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Platform technologies to support brain–computer interfaces

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✓ There is a lack of adequate and cost-effective treatment options for many neurodegenerative diseases. The number of affected patients is in the millions, and this number will only increase as the population ages. The developing areas of neuromimetics and stimulative implants provide hope for treatment, as evidenced by the currently available, but limited, implants. New technologies are emerging that are leading to the development of highly intelligent, implantable sensors, activators, and mobile robots that will provide in vivo diagnosis, therapeutic interventions, and functional replacement. Two key platform technologies that are required to facilitate the development of these neuromimetic and stimulative implants are data communication channels and the devices' power supplies. In the research reported in this paper, investigators have examined the use of novel concepts that address these two needs. These concepts are based on ionic volume conduction (VC) to provide a natural communication channel to support the functioning of these devices, and on biofuel cells to provide a continuously rechargeable power supply that obtains electrons from the natural metabolic pathways. The fundamental principles of the VC communication channels, including novel antenna design, are demonstrated. These principles include the basic mechanisms, device sensitivity, bidirectionality of communication, and signal recovery. The demonstrations are conducted using mathematical and finite element analysis, physical experiments, and animal experiments. The fundamental concepts of the biofuel cells are presented, and three versions of the cells that have been studied are discussed, including bacteria-based cells and two white cell–based experiments. In this paper the authors summarize the proof or principal experiments for both a biomimetic data channel communication method and a biofuel cell approach, which promise to provide innovative platform technologies to support complex devices that will be ready for implantation in the human nervous system in the next decade.

KEY WORDS • brain–machine interface • implantable neural device • volume conduction • biofuel cell

IT has been estimated that in the US alone, there are 1.5 million patients with Parkinson disease; 4.5 million with Alzheimer disease; 2.5 million with epilepsy; 2 million with spinal cord injury, amyotrophic lateral sclerosis, or stroke; 10 million with severe depression; and 1 million who are blind.[39] These numbers will only increase as the population grows and ages, and life expectancy increases. Because of the limitations and high costs of existing therapeutic options, many of these patients are not treated effectively or remain untreated. The rapidly developing areas of neuromimetics and stimulative implants provide hope for the treatment of these diseases, particularly as the level of sophistication of the devices increases and costs are driven down.[1]

Emerging Technologies

Submicron electronics, nanotechnology, and microelectromechanical chips have emerged, all of which will have a profound impact on the structure and performance of devices presently in development, and consequently on the future practice of neurosurgery. Using these technologies, microscopic yet highly intelligent implantable sensors and mobile robots will be built to perform in vivo diagnosis, therapeutic interventions, and functional replacement.[12,21,50,54,55] The eventual integration of these developing devices will depend on the advancement of two critical platform technologies needed to provide their effective support: a wireless data communication link, which allows data exchange between an external computer and an implanted device, and a power supply that does not require external recharging.

Although researchers in laboratories around the world have reported development of a variety of neural implants, most of the devices are only prototypes.[17] Up to the present time, only a few types of neural implants have been routinely used in clinical applications.[12] These include cochlear implants (~ 70,000 cases), deep brain stimulators for treating Parkinson disease and dystonia (~ 30,000 cases), and vagal nerve stimulators for treating epilepsy and depression (~ 30,000 cases). Auditory brainstem implants are also available and have been implanted in approximately 100 patients. It appears that the dawn of clinical applications for neural implants is unfolding, and these devices will provide viable treatment options in the near future.

Abbreviations used in this paper: EEG = electroencephalography; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate; RF = radiofrequency; VC = volume conduction.

Obstacles

We have been investigating two fundamental issues that presently serve as significant obstacles in the function, utility, and efficacy of implantable neural devices, and we are exploring two novel approaches as platform technologies to develop more effective devices of the types previously discussed. The two important issues are as follows: 1) data communication between implantable devices and the external environment; and 2) energy supply and delivery to the implanted device. We are pursuing the development of a wireless data communication system based on the principle of VC, which is the inherent ability of ionic fluids in the body to conduct electrical currents. Our group is also exploring a power supply based on the principle of the interception of electrons released during cellular metabolism.

In this paper we summarize results in both the areas of data communication and power supply. First, we present background information about discoveries that have motivated our investigation of these problems. Second, we summarize our results in the investigation of a VC channel for data communication. These include results of theoretical investigations of the VC approach by using finite element methods, construction of hardware prototypes to assess the feasibility of this approach, and development of signal detection and extraction algorithms for noise removal and to enhance the reliability of data communication. Third, we outline the power extraction approach and present results of experiments demonstrating that implanted devices may be powered by energy scavenged from ongoing cellular processes. Finally, we discuss the implications of this work.

Existing Methods

The explosive advances in information technology, microelectronics, nanotechnology, and microelectromechanical chips have produced technologies that enable the development of highly intelligent implantable devices, even ones that possess biomimetic/neuromimetic features suitable for implantation in the human nervous system.[1] As implantable devices become increasingly sophisticated, they depend on advanced computational/signal processing technology to provide their maximum impact. Therefore, two-way data communication will be required to control their functionality, to monitor their effects, and to download or upload programs or commands from outside the body. Until the present, data communication through tissue was not a major problem, because most implantable devices were relatively primitive from the perspective of information content. Nevertheless, the information content of these devices is rapidly increasing, creating a greater need for efficiency and efficacy in data transfer.

Two Design Approaches

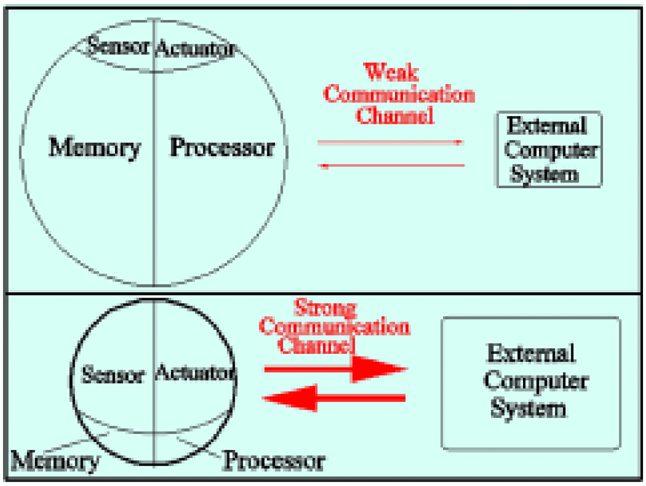

FIG. 1. Schematics showing two design approaches for implantable devices. *Upper:* Strong onboard processing and storage, weak data interface with the external computer. *Lower:* Weak onboard processing, strong data communication link.

There are at least two approaches to the design of information-rich, computationally related implantable devices (Fig. 1). The first approach (Fig. 1 *upper*) is biased toward a self-contained system that consists of a powerful onboard data processor. This device is able to act on its own without a strong data interface to the external world. The second approach (Fig. 1 *lower*) uses a small onboard computer; that is, its data processor and memory are less powerful, and a much larger and more powerful computer is located outside the biological system, requiring a strong internal–external data link.

