

Environmental changes might speed up evolution

Computer simulation stokes debate over genetic variety

By GEOFF KOCH
Staff Writer

A fluctuating environment can change evolution from a meandering stroll to an all-out sprint, a new study suggests.

Rice University scientists David Earl and Michael Deem used a computer to simulate a world where they could turn up or down the rates of environmental change. More change caused the virtual life in this digitized world to radically ramp up its genetic variety, the researchers report in an upcoming issue of the *Proceedings of the National Academy of Sciences*.

"A lot of people are thinking about this idea," says Dr. Earl, whose results provoke discussion about two long-considered questions in biology: How much of evolution can be explained by genetic variety sprinkled into populations in fixed amounts through the eons? And how much is the result of relatively sudden, heap-helpings of genetic change?

Scientists disagree on the answers, but there is consensus about the two ways change is introduced into populations in the first place.

For everything from bacteria to baboons, a dash of genetic variety can come from changes to individual links on chains of their genetic material. A more generous helping of variation comes from wholesale swapping of big chunks of these chains, hundreds or thousands of links long.

As Drs. Earl and Deem programmed in more severe change in their virtual environment — think droughts one year and flooding the next — the rates of wholesale swapping soared.

Their complicated lines of computer code support a simple idea. Nature seems to select for organisms that can speed up the shuffling of their own genes in response to environmental cues.

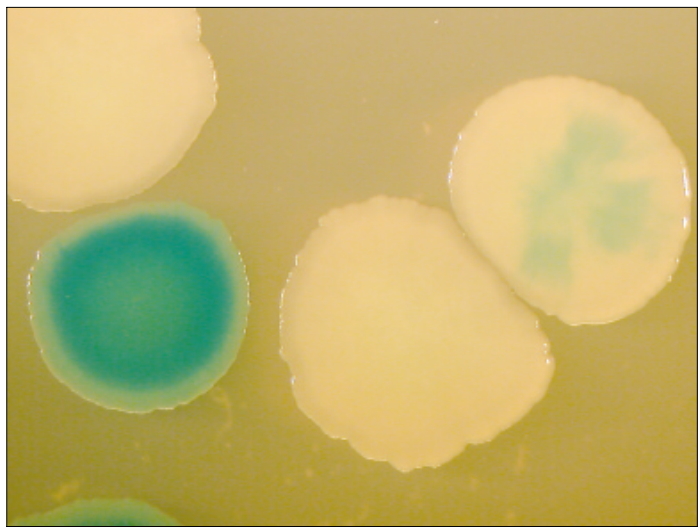
Echoes of the past

The idea that organisms can change in real time isn't altogether new. Two hundred years ago, Jean-Baptiste Lamarck suggested that individuals adapted during their lifetimes and then transmitted acquired traits to their offspring.

Virtually no one agrees with Lamarck today. In fact, "Lamarckism" is practically a slur.

But the Rice research adds to the evidence, accumulating in recent decades, that the Frenchman might not have been completely off base.

"No one thinks that a cold en-



P.J. HASTINGS, SUSAN ROSENBERG/Baylor College of Medicine

Colonies of bacteria respond to changing, stressful environments by increasing their mutation rate, boosting their genetic variety. Here, blue represents more mutations, and thus more variety. Some colonies (blue) respond to stress by radically shuffling their genes. Others (mixed white and blue) introduce a more moderate amount of variety. Some (white) don't suffer mutations at all.

vironment 'speaks' to the genes, telling them to encode more cold resistance," says Susan Rosenberg, a molecular geneticist at the Baylor College of Medicine. But at least some creatures, such as the bacteria Dr. Rosenberg studies, seem to be able to increase their ability to reorder genes as their environments change.

Such increased genetic jumbling usually doesn't work out for the best. "Most of these changes are harmful or without consequence to the organism," Dr. Rosenberg says. "But some rare changes are useful."

Still, arguing that natural selection favors this reshuffling because it sometimes leads to benefits strikes some as specious evolutionary reasoning, a la Lamarck.

