IMPLANTABLE DEVICE FOR LATE-PHASE HEMORRHAGIC SHOCK PREVENTION USING A NOVEL NON-ENZYMATIC FUEL CELL

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ABSTRACT

Autonomous microsystems that have the ability to function on their own, interpret and interact with their environment have many applications for *in-vivo* medical devices. Despite advances in nanotechnology and low power electronics, the development of such devices had been limited in the past decade by slow advances in lithium battery technology. Implantable power sources such as piezoelectric generators and bio-fuel cells have been proposed as alternatives to lithium batteries however those technologies are limited by either poor power output or short lifetime. Non-enzymatic glucose fuel cells are promising replacement candidates because of good long-term stability and adequate power density. Here we have developed a novel single-layer glucose fuel cell with good performance (2µW cm^{-2}) and long-term stability that can be stacked to obtain a high volumetric power density unit (over 16µW cm^{-3}). This represents the first demonstration of a low volume non-enzymatic fuel cell stack and our power density results are an order of magnitude greater than the state-of-the-art. To demonstrate the potential of this new technology, we have developed an autonomous implantable device for vasopressin monitoring and prevention of late-phase hemorrhagic shock. The device consists of a nonosensor, drug delivery device and glucose fuel cell unit.

KEYWORDS

Autonomous implantable devices, glucose fuel cells, vasopressin, biosensor, drug delivery

INTRODUCTION

Non-rechargeable lithium batteries have been successfully used in implantable medical devices for over 40 years, however their life cycle is often much shorter than the desired period of implantation for such devices[1]. In addition, because many new proposed medical devices have much higher power requirements than current batteries, researchers are developing new implantable power sources that can harvest chemical, thermal and mechanical energy from the human body as an alternative to lithium batteries[2]. These include piezoelectric[3] and thermal generators[4] and bio-fuel cells[5]. Glucose fuel cells are particularly interesting because of the abundance of oxygen and glucose in body tissue and the possibility to generate a stable high continuous power output through the coupling of glucose oxidation and oxygen reduction reactions at the electrodes[6]. Here we present a novel non-enzymatic fuel cell that can be manufactured cost-efficiently on single wafers using standard fabrication protocols and integrated in low volume implantable devices. In order to demonstrate the potential of such non-enzymatic glucose fuel cells for powering medical devices we have developed an integrated device for vasopressin monitoring and prevention of late-phase hemorrhagic shock. This is an important application because hemorrhagic shock is the number one cause of preventable death in military battlefield situations. It is also known that progression to the irreversible phase of hemorrhagic shock is indicated by a marked decrease plasma vasopressin levels and that replenishment of vasopressin up to the normal physiological levels has also been shown to rapidly increase the arterial pressure[7]. Therefore our device in Figure 1 integrates an aptamer-based carbon nanotube biosensor currently being developed in our lab and an electrochemically driven microwell drug delivery system similar to a device developed by Chung *et al*[8].

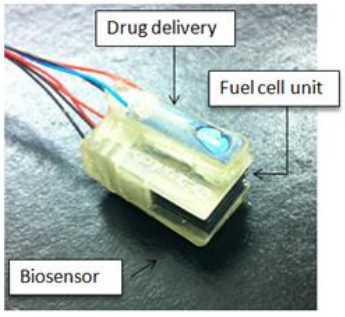

Figure 1: Integrated device consisting of drug delivery unit, biosensor and fuel cell unit for in-vivo monitoring of vasopressin

Here we first demonstrate the integration of the glucose fuel cell into a high volumetric power density fuel cell unit. Secondly we demonstrate that the aptamer-based biosensor can be used to continuously measure changes in vasopressin concentration. Finally we show experiments that demonstrate that that these components can be integrated together to produce an implantable device for late-phase hemorrhagic shock prevention.

NON-ENZYMATIC GLUCOSE FUEL CELL

The single-layer fuel cells (SLFCs) developed here are patterned directly on 500µm thick fused silica substrates and subsequently diced to obtain 1cm^2 fuel cell layers as can be seen in Figure 2a. A concentric design where the anode is surrounded by the cathode was selected because it increases the interface area between the electrodes and it helps increase glucose-oxygen separation when the layers are stacked. In order to achieve high effective surface area, a Raney-type alloy process is used for both the anode and the cathode. This process, first demonstrated by Gebhardt *et al.*[9], involves the annealing of a thin layer of platinum with a non-noble metal followed by the chemical etching of the non-alloyed outer metal layer. By itself, when tested *in-vitro* at physiological levels of glucose and oxygen, the SLFC achieves low power output (0.8µW) because of oxygen cross over at the anode, however when the layers

