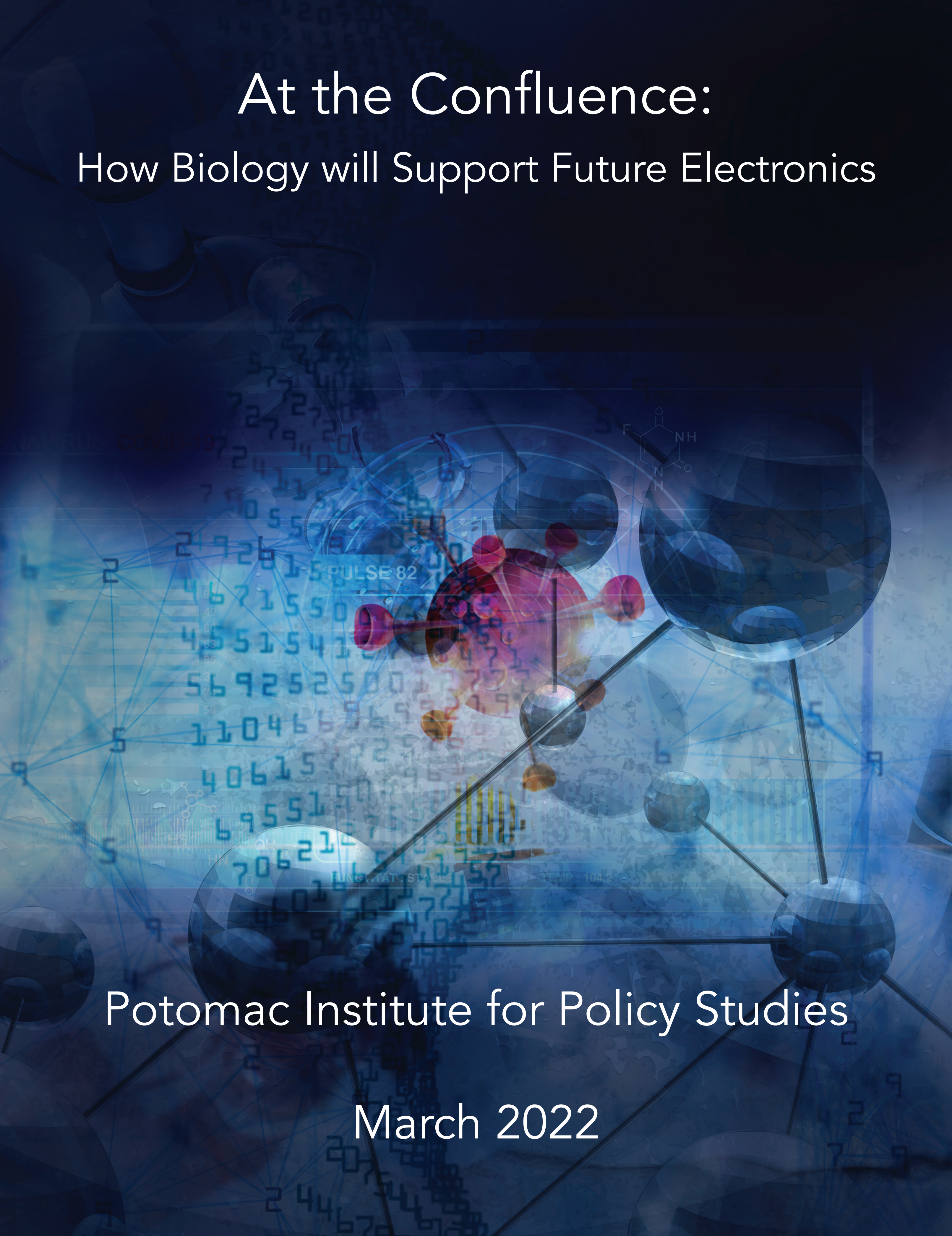
At the Confluence:

How Biology will Support Future Electronics



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Abstract

Biology is poised to offer alternative routes in the development of multiple technical applications. Three example electronics technology areas anticipated to experience further development using biology include sensors, fuel cells, and information systems. There is considerable demand to make devices in these categories smaller, faster, more reliable, more efficient, and/or biocompatible. While there are hurdles to translating these ideas using biology into real commercial products, research efforts indicate these technologies are positioned to offer exciting new capabilities.

Introduction

Biology is poised to offer promising alternative routes to propel innovative technology solutions. Here, we will explore three application areas – sensors, fuel cells, and information systems – where biology offers new possibilities for technology advancements. U.S. economic prosperity and national defense depend on technology innovations, and multidisciplinary approaches are often sources of important new technologies. New understandings of biology and biological processes, converging with electronics and computation, can lead to new capabilities in multiple application areas, and in particular in the ones studied here.

The Fourth Industrial Revolution is intrinsically related to biology, as it emphasizes the increased intersection of digital, biological, and physical innovations.[1] Many believe that biotechnology will experience a fast pace of development in the upcoming years. Some estimates predict the biotechnology market will grow to $2.44 trillion by 2028.[2] Lessons from biology may offer exciting new approaches to critical and emerging technologies important to homeland security.[3] Such advances could indeed herald a revolution in technology available to societies worldwide.

Biology may offer solutions to challenges with electronic devices. Electronic components and material, including semiconductors, transformed the 20th century and have had a radical impact on daily life. With the looming end of Moore's Law, alternatives are being explored to provide the next generation of leading-edge technology.

Fusing biology with traditional technology may involve inspiration from biology as well as using biological components. Merging biological materials, functions, or structures that nature has fine-tuned over billions of years with electronics may offer new avenues to developing sensitive, efficient, biocompatible, biodegradable, and environmentally friendly solutions.

image: Shutterstock

1 Schwab, Klaus. "The Fourth Industrial Revolution." World Economic Forum, Geneva, 2016. https://law.unimelb.edu.au/__data/assets/pdf_file/0005/3385454/Schwab-The_Fourth_Industrial_Revolution_Klaus_S.pdf

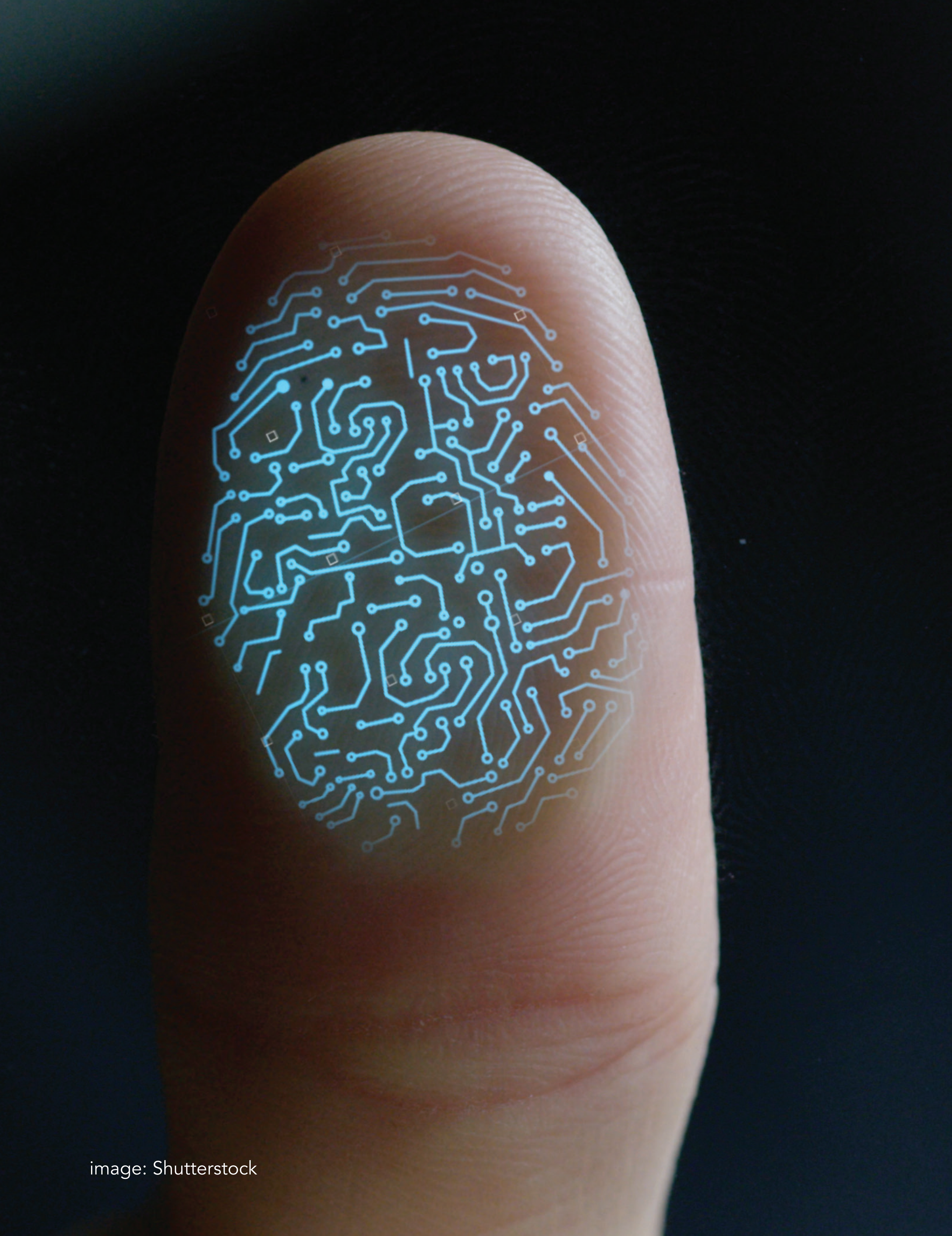
2 "Biotechnology Market Report." Grand View Research, March 2021. https://www.grandviewresearch.com/press-release/global-biotechnology-market

3 For instance, the United States updates its list of Critical and Emerging Technologies (C&ET) that reflects its priorities that includes advanced computing; advanced engineering materials; advanced manufacturing advanced sensing; agricultural technologies; biotechnologies; chemical, biological, radiological, and nuclear (CBRN) mitigation technologies; data science and storage; energy technologies; human-machine interfaces; medical and public health technologies; semiconductors and microelectronics, and others (available at https://www.hsdl.org/?view&did=845571). These highlight an opportunity space where alternative approaches using biology may help with forging ahead.

