

Findings

JANUARY 2012



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...with geneticist
Elizabeth Grice

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of a Human Cell

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

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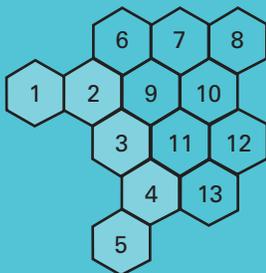
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Up Close With

Elizabeth Grice

GENETICIST

"I didn't know what I wanted to do until relatively recently. I just stuck to what I enjoy doing."

FIRST JOB

Detasseling corn

FAVORITE FOOD

Chocolate

PETS

Two adopted shelter cats,
Dolce and Gabbana

FAVORITE CITY

Athens, Greece

HIDDEN TALENT

Baking creative desserts

BILL BRANSON/INI



The Clone Zone

Body Bacteria

Exploring the Skin's Microbial Metropolis

BY ALLISON MACLACHLAN

Imagine a landscape with peaks and valleys, folds and niches, cool, dry zones and hot, wet ones. Every inch is swarming with diverse communities, but there are no cities, no buildings, no fields and no forests.

You've probably thought little about the inhabitants, but you see their environment every day. It's your largest organ—your skin.

"The skin is like our shell. That's what people see of us first," says Elizabeth Grice, who just finished a postdoctoral fellowship in genetics at the National Institutes of Health (NIH) in Bethesda, Maryland. "It's a defining feature, but it's also an important organ for human health."

Our skin is home to about a trillion microscopic organisms like bacteria and fungi. Together, these creatures and their genetic material—their genomes—make up the microbiome of human skin.

Grice studies the skin microbiome to learn how and why bacteria colonize particular places on the body. Already, she's found that the bacterial communities on healthy skin are different from those on diseased skin.

She hopes her work will point to ways of treating certain skin diseases, especially chronic wounds.

"I like to think that I am making discoveries that will impact the way medicine is practiced," she says.

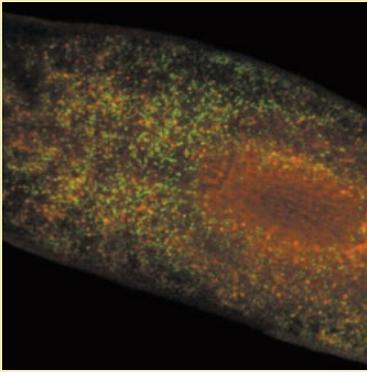
Entering the Field

Growing up in Wisconsin and Iowa, Grice was exposed to biology at a young age—but in a field, not a laboratory.

"My first job was detasseling corn," she remembers. Pulling the tassel, or pollen-producing flowers, off the tops of corn plants is a way to breed high-yield hybrid corn with specific traits.



NIH, NUSANSO, NIH



PHILIP NIEWIAROK

At less than an inch in length, a flatworm called a planarian can regrow its entire body from just a section of tissue. In this image from under a microscope, fluorescent dyes show which cells in the worm have copied their DNA and are ready to split in two.

Making Heads or Tails of Regeneration

A small flatworm called a planarian possesses an extraordinary ability: It can regenerate its entire body from a tiny slice of tissue. Scientists in Massachusetts have discovered how the worm makes heads or tails of what body part to regrow from a wound site.

The process involves a gene called *notum* and a genetic pathway called *Wnt*. Researchers led by Peter Reddien at the Whitehead Institute for Biomedical Research in Cambridge discovered that *Wnt* stops a wounded planarian from sprouting a head. But with *Wnt* around, how do heads ever form?

The scientists found that, if a wound is near the top half of the worm, *Wnt* activates *notum*. The *notum* gene appears to keep *Wnt* in check, dialing down the pathway's activity so a head can form.

In back-end wounds, the researchers noted that *notum* is less active, allowing tails to grow.

Both *notum* and *Wnt* are found in organisms ranging from fruit flies to humans. Could it play a role in repairing—or even regrowing—tissue in these other animals?

Only science can tell.

—Allison MacLachlan



Bacteria aren't all bad.

Summer days in the fields were hot and taxing. “That was when I realized I didn’t want to do manual labor,” Grice laughs.

When Grice was in middle school, her mother went back to college for a bachelor’s degree in biology. Reading off flashcards to help her mom study sparked Grice’s own interest in science.

In high school, Grice trained to become a certified nursing assistant and worked in a nursing home. Then she enrolled at Luther College in Decorah, Iowa for a bachelor’s degree in biology, with dreams of being a doctor.

When biology professor Marian Kaehler announced a summer research opportunity for seasoned students, Grice—a freshman with no lab experience—knocked on Kaehler’s door 10 minutes later and asked for the job.

“She was determined, enthusiastic and confident, and we decided to try it,” Kaehler remembers. “It worked out extraordinarily well.”

Grice studied plant genetics in Kaehler’s lab throughout college. She found the environment, with its experiments and challenges, a more comfortable fit than a career focused on seeing patients—or summers breeding corn.

Several research internships later, Grice earned a Ph.D. in human genetics and molecular biology from the Johns Hopkins School of Medicine before coming to NIH to tackle bacterial genomics.

The Good, the Bad and the Acne

When you use antibacterial hand soap or take antibiotics, it’s easy to think of bacteria as bad guys. After all, *Salmonella* and *E. coli* can give you food poisoning, and *Staphylococcus aureus* (*S. aureus*) can cause pneumonia, meningitis or serious wound infections.

But bacteria aren’t all bad. Many are harmless, and some are actually very helpful. On the skin, *Staphylococcus epidermidis* protects us by taking up



The bacterium that causes acne protects our skin by crowding out other, more dangerous bacteria.

Some are actually very helpful.

space that the harmful *S. aureus* would otherwise colonize.

The common skin bacterium that causes acne works the same way. "It's occupying a niche so that other, more potentially harmful bacteria don't invade," Grice explains.

It might sound unhealthy or even dangerous to have skin that's teeming with bacterial colonies. But as Grice points out, it's completely ordinary.

Your skin was sterile only once in your life—when you were in the womb. Minutes after you were born, bacteria began to colonize it. Your body relies on some of these bacteria as part of its first line of defense.

Many bacteria on the skin defend themselves by secreting antimicrobial peptides, or small proteins that kill harmful invaders. In protecting themselves, they also protect us.

