Interpreting the Dynamics and Patterns of Living Systems

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The understanding and application of physical laws have been indispensable for the development of today's fast-advancing technologies, from automobiles and spacecraft to computers and scanning tunneling microscopes. Are similar laws useful for understanding how living nature works or how life is able to evolve over billions of years? Biology is unique in its investigation of living matter, so progress in this field may not be directly comparable with that in other disciplines. Is biology too complex—too alive—to be understood using similar conceptual methods? Although there is room to debate what constitutes *understanding*, I hold that, in some domains at least, even highly complex biological systems can be modeled using laws based on simple physical principles.

We often use the word *complex* to describe things that are not intuitively understood. In other cases, complexity involves numerous factors that could affect the behavior of an item of interest. The complexity of a process can often affect its predictability, especially if that complexity is combined with insufficient data. So the question of whether physical laws are useful to understanding living nature comes down to whether biology is too complex to be predictable or whether we simply have not yet discovered an adequate model. Consider another physical example: the weather. If we ask a person on the street how the weather will be today, because he or she probably lacks the necessary data (assuming he or she has not heard or seen a weather forecast), a reasonable answer would be based on past and current conditions. If it is sunny in the morning, it will probably also be sunny in the afternoon. However, the answer may not be straightforward, especially during spring or autumn, when there is a higher probability of collisions between hot and cold air masses. These can drastically change conditions within hours or even minutes. The question becomes even more difficult if we ask what the weather will be tomorrow or next week. The complexity of weather systems makes the intuitive prediction of their patterns difficult.

Progress over the past 50 years in nonlinear theoretical physics, mathematics, and engineering—as well as data provided by orbiting meteorological satellites—has meant that it is now possible to predict the weather fairly accurately up to a week in advance. What had been considered to be highly difficult to predict a few decades ago is now reasonably managed for a short time horizon. Can such progress be made in biology? For example, is it possible to predict the dynamic behavior of cells when we perturb them in some way or of cell fates when we change environmental conditions before we perform experiments?

In developmental biology, understanding the process that determines the fate of a cell is pivotal. This explains why much research has been aimed at discovering the secrets of cell diversification along differentiation pathways. In one groundbreaking project, which earned the Nobel Prize for Physiology or Medicine last year, Takahashi and Yamanaka (2006) identified crucial molecules (transcription factors) whose levels can, if they are experimentally modulated, reprogram a differentiated cell type into an undifferentiated one, termed an *induced pluripotent stem* (iPS) cell. Although the discovery is expected to bring about breakthroughs in regenerative medicine, the underlying mechanisms that control the differentiation process of cells remain poorly understood. So researchers do not know whether differentiated cells in a tissue, such as fibroblasts, can all be definitively reprogrammed into iPS cells. The risk remains high that some cells treated with transcription factors might become cancerous because they depart from their original differentiation trajectory. This limits the therapeutic applications for dedifferentiated cells. Biologists need to understand the details of the differentiation mechanisms so that unwanted trajectories (or variability in trajectories) can be eliminated.

Recent studies have, however, shown that fluctuations or variability in cellular dynamics may not always be undesirable. In fact, these fluctuations (also referred to as *biological noise*) have been shown to aid the process whereby cells "decide" their fate. For example, the bacterium *Bacillus subtilis* can survive in two stable forms (vegetative and competent) under conditions of nutrient deficiency. It was previously unknown how *B. subtilis* switched between the states. Today, several studies have shown that modulating noise or stochasticity in the dynamics of certain molecules involved in networks that affect gene transcription can control the switch between the two states. What is noteworthy is that a highly simplified mathematical model, based on rate laws and a stochastic algorithm, was sufficient to predict the cell fate decision of *B. subtilis* (Ozbudak et al. 2002, Maamar et al. 2007). That is, what was initially considered to be a complex decision process is now predictable using a simple model.

Consider another complicated phenomenon in biology, the mammalian immune response. Highly sophisticated cell types are able to recognize and eliminate diverse invading pathogens. The mammalian immune system consists of the innate and adaptive components that work in concert to achieve their goals. The process is considered to be very complex because of the involvement of numerous cell types that interact and release numerous proinflammatory mediators. These orchestrate the entire process. Is the immune process predictable?

To investigate the innate immune response to components of Gram-negative bacteria, which makes use of a cellular mechanism known as *Toll-like receptor signal transduction*, we tracked the temporal profiles of the concentration of various key proinflammatory proteins and of the expression of several genes in mouse macrophages. To interpret the dynamics, we developed a computational model (Selvarajoo et al. 2008) based on the laws of mass action and mass conservation (which were developed in the nineteenth and eighteenth centuries, respectively, to account for the behavior of simple chemical systems). Data from a wild-type macrophage were used to train the initial model, and data from two mutant macrophages were used to test the model's predictive capacity. Despite the widely accepted notion that the immune response is unpredictable, we showed that the intracellular signaling that induces proinflammatory cytokines follows the same simple rules that were first devised to explain nonliving systems (Selvarajoo et al. 2009).

The predictive capability of the model was restricted to the first 1–2 hours of response; after that, the applicability of the model faded. Nevertheless, for suppressing excessive proinflammatory response in common diseases, such as rheumatoid arthritis, the initial response model may be sufficient to identify a crucial therapeutic target. As with the example of the weather system, where predicting severe conditions even just a few days in advance may help save lives, predicting cells' early responses in major diseases could save lives in the future.

As a final example, think about the rules used to explain the complex patterns found in nature. In the 1940s, Alan Turing made seminal contributions to artificial intelligence and computer science that eventually led him to apply the concepts in biology. His work showed that the complex spatial patterns generated during morphogenesis can be modeled by reaction–diffusion equations that use Newton's laws of motion (Turing 1952). Today, scientists know that similar reaction–diffusion models can be used to reproduce the patterns of zebra stripes, leopard spots, seashell structures, fish patterns, and more. The Turing model's drawback is that it is sensitive to model parameters and fails to predict patterns in noisy (i.e., highly stochastic) conditions—for example, the transcriptional machinery that induces gene expressions in cells. But the lesson that complexity can be understood, or at least predicted, with simple assumptions, holds.

In systems biology, we have just started to appreciate the benefits of using formalized theories to understand cellular processes such as those governing cell fate decisions, immune responses, and growth patterns. It is true that we are nowhere near finding a general unifying law that could enable accurate biological predictions beyond a few hours or days in the future (which is also the case for complex systems such as the weather and the stock market). Nevertheless, the knowledge gained from multidisciplinary research efforts in recent years is encouraging the scientific community to apply and test concepts well beyond the areas in which they were originally developed. This is contributing to overcoming the regrettable isolation of some areas of research.

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doi:10.1525/bio.2013.63.9.7