Evolutionary Biology & System Biology – Theoretical Outlook

Table of Contents:

Synopsis

Biological systems represent one of the most complex systems known in terms of their diverse number of basic units. It is commonly accepted that complexity has increased in the process of evolution, which favoured more complex organisms and systems through natural selection. Until recently, it was assumed that in order to reach a comprehensive understanding of complex biological systems, it is necessary to deconstruct every system to its fundamental components, fully analyse and understand them and only then, based on these findings, reach conclusions about the nature of the system. This approach, which regards a system as the sum of its components is often referred to as reductionism.

In the last two decades, thanks to technological advances like genetic engineering and bioinformatics, the scientific community has witnessed enormous progress in many biological fields. One direct result of this was the overwhelming increase in the amount of data available to researchers. While resulting in many advances and successes in both therapeutic and scientific terms, some serious challenges also ensued from this process.

Biological systems now appeared as even more complex entities, with much wider variability than originally thought. Using reductionism approaches failed to provide a complete understanding of those systems. This, in turn, has led to searching of new, complementary, approaches. One of these approaches advocates the viewing of biological systems in integral terms while each having its own qualities and characteristics. This would mean that some systems are more than just the sum of their ingredients, since their complexity is in itself a very important attribute. Examining the complexity of biological systems might also shed some light on complexities and complex systems from other disciplines like physics, management and social science, since it seems that complex systems, interestingly enough, do share many characteristics. Hence, understanding complexity of biological systems might help us understand - and then explain - other complex systems (and, of course, vice versa).

Evolutionary Biology

Evolutionary biology is an interdisciplinary field that includes scientific work covering a wide range of both field and lab oriented disciplines. It pertains to research of particular organisms as case studies aimed at answering general questions in evolution. It also encompasses palaeontology and geology which use fossils to answer questions about the pace and mode of evolution, as well as theories in areas such as population genetics. In the 1990s developmental biology has made a re-entry into evolutionary biology, finishing its previous exclusion from the ***modern synthesis***,[1] through the study of evolutionary developmental biology. Evolutionary biology's frameworks of ideas and conceptual tools are now finding application in the study of subjects ranging from computing to nanotechnology.

Systems biology is the study of the interactions between the components of biological system as well as how these interactions give rise to the function and behaviour of that system. **S**ystems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks. For instance, a cellular network can be modelled mathematically, using methods from chemical kinetics and control theory.

Because of the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Since the objective is a model of all the interactions within a system, the experimental techniques that suit best systems biology are those that are **system-wide** and attempt to be as complete as possible.

Artificial life: This is a sub-field of Bioinformatics that attempts to model, even recreate, the evolution of organisms as described by evolutionary biology. Usually this is done by means of mathematical and computer models.

Evolution

Evolution is change in the heritable traits of a population over successive generations. These traits result from gene expression, which are DNA segments that encode protein or RNA. Therefore, evolution can be defined as changes in genes over time; organisms dynamically changing as result of gene mutations that occur **randomly**. It should be noted that mutations are not directional, in the sense of being affected by the environment. These genetic changes are random and only then natural selection favours beneficial genetic changes. When genetic mutation occurs within an individual organism, it can have a positive, a negative or a neutral effect on the organism’s fitness (survival and ability to reproduce).

Natural selection is the process by which individual organisms with favourable traits (or genes) are more likely to survive and reproduce. If these traits are heritable, they are passed to the organisms' offspring with the result that beneficial heritable traits would become more common in the next generation.

It is important to understand that it is through evolutionary changes, an organism or species adapt to their environment. Should the environment change constantly, it would lead to constant change in the selection parameters. Thus, the effect of each mutation depends on the environment within which the organism operates and it cannot be regarded as “positive” or

[1] integration of Charles Darwin's theory of the evolution of species by natural selection, Gregor Mendel's theory of genetics as the basis for biological inheritance, random genetic mutation as the source of variation, and mathematical population genetics.

"negative" in absolute terms. A very famous example is a mutation in a gene related to sickle-cell Anaemia. This mutation is usually viewed as decreasing fitness, but in areas of high Malaria incidence, this specific mutation would induce a relative protection against Malaria, hence, improving the fitness of the individual that carries it.

Evolution and complexity

Darwinian evolution is a simple yet powerful process. It only requires a population of reproducing organisms in which each offspring has the potential for a heritable variation from its parent. This principle governs evolution in the natural world and it has produced organisms of vast complexity. Through billions of years, organisms and species evolved from relatively simple and "primitive" life forms into extremely complex creatures. This complexity has lead to the development of much larger biological systems (multi-cellular organisms with nerve systems). It has also been responsible for the development of to vast bio-complexity at the cellular level (gene variations, metabolic networks and compartmentalization). Still, whether or not complexity increases through evolution has remained contentious issue.