The convergence of biology and electronics, sometimes called "bioelectronics,"[4] can proceed by a variety of means: via integration of electronics into a biological system, electronics that mimic biology, or inserting a bio-enabled component into an electronic device. Some technologies that are considered bioelectronics interface with the human body to engage electronic or cyberphysical devices, such as a pacemaker, medical imaging tool, artificial limb, or brain-computer interface. However, in what follows, we focus on examples where biological processes are inserted directly into electronic applications.

We explore three applications areas – sensors, fuel cells, and information systems – that highlight where biology can play a role in new electronic applications. We will review what is currently available, anticipated advancements, and research efforts together with drivers and hurdles to commercialization. To provide context and situational awareness of the types of innovation efforts related to these capabilities, this report pinpoints a sample of organizations shepherding advancements — endorsements are not implied.

4 There have been different interpretations of what qualifies as bioelectronics over the years. A 1991 Conference of European Churches (C.E.C.) workshop in Brussels, which brought together leading industry and science experts across Europe, defined bioelectronics as "the use of biological materials and biological architectures for information processing systems and new devices." The 2009 NIST report defined bioelectronics more generally as "the discipline resulting from the convergence of biology and electronics." Others scope it in terms of electrical engineering principles applied only to medical and health related fields. For example, see "Bioelectronics Engineering" page on North Carolina State University Department of Electrical and Computer Engineering available at https://ece.ncsu.edu/research/bee/. This paper will not focus on those devices labeled bioelectronics solely because of insertion in the body, such as brain-computer interfaces.



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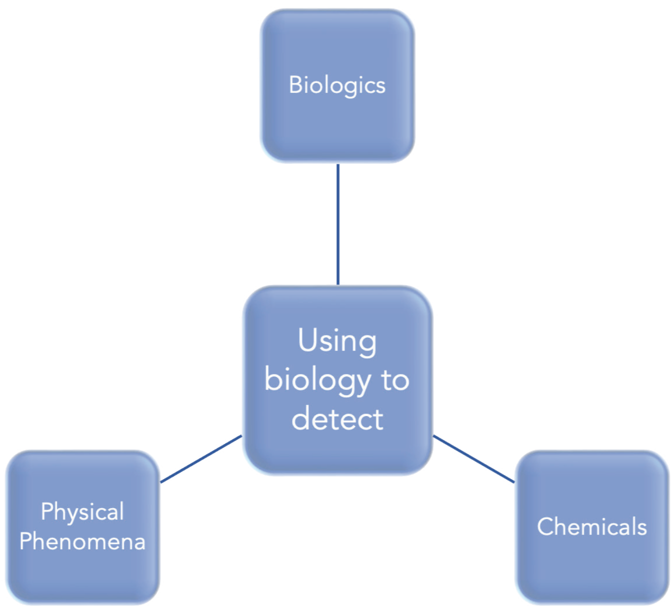
Biosensors

Sensors and sensor systems are designed to translate information about the external world into information that can be used to make decisions. Sensors increasingly translate information collected into electrical signals, either digital or analog, for recording and further processing. Here, we explore some of the possibilities for using modern knowledge of biology and biological processes to develop new sensor types, which will generally involve a convergence of biology with electronic components.

In many cases, bio-enabled sensors[5] will have the advantage of sensitivity, small size, and biocompatibility.



5 The term biosensor has had different meanings. Some apply the term biosensors when detecting something biological by any method. The NIH indicates that "in medicine and biotechnology, sensors are tools that detect specific biological, chemical, or physical processes and then transmit or report this data" ("Sensors." National Institute of Biomedical Imaging and Bioengineering, October 2016. https://www.nibib.nih.gov/science-education/science-topics/sensors.) Some of devices include biometric biosensors (e.g., Fitbit tracking heartrate) which are marketed under this label. Other definitions of biosensor are more exclusive to explicitly utilizing biology to detect certain phenomena. For example, "[a] biosensor is an integrated receptor-transducer device, which can convert a biological response into an electrical signal" (Naresh, Varnakavi and Nohyun Lee. "A Review on Biosensors and Recent Development of Nanostructured Materials-Enabled Biosensors." *Sensors*, 2021, *21(4)*, 1109. https://doi.org/10.3390/s21041109). Such bio-enabled sensors could include systems that utilize biological material like bacteria, enzymes, antimicrobial peptides, lectins, antibodies, aptamers, or a whole organism to assist with detection. The focus of this section is bio-enabled sensors.

Detection of Biologics

Biosensors are ideally suited for the detection of biological materials. While this is especially important for medical diagnostics; biosensors can nonetheless be designed to detect a variety of biologics.

Recently, many have become familiar with sensor technology designed to detect biological materials related to diseases like COVID-19. Tests for SARS COV-2, the virus that causes COVID-19, and evidence of existing or prior infection, have become commonplace. Tests include immuno-diagnostic tests (antigen or antibody tests) and reverse transcriptase-polymerase chain reaction (RT-PCR) tests. By using nasopharyngeal swab, throat swab, or blood or saliva samples, tests can detect viral RNA or protein antigens, or antibodies. Further biosensor development has focused on other approaches such as surface plasmon resonance (SPR)-based tests, electrochemical tests, and field-effect transistor (FET)-based biosensors.[6] Making tests less expensive, less invasive, and more ubiquitous with automated readout for data collection, could help stem future epidemics and improve health outcomes through early detection.

Moreover, long before COVID-19 was upon us, many people worldwide made use of biosensors as blood glucose monitors. Yellow Springs Instrument Company made a commercial glucose biosensor in 1975 using amperometric detection of hydrogen peroxide.[7] Since then, glucose biosensors evolved to become reagent-less and operate as a continuous monitoring system to provide real-time data. By 2004, glucose biosensors were estimated to account for about 85 percent of the global biosensor market.[8] Most tests on blood glucose concentration focus on interaction with enzymes: hexokinase, glucose oxidase (GOx), or glucose-1-dehydrogenase (GDH).[9]

Other consumer bio-enabled tests that are common include biosensors for pregnancy testing and at-home tests that measure cholesterol levels.[10] These tests look for particular biological materials, such as biomarkers, and have been adapted from typical medical laboratory tests for consumer use.

Often, output is read using visual results. However, convergence with electronics embedded into tests might permit continuous data collection that could be used to monitor health conditions using data processing and data analytics, by transferring test information into digital databases. Data analytics can then be used, along with artificial intelligence techniques to discern trends, to provide alerts and other decision-making information without requiring

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6 Lim, Wei Y., Boon L. Lan, and Narayanan Ramakrishnan. 2021. "Emerging Biosensors to Detect Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Review" *Biosensors*, 11, no. 11 (November 2021): pp. 434. https://www.mdpi.com/2079-6374/11/11/434/htm

7 Yoo, Eun-Hyung, and Soo-Youn Lee."Glucose biosensors: an overview of use in clinical practice." *Sensors*, 10, no. 5 (May 2010): pp. 4558-76. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3292132/

8 Ibid.

9 Ibid.

10 Ramirez, Erica and Kristina Galea. "6 of the Best At-Home Cholesterol Tests for 2022." *Medical News Today*, 28 November 2021. https://www.medicalnewstoday.com/articles/3-of-the-best-at-home-cholesterol-tests#what-is-cholesterol

continuous monitoring by humans.

The environmental and food and agriculture industries have also been involved in the development and use of biosensors. Enoveo, a company specializing in environmental biosensors, has developed microbial biosensors for testing of sewage treatment plants, of sewage overflow, industrial effluents, and groundwater to monitor effectiveness of contamination treatments.[11] These tests use specific bacteria existing at the site of interest and detect associated biomarkers. While it would be customary to set thresholds to alert on out-of-range test results, biosensors will increasingly feed data into databases that can discern trends and compare data with other sensor data to provide more diagnostic information.

A new startup PPB Technology is developing its "Cybertongue" technology using protein sensors for rapid dairy diagnostics. This sensor uses bioluminescent reagents that change color if the target, like lactose or specific proteases indicating contamination, is present in samples like milk.[12] Typically, color changes would have to be read by a human, but automated systems could use such changes to generate digital data that can be accumulated in databases.

Detection of Chemicals

Biosensors can also be designed for the detection of chemical substances that are not necessarily products of biological processes. For example, the detection of the presence of gases or toxic chemicals, contaminants, smells, or other substances can be important in a variety of home and industrial applications.

The water monitoring systems company Modern Water uses bioluminescent bacteria to detect toxic substances. Their system Microtox® takes advantage of the bacterium *Aliivibrio fischeri* that usually emits light but has a natural response of decreased emission when toxins are present.[13]

Similarly, the company Quantitative BioSciences, Inc. uses synthetic biology to develop continuous, real-time sensors for monitoring water over long periods with minimal oversight. They have engineered bacteria that produce measurable fluorescent responses in the presence of toxins like arsenic, lead, mercury, cadmium, nitrate, nitrite, ammonium, phosphorus.[14] These measurements can be used for analysis of trends and diagnostic purposes.

