Mathematical Modelling and Analysis of Nanobio-Sensors for Automated Disease Detection and Drug Delivery System

B.N. Shobha, N.J.R. Muniraj

Abstract*— Nano-medicine is the medical use of molecular-sized particles to deliver drugs, heat, light or other substances to specific cells in the human body. Engineering particles to be used in this way allows detection and/or treatment of diseases or injuries within the targeted cells, thereby minimizing the damage to healthy cells in the body. Nanomedicine, it is the innovative combination of nanotechnology and medicine providing us with the most modern cutting edge tool in the field of medicine. It has triggered a whirlwind of medical revolution across the globe. In this paper, the mathematical models required to describe the functionality of nanodevices have been reviewed and mathematical model sensor equivalent circuits have been developed. An experimental setup is developed to analyze the characteristics of IS Field Effect Transistor (ISFET), nanowire and nanosphere devices. The impact of geometrical properties on device performance is estimated based on the experimental setup. Settling time and surface analyte concentration graphs obtained using the experimental setup is used in designing a nanobio-sensor for disease detection. Based on the test results, a mathematical model has been developed in Matlab to model nanodevices. Three different iterations of sensor models are carried out based on the results obtained; curve fitting techniques are adopted to generalize the developed sensor model using Savitzky-Golay Filter (SG Filter). The sensors modeled can be used for automated drug detection and delivery unit

Index Terms*— Nanobio-sensor, drug delivery, cancer detection, diffusion-capture

I. INTRODUCTION

Demands for sophisticated and reliable medical products that can support the timely needs of human being are ever increasing. Miniaturization in device sizes has further led to new generation medications that are automated and are reliable. Quantum dots, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, gold nanowires and many other materials have been developed over the years. Automated drug delivery also called as implantable drug delivery device or biochip have demonstrated their potential in vast areas of medical applications as they provide reliable, controllable and accurate delivery of prescribed drugs without medical intervention.

Valcke and Chizek [1] developed a Closed Loop Drug Delivery (CLDD) system for use with coronary artery disease. In this system feedback control algorithms is used to deliver and monitor the drugs to the patient. The control unit consists of a Proportional-Differential (PD) controller. Woodruff [2] has developed a simulator that can be used to model closed loop cardiovascular drug delivery unit considering multiple model factors. In this work, the developed model was validated against real time results and was published on web. Yu [3] developed a controller that can be used to monitor the cardiac output of a congestive heart failure patient and administer vasodilation and isotropic agents (Nitroprusside and Dopamine). With the emergence of VLSI technology and MEMS attaining maturity, a variety of implantable devices have been designed and demonstrated for chronic diseases, Prescott [4] mentioned that MEMS based devices has advantages of active control and practically possible to perform the drug delivery process. Very recently MEMS technology based drug delivery devices were developed to actively control disease (in vivo) in multiple clinical applications. In order to build such systems, micro-pumps mentioned in, Nguyen [5] electro-chemical or electrical degradation of membranes for multiple-reservoir drug delivery chips as described by Santini [6] and Grayson [7] were used. The availability of MEMS technology enabled miniaturization of micro-pumps, storage and delivery of drugs from single and multiple reservoirs making detection of disease possible with use of sensors. Maloney [8] and Grayson [9], have investigated and developed automated drug delivery systems for use in chronic and non-chronic diseases such as cancer, diabetes and osteoporosis, but still there is a long way to go in making this device more acceptable and reliable. From the survey it is identified that, drug delivery requires the following, Sensors for disease detection, Decision making logic, Controller for drug actuation and monitoring, Drug storage and diffuser. In this work, focus is on modelling and simulation of biosensors for automated disease detection and drug diffusion.

Section II presents introduction to nanostructured devices and biosensors, section III presents discussion on design and analysis of nanobio sensors, section IV presents mathematical modelling of nanobio sensors and conclusion is presented in section V.

