Wireless Graphene-Based Quantum Capacitance Sensors for Continuous Glucose Monitoring

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ABSTRACT

We present a revolutionary concept for *in vivo* biosensing that utilizes the quantum capacitance effect in graphene to realize an ultra-small passive wireless sensor. We provide a review of the quantum capacitance wireless sensing concept in graphene and then describe our recent results toward the application of this concept for use as continuous glucose monitors.

Keywords: graphene, wireless, glucose, sensor

1 MOTIVATION

Continuous glucose monitors (CGMs) are a key component of a closed-loop artificial endocrine pancreas system [1]. Key requirements for such sensors are as follows. The sensor must provide accurate measurements of the glucose levels present at the sensor and, if the sensor does not measure blood glucose directly, these measurements should have a tight correlation with actual blood glucose levels. The CGM should also provide a short time lag between the measured value and blood glucose levels, and must provide accurate readings in the presence of common drugs or other physiological changes. The ideal CGM should also have long lifetime and provide accurate readings over its entire lifetime. The sensor should not cause harmful secondary effect, such as infection or thrombosis, and must be non-toxic. It would also be desirable for the sensor to be small and cause the least amount of discomfort or inconvenience to the patient as possible. Finally, the sensor should be inexpensive relative to alternate methods of measuring glucose.

Current commercial CGMs have been developed over the past 30 years and have made enormous progress since their initial conception [2]. These sensors have several fundamental shortcomings that hamper their application for closed-loop glucose control systems. A key limitation is the fact that they operate subcutaneously, and this mode of operation has a significant time delay between the measured readout and the actual blood glucose level [2]. Therefore, the inherent time-delay associated with subcutaneous CGMs has led to considerable interest in the development of intravascular continuous glucose monitors. However, scaling of conventional CGMs to the sizes needed in order to operate as an intravascular sensor is exceedingly difficult. Wired intravascular sensors based upon conventional amperometric GOx sensors have been investigated, but present significant problems for long-term usage particularly due to the threat of thrombosis, scarring and the need for frequent replacement of the sensor electrode [3]. For this reason, capacitance-based sensors are attractive due to their simplicity, passive operation, their ability to be adapted to non-enzymatic sensing approaches, and their ability to transmit glucose information wirelessly. An excellent example of non-enzymatic wireless capacitance-based sensors is the work of Lei, who utilized a boronic-acid doped hydrogel to create a MEMS-based variable capacitor (varactor) with sensitivity to glucose [4]. However, hydrogel-based sensors have inherently slow response time, negating much of the motivation for intravascular positioning in the first place. Due to the fact that the varactor is based upon MEMS technology, these sensors are still larger (~ 1-2 mm diameter) than desired for intravascular placement.

Therefore, alternative capacitance-based sensors that can be scaled to extremely-small sizes have potential to operate non-enzymatically with fast response time could represent an enabling technology for closed-loop systems. In this work, we describe a fundamentally new method of sensing glucose that has the potential to overcome many of the limitations of conventional glucose sensors. It utilizes a unique property of graphene called the quantum capacitance effect that allows the realization of a variable capacitor with extremely-small size, rapid response and potential for good biocompatibility.

2 QUANTUM CAPACITANCE TRANSDUCTION MECHANISM

The physical structure of the varactor is shown in Fig. 1(a). At its core, the device consists of a metal electrode, a thin high-K dielectric (such as HfO_2) and single-layer graphene. The multi-finger structure is used to reduce the series resistance so that large capacitances can be built up

while maintaining a high quality factor (Q). The variable capacitance comes about due to energy-dependent density of states in graphene. If an external analyte adsorbed onto the surface changes the electron concentration in the graphene, a measurable capacitance change is expected for the device. As the dielectric thickness is reduced, the possible tuning range increases. Fig. 1(b) shows simulated capacitance vs. surface characteristics for graphene varactors, indicating that capacitance tuning ranges of > 3-to-1 are theoretically possible [5]. In addition, due to the extremely high mobility in graphene, the quality factor can be high, a key requirement for wireless readout.

