orbit with an incapacitating headache isn't so wonderful either. Both are symptoms of the space sickness that commonly strikes astronauts during the first few days of flight. Drugs are available to treat the symptoms, but they cause side effects such as drowsiness.

Meanwhile, NASA scientists are at a loss to explain exactly what causes space sickness. But at the meeting, physiologist Alan Hargens of NASA's Ames Research Center described a device that his team is developing to test one hypothesis: that space sickness is the result of pressure buildup inside the skull. If the device—which uses ultrasound to measure fraction-of-a-millimeter changes in skull size—shows that space sickness is associated with surges in intracranial pressure, it could lead to better means of combating the condition.

The pressure hypothesis for space sickness is plausible because without Earth's gravity to pull blood toward the feet, blood volume in the head increases. That increase should boost pressure inside the skull, and increased intracranial pressure is known to trigger nausea, vomiting, and headache in Earthbound patients who have a defect in the drainage of cerebrospinal fluid.

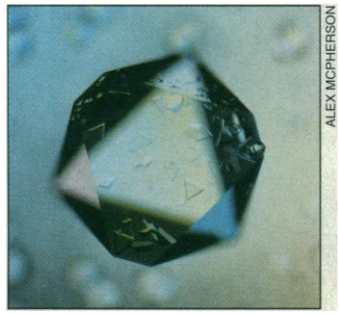
To test the idea, the Hargens team is now adapting a prototype device developed by NASA physicists for detecting stresses in metals used to build rockets. Referred to as the Variable Frequency Pulse Phase-Locked Loop (PPLL) measuring device, it sends a high-frequency sound wave through the head, where it is reflected off the back of the skull and returns to a sensor on the PPLL. By altering the wavelength of the ultrasound, the PPLL maintains a constant distance between the peaks of the outgoing and incoming sound waves. Thus, as the distance between the front and the back of the skull increases with increasing intracranial pressure, so does the wavelength, providing a marker for pressure.

At the Houston conference, Hargens reported that his team had tested the PPLL on seven adults by slowly tilting their bodies so that their heads were just below the horizontal, a position that causes blood to rush to the head as it does in weightlessness. The device could easily measure the tiny increases in skull length, which totaled about 0.1 millimeter. "The more we tilted, the greater the increase in intracranial distance," says Hargens.

Next, the PPLL will be calibrated on cadaver skulls implanted with pressure transducers and infused with fluid to alter pressure. The ultimate aim, says Hargens, is to use the PPLL to monitor intracranial pressure in astronauts "during the launch and into early microgravity, because that is when we think you get the rapid increase in intracranial pressure" that triggers space sickness. The device could be useful on Earth too, says neurosurgeon Lawrence Shuer of Stanford University in Palo Alto, California, who will help test the PPLL. To identify which head-trauma patients need treatment to reduce brain swelling, surgeons now have to implant pressure transducers in their skulls. The PPLL, says Shuer, could provide a noninvasive alternative.

Unpredictable Crystals

There's a common perception that crystal growing in space has failed to live up to its promise of producing protein crystals that are bigger, better, and altogether more suitable for gleaning a protein's 3D structure than those grown on Earth. But that's not quite true, crystallographer Lawrence DeLucas of the University of Alabama, Birmingham, told the meeting. "Of the 100 proteins flown in space, 25 have produced crystals better than anything that can be produced on Earth," said DeLucas, who is also chief scientist for the international space station.



Low-G gem. Crystal of satellite tobacco mosaic virus.

Space provided the superior crystals that helped solve or sharpen the 3D structures of insulin, the HIV protease enzyme, satellite tobacco mosaic virus, and human serum albumin, DeLucas said. And crystallographer Eddy Arnold of Rutgers University in New Brunswick, New Jersey, agrees that space has brought "very significant improvements" in crystal growing, at least for some proteins.

In theory, low gravity aids crystal growth by eliminating convection currents in the crystal-growing fluid that can create imperfections and by keeping the growing crystal from crashing to the bottom of the vessel. But "it's been impossible to predict which proteins will grow better [in space]," says Arnold.

Gaining such foresight has become one of the hottest challenges in crystallization research, says Alex McPherson of the University of California, Riverside. In an upcoming issue of the *Journal of Crystal Growth*, McPherson and his colleagues describe using atomic force microscopy (AFM) to watch crystals grow one molecule at a time. The next step will be to use AFM to find out how crystal growth differs in microgravity. And that, says McPherson, may make it possible to pick out the proteins likely to benefit most from a ride in space.

