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Performance Analysis of Nanowire ISFET Biosensor Towards Bovine Serum Albumin and Liposome

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Abstract: Proteins are necessary to all living organisms for both structural and functional reasons. However, due to their breakdown, some proteins, including Bovine Serum Albumin (BSA) and Liposome, could cause detrimental effects on cells and tissues. Due to its high detection sensitivity, the potential for mass production, and affordable manufacture, the ion-sensitive field-effect transistor (ISFET) biosensor has become increasingly prominent in clinical research for the detection of biomolecules. BSA and Liposome are the target proteins, while collagen is the bioreceptor. ISFET biosensor with a structure of cylindrical nanowire was simulated and examined. The settling time and sensitivity of the biosensor were modeled using Nanohub BioSensorLab software. The cylindrical nanowire ISFET biosensor can be enhanced by reducing the buffer ion concentration, increasing the radius, and increasing the oxide thickness. Compared to liposomes, BSA provides a lower settling time. This is because the diffusion coefficient of liposomes is 3.6 times lower than BSA. Furthermore, settling time is reduced when the analyte concentration is increased. The results are compared with planar ISFET, considered one-dimensional (1D) architecture. The planar ISFET exhibited a quicker settling time than the cylindrical nanowire biosensor. Furthermore, as the amounts of protein and analyte increased, the settling time reduced. The cylindrical nanowire biosensor needs to be in radius of 100nm and 10nm of oxide thickness with 0.1M buffer concentration for it to achieved the highest sensitivity. These results could facilitate researchers to produce the desirable ISFET sensor for different types of proteins.

Keywords: Bovine serum albumin, cylindrical nanowire, ISFET Biosensor, Liposome, planar

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1. INTRODUCTION

All live cells require proteins for structural and functional reasons. However, consuming too many or misusing them might harm the human body; for instance, liver or kidney buildup of cholesterol and saturated fat [1]. In addition, the growth and development of the human body, especially in children and teens, depend on protein for the control of bodily tissues and organs, cell repair, and growth and development [2]. However, improper protein usage can be damaging to the human body. For instance, liposomes are utilized in the medical profession for medication delivery purposes because of their capacity to encapsulate hydrophobic or hydrophilic medicines. However, the creation of undesirable degradants resulting from liposome breakdown will have detrimental effects on cells or tissues.

Additionally, liposome instability will result in drug leakage [3]. BSA, a protein from cows, is frequently used as the benchmark for protein content in various experimental tests. However, BSA can potentially trigger allergic responses in people [4]. In order to mitigate the development of potentially harmful protein effects on the human body, biosensors can be employed.

A biosensor to detect DNA, proteins, enzymes, and cells can help diagnose a clinical illness. It is now possible to identify diseases and monitor the body's reaction to treatment because of advancements in biosensor technology [5]. Identifying and treating the infection is essential to stop the virus from infecting all bodily cells. For instance, detecting deadly diseases like coronary artery disease (CAD), one of the heart diseases that caused 8.8 million deaths in 2015 [6]. Therefore, a reliable and functional biosensor should be a technology worth developing.

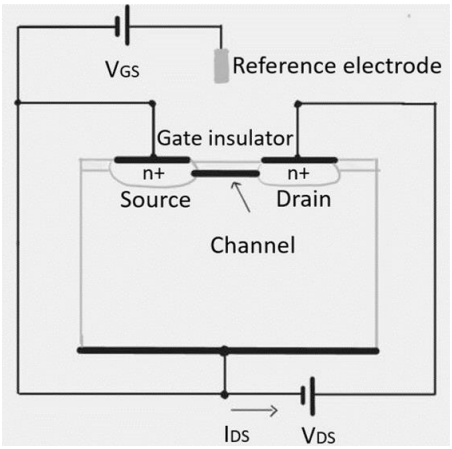
One common type of biosensor is the ion-sensitive field-effect transistor (ISFET). In biomedical applications, it is often used to monitor biological processes such as protein-protein interactions, DNA hybridization, glucose measurement, potential of hydrogen (pH) detection, and antigen-antibody binding [7]. ISFET comprises bioreceptors that can only detect and bind to the target molecules. Receptor molecules are found in enzymes, cells, DNA, and antibodies. The electrolyte functioned as a buffer solution with other molecules and electrically conducted target biomolecules. The bulk electrolyte potential is adjusted using a reference electrode. ISFET conductance modulates the binding and interactions between target and receptor molecules [8]. Target biomolecules are present, as indicated by the change in current. However, ISFET has shortcomings, including the

absence of excellent solid-state electrodes, parasitic sensitivity to light and temperature, and time-dependent instability of sensor characteristics. In addition, using fluorescent labeling and parallel optical detection methods was costly and time-consuming to enhance ISFET performance [9].

