

Battling cancer

Understanding signaling networks

In 2008, more than 41,000 American women died of breast cancer and almost 173,000 others were newly diagnosed with the disease, according to Jason Xuan, an associate professor who is working on breast cancer research.

One of the major therapies to combat this cancer is the administration of antiestrogen drugs. Although most patients with hormone-responsive breast cancers will respond positively to this treatment, many of these cancers will recur and become resistant to antiestrogen drugs, requiring alternative treatments.

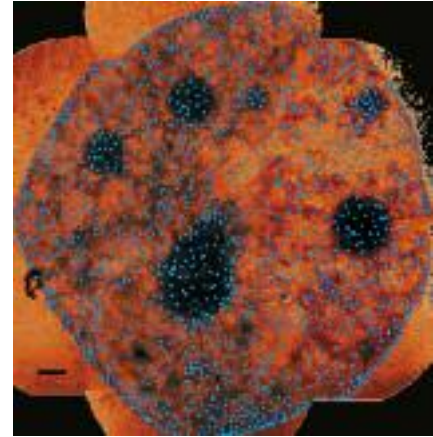
Xuan and ECE's Yue Wang are working with colleagues in molecular biology and clinical oncology at Georgetown University Medical Center to understand why cancer cells become antiestrogen resistant. It has long been known that estrogen can bind to estrogen receptors within cancer cells and initiate a signaling cascade that ultimately causes proliferation. Accordingly, antiestrogen drugs work by binding to estrogen receptors and preventing estrogen from binding, but many details of the signaling network remain unknown as does the cause of antiestrogen resistance.

Xuan and Wang are developing new computational methods

that can be applied to gene expression data to unravel the functioning of the estrogen receptor signaling network for both antiestrogen responsive cells and resistant cells. The ultimate goal of understanding this network is to identify new drug therapies for estrogen resistant cancers, which would have a major impact on breast cancer mortality and improve the quality of life for breast cancer survivors.

The work is funded by a \$350,000 grant from the National Institutes of Health.

A human mammary cell



U.S. Department of Energy Genomes to Life Program

RNA MOLECULES

Noise model overturns accepted notions

Modeling the effects of noise on a system helped a Virginia Tech team of biologists and engineers discover an inconsistency in two commonly accepted notions about single cells: how many messenger RNA (mRNA) molecules are in a cell, and how long they live. Their results affect the understanding of how cells process information and were published this spring in the *Proceedings of the National Academy of Sciences (PNAS)*.

In a cell, information is processed through a molecular network of genes and proteins. Messenger RNA is the molecule that carries information from the gene to the cell's ribosomes, where proteins are made. Because of their small size, cells are sensitive to random fluctuations in the number of molecules being created or destroyed at any given moment. Yet, despite the noise in the system from variations in mRNA molecules,

cells typically have reliable communications for essential processes such as DNA replication and cell division.

Because of the randomness of the mRNA numbers, the team investigated the system through a stochastic modeling perspective. For yeast cell-cycle genes, the literature reported, on average, only one mRNA molecule per gene per cell and that each mRNA molecule lives, on average, for 15-20 minutes before it degrades.

ECE's Bill Baumann worked on the model with John Tyson, University Distinguished Professor of biology, Mark Paul of mechanical engineering, and Sandip Kar, a postdoctoral associate. "When we looked at the effects of noise on our calculations, we found a tradeoff," Baumann said. "If the mRNA molecules are short-lived, then a small number of them are sufficient for the cell to function. If they are long-lived, however,

small numbers are a problem: they create too much noise." The team concluded that since experimental data revealed long lifetimes, there had to be higher numbers of mRNA molecules than conventionally accepted.

"We came to our conclusion based on our model of a yeast cell, and recent experimental work agrees that the numbers of molecules had been underestimated in the past," Baumann said.

Electrical engineers typically model the effects of noise for radio receivers and other communications applications.

"This is a different application of the same theory, except that as a biological system, it's highly nonlinear," he said.

Tyson, Baumann, and Paul are investigators on a National Institutes of Health (NIH) funded research project to build more elaborate and more accurate models of noise in the control system of yeast cells.