Preface to

From the century of the genome to the century of the organism: New theoretical approaches

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This focused issue of *Progress in Biophysics and Molecular Biology* is entitled "From the century of the genome to the century of the organism: New theoretical approaches." It was developed during Ana M. Soto's tenure as Blaise Pascal Chair of Biology 2013-15 at the Ecole Normale Supérieure (ENS, Paris, France). Giuseppe Longo was the Pascal Chair host at the ENS. This ongoing theoretical work was also used as the content of a 10-session course attended by graduate students and post-graduates, which took place at the National Museum of Natural History and at the ENS. The attendants of the course encouraged the guest editors to make this material easily available, hence the origin of this PBMB issue.

The reason for such an issue of the journal is that biology in the 21st century will need such approaches as it tackles more complex interactions in organisms. Unraveling and understanding complexity is a very different kind of investigation from identifying the components of an organism, their structures and their chemical interactions, which formed the basis of successful biological research in the 20th century. Beyond the interactions of a few components, the behavior of complex networks becomes very difficult to predict from the behavior of individual components in isolation, and the behavior of the ensemble is often counterintuitive. This fact has been understood since the work of great theoretical biologists since at least the 1950s (Bertalanffy, 1969; Weiss, 1970; Weiss, 1977). Rigorous development of theoretical approaches is therefore necessary.

Yet, during most of the twentieth century experimental and theoretical biologists lived separate lives. Very few experimental biologists read and studied the work of theoretical biologists. So, the two did not interact in the way they naturally do in other sciences.

For example, it is inconceivable that experiments in physics could be done without extensive mathematical theory being used to give quantitative and conceptual expression to the ideas that motivate the questions that experimentalists try to answer. It would be impossible for the physicists at the large hadron collider, for example, to search for what we call the Higgs boson without the theoretical background that can make sense of what the Higgs boson could be. The gigantic masses of data that come out of such experimentation would be an un-interpretable mass without the theory.

So, how did experimental biology apparently manage for so many years without such theoretical structures?

Actually, it didn't. The divorce was, in a sense, only apparent.

First, there was a general broad theory provided by the theory of evolution, which deals with phylogeny, a large time-scale phenomenon. But it lacks a theory of organisms, which will encompass one life cycle, from conception to death. The main long-term objective of the Pascal Chair research on theoretical biology has been and still is to elaborate a theory of organisms. The immediate objective was to identify principles that could be used to frame such a theory. To accomplish the latter, we formed a research group that we called the ORGANISM group. The members of the group had already been collaborating on theoretical issues with Soto, Longo, or both. For example, Sonnenschein and Soto (Sonnenschein & Soto, 1999) on the default state of proliferation and motility, Longo and Montévil (2014) on the principle of variation, and Mossio, Montévil and Longo on the principle of organization. In addition to this theoretical work, we had also collaborated on related issues such as the inadequacy of concepts derived from mathematical theories, like information, program and signaling (Longo, Miquel, Sonnenschein, Soto, 2012), and philosophical issues, such as downward causation and physicalism (Soto, Sonnenschein & Miquel, 2008). Central to the theoretical work of the ORGANISM group is the realization that there are differences between the inert and the living that require theoretical development. Conservation laws and *a priori* phase-space are central to theoretical development in physics and to the mathematical elaboration of such theories. In biology, instead, ontogenesis and evolution are about relentless changes of symmetries, and the phase-space is being created along, rather than set *a priori*. The ORGANISM group expertise, in addition to theoretical biology, ranged from ecology and experimental biology (Pocheville, Sonnenschein, Soto), mathematics (Longo and Montévil), physics (Montévil), and philosophy (Miquel, Mossio and Perret).

The problem with the standard theory of evolution is that the formulation of the Neo-Darwinist Modern Synthesis ignored much of what the developing theories of complexity showed through using a strongly gene-centric approach. The gene-centric approach is important as a reductive procedure, but it is only one of the ways of studying and interpreting the functioning of organisms. Viewing organisms from the viewpoint of their functional phenotypes is equally important.

