Electrolyte-Gated FET-based Sensing of Immobilized Amphoteric Molecules Including the Variability in Affinity of the Reactive Sites

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***Abstract*— In this work, we developed a unique computational approach that allowed us to detect immobilized amphoteric molecules on the surface of an electrolyte-gated FET-based sensor. Our simulation methodology is based on a combination of the Site-Binding and Gouy-Chapman-Stern models which are solved self-consistently. Our analytical model allows us to describe the surface charge density due to the protonation and deprotonation of the reactive sites of amphoteric molecules. Moreover, we have analyzed the effect of variability in the affinity constant of reactive sites. We also studied the effect of random dopant fluctuations in nanowire FET using in-house simulator NESS to account for the reliability issues in FET-based sensor technology.**

Keywords*— *Amphoteric Molecules, Site-Binding Model, Gouy-Chapman-Stern Model, Fingerprints, Dissociation Constant Variation, Nanowire FET, Random-Dopant Fluctuations, Scattering

I. INTRODUCTION

Amphoteric molecules are found in a variety of biological and chemical systems, including amino acids, and proteins [1]. Amphoteric molecules also have potential applications in the development of sensors and biosensors [2]. However, the affinity of amphoteric molecules can vary greatly, leading to different sensitivities and selectivities of detection d[3]. One important factor that affects the variability in the affinity of amphoteric molecules' reactive sites is the local environment of the molecules, such as pH, temperature, and solvent composition [4]. By gaining a deeper understanding of the factors that affect the affinity of reactive sites, we can develop improved sensing platforms that have a wide range of applications sensing.

Nanowire field-effect transistors (FETs) have emerged as promising transducers for sensing applications [5], [6]. Nanowire FETs' high surface-to-volume ratio and good electrostatic control make this device an ideal architecture for sensitive and selective sensing. However, factors like random dopant fluctuations (RDF) and electron-phonon scattering can have an impact on the sensing capability of nanowire FETs [7], [8]. Variations in dopant concentration can occur within the nanowire channel throughout the fabrication process [9]. These variations cause device-to-device variability, compromising the sensor's sensitivity and reproducibility of the measured device characteristics. To address this issue, improved fabrication techniques such as controlled doping and dopant segregation are being investigated in order to achieve greater control over dopant distribution inside the nanowire channel [10]. The effect of random dopant fluctuations (RDF) on threshold voltage variations in nanowire FETs is well-known [7], [8]. Varying threshold voltages might cause inconsistencies in carrier transport properties, making it difficult to achieve reliable and accurate sensing data. To account for device-to-device variability and increase the dependability of nanowire FET-based sensors, calibration algorithms and statistical analysis approaches are being developed [11].

Scattering effects also have an impact on the sensing performance of nanowire FETs as well [12]–[14]. Scattering occurs as a result of imperfections and structural flaws in the nanowire, resulting in variations in carrier paths. This changes the charge transport parameters of the nanowire, influencing device performance overall. Scattering can disrupt the sensor's output and affect the sensitivity and reaction time of the nanowire FET in the context of amphoteric chemical sensing [15]. Interactions between analyte molecules and the nanowire surface might cause scattering events, reducing sensor performance even furtherI. Surface passivation techniques are used to address this difficulty [16]. These methods involve functionalizing the nanowire surface with appropriate coatings or self-assembled monolayers to reduce scattering in the electrolyte and increase molecule capture and detection efficiency. Optimizing nanowire shape and crystal quality can also assist reduce scattering effects [17]. Improving the structural integrity of the nanowire and reducing surface roughness can improve sensing performance by reducing variations in carrier trajectories and improving charge transport within the device. Adsorption and desorption activities on the nanowire surface can introduce extra scattering events in the presence of amphoteric molecules. These scattering events can impair the sensitivity and selectivity of nanowire FET-based sensors by interfering with the sensor's capacity to detect and measure the concentration of the target moleculesI. Researchers are studying novel surface functionalization strategies to reduce the impact of scattering on sensor performance. It is feasible to improve the interaction between amphoteric molecules and the nanowire

