

# BIOMEDICAL APPLICATIONS

## Understanding ovarian cancer drug resistance

**E**CE researchers are collaborating with researchers from Johns Hopkins University School of Medicine to develop an integrated systems biology approach to study ovarian cancer drug resistance. Ovarian cancer is the fifth leading cause of cancer death among women in the United States and up to 80 percent of patients diagnosed at advanced stages die within five years.

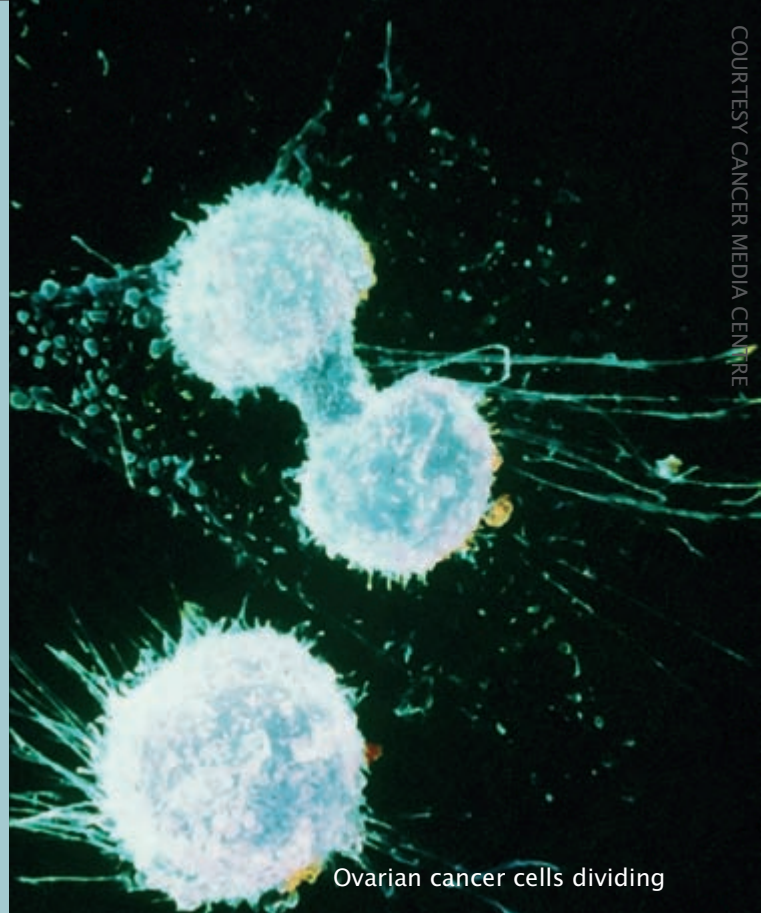
In many cases, the patients initially respond to chemotherapy but later relapse with recurrent tumors that are resistant to the therapy. The Johns Hopkins researchers have produced a cell line model for which they can reversibly turn on and off the cell's drug resistance.

Stimulating this simple biological system with relevant inputs and observing the dynamic response of the protein levels within the cells will provide data that the ECE team will use to build models of the signaling and regulatory networks that are responsible for drug resistance. These models will then be validated experimentally and ultimately used to more precisely target drugs to improve the long-term survival of patients.

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Ovarian cancer cells dividing

COURTESY, CANCER MEDIA CENTRE

## The key risk factors in cardiovascular disease

**T**he Computational Bioinformatics & Bio-imaging Laboratory, in collaboration with the medical team at the Wake Forest University School of Medicine, is working on a genome-wide association study to identify an individual's risk of cardiovascular disease from the joint effects of multiple genetic factors.

Although there are a number of studies underway to collect genetic data from individuals with cardiovascular diseases, the analysis of these massive data sets to identify the key risk factors and their interactions is a critical but unsolved problem. The staggering number of possible combinations of factors that must be considered, coupled with the probable nonlinear nature of these interactions, makes

this problem immensely complex.

Using recent advances in machine learning, such as support-vector machines, conditional mutual information, and cluster computing, Joseph Wang and his colleagues expect to make significant advances over conventional techniques that rely on linear models and simple interaction terms. Ultimately, this work will enhance the ability to predict, treat, and prevent cardiovascular disease.

The ability to identify individuals with a genetic predisposition for disease will allow for more effective preventive interventions, including modifying environmental exposures that have been shown to interact with the genetic predisposition to increased disease risk.

# WINDOWS to the brain

Does changing white matter in the aging brain affect cognitive function? Do the effects of alcohol abuse on the brain begin early in the abuse process? Does childhood exposure to stimulants such as methylphenidate (Ritalin) predispose adolescents to developing substance abuse disorders?