II. NANOSTRUCTURED DEVICES

Nanostructured devices, such as single-walled carbon nanotubes [10] (SWNTs), silicon nanowires [11] (Si NWs) or metal oxide nanowires [12] (e.g., In_2O_3 NWs), are used in biosensors. Devices having very high surface-to-volume ratios are highly sensitive, thus nanotubes and nanowires are used in biosensors for disease detection [13-15]. In this paper, metal oxide NWs (e.g., In_2O_3 and SnO_2), which are traditionally the key materials for sensing are used in detection of prostate cancer. PSA is an oncological marker

Revised Manuscript Received on October 2012.

B.N.Shobha, Dept. of ECE, Sapthagiri College of Engineering, Bangalore, India.

N.J.R. Muniraj, M.E., Ph.D, is currently Principal at Tejaa Shakthi Institute of Technology for Women, Karumathampatti, Coimbatore, India.

for the presence of prostate cancer, which is the most frequently diagnosed cancer among men in India (fourth major cancer among men) [16]. Despite its utmost importance, detection of PSA using nanowires has not been reported. In this paper two major contributions have been carried out. An array of nanowires sensors have been designed to detect PSA density, further the sensor array is designed with planar nanowires and spherical nanowires to increase the sensitivity of detection. Prostate cancer is diagnosed by identifying the presence a protein called the Prostate Specific Antigen (PSA) [17]. PSA will be present in blood of a patient if the PSA level in the blood increases certain levels; the patient is diagnosed with prostate cancer.

2.1 Biomarker:

A biomarker is an indicator of a biological state of disease. A biomarker can be a protein, DNA or RNA-based. Detection of PSA present in the blood is to functionalize the channel surface with anti-PSA antibody (PSA-AB), a specific biomarker for PSA protein. In_2O_3 NW devices were first submerged in a solution of 3-phosphonopropionic acid, resulting in binding of the phosphonic acid to the indium oxide surface with the COOH groups. The COOH groups on the nanowire surface are subsequently converted to a carboxylate succinimidyl ester via incubation in *N-N*'-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide and treated with a buffered saline solution of PSA-AB at 50 *u*M concentration and antibody gets anchored to the nanowire surface [18].

Modelling and analysis of biosensors:

Biosensors that are developed in this work are very generic and are not defined for any particular disease. For a biosensor the most important parameters that are required for detecting diseases are:

- Size of micro channel
- Flow rate of fluid in the channel
- Concentration of antigens in fluid
- Number of antigens through channel per hour
- Total area occupied by Antibodies
- Area of one Si NW occupied by Antibodies
- Target receptor conjugation
- Type of antigen
- Ratio between total occupied area and Si NW
- Mean time between one antigen reacts with one antibody on the Si NW

Based on the above design requirements, three different nanowire sensors are chosen and their performance characteristics are analyzed. Based on the results obtained, one of them is chosen for cancer detection.

III. DESIGN AND ANALYSIS OF NANOWIRE SENSOR

Nanowire sensor required for prostate cancer detection is designed and modeled using simulators that are available for research activities. Naohub.org provides different classes of simulators for sensor analysis. A biosensor lab is one of the simulators for sensor characterization. In this work, we have used the biosensor lab for simulation and characterization of nanowire. Table 1 shows the various set of parameters that have been selected for simulation of nanowire sensor.

Table 1: Nanowire sensor analysis

Parameters - Simulation Options			
Transport Model	Uncoupled mode space	**Drain**	
Average Potential for Schroedinger Solution	yes	Diameter of Silicon nanowire	4nm
Number of Valleys	2	Oxide thickness	1nm
Number of eigenvalues	3	Gate length	8nm
Mesh fineness factor	4	Source and drain extension length	10nm
Orientation of nanowire in transport direction	100	Source and drain doping (n) in	2e+20/cm^3
Geometry and doping		Channel doping (p) in	0/cm^3
Diameter of Silicon nanowire	4nm	**Material**	
Oxide thickness	1nm	Gate work function	4.05eV
Gate length	8nm	Silicon Dielectric Constant	11.9
Source and drain extension length	10nm	Oxide Dielectric Constant	3.9
Source and drain doping (n) in	2e+20/cm^3	Silicon work function	4.05eV
Channel doping (p) in	0/cm^3	Oxide work function	3.1eV
Gate		Longitudinal Effective mass in silicon (Mo)	0.98
Diameter of Silicon nanowire	4nm	Transverse Effective mass in silicon (Mo)	0.19
Oxide thickness	1nm	Effective mass in dielectric (Mo)	0.4
Gate length	8nm		
Source and drain extension length	10nm		
Source and drain doping (n) in	2e+20/cm^3		
Channel doping (p) in	10/cm^3		

