

TRANSFORMATIONAL RESEARCH THROUGH MODELING AND SIMULATION

Pitt Researchers Tackle Some of the Most Complex Issues of Our Times in New Center

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Infectious disease. Global warming. The world economy. These are vastly different subjects, yet all have some things in common. All are complex systems influenced by multiple external stimuli. All have intense importance for humanity, deciding who lives, where they live, and how they live. And the knowledge of all three can be advanced through computer simulation.

With the help of more and ever-faster microprocessors, researchers at the University of Pittsburgh are building powerful models to simulate complex phenomena. They are asking essential questions that would have been unthinkable to address computationally as recently as 10 years ago. Pandemics, climate change, banking meltdowns—all can be described by algorithms, and all can be simulated with powerful computers.

Growing cohorts of researchers from a wide array of disciplines have used computer modeling to tackle some of the biggest challenges in their fields. Yet, despite the phenomenal increase in the speed of computers, traditional simulation tools have been limited because they could not address multiscale modeling, processes occurring across large space and time scales.

A Giant Step Forward in Simulation and Modeling

This limitation is being addressed on a broad scale at the University of Pittsburgh with the creation of the new Center for Simulation and Modeling (SAM), a multidisciplinary research center that will have two critical functions: It will foster collaboration across disciplines on a variety of research challenges as well as focus on developing new multiscale approaches for simulation and modeling.

“Multiscale modeling has the potential to revolutionize the way science is conducted; to foster transformational research; and to stimulate the advancement of new technologies that can have an unprecedented impact on materials, energy, medicine, and many other fields,” says George Klinzing, vice provost for research. “And if multiscale modeling is the challenge, then parallel processing is the solution,” he says. “It is a very competitive environment, and this is how we will distinguish ourselves from others.”

Leaders from the Swanson School of Engineering, School of Arts and Sciences, and schools of the health sciences have carefully designed the new center to reflect the needs of topflight researchers across the campus, with an eye toward making the University a brand name in computational science. Kenneth D. Jordan, Distinguished Professor of Computational Chemistry, and J. Karl Johnson, W.K. Whiteford Professor in the Department of Chemical and Petroleum Engineering, will be codirectors of the center.

According to Jordan, one of the most important aspects of the center is that it will help Pitt researchers and students—from chemistry, physics, biology, and computer science; to materials science and mechanical and chemical engineering; to the health sciences and social sciences—to develop expertise in



SUPERCOMPUTING

University researchers using computer modeling have access to substantial computational resources through the Pittsburgh Supercomputing Center (PSC), a joint effort of Pitt, Carnegie Mellon University, and Westinghouse. Through a processing system known as “BigBen” (pictured), Pitt researchers can address the most demanding large-scale parallel computational projects.

parallel processing. Through the center, researchers also can collectively access the already substantial computational resources available through the Pittsburgh Supercomputing Center.

The new center, which will be housed in Bellefield Hall, will serve as a focal point where almost 50 faculty members (plus more than 100 graduate students) from diverse fields can share their experiences and expertise with one another. The thematic areas of focus at the center will be energy and sustainability, nanoscience and materials engineering, medicine and biology, public health, economics, and other social sciences.

Leaving the Serial World

Computers traditionally have operated in serial, processing one line of code, then another, then another. But microchip speed is topping out; central processing units won't get too much faster than they are now, without major technological breakthroughs. So software designers have begun to write computer codes that run on several different processors at once. The benefits to this kind of programming are obvious: An equation that takes a year to complete on one processor only takes a week if you can get it to run efficiently on 52 processors.

“Leaving the serial world behind is no small task,” says Johnson, who says he grew up in a serial world. “The problem with the shift toward parallel programming is that a lot of people don't know how to do it, and there's a huge demand for people who really understand it.”

When the University asked its faculty what they needed in a computational center, Klinzing says, their answer was, “We need high-level consultants; we don't just need hardware.” In response to that need, the center will provide in-house PhD-level computational consultants who will advise faculty and their students.

The center will allow researchers from across the University to be able to tap more easily into experts like Liz Marai, assistant professor of computer science. Marai's specialty is data modeling and visualization, the conversion of mountains of numbers into visual representations that can then be used for interpretation.