These questions are being investigated using image analysis tools developed by researchers in the Bioimaging Systems Laboratory. The laboratory is a joint effort between ECE and the Virginia Tech/Wake Forest School of Biomedical Engineering and Sciences to accelerate the use of imaging and image analysis in biomedicine. Much of the work is done in collaboration with clinical and basic science researchers at the Wake Forest School of Medicine and the Virginia-Maryland Regional College of Veterinary Medicine.

The nerve fibers that transmit signals long distances within the brain constitute the white matter. As adults age, they can develop patchy white matter lesions, which are referred to as leukoaraiosis (LA). These lesions appear as hyperintensities—or higher contrast spots—in radiologic imaging. LA lesions create a problem for researchers studying how the brain changes with age, as current image registration methods do not perform effectively in regions where tissue contrast has changed.

ECE's Chris Wyatt is developing a new registration approach that can accommodate contrast changes and determine whether the LA changes in white matter correlate with changes in cognitive func-

tion. The project is funded by UCLA's Center for Computational Biology (CCB) and the U.S. National Institutes of Health (NIH).

Investigations into the effects of alcohol and stimulants on the brain are underway in conjunction with research at Wake Forest; also funded by the NIH. The ECE team will apply cutting-edge image analysis techniques used in humans to primates, such as macaques or Rhesus monkeys.

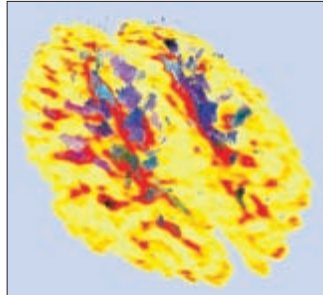


Image estimate of density and direction of white matter connections in a brain.

The alcohol abuse study seeks to understand whether the effects of abuse begin early in the process. Most of what is known of alcohol's effects on the brain is based on studies of individuals who have abused for a long time. Human studies are also complicated by factors including non-alcohol drug abuse, poor nutritional states and other medical conditions.

Although most studies of children and adults with ADHD have suggested that medication with methylphenidate or amphetamine has either no effect or can be protective from substance abuse, it is

impossible to distinguish between the effects of the stimulants and the ADHD itself, according to Linda Porrino, professor of physiology and pharmacology at Wake Forest. "Given that these stimulants can produce dramatic changes in the brain's dopamine system, the question of long-term adverse consequences still remains," she says. The studies on non-human models are designed specifically to answer whether or not stimulant exposure can predispose adolescents to developing substance abuse disorders.

# Applying system identification to biology

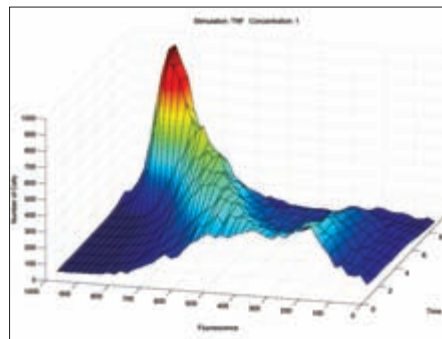
The successful sequencing of the genome for humans and other organisms has provided a "parts list" for these cells, but how these parts function and interact is largely unknown. Understanding these networks in human cells will help us better understand the nature of many diseases and point the way to more effective medical interventions. In microbes, this knowledge can aid in engineering designer bugs that can help with waste remediation or energy production.

Deducing the structure and dynamics of the biochemical networks that control life at the cellular level is of the major goals of systems biology. From an engineering perspective, this work falls into the area known as system identification.

What makes system identification of biological systems so difficult is the sheer complexity of the systems, the fact that they are highly nonlinear, and the difficulty of providing inputs and measuring outputs of the

system. Researchers cannot just hook up a function generator and an oscilloscope, as they might to analyze a radio circuit.

ECE's William Baumann, is working in collaboration with Jean Peccoud of the Virginia BioInformatics Institute, John Tyson of biology and Joseph Wang (ECE) on methods to identify these systems. To understand the basics of this problem, they are measuring the responses of synthetic gene networks engineered in bacteria. In this



The probability over time of an HIV response to a transcription stimulation.

case, where the network can be built up and measured step-by-step, it is possible to verify our techniques and understand the limits of our models. At the next level of complexity, they are looking at stochastic modeling of the cell cycle in yeast and the incorporation of new data from measurements of protein levels in single-cell organisms. At the highest level of complexity, they are investigating the use of gene and protein expression data to model networks of genes involved in diseases such as breast cancer and muscular dystrophy.