



Mouthguard biosensor with telemetry system for monitoring of saliva glucose: A novel *cavitas* sensor

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ABSTRACT

We develop detachable “*Cavitas* sensors” to apply to the human oral cavity for non-invasive monitoring of saliva glucose. A salivary biosensor incorporating Pt and Ag/AgCl electrodes on a mouthguard support with an enzyme membrane is developed and tested. Electrodes are formed on the polyethylene terephthalate glycol (PETG) surface of the mouthguard. The Pt working electrode is coated with a glucose oxidase (GOD) membrane. The biosensor seamlessly is integrated with a glucose sensor and a wireless measurement system. When investigating *in-vitro* performance, the biosensor exhibits a robust relationship between output current and glucose concentration. In artificial saliva composed of salts and proteins, the glucose sensor is capable of highly sensitive detection over a range of 5–1000 $\mu\text{mol/L}$ of glucose, which encompasses the range of glucose concentrations found in human saliva. We demonstrate the ability of the sensor and wireless communication module to monitor saliva glucose in a phantom jaw imitating the structure of the human oral cavity. Stable and long-term real-time monitoring (exceeding 5 h) with the telemetry system is achieved. The mouthguard biosensor will be useful as a novel method for real-time non-invasive saliva glucose monitoring for better management of dental patients.

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1. Introduction

In the last decade, the global burden of diabetes mellitus has increased dramatically (Whiting et al., 2011). Current estimates indicate 380 million people are affected, which is projected to increase by 53% by 2035 (Mena et al., 2014; Aguires et al., 2013). Diabetes is characterized by deranged blood glucose levels and metabolic abnormalities associated with numerous macro- and micro-vascular sequelae and a plethora of additional co-morbidities, as a result of insufficient or ineffective endogenous insulin (Bode and Battelino 2010).

Self-monitoring of blood glucose (SMBG) is traditionally invasive, and is most commonly performed with finger-prick testing using a blood glucose meter. However, compliance is often impaired as this is unpleasant, painful, carries a risk of infection and may induce anxiety or fear. Additionally, finger-prick testing only

provides a single measurement. Continuous glucose monitoring overcomes this limitation, enables short-term fluctuations to be monitored, demonstrates immediate effects of dietary and therapeutic interventions, and can alert patients to hyper- or hypoglycaemia with alarms. It provides better long-term glycemic control as indicated by glycated hemoglobin A1c (HbA1c) measurements. Nevertheless, commercial devices are often equally invasive, and in many cases can only be used as an adjunct to finger-prick testing (Bode and Battelino 2010; Vashist, 2012).

Thus, the requirement for non-invasive, simple and responsive glucose monitoring has been strongly emphasized (Sieg et al., 2003; Scognamiglio, 2013; Ferrante do Amaral and Wolf 2008; Amaral et al., 2009; Chu et al., 2011a, 2011b). Many non-invasive technologies are currently undergoing development. For example, reverse iontophoresis, absorbance spectroscopy and near-infrared spectroscopy have been developed (Pickup et al., 2005; Newman and Turner 2005). However, none of the commercially available non-invasive glucose monitoring devices have the necessary sensitivity and precision to replace finger-prick testing (Tura et al., 2007). Minimally invasive approaches to glucose monitoring

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might therefore offer a reasonable compromise, providing the required sensitivity and precision whilst minimizing impact on quality of life. Though such approaches are sometimes critiqued for discomfort, the need for frequent calibration, and susceptibility to biofouling, effective biosensor design can overcome these limitations. For example, a soft contact lens biosensor to assess blood glucose by monitoring tear glucose concentration was developed (Yao et al., 2011). Monitoring of tear glucose using Japanese white rabbits was demonstrated (Chu et al., 2011a, 2011b).

