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A Continuous Oral-fluid Monitoring of Glucose (O.M.G.) Device with Near-field & Bluetooth Communication Capability

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ABSTRACT

Around 34 million Americans have Type 2 Diabetes (T2D), while 88 million adults have prediabetes. Unlike the traditional invasive needle method, our proposed salivary glucose-monitoring device, OMG, can facilitate self-monitoring through a noninvasive method via Bluetooth modulation using cost-effective material (Nafion, Polydimethylsiloxane [PDMS], Bluetooth chips). The electrodes designed were coated with Glucose Oxidase (GOx), where a biological redox reaction occurs after being in contact with salivary glucose. When the interdigitated electrode (IDE) connects to the Bluetooth circuit, the impedance changes and modulates the electromagnetic reflection from the course, reflecting it as the "change of resistance" (which is proportional to the glucose concentration). Afterward, commercial chemical methods, ex-vivo, and in-vivo styles were employed to assess viability and usability. Data were assessed by creating several different comparisons between OMG and existing alternatives. Scanning Electron Microscope (SEM) images captured OMG GOx's morphology, vector multimeters were used to collect data, and Glucose Assay Kits (Colorimetric) were used for OMG comparative analysis. NOREC (software) transfers measured fluctuations into graphical and numerical data. Testing results suggest that the trendline is reliable: $R^2 = 0.9292$ for colorimetric and $R^2 = 0.9673$ for our Performance Tests (ex-vivo and in-vivo), which was better than the gold standard: $R^2 = 0.8823$. Further, we conducted multiple resistance tests, in which resistance and voltage significance was averaged to be $p < 0.001$ and $p < 0.01$, respectively. The non-invasiveness and portability demonstrate the necessity of developing such applications and novel, cost-effective smartwatch-based alternatives.

Introduction

Diabetes and Progression of Overweightness

Diabetes mellitus is a worldwide epidemic affecting 422 million people and is predicted to be the seventh leading cause of death if the current morbidity trends continue. In the early stages of Diabetes mellitus type 2, it becomes increasingly important to monitor blood glucose as many preventative measures can be taken if the blood glucose seems to have abnormalities (Asif et al., 2014). Obesity- induced insulin resistance is directly linked to increased energy accumulation in tissues, affecting cell responsiveness to insulin (Otero et al., 2014). For instance, disruption in the AKT and PKC kinases contributes significantly to the development of T2D and is associated with all significant features of T2D, including hyperinsulinemia, dyslipidemia, and insulin resistance (Kharroubi et al., 2015). Among the factors associated with the development of insulin resistance, obesity is the most predominant risk factor leading to insulin insensitivity and T2D, which involves the disruption of several pathways that participate in the pathogenesis of the disease.

Monitoring the progression of overweightness is essential as ignorance of such may lead to several health issues, including heart diseases, stroke, kidney disease, blindness, nerve damage, leg and foot amputations, and death. Whereas monitoring using diet-cutting and lifestyle changes can have beneficial effects on preventing diabetes, these only present a subjective study on the severity of the disease; however, these methods do not provide the numerical value of blood glucagon at different times in the day (which can quantify the abnormality of the glucose amount). Specifically, continuous monitoring devices like blood or salivary devices can offer a minimally invasive, or even possibly, non- invasive method to control glucose levels. Blood glucose (BG) concentrations in people with diabetes can undulate significantly throughout the day, leading to severe consequences, including kidney failure, strokes, heart attacks, high blood pressure, blindness, and coma (Berdudi et al., 2020). For maintaining BG within the euglycemic range, the BG concentration should be detected at least twice a day and four times daily for T2D patients.

Combined therapies, including drugs, insulin supply, diet, and physical exercises, are required (Colberg et al., 2010). The emergence of glucose sensors has allowed patients to self-monitor BG levels to manage insulin levels, thus controlling the mortality of diabetes mellitus. Traditional glucose-detecting devices primarily consist of glucose sensors based on electrochemical methods. For instance, the systematic analysis of BG levels requires a small blood sample (<1 μL) obtained by a "finger-pricking" collection method, which is inconvenient and results lower patient usage. Such tests neglect nighttime variations and might cause an approximation of BG variations alongside inaccurate ones (Colberg et al. 2010).

Moreover, instantaneous monitoring sensors cannot provide real-time BG information and thus are unable to warn of hypoglycemic (low blood sugar, <3.0 mM) and hyperglycemic (high blood sugar, > 11.1 mM) in advance (Reddy et al., 2020). There are three generations of glucose biosensors: the first generation relies on using natural oxygen and the production-detection process of hydrogen peroxide. Second-generation sensors employ an electron acceptor to shuttle electrons, thus solving the oxygen deficiency. Third-generation glucose sensors design sensuous glucose monitoring (CGM) devices to replace the currently used portable glucose meters. CGM reports BG levels as trends of glucose fluctuations, and this d, and utilized for various applications, including retrospective analysis, hypo/hyperglycemia detection, and lifestyle suggestions based on artificial intelligence (Gross et al.). The current gold standard glucose biosensors are invasive. While CGM systems are still holistically novel, the poor precision and accuracy of the BG results (along with its delays in tracking methods) represent weaknesses and non-usability. Non-invasive methods, on the other hand, are increasingly prevalent due to the high sensitivity and better patient compliance, contrary to invasive ones. Since there is a delay as glucose is transported from the blood level to the interstitial fluid level, the real-time information detected from CGM sensors might be 15–20 min later than BG from noninvasive sensors. Hence, the rate-of-time of BG measurements in CGM sensors limits the result reliability --- especially in emergencies. Although many enhancements have been implemented to mitigate the inaccuracy of CGM, there is still a lack of approval of CGM data for adjusting insulin since insulin dosage is dependent on the BG level and rate of change of BG. Another barrier is the lifetime of the sensors, as loss of function happens to most implantable electrodes. The calibration would also create problems such as cost, toxicity, inconvenience, and discomfort (Bailey et al., 2015). Integrating noninvasive devices with wireless devices could be an effective method for developing lifesaving, patient-accessible data.

Wearable Sensors

Wearable sensors nowadays have been receiving considerable attention because of their great promise for continuous monitoring of a wide range of relevant parameters for health, fitness, and biomedical-related applications (Ghafar-Zadeh et al., 2015; Andreu Perez et al., 2015). Although most of the existing wearable technologies focus on monitoring physical parameters (e.g., motion, respiration rate, etc.), there is still tremendous interest in developing wearable sensors for important biomarkers relevant to health (Bandodkar et al. 2014). Significant progress has been made in

developing wearable sensors that may detect glucose quantities in sweat, saliva, and tears (Jia et al., 2013; Kim et al., 2015; Yao et al., 2012), though saliva may be the most promising and applicable mechanism.

Saliva is an optimal diagnostic fluid providing an alternative to direct blood analysis without skin piercing for blood sampling. Early work in electrochemical salivary sensors was demonstrated by Graf in the 1960s, measuring pH and fluoride ion levels (Graf et al., 1966). Progressively, efforts have more recently developed salivary sensors based on screen-printing techniques that take advantage of scalable, low-cost fabrication. Though not perfect, Elkington et al. designed a proof-of-concept application that can detect glucose quantities through a vector analyzer in relative proximity using Radio Frequency
Identification (RFID and Oral-fluid Monitoring of Glucose Device (O.M.G.) has expanded upon Elkington et al.'s concept by developing a wearable salivary glucose sensor using both an NFC platform and Bluetooth measuring platform as well (Elkington et al., 2017).

