

A self-powered glucose biosensing system



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ABSTRACT

A self-powered glucose biosensor (SPGS) system is fabricated and in vitro characterization of the power generation and charging frequency characteristics in glucose analyte are described. The bioelectrodes consist of compressed network of three-dimensional multi-walled carbon nanotubes with redox enzymes, pyroquinoline quinone glucose dehydrogenase (PQQ-GDH) and laccase functioning as the anodic and cathodic catalyst, respectively. When operated in 45 mM glucose, the biofuel cell exhibited an open circuit voltage and power density of 681.8 mV and 67.86 $\mu\text{W}/\text{cm}^2$ at 335 mV, respectively, with a current density of 202.2 $\mu\text{A}/\text{cm}^2$. Moreover, at physiological glucose concentration (5 mM), the biofuel cell exhibits open circuit voltage and power density of 302.1 mV and 15.98 $\mu\text{W}/\text{cm}^2$ at 166.3 mV, respectively, with a current density of 100 $\mu\text{A}/\text{cm}^2$. The biofuel cell assembly produced a linear dynamic range of 0.5–45 mM glucose. These findings show that glucose biofuel cells can be further investigated in the development of a self-powered glucose biosensor by using a capacitor as the transducer element. By monitoring the capacitor charging frequencies, which are influenced by the concentration of the glucose analyte, a linear dynamic range of 0.5–35 mM glucose is observed. The operational stability of SPGS is monitored over a period of 63 days and is found to be stable with 15.38% and 11.76% drop in power density under continuous discharge in 10 mM and 20 mM glucose, respectively. These results demonstrate that SPGSs can simultaneously generate bioelectricity to power ultra-low powered devices and sense glucose.

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1. Introduction

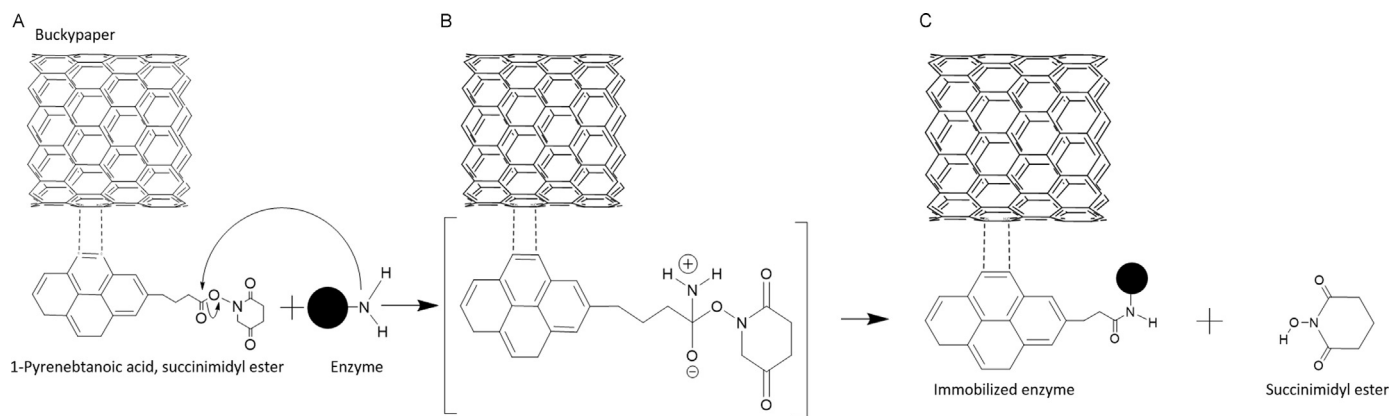
Diabetes is a metabolic disorder caused by the inability of pancreatic β -cells to produce sufficient amount of insulin needed for blood glucose control, thereby leading to high blood glucose levels. According to the 2012 CDC report, 29.1 million people in US suffer from diabetes while 86 million people suffer from pre-diabetes. As many as 234,051 people died due to complications from diabetes in the year 2010, making it the 7th leading causes of deaths (McGlennon et al., 2015). Individuals diagnosed with diabetes are more susceptible to other complications and diseases (Gregg et al., 2014), such as high blood pressure, high cholesterol levels, blindness, eye problems, heart diseases, strokes, obstructive sleep apnoea (Manin et al., 2015) etc. Current continuous glucose monitor (CGM) technologies require the patient to insert a tiny sensor under the skin that measures blood glucose levels. The sensor remains under the skin for several days to a week before it is replaced with a new sensor. This approach to monitoring blood glucose level is very helpful to patients who suffer from

haemophobia. However, CGM uses potentiostatic circuit to acquire blood glucose information, which requires the use of an external power source, such as a battery. Moreover, CGM devices are not as accurate as the standard blood glucose meters and one has to confirm the blood glucose level with glucose meters before making any changes in their treatment regimen.