Comparing the two approaches, it is apparent that the second has many advantages. An implantable device with a small onboard data processor linked to an external computer can be greatly simplified, with only essential components included. Therefore, it can be highly miniaturized, requiring less power. The implantable device based on the second approach may be much "smarter" than that produced by the first approach, because in the external world there exists essentially unlimited computational power. In addition, the second approach always allows changes and updates of software, whereas the first approach is more restricted in this regard. It is clear that to implement the second approach, we must establish a strong, miniaturizable data communication channel.

Communication Methods

There exist several signal transmission modalities that are used for internal–external data communication. Direct wire connections[35] have been used for temporary data recordings, such as in the implantation of subdural electrodes on the cortex of patients with epilepsy. This approach has the obvious drawbacks of possible infection and lack of suitability for long-term use.[27] Radiofrequency telemetry has been commonly used in implantable devices.[21,22,50,54] In this method, an RF signal is transmitted using an antenna, which can be either a dipole antenna similar to the ones used in cell phones, or a coil of wire operating on the principle of magnetic inductive coupling shown in Fig. 2. Use of RF telemetry has a major advantage in that it allows a relatively high rate of data transmission when the carrier frequency is high. The data rate is important in multichannel, multisite neural recording, in which large data sets must be transmitted. However, the

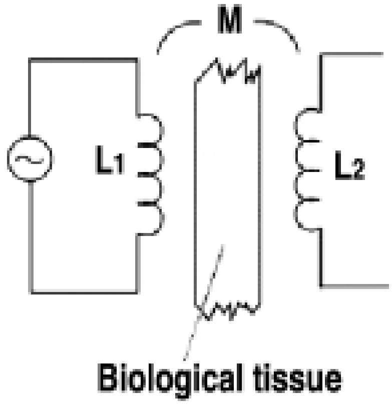

FIG. 2. Drawing showing the principle of magnetic inductive coupling that forms the basis of RF telemetry. L_1 = primary coil; L_2 = secondary coil.

RF method has a low transmission efficiency in biological tissue. Not only do the antenna and certain circuit elements (for example, induction coils) limit the miniaturization of the implantable device, but the ionic fluid is also highly conductive, which makes transmission possible only when the RF signal is strong and its frequency is relatively low.

Optical transcutaneous telemetry systems[10,13,24] involve an optical coupler with an infrared laser diode as the transmitter and a photo diode as the receiver. During data communication, the electrical signal to be sent is first converted to an illumination signal by the laser diode. After passing through the skin, the signal is received by the photo diode, which converts the illumination signal back to an electrical current, from which the transmitted message is resolved. It has been reported that this modality, using phase shift keying modulation, is capable of transmitting data at a rate of 9600 bits per second through semitransparent goat skin 4 mm thick;[13] however, it has the drawback of a short communication range.

There are other less frequently applied data communication modalities, such as those based on ultrasound waves[5] and magnetic fields.[51,52] The ultrasound approaches feature a piezoelectric transducer similar to that used in Doppler flowmeters and acoustic imaging instruments. Because ultrasound attenuates rapidly after traveling through the bone and air, and an accurate alignment between the transmitter and receiver is required, the application of this modality is highly limited. Magnetic field approaches use a controlled magnet that delivers information to a coiled receiver by using a varying magnetic field. This modality has been used to activate reed switches within deep brain stimulators;[51,52] however, this approach also has the disadvantage of limited operational distance as well as lack of miniaturization.

Power Supplies

Battery Power. A nonrechargeable battery is the most popular power source used in commercial neural implants. For example, the Medtronic Soletra neurostimulator uses a 3.7-V lithium ion battery, which is sealed, along with the pulse generator circuit, within an oval titanium case.[52,53] According to the manufacturer's specifications, the battery life varies widely with energy use, depending on the choice of stimulation parameters.

Magnetic Coupling. Besides its use in communications, magnetic inductive coupling is a dominant method for power delivery. It uses a transformer-like device consisting of primary and secondary coils, as shown in Fig. 2. When an RF signal is applied to the primary coil, current is induced in the secondary coil through mutual inductance. The magnetic coupling technique has been applied to several prototype systems.[9,26,57] This simple method has a major drawback in that its efficiency in power delivery is generally poor due to the energy loss in conductive biological tissue.[14] Also, intracranial neural implants must be small, which limits the size of the secondary coil. As the coil size is reduced, there is a rapid decline in magnetic flux captured by the secondary coil. To maintain a sufficient amount of power transfer, however, a strong current must be delivered to the primary coil. This may require patients to carry a large exterior power source, which can be an inconvenience in their daily lives.

Data Channels for VC

We have been investigating the VC properties of the human body as mechanisms for data communication (Fig. 3). When compared with the existing approaches, this one does not require conversion of biological data into RF electromagnetic waves or nonelectrical physical variables. The ionic fluid in the body conducts electric current which, when intentionally manipulated, is capable of transmitting information. This mechanism has been used to send data from inside a dolphin to a pair of remotely located electrodes placed in sea water,[22] to transmit information from a sensor implanted within a leg of a cadaver to perform mechanical measurements,[20,23] and to send information by using a VC body bus.[53] where digital signals are carried along the surface of the body.

Advantages. Electrostatic theory states that a current source within a volume conductor results in an electrical potential distribution within and on the surface of the conductor.[11] Using this physical principle, a data communication system may be built that has the following advantages: 1) the shielding effect of ionic fluid in the body,

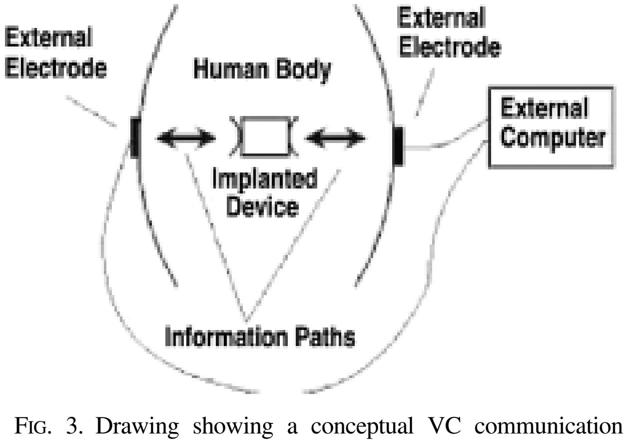

FIG. 3. Drawing showing a conceptual VC communication system.