Despite these recent advances, the realization of wearable biosensors for wireless monitoring of chemical markers is limited by the small number of demonstrated RFID signaling and the lack of integrated wireless data transmission in measurement platforms (Elkington et al.). While it was predicted that the wireless wearable chemo-sensors for personal health/wellness were slated to expand rapidly (Diamond et al., 2008), challenges such as power consumption and size of wireless sensor systems remain. Mannoor et al. reported a novel wireless to-resist metrics sensor for continuous monitoring of bacteria on a silk dental tattoo platform (Mannoor et al., 2014); however, this platform does not measure salivary glucose and requires a sizeable active device to be held near the sensor, which is inconvenient for continuous real-time readout. Another work introduces a radio-frequency identification (RFID) wireless sensor tag with potentiometric input. The tag, the tire for integration in typical anatomically sized platforms, must be positioned near the tag for successful data readout. While developing the O.M.G. system, both NFCs (as a proof-of-concept test) and Bluetooth monitoring with vector analyzer devices were used to implement a near-field environment for detection purposes, which can be reprogrammed to smaller receivers using RFID-like approaches.

As for Bluetooth-based detection methods, many improvements have been made in detecting biometrics, such as urine, sweat, and other bodily fluids (Slaughter et al., 2022; Chen et al., 2020). Specifically, in biosensing using Bluetooth-based detection methods, microneedles and continuous monitoring methods are promoted for a controlled monitoring atmosphere. Even with the advances in noninvasive monitoring by Caduff et al. and Lahdesmaki et al., more advancements to decrease background noise signals and convenience must be addressed (Caduff A. et al., 2003; Lahdesmaki I. et al., 2010). For reference, Caduff et al. used a non-invasive non-optical continuous glucose monitoring system to observe glucose changes in human tissue fluids, and Lahdesmaki et al. integrated triple electrodes to measure glucose in tears. However, sensitivity and background noise signals still occur, pushing the creation of an accurate, effective, and noninvasive glucose measurement in diabetic patients (Chien et al., 2015).

Use of Salivary Glucose

The electrodes of OMG are coated with GOx, where a biological redox reaction occurs after being in contact with glucose. When the interdigitated electrode connects to an NFC tag, the redox reaction strongly changes the impedance of the tag. This finally modulates the electromagnetic reflection from the tag, which will be reflected as the "change of frequency" or delay time. Both the "change of frequency" and delay time are proportional to glucose concentration; thus, the data can be analyzed and calibrated (Keenan et al., 2009). There are three main parts of the OMG: 1) biological recognition; 2) transducer recognition conversion into a signal; 3) a processing system that converts the signal into readable numeric values using the method introduced by Yoo et al., 2010.

Biological recognition is obtained using GOx to capture electron flow through the reduction of FAD+ → FADH2 (since GOx needs a redox factor), thus, acting as an electron acceptor. After the initial catalyzation, GOx catalyzes glucose oxidation and produces gluconic acid and hydrogen peroxide (Weibel et al., 1971). The oxidation of hydrogen peroxide is easily recognizable through the number of electron transfers. Since this electron flow is

proportional to the number of glucose molecules in the blood (Guilbault et al., 1973), O.M.G. can accurately obtain proportional electron-based data.

Transducer recognition can be detected through radio frequency identification (RFID) scanning and electrode pathways. Polydimethylsiloxane (PDMS) as substrate material and the hydrogen peroxide produced by the catalytic reaction of GOx can immobilize particles on the electrode (Kang et al., 2021). However, transducer recognition differs between NFC and Bluetooth-based methods. For voltage-based Bluetooth modules, the strength of the modules in the circuit determines the impendence that the Bluetooth will send to the receiving device. As the glucose concentrations differ between salivary glucose samples, impendency will also differ, presenting varying data. Aside from measuring differences, there are also physical differences in NFC vs. Bluetooth circuit compositions. NFC transducer recognition comes from the O.M.G.'s electrode tag, whereas Bluetooth-based detection consists of many intricate circuits (oximeters, switches, amplifiers) for data transmission. In addition to building an oximeter for O.M.G., oximeter recognition distance, location, and strength also must be calibrated, as demonstrated by Jubran et al. (Jubran et al., 2015).

Signal recognition can be sensed through NFC (emitted at 13.56MHz), capturing electric signals and converting them into a real natural source (Bandodkar et al., 2019). While NFC is battery-less, the limitations of NFC signal detection and transmission are present---the most concerning being the distance and strength of the signal sent (Bandodkar et al., 2019). Because of the compatibility to pair with nearly all NFC signals within 5cm of the NFC, the initial O.M.G. proof-of-concept was made from NFCs. NFC signal recognition also differs between NFC and Bluetooth-based mechanisms. Bluetooth detection is based on readily paired devices that can transmit data (and evaluate data) over longer distances (Leith et al., 2020). Furthermore, different kinds of Bluetooth signal transmission methods (Bluetooth Low Energy, Bluetooth High Energy, Bluetooth Near Field) (Elkington et al., 2014) can have different implications. For a proximity data transferring process, O.M.G. Watch is made and designed upon a Bluetooth Low Energy design.

Literature Review

The detection of glucose was officially formalized through blood glucose meters, which gave an approximate blood glucose number through a droplet of blood (Reddy et al., 2020). Recently, detection has been made more accessible by using Radio Frequency Identification Devices (RFID) and Bluetooth Communication to detect glucose in other bodily fluids than in the blood (Blum et al., 2018; Bankar et al., 2009). As continuous and non-invasive glucose monitoring devices progressed, O.M.G.'s oral fluid (e.g., saliva) sampling methods began their conception.

Salivary-based detection methods for glucose detection through personalized calibrations and organic transistors have been reported (Elkington et al., 2014). Salivary-based detection offers noninvasiveness but is often less accurate than blood-based detection (Chen et al., 2017). Additionally, salivary glucose closely relates to the oral environment in patients with diabetes but may present some problems with calibration (Zhang et al., 2015). Elkington et al. established that glucose oxidase (GOx) can be integrated into low-voltage organic thin-film transistor (OTFT) devices. However, Elkington et al. only demonstrated a "proof-of-concept process" that reflects the ability of OTFTs to measure salivary glucose through biosensors (Elkington et al., 2014). Further, Elkington et al. measured glucose diffusion through a niche method: **polystyrene sulfonate (PEDOT) gate (semiconductor) → Nafion (membrane material) → GOx,** which is slow and unnecessary (Macaya et al., 2007). Complimenting Elkington et al.'s study, subsequent studies used third-party salivary glucose analysis, which is impractical in implementing beyond laboratory research (for both in vivo & ex vivo studies). Understandably, the OTFT voltage decrease for Elkington's preliminary study is expected; however, a ± 13% margin of error (Elkington et al., 2014) from chemical tests raises validity concerns regarding the "Source" & "Drain" methods.

To incorporate noninvasive oral-fluid glucose monitoring with components of NFC technology, GOx & OTFT biochemistry to achieve real-time glucose monitoring and reporting to a personal device (e.g., an iPhone). NFCs are components of smaller data transmissions that integrate into more extensive numerical data databases, providing

dynamic and elaborate real-time data (Cao et al., 2019). The composition of our product based on NFCs is cost-effective and straightforward: an interdigitated electrode (IDE) will be coated with GOx and connected to an NFC tag antenna; the whole device will be covered with polydimethylsiloxane (PDMS) and insulated except the electrode with immobilized GOx (Coskun et al., 2015; Mareli et al., 2013). As the transition from NFC to Bluetooth module encompasses similar low-energy near-field communication features, NFC can be used for proof-of-concept testing; in contrast, Bluetooth can be implemented on more sophisticated devices.

