Systems biology is solving grand challenges by bringing together components from the disciplines of biology, engineering and computation. The new Integrative BioSystems Institute is helping Georgia Tech researchers solve complicated problems in human health and the environment.

Systems Biology:

Solving Grand Challenges at the Crossroads of Biology, Engineering and Computation

By Abby Vogel

In March 2007, when Georgia Tech professors Richard Fujimoto, Jeffrey Skolnick and Eberhard Voit invited colleagues conducting systems biology research to present at a poster session, they expected a few dozen researchers. To their surprise, more than 100 posters were presented that day.

"Systems biology is a relatively new field that focuses on complex networks of biological interactions. When we held the workshop, we were really surprised by the enormous interest on the Georgia Tech campus and also by the broad range of research projects presented that day," says Voit, the David D. Flanagan Chair in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University and Georgia Research Alliance Eminent Scholar in Biological Systems.

Georgia Tech's move toward

Associate professor Frank Löffler and graduate student Elizabeth Padilla-Crespo cultivate bacteria in chemostat vessels.

Photo: Gary Meek

systems biology research was under way. Less than a year later, this initiative was formalized by the launch of the Integrative BioSystems Institute (IBSI) with Voit at the helm as the founding director.

IBSI researchers aim to understand the complex biological systems in which molecules, cells, organs, organisms and ecosystems interact. Their ultimate goal is to solve complicated problems related to human health and the environment.

"Georgia Tech created the Integrative BioSystems Institute to provide our faculty members and students with the opportunity to efficiently and effectively explore the intersection of the traditional science and engineering disciplines with the life sciences," says Gary Schuster, Georgia Tech interim president and provost.

To do this, IBSI brought together a cross-disciplinary group of researchers from Georgia Tech's Colleges of Science, Engineering and Computing. They include:

- Biologists who develop strategies for designing experiments, collect reliable data and suggest important investigations that shed light on grand challenges such as cancer and environmental sustainability;
- Engineers who design new instrumentation that allows rapid, highly parallel, inexpensive and accurate measurements to be recorded of molecules and their characteristics, localization and interactions with other components; and
- Computational experts who manage, analyze and integrate the wealth of biological data and create accurate dynamic models of the system's performance.

"These investigations will lead to the development of new understanding, new tools and new procedures that will help us all to lead longer, healthier lives," adds Schuster.

Georgia Tech researchers plan to understand and fight threatening diseases, develop better pharmaceuticals, create more efficient therapies and determine how to better deal with environmental challenges that affect human health and quality of life.

Developing the Necessary Tools

Systems biology researchers must define all of the components of the system they are studying, including the regulatory relationships between genes and interactions of proteins and biochemical pathways. They can then use this knowledge to formulate conceptual and computational models that test and predict cellular functions and responses.

Complete genome sequences of various organisms are now available, and high-throughput technologies have emerged for molecular-level measurements of gene expression, protein function and protein-protein interactions. These advances make it possible to measure a large number of cellular components simultaneously, and to perform system-level studies at the molecular level with unprecedented breadth and depth.

The available sequenced genomes, however, are not very meaningful until the genes are distinguished from less useful information in the DNA strands. Mark Borodovsky, director of Georgia Tech's Center for Bioinformatics and Computational Genomics and a Regents' Professor in the Wallace H. Coulter Department of Biomedical Engineering and the College of Computing, has developed several algorithms and computer programs that do just that for genomes with different levels of complexity.

"It's like deciphering text when you initially don't have a clue what the sequence of numbers or letters means," he says. "The information you are looking for may be hidden in just five percent of the whole sequence, but you need to find this very important text."

Since 1995 – the start of the genomic era – Borodovsky's line of software pro-

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grams, with the common name GeneMark, has been frequently used in laboratories worldwide to find genes. The program was used to find genes in the first completely sequenced genomes of bacteria and archea.

Borodovsky has long-term funding from the National Institutes of Health. Currently, he is collaborating with the U.S. Department of Energy Joint Genome Institute, the Broad Institute of the Massachusetts Institute of Technology and Harvard University, and genome centers in Europe and Japan to find genes in sequences of novel complex genomes.

Although genes get a lot of attention, it's the proteins produced from the genes that perform most life functions. Unlike the relatively unchanging genome, the dynamic proteome changes every minute in response to thousands of internal and environmental signals.

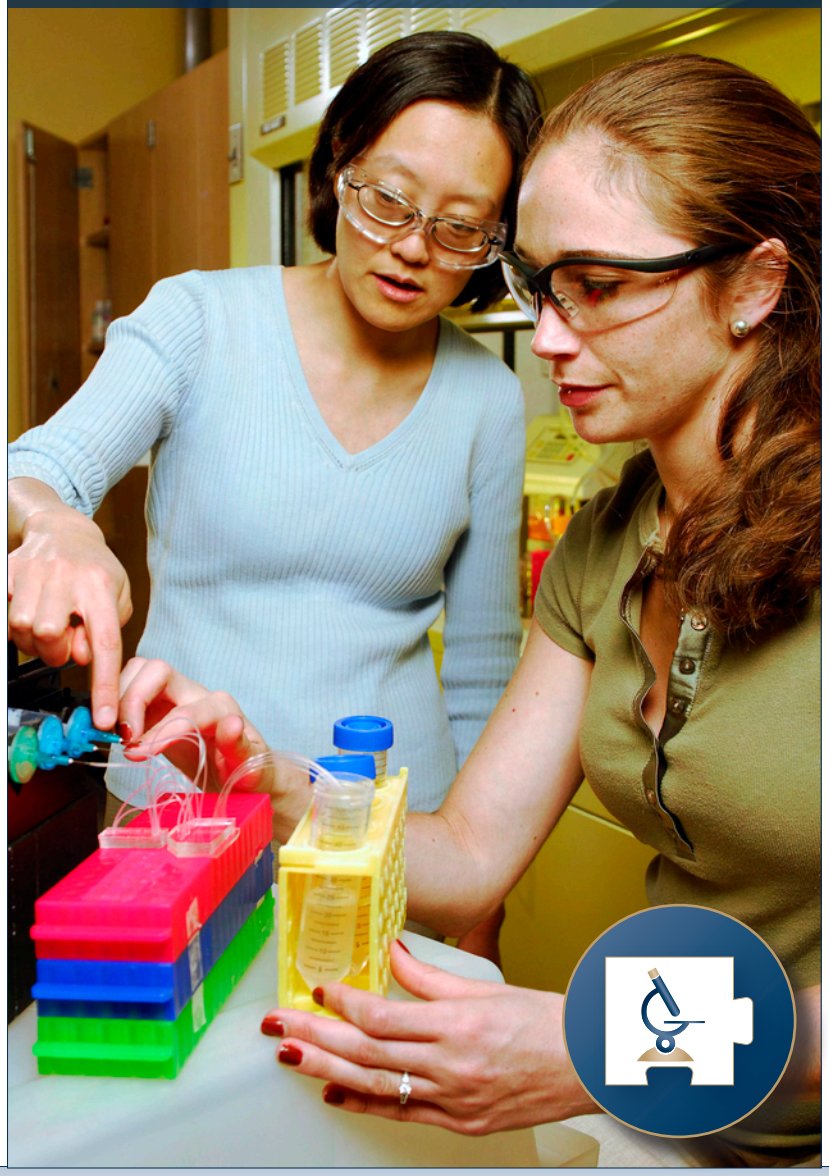
A protein's chemistry and behavior are specified by the gene sequence and by the number and identities of other proteins made in the same cell at the same time and with which that protein associates and interacts. College of Computing professor David Bader and graduate student Kamesh Madduri are using a social networking principle called "betweenness centrality" to analyze cellular proteins interacting in complex systems.

