

REVIEW

Emerging trends in bioenergy harvesters for chronic powered implants

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ABSTRACT

The widening gap between the short battery life (<8 years) and patients' life expectancy (20 years) is a growing concern for long-term implantable devices and adds to outpatient costs. This gap coupled with significant advancements in circuit, device design, and lowered power consumption (<1 mW) has refueled the interest in implantable energy harvesters.

As the complexity of implantable devices is increasing, the size and power requirements of implantable devices have shrunk by more than double over the past few decades. However, the functionality or lifespan of the devices is often found to be limited due to shortage of power. With more than 50% of the device size being occupied by the battery alone, longevity of such implantable devices has garnered huge concern over the years. Fueled by the demand of additional biosensors coupled to such devices, implantable energy harvesters, capable of harvesting the body's chemical, thermal, or mechanical energy over a long period of time, have gained tremendous popularity. Among these technologies, implantable glucose fuel cells provide a promising method to generate a small yet continuous supply of power. Implantable fuel cells tap into the available free blood glucose to generate electricity. With the trend moving toward the use of semiconductor technologies for glucose-based fuel cells, fabrication of reliable and effective technology is within feasible limits. Realization of such implantable power sources can shift the burden from commonly used lithium-ion batteries by utilizing physiological resources. The present review focuses on recent developments on abiotic glucose fuel cell for bioenergy harvesting.

Keywords: biomedical, devices, electrodeposition, energy generation, microelectro-mechanical system (MEMS)

DISCUSSION POINTS

- Currently, automatic implantable cardiac defibrillators (AICDs) last roughly for 8 years, whereas the average patient lifespan is more than 20 years. This gap requires the patient to undergo battery replacement surgery, resulting in additional discomfort and costs. Development of bioenergy harvesters that supplement existing battery life can help bridge this gap.
- Further, additional power supply could power sensors on implantable devices, which could provide clinically important information to the surgeons. Availability of critical information can facilitate rapid decision making and shorter outpatient times.

Introduction

The US implants is a \$54.3B (2014) industry and is expected to grow at a fast rate of 8% compounded annually. Cardiovascular

implants comprise a majority (40%) of all the devices implanted and the remaining 60% of the powered implants market is fragmented into drug delivery, neural, and other small categories. It is estimated that cardiovascular implants itself will be a \$27B industry by 2017 [Fig. 1(a)]. Drug delivery devices come at a close second market, with a compounded growth rate of 4% and forecasted to exceed \$22B by 2017 [Fig. 1(a)].³

The advent of lithium-based batteries spurred the growth of powered implantable devices. Two of the most frequently implanted cardiovascular devices, the automatic implantable cardiac defibrillator (AICD) and pacemaker, still rely on lithium-ion batteries as their sole power source. Table 1 summarizes some of the powered implantable devices along with their power requirements and estimated lifetime.

It is estimated that the average life of an internally implanted battery-powered AICD is less than half of the normal lifespan of a patient after having an AICD implanted [Table 1, Fig. 1(b)]. While the longevity of the average AICD patient has increased to 10 years

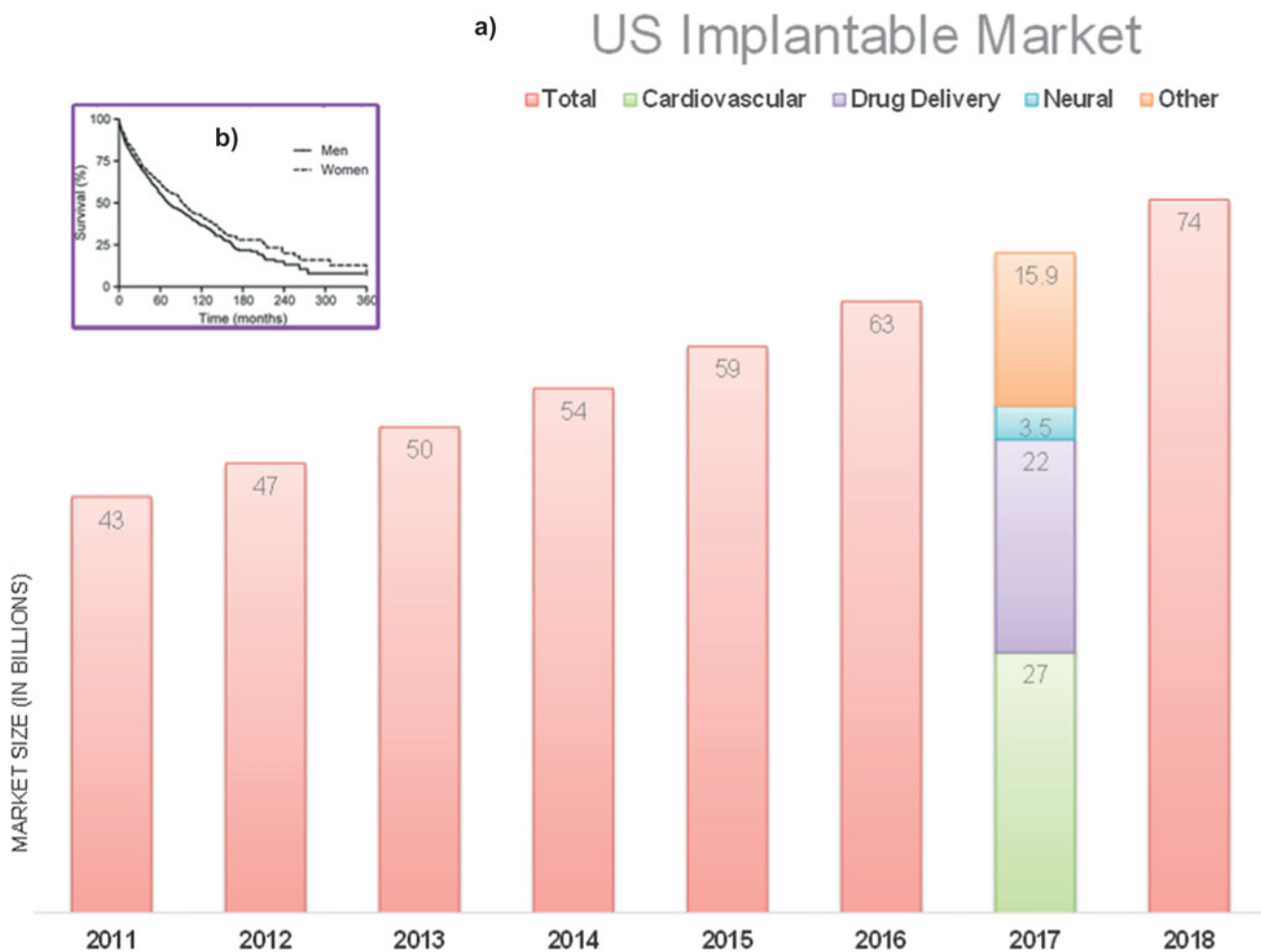


Figure 1. (a) Current and predicted US Implantable Market size (in billions). Estimated market forecast for 2017 showing the distribution among the various implant categories. Data source: Ref. 1; (b) Kaplan–Meier survival analysis of patients with atrial fibrillation, post pacemaker implantation showing a sharp decline in the survival rate as the time increases. Source: Ref. 2. Reproduced with permission. Copyright 2008, Oxford University Press.

post implantation,² only a few implants function for seven years,⁹ and this mismatch poses a significant and ever growing clinical and economic burden. Approximately 90% of AICDs and biventricular pacemakers implanted in 2004 required replacement.⁹ The rate of replacement of pacemakers and AICDs is dependent on the battery capacity and the degree of pacing or occurrence of defibrillation.

