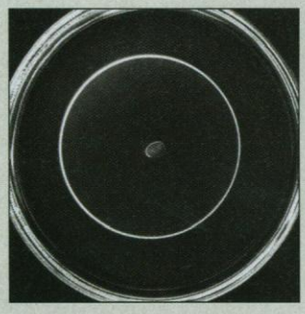
Unraveling Bacteria's Dependable Homing System

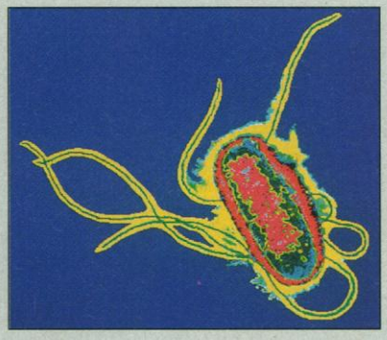
For more than a century, microbiologists have marveled at the ability of bacteria—seemingly simple organisms—to home in on a food source and navigate toward it. Since then they've picked the process apart, identifying some proteins that "smell" the nutrient source, others that propel a microbe toward it by driving flagella, and still others that convey the necessary signals. But they never quite understood how this process could work reliably in spite of variations in the microbes' own genetic makeup or in their environments.



Historical circle. A 1966 experiment showed that bacteria will move from the center of a petri dish outward toward undepleted nutrient supplies, forming a ring.

That's where Stanislas Leibler decided he might be able to make a contribution. Several years ago, this Princeton molecular biologist and Princeton colleague Naama Barkai brought skills from their former lives as physicists to bear on the problem. Today, their success in mathematically representing how this robust behavior arises from the complex interactions of proteins and pathways has earned kudos from both theorists and experimentalists. "They've taken a biological pathway and tried to ask something about its fundamental properties as a unit," says Leland Hartwell, a yeast geneticist at the Fred Hutchinson Cancer Research Center in Seattle. That approach "is really fundamental for the next step in biology."

Leibler and Barkai started with the broader question of how organisms could be different, biochemically speaking, and still carry out the same behavior. Most cellular processes depend on interactions among many different proteins. And many biologists had thought that the cell had to keep tight control over the concentrations and activities of these various molecules to keep everything functioning smoothly.



Mobile microbe. *Escherichia coli* propels itself with flagella.

Yet the more DNA geneticists have sequenced, the more they have realized that the same gene often differs slightly from one individual to the next—differences that affect how much of its protein product a gene produces, or how well the protein works. And even when genes are identical, protein concentrations can vary for other reasons. Yet more often than not, the organism functions just fine in spite of the variations.

When the Princeton duo pondered this puzzle, they wondered whether the biochemical details are less critical than the way the details fit together. Perhaps organisms have evolved networks of interactions that work reliably in spite of either overactive or underactive genes or proteins. "One cannot understand this by looking at one protein," Leibler realized. "One has to consider the whole system ... to see if [this robustness] comes from systemic properties."

They decided to look at this question by trying to make sense of chemotaxis. "There is no simple system," Leibler explains, "but we were able to build on many years of beautiful work done by other people. That made this one tne best known and best studied system." Typically, chemotactic microbes zigzag as they swim, changing direction by tumbling periodically in random directions. However, when a bacterium senses a desirable substance, such as an amino acid, it follows a steadier course toward this target.

In one such microbe, *Escherichia coli*, chemotaxis gets kicked off when an attractant links up with a receptor protein that sits in the cell membrane. Then several Che (for chemotaxis) proteins get involved and alter the movement of the rotating flagella to stop or start a turn. The result is that the bacterium tumbles less frequently, and it moves in a relatively constant direction toward a greater concentration of the attractant. When it no longer senses a rising concentration gradient, it returns to the original tumbling rate, thereby ensuring it can detect further changes in the gradient.

For years, biologists have thought that most aspects of cell function, including this ability to return to a steady tumbling rate over a wide range of attractant concentrations during chemotaxis, depended on precise titration of the various molecular components of the system. If that were the case, too much or too little of any of the Che proteins would throw the system off.

To find out if this is indeed the case, Barkai and Leibler built a mathematical model of the interactions. Like others who had modeled chemotaxis before them, they assumed that the receptor was either on or off, depending mainly on whether an odor molecule had docked at the receptor. They translated this "two-state" model into a series of differential equations that describe the interactions between the various Che proteins.

"The model correctly reproduced the main features of bacterial chemotaxis" when first tested 2 years ago, Leibler recalls. The simulated microbe responded and adapted to changes in the concentration of the attractant much as the real bacterium does. Moreover, it was able to do so even when the researchers changed the amounts and activities of Che proteins by several-fold. These simulations showed "there are some properties which are not sensitive [to perturbation]," Leibler explains.

He and Barkai then teamed up with Princeton physicist-turned-microbiologist Uri Alon and with microbiologist Michael Surrette to examine if this was the way real bacteria worked. They created mutant bacteria that either underproduced or overproduced several Che proteins. Comparing strains that made one protein, Che R, at levels ranging from less than normal to 50 times the normal amount, they found that the time it took the bacteria to return to their usual tumbling rate after sensing an attractant dropped from 23 minutes to less than one. Yet as the model had predicted, all of the mutants, no matter what their Che R activity, were able to return to those precise tumbling rates. The work "shows that for some properties, the cell doesn't seem to care" about the amount of these proteins, says Leibler. A feedback loop that enables the cell to measure the tumbling rate and adjust accordingly must be responsible for this robustness.

Although robustness in chemotaxis may not seem all that important in the grand scheme of cell biology, the work is impressive because "it shows how variability can be accommodated in a circuit," says Hartwell. Some "emergent property" of the chemotactic pathway buffers it against variation in its individual components. Thus each individual can function just fine while being a little different.

This mix of sameness and variation is an asset in the game of evolution. As Harvard cell biologist Marc Kirschner points out, "If you have flexibility, you've essentially designed something that is capable of being modified, [and that's] evolvability." That's a level of understanding that could only come from incorporating the biochemical details of the system into a bigger picture. And, says Hartwell, "this is something that all of us are going to be trying to do." —ELIZABETH PENNISI

CREDIT: (TOP) JULIUS ADLER, *SCIENCE* 153, 708 (1966) (FIGURE 11, P. 712); (BOTTOM) LINDA STANNARD/UCT/PHOTO RESEARCHERS