3.1 Characterization of Nanowire:

The unknown molecules (target) get captured by the receptors in the sensor as they diffuse along the surface of receptors only when the unknown molecule has a conjugate sequence compared to the receptor sequence. It is required to establish the relations ship between number of molecules detected, current, time involved in detection and concentration of molecules.

3.2 Diffusion-capture model:

There are two equations that explain the diffusion-capture activity in a nanobio sensor. The capture equation is given by equation 1

$$\frac{dN}{dt} = k_F (N_0 - N)\rho_s - k_R N \quad (1)$$

N is the number of conjugated molecule, No is the initial number of molecules (receptors, blue y shaped). The numbers of conjugated molecules are proportional to number of unconjugated molecules, this is determined by (N0-N), kF is reaction constant. There are possibilities of molecules that are bound to deconjugate due to chemical reaction, thus the second term kRN represents the number of deconjugated molecules (kR is reverse reaction constant). Deconjugation is very weak in nanobio sensors, thus the diffusion equation can be approximated to equation 2

$$\frac{dN}{dt} \approx k_F N_0 \rho_s \quad (2)$$

ρs is the surface concentration of the captured molecules. As the molecules present in the electrolyte diffuse across the receptors, the diffusion equation is given by equation 3

$$\frac{d\rho}{dt} = D\nabla^2 \rho \quad (3)$$

D is the diffusion coefficient; ρ is the concentration of molecules. This equation defines that the molecules have to diffuse around the sensor surface before they could be captured. It is required to find an analytical solution for the above two equations to understand the sensitivity of sensors. The diffusion-capture equation needs to be solved to understand the behaviour of the sensor. Figure 2 shows experimental setup for prostate cancer detection based on nanowire sensors. Biosensor lab provides the test chamber that is used to analyze the performances of various sensors for prostate cancer detection.

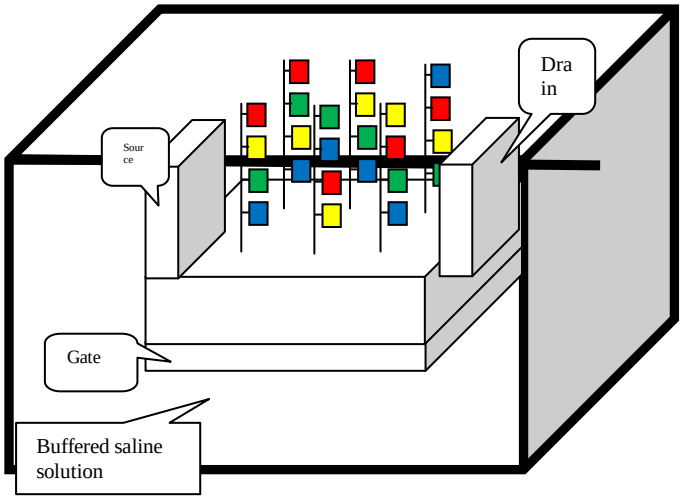
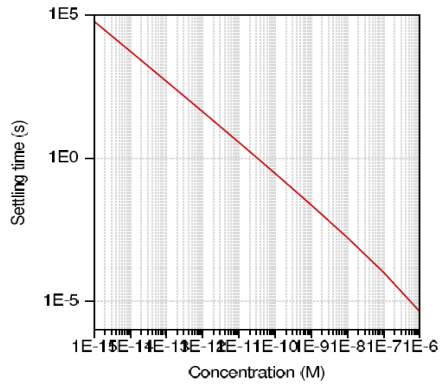
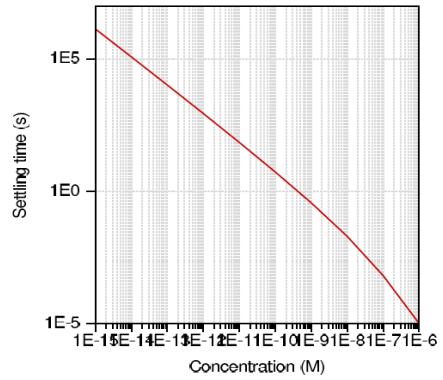


