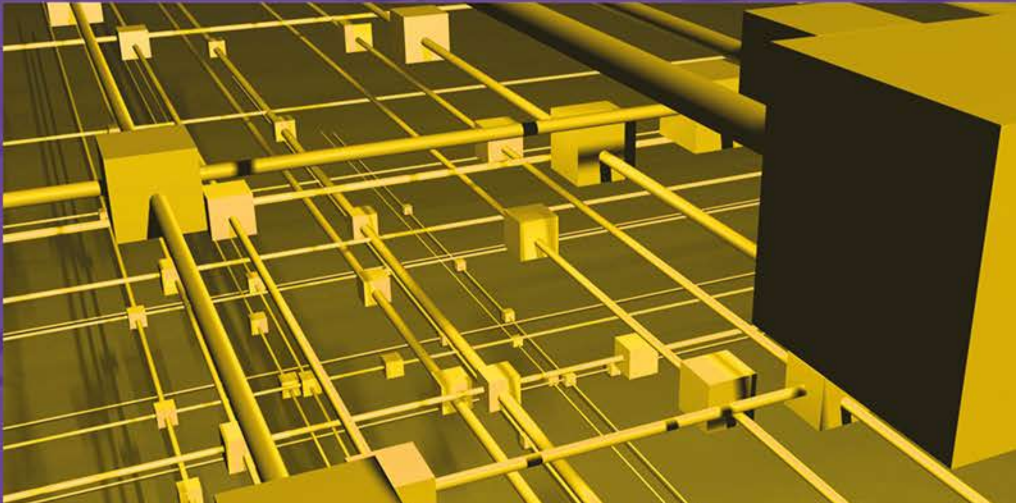
PONTIFICIAE ACADEMIAE SCIENTIARVM ACTA 22

COMPLEXITY AND ANALOGY IN SCIENCE:

Theoretical, Methodological and Epistemological Aspects

Edited by W. Arber, J. Mittelstraß, M. Sánchez Sorondo



The Proceedings of the Plenary Session • 5-7 November 2012

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Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects

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The Proceedings
of the Plenary Session on

Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects

5-7 November 2012

Edited by

Werner Arber
Jürgen Mittelstraß
Marcelo Sánchez Sorondo

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IN CIVITATE VATICANA • MMXV

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The opinions expressed with absolute freedom during the presentation of the papers of this meeting, although published by the Academy, represent only the points of view of the participants and not those of the Academy.

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PONTIFICIA ACADEMIA SCIENTIARVM • VATICAN CITY

My predecessor Benedict XVI likewise proposed "eliminating the structural causes of the dysfunctions of the world economy and correcting models of growth which have proved incapable of ensuring respect for the environment". He observed that the world cannot be analyzed by isolating only one of its aspects, since "the book of nature is one and indivisible", and includes the environment, life, sexuality, the family, social relations, and so forth. It follows that "the deterioration of nature is closely connected to the culture which shapes human coexistence". Pope Benedict asked us to recognize that the natural environment has been gravely damaged by our irresponsible behaviour. The social environment has also suffered damage. Both are ultimately due to the same evil: the notion that there are no indisputable truths to guide our lives, and hence human freedom is limitless. We have forgotten that "man is not only a freedom which he creates for himself. Man does not create himself. He is spirit and will, but also nature". With paternal concern, Benedict urged us to realize that creation is harmed "where we ourselves have the final word, where everything is simply our property and we use it for ourselves alone. The misuse of creation begins when we no longer recognize any higher instance than ourselves, when we see nothing else but ourselves".

Pope Francis, Encyclical Letter *Laudato si'*, para. 6.


C. RUBBIA


P. LÉNA


ES
PÖSCHL
T.-J. CHUANG


PIVS · IIII · PONTIFEX · OPTIMVS · MAXIMVS

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SESSION IV: SCIENCE, EDUCATION AND THEOLOGY

Word of Welcome

I am pleased to see that the ranks are pretty full. I would like to thank all of the present members for taking this opportunity to discuss 'complexity' in our circle. This Plenary Session, which is held every second year, is one of the major activities of our Academy. Here we have the opportunity to bring together scientific aspects that have effects on the daily life, of each one of us, on the whole human population and on the environment, which is our habitat and the habitat of many other living beings. I therefore attach much importance to your help in discussing advances in scientific knowledge and reflections on what these can mean for long periods of time or future development.

We have the possibility to invite non-members to our debates and we feel that we should not use this possibility too much because a debate in a smaller circle is always easier to accomplish than in a large assembly. However, during this Session, we have the chance to have scientist Lilia Alberghina among us, who will present her view on systems biology. I became familiar with her some time ago, we talked about systems biology and we mutually felt that the contribution of her work to our debate on complexity might be very fruitful. So we thank her for coming and look forward to her presentation.

Unfortunately over the last two years we have lost a few of our members and the Council has decided to commemorate them in the Closed Session on Tuesday evening, where we will also hear the presentations of two new members, who we welcome to our circle, Joachim von Braun from Germany, and Vanderlei Bagnato From Brazil.

During the Closed Session we also intend to inform you about the activities that are being planned. We will also talk a little about the publication of our activities, and communicating the information to the Curia, and we will invite you to reflect on renewing your membership. It is clear that we are all getting older from year to year and therefore need some young blood in order to secure the long-term sustainability of our Academy.

Lastly, during the Closed Session, we will hold the commemoration of the Pius XI Medal and shall invite the members to make nominations for possible new candidates for it, and any ideas from your point of view that you wish to discuss. 'Closed Session' means all the members of course, and as such it is important to be present, for those who can. Non-members will not attend at that moment, whilst some guests who are just listening, wives or husbands of members, are welcome to sit in our ranks and listen to us and if you have something important in the discussion to say, you are always welcome to contribute. With these few words I would like to ask Bishop Marcelo Sánchez Sorondo to present his short introduction.

WERNER ARBER

Preface

I would like to add my greetings to all of you who are here. Let me say that we are very satisfied and happy with the work of the Pontifical Academy of Sciences, because in this last year we have had some very important meetings such as the one on *Subnuclear Physics*, organized by Antonino Zichichi and Rolf-Dieter Heuer, Director General of CERN, the one on *New Developments in Stem Cell Research: induced Pluripotent Stem Cells and their Possible Applications in Medicine*, organised by Nicole Le Douarin, and another on *Fate of Mountain Glaciers in the Anthropocene*, organised by Veerabhadran Ramanathan and Paul Crutzen.

This work is very important to show the other academies, but also the Church, the new discoveries that come from the sciences and in this line we are also very happy because the Pope invited our President, for the first time in history, to address the Synod of Bishops, which is a very important institution because it is like the Senate of the Pope and includes all the Bishops of the world. Of course, the President did a very good job in the presence of the Pope and the consequence of this was that our new website was visited infinite times. The Bishops are really very interested in the work of the PAS and I think this is a very important contribution to the work of the Church. Of course, it is not a direct goal of the PAS, but the PAS lives in the Vatican and it is understandable that we have this kind of relationship.

In this sense, because the Pope, as you know, declared this the Year of the Faith, the work of the Academy could be very important, if the Academy presented a sort of hierarchy of the real, proven truth that comes from the sciences, because these truths are very important for the Church which loves the truth, because all truth is a participation of the truth of God.

Thank you for your presence here and thank you for your work, especially the organizers of the workshop and the Plenary Session, and special greetings also to the representative of the Church of Russia who is here because he would like to get to know the Academy of the Pope. I was invited by the Director of the Seminary and the University of the Russian Church and it is a great honour for us to have him here.

Marcelo Sánchez Sorondo

Programme

Monday, 5 November 2012

Welcome

9:00	*Welcome* **Werner Arber**, President of the Pontifical Academy of Sciences **H.E. Msgr. Marcelo Sánchez Sorondo**, Chancellor of the Pontifical Academy of Sciences

Introduction

9:10	*Complexity, Reductionism, and Holism in Science and Philosophy of Science* **Jürgen Mittelstraß**
9:30	Discussion

Session I: PHYSICS, ASTROPHYSICS AND MATHEMATICS

Chair: Werner Arber

9:40	*Complexity at the Fundamental Level* **Antonino Zichichi**
10:10	Discussion
10:20	*Kolmogorov Complexity as a Hidden Factor of Scientific Discourse: From Newton's Law to Data Mining* **Yuri I. Manin**
10:50	Discussion
11:00	Coffee break
11:30	*Scaling in the Complex Systems* **Rudolf Muradyan**
11:40	*Complexity in Space Engineering* **Krishnaswamy Kasturirangan**
11:50	*Complexity and Analogy in the Search of Extraterrestrial Life* **José G. Funes**
12:00	Discussion
12:10	*From Big Bang to Biospheres: The Scope and Limits of Explanation* **Martin J. Rees**
12:20	Discussion
12:30	*Quantum Simulation of Calculationally Intractable Problems and Questions About Emergence* **William D. Phillips**
12:50	Discussion
13:10	Lunch at the Casina Pio IV

Chair: Rafael Vicuña

14:30 *Recurrent Ideas in Mathematical Modelling*
Luis A. Caffarelli

15:00 Discussion

15:10 *Complexity in Chemistry: From Disorder to Order*
Gerhard Ertl

15:40 Discussion

15:50 *Probing the Limits of Quantum Physics by Precision Spectroscopy of Hydrogen*
Theodor W. Hänsch

16:20 Discussion

Session II: Chemistry and Biology

Chair: Veerabhadran Ramanathan

16:30 *Deciphering Complexity in Biology: Induction of Embryonic Cell Differentiation by Morphogen Gradients*
Edward M. De Robertis

17:00 Discussion

17:10 Coffee break

17:40 *Life's Biochemical Complexity*
Rafael Vicuña

18:10 Discussion

18:20 *Systems Biology of Cancer Cell Growth*
Lilia Alberghina

18:30 Discussion

18:40 *Gradual Increases in Complexity Lead to the Emergence of Novel Principles of Information Processing: The Cerebral Cortex as an Example*
Wolf J. Singer

19:00 Discussion

19:10 Dinner at the Casina Pio IV

Tuesday, 6 November 2012

9:00 *Highlights of Nanoscience*
Chintamani N.R. Rao

9:30 Discussion

Session III: Earth and Environmental Sciences
Chair: Paul J. Crutzen

9:40 *Complexity in Climate Change Science*
Mario J. Molina

10:10 Discussion

10:20 Coffee break

10:50 *Climate Change and Protection of the Habitat that Sustains Us: What Can Be Accomplished?*
Veerabhadran Ramanathan

11:10 Discussion

11:20 *Towards a Sustainable Use of Natural Resources by Respecting the Laws of Nature*
Werner Arber

11:40 Discussion

11:50 *Complex Network Analysis of the Virtual Water Trade Among Nations*
Ignacio Rodríguez-Iturbe

12:10 Discussion

12:20 Lunch at the Casina Pio IV

Session IV: Science, Education and Theology
Chair: Jürgen Mittelstraß

14:30 *Analogy, Identity, Equivalence*
Michał Heller

14:50 Discussion

15:00 *Educating to Complexity: A Challenge*
Pierre J. Léna

15:30 Discussion

15:40 *Infinité du monde et infinité de Dieu: quelle corrélation?*
Jean-Michel Maldamé

16:00 Discussion

16:10 Coffee break

Closed Session, Commemorations, Self-Presentations

16:40 Closed Session

Commemorations
Bernardo Colombo (Enrico Berti), **Har G. Khorana** (Werner Arber), **Carlo Maria Martini** (Georges M.M. Cottier), **Rudolf Mößbauer** (Theodor W. Hänsch), **Andrej Szczeklik** (Antonio M. Battro)

Self-Presentations of New Members
Joachim von Braun, Vanderlei S. Bagnato

Future activities of our Academicians. Members' proposals: topics, candidates, etc.

20:00 Dinner at the Casina Pio IV

Wednesday, 7 November 2012

8:45	Visit to the Vatican Museums and Sistine Chapel (optional)
11:00	Pius XI Medal Award Ceremony (Casina Pio IV). *Winners*: Prof. Trees-Juen Chuang, Prof. Ulrich Pöschl
13:00	Lunch at the Casina Pio IV
18:00	Bus leaves the Domus Sanctae Marthae to take the Participants to Villa Madama
18:30	Concert of the Choir of the Italian Spouses Association of the Italian Ministry of Foreign Affairs followed by a dinner at Villa Madama, invited by Foreign Minister Giulio Terzi di Sant'Agata *Villa Madama was designed by Raphael in 1518, just before his death, for Cardinal Giulio de' Medici, cousin of the reigning Pontiff Leo X*

List of Participants

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Address of the President to the Holy Father

8 November 2012

Holy Father,

Your Pontifical Academy of Sciences comes before you on the opening day of the Workshop on *Neurosciences and the Human Person*, which follows its Plenary Session on *Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects*.

Holy Father, we are deeply thankful for your constant solicitude towards our Academy, which is also evident in the appointment of two new Academicians, Physics and Engineering Professor Vanderlei Salvador Bagnato from Brazil and Development and Agricultural Economics Professor Joachim von Braun from Germany, whom we are honoured to introduce to you today. In addition, this year Your Holiness has also awarded the prestigious Pius XI Medal to two young scientists, to the genomics researcher Trees-Juen Chuang from Taiwan who cannot be present today, and to the chemistry researcher Ulrich Pöschl from Austria, now working in Germany.

We are very satisfied with the activity and work of your Academy in the last two years. The three meetings that we have held since our 2010 Plenary Session have focused on three important topics: *Fate of Mountain Glaciers in the Anthropocene*, *Subnuclear Physics*, and *New Developments in Stem Cell Research: induced Pluripotent Stem Cells and their Possible Applications in Medicine*. In addition, this year's Plenary – with its satellite workshop on neurology as an example of complexity – has been crucial in achieving our statutory goals. We will extend our future meetings to any other topic based on available scientific knowledge that may serve for the sustainable development of humanity and the long-term sustainable development of nature. The Pontifical Academy of Sciences tries to fulfil its mission of critically interpreting and establishing a hierarchy of the proven scientific acquisitions and application projects to collaborate at the proper level in your project for a new evangelization, especially during this Year of Faith. We feel very fortunate to have a Pope who has come from our Academy, and we are aware of your understanding and are close to your concerns and your mission to teach Truth, Good and Justice. Therefore, Your Holiness, we look forward to listening to your wise words that will certainly enlighten and guide our Academy's course of action.

We are mindful of the many duties that your high office places upon you, not least the recent and demanding Synod of Bishops, in which I was invited by you to take part, for which I thank you on behalf of our Academicians. We are thus especially grateful to you for granting us this audience today.

■ Werner Arber

Address of His Holiness Benedict XVI to Participants in the Plenary Session of the Pontifical Academy of Sciences

Clementine Hall • Thursday, 8 November 2012

Your Excellencies,
Distinguished Ladies and Gentlemen,

I greet the members of the Pontifical Academy of Sciences on the occasion of this Plenary Assembly, and I express my gratitude to your President, Professor Werner Arber, for his kind words of greeting in your name. I am also pleased to salute Bishop Marcelo Sánchez Sorondo, your Chancellor, and to thank him for his important work on your behalf.

The present plenary session, on "Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects", touches on an important subject which opens up a variety of perspectives pointing towards a new vision of the unity of the sciences. Indeed, the significant discoveries and advances of recent years invite us to consider the great analogy of physics and biology which is clearly manifested every time that we achieve a deeper understanding of the natural order. If it is true that some of the new notions obtained in this way can also allow us to draw conclusions about processes of earlier times, this extrapolation points further to the great unity of nature in the complex structure of the cosmos and to the mystery of man's place within it. The complexity and greatness of contemporary science in all that it enables man to know about nature has direct repercussions for human beings. Only man can constantly expand his knowledge of truth and order it wisely for his good and that of his environment.

In your discussions, you have sought to examine, on the one hand, the ongoing dialectic of the constant expansion of scientific research, methods and specializations and, on the other, the quest for a comprehensive vision of this universe in which human beings, endowed with intelligence and freedom, are called to understand, love, live and work. In our time the availability of powerful instruments of research and the potential for highly complicated and precise experiments have enabled the natural sciences to approach the very foundations of corporeal reality as such, even if they do not manage to understand completely its unifying structure and ultimate unity. The unending succession and the patient integration of various theories, where results once achieved serve in turn as the presuppositions for new research, testify both to the unity of the scientific process and to the constant impetus of scientists towards a more appropriate understanding of the truth of nature and a more inclusive vision of it. We may think here, for example, of the efforts of science and technology to reduce the various forms of energy to one elementary fundamental force, which now seems to be better expressed in the emerging approach of complexity as a basis for explanatory models. If this fundamental force no longer seems so simple, this challenges researchers to elaborate a broader formulation capable of embracing both the simplest and the most complex systems.

Such an interdisciplinary approach to complexity also shows too that the sciences are not intellectual worlds disconnected from one another and from reality but rather that they are interconnected and directed to the study of nature as a unified, intelligible and harmonious reality in its undoubted complexity. Such a vision has fruitful points of contact with the view of the universe taken by Christian philosophy and theology, with its notion of participated being, in which each individual creature, possessed of its proper perfection, also shares in a specific nature and this within an ordered cosmos originating in God's creative Word. It is precisely this inbuilt "logical" and "analogical" organization of nature that encourages scientific research and draws the human mind to discover the horizontal co-participation between beings and the transcendental participation by the First Being. The universe is not chaos or the result of chaos, rather, it appears ever more clearly as an ordered complexity which allows us to rise, through comparative analysis and analogy, from specialization towards a more universalizing viewpoint and vice versa. While the very first moments of the cosmos and life still elude scientific observation, science nonetheless finds itself pondering a vast set of processes which reveals an order of evident constants and correspondences and serves as essential components of permanent creation.

It is within this broader context that I would note how fruitful the use of analogy has proved for philosophy and theology, not simply as a tool of horizontal analysis of nature's realities, but also as a stimulus to creative thinking on a higher transcendental plane. Precisely because of the notion of creation, Christian thought has employed analogy not only for the investigation of worldly realities, but also as a means of rising from the created order to the contemplation of its Creator, with due regard for the principle that God's transcendence implies that every similarity with his creatures necessarily entails a greater dissimilarity: whereas the structure of the creature is that of being a being by participation, that of God is that of being a being by essence, or *Esse subsistens*. In the great human enterprise of striving to unlock the mysteries of man and the universe, I am convinced of the urgent need for continued dialogue and cooperation between the worlds of science and of faith in the building of a culture of respect for man, for human dignity and freedom, for the future of our human family and for the long-term sustainable development of our planet. Without this necessary interplay, the great questions of humanity leave the domain of reason and truth, and are abandoned to the irrational, to myth, or to indifference, with great damage to humanity itself, to world peace and to our ultimate destiny.

Dear friends, as I conclude these reflections, I would like to draw your attention to the Year of Faith which the Church is celebrating in commemoration of the fiftieth anniversary of the Second Vatican Council. In thanking you for the Academy's specific contribution to strengthening the relationship between reason and faith, I assure you of my close interest in your activities and my prayers for you and your families. Upon all of you I invoke Almighty God's blessings of wisdom, joy and peace.

COMMEMORATIONS OF DECEASED ACADEMICIANS

Bernardo Maria Colombo († 26.IV.2012)

Bernardo Maria Colombo died earlier this year on 26 April 2012. Born in Olginate (Italy) on 24 February 1919, he had been a member of this Pontifical Academy for 20 years, since 18 September 1992. The scope of his scientific research is evident by his long list of publications visible in his *Curriculum vitae* in the Academy's Yearbook and on its website. His career began with an Economics Degree from the Catholic University of Milan, followed by an assistant position to the Chair of Statistics at the University of Venice. He then became Visiting Fellow at Princeton, Statistics Professor at the University of Venice and Chair of Demography at the University of Padua where he finished as Professor Emeritus. The mere mention of these disciplines indicates the breadth of interests that characterized Bernardo Colombo's research, from economics to statistics and demographics. It was in this latter area that he gave his greatest contribution as a scholar and teacher. Indeed, the Faculty of Statistical, Demographical and Actuarial Sciences at the University of Padua, the first faculty of its kind in Italy, was established thanks to him.

But despite reaching the highest levels internationally, made evident by his numerous awards from Italy and abroad, scientific research was only one aspect of his job and merits. He was also an expert consultant to major public institutions, at both the national and international level, in the field of population policy. Convinced that demographic studies, while having to meet the most rigorous scientific criteria, are not ends in themselves, but should contribute to social utility, highlighting issues of public interest and suggesting solutions of a political nature, Bernardo Colombo never hesitated to strengthen his commitment towards institutional organizations devoted to the implementation of social policies. For this reason the volume published by the University of Padua on his 90th birthday, titled *Bernardo Colombo. Una vita per la scienza* (*A Life in Science*) (Padua, 2009), while including a valuable interview with him by two of his students, does not do justice to his work, because Colombo's life was not solely devoted to science, or rather it was devoted to science in view of the services that it can render to life.

The first important evidence of his social commitment was his participation in the School Survey Commission, established in 1962 by the Italian government, which produced the *School Development Plan* of 1962. His reputation as an expert in statistics and demography first and foremost at the national level, led Bernardo Colombo to be part of several ISTAT (National Statistics Institute) committees on various subjects such as the Italian population censuses, the revision of the Statistics Yearbook, the respect for the confidentiality of statistics and the sampling distribution of data. Thanks to his reputation, which soon became international, he was included in Committees belonging to the UNESCO, UIESP (International Union for the Scientific Study of Population), and the United Nations, as well as in associations such as the International Statistical Institute and the International Association for Official Statistics.

However, the most remarkable testimony of his human commitment was certainly his involvement as an "expert" in the works of the Second Vatican Council, which later led him to join the Pontifical Commission for the Study of Population, Family and Births. In this capacity, Bernardo Colombo contributed to the drafting of paragraphs 47-52 and 87 of *Gaudium et Spes*, devoted to "Fostering the Nobility of Marriage and the Family" and "International cooperation in the field of population growth". He then published an extremely interesting account of this experience, titled *Discussioni sulla regolazione della sterilità* (*Discussions on the regulation of infertility*), in the journal *Teologia* of the Theological Faculty of Northern Italy (2003/1).

Having thus achieved an international reputation, both in the relations between States and in the life of the Catholic Church, Colombo continued and expanded his commitment to social institutions as an expert on population issues. Further evidence of this was the report he wrote for the closing session of the plenary of the International Population Conference, organized by the International Union for the Scientific Study of Population in Mexico City in August 1977, on the theme "Human rights, ideology and population policies" (the other rapporteur was Simone Veil, the French Minister at the time). The topic demonstrates the breadth and diversity of Colombo's interests, ranging from the concept of ideology to the meaning of human rights, the need for population policies on international migration, internal migration, mortality, marriage, fertility and related problems. He also stressed the importance of demography for the development of these policies in his inaugural speech for the 1977-1978 academic year of the University of Padua.

Another significant milestone in Bernardo Colombo's social commitment was his coordination of the 1992 study week organized by the Pontifical Academy of Sciences on *Resources and Population*. The work ended with a Report prepared by Colombo himself in collaboration with Georges M.M. Cottier, theologian of the Pontifical Household, Ugo Farinelli, scientific adviser of ENEA, Antonio Golini, demography professor, and Alberto Quadrio Curzio, a professor of political economy. The proceedings of that study week were published in 1996 by Clarendon Press, Oxford under the title *Resources and Population. Natural, Institutional, and Demographic Dimensions of Development*, edited by Colombo, P. Demeny and M.E. Perutz, with an Address by His Holiness, Pope John Paul II. The Final Report emphasizes the urgency of the problems created by the enormous increase in world population and provides information and guidance to political and religious authorities to solve these problems in compliance with human dignity and mutual solidarity.

Throughout the course of his life Bernardo Colombo took part in both Italian and Vatican delegations at international conferences, such as UNESCO's International Conference on Education (Paris 1968), the Council of Europe's European Demographic Conference (Strasbourg 1968), the World Population Conference (Bucharest 1974), the World Conference on Population and Development (Cairo 1994), and the World Commission on the Ethics of Scientific Knowledge and Technology (Oslo 1999). The President of the Italian Republic appointed him as member and later chairman of the Commission for the Protection of Statistical Information of the Presidency of the Council of Ministers (1990-1996).

Bernardo Colombo never included any of these roles in his *Curriculum Vitae* for our Yearbook, because his modest, shy, sober nature, far from any form of exhibitionism, prevented him from doing so. His nature dictated his lifestyle, as witnessed by those who knew him personally, in the outside world and even in our Academy. He would generously offer scientific guidance to all who came to him, first of all his students, for whom he created a school of demographic sciences in Padua that was appreciated everywhere. At the same time, in terms of moral guidance he was reserved and respectful of the autonomy of others, and largely limited himself to setting a good example, as one of his pupils said in a speech during the funeral ceremony that was held at the university in his honour. As a scientist and as a man he also demanded scientific rigour in his own research and in that of others, and was critical and at times scathing in the face of undeserved merit. He was also ironic about himself and with those who deserved it, but also extraordinarily willing and kind when it came to listening to what others had to say, trying to understand their reasons and helping them find a common solution to their various problems. Last but not least, he was sincere, quiet and open in testifying to his Christian faith every day. His very long and extraordinarily intense career is an honour for his university, for his country's culture and also for the international prestige of this Academy.

Enrico Berti

Har Gobind Khorana († 3.XI.2011)

Har Gobind Khorana had his roots in India, where he was born on 9 January 1922, in Raipur, Punjab where he also received his basic education. His wide scientific interests were strengthened by his studies at Punjab University, Lahore, where he obtained his B.Sc. in 1943 and his M.Sci. in 1945. He then emigrated to Europe for advanced studies at the University of Liverpool, where he obtained his Ph.D. in 1948. During his postdoctoral training at the ETH Zürich in 1948/49 he became acquainted with his future wife. He then spent another two years at Cambridge University before leaving in 1952 for the University of British Columbia in Vancouver.

Khorana's essential contributions to research in organic chemistry and synthesis strongly benefited from his broad interests in biological problems and they received wide recognition by the scientific community. By the 1950s his laboratory had already been studying energy-rich phosphate esters including polynucleotides. He thereby developed methods for their synthesis. He continued this work after moving to the University of Wisconsin, Madison, USA, in 1960. This then led him to fundamental investigations on the genetic code that serves living organisms as language in the biosynthesis of protein gene products. Carrying out this research with several quite different organisms he came to the conclusion that a particular genetic code is used by all studied organisms and that this code is thus most likely to be of a universal nature, used by all living beings. This fundamental contribution to scientific knowledge found its well merited recognition with the attribution of the Nobel Prize in Medicine in 1968, jointly with Robert Holley and our late Academician Marshall Nirenberg, who had also made essential contributions to the understanding of protein synthesis.

In 1970 Khorana accepted an Alfred Sloan Professorship for Biology and Chemistry at the Massachusetts Institute of Technology in Cambridge, USA, where he worked until his retirement in 2007. On 17 April 1978 he was appointed to our Academy, where he became an active and highly estimated member. Following the elucidation of the universal genetic code, he paid particular attention to the total synthesis of polynucleotides, including genetic information in the laboratory. We can consider him to be an early pioneer of synthetic biology by developing underlying methodology and concepts. His interests also led him to studies of biological membranes, in particular of membrane proteins that transduce light, such as bacteriorhodopsin and essential functions for photoreception and energy transfer in living organisms.

Har Gobind Khorana died on 9 November 2011, after a rich life, leaving very valuable contributions to novel fundamental scientific knowledge. Our Academy is grateful to him for his appraised contributions to its activities.

Werner Arber

Cardinal Carlo Maria Martini († 31.VIII.2012)

I would like to commemorate our Cardinal Carlo Martini. Carlo Maria Martini was born in Turin on 15 February 1927. He entered into the novitiate of the Jesuits in 1944 and studied philosophy and theology in Gallarate, Chieri, Austria and lastly at the Gregorian Pontifical University, during which time he was ordained a priest in 1952. He finished his studies with a doctoral thesis in fundamental theology entitled: *The Historical Problem of the Resurrection in Recent Studies* (1958).

His thesis represented his first contribution to the research field of the sources of Christian origins, where he rigorously applied the historico-critical method. Following this perspective he went on to work at the Pontifical Biblical Institute in Rome, under the guidance of Father Bea, S.J.

He presented his second doctoral thesis in 1965, which was a textual critique entitled: *The Problem of the Recensionality of Codex B in the Light of Papyrus Bodmer XIV,* which contains a group of codices of the Gospel according to Luke. He immediately began his teaching at the Pontifical Biblical Institute. One of his preferred texts for research was the Acts of the Apostles.

I shall now give you some tracts that characterised his personality, which was both intellectual and Christian. The first was his historical culture. He took Erasmus as a reference point and published an essay on Galilei and theology (1967). He was not indifferent to the reality of human misery and always made time to visit the youth detention centre.

On 29 February 1969 he was appointed Rector of the Biblical Institute. He was rector for nearly ten years during the difficult times of the student protests. The Biblical Institute was also criticised but this did not affect his scientific work. His authority was universally recognised. He had contacts with universities from all over the world and was part of the group of five specialists who published the second edition of *The Greek New Testament* (Stuttgart, 1968), which was to serve as a basis for more than eight hundred versions of the Gospel around the world. As soon as he finished his term, he was nominated Rector of the Pontifical Gregorian University in 1978. He was not rector for long however; to general surprise John Paul II nominated him Archbishop of Milan.

He was elected Cardinal on 2 February 1983. This new mission could have distanced him forever from his studies, but it was not the case. His episcopate in Milan lasted until his retirement in February 2002. The extremely intense period was to reveal Carlo Maria's leadership skills, his creativity as well as his great capacity for discernment with regards to problems in the Church and society.

He truly was a man of meaningful dialogue and in 1987 created the lecture series for non-believers entitled *Cattedra dei non-credenti*. Furthermore, during the time of the Red Brigades he strove to build peace, breaking down the logic of violence through dialogue. In June 1984 a group of Brigade members laid down their arms in front of the Archbishop as a sign of renouncing armed conflict. In 1986 he was elected President of the Council of Bishops' Conferences of Europe, where he developed an intense ecumenical activity that culminated in the momentous meeting in Basel in 1989. He published diocesan letters and the texts of his homilies and spiritual retreats, leaving behind a rich patrimony of pastoral thought.

He was nominated a member of our Academy on 13 November 2000. On 15 February 2002, at the age of seventy-five, he asked permission to retire. After receiving approval from John Paul II he transferred to Jerusalem, the place of origin of the privileged object of his studies, and in a short time he prepared the critical edition of the papyrus Bodmer VIII, a papyrus from the third century and the oldest one containing *Peter's Letters*. He then proceeded to work on the critical introduction to the *Greek Vatican Codex 2000*, or codex B, which contains the entire text of the Greek Bible. In Jerusalem he had scientific contacts with the Jewish university, demonstrating that he was a man of dialogue and peace.

After some time however, he began to suffer from Parkinson's disease and the illness progressed until it was necessary for him to return to Italy in 2008 in order to receive care. He returned to the house of his novitiate in Gallarate, and passed away on 30 August 2012. His highly attended funeral was an impressive witness of the gratitude of the people of Milan.

CARDINAL GEORGES COTTIER

Rudolf L. Mößbauer († 14.IX.2011)

In October 1961 a sensational announcement mesmerized post-war Germany. Rudolf Mößbauer, age 32, had won the Nobel Prize in physics for his discovery of the effect named after him. I remember this event vividly, since I had just enrolled at the University of Heidelberg as a new student of physics. Mößbauer, a young German physicist recognized with the highest scientific honor, instantly became our inspiring hero, who symbolized the hopes and aspiration of a new generation of science students.

Rudolf Mößbauer was born on 31 January 1929 in Munich, Germany. He was a talented piano player but decided to study physics at the Technical University of Munich (then called Technische Hochschule). He received his doctoral degree under Professor Heinz Maier-Leibniz in 1958. Since the Technical University was overcrowded with students, he carried out his experiments at the Max-Planck Institute for Experimental Medicine at Heidelberg. After graduating he continued this work for another two years as an assistant at the Technical University. During his experiments he observed for the first time what is now called the Mößbauer effect.

In his research, Mößbauer studied resonance fluorescence of nuclei. Resonance fluorescence is well known for atoms. Atoms emit light at spectral lines, which are determined by the surrounding bound electrons and are characteristic for each atomic species. Resonant radiation can be absorbed by atoms of the same species, but not by different atoms. It was expected that this method of resonance fluorescence would be much more selective for nuclei. The frequencies of gamma rays emitted by long living nuclei are determined much more precisely than the frequencies of light emitted by bound electrons and are usually much higher. A problem arises because each gamma ray photon transfers a small recoil momentum to the nucleus. This changes the gamma ray frequency by a tiny amount. Though very small, the change is large enough so that the radiation can no longer be absorbed by another nucleus.

Rudolf Mößbauer tried to observe resonance fluorescence with Iridium-191 nuclei by heating both source and absorber. However, the effect was very small. When he cooled both samples, he expected the signal to disappear, because the line would become even narrower. However, he observed a stronger signal at lower temperature. The explanation comes from quantum physics. For a certain fraction of atoms, depending on temperature, the gamma recoil momentum is taken up by all the atoms in a crystal, not by an individual nucleus. The crystal acts like an immovable rock from which the gamma photon can jump away so that the frequency change due to recoil becomes negligible.

The observation of nuclear resonance fluorescence enabled by this effect is known as Mößbauer spectroscopy. This technique makes it possible to observe small changes in energy down to one billionth of an electron volt, compared to gamma ray energy of perhaps a hundred thousand electron volts.

This precision enables countless applications in physics and chemistry. To give a few examples:

– In chemical analysis one cannot only determine the atomic species of a sample but also the kinds of chemical bonds.

– In biochemistry, this can be used to elucidate the structure and function of iron containing enzymes.

– In technical chemistry, it has been possible to clarify the function of different catalysts.

– Among the most interesting applications in fundamental physics are precision tests of Albert Einstein's theories of special and general relativity. Already by 1959, Pound and Rebka Jr. had used the Mößbauer effect to observe the red-shift of gamma photons in the gravitational field of the earth.

On the initiative of Richard Feynman, Rudolph Mössbauer went to the California Institute of Technology in 1960. He was a Professor there from 1962 until he returned to the Technical University of Munich in 1964. Following the US model, he introduced non-hierarchical Department structures. Numerous new academic positions were created and new directions of research became possible. These measures contributed significantly to the reputation of physics in Munich.

In the late 1970s, Mößbauer turned his attention to neutrino physics. Neutrinos are, for instance, produced in the nuclear reactions that generate the energy of the sun. It had been observed that much fewer neutrinos arrive on earth than expected from radiated energy. Some physicists speculated that the nuclear reactions powering the sun may have stopped and we are only witnessing some kind of afterglow.

A rather far-fetched explanation was the assumption that neutrinos are changing into some other elementary particle on their way from sun to earth. Mößbauer tried to observe the transmutation of neutrinos from a nuclear reactor, without observing any effect. Although these experiments were belittled by quite a few colleagues, he was fundamentally correct. We know today that neutrino oscillations occur. However, the effect is so small that it was not feasible for Mößbauer to observe it with the techniques available to him. Since then, the effect has been confirmed at large underground neutrino observatories. The experiments led to a Nobel Prize for Raymond Davis and Masatoshi Koshiba. The Journal *Nature* writes in its obituary: "(Mößbauer) saw Science as a language connecting all of the people in the world." He started many international collaborations, and during the Cold War he was one of the first to organize Seminars with Soviet physicists, long before this became feasible for US colleagues.

Rudolf Mößbauer was a charismatic and inspiring academic teacher. His legendary lectures may have motivated quite a few students to choose the Technical University of Munich for their studies of physics.

Despite his high reputation, Rudolf Mößbauer always remained a friendly and modest individual. In this way, he continues to inspire many of us as a role model.

The Pontifical Academy of Sciences is proud to have counted Rudolf Mößbauer among its members.

■ Theodor W. Hänsch

Andrezej Szczeklik († 3.II.2012)

I am honored and grateful to speak in memory of our beloved colleague Andrezej Szczeklik. I met him for the first time at our Academy in 1994 and I will always remember his self-presentation, modest and to the point. He gave a moving testimony of his admiration and love for Pope John Paul II. A few years later he gave me as a gift his inspiring book *Catharsis: On the Art of Medicine* with a foreword by the great Polish humanist and poet Czesław Miłosz. A continuation of this book is called *Koré: On Sickness, the Sick, and the Search for the Soul of Medicine*, a suggestive title that reveals the spirit and mission of a man totally dedicated to his patients and to science.

Andrezej Szczeklik was born in 1938 in Cracow, where he studied medicine. He did post-doctoral training and research at the Karolinska Institut, Uppsala University and North Carolina-Chapel Hill. He became professor and chairman of the Jagiellonian University School of Medicine, Cracow, and president of the Copernicus Academy of Medicine. He was a member of the Polish Academy of Arts and Sciences, the Royal College of Physicians, the American College of Physicians and the Pontifical Academy of Sciences. He became an active participant in all our Plenary Sessions. He received honorary doctorates from the Schools of Medicine of Wrocław, Warsaw, Katowice and Łód . He was awarded the *Gloria Medicinae* Medal by the Polish Society of Medicine. He received the first prize of *The Lancet* for his paper on genetic polymorphism of leukotriene C4 synthase. In 2001 he was awarded the Gold Medal and *The Robert A. Cook Memorial Lectureship* by the American Academy of Allergy, Asthma and Immunology.

His whole life was dedicated to the study and treatment of cardio-pulmonary diseases. He was one of the first to discover the mechanisms of non-steroidal anti-inflammatory drugs that precipitate asthma attacks in sensitive patients by inhibiting cyclooxygenase (COX-1), a key enzyme in the metabolism of eicosanoids (substances produced by arachidonic acid). He was a leader of the *European Network on Aspirin-Induced Asthma* centered in Cracow. He discovered the genetic polymorphism and over-expression of leukotriene C4 synthase in patients with aspirin-induced asthma and the alteration of the metabolism of arachidonic acid common to asthma and urticaria.

He studied the history of salicylates, the forbears of aspirin, the drug that was produced by the pharmaceutical firm Bayer in 1899 and became the most popular drug in the world. His paper *The history of aspirin: the discoveries that changed contemporary medicine* presented at our Plenary Session 2004 and published in *Paths of Discovery* was a remarkable contribution to our understanding of clinical investigations.

He also worked in the mechanisms related to blood clotting after the discovery by his colleague Ryszard Gryglewski in 1976 of prostacyclin in humans, a local substance produced by the lining of blood vessels that produces vasodilation and inhibits blood clotting. In his book *Catharsis* he vividly described the first test of the drug in themselves at the Hospital of Cracow using a sample of the molecule synthesized by Joseph Fried, and how he was affected with high fever after the intravenous infusion (the prostacyclin was contaminated by bacteria) and how Gryglewski lost consciousness (because of the massive vasodilation and the lowering of blood pressure). After further experiments on himself without any complications they started to treat patients with serious diseases of peripheral vessels. I quote "How many days and nights we spent at their bedsides, listening out for the piercing pain in their feet to quieten down, and not believing our own eyes where the deep ulcers on their skin shrank and dwindled as the blood was mixed with a daily dose of prostacyclin". Today stable analogues of prostacyclin are used in the treatment of pulmonary hypertension and also in the treatment of arteriosclerosis. It was further discovered that aspirin inhibits blood clotting and that those statins that reduce blood cholesterol also inhibit blood clotting.

Szczeklik, the remarkable internist and scientist, the mentor of generations of Polish physicians who published more than six hundred papers, was also a humanist, writer, musician, lover of the arts and a man of deep faith that practiced medicine as a sublime humanitarian art. He said "An internist is like a symphony orchestra conductor; specialists are like individual instrumentalists. They do the playing, but only the conductor knows all the instruments and what to expect from them". In his book *Catharsis* he wrote that "Medicine concerns perhaps the strongest of human desires – our longing for love, which is usually unfulfilled". We will miss him.

■ ANTONIO M. BATTRO

SELF-PRESENTATION OF THE NEW ACADEMICIANS

Joachim von Braun

I must say I appreciate how you commemorate those on whose shoulders we are standing; it is very nice. Thank you very much for electing me into this wonderful Academy. Let me briefly say a few words about myself.

My parents came from what is today Poland and Russian parts of former Germany and Silesia and East Prussia. I studied agriculture – on the engineering of plants and animals – at the University of Bonn. My doctoral research was in applied economics. I built demographic economic models, supposedly predicting how many farmers there would be in Germany, in which districts and so on; it was on the modelling of structural change. After that I moved on to what I was really interested in for quite some time, which was addressing issues of development. I lived in Egypt for a couple of years, modelling the river Nile and what would happen to water use and land use if the state-planned economy there became more market-oriented in those days, that is, the early 1980s. Then I spent some time in Washington in an institute of which I later became Director General, called the International Food Policy Research Institute. I got increasingly interested in the relationship between the access and availability of food, technology and what policy can do about addressing hunger. I had a large research programme in about eight countries on the relationships between technology and nutrition. It was research which combined health, that is, weighing children and assessing their health. I lived with my family, including my then small children, in a village in Africa and moved around between various African countries and Central America, weighing children, their health, and assessing the impact of technology on these households and communities, trying to find clues on what to do better. Thus, it was defining the research agenda more from the problem: problem-solving research or applied research.

Some of you may recall the major famine events in Ethiopia in the mid-1980s, which stimulated me to carry out a long-term research programme on Sudan and Ethiopia's hunger crisis. I felt one needed to understand these problems from within so I shuttled back and forth between Sudan and Ethiopia for quite some time and there is a book which is unfortunately still relevant and in print on famines in Africa.

I got deeply involved academically in an international association of agricultural economists, the Association of Agricultural Economists, which was actually founded by Lord Elmhurst, upon the suggestion of an Indian philosopher and writer, Rabindranath Tagore, a Nobel laureate. So it is interesting to note that a philosopher told some early agricultural economists in the 1920s, in the last century, "You people better form some association which addresses food, agriculture and hunger problems".

I was President, Vice-President etc. of that association, which gave me access to a global community of researchers addressing these issues. Then until three years ago, I was Director General of the International Food Policy Research Institute, the leading research institute addressing problems of poverty and hunger in low-income countries. I got deeply involved in trying to explain and address solutions in the last world food crisis of 2007 and 2008, which the teams around me had predicted in 2005. Policy makers actually listened to that in China. I had meetings with the Chinese Prime Minister and the Indian Prime Minister, but less so in the rich world; listening to predictions came late and action came even later. But I learned in that crisis situation that as an academic and researcher we also have to communicate otherwise damage control and the impact of our work is too limited. So I gave speeches at the United Nations, at Davos World Economic Forums and in all the media channels that you can think of, which of course also diverts one from good research; it is a double-edged sword. But I enjoy being back at university and more in academia at the University of Bonn where I am leading the Centre for Development Research, an institute with multi-disciplinary characteristics, which has 120 doctoral students and about 70 post-doctoral students, working on ecological and natural resource issues on economic and technological change and political and cultural change. Such are the names of the three departments of my institute. I've been married to Barbara von Braun for thirty-six years and we have three wonderful daughters. I look forward to working with you.

Thank you.

Vanderlei Salvador Bagnato

Firstly I would like to say that I am very happy to be here and I would like to thank the Chancellor and the President of the Academy for nominating me and, of course, the Pope for accepting the nomination.

I was born in 1958; I am married to Silvia M.F. Bagnato and have a son (Luciano) and a daughter (Renata). I am the second generation of Italians who came to Brazil at the very beginning of the twentieth century to work in the coffee plantations. My father, a first generation Brazilian, was a bluecollar worker who had a firm determination to transfer to his children the value of working hard in order to advance in life. I always studied in Sao Carlos, Brazil. I obtained my Bachelor in Physics (University of São Paulo) and Material Science Engineering (Federal University of Sao Carlos) simultaneously. After that I obtained a Master's Degree in Physics and departed for my PhD, which I obtained from MIT in 1987. In 1989 I received the title of "Livre-Docente" in Physics at University of São Paulo and later, Full Professor at University of São Paulo (1993).

I concentrate my activities on laser cooling and trapping of neutral atoms and biophotonics. Since returning from my PhD I have started to construct a laboratory for advanced studies in both of those areas. Under my guidance, the laboratory has achieved Bose-Einstein Condensation initiating pioneering work with quantum macroscopic matter including the determination of macroscopic global thermodynamic variables and quantum turbulence, with the aim to provide hints to understand the overall concept of fluid turbulence.

My diverse activities include the construction and evaluation of the first atomic clock developed in Latin America and the first pilot plant for the production of high precision microscopes, which served as a seed to spin off optics companies. Recently, in Brazil, my research group implemented a full action, composed of basic and applied research, for the clinical use of Photo-Dynamic-Therapy for the treatment and diagnostic of cancer, as well as for microbial control. About 40 patents originated from our activities are providing subsidies for the products of over 15 companies in the field of Biophotonics.

A strong relation between basic research and industry is one of the characteristics of my work, resulting in the implementation of high technology industries in the field of optics in Brazil. Besides my strong dedication to research, I direct a 24/7 TV channel for the diffusion of science. This channel, together with public science exhibitions and the elaboration of education science kits, has provided many students in Brazil with an important complement to their formal education.

In my carrier I have published over 300 papers in international journals with more than 3000 citations. During my academic life, I have supervised more than 50 graduate students and I am presently advising 17 graduate students involved in several research programs. I like to maintain close international relations with many institutions around the world. Today my research group has more than 90 participants with 4 faculties and 12 researchers. I believe in Science with Social responsibility, science that advances knowledge but at the same time helps create a better life, jobs, education and produces people that are determined to continue doing science for this purpose and not for glorifying their own names. Becoming a member of the Pontifical Academy of Sciences gives me an even higher responsibility to continue my work and to contribute to the initiatives of the other members of this prestigious institution.

THE PIUS XI MEDAL AWARD

Trees-Juen Chuang

Brief Account of Scientific Activity

Comparative and Evolutionary Genomics/Transcriptomics: From Enciphering to Deciphering

Before 1998, T.J. Chuang's work was mainly devoted to the following fields of computer science: Image/Signal Processing, Image Compression/Encryption/Hiding, Pattern Recognition, and Progressive Communication. To increase the security level of image transmission, T.J. Chuang, while working in Ja-Chen Lin's laboratory, proposed several algorithms for enciphering images. After T.J. Chuang received the Ph.D. degree in 1998, he changed his research interests from computer science to life science and devoted himself to deciphering genetic codes. T.J. Chuang's research includes the following four topics.

1. Identification of gene structures and alternatively spliced variants (ASVs)

T.J. Chuang developed a homology-based algorithm named CRASA (Complexity Reduction Algorithm for Sequence Analysis) for a framework annotation of expressed genes in the genome, which efficiently reduced the data complexity and performed gene identification on the basis of the same species EST-to-genome alignments (Chuang *et al.*, 2003, *Genome Res.*). On the basis of cross-species comparisons, several pipelines/Web interfaces, including PSEP (Chuang *et al.*, 2004, *Bioinformatics*), ESTviewer (Chen *et al.*, 2005, *Bioinformatics*), ENACE (Chen *et al.*, 2006, *BMC Bioinformatics*), and PGAA and RiceViewer (Chen *et al.*, 2007, *Plant Physiol.*), were further developed for identification of novel genes/ASVs in mammals or plants. Experimental validations also supported the effectiveness of these methods.

2. Analysis of conflicting arguments in evolution

T.J. Chuang's group first addressed a controversy over whether alternatively spliced exons (ASEs) evolve faster than constitutively spliced exons (CSEs). By examining the synonymous (Ks) and non-synonymous (Ka) substitution rates in human-mouse orthologous exons, ASEs were shown to have higher Ka values and higher Ka/Ks ratios than CSEs, indicating faster amino-acid-level evolution in ASEs. Meanwhile, the majority of ASEs have lower Ks values than CSEs. With reference to the substitution rate in introns, the Ks values in ASEs were shown to be close to the neutral substitution rate, whereas the synonymous substitution rate in CSEs has likely been accelerated (Chen *et al.*, 2006, *Mol. Biol. Evol.*). The effects of multiple features of ASEs on the KA/KS ratio test were also examined (Chen *et al.*, 2006, *BMC Bioinformatics*). Furthermore, different ASE patterns were shown to undergo opposite selection pressure, with CSEs in-between, suggesting that evolutionary analyses of AS should take into consideration the effects of different splicing patterns. (Chen *et al.*, 2007, *Mol. Biol. Evol.*; *BMC Evol. Biol.*). T.J. Chuang's group also addressed the controversy on whether duplicate genes evolve more slowly than singletons by considering gene family size conservation (Chen *et al.*, 2010, *Mol. Biol. Evol.*). Recently, T.J. Chuang tries to address another controversy on whether DNA methylation is correlated with increased or decreased protein evolutionary rates. The preliminary result reveals differential correlations between DNA methylation and the evolutionary rates of coding exons in different genic positions.

3. Genomic/Transcriptomic variations between human and non-human primates

T.J. Chuang's group inferred human-specific (HS) insertions/deletions (indels) using multiple sequence alignments of mammalian genomes and thus identified >840,000 "small" indels, which affected more than 7,000 human genes (>11,000 transcripts). Functional analysis revealed that HS indels might have contributed to human unique traits by causing changes at the RNA and protein level (Chen *et al.*, 2007, *Genome Res.*; *Nucleic Acids Res.*). HS indels were further suggested to have been associated with human adaptive changes at both the species level and the subpopulation level (Chen *et al.*, 2009, *Genome Biol. Evol.*). On the basis of processed pseudogenes (PPGs), which are reverse transcribed ancient transcripts present in the current genome, T.J. Chuang's group also showed that chimpanzee PPGs can be applied to the identification of novel human exons/ASVs and the inference of the ancestral hominoid transcriptome and chimpanzee exon loss events (Huang *et al.*, 2008, *Genome Res.*).

4. Post-transcriptional events in human embryonic stem cells (hESCs)

Post-transcriptional events embrace cis-splicing, trans-splicing, RNA editing, and so on. T.J. Chuang's preliminary results have shown that lineage-specific ASVs (or cis-splicing events) can play important roles in proliferation divergence between human and non-human primate ESCs during early neural differentiation. In addition, T.J. Chuang's group identified and confirmed several trans-spliced RNAs in hESCs, including the first reported trans-spliced large intergenic non-coding RNA. The preliminary results showed that these trans-spliced RNAs are all highly expressed in human pluripotent stem cells and differentially expressed during hESC differentiation. As well, trans-splicing may be significantly associated with the maintenance of pluripotency of hESCs. Like cis-/trans-splicing, RNA editing also lead to the generation of multiple transcript isoforms from a single gene, increasing the complexity of transcriptome/proteome. T.J. Chuang and his laboratory may, within the next few years, develop new computational tools to minimize potential false positives while detecting post-transcriptional events and provide insights into the role of these events in the pluripotency maintenance of hESCs and lineage differentiation.

Ulrich Pöschl

Brief Account of Scientific Activity

The scientific activities of Dr. Ulrich Pöschl encompass the chemistry, physics and biology of the Earth system, climate and public health. His research and teaching deal primarily with multiphase processes, i.e., chemical reactions, mass transport and phase transitions of gaseous, liquid and solid substances linking the atmosphere, biosphere and hydrosphere on molecular to global scales. Focal points are biological and organic aerosols, aerosol-cloud interactions, reactive oxygen species, protein nitration and oxidation, and allergic reactions. The multidisciplinary approach of Dr. Pöschl is to address and combine physical, chemical and biological questions and techniques in environmental observations, laboratory experiments, and mathematical models. His major academic achievements include: (a) global measurements and modeling of biogenic aerosols and cloud condensation nuclei; (b) a universal kinetic model framework and master mechanism of multiphase chemistry and gas-particle interactions in aerosols and clouds; (c) the detection of amorphous solid phases and moisture-induced phase transitions in organic aerosol particles; (d) the discovery of protein nitration as a molecular rationale for the enhancement of allergic diseases by air pollution; (e) the development of interactive open access publishing with a two-stage publication process, public peer review and interactive discussion for improved scientific communication and quality assurance. The results and success of Dr. Pöschl's scientific activities are documented in more than a hundred peer-reviewed journal articles that received over four thousand citations, and in several hundred contributions to conferences, proceedings, and books (http://www.researcherid. com/rid/A-6263-2010).

COMPLEXITY, REDUCTIONISM, AND HOLISM IN SCIENCE AND PHILOSOPHY OF SCIENCE

JÜRGEN MITTELSTRASS

There are concepts that belong to the basic terminology of science but which are not used in everyday scientific work – such as the concepts of natural law and causality. Such concepts touch on the epistemological foundations of science, and thus transcend individual disciplines and presuppose a particular interest, the interest in foundational questions of science, and presumably also special skills and competence. Not everything that belongs to these foundations is self-evident and not everything that is said about them in philosophy of science is universally accepted – which in turn lies in the fact that we are dealing with different theoretical approaches. Theory meets theory, and this does not always go without conflict.

In the following, as an introduction to considerations of a theoretical, methodological and epistemological nature, which especially deal with aspects of complex structures, I offer some brief explications of a conceptual nature oriented towards the concepts of complexity, reduction and holism.

1. In a comprehensive presentation of the role that the concept of complexity plays in the development of modern science we read: "Complexity determines the spirit of twenty-first century science. The expansion of the universe, the evolution of life, and the globalization of human economies and societies all involve phase transitions of complex dynamical systems".[1] And further: "The theory of nonlinear complex systems has become a successful problem solving approach in the natural sciences – from laser physics, quantum chaos, and meteorology to molecular modelling in chemistry and computer-assisted simulations of cellular growth in biology. On the other hand, the social sciences are recognizing that the main problems of mankind are global, complex, nonlinear, and often random, too. Local changes in the ecological, economic, or political system can cause a global crisis. Linear thinking and the belief that the whole is only the sum of its parts are evidently obsolete".[2] In

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[1] K. Mainzer, *Thinking in Complexity: The Computational Dynamics of Matter, Mind and Mankind*, 5th edition, Berlin and Heidelberg: Springer 2007, p. VII.

[2] *Ibid.*, p. 1.

fact, complexity has become not only an important topic but also the key to scientific explanations in all areas of science.

This does not necessarily mean that conceptual clarity has been achieved in questions of complexity. For the concept of complexity displays different (scientific) meanings depending on the area to which it is applied, even while its basic meaning remains constant. Are the concepts used in different disciplines similar, or may a phenomenon be, for instance, biologically complex but physically not? Does the fact that some problems are in principle unsolvable for reasons of complexity (due to limited time and computational power) pose a problem for scientific practice? Shall our practice just ignore problems we cannot currently handle – or can science render apparently complex systems in simple underlying theories? Furthermore, is there a difference between the complex and the complicated such that some complex systems are not actually complicated even though all complicated systems are indeed complex. In general, again, complexity has become an important area of research in many disciplines in the last decades. For instance, the complexity and the ensuing unpredictability of weather systems has been known for a long time. And theoretical tools to master complexity have been developed in biology, where the apparent complexity of organisms has been used to argue against evolutionary theory, as well as in economics and social theory, where so-called "complexity theory" aims to help us understand systems which appear unsystematic.

As to the distinction between complexity and complicatedness:[3] The greater the number of objects and relations of a system, the greater its complexity. Complicatedness depends on the inhomogeneity of the object area. There can thus be systems of high complexity but small complicatedness (for example: organic molecules composed of numerous elements of few different kinds) whereas high complicatedness as a rule leads to complexity (for example: organisms). No wonder that the theory of complex dynamic systems, in which cause-and-effect connections are non-linear (for instance in the motion of more than two bodies under the influence of gravity), is currently becoming ever more influential, especially because of its many applications (another example is the prediction of developments in the weather). This discipline closely joins newer mathematical methods such as chaos theory to older methods from statistics and probability theory.

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[3] The following is taken from K. Lorenz, "komplex/Komplex", in: J. Mittelstrass (Ed.), *Enzyklopaedie Philosophie und Wissenschaftstheorie*, vol. IV, 2nd edition, Stuttgart and Weimar: Metzler 2010, pp. 277-279.

In so far as the reduction of complexity is done in explanatory intent, this is achieved especially by model building. Models serve to simplify complex structures and to visualize abstract structures. Thus, astronomical models (for instance, in the form of orreries) were viewed in the sense of the first purpose (simplifying structures), and physical models (for instance in the form of the atomic model) were viewed in the sense of the second purpose (visualizing abstract, non-intuitive structures) and mechanical models (for instance, in the form of corpuscular models) generally in the sense of both purposes (describing visualizable situations that were nonetheless in need of explanation by the basic concepts of space, time, mass and force). As a rule, we should differentiate between scale models, analogue models and theoretical models. Scale models are enlarged or miniature replicas of real or imaginary objects, for instance, in the three-dimensional representation of the DNA-molecule ("double helix"). Analogue models represent an object in a structurally similar (homomorphic) other object, for instance, in the form of the planetary model of the atom (in physics) or computer-models of the brain in the philosophy of mind. Theoretical models consist of a set of assumptions and equations with which the essential properties of an object or system are to be grasped, for instance (in the intuitive case) in the form of Niels Bohr's atom-model or of billiard-ball models in the kinetic theory of gases.

As a rule a complex state of affairs cannot be completely grasped, even when models are applied. This is for instance the case where chance plays a role. The Copenhagen interpretation of quantum mechanics, that is, the theory of microphysical phenomena, assumes an irreducible, ontological contingency, that is, the existence of absolute chance in the physical world. The assumption is not uncontroversial. For instance, David Bohm's interpretation of quantum mechanics suggests that the quantum world can in fact be grasped with causal-deterministic vocabulary. From this, and from the fact that Bohm's interpretation and the Copenhagen interpretation of quantum mechanics are empirically indistinguishable,[4] it follows that it may not be possible to find out whether there is really absolute chance in the world or not. All arguments for and against seem here to be relative to a physical theory and its interpretation. How are we supposed to know whether – remembering Albert Einstein's admonition that God does not play dice – there is not the possibility of a deeper deterministic description

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[4] See J. Mittelstrass, *Konstruktion und Deutung: Ueber Wissenschaft in einer Leonardo- und Leibniz-Welt*, Berlin: Humboldt University 2001, p. 18.

that excludes accident while coping with complexity. Not only philosophy, but natural science as well has its difficulties with chance and necessity.

Nothing is changed by the circumstance that complex relations cannot be completely grasped. This can in turn be elucidated under the concept of predictability: Even in a deterministic world there are limits to predictability.[5] Two reasons can be given in support of this. First, *deterministic chaos*. This refers to the strong dependence of a system's states on the magnitude of defined parameters. Since the magnitude of these parameters can never been known, the prediction of system's states is bound by uncertainty, which translates into a range of different developments in chaotic systems. Unpredictability as a result of chaos is not limited to complex systems, rather, it can also occur in simple systems that only consist of a few elements. For example, two coupled pendulums constitute a simple system, the relevant laws of which have been known for centuries. But it has only recently become clear that, within such an arrangement, a distinct range of initial conditions – namely system stimulations of medium strength – there can be chaotic and unpredictable oscillations. Second, the problem of a Laplace's demon. This label (credited to Emil Du Bois-Reymond)[6] refers to a fictitious superhuman intelligence, which – under the assumption of a stable, closed and all-determined system typical for a mechanistic worldview – knows of all initial conditions of all possible movements and thus can predict the location of any particle for every point in time. Now, quantum mechanical systems – in contrast to relativistic physics, where differential equations describe deterministic systems with regards to their state variables – are non-deterministic with regard to conjugate variables such as position and momentum. Rather, they are statistical, i.e. incalculable even by Laplace's demon – an implication confirmed by recent developments in physics. But whatever holds for a deterministic world also holds for a complex world and its reductions.

2. With the concept of *reduction* or reductionism philosophy of science denotes, on the one hand, an essential aspect of scientific theory formation and, on the other, a procedure that describes the successful reduction of

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[5] See, in more detail, J. Mittelstrass, "Predictability, Determinism, and Emergence", in: W. Arber *et al.* (Eds.), *Predictability in Science: Accuracy and Limitations*, Vatican City: The Pontifical Academy of Sciences 2008 (Pontificiae Academiae Scientiarum Acta 19), pp. 162-172.

[6] "Ueber die Grenzen des Naturerkennens" (1872), in: E. Du Bois-Reymond, *Vortraege ueber Philosophie und Gesellschaft* (ed. S. Wollgast), Hamburg: Meiner 1974, pp. 56-57.

one theory to another. In general the concept of reduction involves tracing back entities, concepts or theories to others. Reductions serve the goal of unifying the scientific world picture through the use of a conceptual system – and consequently ontology – as uniform as can be and the elimination or replacement of philosophically or methodologically problematical concepts (or the entities they refer to) by unproblematic concepts (ontological reduction). Examples are the reduction of phenomenological thermodynamics to statistical dynamics, the reduction of Mendelian genetics to molecular genetics and the ontological reduction of psychological processes to physical processes via a theory reduction of psychology to neurophysiology.

One expression of a reductionistic programme is so-called *physicalism*, that is, the programme to express all (non-logical) expressions of a unified scientific language in the language of physics. There are two versions: "The strictest version of physicalism restricts all scientific theories to the terms of currently accepted physics. This view demands, for example, that all processes or objects can be assigned a particular quantum of energy. A weaker variant of physicalism demands the completeness of the physics of the time. This conception accordingly takes the historical change of physics explicitly into account. This view of physicalism makes a comprehensive claim for the validity of the theory of inorganic phenomena and asserts that all entities (i.e., including biological and psychological ones) are physical. A further weakening of the concept of physicalism results if only the natural sciences of the time taken as a whole are set to be comprehensive and complete. In particular, this includes the possibility that biology is not reducible to the theory of inorganic phenomena, but must have recourse to special regularities. In this form of physicalism (...) emergent terms and laws are admissible in principle".[7]

Now, a claim for derivability of the reduced theory from the reducing theory presupposes that both are compatible with one another. But since the reducing theory is designed to correct and improve the reduced theory, this in turn presupposes that both are incompatible. That is, the formal and informal conditions of reduction cannot be satisfied simultaneously; the correction of T_1's laws by T_2 precisely excludes their derivation.[8] This, again, is the reason why Karl Popper rejects the idea of reducibility of theories to

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[7] M. Carrier and J. Mittelstrass, *Mind, Brain, Behavior: The Mind-Body Problem and the Philosophy of Psychology*, Berlin and New York: Walter de Gruyter 1991, p. 172.

[8] See again M. Carrier and J. Mittelstrass, *op. cit.*, p. 43. Here too the proof that this difficulty has been solved by applying Tarski's concept of interpretability to the reduction

one another and defends the incompatibility of successive theories. The principle of a critical examination characterizing a logic of scientific discovery requires, according to Popper's concept of falsifiability and the asymmetry of verification and falsification, a pluralism of theories so as to be able to select a "successful" one. Progress among theories is due to the ongoing process of critical revision of existing theories from the perspective of truth or at least verisimilitude.

3. Compared to the approaches represented in the programme of reduction, *analogies* display a weak form of relationship between entities, concepts or theories. Here the point is that this connection can be materially different but formally the same. We should distinguish between *structural* and *functional analogies*: "If the correspondence of particular relationships among the elements of a system with one another is reversibly unique to those among elements of another system (without there needing to be a correspondence between the elements themselves), we say that both systems agree partially in their structure or that a 'structural analogy' holds between them. If one grasps similarity as agreement of two systems in certain (not all) 'characters' in the sense of properties of their elements or element groups, then similar systems agree also in the relationships between the corresponding elements or element groups and are thus structurally analogous".[9] An example would be again Bohr's planetary model of the atom. A "functional analogy" between two systems on the other hand occurs if these are equally suited for a particular purpose, that is, interchangeable for achieving that purpose. An example here: the concept of force in physics and everyday life. Epistemologically speaking, both cases are forms of *similarity*, that is, agreement of two systems in some, but not necessarily all, characteristics. Analogue models accordingly represent a system or an object in a structurally similar (homomorphic) or in a functionally similar system or object.

4. The line of thought pursued here in the case of the concepts complexity, reduction and analogy lead in the philosophy of science to a position that on the one hand turns against the reductionist programme and on the other hand represents the attempt to do justice to the actual complexity of scientific objects, concepts or theories in a different manner as well, namely

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problem (A. Tarski, "A General Method in Proofs of Undecidability", in: A. Tarski *et al.*, *Undecidable Theories*, Amsterdam: North-Holland 1971, pp. 1-35).

[9] Chr. Thiel, "Analogie", in J. Mittelstrass (Ed.), *Enzyklopaedie Philosophie und Wissenschaftstheorie*, vol. I, 2nd edition, Stuttgart and Weimar: Metzler 2005, pp. 117-118.

in the sense of a unity to be regained, a *holistic* unity of disciplinary and transdisciplinary explanations.[10] Under the designation *holism* are to be understood methodological approaches to the explanation of conceptual or empirical phenomena, that take their point of departure from a "holistic" point of view. Conceptually or methodologically, the issue is in particular the distinction between the part-whole relation and the element relation, since wholes are understood as compositions of parts but not merely as the sum of their parts. This is the case because the relations determining the composition make the whole an independent unity, whose qualities cannot be completely traced back to the qualities of the parts. The concept holism was introduced in 1926 in a biological context.[11] It also plays a role in the interpretation of quantum theory, in social-scientific theory formation and in the theory of confirmation.

In biology the concept of holism designates the attempt, in opposition to the particular positions of mechanism and vitalism, to derive all phenomena of life from a holistic "metabiological principle". According to this view biological processes can be adequately explained only if organisms are not grasped as isolated natural bodies (as in physics), but are rather seen in structure and function as standing in inseparable interaction with their own subsystems and the environment. Depending on how this abstract principle is conceptualized, it has either found general recognition in biology or been dismissed as incompatible with the biological facts. For the paleontologist Edgar Dacqué, for instance, holism was a methodological part of a teleological conception of evolution in which humankind, as the primeval form of life, included all the developmental possibilities of the animal kingdom (the animal species appear in this conception as dead ends in biological development).[12] In physics the appearance of so-called entangled states in quantum theory is often viewed as a violation of the principle of separation and as the basis for an *ontological holism*. This principle states that every physical system possesses its fundamental properties independent of other systems distinct from it. The exhibition of these properties, but not their presence, can be influenced by their interactions with other systems. In composite systems the state of the aggregate system results from the states of the subsystems and their interactions.

In entangled states, such as described in the so-called Einstein-Podol-

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[10] I follow closely here my article "Holismus" in the *Enzyklopaedie Philosophie und Wissenschaftstheorie*, vol. III, 2nd edition, Stuttgart and Weimar: Metzler 2008, pp. 427-430.

[11] J.C. Smuts, *Holism and Evolution*, London: Macmillan 1926, 3rd edition 1936.

[12] E. Dacqué, *Leben als Symbol: Metaphysik einer Entwicklungslehre*, Munich and Berlin: Oldenbourg 1928.

sky-Rosen paradox, an aggregate system consisting, for instance, of two initially coupled and later separated particles, has constant properties – it is in a pure state – although this does not hold for the subsystems. The aggregate system exists in a well-defined state, whereas the subsystems do not possess the correlated properties (such as spin and polarization) independently of one another. The probability distribution for the appearance of particular property values of the aggregate system cannot be calculated as the product of such probability distributions for the subsystems. Accordingly the state of the aggregate system does not supervene on the states of the sub-systems. The holism of quantum theory is expressed in the violation of the principle of separation, through which the whole is ascribed primacy before the parts.

In the philosophy of the social sciences *methodological holism* is the view that social relations can only be interpreted and explained in terms of social wholes. This holism is methodological insofar as it primarily refers to the conditions of understanding. The counter-position is so-called methodological individualism, as advocated, for instance by Popper among others. According to this individualism all social relations can be explained out of the actions of individual persons and their interactions, which in turn can be traced back to motives and beliefs and thus need not necessarily refer to social wholes. Opposed to this position, advocates of holism such as Karl Marx and Émile Durkheim postulate the impossibility of abstracting from the influence of social institutions on the behaviour of individuals. According to Marx social conditions and their development can only be interpreted in categories of social "totalities" such as relations of production or classes; for Durkheim institutions such as family or religious communities act as social facts upon the individual.

While biological, quantum-physical and social-scientific elaborations of holistic notions are supposed to serve the particular interpretative and explanatory needs of partial areas of investigation, the so-called *confirmation holism* of philosophy of science deals with the over-arching thesis that theories can only be empirically evaluated as wholes. This form of holism arises in the framework of a hypothetical-deductive conception of empirical testing and confirmation, according to which the investigation of the tenability of a hypothesis, not comprehensively testable by immediate observation, is carried out by deriving empirically accessible consequences. If the consequences turn out to be true, the hypothesis is taken to be empirically confirmed. However, Pierre Duhem pointed out that the derivation of empirical consequences must have recourse to numerous other hypotheses, for instance, those taken from background knowledge or those about the function of the measuring instruments applied. Every successful test confirms not only the hypothesis under consideration, but also the entire group of hypotheses used in the testing process.

Similar arguments are made in philosophy of science in the framework of so-called *meaning holism* or *semantic holism*. Here, the meaning of individual concepts or propositions results from their interactions with other linguistic structures. They do not have meaning in isolation but only in the context of comprehensive language systems. This holism arises out of confirmation holism when it is joined to the verificationist premise that the conditions of empirical testing provide information on meaning. A further ground is the realization that the meaning of scientific concepts is understood only in the context of the corresponding scientific theory and cannot be acquired by knowledge of the appropriate definitions alone. The meaning of a concept like that of force can be clarified only by the role that it plays in the system of the laws of mechanics. According to this context theory of meaning a scientific concept acquires its specific content only through its integration in theory.

As an aside let me remark that holistic approaches of this kind lead to the concept of *emergence* insofar as, both in the sense of the confirmation holism and also in the sense of semantic holism, it is the system-properties that give us information about the behaviour of the system. These properties are in turn *emergent*. Emergence says again that it is impossible to use characteristics of elements and the interrelations between these to describe characteristics of ensembles or make predictions about them. The core element of a *strong* emergence thesis is a non-derivability or non-explainability hypothesis of the system characteristics shaped from the characteristics of the system components. An emergent characteristic is non-derivable; its occurrence is in this sense unexpected and unpredictable. *Weak* emergence is limited to the difference of the characteristics of systems and system components and is compatible with the theoretical explainability of the system characteristics. Weak emergence in turn is essentially a phenomenon of complexity.

Here, too, our considerations return us to the concept of complexity, which is, from the perspective of philosophy of science as well, the key concept of the modern development of science and points to the future, possibly also to the limits, of scientific progress.

