No need for a conductor

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The Music of Life: Biology Beyond the Genome

by Denis Noble

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T o n i g h t , Mahler's 8th Symphony will be performed. As the orchestra prepares, I cannot refrain from a little arithmetic gymnastics. There are almost 1,000 performers on stage, each playing over a range of

two and a half octaves, one octave has 12 tones, that is 30,000 different tones in total. As many as the number of genes in our genome! The coincidence is of course anecdotal, but the sense of wonder is perhaps related: how can harmony emerge from such tumultuous interactions between so many different players? It therefore comes as no surprise that Denis Noble—one of the pioneers of the discipline of systems biology—uses many musical metaphors in *The Music of Life: Biology Beyond the Genome* to illustrate how biology tackles the complexity of living organisms.

In an insightful and audacious demonstration of how metaphors can illuminate the same conceptual problem from different angles, Noble begins by turning one of Richard Dawkins' metaphors upside down. In *The Selfish Gene*, Dawkins wrote, "Now they [the genes] swarm in huge colonies, safe inside gigantic lumbering robots, sealed off from the outside world, communicating with it by tortuous indirect routes, manipulating it by remote control. They are in you and me; they created us, body and mind; and their preservation is the ultimate rationale for our existence." Noble turns this around, and writes, "Now they are trapped in huge colonies, locked inside highly intelligent beings, moulded by the outside world, communicating with it by complex

processes, through which, blindly, as if by magic, function emerges. They are in you and me; we are the system that allows their code to be read; and their preservation is totally dependent on the joy we experience in reproducing ourselves. We are the ultimate rationale for their existence."

By this spectacular inversion, Noble introduces the foundations of his view of systems biology, which is a clear departure from the popular opinion that genetic determinism implies a unidirectional flow of causality going 'upwards' from DNA to protein, cell and organ functions. Noble reminds us that the genome—like many components of living organisms—is just one part of a multicomponent system, which can only work when all parts are put together. Nevertheless, Noble also recognizes that DNA occupies a unique position in the system, in that variations affecting the rest of the system take place much faster than changes of the DNA sequence of the genome. Systems eventually die, whereas genes represent the "eternal replicators".

Biological function generally results from the cooperation between many components. Although clear molecular functions can be ascribed to proteins and other components, evolutionary selection pressure operates, according to Noble, at a higher level of organization—the level of the phenotype at which biological functions are expressed. The outcome of selection thus reveals less the intrinsic—and, even less, 'egoistic'—properties of a given gene product than the intricate set of interactions in which this component is embedded. Crucial to the understanding of biological function is therefore a description of the nature of the interactions and the specific context in which they occur. Accordingly, a main emphasis of molecular systems biology is to characterize the structure and contextual dependencies of biological networks on a genome-wide scale. An understanding of the complex rules of how and why biological components interact—in terms of their physico-chemical properties and spatio-temporal patterns of expression—thus represents the implicit information that we need to interpret the genome and, perhaps one day, hear the music of life as it is written in this difficult score.

Living organisms can be described at several levels of abstraction, corresponding to levels of organization: typically organs, cells and molecules. According to the classical reductionist approach, understanding the

properties of the lower levels provides an explanation for the characteristics of the upper levels, indicating an 'upward' causation. However, the functions resulting from high-level structures also directly affect the lower levels of organization. Noble maintains that a biological system cannot be understood without considering such downward links: for example, the vital property of a heart—its ability to beat—vanishes if the effect of cardiac cell voltage on ion channel behaviour is ignored. Downward causation is an inescapable design principle of biological systems, which means that all levels of organization must be integrated when modelling the behaviour of the full system. Other definitions of systems biology centre on the importance of genome-wide, multidimensional or quantitative measurements, whereas Noble emphasizes the integrative nature of the discipline to account for the multi-level architecture of living organisms.

Discovering that complex patterns and biological functions can emerge from a set of interacting elements contradicts a naive intuition that some mysterious central control unit—a conductor, so to speak—is in fact orchestrating everything. The discovery that there is no need for such a conductor is invariably a source of fascination in biology. As Noble writes, "life is wonderful enough, we don't need to endow it with mystery to appreciate it." The possibilities offered by combinatorial interactions between the seemingly few gene products encoded in our genomes are in fact vertiginous, and this explosion holds at all levels of organization.

The Music of Life also explores the ultimate question of how consciousness emerges from our brains. We might wonder what happens at even higher levels, when human minds interact with each other. At this stage, it might be preferable to leave systems biology and return to the realm of music. Those who have played in a string quartet might have experienced those rare moments when musical inspiration emerges, as if by magic, from the perfect fusion between the musicians' minds into a purely collective musical achievement. In these moments, there is no room for a conductor; only for beauty and contemplation.

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