Navigating via computer-based mathematical models, Pablo A. Iglesias aims to understand—and regulate—how cells move and divide.

By Dave Beaudouin

Call him a control freak, but Pablo A. Iglesias covers more ground than you can imagine in his efforts to direct the movement of cells. Iglesias is steering his considerable knowledge of control engineering down a new path in cell biology that could well lead to extraordinary discoveries.

A professor in the Whiting School’s Department of Electrical and Computer Engineering, Iglesias has joint appointments in the departments of Biomedical Engineering and Applied Mathematics and Statistics. That’s a testament to his own flexibility in pursuing a path. The Venezuelan native earned his doctorate in control engineering at Cambridge University in 1991.

Control engineering is the study of automatic regulating systems, which often take the form of small devices silently managing mechanisms and household appliances. From thermostats to cruise controls, these control systems perform surprisingly sophisticated and dynamic tasks. But they’re nothing new. To make that point, Iglesias turns the clock back to 1903 and the Wright Brothers. “In fact, their greatest contribution to flight wasn’t the aircraft itself,” he notes, “but the control system that allowed them to fly the craft, which is control engineering.”

Today’s control engineers employ not bike chains and canvas but computer-based mathematical modeling systems in order to test-drive controllers in theory before they are actually engineered. Employing the principles of control theory, the control engineer studies and adjusts a mathematical model to create a predictable set of variable responses within a dynamic system.

Pedaling on the Biological Signaling Pathways

For Iglesias and his team at the Cellular Signaling and Control Laboratory, the challenge is applying this discipline to the study of biological signaling pathways, the amazingly complex regulatory system within the human body. “At the simplest level, it’s everything that happens inside a single cell that regulates its well-being,” says Iglesias. From body temperature to cholesterol counts, “No matter the scale, all of the body’s processes are very tightly regulated along much the same lines as apply to control engineering.”

First fascinated by this parallel seven years ago, Iglesias now focuses on two aspects of biological signaling pathways at the cellular level. The first investigation in his laboratory involves the study of chemotaxis, the movement of single cells, or even larger multicellular organisms, in response to the introduction of certain chemicals into their environment. For example, human white blood cells will pursue and destroy invasive bacteria, but only because a bacterium secretes a particular chemical detected by certain sensors on the cell.

In particular, Iglesias seeks to understand a human cell’s biochemical “guidance system” in terms of how it regulates chemotaxis. “Right now, we’re specifically investigating the possibility of feedback loops,” he says. “We have a mathematical model that shows that some of a cell’s observed behavior can be explained by these feedback loops, which measure an outside chemical concentration, produce a response, and then feed it back to the cell’s sensors.” The next step in this study, says Iglesias, will be to move from modeling a cell’s guidance mechanism to developing models of how the cell’s actual locomotion takes place.

Inside a Cellular Split

In a second study, Iglesias and his team are investigating the control dynamics of cell division—and the steps that must occur for a cell to divide successfully. Following division, the resulting two daughter cells must each contain an equal half of the chromosomes from the original cell. However, if these genetic materials are not distributed equally, a condition called aneuploidy occurs. Iglesias notes that aneuploidy is one of the leading causes of genetic disease and cancer.

To gain a greater insight into the control mechanisms governing

By creating computer models, Pablo A. Iglesias studies the control dynamics of *Dictyostelium*, a single-celled organism whose movements are similar to the human white blood cell. The illustration shows the theoretical prediction (top) and experimental result of simultaneous stimulation of the cells.
successful cell division, Iglesias and his colleagues are creating models to analyze cytokinesis, the final step in cellular division, where the two new daughter cells actually separate. To test for the presence of a feedback loop in the cell during this process, Iglesias collaborates with researchers at the Johns Hopkins School of Medicine’s Department of Cell Biology. Together they are developing an apparatus to be used during cell division—a dual micropipette aspirator that can apply pressure to cells through a microneedle less than five microns wide. “When a cell is dividing, we will actually apply some force to it that works against its division,” says Iglesias. “What we think is going to happen is that the cell will then push harder to divide itself. Just like a thermostat that works harder when a window is left open, the cell’s feedback mechanism will kick in to correct the discrepancy.”