Therefore, if the battery is implanted, it must someday be replaced and the battery’s limited capacity accounts for more than 55% malfunctions in conventional pacemaker and AICDs.¹⁰ Every time a surgery is performed, there is an inherent risk and discomfort to the patient.

Moreover, there are now efforts to “piggyback” sensors on all implantable devices for additional functionality such as pressure and volume sensors to warn of impending congestive heart failure (CHF), lung impedance sensors to warn of CHF, and chemical sensors to provide telemetric measures of glucose, potassium, bun and creatinine, all of which would require additional power.^{11–15}

More than four decades ago, alternative sources of energy were considered to be a hot research topic for implants due to

the short lifespan of the mercury-based batteries.^{16–18} The power output of these first implantable fuel cells in the 1970s was in the range of 50 μ W, sufficient to supply a present day-cardiac pacemaker.¹⁹ Introduction of lithium-based batteries in the 1970s²⁰ put all research on alternative energy sources to a grinding halt. While the introduction of lithium-based batteries provided significant step in device lifetime, advancements in battery life have started to slow down [Fig. 2(a)]. Therefore, the research focus has shifted toward the development of compact, efficient, and low-power consuming implants. With the emergence of micro-electro mechanical systems (MEMSs), fabrication of low-power devices can now be realized.^{21–31} But for even very low-power consuming devices, the use of batteries is not considered to be a viable long-term solution. Batteries are bulky for MEMS-based implants and for larger implants such as pacemakers, defibrillators, and cardiac monitors, batteries provide limited lifespan.

As biomedical industry seeks to create smarter, intelligent, and more sophisticated implantable devices, increases in battery

Table 1. Comparison of present day implantable devices along with their power requirements.

Model	Description	Voltage (V)	Current (μ A)	Power (μ W)	Estimated life (years)	Reference
Medtronic Reveal DX	Insertable cardiac monitor	3.6	3	...
Medtronic Maximo	Single chamber ICD	3.2	9.1 (pacing)	29.12	9	...
Medtronic Vitatron	Pacemaker	2.8	14.8–24.2 (pacing)	41.4–68	7–8	...
CardioMEMS EndoSensor	Implantable pressure sensor	3	4
Medtronic MiniMed MIP 2007	Implantable insulin pump	0.08	2500–10,000	200	7	...
Drug delivery pump	Electro-osmotically actuated drug delivery pump	2.8–30	>4000	>30,000	...	5
Closed loop neurostimulator	Neuro stimulator	...	<12,000	...	8	6
	Pulse oximeter	5	...	4800
Cochlear implant	Bionic ear processor	251	...	7
	Glucose sensor
Retinal implant	Retinal stimulator	250,000	...	8
	Volume sensor
	Lung impedance sensor

energy capacity have become a limiting factor rather than a supporting one. Alternative technologies of charging such devices in a continuous and stable manner have become an issue of great importance. Availability of additional energy will not only allow the existing powered implantable devices to carry additional sensors for smarter diagnosis, but also it can help realization of new, smart implants. Table 2 lists the possible alternative technologies along with an understanding of their current limitations.

This study is dedicated to presenting a brief overview of these possible energy generating mechanisms with a focus on one of the most promising avenues of energy generation: abiotic glucose fuel cells (AGFCs).

Batteries and alternative energy sources for implants

Presently, all of the implantable devices rely on electric energy supplied by batteries. The demand of durability between charge cycles can only be satisfied with new power supply

concepts. Batteries with limited capacities will eventually drain long before the service life of the system. Their continuous replacement is a growing burden that adds to outgoing patient costs and concerns. The energy density (energy per unit of volume) and the specific energy (energy per unit weight) of several primary batteries (nonrechargeable) and secondary batteries (rechargeable), which are candidates for power portable devices, are compared in Fig. 2(b). But the trend toward lower power consumption stimulates the investigation for alternative power sources to traditional batteries.

For implantable biomedical devices, internal batteries and ultracapacitors have the disadvantage of duration of power supply because it is often limited by the capacity of the battery, i.e., it is limited by the quantity of the available reactants in the system.³² The energy generated by the battery is based on electrochemical reactions. Once the potential and current levels in the device have reduced, the battery is unusable and replacement of batteries becomes necessary. Replacing batteries³³ in implantable systems can pose a significant issue. Surgical

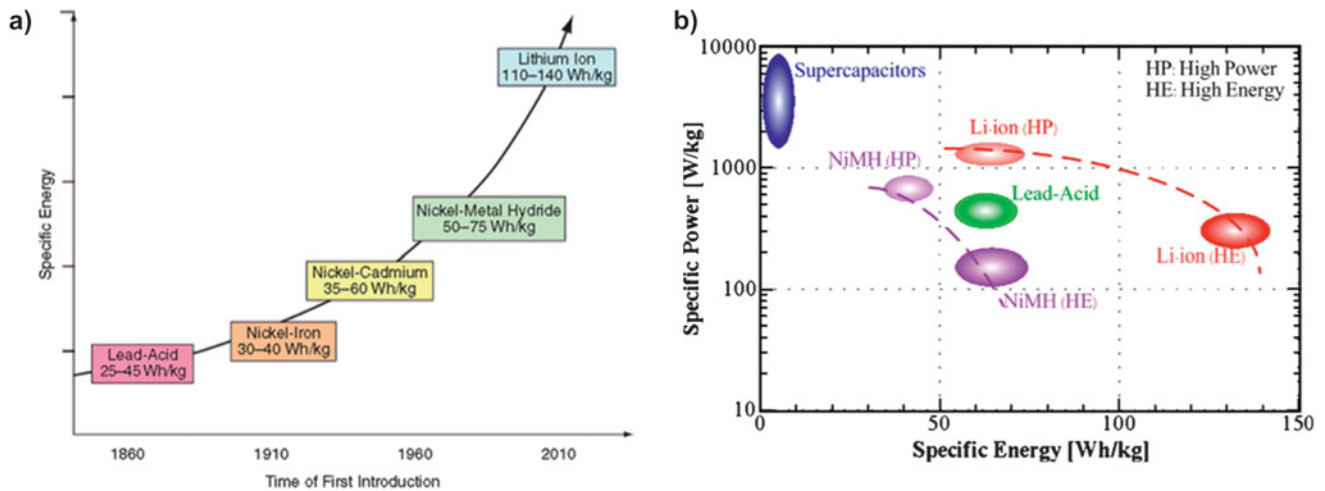


Figure 2. (a) Rapid advancements in increasing power density trend for batteries since the first lead-acid batteries were introduced in the mid-19th century⁴²; and (b) specific power versus specific energy of modern storage devices: supercapacitor, lead-acid, NiMH, and Li-ion battery technology.⁴³

