Beyond Darwin's Die: Does Evolution Have a Direction?

Marco Ferrari
Biologist, journalist and popular science writer

If there is one word that the life sciences view with suspicion, it is "dogma". It is supposed to be a universal and indisputable truth, a principle on which there can be no compromise. This is because there are always exceptions to even the most golden of rules, and any biologist knows dozens of them. So when you hear, in a genetics lecture, that there is a "central dogma of biology", the suspicion that something is amiss immediately arises. First "proclaimed" by Francis Crick – the discoverer of the structure of DNA – this dogma states that information, once it has left the molecules containing the cell's "instructions for use", namely the nucleic acids DNA and RNA, cannot go back. The transfer can only occur between nucleic acids and nucleic acids, or between nucleic acids and proteins, but never from proteins to DNA, which is present in the nucleus. The genetic heritage appears to be a sort of *inner sanctum* inaccessible to external information, which, above all, does not change as a result of what happens during life. It would seem to be a system offering an excellent level of information protection. If every cell were to do as much as it pleased and modify its genome according to environmental conditions or other influences, the risks of improper modifications would be extremely high.

Yet it is precisely this aversion to absolute principles that has, from the 1960s onwards, led to endless technical and philosophical debates on the validity of this "central dogma of biology". The discovery of an enzyme that transfers the genetic message from RNA to DNA (reverse transcriptase) briefly cast doubt on the solidity of the dogma, but it was quickly incorporated into genetic orthodoxy. The announcement of the recent discovery of another enzyme capable of synthesising a long DNA sequence without a template was another surprise and a "refutation" of the dogma. The template from which the molecule draws its inspiration, being an enzyme, is its own protein structure. In reality, even in this case it was immediately pointed out that the information serves to create

long DNA strands, not actual genes. The strands do not integrate into the genetic makeup of the bacterium itself that possesses the enzyme system. For the record, the name of this new group of molecules is DRT3. It is certainly a curiosity, but nothing absolutely revolutionary, for now.

Against the dogma?

Why, over time, has so much effort been put into challenging the so-called "central dogma of biology", which is in itself hardly absolute? Probably because, perhaps unconsciously, many researchers are seeking to challenge another assumption of modern biology, one that dates back to Darwin and the scholars of the early 20th century: the idea that evolution by natural selection is, at least in part, random. According to classical biology, in fact, the process that transforms species and generates ever-new structures depends exclusively on what happens within the molecules contained in the nucleus. No external information can directly alter the cellular genetic material: this is, in essence, the meaning of the central dogma. Two theoretical consequences follow from this. The first is that DNA does not "perceive" what happens outside the nuclear membrane. The second, more important one is that mutations in the DNA sequence, when they occur, are not purpose-driven: they do not serve to modify the life of the cell or organism in a targeted manner. Furthermore, in this view, they could appear with equal probability at any point in the genome.

Yet, accepting that a random process has produced natural wonders such as the blue whale, the lyrebird, the Pando poplar — a forest formed by a single tree spanning tens of hectares — or the bacterium *Deinococcus radiodurans*, capable of surviving in extreme conditions, is not intuitive. This idea, in fact, contrasts with a very ancient mental framework: the tendency to think that everything in life and in the universe has a purpose, a destination, and therefore follows a more or less precise direction. This is what is known as "teleological thinking". According to the historian of biology Ernst Mayr, this view was still widespread among scholars in the first half of the nineteenth century. And even after Darwin, in *On the Origin of Species*, had made it clear that evolution does not proceed towards a predetermined end, this conception did not disappear entirely. Indeed, ideas such as orthogenesis, aristogenesis, and the omega principle remained in circulation — that is, theories according to which an internal force of perfection operates within organic life, capable of directing evolution