Figure 1: Experimental setup for target detection (PSA) using nanowire sensor

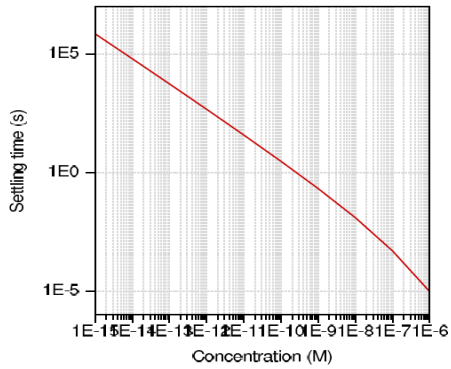
Based on the experimental model for a nanobiosensor, it is required to analyze the following properties of sensor: Settling time vs. Concentration, Surface analyte concentration with time, Conjugate receptor density with time. These three parameters help in identifying the characteristics of a nanosensor that are very critical for characterization. Figure 2- figure 4 presents the results of three different iterations carried out as per the parameters presented in table 1.



(a) Iteration 1



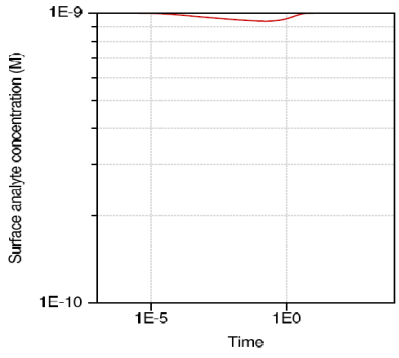
(b) Iteration 2



(c) Iteration 3

Figure 2: Performance limits

From the above results it is found that there is a linear variation between settling time and concentration of analyte. In iteration 1 the linearity is all along the x-axis, in iteration II and iteration III, as concentration increases, the time required to capture the target molecules reduces. Thus, from the above results, parameters in iteration III are chosen for nanowire sensor required for prostate cancer detection.



(a) Iteration 1

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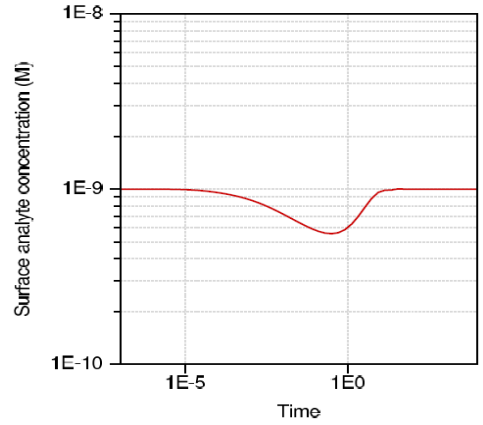
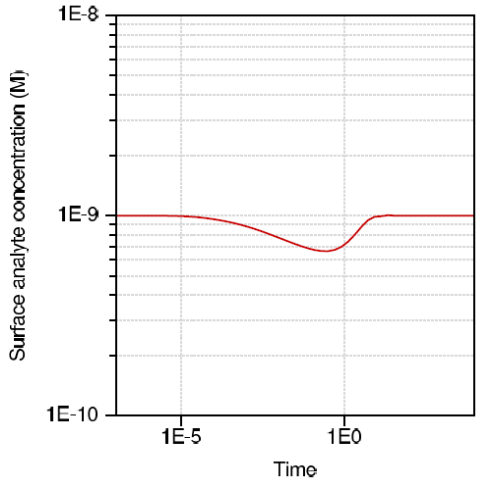