interventions would be the only option to replace the batteries that have failed or that reach the end of its lifetime of operation. These operations could have detrimental effects such as scarring, infection or they could prove to be really expensive.

The increase in power density in batteries trend has started to stagnate. The need for high power densities has led to the development of ultracapacitors. Ultracapacitors are generally created through adding a highly porous, conductive activated carbon to the electrodes of normal capacitors. The additional surface area allows for higher energy densities of up to 100x of traditional capacitors.⁴⁴ Generally, ultracapacitors have only a fraction (~5%) of the energy densities of lithium batteries, but research is attempting novel solutions that could provide comparable results.³⁴

Alternate sources to batteries that could be implanted into biomedical devices were nuclear generator. This idea was conceived in 1960 and brought to the clinical environment in 1970. Numec Corporation developed this prototype where alpha particles emitted by a tiny slug of plutonium 238 bombarded with the walls of its container producing heat that was converted to electrical energy.³⁵⁻³⁷ Although safety was not the primary issue there were concerns about the toxicity of the fuel.

A number of biomedical-based implantable medical devices would benefit from miniaturized MEMS-based implantable power supplies. One of the most important applications are cardiac pacemakers that currently use lithium-ion batteries that power these devices with an operating power of 1 μ W.^{45,46} These batteries have an energy density of 1 W/mL. Biofuel cells

Table 2. Summary of possible fuel-cell technology alternatives and their current limitations.

Fuel-cell alternatives	Description	Current limitations
Batteries	Rechargeable and nonrechargeable types, currently used in many implantable devices	Duration of power supply (Refs. 32 and 33)
Ultracapacitors	Created by adding highly porous, conductive activated carbon to electrodes of normal capacitors	Small energy density compared to lithium batteries (Ref. 34)
Nuclear generators	Emitted alpha particles bombard wall to generate heat, which converts to electrical energy	Toxicity of the fuel (Refs. 35-37)
Wireless charging	Transcutaneous power supply to implanted device via RF, ultrasonic, or optical transmissions	Unwanted heating, tissue damage, attenuation through skin (Refs. 38 and 39)
Piezoelectric energy harvesting	Convert kinetic or mechanical energy from the body into electrical energy	Do not produce sufficiently large current and power densities (Refs. 40 and 41)

created thus far have energy density of 10 mW/mL but this value could be improved to that of conventional lithium-ion batteries. The advantages of biofuel systems are that it can provide constant energy density that is derived from ambient sugars present in the body.

Wireless charging of medical implants is an exciting field that has the ability to not require an implanted power source. Radiofrequency,⁴⁷⁻⁴⁹ ultrasound,⁵⁰ and optical⁵¹ methods have been studied as possible methods for delivering power transcutaneously to implanted medical devices or act as rechargeable batteries. This energy transmission does not require wire leads that penetrate the skin. RF transmissions have shown high efficiency but have also been prone to unwanted heating and tissue damage. Most battery-less implantable devices have the following components⁵²:

- (i) Matching network - used to maximize power delivery efficiency through antenna pairs
- (ii) Rectifier - conversion of AC to DC voltage
- (iii) Regulator - stabilize supply voltage to circuitry
- (iv) Bandgap reference - stable reference voltage for the regulator

Together, these components create the basis for a system that can gather RF power from an external device and provide stable enough supply voltage/current for usage of the implanted device (Fig. 3).⁵²

An alternative method of wireless charging is through focused ultrasound or optical waves to transmit energy. Ultrasound and optical methods have the disadvantage of becoming attenuate through the skin. Optical methods using infrared means is sometimes associated with unwanted heating of the skin.⁵³ Typical setups include a focused transmitting transducer, a receiving transducer, a DC converter (rectifier), and a recharging battery (secondary battery).⁵² The receiving transducer is typically a piezoelectric transducer that converts the mechanical energy into electrical energy. This method has the ability to supplement secondary battery progress to provide a

feasible, long-term solution for power generation for medical implants without requiring battery replacement.

Another mechanism of generating power in implantable devices is thermoelectric modules. Thermoelectric modules use temperature differences between the core body and inner skin surface to generate electric energy. This gradient can be around 0.3-1.5 °C and is enough to generate 70 μW or higher.⁵⁴ This technology at its current stage would not be able to support an implanted device, but could be used to supplement battery power to increase battery lifetime (Fig. 4).

Piezoelectric power sources convert kinetic or mechanical energy into electrical energy. These systems do not produce sufficiently large current and power densities for implantable medical device applications.^{55,56} Recently, researchers⁵⁷ have developed a prototype in the nanometer scale that produces continuous direct current by harvesting energy from the environment such as ultrasound, vibrations, and blood flow. These devices are made of vertically aligned zinc oxide nanowires that generate electricity when they are bent. This piezoelectric device is attractive toward biomedical applications because zinc oxide is nontoxic and biocompatible.

However, ZnO wires are inflexible and brittle (modulus of 21 GPa and fracture strain of several percent⁵⁸). Additional wires in the device could not solve the problem, as fracture of a few would lead to catastrophic failure of other wires since the total mechanical load would be distributed among fewer wires. This fact could compromise the efficacy of implanted AICD with power generation capabilities.

Piezoelectric polymers, such as poly(vinylidene difluoride) (PVDF), have significant advantages over ZnO and other ceramics. PVDF's mechanical properties are better representative of current AICD lead materials (fracture strain of many tens of percent⁵⁹ and modulus an order of magnitude lower than ZnO), indicating that PVDF devices will be more robust, with less impact on lead mechanical properties. PVDF also makes an ideal biomaterial because it is nontoxic, inert, resistant to water absorption (absorbs <0.04% w), biocompatible,⁶⁰ and clean-room friendly.