"It's a metric in which you look at all of the proteins that are interacting and find the most important proteins – the ones where, if you remove them, you most likely disconnect the entire network," explains Bader.

The researchers have examined human protein-pro-

Photo: Gary Meek

Assistant professor Hang Lu (left) and graduate student Alison Paul test microfluidic devices.



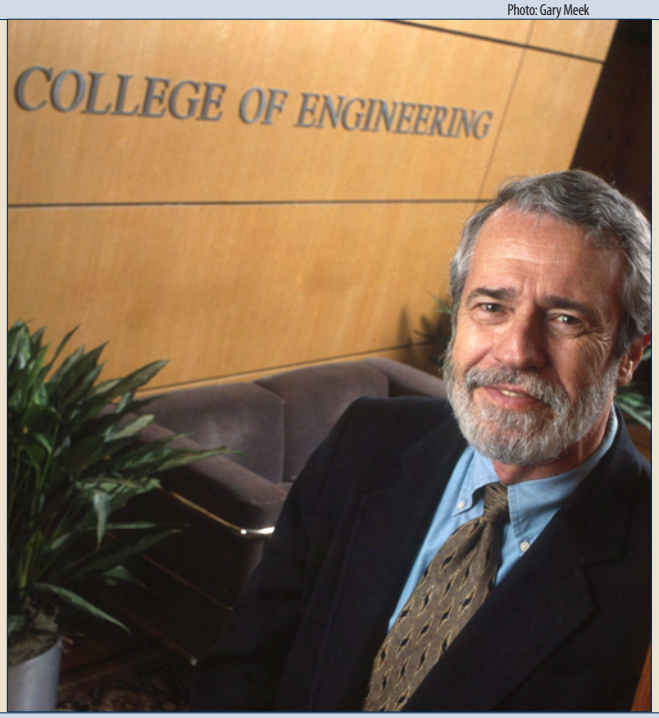
IN BRIEF

DEFINING THE IBSI

"The key words in the name of the Integrative BioSystems Institute are 'integrative' and 'systems.' Many advances in the life sciences today require an integration of what have previously been traditional disciplines, such as biology, computing and engineering. The disciplines provide strong foundations of knowledge and discovery, but the maximum benefits occur when these are integrated to study systems. Creating the Integrative BioSystems Institute is an organizational method of achieving this integration at Georgia Tech."

– Don Giddens, dean of the College of Engineering, the Lawrence L. Gellerstedt Jr. Chair in Bioengineering and a Georgia Research Alliance Eminent Scholar

Photo: Gary Meek



tein interaction datasets and discovered proteins important to the cells, including one that has been implicated in breast cancer. What is intriguing though, says Bader, is that the important proteins are not usually those that interact with the greatest number of other proteins. Bader plans to continue studying protein-protein interactions with other IBSI members.

In addition to genomics and proteomics, another key factor in the rise of systems biology is the rapid development of measurement technologies. Modeling biological systems requires highly accurate, high-throughput, quantitative methods and devices to collect data under many different conditions.

Microfluidic devices show much promise for this, and Hang Lu, an assistant professor in Georgia Tech's School of Chemical & Biomolecular Engineering, has engineered microfluidic devices to collect multiple pieces of data simultaneously from cells and microscopic organisms.

"We've designed a lab-on-a-chip from which we can get lots of data with very high spatial resolution, very high throughput and low error because we've taken out the human manipulation of the organisms – it's all automatic," says Lu. Details about the device were published in July 2008 in the journal *Nature Methods*.

The device Lu developed incorporates complete automation, which allows her to conduct quantitative population experiments to study the genetics of developmental processes in complex systems such as the nervous system and the effects of small molecules on biological networks.

The advances in high-throughput measurement techniques also require innovations from computer science. The volume of data is large and the number of genes or proteins being studied at one time is often much greater than the number of samples.

College of Computing professor Haesun Park uses numerical linear algebra and optimization techniques to develop computer-based algorithms that dramatically reduce the number of genes that must be studied to only those that may be responsible for specific biomedical conditions.

"With careful consideration of the significance of the biological characteristics of the problem and without losing much information, the amount of data can be reduced so that the problem becomes computationally tractable," says Park.

When comparing gene data from a set of cancer patients to comparable information from a set of healthy individuals, it is important to determine which genes are important out of the more than 20,000 in the human genome. Effective algorithms for doing that can potentially increase the new knowledge about the roles of specific genes.

The wealth of biological data and availability of computers with enormous power are beginning to enable realistic models to be designed of living cells and organs that can simulate life in a quantitative fashion. Systems biology connects the wet and dry sciences by an iterative cycle of model-driven experimentation and experiment-driven modeling.

"A good mathematical model of a real world system should be able to quantitatively describe, predict and explain the behavior of the system," says Richard Fujimoto, chair of the Computational Science and Engineering Division in the College of Computing and a member of the IBSI executive committee.

FRONTIERS IN MULTI-SCALE SYSTEMS BIOLOGY CONFERENCE

Georgia Tech's new Integrative BioSystems Institute (IBSI) (www.ibsi.gatech.edu) will officially be presented to the public at the Frontiers in Multi-Scale Systems Biology conference Oct. 18-21, 2008, in Atlanta, Georgia. This conference will highlight topics of integrative systems biology including genomics, proteomics, metabolomics, molecular inventories and databases, modeling and simulation, high-performance computing, enabling experimental and computational technologies, and applications in cancer, neuroscience and the environment.

Photo: Gary Meek

Senior research technologist Bartosz Ilkowski stands in front of the School of Biology computing cluster.

IN BRIEF

Environmental and Health Systems Are Similar

"Modeling biological systems of human health and ecology are not very different. If ecologists draw a community interaction web showing connections among predators and prey, competitors, or host and pathogens and then remove the labels, it will look like a network of protein interactions to the human health biologists. The complexity of interactions and the mandate for considering the system instead of just the parts are similar for both molecular/biomedical and environmental scientists."

– Mark Hay, the Harry and Linda Teasley Chair in Environmental Biology in the Georgia Tech School of Biology

Many researchers begin modeling biological systems with simple organisms, such as bacteria, that can be easy to culture, manipulate genetically, maintain under controlled conditions and examine in the laboratory.

"Understanding small systems is a necessary prerequisite before we can deal with bigger systems, such as the human body and its disease processes," says Voit. "We need to look at microorganisms that have plenty of biological relevance in their own right, but that also allow us to explore the function and coordination of metabolites, enzymes and genes in organisms that are much less complex than humans."

In collaboration with Helena Santos, a professor at the Universidade Nova de Lisboa in Portugal, Voit recently showed that high-precision, dynamic experimental metabolite data could be combined with nonlinear systems modeling to characterize regulatory mechanisms in the bacterium *Lactococcus lactis*. These are difficult to assess with traditional biological analysis.

With a genome of fewer than 300 genes – compared to the more than 20,000 genes in humans – this bacterium served as an attractive model for Voit's biological systems approaches and for the development of new methodologies to analyze metabolites and optimize the production of valuable compounds for the food industry.