978-0-9798064-5-2/µTAS 2012/$20©12CBMS-0001

are stacked 500µm apart, the oxygen gets depleted at the cathode before it reaches the anode as illustrated in Figure 2b. In order to demonstrate the potential of SLFCs to be integrated in implantable devices as highly compact power sources we have assembled a fuel cell unit with stacked SLFCs connected externally in series. The holder was printed using a 3D printer. The assembled device in Figure 2a has a volume of approximately $1cm^3$ and can accommodate 12 SLFCs printed on both sides of 1cm by 1cm diced pieces of 500µm thick fused silica wafers. That represents $12cm^2$ of fuel cell surface area exposed to solution. For comparison purposes an oxygen depletion design type fuel cell that we have previously developed[10] had a thickness of 0.5cm, a total volume of 2 cm^3 and a surface area of $1cm^2$ exposed to solution. The fuel cell had a power output of 2 μWcm^2 corresponding to a volumetric power output of roughly $1\mu Wcm^3$. In Figure 2c it can be seen that the peak volumetric power output is roughly $16\mu Wcm^3$ roughly 16 times higher than for the state-of the art depletion design type fuel cell. It can be also seen by the chronoamperometric response at 100mV that the fuel cell unit shows no power degradation over a period of 12 hours.

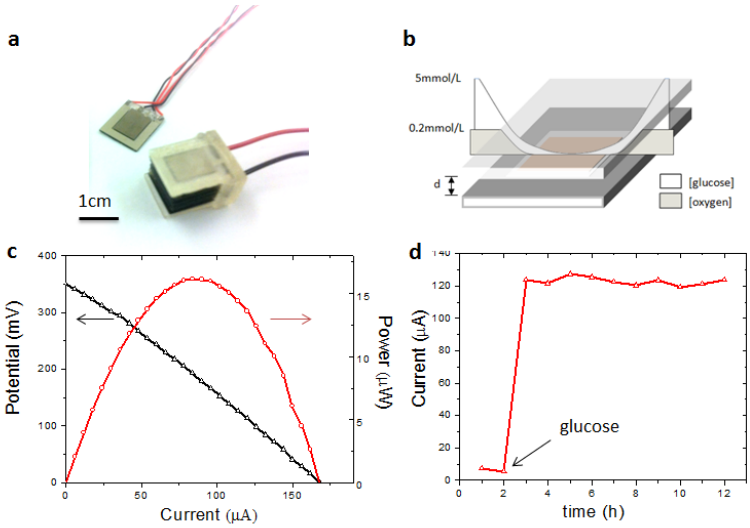

Figure 2: Glucose Fuel Cell Unit. (a) picture of one double sided SLFC along with a stack of 12SLFCs (b) illustration demonstrating how confining the reactants diffusion can reduce oxygen cross over at the anode (c) performance of the 12 SLFCs stack connected in series (d) chronoamperometric response at 0.1V in 0.01M PBS solution for the first 2h and after the addition of $5\times10^{-3}molL^{-1}$ glucose

NANOSENSOR FOR APTAMER BASED DETECTION

The aptamer-based nanosensor that we have developed here works by taking advantage of the conductivity change that occurs due to vasopressin binding at the aptamer-modified carbon nanotubes surface. Aptamers have been widely employed to bind tightly to very specific target molecules, such as amino acids, drugs, and proteins[11]. The binding between aptamer and vasopressin can be transduced to be a readable signal via different approaches in aptamer-based biosensors[12]. The sensor we have developed allows to measure changes in vasopressin binding, and therefore vasopressin concentration by measuring current changes in the sensor. The voltage in the integrated system is provided by the fuel cell unit. Figure 3a shows an illustration of vasopressin binding along the aptamer-modified carbon nanotubes as well as a device that was used to continuously monitor real-time changes in vasopressin concentration. Figure 3b shows that there is 7% decrease in current when 1mM vasopressin is added to the 0.01M PBS solution at potentials of up to 1V. In Figure 3c we demonstrate the real time response to the addition of 10µM vasopressin to the PBS solution. We can see that there is an initial drop when vasopressin flows through the detection area and that the current goes back up to initial levels over approximately 50sec when only PBS is introduced over the detection area. These results demonstrate that the sensor can be used continuously at small applied potentials to measure changes in vasopressin concentration.

