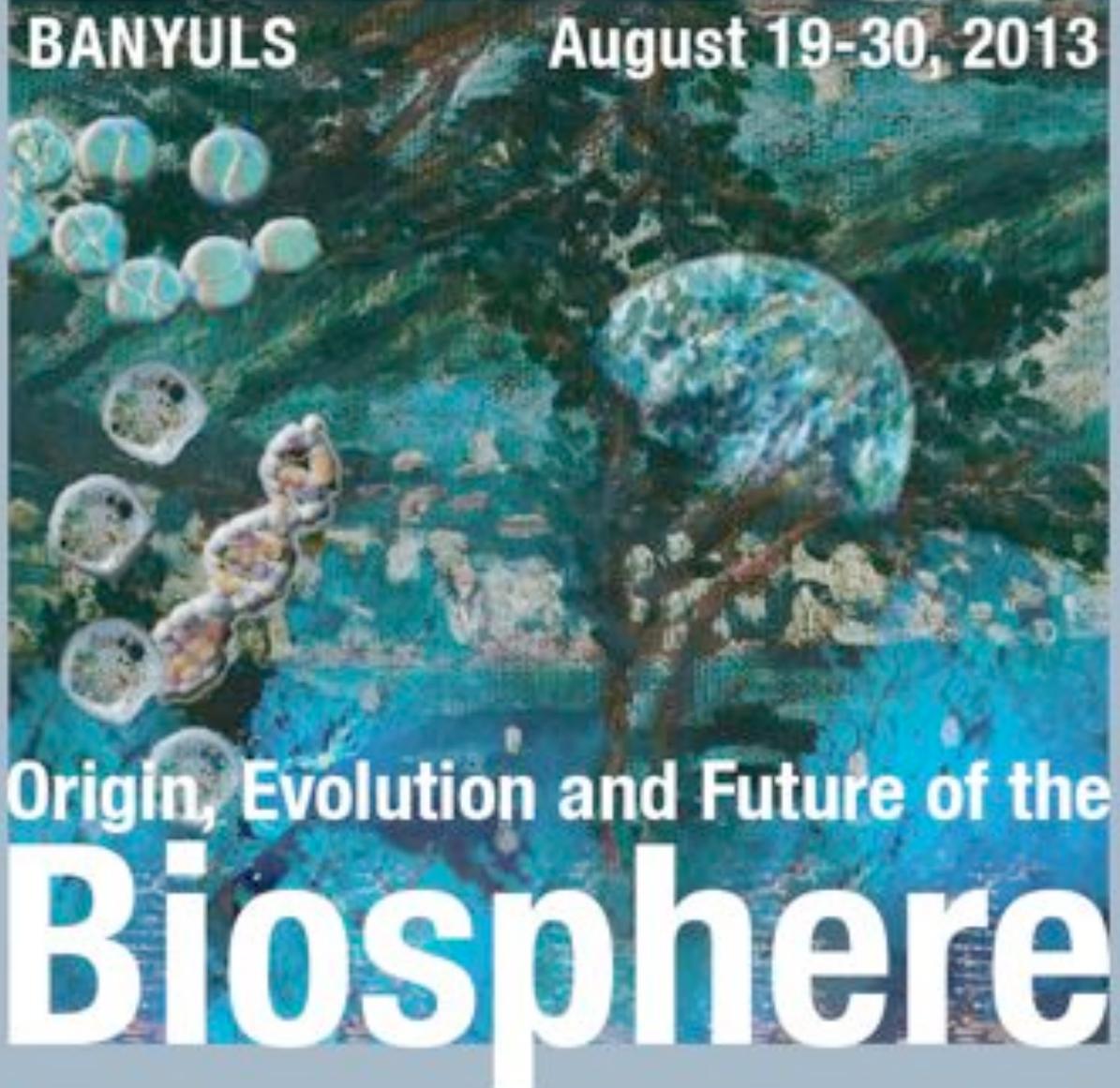


ERASMUS EDUCATION PROGRAMME

BANYULS

August 19-30, 2013



Origin, Evolution and Future of the
Biosphere

COORDINATORS

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Registration by application
to the coordinators

ORGANISATION

Lectures will be given by European specialists on the origins of life, space environment, the role of gravity in molecular, cellular, animal and plant behavior, and the use of molecular tools in space biology. Additionally there will be data analysis workshops, and students working in small multinational groups will present a project design.

OBSERVATOIRE
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OAPEE



BOOK OF ABSTRACTS

First week

	Monday August 19	Tuesday August 20	Wednesday August 21	Thursday August 22	Friday 23	Saturday 24	
09.00	Presentation of the course Marie-Christine Maurel <i>Origins of life: new concepts and experimental results</i>	Kepa Ruiz-Mirazo <i>From protocells to artificial cells: models and experimental vesicle systems</i>	Thijs Ettema <i>Insight into our murky past: Origin of the eukaryotic cell</i>	Juli Peretó <i>Evolution of metabolism (2)</i>	Visit to Tautavel Cave and Museum	Manel Porcar <i>Synthetic life(s)</i>	
10.30	Break						
11.00	Emilie Thomassot <i>The oldest geological archives and the environmental conditions of the primitive Earth</i>	Eugenio Simoncini <i>Chemical disequilibrium in Astrobiology</i>	Juli Peretó <i>Evolution of metabolism (1)</i>	Fernando González-Candelas <i>From the origin of viruses to molecular epidemiology</i>			
12.30	Lunch						
14.00	Antonio Lazcano <i>When the world was made of RNA</i>	Emmanuelle Javaux <i>The first 3 billion years of life evolution</i>	Visit to the Aquarium	Jaume Bertranpetit <i>What will we know when we will have the complete sequence of each of our genomes?</i>		Project session 5	
15.30	Break						
16.00	Presentation of Project sessions and organization of groups	Presentation of students University and country	Evelyne Téoulé <i>GMOs life in biosphere</i>	Jaume Bertranpetit <i>Natural selection revisited in the genome era</i>		Project session 6	
17.30						Project session 7	
19.00	Dinner				Social Dinner		
20.00	Project session 1	Project session 2	Project session 3	Project session 4		Project session 8	