Researchers have been seeking to bridge the gap between glucose monitoring and insulin delivery by developing artificial pancreas, which would consist of a CGM system, an insulin delivery system and a computer program that adjusts the insulin delivery based on changes in the blood glucose levels. Though the bridge between the glucose monitoring and insulin delivery systems have been implemented in the early stages, SPGSs have the potential to overcome the shortcomings of glucose monitors based on potentiostatic circuits by autonomously monitoring blood glucose continuously. This technology uses the amalgamation of glucose biofuel cell and glucose biosensor operation principles. The glucose biofuel cell consist of an anode, a cathode and an electrolyte containing glucose fuel. The oxidation of glucose at anode results in power generation, which could be utilized to power bioelectronics devices as well as provide glucose concentration information. Hence, it will eliminate the need for external power sources and will utilize the glucose fuel in the body

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Scheme 1. Enzyme immobilization scheme. (A) PBSE interact with the buckypaper via π - π stacking and amino functional group on the enzyme reacts with the carboxyl functional group on the PBSE to form a peptide bond. (B) Formation of the unstable intermediate product. (C) Immobilized enzyme along with the byproduct.

to simultaneously generate bioelectricity and monitor blood glucose levels. The power produced by a single biofuel cell is however, not sufficient to power an implantable bioelectronics device (i.e., glucose biosensor). Although stacked multiple glucose biofuel cells (MacVittie et al., 2013) may fulfill the power requirement needed to power a glucose biosensor, it results in an overall bulky device, thereby defeating the purpose of miniaturized implantable biofuel cell device. To overcome this limitation, a charge pump integrated circuit (IC) is used to amplify the minimum input voltage of 0.3 V, which is easily produced by a single glucose biofuel cell to a voltage range of 1.8–2.2 V. The resulting power has been shown to be enough to power implantable bioelectronic devices (Katz and MacVittie, 2013; Falk et al., 2014). Further amplification to 3 V has been achieved using a DC–DC convertor to enable the powering of pacemaker circuit (Southcott et al., 2013; Desmaële et al., 2015).

Significant efforts have been made in the development of SPGSs in past couple of years (Slaughter and Kulkarni, 2015). One such attempt in fabricating a self-powered glucose biosensor comprised of glucose oxidase (GOx) anode and a Pt/C cathode (Liu et al., 2012). In vitro characterization showed that the sensor had a dynamic range of 2–30 mM. When operating in 30 mM glucose, an open circuit voltage of 480 mV and short circuit current of 19 nA was achieved. The power output was observed to be stable over a period of 60 days of continuous operation at 37 °C in 30 mM glucose. Hence, SPGSs can be considered as an alternative to conventionally power sources, specifically for bioimplantable applications. A miniaturized biofuel cell based on glucose dehydrogenase and bilirubin oxidase at screen printed electrodes (Pinyou et al., 2015) produced a maximum power density of 6.8 μ W/cm² and exhibited a dynamic range of 0.1–1 mM. The power generated by this miniaturized biofuel cell was utilized by the electrolyser that detected the glucose concentration dependent dye spectrophotometrically to develop a self-powered glucose biosensor with a dynamic range of 0.1–0.6 mM. Although there have been significant contributions to the field of biofuel cells, there is still a need to develop SPGS systems with long term stability in order to compete with the existing technology. In this paper, we fabricated and characterized a SPGS system by exciting the voltage generated from the glucose biofuel cell via a charge pump IC and the resulting amplified voltage is used to charge the capacitor functioning as a transducer. The combination of charge pump IC and capacitor with the glucose biofuel cell enables the realization of an SPGS system that can simultaneously power ultra-low powered bioelectronics and sense glucose.

2. Material and methods

2.1. Materials

Buckypaper composed of compressed network of multi-walled carbon nanotubes (MWCNTs) was purchased from NanotechLabs in Yadkinville, NC. 1-Pyrenebutanoic acid, succinimidyl ester (PBSE) was purchased from AnaSpec Inc. Pyroquinoline quinone glucose dehydrogenase (PQQ-GDH; E.C. 1.1.5.2) was purchased from Toyobo Co. Ltd. Laccase (E.C.1.10.3.2, from *Trametes versicolor*), potassium phosphate, calcium chloride, D-(+)-Glucose, $\geq 99.5\%$, Dimethyl sulfoxide (DMSO), $\geq 99.5\%$ (GC) Nafion[®] perfluorinated resin solution, 5% wt were purchased from Sigma Aldrich. Ultra-pure water (18.2 M Ω cm) from Milli-Q source was used in all the experiments.