Second, there was theory in biology. In fact, there were many theories, and in many different forms. Moreover, these theories were used by experimental biologists. They were the ideas in the minds of experimental biologists. No science can be done without theoretical constructs. The so-called Central Dogma of Molecular Biology, for example, was an expression of the background of ideas that were circulating during the early heydays of molecular biology: that causation was one way (genes to phenotypes), and that inheritance was entirely attributable to DNA, by which an organism could be completely defined. This was a theory, except that it was not usually formulated as such. It was presented as fact, a *fait accompli*. Meanwhile the pages of journals of theoretical and mathematical biology continued to be filled with fascinating and difficult papers to which experimentalists, by and large, paid little or no attention.

We can call the theories that experimentalists had in mind implicit theories. Often they were not even recognized as theory. But that means that they were not properly developed as rigorous theories in the way that is common in physics. The consequence is that, just as physicists would not know what to do with the gigantic data pouring out of their colliders and telescopes without a structure of interpretative theory, biology has now hit up against exactly the same problem. There is therefore an essential incompleteness in biological theory that calls out to be filled.

The reason that there is no fully-developed current theory of biological organization lies in the multi-level nature of biological interactions, with lower level molecular processes just as dependent on higher-level organization and processes, as they in their turn are dependent on the molecular processes (Soto et al 2008). The error of twentieth century biology was to assume far too readily that causation is one-way.

In an important book, *Perspectives on Organisms: Biological time, Symmetries and Singularities* (Longo & Montevil, 2014), the authors write, "the molecular level does not accommodate phenomena that occur typically at other *levels of organization*." Denis Noble encountered this insight in 1960 when he was interpreting experimental data on cardiac potassium channels using mathematical modeling to reconstruct heart rhythm. The rhythm simply does not exist at the molecular level. The process occurs only when the molecules are constrained by the whole cardiac cell to be controlled by causation running in the opposite direction: from the cell to the molecular components. This insight is general. Of course, cells form an extremely important level of organization, without which organisms with tissues, organs and whole-body systems would be impossible. But the other levels are also important in their own ways. Ultimately, even the environment can influence gene expression levels. Between the genes and the environment there is a whole organism whereby these levels of organization are entangled. Organogenesis, for example, requires the reciprocal interaction between different tissues, a fact that inspired Soto and Sonnenschein to postulate the tissue organization field theory of carcinogenesis, whereby cancer is understood as a relational problem akin to organogenesis and tissue remodeling (Sonnenschein, & Soto, 1999). There is no *a priori* reason to privilege any one level in causation. This is the principle of biological relativity (Noble 2012).

The avoidance of engagement with theoretical work in biology was based largely on the assumption that analysis at the molecular level could be, and was in principle, complete. The articles in this issue of the journal seek to engage at one and the same time with experimentalists and with other theoreticians. They engage with experimentalists by suggesting possible experiments, and with theoreticians by exploring the boundaries of theoretical work, i.e. the metaphysics without which theory is impossible.

We now turn to the articles gathered together in this issue.

Longo & Soto: Why do we need theories? [Preprint] [Edited] The authors present an overview of the role of theories in physics, as well as of the principles of construction and proof is used as a point of departure to identify differences between the observables in physics and those in biology. In contrast to physical objects, organisms are not generic but specific. They undergo incessant changes which represent the breaking of symmetries, and thus the opposite of conservation principles, a central component of physical theories. Additionally, while in physical theories the phase-space is set *a priori*, in biology it is not predetermined, but generated along the way. These distinctions are fundamental for the construction of a theory of organisms.

Perret & Longo: Reductionist perspectives and the notion of information. [Preprint] [Edited] This essay focuses on a critique of two stances that have dominated the practice of biological research in the second half of the 20th century: physicalist reductionism, and the misuse of the notions of information, program and signal, which were transplanted from mathematical theories of information.

