

1970s Nostalgia for the Modern Day

At the beginning of my post-doc, my advisor, Andrew Murray, did the most generous thing anyone has done for me in science. He gave me several months to sit, read, and think. During this time, work from the 1970s became my anchor. I'd make excursions out from it but found myself returning.

Comparing a manuscript from that era to one of today's is almost unfair. There's a universe of difference in science's economics, technology's capabilities, and data's volume. But there is much to praise about that earlier work. Often it's strikingly creative and crisp. Studies begin with a premise that's unique—often a stroke of insight or a hard-won technical advance. The authors' thinking is given pride of place, and authors allow themselves to be wrong.

In those days, a thoughtful exploration of an interesting idea was “enough” for a paper. A favorite example is John J. Hopfield's 1974 work on kinetic proofreading (Proc. Natl. Acad. Sci. USA 71, 4135–4139). This paper contains no data. It builds a mathematical argument carefully and discusses its preconditions in a forthright way. In arguing that biology *could* behave this way, this paper introduced a foundational idea to the scientific enterprise years before any technology or experiment would “prove” it. Reading Hopfield, one gets the feeling that he is saying, “Take my idea, use it, and use it well.” And biology has.

This strikes the *Cell Systems* team as a clear-headed and generous way of doing science. We aim to capture this spirit in a type of article that's new for us; we're calling it “Math | Bio.” These short-format articles will present a concise, accessible mathematical argument and provide a specific biological example of when the ideas presented *might* apply. Our goal is to allow clear thinking to inform science at large without waiting years for an experimentally validated test case. Accordingly, we expect that experimental work will rarely appear in Math | Bio pieces.

The articles themselves will contain two parts: the main text, which will detail a mathematical argument that addresses an interesting question, and a box, which will present a plausible, real-world instantiation of the math. The box is meant to be hypothetical; its point is not to be correct but, rather, to explore ideas more concretely. For example, it could describe the future experiment that would determine, unambiguously, whether the math applies to a particular biological case. We hope that our Math | Bio boxes will provide examples of experiments that could disprove systems-level hypotheses. Meeting this level of rigor has proven to be challenging for our field.

When Math | Bio manuscripts are reviewed, we'll ask the reviewers to pay particular attention to the math. This involves not only making sure that it's right, but also that its preconditions,

underlying assumptions, and inherent trade-offs are appropriate. We'll also ask whether the manuscript is referenced properly. Many seminal papers in this vein pre-date PubMed; they've either fallen off the radar or were not widely appreciated by the biological sciences to begin with. We hope that our Math | Bio papers will bring these papers to the fore, and we ask for the community's help in bringing missed references to our attention. We also ask for more general feedback about whether this format is helpful.

In our inaugural Math | Bio paper on page 238 of this issue, Yonatan Savir, Benjamin Tu, and Michael Springer present a piece of systems enzymology. Their work turned my thinking about a favorite topic—the switch-like response—on its head.

Switches are critical to the cell's ability to launch a concerted response, but as Savir et al.'s work demonstrates, this function can be recast in a different light. A switch compresses a system's dynamic range, restricting its sensitivity to a narrow regime right around the threshold. Accordingly, switches destroy much of the information about the input's concentration.

This is not always biologically useful, at least on its own. Sometimes biology needs to preserve quantitative information about a stimulus and respond proportionally over many orders of magnitude. This presents two challenges: saturation at high input and noise at low input. Savir et al. introduce a kinetic scheme that solves both problems and allows an enzyme to behave as a linear rectifier: below a threshold, the system is unresponsive, but above it, the system responds linearly across its entire dynamic range. They discuss linear rectifiers in the context of the yeast SAGA complex, a molecular-level bridge between metabolism and the cell's massive transcriptional response that ensures growth control.

I'd like to make two points about Savir et al.'s discussion. First, I applaud the authors for being transparent with their thinking and offering the scientific community concrete, compelling experiments despite the prospect of being scooped. Second, there is no technical barrier to doing the work they describe. Rather, any barrier is a sociological one: doing experiments that change two variables systematically is simply uncommon. This highlights one reason that *Cell Systems* is publishing Math | Bio papers. Regardless of whether a favorite enzyme functions as a linear rectifier in a particular case, an atypical experiment—one that shakes up standard ways of thinking—has been proposed. That experiment or its close cousins will bear fruit.

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<http://dx.doi.org/10.1016/j.cels.2015.09.003>