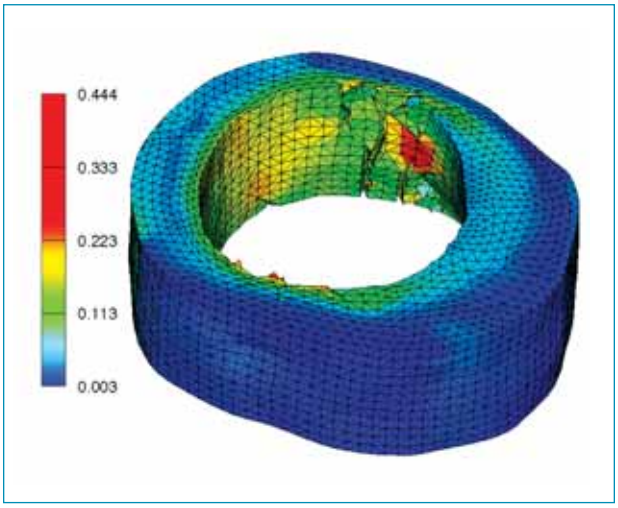
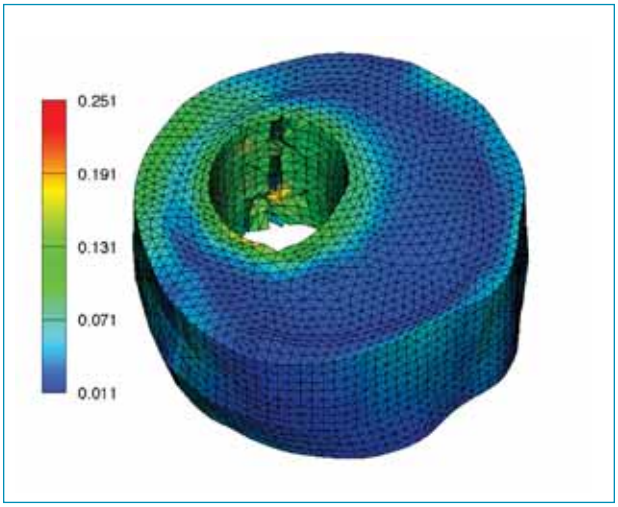
NewsBytes

Modeling Cracks in Clogged Arteries

Every year, doctors in the United States perform more than a million angioplasties: By inflating a tiny balloon inside a clogged artery, cardiologists can compress fatty plaques and restore blood flow. But the balloon also applies high pressure that can crack the wall of hardened, fat-lined arteries—sometimes with disastrous results. Now, structural engineers have created the first fully three-dimensional model to predict how arteries fracture under such stress.

"Once you have the true geometry [of the artery], this model applies pressure to simulate the presence of a balloon and evaluate the possibility of breaking the plaque or rupturing the artery walls," says author **Anna Pandolfi, PhD**, an associate professor of structural mechanics at the Politecnico di Milano in Italy. The research appears in the October 2008 issue of *Computer Methods in Biomechanics and Biomedical Engineering*.





Evolution of cracks in a clogged human artery depends on the geometry of the arterial wall and the pressure inside the artery. In the first simulation (left), a 40-percent-narrowed artery fractures at a blood pressure of 260 mmHg. In the second simulation (right), an 80-percent-narrowed artery fractures at a blood pressure of 380 mmHg. Colors show the distribution of stress on the arterial wall, measured in megapascals. Courtesy of Anna Pandolfi. Reprinted from Pandolfi A and Ferrara A, Numerical modeling of fracture in human arteries, in* Computer Methods in Biomechanics and Biomedical Engineering *(2008) 11(5):563.

In lab experiments, arteries tend to break when exposed to pressures of 0.3 megapascals or more—about 20 times the average human blood pressure. But angioplasty can easily generate such forces, and some areas of diseased arteries are particularly fragile.

To better understand how arteries fracture, Pandolfi and her colleague **Anna Ferrara, PhD**, of the Politecnico di Milano, combined high-resolution magnetic resonance imaging (MRI) of a patient's arteries with a model they previously developed to describe fracture in brittle solids, such as glass. Using a technique called finite element analysis, they divided the artery wall into small volumes and assumed each chunk had a uniform behavior. Then they simulated several high-pressure scenarios and monitored the evolution of arterial cracks.

"What we got was an interesting correspondence with the medical data," Pandolfi says: As others had seen in a clinical setting, cracks usually began at the edge, or "shoulder," of a fatty plaque.

But, Pandolfi says, the model has limitations: An MRI scan can only describe an artery's shape, not its mechanical properties, such as resistance. And these parameters vary from patient to patient, depending on the extent of arterial disease. To get individualized data, Pandolfi says, one must test a piece of artery outside the body or do an *in situ* experiment—dangerous procedures in a patient with unstable arteries.

"The key thing is to get more data and do more tests on human tissue," says **Gerhard Holzapfel, PhD**, professor of biomechanics at Graz University in Austria who published his own model of arterial fracture last year. "When we throw in more data," he says, "I am very certain we can actually define a more optimal stent, on a computer, for a specific lesion."

—By Hadley Leggett, MD

Modeling Muscles From the Inside Out

A new model of skeletal muscle starts from the micro-mechanical properties of the smallest possible unit—the sarcomere—and builds up to the muscle fibers and then to the muscles themselves. In addition, it places the fibers in their natural context—within surrounding soft tissue. The effort brings a new degree of flexibility and realism to muscle simulation.