Second Week

	Sunday August 25	Monday August 26	Tuesday August 27	Wednesday August 28	Thurs 29	Friday 30		
09.00	Free Day	Jack Van Loon <i>Micro-gravity research in life and physical sciences</i>	Dieter Volkmann <i>From cell body to biodiversity</i>	Marcel Egli <i>Biological rhythms of mammals in space</i>	Students oral presentations	Students Travel		
10.30		Break						
11.00		Guy Hervé <i>Life under pressure</i>	Sylvie Vauclair <i>From first elements to exoplanets: is there any life elsewhere?</i>	Ranjan Swarup <i>Evolution of land plants</i>				
12.30		Lunch						
14.00		Project session 9	Project session 13	Michel Cabane <i>Life on other planets, the case of Mars</i>				
15.30		Break						
16.00		Project session 10	Project session 14	Project session 17				
17.30		Project session 11	Project session 15	Project session 18				
19.00		Dinner						
20.00		Project session 12	Project session 16	Project session 19				

The origins of life: new concepts and experimental results

Marie-Christine Maurel
UPMC, Paris

According to the geological records, evidences may be found that life was present on Earth more than 3.5 billion years ago. Furthermore, it is possible to simulate laboratory conditions that may have existed on the prebiotic Earth. Accordingly, the Miller experiment provides several amino acids from an atmosphere composed by methane, ammonia, hydrogen and water. From this discovery great amount of data are known today allowing new molecular approaches mimicking primeval life.

An RNA world at the origin of life?

Auto-replication is a basic property of the living systems. It insures the right reproduction of information, in other words, the correct transmission from a generation to the following, of entities named genes. In contemporary systems, nucleic acids are the parent molecule, which serve as template for its progeny. In the cell they cannot replicate without the help of well-defined protein catalysts and the synthesis of these proteins is impossible without the direction of nucleic acids. How did the early system gave rise to the coupled system of proteins and nucleic acids? A biochemical world that would have existed before the contemporary DNA-RNA-Protein world, and baptized in 1986 «The RNA World» by Walter Gilbert (Gilbert, 1986), such a world had already been proposed during the preceding decades by Carl Woese, Francis Crick and Leslie Orgel (Woese, 1965; Crick, 1968; Orgel, 1968). By demonstrating the remarkable diversity of the RNA molecule, Molecular Biology proved these predictions. RNA present in all living cells performs structural and metabolic functions many of which were unsuspected only a few years ago. This scenario of evolution postulates that an ancestral molecular world existed originally that was common to all the present forms of life; the functional properties of nucleic acids and proteins as we see them today would have been produced by molecules of ribonucleic acids (Benner *et al.*, 1993; Gesteland *et al.*, 1999; Bartel and Unrau, 1999; Joyce, 2002).

Finally, the existence of satellite RNA and viroids possessing ribozymes suggest that they might be vestiges of catalytic nucleic enzymes that is a kind of fossil traces of the past starters of life.

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The oldest geological archives and the environmental conditions of the primitive Earth

Emilie Thomassot

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The purpose of this lecture is to present the state of knowledge on the surface environment of the primitive Earth, i.e. on the physical and chemical properties of its outer envelopes (from rocks to ocean and atmosphere) and the interactions between these different envelopes. From the point of view of this Erasmus IP, this knowledge is a necessary step to analyze and understand the environmental conditions that led to the emergence of life and ensured its development.

The direct study of geological record potentially provides a lot of information. However it strongly depends on the good preservation of the ancient supracrustal rocks (i.e. remnants of the outer part of the Earth's surface) formed by direct interaction with the hydrosphere, atmosphere and possibly the biosphere. For the Archean Eon (2.5 to 3.8 Ga), several supracrustal portions are known, such as Barberton in South Africa, Pilbara in Western Australia (3,5 Ga) or Isua, Greenland (3,8 Ga). Numerous scientific contributions on these rocks have shown the existence of an ocean, clarified its chemistry and temperature. The isotopic composition of the metasedimentary rocks also provided pieces of concerning the atmospheric chemistry and interaction with the biosphere.

In contrast, for the Hadean Eon (before 3.8 Ga), the great majority of knowledge comes from detrital minerals (zircons) crystallized in magmatic rocks that have been weathered, and until recently, no metasedimentary rocks were available.

The recent discovery of a supracrustal belt comprising metasedimentary units as old as 4.3 Ga, (Nuvvuagittuq Greenstone Belt, Nunavik Québec) open a new field of investigation. The geochemical studies of these sediments allow the reconstruction of a restricted range of atmospheric chemistry. This range, comparable with the range known later during the Archean, suggests a very early stability of the external envelopes of the young Earth, a conclusion that has strong implications for the study of the origin of life.



