Metascience (2018) 27:111–115
https://doi.org/10.1007/s11016-017-0255-1

BOOK REVIEW

Relativism as a means to alleviate biology from genomic reductionism: But is the remedy effective?

Denis Noble: Dance to the Tune of Life: Biological Relativity. Cambridge University Press, December 2016, 302pp, £17.99 HB

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Published online: 11 September 2017

For the past several decades, biomedical research has principally been centered on molecular biology and genomic science. Although many molecular pathways and players in different disease and normal biological processes have been elucidated over this period, the much hoped-for "true" understanding of cellular and organismic functions has arguably not been achieved. Furthermore, current mainstream research paradigms from neurodegenerative disease to oncology to evo-devo research do not signal a clear path forward as to how that desired "true" understanding could be achieved. Here three questions can be raised: Why are we where we are in biology? What is the level and type of understanding that should and can be reached? And how do we get there? Denis Noble's recent book makes illuminating contributions to answering these questions, providing a thoughtful analysis of the historical and contextual basis of the current state of biological research.

Noble is a noted cardiovascular physiologist with interests in mathematical and systems biology. He taught at Oxford for 41 years and has been an Emeritus Professor since 2004. In *Dance to the Tune of Life*, he details how his undergraduate and graduate education at University College London from 1955 to 1961 not only allowed him to study and excel in physiology, but also led him to voluntarily explore physics, mathematics, philosophy and computer science, a background that allows for a unique perspective to be brought to biomedical research. It is this perspective that has enabled the book's nine chapters and detailed endnotes to have elements of physiology, history and philosophy of science, and philosophy itself, all combined in one place. It is therefore a very informative read.

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Beginning with a history of Copernican, Galilean and Newtonian science, Noble's main focus is a critique of Neo-Darwinism and gene-centric views of biology propagated in the past century. He writes that "twentieth-century scientists ridiculed the great French biologist Jean-Baptiste Lamarck and sidelined almost completely the brilliant developmental biologist and polymath Conrad Waddington" and that "unnecessary dogmatism has unfortunately haunted evolutionary biology." He identifies with the molecular biologist Max Perutz who thought of DNA as the "score of life" rather than the "secret of life" and reminds us of cytogeneticist Barbara McClintock's prescient statement that the genome is "a highly sensitive organ of the cell" (McClintock 1984). Reiterating this point in a commentary written with other colleagues in 2016, Noble writes:

> The fashion was that all would be revealed once we had read the 'book of life,' the complete human genome. It took a mere decade of the present century for it to become clear that the 'book' is an almost illegible 'database' rather than a readable 'program of life' that would automatically lead to advances in physiology and medicine (Noble et al. 2016).

I think given the multitude of evidence currently available, most scientists, even those who previously supported an entirely gene-centric view of biology, would support this diagnosis. Moreover, it is unfortunate that the field had to go through a circular path to reach a conclusion that might have appeared obvious from the outset, a conclusion set forth, for example, beginning with the work of Waddington. Nevertheless, given where we are now, the question is where we go from here, and how we retool our methods to reach a more thorough understanding of the workings of the cell. To that end, in Chapter 6, Noble formulates a theory of "Biological Relativity," which proposes that no privileged level of causation exists in biology, and to understand the whole one must adopt an integrative approach with an emphasis on "multi-level interactions" in the organism. The theory espouses the position that biological phenomena in an organism are parts of an open system and that we should be against "unwarranted explanatory reductionism." As an example, Noble states that "spiral arrhythmia" in the heart appears random at the cellular level, but is ordered at the level of the whole organ. Therefore, even a seemingly "uncomplicated" arrhythmia cannot be reduced to its encompassing parts. Noble has since further underscored the need for a new theoretical framework that could guide biomedical research beyond what has already been achieved:

> What is needed is a framework of theory within which we can see our way through the forest of data to find the clues to understanding complexity. I see philosophy as playing a major role here since what is required is a mind-shift away from the naïve reductionist paradigm that dominated twentieth century biology. We need reductionist science. But we don't need the naïve and exclusive philosophy that often accompanies it. Reduction and integration in biology go together, rather as they do also in the mathematics of calculus. (Noble 2017b)

