Synthetic Biology, Gödel, and the Blind Watchmaker

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Analysis, Synthesis, and Gödel

Historically, biology is a science that has been caught up in the debate of how to approach living beings: from the analytical or synthetic viewpoint. The analytical view encompasses the most successful biological sciences, particularly genetics, molecular biology, and evolutionary biology. They are considered to be models of a reductionist approach to appraising living beings because, with few exceptions, the conceptual tools and methods they have developed focus on parts, components, or particular traits. In genetics the basic features are the Mendelian trait, the mechanics of inheritance, and the laws governing transmission from one generation to the next. Molecular biology focuses on the chemical nature of genetic traits (i.e., genes) and on the molecular machinery involved in their expression and regulation, giving rise to a particular function. Evolutionary biology focuses mainly on the study of how an organism's fitness is affected by certain genetic traits. Eventually a trait can evolve differentially with respect to any other trait, with or without similar fitness. All three sciences can be considered gene-oriented, which is an accurate description, and during the last 50 years the biology syllabus has been greatly dominated by this gene-centered analytical view. But there is more to the analytical view than that. Analysis means the study of an entity by breaking it down into its parts, and the vast majority of sciences are analytical by definition. Genetics, molecular biology, and evolutionary biology have developed successful methodological tools to study those parts of living organisms that are genes. However, there are many other biological sciences that are analytical, which approach the living entity by focusing on particular parts. Probably one can state that the analytical view is a permanent methodological approach to living beings, no matter which organizational or hierarchical level we consider (Ayala 1968). Historically, biological sciences approaching living entities analytically have been unequally successful, and it is a matter of fact that those sciences focusing on genes have achieved greater success than others focusing on other areas. Current genomic sciences are the typical by-product of the gene-centered approach to living beings.

But can we approach a living being in a different way? Yes and no. The basic perception of many biologists and scientists in general is that living entities (complex entities, broadly speaking) cannot be appraised via an approach that adds up their parts and, less so, by considering that one single part (for instance, the gene, the genome) is enough to gain sufficient understanding of the living entity as a whole. I would like to point out the difference between analytical and reductionist approaches to science, particularly in biology. Analytic approaches do not discard the combination of parts and, then, the rules and/or laws derived by working separately with the parts could eventually be joined in the hope of achieving an increasingly better explanation of the living being as a whole. On the contrary, the reductionist approach discards the explanatory relevance of many parts of the living system because it assumes that once we have discovered the laws governing one particular and essential part, the rest and the whole can be explained. It has been argued that the analytical view is a reductionist view of science when, in reality, it is not. The analytical view probably constitutes the primary methodology of scientific method.

Although both approaches take a different stand on the understanding of complex features, they share a common problem: How to approach or explain the appearance of emergent properties? For the analytical approach, this question is normally solved a posteriori as follows: The emergent property,

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once detected or apparent, is associated or considered as a new part of the whole system. This approach suffers from a consistency problem because it does not consider the relationship between parts and/or their corresponding laws. The reductionist approach considers that emergent properties should be explained a priori, in terms of the laws governing certain parts of the whole system. Although it is consistent, it normally suffers the sufficiency problem because it is unable to explain the appearance of new or emergent properties. The limitations of both approaches are more evident when the entity under scientific appraisal is complex: the perception that there are properties of the entity as a whole that, although present, cannot be explained in terms of the rules or laws derived when working with its parts. This perception is the one that has been expressed for centuries by many reputed biologists and philosophers, who can be ascribed to the synthetic view. As with the use of the term "analysis," "synthesis" also has many connotations and, under their respective umbrellas, there are several research traditions, some of which have vanished, but others which still endure. Vitalistic, holistic, and systemic approaches to living beings can be considered synthetic views that, against different scientific backgrounds, are critics on the capability of the analytic view to have a sound perception of the living being as a whole. But, what are the scientific achievements of such synthetic approaches? As mentioned above, I support the thesis that synthetic views have been presented throughout the history of biology to cite, as expert witness, the problems faced by the analytic view to appraise the living being as a whole, but not as schools of thought, bringing new substantial concepts and/or methods capable of abating the criticisms leveled at the analytic view. This was described beautifully by Mayr (2002):

> It would be ahistorical to ridicule vitalists. When one reads the writings of one of the leading vitalists like Driesch, one is forced to agree with him that many of the basic problems of Biology simply cannot be solved by a philosophy as that of Descartes, in which the organism is simply considered a machine. . . . The logic of the critique of the vitalists was impeccable. But all their efforts to find a scientific answer to all the so-called vitalistic phenomena were failures. . . . Rejecting the philosophy of reductionism is not an attack on analysis. No complex system can be understood except through careful analysis. However, the interactions of the components must be considered as much as the properties of the isolated components.