Photo Pillow Lavas, Nuvvuagittuq (Québec)... The ocean floor 4.3 Ga ago?

When the world was made of RNA

Antonio Lazcano

Facultad de Ciencias, UNAM, Mexico

Although as late as 1942 the possibility that bacteria were endowed with genetic material was held in doubt, the molecularization of biology led several scientists both in the USSR and in other European countries to acknowledge the key role that RNA molecules play in major biological processes and to discuss the idea that RNA could have preceded DNA as genetic material. It was not until the late 1960s when Woese, Orgel and Crick suggested argued that RNA molecules could exhibit catalytic activity, as is now well established –but did life start with an RNA World? The discovery of catalytically active RNA molecules has provided considerable credibility to these suggestions that the first living entities were largely based on ribozymes, in an early stage called the RNA world. There is convincing evidence suggesting that the genetic code and protein synthesis first evolved in such an RNA world, but at the time being the hiatus between the primitive soup and the RNA world is discouragingly enormous. Bioinformatics and comparative genomics provide important insights into some very early stages of biological evolution, but it is difficult to see how their applicability can be extended beyond a threshold that corresponds to a period in which protein biosynthesis was already in operation, i.e., the RNA/protein world. The evidence suggesting that ribonucleotide-derived coenzymes, alarmones and histidines and other imidazole-bearing compounds can be considered vestiges of such early epochs will be discussed.

From protocells to minimal cells: models and experimental vesicle systems

Kepa Ruiz-Mirazo
EHU-UPV, Basque Country

In this seminar I will focus on three main issues. First, I will reason why compartmentation is necessarily an early step in the long and complex sequence of transitions from physical-chemical self-organization phenomena towards biological systems. Then, I will explore different compartment-first models (both theoretical and experimental), paying special attention to Szostak's recent contribution to a better understanding of the properties of hypothetically very primitive (fatty acid) membranes. Finally, I will indicate which is, from my point of view, the most promising avenue of research to move beyond these vesicle models and get closer to protocellular (still infra-biological) systems. At that point, our idea of 'minimal lipid-peptide cell' will be briefly introduced and compared with other proposals (like the so-called 'ribo-cell'). As a general conclusion, I will present a picture that acknowledges the progress being made in the field, but also the big difficulties remaining in order to achieve a bottom-up synthesis of autonomous systems with open-ended evolutionary capacities, i.e., of full-fledged living systems.

Chemical Disequilibrium and its application for Astrobiology

Eugenio Simoncini

INAF – Astrophysical Observatory of Arcetri, Italy

Before looking for life on other planetary bodies, we would first need to appreciate what life has done on the Earth. Lovelock (1965) proposed that an unambiguous sign of the widespread presence of life on Earth is the high degree of chemical disequilibrium associated with Earth's atmospheric composition. A particularly noticeable aspect of the atmosphere's disequilibrium is the coexistence of methane and oxygen, which would be depleted by chemical reactions to carbon dioxide and water if they were not continuously replenished. The high concentration of these compounds, among others, makes the thermodynamic state of the Earth's atmosphere unique when compared to other planets and moons.

A potential application of the quantification of chemical disequilibrium on a planetary atmosphere is the detection of life on exoplanets. The idea is that, with advanced spectroscopic methods that will likely be available in the relatively near future, we should be able to detect the presence of strong chemical disequilibrium in distant planets' atmospheres. Such a disequilibrium may have abiotic causes, such as photochemistry, but if these can be eliminated it may be possible to conclude that the atmosphere's composition is being controlled by a biosphere.

On the other side, life feeds on chemical free energy, thus a high chemical disequilibrium is a *conditio sine qua non* for the emergence of life as well. This consideration can be fundamental for the search of the geological and planetary environment suitable for the emergence of living systems on Earth and on other bodies.

In the lecture, simple conceptual models will be presented, together with actual applications to Earth, Mars and exoplanets.

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The first three billion years of Life evolution

Emmanuelle Javaux
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Rocks are the archives of Earth and life evolution. However the geological and fossil records are fragmentary and sometimes badly preserved. This lecture will explain how geologists and paleobiologists attempt to retrieve information on paleoenvironments and early life from the rock record, to reconstruct the puzzle of evolution. Examples from the Archean through the Proterozoic recording crucial steps in the evolution of life will be presented to illustrate this multidisciplinary approach.

The search for life on the early Earth or beyond Earth requires the definition of biosignatures, or “indices of life”. These traditionally include fossil chemicals produced only by biological activity, isotopic fractionations of carbon and sulphur indicative of biological cycling of these elements, biosedimentary structures induced by microbial mats such as stromatolites, and microstructures interpreted as morphological fossils. However, these traces can in some cases also be produced by abiotic processes or later contamination, leaving a controversy surrounding the earliest record of life on Earth. Geobiological studies can improve our understanding of preservational environments and taphonomic processes, abiotic processes and products, and help us to develop a multidisciplinary approach to establish the biogenicity, endogenicity and syngeneity of these microfossils.

Palaeobiological data are essential for testing hypotheses about relationships between clades and order of branching in phylogenetic trees and for understanding the timing of life diversification. Comparative morphology, wall ultrastructure and microchemistry of microfossils may permit to identify members of early and later clades. Even when a precise identification cannot be achieved, either because the fossil lacks taxonomically informative features permitting to relate it to an extant clade, or because it represents an extinct clade, microfossils do provide direct evidence of early organisms, and document steps in biological and biochemical innovations, and the emergence and rise of biological complexity.

