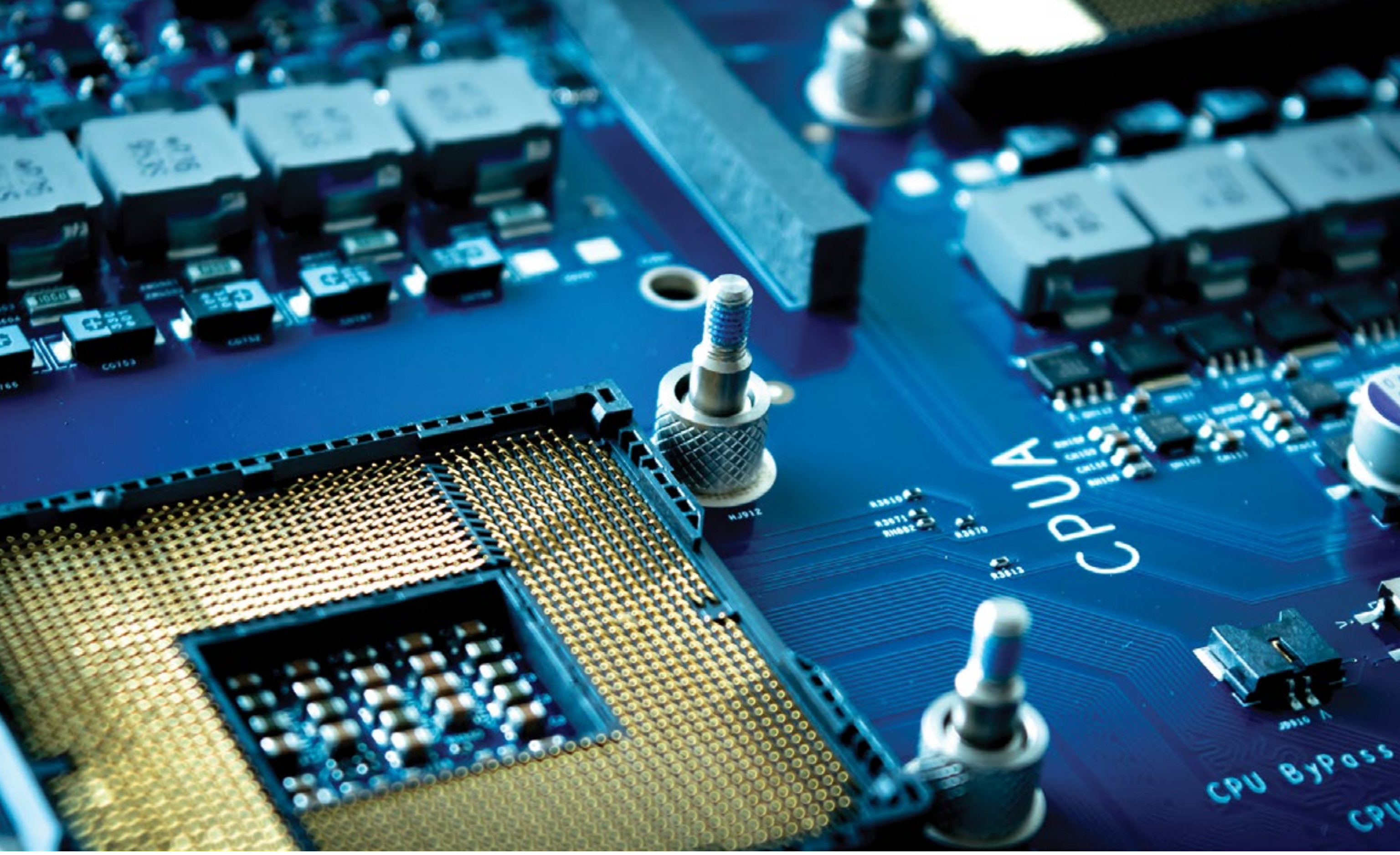


Close up of a computer motherboard. (Image from Adobe Stock)

Biological Electronics

A Transformational Technology for National Security

James J. Valdes, PhD
James P. Chambers, PhD
Diane M. Kotras

Military systems rely on microelectronic components, and the potential for increased efficiency and speed of computing processing made possible by biological components convey potential advantages to mission capabilities. These include, but are not limited to, lower energy requirements, hence reduced battery loads; signature reduction due to reduced heat production; more flexible responses by autonomous systems; and more efficient data manipulation and storage. Next-generation weapons systems are increasingly data-driven and will require computing power beyond the capability of current electronics. The ability to pack more transistors into semiconductor chips is reaching its physical limit, ending the well-known Moore's law, the observation that the number of transistors that could be put on a silicon chip doubles every year. It is simply a matter of limited space, and massive parallel processing or three-dimensional chip architectures are partial but not comprehensive answers. Radical new approaches to next-generation microelectronics are needed.

