Computational Recipes in Enzymology

Michael J. Rust[1,*]
[1]Department of Molecular Genetics and Cell Biology, Institute for Genomics and Systems Biology, 900 East 57th Street, KCBD 10124, Chicago, IL 60637, USA
*Correspondence: mrust@uchicago.edu
http://dx.doi.org/10.1016/j.cels.2015.09.006

How do rich biological behaviors arise from bi-molecular collisions?

Living cells are capable of a remarkably diverse spectrum of behaviors in response to cues from their environment. These behaviors range from switch-like responses, to the ability to detect minute variations in stimulus against a uniform background, to the generation of self-sustaining oscillations. The quantitative properties of cellular behavior can often be usefully summarized by an input-output relationship (similar to a dose-response curve), allowing us to visualize the response of a system as a function of an applied stimulus.

If we zoom into the molecular level, all of these behaviors arise from the seemingly simple rules of biochemistry: molecules colliding with each other, sticking together, falling apart, and catalyzing chemical transformations. A major goal of systems biology is to explain how a rich palette of biologically useful input-output relationships can be built out of a chaotic swarm of colliding molecules. Perhaps the simplest building block of a biochemical network is the binding equilibrium between a site on a macromolecule and a binding partner that can stick to that site, typically present at much higher concentration (e.g., a transcription factor binding to a specific site on DNA or substrate binding to the active site of an enzyme). When no other interactions are present, the resulting input-output function, reflecting the fraction of complexes formed at steady state, is a rectangular hyperbola: a curve that starts off with a linear response when the concentration of the binding partner is low and then saturates at high concentration, a situation in which the binding sites are occupied with high probability (Figure 1A). The logic of the rectangular hyperbola underlies the familiar Michaelis-Menten scheme in enzymology. However, as Savir et al. point out in this issue, this scheme contains a fundamental trade-off: when an enzyme is operating near capacity, it becomes quite insensitive to changes in substrate concentration (Savir et al., 2015).

Much work in biochemistry has gone into asking how the rules of the simple Michaelis-Menten binding scheme can be altered to create biochemical systems with different input-output properties. Early observations indicated that, in some systems with multiple binding sites, most famously hemoglobin, the fraction of bound molecules has a sigmoidal, ultrasensitive dependence on substrate concentration. This behavior can be explained by modifying the simple binding scheme described above to incorporate the powerful idea that different sites in a molecule are allosterically coupled so that binding a ligand in one site exerts an influence on the other sites (Monod et al., 1965). In the case of hemoglobin, binding of the first O_2 molecule to the tetramer induces a conformational change that makes binding the next O_2 more likely.

A conceptually distinct class of mechanisms for producing switch-like, ultrasensitive responses does so by building up biochemical circuitry in such a way that, while the input-output relationship of each underlying element might follow the simple binding curve, the input-output relationship of the whole system is very different. A classic example is the zero-order ultrasensitivity scheme due to Goldbeter and Koshland (1981). Here, two enzymes catalyzing opposing reactions—a kinase and a phosphatase, for example—each act with Michaelis-Menten kinetics. When both enzymes are close to saturation and their binding sites are occupied most of the time, the steady-state concentration of modified substrate becomes a very switch-like function of the relative enzyme activities (Figure 1B).