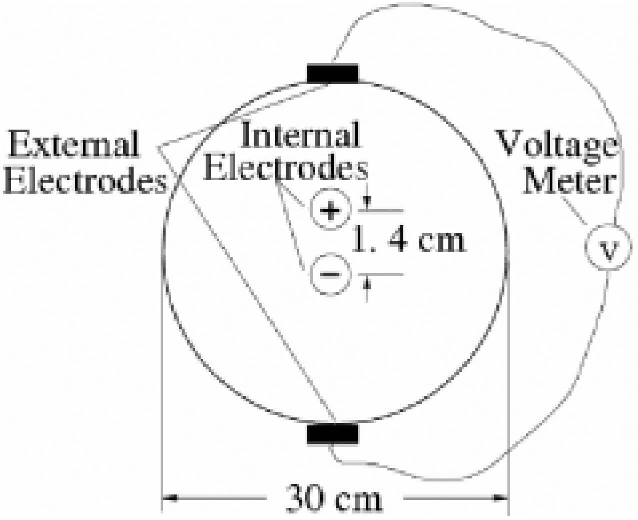

FIG. 4. Drawing showing a spherical torso model with a central dipole of electrocardiogram electrodes on the skin surface of the "torso" at the locations depicted.

rather than being a problem, is instead the information carrier; 2) this method is the simplest, with the exception of a direct wire connection; 3) conversion of data from a biological signal to a different physical variable is not required; 4) the transmitting and receiving elements of the system, which are both electrodes, can be used to pass information bidirectionally; and 5) electrical connection is naturally established as long as the implanted device contacts the fluid environment within conductive biological tissues.

Disadvantages. Although there are significant advantages to the VC approach, there are also limitations, as follows: 1) the bandwidth of the new system is not as wide as systems based on either RF or optical modalities; 2) physical attachment of electrodes to the skin is required to receive from, or transmit to, the implanted device; 3) the information channel provided by VC within the human body may have certain nonlinearities; 4) poor electrode contact to biological tissues or body fluid may cause noise or even interruption in the data communication channel; 5) normal biological activities, such as those of the heart, respiratory, digestive, and nervous systems, generate electrical noise that may interfere with data transmission; and 6) injecting excessive current into tissues may affect the normal functioning of the central nervous system.

Sensitivity Assessment

A fundamental question is whether this mechanism is feasible. Specifically, will this system have sufficient sensitivity? Because the human body is a well-known noise source, if the transmitted signal is not strong enough at a certain distance from the signal source, there could be no hope of detecting it. This sensitivity question is critical. Theory indicates that, for a current dipole in a homogeneous conductor volume of infinite extent, electrical potential attenuates in proportion to the squared distance between the source and the point of measure.[11] Clearly, this attenuation is fairly rapid. Theory also states, however, that the potential never drops to zero as long as the conductor volume is continuous. This is exactly the case with the human body. Therefore, the signal will always be present no matter how great the distance from the transmitter. Nevertheless, how strong is the signal? It must have sufficient strength at a reasonable distance for it to be observable above the noise and to be useful as a data carrier.

To show the feasibility of VC, we performed a simple analysis based on a highly simplified volume conductor model of the torso. We considered the ideal case with absence of noise and the voltage on the surface of the model (at the points of "voltage meter" connection in Fig. 4) in

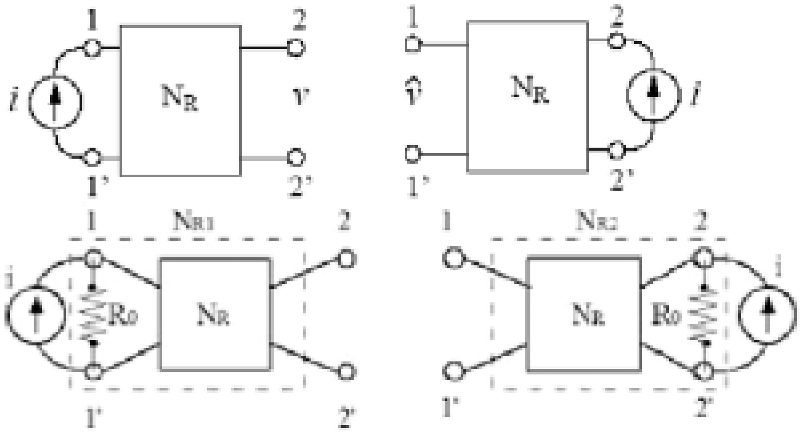

FIG. 5. Schematics showing a proposed VC communication system. *Upper:* In the ideal VC communication system, the transmission and reception can be theoretically modeled as a linear two-port network with a current source input (i) and a voltage (v) output. Based on the reciprocity of the linear system, it can be shown that v and $\hat{v}$ are equal. *Lower:* A more realistic model of the communication system. The output impedance of the transmitter alters the system transfer function.

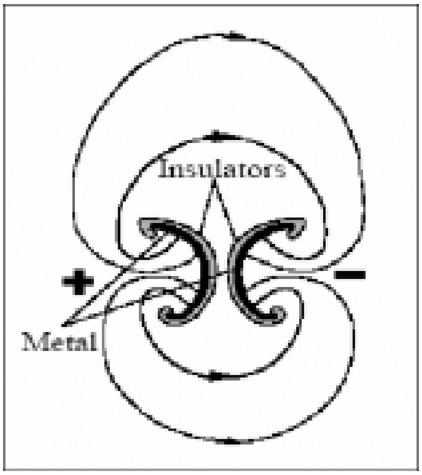

FIG. 6. Drawing showing the *x*-antenna minimizing the near field and maximizing the far field.

response to a current dipole within the model. To facilitate calculations, we approximated the torso of an average adult by a homogeneous conductive sphere 30 cm in diameter, and we assumed that a pair of electrodes located near the center of the model would act as a current source (depicted by the "+"), and a current sink (depicted by the "−"), with a 1.4-cm separation.

We then assumed a weak current injection of only 0.4 mA at the center of the "torso." In our previous publications[44,46] we have derived computationally efficient expressions to calculate surface potentials of spherical models. For the particular case illustrated, the signal strength (v) at the "voltage meter" can be reduced to a very simple expression: $v = 3M/(2\pi\sigma R^2)$, where M is the dipole strength (M = 0.72 mA-cm), σ is the conductance, for soft tissues ($\sigma \sim 1/222\ \text{cm}^{-1}\ \Omega^{-1}$), and R is the radius (R = 15 cm). The result of the calculation is: v = 0.47 mV.

Noise in the VC Channel

As is the case in radio communications, the sensitivity of reception depends not only on signal strength, but also on noise strength. It is clear that the channel provided by the human body is very noisy because of various biological activities. However, the biological noise is mainly in the frequencies below 100 Hz, which can be avoided when communication is performed using modulation at a much higher frequency. Another concern is that the human body acts as an antenna that receives RFs. This problem may not be prohibitive because the conductive body also provides shielding from the RF noise and the shielding becomes increasingly effective in the deeper part of the body. When the VC-based communication system is designed, one has the freedom to choose a frequency band that minimizes the noise effect, achieves good protection against RF interference, and compromises the gradual increase in attenuation at higher frequencies (which occurs above 10 kHz, according to Lindsey, et al.[20]).