Down the Road: Controlling Disease

All of this research, while purely theoretical, has the potential for providing substantial results. For example, malignant tumors in the human body spread through chemotaxis, as do certain other diseases. Short-circuiting the process of how these chemical cues work could effectively halt the progress of such diseases. And, as Iglesias points out, studying cell division shines the light on promising developments in fighting cancer. “A number of the cancer treatments currently being tried are attempting to disrupt cell division in cancer cells,” he says. “So understanding the control system of cell division actually may lead to some treatment.”

The approach Iglesias takes has earned high praise from his colleagues. “The work he is doing is simply fantastic,” says Gerard G. Meyer, professor and chair of Electrical and Computer Engineering. “The promise of his research is enormous, in terms of understanding those biological control mechanisms that govern the onset of disease—and its possible prevention.”

Typically, Iglesias’s response is modest. “I’m often asked why I look at cell biology problems if I’m in electrical engineering,” he says smiling. “My answer is that I find it interesting. The knowledge that I have in systems theory traditionally has not been used in biology. So there are a lot of open problems where I think I can make a contribution.”

For more on Pablo A. Iglesias’s laboratory, visit www.ece.jhu.edu.
The Proof of Truth in Numbers

Node by node in networks, mathematician Edward R. Scheinerman models the motion along direct routes.

By Bob Gray

The Internet...interstate highways...interpersonal relations...e-mails...cell phones...cellular growth...Google. Welcome to a world composed entirely of networks. Edward R. Scheinerman thinks that’s just fine. A professor of mathematics in the Whiting School of Engineering’s Department of Applied Mathematics and Statistics, Scheinerman loves to model and analyze networks—and he uses advanced mathematics to do just that across many engineering disciplines.

“Networks are everywhere,” Scheinerman explains, “from looking inside of a cell at how genes interact to finding your way from Baltimore to Colorado. My field is discrete mathematics, especially graph theory, partially ordered sets, random graphs, and combinatorics, with applications to robotics and networks. The explosion of networks in the world has also led to an explosion in discrete mathematics.

“MapQuest is a perfect example,” Scheinerman observes. “You want to get from point A to point B.” Instead of simply seeking the shortest distance, however, “you have to follow a network. When you come to a stoplight, you have to make a decision. There is no, ‘Well, maybe I’ll take a half left,’” because there is no road there.”

This fall, Scheinerman returned to campus after a year’s sabbatical, during which he completed the second edition of his popular textbook, Mathematics, a Discrete Introduction (now available from Brooks Cole). He also conducted applied mathematics research; began “and mostly completed,” he says, a new book on computer programming for mathematicians; and was a visitor at the Center for Computing Sciences in Bowie, Maryland.

The mathematician has served the Whiting School as chair of his department and recently as interim associate dean for academic affairs. He received his master’s (1981) and PhD (1984) degrees in mathematics from Princeton University, where he was first introduced to the charms of discrete mathematics and graph theory.

In his textbooks, Scheinerman provides a better understanding of discrete mathematics, graph theory, and ways that networks can explain human interaction systems. The first edition of his Mathematics: A Discrete Introduction was published in 2000. Invitation to Dynamical Systems (Prentice Hall) was released in 1996.

“When I started at Hopkins in the mid-’80s,” Scheinerman recalls, “there was no introductory-level course in discrete mathematics, and I thought it was important that there be one.” Much to his surprise, then-department chair Robert J. Serfling suggested he develop one. Out of this experience, Scheinerman produced Mathematics, A Discrete Introduction. “That’s one of the reasons I love Hopkins,” he continues. “It has afforded me the opportunity to make changes, to have some influence, to make a difference.”

Another area where the mathematician is making a difference is in helping computer science more directly address the needs of mathematicians. In fact, the book Scheinerman has almost completed seeks to raise the profile of the programming language C++ among this group. “There has long been a great need” for such a resource, he notes. “C++ is widely used in the computer engineering world, but it has not been widely embraced by the mathematics community.”