Diverse Settlements

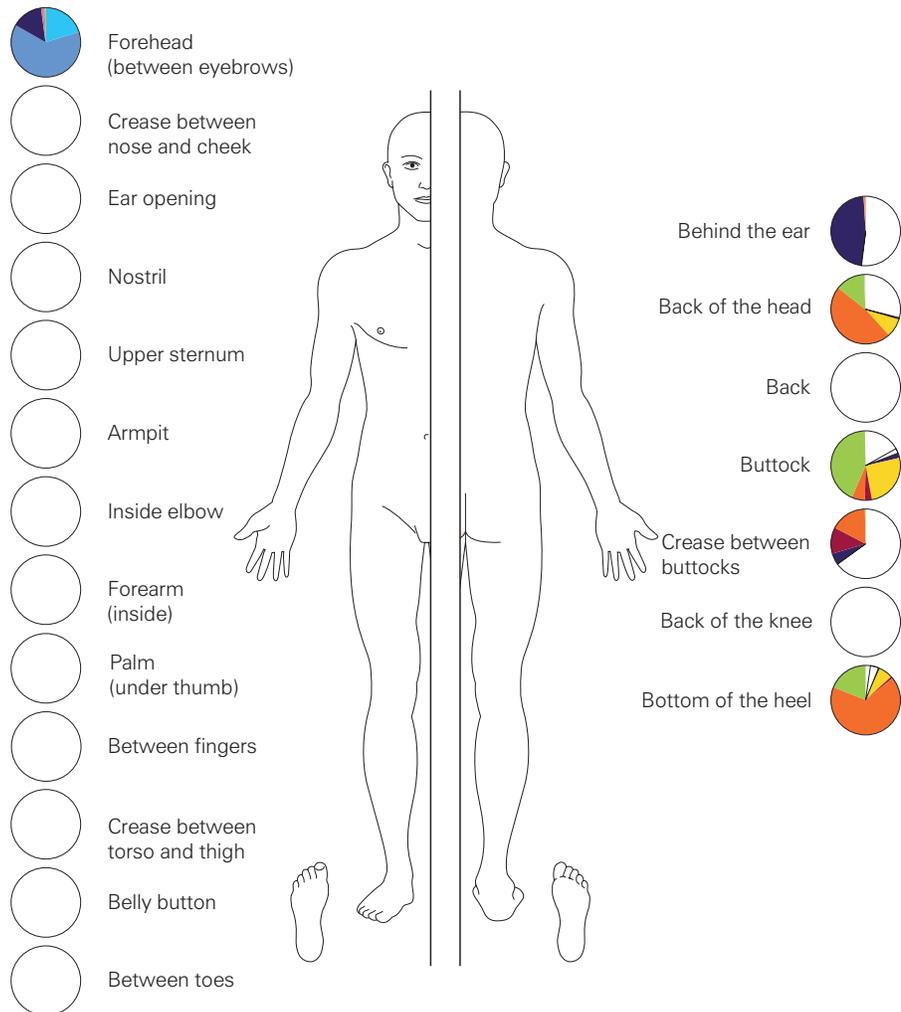
Like plants, bacteria don't all fare well in the same environment. Some are better suited to moist, humid folds like the armpit or navel. Others colonize dry expanses like the forearm or oily nooks like the side of the nostril.

Grice has surveyed the microbial landscape of human skin like a topographer charts a territory and an anthropologist studies its populations.

From a study of 20 different skin sites on a group of healthy people's bodies, Grice and her colleagues identified three types of environments: moist, dry and sebaceous (oily). Then they investigated which types of bacteria colonize what sites.

Scientists have traditionally studied skin bacteria by smearing a sample of them onto a layer of nutrient-rich gel in a Petri dish.

But 99 percent of the microbes won't grow on laboratory plates, because



Types of Bacteria		
Actinobacteria	<input type="checkbox"/> Bacteroidetes	<input type="checkbox"/> Proteobacteria
<input type="checkbox"/> Corynebacteriaceae	<input type="checkbox"/> Cyanobacteria	<input type="checkbox"/> Bacterial types contributing <1%
<input type="checkbox"/> Propionibacteriaceae	Firmicutes	<input type="checkbox"/> Unclassified
<input type="checkbox"/> Micrococciaceae	<input checked="" type="checkbox"/> Staphylococcaceae	
<input type="checkbox"/> Other Actinobacteria	<input type="checkbox"/> Other Firmicutes	

Our bodies are teeming with bacteria. Some bacterial families colonize in warm, moist places like between the toes, while others prefer dry, open spaces like the buttocks.

ADAPTED WITH PERMISSION FROM MACMILLAN PUBLISHERS LTD: NATURE REVIEWS MICROBIOLOGY 9:244-53, COPYRIGHT 2011

they need to interact with other members of the skin's bacterial community to survive. It's also tough to replicate the exact nutrients and environment the skin provides.

Grice calls this "the great plate count anomaly"—bacteria that grow well

in the lab aren't necessarily major players on the skin.

Grice employed a newer technique that uses a gene called 16S rRNA.

story continues on page 6



Bacterial diversity is probably a good thing,

continued from page 5

This gene provides the code for part of a bacterial ribosome, the essential machinery needed to make proteins.

The 16S rRNA gene is present in every known bacterium, but in each one, it has a slightly different DNA sequence. Scientists can use the sequence of this gene to classify the bacteria.

The Petri dish method has uncovered 10 different types of skin bacteria. The method Grice used revealed more than a thousand. Her study was the first to use the technique for such a large survey of human skin.

She found that moist areas tend to host similar bacterial communities in all of her volunteers. The same holds for dry and sebaceous areas. Each skin environment determines its bacterial inhabitants just as an outdoor environment determines its plant life—rainforests support leafy trees, while deserts have cacti.

Even with these patterns, the skin still has a surprising amount of variation from person to person.

Skin microbiomes are like snowflakes: No two are exactly alike. Your unique pattern depends on things like your age, sex, sun exposure, diet, hygiene and even where you live and work.

Microbes in Medicine

By getting a sense of bacteria on healthy skin, Grice hopes to figure out what's different about the microbes on diseased skin—and maybe even find a way to fix the problem.

She's most excited about applying her work to the chronic wounds that are common in people who have diabetes or spend most of their time in beds or wheelchairs.

People with diabetes can lose some of the sensation in their limbs, making it harder for them to feel pain and easier for any of their injuries to fester.

On top of that, they may have poor blood flow, which makes healing tough.

As Grice explains, your body needs blood to deliver oxygen, immune cells and important proteins to the site of an injury to help cells regenerate.

A Problem Afoot

Almost 10 percent of the United States population has diabetes, and up to a quarter of these 24 million people will get a painful wound known as a diabetic foot ulcer.

These ulcers are very difficult and expensive to treat. And the problem is increasing: As obesity rates rise, diabetes—and diabetic foot ulcers—are becoming more common.

