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# Design, Modeling and Simulation of Prostate Cancer Biosensor with ssDNA biomarker and DGFET Biosensor

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***Abstract*— Marker currently available for the detection of prostate cancer and is the forensic marker of choice for determining the presence of azoospermic semen in sexual assault cases. With PSA detection biopsies were also followed to accurately detect prostate cancer and hence lead to delay. Very recent epigenetic alteration in prostate cancer is hypermethylation of the glutathione-S-transferase pi gene (GSTP1) is detected using ssDNA biomarker. DGFET have played a significant role in detection of prostate cancer with ssDNA biomarker. In this work design, modelling and analysis of five different DGFET sensor structures with ssDNA biomarker is analyzed for their performances. A 64 sensor array model arranged in 8 x 8 array with reference bias voltage is designed to improve the sensor sensitivity by increasing the drain current. The sensor is modeled using biosensor lab from nanohub.org and the sensor array is modeled in MATLAB for analysis. The developed sensor and sensor array can be used for prostate cancer detection.**

***Keywords*—** Sensor array, biosensor performances, simulation parameters, device structure and DGFET design parameters

## I. INTRODUCTION

The middle class population in India is increasing with diverse food habits and adoption to western culture. With the transition in food habits and life style there is an increase in non-communicable diseases (NCD) such as cancer and coronary heart disease (CHD) and other epidemic diseases affecting the Indian population. Cancer rates in India are increasing with development progress. According to WHO, cancer rates in India are considerably increasing with the cancer such as lung, oesophagus, stomach and larynx affecting males and cervix, breast, ovary and oesophagus affecting females. Oral cancer in males and females is 12.8% and 7.5% respectively, oesophagus cancer is 5.7% and 2.8% in male and female respectively, breast cancer in females is 19.2%. Cancer that affects only males are prostate cancer and only females is ovary, breast and cervix. Prostate cancer in India is growing at a rate of 4.6%, breast, ovary, cervix and endometrial cancer in females is at rate of 19.1%, 4.9%, 30.7% and 1.7% respectively **[1].** Cancer of the female reproductive tract has a high incidence amongst Indian women. Cervical cancer is the most common cancer among women with approximately 100,000 new cases occurring each year. Prostate cancer is another major cancer affecting men and is also growing at a very significant rate. Prostate cancer is a form of cancer that develops in the prostate [**2**], a gland in the male reproductive system. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. For prostate cancer detection Prostate Specific Antigen (PSA) biomarker has provided a easy solution for early detection, however with low specificity of PSA causing biopsies attention towards other methods have been taken up. One of the technique is the epigenetic alteration in prostate cancer is hypermethylation of the glutathione-S-transferase pi gene (GSTPI). Figure 1 presents the methylation analysis of GSTP1 gene for prostate cancer.

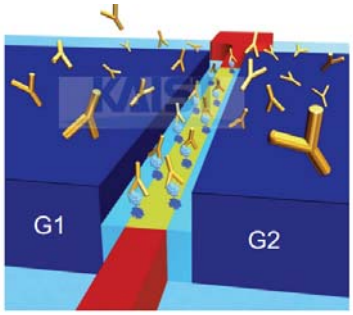



Fig. 1 Double-gate FET with immobilized antibodies and antigens [14 ]

The biomarker for prostate cancer is the single strand oligonucleotide (ssDNA), which is immobilized on the gate of electrode in the electrolyte [**3**]. In [**4**] label free sensors that can detect GSTP1 hypermethylation via hybridization using oligonucleotides is presented. GSTP1 hypermethylation detection for prostate cancer is faster, accurate and nonradioactive, hence many of the biosensors are designed using this biomarker and serves as a method for future research for prostate carcinomas. In this work GSTP1 biomarker is placed in the electrolyte solution for prostate cancer detection. Glutathione S-transferase P1 (GSTP1) is required for metabolism, elimination and detoxification of toxic compounds. Hence GSTP1 helps in protecting mammalian cells from electrophilic metabolites of carcinogens and reactive oxygen species and thus against cancer risk. Suppression of GSTP1 activity or any alteration of this gene could result in DNA damage and increased cancer incidence. Methylation of CpG islands in the promoter region of genes is a frequently acquired epigenetic event in the pathogenesis of many human cancers. This modification inhibits the expression of the affected genes and leads to gene deletions or mutations that can cause loss of gene function **[5].** The genes that are exposed to methylation during the early phases of tumorigenesis could

