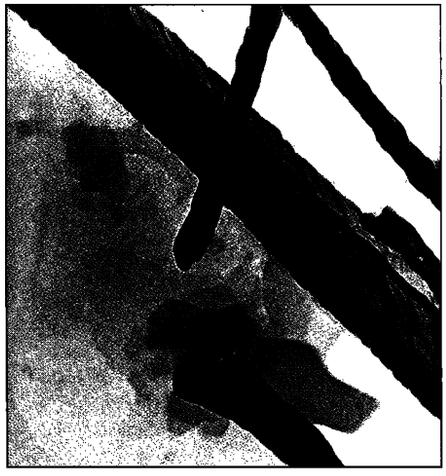
silicon bed. He started by dipping this base into a solution containing molecules with a sulfur atom at one end, a hydrocarbon chain in the middle, and a phosphonate group at the end (see diagram on p. 316). The sulfur atoms tightly bonded to the gold surface, leaving phosphonate groups sticking out at the surface.

These phosphonates carry a net negative charge. So Mallouk placed the structures in a bath containing zirconium ions, which have a positive charge. The zirconium bonded to the phosphonates, forming a single-atom-thick layer of sheet metal. Then Mallouk dipped the structures in a bath containing molecules with phosphonate groups at both end, which readily bound to the zirconium, leaving another group of unbound phosphonates sticking out at the top. From there he could simply repeat the process, building layer after layer.

In general, layered structures are essential for semiconductor devices, which work by separating opposite electric charges between different layers, or at least different levels of the same layer. In conventional solar cells,



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Drawing straws. Used for applications ranging from drug delivery to microwave electronics, strawlike "microtubules" can be as small as half a micron in diameter.

for example, silicon atoms capture photons, emitting negatively charged electrons and positively charged "holes"—effectively the absence of an electron—in the process. These opposite charges migrate to the top and bottom of the silicon layer, where they are collected and shuttled to a battery for storage. If the charges recombine before reaching the battery, the result is heat instead of electricity.

In 1992, Howard Katz and his colleagues at AT&T used Mallouk's so-called "metal-phosphonate" self-assembling system to emulate part of a solar cell. They began by depositing several layers of organic molecules, known as porphyrins and vilogens. Like silicon, porphyrin molecules capture sunlight, giving off electrons and holes. In Katz' layered device, the porphyrins then donate the electrons to the vilogen molecules, allowing the charges to remain separate.

Of course, this is still far from a working solar cell, admits Katz, as he and his colleagues need to figure out how to collect the electrons and pass them to a battery. But if such problems can be solved, self-assembled layers hold the promise of drastically reducing the manufacturing cost of solar cells, since self-assembly makes forming multilayered electronic structures nearly as simple as dipping plates into successive buckets of dishwater and rinse water. With that promise in mind, researchers such as Princeton's Mark Thompson are tinkering with self-constructing layers as possible routes not only to solar cells but to LEDs, which run the same reaction in reverse, combining opposite electric charges and emitting light.

Constructing the field

Whether or not such applications will one day find their way to the marketplace remains to be seen. Applications like liposomes for delivering anti-cancer drugs face not only questions of efficacy but competition from more conventional therapies such as radiation and traditional chemotherapy. For applications such as electronics even proving cost-effectiveness may not be enough, since manufacturers have already spent billions to tool up for making silicon-based microchips. Like many materials science innovations, self-assembled structures are likely to be used for niche applications first, says Leslie Smith, a physical chemist at the National Institute of Standards and Technology in Gaithersburg, Maryland.

Whatever strategies these newcomers adopt for the moment, to insiders "it's clear that self-assembly is here to stay," says Davis. While some scientists refine current techniques in the hopes of proving cost-effectiveness, new applications keep appearing on the horizon. Researchers are trying to get self-assembling molecules to aid in orienting liquid crystal polymers for optical displays, as well in making nonlinear optical materials, which are essential for routing optically transmitted data. And though this quiet revolution is just beginning, one day researchers may be as proficient, if not as happy, as clams.