"It's such a far-reaching problem that it's clearly an area of need," says Grice. "That's what really drives me the most."

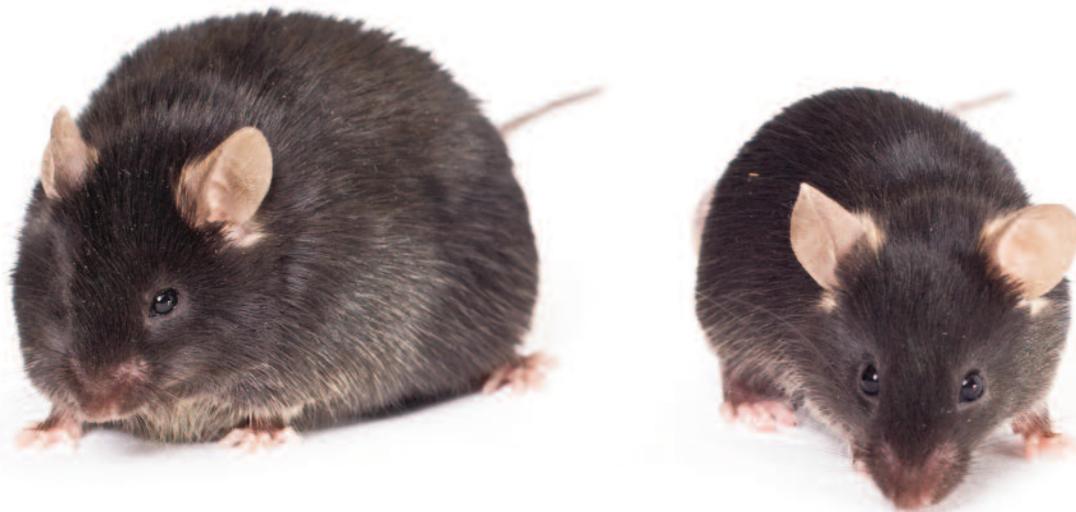
Grice suspects that bacteria make chronic wounds worse because they spur the human immune system to trigger inflammation. Although designed to kill infected cells, inflammation also prevents skin cells from regenerating after an injury.

The immune system acts slightly differently in each of us, thanks to our genetics. Grice's work takes a micro-level look at interactions among human genes, the immune system and the skin's bacterial communities.

Defense Mechanisms

To investigate what role bacteria play in diabetic wounds, Grice used a group of laboratory mice bred to display common features of diabetes—like wounds that don't heal well.

Grice and her colleagues took skin swabs from both diabetic and healthy mice, and then compared the two. Using the 16S rRNA technique, they found that diabetic mice had about 40 times more bacteria on their skin, but it was concentrated into few species. A more diverse array of bacteria colonized the skin of healthy mice.



THE JACKSON LABORATORY

especially in wounds...

"People with diabetes have high blood sugar, which is known to change the skin's structure," says Grice. "These changes likely encourage a specific subset of bacteria to grow."

The researchers then gave each mouse a small wound and spent 28 days swabbing the sites to collect bacteria and observing how the skin healed.

They found that wounds on diabetic mice started to increase in size at the same time as wounds on healthy mice began to heal.

In about 2 weeks, most healthy mice looked as good as new. But most diabetic mouse wounds had barely healed even after a month.

Interestingly, bacterial communities in the wounds became more diverse in both groups of mice as they healed—although the wounds on diabetic mice still had less diversity than the ones on healthy mice.

"Bacterial diversity is probably a good thing, especially in wounds," says Grice. "Often, potentially infectious bacteria are found on normal skin and are kept in check by the diversity of bacteria surrounding them."

Then Grice and her colleagues examined differences between healthy and diabetic mice at the genetic level. They focused on the genes that control aspects of the immune system in the skin.

They found distinctly different patterns of gene activity between the two groups of mice. As a result, the diabetic mice put out a longer-lasting immune response, including inflamed skin. Scientists believe prolonged inflammation might slow the healing process.

Grice's team suspects that one of the main types of bacteria found on diabetic wounds, *Staphylococcus*,

story continues on page 8

Belly Button Bacteria

Your belly button is way more exciting than you probably ever imagined. To bacteria, that is.

The belly button is a good place to look for bacteria because its warm, moist environment is protected, for the most part, from soap and scrubbing.

Some surprising results are coming out of the Belly Button Biodiversity project (<http://www.yourwildlife.org/bellybutton-biodiversity/>). This effort, which focuses on identifying bacteria in the human navel, is part of a broader survey of the life around us called Your Wild Life.

The belly button diversity research team was led by Rob Dunn and Jiri Hulcr at North Carolina State University in Raleigh. They found that swab samples from about a hundred volunteers' belly buttons contained an unexpected 1,400 different strains of bacteria! And that's in a part of the body that Grice found to have the *least* bacterial diversity! (See "Body Bacteria: Exploring the Skin's Microbial Metropolis," page 2.)

To identify the different strains, researchers relied on the same basic technique that Grice used—they looked for variations in the 16S rRNA gene.

They grouped together any bacteria whose 16S gene sequences differed by 3 percent or less. The researchers know 1,400 is an underestimate, because their technique doesn't separate every single strain. For instance, if the technique were used with mammals, dogs and cats would be grouped in the same category.

The biologists were stumped when it came to classifying about half of the strains, because there are no categories for them yet.

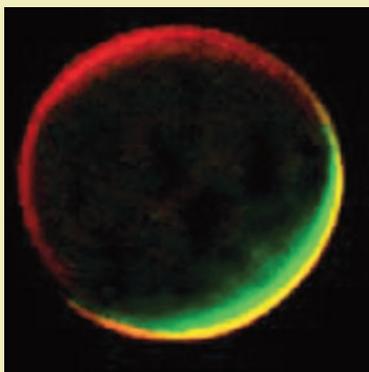
In other words, researchers say, these bacterial strains are about as new to science as African rhinos and elephants were to early European explorers.

Interestingly, 80 percent of the crowd is made up of about 40 main bacterial players.

So, the scientists wonder, are these main players protecting us from other, harmful members of the crowd? Or are they just better suited to survive in a moist environment?

We'll have to wait and see what else the Belly Button Biodiversity project uncovers. Until then, you've got a good excuse to go navel gazing. —A.M.





NEHA KAMAT, UNIVERSITY OF PENNSYLVANIA

The stressed region of this polymersome is evident (in green) before the membrane ruptures.