The mathematical problems that Scheinerman tackles are not merely abstract. “Some of my papers would perhaps be of interest...
“In discrete mathematics, you’re either A or B. You are not something muddled in between.” —Edward R. Scheinerman

only to mathematicians,” he says. “Others deal directly with specific application areas, such as robotics.” What does tie them all together is that they all draw on the relatively new field of mathematics known as “discrete.”

What Makes This Math “Discrete”? 

“Most people study continuous mathematics,” Scheinerman explains. “Calculus, the study of things in motion, is one of the crowning achievements of continuous mathematics.” Calculus developed to answer such questions as, “How does the Moon move around the Earth, and why?” For this reason, he says, “for a very long time, there was no clear distinction between mathematics and physics. To ask whether Newton was a mathematician or a physicist would not have made any sense. In his time, the two things were intermixed.”

Fast-forward to the 20th century, and a world of finite (as opposed to continuous) mathematical problems. “We have invented everything from computers to MapQuest, and Google to the Rubik’s Cube. Not one of these is readily analyzed by continuous mathematics,” Scheinerman says. “Likewise with computers, everything is digital. In discrete mathematics, you’re either A or B. You are not something muddled in between.”

Much of mathematics is application-driven, and the need for a mathematics that can deal effectively with motion through networks—as opposed to smooth and continuous motion—has grown up with the computer era. Using discrete mathematics to model and understand networks finds applications in many fields. “One of my colleagues at Hopkins, Carey Priebe [professor of Applied Mathematics and Statistics], analyzed the e-mail communications of Enron employees to better understand how the social networks differed from corporate networks,” Scheinerman explains. “Nothing happens in engineering these days that doesn’t have a mathematics connection.”

No network, it seems, can escape the discrete mathematician’s ability to capture it in a graph that can be studied to better understand the connections between individuals—human or otherwise.

“Graph” is really somewhat a misnomer, the mathematician says, because the graphs he makes bear little resemblance to a typical pie or bar chart. Scheinerman’s graphs model discrete connections between entities, or nodes. Depending on the network one hopes to graph, there can be hundreds—or thousands—of direct connections between various nodes. Consider for example, the e-mail communication paths within an organization, or the connections represented by the growth and changes inside of a cell. The graphs reveal patterns, and Scheinerman tests theorems against these patterns, looking for mathematical proofs that can be used to discover the “truths” lying hidden in the complex interconnections.

We have a Johns Hopkins mathematician to thank for this specific use of the word “graph.” J. J. Sylvester, the legendary 19th-century British-born mathematician, coined the term “graph” for the kind of representation used by Scheinerman. (Perhaps contributing to Sylvester’s legendary status is the fact that in 1877, as a condition for accepting the position as the University’s first mathematics professor, he stipulated that his annual salary of $5,000 be paid in gold.)

Indeed, language and logic are exceedingly important to mathematics. As the chapter titles in Mathematics: A Discrete Introduction attest, mathematics seems more closely connected with philosophy than science, with which mathematics is often linked. Such chapter titles as “Why?” “The Nature of Truth,” and “If-then,” would sound right at home on a shelf next to Kierkegaard, Bonhoeffer, and Kant.

“The whole idea of ‘definition, theorem, proof’ is key,” Scheinerman explains. “This is universal to all of mathematics, to a mathematical way of knowing.” As it turns out, this is the exact opposite of the scientific method of discovering truth, which is to prove by empiricism. In science, “when you make a statement that has a one-in-a-million exception, no one is going to criticize you,” he says, “especially in a biological or social science.”

In mathematics, however, “truth means 100 percent. When we say a theorem is true, it is true without exceptions. Period. You cannot achieve that by empirical methods,” Scheinerman says with the certainty of a man who speaks mathematical truth. In all probability, he can produce a graph to prove it.

To learn more about Edward R. Scheinerman, visit www.mts.jhu.edu/~ers . To see a graph of how the Applied Mathematics and Statistics faculty members are networked in their research, visit www.ams.jhu.edu/ams/research/general.html .