Theoretical and Computational Modeling

We have conducted a number of extensive studies on the fundamental properties of the VC communication system by using electrostatic and linear system models.[19,29,31–33,41,42,44–49,51,52,56] To solve the channel symmetry problem, which determines whether the same signal transmission system can be used for both uplink and downlink transmissions, we modeled the VC information channel. As illustrated in Fig. 5 *upper*, a pair of linear two-port networks was excited by current sources. By using the reciprocity theorem, we have shown[44] that the ideal VC channel is symmetrical. We then constructed more theoretical models to study the discrepancies between the ideal and realistic systems. A number of practical factors were considered in these models, including transmitter impedance, channel noise, nonlinearity of biological tissues, and ionic–electronic exchange at the electrode–tissue interfaces.[42,44] One of the models is shown in Fig. 5 *lower*, where we used the Thevenin and Norton theorems as described by Desoer and Kuh[4] to represent a realistic transmitter as an ideal current source in parallel with an output impedance. As a result, the two-port networks N_{R1} and N_{R2} are related by the placement of R_0 on either side. Using this model, the channel asymmetry can be estimated regardless of the complexity of the biological VC system.

Antenna Design

As in the RF systems, the VC system requires an antenna to transmit and receive data. We used computer simulations based on finite element methods to study the structure, shape, dimensions, location, and orientation of possible VC antennas.[19,41–46,51,52] We concluded that a pair of insulated parabola-like surfaces rotated at a certain angle from these surfaces normal to the skull provides the optimal performance. These results are more completely described in the following sections.

The x*-Antenna.* We have developed a fundamentally novel structure of the VC antenna called an *x*-antenna. Our main idea, illustrated in Fig. 6, was to maximize the outward propagation of the current field, which contributes to communication, and minimize the direct shorting current, which causes inefficient use of energy.[44–46] The *black* and *gray* regions of the *x*-shaped antenna elements in Fig. 6 indicate a metal layer and an insulator layer, respectively. Because the shorting paths between these elements are blocked by insulation, the current is forced to flow in longer paths, enhancing the outward propagation and reducing the direct shorting current. In addition, because the current flux lines in a volume conductor are initially perpendicular to the surface of the antenna, the curvatures of the flux lines are influenced significantly by the curvature of the antenna. This phenomenon led us to determine the antenna impedance, which is an important parameter in the design of the VC transmitter.[41,49]

Finite Element Simulation. We have performed numerous simulations to understand the potential maps and current field distributions within different biological tissues, explored a variety of antenna structures, and compared their performances.[41,45,49,51,52] The panels in Fig. 7 compare the results of an *x*-antenna with *(left)* and without *(right)* a reflector, which is an insulating film placed below the antenna. In both cases, a slice of the head embedded with the cross-section of an *x*-antenna was studied, and a

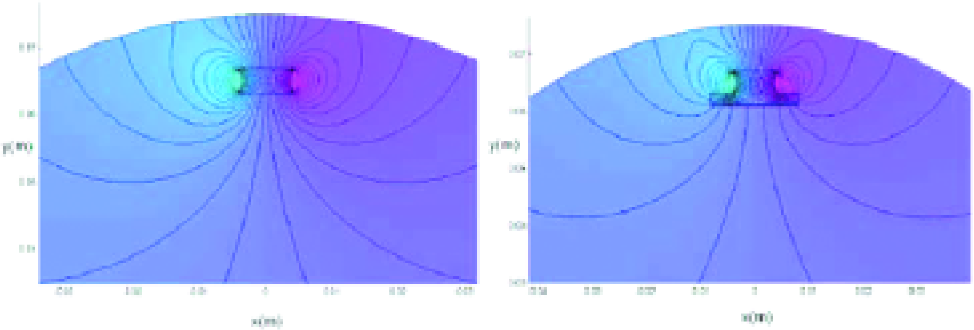

FIG. 7. Computer simulation charts of a spherical head slice (local view). *Left:* Equipotential lines without a reflector (an insulating film placed below the antenna). *Right:* Equipotential lines with a reflector. It can be observed that the reflector helps to block current flowing deep down to the brain. .

homogeneous tissue conductivity of 1/222 $\text{cm}^{-1}\ \Omega^{-1}$ was assumed.[7] It was observed that the reflector effectively blocks the current that flows into the brain (see Fig. 8 for illustrations of this device).

Experiments: Physical Model. We have constructed a physical globe filled with saline fluid to model the VC environment (Fig. 9). This globe has a number of measuring posts around its perimeter to evaluate the VC-based communication system. In addition, a device on top of the globe is able to take measurements at any position within it, using a spherical coordinate system with the top center of the globe as the origin (Fig. 9).

We have acquired experimental data with two different voltage distributions along an actual electrode array antenna. To prevent electrode polarization, an alternating current signal was used. For simplicity, measurements were kept within a two-dimensional slice through roughly the center of the globe. One of our test results is shown in Fig. 10, in which the potential distributions in the vicinities of the antenna elements can be observed. This physical model will help us in preliminary testing of additional antenna electrode setups in the future.

Animal Experiments. As part of this research, we have conducted experiments in pigs. A pair of signal transmission electrodes was implanted on the cortex of the brain, and the electrical signals were transmitted to the skin by VC. We have developed signal processing techniques to extract the transmitted signal from the received waveforms.

For this experiment, a 16-kg Yorkshire pig was tranquilized intramuscular injection of 320 mg ketamine and 32 mg xylazine. A 20-gauge catheter was placed in the ear vein and 320 mg pentobarbital was given as an anesthetic agent. A posterior incision near the left temporal area (Fig. 11) was made. The temporalis muscle was then retracted. A craniotomy approximately 2 cm in diameter was performed and the dura mater was incised. Two dipole sources were then implanted by inserting the wire segments under the dura mater (shaded area in Fig. 11), so that the exposed metal tips were in contact with the cortex. After suturing the dura mater, the craniotomy flap was replaced and secured with bone wax (an electrically insulating material) to seal the gaps in the skull created by surgery. The skin incision was closed with a running stitch of 2-0 Neurolon. We used a segment of insulated parallel wires, with the tips exposed, as a device to simulate a current dipole within the brain of the pig. The wire segment has a flat surface which, when surgically placed on the pig's brain, exerts minimal compression on the delicate tissues and microvessels. In addition, its softness and thinness facilitated surgical manipulation.

We tested this experimental preparation with a linear sinusoidal chirp. We chose the chirp as the test signal because it has a wide range of frequency components and is related to classes of telecommunication signals. This time series was then converted to a sound wave file and played. A 2.5-V output was obtained, which was connected, after voltage attenuation, to a current drive to excite the implanted current dipole. Three channels of potential data, all referenced to the electrode on the snout, were then collected repeatedly over a 5-hour period at a sampling frequency of 256 Hz. Each recording lasted for approximately 2 minutes.

