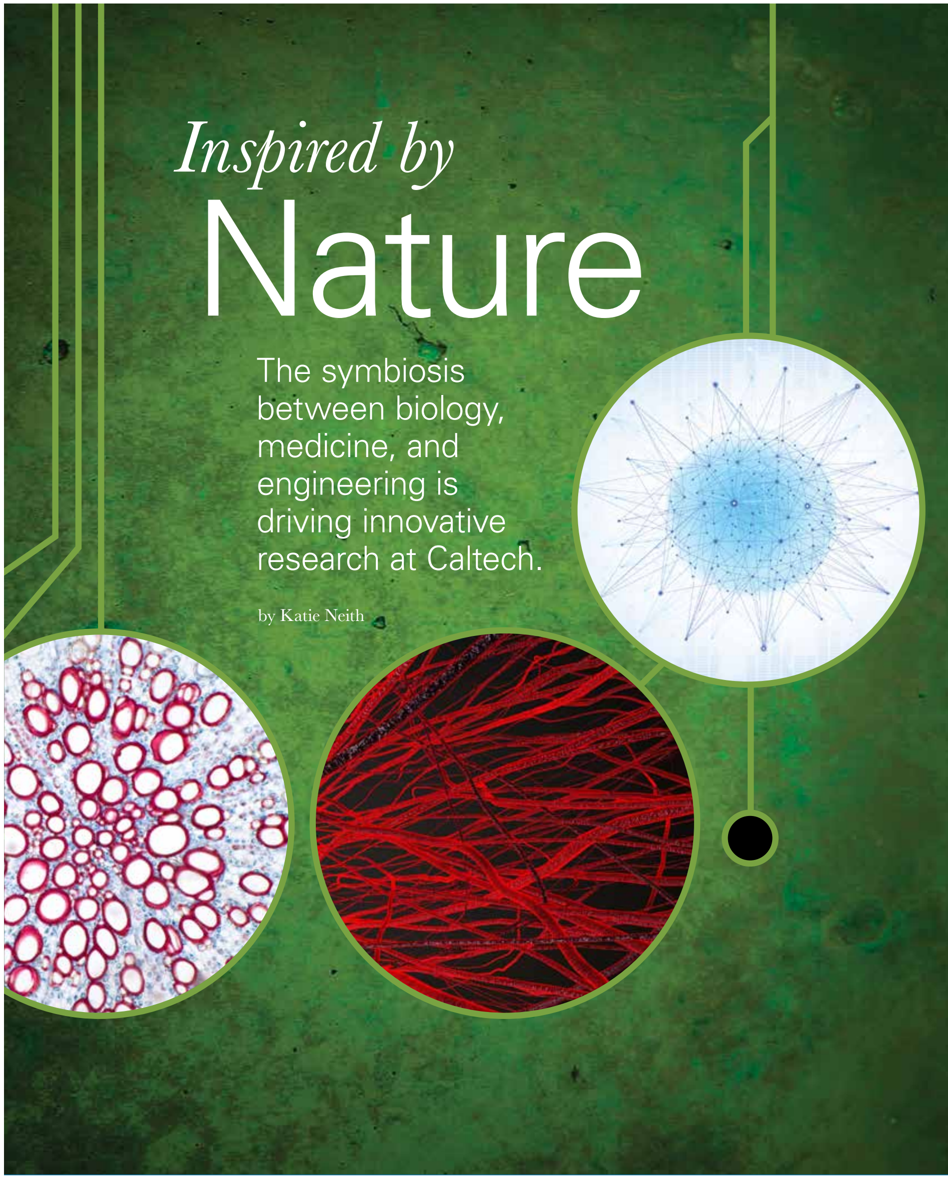
Inspired by Nature

The symbiosis between biology, medicine, and engineering is driving innovative research at Caltech.

by Katie Neith



Learning how to program biological molecules as if they were computers in order to build molecular machines with the ability to process information, make decisions, take actions, learn, and evolve.

Gathering the information gleaned from more than three decades of battling HIV in order to engineer antibodies that can outsmart the virus's attempts to evade destruction.

Detailing the biophysics and biochemistry of the zebrafish heart in order to create man-made artificial pumps that one day might help human hearts beat a little more steadily.

