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ON PREDICTION IN BIOLOGY AND EVOLUTIONARY THEORY

It is widely known that, from a logical point of view, prediction has the same structure as explanation. Given an empirical phenomenon or explanandum, its explanation essentially consists in establishing a set of well-confirmed universal hypotheses and antecedent conditions from which the statement describing the phenomenon can be deduced. In this case, a prediction of the same phenomenon would have consisted in establishing the same set of universal hypotheses and conditions prior to the occurrence of the event itself. Though this view has encountered some difficulties in its application to social and historical disciplines, it adequately describes how these two major concepts are regularly understood and used in scientific activity, specially in the natural sciences.

However, despite their logical identity, explanation and prediction are appreciated by the scientific community in a very different manner. A theory, a law or a general hypothesis with which it is possible to anticipate events that will effectively happen, enjoys of more credibility than the explanation conceived a posteriori in order to account for the same events. The history of science endorses this feeling of the scientific community and, in this sense, the venerable cases of Galileo, Newton and Einstein are repeatedly quoted.

According to scientists' preference of predictive knowledge there are some issues unconnected with philosophical considerations involved, such as the practical value that the power to anticipate events has for human life. But, there are also epistemological questions involved that have to be pointed out in order to understand the high credit of those general statement which allow to anticipate the experience. Among these, it is usual to mention that the difference between explanation and prediction is of a pragmatic character that is given by the temporal situation in which the scientist is placed: after or before the occurrence of the explanandum. But there is more than time. As Lipton (1991, p.145) says: "When the scientist does not know the right answer, she knows that she is not fudging her theoretical system to get it. The fact that her

prediction is of a future event is only relevant insofar as this accounts for her ignorance". On the contrary, explanation would allow for accommodation of the theoretical system to the data. Thus, it is understandable that successful predictions can provide a high regard to those theories which originated them, whereas unsuccessful predictions normally produce their public discredit.

The high consideration of predictive knowledge by the scientific community explains well the reason why the disciplines and theories that can predict are considered more scientific than those that can do it in a lesser degree. Philosophers of science have generally agreed with the view about the supremacy of prediction on explanation, as we can see in the cases of prominent figures of Popper, Hempel and Lakatos. Having said that, it is absolutely understandable that those who have adopted without reservations this view of the value of prediction, could have suspicions on the scientific character of social disciplines because of the limited predictive power of the theories that exist in their fields.

At any rate, biological disciplines are natural sciences; they seem to share, at first sight, the same destination as social ones. Even regarding the evolutionary theory, which, according to the famous dictum of Dobzhansky ("nothing makes sense in biology except in the light of evolution"), is the heart of modern biology, the widespread consensus is that things are more embarrassing. In this article we attempt to demonstrate that this opinion is partially unfounded. The situation regarding prediction in biological knowledge can appear grave to scientists claiming that any prediction has to be exact or to those who adhere to biological theories that are in serious methodological difficulties, such as neo-Darwinism. As soon as we get into molecular biology or precellular evolution, the image of biological sciences as merely descriptive or post hoc explanatories, reveals itself as inadequate.

A distinction will be useful for our purposes. It refers to the precision of the prediction itself. In this sense, we should accurately distinguish between exactness and rigor, on the one hand, and lack of exactness and vagueness on the other. The following examples will provide us with an insight of this distinction and they will exempt us of the requirements of a theoretical discussion that would be more appropriate for another context. What counts as an exact prediction can be illustrated in the case of a scientist who calculates the path of a planet with the help of Newton's mechanics, his law of gravitation and known antecedent conditions. The case of a rigorous prediction, but not an exact one, is different: from the hypothesis that the evolution happened (the fact of evolution) it is possible to predict the past existence of intermediate forms. In this sense, the discovery of *Archaeopteryx*, a fossil with bird and reptile characteristics, constituted an accomplishment of that prognosis. Be-

cause of the fact that the prediction had been made without specifying which concrete forms had to be encountered, it could not be called an exact prediction. Nevertheless, it was a rigorous prognosis because the notion of intermediate form is morphologically unambiguous, i.e., it lacks vagueness.