Scientific Papers

PHYSICS, ASTROPHYSICS AND MATHEMATICS

COMPLEXITY AT THE FUNDAMENTAL LEVEL OF OUR KNOWLEDGE

ANTONINO ZICHICHI*

CONTENTS

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COMPLEXITY AT THE FUNDAMENTAL LEVEL OF OUR KNOWLEDGE

1 THE FIRST REMARK

People speak of 'Complexity' as a source of new insights in physics, biology, geology, cosmology, social sciences and in all intellectual activities which look at the world through the lens of a standard analysis in terms of either Simplicity or Complexity. **But 'Complexity'** is ill-defined, as shown by the existence of at least seven definitions of Complexity.

2 SEVEN DEFINITIONS OF COMPLEXITY

Here are the seven definitions of Complexity.

Definition Number 1

Complexity is a property of systems that are somewhere in between a completely random and a completely regular state, often described by a highly non linear set of equations but sometimes not describable by equations at all.

Definition Number 2 (Gerardus 't Hooft)

Bad ones:

1) Chaos.
2) The need for lengthy calculations.
3) The need for many distinct variables.

Better ones:

4) Unexpected difficulty when attempting to describe something in a precisely formulated theory.
5) What is left over after all systematic approaches failed.

But it could also be that: Complexity is an excuse for sloppy thinking.

Definition Number 3 (Richard Kenway)

The Complexity of a theory (problem) is the minimum amount of computer time and storage required to simulate (solve) it to a specified level of precision.

DEFINITION NUMBER 4 *(Constantino Tsallis)*

If we admit that biological or linguistic evolution, or financial dynamics are complex phenomena, then their typical dynamics is somehow between strong chaos (i.e. positive Lyapunov exponents) and simple orbits (i.e. negative Lyapunov exponents). In other words, Complexity (or at least some form of it) is deeply related to the edge of chaos (i.e. vanishing maximal Lyapunov exponent). Since the edge of chaos appears to be related paradigmatically to an entropy index 'q' different from unity, there must be some deep connection between Complexity and generalized entropies such as 'S_q'.

DEFINITION NUMBER 5 *(Leonard Susskind)*

From the mathematical point of view:

- A problem can be polynomial, which means that it is not to hard to predict surprises.
- A problem can be NP or NP-complete, which represent different degrees of difficulty in predicting surprises.
- •• Surprises means: UEEC event (see later).
- •• That degree of difficulty can be associated with the level of Complexity.

DEFINITION NUMBER 6

A system is 'complex' when it is no longer useful to describe it in terms of its fundamental constituents.

DEFINITION NUMBER 7

The simplest definition of Complexity: '*Complexity is the opposite of Simplicity*'. This is why we have studied the Platonic Grand Unification (Addendum 1) and its extension to the Platonic Superworld (Addendum 2).

These seven definitions of Complexity must be compared with the whole of our knowledge (see Addendum 3) in order to focus our attention on the key features needed to study our real world.

3 COMPLEXITY EXISTS AT ALL SCALES

The Logic of Nature allows the existence of a large variety of structures with their regularities and laws which appear to be independent from the basic constituents and fundamental laws of Nature which govern their interactions.

But, without these laws it would be impossible to have the real world which is in front of us and of which we are part of.

A series of complex systems is shown in figure 1.

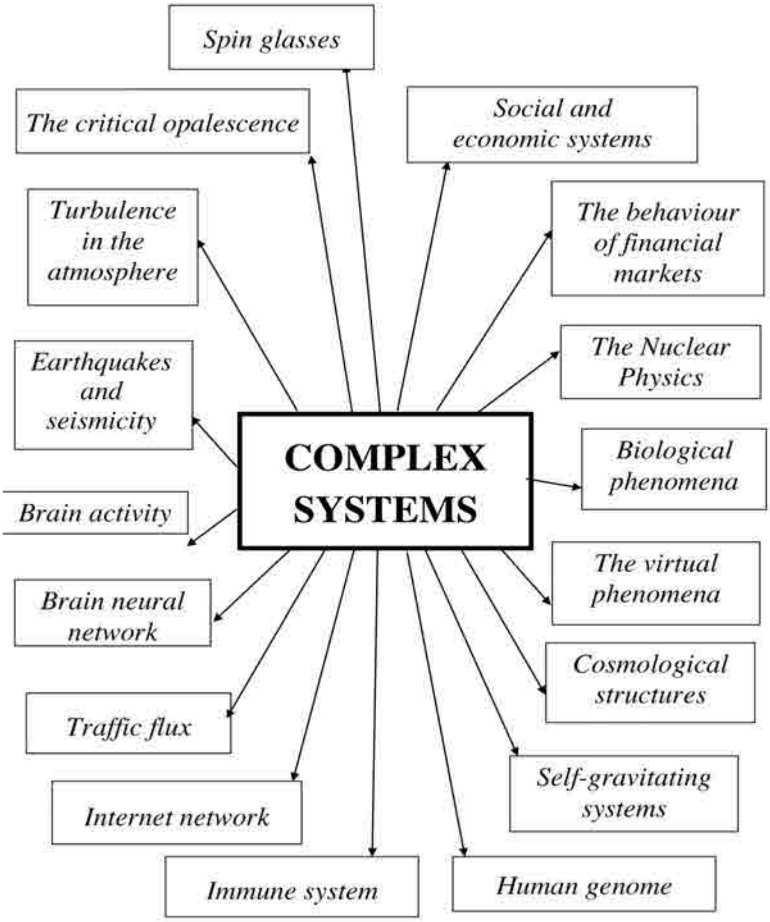


Figure 1

As you can see, we go from traffic flux, to the internet network, to earthquakes and seismicity, to social and economic systems, to the behaviour of financial markets, to the study of cosmological structures, and so on. A recent study proves that Complexity exists at the fundamental level of our knowledge: i.e. Science. Since the queen of all Sciences is Physics (Enrico Fermi) we will discuss the great achievement of the most advanced frontiers in Physics in order to prove that Complexity exists at the fundamental level of our knowledge.

Since History is granted to be the best example of Complexity, the conclusion is that Complexity exists at all scales, as illustrated in figure 2.

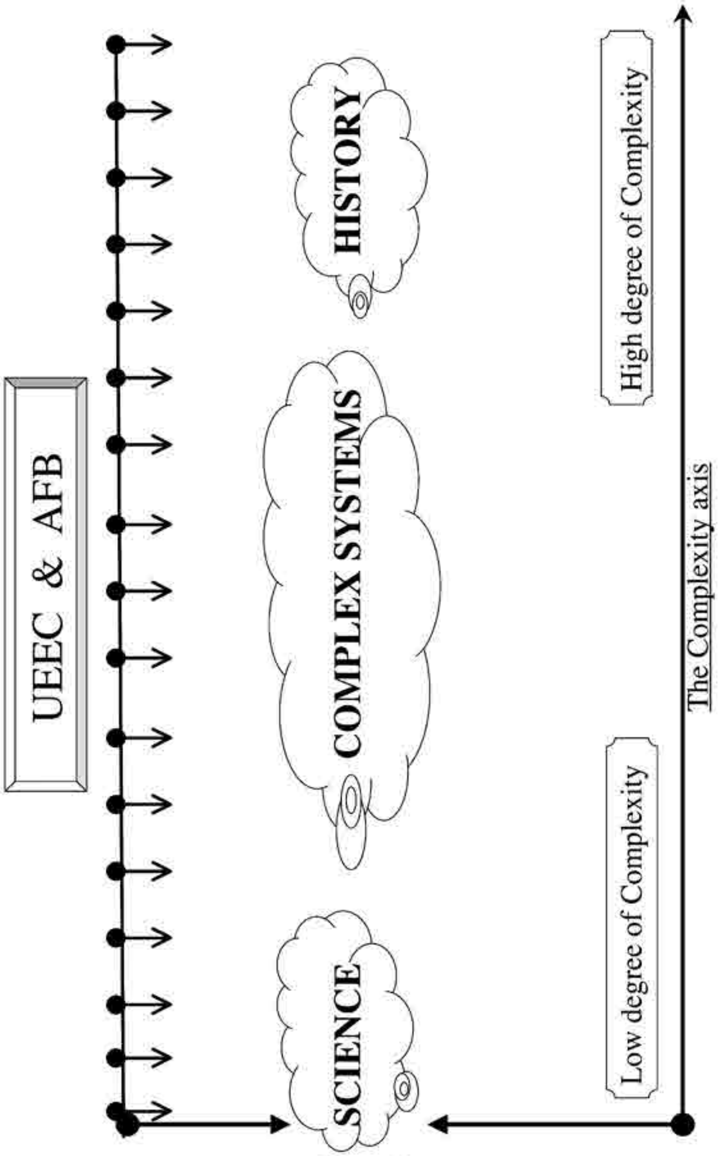


Figure 2

In this figure we have Science and History as the two extreme limits of Complexity. Science is the lowest limit in the degree of Complexity, while History is the highest degree of Complexity. The real world consists of systems with different degree of Complexity. The degree of Complexity of the sample shown in figure 1 is reported in figure 2 as being in between Science and History.

This enormous variety of real structures has in common the same experimental evidence for the property called Complexity.

4 THE EXPERIMENTAL EVIDENCE FOR THE EXISTENCE OF COMPLEXITY

The experimental evidences for the **existence** of **Complexity are two**:

1) The Anderson-Feynman-Beethoven-type phenomena (**AFB**) i.e. phenomena whose laws and regularities ignore the existence of the Fundamental Laws of Nature from which they originate;
2) The Sarajevo-type effects, i.e. Unexpected Events of quasi irrelevant magnitude which produce Enormous Consequences (**UEEC**).

The only certainty about Complexity is the existence of these two experimentally observable effects. The **AFB** will be discussed in chapter 4.1 and the **UEEC** in chapter 4.2. These effects exist at all scales.

4.1 AFB PHENOMENA FROM BEETHOVEN TO THE SUPERWORLD

Beethoven and the laws of acoustics.

Beethoven could compose superb masterpieces of music without any knowledge of the laws governing acoustic phenomena. But these masterpieces could not exist if the laws of acoustics were not there.

The living cell and QED.

To study the mechanisms governing a living cell, we do not need to know the laws of electromagnetic phenomena whose advanced formulation is QED. All mechanisms needed for life are, to a great extent, examples of electromagnetic processes. If QED was not there, Life could not exist.

Nuclear physics and QCD.

Proton and neutron interactions appear as if a fundamental force of nature is at work: the nuclear force, with its rules and its regularities. These interactions ignore that protons and neutrons are made with quarks and gluons.

Nuclear physics does not appear to care about the existence of Quantum ChromoDynamics (QCD), the fundamental force acting between quarks and gluons at the heart of the subnuclear world.

Nuclear physics ignores QCD but all phenomena occurring in nuclear physics have their roots in the interactions of quarks and gluons. In other words, protons and neutrons behave like Beethoven: they interact and build up nuclear physics without 'knowing' the laws governing QCD.

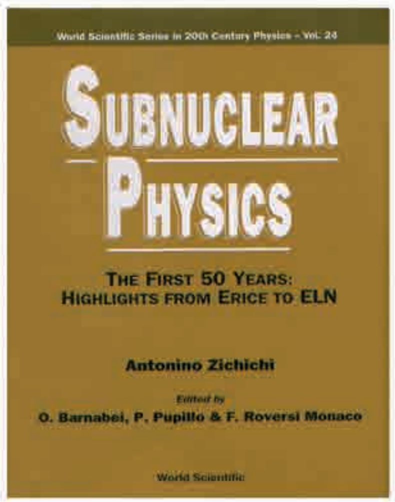
The most recent example of Anderson-Feynman-Beethoven-type phenomenon: **the World could *apparently* not care less about the existence of the Superworld**.

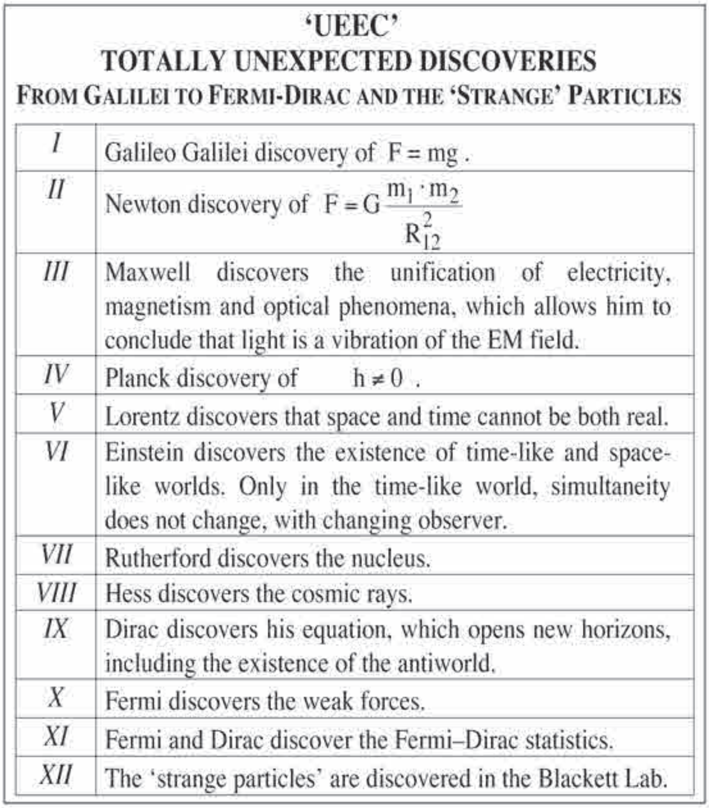
4.2 UEEC EVENTS, FROM GALILEI UP TO SM&B

In figure 3 there is a sequence of **UEEC** events from Galilei to Fermi-Dirac and the 'strange particles'. The series of UEEC events goes on in figures 4, 5, 6 for the construction of the Standard Model. In figure 7 there is the most recent synthesis of UEEC events in what we now call the **SM&B**: the Standard Model and Beyond. In order to discuss, even in a very short way, the contents of all these figures (3, 4, 5, 6, 7) the time needed would exceed by many orders of magnitudes the one allocated to my Lecture. Purpose of these figures is to provide a list of some scientific achievements I have chosen in order to prove that all scientific steps come from totally unexpected events. The contents of all figures (3–7) are far from being complete. The figures (4, 5, 6) cover the first fifty years of Subnuclear Physics, whose detailed description can be found in my book whose front page is reproduced below. In the same volume I discuss the details of figure 7, the **SM&B**, which is the greatest synthesis of all times in the study of the fundamental phenomena governing the Universe in all its structures.

What about Platonic Simplicity? The definition n. 7 of Complexity (reported in chapter 2) forces us to check if Platonic Simplicity plays a role in the Logic of the Fundamental Constituents of matter. An example of Platonic Simplicity is the Platonic Grand Unification (Addendum 1), whose natural extension is in the existence of the Platonic Superworld (Addendum 2). Platonic Simplicity is totally violated in the Unification of all Fundamental Forces and in the construction of the Superworld.

The conclusion is that at the frontier of our scientific knowledge what is needed is not Platonic Simplicity but its opposite. Complexity exists at the fundamental level. In fact, starting from Platonic Simplicity, the **SM&B** needs a series of 'ad hoc' inputs [1] in order to be as it has to be.





'UEEC'
TOTALLY UNEXPECTED DISCOVERIES
FROM GALILEI TO FERMI-DIRAC AND THE 'STRANGE' PARTICLES

I	Galileo Galilei discovery of $F = mg$.
II	Newton discovery of $F = G\frac{m_1 \cdot m_2}{R_{12}^2}$
III	Maxwell discovers the unification of electricity, magnetism and optical phenomena, which allows him to conclude that light is a vibration of the EM field.
IV	Planck discovery of $h \neq 0$.
V	Lorentz discovers that space and time cannot be both real.
VI	Einstein discovers the existence of time-like and space-like worlds. Only in the time-like world, simultaneity does not change, with changing observer.
VII	Rutherford discovers the nucleus.
VIII	Hess discovers the cosmic rays.
IX	Dirac discovers his equation, which opens new horizons, including the existence of the antiworld.
X	Fermi discovers the weak forces.
XI	Fermi and Dirac discover the Fermi–Dirac statistics.
XII	The 'strange particles' are discovered in the Blackett Lab.

Figure 3

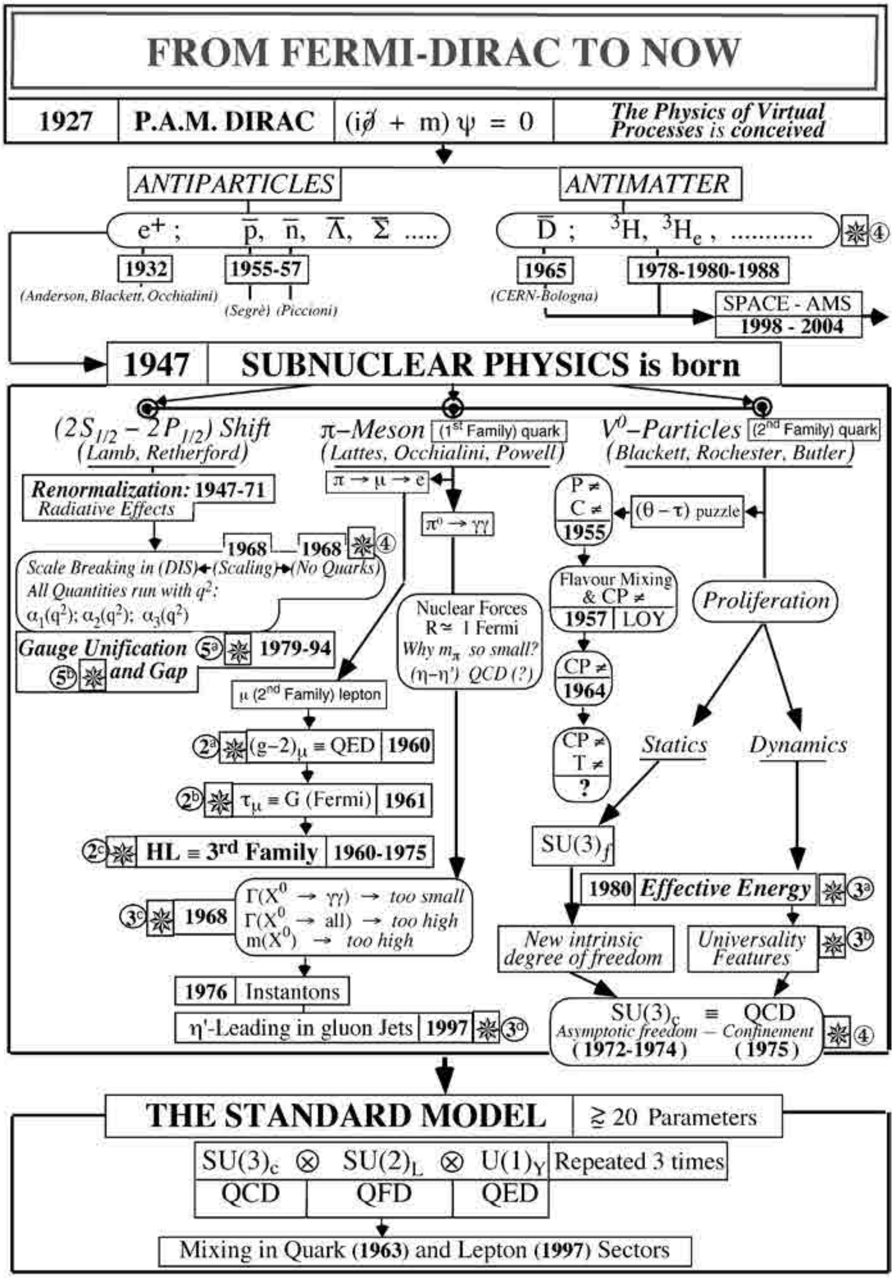

FROM FERMI-DIRAC TO NOW
1927
P.A.M. DIRAC
(i∂̸ + m) ψ = 0
The Physics of Virtual Processes is conceived
ANTIPARTICLES
ANTIMATTER
e+ ; p̄, n̄, Λ̄, Σ̄ .....
D̄ ; ³H, ³He , ...
④
1932
(Anderson, Blackett, Occhialini)
1955-57
(Segrè) (Piccioni)
1965
(CERN-Bologna)
1978-1980-1988
SPACE - AMS
1998 - 2004
1947
SUBNUCLEAR PHYSICS is born
(2S1/2 − 2P1/2) Shift
(Lamb, Retherford)
π−Meson
(1st Family) quark
(Lattes, Occhialini, Powell)
V⁰−Particles
(2nd Family) quark
(Blackett, Rochester, Butler)
Renormalization: 1947-71
Radiative Effects
π → μ → e
π⁰ → γγ
P ≠
C ≠
1955
(θ − τ) puzzle
1968
1968
④
Scale Breaking in (DIS)←(Scaling)→(No Quarks)
All Quantities run with q²:
α1(q²); α2(q²); α3(q²)
Nuclear Forces
R ≃ 1 Fermi
Why mπ so small?
(η−η') QCD (?)
Flavour Mixing
& CP ≠
1957
LOY
Proliferation
Gauge Unification
5a
1979-94
5b
and Gap
CP ≠
1964
μ (2nd Family) lepton
Statics
Dynamics
2a
(g−2)μ ≡ QED
1960
CP ≠
T ≠
?
2b
τμ ≡ G (Fermi)
1961
2c
HL ≡ 3rd Family
1960-1975
SU(3)f
1980
Effective Energy
3a
3c
1968
Γ(X⁰ → γγ) → too small
Γ(X⁰ → all) → too high
m(X⁰) → too high
New intrinsic degree of freedom
Universality Features
3b
1976
Instantons
SU(3)c ≡ QCD
Asymptotic freedom — Confinement
(1972-1974) (1975)
④
η'-Leading in gluon Jets
1997
3d
THE STANDARD MODEL
≳ 20 Parameters
SU(3)c ⊗ SU(2)L ⊗ U(1)Y
Repeated 3 times
QCD
QFD
QED
Mixing in Quark (1963) and Lepton (1997) Sectors

Figure 4

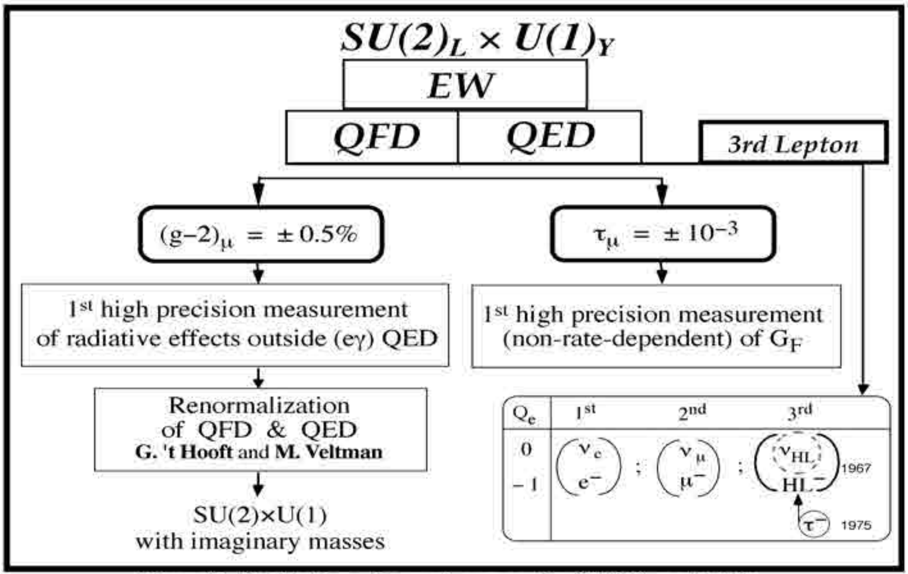


Figure 5: Details from figure 4, concerning $SU(2)_L$ and $U(1)_Y$.

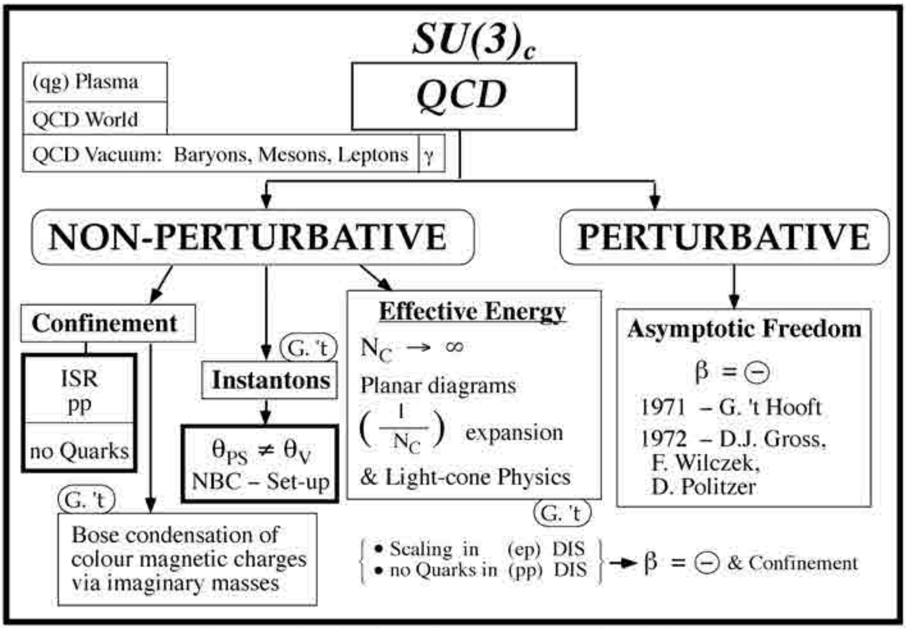


Figure 6: Details from figure 4, concerning $SU(3)_c$.

SM&B

THE STANDARD MODEL AND BEYOND

① RGEs $(\alpha_i \, (i \equiv 1, 2, 3); \; m_j \, (j \equiv q, \, l, \, G, \, H)) : \; f(k^2)$.

- GUT $(\alpha_{\text{GUT}} \cong 1/24)$ & GAP $(10^{16} - 10^{18})$ GeV.
- SUSY (to stabilize $m_F/m_P \cong 10^{-17}$).
- RQST (to quantize Gravity).

② Gauge Principle (hidden and expanded dimensions).

— How a Fundamental Force is generated: SU(3); SU(2); U(1) and Gravity.

③ The Physics of Imaginary Masses: SSB.

— The Imaginary Mass in SU(2)×U(1) produces masses ($m_{W^\pm}$; m_{Z^0}; m_q; m_l), including $m_\gamma = 0$.

— The Imaginary Mass in SU(5)⇒SU(3)×SU(2)×U(1) or in any higher (not containing U(1)) Symmetry Group ⇒ SU(3)×SU(2)×U(1) produces Monopoles.

— The Imaginary Mass in $SU(3)_c$ generates Confinement.

④ Flavour Mixings & CP≠, T≠.

— No need for it but it is there.

⑤ Anomalies & Instantons.

— Basic Features of all Non-Abelian Forces.

Note: q ≡ quark and squark;
l ≡ lepton and slepton;
G ≡ Gauge boson and Gaugino;
H ≡ Higgs and Shiggs;
RGEs ≡ Renormalization Group Equations;
GUT ≡ Grand Unified Theory;
SUSY ≡ Supersymmetry;
RQST ≡ Relativistic Quantum String Theory;
SSB ≡ Spontaneous Symmetry Breaking.

m_F ≡ Fermi mass scale;
m_P ≡ Planck mass scale;
k ≡ quadrimomentum;
C ≡ Charge Conjugation;
P ≡ Parity;
T ≡ Time Reversal;
≠ ≡ Breakdown of Symmetry Operators.

The five basic steps in our understanding of nature. ① The renormalization group equations (RGEs) imply that the gauge couplings (α_i) and the masses (m_j) all run with k^2. It is this running which allows GUT, suggests SUSY and produces the need for a non point-like description (RQST) of physics processes, thus opening the way to quantize gravity. ② All forces originate in the same way: the gauge principle. ③ Imaginary masses play a central role in describing nature. ④ The mass-eigenstates are mixed when the Fermi forces come in. ⑤ The Abelian force QED has lost its role of being the guide for all fundamental forces. The non-Abelian gauge forces dominate and have features which are not present in QED.

Figure 7

5 THE TWO ASYMPTOTIC LIMITS: HISTORY AND SCIENCE

A key feature in our search to understand Complexity is to compare the two asymptotic limits which characterize the world where we live and of which we are part of: History and Science.

The real world seems to be characterized by two basic features, which are one on the opposite side of the other: *Simplicity* and *Complexity*.

It is generally accepted that *Simplicity* is the outcome of *Reductionism*, while *Complexity* is the result of *Holism*.

The most celebrated example of *Simplicity* is *Science* while the most celebrated example of *Complexity* is *History*.

Talking about asymptotic limits, the general trend is to consider ***History*** as the asymptotic limit of *Holism* and of *Complexity*; ***Science*** as the asymptotic limit of *Reductionism* and of *Simplicity*, as illustrated in figure 8.

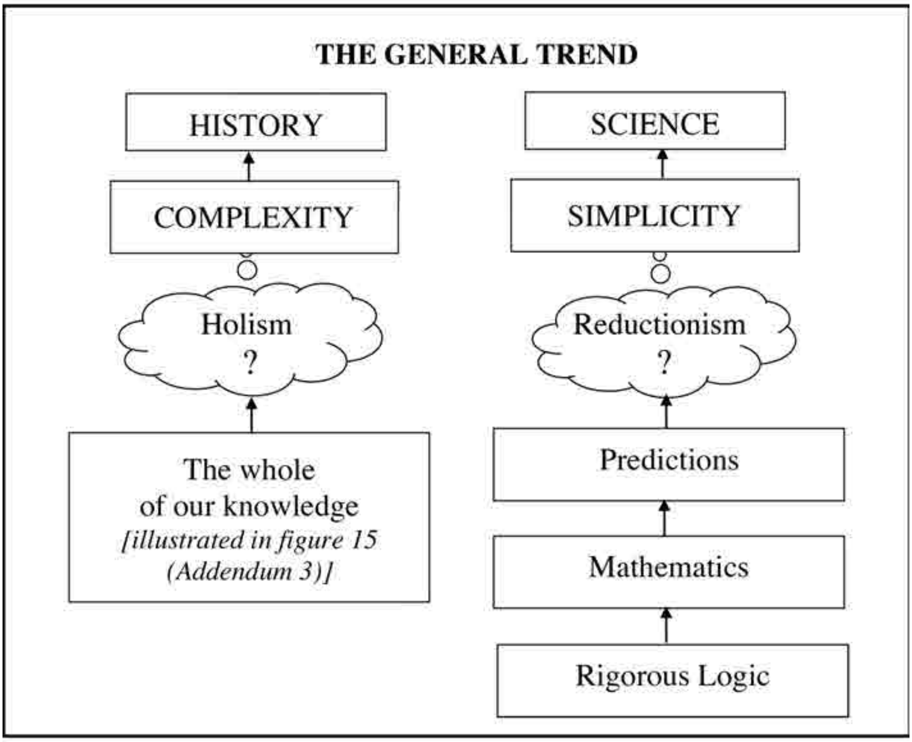


Figure 8

The Logic of Nature allows the existence of ***Science*** (the asymptotic limit of Simplicity) and of ***History*** (the asymptotic limit of Complexity), which **share a property, common to both of them**.

It is interesting to define ***Science*** and ***History*** in terms of this property, **probably the only one**, which they share; i.e. **Evolution**.

- Science is the Evolution of our Basic Understanding of the laws governing the world in its Structure ≡ **EBUS**.
- History is the Evolution of the World in its Real Life ≡ **EWRL**.

In Table 1 we compare these two supposedly asymptotic limits — History and Science — on the basis of 'What if?'; a condition elaborated by the specialists in what is now known as 'virtual history' [2].

On the basis of 'What if?' these specialists conclude [2] that the world would not be as it is, if one, or few, or any number of 'What if?' had not been as History tells us. This is not the case for Science.

The world would have exactly the same laws and regularities, whether Galileo Galilei or somebody else had discovered

$$F = mg \text{ (}F \equiv \text{force; } m \equiv \text{mass; } g \equiv \text{acceleration due to gravity),}$$

and so on for all the other scientific discoveries.

It is in the consequences of 'What if?' that the two asymptotic limits of Simplicity and Complexity seem to diverge, despite the fact that the sequence of 'What if?' in Science belongs to the 'totally unexpected events' (UEEC) exactly like the others listed in the column of History.

TABLE 1

'WHAT IF ?'

	In History ≡ EWRL		**In Science ≡ EBUS**
I	What if Julius Caesar had been assassinated many years before?	***I***	What if Galileo Galilei had not discovered that $F = mg$?
II	What if Napoleon had not been born?	***II***	What if Newton had not discovered that $F = G\frac{m_1 \cdot m_2}{R_{12}^2}$?
III	What if America had been discovered few centuries later?	***III***	What if Maxwell had not discovered the unification of electricity, magnetism and optical phenomena, which allowed him to conclude that light is a vibration of the EM field?
IV	What if Louis XVI had been able to win against the 'Storming of the Bastille'?	***IV***	What if Planck had not discovered that $h \neq 0$?
V	What if the 1908 Tunguska Comet had fallen somewhere in Europe instead of Tunguska in Siberia?	***V***	What if Lorentz had not discovered that space and time cannot be both real?
VI	What if the killer of the Austrian Archduke Francisco Ferdinand had been arrested the day before the Sarajevo event?	***VI***	What if Einstein had not discovered the existence of time-like and space-like real worlds? Only in the time-like world, simultaneity does not change, with changing observer.
VII	What if Lenin had been killed during his travelling through Germany?	***VII***	What if Rutherford had not discovered the nucleus?
VIII	What if Hitler had not been appointed Chancellor by the President of the Republic of Weimar Paul von Hindenburg?	***VIII***	What if Hess had not discovered the cosmic rays?
IX	What if the first nuclear weapon had been built either by Japan before Pearl Arbour (1941) or by Hitler in 1942 or by Stalin in 1943?	***IX***	What if Dirac had not discovered his equation, which opens new horizons, including the existence of the antiworld?
X	What if Nazi Germany had defeated the Soviet Union?	***X***	What if Fermi had not discovered the weak forces?
XI	What if Karol Wojtyla had not been elected Pope, thus becoming John Paul II?	***XI***	What if Fermi and Dirac had not discovered the Fermi–Dirac statistics?
XII	What if the USSR had not collapsed?	***XII***	What if the 'strange particles' had not been discovered in the Blackett Lab?

6 COMPLEXITY AND PREDICTIONS

It is now necessary to establish the relation which exist between Complexity and Predictions.

In the previous chapters 4.1 and 4.2 we have discussed the experimental basis for the existence of Complexity, i.e., AFB and UEEC events.

We will now discuss the experimental evidence for the existence of Predictions and the sequence which correlates UEEC and Predictions.

We will see that Predictions depends on UEEC. The experimental evidences for the **existence** of **Predictions are** the very many results of scientific reproducible experiments.

Quantum Electro-Dynamics, QED, is the best example. The anomalous magnetic moments, in symbols (g–2), of the electron (e) and of the muon (μ):

$$(g-2)_{e,\,\mu}$$

are theoretically computed at an extraordinary level of precision (few parts in ten billion parts for the electron) and are experimentally verified to be correct. Could the

$$(g-2)_{e,\,\mu}$$

be theoretically predicted before the discovery of the Maxwell equations and the existence of Quantum Electro-Dynamics (QED)? The answer is obviously no.

The sequence which correlates UEEC events and Predictions is very clear.

Predictions at the **fundamental level of scientific knowledge** depend on **UEEC events**.

For example: it is the discovery of the laws governing electric, magnetic and optical phenomena (all totally unpredicted) which produced the mathematical structure called QED.

The mathematical structure was not discovered before the innumerable series of **UEEC** events found in electricity, magnetism and optics. This series of UEEC events allowed Maxwell to express 200 years of experimental discoveries in a set of 4 equations.

The mathematical formalism comes **after** a totally unexpected discovery: an **UEEC event** which no one was able **to predict**.

In the whole of our knowledge rigorous predictions exist only in Science. These predictions are based on the mathematical description of a single UEEC event or a series of UEEC events. This description can either be the result of new mathematics (example the Dirac δ-function) or the use of existing mathematical formalism (example: the Einstein use of the Ricci tensor calculus). The UEEC event at the origin of the Dirac equation [3] is the fact that the electron was not a 'scalar' particle but a spin ½ object.

The UEEC events at the origin of Einstein mathematical formulation of the gravitational forces are the discoveries of

$$\text{Galilei } (F = mg),$$

of

$$\text{Newton} \left(F = G \ \frac{m_1 \cdot m_2}{R_{12}^2} \right),$$

and of Lorentz that Space and Time could not be both real and that all electromagnetic phenomena obeyed a new invariance law, now called Lorentz-invariance. These are just two examples of the fact that the greatest steps in the **progress of Science** come from totally unpredicted discoveries. It is the mathematical formulation of these discoveries which allow Predictions to be made. Once made, these Predictions need experimental checks, since they extend our knowledge much further away from the original UEEC event.

Even when we have a mathematical formalism coming from a series of UEEC events, if this formalism opens a new frontier, as it is the case for the Superworld, the experimental proof is needed to verify the validity of the new theoretical frontier.

Today we have a reasonable mathematical formalism to describe the **Superworld**, but in order to know if the Superworld exists we need the experimentally reproducible proof for its existence. And it could be that, while searching for the Superworld a totally unexpected discovery (UEEC) comes in. This is the reason why we need to perform experiments, as Galileo Galilei realized 400 years ago.

7 CHAOS, EVOLUTION AND HISTORY

Two topics in this review devoted to Complexity have not been mentioned: the modern theory of Chaos and the theory of Evolution of living matter.

7.1 CHAOS

One of the most interesting problems in the modern theory of Chaos is the study of the transition to Chaos of dynamical systems.

With my friend and colleague André Petermann, we have published [4] a paper where we prove that the existence of chaos, in a rigorous mathematical language, is still lacking. In this paper [4] we point out that a rigorous Chaos would exist, for example, if a set of strongly coupled non linear differential equations produced all sort of results, inspite of the fact that the initial conditions are exactly the same.

Another possibility for the existence of chaos would be the existence of a finite systems of Axioms followed by Rules.

If the same system brought to different and contradictory conclusions, once again, this would be the proof that Chaos exists in a rigorous logical mathematical structure.

The conclusion is that modern theory of chaos depends on the lack of rigorous knowledge of some parameters in the initial conditions; but this has little to do with chaos [4].

7.2 EVOLUTION OF LIVING MATTER

And now a few remarks on the so called theory of Evolution and origin of our species. Such a theory has never been formulated in terms of a rigorous logic, using the mathematical language.

In order to have an idea of the degree of Complexity in the mathematics needed to describe the evolution of living matter let us see what is needed to describe in a rigorous mathematical language the evolution of the simplest piece of "electricity", discovered in 1897 by J.J. Thomson and called "electron".

After more than a century this particle is established to be "elementary", i.e. without any structure and therefore without Complexity inside its structure since this structure does not exist.

In order to describe the evolution of this "elementary" particle we need a system of four differential equations coupled. This was discovered by P.A.M. Dirac in 1928 [3].

When we go from an elementary particle to the simplest form of "living matter" the interaction with the environment must be taken into account as shown in Figure 9.

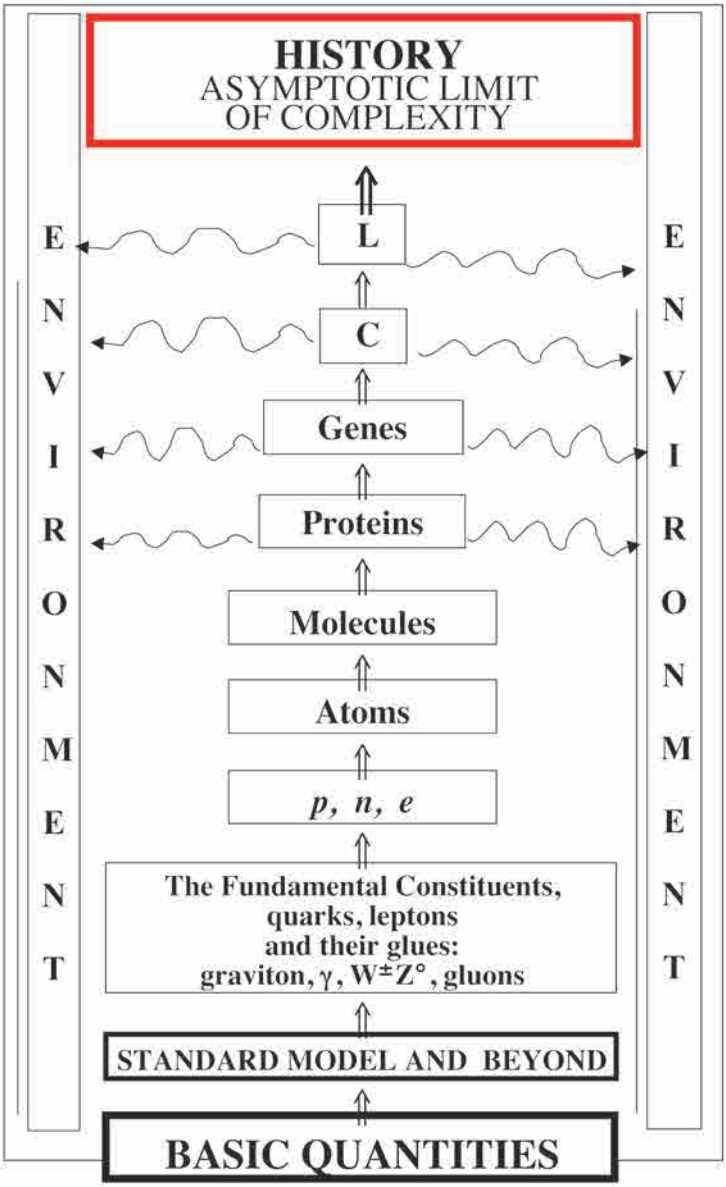


Figure 9

This interaction is a source of a high degree of Complexity. Furthermore the number of "pieces" of inert matter must be at least 10^{11}. This is the maximum limit dictated by Quantum Entanglement. There is no general agreement on this number, the problem being that its value could be much larger. This problem is called "the problem of minimal life" still far from being solved. Notice that hundreds of researchers are at present engaged to study the problem of "minimal life" in many Labs, some of them being secret.

The conclusion is that in order to describe the evolution of the simplest form of living matter we need a (so far unknown) number of differential non linear equations strongly coupled. When this will be attempted, the degree of Complexity will surely be extremely high.

Despite the Complexity of all problems mentioned above, people speak as if not only the evolution but even the origin of the living matter, which we humans are made of, have been scientifically understood.

Let me hope that this telegraphic note will call your attention on the problems which must be taken into account when we go from the elementary form of inert matter to living matter, up to History.

7.3 A FEW WORDS ON HISTORY

No one has ever attempted to describe in a rigorous mathematical language History. If this would be possible "predictions" could be made (as explained in chapter 6), despite the enormous degree of Complexity which characterizes History. Notice that what we call the Queen of all Sciences (Physics) deals with problems where the interaction with the environmental is zero.

8 THE LESSON FOR THE FUTURE

We have proved that AFB and UEEC – which are at the origin of Complexity, with its consequences permeating all our existence, from molecular biology to life in all its innumerable forms up to our own, including History – do exist at the fundamental level [5–8] and [1].

It turns out that Complexity in the real world exists, no matter the mass-energy and space-time scales considered.

Therefore the only possible prediction is that:

- **Totally Unexpected Effects** should **show up**.
- **Effects**, which are impossible to be predicted on the basis of **present knowledge**.

We should be prepared with **powerful experimental instruments, technologically at the frontier of our knowledge**, to discover Totally Unexpected Events in all laboratories, the world over (including CERN in Europe, Gran Sasso in Italy, and other facilities in Japan, USA, China and Russia). All the pieces of the Yukawa gold mine [9] could not have been discovered if the experimental technology was not at the frontier of our knowledge.

Example: the cloud-chambers (Anderson, Blackett, Neddermeyer), the photographic emulsions (Lattes, Occhialini, Powell), the high power magnetic fields (Conversi, Pancini, Piccioni) and the powerful particle accelerators and associated detectors for the discovery – the world over – of the **SM&B** as synthetically reported in chapter 4.2. This means that we must be prepared with the most advanced technology for the discovery of totally unexpected events like the ones found in the Yukawa gold mine.

The mathematical descriptions, and therefore the predictions – for new phenomena to be discovered in the field opened by the given UEEC event – come after the UEEC event, never before.

Recall:

- The **discoveries in Electricity**, **Magnetism** and **Optics** (UEEC).
- **Radioactivity** (UEEC).
- The **Cosmic Rays** (UEEC).
- The **Weak Forces** (UEEC).
- The **Nuclear Physics** (UEEC).
- The **Strange Particles** (UEEC).
- The **3 Columns** (UEEC).
- The **origin of the Fundamental Forces** (UEEC).

The present status of Science is reported in figure 10.

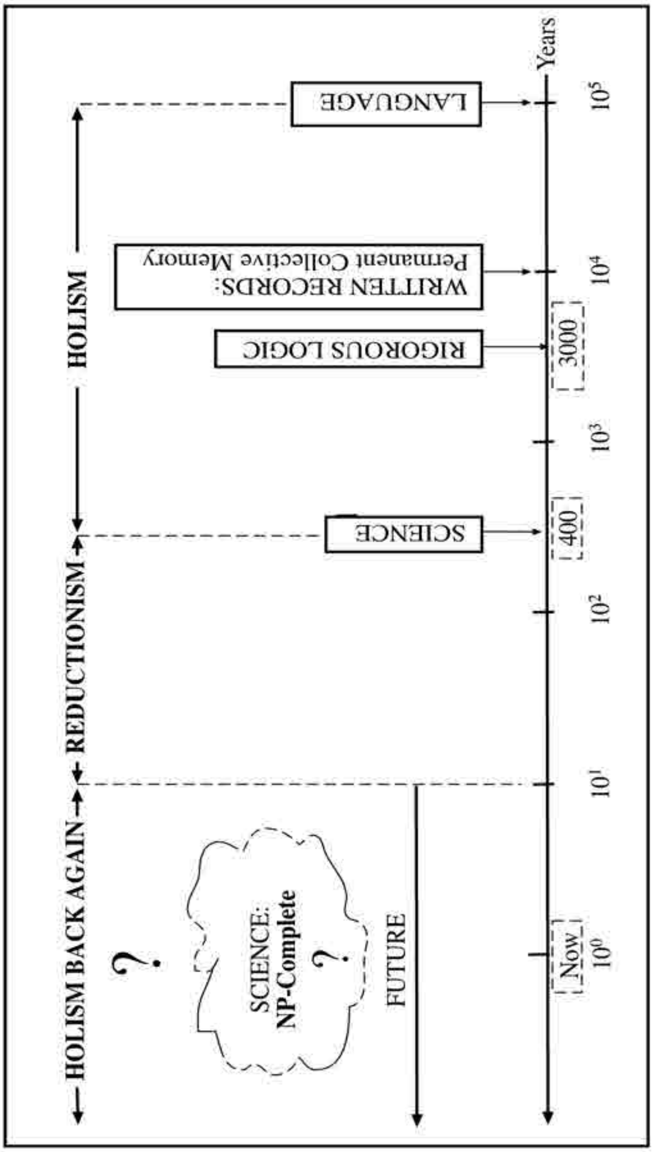


Figure 10

It could be that Science will be mathematically proved to be 'NP-complete'. This is the big question for the immediate future [10].

It is therefore instructive to see how Science fits in the whole of our knowledge as reported in Addendum 3.

Let me point out that Science is the consequence of us being the only form of leaving matter endowed with Reason, from where the sequence of Language–Logic–Science has been originated [11]. The time-sequence of Language–Logic–Science is shown in figure 11.

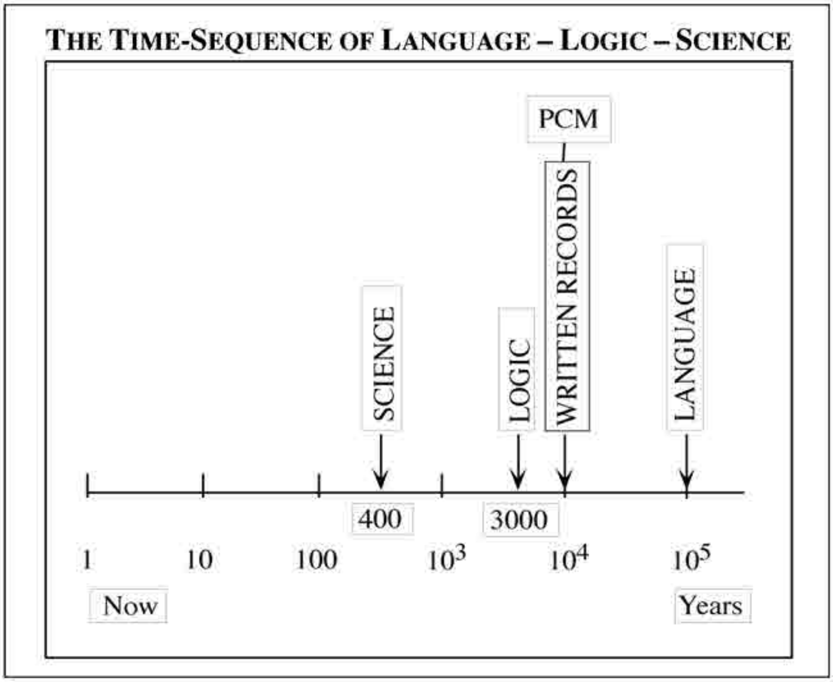


Figure 11

The experimental evidence is that UEEC events dominate our life as we have shown in chapter 5, Table-1, where the evolution of the world in its real life (EWRL ≡ History) and the evolution of our basic understanding of the laws governing the world (EBUS ≡ Science) have been compared.

9 CLOSING REMARKS: FROM PLANCK TO COMPLEXITY

Four centuries of Galilean research work based on Reductionism, i.e. on the identification of the simplest elements in the study of Nature, has allowed us to get the greatest achievements of Science, i.e. the so called **Standard Model** and its extension (**SM&B**), illustrated before in figure 7.

This extension predicts GUT (the Grand Unification Theory), the existence of the Superworld and the resolution of the quantum-gravity problem via the powerful theoretical structure of RQST (Relativistic Quantum String Theory).

These developments started thirty years ago when a great scientific novelty came; all experimental discoveries obtained with our powerful accelerators were to be considered only matters of extremely low energy.

The scale of energy on which to direct the attention to understand the Logic that rules the world, from the tiniest structures to the galactic ones, had to be shifted at a much higher level: to the mass-energy named after Planck, E_{Planck}, something like seventeen powers of ten above the Fermi scale, E_{Fermi}, that already seemed to be an extremely high level of energy.

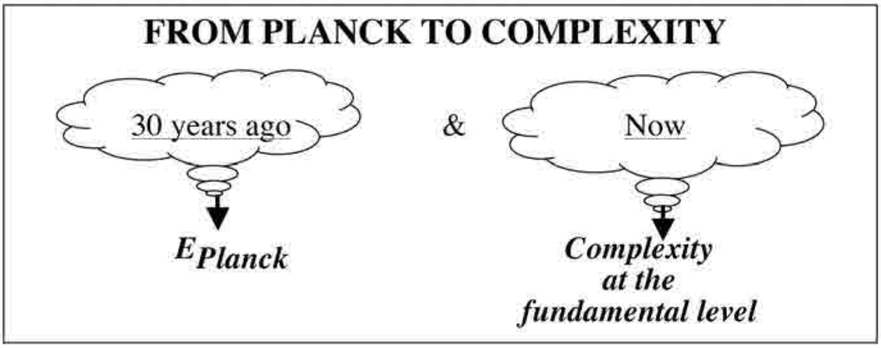


Figure 12

Now, after thirty years, it comes about the novelty of our time: Complexity exists at the fundamental level [1]. In fact, **AFB** and **UEEC** events exist at all scales, as reported all along this lecture.

This result is corroborated from the mathematical structure (the only one) to be in a position of describing all that happens at the Planck scale: the Relativistic Quantum String Theory (**RQST**).

This mathematical structure produces innumerable minima of energy, named **Landscape**.

The theoretical discovery of the **Landscape** (Leonard Susskind) [12], has been followed by another formidable discovery in mathematical physics: the most rigorous model of RQST (Raphael Bousso and Joseph Polchinski) is **NP-complete** (Michael R. Douglas and Frederik Denef) [13].

This discovery corroborates all that we have put in evidence during the last five years [5–8]: **Complexity exists at the fundamental level** [1].

We do not know what will be the final outcome of String Theory.

What we know is that: '*The world appears to be complex at every scale.* ***Therefore*** *we must expect a continued series of surprises that we cannot easily predict*'.

A detail of great interest to me: with the advent of the LHC it will be possible to study the properties of the Quark-Gluon-Coloured-World (QGCW), which is a world totally different from all we have been dealing with since the origin of Science.

10 THE FINAL QUESTION

The final question is: why the greatest achievements of Science have always been generated by UEEC, i.e. totally unexpected events?

ADDENDUM 1
THE PLATONIC GRAND UNIFICATION

In figure 13 is reported the best example of Platonic Grand Unification (the blue straight line). The points have a sequence of 100 GeV in energy. The last point where the 'ideal' platonic straight line intercepts the theoretical prediction is at the energy of the Grand Unification. This corresponds to $E_{GU} = 10^{16.2}$ GeV. Other detailed information on the theoretical inputs: the number of fermionic families, N_F , is 3; the number of Higgs particles, N_H , is 2. The input values of the gauge couplings at the Z^0-mass is α_3 $(M_Z) = 0.118 \pm 0.008$; the other input is the ratio of weak and electromagnetic couplings also measured at the Z^0-mass value: $\sin^2 \theta_W$ $(M_Z) = 0.2334 \pm 0.0008$.

The Platonic Grand Unification should be along the straight line (in blue) but Nature seems to follow the red points.

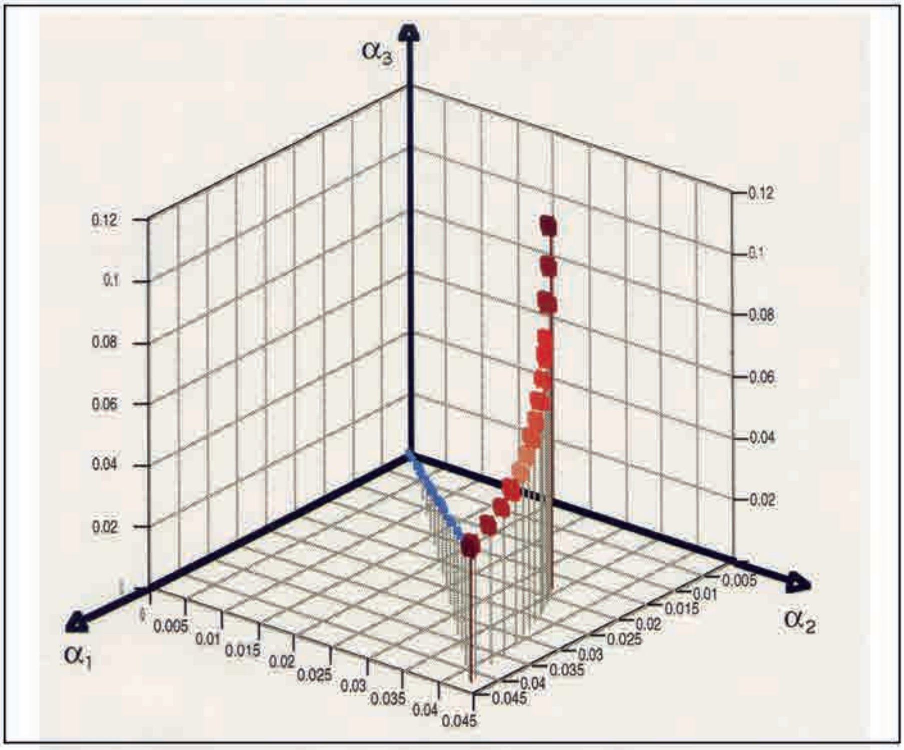
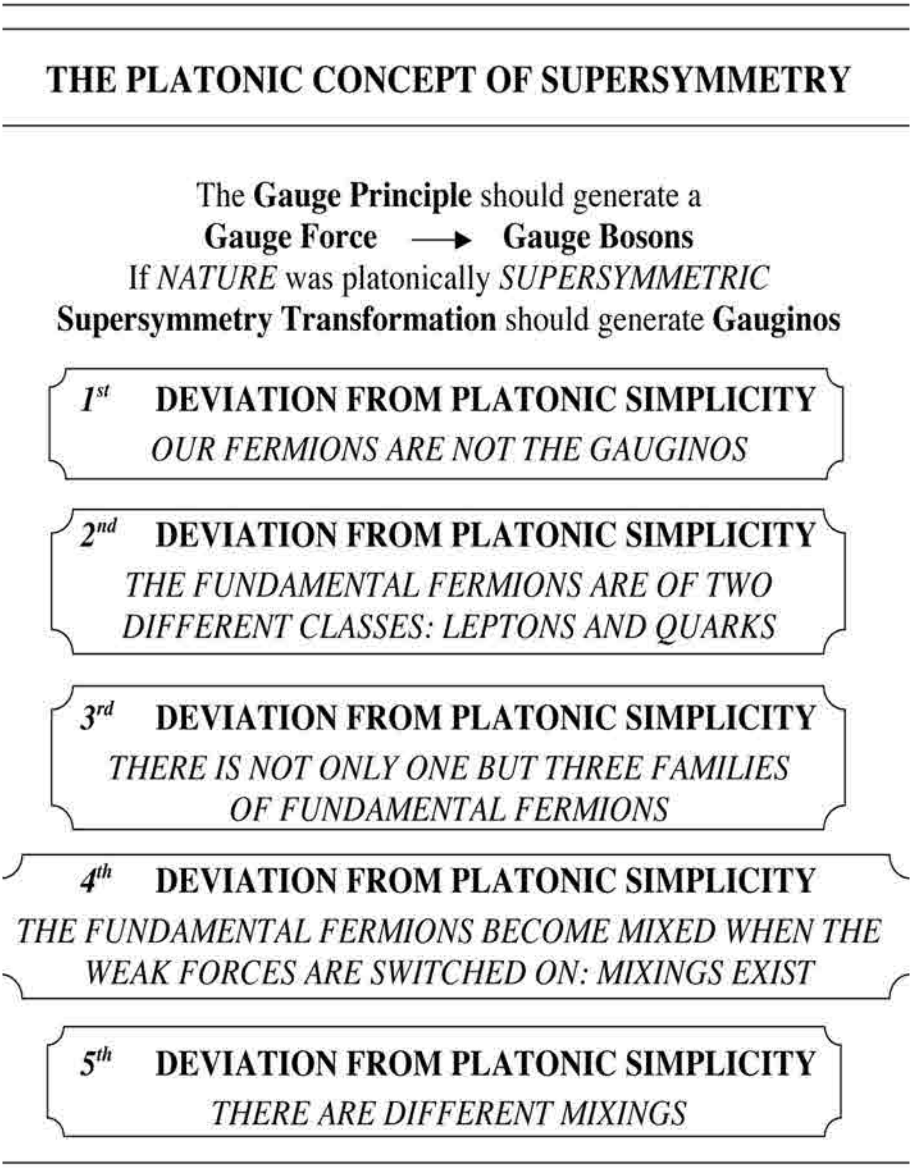


Figure 13

ADDENDUM 2
THE PLATONIC SUPERWORLD



THE PLATONIC CONCEPT OF SUPERSYMMETRY

The **Gauge Principle** should generate a
Gauge Force ⟶ **Gauge Bosons**
If *NATURE* was platonically *SUPERSYMMETRIC*
Supersymmetry Transformation should generate **Gauginos**

1st DEVIATION FROM PLATONIC SIMPLICITY
OUR FERMIONS ARE NOT THE GAUGINOS

2nd DEVIATION FROM PLATONIC SIMPLICITY
THE FUNDAMENTAL FERMIONS ARE OF TWO DIFFERENT CLASSES: LEPTONS AND QUARKS

3rd DEVIATION FROM PLATONIC SIMPLICITY
THERE IS NOT ONLY ONE BUT THREE FAMILIES OF FUNDAMENTAL FERMIONS

4th DEVIATION FROM PLATONIC SIMPLICITY
THE FUNDAMENTAL FERMIONS BECOME MIXED WHEN THE WEAK FORCES ARE SWITCHED ON: MIXINGS EXIST

5th DEVIATION FROM PLATONIC SIMPLICITY
THERE ARE DIFFERENT MIXINGS

Figure 14

ADDENDUM 3
THE WHOLE OF OUR KNOWLEDGE

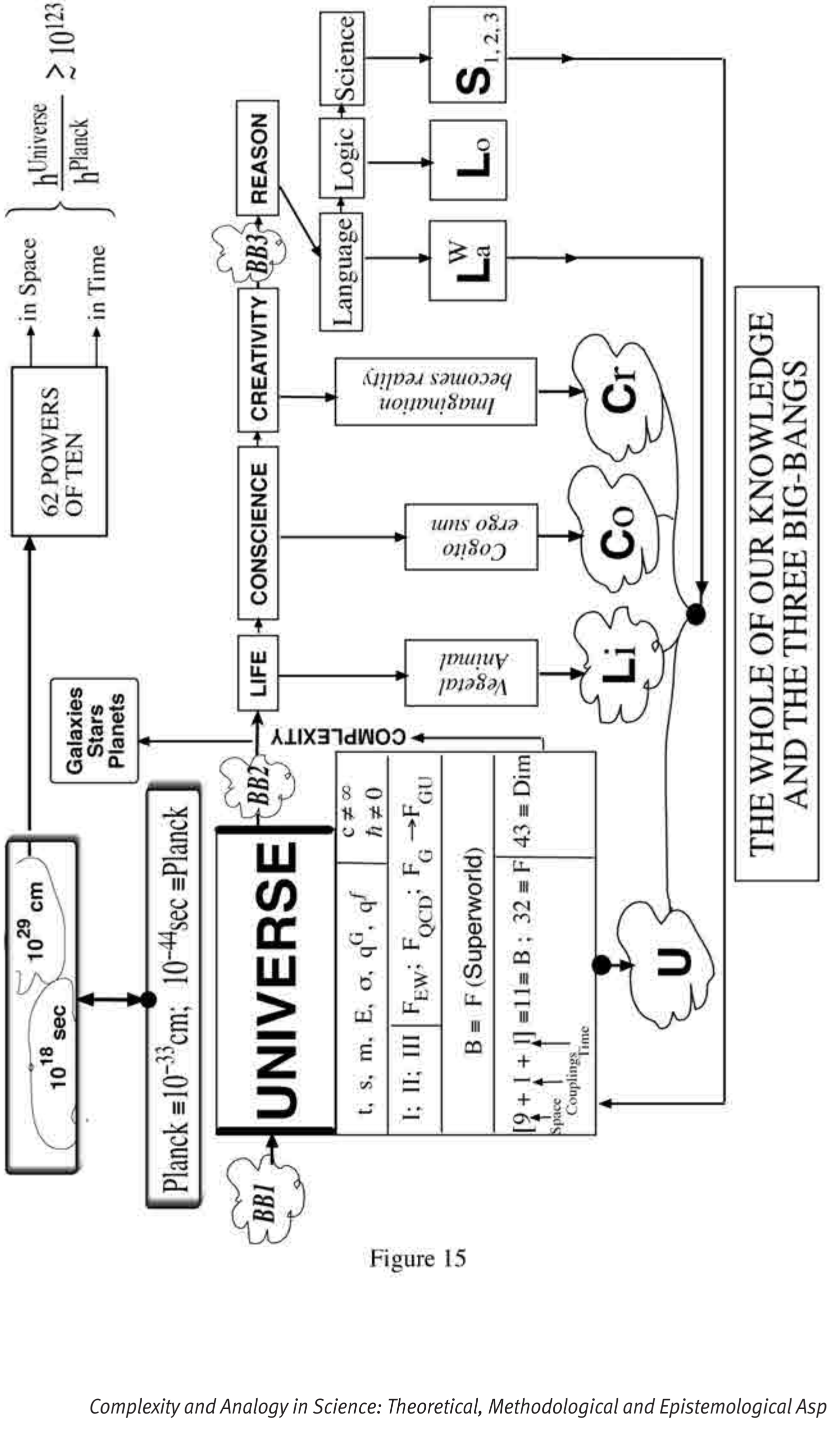


Figure 15

ADDENDUM 4
UEEC EVENTS IN NUCLEAR PHYSICS

Let me dedicate some attention to discuss UEEC events in nuclear physics. In fact in many books it is considered standard wisdom the fact that nuclear physics is based on perfectly sound theoretical predictions. People forget the impressive series of UEEC events discovered in what I have decided to call the 'Yukawa gold mine'.

Let me quote just three of them:

1 The first experimental evidence for a cosmic ray particle believed to be the Yukawa meson was a lepton: the muon.

2 The decay-chain: $\pi \rightarrow \mu \rightarrow e$ was found to break the symmetry laws of Parity and Charge Conjugation.

3 The intrinsic structure of the Yukawa particle was found to be governed by a new fundamental force of Nature, Quantum ChromoDynamics: QCD.

As you know 2007 was the centenary of the birth of Hideki Yukawa, the father of theoretical nuclear physics. In 1935 the existence of a particle, with mass intermediate (this is the origin of 'mesotron' now 'meson') between the light electron, m_e, and the heavy nucleon (proton or neutron), m_N, was proposed by Yukawa [14].

This intermediate mass value was deduced by Yukawa from the range of the nuclear forces. Contrary to the general wisdom of the time, Yukawa was convinced that the particles known (electrons, protons, neutrons and photons), could not explain how protons and neutrons are bound into the extremely small dimensions of a nucleus.

In order to make this 'prediction', Yukawa needed the Heisenberg uncertainty principle: a totally unexpected theoretical discovery.

The origin of it was the totally unexpected discovery of the dual nature of the electron (wave and particle) and of the photon (wave and particle).

Heisenberg himself tried to explain the binding forces between the proton and the neutron, via the exchange of electrons, in order not to postulate the existence of a new particle. The very light electron, m_e, could not stay in the very small dimension of the nucleus.

The author of the uncertainty principle and father, with Dirac and Pauli, of Quantum Mechanics, did not realise this contradiction. The need for a new 'particle' was the reason. What no-one was able to predict was the 'gold-mine' hidden in the production, the decay and the intrinsic structure of this new 'particle'.

This 'gold-mine' is still being explored nowadays and its present frontier is the Quark-Gluon-Coloured-World (QGCW) [15].

I have recently described [9] the unexpected conceptual developments coming from the study of the production, the decay and the intrinsic structure of the Yukawa particle.

Let me just quote the most relevant UEEC events: chirality–invariance, spontaneous symmetry breaking, symmetry breaking of fundamental invariance laws (P, C, T), anomalies, and 'anomaly-free condition', existence of a third family of fundamental fermions, gauge principle for non-Abelian forces, instantons and existence of a pseudoscalar particle made of the quanta of a new fundamental force of Nature acting between the constituents of the Yukawa particle.

ADDENDUM 5
UEEC EVENTS WHERE I HAVE BEEN DIRECTLY INVOLVED

A few cases (seven) where I have been directly involved are summarised in figure 16. Each **UEEC** event is coupled with a **despite**, in order to emphasize the reason why the event is unexpected.

UEEC EVENTS
IN THE CONSTRUCTION OF THE SM&B
MY PERSONAL EXPERIENCE

① ***The 3rd lepton*, HL** (now called τ) with its own neutrino,
ν_{HL} (now called ν_τ),
despite the abundance of neutrinos: ν_e and ν_μ.

② ***Antimatter***
despite S-matrix and C, P, CP, T breakings.

③ ***Nucleon Time-like** EM structure*
despite S-matrix.

④ ***No quarks** in violent (pp) collisions*
despite scaling and Asymptotic Freedom.

⑤ ***Meson mixings***
$\theta_V \neq \theta_{PS}$ **:** $(51^\circ) \neq (10^\circ) \neq 0$ **despite** $SU(3)_{uds}$.

⑥ ***Effective energy:** the Gribov QCD-light*
despite Platonic Simplicity and QCD-confinement not rigorously understood.

⑦ ***The running** of $\alpha_1\ \alpha_2\ \alpha_3$ versus **energy** at **a point*** $\mathbf{E_{GU}}$
1979) (1991) **despite** straight line convergence.
$\boxed{\textit{EGM}}$

Figure 16

All these events have contributed to the construction of the **Standard Model and Beyond (SM&B)**.

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KOLMOGOROV COMPLEXITY AS A HIDDEN FACTOR OF SCIENTIFIC DISCOURSE: FROM NEWTON'S LAW TO DATA MINING[1]

YURI I. MANIN

The word "complexity" is most often used as a meta-linguistic expression referring to certain intuitive characteristics of a natural system and/or its scientific description. These characteristics may include: sheer amount of data that must be taken into account; visible "chaotic" character of these data and/or space distribution/time evolution of a system etc.

This talk is centered around the precise mathematical notion of "Kolmogorov complexity", originated in early theoretical computer science and measuring *the degree to which an available information can be compressed*.

In the first part, I will argue that a characteristic feature of basic scientific theories, from Ptolemy's epicycles to the Standard Model of elementary particles, is their splitting into two very distinct parts: the part of relatively small Kolmogorov complexity ("laws", "basic equations", "periodic table", "natural selection, genotypes, mutations") and another part, of indefinitely large Kolmogorov complexity ("initial and boundary conditions", "phenotypes", "populations"). The data constituting this latter part are obtained by planned observations, focussed experiments, and afterwards collected in growing databases (formerly known as "books", "tables", "encyclopaedias" etc). In this discussion Kolomogorov complexity plays a role of the central metaphor.

The second part and Appendix 1 are dedicated to more precise definitions and examples of complexity.

Finally, the last part briefly touches upon attempts to deal directly with Kolmogorov complex massifs of data and the "End of Science" prophecies.

1. Bi-partite structure of scientific theories

In this section, I will understand the notion of "compression of information" intuitively and illustrate its pervasive character with several examples from the history of science.

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[1] Talk at the Plenary Session of the Pontifical Academy of Sciences on "Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects" , Casina Pio IV, November 5-7, 2012.

Planetary movements

Firstly, I will briefly remind the structure of several models of planetary motions in the chronological order of their development.

