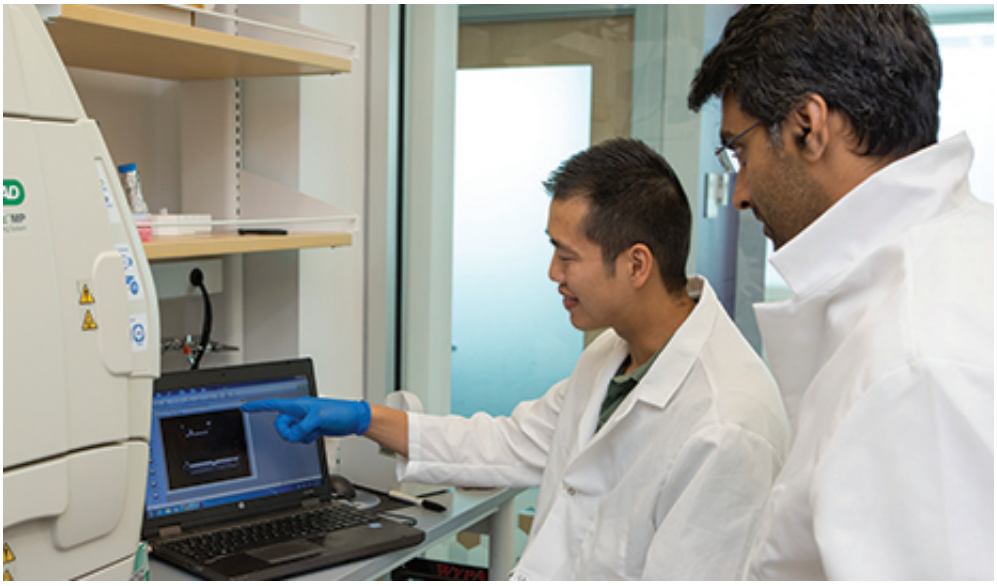
Researchers bring an engineering approach to systems biology efforts

November 24 2015



In addition to numerous faculty members from the School of Engineering & Applied Science, the Systems Biology Institute draws upon renowned geneticists, biologists, and physicists from across the university.

If you've never played chess, the rules are simple to learn. There are two players, each with six types of pieces, and each piece moves in a specific way. Learn the ways each piece can move and you can immediately sit down to play. There is no element of random chance; what happens in a game depends entirely on how the players make their pieces interact. The basic rules are among the simplest and easiest to learn of any strategy game in history.

Yet predicting how a chess game will progress is one of the most challenging modeling problems in the world. Simply by making the first move, the white player sets the game down a certain path; with the following move, the black player veers off down another. The number of possible games of chess has been estimated in excess of 10,000,000. And in all these games, not a single move is made in isolation: every move is a result of the input—the feedback—from the previous move, which was also a result of every move that came before.

This system of feedback loops is what makes chess so difficult to model and predict, but also makes an excellent analogy for a major area of research at Yale: systems biology.

"This is, in some sense, the essence of a systems approach," says Andre Levchenko, John C. Malone Professor of Biomedical Engineering and Director of the Systems Biology Institute at Yale's West Campus. "We are very, very interested in interactions, and put interactions at the center of the analysis—not the components themselves necessarily, but just the interactions."

In Levchenko's Institute, individual cells stand in for rooks, knights and pawns, and the game is much larger: studying (and predicting) the behavior of huge systems of cell networks, whether it's to determine the likely progression of a cancerous tumor or study the development of diabetes.

"Cells are exquisitely sensitive to a variety of different cues, chemical cues and mechanical ones," says Levchenko. "In fact that's the key to their survival, or to their proper function. If you think about what we call disease, that's the inability of cells to mount the response to cues that would be adequate. For example, instead of dying or staying put, cells may start dividing; that's in response to their own state, but also to certain cues they see in the environment. It's misinterpretation of these

cues that may lead to cancer, for example."

In the past, cell studies have been limited to looking at individual pieces of the puzzle: a small group of cells at one time responding to one input, or even a single cell responding to a single input. In a chess game, it would be the equivalent of examining how the white player might move his rook if the black player puts it in jeopardy. This remains a common approach in drug research: cells are exposed to different doses of a drug and the exposure is held constant for a period of time. Researchers study how the cells respond to the various dosages, and hope that the results will be instructive in deciding which candidate drugs to promote for further studies and which to abandon as they are unlikely to be helpful.

But this is only looking at one piece of the system. In the chess game, the white player might not move the rook at all, but sacrifice it to save the queen that is in jeopardy from the same prior move. If you were only looking at the rook, you wouldn't predict that outcome. Similarly, in a living human, many more factors may contribute to how a given drug would affect cells, and actual results could be very different from what you would see with the narrow focus on dosage. Instead of looking at just one small piece of the larger picture, Levchenko and his Institute go several steps further.

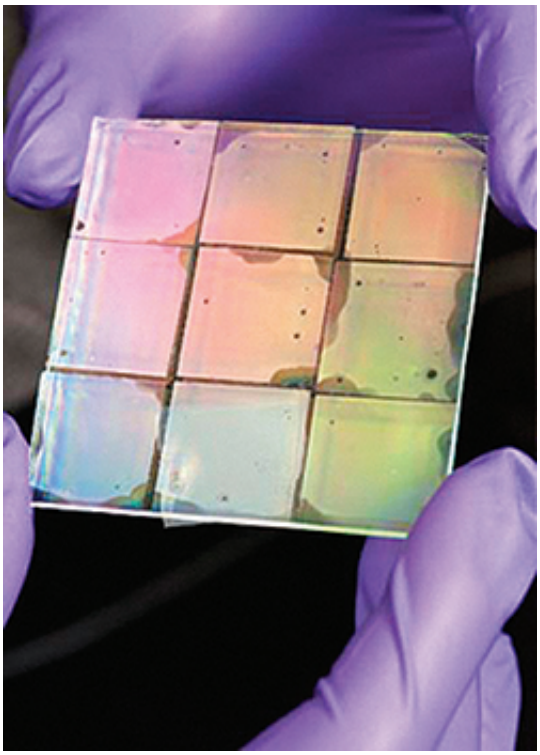
"What we're trying to do is circumvent some of those limitations of current research," he says. "We're trying to be mindful that reality can be complex."

