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U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of General Medical Sciences

NIGMS

What is NIGMS? The National Institute of General Medical Sciences (NIGMS) supports basic research on genes, proteins and cells. It also funds studies on fundamental processes such as how cells communicate, how our bodies use energy and how we respond to medicines. The results of this research increase our understanding of life and lay the foundation for advances in the diagnosis, treatment and prevention of disease. The Institute's research training programs produce the next generation of scientists, and NIGMS has programs to increase the diversity of the biomedical and behavioral research workforce. NIGMS supported the research of most of the scientists mentioned in this booklet.

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computing life

From text messaging friends to navigating city streets with GPS technology, we're all living the computing life. But as we've upgraded from snail mail and compasses, so too have scientists.

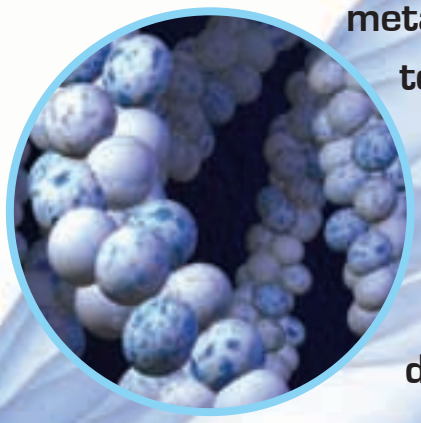
Computer advances now let researchers quickly search through DNA sequences to find gene variations that could lead to disease, simulate how flu might spread through your school and design three-dimensional animations of molecules that rival any video game.

By teaming computers and biology, scientists can answer new and old questions that could offer insights into the fundamental processes that keep us alive and make us sick.

This booklet introduces you to just some of the ways that physicists, biologists and even artists are computing life. Each section focuses on a different research problem, offers examples of current scientific projects

searching for genetic treasures

Imagine finding a treasure chest that contains all of the precious gems and metals ever mined, but you can only lift the lid far enough to see the glint of gold and the sparkle of diamonds. That's how some biologists felt not too long ago. Advances in computer technology have opened the genetic treasure chest all the way, revealing the human genome and answering questions about diseases, drug treatments and even crimes.



We share:

70% of our genes with fruit flies and

98% with chimpanzees and

99.9% with each other.

> side effects: genes and medicines

By Susan Gaidos

MEDICINES that work wonders for you can be ineffective—or even harmful—to others. Why? Age, weight, lifestyle and other medicines each play a role, but so do GENES.

Scientists use computers to find the specific genetic variations that affect the way we respond to drugs. This field of research is called pharmacogenetics, and its goal is to determine the type and dose of medicine best suited for each individual.

Geneticist Gary Peltz at Roche Palo Alto in California leads one research team working in this field. His group has looked for tiny differences that change how mice process, or metabolize, the drug warfarin.

Nearly 2 million Americans, especially those who have heart disease or are recovering from major surgery, take warfarin to prevent deadly blood clots. But warfarin is tricky to prescribe. Too much causes excessive bleeding and too little could allow clots to form. Doctors use a careful, trial-and-error approach to find the right amount for each person.

The California researchers pinpointed the gene that makes an enzyme the mice need to metabolize warfarin. Searching with computers, they then found slight variations in the gene's DNA that could influence how quickly the animals eliminated the drug from their bodies. The scientists were able to use the mice's genetic profiles to predict how the mice would process the drug. Similar studies in humans could ultimately help doctors more quickly and precisely prescribe the right dose of warfarin.

?

In 2005, the U.S. Food and Drug Administration approved a heart-failure drug specifically targeted to African Americans. Why do you think some people raised ethical concerns?

Tishkoff enlists African tribespeople in her project to understand how human genomes have responded to malaria. > Sarah Tishkoff

> answers from africa

By Alisa Zapp Machalek

Geneticist Sarah Tishkoff splits her time between her LABORATORY at the University of Pennsylvania in Philadelphia and remote parts of AFRICA.

She works with and collects DNA from people as diverse as hunter-gatherers in the jungles of central Africa; grain-growing farmers in southern Africa; and nomadic, cattle-raising warriors in eastern Africa.

By designing computer models to compare the DNA of these different populations, she hopes to track down gene variations that make some people less susceptible to malaria — one of the world's leading causes of death.

People in certain African tribes that have been exposed to malaria for thousands of years can contract the disease and survive it. These tribespeople developed genetic adaptations that gave them natural resistance to malaria, which they passed on to their descendants. Through the generations, the resistance genes have become more common in the population.

Tishkoff calls this process the "footprints of natural selection." Following the trail can lead scientists to the genetic basis of innate resistance — and possibly to future therapies — for malaria and other diseases.

So far, the trail has taken Tishkoff to data indicating that innate resistance to malaria is caused by a variant in the gene for a specific enzyme nicknamed G6PD. People with this genetic variant make less of the enzyme, which is needed for several important chemical reactions inside cells.

Up to one-quarter of the people living in malaria-infested regions of Africa have this variant. Everywhere else, fewer than 5 percent have it.

Understanding how the G6PD genetic variant protects people from malaria could eventually help treat and prevent the spread of the disease. The work, Tishkoff adds, is also helping to unravel the history of modern humans in Africa and beyond.

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> word games

If you're hooked on SUDOKU, you should try the letter game called GENETIC CODE. Here's an easy example: Put the following words in a sequence so that each one differs from the previous word by just one letter.

FAN | BIT | BAT | BAN | FUN

Now imagine working with words that contain thousands of letters. And, instead of shuffling around recognizable words, you have long, seemingly random strings of As, Ts, Gs and Cs—the letters of the DNA code.

That's what scientists face when they try to track and analyze changes within an organism's genetic material, or genome. The task may sound tough, but it's easy with the help of computers.

Scientists typically start with a collection of gene sequences from different people or organisms. These sequences could come from blood, bodily tissues or even ancient bones.

To figure out when the variations occurred, researchers use computational tools to put the gene sequences in chronological order. In this way, computers are revealing the genetic changes, combinations and quirks that create the Earth's remarkable biological diversity.—*AZM*

!

make up
your own
3-letter series, and
ask your friends
to arrange them.

