Bio-based communication networks could control cells in the body to treat conditions

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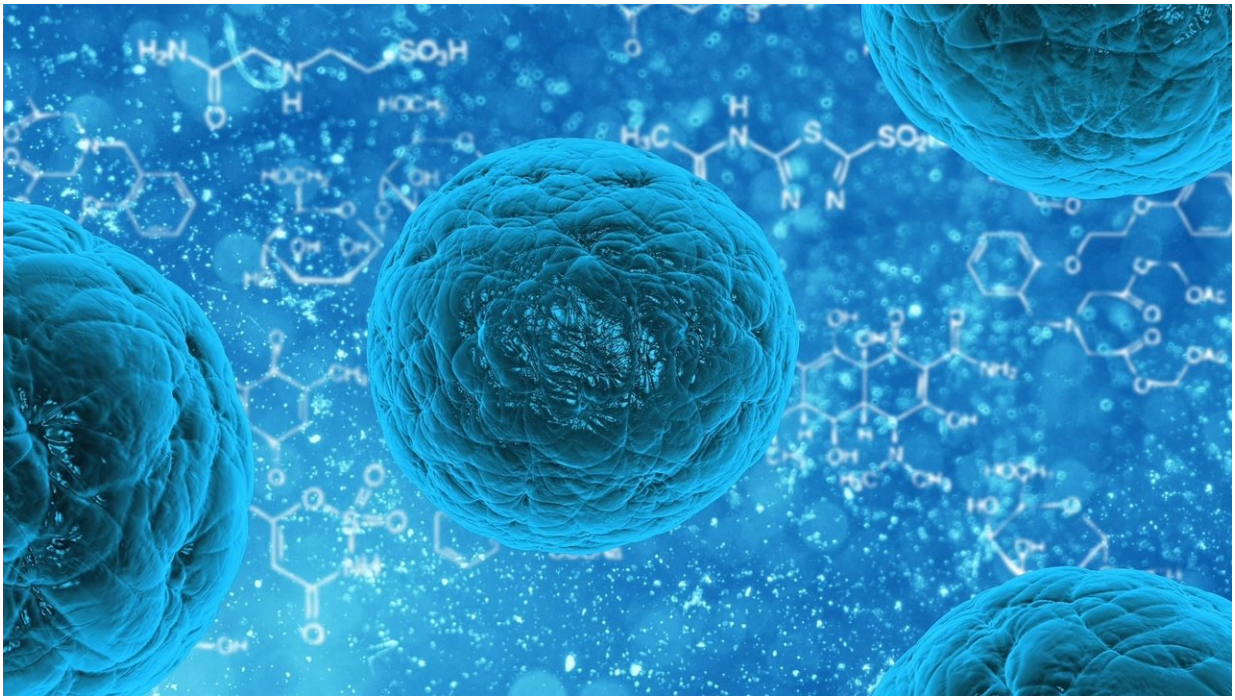

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Like electronic devices, biological cells send and receive messages, but they communicate through very different mechanisms. Now, scientists report progress on tiny communication networks that overcome this language barrier, allowing electronics to eavesdrop on cells and alter their behavior—and vice versa. These systems could enable applications including a wearable device that could diagnose and treat a bacterial

infection or a capsule that could be swallowed to track blood sugar and make insulin when needed.

The researchers will present their results today at the American Chemical Society (ACS) Fall 2020 Virtual Meeting & Expo.

"We want to expand electronic information processing to include biology," says principal investigator William E. Bentley, Ph.D. "Our goal is to incorporate biological cells in the computational decision-making process."

The new technology Bentley's team developed relies on redox mediators, which move electrons around cells. These small molecules carry out cellular activities by accepting or giving up electrons through reduction or oxidation reactions. Because they can also exchange electrons with electrodes, thereby producing a current, redox mediators can bridge the gap between hardware and living tissue. In ongoing work, the team, which includes co-principal investigator Gregory F. Payne, Ph.D., is developing interfaces to enable this information exchange, opening the way for electronic control of cellular behavior, as well as cellular feedback that could operate electronics.