After the discovery that among the stars observable by the naked eye in a night sky there exist several exceptional "moving stars" (planets), several successful models of their movement were proposed, which allowed for the prediction of the future positions of the moving stars.

The simplest of them placed all fixed stars on one celestial sphere that rotated around the earth in a way reflecting nightly and annually visible motions. The planets, according to Apollonius of Perga (3rd century B.C.), Hipparchus of Rhodes, and Ptolemy of Alexandria (2nd century A.D.), were moving in a more complicated way: along circular "epicyles" whose centers moved along another system of circles, "eccentrics" around Earth. Data about radii of eccentrics and epicycles and the speed of movements were extracted from observations of the visible movements, and the whole model was then used in order to predict the future positions at any given moment of observation.

As D. Park remarks ([Pa], p. 72), "[...] in the midst of all this empiricism sat the ghost of Plato, legislating that the curves drawn must be circles and nothing else, and that the planets and the various connectiong points must move along them uniformly and in no other way".

Since in reality observable movements of planets involved accelerations, backward movements, etc., two circles in place of one for each planet at least temporarily saved face for philosophy. Paradoxically, however, the much later and much more developed mathematics of modernity returned to the image of "epicycles", that could since then form an arbitrarily high hierarchy: the idea of Fourier series and, later, Fourier integral transformation does exactly that!

It is well known, at least in general outline, how Copernicus replaced these geocentric models by a heliocentric one, and how with the advent of Newton's

$$gravity\ law\ F = G\frac{m_1 m_2}{r^2}, \quad dynamic\ law\ F = ma,$$

and the resulting solution of the "two-body problem", planets "started moving" along ellipsoidal orbits (with the Sun as one focus rather than the center). It is less well known to the general public that this approximation as well is valid only insofar as we can consider negligible the gravitational forces with which the planets interact among themselves.

If we intend to obtain a more precise picture, we have to consider the system of differential equations defining the set of curves parametrized by time t in the $6n$*–dimensional phase space* where n is the number of planets (including the Sun) taken in consideration:

$$\frac{d^2 q_i}{dt^2} = \sum_{i=1}^{n} \frac{m_i m_j((q_i - q_j)}{|q_i - q_j|^3}$$

Both Newton laws are encoded in this system.

The choice of one curve, corresponding to the evolution of our Solar system, is made when we input *initial conditions* $q_i(0), \frac{dq_i}{dt}(0)$ at certain moment of time $t = 0$; they are supplied, with a certain precision, by observations.

At this level, a new complication emerges. Generic solutions of this system of equations, in the case of three and more bodies, cannot be expressed by any simple formulas (unlike the equations themselves). Moreover, even qualitative behavior of solutions depends in an extremely sensitive way on the initial conditions: very close initial positions/velocities may produce widely divergent trajectories. Thus, the question whether our Solar system will persist for the next, say, 10^8 years (even without disastrous external interventions) cannot be solved unless we know its current parameters (masses of planets, positions of their centers of mass, and speeds) with unachievable precision. This holds even without appealing to Einstein's much more precise description of gravity, or without taking in account comets, asteroid belts and moons of the Solar system (the secondary planets turning around planets themselves).

It goes without saying that a similarly detailed description of, say, our Galaxy, taking in account movements of all individual celestial bodies constituting it, is unachievable from the start, because of the sheer amount of these bodies. Hence, to understand its general space{time structure, we must first construct models involving averaging on a very large scale. And of course, the model of space-time itself, now involving Einstein's equations, will describe an "averaged" space-time.

Information compression: first summary

In this brief summary of consecutive scientific models, one can already see the following persisting pattern: the subdivision into a highly compressed part ("laws") and potentionally indefinitely complex part. The first part in our brief survey was represented by formulas that literally became cultural symbols of Western civilization: Newton's laws, that were followed by Einstein's $E=mc^2$ and Heisenberg's $pq-qp=\frac{h}{2\pi i}$ .The second part is kinematically represented by "initial" or "boundary" conditions, and dynamically by a potentially unstable character of dependence of the data we are interested in on these initial/boundary conditions.

More precisely, a mathematical description of the "scene" upon which kinematics and dynamics develop in these models is also represented by highly compressed mathematical images, only this time of geometric nature. Thus, the postulate that kinematics of a single massive point is represented by its position in an ideal Euclidean space represents one of the "laws" as well. To describe kinematics, one should amplify this "configuration space" and replace it by the "phase space" parametrizing positions and velocities, or, better, momenta. For one massive point it is a space of dimension *six*: this is the answer of mathematics to Zeno's "Achilles and the Turtle" paradox. For a planet system consisting of *n* planets (including Sun) the phase space has dimension 6*n*.

For Einstein's equations of gravitation, the relevant picture is much more complicated: it involves configuration and phase spaces that have *infinite* dimension, and require quite a fair amount of mathematics for their exact description. Nevertheless, this part of our models is still clearly separated from the one that we refer to as the part of infinite Kolmogorov complexity, because mathematics developed a concise language for the description of geometry.

One more lesson of our analysis is this: "laws" can be discovered and efficiently used only if and when we restrict our attention to definite domains, space-time scales, and kinds of matter and interactions. For example, there was no place for chemistry in the pictures above.

From macroworld to microworld: the Standard Model of elementary particles and interactions

From astronomy, we pass now to the deepest known level of microworld: the theory of elementary particles and their interactions.

I will say a few words about the so-called Standard Model of the elementary particles and their interactions, that took its initial form in the 1970s as a theoretical construction in the framework of the Quantum Field Theory. The Standard Model got its first important experimental correlates with the discovery of quarks (components of nuclear "elementary" particles) and *W* and *Z* bosons, quanta of ineractions. For a very rich and complex history of this stage of theoretical physics, stressing the role of experiments and experimenters, see the fascinating account [Zi] by Antonio Zichichi. The Standard Model recently reappeared on the front pages of the world press thanks to the renewed hopes that the last critically missing component of the Model, the Higgs Boson, had finally been observed.

Somewhat paradoxically, one can say that the mathematics of the Standard Model is firmly based on the same ancient archetypes of the human thought as that of Hipparchus and Ptolemy: symmetry and uniform movement along circles.

More precisely, the basic idea of symmetry of modern classical (as opposed to quantum) non{relativistic physics involves the symmetry group of rigid movements of the three-dimensional Euclidean space, that is combinations of parallel shifts and rotations around a point. The group of rotations is denoted $SO(3)$, and celestial spheres are the unique objects invariant with respect to rotations. Passing from Hipparchus and Ptolemy to modernity includes two decisive steps: adding shifts (Earth, and then Sun, cease being centers of the Universe), and, crucially, understanding the new meta-law of physics: *symmetry* must govern *laws of physics* themselves rather than objects/processes etc that these laws are supposed to govern (such as the Solar System).

When we pass now to quantum mechanics, and further to Quantum Field Theory (not involving gravitation), the group of $SO(3)$ (together with shifts) should be extended, in particular, by several copies of such groups as $SU(2)$ and $SU(3)$ describing rotations in the *internal degrees of freedom* of elementary particles, such as spin, colour etc. The basic "law" that should be invariant with respect to this big group, is encoded in the Lagrangian density: it is a "mathematical formula" that is considerably longer than everything we get exposed to in our high school and even college courses: cf. Appendix 2.

Finally, the Ptolemy celestial movements, superpositions of rotations of rigid spheres, now transcend our space-time and happen in the infinite-dimensional Hilbert space of wave-functions: this is the image describing, say, a hydrogen atom in the paradigm of the first decades of the 20th century.

Information compression: second summary

I will use the examples above in order to justify the following viewpoint. Scientific laws (at least those that are expressed by mathematical constructions) can be considered as *programs for computation*, whereas observations produce inputs to these programs.

Outputs of these computations serve first to check/establish a domain of applicability of our theories. We compare the predicted behavior of a system with observations made, we are happy when our predictions agree quantitatively and/or qualitatively with observable behaviour, we fix the border signs signalling that at this point we have gone too far.

Afterwards, the outputs are used for practical/theoretical purposes, e.g. in engineering, weather predictions etc, but also to formulate the new challenges arising before the scientific thinking.

This comparison of scientific laws with programs is, of course, only a metaphor, but it will also allow us to construct a precise model of the kind of complexity, inherently associated with this metaphor of science: Kolmogorov complexity.

The next section is dedicated to the sketch of this notion in the framework of mathematics, again in its historical perspective.

2. Integers and their Kolmogorov complexity

Positional notations as programs

In this section, I will explain that the well-known to the general public decimal notations of natural numbers are themselves programs.

What are they supposed to calculate?

Well, the actual *numbers* that are encoded by this notation, and are more adequately represented by, say, rows of strokes:

$$7:\ |||||||, \qquad 13:\ |||||||||||||, \qquad \dots \qquad , 1984:\ ||||\dots||||$$

Of course, in the last example it is unrealistic even to expect that if I type here 1984 strokes, an unsophisticated reader will be able to check that I am not mistaken. There will be simply too many strokes to count, whereas the *notation-program* "1984" contains only four signs chosen from an alphabet of ten signs. One can save on the size of the alphabet, passing to the binary notation, so that "1984" will be replaced by a longer program "11111000000". However, comparing the length of the program with the "size" of the number, i.e. the respective number of strokes, we see that decimal/binary notation gives an immense economy: the program length is approximately the logarithm of the number of strokes (in the base 10 or 2 respectively).

More generally, we can speak about "size", or "volume" of any finite text based upon a fixed finite alphabet.

The discovery of this logarithmic upper bound of the Kolmogorov complexity of *numbers* was a leap in the development of humanity on the scale of civilizations.

However, if one makes some slight additional conventions in the system of notation, it will turn out that some integers admit a much shorter notation. For example, let us allow ourselves to use the vertical dimension and write, e.g. $10^{10^{10}}$.

The logarithm of the last number is about 10^{10}, much larger than the length of the notation for which we used only 6 signs! And if we are unhappy about non-linear notation, we may add to the basic alphabet two brackets (,) and postulate that $a(b)$ means a^b. Then $10^{10^{10}}$ will be linearly written as 10(10(10)) using only 10 signs, still much less than $10^{10}+1$ decimal digits (of course, 1010 of them will be just zeroes).

So can *all* integers perhaps be produced by notation/programs that are much shorter than logarithm of their size?

No! It turns out that the absolute majority of numbers (or texts) *cannot* be significantly compressed, although an infinity of integers can be written in a much shorter way than can be done in any chosen system of positional notation.

If we leave the domain of integers and leap, to, say, such a number as $\pi = 3{,}1415926\ldots$, it looks as if it had infinite complexity. However, this is not so. There exists a program that can take as input the (variable) place of a decimal digit (an integer) and give as output the respective digit. Such a program is itself a text in a chosen algorithmic language, and as such, it also has a complexity: its own Kolmogorov complexity. One agrees that this is the complexity of π.

The reader should be aware that I have left many subtle points of the definition of Kolmogorov complexity in shadow, in particular, the fact that its dependence of the chosen system of encoding and computation model can change it only by a bounded quantity etc. The reader who would like to see some more mathematics about this matter is referred to the brief Appendix 1 and the relevant references.

Here I will mention two other remarkable facts related to the Kolmogorov complexity of numbers: one regarding its unexpected relation to the idea of *randomness*, and another one showing that some psychological data make explicit the role of this complexity in the cognitive activity of our mind.

Complexity and randomness

Consider arbitrarily long finite sequences of zeroes and ones, say, starting with one so that each such sequence could be interpreted as a binary notation of an integer.

There is an intuitive notion of "randomness" of such a sequence. In the contemporary technology "random" sequences of digits and similar random objects are used for encoding information, in order to make it inaccessible for third parties. In fact, a small distributed industry producing such random sequences (and, say, random big primes) has been created. A standard way to produce random objects is to leave mathematics and to recur to physics: from throwing a piece to registering white noise.

One remarkable property of Kolmogorov complexity is this: *those sequences of digits whose Kolmogorov complexity is approximately the same as their* *length, are random in any meaningful sense of the word*. In particular, they cannot be generated by a program essentialy shorter than the sequence itself.

Complexity and the human mind

In the history of humanity, the discovery of the laws of classical and quantum physics that represent an incredible compression of complex information, stresses the role of Kolmogorov complexity, at least as a relevant metaphor for understanding the laws of cognition.

In his very informative book [De], Stanislas Dehaene considers certain experimental results about the statistics of appearance of numerals and other names of numbers, cf. especially pp. 110-115, subsection "Why are some numerals more frequent than others?".

As mathematicians, let us consider the following abstract question: can one say anything non-obvious about possible probabilities of distributions on the set of *all* natural numbers? More precisely, one such distribution is a sequence of non-negative real numbers p_n, $n=1; 2; \dots$ such that $\sum_n p_n = 1$. Of course, from the last formula it follows that p_n must tend to zero, when n tends to infinity; moreover p_n cannot tend to zero too slowly: for example, $p_n = n^{-1}$ will not do. But two different distributions can be widely incomparable.

Remarkably, it turns out that if we restrict our class of distributions only to *computable from below* ones, that is, those in which p_n can be computed as a function of n (in a certain precise sense), then it turns out that there is a distinguished and small subclass C of such distributions, that are in a sense maximal ones. Any member (p_n) of this class has the following unexpected property (see [Lev]): *the probability p_n of the number n, up to a bounded (from above and below) factor, equals the inverse of the exponentiated Kolmogorov complexity of n.*

This statement needs additional qualifications: the most important one is that we need here *not* the original Kolmogorov complexity but the so-called *prefix-free* version of it. We omit technical details, because they are not essential here. But the following properties of any distribution $(p_n) \in C$ are worth stressing in our context:

(i) Most of the numbers n, those that are Kolmogorov "maximally complex", appear with probability comparable with $n^{-1} (\log n)^{-1-\varepsilon}$, with a small ε: "most large numbers appear with frequency inverse to their size" (in fact, a somewhat smaller one).

(ii) However, frequencies of those numbers that are Kolmogorov very simple, such as 10^3 (thousand), 10^6 (million), 10^9 (billion), produce sharp local peaks in the graph of (p_n).

The reader may compare these properties of the discussed class of distributions, which can be called *a priori distributions*, with the observed frequencies of numerals (number words) in printed and oral texts in various languages: cf. Dehaene, loc. cit., p. 111, Figure 4.4. To me, their qualitative agreement looks very convincing: brains and their societies do reproduce a priori probabilities.

Notice that those parts of the Dehaene and Mehler graphs in loc. cit. that refer to large numbers, are somewhat misleading: they might create an impression that frequencies of the numerals, say, between 106 and 109, smoothly interpolate between those of 106 and 109 themselves, whereas in fact they abruptly drop down.

Finally, I want to stress that the class of a priori probability distributions that we are considering here is *qualitatively distinct* from those that form now a common stock of sociological and sometimes scientific analyses: cf. a beautiful synopsis by Terence Tao in [Ta]. The appeal to the uncomputable degree of maximal compression is exactly what can make such a distribution an eye-opener. As I have written at the end of [Ma2]:

"One can argue that all cognitive activity of our civilization, based upon symbolic (in particular, mathematical) representations of reality, deals actually with the *initial Kolmogorov segments* of potentially infinite linguistic constructions, *always* replacing vast volumes of data by their compressed descriptions. This is especially visible in the outputs of the modern genome projects.

In this sense, such linguistic cognitive activity can be metaphorically compared to a gigantic precomputation process, shellsorting infinite worlds of expressions in their Kolmogorov order".

3. New cognitive toolkits: WWW and databases

"The End of Theory"

In summer 2008, an issue of "Wired Magazine" appeared. Its cover story ran: "The End of Theory: The Data Deluge Makes the Scientific Method Obsolete".

The message of this essay, written by the Editor-in-Chief Chris Anderson, was summarized in the following words:

> *The new availablility of huge amounts of data, along with statistical tools to crunch these numbers, offers a whole new way of understanding the world. Correlation supersedes causation, and science can advance even without coherent models, unified theories, or really any mechanical explanation at all. There's no reason to cling to our old ways. It's time to ask: What can science learn from Google?*

I will return to this rhetoric question at the end of this talk. Right now I want only to stress that, as well as in the scientific models of the "bygone days", basic theory is unavoidable in this brave new Petabyte World: encoding and decoding data, search algorithms, and of course, computers themselves are just engineering embodiments of some very basic and very abstract notions of mathematics. The mathematical idea underlying the structure of modern computers is the Turing machine (or one of several other equivalent formulations of the concepts of computability). We know that the universal Turing machine has a very small Kolmogorov complexity, and therefore, using the basic metaphor of this talk, we can say that the bipartite structure of the classical scientific theories is reproduced at this historical stage.

Moreover, what Chris Anderson calls "the new availability of huge amounts of data" by itself is not very new: after the spreading of printing, astronomic observatories, scientific laboratories, and statistical studies, the amount of data available to any visitor of a big public library was always huge, and studies of correlations have proliferated for at least the last two centuries.

Charles Darwin himself collected the database of his observations, and the result of his pondering over it was the theory of evolution.

A representative recent example is the book [FlFoHaSCH], sensibly reviewed in [Gr].

Even if the sheer volume of data has by now grown by several orders of magnitude, this is not the gist of Anderson's rhetoric.

What Anderson actually wants to say is that human beings are now – happily! – free from thinking over these data. Allegedly, computers will take this burden upon themselves, and will provide us with correlations – replacing the old-fashioned "causations" (that I prefer to call scientific laws) – and expert guidance.

Leaving aside such questions as how "correlations" might possibly help us understand the structure of the Universe or predict the Higgs Boson, I would like to quote the precautionary tale from [Gr]:

> *[…] in 2000 Peter C. Austin, a medical statistician at the University of Toronto, and his colleagues conducted a study of all 10,674,945 residents of Ontario aged between eighteen and one hundred. Residents were randomly assigned to different groups, in which they were classified according to their astrological signs. The research team then searched through more than two hundred of the most common diagnoses of hospitalization until they identified two where patients under one astrological sign had a significantly higher probability of hospitalization compared to those born under the remaining signs combined: Leos had a higher probability of gastrointestinal hemorrage while Sagittarians had a higher probability of fracture of the upper arm compared to all other signs combined.*
>
> *It is thus relatively easy to generate statistically significant but spurious correlations when examining a very large data set and a similarly large number of po-*

> *tential variables. Of course, there is no biological mechanism whereby Leos might be predisposed to intestinal bleeding or Sagittarians to bone fracture, but Austin notes, "It is tempting to construct biologically plausible reasons for observed subgroup effects after having observed them". Such an exercise is termed "data mining", and Austin warns, "Our study therefore serves as a cautionary note regarding the interpretation of findings generated by data mining" [...]*

Coda

What can science learn from Google:
"Think! Otherwise no Google will help you".

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APPENDIX 1. A brief guide to computability

This appendix contains a sketch of the mathematical computability theory, or theory of algorithmic computations, as it was born in the first half the XXth century in the work of such thinkers as Alonso Church, Alan Turing and Andrei Kolmogorov. We are not concerned here with its applied aspects studied under the general heading of "Computer Science".

This theory taught us two striking lessons.

First, that there is a unique universal notion of computability in the sense that all seemingly very different versions of it turned out to be equivalent. We will sketch here the form that is called *the theory of (partial) recursive functions.*

Second, that this theory sets its own limits and unavoidably leads to confrontation with *uncomputable problems.*

Both discoveries led to very interesting research aiming to the extension of this territory of classical computability such as basics of theory of quantum computing etc. But we are not concerned with this development here.

Three descriptions of partial recursive functions. The subject of the theory of recursive functions is a set of functions whose domain and values are vectors of natural numbers of arbitrary fixed lengths: $f : \mathbf{Z}_+^m \to \mathbf{Z}_+^n$.

An important qualification: a "function", say, $f : X \to Y$, below always means a pair $(f, D(f))$, where $D(f) \subset X$ and f is a map of sets $D(f) \to Y$. The definition domain $D(f)$ is not always mentioned explicitly. If $D(f) = X$, the function might be called "total"; generally it may be called "partial" one.

(i) Intuitive description. A function $f : \mathbf{Z}_+^m \to \mathbf{Z}_+^n$ is called *(partial) recursive* iff it is "semi–computable" in the following sense:

there exists an algorithm F accepting as inputs vectors $x = (x_1, \dots, x_m) \in \mathbf{Z}_+^m$. with the following properties:

– if $x \in D(f)$, F produces as output $f(x)$.

– if $x \notin D(f)$, F either produces answer "NO", or works indefinitely long without producing any output.

(ii) Formal description (sketch). It starts with two lists:

– An explicit list of "obviously" semi–computable *basic functions* such as constant functions, projections onto i–th coordinate etc.

– An explicit list of *elementary operations*, such as an inductive definition, that can be applied to several semi–computable functions and "obviously" produces from them a new semi–computable function.

The key elementary operation involves finding the least root of equation $f(x) = y$ (if it exists) where f is already defined function. It is this operation that involves search and makes introduction of partial functions inevitable.

– After that, the set of *partial recursive functions* is defined as *the minimal set of functions containing all basic functions and closed wrt all elementary operations.*

(iii) Diophantine description (A DIFFICULT THEOREM). A function $f : \mathbf{Z}_+^m \to \mathbf{Z}_+^n$ is partial recursive iff there is a polynomial

$$P(x_1, \dots, x_m; y_1, \dots, y_n; t_1, \dots, t_q) \in \mathbf{Z}[x, y, t]$$

such that the graph

$$\Gamma_f := \{(x, f(x))\} \subset \mathbf{Z}_+^m \times \mathbf{Z}_+^n$$

is the projection of the subset $P = 0$ in $\mathbf{Z}_+^m \times \mathbf{Z}_+^n \times \mathbf{Z}_+^q$.

Constructive worlds. *An (infinite) constructive world* is a countable set X (usually of some finite Bourbaki structures) given together with a class of *structural numberings:* intuitively computable bijections $\nu : \mathbf{Z}_+ \to X$ which form a principal homogeneous space over the group of recursive permutations of $\mathbf{Z}_+$. An element $x \in X$ is called *a constructive object.*

Example: X = all finite words in a fixed finite alphabet A.

Church's thesis: *Let X, Y be two constructive worlds, $\nu_X : \mathbf{Z}_+ \to X$, $\nu_Y : \mathbf{Z}_+ \to Y$ their structural numberings, and F an (intuitive) algorithm that takes as input an object $x \in X$ and produces an object $F(x) \in Y$ whenever x lies in the domain of definition of F.*

Then $f := \nu_Y^{-1} \circ F \circ \nu_X : \mathbf{Z}_+ \to \mathbf{Z}_+$ is a partial recursive function.

The status of Church's thesis in mathematics is very unusual. It is not a theorem, since it involves an undefined notion of "intuitive computability". It expresses the fact that several developed mathematical constructions whose explicit goal was to formalize this notion, led to provably equivalent results. But moreover, it expresses the belief that any new such attempt will inevitably produce again an equivalent notion. Briefly, Church's thesis is "an experimental fact in the mental world".

Exponential Kolmogorov complexity of constructive objects. Let X be a constructive world. For any (semi)–computable function $u : \mathbf{Z}_+ \to X$, the (exponential) complexity of an object $x \in X$ relative to u is

$$K_u(x) := \min\{m \in \mathbf{Z}_+ \,|\, u(m) = x\}.$$

If such m does not exist, we put $K_u(x) = \infty$.

Claim: there exists such u ("an optimal Kolmogorov numbering", or "decompressor") that for each other v, some constant $c_{u,v} > 0$, and all $x \in X$,

$$K_u(x) \leq c_{u,v} K_v(x).$$

This $K_u(x)$ is called *exponential Kolmogorov complexity* of x.

A Kolmogorov order on a constructive world X is a bijection $\mathbf{K} = \mathbf{K}_u : X \to \mathbf{Z}_+$ arranging elements of X in the increasing order of their complexities K_u.

The reader must keep in mind two warnings related to these notions:

– Any optimal numbering is only partial function, and its definition domain is not decidable.

– Kolmogorov complexity K_u itself is *not computable*. It is the lower bound of a sequence of computable functions. Kolmogorov order is not computable as well.

– Kolmogorov order of $\mathbf{Z}_+$ *cardinally differs from the natural order* in the following sense: it puts in the initial segments very large numbers that are at the same time Kolmogorov simple.

Example: let $a_n := n^{n^{\cdot^{\cdot^{n}}}}$ (n times).
Then $K_u(a_n) \leq cn$ for some $c > 0$ and all $n > 0$.

Kolmogorov complexity of recursive functions. When we spoke about "complexity of π", we had in mind a program that, given an input $n \in \mathbf{Z}_+$, calculates the n–th decimal digit of π. Such a program calculates therefore a recursive function. However, the set of all recursive functions $f : \mathbf{Z}_+^m \to \mathbf{Z}_+^n$ *do not* form a constructive world, if $m > 0$!

Nevertheless, one can speak about a Kolmogorov optimal enumeration of programs, computing functions of this set, and thus about Kolmogorov complexity of such functions themselves. This is critically important for applicability of our "complexity metaphor" in the domain of scientific knowledge. In fact, both "laws" and descriptions of "phase spaces" that make the scene for these laws belong rather to domains of intuitively computable functions than to the domain of constructive objects.

Mathematical details of constructions, underlying brief explanations collected in this Appendix can be found in [Ma1], Chapter II.

APPENDIX 2. **Lagrangian of the Standard Model**

Source: [ChCoMa]

"In flat space and in Lorentzian signature the Lagrangian of the standard model with neutrino mixing and Majorana mass terms, written using the Feynman gauge fixing, is of the form

$$\mathcal{L}_{SM} =$$

$$-\frac{1}{2}\partial_\nu g^a_\mu \partial_\nu g^a_\mu - g_s f^{abc}\partial_\mu g^a_\nu g^b_\mu g^c_\nu - \frac{1}{4} g_s^2 f^{abc} f^{ade} g^b_\mu g^c_\nu g^d_\mu g^e_\nu - \partial_\nu W^+_\mu \partial_\nu W^-_\mu - M^2 W^+_\mu W^-_\mu -$$

$$\frac{1}{2}\partial_\nu Z^0_\mu \partial_\nu Z^0_\mu - \frac{1}{2c_w^2} M^2 Z^0_\mu Z^0_\mu - \frac{1}{2}\partial_\mu A_\nu \partial_\mu A_\nu - igc_w(\partial_\nu Z^0_\mu (W^+_\mu W^-_\nu - - W^+_\nu W^-_\mu) - Z^0_\nu (W^+_\mu \partial_\nu W^-_\mu -$$

$$W^-_\mu \partial_\nu W^+_\mu) + Z^0_\mu (W^+_\nu \partial_\nu W^-_\mu - W^-_\nu \partial_\nu W^+_\mu)) - igs_w(\partial_\nu A_\mu (W^+_\mu W^-_\nu - W^+_\nu W^-_\mu) - A_\nu (W^+_\mu \partial_\nu W^-_\mu -$$

$$W^-_\mu \partial_\nu W^+_\mu) + A_\mu (W^+_\nu \partial_\nu W^-_\mu - W^-_\nu \partial_\nu W^+_\mu)) - \frac{1}{2} g^2 W^+_\mu W^-_\mu W^+_\nu W^-_\nu + \frac{1}{2} g^2 W^+_\mu W^-_\nu W^+_\mu W^-_\nu +$$

$$g^2 c_w^2 (Z^0_\mu W^+_\mu Z^0_\nu W^-_\nu - Z^0_\mu Z^0_\mu W^+_\nu W^-_\nu) + g^2 s_w^2 (A_\mu W^+_\mu A_\nu W^-_\nu - A_\mu A_\mu W^+_\nu W^-_\nu) + g^2 s_w c_w (A_\mu Z^0_\nu (W^+_\mu W^-_\nu -$$

$$W^+_\nu W^-_\mu) - 2A_\mu Z^0_\mu W^+_\nu W^-_\nu) - \frac{1}{2}\partial_\mu H \partial_\mu H - 2M^2 \alpha_h H^2 - \partial_\mu \phi^+ \partial_\mu \phi^- - \frac{1}{2}\partial_\mu \phi^0 \partial_\mu \phi^0 -$$

$$\beta_h \left(\frac{2M^2}{g^2} + \frac{2M}{g} H + \frac{1}{2}(H^2 + \phi^0\phi^0 + 2\phi^+\phi^-)\right) + \frac{2M^4}{g^2}\alpha_h - g\alpha_h M \left(H^3 + H\phi^0\phi^0 + 2H\phi^+\phi^-\right) -$$

$$\frac{1}{8} g^2 \alpha_h \left(H^4 + (\phi^0)^4 + 4(\phi^+\phi^-)^2 + 4(\phi^0)^2\phi^+\phi^- + 4H^2\phi^+\phi^- + 2(\phi^0)^2H^2\right) - gMW^+_\mu W^-_\mu H -$$

$$\frac{1}{2} g \frac{M}{c_w^2} Z^0_\mu Z^0_\mu H - \frac{1}{2} ig \left(W^+_\mu(\phi^0\partial_\mu\phi^- - \phi^-\partial_\mu\phi^0) - W^-_\mu(\phi^0\partial_\mu\phi^+ - \phi^+\partial_\mu\phi^0)\right) +$$

$$\frac{1}{2} g \left(W^+_\mu (H\partial_\mu\phi^- - \phi^-\partial_\mu H) + W^-_\mu(H\partial_\mu\phi^+ - \phi^+\partial_\mu H)\right) + \frac{1}{2} g \frac{1}{c_w}(Z^0_\mu(H\partial_\mu\phi^0 - \phi^0\partial_\mu H) +$$

$$M\,(\frac{1}{c_w} Z^0_\mu\partial_\mu\phi^0 + W^+_\mu\partial_\mu\phi^- + W^-_\mu\partial_\mu\phi^+) - ig\frac{s_w^2}{c_w} M Z^0_\mu (W^+_\mu\phi^- - W^-_\mu\phi^+) + igs_w M A_\mu (W^+_\mu\phi^- - W^-_\mu\phi^+) -$$

$$ig\frac{1-2c_w^2}{2c_w} Z^0_\mu(\phi^+\partial_\mu\phi^- - \phi^-\partial_\mu\phi^+) + igs_w A_\mu(\phi^+\partial_\mu\phi^- - \phi^-\partial_\mu\phi^+) - \frac{1}{4} g^2 W^+_\mu W^-_\mu \left(H^2 + (\phi^0)^2 + 2\phi^+\phi^-\right) -$$

$$\frac{1}{8}g^2\frac{1}{c_w^2}Z_\mu^0 Z_\mu^0\left(H^2+(\phi^0)^2+2(2s_w^2-1)^2\phi^+\phi^-\right)-\frac{1}{2}g^2\frac{s_w^2}{c_w}Z_\mu^0\phi^0(W_\mu^+\phi^-+W_\mu^-\phi^+)$$

$$-\frac{1}{2}ig^2\frac{s_w^2}{c_w}Z_\mu^0 H(W_\mu^+\phi^- - W_\mu^-\phi^+)+\frac{1}{2}g^2 s_w A_\mu\phi^0(W_\mu^+\phi^- + W_\mu^-\phi^+)+\frac{1}{2}ig^2 s_w A_\mu H(W_\mu^+\phi^- - W_\mu^-\phi^+)-$$

$$g^2\frac{s_w}{c_w}(2c_w^2-1)Z_\mu^0 A_\mu\phi^+\phi^- - g^2 s_w^2 A_\mu A_\mu\phi^+\phi^- + \frac{1}{2}ig_s\,\lambda_{ij}^a(\bar{q}_i^\sigma\gamma^\mu q_j^\sigma)g_\mu^a - \bar{e}^\lambda(\gamma\partial+m_e^\lambda)e^\lambda - \bar{\nu}^\lambda(\gamma\partial+$$

$$m_\nu^\lambda)\nu^\lambda - \bar{u}_j^\lambda(\gamma\partial+m_u^\lambda)u_j^\lambda - \bar{d}_j^\lambda(\gamma\partial+m_d^\lambda)d_j^\lambda + igs_w A_\mu\left(-(\bar{e}^\lambda\gamma^\mu e^\lambda)+\frac{2}{3}(\bar{u}_j^\lambda\gamma^\mu u_j^\lambda)-\frac{1}{3}(\bar{d}_j^\lambda\gamma^\mu d_j^\lambda)\right)+$$

$$\frac{ig}{4c_w}Z_\mu^0\{(\bar{\nu}^\lambda\gamma^\mu(1+\gamma^5)\nu^\lambda)+(\bar{e}^\lambda\gamma^\mu(4s_w^2-1-\gamma^5)e^\lambda)+(\bar{d}_j^\lambda\gamma^\mu(\frac{4}{3}s_w^2-1-\gamma^5)d_j^\lambda)+(\bar{u}_j^\lambda\gamma^\mu(1-\frac{8}{3}s_w^2+\gamma^5)u_j^\lambda)\}+$$

$$+\frac{ig}{2\sqrt{2}}W_\mu^+\left((\bar{\nu}^\lambda\gamma^\mu(1+\gamma^5)U_{\lambda\kappa}^{lep}e^\kappa)+(\bar{u}_j^\lambda\gamma^\mu(1+\gamma^5)C_{\lambda\kappa}d_j^\kappa)\right)$$

$$+\frac{ig}{2\sqrt{2}}W_\mu^-\left((\bar{e}^\kappa U_{\kappa\lambda}^{lep\dagger}\gamma^\mu(1+\gamma^5)\nu^\lambda)+(\bar{d}_j^\kappa C_{\kappa\lambda}^\dagger\gamma^\mu(1+\gamma^5)u_j^\lambda)\right)+$$

$$+\frac{ig}{2M\sqrt{2}}\phi^+\left(-m_e^\kappa(\bar{\nu}^\lambda U_{\lambda\kappa}^{lep}(1-\gamma^5)e^\kappa)+m_\nu^\lambda(\bar{\nu}^\lambda U_{\lambda\kappa}^{lep}(1+\gamma^5)e^\kappa\right)+$$

$$+\frac{ig}{2M\sqrt{2}}\phi^-\left(m_e^\lambda(\bar{e}^\lambda U_{\lambda\kappa}^{lep\dagger}(1+\gamma^5)\nu^\kappa)-m_\nu^\kappa(\bar{e}^\lambda U_{\lambda\kappa}^{lep\dagger}(1-\gamma^5)\nu^\kappa\right)-\frac{g}{2}\frac{m_\nu^\lambda}{M}H(\bar{\nu}^\lambda\nu^\lambda)-\frac{g}{2}\frac{m_e^\lambda}{M}H(\bar{e}^\lambda e^\lambda)+$$

$$\frac{ig}{2}\frac{m_\nu^\lambda}{M}\phi^0(\bar{\nu}^\lambda\gamma^5\nu^\lambda)-\frac{ig}{2}\frac{m_e^\lambda}{M}\phi^0(\bar{e}^\lambda\gamma^5 e^\lambda)-\frac{1}{4}\bar{\nu}_\lambda\,M_{\lambda\kappa}^R\,(1-\gamma_5)\hat{\nu}_\kappa-\frac{1}{4}\overline{\bar{\nu}_\lambda\,M_{\lambda\kappa}^R\,(1-\gamma_5)\hat{\nu}_\kappa}+$$

$$\frac{ig}{2M\sqrt{2}}\phi^+\left(-m_d^\kappa(\bar{u}_j^\lambda C_{\lambda\kappa}(1-\gamma^5)d_j^\kappa)+m_u^\lambda(\bar{u}_j^\lambda C_{\lambda\kappa}(1+\gamma^5)d_j^\kappa\right)+$$

$$\frac{ig}{2M\sqrt{2}}\phi^-\left(m_d^\lambda(\bar{d}_j^\lambda C_{\lambda\kappa}^\dagger(1+\gamma^5)u_j^\kappa)-m_u^\kappa(\bar{d}_j^\lambda C_{\lambda\kappa}^\dagger(1-\gamma^5)u_j^\kappa\right)-\frac{g}{2}\frac{m_u^\lambda}{M}H(\bar{u}_j^\lambda u_j^\lambda)-\frac{g}{2}\frac{m_d^\lambda}{M}H(\bar{d}_j^\lambda d_j^\lambda)+$$

$$\frac{ig}{2}\frac{m_u^\lambda}{M}\phi^0(\bar{u}_j^\lambda\gamma^5 u_j^\lambda)-\frac{ig}{2}\frac{m_d^\lambda}{M}\phi^0(\bar{d}_j^\lambda\gamma^5 d_j^\lambda)$$

Here the notation is as follows:

- Gauge bosons: $A_\mu, W_\mu^\pm, Z_\mu^0, g_\mu^a$

- Quarks: u_j^κ, d_j^κ, collective : q_j^σ
- Leptons: e^λ, ν^λ
- Higgs fields: $H, \phi^0, \phi^+, \phi^-$
- Ghosts: $G^a, X^0, X^+, X^-, Y,$
- Masses: $m_d^\lambda, m_u^\lambda, m_e^\lambda, m_h, M$ (the latter is the mass of the W)
- Coupling constants $g=\sqrt{4\pi\alpha}$ (fine structure), g_s = strong, $\alpha_h=\frac{m_h^2}{4M^2}$
- Tadpole Constant β_h
- Cosine and sine of the weak mixing angle c_w, s_w
- Cabibbo–Kobayashi–Maskawa mixing matrix: $C_{\lambda\kappa}$
- Cabibbo-Kobayashi-Maskawa matrix
- Structure constants of $SU(3)$: f^{abc}
- The Gauge is the Feynman gauge."

SCALING LAWS IN COMPLEX SYSTEMS

RUDOLF MURADYAN

Introduction

There are two types of power scaling distributions in complex systems: a) Discrete distributions, when distribution variable r=1,2,3... is a natural number (*e.g.*, Zipf's distribution); b) Continuous Distribution, when the distribution variable is continuous (*e.g.*, usual power law). Examples of both distributions are considered below.

1. Zipf's Distribution

The Zipf's distribution related to Riemann zeta function is a discrete distribution that is commonly used in statistical linguistic and has probability density function:

$$P(r,s)=\begin{cases}\dfrac{r^{-s}}{\zeta(s)} & s>1;\ r=1,2,3...\\ 0 & Otherwise\end{cases}$$

$\zeta(s)=\sum_{n=1}^{\infty}\frac{1}{n^s}$ Heris is Riemann zeta function.

When it diverges as a sum of harmonic series:

$$\zeta(1)=\sum_{n=1}^{\infty}\frac{1}{n}=1+\frac{1}{2}+\frac{1}{3}+\frac{1}{4}+...=\infty$$

Truncated harmonic series or harmonic numbers at large are defined as

$$H_N=\sum_{n=1}^{N}\frac{1}{n}\rightarrow\gamma+\ln(N)=\ln(1.781N)$$
$$where\,Euler\ const:\ \gamma=0.577,\ e^{\gamma}=1.781$$

American linguist George Zipf was one of the first who noticed that many data in physical and social sciences can be described by Zipfian distribution.

George Zipf (1902-1950)

Zipf suggested the hypothesis "The Least Effort Principle" to explain the origin of his Laws. Benoit Mandelbrot remarked about Zipf's book, *Human Behaviour and the Principle of Least Effort* "...so many flashes of genius, projected in so many directions..."

1.1. Zipf's First Law

If the words in a text are ordered according to the number of times they appear, then if the position of each word in the list is multiplied by its occurrences, the result achieves to the constant: (word occurrences P) x (rank r) = c (const)

$$P(r) \times r = c(const)$$

$$P(r) \approx \frac{P(1)}{r} \quad r = 1,2,3...$$

The first Zipf law in log-log plane represents linear relation

$$\log(\text{occurrences}) = \log(c) - \log(\text{rank})$$

Zipf's law for the example, text of the "Declaration of Independence", created by *Mathematica,* is shown in the figure below.

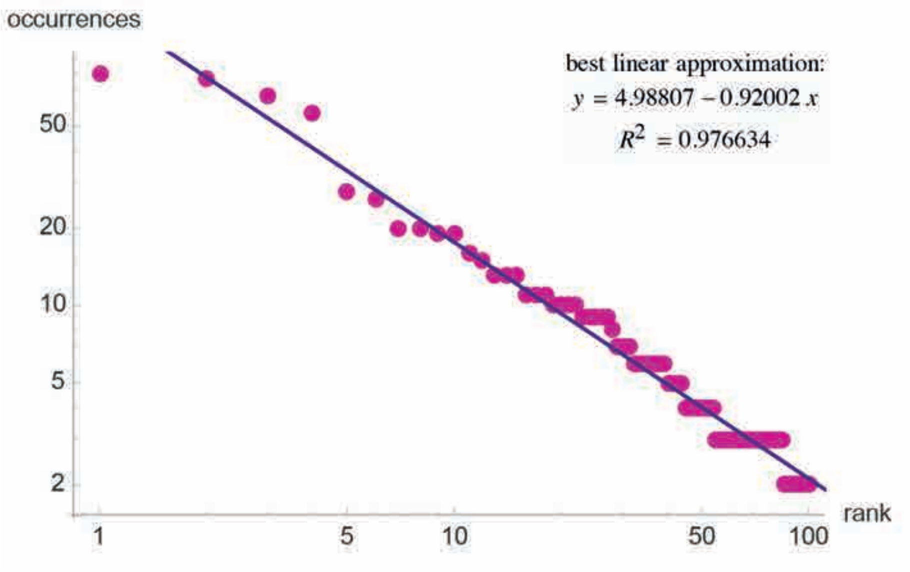


Figure 1. Zipf's law for an example text, adapted from [2]. Omnipresence of Zipf's Law for Complex Systems.

The Least Effort Hypothesis explains the origin of the law as a result of the minimisation of the efforts of speaker and hearer: the tendency of speaker is to use a few words; the tendency of hearer is to demand a specific word (signal) for every event.

Zipf's law today is a well-acknowledged empirical law. Data from various physical and social sciences can be described by Zipf's scaling law. Zipf distribution is ubiquitous in complex systems and well describes different phenomena.

- Frequency of words are Zipf-distributed;
- U.S. firm sizes are Zipf-distributed;
- City sizes are Zipf-distributed;
- Zipf's law governs many features of the Internet;
- Programming language constructs follow Zipf's law;
- Chat robots use Zipf's law.

It is interesting to note that Zipf's book *The Human Behavior and the Principle of Least Effort* and C. Shannon's book *The Mathematical Theory of Communication* were published in 1949 simultaneously. Claude Shannon used Zipf's law to calculate the entropy of an English text.

1.2. *Zipf's Second Law*

According to Zipf, biological organisms strive to spend as little energy as possible. Zipf argues that in speaking, a considerable amount of energy can be saved if linguistic units that are used very often are kept shorter than those which are used less frequently. Thus, the principle of least effort by means of *economy* controls the structural complexity of linguistic items. Zipf formulated his second law as *the shorter a word is, the more often it will be used*.

2. Continuous Scaling

Any polynomial law $f(x)=ax^b$ where constant a has dimension $a=\frac{\dim f}{(\dim x)^b}$ exhibits properties of *scaling* or *scale invariance*. Usually b is called scaling exponent. Function $f(x)$ is shape-invariant with respect to dilatation transformation $x\to\lambda x$

$$f(\lambda x)=a(\lambda x)^b=\lambda^b f(x)$$

According to Euler, $f(x)$ is a homogeneous function of degree b. Differentiating the last equation with respect to λ and $\lambda=1$ we obtain a simple differential equation

$$x f'(x)=b f(x)$$

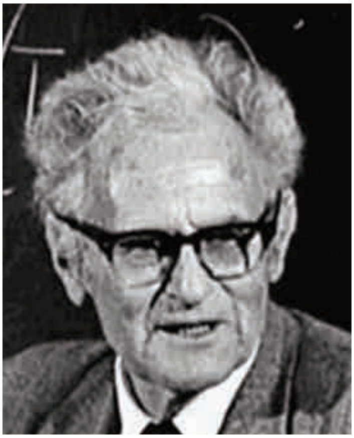
the solution of which brings us back to the polynomial scaling law. There are tremendously many scaling laws in Nature. A Google search for

"*scaling site:nobelprize.org*"

brings nearly 100 results from the Nobel Foundation.

2.1. *Metabolism and Scaling Laws*

Metabolic rate is a fundamental quantity in biology. How does the metabolic rate change from mouse to elephant? A first guess is that the metabolic rate would be proportional to some power of mass. If the metabolic rate is directly proportional to the volume (mass) of an animal, then the exponent would be too. If it depends on the surface area, then we could expect dependence. But in 1932 Swiss-American agriculturer Max Kleiber



Max Kleiber (1893-1976)

published a paper [3] with the so-called "mouse to elephant curve" according to which metabolism increases with body mass with expone$b \approx 3/4 = 0.75$, *i.e.* somewhere in between 1 and $2/3 \approx 0.67$, as demonstrated in the figure below.

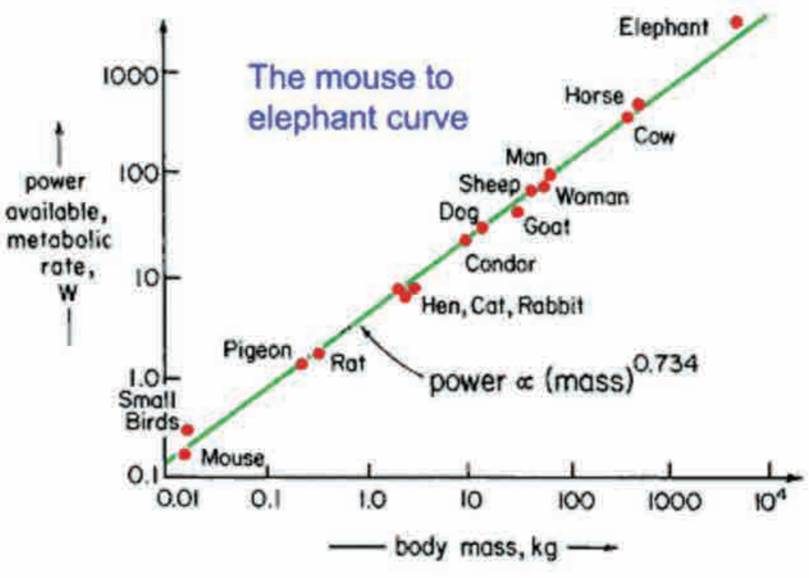


Figure 2. The "mouse-to-elephant" log-log curve shows that the metabolic power of a warm-blooded animal is proportional to its mass to the 0.734 power as established by Max Kleiber in the 1930s. Adapted from K. Schmidt -Nielsen [4].

The dependence of the metabolic rate as as power of the body mass, is known as the Kleiber law. The physical or biological interpretation of 3/4 dependence is not a simple issue. Recent radical ideas of G. West *et. al.* [5]-[7] about *four-dimensional fractal models of life* give impressive support for 3/4 law, but do not satisfy the scepticism of a small minority of supporters of the geometrical 2/3 law. The subject remains in the spotlight of biologists. Recent advancements can probably trigger new insights in the understanding of life's laws.

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COMPLEXITY IN SPACE ENGINEERING

K. KASTURIRANGAN

I. Introduction

Space system design throws interesting challenges in complexity arising out of the need to bring together multiple disciplines of engineering and sciences. Indeed, a satellite launch vehicle provides a fitting example of the complexity involved in the design and control of such a near-cybernetic system – controlled essentially by real-time commands from the on-board computers, though there are necessarily some commands from the ground stations as well. We will address this problem of complexity later in specific terms relevant to the launching of a satellite. But first, let us see what a satellite launch essentially is all about.

Basically, launching an Earth (geocentric) satellite means placing an object (*i.e.,* a payload, of a high level of design complexity, called the satellite) in functionally intact condition in a prescribed orbit around, or a pre-assigned slot above the Earth, using a satellite launch vehicle (LV, essentially a powerful rocket) so as to ultimately serve a set of designed mission objectives. There are, however, many possible variations on this basic theme. Thus, for example, the object, or the payload, could be a communication satellite, a scientific satellite, a weather satellite, etc.; the orbit chosen could be a geosynchronous, Sun-synchronous, equatorial, or a near-Earth polar; the rocket could be a single- or a multi-staged one.

What is, of course, essential is that the rocket engines must generate a thrust, far in excess of the weight of the launch vehicle at lift-off so as to take it to the designed orbital height in short time – of the order of tens of seconds. The rocket is propelled by a chemical fuel that could be liquid/solid, or a combination thereof. Now, the complexity involved in a satellite launch lies in the fact that the system comprises a number of interacting subsystems, components and their functions, and this number is very large. Most importantly, the interactions involved are non-linear, and interactions too interact. This can, therefore, exhibit a range of behavior often at the edge of instability. The on-board control system, therefore, necessarily involves enormous real-time processing of information generated by the sensors. Such systems are naturally unforgiving of any design errors as there is a sensitive dependence on the various conditions involved.

Clearly, the development of any space system calls for the definition of a systemic configuration resulting from the interplay of a number of disciplines including flight mechanics, aerodynamics and various mechanisms, structural and thermal sciences, navigation and guidance, control and propulsion, and so on.

Now, among the many critical phases, *the most* critical phase of a satellite launch is the *atmospheric phase*. During this phase the system is accelerated from rest to high velocities (high Mach/Reynolds numbers) in a matter of seconds, and is, therefore, subjected to excessive and hard-to-predict, randomly fluctuating aerodynamic stresses (mechanical as well as thermal) of great complexity. This could lead to, *e.g.,* a structural failure that may be catastrophic. This paper is intended to give some interesting insights into the role of various inter-related complexities involved by analyzing the possible anomalous behavior of a launch vehicle as illustrated by means of an example taken from our own experience (from a space mission of the Indian Space Programme), namely the catastrophic failure of a developmental Augmented Satellite Launch Vehicle (ASLV-D2), launched from the SHAR Launch Complex, in which the mission was terminated soon after the lift-off when the vehicle broke up catastrophically. This was indeed an object lesson for us in real complexity. Happily, the lesson so learnt led to a subsequent satellite launch that proved to be a great success.

II. Complexity of the Atmospheric Phase of a Launch Vehicle

Before we get to the specifics of the ASLV-D2 launch failure, let us get acquainted with the complexity of controlled flights of a multi-stage rocket system that reveals the extent of critical interactions that often dwell along the thin line between success and failure in meeting the final objective of spacecraft orbit insertion: The overall sizing of the vehicle dictated by the payload capability and consistent with the propulsion and structural technologies; the design of the trajectory and the sequence of events; the aerodynamic shaping, particularly of the bulbous heat shield, protrusions, joints and inter-stages and the internal thermo-fluid-combustion kinetics of the propulsion units are some of the major design considerations. All these have to take cognizance of a variety of optimization processes at each sub-system level. The trajectory design, based on the methods of optimal control of dynamical systems, determines the levels and the timing of the peak dynamic pressures encountered by the launch vehicle in the critical atmospheric phase. These dynamic pressures directly determine the aerodynamic load distribution and drag on the vehicle, which influence the vehicle performance in terms of velocities and altitudes achieved, as well as the structural loads acting on the vehicle. The load distribution is critically influenced by the prevailing wind conditions and the dispersions in propulsion and auto-pilot performances. This in turn can lead to the build-up of vehicle angles of attack and lateral deflections of the long and slender vehicle structure. Stage separation events are mission critical and should be designed to ensure the smooth transition of vehicle control and collision-free dynamics of the separating parts jettisoned under all possible conditions. The spent strap-on jettisoning generally occurs within sensible atmosphere, and hence is influenced by the nonlinear aerodynamic interactions of the separating bodies. An important parameter in the transfer of control is the tail-off thrust profile of the strap-on boosters, and the characterization of the control forces derived from them. The structural deflections, as determined by the vehicle mode shapes and frequencies, affect the vehicle performance and stability through the functioning of the auto-pilot control system. The vehicle attitude is controlled, by the lateral forces derived from the fluid injection thrust vector control system, or directly by nozzle gimballing, both of which depend primarily on the main thrust provided by the propulsion system. Proper functioning of the onboard electronics and computer logic systems depends on limiting the acoustic and vibratory environment created by the high speed jet flow, aerodynamic shock oscillations on the bulbous head shield, flow separations and the shock-boundary layer interactions, and the complex shockwave patterns created due to aerodynamic interactions of the strap-on and the core configurations and the influence of several local body protrusions. These critical parameters are the direct functions of vehicle aerodynamic angle of attack, which in turn is determined by the vehicle flexibility, control, trajectory and atmospheric winds. Thus several loops and sub-loops of mutual interactions determine the complex vehicle dynamics.

It is apt to recall here that the launch vehicle is *not* simply *a rigid body of six degrees of freedom – three rotational and three translational*. (In fact, even such a rigid body in motion can display a complex behavior inasmuch as some of the degrees of freedom (finite rotations) do not commute. In reality, in flight, it is deformable under aerodynamic stresses. The deformations may even subtend zero-angular-momentum turns). All these and more. Extensive six-degrees-of-freedom and flexible vehicle simulations with control-structure-aerodynamics-propulsion interactions of the complex experiment (the ASLV-D2 Launch and its failure) highlighted the need to introduce: (i) event-based ignition of the Core Stage motor based on Strap-on-Stages motor chamber pressure, (ii) appropriate characterization of the fluid injection thrust vector control model in the control of yaw, particularly during tail-off, (iii) extensive short-period, six-degrees of freedom and flexible body dynamics and hardware-in-loop simulations to detect the presence of any critical interactions due to the vehicle system and wind-profile uncertainties, (iv) increasing the inherent stability of the vehicle by providing fins in the pitch-yaw plane with stability coming from the strap on boosters themselves, and (v) reduction of the maximum dynamic pressure to be faced by the vehicle, if necessary by re-designing the motor thrust profiles.

III. Monte Carlo Simulations of Launch Vehicle (LV) Dynamics

When a highly complex system is comprised of (i) a number independent-disciplinary subsystems; (ii) these subsystems themselves are involved in complex physical processes; and (iii) the dynamics of these independent subsystems is dependent on the interactions with the other subsystems of the main process, then the probabilistic outcome of the main system cannot be easily described by a deterministic mathematical model. When the external processes that influence the main system are also random, for example in the context of launch vehicle dynamics amidst the random environmental (aerodynamical) processes of winds and atmospheric parameters, then the system performance is nearly impossible to describe by a deterministic mathematical model. The dynamics of such complex interactive systems can then be studied effectively by system engineers by a Monte Carlo simulation process, which enables the mission analysts to evaluate the mission success probability and make informed decisions on mission-go-ahead (launch-commit) criteria.

Such a process of Monte Carlo Simulations is depicted in a nutshell in the block diagram displayed in Fig.1, in which the main subsystems of a launch vehicle dynamic process are identified as blocks and their mutual interactions are indicated by arrows. As (i) the vehicle lifts off from the launch pad by the propulsive forces of the rocket engines, (ii) picks up a velocity defying gravity forces, and goes through the aerodynamic regimes of subsonic, transonic, supersonic and the hypersonic conditions (which characterize essentially the changes elliptic-to-parabolic-to-hyperbolic mathematical descriptions of the governing partial differential equations), (iii) the vehicle's structural modes are excited by aerodynamic, propulsive and control forces which are interactive, and also the autopilot functions are influenced by the nonlinear sensor dynamics of various actuators, (iv) the vehicle guidance system analyses the current instantaneous state of the vehicle as determined by the onboard rate-gyro and accelerometer packages and determines continuously the immediate attitude orientation changes the vehicle should adopt, and (v) all these processes are influenced by the instantaneous and dynamic wind and atmospheric variations, (vi) the dynamics of the vehicle comprises not only the six-dimensional space of rigid-body motion but also the multi-dimensional nonlinear continuum elastic

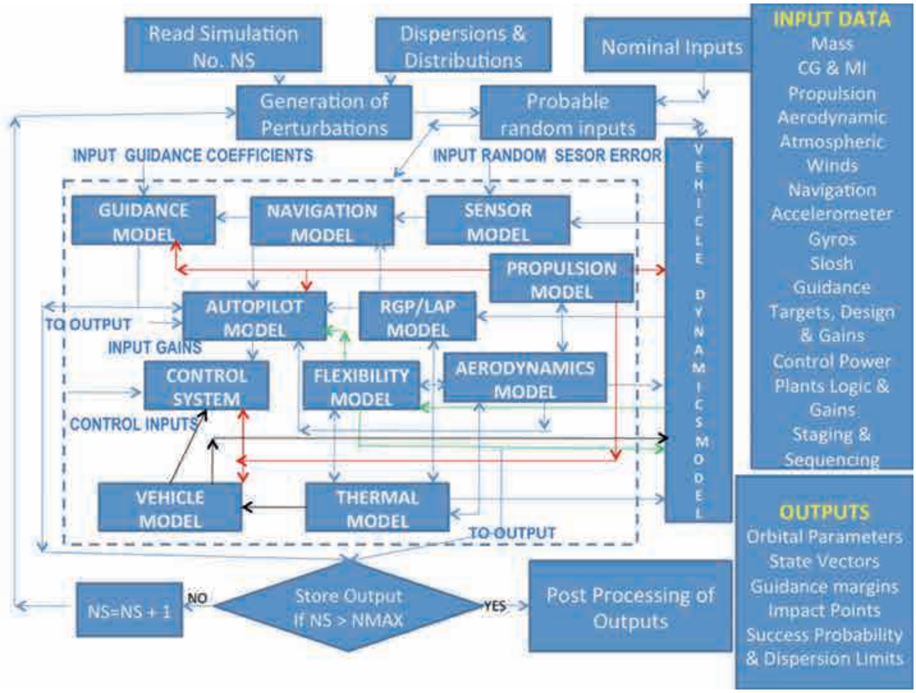

Figure 1. Monte Carlo simulations of L/V dynamics.

deformations and structural modes which modify the aerodynamics and autopilot functions, then the outcome and behavior of such system is not deterministic but becomes stochastic.

Monte Carlo simulation is the right tool for analyzing such systems and making launch decisions that ensure a high mission success probability.

This is done first by a systematic engineering analysis of the dispersion-levels and statistical distributions of all possible parameters (of all the subsystems already mentioned) that influence the vehicle dynamics. This difficult task is usually carried out by a number of ground experiments on the respective subsystems, and then adding any un-modeled uncertainties. A high-fidelity mathematical model of the linked-subsystem processes is made, which reflects the current state of knowledge of the physical processes involved. A random sample of the input-parameters is selected following the statistical distribution determined earlier, and the complete vehicle dynamics is simulated with this set of input parameters. The resulting output parameters of the vehicle state at each important instant (like stage ignition and burnout instants, separation events, satellite injection event) are captured and stored. Then a different set of parameters (as per the dispersion statistics) is randomly generated and the full vehicle dynamics is captured and stored as before. A large number of such simulations are done, the number being determined by the condition to reach statistical stability of the output parameters so that one gets stable mean and statistical distributions of the output parameters at all critical points up to launch. Usually the number of simulations can be of the order of a few thousands. All specific cases in which the vehicle fails to reach a final orbit as desired are carefully analyzed and the reasons for failures understood and ascertained. From a statistical analysis of the output parameters, the mission analyst can ascertain the mission success probability.

IV. An Analysis of the ASLV-D2 Failure

As mentioned in passing in the Introduction, the four-stage all-solid launch vehicle, designated as ASLV-D2, failed after 50 seconds into the flight.

After a detailed analysis of the flight telemetry and tracking data, film and video records of the launch and the flight, specifications and design documents of the vehicle systems, post-flight analysis documents, detailed simulation studies and the analysis of failure modes, it was found that the increase in the angle of attack occurred as the vehicle, which was aerodynamically unstable in the yaw plane (*i.e.,* in the plane containing the strap-on boosters), with a time-to-double-amplitude of about 0.5s, did not have adequate control during a period of about 3-4s, resulting in flight loads exceeding structural limits, and ending in vehicle break up.

Noting that the control forces were derived entirely from secondary fluid injection into the rocket nozzles, this period of inadequate control occurred in three phases of the tail-off region of the strap-on rocket motor. The factors that contributed to the rapid build-up of the vehicle incidence were that the autopilot gain implemented in the flight was lower than the design gain and was not compensated for the tail-off phase of the motor thrust. The Core motor, which was soon ignited, could not provide the required control force, although helping to reduce the yaw rate. The resulting increase in the yaw error at a time when the vehicle was experiencing the maximum dynamic pressure during the flight, led to a continuous increase in the flight loads on the vehicle that exceeded the structural limits and ended eventually in the disintegration of the vehicle.

Other Insights: Oscillation in YAW

The behavior of YAW attitude in ASLV-D2 flight during the period of T+43s to T+52s was extensively simulated, studied and the factors contributing to the flight failure were identified. In this process there were so many other features and aspects of the complex flight behavior that one had the real opportunity to understand and explain the event. The ASLV-D2 flight data indicated that the YAW history shows an oscillation of about 0.3 Hz, which was not appearing in any of the pre-flight simulations. The oscillations in yaw rate have amplitude up to ±0.5 deg/s. Attempts to simulate these oscillations through wind-profile oscillations and the thrust-misalignments have not been successful. The flight SITVC (Secondary Fluid Injection Thrust Vector Control) pintle-opening telemetry data show an on-off behavior that corresponds with the observed YAW-rate oscillations. Simulations show that a dead-zone in SITVC pintle opening until the requirement reached 0.18 mm explains the complex flight behavior in a fairly reasonable manner.

Future Trends

At this moment, the space-faring world is looking ahead towards new frontiers of space science and technology. The main parameters of the new space challenge are low-cost access to space, reaching inter-planetary as well as deep space for scientific exploration, resource utilization, human habitat, and possibly also defending the planet Earth from the disaster of any possible major impact from Near Earth Asteroids.

The future new challenges will be in the area of hypersonic flow research, vehicle control and guidance in severe aero thermal environments, and development of supersonic combustion air breathing propulsion technology, etc. In this context, a number of complex viscous and shock interactions, high temperature boundary-layer transition effects become important. One of the most important factors to be handled in the development of hypersonic technology is the high temperature due to aero heating during re-entry. Some of the important aspects to be considered are: thermal and chemical non-equilibrium, wall catalyticity, communication black out and radiating shock layers. With such systems, the dimensionality of the system-interaction complexity increases – from typical aero-servo-elasticity interactions to aero-thermo-servo-elasticity systems. With the man-in-the-loop space systems, and with long-term space travel and habitation involved, the complexity extends further to include astro-biological and other environmental factors.

In design problems, load analysis, measurements results, material properties, etc., all have inherent uncertainties. Conventional design practices, including engineering design optimization techniques, take these uncertainties into account while designing systems in a very conservative manner, *i.e.,* the worst combination of errors is taken and the design is expected to meet the worst-case scenarios. Explicit factors of safety are considered at all stages of design. This makes the designs sub-optimal. Reliability based techniques need to be applied in design, where the uncertainty distribution is transformed through various sub-system and system analyses.

In addition to Multi-Disciplinary Design Optimization (MDO), substantial effort is now focused also on building algorithms for Reliability Based Design Optimization (RBDO), where input and constraint uncertainty distributions are taken into account, especially in multi-disciplinary scenarios, to obtain reliable optimal designs. The algorithm should optimize the objectives while ensuring that failure probability of constraints remains within acceptable limits. In typical problems, inputs like material properties, etc., are non-deterministic and the optimal designs need to respect these constraints. Future system and sub-system design optimization exercises will necessarily have to be RBDO exercises reflecting the non-deterministic nature of various inputs and constraints. One should also pursue Robust Design Optimization (RDO) where the objective is to minimize the sensitivity of the system performance to input uncertainties. In a complex and uncertain world, these tools permit the scientists and technologists to build systems that evolve and survive. Heuristic development of algorithms should be supported by formal mathematical analysis of their functionality. Thus, this field will continue to provide exciting opportunities for research both in the development of methods and in their application to aerospace technology.

It is tempting to compare the complexity of Space Engineering, epitomized by the design and launch of a near-cybernetic, but will-free space vehicle carrying a satellite, with that of Biology, epitomized by a living organism, evolved through adaptive responses to selective natural pressures over some three billion years, such as a willful human being. Indeed, both are highly complex though in a qualitatively different sense and contexts both possess complex hardware and software, but biology has the `a-ware in addition, and the information is stored in the inheritable genes.

But, really one should resist the temptation to compare these two any further. Instead, it would rather be a reasonable and fruitful, though somewhat distant possibility, namely that biology may, and indeed will get incorporated deeply into the complex Space Engineering Programmes of the future: A remarkably serious example of it would be the Dyson Tree as proposed by Freeman Dyson, developed through nano-biogenetic engineering that could support a natural habitat for living organisms including humans in a spaceship, or on an asteroid!

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A COSMIC END: FROM THE EARTH TO THE UNIVERSE

JOSÉ G. FUNES, S.J.

> *"Human curiosity is the driving force for scientific development, in which belief systems and philosophy still have their valid place"*.[1]

> *"To the scientist, and especially to the Christian scientist, corresponds the attitude to examine the future of humanity and the Earth"*.[2]

Attracted by curiosity about the end of the universe, and encouraged by the words of Pope Francis about the the importance of examing the future, I have tried to consider the cosmic end at different scales.

There is a painting by Paul Gauguin with the title: *Where are we? Where did we come from? Where are we going?*[3] These are the big questions which cut across human culture. The question of the end of the universe is one of those big questions.

To address these questions the scientific method is not the only approach but certainly an important one. Scientific knowledge seeks the explanation of the observed phenomena based on natural causes. It should be able to explain the observed data postulating a new model to predict results that

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[1] Preface of the booklet the Plenary Session of the Pontifical Academy of Sciences on *Evolving Concepts of Nature,* 24-28 October 2014.

[2] Address of Pope Francis to the Plenary Session of the Pontifical Academy of Sciences on the occasion of the inauguration of the bust in honor of Pope Benedict XVI, 27 October 2014.

[3] Gauguin had been a student at the Petit Séminaire de La Chapelle-Saint-Mesmin. His subjects there included a class in Catholic liturgy; the teacher for this class was the Bishop of Orléans, Félix-Antoine-Philibert Dupanloup. Dupanloup had devised his own catechism to be lodged in the minds of the young schoolboys, and to lead them towards proper spiritual reflections on the nature of life. The three fundamental questions in this catechism were: "Where does humanity come from?" "Where is it going to?" "How does humanity proceed?" Although later in life Gauguin was vociferously anticlerical, these questions from Dupanloup's catechism obviously had lodged in his mind (cfr. Wikipedia contributors, *Where Do We Come From? What Are We? Where Are We Going?* Wikipedia, The Free Encyclopedia, http://en.wikipedia.org/wiki/Where_Do_We_Come_From%3F_What_Are_We%3F_Where_Are_We_Going%3F, accessed December 17, 2014).

must be verified with further observations. As Chris Impey has written "Science mostly answers the question of how things got to be the way they are. Yet if we stop at the present day, the job is only half done, as every good story needs an ending".[4]

We can only think the past and the future of the universe from its present, that is, from the local universe and from the data we have collected and interpreted in a theoretical framework. We verify our ideas about the beginning and the end of the universe with a reality check, *id est*, confronting them with experimental data. To survey the local universe we have used telescopes for centuries. I like to think that we are a species with long eyes and that Galileo Galilei is the forefather of this people with long eyes.[5]

We have a good picture of the early universe. As T.S. Elliot said, "*In my beginning is my end*"; in the initial conditions of the Universe is written somehow its end. Though there are many unknowns, our current understanding of Physics allows us to reconstruct the history of the universe since the universe was 10^{-43} seconds old. We cannot go beyond this limit in our look-back time; there we arrive to the present limit of human knowledge.

It is uncertain to predict scientifically the future. Our predictions will depend on the different time scales that we take into account. Thus we can consider the end of Earth, of the Sun, of our galaxy and of the whole universe. In this paper I won't discuss any biological evolution or technical development that would exceed the goal of these considerations.

The Beginning

If we ponder the cosmic end from the Earth to the universe, we should discuss the beginning and evolution of planets, stars, and galaxies. Clearly this would be a gigantic effort, much beyond my abilities. Allow me to say that we have a good comprehension of the formation and evolution of planets, stars and galaxies.

In the last decades we have achieved a very solid foundation for the Big Bang theory, gathering observational, experimental and theoretical evidence to support the case for the standard Big Bang model, which is the best up-to-date explanation of the origin, evolution and current state of the universe. A key component of the standard Big Bang model is the hypothesis of infla-

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[4] C. Impey, *How it ends: From you to the universe*, 2010, W.W. Norton & Company, Inc., New York, p. 11.

[5] Cfr. J.G. Funes, *Preface* in *ASTRUM 2009, Astronomy and Instruments, Italian Heritage Four Hundred Years After Galileo*, edited by Ileana Chinnici, 2009, Edizioni Musei Vaticani and Sillabe, Livorno, p. 19.

tion, an extremely rapid expansion of the early universe, introduced by Alan Guth and Andrei Linde, that is supported by observational evidence.

A good amount of experimental data has been collected to confirm the case for the standard hot Big Bang that I briefly summarize here:

– The expansion of the universe. All galaxies are receding from us with a velocity which is proportional to their distance. This observational evidence was discovered by Edwin Hubble and it is known as Hubble's law. Saul Perlmutter (Supernova Cosmology Project), Brian P. Schmidt and Adam G. Riess (High-Z Supernova Search Team) in 1998 discovered the accelerating expansion of the universe through observations of distant supernovae.
– The Cosmic Microwave Background Radiation. It is the radiation released when the universe was about 380,000 years old. It was detected by Arno Penzias and Robert Wilson in 1965 and observed by NASA's satellites COBE and WMAP, and recently by ESA's Planck mission.
– The Big Bang model predicts the ratio of protons and neutrons during the period of nucleosynthesis. The chemical composition of the universe should be 75% hydrogen, 25% helium and a trace amount of other light elements. This prediction corresponds to observations of cosmic abundances.

According to the current observational evidence the universe is composed 26.8% of dark matter, 4.9% of ordinary matter, and 68.3% of dark energy and has an age of 13.8 billion years.

Taking into account the current knowledge of the beginning and the present of the universe, we expect that, in a very distant future, the universe will continue to expand going toward a final state of cold and darkness. But before discussing the future of the universe, I briefly discuss the cosmic future at different scales.[6]

The Future Earth: A Declining World

It is very challenging to predict the future of Earth since there are many factors that play an important role in its evolution. The Earth has been and will be affected by geological processes. The four geological processes

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[6] In the presentation of the future at different scales I follow A.J. Meadows, *The Future of the Universe*, 2007, Springer-Verlag London Limited, iBook, https://itun.es/us/-MuvB.l; C. Impey, *How it ends: From you to the universe*, 2010, W.W. Norton & Company, Inc., New York; J.O. Bennett, M.O. Donahue, N. Schneider, M. Voit, *The Cosmic Perspective (7th Edition)*, 2014, Pearson Education, Inc., San Francisco.

determine the shape of the surface of the Earth are impact cratering, volcanism, tectonics, and erosion.

