Perspectives on Organisms: Biological Time, Symmetries and Singularities. Foreword

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During most of the twentieth century experimental and theoretical biologists lived separate lives. As the authors of this book express it, “there was a belief that experimental and theoretical thinking could be decoupled.” This was a strange divorce. No other science has experienced such a separation. It is inconceivable that physical experiments 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. Similarly, modern cosmology and the interpretation of the huge amounts of data obtained through new forms of telescopes would be inconceivable without the theoretical structure provided by Einstein’s general theory of relativity. The phenomenon of gravitational lensing, for example, would be impossible to understand or even to discover. The physics of the smallest scales of the universe would also be impossible to manage without the theoretical structure of quantum mechanics.

So, how did experimental biology apparently manage for so many years without such theoretical structures? Actually, it didn’t. The divorce was only apparent.

First, there was a general theoretical structure provided by evolutionary biology. Very little in biology makes much sense without the theory of evolution. But this theory does not make specific predictions in the way in which the Higgs boson or gravitational lensing were predicted for physicists. The idea of evolution is more that of a general framework within which biology is interpreted.

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 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 recognised as theory. When Richard Dawkins wrote his persuasive book *The Selfish Gene* in 1976 he was not only giving expression to many of these implicit theories, he also misinterpreted them through failing to understand the role of metaphor in biology. Indeed, he originally stated "that was no metaphor"! As Poincaré pointed out in his lovely book *Science and Hypothesis* (*La science et l'hypothèse*) the worst mistakes in science are made by those who proudly proclaim that they are not philosophers, as though philosophy had already completed its task and had been completely replaced by empirical science. The truth is very different. The advance of science itself creates new philosophical questions. Those who tackle such questions are philosophers, even if they do not acknowledge that name. That is particularly true of the kind of theory that could be described as meta-theory: the creation of the framework within which new theory can be developed. I see creating that framework as one of the challenges to which this book responds.

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 hit up against exactly the same problem. We also are now generating gigantic amounts of genomic, proteomic, metabolomic and physiomic data. We are swimming in data. The problem is that the theoretical structures within which to interpret it are underdeveloped or have been ignored and forgotten. The cracks are appearing everywhere. Even the central theory of biology, evolution, is undergoing reassessment in the light of discoveries showing that what the modern synthesis said was impossible, such as the inheritance of acquired characters, does in fact occur. There is an essential incompleteness in biological theory that calls out to be filled.

That brings me to the question how to characterise this book. It is ambitious. It aims at nothing less than filling that gap. It openly aims at bringing the rigour of theory in physics to bear on the role of theory in biology. It is a highly welcome challenge to theorists and experimentalists alike. My belief is that, as we progressively make sense of the masses of experimental data we will find ourselves developing the conceptual foundations of biology in rigorous mathematical forms. One day (who knows when?), biology will become more like physics in this respect: theory and experimental work will be inextricably intertwined.

However, it is important that readers should appreciate that such intertwining does not mean that biology becomes, or could be, reducible to physics. As the authors say, even if we wanted such a reduction, to what physics should the reduction occur? Physics is not a static structure from which biologists can, as it were, take things 'off the shelf'. Physics has undergone revolutionary change during the last century or so. There is no sign that we are at the end of this process. Nor would it be safe to assume that, even if it did seem to be true. It seemed true to early and mid-nineteenth century biologists, such as Jean-Baptiste Lamarck, Claude Bernard, and many others. They could assume, with Laplace, that the fundamental laws of nature were strictly deterministic. Today, we know both that the fundamental laws do not work in that way, and that stochasticity is also important in biology. The lesson of the history of science is that surprises turn up just when we think we have achieved or are approaching completeness.

The claim made in this book is that there is no current theory of biological organisation. The authors also explain the reason for that. It lies in the multi-level nature of biological interactions, with lower level molecular processes just as dependent on higher-level organisation and processes, as they in their turn are dependent on the molecular processes. The error of twentieth century biology was to assume far too readily that causation is one-way. As the authors say, "the molecular level does not accommodate phenomena that occur typically at other *levels of organisation*." I encountered this insight in 1960 when I was interpreting experimental data on cardiac potassium channels using mathematical modelling 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 organisation, 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. There is no *a priori* reason to privilege any one level in causation. This is the principle of biological relativity.

The principle does not mean that the various levels are in any sense equivalent. To quote the authors again: "In no way do we mean to negate that DNA and the molecular cascades that are related to it, play an important role, yet their investigations are far from *complete* regarding the description of life phenomena." Completeness is the key concept. That is true for biological inheritance as well as for phenotype-genotype relations. New experimental work is revealing that there is much more to inheritance than DNA.

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. In contrast, the authros write, "these [molecular] cascades may causally depend on activities at different levels of analysis, which interact with them and also deserve proper insights." Those 'proper insights' must begin by identifying the entities and processes that can be said to exist at the higher levels: "finding ways to constitute theoretically biological objects and objectivise their behaviour." To achieve this we have to distance ourselves from the notion, prevalent in biology today, that the fundamental must be conceptually elementary. As the authors point out, this is not even true in physics. “Moreover, the proper elementary observable doesn’t need to be “simple”. “Elementary particles” are not conceptually/mathematically simple.”

There is therefore a need for a general theory of biological objects and their dynamics. This book is a major step in achieving that aim. It points the way to some of the important principles, such as the principle of symmetry, that must form the basis of such a theory. It also treats biological time in an innovative way, it explores the concept of extended criticality and it introduces the idea of anti-entropy. If these terms are unfamiliar to you, this book will explain them and why they help us to conceptualize the results of experimental biology. They in turn will lead the way by which experimentalists can identify and characterize the new biological objects around which a fully theoretical biology could be constructed.

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June 2013