"In one project that we are reporting on at the meeting, we engineered cells to receive electronically generated information and transmit it as molecular cues," says Eric VanArsdale, a graduate student in Bentley's lab at the University of Maryland, who is presenting the latest results at the meeting. The cells were designed to detect and respond to hydrogen peroxide. When placed near a charged electrode that generated this redox mediator, the cells produced a corresponding amount of a quorum sensing molecule that bacteria use to signal to each other and modulate behavior by altering gene expression.

In another recent project, the team engineered two types of cells to

receive molecular information from the pathogenic bacteria *Pseudomonas aeruginosa* and convert it into an electronic signal for diagnostic and other applications. One group of cells produced the amino acid tyrosine, and another group made tyrosinase, which converts tyrosine into a molecule called L-DOPA. The cells were engineered so this redox mediator would be produced only if the bacteria released both a quorum sensing molecule and a toxin associated with a virulent stage of *P. aeruginosa* growth. The size of the resulting current generated by L-DOPA indicated the amount of bacteria and toxin present in a sample. If used in a blood test, the technique could reveal an infection and also gauge its severity. Because this information would be in electronic form, it could be wirelessly transmitted to a doctor's office and a patient's cell phone to inform them about the infection, Bentley says. "Ultimately, we could engineer it so that a wearable device would be triggered to give the patient a therapeutic after an infection is detected."

The researchers envision eventually integrating the communication networks into autonomous systems in the body. For instance, a diabetes patient could swallow a capsule containing cells that monitor blood sugar. The device would store this blood sugar data and periodically send it to a cell phone, which would interpret the data and send back an electronic signal directing other cells in the capsule to make insulin as needed. As a step toward this goal, VanArsdale developed a biological analog of computer memory that uses the natural pigment melanin to store information and direct cellular signaling.

In other work, Bentley's team and collaborators including Reza Ghodssi, Ph.D., recently designed a system to monitor conditions inside industrial bioreactors that hold thousands of gallons of cell culture for drug production. Currently, manufacturers track oxygen levels, which are vital to cells' productivity, with a single probe in the side of each vessel. That probe can't confirm conditions are uniform everywhere in the bioreactor, so the researchers developed "smart marbles" that will

circulate throughout the vessel measuring oxygen. The marbles transmit data via Bluetooth to a cell phone that could adjust operating conditions. In the future, these smart marbles could serve as a communication interface to detect chemical signals within a bioreactor, send that information to a computer, and then transmit electronic signals to direct the behavior of engineered cells in the bioreactor. The team is working with instrument makers interested in commercializing the design, which could be adapted for environmental monitoring and other uses.

More information: Connecting biology to electronics through a redox communication network of tyrosine, tyrosinase, and eumelanin:

Abstract
Systemic control of cellular physiology will allow for the design of synthetic electronic-biological communication networks, capable of coordinating physiology across large distances, disparate environments, and varied time scales. In order to achieve this connectivity, we have begun to develop cellular equivalents of network technology. To do this, we have engineered a coculture transducer system in which cells convert molecular communication into a redox signal by synthesizing both the catalytic and reagent components of an oxidative reaction. The "catalytic" transducer cell population integrates molecular cues to regulate the expression of a surface-linked tyrosinase. Similarly, the "reagent" transducer cell population regulates the synthesis of the enzyme-substrate L-tyrosine, which is converted by the catalytic transducer cell population into the redox signal L-DOPA. In cocultures, this system enables real-time electrochemical detection of molecular information by measuring the oxidative current of L-DOPA. This system was able to eavesdrop on cell-cell molecular communication, which we demonstrate by intercepting the quorum sensing signals of Pseudomonas aerugionosa. We have also adapted this system to receive electronic signals through "transmitter" cells that produce quorum sensing signals in response to electrochemically generated hydrogen peroxide. Finally, we

have stored cellular and electronic information in cellularly-produced "hard drives" to store redox memory, through controlled oxidation and reduction of the catechol-quinone groups of eumelanin with redox mediators. The melanin memory units were capable of directing cellular signaling, either by attenuating or amplifying the oxidative signature of a mediator mixture. Together, these cellular units allow for regulated information exchange with biology to allow for rational, user-guided cellular communication and physiology.

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