potentially be used as prognostic markers [**6]**. Many studies have reported the use of GSTP1 methylation as a biomarker to detect prostate cancer [7]. Hypermethylation of the GSTP1 gene pro-moter region is found in the majority (>90%) of primary prostate carcinomas, but not in normal prostatic tissue or benign hyperplasia of prostate [8]. Thus, promoter hypermethylation of GSTP1 is the best DNA-based biomarker for the disease. To date, many different approaches have been developed to analyze DNA methylation, such as methylation-specific PCR (MSP), methylation-sensitive restriction digestion, bisulfite sequencing and microarray analysis [9]. Bisulfite treatment of DNA has been the most popularly used approach to detect DNA methylation[10]. The basic principle of this method is that the cytosines are completely deaminated to uracil, whereas the 5-methyl cytosines remain unmodified; the sequences under investigation are then amplified by PCR, especially with MSP, using a set of primers specific for the converted sequence. The specificity of MSP is higher than that of other methylation detection techniques due to specific primer design. With biomarkers being DNA and FET being the active element, together would form a suitable device for prostate cancer detection. In this paper the structural and biological properties of DGFET is designed and analyzed using Biosensor lab from nanohub.org. Section II discusses the structure of biosensor and mathematical analysis of biosensor, section III discusses the performances design and modeling of DGFET as biosensor and section IV discusses the results of DGFET biosensor and section V discusses the results of DGFET array sensors and section VI is conclusion.

## II. DGFET BIOSENSOR

Techniques that have been developed for biomolecule detection with different types of biosensors are nanomechanic device, nanowire-based device, conductometric devices, optoelectronic device, ion-sensitive electrode, piezoelectric device and electrochemical sensor [11]. Numerous kinds of biosensors existing among those electrical detection methods are viable for transducers because there is no need to use labeling process with indispensible in optical detection and no need to use ultrahigh vacuum apparatus for mass spectrometric detection. Field effect transistor (FET)-based biosensors are fabricated based on the standard complementary metal-oxide-semiconductor (CMOS) process, have attracted a great deal of advantage. In particular, FET based biosensors are suitable for integration of sensors and readout circuits. Numerous reports have recommended FET-based biosensors for cancer detection due to its ultrasensitive and low cost process. FET biosensors operates on charged based detection principle that detects the presence of biomolecules in the analyte solution. Detection of DNA in analyte solution using FET has offered higher sensitivie as DNA carries negative charge under normal conditions. Limitations in FET based biosensor is overcome by use of double gate FET, as one of the gate which is floating gate can be charged with modulation applied with propoer biasing terminal. Sensitivity is one of the major advantages of DGFET biosensor [**12**]. With comparison of conventional FET biosensor activated by single back gate, the advantage of double gate FET is that the symmetric/asymmetric biases can be applied to two gates, with precise and independent control on the conduction path. Figure 1 shows a double gate nanowire FET biosensor which has double gates G1 and G2 that are placed vertically on the silicon nanowire. The double gate FET is immobilized with biomolecules, the antibodies are difused through solution and the antigens bind to the antibodies selectively on top of the nanowire channel. The current flow between source drain regions provide information on density of cancer cells in the given analyte.

In order to detect the target molecules in the analyte solution, it is required to immobilize the surface of biosensor with capture molecules. Immobilization can be arried out with DNA, protein and charged polymers as biomarkers. DNA biomarker immobilization are of two methods, DNA bonding with covalent bond and second with eletrostatic interaction [**13**]. Figure 2 shows the DGFET biosensor with three different biomarkers such as ssDNA, dsDNA and cDNA. In this work single strand DNA is used as a biomarker for detection of prostate cancer cells.

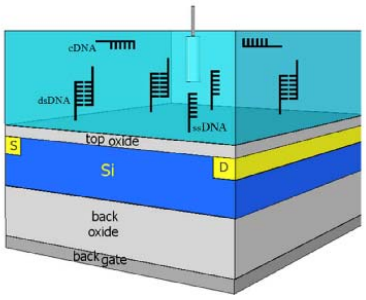



Fig. 2 Structure of DGFET biosensor with DNA receptors [ ]

In a typical electrochemical DNA detector, ssDNA is immobilized with conjugated polymer film which is polypyrrole (PPy). The PPy is prepared with simultaneous electrooxidation of pyrrole and polymerization on platinium electrode that is inserted in the solution of electrolyte containing anion X- perchrolyte or chloride as shown in Figure 3

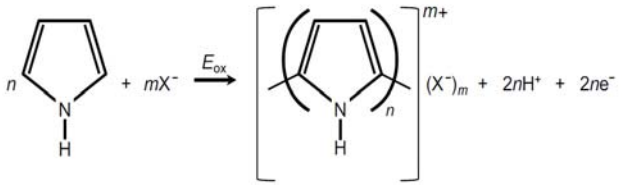



Fig. 3 Preparation of ssDNA biomarker [3]

During the oxidation of PPy the electrons removed from the polypyrrole pi electron orbitals takes place. The electrons that travel to the positively-charged Pt electrode on which the PPy is deposited [**13**]. In this work, the ssDNA is used with DGFET for detection of prostate cancer. The mathematical modeling of the biosensor is requried to analyze the perfromances of DGFET biosensor for prostate cancer detection.

The change of the drain current is proportional to the concentration of target molecules capturd by the receptors.

