engineering frontiers

Cells *into* Systems

A new research center will work with the basics of life to build complex biological machines.

By Roger D. Kamm, Robert M. Nerem, and K. Jimmy Hsia

One of the cutting-edge frontiers of engineering research sounds almost like familiar territory. The confluence of the mechanical and the biological—Terminator or Robocop, for instance—has been explored in science fiction for generations. But ever since Jules Verne invented the *Nautilus*, science fiction has from time to time proved to be uncannily prescient.

Imagine if….

Plants had a collection of neurons that could process information and generate a signal when they need water;

"Noses" could be grown with the sensitivity comparable to that of dogs and be used to identify explosives or toxic substances during airport screenings;

Drugs could be screened using microfluidic systems that mimic the behavior of a human heart, liver, or lung, minimizing the need for expensive and time-consuming animal studies, and thereby speeding drug development;

Biological robots in an assembly line could repair themselves and adapt to optimize their performance;

New "organs" could be developed and implanted, capable of sensing the level of a particular drug in the bloodstream, processing that information, and instructing a collection of secretory cells to turn on or off drug synthesis;

Organisms could be grown that swim toward an oil spill, enzymatically degrade it into harmless byproducts, replicate as needed to finish the job, then return to a host ship for processing.

As far-fetched as some of these ideas may sound, many scientists and engineers believe that in the near future some or all of them may become reality. The National Science Foundation agrees, and has just awarded a Science and Technology Center grant to a group of researchers to explore ways in which these biological machines can be created.

The new center is named Emergent Behaviors of Integrated Cellular Systems, or EBICS (www.ebics.net). It consists of scientists and engineers from the Massachusetts Institute of Technology, the Georgia Institute of Technology, the University of Illinois at Urbana-Champaign, and three minority-serving institutions, the City College of New York, Morehouse College in Atlanta, and the University of California at Merced. EBICS's mission is to create a new scientific discipline for building living, multicellular machines that solve real-world problems in health, security, and the environment.

The goal of building biological machines may be achieved through either of two distinct pathways—engineered systems and emergent systems—and the distinctions between them are important and fundamental. Both approaches start by creating the building blocks—component cell types of biological machines such as neurons, muscle cells, and endothelial cells through stem cell differentiation—but the process used in each case is different.

Engineered systems are produced by first inducing a group of stem cells to differentiate into one of several distinct cell types: e.g., neurons, muscle cells, vascular cells. These separately differentiated cells are the components that are ultimately assembled to produce machines with desired functionalities. This parallels the process used to produce nearly every non-biological machine. It, there-

