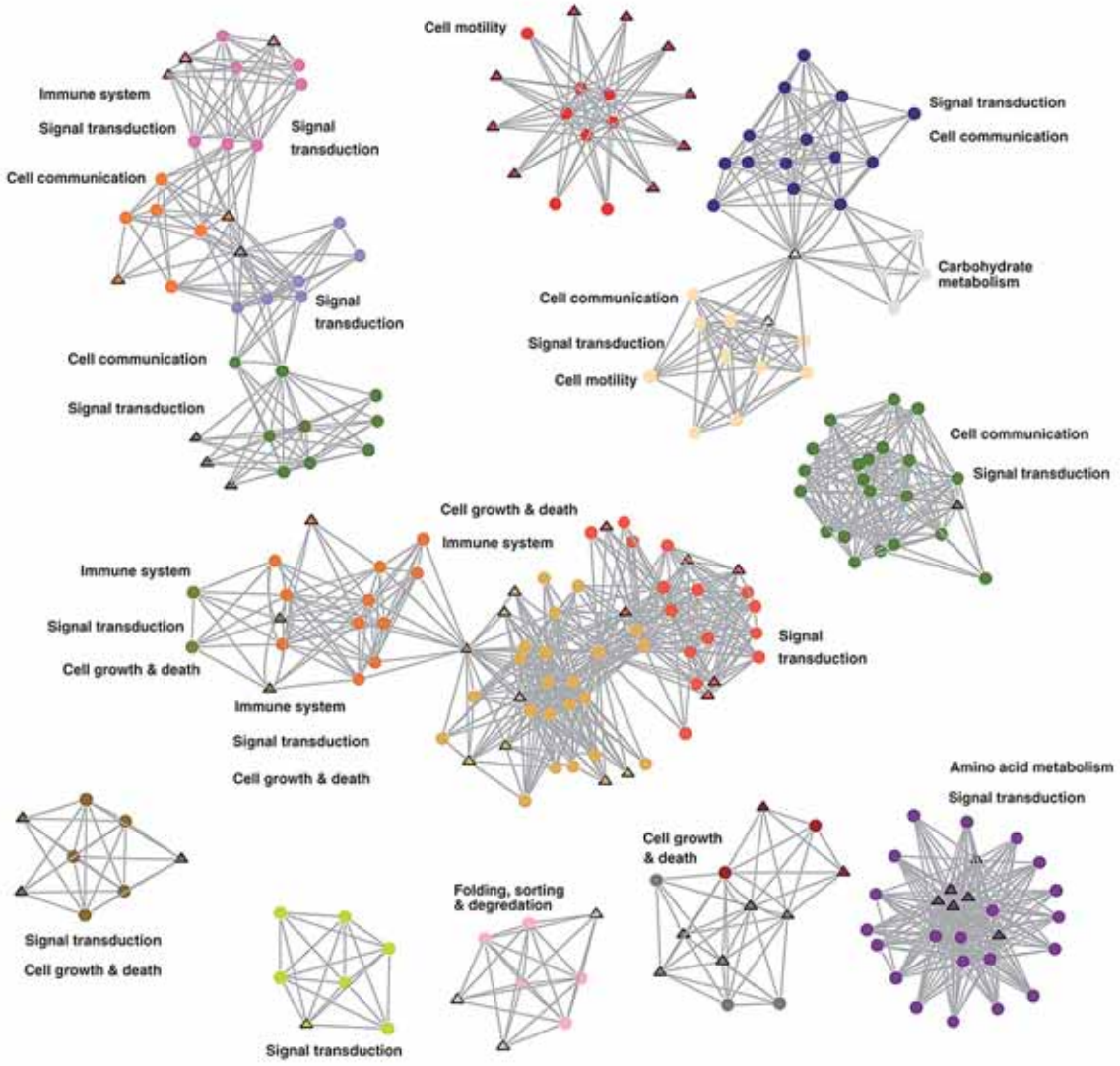


A sampling of protein communities identified in the interactome. Each community is labeled by the general classes of functions in which it belongs. Cancer proteins are shown as triangles. Note that this figure shows only one community assignment per protein, although they can belong to more than one. Courtesy of Pall Jonsson and Paul Bates.

The average cancer protein is linked to 23 other proteins in the network, more than twice as many as the typical protein.

date at the University of California, Davis, says the results are hard to interpret. The mapped cancer proteins were based on genetic information rather than experimental data on how they interact, he says. "A gene may perform a function in the cell, but the mutation could either reduce the function or result in higher activity. ... It could go either way," says Wachi, who has studied the network properties of proteins in lung cancer tissues. Wachi also cautions that because the list of cancer genes is changing dramatically, the researchers may soon need to re-examine their model.

Bates would like to do further analysis. "We've only got 108,000 interactions. There's likely to be more than that—400,000, maybe 700,000," he says. "We want to increase the map and validate it further."

—Rachel Courtland

Watching Blood Vessels Grow and Shrink

Microscopic capillaries grow on demand, snaking toward hungry cells needing their blood supply. Understanding how to control this process could help scientists promote wound healing or halt cancer in its path. A new computer model simulates how a key molecule (VEGF, or vascular endothelial growth factor) summons vessels to sprout: It spills out of a hungry cell and travels toward a vessel, with increased concentrations in areas with few vessels. The two-dimensional model also predicts the actual number of VEGF molecules at that edge, another novel advance.

"There have been over 10,000 papers published on VEGF and not one shows a molecular-level computation," says **Aleksander Popel, PhD**, professor of biomedical engineering at the Johns Hopkins

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.

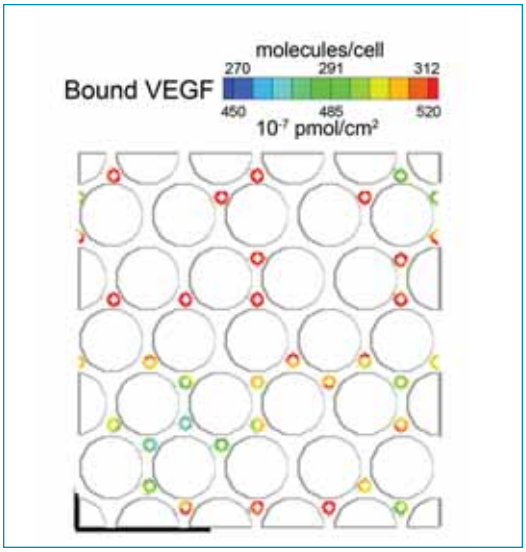
"We can model the behavior of therapeutics that you just can't do *in vivo*," Mac Gabhann says.

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

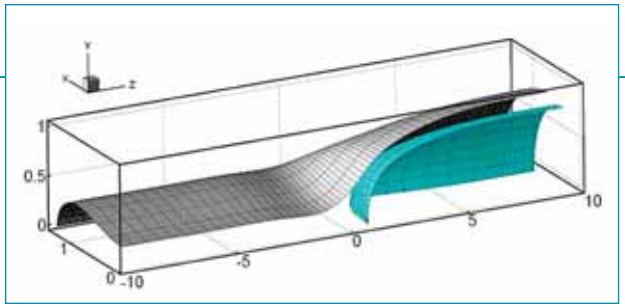


This image shows skeletal muscle (gray circles) interspersed with capillaries color-coded to show the amount of VEGF bound to each capillary. Red capillaries have more VEGF bound and may sprout new vessels in response to the signal. Courtesy of Aleksander Popel and Feilim Mac Gabhann.

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