Three dimensional graphene transistor for ultra-sensitive pH sensing directly in biological media

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HIGHLIGHTS

- A three-dimensional graphene transistor for pH sensing is presented.
- It shows sensitivity of 71 ± 7 mV/pH even in high ionic strength media.
- High sensitivity attributed to 3D foam structure and all-around liquid gating.
- Enables real-time pH sensing in biological media without need of desaltation.

GRAPHICAL ABSTRACT
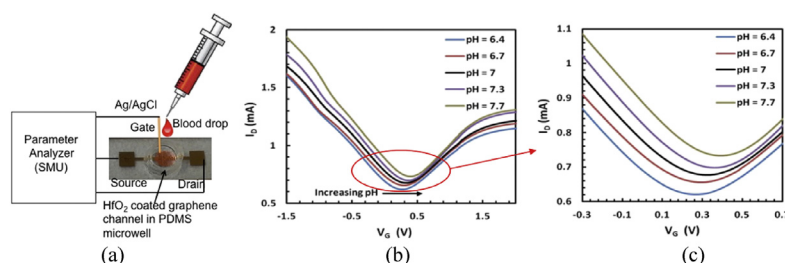
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ABSTRACT

In this work, pH sensing directly in biological media using three dimensional liquid gated graphene transistors is presented. The sensor is made of suspended network of graphene coated all around with thin layer of hafnium oxide (HfO_2), showing high sensitivity and sensing beyond the Debye-screening limit. The performance of the pH sensor is validated by measuring the pH of isotonic buffered, Dulbecco's phosphate buffered saline (DPBS) solution, and of blood serum derived from Sprague-Dawley rat. The pH sensor shows high sensitivity of 71 ± 7 mV/pH even in high ionic strength media with molarities as high as 289 ± 1 mM. High sensitivity of this device is owing to suspension of three dimensional graphene in electrolyte which provides all around liquid gating of graphene, leading to higher electrostatic coupling efficiency of electrolyte to the channel and higher gating control of transistor channel by ions in the electrolyte. Coating graphene with hafnium oxide film (HfO_2) provides binding sites for hydrogen ions, which results in higher sensitivity and sensing beyond the Debye-screening limit. The 3D graphene transistor offers the possibility of real-time pH measurement in biological media without the need for desaltation or sample preparation.

1. Introduction

Graphene has attracted a lot of attention in recent years for various electronic [1,2], sensing and bioelectronics [3–7] applications due to its high carrier mobility, high carrier concentration, biocompatibility, atomic thickness, electrochemical stability and mechanical reliability [8]. Many different biomolecules have been sensed using liquid-gated graphene devices where a solid-state dielectric is replaced by electrolytic double layer capacitance formed at the liquid-graphene interface [9,10]. Such configuration enables direct sensing in the liquid environment. Due to atomic thickness of graphene, its carrier density is very sensitive to the charge species in environment which enables charge-based detection of charged molecules and ions [10–12]. Using liquid

gated graphene FETs for pH sensing, has been reported in literature, however reported pH sensing performance has not been consistent and sensitivities vary widely from 17 to 99 mV/pH [10,13–16]. Recently, it has been shown that a perfect defect-free graphene transistor is in fact not sensitive to the ions in the environment and the pH sensing may be mediated by the existence of defects and dangling bonds on the graphene surface and edges, and leakage current through bare source and drain gold contacts [16].

Another challenge in charge-detection based sensing of pH, especially for biological applications is the limited dynamic range due to charge screening in high ionic strength biological medium. Presence of electrical double layer at graphene/electrolyte interface results in exponential drop-off in the potential, away from the graphene/electrolyte interface. This effect is captured by the characteristic length known as Debye length beyond which the electrostatic effect of ions on the graphene channel is minimal. Debye length is defined as [10]

$$\lambda_D = \sqrt{\frac{\varepsilon kT}{e^2 \sum_i Z_i^2 n_{i0}}} \qquad (1)$$

where ε is permittivity, K is the Boltzmann's constant, T is temperature, e is electron charge and Z_i is charge of the species i and n_{i0} is the concentration (number per volume) of the species i under equilibrium neutrality. At a constant temperature, Debye length just depends on the permittivity and ionic strength of the electrolyte. As an example, in a 100 mM aqueous electrolyte at room temperature, the Debye length is only about 1.3 nm, beyond which the charge carriers in the bulk will not have effect on the channel potential. In most biological medium, ionic concentration is higher than 100 mM. The osmolality of extracellular fluids and human blood serum is between 277 and 305 mOsmol/Kg, which correspond to 270–297.4 mM [17],; and Debye length in such high concentration medium will be even smaller. Therefore to be able to perform charge-detection based sensing of charged molecules and ions in biological samples, such as blood serum, urine and extracellular fluids, one needs to perform desaltation of the sample to reduce the overall ionic strength [18]. Sensing pH using graphene has not been reported in medium with concentration more than 100 mM due to such charge screening effect [13–16]. This limits the practical use of current graphene based sensors in real time monitoring of pH and other ions directly in the blood and biological fluids, which can be extremely useful especially in emergency medical care. For example, it is known that if arterial blood pH falls below 7.37 (normal range is 7.37–7.42), acidosis occurs [19]. Severe acidosis can lead to shock and death [20]. Therefore real time monitoring of pH of blood serum can be very valuable.