As stated clearly by Mayr, analysis is a necessary step in any science, particularly in biology, and we can wonder about the nature of synthetic inquiry, considering the current status of biological research, particularly at the cellular level. Mayr makes reference to the nature of such inquiry because for him it is also very important to know more about the interaction between components. Is there any type of behavior in the whole system that requires some sort of experimental combinatorial game of the parts to predict and/or to explain it? Moreover, do we possess methods, concepts, and tools to take on such a challenge? The quest of the synthetic view changes in line with our expanding biological knowledge, and current questions are of a different nature than previous ones, probably due to recent and astonishing advances in genomics and computational sciences. Now, more than ever before, we can combine many parts of a living being; moreover, we can detect many parts functioning at any given moment in a living being and, also, how such parts interact. If we are interested in the interaction between components, it is because many properties of living beings are supposedly the by-products of such interactions. One particular but extremely important class of interactions concerns emergent properties. Within the current panorama, the living being is being approached via a combination of powerful and successful conceptual and experimental analytical tools, with synthetic biology enabling us to simulate *in silico* the behavior of cell systems, about which we have more and more detailed knowledge. The simulated systems are governed by a set of defined rules (i.e., axioms) that can approximate the natural ones gradually, but where emergent properties may or may not appear. Let us suppose that we are able to fully mimic any given natural living cell because we have a set of predefined rules and components that enable us to reproduce the properties of the natural one. Such a situation may represent the threshold of our knowledge of a particular living being and, in some way, represents the most ideal approach to acquiring biological knowledge: the combination of the analytic and synthetic views. Let me define as the final integrative stage, the state of biological knowledge of that particular living being we call a cell. Following are the key questions to be asked at such a state of knowledge: Is the simulated system completely predictable? Is it more predictable that the natural one? Do we really think that any behavior demonstrated by the natural cell will also appear in the simulated one? The answer to all three questions is "no." The main reasoning behind this answer lies in the Gödel theorems and later derivations in what is known as the Gödel–Turing–Chaitin limit (for a more detailed and technical description, see Moya et al. in press).

Applied to any biological system (particularly a cell), the Gödel theorem of undecidability states that *properties exist within a cell that are neither provable nor disprovable on the basis of the rules that define the system*. This means that on the basis of the rules and component elements or parts that govern cell behavior, there might be properties from which we cannot tell whether they can or cannot be derived from the rules of the cell system. Emergent properties belong to this type of property.

On the other hand, the Gödel theorem of incompleteness states that *in a sufficiently well-known cell in which decidability of all properties is required, there will be contradictory properties*. The biological translation of that theorem is extremely important because it asserts that no matter how well we know a particular cell system, we can find properties and/or behaviors that seem to contradict each other. Contradiction is applied to formal systems and is not a proper empirical description when talking about biological features. Contradiction is the syntactic metaphor when referring to examples where we can find a particular in silico cell showing properties (some of which may be emergent) that are the opposite ones to another that, like the first, is based on the same operational rules and starting components.

Gödel theorems on living cells admit a translation within the framework of Turing machines. The statement may be formulated as follows: *There may appear functions, structures, properties in general of living cells that cannot be computed by any logical machine*. If we consider the cell as a Turing machine (for an extensive review, see Danchin 2009), then a finite procedure (i.e., an algorithm) should exist showing us how to compute its behavior. As mentioned above, we can imagine an integrative stage of biological knowledge where we can define the rules and all the components of a living cell. Then, supposedly we can compute the cell and the corresponding algorithm can be executed by using a mechanical calculation device, provided we have unlimited amounts of time and storage space. But if Gödel theorems apply to physical and/or biological entities (Penrose 1989), they tell us that we cannot anticipate the appearance of new properties in the cell or the lack of them and sometimes properties will appear that follow contradictory trajectories, no matter how deep is our knowledge of the cell.