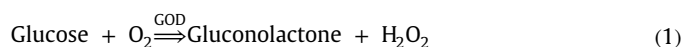
Saliva glucose concentrations range approximately from 20 to 200 $\mu\text{mol/L}$ in normal and diabetic individuals, closely follow circadian blood glucose fluctuations (Yamaguchi et al., 1998), and offer promising opportunities for non-invasive monitoring (Mascarenhas et al., 2014). Saliva and blood glucose levels correlate reasonably in a sample of individuals (Sener, et al., 2009; Abikshyeet et al., 2012; Liu et al., 2015; Soni and Jha 2015). However, a much stronger correlation is observed within the same individual, enabling blood glucose concentrations to be estimated from saliva glucose measurements (Zhang et al., 2015). A mouthguard biosensor for continuous monitoring of salivary lactate and other chemical components was reported (Kim et al., 2014; Kim et al., 2015). Hence, a novel wearable mouthguard glucose sensor produced using micro electromechanical systems (MEMS) techniques would offer promise as a minimally-invasive, painless, continuous, custom-fitted and wireless solution for self-monitoring of glucose.

In this study, we developed novel “cavitas sensors” to apply to the human oral cavity for non-invasive monitoring of saliva glucose. *Cavitas* is the etymological origin of the word “cavity” in Latin. Hence collectively, *cavitas* sensors provide biological information from within a body cavity. The mouthguard glucose sensor consisted of a platinum and silver/silver chloride electrode, with glucose oxidase (GOD) immobilised by entrapment with Poly (MPC-co-EHMA) (PMEH), on a custom-fitted monolithic mouthguard support with a wireless transmitter, thereby enabling telemetric measurement of saliva glucose. We also demonstrated the capability of the sensor and wireless communication module to monitor saliva glucose in a phantom mandible replicating the environment of the human oral cavity.

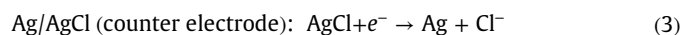
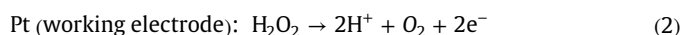
2. Experimental methods

2.1. Measurement of glucose

Glucose oxidase (GOD) catalyses the oxidation of glucose in the presence of oxygen, to produce gluconolactone and hydrogen peroxide at the working electrode through the following enzymatic reaction:



Thereafter, the following redox reactions take place:



The output current produced can be measured by amperometry, and is directly proportional to the H_2O_2 concentration at the working electrode, and therefore also directly proportional to the glucose concentration in solution, thus enabling continuous measurement of saliva glucose.

2.2. Solution preparation

All solutions were prepared using deionised distilled water from a Millipore Milli-Q purification system. 20 mmol/L, pH

7.4 PBS was prepared from disodium hydrogen phosphate and potassium dihydrogen phosphate (Kanto Chemical Co., Inc., Japan). Artificial saliva containing various proteins, was prepared from disodium hydrogen phosphate, anhydrous calcium chloride, potassium chloride, sodium chloride, urea (Kanto Chemical Co., Inc., Japan) and type II mucin from porcine stomachs (Sigma-Aldrich Co., USA) according to a protocol reported by Fusayama et al., 1963.

Glucose solutions were prepared from D(+)-glucose (Wako Pure Chemical Industries Ltd., Japan) and PBS. 100 mmol/l galactose, fructose, mannitol, sorbitol and xylitol solutions were prepared from D(+)-galactose, D(–)-fructose, D(–)-mannitol, D(–)-sorbitol and xylitol (Wako Pure Chemical Industries Ltd., Japan), respectively and PBS.

10 wt% PMEHE was previously obtained by copolymerising 2-methacryloyloxyethyl phosphorylcholine (MPC) with 2-ethylhexyl methacrylate (EHMA) by a free-radical polymerisation method previously reported (Chu et al., 2011a, 2011b). Immediately prior to application 10 wt% PMEHE was diluted with 99.5% ethanol (Kanto Chemical Co., Inc., Japan) to produce the required percentage by mass PMEHE solution. GOD mixture was also prepared prior to application by mixing GOD from *Aspergillus niger* (EC 1.1.3.4, 900 units/g, Sigma-Aldrich Co., USA) with 10 wt% PMEHE in a 1 mg: 10 μL ratio using a vortex.

