





by Benjamin Lester | illustration by Josh Cochran

Scientists are applying the tools and approaches of engineering to solve some practical problems and fathom the basic nature of things.

When Intel comes out with a new microprocessor, its competitors' inquisitive engineers soon have that chip under a microscope, figuring out how the device works by tracing the patterns of transistors on its surface. Dmitri Chklovskii, a group leader at HHMI's Janelia Farm Research Campus, is applying much the same technique to fruit flies.

His colleagues dissect the flies' brains, 50 nanometers at a time. "It's like slicing prosciutto," he says. Extremely thin prosciutto—1/1,000th the thickness of a human hair. Each slice reveals a new layer of neurons and synapses, which are carefully photographed with an electron microscope. Later, Chklovskii's team uses computers to trace each neuron's axon and dendrites as they snake through the brain.

Chklovskii is using computer algorithms to trace neural networks, and he thinks the principle of economy underlying microchip design may also govern the "wiring" of a neural network. Nature and microchip engineers may be working from the same playbook.

With its neuroscience focus and interdisciplinary character, Janelia Farm is a perfect place for Chklovskii, who was trained as a theoretical physicist and is now working to understand how the brain functions. "I consider myself a neurobiologist because I publish in neurobiology journals and go to neurobiology conferences," he says. "But I try to think like an engineer."

What does it mean to think like an engineer? In some circles, engineering is linked to the quest to build things and solve practical problems—for example, putting a man on the moon. ABET, Inc., formerly known as the Engineers' Council for Professional Development, has defined the discipline as: *the creative application of scientific principles to design or develop structures, machines,*

apparatus, or manufacturing processes.... By that credo, engineering serves not to expand the boundaries of knowledge but rather as the link between existing scientific discovery and technological benefit.

But Chklovskii and others see engineering as a broader set of ideals: simplicity, practicality, systematic thinking, and the idea that understanding a thing—or a process or a cell—isn't ensured until that thing can be built.

The line between science and engineering is blurring as engineers and tool makers set their sights—and their engineering minds—on unanswered biological questions, both as a means to solve practical problems and because they too are fascinated by the basic nature of life. And biomedical researchers, those who are after practical solutions to disease and those who seek to push the boundaries of knowledge, are reaching over and borrowing techniques and ideals from the engineers' toolbox.

Rebecca Richards-Kortum, an HHMI professor and biomedical engineer at Rice University, sees science and engineering along a spectrum. "At one end, there is pure science, where we just want to understand how the world works, and at the other is pure engineering where we just want to solve a problem like 'I need a rapid test for HIV that's 99 percent accurate and costs less than a dollar.'" There's a lot of overlap among individual researchers, she says.

Eminently Practical

HHMI INVESTIGATOR KRISTI ANSETH HAS AT THE ROOT OF all her endeavors a fundamental question: how does a cell get information from its surrounding environment? But she has ambitious practical applications for her findings.

"I want to design materials that I can use to culture cells"—cells for use in reconstructing damaged tissues, such as knees and hearts, says the chemical engineer at the University of Colorado at Boulder.

It is not yet possible to grow new tissues in a dish. A bit of structural engineering is necessary. Anseth creates an artificial

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A replacement heart valve that expands as a child grows is one of Kristi Anseth's engineering aims. Dmitri Chklovskii wants to know if neural networks follow the same design logic as microchips.

scaffold that supports cells from her patients while delivering the proper molecules to encourage growth. The crux of the problem is figuring out what signaling molecules are needed—and the answer varies, depending on the tissue being regenerated.

According to Anseth, with such a complex subject, it's easy to get overwhelmed. "You can't understand every pathway within the cell, let alone what happens to that cell when it interacts with other cells," she says.

She uses her engineer's training to reduce the scope of the problem. "I look at a complicated problem where we don't have enough information," she says, "and I try to figure out what's the critical information, and make a judgment that's 90 percent correct." In most cases, Anseth says, that approach is enough to learn what she needs and move forward. In one project, she is building a replacement heart valve for children with congenital valve defects. "There's no good option for them right now," she says. "Most treatments require many surgeries because the children are growing so fast. If we could create a living, reengineered valve structure that could grow with a child, that would have lots of benefits."

