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Directed evolution: pruning the tree of life from Darwin's demon to nanobiotechnology

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Abstract

In recent years the expression "directed evolution" has acquired a very specialized and narrow connotation in the scientific literature. It refers to a system of methods and techniques for synthesizing new molecules, such as proteins and nucleotides, by exploiting the action of natural selection. This form of "applied Darwinism" opens new possibilities for designing and manufacturing molecules not spontaneously produced by organisms, in order to fulfill specific requirements in pharmaceutics, agriculture and various industrial fields.

In honor of this year's commemoration of Darwin's second centenary it seems appropriate to give here a brief sketch of the history of the concept of **directed evolution** understood in a much wider sense. This purpose will take us back to a sort of *gedanken* experiment Darwin reported in the notebooks and essays that preceded the *Origin*. Some authors refer to this imaginary experiment as the introduction of a "Darwin's demon," in analogy to the role played by other similar *gedanken* creatures that grace the pages of the history of science.

Finally a brief sketch is presented of the ups and downs of the idea of evolutionary directionality, from Darwin and Spencer to the current impact of self-organization and complexity approaches upon orthodox neo-Darwinian views on evolution.

Of cabbages and pigeons

At present a search of the scientific literature under the heading **directed evolution** yields hundreds of references to highly technical articles with little relationship to the preoccupations this expression has stirred in the minds of biologists and philosophers since de mid-nineteen century In its current, non-philosophical use it designates a complex of techniques directed at the production and selection of new kinds of biomolecules (e.g. proteins and amino acids) with desirable pharmaceutical or industrial properties. These properties are obtained by repeated random recombination and selection of the "fittest" molecules among a great many recombinants, through a process of *in vitro* "shuffling" and screening that mimics the workings of Darwinian optimization in the natural selection of organisms.[1]

In this presentation I would like to call attention to the important role played by a less sophisticated but similarly successful method of "directed evolution" in the

genesis of Darwin's basic theory. This method has been applied through the ages by plant cultivators and animal breeders, and consists in the culling and crossbreeding of specimens that display randomly produced properties which happen to be useful or desirable to humans. All of the varieties of our domesticated crops, pets and livestock are products of this forced selection, directed at achieving results which are quite at variance from those that natural selection would have spontaneously reached. Although the importance of the study of domestication for Darwin has been repeatedly downplayed by historians and biologists, there is ample evidence that reflection on this method, in conjunction with his reading of Malthus, precipitated Darwin's adumbration of the basic schema that grounds his mature theory of descent with modification through natural selection.

Darwin states this quite clearly in several of his published works, starting with the Introduction to the first edition of the *Origin*:

> At the commencement of my observations it seemed to me probable that a careful study of domesticated animals and of cultivated plants would offer the best chance of making out this obscure problem. Nor have I been disappointed; in this and in all other perplexing cases I have invariably found that our knowledge, imperfect though it be, of variation under domestication, afforded the best and safest clue.

Many years later he writes in his *Autobiography*, a book not intended for publication, that

> In October 1838, that is, fifteen months after I had begun my systematic inquiry, I happened to read for amusement Malthus on *Population*, and being well prepared to appreciate the struggle for existence which everywhere goes on from long-continued observation of the habits of animals and plants, it at once struck me that under these circumstances favourable variations would tend to be preserved, and unfavourable ones to be destroyed. The result of this would be the formation of a new species. Here, then, I had at last got a theory by which to work; but I was so anxious to avoid prejudice, that I determined not for some time to write even the briefest sketch of it.

The analogy of natural and artificial selection animates Darwin's early groping attempts toward a mechanism for "transmutation" of species, from his secret notebooks to the early drafts of 1842 and 1844, and continues to appear in his epistolary summaries and throughout his later published works. He studied the effects of directed domestication in a great number of species and their varieties. Darwin traced the genealogy of cabbages, including Brussels sprouts, broccoli, kale and other cultivars of the genus *Brassica* to a common wild ancestor. He consulted with breeders of cattle, sheep and dogs and finally got deeply involved in experimentation with "fancy pigeons" by becoming a member of pigeon hobby clubs and raising many birds himself. As Stephen Jay Gould has remarked in an essay aimed at debunking the myth of Darwin's finches:

> Darwin's finches are not mentioned at all in the *Origin of Species* (1859); the ornithological star of that great book is the domesticated pigeon. (Gould 1985 p. 356).

Of demons and machines

Darwin was an exceptional thinker and scientist in manifold ways. Besides his extraordinary powers of observation, in going through his writings one is struck by his capacity for bringing together a variety of apparently unrelated examples through a marvelous knack for exploiting recondite analogies and metaphors. Another original but seldom noticed novelty of Darwin's argumentation is his use of thought experiments.

