Assembly and Creativity: An Interview with Three Founders of Caltech's Newest Option

NATURE HATH NO GOAL THOUGH SHE HATH LAW—or so observed the seventeenth-century poet John Donne. While we can only speculate about the former, we are certain about the latter, and researchers in the new Caltech interdisciplinary Option of Bioengineering aim to analyze, understand, and adopt the laws governing Nature's handiwork for the extreme benefit of multiple areas of science and engineering. Centered in the Division of Engineering and Applied Science, the graduate Bioengineering Option will be a full collaboration with the Division of Biology and the Division of Chemistry and Chemical Engineering.

At a variety of levels of order—from the molecular to the cellular to the organismal—biology is becoming more accessible to approaches that are commonly used in engineering, such as mathematical modeling, systems theory, computation, and abstract approaches to synthesis. Conversely, the accelerating pace of discovery in biological sciences is suggesting new design principles that may have important practical applications in man-made system design. Thus, the research synergism created at the interface of the enhanced understanding of complex biological systems and the design and synthesis of complex biological systems offers unprecedented opportunities to meet challenges in both biology and engineering.

The educational mission of the Option is to create a new generation of bioengineers superbly trained in both engineering and biological science, ready to realize the possibilities of reverse engineering of biological systems and produce biological structures from man-made materials. The faculty and students are drawn from diverse disciplines such as biology, computational and neural systems, mechanical engineering, electrical engineering, computer science, aeronautics, chemistry, and chemical engineering.

Some of the questions driving the research of this approach-integrating group include how can we engineer robust and controllable components (at levels of molecules, gene networks, and organelles) that can be inserted into organisms for clinical and research use; how can emerging engineering technologies, such as robotics, MEMS, and nano-scale systems technology, be used to improve our ability to carry out biological research, as well as enhance medical clinical practice; and how can biological discoveries be used to guide the development of new engineering components and systems?

Caltech has the distinct opportunity to redefine traditional "bioengineering," which typically concentrates on biomechanics, to include new areas of molecular biophysics and neurobiology, both of which are ripe for the application of engineering tools to analyze and synthesize biologically based and inspired systems. To learn more about the new Option, ENGenious interviewed Mory Gharib, Professor of Aeronautics and Bioengineering, Steven Quake, Associate Professor of Applied Physics, and Paul Sternberg, Professor of Biology.


Professor Steven Quake


Professor Mory Gharib


Professor Paul Sternberg

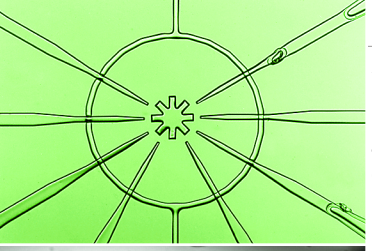
bioengineering

interview

ENGENIOUS: What's the Bioengineering Option all about?

GHARIB: I think one can claim the Caltech version has converged with something that we think will address very certain principles of bioengineering, biosynthesis and biomimetics, and learn from nature's design, to come up with physics, analysis, and better devices. But you know, we can't just jump into it. You cannot just mimic nature. You have to first understand it. You have to mimic both function and, for example, geometry, in terms of reality. So, that's why we put together this program. It's not 100% complete, but there are different aspects that require a strong synergy between biology, engineering, chemistry, chemical engineering, and physics. Paul and Steve can add to this from their perspectives…

STERNBERG: As an experimental biologist, I'm trying to reverse engineer nature, to look at these organisms, to figure out how they do the wonderful things they do. And at some point, you say, we think we understand how it works. But, the proof of that



A microfabricated rotary pump device. Such a device consists of two layers: fluid channels on the bottom and pneumatic actuation channels on top. Fluid channels are 100 µm wide and 10 µm high. Two applications based on this rotary pump have been demonstrated: efficient on-chip fixed-volume and continuous flow mixing of two streams; and accelerated sensitivity in a surface binding assay.

A 1.5 mm long zebrafish (*Danio rerio*) embryo 48 hours post fertilization. Analysis of intracardiac fluid dynamics of the early embryonic heart may represent a useful approach to understand the interplay between physical forces, developmental gene expression, and cardiac pathogenesis.

understanding is turning it into engineering. And really, that's part of the excitement here—to demonstrate that for certain systems, whether they be molecular systems or gadgets, we can make something that's new.

