Modelling And Identification Of Suitable Matrix For Uric Acid Biosensor Using Comsol Multiphysics

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Abstract: Uric acid biosensor was designed in COMSOL Multiphysics simulation software for the suitable identification of sensing materials for the application of arthritis disease diagnosis. The detection of biomarkers (proteins, DNA, nucleic acid, uric acid or antigens) from biological samples such as serum, urine or blood in high-throughput manner with high specificity is the beginning stage of creating compelling treatment for some maladies. Right now, accessible bio detecting methods that are including in the recognition of biomarker particles in patients' samples don't have the sufficient affectability and point of confinement of discovery to be successfully recognize beginning time of joint pain or any cardiovascular infection. Especially, the limit of detection, materials used as a sensing region and sensor design limits its application for early detection of arthritis and heart disease. This work builds up a Multiphysics computational model to study the uric acid concentration effect on human blood serum in the designed biosensor system. TiO₂ based - metal oxide semiconductor materials as a sensing matrix with immobilized uricase enzyme as a detector was developed and comparison made between various other materials like SnO₂, ZnO and NiO. Among all other materials used for the biosensor design, Titanium dioxide gives more sensitivity, lower detection limit and linear concentration range between 0.1 to 5 mg/dl and it can be used as sensing material for the application of arthritis disease diagnosis.

Index terms: Biosensor, Uric acid, COMSOL Multiphysics, Titanium dioxide, enzyme layer, thin film, modelling.

1. INTRODUCTION

Biological detection procedures exist in huge numbers of parts of human's everyday life, particularly in the region of science. Various gadgets have just been exhibited for the discovery of DNA [1, 2], proteins and some hurtful acids in the human body [3-5]. Uric acid (2, 6, 8-trihydroxypurine) is the main final end product of purine metabolism in humans and the high level of uric acid concentration in blood is associated with several diseases, such as gout, arthritis [6], cardiovascular diseases [7], neurological diseases [8], insulin resistance, hypertension, and renal insufficiency [9, 10]. A healthy adult human excretes uric acid at a rate of 0.6 g/24 hr the excreted product arises in part from turnover of the purine nucleotide of nucleic acids. The typical level is between 0.13 and 0.46 mM (2.18–7.7 mg/dl) [11, 12] for uric acid in serum. Therefore, uric acid determination is of foremost significance in the diagnosis and medical administration of maladies caused by some metabolic disorder. As of now accessible gadgets or any recognition techniques accessible in therapeutic businesses or clinical research centres for recognizing uric acid substance in the human body don't have the ability of distinguishing uric acid precisely and exactly. Quick development in the advancement of new materials and change in detecting methods have prompted the development of cutting edge biosensors which have strong application in environment monitoring, healthcare, food industries and biological analysis. It might be seen that the greater part of the Metal-oxide Semiconductor materials-based bio-electrodes experience the ill effects of specific issues in uric acid determination, for example, tedious example readiness including multiple steps, cumbersome fabrication of the bio-electrode based on cross linkers, which exhibited lack of stability, a poor linear detection range, thereby limiting their application in development of uric acid biosensors. The main problem is with the development of the device and materials used for the detection of UA in the blood serum having low physical and chemical properties of the materials. So, at a treatable stage many patients were not treated successfully. Therefore, choosing the materials used for the fabrication of bio-sensor is a vital one. Thus, its effective detection at an initial step is imperative which requires distinguishing proof of an appropriate sensing matrix having high electron communication highlight and high adsorption capacity. Other than this, effective immobilization of an enzyme on the anode surface is additionally essential. In the previous couple of years, wide band-gap metal oxide semiconductors (ZnO and SnO₂) have increased much consideration as a framework for immobilization of different bio-particles due to their profile good nature other than solid adsorption capacity and plenitude in nature [13-17]. SnO₂ experiences the dependability issue while ZnO based bio-electrode offer restricted affectability. Subsequently, there is a critical need to distinguish another framework which gives steady and improved biosensing response characteristics. So, for the cost and other issues, before fabrication process, numerical or simulation modelling is required for the development of bio-sensor for the selection of suitable matrix to increase the sensitivity, selectivity and reliability of the biosensor.