Geobiological studies illustrate what can be preserved during fossilization, after diagenesis and metamorphism, in various environmental conditions, and provides a rationale to tentatively define diagnosis criteria for microfossils or ways to look for life on Earth or in extraterrestrial environments.

Insight into our murky past: The origin of the eukaryotic cell

Thijs Ettema

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Life on our planet can be divided into three Domains: the Bacteria, the Archaea, and the Eukarya, to which we, humans, belong (Woese and Fox, 1977). When looking at the cellular level, eukaryotic life forms appear to extremely complex as compared to their bacterial and archaeal counterparts. Eukaryotic cells are much larger and are vastly compartmentalized with structures such as the nucleus, organelles, and all sorts of other membrane structures. This apparent cellular complexity is hard to explain from an evolutionary perspective (Martijn and Ettema, 2013). Yet, in the current overview I will give an overview of the current insights in this enigmatic evolutionary puzzle.

A first and important clue regarding the eukaryotic origin comes from analyses of their genomes. Comparative analyses of eukaryotic gene content have revealed that these are chimeric in nature (Riviera *et al*, 1998). Roughly, we can distinguish two types of gene-classes: First, eukaryotic genes involved in so-called ‘housekeeping’ functions (such as replication, transcription and translation) are more closely related to those of Archaea. Conversely, eukaryotic metabolic genes are more related to those of Bacteria.

To explain the chimeric nature of eukaryotic genomes, we need to take a look at a central, energy-producing organelle present in all eukaryotes: the mitochondria. Mitochondria evolved from a once free-living bacterium via an endosymbiotic interaction. During this symbiosis, the bacterium has transferred many of its metabolic genes to the host cell, causing the host genome to become chimeric in nature.

A final, yet imminent question entails the nature of the host cell that took up the mitochondrial ancestor: was this a readily complex cell (a “proto-eukaryote”), or was this a relatively simple cell? Recent studies seem to lend support for a scenario in which a fusion-event stood at the basis of the emergence of eukaryotic life, and that this event entailed a fusion between an archaeon and an alphaproteobacterium (Guy and Ettema, 2011; Koonin, 2010).

Despite that we currently can provide a rough scenario for how the eukaryotic cell might have emerged, many important pieces of this evolutionary puzzle are still missing: What was the biological basis of the presumed endosymbiosis from which eukaryotic life originated? And which evolutionary forces were responsible for the emergence of the cellular complexity that is so characteristic

for eukaryotic cells? With the development of novel, powerful genomics technologies in recent years, it will become possible to identify some of these missing puzzle-pieces, and gain some new, exciting insights into our murky past.

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Evolution of metabolism

Juli Peretó

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In the first part of my talk I will complement Thijs Ettema approach to evolution by symbiosis. The theory of symbiogenesis, proposed by Boris Kozo-Polyansky Mikhaylovich (1890-1957) and deployed in all its explanatory power by Lynn Margulis (1938-2011), allows the study of the emergence of new structures, metabolisms and behaviors from the association of different species. Actually there is an ancient connection between endosymbiosis and metabolic evolution in eukaryotes since associations with prokaryotic microorganisms have been present and repeated throughout their evolutionary history. One of the best studied cases are the metabolic symbiogenesis between insects and bacteria, which have occurred independently many times during the last 300 million years, producing numerous mergers of the branches of the tree of life (Moya et al. 2008). A conspicuous outcome of symbiogenesis is that all eukaryotes are really metabolic mosaics (Peretó 2011).

Another aspect of metabolic evolution is the study of its origin and early evolution. We still do not know when and how life originated. But useful hints can be inferred from extant metabolic pathways, as well as from their correlation with environmental changes through planetary history. Although we still lack a narrative for the origin and evolution of metabolic pathways, a true natural history of biochemistry, we are gaining insights from comparative genomics and molecular cladistic analyses of individual enzymes. The fruitfulness of this approach is in debt to the vision of evolution as a tinkerer rather than an engineer. Using the words of Jacob (1977), inspired by Darwin (1862): In contrast to the engineer, evolution does not produce innovations from scratch. It works on what already exists, [...] like a tinkerer who, during millions of years, has slowly modified his products, [...] using all opportunities to transform and create.

But how the metabolic pathways did evolve? Horowitz (1945, 1965) suggested that pathways emerged in a retrograde manner, backwards, whereas Granick (1957, 1965) proposed a forwards order for the origin of biosynthetic pathways. Only a very few examples would give support to both models, but the view of a patchwork assembly of pathways (based on ideas by Waley 1969, Ycas 1974 and Jensen 1976) has more explicative power (Lazcano et al. 1992, Peretó et al 1994, Fani and Fondi 2009, Peretó 2011). A semi-enzymatic mode of evolution has also been proposed (Lazcano and Miller 1999). In essence, metabolic pathways may have been assembled by the recruitment of primitive enzymes that could react with a wide range of chemical related substrates. Such relatively slow, unspecific enzymes may have represented a mechanism by which primitive cells with small genomes could overcome their limited coding abilities. Accordingly, new enzymes with narrow specificities would result from gene duplication and divergence events. In reductive metabolic evolution the inverse process has been observed. Thus, substrate ambiguity and enzymatic sloppiness have been a leitmotif during the origin and evolution of metabolisms (Tawfik 2010, Peretó 2012).