Although *gedanken* experiments had been common fare in physics since before the time of Galileo their repeated used in biology (see Lennox 1985) is another mark of Darwin's originality. Some of the important functions of thought experiments in physics are the sharp articulation of previously nebulous concepts, of showing the plausibility of processes originally thought implausible and of proving the impossibility of processes originally conceived as plausible. Thought experiments often have recourse to *gedanken* devices, the most common of which are imaginary demons and machines These are idealized creatures and artifacts often endowed with superhuman (but strictly finite) powers. Laplace's demon articulates the idea of strict determinism; Maxwell's demon demonstrates the statistical nature of the second law of thermodynamics, Kelvin's perpetual motion machines illustrate the first and second laws, Carnot's machine shows the limits of energy efficiency, Turin machines serve to give precise meaning to the concept of algorithm and demonstrate the limits of digital computation. Finally we should of course mention **Darwin machines**, which are used to model sequential processes in the brain (see e.g. Calvin 1987).

Silvan Schweber has identified another such *gedanken* devise in Darwin's argumentation: **Darwin's demon** (see Schweber 1991 and also Keller 1995, p.54 *et passim*). The demon helped Darwin combine the ideas he extracted from his domestication studies and the population conceptions of Malthus to arrive at the recognition that natural selection is the main force driving the evolutionary process. Here is Darwin's portrait of the creature (he does not call it a demon):

> Let us now suppose a Being with penetration sufficient to perceive differences in the outer and innermost organization quite imperceptible to man, and with forethought extending over future centuries to watch with unerring care and select for any object the offspring of an organism produced under the foregoing circumstances; I can see no conceivable reason why he could not form a new race (or several were he to separate the stock of the original organism and work in several islands) adapted to new ends.

The analogue of the demon in nature is then identified as the relentless culling of the offspring, spontaneously brought about by differential survival capacities in the competition for scarce resources.

The direction of evolution: science, theology and ideology

I think it is safe to say that in the history of its conceptual evolution no other major scientific theory has suffered as much as Darwin's at the hands of ideologues, metaphysicians and theologians. Copernican astronomy had its misfortunes, as we all know, but in the main they turned out to be short-lived and conceptually harmless. Evolution by natural selection, on the contrary, has remained the plaything of extra-scientific intellectual interests since its inception until the present. From social Darwinism in the nineteenth century to the diametrically opposite agendas of creationists on the one hand and of militant atheists like Dawkins or Dennet on the other, Darwin's theory continues to be fodder for metaphysical rumination of the most diverse sorts. Far from being a defect, this feature of the theory bears witness to the fertility and depth of its philosophical import. It is to be noted that the ideological and philosophical exploitation of Darwinism is not confined to mere interlopers —several main contributors to its scientific development (e.g. Gould or Dawkins) have written quite eloquent philosophical elaborations for popular consumption.

There is no room in this brief communication for reviewing the ideological vicissitudes of Darwinism and the copious literature they have spun.[2] A few remarks on the fortunes of "directed evolution" must suffice to illustrate some important issues.

After a brief eclipse in the early decades of the last century Darwin's theory was rejuvenated through its successful amalgamation with the concepts and facts of Mendelian genetics. The New Synthesis—as that outcome is generally known—was the fruit of a gigantic effort by some of the most gifted biologists of the first half of the century (including Fischer, Huxley, Haldane, Simpson and many others). This formulation soon became entrenched as a dominant orthodoxy (neo-Darwinism). Two closely related philosophical tenets often associated with the Synthesis are part of our story: the exclusive role of natural selection as explanatory mechanism and the concomitant characterization of the course of evolution as totally blind, contingent and directionless.

Darwin had rejected both of these positions. With respect to natural selection he had said in the last edition of the *Origin* (1872):

> As my conclusions have lately been much misrepresented, and it has been stated that I attribute the modification of species exclusively to natural selection, I may be permitted to remark that in the first edition of this work, and subsequently, I placed in a most conspicuous position—namely at the close of the Introduction—the following words: "I am convinced that natural selection has been the main but not the exclusive means of modification." This has been of no avail. Great is the power of steady misrepresentation. (Quoted in Gould 1997, p.34)

With respect to directionality Darwin thought that evolution is progressive (see Richards 2009). In Chapter 10 of the first edition of the *Origin* he states:

> …the more recent forms [of organisms] must, on my theory, be higher than the more ancient; for each new species is formed by having had some advantage in the struggle for life over other and preceding forms (Darwin 1859, 336-37).

Stephen J. Gould, who rejected the exclusivity of natural selection, was nevertheless convinced of the utter contingency and lack of directionality of evolution. In *Wonderful Life* (Gould 1989) and other places he bolstered this contention with a thought experiment that employs a *gedanken* devise (let us call it a **Gould Machine**): the *tape of life*. One imagines a recording device that would record the course of evolution starting from some set of contingent initial conditions in the past. If one now rewinds and erases the tape and plays it forwards starting from different contingent conditions, the indeterminism inherent in biological transactions would result in a pathway radically different from the one that it previously followed. One cannot expect that complex animals similar to us will turn out the second time.

