Sudan University of Science And Technology

College of Engineering

Biomedical Engineering Department

Design of Biosensor using COMSOL Multiphysics

Submitted by:

Israa Isahge Gadora Mohammed

Kholod Hajo Hassan Ibrahiem

Nosiba Khider Alrofai Ali

Supervisor:

Dr. Fragoon Mohamed Ahmed

Thesis submitted in partial fulfillment for the degree of B.Sc. in Biomedical Engineering

October 2016

الآية القرآنية

قال الله تعالى :

(شَهِدَ اللَّهُ أَنَّهُ لَا إِلَهَ إِلاَّ هُوَ وَالْمَلائِكَةُ وَأُوْلُو العِلْمِ قَائِمًا بِالْقِسْطِ لَا إِلَهَ إِلاَّ هُوَ العَزِيزُ الحَكِيمُ)

سورة آل عمران: الآية .[18]

صدق الله العظيم

Dedication

To our beloved parents

Who wait so long to see successful project carried

their daughter's names

To our family and friends

Who stand with us in good and bad

To our teacher's

For their support and encouragement

Acknowledgement

Our prays and Thanks should be first and last to ALLAH, the almighty most gracious and most merciful who enabled us to conduct the project by the grace of him, giving us the confidence and patience to accomplish this work.

All gratitude and respect to our supervisor Dr.Fragoon Mohammed for his supervision and constant support to help us to bring up this work and all teachers and staff of biomedical engineering department .

Our sincere thanks go to our family and friends for their continuous support.

We are indebted to our wonderful mothers and fathers for their patience, encouragement and moral support during this project.

Table of Contents

CHAPTER THREE: Background Studies

CHAPTER FOUR: Methodology

CHAPTER FIVE: Results and Discussion

List of Tables

List of Figures

List of Abbreviations and Symbols

COMSOL	Computer solution
GNPs	Gold Nanoparticles
Nm	Nanometer
PH	Power of Hydrogen
Au NPs	Gold Nanoparticles
SPR	Surface Plasmon Resonance
HAuCl	Aqueous gold Nanocage
NPs	NanoParticles
ESM	Egg shell membrane
TiO2	Titanium dioxide
IUPAC	International Union of Pure and Applied Chemistry
FET	Field effect transistors
ENFET	Enzyme sensitized field effect transistors
ISE	Ion-Selective Electrodes
ISFET	Ion-Sensitive Field Effect Transistors
BAW	Bulk acoustic wave
SAW	Surface acoustic wave
LFIA	Lateral Flow Immunoassay
ICT	Immunochromatographic
NALFIA	Nucleic Acid Lateral Flow Immunoassay
LED	Laser or Light-Emitting Diode
FEMLAB	Finite Element Analysis
PDEs	Partial Differential Equations
CNTs	Carbon Nanotubes
AFM	Atomic Force Microscope
SEM	Scanning Electron Microscope

LFBs	Lateral Flow Biosensors
EDX	Energy Dispersive X-ray spectroscopy
XRD	X-ray Diffractometer
UV-VIS	Ultra Violet/visible spectroscopy
FTIR	Fourier Transforms Infrared spectroscopy
LF	Lateral flow
EKF	Extend Kalman Filter
IDEs	Interdigitated Electrodes
SMA	Steric Mass Action Approximation
P	Analyte molecules
S	Surface sites
PS	Adsorbed analyte
QS	Quenched state
Cp	The species concentration
Cps	Concentration of surface adsorbed species
DP	The diffusion coefficient
U	The velocity vector
E	Refractive index
Er	Relative permittivity
k0	The free space wavenumber
δ	Skin depth
$\gamma 0$	The initial site density

Abstract

Lateral flow biosensors (LFBs) provide advantages in low cost, simplicity, rapidity, stability and portability thus making LFBs popular in biomedical, agriculture, food and environmental sciences. Currently, Computer simulation has become an essential part of biosensor design .In the past two decades, COMSOL Multiphysics Software Package have emerged as a powerful tool for simulation, particularly in Nanotechnology and most importantly in biomedical application and various application involving fluid and solid interactions. Compared with conventional component or system design, distinctive advantages of using COMSOL software for design include easy assessing to the significant parameters in various levels of design, higher throughput, process monitoring with lower cost and less time consuming.

The research is Firstly focused on simulation model of biosensor based on gold nanoparticles(GNPs) designed by using Software Package (COMSOL Multiphysics), the magnitude of the laminar velocity field in the flow cell , concentration distribution in the analyte stream and surface coverage of adsorbed species and Average fractional surface coverage of adsorbed analyte were discussed from the model. Secondly the GNPs is modeled in Multiphysics then the far-field radiation pattern and the heat losses in gold nanoparticles were studied .Finally the protein adsorption is modeled in COMSOL and the concentrations of the reacting species change with the time, behavior of protein B after 5 sec and 30 sec and the velocity field were discussed and couples of suggestion are given in order to functionalize GNPs and to increase the accuracy of the biosensor design, It was obtained acceptable results.

مستخلص

يتميز المحساس الحيوي بقلة التكلفة ،البساطة ،الاستقرارية ،السرعة والقابلية للنقل مما يجعله شائع الاستخدام في كثير من المجالات مثل الطب ،الصناعة وعلوم البيئة . حاليا اصبحت المحاكاة بواسطه الكمبيوتر جزء اساسي في تصميم المحساس البيولوجي . في العشر سنوات الاخيرة اصبح استخدام البرنامج الحاسوبي (كومزول) اداة فعالة في المحاكاة خاصة في علوم النانو تكنولوجي والتطبيقات الطبية وكثير من المجالات الاخرى التي تتضمن تفاعلات المواد. ويتميز استخدام برنامج الكومزول في المحاكاة والتصميم مقارنه بالبرامج الاخرى انه فعال في مراقبة ونقل البيانات باقل تكلفه واقل استهلاك للزمن. في هذا البحث تم التركيز على استخدام جزئيات الذهب النانوية في تصميم المحساس البيولوجي ،وتم استخدام برنامج الكومزول كأداة مساعده في عملية التصميم باقل تكلفة واستهلاك للوقت.

في هذا البحث أولا تم التركيز علي نموذج المحاكاة للمحساس البيولوجي اعتمادا علي جزيئات الذهب النانوية والذي صمم باستخدام برنامج المحاكاة(كومزول) وتمت دراسة قيمة السرعة في خلايا التدفق وتوزيع التركيز في مجري العينات وأيضا متوسط الاحتكاك السطحي للعينات الممتصة . ثانيا تمت نمذجة جزيئات الذهب النانوية وتمت دراسة نمط المجال الاشعاعي وفقدان الحرارة في جزيئات الذهب النانوية . بالإضافة لذلك تمت نمذجة الامتصاص الكيميائي للبروتين ودراسة تراكيز العينات المتفاعلة كدالة متغيرة في الزمن وسلوك البروتين بعد خمس ثوان وايضا بعد ثلاثون ثانية ومجال السرعة .وتم التحصل علي نتائج مقبولة وفي النهاية تم وضع عدد من الاقتراحات لزيادة الدقة في تصميم المحساس البيولوجي .

CHAPTER ONE

Introduction

1.1 Project Overview :

The term “biosensor” is very broad and is used with various different meanings. In the most general of terms, a biosensor is any biological entity capable of being used to identify (either qualitatively or quantitatively) a response to some environmental change[1].

From general point of view, a biosensor is a device which is able to detect certain compounds through an electrical or optical signal. These devices consist of basically two components: a transducer , and a biological element able to produce a specific reaction with the substance that it is required to be measured, which in turn should be able to generate a signal that can detected by the transducer.

A biosensor is the combination of a biological element (which is able to produce a perturbation) with a conventional transducer (which is able to generate a measurable signal). Enzymes, antibodies, tissue and microorganisms have principally been used as biological element, although DNA and cell receptors have found applications as well. Biosensor will revolutionize the way in which analytical information is retrieved. This will allow the detailed study and automatic control of certain processes, mainly in the fields of clinical analysis, fermentation, food technology and wastewater treatment. Each particular type of biosensor has to be evaluated in terms of its detection range, selectivity, reliability, shelf life, versatility, size and, for some application, biocompatibility, sterility and suitable packing is crucial. In the specialized literature, hundreds of biosensors have been described for the determination of very large number of analytes and properties [1] .

1.2 Problem Statement:

Biosensors were become used as experts in various fields especially in engineering and medicine, which need large number of trials to overcome the best result. The manufacture of biosensor need integrated laboratory with materials, structures and equipment and this insufficiency in the world. To avoid this problem the simulation is designed by used of COMSOL Multiphysics as tool to complete the design with approximate result.

1.3 Project Objectives:

1.3.1 general objective

Design of Biosensor using COMSOL Multiphysics as modelling tool.

1.3.2 Specific Objectives

1. Design biosensor based on nanotechnology with low cost to use in medical application by using plant seeds extract.
2. Model the biosensor as a software using COMSOL Multiphysics.
3. Introduce functional gold nanoparticles in the biosensor design.

1.4 Project Organization:

In this research, chapter two contains a theoretical background, while literature review is contains in chapter three, the methodology is explains in chapter four, next in chapter five results and discussion are explains, and finally chapter six includes conclusion and recommendation.

CHAPTER TWO

Theoretical Fundamentals

2.1Nanotechnology

Nanotechnology is the science that deals with matter at the scale of 1 billionth of a meter (i.e., 10^{-9} m = 1 nm), and is also the study of manipulating matter at the atomic and molecular scale[2]. Nanotechnology is an anticipated manufacturing technology that allows the long-established trend toward smaller, faster, cheaper materials and devices[3]

2.1.1 Nanoparticles:

Nanoparticles are those particles which have two or more than two dimensions and are in the size range of 1 – 100 nm. These particles have special and enhanced physical and chemical properties as compared to their bulk materials due to their large reactive and exposed surface area and quantum size effect as a result of specific electronic structures. These particles have been widely used in many fields such as electronics, photochemical, biomedicine and chemistry .Nanoparticles cover a broad area of interest including electronics, medicine, food industry, environmental applications and cosmetics. Furthermore due to the metallic properties these metal nanoparticles exhibit photoelectric effect which neutralizes the photo bleaching concerns related with the conventional fluorescent dyes. Surface modification of the nanomaterial's have strong effect on the interaction of these nanomaterial's with cells, in addition to this it also helps to convert toxic nanomaterial's to the less toxic or less toxic to more toxic nanomaterial's[4].