According to some views, it would be inaccurate to view evolution as complexity oriented, that leads ***always*** to more and more complex organisms and systems. However, it is agreed by most (if not all) scientists that evolution has enabled organisms to be more adaptive to their niche - which in many cases (but not always) this meant becoming more complex. Complexity may be very advantageous for an organism in order to either specialise in a certain biological niche or rather, broaden the spectrum of its functions. This would ultimately lead to greater fitness compared with competitors.

Gould[2], for example, argues that any recognisable trend can be explained by the "drunkard's walk" model, where "progress" is measured simply in terms of a fixed boundary condition. McShea[3] investigates trends in the evolution of certain types of structural and functional complexity and finds some evidence of a trend but not of anything conclusive. In fact, he concludes that "something may be increasing. But is it complexity?"

Bennett[4] on the other hand, defines complexity as "that which increases when self-organising systems organise themselves."

Biological networks are the most complex outcome of evolution and natural selection since they are formed by interactions between DNA, RNA and proteins and organisms. Their existence is what has led to the bio-diversity and bio-complexity, so they might be seen as the essence of living creatures. Recently, some questions arose regarding the effectiveness of current tools provided by molecular and evolutionary biology to understand and analyse these networks. The central idea in biology, like other exact sciences, is that complex systems should be analysed through ***reductionism***. According to this philosophy first introduced by ***Descartes*** in 1637, higher-level processes can generally be better understood by looking at their components or lower-level processes. For example, in order to understand how the human body works, it is necessary to understand how the organs and the tissues work. In order to fully understand the different tissues, one must investigate the cells from which they are built. In order to fully understand how cells operate, it would be necessary to understand how its proteins function within the cell etc. One of the main questions was whether the

2 Gould, *Full House*, Harmony Books, New York (1996)
3 McShea, *Evolution*, (Lawrence, Kans) 50, pp. 477–492. (1996)
4 Bennett, C. H. *Physica* D 86, pp 268–273. (1995)

molecular dynamics or chemical kinetics description of such network can be described in way of reduction to the smallest parts in each system. Some would argue that in addition to reductionism, other approaches like ***holism*** and ***complexity*** should be used.

Evolution of Complex Systems - Self Organisation

Ozkul[5] tries to mimic evolutionary development (complexity and organisation) by sophisticated computer programmes. He argues that systems created by complicated algorithms can be very similar to cellular organisms. The question that remains unanswered is whether these complex systems can evolve and mature as cellular organisms do.

It is assumed that it is possible to base an evolutionary system on a pure functional language. Functional languages are so elegant that:

> They are mathematically reducible. Straightforward optimisations are possible. Equivalence of programmes can be shown.
> The semantics of a functional language can be written in itself. The best way is to have an interpretation written by the language itself.
> They easily allow object oriented extensions.
> They can be compiled for massive concurrence.
> They can be very intuitive and pedagogic.
> They can enhance programmes striving for artificial intelligence.
> Data are constant functions or vice versa: functions are data.

Thus, the evolutionary system is promising to allow programmes to evolve, processing other programmes (or its own self)! These properties of functional languages might lead to some rather interesting developments.

Currently, genetic programming, genetic algorithms, artificial life are all use extensively random number generators. Unfortunately, to generate every single random number, up the 5 million transistors are used for a considerable fraction of a second. This makes genetic programming a very demanding task in terms of processing power and as a result there are limitations to the complexity that can be achieved.

Evolution has progressed from simple proteins up to human societies. Simple cells have become complex cells with autonomous internal elements. Cells have formed animal and plant bodies. Animals have formed societies. Ecological structures have emerged. This process can be described as follows:

Stage I - Independent units compete for maximum fitness. Without regard to their elaboration, this is what state of the art genetic programmes and algorithms seem to do.

Stage II - Some competitors begin to cooperate. This has never been actually accomplished in genetic algorithms.

Stage III - Cooperation continues within the border to protect resources from parasites.

Stage IV - Higher hierarchical units continue to evolve. We are back to "standard" genetic algorithm.

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5 Umur Ozkul, "Evolution of Complex Systems" - Self Organisation, via internet (1996)

This process repeats itself into higher hierarchies whenever it has enough resources. Real life indicates that whenever resources are scarce, competition is beneficial. What is striking in life is the evolution of reusable and modular lower level units. Life uses the same components again and again in different designs.

This process is viewed as a reasonable mechanism through which Eukaryotic cells have emerged as endo-symbiotic systems between several primitive organisms. It is suggested that eukaryotic organelles such as mitochondria and the chloroplast[6] (in plants and photosynthetic micro-organisms) and even the nucleus itself[7] were all independent organism that have integrated into the eukaryotic cell.