The answer is: BIT, BAT, BAN, FAN, FUN.

> mutiny against antibiotics

What can dirty DIAPERS teach us about MEDICINE? That infectious bugs are cagey.

When scientists designed the first antibiotics more than 50 years ago, they called them medical marvels. The drugs cured common infections caused by bacteria in just days, slashing death rates and transforming medical care.

But through tiny genetic changes, prompted in part by our own overuse and misuse of antibiotics, super bugs now outsmart our once super drugs. Certain bacterial strains have developed resistance to antibiotics that once killed them and passed this ability to their descendants. Today, a few of these strains can even overcome every existing antibiotic.

Scientists thought that after many generations without exposure to antibiotics, the bacteria would eventually succumb to the drugs once again. Unfortunately, that doesn't seem to be the case, says Bruce Levin, a population geneticist at Emory University in Atlanta, Georgia.

Levin analyzed *E. coli* bacteria—the harmless kind in our colons—found in 70 dirty diapers from a day care center. One-quarter of the bacteria in the used diapers were resistant to streptomycin, an antibiotic rarely prescribed in the previous 30 years.

Levin's diaper discovery was buoyed by research led by Richard Lenski, a microbiologist at Michigan State University in East Lansing who trained in Levin's lab.

Since 1988, Lenski has monitored flasks of streptomycin-resistant *E. coli*. After 10 years and 20,000 bacterial generations, he flooded the bugs with streptomycin for the first time. They remained unfazed by the drug.

Levin and others have run thousands of computer simulations to come up with strategies that slow the development and spread of resistance.

!

blow
your nose.

There's a good chance that your tissue contains *Staphylococcus aureus,* or "staph" bacteria. Normally, this common bug doesn't cause sickness, but it occasionally can be life-threatening. Computer models can help identify strategies for keeping the spread of these infections at bay, especially in hospitals, where they can be the most dangerous.

Because drug-resistant bacteria will continue to plague us, Levin jokes that research on antibiotic resistance offers the perfect career opportunity. He says, "We must continually discover new ways to deal with bacterial infections. I tell students that when you graduate from school, there are plenty of things for you to do!"—*AZM*

By 2010, the Innocence Project, which offers legal assistance to people who claim they've been wrongfully accused, says that DNA fingerprinting had led to the freeing of more than 240 people.

> csd: crime scene dna

In 1995, a Louisiana nurse accused her ex-boyfriend, a doctor, of attempted MURDER. She claimed he gave her the AIDS virus by injecting her with blood from an HIV-positive patient. Lawyers from both sides recruited scientists to analyze viral DNA from the nurse.

To prove its case, the prosecution had to convince the jury that the virus from the nurse and the virus from the patient were close relatives. So, scientists dusted for DNA fingerprints!

The investigative team, led by computational biologist David Hillis at the University of Texas at Austin and virologist Michael Metzker at Baylor College of Medicine in Houston, Texas, used a technique called DNA fingerprinting to compare the DNA sequences from the two viral samples. The team also used a number of different computer programs to piece together how the viral sequences most likely changed between the alleged injection in 1994 and the trial in 1998.

The results showed that certain genetic sequences from the nurse's virus were identical to those of the patient's virus. The doctor was convicted of attempted second-degree murder and sentenced to 50 years in prison. Lawyers appealed his case all the way up to the U.S. Supreme Court, which let the conviction stand in 2002.

The case marks the first time that such genetic analysis, called phylogenetics, was used as evidence in a U.S. criminal court.—*AZM*

Computational biologists helped prove that a doctor tried to murder his ex-girlfriend using a syringe filled with the AIDS virus.

? who do you think is guilty?

Evidence from a crime scene leads police to five suspects. Compare DNA from the perpetrator's blood left at the crime scene with the suspects' DNA below.

DNA sequence from perpetrator's blood found at the crime scene:
AGGCTGCCTACGCGGTTAGG

DNA sequences from suspects:
#1 AGGATGGCTACCCGGTTAGG
#2 AGGCTGCCTCAGCGGATAGG
#3 AGGCTGCCTACGCGGTTAGG
#4 CGGCAGCCTACTCGGTTAGG
#5 AGGCTGGATACGCGGCTAGG

In the Louisiana murder trial, scientists compared more than 2,000 letters of HIV from about 30 people. Computers did most of the work!

The answer is: #3.

the next top protein model

From building muscles to healing wounds, our bodies rely on proteins—chains of small molecules called amino acids that fold into unique shapes. Incorrectly folded proteins can cause disorders like sickle cell disease or cystic fibrosis. Ever-improving computer power is making it easier for researchers to predict how proteins fold and interact with other molecules, possibly leading to new treatments for protein-related disorders.

> tailor-made proteins

By Emily Carlson

Scientists can easily determine a protein's amino acid sequence, but they can't reliably PREDICT how this sequence will fold into a three-dimensional STRUCTURE.

So computational biologist David Baker at the University of Washington in Seattle took a different approach. He started by sketching a protein structure that nobody had ever seen. Next, he relied on a computer modeling program he developed called Rosetta to tell him what amino acid sequence would form the three-dimensional shape of his made-up molecule. Baker used that sequence to build an actual protein that was stable and quite similar in structure to the one he had drawn, validating his approach.

With the ability to whip up new proteins, Baker's research may make it possible to customize proteins that could be used as drugs or tiny biological machines to treat certain diseases.

Baker used his computer program to design a small protein not found in nature. > Brian Kuhlman, Gautam Dantas, David Baker

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> modeling@home

In high school, Johnathon Tinsley had MIXED feelings about MATH and SCIENCE. "Math was very challenging," he recalls. "I enjoyed some parts of biology, but not physics."

This British teenager helped search for cures for diseases like AIDS and Alzheimer's just by letting researchers use his computer when he wasn't. You can get involved, too!

Tinsley is part of a tech trend called distributed computing that relies on the public to help advance health and medicine. Through this approach, researchers harness the power of personal computers to answer important questions about biology. The typical computers in a scientist's lab can't perform all of the required number crunching, but a network of hundreds and even thousands of personal computers can.