2.3. Fabrication of the electrode sensor

Electrodes of the glucose sensor consisted of a 0.2 mm² Pt working electrode and a 4.0 mm² Ag/AgCl (reference/counter electrode), insulated with polydimethylsiloxane (PDMS) (Fig. 1A). 0.5 mm thick polyethylene terephthalate glycol (PETG) was selected to form the supporting structure based on a previous experiment demonstrating stronger adhesion of Pt and Ag to PETG. Additionally, electrode sensors capable of glucose measurement had GOD and a PMEHE overcoat applied to the sensing region.

Firstly, for the mouthguard support material, an Erkodent ϕ 120 mm, 0.5 mm thick thermoforming PETG disc (Erkodent, Erich Kopp GmbH, Germany) was cut into a rectangle, the protective film was removed, and it was cleaned in an ultrasonic cleaner half-filled with 95% ethanol (Kanto Chemical Co., Inc., Japan) for 15 min. Once dry, the PETG was secured with Kapton tape onto a dummy 100 mm ϕ , 525 μm thick Si wafer. For the sputtering process, two types of polypropylene stencils, for the Pt and Ag electrode respectively, were designed with Roland Cut Studio 1.30 software and produced with a vinyl cutter. Sputtering was then undertaken as indicated in Fig. 1.

To insulate the electrodes, base and catalyst of SILPOT 184 PDMS (Toray Dow Corning Co., Ltd.) were mixed in a 9:1 ratio and deaerated for 2 min with a planetary centrifugal mixer. The PDMS mixture was then applied as a thin film to provide insulation on the sensor electrodes. The electrode sensors were left to dry on a hot plate at 60 °C for 1 h. Finally, the Ag electrode was electrochemically chloridized to form the Ag/AgCl electrode at the sensing region, by immersing each electrode sensor in 0.1 mmol/L hydrochloric acid solution (Wako Pure Chemical Industries Ltd.) along with a layer of platinum to which a constant voltage of –120 mV was applied versus the Ag/AgCl reference/counter electrode with a potentiostat until the output current dropped below –0.35 mA. To produce electrode sensors capable of glucose measurement, GOD and PMEHE were applied as depicted in Fig. 1. Finally, the sensing region of each electrode was rinsed by immersion in PBS for 30 min. Thereafter, the electrode sensors were rinsed with distilled water, dried and stored.