Microscopic Mood Rings

Scientists have designed tiny, glowing capsules that shine in stressful situations—literally. A team led by Daniel Hammer and Ivan Dmochowski at the University of Pennsylvania in Philadelphia engineered polymersomes, membrane-encased spheres only a few microns in diameter. The polymersomes act as miniscule mood rings, changing color in response to stresses like heat, membrane-disrupting chemicals and the mechanical stress of being sucked into a glass tube.

Here's how it works: The polymersomes are studded with natural light-emitting pigments called porphyrins that change shape when exposed to environmental stress. For porphyrins, a shape change means a change in the wavelengths of light they emit—their color. The new color reveals when and where the membrane is stressed.

The scientists suggest lots of potential applications. Polymersomes could be injected into the bloodstream to provide clues about nearby stresses, such as arterial blockages. They might carry a medicine into the body and reveal its release over time. They could even be used in body-scanning technology that would rely on light rather than radiation. —A.M.



Skin isn't the only place in the

continued from page 7

makes one of the inflammation-causing genes more active.

Now that they know more about the bacteria that thrive on diabetic wounds, Grice and her colleagues are a step closer to looking at whether they could reorganize these colonies to help the wounds heal.

More Than Skin Deep

Skin isn't the only place in the body that's crawling with bacteria.

Grice also spends time studying bacteria that live in the intestines. There too, microbes can be helpful.

Certain strains of *E. coli* in our digestive tracts help keep dangerous bacteria at bay and produce K- and B-complex vitamins, which our bodies can't make enough of on their own.

Grice is involved with a study of Hirschsprung disease, a genetic disorder that leaves parts of the digestive tract without enough nerve endings to push wastes out.

Some children born with the disease get enterocolitis, a painful inflammation in the gut, and others don't. Together with geneticist Bill Pavan, who also works at NIH, Grice is looking at gut bacteria to see if their distribution differs between the two groups.

If the researchers find a pattern, it might help predict which patients will need surgery to reduce inflammation. Grice and Pavan also think that redistributing some of the bacteria in inflamed intestines might help.

Pavan admires Grice's confidence and dedication to her science, and he also says that working with her is a lot of fun.

"She is driven to get high-quality research done, but she's still extremely friendly and interactive on a personal level," he says. "She has an infectious laugh."

Pavan said Grice is well known for whipping up impressive treats like miniature chocolate mice, which are very popular in the lab. And whenever a lab-mate has a birthday, Grice brings in a custom-baked cake with whatever flavor and frosting the person wants.

"Most people wouldn't suspect that I'm very domestic," says Grice, who lists cooking as one of her hobbies. "You get to a point where you're comfortable experimenting with recipes and seeing what works."

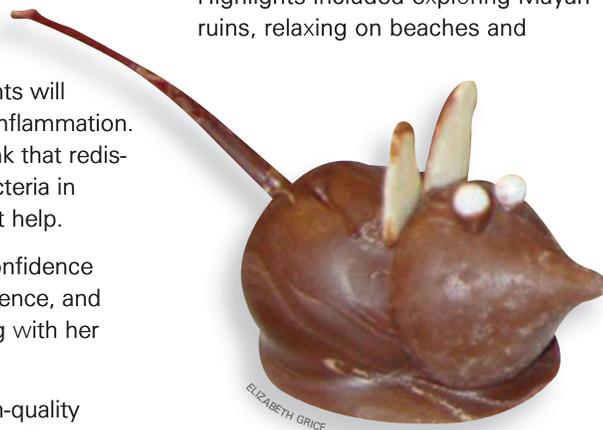
Grice likes getting creative with her experiments in the kitchen as well as in the lab. "My husband doesn't really eat vegetables, so it's always a challenge to work around that," she laughs.

Taking Exploration Global

For Grice, exploring diverse landscapes and populations goes far beyond skin samples. Outside of her work, she enjoys traveling to exotic locations to soak up the culture.

She and her husband were married in Belize, a country they chose for its natural beauty and its preserved culture. "It's one of those places that you feel isn't overrun by civilization," she says.

Highlights included exploring Mayan ruins, relaxing on beaches and



Grice enjoys cooking, baking and creating playful sweets like these chocolate mice.

body that's crawling with bacteria.



Grice loves to experience the natural beauty and local culture in countries like Belize, Greece and Costa Rica.

snorkeling in the striking coral reefs off the coast.

Grice also counts Greece among her favorite destinations because of its architecture and the laid-back Mediterranean attitude. "I love Athens and all the old ruins that are just integrated into the city," she says.

When she's home, Grice likes to explore other cultures and civilizations by reading. A self-professed bookworm, her favorite genre is historical fiction, including novels about the Tudor period in Britain.

Tying her hobbies to her career choice is easy for Grice. "I really like experiencing different cultures, and science is so multicultural—you get to interact with a diverse group of people," she says.

Charting New Ground

During the preparation of this article, Grice was considering job offers for a faculty position. She decided to join the University of Pennsylvania's

dermatology department and will start working there in January 2012.

In her new job, she will continue her research on the wound microbiome and teach graduate and medical students.

She hopes that she, like her longtime mentor Marian Kaehler, will inspire and challenge her students.

"She was just so tough, and I really respected that," Grice says of Kaehler.

"Having a female mentor was also really important to me, because otherwise, how do you picture yourself in that role?"

Even now that she's landed that role, Grice's ambition isn't flagging. She aims to sustain a successful research program, improve the way chronic wounds are managed and keep time for personal goals like traveling to new continents.

Kaehler, for one, is confident that Grice will succeed. "She has a very strong sense of self, and there's nothing more important for people making career decisions than knowing where you're going to find a niche that makes you satisfied and challenged," she says.

Like the bacteria she studies, Grice knows where she thrives. ● ● ●

FIND MORE @

See a video of Grice explaining her research at <http://www.scivee.tv/node/10037>

To read about other geneticists, select "Genetics" in the "By Topic" search on <http://publications.nigms.nih.gov/findings>

For a story about another scientist who studies wound healing, go to <http://publications.nigms.nih.gov/findings/sept07/healing.html>



Drakes: A Mythological Model Organism

By *Rahkendra Ice*

Ever watched a teenager play a video game? The trance-like concentration. The long, frustrating hours spent puzzling over the same level. The determination to sit in the same spot all day, without eating or sleeping—whatever it takes to win. If you watch long enough, you'll see that the teen isn't just playing the game anymore but has become the game.

Captivated by the story, the players insert themselves into the game and live vicariously through the characters—saving villagers, fighting invading aliens and slaying evil dragons! I would know. I was one of them.

Science educators are now taking advantage of this “gaming effect” to teach biology in high schools. With the aid of Web-based programs that use dragons, high school students are learning about complex concepts and gaining an appreciation for how science is really done—all while having fun.