"The idea behind micromechanical modeling is to imitate the behavior of the material as well as possible," says lead researcher **Markus Böl, PhD**, professor of mechanics of polymers and biomaterials at the Braunschweig University of Technology in Germany. "We're trying to include all the micro-parameters we can. In this way we do not have to fit the material behavior to the experimental data." His work appears in the October 2008 issue of *Computer Methods in Biomechanics and Biomedical Engineering*.

Scientists started making mathematical models of muscles in the 1920s. Most attempts to date were one-dimensional, and they ignored the soft tissue surrounding muscle fibers, Böl says. Also, they usually were built from the outside in: Scientists would look at the way a muscle behaved and tweak their

model's parameters (such as the number of contractions per second) until it matched the behavior. This led to some accurate but limited simulations.

Böl's work builds muscles from the inside out. He uses the finite element method, originally developed by aerospace engineers to design planes, to divide a muscle into discrete parts that each behave differently. Previous finite element muscle models used a continuum-based approach, which lumped all muscle fibers together and treated them as a single unit. But Böl gets into the nitty-gritty of each tiny fiber. In essence, his modeled muscles behave like a bunch of ropes of different thicknesses attached at the same point. Because the model describes each rope independently, Böl can plug in any parameters he wants and get realistic behavior back out.

In his model, Böl splits the muscle into an active element (the contractile muscle fibers) and a passive one (the incompressible tissue that surrounds them). Putting the "ropes" into the realistic environment of soft tissue yields a more complete picture, he says.

The model has both experimental and clinical value, Böl says. Scientists will use it to test the properties of living muscle, or to help doctors design unique treatments for patients, he believes. He is now working with sports doctors to refine and implement his approach. "But I have to say, these are first trials and work is still in progress," he cautions.

The new model can simulate any biological tissue that contracts, not just skeletal muscles, says **Ellen Kuhl, PhD**, professor of mechanical engineering at Stanford University. Kuhl was so impressed that she is now working with Böl to model heart tissue, with the goal of helping researchers develop a patch to replace dead tissue after a heart attack. "I think the cardiac application is even more sexy, because many more people could benefit from it," she says.

—By Lisa Grossman

"Digital Embryo" Created

How does a humble zygote grow into a fully functioning animal, billions or trillions of cells strong? This question has intrigued biologists for centuries. Now scientists have generated the first complete developmental blueprint of a vertebrate—a "digital embryo" mapping the positions, divisions, and movements of every cell during the first 24 hours of a zebrafish's life.

"Such reconstruction of a complex vertebrate embryo had not been achieved before," says **Philipp Keller**, a PhD candidate at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. Keller is lead author of the paper, which appeared in the October 9, 2008 issue of *Science*.

Developmental biologists have long coveted such a tool, but imaging a complex organism's growth presents a serious hurdle. After just one day, for example, a zebrafish already has 20,000 cells and a beating heart. To meet that challenge, Keller and his colleagues developed a new technique called digital scanned laser light sheet fluorescence microscopy (DSLM).

DSLM generated a three-dimensional image of the embryo by combining about 400 pictures taken along slightly different planes. The team repeated this process every 60 to 90 seconds, tracking changes as the zebrafish developed. In 24 hours, this amounted to about 400,000 images for each embryo.

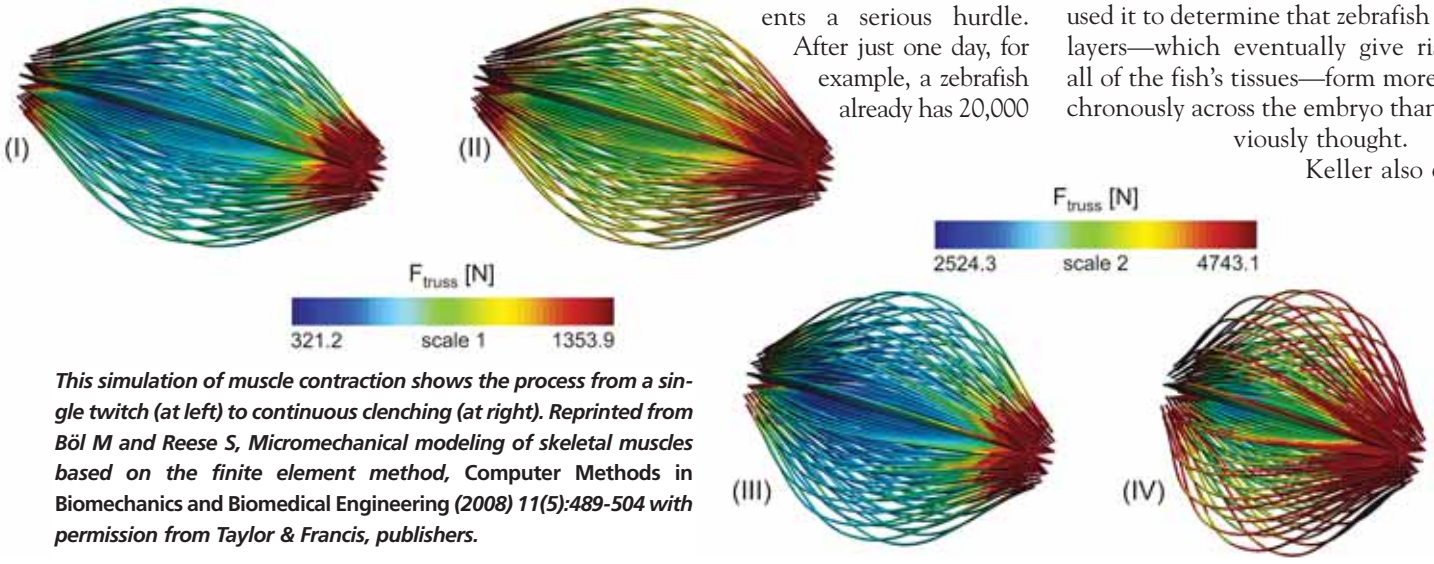
To deal with this deluge of data—three terabytes per embryo—the researchers developed a computational pipeline. They wrote algorithms defining the structure of cell nuclei, then ran the microscopy data through a network of more than 1000 computers at EMBL and the Karlsruhe Institute of Technology in Germany.