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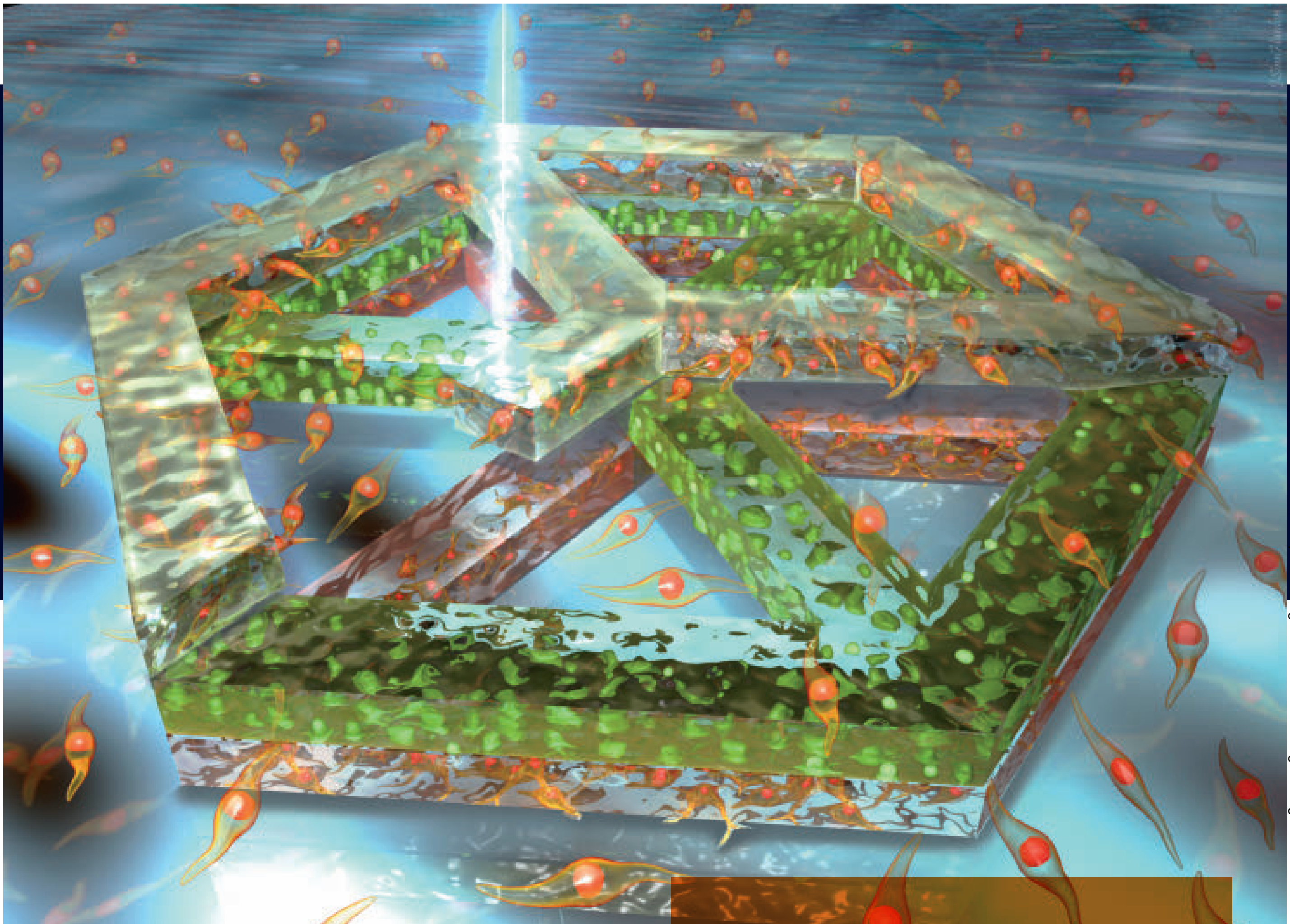

▲ A depiction of how biological machines might be made, using a photopolymerizable gel containing cells of various types arranged in different regions or layers. This method was developed by Rashid Bashir, one of EBICS's lead researchers, and published recently in *Lab on a Chip*.

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fore, has the advantage of drawing upon an enormous body of research and practical engineering experience.

Emergent systems, on the other hand, rely on the methods used by nature, as in the case of biological development of an organism from embryo to adult. In this case, a small number of undifferentiated cells differentiate into different cell types as a consequence of their own interactions and communication, using either chemical or physical (mechanical, electrical, thermal, etc.) cues or signals. These differentiated cells self-segregate into different components that interact naturally, with little or no external intervention.