In an approach to airborne chemical detection, the small biotechnology company Koniku is developing a bioelectronic sensor (the "Konikore") that detects smells with a very fast

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11 "Microbial Biosensors." Enoveo, accessed 13 February 2022. https://enoveo.com/en/services/biosensors/

12 Whitehead, Richard. "Cybertongue has protein detection licked." Dairy Reporter, 5 December 2018. https://www.dairyreporter.com/Article/2018/12/05/Cybertongue-has-protein-detection-licked

13 "Toxicity." Modern Water, accessed 10 February 2022. https://www.modernwater.com/monitoring/toxicity/

14 "Customized Sensor Strains." Quantitative Biosensors, Inc., accessed 13 February 2022. https://www.qbisci.com/sensor-technology

response time. They are designing computer chips that incorporate lab-grown genetically modified neurons to identify compounds by smell, marketing products for military, security, agriculture, and health applications.[15]

Others continue to study olfactory receptors that bind to molecules with specific odors.[16] The University of Tokyo's Biohybrid Systems Laboratory is studying ways to make a portable odorant sensor using mosquito cells to detect airborne chemicals.[17]

Detection of Physical Phenomena

Using bio-enabled sensors to detect physical phenomena, such as light, heat, sound, or pressure might seem less obvious than the detection of biological or chemical compounds, but since evolution has endowed the world with natural such sensors, there are many possibilities for biosensor systems to sense such physical system manifestations. Other phenomena, such as radiation or magnetic fields might also have biological sensor possibilities.

Light-responsive proteins are found in many organisms, including the human retina, and can enable sensing of light by biological means. Bacteria have been engineered that can specifically detect and respond to specific colors of light – a type of electromagnetic radiation – including ultraviolet, near-infrared, blue, green, and red light.[18] Currently, the genes that encode light-sensing proteins are available from the non-profit plasmid repository Addgene solely for research purposes,[19] but sensors employing these bacteria might someday be commercially available.

Detection of infrared radiation is particularly interesting for biological systems. Certain animals, like snakes, use infrared light to detect prey in the nighttime, using receptors tuned to colors that use longer wavelengths than visible light.[20] Biological infrared detection might provide an alternative approach to night vision sensors.

A different approach to light sensing is to use photosynthetic organisms. While typical solar cells use photovoltaics to produce electricity, a microbial solar cell produces a small amount of electricity when exposed to light and could therefore be used to sense extremely low

15 "Frequently Asked Questions." Koniku, accessed 13 February 2022. https://koniku.com/faq

16 Cepelewicz, Jordana. "Secret Workings of Smell Receptors Revealed for First Time." *Quanta Magazine*, 21 June 2021. https://www.quantamagazine.org/secret-workings-of-smell-receptors-revealed-for-first-time-20210621/

17 Fan, Shelly. "Scientists Made a Biohybrid Nose Using Cells from Mosquitoes." Singuilarity Hub, 26 January 2021. https://singularityhub.com/2021/01/26/scientists-made-a-biohybrid-nose-using-cells-from-mosquitoes/

18 Zedao, Liu, Zhang Jizhong, Jin Jiao, Geng Zilong, Qi Qingsheng, and Liang Quanfeng. "Programming Bacteria With Light—Sensors and Applications in Synthetic Biology." *Frontiers in Microbiology*, 9, no.8 (November 2018). https://www.frontiersin.org/articles/10.3389/fmicb.2018.02692/full

19 "*Optogenetics Guide*." *Addgene, accessed 7 March 2022*. https://www.addgene.org/guides/optogenetics/

20 "Pit Vipers Can Detect Prey Via Heat." American Museum of Natural History, 25 January 2018, https://www.amnh.org/explore/news-blogs/news-posts/pit-vipers-can-detect-prey-via-heat.

levels of light.[21]

Detection of other electromagnetic (EM) fields, such as EM radiation or magnetic fields, is not usually considered part of biology's purview. But various organisms respond to EM fields, and so there are possible biological sensors that can be developed for specialized detection purposes.

We previously discussed detection of visible and infrared light by biological means, but detection of high energy radiation (e.g., gamma rays) is of particular interest to NASA. NASA's project BioSentinel measures the impact of radiation on living organisms over long periods beyond low earth orbit by using a biosensor that utilizes the yeast *Saccharomyces cerevisiae*. It compares the DNA double strand breaks after radiation exposure in the wild-type strain of yeast to those in a mutated strain that cannot repair DNA damage. In this way, they can study the effects of deep space radiation and the importance of DNA repair mechanisms.[22] A separate study by a researcher at Clemson University uses single-celled organisms (bacteria and yeast) to detect radiation damage based on changes in gene expression; they also studied the effects of low-level radiation on these organisms.[23]

At the other end of the EM spectrum from ionizing radiation, radio waves can cause effects in biological materials. A DARPA project called RadioBio is investigating whether a class of cells inside a marine invertebrate known as a "brittle star" has surface structures that serve as tiny radio antennae.[24] It may be possible that those organisms can sense radio frequencies using molecular units with novel antennae structures. Within radio frequency studies there are mysteries concerning the effects of microwaves on humans, including pain that can be induced by high powered microwave as anti-personnel weapons or as non-lethal crowd-control, and suspicions that certain syndromes might be due to directed microwave energy. Wearable detectors might be able to warn of such effects.

Further on the extreme end of the spectrum, static fields are also known to have biological effects. Magnetoreception allows certain organisms to detect a magnetic field. It is known that many animals use magnetic fields to help with direction, altitude, or location.[25] One research effort suggests that proteins called cryptochromes respond to magnetic fields in a living cell,[26] and could thus be the basis for a biology-based detection or measurement of

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21 Mohammadifar, Maedeh, Mehdi Tahernia, and Seokheun Choi. "A Miniaturized, Self-Sustaining, and Integrable Bio-Solar Power System." *Nano Energy*, 72 (June 2020): pp. 104668. https://doi.org/10.1016/j.nanoen.2020.104668.

Also discussed in more detail in subsequent section on "Microbial Fuel Cells."

22 "BioSentinel." NASA, 8 October 2021. https://www.nasa.gov/centers/ames/engineering/projects/biosentinel.html

23 "New Biosensor Could Help Search for Nuclear Activity." *CBRNE Central*, 22 February 2017. https://cbrnecentral.com/new-biosensor-could-help-search-for-nuclear-activity/10601/

24 Monroe, Robert. "Can Organisms Sense via Radio Frequency?" *UC San Diego News Center*, 31 October 2017. https://ucsdnews.ucsd.edu/pressrelease/can-organisms-sense-via_radio-frequency

25 Irving, Michael. "Scientists Observe Live Cells Responding to Magnetic Fields for First Time." *New Atlas*, 6 January 2021. https://newatlas.com/biology/live-cells-respond-magnetic-fields/

26 Bressan, David. "Scientists Observe Cells Responding To Magnetic Fields For First Time." *Forbes*, 8 January 2021. https://www.forbes.com/sites/davidbressan/2021/01/08/scientists-observe-cells-responding-to-magnetic-fields-for-first-time/

fields.

Similarly, electricity is perceived in biological systems through electroreception. Static fields (static electricity) are perceived in bumblebees to detect weak electrical fields surrounding flowers.[27] Certain fish use electrical signals for communication — the Mormyrid electrical fish has certain receptors to sense electric signals.[28]

Heat is another type of physical phenomenon that can be detected via biological means. Thermoreceptors in our body help with the sensation and perception of temperature, and certain nerve endings that can sense heat.[29] Stimuli-responsive materials for sensing heat can be used for applications where temperature control is important, and biological materials might provide increased sensitivity at particular temperatures. The protein engineering company BioHybrid Solutions is creating stimuli-responsive protein-polymer hybrids that can respond to changes in temperature and pH,[30] for medical purposes. The technology for polymer-based protein engineering is championed by a center at Carnegie Mellon University.

We normally use microphones and signal analysis to detect physical vibrations that can represent sounds, but biological systems have evolved to detect and process sounds as well. For example, bats are known to emit ultra-high frequency sounds directionally for echolocation, with detectors to locate prey.[31] Katydids are likewise capable of ultrasonic hearing despite very small and simple ears.[32] A cochlear organ in bush-crickets can distinguish components of different frequencies in a complex sound.[33] Slits in the exoskeletons of spiders are known to detect sounds for hunting the dark.[34] Some of these biology technologies might provide sensor applications for special sound detection. Applications might include detection of heart anomalies using biological implants, or restoration of hearing in deaf people.

Furthermore, the sense of touch is important to many biological organisms. In some cases, hair-like structures called cilia are used to detect minute pressure changes for a variety of

27 "Floral Signs Go Electric." *University of Bristol / News and Features*, University of Bristol, 21 February 2013. https://www.bristol.ac.uk/news/2013/9163.html

28 Ogliore, Talia. "New Maps Hint at How Electric Fish Got Their Big Brains." The Source: Washington University in St. Louis, 15 November 2018. https://source.wustl.edu/2018/11/new-maps-hint-at-how-electric-fish-got-their-big-brains/

29 Mulders, M. A., editor. "4. Detection of Electromagnetic Radiation." *Developments in Soil Science*, 15 (1987): pp. 93–124. https://doi.org/10.1016/S0166-2481(08)70030-8

30 "Expanding the Possibilities." BioHybrid Solutions, accessed 14 February 2022. https://biohybridsolutions.com/company/

31 Hickey, Hannah. "Fruit bat's echolocation may work like sophisticated surveillance sonar." UW News, 7 February 2018. https://www.washington.edu/news/2018/02/07/fruit-bats-echolocation-may-work-like-sophisticated-surveillance-sonar/

32 "ERC: The Insect Cochlea." University of Lincoln, Bioacoustics & Sensory Biology Lab, accessed 14 February 2022. http://bioacousticssensorybiology.weebly.com/erc-the-insect-cochlea.html

33 Ibid.

34 Krisch, Joshua A. "A Mechanical Sensor Inspired by Spider Biology." *Scientific American*, 12 December 2014. https://www.scientificamerican.com/article/a-mechanical-sensor-inspired-by-spider-biology-video1/

purposes.[35] Simulants to cilia are being developed for biosensing of pressure phenomena.[36] Piezoelectric pressure sensors are also being fashioned from biodegradable glycine and chitosan found in the shells of crustaceans and insects. Using self-assembly of glycine molecules within a water-based chitosan solution, these sensors could be used for monitoring force/pressure. Chitosan polymers are an appealing material for biomedical applications such as wound dressing because they are biodegradable, biocompatible, nontoxic, and antibacterial.