The computational analysis picked out every nucleus. Keller's team then processed this information into comprehensive databases of cell positions, divisions, and migratory tracks. In all, they catalogued 55 million nucleus entries.

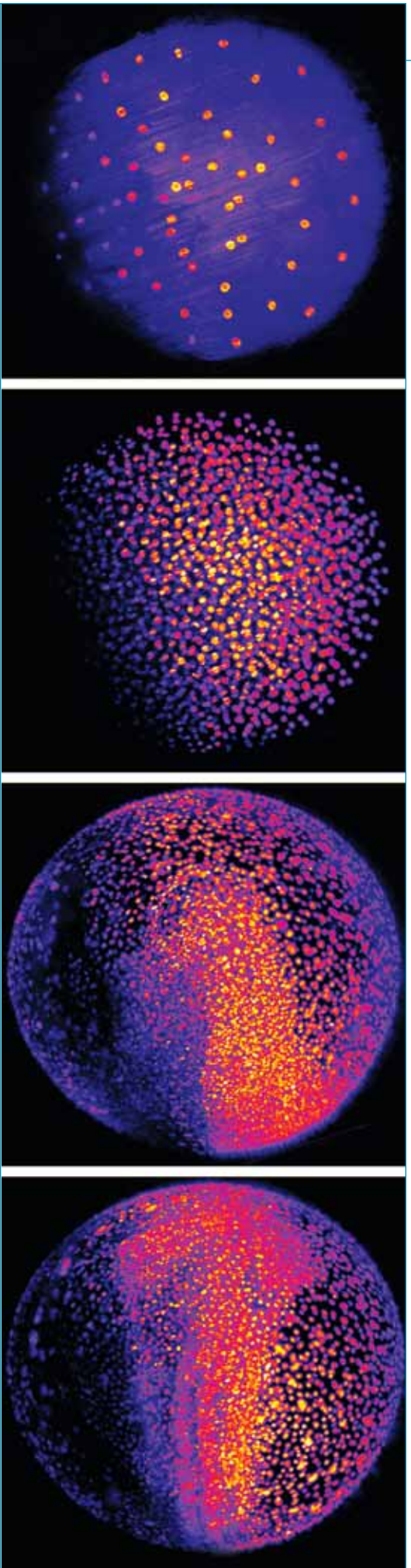
Digitizing the data was key. "Microscopy tells you about phenomena from a qualitative point of view," Keller says. "But with digital embryos, we can count the number of cells that are involved in a process and see what they do."

The digital embryo has many potential uses. For example, the researchers used it to determine that zebrafish germ layers—which eventually give rise to all of the fish's tissues—form more synchronously across the embryo than previously thought.

Keller also envi-



This simulation of muscle contraction shows the process from a single twitch (at left) to continuous clenching (at right). Reprinted from Böl M and Reese S, Micromechanical modeling of skeletal muscles based on the finite element method,* Computer Methods in Biomechanics and Biomedical Engineering *(2008) 11(5):489-504 with permission from Taylor & Francis, publishers.



sions applications in tissue engineering and the study of tumor growth. Overlaying the digital embryo with genomic data also could be powerful, he adds. Researchers could learn which genes regulate vital developmental processes, such as organ formation. To encourage such progress in multiple fields, the researchers made their data public.

"Microscopy tells you about phenomena from a qualitative point of view," Philipp Keller says. "But with digital embryos, we can count the number of cells that are involved in a process and see what they do."

DSLM images of a zebrafish embryo at four different time periods, between 1.5 and 20 hours post-fertilization. Different colors indicate different densities of nuclei (blue and purple are least dense, while yellow is most dense). Courtesy of Philipp Keller.

"This paper is groundbreaking," said **Kees Weijer, PhD**, professor of developmental physiology at the University of Dundee in Scotland. "And making all the data available is very helpful since these coordinates will be used to compare the development of mutants."
—By Michael Wall, PhD

The Circuitry of Yeast

For centuries, yeast has helped scientists understand how cells work. Now, two inventive teams have applied an engineering approach coupled with computer modeling to reveal new details about key biological pathways by which yeast cells regulate themselves in a changing environment, as reported in the January 25, 2008 issue of *Science* and the August 28, 2008 issue of *Nature*.

"What's interesting to me was looking at this biological system from an information-processing perspective," says **Jerome Mettetal, PhD**, a physicist at the Massachusetts Institute of Technology and lead author of the Science paper. "By applying temporally varying inputs, you can find out a lot about the system that you wouldn't be able to see otherwise."