Environmental Systems Linked to Human Health

Once researchers understand microorganisms in controlled laboratory systems, they can begin to study them in their more complicated natural environments. The challenge is that although the genomes of hundreds of microbes have been sequenced, microbial ecosystems can encompass hundreds or thousands of different populations, each comprising large numbers of cells that often cannot be differentiated as individuals and must be considered as communities.

Frank Löeffler, the Carlton Wilder Associate Professor of Environmental Engineering, is analyzes complex soil microbial ecosystems so that he can improve the efficiency of environmental decontamination processes. His work focuses on remediating groundwater contaminated by toxic chlorinated solvents, such as those used in dry cleaning and metal degreasing operations.

Löeffler found microorganisms that detoxify these chemicals by biodegrading them into ethylene gas, a harmless end-product. The genomes of some bacteria involved in this process have been sequenced, and current efforts are aimed at determining the expression levels of thousands of genes and proteins to identify those responsible for the detoxification processes.

"With computational models, we can better understand the cellular regulatory networks, including how different components in the microbe interact and how populations of microbes interact," says Löeffler. This work is sponsored by the U.S. Department of Defense's Strategic Environmental Research and Development Program and the National Science Foundation.

Löeffler also has funding from the U.S. Department of Energy's Environmental Remediation Sciences Program to investigate uranium contamination. Uranium is radioactive and can be mobile – that is, it can be transported with the groundwater flow and cause widespread subsurface contamination.

Remediation is difficult, he says, because the actions of one set of microbes

RNA Folding

Christine Heitsch, an assistant professor in the School of Mathematics, is collaborating with School of Biology professor Steve Harvey and College of Computing professor David Bader to understand how ribonucleic acid (RNA) folds in two and three dimensions and how structural information is encoded in large RNA viral genomes. Because current prediction methods cannot reliably and efficiently treat these lengthy sequences, the researchers are developing novel combinatorial and computational approaches to the analysis, prediction and design of viral RNA secondary structures. "Once we know how things fold, we can design drugs to dock at the right places and design a sequence to fold into a specific shape," says Bader.

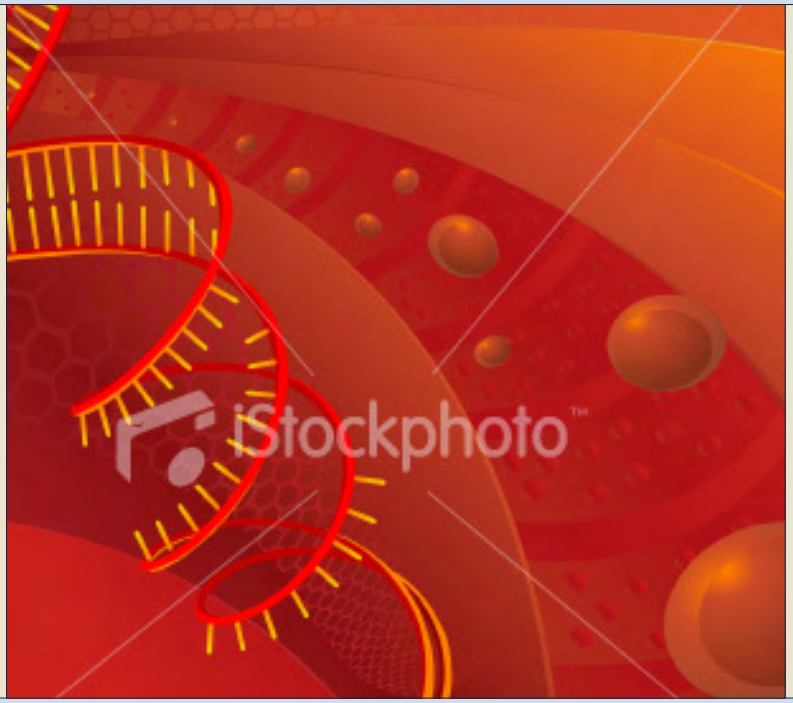
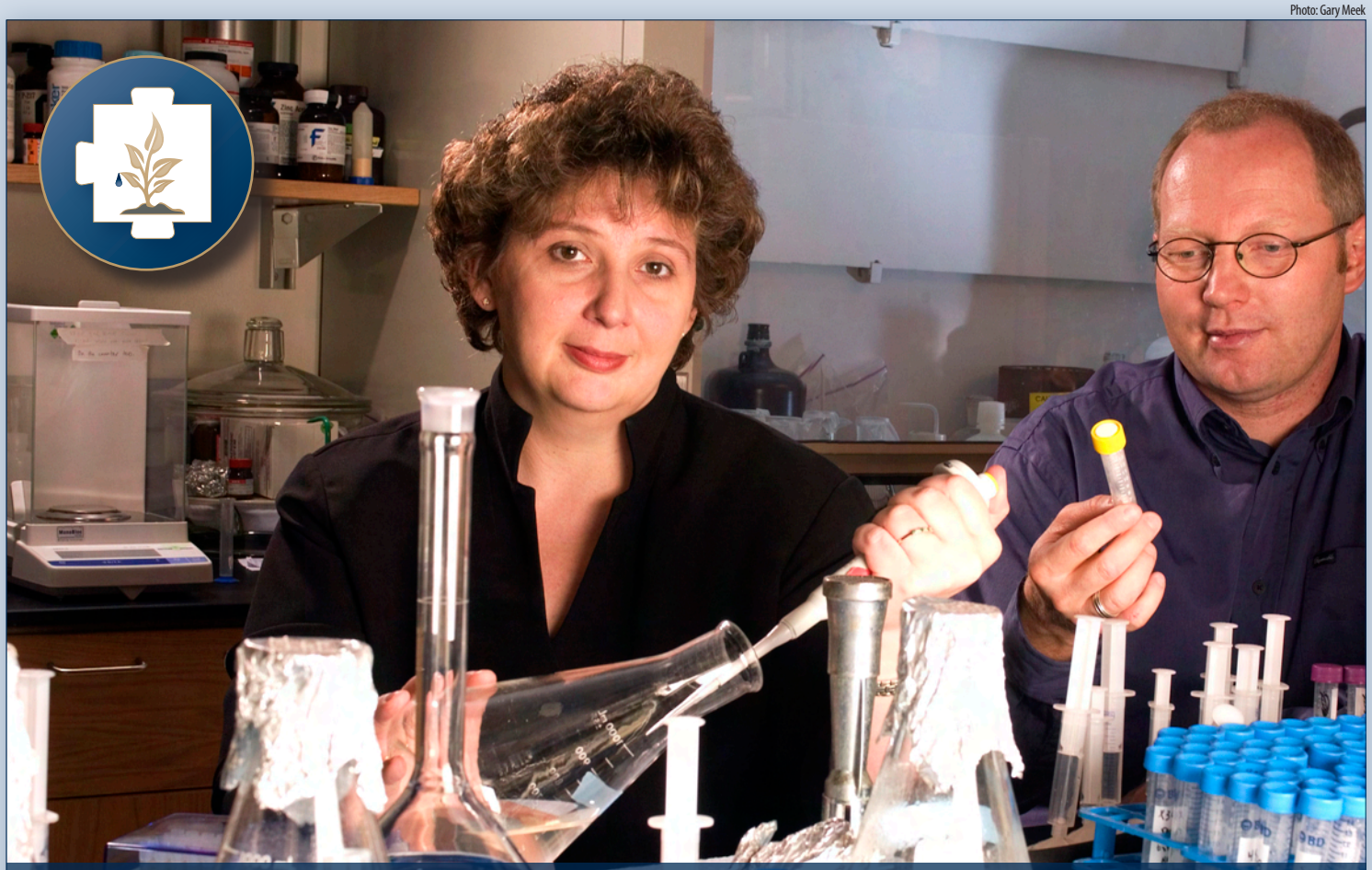


Photo: Gary Meek



Associate professors Patricia Sobecky (left) and Martial Taillefert analyze soil samples.

can undo the work of another. Microbes transform the soluble form of uranium into an insoluble form that won't travel or spread, but certain microbes can re-mobilize the uranium. Löeffler aims to understand these microbial processes so that computational models can be used to predict how best to remediate a contaminated area.