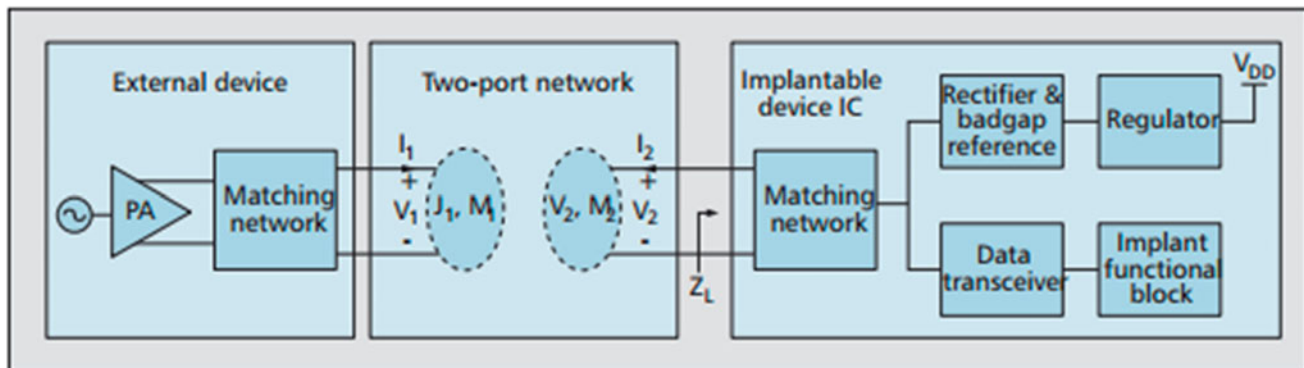


Figure 3. Block diagram showing the various components of a wireless transmission system utilizing RF antennas for energy transfer. Key components include the matching network, rectifier, regulator, and band gap reference. Source: Ref. 52.

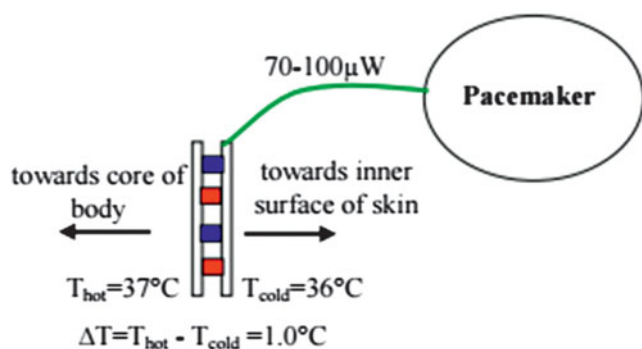


Figure 4. Schematic of a thermoelectric module showing the module attached to a pacemaker as an energy supplement to extend the lifetime of the pacemaker battery. The diagram demonstrates the approximate temperature difference available in the body. Source: Ref. 54.

In contrast, ZnO is difficult to pattern, assemble into devices, stack in multiple layers, and encapsulate.^{61–65}

Several groups have worked on developing piezoelectric energy harvesting for implantable devices.⁶⁶ Some groups have worked with PZT 5A, PZT 5H, and PVDF membranes to produce power from fluctuating blood pressure. Although most of these devices produced power, the power was insufficient to run the device for the proposed application.

The most successful power recovery schemes from body motion using PVDF devices were able to convert ~1% of mechanical energy into electrical energy.⁶⁷ Assuming similar efficiencies for PVDF devices implanted into AICD leads, it could be possible to generate 10–50 mW (1–5 W mechanical power from heart⁶⁸), which is higher than the ~5 mW used by typical pacemakers with 4–5 years of battery lifetime. While PVDF devices have not been utilized for heart applications, they have been incorporated to harvest energy from respiration as early as the 1980s. It was determined that 1 mW of electrical power could be generated from respiration processes (~1 W total mechanical energy).^{69–71} While few advances have been made beyond these initial demonstrations, the understanding of piezoelectricity of bulk PVDF was just emerging in 1984 (Ref. 72) and has since developed substantially. Recent work utilizing PVDF nanofibers⁷³ and the enhancement of the properties of crystallizing polymers using 10–100 nm layers provides future opportunities in this area.

Implantable fuel cells

Basic principle

In a chemical fuel cell, electrical energy is generated by the electrochemical reaction of fuel and oxidant at two spatially separate electrodes.¹⁶ Electrons, released upon the electro-oxidation of the fuel, flow from the anode through an external load circuit to the cathode, where the terminal electron acceptor, usually oxygen, is reduced (Fig. 5). A number of groups, such as Aston et al.,⁷⁴ Benneto,⁷⁵ Katz,^{76,77} Barton and Atanasso,⁷⁸ etc. have

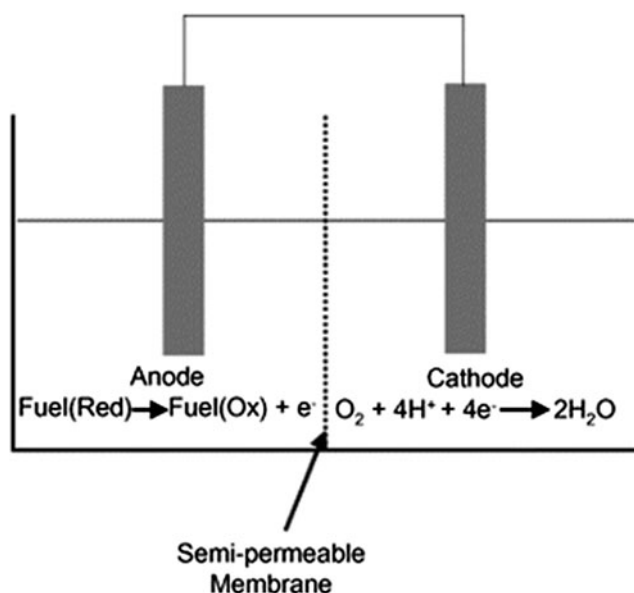


Figure 5. Schematic of a basic biofuel cell consisting an anode, cathode, and a semipermeable membrane.⁷⁹

worked on bioelectrochemistry that use compounds such as sugars found in vivo. Glucose, being the most abundant molecule, is also the most commonly targeted preferred fuel for an implantable fuel cell. The driving force of the electron flow is the difference in electrochemical potential of electrolyte near the anode and the cathode.

In general, glucose-consuming fuel cells can be divided into three main types according to the type of catalyst that is used to enable the electrode reactions: *enzymatic, microbial, and AGFCs*. Table 3 provides an overview of the various types of biofuel cells along with their advantages and disadvantages while Table 4 gives a few examples of the common types of biofuel cells and their characteristics.