Traditionally, biologists measure how cells respond by adding or taking something away in a steady-state context. But in real cells, inputs from the environment vary constantly. To understand the mechanisms by which cells respond to changes, the two teams created microfluidic arrays that confine yeast cells in a chamber and feed them in regular cycles, controlled by software. Based on the output, each team generated a model of the inner workings of the cells.

Mettetal's team added bursts of salt to the microfluidic array in order to tease out how yeast responds to changes in osmotic pressure—the salt level in the surrounding medium. They then built a model based on the response generated by the yeast. When they compared their model to known cell responses to osmotic changes, they discovered new roles for three different negative feedback loops—the processes by which a biological system reestablishes equilibrium.

The research team on the *Nature*

paper applied a similar engineering approach to better understand how yeast cells respond to fluctuations in nutrient levels. If yeast is deprived of its favorite sugar (glucose), it will consume an alternative and less nutritious sugar (galactose). The researchers created a sinusoidal input by alternately feeding and starving yeast of glucose on different time scales while galactose was constantly present in the environment. The cells responded to long-term changes in glucose, but not to faster fluctuations.

The researchers then made a model based on the well-known metabolism of galactose. But the experimental yeast was responding much faster to the glucose fluctuations than the model predicted. "This suggested something was crucially missing from the model," says co-author **Jeff Hasty, PhD**, associate professor of bioengineering at the University of California, San Diego. Studying live yeast provided the answer: The messenger RNA necessary for the galactose metabolic pathway was degraded when glucose was present. "The most exciting thing is that without the model, none of this would have happened," said Hasty.

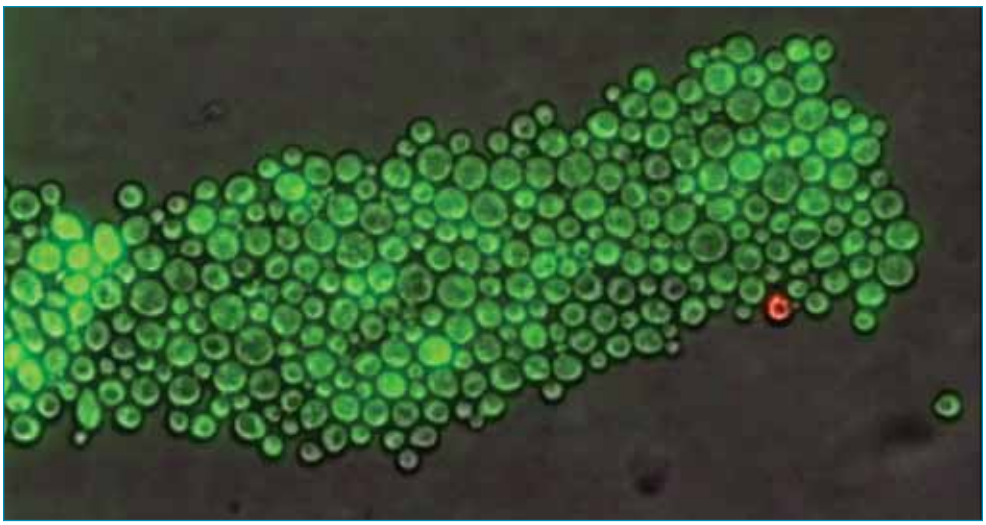
"The broader contribution of each of these pieces will be to point to the value of using periodic input signals as a means to tease out the structure and function of the underlying system," says **James Collins, PhD**, professor of biomedical engineering at Boston University. "I am already beginning to think about how these might be interesting tools to use to look at other systems, bacteria in particular."

—By Cassandra Brooks

Watching a Molecule Bind

Like a paper clip being pulled to a magnet, a small molecule called ADP gets pulled into its port in a new simulation. Because of a simple case of opposites attract, it's the first time computational biochemists have successfully simulated a molecule—or ligand—being drawn into its binding site in an unbiased simulation.

"Nobody has been able to capture and describe the full process of ligand binding to a binding site while permitting natural motion of the ligand," says **Emad Tajkhorshid, PhD**, assistant professor of biochemistry, pharmacology and biophysics at the University of Illinois at Urbana-Champaign. "We think we are getting the most faithful representation of the binding site, because in our simulations, the protein is dynamic and allowed to freely react to and establish new interactions with the ligand as it binds."



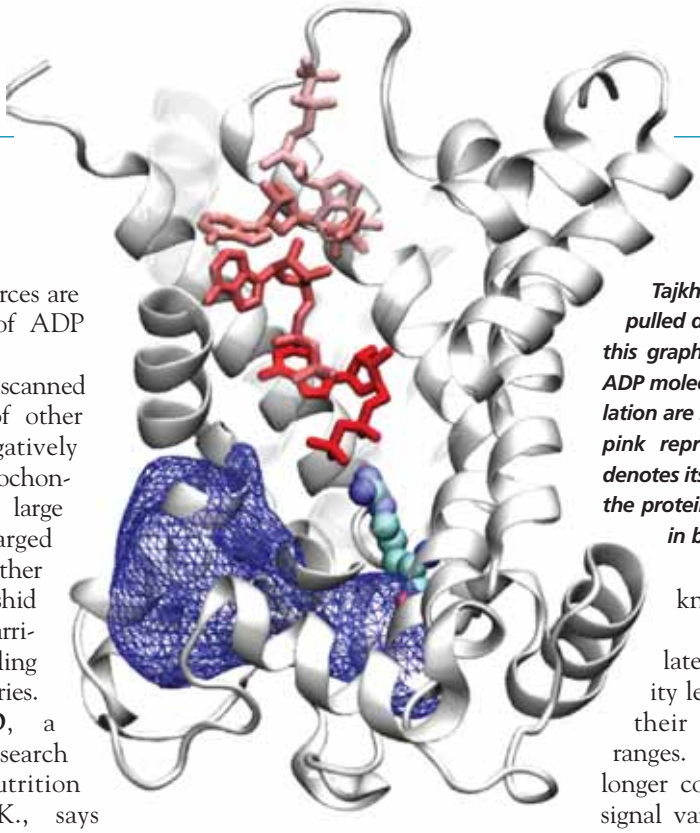
Yeast grows in a microfluidic chamber designed at the University of California, San Diego. Regular nutritional inputs, generated in a wave-like pattern, reveal aspects of how the cells regulate their metabolism and internal environments. The green background color signals that it is a galactose rich environment. Photo credit: UC San Diego Jacobs School of Engineering.