Capturing of target molecules is based on the complement property of target molecules with the receptor molecules. The dynamic capture of target molecules is based on diffusion capture model based on first order chemical reaction, the diffusion of target molecule to the sensor surface is given by Eq. (1),

$$\frac{d\rho}{dt} = D\nabla^2\rho \qquad (1)$$

Where, D is the diffusion coefficient and ρ is the concentration of target bio-molecules in a solution. The capture of bio-molecules by the receptors on sensor surface is given by Eq. (2),

$$\frac{dN}{dt} = K_F(N_o - N)\rho_s - K_R N \qquad (2)$$

Where, N represents the density of conjugated receptors, No is the total density of receptors on sensor surface. $K_F$ and $K_R$ are the capture and dissociation constants respectively. The solution to the equation is given as in Eq. (3)

$$-\frac{K_F N_O + E - K_F N_{equi}}{K_F\rho_O + K_R}\log\left(1 - \frac{N}{N_{equi}}\right) + \frac{K_F}{K_F\rho_O + K_R}N = Et \qquad (3)$$

Where E = Navg CD (t)/ AD, Navg is the Avogadro's number, CD(t) is the time dependent diffusion equivalent capacitance, AD is the dimension dependent area of the sensor

$$N_{equi} = \frac{K_F N_O \rho_S}{K_F\rho_O + K_R} \qquad (4)$$

is the equilibrium concentration of the conjugated biomolecules.

## III. MODELING OF DGFET BIOSENSOR

Figure 4 shows the double gate FET biosensor structure. The biosensor consists of a nanoscale FET, with electrolyte replacing the polysilicon gate. The electrolyte is connected to a reference electrode that (which is usually made up of Ag/AgCl) is immersed in the electrolyte solution to provide a reference potential (electrostatic) in the electrolyte solution.

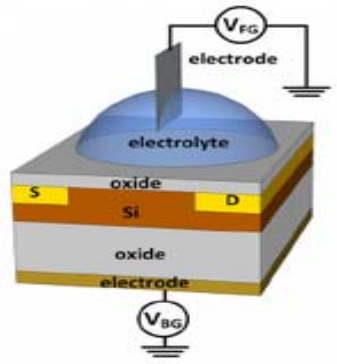



Fig. 4 Double gate FET with electrolyte and reference electrode

The DGFET consists of two gates one is the electrolyte gate and the other is the back gate at the bottom of the transistor. The structure of DGFET is made up of four regions, electrolyte-electrode interface, the electrolyte, oxide-electrode interface and the oxide-FET interface. The electrode immersed in the electrolyte exchanges electrons with ions in the electrolyte hence there will be no potential drop at this interface. The electrode-electrolyte interface can be described as in Eq. (5),

$$\Psi|_{\text{elec}} - V_{\text{elec}} \quad (V_{\text{elec}}: \text{fluid gate bias}) \qquad (5)$$

where Ψ is the electrostatic potential at the electrode-electrolyte interface.

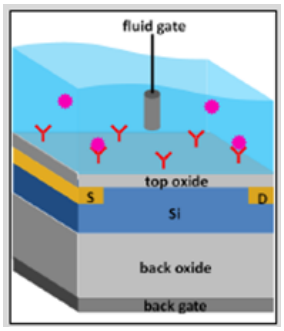



Fig. 5 Double Gate FET with DNA biomarkers

Figure 5 shows the structure of DGFET with DNA biomarker as per the models provided in the biosensor lab from nanohub.org. Table 1 presents the DGFET design parameters that have been set for the simulation of biosensor. Device parameters, biological parameters and ambient conditions are set prior to simulation of biosensor model. The biosensor lab provided two options for biomarkers (DNA/Protein), ssDNA biomarkers are selected for analysis.

**TABLE 1:**
**DGFET DESIGN PARAMETERS**

| Sl | Parameters | Values | Range |
|---|---|---|---|
| | **Device Parameters** | | |
| 1 | Device width (um) | 1 um | 0.1 – 10 (um) |
| 2 | Device length (um) | 1 um | 0.25 – 10 (um) |
| 3 | Top Oxide thickness (cm) | 4e-07 cm | ------- |
| 4 | Back Oxide thickness (cm) | 1.5e-05 cm | ------- |
| 5 | Silicon Body thickness (cm) | 8e-06 cm | ------- |
| 6 | Doping density | 1e+19/cC | 1e+15 – 1e+21 |
| | **Biological Parameters** | | |
| 1 | Type of Analyte | DNA | DNA/Protein |
| 2 | kf | 3e+06 | 1e+03 - 1e+03 |
| 3 | kr | 1 | 0.01 - 10 |
| 4 | Receptor density | 1e+12 | 1e+10 - 1e+15 |
| 5 | DNA strand length (base pair) | 12 | 1 - 100 |
| 6 | Diffusion parameters | Diffusion coefficient | Diffusion coefficient/ DNA diffusion model |
| 7 | Diffusion coefficient | 1e-06 | 1e-09 - 1e-03- |
| | **Ambient conditions** | | |
| 1 | Incubation time (mins) | 60 min | ------- |
| 2 | Temperature in ($^0$K) | 300 K | ------- |

With design parameters set for the biosensr structure, simulation settings are also set as per the specifications in Table 2. It is requried to analyze settling time versus analyte concentration with minimum number molecules set to 10, the total time before saturation is also required to be captured with analyte concentration, pH parameters with surface density, protonation constants are defined for the simulation settings. Ion concentration and pH level is also set for simulation purpose.