It is understandable that the question of prediction in biology causes great concern among biologists and philosophers of biology because any scientific theory should produce some kind of prediction. But this just does not occur with neo-Darwinism, which enjoys a prominent place in contemporary life sciences. It should be noted that we speak of "a" theory of evolution and not "the" theory of evolution. A theory of evolution – whatever it be – should be understood as the set of general hypotheses about mechanisms according to which species evolved up to today's living forms, and should be carefully distinguished from the existential hypothesis of the fact of evolution. Besides neo-Darwinism, of which the central hypotheses are the creative role of natural selection, the theory of micromutation and, in some versions, Spencer's law "the survival of the fittest" (Gould 1982), other alternatives are possible. So, we may consider the epigenetic theory, which asserts that the creation of the living forms occurred during the process of ontogenesis, and particularly embryogenesis. Among other titles, this alternative approach is supported by that revealed by the fossil record and by a historical taxonomy that has been carried out regardless of specific evolutionary tenets (Løvtrup 1986-87, 1987; Amundson 1994).

The problem of neo-Darwinism regarding prediction is mainly due to two factors. The first is the discovery by Scriven (1959), Popper (1992) and many others of the tautological character of the Spencer's maxim "the survival of the fittest", that many neo-Darwinians, as Ruse (1973), thought was a central tenet of the theory. But tautologies say nothing about the empirical world, thus they cannot constitute the grounds for any prediction in natural sciences. The second factor is the fact that the other two neo-Darwinian principles (the theory of micromutation and the theory of natural selection as creative force) together generate the prediction that the fossil record must exhibit a gradualistic character. The rationale is simple: if it is supposed that the evolution of species is produced by natural selection acting on slight phenotypical variants in individuals during long periods of time, then the testable result should be a fossil record displaying the gradual origin of evolutionary novelties. However, paleontological evidence shows us that the intermediate forms predicted by Darwinians and neo-Darwinians never existed and that the dominant pattern is made up of recurrent gaps between genera and higher taxa. In other words, there is no evidence of intermediate stages (Stanley 1979; Eldredge & Gould 1972).

The problem pointed out has produced a critical methodological situation for neo-Darwinians. This is so because predictions not only anticipate facts, but they simultaneously perform the role of testable hypotheses, the falsification of which implies -at least in principle- the falsification of the central tenets which generate the predictions themselves. Darwinians and neo-Darwinians have been sensitive to the point and, in this sense, provided motives for the failure of such an important prediction, which comes directly from the heart of their theory. Different auxiliary hypotheses can be supplied in order to explain the failure (incorrect interpretation of paleontological data, past existence of perturbing factors operating on the evolutionary mechanisms, etc.). So did Darwin himself, G.G. Simpson (1944) and E. Mayr (1982), to quote only the most prominent efforts in this sense. However, an analysis of their additional explanations is out of our scope. The rationale for the present purposes is to manifest that this critical situation has generated a feeling of doubt about biological sciences that is fueling, now fundamentalisms (unable to distinguish between the obstacle of a specific theory and the scientific value of the evolutionist perspective), now the apprehensions of the scientific community regarding any evolutionary attempts.

Fortunately, in the field of precellular evolution, which focuses on a fundamental period of the historical process of life, we find successful predictions, hypotheses that can anticipate facts that were unknown when these hypotheses were coined. Certainly, the relative simplicity of the systems capable to imitate some kind of precellular processes, allows an experimental approach that would be very difficult to achieve in the field of the evolution of organisms. However, complexity is never a valid excuse for lack of prediction. The question here is not to predict the future of life, but to demonstrate that evolutionary mechanisms work in full accordance with the predictions deduced from the theory (Løvtrup 1988).