Until now, says Emad Tajkhorshid, "nobody has been able to capture and describe the full process of ligand binding to a binding site while permitting natural motion of the ligand."

Tajkhorshid and graduate student **Yi Wang** describe their simulations in the July 15, 2008 issue of the *Proceedings of the National Academy of Sciences*.

Tajkhorshid and Wang simulated the binding of adenosine disphosphate (ADP), a molecule involved in fueling the cell, to the ADP/ATP carrier protein (AAC) located in the membrane of mitochondria—the cell's power generation plants. For ADP to be shuttled into the mitochondria, it must first float into a cavity inside AAC and bind to it—an event that lasted 100 nanoseconds in the simulations.

Previously, simulations of molecular binding have required an active force to produce the attachment. But placing the ligand (in this case ADP) at the mouth of the ligand binding site (here, the AAC cavity) in molecular dynamics simulations is more faithful to biological reality. Initially, Tajkhorshid thought that the ADP would just float away. Instead it moved right into place. He and his colleagues found that AAC uses a special bait to lure ADP to its binding site: Positively charged amino acids line the sides and bottom of the AAC cavity, creating a surprisingly strong electrostatic potential that attracts the negatively charged ADP. They called this process "electrostatic funneling." And



Tajkhorshid and Wang watched as ADP was pulled down into the cavity of the AAC protein. In this graphic, the AAC structure is outlined in black. ADP molecules at different stages of the 100 ns simulation are shown in colors ranging from pink to red—pink represents ADP's starting position and red denotes its final binding state. The strongest region of the protein's positive electrostatic potential is shown in blue mesh. Courtesy of Emad Tajkhorshid.

because of it, no additional forces are needed in the simulations of ADP binding to AAC.

In addition, when the team scanned the amino-acid sequences of other molecules that shuttle negatively charged molecules across mitochondrial membranes, they found large numbers of positively charged amino acids not present in other membrane proteins, Tajkhorshid says. He suspects these other carriers also use electrostatic funneling to pull in their molecular quarries.

Alan Robinson, PhD, a researcher at the Medical Research Council Dunn Human Nutrition Unit in Cambridge, U.K., says Tajkhorshid has "published what looks like the most reasonable structure of ADP bound to the carrier." This structure may serve as the starting point for more detailed studies of how ADP binds to AAC and how it triggers the protein to open, he says.

— By Michael M. Torrice, PhD

Identifying a Cell's Weakest Link

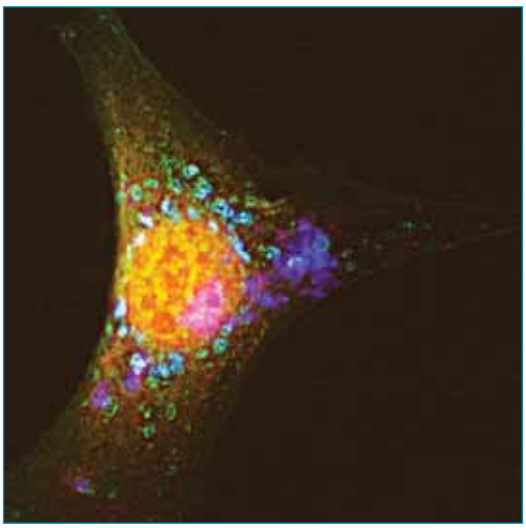
To understand why bridges collapse or computers fail, engineers might create models of these systems and push them beyond their limits. Now, computational biologists are using a similar approach to understand the causes of cell death. By driving their model of the cell beyond experimentally observed values of certain important cellular ingredients, they push it to the "breaking point"—uncovering the weakest links. The process revealed some new biological roles for several key signaling molecules—the kinases ERK, Akt, and MK2.

"It showed us things that, in retrospect, we couldn't see looking by inspection of the original model," says co-author **Michael Yaffe, PhD**, associate professor of biology and biological engineering at the Massachusetts Institute of Technology (MIT). The work was published in the October 17, 2008 issue of *Cell*.

The mechanisms by which proteins influence cytokine-induced apoptosis, or cell death, are poorly understood. So Yaffe and colleagues **Kevin Janes, PhD**, a recent MIT graduate, and **H. Christian Reinhardt, PhD**, a postdoctoral associate at MIT, built a model of the cell using carefully collected data. Included in the model were nearly 8,000 measurements of protein signals in response to combinations of three cytokines that help dictate the fates of cells: tumor necrosis factor (TNF), known as the "death stimulus," and epidermal growth factor (EGF) and insulin, known as "survival stimuli."

