



Bringing cartoons to life

To understand cells as dynamic systems, mathematical tools are needed to fill the gap between molecular interactions and physiological consequences.

John J. Tyson

Open any issue of *Nature* and you will find a diagram illustrating the molecular interactions purported to underlie some behaviour of a living cell. The accompanying text explains how the link between molecules and behaviour is thought to be made. For the simplest connections, such stories may be convincing, but as the mechanisms become more complex, intuitive explanations become more error prone and harder to believe.

A better way to build bridges from molecular biology to cell physiology is to recognize that a network of interacting genes and proteins is a dynamic system evolving in space and time according to fundamental laws of reaction, diffusion and transport. These laws govern how a regulatory network, confronted by any set of stimuli, determines the appropriate response of a cell. This information-processing system can be described in precise mathematical terms, and the resulting equations can be analysed and simulated to provide reliable, testable accounts of the molecular control of cell behaviour. To make these ideas clear, I will use a simplified example.

Sometimes the best response a cell can make is suicide. Programmed cell death involves activation of proteases, called caspases, that disassemble the doomed cell in a tidy fashion, avoiding the inflammatory consequences of cell breakdown. Cells stockpile caspases in precursor forms and activate the precursors under carefully regulated conditions. The network that activates caspase is extremely complex, with many levels of control to keep caspase activity switched off in healthy cells and to turn it on in cells that need to die.

Various sets of conditions can activate cell death. When the control system senses such conditions, it must trigger death irreversibly — the suicide command should not be withdrawn, even if the initiating signals are cancelled. In addition, the control system must not respond to inevitable pro-death fluctuations that are beneath the threshold for commitment to programmed cell death. These essential properties of cell death suggest that its molecular regulatory network is bistable (either off or on) at zero signal strength and monostable (on) for signals above the threshold.

Bistable behaviour of a chemical reaction system typically results from positive feedback, of which there are several

possibilities in the programmed-cell-death network. For instance, small amounts of caspase in the cell are neutralized by binding to an inhibitory protein XIAP — whose function is to prevent accidental firing of the suicide pathway by inadvertent activation of a few caspase molecules. But if enough caspase is activated

to saturate the XIAP pool, then the excess caspase triggers release of a protein whose job is to eliminate XIAP and free up even more caspase. These sorts of interactions might generate the kind of dynamic responses so characteristic of programmed cell death. But can we be sure our intuition is correct? Under what conditions is

the off state stable to small signals but switched irreversibly to the on state by large signals? How might the regulatory system fail? What are the most effective ways to intervene pharmaceutically to repair the cell-death pathway?

In the face of such quantitative questions about a complex molecular regulatory system, our intuition needs some guidance. The network of biochemical reactions among caspases, inhibitors, activators, inhibitors-of-inhibitors and so on, can be cast into a set of kinetic equations describing how the rates of the reactions cause the concentrations of the network components to increase or decrease in time. The 'state' of the control system can be represented as a point in a multidimensional coordinate system, and the kinetic equations define little vectors in this space, telling how every component of the control system will change over the next small increment of time. By following the arrows, a computer can simulate the temporal evolution of the control system under any specified experimental conditions. Computer simulations can then be compared with experimental observations to judge the adequacy (or inadequacy) of hypotheses based on the molecular interactions in the network.

More importantly, for nonlinear differential equations, a well-developed mathematical theory describes qualitative properties of equation solutions, and these properties accord well with our intuitive

notions; for example, 'bifurcation points' correspond to thresholds. Bifurcation analysis is a powerful tool for deducing qualitative dynamical features of complex reaction networks. In this fashion, dynamical systems theory forges a rigorous chain of deductions from molecular interactions to kinetic equations

to vector fields to physiological consequences.

This 'dynamical perspective' has proven its merits in many areas of molecular cell biology. Calcium signalling shows a variety of fascinating behaviours, none of which can be understood in quantitative detail without mathematical models. The molecular basis of circadian rhythms

is another area in which mathematical modelling is essential

to understanding such physiologically significant features as spontaneous oscillations, entrainment, temperature compensation and jet lag. In the study of cell-cycle regulation, bifurcation theory has led to novel predictions of excitation thresholds, time lags, checkpoint delays and oscillatory damping, all of which have been confirmed experimentally.

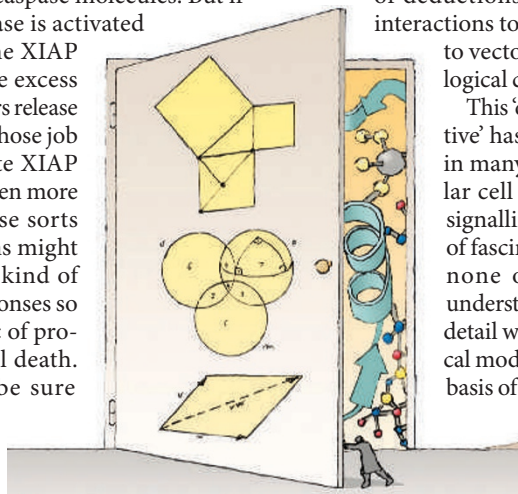
The dynamical perspective promises to revolutionize how we think about the molecular basis of cell physiology. For instance, the molecular correlates of programmed cell death are still subject to disagreements. I predict that, in the next few years, these uncertainties will be resolved largely by experiments driven by theoretical issues such as the importance of bistability, the roles of feedback and feed forward, and robustness in the face of noise. ■

John Tyson is university distinguished professor of biological sciences at Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA.

FURTHER READING

Goldbeter, A. *Biochemical Oscillations and Cellular Rhythms* (Cambridge Univ. Press, 1996).
 Legewie, S., Bluthgen, N. & Herzog, H. *PLoS Comput. Biol.* **2**, e120 (2006).
 Locke, J. C. et al. *Mol. Syst. Biol.* doi:10.1038/msb4100018 (2005).
 Pomeroy, J. R., Kim, S. Y. & Ferrell, J. E. Jr *Cell* **122**, 565–578 (2005).

For other essays in this series, see <http://nature.com/nature/focus/arts/connections/index.html>



J. KAPUSTA/IMAGES.COM

CONNECTIONS