The French naturalist suggested that giraffes' necks might grow ever so subtly from all the stretching and craning to reach the high, leafy branches. The idea that the animals might subsequently pass down these newly acquired longer necks to their offspring is lampooned today.

Those who cry "Lamarckism" today are engaged in a bit of name-calling, says James Shapiro, a University of Chicago microbiologist. Scientists first studied mutations, small changes to genetic material, by observing how harsh X-rays damaged DNA. This early work might have contributed to the idea that genetic change is a random phenomenon, outside a creature's control, Dr. Shapiro suggests.

Actually, "it's clear that organisms have built-in systems responsible for the vast majority of change seen in their genetic material," says Dr. Shapiro, the first person to describe sections of mobile DNA in bacteria, in the

1960s.

Further evidence

There's little doubt that this same swapping is happening in people. The Human Genome Project showed that nearly half of the human genome is mobile, made up of discrete chunks of genetic material that can plug themselves in at different places along a strand of DNA.

Part of the resistance to the notion of self-shuffling genes might be its resemblance to vitalism, the idea that some nonmaterial vital spark or energy is what animates life.

Vitalism was vanquished by science decades ago. But the idea of genes possessing some mysterious, quasi-autonomous ability to change almost smacks of vitalism, and thus may explain some of the consternation, Dr. Shapiro says.

Dr. Rosenberg points to several examples in nature of organisms that possess the ability to reorder their genetic material in response to harsh environments.

The bacteria that causes gonorrhea, another that commonly causes infections in patients with cystic fibrosis, and the tiny creature that causes sleeping sickness all seem to be especially adept at cranking up the rate of change in their genomes.

Many early evolutionists rejected the idea that change came from anything but sexual reproduction and random mutation because they couldn't find any other way to explain the variation they observed in bacteria, baboons and all other life under the sun.

"Well, nowadays," says Dr. Shapiro, "we can explain it."

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It's Mercury's turn to be target of space mission

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dio telescopes, which shoot radio waves toward Mercury and measure how they bounce off the surface. Using such telescopes in Puerto Rico, California and New Mexico, scientists have spotted odd reflections from craters near Mercury's south pole.

The reflections could indicate the presence of water ice — or sulfur, or a rocky silicate-type material, or some other unknown substance frozen in the craters since the birth of the solar system, says Dr. Sprague.

"That's a very exciting discovery, and we're hoping Messenger will be able to shed some real knowledge on that subject," she says.

Similar deposits seen on Earth's moon have triggered speculation about a possible water resource for future lunar astronauts.

With all Mercury's mysteries, it may seem strange that scientists haven't been back for so long. But there are two major problems: how to get there, and how to survive the heat once you do.

Getting to Mercury is essentially a question of cost, says Robert Farquhar, mission manager at the Johns Hopkins University Applied Physics Laboratory in Laurel, Md.

Zooming straight from Earth to Mercury, a spacecraft could get there in 3½ months, he says. But that would require carrying enough fuel to slow down the craft so that Mercury's gravitational pull could capture it directly into orbit. More fuel means a bigger launch vehicle and much greater costs.

As it stands, Messenger weighs 1,100 pounds when empty and carries 1,300 pounds of propellant — making it almost 55 percent fuel. The spacecraft will launch on a Delta 2 rocket, at a total cost of \$426 million. Had it carried enough fuel to get to Mercury directly, it would have been 85 percent fuel, says Dr. Farquhar.

But as a tradeoff, the mission won't get to Mercury until 2008 and won't start orbiting it until 2011. Messenger is designed to fly by Earth once, Venus twice and Mercury three times, with each pass acting as a gravitational brake to place the spacecraft on the proper trajectory. By the time Messenger finally enters orbit around Mercury, it will have looped around the sun more than 15 times and traveled nearly 5 billion miles.

Once there, the spacecraft will have to cope with the sun's intense heat, as temperatures vary more than 1,100 degrees from night to day in some places.

To keep its cool, Messenger is made entirely of a composite material that radiates heat away quickly. It also features a large ceramic-fiber sunshade that can get as hot as a pizza oven while keeping the electronics behind it near room temperature, says mission engineer James Leary.



