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Postulated Randomness

Nicolas Bouleau
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Very often adopted in biology articles and even more so in popularizations, the common interpretation of Jacques Monod's philosophy considers that the process of evolution resides in random mutations of DNA that are independent of each other and of the molecular and environmental context. Here we point out the lack of arguments for this postulate and show that this schematic vision, by its apparent simplicity, is becoming a form of slogan, whereas a great deal of work in progress is focused on correcting it.

The article begins with a historical overview of the positions taken on this issue, and then discusses the methodological framework in which this vision takes place. Finally, we draw some conclusions about the distinction between GMOs and non-GMOs and about a certain ethical imprudence.

1. Historical milestones

The few passages where Darwin mentions chance are not formal enough, according to our contemporary criteria, to decide on the role he attributed to randomness.

*I have hitherto sometimes spoken as if the variations [...] were due to chance. This, of course is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation.*¹

As early as *On the Origin of Species* he encounters a problem that will remain to this day :

It is, however, difficult to decide and immaterial for us, whether habits generally change first and structure afterwards; or whether slight modifications of structure lead to changed habits; both probably often occurring almost simultaneously.

Darwin quotes Lamarck rather positively. It could hardly have been otherwise at the time, since his great book appeared at the same time as the controversy in the French Academy of Sciences over spontaneous generation, and since atoms were still only a hypothesis, rejected until the beginning of the 20th century by eminent scientists, including chemists.²

A long period then began, the beginning of which can also be marked by Boltzmann's important formula in statistical thermodynamics (1875) and which was to continue until the discovery of the double helix after the Second World War and that of the metastable equilibria of open systems. It was marked by a prodigious development of physics which encouraged reductionist views, and, on the contrary, by the increasingly numerous and detailed observations of naturalists and physiologists on which eminent thinkers based themselves to defend a "vital principle" or at least the insufficiency of physical and chemical causalities to understand the living. The philosopher Henri Bergson uses the example of the horse Bot, a species of fly that bites the animal which, by licking itself, swallows the insect's eggs whose larvae pass through its digestive system until they give rise to new adults, and that of the Sitaris beetle which parasitizes the nest of certain

¹ Charles Darwin 1876.

² Cf. Henry Le Chatelier 1908.

bees, to support the relevance of a creativity of the living distinct from that of science which he classifies as "mechanistic".³

At the turn of the 19th and 20th centuries, science underwent successive revolutions, in the sense of Thomas Kuhn, which often took the form of impossibilities, growth of entropy, non-transmissibility of acquired characteristics (August Weismann), non-additivity of speeds close to the speed of light. As for the last reservations about the abstraction of the atomic theory (Pierre Duhem, Louis Le Chatelier), they were overcome thanks to the meticulous counting of Jean Perrin and Léon Brillouin, who provided Avogadro's number. The rediscovery in 1900 of Gregor Mendel's work, which had been completely ignored, gave biology its first quantitative foundations, which were then developed by the English school of mathematical statistics with the first models of population dynamics (Francis Galton, Ronald Fisher, and Sewal Wright in the United States).

After the First World War, when physics underwent a metamorphosis leading to quantum mechanics, which mobilized advanced mathematical tools such as Hilbert spaces, statistics seemed to be a method that was well suited to the human and life sciences. This was already the opinion of Condorcet and Buffon; they allow rigorous classifications thanks to the concept of correlation without necessarily mobilizing a causal relationship.⁴ The observations of naturalists and physiologists are accumulating, revealing the prodigious wealth of plants and animals and their curious ways of life.

The gap between the methodological tools of physics and those of biology has certainly contributed to seeing the creative inventions of living nature as an enigma. How could wave functions and Von Neumann algebras explain the making of an eye or the construction of a bird's nest? If we rule out any divine intention, in what game can chance draw such varied cards? Lucien Cuénot, after having assembled an impressive collection of cases where evolution seems to intentionally follow a direction, comes to seek the philosophical consistency of an anti-chance to correct the disorder of randomness.⁵ He sees this register on the side of what makes sense to us humans.