2.2. Bioelectrode preparation

1.0 cm $\times$ 0.2 cm strips of buckypaper were used as the electrode material because of the high surface area for enzyme loading afforded by the mesh network of carbon nanotubes (Zebda et al., 2011; Reuillard et al., 2013; Holzinger et al., 2012). Initially the electrodes were rinsed in 2-propanol to remove any impurities present on the surface of the buckypaper as a result of the manufacturing process. In order for the polyaromatic pyrenyl group of the PBSE, a heterobifunctional cross-linker, to interact with the MWCNTs via π - π stacking (Roman et al., 2006) as seen in Scheme 1A, the electrodes were immediately incubated with 10 mM PBSE, in DMSO with moderate shaking for 1 h in the dark. Following the incubation period, the electrodes were subsequently rinsed with DMSO and 100 mM phosphate buffer solution (pH 7) to remove any loosely bound PBSE and any traces of DMSO on the electrodes, respectively. The bioelectrodes were prepared by immobilizing anodic and cathodic enzymes, PQQ-GDH and laccase on a separate PBSE-functionalized electrodes. The bioanode was prepared by incubating the PBSE-functionalized electrodes in a solution of PQQ-GDH in 10 mM PBS containing 1 mM CaCl₂ (pH 7). Whereas, the biocathode was prepared by incubating the PBSE-functionalized electrodes in the solution of laccase in 10 mM PBS (pH 7). The immobilization reactions were conducted at room temperature with moderate shaking at room temperature for a period of 1 h.

The amino functional groups from the enzymes react with the carboxyl functional group from the PBSE (Scheme 1A) by breaking the double bond between the carbon and oxygen atom. The π electrons present in the pi bond moves towards the oxygen atom making it formally negative charged. In addition, nitrogen atom

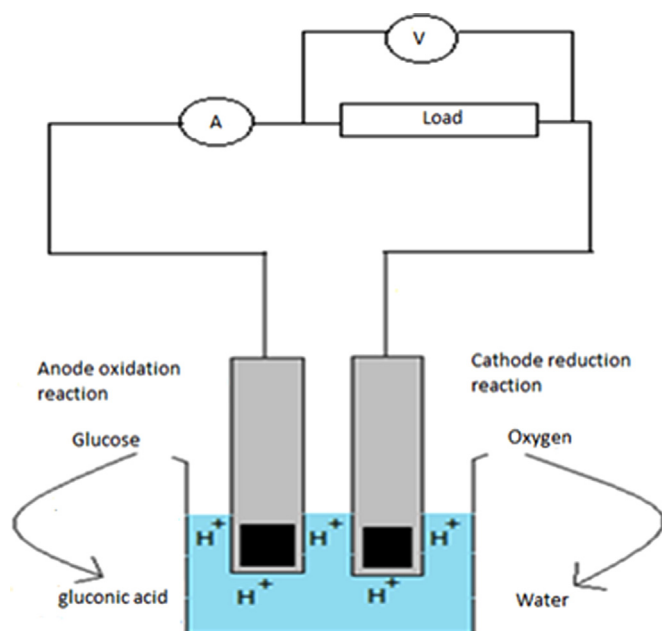
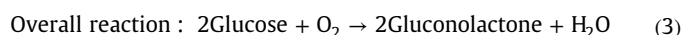
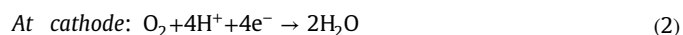


Fig. 1. Illustration of the experimental setup for the glucose biofuel cell consisting of a cathode, an anode and an electrolyte containing glucose fuel and the redox reactions that occur within the glucose biofuel cell.

reacts with the carbon atom to donate an electron making it formally positive. These formally positive and negative states result in the formation of an intermediate product that is unstable (Scheme 1B). As a result, the π electron returns back to form a double bond and releases the $R'-O$ group along with one hydrogen atom. This reaction enables the nitrogen atom to become electrically neutral and hence, stable. Overall, this reaction results in the formation of a peptide (amide) bond ($-CO-NH-$) between the amino and carboxyl functional groups (Katz et al., 2015), thereby resulting in the enzyme-modified electrodes as shown in Scheme 1C. Furthermore, the bioelectrodes were additionally coated with 2 μ L of a 10-fold diluted 5 wt% Nafion 117 solution and left to dry in a desiccator for 15 min. The resulting bioelectrodes exhibited an active surface area of 0.08 cm^2 and a volume of 0.024 cm^3 . The bioanode was stored in 100 mM PBS (pH 7) and the biocathode was stored in 100 mM PBS (pH 6) in the refrigerator when not in use.

