ENGINEERING BIOLOGY

I
n a lab on the second floor of the Technological Institute, a robotic arm whirs behind glass, picking up pipette tips and dropping their contents onto a metal surface. But this is not just any surface: No bigger than a postcard, the plate is dotted with hundreds of tiny circles made of the thinnest layer of gold—the perfect surface for testing particular biological reactions. Upon these dots, in tiny droplets of liquid, proteins mix with one another in ways that science has yet to comprehend fully, spurring reactions identical to those that occur inside human cells. “It’s been a three-year process to learn to do all this,” says Milan Mrksich, standing in his newly transplanted lab. “It’s gotten to the point now where it’s ready for prime time.”

Just a few months ago these robots were humming at the opposite edge of the city, at the University of Chicago, where Mrksich held a professorship for 15 years. Last September Mrksich brought his lab to Northwestern, where he holds joint appointments in McCormick, the Judd A. and Marjorie Weinberg College of Arts and Sciences, and the Feinberg School of Medicine in biomedical engineering, chemistry, and cellular and molecular biology. “Those departments all have strengths in the areas we are active in, and Northwestern offers us a broader community that will allow us to take our science further,” Mrksich says. “After my first three months on campus, it was clear to me that I had made the right decision.”

Mrksich is perhaps the world’s leading engineer of the interfaces between materials and biological environments, a research area that blurs the line between the physical and biological sciences. “When we look at a cell, we don’t just see biology,” he explains. “We see the opportunity for using the cells in the physical sciences.” Throughout Mrksich’s career, that research has translated into the pursuit of “hybrid devices,”
man-made machines made partly of living cells (such as instruments that use beating heart cells as a power source), and the development of materials that mimic the structural matrix that organizes cells in tissue.

But on this wintry afternoon, watching the robotic arm zip back and forth in its glass housing, Mrksich is focused on a relatively new research area: a process he’s named self-assembled monolayers desorption ionization (SAMDI) mass spectrometry, a super-fast, low-cost, and “label-free” method of measuring biochemical activities on a surface—in today’s case, reactions between various proteins, peptides, and carbohydrates. While reactions performed in a solution can be easily characterized in minutes or hours, those performed on a surface, while less expensive, could take weeks to characterize—until now.

For Mrksich, studying the interactions between cells and their parts boils down to one overarching idea: living organisms are far better designed than any feat of human engineering, and it is only by truly understanding biology that we can begin to match its efficiency. “Our interest is in the engineering principles of biology,” he explains. “When we learn how biological networks operate, not only can we pursue more effective interventions in medicine, but we also can build nonbiological systems that operate by biology’s rules and that, unlike man-made systems, display the tantalizing properties of biological systems.”

He has his work cut out for him. Despite incredible scientific advances, Mrksich says, researchers remain relatively ignorant about how biological systems actually work. While we have made great strides in understanding individual parts—we know the parts of a cell, for instance, and we can sequence the DNA of whole genomes in a single day—we don’t know how these parts work together. “Take a cell,” Mrksich says. “We know, in principle, it’s not that complicated: It’s half the width of a hair, it’s got about 3 billion base pairs of DNA, maybe 50,000 proteins. But we still don’t understand how these parts interact with each other to make a cell alive, to make it carry out its functions.”

To understand the cell, it’s vital to understand proteins, Mrksich explains. Proteins are the functional units, or the “doers,” in a cell; they catalyze reactions, transmit signals between cells, and their actions can even be linked to various cancers. But when it comes to specifics, things get fuzzy. Of 50,000 proteins, we understand the functions of fewer than half. “That’s really quite remarkable. After many years of research by thousands of research groups, we still don’t understand what roles these proteins play in biology,” Mrksich says. “It’s like flying an airplane and not knowing what half the switches control or why they’re there.”

That’s largely because we haven’t had the right tools, Mrksich says. Traditionally, discovering protein function has been a slow, tedious process of trial and error. Since it’s impossible to see proteins directly, researchers use labels—chemical additives that will leave their mark in a reaction, such as radioactivity or antibodies—to determine whether a protein is active in a reaction. But labels are inherently limiting; they can only test to see whether a specific reaction is occurring, which means researchers have to know what they’re looking for in order to find it.

Mrksich has developed another way, which hinges on those gold-plated surfaces. In SAMDI mass spectrometry, each dot—as many as 6,000 per plate, each with its own “address”—is the site for its own reaction. Proteins are tethered to each spot with a sulfur molecule, which has an affinity for gold, and a particular solution is delivered to each site. After the reaction is complete, the plate is put into a vacuum and each dot is struck with a laser that releases the molecules from the gold base. The robot then weighs the contents of each site, allowing researchers to make an educated assumption about what occurred in each reaction.

The result is a highly streamlined, relatively inexpensive process that delivers an enormous amount of data. “Half a dozen years ago, doing 100 experiments in a day would have been considered a good day,” says Mrksich. “We do 100,000 experiments in a day. In 18 months we’ll be capable of running half a million in a day.” Mrksich estimates that each reaction in SAMDI mass spectrometry costs just pennies, compared with about $10 in a standard laboratory.

Mrksich’s research is already finding its way into industry. Last summer he founded a company, SAMDI Tech, to commercialize the process for the pharmaceutical industry. The process is especially well suited to the drug discovery process, which currently is extraordinarily lengthy.

“You have a freezer full of different compounds in a lab. In a pharmaceutical company the number is a few million,” Mrksich says. “You have one enzyme, and one by one you test small molecules to find those few that block the enzyme function. Instead of trying 10 combinations in a day, imagine trying 1,000—maybe 100,000. Imagine the discoveries we will make.”

Watch a video about Mrksich’s research at www.mccormick.northwestern.edu/magazine.