Here Levchenko, who comes from an engineering background, draws a parallel.

"To understand a system that someone else, or even we, have designed, that's reverse engineering," he says. "When you grow up in an engineering community, you develop appreciation for the complexity of

systems, because when you try to build systems—to engineer them—you do it by design, but also by tweaks and tinkering and trying to figure out what works and doesn't work.

"Biology is very much engineering in that sense—an engineering science, because that's what we do all the time," says Levchenko.



Anatomical features of highly oriented extracellular matrix in various tissues.

It's no surprise, then, that among the many Yale researchers collaborating with Levchenko's Institute are several faculty members from SEAS, including Kathryn Miller-Jensen, Rong Fan, and recent hire Michael Murrell.

Fan's research will be familiar to readers of Yale Engineering (see "The

Translator," 2013-2014 issue). The associate professor of biomedical engineering was a chemist by training, but insists he was always an engineer at heart.

"My early training was more toward technology development, and my role in systems biology research was to develop better tools," says Fan.

Among Fan's primary interests is how cells communicate. Cells can respond to their environment based on several different cues, including mechanical forces and chemical signals. Given his background in chemistry, Fan has focused on cells' chemical signaling.

"Cells talk to each other, but it's unfortunate they don't understand English," laughs Fan. "They talk, but it's in a different language—they secrete proteins and bring those proteins throughout the cells and to the surface of the neighboring cells.

"The proteins secreted by one cell can mediate another cell," says Fan. "It's essentially a conversation. I think once we can measure a large protein panel, you'll be able to get an understanding of what they talk about. Then you know what they are going to do."

But the need for these kinds of large-scale measurements brings back the chess analogy: looking at just a piece of the board doesn't tell you how the game is going to progress.

"If you look at one or two proteins, that will not give you a systems-level view of a whole biological mechanism," says Fan. "In my lab, we develop a kind of microchip technology that we can use to interrogate individual cells, but also very large protein panels."

Fan has shared the device he developed for this purpose with Miller-Jensen, associate professor of biomedical engineering and molecular,

cellular, and developmental biology, who studies the way that cells communicate to mount an immune response in the face of viral infections. Viruses can hijack cell signaling for their own benefit, allowing them to evade immune response and replicate. Among many avenues of exploration, Miller-Jensen's group uses single-cell analysis to reverse engineer the signals sent during an immune response—work for which Miller-Jensen won an NSF CAREER Award earlier this year.

Feedback from Miller-Jensen's group, in turn, is used to further develop Fan's device.

"It's a mutual scientific exchange," says Fan. "It's a way of developing a tool by testing the device on cells. Sometimes we'll see something weird and then analyze the data in depth, and realize we need to take out a protein or replace it, improving the device. So that's a mutually beneficial process, I think."

This is a critical element of modeling efforts in systems biology, as Levchenko sees it.

"The most interesting times are the times where we see that a model doesn't work, doesn't give us a correct prediction," he says. "That's an opportunity for us to learn how these systems work, because there's clearly something we don't yet understand—something we haven't taken into account. Frequently it's just the telltale sign that we can find something new and different, and that's a great thing for us."

This kind of research calls for a wide range of expertise. In addition to the aforementioned SEAS researchers, key faculty at the Institute include Farren Isaacs, assistant professor of molecular, cellular, and developmental biology; Gunter Wagner, the Alison Richard Professor of Ecology and Evolutionary Biology; Murat Acar, assistant professor of molecular, cellular, and developmental biology and of physics; and Jesse

Rinehart, assistant professor of cellular and molecular physiology.

Together, the researchers' efforts have wide-ranging translational applications. In diabetes, for example, multiple types of cells are involved, including pancreas and liver cells. Many studies focus solely on the pancreas, guaranteeing from the start that they will never get a full picture of the system. Similarly, cell signaling is critical in the development of cancer; when signaling is interrupted or altered, cells can begin multiplying wildly, leading to the development of tumors. This has become an important focus of the Institute, particularly for aggressive types of cancer cells, and complements the cutting-edge cancer initiatives currently led by Joseph Schlessinger at the Cancer Biology Institute at Yale's West Campus.

Given the current state of systems biology, it's natural that SEAS research would relate to work being done at the Systems Biology Institute, and Levchenko sees it as an expected evolution.

"For a very long time, biology was just cataloging parts science," says Levchenko. "Cells are very complicated; let's take this protein, categorize this protein, take another protein, categorize that protein, and so on. That was an important, necessary step in the development of our new approaches to biology.

"Systems biology now is a step beyond that," he says. "It's thinking about how parts interact with each other—very much an engineering approach, because in engineering—yes parts are important—but how do we build something that performs as we want? How do we understand something that's been built before?"

"It's exceptionally easy for a systems biologist to talk to an engineer," says Levchenko, "because we share the appreciation for the importance of complexity for proper function. It's a synergy of philosophy; it's a

synergy of techniques."

Provided by Yale University