2.3. Glucose biofuel cell measurements

Fig. 1 provides a depiction of the experimental setup of the glucose biofuel cell consisting of bioanode and biocathode previously described by using glucose analyte and oxygen in air-saturated environment as fuel and oxidant, where the load represents external variable load resistor. At the bioanode, PQQ-GDH oxidizes glucose to produce gluconolactone by releasing electrons and positive ions. The electrons travel through the external circuitry, thus producing current and the positive ions travel through the electrolyte containing the glucose fuel and recombine at biocathode, where laccase reduces oxygen to water. The half reactions and the overall cell reaction is as follows:



The glucose biofuel cell was characterized in the presence of various concentration of glucose analyte. The current and voltage values were monitored across and in series with the load resistor respectively at 37 $^\circ\text{C}$ and pH 7. The glucose biofuel cell was then combined with the charge pump IC and the capacitor functioning as the transducer in the self-powered glucose biosensing system.

3. Results and discussion

3.1. Glucose biofuel cell characterization

The bioelectrodes display a huge advantage of providing a dense network of MWCNTs for electrically wiring large amounts of enzymes. The electrocatalytic activity of the bioanode and biocathode using cyclic voltammetry (CV) affirmed the direct electron transfer between the active center of the bioelectrodes and the MWCNTs. The CV experiments were performed at 37 $^\circ\text{C}$ at a scan rate of 20 mV s^{-1} (Fig. 2). The catalytic electrooxidation of 20 mM glucose was detected at an onset voltage of -190 mV vs Ag/AgCl (Fig. 2A), whereas the reduction of oxygen due to the laccase modified biocathode exhibited an onset voltage of $+380$ mV vs Ag/AgCl (Fig. 2B).

The open circuit voltage of the glucose biofuel cell operating in 20 mM glucose was 530 mV, which is very similar to the potential difference at which glucose oxidation and oxygen reduction start

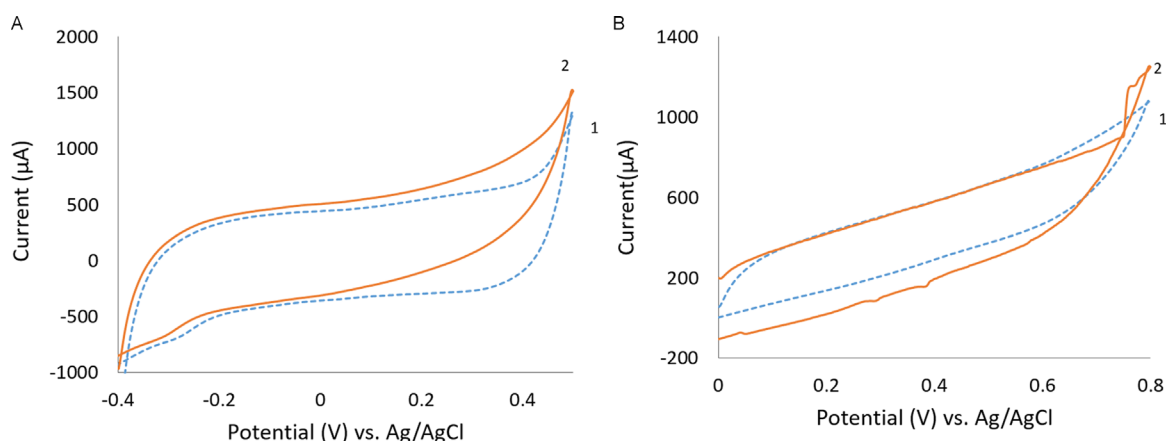


Fig. 2. Cyclic voltammogram of (A) bioanode in the absence of glucose pH 7 (—) and presence of 20 mM glucose (—). (B) Biocathode in 100 mM phosphate buffer (pH 6) saturated with N_2 (—) and in the presence of O_2 (—). All CVs were performed at 37 $^\circ\text{C}$.