The transition from micro particles to nanoparticles can lead to a number of changes in physical properties. Two of the major factors in this

are the increase in the ratio of surface area to volume, and the size of the particle moving into the realm where quantum effects predominate.

The increase in the surface-area-to-volume ratio, which is a gradual progression as the particle gets smaller, leads to an increasing dominance of the behavior of atoms on the surface of a particle over that of those in the interior of the particle. This affects both the properties of the particle in isolation and its interaction with other materials. High surface area is a critical factor in the performance of catalysis and structures such as electrodes, allowing improvement in performance of such technologies as fuel cells and batteries. The large surface area of nanoparticles also results in a lot of interactions between the intermixed materials in nanocomposites, leading to special properties such as increased strength and/or increased chemical/heat resistance[3]

2.1.1.1Methods of Nanoparticles Synthesis

Various preparation techniques for nanoparticles (nanomaterial's) are summarized in Figure(2.1). Two approaches have been known in the preparation of ultrafine particles from ancient times which shown in Figure(2.2). The first is the breakdown (top-down) method by which an external force is applied to a solid that leads to its break-up into smaller particles. The second is the build-up (bottom-up) method that produces nanoparticles starting from atoms of gas or liquids based on atomic transformations molecular condensations.

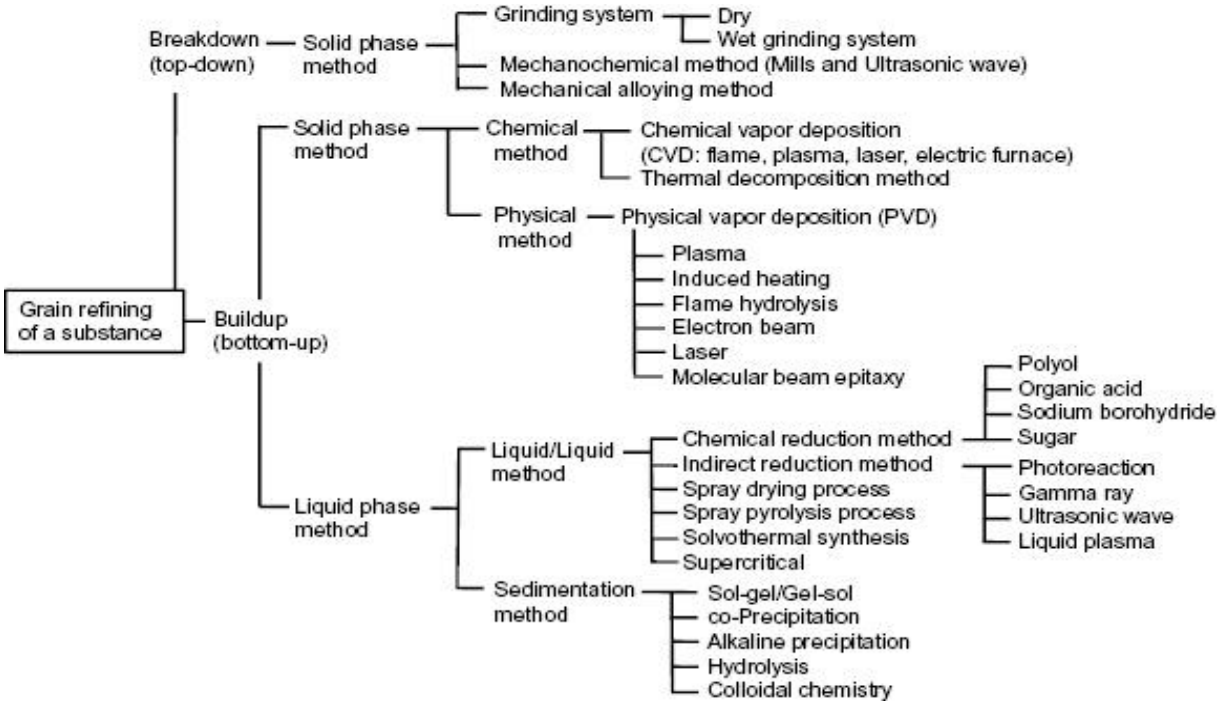
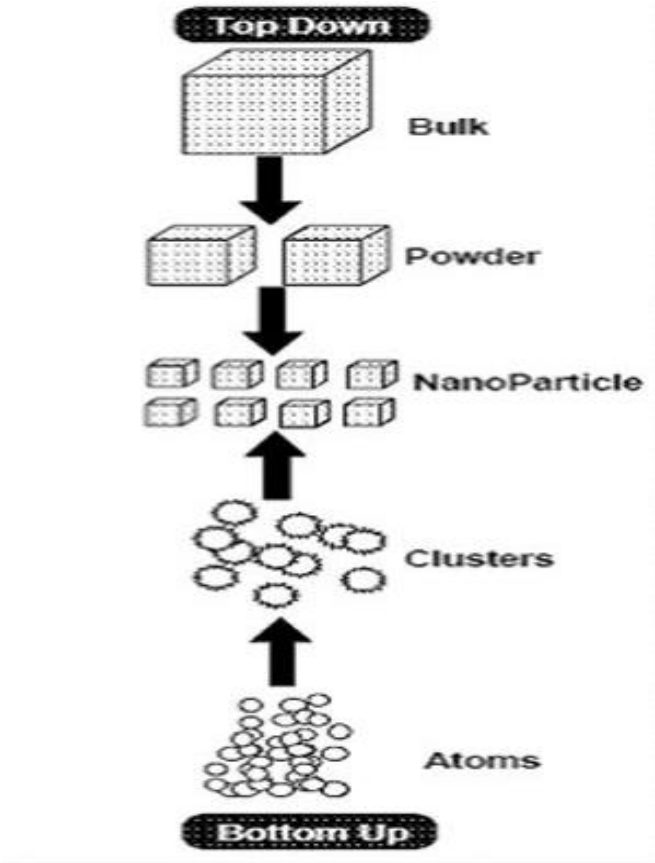


Figure (2.1): Typical synthetic methods for nanoparticles for the top-down and bottom-up approaches[2].



Figure(2.2): Main methods for the creation of nanoscale material [2] .

2.1.2Gold Nanoparticles:

Gold is a rare metallic element with a melting point of 1064°C and a boiling point of 280°C. Several properties of gold such as its excellent conductive properties and its inability to react with water or oxygen, have made it very useful to mankind over time[5],Gold nanoparticles (Au NPs) have larger surface area and higher dispersion owing to their very small size. Moreover, colloidal gold solutions are the subject of an increased interest for investigation of their cytotoxicity properties for applications in pharmacology, medicine, food industry, and water purification[6],Gold nanoparticles have advantages over other metal nanoparticles due to their biocompatibility and non-cytotoxicity. Gold is used internally in human from last 50 years due to their chemical inertness. The size of gold nanoparticles can be controlled during their synthesis and fictionalization with different groups. Gold nanoparticles accumulate in the tumor cells and show optical scattering. So these can act as the probe for the microscopic study of cancer cells. These are also used in chemotherapy and diagnosis of cancer cell. Gold nanoparticles have a great application not only in bio-sensing drugs but also in drug, gene and protein delivery. Gold nanoparticles occur in various sizes ranges from 2 to 100 nm. But 20 to 50 nm particles size range show the most efficient cellular uptake. Specific cell toxicity is shown by 40 to 50 nm particles[7].

Properties of gold nanoparticles are different from its bulk form because bulk gold is yellow solid and it is inert in nature while gold nanoparticles are wine red solution and are reported to be anti-oxidant. Inter particle interactions and assembly of gold nanoparticles networks play key role in the determination of properties of these nanoparticles. As shown in Figure(2.3) Gold nanoparticles exhibit various sizes ranging from 1 nm to 8 nm and they also exhibit different shapes such as spherical, sub-octahedral, octahedral, decahedral, icosahedra multiple

twined, multiple twined, irregular shape, tetrahedral, nano-triangles, nano-prisms, hexagonal platelets and nano-rods.

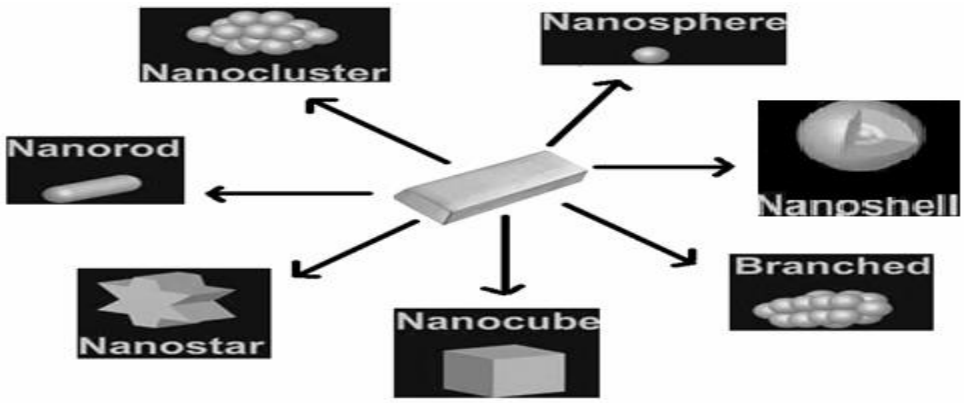


Figure (2.3): Various shapes of gold nanoparticles [4].