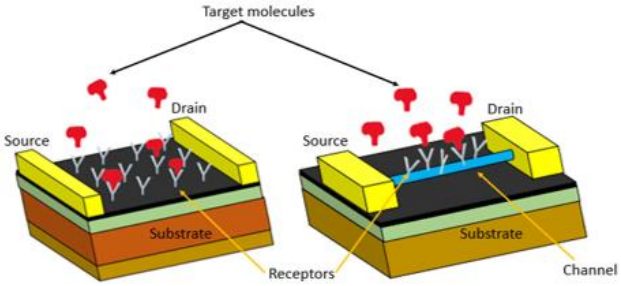
Therefore, further improving the ISFET biosensor by increasing the surface-to-volume ratio could be a superior strategy for rapidly detecting biomolecules with low concentration. Additionally, Si-NW biosensors have already been demonstrated for ultrasensitive detection of DNA [10], proteins [11], and pH levels [12]. However, the influence of factors like buffer ion concentration, nanowire radius and ISFET oxide thickness is generally overlooked in most sensor designs. In this simulation study, we unveil the influence of parameters like the dimension of the Si-NW (radius), surrounding environment (the ions concentration in the buffer solution) and the oxide thickness for the performance optimization in terms of settling time and sensitivity of the Si-NW biosensor towards BSA and liposome proteins. In addition, the results from the Si-NW biosensor are compared with planar ISFET to analyze the degree of performance improvement. A simulation tool named BioSensorLab is used for the numerical simulation [13].

2. BIOSENSOR SIMULATION

ISFET has a similar basic structure and working principles as metal oxide semiconductor field-effect transistor (MOSFET). In ISFET, the metal gate is replaced by an ion-selective membrane, electrolyte and a reference electrode as shown in Fig. 1(a). The surface of the sensor is functionalized with specific receptors for the target protein molecules called the analytes. The diffusion of analyte particles towards a planar device (ISFET) is 1D, and towards a cylindrical nanowire surface is 2D. The Diffusion-Capture (D-C) model assumes that the molecule transport is diffusion limited and the target-receptor conjugation is treated as a first-order chemical reaction [14].



(a)



(b) (c)

Figure 1. (a) General ISFET's structure (b) Planar ISFET design (c) Cylindrical nanowire design

Table 1. Parameters settings for the cylindrical nanowire biosensor simulation

Parameters	**Value**
Radius (nm)	5
	30
	100
Oxide thickness (nm)	1
	5
	10
Buffer ion concentration (M)	0.1
	0.2
	0.3

Sensitivity is the relative change in sensor characteristics upon attachment of target molecules on the sensor surface [15]. For the sensitivity analysis of cylindrical nanowire biosensor, the radius, oxide thickness, and buffer ion concentration were varied as shown in Table 1. The impact of each of these parameters on biosensor sensitivity is analyzed in terms of the device conductance modulation. When one of the parameters in Table 1 is varied, other parameters were fixed to the default values. The default values for radius, oxide thickness and buffer ion concentration of cylindrical nanowire are 30 nm, 1nm, and 1×10^{-5}M, respectively.

Table 2. Parameters for settling time analysis

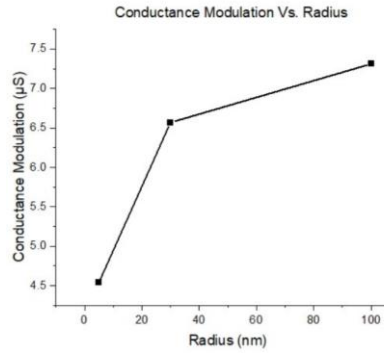
Measurement	**No**	**Parameters**	**Value**
Settling Time vs Analyte Concentration	1	The lower value of analyte concentration (molar unit)	0.00533
	2	The upper value of analyte	0.016

		concentration (molar unit)	
Time-Dependent Capture of Target Molecule	1	Analyte Concentration (molar unit)	0.001
Diffusion Coefficient of Proteins in Collagen (cm^2/s)	1	Liposome	25×10^{-8}
	2	Bovine Serum Albumin (BSA)	90×10^{-8}

The diffusion coefficients in collagen of both Liposome and BSA is different and tabulated in Table 2 [16]. The lower and upper values of analyte concentration were set to obtain the settling time against analyte concentration graph. Meanwhile, the analyte concentration was fixed at 0.001 M to obtain the transient capture of target molecules-analytical simulation graph.