Methodology

Phases of O.M.G. Development

In **Phase 1** of O.M.G. development, the wireless circuit electrode, paired with a communication system-on-chip (SoC) NFC design for miniaturized and low-power operation, is fully integrated into a novel salivary biosensor for continuous monitoring. The enzyme glucose oxidase (GOx) is applied onto the electrode to exhibit the redox reaction, which results in the product of electrons will be sensed through the interdigitated electrodes (IDE). While blood glucose (BG) measurements require invasive blood collection, salivary glucose (SG) measurements could be carried out non-invasively and in a continuous real-time manner. Others have found a good correlation between blood and saliva glucose levels in their previous studies, demonstrating that saliva can be monitored in a non-invasive way without the need for blood sampling. O.M.G.'s design provides the same discreteness and reliability shown in OMG's prototype. The size of the wireless system can potentially be decreased by transitioning from traditional NFC readers, which require a sizeable proximal reader device, to RFID-like approaches that communicate with tiny receivers that can be placed far away. Endo et al. (2009) and Hibi et al. (2012) reported wireless monitoring of blood glucose and lactic acid levels in fish. In another work, a portable smartphone-based impedance monitoring system has been reported (Zhang et al. 2015). The conjunction of device integration, wireless calibration, and aspects of RFID-incorporated NFC-oriented prototypes holistically contribute to O.M.G.'s structure and application as seen in **Figure 1**.

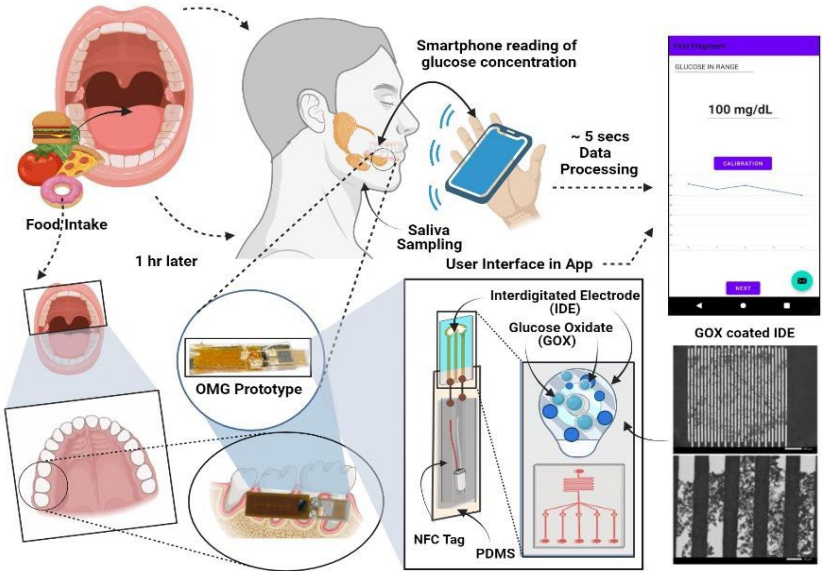


Figure 1: Schematic of Phase 1 of OMG Development. Phase 1 is a proof-of-concept model for OMG.

In **Phase 2** of O.M.G. development, Bluetooth-dependent systems (Wang et al., 2019) have been identified and are used daily to communicate results from device to device. However, oximeter differences and data capacity have the Bluetooth module must be identified and tested for implementation in app-to-device communication. This is the "product" step of O.M.G seen in **Figure 2**.

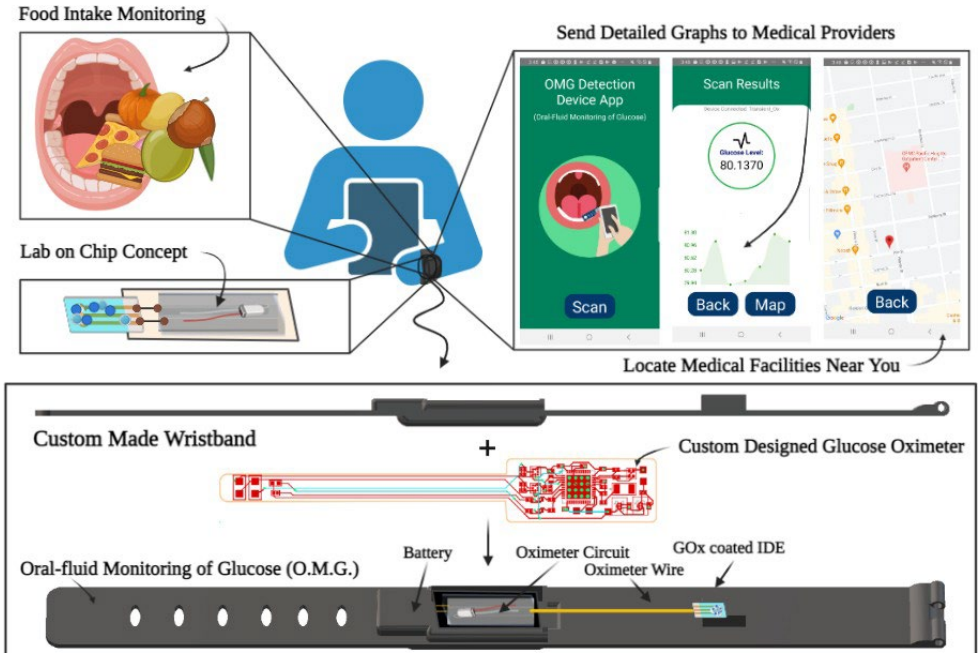


Figure 2: Schematic for Phase 2 of OMG design. Using data collected from proof-of-concept testing in Phase 1, Phase 2 aims to translate this data into a device that is wearable, accessible, and provides a "lab on chip" concept for all patients.

Materials

For Phase 1, the interdigitated electrode (IDE) was purchased from Newvision1981 (USA) and is used to detect and relay the electron activity back to the NFC readers. The polyethylene terephthalate (PET) substrate had a relative thickness of 60 µm, measuring roughly 10mm x 5mm. Each PET substrate also contained a specific conductor layer structure (Cu/Ni/Au) for better conductivity, thickness measuring 12 µm, three µm, and one µm, respectively. Each PET substrate contained several interdigital pairs (roughly 15-30 fingers). Each finger measures roughly 3300 nm and works to relay signal detection from the IDE to the NFC Tag for detection through a "RECEIVING" device (e.g., Vector Analyzer).

Subsequently, the prototype was also composed of the NFC Tag (Begin Industries, USA), which had a constant frequency of 13.56 MHz. A Nafion solution (1% wt), bought from DuPont Biomedical (USA), will aid OMG as a selective, semi-permeable membrane to facilitate absorption, guiding glucose molecules to the redox reaction site. The polydimethylsiloxane (PDMS) of the prototype was made with the PDMS base and mixer, both from ThermoFisher (USA). PDMS is used to aid in protective measures for the devices, concealing everything except for the immobilized GOx---on the OMG electrode. The GOx is made through a specialized GOx-chitosan mixture (Sigma, USA) and is used to catalyze the redox reaction on the OMG electrode.

For Phase 2, the oximeter for O.M.G. was self-made and had built-in laboratory space. The Bluetooth chip (Begin Industries, USA) measuring 5mm x 5mm, resistors, amplifiers, and circuits (Sigma Aldrich, USA) were

outsourced and soldered together for the functionality of the oximeter. The oximeter also required the same IDE from Newvision1981 (USA), except in a Bluetooth-based design, the IDE will detect and relay electron activity back to the Bluetooth reader, which will output data to the O.M.G. application. The battery (Hoottracker, China) was 3.7V, 650mAh, and is rechargeable after use. The watch strap (Flexninja Polyester) was self-CAD (Shapr3D, USA) and outsourced (Xometry, USA) for the oximeter component to be held. The GOx is made through a specialized GOx-chitosan mixture (Sigma, USA) and is used to catalyze the redox reaction on the OMG electrode.

