Biochemical networks

Notes for APC591: Special Topics in Biological Dynamics

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1 What are we trying to explain?

Networks of biochemical reactions in cells perform many different functions, and before launching into models we should try understand what functional behaviors these models must reproduce. This will be a somewhat qualitative introduction, with examples of amplification, adaptation, switching and (maybe) oscillation. A theme that runs through all of these examples is that functions often are accomplished with surprisingly small numbers of molecules. At the same time, many of these networks are robust to substantial changes in the concentrations or copy numbers of key molecular components.

This is a partially annotated set of references for some of our examples. I don't expect that you read everything in the first week, since we will be going back to these problems once we have built up some mathematical tools.

Amplification and noise in the first steps of vision

Single photon detection by rod cells of the retina. F Rieke & DA Baylor, *Revs. Mod. Phys.* **70,** 1027–1036 (1998). Gain and kinetics of activation in the G-protein cascade of phototransduction. TD Lamb, *Proc. Nat'l. Acad. Sci. (USA)* **93,** 566–570 (1996).
Rieke and Baylor provide a general overview and history, explaining how we know that these cells can count single photons, and outlining the molecular mechanisms of amplification. Lamb gives a more focused review of the biochemistry.

Molecular origin of continuous dark noise in rod photoreceptors. F Rieke & DA Baylor, *Biophys J.* **71,** 2553–2572 (1996). Origin of reproducibility in the responses of retinal rods to single photons, F Rieke & DA Baylor, *Biophys J.* **75,** 1836–1857 (1998).
In these two papers Rieke and Baylor use a combination of electrical recordings and clever biochemical manipulations to dissect the contributions of different biochemical events to the signals and noise in the rod cell. The single photon response is distinguished both by its large size relative to the background of dark noise and by its reproducibility from event to event; both make obvious (and not so obvious)

contributions to visual detection and discrimination performance; these papers address these issues in turn. Some very clear answers, lots of details, rather careful and explicit discussion of the models, and enough loose ends to keep it interesting.

The gain of rod phototransduction: reconciliation of biochemical and electrophysiological measurements. IB Leskov, VA Klenchin, JW Handy, GG Whitlock, VI Govardovskii, MD Bownds, TD Lamb TD, EN Pugh Jr & VY Arshavsky, *Neuron* **27,** 525–537 (2000). Although the rod amplification pathway is often presented as one of the best understood examples of cellular signalling (and it is!), this paper highlights the difficulties of "knowing" all the biochemical parameters needed to explain quantitative measurements of cellular behavior.

Engineering aspects of enzymatic signal transduction: photoreceptors in the retina. PB Detwiler, S Ramanathan, A Sengupta & BI Shraiman, *Biophys J.* **79,** 2801–2817 (2000). As the details of different networks become clear, it is important to ask *why* they are the way they are. This is a serious and very interesting attempt to identify design principles in the rod transduction network.

Bacterial chemotaxis

Physics of chemoreception. HC Berg & EM Purcell, *Biophys. J.* **20,** 193–219 (1977).
This is the great classic, covering many different issues in the physics of bacterial behavior. For our purposes the most important discussion centers on the role of fluctuations and noise, leading to the conclusion that bacteria must be capable of counting single molecules. Along the way the authors develop a rather idiosyncratic approach to the analysis of fluctuations in chemical kinetics, and it will be worth our while to show how their (correct!) results can be derived with more general and rigorous methods.

Impulse responses in bacterial chemotaxis. SM Block, JE Segall & HC Berg *Cell* **31,** 215–226 (1982). Adaptation kinetics in bacterial chemotaxis. SM Block, JE Segall & HC Berg, *J. Bacteriol.* **154,** 312–323 (1983). Temporal comparisons in bacterial chemotaxis. JE Segall, SM Block & HC Berg, *Proc. Nat'l. Acad. Sci. (USA)* **83,** 8987–8981 (1986).
This trio of papers provides evidence on several key points. First, measurements of the response dynamics confirm (at least in outline) the theoretical predictions of Berg and Purcell regarding what the cell *must* do in order to make effective use of the available signals given the physical limits. Second, there is a more direct estimate of sensitivity, confirming that the system counts single molecules. Finally, there is the argument that the switching behavior of the bacterial motor is inconsistent with a model in which the switch corresponds to some internal messenger molecule crossing a threshold concentration. This last argument is widely cited as justification for a highly stochastic picture of the system, and I think the argument is wrong.

Robustness in simple biochemical networks. N Barkai & S Leibler, *Nature* **387,** 913–917 (1997). Robustness in bacterial chemotaxis. U Alon, MG Surette, N Barkai & S Leibler, *Nature* **397,** 168–171 (1999).
These are the now rather well known (especially locally) papers in which Leibler et al. drew attention to the problem of robustness. Already from Berg and Purcell

we knew that bacteria need to take temporal derivatives, and in conventional models of the biochemical network this is accomplished by balancing "amplification" and "adaptation" processes. But looking more closely one finds that these models require the balancing to be accomplished by fine tuning of the biochemical rate constants or protein copy numbers. As in other areas of physics, such fine tuning is *not* an explanation. The first paper offers alternative models, and the second a direct experimental demonstration that the balancing is achieved even in the presence of (large) copy number fluctuations. I think that one might like to look at the issues of robustness in a larger context; for example, models for neural dynamics are not robust to changes in the number or density of each kind of channel, and there is earlier theoretical work on how real neurons might solve this problem [G LeMasson, E Marder & LF Abbott, *Science* **259,** 1915–1917 (1993)].