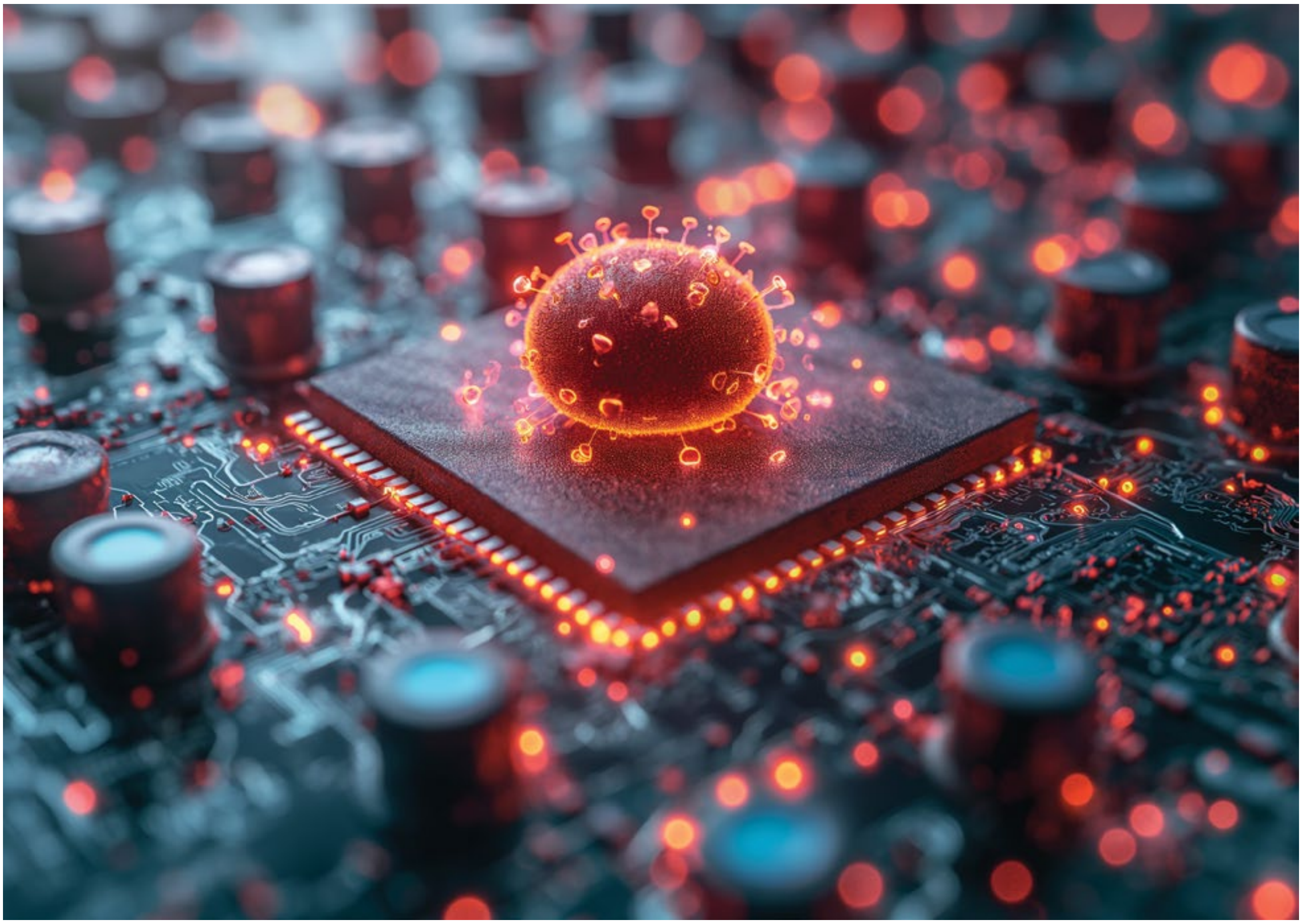
Biological structures and organisms perform many of the same functions as electronic and optical devices, including electron transfer; signal generation, transduction, and amplification; data analysis, reduction, and storage; and energy harvesting. The languages of biology and electronics are quite different. The former is primarily represented by small molecules and ions and the latter by electrons and photons, which operate at different space and time scales.