The molecular tinkering associated to protein function evolution has long been recognized (Jacob, 1977), one classic example being the use of some metabolic enzymes as lens proteins in animals. The conventional view of an extremely specific and proficient enzyme performing a well-defined and unique function must be substituted by the appreciation of several properties –like promiscuity, ambiguity, and plasticity– of crucial importance for the

comprehension of enzyme evolvability, defined as «the ability of proteins to rapidly adopt (i.e., within a few sequence changes) new functions within existing folds or even adopt entirely new folds» (Tokuriki and Tawfik 2009).

As a complementary activity some basics on tree thinking will be introduced and students will solve a short quiz on phylogenetic understanding.

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GMOs life in biosphere

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Genetically modified organisms (GMOs) are presently used in agriculture, expressing traits of interest as insect or herbicide resistance. Soybean, maize, cotton and oilseed rape are the main crops concerned by this innovative technology. Despite hard controversy in some countries, especially in Europe, acreage around the world is increasing every year and is now around 10 % of cultivated area. Risks associated with release of GMOs in environment are largely debated, but very often from a global point of view while it seems really important to consider each situation as a special case. During this lecture, essential technique data, allowing clear interpretation of what GMOs are will be given. Then different examples of applications will be developed in order to underline risks and benefit of each situation. Animal transgenesis will be evoked too.

Finally, arguments in favour of and against release of GMOs in wild environment will be discussed.

Evolution at the frontiers of life: from the origin of viruses to molecular epidemiology

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Evolutionary processes occur at many different scales. From the initial steps of life on this planet to the differential survival of cancer cells in a growing tumor, we can observe evolution whenever the differential reproduction of evolving units depends on hereditary variants that are passed to the offspring. In fact, the capacity of undergoing biological evolution is an essential property of living organisms. This capacity has even been adopted as the distinguishing feature to identify and define life. In fact, depending on the definition of life that one accepts, viruses will be included or not in the domain of life organisms/entities. Naturally, opposing views on the definition of life have led to bitter controversies about the live or non-alive nature of viruses but one thing is certain: viruses evolve, and they do it fast and efficiently. Sometimes too much.

In this talk we will consider viral evolution at three different levels. First, we will have a quick look at the origin(s) of viruses. There are seven major virus types defined on the nature of their genetic material although, according to the ICTV (International Committee on Taxonomy of Viruses), there are only seven recognized orders encompassing 25 families plus 71 additional families not assigned to any higher taxonomic order. These groups have markedly different structures, ecology, host-ranges and impact on human health or economy, and the analyses of their origins could shed some very much needed light for their evolutionary classification. However, the fast pace of viral evolution prevents the application of usual molecular evolution methods for tracing the ancestry of organisms and different strategies have been used to gain insight on these issues.

Secondly, we will study the origin of a specific virus. There are many interesting candidates to be considered. For instance, the origin of HIV-1 and HIV-2, the two retroviruses causing AIDS, can be traced to several separate introductions from related viruses infecting primates in Central and Western Africa, which have become established in the human population only in the last century, or the until very recently mysterious origin of HCV (hepatitis C virus), for which no relative was known until the discovery of other Hepaciviruses in rodents, bats, dogs and horses. However, we will analyze in more detail the recent and complex origin of the causative virus of the latest global pandemic, influenza A (H1N1)pdm, which appeared in the late winter-early spring of 2009 in Mexico and spread in a few weeks all over the world, causing a global health alert and, luckily, not as many fatalities as initially foreseen.

But the rate of viral evolution can be as fast as to allow the observation during a fraction of an individual's life. This has many important consequences, mostly negative as the virus is capable of evolving in response to drugs during treatment and become resistant to them, thus rendering the antiviral therapy inefficient. But it also allows tracking its spread in a population and determining who has infected whom. We have applied a series of molecular evolutionary techniques to study a large outbreak of hepatitis C caused by a single person who infected over 275 patients along a 10-year period. The case was brought to court and this person was sentenced to almost 2,000 years in prison. We were capable of determining whom

he had infected, from a larger population of potential victims, and when the infections had likely occurred, thus providing an individual link between the two viral populations and the additional information gathered by the prosecution in the trial.

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What will we know when we will have the complete sequence of each of our genomes?

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The ease of obtaining DNA sequence is reaching levels that were unthinkable a few years ago. After two decades of use of technologies now considered classical, we can now examine with relative ease millions of positions (SNPs or SNVs) in the genome, the genome functional part of the genome (exome and conserved regions) or the whole genome (more than three billion bases) at affordable prices (about 2,000 euros per genome, which will fall below 1,000 soon).

We therefore have a lot of information and a lot more soon, including the complete genome of each of us. The key question, however, is how we understand this information and whether we can make a reasonable use of it. This presentation will review the state of our knowledge of the genome, the contributions of current and prospective technologies and the future technological and scientific challenges.

We will mainly discuss the implications (scientific, technological, social, medical) of the massive knowledge of the genomic information:

1. The genome of our species.
2. The human genome in perspective: genomes of other species and comparative genomics.
3. The human genome diversity seen with thousands of genomes.
4. The genome of the human past: ancient DNA.
5. The individual genome. Ancestrality information and health information.

As an example we will discuss the interest of knowing my own genome and the implications it has and will have in the future.