Geological activity depends on the fundamental properties of the planet, especially the size. Earthquakes release energy from the earth's crust through seismic waves. The core and mantle are changing continuously. In its final state, about 3 billion years from now, the Earth will be a cold solid body. At this point, there will be no earthquakes on the surface.

Another factor to be taken into account is the change in the atmosphere and in the oceans. The Earth's surface has gone through periods of warmer and colder climates. The timescale on which major ice ages have occurred corresponds with the timescale for continental drift (about 400 million years).

We also need to consider the dynamical evolution of the Earth-Moon system. Some calculations suggest that, within the next 4.5 billion years, the Sun would be overhead at the poles rather than the equator. Changes of this sort will alter considerably the distribution of temperature across the terrestrial surface.

Prolonged periods of high volcanic activity can act as a trigger for climatic change. Also, the world will be warmer or colder depending on how freely equatorial currents can flow as the final layout of continents is approached. The winds too will adapt to the final continental pattern.

If the level of carbon dioxide in the atmosphere continues to rise, as at present, the average temperature in 2100 could be between 2 and 5°C above its current value. Cities around the globe that currently have moderate summer temperatures would be substantially hotter. At the same time, the higher temperatures could well lead to more violent hurricanes. As a consequence in 2-3 billion years the Earth would be a declining world.

In this timescale the Sun will considerably grow in size turning into a red giant (200 times bigger than its current size). The Sun will expand out as far as the Earth's present orbit. This will happen some 8 billion years from now. In its expansion, the Sun will blow off a considerable part of its mass into space. As a result the Earth will move into a more distant orbit. By the time the Sun expands to the Earth's present orbit, the Earth itself will have moved out to nearly twice its current distance from the Sun.

In this very rough description of the Earth's future, I have not taken into account the magnetic fields of the Earth and the Sun.

Impacts on the Earth

Geological data shows that large impacts that happened in the past caused mass extinctions. More recently, Earth experienced the smaller but well-documented entrance of the Chelyabinsk meteor in Earth's atmosphere over Russia on February 15, 2013. This kind of event may occur every couple of years though the probability of major impact is very low in our lifetime.

The range of impactor size could go from small bodies to large objects like asteroids and comets. At the moment no one knows for sure if with the current technology we would be able to destroy or divert a potential large object such as an asteroid or comet.

The Solar Neighborhood

The next step is to consider nearby stars and how they could affect life on Earth. Taking into account the solar neighborhood, a star would wander to within a distance of 3 light-years from the Sun every 100,000 years on average, and a nearby star could pass by about a light-year from the Sun. This is far away enough to have little effect on the Sun and planets. The closest approach to the Sun by any other star over the next few billion years is likely to be at a distance of about 10,000 AU.[7] The gravitational pull of the star would disturb comets, especially the outermost ones. The shower of comets that would result may well increase the impact rate on the planets for a prolonged period after the encounter with the passing star.

A galaxy is a system of stars, gas, dust and dark matter gravitationally bound together with a total mass ranging from 10 million to 1000 billion times that of the sun. Gas and dust are the material between stars and it is called interstellar medium. This is the material from which new stars form.

Collisions between stars may be unlikely in the solar neighborhood but collisions between stars and interstellar clouds are possible. The Sun is likely to encounter a molecular cloud once or twice every billion years. The gravitational pull of the cloud as the Sun moves through it would disturb comets, causing a major shower of comets into the inner regions of the solar system.

In addition, within a molecular cloud, the solar wind will be almost entirely suppressed, and the Earth will be surrounded by interstellar material. This may affect the upper atmosphere, and also what happens at the Earth's surface. It could affect the ozone layer and the amount of sunlight that the Earth receives. Encounters with dense clouds could affect the longer-term future of the Earth.

Any supernova that occurs within 150-200 light-years of the Sun is likely to have a noticeable effect on the solar system. The particles and ra-

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[7] 1 AU (astronomical unit) = distance from the Earth to the Sun, or approximately 150 million km.

diation from a nearby supernova could produce significant, though temporary, changes in the Earth's atmosphere. Examination of the radioactivity in meteorites suggests that cosmic-ray bombardment of the solar system originated by a supernova becomes stronger every 100-200 million years.

In the present the atmosphere and the magnetic field of the Earth protect us from the direct effects of cosmic rays. Cosmic rays can interact with the Earth's upper atmosphere, altering the ozone layer and letting through a flood of ultraviolet light. It also seems that an abundance of cosmic rays could affect the greenhouse effect lowering temperatures at the terrestrial surface.

A supernova also produces gamma rays that would cause cellular damage to all land creatures within thirty light-years and inflict destruction on the food web. An even more dramatic stellar cataclysm could disrupt genetic material at a distance of a thousand light-years. Luckily, violent star death is rare.[8]

Galaxy Future

Galaxy formation and evolution is a complex combination of hierarchical clustering, gas dissipation, merging, and secular evolution. Galaxies are tracers of cosmic evolution over the last 13 billion years. Galactic time scale is the combination of two clocks. One time scale is the cosmological one (the Hubble time, i.e. basically the age of the universe) and the other scale is related to stellar evolution. The combination of both gives rise to galaxy evolution.

Our knowledge of galaxy evolution showcases our understanding of cosmology, stellar evolution, and galaxy dynamics. It is an excellent example of how scientific knowledge achieved independently can be put together to shed light on a complex process that involves other physical processes at different scales.

As we know from Hubble's law, galaxies move farther apart over time, and within them stars are born and die. Meanwhile stars are born and die within the galaxies. They are born from the gravitational collapse of gas clumps in molecular clouds. Massive stars, when they die, enrich the gaseous environment with new and heavier elements. Eventually this gas cools off in molecular clouds completing the star-gas-star cycle. Looking to the far future, in a trillion years, the cycle will be broken as more gas is trapped in stellar corpses (white dwarfs, neutron stars, and black holes) and less is left over to form new stars.

In each and every galaxy, the lights will gradually go out. In 10^{100} years (10^{90} times the age of the universe) clusters of galaxies will become clusters

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[8] Cfr. C. Impey. "Humble before the Void." iBooks. https://itun.es/us/XUKw0.l, chapter 3.

of black holes; finally black holes will evaporate. The Milky Way will be one of those galaxies fading into darkness.

The Fate of the Universe

According to our current comprehension of the universe, dark energy seems to be the driving force for the accelerated expansion of it. If this is the case and dark energy does not change with time and there are no other factors, in the very distant future the universe eventually will be shredded. This final stage of the universe is known as the *Big Rip*. Some cosmologists propose that the universe could not have a single final end but even multi-ends.

Thus the universe is going toward a final state of cold and darkness, thermal death, which says that the universe will go toward a state of maximum entropy (*Big Freeze*). The long-term scenario, with everything in the universe gradually dying, is obviously hostile to life.

Emptiness and Questions

Using the poetic language of T.S. Eliot, the end of the universe can be metaphorically described as follows:

> *"This is the way the world ends*
> *This is the way the world ends*
> *This is the way the world ends*
> *Not with a bang but a whimper"*

Our scientific journey to the end of the universe is also a spiritual one to the last frontier, to our existence in this cosmos. Looking at a not very bright perspective for life we may experience what Friedrich Nietzsche sums up effectively in few words: *"When you look long into an abyss, the abyss looks into you"*. Similarly we could feel emptiness in front of the vastness of the cold and dark universe in its final stage as the sacred author of the book of Ecclesiastes sees the fragility and contingency of this world: *"A vast emptiness – Qoheleth says – an immense void, everything is empty"*.[9]

In the previous sections I have tried to summarize what is possible to say about the future of the universe from the scientific point of view. This perspective poses many questions regarding life in the universe:

- If our location in the universe is crucial for life, will all life end with Earth?

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[9] Ecclesiastes 1:2.

- Is life a common phenomenon?
- What will happen with life in trillions and trillions of years when the universe fades?
- If there are other universes will life survive in those places?
- What is the Christian perspective on the end of the Universe?
- What can we say about the *Last Day*?

At this point I would like to quote Martin Rees who put in evidence our crucial position regarding the future:

> "*The most crucial location in space and time (apart from the big bang itself) could be here and now*".[10]
>
> "*The wider cosmos has a potential future that could even be infinite. But will these vast expanses of time be filled with life, or as empty as the Earth's first sterile seas? The choice may depend on us, this century*".[11]

Christian Realism

It is very difficult to dare to make any statement or hypothesis about the future of life in the universe. However we know from direct observation on Earth that life is resilient, it has an extraordinary capacity to adapt and evolve in hostile conditions. Life could have spread elsewhere in the universe or in other universes if the idea of the multiverse were confirmed.

The good scientist should remain open to the interpretation of reality being aware that the scientific knowledge is incomplete, as Pope Francis pointed out for theologians and philosophers:

> *"The theologian who is satisfied with his complete and conclusive thought is mediocre. The good theologian and philosopher has an open, that is, an incomplete, thought, always open to the maius of God and of the truth, always in development…"*.[12]

There are many incomplete issues in science and this paper is incomplete in many aspects, however I would like to conclude with the Christian ap-

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[10] *M. Rees, Our Final Hour,* 2003, iBooks*, https://itun.es/us/X9EXw.l,* Basic Books, New York, Chapter 1.

[11] *Ibid*. Chapter 14.

[12] Address of Pope Francis to the Community of the Pontifical Gregorian University, 10 April 2014.

proach to the *Last Day*. I find Joseph Ratzinger's words very illuminating in this regard:

> *"Christian realism goes beyond the physical, as realism of the Holy Spirit".*
>
> *"If the cosmos is history and if matter represents a moment in the history of the spirit, then matter and spirit are not forever next to each other in a neutral manner, it is necessary to consider one last "complexity" in which the world finds its Omega and unity. Then there is one last link between matter and spirit in which the destiny of man and the world finds compliance, even if today we cannot define the type of such a connection. Then the "last day" is one in which the fate of each man will be fulfilled because the fate of humanity* (... and of the universe I would add) *has found fulfillment".*[13]

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[13] J. Ratzinger, *Introduzione al Cristianesimo*, 2010, Queriniana, Brescia, 347-348.

FROM BIG BANG TO BIOSPHERES: THE SCOPE AND LIMITS OF EXPLANATION

MARTIN J. REES

Our present complex cosmos manifests a huge range of temperature and density – from blazingly hot stars, to the dark night sky. People sometimes worry about how this intricate complexity emerged from an amorphous fireball. It might seem to violate a hallowed physical principle – the second law of thermodynamics – which describes an inexorable tendency for patterns and structure to decay or disperse.

The answer to this seeming paradox lies in the force of gravity. Gravity enhances density contrasts rather than wiping them out. Any patch of the expanding universe that started off slightly denser than average would decelerate more, because it would 'feel' extra gravity; its expansion would lag further and further behind, until it eventually stopped expanding and separated out. Cosmologists are now able to generate computer simulation of a segment of a 'virtual universe'. These simulations start off with a dense and almost-uniform universe, and depict how, as it expands, incipient structures unfold and evolve into the precursors of the first galaxies. In these galaxy-scale clumps gravity enhances the contrasts still further; gas is pulled in, and compressed into stars. Each galaxy is an arena within which stars, planets and perhaps life can emerge.

The conditions prevailing in the very earliest stages of the universe – within the first tiny fraction of a second – are uncertain. This is primarily because the densities and energies were more extreme than can be achieved on Earth, even in a machine like CERN's Large Hadron Collider. However, at the later stages, our models have a firmer foothold in experiment (corroborated now by astronomical observations), and we can identify some key stages:

(i) Protons and neutrons combine in the first three minutes to make deuterium and helium.

(ii) Everything expands, cools and dilutes until the gas becomes neutral and transparent. And the universe enters a literal dark age when the cooling shifts the primordial light into the infrared.

(iii) After about 100 million years the first stars form and light up the universe again.

(iv) The stars then assemble into galaxies. Fusion processes within the stars synthesis the periodic table from pristine hydrogen. Short-lived stars of high mass end their lives as supernovae, and fling this processed material back into space. Second-generation stars (our Sun among them) condense from interstellar clouds already contaminated by the debris from earlier supernovae. Indeed each of us contains atoms of carbon, oxygen and phosphorus that were forged in hundreds of ancient stars spread across the Milky Way.

Crucial to the whole process is gravity. This force has the perverse thermodynamic property of driving things further from equilibrium. Gravitating structures have a negative specific heat. As they lose energy, they get hotter. If the nuclear reactions that generate its power were switched off, the Sun would gradually contract, but in the process its centre would get hotter: higher pressure is needed to balance gravity as it gets smaller.

Gravity is a very weak force. On the atomic scale, it is about 40 powers of ten weaker than the electric force between an electron and a proton. Chemists do not need to worry about the gravitational forces within the molecules or crystals they study. But in any large object, positive and negative charges almost exactly cancel. In contrast, everything has the same 'sign' of gravitational charge so when sufficiently many atoms are packed together, gravity wins.

Figure 1 depicts this trend. It shows, on a logarithmic scale, the masses and radii of various objects. Black holes, with mass proportional to radius, lie along a line of slope 1. Note that a black hole the size of a nucleus has the mass of about 10^{38} protons – billions of tons. Small holes are so massive because gravity is weak. Solids – sugar lumps, rocks, and asteroids, lie on a line of slope 3. The gravitational binding energy per particle grows as the 2/3 power of mass, so solid objects get closer to the black hole line as their mass goes up. Gravity is unimportant up to asteroid-size lumps. But it makes planets round, and any object more massive than Jupiter is squeezed to make a star. We see clearly from this diagram why the characteristic number of protons in a star is the 3/2 power of the large number that reflects the weakness of gravity on the atomic scale (right on the left, is where quantum theory and gravity meet. The Planck mass – when a black hole is no bigger than its Compton wavelength).

From diagrams like this you could predict what stars were like even if you lived on a perpetually cloud-bound planet. Were gravity not so weak, this graph would have the same shape, but there would be fewer powers of ten between the micro and the cosmic scales – and less space and time for complexity.

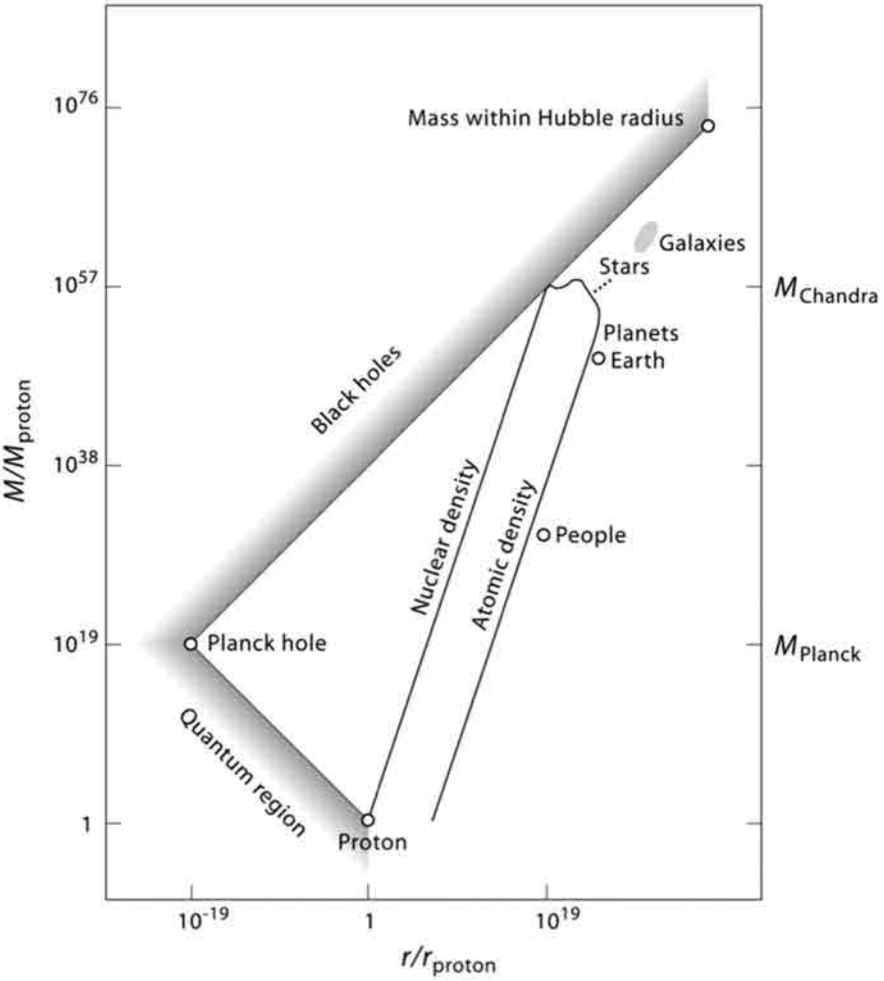

Figure 1.

Let's now step back a bit and ask what are the essential features of our universe that allow it to evolve from an amorphous dense beginning into its present complexity.

(i) As already mentioned, gravity is crucial. It has to be very weak. Indeed, up to a point, the weaker the better. We might live in a more interesting universe if gravity were (say) ten times weaker than it actually is. Stars would be bigger and would live longer. Objects could grow larger without being crushed by gravity, and evolutionary emergence could extend over an even longer timespan.

And there are other requirements:

(ii) There could be no complexity if the universe stayed in thermal equilibrium, as it was for its first half million years. The emergence of life requires temperature contrasts. We and all living things depend on 'high grade' energy from the Sun; this is processed via photosynthesis and re-emitted from the Earth as infrared radiation; it escapes into intergalactic space where the temperature is only 2.7 degrees above absolute zero.

(iii) There must be an excess of matter over antimatter in the hot early universe. Otherwise almost all particles would annihilate with antiparticles as the universe expanded and cooled, leaving just radiation. The detailed mechanism that establishes a 'favouritism' for matter over antimatter is still a matter of discussion.

(iv) Another requirement for stars, planets and biospheres is the possibility of complex chemistry. If hydrogen were the only element, chemistry would be dull. The existence of a periodic table of stable elements requires a balance between the nuclear force (the so called 'strong' interactions that bind together the protons in a nucleus) and the electric repulsive force that drives them apart. And if complex nuclei were not strongly bound together, the energy that powers the stars would not exist.

(v) There must be stars. Indeed there must be at least two generations of stars. The first synthesizes the elements of the periodic table. A second generation of protostars then contracts from slowly rotating interstellar clouds enriched in heavy elements (in dust and gaseous form). During the contraction, the protostar conserves angular momentum and spins faster, eventually spinning off a dusty disk from which planets form.

(vi) The universe must expand at the 'right' rate – neither collapsing too soon, nor expanding so fast that gravity can't pull together the structures. This requires two conditions to be fulfilled. First, the universe must be nearly 'flat' in the technical sense that the angles of triangles add up to 180 degrees. The theory called 'inflation' suggests how this might have come about. But a second requirement is that the so-called 'cosmological constant', in effect a repulsive force generated by space itself, should not be so large that it overwhelms gravity, causing the cosmic expansion to accelerate, before the first stars and galaxies have condensed out. The fact that this force is non-zero, but so small, is a mystery that will not be solved until we understand the bedrock nature of space. It is suspected that space will have a 'grainy' structure, but on the Planck scale (see Figure 1) which is a trillion trillion times smaller than an atom.

(vii) There must be some initial fluctuations for gravity to amplify – sufficient in amplitude to permit the emergence of structures. Otherwise the universe would now be cold ultra-diffuse hydrogen – no stars, no heavy elements, no planets and no people. There are theories which suggest that these fluctuations could have been generated at an ultra-early stage in the cosmic expansion by microscopic quantum fluctuations, these fluctuations being stretched by the subsequent expansion right up to the scales of galaxies, and beyond.

Firming up our understanding of these requirements (and deciding which are 'necessary' and which are contingencies) requires progress on meshing general relativity and the quantum principle into a single unified theory. This is unfinished business for the 21^{st} (or maybe even the 22^{nd}) century. In most contexts, the lack of such a theory does not impede us because the domains of relevance do not overlap. Astronomers can ignore quantum fuzziness when calculating the motions of planets and stars. Conversely, chemists can safely ignore gravitational forces between individual atoms in a molecule because they are nearly 40 powers of ten feebler than electrical forces. But at the very beginning, *everything* was squeezed so small that quantum fluctuations could shake the entire universe. To confront the mystery of what banged and how it banged requires a synthesis between our current separate theories of the very large and the very small.

The bedrock nature of space and time, and the unification of cosmos and quantum are surely among science's great 'open frontiers'. But calling this the quest for a 'theory of everything' is hubristic and misleading. It is irrelevant to 99% of scientists. Problems in biology, and in environmental and human sciences, remain unsolved because it's hard to elucidate their complexities – not because we don't understand subatomic physics well enough. Even an insect, with its layer upon later of complexity – is harder to understand than a star, where intense heat and compression by gravity precludes complex chemistry.

The sciences are sometimes likened to different levels of a tall building – particle physics on the ground floor, then the rest of physics, then chemistry, and so forth: all the way up to psychology – and the economists in the penthouse. There is a corresponding hierarchy of complexity – atoms, molecules, cells, organisms, and so forth. But the analogy with a building is poor. The 'higher level' sciences dealing with complex systems aren't imperiled by an insecure base, as a building is. Each level has its own autonomous concepts and theories. Everything, however complicated – breaking waves, migrating birds, and tropical forests – is made of atoms and obeys the equations of quantum physics. But even if Schrodinger's equation could be solved for one of these macroscopic systems, its solution wouldn't offer the enlightenment that scientists seek. Reductionism is true in a sense. But it's seldom true in a *useful* sense.

I conclude with a speculation. Einstein averred that, "The most incomprehensible thing about the universe is that it *is* comprehensible". He was right to be astonished. Our minds, which evolved to cope with the life of our remote ancestors on the African savannah, can also comprehend the counterintuitive microworld of atoms, and the vastness of the cosmos.

But some aspects of reality might elude us simply because they're beyond human brains, just as surely as Einstein's ideas would baffle a chimpanzee. Perhaps complex aggregates of atoms, whether brains or machines, can never understand everything about themselves. I'm not suggesting that the 'big problems' that we've identified won't be solved – least of all would one wish to demotivate those who are now talking them – but we should be open to the prospect that some problems (and some aspects of reality) exist that we are not aware of.

However, our intellectual limitations are less cause for dismay if we are mindful of another important inference from cosmology: the time lying ahead is at least as long as the time that has elapsed up until now. Our Sun is less than half way through its life; and our universe may continue for even longer – perhaps forever. So humans may be far from the culmination of the evolutionary process. This process could have much further to run, here on Earth and perhaps far beyond. Indeed in future the changes could be fast, because they would be determined (or at least modulated) by conscious choices of intelligent beings rather than being the outcome of Darwinian selection. In this perspective, we should be hopeful, and consoled, that post-human intellects may, in the far future, elucidate mysteries that are beyond our grasp.

QUANTUM SIMULATION OF CALCULATIONALLY INTRACTABLE PROBLEMS AND QUESTIONS ABOUT EMERGENCE[1]

WILLIAM D. PHILLIPS

I am from a place called the Joint Quantum Institute. This is a new institute that was set up just a few years ago to study quantum coherence.

A number of people at this meeting have quoted from the prologue to the programme of this meeting, which I think is an indication of how good that prologue was in guiding our thinking. The quotation that I wish to highlight is really a question:

> "Is there a difference between complex and complicated, such that some complex systems are not actually complicated even though all complicated systems are indeed complex?"
> (Werner Arber and Jürgen Mittelstraß, Prologue to the Program of the Plenary Session)

I intend to answer the first part of this question in the affirmative, from the perspective of a quantum physicist. I also want to say that I am not at all sure about the second part of this question. That is, there is an assumption made that all complicated systems are indeed complex. I'm not sure that that's true – but I'm not really prepared to discuss that yet. I think it might be in an interesting thing to discuss later.

Part of the problem is that we've been struggling with the definitions of what we mean by complex and complicated, and even simple. So I'm going to give you my definitions and they're the ones that I'm using for this talk. I'm saying that a problem is complicated if it's hard to state what the problem is, if it takes a lot of description to tell you what the problem is. My definition of complexity is that a problem is *complex* if it is difficult to solve. I think this is very much in line with the spirit of Kolmogorov Complexity.

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[1] This text is a verbatim transcript of the talk given by William D. Phillips at the November 2012 Plenary Session of the Academy. The transcript has been slightly edited for clarity, and figures of slides to which the transcript refers have been inserted.

So *complicated* means that it is hard to state and *complex* means that it is hard to solve. This may not be the definition that everyone is using, but it is the one I'm going to use for this talk. An example of a problem that is both complicated and complex is the human brain. It would be very difficult to describe the problem in the first place, to describe all the neurons, and even more difficult to describe the initial conditions, and then it would be essentially impossible, even given all that description, to predict what happens next.

On the other hand, a pendulum is a very simple thing. You typically only need one parameter to tell you about the pendulum: the length of its suspension. Then, if you know the initial position and velocity, you know how the pendulum behaves after that. There is no chaos, everything behaves in a very nice way. So these are two extremes, a problem that is both complicated and complex, and a problem that is simple and *not* complex.

An example of what I consider to be an uncomplicated problem that is nevertheless complex is the Hubbard Model of Condensed Matter Physics. The idea is that you have a certain number of lattice sites. These might be the lattice sites on a crystal. And you have a certain number of particles. These might be electrons that can move through the crystal. In this model you only think about two physical parameters: one is the rate at which a particle can tunnel, that is, hop from one site to the next, and the other one is, what is the energy cost for putting two particles on the same site? That is, if I have two electrons, and they are on the same site, there is a Coulomb repulsion between them, and that costs a certain amount of energy. So the hopping makes things want to be everywhere throughout the crystal and the on-site energy cost wants to spread things out so that they stay in their own sites. Now this is a very simple problem to state, but if you wanted to calculate what happened, even at zero temperature, and you had more than a few tens of lattice sites and particles, no computer in existence can calculate this problem directly. And if the problem were even slightly larger than a few tens, then no computer that you could even imagine would be capable of calculating this problem. Why is that the case?

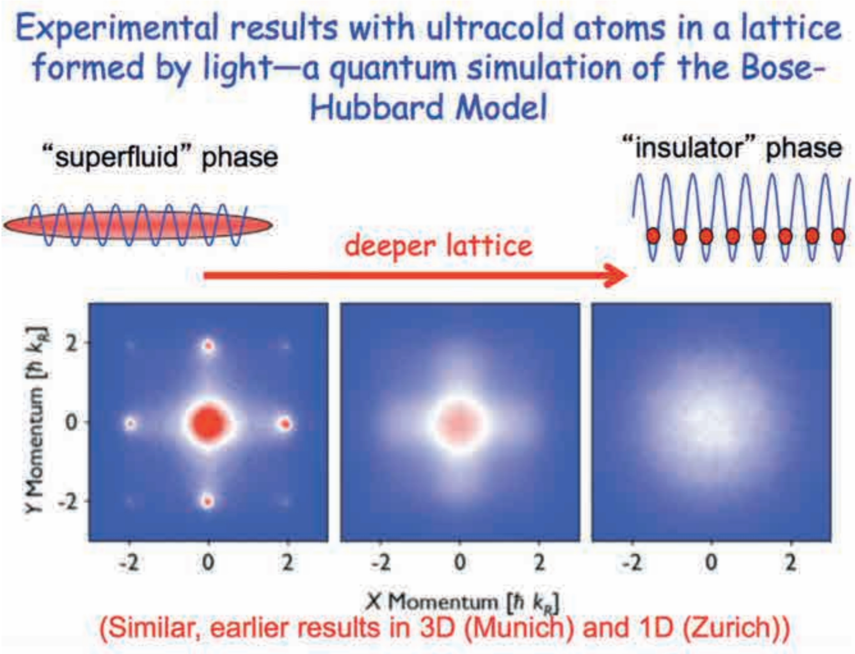
Consider a somewhat simpler situation. Imagine that I have N sites and on each one of the N sites is an atom, and that atom can be in one of two different states, and I'm going to call those two states '0' and '1'. If I've only got one site, then there are just two possibilities: the site is either 0 or 1. If I have two sites then there are four possibilities: I can have 00, 01, 10 or 11. If there are three sites then there are eight possibilities. So you see the number of possibilities grows exponentially with the number of sites. If I have just 300 sites, which is a very modest number, then that means I have 2^{300} different states. And that number is larger than the number of particles in the universe.

This means that a direct calculation for a quantum problem like this, would be really hard. Quantum mechanically the system can be in ALL of those states simultaneously. So that means there could be 2^{300} states simultaneously describing this system, and obviously no computer could handle that calculation, because the computer would have to be larger than the visible universe. So, it is fundamentally impossible to calculate a problem like this.

Why do we care? There is an important problem that is like the first one that I told you: the problem of electrons on lattice sites. One of the reasons why this is an important problem is that some people believe that this problem can describe high temperature superconductivity. Now this is not the ordinary kind of conductivity that, for example, Professor Zichichi mentioned in his talk. Superconductivity means the complete absence of electrical resistivity. Certain kinds of materials become superconducting at quite high temperatures, that is, temperatures on the order of a 100 degrees above absolute zero, whereas most ordinary superconductors are superconducting at a few degrees above absolute zero.

Such a "high temperature" is still very cold by the standards of daily human life, but very high compared to the temperatures of ordinary superconductors. And no one understands what causes this high temperature superconductivity. But some people guess that this very simple model that I described to you, will explain it. The problem is that even though the model is very simple, it is so complex that no one can calculate whether this model leads to superconductivity. So here is a model that is very easy to state, but the computational complexity of solving this model is so great that we do not know whether this answers the question of why we have high temperature superconductivity. And it's a very important question because being able to answer that question could help us to develop these materials for practical uses, which could be very important.

So the question is: is there any way out of this problem? And the answer is: yes, maybe (see Fig. 1). There are some approximation methods, but none of them work well for this problem. So that's not the way this is going to work, at least not for the moment. That is, calculational approximations so far have not been able to give us the answer to this problem. But there *is* a possible answer, and that is: doing experiments. It is something that I am particularly interested in because in my own laboratory, we can do experiments to, in fact, solve the problem that you see in Figure 1. This is one where the particles are not electrons, which are more complicated because they are fermions (they obey Pauli's Exclusion Principle, and I can't have two in the same state on the same site, so that makes things more complex as it turns out).



Experimental results with ultracold atoms in a lattice formed by light—a quantum simulation of the Bose-Hubbard Model

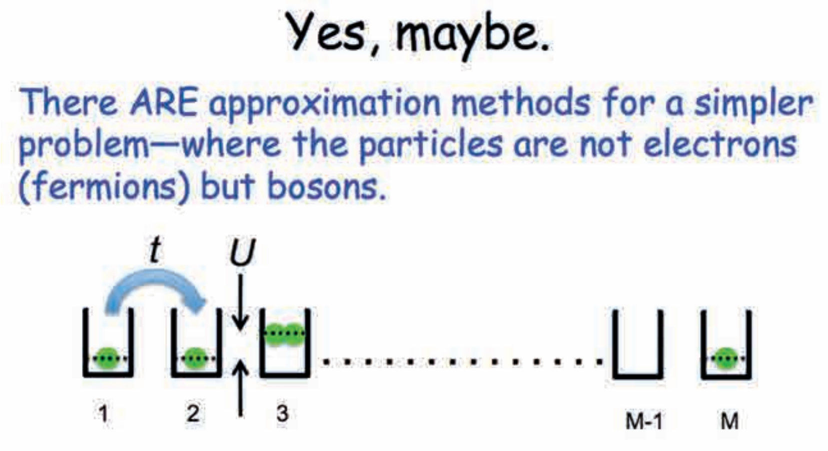
(Similar, earlier results in 3D (Munich) and 1D (Zurich))

Figure 1. The Bose-Hubbard model.

This is the problem of what are called 'bosons', of which there are a number of examples (and the Higgs boson is perhaps the most famous one today) but the ones we use in the laboratory are things like rubidium atoms, which are bosons. It's an easier problem. We can solve the problem by approximation methods and we can solve the problem in the laboratory by making, in the laboratory, a physical realisation of the model. So it's not that we make something that is the same as some solid-state system that we think might be described by this model. We make the actual model in the laboratory. And what we find is that this laboratory model gives the same result as these approximation methods. So this gives us confidence that these approximation methods, in fact, work.

Figure 2 shows some of the results from our laboratory. I won't explain what these are because we don't have enough time. This is just to show that we *can* make measurements in the laboratory. And, by the way, I should say that the measurements that we've made in the laboratory have come after some pioneering measurements made in Theodor Hänsch's lab in

Munich, which is noted at the bottom of the slide. But the point is that in the laboratory we can make a physical realisation of this simple model, and we can show that it agrees with some of the most advanced approximation methods for the problem that we cannot solve directly, by brute force. Now the important thing is that we may be able to do the slightly more complex problem, the one with fermions instead of bosons, the one for which no one has solutions – we can also do that in the laboratory, or at least we hope that in the coming few years we will be able to make this model in the laboratory.



Yes, maybe.

There ARE approximation methods for a simpler problem—where the particles are not electrons (fermions) but bosons.

Figure 2. Experimental results for a laboratory realization of the Bose-Hubbard model.

What this means is that we have a problem that is so complex that, computationally, no one can solve the problem, no one expects to ever be able to solve the problem directly, and no one has yet been able to come up with an approximation method to solve the problem mathematically. And we believe that we can solve the problem in the laboratory by building a laboratory model of the mathematical model, and find out what the solution is we don't know.

What if it turns out that this model *does* show that there is superconductivity? Well then many people would say that what we have shown is that superconductivity, high temperature superconductivity, is an emergent phenomena, and I think this would fall under the category of what Jürgen

Mittelstraß called 'strong emergence', where if there is no possibility of calculating what the result is, but we know what the result is, in this case because we did an experiment, but in a certain sense that experiment is a kind of calculation.

So we might ask the question: what is emergence? And the answer is: I don't know! But I've been reading lots of definitions and some of them seem to be more philosophical than scientific. And, in fact, I was asked to give a talk at a meeting, in which the topic was 'Emergence at the mesoscale', and I complained to the organisers that I didn't know anything about emergence and I didn't know anything about the mesoscale. And they said, "Oh it doesn't matter, come anyway and just talk about whatever you know". So I did and I began my talk by telling people this: atomic physicists are confirmed reductionists. We are wedded to the belief that we can understand the beauty of nature on the basis of microscopic properties and principles. To us, emergence is just another name for *ignorance*. And I added a little winking emoticon to try to soften the harshness of this statement, but still I believe, as an atomic physicist, that emergence is just another name for ignorance.

So what is an emergent property? Here is my naïve attempt at a few definitions: it's a property of an ensemble, a macroscopic property that is not evident from the behaviour of the individual parts. Now, there are two possibilities, and I think that these two possibilities correspond to what Jürgen has called weak and strong emergence. One is that it's a macroscopic property that is not evident, and that no one would have been able to calculate beforehand from the microscopic behaviour, but that once that macroscopic behaviour becomes evident then you can figure out how to calculate it from the microscopic properties. That's the first possibility.

The second possibility is an ensemble property that *cannot* be calculated from the microscopic properties, even once the ensemble property, the macroscopic property, has been discovered. And that would apparently be the situation with the Fermi-Hubbard model and high temperature superconductivity.

So now I pose the following question: what happens if an incalculable problem becomes calculable because I change the hardware? In other words, I have now developed a new kind of computer. In my laboratory the computer is a bunch of atoms in a vacuum, and these atoms do the computation that no ordinary computer can do. So if a complex problem, one that was incalculable, all of a sudden were to become simple, or at least tractable, because of this new kind of computer, then how would this change our notions of emergence?

Consider another candidate for emergence, one that I have brought up before: human consciousness, that is, the awareness of self and all that that implies. How does that arise from chemistry and physics? I don't think anyone knows, and I suspect that no one will know anytime soon. Some people say that consciousness is an emergent phenomenon. Surely, if it is, it falls into the second category of being strongly emergent. So I offer that as a candidate for strong emergence.

Now in reading about emergence I found this quotation from Mark Bedau, who is a philosopher. He said that, "Although strong emergence is logically possible, it is uncomfortably like magic".

In the case of human consciousness, let's substitute the word "transcendence" for "magic". I am a person of faith and I have often been attracted to the notion that consciousness – whatever that really means, and I'm not sure I know – as well as free will – whatever that really means, and I don't think I know either – are transcendent phenomena. That is, they are gifts from God that are given to a sufficiently complex structure, maybe not just to humans. Is this notion any different from the idea of emergence? Is the idea that consciousness is a transcendent phenomenon, that is, something that has to do with the divine, any different from the idea of emergence, and is it any different from the idea of magic, as was indicated by Mark Bedau?

And then finally, is it any different from what I would call the old fallacy of ascribing to God everything that you cannot explain? This is sometimes called the 'God of the gaps'. Would the notion of transcendence or emergence change if we had a sufficiently powerful computational method like quantum simulation or quantum computation?

So why am I posing all these silly questions? It's simple. It's because I want to know the answers. I don't know the answers to any of these questions, and I'm not even sure that I even understand what the questions mean. And I excuse myself by saying: well, I think I'm a reasonably competent physicist; I'm certainly a bad philosopher, and an incompetent theologian. So I hope that a discussion of these questions will occur here in the Academy, and I welcome that discussion, because I hope that it will help me to become better educated.

Finally, I want to acknowledge the people that I work with, especially Gretchen Campbell, Ian Spielman, Paul Lett and Trey Porto, who are the permanent members of my group. They are all working together to try to provide the physical means of calculating problems that are impossible to calculate on computers.

I now want to invite your questions. The fact is that this talk is designed not so much to invite questions from you as to invite answers from you.

Let me summarize the questions to which I want answers, starting with a question that I didn't address: can a complicated system be other than complex? What is emergence – and this I think is strong emergence – and is it any different from magic? Does the idea of emergence change if you have new computational tools that change the tractability of a problem? Is there any validity in connecting emergence to transcendence? And does making such a connection bring one back to the old trap of ascribing to God the things that one doesn't understand. Normally I wouldn't be raising these last two questions. But in an Academy where some of the members are philosophers and theologians, I feel justified in raising such questions.

Thank you very much.

COMPLEXITY IN CHEMISTRY: FROM DISORDER TO ORDER

GERHARD ERTL[1]

This contribution will address two questions raised in the prologue of this conference:

1. Can science render apparently complex systems in simple underlying theories?
1. Has a complex system necessarily to be complicated?

Our starting point will be disorder as to be expected from a closed system consisting of non-interacting elements, and the role of accident had already been pointed out in 1921 by E. Schrödinger in his Inaugural Lecture at the University of Zürich: "Physical research has unequivocally demonstrated that for the majority of observed phenomena, whose regularity and continuity led to the formulation of the postulate of general causality, the common root for strict laws has to be sought in the accident" [1].

Nevertheless the surrounding nature exhibits objects of considerable order, the most simple of which is found in the inorganic world of minerals and crystals. This order extends frequently down to the atomic scale as can be seen from Fig. 1* showing a section from the (111) surface of an aluminum single crystal surface recorded by scanning tunneling microscopy (STM) with atomic resolution. In order to illustrate the principles of order formation in simple chemical systems I shall focus my presentation in the following on experiments with well-defined single crystal surfaces of this type interacting with molecules from the gas phase.

Fig. 2 shows the image from a Pt(111) surface which had been exposed to a small quantity of O_2 molecules which dissociate upon interaction with the surface and give rise to the bright extra dots (surrounded by dark holes) from the adsorbed O atoms [2]. The energetics of such adsorbed atoms are illustrated by Fig. 3: Motion of the atom perpendicular to the surface is associated with a potential minimum E_{ad} (characteristic for the bonding to the surface) giving rise to the lifetime t_{surf} of the adsorbed species. Motion parallel to the surface is associated with a periodic variation of the potential whereby the barrier $E^\star$ denotes the activation energy for surface diffusion

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[1] Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin, Germany.

* Figures begin on p. 149.

which is much smaller than E_{ad} so that the particle has a residence time t_{site} and makes many jumps between neighboring sites before A eventually desorbs into the gas phase. Fig. 4a shows a snapshot (taken in 0.07 s) from O atoms randomly distributed over a Ru(0001) surface at T=300K. The mean residence of an isolated particle is now reduced to 60 ms, but increases to about 220 ms when two atoms approach each other to a distance of two lattice constants. This is a consequence of weak attractive interactions between neighbors over such a separation. As a consequence the distribution of adsorbed atoms at higher coverages is no longer random, but is characteristic by the formation of two phases as represented by the image of Fig. 4b: A diluted 'gas' phase and a well-ordered quasi-crystalline phase being in equilibrium with each other. The occurrence of phase formation and the formation of a ordered structure has in this case to be attributed to the establishment of thermodynamic equilibrium which is governed by the minimum of the Free Energy F=U–TS=min, with U=(Internal) energy, T=temperature, and S=entropy. In this case the attractive interaction between the adsorbed atoms lowers U and overcompensates disorder by the entropy term. This equilibrium condition holds for *closed* systems which can only exchange heat with the surrounding. We may call the resulting state as 'dead order' since the system is not nurtured by another source of Free Energy.

By contrast, there is another class of observations which we may classify as 'living order', because these are mainly – but not exclusively, as will be shown – found with living systems as exemplified by Fig. 5: The fur of the animal not only exhibits a pattern on macroscopic scale, but periodic motion reflects an addition also temporal order. These effects may certainly not be described on the basis of thermodynamic principles governing equilibrium.

In 1943 E. Schrödinger held a series of lectures which were later published under the title "What is life?" [4]. This book is considered to be a landmark in the development of molecular biology, since it pioneered the concept of molecular (i.e. chemical) basis of the genes. The author, however, admits that his real intention was to find an answer to the question of how living systems may develop into a state of higher order under conditions of an open system far from equilibrium, but he was in fact not able to find a satisfactory answer on the basis of the then known physical laws. However, a theoretical model for this type of structure formation was presented a few years later by the famous mathematician A. Turing in a paper entitled "The chemical basis of morphogenesis" [5], whose abstract reads: "It is suggested that a system of chemical substances, reacting together through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous state. With such reaction-diffusion systems stationary waves may appear. The theory does not make any new hypothesis; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts".

At present, reaction-diffusion systems of the Turing type are indeed generally accepted as mechanism underlying (macroscopic) structure formation in biological systems [6,7]. The essential aspect is that we are no longer dealing with closed systems attempting to reach thermodynamic equilibrium, but with open systems far from equilibrium in which e.g. an ongoing chemical reaction serves as a continuous source of Free Energy. In Turing's concept chemical reaction is coupled to diffusion, and mathematical description is achieved in terms of coupled nonlinear differential equations. The theoretical framework for the chemical systems of the present context was essentially developed by Prigogine [8] who denoted the resulting effects of order as 'dissipative structures' because the supply of Free Energy is dissipated in the form of heat. An even more general concept was developed by Haken [9] and denoted as "synergetics". The consequences of complexity resulting along these principles for chemical systems will be presented with the catalytic oxidation of carbon monoxide on a Pt(110) surface whose mechanism is illustrated in Fig. 6. This reaction which is of importance for car exhaust removal comprises bonding (chemisorption) to the surface of CO through the carbon atom and dissociative adsorption of O_2, followed by recombination of both surface species (CO_{ad} and O_{ad}) to CO_2 which is then immediately released into the gas phase. Under steady-state flow conditions the rate of CO_2 formation will usually be constant and determined by temperature T and the partial pressures for the reactants, p_{CO} and p_{O_2}, respectively. In special cases, however, this is not the case, but the rate will start to oscillate periodically with time. This is shown in Fig. 7 where for constant T and p_{CO} at the point marked by an arrow the O_2 partial pressure is stepwise increased where after the rate slowly grows and then oscillates [10].

Another example of this kind is presented in Fig. 8 which shows the variation with time of the number of furs from hares and lynxes delivered to the Hudson's Bay Company [11]. The oscillating populations of both species are coupled to each other with some phase shift. The reason seems to be quite obvious: If the lynxes find enough food (=hares) their population will grow, while that of the hares will decay as soon as their birth rate cannot compensate the loss any more. When the supply of food ceases, the lynxes begin to starve and their population decays so that of the hares can recover. Although the actual situation is somewhat different, the essential features of the concentrations x and y of the two species can be approximately modelled by two coupled, nonlinear ordinary differential equations (Lotka-Volterra model) as shown in Fig. 9 together with their solution for properly chosen parameters a and b which reproduces qualitatively the observed behavior.

An essential aspect of mathematical modelling consists in the description in terms of nonlinear coupled differential equations, hence also the denotion 'nonlinear dynamics' for this actual field of research.

In a similar manner the temporal oscillations in the CO oxidation on a Pt(110) surface as reproduced in Fig. 7 can be modeled with a set of three coupled nonlinear differential equations, with the coverages of CO and O and the fraction of the surface structure being present in the 1x1 phase. Solution for properly chosen kinetic parameters (derived from experiment) is reproduced in Fig. 10 and reproduces indeed the observed behavior [12].

However, the theoretical description is so far not yet complete: If an extended system exhibits temporal oscillations as a whole, lateral coupling between different parts is required in order to reach synchronization. Hence the state variables c_i (i.e. the surface concentrations in our case) depend not only on temporal, but also on spatial coordinates. Coupling takes place through diffusion so that description is achieved through a set of coupled nonlinear partial differential equations of the type $\frac{\partial c_i}{\partial t}=f_i\left(c_j,p_k\right)+D_i\nabla^2 c_i$ whereby f_i denotes the kinetics (depending on the concentrations and on the external parameters) and the last term (generalized) diffusion. The length scale of the resulting spatio-temporal concentration patterns is no longer determined by atomic dimensions but by the diffusion length which in our case is of the order of micrometers [13]. These patterns can be imaged by the technique of photoemission electron microscopy (PEEM) [14]: Adsorbed O and CO species are accompanied by different dipole moments and hence different intensities of electrons emitted by UV light. Dark areas in the images are mainly O-covered while brighter patches are CO-covered. As an example, Fig. 11 shows so-called target patterns, concentric elliptic waves propagating somewhat faster in direction of the Pt(110) surface along which direction CO diffusion is also faster, on a background changing periodically between bright (=CO-covered) and dark (=O-covered), reflecting the periodic variation of the integral reaction rate while the external parameters of temperature and partial pressures of the reactants are kept constant [15].

Under other external parameters, typical spiral waves may develop as reproduced in Fig. 12, propagating with front velocities of several micrometers per second [16]. Spiral waves are ubiquitous in nature, ranging from galaxies to hurricanes to animals. In our case the underlying mechanism is well established and can be formulated in terms of the set of reaction-diffusion equations shown in Fig. 13 which contain for simplicity only diffusion of the fastest species, adsorbed CO (=u) [17]. Numerical solution of these partial differential equations yields for properly chosen parameters, indeed the evolution of spiral patterns from a random initial distribution as reproduced in Fig. 14. Slight changes of the parameters, however, yield breakup of the spirals and development of a turbulent (chaotic) state as shown in Fig. 15, and Fig. 16 presents experimental verification of this situation.

If we now return to the questions posed at the beginning, clear answers can be given: The example of catalytic oxidation of CO at a Pt(110) single crystal surface is certainly a simple system for which the details of the mechanism are known down to the atomic scale. Nevertheless it exhibits all features of complexity from pattern formation to chaos. This complex system can be successfully modeled theoretically on the basis of three differential equations derived from the experimentally established mechanism. Thus a complex system has by no means to be complicated.

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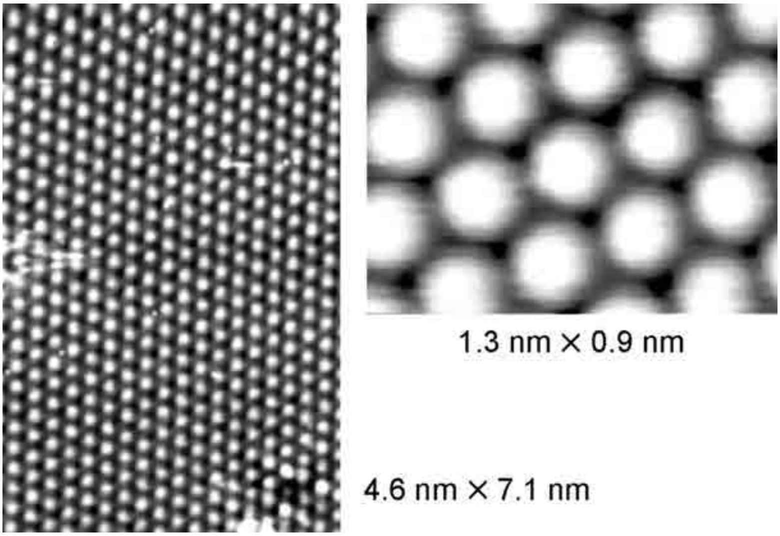

Figure 1. Al(111) single crystal surface as imaged by scanning tunneling microscopy (STM).

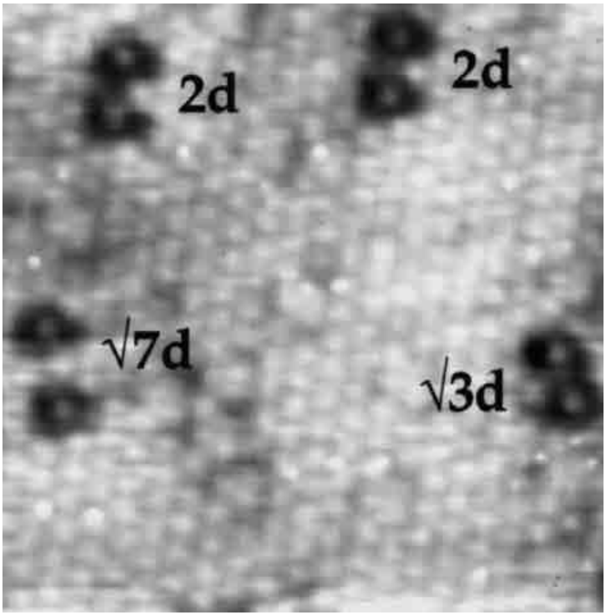

Figure 2. STM image from a Pt(111) surface (5.3x5.5 nm^2) after exposure to a small quantity of O_2 molecules at 165 K showing the formation of adsorbed O atoms.

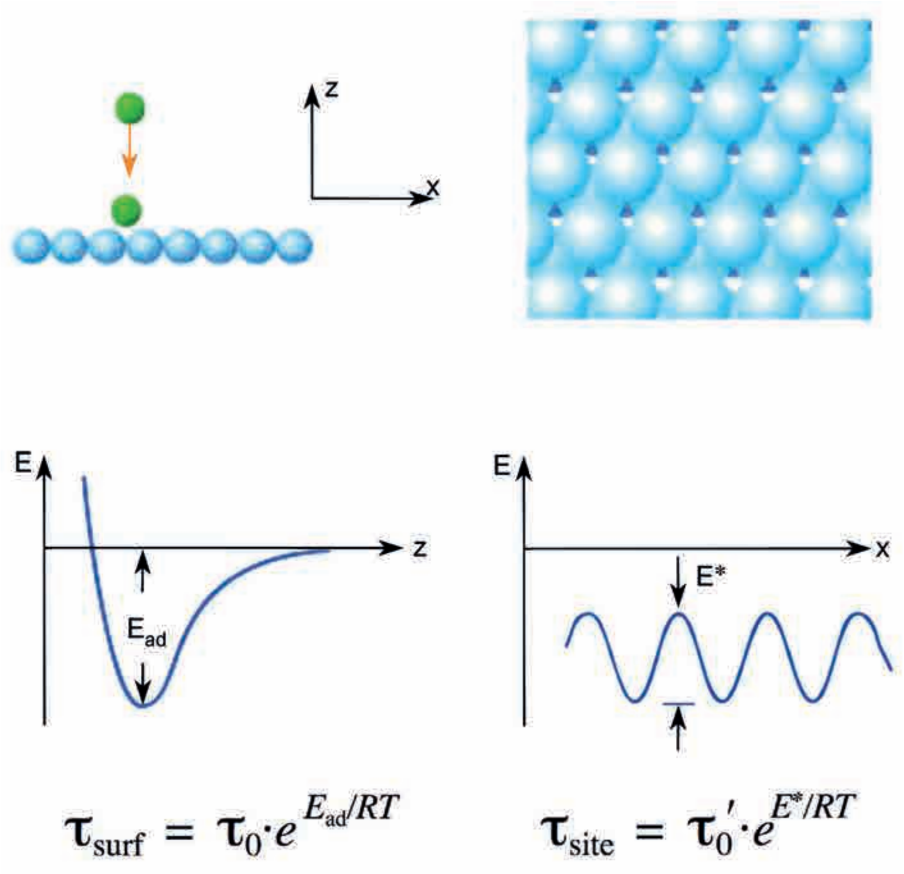

Figure 3. Potential of an atom interacting with a surface along the z- and x-directions.

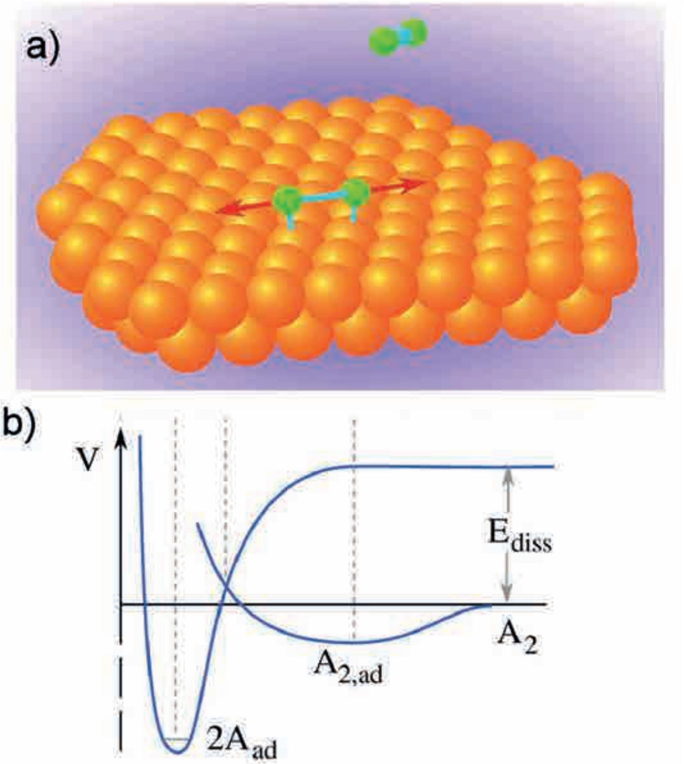

Figure 4. STM snapshots from O atoms adsorbed on a Ru(001) surface at 300 K. a) at very small coverage, b) at higher coverage.

Figure 5. The fur of a cheetah exhibits patches reflecting ‘living order’.

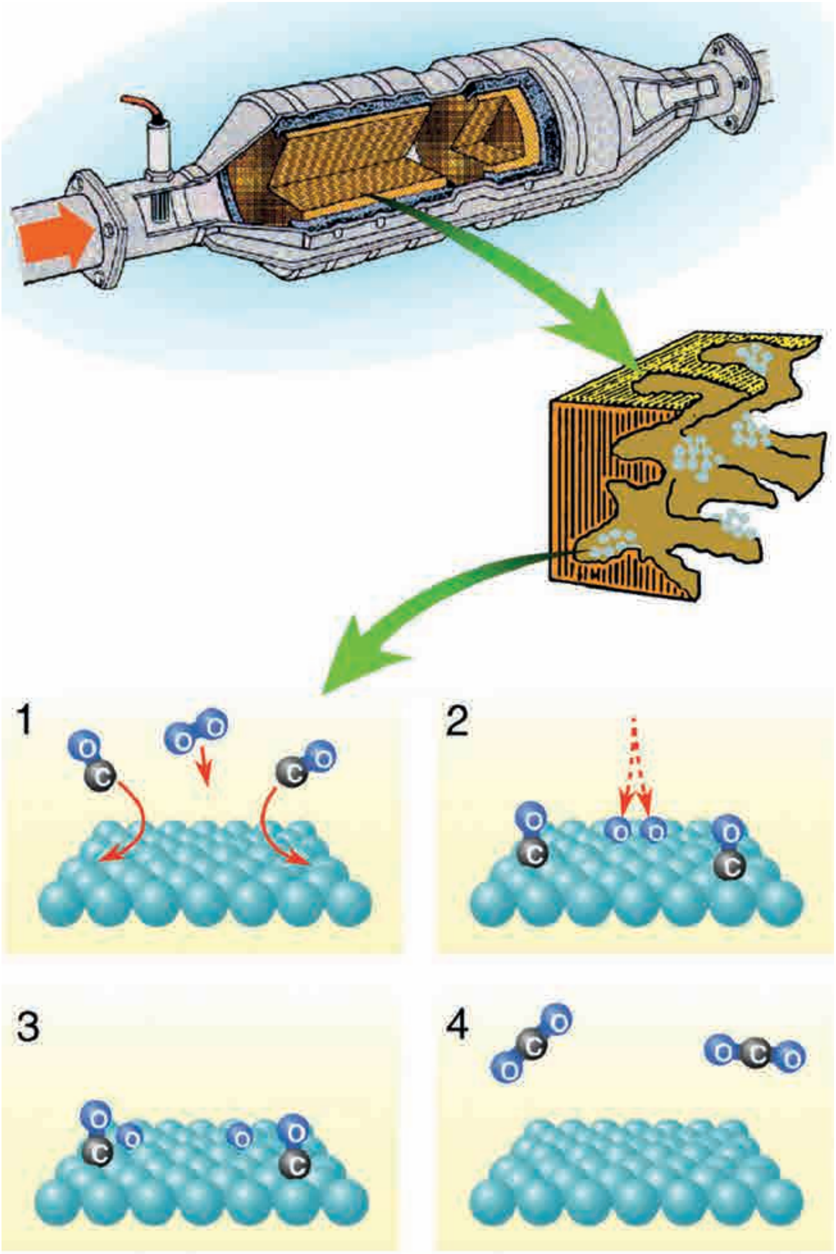

Figure 6. Schematic illustration of the mechanism of catalytic CO oxidation.

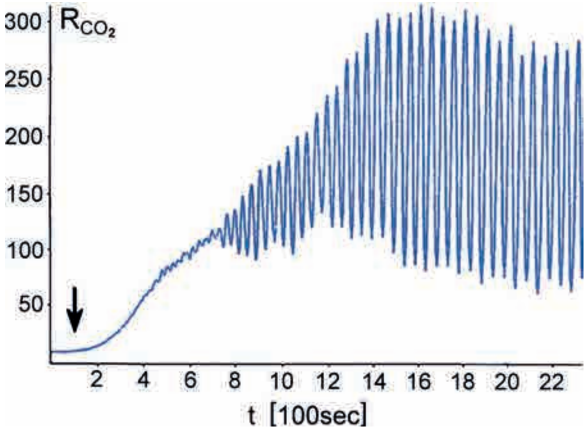

Figure 7. The rate of the catalytic CO oxidation on a Pt(110) surface as function of time when at the point marked by an arrow the steady-state partial pressure of O_2 is stepwise increased.

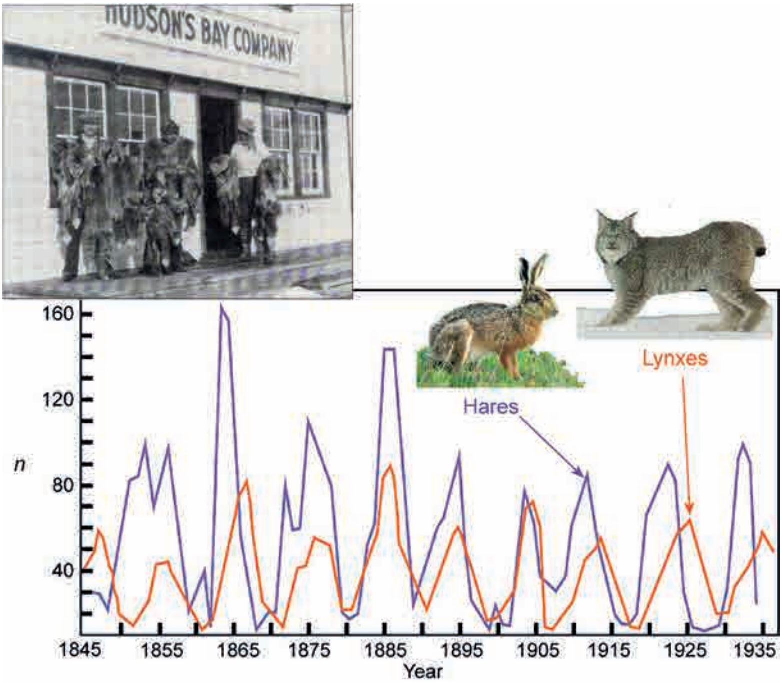

Figure 8. Variation of the number of furs n (in thousands) from hares and lynxes delivered to the Hudson's Bay Company over the years.

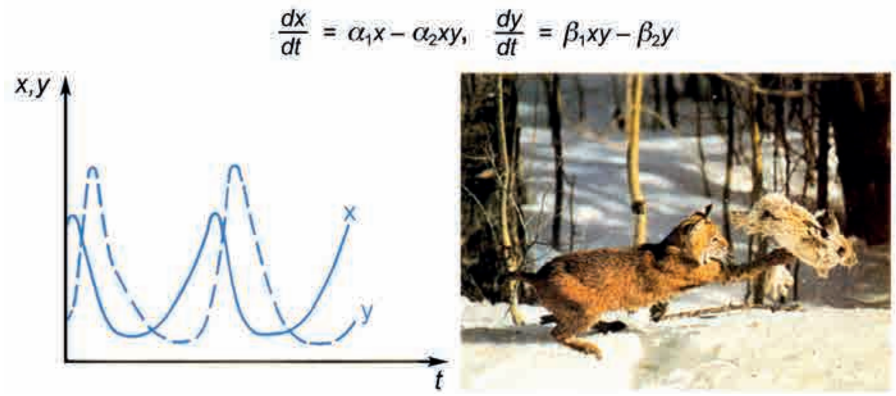

Figure 9. The Lotka-Volterra model for the concentrations of hares x and lynxes y and the solution of the two coupled ordinary differential equations.

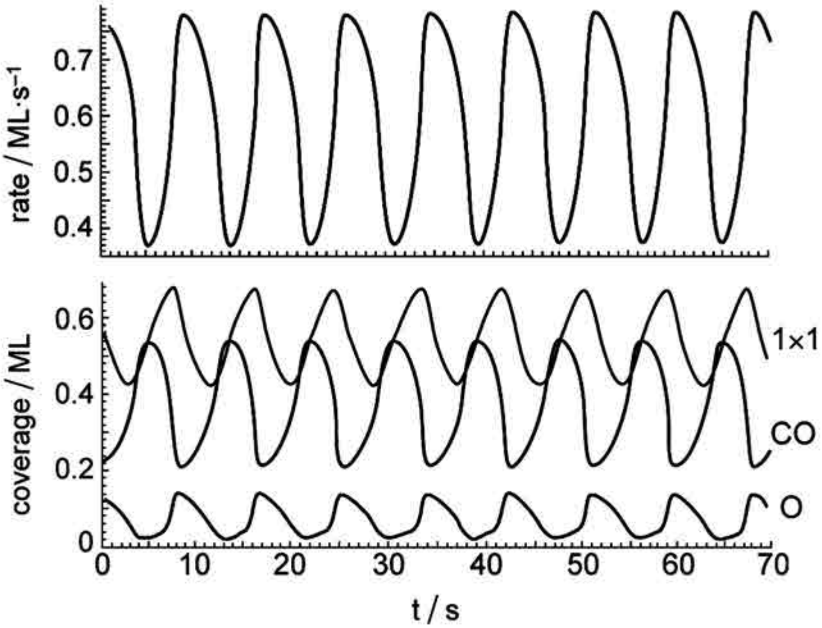

Figure 10. Solutions for the differential equations describing the reaction rate, as well of the concentrations of adsorbed O and CO and 1x1 surface phase during the catalytic CO oxidation on a Pt(110) surface at T = 540 K, =6.7x10^{-5} mbar, p_{CO} =3x10^{-5} mbar.

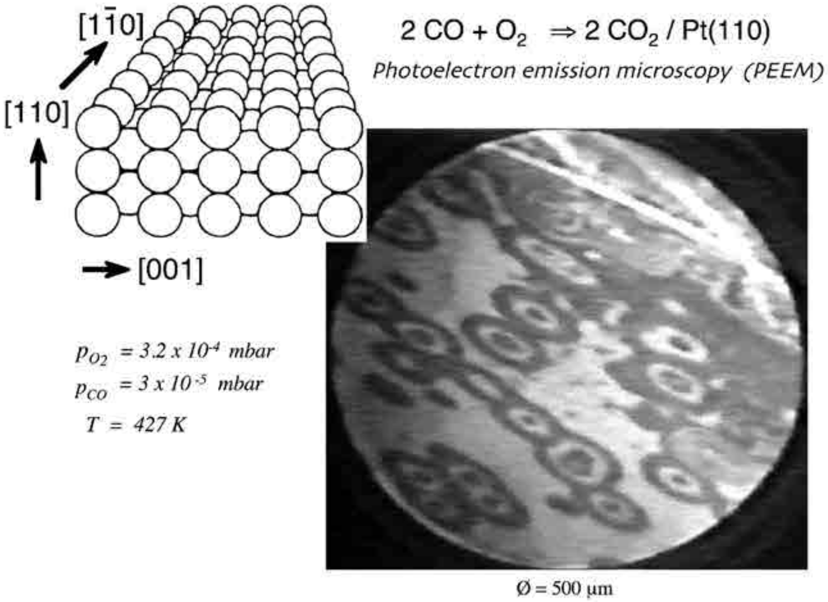

Figure 11. Target patterns during the catalytic CO oxidation on a Pt(110) surface as imaged by photoemission electron microscopy (PEEM).

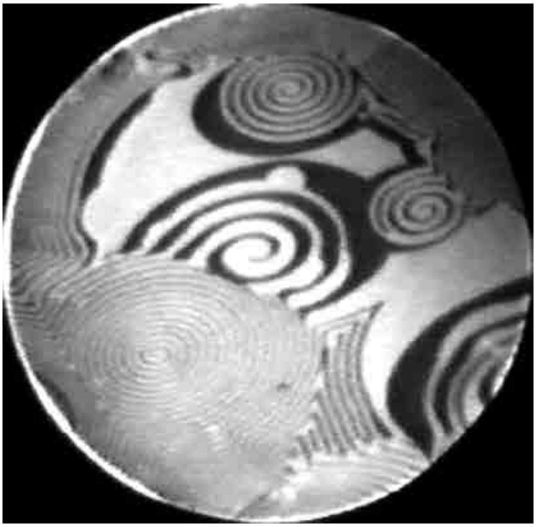

Figure 12. PEEM image from a typical spiral wave formed on a Pt(110) surface during catalytic CO oxidation.

$$CO + \tfrac{1}{2}O_2 \rightarrow CO_2 \,/\, Pt(110)$$

Reaction-diffusion model:

$$\theta_{CO} \equiv u;\ \theta_0 \equiv v;\ \theta_{1\times1} \equiv w\ (\theta_{1\times2} = 1 - w)$$

$$CO + * \rightleftarrows CO_{ad}$$

$$O_2 + 2* \rightarrow 2\,O_{ad}$$

$$O_{ad} + CO_{ad} \rightarrow CO_2 + 2*$$

$$(1\times2) \xrightarrow{CO_{ad}} (1\times1)$$

$$\frac{\partial u}{\partial t} = s(CO)p_{CO} - k_2u - k_3uv + D\nabla^2u \qquad (1)$$

$$\frac{\partial v}{\partial t} = s(O_2)p_{O_2} - k_3uv \qquad (2)$$

$$\frac{\partial w}{\partial t} = k_5[f(u) - w] \qquad (3)$$

$$s(CO) = k_1(1 - u^3)$$

$$s(CO_2) = k_4[s_1w + s_2(1 - w)](1 - u\text{-}v)^2$$

Figure 13. The set of 3 partial differential equations (reaction-diffusion equations) modeling the formation of spatio-temporal concentration patterns for adsorbed CO(=u) and O(=w) on a Pt(110) surface during the catalytic CO oxidation.

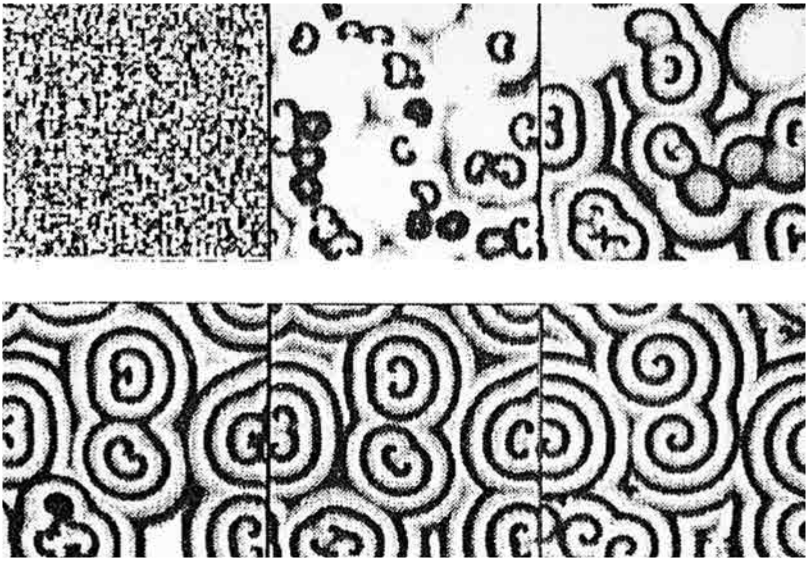

Figure 14. Numerical solutions of the preceding differential equations for a certain set of parameters with progressing time.

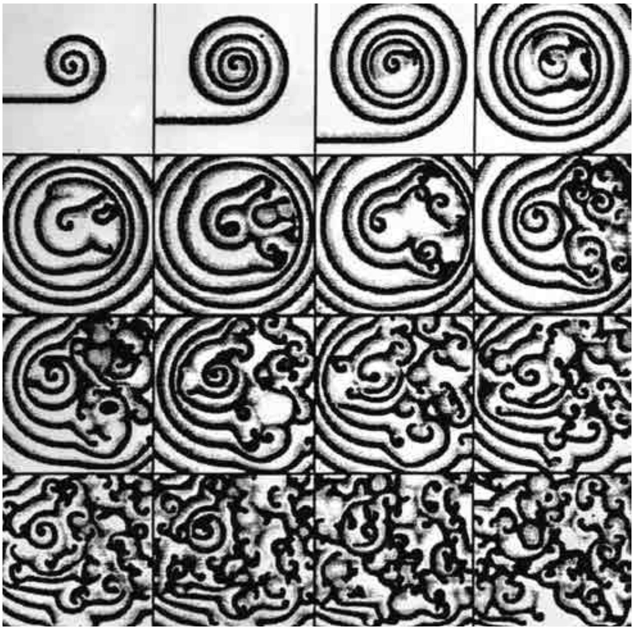

Figure 15. Upon slight variation of the parameters the computer simulations exhibit the break-up of the spiral waves and the transition to chemical turbulence (chaos).