Enzymatic fuel cells use enzymes such as glucose oxidase and laccase in their isolated forms as the anodic catalyst. Figure 6(a) demonstrates the layout of their enzymatic cell. An extensive review of enzymatic fuel cells has been reported previously by a number of research groups. Palmore and Whitesides^{88,89} have summarized the concepts, device designs, and performance of biofuel cells. Katz and Willner^{63,76,77,90–98} have discussed the progress of novel electrode designs and chemistries for enzymatic fuel cells. Heller^{99–101} reviewed the advances in miniaturized biological fuel cells. Such fuel cells can potentially run in living systems, taking the oxygen and the fuel required for operation from the environment. Since the enzymes are coated on a flat electrode surface, channeling of electrons from the catalysis site to the current collector remains a huge issue. Hence, suitable electron mediators are used that can shuttle between the site of catalysis and the current collector facilitating the transfer of electrons. However, most of the suitable electron mediators are toxic in nature, making them unsuitable for implantable application. Heller came up with the concept of

Table 3. Potential fuel-cell technologies along with their pros and cons for powering implantable devices.

Potential fuel-cell technology	Description	Pros	Cons
Enzymatic fuel cells	Use enzymes in their isolated forms as the anodic catalyst	Biocompatible, ⁸⁰ biodegradable, ⁸⁰ feasibility of implantation proven ^{81–84}	Ability to channel electrons to current collector, long-term durability, ease of sterilization, limited stability of enzymes ⁸⁵
Microbial fuel cells	Utilize enzymatic system of a whole electroactive micro-organism	Cheapest, highest power output (Table 2)	Biocompatibility and safety issues ^{96,121,127–129}
Abiotic glucose fuel cells	Use mainly nonbiological, abiotic catalysts	Sterilizability, ⁸⁶ long-term stability, ⁸⁷ biocompatibility ⁸⁶	Nonselectivity toward oxygen/glucose, low electrocatalytic activity of metals ⁸⁷

wired enzymes that enable rapid transfer of electrons from enzyme domains to the current collector.⁹⁹ They can be used for a wide variety of implantable medical devices. Recent developments have created a fully biocompatible and biodegradable enzymatic biofuel cells utilizing single-walled carbon nanotubes bioconjugated with glucose oxidase and with a catalase anode. In this cell, Stolarczyk et al. were able to create a power density of 60 $\mu\text{W}/\text{cm}^2$ with the ability to increase power output further through aligning multiple fuel cells in series.⁸⁰ Further innovations in the field of enzymatic biofuel cells include the nanofabrication of electrodes using carbon nanotubes, allowing for tight packing of electrodes. This has allowed a much higher power density to be achieved (18 mW/cm^2) than is typically seen in enzymatic cell.¹⁰² Further, many trials have shown the feasibility of implanting enzymatic biofuel cells into hosts ranging from rats to snails.^{81–84} However, it is unlikely that these trials will lead to their implementation in human hosts anytime in the near future due to multiple unaddressed issues,⁸⁵ including the long-term durability, ease of sterilization, and limited stability of enzymes.

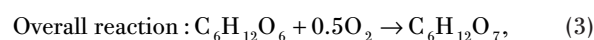
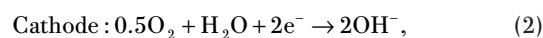
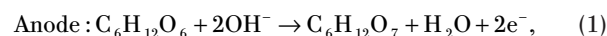
In microbial fuel cells, the enzymatic system of a whole electroactive micro-organism is used. The use of microorganisms in biological fuel cells eliminates the isolation of individual enzymes. Hence, microbial fuel cells are the cheapest among all biological fuel cells. There has been exciting progress on the energy obtained from microbial fuel cells based on the different microbes,^{116–123} electrode materials,^{124–129} electron mediators,^{107,130–133} bioreactors,^{116,134–137} and substrates.¹³⁸ Even though microbial fuel cells provide the highest power output among the different types of fuel cells (Table 2), power-supply systems based on microbial fuel cells are not seriously considered for implantation due to concerns of safety and biocompatibility of implanting bacteria.^{107,133,139–141}

Abiotic glucose fuel cells (AGFCs)

Abiotically catalyzed fuel cells use mainly nonbiological, abiotic catalysts (noble metals or activated carbon) and are therefore considered to be advantageous regarding their sterilizability, long-term stability, and biocompatibility.⁸⁶

The power output of these initial AGFCs was in the range of 40 μW ,¹⁹ when implanted outside the abdomen cavity of dogs, sufficient to run a present-day ICD independent of a battery (Table 1). The duration of early AGFCs in animal trials amounted to more than 150 days¹⁹ of continuous energy production. AGFCs provide superior advantages over conventional batteries by eliminating patient costs associated with battery replacements, and allowing newer devices which require energy to be piggy-backed onto AICDs and biventricular pacemakers. Among the fresh research carried out on implantable AGFCs, the body of work done by Kerzenmacher and Stetten^{109,110,113,142–149} is the most extensive and in-depth.

Theoretically, glucose can be completely oxidized to carbon dioxide and water, releasing 24 electrons per molecule glucose.¹⁴² To simulate the physiological environment for testing the implantable AGFC, glucose solution in phosphate-buffered saline (PBS; pH = 7.4) is most commonly used. However, the transfer of 24 electrons per molecule glucose has not yet been achieved. Rao and Drake reported gluconic acid to be the only reaction product that could be identified by thin layer chromatography.⁸⁶ The oxidation of glucose to gluconic acid only yields two electrons per molecule of glucose and the corresponding electrode reactions are given by:



$$\Delta G^\circ = -2.51 \times 10^5 \text{ J/mol}; V^\circ = 1.30 \text{ V}. \quad (4)$$

where ΔG° is the change in standard Gibbs free energy and V° is the standard reaction potential. This correlates to a maximum coulombic efficiency of 8%.^{88,115}

In practice, the theoretical voltage is never achieved due to the lack of a metal catalyst that can selectively oxidize glucose from blood. The presence of oxygen (along with other amino acids) in blood interferes with glucose oxidation

Table 4. Comparison for various cells.