BRUCE WEAVER/EPA

The Messenger spacecraft sits atop a transporter on July 14 as workers discuss its sun shield (front).

Messenger's seven scientific instruments have a wide range of tasks. A magnetometer will measure Mercury's magnetic field, attempting to determine if it is created by the sloshing motions of a liquid outer core, as Earth's magnetic field is. Cameras will photograph the surface in great detail, checking for volcanic flows, meteorite impacts and other geological signs. Other instruments will map the chemical makeup of Mercury's crust, as well as measure gases and charged particles in the atmo-

sphere.

Mission controllers hope that Messenger will spend an entire Earth year orbiting Mercury. Eventually, it will crash into the surface, taking with it a U.S. flag, says Dr. Farquhar.

Other countries may not be far behind. The European Space Agency is collaborating with Japan on a two-pronged Mercury mission called BepiColombo, which could be launched as early as 2012.

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MERCURY IN A MINUTE

Average distance from sun: 36 million miles
Size: About 3,000 miles across (a bit larger than Earth's moon)
Surface temperature: Varies from plus 850 degrees to minus 300 degrees Fahrenheit, the greatest range of any planet
Year (time taken to travel around the sun): 88 Earth days
Solar day (sunrise to sunset): 176 Earth days, making Mercury's day longer than its year
SOURCE: Encyclopedia of the Solar System

RESOURCES

- The Messenger mission's home page is <http://messenger.jhuapl.edu>
- Learn more at www.nineplanets.org/mercury.html
- *Exploring Mercury: The Iron Planet*, by Robert Strom and Ann Sprague (Springer-Verlag, 2003)

Trying to identify blood-borne boon to longevity

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clair.

Scientists have known for years that when yeast are stressed by near-starvation, the tiny organisms turn on their miniature sirtuin factories. Dr. Sinclair and collaborators recently showed that the same thing happens in flies. And last month in the journal *Science*, Dr. Sinclair and others reported that rats on reduced-calorie diets also produced more sirtuins.

Whatever turns on production of this anti-aging enzyme seems to be in the blood. Human cells in test tubes start pumping out sirtuins when exposed to blood from these slim, trim rats. Dr. Sinclair and others are working to identify the blood-borne boon to longevity.

Sirtuin factory

In the meantime, a finding published online recently in the journal *Nature* hints at a less unpleasant way to forestall aging. The paper identifies a molecule called resveratrol — serendipitously, red wine is one of the best sources — that turns on the body's sirtuin factory even when actual calorie intake is unchanged.

"It's a molecule that might allow you to have your cake and eat it, too," says Dr. Sinclair, one of the study's authors. "It works on every animal we've fed it to so far."

Seeing dollar signs, Dr. Sinclair and his former mentor, Leonard Guarente of the Massachusetts

Institute of Technology, have founded competing companies to try to reap benefits of this sirtuin-activating stuff.

The NIH's Dr. Levine says that while the news on sirtuins is exciting, it's too soon to say the enzymes are the lone substances responsible for regulating and extending life span.

"It may be that sirtuins are intimately related to other mechanisms," says Dr. Levine, whose work focuses on how protein damage may relate to aging.

Dr. Levine studies the way proteins gradually accumulate damage, especially in the last third of life. Proteins, composed of building blocks called amino acids, do everything from turning on and off important chemical reactions in the body to maintaining cellular structure. Damaged proteins don't work well or at all, leading some scientists to suspect that protein damage is associated with aging.

Methionine protection

Proteins take a pounding from a variety of compounds, but they're not defenseless. In the last decade, Dr. Levine has focused on methionine, an amino acid that seems to absorb some of this pounding and to protect crucial parts of proteins.

"It may be the sacrificial amino acid," says Dr. Levine.

The body produces an enzyme that fixes fouled-up methionines. John Tower of the University of Southern California engineered

flies to crank up their methionine repair factories and produce more of the enzyme. The flies lived twice as long, he reported in the *Proceedings of the National Academy of Sciences*.

