Computer model reveals cells' inner workings

October 16 2008

(PhysOrg.com) -- After spending years developing a computational model to help illuminate cell signaling pathways, a team of MIT researchers decided to see what would happen if they "broke" the model.

The results, reported in the Oct. 17 issue of the journal *Cell*, reveal new ways in which cells process chemical information and could indicate how to maximize the effectiveness of disease treatments such as chemotherapy.

A couple of years ago, MIT faculty member Michael Yaffe and colleagues reported a data-driven computational model that allows them to simultaneously investigate the relationships between several cell signaling pathways, which control the cell's response to inflammation, growth factors, DNA damage and other events.

Such a model can help researchers figure out how cells will respond to growth factors and treatments like chemotherapy, allowing them to potentially tailor treatments to individual patients.

In the Cell paper, the team took a new approach to wring more information out of their model: They looked at what happens in cells under conditions where the model fails catastrophically. This approach, which the authors call "model breakpoint analysis," is an extension of more traditional failure analysis methods commonly used by engineers to figure out what design changes would make a bridge fall down or an engine fail.

"In traditional engineering sciences, you frequently use computational methods to predict what effect a faulty strut or a broken wire will have on a plane or an electronic circuit — will it fail, and if so, when and how?" said Yaffe, associate professor of biology and biological engineering and senior author of the new paper.

Doing the same thing in cellular models can reveal important and previously unexplored aspects of the signaling pathways.

To "break" the computer model, the researchers entered increasingly implausible inputs to the model until it no longer correctly predicted cell fate. To their surprise, they found that the model remained accurate for a long time.

"As the data we used to build the model got progressively worse and worse — more and more biologically inaccurate — the model would work fine, and then when you got to a certain threshold — the breakpoint — the model suddenly wouldn't predict anymore," said Yaffe, who is affiliated with MIT's David H. Koch Institute for Integrative Cancer Research, the Broad Institute of MIT and Harvard, and Beth Israel Deaconess Medical Center.

"By going back and looking at what happened in the model when the predictions failed, we discovered a surprising amount of new biology that was actually happening in the living cell," Yaffe said.

One significant, unexpected finding is the observation that both overactive and underactive mutations within a particular gene, such as those found in cancer, reduce cell death compared to the normal gene. This suggests that normal cells are poised to die whenever there is trouble, but perhaps not tumor cells.

That means the dynamic range of cell signaling — the spread between

the highest and lowest levels of a biological signal, like the range of volumes you can hear on your stereo — may be a greater determinant of what cells do than the absolute level of a particular signal, said Yaffe.

The computer modeling approach offers the chance to learn about biological phenomena that might take thousands of hours in the laboratory to uncover, according to Yaffe.

"In addition, rather than looking at one pathway in the cell in isolation, we could look at five pathways or eight pathways simultaneously," he said. "It also reinforces how engineering ideas can really illuminate biological mechanisms."

Provided by Massachusetts Institute of Technology