Fig.1 A general schematic of TiO₂ based uric acid biosensor
The aim of the COMSOL Multiphysics modelling of the TiO$_2$ structures is mainly focused on the device response at different types of energy stimulus reaching the dynamic surfaces of the 3D bio-detecting structures under the principle limitations of biocompatibility and non-harmfulness. A simple schematic and flow of TiO$_2$ biosensor for uric acid sensing is shown in the figure 1. This article describes the modelling of the uric acid bio-sensor based on TiO$_2$ as a matrix and uricase as an enzyme arranged like a pillar shaped structure using COMSOL Multiphysics simulation software and comparison of uric acid concentration has been made for various metal oxide semiconductors.

2. USE OF COMSOL MULTIPHYSICS

COMSOL Multiphysics is a coordinated domain for understanding arrangement of time-dependent or stationary second request in space halfway differential conditions in one, two, and three dimensions. In addition, such conditions might be coupled in a relatively subjective way. COMSOL Multiphysics give refined (and advantageous) instruments for geometric displaying. Along these lines, for some standard issues, there exist predefined alleged application modes which act like formats to conceal a great part of the perplexing points of interest of demonstrating by conditions. The application modes make utilization of the dialect utilized as a part of the individual building discipline [18]. COMSOL (in the past known as FEMLAB) is a limited component investigation and solver programming bundle for different material science and building applications, particularly coupled wonders, or Multiphysics. It incorporates an entire domain for demonstrating any physical marvel that can be portrayed utilizing standard or PDEs. It has turned into the business standard for Multiphysics displaying, research, plan, and improvement (COMSOL 2008b; Zimmerman 2006). The product bundle underpins almost all stages (e.g., Windows, Mac, Linux, and UNIX). COMSOL takes into consideration building coupled frameworks of PDEs. The PDEs can be entered specifically or utilizing the alleged frail shape. COMSOL likewise offers a broad and very much oversaw interface to Math Works MATLAB and its tool compartments for an expansive assortment of programming, pre-handling, and post preparing potential outcomes [19]. COMSOL Multiphysics is an effective intuitive condition for displaying and settling a wide range of logical and designing issues in view of fractional differential conditions (PDEs). With this item you can without much of a stretch broaden regular models for one sort of material science into Multiphysics models that unravel coupled material science wonders and do as such at the same time. Through COMSOL Multiphysics, demonstrating and reproduction were distinguished the best fitted answers for bio-detecting gadget structures. The model of dynamic surface plan depends on COMSOL Multiphysics which is a limited component investigation, solver and recreation programming bundle for different material science and building applications.

In this article we designed and studied a bio-sensor model (in figure 2) as flow strip based on curved pillar structure using COMSOL Multiphysics simulation software for the application of uric acid determination for arthritis disease [20].

2.1 MODEL DEFINITION

A flow cell model is designed which contains an array of micro-pillars coated by TiO$_2$ and Uricase enzyme to detect bio-molecules (uric acid), for example antibodies in aqueous solutions. The selective absorption of bio-molecule in the sample stream is due to the active sensing material coated over the curved pillars. These bio-molecules then react on the surface of the metal oxide layer. A signal proportional to the surface coverage can be detected in a sensor and the corresponding analyte composition is also detected with the help of curved pillar surface. This application enables the client to change the plan of the sensor by modifying surface parameters, for example, pillar dia. measurement, spacing, and inlet velocity of the solution to examine how the design influence the detection results [20].

![Fig.2 COMSOL work flow for bio-sensor design](image)

Detection range is almost depending upon the layer thickness of the pillar coated with the materials. The adsorbed species or any bio-molecules on the pillar will produce a signal proportional to the analyte concentration which depends on the concentration at the curved pillar surface. This researches the surface concentration...
distribution while an analyte is gone through it. It additionally studies about the impact of an extinguishing surface response where adsorbed species are changed over into an inert state.