3. RESULTS AND DISCUSSION

3.1 Analysis of Sensitivity



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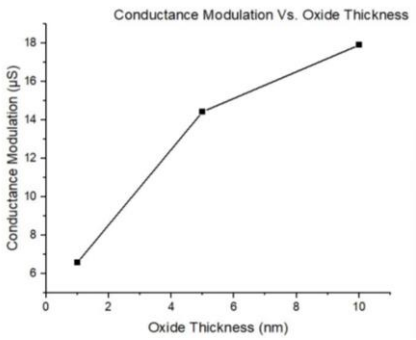

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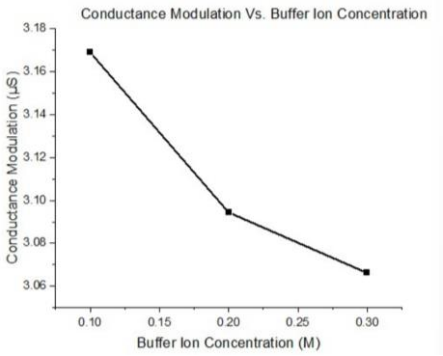


(c)

Figure 2. Conduction modulation against (a) radius (b) oxide thickness (c) buffer ion concentration of cylindrical nanowire biosensor

The diffusion coefficient of protein, device length, and doping are found to have no impact on the sensitivity of the cylindrical nanowire biosensor.

From Fig. 2, the conductance modulation increased when the nanowire's radius and oxide thickness increased. However, the conductance modulation reduced when the buffer ion concentration is increased. Higher modulation in biosensors indicate higher sensitivity and thus better performance. Hence, a greater conductance modulation value is desired. From the plots, the highest conductance modulation was achieved at 18 μS when oxide thickness is at 10 nm. Table 3 shows the optimized parameters for the nanowire radius, oxide thickness and buffer ion concentrations, respectively.

Table 3. Parameter values to produce the best ISFET biosensor

Parameters	**Value**
Radius (nm)	100
Oxide thickness (nm)	10
Buffer ion concentration (M)	0.1

Parameter values from Table 3 can be applied to achieve a high sensitivity cylindrical nanowire biosensor. Fig. 3 shows the logarithmic dependency of sensitivity on analyte concentration for the optimized parameters. The conductance modulation which translates to the sensitivity of the cylindrical nanowire biosensor improves as target molecule density increases.

From the result shown in Fig. 3 one can easily predict the range of analyte concentration over which log dependency is observed. A modulation of 3.203×10^{-6}S at analyte concentration of 1×10^{-12}M of buffer ion concentration is observed from this numerical simulation.

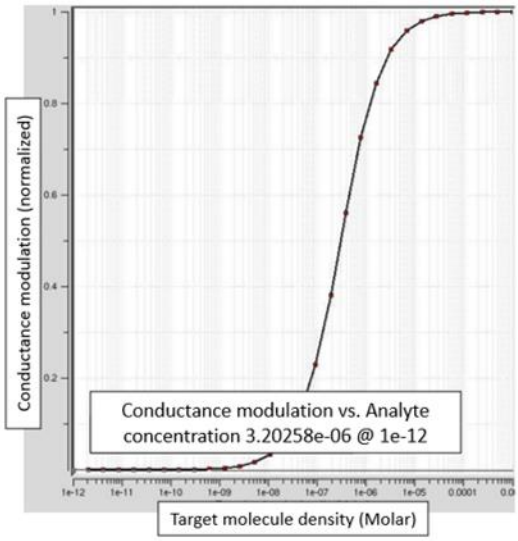


Figure 3. The sensitivity graph for the cylindrical nanowire

For a cylindrical nanowire biosensor, increasing the radius and oxide thickness while lowering the buffer ion concentration is desirable to achieve high sensitivity characteristics. The sensitivity of the cylindrical nanowire biosensor is measured by the ratio of threshold voltage to charges on the sensor surface [9].