Those Darwinian geneticists working with *Drosophila* are conscious of the fact that they attempt to demonstrate the reality and the importance of Darwinian mechanisms to explain the origin of new species, but they do not attempt to know the future of evolution. Up to now, their efforts have been fruitless, unless the extrapolation of the results obtained in the field of microevolution to that of macroevolution can be considered a legitimate maneuver. But methodologically speaking, it is nonsense because that is just what has to be demonstrated (the onus probandi).

Any evolutionary system (natural or social) entails some kind of transference of what is achieved at a stage to the subsequent one. In other words, inheritance is always a necessary condition for evolutionary processes. On this premise, i.e., on the requirement of a certain continuation of information, Sol

Spiegelman embraced very early the hypothesis that says that the material of precellular evolution had been the genetic substance (Spiegelman 1945). In this way, Spiegelman adhered to the ideas of H.J. Muller and J.B.S. Haldane, who had conjectured by the 1920s that the substance of primitive life had been the substance of inheritance. From a historical point of view, it should be pointed out that by that time the genetic substance had not been yet identified. However, biologists alternatively opted for one or the other of the two currently well-known biological macromolecules, by giving priority to their respective external characteristics, now to the metabolism (Oparin), now to the inheritance (Haldane).

The hypothesis undertaken by Spiegelman, many years after its enunciation, had been enriched by data that Haldane and Muller could not have at hand, specially the chemical structure of nucleic acids and thereby the way in which they could store information and pass on their structure. It was also decisive for the preference of Spiegelman and coworkers the failure of Sidney Fox and colleagues in demonstrating how polyaminoacids (proteinoids) could pass on their structures to other polyaminoacids and generate evolution (Orgel 1968). Naturally, the elimination of one of the two possible candidates clearly indicated to Spiegelman the direction that this research should follow.

In spite of the fact that nucleic acids appeared to be the unique option, Spiegelman had to find independent confirmation for his hypothesis. In first place, biology is not a formal science that progresses by purely theoretical decisions. In second place, independent confirmation of central hypotheses by means of derived testable ones is a methodological rule, otherwise there would not be any contact between scientific thought and experience. In addition, there were strong obstacles to the consideration of nucleic acids as the substances of precellular evolution (substances that according to Spiegelman, they would have associated afterwards to proteins in order to enhance their own work). On the one hand, the substance of life not only had to be able to store and transmit information, but also to perform some functions (e.g., to catalyze replicative processes). On the other, the DNA – the chemical structure and mechanism of duplication of which, were well known by the 1960s – could not offer all that any evolutionary process by selection demands: phenotypical variants. In this sense it was clear that the perfectly paired double helix of DNA would have been unable to offer options to the demands of a primitive environment (see Sagan's curious attempt of 1957).

With regard to the independent confirmation of the central assumption of Spiegelman and coworkers (that a nucleic acid had been the substance of precellular evolution), the derived testable hypotheses were two. That is, two were the predictions made in this sense by researchers:

- the nucleic acid should have been able to offer phenotypical variants to the precellular environment, which operated directly on the naked molecules;
- these variants should have had a biological significance, i.e., they should have been characteristics of adaptation from a biological point of view.

The accomplishment of the first prediction took place when advances in the studies of RNA, specially those related to RNA virus, revealed that – contrarily to DNA – RNA entities (e.g., viral genomes) could present very different structures (or "molecular phenotypes") by virtue of the chemical peculiarities of RNA. Particularly, the genome of the Q_β virus (and its derived species, i.e., fragments of the original Q_β genome that are able to instruct their own synthesis to their protein machinery) "contains a surprising number of intrastrand antiparallel complements, a peculiarity generating the potentiality for extensive secondary and tertiary structures containing antiparallel stems and loops. This possibility would allow these molecules to go beyond their primary sequences and exploit the selective advantages of their two- and three-dimensional consequences: a distinction between genotype and phenotype could thus arise before the primary sequence was used for translational purposes" (Mill et al. 1973, p. 916).