QUAKE: Bioengineering at Caltech is M.S.G.: molecules, systems, and gadgets. Those are the three broad categories that capture what the central people in our Option are doing. In the area of molecules, we have some really clever and sharp faculty who are interested in this problem of molecular design, particularly for biological molecules. So Nature, the tinkerer and the designer, she's handed us 200,000 proteins to play with, but people at Caltech aren't satisfied with that. They're trying to come up with very clever ways to make new molecules. We have a very strong group in this respect. It's cool because they have a nice interplay between biology and engineering. For example, one of the ways Frances Arnold [Dickinson Professor of Chemical Engineering and Biochemistry] tries to design is to design by using evolution, which is not something that's in a normal engineering tool kit. But she's taking the principles of biological evolution and applying them to protein design.

Guys like Steve Mayo [Associate Professor of Biology and Chemistry; Associate Investigator, Howard Hughes Medical Institute] are trying to use very sophisticated computational methods to do evolutionary design. Systems engineers are good at making systems and have worked out a number of principles for doing that. Nature has done it, too, but historically biologists just haven't really appreciated that part of nature's designs. This has become a very interesting area to look at: to try to understand how biological systems function as a whole. Many people think that maybe nature uses similar design principles that engineers have worked out and they're trying to push that analogy and see how far it will take them.

GHARIB: These collaborations between biologists and engineers are not new. They work together on devices and approaches to systems. All the devices that helped the genomic revolution were designed by engineers and biologists working together. But, now that we have sequenced DNA, we ask ourselves how to put it back together in order to reconstruct big molecules, and eventually organs and systems.

QUAKE: The third area is gadgets. That's what engineers do—they make gadgets. And again we have a very strong group at Caltech. Guys like Mory are trying to take lessons from nature and look at the fundamental physics of how nature makes devices. How a growing heart develops, and how a heart pumps.

GHARIB: How does nature pump in general?

QUAKE: So he's trying to look at nature, understand what nature does and then try to engineer man-made gadgets that use those principles. Because in many cases, they're actually quite transposable and useful.

ENGENIOUS: So it's a very different viewpoint from a strict engineering perspective.

GHARIB: That's right. And also different from other bioengineering or biomedical programs because most of them try to build the pump that works inside someone's body. They build micro-fluidic devices without looking at the concept in nature. They have good solutions, but that's different from what we're trying to do.

ENGENIOUS: Look at nature and work backwards? So you're taking a much more biologically focused approach?

STERNBERG: Philosophically biological in approach, yes, but the outcomes might be different. You don't actually have to make it look like something in nature. You could use the principle, a design principle, and then come up with something new.

QUAKE: There's a very famous example of that which was done here at Caltech in the '80s. Done by the CNS group [Computation & Neural Systems], right? The general idea was trying to understand how the brain computes. The mathe-

matical, physical models—neural networks—were sort of discovered and explored, and the pioneers were here. At the end of the day, I think they weren't that useful for understanding biology, but the principles that came out of them have found a number of applications in the engineering world. And so you'll find neural nets all over the place now as a computational tool. It's something that was inspired by biology, but it's got applications in engineering.

STERNBERG: But again, the interface is pretty interesting. Here's a little historical project that led to gadgets: Shuki Bruck [Gordon and Betty Moore Professor of Computation and Neural Systems and Electrical Engineering], some students, and I were trying to model certain aspects of development and function of a worm we were working on. We realized immediately that we were not collecting data fast enough. To get a good model you need a great deal of data. And the biologists, you know, are used to painstakingly doing it by themselves without any gadgets.

So we started to design something that could look at the worm to see how it wiggles, and where it moves in a sine-like wave. We developed a system that's proven to be very useful to quantitatively obtain information about what the worm looks like as a function of time. We could see how it wiggles and you can basically use that information to do the genetics of a sine-like wave, and try to model it.

QUAKE: Science always advances on gadgets. There's a long history of this. You can look in physics how it's happened. Physics in the 20th century has been driven by essentially two big projects from World War II. One is the radar lab at MIT. The development of microwave radar led to the development of the maser, development of the laser, atomic clocks, the precision frequency standards, high precision tests of QED [quantum electrodynamics]. You can trace it all very clearly back to the development of laser technology. And likewise Los Alamos had a huge influence on the development of particle physics.