Semiconductors are the building blocks of electronic brains in military systems. They conduct electrons over relatively long distances, such as between transistors, whereas cells transfer electrons over very short ranges between molecules. Early work on biosensors focused on immobilizing cells or cellular components onto the surface of optical fibers similar to those used for telecommunications or on the surface of semiconductors to exploit the ability of cells to recognize and respond to many thousands of environmental stimuli (see figure 1).[1] These stimuli include, for example, chemicals, toxins, biological molecules, radiation, heat, and magnetic fields. More recent observations suggest that cells may be incorporated into electronic devices, conveying information processing capabilities many orders of magnitude beyond that of current *in silico* (silicon-based) systems alone while using far less energy per task.[2] The combination of *in carbo* (carbon-based) and *in silico* components has the potential to significantly disrupt the semiconductor industry, which the Semiconductor

James J. Valdes received a PhD in neuroscience from Texas Christian University and was a postdoctoral fellow at Johns Hopkins University. He was the Army's scientific advisor for biotechnology, a senior professional position within the Senior Executive Service, and he received Presidential Rank Awards from President George W. Bush for his development of biosensors and from President Barack H. Obama for his development and deployment to Iraq of a tactical energy system. Valdes was a participant in studies by the DOD Office of Net Assessment and, separately, the National Research Council on military applications of biotechnology. As a senior research fellow at the National Defense University, he was senior editor of *Bio-Inspired Innovation and National Security*. Valdes is the author of more than 130 scientific papers, forty Army and NDU technical reports, and seven patents. He is currently technical director of the MSI STEM R&D Consortium, a group of seventy-five minority serving universities.

James P. Chambers received a PhD in biochemistry from the University of Texas Health Sciences Center at San Antonio and was a postdoctoral fellow in biochemistry at the University of Pittsburgh and in biochemical genetics at the Washington University School of Medicine. He served as the director of the Metabolic Disease Laboratory at the University of Texas Health Sciences Center at Houston and is currently professor of biochemistry at the University of Texas at San Antonio. Chambers is editor in chief of the *Journal of Pathogens* and the author of more than 175 scientific publications.

Diane M. Kotras is an intelligence strategist and policy principal with the MITRE Corporation. She specializes in artificial intelligence (AI) national security policy, AI adoption, and emerging threat technologies. Her portfolio focuses on enabling AI adoption across organizations, advancements in AI technology, international AI engagement, and counter-threat. She served in the Office of the Undersecretary of Defense for Policy and the Intelligence Community prior to joining MITRE in 2017. She holds a BA degree in natural sciences from Johns Hopkins University and an MS in national security studies from the National War College.



In this artist's conception of a biosensor, biological molecules such as antibodies and enzymes are coupled with an electronic microchip that processes data. (AI illustration by Gerardo Mena, Army University Press)

Figure 1. Artist's Conception of a Biosensor

Industry Association estimated to be more than $400 billion in 2018.[3]

The Biden administration's Executive Order 14081 explicitly calls for "genetic engineering technologies and techniques to write circuitry for cells and predictably program biology in the same way in which we write software and program computers."[4] Finally, the 2022 Creating Helpful Incentives to Produce Semiconductors (CHIPS) and Science Act recognizes the critical importance of developing advanced next-generation semiconductors.[5]

Background

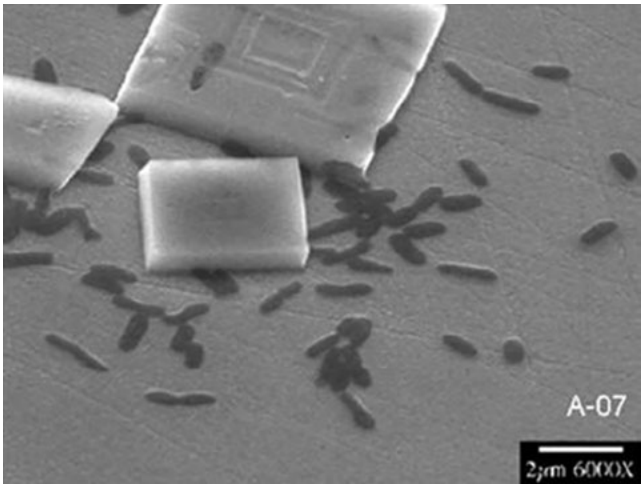
Extremophiles are organisms that live at the extremes of environmental conditions such as very high or low temperatures, high ambient radiation, or low oxygen or nutrient conditions. Robert Baier, of the National Science Foundation's Center for Biosurfaces at the State University of New York at Buffalo, as well as Anne Meyer and Robert Forsberg, observed that the extremophile bacterium *Pseudomonas syzgii* could "armor" themselves with semiconductor crystals by embedding them in the cell membrane and, more amazingly, these bacteria penetrate and survive within semiconductor wafers under zero oxygen conditions during the chip fabrication process (see figure 2).[6] While this was initially viewed as a contamination problem for semiconductor fabrication, it became the impetus for the idea that biological cells could be incorporated into electronic devices to confer enhanced properties that traditional semiconductors lack. Living bacteria have also been found to be encased in minerals, and their intact biological functions under these extreme conditions suggest that these bacteria almost certainly engage in electronic communication via the movement of electrons as with electricity, opening the possibility for functional organism-based biological semiconductor fabrication.[7]