There is an obvious opposition [...] on the one hand blind determinism, without design, and exclusion of finality, on the other teleological determinism directing mechanical determinism towards a goal. On the one hand, chance, on the other hand, anti-chance. [...] We only know the plant and animal species and ourselves through the phenotype, i.e. through the result of the reaction of the hereditary substratum to the actions of the environment, which can modify the expression of the genotype to a greater or lesser extent.

Should we admit a kind of rigged chance ? Chance that would mean something ? But if it makes sense, it cannot be pure chance. The physicist Charles-Eugène Guye, for his part, launches into probability calculations to show how obvious improbability is.⁶ In this respect, Erwin Schrödinger's *What is life?* which postulates the crystalline nature of the maintenance of permanence in heredity appears to be a promising path towards causality in biology.⁷

³ Henri Bergson 1907.

⁴ Should biology be limited to a descriptive role? The question of the place of causality in the life sciences is a permanent one (Ernst Mayr 1961, Jean Gayon and Thomas Pradeu 2021).

⁵ Lucien Cuénot 1941 and 1944.

⁶ Charles-Eugène Guye 1941, p213 *et seq.*

⁷ Erwin Schrödinger 1944.

The discovery of the double-stranded structure of DNA by Francis Crick, James Watson, Maurice Wilkins and Rosalind Franklin, shortly after the Second World War, was a major epistemological breakthrough which gave Schrödinger's book a premonitory value, strengthened the reductionist trend and rapidly gave rise to a schematic popularization based on computer science. The question of the importance of lived experience remained, and Conrad Waddington introduced the concept of *genetic assimilation*, which aimed to provide a better circumscribed framework for a form of Lamarckism. These ideas were discussed in a famous symposium led by Arthur Koestler and J. R. Smythies, *Beyond Reductionism, New Perspectives in the Life Sciences* (1969), which mentioned the early work of the American Walter Baldwin (1896). Although according to Waddington this reference is debatable, the repeated use of this quotation has led to the concept of the *Baldwin effect*, which today refers to the fact that when the environment changes, certain individuals in a population may display traits that selectively favor them, even if these traits were not previously observable.

Shortly after the Nobel Prize was awarded to Jacques Monod, François Jacob and André Wolf (1965), Jacques Monod published his very famous book, which we shall now look at. As Laurent Loison clearly shows⁸, this book confirms a turning point in Monod's epistemic vision. Starting from a widespread conception where the microscopic could only have a direct macroscopic effect in a statistical way⁹, he now defends a molecular determinism based on "non-covalent stereospecific complexes" and he unravels the opposition with statistical thermodynamics by appealing to Léon Brillouin's interpretation and the notions of information and negentropy. He placed Koestler and Smythies' work in "the organicist or holist schools which, like a phoenix, are reborn with each generation" and turned away from the idea of a "general theory of systems" by Von Bertalanfy.

But the strongest thesis of his book, as the title suggests, is the role he gives to chance in evolution (Chapter 7). Building on the work of Brenner and Crick, he lists various types of discrete accidental alterations that can occur in the DNA double fiber and makes the famous postulate :

We say that these alterations are accidental, that they take place at random. And, since they constitute the only possible source of modifications to the genetic text, the sole repository in turn of the hereditary structures of the organism, it necessarily follows that chance is the only source of all novelty, of all creation in the biosphere. Pure chance, the only chance, absolute freedom but blindness, at the very root of the prodigious edifice of evolution." (p.147).

Monod's book is clearly written and does not shy away from any radicality: "*this central notion of modern biology is not today a hypothesis, among other possible or at least conceivable ones. It is the only one conceivable, as the only one compatible with the facts of observation and experience*" (p.148). He depicts evolution (chap. 7) as the result of "the roulette of nature" (p. 159).

⁸ Laurent Loison 2016.