And guess what? The dragons get to be the good guys for once.

You may be wondering: Of all the creatures that scientists use to study biology, why pick dragons? The answer is more straightforward than you might guess. Scientist-developers of the game were most familiar with the mouse genome, but knew it was too complicated for students to work with. So, they tossed out 99 percent of the genetic information and used the remaining 1 percent to create a simpler model organism called a drake. In the game, drakes are used to help figure out the diseases of dragons in a way that's similar to how scientists use mice to understand human genetic diseases. The drakes weigh about 50 grams and breed four times each year, always producing a brood of 20.



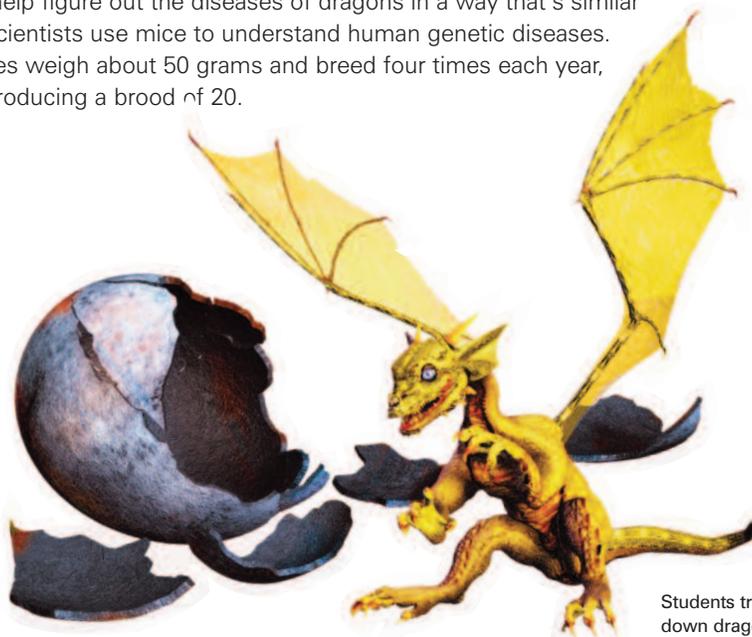
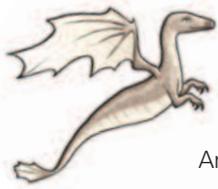
As with many games, the goal for players is to advance to the next level. To do that, they must solve the species' genetic problems.

One of the games, GenetIF, is the work of Randy Smith, director of educational programs and educational coordinator for a systems biology center at the Jackson Laboratory in Bar Harbor, Maine.

In this interactive fiction game, which is played mostly in specialized or magnet high schools, students work at a drake research facility. They have three biological challenges to solve: identifying eye color (which is based on human blood types), scale color (which is modeled after mouse coat color) and disease genes (which are modeled after a metabolic condition called PKU). To study up, the students must visit the drake library.

“The game is based on real biology with a narrative thread that interests and excites students in science,” says Smith, adding that the tools the students use in the game are the same ones used by actual postdocs.

Geniverse, a collaborative project led by the Concord Consortium and directed by Frieda Reichsman, tests the usefulness of this dragon theme to teach genetics in ordinary classroom environments. The Geniverse storyline follows a similar concept as GenetIF but uses more traditional gaming techniques. In this game, students begin as trainees in a “Drake Breeders' Guild” and must



Students try to breed a rare golden drake (a scaled-down dragon) in the online video game Geniverse. As they advance in the game, they learn principles that underlie real-world genetics.

solve genetic challenges to work their way up to becoming masters. They're also on a quest to breed the legendary "gold drake," a species that hasn't been seen for centuries.

As the game levels advance, so too does the players' genetic mastery. At each level, students are presented with the 20-drake brood and must use concepts from genetics to either predict traits or trace them back to the parents.

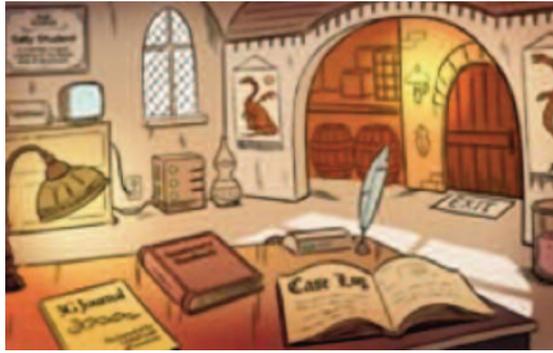
In the beginning, the students learn about dominant and recessive genes in a hands-on way by changing one gene allele and then observing the physical effect, such as a lack of horns.

Later, complex phenomena like incomplete dominance, where more than one allele is physically expressed, come into play. The master level focuses on the four genes involved in drake scale color (also based on real-life mouse coat color) that may lead to the fabled gold beast.

For future versions of the games, some players (and even scientists) have suggested giving dragons back their fire-breath. But, staying true to the premise of the game, Smith asks, "What's the real underlying biological trait?" (If we think of any, we should let him know.)

Sharing findings and backing them up with evidence are important components of both games. The students' colleagues (read: classmates) can then support or refute the claims. This encourages reading, writing and record-keeping skills, which Smith says teachers stressed the need for.

Speaking as a gamer, using these programs to teach genetics and the scientific process seems like both a novel and obvious concept.



CONCORD CONSORTIUM

Enter into the world of Geniverse. This illustration and all the others in the Geniverse game were drawn by Stephanie Dziezyk, a student at the University of Maine in Orono, who is studying studio art with a minor in zoology.

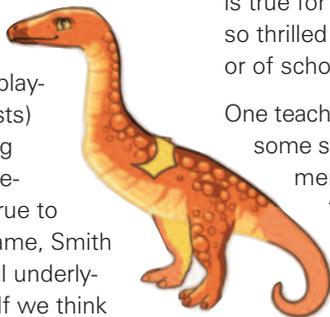
Science is more than numbers and formulas—it's about exploration and learning.

Reichsman says that changing the context of science from didactic to interactive relieves the academic pressure some students feel to just get the right answer. In doing so, it frees the students to actually learn instead of memorize. The same is true for students who may not be so thrilled by the thought of science or of school, for that matter.

One teacher credited the games for some students' academic improvement and told Reichsman:

"Three of my top kids in the class right now were kids [who] had pretty much been failing. They were understanding this [game] and coming up with explanations."