Natural selection revisited in the genome era

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Evolutionary analysis at the molecular level provide new tools to biology when considering the action of natural selection in genes and sets of genes in their functional setting of physiological pathways. Their analysis is illuminating by one hand the molecular bases of complex adaptations and, moreover, may help in advancing at a higher pace the basic understanding of function at the gene-product (or protein) level. These processes can be seen comparing genome data of different species or of populations within a single species. Examples will be provided for humans and primates.

The initial point is the interest of detecting natural selection in the form of positive (or adaptive) selection, purifying (or negative) selection and balancing selection. From the theoretical models now it is possible to interrogate whole genomes in the search of footprints of selection. And the genes and genome regions having been under positive selection will tell us the specific adaptations that have driven a species (in the examples, our own species) to have unique adaptations, a framework that may be translated into the differences among human populations.

Comparative analysis of selective pressures on sets of genes involved in a complex pathway or functional network may help disentangle the fine tuned purifying selection pressures that may be converted in terms of “biological importance” or relative dispensability in sets of genes. Results in functional networks and gene families show differences in selective pressures (and thus in function) that are not being detected by standard experimental methods. Second, the evolutionary analysis among humans may unravel the specific role of genetic variants in different populations having been exposed to different selective forces. When looking at genes that may be related to the pathogenic environment (of strong stratification in humans), not only genes related to immunity or inflammation are of interest, but also those related to glycosylation of the membrane proteins. Where in the functional network these forces have been acting may help to understand the basic forces of adaptation and genotype-phenotype relationships.

These evolutionary studies are nothing but the analysis of the results of long term adaptation and thus of functional analysis of variation naturally produced by mutation and natural selection having shaped the resulting phenotypes. Their comprehension, as in all genotype-phenotype relationships, will only be possible through the analysis of complex biological networks.

Artificial life(s)

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In 2010, a team led by the American scientist, business and marketing expert Craig Venter announced the creation of the first synthetic cell, “Synthia”, and stated in a press release that it was “the first organism on Earth whose parent is a computer”. Beyond the hyperbole, the fact is that Venter’s accomplishment was indeed a technical milestone. For the first time, we humans do have the technical proficiency that allows us to chemically synthesize functional avatar genomes, synthetic copies of existing wild-type, simple bacteria. This accomplishment, though, requires deep reflexion: the fact that we can *copy* genomes does not mean that we can *write* them yet. There is not true writing without understanding and although our insight into life complexity is increasing, modelling and experimental approaches still do not suffice for re-creating life *de novo*. Quite paradoxically, one of the few watermarks introduced in Synthia’s artificial genome was a DNA-encoded quotation of physicist R. Feynman’s, found on his backboard after his death: “what I cannot create I do not understand”. Can we build what we do not fully understand? Can life be engineered in the way machines are engineered? In order to ask these questions, I will give a speech on Synthetic Biology, the newborn framework in biotechnology, which specifically aims at making life easier to engineer. I will describe the pillars of Synthetic Biology, standardization, abstraction and decoupling and I will give examples of SB-based successful approaches, such as the synthesis of the anti-malaria drug artemisinin in *E. coli* and yeast, the design and construction of biological logic gates, and the unorthodox international Genetically Engineered Machine competition (iGEM) projects. This competition, created and organized by the MIT, is one of the flagships of Synthetic Biology. Students worldwide present SB-based projects such as re-creation of biofactories in engineered bacteria, biological displays with electrically stimulated glowing yeasts as living pixels, or detection or biodegradation biological devices of toxic compounds by a set of engineered microorganisms. However, and no matter how wonderful this competition is, a close analysis sheds light, as I will describe, on both the potential and the contradictions of the discipline.

By the end of the talk, I will compare cells and machines, stressing the similarities and differences between them. In fact they are both functional and flexible complex systems capable of an outstanding range of processes. Rather than a childish comparison on their performance, the point I will raise is the origin of complexity in living forms compared to the origin of complexity in machines, and the key role of evolution and design, respectively. Finally, I will stress the limitations of engineering life, the theoretical –and practical– obstacles synthetic biologists will have to tackle in order to turn real one of the oldest, most universal and fantastic collective dreams of Humanity: the creation of living forms.

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(Micro-)Gravity Research in Life and Physical Sciences

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In this lecture we will try to address, as broadly as possible, the research concerning gravity (or the lack thereof) in the fields of life and physical sciences. We will focus on some physical phenomena either studied or used in gravity related research. Phenomena like convection, sedimentation, buoyancy, and diffusion will be addressed. In the field of life sciences the current status in cell mechanics, mechanomics or physicomics shall be explained. The rationale behind the various facilities used in this field of research on Earth and what could (or better should) be done in space.

Going from cell biology also animal and human studies shall be discussed, especially ground-based hypergravity studies making use of centrifuges or microgravity simulators such as clinostats, levitating magnets and random positioning machines. We will discuss their application but also their limitation in gravity related research.

Life under pressure

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There are several reasons to consider the implication of hydrostatic pressure in biology. Investigations on the influence of this thermodynamic parameter on biomacromolecules and enzymatic reactions can provide information about the molecular mechanisms involved in the adaptation of organisms living under high pressure, like in the biotops wich developed around the deep-sea hydrothermal vents (see figure). Experimental pressure studies allow also deciphering structure-function relationships in biomacromolecules belonging to organisms living under atmospheric pressure. This parameter is also involved in some physiological aspects in organisms living at atmospheric pressure. In addition, these studies are of use to hypothesize on the prebiotic chemical world, the proposed emergence of life around the volcanic deep-sea vents and the putative existence of extraterrestrial life.