The simulations are set to selectivity analysis with receptor size of molecules and parasitic molecules. The simulation steps is set to 50 so as to be more accurate with rate constant of 0.1.

**TABLE 2**
**DGFET BIOSENSOR SIMULATION SETTINGS**

| Sl | Simulation Settings | Values | Range |
|---|---|---|---|
| | **Settling Time vs Analyte Concentration** | | |
| 1 | Lower value of analyte concentration (molar units) | 1e-15 | 1e-20 - 1 |
| 2 | Lower value of analyte concentration (molar units) | 1e-06 | 1e-15 - 10 |
| 3 | Number of intermediate concentration steps | 30 | 10 - 100 |
| 4 | Minimum number of molecules | 10 | ------- |
| | **Time-dependent Capture of target Molecules** | | |
| 1 | Analyte Concentration | 1e-09 | 1e-15 - 1e-03 |
| 2 | Start time for transient response (s) | 1e-06s | 1e-07 - 1e+05 |
| 3 | Final time for transient response (s) | 10000s | 1e+02 - 1e+06 |
| 4 | steps | 100 | 100 -1000 |
| | **Numerical Simulation** | | |
| 1 | Numerical Simulation | No | Yes/No |
| | **pH Parameters** | | |
| 1 | Surface density (/$cm^2$) | 5e14 | ------- |
| 2 | Protonation constant (pKa) | -2 | ------- |
| 3 | De-protonation constant (pKb) | 6 | ------- |
| | **Conductance modulation vs Analyte Concentration** | | |
| 1 | Lower value of analyte concentration (Molar) | 1e-15 | 1e-20 - 1e-12 |
| 2 | Upper value of analyte concentration (Molar) | 1e-06 | 1e-09 - 1e-03 |
| 3 | Number of steps | 30 | 10 - 100 |
| 4 | Buffer Ion Concentration (M) | 1e-05 | 1e-07 - 10 |
| 5 | Vfg(V) | 1.0 | ------- |
| 6 | Vbg(V) | 0.0 | ------- |
| 7 | pH | 4 | ------- |
| | **Conductance modulation vs Buffer ion Concentration** | | |
| 1 | Lower value of electrolyte concentration (Molar) | 1e-05 | 1e-07 - 10 |
| 2 | Highest value of electrolyte concentration (Molar) | 2 | 1e-07 - 10 |
| 3 | Step number | 20 | 1 - 100 |
| 4 | Vbg(V) | 0 V | ------- |
| 5 | Analyte concentration (Molar) | 1e-09 | 1e-20 - 1e-03 |
| 6 | Vfg(V) | 1.0 | ------- |
| 7 | Vbg(V) | 0.0 | ------- |
| 8 | pH | 4 | ------- |
| | **Conductance modulation vs pH** | | |
| 1 | Lower value for the pH | 1 | 1 - 14 |
| 2 | Upper value for the pH | 10 | 1 - 14 |
| 3 | Number of steps | 20 | 1 - 30 |
| 4 | Buffer Ion Concentration (M) | 1e-05 | 1e-07 - 10 |
| 5 | Vfg | 1.0 | ------- |
| 6 | Vbg | 0.0 | ------- |
| | **Selectivity** | | |
| | **Molecule Parameters** | | |
| 1 | Size of receptor molecules | 2e-07 cm | 0.1e-07 - 3e-07 |
| 2 | Size of parasitic molecules | 1e-07 cm | 0.1e-07 - 3e-07 |
| 3 | Concentration of Target molecules (Molar) | 1e-12 | 1e-15 - 1e-06 |
| 4 | Parasitic of Parasitic molecules (Mlar) | 1e-06 | 1e-09 - 1e-03 |
| 5 | Charge of individual Target Molecules (eu) | 10 | ------- |
| 6 | Charge of Parasitic Molecules (eu) | 1 | ------- |
| | **Other Parameters** | | |
| 1 | Maximum surface coverage | 0.54 | 0.54 - 1 |
| 2 | Lower value of Receptor density | 1e+11/cm2 | 1e+09 - 1e+12 |
| 3 | Upper value of Receptor density | 5e+12/cm2 | 1e+12 - 5e+13 |
| 4 | Number of Steps | 50 | 10 -100 |
| 5 | Rate Constant | 0.1 | 1e-03 - 1e+02 |

