Molecular Computing in a DNA Soup

Putting on a lab coat, getting out test tubes, and handling chemicals aren't normally part of a computer scientist's routine for solving a mathematical problem. But when the answer is encoded in strands of DNA, hands-on computing in the biotechnology laboratory becomes necessary.

Computer scientist Leonard M. Adleman of the University of Southern California in Los Angeles has taken just such a route. He has ventured into the laboratory to use the tools of molecular biology — simple DNA manipulations — to explore the possibility of computing directly with molecules.

In the Nov. 11 SCIENCE, Adleman describes a laboratory experiment in which he solved a computational problem that involved finding a particular path through a maze of points and links. "This is the first example, I think, of an actual computation carried out at the molecular level," Adleman says.

Adleman's guinea pig was a particular network, or graph, consisting of seven points (called nodes or vertices) and 14 links (known as edges) connecting the points in various ways (see diagram). Identifying each node as a city and each link as a one-way, nonstop flight between two cities, one has to determine whether there is a route that takes a traveler from a given starting point to a given end point and passes through each city exactly once. For this example, Adleman knew, there is only one solution.

Mathematically, this is known as the directed Hamiltonian path problem, and it serves as a surrogate for a wide variety of practical computational problems.

Adleman proceeded by assigning each of the seven cities a unique code name in the form of a short DNA sequence made up of 20 nucleotides. The four different types of nucleotides are designated C, G, T, and A, and the cities' codes were written as some combination of these letters.

By replacing A with T, T with A, G with C, and C with G, he also created a complementary DNA sequence for each city code. Such a string of nucleotides would stick to its mate.

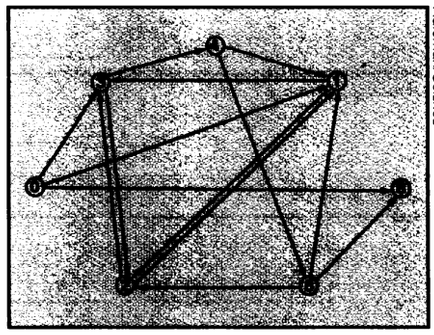
Adleman then constructed each of the 14 links by attaching the last 10 nucleotides of the DNA code for the originating city to the first 10 of the destination city. To begin his experiment, he obtained small quantities of each of the DNA sequences representing the 14 links and the complement codes for the seven cities.

Adleman then mixed together pinches of each of these 21 powders in a test tube and dissolved them in water. This caused the DNA strands to join end to end, forming longer sequences. The complementary strands served as splints to hold the pieces together. This reaction resulted in the formation of DNA molecules encoding an enormous number of random paths through the graph.

The remaining steps involved isolating out of the trillions of molecules present the one type of DNA strand that corresponds to the solution of the route problem.

"What you know about the winning molecule is that it has to start with the right DNA name and it has to end with the right DNA name, and it must have the DNA names of all the cities in between," Adleman says. "You [will also know] how much it will weigh and how many nucleotides long it will be."

Advances in molecular biology have made such separations practically routine. Adleman spent a week in the laboratory obtaining his result. "In the end, you wind up with a test tube in your hand containing just the Hamiltonian path molecules," he remarks.



Adleman/SCIENCE

This graph shows seven nodes and 14 one-way links. It has a unique Hamiltonian path, starting at 0, running through each of the other nodes exactly once, and ending at 6.

"In essence, Adleman has used the enormous parallelism of solution-phase chemistry to solve a hard computational problem," David K. Gifford of the Massachusetts Institute of Technology comments in the same issue of SCIENCE.

"My goal was to show feasibility," Adleman says. "Whether it really turns out to be practical remains to be seen."

— I. Peterson

One team, two clues in Alzheimer's puzzle

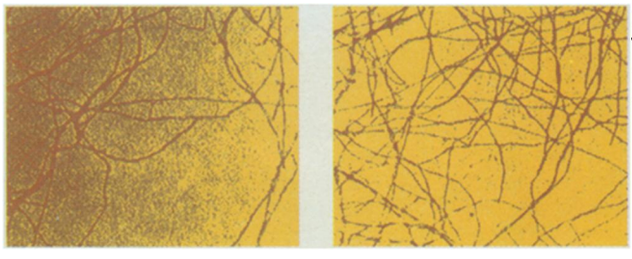
Collaboration between clinical and basic researchers in Boston has yielded two findings that should help physicians, scientists, and patients fight Alzheimer's disease. Their work may explain how a chemical in the brain, apolipoprotein E, can increase a person's risk of developing Alzheimer's disease (SN: 8/13/94, p.111). Other results suggest that these researchers have devised a simple diagnostic test for the disorder.