–Rachel Nowak

COMPUTER SCIENCE

A Boom in Plans for DNA Computing

Five months ago, when Leonard Adleman reported building a "DNA computer," few of his peers in the computer science community thought it would ever be more than a toy. They were impressed by how cleverly the University of Southern California researcher had solved a variation of the "traveling salesman" problem, coaxing strands of DNA to link up in a way that identified a route through each of a series of destinations. But they suspected the technique would be a one-trick pony. Nature, it seemed, offered a tailor-made approach to attacking one specialized problem, but even Adleman himself was unsure of the next step—or whether there was one. "Wider applicability wasn't apparent," he says.

It is now. Early this month nearly 200 computer scientists, molecular biologists, and other researchers gathered at a hastily arranged meeting at Princeton University to discuss what has suddenly become the hottest field in computer science: computing with DNA. One speaker after another described schemes to apply the techniques of molecular biology to computational problems from cracking codes to building a "universal computer," a device that can carry out any combination of logical and arithmetic operations. And on page 542 of this issue of *Science*, Princeton computer scientist Richard Lipton details a scheme that helped spark the excitement: a way to use DNA to solve a problem that requires searching a universe of solutions so large it would defeat any conventional computer.

So far, no one but Adleman has actually built a DNA computer, and the practical difficulties may be formidable. "Nobody knows if any of this stuff works," says David Gifford, a computer scientist at the Massachusetts Institute of Technology, noting that Adleman's computer had to consider fewer than 100 possibilities and that errors may creep in as the size of the problems increases. Nevertheless, the excitement has a very real basis: Working with DNA offers the chance to perform billions of operations simultaneously, compared with only a few thousand parallel operations in even the most advanced electronic computers.

A single flask, Adleman says, might hold 10^{19} to 10^{20} strands of DNA, each encoding a string of data in its sequence of nucleotides. These data can be manipulated in various ways by the techniques of molecular biology:

ILLUSTRATION: E. CARROLL

combining strands, splitting them at well-defined points, copying them, extracting strands with a given nucleotide sequence, and so on. Although a single operation is slow—taking minutes or hours to perform, compared with microseconds in an electronic computer—the operation is done on all of the DNA in the flask at once. Harnessing those simultaneous chemical reactions could produce a device that performs millions of times as many operations per second as a state-of-the-art supercomputer.

Computer scientists had long been aware of this potential, but no one knew how to exploit it until Adleman published his description of a working DNA computer (*Science*, 11 November 1994, p. 1021). Even then, only a few researchers realized the implications. "After I heard the result, I talked to a lot of people who thought it was a dead end," recalls Lipton. After all, the traveling salesman problem he solved—in essence, finding a path through seven cities connected by one-way streets—could be done by any seventh-grader with a pencil and paper. Furthermore, calculations indicated that even an optimized version of the DNA device could not solve path problems as large as those that can be done by conventional computers: One would need to fill a lake or ocean with DNA.

Lipton, however, saw the seeds of something larger. Before the end of the year, he had figured out how to modify Adleman's approach to solve a more difficult and interesting computational task: the famous satisfaction problem, or SAT (see box). His approach—starting with strands representing all possible solutions and then discarding the ones that don't work—shows how a DNA computer could serve as a powerful "search machine," combing through astronomical numbers of possible answers in search of the correct one. It offers the possibility of solving satisfaction problems much larger than are feasible with silicon-based computing. And early reports of it on the Internet sparked a flurry of interest from other researchers, culminating in the Princeton meeting.

The results described at that meeting prove that the field has come a long way in just a few months, Adleman says. For example, Lipton and two of his students, Dan Boneh and Christopher Dunworth, have developed a method for breaking the data encryption standard system (DES) developed by the National Security Agency and widely used by government agencies and private corporations. The DES uses one of 2^{56} keys to scramble messages; ordinarily, breaking the code demands testing the keys one by one, which would take an impossibly long time with current computers. But Lipton, Boneh, and Dunworth came up with a plan for encoding every possible key as a strand of DNA and then testing them all simultaneously. The search for the key would consist of a series of extractions, replications, and other DNA-processing steps taking several months, Lipton says, and would yield the single DNA strand corresponding to the DES key: "It's not practical at this time, but we could probably do it if there were a commercial reason for it."