The researchers then manipulated the model to drive the activity levels of the proteins outside of their experimentally observed ranges. When the model could no longer computationally fit one of the signal variables, it would stop making predictions. This "breaking point" highlighted the protein that caused the failure. Thus, the technique acts as a sort of high-throughput screen, revealing new hypotheses about proteins previously thought to have well-defined roles within the cell. The team then verified these hypotheses experimentally, leading to surprising new insights about how the signaling proteins communi-

"Signaling networks are so complicated right now that common sense doesn't always hold true," Michael Yaffe says.



Breakpoint model analysis pushes cellular ingredients beyond their normal ranges to see which ones are critical to a particular cellular process. Here we see fluorescent proteins highlighting the subcellular location of several different key signaling molecules (phosphoinositide-binding domains), which function together with lipid and protein kinases and phosphoserine/threonine-binding domains, to control a wide variety of cellular events. These are the kinds of molecular interactions that could be studied using breakpoint model analysis. Courtesy of Seth J. Field and Michael Yaffe.

cate. "Signaling networks are so complicated right now that common sense doesn't always hold true," Yaffe says.

"The thing that makes me really stop and pay attention is the methodology, which I found of special note," says **Raphael Levine**, **PhD**, distinguished professor of chemistry at the University of California, Los Angeles. "Instead of trying to see if the model can predict something new, they tried to drive it to say something which they know it shouldn't say. As a result, they were successful in finding some new biology."
—By Kayvon Sharghi

Diagnosing Cell Circuitry

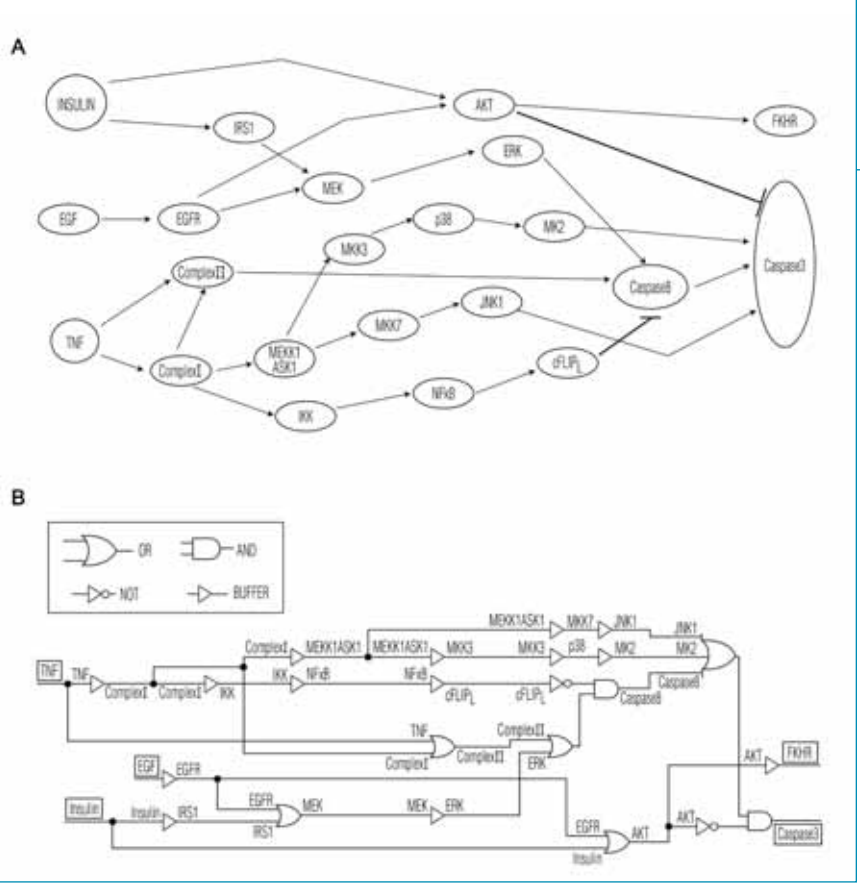
To biologists, a computer's motherboard may just look like highways of circuitry connecting various chips. But if they focus harder, they might see a model for disease, according to new research.

Just as a single corrupt circuit can foul a computer's operation, a faulty molecule can upset a healthy body. "If your body is not functioning correctly, then the molecules inside your cells are causing the problem," says **Effat Emamian**, **MD**, president and CEO of Advanced Technologies for Novel Therapeutics in New Jersey.

The parallels between signal transduction pathways in a cell and circuit networking in a motherboard inspired Emamian's team to identify defective cell pathways in the same way that engineers inspect faulty circuits. This technique, known as fault diagnosis, can pinpoint the molecules that are most critical to a cell's function.

Such an accurate assessment may lead to more precise medicines. Most new drugs in trial are toxic, Emamian says, because they often target molecules essential for cell function. Fault diagnosis can reveal safer molecules to target. The work appears in the October 21, 2008 issue of *Science Signaling*.

Lead author **Ali Abdi**, **PhD**, associate professor of electrical and computer engineering at the New Jersey Institute of Technology, helped test Emamian's theory. Abdi re-envisioned three previously studied cell pathways as electronic circuits: tumor suppressor p53, cell death regulator caspase3, and a nerve-cell network called CREB. His reconstructions used binary language to characterize a molecule's state in its pathway as "active" or "inactive." Relationships between molecules were organized into decision-making operations using Boolean logic where each relationship contains only two possible values—on or off. This allowed the researchers to write algorithms predicting which molecules were critical to a pathway's smooth functioning. The algorithms confirmed what was known about p53 and caspase3, but they also revealed new critical molecules in the CREB network.