It has been shown that by adding oxide on graphene, the OH groups at the surface of oxide in contact with electrolyte can be protonated or deprotonated based on the pH of the solution and oxide surface composition [21–24]. In this case, the sensitivity of the device is not dependent on the electrolyte concentration [25]. Sensing pH using graphene-based liquid-gated field effect transistor (FET) with aluminum oxide dielectric acting as an ion sensitive layer has been reported [16]. It is shown that by growing less than 2 nm of Al_2O_3 using atomic layer deposition (ALD) at low temperature, the sensitivity of the sensor increases from 6 mV/pH to 17 ± 2 mV/pH[16]. In another work, the sensitivity of 40–50 mV/pH was achieved by adding high quality of aluminum oxide on the graphene [22]. The low sensitivity of earlier work is attributed to the poor quality of the oxide grown on graphene, due to low temperature growth process and low thickness of oxide (less than 2 nm). The sensitivity of such devices also depends on the type of oxide used as a sensing surface. It has been shown that using

hafnium oxide, HfO_2, provides higher pH sensitivity of FET up to 59 mV/pH[26].

The pH sensitivity of conventional FETs and ISFETs is theoretically obtained using Nernst equation. Based on this equation the maximum sensitivity in such devices to pH is limited to 59 mV/pH, which comes from the relation between changes of electrostatic potential at the insulator-electrolyte interface, φ_0, with change of bulk electrolyte pH, pH_B, given by Ref. [25]

$$\frac{\partial \varphi_0}{\partial pH_B} = -2.3 \frac{kT}{e} \alpha \qquad (2)$$

$$\alpha = \frac{1}{\left(\frac{2.3kTC_{dif}}{e^2 \beta_{int}}\right) + 1} \qquad (3)$$

where α is dimensionless sensitivity parameter, C_{dif} is differential capacitance, β_{int} is intrinsic buffer capacity, k is Boltzmann constant, T is temperature, and e is electron charge. The sensitivity parameter is the function of differential capacitance and buffer capacity, which depends on the density of sensing sites on the surface and the ions in the sensing liquid [25]. As mentioned earlier, the maximum value of pH sensitivity given by equation (2) is 59 mV/pH at room temperature, known as Nernst limit. But one should notice that to derive Nernst equation, the oxide/electrolyte interface is modeled using either Hg/electrolyte or AgI/electrolyte interface so this equation is not valid at the oxide/electrolyte surface where variation of charge density with electrostatic potential, φ_0, is very different than Hg/electrolyte and AgI/electrolyte interfaces and in most of the oxides the surface charge density and differential capacities are higher than those in Hg and AgI [25–28]. It has been shown that sensitivity of the field effect transistors can be tuned by using different gate oxide materials and different configuration of transistor [22,23,29]. The pH sensitivity reported in dual gated FETs is considerably higher than Nernst limit [30,31]. The second gate in dual gated FETs enables compensation of the change in current induced by the first gate in response to pH which results in an effective amplification of the sensitivity. The super sensitivity of porous gate ISFET has also been reported where the effect was attributed to the 3D structure of the gate, results in the effective increase in the adsorption surface area and increased buffer capacity [32].

In this work, a three-dimensional suspended graphene is used as the channel of a liquid gated transistor. Graphene is coated with 20 nm hafnium oxide using atomic layer deposition (ALD) which acts as a pH sensing surface. The three-dimensional nature of this oxide-coated graphene foam results in a considerably larger sensing surface area. Moreover, the suspended structure of the liquid gated FET enables ions to accumulate all around, on exposed surfaces, resulting in significant improvement in liquid gate/channel coupling efficiency [33]. These effects have resulted in the proposed graphene transistor device to demonstrate a pH sensitivity of 71 ± 7 mV/pH, with the advantages of biocompatibility, potential flexibility and sensitivity in biological media with high ionic concentration.

2. Methods

The fabrication process flow of pH sensor is shown in Fig. 1. Process begins with placing CVD grown graphene (Graphene Supermarket Inc. USA) in ferric chloride solution ($FeCl_3$, 0.06 M) to etch away copper and then rinsing it with sufficient amount of deionized water (DI water) to remove the residue left over from the etching process. Titanium and gold were deposited through