Building an understanding of the basics of a phenomenon so that you can pursue the best and most practical way to apply those findings—often within the same research group or collaboration—is the crux of bioengineering at Caltech. Instead of handing knowledge off, Caltech's scientists and engineers use what they've learned to solve the problems they are most interested in.

To acknowledge and formalize its commitment to this kind of continuity and collaboration, last fall the Institute combined the disciplines of biology and biological engineering into the Division of Biology and Biological Engineering (BBE). It was a move that created an academic division unlike any other among its peer institutions, and the first time a Caltech division has been renamed since 1970. Simultaneously, the Division of Engineering and Applied Science (EAS) announced it would be providing a more solid platform for the in-depth exploration of bench-to-bedside medicine by dedicating an entirely new department to medical engineering (MedE).

"We've been doing bioengineering work at Caltech for a long time, but we've never organized it in such a way that the connection between the science and the engineering was so clear," notes Caltech vice provost Mory Gharib, whose own research focuses on what he calls bioinspired engineering. "Now we're set up so that we can not only develop the scientific understanding of biological engineering and then apply it, but we can also translate it to a clinical setting. This, I believe, is creating a model for the rest of the country. Instead of putting researchers in boxes, we are trying to nurture them in a collaborative, fluid way."

BUILDING FROM BASICS

The study of nature—of what goes on in the living world around us as well as the one inside our own bodies—is among the oldest fields of human inquiry. Scientists working in biology have long examined plants, animals, and other organisms to determine how they are structured, as well as to better understand how they function and how they evolve.

But even before we were able to understand our surroundings, we worked to improve them, to solve the various problems we encountered by using the raw materials around us to develop tools, machines, and other technological solutions. It's a most basic of human endeavors; a pursuit we refer to today as engineering.

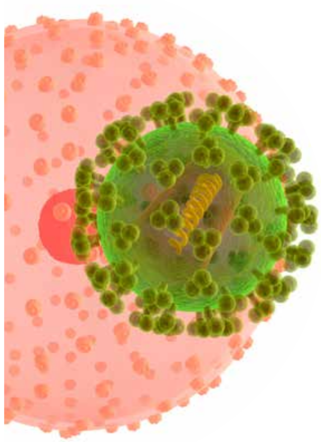
Those two approaches—that of basic science and that of engineering—tend to address similar questions and problems from different angles, says Gharib. As, he adds, do biological and medical engineering, as exemplified by the fundamental approaches taken by researchers in BBE and MedE, respectively. "In trying to understand how biology works and then building upon that to get to the point where it can contribute to the field, biological engineering is bottom-up. Medical engineering, on the other hand, is top-down. We look at the problems that are currently challenging to the field and try to come up with devices and techniques to help clinicians do their job better or make breakthroughs. Essentially, we're looking at the same wall from two different sides."

This kind of dedicated focus on bioengineering, no matter which side of the wall a researcher is on, Gharib notes, "will not only help coordinate scientific work at Caltech but will also give outsiders a more accurate impression of how we at Caltech are taking a multifaceted approach to the challenges of this field across disciplines."

According to BBE chair Stephen Mayo, who guided BBE through its reorganization, melding biological engineering with the fundamental science of biology is a unique way of approaching this area of research. "Although other schools have biological engineering programs within their schools of engineering," he notes, "none has a college or school in which biological engineering is integrated directly with biology, so that they can enhance each other—allowing those people who are doing engineering to interact more closely with those who are doing fundamental work and obtaining basic knowledge."

Caltech's Division of Biology was originally founded in 1928 by Nobel Prize–winning geneticist Thomas Hunt Morgan. As part of its transformation into BBE, it has added 11 faculty members who also work within other Caltech divisions; their research areas include genetic engineering, translational medicine, synthetic biology, and molecular programming.

"The formation of BBE is a reflection of the diversity and breadth of activities in engineering and the biological sciences at Caltech—from the structure and function of proteins at the atomic level to developing nanoprobe electrodes that can simultaneously measure the activity of thousands of neurons in the brain," says Mayo. "Putting these activities into one division increases the potential and the pace for providing transformative solutions to some of the biggest problems in science, medicine, and health."



