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

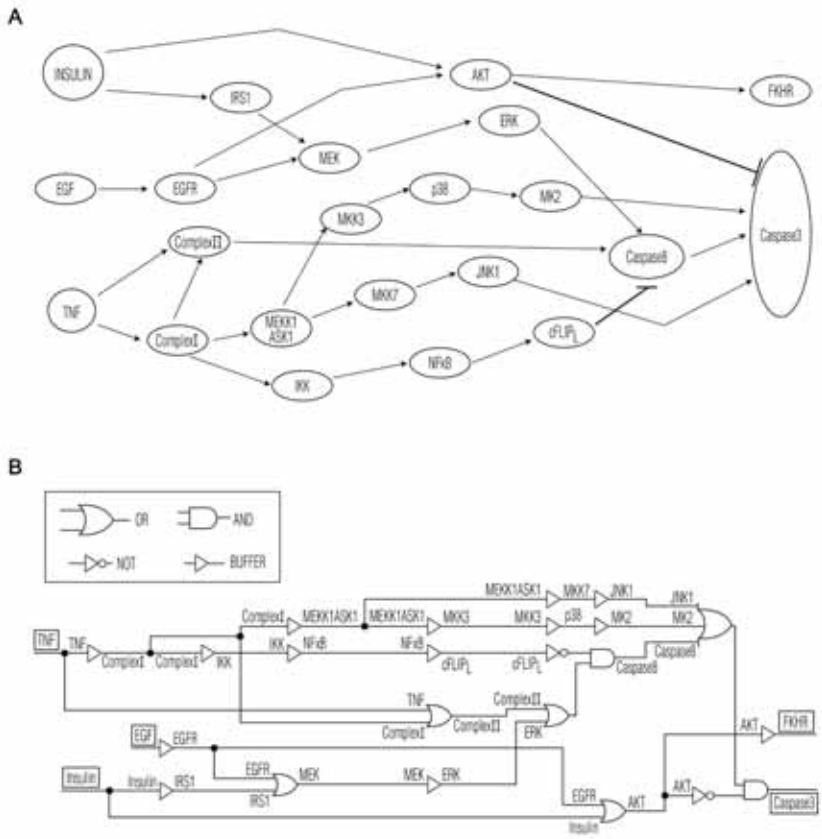
To biologists, a computer's motherboard may just look like highways of circuitry connecting various chips. But if they focus harder, they might see a model for disease, according to new research.

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-