Among all these shapes triangular shaped nanoparticles show attractive optical properties as compared to the spherical shaped nanoparticles. Using of single active substance from plant extract in the synthesis of gold nanoparticles is an important biosynthesis technique to purify gold nanoparticles and to investigate about their medical uses. Gold nanoparticles have been widely used in the field of radiation medicine as radiation enhancer. Gold nanoparticles are widely used in biomedical science including tissue or tumor imaging, drug delivery, photo-thermal therapy and immunochromatographic identification of pathogens in clinical specimens due to the surface Plasmon resonance (SPR)[4]

2.1.2.1 Characteristics of Gold Nanoparticles:

- Gold nanoparticles are chemically inert.
- These have greater biological compatibility.
- Optical properties like Plasmon resonance are exhibited by gold nanoparticles.
- These exhibit versatility because of their ready fictionalization through thiol linkages.

●Gold nanoparticles provide microscopic probes for the study of the cancer cell.

●Gold nanoparticles accumulate in the cancerous cell and show the cytotoxic effect i.e. apoptosis or necrosis of the specific cell and cell specific receptor.

●These have high stability due to the gold-Sulphur bonds.

●Their photo physical properties can be exploited for drug release at remote place.

2.1.2.2 Types of Gold Nanoparticles:

● Gold Nanorods:

These are synthesized by template method. These are prepared by electrochemical deposition of gold within the pores of nonporous polycarbonate template membranes. Gold nanorods diameter is according to the diameter of pore of the template membrane.

● Gold Nanoshells:

Surface Plasmon resonance peaks (ranging from visible to near I.R. region) is used for the designing and fabrication of gold nanoshells. The core of gold nanoshells is made up of silica and outer surface is made up of gold. Gold controls the thickness of the shell.

● Gold Nanocage:

Through galvanic replacement reaction between truncated silver nanocubes and aqueous HAuCl gold Nanocage is synthesized.

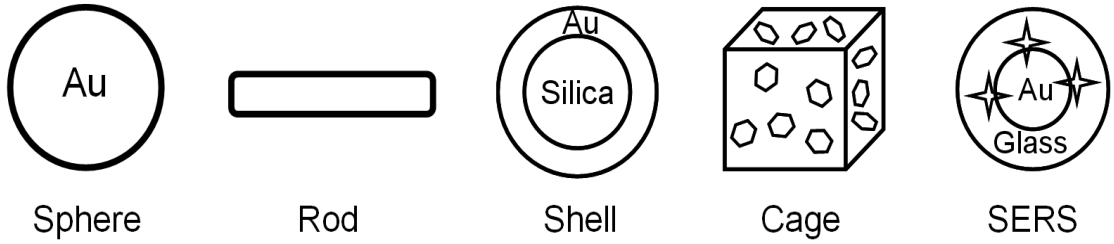
● SERS Nanoparticles:

SERS is an optical technique like fluorescence and chemiluminescence having better sensitivity, high levels of multiplexing, robustness and greater performance in blood and biological.

● Gold Nanosphere:

These are synthesized by reduction of an aqueous HAuCl by 4 using citrate as reducing agent. Through citrates / gold ratio the size of

nanospheres can be controlled. By two-phase ratio, the size of nanospheres can be affected by thiol / gold molar ratios .[7]



Figure(2.4): Shapes of Gold Nanoparticles[7] .

2.1.2.3 Synthesis Strategies

Various methods have been developed for the synthesis of gold nanoparticles and these methods follows the same rules as the preparation methods of other particles. General methods for the synthesis of gold nanoparticles include chemical, physical, and biological methods which are explained below[4].

- **Chemical methods**

Means use chemicals in synthesis of NPs, Most important synthesis agents are used Tri sodium citrate (Citrate synthesis) and sodium borate (Borate synthesis)[9].

- **Physical methods**

In this method nanoparticle is obtaining by breaking of metal parts into small particles. Have several methods such as: Laser ablation this technique was developed to produce Au nanoparticles in surfactants. A laser was used to irradiate the metal source to produce GNPs in solution [10-11].

- **Green methods(biological syntheses)**

Green chemistry synthesis routes are environment friendly and non-toxic, A facile green biosynthesis method for the preparation of gold

nanoparticles of size 25 + 7 nm was reported by using natural biomaterial egg shell membrane (ESM) [4] .

2.1.2.4 Application of gold nanoparticles:

●Gold Nanoparticles for the Delivery of Protein, Peptides and Nucleic Acid These can be employed as a carrier for delivery of peptides, proteins and nucleic acid like DNA due to their tunable size. Gold nanoparticles are functionalized with cationic4° ammonium group, can bind DNA plasmid through electrostatic interactions and protect DNA from enzymatic digestion Gold nanoparticles can work as a carrier for peptides and proteins, have reported that the cationic tetra alkyl ammonium functionalized GNP's recognize the cell surface receptor Gold nanoparticles act as a carrier of insulin. Chitosan coated gold nanoparticles easily adsorb insulin on their surface and the trans mucosal delivery of insulin is enhanced [7]**.**

●Coating: All the traditional coating technology can be used or modified into forms of Nano coating. Coating with nanoparticles has higher hardness, wear resistance and toughness. The nanoparticles were also applied on the surface coating, reducing the friction coefficient of the effect and forming self-lubrication material.

●Solar Cells: A major application of Au nanoparticles is Solar Cells, which include inorganic and organic devices. In organic devices, polymer film with semiconductor spots rather than the silicon crystal absorb the photon and transfer the light energy into electro energy. The solar cells with GNPs have a wider absorption wave length, making the organic photovoltaic device would absorb more light, resulting in a higher photovoltaic efficiency.

● Sensors: Metal nanoparticles have large specific surface areas, making them born sensors. For example, fixing the functional

nanoparticles on biological macromolecules, such as peptides, proteins, nucleic acids, can be used in biological signal detection, signal conversion and amplification of the sensor. It can be divided into acoustic, optical, magnetic and electrochemical species.

●Cancer Therapy: One of the important applications that nanotechnology is applying is on medicine and therapy, such as drug delivery, cancer cell diagnostics, and therapeutics. Images of cancer cell could be obtained by using co focal microscopy and simple dark-field microscopy through the scattering properties of gold nanosphere. While the absorption properties of gold nanoshells and solid gold nanosphere conjugated with anti-body has been demonstrated to selectively kill cancer cells, leaving the healthy cells unaffected, which is called the photo-thermal therapy.

●Catalyst: Au nanoparticles have great potential in catalyst because of their unusual and unexpected catalyst properties. It was found that GNPs supported on metal oxides, such as TiO2, exhibits an extraordinary high activity for low-temperature catalytic combustion, partial oxidation of hydrocarbons, hydrogenation of unsaturated hydrocarbons, and reduction of nitrogen oxides. GNPs with size of 1.4nm, which are derived from 55-atom gold clusters and supported on inert materials, are efficient catalysts for the selective oxidation of styrene by dioxygen. The catalyst effect of GNPs is so sensitive to the sizes that particles with diameters of 2nm and above are completely inactive [14].

● Electronics: nanoparticles are important components in the chip design.

● Photodynamic Therapy: When light is applied to a tumor containing gold nanoparticles, the particles rapidly heat up, and killing tumor cells in a treatment also known as hyperthermia therapy.

●Probes: Gold nanoparticles also scatter light and can produce an array of interesting colors under dark-field microscopy.

●Diagnostics : Gold nanoparticles are also used to detect biomarkers and common in lateral flow immunoassays [15].

2.2 Biosensor

The first demonstration of the biosensor concept, was given by the same Leland C. Clark Jr. in 1962 [8]. Since then various biosensors have been developed and applied in point-of-care testing, home diagnostics, environmental monitoring, research laboratories, process industry, security and biodefense and others [9]. In the medical field, a majority of biosensors are included in glucose meters; blood gas analyzers, electrolyte analyzers, metabolite analyzers and various drug detectors. Biosensors are widely applied in the above mentioned areas, because they are relatively cheap to construct, reliable and highly sensitive devices.

As shown in **Figure (2.5)** Biosensor consists of three major parts: sensitive biological element (bioreceptor), element that transforms the signal of interaction between substrate and biological element into another signal (transducer element) and associated electronic device which displays the result. As a result of this separation by parts, biosensors are classified according to bioreceptor and transducer elements[10] .

Three classes of bioreceptors are distinguished: Biocatalytic, bio affinity and hybrid receptors. Biocatalytic receptors are systems containing enzyme (single or multiple enzymes might be used), whole cells (bacteria, fungi, eukaryotic cells, yeast), cells organelles and tissues (plant or animal) [10][11].

International Union of Pure and Applied Chemistry **(IUPAC) defines biosensor as** "*A* device that uses specific biochemical reactions mediated by isolated enzymes, immune-

systems,tissues,organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals"[12]

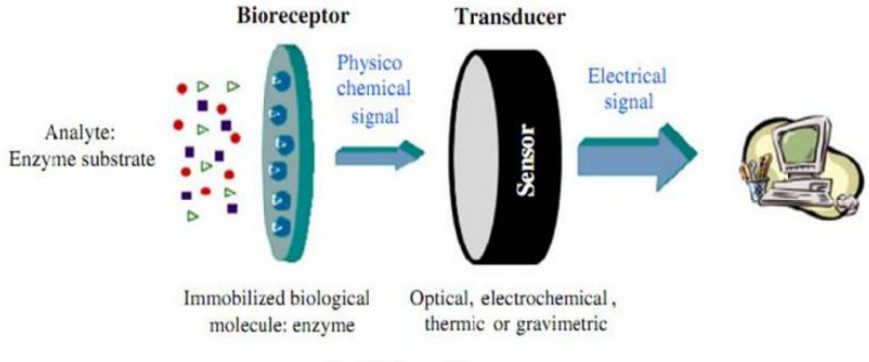


Figure (2.5): Scheme of biosensor[12].

2.2.1 Biosensor characteristics

Biosensors are usually characterized by the following parameters:

• **Sensitivity** is the response of the sensor to changes in analyte concentration.

• **Selectivity** is the ability of the sensor to respond only to the target analyte. That is, lack of response to other interfering chemicals is the desired feature.

