University School of Medicine. The work appeared in the September 2006 issue of *PLoS Computational Biology*.

VEGF promotes the growth of blood vessels, a process known as angiogenesis. Developing treatments to halt or promote angiogenesis is rife with complex issues: Too much VEGF can lead not only to cancer but also to abnormal blood vessel growth. And VEGF concentration is not the only issue; to control vessel growth one needs to control the VEGF gradient across the tissue—a challenging task. Previous computational models have addressed this question *in vitro*. But this model takes that work a step further, modeling VEGF gradients in a complex *in vivo* environment.

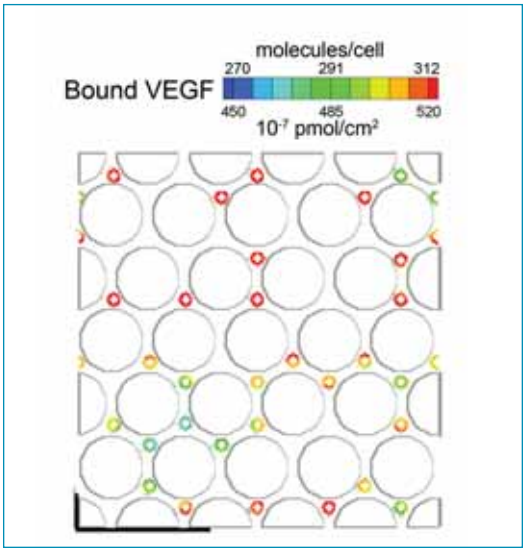
"We can model the behavior of therapeutics that you just can't do *in vivo*," Mac Gabhann says.

Feilim Mac Gabhann, PhD, now a postdoctoral fellow at the University of Virginia, built the model from electron micrographs and *in vitro* data on the size and shape of vessels, muscle cells, and the organic matrix between them. He simulated different scenarios to analyze how VEGF moved between muscle and vessel. He found that VEGF concentrations increased dramatically when the model mimicked oxygen-starved muscle. In addition, the model predicted a 12 percent change in VEGF concentration over 10 microns—a characteristic no other research had attempted to quantify. This gradient may be significant for capillary sprouting, the researchers suggest.

"This research is right on the edge," says **Dan Beard, PhD**, professor of physiology at Medical College of Wisconsin. "They are just at the point where they've put everything together. They are ready for applications where there is potential for big payoffs." But Beard warns they need to prove the model truly mimics *in vivo* angiogenesis—a task the team admits will be difficult.

Mac Gabhann and Popel next want to mimic drug activity to watch molecules interacting with VEGF. If a drug can reduce VEGF to a trickle instead of a flow so that vessels don't grow, it might help fight cancer. If a drug increases VEGF diffusion, or guides blood vessel formation more precisely, it might help with wound healing. "We can model the behavior of therapeutics that you just can't do *in vivo*," Mac Gabhann says.

—Megha Satyanayarana

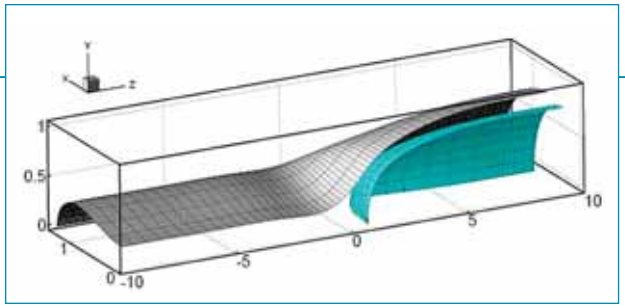


This image shows skeletal muscle (gray circles) interspersed with capillaries color-coded to show the amount of VEGF bound to each capillary. Red capillaries have more VEGF bound and may sprout new vessels in response to the signal. Courtesy of Aleksander Popel and Feilim Mac Gabhann.

Opening Airways

Scientists are breathing new life into airway modeling. Using a three-dimensional mathematical model of the delicate passages in the lungs, researchers have found that strongly collapsed airways are actually easier to reopen than partially collapsed ones.

"Everybody I have mentioned it to has said, 'No, but surely, that's the wrong way around,'" says **Matthias Heil, PhD**, a reader in applied mathematics at the University of Manchester, United Kingdom.



A computational model of pulmonary airway reopening. An air finger propagates (from right to left) into a strongly-collapsed fluid-filled airway. The finger reopens the airway and deposits a thin layer of fluid on its wall. The grey and cyan surfaces show the airway wall and the air-liquid interface, respectively. Courtesy of Matthias Heil and Andrew Hazel.

Heil and **Andrew Hazel, PhD**, a mathematics lecturer at the University of Manchester, created a model of the respiratory tracts to study how a stream of air can open a closed airway. The work was published in the August 2006 issue of the *Journal of Biomechanical Engineering*.

A surfactant layer of proteins and lipids normally lines airways, reducing surface tension along the fluid-covered walls. However, many premature babies lack surfactant, and adults who have gulped air filled with smoke or noxious fumes can destroy their surfactant layers. In these cases of respiratory distress syndrome, the surface tension increases, the airways collapse, and the fluid lining becomes a blockage. Doctors treat this collapse by forcing pressurized oxygen vigorously into the airways to redistribute the fluid. They often add surfactant to avoid damaging lungs with over pressure.

"You want to reopen the lung as soon as possible," says Heil. "The easiest way to do this is to apply an enormous amount of pressure, but then you can actually damage the lung tissue. So there's a fine balance to be found."