The physico-chemical effects of pressure result from the volume changes associated to the chemical and biochemical reactions, the $PV=RT$ relationship and the Law of Le Chatelier. Basically, in any equilibrated reaction, pressure will favor the side of the equilibrium for which the volume of the reactants solution is the smallest. Pressure influences the interactions involved in the structure of the macromolecule. It has also an effect on the properties of the solvent in which this macromolecule is dissolved (pH, dielectric constant, viscosity...), thus altering the interactions between the two partners and, consequently, the properties of the macromolecule.

On the basis of the same principles, pressure will influence the rate constant of reactions as a function of the sign and value of the activation volume involved in the formation of the transition state. Thus, this experimental approach provides information about conformational changes in biomacromolecules and changes in their hydration.

Special apparatus were constructed in various laboratories, especially in Europe, in order to perform, under pressure, the main experimentations involved in Microbiology, Biochemistry, Enzymology and Biophysics, allowing multidisciplinary approaches, and a Web site was opened in order to promote collaborations.

Examples will be given which illustrate the specificity of the information obtained using the high-pressure methodologies.

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From cell body to biodiversity

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The origin of organic molecules, formation of cellular structures and finally generation of species and biodiversity are most important steps in evolution of organisms and biodiversity of the biosphere. Formation of cell structures on the basis of organic molecules is a fascinating field of research and speculations resulting in several actual concepts and hypotheses:

1. Cell body concept of Daniel Mazia (1), extended by František Baluška (2 and 3)
2. Symbiont hypothesis of Lynn Margulis (4)
3. Symbiont hypothesis revisited by Bill Martin (5).

Result of these millions of years lasting processes are well structured and functioning cells and organisms living in water. In particular when those water living organisms entered land, the Earth gravitational force as one of the most constant environmental factors played an important role by guiding and affecting the evolution of organisms.

Mechanical load on organisms is approximately 1000 times larger on land than in water, due to large differences in density ($\Delta\rho$) of the surrounding medium. Increasing heterogeneity of the habitat conditions, e.g. for nutrition, transpiration and respiration, is strongly correlated with the biodiversity. Just 5% of estimated plant species live in the water habitat – salt as well as fresh water – whereas 95% evolved on land. Mechanical load resulting in anti-gravitational material might be, among others, an important factor in the evolutionary explosion of organisms into the new and extremely heterogeneous biotope of dry land (6).

Anti-gravitational strategies in land plants are related to production and composition of the cell wall (extracellular matrix). Besides cellulose, which is the most abundant polymer on the Earth, the most important anti-gravitational component of land plants is lignin which is also called the backbone of plants (7). It is interesting to compare the anti-gravitational mechanisms in land plants with anti-gravitational strategies known in animals living on land.

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From the first elements to the exoplanets: Is there any life elsewhere?

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The talk will be in two parts. First I will explain how the chemical elements, which constitute the molecules of both living and inanimate systems, have been formed since the beginning of times. Whereas most of the molecular systems that we know and study have been formed on the Earth since its birth, the constituents of these molecules, namely the atomic nuclei, were present in the Universe long before the existence of the Sun and the Earth. The elements that constitute our own bodies were already in the large galactic cloud out of which the solar system emerged, 4.5 billion years ago. I will recall the observations and theories leading to our present knowledge on the Universe since its primordial stage. Then I will discuss how, in this expanding space, light elements first emerged from the chaos. Later on, the first stars came up, and heavier atomic nuclei could then be formed in their hot cores. Stars evolve with time, and their energy comes from the nuclear reactions that occur in their deep interiors. At the end, the more massive ones explode and reject into the Galaxy the matter that contains all the heavy elements they have built during their existence. This was a necessary condition for our existence on Earth at the present time.

Second I will discuss the present knowledge on planetary systems in space. More than 500 exoplanets, or planets orbiting around stars other than the Sun, have already been discovered. How can we detect them? Are there planets like the Earth in space? Are there any other living systems than the ones we know at home? I will answer some of these questions, but that of living systems is still open. I will explain how we can, step-by-step, work to be able to reach an answer in the (near) future

Biological rhythms of mammals in space

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Life on earth has evolved in an environment that is showing rhythmic changes like the lighting conditions or temperature fluctuations constantly. Most organisms have responded to these naturally occurring rhythms by developing their own internal timing system because temporal organization of activities has remarkable evolutionary advantages. Energy can be saved by the organism when raising its body metabolism during the active phase only when food is available for example. Actually, many physiological parameters of mammals are showing such daily/seasonal rhythms like the body temperature (1-3). Because most of the biological rhythms of organisms demonstrate a period of about 24 hours, they are therefore called circadian rhythms (circadian = about a day).

Core function of the internal circadian timing system is the temporal coordination of endogenous physiological processes and their adjustment to external time cues. Severe consequences occur without temporal orchestration of these parameters. Many of us have already experienced de-synchronization of internal circadian rhythms after a transatlantic flight by suffering under the “jet-lag” syndrome at the destination (4). Studies showed that constant disruption of internal rhythms can even lead to health problems like the increased cancer risk (5, 6, 7).