An exotic use of pressure sensitivity for the military involves detecting the undersea passage of enemy subs, underwater vessels, or even divers. A government effort has been directed toward genetically engineering common marine microorganisms to make living tripwires to provide signals based on indicators of small pressure waves.[37]

Bio-Field Effect Transistors

Throughout, we have seen that biological materials can be used to detect (or measure) particular phenomena. Designs utilizing biology in sensors are looking to tackle challenges such as efficiency in capturing and transforming signals, enhancing transduction performance, and size of devices. Key features within bio-enabled sensors include the bio-recognition element where the bioreceptor[38] detects an analyte and signal transduction method which converts the biorecognition event into a measurable signal. As part of the convergence of biology with electronics, Bio field-effect transistors (Bio-FETs)[39] are a promising means wherein biology can interact with an electronic device.

Bio-FETs sensors are based on modified standard silicon CMOS transistors of the type that use field effects for gate functions. In Bio-FETs, the interaction with biological analytes is measured as a small change in the electrical field of the gate, which is amplified as a change in electrical conductance. In a Bio-FET, the transistor gate is replaced with a material, such as a polymer material,[40] to which target molecules stick and thereby alter the potential in the conductive channel below. Small changes in the gate potential cause large changes in source-drain current in the transistor, allowing detection of small amounts of biotarget materials.

In addition to providing high sensitivity for various analytes, Bio-FETs offer the possibility of

35 "Cilia Revolution." National Science Foundation, News Release 10-171, 23 September 2010. https://www.nsf.gov/news/news_summ.jsp?cntn_id=117670

36 Johns Hopkins Medical Institutions. "Can You Feel The Heat? Tiny Hair-like Cell Structures, Your Cilia, Can." ScienceDaily, 24 October 2007. www.sciencedaily.com/releases/2007/10/071022203111.htm

37 Tucker, Patrick. "The US Military Is Genetically Engineering New Life Forms To Detect Enemy Subs." *Defense One*, 1 December 2018. https://www.defenseone.com/technology/2018/12/us-military-genetically-engineering-new-life-forms-detect-enemy-subs/153200/

38 Examples of bio-recognition elements or bioreceptors include enzymes, DNA, and antibodies.

39 Other names also include FET-based biosensors, FET biosensors, biosensor field-effect transistor.

40 This polymer material has a bio component to it.

mass-production and low-cost manufacturing.[41] While still largely in research phases, Bio-FETs have been created using several biorecognition elements[42] and with different transduction materials for analyte detection.[43] Commercial applications are close. For example, the company Cardea Bio is developing graphene-based biosensor hardware, software, and molecular detection platforms. Its Cardean Transistor™ is a graphene-based biology-gated transistor, that uses the CRISPR-Cas9 technology to detect particular DNA molecules using a hand-held device.

Development Considerations

Industries, such as medical, food, environment, defense, and others [44] desire increased sensing capabilities. The global biosensor market was valued at $18.2 billion in 2018[45] and expected to reach $27.1 billion by 2022.[46] Improvements including more rapid data, improved accuracy, or generating more data via biology could provide substantially improved decision-making.

While health and medical applications dominate, especially for blood glucose monitoring, testing for drug discovery and infectious diseases; the agricultural industry is also projected to grow rapidly from 2021-2028.[47] There has been increased interest in development in the materials used as platform, including wearable, implantable, and most recently, ingestible biosensors, and other forms of degradable.[48] Medical applications also demand portability, rapid responses, and disposability,[49] and these requirements exist for non-medical use cases too.

Biosensor development still needs to work on hurdles like durability, detection time, and reusability of biological components, which are often sensitive to changes in temperature or pH.[50] Across all sector applications, sensors need to have specificity, sensitivity, and reliability.

41 “Biosensors using field-effect transistors show great promise.” EurekAlert, 21 December 2021. https://www.eurekalert.org/news-releases/938311

42 Sung, Daeun, and Jahyun Koo. “A review of BioFET’s basic principles and materials for biomedical applications.” *Biomedical engineering letters*, 11, no. 2 (9 April 2021): pp 85-96. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8034276/

43 For example, CNT (Y2O3), CNT (Au), Graphene, Silicon Nanowires, ZnO2 rods, Metal Organic Framework (MOF).

44 Vigneshvar S, CC Sudhakumari, B Senthilkumaran, and H Prakash. “Recent Advances in Biosensor Technology for Potential Applications – An Overview.” *Frontiers in Bioengineering and Biotechnology*, 4, no. 11 (2016). https://www.frontiersin.org/articles/10.3389/fbioe.2016.00011/full

45 “Global Biosensors Market to Register 8.1% CAGR through 2026: Grand View Research.” *Printed Electronics Now*, 9 July 2019, https://www.printedelectronicsnow.com/contents/view_breaking-news/2019-07-09/global-biosensors-market-to-register-81-cagr-through-2026-grand-view-research/

46 “Biosensors Market Size, Share, Trends | Forecast Report 2022.” *P&S Intelligence*, June 2018, https://www.psmarketresearch.com/market-analysis/biosensors-market

47 “Biosensors Market.” Emergen Research, Report ID: ER_0042, September 2020. https://www.emergenresearch.com/industry-report/biosensors-market

48 Zucolotto, Valtencir. “Specialty Grand Challenges in Biosensors.” *Frontiers in Sensors*, 1 (August 2020). https://www.frontiersin.org/article/10.3389/fsens.2020.00003

49 Ibid.

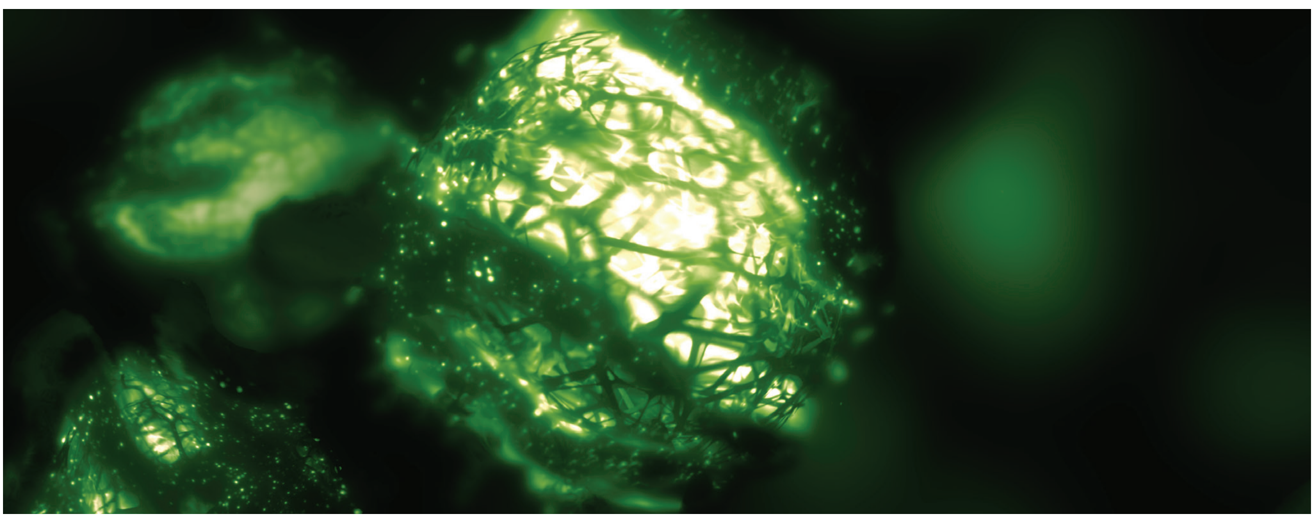
50 Mehrotra, Parikha. “Biosensors and Their Applications – A Review.” *Journal of Oral Biology and Craniofacial Research*, 6, no.2 (2016): pp. 153–59. https://doi.org/10.1016/j.jobcr.2015.12.002

Biology-Based Energy Production: Biofuel Cells

Fuel cells produce electrical energy by consuming a fuel, such as hydrogen or some other chemical. Unlike batteries, which are closed systems with an internal source of fuel, fuel cells require a constant external source of reactants.[51] This section will focus only on fuel cells solely for energy production that are based on biological processes.[52]

In niche scenarios, biology may offer benefits compared to contemporary energy sources. Biofuel cells offer smaller long-duration low power sources that might also provide biocompatibility and environmentally friendly features. Living organisms derive power from food sources — mostly sugars and other carbohydrates which have high energy density and are safe and easy to transport.[53] Bio-energy systems are appealing due to their use of non-toxic, biodegradable materials.[54]

Research has focused primarily on enzymatic fuel cells and microbial fuel cells.