⁹ This point of view is well expressed by Ch. E. Guye: "If, therefore, we admit the hypothesis according to which the origin of life would coincide with the appearance, in the molecular constitution, of a dissymmetrical fluctuation of a relatively very rare species, we can immediately conceive why we have always been unable to bring life out otherwise than from life itself. This follows immediately from the fact that we are not Maxwell's demon and that we are powerless to act on individual fluctuations by the crude means of our physico-chemical (statistical) manipulations which only we are capable of performing."

Several authors quickly reacted to this statement, whose provocative nature for a part of the intellectual world did not in itself constitute a validation, and pointed out its weakness as an epistemological apriorism, notably Ernest Schoffeniels and Albert Jacquard, who emphasized that the appeal to chance is a facility that can hinder the search for new understandings.

It should be emphasized that, beyond a popular image, the notion of "roulette of nature" has a fundamental epistemological, I would even say mathematical, significance. It means that mutations are not only subject to randomness, but that this randomness is like that of the roulette wheel: not dependent on any framework, on any influence, independent in the stochastic sense of any other chance, of any mutation in another individual, outside any context. At most, it will be granted that this randomness depends on the DNA to which it is applied, the DNA as an abstract text without folding, without metastable quantum states, without correlation with anything. Henceforth we shall refer to this chance as chance-roulette.¹⁰

Among Monod's criticisms, that of the statistician Georges Matheron (Matheron 1978) is particularly interesting because it is right where the problem is epistemologically difficult. As a statistician he observes that amino acids are not distributed in nature as if they had been drawn at random. Even if we consider that biological phenomena are the result of chance, of this chance we have only one draw, one trajectory; and what nature is today — and what it was in the past — induces a host of determinisms, so that the problem is to share the sources of chance if there are any, and the multiple and contextual causalities. There is indeed only one nature with one course, however diverse and rich it may be, and on one planet. The comparison with the chance of the roulette wheel with multiple independent draws is thus a pure abstraction. We can see that the question concerns the method itself of the natural sciences.

The case of René Thom is more complicated. A distinction must be made between a pamphlet against the abuse of probabilistic models in many disciplines (Thom 1980) because they are not very informative and are difficult to refute, and the application of *catastrophe theory* to biology, which was the subject of two books (Thom 1972) (Thom 1991) which, despite a reserved reception from many biologists, open up a very new and now better accepted way of elaborating a discourse at the level of development and phenotype that goes further than a simple statistical description. The approach is platonic and typically that of a mathematician to construct more abstract but simpler notions than what is observed and measured.

At the same time as Monod's book, Kimura and Ohta's paper (1971) was published, which emphasized the existence of mutations with no visible effect on the phenotype and stressed the phenomenon of drift by deletion of alleles in small populations. In one of his many books (1987) Stephan Jay Gould, an outstanding storyteller, argues in favor of Kimura's neutralist theory rather than Koestler's organicism.

Another way of talking about the inventiveness of nature is that of François Jacob who speaks of "bricolage" or of Antoine Danchin (Danchin 1991) who uses the term *opportunism* and takes the example of the eye in various animals where the tissues used for the transparent bodies are different proteins found on occasion, from other uses.

¹⁰ The last chapter of his book explains why Monod adopts this position. It also seems to contradict the role he gives, based on his own work, to "non-covalent stereospecific complexes", a notion that goes beyond "Anfinsen's hypothesis" that the action of proteins would only take place through their amino acid sequences.

Also, the mathematician and linguist Marcel Schützenberger (Schützenberger 1992), a collaborator of Noam Chomsky, discusses the "convergence" of the process of natural selection as a form of simulated annealing algorithm.

2. Jean-Claude Milner's dialectic

It is not surprising that the duality highlighted by Cuénot and many others between phenotype and genotype should have interested linguists, since language is typically the play of a formal that is susceptible to interpretation: the signifier and the signified.

