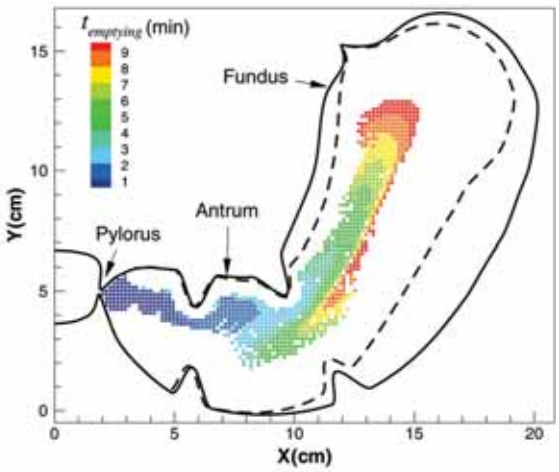
who created the model for studying drug delivery. But this was one such time.

The curious finding could help explain the wide variability in drug activation time: A drug might get swept along in this fast digestive current one time, and not another. The work appeared online in the *Journal of Biomechanics* in August 2006.

In 2004, Brasseur and research associate **Anupam Pal**, **PhD**, had published a computer simulation of gastric flow and mixing. In the current work, they used the same basic simulation, but studied gastric emptying. They gave unique numbers to thousands of points (fluid particles) uniformly distributed around the stomach. They then watched the order in which these particles left the stomach during a 10 minute simulation, while keeping track of each particle's position at each time-step. When they then ran the simulation in reverse, they could watch the particles' changing positions. After color-coding the points by time of leaving, they observed a ribbon-like path of gastric emptying that originates in the top of the stomach and passes along its side of least curvature. The entire animated sequence can be seen at http://mne.psu.edu/Brasseurlab/gastric/.



This image of Brasseur's two-dimensional stomach model shows the initial locations of all particles that left the stomach over the course of 10 minutes. The pattern of gastric emptying suggests the existence of a Magenstrasse in the stomach. The dashed line shows the shape of the stomach after 10 minutes. Courtesy of James Brasseur.

The researchers dubbed their discovery the "Magenstrasse," which means "stomach road" in German. It is a sort of passing lane, where digested matter reaches the intestines more quickly than food and liquids outside the road. "We do not know if the Magenstrasse has a physiological function or if it is only a byproduct of the contraction waves in the distant stomach," says Brasseur. The team showed that when the simulation excluded contractions known to exist at the bottom of the stomach, the Magenstrasse didn't form.

"Brasseur's modeling has revealed a potential new mechanism of liquid emptying that can explain why some patients take a very short time to absorb drugs in their bloodstream," says **Michael Fried**, **MD**, director of the division of gastroenterology and hepatology at the University Hospital Zurich, Switzerland. He says pharmaceutical companies who wish to achieve constant and reproducible patterns of absorption of drugs must take this study into account. However, Fried notes, the model "has to be validated in animals or in humans."

Brasseur agrees more research is necessary. "We would need further studies that checked how the path works with nutrients and drugs of different densities," he says. He believes the Magenstrasse would still exist if the stomach contents are thicker than the viscous liquid used in his team's simulations, but it may assume a different shape.

—Maria José Viñas

Stem Cells' Existential Crisis Explained

To differentiate or not to differentiate? That is the question constantly faced by embryonic stem cells. And they seem to answer it decisively at the behest of a molecular trio of transcription factors. A new computational model shows how it is possible for three proteins to control the switch in the observed, clear-cut manner. The model also gives researchers a hypothesis they can test in the lab.