Ralph Calvin, Paolo Lugli, and Victor Zhirnov point out that living cells process complex inputs and outputs spanning multiple modalities (e.g., chemical, electrical) and accomplish these computational operations at decreased energies, which cannot be matched by today's silicon-based electronic systems.[8] In a comparison of a theoretical silicon "cell," represented by a 1 um^3 memory and logic circuit, with a biological cell, they calculate that the silicon cell has 10^5 bits of memory, 300 to 100,000 logic bits, consumes 10^{-7} W of power, and generates 1 W/cm^3 of heat. In comparison, the biological cell has 10^7 bits of memory, $> 10^6$ logic bits, uses 10^{-13} W of power, and generates 10^{-6} W/cm^2 of heat, a difference of six orders of magnitude of energy use in favor of the biological cell. This is a million-fold difference. The military's reliance on technology requires a lot of power and biological systems' efficiency in this area could reduce logistics and sheer weight burden of batteries.

The "Grand Challenges" to electronics are to reduce energy consumption and heat generation while increasing processing power. Biological systems are clearly superior to traditional electronics with respect to these characteristics. The advantages to military systems in efficiency and computational power and the potential to design intrusion or hacking resistant, self-healing circuits can scarcely be overstated.

Current State-of-the-Art

Current concepts of hybrid bioelectronic devices focus on using the biochemical processes in living systems as a "biological front-end," biological recognition elements such as antibodies, which would interact directly with the external environment and share information with a silicon semiconductor "back-end," the physical component that processes the data. Biochemical processes, which operate at small scales that semiconductor devices cannot match, react to the environment and transduce a signal that is usually either ion transport through a cellular membrane, or activation of proteins within the cell. In some cases, ephaptic transmission, direct stimulation of one cell by another via magnetic fields, may occur. Mechanisms, whereby cells can use electro-conductive pili (structural fibers protruding from a cell) to transport electrons as electrical current, will be discussed in clarifying detail later in this article. The pili can be utilized as part of the cell assembly itself or manufactured and used as stand-alone electronic components.[9] In a scenario in which a cell is the component that interacts with the environment, the biological front-end transmits its information to the semiconductor back-end that handles computation, control, and information storage (see figure 3).



