Implanted biofuel cells

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***Abstract*—This article explores the feasibility of using Implantable Biofuel Cells as a sustainable alternative to the lithium-based batteries currently powering medical implants. While conventional batteries offer reliability, their finite lifespan necessitates repeated and risky surgical replacements. In contrast, enzymatic biofuel cells offer the potential of a replenishable power source that harvests energy directly from the host's metabolism. This report first outlines the fundamental classifications of biofuel cells before focusing on the most promising architecture: the enzymatic glucose biofuel cell. Critical design considerations are discussed, ranging from enzyme selection and immobilization to the optimal anatomical location for implantation. By reviewing a progression of key *in vivo* experiments, the report highlights essential engineering lessons and achievements from each. Furthermore, specific attention is given to the challenge of power management, detailing the interface circuitry required to boost low-voltage outputs to levels usable by external electronics. The assessment concludes that while the technology demonstrates significant potential, substantial advancements in biocompatibility, enzymatic stability, and conversion efficiency are required before translation to human applications can be realized.**

I. Introduction: The Energy Crisis in Implantable Devices

Currently, deep-tissue medical implants are solely relying on batteries. Batteries are not ideal because they need to be replaced surgically. Implantable biofuel cells (IBFC) are a solution for the sustainable power problem that rises from current implantable technologies. By implanting bio-catalytic electrodes, electrical power can be harnessed chemically from the hosts metabolism. Which ideally means that a replenishable and sustainable power source could be acquired by implanting BFCs into humans, which are only limited by the hosts metabolism. These implantable devices are challenging to design due to bio-and hemocompatibilty issues but serves as a major research area for sustainable power [1].

IBFCs could either be enzymatic or abiotic. Regardless, they oxidize their corresponding substrate in the hosts body, converting the chemical energy stored in the chemical bonds to electrical energy [2]. The amount of different substrates that could be used as biofuel is quite considerable as different sugars like glucose and fructose can be utilized, but also salts and alcohols like ethanol are viable. As glucose circulates through all organs in the body and serves as the key molecule in human metabolism, it is one of the primary substrates for IBFCs. It is constantly produced and decomposed in the body's metabolism, which makes it an ideal target for producing sustainable power [3]. Because of the abundance and qualities of glucose, glucose biofuel cells (GBFCs) are the most researched type of cells. In the GBFCs, glucose is oxidized either enzymatically or abiotically to harvest electrons. These electrons can be used as electrical power to support implantable technologies such as pacemakers. The most widely successful GBFCs use an enzymatic approach, therefore this article focuses purely on EBFCs (enzymatic biofuel cells) [1], [2], [3].

II. Development of Implanted biofuel cells

1) Working method: EBFCs are constructed with an anode and a cathode. It produces electrical energy by transporting the electrons from the anode through external circuitry, and back to the the cathode as shown in fig. 1. In an EBFC, electrons are harvested from the oxidized substrate by the enzyme at the anode according to this reaction: $C_6H_{12}O_6 \longrightarrow C_6H_{10}O_6 + 2\,H^+ + 2\,e^-$. The electrons are thereafter transferred to the cathode where the second enzyme can utilize the electrons to convert oxygen to water according to this reaction: $\frac{1}{2}\,O_2 + 2\,H^+ + 2\,e^- \longrightarrow H_2O$ [3], [4].

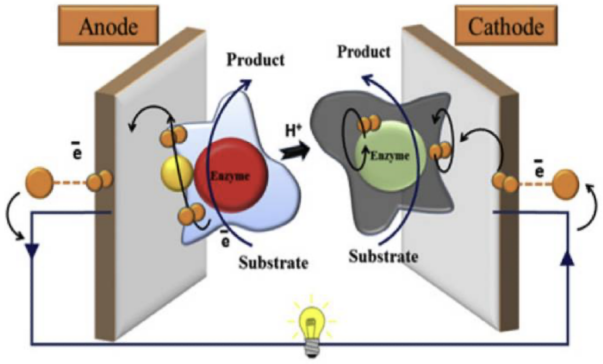

Fig. 1. Schematic of how electrons are transferred between the anode and the cathode in a biofuel cell [3]

There are two methods of electron transfer, direct electron transfer (DET) and mediated electron transfer (MET) [3]. DET means that electrons are transferred directly without the help of a mediating molecule. MET uses a mediator, which generally generates a higher current density than DET but requires more attached components to the biofuel cell, which could make the fabrication more complex [5].