Fabrication

To fabricate the battery-less NFC tag biosensor **(Phase 1)**, an interdigitated electrode (IDE), which was coated with a layer of glucose oxidase (GOx), was connected to an NFC tag antenna. The whole sensor was covered with polydimethylsiloxane (PDMS) and insulated except for the electrode (which was later immobilized by GOx). For the immobilization of GOx with IDE, chitosan was mixed with GOx to enhance the mechanical strength. Specifically, 15 mg of GOx was dissolved in 1 mL PBS to make a stock solution. After stirring the solution, 5 mg chitosan and 1 mL acetic acid solution was added and stirred for roughly 1 hour. Then, they were stirred for another hour after the preparation and sonication of equal volumes of the GOx solution and prepared chitosan. To modify the IDE before GOx immobilization, a Nafion solution (1% wt) was prepared and dropped (10 µL) onto the IDE. After the Nafion layer was dried thoroughly, 15 µL of GOx-chitosan mixture solution was prepared and dropped onto the IDE, which was dried at four °C overnight. To remove the non-immobilized GOx, the IDE was rinsed using water.

To fabricate the noninvasive Bluetooth biosensor watch **(Phase 2)**, the preparation of Gox and the immobilization of Gox onto the IDE were the same. However, the construction of the oximeter differs.

The oximeter design **(Figure 3)** consists of an antenna on port: C13, a Bluetooth chip on the central port; two amplifiers on ports: U2, U3; 2 resisters on ports: Y1, and Y2; multiple different signals switches on ports: R1, R4, R9, R10, T1, T2, C4, C5, C6, C7, C9, C19, and C44; and battery connectors on ports: BAT+. The IDE was connected to ports: U$ and U$2.

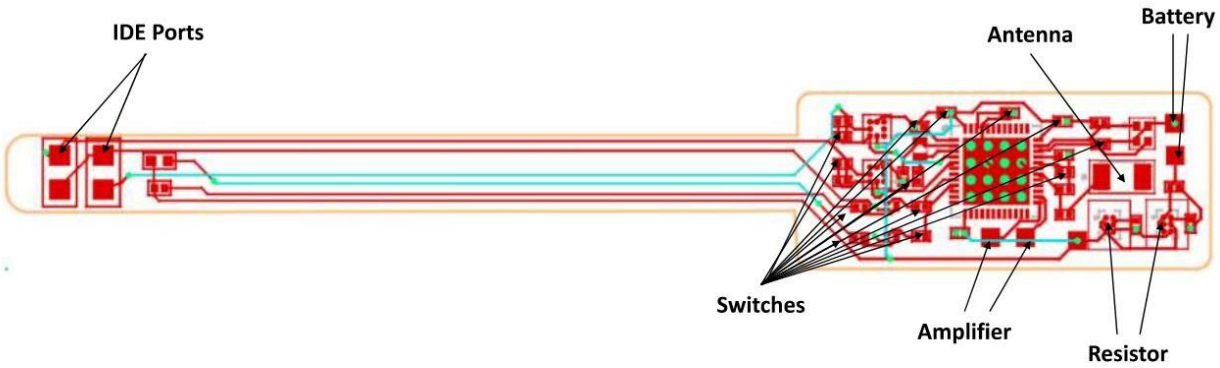


Figure 3: Visual concept of the O.M.G. oximeter and its various components

Phase I (Near-fluid Communication Chip) Methodology

Glucose Colorimetric Testing

Multiple test tubes were prepared and labeled into three categories: Blank, Standard, and Test. Glucose Reagents and Glucose Standards were warmed to room temperature before use. Then 3 ml glucose reagent was pipetted into all

three tubes. 30 µl of demineralized water was pipetted into a Blank, 30 µl of Glucose standard into the Standard tube, and 30 µl of sample into the Test. Afterward, all three tubes (Blank, Standard, and Test) were mixed well and incubated at 37°C for 10 minutes. All tubes were shaken two or three times to ensure an adequate reaction. Afterward, three mixtures were separated into six different rows (18 total wells), and varying concentrations of glucose samples (5 mg/dl, 25 mg/dl, 50 mg/dl, 100 mg/dl, 200 mg/dl, 300 mg/dl)) were pipetted into each good sample and tested the absorbance through a colorimetric machine. The absorbance was read at 630 nm against a reagent blank within 15 minutes using a spectrophotometer. The test was performed in triplicate to generate average results.

Scanning Electron Microscope

After drying, the samples were carefully mounted on an aluminum stubbed using either silver paint or a double stick carbon tape. Later, all samples were introduced into the chamber of the sputter coater and coated with a fragile film of gold/palladium before SEM examination. After the SEM was pressurized, the morphology of various samples was captured and characterized, thereby noting disruptions that GOx had on the fingers of the IDE. Saving and annotating in the system will save the files from being translated into figures. O.M.G.'s fingers were examined after applying GOx to see whether the fingers were damaged or not.

Vector Analyzer

Vector analyzers use a radio frequency signaling set using a variable attenuator. Detection of differing radiofrequency waves (through level adjustments) determines O.M.G. data. O.M.G was tested in a triplicate assay of 5 different intervals---rendering five different points (averaged) and recorded based on set time intervals. To set up the Vector Analyzer for O.M.G. testing, it first must be traced to only frequency (disregarding static, sound, etc.) to quantify frequency values. Afterward, the display (range) of the Vector Analyzer is to be set to 0.1 x 1 since the frequency emitted is weaker than other NFCs. Afterward, the inductor coil (self-CAD) and the transponder are connected to the measuring port to measure frequency-based values of salivary glucose concentrations.

Saliva Sampling

For *ex vivo* saliva sampling, samples (roughly 500 µL) were collected from unidentifiable participants. Glucose levels were tested using our device and compared to their blood glucose level with traditional methods. After calibration, the OMG device was tested under various saliva environments (e.g., before eating, during eating, after eating, drinking water, drinking sugary drinks, etc.), and data was collected from a triplicate assay as well (a total of five samples). The accuracy was compared to gold standard glucose meters, Accu-Check© Performa Nano, evaluating the product's usability. Results were documented in numerous excel sheets and converted into GraphPad graphs for correlation analysis.

Phase II (O.M.G.) Procedures

Voltage Measurement through DK-Board

The DK-Board (Development Kit Board) is a custom-coded board using nRF Low Energy Bluetooth (LEB) components. The Dk-Board is coded to measure voltage and has a central Bluetooth chip for data from the O.M.G. watch to send to. The DK-Board ran O.M.G.'s first tests as it provided O.M.G.'s preliminary results on voltage significance when testing for glucose concentrations versus when it is "dry" testing. When testing with O.M.G., the DK-Board first

switches onto the O.M.G. protocol and receives its respiratory (as well as O.M.G.'s Bluetooth information). After connection, the DK-Board will receive fundamental time changes in the device voltage and graph them on a linear scale for visualization. Then, the DK-Board will calculate significance (*p*) and plot the significance value alongside its raw values (measured every 2 seconds). The DK-Board was coded in Python using VSCode and is implemented in Script form on Local hosting servers.

Voltage Measurement through DDM Machine

Data Diffusion Machine (DDM) testing for Voltage Curve Significance is another test for testing the effects of applying salivary glucose. Before testing, the range calibration must be set (based on normalized values of Voltage from the O.M.G. module. Then, the DDM will calculate significance (*p*) and plot the significance value alongside its raw values (measured every 1 second). The DDM was outsourced (Sigma Fisher, USA) and provides another source of validation for voltage accuracy in O.M.G.

Application Design

The O.M.G. compatible application was made through an Android Application Package (APK). The application was first coded using JavaScript and later hosted on Firebase servers when a user needed spatial communication. The application has a total of 7 screens, namely: "Home," "Error," "Result Normal," "Result Critically Low," "Result Critically High," "Links," and "Map." After designing the application's User Interface (UI), the O.M.G. standard curve was implemented to calculate salivary glucose based on electron activity received from the Bluetooth sensors. Based on the number given for the salivary glucose, different screens will show how critically high/low the concentration is and will give automatic warnings if the range falls outside 80-160. The data points will also translate in real-time into a chart---in which patients can save the graph and send it to their healthcare providers. Lastly, the "Map" and "Links" feature aim to provide resources to struggling diabetics about the most asked questions or pinpoint the nearest shelter. O.M.G. was coded in JavaScript using VSCode and is implemented in APK form on Firebase hosting servers.