But, were those molecular phenotypes, or dimensional consequences of the RNA primary strands, actually relevant for selective processes? How can we find it out? The chance for an answer arrived when the isolation of the first self-replicating system, the Q_β replicase system, took place. The Q_β replicase, an RNA-dependent RNA polymerase, has been discovered and purified by Spiegelman and coworkers in 1965 and was capable of mediating in vitro extensive and continuous replications of viral RNA (Haruna & Spiegelman 1965a, 1965b). This particularity opened the possibility of studying the replicative act in a system that was very simple due to the few components involved in the process: the Q_β replicase and the viral genome. This situation encouraged the exploration of selective processes outside a living cell by imposing diverse and specific selective pressures on the system and then observing the unambiguous answers. In Spiegelman's words:

An opportunity is thus provided for studying the evolution of a self-replicating nucleic acid molecule outside a living cell. It should be noted this situation mimics an early precellular evolutionary event, when environmental selection presumably operated directly on the genetic material. The comparative simplicity of the system and the accessibility of its known chemical components for manipulation permit the imposition of a variety of selection pressures during the growth of the replicating molecules (Spiegelman 1967, p. 256).

Among the experiments carried out with the Q_{β} system, we want to focus on the so-called "serial transfer technique". By means of its application, where the intervals of synthesis between the transfer are adjusted to select the first molecules completed, the molecules are forced to reproduce as soon as possible (Mills et. al. 1967). Or put in another way, "What will happen to the RNA molecules if the only demand on them is the Biblical injunction 'multiply', with the biological proviso that they do so as rapidly as possible?"

As the experiment progressed, the RNA molecules became shorter. By the 74th transfer the 83% of the original Q_{β} genome (4500 nucleotides long) had been eliminated. The Q_{β} genome progressively prescinded of those parts that codify for proteins not needed by a virus during its life in a test tube (infection proteins, the replicase, etc.). In order to reproduce itself, the Q_{β} prescinded of those parts that constituted a burden under the critical circumstances created by the experiment for quick replication (a complete account of Spiegelman and coworkers' experiments of the 1960s. – in Spiegelman 1971; a critical study on Q_{β} system in connection with the theory of the hypercycle – in Küppers 1979, 1990).

The self-replicating fragments produced during this process and others formed the so-called " Q_{β} Zoology". We should keep in mind that these fragments were not random polynucleotides because they could instruct their own synthesis; thus they were truly self-replicating RNA species. Among them, we can mention the V-1 (550 nts.), the MDV-1 (218 nts.), the microvariant (114 nts.), and the 6S (100 nts.) As it was said in connection with the necessity of the subject of an evolutionary process to offer phenotypical variants to a selective environment, each RNA species had its own peculiar molecular phenotype. These Q_{β} species showed different properties of biological value; examples of these were the replication in the presence of well known inhibitors of RNA synthesis (as ethidium bromide), resistance to inhibitor analogues or the more effective use of CTP to suboptimal concentrations. The crucial point is that the above mentioned characteristics and others were results of the molecular phenotypes of the Q_{β} species, the RNA strands of which were not involved in informational tasks. By demonstrating the importance of molecular phenotypes with regard to selective pressures, Spiegelman verified a testable hypothesis (or prediction) originated from his central one: the RNA had been the substance of precellular evolution.

Some final considerations. In first place, predictions are testable hypotheses capable of falsifying (when they fail) central assumptions. But when predictions are successful, they cannot verify the hypotheses that originated them (fallacy of affirming the consequent). In this sense, Spiegelman and coworkers' achievements cannot constitute a ground to support, beyond any doubt,

the hypotheses of RNA as the substratum of precellular evolution, instead they can only provide some empirical (important) foundation about it. Second, we should not forget that replicase is an evolved catalyst and, in this sense, the results obtained from the experiments with the Q_{β} system may only be extrapolated to the precellular period with serious reservations. However, Spiegelman's prognosis in the field of precellular evolution was accomplished rigorously, because it was possible to determine the biological importance of RNA phenotypes in selective processes. Thus, some predictions are not only possible, but also successful in evolutionary theory (quod erat demonstrandum).

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