Like everyone else involved in the treatment or study of this dementia, Huntington Potter of Harvard Medical School in Boston has long sought an easy, certain way to diagnose Alzheimer's, a disease characterized by progressive loss of memory and other brain functions. Currently, researchers depend on a battery of neurological and psychological tests that can be confirmed only by examining the patient's brain after death.

Now, preliminary results indicate that monitoring pupil dilation after exposure to a chemical commonly used by eye doctors may one day accomplish just that, Potter says.

Because of similarities between Alzheimer's disease and Down's syndrome, Potter had combed the scientific literature for unusual traits in Down's patients that people with Alzheimer's might share. As early as 1959, others had noticed that Down's patients react strongly to chemicals that block transmission of the nervous system messenger acetylcholine: Their pupils dilate and their heart rates increase more than normal.

Leonard F.M. Scinto, now at Brigham and Women's Hospital in Boston, tried one such chemical, tropicamide, on 58 individuals. Of those 58, 14 were already diagnosed as having Alzheimer's, 5 were suspected of having Alzheimer's, 4 suffered from other dementias, 3 showed some loss of mental function, and 32 had scored well on the



Jianyi Ma *et al.*/ NATURE

Apo E-III promotes less amyloid filament formation (left) than apo E-IV (right).

initial screening tests of brain function.

Each participant first watched television in a dimly lit, quiet room for a few minutes. A researcher measured the viewer's pupils, then administered a drop of sterile water into one eye and a drop of tropicamide into the other. The researcher did not know which drop was which. For the next hour, a special infrared video camera monitored changes in the pupils.

The eyes of Alzheimer's patients and people suspected of having the disease reacted similarly to the eyes of the three volunteers with some loss of mental function, Scinto, Potter, and their colleagues report. This reaction differed most from that of healthy individuals one-half hour into the test, the group reports in the Nov. 11 SCIENCE.

Pupils dilate about 5 percent in normal individuals and in those with other types of dementia but 23 percent in those with or possibly suffering from Alzheimer's. This test pointed to Alzheimer's in 18 of the 19 people having or believed to have this disease, the researchers note.

Furthermore, pupils seem to become sensitive to tropicamide very early in the course of the disease. A man with slightly abnormal brain function who had tested positive for Alzheimer's now shows signs of being in the early stages of the disease, Potter says.

"[The test] is very provocative if it holds true," comments Zaven S. Khachaturian of the National Institute on Aging in Bethesda, Md. He adds, however, that the test must be studied in many more people to determine whether it holds up in different types of people with different types of Alzheimer's.

Even Potter cautions against physicians trying this test out yet. "[It] requires rather specialized equipment," he warns. "You can't just use an eyedropper and ruler."

In the second study, reported in the Nov. 3 NATURE, Potter's group demonstrated that the cholesterol-carrying molecule apolipoprotein E (apo E) promotes the formation of deposits, called amyloid plaques, in the brain. These plaques serve as a hallmark of Alzheimer's disease.

Apo E-IV, the version of the molecule associated with increased risk of Alzheimer's, stimulates plaque formation the most, while apo E-III works less well, and apo E-II can even slow plaque formation, the team reports. These findings agree with those of earlier epidemiological studies (SN: 1/1/94, p.8).

The researchers had already established that the protein ACT helps stimulate the creation of filaments, which clump into amyloid plaques. These new experiments, done by mixing high concentrations of the substances involved in a test tube, demonstrate that ACT links with one part of the amyloid fragment and apo E with another part. Other studies indicate that ACT and apo E are more abundant in the parts of the brain most affected by Alzheimer's, Potter notes.

— E. Pennisi

Hubble: Evidence of oceans on Titan?