The students, who described themselves as gamers—not geeks—said that the game gave them something to work with. Now, thanks to programs like GenetIF and Geniverse, they may one day be scientists. ●



FIND MORE @

Learn more about the dragon games by watching this video <http://publications.nigms.nih.gov/multimedia/video/dragons-captions.html>

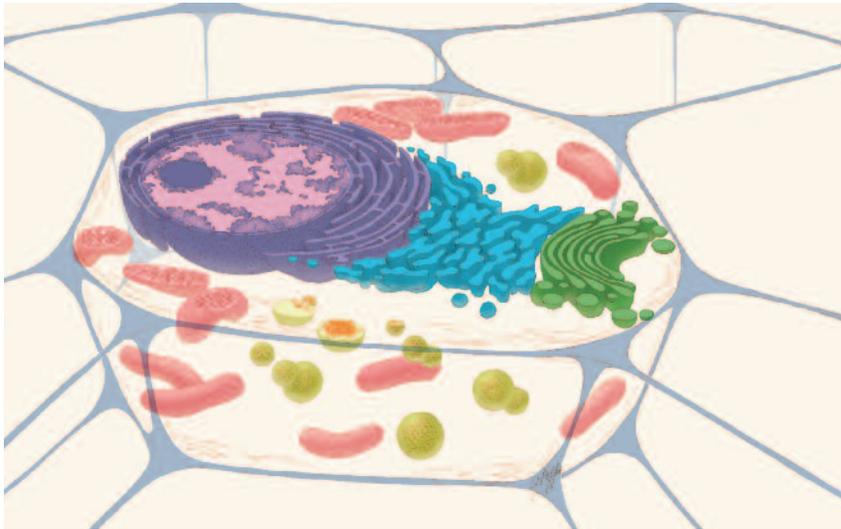
Check out Geniverse at <http://www.concord.org/projects/geniverse> (the game works best with Chrome browser)

A version of this story and other articles about the use of computers in biology are available at <http://publications.nigms.nih.gov/computinglife>



The Amazing World Inside a Human Cell

By Alisa Zapp Machalek and Emily Carlson



A typical animal cell, sliced open to reveal cross-sections of organelles.

JUDITH STOFFER

As you read these words, electricity is zinging through your brain, voracious killers are coursing through your veins and corrosive chemicals bubble from your head to your toes. In fact, your entire body is like an electric company, chemical factory, transportation grid, communications network, detoxification facility, hospital and battlefield all rolled into one. The workers that drive these activities are your cells.

Our bodies contain trillions of cells, organized into more than 200 major types. At any given time, each cell is doing thousands of routine jobs, like creating and using energy, manufacturing proteins and responding to environmental cues. Different cell types also have special duties, like building skin or bone, pumping out hormones or making antibodies.

Let's take a quick trip inside to see how cells carry out their major tasks.

Imagine you've shrunk down to 3 millionths of your normal size and are now about 0.5 micrometers (0.00002 inches) tall—way smaller than a dust mite or the width of a hair strand. At this scale, a medium-sized human cell looks as big as a football field.

Nucleus

From your new perspective, the cell's somewhat spherical nucleus catches your attention. It looks about 15 meters (50 feet) wide. Occupying up to 10 percent of the cell's interior, the nucleus is the most prominent organelle, or cellular compartment. It contains the cell's genetic material, DNA, which guides the making of billions of protein molecules that participate in nearly every cellular process.

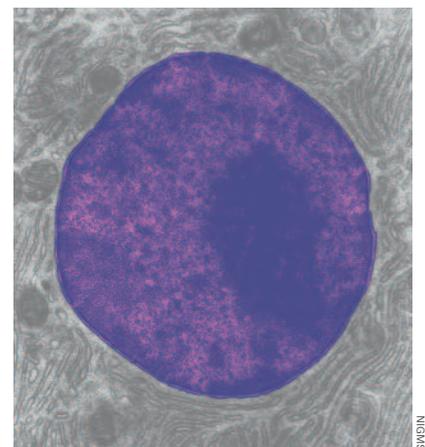
Membranes

Encasing the cell is a membrane with special gates, channels and pumps that let in or force out selected molecules. The membrane protects the cell's internal environment—a thick brew called the cytosol made of salts, nutrients and proteins that accounts for about half the cell's volume (organelles make up the rest). In addition to the outer membrane, which is made up of proteins and lipids (fats), the cells of humans and other higher organisms have a pair of porous membranes that envelop the nucleus. Each organelle also has an outer membrane.

Endoplasmic Reticulum and Partners

Next to the nucleus are enormous, interconnected sacs called the endoplasmic reticulum or ER. From your shrunken view, each sac is only a few inches across, but they can extend to lengths of 30 meters (100 feet) or more. The sacs come in two types: a "rough" version covered with protein-making ribosomes and a "smooth" version that makes lipids and breaks down toxic molecules.

The ER sends newly made proteins and lipids to the Golgi complex, a short and narrow structure inside the cytosol. The Golgi complex



The nucleus contains the cell's DNA.

BYRON



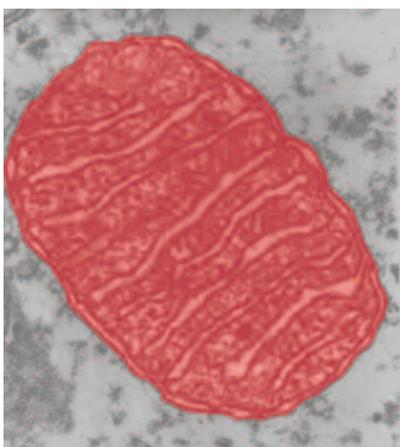
The nucleus (far left) connects to the ribosome-studded rough endoplasmic reticulum (purple) which manufactures proteins. The smooth endoplasmic reticulum (blue) makes lipids. The Golgi complex (green) puts the finishing touches on proteins and lipids and routes them to their assigned destinations.

JUDITH STOFFER

processes them and sends the molecules to their final destinations inside or outside the cell.

Mitochondria

About the size of pickup trucks from where you're floating, the organelles called mitochondria convert energy from your food into adenosine triphosphate, or ATP, to power biochemical reactions. A typical cell burns through 1 billion molecules of ATP every 1 to 2 minutes.



D.S. FRIEND, BRIGHAM AND WOMEN'S HOSPITAL

Mitochondria convert molecules from your food into cellular energy called ATP.

Like all other organelles, mitochondria are enclosed in an outer membrane. But they also have an inner membrane that's actually four or five times larger than the outer one. The inner membrane doubles over in many places so it can fit, extending long, fingerlike folds into the center of the organelle. These folds vastly increase the surface area for ATP production.

