The price of accuracy

Biological systems can adapt to changes in their environment over a wide range of conditions, but responding quickly and accurately is energetically costly. A study pins down the relationship between energy, speed and accuracy.

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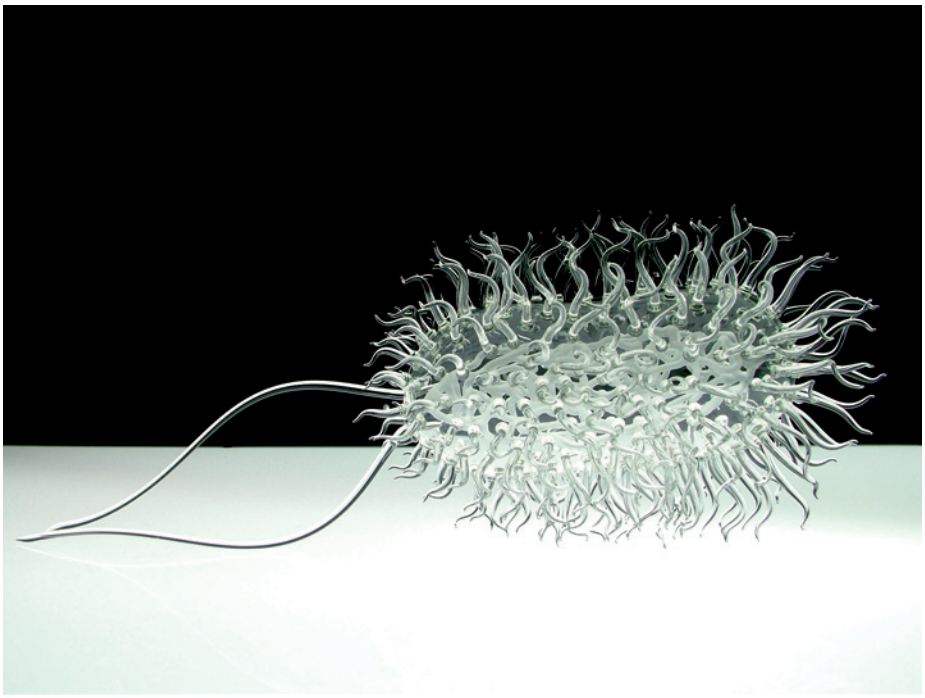
Systems that are in thermodynamic equilibrium are quite literally dead. By contrast, living systems are constantly driven out of thermodynamic equilibrium by burning chemical energy. Cells use this chemical energy to generate the forces necessary to pull chromosomes apart during cell division, or to propel themselves through their environment to find food. Yet energy is used not only to perform mechanical work, but also chemical work. Biomolecules such as proteins and DNA carry out calculations to determine when a cell should divide or in which direction food can be found, by chemically and physically interacting with one another through biochemical networks. The energetic cost of such computations has so far remained obscure. Now, writing in *Nature Physics*, Ganhui Lan and co-workers have used an adaptive sensory system to report on the rate of energy dissipation — and its relationship with the speed and accuracy of adaptation[1].

Adaptation is the ability of a system to reset its state after having been in a new environment, and constitutes a key characteristic of many sensory systems in biology. Indeed, some of our own sensory systems involve very familiar adaptation — when we walk into a dark room, our eyes take a few moments to adjust to the low-level light. Adaptation is crucial, because it enables sensory systems to respond to changes in the environment over a broad range of environmental conditions.

Most sensory systems, ranging from the osmotic-pressure-sensing system in yeast to the olfactory and light-sensing systems in mammalian cells, implement adaptation through biochemical networks that employ negative feedback. This is perhaps best understood in the chemotaxis system that allows bacteria to swim towards higher concentrations of nutrients and away from higher concentrations of various noxious chemicals.

The central players in this system are the receptor proteins at the surface of the bacterium, which detect chemicals — or ligands — by binding them. Ligand binding rapidly changes the activity of the receptor proteins, which in turn leads to a chemical change in the messenger proteins that relay the signal to the motors propelling the bacterium forward. Importantly, the change in receptor activity is recognized not only by the messenger proteins, but also by enzymes that continually methylate and demethylate the receptor proteins. Methylation counteracts the effect of ligand binding, and this negative feedback resets the activity of the receptors to its pre-stimulus level — closing the cycle of adaptation. Despite being one of the best characterized systems in biology, both theoretically and experimentally, the cost of this adaptation process has yet to be determined.



The bacterium *Escherichia coli* (depicted here in a glass model by artist Luke Jerram) undergoes chemotaxis through a sensory system that conforms to an energy–speed–accuracy relation for adaptation, which may describe a general principle for the design of sensory systems in biology.

Lan and co-workers took on this challenge by constructing a minimal model of the network, which also applies to other sensory systems[1]. They first showed that the negative feedback leads to a breakdown of detailed balance — an interesting observation in itself, because it implies that the system must be out of equilibrium. In the chemotaxis system, detailed balance is broken by the cycles of receptor methylation and demethylation, which create fluxes in state space. Maintaining these currents costs energy, and this energy is provided by the hydrolysis of the molecules that donate the methyl groups to the receptors. These molecules provide the fuel for adaptation, and their constant turnover represents chemical work performed on the system, keeping it out of thermodynamic equilibrium. However, part of the reaction energy is wasted, being dissipated as heat into the environment, leading to an increase in the entropy of the surroundings.

This brings us to the second and central result of the paper. Lan *et al.*[1] calculated the rate of energy dissipation for the minimal model and found that it is proportional to the accuracy and speed of adaptation: more accurate and/or faster adaptation inevitably

requires more energy dissipation per unit of time. To test this energy–speed–accuracy relation, Lan *et al.*[1] considered a microscopic model of the chemotaxis network of the bacterium *Escherichia coli*, finding that as the system is driven further away from equilibrium, the energy-dissipation rate approaches that predicted by the energy–speed–accuracy relationship. Moreover, by comparing the network with a large class of models, they found that the design of the *E. coli* network is close to optimal — for a given energy-dissipation rate and adaptation time, the uncertainty cannot be reduced much by choosing different model parameters.

Last, although the energy–speed–accuracy relation shows that the energy-dissipation rate is proportional to the adaptive speed and accuracy, it does not predict whether energy is traded for accuracy or speed (or a combination of both) under biological conditions. To test this, the authors performed experiments on starving *E. coli* cells, showing that in the stressed system, the adaptive speed becomes progressively slower, whereas the adaptive accuracy remains constant.

Many signalling systems employ futile cycles, in which two pathways run in opposite directions with no apparent function. The results of Lan *et al.*[1] show that these cycles can have a function: they enable accurate adaptation. At the same time, they come at an energetic cost. This trade-off between accuracy and energy is emerging as a general design principle of biological systems. The classical example is kinetic proofreading[2,3], in which energy is consumed to discriminate between two possibilities — the binding of the 'right' molecule instead of the 'wrong' molecule, for example — with higher fidelity than that allowed by equilibrium thermodynamics.

Recently, it was shown that there is a trade-off between the energetic cost of making a regulatory network and the precision of its regulatory function[4,5]. In the coming years, new examples of this interplay between precision and energy will undoubtedly be revealed. Given the tremendous progress that has recently been made in describing systems driven arbitrarily far from equilibrium, such as the Jarzynski relation[6] and new fluctuation theorems[7–9], the study of precision and energy in living systems holds great promise for the future of non-equilibrium physics.

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