A simple model of the caspase3 network (top) shows the various regulatory molecules and their relationships to each other. Depending on which regulatory molecules are active or inactive, caspase3 will induce cell death. This network can be re-envisioned (below) as an electronic circuit after organizing previous knowledge of the molecules' relationships using Boolean logic. Algorithms applied to this circuit can predict molecules to which a pathway's signal is most vulnerable. Reprinted with permission from Abdi A, et al., Fault Diagnosis Engineering of Digital Circuits Can Identify Vulnerable Molecules in Complex Cellular Pathways,* Science Signaling*, (2008) 1(42):ra10.

The approach is a good start for quickly identifying essential points in cell networks, says **Kevin Janes**, **PhD**, assistant professor of biomedical engineering at the University of Virginia. But while Boolean logic can make good approximations, it may oversimplify the relationships for some networks, he says. For example, Emamian's approach doesn't allow consideration for graded responses between "active" and "inactive." "But it's not a fundamental flaw," Janes adds.

The team acknowledges these limitations in its *Science Signaling* paper. The next step, Emamian says, is to focus on larger networks, and not necessarily just signaling pathways. "We can analyze metabolic pathways, or pathways that also have several critical enzymes playing in the whole game."
—By Emmanuel Romero

Cancer's Signature—Written in Blood

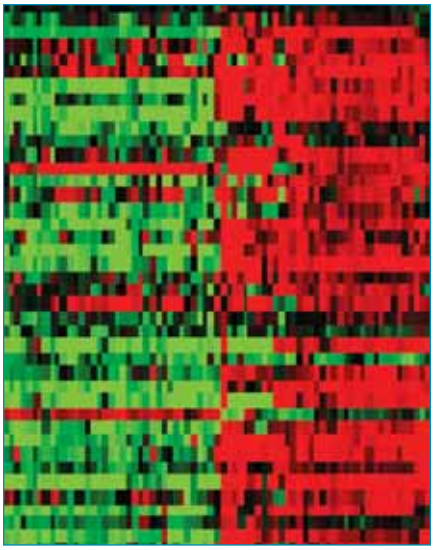
When it comes to deciphering the health of the body, the blood carries a potential mother lode of protein clues. Given the ease of extracting blood, such proteins could serve as efficient health barometers. But it's tough to distinguish between the multitude of proteins naturally found in blood and those that are secreted into the blood—including those secreted by diseased tissue such as cancer. Their signal may get swamped by the many other proteins present in blood, thwarting efforts to discover useful infor-

"Figuring out which proteins are secreted into the blood is like searching for a needle in a big, big haystack," says Ying Xu, PhD. "This [algorithm] sorts through all that hay."

mation. Now, scientists have developed an algorithm that sorts through the multitude, expediting the search for blood-based cancer biomarkers.

"Figuring out which proteins are secreted into the blood is like searching for a needle in a big, big haystack," says **Ying Xu**, **PhD**, professor of bioinformatics and computational biology at the University of Georgia. "This [algorithm] sorts through all that hay."

To develop their algorithm, Xu and his colleagues began by scouring the literature for all proteins known to be secreted into the blood, regardless of their origins. They then analyzed the amino-acid sequences of these proteins to identify common features, such as signal peptides, transmembrane domains, solubility, and secondary structure. They discovered 18 features that were powerful predictors of blood secretion, and used them to train a computerized classifier.



This microarray shows genes that differ in regulation between cancerous and non-cancerous lung tissue. Ying Xu's classifier can predict which of the proteins made by these genes may be useful as blood-based biomarkers. Courtesy of Ying Xu.

When the researchers applied the classifier to other data sets, it could distinguish proteins secreted into the blood from all other proteins in the blood with more than 80 percent accuracy. The results appear in the October 2008 issue of *Bioinformatics*.

Xu and his colleagues are now using microarrays to identify differences in gene expression levels between cancerous and non-cancerous stomach tissue. Using their classifier, they can then sift through the data to zero in on genes that produce proteins that are most likely to be secreted into the blood, followed by validation with mass spectrometry.

"We've already identified proteins that are elevated during different stages of stomach cancer," Xu says. "Typically, in order to find out what stage it's in, you'd have to actually cut the patients open and do a biopsy. Our markers could be the first markers to provide information about cancer stage."

By applying his biomarker discovery pipeline to a range of cancers, Xu ultimately hopes to identify general biomarkers that apply to any cancer. He envisions doctors detecting various cancers at early stages with a simple blood test.

Bo Huang, **PhD**, a post-doctoral fellow at Vanderbilt University, hopes to use Xu's classifier to find biomarkers for breast cancer. "These results provide a powerful method to discover potential biomarkers, not only for cancers but also for many other diseases," Huang says.

—By Lizzie Buchen

Blurring Data for Privacy and Usefulness

Hospitals with research agendas share a common problem: how to use medical records for research while protecting patient privacy. One approach—the data-protection equivalent of blurring the face of an anonymous source on television—has now been tested using real-world data. The results, which show promise for protecting privacy without rendering the data set useless, appear in the September/October 2008 issue of the *Journal of the American Medical Informatics Association*.

"It's not a theoretical problem," says **Khaled El Emam**, **PhD**, associate professor at the University of Ottawa and Canada Research Chair in electronic health information, who collaborated with **Fida Kamal Dankar**, **PhD**, on the paper. "We're trying to protect privacy, but we need the tools."