40,000-Foot View

Back in the human-sized world, many scientists are studying these cellular structures—and many others not listed here—because knowledge about them underpins our understanding of health and disease. For instance, recent research suggests why the nucleolus (a cellular compartment found in a range of species) is crucial for proper cell division, and how a special arrangement of microtubules (cellular highways that transport raw materials) may help nerve cells rebuild after injury. ●

FIND MORE @

Read more about cells in the booklet *Inside the Cell* at <http://publications.nigms.nih.gov/insidethecell>

Find out how researchers see and study cells, organelles and individual molecules at http://publications.nigms.nih.gov/insidelifescience/visualize_invisible.html



Solving the Sleeping Sickness 'Mystery'

By Emily Carlson

Since before the 1300s, people living in many parts of Africa have been dying from a disease known as sleeping sickness. Despite public health campaigns that explain ways to stop infection—primarily by killing the disease-spreading tsetse fly—successful eradication has remained out of reach. That's partly because epidemiologists can't predict where cases will emerge next.

"It's in places where people thought it shouldn't be, and it's not in places where they're sure it should be," says Joseph Messina, a geographer at Michigan State University in East Lansing.

Now, Messina's effort to map future tsetse fly distribution may help solve this sleeping sickness "mystery."

No Ordinary Bug

The tsetse fly isn't like most insects. For instance, it has a very low reproductive rate, laying a single live pupa in the soil just a few times each year. The flies travel so fast that they can dart into a moving car to bite someone. The good news is that they're also very dependent on environmental conditions, meaning they die off quickly if it's too hot, too cold or too dry.

"As long as you have the right kind of climate for part of the year and a corridor for tsetse to move through, you'll find it," says Messina.

The tsetse is also an efficient carrier of trypanosomes, the parasite that causes sleeping sickness. When the fly bites into its host, it injects the parasite. The parasite eventually reaches the bloodstream, where it can travel to other sites

in the body. If left untreated, the host may experience neurological problems, including confusion, fatigue and disrupted sleeping patterns—hence, a "sleeping sickness." Coma and death may follow. The disease's annual toll is about 50,000 human fatalities and \$4.5 billion in livestock losses.

"If I can do anything to reduce the number of people burdened by the disease," says Messina, "I'll be very happy."

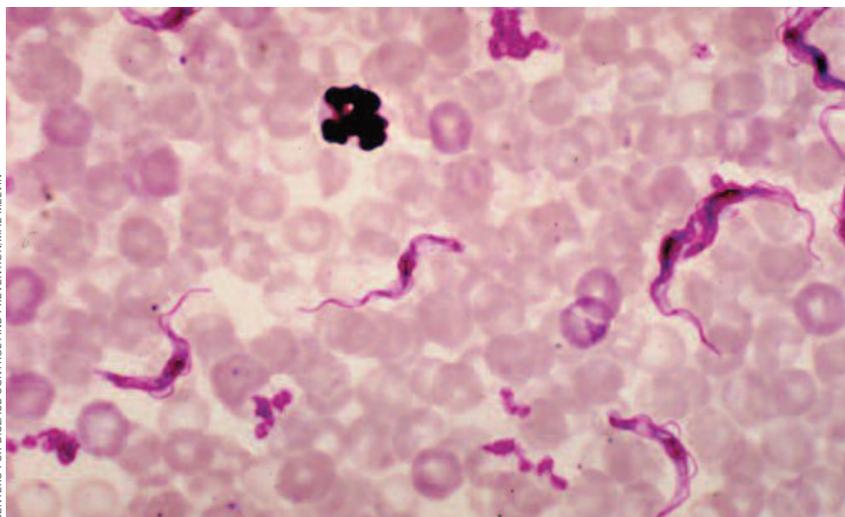
Mapping Distribution

Four years ago at a meeting in Nairobi, Kenya, Messina and his colleagues hatched a plan to use climate and land cover data to model tsetse fly distribution in that east African country, where the tsetse fly has started to move into more areas. The goal was to predict future hotspots of sleeping sickness, which would aid efforts to strategically trap and spray tsetse fly populations and prevent an epidemic.

Messina and his team tapped into NASA's free resource of worldwide vegetation, temperature and land cover data that are updated every 16 days. This information, along with knowledge about tsetse ecology, enabled the researchers to make educated guesses about where the fly was likely to be. After spending a year experimenting with the design of a predictive mathematical model, they now can enter the NASA data into a model to generate detailed maps of Kenya that show tsetse locations.

"The model has been doing a very good job of locating the fly," says Messina.

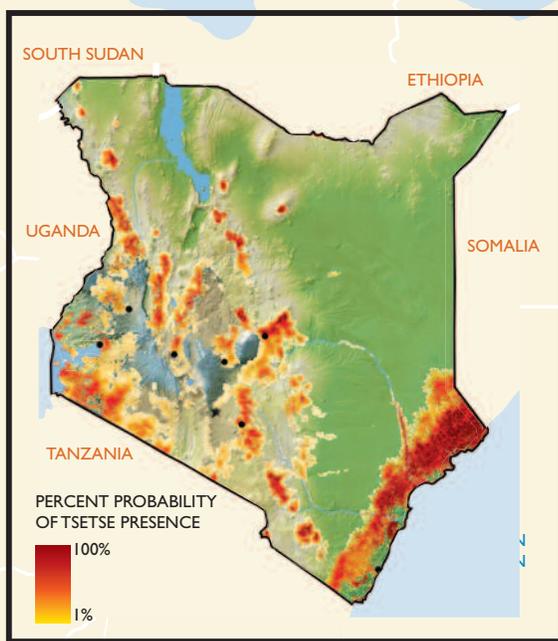
He notes that it also has revealed some surprising distribution patterns. For instance, the model shows that the amount of land the fly occupies from month to month and year to



Trypanosoma brucei (bright pink, thread-like), the parasite that causes African sleeping sickness.

AFRICA

This map, which was generated using climate and land cover data, shows the presence of the disease-carrying tsetse fly across the country of Kenya. Information like this could help control the insect population and resulting cases of sleeping sickness.



year varies. This makes sense when you consider that climate is not consistent across Kenya. Yet the model also has pointed to particular areas—tsetse “reservoirs” and “refugia”—where the flies always can be found. Messina says these places may be good spots for routine trapping and spraying.

The next goal for the modeling effort is to incorporate weather prediction data, so that the research group can make real-time estimates of fly distribution in the near future.