Dr. Levine calls this result stunning.

It's also stunning, though, how difficult it is to definitively say what causes aging. Dr. Tower, for instance, compared young flies with artificially boosted protein damage to old flies that naturally accumulated a similar amount of damage. The older flies' metabolisms gradually slowed, and their immune systems seemed to be turned up full blast — two important differences from the younger, prematurely damaged flies.

Free radicals

Bacteria accumulated over a lifetime might be associated with the elevated immune activity, and perhaps with aging. "But no one knows for sure," says Dr. Tower.

Further gumming up the idea that damage to proteins causes aging is Vadim Gladyshev at the University of Nebraska, Lincoln. Dr. Gladyshev studies yeast, an organism unique for its ability to grow whether or not oxygen is present. Oxygen is an essential part of molecules known as free radicals that pummel proteins and other parts of cells.

In a recent paper in the *Proceedings of the National Academy of Sciences*, Dr. Gladyshev described how yeast grown in environments free of oxygen, and thus

without the pugilistic molecules, actually showed a decreased life span.

"At the very least, this shows that free radicals are not the universal cause of aging," he says.

Dr. Levine cautions about interpreting experiments that shorten the lives of animals used to study aging. "It's not that hard to screw things up to shorten life span," he says.

Human study not easy

Crafting an experiment that can answer with any certainty what causes aging is difficult, he says.

And it's hard to study aging directly in humans. People live so long that any sustained attempt to study one group of individuals as they get older necessarily involves coordinated work by generations of researchers.

In contrast, the genetic engineering approach to aging research yields powerful results to small teams and even individual researchers. But it is a young field that is already pockmarked with ethical land mines and scientific hurdles. Any attempt to subject humans to the genetic manipulation that has produced such promising results in yeast, flies and mice is years or decades away.

But maybe sooner, Kerry Kornfeld's decidedly low-tech and noninvasive study of worms could be tried on humans. Dr. Kornfeld, a professor at Washington University in St. Louis, monitors a variety of physical processes

for the worms — body movement, pumping of the gut and production of sex cells — and compares how they change with age.

In the gut

By measuring the decline of these processes, especially body movement and gut action, Dr. Kornfeld can accurately predict the worms' life spans. He and other collaborators published their findings recently in the *Proceedings of the National Academy of Sciences*.

"Almost certainly, yes, tests could be developed to represent degrees of degeneration in humans," says Dr. Kornfeld. But ethical questions abound, and it remains an open question whether there would be any demand, other than from life insurance companies, for tests that accurately predict how long a person might live.

Dr. Kornfeld predicts that eventually aging will be revealed to be an interconnected process that involves multiple systems in the body.

"We don't want it to be so complicated," he says. "People want it to be one hormone that diffuses through the animal and controls the entire process."

But aging, he says, may turn out to be best explained by thinking of a coordinated developmental program that takes an animal from conception to maturity and then lets it go. He compares this to NASA's development of probes to explore Mars.

NASA designs the probes to

handle every environmental challenge the engineers can imagine for a multi-month mission. But beyond this time horizon, beyond the developmental program designed in by the engineers, the probes are on their own. Eventually some unforeseen crater or dust storm, or even just battery limits, will do them in.

Still a mystery

Dr. Kornfeld believes that despite recent progress, researchers quickly bump up against the limits of their knowledge when they ponder fundamental questions about aging.

"What's life span? What's aging? Life span is the dominant measure in this field, but it's an open question whether life span is really about aging," he says. "Aging is fundamentally mysterious; it's why scientists are drawn to it to study."

Fundamental mystery does not equate with doddering and sclerotic, though. The competing and complementing theories keep the study of aging vibrant.

Dr. Sinclair says that research on aging is 50 years ahead of where he expected it to be when he began his work a decade ago. There's even a feeling among scientists, he says, that a Nobel Prize may be awaiting someone who finally cracks the molecular code that controls aging.

"I hope I live long enough to see it happen," says Dr. Sinclair.

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