WOLD: There is a computing revolution going on across the board in many areas of biology—from molecular, to cellular, to developmental and neurobiology. At an obvious level, the revolution is driven by rapid changes in the kind and amount of data we work with, beginning with entire genome DNA sequences and everything that now flows from them. The basic challenge is to turn data into real information, then turn that information into real understanding. At another level, biologists have long been interested in information in living systems—how it is encoded, stored, recalled, and transmitted from one site to another. These are themes that the faculty in this Center will be addressing in a very particular way.

After talking to many of our faculty and colleagues, in and out of the Biology Division, we hit upon the idea of focusing on biological circuit design. In some sense, you don’t really understand the properties of something until you can sit down and—from scratch—design it, test it, and see if it behaves as you predicted: have you got it right? We break things and see what happens. That’s the heart of classical genetics. Or, we take things out of the cell and make them work in a test tube—that’s biochemistry’s challenge. So at this point, from all of our tweaking, the biologists have learned a lot about the molecular components of gene circuits. Similarly, neurobiologists know a lot about the cellular components of neural circuits that ultimately lead to brain function and behavior. In the middle are the people studying signal transduction—that is, how signals travel from the outside of the cell to the inside of the cell, or from one cell to another.

The state of the art is this: we know an enormous amount about what the circuit components are, and something about how they’re hooked together. We know a good deal about how the inputs work, and, globally, what the outputs are. But what gives a biological system its real properties—for instance, its robustness in the face of various kinds of insults? What are the dynamical properties of important circuits? How is information really encoded or stored by a given molecular or cellular circuit? Getting at these questions using a design focus is the core mission I see for the CBCD: it will take the fruits of all the research of past decades, combine it with the current revolution in biological information processing, and focus on circuit design. This is tremendously exciting, and central to deep understanding of biological systems.

STERNBERG: Another way to describe what we want to do is the “reverse engineering” of biological systems and circuits. But it’s going to be much easier to learn how to do it with, for instance, a Model T rather than a Boeing 777. Organisms have been around for a billion years, making nature’s designs incredibly complex and sophisticated. Even the simplest organisms are intricate integrated machines. They have embedded controls that are really hard to tease out. It’s a lot easier to build something from scratch and then learn how to model it.

In my lab, we’ve looked at signal transduction and we’ve come up
with very nice models that are powerful. But when we go into the real cell, they fall apart, because every little detail has been tuned by processes of evolutionary selection to make it work. That means you really want to start very simple. That’s where the synthetic approach comes in. To build biological circuits, we need to define components and interactions. We have to determine which components are really going to be robust. You can liken this to creating a system using Lego bricks. You want to have the equivalent of those bricks, and that takes a lot of thought. Right now, Niles Pierce, Steve Mayo, Frances Arnold, and their colleagues are thinking about how to make those components.

PIERCE: We have three different types of people at Caltech who are all working in areas that contribute directly to progress on this very challenging topic. First, as Paul said, we have the tool builders who have been working on components. Steve Mayo’s lab uses computational methods to design proteins with enhanced stability or novel functions. Frances Arnold’s lab, by contrast, uses directed evolution to obtain molecules with new or enhanced functions. Richard Roberts’ lab has developed a novel approach for in-vitro selection to screen for molecules with particular functions. My lab works on computational algorithms for designing molecular machines out of DNA and RNA. Erik Winfree’s group is interested in biological computation and issues of how biological systems can be designed to process information. Steve Quake, Jared Leadbetter, and Frances Arnold are collaborating on the design of cellular signal-processing circuits in bacteria. Finally, we have a number of biologists [here and elsewhere] who study the structure and function of naturally occurring circuits, including Mel Simon, Elliot Meyerowitz, Stan Leibler, Paul Sternberg, Eric Davidson, Mary Kennedy, Thanos Siapas, Jim Collins, John McCaskill, Ron Weiss, Tom Knight, and Barbara Wold, among others. So there is a diverse set of people working on component-level issues for circuit design, creating synthetic circuits, or studying naturally occurring circuits. The latter have a deep understanding of how those circuits function and how they’re structured. All three communities are well positioned, right now, to try to approach biological circuits from a synthetic point of view.

STERNBERG: There’s a critical mass of talent, including researchers in the neural biology community—the Computation and Neural Systems program—who are thinking about how naturally occurring circuits work, and how one might like to design new ones. Because of the properties of the systems they study, they have a different view of how to analyze a complex circuit. Thanos Siapas and Gilles Laurent record information from multiple places in one structure simultaneously. They are good at articulating this approach and figuring out how to apply it to other complex systems—for instance, in a cell. Bringing in their expertise and interests allows us to make bridges all the way from chemical engineering to brain neuroscience in this quest to design and understand biological circuits.
Caltech is more than ready to make this very interdisciplinary, very ambitious goal happen. And again, it can only happen here, because in all the divisions you have people who are really good at what they are doing, of course, but also imaginative enough and interested enough to be able to learn other approaches. I think what will happen in the Center is that at the start, everybody will come in with his or her own ideas, leading to an incredible effervescence. Then we’ll condense our focus on a couple of projects that seem tractable and seem to be the right way to learn to prove principles that will lead to new technology. The new technologies will then be applied in many directions and spawn new industries.

**WOLD:** One of the other things the CBCD will spawn will be an entirely new generation of students and post-docs with a worldview that is some interesting combination of all these inputs. Without the Center, a few students might make the interesting connections that biological circuit design requires. With the Center, and the concomitant “lowering of the energy barrier,” so to speak, the path toward this kind of research training will be much more easily and frequently traversed. So the impact—through these people—ultimately goes far beyond Caltech.