With funding from the U.S. Department of Energy, Patricia Sobecky, an associate professor in the Georgia Tech School of Biology, and Martial Taillefert, an associate professor in the School of Earth and Atmospheric Sciences, are analyzing aerobic processes that contribute to the remediation of uranium.

In articles published in the August 15, 2007 issue of the journal *Environmental Science & Technology* and the December 2007 issue of the journal *Environmental Microbiology*, Sobecky and Taillefert showed that certain bacteria could promote uranium immobility through the activity of phosphatases. This process, which can occur aerobically and anaerobically, can be included in models to remediate contaminated areas.

"While investigating phosphatase genes, we found that another gene was being transferred between organisms that allowed the organisms to pump heavy metals back out to help them adapt and detoxify their environment," explains Sobecky.

Currently, Sobecky is developing and applying systems approaches to better understand how these complex processes such as horizontal (or lateral) gene transfer operate. By studying the genetic material of these organisms, scientists can begin to understand how these microbes have evolved and adapted to life in extreme conditions, and isolate the genes that give them their unique abilities to survive and proliferate.

Horizontal gene transfer is also important in human disease because the process is thought to be a significant cause of increased drug resistance. When one bacterial cell acquires resistance, it can quickly transfer the resistance genes to many species. Cells commonly transfer genetic material between one another via bacteriophages, also known as phages, which are diverse and abundant viruses that exclusively infect bacteria.

Joshua Weitz, an assistant professor in the School of Biology, is modeling the mechanisms behind the diversity that can emerge from interactions between phages and bacteria. This is particularly difficult because the evolution of bacterial viruses is intimately linked to their hosts.

"I am trying to understand the strategies by which viruses interact with bacterial hosts at the cellular scale and the diversity of such strategies in different environments," says Weitz, who is funded by the Defense Advanced Research Projects Agency and the Burroughs Wellcome Fund.

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FACULTY COLUMN:

Systems Biology—What's All the Buzz About?

The buzzword "systems biology" entered the vocabulary of the scientific community only a few years ago, but what does it really mean?

Front and center is a clear focus on systems, which are collections of components that interact with each other and in the process make something happen. Typical components in the engineering world – screws, wires, wheels and transistors – don't do much when left to their own devices. However, let clever engineers put them together and the parts seemingly come to life, with the creation of a television set or a car. Something dynamic emerges out of a collection of objects.

On a coarse level, biological systems have quite a few similarities with engineered systems, but they are incomparably more complicated and intriguing. Not only do they move, but they also reproduce and develop on their own out of a single cell.

In contrast to cars, they search for their own food and adapt to new situations and even to entirely novel environments. They respond to challenges appropriately and intelligently, although the latter is sometimes disputed.

The grand challenge of systems biologists is to understand how biological systems function. This is an important goal, not just from an academic perspective, but also for very practical reasons.

Understanding how cellular control works—or fails—will suggest new options for cancer treatment. Insights into the organization of bacterial pathways will help harness the power of microorganisms for the biotechnological production of valuable organics or bulk products like ethanol and for novel, yet natural, means of cleaning up the environment.

Integrative systems biology adds a new and exciting set of tools to the repertoire of biological research techniques. It uniquely complements the more traditional paradigm of "reductionist" experimentation in which well-controlled experiments crisply focus on the characterization of select components or processes.

Reductionist biology has provided researchers with a rapidly growing list of molecular building blocks, along with details on their features and functions. The results of this reductionist paradigm have been truly amazing and have affected every aspect of life. Just look at the advances in medicine over the past decades!

Systems biology complements the reductionist paradigm by revealing how higher-level functionality emerges from interactions among the building blocks. They are intimately interwoven – after all, how could systems biology succeed without detailed knowledge of the players in a system? And why would anyone be interested in one particular gene or signaling process if it did not contribute to some higher-level function that is important in a cell, organism or ecological system?

Biological systems are complex and modeling them requires researchers in many areas of expertise to unite. The three main areas of expertise are described here. The first typically uses high-throughput experiments that, for instance, simultaneously measure the expression of thousands of genes in an organism. The ultimate goal of these researchers is to establish complete molecular inventories and characterize the function of each biological component.

The second area of expertise falls into the realm of engineering. Without innovative machinery, none of the high-throughput biology would be possible. Brilliant engineering advances in sensing, probing, miniaturization, robotics and many other areas allow biological building blocks to be investigated rapidly and with a clarity and resolution never seen before.

The third area of expertise is computational. Here the goal is the construction of numerical models that reliably quantify the interactions among the many components and processes within a biological system. Following Richard Feynman's observation, "What I cannot create, I do not understand," and glancing at the enormous successes in engineering, the "creating" is accomplished first with computer models, whose results later guide the creation of actual, yet synthetic, biological systems.

The technical aspects of experimentation, device creation and computation will certainly be the crucial drivers of the success of systems biology. Motivating these drivers is a systems-oriented mindset.

Systems biology encourages us to look at the living world with different eyes. Systems biologists appreciate the role and function of each biological building block – not in isolation, but as a vital part in the larger context of intricately fine-tuned machines that hierarchically form larger ensembles and, in concert with all parts, bring innate molecules to life.

Systems biology is a fascinating, mind-altering endeavor. So beware – engaging in systems biology may irreversibly change your views of the living world!

By Eberhard Voit

Voit is the The David D. Flanagan Chair in the Coulter Department of Biomedical Engineering, Georgia Research Alliance Eminent Scholar and director of Georgia Tech's new Integrative BioSystems Institute.

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With his research team that includes biologists, physicists, mathematicians and bioinformaticians, Weitz has developed simulation models of host-phage dynamics that begin at the site of infection. The researchers analyze the fate of the infected cell and infecting phage, followed by long-term population changes as both viruses and hosts respond to the emergence of newly reproduced – and in some cases newly evolved – strains.

Weitz's expertise in environmental host-phage interactions led him to begin studying the dynamics of diseases mediated by aquatic reservoirs, such as cholera. Cholera transmission occurs by ingesting contaminated water or food – infection doesn't require contact with a person already infected.

He has teamed with School of Mathematics professor Howie Weiss, physics graduate student Richard Joh and postdoctoral scientist Hao Wang to mathematically model the transmission of cholera and predict what conditions lead to endemic or epidemic outbreaks of the disease. The study of cholera dynamics is a multi-scale systems biology problem because the emergence of an outbreak depends on information about how an individual's immune system contends with a pathogen as well as how the pathogen spreads among a population.

