



Hip Bone Is Connected to . . .

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Every living cell employs a network of chemical reactions to construct and control a huge variety of chemical compounds. Biologists, physicists, and mathematical scientists have developed and applied techniques of network analysis to study how biochemical compounds interact with one another. The studies suggest that very complex biological systems may result from the interconnection of far simpler processes, and further suggest that insight into complex systems may be gained from models that are themselves conglomerates or networks of simpler models.

Here I discuss four theoretical papers, each describing how a specific network carries out a function in a particular group of organisms. Painstaking work of biologists has filled in tens of thousands of reaction processes occurring in cells and has told us what reactions are important for a given biological function. Thus the biologists traced out the interactions among the different chemical compounds that work together. Those connections have given us a partial topology of some of the most important biological networks. Further, the biologists have isolated some modules—interconnected processes that work together to produce a given biological function.

Fruit-fly embryo

One much-studied example looks at the development of an effectively one-dimensional chain of cells along the body of a developing fruit-fly embryo. Starting roughly three hours after fertilization, a simple pattern, with a spatial period of four cells, is turned into a much more complex and sharply defined pattern, with each repetition eventually becoming a segment of the adult *Drosophila* insect. A University of Washington group has modeled each cell as the interaction of the chemical products of five genes. The model involves 14 ordinary differential equations that embody the time history of each cell's concentration of its different chemical species.¹ The model, which

has roughly 50 parameters, includes the interaction of a given cell with its closest neighbors. After a little adjustment of network topology, including the introduction of some new interactions that inhibit formation of two chemical species, the Washington group found a satisfactory set of parameters. The set produces a steady-state behavior that reflects well the pattern of concentrations known to exist in *Drosophila* at the termination of the developmental stage under study.

The investigators studied some 200 000 parameter sets, with each parameter varying over a wide range, usually several factors of 10. Roughly 1 in 200 of these randomly picked sets of parameter values yielded qualitatively correct behavior. The word "robust" is used to describe models or biological systems in which the proper functioning seems to persist across a wide range of parameter values or external conditions. The main result of the University of Washington work is the suggestion that this developmental module is sufficiently robust against variation of parameters that once one gets the network topology right, it is relatively easy to find parameters that give the biologically observed outcome.

Despite the fact that the authors were working with a continuum model, they described their desired outcome as a steady state in which some chemical compounds are present and others are absent. Indeed, much biological work is expressed in very qualitative form, using this kind of binary description of the overall chemical state of the system. A system is described as a network consisting of nodes and links. Each node is a particular chemical species. Each link is a line between nodes that shows how an existing chemical compound inhibits or enhances the formation of a product chemical compound. Starting from this description, it is natural to build a computer model based on a large number of statements like "If at time t , compound A is present and compound B is absent, then at time $t + 1$, compound C will be present." Putting together a large number of

statements of this kind can produce a model that completely specifies the behavior of the system. Doing exactly that, Réka Albert and Hans Othmer constructed a model using the same connections as in the Washington study but built upon binary variables.² In every step of their model, the presence or absence of the different chemical species determined, via single or pairwise interactions, what species were available in the next step. The idea is that, given the robustness of the network topology studied by both groups, it is plausible that these simplified interactions might capture the essence of the underlying processes.

The modeling seems to be successful in that it captures some of the basic characteristics of the developmental system. Starting with any set of initial data, the model system will fall into one of ten different time-independent patterns, one of which (the "wild type") corresponds to the actual state of a viable *Drosophila* embryo. The effects of mutations that cause changes in the behavior in several of the genes have been investigated experimentally and these effects are apparently properly reflected in Albert and Othmer's simplified model. Thus the model can be used both to represent the known behavior of this biological module and to extrapolate the behavior to unnatural or new situations.

Albert and Othmer, and other authors as well, argue that their model of a developmental module has properties that are quite different from a randomly chosen network with a similar number of nodes. In general, a given complex network with binary variables will permit many different long-term behaviors involving mostly time oscillations. Instead, the model networks studied tend to have only a few different long-term behaviors, each one a steady state. In general, binary-variable networks will show vastly changed behavior after the flip of an initial value at a single node. But the models of biological networks each come to the same long-term behavior for many values of the initial state of the system. Perhaps these special features reflect the effects of evolution-

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