Evolution of biological complexity

Adami *et al.* argue that in order to make a case for or against a trend in the evolution of organism complexity, we must first define biologic complexity. Through separating genomic complexity from structural or functional complexity, they have established an information-based theoretical method for gauging complexity. Their mathematics permits genomic complexity to be extrapolated, to a degree, into knowledge about the world in which that complexity has arisen.

They have investigated the evolution of genomic complexity in populations of digital organisms and had monitored in detail the evolutionary transitions that have increased complexity. They showed that because natural selection forces genomes to behave as a natural "Maxwell Demon"[8] within a fixed environment, genomic complexity is forced to increase.

In their system, they created computer programmes that were, actually, sequences subject to evolution with the ability to self-replicate through the execution of their own code. In this respect, these sequences have been computational analogues of catalytically active RNA sequences that would serve as the templates of their own reproduction. In populations of such sequences that adapt to their world (inside of a computer's memory), noisy self-replication coupled with finite resources and an information-rich environment leads to a growth in sequence length as the digital organisms incorporate more and more information about their environment into their genome. Evolution in an information poor landscape, on the other hand, would lead to selection for replication only, and shrinking in genome size[9].

How the Leopard Changed its Spots: The Evolution of Complexity[10]

It is postulated that all organisms on the planet share a common ancestor and that evolution represents a very gradual mechanism of change. These assumption lead to a paradox: on the one hand, bio-diversity is so rich and versatile that it leads to substantial differences between different species. On the other hand, it is very hard to understand such large differences by a deterministic way of thinking. While it is not hard to grasp the notion that dogs and cats are evolutionarily related, the evolution link between a mammal and a plant seems bizarre. "The large-scale differences between the species seem to require another principle other than

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6 Johnson *et al.*, *Science* 304 pp. 253 – 257 (2004)

7 Lake *et al. PNAS* 91 pp. 2880. (1994)

8 Maxwell's demon is a 1867 thought experiment by the Scottish physicist James Clerk Maxwell that was meant to raise questions about the possibility of violating the second law of thermodynamics.

9 Spiegelman, *et al PNAS*. 58 pp. 217–224. (1967)

10 Goodwin, B. C. How the Leopard Changed Its Spots. Charles Scribner's Sons, New York. 1994 natural selection operating on small variations." Moreover, recent advances in relevant basic science (genomics, proteomics, bio-informatics, etc.) have generated abundance of information about even more complex and versatile biological systems originally thought. Another change resulting from these advances is that fundamental units of biology become smaller: from whole organisms to cells, from cells to organelles, from organelles to proteins and from proteins to genes. Thus, in order to analyse a biological system, the scientist must cope with an incomprehensible number of variants which surprisingly lead to a well ordered and organised system.

This phenomenon, in which highly complex, sometimes chaotic, systems lead to very ordered and sophisticated ones poses immense challenges to scientists and may require an inter-disciplinary approach combining other disciplines and sciences, such as "complexity science" that deals with highly diverse and complex systems.

Goodwin compares the "geno-centric" biology to the geo-centric cosmology that was popular until Copernicus had developed his "helio-centric" cosmology. Geno-centric biology has presumed that organisms' properties could be fully understood by recognising and analysing the genes involved. Goodwin argues that there is always a risk in science, where particular way of looking at things would result in "***tunnel-vision***" (the assumption that everything can be explained while, in fact, it is impossible to recognise the limitations embedded in this very approach). Just like the geo-centric cosmology was good enough for observations made before Copernicus, geno-centric biology was sufficient until recently. Geno-centric biology was an extremely powerful tool in understanding biological systems, but it has its limitations and as a result, there are certain areas in which it fails. Organisms simply cannot be reduced to the properties of their genes. They must be understood as dynamic systems with distinctive properties that characterise the living state. The complementary approach should be "organo-centric" that entails seeing the whole organism as a fundamental unit.

It is important to note that this approach is **not aimed at replacing** the geno-centric approach that has proved - indeed still is – of vital importance, but reframe and re-integrate biology from different points of view.