Figure 16. PEEM image (0.36x0.36 mm^2) from a Pt(110) surface in the state of chemical turbulence during catalytic CO oxidation at T=548 K, =4x10^{-4} mbar, p_{CO}=1.2x10^{-4} mbar.

CHEMISTRY AND BIOLOGY

DECIPHERING COMPLEXITY IN BIOLOGY: INDUCTION OF EMBRYONIC CELL DIFFERENTIATION BY MORPHOGEN GRADIENTS

EDWARD M. DE ROBERTIS

Introduction

One of the most complex and mysterious processes in nature is the development of a vertebrate animal from a single cell into an organism consisting of hundreds of differentiated cell types that are reproducibly arranged in specific spatial patterns. Understanding developmental mechanisms is essential because it is during development that the information contained in the DNA (the genotype) is interpreted into morphological phenotypes.

Historically, developmental biology has attempted to study the embryo as a complete system that develops seamlessly into a perfectly shaped organism. For example, embryologists were fascinated by the fact that when an embryo is divided into two halves perfectly patterned twins can form. Fortunately, this vocation of embryology towards studying the whole is now paying off and we are beginning to understand how cells can communicate with each other over long distances spanning hundreds of cells.

In this essay I will examine how complexity can be deciphered in animal development. Three issues will be addressed:

First, in biology physiological mechanisms are determined by the historical twists and turns a species had to endure in order to survive during its evolution. Although humans share a common gene tool-kit with other animals, each species found unique solutions to the obstacles presented by the selective pressures of natural selection. Consequently, in biology it is difficult to uncover invariant universal laws that can be expressed as mathematical equations.

Second, we will examine how the researcher usually constructs a mental model of how the mechanism might work, and then tests it by experiment. To be productive, a hypothesis must be testable using the techniques available in that particular period. Consequently, our level of understanding changes over time. The new ability to readily sequence and clone DNA through molecular biology opened the door for great advances in recent decades.

Finally, the main part of this essay will describe how this step-by-step approach of simple hypotheses tested by experiment allowed the deciphering of one of the most complex regulatory systems imaginable, the molecular mechanism of induction of an invariant pattern of cell differentiation in the early vertebrate embryo. We will examine how a network of extracellular proteins that generates a dorsal-ventral (D-V) morphogenetic gradient of growth factor signaling was discovered. This system has the remarkable capacity of regenerating a perfect pattern after the morphogen gradient is perturbed. This property of self-regulation is one of the most fascinating phenomena in living organisms, which could start to be addressed from a physico-chemical perspective only after recombinant DNA technology made possible the purification of the proteins involved in the network.

1. Living organisms are shaped by their evolutionary history

Physics and chemistry obey universal laws that can be expressed by mathematical equations. These laws have remained unchanged since the beginning of the universe. Life on earth has a single origin, as revealed by the fact that all living organisms share the same basic genetic code as the one in human DNA (Collins, 2006). Recent advances in DNA sequencing have allowed entire genomes to be sequenced readily. Bioinformatic "systems biology" approaches allowed scientists to describe the expression of thousands of genes in many cell types. Computational analyses of DNA sequences led to detailed catalogues of functional sites in humans. An ENCyclopedia of DNA Elements (ENCODE) in humans was recently published in a paper with almost 450 co-authors (Dunham *et al.*, 2012); it provides one of the best examples of current "big science" efforts. Computers are very efficient at comparing linear sequences of A, G, T and C. However, despite these extensive computer analyses of the complexity of the human genome we are still very far from understanding the principles by which the genotype is converted into phenotype. We know the sequence of nucleotides, but do not understand how the genetic program is interpreted to produce a perfect organism generation after generation.

The main obstacle to revealing general laws in biology is the historical nature of life. Animals are shaped by evolution. To survive the strictures of natural selection a species acquires mutations, duplications, and gene losses that record within its DNA its previous history (Gould, 2002; De Robertis, 2008). For this reason it is very difficult to uncover invariant laws beyond those of physics and chemistry. Nevertheless, extraordinary advances have been achieved using the experimental method. The main goal of this paper is to illustrate how the enormous complexity of embryonic development can be interrogated productively using an hypothesis-driven approach.

2. Conceiving hypotheses that can be tested by experiment

How is new knowledge acquired in biology? The best description I know of the mental process involved is presented in an old book by French physiologist Claude Bernard (1865). Entitled *Introduction to the Study of Experimental Medicine*, its lessons are still valid today. Bernard was a noted physiologist, who discovered that the function of the liver and other organs was to deliver internal secretions into the blood. He also proposed that "animals have really two environments: a *milieu extérieur* in which the organism is situated, and a *milieu intérieur* in which the tissue elements live", and that physiological mechanisms were directed at maintaining the *milieu intérieur* constant.

The leitmotif of C. Bernard's book on the epistemology of experimental biology is that discovery starts with an *a priori* idea or hypothesis of how a phenomenon might occur. Using our reason we then devise experiments that might support or falsify the hypothesis and finally subject the hypothesis to proof by experiment. "The true scientist is one whose work includes both experimental theory and experimental practice. (1) He notes a fact; (2) *à propos* of this fact an idea is born in his mind; (3) in the light of this idea, he reasons, devises an experiment, imagines and brings to pass its material conditions; (4) from this experiment, new phenomena result which must be observed, and so on and so forth". In modern terms we call this approach hypothesis-driven research. To conceive an experiment we first need an idea or mental picture of how the process might work. "The experimental idea is the result of a sort of presentiment of the mind which thinks things will happen in a certain way. In this connection we may say we have in our minds an intuition or feeling, as to the laws of nature, but do not know their form. We can learn it only from experiment". In general, the new hypothesis is based on previous knowledge that pointed our attention to areas that remained unexplained.

The experiment puts the question to the natural world, which gives an answer independent of our own prejudices. At this point, the observer evaluates the results without preconceptions and decides whether the experimental hypothesis is verified, disproved, or suggests an alternative hypothesis. The key to the experimental method is that we must accept the result offered by nature and not replace it with our own reason. "Experimenters must doubt their intuition, i.e., the *a priori* idea or the theory which serves as their starting point; this is why it is an absolute principle always to submit one's idea to the experimental criterion so as to test its value". In my experience, when an idea is confirmed by experiment it frequently opens doors for new discoveries. If the hypothesis is incorrect, we rapidly encounter a wall of repeated obstacles and the verdict becomes evident. At some point even a productive experiment ceases to yield new insights; this indicates that new theories or methods will be required to advance further.

The story of the molecular dissection of the dorsal-ventral morphogen gradient provides an example right out of Claude Bernard's book. Experiments on the self-regulation of embryonic development suggested ideas that changed over time as new technical advances allowed deeper levels of understanding of development at a physico-chemical level.

3. Unraveling the induction of embryonic tissue differentiation

3.1 Self-regulation in development

One of the most remarkable properties of embryos is that they are able to regenerate missing parts. After experimental manipulations the embryo attempts to self-regulate towards the whole. This property ensures that the most perfect embryo possible is produced time after time despite variations in egg size or environmental changes such as temperature. The experimental approach in embryology started in 1883 when Roux killed one of two cells of a frog egg with a hot needle and found that the surviving half gave rise to a partial embryo. However, in 1891 Driesch separated the two first cells (called blastomeres) of a sea urchin embryo and found that each was able to form a complete, although smaller, embryo.

Amphibian embryos provide a very good material for these experiments because the dorsal (future back) and ventral (future belly) sides can be distinguished from each other. Even before the first cell division, the future dorsal side can be recognized by a less pigmented dorsal crescent (resulting from a rotation of the egg cytoplasm along microtubules). In 1901 Hans Spemann used a baby hair loop to constrict salamander embryos into two halves. Much later, we found that the embryo can self-regulate a perfect pattern even after bisection with a scalpel blade at the late blastula (9000-cell) stage (for a timeline article on experimental embryology see De Robertis, 2006). In modern times researchers use the South African frog *Xenopus laevis* (Gurdon and Hopwood, 2000), which provides large numbers of eggs all year long.

If the embryo fragments contain both dorsal and ventral components identical twins can result. This provides one of the most extreme examples of regeneration since the entire missing half of the body, with all its organs, is perfectly replaced. The resulting embryos are "scaled" so that they are smaller in size but perfectly patterned. If the half embryo contains only ventral cells a spherical "belly piece" consisting of ventral tissues such as epidermis and blood is produced (Spemann, 1928). However, the dorsal half of the embryo is able to scale, forming a smaller but well-proportioned embryo containing dorsal tissues such as the central nervous system (CNS) and notochord, as well as ventral tissues. These experiments suggested that the dorsal side contained an activity able to organize embryonic tissue differentiation.

The key experiment for understanding embryonic patterning was performed by Spemann's graduate student Hilde Mangold, who transplanted a small region of the gastrula (10,000-cell stage) called the dorsal lip of the blastopore into the ventral side of a host embryo (Spemann and Mangold, 1924). The blastopore is the region through which the cells that will form the endoderm and mesoderm layers of the embryo invaginate. The cells that remain on the outside form the third germ layer, the ectoderm. A small grafted dorsal region had a very potent effect on the embryo, dividing the pattern of the whole into two Siamese twins:

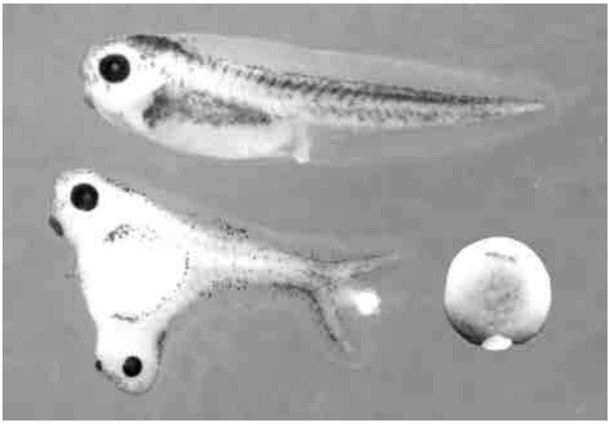

Figure 1. The Spemann experiment: transplantation of a small fragment of dorsal tissue from the dorsal lip can induce twinning. Note the less pigmented grafted tissue in the ventral side of an early Xenopus embryo.

The tissue used by Hilde Mangold for the transplantation was from an unpigmented species of salamander, so that the lineage of the grafted cells could be distinguished from the pigmented host. The transplanted cells differentiated into notochord and induced neighboring cells to differentiate into somite (the embryonic tissue segments that give rise to skeletal muscle, bones and connective tissue of the dermis) and kidney in the mesoderm, and brain and spinal cord in the ectoderm. This was the crucial experiment that demonstrated that during development groups of cells can direct the differentiation of other cells. Spemann called the dorsal lip tissue the "organizing center" of the embryo. His thinking borrowed heavily from physics, which was the dominant science at this time. From electromagnetism he borrowed the term embryonic "induction" to designate the ability of organizer tissue to change cell differentiation and considered that cells in the embryo formed a morphogenetic "field" that was capable of self-regulation.

The organizer experiment represented the highest point of experimental embryology and Spemann received the Nobel Prize for Medicine or Physiology in 1935 for the discovery of embryonic induction. This experiment firmly established that the dorsal side of the embryo had inductive abilities and that organizer tissue played a crucial role in self-regulation. A molecular analysis would have to wait for many decades until gene cloning made molecular embryology a practical possibility. However, a new working hypothesis had been formulated by the Spemann-Mangold experiment: that dorsal organizer tissue secretes signals that induce cell differentiation at a distance.

3.2 Morphogen gradients

Another important advance took place in the 1950s. It was not an experimental advance but rather a theoretical one. Mathematician Alan Turing proposed a simple yet powerful theory to explain the behavior of differentiating biological systems. He suggested that anatomical structure might result from the diffusion of hypothetical substances that he called morphogens. He took the complex embryonic system and rendered it much simpler. Turing realized that simple physico-chemical laws were able to explain many of the facts of embryonic morphogenesis. He imagined that a system of chemical substances capable of reacting with each other and diffusing through a tissue would be able to generate pattern (Turing, 1952). "The systems actually to be considered consist therefore of masses that are not growing, but within which certain substances are reacting chemically, and through which they are diffusing. These substances will be called morphogens, the word being intended to convey the idea of a form producer". The D-V patterning system that was later uncovered in the frog *Xenopus* indeed contained many interacting protein molecules, which are able to diffuse over long distances in the embryo.

The reactions between morphogens depended on their concentration (law of mass action) and on their diffusion according to Fick's law of diffusion in fluid medium. Turing formulated a general partial differential equation to describe quantitatively the changes in concentration of a morphogen (C) over time (δt):

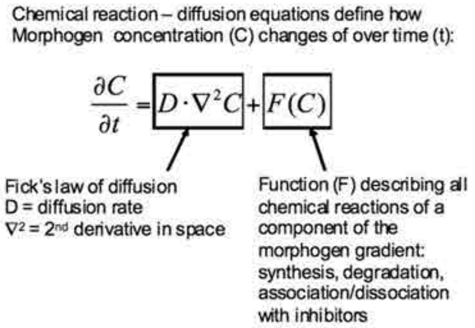

Figure 2. Evolution of morphogen (C) concentration in time and space.

The right side of the equation describes that, following Fick's law of diffusion, the change in concentration of the morphogen (C) is proportional to its diffusion rate (D) and to the second derivative in space of the morphogen concentration (∇^2C). In addition, the change in morphogen concentration is also a function (F) of all the chemical reactions it undergoes (such as synthesis, degradation, and association and dissociation with other proteins such as antagonists). From this initial insight a large number of "reaction-diffusion" computer models to explain the behavior of developing systems have been derived (reviewed in Meinhardt, 2008; Plouhinec and De Robertis, 2009).

A further advance was the realization by Gierer and Meinhardt (1972) that in theory a pair of morphogens composed of an Activator and an Inhibitor originating from the same cells can generate stable patterns:

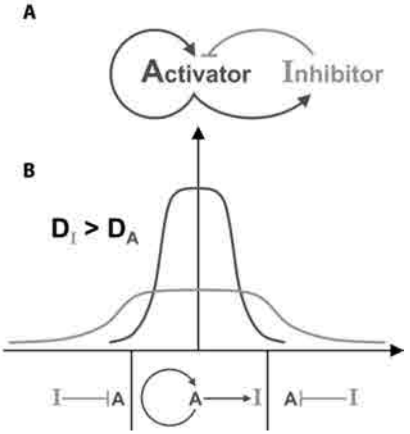

Figure 3. An Activator/Inhibitor pair of interacting morphogens.

The system shown in the figure consists of two diffusible morphogens secreted by the same source. In panel A we see that the Activator turns on its own production and also the synthesis of an Inhibitor that interacts with the Activator. In panel B we see how a field of cells can be patterned into two different zones provided the inhibitor diffuses faster than the activator. Activator (A) and Inhibitor (I) are secreted by the source at the center and turned off by a preponderance of inhibitor in the periphery. Such pairs of Activators and Inhibitors were found decades later to play prominent role in maintaining the dorsal and ventral signaling centers present in the frog embryo.

It is remarkable that these mathematicians could provide a theoretical framework for understanding long-range diffusion-reaction of morphogens at a time when the chemical nature of not even a single morphogen was known. A new working hypothesis was formulated, that morphogens would form gradients of signaling activity that could cause the differentiation of different cell types at different thresholds of activity. Further, these morphogens would be expected to react with each other, an idea that was fully vindicated by work on the D-V patterning system. Respecification of an embryonic morphogen gradient by the organizer graft could explain the amazing Siamese twins observed in the Spemann transplantation experiment.

3.3 A Dorsal-Ventral gradient of BMP signaling controls histotypic differentiation

D-V patterning results from a gradient of activity of a family of secreted growth factors called Bone Morphogenetic Proteins (BMPs). The first correlation between tissue differentiation and BMPs came from the study of *Drosophila* mutations in a gene called *decapentaplegic* (*dpp)*, which is the homolog of vertebrate BMP2/4 (Ferguson and Anderson, 1992). In mammals, BMPs had a long history of being involved in bone differentiation. It was first noted that bone fragments transplanted subcutaneously or intramuscularly in rabbits could induce bone differentiation even after all cells had been killed with ethanol (Levander, 1938). Marshall Urist, an orthopedic surgeon working at the University of California, Los Angeles, found that the proteinaceous bone extracellular matrix, obtained by removing Calcium from bones by soaking them in Hydrochloric acid (HCl) for several days, had potent ectopic bone morphogenetic activity after transplantation into rabbits or rats (Urist, 1965). The active proteins were purified and cloned by a biotechnology company, and found to correspond to growth factors designated BMP2 to BMP7 (Wozney *et al.*, 1988).

Growth factors are proteins that are secreted into the extracellular space, where they bind to surface receptors in other cells, triggering changes in cell signaling. They provide the main mechanism by which cells communicate with each other. BMP2 to BMP7 belong to the larger Transforming Growth Factor-beta (TGF-β) family of growth factors, which consists of 30 different genes in humans. Although first discovered because of their bone morphogenetic properties in mammals, BMPs play a central role in D-V embryonic patterning.

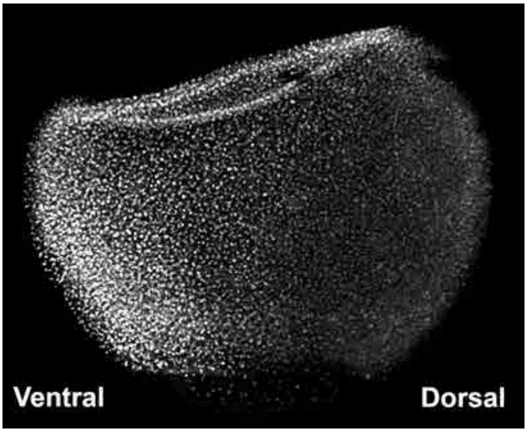

Figure 4. D-V gradient of BMP signaling revealed by phospho-Smad1 in Xenopus.

In zebrafish and *Xenopus* embryos it is possible to visualize the gradient of BMP signaling activity. This is done indirectly, by staining whole-mount embryos with an antibody specifically directed against the phosphorylated form of the Smad1 transcription factor. In Figure 4 one can see that BMP activity is lowest on the dorsal side and gradually increases towards the ventral side, in which the cell nuclei accumulate higher amounts of phospho-Smad1.

BMPs (or other members of the TGF-β superfamily) bind to two receptors on the cell surface, which become activated. The BMP receptors are transmembrane proteins containing a cytoplasmic enzymatic domain able to phosphorylate hydroxyl groups of Serine or Threonine amino acids in proteins. Their main target is a transcription factor called Smad1, which becomes phosphorylated at its carboxy-terminal end. Phospho-Smad1 (pSmad1) binds a second protein called Smad4 (also known as Deleted in Pancreatic Carcinoma). These two proteins together translocate inside the nucleus where they bind to DNA. Smad1/4 do not have a very high DNA-binding affinity and therefore require additional partner transcription factors bound to nearby DNA sites in order to activate or repress gene activity

(Massagué, 2000). BMP/TGF-β can activate different genes in different germ layers because these differ in the types of partner transcription factors they contain, according to their previous developmental history. This process, by which a protein bound to the outside membrane of the cell can change the activity of genes in the nucleus, is called signal transduction.

3.4 Cloning the Spemann organizer genes

When molecular biology, the great equalizer of modern biology, became practical the search for the signals produced by the dorsal organizer tissue that mediate embryonic induction was on. In our laboratory a gene library from manually-dissected dorsal blastopore lips from *Xenopus* was prepared. We succeeded in isolating a homeobox gene designated *goosecoid* (Cho *et al.*, 1991). This gene allowed us to visualize Spemann's organizer using *in situ* hybridizations to its mRNA. Previously, the existence of organizer tissue had to be deduced from its effects after transplantation experiments.

Overexpression of *goosecoid* mRNA was able to induce twinned axes. However, *goosecoid* encodes an intracellular DNA-binding protein and we knew from Spemann's experiments that the factors responsible for embryonic induction had to be diffusible over long distances. This suggested the hypothesis that *goosecoid* might activate the synthesis of secreted proteins.

In 1994 we were able to isolate *chordin*, a gene activated by *goosecoid* from our *Xenopus* organizer library (Sasai *et al.*, 1994). Richard Harland had also isolated *noggin* (Smith and Harland, 1992) and Douglas Melton *follistatin* (Hemmati-Brivanlou *et al.*, 1994). It was later found that all three gene products were able to inhibit BMP signaling (Sasai *et al.*, 1995). The dorsal side of the gastrula embryo secretes BMP antagonists and the ventral side BMP4 and BMP7:

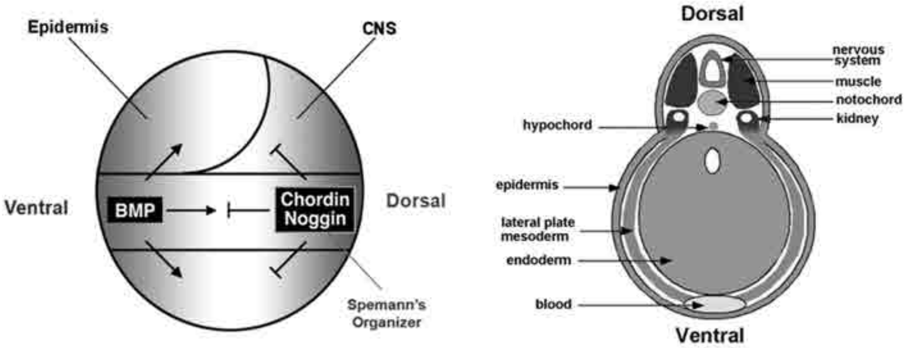

Figure 5. BMP antagonism patterns the three germ layers, leading to the stereotypical arrangement of tissue differentiation in the vertebrates.

Our initial hypothesis was that dorsal tissue would be the source of novel growth factors. Spemann's organizer proved a fertile fishing ground for new molecules, but what was found instead was that it secreted a large number of secreted growth factor inhibitors (reviewed in De Robertis and Kuroda, 2004).

Curiously, BMP signaling levels were able to regulate cell differentiation in the ectoderm, mesoderm and endoderm layers simultaneously. Explants of future ectoderm (cells from the animal cap of the embryo) differentiate into CNS at low BMP levels (*e.g.*, in the presence of BMP antagonists) and into epidermis when BMP signaling levels are high. Similarly, in the mesoderm low BMP gives rise to notochord (a flexible rod used by chordate embryos for swimming), at slightly higher levels skeletal muscle (arranged in repeated segmental structures called somites), then kidney (each embryonic segment develops a kidney tubule), then lateral plate (which gives rise to the body wall) and at the highest BMP levels blood islands (Figure 5). These tissues represent the invariant body plan shared by all vertebrates. This then raises the question of how many morphogen gradients exist. Is there one gradient per germ layer? How would each gradient be regulated coordinately so that a perfectly harmonious embryo is formed?

The embryo has only one chance to allocate these tissues perfectly so it is not surprising that the BMP gradient is tightly regulated. While there are many growth factor antagonists secreted by Spemann's organizer cells, Chordin proved the most informative for the regulation of the D-V signaling gradient; it was at the heart of the organizer phenomenon.

3.5 Chordin regulates the D-V BMP gradient

When Chordin is microinjected into a ventral cell (in the form of synthetic mRNA prepared in the test tube) it recapitulates the organizer experiment, forming a second neural tube, somites and even a second gut cavity. Chordin can be depleted in *Xenopus* embryos using microinjected Morpholino oligos (MO). These antisense reagents (which resemble RNA but have a morpholine ring replacing the ribose, so they not degraded easily by cellular enzymes) hybridize to mRNA and prevent its translation into protein. Depletion of Chordin produced embryos that developed with smaller heads and dorsal tissues and enlarged ventral structures. However, an embryonic axis was still formed. Later, Harland found that the combined depletion of Chordin, Noggin and Follistatin led to a catastrophic loss of all dorsal tissues (Khokha *et al.*, 2005). Similarly, in the mouse double knockout of Chordin and Noggin the forebrain, midbrain and notochord and are lost (Bachiller *et al.*, 2000). Thus, the BMP antagonists secreted by organizer tissue are able to compensate for each other.

Chordin is absolutely essential for the activity of Spemann organizer grafts. An organizer transplanted to the ventral side of the gastrula invaginates inside the embryo, inducing new dorsal tissues. This is particularly clear when a pigmented graft is placed in an albino embryo. When the organizer was depleted of Chordin it remained as a patch of epidermis that was completely devoid of inducing activity (Oelgeschlager *et al.*, 2003). Transplantation is a very powerful tool in biology. In this case, when dorsal cells were challenged by placing them in a new ventral surrounding their diminished biological capacity due to the loss of the Chordin gene product was strikingly revealed.

3.6 Chordin is used throughout the animal kingdom

We realized that Chordin had to be a very important molecule very early on. A gene of similar sequence was cloned in the fruit fly *Drosophila* called *short gastrulation* (*sog*). We collaborated with F. Michael Hoffman and Edwin "Chip" Ferguson to show that microinjected *chordin* and *sog* mRNA induced neural tissue both in *Drosophila* and frog embryos (Holley *et al.*, 1995). This led to the realization that we had discovered an ancient molecule that had been conserved in evolution between fly and amphibian embryos.

Extensive genetic screens in the zebrafish *Danio rerio* by Christiane Nüsslein-Volhard supported the discoveries from our work in *Xenopus* described below. In a satisfying convergence, zebrafish loss-of-function mutations that affected the allocation of dorsal-ventral tissues were found to affect genes in the Chordin pathway. Loss-of-function mutations that increased ventral tissues eventually corresponded to Chordin and Sizzled, and mutations increasing dorsal tissues corresponded to BMP7, BMP2b, a BMP receptor, Smad5 and Tolloid (Little and Mullins, 2006).

These genetic findings greatly increased confidence that we had uncovered a patterning mechanism that was generally applicable across animal embryos. Importantly, the effects of *sog* mutations were known to be enhanced when the number of *dpp*/BMP4 genes was increased in *Drosophila* (Ferguson and Anderson, 1992). This led us to the new hypothesis that Chordin and BMPs worked on a common signaling pathway.

3.7 Chordin is part of a biochemical pathway

Chordin mRNA is expressed at high levels in dorsal cells in the exact region that has inducing activity after transplantation. We measured the amount of Chordin secreted by the frog embryo during gastrulation and found that it is produced in prodigious amounts. If distributed uniformly in the extracellular space, Chordin protein would reach concentrations of 33 nanomolar (nM). In the dorsal side, where it is produced, Chordin must reach much higher extracellular concentrations. BMP concentrations have not been measured in embryos, but in other tissues they are in the picomolar (pM) range. Thus, a vast excess of Chordin exists during early development.

Since Chordin is a BMP antagonist, in principle its localized expression in the dorsal side could be sufficient to account for the BMP signaling gradient, even if BMP expression were uniform. However, our investigations discovered that Chordin is part of a biochemical network of extracellular proteins that encompasses the entire embryo. It gradually became clear that the organizer effect is not due only to the action of the dorsal side but also to the reaction of ventral cells.

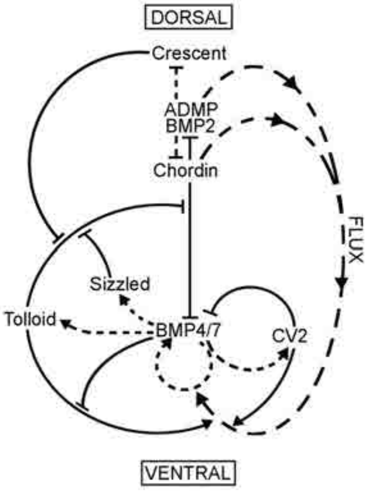

Figure 6. The extracellular biochemical network of interacting proteins that explains self-regulation of D-V patterning.

We found that several secreted proteins are synthesized by the same cellular sources. The embryo has a dorsal and a ventral center that communicate through secreted proteins that interact with each other (indicated by solid lines). Dorsal genes are expressed when BMP levels are low, while ventral genes are expressed when BMP levels are high (transcriptional activity is indicated by lines with short stipples). The two centers adapt to changes in signaling because all the components of the system are under opposing transcriptional control by BMP. The long stippled arrows indicate the flux or flow of Chordin bound to dorsal BMPs, BMP2 and ADMP, towards the ventral side (ADMP stands for anti-dorsalizing morphogenetic protein, Moos *et al.*, 1995). The function of each of the extracellular proteins of this pathway was determined by a combination of biochemical and embryological experiments, as explained below.

3.8 Chordin is a BMP antagonist regulated by a metalloproteinase

Chordin encodes a large protein containing four Cysteine-rich (CR) domains that serve as BMP-binding modules. It has a cofactor called Twisted gastrulation (Tsg) that helps keep BMPs soluble and binds to both Chordin and BMPs. The ternary complex of Chordin, BMPs and Tsg prevents binding of BMPs to BMP receptors on the cell surface and in this way inhibits BMP signaling.

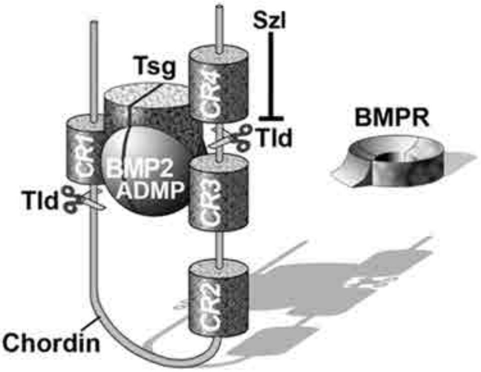

Figure 7. The ternary complex of Chordin (Chd), BMP4 and Tsg inhibits binding to BMP receptor (BMPR).

Purified Chordin binds BMPs with an affinity (dissociation constant, K_D) in the low nM range (Piccolo *et al.*, 1996). However, the inhibitory action of Chordin is not permanent and can be reversed by metalloproteinases of the Tolloid family. Tolloid was identified in classical *Drosophila* genetic screens (Wieschaus and Nüsslein-Volhard, 1980) as a gene that increased Dpp/BMP signaling. In collaboration with Leslie Dale, we showed that the metalloproteinase Xolloid-related (indicated as Tld and represented by scissors in Figure 7) was able to cleave Chordin at two precise sites. When this happens, the affinity of the cleaved Chordin for BMP decreases precipitously and the complex of BMP and Tsg is able to bind to BMP receptors, restoring signaling (Piccolo *et al.*, 1997). Because Tolloid/Xlr is expressed in the ventral side, it serves as a ventral sink that degrades Chordin originating from Spemann's organizer, allowing the flux of BMPs from more dorsal regions to the ventral side in which BMP signaling is maximal. Activity of the Tolloid protease is the rate-limiting step in D-V patterning and is subjected to stringent regulation.

3.9 Sizzled and Crescent are inhibitors of Tolloid activity

Sizzled is a ventral center molecule that is expressed at high BMP signaling levels (Collavin and Kirschner, 2003). In zebrafish the Sizzled mutation (called *ogon/mercedes*) had a phenotype intriguingly similar to that of Chordin mutants (Yabe *et al.*, 2003). We microinjected *sizzled* mRNA into dorsal or ventral half-embryos in *Xenopus* and noted that it had strong dorsalizing effects on dorsal fragments (expansion of the CNS) but none at all in ventral fragments. Thus, *sizzled* function required a dorsal component, giving rise to the idea that it might inhibit the degradation of Chordin by Tolloid.

Sizzled encodes a secreted Frizzled-related protein (sFRP). This class of protein is normally involved in inhibiting Wnt signaling. However, in the case of Sizzled the protein has evolved so that it is able to bind to the Tolloid proteolytic site, but is unable to be cleaved by this enzyme. In this way, Sizzled acts as a competitive inhibitor of Tolloid. Like most components in the pathway shown in Figure 6, the Sizzled/Tolloid binding has an affinity in the 20 nM range (Lee *et al.*, 2006).

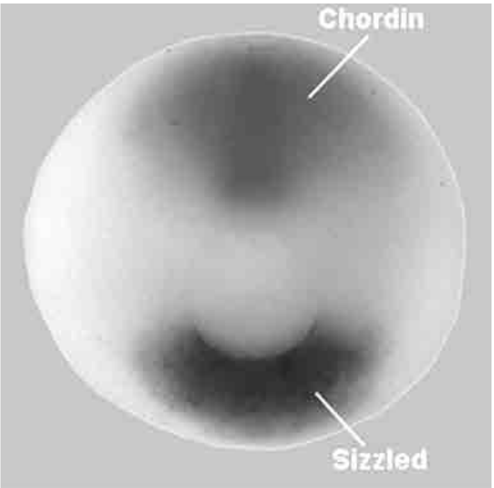

Figure 8. Sizzled is expressed in the ventral side and Chordin in the dorsal organizer at the circular blastopore stage (the blastopore will later become the anus).

Sizzled depletion by antisense morpholinos results in the same phenotype as Chordin loss-of-function, because in its absence the activity of Tolloid increases and Chordin is degraded. When overexpressed Sizzled has an anti-BMP effect because it inhibits Tolloid, causing the accumulation of Chordin. The increase in Chordin levels then inhibits BMP signaling. On the dorsal side of the embryo, a protein structurally related to Sizzled called Crescent also serves as a Tolloid inhibitor, but under the opposite transcriptional regulation (Figure 6; Ploper *et al.*, 2011).

Sizzled acts as a feedback inhibitor of Tolloid and is expressed in copious amounts in the *Xenopus* embryo. Like Chordin, it would be present at concentrations of 30 nM if distributed uniformly in the extracellular space (Lee *et al.*, 2006). Tolloid and Sizzled behave as an Activator/Inhibitor pair in the sense described in Figure 3. Tolloid will activate its own synthesis by increasing BMP signaling, while Sizzled will inhibit Tolloid activity competitively.

Tolloid activity is also regulated by direct binding of BMP to protein domains outside its catalytic region. If BMP levels become high it binds to domains in Tolloid called CUB domains, inhibiting enzyme activity in a non-competitive fashion (Lee *et al.*, 2009). This new negative feedback loop provided a molecular explanation for an old mystery in the field. When the first peptide sequences were obtained from extracts with bone-inducing activity (Wozney *et al.*, 1988) the first protein identified, designated BMP1, had the sequence of a Tolloid enzyme containing three CUB domains. The reason why BMP1 was purified together with the BMP2 to 7 growth factors was simple: Tolloids are BMP-binding proteins. In conclusion, Tolloid activity is highly regulated and plays a key role in the communication between the dorsal and ventral sides of the embryo.

3.10 Crossveinless 2 concentrates Chordin/BMP complexes in the ventral side

Another component of the Chordin/BMP pathway is Crossveinless 2 (CV2). We first identified it by searching sequencing databases for vertebrate genes that contained CR domains similar to the BMP-binding modules of Chordin. Once the complete sequence was obtained, it became clear that it was homologous to a gene previously described in *Drosophila* called *Crossveinless 2* (Conley *et al.*, 2000). In the fly wing, CV2 is required to reach the maximal BMP signaling required for formation of cross vein structures. Like Chordin, overexpressed CV2 can act as a BMP antagonist through its BMP-binding modules. CV2 expression is activated by high BMP levels and is therefore produced in the ventral center. When one depletes Chordin, CV2 expression increases, compensating for the loss of

Chordin from the opposite side of the embryo. When both Chordin and CV2 are depleted, ventral tissues are greatly expanded (Ambrosio *et al.*, 2008). One difference with Chordin is that CV2, although it is a secreted protein, is not able to diffuse through the extracellular space because it remains anchored by glycosylated proteins (called glypicans) to the surface of the cells that secrete it (Serpe *et al.*, 2008).

Why does CV2 have pro-BMP effects in *Drosophila* wing? We addressed this by asking whether CV2 interacted with other components of the D-V patterning system. Using a biochemical approach we found that CV2 has a second activity. It binds with considerable affinity (dissociation constant 1.4 nM) to Chordin and with even higher affinity to Chordin/BMP complexes. In the frog embryo, CV2 acts as a molecular sink concentrating Chordin/BMP complexes in the ventral side. Once there, Tolloid proteases can cleave Chordin, allowing BMP to signal through its receptors. In this way BMP signaling is boosted on the ventral side by the combined action of CV2 and Tolloid, which facilitate the flux of BMPs produced in more dorsal regions of the embryo and transported by Chordin.

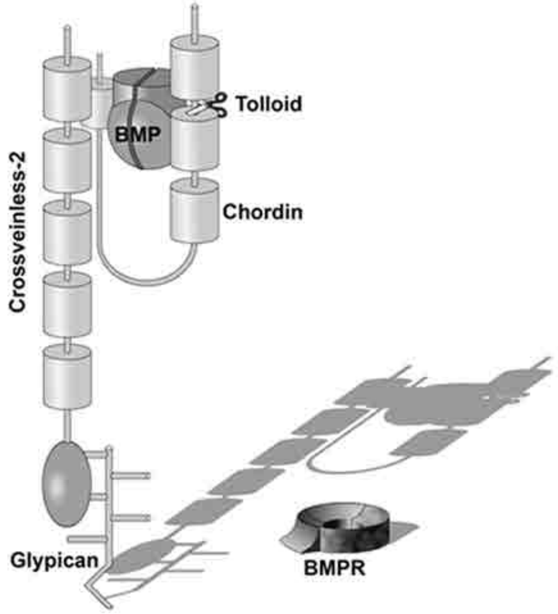

Figure 9. Crossveinless 2 (CV2) serves as a molecular sink that concentrates Chordin/BMP complexes on the ventral side, where BMPs are then released by cleavage of Chordin by Tolloid. CV2 does not diffuse far from the cells where it is produced because it binds to glypicans on the cell surface.

Starting with the isolation of Chordin we were able to identify, one at the time, multiple components that react molecularly in this morphogenetic pathway that comprises the entire embryo. At the stage being studied, the embryo is composed of 10,000 cells, raising the question of how the information in the dorsal and ventral centers is transmitted long range to produce a self-regulating morphogen gradient. We address this next.

3.11 Opposite transcriptional regulation of D-V molecules is the key to self-regulation

The dorsal and ventral centers are under opposite transcriptional control by the BMP signaling pathway. Dorsal center molecules are produced when BMP levels are low while ventral molecules are secreted when BMP signaling is high (Figure 6, stippled arrows). Interestingly, the dorsal and ventral poles of the embryo express proteins of similar biochemical activities but under the opposite regulation.

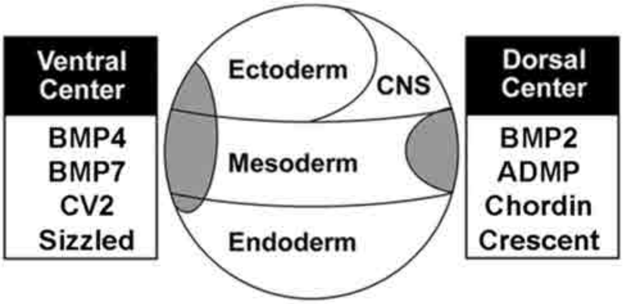

Figure 10. Proteins of similar structure and function in the ventral and dorsal sides, but under opposite transcriptional control.

The dorsal side produces BMP2 and ADMP, while the ventral side secretes BMP4 and BMP7. All have similar activities, activating BMP receptors that phosphorylate Smad1. Chordin is secreted by Spemann's organizer while on the ventral side CV2, which contains similar BMP-binding modules, is produced. Similarly, the ventral center secretes Sizzled and the dorsal side the closely related molecule Crescent. These molecules can compensate for each other from different poles of the embryo. For each action of Spemann's organizer there is a reaction in the ventral side of the embryo.

The self-adjusting nature of this system is illustrated by an experiment in which the cavity of blastula embryos (called the blastocoele) was injected with Chordin protein to decrease BMP signaling or with BMP4 protein to increase signaling. When BMP levels were decreased, expression of ADMP mRNA went up, increasing BMP signaling. When BMP4 was injected, Sizzled transcription went up, indirectly dampening BMP signaling levels (via the inhibition of Tolloid, causing an increase in Chordin that antagonizes BMP). The embryo behaves as a molecular seesaw, forming a self-adjusting BMP gradient (Reversade and De Robertis, 2005).

3.12 BMPs and self-regulation

The *Xenopus* embryo expresses four main BMPs: ADMP, BMP2, BMP4 and BMP7. When we depleted embryos of BMP2, 4 and 7, we found that ventral half-embryos differentiated profuse amounts of dorsal tissues such as CNS, but dorsal half-embryos scaled to an almost normal embryonic pattern. This suggested that the organizer, which is the region of lowest BMP signaling, also contained a ventralizing signal.

This led us to formulate the hypothesis that ADMP was produced on the dorsal side but its activity blocked by the presence of Chordin secreted by the same cells. Indeed, when the four BMPs were depleted a spectacular transformation was observed, in which the entire ectoderm of the embryo became converted into CNS tissue (Reversade and De Robertis, 2005). Embryos were pear-shaped (radial) and covered mostly by forebrain, with a small amount of spinal cord near the blastopore.

The availability of these radial embryos covered in neural tissue gave us a new experimental opportunity. Would wild-type tissue be able to secrete BMPs in sufficient amounts to restore epidermal differentiation at a distance? Transplanted ventral tissue was able to restore D-V pattern and epidermal differentiation, making the important point that a long-distance ventral signaling center exists. An even more interesting result was obtained by transplanting lineage-traced wild type dorsal grafts into BMP depleted embryos. The grafted gave rise to notochord and restored D-V patterning. Epidermis was formed in embryos that otherwise would have developed only neural tissue in the ectoderm. Importantly, there was no epidermal induction near the dorsal graft, which was the only source of BMP in these embryos. Epidermis differentiated on the ventral side at a great distance from the transplant. This suggested that ADMP and BMP2 from the organizer grafts diffused, presumably bound to Chordin and unable to signal, and were released for signaling when Chordin is cleaved by Tolloid enzyme in the ventral side (Reversade and De Robertis, 2005). This was our best, although indirect, evidence for long-distance flux of morphogens in *Xenopus* for many years.

3.13 Chordin forms a gradient in the space that separates ectoderm from endomesoderm

We have recently been able to visualize Chordin protein by immunohistochemistry in the *Xenopus* gastrula. This required technical improvements since amphibian embryos have autofluorescent yolk particles. Chordin mRNA is produced in 60° of the arc of the dorsal side. However, Chordin protein was present as a gradient extending from the dorsal side to the ventral-most part of the embryo. The staining was specific because it was eliminated by depletion of Chordin. The unexpected surprise was that Chordin does not diffuse randomly in the space between cells but instead is found specifically in the extracellular space that separates the ectoderm from the endomesoderm.

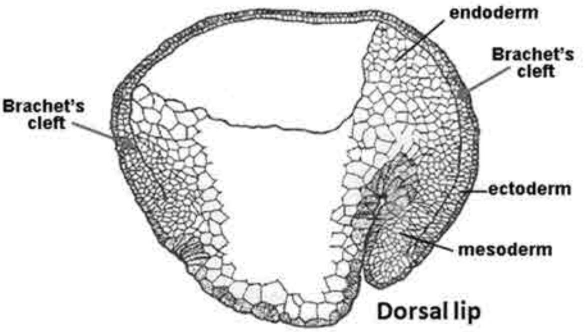

Figure 11. Brachet's cleft separates ectoderm and endomesoderm (modified from Nieuwkoop and Florschütz, 1950).

In amphibian embryos this virtual cavity is called Brachet's cleft (in honor of Albert Brachet, the distinguished Belgian embryologist). All vertebrate embryos have an extracellular matrix containing Fibronectin and other proteins separating ectoderm and mesoderm. Therefore, Brachet's cleft is not an amphibian-specific structure. Confocal optical sections revealed a smooth gradient of Chordin extending from the organizer to the ventral side through this space. From Brachet's cleft Chordin protein can be seen diffusing into both the ectoderm and the mesoderm. Within this narrow cleft, Chordin behaves as predicted by our biochemical pathway. For example, when Tolloids are depleted with antisense morpholinos nuclear phospho-Smad1 (a measure of BMP signaling) decreases while Chordin protein accumulates to high levels in Brachet's cleft. This increase in Chordin protein is particularly obvious in the ventral cleft. These experiments directly demonstrate the long-range diffusion of the Chordin morphogen in the gastrula embryo.

It appears that the embryo has a single gradient of Chordin that can pattern all three germ layers at the gastrula stage. This provides a simple solution to the question of how many BMP gradients exist: only one. As mentioned above, Chordin reaches high concentrations in the embryo. The fact that it diffuses through a narrow region suggests that Chordin, and probably other components of the D-V patterning pathway, must reach very high concentrations in the space between ectoderm and endomesoderm. During gastrulation the germ layers undergo extensive morphogenetic movements; it is possible that cells might read the Chordin/BMP gradient contained in this extracellular matrix as they move along its surface.

The most intriguing property of the D-V patterning system is its ability to self-regulate. The ability to visualize gradients allowed us to examine embryos bisected in D-V fragments (unpublished results). A phospho-Smad1 gradient was re-formed on dorsal halves, while in the ventral half, where BMP signaling is not opposed by antagonists, very high uniform levels of BMP signaling were found. Using Chordin antibodies, the Chordin gradient in Brachet's cleft was re-formed in dorsal halves, but not in ventral ones. Thus, the BMP/Chordin gradient is able to rescale pattern after experimental perturbation of the system, opening new opportunities for investigating the mechanisms of D-V cell differentiation.

Conclusions

The considerable complexity of the D-V patterning biochemical pathway was deciphered using the hypothesis-driven experimental approach outlined by Claude Bernard (1865). The investigator formulates an idea in his mind, reasons an experiment that might prove it or disprove it, allows the experiment to give an objective answer, and finally designs new hypotheses based on the observed results. Embryologists were always fascinated with the self-regulating properties of embryos. Spemann found that dorsal organizer tissue could induce cell differentiation over long distances. Mathematicians proposed that the long range diffusion of morphogens according to the laws of physics could account for biological phenomena and proposed that morphogens reacting with each other could generate stable patterns provided they arise from the same source and have different diffusion rates.

With the background of these hypotheses, a large number of extracellular proteins that mediate the dorsal-ventral pattern were isolated from the frog embryo. Key supporting insights came from *Drosophila* and zebrafish genetics. Using a combination of biochemistry with purified proteins and embryological studies involving the simultaneous depletion of multiple gene products with morpholinos in combination with transplantation experiments, it was possible to construct the biochemical pathway shown in Figure 6. All its components are secreted proteins that are able to directly interact with each other, forming negative feedback loops of activators and inhibitors synthesized by cells in the dorsal and ventral poles of the embryo.

Dorsal genes are expressed when BMP signaling is low and ventral genes when it is high. The genes that are turned on and off also interact with each other at the protein level. The D-V gradient is adjusted redundantly by regulating the synthesis of its components, by direct protein-protein interactions between morphogens, and by diffusion. The entire embryo participates in maintaining the D-V BMP gradient, so that for each action in the dorsal side there is a reaction in the ventral side. The dorsal and ventral centers are able to communicate with each other through the flux of Chordin, a protein that transports BMPs ventrally, and through the metalloproteinase Tolloid that cleaves Chordin. A gradient of Chordin is formed in the extracellular matrix that separates ectoderm from endomesoderm. It appears likely that a single gradient of Chordin/BMP provides patterning information for all germ layers. The Chordin/BMP pathway is self-regulating and able to scale to a perfect pattern in the dorsal half of bisected embryos. These findings illustrate how the complexity of an embryonic self-regulating system can be unraveled one gene at a time while keeping in mind the behavior of the whole system.

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LIFE'S BIOCHEMICAL COMPLEXITY

RAFAEL VICUÑA

> *"In vain we force the living into this or that one of our moulds... Our reasoning, so sure of itself among things inert, feels ill at ease on this new ground".*
> Henri Bergson, Creative Evolution.

Introduction

Since our childhood we have been able to sense that the world that surrounds us comprises living things and inert objects, which usually differ from each other by qualities that seem easily recognisable. Thus, we can distinguish that a plant, a fish or an insect belong to the first group of entities, while any liquid substance, air, stone or machine belong to the second.

Biology, with its numerous subdivisions (ecology, physiology, genetics, biochemistry, etc.) is the science that studies living beings. Despite the extraordinary advances of this science in both basic and applied (biotechnology), it is paradoxical that the efforts of biologists to reach a formal definition of life have proved unsuccessful.[1]

This issue does not only have intrinsic intellectual or academic interest. Astrobiology, which is the science that studies the existence and evolution of life in the universe, requires certain criteria, if the opportunity ever arose, to be able to conclude that life has been found on a celestial body other than earth. Furthermore, there have been attempts by synthetic biology to obtain life *de novo* in the laboratory. What qualities should an entity fabricated by scientists possess so that we would consider it to be alive? Finally, if we concurred that the origin of life on earth did not come about suddenly by a fortuitous coincidence of numerous environmental conditions, but that it happened gradually, would we all unequivocally agree to distinguish at what point during these successive stages life began?

Efforts made from other natural sciences to define life, such as in physics or chemistry, have also proven unsuccessful. The difficulty undoubtedly stems from the fact that life is a complex phenomenon that transcends the

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[1] There are at least five books with the title "What is life?" and none of them seem to have given a satisfactory answer to this question: Erwin Schrödinger, Cambridge University Press, 1967; Ed Regis. Farrar, Straus and Giroux, New York, 2008; Lynn Margulis and Dorian Sagan. University of California Press, Berkeley and Los Angeles, 1995; Joseph Seifert. Rodopi, Amsterdam and Atlanta, 1997; P.H. Pinter. Arima Publishing, ASK House, UK, 2006.

scope of individual disciplines and cannot be explained on the basis of its component material parts.

This complexity of life is manifested in various ways. In terms of the molecular components of each cell, the minimal structural and functional unit of all living things, a hierarchical arrangement is observed: monomers, polymers, supramolecular structures, organelles and the external membrane. The resulting cellular architecture shows a remarkable stability despite the constant turnover of the molecular constituents. At the same time, there is an intricate network of interactions among these components, with multiple connections and feedback controls. These include those that occur in the domains of the metabolic pathways and of the genetic material, as well as those that are established between both domains. Just as the structure is hierarchical, the level of organisation is also hierarchical.[2] Thus, within the cell, there are simple networks that are the basis of other more elaborate ones.[3] There are also interactive networks among cells in a colony of microorganisms or those in a multicellular organism and ultimately, among all organisms that make up an ecosystem. Finally, life is also complex in its expansion, a characteristic that is reflected in its dynamic evolution, in its niche construction ability and in processes such as cell differentiation and morphological development.

In search of a definition

Faced with this difficult scenario, researchers have adopted different strategies to agree on a definition of life. One of these has been to distinguish its most distinctive characteristics, such as nutrition, homeostasis, irritability, etc. To Claude Bernard, for example, these qualities are organisation, generation, nutrition, embryonic development and disease or death.[4] The problem is that there are always situations that do not seem to satisfy one or more of these requirements. Could we say that a mule is not a living being because it is incapable of reproducing? There are also the typical borderline cases, such as viruses, frozen bacteria, spores and dormant seeds. More recently, Daniel E. Koshland described the seven essential pillars

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[2] Bairns, W. The parts of life. *Nature Biotechnol.* 19, 401-402, 2001.

[3] There are authors, however, that argue that the idea of organisational hierarchy should not be applied to living beings given that the components are self-produced by organisms themselves in a closed system of metabolic reactions. See for example Letelier, J.C., Cárdenas, M.L., Cornish-Bowden, A. From l'homme machine to metabolic closure: Steps towards understanding life. *J. Theor. Biol.* 286, 100-113, 2011.

[4] Bernard, C. *Phenomena of life common to animals and plants*. Trans. R.P. Cook and M.A. Cook. Dundee, Cook & Cook, 1974.

of life, which are worth mentioning given the great prestige attained by this scientist: these are programme, seclusion, energy, improvisation, regeneration, compartmentalisation and adaptability.[5] However, Koshland's proposition did not receive much consideration. According to Franklin Harold, on the other hand, there are four criteria that would allow life to be distinguished anywhere in the universe: flow of matter and energy, reproduction, organisation and adaptation by random variation and natural selection.[6] In turn, for Michael Morange there are only three pillars: a high molecular complexity, a system of very specific chemical reactions in which an exchange of matter and energy is produced with the environment, and reproduction.[7] But as Morange himself has pointed out, the strategy to describe the distinctive qualities of life is only partially correct, since instead, the real issue is how they emerged and became integrated within organisms.[8] Another drawback of this approach is that some statements are not simple to prove, or are in fact unprovable. For example, the most widespread definition of life is the one proposed by Gerald Joyce now almost two decades ago[9] and which was later adopted by NASA for its astrobiology programme: "Life is a self-sustaining chemical system capable of undergoing Darwinian evolution". How long would it take a probe sent to another planet to confirm these qualities?

A second strategy bypasses the problem by offering definitions from different perspectives: physiological, metabolic, biochemical, thermodynamical, etc. Initially proposed by Carl Sagan, this is what has been adopted by, among others, the prestigious *Encyclopaedia Britannica*. It also seems to be a valid option, although as long as these different approaches are not integrated in one overall vision, it will remain incomplete.

A third strategy has favoured a systemic approach that sees life as a process. According to the concept of autopoiesis, originally enunciated by Humberto Maturana and Francisco Varela, living things consist of a network of processes of production, in which the function of each component is to participate in the production or transformation of the other components in the network, including the production of an external limit that specifies

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[5] Koshland, D.E. The seven pillars of life. *Science* 295, 2215-2216, 2002.

[6] Harold, F. *The way of the cell. Molecules, organisms and the order of life*. Oxford University Press, New York, 2001.

[7] Morange, M. *Life explained*. Yale University Press 2008.

[8] Tirard, S., Morange, M., Lazcano, A. The definition of life: A brief history of an elusive endeavor. *Astrobiology* 10, 1003-1009, 2010.

[9] Joyce, G.F. Foreword in *The origin of life: The central concepts*, eds. D.W. Deamer & G. Fleischaker. Jones and Bartlett, Boston, 1994.

the domain of the autopoietic organisation.[10] This definition, probably inspired by another previous proposal by J. Perret and J.D. Bernal,[11] points to a very particular aspect of life: its immanent action. In the words of Robert Rosen, organisms themselves are their own efficient cause.[12] However, for many, the autopoietic approach is not sufficient since it leaves out an aspect essential to life such as its ability to undergo Darwinian evolution.[13] That is why Franklin Harold proposes to combine both qualities in one single statement: "living organisms are autopoietic systems capable of evolution by natural selection".[14] Being very similar to the definition adopted by NASA, it has not prevailed among the scientific community.

Interestingly, the previous difficulties have not been an obstacle for the vertiginous progress of the diverse branches of biology, as has been the case for molecular genetics, bioinformatics and neurobiology, to name but a few. We have come to know in great detail intricate processes such as the replication and expression of genetic material, protein synthesis, signal transduction, cellular transport, etc., but reaching a distinctive understanding of what life exactly is remains elusive. By the middle of the last century, Max Delbrück had stated that "biology is a very interesting field to enter for anyone, by the vastness of its structure and the extraordinary variety of strange facts it has collected. But to the physicist, biology is also a depressing subject, because, insofar as physical explanations of seemingly physical phenomena go, like excitation, or chromosome movements, or replication, the analysis seems to have stalled around in a semi-descriptive manner without noticeably progressing towards a radical physical explanation".[15] Subsequent testimony such as that of Franklin Harold ("life is fundamentally a mystery"),[14] Wendel Berry ("life is a miracle")[16] and Erwin Chargaff ("life is the con-

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[10] Maturana, H. and Varela, F.J. *De Machines and living things – A theory of biological organisation*. Editorial Universitaria, Santiago, Chile, 1973.

[11] J. Perret had defined life as a system of organic reactions that was self-perpetuating, sequentially catalyzed, almost isothermically, by complex and specific organic catalysts that are themselves produced by the same system (*New Biol.* 12, 68 1952), assertion reiterated by J.D. Bernal in 1965.

[12] Cfr ref. 3.

[13] See ref. 3 for a recent and very complete discussion of the diverse approaches that life has received as to what constitutes a closed-circuit reaction.

[14] Harold, F.M. Postcript to Schrödinger: So what is life? *ASM News* 67, 611-616, 2001.

[15] Delbrück, M. A physicist looks at biology. *Trans. Connect. Acad. Arts Sci.* 38, 173-190, 1949.

[16] Berry, W. *Life is a miracle*. Counterpoint, Washington, 2001.

tinuing intervention of the inexplicable")[17] appear to give an eloquent testimony of this situation. The laws of natural science, which are applicable to life, seem insufficient to explain it fully.

Different approaches to the understanding of life

There are two main perspectives to address the phenomenon of life. One of these, with a mechanistic or reductionist orientation, is well illustrated by the words of Francis Crick: "The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry".[18] In his classic work, *What is life*, Schrödinger stated that new laws could possibly be needed to explain life, but always in the field of physics. Consequently, representatives of this view see the functioning of an organism as a machine. The mechanisms that operate both are equivalent.

The reductionist approach has been extraordinarily successful regarding the generation of new knowledge, though always relative to localised or partial phenomena. The situation becomes complicated when attempting to establish a linear causality between these and the behaviour of the cell or the entire organism. Molecular genetics itself, which originally appeared so promising to this deterministic vision, has been the source of findings that, instead of facilitating this task, are making it more arduous. By way of example, one can mention (among others) RNA splicing, RNA editing, prions, genetic redundancy, epigenetics, pleiotropy and the fascinating new scenario displayed by the various types of non-protein coding RNAs. Today we know the complete genome sequences of many organisms but we don't know how genomes sharing a high degree of homology can give rise to very different organisms. On the other hand, establishing the relationship between genotype and phenotype is also proving very difficult. To the well-known c-value paradox, which shows a profound lack of correlation between the amount of genetic material and the complexity of organisms, the g-value paradox has been added, which surprisingly shows no correlation either with the number of genes that their genomes possess. A recent study of the systemic inactivation of genes in two virtually identical yeast strains, showed that out of the 5,100 genes analysed, just over 900 are essential. But apart from the latter, the same work revealed that a few dozen genes were only essential for one strain or the other, an unexpected result

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[17] Chargaff, E., in *Heraclitean fire: Sketches from a life before Nature*. Seabury, New York, 1977.

[18] Crick, F.H. *Of molecules and man*. University of Washington Press, Seattle, USA, 1966.

given their high sequence identity.[19] Results like these help to explain why finding the genetic causes of diseases that affect humans is so problematical. However, it gives the impression that these difficulties are not so relevant for the materialistic view, since after all, its supporters do not see a radical difference between living things and inert bodies. Life only represents an intricate shape of the motion of matter and therefore there is no reason to treat it like a phenomenon that transcends the laws of physical chemistry. Recently, an editorial in the journal *Nature* stated "there is a popular belief that life is something that appears when one crosses a threshold. It would be desirable if the perception of a qualitative difference between living and inert matter had disappeared just as the concept of spontaneous generation emerging from non-living matter did".[20]

On the other hand, there is also a more holistic approach to life, which envisions it as a complex phenomenon that cannot be deduced from its material components. According to this, organisms and machines differ in fundamental attributes. Among these, the most obvious is that organisms can form themselves, while an external agent manufactures machines. Another one is that the network of interactions between the constituents of a living being is synchronously established with the production of said constituents, whereas for machines the interactions between the different parts are established once they have been assembled after being separately manufactured. A third attribute is that the properties of a machine can be deduced from their material components, something that is not possible in the case of organisms. Additionally, the rigidity of the parts of a machine sharply contrasts the structural dynamics that cell components exhibit (membranes, proteins, nucleic acids, etc.), a quality that contributes to its resilience during changes in the environment. Finally, for machines, it is possible to replace one part or another and assembled it with the old parts, whereas in living organisms the components are continuously replaced.

The previously cited physicist Max Delbrück, a disciple of Niels Bohr and one of the fathers of molecular genetics, boldly upheld the argument that biological analysis must be done in terms of the living cell and theories must be formulated without fear of contradicting molecular physics. In a somewhat more cautious, but innovative way, the biologist Sidney Brenner made the following prediction years later: "I think in the next twenty-five years we are going to have to teach biologists another language ... I don't

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[19] Dowell, R.D., Ryan, O., Jansen, A. *et al*. Genotype to phenotype: a complex problem. *Science* 328, 469, 2010.

[20] Meanings of "life". *Nature* 447, 1031-1032, 2007.

know what it's called yet, nobody knows ... It may be wrong to believe that all the logic is at the molecular level. We may need to get beyond the clock mechanisms".[21] More recently, the microbiologist Carl Woese, recognised worldwide for his proposal of a tree of life composed of three domains (Bacteria, Archaea and Eukarya), maintained that the great advances in molecular genetics have produced mixed results. On the one hand, the aspects that could be addressed with an objective scientific method based on hypothesis testing were greatly benefited. But this reductionist approach, which came to permeate all of biology, was also pernicious, as it produced a distortion in twentieth-century biology. Not only did it leave the most holistic problems unresolved, but it also succeeded in producing a change to the concept of life itself. According to Woese, this approach stripped the organism of its surroundings, it separated it from its history and evolutionary flow, and it reduced it to unrecognisable parts, this being the cell, a multicellular organism or the entire biosphere. Therefore, Woese makes a fervent appeal for a new biology, with less attention on the deterministic mechanisms and a greater emphasis on the holistic aspects. That is to say, to see living beings for everything that they are, not to break them into parts as required by the reductionist scientific method.[22] Hans Westerhoff and collaborators have contributed to this line of thought with new arguments. According to these scientists, organisms do not fit into two basic attributes that are typical of physical systems, namely, maximum simplicity and minimum potential energy state. The high complexity of living organisms and their functioning as open thermodynamic systems that store energy, distinguishes them from inert matter. Therefore, they propose to give impetus to systems biology with its own principles equipped with quantitative laws that differ from traditional biology.[23]

A sample of the valuable contribution of the reductionist approach

Criticism of the application of the reductionist scientific method that has prevailed in biology is justified if it is thought to constitute the only way to explore life. Nevertheless, one must not lose sight that its contributions to biology have been very beneficial and will remain so as a comple-

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[21] Cited in Judson, H.F. *The eighth day of creation*. Simon & Schuster, New York, 1979.

[22] Woese, C.R. A new biology for a new century. *Microbiol. Molec. Biol. Rev*. 68, 173-186, 2004.

[23] Westerhoff, H.V., Winder, C., Messiha, H., Simeonidis, E., Adamczyk, M., Verma, M., Bruggeman, F.J., Dunn, W. Systems biology: The elements of life. *FEBS Lett.* 583, 3882-3890, 2009.

ment to new studies of a more systemic orientation. In this sense, one of the more fruitful branches of biology has been biochemistry, a discipline that studies the structure, function, organisation and transformation of the cellular constituents. Biochemistry also serves to support all other branches of biology, because in the search for understanding biological processes, it is common that the inductive method ultimately leads to the molecular level. That is why it may be illustrative to mention some fundamental aspects that biochemistry has demonstrated to us, as a sample of how relevant the use of the experimental method has been for biology.

Firstly, we know that the **materials of life** are developed in an aqueous medium. Its bipolar structure, its smooth tendency to ionise, its ability to form hydrogen bonds, its high specific heat and the lower density of ice, makes water the optimum solvent for life on earth. But water also plays other important roles: it is a source of electrons in photosynthesis, it is the final product of cellular respiration (oxidative phosphorylation), it is also a product of condensation reactions and a substrate of hydrolysis, etc. Biochemistry has also taught us that the molecules of life are the same in all organisms of the biosphere, although some of them may also be formed in environments devoid of life. For example, meteorites that come from space contain amino acids, sugars, lipids, nucleotide bases, etc. These same compounds can be synthesised abiotically in the laboratory simulating environmental conditions of early earth. Among those, and of particular interest, are lipids, compounds that compose the membrane providing confinement and identity to the cell. Far from playing a passive role, membranes participate in the flow of compounds towards the interior and exterior of the cell and in the electron transport systems related to cellular energetics.

One can wonder whether life could arise with a solvent other than water or with other types of molecules. The scientist Michael Denton has devoted an entire book to the argument that the cosmos is particularly conditioned to one type of biology – the one that exists on earth – and the phenomenon of life cannot be sustained in any other exotic chemistry.[24] In agreement with him is the microbiologist Norman Pace, for whom the biomolecules of life that we know of are unsurpassable because of their individual characteristics and their ability to form polymers. Wherever life develops, according to Pace, will be composed of macromolecules, for only they can contain and transmit information.[25] Furthermore, the cellular scaffold re-

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[24] Denton, M.J. *Nature's destiny*. The Free Press, NY, 1998.

[25] Pace, N.R. The universal nature of biochemistry. *Proc. Natl. Acad. Sci.* USA 98, 808-808, 2001.

quires a versatile element that is capable of forming different links with itself and with other atoms of life, such as hydrogen, nitrogen, oxygen, sulphur and phosphorus. Carbon, which is abundant in the universe, is superior to silicon, the only other element that could compete with this function, because the linkages that silicon forms to itself are weaker and thus less stable than carbon-carbon bonds. In addition, several metals that are essential in cellular biochemistry and that probably played a leading role in the origin of life on earth, act harmoniously in this carbon-based biochemistry. The universal phylogenetic tree based on ribosomal RNA sequences is the best proof of the interrelationship between living things on earth and a unique molecular logic for all of them. Pace adds that the extreme conditions of temperature, pressure, pH and aridity, that are capable of bearing life on earth makes one presume that be it anywhere, the fundamental biochemistry should be the same.

But there are also other views regarding the material components of life. In a provocative article, Benner *et al.* argue that a self-sustaining chemical system capable of Darwinian evolution could allow for a great diversity of chemical compounds, including a non-aqueous solvent that could well be ammonium. A similar viewpoint is stated in an extensive report elaborated by a committee convened by the U.S. National Research Council to analyse the boundaries of life on earth and to help NASA to adopt criteria to recognise, conserve and study life that could exist in other parts of the universe. According to this committee, it is easily conceivable that the fundamental requirements of life, that is, a thermodynamic disequilibrium, stable bonds between atoms, a liquid environment and an ability to undergo Darwinian evolution, could satisfy a chemistry that is not based on carbon, that does not use water as a solvent and where oxygen does not participate in electron transfer reactions. The report calls to set aside the prevailing "terracentristic" view and explore the possibility of new scenarios. Besides proposing various options of small biomolecules, macromolecules and solvents, it extends to analyse the possibility of life in solid and gaseous states.

An intermediary position between a universal biochemistry and the existence of several biochemistries is that of Paul Davies, who has promoted the concept of the "shadow biosphere" originally coined by Carol Cleland and Shelley Copley. According to Davies, given that it is possible that life arose more than once on earth, there could be organisms that exist (meaning microorganisms) whose biochemistry partially differs to that of what we know. For this reason, we have not known how to detect it. Davies, who recently co-authored a controversial article describing a bacterium that replaces phosphorus with arsenic, invites us to search for this shadow life in isolated environments such as underwater hydrothermal vents or the Dry Valleys of Antarctica.

An additional distinguishing characteristic of biomolecules is their chirality (derived from the Greek *kheir*, hand). This concept applies when an object and its mirror image are not super imposable. A textbook example to illustrate this situation is that of hands. Something similar happens with several molecules of life, including amino acids and sugars. In these cases, the chirality arises when a carbon atom binds to four different chemical groups. There can be two types of configuration or spatial distribution of these groups, one being the mirror image of the other. These are known as optical isomers. In life, as we know it, there is only one type of configuration in both amino acids and sugars. That is, in each case life chose only one of the optical isomers. By contrast, the analysis of the organic molecules found on meteorites or those obtained in the laboratory always show the presence of both optical isomers. This selection that resulted in life on earth is explained by reasons of stabilisation of the three dimensional structure of the macromolecules and the specificity in enzymatic reactions. The reasons why life chose a particular isomer in each case is unclear and the mechanisms involved in this selection are the subject of intense studies. It could well be that elsewhere in the universe there is a life based on the same biomolecules as our biosphere but of opposite chirality.

One aspect of the molecular logic of life that does not cease to attract attention is its **metabolism-genetic duality**. The integrated and harmonic coexistence of a component of chemical reactions with an informational one evokes the before mentioned autopoietic and evolutionary processes of Harold's definition, respectively. It is possible that self-replicating informational macromolecules such as RNA, or maybe another initially simpler molecule, may have appeared at the origin of life on earth. There are also supporters of the theory that metabolism was born first and that genetics appeared later. It may be that both began at the same time. Whatever the case, it is difficult to imagine how this association and interdependence between metabolism and genetics was produced.

Would we consider to be alive an RNA molecule that makes copies of itself? Or, could we say that a system of chemical reactions sustained by an external power source and which lacks informational polymers is alive? Neither of these situations exists in natural environments nor have they been obtained experimentally in controlled conditions in the laboratory.[26]

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[26] With the exception of the autocatalytic system of reactions known as the formose cycle, which gives rise to sugars based on formaldehyde.

The self-replication of an informational polymer such as RNA proves particularly problematic, since it implies a series of difficult obstacles to overcome: i.e. the abiotic synthesis of precursors, the initial copy of a complementary RNA that will later serve as a template for the synthesis of the original RNA, accuracy of the copy so as not to lose the self-replicative capacity. Moreover, one can speculate that if at the origins of life certain conditions were present, such as an energy source, availability of precursors, an external boundary and the presence of catalysts, reaction systems could have appeared with the capacity to grow and "evolve" by incorporating new ingredients.[27] This hypothesis has both supporters[28] and detractors.[29] If this had been the case, there is no doubt that the genetic-metabolism duality of life that we know of would have constituted a substantial improvement, since the presence of a genome provides many advantages. Among them, a mechanism of replication, variation, and evolution of organisms; a mechanism of internalisation of its phylogenetic history; an expression of functions program (i.e. metazoan development, tissue-specific expression, energy saving in the adaptation mechanisms, etc.) and the encoding of catalysts that are much more efficient and specific than minerals. But above all, the genome provides stability and gives identity to all organisms.