Anode/Catalyst	Separator	Cathode	Electron mediator	Open circuit voltage (V)	Power ($\mu\text{W}/\text{cm}^2$)	Reference
Enzymatic fuel cells						
Carbon felt/Nafion NBU ₄ + salt alcohol + aldehyde dehydrogenase	Nafion	Pt/C	1550, 2040	104
Carbon fiber/GO _x	None	Carbon fiber/laccase	Modified Os redox polymer	0.78	4300	105
Microbial fuel cells						
Carbon paper	...	Carbon cloth + Pt	Wastewater organics	0.52	494	106
Sn–Pt/MWNT/ <i>E. coli</i>	Nafion	Sn–Pt/MWNT	Neutral red	0.84	2400	107
Abiotic glucose fuel cells (AGFCs)						
Platinized activated carbon	PVA-PAA	Activated carbon	None	...	100	108
Activated Carbon + 5% Pt + 5% Bi	PVA-PAA	Activated carbon	None	0.33	3.3	109
Roughened Pt from Pt–Cu deposition	Supor-450	Pt-black on track-etched membrane	None	0.49	3.1	110
Gold	PVA/PAA	Carbon cloth	None	1.25×10^{-4}	14×10^{-3}	111
Raney type from Pt–Ni alloy over silicon	None (used SU-8 as the separator)	Pt (100 nm) sputtered on carbon paper	None	0.35	2	112
Raney type from Pt–Al alloy over silicon	Porous silicon substrate along with Supor-450	Raney type from Pt–Zn alloy over silicon	None	0.69	4.4	113
Pt thin film	Nanoporous silica	Graphene	None	0.31	5.3	114
Raney type from Pt–Al over silicon	Nafion	Carbon nanotubes in Nafion ionomer	None	0.275	3.4	115

at the anode. Hence, there has been significant effort to develop better anodic catalysts for AGFCs. Commonly used sandwiched-electrode design [Figs. 6(b) and 7(a)–7(c)] helps circumvent this problem to a certain extent by consuming oxygen at the oxygen-selective cathode (usually carbon based), leaving glucose for oxidation at the anode.¹⁰⁹ Various AGFC designs have been described in detail previously by various authors and summarized by Kerzemer et al.^{142,148}

Cathode

Conventionally, platinum is the most favorable material of choice for oxygen reduction. Historically, platinum was kept restricted to the anode material due to the ability of platinum to adsorb and oxidize glucose under low oxygen conditions. As the fabricated cathodes were thick (several hundred micrometers in thickness), simultaneous reduction of oxygen and oxidation of glucose on the same cathode material would drastically lower AGFC power output.

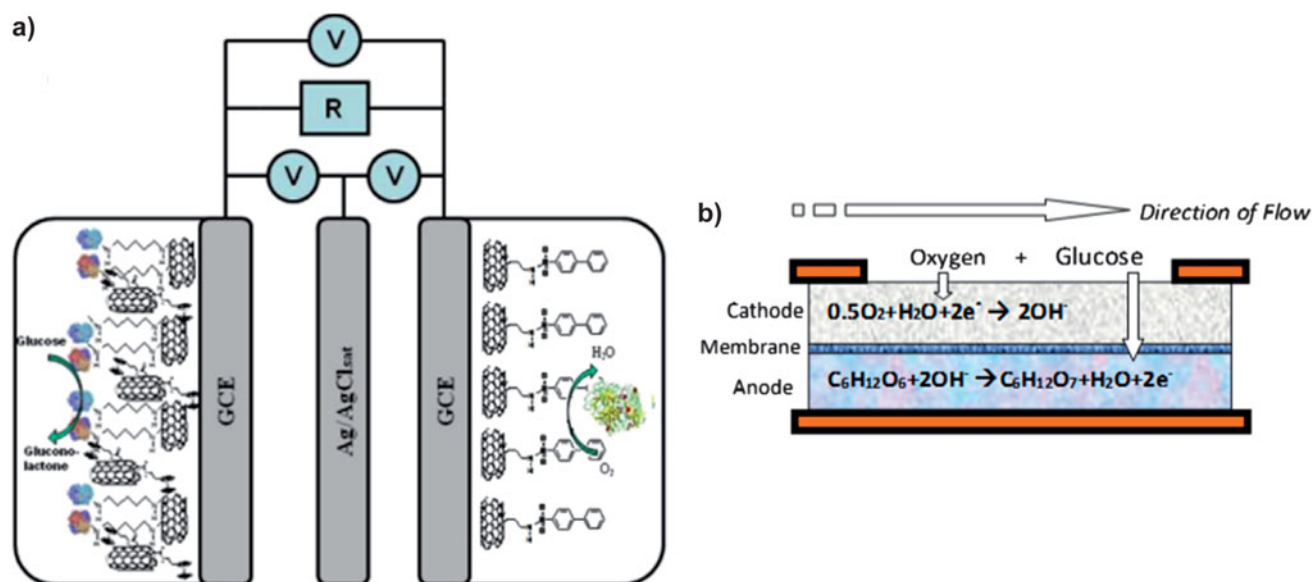


Figure 6. (a) Schematic of enzymatic biofuel cell demonstrated by Stolarczyk et al. showing mechanism of oxidation at the biological – gold-coated electrode (GCE) anode and reduction at the cathode⁸⁰; and (b) schematic of AGFC showing mechanism of selective glucose oxidation by oxygen depletion at the cathode. Source: Ref. 103.

Hence, most of the studies reported the use of activated carbon as the cathode material^{109,142,145,149} (Table 4). Activated carbon does not show any affinity toward glucose and exhibits a better oxygen reduction performance compared to silver.¹⁴² An inherent problem associated with the use of activated carbon is the bulk resistivity and the electrical connectivity of the powdered materials.¹¹³ Carbon-based cathode materials are usually mixed with a binder such as polyvinyl alcohol – polyacrylic acid (PVA-PAA), polytetrafluoroethylene (PTFE), or Nafion as a

support for the catalyst material. The binders add to the bulk resistivity of the cathodes, however.

It has been shown that the oxygen adsorption on activated carbon occurs on the graphene edges of activated carbon and the mechanism of oxygen reduction involves oxidation of such sites.¹⁵⁰ Hence, activated carbon might not be a long-term solution for implantable biofuel cells. In other words, the mass of activated carbon to be used for building cathode materials in AGFCs needs to be estimated before long-term claims can be made.