**WINFREE:** One of the problems engineers face is understanding which aspects of a given component are important and which are just implementation details, not really relevant to the function. This leads to new levels of abstraction. For instance, we ask: “Is this atom over here the critical atom, so I need to focus my attention down here at the molecular level? Is it critical to the function or not?” Researchers try to understand that by making mutations, changing a moiety here or there, and so on. This is another approach for determining which parts of a system are important, and which are merely accidental. I hope that going through the design process will help elucidate this completely.

Many advances in biology have been driven by instrumentation. Programming with biochemical reactions rather than with logical “and gates” and “or gates” is a whole different beast.

**ENGENIOUS:** What are the practical goals of the CBCD?

**PIERCE:** One way to encapsulate a long-range objective for the CBCD is to say that we’re going to try to recreate the remarkable technology of the compiler. A compiler takes an algorithm written in a programming language and turns it into instructions that a computer can understand. Given a conceptual design for a circuit, we’d like to be able to “compile” a set of molecules that can be introduced into a test tube and be observed to function according to the principles for which that circuit was designed. This outcome would be tremen-
dously exciting not only for its biotechnological and medical applications, but also for the sheer challenge of working with a complex array of components to develop a design framework robust enough to produce working molecules and circuits. This goal sets a high standard, but I think we have a real shot at meeting it.

ENGENIOUS: Will principles of evolutionary biology be useful in this work?

WINFREE: Exploiting evolutionary principles in the design process is already being done at Caltech. For instance, Richard Roberts does in–vitro selection to design protein sequences with functional properties. Frances Arnold applies directed evolution to both circuits and proteins. These are important tools. It will be interesting to integrate this “irrational” approach, where you try a bunch of things and select one that works, with rational, systematic design, where you put together a system based on your ability to predict how it will function.

WOLD: A hybrid approach is to design first, then subject the system to very rapid evolution for optimization. This allows you to see how close you were to optimal in the first place.

WINFREE: Absolutely. I think that’s an important approach, and the way you might design components—a particular protein, for example—by some kind of directed evolution, then characterize it, put it in your toolbox, and fit it into a circuit in a rational way. Then, perhaps, do another level of evolution to optimize that circuit.

STERNBERG: Then you can look at evolution to see what’s worked—which components have been used in many circumstances, but have maintained their central character. Neurons, for instance, are very successful. Our neurons are the same as many other creatures’ neurons, but they’re wired together in different ways. It’s the circuit design that makes us different. That’s something that was discovered at Caltech, by John Allman and his colleagues, and elsewhere. Neurons are one type of component. At the molecular level, we have the G protein, a molecule that Mel Simon has been obsessed with for years. It acts as a little molecular switch or timing device. We could start with these known robust components and learn how to build things with them. But given the collaborations that will take place, each person’s research approach might be wonderfully and radically changed.

WOLD: That may be the most important bit of “evolution” from our immediate point of view. We exert intellectual pressure on each other to look at a problem in a different way and to use somebody else’s point of view—intellectual evolution in action.

STERNBERG: And that’s why articulating and committing to a focus on designing circuits is going to change the direction of many people. There are a lot of our colleagues we think will be involved, but they don’t even know it yet…

WOLD: But we have faith that they will be attracted by the theme and know exactly what to do.

One last thing concerning potential practical outputs. Our greatest passion is for the deep underlying principles. At the end of the day, to us, a practical result would be having the compiler. But as viewed by many other people, that’s not a practical output. Certainly the implications of this work will have a significant biotechnological spillover. What Caltech does best is getting fundamental ideas and technologies to a level where they can radiate out to the tech sector.

WINFREE: And the possible technological implications here are not restricted to the medical or biological realm. The ability to program things and to automate tasks has profoundly affected science, engineering, and technology in the last 50 years, a very short time historically. Most programs exist in microprocessors, which are quickly becoming ubiquitous in our lives. They are in your microwave oven, in your car, in your digital camera. We know how to program and...
exert embedded control over macroscopic electromechanical systems, and this has revolutionized technology.

Nature, through biological processes, has transformed the earth by exploiting algorithms and embedded control at the chemical level to fabricate cells, bodies, and ecosystems; to build forests from light and chemical nutrients, for example. Intellectually, we don’t really understand how these things exert an influence over chemistry and organize it into meaningful constructs. Biochemistry is where we see most clearly that information and algorithms are fundamental elements of the chemical process. Nature has polymers, like DNA, which contain information. The cell interprets that information as a program for directing its behavior. Evolution changes the program to carry out an incredibly wide range of functions. This is a technology that isn’t just biological: biology is only one possible result of programming biochemistry. Working with atoms and molecules in systems will turn out to encompass a wide world, and is going to be very fun.

**WOLD:** Actually, at the end of the day, that’s the point. We don’t usually start with that. What’s the goal of your Center? To have fun. But we know it will be...

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**Center for the Physics of Information:** The Impending Overthrow of the Silicon Monopoly: Revolutionary Substrates Unite!
A Conversation with André DeHon, John Preskill, and David Rutledge

Silicon is a superb computational substrate...but sooner or later it will run out of room. The CPI is devoted to inventing the new computational substrates, architectures, and algorithms for the computing devices of the future.

**PRESKILL:** We’re kind of an odd mix of people, you know. I’m a theoretical physicist, Dave’s an electrical engineer, André is a computer scientist. But I think we have some things in common. In those areas of overlap there’s a potential for some really exciting scientific and technological developments. We know that the advance of our information technology, which has been dazzling for so long, is confronting limitations that come from physics and, in particular, from the size of atoms. And we don’t know beyond say, a decade, what we are going to...