51 Dunn, Katherine E. "The Emerging Science of Electrosynbionics." *Bioinspiration & Biomimetics*, 15, no. 3 (May 2020): pp. 033001. https://doi.org/10.1088/1748-3190/ab654f

52 While some do use the terms biobatteries and biofuel cells interchangeably, distinctions exist between them. In other words, "Technically, the term fuel cell implies that the fuel is supplied from a source external to the device, whereas the term battery implies an internal fuel source, but in practice some papers use the terms interchangeably, in part because some devices can be used in either way" (https://iopscience.iop.org/article/10.1088/1748-3190/ab654f/pdf). Batteries and fuel cells are similar, however, in that both use redox reactions to convert chemical energy to electrical energy.

53 Vasilenko, Violetta, et al. "Glucose-Oxygen Biofuel Cell with Biotic and Abiotic Catalysts: Experimental Research and Mathematical Modeling." *Energies*, 13, no. 21 (October 2020): pp. 5630. https://doi.org/10.3390/en13215630

54 Proffitt, Kyle. "Releasing the Potential of Biobatteries." *Bio-IT World*, 9 February 2022. https://www.bio-itworld.com/news/2022/02/09/releasing-the-potential-of-biobatteries

Enzymatic Fuel Cells

Enzymatic fuel cells use enzymes to catalyze chemical reactions that convert the chemical energy of a biofuel into electricity. Biocatalysts contrast with metal catalysts used in traditional fuel cells. They offer the benefit of cheaper fuels and a wider range of fuel types, as well as avoiding the need for metals.[55] Further, enzymatic fuel cells offer improved safety and biocompatibility. Electrolytes in conventional fuel cells function best in very acidic or very basic solutions,[56] compared to enzymatic fuel cells. Thus, there is substantial research into using enzymatic fuel cells to power wearable or implantable devices that have more neutral pH.[57]

Enzymes are selective for their fuel targets and will still function even if the concentration of the target is low. Thus, the fuel can be inexpensive, impure substances.[58] For example, some enzymatic fuel cells use lactate directly from sweat or tears, allowing them to be powered by the human body, which could yield inexpensive portable devices for low-power applications.[59]

In enzymatic fuel cells, the selectivity of the enzymes means that the chemical reactions can take place in a single compartment, which reduces size requirements,[60] and can result in extremely small fuel cells.[61]

Living cells can use all available energy in sugars through a multi-step process that uses a sequence of different enzymes to fully break down the fuel. Considerable research has been devoted to replicating this process in enzymatic fuel cells, to greatly increase power densities.[62,63] However, many challenges confront implementing a multiple enzyme fuel cell.[64]

55 Dumé, Isabelle. "Improving electron transfer in enzymatic fuel cells." *Physics World*, 11 June 2018. https://physicsworld.com/a/improving-electron-transfer-in-enzymatic-fuel-cells/

56 Xiao, Xinxin, Hong-qi Xia, Ranran Wu, Lu Bai, Lu Yan, Edmond Magner, Serge Cosnier, Elisabeth Lojou, Zhiguang Zhu, and Aihua Liu. "Tackling the Challenges of Enzymatic (Bio)Fuel Cells." *Chemical Reviews*, 119, no. 16 (25 June 2019): pp 9509–9558. https://doi.org/10.1021/acs.chemrev.9b00115

57 Shitanda, Isao, et al. "Paper-Based Lactate Biofuel Cell Array with High Power Output." *Journal of Power Sources*, 489 (March 2021): pp. 229533. *ScienceDirect*, https://doi.org/10.1016/j.jpowsour.2021.229533

58 Xiao, Xinxin, Hong-qi Xia, Ranran Wu, Lu Bai, Lu Yan, Edmond Magner, Serge Cosnier, Elisabeth Lojou, Zhiguang Zhu, and Aihua Liu. "Tackling the Challenges of Enzymatic (Bio)Fuel Cells." *Chemical Reviews*, 119, no. 16 (25 June 2019): pp 9509–9558. https://doi.org/10.1021/acs.chemrev.9b00115

59 Ibid.

60 Yu, Sooyoun, and Nosang V. Myung. "Recent Advances in the Direct Electron Transfer-Enabled Enzymatic Fuel Cells." *Frontiers in Chemistry*, 8 (February 2021). https://doi.org/10.3389/fchem.2020.620153

61 Chen, Ting, et al. "A Miniature Biofuel Cell." *Journal of the American Chemical Society*, 123, no. 35 (September 2001): pp. 8630–31. https://doi.org/10.1021/ja0163164

62 Arechederra, Robert L., et al. "Mitochondrial Bioelectrocatalysis for Biofuel Cell Applications." *Electrochimica Acta*, 54, no. 28 (Dec. 2009): pp. 7268–73. *ScienceDirect*, https://doi.org/10.1016/j.electacta.2009.07.043

63 Sokic-Lazic, Daria, and Shelley D. Minteer. "Citric Acid Cycle Biomimic on a Carbon Electrode." *Biosensors & Bioelectronics*, 24, no. 4 (Dec. 2008): pp. 945–50. *PubMed*, https://doi.org/10.1016/j.bios.2008.07.043

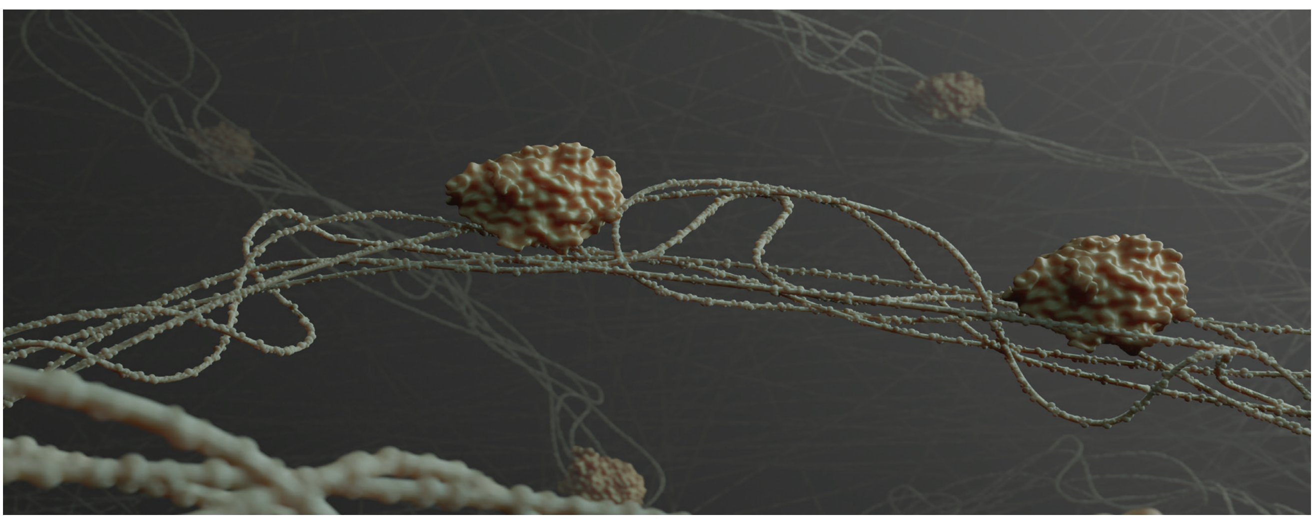
64 Xiao, Xinxin, Hong-qi Xia, Ranran Wu, Lu Bai, Lu Yan, Edmond Magner, Serge Cosnier, Elisabeth Lojou, Zhiguang Zhu, and Aihua Liu. "Tackling the Challenges of Enzymatic (Bio)Fuel Cells." *Chemical Reviews*, 119, no. 16 (25 June 2019): pp 9509–9558. https://doi.org/10.1021/acs.chemrev.9b00115

Other research seeks ways to improve the efficiency of electron transfer with enzymatic fuel cells. One approach is striving to improve electron transfer by enabling direct electron transfer between the enzyme and electrode.[65] Researchers are improving techniques for immobilizing enzymes on the surface of the electrode to perform electron transfer more efficiently. Example research groups in this line of research include the Minteer Research Group at the University of Utah and the Uppsala University's Ångström Laboratory.[66] Promising strategies include using the double-helix structure of DNA to immobilize enzymes on the electrodes,[67] and using conducting polymers such as polyaniline to enhance electrical conductivity between the enzyme and the electrode.[68]

Microbial Fuel Cells

Microbial fuel cells are devices that convert chemical energy to electrical energy using the activities of microorganisms. Microbial fuel cells have the unique advantage of using a variety of microorganisms that can grow, adapt, and regenerate as catalysts.[69]

The realization that microorganisms generate power is not new. As early as 1911, botanist M.C. Potter showed that electricity could be generated from *E. coli*.[70] Since then, studies



65 Yu, Sooyoun, and Nosang V. Myung. "Recent Advances in the Direct Electron Transfer-Enabled Enzymatic Fuel Cells." *Frontiers in Chemistry*, 8 (February 2021). https://doi.org/10.3389/fchem.2020.620153

66 Pollitt, Michael. "Sweet Smell of Success for Biofuel Expert." *The Guardian*, 26 April 2007. https://www.theguardian.com/technology/2007/apr/26/energy.environment

67 Caballar, Rina Diane. "Living Power: This Bio-Battery Is Harnessing the Power of DNA." *Built WithBiology*, April 2021. https://www.builtwithbiology.com/read/living-power-this-bio-battery-is-harnessing-the-power-of-dna

68 Yu, Sooyoun, and Nosang V. Myung. "Recent Advances in the Direct Electron Transfer-Enabled Enzymatic Fuel Cells." *Frontiers in Chemistry*, 8 (February 2021). https://doi.org/10.3389/fchem.2020.620153

69 Obileke, KeChrist, et al. "Microbial Fuel Cells, a Renewable Energy Technology for Bio-Electricity Generation: A Mini-Review." *Electrochemistry Communications*, 125 (April 2021): pp. 107003. https://doi.org/10.1016/j.elecom.2021.107003

70 Pop, Magdalena. "Microbial Fuel Cells." Let's Talk Science, 23 July 2019. https://letstalkscience.ca/educational-resources/stem-in-context/microbial-fuel-cells

have used bacteria like *Geobacter sulfurreducens* to produce tiny electrical currents,[71,72] for applications such as to convert wastewater organic compounds into electricity.[73,74] Other tests have also been conducted using inexpensive common baker's yeast (*Saccharomyces cerevisiae*).[75,76]

Microbial power generation can use many different types of microbes in conjunction, as well as using existing microbes at the site of their intended use. A Spanish start-up called Bioo is developing a microbial fuel cell that uses existing microbes and organic matter in dirt to produce a small electrical current.[77] Bioo is hoping to commercialize their technology as a power source for agricultural sensors and small garden lights.