Of all the solar system bodies other than Earth, planetary scientists believe just one may harbor oceans or lakes. Researchers have long debated whether Saturn's moon Titan, cloaked in a methane-rich atmosphere, contains hydrocarbon oceans or lakes.

In penetrating much of Titan's haze, the Hubble Space Telescope has taken a new step in clearing up the mystery. Peering through a "window" that allows near-infrared light to escape through the smog and methane engulfing Titan, Hubble has imaged intriguing bright and dark patches that seem to lie on the moon's surface. One explanation for the dark patches: They represent oceans of hydrocarbons; the brightest patch could be a continent-size chunk of frozen water and ammonia ice.

Peter H. Smith of the University of Arizona in Tucson and his colleagues presented the findings last week in Bethesda, Md., at the annual meeting of the American Astronomical Society's Division for Planetary Sciences.

He cautions that the dark patches could have more mundane explanations. Hydrocarbon tars coating parts of the moon's surface, for example, could also lower Titan's reflectivity and account for the dark features.

Because the near-infrared wavelengths at which Hubble observed don't penetrate all of Titan's haze, Smith and his colleagues had to subtract the murky atmosphere to produce the final images. Some astronomers express concern that the pictures may show a mix of surface and lower-atmosphere features rather than just the surface.

But Smith notes that the light and dark regions imaged by Hubble match several ground-based observations. Unlike Hubble, telescopes on Earth must contend with Earth's wavering atmosphere and for now can't resolve individual features on Titan. But near-infrared observations from Earth taken over several years reveal that the regions of Titan that reflect the most and least sunlight are the same ones in which Hubble finds the brightest and darkest patches, respectively.

"The real proof of the pudding that these are surface features is that our bright spot and our dark spot line up precisely with the ground-based measurements," Smith says.

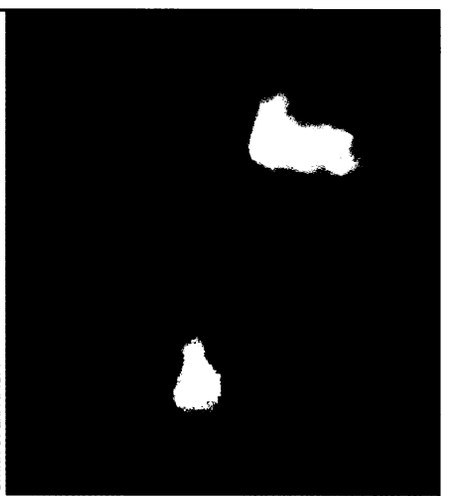
Jonathan I. Lunine of the University of Arizona, a proponent of the ocean hypothesis, says the Hubble images suggest that the composition and topography of the moon's surface vary considerably. Both hydrocarbon tars and a small ocean might reside within the same dark patch, he notes.

Researchers proposed Titan's hydrocarbon ocean in order to solve a dilemma. They realized that to sustain the amount of methane found in Titan's atmosphere, the moon must have a reservoir of the hydrocarbon. Without it, sunlight would have long ago destroyed the atmospheric methane.

Given Titan's temperature and surface pressure, scientists suggested that the reservoir took the form of methane and ethane oceans and lakes. Radar studies later ruled out an ocean covering the entire moon but allowed for individual lakes or seas.

Several developments may help identify what lies on Titan, even before a space probe parachutes onto the moon in 2004. New techniques to compensate for Earth's blurry atmosphere should enable ground-based infrared telescopes to image individual features on Titan. Similarly, an upgrade of the Arecibo Observatory's radio telescope in Puerto Rico, to be completed in 1996, should provide higher-resolution radar images. In space, NASA plans to install a new infrared camera on Hubble in 1997. This should enable the telescope to get an even clearer view of Titan's surface.

— R. Cowen



Smith et al./NASA

Hubble images of Titan. The false-color pictures are projected global views of the moon, each separated by 90° of longitude. Assuming that Titan rotates at the same rate that it orbits Saturn, upper left image shows the hemisphere facing Saturn; upper right is the hemisphere that leads in the moon's orbit; lower left is the hemisphere facing away from Saturn; and lower right is the trailing hemisphere. Poles were not imaged.