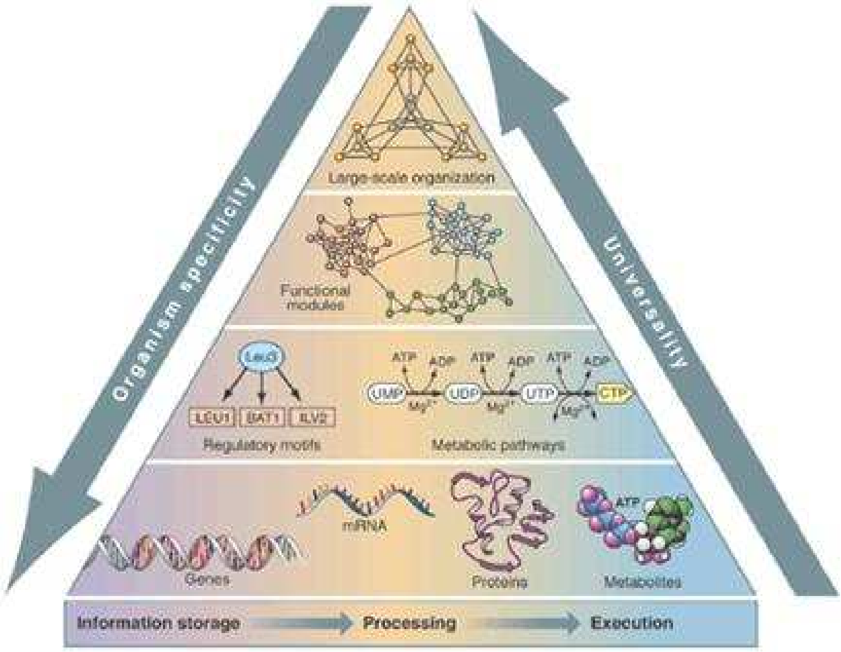
Life's Complexity Pyramid (Oltvai and Barabási)

When looking at cells or micro-organisms, one cannot cease to be amazed by the impressive abilities and sophistication a single cell possesses. Each cell can operate as an independent biological system, as it can adjust its intracellular machinery in response to the environmental changes and developmental state. The amazing ability to regulate and respond to problems like DNA damage, error in replicating DNA and mis-folded proteins increases even further the complexity and diversity of each cell. This brings the scientific community onto a major issue in contemporary cell biology: the need to comprehend the staggering complexity, versatility and robustness of living systems.

The basic dogma of molecular biology that deals with the flow of biological information and processes within a cell, presents a directional scheme in which each component is responsible for a specific function. For example, DNA is responsible for the genetic information storage and proteins are responsible for information processing and execution of cellular programmes. Each level of organisation was supposed to be distinct - relative to other organisational levels. Recently, however, this hypothesis has been challenged when it has been discovered that the borders between these levels are "leaky". One example could be the proteome's ability to store short-term information.[11]

These overlap and integration between the different organisational levels may require scientists to view cellular functions as distributed between groups of heterogeneous components that interact with one another within large networks.[12]

Oltvai and Barabási propose a different way of looking at cellular systems: A **simple complexity pyramid**[13]



The basis of the pyramid features the traditional basic units known from molecular biology: DNA, RNA, proteins and metabolites. These units interact to create small recurrent patterns, called pathways in metabolism and motifs in genetic regulatory networks. These motifs and pathways are integrated to form functional modules that are responsible for discrete cellular functions. These modules are nested in hierarchical manner and define the cell's large-scale functional organisation. Universality increases as the units become bigger and more complex while specificity decreases.

When examining the upper layers of the complexity pyramid (levels 3 & 4), it becomes clear that there might be universal patterns common to all biological systems and even to non-biological ones.

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11 D. Bray, *Nature* 376, 307 (1995); U. S. Bhalla, R. Iyengar, *Science* 283, 381 (1999)

12 L. H. Hartwell *et al*., *Nature* 402, C47 (1999); H. Jeong et al., *Nature* 407, 651 (2000)

13 Life's Complexity Pyramid - Z. N. Oltvai, A.-L. Barabási, *Science* 298, 763 (2002)
The pyramid is divided to 4 levels: Level 1 represents the functional organisational units (genome, transcriptome, proteome and metabolome). There is remarkable integration between these units as they can form genetic regulatory or metabolic motifs (level 2). These motifs are the basis of functional modules (level 3), which in turn generate a scale-free hierarchical architecture (level 4).

Milo *et al.*[14] argue - and provide evidence to their claim - that the motifs and modules are not unique to cellular regulation but can be found in a wide range of networks such as food webs, neural networks and computer circuits. Their study raises the possibility that the complexity pyramid may not represent only biological networks may but be relevant to understanding non-biological complex networks as well. This may lead to the conclusion that universal organising principles apply to all networks, from the cell to the World Wide Web.

This attitude of looking at the level of the entire system might complement molecular biology's reductionism. Furthermore, such system-level laws and patterns might be relevant to other disciplines like physics, sociology and computer engineering and as such, they can help researchers to understand many types of complex networks. There is a true need to develop inter-disciplinary models that are relevant for complex networks - whether biological or mechanical; mathematical or social. The new tools that would have to be invented *en route* may prove useful in other areas such as management and society.

[14] R. Milo *et al., Science* **298**, 824 (2002)