Chemotactic responses of *Escherichia coli* to small jumps of photoreleased L–aspartate. R Jasuja, J Keyoung, GP Reid, DR Trentham & S Khan, *Biophys. J.* **76,** 1706–1719 (1999).
Response tuning in bacterial chemotaxis. R Jasuja, Y Lin, DR Trentham & S Khan, *Proc. Nat'l. Acad. Sci. (USA)* **96,** 11346–11351 (1999).
Most of the early experiments on chemotaxis relied either on spatial gradients or on rapid mixing in small volumes (e.g., with tethered cells). Now (largely with techniques developed for neurobiology) it is possible to change the concentration of relevant molecules on a much more rapid time scale and also (although this isn't exploited much here) with micron scale localization. This gives us a new view of the dynamics of chemotaxis, which is sampled by these papers.

Heightened sensitivity of a lattice of membrane receptors. TA Duke & D Bray, *Proc. Nat. Acad. Sci. (USA)* **96,** 10104–10108 (1999).
Despite the fact that Berg and Purcell sit somewhere near the beginning of the subject, one of their observations about bacterial behavior has eluded essentially all models, and this is the extreme sensitivity of the system. This paper explores the possibility that cooperative interactions among closely packed molecules in the cell membrane could enhance the sensitivity of the system, in effect poising the receptor array near a phase transition. I don't know if this really works, but it is thought provoking. Someone needs to do a careful job on the role of cooperativity in shaping both signals and noise in biochemical systems.

An ultrasensitive bacterial motor revealed by monitoring signaling proteins in single cells. P Cluzel, M Surette & S Leibler, *Science* **287,** 1652–1655 (2000).
Again, new methods give us a better look at an old problem. This connects back to the issues above about stochasticity vs. thresholding.

Switches

Regulation of brain type II Ca^{2+}/calmodulin–dependent protein kinase by autophosphorylation: A Ca^{2+}–triggered molecular switch. SG Miller and MB Kennedy, *Cell* **44,** 861–870 (1986).
This presents the discovery (as far as I know) of the basic facts about switching dynamics in the CaMKinase system.

A mechanism for memory storage insensitive to molecular turnover: A bistable autophosphorylating kinase. JE Lisman, *Proc. Nat. Acad. Sci. (USA)* **82,** 3055–3057 (1985). Feasibility of long–term storage of graded information by the Ca^{2+}/calmodulin–dependent protein kinase molecules of the postsynaptic density. JE Lisman and MA Goldring, , *Proc. Nat. Acad. Sci. (USA)* **85,** 5320–5324 (1988).

These two papers lay out a (semi–)quantitative model for the autophosphorylation dynamics of CaMKinase, and show how it leads to switching behavior (or maybe more). In the very first paper (and quite early in this whole discussion) Lisman realized that networks with dynamics that reach stable states can have these states be robust against molecular turnover. In a sense this is a solution in principle to one of the most profound problems in memory storage; even if the details are wrong this message is very important.

A Genetic Switch: Phage λ and Higher Organisms, 2nd Edition. M. Ptashne (Blackwell, Cambridge MA, 1992).

A classic text which explains, in some detail, what we know about the λ switch and how we know it.

Stochastic mechanisms in gene expression. HH McAdams & A Arkin *Proc. Nat'l. Acad. Sci. (USA)* **94,** 814–819 (1997). Stochastic kinetic analysis of developmental pathway bifurcation in phage lambda-infected Escherichia coli cells. A Arkin, J Ross & HH McAdams *Genetics* **149,** 1633–1648 (1998).

Arkin and coworkers certainly played a big role in reviving interest in the problem of noise in biochemical systems. For my taste, they seem to be trying to simulate lots of details rather than isolating a theoretical question. On the other hand, the long paper is a place where you can find many details! An interesting question that comes out of reading these papers concerns the level of detail and simulation that you need in order to understand things. For a contrasting view, see the next papers.

Stability and noise in biochemical switches. W Bialek, in *Advances in Neural Information Processing 13,* TK Leen, TG Dietterich & V Tresp, eds., pp. 103–109 (MIT Press, Cambridge, 2001). cond-mat/0005235.

My own effort to isolate some of the theoretical issues.

Stability Puzzles in Phage Lambda. E Aurell, S Brown, J Johanson, & K Sneppen, cond-mat/0010286. Epigenetics as a first exit problem. E Aurell & K Sneppen, cond-mat/0103080.

In these papers Sneppen et al. try to isolate the problem of building a stable switch, using λ as an example. They make some interesting mathematical points about how one can actually calculate spontaneous (noise–driven) switching rates in biochemical networks, and cite evidence of the extreme stability of the λ switch even though the number of molecules involved is quite small. They claim (as I understand it) that this stability can be explained in terms of a generally agreed upon network model, but that this picture is not sufficiently robust to explain the behavior of mutants.