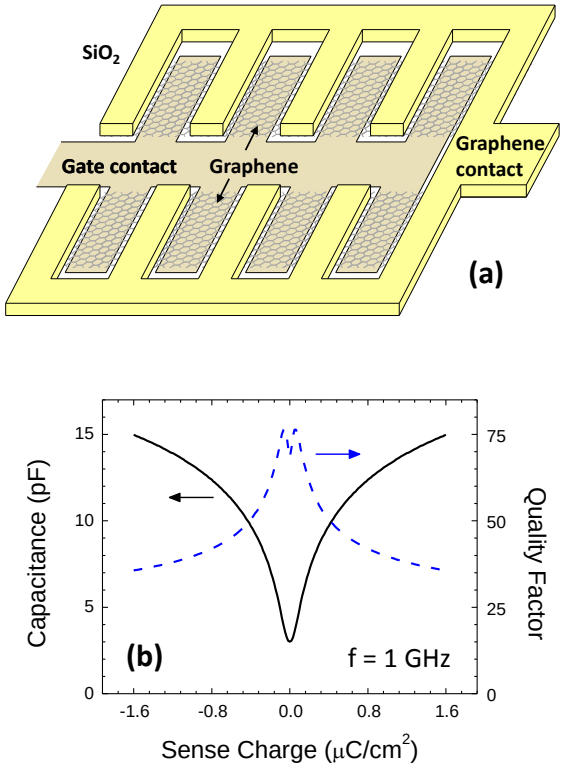

Figure 1: (a) Cartoon showing basic graphene varactor device design. (b) Simulated results showing ideal graphene varactor capacitance and quality factor tuning vs. adsorbed surface charge.

As an initial step toward realizing this type of novel sensor, we have developed a fabrication process for these devices. The detailed results are reported in [6], and a brief summary is described here. Devices were fabricated on a Si substrate upon which 90 nm of SiO_2 has been grown by thermal oxidation. Next, the gate contact electrode was patterned using optical lithography and 10 nm Ti and 40 nm of Pd was deposited. After the gate metallization, 20 nm of HfO_2 was deposited on the entire sample using atomic-layer deposition (ALD). Next, graphene that was grown by chemical vapor deposition on a Cu substrate was transferred onto the sample using a poly(methyl methacrylate) (PMMA) handle layer, and the graphene removed everywhere except in the region shown in the figure. To complete the device fabrication, metal electrical contacts to the graphene (10 nm Ti and 100 nm of Au) was patterned and deposited. An optical micrograph of a completed graphene varactor is shown in Fig. 2(a). It should be pointed out that the active area of the device is only where the graphene is situated above of the buried gate electrode.

The measured results for the varactor described above are shown in Fig. 2(b). The data has been obtained by measuring the capacitance between the gate contact and graphene contact where the voltage between the two contacts has been swept from -2 V to + 2V. In a "normal" parallel plate capacitor, the capacitance would be constant as a function gate voltage. However, in graphene, a change in the capacitance is observed, which occurs when the Fermi-level in graphene coincides with the so-called Dirac (or charge-neutrality) point. The Q value vs. gate voltage is also shown (blue curve), and a value of $Q \sim 10$ at 5 MHz is observed.

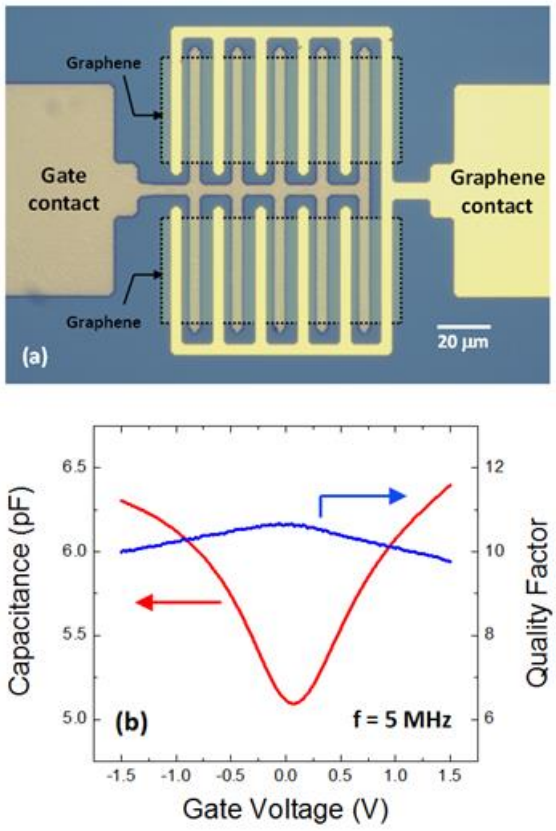

Figure 2: (a) Optical micrograph of fabricated multi-finger graphene varactor with HfO_2 thickness of 20 nm. (b) Measured capacitance and quality factor vs. gate voltage at a frequency of 5 MHz.