We delivered a very low excitation current (20 μA-cm in terms of the root mean square value of the current dipole moment) to the implanted dipole. This level was chosen to make the excitation current as low as possible. As a result, noise contamination in the recorded data was significant (Fig. 12a). Because this signal is highly nonstationary, we applied a discrete Gabor analysis and synthesis technique.[48] Figure 12b shows the amplitude values of the Gabor coefficients (matrix size 33 × 128). In this image, horizontal and vertical axes represent the time and frequency variables, respectively. The chirp signal (diagonal component), the 60-cycle interference and its harmonics (horizontal stripes), and the spontaneous EEG signal in

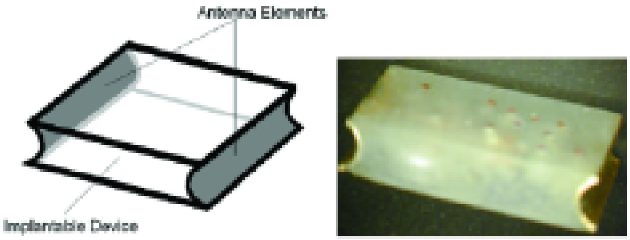

FIG. 8. *Left:* Drawing of a finite element model of a neural implant *x*-antenna. *Right:* Photograph of the constructed device ($12 \times 8 \times 3\ \text{mm}^3$) based on the results of finite element modeling.

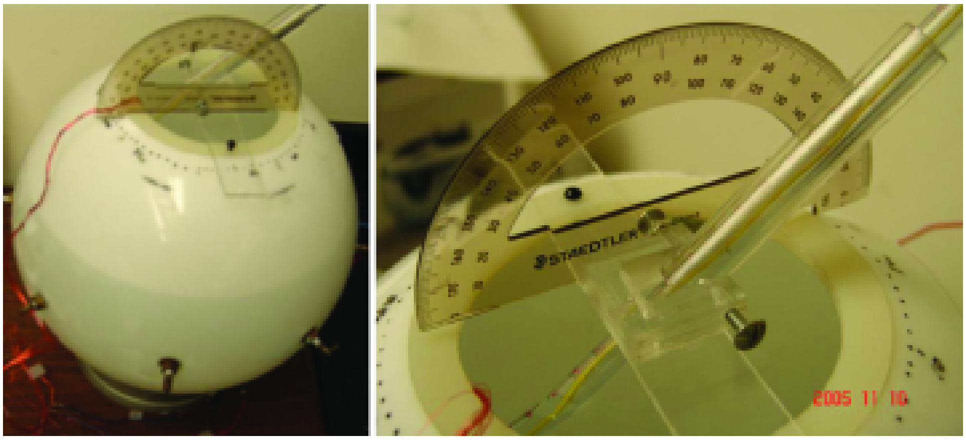

FIG. 9. Photographs of the physical test globe *(left)* filled with saline fluid and equipped with electrode posts and coordinate measuring devices *(right)*.

the lower part of the image can be clearly observed. A special filter with varying frequency characteristics over time is shown in Fig. 12c, the filtered Gabor coefficients after four iterations in Fig. 12d, and the reconstructed signal in Fig. 12e. The noise originally present in the data has been virtually eliminated (compare Fig. 12a and e).

Data Communication System Design and Construction

Design. We have constructed prototype implantable devices equipped with a VC communication channel. To conduct animal experiments with implantable devices, we must fit all electronic chips and components within a tiny space of approximately 11 × 10 × 3 mm^3, which has been a very challenging task. Figure 13 shows the block diagram of a neural recording prototype (only one channel is shown). Two miniature batteries provide a 3.1-V power supply (rail-to-rail). The cortical EEG signal from subdural electrodes is amplified, high-pass filtered, modulated, multiplexed, and fed to the output antenna. To minimize noise and unwanted cortical stimulation, a modulation frequency between 6 and 20 kHz was chosen, which was well beyond the frequency range of the subdural EEG signal.

Construction. To implement the minicircuit containing both analog and digital components, we used computer software to design a printed circuit board.[29] Using in-house printed circuit board construction methods and standard surface mount chips and discrete components, the circuitry was carefully assembled. It was then coated with epoxy to form a small, watertight package with embedded recording electrodes and a transmitting antenna. Although delicate procedures were required, we have found that at this initial research stage, a manual approach is very flexible and cost-effective. In Fig. 14 *left* a minicircuit constructed in our laboratory is pictured, and the *right* panel shows a prototype device for cortical recording.

Packaging the Circuit. To facilitate testing flexibility after packaging the constructed circuit into an implantable capsule, we leave some wires protruding from the capsule during construction (Fig. 15 *left*). After the epoxy resin hardens, the wires are cut off at the surface (Fig. 15 *center*) and then polished. As a result, the wire ends are smoothly integrated with the epoxy surface of the capsule, and the boundaries between the wire ends and epoxy become watertight. Just before performing an experiment, the wire ends, now acting as connecting posts, are temporarily connected by painting a thin conductive layer of paint between desired posts (Fig. 15 *right*). This allows the circuit to be designed with optional components that can easily be connected during testing to vary the circuit parameters. After or during experiments, the points in the circuit can be disconnected easily by scratching off the paint. Connections to the battery are also made in this way to preserve battery life between experiments.

Modulation/Demodulation. The VC communication system requires considerable signal processing to modulate/demodulate and multiplex/demultiplex signals. We have investigated signal processing methods and their hardware and software implementations to perform these tasks. After considering power consumption and complexity in circuit design, we chose a switching modulation method that was implemented using small, extremely low-power solid-state analog switches.[31–33] Outside the biological system, the signal received from skin-surface electrodes was demodulated/demultiplexed by software that not only facilitated implementation, but also allowed the use of advanced signal processing techniques, such as the wavelet transform,[31,48] to reduce noise and enhance performance.[33]

Energy Delivery

The issue of energy delivery to implantable devices has been a significant and challenging problem for many years. Today, external and internal batteries as well as transcutaneous energy transmission via RF links are most commonly used. The previously described approaches function satisfactorily for their individual applications; however, they can also pose problems and even health risks to patients. External batteries require wire leads that penetrate the skin to reach the implanted device, and infections at the site of skin penetration can occur. Internal batteries implanted with the device, such as those used for cardiac pacemakers, also have a limited lifespan and con-