Voltage Ex-Vivo Testing

For *ex vivo* saliva sampling, participants (nondiabetic and diabetic) (n=10) were asked to test their glucose levels through O.M.G. and a standard blood glucose monitor, *AccuChek* ©, at around the same time. Participants were also asked to rinse their mouths before testing and to clean the oxidized GOx afterward by rinsing with tap water. To normalize for enzymatic content after testing, all O.M.G. IDEs were cleaned, and GOx was replaced after every test. Data was transported directly from the application discussed above and visualized through graphs. This data was then compared to the commercial gold standard for data analysis (R^2).

Phase I Results

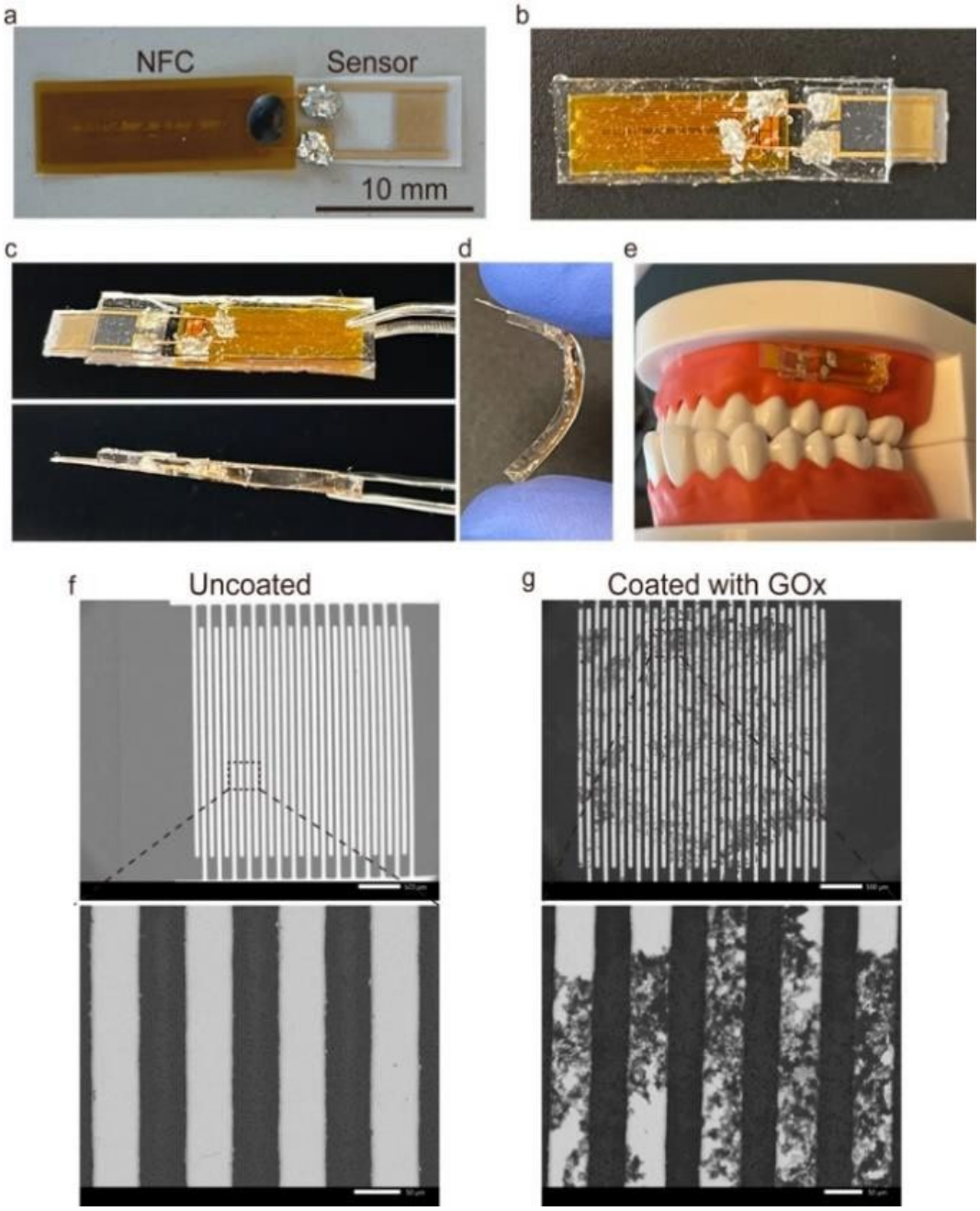
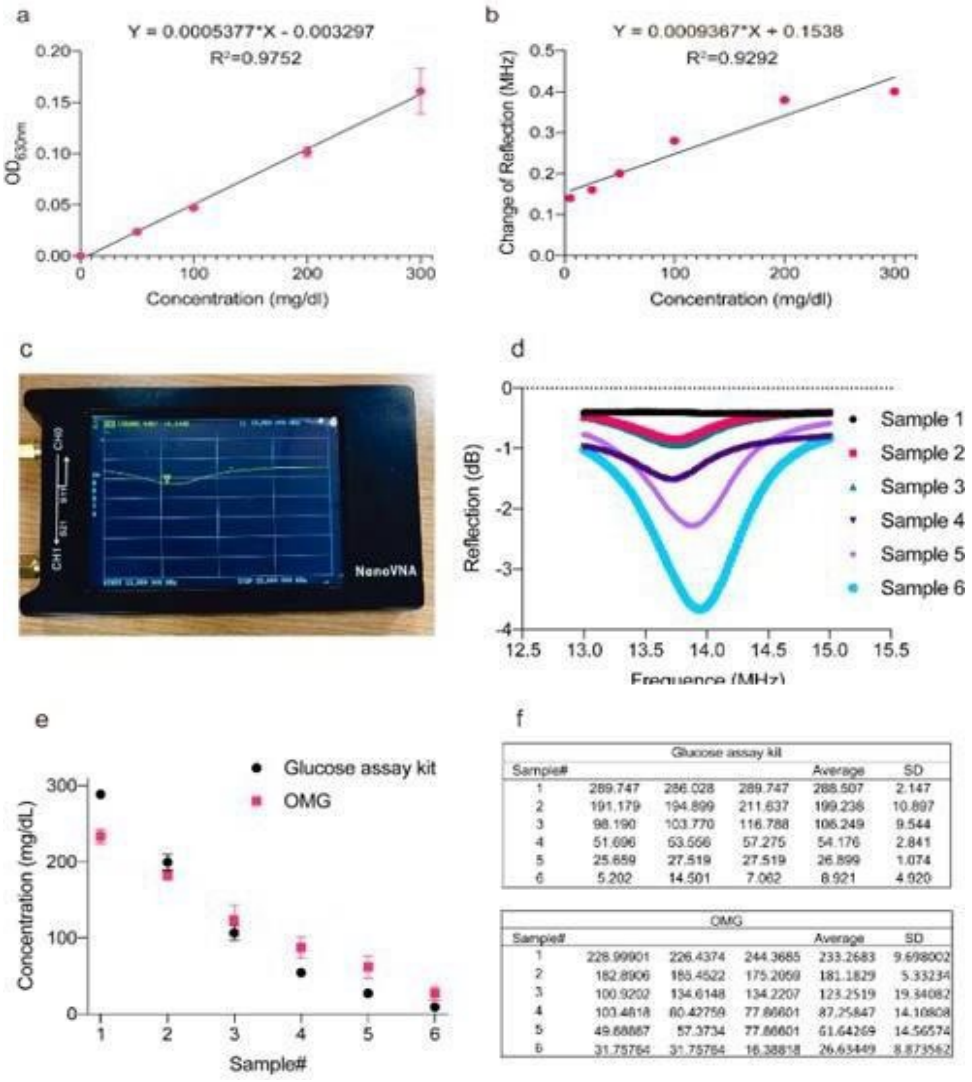


Figure 5: System design of OMG device integrated with an NFC tag. (a) Photograph of the product prototype including NFC and sensor parts. (b) The prototype after polydimethylsiloxane (PDMS) covering. (c) Side-view and vertical dimensions of OMG. (d) Imaging showing the flexibility of OMG. (e) OMG attached on a human gum model. SEM images of the IDM sensor before (f) and after (g) coating with GOx.