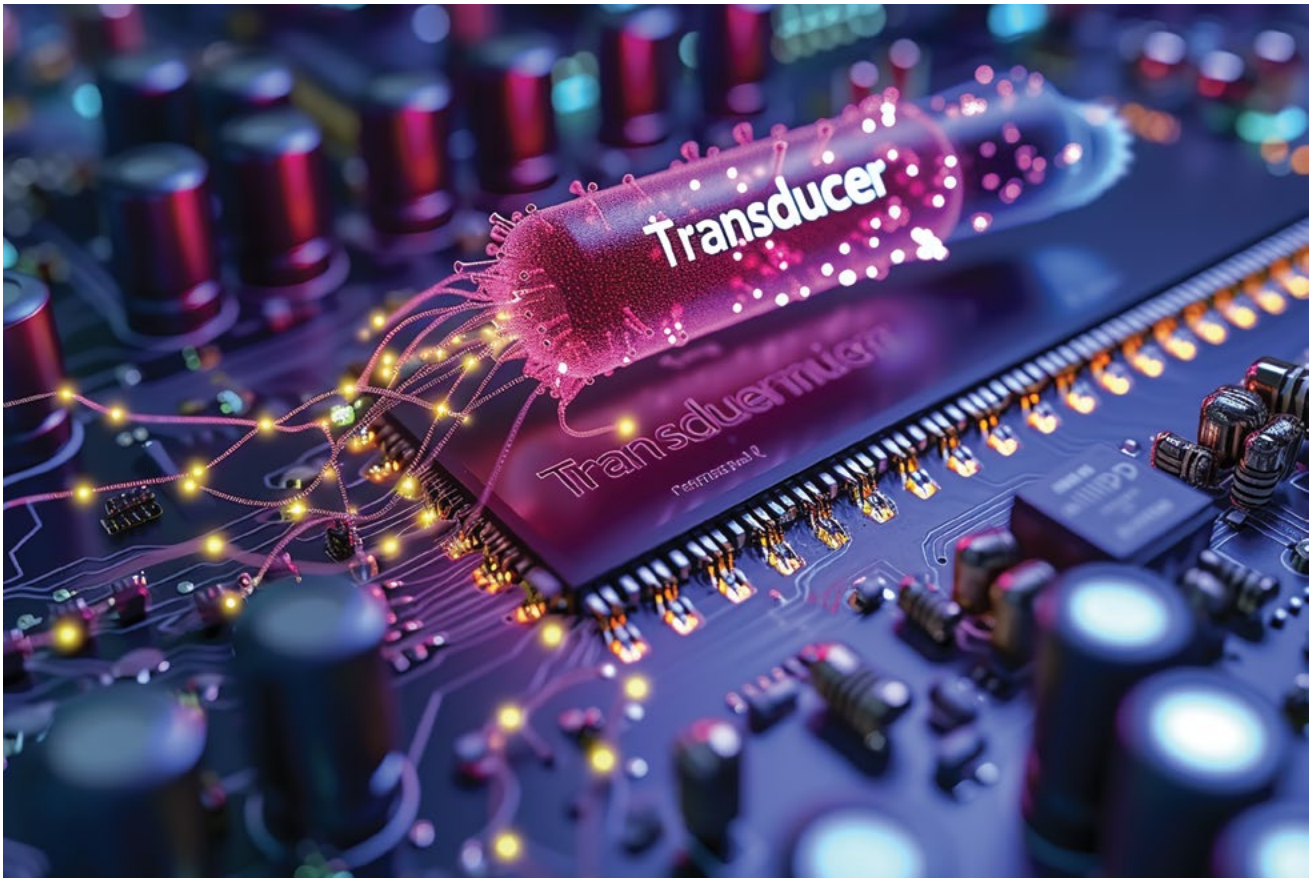
An image from a scanning electron micrograph of live bacteria interacting with semiconductor materials. (Figure courtesy of the Baier Lab, State University of New York at Buffalo)

Figure 2. Live Bacteria Interacting with Semiconductor Materials

Long-Term Vision for Future

In the short-term, living cells or their components would be used to build bioelectronic devices, but the longer-term focus is to design programmable abiotic (nonliving), artificial "cells" with many of the functions of biotic (living) cells. These functions include sensing, information processing, and self-repair. There is considerable similarity between mathematical models that describe noisy electron flow in transistors and noisy molecular flows in biochemical reactions in living cells, and both are subject to the laws of thermodynamics. In other words, they both follow the same natural rules, and their similarities suggest that *cells and electronic components could interact in a predictable and controllable manner*.

The Department of Defense (DOD) Community of Interest for Advanced Electronics listed "bioelectronics"



A conceptual schematic of transduction of biological signals into electronic data impulses, which are then processed. (AI illustration by Gerardo Mena, Army University Press)

Figure 3. Conceptual Schematic of Transduction of Biological Signals

as one of the technologies to watch for in the future, and the National Institute for Standards and Technology Advanced Manufacturing Technology Program awarded funding to the Semiconductor Research Corporation in 2015 to develop a Semiconductor Synthetic Biology Consortium (known as SemiSynBio). The mission is to bring together the semiconductor and biotechnology industries to develop new energy-efficient information technologies.[10] The short-term goals of SemiSynBio are to develop biological self-assembly for features that are on a much smaller scale than the resolution of lithography, the current semiconductors manufacturing technology. The long-term goal is to design new types of artificial cells or their components that can be integrated into semiconductors. In 2022, the National Science Foundation announced SemiSynBio III, "Semiconductor Synthetic Biology Circuits and Communication for Information Storage." The age of biological electronics, once the stuff of science fiction, is becoming reality.

Issues and Obstacles to Advances in Bioelectronics

The current national and commercial efforts to "onshore" manufacture critical technologies such as semiconductors is especially supportive of bioelectronics. The potential for supply chain disruptions for critical electronic materials and components is relevant to the DOD. For example, there are few trusted second sources for field programmable gate arrays and application-specific integrated circuits. By contrast, the precursors for manufacturing biological components are abundant, inexpensive, and freely available.

Microbes and bioelectronic devices. Bacteria communicate with each other and the physical environment through various biochemical and electrical mechanisms. Many microorganisms are known to be electroactive and electron transport, a form of bioelectric communication, has been demonstrated between different species (*Geobacter metallireducens* and *G.*

sulfurreducens).[11] Many bacteria form biofilms, and the movement of electrons between bacteria is believed to be the mechanism by which the biofilms are electrically active. These slimy biofilms are essentially colonies whose inhabitants (bacteria) communicate to regulate metabolic processes, such as growth, energy production and use, waste disposal, and reproduction.

