Kinase cascades are binary to the bone

Like electronic relays, many biological signaling pathways are bistable, able to turn “on” or “off” in response to a stimulus, but unstable in intermediate positions. The conventional view is that bistable cellular signaling requires a distinct positive or double-negative feedback signal; but on page 353, Markevich et al. prove that it does not. Instead, signaling pathways like the common MAPK cascade are intrinsically bistable, suggesting that feedback loops function primarily to increase the repertoire and flexibility of cellular responses.

The authors performed a mathematical analysis of a generic MAPK phosphorylation/dephosphorylation cycle, in which MAPK can be phosphorylated or dephosphorylated on two sites. Their assumptions were that the monophosphorylated and diphosphorylated forms of MAPK compete for either kinase or phosphatase, and that the enzymes are nonprocessive. Under these conditions, the equations reveal bistability in the absence of a distinct feedback system. Instead, the competition of substrates for enzymes automatically reinforces a stable “on” or “off” state and makes intermediate states unstable.

Nonetheless, the ubiquity of biochemical feedback loops implies that they serve some purpose. One possibility is that the combination of intrinsic bistability and a feedback loop could confer multistability, allowing systems like the MAPK cascade to signal varying degrees of “on.”

Switching mating types with one arm tied

The mating type (MAT) locus on *Saccharomyces cerevisiae* chromosome III can recombine with the HMRa locus near the right telomere or the HMLa locus near the left telomere of the same chromosome. On page 361, Bressan et al. show that the current mating type of a cell determines the spatial configuration of these three loci in the nucleus, suggesting that the outcome of mating type switching is directed by the restraint or release of the left arm of chromosome III.

GFP tagging of chromosomes in the nuclei of living cells showed that movement of the left arm of chromosome III is tightly constrained in MATa cells, but relatively free in MATα cells. Deleting the recombination enhancer (RE) sequence on chromosome III keeps the left arm constrained in both types of cells.

RE activity requires the transcriptional activator Fkh1p, and Bressan et al. suggest that Fkh1p competes for DNA binding with tethering factors that restrain the chromosome. In MATa cells, Fkh1p binding prevails, releasing the left arm and allowing HMLα to recombine with the MAT locus, whereas in MATα cells, restraint of the left arm leaves HMRα as the recombination donor. By directing cells to switch periodically to the opposite mating type, the system assures the availability of mating partners in a haploid population.

Actin organizer takes pathogens for a ride

*Escherichia coli* causes a dramatic actin reorganization in intestinal epithelia, erecting intracellular pedestals on the host cells beneath the attached bacteria. On page 407, Campellone et al. reduce this complex phenomenon to twelve amino acids, showing that clustering a small domain of the bacterial Tir protein, which is translocated to the host cell, is sufficient to induce actin rearrangement. The results highlight an interesting evolutionary convergence, and provide a simple model system for studying actin assembly.

After discovering that Tir is the only *E. coli* component required for pedestal formation, the authors further whittled the system down to the C-terminal cytoplasmic domain of Tir. Clustering this domain at the plasma membrane causes its phosphorylation, allowing it to bind to the host protein Nck. Nck binding leads to the recruitment of N-WASP and the Arp2/3 actin nucleating complex, followed by actin pedestal formation. A 12–amino acid piece of the Tir COOH terminus triggers actin assembly in *Xenopus* egg extracts. Interestingly, a similar peptide sequence in vaccinia virus allows the virus to be transported on actin tails, suggesting that two unrelated pathogens have evolved to exploit Nck in similar ways. The authors now hope to determine how Nck binding to the Tir sequence leads to actin rearrangement.