THREE PRINCIPLES FOR A THEORY OF ORGANISMS

I. Soto, Longo, Montévil & Sonnenschein: The biological default state of cell proliferation with variation and motility, a fundamental principle for a theory of organisms. [Preprint] [Edited] Unlike physical objects living ones such as cells are characterized by agency (the capacity to initiate action), normativity (the capacity of generating their own rules) and individuation (the ability to change one's own organization). Agency is at the core of the default state. In analogy to Galileo's inertia, we propose a foundational principle, the biological default state. The biological default state is implied in Darwin's "descent with modification". Like the principle of inertia, the biological default state does not require an explanation; what require an explanation are departures from it (quiescence, lack of variation and lack of movement).

II. Mossio, Montévil & Longo: Theoretical principles for biology: organization. [Preprint] [Edited] A succinct historical survey of the understanding of organization in the organicist tradition provides the bases for a specific characterization of organization in terms of the closure of constraints. Organization provides a framework for a systemic understanding of the notion of function. In the authors' framework, organization as a principle also provides a basis for biological stability.

III. Montévil, Mossio, Pocheville & Longo: Theoretical principles for biology: variation. [Preprint] [Edited] The principle of variation extends Darwin's notion of random variation. In physics, objects are generic and evolve in well-defined phase spaces, whereas in biology, objects are specific and the phase space is not set a priori. Biological objects show randomness, historicity and contextuality. The principle of variation is expressed in terms of symmetry changes, where symmetries underlie the theoretical determination of the object.

Miquel and Hwang: Physical and biological individuation. [Preprint] [Edited] Based on Simondon's work the authors start from the assumption that an individual is the result of individuation, and not with the classical philosophical claim according to which, individuation is a property of an individual. Individuation occurs in complex physical systems by the coupling between the system and its outside conditions. The system is not entirely defined by its structure at a given time because this structure will change and global emergent properties will appear. Thus physical individuation is defined both by the coupling of a physical system with its environment and by the diachronic dynamics taking place. Biological individuation is interpreted as a recursive procedure through which physical individuation is also acting in "its own theatre".

Montévil, Speroni, Sonnenschein & Soto: Modeling mammary organogenesis from biological first principles: cells and their physical constraints. [Preprint] [Edited] The typical approach for mathematical modeling in biology is to apply mathematical tools and concepts which originated from theoretical principles in physics and computer sciences. Instead, the authors propose to construct a mathematical model based on proper biological principles. Specifically, they use principles identified as fundamental for the elaboration of a theory of organisms, namely i) the default state of cells and ii) the principle of organization. Cells display agency and move and proliferate unless constrained; they exert mechanical forces that i) act on collagen fibers and ii) on other cells. As fibers organize, they constrain the cells on their ability to move and to proliferate. The model exhibits a circularity that can be interpreted in terms of a closure of constraints. Implementing the mathematical model shows that constraints to the default state are sufficient to explain ductal and acinar formation, and points to a target of future research.

Sonnenschein & Soto: Carcinogenesis explained within the context of a theory of organisms. [Preprint] [Edited] The tissue organization field theory (TOFT) posits that cancer is a tissue-based disease whereby carcinogens (directly) and mutations in the germ-line (indirectly) alter the normal interactions between the diverse components of an organ, such as the stroma and its adjacent epithelium. The TOFT explicitly acknowledges that the default state of all cells is proliferation with variation and motility. When taking into consideration the principle of organization, the authors posit that carcinogenesis can be explained as a relational problem whereby the release of constraints created by cell interactions and the physical forces generated by cellular agency lead cells within a tissue to regain their default state of proliferation with variation and motility.

Soto, Longo, Miquel, Montévil, Mossio, Perret, Pocheville & Sonnenschein: Toward a theory of organisms: Three founding principles in search of a useful integration. [Preprint] [Edited] Organisms are agents capable of making their own norms thus creating novelty and stability. The three principles for a theory of organisms (the default state of proliferation with variation and motility, the principle of variation and the principle of organization) provide understanding of the organism's ability to create novelty and stability and to coordinate these apparent counterparts. These principles profoundly change both biological observables and their determination with respect to the theoretical framework of physical theories. This radical change opens up the possibility of anchoring mathematical modeling in biologically proper principles.

We believe that these articles present the current state of play in developing a theory of organisms.

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