Lori Zacharoff and Mohamed El-Naggar suggest that multistep "hopping" of electrons allows conduction over long-length scales previously thought to be impossible in biological systems and further suggest that understanding these processes is critical to the design of a new generation of "living electronics."[12] Recall that length scales in traditional electronics are much longer than those in cellular systems; this mismatch is a drawback for the former and a potential obstacle for designing bioelectronic systems. The structural foundation of this electron transport is thought to be the electrically conductive pili (cellular fibers known as e-pili), which microorganisms have evolved to interact with the environment and with each other.[13] The composition of the e-pili is critical in that increasing the content of aromatic amino acids facilitates electron transport, providing a genetic technology by which designers can "tune" e-pili electrical characteristics by manipulating the content of these amino acids along the length of the fiber. Derek Lovley further posits that *the ability to genetically engineer the composition of e-pili suggests the possibility of manufacturing a "green" electronic material from bacteria that can be easily manufactured via fermentation. These renewable feedstocks have the added benefit of being biodegradable* (see figure 4).[14]

Yang Tan et al. have used the electrically conductive pili of *G. sulfurreducens* to produce "microbial nanowires."[15] They genetically manipulated the bacteria by substituting tryptophan for the carboxyl terminus phenylalanine and tyrosine to produce high aspect ratio (extreme length-to-width ratios) electrically conductive nanowires that are physically robust and suitable for use as electronic components. To illustrate scale, a human hair is about 70,000 nm thick, a bacterial cell is about 1,000 nm, and nanowires are several nanometers. Other microbial species, such as *Aeromonas hydrophila*, express electrically conductive filaments that appear to facilitate intercellular communication. Laura Castro et al. genetically manipulated such nanowire formation by adding synthetic acyl-homoserine and suggested that these components could be useful as biological conductors in electronic devices.[16]

The large number of microorganisms that express e-pili, the relative ease with which these can be genetically manipulated, and their nanoscale structures suggest that there exists a large natural reservoir of biomaterials that can lend new characteristics to traditional electronic devices. These biomaterials can be produced with minimal environmental impact compared to today's semiconductor manufacturing methods, offering another advantage of biological systems versus electronic components.

Combining Bioelectronic Power Generation with Devices

In a seminal review paper, Michael Stroscio and Mitra Dutta describe the many subtle ways in which biological structures and processes could be combined with electronic devices to provide new functionalities.[17] They point out that the nanoscale of electronic devices permits direct contact with electroactive cells and subcellular structures such as ion channels, receptors, and other proteins that span the cell membrane and communicate with the external environment. A growing scientific literature exists in which the transmembrane protein bacteriorhodopsin (BR) is used as a sensing element—the "front end," as previously described—for electronic devices. For example, Yu-Tao Li et al. reviewed the BR literature specifically as it pertains to the design of bioelectronic devices.[18] They describe photochemical and electrochemical applications and speculate on new designs for high-performance BR-based hybrid bioelectronic devices.