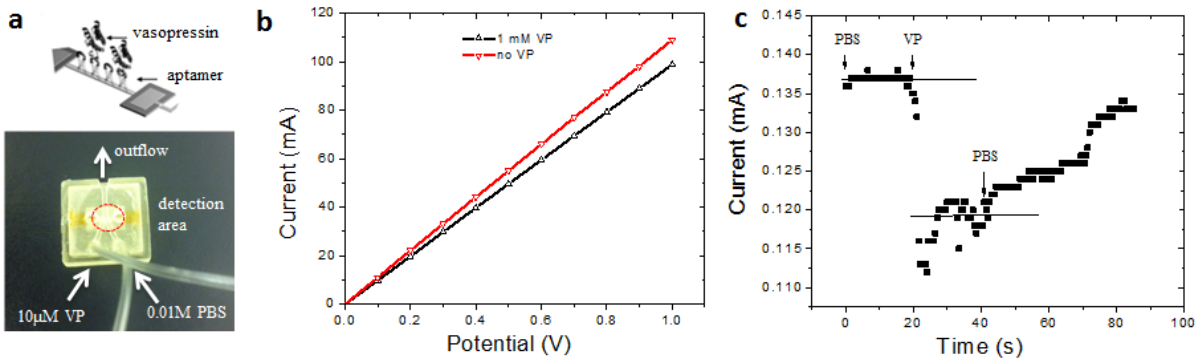

Figure 3: Sensor Unit. (a) illustration of vasopressin binding along the aptamer-modified carbon nanotubes and device for continuous monitoring of changes in vasopressin concentration (b) current-potential curvesfor 1mM

vasopressin in PBS(black) and just PBS solution(red) (c) real-time response to addition of 10 μM vasopressin, followed by just 0.01M PBS 20 sec later

INTEGRATED DEVICE FOR CONTINUOUS VASOPRESSIN MONITORING

The device in Figure 4a, composed of 2 stacked SFCLs and a biosensor, was used to demonstrate that the fuel cell unit can be used to continuously detect changes in vasopressin concentration. In Figure 4b it can be seen that the voltage decreases by an average of 2.56% when vasopressin flows over the detection area. This change can be easily detected despite only using 2 fuel cell layers (corresponding to 0.1cm^3) to power the sensor. To increase accuracy, a larger fuel cell unit can be connected to the sensor.

The electrochemically driven microwell drug delivery system developed previously has been modified to be more easily integrated in a small compact implantable device[8]. The reservoir of the drug delivery device contains approximately 15μl of 0.05g/l vasopressin for release. When drug release is desired, an electrical potential is applied and the gold membrane holding off the vasopressin ruptures. Figure 4c shows that the vasopressin drug delivery can be achieved in approximately 7seconds at an applied potential of 12V. In the devices presented in Figure 1 all the connections were made externally and the voltage to the drug delivery system was provided by an external power source. We have demonstrated here that the glucose fuel cell unit that we have developed here can be used to detect changes in vasopressin concentration. In addition the glucose fuel cell unit can also be used to charge a capacitor that can subsequently be used to apply a one-time 12V potential in order to initiate drug delivery.

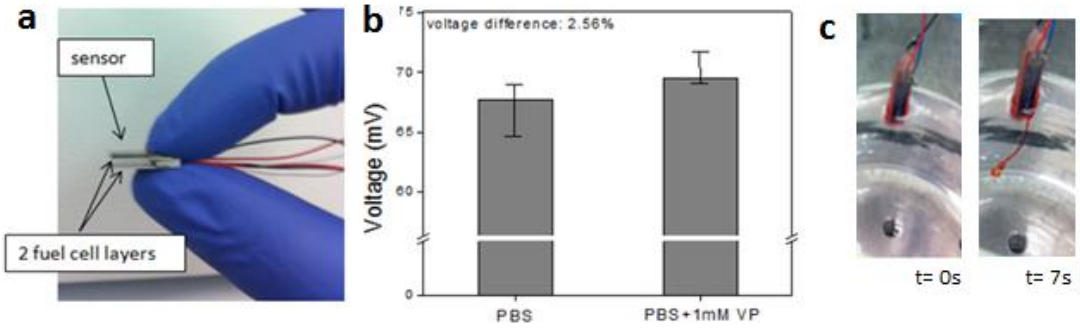

Figure 4: Integrated device. (a) integrated stacked fuel cell unit and sensor device (b) voltage drop across the sensor when the current is generated by the fuel cell unit (c) drug deliver system in 0.01M PBS solution at t=0s (time when 12V is applied) and at t=7s

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