VIEWPOINT

Biological Networks: The Tinkerer as an Engineer

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This viewpoint comments on recent advances in understanding the design principles of biological networks. It highlights the surprising discovery of "good-engineering" principles in biochemical circuitry that evolved by random tinkering.

François Jacob pictured evolution as a tinkerer, not an engineer (*1*). Engineers and tinkerers arrive at their solutions by very different routes. Rather than planning structures in advance and drawing up blueprints (as an engineer would), evolution as a tinkerer works with odds and ends, assembling interactions until they are good enough to work. It is therefore wondrous that the solutions found by evolution have much in common with good engineering design (*2*). This Viewpoint comments on recent advances in understanding biological networks using concepts from engineering.

Biological networks are abstract representations of biological systems, which capture many of their essential characteristics. In the network, molecules are represented by nodes, and their interactions are represented by edges (or arrows). The cell can be viewed as an overlay of at least three types of networks, which describes protein-protein, protein-DNA, and protein-metabolite interactions. Inherent in this description is suppression of detail: many different mechanisms of transcription regulation, for example, may be described by a single type of arrow. Furthermore, the interactions can be of different strengths, so there should be numbers or weights on each arrow (*3*). Whenever two or more arrows converge on a node, an input function needs to be specified (for example, AND or OR gates) (*4*, *5*). At present, many of the connections, numbers and input functions are not known. However, something can still be learned even from the very incomplete networks currently available (*6*–*8*). First, the network description allows application of tools and concepts (*9*) developed in fields such as graph theory, physics, and sociology that have dealt with network problems before (see D. Bray on pg. 1864 in this issue). Second, biological systems viewed as networks can readily be compared with engineering systems, which are traditionally described by networks such as flow charts and blueprints. Remarkably, when such a comparison is made, biological networks are seen to share structural principles with engineered networks. Here are three of the most important shared principles, modularity, robustness to component tolerances, and use of recurring circuit elements.

The first principle, modularity (*10*–*12*), is an oft-mentioned property of biological networks. For example, proteins are known to work in slightly overlapping, coregulated groups such as pathways and complexes. Engineered systems also use modules, such as subroutines in software (*13*) and replaceable parts in machines. The following working definition of a module is proposed based on comparison with engineering: A module in a network is a set of nodes that have strong interactions and a common function. A module has defined input nodes and output nodes that control the interactions with the rest of the network. A module also has internal nodes that do not significantly interact with nodes outside the module. Modules in engineering, and presumably also in biology, have special features that make them easily embedded in almost any system. For example, output nodes should have "low impedance," so that adding on additional downstream clients should not drain the output to existing clients (up to some limit).

Why does modularity exist in biological networks? It is important to realize that not all networks that evolve by tinkering are modular. A well-studied example is computer-science neural networks (NNs). NNs are a set of interconnected nodes, each of which has a state that depends on the integrated inputs from other nodes (*14*). As do protein signaling networks, NNs function to process information between input and output nodes (*15*). In a way analogous to biological networks, NNs are optimized by an "evolutionary" tinkering process of adding and removing arrows and changing their weights until the NN performs a given computational goal (gives the "correct" output responses to input signals). Unlike biological networks, however, NNs are nonmodular. They typically have a highly interconnected architecture in which each node participates in many tasks. Viewed in this perspective, the modularity of biological networks is puzzling because modular structures can be argued to be less optimal than NN-style, nonmodular structures. After all, modules greatly limit the number of possible connections in the network, and usually a connection can be added that reduces modularity and increases the fitness of the network. This is the reason that NNs almost always display a nonmodular design. A clue to the reason that modules evolve in biology can be found in engineering (*16*). Modules in engineering convey an advantage in situations where the design specifications change from time to time. New devices or software can be easily constructed from existing, well-tested modules. A nonmodular device, in which every component is optimally linked to every other component, is effectively frozen and cannot evolve to meet new optimization conditions. Similarly, modular biological networks may have an advantage over nonmodular networks in real-life ecologies, which change over time: Modular networks can be readily reconfigured to adapt to new conditions (*16*, *17*).

The second common feature of engineering and biological networks is robustness to component tolerances. In both engineering and biology, the design must work under all plausible insults and interferences that come with the inherent properties of the components and the environment. Thus, *Escherichia coli* needs to be robust with respect to temperature changes over a few tens of degrees, and no circuit in the cell should depend on having precisely 100 copies of protein *X* and not 103. This point has been made decades ago for developmental systems (*17*, *18*) and metabolism (*2*, *19*, *20*). The fact that a gene circuit must be robust to such perturbations imposes severe constraints on its design: Only a small percentage of the possible circuits that perform a given function can perform it robustly. Recently, there have been detailed experimental-theoretical studies that demonstrate how particular gene circuits can be robust, for example, in bacterial chemotaxis (*21*, *22*) and in fruit-fly development (*23*).