She has collaborated with biologists, orthopedists, and bioengineers to create visual, individual-specific models of how the joints in the human body work. “We take numbers and measurements and try to generate insight,” says Marai. “We run a tight loop between data, visualization, and analysis.”

Marai believes that the center will allow computational research at Pitt to take a big step forward. “It will foster collaboration among experts from different fields. It's not just adding computing power, it's combining methodologies across disciplines to look at these really important questions—how galaxies are formed, how the human body works. Expert collaboration across disciplines can solve really big problems.”

Toward Energy and Sustainability

Other important questions include those being asked about energy, sustainability, and the environment.

Jordan uses models to analyze the structure of methane hydrate, a compound formed from water and methane under high pressures at low temperatures. It is most abundant in deep ocean water and under the permafrost near the Arctic. The methane embedded in these deposits contains more potential energy than all known oil and natural gas reserves on the planet. It also represents a major potential contributor to global climate change. Methane is a potent greenhouse gas, 20 times more potent than carbon dioxide (CO₂), and as the polar region warms, the melting permafrost may release the vast supply of methane beneath it.

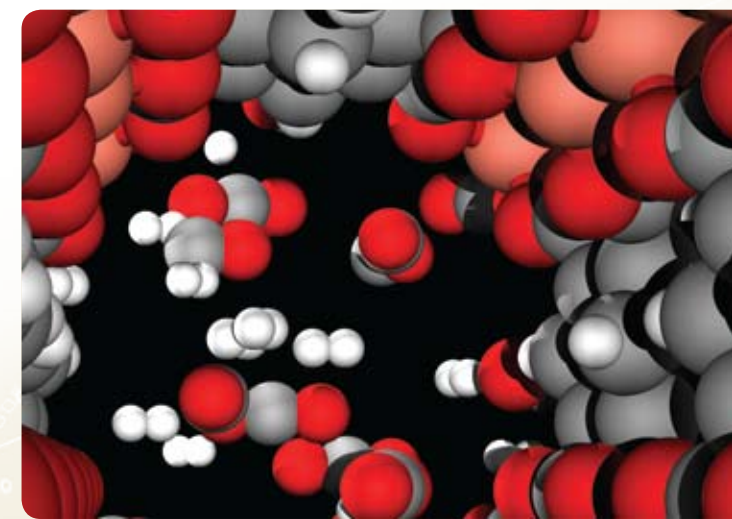
Either way, understanding its mysterious properties is crucial. Jordan is working with the U.S. Department of Energy's National Energy Technology Laboratory to simulate the structure and dynamics of methane hydrate. In hydrates, water molecules form polyhedral cages around methane molecules. Simulations allow Jordan's team to explore questions about methane hydrate that would be nearly impossible otherwise. “On the computer, we can study the network of cages without the methane molecules—something that cannot be done experimentally,” he says.

Jordan's group also is studying a hydrate that is formed from water and CO₂ molecules, which may be useful in sequestering CO₂, the world's most abundant greenhouse gas.

Like many researchers at the University, Jordan collaborates with experimentalists at numerous institutions, including Yale University and Purdue University, to combine his research with state-of-the-art experimental approaches.

Carbon dioxide also is an area of inquiry for J. Karl Johnson, who is using computational modeling to understand its basic physics. Johnson and his collaborators are hoping that the materials they help to design will one day be used to capture CO₂ and slow global climate change.

“For the next 20–50 years, we're going to be relying heavily on fossil fuels for energy,” Johnson says. “How can we use that resource without releasing CO₂ into the atmosphere?” Johnson's group is modeling a class of nanoporous material compounds with “pores” 1/1000th the width of a human hair in diameter to understand how they interact with CO₂. He hopes their modeling will lead to the design of a material that can capture CO₂ from emissions that can then be stored through carbon sequestration.