• **Range** is the concentration range over which the sensitivity of the sensor is good. Sometimes this is called dynamic range or linearity.

• **Response time** is the time required for the sensor to indicate 63% of its final response due to a step change in analyte concentration.

• **Reproducibility** is the accuracy with which the sensor's output can be obtained.

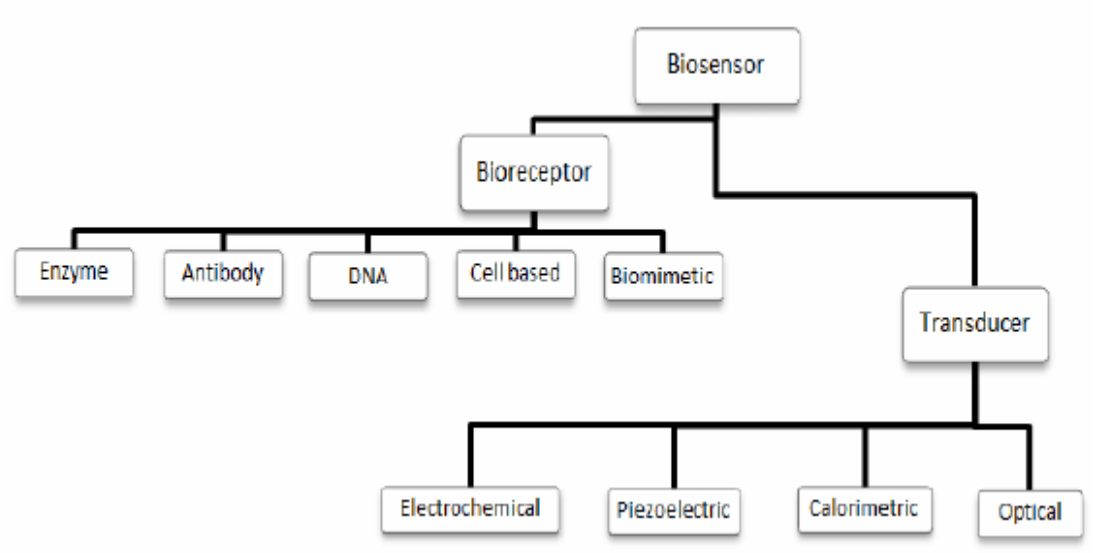
• **Detection limit** is the lowest concentration of the analyte to which there is a measurable response.

• **Life time** is the time period over which the sensor can be used without significant deterioration in performance characteristics.

• **Stability** characterizes the change in its baseline or sensitivity over a fixed period of time.[13]

2.2.2 Type of Biosensors

Biosensors can be broadly categorized as either transducer or bioreceptor which can bioaffinity devices or biocatalytic devices as shown in **Figure(2.6)**. In the bioaffinity devices, the analyte in the solution binds selectively to a receptor immobilized on the biosensor surface. In the biocatalytic devices, an enzyme immobilized on the biosensor surface catalysis the target substance.[13]



Figure(2.6):classification of biosensor [13].

2.2.2.1 Biosensors According to the transducer type

- **Electrochemical biosensors**

Electrochemical is very big field and there a lot of applications, currently applications electrochemical sensor by using COMSOL one of those used is applications Amperometric with potentiometric transducers are the largely usually used electrochemical transducers. as well In amperometric transducers, can the possible between the two electrodes is set and the current produced by the rust or decrease of electro active type

is measured and can related to the concentration of the study of attention. In other hand, platinum, silver, gold, or carbon, be able to are create electrodes of -based materials that are inert at the potentials at which the electrochemical reply takes place. Is very low current of the Potentiometric transducers measure the potential of electrochemical cells Field effect transistors (FET) are potentiometric devices based on the measurement of potential at an insulator– electrolyte interface. Also the metal gate of a FET can be substituted by an ion selective membrane to make a pH transducer (pH ISFET). They can show Enzymes on the face of such pH ISFET to create enzyme sensitized field effect transistors (ENFET). [14]

●Amperometric Biosensors:

In amperometry, the current produced by the oxidation or reduction of an electro active analyte species at an electrode surface is monitored under controlled potential conditions. The magnitude of the current is then related to the quantity of analyte present [15]. Clark oxygen electrodes perhaps represent the basis for the simplest forms of amperometry biosensors, where a current is produced in proportion to the oxygen concentration. This is measured by the reduction of oxygenate a platinum working electrode in reference to a Ag/AgCl reference electrode at a given potential. Typically, the current is measured at a constant potential and this is referred to as amperometry. If a current is measured during controlled variations of the potential, this is referred to as voltammetry.

●Potentiometric Biosensors

These biosensors are based on ion-selective electrodes (ISE) and ion-sensitive field effect transistors (ISFET). The primary outputting signal is possibly due to ions accumulated at the ion-selective membrane interface. Current flowing through the electrode is equal to or near zero. The

electrode follows the presence of the monitored ion resulting from the enzyme reaction. For example, glucose oxidize can be immobilized on a surface of the pH electrode. Glucose has only minimal influence on pH in the working medium; however, the enzymatically formed gluconate causes acidification. A biorecognition element is immobilized on the outer surface or captured inside the membrane.

●Optical Biosensors

Optical detection biosensors are the most diverse class of biosensors because they can be used for many different types of spectroscopy, such as absorption, fluorescence, phosphorescence, Raman, SERS, refraction, and dispersion spectrometry. In addition, these spectroscopic methods can all measure different properties, such as energy, polarization, amplitude, decay time, and/or phase. Amplitude is the most commonly measured as it can easily be correlated to the concentration of the analyte of interest [16]. In optical biosensors, the optical fibers allow detection of analyte on the basis of absorption, fluorescence or light scattering. Since they are non-electrical, optical biosensors have the advantages of lending themselves to in vivo applications and allowing multiple analyses to be detected by using different monitoring wavelengths.

●Acoustic Biosensors:

Electro acoustic devices used in biosensors are based on the detection of a change of mass density, elastic, viscoelastic, electric, or dielectric properties of a membrane made of chemically interactive materials in contact with a piezoelectric material. Bulk acoustic wave (BAW) and surface acoustic wave (SAW) propagation transducers are commonly used. In the first, a crystal resonator, usually quartz is connected to an amplifier to form an oscillator whose resonant frequency is a function of the properties of two membranes attached to it.

●Bimolecular sensor:

A biomolecule is very interested field part of bio sensing and nanotechnology and simulation COMSOL Multiphysics, is any molecule that is produced by an income organism, including many types of bimolecular large macromolecules such as proteins, DNA and nucleic acids, as well as small molecules such as metabolites, and natural products. In this review they present in Bimolecular detection has become very clear popularly employed in biomedical diagnostics, environmental monitor, forensic and civil defense. COMSOL Multiphysics simulation start in this field of Biosensors are chiefly interesting since they due can compared between high sensitivity of optoelectronic transducers and the high selectivity of bio molecule recognition, which successfully physical and chemical properties. In other hand, nanotechnology give high develop to offers unprecedented opportunities for make the design of highly sensitive and selective bio sensing devices. Can see In the Metal nanoparticles are particularly and use fulin this regard due to their different properties.[14]

2.2.3 Biosensing Techniques

Biosensors can be classified either by the type of biological signaling mechanism they utilize or by the type of signal transduction they employ. Transduction can be accomplished via a great variety of methods. Most forms of transduction can be categorized in one of three main classes. These classes are:

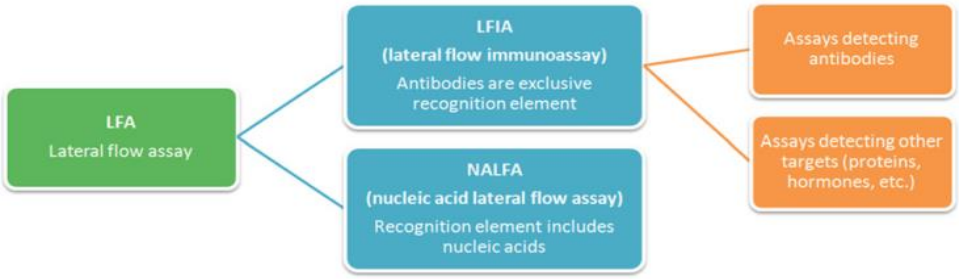
1) Electrochemical detection methods.
2) Optical detection methods.
3) Mass detection methods.

However, new types of transducers are constantly being developed for use in biosensors. Each of these three main classes contains many

different subclasses, creating a nearly infinite number of possible transduction methods or combination of methods.

2.2.4 Overall Design

The type of biosensor which used were immunochromatographic test strip, also known as lateral flow immunoassay (LFIA), A typical biosensor is composed of a reaction membrane, usually made out of nitrocellulose, a sample pad, a conjugate pad, and an absorbent pad. The conjugate pad, commonly made out of glass fiber filter, paper filters, and surface-treated (hydrophilic) propylene filters, is used to store and deliver the detector agent, which are dye encapsulating liposomes in this case. The absorbent pad, which is placed at the end of the test strip, serves as the sink for the sample as it migrates through the strip. The absorbent pad is often made out of cellulosic paper. It works to enhance the assay sensitivity by increasing the total amount of volume of sample that can be accommodated on the membrane. Lastly, the sample pad, which will be placed at the beginning of the test strip, acts as a filtration device by removing undesirable fractions of the liquid sample. It also serves to absorb the sample and provide a uniform flow on the test strip. For high viscosity and high concentration of particles in fluid, such as whole blood samples, special blood separation filters should be used.



Figure(2.7): Classification of lateral flow assays [17] .