The third feature common to engineering and biological networks is the use of recurring circuit elements. An electronic device, for example, can include thousands of occurrences of circuit elements such as operational amplifiers and memory registers. Biology displays the same principle, using key wiring patterns again and again throughout a network. Metabolic networks use regulatory circuits such as feedback inhibition in many different pathways (*24*). The transcriptional network of *E. coli* has been shown to display a small set of recurring circuit elements termed "network motifs" (*25*). Each network motif can perform a specific informa-

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tion processing task such as filtering out spurious input fluctuation (*25*), generating temporal programs of expression (*3, 25*) or accelerating the throughput of the network (*2, 26*). Recently, the same network motifs were also found in the transcription network of yeast (*7*, *27*). It is important to stress that the similarity in circuit structure does not necessarily stem from circuit duplication. Evolution, by constant tinkering, appears to converge again and again on these circuit patterns in different nonhomologous systems (*25*, *27*, *28*), presumably because they carry out key functions (see Perspective (*29*) STKE). Network motifs can be detected by algorithms that compare the patterns found in the biological network to those found in suitably randomized networks (*25*, *27*). This is analogous to detection of sequence motifs as recurring sequences that are very rare in random sequences.

Network motifs are likely to be also found on the level of protein signaling networks (*30*). Once a dictionary of network motifs and their functions is established, one could envision researchers detecting network motifs in new networks just as protein domains are currently detected in the sequences of new genes. Finding a sequence motif (e.g., a kinase domain) in a new protein sheds light on its biochemical function; similarly, finding a network motif in a new network may help explain what systems-level function the network performs, and how it performs it.

Will a complete description of the biological networks of an entire cell ever be available? The task of mapping an unknown network is known as reverse-engineering (*3*, *31–33*). Much of engineering is actually reverse-engineering, because prototypes often do not work and need to be understood in order to correct their design. The program of molecular biology is reverse-engineering on a grand scale. Reverse engineering a nonmodular network of a few thousand components and their nonlinear interactions is impossible (exponentially hard with the number of nodes). However, the special features of biological networks discussed here give hope that biological networks are structures that human beings can understand. Modularity, for example, is at the root of the success of gene functional assignment by expression correlations (*11*, *34*). Robustness to component tolerances limits the range of possible circuits that function on paper to only a few designs that can work in the cell. This can help theorists to home in on the correct design with limited data (*21–23*). Network motifs define the few basic patterns that recur in a network and, in principle, can provide specific experimental guidelines to determine whether they exist in a given system (*25*). These concepts, together with the current technological revolution in biology, may eventually allow characterization and understanding of cell-wide networks, with great benefit to medicine. The similarity between the creations of tinkerer and engineer also raises a fundamental scientific challenge: understanding the laws of nature that unite evolved and designed systems.

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VIEWPOINT

Social Insect Networks

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Social insect colonies have many of the properties of adaptive networks. The simple rules governing how local interactions among individuals translate into group behaviors are found across social groups, giving social insects the potential to have a profound impact on our understanding of the interplay between network dynamics and social evolution.

The formal exploration of social insect colonies as networks is in its infancy. However, social insects such as wasps, ants, and honeybees provide a powerful system for examining how network dynamics contribute to the evolution of complex biological systems. Social insect colonies (and social groups generally) have key network attributes that appear consistently in complex biological systems, from molecules through ecosystems; these include nonrandom systems of connectivity and the self-organization of group-level phenotypes (*1–3*). Colonies exhibit multiple levels of organization, yet it is still possible to track individuals, making these societies more accessible to experimental manipulation than many other complex systems.

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How can viewing insect societies as networks shape our understanding of social organization and evolution? First, they have become one of the central model systems for exploring self-organization: the process by which interactions occurring locally between individuals produce group-level attributes. Self-organization in a social insect colony produces emergent properties: social phenotypes that are greater than a simple summation of individual worker behaviors (*2*). The basic rules generating these dynamics are broadly applicable across taxa whose members show social behavior, and they produce ubiquitous patterns of social organization, including mass action responses, division of labor, and social hierarchies (*2*, *4*).