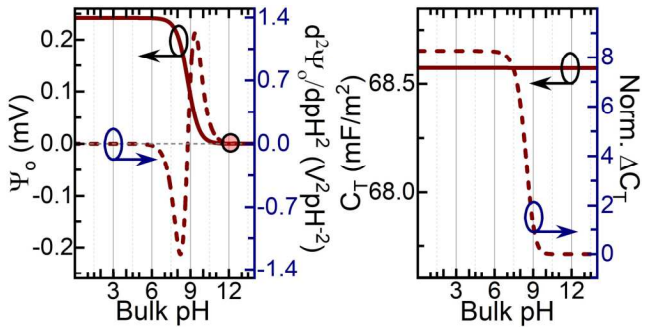

Figure 1. (a) Surface Potential (solid line) and 2nd Gradient of Surface Potential (×10^{-4} $d^2\Psi_o/dpH^2$) (dashed line) for Asparagine (N) (b) Total Capacitance (C_T) (solid line) and Normalized ΔC_T [×10^{-6} (C_T-min(C_T))/(min(C_T))] (dashed line) of EG-NWFET with respect to the pH for Carboxy-terminal immobilized N. [Note: Calculated for electrolyte concentration = 0.001M and density = 10^{12} mol.cm^{-2}]

surface while minimizing scattering effects by adjusting the surface features of nanowires, such as inserting certain functional groups or utilizing nanomaterial coatings.

II. Methodology

In this paper, we presented a unique methodology that combines the Site-Binding and Gouy-Chapman-Stern models to create an analytical model for examining amphoteric molecular fingerprints [18], [19]. Also, the obtained results from the analytical models are transferred to our in-house simulator called NESS in order to evaluate the impact of RDF and scattering on the ISFET output characteristics. Site-Binding model takes into account the adsorption of charged species on specific sites of the amphoteric molecule. This model enables us to assess the distribution of charged sites and their interactions with their surroundings. We also included the Gouy-Chapman-Stern model, which describes ion dispersion around the charged surface [20], [21]. By integrating these two models, A self-consistent solution was established that appropriately describes the behaviour of amphoteric molecules.

To demonstrate the efficacy of our methodology, two different amino acids are analyzed. These amino acids were chosen because of their unique characteristics and variances in surface charge density (σ_o). By evaluating the changes in surface charge density among different amino acids while eliminating the impact of the immobilized carboxylic terminal, we can acquire useful insights into the reactivity of amino acids and their interaction with their surroundings.

$$\sigma_{o1} = qN_S\left(\frac{cH_S}{cH_S + K_a}\right) \quad \textbf{(1)} \qquad \sigma_{o2} = qN_S\left(\frac{cH_S^2 + cH_S K_a}{cH_S^2 + cH_S K_a + K_a K_b}\right) \quad \textbf{(2)}$$

Several characteristic parameters such as surface charge density along with surface potential, total capacitance, etc. are calculated and compared for each amino acid using our analytical model. Based on the results gathered from the model we are able to predict the peculiarities in the behaviour of these amphoteric molecules, giving light on their distinct properties and prospective applications.

Here, for transducing the signal of the amphoteric molecules, we have considered an Electrolyte gated Nanowire-FET (EG-NWFET) which consists of highly n-type (10^{20}cm^{-3}) source, drain regions and p-type (10^{17}cm^{-3}) doped channel. The Silicon nanowire has a width and thickness of 5nm with a channel length of 10nm. The nanowire is covered with a thin insulating layer (Silicon Dioxide), known as the gate oxide, which separates it from the surrounding electrolyte solution. The EG-NWFET is immersed in an electrolyte solution, which can be adjusted to different pH levels with a reference electrode (gate electrode) to control the operating regime of the device. The pH of the electrolyte directly affects the concentration of hydrogen ions (H^+) in the solution.