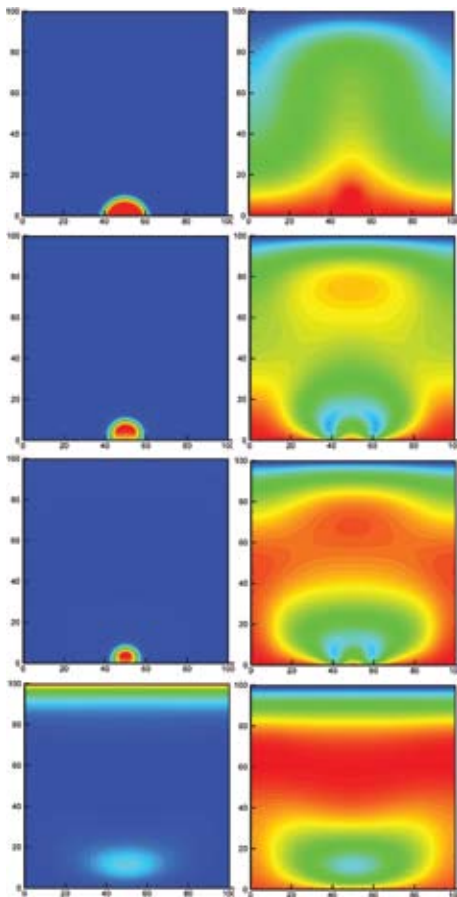


ENERGY

Shown here is an inside view of gas molecules entering a nanoporous material, as computed by molecular modeling in J. Karl Johnson's group. The gas molecules at the mouth of the pore are CO₂, H₂, and CO. The walls of the nanoporous materials are composed of carbon (gray), hydrogen (white), oxygen (red), and copper (salmon).

Hutchison and his collaborators put together a group of 100 potential molecules and, through simulations, gleaned five or six to be good candidates for solar cells. "A lot of these molecules look like things we could make, but we want to understand whether to put in the effort to make them," he says.

Laura Schaefer, associate professor of mechanical engineering and materials science, Bicentennial Board of Visitors Faculty Fellow, and deputy director of the Mascaro Center for Sustainable Innovation, uses computer modeling to develop green alternatives to CFCs and related polymers.



SUSTAINABILITY
As part of an effort to implement a safer, more energy-efficient refrigerant, modeling done by Laura Schaefer shows the evaporation of a liquid droplet into a vapor field.

Chlorofluorocarbons (CFCs) have long been used as refrigerants in air conditioning because their chemical profile allows them to draw away heat from the air around them efficiently and safely. But CFCs deplete the Earth's ozone layer, which blocks harmful solar radiation, and these chemicals will be phased out completely by 2010.

Hydrochlorofluorocarbons (HCFCs), the chemicals used to replace CFCs, are more environmentally friendly but still have a negative impact on the ozone layer. Regulators will begin phasing out the most common HCFCs by 2010.

Schaefer, who also has used computer modeling to study the use of acoustics for refrigeration, is simulating how different combinations of chemicals would react to find a safe, efficient alternative. Her work involves multiscale modeling that predicts not just what individual molecules will do but also how the system as a whole will perform.

The urgency to develop a safer, more energy-efficient refrigerant is great; air conditioning accounts for one-sixth of U.S. household electricity use. Schaefer's work is leading to new understandings in the basic science of fluid dynamics, she says. "The theoretical insights have been really fascinating. We're learning a lot on how complex fluids behave at a small level. This could have far-reaching impacts for researchers in other fields."

Tracking Global Health

Computer modeling tools have become increasingly important to understanding and addressing global health problems. By using informatics and computational modeling and simulation, researchers and policymakers can understand more about current public health challenges and determine the best strategies to prevent disease and improve human health.

Modeling also can show how disease spreads through whole populations, as demonstrated by the work of Donald Burke, dean of the Graduate School of Public Health, UPMC-Jonas Salk Chair of Global Health, and associate vice chancellor for global health. Burke is a pioneer in using computer modeling to understand the behavior of pandemic disease.

For decades, Burke tracked infectious diseases like HIV/AIDS and dengue fever throughout the developing world. In the 1990s, he began to think of pandemics as computable processes. "I now think of virus transmission as an algorithmic process, with underlying subprocesses and patterns," Burke says. "I never would have thought that way before I started to use computer modeling and simulation."