OMG is composed of an NFC chip and an interdigitated electrode (IDE) **(Figure 5a and 5b)**, which serves as data transmissions and biological sensor. The whole sensor is covered with polydimethylsiloxane (PDMS) to protect the electronic components from saliva and makes OMG flexible **(Figure 5c and 5d)**. This also allows OMG to be conformably mounted on human gum for in situ glucose analysis **(Figure 5e)**. For glucose detection, the IDE was coated with GOx, where a biological redox reaction occurs after being in contact with glucose. As demonstrated in the SEM image **(Figure 5f and 5g)**, GOx was maintained on the sensor compared to the uncoated IDE.



Glucose assay kit

Sample#				Average	SD
1	289.747	286.028	289.747	288.507	2.147
2	191.179	194.899	211.637	199.238	10.897
3	98.190	103.770	116.788	106.249	9.544
4	51.696	53.556	57.275	54.176	2.841
5	25.659	27.519	27.519	26.899	1.074
6	5.202	14.501	7.062	8.921	4.920

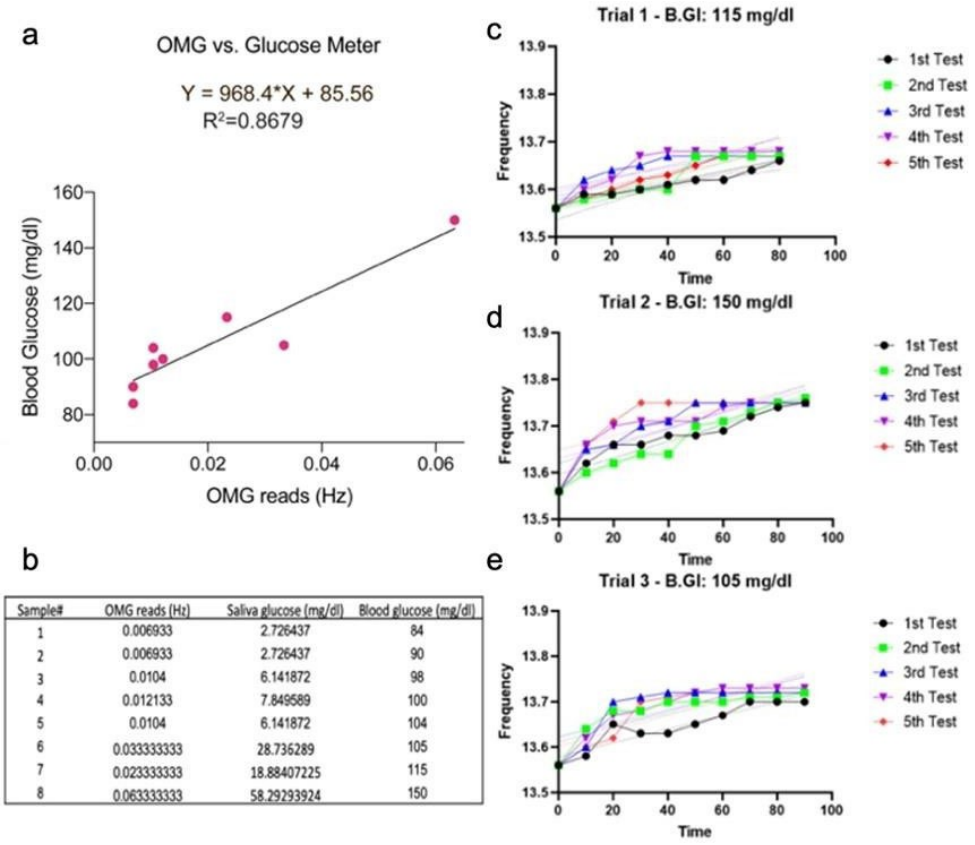
OMG

Sample#				Average	SD
1	228.99901	226.4374	244.3685	233.2683	9.698002
2	182.8906	183.4522	175.2059	181.1829	5.33234
3	100.9202	134.6148	134.2207	123.2519	19.34082
4	103.4618	80.42759	77.86601	87.25847	14.10808
5	49.68887	57.3734	77.86601	61.64269	14.56574
6	31.75784	31.75784	16.38818	26.63449	8.873562

Figure 6: The evaluations of the electrochemical system. (a) The standard curve for the colorimetric method. (b) The standard curve for our initial prototype respectively. (c) Representative photograph of the vector network analyzer used to detect the RFID signal. (d) The responses of all samples, classified through frequency changes. (e) The comparation of samples 1-6 measured by both the glucose assay kit and our initial prototype. (f) Full quantitative results of the test.

The electrodes that we designed were coated with GOx, where a biological redox reaction occurs after being in contact with glucose. When the interdigitated electrode connects to an NFC tag, the redox reaction strongly changes the impedance of the tag. This finally modulates the electromagnetic reflection from the tag, which will be reflected as the "change of frequency" or delay time. Both the "change of frequency" and delay time are proportional to the concentration of glucose; thus, the data can be analyzed and calibrated (Keenan et al.).

To confirm the precious of OMG for saliva glucose detection, we compared the glucose detection results from OMG with a commercial chemical method. For reference, the chemical method uses colorimetric testing at an absorbance rate of 630 nm **(Figure 6a)**. **Figure 6b** exhibits the frequency responses of the OMG to glucose, which shows that the "change of frequency" was linearly proportional (with R^2= 0.9292) to glucose concentrations in the range of 0 to 300 mg/dl. Within the same range of glucose concentration, the standard curve for the chemical detection method showed a linearly proportional with R^2= 0.9752. Besides, we have compared the results regarding the glucose concentration in prepared glucose samples by OMG and standard chemical approach. The reflection was obtained through NanoVNA **(Figure 6c)**. As the concentration of glucose rises from sample 1 to sample 6, the changes of reflection also increased **(Figure 6d)**. Thus, the change of frequency was quantified and transformed into glucose concentration using the format from the standard curve. As compared to the commercial chemical method, the glucose concentration detected using OMG showed good accuracy **(Figure 6e and 6f)**.



Sample#	OMG reads (Hz)	Saliva glucose (mg/dl)	Blood glucose (mg/dl)
1	0.006933	2.726437	84
2	0.006933	2.726437	90
3	0.0104	6.141872	98
4	0.012133	7.849589	100
5	0.0104	6.141872	104
6	0.033333333	28.736289	105
7	0.023333333	18.88407225	115
8	0.063333333	58.29293924	150

Figure 7. Ex-vivo glucose detection using saliva samples from human. (a) and (b) displays preliminary testing using saliva samples from human (measured with OMG) compared to their blood samples in the same time range (measured with Accuchek). (c), (d) and (e) show three total trials with differing blood glucose values compared to frequency values measured throughout 100 seconds, (c) before, (d) 1 hour, and (e) 2 hours after food consumption.

After the correlation of glucose concentration with frequency change, a preliminary comparison was performed using human saliva samples and corresponding blood samples in the same time range. As shown in Figure **7a and 7b**, both blood glucose level (measured with blood glucose meter) and saliva glucose level (measured by OMG) were recorded from eight samples. A good linear correlation (R^2= 0.8679) was found between OMG reads and blood glucose. To confirm the reliability of OMG, the test was performed at three time points, before food consumption, 1 hour and 2 hours after food consumption **(Figure 7c, 7d and 7e)**. The frequency values were measured throughout 100 seconds, which showed good reproducibility.