Just as systems approaches improve knowledge of human health, they also provide management options for sustaining and improving the health of natural ecosystems upon which humans depend. Georgia Tech researchers are developing novel approaches to conservation and ecosystem restoration with the goal of sustaining ecosystem services such as food production and water and air purification. Mark Hay, the Harry and Linda Teasley Chair in Environmental Biology, explores tropical coral reefs in the Caribbean and South Pacific to understand the complex network of interactions that sustain these biodiverse systems.

Hay conducts field experiments by adding or removing different consumers, competitors and nutrients to ecosystems. The goal is to understand complex networks of interactions as a way to maximize the ecosystem's health and its ability to recover from environmental damage. This work is funded by the National Science Foundation and the National Institutes of Health.

Hay anticipates that this understanding will be used to develop models for predicting, avoiding and recovering from the effects of global change, invasions of non-native species and environmental stressors. He also hopes that this type of system-wide, multi-scale exploration will lead to better stewardship of the natural environment in the face of a growing human population that both values natural ecosystems and depends on the critical services they provide.

All organisms, regardless of their complexity, live in and rely on diverse and interconnected communities. At Georgia Tech, environmental systems that affect human health are being modeled on the scale and complexity of real living systems and processes.

Improving Drug Discovery

Modeling and simulation have played relatively minor roles in pharmaceutical research and development to date. Each drug and target combination is typically considered in isolation, which can often be

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Joint Research Proposals and Graduate Students

The Integrative BioSystems Institute (IBSI) has established a collaborative graduate student fellowship program and a pilot research program. The fellowship program promotes new collaborations between faculty members at Georgia Tech by funding a graduate student to be supervised by two faculty members from different disciplines. The research program supports pilot research projects that combine in a new way the expertise of at least two faculty members in different units within Georgia Tech. The typical award is about $30,000 for one year, with the possibility of extension.

Images: Vickie Okrzesik

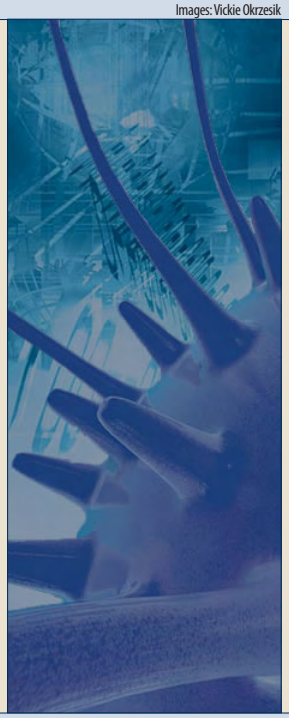
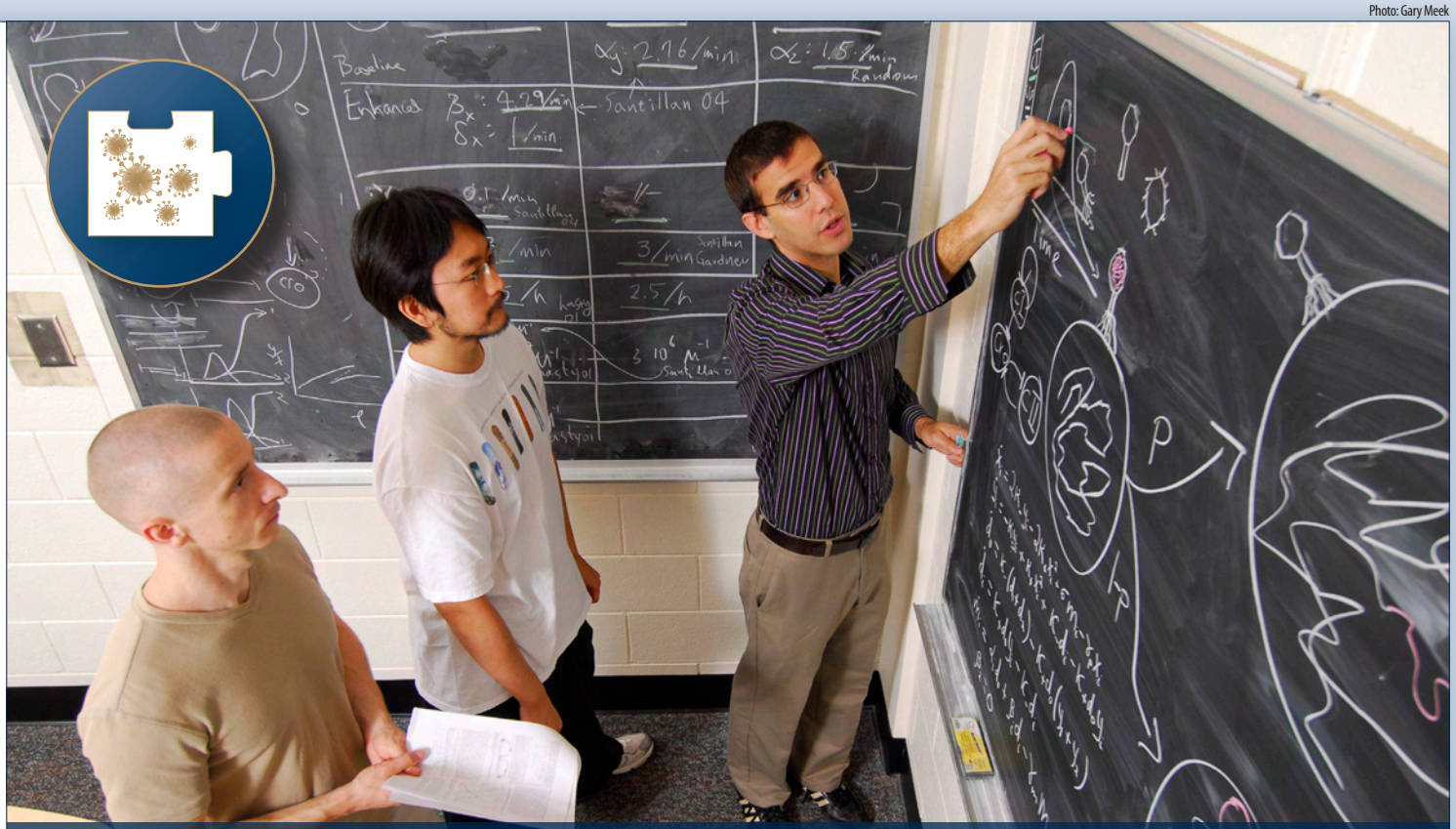


Photo: Gary Meek



Assistant professor Joshua Weitz discusses cholera transmission with postdoctoral scientist Yuriy Mileyko and graduate student Richard Joh.

misleading because the mechanisms contributing to the development of disease are complex and not just the result of the contribution of a single gene or its protein product.

With the increased use of antibiotics to treat bacterial infections, pathogenic strains have acquired antibiotic resistance, prompting extensive effort in the design of new or improved antibacterial agents. One target of antibiotics is the ribosome – the cellular workhorse that translates the genetic code into proteins.