Note that microbes can regenerate themselves if supplied with nutrients, unlike enzymes and metallic catalysts used in traditional fuel cells, for applications requiring long-term low-maintenance power sources such as environmental sensors.[78] One application involves measuring the power output of the fuel cell to determine if toxins are present, as the harm to the bacteria will cause a corresponding decrease in electricity production.[79]

Another line of research investigates microbial solar cells that uses photosynthetic microorganisms to produce bioelectric power.[80] Photosynthetic microbes can produce small

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71 "Microbial Fuel Cells 1 Bacterial Power." Oregon State University, Bioenergy Education Initiative, accessed 7 March 2022. https://agsci.oregonstate.edu/sites/agsci.oregonstate.edu/files/bioenergy/microbial-fuel-cell-1-activity-v1.3.pdf

72 "Batteries Made of Bacteria?" National Science Foundation, Research News, 19 November 2008. https://www.nsf.gov/discoveries/disc_summ.jsp?cntn_id=112597

73 Ibid.

74 Another promising application for microbial fuel cells is its potential assistance with waste management. Traditional wastewater treatment consumes up to 1-2% of electricity in developed countries, due to high-powered air pumps that oxygenate the water and allow oxygen-requiring microbes to digest the waste. Researchers in Switzerland demonstrated a 1000-liter wastewater fuel cell using anaerobic and electrogenic microbes; the fuel cell was operational for a year, and removed ammonium, phosphorus, and micropollutants from the water, while generating between 0.015 and 0.06 kWh/m3. See: Blatter, Maxime, et al. "Stretched 1000-L Microbial Fuel Cell." *Journal of Power Sources*, 483 (January 2021): pp. 229130. *ScienceDirect*, https://doi.org/10.1016/j.jpowsour.2020.229130

75 Chaturvedi, Venkatesh, and Pradeep Verma. "Microbial fuel cell: a green approach for the utilization of waste for the generation of bioelectricity." *Bioresources and Bioprocessing*, 3, no. 38 (2016). https://bioresourcesbioprocessing.springeropen.com/articles/10.1186/s40643-016-0116-6

76 Silveira, Gustavo, Masaharu Ikegaki, and José Maurício Schneedorf. "A low-cost yeast-based biofuel cell: an educational green approach." *Green Chemistry Letters and Reviews*, 10, no.1 (January 2017): pp. 32-41. https://www.tandfonline.com/doi/full/10.1080/17518253.2016.1278280

77 "Research & Development." Bioo, accessed 7 March 2022. https://www.biootech.com/research

78 Hao, Shuai, Xiaoxuan Sun, He Zhang, Junfeng Zhai, and Shaojun Dong. "Recent development of biofuel cell based self-powered biosensors." *Journal of Materials Chemistry B*, 8 (2020): pp. 3393-3407. https://pubs.rsc.org/en/content/articlelanding/2020/tb/c9tb02428j

79 Chouler, Jon and Mirella Di Lorenzo. "Water quality monitoring in developing countries; can microbial fuel cells be the answer?" *Biosensors*, 5, no. 3 (2015): pp. 450-470. https://purehost.bath.ac.uk/ws/portalfiles/portal/126884381/biosensors_05_00450.pdf

80 Liu, Lin and Seokheun Choi. "Miniature microbial solar cells to power wireless sensor networks." *Biosensors and Bioelectronics*, 177 (April 2021): 112970. https://www.sciencedirect.com/science/article/abs/pii/S0956566321000063

amounts of electricity fueled only by carbon dioxide, water, and sunlight. To date, microbial solar cells have been far less efficient than other microbial fuel cells,[81] but combining non-photosynthetic microbes into a single fuel cell shows promise: one such device demonstrated self-sustained power for 13 days.[82] Microbial solar cells could be well suited for wireless sensor networks but face many challenges.[83]

Development Considerations

The global fuel cell market is estimated to be around $263 million in 2020 and expected to grow to $848 million by 2025,[84] of which biofuel cells are a negligible component. However, biofuel cells show the most promise for bio-compatible and low power devices such as biosensors,[85] and so could grow as the technology matures.

Currently, both enzymatic and microbial fuel cells can generate only low amounts of power. Increasing power efficiency involves improving electron transfer between the enzymes or microbes and the electrodes, and multiple lines of research are exploring different methods to address this problem. Potential solutions for enzymatic fuel cells include using enzyme engineering to change the shape of the enzyme or improving immobilization techniques to keep enzymes in place on the electrode.[86] For microbial fuel cells, electron transfer can be improved by adding chemical mediators,[87] or by using nanowires or conductive pili.[88] The efficiency of the electron transfer process is determined partly by the material of the electrodes, and most highly conductive metals are not suited to microbial fuel cells due to toxicity of metals such as nickel and copper, or surfaces that are too smooth to allow microbes

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81 Rosenbaum, Miriam, Zhen He, and Largus T Angenent. “Light energy to bioelectricity: photosynthetic microbial fuel cells.” *Current Opinion in Biotechnology*, 21, no. 3 (June 2010): pp 259-264. https://www.sciencedirect.com/science/article/abs/pii/S0958166910000510

82 Mohammadifar, Maedeh, Mehdi Tahernia, and Seokheun Choi. “A Miniaturized, Self-Sustaining, and Integrable Bio-Solar Power System.” *Nano Energy*, 72 (June 2020): pp. 104668. https://www.sciencedirect.com/science/article/abs/pii/S2211285520302251
In this type of symbiotic microbial fuel cell, the photosynthetic microbes do not directly produce electricity, but instead support the power production of non-photosynthetic microbes.

83 One obstacle to truly self-sustaining microbial solar cells (MSCs) is the requirement for a constant supply of water. Several attempts to deploy MSCs in harsh non-laboratory environments have been foiled by functional failure due to inconsistent access to water. https://www.sciencedirect.com/science/article/abs/pii/S0956566321000063

84 “Fuel Cell Market.” Markets and Markets, Report Code EP 2762, December 2020. https://www.marketsandmarkets.com/Market-Reports/fuel-cell-market-348.html

85 Koffi, N’Dah Joel, and Satoshi Okabe. “High voltage generation from wastewater by microbial fuel cells equipped with a newly designed low voltage booster multiplier (LVBM).” *Scientific Reports*, 10 (4 November 2020): 18985. https://www.nature.com/articles/s41598-020-75916-7

86 Yu, Sooyoun, and Nosang V. Myung. “Recent Advances in the Direct Electron Transfer-Enabled Enzymatic Fuel Cells.” *Frontiers in Chemistry*, 8, 10 February 2021. https://www.frontiersin.org/articles/10.3389/fchem.2020.620153/full

87 Logan, Bruce, H.V.M. Hamelers, Rene Rozendal, Uwe Schröder, Jürg Keller, Stefano Freguia, Peter Aelterman, Willy Verstraete, and Korneel Rabaey. “Microbial Fuel Cells: Methodology and Technology.” *Environmental Science and Technology*, 40, no. 17 (October 2006): pp. 5181-92. https://www.researchgate.net/publication/6795702_Microbial_Fuel_Cells_Methodology_and_Technology

88 Aiyer, Kartik.S. “How does electron transfer occur in microbial fuel cells?” *World Journal of Microbiology and Biotechnology*, 36, no. 19 (January 2020). https://link.springer.com/article/10.1007/s11274-020-2801-z

to attach to metal such as titanium, platinum, and stainless steel.[89] Therefore, there is a great deal of interest in using novel materials such as conductive polymers or nanomaterials to coat electrodes.[90]

Biofuel cells are primarily appealing for applications such as wireless sensor networks, remote water quality monitoring devices, and other transient electronics.[91,92,93] The self-regenerating nature of microbial fuel cells is an advantage. Enzymatic fuel cells, on the other hand, are likely best suited for portable and short-term applications, particularly wearable and implantable devices which are conducive to being powered by human bodily fluids such as sweat or urine.[94]

All types of biofuel cells face challenges of stability. Enzymes in enzymatic fuel cells are susceptible to denaturation when exposed to elevated temperatures, pH extremes, or high concentrations of certain chemicals, while microbial fuel cells contain living organisms that must be kept alive. In general, microbial fuel cells are more stable than enzymatic fuel cells due to microbes' capacity to regenerate.[95] Research is ongoing to improve stability of enzymatic fuel cells, including using enzymes derived from microbes that naturally live in extreme conditions, modifying the structure of the enzyme, or encapsulating enzymes in a protective polymer.[96]

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89 Akçay, Gizem, and Irfan Ar. "Review on microbial fuel cell technologies: Recent developments in electrode materials." Proceedings Book, International Eurasian Conference on Biotechnology and Biochemistry (BioTechBioChem 2020), Ankara, 16-18 December 2020. https://www.researchgate.net/publication/347491641_Review_on_microbial_fuel_cell_technologies_Recent_developments_in_electrode_materials

90 Xiao, Xinxin, Hong-qi Xia, Ranran Wu, Lu Bai, Lu Yan, Edmond Magner, Serge Cosnier, Elisabeth Lojou, Zhiguang Zhu, and Aihua Liu. "Tackling the Challenges of Enzymatic (Bio)Fuel Cells." *Chemical Reviews*, 119, no. 16 (June 2019): pp 9509–9558. https://pubs.acs.org/doi/10.1021/acs.chemrev.9b00115

91 Knight, Chris, Kate Cavanagh, Christopher Munnings, Tim Moore, Ka Yu Cheng, and Anna H. Kaksonen. "Application of Microbial Fuel Cells to Power Sensor Networks for Ecological Monitoring." *Wireless Sensor Networks and Ecological Monitoring*, 3 (2013): pp. 151-178. https://link.springer.com/chapter/10.1007/978-3-642-36365-8_6

92 Microbial fuel cells could enable powering of transient (or "disposable") electronic devices, which have many advantages for sensor applications, including reduced risk of cross-contamination if testing multiple samples and lower changes of information leakage. See https://par.nsf.gov/servlets/purl/10106011 for more information.