An increased in nanowire radius indicates an increase in surface area. Hence, more target molecules can interact with the ion-sensitive membrane at a time. Furthermore, when the oxide thickness is decreased results in an increase in oxide capacitance which cause a decrease in modulation. Therefore, the optimum value of oxide thickness for nanowire is 10nm. Subsequently, the sensitivity can be improved. This value is similar to the value obtain from a paper written by Jadhav, M. et.al [17].

Besides, when buffer ion concentration increased, the concentration of both target molecules. and parasitic molecules are increased. The sensor needs a longer time to identify and capture the desired target molecules. Hence, a lower buffer ion concentration is preferable for high sensitivity detection.

3.2 Settling Time

Figure 4 shows the settling time against the analyte concentration for both liposome and BSA protein. Settling time is the amount of time a sensor needs to achieve a steady signal change [15]. It is found that the settling time decreased when the analyte concentration increased. Furthermore, from Figure 4, the settling time of liposomes is higher than BSA. This is because the diffusion coefficient of liposome is 3.6 times lower than BSA. Diffusion coefficient indicates the rate of diffusion of the protein molecules. Hence, as the diffusion coefficient rises, more target protein molecules diffuse into the sensor membrane per second. Therefore, BSA has shorter settling time than Liposome. Furthermore, settling time reduced when the analyte concentration increased. As the analyte concentration increases, more target molecules presence in the solution and interact with the ion-sensitive membrane of the biosensor. As a result, the settling time is shortened.

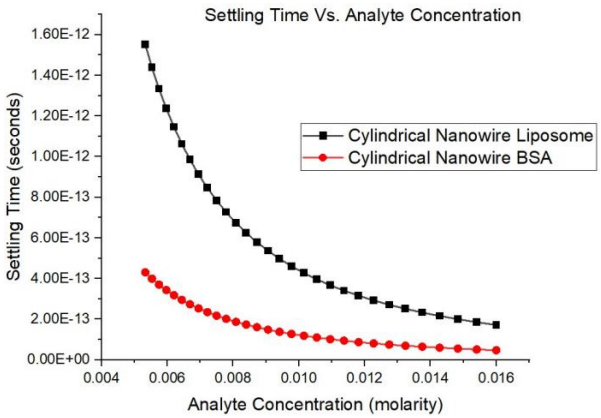
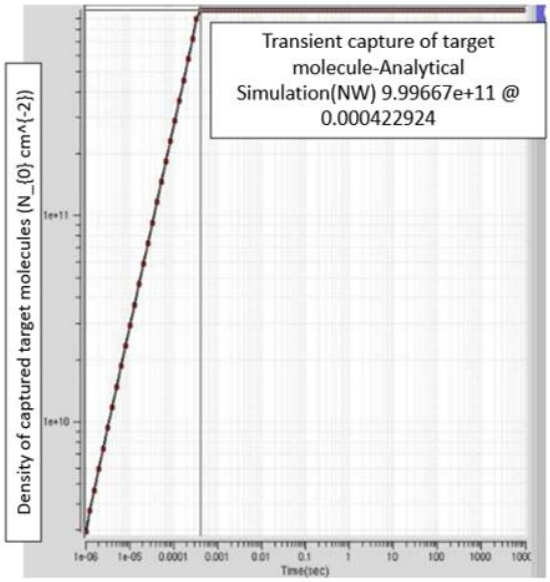
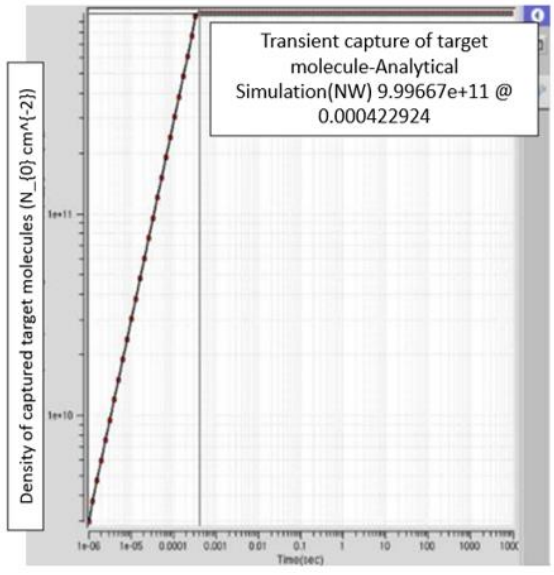