—**Robert F. Service**

Additional Readings

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EVOLUTIONARY BIOLOGY

A Boost for "Adaptive" Mutation

British geneticist John Cairns touched off a firestorm in genetic and evolutionary circles 6 years ago by proposing that bacteria could, in his words, "choose" the mutations they acquire. Assigning such freedom of choice to bacteria violates a basic tenet of evolutionary theory, which holds that mutations arise at random. But Cairns and his colleagues claimed to have evidence for their view: They put bacteria unable to digest lactose into a petri dish with only lactose for nourishment—and found that the bacteria preferentially acquired the crucial mutations they needed to become lactose-eaters.

Then came the firestorm. Other researchers also saw evidence of these apparently nonrandom mutations in their counts of various bacterial and yeast colonies. But a legion of neo-Darwinists and population geneticists, who considered Cairns' idea heresy of the first order, pounced on this work, charging that the results were due to experimental artifacts. Now, according to two papers in this issue of *Science*, a distinct type of mutation is indeed at work under certain selective conditions—but neither paper proves that useful mutations arise faster than non-useful ones.

In essence, some critics had claimed that Cairns and others had miscounted garden-variety mutations. Patricia Foster and Jeffrey Trimarchi of Boston University, on page 407, and Susan Rosenberg of the University of Alberta and her colleagues, on page 405, go beyond colony counts to present gene sequence data from *Escherichia coli*, showing that under selection pressure, a novel mutation mechanism is creating specific types of mutations. Says geneticist Franklin Stahl of the University of Oregon, "With essentially one [stroke], this qualitative observation rules out the possibility that the whole thing was an unintentional fake."

Not only do these papers show that something exceptional was happening in Cairns' experiments, they offer clues to the molecular nuts and bolts of the mutational mechanism, implicating the same kind of genetic mistake that has recently been linked to colon cancer and some inherited diseases. With these results in hand, even longtime skeptics like Richard Lenski of Michigan State University say they are now persuaded that an unusual mutational process is at work—at least in this experimental system.

But Lenski is quick to point out that

these findings haven't really doused the fiery debate Cairns ignited. Neither paper addresses the most controversial issue Cairns posed: Do mutations arise because they are useful? On that question, Lenski and other critics insist, the answer is still no.

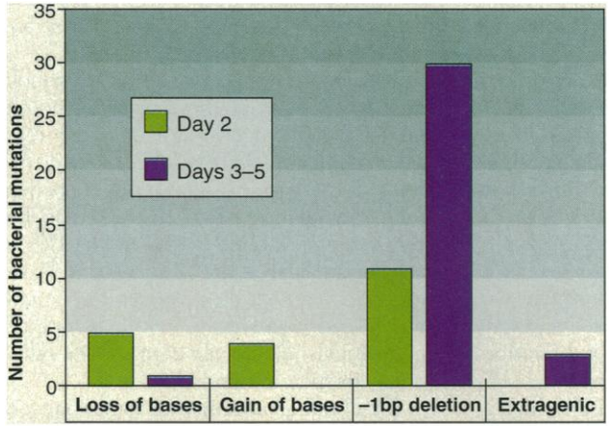
Foster, a veteran of the mutation wars who has worked with Cairns, and Rosenberg, a genetic recombination specialist who only recently entered the fray, worked simultaneously but independently to probe the molecular basis of what they call "adaptive mutation." Both followed the outline of Cairns' early work, using an elegant experimental system developed by Foster and Cairns. They employed a strain of *E. coli* with an inactive copy of the *lacZ* gene, which encodes the enzyme needed to digest lactose. They put the bacteria in a petri dish with only lactose for food, and then analyzed the mutant colonies that had acquired the ability to grow on lactose.

In this particular strain of *E. coli*, lactose fermentation can be turned on by a variety of mutations, some simple and some complex. But when the researchers sequenced the relevant region of the genome, they found that most of the DNA changes consisted of simple deletions of one nucleotide in a run of repeated bases, such as dropping one "C" from the sequence "CCCC." Mutations that arose under normal conditions, which are called spontaneous mutations, included a more diverse spectrum of DNA changes, such as duplications or longer deletions.

This type of bias in mutation sequence is considered good evidence that the mutagenic processes operating under normal and selective conditions are different, says geneticist David Thaler of Rockefeller University. And that makes it hard to sustain one type of criticism of Cairns' work—what Thaler calls the "growth-on-the-plate arguments." These critics contended that mutations arising under selection pressure are simply spontaneous mutations growing at unusual rates for various artifactual reasons. "The most trivial explanations, which were technically very hard to refute, are now not relevant," says Thaler.