along a more or less linear trajectory. Despite the robustness of the Darwinian framework, the allure of a directed evolution thus continued to captivate some biologists. This interpretation also implies the idea that living beings have progressively "improved", without, however, clarifying what this progress actually consists of. Traces of this approach can still be found today in scientific discourse, where it is sometimes suggested that present-day life forms are more advanced or better adapted than those of the past. Thus, for example, it is said that highly successful groups such as trilobites and dinosaurs became extinct because they were "more primitive" than the species that replaced them. Yet one need only observe the enormous variety of Mesozoic dinosaurs to realise that the mammals, which took over after the extinction of their predecessors 66 million years ago, were by no means more advanced or complex. Returning to the central dogma and the randomness of mutations, it was precisely the idea of DNA as impervious to external influences and of mutations as devoid of purpose that had temporarily overshadowed the search for a possible "direction of evolution". The hardest blow to theories of directed mutations came in 1943 with the famous experiment by Luria and Delbrück. Studying the bacterium *Escherichia coli*, the two researchers showed that mutations conferring resistance to viruses appeared before exposure to the virus, and not as a response to it. The result reinforced the idea that mutations are not aimed at producing beneficial effects. Within this theoretical and experimental framework, evolution thus appears as a process that has a random component at its origin and precisely for this reason does not allow a specific direction to be determined in advance.

Delving deeper

Beyond the unlikely return to pre-Darwinian ideas — or even Lamarckian ones, such as the inheritance of acquired characteristics or the notion that a species tends towards a specific goal — contemporary biology has begun to truly penetrate the "fortress" of DNA to understand how it functions. The aim is to clarify how certain crucial steps in the history of life occurred. Over time, studies have thus at least partially corrected the image of absolute randomness. New technical possibilities for analysing the structure and sequence of nucleic acids in depth have paved the way for a more precise understanding of genetic material. This has allowed us to observe that factors such as the environment or the architecture of the genome can influence, to some extent, the fate of populations, their evolution, and perhaps even its

direction — not directly, as theories such as orthogenesis had hypothesised, but in much more indirect and nuanced ways.
To understand the current situation, it is important to recognise that determining the extent to which — and indeed whether — evolution is predictable can be approached at various levels. These range from the molecular level to the population level, and to the history of life on the planet. A first step in introducing the topic is the obvious fact that mutations are entirely random. While this is true, it masks a significant complexity: mutations are not distributed uniformly across the genome. Mutations are not distributed uniformly across the genome, yet randomness with regard to genomic position has no direct influence on so-called *fitness*, that is, the reproductive success of an individual or a population. *Randomness*, one might say, is relative, not absolute. In particular, in a famous 2022 article published in the journal *Nature*,[1] the authors, Monroe et al., state that *de novo* mutations occur at a significantly reduced rate in functionally constrained regions: their frequency is reduced by two-thirds in essential genes. There are mechanistic explanations for this finding: DNA damage repair appears to be particularly effective in the regions that are most important biologically. Other studies have established that the genes most protected, from this perspective, are those involved in reproduction. Conversely, in animals, genes of the immune system and olfactory receptors show extraordinarily high rates of evolution because variability in these regions is a selective advantage. It is not noise: it is the ability to respond to a constantly changing biological environment. The paper by Monroe et al. has been criticised because, from certain perspectives, it appears to defend a position that states «this situation tends to produce a certain type of mutation more than others», which does not seem to correspond with other observations. The distinction that Monroe sought to defend is, however, subtle: it does not claim that mutations are directed in a strict sense, but that the so-called mutational supply profile — specifying which mutations are more likely — is itself a product of selection and thus creates a feedback effect on the variability available for future evolution. It is the difference between «mutations point in a certain direction» and «the input to selection is not uniformly distributed, and this can influence which evolutionary

[1] MONROE, J.G. – SRIKANT, T. – CARBONELL-BEJERANO, P. *et al.* "Mutation Bias Reflects Natural Selection in *Arabidopsis thaliana*." Nature 602, 2022, pp. 101-105.

trajectories are viable or exclude others». The second is a much more defensible thesis, but it is also far less surprising. This would be the mechanism: natural selection, over time, has built more efficient DNA repair systems in certain contexts — in germ cells, in essential genomic regions. In no case, therefore, are mutations "targeted" in a teleological sense. They are simply less frequent because the surveillance and repair mechanisms work better there. It is not a true "direction", but an increase or decrease in the probability of certain mutations. From this perspective, the dogma holds firm. DNA is protected, and the responsibility falls to the generation, frequency, and randomness of mutations.

Enter evolution

These findings already confirm what might be described as a kind of mutational *bias*, currently based on regions of the genome. This concept serves to introduce the concept of true *mutation bias* — that is, systematic differences in mutation rates, which can vary depending on the type of mutation and the bases involved, as well as the DNA regions that are "affected".