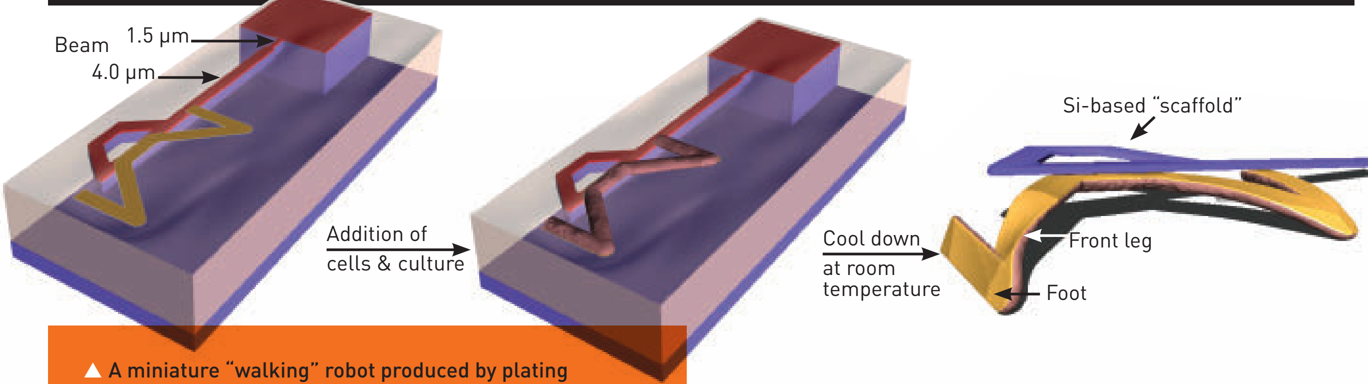
Using this approach for biological machines, we hope to steer the differentiation process by manipulating the interactions among the stem cells. This is a more natural way to evolve a single cluster of interacting cells (e.g., heart tissue with myocytes perfused by an integral vascular network that might be used either to repair a damaged, non-functional region of the heart or to propel a bio-bot). In this case, we say that the functional behavior "emerges" rather than being "engineered."

While nature has refined this process, we are just beginning to understand it. Such understanding enables us to generate replacement tissues from an individual's own stem cells, to produce tissues for individualized drug screening, or to create complex biological machines such as bio-robots with defined functionalities, such as autonomous sensing and subsequent annihilation of toxins in water.

To effectively carry out EBICS-STC's mission, we need not only to produce innovative research results and develop new technologies, but also to train the next generation of research and education leaders. The leaders of this new field should be knowledgeable in engineering and physical sciences, and in biology. They should be not only competent in these scientific disciplines, but also familiar with other big-picture issues such as public policies, intellectual property and patent law, entrepreneurships, and ethics. They should possess strong communication skills and leadership qualities. Furthermore, the new generation of research and education leaders should be a diverse group including women and underrepresented minorities.

As one can imagine, whenever the issue of creating living systems with new functionalities is raised, caution must be exercised. Indeed, a number of ethical issues will need to be addressed. Will these machines

A WALKING BIOMACHINE



▲ A miniature "walking" robot produced by plating rat neonatal cardiomyocytes onto a flexible substrate, designed so that it crawls along a surface when the muscle periodically contracts and relaxes.

REPRODUCED WITH PERMISSION FROM XI, SCHMIDT, AND MONTEMAGNO, NAT MAT, 2005.

be endowed with the capability to self-repair, adapt, and self-replicate? If so, they become indistinguishable from natural organisms and need to be considered in a similar light. If stem cells are used, from what source may they be taken? What protections and regulations need to be in place? These and many other questions will be openly debated within EBICS and with the larger community in parallel with the development of advancing technologies.

How close are we to realizing such engineered biological machines? Perhaps closer than you might think. Synthetic biology, the design of new forms of life using a combination of engineering and biological approaches, has made tremendous gains. It is now possible to reprogram the genetic machinery of single cells so that they can perform functions not possible in any naturally occurring biological system. For example, recent work by Ron Weiss, one of EBICS's lead researchers, and his colleagues has demonstrated creation of neuronal circuits capable of performing simple functions of switching on and off chemical secretion. Others have produced micro-scale systems that walk along a surface due to the reflexive contractions of engineered muscle.

But the engineering of multicellular biological machines represents a major step beyond what is currently being done. Most of the advances in synthetic biology have occurred in bacteria, not mammalian cells. And the muscle-driven robots developed in mammalian systems simply move in a reflexive manner, with no sense of where they are going or what they would do when they get there. These robots lack the sensing and information-processing capabilities, which are needed to move them in a desired direction.