A growing body of evidence demonstrates that also gravity can function as exogenous time cue that influences rhythms of mammals. Astronauts experience the importance of 1 g (Earth gravity force) while in space when developing health problems like motion sickness, bone mass reduction, muscle atrophy and impaired immune response (8). First evidences of microgravity induced alteration of the circadian rhythms in mammals were obtained by studying *Macaca nemestrina* monkeys on board Biosatellite 3 in 1969. Substantial changes occurred in the sleep-wake rhythm and the core body temperature rhythm (9). Similar disruptions of internal circadian rhythms were observed in rats on board Spacelab 3 (12). Additional investigations carried out on astronauts verified these results, showing changes in the core body temperature rhythm, sleep and performance rhythms (10, 11). Likewise, hypergravity studies demonstrated that increased gravity has a comparable effect on the mammalian body. Homeostatic regulation of the rat body temperature, heart rate, and activity become depressed under 2 g, an effect from which rats recover within 5-6 days (13).

The master clock that coordinates the circadian timing system of mammals is localized in the hypothalamic suprachiasmatic nucleus (SCN) of the brain. SCN cells generate a 24 h output rhythm to which peripheral slave oscillators synchronize. Furthermore, SCN rhythms entrain to the ambient light/dark cycle, in the absence of which, it maintains a free-running endogenous rhythm. Mice under constant darkness for example do continue to display activity rhythms, but the period being shorter than 24 hours. Whereas rats and humans under constant environmental conditions show free-running periods longer than 24 h (14). SCN originated circadian rhythms show cell-autonomous properties produced by an autoregulatory transcriptional/translational feedback loop of clock genes and their protein products. Studies discovered that these clock genes are not only expressed in SCN (15), but also in numerous extra-SCN brain regions (16, 17) and peripheral organs (16, 18, 19).

We have just started to understand the importance of biological rhythms on physiological processes and performance in humans. More data needs to be gathered before we fully understand the underlying mechanisms how SCN orchestrates the internal timing system, on which we all depend on.

In the lecture, core principles of the circadian timing system of mammals will be explained and problems discussed which occur when the system gets de-synchronized. Thereafter, we will focus on major problems of circadian rhythms in space and on applicable countermeasures.

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Evolution of land plants

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There are over 275000 plant species known today. But the situation was very different when first land plants evolved from green algae. This transition of life from aquatic habitat to drier land conditions is considered to be one of the most important adaptation events in the history of life.

When did this happen?

Paleontological studies have identified five key segments in the evolution and diversification of life on land.

476 MY*	First land plants evolved.
410-380 MY	This is one of the most important periods of evolution of land plants. Studies suggest that evidences of virtually all plant adaptations that made the life possible on drier lands are present in these fossils. This rapid appearance of so many plant groups and growth forms has been called the Silurian-Devonian Explosion.
350-290 MY	This period is known as Carboniferous period because fossil records show extreme coal deposits. Coal formation starts only in presence of water indicating the presence of extreme forested swamps.
250-120 MY	Age of Gymnosperms
140 MY-present	Age of Angiosperms
(* million years ago)	

What were the key challenges for transition of life from aquatic habitat to drier land conditions?

Preventing water loss. Plants solved this problem by evolving a wax like coating called cuticle. But this created problems for gas exchange. Plants solved this problem by evolving stomata.

Transporting water from tissues with access to water to tissues without access. Plants solved this problem by evolving vascular tissues. Not only they solved water problem, vascular tissues provided rigidity to pave the way for erect growth against the forces of gravity.

Transporting gametes without water. Early land plants had male gametes that swim to the egg to perform fertilization but evolution of pollen enabled plants to break their aquatic habitat.

Another key event that paved the way for future evolution of life on land took place a long time before plants evolved on land. This was evolution of oxygenic photosynthesis. The talk will cover briefly how land plants have diversified in ways that affect their ability to capture photons and make sugar and perhaps reflect their growth habits.

The talk will also provide a brief description of molecular basis of evolution including genome duplication and how duplicate genes may sub-functionalise or acquire new functions to enable further diversification of life of land plants.

Life on other planets, the case of Mars

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It is difficult to have a clear idea of the paths between carbon-hydrogen complex abiotic molecules that were on Earth about 3.5 billion years ago, and organized bodies that obey to the rules of life. If we leave the Earth and look to the Solar System, the habitability zone, around the Sun, in which water exists under a liquid form, comprises only the Earth, then life. Nevertheless on the borders of this zone, one sees Venus and Mars. No doubt that Venus was –and is– too hot to sustain life, but, at its beginnings, Mars was very similar to Earth. Then, even if, at the present time, Mars seems unable to sustain living organisms, it may be possible that, at the time when life appeared on Earth, mild conditions existed on Mars; then, looking at Mars may help to understand the way life appeared on our planet. From the sixties to now, our knowledge of Mars has evolved; complex missions are sent to Mars, a part of which is devoted to the search for complex molecules. We will have a quick look at the mineralogy of Mars surface, and its links with the search for fossil (pre)biotic molecules, at the experimental content of the ‘laboratories’ arrived at Mars surface in August 2012, and at the present clues or mysteries (methane on Mars?). The first 9 months of Mars exploration, by Curiosity rover, sustained the idea that Mars has been habitable, and some fresh news will be detailed. Other bodies of the Solar System (*e.g.* Titan) will also give different points of view on this complex organic chemistry.

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