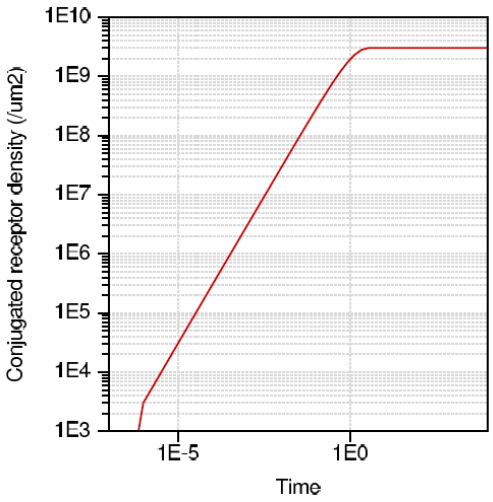
(b) Iteration 2



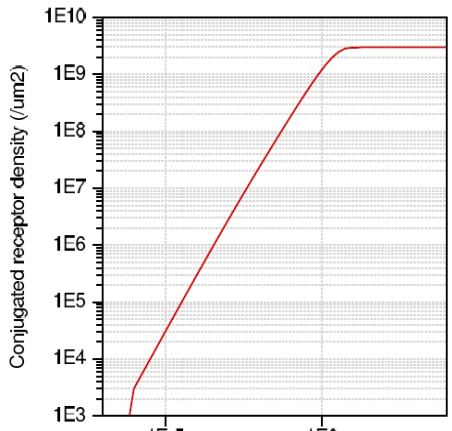
(c) Iteration 3

Figure 3: Surface analyte concentrations

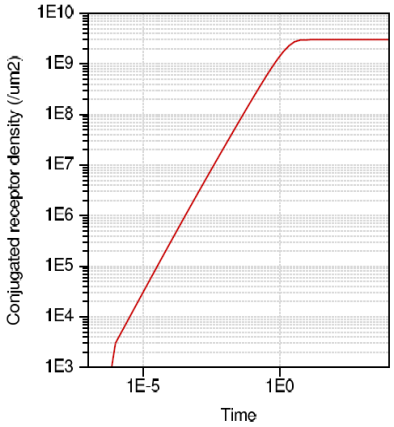
Surface analyte concentration varies with detection of target molecules, as shown in figure 3, the concentration of analyte at corresponding time indicates the presence of target molecules. Iteration II produces larger dip in analyte concentration, thus assisting detection of target molecules. Hence based on these results, parameters in iteration II are chosen for nanowire sensor design. From the test results shown in figure 4, transient response for all the three sensors are identical, the detection time is ideal between few microseconds to a second.



(a) Iteration 1



(b) Iteration 2



(c) Iteration 3

Figure 4: Transient response

Based on the analysis carried out the nanowire sensor with the following characteristics is chosen for prostate cancer detection as shown in Table 2.

Figure 5 shows the VI characteristics of nanowire sensor, from the results shown it is found that the sensor has current variations in few micro amps that aides in detecting the presence of prostate cancer, as the concentration of PSA increases the current in the sensor increases for a given analyte concentration.

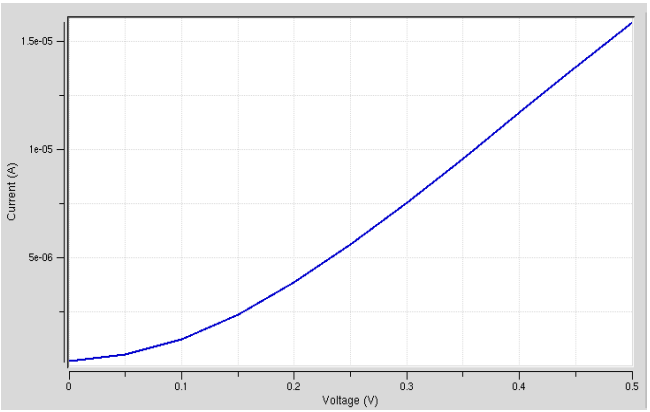


Figure 5: VI characteristics of nanowire sensor

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Table 2: Selected design parameters for nanowire