## IV. RESULTS AND DISCUSSION

DGFET biosensor with DNA marker simulations are shown in Figure 6. Figure 6(a) presents the results of analyte concentration versus settling time for various diffusion coeffieicnts in the range 1e-09, 1e-08, 1e-07, default(1e-06), 1e-05, 1e-04, 1e-03. From the results shown the settlign time exhibits linear variation with increase in analyte concentration. Higher the diffusion coefficient sensor response time is reduced, for response time less than one second analyte concentration greater than 1e-10 is recommended. Similarly figure 6(b) shows the variation in drain current with analyte concentration. The drain current increases by 0.01 microA for change in analyte concentration, exhibiting very poor response. Hence sensor array is recommended that could improve the current rating. Figure 6(c) presents the drain current variation with regard to ion concentration which is in molar units. And Figure 6(d) presents the DGFET drain current with pH variations. From the results the linear region for drain current variation is between 0.0001 molar units to 0.1 molar units and 4 to 8 buffer ion concentration and pH level respectively.

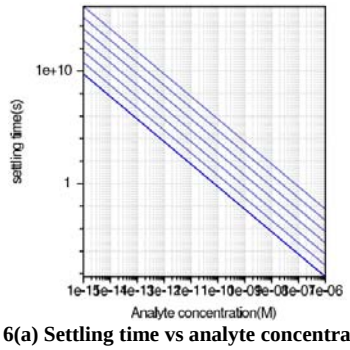



**Fig 6(a) Settling time vs analyte concentration**

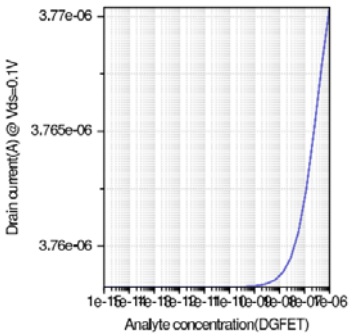



**Fig 6 (b) Drain current vs analyte concentration**

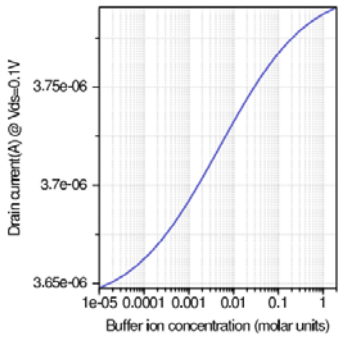



**Fig 6 (c) Current vs Buffer concentration**

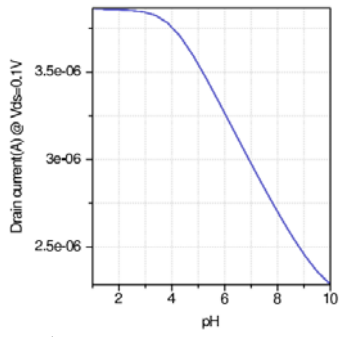



**Fig 6 (d) DGFET Current vs pHDGFET**

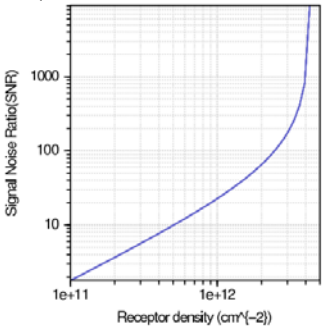



**Fig 6 (e) SNR of biosensor**

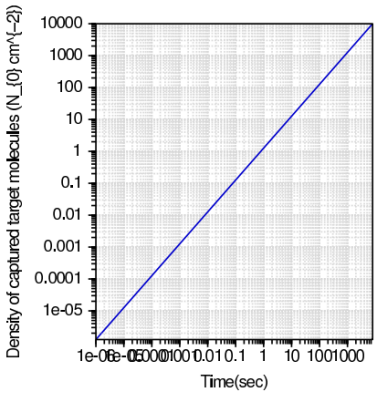



**Fig 6 (f) Density of target molecules**

**Figure 6: Current vs Analyte concentration DGFET**

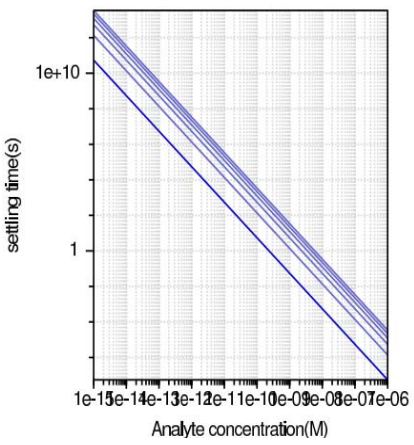
Figure 6(e) is a graph of SNR versus receptor density, with receptor density variation SNR is linear however with larger receptor density SNR reaches nonlinear state. Figure 6(f) presents the density of captured target molecules with time, from the graphs showsn with time the target molecule capturing increases.