**SURFACE REACTIONS**

Adsorption and desorption of analyte molecules ($A_m$) from surface sites ($S_x$) on the micropillar surfaces according to

\[ A_m + S_x \stackrel{k_a}{\longleftrightarrow} A_m S_x \]  
Equation 1

The adsorbed analyte $A_m S_x$ can transform into a quenched state $Q_x S_x$ that does not contribute to the sensor signal. The quenching reaction is reversible:

\[ A_m S_x \stackrel{k_1}{\longleftrightarrow} Q_x S_x \]  
Equation 2

The rate of adsorption is

\[ \text{r}_{ads} = k_{ads} c_{A_m} \]  
Equation 3

where $c_{A_m}$ is the concentration of $A_m$ in the stream.

The desorption rate is linear in the concentration of surface adsorbed species $c_{A_m S_x}$:

\[ \text{r}_{des} = k_{des} c_{A_m S_x} \]  
Equation 4

The rate of the reversible quenching reaction is given by

\[ \text{r}_{quench} = -k_1 c_{A_m S_x} + k_2 c_{Q_x S_x} \]  
Equation 5

**MASS TRANSPORT IN THE ANALYTE STREAM**

The equations in the Transport of Diluted Species interface describe the transport of the species $A_m$, in the analyte stream according to

\[ \frac{\partial c_{A_m}}{\partial t} + \nabla \cdot \left( -D_{A_m} \nabla c_{A_m} \right) + \mathbf{u} \cdot \nabla c_{A_m} = 0 \]  
Equation 6

Here, $D_{A_m}$ denotes the diffusion coefficient (SI unit: m$^2$/s), $c_{A_m}$ denotes the species concentration (SI unit: mol/m$^3$) and $\mathbf{u}$ is the velocity vector (SI unit: m/s). The adsorption and desorption of analyte at the dynamic pillar surfaces offer ascent to a net flux at the corresponding boundaries:

\[ N_f = -r_{ads} + r_{des} \]  
Equation 7

**3. RESULT AND DISCUSSION**

The below model shows the bio-sensor model designed in COMSOL Multiphysics using surface reaction and transport module and it includes study module based on time dependent analysis.
Concentration distribution in the analyte stream and surface coverage of adsorbed species are shown in the above figures. The velocity distribution of the stream field makes pillars near the wall to achieve their greatest adsorption level at a later time contrasted with columns in the focal point of the stream. Pillars near the wall also take longer to discharge adsorbed analyte and the position of a pillar in a row also has an effect on the maximum adsorption level.

It may be clearly seen that the curve between current and uric acid concentration of TiO₂ coated pillar for biomolecules sensing is linear and the current reached maximum of 2.65 µA which is the maximum current obtained for the uric acid concentration range of 100 mg/dl when compared with some experimental works [21]. This might be because of the way that the covered layer of the pillar surface and it is a key parameter for bio-detecting applications. It is the quality and surface region of the thin pillar surface which assume a vital part for powerful and conformal immobilization of the compound over the TiO₂ surface. The investigation moreover demonstrates the great direct connection amongst current and uric acid concentration and furthermore the plot amongst time and current is additionally demonstrated as follows.

The plot between concentration species and current is plotted and its shows a linear relationship between biosensor response (i.e. current) and uric acid concentration ranging from 0.1 to 100 mg/dl (pH 7.5), which is better than previous reports of some experimental work of TiO₂ based biosensor, 0.05–0.5 [21].
3.1 DEPENDENCE ON ENZYME LAYER THICKNESS
Some experimental work illustrated that, manufacturing of highly active biosensors is mainly depend upon the uricase enzyme and its thickness deposited on the conducting substrate by using various deposition techniques [22]. So, it is necessary to choose an enzyme layer thickness to design a highly active biosensor. By considering that in to an account here, we modelled biosensor based on the response of Uricase layers to uric acid as a function of the thickness of the pillar structure coated with active enzyme [23]. Immobilization of enzymes is used in biosensors to detect the concentration of a specific analyte because of the biological recognition between the analyte and the immobilized enzyme. The response of current as function of enzyme thickness layer of pillar coated with uricase enzyme is plotted for various values of thickness. It is clearly seen in the figure 10, that the current reaches maximum of 2.34µA with the enzyme thickness of 0.8mm. This behaviour can be understood as follows: when the film is very thin, almost no uric acid is changed over to hydrogen peroxide and the current is small. As the film thickness expands/increases, more and more uric acid reacts to hydrogen peroxide and the current increases. At a specific thickness of 0.8 mm, the majority of the uric acid that enters the film is converted to hydrogen peroxide and the current reaches an extreme and saturation value as shown in the figure 11.