2.4. Fabrication of the mouthguard glucose sensor

Fabrication of the mouthguard glucose sensor involved

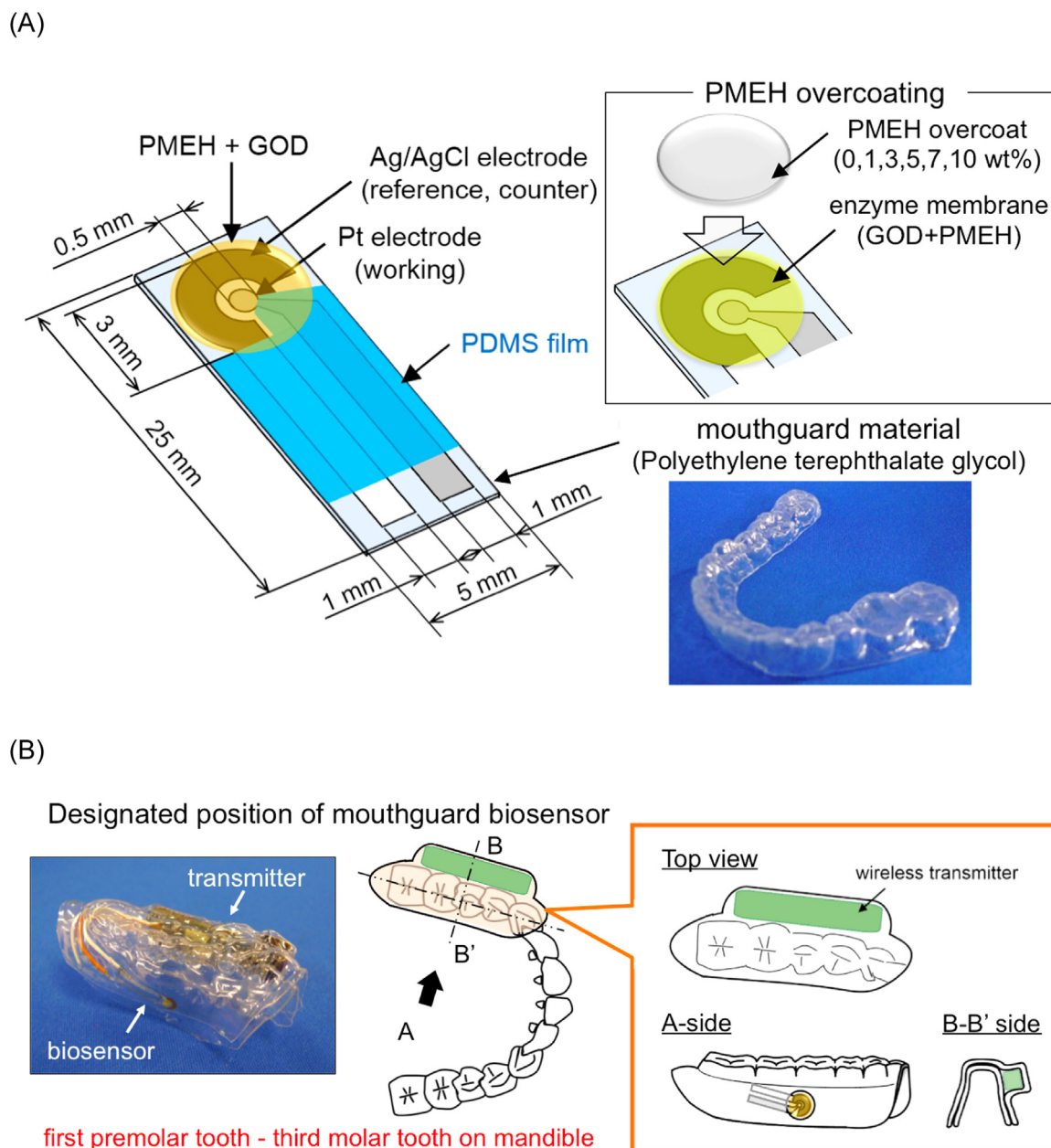


Fig. 1. (a) Schematic image of the glucose biosensor on the polyethylene terephthalate glycol mouthguard support. Pt and Ag electrodes were formed on the PETG through a sputtering process. Each electrode sensor consisted of a 0.20 mm^2 Pt working electrode and a 4.0 mm^2 Ag/AgCl reference/counter electrode, both insulated with PDMS on a 0.5 mm thick PETG layer. 30 units of GOD were applied to the sensing region of the working electrode. In order to optimize enzyme entrapment, $2.0 \mu\text{L}$ of $1.0 \text{ wt}\%$ PMEHE solution was spread over the sensing region to form the PMEHE overcoat. (b) Schematic image of the mouthguard biosensor to custom-fit the patient's dentition. The device consisted of a glucose sensor and wireless transmitter incorporating a potentiostat for stable glucose measurement. The sensor was designed to fit the mandibular dentition from the first premolar up to the third molar. The wireless transmitter was neatly encased in PETG.

production of a dental cast, vacuum forming of the PETG mouthguard support, electrode sensor fabrication on the mouthguard support, wireless transmitter installation, packaging, and GOD and PMEHE application (Fig. 1B).

Firstly, half a cup of Aroma Fine Plus Normal Set Alginate Impression Material (GC Corporation, Japan) was spatulated with distilled water until homogeneously viscous and poured into a Directed Flow Disposable Jaw Impression Tray (3 M Deutschland GmbH, Germany), which was held in the mouth for 3 min to produce a dental impression. 40 mL of Zo-Stone hard plaster (Shimomura Gypsum Co., Ltd., Japan) and 40 mL of Hera Xanthano special plaster (Heraeus Kulzer GmbH, Germany) was mixed with distilled water until homogenous and poured into the dental impression to produce a dental cast. After 1 h the cast was separated

from the impression and imperfections were trimmed. Thereafter, PETG was vacuum formed over the dental cast with a vacuum forming machine. The resulting structure was cut to produce the mouthguard support.