The simulation parameters and device structures are varied to analyze the performances of biosensor with ssDNA biomarker with DGFET. In this work four case studies are consider for the analysis of biosensor.

Case 1: M**inimum number of molecules** is varied from 1, 5, (default)10, 15, 20, 25 and the following performance graphs are captured.

a. Settling time vs analyte concentration
b. Current vs Analyte concentration DGFET
c. Current vs Buffer concentration DGFET
d. Current v spHDGFET
e. SNR ofbiosensor in the presence of parasitic molecules
f. Transient capture of target molecules Analytical Simulation DGFET

Figures 7 shows the performances of nanobio sensor for the given case study. As the values are varied in the above order, the curves shift upwards for Settling time vs analyte concentration.



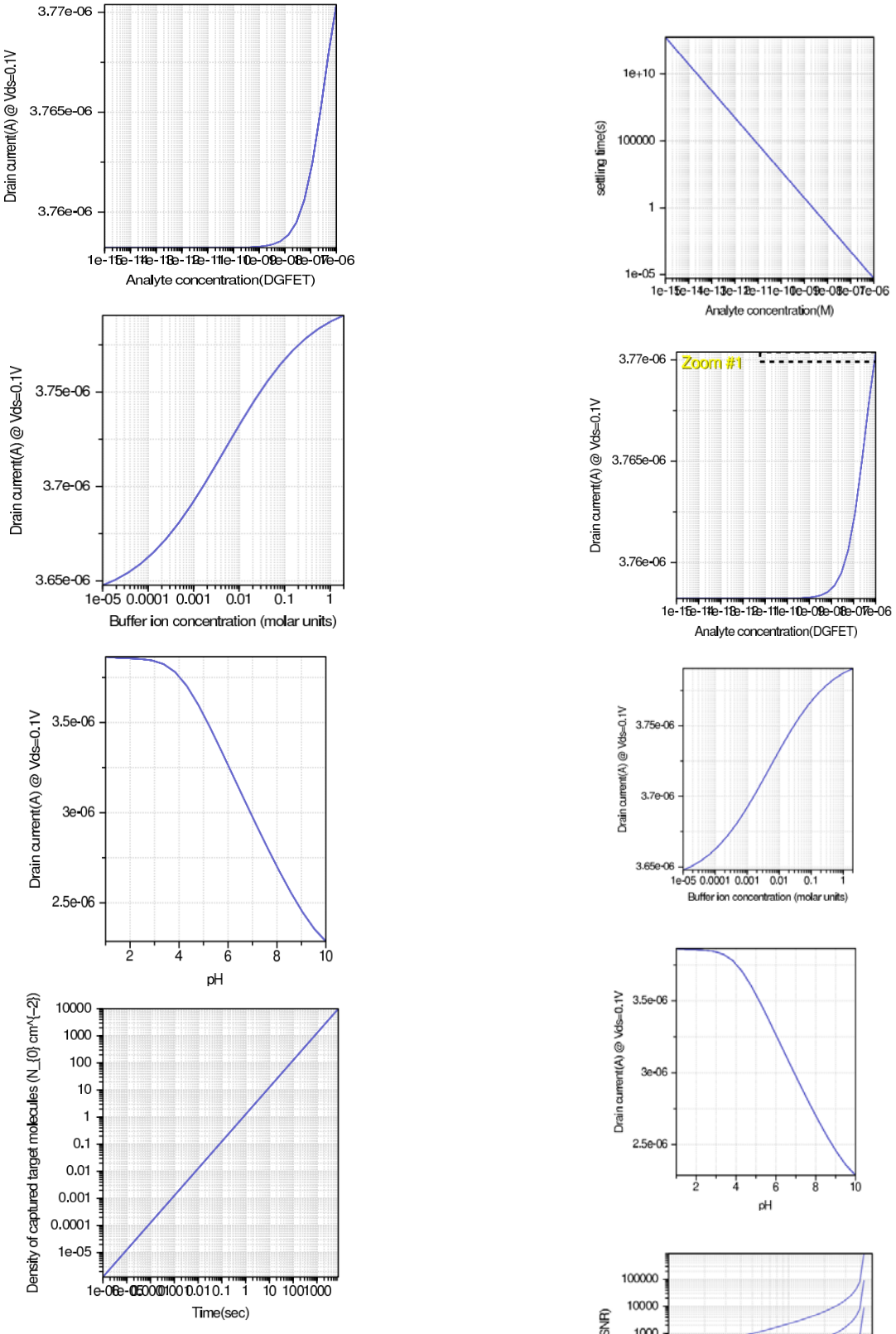



**Fig. 7 Simulations results for case study 1**

Case study 2: R**ate constant** is varied from 0.001, 0.01, (default)0.1, 1, 10, 100 and the following performance graphs are captured and is presented in figure 8. As the values are varied in the above order, the SNR vs Receptor Density. SNR decreases with increase in the rate constant.