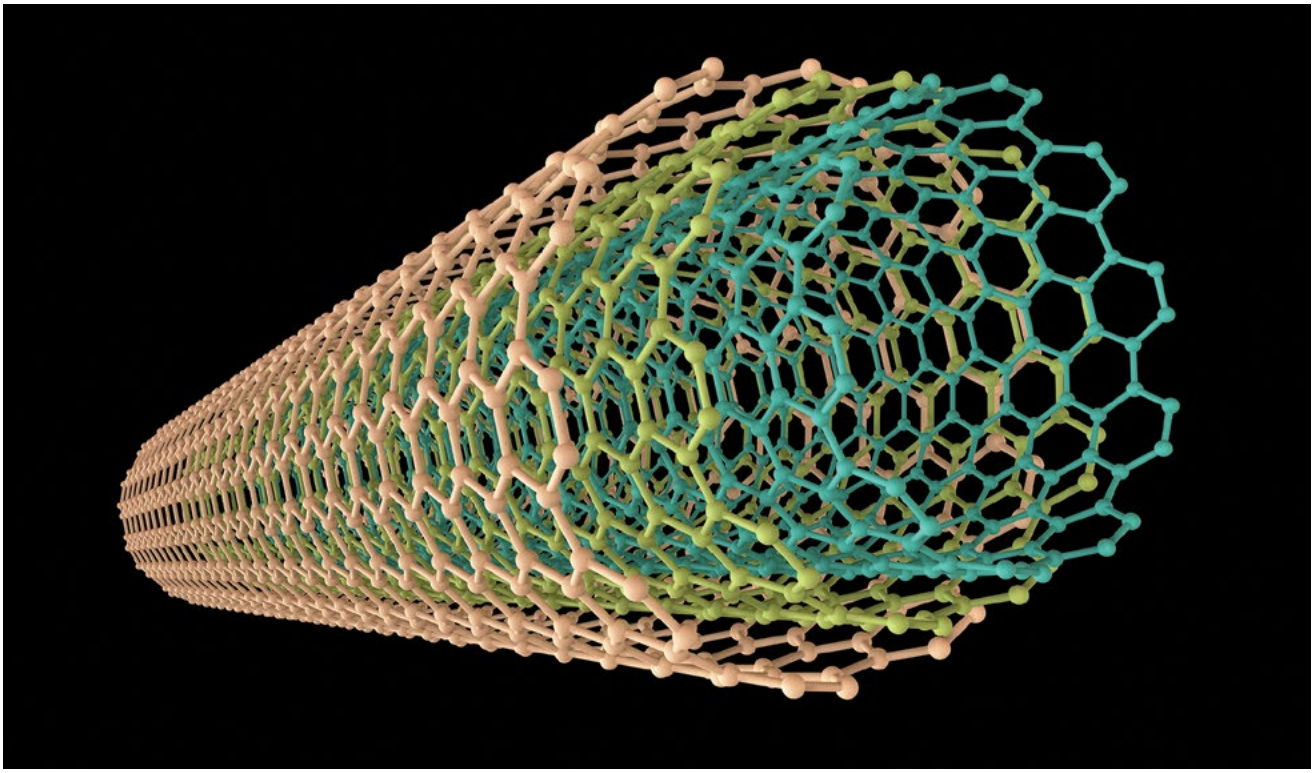
Special properties of biological components. Ion channels and receptors further offer an "analog" capability in which responses to environmental stimuli are not necessarily "on" or "off" as with traditional electronic devices but are graduated with initial responses to very small chemical, physical, and electrical perturbations in the environment and that can be tuned for sensitivity and specificity. The increasing reliance of tactical missions on precision smart weapons and, more specifically, autonomous systems require the ability to respond to input of very low signal-to-noise ratios; this analog aspect of biological systems would permit finely graded responses.

In this artist's conception, a bacterium is shown interacting with an electronic chip via its conductive nanowire pili. (AI illustration by Gerardo Mena, Army University Press)

Figure 4. Bacterium Interacting with an Electronic Chip

Leon Juarez-Hernandez et al. describe a bio-hybrid interface between cells and a poly(aniline) semiconducting polymer.[19] The cells remain functional as assessed by standard electrophysiology, which measures a cell's electrical activity, hence viability, and this was achieved with heart, skeletal muscle, and nerve cells. These bio-hybrid interfaces also demonstrated memristive properties; that is, the ability to alter function in response to prior electrical activity (experience). This is a primitive model for learning and memory and analogous to the concept of Hebbian circuits in the human brain, a circuit of brain cells that becomes either more or less sensitive and responsive with use and can "remember" previous actions. Thus, coupled with artificial intelligence, the bioelectronic component could add flexibility to the response repertoire of autonomous systems. Leon Chua first proposed the concept of the memristor and it has now become an active area of research.[20]

There have been other remarkable instances in which organic components have demonstrated semiconducting properties.[21] That organic polymers could serve as semiconductors has been well known and, in fact, was the subject of a Nobel Prize.[22] The demonstration that a small peptide composed of two phenylalanine amino acids has the optical and electronic properties of semiconductor nanocrystals was completely unexpected and adds important new dimensions to this area.[23] These can form the building blocks of quantum dots, which are nanoscale crystals with semiconductor properties intermediate in size between meso- and molecular-scale materials, "meso" being a size between materials of molecular size and the large objects of everyday experience. This peptide



(Image from Adobe Stock)

Figure 5. Molecular Structure of a Carbon Nanotube

also self-assembled to form nanotubes composed of millions of quantum dots. The authors point out that, unlike metal-based quantum dots, these are biodegradable and nontoxic, and because they are formed with a single peptide bond, they are cheap and easy to manufacture and have minimal environmental impact upon disposal. Because there are twenty natural amino acids and many hundreds of noncanonical (man-made, not found in nature) amino acids, the likelihood of designing quantum dots with properties not found in traditional electronic materials is almost limitless (see figure 5).