Identical steps involved in fabrication of the electrode sensor were then undertaken, including ultrasonic cleaning, sputtering, insulation with PDMS, and formation of the Ag/AgCl electrode. Thereafter, a custom-manufactured wireless transmitter containing an A/D converter was fitted with a LR41 1.5 V battery and installed by securing it in position with kapton tape and attaching the Pt and Ag/AgCl electrodes, respectively, with electrically conductive TK Paste CN-3160L (Kaken, Japan). The kapton tape was subsequently removed, and the medial edge between the cover and support was sealed with Unifast III Quick Self-Curing Acrylic

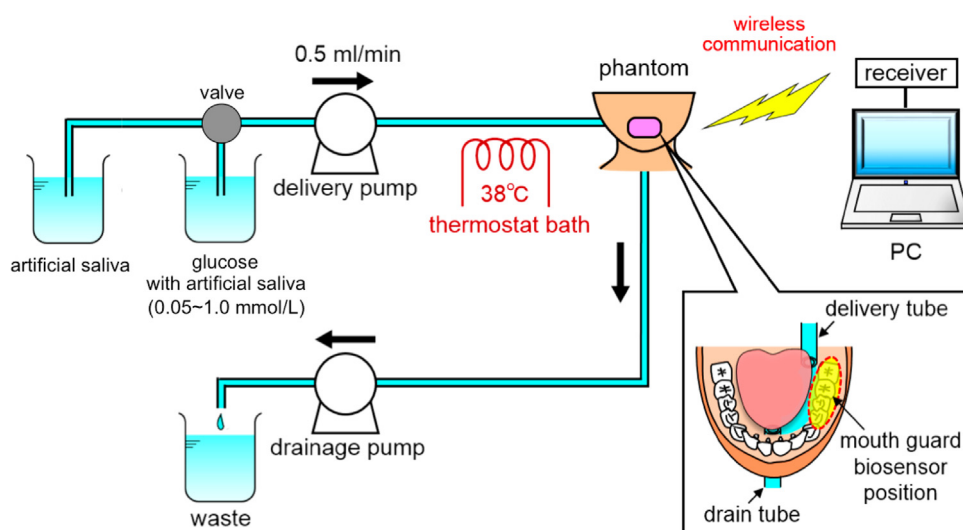


Fig. 2. The mouthguard biosensor was mounted onto the phantom jaw and open-loop injection system. A silicone tube was placed in 20 $\mu\text{mol/L}$ glucose solution in artificial saliva being continuously stirred. The tube was passed through a peristaltic pump set to a flow rate of 0.5 mL/min, and subsequently multiple coils were passed through a thermostat water bath, consisting of a large beaker of water. The opposite end of the tube was positioned medially to the left second premolar, and the temperature of the thermostat water bath was adjusted to deliver an input stream at 38 °C.

Resin (GC Corporation, Japan) and left to dry at room temperature for 24 h to complete the sensor packaging. GOD mixture and 1.0 wt% PMEHE were then applied, as described for the electrode sensor.

2.5. Evaluation of the mouthguard glucose sensor

In vitro measurement of glucose in artificial saliva with the mouthguard biosensor was demonstrated on a phantom jaw as shown in Fig. 2. After an initial stabilisation period, output current was recorded on a computer via a custom-manufactured wireless receiver. After 5 min, the artificial saliva solution beaker was switched for one containing 0.05, 0.1, 0.2, 0.5, and 1.0 mmol/L glucose solution in artificial saliva. We monitored changing output current at 1.0 s intervals using the mouthguard biosensor with the built-in wireless transmitter.

3. Results and discussion

3.1. Response of the glucose sensor in buffer solution

A glucose sensor on a PETG mouthguard support was fabricated using MEMS techniques. After GOD immobilisation on the Pt electrode with PMEHE coating and subsequent rinsing in PBS, the sensor response was shown to be dependent on glucose concentration. Output current increased as the glucose concentration of the PBS increased, and reached steady-state values soon after the start of each 180 s interval. Glucose concentration (dynamic range 1.0–1000 $\mu\text{mol/L}$) was strongly correlated with mean Δ output current ($R=0.999$) (data not shown). This adequately encompassed the range of saliva glucose in healthy people and diabetic patients (20–200 $\mu\text{mol/L}$).