2) Components of EBFCs: The design of EBFCs is built around principles regarding efficiency, biocompatibility and choice of substrate [6]. As stated previously, glucose is one of the major researched fuels for a biofuel cell due to its abundant nature in the human body. For an EBFC, the enzyme needs to

be compatible with the substrate, which ultimately means that glucose oxidase is a common used enzyme, especially *in vivo*. However, there are other alternatives like pyrroloquinoline dependent glucose dehydrogenase (PQQ-GDH) as it provides the same functionality as the glucose oxidase without producing hydrogen peroxide H_2O_2 as a byproduct [1], [6]. Hydrogen peroxide is toxic when released in an implanted biofuel cell which makes the PQQ-GDH a more suitable choice of enzyme for a robust BFC [1]. For the enzyme at the cathode, where the electrons are utilized for the conversion of oxygen to water, laccase and bilirubin oxidase (BOD) are commonly used, as they are well studied and effective at low potentials [1], [4], [6].

As for the electrode material, EBFCs require materials with high surface area, durability and enzyme loading density. Additionally, its crucial that the material is highly conductive as well as biocompatible [7]. Materials with these properties can enhance the efficiency of the BFC [4]. Carbon-based nanomaterials such as buckypaper [1], carbon fibers [6] or multi-walled carbon nanotubes are examples of enzyme immobilization materials that fits this description [4], [7], [8].

III. 3. Limitations of Enzymatic Biofuel Cells

1) Location of implant: Where to implant the biofuel cell has been a contested topic. A rich source of glucose and oxygen with constant flow can be found in be the blood vessels, making it an obvious first choice. The downsides of choosing the blood vessels is that the added turbulence can slow down the bloodstream, putting unwanted strain on the heart to overcome the resistance. Thrombosis is another consideration, that blood clots can occur around the device and potentially move around the body. These risks could be minimized by smaller implants or redirecting the blood, but are still risks [6].
Others propose to use another region of the body, the retroperitoneal space [8], [9]. This space around the kidneys is highly vascularized, meaning that distance from the glucose and oxygen carriers (blood vessels) is very low. Thus the diffusion into the implant is adequate without the many medical risks of having implants directly in the bloodstream.

2) Enzyme Limitations: In EBFCs, there are challenges regarding the enzymes immobilization, function and longevity. Firstly, enzymes are immobilized on the immobilization material prior to implantation. This means that any delamination of enzymes post implantation will result in permanent loss of reactions per second. Consequently, there will be a loss of power-output from the biofuel cell. Secondly, some enzymes need to be oriented in specific ways in regard to each other or the electrode to function properly. However, it is not uncommon for enzymes to reorient themselves after immobilization due to surface shifts which could heavily impact the generated power of the BFC. Structural issues stated above could be decreased and nullified with protective membranes or other additional elements. Past experiments have for instance used

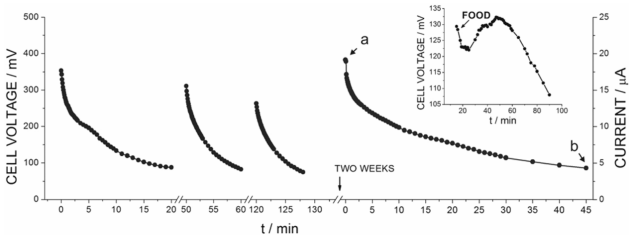

Fig. 2. Voltage generated by the implanted biofuel cell operated in vivo in a snail on a 20 kΩ load resistance as a function of time. Inset: Restoring the cell voltage in real time upon feeding the snail. (figure from [1])

layers of carbon nanotubes and metaloxide frameworks to improve the orientation of the enzymes [4].