GHARIB: Every time you have a new device, it leads to new understanding and, boom, new information comes.

STERNBERG: Much of this is on the analytical side and that's very useful. And then as you start to build things, you can say, all right, we have this device which has part of a living organism. Now we can start engineering. We can use things that we know that we've done in the laboratory to make this organism do something to our specifications. It's a very different kind of approach and there are some simple things you may find out that you never even asked about before—low hanging fruit.

ENGENIOUS: For example?

STERNBERG: Well, let's just say a lot of research in biology has been on merely finding the new components. Finding new parts and not saying how they work together: to really think about how it's working as a system, to understand in detail. Okay, you're limited by imagination, but when you start applying it, you immediately say, wait a second. If we want to get more sensitive, what's the tradeoff? And then we go do measurements. We would never have thought about those sorts of engineering issues before.

GHARIB: Let me give you a couple of examples of how we learn from nature. In the macroscopic realm, let's look at the heart. Let's say it, a mature heart, has four valves, a complicated thing. But if you look at the embryonic stages, the heart works without valves. How do you make it pump and pump without rest? For example, in a collaboration with Scott Fraser [Director, Biological Imaging Center Anna L. Rosen and Professor of Biology], we study the embryonic heart of the zebra fish. We've learned how to actually build valveless pumps. Then you try to use that new pumping technology in other applications. We try to put back into nature what we learn from it—to help people who have problems with their hearts.

Another example has to do with photosynthesis. We'd like to see how we can build VLSI circuits on lettuce leaves. Chlorophyll can be used as a capacitor, the power supply, and wire. So if the program is right, you can probably build a real circuit. This sounds like science fiction. But there are people at JPL who have already started to model this.

STERNBERG: Yeah, that's the spirit of the bioengineering field. Open it up. Go back to the science fiction. You know, let's mix up dif-

Medical robot prototype. The goal of this device is to access, in a minimally invasive fashion, the portions of the small intestine that cannot be accessed by conventional endoscopes.

ferent talents, different perspectives, see what happens.

ENGENIOUS: How is all this being communicated to students? What kinds of courses are being taught? They must be radically different from other courses.

QUAKE: It's a big challenge because we're bringing together two communities that historically had very little in common. And so, when we recruit graduate students we try to get them to come here from different backgrounds, from both engineering and the biology communities. So how can you make a curriculum that will address their needs, fill in the gaps, and take them to places we want them to go?

The way we've chosen to address that is to think about tailoring each student's curriculum to his or her background. The engineers take biology courses. The biologists take engineering courses. The centerpiece of the curriculum is our core course, Bioengineering 200, which they take together as a lecture and a lab component, that will help synthesize the two fields for them and lay the foundation for what we think are the important issues to look at in bioengineering.

ENGENIOUS: How long does it take before they get to the core course?

GHARIB: Well, we start them with this one year course in bioengineering—covering the principles of bioengineering. This first year is taught by three different instructors and each one brings a different aspect into the picture. [For a list of course descriptions visit the BE website at *http://www.be.caltech.edu.*] In the meantime they also take a vigorous program in mathematics, mechanics, chemistry, and biochemistry. It's a real challenge.

STERNBERG: But they're going to have to take risks to get the rewards.

QUAKE: This term [in BE 200] they're doing an extended experiment where we teach them how to program computers, if they haven't done that already. We're also going to have them do a very simple bioinfomatic analysis of a bacterium. This bacterium has the smallest known genome, 500 base pairs. So it's something that they can manage to analyze on a small PC. We're going to have them write, what I call, a toy version of algorithms that will find genes and find relationships between genes. We want them to kind of have the thrill of playing with the entire genome of an organism and try to do some computations on them.

The second month we're going to have them play with a real genetic circuit. We're going to take one of the existing genetic circuits that a group, just a couple of years ago, had managed to engineer a toggle switch in *E. coli* by using principles of visual design. We're going to have them make measurements on this bacterium and characterize this toggle switch, explore the boundaries of its performance, and do some basic molecular biology on it. We'll use it as a vehicle to teach elementary microbiology skill to the group. I think the biologists will have no problem with it but the engineers may have to explore new territory.