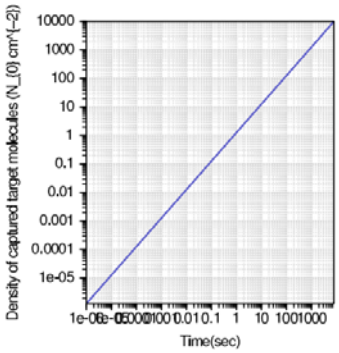
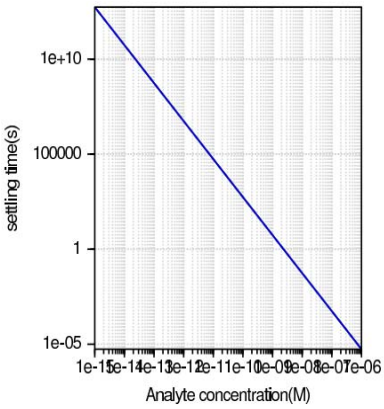
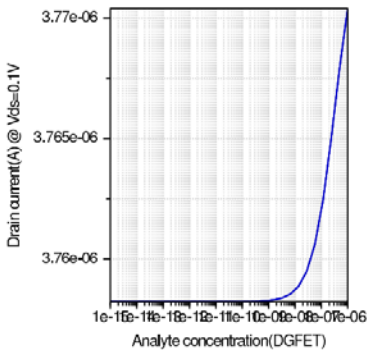
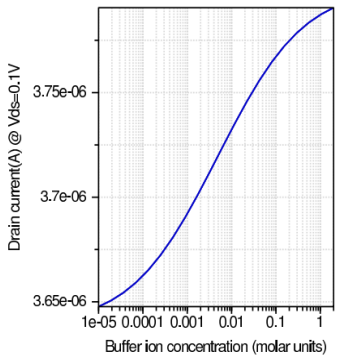



**Fig. 8 Simulation results for case study 2**

Case study 3: V**alue of pH** is varied from 1, 2, 4, 6, 8, (default)10, 12, 14, and the following performance graphs are captured and is presented in figure 9. As the values are varied in the above order, the curves the values stop at the corresponding pH values.



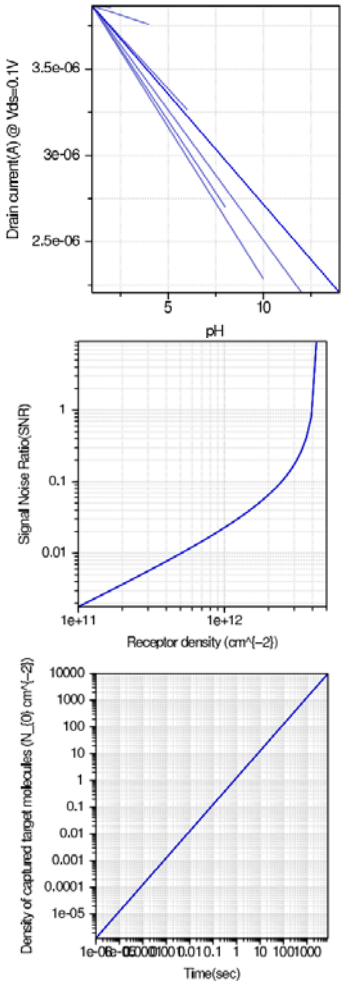
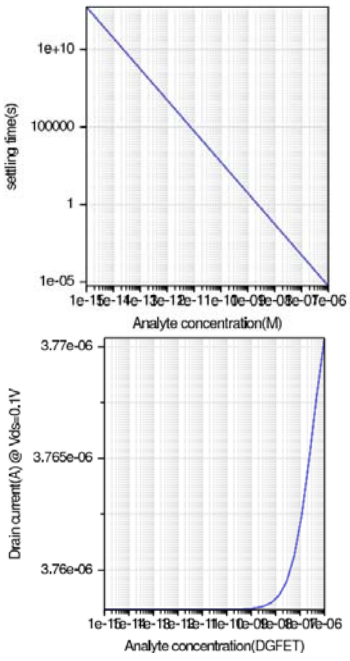




**Fig. 9 Simulation results of case study 3**

Case study 4: **Analyte Concentration** is varied from 1e-20, 1e-18, 1e-15, 1e-12, (default) 1e-09, 1e-06, 1e-03 and the performances are presented in Figure 10. There is no variation in any of the graphs for the variation in the analyte concentration.