Figure 4. Settling time against Analyte Concentration of a cylindrical nanowire for liposome and BSA protein



(a)



(b)

Figure 5. Transient capture of target molecules-analytical

simulation (ISFET) of cylindrical nanowire biosensor for (a) liposome (b) BSA

Figure 5 shows the transient capture of target molecules-analytical simulation of cylindrical nanowire biosensor ISFET. Both Liposome and BSA took 0.423 ms to obtain maximum density of captured molecules of $9.997 \times 10^{11} cm^{-2}$. Both proteins consumed the same amount of time to capture all the target molecules in cylindrical nanowire biosensor. This shows that the surface of the nanowire is saturated within the same time regardless of the type of protein it is detecting.

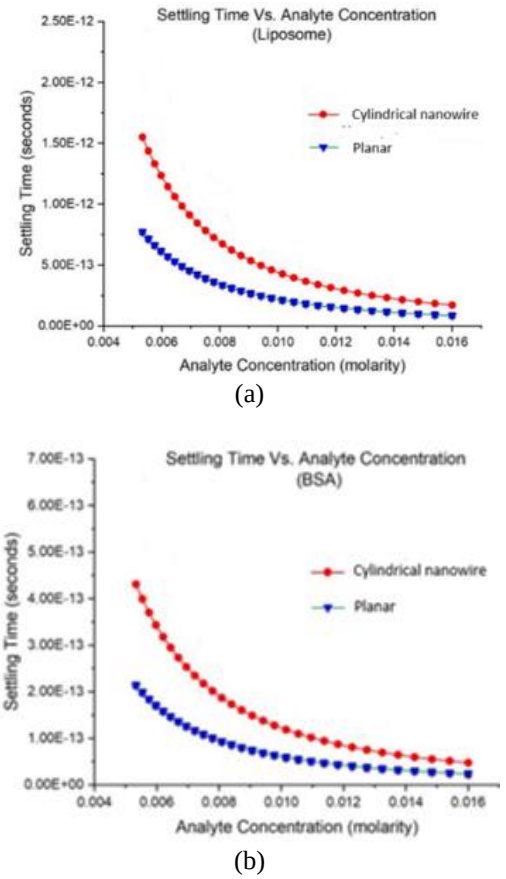


Figure 6. Settling Time against Analyte Concentration in Planar and Cylindrical Nanowire for (a) liposome (b) BSA

In order to analyze further the impact of cylindrical nanowire ISFET sensor, a comparison with planar ISFET was conducted. The planar ISFET has a dimension of length = 30 nm, width = 30 nm and oxide thickness of 1nm with electrolyte concentration of 0.1M. Figure 6 shows the settling time against analyte concentration plots for both planar and cylindrical nanowire. The planar ISFET biosensor consumed less amount of time to detect protein molecule, followed by cylindrical nanowire biosensor. The different structure of biosensors significantly affects the settling time. Planar ISFET biosensor has a one-dimensional (1D) structure while cylindrical nanowire biosensor has a two-dimensional (2D) structure in the context of biosensing. As the structure's dimension grows, target biomolecules will interact with the biosensor in a more multi-directional manner. This will cause instability and would need longer time to produce a stable output signal change in the biosensor.

4. CONCLUSION

The sensitivity analysis was carried out uniquely as the evaluation graphs are different for each biosensor. Increasing the radius and oxide thickness and lowering the buffer ion concentration will enhance the performance of the cylindrical nanowire biosensors. The findings demonstrate that the protein's diffusion coefficient has no bearing on the biosensor's sensitivity. The settling time decreases when diffusion coefficients of protein are increased. Lower settling time is desired because it leads to faster response of the biosensor. The settling time also exponentially decreases with the analyte concentrations and also affected by the ISFET structure. It increases as the structure dimension grows. Therefore, planar ISFET had a shorter settling time than cylindrical nanowire biosensors because of its one-dimensional (1D) forms. These results could facilitate researchers to produce the desirable ISFET sensor for different types of proteins.

ACKNOWLEDGMENT

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