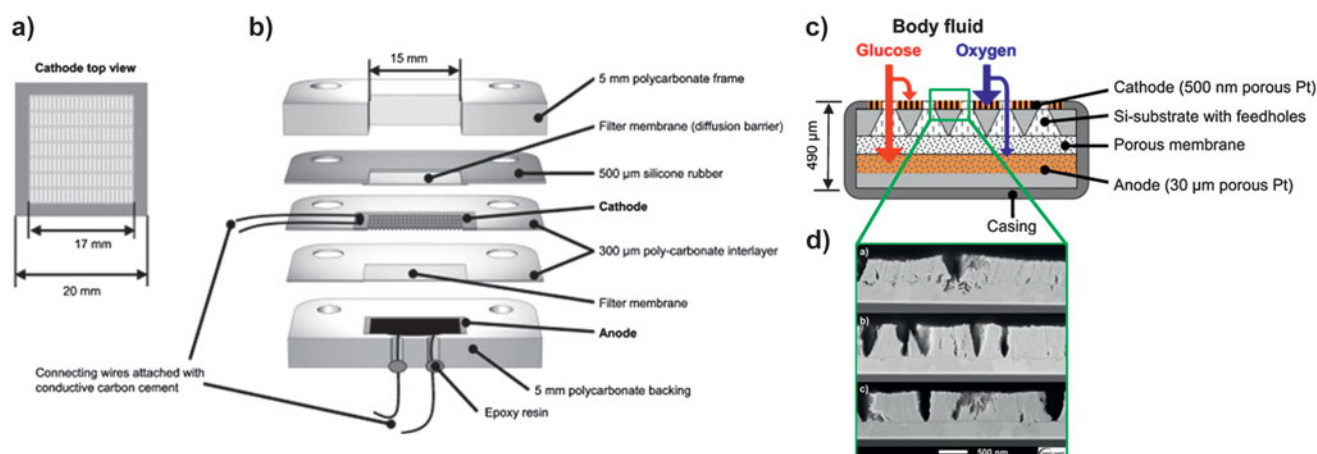


Figure 7. Abiotic glucose fuel cell construction details. (a) Top view of a permeable cathode, (b) cross-sectional view of the binder-less glucose fuel cell assembly. (c) Schematic of binder-less cathode, and a self-supporting platinum anode-based glucose fuel cell. Source: Ref. 113; and (d) cross-sectional views of (a) Pt–Al₆₀, (b) Pt–Al₁₂₀, and (c) Pt–Al₂₄₀ Raney-platinum cathodes fabricated for oxygen depletion. Source: Ref. 147. Copyrights permission 2014 Elsevier.

Kerzenmacher et al.¹⁰⁹ demonstrated a glucose fuel cell running on activated carbon for 234 days, which could generate energy capable of powering an artificial pacemaker. However, they also showed that with time, appreciable oxygen crossover takes place from the cathode to the anode, leading to degradation in the cell performance. Moreover, the highly tortuous structure of activated carbon-based cathode also decreases diffusion to the anode.

By using a thin (<500 nm) film of porous Pt, Kerzenmacher et al. were able to avoid the generation of oxygen-depleted sites on the same electrode [Fig. 7(d)].¹⁴⁷ This allowed fabrication of a platinum-based binderless cathode whose performance was comparable with that of activated carbon at 7% oxygen saturation (physiological conditions)¹⁵¹ [Fig. 7(c)].

Membrane

Separator membranes provide electrical insulation between the electrodes while at the same time they serve as a diffusion barrier to certain chemicals. Given the electrolytic character of body fluids, it would be sufficient to apply a mesh-like hydrophilic spacer as separator membrane, its pores filled with body fluid.

However, the ionic nature of the separator and the corresponding capability to transport either OH⁻ or H⁺ ions influences the electrode reactions. In the case of AGFCs using an oxygen-selective cathode catalyst the separator must not only be an ionic conductor but also allow for the diffusion of fuel and its reaction products to and from the anode.

For conventional membrane use, a variety of materials are reported to be suitable, among them weak cation exchange hydrogels of the poly(vinyl alcohol)-poly(acrylic acid) type, glycolmethacrylate, cuprophane, sulfonated PTFE membranes.^{17,19,109} Difficulties were encountered with hydrogels based on poly(vinyl alcohol)-poly(acrylic acid) (PVA-PAA) and glycolmethacrylate, that were disconnected after prolonged fuel cell operation, presumably due to hydrolysis or the oxidative effect of electrocatalysts.¹¹³ Nafion is another popular membrane among all due to its excellent proton conducting properties. Extensive research on Nafion membrane due to hydrogen fuel cell research makes it an easy favorite.¹¹⁵ A common challenge with polymer membranes is the nonisotropic polymerization, which leads to high variation in the localized physical properties of the membrane. Further, the thickness of the membranes is typically on the order of a few hundred micrometers, increasing the overall AGFC thickness and presenting a significant diffusion barrier for glucose. Moreover, polymer membranes are prone to swell and delaminate, and have been a nidus for infection when implanted *in vivo*.^{19,152} An advantage of using Nafion is that it can be easily spin coated and patterned using photoresist.¹¹⁵ Fabrication of uniform films and patterning of the membrane, with high precision, will be of great importance moving forward if mass production of AGFCs is to be realized.

In recent studies, the use of patternable inorganic membranes has been realized. In particular, Sharma et al.¹¹⁴ used 300 nm thin mesoporous (nanoporous) silica films as the separator membranes. Since mesoporous silica films are obtained from

spin-coated films of organosilicates, it can also be used to fabricate conformal coatings for uneven surfaces. Kerzenmacher et al.^{113,147} used silicon substrate with patterned feedholes as the membrane. Both the fuel cell setups showed promising power output and performance (Table 4). In general, inorganic membranes do not swell, can be fabricated into thin films, offer good opportunity for custom surface chemistries over organic membranes. Clearly, the use of inorganic membranes demonstrates the critical role of a membrane in maximizing the AGFC efficiency.

AGFCs without membrane have also been created, leading to lower ohmic resistance and better glucose diffusion.¹¹² Separation of glucose and oxygen was achieved instead through using a stacked electrode design, where layer of patterned SU-8 was used as the spacer. The peak power output of the cell was approximately 2 μWcm^{-2} with a sustainable output of 1.5 μWcm^{-2} at 10 μAcm^{-2} . This design of membrane-less AGFCs is sustainable as long as a gap is maintained between the cathode and anode, preventing them from shorting.

Anode

Noble metal catalysts are well known for oxidation of carbohydrates.^{17,86,108,152} Gold-based electrodes have been popular for oxidation of glucose under alkaline conditions. However, it tends to have extreme instability and low oxygen tolerance,¹⁵³ making it inappropriate as anode for implantable application. Alternative metals act as better catalysts for AGFCs. But they fail to deliver under the physiological conditions.¹¹¹ Since pure platinum undergoes irreversible oxidation and poisoning easily, roughened platinum has exhibited better, stable performance. In attempts to develop thin and highly active glucose anodes which permit generation of the required energy in the smallest possible volume, Raney noble metal catalysts supported on a metal foil followed by dissolution of the metal catalyst was adopted.^{110,142} Rao et al.^{17,19,154} showed using this method that they could dissolve 79% of the nickel content starting from an initial Pt-Ni (1:6) alloy, resulting in 50–60 μm deep cracks perpendicular to the surface while still being active and shear resistance. While this set of experiments were done about four decades ago, Kloke et al.¹¹⁰ were able to recreate an AGFC with 3.1 $\mu\text{W}/\text{cm}^2$ using a similar technique. They were able to create a highly porous platinum anode through alternation of electrodeposition of a platinum-copper alloy followed by electrochemical extraction of the copper. To fabricate a permeable cathode, the group deposited platinum black on a gold-coated polycarbonate track-etch membrane (PC-TEM).