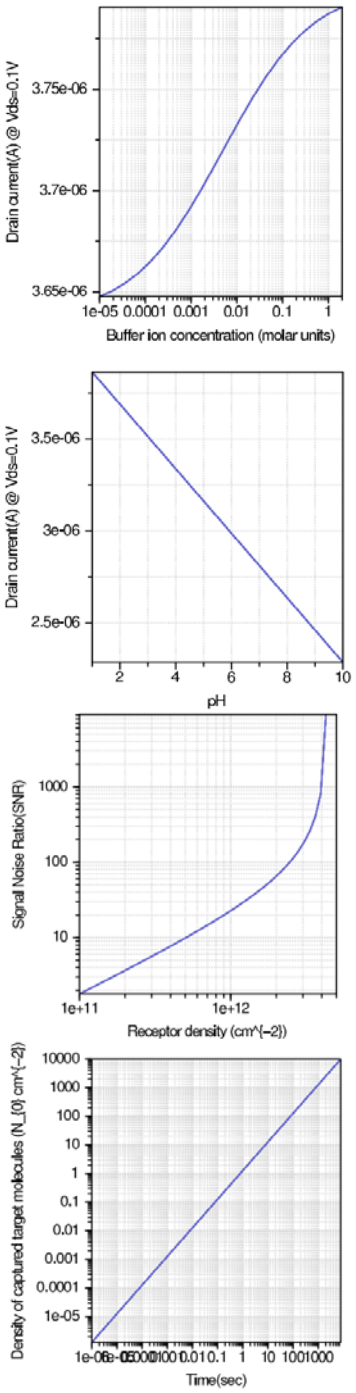



**Figure 10: Simulation results of case study 4**

## V. DESIGN OF BIOSENSOR ARRAY WITH DGFET

From the results discussed in the previous section, the drain current variation is in terms of 0.01 microA, for improving the sensitivity of sensing, it is imperative to implement the sensor in an array format. The detectors in array systems need to measure the analyte quantity at different locations, which is typically carried out sequentially by a single detector across the array or to dedicating an individual detector to each location. Most array systems require a single measurement (usually when the array reaches its biochemical equilibrium) per detection site. Others require the capturing of the reaction kinetics, necessitating multiple measurements per pixel. Independent of the application and sensor, signal-to-noise ratio (SNR) is always defined as the power of the detected signal to the power of the noise. SNR is a good measure of detection system sensitivity. The higher the SNR (for a certain input), the more sensitive the detection system. In a detection system, SNR generally decreases as signal power is reduced, assuming that the noise power remains rather constant. Figure 11 shows the arrangement of biosensors in array for improving the sensitivity of detection.

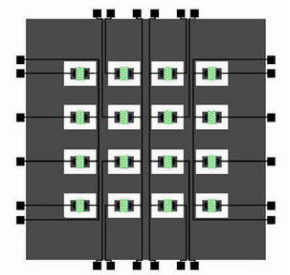


**Figure 11: Biosensor array with DGFET**

In this work in order to improve the sensitivity a sensor array model with 64 sensors are designed, that consists of the DGFET biosensor with ssDNA biomarker. The reference voltage connected to the electrode biases the top gate of all 64 sensors to attain biological equilibrium. The back gate voltage is set a predefined bias depending upon the electrolyte concentration.

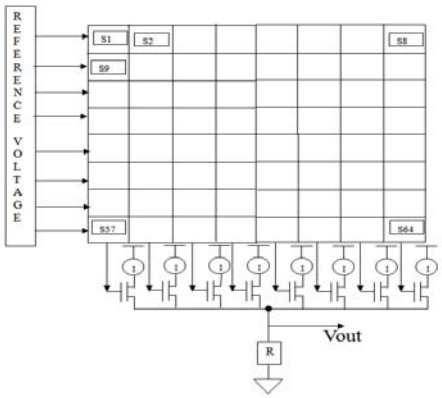



**Figure 12: Biosensor array with 64 sensors**

Each sensor node output current is connected in series to the adjacent sensor and all the sensor nodes currents are connected in series in column wise. The current potential drop of 8 sensors is sufficient to switch the transistor at the bottom of the sensor array, which is connected to a predefined bias current. The sensor voltage switches on the corresponding transistors and the corresponding bias current flows in the output loop of the array sensor. With 64 sensors reacting to the electrolyte solution, the presence of biomarker on the gate regions of 64 sensors enhances the detection process. The drain current in single biosensor varies by 0.01uA, in the sensor array model the drain current is variation is increased by 10 times hence improving the sensing accuracy. It is required to design the structure of sensor array model and perform accurate simulations.

## VI. CONCLUSION

Prostate cancer is the one of the most diagnosed cancer among men in India, with 3.6% deaths leading to prostate cancer there is need for early diagnosis of prostate cancer. DNA biomarkers are used as one of the most popular biomarkers for detection of prostate cancer, with DGFET being the active device. In this work, design modelling and analysis of DGFET with ssDNA biomarker is carried out for prostate cancer detection. Five different structures of DGFET with DNA biomarker is modeled to analyze the performances of biosensor using biosensor lab from nanohub.org. A sensor array consisting of 64 biosensors are designed to improve the sensitivity of detection. The sensor array is connected in series column wise to improve the drain current with increase in analyte concentration. The designed sensor array is suitable for detection of prostate cancer with high sensitivity.

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