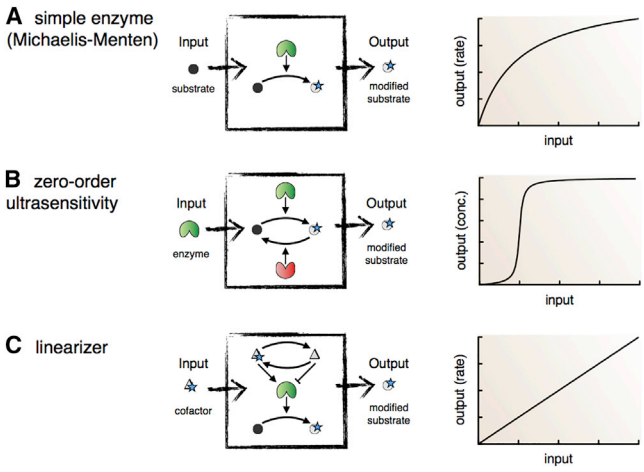

Figure 1. Biochemical Systems Viewed as Black Boxes Generating Input-Output Relationships
(A) A simple Michaelis-Menten enzyme produces an input-output relationship that is linear at low substrate concentrations but saturates when the enzyme binding site is almost always occupied at high concentration.
(B) Goldbeter-Koshland zero-order ultrasensitivity. Two Michaelis-Menten enzymes opposing each other can produce a sharp switch in the concentration of the reaction product as the velocity of one of the enzymes is increased.
(C) Linearizer scheme described by Savir et al. A Michaelis-Menten enzyme uses a charged cofactor to catalyze a reaction but is inhibited by the uncharged form of the cofactor. The total concentration of cofactor is held constant in the cell. The result is a linear dependence of reaction rate on the concentration of charged cofactor.

More recently, systems biologists have become interested in simple biochemical schemes that can produce the opposite effect: outputs that are proportional to inputs over a wide range. For example, an incoherent feedforward loop of transcriptional elements, each obeying simple binding rules, can respond proportionally to fold changes in the input to the circuit rather than its absolute concentration (Goentoro et al., 2009). In this issue, Savir et al. propose an elegant class of mechanisms that allow the input-output relationship for an enzyme to vary linearly over the full range of substrate concentrations in the cell. This insight is based on the idea that many key molecules—for example, ATP, ADP, and AMP—are interconverted in the cell so that their total concentration stays approximately constant. Enzymes that consume these molecules are often competitively inhibited by their products: an ATPase inhibited by ADP (Drobinskaya et al., 1985). Under these conditions, when substrate concentration increases, inhibitor concentration necessarily decreases. When the enzyme binds both substrate and product with similar affinity, the result is that the input-output relationship for the enzyme is linearized (Figure 1C).

Savir et al. point out that this scenario may very well apply to the SAGA histone acetyltransferase complex, which consumes acetyl-CoA and may be competitively inhibited by CoA. Interestingly, assembly of the SAGA complex is itself promoted by acetylation. Positive feedback, in this case mediated by self-acetylation, can impose a threshold so that the input-output relation is not responsive below a critical level of input (Gunawardena, 2005). The combination of both effects produces a "linear rectifier," an element that requires a critical level of input to respond and then produces output that grows linearly with input.

In addition to demonstrating that a simple set of biologically reasonable conditions can extend a response's linear range, the analysis of Savir et al. generates concrete hypotheses that can help to explain features of biological systems that might otherwise seem like extraneous details. Faced with the challenge of trying to understand the complexity of the dense network of signaling interactions in a cell, it is tempting to draw parallels to the architecture of human-created electronic circuits (Lazebnik, 2002; Milo et al., 2002; Sorger, 2005). Our engineered systems rely on carefully designed modularity, where small groups of components perform well-defined functions, such as filtering or amplifying an upstream signal and then passing it on to the next module in the circuit. How far this analogy can take us in cell biology remains unclear, but it has been remarkably fruitful as a guiding principle for research, as Savir et al. demonstrate.

REFERENCES

Drobinskaya, I.Y., Kozlov, I.A., Murataliev, M.B., and Vulfson, E.N. (1985). FEBS Lett. *182*, 419–424.

Goentoro, L., Shoval, O., Kirschner, M.W., and Alon, U. (2009). Mol. Cell *36*, 894–899, http://dx.doi.org/10.1016/j.molcel.2009.11.018.

Goldbeter, A., and Koshland, D.E., Jr. (1981). Proc. Natl. Acad. Sci. USA *78*, 6840–6844.

Gunawardena, J. (2005). Proc. Natl. Acad. Sci. USA *102*, 14617–14622, http://dx.doi.org/10.1073/pnas.0507322102.

Lazebnik, Y. (2002). Cancer Cell *2*, 179–182.

Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., and Alon, U. (2002). Science *298*, 824–827, http://dx.doi.org/10.1126/science.298.5594.824.

Monod, J., Wyman, J., and Changeux, J.P. (1965). J. Mol. Biol. *12*, 88–118.

Savir, Y., Tu, B.P., and Springer, M. (2015). Cell Systems *1*, this issue, 238–245.

Sorger, P.K. (2005). Curr. Opin. Cell Biol. *17*, 9–11, http://dx.doi.org/10.1016/j.ceb.2004.12.012.