BACK TO THE FUTURE: ARISTOTLE AND MOLECULAR BIOLOGY

ARMANDO ARANDA ANZALDO

Molecular biology was born in the first half of the twentieth century when some European physicists decided to apply the methodology of physics to the detailed study of biological molecules so as to establish how molecular structure determines biological function. This scientific approach implied the Aristotelian axiom: function follows form, which was impressively instantiated by the discovery of DNA structure by Watson and Crick in 1953, a feat that immediately lead to depth insights into the functioning of the genetic material. Thus, genetics also became molecular and in spite of the further successes of molecular biology in clarifying the relationship between form and biological function at the molecular level, the fascination with genes—identified within the neo-Darwinian paradigm as the ultimate targets upon which the sieve of natural selection acts by differential reproduction of the organisms carrying such genes and then ushering changes in their frequency within a given population[1] —led to a gene-centered notion of biology and so genes became the all-powerful determinants of organismic structure [2]. Indeed, the genes constituted by specific strings of DNA have been endowed with almost magical properties such as the capacity for "self-replication" (a completely meaningless term) and, in the same vein, it is thought that an atomized jumble of gene products (i.e., proteins) taking place within cells, that grow, proliferate and get together but always by unfathomed 'genetic' reasons, nevertheless conforms organisms endowed with complex structure and behavior. This rather odd logic culminated in the expensive sequencing of the DNA nucleotides constituting the human genome that was justified on the basis that knowing the genome was equal to knowing the organism. However, as Richard Lewontin has clearly stated: "genes can make nothing" since the proteins coded by such genes are the result of a very complex system of chemical production involving a pre-existing and renewable molecular machinery [3]. Proteins cannot be produced without either the genes or the

Laboratorio de Biología Molecular, Facultad de Medicina, Universidad Autónoma del Estado de México. Apartado Postal 428, C.P. 50000, Toluca, Edo. Méx., México. / aaa@uaemex.mx
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molecular machinery. On that account, regarding the gene as the "master molecule" is more an ideological posture than a true scientific statement. In any case, what is being reproduced is the entire organism as a complex system and not only the genes or the genome. A further derive of this gene-centered ideology arrived to the rather silly notion that by comparing the human genome with that of the chimpanzee we would know what genes actually hold the key to humanness. Yet the result of such an effort showed that humans and chimps are basically isogenic and so no specific human genes responsible for our human properties could be identified [4]. Given the failure of the aforementioned enterprise now the trend is to assume that modifications of gene-regulatory networks in the course of evolutionary time are behind the fact that animals with isogenic genomes like the rat, mouse, dog, chimp and human, nevertheless display clearly disparate features at both structural and behavioral levels [5]. Such an assumption is currently very difficult to prove but is the stepping-stone for the actual hijacking of the new research program of *evo-devo* by genetic reductionism.

Evo-devo, the marriage of evolutionary and developmental biology, is a possible path for recovering the organism as the centre of biological thought. Indeed, neo-Darwinism explains evolution as the effect of differential fitness of different phenotypes but tells nothing about the actual origin of such phenotypes. To enunciate that the adaptive traits of the fittest are passed on to its progeny says nothing about the origin of such traits, thus evolutionary biology needs developmental biology to adumbrate the problem of origins. Yet development is much more than the sum of the expression patterns of a long list of genes and it is certainly not the result of a "genetic program" loaded into the zygote analogized as a computer, because the distinction between 'genetic' and 'epigenetic' is not the same as the distinction between 'program' and 'data' [6], and in the game of analogies the genetic information might actually be a set of data to be processed by the program embodied in the structure of the cell. So far cells beget cells and after each cell division what is inherited is more than a genome: a complex structural and spatio-temporal order that is certainly not codified in the genes and yet it is fundamental for understanding the complex behavior of the cell. Self-assembly of molecular constituents is not the answer for building a cell: a new cell needs a pre-existing cell as template. In multicellular organisms development can be understood as a self-perpetuating dynamic resulting from the coupling of molecular synthesis, gene activation, spatial patterning of substances, cell interactions, cell sorting and morphogenetic movements [7], thus achieving the transmission of structure and form that is not exclusively dependent on genetic information [8]. Moreover, a lot of fundamental physics is involved in the many morphogenetic and patterning effects in living systems that are the outcome of the basic physical properties of cells and tissues.

Therefore, generic mechanisms are equally or more important than genetic mechanisms in determining organic form [9].

For Aristotle, form was the principle of intelligibility since it is through forms that we apprehend the complexity of the world; in this way Aristotle founded natural history or what we actually know as biology with the central aim of understanding how organic form comes into being [10]. Biological development implies the process of morphogenesis consisting in the formation of biological structure by changing the spatial relationships of cells and tissues, leading to several intermediate forms in the pathway that culminates in achieving the full organic form which is proper to an individual organism of a given species. Several years ago it was suggested that this process unfolds upon an 'epigenetic landscape' of necessary paths or *chreodes* that canalize development towards definite end points [11]. Moreover, the overwhelming experimental evidence showing that cellular developmental fate is a function of position implies that material (molecular) constituents acquire the power to produce specific morphological structures as a result of qualitative changes in their spatial relationships, but since spatially-related entities are not connected, it is logically necessary to assume the existence in developing organisms of a spatially organized system of constitutive relations: a morphogenetic field like the other fields currently known to physics (gravitational, magnetic, electrical, etc.) that guides and controls interactions between matter and energy. Current evidence suggests that morphogenetic fields are wholes actively organizing themselves since they posses active powers and their essence is a dynamical structure within which genetic and environmental factors determine parametric values in the equations describing the actual structure of the field, thus acting as stabilizers of one empirical form from a set of forms that are possible for a particular type of field [12]. In recent years, the late René Thom lead the effort to create a general mathematical theory of morphogenesis that might help to understand and model any kind of morphological process, be it related to language, behavior or biological development [13].

My view is that molecular biology must go back to its roots in physics and in the foundational axiom that function follows form so as to undertake the study of development and morphogenetic fields. Yet for that purpose molecular biology must leave behind the narrow-minded notion of causality that permeates the neo-Darwinian gene-centered view, and recover the spirit of classical natural history and its four types of causation: material, efficient, formal and final, in their original non-theological but Aristotelian fashion. For Aristotle it is not the end or *telos* that directs or causes a given process from its inception, yet it is form that directs the process of its own development from a potential to an actual condition. For Aristotle potential form is a natural force operating in nature, matter

is endowed with certain necessary properties, but the necessity that is truly important in the process of organic generation is the hypothetical necessity *(to anakaion ex hypotheseos: Physica* II.9, 200a13); such is a necessity that flows backwards from the achieved *telos* to the process that leads to such an end or towards the structure of the parts that contribute to such an end [14]. The several global or local organizers described in varied embryonic developmental processes, such as the Spemann organizer in amphibians, the Hensen node in the chick, and the equivalent node region in the mouse, might be the embodied manifestations of the hypothetical necessity that establishes a set of 'attractors' along the developmental pathway that allow us to rationalize in a retrospective fashion the process of ontogeny, in the same way that a satellite view of an earthly landscape allows us to understand and then predict the course taken by water flowing upon such a landscape in its relentless voyage towards the ocean. By linking the spatio-temporal order and underlying structural constraints that control cellular physiology to the field properties manifested in the process of ontogeny, molecular biology might finally explain the organism and thus find its meaning as a true science.

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