In this respect, in a very interesting article "Hasard et langage", the linguist Jean-Claude Milner (Milner 1991) points out what can be called a dialectic of the scientific approach to language. Initially, knowledge is placed under the reign of chance, which is what Ferdinand de Saussure calls *the arbitrariness of the sign*. And Milner points out that the word *hasard* itself, which came into French from Arabic where it designates a game of dice, could be different, which gives a founding meaning to Mallarmé's famous poem "Un coup de dé jamais n'abolira le hasard". He adds :

But, this first time, nothing can be done with it. From the moment we say that linguistic configurations are totally random, and therefore that they could be entirely other than what they are, the problem of the science of language is not to explain how they could be other, but how they are. The second stage therefore consists in covering up, in obliterating the first [...] it remains to show that this or that character can be explained in relation to another. In the best of cases, this linking will take the form of a deduction.

Monod's radical stance is akin to the first stage, from which nothing can be done, and to the reproaches of Albert Jacquard¹¹ and others who call for a different approach to biology. Let us not forget that this randomness is supposed to govern the choice of functions and forms which, during evolution, will come to be related to those of the existing phenotypes.

Let us digress for a moment to mention a situation that is more than just an anecdote.

It concerns Ferdinand de Saussure, a famous philologist, who during the same years in which he was teaching his masterly *Course in General Linguistics* in Paris, was engaged in research on ancient poetry, the main thread and motivation of which was that he guessed the names of gods from the music of the verses without these names being explicitly written. Why did he not publish this very thorough work, which he covered in dozens of notebooks kept in the Geneva library? Because this great scholar feared that people would say that his findings were due to chance. This case illustrates the ideological pressure that the notion of chance can exert.¹²

Recently, this issue of the mutual influences of the genome, epigenesis and development has gained considerable attention in research and publications, and the remarkable reviews by Mary Jane West-Eberhard (2003) and David Pfennig *et al.*

¹¹ " I believe that Jacques Monod has done us a great disservice by giving the impression, following Democritus, that there was either chance or necessity, and that everything depended on them. This service is all the worse because he gave the image of chance as a little Greek god." (Jacquard 1991).

¹² Saussure's research has been published and commented on by J. Starobinsky, *Les mots sous les mots*, Gallimard 1971.

3. The syntheses by Mary Jane West-Eberhard and David Pfennig *et al.*

Mary Jane West-Eberhard's work is a sum of 800 pages of impressive richness both in the analysis of the scientific literature and in the ideas and personal insights she gives on delicate issues. It is fascinating and this book has undoubtedly contributed greatly to reorienting the motivation of researchers on issues related to developmental plasticity.

A key concept she puts forward is that of *genetic accommodation*, which extends the concept of genetic assimilation introduced by Waddington. She defines it as follows :

Genetic accommodation improves a novel phenotype in at least three different ways: (a) by adjusting regulation, to change the frequency of expression of the trait or the conditions in which it is expressed; (b) by adjusting the form of the trait, improving its integration and efficiency; and (c) by reducing disadvantageous side effects. Genetic accommodation occurs whether a novel trait is mutationally or environmentally induced, for it depends on genetic variation at numerous loci brought under a new selective regime by the phenotypic change induced.

Note that this definition is not completely explicit about the process by which this accommodation will be achieved. Indeed, if the new, supposedly advantageous, trait is due to developmental plasticity and is not genetically inscribed at the outset, it is understandable that the genome of this individual will spread throughout the population if its carrier is prolific. But how will this genome, once more widespread, "know" which mutation to make to fix the trait ? The mutations that will occur in the individuals born of the new genome are unlikely to find out what modification of the genome is needed to obtain the trait. Because whether the lived trait is recorded on the genome or not, it is not seen, so it is not subject to selection.

Let us add that — remaining in the hypothesis of chance-roulette — mutations on an individual's descendants do not go everywhere. In the Monod hypothesis, mutations induce all changes. This means that they cause all hereditary changes in phenotype. But this is not contradictory with the fact that if a change is fixed in advance, successive mutations can pass by without ever reaching it. This very important phenomenon can be understood by similarity with the fact that a random walk in dimension 3 and beyond goes to infinity without having had time to visit all the eventualities (cf. Kesten 1978), taking into account that a phenotype, however simple, always evolves in a high dimensional state space.