To discover where new drugs will bind to the ribosome, researchers must know the structural shape of the ribosome, which includes two subunits that assemble to

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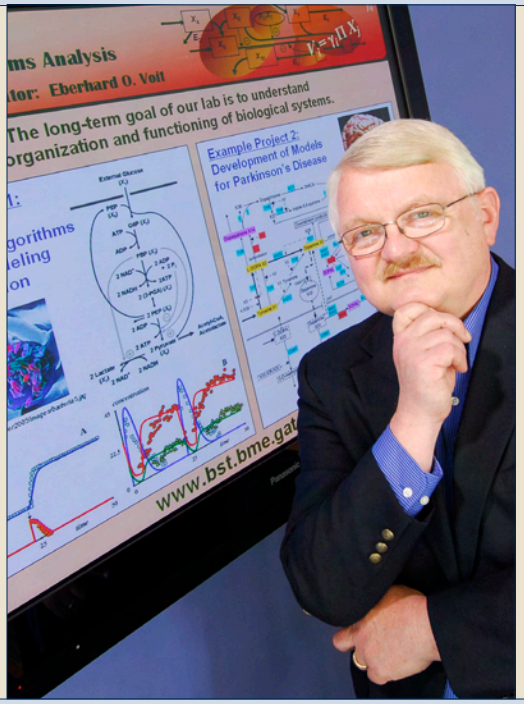
Modeling Neurological Disorders

Eberhard Voit, the David D. Flanagan Chair in the Coulter Department of Biomedical Engineering, postdoctoral fellow Zhen Qi and Gary Miller, an associate professor in Emory's Department of Environmental and Occupational Health, are developing a mathematical model of the dopamine network. They hope to use it to better understand how genetic, environmental and pharmacological factors alter how dopamine functions in healthy neurotransmission and in neurodegenerative diseases like Parkinson's disease and schizophrenia.

The researchers plan to use the model in conjunction with biological and clinical studies conducted at Emory University to screen novel therapeutics aimed at altering dopamine function and decreasing the symptoms of both disorders. This interdisciplinary research is being funded by the Woodruff Health Sciences Center's Predictive Health Initiative at Emory University.



Mass Spectrometry:

Techniques Offer Molecular Information to Help Solve Systems Biology Problems

Understanding biology at the systems level is difficult, especially when studying complex specimens like tissue slices or communities of organisms in a biofilm. Scientists must be able to identify, quantify and locate the molecules present in the samples.

Mass spectrometry imaging is a powerful analytical technique with the potential to unravel the molecular complexities of such biological systems. It allows researchers to visualize the spatial arrangement and relative abundance of specific molecules – from simple metabolites to peptides and proteins – in biological samples.

At Georgia Tech, researchers from the Colleges of Sciences and Engineering have joined forces to create the Center for Bio-Imaging Mass Spectrometry (BIMS) that aims to tackle these types of challenges.

"We organized this center in 2007 when we saw the enormous potential of mass spectrometry imaging tools and realized that we had a unique ensemble of people at Georgia Tech that would enable us to excel in this field," says Al Merrill, a professor in the School of Biology and the Smithgall Chair in Molecular Cell Biology.

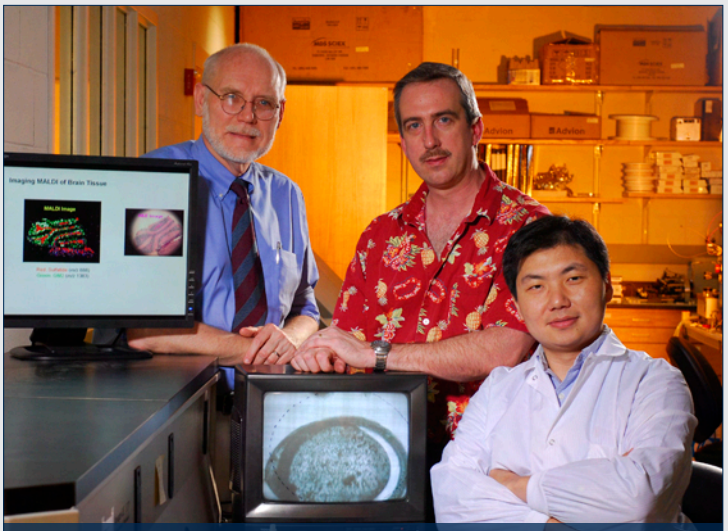
Mass spectrometry imaging takes advantage of the ability of biological molecules to be converted into ions that can then be separated and analyzed by a mass spectrometer. When data is collected from different regions of a sample, the distribution of molecules can be used to create multidimensional images of that sample.

As a cell biologist, Merrill sees the technique's potential in its ability to detect all of the important molecules that control cell behavior instead of just a few. Another advantage to mass spectrometry is the ability to test whether all of the cells are being affected in the same ways.

His laboratory uses mass spectrometry to profile sphingolipids, a family of thousands of metabolites that are involved in cell-cell communication and intracellular signaling. He also studies the types and amounts of these metabolites that control whether cells grow or die.

"With mass spectrometry, we have not only been able to profile these compounds, but also to find new metabolites we think are important in inflammation, aging and cancer," says Merrill.

The BIMS center includes researchers like Merrill who propose biological and clinical problems that may be solved by mass spectrometry imaging. It also brings together researchers who are improving current mass spectrometry imaging technologies and developing innovative techniques, and researchers who are analyzing the large sets of complicated data collected by mass spectrometry systems.



Professor Al Merrill, principal research scientist Cameron Sullards (left to right standing) and research scientist Yanfeng Chen display mass spectrometry results.

Photo: Gary Meek

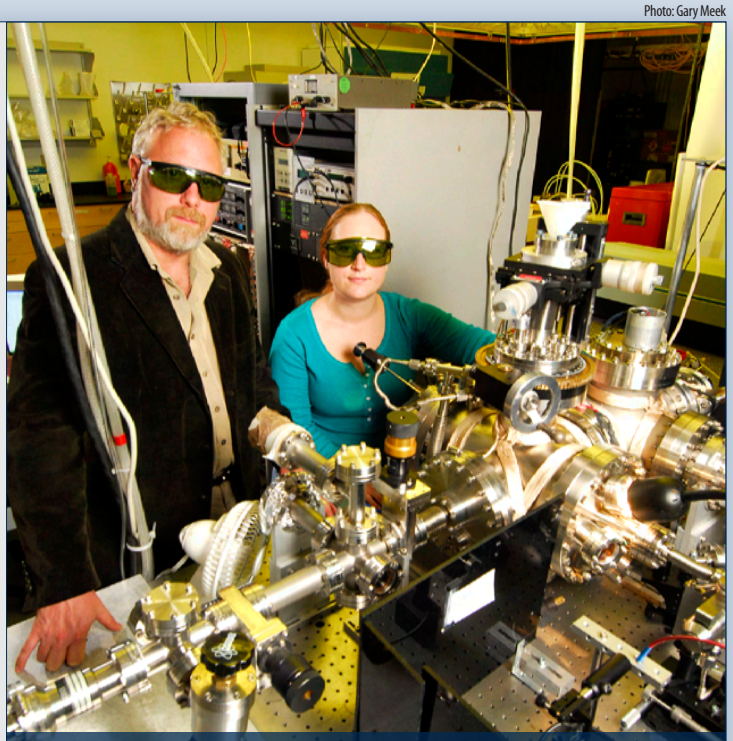
Improving Current Technology

Today, a popular technique for studying biological samples is matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). In this technique, sample preparation plays a very important role in image quality because it requires that a matrix compound be uniformly deposited over the surface of a histological tissue slice mounted on a special plate.