WARNING!
Before you download distributed computing software onto a public computer, like the ones at school or work, ask if it's OK. If you don't, you could get into serious trouble!

How It Works

You join a distributed computing network by downloading free software.

When your computer isn't busy, it sends a message to a server in the researcher's lab basically saying, "Hey, I'm available. Can I help?" The server assigns a chunk of a large calculation that it knows the home computer can solve.

The donated computer may spend several days working out the problem. When it's done, it hands in the answer. Just like teachers, people in the lab check the result, also making sure that no one has tampered with the information.

You can volunteer your computer, whatever the make or model. The computer must be connected to the Internet—the type of connection doesn't matter. Older computers can do the job, although they generally get simpler calculations. You can also choose how much computer memory you want to donate.

You don't need to worry about hackers breaking into your computer system. Security checks protecting the main servers and the limited capabilities of the required software make participating in the projects considerably safer than surfing the Internet.

If you visit the Web sites of distributed computing projects, you'll likely find computerese. Here's a brief glossary.

DC	Distributed computing
@home	Most likely a distributed computing project
Credit	Points received for solving a calculation
Work Unit	Problem sent to a donated computer
BOINC	The Berkeley Open Infrastructure for Network Computing, or the free software program used by many DC projects
PC	Personal computer
Server	Computer that sends information to other computers in a network

Wanna Volunteer?
Folding@Home: http://folding.stanford.edu
Rosetta@home: http://boinc.bakerlab.org/rosetta
FightAIDS@Home: http://fightaidsathome.scripps.edu

While you're sleeping, your computer could be doing scientific research.

Distributed Computing in Action

"The science we can do is unmatched by what we could do with any other available tools," says Vijay Pande, a scientist at Stanford University in California who started a distributed computing project called Folding@Home.

Pande studies the dynamics of how proteins fold into their unique shapes. By studying how they fold, Pande can see what goes wrong and how drugs might patch misfolded proteins.

Proteins fold much faster than you can fold a shirt. The quickest one is done in just 5 millionths of a second.

Pande says that it would take a very fast desktop computer more than a thousand years to completely simulate the process! But with the help of nearly 250,000 personal computers and more than 1 million PlayStation® 3 gaming consoles, Pande can do the job in less than a week.

Tinsley donated about 40 hours of processing time every day between his two computers. He liked knowing that his computers were doing something useful. Tinsley says, "They're not just sitting there like stuffed lemons"—British slang for being idle.

For his distributed computing projects, Tinsley tracked how much work his computer contributed compared to others'. If his computer helped predict a protein structure, he saw his name on the project's Web site and maybe even published in a scientific journal. Some projects also would award special certificates.

"Seeing the impact makes a big difference," says Pande. "When you donate to many charities, you don't see a direct link between what you give and how it's used. For us, you can actually see what your computer has donated and the results."

Serving science, though, is not the only benefit. Distributing computing also offers its participants an active social network. Many projects have message boards where donors can post questions about the science or random thoughts about life.

Donors who really want to be ranked at the top often will form competitive teams.

"I like competing to get my stats above my team members'," says Tinsley. But he also has enjoyed the social aspect. For one team, he explains, "The main aim is to meet and talk with friends and do something good and worthwhile while we're at it."—*EC*

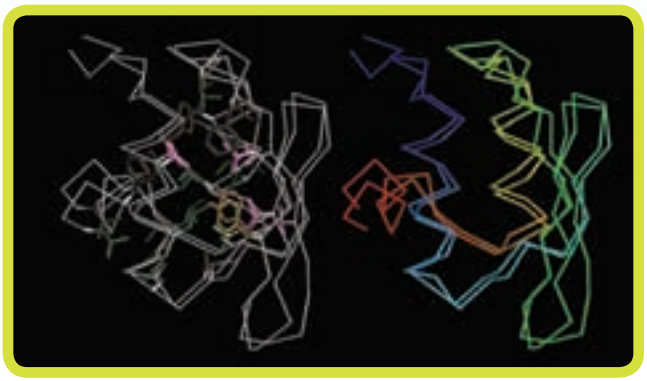
Scientists often are rewarded for making big breakthroughs, with the Nobel Prize being the ultimate honor. Read about the winner of a high school science competition on page 18.

> project structure

Most people enjoy a little friendly COMPETITION, and protein structure prediction researchers are no exception. Every other year, these experts go head-to-head to see whose computer MODELS make the best predictions.

The goal is to most accurately model the shapes of pre-selected proteins. The contestants don't know the actual structures of these molecules, but the judges do. After reviewing the entries, the judges invite the most successful modelers to an international meeting where they talk about the approaches they used. The entire group discusses how all can do an even better job in the future.

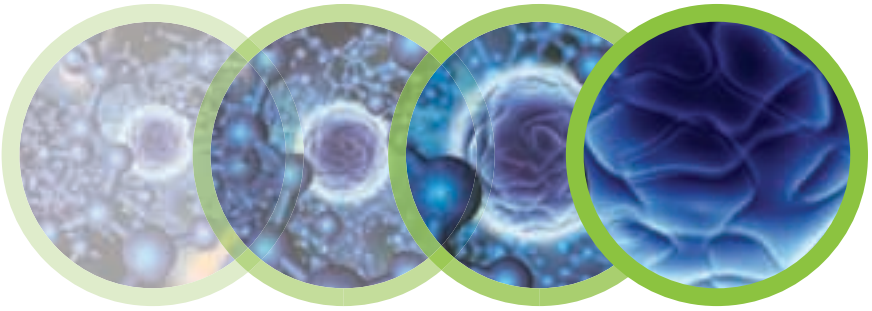
The scientists don't actually call the event a "contest" or even a "competition." It's a "community-wide experiment" to improve the accuracy of protein prediction modeling so researchers can discover new drugs more quickly and cheaply.—*EC*



The computer model generated by David Baker's team for the 2004 community-wide experiment (left) was strikingly similar to the protein's actual structure (right). > Philip Bradley, David Baker

movie mania

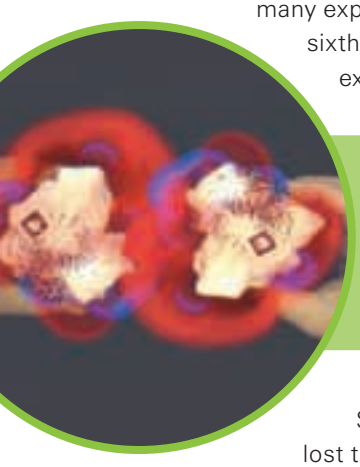
Just as sound and color revolutionized the film industry, computer technology has changed the way scientists view biology. Researchers today not only can take snapshots of biology, they can animate entire biological processes, thrusting viewers deep into never-before-seen worlds.