As with peptide quantum dots, many biological materials self-organize. Recent advances in additive manufacturing have also led to the use of inkjet printing to manufacture organic semiconductors. Yoon-Jung Kwon, Yeong Don Park, and Wi Hyoung Lee describe the printing of an organic field effect transistor using inkjet printing and organic semiconductor inks. Organic field effect transistors have the advantage of being cost-effective, compatible with most plastics, and can be tailored with specific mechanical properties.[24] This makes them suitable for devices that must function in a physiological environment, such as human-machine interfaces and prostheses for physical or cognitive enhancement, and as components for soft robotic systems. Petri Ihalainen, Anni Määttänen, and Niklas Sandler published a review of roll-to-roll and inkjet printing of proteins, biomacromolecules, and cells, and the application of these techniques to biosensors, diagnostics, and DNA sequencing.[25] The inverse relationship of biology and semiconductors is also worth noting, as many organisms have been shown to synthesize inorganic metallic nanoparticulate semiconducting materials with unique optical, electronic, and mechanical properties and with potentially high value to industry.[26]

Technical hurdles. There is little question that biological cells, their components, and their synthetic analogs will enable the design of new classes of semiconductors and other bioelectronic devices with unique properties and distinct advantages in information processing capacity and vastly reduced energy consumption and heat generation. As would be expected in such a new area of inquiry, we have identified several theoretical and practical problems that will need to be addressed. The most challenging of these is the precise immobilization of cells and/or their functional components within or onto semiconductors, genetic engineering of cells to introduce genetic control switches with which to control cellular activity, reconciling the differences in space and time scales of the languages of biology and electronics so they can communicate seamlessly, and engineering completely artificial cells with designer properties and the functional equivalents of living cells. Synthetic biology will be a critical technology in realizing fully integrated bioelectronic devices, which is the ultimate goal of the SemiSynBio consortium.[27] More prosaic considerations are to define the design parameters for a benchtop foundry simulator, a small-scale model of a semiconductor foundry with which to conduct the required experiments, and the selection and adaptation of analytical techniques such as cryo-electron microscopy for real-time morphological and electrochemical characterization of immobilized microbes as they exist in an electronic device.

Discussion and Conclusions

The semiconductor industry is rapidly nearing the physical limits of traditional materials. It has already started to look at alternate techniques with which to pack more computing power into very limited space. As previously noted in this article, a biological cell consumes approximately six orders of magnitude less energy and generates approximately six orders of magnitude less heat than comparable *in silico* semiconductors. While these numbers are somewhat theoretical, they point out the relative advantages that biological systems have over electronics and the potential to disrupt the semiconductor industry if biological cells, whether natural, bioengineered, or artificial, could be integrated with traditional semiconductors. In addition, the cell's ability to process many modalities of input/output simultaneously is advantageous, as are the redundancies and feedback loops that allow for self-correction and self-repair. In fact, the ability of cellular circuits in the brain to self-modify their sensitivities, the Hebbian circuits described earlier, is a key component of memory and underpins the theoretical description of memristors, described earlier in this article. A hybrid biological semiconductor could also confer the advantage of self-healing to computer networks.[28]

The concept of hybrid biological semiconductors is likely DOD Technical Readiness Level-2, defined as a concept whose application has been formulated. As described earlier, the National Institute for Standards and Technology's Advanced Manufacturing Technology Program has funded the development of a roadmap by the SemiSynBio consortium, and the National Science Foundation's SemiSynBio III is the more recent iteration. New classes of biologically based semiconductors would have wide applications in intelligent process control for autonomous systems, chemical and biological detection, integrated medical devices for enhanced human performance, advanced manufacturing processes, DNA-based memory storage, environmental monitoring and control, and would save enormous amounts of energy now used to cool server farms, and reduce heat signatures of military systems in the field. The overlap of biological semiconductors with the broader field of biomaterials presents opportunities to develop biosensors, other implantable biomedical devices, and tissue scaffolds based on novel hydrogels, three-dimensional polymers in which the liquid component is water, that have important implications for military medicine such as wound healing and smart physical and cognitive prostheses.

In summary, capitalizing on the ability of biological systems to process information more efficiently than current *in silico* semiconductors presages a new frontier in information technology. Biological electronics offer the possibility of intrusion-resistant and self-healing networks, and microbes' ability to modulate signals may provide resistance to electromagnetic pulses.

The DOD's recent investments in synthetic biology and biotechnology have it well-positioned to assess the potential for military applications. Future military systems will benefit from heretofore unimaginable advances at the nexus of biology, materials science, and physics. The resulting breakthrough discoveries will provide the Nation's security posture with greater operational capabilities and cost benefits. ■

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