Actually, Thaler and others—including Foster and Rosenberg—were already persuaded that a different type of mutation was at work. Foster and Cairns had previously shown that adaptive mutation in these cells required a gene called *recA*. The protein encoded by this gene causes portions of DNA strands to recombine, or swap positions, but the gene is apparently irrelevant for most mutations during cell growth. Rosenberg and colleagues confirmed and extended this conclusion in a recent *Science* paper (8 April, p. 258). Other studies had even suggested that adaptive mutation generates a different spectrum of mutants. But none of the earlier results have been as persuasive as the sequence data, says Foster. "You can show curve after curve of colonies on plates, but there's something about sequence data that just really thrills people." Cairns, now retired, put it this way: "The spectra are different, the papers agree, and hurray."

The papers also provide clues to the molecular mechanism operating in this system. The particular type of sequence change observed—deletion of a repeated nucleotide—is typical of errors made when enzymes responsible for synthesizing DNA, the DNA polymerases, make a mistake. Dropping a repeated base could also be a sign of flaws in mismatch repair, the molecular machinery responsible for editing out mistakes in the new DNA strand.



Mutants under pressure. Experiments show a distinctive type of mutation predominates when bacteria are starving.

DNA synthesis and mismatch repair are known to occur frequently during recombination, knowledge that has helped researchers develop a preliminary molecular model of adaptive mutation. The new data, in fact, support one of two models that Rosenberg suggested in the April report. In this view, adaptive mutation might start with breaks in DNA strands in starving cells, which prompt recombination involving DNA synthesis. The new DNA has more errors than usual, because of an error-prone polymerase, faulty mismatch repair, or both.

But how is this related to the selection pressure? Rosenberg is considering an adaptation of a model developed by geneticist Barry Hall of the University of Rochester. He proposed that a small number of the starving bacteria begin to mutate rapidly, producing a raft of mutations that either do or do not confer the needed trait. Bacteria that don't develop the right mutation accumulate breaks in their DNA and die, says Rosenberg. Useful mutations allow bacteria to grow, leave this "hypermutable state," and survive.

There are plenty of other models out there, and there is plenty of controversy over the evolutionary implications. Evolutionary theory doesn't demand that all mutations occur at a constant rate; indeed, it's been known for decades that radiation increases mutation rates. That's why even critics such as Lenski are comfortable with the notion that a distinct type of mutation is turned on when cells are in so-called stationary phase, meaning they aren't growing. Lenski and John Mittler, now of Emory University, themselves showed that certain types of mutation happen faster in starving cells.

But neo-Darwinian theory does insist that mutations arise at random *with respect to their usefulness*. In contrast, Cairns raised the possibility that selection pressure for a specific trait preferentially sparked mutations that conferred that trait, as though bacteria could call up the mutation they needed on demand. To some, that proposal raises the ghost of 19th-century naturalist Jean-Baptiste de Lamarck. The key question, as Rosenberg puts it, is "are cells so smart that they only make mutations in *lac* genes?"

But in these papers, neither she nor Foster looked at whether the single-base deletions arose only in the *lacZ* gene or in other parts of the genome as well. And though Cairns and others found that only useful mutations arise, that work remains controversial, in part because it's hard to prove the *absence* of other mutations. "That part is still wide open," admits Hall.

In fact, both Rosenberg and Foster are considering models that involve random genetic changes and selection. Foster's model invokes selection at the molecular, rather than the individual, level, thus avoiding cell death. "The question becomes not whether the process is random, but where does the randomness appear?" she says .

In Lenski's view, the fact that most models of adaptive mutation now include this element of randomness shows that his opponents have, in recent years, "retreated from anything that challenges evolutionary dogma, from anything goal-directed." Mittler agrees: "The debate is getting down to bacterial physiology in stationary phase now. It's an important area of investigation—but it's unlikely to be Lamarckian."

What hasn't been narrowed down, however, is a name for this phenomenon. Cairns originally used the term "directed mutation," which to many scientists implied that the bacteria themselves were directing which mutations arose. Others have called it "Cairnsian," "stationary phase," and "starvation-associated" mutation. Foster and Rosenberg both used "adaptive" in print, but on the job in Rosenberg's lab, they call it SPAM—Selection-Promoted Additional Mutations. Foster's idea: Just call it "Fred."

–Elizabeth Culotta