Anseth is not tackling the complex problem on her own: her team is collaborating with molecular biologists who specialize in



diseases of the heart. "We're learning about cells in heart valves and what goes wrong that leads to these valve defects," she says. "Once we understand what cues may be used to reverse this process, we can try to regenerate and grow healthy valve structures."

Robert Sah, an HHMI professor at the University of California, San Diego (UCSD), wants to create whole replacement joints—bone, cartilage, and all—outside the body that can then be surgically implanted into patients with osteoarthritis.

The vastness of the problem is one of the things that appeals to Sah, who runs the UCSD cartilage tissue engineering laboratory. "Theories of many materials and systems are very simple and predictable in terms of the phenomena underlying them—one electrical circuit component can be made almost the same as the next," he says. "In biology, it's orders of magnitude more difficult to [develop] useful quantitative theories." The engineering approach works well, he says, because engineers disregard the information they don't need. "Engineers reduce a model to its essential components," he says.

To fashion his biological joints, Sah needs to answer some fundamental scientific questions. "We need to understand the physiology of the joint. How is the joint lubricant made and maintained? How do mechanical forces cause wear and tear or induce biological responses that may be healthy or damaging?" he says. "During the past decades, scientists and engineers have worked on the individual pieces, and now some of us are trying to put them all together."



Loren Looger is motivated by the audacity of his plan: to redesign the way we think. For Robert Sah, it's the remarkably practical: to engineer biological replacement joints.

Grasping the Fundamentals

ANSETH AND SAH ARE ENGINEERS BY TRAINING, AND THEY seek answers to basic scientific questions as a way to solve practical medical problems. But there are scientists looking through the binoculars from the other end, borrowing engineering methods to improve their grasp of fundamental concepts—sometimes along the way they address practical problems, but that's a secondary benefit.

At the University of Washington (UW), HHMI investigator David Baker is fascinated by how the amino acid chains that make up proteins fold into the specific three-dimensional shapes that allow them to function. In nature, proteins always fold into the most thermodynamically stable shape—spontaneously and rapidly—and Baker is trying to mimic the process on computers. He compared his predictions with data from direct methods of structure determination, such as x-ray crystallography. “That was a way of testing our understanding of the process,” he says.

Once passing that way station, “we realized that another, just as stringent, challenge was to design new protein structures by changing the sequences or coming up with new sequences,” he says. “One of the best tests of understanding is building something.”

Baker admits to seeing the practical side of his work. “I’m very interested in creating new enzymes to do useful things, which is pretty much an engineering problem,” he says. For example, one of his students is developing an enzyme that can turn carbon dioxide—CO₂—into sugar, possibly helping to reduce greenhouse gases. Other conceivable applications for new enzymes include proteins that could speed up pharmaceutical manufacturing or other industrial processes. Baker makes the point, though, that while these are problems with eminently practical goals, he’s not tackling them for practicality’s sake. Instead, he hopes to use the process of building enzymes as a way to learn more about the fundamental principles that govern how they work.



The purely practical applications that follow, says Baker, can be handled by others. For the past few years, he has run the calculations necessary to predict protein shape with help from the computers of laypeople around the world. The distributed computing network is called Rosetta@home and has more than 200,000 members from all walks of life. Now, Baker and his colleagues at UW have devised a multiplayer game for them called Foldit. Players score points for folding amino acid sequences into the most stable shapes. Later this year, the Foldit team plans to introduce a design element to allow players to create brand new proteins. The design game aims to turn people all over the world into competitive molecular engineers. “I imagine a 12-year-old in Indonesia who can visualize proteins in his head and build a cure for HIV,” Baker says.

Like Baker, Loren Looger, a group leader at Janelia Farm, likes to build. At the moment, Looger thinks of his lab as a one-stop tool shop for his colleagues at Janelia—making new molecules to assist their research. “People want sensors for all the hot neurotransmitters—serotonin, GABA, glutamate, dopamine,” he says. “We also make brighter fluorescent proteins, and fluorescent proteins that can switch colors. Those are useful for different modes of imaging.”

According to Looger, whose training is in math, synthetic chemistry, and computer science, making sensors and fluorescent proteins isn’t exactly easy, but “it’s pretty obvious what needs to be done.” In a year or so, after he’s taken care of his colleagues’ pressing needs, Looger plans to turn his prowess in manipulating molecules to the wiring of neurons. “We’ll start to swing the pendulum back toward crazier things, like getting inside neurons and whole-scale

A TOOL-DRIVEN REVOLUTION

Occasionally, the tools built to make an experiment possible attain significance far beyond the experiment that spawned their creation.