Biologist Pamela Bjorkman is working to engineer antibodies that function more effectively against HIV, seen above (in green) infecting a cell.

EAS's new MedE department, spearheaded by EAS chair Ares Rosakis and a core group of faculty, joins six other departments in the division, each of which is grounded in a specific engineering discipline. "We have been engaged in medical engineering for several decades, but are now formalizing our commitment to this area by focusing more resources on finding fresh avenues for developing diagnostic tools, medical devices, and treatment options, in an approach sometimes known as translational, or 'bench-to-bedside,' medicine," says Rosakis. "The evolution of MedE reflects the desire of many faculty members and of local research hospitals and medical foundations to engage jointly in engineering-centric technology-development efforts for medical applications."

To that end, MedE is already partnering with the Keck School of Medicine of USC, UCLA's David Geffen School of Medicine, City of Hope, the UCSF School of Medicine, and Huntington Memorial Hospital, among others. Alongside the newly established BBE division, MedE positions Caltech to become an even more dynamic force in the field of bioengineering, says Rosakis.

"Caltech really has an opportunity here," says Yu-Chong Tai, the inaugural executive officer for MedE. "While there are more than 60 accredited biomedical engineering programs in the United States, and there are about 100 biomedical programs at various universities and institutes, Caltech is engaged in a very unique pursuit. The work we want to do relies on deep engineering, which is our strength at Caltech. That's why our intention is to build the Caltech medical engineering department in a way that is rooted in really first-class engineering, moving from that base toward medical applications."

Not every aspect of bioengineering at Caltech is undergoing an evolution, however: the Institute's Donna and Benjamin M. Rosen Bioengineering Center, founded in 2008 through an $18 million gift from the Benjamin M. Rosen Family Foundation, will remain an intellectual hub for bio- and medical engineering resources and activities, and will continue to be jointly administered by BBE, EAS, and the Division of Chemistry and Chemical Engineering.

"The Rosen Center acts as a kind of glue that ensures that the broad bio-related engineering activities on campus have a central point of coordination and support," Mayo says.

TRANSFORMATIVE SOLUTIONS

For bioengineer Lulu Qian, this renewed recognition of the importance of her field for Caltech plays out every day in her lab, where she and her team apply engineering's computer programming principles to biological molecules like DNA and RNA. Qian, who became one of the first new members of BBE when she joined the Caltech faculty last year as an assistant professor, is bringing to this problem both the biological knowledge and the computational expertise she gained when she spent time as a Caltech postdoc working with Shuki Bruck, the Gordon and Betty Moore Professor of Computation and Neural Systems and Electrical Engineering.

"Nature has been very successful in evolving and selecting the most efficient and powerful biological systems made of simple individual molecules," says Qian. "If we want to use the full potential of molecules to create complex and programmable systems, we'll need to borrow biology's own information-processing principles."

For example, Qian and her lab members, inspired by learning and memory-forming rules in the brain, are working to create synthetic DNA neural networks that can learn from their biochemical environment and recall patterns of biochemical signals. Such circuitry could, in the future, lead to molecular robots that respond intelligently to unexpected events they encounter during autonomous operations such as delivering drugs in the body. Inspired by collective behaviors such as foraging in ants and swarming in termites, Qian's group is working to build molecular robots that may have simple functions as individuals but are able to perform remarkably complex tasks when in groups.

"I take inspiration from biology and apply the conceptual frameworks and tools of computer science to molecular engineering," says Qian. "My research aims to extend computer science with new molecular substrates, and to create new frontiers in chemistry and the biomedical sciences."

While Qian is applying what she's learned from biology to her engineering pursuits, biologist Pamela Bjorkman is attacking from another angle—applying engineering principles to the development of innovative ways to counter the human immunodeficiency virus (HIV), the infectious agent that causes acquired immunodeficiency syndrome, or AIDS. A worldwide scourge, AIDS has killed an estimated 35 million people, according to the World Health Organization. Another 34 million are believed to be living with HIV.

Specifically, Bjorkman and her team are trying to create—or, rather, engineer—antibodies that can work more effectively against HIV, which is difficult for the human immune system to clear from the body once it has been infected. There's only one clear target on the virus for antibodies to go after—spikelike proteins that stick out of the outer coat of the virus.