When something is discovered that could have consequences for evolutionary outcomes — that is, at the population level and not just in the life of a single individual — researchers are also encouraged to engage in theoretical reflection. One of the most interesting leads to another type of constraint, the so-called *arrival bias*. This is the proposal by Yampolsky and Stoltzfus,[2] which stems from the so-called Modern Synthesis of the 1930s-1940s. It was a time when mathematics, modelling, and other more quantitative approaches such as population genetics entered evolutionary theory. Theorists, from Ronald Fisher to Thomas Hunt Morgan to Theodosius Dobzhansky, modelled natural selection as if it always had the fittest variants at its disposal. The possibility that mutational *biases* might shape adaptive outcomes had been overlooked by scholars at the beginning of the last century. In a computer simulation, Yampolsky and Stoltzfus thus considered a model with two incompatible adaptive mutations — one common but less advantageous; the other rarer but more "fit". The essence of this idea is effectively summarised as follows: adaptive evolution proceeds not

[2] YAMPOLSKY, L.Y. – STOLTZFUS, A. "Bias in the Introduction of Variation as an Orienting Factor in Evolution." *Evolution & Development*, 3, 2001, pp. 73-83.

merely according to the survival of the fittest, but rather of the "most likely among the fittest".
So far, it would seem that mutations still retain their usual random nature, at least in terms of their origin, even though they tend to affect certain regions and molecular structures within the DNA in particular. But what about another consideration? It is at this point that we move from individual history, with consequences for the population, to the possible emergence of new species. According to a recent article, mutational *bias* is also an important factor in determining the diversity of genetic variants available for selection, not only in an individual but also in a population.[3] As adaptation proceeds and certain advantageous mutations become established in the population, new beneficial mutations become rarer, because there is literally no more room for others. This is how this "bias", which favours one direction of mutation over others, could alter the fate of populations, because by modifying or reversing this very same mutational *bias* (as shown in the paper), new mutations are made available to populations, along with new combinations upon which natural selection can act.
Would it finally be possible at this stage to discern even a vague direction of evolution? Probably not, partly because it would be necessary to know the entire genomic structure of the individuals involved inside out. They might be subject to mutations to a greater or lesser extent, without it being possible to say whether these would be neutral, negative, or positive. There are also more controversial and less well-established theoretical hypotheses, such as *complex conditional mutations*.[4] These are non-Lamarckian mutations (they do not respond to the environment) but are also "non-accidental". One example is the HbS mutation in human haemoglobin, which confers protection against malaria. Recent high-resolution studies have revealed that this specific mutation arises *de novo* with a significantly higher frequency in African populations historically exposed to malaria than in European populations. This does not happen because the body "sees" malaria and mutates accordingly (which would indeed be Lamarckism), but because past natural selection has shaped mutational mechanisms that favour certain variants in specific regions of the DNA. To summarise and

[3] SANE, M. – PARVEEN, S. – AGASHE, D. "Mutation Bias Alters the Distribution of Fitness Effects of Mutations" *PLoS Biol.* 14 July 2025, 23, 7.
[4] LIVNAT, A. – LOVE, A.C. "Mutation and Evolution: Conceptual Possibilities." *BioEssays*, 46, e2300025M, 2024.

return to the beginning, in this case too, mutational *bias* exists, but it is certainly not the same thing as orthogenesis. In short, the reduction or change in the frequency of mutations is not a precise evolutionary direction.

Theory and reality

Moving from "regions of the genome that are more or less prone to mutation" to "what happens in the evolutionary process" might seem like too great a leap to make. But one might ask: if the genome has regions that are more and less protected, does it also have regions that are more and less capable of generating variation, and are therefore subject to natural selection – as demonstrated by the example of haemoglobin? At this point, evolutionary theorists have introduced the concept of differential evolvability, that is, the capacity to generate heritable variations that are phenotypically significant, and indeed that promote evolution through natural selection. A highly evolvable genome is not one that mutates a great deal — it is a genome organised in such a way as to produce variation that can be exploited by selection without dismantling everything that already works. But is this characteristic of the genome itself the result of the evolutionary process? These discussions, which largely take place far removed from the spotlight of scientific communication, also demonstrate that the study of evolution is far from dormant. Darwin was a pivotal figure, but he merely set in motion the avalanche of research that still fills scientific journals today. Finally, it is important to note that the very concept of evolvability is not without its critics, as demonstrated in this brilliant essay by Mauro Mandrioli, who teaches genetics at the University of Modena and Reggio Emilia.[5]