3.2 COMPARISON BETWEEN DIFFERENT METAL-OXIDE SEMICONDUCTORS FOR URIC ACID SENSING
Among different strategies and principles methods used to identify uric acid, biosensors in view of electrochemical recognition techniques are known to be the most famous in the experimental oriented type because of a lower detection limit, high selectivity and affectability can be effortlessly obtained where sensing matrix assumes a critical part. Different frameworks have been accounted for to immobilize uricase for the investigation of uric acid. Here we modelled a biosensor based on SnO₂ coated layer over which uricase enzyme is coated. The same pillar type Multiphysics model is designed to measure the concentration range for uric acid. The figure 11 shows the maximum current value of 1.6 µA for UA concentration of about 140 mg/dl which is lower than that of the material we used in the previous model in the same work.

![Fig.9 Graph between Time (sec) and Current (µA)](image)

![Fig.10 Surface covered area of analyte over pillar](image)

It is clearly seen from the figure that, the fractional covered area of pillar when analyte is passed over the pillar surface. The surface fraction is high when it is passed through the centre row of pillar in the interval of 55 sec and same way it is very low in the pillar sections nearer to the walls of the surface. So, the adsorbed analyte is high in the centre row of the pillar which gives maximum current in the present area.

![Fig.11 Plot between enzyme layer thickness and current (µA)](image)

![Fig.12 Plot between UA concentrations Vs Current for SnO2 coated layer](image)
Thus, uric acid determination is of principal significance in the analysis of the sicknesses caused by disorder of purine biosynthesis and catabolism. Different matrices including metal nanoparticles, polymers, metal oxide thin films etc. have been utilized to immobilize uricase to design a uric acid biosensor. Among them, we used some Metal oxide semiconductor like ZnO, NiO and SnO2 for modelling uric acid-based bio-sensor. The figure 12 shows the plot between analyte concentration of uric acid for various materials and current range. It is figure from the figure that the maximum value for reaches up to only 1.5 μA and the linear concentration range is between 0.1 to 2.0 mg/dl which is very low when it is compared with TiO2 coated pillar curved layer.

![Fig.13 Plot between UA concentrations Vs Current for SnO2, ZnO and NiO coated layer](image)

**Fig.13 Plot between UA concentrations Vs Current for SnO2, ZnO and NiO coated layer**

### 4. CONCLUSION

Design and model of biosensor based on TiO2 material were performed using finite element analysis which was solver software package via simulator COMSOL Multiphysics. The biosensor module was a useful tool used to characterize the thermodynamics and kinetics interaction of bio-molecules. In this article, a Multiphysics computational model has been developed to study the bio-molecular detection process. Biosensor design in COMSOL Multiphysics has becoming the most powerful tool to quantify, analyze and selection of suitable matrix for the uric acid bio-sensors. TiO2 based biosensor is modelled and successfully studied for sensitivity and uric acid concentration analysis in blood samples for the application of arthritis disease diagnosis. Additionally, comparison between various metal oxide semiconductors as a sensing matrix has also been made. Among various materials used as a matrix to detect uric acid, TiO2 attains more sensitivity, lower detection limit and linearity in the range between 0.1 to 5 mg/dl. Since the selection of suitable materials has been made by using COMSOL Multiphysics, it will be more useful for the selection of biosensing materials to fabricate a bio-device in the future.

### 5. REFERENCES


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