The computer model Burke and his collaborators designed to simulate an outbreak of avian flu in Southeast Asia—using transmission statistics from past epidemics, census data, and other social patterns—has helped the U.S. Department of Health and Human Services, U.S. Department of Homeland Security, and Centers for Disease Control and Prevention develop policies on travel restrictions, vaccinations, and school closures in the event of an outbreak. The Bill & Melinda Gates Foundation, which funds projects to help eradicate infectious disease, committed \$10 million to Burke's group to build a model for the use of vaccines to contain epidemic diseases.

"Computer modeling allows us to test our ideas on populations in silicon," says Burke, and not just for epidemics of infectious diseases. Smoking, obesity, and drug use are all examples of public health problems where social behaviors spread from person to person, similarly to contagious microbes, and where modeling can help people think through and evaluate public policies designed to limit or reverse the spread of the behaviors, according to Burke.

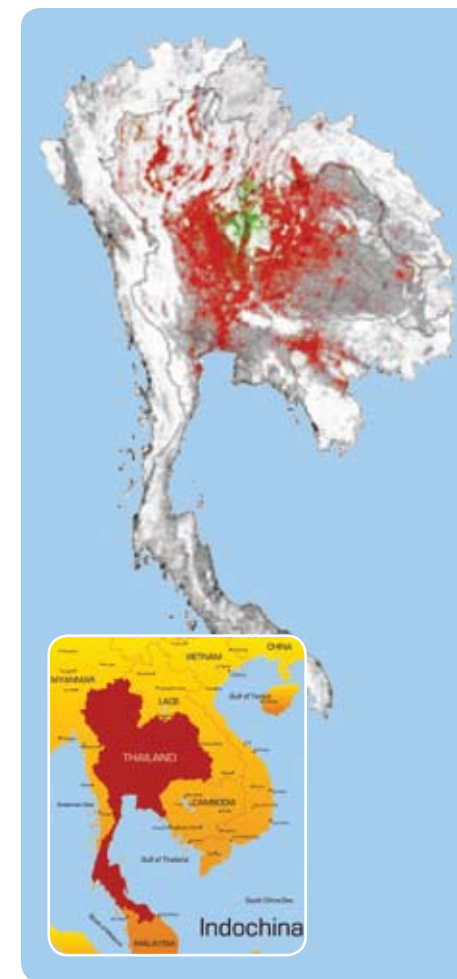
Pitt can be an international leader in this exciting new field, he says. "We're definitely on the front edge. My intuition is that soon, virtually every aspect of public health research and policy development will be supported by modeling and simulation, and Pitt will be extremely well positioned to lead the field."

Embracing Turbulence

Anyone who's puzzled at an inaccurate weather forecast can appreciate why turbulence is one of the great problems of modern science. "Albert Einstein advised all his associates not to get involved with the problem of turbulence; it's a very chaotic phenomenon," says Peyman Givi, William Kepler Whiteford Professor in the Department of Mechanical Engineering and Materials Science and director of the Laboratory for Computational Transport Phenomena.

Givi hasn't stayed away from turbulence—he's embraced it by developing unique methods of modeling the phenomena of turbulent combustion and high-speed combustion inside engines. He's gained attention for a novel way to combine two modeling methods—one employing exact calculations and another using probability—to provide an accurate way for engineers to experiment with engines even before they're built.

Rolls-Royce Motor Cars and NASA engineers already use his model to predict temperature differential, fuel usage, and emissions for different engine and fuel combinations. Givi's models plot billions of fluid particles across hundreds of thousands of time intervals. It's a lot of work, but it saves countless amounts of time and energy for engineers trying to create more efficient, cleaner-burning engines. "When you design an engine, you'd like to be able to know how it will work before you build it," Givi says. "This lets people do that."



GLOBAL PUBLIC HEALTH

As principal investigator on a National Institutes of Health grant, Donald Burke worked with collaborators to create a simulation of a hypothetical outbreak of transmissible avian flu in Thailand and then used the model to determine whether intervention strategies could quench an epidemic before it spread worldwide (results published in *Nature*, 9/8/05).

Designer Materials and Nanotechnology

Similar to the way Givi's models depict how engines will work before they are built, computer modeling allows researchers to test the properties of new materials and novel chemical compounds prior to building them.