2.2.5 Principle of the lateral flow immunoassay

The principle behind the LFA is simple: a liquid sample (or its extract) containing the analytes of interest moves with- out the assistance of external forces (capillary action) through various zones of polymeric strips, on which molecules that can interact with the analyte are attached. Atypical lateral flow test strip consists of over- lapping membranes that are mounted on a backing card for better stability and handling. the sample is applied at one end of the strip, on the adsorbent sample pad, which is impregnated with buffer salts and surfactants that make the sample suitable for interaction with the detection system. The sample pad ensures that the analyte present in the sample will be capable of binding to the capture reagents of conjugates and on the membrane. The treated sample migrates through the conjugate release pad, which contains antibodies that are specific to the target analyte and are conjugated to colored or fluorescent particles –most commonly colloidal gold and latex microspheres. The sample, together with the conjugated antibody bound to the target analyte, migrates along the strip into the detection zone. This is a porous membrane (usually composed of nitrocellulose) with specific biological components (mostly antibodies or antigens) immobilized in lines. Their role is to react with the analyte bound to the conjugated antibody. Recognition of the sample analyte results in an appropriate response on the test line, while a response on the control line indicates the proper liquid flow through the strip. The read-out, represented by the lines appearing with different intensities, can be assessed by eye or using a dedicated reader. In order to test multiple analytes simultaneously under the same conditions, additional test lines of antibodies specific to different analytes can be immobilized in an array format ,The principle and construction of lateral flow assay is presented in **Figure (2.8)** [17] .

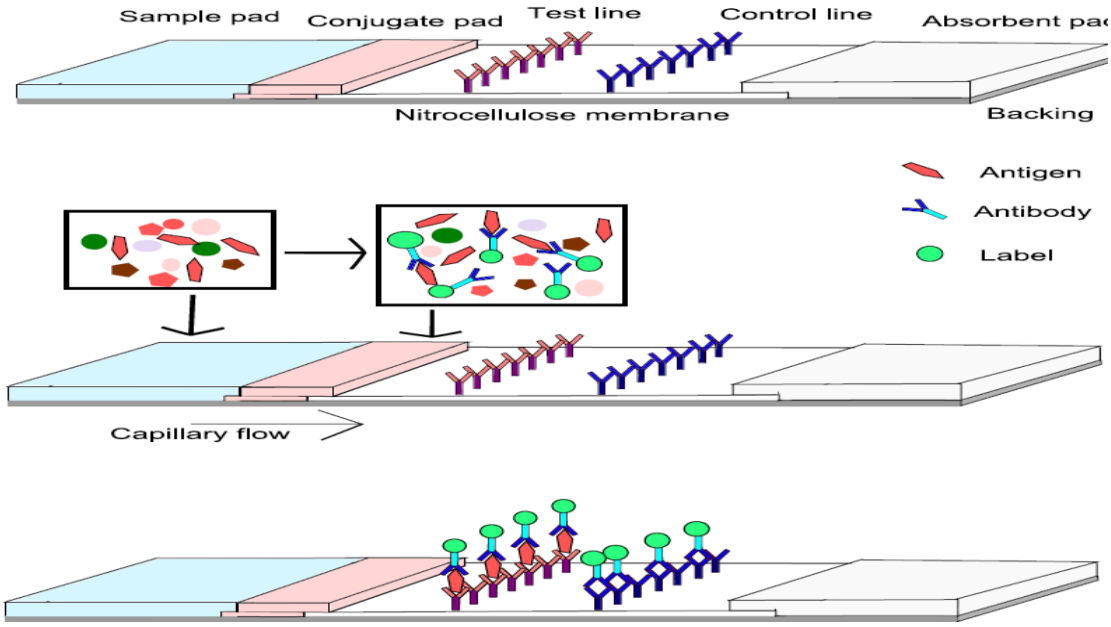


Figure (2.8): the principle of lateral flow strip presented with sandwich assay.

2.2.6 Detection methods

Since the LFIA is an antibody-based technique, specificity and sensitivity may be affected by other chemicals with similar structures, leading to false positive results. The sensitivity of assays is limited by the Kd (dissociation constant) of the antibody–antigen conjugate and by the colorimetric read-out. In order to overcome these limitations, both readers and novel biochemical techniques have been developed to improve product quality and customer convenience. The selection of a detection system is mainly determined by the label employed in the analysis. Fluorescent dyes or paramagnetic particles cannot be detected directly by the naked eye and require dedicated readers for quantitative analysis (Table 2.1).Moreover, automated detection methods provide advantages over manual imaging and processing in terms of time consumption, interpretation of results and adjustment of variables[17].

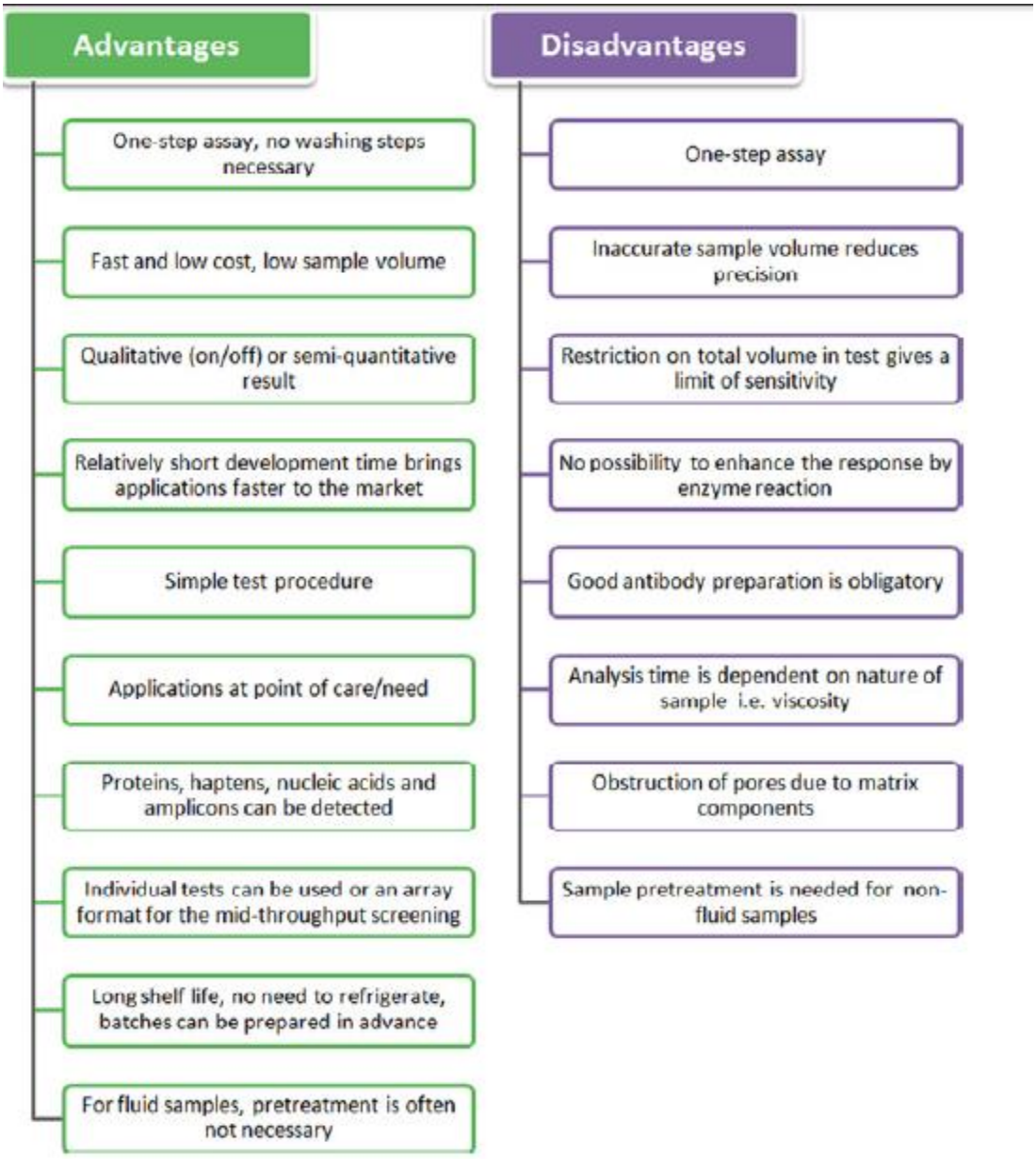
Table(2.1): The most commonly used detection methods employed in lateral flow assays[17].

Labels \ Results	Quantitative	Semi-quantitative	Qualitative
Colour labels e.g. gold nanoparticles, coloured latex	Optical strip readers or camera (with imaging software) for measurement of the intensity of colours produced at test and control line	Visual inspection of ladder bar, where the number of coloured lines is an indication of analyte concentration	Visual inspection of line colours
Fluorescent labels e.g. quantum dots, ruthenium complexes	Fluorescent strip reader, recording fluorescence intensity		
Other labels e.g. paramagnetic labels, enzyme labels, carbon nanoparticles	Magnetic strip readers; Electrochemical detectors; Chemiluminescence readers		

2.2.7Advantages and disadvantages of LFAs

Many LFIAs are designed for use at point-of-care/need, providing cheap, rapid and easy tests desirable in many industries. However, regulatory bodies often require confirmation of results using an independent method. Therefore, LFIA are only suitable for primary screening at point-of-care/need. Because of their long shelf life and the fact that refrigeration is not required for storage, these tests are very well adapted for use in developing countries. As the visual result is usually clear and easily distinguished, no additional specific equipment was needed[17].

As shown in **Figure(2.9)** Advantages and disadvantages of the lateral flow assay was presented.



Figure(2.9) Advantages and disadvantages of the lateral flow assay [17].

2.2.8 New strategies in LFAs

In recent years, the major advances in LFA development have included novel signal-amplification strategies, applications of new labels, improved quantification systems and simultaneous detection. Some of the new strategies used to enhance the signal from the colloidal gold nanoparticles (GNPs) have adopted silver enhancement technology or combinations of GNPs with an enzyme (such as horseradish peroxidase),which results in catalytic amplification of the signal [18]. To

improve the detection sensitivity, novel reagents have been identified, including magnetic particles such as Nano-gold microspheres, or immune-nanoparticles, which reduce the detection limits to at least 0.1 ng/ml . Another way to increase assay sensitivity is the implementation of a suitable quantity system such as a thermal contrast, laser or light-emitting diode (LED), which can result in signal amplification up to 1000-fold . Some successful developments of simultaneous detection techniques have been described. These include a combination of colloidal gold nanoparticles and oligonucleotides for the simultaneous detection of antigens and antibodies and the use of two conjugate pads for the simultaneous detection of two proteins .Moreover, combinations of LFAs with computational methods have led to the first example of combinations with electronic logic gates such as 'OR' and 'AND', providing a novel logic-sensing platform[19]-[17].