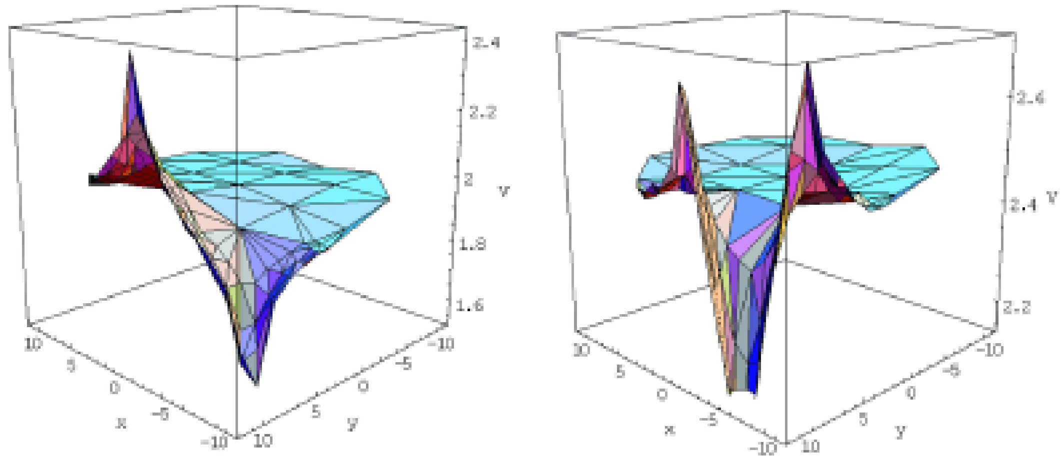

FIG. 10. Computer models of measured voltage levels across a two-dimensional slice of the test globe model. *Left:* Linear voltage distribution. *Right:* Symmetrical voltage distribution.

sequently need to be replaced by surgical intervention after several years.[18] They can also be quite bulky, accounting for a significant portion of the overall weight of the implanted device. Rechargeable batteries can be used and would be preferable to nonrechargeable ones for certain applications, because they can be made smaller and lighter (less fuel is needed) than the latter. In this instance, a method for recharging the battery is needed. Transcutaneous energy transmission via an RF link or magnetic coupling is often used.[39] However, this method can be associated at times with unwanted heating and tissue damage.[6] Rechargeable lithium ion batteries are often used as backup power sources. There is also the issue of convenience to the patient, one that should be taken into careful consideration. The process of recharging the battery, if left to the patient, becomes a task that would need to be incorporated into the daily routine, essentially disrupting the patient's way of life. The ideal solution would be to develop a power source that requires minimal to no maintenance and lasts at least as long as the implanted device.

Human beings, like all other animals, acquire energy from the foods they eat. The process of respiration involves the oxidation of sugars (glucose) within the mitochondria and subsequent storage of that energy as adenosine triphosphate. Different organs have varying energy needs, and therefore metabolize sugars at different rates. The power consumption of the brain alone is approximately 0.29 kcal/minute (~ 20 W),[28] representing approximately one fifth of the total energy used by the body. Even a small fraction of this energy would be sufficient to power a neural implant.

We have recently undertaken a novel research project investigating biofuel cells for power generation within the body. A biofuel cell couples the oxidation of a renewable fuel (such as glucose) to the reduction of molecular oxygen to water. An electrical current output can be generated by such electrochemical cells as long as sufficient quantities of the biofuel are supplied. In previous studies investigators have demonstrated the feasibility of producing electricity from biofuel cells by using whole cells (primarily bacterial cells).[2,30,34,38] In these microbial fuel cells,

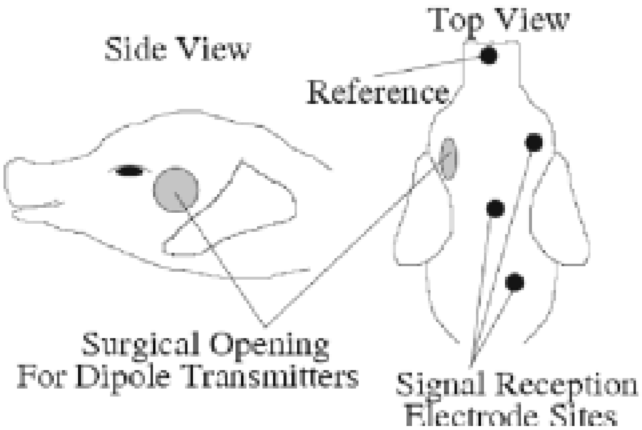

FIG. 11. Drawing showing surgical opening and recording electrode locations for the experiment performed in a pig.

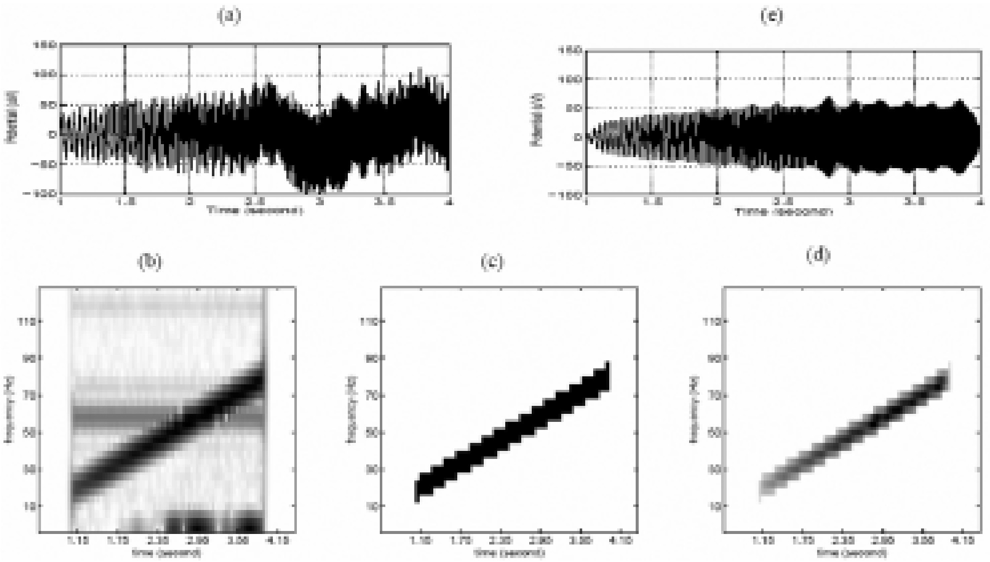

FIG. 12. Readouts of Gabor time-frequency analysis and synthesis. a: A noisy signal segment. b: Amplitude of discrete Gabor coefficients. c: Mask function for selecting the desired time-frequency component. d: Gabor coefficients after four iterations. e: Result of Gabor synthesis.

bacteria are able to transfer their high-energy electrons either directly, through membrane-bound electron transport chain proteins,[2] or indirectly, through artificial redox mediators[34] or metabolic products excreted into the extracellular environment[18] (Fig. 16). Current densities of up to 1.5 mA/cm^2 and power densities as high as 3.6 W/m^2 have been reported for these microbial fuel cells.[38]

Our research group is interested in replicating such experiments using human cells as opposed to microbial cells. We believe that certain human cells, like microbes, can directly or indirectly mediate the transfer of electrons to an interfacing electrode. Direct electron transfer would likely occur through NADPH oxidase, an enzyme complex that resides in the cell membranes of phagocytic white blood cells[37] and microglia.[8] It has been shown previously that NADPH oxidase is an actual electron transport chain, serving as a channel for transfer between the pentose phosphate pathway of glucose metabolism and extracellular oxygen. Electron transfer may also occur indirectly through the release of chemical compounds or metabolic products into the extracellular environment.