"If you can understand what's happening at the level of atoms, you can build things from the bottom up and create designer materials," says Johnson. His lab is using models to probe the physical properties of carbon nanotubes—long, straw-like molecules with very narrow diameters that scientists think may be useful for separating different gases or liquids. For example, a carbon nanotube membrane that selectively separates water from sodium chloride could be used as an easy, low-energy way to desalinate seawater.

Johnson and his group model how specific mixtures of molecules could interact with these structures, including showing how quickly these materials flow through the nanotubes. Unless the flow rate is fast, the membrane will not be useful in practical terms for separating fluids. The model created by Johnson and his collaborators found that gases would pass much more quickly through the nanotubes than expected. Laboratory results published in a 2006 *Science* article by a separate research team supported some of the predictions Johnson's team made: The measured flow of gases and liquids was about 1,000 times faster through the nanotubes than through conventional porous membranes.

Jordan is using modeling to study one of the most abundant materials on Earth: water. "Although water is probably the most studied substance on Earth, we still don't understand all of its properties, many of which are quite unique," Jordan says.

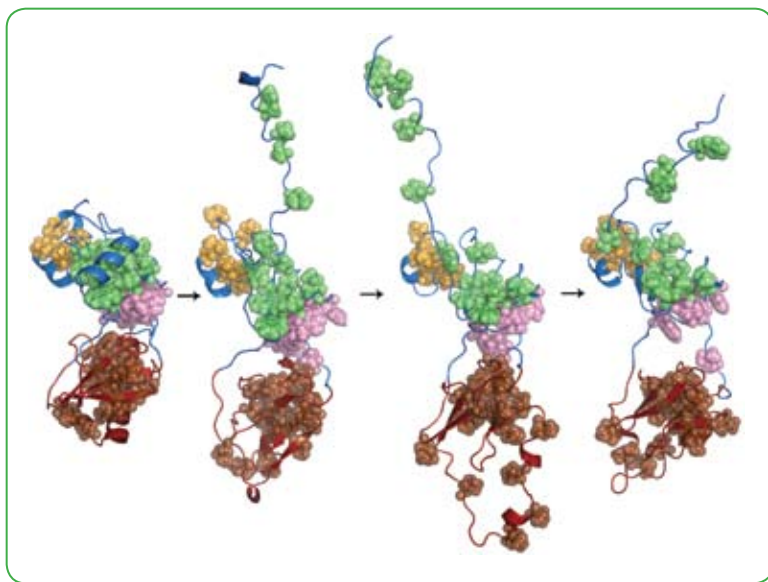
Jordan's group simulates the behavior of small clusters of water containing up to 100 molecules. These studies are shedding new light on a wide range of processes, including chemical reactions in the atmosphere, and on electrochemistry. One of the most important problems on which Jordan's group is working is whether charged particles, such as electrons and protons, prefer to be on the surface or in the

interior of water clusters. This fundamental science question turns out to have far-reaching consequences, including those of environmental importance, in atmospheric chemistry.

One researcher is using computers to model “sticky stuff”—wet or very fine granular material. Joseph McCarthy, associate professor and William Kepler Whiteford Faculty Fellow in the Department of Chemical and Petroleum Engineering, studies the science of mixing sticky material. This is an important process in fields like pharmaceuticals, where a thimbleful of active chemicals must be mixed evenly into a roomful of flour-like substance. McCarthy and his collaborators build intricate models to see how best to mix these materials based on their size, density, and whether they are attracted to or repelled by water. They calculate the behavior and mechanics of billions of particles interacting over hundreds of thousands of time segments. This takes months to run across several high-powered processors. The time put into these models saves McCarthy and his colleagues from having to build time-consuming physical experiments.

The McCarthy group simulated a “chute flow” experiment, in which a substance is poured down a surface with a series of zigzags built into it. To construct a physical experiment, the team would have had to build a chute as high as 12-story Benedum Hall, which houses the Swanson School of Engineering. “We can make a lot of measurements you can’t do when you’re working experimentally,” McCarthy says.