An essential requirement of the chemical reactions of life is **catalysis**. Without catalysis, these reactions would be extraordinarily slow and, we presume, life would not be possible. At the origin of life, it is presumed that metals fulfilled this role, a hypothesis that is reinforced by the participation of these in numerous cellular reactions. However, enzymes, proteins that greatly exceed metals because of both their efficiency and specificity, catalyse the vast majority of the reactions. The information for the synthesis of all enzymes is encoded in the DNA, reinforcing the functioning of the metabolic and genetic domains as a whole. There is another layer of complexity to catalysis, though, as for some years now we know that some reactions in the cell are catalysed by RNA (ribozymes), which could be a remnant of a catalysis that preceded that of proteins.

Finally, a few words about the **energy** that sustains life. The laws of thermodynamics tell us that the high organisation and complexity of life cannot occur spontaneously. The increase of the internal order, which is compen-

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[27] Shapiro, R. A simpler origin of life. *Sci. Am.* 46-53, February 2007.

[28] Segré, D., Ben-Eli, D, Lancet, D. Compositional genomes: Prebiotic information transfer in mutually catalytic noncovalent assemblies. *Proc. Natl. Acad. Sci.* USA 97, 4112-4117, 2000.

[29] Orgel, L.E. Self-organizing biochemical cycles. *Proc. Natl. Acad. Sci.* USA 97, 12503-12507, 2000.

sated with an increase in disorder (entropy) of the environment, is made possible thanks to a constant flow of energy. Because of this, it is said that life is in thermodynamic disequilibrium with its environment. When this flow of energy is detained, death occurs and the molecular components of the organism are dispersed and eventually degraded, thus terminating the state of imbalance. We know that there are two primary energy sources to sustain life: sunlight and inorganic redox reactions. Organisms that use them (plants and bacteria) are also capable of manufacturing their biomolecules from atmospheric CO_2, although there are some bacteria that use sunlight for energy purposes only and are dependent on the supply of organic compounds as a carbon source. There is also an important group of organisms, including humans and all animals, which use organic compounds synthesised by plants as their source of energy and carbon.

Whatever the source of energy, all living beings follow the same strategy to capture and store it for later use. This consists of a flow of electrons from levels of high energy to lower energy, which produces a proton gradient whose natural tendency balances and culminates in the synthesis of ATP. This molecule, which constitutes the universal energy reserve of the cell, is principally used for the synthesis of biomolecules and polymers, and for mechanical work. The formation of a proton gradient due to the flow of electrons activated by solar photons or redox chemistry is undoubtedly one of the most unique and ingenious signatures of life on earth. It is the fundamental support of the distinctive autonomy of living things to be permanently sustained in disequilibrium with the environment. This could be the reason that inspired Hungarian Nobel Prize winner Albert Szent-Györgyi to metaphorically say that life is nothing but an electron looking for a place to rest. Therefore, it should not surprise us that upon finding extraterrestrial life, the same strategy to provide energy could be used.

A renewed impetus in the studies of the complexity of life

Leaving aside that some might consider that an isolated self-replicating polymer possesses life, the simplest autopoietic system seems to be a polymer that self-replicates and that replicates another polymer involved in the synthesis of membrane lipids that confines both.[30] Indeed, this would be hypothetically possible if the precursors of both polymers are synthesised abiotically using any available energy source. However, life as we know it has a threshold of complexity far higher than the previously mentioned minimum. *Mycoplasma genitalium*, one of the simplest bacteria known to

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[30] Szostak, J.W., Bartel, D.P., Luisi, P.L. Synthesizing life. *Nature* 409, 387-390, 2001.

exist, has a total of 580 genes, of which 482 code for proteins. Several years ago, while trying to answer the question of what could be the smallest genome of a microorganism that is not exposed to any form of stress and that has all the nutrients it needs, Craig Venter and collaborators methodically inactivated each of the genes of *M. genitalium* and discovered that 382 protein-coding genes are absolutely essential for the viability of the bacterium.[31] To these we must add 43 genes that code for RNA. This seems to be the minimum size that a system requires to be autopoietic, that is to say, to function autonomously, far from equilibrium, and exchanging matter and energy with the environment.

Autopoiesis is a process that involves several interconnected systems of metabolic reactions. Some may be intended for energy production, others for the supply of macromolecule precursors, others for biosynthetic purposes. Indeed, also included in these reaction systems are compounds destined for replication and expression of genetic material. One approach to studying the complexity of life is precisely the comprehensive analysis of macromolecular complexes and of the networks within the cell, which seem to represent a growing trend in contemporary biochemistry.[32] This view of systems biology is in line with the more holistic approach proposed by Woese and provides a complimentary perspective to that of the traditional work at the molecular level. Always within the scope of the scientific method, systems biology operates by gathering, processing and integrating information to later develop mathematical models that describe the structure and organisation of a particular system. These models are also useful for analysing the robustness of the systems, allowing the simulation of different disruptions to the structure. This networks approach is even being used as a tool in evolutionary studies, analysing the effect that a mutation produces in the functioning of a network and how its alteration is translated into a phenotypic change.[33]

There are different types of interaction networks, such as: protein-protein, signal transduction, metabolic networks and regulation circuits of gene expression. While each network has its own identity, all together they form an interactive system. This systemic approach is not simple. It firstly requires the identification of the components of the network, taking into account

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[31] Glass, J.I., Assad-García, N., Alperovich, N., Yooseph, S., Lewis, M.R., Maruf, M., Hutchinson, C.A., Smith, H.O. and Venter, J.C., Essential genes of a minimal bacterium, *Proc. Natl. Acad. Sci.* USA 103, 425-430, 2006.

[32] Arkin, A.P., Schaffer, D.V. Network news: Innovations in 21st century systems biology. *Cell* 144, 844-848, 2011.

[33] Moore, A. Towards the new evolutionary synthesis: Gene regulatory networks as information integrators. *Bioessays* 34, 87, 2012.

that some of them may have a transient presence. It is then necessary to establish interactions with the corresponding cooperative and feedback elements. It requires also an idea of its spatial topology: participation of elements in solution, associated with membranes or within an intracellular compartment. Next, the robustness of the network must be analysed: how it responds to external stimuli, to states of stress or disease, how it varies during the cell cycle or in cells of different tissues. Finally, it is necessary to integrate all the networks of the cell, establishing the connectivity map and the spatiotemporal relationship that exists between them.

Computer modelling and the availability of software that allows the integration of data, together with new high-performance technologies, are greatly facilitating network analysis. For example, a recent study detected the presence of 178 protein complexes with some multifunctional proteins participating in several of these complexes in a different species of *Mycoplasma* to the aforementioned one.[34] The case of *Saccharomyces cerevisiae* is paradigmatic, because of its unicellular eukaryote nature. Studies from two groups with this microorganism have identified 547 protein complexes, although it is estimated that these could be about 900. The average amount of polypeptides per complex is close to four and they have found 429 additional interactions between pairs of complexes.[35,36] Another study that analysed more than 5.4 million possible interactions between gene products, led to a functional map of the yeast cell, in which genes that participate in the same processes show connections between them.[37]

Apart from yeast, another organism used extensively in diverse types of molecular studies is the worm *Caenorhabditis elegans.* Its close to a thousand cells and the sequencing of its genome make it a very good study model. Several groups have contributed to building networks of protein-protein interactions, networks of transcription factors with promoters and with mi-

[34] Kühner, S., van Noort, V., Betts, M.J., Leo-Macias, A., Batisse, C., Rode, M., Yamada, T., Maier, T., Bader, S., Beltran-Alvarez, P., Castaño-Diez, D., Chen, W-H., Devos, D., Güell, M., Norambuena, T., Racke, I., Rybin, V., Schmidt, A., Yus, E., Aebersold, R., Herrmann, R., Böttcher, B., Frangakis, A.S., Russell, R.B., Serrano, L., Bork, P., Gavin, A-C. Proteome organization in a genome-reduced bacterium. *Science* 326, 1235-1240, 2009.

[35] Gavin AC, Aloy P, Grandi P, Krause R, Boesche M, Marzioch M, Rau C, Jensen LJ, Bastuck S, Dümpelfeld B, *et al.*: Proteome survey reveals modularity of the yeast cell machinery. *Nature* 2006, 440:631-636.

[36] Krogan NJ, Cagney G, Yu H, Zhong G, Guo X, Ignatchenko A, Li J, Pu S, Datta N, Tikuisis AP, *et al.*: Global landscape of protein complexes in the yeast *Saccharomyces cerevisiae*. *Nature* 2006,440:637-643.

[37] Costanzo, M. *et al.*, The genetic landscape of a cell. *Science* 327, 425-431, 2010.

croRNA, networks of interactions between gene products, and signal transduction networks.[38] Moreover, the phenotypic effects that have disruptions in some of these networks have been studied, a strategy already being applied to study the genetic causes of human diseases.[39]

Another approach to the three-dimensional architecture of the cell is the study of the spatial arrangement of the different regions of the genome. One of them made with the fly *Drosophila*, reveals that the active genes are grouped in different domains to those that are not expressing, producing physical interactions between them despite the fact that they can be found on different chromosomes.[40] Since it would seem that the gene sequence is not sufficient to express a phenotype alone but that the structural organisation is also critical, this methodology is being applied to study human diseases, particularly cancer.

Is science sufficient to explain life?

Lord Rutherford argued that physics is the only science. Anything else was the equivalent to collecting stamps.[41] Though entitled to his opinion, his judgement seems like an insult to biologists. It has to be considered that it was a type of "philatelic" activity that led Darwin and Wallace to the theory of evolution. It is possible that descriptive biology at that time motivated Lord Rutherford to deliver such an arrogant judgement. Possibly, had he witnessed the progress of contemporary biology, his opinion would have been different.

The current outlook, with its impressive achievements, is mainly the result of a successful application of the experimental method. First, enzymology, then molecular genetics, followed by structural studies of macromolecules, and more recently by massive genome sequencing, has led to the accumulation of information that is only possible to analyse with computational tools. It has been a successful journey and it is compulsory to continue along this path, because it is the only way to know how the molecular components of life function. But this approach has its limitations, because it is methodologically reductionist. A subsystem is isolated and is

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[38] See Gunsalus, K.C., Rhrissorrakrai, K. Networks in Caenorhabditis elegans. *Curr. Op. Genet.& Develop.* 21, 1-12, 2011 and the references included.

[39] Cordell, H.J. Detecting gene-gene interactions that underlie human diseases. *Nature Rev. Genet*. 10, 392-404, 2000.

[40] Sexton, T., Yaffe, E., Kenigsberg, E., Bantignies, F., Leblanc, B., Hoichman, M., Parrinello, H., Tanay, A., Cavalli, G. Three-dimensional folding and functional organization principles of the Drosophila genome. *Cell* 148, 1-15, 2012.

[41] Birks, J.B. *Rutherford at Manchester*, Ed. Heywood. London, 1962.

studied outside the multiple connections that it normally has with other systems within a cell or the whole organism. For this reason, the application of systems biology and the development of complexity science are giving a new impetus to biology, always within the scope of the scientific method of exposition and refutation of hypotheses. Most likely, problems such as the lack of correlation between gene number and the complexity of organisms, the significance of RNA editing or the consequences of pleiotropy, will be solved this way.

However, the underlying question is whether the exclusive use of this method and the mere knowledge of the molecular mechanisms will lead us to an exact understanding of not only life, but also living beings. Nowadays, no one disputes that molecular mechanisms do not violate the laws of physical chemistry. Is this, however, sufficient to explain life? The analysis of such a distinctive aspect of life, such as its autonomy to operate far from the thermodynamic equilibrium while exchanging matter and energy with the environment, seems to require more than experimental data. The same could be said about self-organisation and emergent properties, or about the effect of the relationship between parts of a system in the behaviour of said parts (*downward causation*).[42] Supposedly, a science of complex systems should be able to explain these aspects, but it is not at all clear that that is how it will be.

In his *Critique of Judgement*, Kant maintained that mechanical causes are not sufficient to understand the phenomenon of life and that teleological arguments are indispensable for its systematic and complete comprehension.[43] Later on, Niels Bohr would reaffirm this line of reasoning.[44] By this time, Bohr had already proposed the principle of complementarity in physics, ac-

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[42] Mazzocchi, F. Complementarity in biology. *EMBO reports* 11, 339-344, 2010.

[43] "For it is quite certain that in terms of merely mechanical principles of nature we cannot even adequately become familiar with, much less explain, organized beings and how they are internally possible. So certain is this that we may boldly state that it is absurd for human beings even to attempt it, or to hope that perhaps some day another Newton might arise who would explain to us, in terms of natural laws unordered by any intention, how even a mere blade of grass is produced. Rather, we must absolutely deny that human beings have such insight. On the other hand, it would also be too presumptuous for us to judge that, supposing we could penetrate to the principle in terms of which nature made the familiar universal laws of nature specific, there simply could not be in nature a hidden basis adequate to make organized beings possible without an underlying intention (but through the mere mechanism of nature)". Immanuel Kant, *Critique of Judgment*, 1790.

[44] "The asserted impossibility of a physical or chemical explanation of the function peculiar to life would in this sense be analogous to the insufficiency of the mechanical

cording to which, matter at the atomic level should be studied as a particle and as a wave. Similarly, he thought, the reductionist and holistic approaches, mutually exclusive epistemological concepts, could be used in a complementary form for a complete understanding of life. The first one is called to account for molecular mechanisms, while the second is directed towards the functioning of living organisms as such, even taking teleological arguments into consideration. This is not to later make an amalgam of both, but to accept the idea that the understanding of life may require approaches from different points of view.

In more recent years, Vicuña and Serani-Merlo[45] have made an epistemological proposal comprising three types of approaches to the study of life, as follows: a) an experimental one, appropriate to answering questions that can be resolved with the scientific method in the areas of biochemistry, physiology, cytology, genetics, etc; b) a historical one, to address scientific aspects that cannot be answered experimentally, such as evolutionary speciation, the effects of mass extinctions, etc.; palaeontology and dating methods are valuable tools of the latter approach; and c) a third one, from the standpoint of philosophy of nature, for matters that cannot be studied with the experimental method either, such as the existence or nonexistence of purpose or design of living things. In a similar vein, Powell and Dupré have recently indicated the importance of looking at both sides when studying the transition from molecules to systems, also suggesting that philosophical ideas can be valuable in this exercise.[46]

It is difficult to estimate the degree of acceptance the invitation that Kant and Bohr gave us would have today, namely, to resort to arguments from natural philosophy together with those from the natural sciences to attain a better understanding of the phenomenon of life. Given the so far unsuccessful efforts of biologists to attain this goal, this seems to be a path worth exploring.

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analysis for the understanding of the stability of atoms….It is due to this situation, in fact, that the concept of purpose, which is foreign to mechanical analysis, finds a certain field of application in problems where regard must be taken of the nature of life". Bohr, N. Light and life. *Nature* 133, 421-423, 457-459, 1933.

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TOWARDS AN UNDERSTANDING OF THE MOLECULAR COMPLEXITY OF CANCER

LILIA ALBERGHINA

Introduction

The molecular biology of cancer cells has a crucial role not only in promoting scientific knowledge, but also in developing better treatments for patients of a disease that is still in strong medical need. Since the eighties of the last century, the research in this field has been characterized by a genetic approach. The recombinant DNA technologies, developed in those years, allowed to isolate genes (called "oncogenes"), which were shown to be able to promote both *in vitro* and *in vivo* cancer growth. More than one hundred oncogenes have been described, together with a few "oncosuppressors", genes whose function is, on the contrary, to block cancer cells proliferation.

Extensive analysis of the molecular functions of both oncogenes and oncosuppressors has shown, to the surprise of the scientific community, that they encode for mutated or overexpressed proteins, which, in the wild type form and at normal level, are constituents of healthy cells. The large part of these proteins are involved in signaling, that is in the cascade of biochemical reactions that convey the cues coming from the environment (from nutrient availability and/or from the presence of growth factors) to the cell machinery.

Given that oncogenes are found to activate signaling, thereby allowing cancer cells to grow under conditions in which normal cells do not, a new drug discovery strategy was developed: to construct molecules able to block, in a specific way, the various oncogenes, whose activation underlays each given cancer type. Although these new drugs present, at first, very positive clinical responses, quite often, after several months of treatment, there is a recurrence of the disease, due to innate or acquired resistance (1, 2). New signaling pathways, able to sustain the growth and survival of cancer cells, are activated, mostly by mutations, generated by the genomic instability of cancer cells (3), so to bypass the oncogenic signaling pathway which was the initial target of the therapeutic treatment. It has become clear, therefore, that the genetic approach, which polarized the interest on specific oncogenes (and on the signaling pathways in which they are involved), while it considered the growth and survival of cancer cells as a "read out" of the genetic analysis, is no longer tenable, and instead investigations have to be directed to the molecular basis of the specific "read out" of cancer cells.

The molecular setup of a human cell is extremely complex: while we have about 50,000 billion cells in a human body, each cell contains, on average, about 1 billion proteins of about 10,000 different sequences, being the proteins the components that carry out the large majority of the activities of the cell. Furthermore, each of these proteins may be localized in different compartments of the cell (having a distinct role in each compartment) and may be modulated in its activity by a number of different post-translational modifications (i.e. phosphorylation, acetylation, etc.) that are under the control of the signaling apparatus.

Molecular complexity of cancer cells

The "omics" technologies (transcriptome, proteome and metabolome analyses), together with the classical approaches of cellular and molecular biology, have collected a wealth of information on molecular changes observed in cancer cells, when compared with normal ones. The various types of tumors and the many cancer cell lines that have been analyzed, show changes, for instance, in several thousand gene products, which are largely different between one type and another type of tumor or cell line (4). The necessity thus emerged to develop automatic, computational algorithms able to extract information from those sets of Big Data (5). Statistical analysis and graph theory have offered the first tools used to extract an order from this deluge of data (6), but they have obtained a very limited success in terms of a better understanding of the disease.

Following a line of thought first elaborated by René Descartes on how to treat complex problems to be solved: "to divide each difficulty which I examined into as many parts as possible and as might be necessary to resolve it better", Hanahan and Weiberg (7) recognized that, under the vast catalogue of different cancer phenotypes, there are a small number of essential alterations in cell biochemistry and physiology (that they called "hallmarks"), which, integrated in various ways, generate the features of cancer disease.

Some of these hallmarks are specifically expressed in the organism, for instance the ability to metastasize, others are properties that can be investigated, under controlled conditions, also in cancer cells growing "in vitro". A reorganization of cancer hallmarks, following a systems approach, identified a number of functional modules, each one characterized by a measurable input, a molecular network that elaborates the input, to produce a measurable output (8).

Systems Biology is emerging as the necessary approach to investigate how the interactions of a large number of molecular players generate the functional properties of living cells (9). The integration of molecular analysis with mathematical modeling and simulation, in an iterative process, characterizes the systems biology approach, since it allows to investigate the role of non-linear dynamic steps in the network under investigation (10). Mathematical models may be constructed at different levels of resolution (11) and based on different rationales (12, 13).

Due to the non-linearity of biological complex processes, their functions emerge as a system-level property, making the relation between genotype and phenotype not straightforward (as it may happen for simple functions, like the transport of respiratory gases by hemoglobin), but very difficult to predict, if one knows only the properties of the individual components and not the map and the strength of their interactions, organized in a dynamic mathematical model. This is the reason why a purely reductionist approach is not, and will not, be able to explain complex functions, as cancer, and systems biology is needed to move towards the understanding of complex functions as emergent properties.

Going back to the cancer hallmarks, the more basic property, necessary for the development of the disease, is the uncontrolled, enhanced cell growth, that is well characterized under "in vitro" conditions. Extensive transcriptome analysis has shown that almost 3000 gene products are differentially expressed in cancer cells as compared to their normal counterparts (14). Clustering analysis has identified, among various changes, alterations in metabolism, both glycolytic and mitochondrial (15).

Cancer metabolism rewiring

In 1956 Otto Warburg reported that most cancer cells present a high rate of glycolysis, even in the presence of oxygen. Pyruvate, instead of being oxidized by mitochondria, as normal cells do, is converted to lactate. He postulated that this change of metabolism be the fundamental cause of malignant transformation (16).

The Warburg hypothesis was scoffed at, and later forgotten in the period in which the genetic approach to oncogenes was popular. Things started to change when evidence accumulated to show that different oncogenes have as a common "read out": the stimulation of glycolysis (17).

The turnaround occurred a few years ago, when it was shown that, besides having stimulated glycolysis, several cancer cells are "glutamine addicted", that is, they require glutamine (a non essential aminoacid in humans) for proliferation (18, 19). Glutamine is utilized by reductive carboxylation, an unusual pathway which may lead to lipid synthesis (20).

In K-Ras transformed cells, utilization of glucose and glutamine has been shown to be decoupled: glucose goes to lactate, producing ATP on the way, while glutamine is utilized both as a carbon and nitrogen source for biomass production (21). One has to recall that normal cells utilize glutamine only as a source of organic nitrogen and excrete the remaining glutamic acid (the carbon moiety). It should be added that in the same transformed cells, mitochondria are quite inefficient, having the Complex I dysfunctional (22).

Is it possible to connect all the information that we have by now on the ample cancer metabolic rewiring (CMR): stimulated glycolysis and reductive carboxylation of glutamine, mitochondrial dysfunction, enhanced lipid synthesis, sustained protein and nucleic acid production, etc.? This is going to be a great task for systems biology.

First of all, we need to reconstruct the large metabolic network that underlays CMR. A redox control has been identified from the analysis of the map, linking the various areas of the metabolism and explaining their interlocking (23). Advanced computational approaches are required to unravel the complexity of metabolism and of its regulation (24). Of particular interest are constraint-based models (12, 13). This ingenious approach, that requires to know the stoichiometry of the reactions involved without asking for their kinetics parameters, which are very difficult to obtain by experimental analysis, allows to estimate the flux, that, in steady state, traverse the various pathways of the metabolism, thereby offering an informative description of the functionality of the entire network. Flux Balance Analysis has been developed both for small networks and for genome-scale networks (25, 26). Given that experimental findings indicate that various types of tumors may have different metabolic pathways (some are reported to be glycolytic while others are oxidative), an ensemble evolutionary constraint-based approach was developed to better understand how various phenotypes of CMR metabolism may be generated (27).

Studies, now underway in my laboratory, based on the various computational approaches indicated above, are recognizing the design principles that underlay CMR in various cancer cells.

Conclusions and perspectives

Analytical technologies, based on mass spectrometry, allow to obtain experimental findings not only on metabolic profiling and on metabolic pathway analysis, but more importantly also on metabolic flux analysis (25, 26), which can be used to ascertain the validity of the indications coming from computational Flux Balance Analysis, for various tumors and cell lines. The details of CMR in various types of cancer are thus going to be ascertained. Given that inhibition of CMR has been shown to block cancer cell growth, the knowledge of the biochemical pathways involved in CMR is going to be the stepping-stone for a new strategy of anticancer drug discovery.

The molecular complexity of cancer is a very clear example of the "organized complexity" anticipated by Warren Weaver (28). While classical physics has been devoted to few-variable problems and many areas of scientific investigation are analyzing "disorganized complexity", in which numerous variables can only be treated by probability analysis, biology offers problems of "organized complexity".

A moderate number of variables, often linked by non-linear relationships, generate functions as emergent properties. As discussed above, only the integration of extensive molecular analysis and of computational algorithms and models may allow to understand how biological functions are generated by organized molecular complexity.

As shown in this note, science has become able to tackle with success this new frontier, having developed appropriate experimental and computational approaches. It is a real paradigm change: from the consolidated molecular and reductionist approach, biology is moving towards a new integrated, multidisciplinary approach, that is going to be "Big Science" oriented. As predicted by Weaver, large communities of scientists are going to collaborate to reach macro-objectives: from a better understanding of major diseases to unraveling the relations brain/mind.

The flourishing of biological organized complexity studies is expected to elucidate new concepts that are going to impact also on the analysis and management of man-made organized complexity, such as that found in social or financial organizations.

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COMPLEXITY AS SUBSTRATE FOR NEURONAL COMPUTATIONS

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Abstract

Recent discoveries on the organization of the cortical connectome together with novel data on the dynamics of neuronal interactions require an extension of classical concepts on information processing in the cerebral cortex. These new insights justify considering the brain as a complex, self-organized system with non-linear dynamics in which principles of distributed, parallel processing coexist with serial operations within highly interconnected networks. The observed dynamics suggest that cortical networks are capable of providing an extremely high dimensional state space in which a large amount of evolutionary and ontogenetically acquired information can coexist and be accessible to rapid parallel search.

The question that I would like to address is, whether evolutionary increases in the complexity of the cerebral cortex led to the implementation of unconventional computational strategies that have not yet been investigated much in the brain nor implemented in technical systems.

The evolutionary increase in the brain's complexity has led to the emergence of ever more efficient cognitive and executive functions. While neurobiological investigations have been very successful in elucidating the neuronal mechanisms underlying the behaviour of simple organisms such as molluscs, worms and insects, the search for mechanistic explanations of higher cognitive and executive functions, in particular of the human brain, remains a major challenge.

One conundrum is related to the evidence that memories can be accessed nearly equally fast, within fractions of a second sometimes, irrespective of whether they are recent or whether they are from early childhood. This implies that the huge number of memories that have been acquired over a lifetime must be stored in a way that permits equal and fast access. Thus, a space

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must be configured in which all these memories can be superimposed and accessed in parallel. A serial search process as it is realized in digital computer memories is not conceivable because neuronal processes are orders of magnitude slower than electronic computations. Serial search strategies in neuronal systems would consequently be orders of magnitude too slow.

A related conundrum is the fast readout of priors that need to be called upon for the interpretation of sensory signals. There is consensus that perceptions are the result of a reconstructive process. The sparse signals provided by the sense organs can only be disambiguated and interpreted because they are compared with models of the world that are stored in the functional architecture of the brain. This architecture is specified by essentially three processes: Evolutionary selection, epigenetic modification by experience dependent developmental processes, and normal learning. All three processes store knowledge about the features of the embedding world, so called priors, in the brain and this knowledge is subsequently used for the construction of our perceptions. Primates change the direction of their gaze on average four times in a second. This implies that new information needs to be matched with the corresponding priors approximately every 250 ms, the time it takes to interpret a visual scene. How the nervous system is able to retrieve the relevant priors from the immense reservoir of priors within such short intervals is enigmatic. Again, a very large space needs to be configured in order to store these priors and a search mechanism has to be implemented that is capable of retrieving any of these priors with equal probability.

Our ability to explore the huge database of stored knowledge in a surprisingly short time is also revealed by the fact that we immediately know if something is known or unknown to us.

Classical theories on information processing in neuronal networks fall short of explaining how the immense amount of memories and priors can be stored without fusing and retrieved with remarkable speed and accuracy. Here I shall propose a computational strategy that has so far not received much attention by neuroscientists, which goes back to recent theoretical work in the field of non linear dynamics and capitalizes on the extremely rich dynamics of recurrently coupled complex networks. The idea is that such networks are capable of providing a very high dimensional state space that allows the superimposition of an equally large number of dynamic patterns that can be kept separate because of the high dimensionality of the available space.

Options to create high dimensional coding space

Artificial neuronal networks of the Hopfield type are in principle capable of simultaneously representing different objects, i.e. constructs defined by specific constellations of features and the relations among those features. However, such systems cannot cope easily with the representation of large numbers of superimposed relational constructs, in particular if temporal relations also need to be stored. One reason is their restricted temporal dynamics that limits the dimensionality of states (Hopfield & Tank 1991; Rumelhart & McClelland 1986). Another, more recently developed class of models capable of dealing with relational constructs and providing high dimensional spaces for coding is derived from concepts of reservoir computing, also addressed as echo-state or liquid computing. These networks consist of self-active nonlinear units with random recurrent coupling that maintain their own dynamics and are engaged in active processing (Buesing *et al.* 2011; Buonomano & Maass 2009; Jaeger 2001; Maass *et al.* 2002; Lukoševičius & Jaeger 2009).

In this computational framework, the reservoir consists of a network of self-active, randomly coupled neurons (nodes). If a specific input constellation is driving a subset of these nodes, a complex, transient, high dimensional and stimulus specific activity pattern emerges in this recurrently coupled network, the "liquid", and is then further propagated by waves of recurrent interactions among neurons. Such reverberation provides the "liquid" with a fading memory of recent inputs that allows it to integrate input sequences (e.g. several frames of visual input) while keeping track of sequence order. The readout of the relational code is achieved with conventional machine learning strategies for the classification of high dimensional vectors of activity. This readout function can again be implemented by neuron-like elements, that sample activity from the nodes in the "liquid" and adjust the coupling strength of the sampling lines through supervised learning until they become optimally activated by a particular state of the "liquid" (Nikolic *et al.* 2009). However, the readout stage could also consist of cell assemblies that are in turn ignited by specific states of the "liquid" after appropriate adjustment of the synaptic weights of the connections between the liquid and the readout stage. This strategy increases the robustness of decoding and at the same time generates low dimensional readout patterns that can directly be used to control effectors, e.g. orchestrate the population vector for a composite movement. The principle of this computing strategy is simple and powerful: a low dimensional input configuration is transformed into a high dimensional dynamic representation. In this high dimensional state space stimulus evoked vectors remain compact, cluster in well segregated subspaces and can be more easily discriminated based on their spatiotemporal signatures. The segregation of clusters can be improved further, if the network is endowed with Hebbian synapses and given the opportunity to "learn" in an unsupervised fashion about the features of the stimulus sample by repeated presentation of the stimuli (Lazar *et al.* 2009). As a matter of principle the performance of the liquid increases with the dimensionality of the space it is able to explore. Thus, if the nodes are configured as oscillators (e.g. relaxation oscillators or damped harmonic oscillators), phase comes into play in addition, which allows for a further expansion of the dimensionality of the "liquid" (see also Wang *et al.* 2011). Because of their high dimensionality, such "liquids" are in principle capable of storing and superimposing very large numbers of "memories" and learned associations that can be accessed and readout nearly instantaneously. The astounding ability of our brains to solve with such ease problems that are still computationally intractable, such as e.g. the fast processing of complex scenes, suggests that the brain might indeed capitalizes on computational algorithms which permit parallel storage and fast readout of complex relational constructs.

Analysis of the anatomy and the dynamics of the cerebral cortex suggests indeed that some of the above mentioned strategies might be implemented (for review see Deco & Jirsa 2012).

Developmental studies indicate that the statistics of feature conjunctions in the outer world get translated into the strength of coupling between cells tuned to the respective features. Early evidence for such internalization of contingencies has been obtained in kittens, which had exclusive experience with vertically oriented, unidirectionally moving gratings that had a constant stripe separation of 10 degrees visual angle (Singer & Tretter 1976). As expected, this selective rearing biased the numerical distribution of orientation and direction selective neurons towards the experienced stimulus (see also Blakemore & Cooper 1970). However, most importantly, a substantial fraction (~30%) of the neurons in supragranular layers of area 17 developed multiple, well-segregated receptive fields whose spacing frequently corresponded to the spacing of the experienced stripes. Because intercolumnar connections are shaped by experience according to a Hebbian mechanism (Löwel & Singer 1992) the ectopic receptive fields are most likely due to selective strengthening of intrinsic cortical connections linking those columns that were activated synchronously by the grating. In conclusion the weight distributions of the connections among cortical neurons likely reflect not only evolutionary adaptation to regularities but also the immensely complex statistics of the feature relations experienced throughout life (Heisz *et al.* 2012). Somehow, these countless, content-specific weight distributions must coexist in a very high dimensional space so as to remain flexibly addressable as contextual priors (Rabinovich *et al.* 2001; 2008). As discussed in the following paragraph, the dynamics emerging from cortical networks are indeed high dimensional, allowing for the coexistence of a large number of potentially realizable states (Schittler, Neves & Timme 2012).

The fingerprints of high dimensional dynamics

The dynamics of complex systems can vary between two extremes. All elements of the system could be active independently and exhibit stochastic activity (high dimensionality) or, alternatively, all elements could be synchronized (low dimensionality). Both extreme states have low computational potential. However, under normal conditions the cerebral cortex operates in an intermediate regime where the emergent dynamics are complex and computational power is high (see below). Interestingly, this is also true for the architecture of the anatomical connections. The connectivity graph constitutes a compromise between randomness and regularity where complexity and dimensionality are high (Sporns & Tononi 2002; Tononi *et al.* 1998).

Analysis of the resting state dynamics of cortical networks suggests that they operate close to a self-organized critical (SOC) state (Deco & Jirsa 2012; Linkenkaer-Hansen *et al.* 2001; Plenz & Thiagarajan 2007; Priesemann *et al.* 2013; Wang *et al.* 2011). The SOC state provides favourable conditions for computations: Its memory capacity is maximal (Bertschinger & Natschläger 2004), the information transfer is most reliable (Shew *et al.* 2009; 2011), it can optimally separate between different inputs (Bertschinger & Natschläger 2004), and it shows the largest dynamical range (Shew *et al.* 2009; Kinouchi & Copelli 2006).

Predictions

If mechanisms posited by the hypothesis formulated above are exploited by the cortex, one can make the following predictions: i) Internal models of the world are stored in the architecture and weights of neuronal connections. ii) The highly complex dynamics that evolve on the backbone of this architecture provide the high dimensional space for the accommodation of an immense repertoire of potential states (memories, priors). iii) The complex spatio-temporal patterns of cortical activity reflect the superposition and coexistence of latent prior distributions, both inborn and acquired. iv) In response to input signals the initially unconstrained, high dimensional internal network dynamics (the internal model) rapidly assume metastable subregions of the state-space. v) These selected substates are distinguished by enhanced coherence (synchrony, covariance) of neuronal responses and constitute the solution of the search process. Hence the transition of the system towards a stabilized substate should be associated with a reduction in dimensionality. vi) The increased coherence of selected substates should promote their long term stabilization by Hebbian modifications of recurrent connections and this, in turn, should facilitate retrieval of familiar substates in future matching operations and their recruitment by down stream processes. vii) Robustly consolidated substates should be manifest in resting state activity and be detectable as replayed vectors or manifolds. viii) Simple stimuli drive the network in one of its normal modes and thus into states with low dimensional correlation structure while complex stimuli (natural scenes) evoke numerous normal modes simultaneously that superimpose and lead to high dimensional states. ix) Cortical networks should operate in a dynamic range close to Self Organized Criticality (SOC) because the intermediate level of existing correlations and the long correlation distance in SOC states facilitate the rapid relaxation of a dissipative system into coherent substates.

As reviewed recently (Singer 2013), some of these predictions are supported by data. Developmental studies indicate that the statistics of feature conjunctions in the outer world are translated into cortical connectivity according to a Hebbian mechanism (for review, Singer 1995). The anisotropy of this connectivity is reflected by the correlation structure of resting activity (Fries *et al.* 2001a), and the latter can be modified by learning (Lewis *et al.* 2009). Ample evidence is also available for the propensity of cortical circuits to engage in oscillatory activity in a wide range of frequencies and for stimulus dependent changes of correlation structure mediated by intracortical connections. Both features are hallmarks of recurrently coupled networks (for reviews see Singer 1999; Buzsáki *et al.* 2013). The fact that both sensory stimulation (Gray *et al.* 1989; Churchland *et al.* 2010) and top down signals related to attention (Fries *et al.* 2001b; Lima *et al.* 2011) enhance synchronized oscillatory activity in distinct frequency bands is compatible with processes of dimensionality reduction. There are also indications that cortex operates in a SOC state (Linkenkaer-Hansen *et al.* 2001; Plenz & Thiagarajan 2007; Wang *et al.* 2011). Finally, in a recent electrophysiological study (Nikolic *et al.* 2009) in the visual cortex of anesthetized cats we were able to demonstrate features characteristic of reservoir computing. We found that i) stimulus identity can be determined by a linear classifier fed with the responses of 60 randomly selected simultaneously recorded neurons, suggesting that information about stimuli is distributed, ii) stimulus-specific information persists up to a second, which supports the existence of fading memory, and iii) information about the nature and sequence of stimuli is retrievable for at least two successively presented stimuli, suggesting superposition of representations. Most importantly, in these pilot experiments we have obtained indications (unpublished) for unsupervised learning and replay of stimulus specific vectors in spontaneous activity. Classification improved for frequently presented stimuli because their response vectors became increasingly different and these vectors occurred spontaneously in resting states. Thus, in contrast to liquid state machines, where plasticity is neglected, real neuronal networks exhibit experience dependent long term modifications of their state.

Conclusions

In conclusion, I believe that theoretical arguments and available experimental results now provide sufficient ground to support the hypothesis that neocortex exploits the fantastic computational capabilities offered by complex systems with high dimensional, non linear dynamics in order to i) superimpose information about relational constructs and sequences, ii) perform computations for matching, pattern completion and invariance extraction, and iii) obtain fast results by relaxation into metastable substates of lower dimension, thereby simplifying classification and enhancing stability.

Thus, it appears as if nature had found a way to realize extremely powerful computational strategies by increasing the complexity of neuronal dynamics. The anatomical substrate for this increase in complexity is the cerebral cortex, the most recent invention of evolution. The prevailing principle appears to be dense reciprocal coupling among large numbers of nodes, whereby the nodes already possess highly diverse and non-linear dynamic properties and the connections differ in conduction time and coupling strength. These features generate a maximum of diversity and because of the high degree of non-linearity of the emerging dynamics, such networks provide an extremely high dimensional space for the storage and processing of information.

As is evident from comparisons with artificial intelligent systems, the computational abilities and the energy efficiency of cortical computations exceed by far those of man made systems. If the hypotheses formulated above should turn out to be correct, this is bound to have a strong impact on both neuroscience and artificial intelligence. In neurosciences, it will encourage the incipient paradigm shift from behaviourist stimulus-response concepts towards notions of predictive coding in self-organizing recurrent networks with high dimensional dynamics. It will also provide a new framework for the interpretation of pathological cognitive and executive functions and their experimental analysis, as there is first evidence that diseases such as schizophrenia and autism are associated with abnormal brain dynamics (Uhlhaas & Singer 2012). In the computational sciences it will further encourage and perhaps even instruct the already intense search for novel, biomorphic or brain inspired computer architectures. Finally, at the epistemic level, it would provide a first hint that evolution, by exploiting complex dynamics, has found a way to realize in a classical system functional aspects like fast parallel search and computation that so far were thought to be realizable only with quantum computers. The analogy with processes known to exist in the quantum world such as the coexistence of a large number of potentialities by the superposition of wave functions and the fast realization of one of these potentialities by the collapse of the wave function is fascinating. As quantum processes cannot play a role at the macroscopic scale at which neuronal network computations occur, this similarity suggests that increases of complexity of classical systems can lead to the emergence of qualities that bear a certain resemblance with features of the quantum world. Thus, the boundaries between the quantum world and the macroscopic world may turn out to be not as sharp as generally assumed.

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GLIMPSES OF THE NANOWORLD

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Abstract

Nano science and technology have added a new dimension to the frontiers of physical and biological sciences. The novel and unexpected properties of novel materials are indeed fascinating and many of them can be exploited for useful applications. In this article, various aspects of nanoparticles and nanotubes are examined. Some highlights of the newly discovered two-dimensional sensation, graphene, are presented.

Historical

The Lycurgus Cup is the only surviving example of a very special type of glass, the dichroic glass. The cup changes colour when it is held up to light. The cup is opaque green but when light is shone through it, it turns to a glowing translucent red cup. This is due to the small amounts of colloidal gold and silver present in it. The cup is an example of 'cage-cup' method of glassmaking. An episode from the myth of Lycurgus is the theme of the scene on the cup. The cup depicts Lycurgus trapped by the branches of a vine and tormented by Dionysus for his cruelty. In the Roman period, colloidal metals were used to dye fabrics, colour glass and to treat diseases. The Romans used metal particles together with glass to achieve dramatic effects. A popular dye, the Purple of Cassius, formed on reacting stannic acid with chloroauric acid is made up of tin oxide and gold nanoparticles. Maya blue used by the Mayas consists of indigo, silica and metal oxide nanocrystals. Damascus swords were first made in the eighth century. They were famous for their strength and sharpness. Peter Paufler and his colleagues in Germany studied samples from the blade of the Damascus sword and found tiny nanowires and nanotubes in the sample. They revealed the first ever carbon nanotubes present in steel. The swords were forged from Wootz steel first made in India around 300 BC.

Nature makes use of nanoparticles for specific purposes. For example, there are bacteria containing magnetite particles which are used for navigation.

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The first laboratory synthesis of nanomaterials was by Michael Faraday in the year 1857, who prepared gold nanoparticles. He called these materials divided metals since he actually did not know their dimensions. What is amazing is that he could make colloidal metal particles dispersed in solvents and recognized that they exhibited different colours depending on the size. Interest in the nanoworld of today seems to have been kindled by the famous statement of Feynman, 'There is plenty of room at the bottom'. Today, the subject has become extremely competitive and sophisticated. We shall now briefly trace the recent developments in this area.

Nanomaterials

More than a decade ago, nano structures fabricated by the manipulation of atoms were demonstrated in the United States in the IBM Corporation as well as in Hewlett Packard laboratories. Today, nanomaterials are made routinely by various methods. Nanomaterials include zero-dimensional nanocrystals or quantum dots, one-dimensional nanowires and nanotubes and two-dimensional nanofilms or sheets. The different forms of nanomaterials of metals, oxides, sulphides and a variety of other materials have been prepared. We can say that given any material, we can make it in the form of some nanostructure.

The main feature of nanomaterials is that their properties depend on size. This is unlike our experience in the normal world. The most well known example is that of cadmium selenide which on optical excitation emits light of different colours depending on the size of the particles. While 3.5 nanometer crystals of CdSe give out green light and 5 nanometer nanocrystals give out red light (Fig. 1). A good example of a size-dependent property in the nano regime is provided by metal nanoparticles. Gold, which is a shining metal, becomes a non-metal when the particle is small. A gold nanoparticle containing about 200 atoms is non-metallic. Small particles of gold (1-2 nm) are chemically reactive and do not exhibit the characteristic absorption band in the visible spectrum due to surface plasmons. Similarly, mercury ceases to be metallic when the particle has less than 250 particles. Small nanoparticles have all the atoms on the surface and the fraction of surface atoms decreases with increase in size.

To prepare nanoparticles, what one does is to choose an appropriate chemical reaction, prepare the particles dispersed in a suitable solvent first, and determine the distribution of size of the particles by electron microscopy. X-ray diffraction gives the structure of the nanoparticles. The structure may or may not correspond to the stable structure. Small particle size often favours metastable structures. Today there are many methods of

Figure 1. Fluorescence images of CdSe QDs as a function of size.

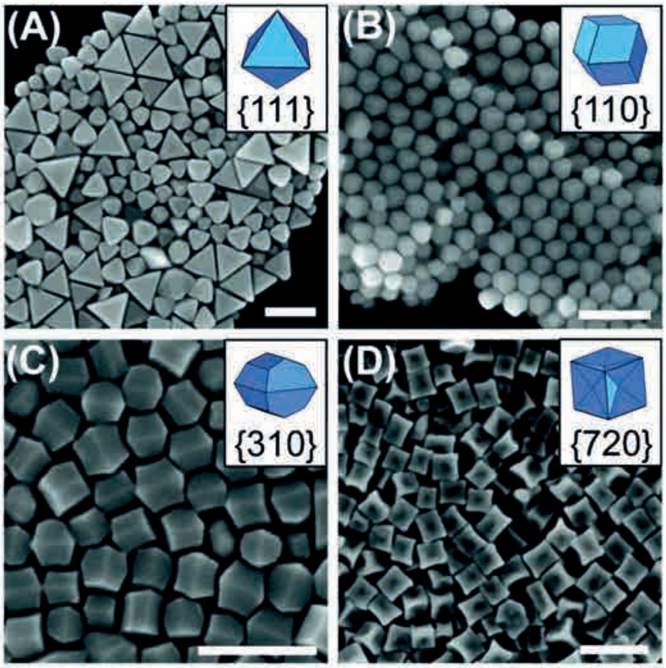

Figure 2. SEM images of (A) octahedra, (B) rhombic dodecahedra, (C) truncated ditetragonal prisms, and (D) concave cubes synthesized from reaction solutions containing Ag^+/Au^{3+} ratios of 1:500, 1:50, 1:12.5, and 1:5, respectively. Scale bars: 200 nm. Note the octahedra form concomitantly with {111}-faceted twinned truncated bitetrahedra, which are larger in size (from Chad Mirkin *et al.*).

making nanoparticles and other nanostructures. Nanoparticles of different shapes have also been generated (Fig. 2). For example, by using the interface between oil and water (or between an organic liquid and water), it is possible to make films of nanocrystals. Carbon nanotubes became famous in the year 1991. They are nothing but extended fullerenes (Fig. 3). They were first made by arc-discharge between graphite electrodes. The deposit near the cathode contains nanotubes. Since then, many methods have been devised to make carbon nanotubes which include the decomposition of metal organic precursors. In the last few years, inorganic analogues of fullerenes as well as nanotubes have been made. For example, nanotubes of molybdenum disulphide, boron nitride and many other layered inorganic materials have been prepared (Fig. 3).

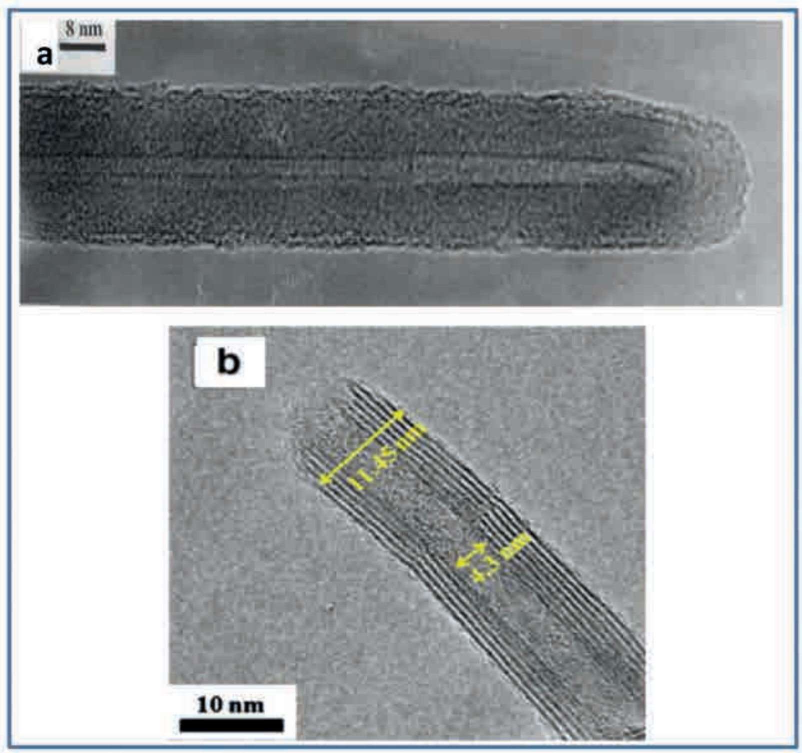

Figure 3. High resolution TEM image (a) of a multiwalled carbon nanotube, (b) of a multilayer TiO_2 nanotube.

Graphene

One of the greatest sensations in physical sciences in recent years is the discovery of graphene with unusual properties. Graphene is nothing but a single two-dimensional sheet of sp^2 bonded carbon atoms. It consists of six-membered rings and shows electronic properties which are most unusual, such as ballistic conduction and high mobility of electrons, quantum Hall effect at ordinary temperatures and a band structure wherein the valence and conduction bands meet at a unique point. A single sheet of such carbon atoms is normally referred to as graphene, but one can have two-, three- and few-layered graphenes as well. Anything beyond ten or twelve layers would be considered to be graphite. Single-layered graphene was prepared a few years ago by using the scotch-tape technique wherein the top layer of a graphite crystal was peeled off. Since then, many chemical and physical methods have been reported for the preparation of single- as well as few-layered graphenes. The edges in graphene sheets which have lone pair orbitals give rise to magnetic properties of these materials. An important form of graphene is provided by graphene nano-ribbons which have even more unique properties. They have more edges. When incorporated in polymers, graphene improves the strength and elastic modulus. Graphene can also be used as a field emitter and an infrared radiation detector. Field-effect transistors based on graphene have been fabricated. Graphene can be doped with elements like boron and nitrogen. Recently analogues of graphene of inorganic layered materials such as molybdenum disulphide and boron nitride have been prepared. They also exhibit certain unusual properties.

Applications

Nanomaterials have found a variety of applications in lithography, photovoltaics, catalysis, nanoelectronics and so on. Thus, many of the nanowires and nanosheets including graphene have been used to prepare field-effect transistors. Dip-pen lithography is a useful technique that makes use of nanoparticles as the ink. Nanoparticles of semiconductors have been used as biological sensors. Nanoparticles of semiconductors and metals can also be used to generate hydrogen. What should be noted is that nanowires of even ordinary materials such as zinc oxide are found to have a variety of applications. Thus, lasers and sensors based on zinc oxide have been fabricated.

Of all the applications of nanomaterials, those in medicine are catching great attention. Thus, gold nanoparticles can be used for destroying cancer cells. The gold particles are directed towards the tumours and on irradiation of these particles, they absorb light and give out the energy as heat. The temperatures reach very high values and burn the cancer cells. Many other types of therapies based on nanomaterials, have been proposed in recent times. Specially noteworthy is the nano nose device prepared in Israel which detects molecules specific to different types of cancers that the patient breathes out. The nano nose is truly impressive. Tissue engineering has emerged to be an important part of nano medicine. Scientists have grown artificial skin, spinal cords and such biologically (and medically) important components of the human body.

Conclusions

Nano science and technology has become the flavour of the day and promises to deliver many new innovations in physical, biological and medical sciences which are of important significance to the welfare of the human beings and society as a whole.

EARTH AND ENVIRONMENTAL SCIENCES

COMPLEXITY IN CLIMATE CHANGE SCIENCE

MARIO J. MOLINA

Summary

The Earth's climate is a complex system, and yet the basic science of climate change is clear: the average temperature of the Earth's surface has increased about 0.8 degrees Celsius since the Industrial Revolution. Deniers of climate change science have taken advantage of its complexity to discredit the consensus conclusion that the climate is changing most likely as a consequence of human activities, with potentially very negative impacts on society. Examples of findings that are often questioned include the average surface temperature increase inferred from global measurements, and the conclusion that the recent waves of extreme weather events are most likely connected with such an increase.

Climate change represents one of the most important challenges for society in the 21st century. Drastic cutbacks in activities such as burning of fossil fuels and deforestation are needed in order for mankind to limit its impacts on the Earth's climate.

There is little doubt that the climate of our planet is a complex system. A consequence is that there are uncertainties in our understanding of the science of climate change; nevertheless the scientific basis of the problem is very well established. From the Industrial Revolution to the present day the average temperature of the Earth's surface has increased by around 0.8°C, and the consensus among experts is that the probability that this increase has been caused by human activities is extremely large.

The risk of causing changes in the climate system with potentially catastrophic consequences rises rapidly if the average temperature of the Earth's surface is increased by more than 2 or 3°C. Thus, according to most energy and economics experts a reasonable goal for society is to limit the average temperature increase of the Earth's surface below 2°C in order to prevent dangerous interference with the climate system. Achieving this goal will require most likely an international agreement that places directly or indirectly a price on the emission of greenhouse gases.

It is often stated that the two-degree goal is what science tells us; it is clear, though, that science does not tell us what to do; it only advises us what might happen as a result of different courses of action. The 2°C figure comes in part because the risk of triggering nearly irreversible and potentially very damaging changes in the Earth's climate increases rapidly if the temperature increases by more than 2°C. But equally important is the fact that there are technological solutions to the problem at hand, and that the cost of taking the necessary measures to achieve the 2°C goal is relatively small, namely of the order of only one or two percent of the gross world economic product. But, most importantly, the consensus among economic analysts is that the cost of not implementing such measures is very likely significantly higher. In fact, postponing action and thus risking a temperature increase of five or more degrees could imply astronomical costs for future generations, threatening both our economic systems and our governance systems, and making it truly difficult to eradicate poverty on the planet.

There are, in fact, a number of well-documented scientific findings that tell us that if we continue with unabated emissions of greenhouse gases there is a significant risk of achieving a temperature increase of 5°C or more towards the end of the century, with the likelihood of reaching certain tipping points that could lead to changes in the Earth's climate system that, for all practical purposes, will be irreversible, such as melting of the poles, drying of the Amazon forest, or a disappearing Indian monsoon. Such catastrophes could have devastating consequences for literally hundreds or even thousands of millions of the Earth's inhabitants. And even if the probability that such events will occur is a mere five or ten percent, if society chooses to continue to move along a business-as-usual path, economics experts agree that this risk is the one that should actually dominate economic considerations, let alone ethical considerations, rather than the risk associated with the most probable outcomes.

If the basic conclusion of the scientific community is that the climate is indeed changing as a consequence of human activities with potentially very serious consequences for society, why, then, has the problem not been solved? The main reason is that there remain many political difficulties, and furthermore there are powerful interest groups that have mounted a very successful public relations campaign to discredit climate change science. The consequence has been that all sorts of media reports have stated that the basic scientific conclusion connecting climate change to human activities is questionable.

As stated above, the scientific community is, of course, aware that because of its complexity the current understanding of the science of climate change is not perfect, and that much remains to be learned, but nevertheless enough is known to estimate the probabilities that certain events will take place if society continues with "business as usual" emissions of greenhouse gases. The existing body of climate science is robust and extensive, and is based on many hundreds of studies and measurements conducted by thousands of highly trained scientists, with transparent methodologies, and with publications in the open scientific literature which have been rigorously peer-reviewed. The point is that the available scientific information is quite sufficient for society and decision-makers in government to assess the risk associated with the continued emissions of gases that affect the climate.

Furthermore, there are now numerous scientific studies that conclude that climate change is indeed the cause of many of the extreme weather events that are occurring with increasing frequency. The scientific understanding is not that such events would not have occurred in the absence of human-induced climate change; instead, it is the severity of the events in question that has been affected by this change in climate, which is of human origin.

In closing, the climate change challenge is urgent and society should adopt the necessary measures to reduce greenhouse emissions as soon as possible. Here I am not speaking as a scientist, but rather as an individual who strongly supports universal ethical values, and who values the wellbeing of future generations. We have an ethical responsibility to leave future generations a planet where its inhabitants can enjoy a quality of life on a par with, or better than, that of the present day. There is still time to act, although the window of opportunity is rapidly closing.

CLIMATE CHANGE AND PROTECTION OF THE HABITAT: EMPIRICAL EVIDENCE FOR THE GREENHOUSE EFFECT AND GLOBAL WARMING

V. RAMANATHAN*

Summary

Our understanding of the greenhouse effect and global warming is based on fundamental laws of physics, chemistry and thermodynamics. The greenhouse effect has been measured directly by high precision radiometers on satellites and the feedback processes through which the greenhouse effect warms the planet have also been measured. In addition, there is unambiguous empirical evidence for the link between the greenhouse effect and global warming. In this paper I will document these compelling observational evidence for the link between chemical pollution, increase in greenhouse gases and global surface warming. These empirical data lead us to conclude that the observed increase in the greenhouse gases is sufficient to ultimately warm the planet by more than 2°C during this century.

I. Background

i) Human Activities and Climate Change

Burning of fossil fuels leads to emission of carbon dioxide and several pollutant gases and particles into the atmosphere. Some of these gases and particles interfere with the flow of energy into and out of the planet thus altering the climate.

ii) Fundamental Drivers of Climate

The temperature of the surface and that of the atmosphere is largely determined by the flow of incoming solar radiation energy and the outgoing infrared radiation energy. About 30% of the solar radiation is reflected back to space by clouds, atmosphere and the surface. The remaining 70% heats the surface and the atmosphere, which in turn gives the energy back to space by emitting it as infrared radiation. So this process of net (incoming

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* University of California at San Diego.

minus the reflected solar) incoming sunlight warming the planet and the warmer surface-atmosphere system emitting more outgoing infrared energy goes on until the two (net incoming solar and outgoing infrared) balance each other. On a long time average basis, the absorbed solar radiation (incoming minus the reflected solar) is balanced by the outgoing infrared radiation. So that's what determines the climate of the Earth. Gases and particles in the air regulate the outgoing infrared while particles regulate the reflected solar radiation and thus regulate the climate.

iii) The Natural Greenhouse Blanket

Certain polyatomic gases such as water vapour and carbon dioxide absorb the infrared energy from the surface and thus inhibit its escape to space. As a result not as much infrared energy escapes to space to balance the net incoming solar. I think the way the greenhouse effect works is similar to that of a blanket. On a cold winter night the blanket keeps us warm, not because the blanket gives us heat, but it traps body heat. That's exactly how the gases behave. They trap the infrared energy coming from the Earth. Nature has provided us with a thick blanket in the form of water vapour and carbon dioxide, without which our planet would be frozen like Mars. The greenhouse effect, which is a well-understood phenomenon, is based on fundamental laws of quantum mechanics and Planck's black body radiation. While oxygen and nitrogen are the most abundant gases in the atmosphere, these two gases do not exert a greenhouse effect. Earth's dominant greenhouse effect is primarily due to water vapour and carbon dioxide. Both are naturally occurring greenhouse gases. Human activities have increased the concentration of carbon dioxide by about 40%. They have also increased the concentration of numerous other greenhouse gases such as methane, nitrous oxide, and halocarbons among others.

iv) The Albedo Effect

The percentage of incoming solar radiation that is reflected to space is referred as the planetary albedo, or simply the albedo. The particles in the air intercept the solar radiation and thus reduce the solar radiation that reaches the surface and the albedo. The reduction of solar radiation reaching the surface is called dimming. Some of these particles, like sulphates from coal combustion, reflect solar radiation like mirrors, increase the albedo and cool the surface while other particles, like soot, trap solar radiation, decrease the albedo and warm the atmosphere.

I will start with the most spectacular example of the warming effect of carbon dioxide.

II. Empirical Evidence of the Greenhouse Effect

i) Greenhouse Effect of Venus, Earth and Mars [Fig. 1]

For my PhD work I looked at the energy budget of Venus and Mars (Ramanathan, 1974). After graduation, I could not get a job in that field. By sheer luck, I found a post-doctoral fellowship at NASA to study the impact of ozone destruction on Earth's climate. This is how I started working on Earth's climate and was able to use my graduate studies to compare the greenhouse effect of the three planets.

Let us compare Venus with Earth. Earth receives 340 Wm^{-2} of solar energy compared with 650 Wm^{-2} for Venus, since it is much closer to the sun. The unit of Wm^{-2} is Watts of energy per square meter of surface. The average temperature of the Earth's surface is 15°C whereas Venus is superhot at 430°C. It is tempting to conclude that the hot temperature of Venus is due to the fact that it receives nearly twice (650 Wm^{-2} compared with 340 Wm^{-2}) as much solar energy as Earth. However, if we compare the albedo (percentage of solar radiation reflected by the planet) of the two planets, we

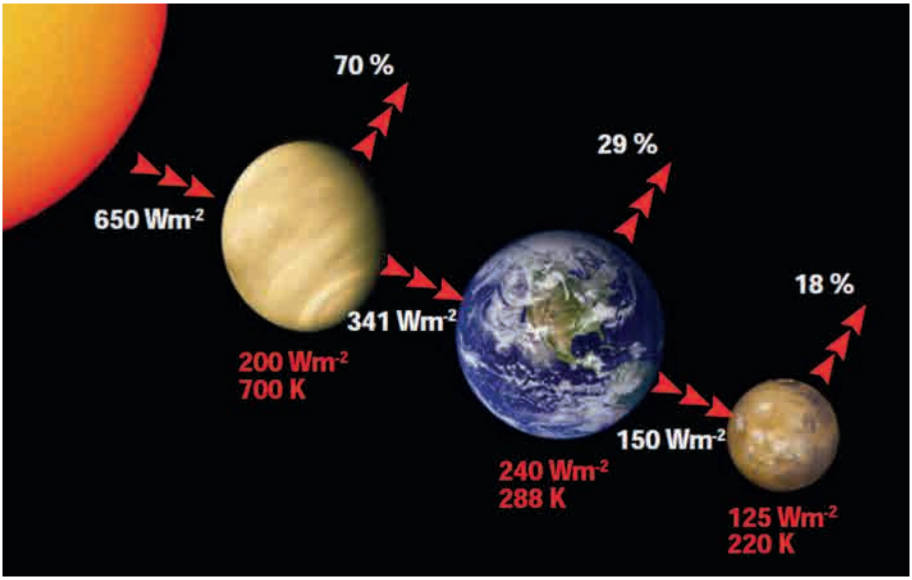

Figure 1. Why is Earth's albedo 29% and Was it always 29%? V. Ramanathan, Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California, USA. iLEAPS Newsletter Issue No. 5, April 2008. Space Images http://solarviews.com/ Photo copyrights: NASA/MODIS/USGS and Calvin J. Hamilton.

find that incoming solar radiation cannot explain the hotter Venus. Earth's albedo is only 0.29 whereas Venus' albedo is 70%. Earth is only partially cloud covered, whereas Venus is overcast all the time and that too by massively thick clouds (more than 40 km thick). As a result the solar radiation that is absorbed by Venus is only 200W^{-2} which is slightly even less than the 240Wm^{-2} absorbed by the Earth.

So solar energy is not the explanation for why Venus is hot. Venus is hot because of the greenhouse effect. It has about three hundred thousand times more carbon dioxide, and it is the greenhouse effect of carbon dioxide which maintains the superhot temperature of Venus at 425°C.

ii) Measuring the thickness of the greenhouse blanket from space [Fig. 2]

When I joined NASA in 1974 to model the climate impact of stratospheric ozone destruction I teamed up with engineers at NASA to design a satellite experiment, the Earth Radiation Budget Experiment [ERBE], to study the flow of solar energy and infrared energy in and out of Earth. ERBE had calibrated radiometers to measure both the incoming and the

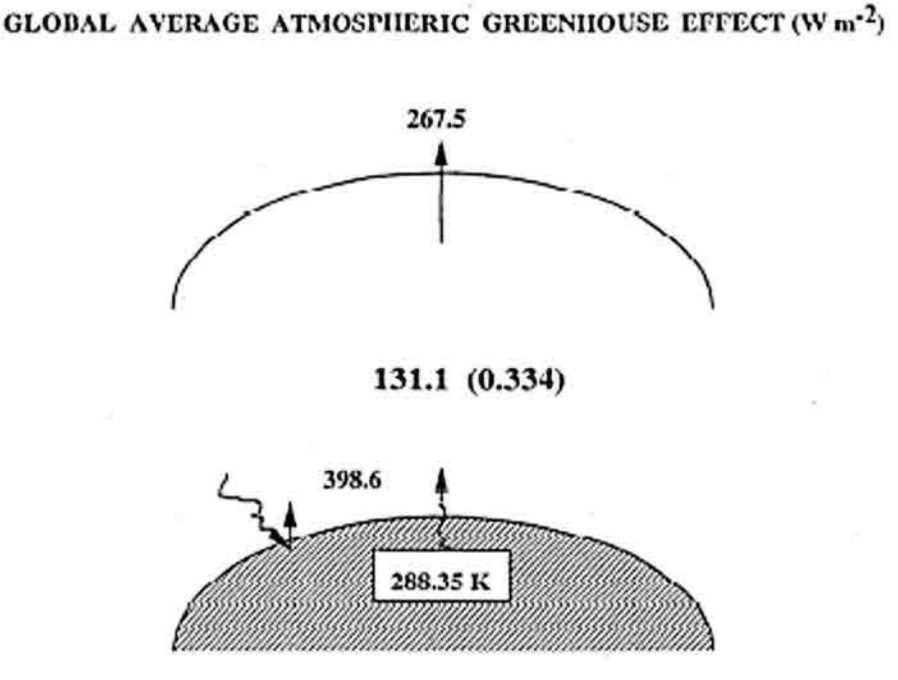

Figure 2.

reflected solar radiation and the outgoing infrared radiation. I proposed to use the infrared radiometer to determine the atmospheric greenhouse effect for the first time (Ramanathan, 1987; Raval and Ramanathan, 2000; Inamdar and Ramanathan, 1998). The method was very simple. We took the scanning radiometer to determine the outgoing infrared [OIR] from cloudless skies, i.e., the OIR escaping to space in-between overcast skies. The next step was to determine the infrared radiation from the surface. This was estimated from the surface temperature using black body radiation laws. The difference between the infrared energy emitted by the surface and that escaping to space is the energy trapped by the atmosphere and is a measure of the greenhouse effect in energy units [Wm^{-2}]. For the 1988 to 1990 period used in the study, the infrared energy from the surface was 398.6 Wm^{-2} [95% uncertainty of 1%] while the energy escaping to space (under clear skies) was only 267.5 Wm^{-2} [95% uncertainty 2%]. The trapping of the IR energy by the intervening atmosphere led to the reduction of IR by 131 Wm^{-2} (398.6-267.5) Thus the greenhouse effect was determined to be 131 Wm^{-2} [95% uncertainty of 4%]. This greenhouse effect of 131 Wm^{-2} is the sum of natural and anthropogenic effect and could be considered as the thickness of the blanket in energy units. Roughly 80% of the 131 Wm^{-2} greenhouse effect is due to naturally occurring water vapour.

III. Empirical Evidence for the Role of Human Activities on the Greenhouse Effect

i) How much have we added to the thickness of the greenhouse blanket?

Several international reports (Ramanathan *et al.*, 1985; IPCC-WGI 2013 report) have adopted the observed increase in the concentrations of greenhouse gases (CO_2; CH_4; N_2O; Halocarbons; Ozone; etc.) since the 1850s and integrated them with the quantum mechanical parameters for absorption of infrared radiation and estimated the infrared energy trapped in the atmosphere. The increase in the IR energy trapped by the greenhouse gases emitted by human activities is estimated to be 3 Wm^{-2} (with an uncertainty of 25%). Comparing this number with the 131 Wm^{-2} inferred from the satellite data for natural and anthropogenic greenhouse effect, we infer that: The Natural Greenhouse Effect by the atmospheric gases (water vapour; CO_2; and others) is 128 Wm^{-2} and the anthropogenic effect is 3 Wm^{-2}. Thus, human activities have thickened the greenhouse blanket by 2.3%. The build-up of carbon dioxide since the 1850s has contributed 1.7 Wm^{-2} – or about 57% – of the total anthropogenic effect of 3 Wm^{-2}.

ii) How long have we known about the anthropogenic greenhouse effect?

The first authoritative study on the greenhouse effects of carbon dioxide was published in 1896 by the Nobel Chemist Svante Arrhenius. For nearly 78 years we thought CO_2 was the only manmade climate pollutant of concern (see SMIC Report, 1972). That changed overnight when the greenhouse effect of a class of compounds called halocarbons was discovered in a study I published in 1975 (Ramanathan 1975). CFCs, one of the most popular refrigerants used then, was one such Halocarbon. I showed that the addition of one molecule of CFCs had the same warming effect on the planet as the addition of over 10,000 molecules of CO_2. CFCs were banned because of their effects on destroying the ozone layer (Molina and Rowland, 1974) under the Montreal Protocol. But now my work on the greenhouse effect of halocarbons has finally been recognized and last year, *The Economist* journal called the Montreal Protocol the most successful climate mitigation policy. CFCs were replaced by another halocarbon, called HFCs, also a potent greenhouse gas... There is now a global move to ban HFCs because of their global warming effect under the Montreal Protocol. What that means is that about 6% of the total anthropogenic greenhouse effect can be mitigated by the end of this century.

IV. Quantitative Link Between the Greenhouse Effect and Global Warming

Now that we have quantified the increase in the thickness of the blanket [since the time the British Engineer James Watt invented the improved steam engine], we have to address two important questions: *How large is the warming? & How soon will it descend on us?*

The thickening of the blanket has added 3 Wm^{-2} to the IR energy to the planet. In response, the planet will warm and radiate this energy to restore the energy balance between the net solar energy flowing in and the infrared energy flowing out. We will begin this discussion by making the simplest assumption possible, which is that the surface and the atmosphere behave like Max Planck's black body, in which case it will radiate energy to space as a black body, which is given by σT^4, where σ is a fundamental constant derived by Max Planck and T^4 denotes the fourth power of temperature T. Based on this law, the surface and the atmosphere will radiate 3.3 Wm^2 per 1°C of warming. In other words, the planet can get rid of 3.3 Wm^{-2} for every degree warming. So to get rid of the 3 Wm^{-2} energy trapped by manmade greenhouse gases, the planet will warm by (3/3.3=) 0.9°C. This analysis ignores some major feedbacks between warming and atmospheric greenhouse effect and planetary albedo.

i) Empirical evidence for the thermodynamic feedbacks between warming and the greenhouse effect of H_2O [Figs 3 & 4]

The water vapour (H_2O) in the atmosphere is to zeroth degree determined by the temperature of the air. It is an exponentially increasing function of temperature. For each degree (°C) rise in temperature, H_2O will increase by about 6% to 10% (depending on the value of temperature). With the increase in H_2O, the H_2O greenhouse blanket will increase (logarithmically). This increase is substantial since H_2O is the most powerful greenhouse gas in the planet. So, following the line of thought-experiment so far, increase in the concentration of greenhouse gases since the 1850s has increased the greenhouse effect by 3 Wm^{-2}. In response to this increase, the system begins to warm. The warmer surface and the atmosphere begin to

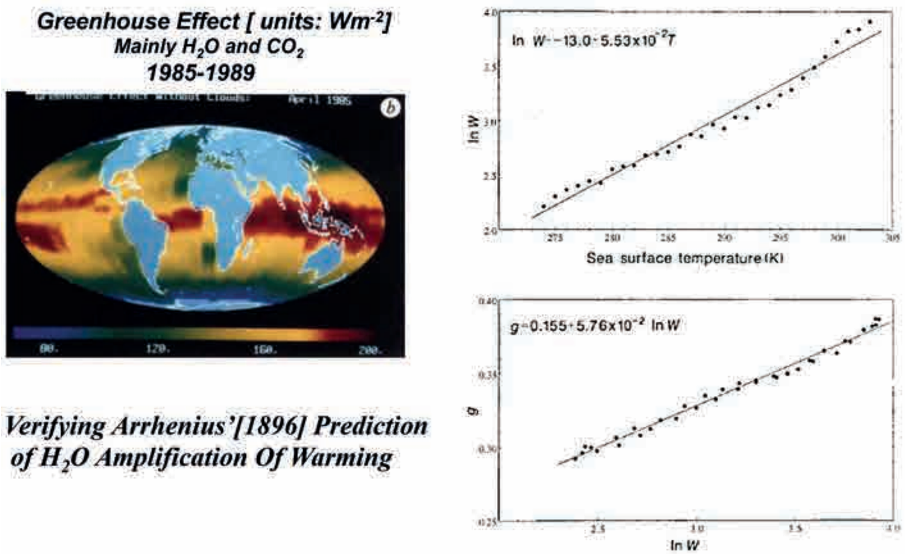

Figure 3. Atmospheric Greenhouse effect derived form satellite observation. Raval and Ramanathan, 1989. A: Natural logarithm of the atmospheric water content (*W*, kg m^{-2}) as a function of surface temperature, April 1982, monthly averages for 3° X 5° regions. The water content was derived from microwave satellite soundings available for 1979-1983. The error in *W* is ~ 10% (ref. 13). The strong positive correlation indicates that the behaviour of W follows simple thermodynamic laws; the slight upward and then downward deviations are consistent with the latitudinal variations in relative humidity and lapse rate which are governed by the dynamics of the atmosphere. B: Normalized clear-sky greenhouse effect (g) for April 1985 plotted against in *W* for April 1982. ERBE data is not available before 1985 whereas *W* is not available after 1983. To minimize the effect of year to year variations in W, we have used zonally averaged values.

radiate more IR energy, and with just this black body radiation and no feedbacks, the climate system should have warmed by about 0.9°C. However, as the atmosphere begins to warm, the water vapour content begins to increase and with it the water-vapour greenhouse effect begins to increase as well. In other words, the thickness of the greenhouse blanket, which increased due to human activities, is increasing further due to the Temperature-H_2O greenhouse effect feedback, and additional energy is being trapped and the temperature will increase further.