> scientists develop sixth sense

Thanks to a HIGH-TECH tool, scientists just regained their "SIXTH SENSE."

Before you think of a certain flick starring Bruce Willis, think about feeling your muscles flex as you push a box across carpet or plunging forward as your car suddenly stops. These physical responses to external cues are what many experts consider the sixth type of sensory experience.



A scientist manipulates plastic models of two proteins while the computer tracks and displays their electrostatic properties, shown here as **red** and **blue** clouds. > Arthur Olson

Some scientists lost this sense in the computer age. They no longer used physical models of biological molecules, like proteins or DNA, to see how they fit together. Instead, they used computer-generated models.

"Many scientists stopped working with physical models altogether," says Arthur Olson, a structural molecular biologist. "The nature of spatial perception changes and the kind of understanding you get from interacting with your surroundings were lost when computer graphics took over."

Olson and his team at the Scripps Research Institute in La Jolla, California, have developed a tool that allows them to do both: physically manipulate a model of a biological molecule while watching its chemical and biophysical properties change on a computer screen. Olson says combining the two experiences will let researchers approach and understand biological problems in new ways.

The scientists use special printers that generate plastic or plaster 3-D shapes as easily as other printers produce 2-D pictures. As Olson and others hold and interact with the models, a camera records a close-up shot of the models in motion. A computer program then superimposes graphics, like the arrangement of atoms or the energy between modeled molecules.

Olson combines the model and computer graphics into one image that allows him to study all the different facets of the biological molecule. Olson hopes that one day his interface could double as a video game that lets students explore and play at the molecular level. —*EC*

! pick up

a nearby object.

Rotate it so you see all its sides. Does it feel heavy? What about cold? Smooth? How would you determine these qualities if you only saw the object on a computer screen?

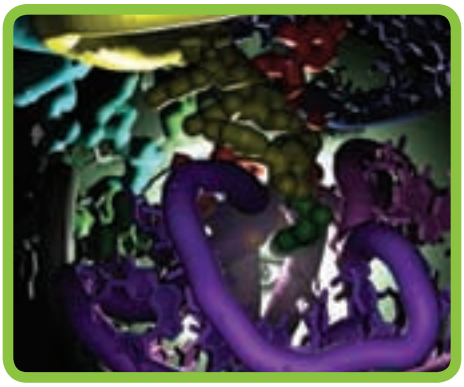
> now playing on a computer near you

By David Bochner

Superman is super strong, super fast and generally super fly. But in a COMIC book, he's also super FLAT, leaving many of his superhero feats up to your imagination. But when the comic book turns cinematic, Superman truly comes ALIVE.

Sometimes scientists only get to see the comic book view of biology: Experimental data gives researchers just snapshots of what a biological process looks like at a specific time. So, computational biologist Kevin Sanbonmatsu at the Los Alamos National Laboratory in New Mexico is bringing those processes to life.

Sanbonmatsu uses high-performance computers to create movies of a tiny molecular machine present in every living organism. This machine—called the ribosome—builds proteins from the genetic instructions encoded in DNA.



The ribosome plays itself in this molecular movie, now appearing on the *Computing Life* Web site. > Kevin Sanbonmatsu

Interested in understanding the origin of life, Sanbonmatsu says he studies the ribosome because "it may be the oldest artifact in the cell."

But there's more to it than curiosity. Sanbonmatsu also says that about half of all antibiotics used to treat bacterial infections target the ribosome, meaning that a better understanding of this biological machine could lead to super-strong drugs.

To make his movies, Sanbonmatsu starts with experimental data, like the structure of a ribosome in a particular instance, and generates a storyboard of sorts. Hundreds of connected computer processors—or a supercomputer—then turn the snapshots into an entire movie filled with information scientists couldn't otherwise see or even imagine.

"You can look at static structures of the ribosome," says Sanbonmatsu, "but the only way to watch it in motion is the supercomputer simulation."

His team has created one of the largest biological simulations ever, bringing new life to characters in the old story of protein synthesis.

> the art of animation

By Karin Jegalian

Amid a network of BLOOD vessels and star-shaped support cells, neurons in the BRAIN signal each other. The mists of COLOR show the flow of important molecules, such as glucose, oxygen and nitric oxide.

An artist's rendering of how chemicals change and move among cells in the brain. Watch the animation on the *Computing Life* Web site. > Kim Hager

This image is a snapshot from a 52-second simulation created by Kim Hager, an animation artist working with the Laboratory of Neuro Imaging at the University of California, Los Angeles. The animation, which portrays how chemicals change and move among cells in the brain, took about 300 hours to create. To put it all together, Hager worked closely with Neal Prakash, a neurobiologist in the same lab. Prakash initially asked for a drawing to illustrate a research paper, but the director of the lab suggested producing an animation instead.

Hager, who studied photography, video and graphic design in college and later earned a graduate degree in media arts, does not draw movies frame-by-frame. Instead, she builds "virtual sculptures" filled with color, light, texture and motion and then guides the viewer's eye through the scenes.

The lab features this animation, along with dozens of others, on its Web site and also plays it in a state-of-the-art theater during presentations for scientists, students and other visitors.

Hager says her role is to make the research more accessible to different audiences. "Seeing an animation," she explains, "makes it easier to comprehend what a researcher is saying."