A research team including Merrill, along with Cameron Sullards, director of Georgia Tech's Bioanalytical Mass Spectrometry Facility, and Yanfeng Chen, a research scientist in the School of Chemistry and Biochemistry, recently showed that the homogeneity of the matrix could be improved. With this development, broader categories of compounds, such as lipids, could be analyzed.

The researchers used an oscillating capillary nebulizer to spray small droplets of matrix aerosol onto the sample surface – a process similar to airbrushing. Using histological samples provided by Timothy Cox, a professor of medicine at the University of Cambridge, the researchers could profile and localize many different lipid species in the samples. Specifically, they localized sphingolipids that accumulate in the brain when there is a genetic defect. This research was published in the April 15 issue of the journal *Analytical Chemistry* and was funded by the National Institutes of Health.

Photo: Gary Meek



Professor Thomas Orlando and graduate student Irene Anestis-Richard conduct an experiment with the single photon ionization mass spectrometer.

Developing New Technologies

While MALDI samples must be analyzed in a vacuum, recent advances allow samples to be studied under ambient conditions. Facundo Fernandez, an assistant professor in the School of Chemistry and Biochemistry, has been using a technique called desorption electrospray ionization (DESI).

With DESI, a high-speed, charged spray containing alcohol and water is directed at a sample a few millimeters away. The solvent droplets pick up portions of the sample through interaction with the surface and then form highly charged ions that can be analyzed.

Fernandez and his research team recently used DESI to analyze nearly 400 drug samples provided by public health authorities to identify counterfeit anti-malarial drugs.

"We have done a lot of work using DESI to analyze pharmaceutical formulations, but we are moving into new avenues of research including looking at algae samples, as well as ovarian cancer tissue samples provided by the Ovarian Cancer Institute, which is housed at Georgia Tech and headed by School of Biology chair John McDonald," says Fernandez.

In ovarian cancer research, little is known about how biomarkers and low-mass signaling molecules increase or decrease in abundance with treatment. Fernandez has teamed with Thomas Orlando, chair of the School of Chemistry and Biochemistry, to use laser desorption single photon ionization mass spectrometry (LD/SPI-MS) to investigate this issue.

Because it does not use a matrix, LD/SPI-MS can detect low-mass molecules – such as sugars, amino acids, small peptides and cytotoxic compounds – formed as result of cancer treatment. It can also achieve higher spatial resolution than is typically possible with a desorption laser, according to Orlando.

"We hope LD/SPI-MS will lead to a better understanding of the molecular basis of ovarian cancer at its various stages and how treatment affects regulation of low-mass biomarkers in ovarian cancer cells," says Orlando.

The Information Challenge

Mass spectrometry experiments produce incredible volumes of data, each composed of thousands of spectra and thousands of peaks, which makes finding molecules of interest very difficult.

"We've focused on researching computational methods that can clean up, visualize and look for interesting patterns in thousands of mass spectrometry tissue images that you wouldn't necessarily be able to find or have time to find with the naked eye," says May Dongmei Wang, an assistant professor in the Wallace H. Coulter Department of Biomedical Engineering and a Georgia Cancer Coalition Distinguished Cancer Scholar.

Wang, post-doctoral fellow Mitchell Parry and graduate students Richard Moffitt and Peter Siy are providing software systems to BIMS center users. The systems acquire the thousands of ion spectra collected from every tissue slide matrix, perform quality control and visualize the distribution of ions on the tissue matrix. The researchers then use data mining methodologies – including principal component analysis, independent component analysis and multivariate analysis – to identify and compare ions of interest present in different locations.

With the advances in software and hardware, the use of mass spectrometry in the life sciences promises to become even more prevalent and diversified for systems biology research.

By Abby Vogel

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produce a functional particle at the beginning of the process of protein biosynthesis. School of Biology professor and Georgia Research Alliance Eminent Scholar Steve Harvey uses computer models to investigate the structural shape, and in turn, function, of the ribosome.

He developed a structural model of the large subunit of the mammalian ribosome by combining molecular modeling techniques with cryo-electron microscopic data that will allow him to screen where novel drugs will bind to the ribosome and affect its function.

Jeffrey Skolnick, a professor in the School of Biology, a Georgia Research Alliance Eminent Scholar and associate director of IBSI, has worked with postdoctoral scientist Michal Brylinski to develop a method for predicting where signal-triggering molecules called ligands will bond to target proteins. The prediction can be made without knowing the protein structure.

To complete the complex calculations required for the prediction, Skolnick has a computing facility that contains 4,600 core processors that perform calculations 24 hours a day, seven days a week. The computer rates the quality of the fit to various sites on the protein, analyzing the molecules' abilities to either enhance or disable the function of the protein, depending on its function in the cell.

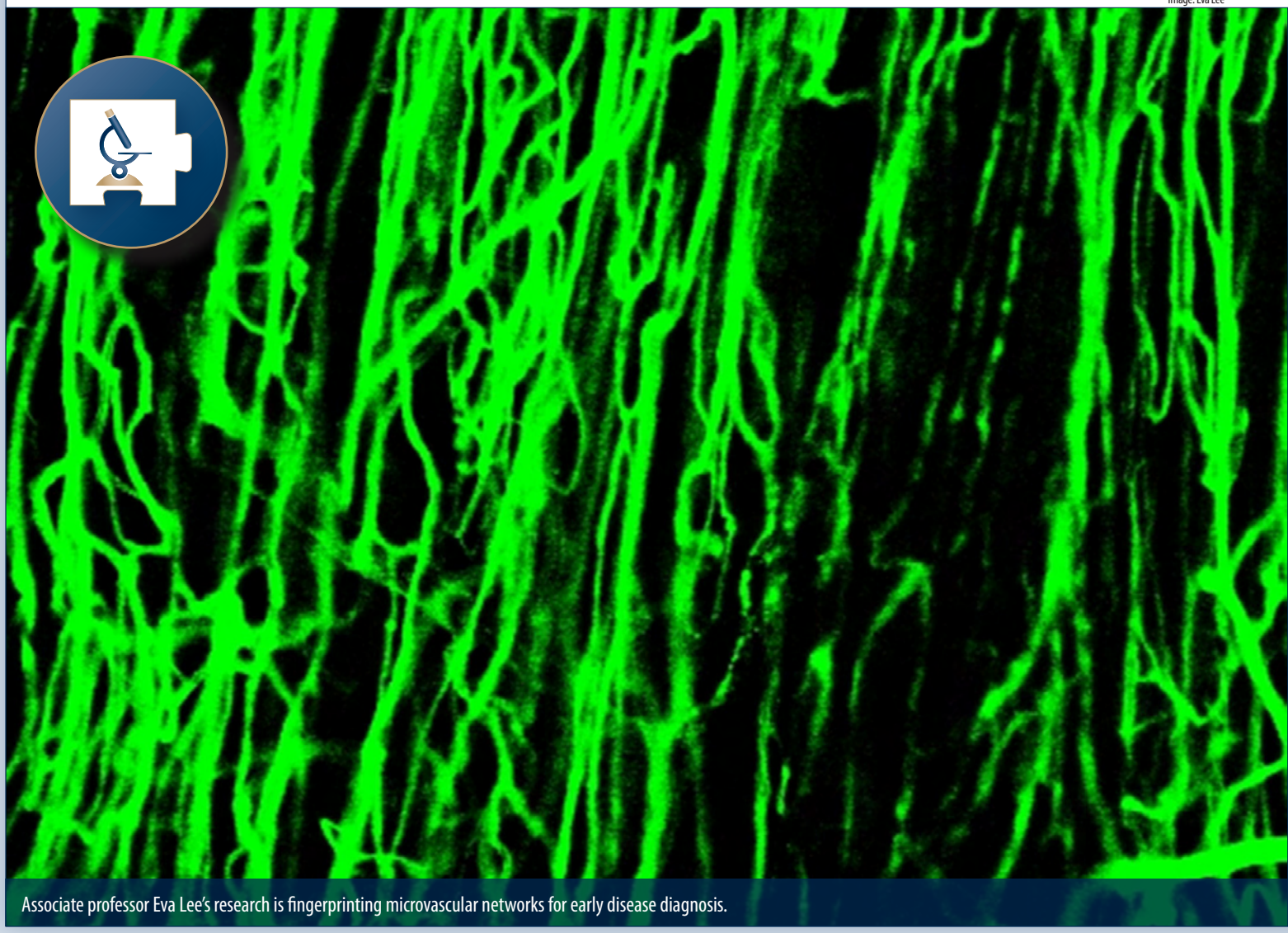
Identifying the ligand-binding site is often the starting point for protein function determination and drug discovery. Details of the method were published in January 2008 in the journal *Proceedings of the National Academy of Sciences*. This work was funded by the National Institutes of Health.