All these characteristics of the genome and the evolutionary process are interwoven with and enriched by a theoretical concept proposed several decades ago: the so-called evolutionary landscape. This metaphor, coined by the American geneticist Sewall Wright, was also put forward during the Modern Synthesis period. The idea explains how, over the millennia, the genomes of entire populations of animals or plants do not face an endless plain on which to "roam" – that is, to be modified by natural selection. The ideal, modelled terrain across which they move over time is instead rugged – full of valleys and peaks, or positions

[5] https://pikaia.eu/evolvibilita-un-concetto-paradossale-o-innovativo-nella-biologia-evoluzionistica-moderna

where *fitness*, that is, potential evolutionary success, is greatest. In the valleys, *fitness* is slightly lower. In this landscape, it is clear that not all evolutionary paths are possible or equally likely (climbing through a steep valley towards a *fitness* peak can be difficult). Combined with the concept of evolvability, the metaphor thus becomes more nuanced and useful. The formulation of the evolutionary landscape has also been modified over time. Now the concept is no longer static, as conceived by Sewall Wright, but dynamic: a valley can become a hill, a peak can become lower and more accessible. Everything changes according to time and geological and environmental conditions; the landscape is also shaped by the evolution of other species, whether in competition or in symbiosis. Finally, the Austrian scholar Andreas Wagner has also added vast *plateaus* to the landscape, where mutations can occur without significantly altering the fitness of the population, thereby allowing them to explore new territory without running the risk of extinction.

The history of the species and its evolution thus become the story of a journey through time within a landscape where not all paths are equally accessible. Are there, then, some that are so "easy" that they become almost inevitable? And so, returning once again to the recurring question: is evolution (a little more) predictable? After decades and decades, we can say that the technical and genetic details are still in a state of tumultuous development, as the scientific literature demonstrates. For example, in 2006 an article describing a wonderful empirical case showing that in an evolutionary landscape, almost all possible paths towards a more efficient protein pass through the same sequence of mutations was published.[6]

A historical dispute

However, it is on a less technical, almost philosophical level that our question gave rise to one of the most fruitful debates on the greater likelihood, or even the inevitability, of certain evolutionary pathways. It dates back a few decades and features two leading theorists and scholars: on the one hand, Stephen Jay Gould; on the other, Simon Conway Morris. The former, an American paleontologist, a great populariser and theorist of evolution, asserted «if we rewound the tape

[6] WEINREICH, D.M. *et al*. "Darwinian Evolution Can Follow Only Very Few Mutational Paths to Fitter Proteins." *Science New Series*, 312, 5770, 7 April 2006, pp. 111-114.

of life, the results would have been different». He also emphasised the role of contingency and chance, on a different level from that of mutations. For Gould, a contingent event was the meteorite that wiped out most of the dinosaurs, or the profound environmental change that struck East Africa some 5 million years ago and also paved the way for the evolution of the primate species that preceded us. Gould argued, for example, that the survival of particular lineages, such as the chordate *Pikaia* in the Cambrian seas, was the result of a fortuitous contingency rather than an intrinsic superiority over other contemporary species. Had that particular species not survived a mass extinction — a contingent event — the entire history of vertebrates would have changed. The very existence of humankind would have been almost impossible. He explained his position in a highly acclaimed book, *The Wonderful Life* (Italian translation *La vita meravigliosa*: Feltrinelli, 1995). Instead, Conway Morris, an English paleontologist, argued that well-known phenomena, such as evolutionary convergence or parallel evolution, demonstrate the opposite. Convergence itself occurs when independent lineages develop similar solutions to the same ecological problems; examples include wings in birds and bats, or the hydrodynamic shape in fish and marine mammals. For Conway Morris, this demonstrates that evolution is constrained by rigid biological, chemical, and physical constraints, which act as "attractors" towards stable and always identical – or very similar – anatomical configurations. From this perspective, evolutionary pathways are limited and the final outcomes are, to a large extent, inevitable and therefore predictable. His counter-manifesto is *Life's Solution: Inevitable Humans in a Lonely Universe* (Cambridge University Press, 2003). Each of the two scholars presented paleontological evidence in their favour, and even biochemistry and arcane fields such as protein physics now confirm one scenario or the other. In favour of Conway Morris, nature often displays phenomena of convergence, including at the molecular level, suggesting the existence of "fast tracks" dictated primarily by functional constraints, by steep valleys or peaks in the evolutionary landscape, or by very strong mutational *biases*. There may thus be identical mutations in the same nucleotide (the building block of the DNA molecule), amino acid changes in the same gene, or similar alterations in the number of gene copies and gene expression. A classic example is fish from different groups (living in very distant locations, such as Antarctica and the Arctic) that have independently evolved