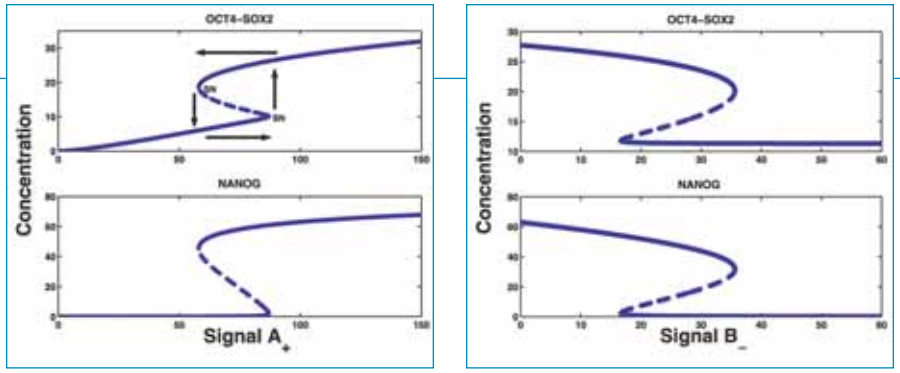
"We've shown that these three players are able to define the embryonic stem cell switch," says **Carsten Peterson**, **PhD**, professor of computational biology at Lund University in Sweden and lead author of the study. By explaining this either/or molecular circuitry, the model could eventually help scientists harness stem cells for treatments. The work appears in the September 2006 issue of *PLoS Computational Biology*.

Embryonic stem cells have two defining traits: They can divide forever to remain stem cells, and they are pluripotent, meaning they have the potential to become any type of somatic cell in the body—gut, muscle, skin, blood or nerve. But whether in a Petri dish or the body, stem cells receive a barrage of molecular signals that they must interpret and respond to with a binary decision. "Either you are a stem cell or you commit yourself," says Peterson.

Over the last few years, biologists have discovered that a handful of proteins determine an embryonic stem cell's fate. Three in particular—named OCT4, SOX2 and NANOG—seem to coordinate the decision by cueing the actions of hundreds of target genes.

Peterson's team derived mathematical equations governing the rate at which these three transcription factors bind and unbind to DNA, thereby regulating the expression of differentiation genes and stem cell genes. The team then used the Systems Biology Workbench to simulate how this trio controls other genes to engineer opposing outcomes: self-renewal or differentiation. They infer that the proteins reinforce one another's actions through a positive feedback mechanism, creating a bistable switch: either on or off, with no middle ground. When all three proteins are active, stems cells remain stem cells; when the trio is inactive, the cells differentiate, with no middle ground. Peterson and others hypothesize that stem cells receive external signals to control the switch. Because of the positive cascade of interactions, the cells effectively ignore slight changes in those signals and respond with a single outcome every time.

The model was based on previous work by **Laurie Boyer**, **PhD**, a postdoctoral fellow at the Whitehead Institute in



A+ represents hypothetical factors that activate OCT4 and SOX2. In response to increasing that signal, the OCT4-SOX2 dimer and NANOG switch from all off to all on. B- represents factors that repress NANOG, which has the effect of turning the switch off. Courtesy of Carsten Peterson.

Cambridge, Massachusetts. She thinks other components must function with the trio of proteins. However, she says, the work "provides a testable model to explain how OCT4, SOX2 and NANOG may contribute to these seemingly opposing activities."

The heart of the model—explaining how stem cells reconcile their dual identities—is vital, says Boyer. "If you are ever going to realize the therapeutic potential of these cells, you really need to find the key for understanding how embryonic stem cells balance their ability to self-renew or differentiate."

—Ewen M. Callaway

Connecting the (Microarray) Dots from Drug to Disease

Normal cells, diseased cells and cells on drugs share a common language: They all produce their own patterns of gene expression. And the patterns can be compared in useful ways—given a disease in which a certain set of genes are up- and down-regulated, one would like to find a drug that specifically counteracts those changes. A powerful new web-based tool allows researchers to draw just such connections. Researchers from all around the world can use the tool, called the Connectivity Map, to identify potential new drugs for a variety of diseases, and potential new uses for existing drugs.