Thus, the challenge for EBICS, with a program that has the potential to be truly transformative, is immense. It starts, however, with developing the necessary components for building biological machines, and achieving a better understanding of integrated cellular systems and their emergent behaviors.

Engineers have been instrumental in the development of biological "parts" that might eventually be used to construct a machine. From various cell sources, such as stem cells, multipotent cells extracted from bone marrow, or even fat, a variety of mature cell types, needed for higher-level functions, can be derived. Stem cell differentiation controlled by the local extra-cellular environment, such as stiffness of the matrix or certain biochemical factors, can lead to creation of machine components such as sensors (neurons), actuators (muscle cells), and processors (neuronal networks). Indeed, methods to induce these uncommitted cells to differentiate into beating heart cells, neurons capable of processing and transmitting information, or endothelial cells to generate a vascular network have already been demonstrated. There are also numerous examples of achievements in the field of tissue engineering, as reported in a paper by Stephen F. Badylak and Robert M. Nerem earlier this year in the *Proceedings of the National Academy of Sciences*.

While a great deal of progress has been made developing the components for biological machines, where we are most deficient is in our ability to combine the parts into a functional whole. One key challenge is our limited understanding of how cells interact with each other and with their environment. According to Nerem, cells clearly respond to a "symphony of signals" provided by their local microenvironment, sensing signals or cues from neighboring cells and tissues, from the local soluble molecules, and from the mechanical environment in which the cells reside.

To create a biological machine, we will need to understand the language that cells of different types use to communicate with each other. In the case of neurons controlling muscle, this communication takes place in a neuro-muscular junction consisting of an exchange of neurotransmitters across a synapse between the two cells. In other cases, communication can occur over larger distances with the signaling molecules secreted by one cell type diffusing through a matrix and ultimately activating a receptor to direct activity in a second cell of a different type.

Understanding the nature of these cues and the responses to them will be essential if we hope to take advantage of the emergent behaviors to develop biological machines.

We also have rather limited knowledge of the complex, emergent behaviors of cell clusters. For example, under what conditions does complex, cooperative behavior emerge in a cluster of cells? Is it the size of a cluster, the number of cells in a cluster, or the environment, or are all of these critical to the emergent behavior? What instructions are needed for different types of cells to assemble into functional organs? Answers to many such questions are again essential to building biological machines.

Some things we know. Forces or mechanical factors have been shown to be critical in the process of biological development. Dennis E. Discher, Paul Janmey, and Yu-li Wang reported in a 2005 paper published in *Science* that stem cells grown on gels of different stiffness differentiate into different cell types. Hydrodynamic forces have been shown to guide the process of development. Fundamental understanding of such emergent behaviors will guide us in making integrated biological machines directly from basic processes such as stem cell differentiation.

Along with cell and molecular biologists, mechanical engineers will be essential players in advancing this new field. Biological machines of the future will encompass the complexities of nature, the intricacies of which we are just beginning to comprehend. Engineers have developed effective methods to deal with large, complex manufactured systems (e.g. the modern automobile), and similar approaches will be needed for building the biological machines of the future. The resulting complexities, especially extending down to the genetic level, will no doubt require computational models that embody our growing understanding of these critical processes. Engineers in general and mechanical engineers in particular, among all scientific and engineering professions, are trained to build machines, and this expertise will be indispensible.

Bio-design will need to encompass all of our current design practices, but with additional critical elements from biology. There is much that we can learn from nature (think of the entire field of biomimetics), and this newly gained knowledge has to be incorporated into the process of designing biological machines.