Both the capacitance tuning range and quality are less than theoretical predictions and work is ongoing to improve he basic device performance. However, these results are still adequate for initial sensing experiments, and we have recently demonstrated the operation of bare (non-functionalized) graphene varactors as wireless vapor sensors [7].

3 SURFACE FUNCTIONALIZATION FOR GLUCOSE SENSING

The results described above validate the basic graphene varactor transduction mechanism. However, in order to operate as a glucose sensor, the surface of the graphene must be functionalized in such a way to make it selective to the target analyte (in this case glucose). Previous work in the literature has suggested an initial approach based upon glucose oxidase [8]. In this functionalization scheme, GOx is attached to the graphene using the pyrene-based linker molecule 1-pyrenebutanoic acid succinimidyl ester (1-PASE), as shown in Fig. 3(a). The π-π bonds provide a strong and stable bond between the graphene and the linker molecule. The sensing mechanism occurs when the GOx oxidizes glucose and produces H_2O_2 which acts as an electron acceptor, thus depleting the electrons from the graphene. This mechanism is distinctly different than the conventional amperometric sensing mechanism, where a biased electrode reduces the H_2O_2 and the resulting current is proportional the glucose concentration. We have demonstrated the attachment of GOx to graphene as shown by the atomic force microscope image in Fig. 3(b), and have further confirmed that GOx-functionalized graphene produces H_2O_2 using luminol chemiluminescence, as shown in Fig. 3(c).

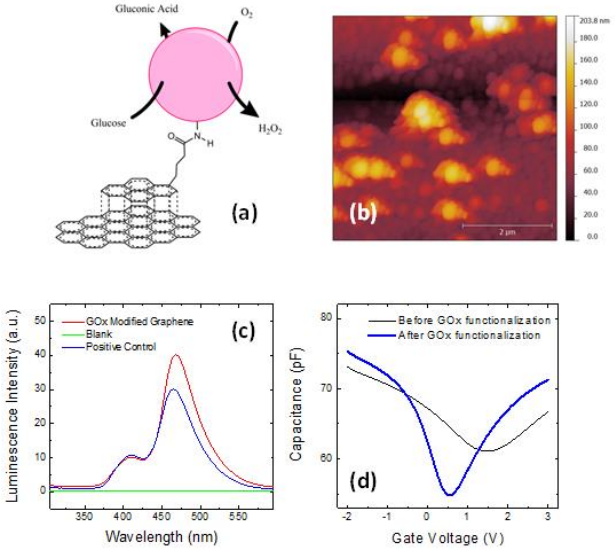

Figure 3: (a) Cartoon depicting GOx attachment to graphene, (b) AFM of GOx-functionalized graphene, (c) Luminescence spectra confirming H_2O_2 production from GOx-modified graphene, (d) Capacitance vs. gate voltage for graphene varactors before and after functionalization.

We have applied this surface functionalization method to actual graphene varactors and measured their performance before and after functionalization. The results shown in Fig. 3(d) indicate improved capacitance tuning range after functionalization, most likely to the displacement of moisture from the graphene surface by the 1-PASE linker.

4 PRELIMINARY SENSING RESULTS

As a final preliminary step before actual glucose sensing, we have shown that graphene varactors exhibit a strong response to H_2O_2. Here GOx-functionalized graphene varactors were exposed to varying concentrations of H_2O_2 ranging from 0.4 mM to 8 mM. The devices show a clear rightward shift, indicating that at fixed bias, strong capacitance tuning can be achieved. It should be pointed out that these devices were tested by sweeping the gate bias voltage and measuring the capacitance-voltage characteristic at different concentrations, while in actual sensor operation, the device would be biased at 0 V, with the capacitance shifted by different analyte concentrations. We currently are working to demonstrate actual glucose sensing using glucose in phosphate buffered saline (PBS) using these devices. Such demonstrations require a slightly more complex fabrication process owing to the ionic nature of the PBS. Preliminary results of these experiments will be reported at the conference.

5 DISCUSSION

The primary benefit of the graphene varactor over other capacitance-based sensor concepts, particularly those based upon MEMS technology, is layout area. The calculated total layout area of varactors with EOT = 1 nm from in Fig. 1 is 1.21 x 10^3 μm^2 with a corresponding capacitance range of ~ 3-10 pF. This area is < 50 x 50 μm^2 and, if transferred to a membrane substrate, could be roughly comparable in thickness. Such a minutely sized sensor could readily be mounted onto the inside of a blood vessel. As a comparison, typical MEMS-based sensors [9] require layout areas > 10^5 μm^2 in order to produce comparable capacitances, owing to the large spacing between the capacitor electrodes.