Moreover, enzymatic function can be heavily altered by the environment surrounding the implant, which ultimately also affects performance of the BFC. Enzymes are sensitive to pH as well as temperature, changes to either of these could lead to enzyme malfunction. Additionally, interfering molecules could inhibit the enzymes both at the cathode and anode, therefore leaving them non-functional. Some common inhibiting molecules for the enzymatic GBFCs are hydrogen peroxide, chloride ions, uric and ascorbic acids. Therefore, it is crucial that the enzymes are protected against interfering molecules to preserve function and reliability. There are several ways to tackle this problem but one approach is by engineering the enzymes prior to immobilization. Engineering enzymes means to reshape the enzyme by substituting amino acids to get the desired function and characteristics. Enzymes can therefore be altered to be resistant to inhibiting molecules [4], [6].

Lastly, enzymes longevity is not ideal for a long lasting implanted biofuel cell. Enzymes in the human body are constantly being denatured and reproduced. However, in the EBFCs, enzymes have no way of being reproduced, causing the whole system to falter. Ultimately, this is one of the hardest obstacles to overcome for the enzymatic biofuel [4].

3) Biocompatibility and Sterilization: Implanting devices triggers a natural foreign body response, necessitating robust packaging to prevent inflammation or rejection [6]. For BFCs, this presents a paradox: the device must be biologically isolated to prevent immune attack, yet remain permeable to fuel sources. To reconcile these conflicting requirements, bioelectrodes are typically encapsulated within selectively permeable membranes such as dialysis tubing or Dacron® sleeves [6], [9].

Sterilization poses a significant engineering challenge. Standard sterilization protocols, such as autoclaving, irradiation, or chemical treatment, cause the denaturation of enzymes, rendering the fuel cell useless [6], [10]. Consequently, BFCs cannot be sterilized as a whole unit. The proposed solution is aseptic manufacturing: non-biological components are sterilized using standard methods, while enzymes are purified via filtration. The final device is then assembled in a sterile environment immediately prior to implantation [6], [9].

Another element of biocompatibility is the mechanical inter-

action between the implant and the surrounding tissue during movement. Rigid electrodes can pose an issue by interfering with the natural movement of the tissue, potentially provoking inflammation and fibrosis [8]. While this is not only dangerous for the subject, it also negatively impacts the performance of the BFC since fuel has a harder time diffusing into the electrodes [8]. To combat this issue, researchers are developing flexible architectures for the electrodes which will be explored later in this article [8].

IV. Past experiments

1) In vivo experiments in invertebrates: The first long-term study in living animals using implanted EBFCs was carried out in 2012 on snails (see fig. 3 a). Here the researchers implanted the electrode through cut slits in the shell into the hemolymph of the snail with an external variable load resistance for monitoring [1].
Interestingly, the output voltage quickly declined after putting a resistive load on the BFC. In figure 2 it can be seen that the output voltage nearly halved after only 5 minutes of load. This voltage can be restored by removing the load which allows the glucose levels to rise again.
The experiment found that feeding the snails while loading the EBFC partially recovered the power output. Full recovery was only observed after prolonged time of rest. See fig 2 for more detail.
Tuning the load resistance to allow continuous operation where the glucose levels were regenerated at the same rate as drained by the BFC, an output power of $0.16\mu W$ at $1M\Omega$ was maintained for one hour.
After 2 weeks of no applied load, the biofuel cell was still operable. The enzymes were not significantly degraded, and the BFC showed no signs of biofouling. The researchers found the root cause of the output power drop to not be from BFC degradation or snail exhaustion. Rather it was the local glucose levels around the EBFC since the biology of snails does not support rapid transfer of glucose around its hemolymph [1].

The same research group later experimented on a larger invertebrate - namely lobsters [11]. A single implanted EBFC yielded ~ 540 mV and 1 mA (0.16 mW peak power), falling short of the 700 mV threshold required for powering an arbitrarily chosen commercial circuit. An attempt at boosting the voltage was done by implanting two cells in series within the same body. This failed since the low resistance of tissue ($\sim 180k\Omega$) shorted the two cells, thus only slightly increasing output voltage.

