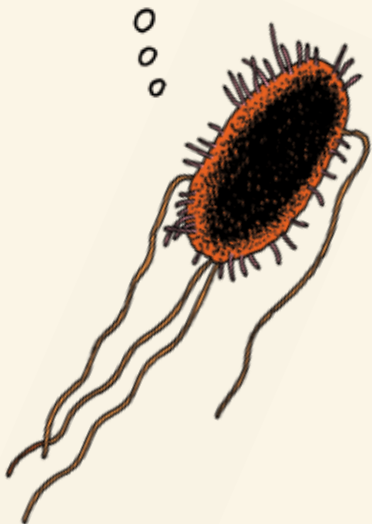




Judges Flip for Bacterial Computer



So, you've whipped up a big stack of pancakes, but you burned them on one side—too busy turning out pancakes to notice. Your folly is a pile of flapjacks in random order of size, burnt side up or down. Being a scientific type, you decide to make a cool puzzle out of figuring how to flip them into a neat stack, in order by size, with all the embarrassingly burnt sides down.

This pancake puzzle was actually tackled by a “bacterial computer” engineered by a predominantly student team of gene tinkerers at Davidson College (Davidson, North Carolina). Their synthetic-biology solution to the breakfast blunder won them a sweet stack of awards at the 2006

international Genetically Engineered Machine competition. This small-college team, competing against such powerhouses as Harvard, the Massachusetts Institute of Technology, and Princeton, took second prize in three categories, as well as third prize for Best Conquest of Adversity.

The students' conceptual equivalent of a stack of pancakes was a set of gene segments that they inserted into the DNA of the bacterium *Escherichia coli*. When those pieces are all correctly oriented in a piece of carrier DNA called a plasmid, the gene works normally, but if any functional piece is inserted backward, the gene sits inactive. Thus, an active gene is the equivalent of a properly ordered stack of burnt-side-down pancakes.

As an indication that their “pancakes” were all flipped into the right orientation, the students chose a gene that, when activated, confers antibiotic resistance to the *E. coli*. Therefore, they could treat the cultures with an antibiotic to winnow out those that “failed.”

A daunting engineering challenge, however, was how to get the inserted gene segments to flip like pancakes in the first place. The students' solution was to engineer gene-inverting machinery, borrowed from *Salmonella* bacteria, into *E. coli*. Wily *Salmonella* ordinarily uses such “flipping” as part of its infectious process—which

Illustration: Peter Arkle

A Brew of Bitter

If you mix lab skills, nostalgia, and a hankering for diversion, what do you get? For HHMI professor Graham F. Hatfull, the answer is The Plowman's Lunch: bread, cheese, and beer.

Hatfull is a professor of biotechnology at the University of Pittsburgh. His day job is studying mycobacteriophages—viruses that infect mycobacteria, like the kind that cause tuberculosis. Outside the lab, he likes to plumb the mysteries of bread, cheese, and beer. Especially beer.

"Maybe this is coincidence," he says, "but the things I really like to eat and drink are, fundamentally, experiments in microbiology."

His quest: "the perfect pint of British bitter." For beer drinkers in this country, a bitter is a pale ale, with what Hatfull calls an "artisanal" touch. He cultivated that touch during a 1980s flirtation with kitchen-sink brewing, while earning his Ph.D. in molecular biology at the University of Edinburgh. By 2006, an established researcher plagued by bureaucratic chores, he thought, "I really need something to take my mind away from the administrative details." So he blew the dust off his British-made equipment, sorted out voltage differences, located a Pittsburgh source of hops and grain, and was soon happily brewing away in his garage. Five gallons at a time, no two batches exactly alike.

With afternoon sunlight glancing off his John Lennon glasses, Hatfull elaborates in his campus office. "Both brewing and what we do in the lab require appreciation and respect for the power of microorganisms. They can make you very ill, but you can view them as essential pieces of civilization." He bakes bread as well—another traditional mainstay that uses yeasts. "And I just started getting into cheese, which is microbiology of yet another sort."



Each new brew is a mild surprise, and Hatfull relishes the impact of tiny, random variations in taste, aroma, and color. "I like the sense of being an artisan. It depends, from batch to batch, on you, and on the microorganisms, and what their particular behaviors are."

At the same time (here he slips into a mock-professorial tone), "There are clearly a lot of scientific elements: You have a hypothesis as to how a particular brew is going to be made. You devise a recipe that you hypothesize will give you that kind of brew. You go in and do the experiment—right?—and at the end, you get to drink the experiment." —George Heidekat

enables it to evade immune detection during an infection.

Inserting the *Salmonella* machinery into *E. coli* was no piece of cake, says Karmella Haynes, an HHMI research-teaching fellow in biology and one of the team's faculty leaders. The students had to engineer the inserted gene segments so that they were flanked by short DNA sequences that the gene-flipping machinery would target. This allowed them to persuade the *Salmonella* snipping-and-flipping enzyme, called an invertase, to flip DNA fragments that it does not normally flip.

"What I admire about the group is their gutsiness," says Haynes. "They went ahead and said 'Let's reconstitute this thing in *E. coli*. Let's strip out the bare minimal components and adapt it so that we can flip any segment of DNA we want.'" Besides Haynes, two of the students—Sabriya Rosemond from Hampton University (Hampton, Virginia) and Lance Harden from Davidson—were supported by an HHMI undergraduate science education grant to Davidson. Collaborators

included other Davidson students and students from Missouri Western State University (St. Joseph, Missouri).

"Besides learning a good deal about synthetic biology," says Harden, "we also learned a lot about communication between people in different disciplines, in this case, biologists and mathematical modelers. Our weekly lab meetings really served a dual role of educating each other and teaching us technical public speaking."

Haynes is excited about the gene-flipping bacteria's potential to help solve huge mathematical problems. "This system has tremendous parallel-processing capacity. Just one liter of cell culture has about a hundred million bacteria, all working on the problem at the same time."

The students' name for their system? "E.HOP," of course! —Dennis Meredith



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KARMELLA HAYNES