3.2. Response of the glucose sensor in artificial saliva

Artificial saliva adjusted to pH 7.4 containing electrolytes and proteins was produced according to previously reported methods (Fusayama et al., 1963) (Supplemental Fig. 1), with disodium hydrogen phosphate, calcium chloride, potassium chloride, sodium chloride, porcine mucin and urea. Mucin is a family of high molecular weight protein. When glucose was measured in artificial

saliva instead of PBS, output current was observably lower at each glucose concentration (Supplemental Fig. 1). This suggests a component of the artificial saliva, such as high viscosity protein in the mucin, might inhibit sensor response by non-specific binding to GOD and the electrode surfaces; hence the need to protect the GOD with an overcoat.

When comparing PMEHE overcoats, from no PMEHE overcoat to a 10.0 wt% overcoat in artificial saliva, the optimum percentage by mass was identified at 1.0 wt% (Fig. 3). Output current increased sharply from 0 to 1.0 wt%, then decreased initially and thereafter decreased at a progressively slower rate from 1.0 to 10.0 wt%. For a PMEHE overcoat of 1.0 wt%, a CV of 2.4% ($n=3$) was obtained. For the sensor without a PMEHE overcoat, a much larger error bar was obtained as output current decreased with each successive use, until only a negligible change in output current was detected on the third use. This is because GOD is progressively washed off the

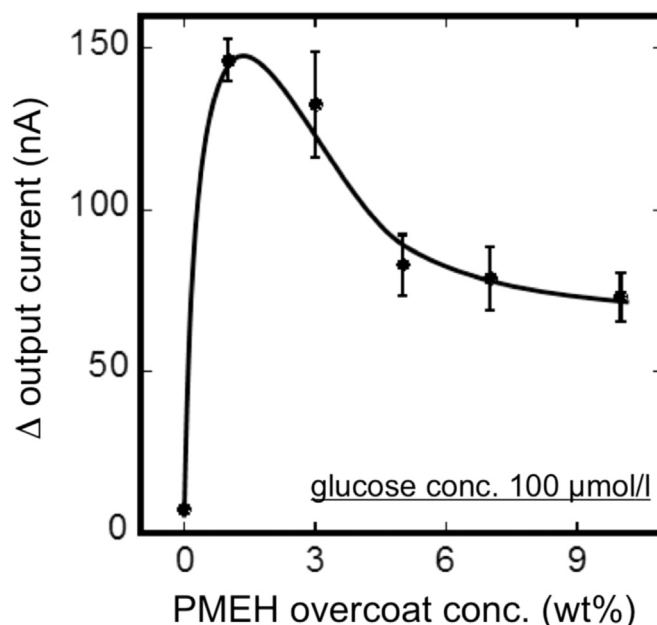


Fig. 3. Comparison of the glucose sensor response with 0–10.0 wt% PMEHE overcoats in artificial saliva. Glucose concentration: 100 $\mu\text{mol/L}$.

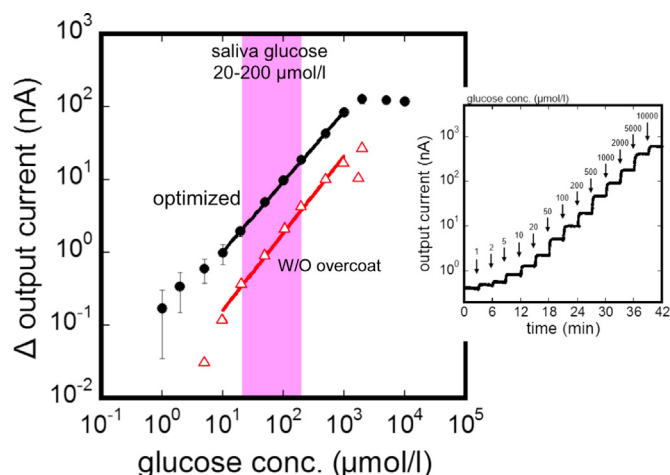


Fig. 4. Calibration curves of the optimized glucose sensor on PETG. An electrode area of 16.8 mm² and a 1.0 wt% PMEHE overcoat was identified as the optimum. The calibration range was 10–1000 μmol/L which encompassed the physiological saliva glucose range in humans (20–200 μmol/L). Output current of the glucose sensor without a PMEHE overcoat was substantially decreased, because of proteins in artificial saliva adhering to the electrode surface.