We have investigated an in vitro biofuel cell in which white blood cells that had been isolated from whole human blood and suspended in 1x phosphate-buffered saline were placed at the fuel cell anode. The cathode compartment contained a solution of potassium ferricyanide, which has a high electron affinity. The ferricyanide solution mediates electron transfer between the cathode and dissolved oxygen. In the absence of the ferricyanide solution, very low efficiencies in electron transfer would occur, resulting in significantly smaller currents and open circuit potentials, due to greater internal resistances and greater polarization effects. Carbon felt electrodes were used for both the anode and cathode. The high surface area of these electrodes would facilitate increased current outputs and would increase current densities relative to the

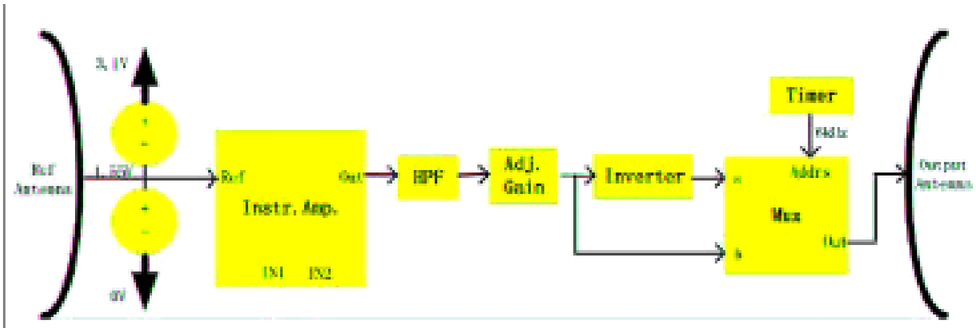

FIG. 13. Block diagram of implantable chip design. Addrs = address; Adj. = adjustable; HPF = high pass filter; Instr. Amp. = instrumentation amplifier; Mux = multiplexor; Ref = reference.

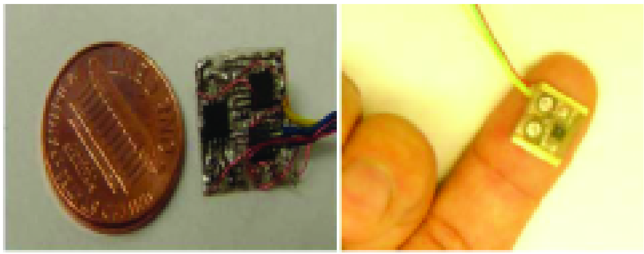

FIG. 14. *Left:* Photograph of a minicircuit built on a double-sided printed circuit board. *Right:* Photograph of a completed neural implant sealed within clear epoxy with installed *x*-antenna elements. The wires are used to connect the recording electrodes implanted on the cortex. Two tiny button batteries *(circular objects)* provide power to the prototype device.

geometric surface area. Electrical currents between 1 and 3 μA/cm^2 were observed when the biofuel cell was allowed to discharge across a 100-Ω resistor.[15,16] Open circuit potentials on the order of 300 to 500 mV were also observed.

Based on these studies, the mechanism of electron transfer is not immediately obvious. A galvanic cell can often be a black box, requiring an arsenal of electrochemical techniques to elucidate the chemical events within the system. Cyclic voltametry is one electrochemical technique that has been widely used to explore various electrochemical phenomena, including the redox activity of human red and white blood cells.[3,25] A number of studies have revealed that the cells release electrochemically active compounds into the extracellular environment. Serotonin has been proposed as one such candidate compound. In the biofuel cell experiments in which white blood cells were used, a possible mechanism of electron transfer may be that serotonin released by the cells reacts at the electrode surface, yielding its oxidation product, 5-hydroxyindoleacetic acid (Fig. 17).

Previous electrochemical studies of serotonin oxidation-reduction reactions at electrode surfaces have been performed.[36] At the cathode, oxygen would be reduced to water. The electrode potential of serotonin normally lies within the range of 300 to 450 mV compared with an Ag/AgCl electrode (0.5–0.65 V compared with a normal hydrogen electrode. Because the potential for the reduction of molecular oxygen to water is 1.229 V compared with NHE, one would expect an open circuit potential between 550 and 700 mV, a range that is a bit higher than that obtained in our biofuel cell studies. The positive potential demonstrates the thermodynamic feasibility of the coupled oxidation–reduction reactions.

There is obviously much more work to be done in this area, and this work is still far from producing an actual implantable product. Further research in this area will tackle issues related to three major problems: 1) biocompatibility of the electrodes and the overall device; 2) improving efficacy of the electrode surface reactions; 3) eliminating the need for the proton exchange membrane used to separate the anode and cathode compartments; 4) eliminating the need for the ferricyanide solution; and 5) increasing power and current densities.

Discussion

We have presented two novel platform technologies to tackle directly some of the most important challenges facing the development of implantable diagnostic and therapeutic devices. The first is a technology based on VC, which may be used to establish data communication channels between an internal device and an external computer. The second platform technology deals with the power supply issue, whereby biofuel cells based on cellular metabolic processes may be used to provide electrical energy to the implanted device. We have demonstrated both theoretically and experimentally the fundamental capability of VC as a communication channel. The VC channel takes advantage of the natural conductive properties of the ionic fluid in the body and provides an efficient method for data communication in living tissue. The computational model based on the reciprocity theorem reveals a nearly symmetrical channel with respect to the transmitting/receiving sensitivity. The linearity and information capacity of this channel have yet to be investigated. Quantitative analysis of these two issues would provide physical principles that could be used in the future design of communication for better data transmission rates, error resilience, and power consumption.

Biofuel cells offer a biomimetic approach to energy transduction. Our bodies derive energy through the process of respiration, whereby glucose is oxidized to create carbon dioxide and water. We are able to harness the energy that we need as long as our bodies receive ade-

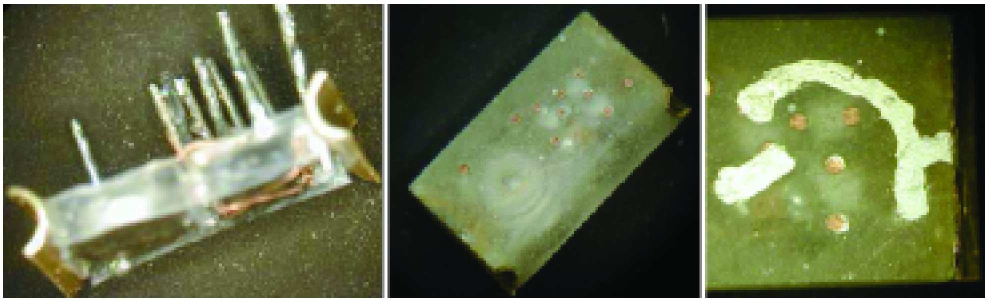

Fig. 15. Photographs of a device constructed based on a scheme for adding flexibility during testing. The protruding wires in the *left* panel, which are cut off in the *center* one, can be connected with conductive paint *(right)* to establish contact for various circuit components on the internal board.