More recently, Kerzenmacher et al. revived the Raney type metal catalyst anodes by dissolving zinc and aluminum from platinum alloys to improve the biocompatibility of the fuel cell.¹⁴⁵ The Raney type anode was also tested in the presence of various amino acids, resembling physiological fluid. Zinc or nickel leakages during fuel cell operation were found to be negligible, making it suitable for implantable devices. This new structure showed a significant improvement in mechanical and chemical stability while still showing comparable glucose oxidation performance. The complete fuel cells showed a maximum

power density of up to $4.4 \mu\text{W}/\text{cm}^2$ with open circuit potential of 0.7 V at 7% oxygen saturation.¹¹³

Fuel cell assemblies

Nonselectivity toward oxygen or glucose and the low electrocatalytic activity of metals are still problems slowing the use of AGFCs. However, their long-term stability makes them attractive for future development in implantable devices.⁸⁷ Several significant milestones have been achieved in the field of AGFCs within the last decade itself. Demonstration of the Raney type platinum-based electrodes as both the anode and cathode eliminated the necessity to rely on bulky, resistive hydrogel binder-based cathodes for oxygen reduction. Studies have used 500 nm thin films of porous platinum as the cathode material to demonstrate the feasibility. The thickness of cathode is critical in maximizing the cell potential; also affected by or dependent on the diffusion properties across the various membrane barriers used by the assembled AGFC. Greater than required thickness can lead to glucose and oxygen redox reaction taking place on the same electrode. Thinner than required electrodes would lead to oxygen diffusion to the anode, thereby causing the same redox reaction on the anode. The thickness of the cathode in such a case can be further optimized using advanced computational models, to balance between oxygen crossover and glucose oxidation at the porous platinum-based cathodes. Such computational models would also need to account for the complex diffusion across the membrane.

Computational models can also give insight into better design for membranes and implantation sites as well. Implant sites determine the concentrations of free dissolved oxygen, glucose, and other fibrinogenic factors. Earlier studies have considered implanting in body cavities due to the bulkiness of AGFCs.

Such cells could be incorporated as an external coating of the implantable devices and would harness energy from the ambient glucose and oxygen supplied to the body tissue. Redesigning the biofuel cell for vascular implant, on the other hand, would require development of ultrathin AGFCs. The recent increase in neural and cerebral implants have led to development of ABFCs for cerebrospinal implantation as well.¹¹⁵ The cerebrospinal fluid is virtually acellular, is under minimal immune surveillance, has a 100-fold lower protein content than blood and other tissues and is therefore less prone to induce biofouling of implanted devices, and its glucose levels are comparable to those of blood and other tissues. Rapoport et al. were the one of the first to develop and test AGFCs specifically for implant in the brain.¹¹⁵ They also used Raney type platinum film patterned on silicon wafer as the anode (Table 4).

While using Raney type platinum films as electrodes hold great potential for future cell designs, commercialization of AGFCs would need development of patterned electrodes and membrane for consistent, predictable performance. Recent studies have started to integrate electrodes using silicon as the main substrate^{112,115,151,155} (Fig. 8). This also allows patterning of the required CMOS circuitry on the same substrate. Rectifier-based energy harvesting circuits¹⁵⁶ can be used to tap the maximum energy from the system. Further, development of flexible AGFCs would facilitate its use as a conformal coating on the surface of the powered implantable device.

Summary

While there are many potential sources of power, fuel-cell technologies have shown great potential for implantable applications and are the focus of research over the past few decades.

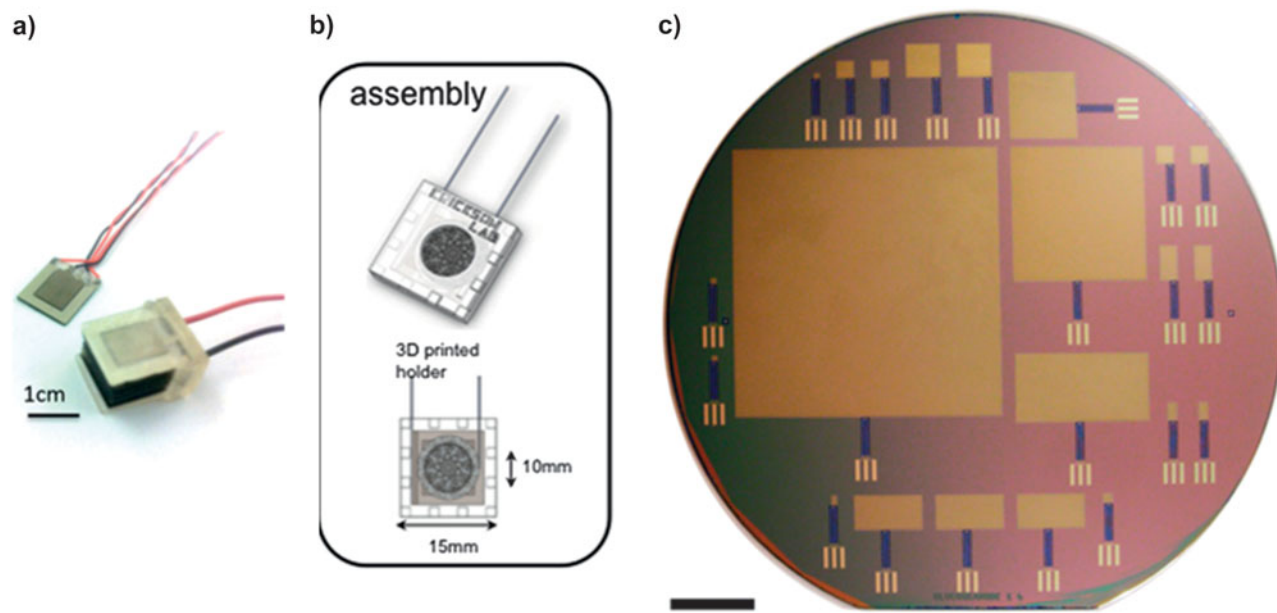


Figure 8. Photographs showing various AGFCs using custom silicon patterned electrodes for low-power implantable devices. Sources: Refs. 155, 112, and 115.

Biofuel cells have the advantage over existing technologies, such as lithium-iodine batteries, in implantable devices such as heart pacemakers. Ideally, an implanted biofuel cell would use metabolite fuel such as glucose or lactate, both of which are readily available in the human body. Clearly, implantable fuel cell has come a long way since the 1960s. And the vast scope of opportunities opens up lot of gray areas as well. Rapid progress in this field requires interdisciplinary efforts in instrumentation, material sciences, microfabrication, and biomedical engineering. Biofuel cells hold great promise moving forward for cardiovascular and neural powered implants.

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