Every living cell employs a network of chemical reactions to construct and control a huge variety of chemical compounds. Biologists, physicists, and mathematicians 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 biochemical function. Thus the biologists traced out the interactions among the different chemical compounds that work together. These connections have given us a partial topography 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 experiment 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. The model, which has roughly 50 parameters, includes the interaction of a given cell with its closest neighbors. After a slight 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 the pattern of concentrations known to exist in Drosophila at the termination of the developmental stage under study.

The investigators studied some 280,000 parameter sets, with each parameter varying over a wide range, caused by several factors of 10. Roughly 1 in 200 of these randomly picked sets of parameter values yielded qualitatively correct behavior. The word "validated" is used to describe models or biochemical 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 exist once one goes the network toplogy right, it is relatively easy to find parameter that give the biologically observed outcome.

Despite the fact that the authors were working with a relatively fine-tuned parameter model, they described their designed outcome as a steady state in which some chemical compounds are present and others are absent. Indeed, much of the biological work is organized in very qualitative form, using this kind of binary description of the overall chemical state of the systems. 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 allows 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, relic Albert and Hans Othmer constructed a model using the same connections as in the Washington study but built open binary variables. 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 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 module. Thus the model can be used both to represent the known behavior of this biological module and to simulate the behavior to untested or new situations.

Albert and Othmer, and other authors as well, argue that their model of a developmental module has general utility. It will provide differential equations for a randomly chosen network with a similar number of nodes. In general, a given complex network with binary variables will permit many different behaviors involving nearly the same 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 time. 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 effect of evolution.
connections matter

All of these examples are hinges at the same, very exciting idea. Ten or a dozen or 20 linked elements produce a mildly complex machine, perhaps analogous to a little thermostat. We can, with study, understand its work-

other higher animals.* This particular network is interesting because it shows a different response to a transient exposure to its activating chem-

ical species (the cells proliferate) compared to a sustained exposure (the cells change into nerve cells). The model makes 5 start using biol
generated knowledge about which chemical interactions are important for the biological process. To describe in mathematical terms the reactions that produce the dozen or so import-

ant chemical compounds, the model makes the chemical concentrations vary in time via a set of first-order dif-
f
erential equations. The equations contain 50 free parameters. For many different sets of parameter values, the model is run to generate a set of data giving the concentrations of the chemi-

cals as a function of time. Each data set is then compared to a set of data obtained from experiments on rats. A sum of squares of differences between experimental data and model data is used as a measure of the disagree-

ment produced by the particular pa-

tamer set. After the parameters are each varied over a very wide range, the set of parameters that produce the best fit is selected. The calculated fit matches reasonably well the experi-

mental data used to construct it and, in addition, accurately predicts the re-

sults of additional experiments.

But that's not the point. As in the work of the University of Washington group, a wide range of parameters fit the data reasonably well, that is, pre-

duced a fit indistinguishable from that of the best fit. One conventional way of thinking is to visualize a land-

sc ape in which directions to x, y, and so on describe parameter variation while depth represents the parameter that describes the sum of squares of fits. With this definition, the measured goodness of the fit, in a sense used by James Sethna, be imagined as a river at the bottom of a canyon meandering and branching through a landscape of the parameter space. Some correlated changes in parameter space could produce substantial changes in parameter, but an equivalent fit. Those changes are, then, motion along the river. 

Changes in other directions in parameter space would swiftly drive an observer away from a viable solution and up the canyon walls. Underlying everything is some process, the base process of the module, produced by the topology of connections and removing fit for it within some volume in parameter space. That volume is Sethna's river. The network's topology produces the branching topology of the river, as yet unknown.

Tissue differentiation

The University of Washington model of the neural network is robust in that its behavior does not change much as model parameters are varied. As I mentioned, its variables are not bi-

ology, but instead are numbers de-

scribing concentrations of various chemical compounds in the cell. The differential equations for concentra-

tions contain the model's parameters. One might wish to understand in more detail the result of parameters variation. A Cowen University study wi-

the network involved in tissue differentiation in the development of rate and

*In this model, the researchers used a form of network engineering called the "wiring model" that represents the network's specific biological function.

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