Computer modeling is allowing Anna Balazs, Distinguished Professor of Chemical Engineering and Robert



MOLECULAR MACHINES
Lillian Chong’s lab uses simulations to study protein dynamics. Shown is a simulation exhibiting the mechanically induced unfolding that results from the fusion of two proteins.

Von der Luft Professor, to explore the creation of nanomachines that behave in much the same way human cells do.

Balazs uses simulations to study how microcapsules—synthetic bubbles roughly the size of a human blood cell—moving across a surface could form an artificial “skin” on a damaged material. She also has simulated communication between these synthetic bubbles using a route similar to processes that occur in cell signaling. These materials one day could form the basis for chemical sensors that “heal” defective surfaces.

“This artificial skin is essentially a coating that could indicate where a surface has been damaged,” Balazs says. She believes that her simulations will help experimentalists to follow the “recipe” for the nanomachines her team has created using computational modeling.

Through models, David J. Earl, assistant professor of chemistry, explores structures called zeolites, a class of crystalline materials whose tiny channels make good places for chemical reactions to take place. “These pores are about the same size as molecules, so you can use zeolite to sieve different molecules,” says

Earl. Because of their unique porous structure, zeolites are used as catalysts in crude oil refinement and water softening. Zeolites also can be introduced into the bodies of people exposed to radiation to swap harmful radioactive ions out with benign ions floating inside its many pores.

There are 176 known zeolite structures, and Earl and his collaborators are trying to see if more structures are possible. Using computational methods, they discovered 3 million possible zeolite structures; extra analysis concluded that 450,000 were more likely than others to be synthesized.

Earl also has used computer simulation to study the structure of liquid crystals and research the relationship between molecular structure and the types of phases (liquid, liquid crystal, solid, or gas) a molecule forms. He also has used simulations to study evolvability, the ability of organisms to evolve more quickly when confronting stress in their environment.

In all of his explorations, Earl says the speed with which computers can solve complex equations makes them

invaluable tools for scientists. “Over time, as computing power increases, we’re able to tackle harder and harder problems, so computer modeling is becoming more and more important.”

Unlocking the Body’s Mysteries

Modeling is becoming an invaluable tool for many researchers in medicine and biology at Pitt. From studying proteins at the atomic level to the body’s immune system, models let these researchers quickly test theories—enabling innovations that could help to save many lives down the road.

Lillian Chong, assistant professor of chemistry, uses computer simulations to study proteins, the body’s workhorses, in order to understand better the roles they play in the biological pathways of the cell. Chong studies natively unfolded proteins—so named for their seemingly disordered structure—which include a protein called tumor suppressor p53, thought to play a role in cancer. Proteins initiate important chemical functions in the body by “folding” into target molecules.

Chong’s group simulates the kinetics of these protein interactions on tiny time intervals of femtoseconds (that’s 10^{-15} second). “There’s no way you could get that level of time detail without a computer,” Chong says. These simulations run through Folding@home, a unique collaboration based out of Stanford University in which scientists use distributed computing to take advantage of idle computers around the world. They can run protein folding simulations on a network of more than 600,000 idle personal computers and Sony PlayStation 3s.

The Center for Simulation and Modeling will help researchers like Chong to share their expertise and experience with others at Pitt. “It makes a lot of sense to have a center that supports that kind of faculty collaboration so we can leverage that kind of expertise from so many people in this community,” she says.

Rob Coalson, professor of chemistry and physics, and his team model ion channels, one of the body’s least understood, but most important, protein structures. These nanoscopic channels enable the passage of charged atoms such as hydrogen, potassium, and chlorine through the body and are essential for everything from the creation and propagation of nerve signals and muscle contraction to the production of such chemicals as insulin.

“Malfunction of ion channels is implicated as the root cause of many serious diseases and neuropsychiatric disorders, including cystic fibrosis, certain types of epilepsy, and migraine headaches,” Coalson says.

According to Coalson, it’s difficult to test ion channels in their natural environment within a living organism, but it’s important that they be better

understood, as about half of the drugs on the market today target ion channels and their protein cousins. Coalson’s group has developed simulations that calculate the rate of ion flow through channels in cell membranes for various transmembrane voltages and electrolyte concentrations in order to gain insight into the relationship between channel structure and function.