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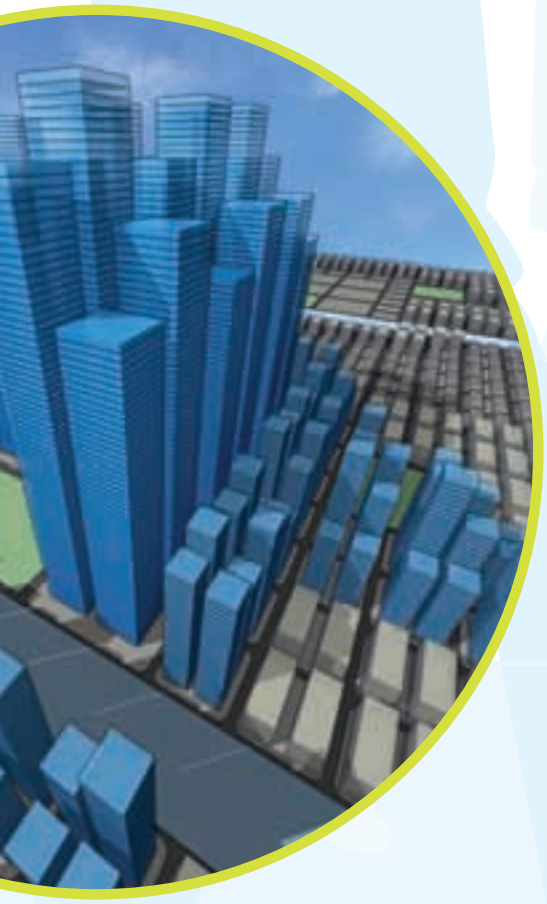
sim sickness

Scientists are creating their own virtual worlds where people live and work—and get sick. Here, researchers can mimic viruses and predict the spread of contagious diseases through a community. Successful simulations can help us better prepare for real-life outbreaks.



> preparing for a pandemic

Just months after the first cases of SWINE FLU appeared in April 2009, millions of Americans had gotten sick and some had even died. By the end of the year, the virus had spread worldwide, creating the first influenza PANDEMIC since 1968.

As drug companies produced a vaccine that prevented millions more from catching this flu, researchers participating in an international project called MIDAS were simulating disease spread. The simulations let them explore how the pandemic might unfold, who was more likely to get sick and which interventions might protect the most people. The results helped inform public policy decisions.

MIDAS, not to be confused with the king who turned everything to gold, stands for Models of Infectious Disease Agent Study.

Flu and You

To create the pandemic flu simulations, the MIDAS researchers use computer models to build virtual cities, countries and even continents. Here, thousands of pretend people go to school, work, stores and other places. The researchers base the residents' activities on information about actual people like you.

Stephen Eubank, a physicist at Virginia Tech University in Blacksburg and part of the MIDAS team, has modeled virtual versions of major U.S. metropolitan areas using local transportation and census data. In Eubank's cities, there really are six (or fewer) degrees of separation between any two people—making it easy for germs to spread.

"Viruses don't care much about geography," says Eubank. "They care about social networks and how people come into contact with each other."

? **How would your simulated life be different from your best friend's?**

Virtual Viruses

Another key part of studying the spread of infection with computers involves developing a virtual version of the germ. To model its spread as realistically as possible, the researchers track down everything known about the infectious agent. Eubank, who has studied plague, smallpox and anthrax, has gathered information on how each agent spreads between people, how contagious it is and how long it takes for an infected person to show symptoms.

When they don't know the actual characteristics of an infectious disease, the MIDAS researchers use health reports and scientific data collected during earlier outbreaks to estimate what a future one might be like.

During graduate school, Christina Mills modeled a pandemic flu before we had ever heard of swine flu (also called H1N1). She did a lot of her research in the library, scouring the shelves for scientific articles that discussed the 1918 Spanish flu—a pandemic that killed between 20 and 40 million people worldwide.

"It was very old-fashioned," says Mills, who was studying international health at Harvard Medical School in Boston, Massachusetts. "I couldn't just type a search word into Google™ and get the necessary information." The hunt eventually led her to the 1918 transmission rates.

Asking Questions

With all the modeling pieces in place, the MIDAS researchers invite policymakers to ask questions that can be answered using the models. Questions range from *What happens if we don't do anything?* to *How many people could be protected if we intervene?*

The researchers create different simulations that change the variables, like the contagiousness of the virus or the number of people taking "snow days"—Eubank's term for people who voluntarily hang out at home to avoid infection.

"What's so great about the computer simulations is that you can try out different situations that you can't create in real societies," says Eubank.

With more than 250 possible combinations to simulate, Eubank says he relies on statisticians to help him determine which arrangements will produce the most informative results.

"It's easy to come up with questions," says Mills. "The hard part is figuring out which ones we should—and could—answer."

? **What questions would you want to ask the models?**

Because of the amount of data and calculations involved, the simulations run on high-performance computers that can simulate a 180-day outbreak in a matter of hours. Eubank uses software programs to take snapshots of the pretend pandemic as it occurs.

"I know exactly when a virtual person gets infected, shows symptoms and recovers," says Eubank, explaining that the computer records every change in disease state.

>>>

Meet the Simulators

Stephen Eubank started out studying high-energy physics but then got into modeling the dynamics of nonlinear systems, which are systems that can't be solved by adding up all of the parts. He has developed computational models to study natural languages, traffic patterns and financial markets. He plans to use the infectious disease models to study how behaviors, like smoking, spread through society.

Christina Mills has a Sc.D. (like a Ph.D.) and an M.D. For her, modeling infectious diseases is a dream job because it combines her interests in math, biology and human health. While most of her colleagues with double degrees practice "bench-to-bedside" research in which they translate lab findings into patient care, Mills says she'll stick with the "computers-to-clinics" approach.