2) In vivo experiments in mammals: The first demonstration of a single EBFC capable of powering electronics in a mammal was reported in 2013. The device used in the test was implanted in the retroperitoneal space of a freely moving rat, with flexible wires leading to a connector fixed on the skull [9].
The EBFC consisted of bioelectrodes formed by compressing multi-walled carbon nanotubes (MWCNTs) and enzymes into rigid pellets. The anode utilized glucose oxidase (GOx) for glucose oxidation, combined with catalase, while the cathode utilized laccase for oxygen reduction. To ensure biocompatibility and stability, the electrodes were wrapped in dialysis membranes to retain enzymes, housed in perforated silicone tubes for mechanical support, and finally sutured inside a Dacron® sleeve.
The same issue of local glucose and oxygen depletion seen in the invertebrates were present in the rats, but here the decay was slower, and recovery faster. With a discharge of $50\mu A\ cm^-2$ for 5 minutes, and resting for 7 minutes, the EBFC could output a stable voltage of $\sim 0.6V$ only dropping $20mV$ under load for four cycles.

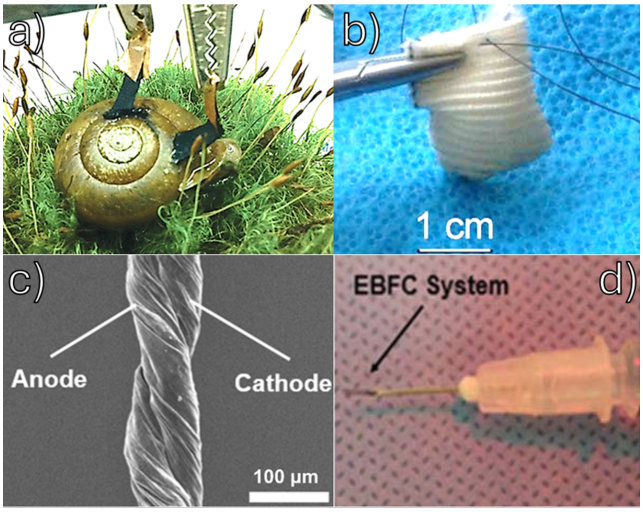

Fig. 3. a) photo of the first EBFC implanted long term in a living animal [1]. b) photo of a rigid EBFC with Dacron® sleeve before implanting into a rats peritoneum [9]. c) SEM image of a flexible carbon-nanotube EBFC system [8]. d) Optical image of the same system in a 26 G (0.464mm outer diameter) syringe needle [8].

The implants in the rats failed after 6-8 days because of unstable wiring and production method, thus not allowing for study of long term degradation of enzymes. A study of the tissue around the BFC was carried out after 110 days of being implanted, showing positive signs of biocompatibility with highly vascularized tissue.

In 2020, a research group engineered a submillimetric EBFC made of MWCNT [8]. The chosen enzymes were glucose oxidase (GOx) and bilirubin oxidase for the anode and cathode respectively. Here the sheets of MWCNT were rolled into long "strings" and then twisted to keep the enzymes trapped in the structure without the need of a dialysis bag. The flexible anode and cathode were coated in Nafion, then twisted together to form a flexible EBFC with a diameter of $\sim 70\mu m$, see fig 3 c) and d). Due to the size of this implant a minimal invasive implantation method of direct injection with syringe into a mouse could be carried out. The results of the paper was a very power-dense BFC of $0.3mW\ cm^-2$.

The power density reached here is a huge engineering feat, but still only output $4.7\mu W$ After a histology analysis, it was evident that the EBFC was biocompatible, but the grown tissue still acted as a barrier for glucose transport, thus degrading perfomance heavily. This tissue buildup resulted in a 55% drop in measured OCV, and a 19% drop in areal power density [8].