The extremely-small size of the graphene varactors could allow the realization of intravascular glucose sensors, particularly if combined with an arterial stent used as an

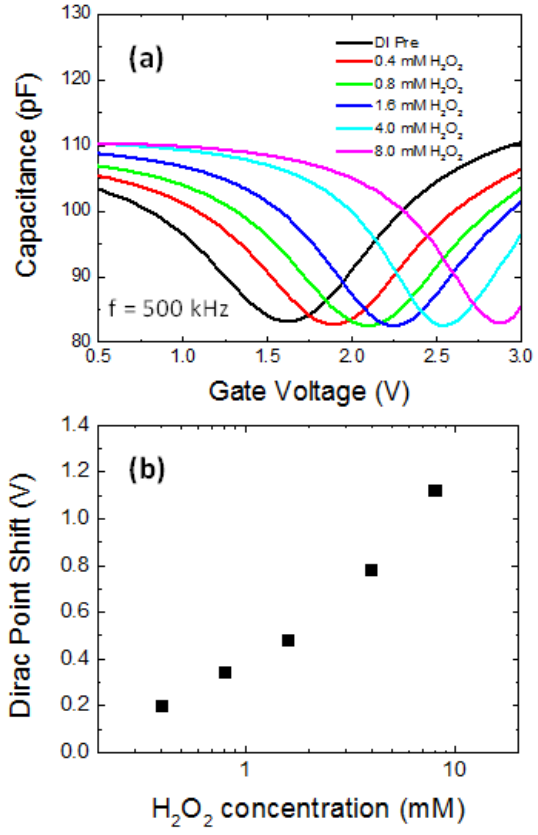

Figure 4: (a) Capacitance-voltage characteristic of GOx-functionalized graphene varactors exposed to different H_2O_2 concentrations. (b) Plot of voltage shift vs. H_2O_2 concentration for data shown in (a).

inductor. This would allow the sensing scheme shown in Fig. 5. Here, the functionalized graphene varactor could be located on the inside of a blood vessel and attached to the ends of a stent designed to also act as a inductor. If an external inductor is placed near to the blood vessel outside of the body, and its impedance measured continuously vs. frequency, then a "dip" in the impedance phase occurs at the resonant frequency of the LC sensor. In this way, the glucose concentration can be encoded into the measured frequency, a very robust and noise-immune sensing mechanism.

Despite the promising results, numerous challenges remain to this sensor concept. In addition to demonstrating the full wireless sensing mechanism using glucose standards, numerous properties have to be studied. Among these include the sensitivity to both low and high glucose levels, their stability, immunity to biofouling, reproducibility, and need for calibration. A particularly intriguing feature of this sensor is the fact that the graphene varactors do not rely upon a glucose-based redox reaction, and therefore could utilize non-enzymatic methods of sensing. Such techniques could simply involve the localization of glucose near the graphene surface using an appropriate receptor.

In conclusion, a novel glucose sensor concept has been reported for graphene and preliminary results have been shown that suggest this concept could lead to the realization of a new class of ultra-small wireless continuous glucose monitors. This work was supported by the Minnesota Partnership for Biotechnology and Medical Genomics Decade of Discovery Initiative.

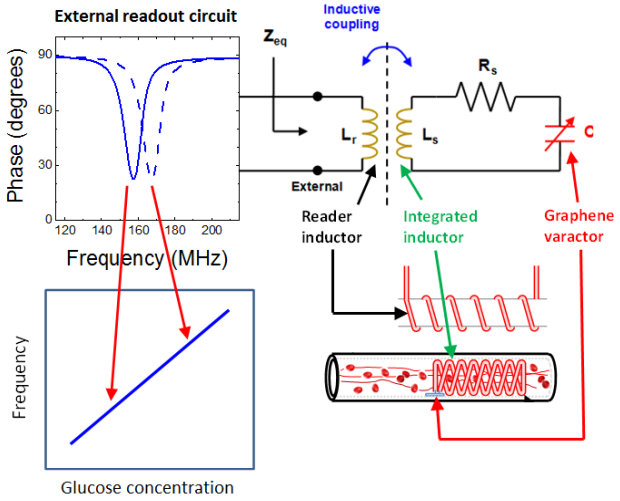

Figure 5: Diagram showing envisioned intravascular wireless glucose sensing scheme.

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