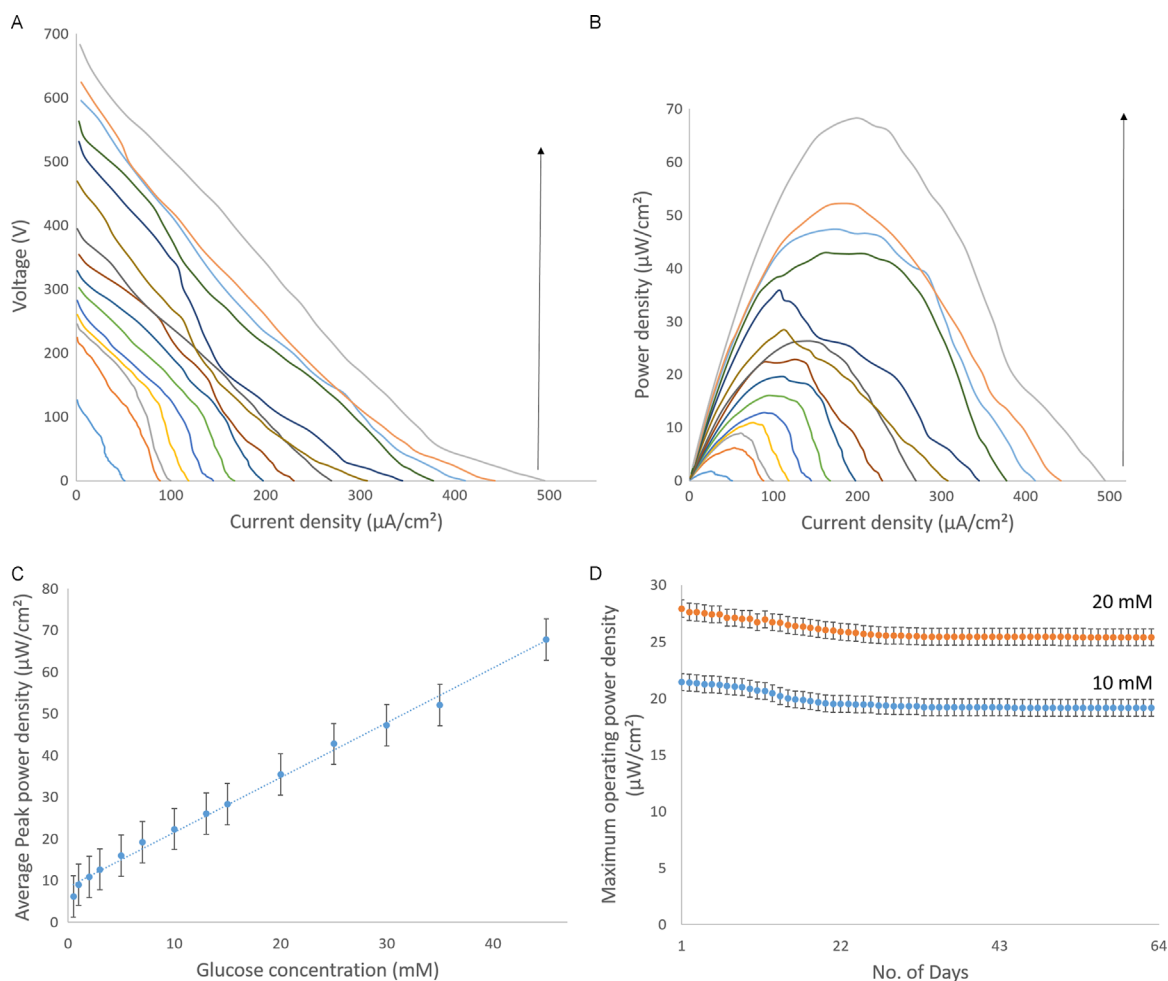


Fig. 3. Glucose biofuel cell characterization. (A) Polarization curve and (B) corresponding power curves of glucose biofuel cell at varying glucose concentrations in 0.1 M PBS (37 °C, pH 7). (C) Calibration curve of glucose biofuel cell response to glucose analyte (error bars indicated the RSD). (D) 30 day stability profile in the presence of 10 mM and 20 mM glucose (37 °C, pH 7).

to occur in the cyclic voltammogram under air-saturated environment, which is comparable or superior to those previously reported using GOx or PQQ-GDH (Miyake et al., 2013; MacVittie et al., 2013; Halamkova et al., 2012). The high open circuit voltage could be attributed to the fact that the oxidation of glucose by PQQ-GDH does not produce hydrogen peroxide in contrast to GOx or mixture of various enzymes (Sales et al., 2013; Rasmussen et al., 2012; Giroud et al., 2012; Cinquin et al., 2010; Barrière et al., 2006). The production of hydrogen peroxide as a byproduct in glucose oxidation reaction leads to the denaturing of the enzyme. Thus, bioanode based on PQQ-GDH enhances the bioanode performance.