“Given the current climate scenarios, it’s likely that many parts of Kenya, including the agricultural areas, will become suitable habitat for tsetse,” says Messina. “If we can predict where tsetse will be, we can say, ‘Set up your traps now because they’ll be here in 2 weeks.’ Because of this, we’ll be able to control the disease so much more effectively than ever before.” ●

FIND MORE



See the complicated and bizarre life cycle of the parasite that causes sleeping sickness at <http://www.cdc.gov/parasites/sleepingsickness/biology.html>

A version of this article appears in *Inside Life Science* at <http://publications.nigms.nih.gov/insidelifescience>



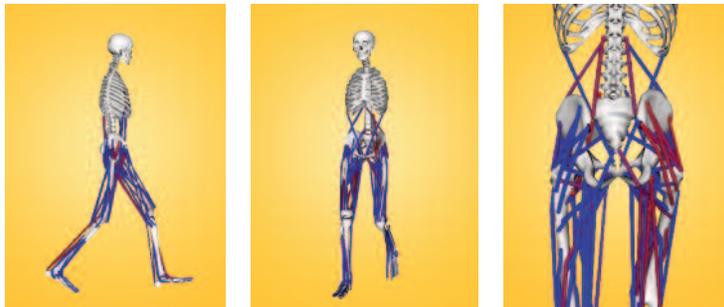
Walking the Line

By Emily Carlson

Quads, glutes, hamstrings, calves — these are all leg muscles that we try to slim down or bulk up by running, biking, squatting and lunging for hours at the gym.

While we're busy pumping iron to perfect these muscles, people like Chand John at Stanford University in Palo Alto, California are computationally modeling them to understand their role in walking disorders.

John and his colleague Eran Guendelman developed a computer simulation—a movie—that shows the activity of different leg muscles during a casual stroll. Red lines indicate muscles that have received signals from the nervous system to contract and generate force. Blue lines indicate muscles that are receiving no such signals.



These images come from a computer simulation of walking. The simulation is helping researchers understand the activity of different leg muscles. The work might help improve speed, balance and posture in people with movement disorders and enhance the training of athletes. CHAD JOHN AND ERAN GUENDELMAN, STANFORD UNIVERSITY

"With the simulation, you can tell what muscles are 'on' at certain times," says John, currently a graduate student. "This is something that is not well understood—and even less understood in walking disorders."

Injuries or impairments that affect the nervous system can disrupt the signals sent to muscles, sometimes causing abnormalities in one's step. Knowing how muscles are involved in normal walking could aid the development of treatments to improve speed, balance and posture.

The movement of this animated skeleton is based on measurements taken from a real person. John and others invited a healthy adult man about 6 feet tall to a motion lab for experimental studies. They measured his walking movements by attaching reflective markers all over his body and asking him to walk on a treadmill that recorded the forces exerted by his feet. Video cameras captured all the action.

John and Guendelman entered this force and motion data into a customized software program that calculated when the muscles "turn on."

The end result was a computer simulation. The project took about a year to complete.

The work is an example of computational modeling that uses concepts from physics—force, acceleration and energy—to simulate human movement in a particular way. The software behind it is freely available to others studying movement disorders and one day may be used by coaches to improve athletic training.

John, who studied computer graphics in college and is working toward a Ph.D., says he will continue to apply his knowledge in computer sciences and mathematics to investigate the biomechanics of humans, develop more realistic animations and even create robots that can assist with different physical tasks.

"In computer graphics, the end goal is to make nice pictures," John says. "Biomechanics enables me to have the end goal be scientific discovery and results that are important to humanity." ●

FIND MORE @

To see the animated skeleton walk, go to http://publications.nigms.nih.gov/multimedia/10gc_big.mov

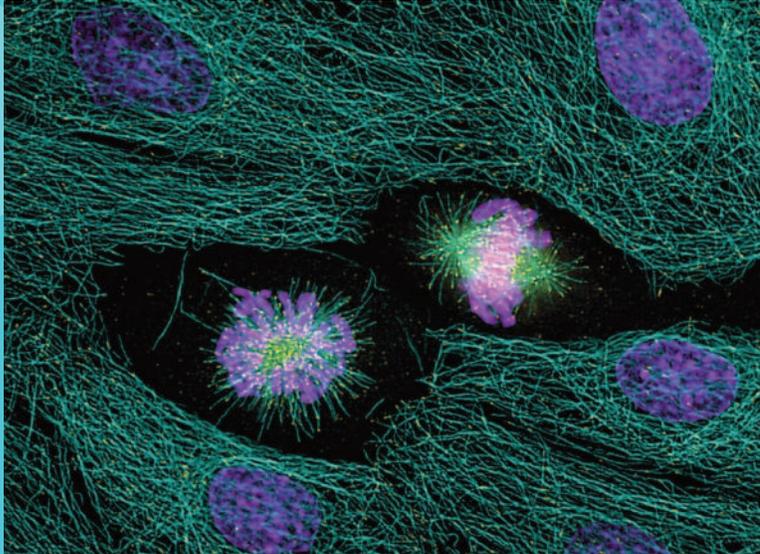
Use computer modeling to decide the best treatment for a person with a walking abnormality. Download OpenSim (<https://simtk.org/home/opensim>), free software for simulating movement and understanding muscle forces. Follow tutorial #1 (https://simtk.org/frs/download.php?file_id=1166)



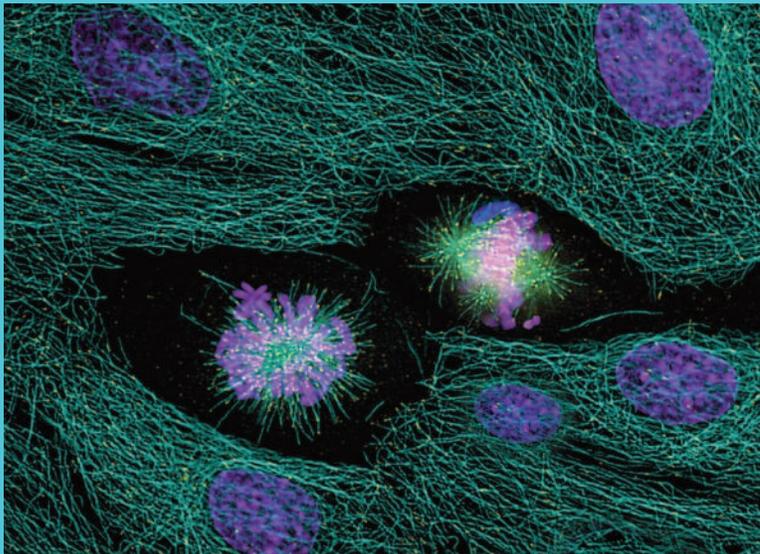
SPOT THE DIFFERENCE

CHECK YOUR POWERS OF OBSERVATION

Find 10 differences between these two photographs of dividing cells.



TORSTEN WITTMANN, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO



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