Parameters	Sensor design
Geometry and doping	
Diameter of Silicon nanowire	10nm
Oxide thickness	2nm
Gate length	10nm
Source and drain extension length	8nm
Source and drain doping (n) in	12e+20/cm^3
Gate	
Diameter of Silicon nanowire	6nm
Oxide thickness	2nm
Gate length	6nm
Source and drain extension length	8nm
Source and drain doping (n) in	6e+20/cm^3
Drain	
Diameter of Silicon nanowire	4nm
Oxide thickness	2nm
Gate length	6nm
Source and drain extension length	8nm
Source and drain doping (n) in	6e+20/cm^3
Material	
Gate work function	3eV
Silicon Dielectric Constant	14
Oxide Dielectric Constant	4.2
Silicon work function	3eV
Oxide work function	3eV
Longitudinal Effective mass in silicon (Mo)	0.8
Transverse Effective mass in silicon (Mo)	0.17
Effective mass in dielectric (Mo)	0.2

From the results obtained, it is concluded that the designed nanowire sensor that is used to detect PSA present in blood by use of biomarkers achieve good sensitivity within 100mseconds. Thus when the analyte solution consisting of target molecules are passed on to the nanowire sensor, it takes less than 100mseconds to capture the target molecules and correspondingly change the conductivity of the transistor. The current levels obtained due to change in conductivity are less than 1uA. Figure 6 shows the graphical display of three different iterations of the sensor model. From the graphs shows that the variation in sensor currents is nonlinear and also consists of noise.

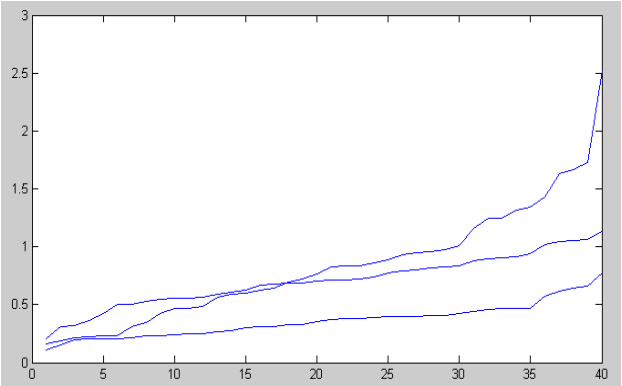

Figure 6: Concentration Vs. Sensor Currents for Three Iterations

IV. MATHEMATICAL MODELS FOR NANOWIRE SENSOR

From the results obtained using biosensor lab, a Matlab model is developed for silicon nanowire. The experimental setup developed using biosensors lab is used to identify the equivalent current values that flow in the drain of nanowire sensor with changes in analyte concentration. During the experimental setup, 135 different values of analyte concentration are set to identify the variations in drain current. The analyte concentration is varied from 0.1 to 0.5 mmol/L, corresponding drain currents are identified and recorded. The Matlab model is a look up table of these values obtained in the biosensor lab. Figure 7 shows the top level diagram of Matlab model for nanowire sensor.

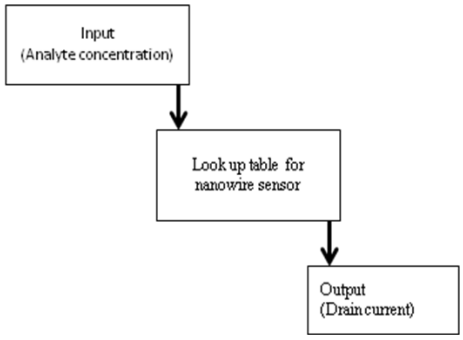

Figure 7: Matlab model developed using look up table

In order to generalize the sensor models for all possible input conditions, it is required to extend the sensor model for generic inputs. In this work, curve fitting techniques have been adopted to improve the performance characteristics of sensor models. Next section discusses the curve fitting techniques for sensor model development.

4.1 Curve fitting techniques

There are four different steps in curve fitting, they are 1) Data Transformation, 2) Smoothing and filtering 3) Curve Fitting and 4) Residual Analysis.