The problem is that HIV-1 can easily evade these antispike antibodies because its spike proteins—which are used to bind to receptors on the host cells it wants to infect—are able to rapidly mutate so that the antibodies are no longer able to recognize or glom onto the spikes.

It's that evasive technique that Bjorkman and her team are trying to counter in the lab. "We are using structure-based protein design methods to engineer antibodies that can fight back against some of the common routes of HIV mutation," says Bjorkman.

The production of ever-changing types of antibodies in response to an infection is a remarkable example of real-time evolution, Bjorkman says. The immune system begins churning out huge numbers of antibodies when it detects a pathogen in the body; the ones that bind best to that pathogen are then made in large quantities. By studying the natural antibodies produced by an infected host, she hopes to learn what makes certain antibodies—in particular those targeting HIV—effective, and to then take the optimal properties found in various anti-HIV antibodies in order to engineer new versions specifically created to have many of those advantageous properties.

"It's this ability to draw on both the quantitative and engineering aspects of biology that puts those of us in the Caltech community in a unique position to conduct both fundamental and applied research," Bjorkman says. "And that's what will ultimately help us to make real improvements in human health."

ADDRESSING SOCIETAL NEEDS

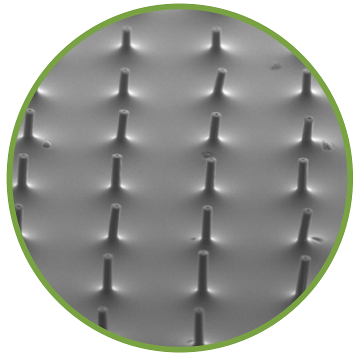
The researchers who make up the MedE department—brought together from a broad range of engineering and science specialties both within EAS and outside it—are, for their part, focusing on improving human health though interdisciplinary collaboration in those critical areas of medicine and engineering that can positively effect well-being, says electrical engineer Hyuck Choo, who is part of the new department.

"The outcomes of biomedical engineering research impact our lives directly and can greatly improve the span and quality of human lives," says Choo, who is working on building implantable sensors to improve the management of glaucoma and diabetes. "Our society is aging and, as a result, the medical care burden on our society will continue to increase. It's a great responsibility and also opportunity at the same time. Because it is a large-scale societal burden that we have no other choice but to deal with, you can easily foretell that new, useful medical engineering technologies will create economic engines for our society."

The nanoscale biomedical implants that Choo is engineering in his lab will provide pressure readouts for people with glaucoma, an eye disorder associated with increased fluid pressure in the eye that can lead to optic-nerve damage, including blindness. He is also working on glucose-monitoring sensors that can be implanted in diabetes patients to help them know how to regulate their glucose levels, which is key to managing the disease. In addition, his lab works on developing imaging techniques that give both literal and figurative insights into human diseases; the team is also involved in building nanoscale power generators for its and others' implantable medical electronic devices, all of which require robust power sources in small spaces.

Choo says that, as an engineer, he finds it fascinating to learn more about how our bodies work and why they sometimes malfunction, and to consider how he and others might use engineering technologies to solve health problems and improve our functioning.

"Frequently, while studying how our bodies work, I find a lot of similarities between independently human-engineered devices and their naturally evolved counterparts, which are often



Mory Gharib was inspired by the thorns of cacti when developing microneedles for drug delivery (above, right). Lulu Qian is exploring how knowledge of biological systems can help her create synthetic DNA neural networks (next page, left).

better designed and optimized than human devices," he says.

BLURRING THE LINES

Several faculty members are so deeply embedded in both the biological and the engineering worlds that they are part of both the renamed BBE division and the new MedE department.

Mory Gharib is one of those with a joint appointment. Gharib and his research team work to better understand how our most important physiological machines—such as our hearts and our eyes—actually work. He uses these insights to design and build devices for drug delivery and other medical applications.

Take, for example, zebrafish. Gharib and his team have been looking at how the hearts of these small vertebrates work, using advanced imaging techniques to understand the physics and chemistry of the mechanisms responsible for what he calls "these amazing machines that work on all scales." By deciphering the science and engineering principles underlying those mechanisms, he has been able to build small pumps that might one day be used for cardiovascular medical applications.