Heil and Hazel's three-dimensional model surpassed previous two-dimensional models by taking the fluid's viscosity, inertia, and surface tension into account. With this more realistic model, they revealed that less pressure is required to reopen airways that have collapsed more completely. The smaller cross-section of fully collapsed airways means a smaller volume of fluid to redistribute. This takes less energy, and less

air pressure, than moving around fluid that clogs a partially collapsed airway.

However, the researchers acknowledge shortcomings in their model. Airways are not infinitely long tubes, as Heil and Hazel assumed. "The airway branches are relatively short before they branch again," says Heil. "You have this tree structure, and that is something we do not take into account."

Oliver Jensen, **PhD**, professor of applied mathematics at the University of Nottingham, United Kingdom, says the new model is a step forward compared to older ones. "They've developed an absolutely wonderful tool," says Jensen. He notes the model also should apply to other systems with fluid-lined tubes, such as blood vessels.

For doctors who treat collapsed airways, Heil and Hazel's work eventually could lead to fine-tuned air pressure for different patients. For now, when doctors sit down to use a ventilator, says Jensen, "It's nice if they can at least understand what is happening in the airways."

—Sarah CP Williams

New Algorithm Finds Stories in Biomedical Literature

A good story ties up all the loose ends. A new data-mining tool takes a stab at doing the same. Dubbed *storytelling*, the algorithm may make it easier to unearth unexpected connections in the avalanche of freshly published research, or among high-throughput datasets. For example, *storytelling* can sift through tens of thousands of PubMed abstracts to discover scientific links between two apparently unrelated topics; or draw connections across a knowledge structure such as the Gene Ontology.

"What we are trying to do is link data sets very far apart," says **Richard Helm**, **PhD**, associate professor of biochemistry at Virginia Polytechnic Institute. "In the end, we link data set A with data set Z in the form of a story." The work was presented at the Twelfth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining (KDD 2006), in August 2006.

Researchers might not have time to find complex relationships waiting for discovery in the literature, but *storytelling* does. It finds key documents bridging from one research publication (the starting point) to another (the end point). Using System X, a Virginia Tech supercomputer, the algorithm first classifies each PubMed article's abstract into an organized branched set of terms. It can then make thousands of comparisons and join related publications into a chain connecting start to finish.

For example, Helm and his colleagues, used *storytelling* to dig through the literature seeking ties between two remotely related papers: one on tomato genes expressed in yeast and another on how chemical stress affects yeast gene expression. The supercomputer boiled down 140,000 yeast publications to nine abstracts—stepping stones from paper one to paper two. The results included a paper that identified a novel protein, expressed only when yeast cells are exposed to cadmium, which researchers might not have immediately connected with the first two papers. Although the paper might have surfaced in an ordinary PubMed search, it would have required much sifting to find it. While not every search will yield treasures, hopefully most results from *storytelling* will provide new insights and hypotheses that researchers can test at the bench, Helm says.

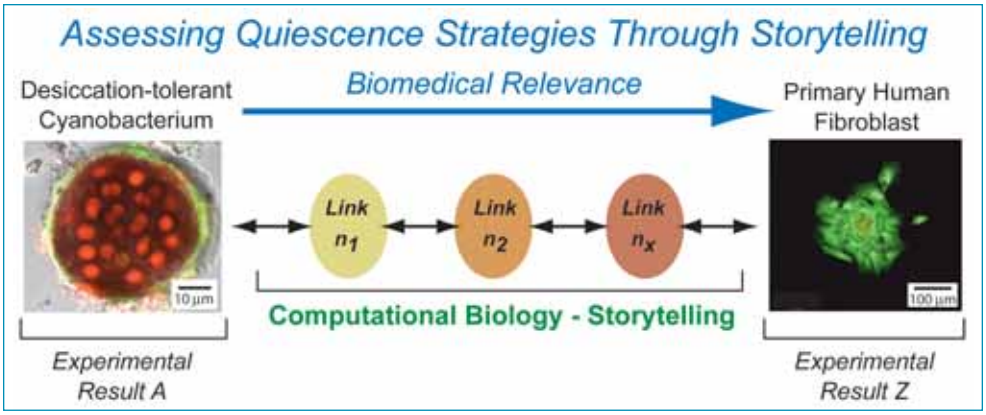
Bud Mishra, **PhD**, professor of computer science and cell biology at New York University, thinks *storytelling* can help biologists make new connections. "In some sense it closely resembles what biologists do, and it works in the same way that biologists think," says Mishra.

—Brian Lee

A Fast Lane Through the Stomach

What goes into the stomach must come out, but perhaps not in the same order in which it entered, as gastroenterologists have long assumed. A two-dimensional computer model of human stomach digestion reveals a previously unknown narrow pathway that can funnel liquids from the top of the stomach to the intestines within 10 minutes.

"There are very few times you discover something that you weren't expecting to find when you designed the experiment," says **James G. Brasseur**, **PhD**, professor of mechanical engineering, bioengineering and mathematics at Penn State University and one of the researchers



As shown here, one might use* storytelling *to understand the pathways into and out of a quiescent state. Datasets evaluating desiccation-tolerant cyanobacteria (left, coccoid cells stained red and encased in an extracellular matrix, the exterior of which is stained green) could potentially be linked to studies involving the metabolic arrest and recovery of primary human fibroblasts (right, Live/Dead stain; image taken 72 hours after a two week metabolic arrest).* Storytelling *allows the biologist to link disparate datasets, allowing for the development of new hypotheses that can be tested at the bench and re-evaluated within the algorithm, ultimately resulting in new insights into the process of interest. Courtesy of Richard Helm.