Other schemes presented at the meeting were even further from practical application, such as a universal computer. But that's to be expected, Adleman notes: "DNA computers are less than 6 months old. It's too early for either great optimism or great pessimism."

It's not too early, however, to identify the two biggest question marks facing DNA computers. First, will it be possible to put great quantities of DNA through hundreds of processing steps without the sorts of errors that will give wrong answers? So far, Gifford notes, only Adleman has moved from paper to practice, and that was for one very small problem with only a dozen different kinds of DNA strands and a few processing steps: "It's an open question whether this will scale up." And even if it does, Adleman asks, how important are the sorts of problems that DNA computers can handle better than their silicon cousins? "Is anybody walking around with a big satisfiability problem he's dying to solve? I don't know of anyone."

But Lipton thinks that once people start thinking about the sorts of problems solvable by a computer that performs 10^{18} or 10^{20} operations at once, "we're going to find a lot of things that fit that model." He and his colleagues say that the union of two of science's most fertile fields—molecular biology and computer science—is sure to produce some remarkable offspring.

–Robert Pool

Getting Satisfaction From DNA

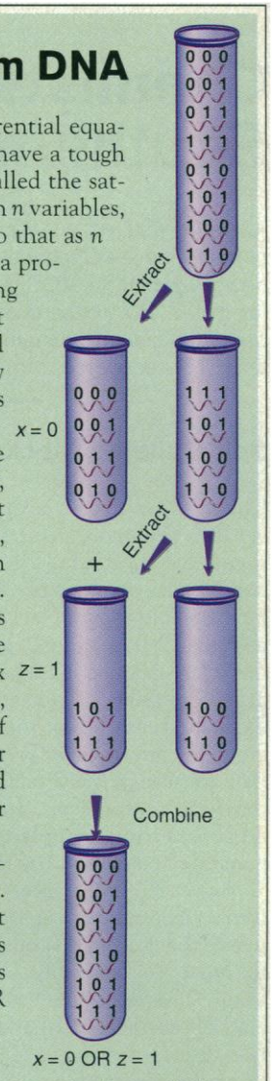
Although electronic computers can crunch complex differential equations in a jiffy and factor 100-digit numbers with ease, they have a tough time with a seemingly simple task in mathematical logic called the satisfaction problem, or SAT. The reason is that for an SAT with n variables, the computer must test 2^n possible solutions one by one, so that as n increases, the computing time goes up exponentially. But in a proposal that has helped spark the new field of DNA computing (see main text), Princeton University computer scientist Richard Lipton describes a DNA computer that could test all the possibilities simultaneously. The scheme points the way to solving SATs with dozens of variables—far more than is now feasible.

To see how Lipton's scheme works, consider a simple three-variable SAT, where x, y, and z are Boolean variables, each representing a simple statement such as "It is raining" that can be either 0 (false) or 1 (true). The problem is to assign x, y, and z the values true or false so that they satisfy the expression $(x = 0 \text{ OR } z = 1) \text{ AND } (x = 1 \text{ OR } y = 0) \text{ AND } (y = 1 \text{ OR } z = 0)$.

The first step in the biological solution is to create strands of DNA, each 20 nucleotides long, that correspond to the values of the variables. Because there are three variables, six types of strands are needed: one each for $x = 0$, $x = 1$, $y = 0$, and so on. In a test tube, the strands are mixed with bits of complementary DNA that link them at random to form longer strands representing possible solutions. Each longer strand codes values for all three variables: $x = 1$, $y = 0$, and $z = 1$, for example, is one strand.

Finding the solution entails using molecular-biology techniques to sort through the test tube of DNA (see diagram). First, extract all those sequences that code for $x = 0$ and put them in a separate test tube. Then extract all the sequences that code for $z = 1$ and mix them with the $x = 0$ strands. This subset of the original DNA satisfies the statement $(x = 0 \text{ OR } z = 1)$. Working from this DNA, do a second set of extractions that correspond to $(x = 1 \text{ OR } y = 0)$. This produces a new subset of DNA—the starting point for one more extraction step corresponding to $(y = 1 \text{ OR } z = 0)$. The resulting DNA contains the sequences $x = 0$, $y = 0$, $z = 0$ and $x = 1$, $y = 1$, $z = 1$—the solutions to the SAT problem.

–R.P.



One step toward SAT. A DNA computer operates on strands encoding values for x, y, and z.