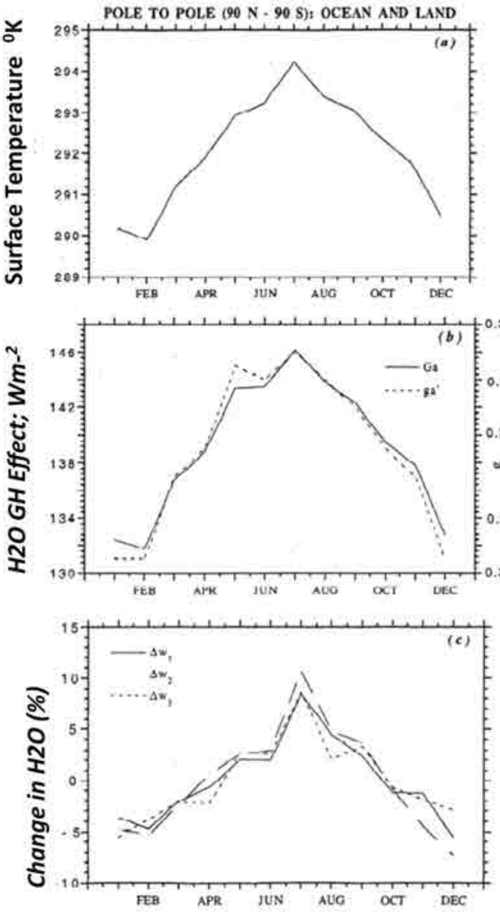

Figure 4. Observed data for climatological monthly variations in surface temperature (top), atmospheric greenhouse effect (middle) and water vapor amount (bottom) in lower (DW1), middle and upper troposphere (DW3). Ref: Inamdar and Ramanathan, 1998.

The link between atmospheric temperature, atmospheric water vapour content and its greenhouse effect was first proposed by Arrhenius in 1897. It has now been verified with satellite data (Raval and Ramanathan, 1988; Ramanathan and Inamdar, 1997) for the first time. Global distribution of the thickness of the blanket as obtained by the Earth Radiation Budget Experiment (see earlier discussion) reveals (Fig. 3, left hand panel) that the IR energy trapped in the humid tropics is twice as much as that in the drier extra-tropical regions. To look at it more quantitatively, the right hand panels plot the observed water vapour amount as a function of observed sea surface temperature (top panel) and the observed thickness of the blanket as measured in terms of the energy trapped in Wm^{-2} (vertical Y-axis) as a function of the observed water vapour amount (horizontal X-axis). The increase in water vapour amount with temperature is within 10% of the slope predicted by thermo-dynamical laws (top right hand panel). On the bottom panel the thickness of the blanket has been normalized by the surface emission. If the value of this normalized thickness is 0.3, it means 30% of the IR energy emitted by the surface has been trapped by the atmosphere. The bottom panel shows the normalized thickness increases with water vapour amount and furthermore it increases as the logarithm of the water vapour amount as predicted by quantum mechanics of the water vapour molecule. Thus far, our analyses use the observed spatial variation of water vapour and surface temperature to show the link between surface temperature, the water vapour amount and the thickness of the greenhouse blanket. It demonstrates that this link is governed by the thermodynamics of water vapour combined with the quantum mechanics of water vapour absorption of IR radiation. We will now look at a more critical test of the water vapour feedback.

Fortunately, the planet does a spectacular experiment every year. Each year, when we integrate temperature, water vapour amount and its greenhouse effect over the whole pole, from North Pole to South Pole, July is warmer by about 4° than January (Fig. 4 right hand top panel). We have millions of observations from satellites on this. As the planet warms from January to July, the humidity (measured by a microwave instrument on a NASA satellite) increases almost exactly by the amount (middle panel) predicted by the thermodynamics of water vapour (Fig. 4 middle panel). The humidity increases at all levels of the lower part of the atmosphere called the Troposphere. In conjunction with increase in surface temperature (top panel) and water vapour amount (middle panel), the atmospheric greenhouse effect increases proportionately (logarithm of the water vapour amount). The data in Fig. 4 shows that the greenhouse effect of water vapour increases by about 1.4 Wm^{-2} for each degree in warming. In the earlier analyses, we ignored all feedbacks, and estimated that the forcing of 3 Wm^{-2} due to the stock of greenhouse gases in the atmosphere as of 2010 should have warmed the planet by 0.9°C. The inclusion of the water vapour feedback would increase the projected warming from 0.9°C to 1.7°C.

ii) Empirical evidence for the ice-albedo feedback [Fig. 5]

In 1969 two studies, one by a Russian climatologist (Budyko, 1969) and another by an American meteorologist (Sellers, 1969) suggested that surface warming by CO_2 (or any other warming agent) would lead to an increase in the melting of snow and ice and the exposure of the underlying darker surface would lead to more absorption of solar radiation. The albedo (percent reflection of solar radiation) of fresh snow is about 0.8 or more, whereas land surface albedo is typically about 10% to 40%, while that of the underlying ocean is about 5% to 20%. Budyko and Sellers hypothesized that this link between warming, retreat of sea-ice and snow would lead to amplification of global warming. This hypothesis was verified recently by Pistone, Eisenman and Ramanathan (2014) using microwave data for sea ice and radiation budget data for albedo. They showed that from 1980 to 2010, the arctic warmed by about 2.5°C, annual mean sea ice retreated from 63% to 53% and the arctic averaged albedo decreased from 52% to 48%. The increased solar energy absorbed by the Arctic Ocean was about the same as the added energy trapped by thickening the CO_2 greenhouse blanket by 25%. This positive feedback between increase in the greenhouse gases, arctic warming and darkening of the arctic confirmed the Budyko-Sellers' hypotheses. Inclusion of this positive feedback to our estimates thus far, would amplify the projected warming from 1.7°C (with water vapour feedback) to about 2°C.

iii) Comparison of the empirically estimated warming with observed warming

Using observations from the ground and from satellites, we have concluded that the observed build up of greenhouse gases and the resulting thickness of the greenhouse blanket (by 3 Wm^{-2}) should have warmed the planet already by 2°C. In contrast, the planet has thus far warmed by about 0.85°C (as of 2010) since about the late 1880s.

So, where is the missing heat? Our estimate of 2°C is for so-called equilibrium warming, which is the warming of the system after it has had sufficient time to respond to the added heat. This inertia of the system is governed by the ocean, which has a huge heat capacity. Ocean observations suggest that the heat added by the blanket has penetrated to about 1000 meters in the ocean and, as a result, about 0.6°C is stored in the ocean and within several decades the system will warm by another 0.6°C, even if we stop adding greenhouse gases as of today. If we add this to the 0.6°C observed warming, the warming will increase from 0.85°C to 1.4°C compared with our predicted value of 2°C. We still have to account for another 0.6°C of the missing heat. It turns out that human activities, particularly coal combustion, diesel combustion and biomass burning, have also resulted in addition of particles to the air (aerosols) and these particles (with the exception of black carbon in soot) reflect the incoming sunlight and enhance the albedo, thus adding mirrors to the greenhouse blanket.

This cooling effect of these particles is an area of intense research by several hundred researchers around the world and suffers from a large uncertainty range, but the best value for the cooling effect of manmade particles is about -0.6°C (-0.2 to -1.8°C). This cooling effect is not a permanent effect and it should at best be considered as a mask behind which resides the greenhouse blanket.

So why should the aerosol cooling effect be treated as a mask? These particles are part of air pollution which kills about 7 million each year. Worldwide there are efforts to clean the air of these particles, as has already happened in many industrial nations. The lifetime of these particles is only of a few days. So mitigation efforts to clean the air (e.g. putting sulphur scrubbers in coal plants) will get rid of the particles and their cooling effects in a few weeks, which will then expose the planet to the full effect of the manmade greenhouse blanket and the planet will warm by additional 0.6°C of warming, which will increase the total warming from 1.4°C to 2°C in agreement with the predictions based on empirical data.

V. What Were The Predictions and How Do They Compare With Observations?

Every theory must be judged by the predictions it makes. We must judge the greenhouse theory of climate change accordingly. So what were the predictions? This is not an exhaustive list but includes the most important ones:

- *Warming will be amplified due to water vapour feedback (Arrhenius, 1896)*
- *Warming will rise above background noise by 2000 (Madden and Ramanathan, 1980)*
- *Warming will be amplified in polar regions due to snow/ice albedo feedback (Budyko, 1950s)*
- *Both land and oceans will warm (Manabe and Wetherald, 1975)*
- *Stratosphere will cool (Manabe and Wetherald, 1967 & others)*
- *Global average precipitation will increase (Manabe and Wetherald, 1975)*

The first five predictions have been confirmed by observations (see earlier descriptions for the feedbacks due to water vapour and snow/ice albedo feedback). The last one dealing with global average precipitation is yet to be verified. One issue is that the particles' effect is to decrease precipitation and this offsetting effect, coupled with the noisiness of the precipitation data, has obscured the greenhouse gas signal.

TOWARDS A SUSTAINABLE USE OF NATURAL RESOURCES BY RESPECTING THE LAWS OF NATURE

WERNER ARBER

Introduction

On our planet Earth a remarkable diversity of living organisms exists which make use of a great number of diverse habitats. This represents a highly complex global system of mutual interdependencies, both between different forms of life and of living organisms with their used habitats (1). Although this global setup reflects a relatively comfortable stability, both the living world and its habitats undergo a slowly progressing but steady evolution (2).

Most kinds of living organisms are forced to use a number of natural resources such as available nutrition, potable water, sources of energy and other life-supporting elements. Thanks to its remarkable intelligence the human species has been quite successful in doing so. It is in particular in recent centuries that our impressive acquisition and progression of scientific knowledge together with its beneficial applications has provided various kinds of benefits and facilities to human life. This raises the question of responsibility to ensure a long-lasting sustainable development on our planet. Answers to this question will be sought in the following sections.

Appreciation and cultural values of scientific knowledge

In the course of recent times, ever more powerful methodology has allowed the scientific community to acquire in fundamental research a remarkable treasure of scientific knowledge. This basic knowledge includes deep insights into the fundamental laws of nature and represents cultural values for our civilization (3). On the one hand, scientific knowledge enriches our worldview, which forms part of man's orientational knowledge influencing his decisions, including those which impact on sustainable development. On the other hand, it is often novel scientific knowledge together with appropriate methodology that can lead to practical applications to the benefit of human life, as well as of the wider environment. Good examples for this general outline can be found in many disciplines of scientific investigations. In the life sciences, striking developments currently occur in genomics and its applications (4).

Insights into cosmic/terrestrial evolution

Astrophysical investigations indicate that the Universe in which we live must have steadily but slowly evolved since about 14,000 million years ago. At the microlevel, fundamental particles contributed to form atoms, chemical elements, composing matter. At the macrolevel, numerous galaxies appeared in the course of time. Their stars are solar systems with extremely long but limited life times. Our solar system with its planets must have an approximate age of 4,500 million years. Our sun can be expected to continue to provide energy to the Earth still for a few thousand million years.

Insight into biological evolution

Life on our planet is postulated to have its origin some 3,500 million years ago and it must have slowly evolved ever since that time to reach by today a remarkable diversity of forms of life. These have in common to be able to replicate and to have the potency to undergo evolution at the level of their populations.

Molecular genetic research has revealed that diverse specific molecular mechanisms contribute stepwise to the evolution process by occasionally forming a genetic variation in an individual organism. The so far closely studied specific molecular mechanisms can be assigned to three qualitatively different groups that we call natural strategies of genetic variation (5).

A first strategy brings about a local change in the nucleotide sequence of the genome. Such local changes can be a nucleotide substitution, a deletion or an additional insertion of one or a few nucleotides, or a scrambling of a few adjacent nucleotides. Local genetic variants can have their origin upon DNA replication or by the impact of a mutagen. Local mutations occur quite rarely thanks to the preventive action by repair enzymes that modulate the rate of local genetic variation. Only occasionally a local mutagenesis brings about an improvement of a biological function. This then provides the organism in question with a selective advantage in comparison with its parent. More frequently, a new genetic variation results in a selective disadvantage by an impaired or lost function.

A second natural strategy of genetic variation consists in an intragenomic rearrangement of DNA segments. Recombination enzymes are thereby usually involved. Such rearrangements can bring about the duplication, the deletion, the transposition or the inversion of a DNA segment. This can lead to the loss of function or the novel fusion of previously independent functional domains. In the latter case, the DNA rearrangement may, by chance, result in an improved or even in a novel function providing a selective advantage. Segment-wise DNA duplication provides means for subsequent further mutagenesis in one of the copies while the second one may maintain its inherited essential function.

A third strategy of genetic variation consists in the acquisition by horizontal DNA transfer of a segment of genetic information from another kind of living organism. The DNA acquisition strategy can provide an elsewhere developed, useful biological function to the receiving organism in only one step. This strategy is a sharing in the evolutionary success of others. The universality of the genetic code, i.e. of the genetic language used, favors the success of this strategy (6).

These three natural strategies have in common to affect in each step of genetic variation only a tiny fraction of the whole genomic information. This ameliorates the chance of spontaneous mutagenesis to bring about a functional improvement (rather than a functional disharmony) to the organism in question. But we have to be aware that spontaneous mutagenesis events are largely conjectural (7). As a matter of fact, this makes sense, if we look at the global system of evolving life in evolving environments. Living beings can, of course, not predict which different kinds of environmental living conditions they are going to encounter. Adaptation goes stepwise by the impact of natural selection on populations of different genetic variants and their parents. Natural selection reflects the capacity of a living being to deal with its environment, i.e. with the physico-chemical composition of the environment and with other forms of life in the given ecosystem.

Self-organization or intelligent design?

A critical evaluation of the scientific knowledge on biological and on cosmic evolution indicates that these processes reflect nature's self-organization. This points to intrinsic potencies to undergo steps of alterations: genetic variation as the driving force for biological evolution and steps of various kinds of structural and compositional transformations in cosmic/terrestrial evolution. We, human observers, can be particularly impressed by the logical nature of these processes. This raises the question of a possible direction of evolution by "intelligent design". So far, we have no scientific argument that would point to this concept of a designer, a planning authority for the macro system of evolving life in an evolving environment. Nevertheless, the encountered situation representing permanent creation can appear wonderful and miraculous to the human observer. This requires and justifies a deep respect for the natural processes of evolution and a particular care not to interfere drastically with the evolutionary processes on our planets.

Additional facts to be considered

We have become aware that living beings do not only depend on their own genetic information; rather, they may profit, or sometimes suffer, from impacts by their environment. Many epigenetic effects are responses to environmental contacts and can influence various life performances. On the other hand, living organisms often show genetically anchored possibilities to live in various kinds of environment. Think, for example, of bacteria able to grow on different alternative sources of energy. Genetic expression can thereby respond to the encountered environment. Another situation largely neglected until recently is the cohabitation of various living organisms. Symbiosis between microorganisms and higher forms of life (humans, animals, plants) greatly facilitates life of the cohabiting partners. Only rarely microorganisms can thereby become pathogenic, either by novel mutations or by environmental impacts. These few indications can remind us of the long-neglected complexities of sustaining life in evolving environments.

Fundamental laws of nature can provide guidance for a sustainable development

Fundamental laws of nature are known to influence and regulate capacities and processes intrinsic to the living world and/or the inanimate world. We have here already referred to the situation in biological and in cosmic/terrestrial evolution. Another example can be the laws controlling chemical and physical stabilities of atoms and molecules including tautomery and atomic decay. Generally speaking, it is a good precautionary principle to respect the laws of nature in the inventive application of acquired scientific knowledge to the benefit of the human population and its environment; together with other measures this can insure sustainability of the development. Other measures can involve, for example, the prediction of possible impacts by a scientifically based technology assessment before an envisaged innovation becomes introduced. Similarly, it is advisable to carry out scientifically based policy assessment before political measures to either favor or hinder the introduction of possible innovations become activated.

Genetically modified food plants

As an illustration to these suggestions, let us turn our attention to genetic engineering applied to essential food plants. Genetic engineering was inspired by, and it generally follows, the three natural strategies of genetic variation: i.e. local DNA sequence changes, intragenomic rearrangement of DNA segments and insertion of a DNA segment from another kind of living organism. These manipulations are not done randomly but with good knowledge of the specific biological functions involved. These experimental approaches are most successful if only small amounts of genetic information are involved, as it is also the case in spontaneous genetic variation. In addition, we have to note that any engineered genome will reveal its activities and viability under the pressure of natural selection, as it is the case in spontaneous genetic variation. We can conclude that directed evolution by genetic engineering follows fundamental laws of nature and should thus not be expected to be associated with method-specific unforeseeable dangers (8). This holds at least as long as horizontally transferred genes are actually taken from a living organism.

As a suggestion for a sustainable contribution to provide accessible and healthy nutrition to all human beings, we have discussed a road map to enrich nutritional values as well as the plant's health of a number of widely used food crops (9). It should be possible to reach this goal by genetic engineering based on our increasing knowledge in genomics and metabolomics accompanied with careful experimental testing for the envisaged results. If successful, this approach may, in fact, lead to a largely vegetarian diet. This might, at a longer term, free large surfaces of agricultural land from growing animal feed and render it available for growth of food plants for human nutrition.

Limited carrier capacity of our planet

As we have seen, we find on our planet Earth a very rich diversity of forms of life using a remarkable diversity of habitats. But the space available on our planet must have remained constant during many million years of past evolution. We have good reasons to expect and to hope that this remarkable richness will continue to evolve on the basis of the present diversity. Thus, our civilization should avoid drastically disturbing the natural process of this slow but steady evolution of forms of life and of potential habitats for a rich biodiversity. This strongly requires humanity to abstain from claiming more and more fertile soil to exclusively produce food crops by agricultural practice with monocultures. These requested limits to overuse the available carrier capacity of our planet mainly for human beings requires the human population to reach an equilibrium that may allow for a largely undisturbed, further biological evolution of many different forms of life in a rich diversity of habitats. Let us remember that our sun can be expected to send energy to Earth still for many million years. Sustainable development should avoid strongly interfering with the ongoing process of biological evolution in the context of terrestrial evolution.

Tasks of education

It will be an important educational task of the scientific community and the political leadership to spread and to validate the fundamental principles discussed here. This can enrich our worldview as part of our orientational knowledge, the basis for our behavior and activity. A well-informed population can be expected to contribute to a long-term sustainable development of life on Earth.

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WATER FOR FOOD: EVOLUTION AND PROJECTIONS OF WATER TRANSFERS THROUGH INTERNATIONAL AGRICULTURAL TRADE

CAROLE DALIN[1] AND IGNACIO RODRÍGUEZ-ITURBE[2]

Summary

Water resources are unevenly distributed on the planet. In some regions, while population grows and diets shift toward water-intensive products like meat, water resources are placed under increased pressure, leading to water and food security issues. Besides, many areas of the world are expected to suffer from increasingly frequent and intense droughts under climate change, which will strain water resource use in agriculture even more and potentially lead to crop failures (Field *et al.*, 2012). However, other regions have abundant water resources, prosperous agriculture and might slightly benefit from climate change in terms of crop yields (Parry *et al.*, 2007). Thus, among different strategies to increase agricultural water-use efficiency (i.e. mechanization, water-saving irrigation, fertilizers, etc.), trade of water-intensive products (e.g. agricultural commodities), or virtual water trade (VWT), is a way to improve global water-use efficiency by virtually transferring water resources to water-stressed regions.

In two articles published in peer-reviewed journals, (Dalin *et al.*, 2012a) and (Dalin *et al.*, 2012b), forming part of the Ph.D. dissertation of Carole Dalin (Dalin, 2014), we focus on the virtual water trade network associated with international food trade, built with annual trade data (FAO, 2010) and annual estimates of the virtual water content of food commodities (the amount of water required to produce a unit of product in each country (Hanasaki *et al.*, 2008b)).

In the first study, the evolution of this network from 1986 to 2007 is analyzed and linked to trade policies, socio-economic circumstances and agricultural efficiency. We find that the number of trade connections and the volume of water associated with global food trade more than doubled

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in 22 years. Despite this growth, constant organizational features were observed in the network. However, both regional and national virtual water trade patterns significantly changed. Indeed, Asia increased its virtual water imports by more than 170%, switching from North to South America as its main partner, while North America oriented to a growing intra-regional trade (Figure 1). A dramatic rise in China's virtual water imports is associated with its increased soy imports, following a domestic policy shift in 2000. Significantly, this shift has led the world's soy market to save water on a global scale, but also relies on expanding soy production in Brazil, which contributes to deforestation in the Amazon. We find that the international food trade has led to enhanced savings in global water resources over time, indicating its growing efficiency in terms of global water use.

In the second study, we determine which variables control the virtual water trade network's structure and temporal evolution from 1986-2008, and estimate changes in the network under future scenarios. Our fitness model reproduces both the topological (connections) and weighted (flows) characteristics of the network for the whole period. Undirected and directed network properties are well reproduced in each year, assuming as sole controls each nation's GDP (Gross Domestic Product), mean annual rainfall, agricultural area, and population. The future structure of the network is estimated using climate and socio-economic projections, showing that volumes of virtual water traded will become increasingly heterogeneous and the importance of dominant importing nations will further strengthen.

Evolution of global virtual water trade flows[3]

On a global average, agricultural water productivity has improved during the 22-year period from 1986-2007 (crop yields increased by 10-47%). In particular, major soy exporters significantly reduced their water use for soybean production, notably by increasing soy yield (72% increase in Argentina from 1997-2007). Interestingly, Brazil and Argentina changed their soy yield and water productivity fast enough to reach a slightly higher level of soy water productivity than the USA by 2007 (around 1,500 *kgwater/kgsoy* vs 1,650 *kgwater/kgsoy* in the USA). Thus, as countries become major exporters of a certain crop, they tend to increase their agricultural water productivity for this crop – notably through higher yield per area – more than other countries do on a global average. This is also reflected by the positive global

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[3] Additional findings, as well as detailed material and methods, can be found in the published article (Dalin *et al.*, 2012a) and its appendix.

water savings from food trade, corresponding to trade flows from relative more water-productive areas to less productive ones.

Despite water being only one of the many factors of agricultural production and trade (other factors include the economy, labor, agricultural land, etc.), we find that in 2000, global water savings represented 4% of the water used in agriculture, and this percentage increased to 9% in 2007. This illustrates that food trade actually reduces global water use by transferring commodities to relatively less-productive regions, as irrigation requirement per unit of crop vary widely among world regions (Hanasaki *et al.*, 2008b, a; Foley *et al.*, 2011). Particularly, the soy trade dramatically re-organized and changed from a system that lost water at the global scale to the most efficient food trade system in terms of water. However, deforestation of the Amazon rainforests, partially due to the expansion of Brazil's soybean production (Fearnside, 2001), has important impacts on the water cycle (Shukla *et al.*, 1990).

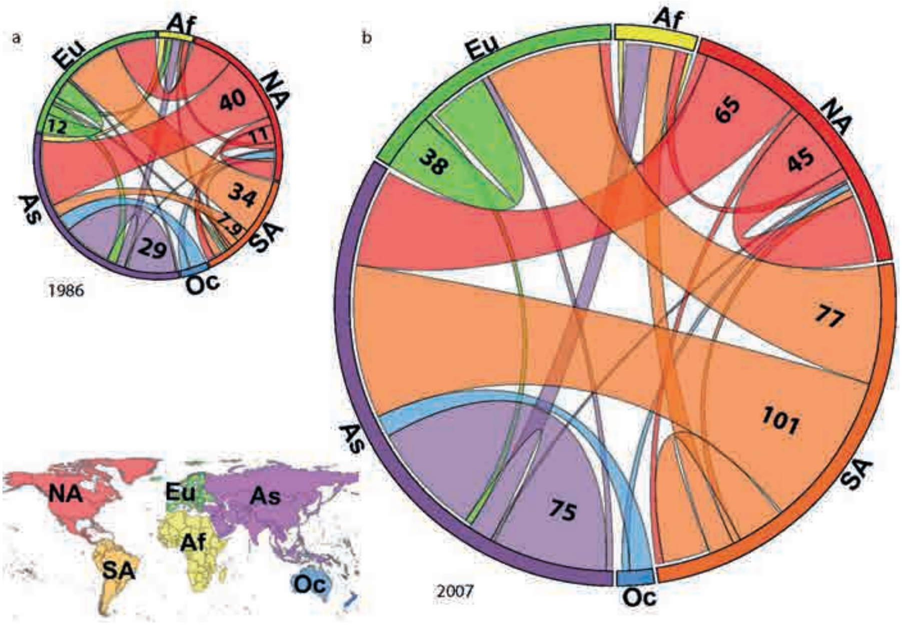

Figure 1. Virtual water flows between the six world regions: Africa (Af), North America (NA), South America (SA), Asia (As), Europe (Eu), and Oceania (Oc). Panel a: Regional VWT network in 1986. Panel b: Regional VWT network in 2007. Numbers indicate the volume of virtual water trade in billion of cubic meters (*km*^{3}), and the links' color corresponds to the exporting region. The regional map at the bottom left provides a key to the color scheme and acronyms of regions. The circles are scaled according to the total volume of VWT. Note the large difference between total VWT in 1986 (259 *km*^{3}, panel a) and 2007 (567 *km*^{3}, panel b). Taken from Dalin *et al.* (2012a).

We have quantified the important changes in the water and food systems as linked through trade. The imprint of globalization and trade policies are evident in the dynamics of the global virtual water trade network (Figure 1). Importantly, the food trade has become more efficient in terms of global water resources use over time, highlighting the important role of international trade in driving efficient allocation of resources.

Structure and controls of the global virtual water trade network over time[4]

We have shown food trade has increasingly saved water over time (Dalin *et al.*, 2012a; Konar *et al.*, 2012), as countries with low agricultural water productivity tend to import food from more productive countries. These global water savings exist even though water is usually not a strong driver of international trade. Thus, it is important to understand the major factors controlling water transfers through international food trade, or global virtual water trade.

Suweis *et al.* (2011) built a fitness model that reproduces the global structure of the international VWT network in 2000 using a few controlling variables: national GDP, rainfall, and agricultural area. This model can be used to predict the future global structure of the network under climate

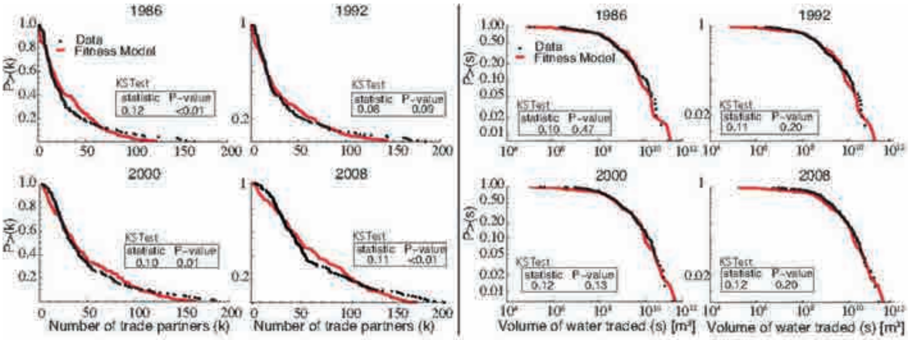

Figure 2. Exceedance probability distribution of the undirected node degree (*k*, panel a) and strength (*s*, panel b): comparison of data and model results in 1986, 1992, 2000 and 2008, using GDP and RAA, respectively. The similarity between data and model is confirmed by a Monte-Carlo Kolmogorov-Smirnov test; test results are shown in the "KS test" box. Taken from Dalin *et al.* (2012b).

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[4] Additional findings, as well as detailed material and methods, can be found in the published article (Dalin *et al.*, 2012b) and its appendix.

and socio-economic changes. Here we compare the structure of the empirical network each year with the structure obtained from the fitness model using input variables specific to each year. Finally, we show the predicted structure of this network under socio-economic and climate scenarios.

In the undirected version of the network, a node's degree is the number of export and import partners of each country and a node's strength is the nation's volume of virtual water exports and imports. We find that the distribution of node degree is well fit by an exponential distribution every year. Similarly, the distribution of node strength is well fit by a stretched exponential distribution every year, presenting larger heterogeneity than the node degree distribution. This reflects the dominance of a few countries concentrating large parts of the global VWT volume.

To model the nodes' degree and strength, we attribute to each node two fitness variables: one based on the country's annual GDP (time series from 1986-2008 (The World Bank, 2012)) and the other on the nation's long-term average annual rainfall (Aquastat, 2010) and agricultural land area (time series from 1986-2008 (Food and of the United Nations (FAO), 2010)). The two fitness variables assigned to each node i, normalized GDP and normalized Rainfall times Agricultural Area (RAA), are used to characterize the undirected network properties in each year from 1986-2008. Both for node degree and node strength, we observe that the model and data match closely for all years studied (Figure 2).

In the directed version of the network, each node has two weighted properties: in-strength, s_{in} (i.e. import volume), and out-strength, s_{out} (i.e. export volume). To characterize the asymmetry of the directed and weighted network, the fitness variable assigned to each node needs to be different whether the country participates in the trade as an exporter or as an importer. Thus, in this paper (Dalin *et al.*, 2012b), we choose for the first time two different fitness variables for exporting and importing nodes. As RAA represents well the nation's potential to produce and thus export food, we use this variable for exporting nodes (y), and for importing countries, we choose a variable related to food demand, represented by the national population (z). We then attributed to each link directed from i to j a weight based on y_i^n and z_j^n. Using this procedure, we obtain a close match between the modeled and observed distributions of directed strengths over the period. Thus, simple node properties such as rainfall, agricultural area and population allow us to model the two distinct distributions of exports and imports in the network.

Having shown the good performance of the fitness model to reproduce the statistical properties of the network using a few external variables, we apply this model to predict the future structure of the network under different scenarios for the year 2030.

We observe that the difference between projected node strength distributions with the driest and with the most humid climate scenario appears to be negligible. Both rainfall projections correspond to an increased strength of all countries, particularly for dominant nations. Indeed, the projected strength distributions present remarkably large tails, implying that the dominance of a few countries in the network will increase and the heterogeneity among nations will grow.

We have shown that our fitness model reproduces well the topological and weighted properties of the undirected and directed virtual water trade network via food trade over a time-period of significant changes (1986-2008), assuming as sole controls each nation's GDP, rainfall on agricultural area, and population. The population variable is shown for the first time to reproduce the crucial directed flows of virtual water over time. The simplicity of these input variables implies that future scenarios may be easily run to predict the future global structure of the global VWT network. The tendency for a few countries to concentrate most virtual water trade flows has been observed in the past, in particular with the emergence of China as a major importer (Dalin *et al.*, 2012a). We found that the distribution of network flows is expected to become increasingly heterogeneous, and, thanks to our directed network modeling framework, that a few importing countries are likely to concentrate a significant portion of virtual water trade through food commodities.

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SCIENCE, EDUCATION AND THEOLOGY

ANALOGY, IDENTITY, EQUIVALENCE

MICHAEL HELLER*

Abstract

Category theory, possibly more than any other mathematical theory, has a rich philosophical significance. The reason why it has not been so far exploited by philosophers is that they know it, if at all, only superficially. In the present essay, I shall explore only one aspect of this theory, namely the way it contributes to our understanding of such concepts as: analogy, identity, equivalence. It goes without saying that these concepts play a paramount role not only in many scientific disciplines, but also in philosophy of science and in some fundamental ontological questions. They are notoriously difficult to be defined, and most often are used intuitively or only with the help of purely verbal clarifications. Within the category theory their meaning can be rigorously determined, and their definitions are not arbitrary but imposed, so to speak, by the mathematical context. And even more importantly, these definitions often reveal the variety of meanings never suspected outside the categorical context – the meanings that can doubtlessly be adapted to enrich many traditional philosophical discussions.

1. Introduction

In 1945 Samuel Eilenberg and Sounders Mac Lane published a lengthy paper entitled "General Theory of Natural Equivalences"[9] in which they introduced the concept of category. Many years later Mac Lane confessed that in this paper "they had written what they thought would perhaps be the only necessary research paper on categories" [14, p. 345]. Today every textbook on the category theory quotes this paper as the one that gave birth to one of the most comprehensive mathematical theories.

Category theory, possibly more than any other mathematical theory, has rich philosophical significance. The reason why it has not been so far exploited by philosophers is that they know it, if at all, only superficially. In

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the present essay, I shall explore only one aspect of this theory, namely the way it can contribute to our understanding of such concepts as: analogy, identity, equivalence and the like. It goes without saying that these concepts play a paramount role not only in many scientific disciplines, but also in philosophy of science and some fundamental ontological questions. They are notoriously difficult to be defined, and most often are used intuitively or with the help of purely verbal clarifications. One of my motivations to embark on this study was the reading of an essay by R. Brown and R. Porter under the telling title "Category Theory: an Abstract Setting for Analogy and Comparison" [6]. Although my argument goes along slightly different lines, to quote almost literally the abstract of this essay could be the best summary of my aims. "Comparison and analogy are fundamental aspects of knowledge acquisition. One of the reasons for the usefulness and importance of the category theory is that it gives an abstract mathematical setting for analogy and comparison, allowing an analysis of the process of abstracting and relating new concepts. This setting is one of the most important routes for the application of mathematics to scientific problems".

My argument runs as follows. In section 2, I introduce categories and functors in the context of philosophical controversy between objectivist and relativist positions. In section 3, I present natural transformations and adjoint functors. In section 4, I discuss the concept of equivalence, and compare set-theoretic and categorical ontologies. And finally, in section 5, I collect conclusions related to the concept of analogy.

2. Categorical Structuralism

In the philosophy of mathematics there is a long lasting controversy between those who claim that the primary mathematical entities are objects and those who support the view that the primary mathematical entities are structures (roughly speaking, networks of relations) and objects are but "places" within structures (see, for instance [22]). In physics this controversy assumes the form of the question: are space and time collections of object-like points or instances (Newton's view on the absolute space and time), or ordering relations between events (Leibniz's view on the relational nature of space and time) (see, for instance [8])? These polemics are but an echo of what is discussed in metaphysics since Aristotle or even presocratics: are fundamental bricks of reality substances or should the world be regarded as a network of relations? The strength of mathematics consists in its idealization of our intuitive concepts and converts them into formal theories which, in turn, sharpen our understanding of the world. The category theory does this with respect to objectivist versus relational controversies.

A category is a system consisting of:

- Objects: $A, B, C, \ldots$
- Morphisms (also called arrows): $f, g, h, \ldots$ between objects, for instance
$$f : A \to B,$$
A is called domain of f and B is called codomain of f.
- Morphisms can be composed, e.g. if $f : A \to B$ and $g : B \to C$ then
$$g \circ f : A \to B.$$
- The composition is associative, i.e. for all $f : A \to B, g : B \to C, h : C \to D$,
$$h \circ (g \circ f) = (h \circ g) \circ f.$$
- For each object A there is a morphism $1A : A \quad A$, called identity morphism of A, such that
$$f \circ 1_A = f = 1_B \circ f$$
for all $f : A \to B$.

For instance, sets as objects and functions between sets as morpisms form a category, but in general objects need not be sets and morphisms need not be functions.[1]

If in the afore mentioned philosophical discussions we substitute "morphisms" for "relations", we can draw preliminary conclusions important for these discussions. For instance, if we do so with respect to the question: "can objects be entirely eliminated and replaced by a network of relations?", we get a clearly formulated program to be considered in the category theory, namely, can we get rid of objects in the category definition? The result of such an attempt is the so-called objectless category theory [21, pp. 44-46]. The only primitive concept in it is that of morphism, and the axioms assure the composition of morphisms and the existence of the identity morphisms. However, the elimination of morphisms is here only apparent since in fact there is a one to one correspondence between identity morphisms and ob-

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[1] For the full definition and more examples see, for instance, [2, chapter 1].

jects, and without identity morphisms categories cannot be defined. But the conclusion that objects are on equal footing with morphisms would also be premature. It turns out that all relevant information on an object can be recovered by considering all morphisms (arrows) ingoing to and outgoing from a given object [15, p. 47]. This recalls Leibniz's idea of monads "which are windowless (we would say they have no internal structure), and the only things that matter are their mutual relationships" [7].

Here we should be warned that in this context the term "relation" is too set-theoretic and too laden with philosophical connotations to correctly render the message coming from the category theory. Traditional relational structuralism is a bottom-up structuralism in which "every relation had to be a relation on some things which, even if they were themselves analyzable into relations, had to be among some other things, ... , and either this process had to stop somewhere (atoms), or an account had to be given of infinite analysis" [3, p. 61]. The categorical structuralism, on the other hand, can be called top-down structuralism. As it is expressed by Awodey, "If we take instead the perfectly autonomous notion of a morphism in a category, we can build structures out of them to our heart's content, without ever having to ask what might be in them" (ibid.). The best solution would be to regard categories themselves as "building blocks" of the categorical structuralism,[2] that is to say to regard them as "objects of a higher order", and look for suitable "morphisms" between them. Such a "morphism" is called functor and is one of the corner stone concepts of the category theory.

A functor from a category $\mathcal{C}$ to a category $\mathcal{D}$ transforms the objects of $\mathcal{C}$ into objects of $\mathcal{D}$, and the morphisms of $\mathcal{C}$ into morphisms of $\mathcal{D}$ in such a way that the structure of the category $\mathcal{C}$ is preserved (for definition see, e.g., [2, pp. 8-9]). The above discussion concerning the relationship between objects and morphisms could in principle be repeated with respect to categories as objects and functors as morphisms. It is obvious that we could proceed further and further along subsequent steps of generalisations, and finally we should consider what is called category of categories. It is a hot topic in the philosophy of mathematics. It was F. William Lawvere who, in his Ph.D thesis [12], tried to consider the category of all categories in the context of the foundations of mathematics, but the very existence of such a category is uncertain. I shall not immerse myself into this discussion (see, for example [17]; this would take us aside from our main line of reasoning.

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[2] The discussion on a "categorical structuralism" in the philosophy of mathematics is very much alive; see, for instance [1, 11, 18].

I would like to argue that there are functors that reveal the nature of the categorical structuralism.[3]

3. Natural and Adjoint

In this section we introduce two concepts which play the crucial role in our further analysis; these concepts are: natural transformation and adjoint functor.

Mathematicians often say that a structure or an operation is natural, and usually know what they have in mind, although the concept has not been defined so far. Eilenberg and Mac Lane in their seminal work [9] faced the problem of formally defining the meaning of natural transformation. The result of their effort is this. Let us consider two functors $F, G : \mathcal{C} \to \mathcal{D}$ (of the same variance)[4] from a category $\mathcal{C}$ to a category $\mathcal{D}$. A natural transformation between these two functors, written as $\tau : \mathcal{C} \to \mathcal{D}$, is a family of morphisms in the category $\mathcal{D}$, $\tau_A : FA \to GA$, indexed by objects A of the category $\mathcal{C}$ with some rather obvious conditions supposed to be satisfied (for the definition see, for instance, [23, pp. 90–91]).

Eilenberg and Mac Lane, in their original paper, introduced the concept of an isomorphism of categories more or less in the standard way: A functor $F : \mathcal{C} \to \mathcal{D}$ is said to be an isomorphism if there is a functor $G : \mathcal{D} \to \mathcal{C}$ such that $G \circ F = \mathrm{id}_{\mathcal{C}}$ and $F \to G = \mathrm{id}_{\mathcal{D}}$. A natural transformation between functors F and G is said to be a natural isomorphism if, for each object A of the category C, the morphism $\tau_A : FA \to GA$ is an isomorphism in the category $\mathcal{D}$.

The concept of an adjoint functor was introduced by Daniel Kan in 1958 in [13]. This work truly revolutionised category theory, changing it from a convenient shorthand of some complicated constructions into one of the most fundamental theories of modern mathematics.

Let us consider, as above, two categories $\mathcal{C}$ and $\mathcal{D}$, and let $F : \mathcal{C} \to \mathcal{D}$ and $G : \mathcal{D} \to \mathcal{C}$ be two (covariant) functors as shown below

$$\begin{tikzcd}
C \arrow[r, shift left, "F"] & D \arrow[l, shift left, "G"]
\end{tikzcd}$$

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[3] It is a modification of McLarty's "The main point of categorical thinking is to let arrows reveal structure" [16, p. 366].

[4] This means that both functors are either covariant or contravariant.

Let A, B be objects of the category $\mathcal{C}$ and S, T objects of the category $\mathcal{D}$. Let further $\mathrm{Hom}_{\mathcal{C}}(A, B)$ denote all morphisms from the object A to the object B in the category $\mathcal{C}$, and analogously $\mathrm{Hom}_{\mathcal{D}}(S, T)$ in the category $\mathcal{D}$. We want to compare objects A and S, but they live in different categories. Therefore, we either move S, with the help of the functor G, to the category C to compare it with A or, equivalently, we move A, with the help of the functor F, to the category $\mathcal{D}$ to compare it with S. This idea is encoded in the following way

$$\alpha : \mathrm{Hom}_{\mathcal{C}}(A, GS) \to \mathrm{Hom}_{\mathcal{D}}(FA, C)$$

where α is supposed to be a natural isomorphism. If this is the case, F is said to be a left adjoint of G, and G a right adjoint of F, denoted $F \dashv G$ (for the full definition see [23, pp. 148–151] or [2, p. 215]).

As we can see, the functor G is almost an inverse of the functor F, but not quite an inverse [15, p. 159]. Adjoint functors were not known prior to Kan's work, but it has turned out that they play the fundamental role both in the category theory itself and in the whole of mathematics. One often discovers that there exist adjoint functors between categories that are "far away from each other" so that no connection between them was so far suspected. Such a discovery usually leads to new interesting mathematical results.

Suppose we have two structures (categories) between which there exists a pair of adjoint functors. Then one of these structures gives rise to the other structure, and this relationship is reciprocal. Very often, to establish this relationship without the help of adjoint functors would require a long chain of deductions or even would have never been identified.

Suppose we have to solve a problem related to two categories between which there exists a pair of adjoint functors. The merit of formulating the problem in terms of these functors is that if we get a solution, it is guaranteed that the solution is optimal in the strictly defined sense.

4. Set-Theoretic and Categorical Ontologies

In mathematics objects are defined "up to isomorphism", i.e. two isomorphic objects are regarded as two "representations" of the same object. In other words, it is isomorphism that gives to an object its identity. We could call this "set-theoretic ontology".[5] It was Alexander Grothendieck who noticed that this ontology is not suitable for categories: there are some categories that are

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[5] The term "ontology" is used here in the sense close to that proposed by W. Quine [19].

not isomorphic with each other that should nevertheless be regarded as "the same" from the categorical point of view[10]. He thus proposed the following definition. Two categories $\mathcal{C}$ and $\mathcal{D}$ are equivalent if there are functors $F:\mathcal{C}\to\mathcal{D}$ and $G:\mathcal{D}\to\mathcal{C}$ such that $\mathrm{id}_{\mathcal{C}} \cong G\circ F$ and $\mathrm{id}_{d} \cong F\circ G$ are natural isomorphisms. The fact that, in this definition, the concept of natural isomorphism appears, makes it natural for the category theory. If we use the equivalence in the Grothendieck sense to equipp categories with their identity, we can speak about a categorical ontology.

It is easy to see that two equivalent (in the Grothendieck sense) functors F and G are adjoint, $F \dashv G$ (but not necessarily *vice versa*). As the consequence, the equivalence of categories is a special case of adjointness. Therefore, if two categories C and D are equivalent, there exists a pair of adjoint functors $F:\mathcal{C}\to\mathcal{D}$ and $G:\mathcal{D}\to\mathcal{C}$, but these functors need not be the inverses of each other, i.e. they need not define an isomorphism of categories. If they do, the functors are trivially equivalent. Here we have a surprise: it can happen that this deviation from triviality can lead to interesting theorems.[6] We can see here that the "space of categories" is not a loose agglomeration of categories, but rather a highly structured "field" that reacts on "perturbations" of its substructures in a sophisticated manner.

We can go even further in comparing the "set-theoretic world" with the "categorical world". In the set-theoretic approach, the *univers de discourse* of mathematics is the "space of all sets" (we abstract here from paradoxes of the set-of-all-sets type); in the categorical approach the *univers de discourse* of mathematics is the "space of all categories" as mentioned above (we abstract here from the discussions around the category of categories). Therefore, a single category is a point in this space. But the category of all sets as objects and all functions between them is only a one category among many others, that is to say, just one point in the space of categories. This shows vastly different perspectives of both these approaches.

Could this vast multiplicity of categories be made of an immense number of families of sets and functions between them? If so, the categorical ontology would finally be reducible to the set-theoretic ontology. This problem has been, at least in part, elucidated by some consequences following

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[6] Here is an example: Let C be a category the objects of which are locally compact Abelian groups and the morphisms are continuous group homomorphisms. Let also *Cop* be the category opposite to C. These two categories are equivalent (in the Grothendieck sense), and this equivalence is nothing else but the well known Pontryagin theorem. For more examples see [20].

from the so-called Yoneda lemma. The following remarks should give the reader the general idea (for details see [2, pp. 185-192]).

Let $\mathcal{C}$ be any locally small category.[7] It can be represented by functors from the category $\mathcal{C}^{op}$ opposite[8] to $\mathcal{C}$ to the category **Sets** of sets as objects and functions as morphisms. More technically, the representation is given by a functor, called Yoneda embedding,

$$y : \mathcal{C} \to \mathbf{Sets}^{\mathcal{C}^{op}} .$$

It says that the category C can be identified with a subcategory of functors from $\mathcal{C}^{op}$ to **Sets**. In other words, any (locally small) category can be represented in terms of a functor category. Here is a short comment given by Marquis: "This might seem innocuous but it constitutes an extremely important shift that has tremendous implications, both mathematically, and philosophically, that is in the way one thinks about what mathematics is *about*. For now, objects of a category are not fundamentally structured sets, they are first and foremost *functors*" [15, p. 105]. Categorical ontology is a functorial ontology. Even if the majority (at least all locally small categories) can indeed be translated into families of sets and families of functions between them, the categorical perspective is totality different: the space of categories is "spanned" by functors rather than by functions, and this makes the difference. Functors are not only much richer, but also much more flexible. A lot of possibilities that are excluded in the set-theoretic ontology in the categorical ontology are quite "ordinary". Many of our scientific and philosophical concepts if looked upon from this new perspective could reveal their unexpected aspects. This is also true as far as the concept of analogy is concerned.

5. Analogies

The concept of analogy belongs to the family of those concepts that being important for scientific or philosophical discourse, are at the same time fuzzy and change their meaning depending on the context. In spite of some heroic attempts, undertaken mainly by philosophers, linguists and

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[7] A category C is locally small if, for all its objects X, Y the collection of all morphisms from X to Y is a set.

[8] The category Cop , opposite to the category C, has the same objects as C, and the same arrows but in the reversed direction.

logicians,[9] we use them by basing them on our intuition rather than on some hard analyses. There is a strong connection between our intuitions and the set-theoretic ontology. No wonder since a set-theoretical thinking was created by formalizing and idealizing our every-day intuitions. My view is that our intuitions, contaminated by a set-theoretic thinking, do not grasp the full content of the concept of analogy as it reveals itself in the manifold of its applications. To this end the category theory seems to be much better suited. The concept of analogy seems to be, from its very nature, multi faced and adapting its meaning to various situations. It is a dynamic concept. This is why the categorical ontology seems to offer more effective means to deal with the issue of analogy.

Looking at analogy in the categorical environment and with the help of categorical tools is so promising that it would require a more profound study; here I offer only a few hints or remarks suggesting some perspectives:

- Classically analogy is defined or described in terms of relations between objects; categorical concept of morphism, together with its “dom inance” over objects, enables us to disclose more shades of the notion of analogy. For instance, the very concept of object in the categorical setting reveals its dynamical nature: the usual question “what is object?” is replaced by the question “what is object doing?”.

- Even more so as far as the concept of functor is concerned. Owing to this concept we can speak about “analogous” categories, and the category concept is so rich that it embraces structured sets, relations, relations between relations, abstract and concrete processes, etc., etc. One can deal with this variety of situations not only at the intuitive level, but also in a mathematically precise way. If we want to decide whether two things or situations deserve the name “analogous”, we must compare them. In the category theory we compare categories with the help of functors, and the enormous variety of functors offers a great richness of comparing methods. Since there are functors between functorial categories (i.e. such categories the objects of which are functors), we can also explore “analogy between analogies”. It seems that natural transformations and adjoint functors are especially suitable to this end.

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[9] From the formal point of view analogy was analysed by the Polish School of Logic (see [24]). The most known are the works of J.M. Bocheński [4, 5].

- A natural transformation compares two functors between two categories. The way of comparing seems complicated, but it effectively detects a certain *affinity* between them. It is tempting to call this affinity of functors, at least in some situations, analogy.

- If we agree to relate analogy to natural transformations, we must acknowledge that analogy is involved, via the natural isomorphism α (section 3), into the concept of adjointness. The fact that the isomorphism α is natural means that if we transform the object A into an object B (in the category $\mathcal{C}$), or the object S into an object T (in the category $\mathcal{D}$), the correspondence (analogy) between the two hom-sets will be preserved. Two adjoint functors between two categories are "almost inverse of each other, but not quite an inverse". If they were inverse, the two categories would be isomorphic, and the fact that they are not, allows us to call them analogous. As put by Brown and Porter, "the partial matching, via a comparison, of the properties of A and B leads to analogy" [6, p.3].

I am far from thinking that with natural transformations and adjoint functors the analogy problem in relation to category theory has been closed; they are only examples of what could be achieved.

One more lesson from the above analysis. After all, it is not that important how we call our concepts (analogous or not) as long as we have effective tools to compare them, and it is category theory that offers such tools. We should only learn how to use categorical models in the service of philosophical investigations. Mathematical tools are much richer than our every-day intuitions and purely verbal distinctions; they are able to reveal unexpected aspects of reality.

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EDUCATING TO COMPLEXITY: A CHALLENGE

PIERRE LÉNA

> *Je tiens pour impossible de connaître les parties en tant que parties sans connaître le tout, mais je tiens pour non moins impossible la possibilité de connaître le tout sans connaître singulièrement les parties.*
>
> *Blaise Pascal – Pensées*

Abstract

Education today faces difficult tasks: the traditional model of science education - disciplinary, analytical and deductive - is challenged by the complexity of the world to be deciphered and the complexity of the science to be communicated. Yet, more than ever, a scientific knowledge is needed for everyone. Some aspects and examples of this modern challenge shall be discussed, dealing with primary, secondary and post-secondary education.

Introduction

The physicist and Nobel laureate (1926) Jean Perrin first demonstrated experimentally in 1908 that atoms existed. For him, science was a way *to replace the complexity of what is seen by the simplicity of the invisible.* As any child, any student apprehends the world while perceiving it by the senses, an education aimed at understanding and eventually mastering science is exactly confronted to this step, namely to jump from the visible to the invisible. One has to move from the real object to the mental object, from the concrete to the abstract, from the obvious to the counter-intuitive. Even if today, we can show pictures of atoms in crystals or proteins to our students, the invisible is still there, hidden in the quarks, the dark matter, the equations and the symbols. Science education is difficult, because we can say with Gaston Bachelard that "*There is no such thing as the simple, we just know the simplified*". And science education becomes more difficult, as the complexity of science immensely increases.

Traditional science education aims at training specialists, focusing on excellence in one discipline such as physics, with little or no exposure to epistemology or philosophy. But today, the complexity of modern physics (or biology) and the ethical issues met by the applications of physics (or biology) question this traditional approach. Traditional education pays more attention to technical ability or learning facts than to the understanding of what is a scientific process. But today, the importance of science and technology in the life of every citizen also questions this traditional attitude.

In front of such inadaptations, deep changes may be necessary. In a first section, with a few examples, I give some signs detailing why these changes are needed. In the second one, I examine possible evolutions for an advanced science education, with some examples in physics, my own field. In the third, I discuss how the goal of a *science for all* reintroduces the person to the objective realm of natural sciences, and forces one to abandon over-specialized subjects for an interdisciplinary vision of education. I will focus essentially on primary and secondary education, but many observations may also apply to tertiary education.

1. A new vision of sharing science

Traditionally, science education aims at preparing a small number of specialists, mastering a well-defined field of knowledge. Because of the ever growing complexity and abstraction of the concepts, a hyper-specialization of individuals is practiced and keeps increasing. Related to this complexity, modern and central concepts in physics, such as special or general relativity, or quantum mechanics, are so distant from familiar representations of nature that secondary education often ignores them, transmitting a physics apparently simpler, but older than a century and disconnected from today's applications.

In addition, physics education observes a strict, although recent (20th century), separation between the objectivity of natural sciences and the various facets of subjectivity explored by the humanities. As a consequence, in our secondary or post-secondary lectures when training physicists, the historical emergence of scientific concepts, the epistemological difficulties, the interfaces with other fields such as biology or neurosciences are often ignored, not even to speak of ethics. Developed countries are facing a serious shortage of students choosing to study physics at the end of secondary school (Depp 2012), and one may question whether there is not here a causal relation with the way physics is presented to them.

On top of this, a new challenge emerged in the last two decades. Today, science and technique invade almost every aspects of individual life, deeply modify our representations of nature, impact the development of societies and aim at shaping the future. The whole society is concerned by such a massive transformation and a good science education for all students on our planet is requested. But implementing such a *science for all* education faces two difficulties.

The first difficulty occurs when science has to deal with societal issues where scientific disciplines are mixed in intrinsically complex and challenging problems, often highly non-linear: climate or energy issues are good exemples.

Contrary to the classical separation of science in disciplines being taught separately, a cooperation, even at an elementary level, between different fields of knowledge is needed to help understanding or solving these complex problems (Morin 2005). The probabilistic or statistical aspects are also present, e.g. in health issues (vaccination, epidemics), natural or human-related extreme events (earthquakes, nuclear accidents), financial decisions. Here, interdisciplinarity seems the unescapable road education has to explore.

The second difficulty deals with the intrication of objectivity and subjectivity in these issues. Indeed science may provide objective answers: e.g. Is global warming real? Is it caused by an increasing carbon dioxyde concentration? What is the probability of a nuclear accident? On the other hand, choices made by citizens involve many subjective factors, face hazards of all sorts, meet with religious convictions and are deeply entangled in the person's subjectivity. The good old separation between the object and the subject seems no longer to work. Here, a reconciliation between the person and the scientific knowledge seems the road to explore (Serres 2011).

Hence, as science itself is moving further and further into the realm of complexity, making it more difficult to be explored, to be taught, understood or mastered, science education has to think itself anew (Sánchez Sorondo *et al.* 2007).

2. Teaching advanced science

In the following and with a few examples, I question how high quality scientific training could give students (from secondary to bachelor level) a solid basis to lead a professional life as scientists, without remaining blind to the global development of a complex science or to the complex expectations of the society. Namely: to master the tools of a specialized domain, in order to use them efficiently; to know and understand the conceptual revolutions (epistemology) which have led to modern physics; to stimulate their creativity by avoiding to format them; to open their mind to the borders between disciplines, to the unexpected analogies and metaphors which, in the past, have often led to great discoveries (history); to foster a sense of ethical issues, both internal to science (respect of truth and modesty) and external (applications of science).

A century ago, special relativity shook the classical visions of space and time, built by human brains on the basis of their concrete experience. Teaching a relativistic world encounters deeply embedded representations, which often hamper the student's understanding or creativity. After the *thought experiments* of Einstein, Victor Weisskopf in the 1960s had already adressed this difficulty (Weisskopf 1960). I quote here an interesting use of the new tool called augmented reality,[1] from a recent PhD project developed by Tony Doat (Doat 2012) and used for undergraduate students (De Hosson *et al.* 2011, Ladeveze *et al.* 2012). Palets or pucks on a carom billiard table are put in motion by a cue and hit, the velocity of light being brought to 1 m/s. Several frames of reference are available for the spectator, who is fully immersed in a 3-dimensional scene, each frame being seen with its own time and relative velocity (Fig. 1). Collisions are observed at will from the different frames, while the observer frame, with its 6 degrees of freedom, is constantly monitored by infrared sensors and computed. In addition to the understanding of kinematics, a haptic cue provides a direct muscular feeling of the dynamical properties encountered in special relativity.

This example, using augmented reality, is far from unique. The power of computers allows to make concrete for students and researchers the modern complexity of scientific domains, such as fluid dynamics (Crane *et al.* 2007), or plant growth (Diao *et al.* 2012).

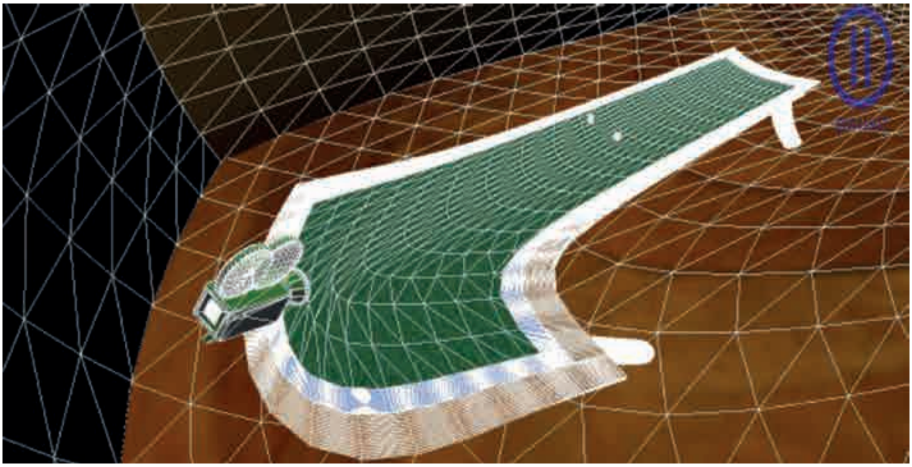

Figure 1. A scene being deformed under the relativistic aberration of light (From Doat T, PhD Thesis, 2012).

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[1] Following Wikipedia's definition, **augmented reality** is a live, direct or indirect, view of a physical, real-world environment whose elements are *augmented* by computer-generated sensory inputs such as sound, video, graphics or GPS data. It is related to a more general concept called mediated reality, in which a view of reality is modified (possibly even diminished rather than augmented) by a computer. As a result, the technology functions by modifying one's current perception of reality.

Simply observe the slow and timid pace with which the complexity of quantum physics penetrates secondary schools in France, despite three Nobel prizes in our country on the subject (Alfred Kastler, Claude Cohen-Tannoudji, then Serge Haroche in 2012). A careful study of French physics textbooks over the last fifty years shows a slow, extremely cautious and mostly qualitative presentation, on the prerequisite that the adequate mathematical language of quantum physics was not then available to students (Lo Bello 2012).

My second example deals with the compartimentalized manner in which many science introductory courses are commonly taught. *Students fail to view even physics itself as a coherent of structure knowledge. This failure suggests that students would not be able to relate what they study in physics to phenomena encountered in other fields such as chemistry and biology* as expressed in a recent paper by a group of Jerusalem physicsts and education researchers (Langbeheim *et al.* 2012). Reforms in universities are adressing this failure, with the goal of motivating students to focus on complex systems, without neglecting the necessary core of disciplinary contents. This group proposes an interesting integrated unit on soft matter. Typical topics in soft matter,

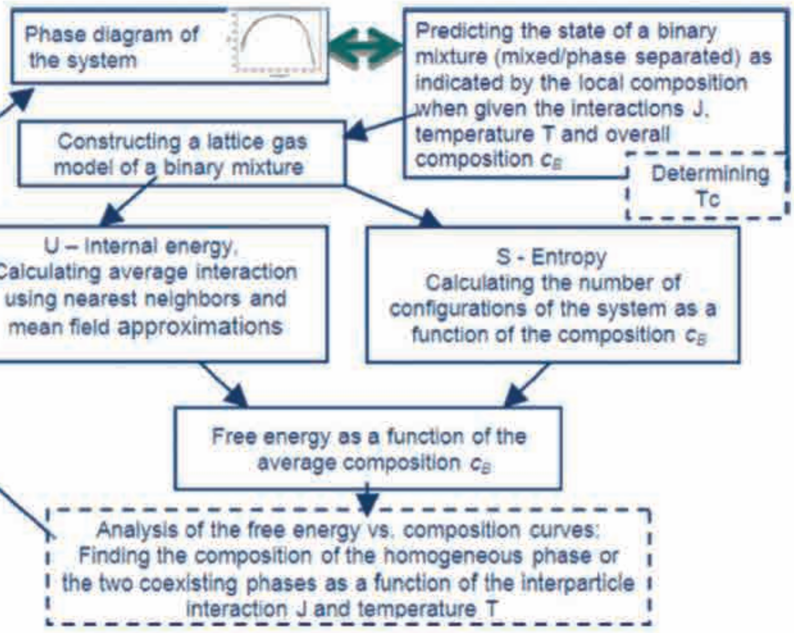

Figure 2. Soft matter: a proposed concept map for the derivation of free energy in a binary mixture (from Langbeheim *et al.* 2012).

such as the conformation of polymers in solvents, the cause of bending energy and shapes of membranes require thermodynamics and chemistry (Fig. 2). Despite the complexity of the objects, such study of soft matter, with an inquiring pedagogy, can focus on everyday materials which are familiar to students and important in materials science and biology.

My third example deals with language. It represents another communication difficulty introduced by the complexity of modern science. Traditionaly, a language made of differential/integral calculus and chemical symbols was sufficient to cover most, if not all science. Today, in physics, electronics (descriptive tools), chemistry, biology (genes), quantum mechanics (Feynman diagrams), the multiplication of symbolic tools create barriers between disciplines. Some introduction of the students to epistemology, including elements of a general theory of language, would bridge this gap and help moving into the expression of abstract concepts (Dowek 2012).

3. Science for all students

In the introduction, I underlined the challenge of a renewed science education preparing all students to deal with complex issues involving science and society, accounting for the complexity of science itself. In the last two decades, this theme has been adressed by numerous reports at international levels such as OECD, UNESCO (UNESCO 2010), regional (European Union, Rocard 2007) or national levels (Royal Society 2010) as well as by the Pontifical Academies (Sánchez Sorondo *et al.* 2007). Without entering here into the richness that these detailed analyses provide, I would focus on the concept of *big ideas* in science.

When observing the complex world surrounding them and interacting with it, babies and children ask questions which, in their freshness and spontaneity, represent the early seeds of the whole scientific venture (Gopnik *et al.* 2000). Later, becoming adults, many will give up this curiosity and decide that science, its language and its machines, as often presented by the media, are too complex to be understood. They may even enter into relativism, forgetting that science is a search for truth. Or, conversely, discouraged by the complexity, they may entirely rely on the word of experts, renouncing their prerogatives of free thought.

How can we conceive the goals of science education (K-9 or so) for modern pupils facing this complexity? Not in terms of knowledge of a body of facts and theories but as a progression towards key ideas which together enable the understanding of events and phenomena which are of relevance to students' lives and later to citizen's. This vision of 'big ideas' in science (Millar R & Osborne J 1998) emerged in the 1990s and was explored in depth in a recent effort (Harlen 2011) built around the Interacademy Panel (IAP) Science education program, in parallel with the worldwide development of an inquiry pedagogy (Allende & Léna 2012) – in the spirit of *La main à la pâte* as developed in France (Charpak *et al.* 2005, Léna 2012).

I use here the term 'idea' to mean an abstraction that explains observed relationships or properties. A *big idea* in science is an idea that applies to a wide range of related objects or phenomena, whilst what we might call *smaller ideas* apply to particular observations or experiences. For instance, that worms are well adapted to living in the soil is a *small idea*; a corresponding *big idea* is that living things have evolved over very long periods of time to function in certain conditions. *Big* ideas, with their rich and wide encompassing power, not only provide explanations of observations and answers to questions that arise in everyday life when facing complexity, but they also enable a prediction capability to deal with previously unobserved phenomena. Big ideas are more abstract than small ones, they require more elaborate cognitive abilities, which are age- and intelligence- dependent. Science education has therefore to establish adequate progressions as for example it has been proposed for genetics at grades 5 to 10 (Duncan R.G. *et al.* 2009).

Table 1 presents a preliminary result of the exercise, aiming at a reasonably short list of big ideas, to be progressively explored from kindergarten to 9th grade.

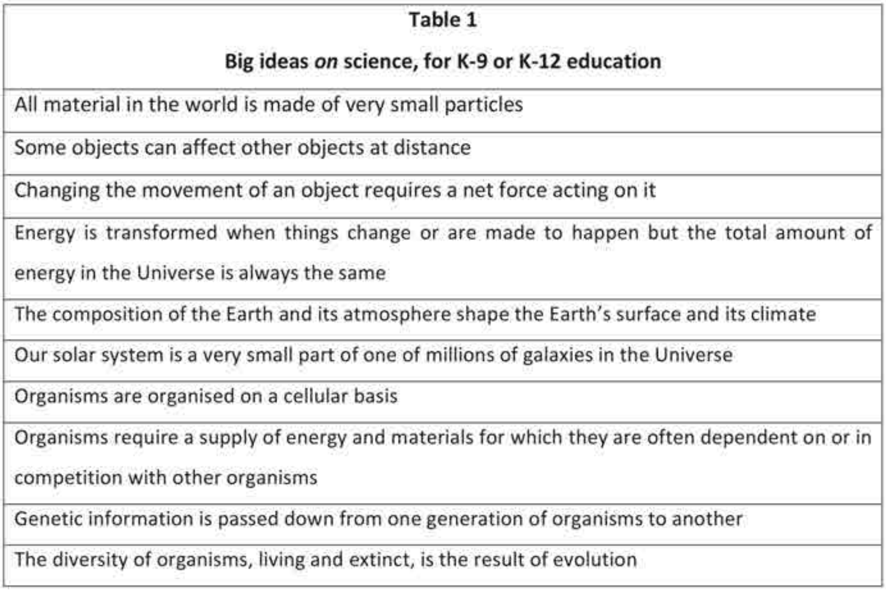

Table 1 **Big ideas *on* science, for K-9 or K-12 education**
All material in the world is made of very small particles
Some objects can affect other objects at distance
Changing the movement of an object requires a net force acting on it
Energy is transformed when things change or are made to happen but the total amount of energy in the Universe is always the same
The composition of the Earth and its atmosphere shape the Earth's surface and its climate
Our solar system is a very small part of one of millions of galaxies in the Universe
Organisms are organised on a cellular basis
Organisms require a supply of energy and materials for which they are often dependent on or in competition with other organisms
Genetic information is passed down from one generation of organisms to another
The diversity of organisms, living and extinct, is the result of evolution

But to understand how science seizes complexity, ideas *about* science must also be conveyed. Table 2 proposes four of them.

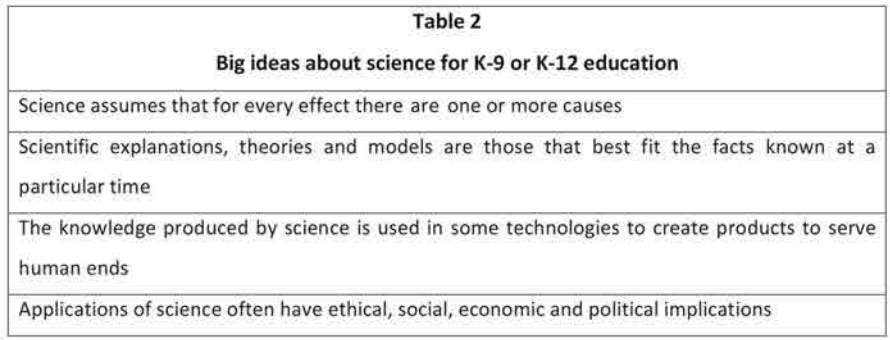

Table 2 **Big ideas about science for K-9 or K-12 education**
Science assumes that for every effect there are one or more causes
Scientific explanations, theories and models are those that best fit the facts known at a particular time
The knowledge produced by science is used in some technologies to create products to serve human ends
Applications of science often have ethical, social, economic and political implications

Conclusion

With the triple irruption of complexity in modern natural sciences themselves, in their transmission and in their interfaces with society, scientists meet a new and difficult responsibility, if they wish their activity to remain recognized, respected and understood. The primary goal of science, namely the search of the truth and the creation of adequate languages to express it remains indeed unchanged. But a new articulation has to be found between this quest of objectivity and the subjectivity of our contemporaries, whether they are themselves scientists or simple laymen.

We had a classical methodology, quantitative, deductive, determinist and reductionist, which has proven its efficiency. Even when it keeps demonstrating its value in dealing with the complexity of the cosmos, the cell, the history of life or climate, it may meet today certain limits. The modern subject, becoming himself/herself an object for science and technology, resists.

I conclude by quoting a very recent editorial published in the French newspaper Le Monde, signed by a reputed surgeon under the title "Biology and homoparentality": *Experience shows that the speed at which one slides from the "forbidden" to the "tolerated", the "allowed", or even the "mandatory" essentially depends on the rhythm of scientific discoveries, no matter what the ethical issues are.* It seems to me that the question of the complex interaction between modern science and the person cannot be expressed in a better way.

