Getting Your Loops Straight

COMPLICATED BIOCHEMICAL SIGNALING PATHWAYS REGULATE THE FUNCTION OF living cells. Such regulatory networks often have “downstream” components that provide input to components that act earlier in a pathway, creating feedback loops. These feedback loops have the potential to greatly alter the properties of a pathway and how it responds to stimuli. To fully understand these regulatory systems and exploit their vast potential as targets of therapeutic strategies, we need quantitative information on the flow of signals through a pathway and on the timing and location of signaling events within cells. We need to explore the properties that determine, for example, whether a system shows a graded response to a stimulus or turns on and off like a switch, how long a pathway stays activated, whether its output oscillates, which components can be perturbed to control the output of the system, and so on. The papers assembled in this special issue and in the companion issue of Science Signaling highlight recent progress in tackling these challenges.

The systems-level approaches required to understand signaling networks often integrate mathematical modeling with traditional biochemical analysis. Brandman and Meyer (p. 390) describe the ways in which feedback loops allow sophisticated regulatory responses, such as adaptable sensors that respond to changes in the amplitude of an input signal rather than the absolute amount of that signal. Lewis (p. 399) summarizes recent examples in which modeling approaches allow new insights into classical problems in development. Spemann’s organizer, for example, emits a gradient of signaling molecules, and recent work explains how the system adjusts when an embryo is damaged, to recreate a complete body axis. Tools that allow precise noninvasive control and monitoring of biochemical components facilitate sorting out how a system responds. As Gorostiza and Isacoff explain (p. 395), it is now possible not only to sample the output of signaling systems by monitoring the fluorescence of reporter molecules but also to engineer proteins with light-dependent isomerization switches that, when reintroduced into cells, can be controlled precisely in time and space by exposure to light.

At Science Signaling (see www.sciencemag.org/cellsignaling08), an original research paper by Abdi et al. takes strategies that engineers use to understand the vulnerability of digital circuits and applies them to biological systems to identify key elements of cellular signaling networks. In Perspectives, Dohlman discusses how scaffolding molecules can determine the graded or switchlike response of a pathway. Elston summarizes how responses to pulsatile inputs are used to understand the dynamic behavior of a signaling system in yeast. Chiang and Muir outline advances in chemical approaches providing deeper insight into signaling mechanisms.

Getting your loops straight—or understanding how a complicated signaling network might respond in any given situation—does not come easily or intuitively. But the approaches mentioned here are clearly opening a large area of investigation of enormous practical potential.

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Editor's Summary

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