When a charged amphoteric biomolecule, such as a protein or DNA, interacts with the electrolyte solution, it undergoes changes in its charge state depending on the pH. For example, at low pH (acidic conditions), the biomolecule may carry a net positive charge, while at high pH (basic conditions), it may carry a net negative charge. The charged biomolecules in the electrolyte solution can interact electrostatically with the nanowire channel and the gate oxide. These interactions induce a change in the surface charge density and the electric field within the nanowire channel. The changes in the electric field caused by the charged biomolecules alter the conductivity of the nanowire channel. As the biomolecules adsorb onto the surface of the nanowire, they effectively change the doping profile of the semiconductor material, leading to a change in the transistor's output current.

The EG-NWFET measures this change in the output current and converts it into an electrical signal that can be detected and analyzed. By monitoring the variation in the transistor's conductance, it is possible to determine the

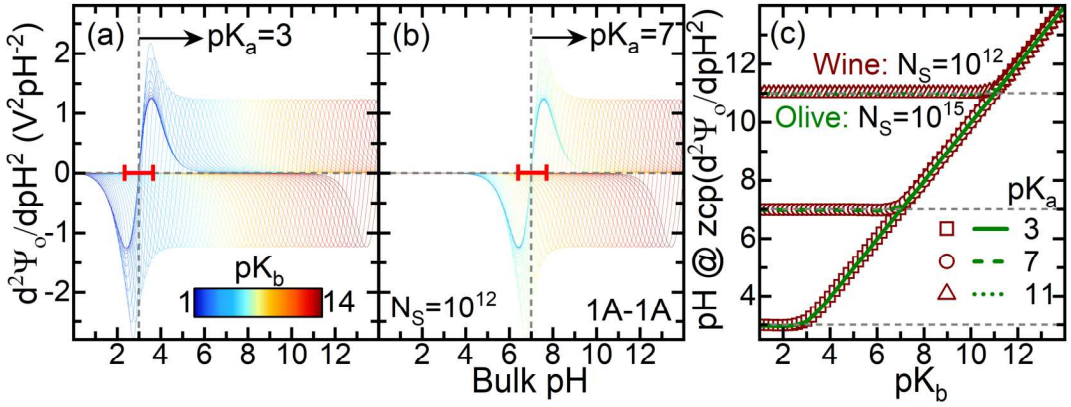

Figure 2. 2nd order Gradient of Surface Potential ($d^2\Psi_o/dpH^2$) of EG-NWFET with respect to the pH for Carboxy-terminal immobilized amino acid (example: Lysine) having two free amine reactive sites (one α-amine and one amine sidechain) for varying pK_b and fixed (a) pK_a=3 (b) pK_b=7 [Note: Calculated for electrolyte concentration = 0.001M] (c) Zero-crossover point (in terms of pH) of $d^2\Psi_o/dpH^2$ of EG-NWFET with respect to the varying pK_b and fixed pK_a (3, 7 and 11) of Carboxyl-terminal immobilized Amino acid on the sensing surface of EG-NWFET for different surface density (10^{12} and 10^{15} cm^{-2}).

presence and concentration of charged amphoteric biomolecules in the electrolyte solution. The pH sensitivity of EG-NWFETs allows them to discriminate between different pH levels and correlate them with the charge state of the biomolecules. By calibrating the device response with known pH values, the relationship between the charge of the biomolecules and the pH of the electrolyte can be established.