In another project, Skonick and postdoctoral scientist Roman Mezencev, research scientist Adrian Arakaki and School of Biology chair John McDonald aim to discover drug targets for treating ovarian cancer. Their goal is to enhance the non-cancerous pathway by promoting production of specific molecules whose production is reduced by the disease.

"It's much easier to feed cells a molecule that's been inhibited because of a disease rather than designing a drug to inhibit a molecule that's being produced in excess due to a disease," explains Skolnick.

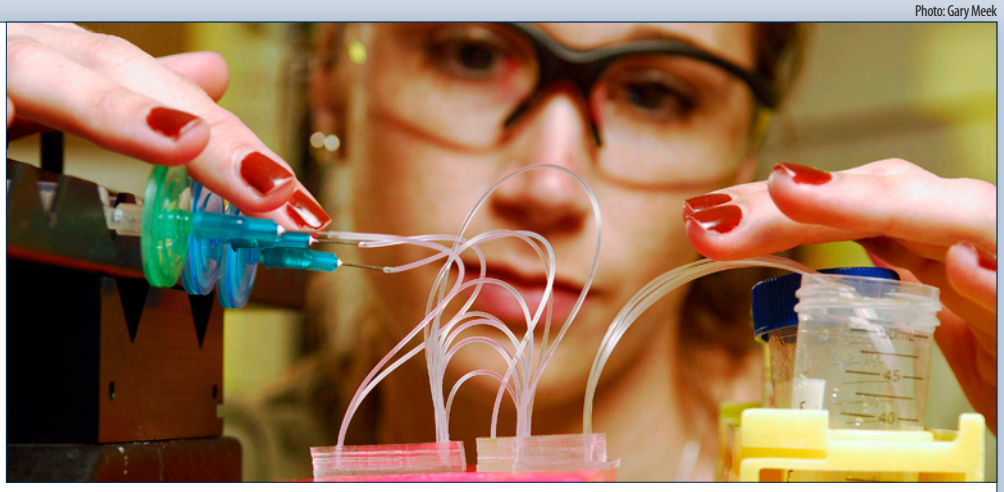
The researchers have developed a list of metabolites whose production has been

Image: Eva Lee



Associate professor Eva Lee's research is fingerprinting microvascular networks for early disease diagnosis.

Photo: Gary Meek



reduced in diseased cells, but which may stop cancer cells from multiplying if metabolite production resumes. They have tested these metabolites on leukemia and ovarian cancer cell lines and results have shown a reduced growth rate of the cancer cells by 90 and 50 percent, respectively. This work was published in June 2008 in the journal *Molecular Cancer*.

Predicting Health Risk, Improving Disease Diagnosis and Treatment

A wealth of biological and clinical data is available for health professionals to examine, but existing modeling and computational techniques limit their ability to handle such heterogeneous large-scale data sets. This limits the ability of researchers to uncover discriminatory factors that might assist in predicting health risk, detecting disease early and predicting treatment outcome.

Working with clinicians and experimental biologists, Eva Lee, an associate professor in the School of Industrial and Systems Engineering and director of Georgia Tech's Center for Operations Research in Medicine and Healthcare, has developed a general-purpose predictive modeling and software system that determines predictive rules for a wide range of biological and medical problems. These rules can assist in early disease prediction and diagnosis, identification of new target sites – genomic, cellular and molecular – for treatment and drug delivery, disease prevention and early intervention and optimal treatment design.

For one project, Lee has developed a model to predict atherosclerosis by examining inexpensive physiological measurements, traditional risk factors and novel biomarkers. In another, she has completed genomic analyses to predict the abnormal methylation of certain genomic regions. Methylation is a process that has been shown to silence genes responsible for tumor suppression.

Lee is also fingerprinting microvascular networks to provide early diagnosis of diabetes, premature aging, macular degeneration and tumor metastasis. Her predictive models have yielded correct classification rates ranging from 80 to 100 percent. Lee and her medical collaborators have also conducted blind tests, where diagnoses are predicted for new patient data based on a developed rule. These tests resulted in correct predictions more than 83 percent of the time.

These results provide a strong basis for pursuing their use as medical diagnostic, monitoring and decision-making tools, Lee says. This research is supported by the National Institutes of Health and the National Science Foundation.

In addition to diagnoses, systems biology approaches can also be used to improve disease treatments. Hang Lu and Melissa Kemp, an assistant professor in the Coulter Department of Biomedical Engineering and Georgia Cancer Coalition Distinguished Professor, aim to improve a new cancer therapy called adoptive transfer of T-cells.

During this process, clinicians remove T-cells from a cancer patient, multiply them in the laboratory and then infuse them back into the patient's body to attack the cancer. However, this type of therapy is limited by the difficulty of generating sufficient numbers of active T-cells in the laboratory.

"Researchers use an artificial method of population growth that may cause the cells to divide too many times and become unresponsive and inactive," says Kemp.

Kemp and Lu are using microfluidic devices to stimulate and break open T-cells to analyze their properties dynamically. By measuring molecules downstream from the T-cells in a high-throughput manner, Kemp and Lu can build mathematical models to assess the quality of the T-cell population before infusing the cells into the patient. That could potentially improve the therapeutic outcome.

As the field of systems biology expands, Georgia Tech's Integrative BioSystems Institute is working to be on the forefront. The Institute will continue to encourage the integration of information about cells and organisms at multiple levels and the integration of knowledge from biological science and tools from mathematics and computer science for a better understanding of the biological systems.

"Georgia Tech has a culture of interdisciplinary research and education that goes back several decades and enables us to address issues such as systems biology in ways that other institutions can't," notes Don Giddens, dean of the College of Engineering, the Lawrence L. Gellerstedt, Jr. Chair in Bioengineering and a Georgia Research Alliance Eminent Scholar.

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