2.3 COMSOL Multiphysics

2.3.1History

The COMSOL Group was founded by Mr. Svante Littmarck and Mr. Farhad [20] in Sweden in 1986. It has now grown to United Kingdom, U.S.A, Finland and so on. Nowadays, The COMSOL Multiphysics software has been widespread used in various domains of science research and engineering calculation, for example, it was used in global numerical simulation. [20]–[21].COMSOL Multiphysics is a finite element analysis, solver and Simulation software package for solving various physics and engineering applications. The first version of COMSOL Multiphysics software was published in 1998 by COMSOL group and it was 33 named as Toolbox. At the beginning time, this software is only applied in the field of Structural Mechanics. ―The COMSOL Multiphysics simulation environment facilitates all steps in the

modeling process —defining your geometry, specifying your physics, meshing, solving and then post-processing your results [22].

2.3.2 Introduction

COMSOL Multiphysics is an integrated environment for solving system of time-dependent or stationary second order in space partial differential equations in one, two, and three dimensions. Moreover, such equations may be coupled in an almost arbitrary way. COMSOL Multiphysics provide sophisticated (and convenient) tools for geometric modeling. Therefore, for many standard problems, there exist predefined so-called application modes which act like templates in order to hide much of the complex details of modeling by equations. The application modes make use of the language used in the respective engineering discipline[23]**.**

COMSOL (formerly known as FEMLAB) is a finite element analysis and solver software package for various physics and engineering applications, especially coupled phenomena, or Multiphysics. It includes a complete environment for modeling any physical phenomenon that can be described using ordinary or PDEs. It has become the industry standard for Multiphysics modeling, research, design, and development (COMSOL 2008b; Zimmerman 2006). The software package supports nearly all platforms (e.g., Windows, Mac, Linux, and UNIX). COMSOL allows for building coupled systems of PDEs. The PDEs can be entered directly or using the so-called weak form. COMSOL also offers an extensive and well-managed interface to Math Works MATLAB and its toolboxes for a large variety of programming, preprocessing, and post processing possibilities[24].

COMSOL Multiphysics is a powerful interactive environment for modeling and solving all kinds of scientific and engineering problems

based on partial differential equations (PDEs). With this product you can easily extend conventional models for one type of physics into Multiphysics models that solve coupled physics phenomena— and do so simultaneously. Accessing this power does not require an in-depth knowledge of mathematics or numerical analysis. Thanks to the built-in physics modes it is possible to build models by defining the relevant physical quantities—such as material properties, loads, constraints, sources, and fluxes—rather than by defining the underlying equations.

2.3.3 PDE modes

COMSOL Multiphysics internally compiles a set of PDEs representing the entire model. Accessed the power of COMSOL Multiphysics as a standalone product through a flexible graphical user interface, or by script programming in the MATLAB language. As noted, the underlying mathematical structure in COMSOL Multiphysics is a system of partial differential equations. In addition to the physics mode and the modules, these provide three ways of describing PDEs through the following PDE modes:

- Coefficient form, suitable for linear or nearly linear models.
- General form, suitable for nonlinear models.
- Weak form, for models with PDEs on boundaries, edges, or points, or for models using terms with mixed space and time derivatives.

Using the application modes in COMSOL Multiphysics, that can perform various types of analysis including:

- Stationary and time-dependent analysis.
- Linear and nonlinear analysis.
- Eigen frequency and modal analysis.

To solve the PDEs, COMSOL Multiphysics uses the proven finite element method (FEM). The software runs the finite element analysis

together with adaptive meshing and error control using a variety of numerical solvers[25]

2.3.4 Work flow

To Set Up and Run a Simulation with COMSOL Multiphysics the next work flow must done as shown in **Figure (2.10)**:

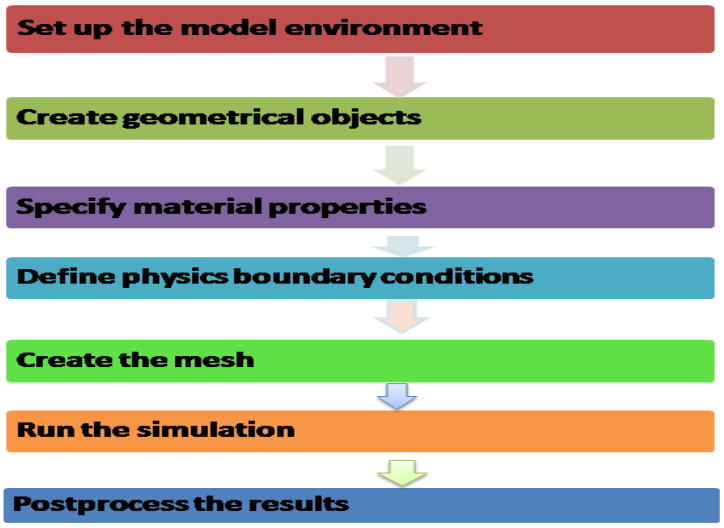


Figure (2.10):flow chart of COMSOL Multiphysics[26].

2.6.5 Application areas

There are several application-specific modules in COMSOL Multiphysics. The most common applications are [20]:

AC/DC Module, Acoustics Module, CAD Import Module, Chemical Engineering Module, Earth Science Module, Heat Transfer Module, Material Library. In this thesis, only Heat Transfer Module will be introduced and used in order to solve the relating problems of heat transfer.

2.6.6 Characteristics

The spread usage of COMSOL Multiphysics in various domains largely depends on its marked characteristics. These characteristics are [20]:

●It can be used to solve multi-physics problem.

●The user can specify their own Partial Differential Equations.

● Professional predefined modeling interfaces.

●CAD models can be made directly.

●CAD package can be added.

● Exuberance of simulation capability.[21]

One unique feature in COMSOL Multiphysics is something we refer to as extended Multiphysics, the use of coupling variables to connect PDE models in different geometries. This represents a step toward system-level modeling.

Another unique feature is the ability of COMSOL Multiphysics to mix domains of different space dimensions in the same problem. This flexibility not only simplifies modeling, it also can decrease execution time. In its base configuration, COMSOL Multiphysics offers modeling and analysis power for many application areas. For several of the key application areas we also provide optional modules. These application-specific modules use terminology and solution methods specific to the particular discipline, which simplifies creating and analyzing models.[25]

2.6.7 Application Modes in COMSOL Multiphysics

● The physics mode

Use the physics modes to instantly access convenient templates for specific application areas. Here can specify physical properties for models in fields such as acoustics, diffusion, or electromagnetic.

●The deformed mesh application modes

These application modes provide support for applications with moving boundaries using the Moving Mesh (ALE) application mode and for parameterized geometries in 2D.

•The optimization and sensitivity analysis application modes

The Sensitivity Analysis application mode adds sensitivity analysis to any type of Multiphysics model. The Optimization application mode provides functionality for combining Multiphysics modeling with optimization (for example, topology optimization and inverse modeling).

The PDE modes

Turn to these modes to model directly with PDEs when there cannot find a suitable physics mode. With these modes when define the problem in terms of mathematical expressions and coefficients. COMSOL Multiphysics includes three PDE modes:

• The Coefficient form allowed solving linear or almost linear problems using PDEs and coefficients that often correspond directly to various physical properties.

• The General form provides a computational framework specialized for highly nonlinear problems. Consider using a weak form for these problems, too.

• The Weak form makes it possible to model a wider class of problems, for example models with mixed time and space derivatives, or models with phenomena on boundaries, edges, or points as described with PDEs. In terms of convergence rate, these modes also set a computational framework suited for all types of nonlinear problems.

2.6.8 Selecting an Application Mode

• Modeling using a single application mode

Most of the physics application modes contain stationary, Eigen value, and dynamic (time-dependent) analysis types. As already mentioned, these modes provide a modeling interface that lets performed modeling using material properties, boundary conditions, and initial conditions. Each of these modes comes with a template that automatically supplies

the appropriate underlying PDE. If cannot found a physics mode that matches a given problem, try one of the PDE modes, which allowed to define a custom model in general mathematical terms. Indeed, COMSOL Multiphysics can model virtually any scientific phenomena or engineering problem that originates from the laws of science.