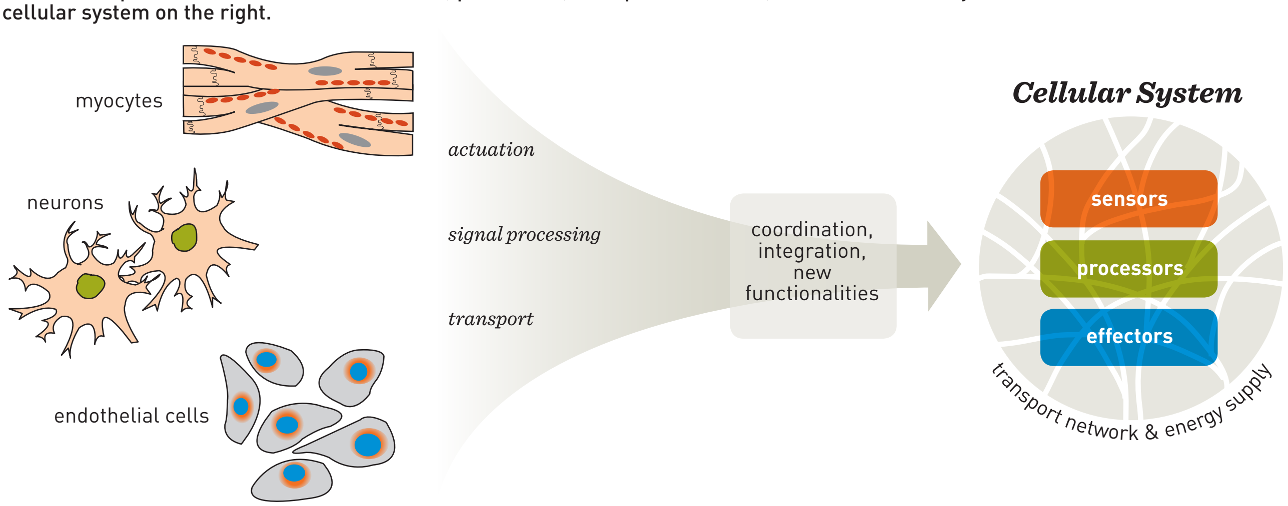
Many of the needs for biological machines will naturally emerge from our existing, mechanical technologies. Consider the parallels between biological and mechanical robots. Sensing currently performed by mechanical means will be accomplished by cell clusters that can see, feel, hear, and smell, rather than by the now familiar mechanical transducers. Signals from sensing cell clusters will be transmitted to collections of neurons through neurites and synaptic junctions (the wires and connectors), and will be processed through biological computers.

Just as the first robots bear little resemblance to the robotic systems in a modern manufacturing plant, biological machines, too, will go through a period of refinement and optimization. Performance will need to be quantified, and the processes of both manufacture and design will need to be gradually improved over time.

How can we, as mechanical engineers, prepare as a profession? First and foremost, engineers in this emerging field will need to have a working knowledge of molecular and cell biology. Several universities already require all engineering students to take a biology course, and many engineering students elect to take biology, recognizing it as part of an essential scientific knowledge base. Beyond that, new graduate programs need to be developed that bring engineers and biologists together so they come to speak a common language. Some programs of this type already exist, at

NEW IDEAS IN ASSEMBLY

Schematic of the process of engineering biological machines. Various cell types on the left (derived, e.g., from stem cells) are combined into the components of the machine (actuators, processors, transport networks), which are ultimately assembled into the functional cellular system on the right.



Georgia Tech, MIT, and UIUC, for example, but more are needed.

We envision that, through the efforts of building biological machines, mechanical engineers will play an instrumental role in creating this new field. Mechanical engineering, defined in much broader terms, will then become an integral part of a truly multidisciplinary field.

When we can expect to see biological machines and what impact they will have on society are open questions.

We have learned from history, that for new, transformative technologies, the hype often precedes the reality. Take, for example, the cover article in *Time* magazine in 2000, proclaiming tissue engineering as one of the top ten professions of the decade that just ended. While excellent progress is being made on a number of fronts, the commercial success suggested by this article is still some years off.