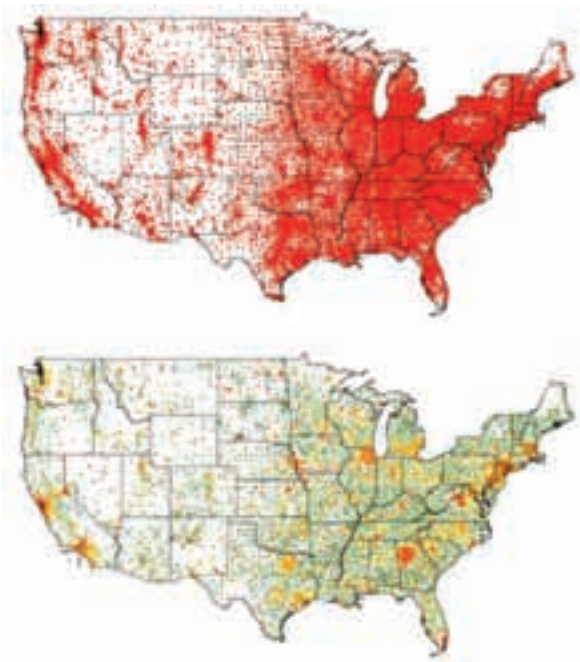
create a timeline

of what you did yesterday. List all the people (even if you don't know their names) you came into contact with. If you were contagious with the seasonal flu, how many of these people do you think you would have infected? The answer is surprisingly low. Estimates suggest that you'd pass the virus to no more than three people. But if more than one other person catches it from you, the bug will continue to spread.

Flu Forecast

Eubank and other researchers modeling the 2009 H1N1 pandemic flu simulated outbreak scenarios in communities across the United States. The results suggested that early vaccination of school kids best reduced disease spread, while vaccinating elders became more important later on. The simulations also indicated that people at risk for serious complications—like pregnant women or individuals with pre-existing health problems—should be given antiviral medicines to take at the first signs of illness.

While the results generated by the simulations are useful, Eubank stresses that they're not a guarantee of what actually will happen. He and others often will ask different models the same questions and, when the models agree, they'll have more confidence in the predictions.—*EC*



In 2006, MIDAS modelers mapped the potential spread of pandemic flu in the United States. Each dot changes from green to red as more people in that area get sick. The top map shows what could happen if we didn't do anything. The bottom map shows the effect of giving people a less effective vaccine while a better one is being developed. > *Proceedings of the National Academy of Sciences*

Watch this pandemic flu spread on the *Computing Life* Web site.

web exclusives @ http://publications.nigms.nih.gov/computinglife/simsickness.htm

> the rise & fall of deadly dengue

By Alison Davis

If you live in the United States and don't travel ABROAD, chances are you'll never come down with DENGUE fever. That's not the case for people living in tropical and subtropical climates, like South America, Africa and the Caribbean.

Between 50 and 100 million of these people catch the mosquito-transmitted dengue virus every year. Most of them will bounce back after 2 weeks of rest and extra fluids. A small percentage, however, won't be so lucky. After contracting dengue a second time, some people may develop a potentially fatal dengue hemorrhagic fever.

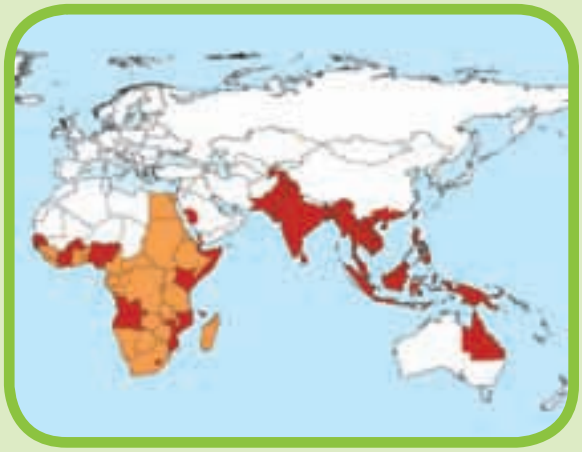
Scientists suspected that the human immune system might be to blame for making the second infection more dangerous, but until recently they weren't sure how.

Using computer simulations, epidemiologists at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, learned that the infected person's antibodies—proteins that should fight off dengue—actually help the virus copy itself. More copies make the virus a better predator, allowing it to spread faster and infect more people.

But the researchers—Derek Cummings and Donald Burke, who is now at the University of Pittsburgh in Pennsylvania—also learned that the virus actually causes its own demise. Like a hungry wolf pack that clears out the local deer population, the virus eventually starves itself. Infecting too many people reduces its "food" supply.

This work is just one example of how researchers can develop models to answer questions about outbreaks of dengue or other diseases. With a mathematically based model, ecologist Pejman Rohani at the University of Georgia in Atlanta examined 30 years of epidemiological data from Thailand, a hot spot for dengue. He learned that environmental factors, like warmer temperatures, can re-route mosquito flyways and in turn change dengue infection rates.

Dengue is common in Haiti, and survivors of the massive earthquake that devastated the country's capital in 2010 faced a greater risk of infection due to standing water and contaminated sanitation systems.



This map from 2007 shows areas infested with the mosquito that carries the dengue virus (orange) and areas with both the mosquito and dengue epidemic activity (red). > Centers for Disease Control and Prevention

integrating biology

Identifying all the parts of a cell or organism won't necessarily tell you how those parts work together to make the system run. To do this, scientists have turned to a relatively new field called systems biology that combines experimental data and computational models to diagram everything from how cells move to how hearts beat. With the diagrams, the researchers can tinker with different parts and begin to explore questions nearly impossible to answer through traditional lab experiments.

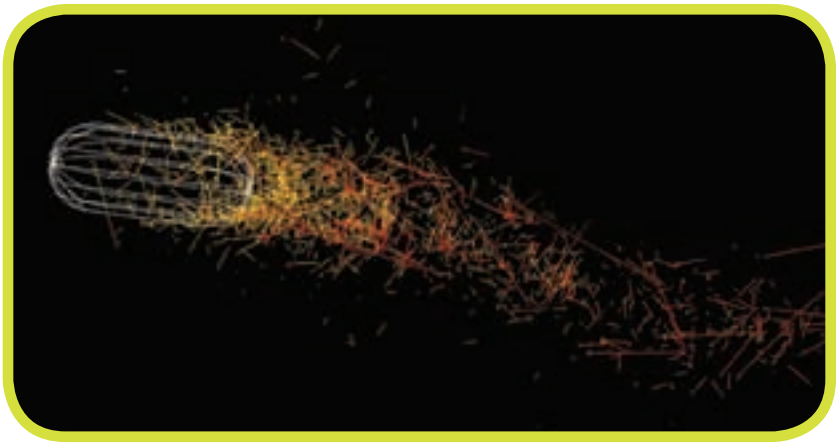
> bacteria blast off

Ten, nine, eight, seven, six, five, four, three, two, one . . . BLAST OFF!