Through computational models, Ivet Bahar, John K. Vries Chair and professor of computational biology, and her colleagues at Pitt’s School of Medicine simulate the interactions of proteins with potential inhibitors, small compounds that can limit the undesirable activities of some proteins. In collaboration with the Drug Discovery Institute, Bahar’s lab members screen libraries of hundreds of thousands of chemical compounds for their potential to interact with target proteins in the search to identify promising drugs for further development.

By doing “virtual screening,” Bahar says, she and her collaborators can not only increase the likelihood of identifying more potent inhibitors but also speed up the process of drug discovery. Other members of the computational biology department also use computational tools to study the role of microRNA, tiny



BENCH TO BEDSIDE

By creating mathematical models of the nervous and immune systems, G. Bard Ermentrout and his colleagues are seeking to help medical practitioners (like the one pictured) improve patient care.

TRANSFORMATIONAL RESEARCH THROUGH MODELING AND SIMULATION

strands of genetic material, in regulating the immune response with respect to cancer and in understanding the complex biophysics of cell signaling.

G. Bard Ermentrout, University Professor of Computational Biology and professor of mathematics, uses computational modeling to simulate complex medical phenomena. Ermentrout, who's used modeling to study everything from the trail-making properties of ants to the pigmentation design of mollusk shells, frequently collaborates with colleagues in the fields of medicine, neuroscience, and biology to study how certain patterns occur.

Ermentrout and his collaborators use models to understand the immune response during sepsis, a potentially fatal condition in which the body's response to infection inflicts "collateral damage" on internal organs like the lungs. They are trying to model how the immune system response in sepsis reaches a tipping point after which the body's own immune defenses start causing more harm than good. "At what point does the immune feedback become overwhelming and start to avalanche and cause problems?" Ermentrout asks.

Ermentrout also has used modeling to study phosphenes, the geometric visual patterns that occur when one looks at strobe lights, hallucinates, or enters a pre-epileptic state. He thinks that the patterns represent neural activity transposed directly onto the brain during those instances when the brain's visual apparatus is knocked off its usual setting.

"There are some problems in science that really lend themselves to modeling," says Ermentrout. "We're trying to find the algorithms that generate these patterns."

Forecasting the Uncertain

Predicting how the world economy will react to a laundry list of economic contingencies—wars, resource shortages, or banking meltdowns, to name just a few—is no task for the faint of heart. "The devil is in the details," explains David N. DeJong, professor and chair of the Department of Economics. DeJong is trying to harness the power of computational methods to create economic forecasting models designed in part to chart reactions to such contingencies.

DeJong uses computer simulations to reconcile two branches of the field that don't always communicate with one another: theory and statistics. Statistics are invaluable in unearthing the details of economic trends, but, DeJong explains, "They don't really answer the question, 'How come?'"

DeJong has already begun this task, mapping theoretical models of economic behavior onto statistical models. He understands that, because models are simplifications of reality, there are some things that models will have difficulty accounting for: "No matter how rich our understanding of the aggregate economy is, we're never going to get everything." For instance, how do you account for the reaction of consumers to unforeseeable changes in their environment not built explicitly into the model, like the recent foreclosure crisis or instabilities in the banking sector?

But as our understanding of the relationship between tax policy, investment, and consumption increases, DeJong and other economists increasingly will use structural models to read the economic tea leaves.

"What I'd like to do is to be able to answer questions like 'Should the Federal Reserve Board be more worried about interest rates or inflation?' or 'What are the effects of a tax holiday going to be?' I'll fire up the model and give you an answer," DeJong says.

Traditional Methods, New Tools

No matter what kind of modeling they do, researchers at Pitt and elsewhere will continue to refine their understandings of the complicated systems they're modeling. They will collaborate heavily with experimentalists to test their theories against real-world data and explore new ways to make computational modeling even faster. In these ways, computational modeling is not so far removed from the most rudimentary forms of scientific inquiry that have been around for centuries: observe, experiment, analyze.

As Givi says, "In almost anything we do in science, we use what we know and model what we don't. The issue is how do you combine these two worlds to come up with a unified methodology? That's where we are putting our efforts."



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