almost identical antifreeze glycoproteins from different genomic sequences.
Research conducted at Princeton University also demonstrates how evolution can be surprisingly "predictable".[7] By examining 29 distantly related insect species (such as butterflies, beetles, and aphids), the researchers discovered that 14 of them had developed identical resistance to cardenolides, toxins produced by plants such as milkweed. Despite being separated by millions of years of evolution, these insects have modified the same key protein — the sodium-potassium pump — through almost identical mutations at the same sites in their DNA. This phenomenon of parallel evolution suggests that there are such tight molecular constraints that the environment "drives" different species towards the same genetic solution. This demonstrates that similar environmental problems can force similar anatomical, and above all genomic, solutions.
At the same time, however, following Gould, the problem of swimming was solved by forms such as fish and marine mammals in the same way, but by molluscs using a completely different (reactive) technique. The problem of vision, too, has been evolved by various animal lineages in dozens of different ways. One need only compare the eyes of vertebrates (and molluscs such as octopuses) with those of insects. The former consist of a single chamber, the latter of dozens and dozens of small separate sensors. One aspect of the debate between Gould and Conway Morris also concerns our own species. For Gould, as we have seen, it is by no means certain that rewinding the "tape of life" would inevitably result in the emergence of an intelligent species similar to *Homo sapiens*. For Conway Morris, on the other hand, "humans" not very different from us – intelligent and, above all, endowed with a religious sense – would also emerge on other planets. An important detail in this case is precisely the fact that Conway Morris is a Catholic, and Church doctrine has always viewed with favour, if not prioritised, strongly teleological positions aimed at an ultimate end or a final purpose. The "omega principle" mentioned at the beginning is in fact a proposal by the Jesuit paleontologist Teilhard de Chardin in *The Human Phenomenon* (Italian translation *Il fenomeno umano*: Queriniana,

[7] DOBLER, S. – DALLA, S. – WAFSCHAL, V – AGRAWAL, A.A. "Community-Wide Convergent Evolution in Insect Adaptation to Toxic Cardenolides by Substitutions in the Na,K-ATPase." *Proc Natl Acad Sci U S A.* 7 August 2012, 109, 32, 13040-5.

2014). This idea, as we have seen, runs counter to the modern understanding of the theory of evolution.

A clearer future?

On this and other points, modern evolutionary biology seeks a synthesis between Gould and Conway Morris. Although evolution may be determined on a large scale by functional constraints (leading to seemingly convergent outcomes), it remains contingent and unpredictable at the molecular and genetic levels. Predictability also depends on population size. Intermediate-sized groups tend to follow paths that maximise immediate *fitness* gains, making the results more repeatable; very large populations may go through periods of modest *fitness*, exploring unexpected paths in the famous evolutionary landscape. In conclusion, although the "ribbon of life" may display general, predictable patterns dictated by the laws of nature, the specific details of the path remain captive to the physical complexity of molecular systems and the accidents of history, making evolution a fascinating dance between the inevitable and the unforeseen. Life forms can thus arrive at the same outcome, and sometimes the same physical form, via entirely different pathways.

Therefore, although the source of all new information in the genome — mutation — is not "random" in the sense of being equally likely or entirely unpredictable to modern science, it remains random in the Darwinian sense. One cannot predict with certainty the success of an individual or a population because this is due to natural selection. Evolution is neither a straight line nor total chaos. It is rather a system of facilitated variation, where perhaps the genome seems to "learn" from its own history to generate new variation more efficiently. In conclusion, although the grand schemes of biology may display a certain regularity dictated by convergence and physics, the detailed (re)writing of the genetic heritage remains captive to an intrinsic complexity that makes rewinding "tape of life" a task that is always unique and never entirely predictable.