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L’INFINI

Jean-Michel Maldamé

Le thème général de notre rencontre a regroupé deux termes fondamentaux pour la pensée humaine. Le premier fait partie du discours scientifique, celui de complexité; le second fait partie de l’épistémologie ou philosophie de la connaissance, celui d’analogie. Il m’est venu à l’esprit en lisant l’annonce de notre rencontre que le terme «infini» permettrait de lier les deux aspects de notre échange: l’aspect scientifique et l’aspect philosophique, avec une ouverture sur la théologie.

Une première raison du choix est que l’on parlait de l’infini de manière traditionnelle pour l’infiniment grand et l’infiniment petit. Au cours du XXe siècle on a parlé d’un troisième infini: l’infini de complexité. Il m’a semblé que l’analyse de l’emploi du terme «infini» permettrait d’honorer le thème de nos réflexions.

En deuxième lieu, l’emploi du terme «infini» ne peut pas éluder la nécessité de traiter de deux choses. D’abord, du statut du savoir mathématique; ensuite, de la théologie, puisque la notion d’infini fait partie de la métaphysique.

Il y a enfin une troisième raison. En choisissant de parler de l’infini, j’ai conscience d’entrer dans un champ habité de vives polémiques dans le rapport entre sciences de la nature et religions. La question de l’infini est au cœur des débats qui ont agité l’Europe à la fin du XVIe siècle et qui ont conduit à la condamnation de Giordano Bruno dont la statue orne une belle place de Rome (*Campo de’ Fiori*). On ne peut évoquer la question de l’infini sans rencontrer cette figure.

Je commencerai donc par donner quelques éléments à propos des débats sur l’infini; puis je traiterai de l’infini des mathématiciens, des physiciens et cela nous conduira à préciser les règles de l’analogie à propos du passage des sciences à la théologie.

1. Genèse du concept d’infini

Pour comprendre le sens du terme infini aujourd’hui, il est bon de revenir à l’origine du savoir scientifique de la culture fondée sur l’estime de la raison.

1.1. Les Anciens

Chez les Anciens, le terme «infini» est péjoratif. Il désigne ce qui est inachevé, ce qui n'est pas arrivé à son terme. Le mot qui le désigne en grec, *apeiron*, est construit avec un préfixe privatif (*a*). Il s'agit donc du «non-fini» ou du «non-mesurable». Le passage au latin et aux langues qui en dépendent garde cette signification: est «infini» ce qui n'est pas fini, l'inachevé ou encore l'imparfait. Il désigne l'imperfection et donc ce qui échappe non seulement à la mesure, mais plus encore à la pensée. Pour ne pas laisser l'esprit sur un échec on distinguait entre l'infini de grandeur et l'infini potentiel – l'infini mathématique n'existant que potentiellement, puisque jamais atteint par un chiffre à l'écriture finie – comme le nombre *pi*!

Malgré cet aspect «négatif», le terme «infini» a pris une grande importance, parce qu'il s'enracinait dans l'expérience humaine la plus fondamentale: l'expérience de la finitude. Par contraste, le terme infini est devenu une qualité attribuée à Dieu, le Dieu transcendant et unique de la Bible.

1.2. Théologie

1.2.1. Monothéisme classique

Dans la théologie classique, dont saint Thomas d'Aquin est la figure emblématique, le qualificatif «infini» n'est pas le premier dans la liste des qualités attribuées à Dieu. Les notions qui viennent en premier sont les notions d'être et d'unité. L'affirmation de la grandeur de Dieu insiste sur l'unité et sur la plénitude de son être. Cette affirmation est commune aux trois monothéismes abrahamiques – avec des différences notables qui ne concernent pas notre débat. La question de l'infini ne se posait pas dans les termes qui sont apparus ensuite dans un autre contexte.

Pourquoi cette situation? Il me semble que la notion d'infini est placée au second rang, car elle se réfère à ce qui se donne à l'expérience et donc à ce qui est mesurable «à la règle et au compas» où il n'y a pas de mesure de l'infini. Par ailleurs, le cosmos est pensé selon le modèle cosmologique de Ptolémée selon le principe que le mouvement circulaire uniforme est la forme du mouvement «parfait».[1]

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[1] Aristote, *Physique:* «Il est évident que le transport circulaire est le premier des transports. En effet, tout transport, comme nous l'avons dit précédemment, est, ou circulaire, ou rectiligne ou mixte; ceux-là sont nécessairement antérieurs à celui-ci, puisqu'il en est composé; et le circulaire est antérieur au rectiligne, car il est plus simple et plus parfait. En effet il n'y a pas de transport sur une droite infinie, car un tel infini n'existe pas; et, s'il existait, rien ne serait ainsi mû, car l'impossible ne se produit pas et parcourir l'infini est impossible. […] Il nous a paru d'autre part raisonnable que le mouvement circulaire

La notion d'infini est, elle aussi, liée à l'expérience humaine du temps. Là encore la finitude est reconnue, car la théologie monothéiste affirme que le monde a eu un commencement et qu'il aura une fin. Le débat des monothéismes religieux contre la cosmologie grecque se portait sur le refus de l'éternel retour. L'éternité du monde étant un perpétuel recommencement. La question de l'infini ne se posait donc pas dans les termes qui sont apparus ensuite dans un autre contexte.

1.2.2 Mystique et infini

La notion d'infini a été prise en compte de manière neuve à partir de la théologie mystique. En effet, les mystiques font l'expérience que leur quête de Dieu ne peut cesser. Plus ils avancent, plus ils expérimentent que celui qu'ils désirent rencontrer est au-delà de tout. Il n'est pas sans intérêt de constater que cette expérience transforme la place de l'infini dans la pensée théologique. La notion d'infini passe au premier plan. Il en résulte une révolution conceptuelle dont Nicolas de Cues est fondateur; pour lui les contraires se complètent: *Contraria sunt complementa*. Ceci est possible à raison du caractère infini de la divinité. La notion d'infini devient de la sorte la clef de la théologie ouverte sur la mystique.[2] Cette révolution logique et conceptuelle concerne les sciences de la nature.

Nicolas de Cues pense qu'il n'y a aucune difficulté à reconnaître que Dieu ait créé d'autres mondes. Ainsi l'Univers peut être infini dans ses dimensions spatiales et temporelles. Plus encore: il convient qu'un créateur infini fasse exister une pluralité de mondes. La pluralité des mondes atteste la perfection de Dieu. L'infinité de l'espace et du temps est une attestation de la gloire de Dieu.[3]

1.3.3. Physique du mouvement et recours à la notion d'infini

Dans la science après Galilée il y a une correspondance entre la beauté de la science moderne fondée sur l'usage des mathématiques et la vision d'un univers dont la richesse ne cesse de se développer. La mathématisation permet en effet de décrire le mouvement des corps par des équations. Or

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fut un et continu, et que le rectiligne ne le fut pas. [...] En outre, seul le transport circulaire peut aussi être uniforme. En effet, les choses mues sur une droite ne sont pas transportées uniformément du commencement vers la fin; car plus elles s'éloignent de l'état où elles sont en repos, plus rapide est le transport», VIII, 265a-265b; Paris, Les Belles Lettres, 1969.

[2] Sur la rencontre des religions de manière éminente.

[3] Cette idée a été reprise par Giordano Bruno; elle n'est en rien le motif de sa condamnation par l'Inquisition romaine.

celles-ci portent l'esprit vers un infini numérique. De même, le principe d'inertie rompt avec le modèle du mouvement circulaire uniforme. Il invite donc à une considération sur le déroulement d'un temps et l'extension d'un espace sans commencement ni fin. Le concept d'infini se confronte aux difficultés de la physique du mouvement. Elles ne pouvaient avoir de réponse avant que la notion mathématique d'infini ait été clarifiée.

2. L'infini des mathématiciens

L'articulation étroite entre la théologie et la science – et donc la nature du rapport d'analogie entre les deux domaines de savoir – est liée à la notion même d'infini: si le terme est réservé à Dieu seul, la qualité d'infini peut-elle être attribuée à des objets créés qui ne peuvent qu'être finis? Le processus de géométrisation de la nature invite à poser radicalement cette question. C'est sur ce point que se situe le cœur de la pensée de Giordano Bruno. Il met l'infini dans l'univers, mais il lui garde des attributs divins dans une vision où la matière est énergie.[4]

2.1. *La science mathématisée*

La science est platonicienne, elle accorde au chiffre une dignité, celle de participer aux idées éternelles qui constituent l'archétype du monde dont l'homme a l'expérience. Galilée en hérite, Descartes, Huygens, puis Leibniz, en prolongeront les exigences.[5] Le recours aux mathématiques ouvre le champ d'intelligibilité tant sur un infini de grandeur que sur un infini de petitesse. Pascal explicite cette liberté de l'intelligence mathématique dans son étude, *De l'esprit géométrique*.[6] La science moderne se donne les moyens

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[4] Giordano Bruno, *De l'infinito, universo e mundi*: «Il n'y a pas de fins, termes, limites ou murailles qui entravent et arrêtent l'abondance infinie des choses. C'est par elle que la terre et la mer sont fécondes; c'est par elle que se perpétue l'éclat du soleil […] car une nouvelle abondance de matière est engendrée éternellement par l'infini». Dans cette phrase le mot infini se réfère à la fois à l'extension spatiale et temporelle et à la puissance créatrice immanente au processus de production.

[5] Galilée, *Il Saggiatore*: «La philosophie est écrite dans cet immense livre qui se tient toujours ouvert devant nos yeux, je veux dire l'Univers, mais on ne peut le comprendre que si on ne s'applique d'abord à en comprendre la langue et à connaître les caractères avec lesquels il est écrit. Il est écrit en langage mathématique», Rome, 1923, trad. Les Belles Lettres, 1979, p. 141.

[6] «Quelque grand que soit un nombre, on peut en concevoir un plus grand, et encore un qui surpasse le dernier, et ainsi à l'infini, sans jamais arriver à un qui ne puisse plus être augmenté. Et, au contraire, quelque petit que soit un nombre, comme le centième ou la dix millième partie, on peut en concevoir un moindre, et toujours à l'infini, sans

de formaliser et donc de traiter la connaissance de la nature par l'expression de lois où les chiffres et les lettres tracent le chemin de la pensée.

Le mouvement même de la science conduit à étudier le mouvement et à introduire ainsi le calcul différentiel qui permet l'essor de la mécanique analytique.[7] La science du mouvement rencontre alors une difficulté conceptuelle: les éléments du calcul différentiel sont-ils un artifice sans statut clairement défini ou bien sont-ils des entités mathématiques qui doivent être pensées pour elles-mêmes? La question est posée par des scientifiques chrétiens qui savent que seul Dieu peut penser l'infini, puisque son intelligence est infinie. L'esprit humain peut utiliser l'infini, mais il ne le pense pas comme tel. L'infini est toujours «potentiel».

Dans l'étude du mouvement, le premier traitement de l'infinitésimal a été opéré par Leibniz qui considéra que les termes écrits dans les équations étaient des artifices de calcul, puisque le résultat était exprimé en termes finis. Le passage par l'infinitésimal (les *dx* du calcul différentiel) sont, selon ses termes, des «fictions»[8]. On peut donc faire référence à l'infini dans les calculs, sans qu'il y ait d'infini réel, au sens d'une quantité définissable par ce terme, donc pas de nombre et encore moins de réalité physique.[9] Cette vision des choses change avec Bolzano.

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arriver au zéro ou néant. De même quelque grand que soit un espace, on peut en concevoir un plus grand, et encore un qui le soit davantage; et ainsi à l'infini, sans jamais arriver à un qui ne puisse plus être augmenté. Et au contraire quelque petit que soit un espace, on peut encore en considérer un moindre, et toujours à l'infini, sans jamais arriver à un indivisible qui n'ait plus aucune étendue», Blaise Pascal, *De l'esprit de géométrie*, édit. de la Pléiade, Paris, 2000, p. 162-163.

[7] Cf. Michel Blay, *La Naissance de la mécanique analytique*, Paris, PUF, 1992.

[8] Cf. Leibniz, *Lettre à Des Bosses* du 1^er^ septembre 1706: «Le calcul infinitésimal est utile, quand il s'agit d'appliquer les mathématiques à la physique, cependant ce n'est point là que je prétends rendre compte de la nature des choses». La divisibilité des opérations mathématiques du calcul ne portent pas sur le réel; l'infini relève de la pensée: «Les infinis ne sont pas des touts et les infiniment petits ne sont pas des grandeurs». Il dit également: «On ne conçoit l'infini que par une pure fiction de l'esprit». (*Philosophische Schrifften*, II, p. 315). Ce qui est infini, c'est donc le processus, mais pas la réalité. Aussi «il n'y a pas de nombre infini, ni de ligne ou autre quantité infinie, si on les prend pour de véritables touts» (*Nouveaux Essais sur l'entendement humain*, II, chap. XVII).

[9] Cf. Karl Friedrich Cauchy (1777-1855): «Je conteste qu'on utilise un objet infini comme un tout complet; en mathématiques, cette opération est interdite; l'infini n'est qu'une façon de parler», cité par Jean-Pierre Luminet et Marc Lachièze-Rey, *De l'infini*, Paris, Dunod, 2005, p. 109.

2.2. Bernard Bolzano: la réflexibilité

L'œuvre de Bolzano consacrée à cette question est présente dans *Les Paradoxes de l'infini*. Bolzano reprend la distinction entre infini potentiel et infini actuel pour reconnaître l'existence d'infini actuel dans le domaine des choses familières.[10] Une relation de récurrence simple définit la suite des entiers; la donnée de deux points détermine un segment de droite. Bolzano examine les divers sens du mot infini chez les mathématiciens[11] pour dire que l'infini doit être une propriété intrinsèque.[12] Bolzano introduit la distinction entre penser une totalité comme telle ou penser chacun des éléments qui la constituent. La notion d'infini se rapporte à la totalité comme telle; c'est ce qui fonde son objectivité (*Gegenstandigkeit*).

Pour montrer l'existence de cet infini actuel, Bolzano affronte le paradoxe dit de la réflexibilité. Il se rapporte à la situation suivante: si on considère un ensemble, si l'ensemble est fini, toute partie de l'ensemble est moindre que la totalité de l'ensemble. Ainsi dans l'ensemble des entiers de 1 à 100, les chiffres pairs sont moins nombreux que ceux de l'ensemble. Ce n'est pas le cas quand on considère les nombres réels. Par exemple, si on compare la grandeur d'un segment de droite compris entre 0 et 1, avec celui qui est compris entre 0 et 2, le premier segment est contenu dans le second; mais on passe de l'un à l'autre en multipliant par 2 tous les chiffres du premier et inversement par division par 2. Il y a donc à la fois égalité et non-égalité. Tel est le paradoxe: pour un ensemble de grandeur infinie, une partie de l'ensemble peut être aussi grande que l'ensemble; ce qui contredit le principe selon lequel le tout est plus grand que la partie. Cette propriété que l'on appelle «réflexibilité», qui servait jusqu'alors à récuser la notion d'infini actuel, doit être considérée comme ce qui définit l'infini.[13]

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[10] Pour ce faire, Bolzano considère les concepts mathématiques familiers (celui de nombre entier ou de fraction); il constate qu'il existe des ensembles infinis en acte, que rien logiquement n'empêche de concevoir comme des touts achevés: ainsi l'ensemble des entiers, une droite infinie et même un segment comportant une infinité d'éléments conceptuellement déterminés et saisissables. Il n'est pas nécessaire d'énumérer tous ces éléments pour concevoir la totalité. Il suffit de caractériser par une propriété (ou plusieurs propriétés).

[11] Bernard Bolzano: «Il reste à savoir si une simple définition de ce qu'est une pluralité infinie nous met en état de déterminer ce qu'est un infini en général» (*Paradoxes de l'infini*, § 10).

[12] Bernard Bolzano: «Donner aux mots fini ou infini un sens tel qu'ils désignent une propriété intrinsèque déterminée des objets ainsi nommés finis ou infinis, mais en aucun cas le simple rapport de ces objets à notre pouvoir de connaître» (*Paradoxes de l'infini*, § 12, p. 71).

[13] On dit aujourd'hui qu'un ensemble infini est équipotent à l'un de ses sous-ensembles propres. Cette formulation suppose une conceptualité qui viendra après Bolzano; elle sera introduite par la lecture des *Paradoxes sur l'infini* par Dedekind et Cantor.

Le concept d'infini est ainsi introduit de manière claire; il sera pleinement intégré dans le formalisme mathématique, quand Georges Cantor proposera l'écriture de nombres qui différencient diverses formes d'infini mathématique. L'apport le plus décisif de Cantor est qu'il y a une diversité d'infinis, et même une infinité.

2.3. L'infini en logique

Les travaux de Bolzano ont libéré la recherche mathématique et permis ensuite à Cantor de faire de l'infini un nombre, écrit avec la première lettre de l'alphabet hébreu aleph, , avec des index pour l'employer à tous les ordres de numération $(\aleph_1, \aleph_2, \ldots\aleph_n\ldots)$.

Un tel travail ne se réduit pas à la définition des nombres. Il repose sur des questions de logique. Aussi la question de l'infini est-elle une question de logiciens qui raisonnent dans une perspective ensembliste. La théorie des ensembles rencontre des questions nouvelles quand il s'agit d'ensembles infinis. Les questions posées invitent à un examen logique des fondements et cela conduit à poser des axiomes dont il faut ensuite vérifier la cohérence. La thématisation par Zermelo-Fraenkel a formalisé les opérations habituelles sur les ensembles complétés par «l'axiome du choix».[14] Cette formalisation est ouverte sur de nouvelles extensions de la logique, comme par exemple la «Ω-logique» qui généralise la logique habituelle en mathématique qui permet d'étudier tous les infinis mathématiques sans déroger au principe de non-contradiction.

Le travail des logiciens a permis à Gödel de démontrer que le souci d'une démonstration totale ne peut être réalisé, car les premiers éléments sont posés en principe; s'ils servent à établir par démonstration la cohérence des raisonnements, ils ne peuvent se justifier eux-mêmes.[15]

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[14] Dans plusieurs ensembles, on peut prélever un élément de chaque pour former un nouvel ensemble. Il y ainsi une infinité d'infinités quand on part d'un ensemble infini.

[15] Blaise Pascal: «Je reviens à l'explication du véritable ordre, qui consiste, comme je le disais, à tout définir et à tout prouver. Certainement cette méthode serait belle, mais elle est absolument impossible; car il est évident que les premiers termes qu'on voudrait définir en supposeraient de précédents pour servir à leur explication, et que de même les premières propositions qu'on voudrait prouver en supposeraient d'autres qui les précédassent; et ainsi il est clair qu'on n'arriverait jamais aux premières. Aussi en poussant les recherches de plus en plus, on arrive nécessairement à des mots primitifs qu'on ne peut plus définir, et à des principes si clairs qu'on en trouve plus qui le soient davantage pour servir à leur preuve. D'où il apparaît que les hommes sont dans une impuissance naturelle et immuable de traiter quelque science que ce soit dans un ordre absolument accompli» (*De l'esprit géométrique*, édit. de la Pléiade, Paris, 2000, p. 157).

Ainsi la question de l'infini en logique et en mathématique montre que le chemin de la pensée renvoie à une référence qui échappe à sa maîtrise. Elle oblige à considérer le travail de la pensée et de la science comme une aventure, toujours ouverte.

3. Les jeux de l'analogie

Notre colloque portant explicitement sur l'analogie, il me semble important de consacrer la troisième partie de cet exposé à l'examen de cette procédure de la pensée. Il est apparu en effet que le terme infini renvoie à plusieurs réalités pensées ou représentées. On peut dire en simplifiant qu'il y a trois sortes d'infinis.

3.1. Démarche théologique

Nous avons vu avec Nicolas de Cues la naissance d'une théologie où la logique est repensée pour éclairer les richesses de la notion d'infini.

Cette affirmation théologique n'est pas restée dans le seul domaine de la foi ou du discours religieux; elle a une influence sur la manière de voir le monde, pensé comme création de Dieu. En effet, la confession de foi reconnaît que si Dieu est parfait en tout ce qu'il est de manière éminente, il possède un savoir qui a deux propriétés: d'abord il est illimité – à la différence de l'esprit humain borné – ceci est important pour fonder une physique qui découvre l'ampleur de l'acte créateur. La seconde propriété est importante au plan mathématique. En effet à raison de son éternité, la connaissance de Dieu n'est pas progressive et dispersée dans le temps – à la différence de la connaissance humaine qui est tendue entre des exigences opposées qu'elle ne peut tenir au même moment. Aussi les nombres qui se présentent comme une suite infinie (en premier lieu le chiffre *pi*) ne sont pas connus par examen de tous les chiffres nécessaires à son écriture; ils sont connus comme tels dans la simplicité d'un seul acte qui, au sens plénier du terme, les comprend. L'esprit humain peut donc poser un infini actuel. Ainsi les mathématiques et la logique peuvent traiter l'infini dans leur démarche propre.

3.2. La pensée de l'infini

L'esprit humain est donc fondé à penser l'infini. Une perspective religieuse en conclut qu'il participe à l'entendement divin. Ainsi naît un usage de l'infini dans le monde des religions – C'est l'ambiguïté de G. Bruno! La mise en place rigoureuse d'un concept d'infini par Bolzano et Cantor permet de sortir de cette équivoque. L'infini est un nombre qui joue un rôle essentiel quand il est pris dans les rigueurs du concept qui l'introduit dans le formalisme des équations. Il y a bien un infini actuel; ce n'est pas une fiction ou un artifice. L'infini dont il s'agit alors est de l'ordre strictement mathématique, il est opératoire.[16] Très précisément défini, il est pris dans des exigences de pensée que l'on appelle à bon droit «limitations internes du formalisme». La multiplicité des infinis et la mise en place de logiques de plus en plus générales ne suppriment pas cette exigence de finitude.

3.3. Infini des physiciens

Il est sûr qu'il y a un infini actuel au sens mathématique du terme. Pour les physiciens, il n'en est rien, puisque les mesures doivent donner des résultats chiffrés de manière finie.[17] En physique, la question posée est celle de la divisibilité de la matière. Le concept d'atome est alors introduit. S'il a été longtemps pensé comme une limite, il a cessé de l'être comme tel puisque composé d'éléments plus «fins» qui constituent le noyau et les électrons. Mais l'analyse va plus avant par une représentation qui ne se contente pas de trouver «un objet plus petit». La physique porte sur des entités qui ne laissent pas réduire à la mécanique classique qui étudie des «forces» sur des «corps matériels». La physique quantique porte sur des interactions – présentes dans toute mesure. Ainsi les grandeurs sur lesquelles se fondait la formation de l'infini mathématique sont prises entre des limites. La notion de «mur de Planck», l'exprime, car elle trace une frontière indépassable. Les physiciens n'aiment pas l'infini – il y a là un trait qui est lié à la philosophie immanente à leur travail scientifique.

La question de l'infinité de l'univers renvoie elle aussi à des exigences qui relèvent de la philosophie. Ainsi en cosmologie, il apparaît que les équations présentent des valeurs infinies lorsqu'il s'agit de singularités. Cette situation est donc écartée. On le voit dans la formulation de modèles cosmologiques dont une des caractéristiques est qu'il n'a pas de «bord»[18] comme dans le mo-

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[16] La notation des nombres transfinis par la lettre Aleph, atteste que cette limitation dans l'exercice de la pensée n'est pas sans ouverture puisque dans la kabbale, la lettre désigne l'*En Soph*, la divinité illimitée et pure.

[17] Cf. Jean-Pierre Luminet et Marc Lachièze-Rey, *La Physique de l'infini*, Paris, Flammarion, 1994.

[18] L'expression demande à être entendue au sens strict. Le «principe cosmologique», en vertu duquel l'Univers homogène est partout le même, écarte le concept de centre et le «principe de contenu», en vertu duquel l'univers contient tout ce qui est physique, exclut l'idée de bord. L'espace et le temps ne sont pas des réceptacles vides dans lesquels le monde matériel peut être placé, à la façon d'un objet. Nicolas de Cues disait: «La fabrique du monde a son centre partout et sa circonférence nulle part» (*Traité de la docte ignorance*).

dèle de Stephen Hawking. On le voit aussi dans les recherches actuelles sur la «théorie des cordes». Une des raisons de promouvoir ces recherches, qui restent à l'état d'hypothèse, est d'écarter les valeurs infinies au voisinage de la singularité initiale présentée par le modèle standard.

La difficulté invite à voir que la cosmologie n'est pas une partie de l'astrophysique, car son objet est l'univers, donc une totalité qui est unique. La notion de limite est donc différente de la physique où tout objet d'étude est entouré par d'autres objets – à commencer par les appareils de mesure.

Conclusion

Le thème de l'infini nous permet de voir comment le langage des sciences ne peut s'enfermer dans les limites du langage formel des exposés scientifiques.

La vie de la science repose sur l'esprit et sur la créativité de l'esprit humain qui est capable de dépasser les limites de l'expérience immédiate liée aux sens.

Dans le débat sur l'infini, la pensée humaine se découvre elle-même en excès par rapport au fini qu'elle appréhende. La réflexion montre que l'esprit se trouve interrogé et ainsi renvoyé à lui-même. En formalisant l'infini avec les mathématiciens, en rapportant l'expérience de la quête d'un Dieu au-delà de toute prise et en se confrontant à la réalité sensible selon les exigences de la méthode scientifique, l'esprit humain expérimente qu'il est fait pour aller toujours plus avant, dans la recherche scientifique, mais aussi dans la quête du sens. La fécondité de l'activité humaine est au prix de sa confrontation avec l'inconnu – cet inconnu dont la notion d'infini marque l'horizon.

La référence à l'infini à la croisée des chemins de la pensée et de l'action humaine marque l'ouverture irréductible de l'esprit humain sur un au-delà de lui-même.

INTERACTION BETWEEN TWO READINGS: THE NATURALISTIC AND THE SOCRATIC "KNOW THYSELF"

MARCELO SÁNCHEZ SORONDO

Knowledge about Man: the possibility of two approaches

There was no great problem between the different domains of knowledge until a border was drawn between nature understood as having a soul or surrounded by a soul, and a soul which was in itself characterised by an end: this was the age of Aristotle's *Physics*, *De Anima* and *Ethics*. This border was drawn at the end of the Renaissance, which had not assimilated the originality of the thought of St. Thomas.

The problem became acute when nature became the subject of a science based on pure observation, mathematical calculation, and experimentation. This was the meaning of the Galileian and Newtonian revolution, as Kant (1787) defined it.[1] The human mind thought that it did not have access to the principle of the production of nature in itself or in something other than itself, what Aristotle called form or the formal principle as principle of operation: 'every essence in general is called "nature", because the nature of anything is a kind of essence'.[2] Therefore one can only gather natural gifts made known through their appearance in space and time and try to 'save the phenomena – τὰ φαινόμενα σώζειν', as Plato himself suggested, who in this was Galileo's mentor. This is no minor endeavour given that the field of observation is so unlimited and that the imaginative ability to form hypotheses with a mathematical formula, to enlarge and replace models, to vary the character of models, and to invent procedures of verification and falsification, is so powerful. This is no minor endeavour, also, because mathematics, which is in part a construction of the mind of the human being, corresponds to the quantity that indeed constitutes the specific matter of every individual and expresses in bodies the realisation of individuality through the parts of such material structure. There is quantity in the mind of man and in the corporeal structure (atoms and sub-atomic structures,

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[1] Kant, Immanuel, *Critique of Pure Reason*, Preface to the second edition (1787). Available online: http://etext.library.adelaide.edu.au/k/kant/immanuel/k16p/k16p2.html.

[2] Aristotle, *Metaph.*, 5, 1015 a 12 f.

molecules, cells, organs, etc.). Thus, although there is no ancient Aristotelian correspondence between the mind and reality through the notion of form, there is the modern correspondence through quantity inspired in Pythagoras of Samos and Plato – something that has been pointed out on more than one occasion by Benedict XVI in his Magisterium.

However, as regards phenomena relating to human beings, this asceticism of hypotheses, of the creation of models, and of experimentation, is in part compensated for by the fact that we have partial access to the production of certain phenomena that can be observed through philosophical self-reflection (and of course, for believers, through faith). Thus we are dealing with what in the praxes that are different from this scientific theory and technologies can be deemed the genetics of action that belong to fundamental anthropology and to ethics. Reflection on human praxes expresses the point of convergence because it indicates the path that leads to the end, i.e. perfect human work as fullness of the act. The success of work (ἐργόν) can only be observed in the perfection of praxis itself (ἐνέργεια) in relation to its end.

Thus the action shows that every man and every woman as individuals proceeds for an end and thus that they themselves are the principle of action: '*hic homo singularis intelligit, vult, amat*'. As will be discussed, this is the starting point of St. Thomas against Averroism which anticipates in many ways some decisive modern philosophies and of Ricœur against the "masters of suspicion" (Marx, Nietzsche and Freud) for their methodological and substantial naturalism. In the vast field of activity, the human being considers himself responsible for his own action. This means that he can go back from the observable effects of his actions to the intention that gives them meaning and even to the mental acts which create finalities that generate the intentions and the observable results. Thus the action not only exists to be viewed from the outside, like all the natural phenomena of which it is part: it exists to be understood beginning with expressions that are at one and the same time the effects and signs of the intentions that give meaning to it and with the acts that create meaning that at times sometimes produce such intentions. It follows from this that man's knowledge is not a matter of a single plane or level – that of external observation, explanation, and experimentation (as a reproduction of phenomena) beginning with his body and brain: this knowledge develops in the interface between the observation of nature and reflective understanding. Therefore the human being is simultaneously an observable being, like all the beings of nature in which he participates, and a being who interprets himself, who knows himself, as Heraclitus, Socrates, Aristotle, Thomas Aquinas, Hegel had already suggested (a 'self-interpreting being' to employ the phrase of Charles Taylor or Paul Ricœur).[3]

This statement on the various objective levels of knowledge and of the science of knowledge, or epistemology, and to begin with on the different levels of knowledge and self-awareness of the human being, can provide an answer of reconciliation and pacification to the question raised by the status of the human being in the age of predominance of the natural sciences, as long as, that is, positivist ideology does not claim the right to abolish the border between the sciences of nature and the sciences of man and to annex the latter to the former. Regretfully, contemporary philosophy answered this challenge by simply juxtaposing an abstract anthropology or a phenomenology of the concrete man, without articulating its discourse on the way this acting and suffering being behaves in the world with scientific discourse. It may be difficult to ask today's philosophers or theologians to become scientists or specialists and vice versa: however, the needs of the condition of contemporary man strongly encourage us to open up to an indispensable participation in interdisciplinary research where theologians, philosophers, thinkers and scientists are willing to work together. We are trying to do this in our workshop.

The Neurosciences and Self-understanding

A controversial point to achieve this pacification might be the field of the neurosciences. In terms of this approach, the scientist is expected to seek at the cortical level the correlation between the observable structures and the functions where the structures are the bases, the supports, the nervous material or whatever we may want to call it. The scientist only observes quantitative and qualitative changes, the ever more complex hierarchies of observable phenomena; but the meaning of the function which corresponds to the structure is understood only by the speaking subject who says that he perceives, that he imagines, and that he remembers. These oral statements, together with behavioural signs that the human being shares to a large extent with the higher animals, fall within a type of analysis where there is no mention of neurons, synapses etc. but reference is made to impressions, intentions, dispositions, wishes, choices, ideas etc. We again find

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[3] On this point we find an illuminating text in the Encyclical *Fides et ratio* which declares: 'Metaphysics should not be seen as an alternative to anthropology, since it is metaphysics which makes it possible to ground the concept of personal dignity in virtue of their spiritual nature. In a special way, the person constitutes a privileged locus for the encounter with being, and hence with metaphysical enquiry' (§ 83).

here a certain semantic dualism, if we can use this phrase, which does not, however, jeopardise the integral knowledge about the human being. An important corollary of such semantic dualism lies in the fact that we speak in similar terms of the body, of the same body, in both analyses: there is the body-object, of which the brain is the guiding force with its marvellous architecture, and the body proper, this body that is the only one that is mine, that belongs to me, which I move, which I suffer; and there are my organs, my eyes 'with' which I see, my hands 'with' which I grasp. And it is on this body proper that all the architecture of my powers and my non-powers is built: the power to do and not to do; the power to do this or that; the power to speak, to act, to attribute to myself my own actions, given that I am their real author, and thus free. In short, I find in my body something radical which is my free capability to act, which in Latin may be defined as *capax*, the human being as capable to act and to be aware and free of it through his body and brain.

There is thus raised the question of the relationship between the two analyses or approaches – that of the neurologist and that of the philosopher and metaphysician. And it is here that the analyses cross over without ever dissolving each other. The scientist and the philosopher can agree on calling the body-object (and its marvel, the brain), the 'reality without which we cannot speak, or think or decide or feel or live or act'. The scientist can continue to have a naturalistic viewpoint in his analysis which enables him to work without direct metaphysical perspectives. The philosopher speaks about the brain in terms of recipient structure, of support, of substrata, of basis, of potency, of encephalic matter, of part of the person. It must be accepted that, for the moment, we do not have a sort of third analysis where there is awareness that this brain-body and my living body are one and the same being. However, the analysis of the brain-body must have a certain opening towards the analysis of my living body and vice versa, namely that while the analysis of my living body gives to me in itself my experience and philosophical reflection, it must be open or enable indirectly or *per accidens* the analysis of the mind-body and vice versa.

We notice here that we do not have direct access to the very origin of the being that we are, in other words we do not have a sort of self-transparency of ourselves and of our selfhood and, starting from this centre, a self-transparency also of all of our actions. In this sense we cannot understand ourselves immediately through our being and essence by essence. On the contrary, our being attests to its existence in the concrete and current exercise of our life. In a realistic clime and vision, St. Thomas indicates this clearly: 'For one perceives that he has a soul, that he lives, and that he exists, because he perceives that he senses, understands, and carries on other vital activities of this sort' ('*In hoc enim aliquis percepit se animam habere, et vivere et esse, quod percepit se sentire et intelligere et alia huiusmodi opera vitae exercere'*).[4] For this reason Aristotle declares: 'We sense that we sense, and we understand that we understand, and because we sense this, we understand that we exist'.[5] In the perception of our praxis or activity there is the co-perception of the beginning: 'from a perception of the acts of the soul we perceive the principle of such acts' ('*perceptis actibus animae, percipitur inesse principium talium actum'*)'.[6] St. Thomas assures us that our soul, since it grasps universals, perceives (*percepit*) that is has a spiritual form; he argues that we are aware of the very becoming of the universal in the soul and even that the very light of intelligence makes its presence known to us by means of the soul. This signifies affirming in an explicit manner a perception proper to the spiritual reality in a positive way but by means of the spiritual operation of implementing the intelligible: 'And we know this by experience, since we perceive that we abstract universal forms from their particular conditions, which is to make them actually intelligible' ('*Et hoc experimento cognoscimus, dum percipimus nos abstrahere formas universals a conditionibus particularibus, quod est facere actu intelligibilia*').[7]

The ultimate originality of this perception of our spiritual reality is the absolutely original fundamental situation which we may call the genetics of the act or 'the emergence of freedom' as a move from potency to act or the capability to act freely or the capability of acting or of non-acting and our awareness of it. Quite rightly Christian thought, long before, and with more precision than the moderns, when considering this reality of the spiritual subject called freedom the '*motor omnium*' of the activity of the person, and the protagonist of the person, the 'I', the self (selfhood), the human subject that we discover through praxis. This perception is so radical that it is more than an opinion and it is prior to every science, whether theoretical or practical; indeed it is converted into the principle of the foundation of the different

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[4] St. Thomas Aquinas, *Q. d. De Veritate*, q. 10, a. 8.

[5] Aristotle, *Ethica Nicomachea*, IX, 9, 1170 a 30.

[6] St. Thomas Aquinas, *Q. d. De Veritate*, q. 10, a. 9.

[7] St. Thomas Aquinas, *S. Th.*, I, q. 79, a. 4. Available online: http://www.corpusthomisticum.org/sth1077.html He also states: 'The human soul understands itself through its own act of understanding, which is proper to it, showing perfectly its power and nature' i.e. '*Anima humana intelligit seipsam per suum intelligere, quod est actus proprius eius, perfecte demonstrans virtutem eius et naturam*' (*Ibidem*, I, q. 88, a. 2 ad 3; available online: http://www.corpusthomisticum.org/sth1084.html).

praxes. We can say that it is a form of belief, a *Glauben*, in the non *doxic* sense of the term, if we reserve the term *doxa* for a degree lower than *episteme* and in the order of the phenomena of nature and also in that of human phenomena liable to being treated they themselves as observable. The belief proper to the attestation of our freedom is of another order; it is of the order of conviction and confidence; its opposite is suspicion, not doubt, or doubt as suspicion (P. Ricœur); it cannot be denied, but refused; it cannot be re-established and strengthened if not through resorting again to attestation, and is rescued by the approval of the other, indeed thanks to some kind of gracious divine support. In this context to which fundamental anthropology refers, one can observe that one is dealing with a truth that is closely connected with the fundamental conviction that the human being has of himself and which is not temporary as is the case with the acquisitions of the arts and sciences and philosophy itself with which, however, it has a close relationship, and thus one speaks of 'philosophical anthropology' to refer to its specific genre of knowledge through reflection that takes place by stages.

Brain, Mind, Soul and Being

Aware of the lack of a direct and perfect self-transparent knowledge of such a founding origin, scientists and philosophers should aim to seek an increasingly precise adjustment between a neuroscience which is increasingly expert in material architecture and phenomenological and anthropologic descriptions centred on human operations (seeing, understanding, living well, acting) where praxis is subject to philosophical analysis. So, the point of departure and turning point to both approaches is human praxis. In Aristotle, the act that achieves a human praxis is clearly dissociated from the act of movement (κίνησις) and is, instead, associated in a privileged way with that of action, in the sense of praxis (πρᾶξις): 'Since no action which has a limit is an end, but only a means to the end, as, e.g., the process of thinning; and since the parts of the body themselves, when one is thinning them, are in motion in the sense that they are not already that which it is the object of the motion to make them, this process is not an action, or at least not a complete one, since it is not an end; it is the process which includes the end that is an action. E.g., at the same time we see and have seen, understand and have understood, think and have thought; but we cannot at the same time learn and have learnt, or become healthy and be healthy. We are living well and have lived well, we are happy and have been happy, at the same time; otherwise the process would have had to cease at some time, like the thinning-process; but it has not ceased at the present moment; we both are living and have lived. Now of these processes we should call the one type motions, and the other actualisations. Every motion is incomplete – the processes of thinning, learning, walking, building – these are motions, and incomplete at that. For it is not the same thing which at the same time is walking and has walked, or is building and has built, or is becoming and has become, or is being moved and has been moved, but two different things; and that which is causing motion is different from that which has caused motion. But the same thing at the same time is seeing and has seen, is thinking and has thought. The latter kind of process, then, is what I mean by actualisation, and the former what I mean by motion'.[8] What makes this text remarkable is that the disjunction between action and movement is upheld by a criterion that involves a phenomenology of a metaphysical character, namely the possibility of saying, 'at the same time', we are seeing and we have seen, we are living well and have lived well, we are happy and we have been happy. The interaction of the tenses of verbs, and in a certain sense its overcoming which is arranged around the difference between movement and human praxis, reveals a fundamental phenomenon that bears upon the temporality of human acting. The fact that the perfect and the present are 'together' implies that everything that the perfect contains of the past is recapitulated in the present and *vice versa*. The human being, therefore, not only is capable of measuring temporal succession according to a first and then but is also, after a certain fashion, above time and the foundation of its succession which is matter. In spiritual operations the human being transcends the movement of nature and lastly matter itself, and is directed, according to the suggestive statement of St. Thomas, towards the Infinite: '*Simpliciter quidem, sicut intelligere, cuius obiectum est verum, et velle, cuius obiectum est bonum, quorum utrumque convertitur cum ente; et ita intelligere et velle, quantum est de se, habent se ad omnia*'.[9] If this kind of praxis transcends pure movement it is because it is a more perfect kind of act, that is to say it has all the perfection of the act of movement but its imperfection is not linked to the succession of matter.[10]

This connects the investigation of the being of the self to the interpretation of one of the four primordial meanings of being, which Aristotle

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[8] Aristotle, *Metaph*, IX, 6, 1048 b 18-35.

[9] *S. Th*, I^a, q. 54 a. 2 co.

[10] Cf. Paul Ricœur, 'Tenth Study: What Ontology in View?', in *Oneself as Another* (Chicago-London, 1992), pp. 302-308; 'Que la science s'incrit dans la culture comme "pratique théorique"', in *The Cultural Values of Science* (The Pontifical Academy of Sciences, Vatican City, 2003), pp. 14-23.

placed under the distinction of act and of potency.[11] Now, it is essential for an ontological exploration of human acting, understood as being different from the movement of nature, that the same examples taken from human praxis appear at the same time as *centred* and *decentred*. In others words, if the meanings of being such as *dynamis-energeia* were only another way of saying *praxis,* the metaphysical lesson would be meaningless. And rightly to the extent that *dynamis-energeia* can irrigate other fields of application different from human action that manifests its analogical fecundity. The essential is the decentring itself towards the bottom and towards the top, in Aristotle, (and in St. Thomas during the Middle Ages and in Ricœur in our contemporary time), in virtue of which the *dynamis-energeia* indicates a basis of being, at one and the same time powerful and effective, on which human acting stands out. In other terms, it appears equally important that human acting is the privileged place of the readability of this meaning of being because it is distinct from all the acts of physical nature, and that being as act and potency has other fields of actuation that are different from human acting. Centrality of acting and decentring or better *re-centring* in the direction of a basis of act and potency which Aristotle himself defines as 'first act' because it is distinct from all the others, when it is a matter of explaining the soul as form. This analogy attests that for Aristotle the being of man is that basis of being as first act starting with which he can be an agent and receiver that transcends matter and is capable of measuring time.

And it is here, in that higher sphere of human praxis which is knowing, that Aristotle distinguished in a new way for the first time two acts and two potencies: the quiescent act, which is acquired science, and the working act, which is the exercise of science by he who possesses it: 'he who has science thinks' (θεοϱοῦν γὰϱ γίγνεται τὸ ἔχον τὴν ἐπιστήμεν – 417 b 6). The second is a special process, different from the first which is from ignorance to science (said in its own way to be an alteration), but it presents itself as an increase in itself and in the act: 'For it is by exercise of knowledge that the possessor of knowledge becomes such in act: and this is not an alteration – for the thing develops into its own perfection and act' (εἲς αὖτὸ γὰϱ ἥ ἐπίδοσις καὶ εἲς ἐντελέχειαν – b 7). And this must be another kind of act and thus another kind of process; certainly not a process from potency to active potency, but from act to act. Here, then, the dynamic of acting expresses the intertwining of the act as first act and the second act, which is the point of departure of the metaphysical approach of St. Thomas.

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[11] Aristotle, *Metaph.*, V, 7 and 12; IX, 1-10.

Indeed, being, the mode of being, is revealed by operating, that is to say by the mode of operating. Thus from the point of view of the *via inventionis* one can say: *esse sequitur operari*. If we decentre, therefore, the activity of man towards the bottom and towards the top of each one of us, we find with a base of being, which is potent and effective, a first act for Aristotle that is not immersed in matter and is of a different kind from the rest of nature. Each man has the capacity to act according to what he is, and thus if our actions attest to the just, good and the true, it is necessary that the being of this capacity that works spiritually, which makes man in part a being heterogeneous with nature, is a being (*esse, actus essendi*) that has an emergent form above corporeal matter and not dependent on the body or the composite. Thus this being belongs inseparably to the intellective soul, like the rotundity of a circle. The human soul is a 'subsistent form' because it has the being in itself that transmits to the body and conserves it in itself when the body with death is no longer able to receive the life of the soul. The reasoning of St. Thomas is rather convincing: 'the most perfect of forms, the human soul, which is the end of all natural forms, has an activity that goes entirely beyond matter, and does not take place through a corporeal organ; namely, understanding. And because the actual being of a thing is proportioned to its activity, as has been said, since each thing acts according as it is a being (ens), it must be the case that the actual being of the human soul surpasses corporeal matter, and is not totally included in it, but yet in some way is touched upon by it. Inasmuch, then, as it surpasses the actual being of corporeal matter, having of itself the power to subsist and to act, the human soul is a spiritual substance; but inasmuch as it is touched upon by matter and shares its own actual being with matter, it is the form of the body'.[12]

This appears clearly even if one considers the specific activity capable of developing the human being. The perfection of understanding and willing as such lies in the possession of what is understood as intelligible in the intellect and what is loved as love in he who loves. It corresponds therefore to the human capacity to have a potentiality such as to be proportionate to

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[12] '*Perfectissima autem formarum, id est anima humana, quae est finis omnium formarum naturalium, habet operationem omnino excedentem materiam, quae non fit per organum corporale, scilicet intelligere. Et quia esse rei proportionatur eius operationi, ut dictum est, cum unumquodque operetur secundum quod est ens; oportet quod esse animae humanae superexcedat materiam corporalem, et non sit totaliter comprehensum ab ipsa, sed tamen aliquo modo attingatur ab ea. In quantum igitur supergreditur esse materiae corporalis, potens per se subsistere et operari, anima humana est substantia spiritualis; in quantum vero attingitur a materia, et esse suum communicat illi, est corporis forma*' (St Thomas Aquinas, *De spiritualibus creaturis*, 2).

the taking on of intelligible and lovable reality. Now, 'the potency of prime matter is not of this sort, for prime matter receives form by contracting it to the individual being. But an intelligible form is in the intellect without any such contraction; for thus the intellect understands each intelligible as its form is in it. Now the intellect understands the intelligible chiefly according to a common and universal nature, and so the intelligible form is in the intellect according to its universality (*secundum rationem suae communitatis*). Therefore, an intellectual substance is not made receptive of form by reason of prime matter, but rather through a character which is, in a way, the opposite (*sed magis per oppositam viam*)'.[13]

Dual Act and Dual Potency from the Operative to the Ontological

And more precisely, in analogy with the statement of Aristotle about the dual potency and dual act in the analysis of the human praxis of knowledge, both as habit and as *theoresis*, St. Thomas in going towards the depths of our

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[13] *Ibidem*, 1 co. In a parallel passage of *The Treatise on Separate Substances*, the Angelic Doctor expressed himself in an analogous way: 'The matter of corporeal things, however, receives the form in a particular way, that is, not according to the common nature of form. Nor does corporeal matter act in this way insofar as it is subject to dimensions or to a corporeal form, since corporeal matter receives the corporeal form itself in an individual way. Accordingly, it becomes clear that this befits such a matter from the very nature of the matter which, since it is the lowest reality, receives form in the weakest manner; for reception takes place according to the mode of the receiver. Thereby matter, by receiving that form in a particular way, falls short in the greatest degree of that complete reception of form which is according to the totality of the form. Now it is clear that every intellectual substance receives the intellected form according to its totality, or otherwise it would not be able to know it in its totality. For it is thus that the intellect understands a thing insofar as the form of that thing exists in it. It remains therefore that if there be a matter in spiritual substances, it is not the same as the matter of corporeal things, but much nobler and finer, since it receives form according to its totality' i.e. '*Materia autem corporalium rerum suscipit formam particulariter, idest non secundum communem rationem formae. Nec hoc habet materia corporalis inquantum dimensionibus subiicitur aut formae corporali, quia etiam ipsam formam corporalem individualiter materia corporalis recipit. Unde manifestum fit quod hoc convenit tali materiae, ex ipsa natura materiae, quae quia est infima, debilissimo modo recipit formam: fit enim receptio secundum modum recipientis. Et per hoc maxime deficit a completa receptione formae, quae est secundum totalitatem ipsius particulariter ipsam recipiens. Manifestum est autem quod omnis substantia intellectualis recipit formam intellectam secundum suam totalitatem; alioquin eam in sua totalitate intelligere non valeret. Sic enim intellectus intelligit rem secundum quod forma eius in ipso existit. Relinquitur igitur quod materia, si qua sit in spiritualibus substantiis, non est eadem cum materia corporalium rerum, sed multo altior et sublimior, utpote recipiens formam secundum eius totalitatem*' (*De substantiis separatis*, c. 7).

self itself can speak about a dual act and a dual potency that are ontological: 'in composite things there are two kinds of act and two kinds of potency to consider. For first of all, matter is as potency with reference to form, and the form is its act. And secondly, if the nature is constituted of matter and form, the matter is as potency with reference to existence itself, insofar as it is able to receive this. Accordingly, when the foundation of matter is removed, if any form of a determinate nature remains which subsists of itself but not in matter, it will still be related to its own existence as potency is to act. But I do not say, as that potency which is separable from its act, but as a potency which is always accompanied by its act'.[14]

An explorer of these metaphysical sublimes, St. Thomas manages to affirm something that is surprising as regards the very high dignity of the human being: 'we see a certain gradation of infinity in things. For a material substance is finite in a two-fold manner, namely, on the part of the form which is received in matter and on the part of the "to be" itself, in which it shares according to its own mode, as being finite from below and from above. A spiritual substance – the Angel and the human soul –, however, is finite from above, inasmuch as it receives "to be" from the First Principle according to its proper mode; it is infinite from below, insofar as it is not received in a [material] subject. But the First Principle, God, is infinite in both'.[15]

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[14] '*In rebus compositis est considerare duplicem actum, et duplicem potentiam. Nam primo quidem materia est ut potentia respectu formae, et forma est actus eius; et iterum natura constituta ex materia et forma, est ut potentia respectu ipsius esse, in quantum est susceptiva eius. Remoto igitur fundamento materiae, si remaneat aliqua forma determinatae naturae per se subsistens, non in materia, adhuc comparabitur ad suum esse ut potentia ad actum: non dico autem ut potentiam separabilem ab actu, sed quam semper suus actus comitetur*' (*De spiritualibus creaturis*, a. 1 co.).

[15] '*Sic igitur apparet gradus quidam infinitatis in rebus. Nam materiales substantiae finitae quidem sunt dupliciter: scilicet ex parte formae, quae in materia recipitur, et ex parte ipsius esse, quod participat secundum proprium modum, quasi superius et inferius finita existens. Substantia vero spiritualis est quidem finita superius, inquantum a primo principio participat esse secundum proprium modum; est autem infinita inferius, inquantum non participatur in subiecto. Primum vero principium, quod Deus est, est modis omnibus infinitum* (*De substantiis separatis*, c. 8). Cf. also the general principle: 'According to the Philosopher (*Phys.* ii) there is an order of precedence even in formal causes: so that nothing prevents a form resulting from the participation of another form: and thus God who is pure being, is in a fashion the species of all subsistent forms that participate of being but are not their own being' i.e. '*secundum philosophum, etiam in causis formalibus prius et posterius invenitur; unde nihil prohibet unam formam per alterius formae participationem formari; et sic ipse Deus, qui est esse tantum, est quodammodo species omnium formarum subsistentium quae esse participant et non sunt suum esse* (*De Pot.*, q. 6, a. 6 ad 5).

The Metaphysical Unification of Being and Human Activity

Now Averroes and many neo-Aristotelians, who in some sense anticipate Cartesian modernity, differently from Avicebron and the neo-Augustinian theologians, agree on the idea that thinking is the action of a spiritual substance, but they deny that this is united to the body as its substantial form. St. Thomas, instead, begins from the incontestable fact that this human praxis of thinking and willing is achieved by every man and every woman as individuals: '*hic homo singularis intelligit, vult, amat*'.[16] The '*cogito*' – in inverted commas – of St. Thomas does not finish in the separate intellect of Averroes and not even in the impersonal transcendental of the Kantian self like the modern *cogito* of Descartes because 'no one can assent to the thought that he does not exist. For, in thinking something, he perceives that he exists'.[17] There is an inseparable belonging between the thinking and the being of each human being. If, then, understanding is to the advantage of every human being and 'as an individual man', 'because it is obvious that understanding belongs to "this particular man" (as, for instance, Socrates or Plato)', one should say that it proceeds from a present principle that determines the human being as rational nature. This principle is the spiritual soul which is thus the substantial form of the human being: 'Accordingly, it must be the case that the principle of that activity which is understanding should be in "this man" in the way of a form. Now the principle of this activity is not a form whose actual being is dependent on matter and tied down to or immersed in matter, because this activity is not effected by means of the body, as its proven in III *De Anima* [4, 429 a 24]; hence the principle of this activity possesses an activity that has nothing in common with corporeal matter. Now, the way in which each thing acts is a consequence of its being. Hence the actual being of that principle must be an actual being which is raised above corporeal matter and not dependent on it. Now this is characteristic of a spiritual substance. It is necessary to say, therefore, if the preceding considerations are put together, that some kind of substance is the form of the human'.[18]

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[16] The principle *hic homo singularis intelligit* is repeated 14 times, cf. *De unitate intelectus contra Averroistas*, capp. 3 e 4. For *vult* cf. *De Malo*, q. 6 art. un.

[17] '*Nullus potest cogitare se non esse cum assensu: in hoc enim quod cogitat aliquid, percipit se esse*' (De veritate, q. 10, a. 12 ad 7).

[18] '*Oportet igitur principium huius operationis quod est intelligere, formaliter inesse huic homini. Principium autem huius operationis non est forma aliqua cuius esse sit dependens a corpore, et materiae obligatum sive immersum; quia haec operatio non fit per corpus, ut probatur in III de anima; unde principium huius operationis habet operationem sine communicatione materiae corporalis. Sic*

Having rejected this *Averroist* opinion as impossible, St. Thomas takes into consideration the opinion that most seduced Patristic thinkers and the neo-Augustinian theologians who, following Plato, argued that the concrete individual thinks but nonetheless the spiritual substance is not united to the body as its form but has the same function as that of a sailor for a ship. Now, if the soul were not the form of the body, it and its parts would not obtain from the soul its specificity and identity, which appears evidently false, because, on separating from the soul the eye, the brain, the heart, the flesh and bone can longer be said to be such 'except equivocally, like an eye in stone or in a picture'.[19]

This metaphysical union of human activity, and thus of individuality and personality themselves constitutes a 'new event in thought', that is to say an absolute innovation in Christian thought that was unknown to Patristic thought, which St. Thomas managed, however, to develop thanks to the principle of the ontological continuity of the species of the Pseudo-Dionysius '*Supremun infini attingit infimum supremi*'. Thus: 'the human soul, which is the lowest in the order of spiritual substances, can communicate its own actual being to the human body, which is the highest in dignity, so that from the soul and the body, as from form and matter, a single being results'.[20] And, concluding in a masterful way, St. Thomas demonstrates to his neo-Augustinian colleagues of the Faculty of Theology, with an extraordinary beat of his intellectual wings, the defeat to which their theory exposed them in relation to the followers of Averroes of the Faculty of Philosophy: 'But if a spiritual substance were composed of matter and form, it would be impossible for it to be the body's form: because it is essential to matter that it be not in anything else, but that it should itself be the primary subject'.[21]

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autem unumquodque operatur secundum quod est; unde oportet quod esse illius principii sit esse elevatum supra materiam corporalem, et non dependens ab ipsa. Hoc autem proprium est spiritualis substantiae. Oportet ergo dicere, si praedicta coniungantur, quod quaedam spiritualis substantia, sit forma humani corporis' (*De spiritualibus creaturis*, a. 2 co.).

[19] Aristotle, *De Anima*, II, 1, 412 b 20 f.

[20] '*Attingitur autem a materia corporali ea ratione quod semper supremum infimi ordinis attingit infimum supremi, ut patet per Dionysium VII cap. de Divin. Nomin.; et ideo anima humana quae est infima in ordine substantiarum spiritualium, esse suum communicare potest corpori humano, quod est dignissimum, ut fiat ex anima et corpore unum sicut ex forma et materia* (De spiritualibus creaturis, a. 2 co).

[21] '*Si vero substantia spiritualis esset composita ex materia et forma, impossibile esset quod esset forma corporalis: quia de ratione materiae est quod non sit in alio, sed quod ipsa sit primum subiectum*' (*loc. cit.*). Averroism, together with *Alexandrinism*, were expressly condemned by the Fifth Lateran Council under Leo X with the Bull *Apostolici regiminis* (1513): 'Now,

Freedom of Will and the Divine Conatus

It appears that during this same period St. Thomas was the first to grasp the corollary that was most destructive of the Averroist position on the basis of which the human being does not specifically have free choice in his acts but, rather, his will is moved to choosing out of necessity, although it is not subjected to coercion. Indeed, not every necessary thing is violent but only that which has an external principle, and it follows from this that the will is necessarily moved without violence by an internal principle such as the intellect. For St. Thomas 'this opinion is heretical. For it takes away the reason for merit and demerit in human acts, as it does not seem meritorious or demeritorious for persons to do necessarily what they could not avoid doing. It is also to be counted among the oddest philosophical opinions, since it is not only contrary to faith but also subverts all the principles of moral philosophy. For if nothing is within our power, and we are necessarily moved to will things, deliberation, exhortation, precept, punishment, and praise and blame, of which moral philosophy consists, are destroyed'.[22] For St. Thomas, instead, if it is true that the intellect as a faculty of the true precedes the will and guides it, and he indeed states that '*primum principium motionis est ex intellectu: hoc enim modo bonum intellectum movet etiam ipsam voluntatem*', however in the order of the exercise of the act, which is that of the real actuating itself of the freedom of the person, the relationship is overturned and it is the will which has as an object the end, or the good, that decides the action and confers a moral quality on the exercise of the intelligence and all the other faculties and habits. St. Thomas managed to demonstrate the freedom of the will which is another new 'event of thought' or an absolute innovation in the history of philosophy and he found for it the formula: '*Intelligo enim quia volo; et similiter utor omnibus po-*

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the sower of tares has dared to sow and multiply extremely dangerous errors…above all on the nature of the rational soul, according to which it is mortal or unique for all men…we condemn and rebuke all those who state that the intellective soul is mortal or unique for all men…in fact the soul is not only truly, of itself and essentially, the form of the human body…but it is also immortal, and, given the multitude of bodies in which it is individually infused, it can be, must be and is multiplied' (*Doctrine on the Soul, against the Neo-Aristotelians*, Denzinger-Huenermann, 1440, p. 621).

[22] '*Haec autem opinio est haeretica: tollit enim rationem meriti et demeriti in humanis actibus. Non enim videtur esse meritorium vel demeritorium quod aliquis sic ex necessitate agit quod vitare non possit. Est etiam annumeranda inter extraneas philosophiae opiniones: quia non solum contrariatur fidei, sed subvertit omnia principia philosophiae moralis. Si enim non sit liberum aliquid in nobis, sed ex necessitate movemur ad volendum, tollitur deliberatio, exhortatio, praeceptum et punitio, et laus et vituperium, circa quae moralis philosophia consistit*' (De malo, q. 6 co).

tentiis et habitibus quia volo’, clearly bringing out – against any rationalist determinism – the real dominion of freedom and this of the end, which is the good, in the behaviour of a person. And here St. Thomas with sophistication that is specific to him brings out the contradiction of his Averroist colleagues by referring to the authority of their mentor, Averroes: ‘And so also the Commentator in his *Commentary on the De anima* defines habit as what a person uses at will’.[23]

Now, because it is not possible to dwell on this subject *ad infinitum*, one should necessarily state that, as regards the first movement of the will, that is to say the move from potency to act or the placing in act of freedom, the will of every human being is moved by an agent by impulse of which it begins to will freely. This agent cannot be a celestial body nor anything material or of the organism such as the genes, as some affirm today, because the will is not corporeal potency. ‘Therefore, we conclude’, St. Thomas observes, ‘as Aristotle concludes in the chapter on good fortune in the *Eudemian Ethics*, that what first moves the intellect and the will is something superior to them, namely, God’.[24] We owe to Aristotle the introduction of the divine conatus as the founding basis of human freedom, which St. Thomas read in *Eudemian Ethics* where an instinct is affirmed, that is to say a ‘starting-point of motion in the soul’[25] which passes by way of Spinoza and reaches P. Ricœur.[26]

The Existential and Metaphysical Aristotelian-Thomistic Approach: the Circularity of Science and Knowing Yourself

We can recapitulate by observing that the approach of Aristotle, in this determining of the human being in the two moments of potency and act, of the first act and the acts of the faculties and habits, and of act as the habit of science and as exercise of it, followed by St. Thomas with the act of form and the act of being, is very acute, existential and metaphysical at one and

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[23] ‘*Unde et Commentator definit habitum in III de anima, quod habitus est quo quis utitur cum voluerit*’ (*loc. cit*).

[24] ‘*Relinquitur ergo, sicut concludit Aristoteles in cap. de bona fortuna, quod id quod primo movet voluntatem et intellectum, sit aliquid supra voluntatem et intellectum, scilicet Deus* (*loc. cit.*)

[25] *ὁ δὲ ζητούμενον τοῦτ᾽ ἐστί, τίς ἡ τῆς κινήσεως ἀρχὴ ἐν τῇ ψυχῇ. δῆλον δὴ ὥσπερ ἐν τῷ ὅλῳ θεός, καὶ κἀν ἐκείνῳ. κινεῖ γάρ πως πάντα τὸ ἐν ἡμῖν θεῖον: λόγου δ᾽ ἀρχὴ οὐ λόγος, ἀλλά τι κρεῖττον: τί οὖν ἂν κρεῖττον καὶ ἐπιστήμης εἴη καὶ νοῦ πλὴν θεός;* (*Eth. Eudem.*,VIII, 1248 a 25 ff.). Cf. C. Fabro, ‘Le liber de bona fortuna chez Saint Thomas’, *Revue Thomiste*, 1988, p. 356 ss.

[26] P. Ricœur, *Oneself as Another*, cit., pp. 315-317.

the same time: existential because it is drawn from the analysis of human praxis as an increase of the life of the spirit (intelligence and freedom in St. Thomas), and at the same time metaphysical because it draws on the being as being as potency and act, and then as act in act in its foundation which is Logos and Principio at one and the same time. The essential in this anthropological legibility of being is the analogical decentring towards the bottom, that is to say the self of each human being, and the re-centring towards the top, that is to say God; this is what the late St. Thomas does: '*Deus est et tu: sed tuum esse est participatum, suum vero essentiale*' (*In Psal*. 34, 7).

Therefore, neuronal and philosophical centrality in acting and decentring in the direction of a foundation of act and potency are equally and jointly constitutive of an ontology of the human being in terms of act and potency. Therefore only the human being has this double legibility: the external objective reading, common to all the beings of nature, which is the subject of the sciences (*epistémê*), and the approach of auto-reflection, which belongs to philosophy (*sophia*), according to the Socratic precept 'know yourself', which understands being as an act of an active potency which we call the 'soul'.[27] Thus only a human being is able to create a circularity between this double legibility, seeing, so to speak, externally, the functioning of his brain with new sensors that portray it in film-like fashion, and interpreting from the inside this film-like portrayal starting from auto-reflection on himself.

There is nothing that is more ours than our brain, yet there is nothing that we know less about. The ancients thought that the heart was the centre of life because it beats constantly like a pump and tells us 'I am here'.[28] On

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[27] Saint Thomas Aquinas, *Q. d. De Spiritualibus Creaturis*, a. 1.

[28] Indeed, St. Thomas says: '*Secundum igitur quod anima est forma corporis, non potest esse aliquid medium inter animam et corpus. Secundum vero quod est motor, sic nihil prohibet ponere ibi multa media; manifeste enim anima per cor movet alia membra, et etiam per spiritum movet corpus*' (*Q. d. De Spiritualibus Creaturis*, a. 3 co.). Also: '*unumquodque operatur in remotiora per id quod est maxime proximum. Sed vires animae diffunduntur in totum corpus per cor. Ergo cor est vicinius quam ceterae partes corporis; et ita mediante corde unietur corpori*' (*Q. d. De Anima*, a. 9, arg. 13). Also: '*cor est primum instrumentum per quod anima movet ceteras partes corporis; et ideo eo mediante anima unitur reliquis partibus corporis ut motor, licet ut forma uniatur unicuique parti corporis per se et immediate*' (*Q. d. De Anima*, a. 9, ad 13). Again, from a general point of view: '*cum anima rationalis sit perfectissima formarum naturalium, in homine invenitur maxima distinctio partium propter diversas operationes; et anima singulis earum dat esse substantiale, secundum illum modum qui competit operationi ipsorum. Cuius signum est, quod remota anima, non remanet neque caro neque oculus nisi aequivoce. Sed cum oporteat ordinem instrumentorum esse secundum ordinem operationum, diversarum autem operationum quae sunt ab anima, una naturaliter praecedit alteram, necessarium est quod una pars corporis moveatur per aliam ad suam*

the contrary, the brain was, so to speak, the great silence or the sealed box of our body.[29] Today however the brain opens itself up and shows itself, in part because of the neurosciences, as being the centre of the body, and this may turn out to be a turning point for a new beginning where external experience can be joined to internal experience and science can be joined to philosophy, each in their respective functions and consistencies and in their mutual circularity. This was not present in ancient philosophies, or in medieval, modern or contemporary thought, and if the human being is analysed, he is analysed from a formal point of view without these dynamic and circular links with scientific knowledge and auto-reflective knowledge of my body and my brain. In truth, it is not that I am my body, not even its masterpiece, the brain: I am neither my brain nor my body; I have a brain

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operationem. Sic ergo inter animam secundum quod est motor et principium operationum et totum corpus, cadit aliquid medium; quia mediante aliqua prima parte primo mota movet alias partes ad suas operationes, sicut mediante corde movet alia membra ad vitales operationes: sed secundum quod dat esse corpori, immediate dat esse substantiale et specificum omnibus partibus corporis. Et hoc est quod a multis dicitur quod anima unitur corpori ut forma sine medio, ut motor autem per medium. Et haec opinio procedit secundum sententiam Aristotelis qui ponit animam esse formam substantialem corporis. Sed quidam ponentes secundum opinionem Platonis animam uniri corpori sicut unam substantiam, alii, necesse habuerunt ponere media quibus anima uniretur corpori; quia diversae substantiae et distantes non colligantur, nisi sit aliquid quod uniat eas. Et sic posuerunt quidam spiritum et humorem esse medium inter animam et corpus, et quidam lucem, et quidam potentias animae, vel aliquid aliud huiusmodi. Sed nullum istorum est necessarium, si anima est forma corporis; quia unumquodque secundum quod est ens, est unum. Unde cum forma secundum seipsam det esse materiae, secundum seipsam unitur materiae primae, et non per aliud aliquod ligamentum' (*Q. d. De Anima*, a. 9 co.).

[29] However, Saint Thomas had already acutely observed the absolute necessity, for the working of the mind, of the state of perfection of the body: '*naturale est animae quod indigeat phantasmatibus ad intelligendum; ex quo tamen sequitur quod diminuatur in intelligendo a substantiis superioribus. Quod autem dicitur, quod anima a corpore praegravatur, hoc non est ex eius natura, sed ex eius corruptione, secundum illud Sapient. IX: corpus quod corrumpitur aggravat animam. Quod vero dicitur quod abstrahit se a nexibus corporalibus ut se intelligat, intelligendum est quod abstrahit se ab eis quasi ab obiectis, quia anima intelligitur per remotionem omnis corporeitatis; non tamen ab eis abstrahitur secundum esse. Quinimmo, quibusdam corporeis organis laesis, non potest anima directe nec se nec aliud intelligere, ut quando laeditur cerebrum*' (*Q. d. De Spiritualibus Creaturis*, a. 2 ad 7). Also: '*Hanc igitur oportet esse dispositionem corporis cui anima rationalis unitur, ut scilicet sit temperatissimae complexionis. Si quis autem considerare velit etiam particulares humani corporis dispositiones, ad hoc inveniet ordinatas, ut homo sit optimi sensus. Unde, quia ad bonam habitudinem potentiarum sensitivarum interiorum, puta imaginationis et memoriae, et cogitativae virtutis, necessaria est bona dispositio cerebri. Ideo factus est homo habens maius cerebrum inter omnia animalia, secundum proportionem suae quantitatis; et ut liberior sit eius operatio habet caput sursum positum; quia solus homo est animal rectum, alia vero animalia curva incedunt*' (*Q. d. De Anima*, a. 8 co.).

and a body but – as I have tried to show – in order to understand my 'being' I must know what to have a brain means, to have a body means, through that knowledge of them that experience and science offer to me.

Philosophy follows its own synthetic method: it acts with the experimental data provided by science and neuroscience and the principles of reason but moves them within the transcendent reality of the soul as a spiritual free subject[30] and of God the Creator. Thus experience, science and philosophy are fused in their respective functions and consistencies and a 'breach' of movement is made towards the limit that always keeps the consciousness of a person alert and vigil.

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[30] The fact that sensitive knowledge precedes intellectual knowledge in the human being, the sensitive origin of human intellectual knowledge and the affirmation that the soul (the profound self of each of us) can come to know itself as spiritual only through the intellectual species that are abstract from the sensitive ones, have prevented most of the time not only the understanding but also the actual reading of the texts of St Thomas who focuses on the real issue in question and shows that "the principle of human knowledge comes from sense. However, it is not necessary for everything that man knows to be submitted to sense or that it is immediately known only by means of a sensitive effect". Indeed, he affirms what we may call the decisive epistemological position of the Socratic principle of "know yourself": "The very intellect knows itself by means of its own act, which is not submitted to sense. In the same way, it also knows the interior act of will, since will is somewhat moved by the intellectual act and since intellectual act is caused in another way by will, like the effect is known by means of the cause and the cause by means of the effect" i.e. "principium humanae cognitionis est a sensu; non tamen oportet quod quidquid ab homine cognoscitur, sit sensui subiectum, vel per effectum sensibilem immediate cognoscatur; nam et ipse intellectus intelligit seipsum per actum suum, qui non est sensui subiectus: similiter etiam et interiorem actum voluntatis intelligit, in quantum per actum intellectus quodammodo movetur voluntas, et alio modo actus intellectus causatur a voluntate, ut dictum est, sicut effectus cognoscitur per causam, et causa per effectum" (*De Malo*, q. 6, a. un. ad 18). This is a decisive point because St. Thomas also states that 'we would not be able to obtain knowledge about separate intellectual substances either though reason or through faith, unless our soul knew on its own to be an intellectual being': '*Cum enim de substantiis separatis hoc quod sint intellectuales quaedam substantiae cognoscamus, vel per demonstrationem vel per fidem, neutro modo hanc cognitionem accipere possemus nisi hoc ipsum quod est esse intellectuale, anima nostra ex seipsa cognosceret*'' (*Summa contra Gentiles*, III, 46). Thomas also accepts that is it because of the spiritual soul that the human intellect can raise itself to God: 'the soul itself, through which the human intellect ascends to knowledge of God': *'etiam ipsa anima per quam intellectus humanus in Dei cognitionem ascendit'* (*Ib.*, I, 3).