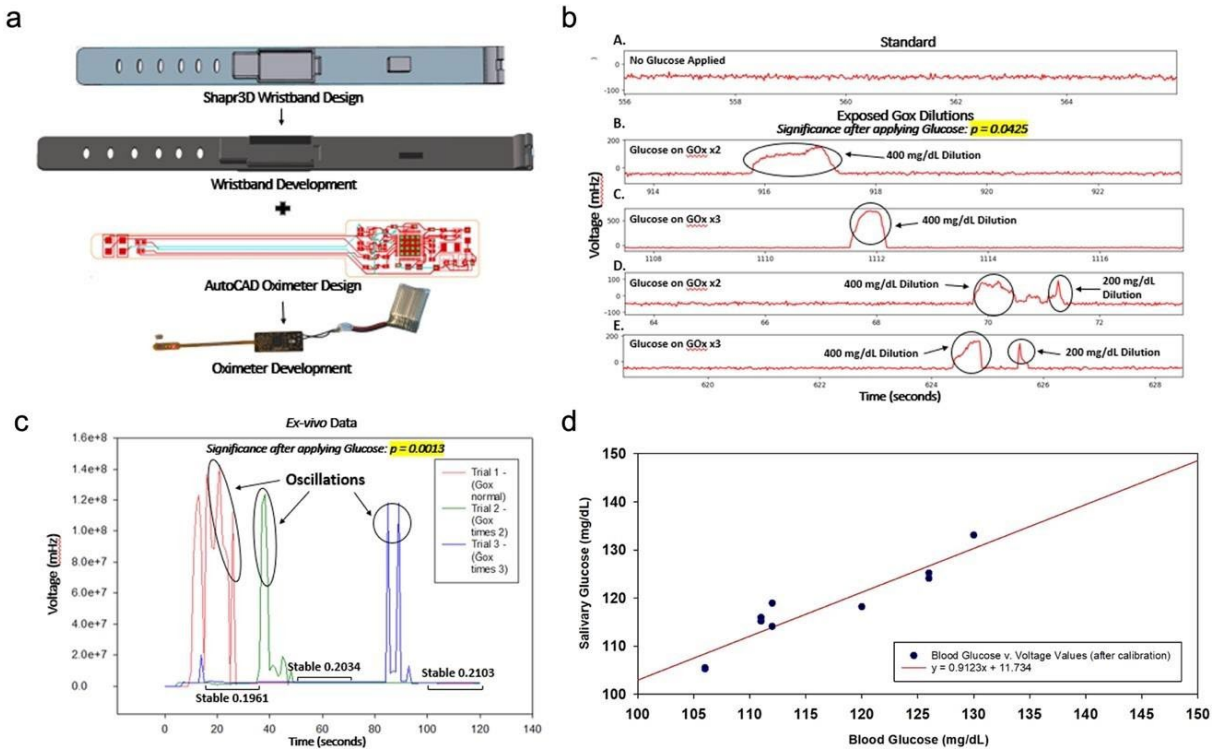


Figure 8. Fabrication of OMG wristband. (a) Assembling schematic and design involves a 3D printed wristband (Flexninja Filament), a custom-made oximeter, and extension with OMG. (b) Development board testing for voltage curve significance. (c) Data diffusion machine (DDM) testing for voltage curve significance. (d) OMG vs. Standard blood glucose test to establish line of best fit in voltage values versus blood glucose values.

Using data collected from proof-of-concept testing, a wristband was fabricated to translate this data into a device that is wearable, accessible, and provides a "lab on chip" concept for all patients **(Figure 8a)**. **Figure 8b** showed the development board testing for voltage curve significance. Standard (A) shows that when no glucose was applied, the voltage (mHz) seemed stagnant. (B) is based on twice the normal Glucose Oxidase concentration on 400 mg/dL dilution, (C) is triple the normal Glucose Oxidase concentration on 400 mg/dL dilution, (D) is twice the normal Glucose Oxidase concentration on 400 mg/dL dilution followed by a 200 mg/dL dilution, (E) is triple the normal Glucose Oxidase concentration on 400 mg/dL dilution followed by a 200 mg/dL dilution. All measurements were taken across 5 second intervals and measured in voltage (mHz). The DDM testing for voltage curve significance was further performed **(Figure 8c)**. By testing with normal GOx concentration, double the GOx concentration, and triple the GOx concentration, significance can be calculated between stable (0.1961, 0.2034, 0.2103 respectively) and oscillating patterns (1.38e+8, 1.22e+8, 1.16e+8 respectively). Taken from a sample of 10 patients (who wore the device and

tested through salivary direct contact with OMG, the line of best fit was determined and implemented in application models (**Figure 8d**). The values shown were readily calibrated through y = 0.9123x + 11.734.

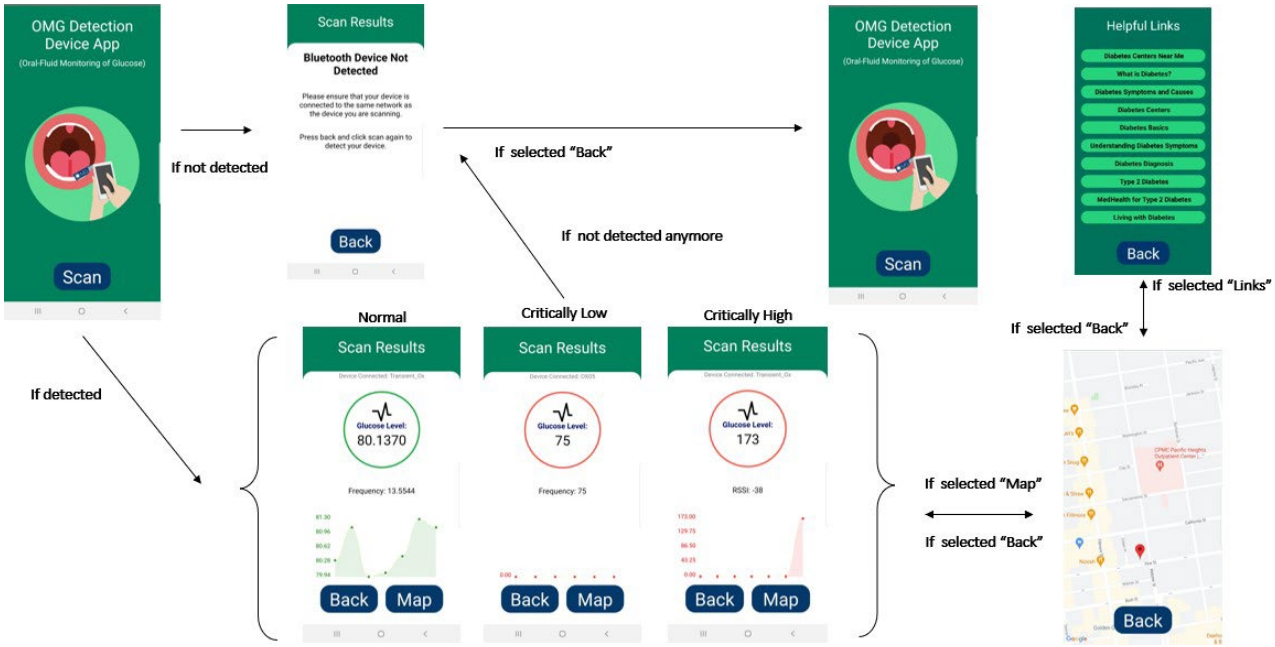


Figure 9: Creation of an App-based module for ease of access. In this APK, it includes a display screen, a path for "not detected," a path for "connected," a chart for visual analysis, a display value of "too high!" or "too low!", resources to help patients, and an interactive map to locate the closest hospitals.

Creating an OMG-based application is warranted to suit consumer usage and monitoring without the use of complex machinery. OMG application provides a simplistic interface of data display and contains complex data storage systems and links/maps for data implementation. Lastly, OMG incorporates an emergency beeping mechanism in case patients experience too high or too low glucose concentration in their blood.