Furthermore, the glucose biofuel cell was characterized in vitro at various standard glucose solutions by measuring the voltage and the current values at varying resistances. The current and power densities were calculated using the geometrical surface area of the bioanode. Fig. 3A depicts the polarization of the cell, wherein the open circuit voltage and the short circuit current increased with increasing glucose concentrations due to the availability of more glucose molecules. The maximum cell parameters were obtained in the presence of 45 mM glucose in air-saturated environment (37 °C, pH 7) with an open circuit voltage, short circuit current and power density of 681.8 mV, 39.6 μA , and 67.86 $\mu\text{W}/\text{cm}^2$ at a cell voltage of 335 mV, respectively. This compares favorably to previously published glucose biofuel cells employing GOx and PQQ-GDH (Yang et al., 2015; Desmaële et al., 2015; Szczupak et al., 2012; Falk et al., 2012; Miyake et al., 2011; Pizzariello et al., 2002). At physiological glucose concentration

(5 mM glucose at 37 °C, pH 7), the cell exhibits an open circuit voltage of 302.1 mV, a maximum power density of 15.98 $\mu\text{W}/\text{cm}^2$ at a cell voltage of 166.3 mV (Fig. 3B). Triplicate testing of the cell parameters to various glucose concentrations yielded a dynamic linear range of 0.5–45 mM glucose with the following regression equation ($n=14$, $r^2=0.995$):

$$\text{Cell response } \left(\frac{\mu\text{W}}{\text{cm}^2} \right) = 1.3128 [\text{glucose}] (\text{mM}) + 8.4841 \left(\frac{\mu\text{W}}{\text{cm}^2} \right)$$

As illustrated in Fig. 3C, the biofuel cell performance (power density) significantly increased upon increasing the glucose analyte concentration from 0.1 mM to 45 mM. The biofuel cell stability was further investigated separately in 10 mM and 20 mM glucose solutions under constant load discharge by applying a load resistance of 90 and 84 $\text{k}\Omega$ for 1 h each day over a period of 63 days. Fig. 3D shows the successive 1 h constant load discharge curve acquired during the 63 day periods. A 2% and 3% drop in power density was observed after 1 week of operation in 10 mM and 20 mM glucose, respectively. The overall drop in power density after 63 days of operation in 10 mM and 20 mM glucose at 37 °C and pH 7, was 10.61% and 9.11%, respectively. This slight drop in power density is attributed to the use of PQQ-GDH and nafion, which provided a hydrophobic surface and improved the durability of the bioelectrodes (Reuillard et al., 2013), thus, improving the biofuel cell stability. The peak power density produced by the biofuel cell was higher than that reported by Pinyou et al. (2015), which was stable for 1 week. Nevertheless, more than 90% of the

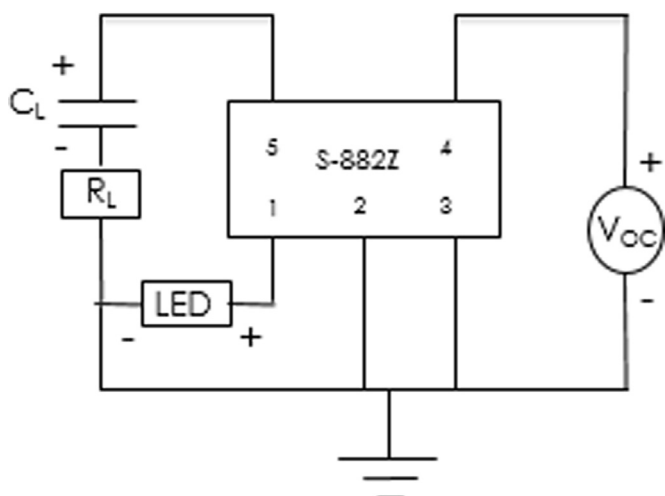


Fig. 4. Charge pump circuit consisting of a $0.1 \mu\text{F}$ capacitor functioning as a transducer C_L , a charge pump IC powered by the glucose biofuel cell.

glucose biofuel cell activity was maintained after the 63 days of operation in air-saturated 10 mM and 20 mM glucose, proving the stability of the bioelectrocatalytic ensemble achieved with the compressed MWCNTs, enzymes and nafion coating.