- **Modeling Multiphysics or systems with several dependent variables**

When modeling a real-world system, you often need to include the interaction between different kinds of physics. For instance, the properties of an electronic component such as an inductor vary with temperature.[25]

2.7 Modelling of biosensor

2.7.1 Mathematical modelling

A mathematical model of a physical law is a description of that law in the language of mathematics. Such models make it possible to use mathematical methods to deduce results about the physical world that are not evident or have never been observed. Mathematical modelling is a technique which builds on a firm understanding of the basic terminology, notation, and methodology of mathematics. It involves the following steps. First, the problem or objective of the study must be stated in a way that reflects accurately the needs of the organization. The second step includes finding data relevant to the problem which can be applied to the model, and often includes the scaling of these measurements. This process often yields a more realistic model, the results of which are more easily comprehended. The third step in the modelling process is the development of a mathematical model that addresses the concerns of the organization. In developing the mathematical model, the primary goal is to provide a quantitative structure for analyzing a large group of possible

situations. Model formulation frequently includes the selection of the appropriate mathematical functions to explain the phenomenon. In the fourth step, the data collected at the second step are applied to the mathematical model to obtain quantitative results. Step five involves the interpretation of the analysis completed in the previous step. It is very important that the results are interpreted in a clear and comprehensible way. Next, the results of the analysis are verified as to their applicability to a wide range of possibilities for the organization. The ability of a model to predict accurately is fundamental to verification. If the model is verified as useful to the organization, then it will be implemented. After implementation, use of the model may lead to additional applications for similar models, adjustments and refinements of the model. Or eventual rejection of the model if it is found inapplicable to function.Mathematical models and the modelling process serve as learning aids by emphasizing the applied aspects of mathematical analysis.[13]

2.7.2 Computational modelling

The computational modelling is applied in various scientific areas, including more theoretical ones (alternating direction method for solving Poisson [27]. and parabolic equations [[28]- [29]] as well as for solving applied problems when modelling blood glucose dynamics , anisotropic media , moisture diffusion in wood [30], piezoelectric and ultrasound actuators , protein spot detection and others. Computational modelling is the only way to solve the problems presented by the mathematical models of the biosensors since the analytical solutions exist only at extreme set of parameter values[10]

CHAPTER THREE

Background Studies

3.1 Studies about Applications of Gold Nanoparticles

In 2013 in Meerut Institute of Engineering and Technology, Department of Pharmaceutical Technology, NH-58, Baghpat Crossing, Bypass Road, Meerut, U.P. 250005, India, Avnika Tomar and Garima Garg developed study about:

”Short Review on Application of Gold Nanoparticles”

Nanoparticles have several biomedical and industrial applications in diagnosis of disease, targeted chemotherapy and in drug delivery. Multifunctionality and sub Micronics size is the main characteristics of nanoparticles. Nanoparticles can be integrated with ligands, imaging labels, therapeutic agents and other functionalities for site specific drug delivery and cellular uptake. In the present review we are discussing the application and synthesis of gold nanoparticles which is the most studied among all metallo-nanoparticles. Various anticancer drugs are available but these are cause the necrosis of cancerous cell as well as normal cells. But gold nanoparticles cause the necrosis of only cancer cells. These are targeted drug delivery systems which are smaller than human cells so can easily penetrate the tumor and destroy the cancerous cell. Various anticancer drugs conjugated with gold nanoparticles result in increased efficiency of anticancer drug. Gold nanoparticles are beneficial for chemotherapy and also for diagnosis of cancer due to their photo physical property and optical property. Gold nanoparticles can be functionalized with protein, peptides and nucleic acid. So these have a great application not only in bio-sensing drugs but also in drug, gene and protein delivery [7].

3.2Studies about Design Biosensor Based on Nanotechnology

In 2006, Kannan Balasubramanian, Marko Burghard Biosensors they are developed study about:

“Biosensors based on carbon nanotubes”

Carbon nanotubes (CNTs) exhibit a unique combination of excellent mechanical, electrical and electrochemical properties, which has stimulated increasing interest in the application of CNTs as components in (bio) sensors. This review highlights various design methodologies for CNT-based biosensors and their employment for the detection of a number of biomolecules. In addition, recent developments in the fields of CNT-based chemiresistors and chemically sensitive field-effect transistors are presented. After a critical discussion of the factors that currently limit the practical use of CNT-based biosensors, the review concludes with an outline of potential future applications for CNTs in biology and medicine [31] .

In June 2009, Jonas Ljungblad, in Department of Physics, Chemistry and Biology developed thesis about:

“Antibody-conjugated Gold Nanoparticles integrated in a Fluorescence based Biochip "

Gold nanoparticles exhibit remarkable optical properties and could prove useful in sensitive biosensing applications. Upon illumination gold nanoparticles produce localized surface Plasmon, which influence nearby fluorophores and an enhancement in their fluorescence intensity can be observed. This property makes gold nanoparticles attractive for enhancing optical signals. In this project gold nanoparticles were functionalized with an antibody and immobilized to the surface of an existing biochip platform based on fluorescence. The aim was to investigate the possibility of obtaining an increased fluorescence signal from the gold nanoparticles. Two different conjugation procedures were

investigated, direct physisorption and covalent attachment of the antibodies to the particles. Activity of bound antibodies was confirmed in both cases. The on-chip fluorescence intensity produced by the different conjugates was monitored by use a specialized fluorescence reader designed for point-of-care use. AFM and SEM were used to determine the surface concentration of particles. A correlation between the produced fluorescence intensity and the surface concentration could be seen [32].

In 2014 in University of Science & Technology Beijing, China, University of South Florida, FL, USA and North Dakota State University, Fargo, ND, USA, Xuefei Gao1, Li-Ping Xu1, Surfing Zhou, Guodong Liu, Xueji Zhang, they developed study about:

"Recent Advances in Nanoparticles-based Lateral Flow Biosensors" Lateral flow biosensors (LFBs) provide advantages in low cost, simplicity, rapidity, stability and portability, thus making LFBs popular in biomedical, agriculture, food and environmental sciences. This article reviews recent advances of LFBs for bioassays, including the investigation of the improvements achieved by signal-amplification strategies, the application of new nanoparticle labels, novel quantitative system and simultaneous detection. This summarized the outstanding performances of LFBs such as high detection sensitivity, specificity, reproducibility and reliability[33].

In 2015 in Sudan university sciences and technology department of biomedical engineering, Eiman Mohamed developed research about: "Fabrication of an Immunochromatography Biosensor Using Green Synthesis Gold Nanoparticles"

This project synthesis GNPs useful for many applications then study properties of these particles as a models for rapid, simple, more sensitive and more specific detection method that was based on one step membrane based. Synthesis nontoxic and low cost gold nanoparticles using plant

seed extraction Characterize GNPs by TEM images, and different types of spectroscopes (UV-VIS, XRD, EDX, and FTIR) .The ecofriendly synthesized GNP by fenugreek and black seeds extract studied using spectrometry and imaging methods to determine the formation of gold nanoparticles, its size and shapes .the Uv-vis spectrometer peaks between 534-536 for both depending on extract volume. XRD peaks are found to be broad indicating the formation of nanoparticles. FTIR measurements were carried out to identify the possible biomolecules present in fenugreek seed extract which are responsible for the reduction of gold NPs. TEM image depicts the presence of spherical nanoparticles in black seed sample size range from 9nm to 29nm, for fenugreek seed GNPs presents in different shapes in same rang, when using 8ml extract the size increase [34].

3.3 Studies about Mathematical model

In 2003 in University of Pennsylvania, Shizhi Qian, Haim H. Bau, they developed study about:

"A mathematical model of lateral flow bioreactors applied to sandwich assays"

Lateral flow (LF) bio-detectors facilitate low-cost, rapid identification of various analytes at the point of care. The LF cell consists of a porous membrane containing immobilized ligands at various locations. Through the action of capillary forces, samples and reporter particles are transported to the ligands sites. The LF membrane is then scanned or probed, and the concentration of reporter particles is measured. A mathematical model for sandwich assays is constructed and used to study the performance of the LF device under various operating conditions. The model provides insights into certain experimental observations including the reduction in the level of the detected signal at high target analyte concentrations. Furthermore, the model can be used to

test rapidly and inexpensively various operating conditions, assist in the device's design, and optimize the performance of the LF device[35].

In 2011 in Nianyin Zeng, Zidong Wang, Yurong Li, Min Du and Xiaohui Liu, they developed study about:

"Inference of Nonlinear State-space Models for Sandwich-Type Lateral Flow Immunoassay Using Extended Kalman Filtering"

A mathematical model for sandwich-type lateral flow immunoassay is developed via short available time series. A nonlinear dynamic stochastic model is considered that consists of the biochemical reaction system equations and the observation equation. After specifying the model structure, we apply the extend Kalman filter (EKF) algorithm for identifying both the states and parameters of the nonlinear state-space model. It is shown that the EKF algorithm can accurately identify the parameters and also predict the system states in the nonlinear dynamic stochastic model through an iterative procedure by using a small number of observations. The identified mathematical model provides a powerful tool for testing the system hypotheses and also inspecting the effects from various design parameters in a both rapid and inexpensive way [36].

3.4Studies about Modelling Biosensor using COMSOL Multiphysics

In 2013 in University Malaysia Perlis, (UniMAP),Kangar, Perlis MalaysiaM,Wesam Al-Mufti,U,Hashim and Tijjani Adam they developed study about.

"Simulation of Nano lab on chip devices by using COMSOL Multiphysics"

A Simulation in engineering and science has become the back bone of analysis and characterization of semiconductor components, in particular, when developing new products or optimizing designs. Today a broad

spectrum of options for simulation is available; researchers use everything from basic programming languages to various high-level packages implementing advanced methods. Though each of these techniques has its own unique attributes, they all share a common concern. Hence, the paper present a COMSOL simulation on Nano lab on chip devices simulation the past and recent development nanostructures design and simulation for lab on chip application [14].

In 2015 in University of Alberta, Scott MacKay 1, Peter Hermansen, David Wishart and Jie Chen, developed study about :
"Simulations of Interdigitated Electrode Interactions with Gold Nanoparticles for Impedance-Based Biosensing Applications"

This paper, describe a point-of-care biosensor design. The uniqueness of our design is in its capability for detecting a wide variety of target biomolecules and the simplicity of nanoparticle enhanced electrical detection. The electrical properties of interdigitated electrodes (IDEs) and the mechanism for gold nanoparticle-enhanced impedance-based biosensor systems based on these electrodes are simulated using COMSOL Multiphysics software. Understanding these properties and how they can be affected is vital in designing effective biosensor devices. Simulations were used to show electrical screening develop over time for IDEs in a salt solution, as well as the electric field between individual digits of electrodes. Using these simulations, it was observed that gold nanoparticles bound closely to IDEs can lower the electric field magnitude between the digits of the electrode. The simulations are also shown to be a useful design tool in optimizing sensor function. Various different conditions, such as electrode dimensions and background ion concentrations, are shown to have a significant impact on the simulations. Conclusions: A method for simulating impedance-based IDE biosensor systems was developed using COMSOL Multiphysics software. These

simulations can be used to show the effects of ions in solution over time in the establishment of electric screening layers above electrodes as well as the electric fields between the digits of the electrodes. The effect of bound gold nanoparticles under different conditions was also simulated although smaller digits and interdigital gap spacing resulted in higher percent differences, the benefit of smaller dimensions diminishes as dimensions decrease. The size of the nanoparticles in the simulations did not greatly affect the results. Future work with these simulations will be focused on further optimization of conditions to maximize results and make the simulations more in line with real-world devices and comparisons between simulated and actual device results. These simulations can be used as a tool for designing effective biosensor devices. The validity and effectiveness of these simulations will be evaluated by comparison to actual results from fabricated devices as we [37].