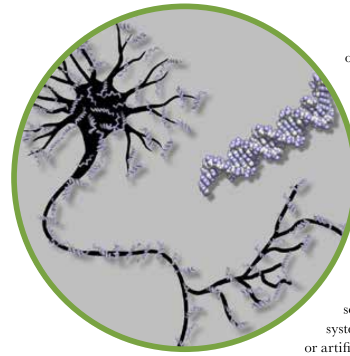
But his biology-derived motivation doesn't stop there. Gharib has designed visualization systems based on spider eyes, is investigating carbon nanotubes for their ability to be super hydrophobic (meaning they stay very clean because nothing attaches or sticks to them, including microbes), and has engineered microneedles based on the design of the thorns found on cacti, that are now being used for drug delivery.

"There are medical needs that we are trying to respond to," says Gharib. "There are some areas where no one else is doing research because they don't believe a solution is possible. Those are the problems we like to attack and where we believe bioengineering can provide an answer."

Bioengineer Changhuei Yang is also a member of both BBE and MedE.

"There is a lot of cross-talk and cross-fertilization between the two," he says. "I participate in both options because a lot of my research crosses that diffuse boundary."

Yang's research focus is on optical imaging techniques that have biomedical applications. One example he points to is a suite of microscopy technologies he has developed,



which—designed for a wide field of view—can have a direct impact on digital pathology, giving pathologists accurate and efficient ways to digitize pathology slides. As it turns out, Yang says, these same technologies are useful for laboratory biologists as well, because they allow the scientists to track cell cultures over long periods of time.

"Bioscience research is actually a very good staging ground for the eventual translation of technologies into the medical arena," he says. "Our eventual research goal is to translate this technology into medical applications such as incisionless surgery, deep brain stimulation, and targeted optically activated drug therapy."

Lulu Qian says Caltech's increasing emphasis on bioengineering highlights two general directions for research at the intersection of bio-medicine and engineering.

"In my view, the importance of bioengineering derives from two related facts," says Qian. "First, bioengineering helps us bring engineering approaches from the macroscopic scale down to the microscopic scale, and creates real-world applications in areas such as biology, materials science, and medicine by improving our capability for precisely manipulating matter at the finest level. Second, by building artificial molecular systems, bioengineering helps us to better understand the brilliance of nature, the powerful principles it exploits, and the incredible potential of self-organized biochemical systems—whether natural or artificial."

The consensus, it seems, is that a robust focus on bioengineering will benefit both Caltech and society as a whole.

"Before, it was a hodgepodge, and no one was sure which area to focus on, but now we've given importance to both—to biological engineering and to medical engineering, says Gharib. "The outside world will see it as something that is being taken seriously at Caltech. We are not just sending rovers to Mars, we are also responding to the immediate needs of society." ESS

Pamela Bjorkman is the Max Delbrück Professor of Biology at Caltech and an investigator with the Howard Hughes Medical Institute. Her work on HIV antibodies is supported by the Bill and Melinda Gates Foundation, and the National Institute of Allergy And Infectious Diseases.

Hyuck Choo is an assistant professor of electrical engineering.

Morteza Gharib (PhD '83) is a vice provost at Caltech and the Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering.

Stephen Mayo (PhD '88) is Bren Professor of Biology and Chemistry and William K. Bowes Jr. Leadership Chair of the Division of Biology and Biological Engineering.

Lulu Qian is an assistant professor of bioengineering. Her work in synthetic molecular systems is funded by the Burroughs Wellcome Fund, the Okawa Foundation, and the National Science Foundation. Ares Rosakis is Theodore von Kármán Professor of Aeronautics and Mechanical Engineering and Otis Booth Leadership Chair of the Division of Engineering and Applied Science.

Yu-Chong Tai is Anna L. Rosen Professor of Electrical Engineering and Mechanical Engineering and executive officer for medical engineering.

Changhuei Yang is professor of electrical engineering and bioengineering. His work on optical imaging is funded by the National Institutes of Health and Clearbridge BioPhotonics.