While this object might look like a rocket blasting through space, it's really a fake bacterium jetting around a virtual cell. It represents *Listeria*, a type of bacteria best known for causing food poisoning.

Computational biologist Jonathan Alberts and mathematical biologist Garrett Odell at the University of Washington's Center for Cell Dynamics in Friday Harbor created it to study how the bacterium moves around the cells it infects, ultimately making you sick to your stomach.

By combining experimental data with computer-based approaches, Alberts and Odell have created virtual models of *Listeria* that show it moving through time. This more complete picture may enable the researchers to identify new ways to prevent food-borne illnesses.—*AD*



In this computer model, a *Listeria* bacterium propels itself through an infected cell by stimulating the growth of cellular filaments (yellow and red) at the cell's surface. > Jonathan Alberts, Susanne Rafelski, Garrett Odell

web exclusives @ http://publications.nigms.nih.gov/computinglife/integratingbiology.htm

> connected worlds

For scientists, the INTERNET is more than an information superhighway and AIRPORTS aren't just places where planes take off and land. They are examples of complex NETWORKS that can help researchers study even more complicated ones in the body.

Networks, whether social or cellular, share a number of features. Each one is a system made up of different elements that connect through important centers of activity called hubs. Hubs could be Web pages linked to many other sites or major airports that route passengers to additional cities. Communication occurs within the network, letting it organize itself and even change over time.

Any network can serve as a model for understanding another because all these systems operate by a similar set of rules, says physicist Luis Amaral at Northwestern University in Evanston, Illinois.

Amaral models the networks of the Internet and air travel, but he also maps metabolic networks — the intricate pathways by which cells generate the energy needed to carry out biological processes spanning the production of proteins to the breakdown of drugs. He creates simple computational models that show how the paths of these complicated networks connect and communicate.

Knowing all the details about the body's networks may help scientists learn to re-wire them to prevent certain diseases, just like air traffic controllers re-route planes to avoid thunderstorms. — *AD*

Each spot on this globe represents a city, and each color corresponds to a community of easily connected cities. > Luis A.N. Amaral, Roger Guimerà

This sphere represents all the known chemical reactions in the *E. coli* bacterium. > Luis A.N. Amaral

? **Did you know that some cells form ladders so other cells can climb up them?**

> on the move

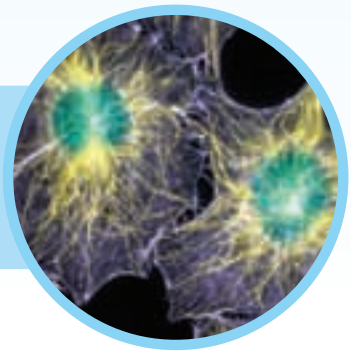
Like us, CELLS rely on transportation to do their daily activities. But while we can choose to take cars, busses, bikes and even Segways®, cells take the pedestrian approach: They MOVE themselves.

A cell moves by grabbing onto something, like the wall of a blood vessel, and then pulling itself forward. This mobility is an essential part of wound healing. When you cut yourself, your white blood cells speed to the wound like paramedics.

But cellular movement can also cause health problems, like when cancer cells spread to other parts of the body.

Scientists want to understand how cells move so they can develop new drugs that can rev up or stop cell migration altogether. But like most biological processes, cell movement hasn't been easy to figure out because it involves hundreds of proteins.

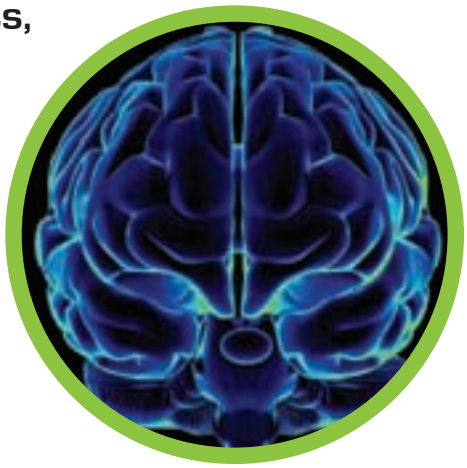
Cell biologist Clare Waterman-Storer at the National Institutes of Health in Bethesda, Maryland, takes a systems biology approach to studying cell movement. She uses mathematical equations and computer software to piece together the various components that make cells motor along. — *AD*



This image, taken with a microscope-camera, shows the intricate network of fibers that builds a cell's structure. These fibers are called microtubules (**yellow**) and actin filaments (**blue**). > Clare Waterman-Storer

made possible by...

You've learned a lot about how computing power gives us new perspectives on biology. At the center of it all is a component more advanced than any silicon chip inside a computer processor. It's the human brain. Biologists, engineers, physicists, computer scientists, epidemiologists, geneticists and even writers and artists have brought their brainpower to the table to solve these old and new problems.



> time for computation

By Jilliene Mitchell

Going from Mom's or Dad's savory home cooking to the CAMPUS cafeteria's "mystery meat" can be a big adjustment for any COLLEGE freshman. But for Ryan Harrison, a BIOMEDICAL engineering and economics major at Johns Hopkins University in Baltimore, Maryland, it wasn't a big deal.

While most of his high school friends took it easy their last year to fully enjoy "senioritis," Harrison spent his downtime at Hopkins, where he worked in the chemical and biomolecular engineering lab of professor Jeff Gray. Harrison got the chance through his high school, which offers a program that pairs students with researchers.

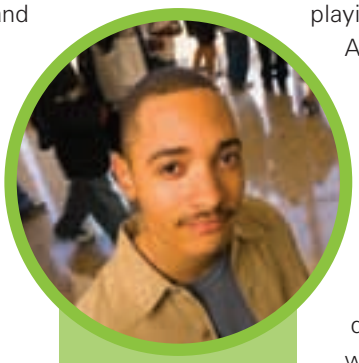
Harrison had been writing his own computer programs since the 4th grade. So when his high school biology teacher introduced him to Gray, everything fell into place. "He was into computational biology and we immediately hit it off!" says Harrison.