Mary Jane West-Eberhard's essay (p148 *et seq.*) explaining genetic accommodation describes a phenomenon and gives examples where the genome changes to accommodate an advantageous trait discovered through developmental plasticity. But this text does not explain how this inscription in the genome occurs in the chance-roulette case, so that this essay can be understood as a critique of the chance-roulette hypothesis, rather than as a confirmation of this hypothesis, depending on future advances in knowledge. This is cautious. It suggests that she does not blindly subscribe to Monod's hypothesis and that she considers that detailed explanations will come from research and could vary according to various experimental circumstances (she cites changing alleles at a plurality of loci, etc.).

The collective work coordinated by David Pfennig takes up this issue some twenty years later. It is logically rigorous. Pfennig's own contribution is particularly clear.

In the 4th of his "key questions" on phenotypic plasticity David Pfennig shows that according to the "modern synthesis", which reconciled Darwin's theory with Mendelian genetics, plasticity could not affect evolution since evolution requires hereditary change. But he makes two corrections to this argument: first, that plasticity can have an impact on

evolution even if the specific plastic response is not itself inherited, and second, that in fact some plastic responses are inherited. And he identifies three cases where plasticity facilitates evolution :

First, plasticity can facilitate evolution indirectly by promoting population persistence in novel environments, thereby allowing populations to remain viable until adaptive evolution can occur (the 'buying time' hypothesis). Second, plasticity can facilitate evolution directly by exposing formerly unexpressed genetic variation to selection, thereby fueling adaptive evolution (the 'plasticity-led evolution' hypothesis). Lastly, plasticity can facilitate evolution directly by forming the basis for an alternative inheritance system on which adaptive evolution can unfold (the 'non-genetic evolution' hypothesis).

He illustrates these situations with detailed cases. I refer you to the book, where the work of his colleagues is also rich in factual knowledge and observations that specify behaviors where an influence of development towards heredity is at play. This is the crucial question of "development first".

Any particular situation can often be read as a "random mutation first", (cf. Saussure's fear), but this facility is becoming more and more artificial as cases accumulate and certain experiments provide confirmation. The case of the *Daphniae*, these small freshwater crustaceans, is without doubt the most spectacular.

It seems to me that we can interpret, if not all, at least several of these examples, by suggesting that, by a process of which we do not have the details and perhaps in several ways, *the development drawn by an experienced journey in phenotypic plasticity intervenes in the form of a bias favoring, at least slightly, mutations that modify only a little this development.*

Contrary to what happens in the chance-roulette hypothesis, where nothing but a new chance alien to the scene can influence mutations, a simple correlative influence between epigenesis and the genome would have a decisive effect on adaptation and gradualism because it would subject the mutations supporting the lived experience to a favorable selectivity.

Such a principle would follow the influence imagined by Raymond Hovasse some fifty years ago (Hovasse 1972, p1679):

The fact that a given organism can react to an action of the environment by somation, implies, in its cytoplasm, independently of its genes, the possibility of a realizing mechanism, deviation from a gene mechanism, or perhaps plasmagenic. Once this mechanism has been realized, can it not be triggered again more easily by a gene phenomenon? Somation would, in a way, initiate the mutation.

In recent publications, there are investigations that show at least that epigenesis can be influenced by experience and can influence the genome by qualifying the type of chance that intervenes: bias, correlation, memory, etc.

All this research shows that we are now clearly in the second phase of Milner's dialectic.

4. The two precepts of Jacques Monod

To understand the ethical aspects, we must place ourselves in this extraordinary historical situation where the discoveries on DNA seem to finally provide an answer to the great

question of life on which religions had built feelings and beliefs, and where a new scientific activity, molecular biology, is opening, promising a truly concrete approach to the mechanisms of life. A whole programme. Darwin's vague ideas must be rethought in a new operational reality for agriculture, breeding and medicine. The interpretations shaped by culture, the empathy with living beings that we also are, the resemblance between our infants and small animals, all that intuition that constituted what was called life, ours and our death as well, and was at the heart of the highest philosophies, all this remains but changes role, it becomes the sources of biological questioning, no longer the basis of the truth but the setting where the scientific play is played out. It is at this unique historical moment that Jacques Monod takes the floor, legitimized by his recognized knowledge of the techniques involved, and puts into words the adventure and the potentialities facing humanity.