3.2. Self-powered glucose biosensing system characterization

Although the power produced by a single glucose biofuel cell has been shown to be incapable of powering any bioelectronic device, significant work has been done by stacking multiple glucose biofuel cell to enhance the electrical parameters (Miyake et al., 2013; Renaud et al., 2015) to power low-powered bioelectronic devices. Due to implantation and power constraints, several research groups have implemented a charge pump IC (Palumbo and Pappalardo, 2010) to excite the voltage generated by biofuel cells. Here we demonstrate the application of the glucose biofuel cell as a self-powered glucose biosensing system by constructing a power amplifying circuit (Fig. 4) using printed circuit board, wherein the charge pump IC requires an input voltage of at least 0.25 V. The charge pump IC boosts the voltage generated by the biofuel cell to 1.8 V. The 302.5 mV generated by the glucose biofuel cell operating in 5 mM glucose is sufficient to serve as the input voltage to the charge pump IC, which in turn supplied a

continuous burst of power via the $0.1 \mu\text{F}$ capacitor to power a light emitting diode (LED) as a small portable electronic devices.

For indicating glucose concentration, the charging/discharging frequency of the $0.1 \mu\text{F}$ capacitor could be controlled by the performance of the glucose biofuel cell, specifically the glucose responsive bioanode because the bioelectricity (power) generated by the biofuel cell is used to charge the capacitor via the charge pump IC. Once the capacitor is fully charged, the charge pump IC discharges the capacitor until the potential reaches 1.4 V. This charging/discharging of the capacitor continues and is observed to be directly proportional to the biocatalytic reaction at the glucose anode. Thus, by monitoring the charging frequency of the capacitor, the glucose analyte concentration can be determined. Triplicate testing of the charging frequency to various glucose concentrations yielded a dynamic linear range of 0.1–35 mM glucose with the following regression equation ($n=14$, $r^2=0.993$):

$$\text{Frequency response (Hz)} = 0.8044[\text{glucose}] \text{ (mM)} + 17.441 \text{ (Hz)}$$

Fig. 5 shows that the average frequency increased linearly with increasing glucose concentration. This indicates that the present SPGS system is capable of sensing the changes in glucose levels from hypoglycemic (0.5 mM) to hyperglycemic (20 mM) conditions. An extensive linear dynamic range was achieved with this SPGS system and was found to exceed those previously reported (Liu et al., 2012; Zenghe et al., 2012). The frequency of charging the capacitor was stable for 1 week following which the power density dropped by 3% after a week of operation separately in both 10 mM and 20 mM glucose. The overall drop in the frequency was 15.38% and 11.76% over a period of 63 days of operation in 10 mM and 20 mM glucose, respectively (Fig. 5). The stability observed here supersedes the stability of the biofuel cell powering the contact lens reported by Reid et al., whose stability reduced by 80% within the initial 4 h of operation.

The SPGS system was also characterized under various pH and temperature conditions in the presence of 10 mM glucose and 20 mM glucose solution. The temperature dependent profile in response to 10 mM and 20 mM glucose for the present SPGS is shown in Fig. 6A with a stable working temperature range of 35–40 °C. The pH dependent profile in response to 10 mM and 20 mM glucose for the present SPGS are shown in Fig. 6B with a stable optimal working pH of 7. The charging/discharging frequency of capacitor steadily improved with increasing pH and peaked at pH 7 at which both PQQ-GDH and laccase enzymes are still active.