93 Chouler, Jon and Mirella Di Lorenzo. "Water quality monitoring in developing countries; can microbial fuel cells be the answer?" *Biosensors*, 5, no. 3 (2015): pp. 450-470. https://purehost.bath.ac.uk/ws/portalfiles/portal/126884381/biosensors_05_00450.pdf

94 Nasar, Abu, and Ruma Perveen. "Applications of enzymatic biofuel cells in bioelectronic devices – A review." *International Journal of Hydrogen Energy*, 44, no. 29 (June 2019): pp. 15287-15312. https://www.sciencedirect.com/science/article/abs/pii/S0360319919316155

95 Gao, Yang, Maedeh Mohammadifar, and Seokheun Choi. "From Microbial Fuel Cells to Biobatteries: Moving toward On-Demand Micropower Generation for Small-Scale Single-Use Applications." Advanced Materials Technology (2019), 1900079. https://par.nsf.gov/servlets/purl/10106011

96 Xiao, Xinxin, Hong-qi Xia, Ranran Wu, Lu Bai, Lu Yan, Edmond Magner, Serge Cosnier, Elisabeth Lojou, Zhiguang Zhu, and Aihua Liu. "Tackling the Challenges of Enzymatic (Bio)Fuel Cells." *Chemical Reviews*, 119, no. 16 (June 2019): pp 9509–9558. https://pubs.acs.org/doi/10.1021/acs.chemrev.9b00115

Biology-Based Information Systems

An intriguing but nascent possibility is the development of information systems based on biology. The possibilities include future processing infrastructure and long-term data storage of massive amounts of data.

Traditional computing methods based on semiconductors and silicon chips are approaching fabrication limits as Moore's Law physical scaling ends. Processor power dissipation is now the key factor defining performance for computing. Biological processes offer the possibility of tremendous power efficiencies, resilience, and temperature stability. Biological systems naturally permit highly parallel processing. Most importantly, DNA can achieve unprecedented data storage densities. Biological means for processing and storing data could become a new paradigm for information systems.

Storage

Incredible data densities can be achieved by using DNA sequences to represent digital data. As reported in a Scientific American article on the topic, 33 zettabytes can be crammed into a volume the size of a ping-pong ball,[97] equivalent to the estimated total amount of data generated by humanity by 2025. DNA-based storage might be the ideal way to archive massive continuous data collection, as in, for example, a life-log.[98] Once a sequence is constructed, it is highly stable and easily replicated. While retrieval to readout the data will always be slow, random-access retrieval of data could be achieved through efficient indexing schemes.[99] Retrieval through associative search (i.e., finding content that matches a key word) should also be possible using enzyme processes.

Another effort in DNA storage is based on a system composed of single strand DNA conjugated with a protein.[100] This enables functions including "information reinforcement," "information regulation," and "information amplification," based on changing oxidation and reduction states in the protein.

While the DNA storage concept is mostly theoretical, there is preliminary industry interest. For example, the IMEC research consortium in Belgium is part of an alliance to explore the

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97 Ionkov, Latchesar and Bradley Settlemyer. "DNA, The Ultimate Data Storage Solution." *Scientific American*, 28 May 2021. https://www.scientificamerican.com/article/dna-the-ultimate-data-storage-solution/

98 "Pentagon Explores a New Frontier In the World of Virtual Intelligence." *The New York Times,* 30 May 2003. https://www.nytimes.com/2003/05/30/us/pentagon-explores-a-new-frontier-in-the-world-of-virtual-intelligence.html

99 Organick, L., Ang, S., Chen, YJ. *et al.* "Erratum: Random access in large-scale DNA data storage." *Nature Biotechnology*, 36, no. 660 (2018): pp 242–248. https://www.nature.com/articles/nbt0718-660c

100 Choi, Jeong-Woo, Taek Lee, and Jun Hong Min. "Bioprocessing Device." United States and Trademark Office, United States Patent Application 20150005479, filed October 4, 2013, and issued August 1, 2017. https://appft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/srchnum.html&r=1&f=G&l=50&d=PG01&s1=20150005479.PGNR

DNA data storage concept, developing a corresponding roadmap.[101]

Computing

Beyond storage, it is observed that biological processes might enable new approaches to computing. There is much academic interest in the concept of using DNA to perform computation,[102] and more broadly in biological computing, which uses biologically derived molecules to perform either digital or analog computations.[103] These concepts are a subfield of the field of nanotechnology.

Most applications of biological principles to computing applications are still in very early stages of development. The notion of "cellular supremacy" is defined as when a biological process clearly outperforms a standard electronics process (e.g., in terms of power efficiency, speed, parallelism, resiliency), but to date it cannot claim to have been achieved.[104]

As with DNA storage, an advantage of biological computing is that processing elements can be extremely compact. Computation can be implemented by altering segments of the coded DNA patterns, using enzyme processes similar to those involving CRISPR-Cas9. Industries that have shown interest in developing these capabilities include Microsoft, Twist Bioscience Inc, and Western Digital.

Biological computing might also offer faster, more efficient ways to solve certain problems using analog techniques. For example, analog based computation might be used for certain combinatorial optimization problems.[105] Network-based bio-computation principles are being explored by a Fraunhofer Institute for Electronic Nano Systems (ENAS) group.[106] Nanopatterned structures are leveraged together with biological microtubules to perform basic computations. The nanopatterned network route chosen by the biological materials transiting the system represents the answer to an optimization problem. The work is part of an EU-funded project called Bio4Comp,[107] which in turn is presented at a conference of the

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101 "Twist Bioscience, Illumina and Western Digital Form Alliance with Microsoft to Advance Data Storage in DNA." IMEC, 12 November 2020. https://www.imec-int.com/en/press/twist-bioscience-illumina-and-western-digital-form-alliance-microsoft-advance-data-storage

102 "27th International Conference on DNA Computing and Molecular Programming." Institute of Physics, September 2021. http://dna27.iopconfs.org/home

103 Uppal, Rajesh. "Highly Energy Efficient Biological Supercomputers Being Achieved by Bio Breakthroughs." International Defense Security & Technology Inc., 24 January 2020. https://idstch.com/technology/ict/biocomputers-dna-computers-future-low-energy-low-cost-parallel-supercomputers/

104 Grozinger, L., Amos, M., Gorochowski, T.E. *et al.* "Pathways to cellular supremacy in biocomputing." *Nature Communications*, 10 (2019): pp. 5250. https://www.nature.com/articles/s41467-019-13232-z

105 Sarpeshkar, R. "Analog synthetic biology." *Philosophical transactions. Series A, Mathematical, physical, and engineering sciences*, *372* (2012): 20130110. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928905/

106 "Demonstration on the Fabrication of Biocomputational Devices." Fraunhofer ENAS, accessed 1 February 2022. https://www.enas.fraunhofer.de/en/business_units/micro_and_nanoelectronics/Beyond_CMOS_and_RF_devices/Demonstration_on_the_Fabrication_of_Biocomputational_Devices.html