working electrode and lost in solution in the absence of a PMEHE overcoat, suggesting that entrapment of GOD with a PMEHE overcoat is essential to allow the biosensor to be reused consistently. A PMEHE overcoat exceeding 1.0 wt% may begin to interfere with the exposure of GOD to glucose in solution, resulting in a lower output current. Hence, optimisation of the PMEHE overcoat is a balance between ensuring entrapment of GOD without compromising exposure of the enzyme to its substrate.

When comparing electrode surface areas of 4.20 mm² and 16.8 mm², a greater output current was observed with a greater area as this enables Eqs. 1, 2 and 3 to proceed at a faster rate. For both areas, output current increased as the glucose concentration of the artificial saliva increased, as expected. In both cases, glucose concentration (dynamic range 1–1000 μmol/L) was strongly correlated with output current.

The response of the optimised sensor in artificial saliva with a 1.0 wt% PMEHE overcoat and an area of 16.8 mm² was then compared to the response of the sensor in PBS before optimisation without a PMEHE overcoat and an electrode area of 4.20 mm² (Fig. 4). Biosensor optimisation restored Δ output current in artificial saliva to levels exceeding those recorded in PBS. Glucose concentration was strongly correlated with output current, with the following exponential relationship:

$$\Delta \text{Output Current } (\mu\text{A}) = 0.077 [\text{Glucose } (\mu\text{mol/L})]^{0.90}$$

Furthermore, the signal-to-noise ratio was greater than three. The calibration range of the optimized glucose sensor with the telemetry system was 5–1000 μmol/L glucose solution in artificial saliva ($R=0.999$, $n=5$).

3.3. Selectivity of the glucose sensor

Selectivity of the glucose sensor was evaluated by comparing output current in response to 100 μmol/L glucose, galactose, fructose, mannitol, sorbitol and xylitol solutions after 180 s. The glucose sensor was shown to be highly selective for glucose based on the substrate specificity of GOD (Fig. 5). Fructose, mannitol, sorbitol and xylitol, which are contained in some foods, were not detected, producing a negligible output current less than 0.05% of the magnitude of the output current produced by glucose. Galactose was detected to a minimal extent, producing an output

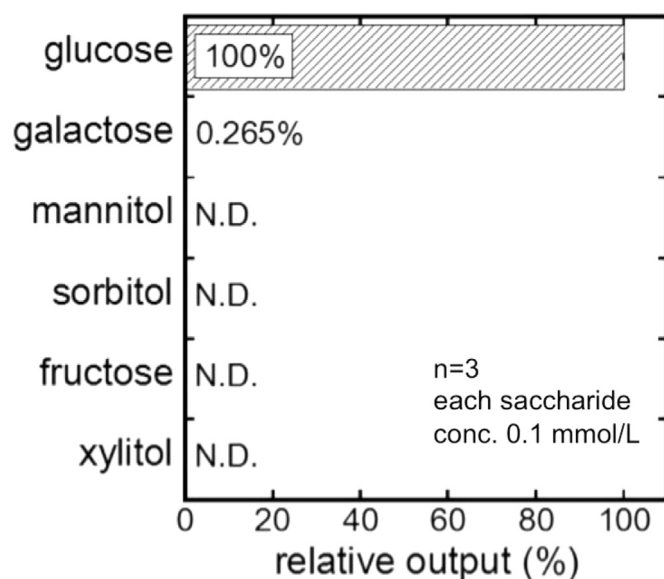


Fig. 5. Selectivity of the glucose sensor was evaluated by comparing mean relative Δ output current in response to 100 μmol/L glucose, galactose, fructose, mannitol, sorbitol and xylitol solutions.

current at 0.265% of the magnitude of the output current produced by glucose.