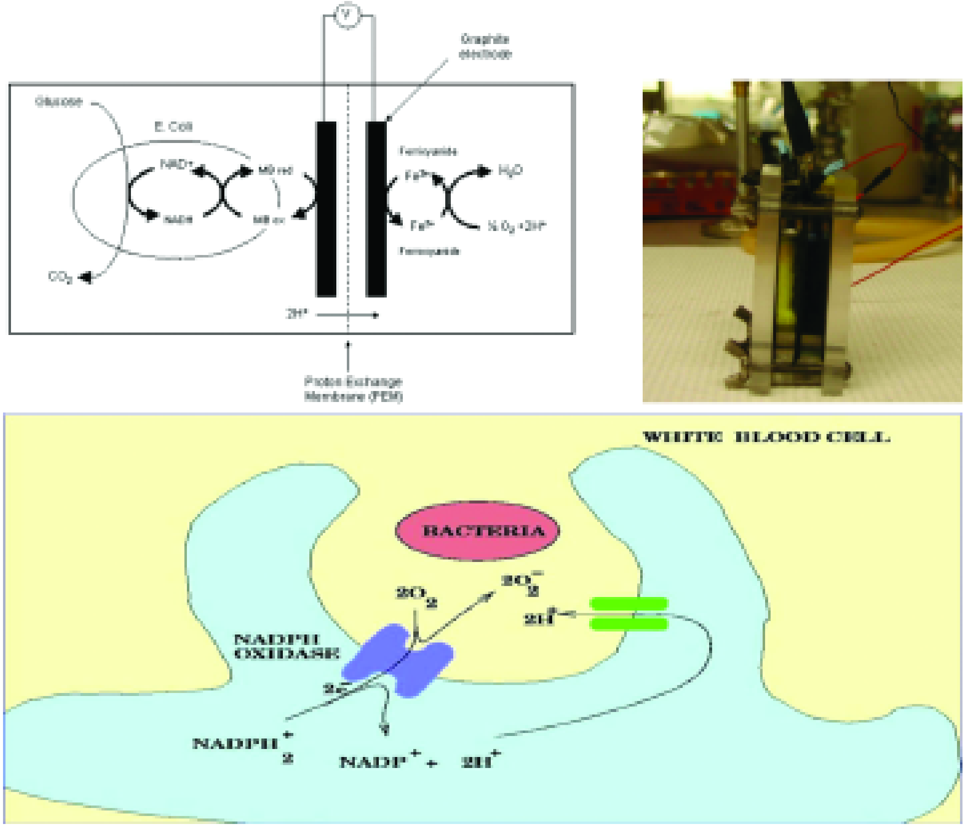

FIG. 16. *Upper Left:* Schematic of a microbial fuel cell with methylene blue as the electron mediator. Such mediators increase the efficiency of electron transfer to the anode. *Upper Right:* Photograph of an in vitro biofuel cell assembled in our laboratory. The total working volume of the apparatus is approximately 20 ml. *Lower:* Schematic of energy production in a biofuel cell. Respiratory burst by phagocytic white blood cells is associated with the generation of reactive oxygen species, such as superoxide, by activated NADPH oxidase.

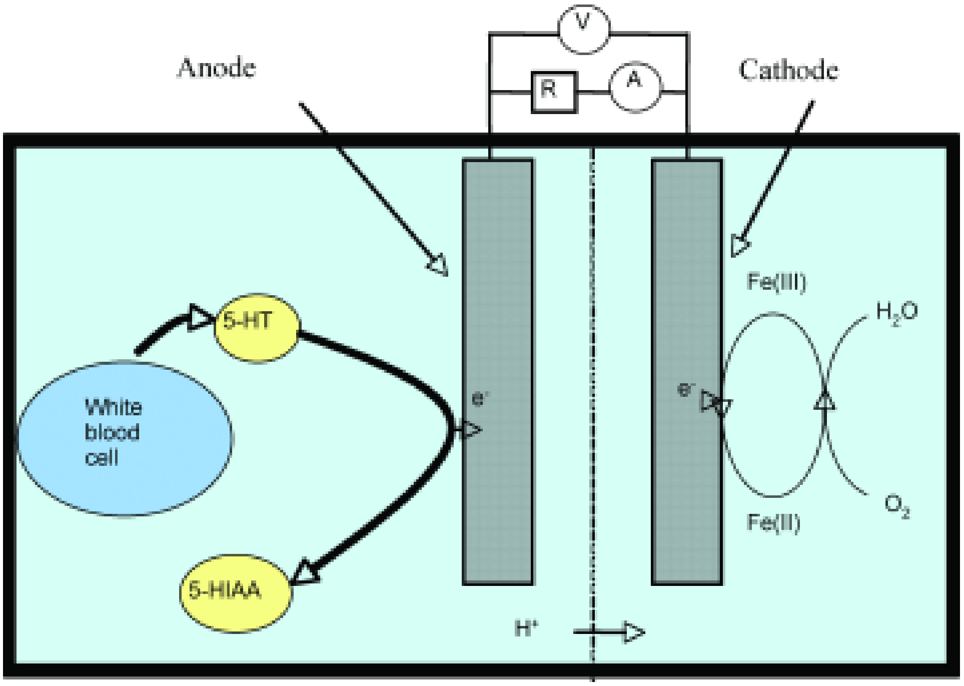

FIG. 17. Schematic drawing showing possible chemical reactions occurring at the anode and cathode of a biofuel cell incorporating white blood cells at the anode. Release of serotonin (5-hT) from activated white blood cells may be followed by oxidation of the neurotransmitter to 5-hydroxyindoleacetic acid (5-hIAA). The *dotted line* represents the proton exchange membrane used to separate the anode and cathode compartments. The objects labeled V, R, and A in the external circuitry represent the voltmeter resistor and ammeter, respectively. Fe(II) = reduced form of potassium ferricyanide; Fe(III) = oxidized form of potassium ferricyanide.

quate quantities of glucose and oxygen from the environment. Similarly, a biofuel cell is able to generate energy continuously in the form of electrical potentials and currents, as long as it receives sufficient quantities of fuel and oxygen at its electrodes. In this way, fuel cells are different from batteries. One of the primary limitations of batteries is the fact that they carry a finite amount of fuel, that when completely expended results in a loss of electrical potential and current levels. For this precise reason, batteries are often bulky and their accommodation needs to be taken into consideration in the design of any implantable device. Batteries often contribute a significant portion of the weight of an electronic device. With a fuel cell, however, the problem of an expendable, finite load is not an issue. Potential energy in the form of chemical bonds can be converted into electrical energy, using organic compounds such as glucose as the source. One mole of oxidized glucose yields 2870 kJ of free energy. A fraction of this energy would be sufficient to power most implantable devices. With the prospect of an unlimited source of this fuel from the body, biofuel cells would be able to supply all necessary energy to an implantable device during its entire lifetime, while simultaneously eliminating the bulky size, weight, and additional surgeries associated with the use of traditional batteries.

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