III. Results and Discussion

The solid line in Fig. 1(a) represents the surface potential (Ψ_o) as a function of pH which clarifies the presence of different reactive sites on the considered carboxylic-terminal (C-Imm.) immobilized amino acids (Asparagine, N) [5]. The density of the asparagine (or amino acid sample) on the EG-FET surface is 100 molecules/μm^2. Asparagine is a bifunctional amino acid with only a free α-amine reactive site which acquires a positive charge at very acidic pH values and loses the charge due to deprotonation at alkaline pH values after the dissociation constant of the α-amine reactive sites. The presence of α-amine reactive sites in C-Imm. N shows the Ψ_o variation from positive to zero value due to protonated state at acidic pH values and deprotonation with respect to higher bulk pH. Moreover, the 2nd order gradient of surface potential ($d^2\,\Psi_o/dpH^2$), presented with a dashed line in Fig.1 (a), shows the exact correlation of dissociation constants of the asparagine with the zero-crossover points. $d^2\,\Psi_o/dpH^2$ captures the significant transition of charged Asparagine (N) at the zero-crossover point. Even the minima and the maxima of $d^2\,\Psi_o/dpH^2$ can be considered as the fingerprints of the asparagine resulting from the slope of the surface potential. Fig. 1 (b) shows the change of the total capacitance (C_T) and of the capacitance (ΔC_T) as a function of pH. In general, C_T consists of differential capacitance along with the intrinsic capacitance due to the length and permittivity of the amphoteric molecule, for which the first minimum of the normalized ΔC_T from acidic to alkaline pH signifies approx. the same value of dissociation constant. The value of the capacitance is large enough (mF/m^2) to be detected experimentally but due to a small variation in differential capacitance with respect to pH, the variation in the C_T can be observed in normalized value.

Fig. 2 shows the variation of $d^2\,\Psi_o/dpH^2$ as a function of pH for different dissociation constant values of the amino acid sample with an amine sidechain. For the affinity constant variations, the pK_a is kept the same to values 3 (Fig. 2(a)), 7 (Fig. 2(a)), & 11 and pK_b is varied throughout the pH range which shows that as the pK values get close to each other within approx. pH=2units, the zero-crossover point of $d^2\,\Psi_o/dpH^2$ deviates from the values of affinity constants confirming the interactions of the reactive sites of amphoteric molecules. Fig. 2(c) shows that with the variation of pK_b, the zero-crossover point remains the same even for different densities of amino acid on the sensing surface. The obtained results will help in distinguishing amino acids whose pK values are distinct from amino acids with very similar pK values even with random perturbations in the sensing system.

To capture the perturbations in biomolecule charge density, we confirmed that the variability due to random dopant fluctuations and scattering is lower than the sensing signal obtained from the charged biomolecules. To analyze the results, we considered 3 samples of 5nm x 5nm nanowires with different random dopants (13 (sample-2), 15 (sample-3), 16 (sample-1) RDDs) operating at low (V_{DS}=0.05V) and high drain bias (V_{DS}=0.7V). The random dopants are distributed

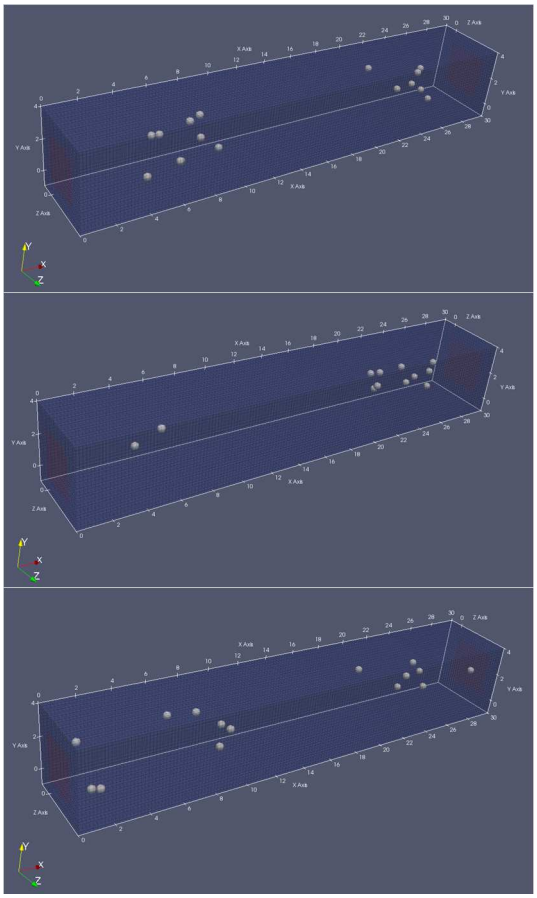

Figure 3. 5nm x 5nm Nanowire samples with gate length (L_G) of 20nm for different random dopant fluctuations in the source and drain regions (a) 16 RDDs (sample 1, top figure) (b) 13 RDDs (sample 2, middle figure) and (c) 15 RDDs (sample 3, bottom figure)