ENGENIOUS: Do we have any joint programs with any medical school?

GHARIB: Yes. UCLA and USC. So Bioengineering is part of the consortium of the MD/PhD programs that Caltech has with UCLA and USC.

STERNBERG: There are approximately two students a year from the UCLA and USC programs.

GHARIB: Students who were accepted this year into our program all had admission to at least one of the top five bioengineering departments in the country. They chose to come here because of the quality of the faculty.

ENGENIOUS: What really distinguishes the Caltech program from all the other distinct programs? How is Caltech unique?

GHARIB: I think it's the philosophy that's different. We try to teach them to learn about life's devices. There are other programs that study tissues left and right, top and bottom. But we're trying to understand how the tissues are being made.

STERNBERG: We have no boundaries. We're going to take a very broad look at things. We have three divisions coming together out of necessity, and we're going to get access to every possible great idea, and many great minds.

GHARIB: Each faculty member here acts like a biological system. If you look at a biosystem like a muscle, it doesn't do just one thing. It's capable of performing different functions. Caltech faculty immerse themselves in different fields. You may think I work on heart valves, but the next day you'll see me working on laser devices. It's very

important that each one of us has interests, professional interests, in different fields of science and engineering. That's why I think we're different. Each student receives lots of exposure from our experience.

STERNBERG: That's what makes it different. Of course it's just starting. We'll see. But we're excited about the timing.

ENGENIOUS: How did you become involved in this and become an active participant, get the Option going?

QUAKE: Well, you know, my own career has been sort of on the boundary of physics and biology. As a one-person show, you can only go so far. To have a whole option set up where everyone is trying to do the same thing, incorporate different areas and philosophies, is tremendously attractive to me. Paul had also spontaneously started trying to incorporate ideas from engineering into his research. Mory was the one who got us all organized.

GHARIB: I think the idea of having bioengineering here at Caltech is not new. If you look at the top programs in this country, three of them were started by Caltech graduates: Georgia Tech, UC San Diego, and UC Berkeley. I think what's new here is that a new generation came in at about the time of the new revolution in biology. Suddenly we realized that it's more exciting than ever. We looked at the levels the students were looking at, cell sequences and cell sorters. Those are things that, ten years ago, it was hard to even imagine. Now we can tackle the problem, learn about it, and work with people like Paul and come up with better ideas.

QUAKE: Yeah, it's sort of a grass roots effort. Mory just pointed out, hey, everyone's doing all this great stuff. Let's build a real quality program around it and create an infrastructure that educates students in an organized way, rather than piecemeal.

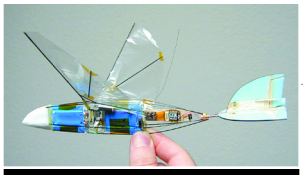
STERNBERG: I think part of it is giving support to students. I have several areas of research: bioinfomatics, databases, generating devices in modeling, and computational biology that I can offer support in. You know, it's always a struggle when students are torn because they don't have the peer support when it comes to what to do, how to go about things. So this program is a potential source for that support network. The other thing is it's just so exciting.

ENGENIOUS: What kinds of devices or what kinds of fundamental results might we expect in the next 5 to 10 years?

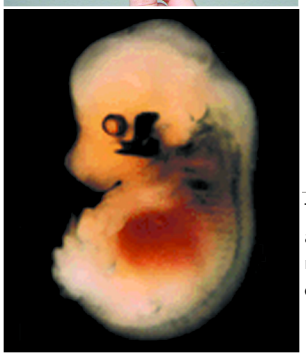
QUAKE: We're pursuing a program to attempt to make very highly integrated chip-based devices to do biology, lab on a chip as it were. There's a huge number of very basic scientific problems that one can address with new gadgets. We have already made the world's smallest valves and pumps and we recently figured out ways to integrate them so you can have thousands of these valves on a chip and do very complex plumbing. A fundamental problem we're particularly interested in is microbial diversity. Look around the world, pick any environmental sample, whether it's sea water, soil, something from your gut, or a termite gut. You'll find that there is an incredibly diverse ecosystem of bacteria living in there. And in large measure, these ecosystems are completely uncharacterized. How do you characterize bacteria? Well, you've got to grow them in a culture. And when you start growing…

STERNBERG: And many of these things can't be cultured because they need 15 different friends.