At present Neo-Darwinian orthodoxy is being increasingly challenged by new experimental and theoretical developments. As Darwinism evolves to meet these new realities it is likely that it will be forced to renounce the two philosophical principles of the causal monopoly of natural selection and the directionless course of evolution. Several recent discoveries and ideas seem at odds with them. Let us briefly mention some.

- **Self-organization.** The rapid, spontaneous emergence of complexity and order is characteristic of some dissipative thermodynamic systems far from equilibrium, such as tornados, organisms and ecosystems.[3] Natural selection from random mutations creates adaptive complexity and variety at a rate that appears too slow to account for the timing indicated by the paleontological record. Many researchers are now inclined to consider natural selection as a pruning adjunct to self-organized variety (see e.g. Kaufman 1993 and 2000, Edelmann and Denton 2007). In summary, in the words of Batten *et al*, “self-organization proposes what natural selection disposes” (Batten *et al*. 2008).
- **Cooperation**. Faithful to its Malthusian roots Neo-Darwinism sees nature as the stage of ruthless competition among selfish individuals, pretty much as human society is conceived by *laissez-faire*, free market ideologues. Two important discoveries emphasize the opposite, positive role of cooperation in evolution: 1) **Symbiogenesis**, the fusion of two different organisms to create new, completely different ones. This process is responsible for some of the most revolutionary transitions in evolution (see e.g. Margulis 1993) and 2) **Horizontal gene transfer** (HGT). Darwin’s theory is based on the reproductive mechanism of multicellular Eukaryotes (i.e. mostly plants, fungi and animals, relatively late newcomers in evolution) and especially on their sexual reproduction, where genes are transferred vertically from two individuals of the same species to their offspring. HGT is a cooperative free exchange of genes between

organisms of totally different kinds that now appears to be pervasive throughout the biosphere. In his seminal article on “a new biology for a new century” (Woese 2004), Carl Woese speculates about a pre-Darwinian era best described in the words of Freeman Dyson (Dyson 2004):

> Evolution was a communal affair, the whole community advancing in metabolic and reproductive efficiency as the genes of the most efficient cells were shared. Evolution could be rapid, as new chemical devices could be evolved simultaneously by cells of different kinds working in parallel and then reassembled in a single cell by horizontal gene transfer. But then, one evil day, a cell resembling a primitive bacterium happened to find itself one jump ahead of its neighbors in efficiency. That cell, anticipating Bill Gates by three billion years, separated itself from the community and refused to share. Its offspring became the first species of bacteria—and the first species of any kind—reserving their intellectual property for their own private use.

- **Neo-Lamarckian facts and ideas**. Writing before Darwin Lamarck advanced two mechanisms of evolutionary novelty: an inherent tendency in living matter toward increasing complexity, and the inheritance of acquired characteristics. These ideas, rejected upon the success of natural selection, have returned in the wake of new discoveries and the emergence of “Evo-Devo,” a theory of the evolution of embryonic development that must confront serious limitations of classic neo-Darwinism in the explanation of developmental change. One of its key concepts is **epigenetic inheritance**, the transmission of developmental variations which are independent of gene transfer, such as chemical modifications of genes that are transmitted from one cell generation to the next, and that affect gene expression without altering the DNA sequence. The transmission of learnt behavior and of song dialects in birds are other examples (see e.g. Jablonka 2006a and 2006b).
- **Homeostatic action.** J. Scott Turner has advanced a theory of evolution in which homeostatic mechanisms are more important than natural selection. Homeostasis is a process of dynamical equilibrium through the action of negative feedback loops. He illustrates his ideas with the actions of **Bernard Machines**, yet another *gedanken* artifact, named after Claude Bernard, the originator of the homeostasis concept (see e.g. Turner 2007).

Finally, several authors increasingly consider the directionally of the evolutionary process to be a consequence of the directionality imposed on living and non-living systems by the maximum entropy production principle of nonequilibrium thermodynamics. The drive to more probable states leads spontaneously to the organization of matter into functional hierarchies (see e.g. Kleidon 2004, Kaila and Annila 2008).

This list of heterodox ideas can be greatly extended. It must be noted that they are more in opposition to neo-Darwinism than to Darwin's original ideas. As a matter of fact, some of them seem to evoke undeveloped intuitions and observations still slumbering in the seldom read pages of Darwin's great and multifarious opus.

NOTES

[1] For the role of directed evolution in present-day bionanotechnology see Kim 2008.

[2] Readers interested in going deeper will find an excellent starting point in Lennox's work-in-progress under the heading **Darwinism** in the *Stanford Encyclopedia of Philosophy*, at http://plato.stanford.edu/entries/darwinism.

[3] The concept of self-organization and its relation to circular causation and purposive action in organisms was anticipated by Kant in his *Critique of Judgment* (see e.g. Fernández 2008).

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