When we as readers consider Biological Relativity as one such framework of theory, certain ambiguities and questions might arise that warrant further consideration and could perhaps be addressed in future work. To begin with, if genes are always “passive, not active, causes,” how would we account for monogenic diseases with a very clear cause-and-effect relationship to the phenotype? This causal structure could also manifest itself not at the level of genes, but at the level of proteins, for example in human amyloid diseases (Wang et al. 2017) or heritable yeast prions (Newby and Lindquist 2013), to name a few. Furthermore, if there is no “privileged scale,” how can there be any structure in biology, and anything beyond ameboid organisms? Hierarchies and “privileged scales,” if I understand the latter phrase correctly, abound in biology, from embryo development all the way to the language faculty. In this context, Noble quotes from the philosopher Nicholas of Cusa that “the world will have its centre everywhere and circumference nowhere.” But, analogously, can we say that the cell has its nucleus everywhere and plasma membrane nowhere? A cell’s nucleus and plasma membrane are not mere conventions and metaphors. This is not to say that everything inside the cell is orchestrated in the nucleus, but rather that every biological structure has an inherent nonrelativistic framework. Moving beyond the cell and to the level of the organism, does relativism hold at that larger scale? I think the answer is still unclear even there. For example, if we consider the language faculty [“I-language” (Chomsky 2006) to be precise], what arguably makes us human (Berwick and Chomsky 2015), can we say that our inherent language faculty is part of an open system, one that “dance[s] to the tune of the organism and its social context?”

Furthermore, there is always room for pause when concepts and ideas from physics are applied to biology, which is many orders removed from the physical sciences and where scientific reasoning and explanations cannot be as exact. For example, describing “stochasticity” and randomness in a recent article, Noble writes:

> Stochasticity is harnessed by organisms to generate functionality. Randomness does not, therefore, necessarily imply lack of function or ‘blind chance’ at higher levels. In this respect, biology must resemble physics in generating order from disorder (Noble 2017a).

As concepts, “generating order from disorder,” are valuable guideposts in framing our perspective toward biological questions, how can they be applied to formulating an inherently testable hypothesis? Many “laws” of physics do not even completely and accurately describe and predict atomic-scale physical phenomena. So how can biological phenomena be reasonably explained by them? This is not to suggest that concepts from physics have no use in biology. For example, I found two ideas about randomness and the ascribing of functions particularly interesting in the book. As for randomness, Noble suggests an alternative definition of “random with respect to what?” framework. And as for functionality, he writes: “It is an important consequence of the theory of Biological Relativity that we should ascribe functions and purposes to the level at which they make sense, which is the level at which they constrain the interactions of the system at lower levels.”

Another reservation with Biological Relativity, a theory that may be categorized as a branch of systems biology, is whether it can really simplify our understanding of cellular phenomena and contribute to science's ultimate goal of simplifying complexity. Research programs exist in the physical sciences that focus on complex adaptive systems, perhaps best epitomized by the work of the Santa Fe Institute in New Mexico founded in 1984. "Complexity science" in general utilizes mathematical modeling to tackle topics such as emergence, chaos theory and complex networks, among other topics. It remains to be seen if these lines of research can really simplify the cloud of uncertainty and noise that separates us from a true understanding of the workings of a biological cell, even before we get to the level of the organism.

To gain deeper insights into cellular functions, perhaps a good working plan could be to go back to serious and elementary rational inquiry, starting with the low-hanging fruit(s), in any discipline that we choose to study. If we decide to study the behavior of a collection of cells in an organ, one could start by looking at the systems dynamics of the interacting proteins in each cell or deciphering the transcriptional and epigenetic network behind those protein interactions. But how can we arrive at a serious understanding of these cellular events if we are still unclear about the structural elements and "disordered" regions of each single protein, or what really constitutes an "interaction" between two proteins? These questions are not meant to imply that we are aiming to reduce cellular functions to structural elements at a single protein level, but they do suggest that rational inquiry should proceed in a hierarchical fashion. Biology cannot reasonably be reduced to chemistry and physics, but should eventually be unified with them, and we cannot get there before seriously pursuing the basic and seemingly pedantic questions that are still unanswered in biology.

Noble's *Dance to the Tune of Life* is an illuminating account of why philosophy is necessary in doing science. Philosophy was always part and parcel of science and it must remain so if we are to achieve science's enduring goal of simplifying our understanding of the world around us. Following with this theme, Noble writes:

> [Immanuel Kant] showed that we always need a framework within which to interpret the world, but that the framework itself may not be derivable from what we already know. That is why all science requires a metaphysics if it is not to be mere cataloguing. That metaphysics may not be derivable from purely empirical observations.

The quest for that ideal framework continues.

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