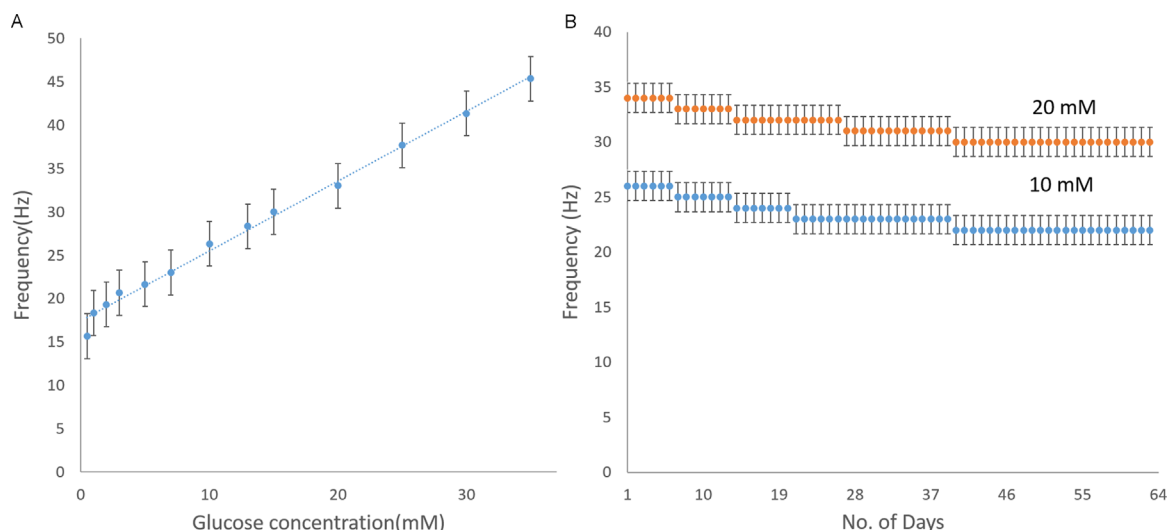


Fig. 5. (A) Calibration curve of SPGS response to glucose analyte and (B) 63 day stability profile in the presence of 10 mM and 20 mM glucose (37 °C, pH 7; error bars indicated the RSD).

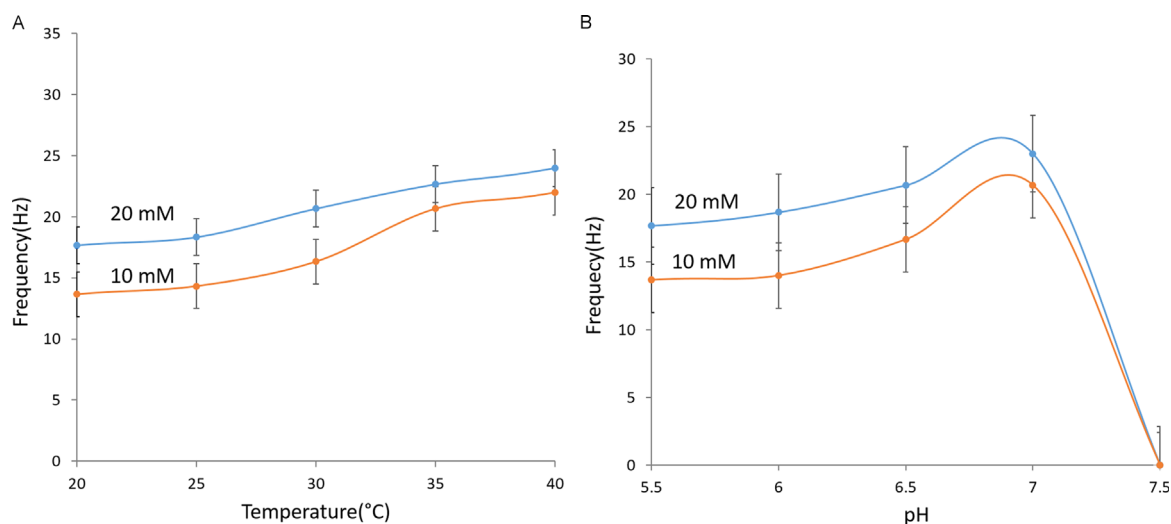


Fig. 6. (A) Temperature and (B) pH response of the present SPGS in response to 10 mM glucose (orange dots) and 20 mM glucose (blue dots). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Importantly, laccase from *Trametes versicolor* exhibits optimum biocatalytic activity at pH 5.5–6.0 and its activity is reduced at neutral pH. Therefore, beyond pH 7, laccase becomes inactive and as a result little or no power is generated to supply the present SPGS system. Overall, the activity of the present SPGS system in the presence of 20 mM glucose solution retains greater than 91% activity over the entire 63 days of investigation when compared to the SPGS system operating in 10 mM glucose solution, which retained 88.5% of its activity over the 63 day period.

4. Conclusions

This work demonstrates a stable self-powering glucose bio-sensing system constructed by combining a charge pump IC and a capacitor functioning as a transducer with a glucose biofuel cell. The glucose biofuel cell design when applied to various concentration of glucose analyte, demonstrated linearity up to 45 mM glucose. The charge pump IC was successfully demonstrated in supply burst of power to light an LED via a single glucose biofuel cell. The SPGS system exhibited linearity up to 35 mM glucose. The concentration ranges of both the glucose biofuel cell and the SPGS system effectively covers the hypoglycemic and hyperglycemic range. This work constitutes the first stability study of SPGS of this kind that is still able to deliver greater than 91% of its initial maximum power density after 63 days of operation. The present SPGS exhibits the potential to function as a stable, continuous glucose biosensors and has potential application in the development of a “closed-loop” insulin delivery system for simultaneously monitoring blood glucose levels and delivery of insulin.

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