V. Power Management and Interfacing with Electronics

The output voltage of the proposed EBFCs is in the range of 300–$600mV$, which is insufficient to power standard implantable medical devices which run on Lithium-Iodine batteries generating a stable $2.8V$ [11].
This low output voltage is fundamentally restricted by the harnessed fuel. It is determined by the fixed energy difference between the glucose reaction at the anode, and oxygen reaction at the cathode. As observed in the *in vivo* experiments with lobsters, attempting to increase this voltage by having multiple EBFCs in series in the same body is ineffective [11]. This was due to the short circuiting nature of the low resistance paths inside the tissue of bodies.
The most promising solution to increase the output voltage of the EBFCs is to have external circuitry, which modifies the characteristics of the electrical signal. Several groups have successfully used commercial boost-converters to power electronic devices from light-emitting diodes (LEDs) to pacemakers [9][12].
Even the boost-converters require a higher rail voltage than the EBFCs can provide, necessitating a charge pump as an interface.
The *in vivo* experiment in rats discussed previously in section IV-2 used a BQ25504 boost-converter to power external circuitry [9], [13]. The BQ25504 requires a high voltage for starting the operation (600mV), where it afterwards can operate at a lower voltage (130mV) which is usual for boost-converters. The starting voltage can be acquired by utilizing the integrated charge-pump, which accumulates charges within a capacitor and releases it in discrete bursts. These high power bursts can power energy-demanding circuits, and can have an efficiency up to 75%. This architecture can be useful for monitoring and transmitting devices, which only needs a few milliseconds of high power to operate.

To power implanted devices that require continuous operation, such as pacemakers, an another architecture is necessary. Southcott et al. demonstrated that a stable, continuous supply can be achieved by decoupling the startup and regulation functions into two distinct circuits [12]. In their *in vitro* pacemaker experiment, a separate charge pump (Seiko S-882Z) was used solely to boost the low input voltage ($0.3\,\mathrm{V}$) to $\sim 2.0\,\mathrm{V}$. This intermediate voltage was then fed into a separate boost-converter (Seiko S-8353), which regulated the output to the stable $3.0\,\mathrm{V}$ required by the pacemaker's logic.

Although this dual-stage approach reduces overall efficiency to 60% [12], it provides the constant current necessary for life-support devices, unlike the intermittent bursts of single-chip harvesters. Using this configuration, researchers successfully powered a commercially available pacemaker for 5 hours using a single EBFC [12].

It is crucial to note that in all of the explored experiments, the power management circuitry was located *ex vivo*. The BFCs were connected to external circuitry containing the boost-converters and charge-pumps. Consequently, a significant engineering challenge remains in the miniaturization and encapsulation of these interface circuits to allow for their full integration into a single, implantable package. Next-generation bioelectronics are expected to operate on increasingly lower power budgets which will better fit the inherently constrained power output of the EBFCs.

VI. Conclusion & Future Outlook

Currently, Lithium-based batteries outmatch the performance of modern EBFCs in all aspects. However, the potential of a replenishable energy source derived directly from the hosts metabolism is too promising to ignore. While researchers have achieved several successful proof of concept experiments of *in vivo* energy harvesting, the technology has not yet reached viability. The technology is hindered by the critical limitations of enzyme stability and the challenges of biocompatibility. As observed in all the trials, a combination of tissue buildup and enzyme degradation severely hindered the theoretical power output of the EBFCs. Even with modern biocompatible electrodes, the output voltage plateaued at 55% of its initial value within one week [8].
Additionally, the current reliance on external voltage-boosting circuitry is mandatory, yet these circuits currently remain too bulky and inefficient for full integration into a single implantable package.

The future of implantable EBFCs lies in the development of materials that bridge the mechanical and biological gap between the device and the host tissue. The field is swiftly shifting from rigid components toward soft electrodes. Recent successes with flexible carbon nanotube yarns [8] illustrate that flexible implants significantly increase the biocompatibility for the host body, but still struggle with long-term performance.

Instead of relying on fragile enzymes, researchers are exploring abiotic catalysts as an alternative. The development of ultrathin ceramic-electrolyte BFCs result in devices that are autoclavable and immune to enzymatic degradation, potentially extending the lifetime of the BFC [10]. Lastly, as the power consumption of medical implants continues to decrease, the reliance on inefficient boost converters may diminish.

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