His discourse has two pillars: 1°) chance reigns supreme, and 2°) the scientist's conscience can take the place of ethics for the future.

But contrary to what he assumed, evolution does not work with purely random mutations, independent of each other and independent of context as if they were drawn at roulette. It is instead a vast subject of study to understand the influences, the induced biases, their degree of causality or only correlation between changes in the genome and those in the epigenetic matrix and development. Monod, seeking a hard-hitting discourse against all forms of spiritualism, seized on chance as an absolute weapon and, in so doing, opened wide the moral license to do anything. By proclaiming an easy and caricatured explanation of nature, he made its preservation more difficult and gave a ready-made slogan to the ethically unscrupulous molecular manipulators.

The last chapter of his treatise entitled "The Kingdom and the Darkness" constitutes, in twenty pages, a veritable manifesto of an ethics drawn from the "modern conception of science". To respond to Man's anguish in the face of his destiny, it is a question of maintaining an "authentic discourse" which consists of linking scientific truth and values but keeping them distinct without confusing them. This is a discipline that the man of science imposes on himself for the authenticity of any discourse or action: "*The ethics of knowledge, creator of the modern world, is the only one compatible with it, the only one capable, once understood and accepted, of guiding its evolution.*"

But is this faith in the man of science well founded? If God does not exist, the prudent and disinterested man of science is an even greater fiction. Let us think of the birth in 2018, on the sly, of genetically modified girls by He Jiankui's Chinese team¹³, let us think of the many private laboratories that trade in information taken from human genome databases to help select embryos at the blastomere level, let us not forget DARPA, which finances synthetic biology, not to mention the countries where information is controlled and which carry out a number of tests that are kept secret. This immaculate science does not exist. Letting people believe it amounts to absolving all slippages in advance.

Monod had a rather schematic idea of the social, and this misled him about the future of his own discipline. He wrote: "*It will no doubt be possible to remedy certain genetic defects, but only for the individual affected, not for his descendants. Not only does modern molecular genetics offer no means of acting on the hereditary heritage to enrich it with new traits, to create a genetic 'superman', but it also reveals the vanity of such a hope: the microscopic scale of the genome forbids such manipulations for the time being and probably*

¹³ These are three girls about whom we have little information (cf. H. Morin *Le Monde* 19 April 2022).

for ever". However, with the modifications of the human genome, the limits of which he speaks have already been exceeded and the ethical recommendations made at the 1975 Asilomar conference are no longer appropriate.

4. Conclusion

All over the world, researchers are preoccupied with understanding the numerous and circumstantial passages that nature shows us between the experiences of living beings and their DNA. There is not only the astonishing case of *Daphniae*, in California it is about lizards, etc. In France, a research grouping (GDR) has been created under the aegis of the CNRS, comprising 37 laboratories on the theme of phenotypic plasticity.¹⁴ This is a huge research stream, and I would like to add to the previous mentions the work of Jonathan B. Losos, Kevin J. Parsons, Ammon Cori, and Blair W. Perry. We have begun to understand that there is a kind of continuity between the permanence of the epigenetic matrix and that of the genome, as well as a progressive relationship between changes in one and the other. To what extent, on what scale? Work in progress...

However, institutional bodies of collective wisdom are slow to emerge.¹⁵ Last month the Court of Justice of the European Union (CJEU) did not classify as regulated GMOs the products of *random in vitro mutagenesis* which nevertheless modify the cellular framework of DNA.

Let's sum up: Jacques Monod has built a doctrine that validates the message to scientists "you can try anything", and whose moral for the whole world is "trust the scientists".

This is the main origin of the deontological blank check that has spread in biology. Biology must now move away from these radical and reckless visions.

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¹⁴ <https://plasticite-phenotypique.cnrs.fr/>

¹⁵ See *Global BioLabs Report 2023*, on line.

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