While in the Gray lab, Harrison improved the Rosetta computer program that predicts how proteins fold and attach to other biological molecules.

By the time he graduated from high school, Harrison had presented his research to scientists older than his parents and received numerous awards, including a top prize in the 2005 Intel Science Talent Search—the nation's oldest and most prestigious high school science competition.

After graduation, Harrison returned to Hopkins and the Gray lab. Even with a full college course load, he still found time to work on Rosetta.

Don't be fooled, though. Just because he was an award-winning researcher at age 17 doesn't mean he's a whiz at everything! When he started losing the battle in a high-level algebra course, he says he knew it was time to visit the math help room, where students could work with tutors. The effort paid off. Harrison finished the class with a B-, which, considering how tough the class was, he says felt more like an A+.



Harrison in high school, when many scientists mistook him for a college or graduate student!

> Stephen Spartana

"I study a lot," admits Harrison. "But I still make time to do things that I enjoy."

Among his hobbies: directing a one-act play, experimenting with light and sound for student theater productions and playing his favorite computer game.

And he taught disadvantaged kids in Baltimore how to play chess, explaining that it was also good practice for him.

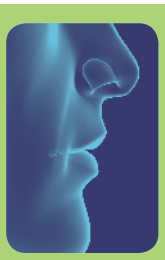
With so many interests, one of Harrison's biggest challenges in college was finding time for all of his activities—and deciding what he ultimately wanted to do professionally. As he wrote in his online diary (see excerpts on the next page), "I have more questions now about my future than ever before. But, I guess that's … a normal part of growing up."

> excerpts from an internship

Ryan Harrison spent his first SUMMER off from college in New York City, where he did a 10-week INTERNSHIP at Weill Medical College of Cornell University.

Instead of working in a computer lab, he worked in a "wet lab," complete with live organisms, chemicals and petri dishes. He studied how a particular protein affects the life cycle of the parasite that causes malaria.

Harrison wrote about his summer experience in his blog, "Verdant Force: Discoveries in Life and Proteomics."



BLOG

NAME: Ryan Harrison

Thursday 8:37pm

"I've been in New York City for almost a month now. Settling in well to my new lab environment and even forgetting that I'm in NYC occasionally. . . . Wish I could work a little more independently, but I understand that I just don't have the proper laboratory background/experience to handle my own independent project. I guess I was expecting a Gray lab type arrangement—where I work at my own pace at a problem I selected and I am the only one responsible for the outcome (good or bad). . . . Whatever I decide to do, I think it will combine computational with "wet lab" work. Since I haven't the slightest idea how my life is going to unfold, I am just going to do what I enjoy."

To find out what Harrison is doing now, visit this story on the Computing Life *Web site.*

> programming biology

Drew Endy likes taking things APART and putting them back together—bikes, cars, lawn mowers. He essentially does the same thing when he tries to understand BIOLOGY. A professor at Stanford University in Palo Alto, California, Endy assembles and PROGRAMS living machines. I asked him a few questions about his work and why he likes it.—*DB*

Q *What got you interested in science?*

A I'm curious. It bothers me when I don't understand how things work.

Q *You're trained as an engineer. How does that influence your approach to biology?*

A If you ask engineers what they want to do in their heart, they want to make something. My interest is to be able to routinely, reliably, quickly, easily and cheaply put together the bits and pieces of biology to make new and useful things.

Q *You're in a new field called synthetic biology. What's the goal of this field?*

A It's to make routine the engineering—the programming—of living organisms.

Q *Why do you want to do this?*

A I started to think about why it's been so hard to understand biology. The conclusion I've come to is that the biological systems we find in nature aren't easy to understand. I figure that if I want to have biology that I understand, I'd be better off building it myself.

Q *What makes the field so hot right now?*

A Seventy years ago, physicists came into biology and really shook things up. I suspect that what's happening now is that the engineers are coming into biology, and they're going to shake things up.

>>>

With the help of a Hollywood illustrator and others, Endy created a comic book called *Adventures in Synthetic Biology*. He hopes to use it as a teaching tool. To read the entire comic, visit this story online. > Drew Endy

Q *Describe your typical day.*

A I feel like I'm an enzyme, helping stuff happen. I teach courses on synthetic biology, and I supervise the research in my lab. Every now and then I get a little bit of time to think.

Q *What have you thought about lately?*

A Are we discovering biology faster or slower than nature is inventing new biology? I did some back-of-the-envelope calculations, and this number could be completely wrong, but sometime between the year 2085 and 2105 we should be able to sequence all the DNA on the planet in a month.

Q *What do you like most about your job?*

A The people in research are some of the coolest, [most] interesting [and] nicest people you're ever going to meet. It's just a great experience.

Q *What do you think makes for a successful scientist?*

A The best, most fun-loving, happy scientists I've seen are the people who recognize when an idea isn't working and abandon it for a better idea without feeling too bad.

Q *Do you think you'll always be a scientist?*

A I'm doing what I want to be doing, and if I wasn't, I would change it. If at some point in the future, I'd rather be raising pheasants in southern France, or northern France, or wherever they raise pheasants in France, I presume I would go do that. Of course, I'd have to learn French.

Q *Last words?*

A People express great wonderment, excitement and almost a magical relationship with the living world. But I think over the coming years—faster than most expect—we'll see a transition in biology where it becomes much simpler and easier to engineer living systems. We don't actually know how to do that right now, but there are lessons buried in the lore and wisdom of other engineering disciplines.

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"When I was in high school, I never thought there was a field that combined all my interests."

—Christina Mills, a scientist who uses modeling to study infectious diseases

> think you want to compute life?

People with many different talents can join in COMPUTING LIFE. If you're interested, ask yourself what aspects of the research featured here you find EXCITING. Do the projects blend many of your academic interests? Are there particular biological problems you'd like to solve?

Here are a few tips on how to get started looking into COMPUTING LIFE as a career.

> Ask your science teacher or guidance counselor about opportunities to work with a researcher at a nearby college or other institution.

> Search the Web for scientists working at the crossroads of biology and computation.

> E-mail scientists at your local college or university for more information.

> Enter a science fair to get experience presenting research results.

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