Milan Mrksich loves pointing this out. “New directions in science are launched by new tools much more often than by new concepts,” he says, quoting the physicist Freeman Dyson. “The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained.”

That sentiment explains why Mrksich, an HHMI investigator at the University of Chicago, tackles questions in biology by building new tools. The revolutionary advances within modern biology are often associated with the development of a new tool, he points out. “The polymerase chain reaction, green fluorescent protein, DNA

synthesis—these are the tools that allow life scientists to do their work,” he says.

Mrksich is studying the interplay between cells and the extracellular matrix of proteins that surrounds them, supports them, and guides their development. “The matrix is dynamic,” he says. “Proteases are degrading the matrix, cells are remodeling it, and growth factors and other proteins are binding to it so that they can interact with cell-surface proteins. It’s very challenging to study.”

Right now, the best available way is to affix a single layer of a matrix protein of interest in a Petri dish. “Once you do that, the cells will attach, they’ll spread, and one can then study the relationship between the protein layer [and] the cells,” he says. But that technique can’t mimic the matrix’s constant remodeling.

So Mrksich engineered a better Petri

dish that can mimic the dynamic matrix by turning the signaling molecules, called ligands, on and off. The engineered surface consists of a glass slide coated with a layer of gold thin enough to be transparent. Carpeting the gold is a layer of molecules that anchor ligands. The ligands are “hidden” from cells growing on the dish by a small molecule that pops off in the presence of voltage, allowing the ligand to interact with receptors on the cell. “So we can grow cells on the layer, and then, when we want, flip a switch and turn those ligands on [or off] and see how the cell responds to the changes,” he says.

Mrksich has a history of sharing tools he developed with other labs. Eventually, he will do the same with this matrix mimic. But not yet. “We’ve spent a long time developing this tool. Now we’re applying it to questions,” he says. —B.L.

rewiring,” he says. “There’s that idiom that you don’t really understand a system until you can redesign how it works.”

In his drive to test his understanding of how neurons function, Looger will change the sequence of amino acids in neuronal proteins, basically reengineering the proteins that control the way neurons communicate. “That work is mainly driven by curiosity ... the sheer audacity of trying to redesign the way we think,” he says.

Principles of Economy

DOWN THE HALL FROM LOREN LOOGER’S OFFICE AT JANELIA Farm, Dmitri Chklovskii is looking for simple engineering principles in the dizzying structure of neural networks.

Chklovskii is investigating a century-old tenet called “the wiring economy principle.” The idea was formulated by Santiago Ramón y Cajal, a Spaniard who won the 1906 Nobel Prize in Physiology or Medicine for his work on the structure of the nervous system.

Ramón y Cajal believed that evolution would act to reduce the length of connections between neurons to conserve energy and materials. The same principle is a key part of microchip design: fitting transistors close together on chips allows engineers to reduce the distance electrons must travel along wires, thereby increasing processing speed. In addition, says Chklovskii, “wires are mostly what take up the room on a computer chip. If you

don’t optimize their length, you can’t fit a significant circuit on a chip of a limited size.”

Testing the wiring economy principle on the scale of a whole brain in fact involves borrowing the tools of a microchip engineer: tracing every nerve connection in an organism’s nervous system, then feeding the connection data into a computer and comparing its “optimal” layout with the reality of what’s there.

A complete wiring diagram for an organism didn’t exist until Chklovskii’s group created one by finalizing a partially completed, decades-old schematic for a roundworm called *Caenorhabditis elegans*, whose 302 neurons make it easy to map. The diagram was started by Nobel laureate and Janelia Farm senior fellow Sydney Brenner, who first realized the worm’s potential as a model organism. Using the roundworm diagram, the team tested the economy principle. “In most situations, we were able to predict neuronal locations pretty well,” Chklovskii says, “but some were way off. Some neurons [didn’t] fit into the optimization scheme.” Identifying the discrepancies between the wiring economy principle and real brain wiring is helping Chklovskii refine his thinking about the principles that govern neuronal circuitry.

The project served as a warm-up for his team’s *Drosophila* endeavor, which entails mapping connections among more than 250,000 neurons. “The idea is not just to get the structure of the neuronal circuit, but to be able to infer function—to understand how the brain works,” he says. ■