The response of nanowire sensor computed based on the model developed is used in detection of various diseases and is used in design of automated drug delivery unit. In order to validate the interpolated sensor model, a new iteration (iteration 4), is considered with change in input parameters as presented in figure 7. The sensor model parameters are varied and a new experiment is conducted to measure the variation in sensor current for different sets of molecular concentration. In figure 8, the graph (blue) is the variation in sensor currents for variation in molecular concentration. Graph (green) is the sensor current obtained based on curve fitting techniques. From the comparison of these two graphs, it is found that the variation in the actual model and the curve fitted model are similar, but there is a scaling difference. This is due to amplification factor in the mathematical equation. In order to improve the linearity between actual models and the mathematical model, SG filtering is adopted on the captured signal from the simulation results. Curve fitting techniques are adopted after filtering, thus eliminate the noise in the captured signal as well as reduce the intensity of scaling factor.

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The results are obtained based on SG filtering and curve fitting is shown in Figure 8. From the obtained results it is found that the curve fitted model after SG filtering matches with the actual sensor model in terms of both variation and intensity. From the results obtained it is found that the error between actual and improved sensor model is less than 0.8.

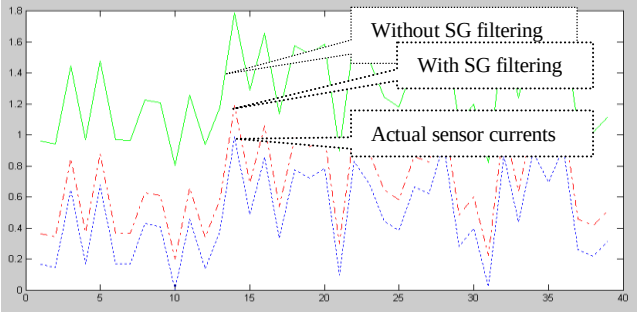

Figure 8: Perfromance Comparison of Sensor Models

V. CONCLUSION

The approaches to nanomedicine range from the medical use of nanomaterials to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology. In this paper, we have analyzed the mathematical models for nanowire sensors and the variation in sensor properties with geometrical parameters. Experimental setup is developed to simulate three different nanosensors (ISFET, nanowire and nanosphere). Sensitivity of nanosphere is found to be better than nanowire and ISFET, however, it is practically difficult to realize nanosphere. Thus nanowire sensor is selected for system level design (prostate cancer detection), nanowire sensor is simulated and its response to variations in analyte concentration is identified. The developed mathematical model is validated against biosensor model, the results shows that both the models have linear variations for changes in analyte concentration, but there is an error of 0.8 (maximum), between the drain currents of biosensor model and Matlab model. This can be minimized by developing accurate results using the biosensor model for large number of analyte concentration. The mathematical model developed can be used to model different sensors using Matlab. The sensors can be interfaced with signal conditioning circuits and control unit for automated disease detection and drug delivery.

ACKNOWLEDGEMENT

The authors would like to acknowledge Nanohub.org for providing permission to access the biosensor labs simulation tools and to carry out the experiments. The authors also acknowledge the support and guidance provided by Cyril Prasanna Raj P., MSR School of Advanced Studies, Bangalore. His inputs and timely guidance has helped us to carry out the experimental analysis.

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AUTHOR PROFILE

Mrs. B.N.Shobha is a Associate Professor, Sapthagiri college of Engineering, Bangalore. She received B.E. degree in Electronics and Communications and M,E degree in Electronics from Bangalore University. She has been associated with various Academic activities in UG and PG courses since 20 years. Her areas of interest are in Biosensors, Image processing, Computer vision and Operating Systems. She has around 17 publications to her credit.

Dr. N.J.R.Muniraj, M.E., Ph.D, is currently Principal at Tejaa Shakthi Institute of Technology for Women, Karumathampatti, Coimbatore, India. He has taught UG and PG courses in ECE in diverse fields for 21 years. He is a member of ISTE, IEEE and VLSI Society of India. He is Guiding 30 Ph.D. Scholars, Presented papers in 12 International conference, 6 National conference and symposium and 42 International Journals. He has organized three International Conferences, eleven national level conferences and workshops. He has headed the R&D Center of Vlsi Embedded systems Dsp Innovation Center, headed the Nodal Centre for MEMS sponsored by IISC and NPMASS, headed the research and development centre for the Karpagam College of Engineering.

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