On the other extreme, even some of the pioneers of the computer industry failed to foresee the impact that computers would have on our lives.

"There is no reason anyone would want a computer in their home," Ken Olsen, the founder of DEC, said in 1977. Thomas Watson, chairman of IBM, said in 1943, "I think there is a world market for maybe five computers."

The bottom line is that it is impossible to predict either the time-line for the development of biological machines or their ultimate impact on health, security, and the environment. We do, however, fully expect to have created several simple machines within the next five years. During that same period, we expect that industry will begin to recognize the potential of biological machines and will initiate research and development programs. Initial interest will likely come from the pharmaceutical and medical products industries, but others, as well, should begin to show interest.

But the barriers to success are considerable and much basic research is still needed to lay the foundation for engineering successes in the future. A current program, the National Academies Keck Futures Initiative, has focused on a number of the key issues. Some of the questions they raise have direct bearing on the future of biological machines:

How can self-synchronizing cell populations that behave coherently be engineered despite cell-to-cell variability?

How do we achieve effective cell communication over distance and time?

How do we design cells to organize themselves into defined three-dimensional structures?

Similar issues have been raised in a recent report from the National Academies, *A New Biology for the 21st Century*. The authors write that, despite recent advances, there is still much to be done "to move from identifying parts to defining complex biological systems, to systems design, manipulation, and prediction."

These and many other fundamental issues will need to be resolved before we can realize the full potential of this new technology. But the foundation is laid and it is only a matter of time before biological machines come to the mainstream.

It is thus the goal of this new NSF-funded Science and Technology Center not only to imagine what many may think is unimaginable, but also to make possible through engineering what many say is impossible. In doing so we hope to address many of the problems facing society so as to make the world tomorrow a better place for future generations. ■

To Follow Up

Readers interested in learning more about some of the subjects discussed in this article can find a digital version of *A New Biology for the 21st Century* available free at the National Academies Press Web site, www.nap.edu/catalog.php?record_id=12764. A paperback edition can be purchased at the site.

The following are representative papers exploring the connection of the biological and mechanical.

›› Dennis E. Discher, Paul Janmey, and Yu-li Wang, "Tissue cells feel and respond to the stiffness of their substrate," *Science*, Nov. 18, 2005; Vol. 310 No. 5751, pages 1139-43.

›› Boris Guirao, Alice Meunier, Stéphane Mortaud, Andrea Aguilar, Jean-Marc Corsi, Laetitia Strehl, Yuki Hirota, Angélique Desoeuvre, Camille Boutin, Young-Goo Han, Zaman Mirzadeh, Harold Cremer, Mireille Montcouquiol, Kazunobu Sawamoto, and Nathalie Spassky, "Coupling between hydrodynamic forces and planar cell polarity orients mammalian motile cilia," *Nature Cell Biology*, April 2010, Vol. 12 No. 4, pages 341-50.

›› Parth Patwari and Richard T. Lee, "Mechanical control of tissue morphogenesis," *Circulation Research*, 2008, Vol. 103 No. 3, pages 234–43.

›› Jay R. Hove, Reinhard W. Köster, Arian S. Forouhar, Gabriel Acevedo-Bolton, Scott E. Fraser, and Morteza Gharib, "Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis," *Nature*, Jan. 9, 2003, No. 421, pages 172–77.

›› Stephen F. Badylak and Robert M. Nerem, "Progress in tissue engineering and regenerative medicine," *Proceedings of the National Academy of Sciences*, Feb. 23 2010, Vol. 107 No. 8, pages 3285-86.

›› Vincent Chan, Pinar Zorlutuna, Jae Hyun Jeong, Hyunjoon Kong, and Rashid Bashir, "Three-dimensional photopatterning of hydrogels using stereolithography for long-term cell encapsulation," *Lab on a Chip*, published by the Royal Society of Chemistry, 2010, Vol. 10 Issue 16, pages 2062-70.