Just as the nightly news renders the faces of anonymous sources unrecognizable, the approach known as k-anonymity blurs distinctive variables to reduce the risk that someone could trace patients with distinctive characteristics. For example, the approach might cut birthdates down to birth years. And easily identifiable outliers—the octogenarian in a college town, the teenager in a retirement community—are omitted. The remaining information contains at least k data points that look identical, where $1/k$ is deemed an acceptable level of risk.

That works in theory, but the actual risk depends on the type of data set and what an intruder wants from it. A prosecutor digging up dirt on a defendant would try to re-identify a specific person in the database. A journalist trying to discredit an organization's data-security procedures would also only need to re-identify one person, but it wouldn't matter who. El Emam set out to test whether k-anonymity works in both circumstances. His findings: k-anonymity correctly predicts the risk of re-identifying one specific individual with minimal harm to the value of the database (the prosecutor example). But using k-anonymity to protect against re-identifying an arbitrary person (the journalism example) is unnecessarily strict and compromises the research quality of the data.

Since researchers choose *k* based on statistical theory, El Emam suggests data custodians run test cases to verify if the *k* is sufficient, or if it's overprotective, as in the journalism example, before making the data available to researchers. If needed, the number of groupings of *k* identical data points could then be adjusted to ensure that the actual risk approximates the theoretical risk of 1/*k* and, in this way, keep the risk acceptably low while preserving data.

"What is needed are the steps to turn this article into a practical tool that custodians can use in conjunction with researchers," says **Joan Roch**, chief privacy officer for Canada Health Infoway in Montreal, Quebec.

El Emam says he plans to continue exploring actual risks in various data-security scenarios: "It's a big problem, and we've solved part of it."

—By Stephanie Pappas

Modular Modeling

Biological models can quickly become as complex as the systems they represent. And minor changes can necessitate a complete rewrite of the model. But researchers may soon snap their models together like LEGOs, using a new programming language called Little b, which uses modularity to simplify biological modeling. Eventually, the authors hope to turn Little b into an easy-to-use tool for biology labs.

"I think that as an everyday tool, it [Little b] is going to be kind of like the microscope," says **Aneil Mallavarapu, PhD**, lead developer of Little b and a senior research scientist in systems biology at Harvard Medical School. "We're essentially building a new kind of gel, a new type of microscope for the lab." The work appears in the June 2008 issue of the *Journal of the Royal Society Interface*.

Biologists traditionally create models to describe unique systems, such as the development of fruit fly embryos or the actions of a phosphorylation cascade on gene transcription. Such computational models are usually based on lists of the system's properties, which detail every molecular interaction in the system. This allows researchers to tailor models to the precise questions being asked, but it also constrains the model's usefulness, because it can only probe into one area.

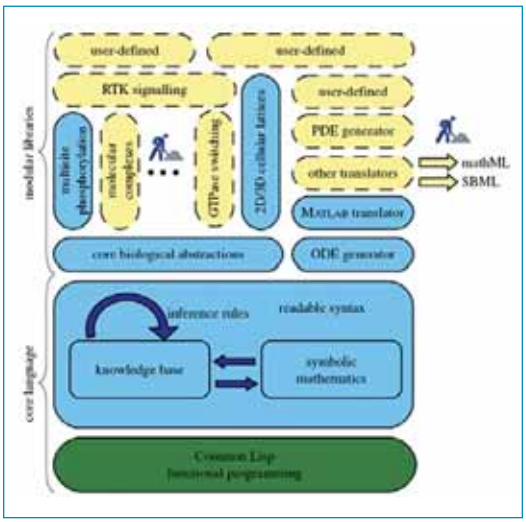
Little b strives to break down biological systems into modules that can be used regardless of the specific context, such as "nuclear export" or "membrane localization." It then defines those parts in a mathematical language. Researchers can use Little b to put together assorted modules to describe their system; Little b then uses those symbolic modules to write out executable code that a scientist could use in a simulation program like MATLAB. "I've given Little b the power to reason about biological objects," Mallavarapu says.

Mallvarapu is excited about the possible use biologists might make of Little b. He would like to see the language help uncover the complex pathways involved in diseases. He hopes that researchers will eventually build entire virtual cells or virtual plants collaboratively, increasing their ability to study their projects *in silico*.

> "I've given Little b the power to reason about biological objects," Aneil Mallavarapu says.

While the idea of breaking down biological systems into modular chunks may seem logical, Little b may not arrive in the lab immediately, says **Birgit Schoeberl, PhD**, a senior director of research at Merrimack Pharmaceuticals, Inc, in Cambridge, Massachusetts. "I'm excited about the concept and what I see, but in my own experience, it isn't straightforward," Schoeberl says. "I think it's not quite ready for non-developers. I hope he keeps developing it, or someone takes it on to keep working on the idea."

—By Molly Davis □



Little b is based on a core language, which includes the Lisp language it was created in (green) and the knowledge base, symbolic mathematics and syntax modules that allow Little b to reason about biological systems. It also includes modular libraries that describe specific biological interactions, and translators that can generate code used in simulations. Blue areas exist within the current framework; yellow areas are currently under development or are envisioned for future work. Reprinted with permission from Mallavarapu, A, et al., Programming with models: modularity and abstraction provide powerful capabilities for systems biology,* Journal of the Royal Society Interface, *online publication, July 23, 2008.