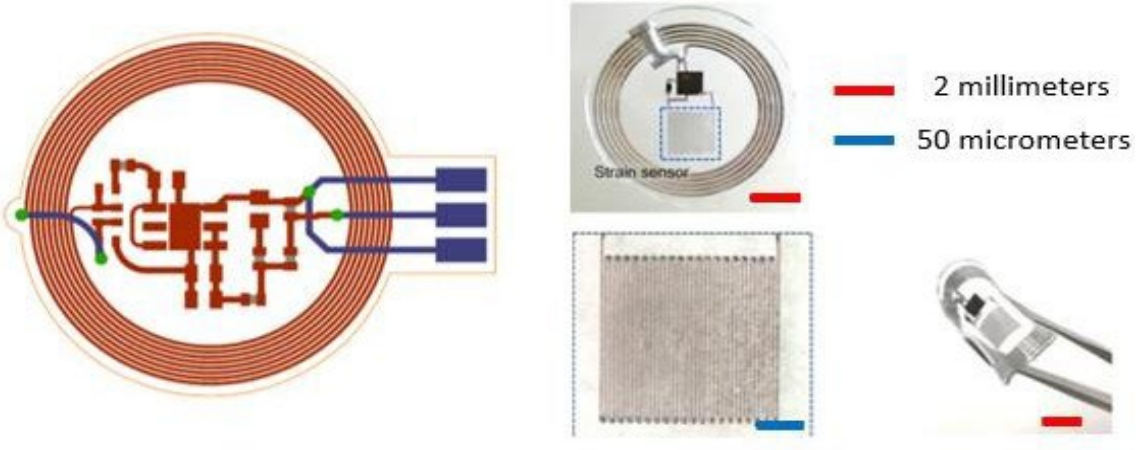


Figure 10: A custom CAD file, measuring 5mm – 7 mm in hopes of developing a slimmer, resource-efficient model, with higher resonance and distance detection.

Future designs of OMG may be smaller-fitted and provide a stronger resonance to a smartphone (and provide combability over a more extended period and distance). Further, the fingers of the IDE may be more compact and provide more specific resonance to the receiving device. The circular design and battery connectors (below) will provide longer charging and more concentrated signaling from the device to the responder.

Discussion

SEM Imaging

SEM Imaging Covering the electrodes with polydimethylsiloxane (PDMS) may raise concerns about the effectiveness of the design. However, current data shows that the electrodes were not disturbed through the morphology of scanning electron microscope (SEM) tests; the particles of GOx are also readily immobilized. Since SEM imaging uses scanning electrons to determine an object's morphology, we could also determine the rigidness of OMG's electrode component, the size of the fingers, and finger impairment after immobilized GOx coating.

Glucose Colorimetric Assay

Glucose Colorimetric Assay Though glucose colorimetric correlates $R^2 = 0.9752$, OMG's $R^2 = 0.9292$ also proves its reliability. The MHz/dB chart noted a frequency of change, meaning that OMG can quantify differing frequencies based on glucose concentration. OMG can also be quantified on the mg/dB scale and thus calibrated/compared with chemical samples. The standard deviation for glucose colorimetric is: [2.147, 10.897, 9.544, 2.841, 1.074, 4.920] and OMG [6.315, 8.668, 9.548, 3.323, 0.597, 1.034], respectively, showed acceptable deviation, justifying our correlation and OMG's accuracy.

OMG vs. Blood Glucose Performance Testing, Triplicate Testing, and In-Vivo Analysis

Through the comparative analysis between blood glucose (BG) and OMG in proof-of-concept testing, its total correlation is $R^2 = 0.8629$, which proves its correlatability and assures some pattern between both testing methods. OMG readings (Hz) show OMG raw data minus the constant 13.56 Hz from each test. OMG → Saliva glucose (mg/dl) is calculated using the saliva-OMG equation ($Y = 0.00093867*X + 0.1538$), calibrating the saliva glucose. OMG → Blood glucose (mg/dl) is calculated using the blood-OMG ($Y = 3013*X + 67$). Double variable testing can help increase the validity of the results through blood v. saliva and OMG v. saliva & blood quantities. There was a ~ 10-second time buffer from saliva detection to data calibration, seeing that the data for ex-vivo only included ~ 10 seconds of testing. Meanwhile, the in-vivo analysis between 10 samples of diabetic data matched well with the values of AccuChek Performa Nano; AccuChek Performa Nano even had fluctuations in data which caused two separated lines to occur in both (a) and (b).

Voltage Testing with DK-Board

Through DK-Board Testing (Development Kit Board Testing), oximeter values fluctuated consistently with the application of glucose onto the GOx. Varying amounts of glucose concentration will render various heights of the oximeter curve, particularly as the DK-Board is connected to a data-fetching Bluetooth chip itself; OMG validity through voltage testing can be measured, and significance can be measured through both student *t-test* and ANOVA-2-way testing. Moreover, the time the voltage curve slows down can be measured and quantified (inputted into OMG's latest

algorithm in its smartphone app). OMG's structure was integrated with different GOx levels to quantify different steps of glucose diffusion. The amount in which the voltage current was diluted was recorded as "steps" in glucose level concentration.

Voltage Oscillation with DDM

Through the Data Diffusion Machine (DDM), OMG oscillation could be quantified. GOx 1, GOx 2, and GOx 3 were applied and immobilized onto varying IDE chips. Oscillation was then measured by applying a glucose control (400 mg/dL) to all samples of GOx variation. OMG validity can be measured through voltage oscillation peaks, and stable bases, and significance can be measured through student *t- test* and ANOVA-2-way testing. Intricately, as time passes with higher GOx concentrated IDEs, the peak will be delayed (and occur after a more extended application period).

OMG vs. Blood Glucose Performance Testing and In-Vivo Analysis

Through the comparative analysis between blood glucose (BG) and OMG in performance testing, its total correlation is $R^2 = 0.9527$, which proves its correlatability and assures some pattern between both testing methods. OMG readings (Hz) show OMG raw data minus the constant 13.56 Hz from each test. OMG → Saliva glucose (mg/dl) is calculated using the saliva-OMG equation ($Y = 0.00093867*X + 0.1538$), calibrating the saliva glucose. OMG → Blood glucose (mg/dl) is calculated using the blood- OMG ($Y = 3013*X + 67$). Implementing both equations within the OMG watch leads to the regression graph incorporated in the OMG application. Double variable testing can help increase the validity of the results through blood v. saliva and OMG v. saliva & blood quantities.

Conclusion

In this study, a salivary glucose-monitoring device (OMG) was fabricated, showing noninvasive blood glucose monitoring performance. The sensor of OMG is composed of a wireless circuit electrode and a communication system-on-chip (SoC) NFC, which achieved miniaturized and low-power operation. Glucose oxidase (GOx) is applied onto the electrode to exhibit the redox reaction, which results in the product of electrons and sensed through the IDE. The whole system is fully integrated into a chip like biosensor for continuous monitoring and showed response to salivary glucose. A good linear correlation was established between glucose level and electronic signal, which demonstrated a good proof-of-concept for further device fabrication. When the IDE connected to the Bluetooth circuit, the impedance changed and modulated the electromagnetic reflection from the circuit, reflecting it as the "change of resistance" and was proportional to the glucose concentration. The resistance and voltage significance were averaged to be $p < 0.001$ and $p < 0.01$ respectively, showing the reliability of the device. Finally, the custom-CAD smartwatch and a compatible application of OMG were developed, which would be a promising candidate for non-invasive blood glucose detection.

Limitation

This study mainly focused on the transmission of salivary glucose data through NFC and Bluetooth means to serve as proof of concept for future testing. Subsequent studies should aim to measure GOx concentration after each reaction, the effect the amount of saliva has on chip performance, how long the watch can last before replacement, and ways to sanitize the chip after every test.

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