Simplicity in biology

Networks of interactions between thousands of molecules within cells seem to defy comprehension, but shared principles of design may simplify the picture.

Uri Alon

'Complex' is perhaps the most common adjective used to describe biological phenomena. In every cell, complex networks of interactions occur between thousands of metabolites, proteins and DNA. Every interaction is itself a complex dance between exquisitely shaped proteins, designed to interface with each other if the conditions are right. And every protein looks like tangled strands of spaghetti festooned with atomic appendages. So where is the simplicity?

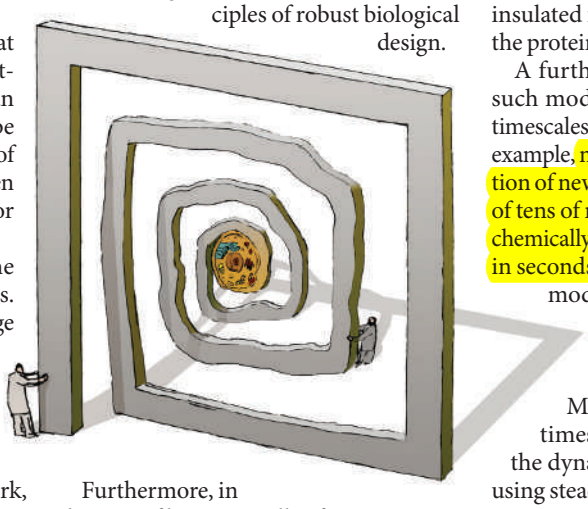
The point I wish to make is not that biology is simple, but that biological networks of interactions are simpler than they might have been. There seems to be a degree of simplicity in several aspects of these networks, which is intriguing given that cells evolved to survive, and not for scientists to understand.

One level of simplicity occurs in the structure of networks that regulate genes. In large networks there is normally a huge number of possible interaction patterns, but biological networks seem to be built, to a good approximation, from only a few types of patterns called network motifs. These motifs appear again and again throughout the network, each time having the same pattern of interactions but with different genes.

Theoretical modelling, and experiments that monitor the dynamics of networks in real time inside living cells, have revealed specific functions of different motifs — such as filtering out fluctuations in input signals. For example, a common network motif in *Escherichia coli* allows the bacteria to respond appropriately to stress even if the signal that triggers the response is disrupted.

When stressed, *E. coli* produce proteins that self-assemble into whip-like projections called flagella, and these enable the bacteria to swim in search of better conditions. A network motif known as a coherent feedforward loop senses the stress signal and coordinates the production of flagella proteins. The motif allows the cells to start making flagella proteins when a stress signal appears, but when the signal is lost, keeps production going for an hour — about the time it takes to assemble a flagella. In this way, this motif protects flagella production from a brief loss of input signal. The same motif appears in hundreds of systems in bacteria and other organisms.

Why are gene-regulation networks built out of only a handful of network motifs? The small number of motifs seems to result from the strict constraints that biological circuits must meet. For example, circuits must operate despite random fluctuations in the concentrations of the component parts, because such fluctuations seem to be an inherent feature of cells. This demand for robustness reduces the large number of circuits that perform a given function on paper to only a few that can work in the cell. Theoretical and experimental studies have begun to outline the basic principles of robust biological design.



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Furthermore, in the case of bacteria, cells often seem to economize; network motifs tend to be the circuits with the fewest components that are able to robustly perform a given function. Also, in many of the systems studied so far, the motifs are wired to each other in a way that does not spoil the independent function of each motif. As a result, combinations of motifs can give rise to new dynamical functions.

The same small set of network motifs, discovered in bacteria, have been found in gene-regulation networks across diverse organisms, including plants and animals. Evolution seems to have 'rediscovered' the same motifs again and again in different systems: circuit duplication, where an ancestral network motif gave rise to existing motifs in several species, would lead to a 'family resemblance' between the proteins that appear in different instances of the motif, but this is rarely found. Such convergent evolution suggests that specific motifs are repeatedly selected because of their properties.

A second type of simplicity is found when one considers the kind of models needed to understand the dynamics of biological networks. Instead of having to include many of the molecular details referred to at the start of this essay, the dynamics of each motif can be described using mathematical models that have a certain degree of universality. In many cases the models do not require plunging into the details of how every protein works; they only need to include information on whether X activates or inhibits Y, and at what concentration (and perhaps a few additional parameters). Such models seem to capture the essential dynamics of protein circuits, while being, in a sense, insulated from most of the complexity of the proteins themselves.

A further source of simplification in such models is the strong separation of timescales between different processes. For example, networks that control the production of new proteins work on the timescale of tens of minutes, whereas networks that chemically modify existing proteins operate in seconds. Thus, circuits that chemically modify proteins can complete their work before the slower interactions have begun to change the concentrations of proteins. Mathematically, the separation of timescales allows us to understand the dynamics on the slow timescale by using steady-state approximations for the interactions on fast timescales.

Some of the biological networks studied so far seem to contain a degree of simplicity. Simplifying principles gives hope that the behaviour of seemingly incomprehensible biological networks will eventually be deciphered. I have emphasized simplicity in biology to encourage the point of view that general principles can be discovered. Without such principles, it is difficult to imagine how we might ever make sense of biology on the level of an entire cell, tissue or organism. ■

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FURTHER READING
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