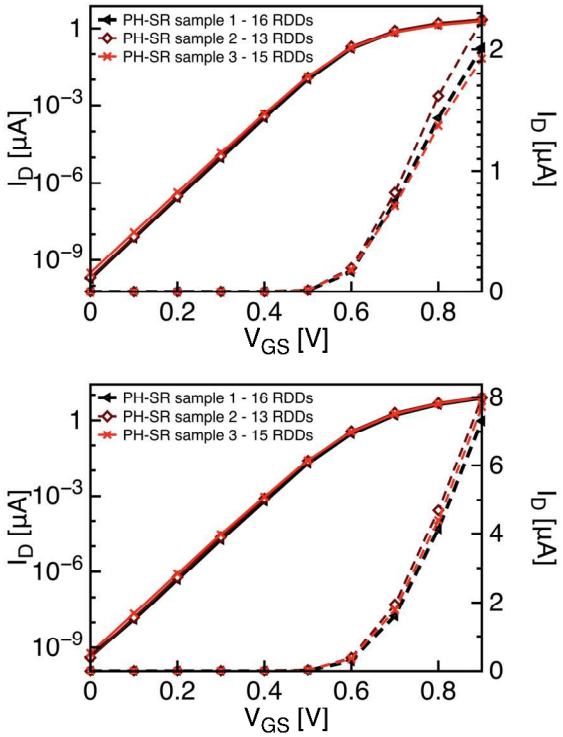

Figure 4. Drain current vs Gate voltage characteristics for the nanowire samples with different RDDs including the phonon scattering and surface roughness for (a) Low Drain Bias (0.05V) (b) High Drain Bias (0.7V)

randomly across the source and drain regions as shown in Fig. 3. The devices shown in Fig. 3 were simulated with phonon scattering and surface roughness using effective-mass based Non-Equilibrium Green's Function module from the in-house simulator NESS. Fig. 4 shows the different current-voltage characteristics (I_{DS}-V_{GS}) with included phonon scattering and surface roughness for different RDF samples in Nanowire FET. It is observed that there is negligible change in the OFF-current and subthreshold slope for all three samples operating at low and high drain bias. However, the ON-current (I_{ON}) is highest for sample-2 (RDFs-13) for both operating biases, but I_{ON} is higher for sample-1 (RDFs-16) than sample-3 (RDFs-15) at lower drain bias and vice-versa at higher drain bias due to bunched RDFs at the source-channel junction (sample-1) which increases the scattering at higher drain bias. Even at higher drain bias, the variation in I_{ON} is less than 1μA which is smaller than the variation obtained from the charged biomolecules across the pH range. The proposed work can help in designing a robust sensing methodology for amphoteric molecule sensing using Design Technology Co-Optimization of nanowire FET that can be used for designing sensitive and reliable sensors for commercial applications.

IV. Conclusion

This work presents a novel computational approach for detecting immobilized amphoteric molecules on the surface of an electrolyte-gated FET-based sensor. By combining the Site-Binding and Gouy-Chapman-Stern models, a self-consistent analytical model was developed to describe the behavior of amphoteric molecules. The methodology was validated using two different amino acids, and characteristic parameters such as surface charge density, surface potential, and capacitance were calculated and compared. Furthermore, the work focuses on the utilization of an Electrolyte Gated Nanowire-FET (EG-NWFET) as the transducing element for detecting amphoteric molecules. Moreover, the study addresses the reliability challenges in FET-based sensor technology by investigating the impact of random dopant fluctuations in nanowire FETs. The results demonstrate that the variability due to random dopant fluctuations and scattering is smaller than the sensing signal obtained from charged biomolecules. These findings contribute to the design of a reliable and efficient sensing system for amphoteric molecule detection, further facilitating the development of commercial applications in molecular sensing.

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