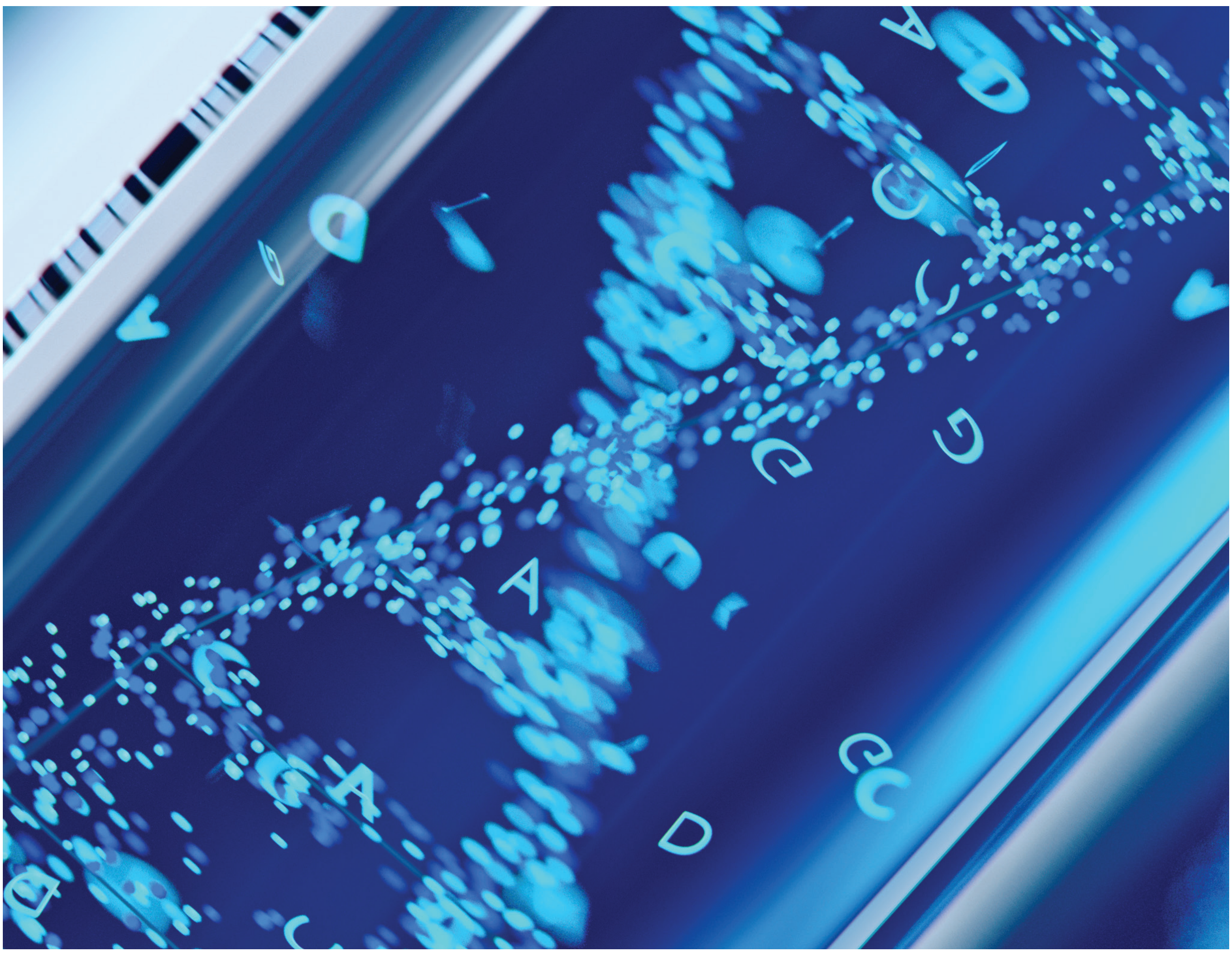
107 "Functional nano structures for biocomputing." Fraunhofer ENAS, accessed 1 February 2022. https://www.enas.fraunhofer.de/en/business_units/micro_and_nanoelectronics/Beyond_CMOS_and_RF_devices/Functional_Nano_Structures_for_Biocomputing.html

European Materials Research Society.[108]

Development Considerations

Market estimates indicate the global DNA data storage market could grow to $525.3 million by 2025 from an estimated $36.4 million,[109] under the assumption that the technology works out.

Practical developments of biological computing are yet more speculative. Challenges for commercialization include the overall cost and time required to read and write DNA sequences, along with error correction methods. Nonetheless, biological computing mechanisms hold potentially attractive prospects in a "post-Moore" world.



108 "E-MRS-Symposium Biocomputation 2020 – Call for abstracts, deadline January 15, 2020." Fraunhofer Institute for Silicate Research ISC, accessed 7 March 2022. https://www.isc.fraunhofer.de/en/fairs-and-events/fairs-and-events-2020/e-mrs-symposium-biocomputation2020.html

109 "DNA Data Storage: Global Markets and Technologies." Research and Markets, Report ID 5232553, December 2020. https://www.researchandmarkets.com/reports/5232553/dna-data-storage-global-markets-and-technologies?utm_source=BW&utm_medium=PressRelease&utm_code=jkwl29&utm_campaign=1531334

Concluding Comments

The growing convergence of biology and electronics will lead to new applications and new capabilities. The example application areas discussed here all employ some biological process or insight which is then integrated into an electronic device, to provide new capabilities in sensors, fuels, and processing systems. The resulting technologies, when properly developed, would be a significant part of a future bioeconomy.

Other application areas might benefit from the convergence. As living organisms have unique capabilities such as sensing, self-propagation, and autonomous action, opportunity is ripe to explore mimicking biology's designs. Currently, healthcare and medical applications dominate forward momentum in the transition to initial products. Further research will have to demonstrate biology's potential to provide a competitive advantage over current techniques.

Much of the anticipated applications surrounding biology in electronics are still in early research stages. Biosensors are the most developed due to the interest of the health industry. Academia continues work on the fundamentals for monitoring phenomena in the environment and developing tests for engineering applications. Biofuel cell technology, applicable to specialized applications, faces engineering challenges before major market insertion. Information technology applications of biological processes will need to outperform current silicon-based electronics. In all cases, however, further research and development is likely to overcome challenges.

As part of the R&D process, researchers are likely to reveal knowledge about how nature operates. For example, some animals detect certain phenomena more efficiently than humans, and the behavior of different types of bacteria might be unlocked.

Furthermore, interdisciplinary research is often challenged by inconsistencies in terminology. There are struggles between groups with the meanings of biosensor, biobattery, and bioelectronics as examples. However, the benefits of convergence of fields provides great progress in turning knowledge into new applications.

The hurdles involved in scaling up technologies to production also pose challenges. Much might be learned about manufacturing techniques, particularly in the nano-technologies areas.

In the development of new technologies, the newcomer is rarely significantly "better" than the incumbent at first. The newcomer realizes big advantages in smaller "niche" applications and must continue development before it can dethrone incumbent technologies. Compelling motivations for adopting biological approaches will ultimately drive applications. For the applications that have been surveyed here, there are not yet substantial commercial markets. However, we believe that these areas will provide important new capabilities in the future as envisioned by the science, and thus the motivation for transitioning innovative research into development is strong. Indeed, biologically enabled approaches to developing commercially viable products could easily be the cause of the next industrial revolution.

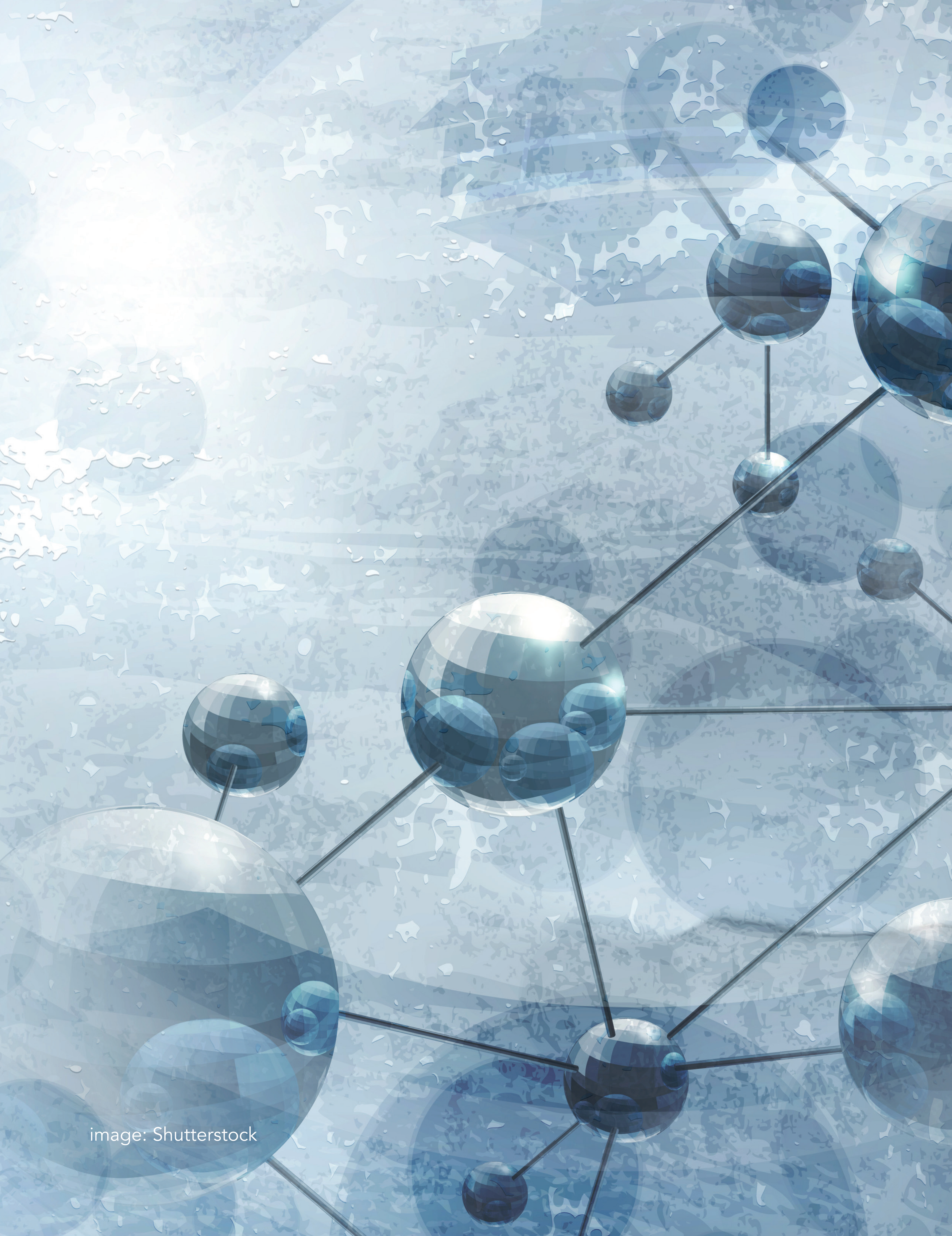


image: Shutterstock