"The objective is to connect diseases with the genes that underlie them and the drugs that treat them," says **Justin Lamb, PhD**, a senior scientist at the Broad Institute of Harvard and MIT. He and his colleagues described their work in the September 29, 2006, issue of *Science*.

The advent of DNA microarrays more than a decade ago made the Connectivity Map possible by allowing scientists to study thousands of genes all at once. Lamb and his colleagues used microarrays to determine which genes were turned up or down in cells treated with 164 different biologically active compounds (mostly drugs). They also gathered together previously published gene expression data for various diseases, including obesity, Alzheimer's Disease, and various types of cancer. Using pattern-recognition software the team developed, any researcher around the world can query the database at http://www.broad.mit.edu/cmap to identify drugs or diseases with patterns that are either the same as or opposite to a particular gene signature of interest.

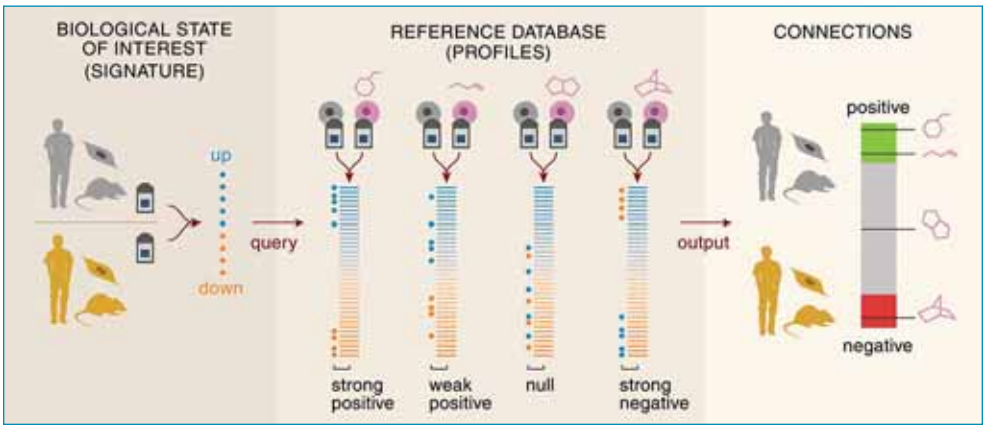
The most exciting use of this approach is in suggesting potential drug therapies for real diseases, Lamb says. In one of the team's initial tests, gene signatures exposed a possible new treatment for children with drug-resistant acute lymphoblastic leukemia. The researchers also have used the database to seek novel treatments for obesity and Alzheimer's disease.

The Connectivity Map also can unveil how drugs work on a molecular scale, says Lamb. For instance, similar genomic patterns in the database pointed to a connection between a compound called gedunin and a class of well-understood drugs. This implies gedunin might operate in a similar fashion to disrupt hormone signals in cancerous cells.

Having completed the Connectivity Map's pilot stage, the team intends to expand to cover all drugs approved by the Food and Drug Administration. One limitation is that it is restricted to specific cells in a petri dish, which neglects other interactions that occur in a human body, says **Eric Schadt, PhD**, senior scientific director of Rosetta Inpharmatics in Seattle. Still, Schadt says, "It's a great piece of work. It's a great tool, and it will be well-used."

"The whole field is on fire with these large-scale experiments," Schadt adds. "It's the only way you can uncover these networks that drive diseases. I think it's right on the money."

—Marcus Woo □



The Connectivity Map lets users compare the gene expression signature of any cell state of interest (left) with a reference database of profiles from cultured human cells treated with various drugs. Pattern-matching algorithms score each reference profile for the direction and strength of enrichment with the query signature to produce a "connectivity score." Here the columns for the first and second drug treatments show a positive connection to the state of interest; the third has no relationship to it; and the fourth has a negative connection. From: The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease, by Lamb, et al.,* Science *2006 Sep 29;313(5795):1929-35. Reprinted with permission from AAAS. http://www.sciencemag.org/cgi/content/full/313/5795/1929