QUAKE: That's right. Many of these things can't be cultured



The Microbat—a flapping wing microelectromechanical (MEMS) device may one day go where man would rather not.



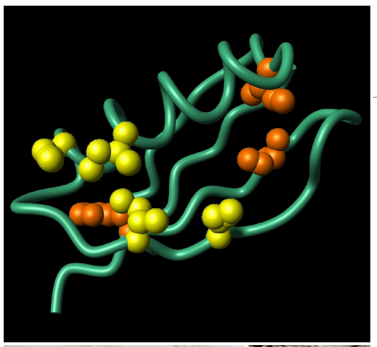
The mouse embryo is studied to understand the regulation and execution of developmental decisions that lead from multipotential,undifferentiated precursor cells to their specialized differential products.

because they need friends. Or what happens is that when you try to culture, the fastest growing ones completely overwhelm the population. So instead of having this incredibly diverse population, you have a fairly simple one. The conventional tools in biology left that aside. We think our microfluidic chips are going to allow us to take a peek at this microbial diversity because we developed the tools to manipulate and analyze single cells. What we'd like to do is take a population, divide it up, and then analyze each cell independently. This is something that has more value than basic science. There's a large number of diseases that are associated with bacterial populations, either from getting a bacteria or getting an imbalance in the community. And actually it's suspected that many current diseases that aren't associated with bacteria just might be of bacterial origin. So there's a whole field of emerging infectious diseases and the next easiest tool is to try to track them down and nail the associations.

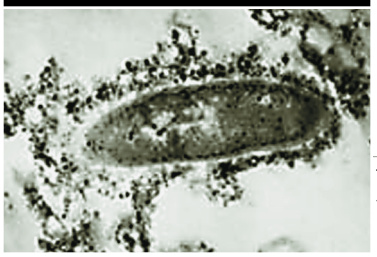
GHARIB: There are many new fields like nanotechnology that we'll be using. JPL has many programs in this area and gives another flavor to our program. That's the space side of bioengineering. For example, we get many good students here because they associate Caltech with JPL and GALCIT. And they'll grab benefits from having access to all. Maybe one day we can come up with a true implantable heart system, a cardiovascular system that can be implanted that's self-sufficient, takes energy from the body, and is efficient enough that it works like a real heart. But it will take five, ten or more years. And many technological revolutions have to occur before we can offer such things.

ENGENIOUS: And Paul, what kinds of things, in the next five to ten years, are you looking forward to?

STERNBERG: I think building circuits within cells and building gadgets within cells that communicate with each other and do other things. That's where we come to the self-assembled device, one of the mysteries of life.



In the ever expanding knowledge of the chemistry of life, Caltech researchers are exploring the intimate details of protein structure and stability and using this knowledge to design, build, and test proteins with novel biochemical properties.



The continued study of bacteria may reveal how they transfer electrons to insoluble minerals via organic compounds.

ENGENIOUS: How are you recruiting the best students?

QUAKE: By doing the best science.

GHARIB: Steve is right, indirectly. The faculty is the best asset of the program. And the reputation of our program is helping with recruitment.

This year, we started registering the program with different organizations, to try to bring our strengths to the attention of the best students in different departments, and encourage them to apply. We write and ask them to come here for an interview. We are very selective. Last year out of the 45 who applied, we picked six.

STERNBERG: Generally we just talk. Once you're in the program, you're excited about it and you talk it up. I was on jury duty and I was sitting there waiting to get called, and the guy sitting next to me was excited about applying to the program. He was a former Caltech student, out for ten years. But that's where he got the idea.

ENGENIOUS: Any wrap-up thoughts that you want to communicate particularly to an alum audience?

GHARIB: The message is that this is a new, exciting option with lots of promise. It's got some of the best faculty that we can put together here at Caltech. They're all eager and energetic to bring their talents and energies here. So as a result it's very fun to work with this group. Lots of good ideas, lots of challenging ideas. It makes it more challenging for us to accommodate other faculty because the expectations are very high for the Option. ENG

Caltech's Bioengineering webpage is at
http://www.be.caltech.edu