Evolutionary Theory and Gödel's Theorems

As envisioned by Darwin, the history of living beings can be represented in a tree-like form and now we know that a set of events or major transitions have taken place but not necessarily sequentially (i.e., from single replicons to chromosomes, from prokaryotes to eukaryotes, from unicellular to multicellular organisms, etc.), playing an important role in shaping the diversification of life. The theory of evolution deals with the nature of the causative and casual factors able to account not only for those major transitions but also for the astonishing range of biodiversity (i.e., species and also more inclusive phylogenetic taxa) and the associated extinction events (regular or sporadically dramatic) that have populated our planet since life first appeared. Throughout its history, life has displayed a plethora of emergent properties and, in some way, life is the perfect model in which to study emergence.

Is there any relationship between the continuous appearance of evolutionary novelties and Gödel's theorems? Or, to pose the question in another way, what is the relationship between Gödel's theorems and evolutionary theory? The neo-Darwinian theory of evolution states that evolution proceeds by selecting those genetic variants that display higher relative fitness. Random genetic drift can also promote evolutionary change by randomly choosing among genetic variants that are selectively neutral. Evolutionary change is then governed by these two forces, although others cannot be ruled out, constituting another major debate in the history of biology (Gould 2002).

Let us consider the evolutionary process as some sort of executable algorithm that we may call the "blind watchmaker 1" (BW1) and from which we know exactly all the forces (rules) acting on populations of living and genetically diverse objects. Can we predict the expected outcomes of BW1? No, if we agree that Gödel's theorems, as when applied to formal languages, also apply to the physical (biological) or materialistic phenomena that can be described algorithmically (Penrose 1989). I am not stating that life is totally unpredictable—it often is for a certain number of situations. But from time to time, through evolutionary history, emergent phenomena have appeared. It seems that evolution, emergent phenomena, and the unpredictability of the history of life as a whole are perfectly compatible with Gödel's statements. As beautifully described by Danchin (2009), contrary to interpreting Gödel's statements and referring to later derivations by Turing and Chaitin in the negative sense of an upper limit to our capacity of knowledge (Moya et al. in press), what we observe is the intrinsic ability of living systems to permanently create new information and then to evolve. This is possible because in the early stages of evolution of life a living device appeared, formed by a unit of coded information (DNA) and another device (the protein machinery) that decodes and recodes the genetic information.

Let us suppose that we add new rules to the BW1 in such a way that we are now in a position to explain that particular phenomenon, which was an emergent phenomenon within BW1. Let us call this new system BW2. Although BW2 is more sophisticated and far-reaching than the former, it will be exposed, following Gödel's statements, to new unpredictable phenomena. And so on.

Lessons for Synthetic Biology

As I have shown, many biological features are not predictable. Emergent phenomena will appear within any sufficiently complex living system. Accordingly, we need to think about how methodologies in synthetic biology are conceptualized and developed. There are two prevailing views: engineering and systems standpoints.

From the engineering viewpoint, synthetic biology is an engineering discipline (Endy 2005) whereby both the whole cell and any natural or artificial cellular components can be standardized. From such a perspective, how they behave should be both predictable and controllable. The emphasis on control is of great relevance because it entails that any man-made biological device should always behave as expected in any suitable environment. With respect to BW1, BW2, etc., here we have a case of a "not-blind engineer-watchmaker" (NBEW). Although NBEW is better able to predict the outcomes than BW, can we rule out Gödel uncertainties? Unlike BW, we can apply, for instance, two levels of quality control: (1) exploring all imaginable environmental circumstances during the design stage, and (2) when the device is put into a biological chassis and released. It is probably much easier to control simple biological devices than living cells and, within cells, much easier to control a single minimal cell than a complex one. But no matter whether we choose to work on simple devices or minimal cells, we cannot exclude a priori the appearance of an emergent property and, in consequence, we will need to move from NBEW1 to NBEW2 and so on, as explained in the previous section.

Synthetic biology can also be considered as an applied methodology to create biological systems from which we gain knowledge. I call this a "not-blind systems-watchmaker" (NBSW) view. Complementary to NBEW, this view directly embraces complex phenomena and emergent properties. Advances in all areas of molecular biology and computational biology coupled with recent developments in network and graphs theory allow us to simulate cellular behavior, tinker with the cell, and observe the outcome of such interventions (Serrano 2007). Although NBSW is also subjected to Gödel's uncertainties, it is conceptually and empirically better prepared to delay the transition from NBSW1 to NBSW2 than NBEW1 to NBEW2. NBSW is probably better suited to meet the expectations of professional biologists. NBSW also falls under the umbrella of the particular stage of the history of biology that I called "integrative" in the first section, which is currently merging convergent analytical and synthetic traditions.

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