3.4. Response of the mouthguard glucose sensor in the phantom jaw

The mouthguard glucose sensor response was dependent on glucose concentration (Fig. 6). Output current increased in response to higher glucose concentrations in the artificial saliva as expected, but took longer to reach steady-state values than the output current of the electrode sensors. This prolonged response can be accounted for by the time it takes for the concentration of the glucose solution within the phantom jaw to change based on the flow rate of 0.5 ml/min, after changing the glucose concentration at the input to the phantom jaw. An increase in output current accompanying each injection of glucose solution was observed. Stable responses within approximately 60 s were obtained when changing from 0.05 to 1.0 mmol/L. Likewise, a decrease in each output current, with stabilisation within 180 s, was obtained when changing back from 1.0 to 0.05 mmol/L. Output current at lower and higher glucose concentrations also became progressively stable after each injection of glucose solution. Interference noise will also have affected output current throughout all experiments. For instance, at a macroscopic level, fluctuations in output current were observed whenever the apparatus was disrupted by motion. Coexisting electro-active compounds might also have introduced interference, though these were somewhat blocked by the PMEHE overcoat.

The mouthguard biosensor was capable of long-term monitoring of salivary glucose concentration in the phantom jaw. The sensor consisted only of a PETG support, a Pt electrode, an Ag/AgCl electrode, and GOD enzyme covered with PMEHE, to maximise biological compatibility. The telemetry device was fully encased and neatly sealed with dental composite resin to prevent exposure to liquid. Hence, the mouthguard biosensor has potential utility as a novel tool for real-time non-invasive saliva glucose monitoring within the oral cavity.

4. Conclusions

This research demonstrated *in vitro* development of a mouthguard biosensor capable of real-time continuous wireless

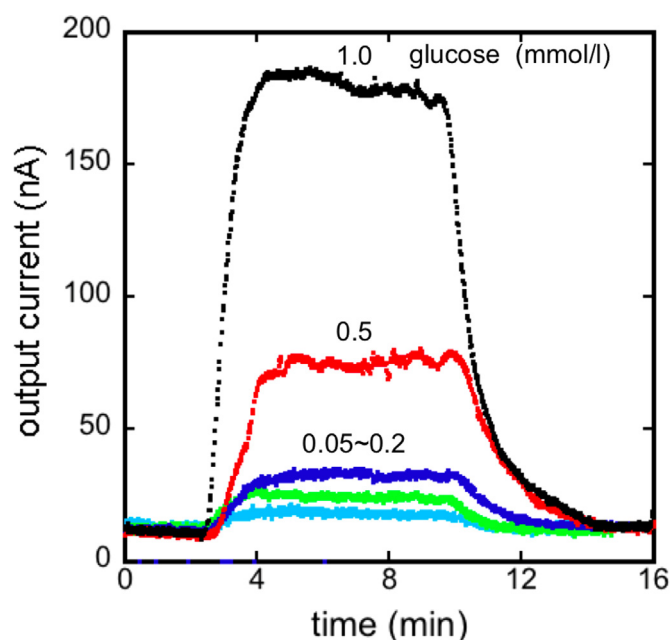


Fig. 6. Response of the mouthguard glucose sensor using the phantom jaw and open-loop injection system. A response was observed with a change in glucose concentration at 0.05, 0.1, 0.2, 0.5 and 1.0 mmol/L. The phantom jaw system accurately matches flow rates of the delivery and drainage pumps to maintain a constant level of artificial saliva.

measurement of saliva glucose. Following application of GOD and a PMEHE overcoat, the electrode sensor was capable of highly sensitive and selective measurement of glucose in PBS and artificial saliva. The sensor's dynamic range encompassed the range of saliva glucose concentrations in healthy and diabetic individuals. Optimum sensor characteristics for measuring glucose in artificial saliva were a 1.0 wt% PMEHE overcoat and an electrode surface area of 16.8 mm². To produce the mouthguard sensor, the electrode sensor was applied to a custom-fitted mouthguard support with a wireless transmitter. The mouthguard biosensor was capable of real-time continuous wireless measurement of glucose in artificial saliva from 0.05–1.0 mmol/L with a phantom jaw.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bios.2015.12.014>.

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