CHAPTER FOUR

Methodology

In this chapter the methods used to design biosensor model as lateral flow immunoassay strip using COMSOL Multiphysics software is defined, as shown in **Figure (4.1)** the computational modelling of biosensor based on gold nanoparticles'(GNPs),and introduce functional GNPs in the biosensor model.

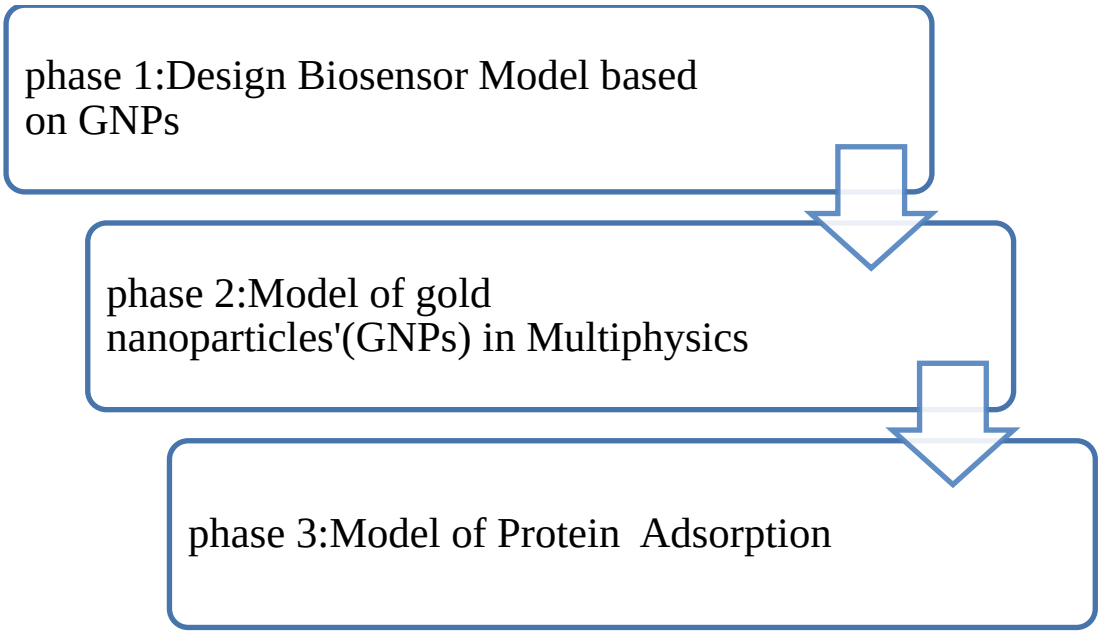


Figure (4.1): Methodology Block Diagram

4.1 Phase One:

4.1.1 Biosensor Design

A flow cell in a biosensor contains an array of micropillars used to detect biomolecules, for example antibodies in aqueous solutions. The pillars are coated with an active material that selectively adsorbs biomolecules in the sample stream and the gold nanoparticles(GNPs) were used as optically active material . These biomolecules then react on the surface. A signal proportional to the surface coverage can be detected

in a sensor. The geometry and operating conditions have impact on the signal strength and diffuseness which is visualized in plots. Also, manufacturing constraints, set by a minimum distance between pillars.

4.1.2 Input

Table(4.1) and Table(4.2) show the parameters and variables of biosensor model obtained from COMSOL Multiphysics which contain the abbrivation,expression,value and description of input .

Table (4.1): Parameter of Biosensor model.

Name	Expression	Value	Description
k_ads	1e-2[m/s]	0.01 m/s	Forward rate constant
k_des	0.5[mol/m^2/s]	0.5 mol/(m²·s)	Backward rate constant
D	5e-9[m^2/s]	5E−9 m²/s	Gas diffusivity
Kf	2e-7[mol/m^2/s]	2E−7 mol/(m²·s)	Forward rate constant
Kr	4e-8[mol/m^2/s]	4E−8 mol/(m²·s)	Reverse rate constant
u_in	2e-4[m/s]	2E−4 m/s	Inlet velocity
N_w	4	4	Number of pillars across
R_pillar	0.4[mm]	4E−4 m	Radius of pillar
R_c	6e-4[m]	6E−4 m	Radius of carve-out
d_c	1.5e-4[m]	1.5E−4 m	Cut depth of carving
x_c	R_pillar + R_c - d_c	8.5E−4 m	x-position of carving circle
R_c_1	6e-4[m]	6E−4 m	Radius of carve-out
d_c_1	1.5e-4[m]	1.5E−4 m	Cut depth of carving
x_c_1	R_pillar + R_c - d_c	8.5E−4 m	x-position of carving circle
W_tot	6.8e-3[m]	0.0068 m	Total width of pillar grid
L_tot	5.6e-3	0.0056	Total length of pillar grid (outer row)
d_wall	0.5e-4[m]	5E−5 m	Distance from pillar edge to cell side wall
d_z	(W_tot - 2*R_pillar)/(N_w - 1)	0.002 m	z-spacing between pillars

Name	Expression	Value	Description
d_x	(L_tot - 2*R_pillar)/(N_w - 1)	0.0016 m	x-spacing between pillars
W_box	12e-3[m]	0.012 m	Width of cell
D_box	1e-3[m]	0.001 m	Depth of cell
H_box	6.9e-3[m]	0.0069 m	Height of cell
d_pillar	sqrt(d_z^2 + d_x^2)/2 - 2*R_pillar	4.8062E−4 m	Current closest distance between two pillar edges
d_pillar_allowed	0.1e-3[m]	1E−4 m	Allowed minimum distance between two pillar edges
R_max_allowed	sqrt(d_z^2 + d_x^2)/4 - d_pillar_allowed/2	5.9031E−4 m	Allowed maximum pillar radius
c_00	400[mol/m^3]	400 mol/m³	Injection pulse amplitude
sol_tol	0.01	0.01	Relative tolerance of solvers
end_time	250	250	Simulation end time
d_time_value	0.5	0.5	Dimensionless time for concentration plot
time_value	35	35	Time for time dependent plots

Table (4.2): Variable of Biosensor model.

Name	Expression	Unit	Description
r_ads	(k_ads*c_p*sr.theta_free)	mol/(….	Adsorption rate
r_des	(k_des*sr.theta_i_cs_p)	mol/(….	Desorption rate
r_quench	(kf*sr.theta_i_cs_pkr*sr.theta_i_csQ	mol/(….	Quench rate
C0	C_00*gp1(t[1/s])	mol/m^3	Inlet concentration

4.1.3 Model Definition

Surface Reactions

Analyte molecules (*P*) can adsorb and desorb from surface sites (*S*) on the micropillars surfaces according to

$$P + S \underset{k_{des}}{\overset{k_{ads}}{\rightleftharpoons}} PS \quad (1)$$

The adsorbed analyte (*PS*) can transform into a quenched state (*QS*) that does not contribute to the sensor signal. The quenching reaction is reversible:

$$PS \underset{k_2}{\overset{k_1}{\rightleftharpoons}} QS \quad (2)$$

The rate of adsorption

$$r_{ads} = k_{ads} c_p \quad (3)$$

where *cp* is the concentration of *P* in the stream. The desorption rate is linear in the concentration of surface adsorbed species, *cPS*:

$$r_{des} = k_{des} c_{ps} \quad (4)$$

The rate of the reversible quenching reaction is given by :

$$r_{quench} = k_1 c_{ps} + k_2 c_{Qs} \quad (5)$$

Mass Transport in the Analyte Stream

The equations in the Transport of Diluted Species interface describe the transport of the species, *P*, in the analyte stream according to:

$$\frac{\partial c_p}{\partial t} + \nabla . \left(-D_p \nabla c_p\right) + u \, . \nabla c_p = 0 \quad (6)$$

Here, *DP* denotes the diffusion coefficient (SI unit: m2/s), *cP* denotes the species concentration (SI unit: mol/m3), and is **u** is the velocity vector (SI unit: m/s).

The injected sample concentration is given by the user and is 400 mol/m3as default during 2.5 ms. Due to the diffusive spreading just

before the inlet section, a smooth pulse enters the sensor, which is described by a Gaussian distribution at the flow cell inlet with a maximum concentration of 80 mol/m3 (at default input settings) and a standard deviation of 2.

The adsorption and desorption of analyte at the active pillar surfaces give rise to a net flux at the corresponding boundaries

$$N_p = -r_{ads} + r_{des} \quad (7)$$

The mass flux due to desorption is dependent upon the local concentration of adsorbed surface species and is hence coupled to the equations in the Surface Reactions, described next.

Mass Transport and Reactions on the Active Surfaces:

surface diffusion is ignored on the active surfaces. Therefore, using the reactions described by Equation 1, Equation 2, and Equation 3, the balance equations for the surface species *P* and *Q* will be:

$$\frac{dc_{s.p}}{dt} = r_{ads} - r_{des} - r_{quench} \quad (8)$$

$$\frac{dc_{s.Q}}{dt} = r_{quench} \quad (9)$$

The rate of adsorption depends on the concentration of the *P* species in the analyte stream and therefore the equations describing the surface reactions (above) are coupled to that of the free analyte flow, Equation 4.

Fluid Flow : The flow regime is laminar in the cell, The calculated flow field serves as input to the Equation 4, to describe the convective mass transport.

Figure (4.2)and Figure(4.3)show the 3-dimension biosensor design ,biosensor mesh respectively obtained from COMSOL Multiphysics.

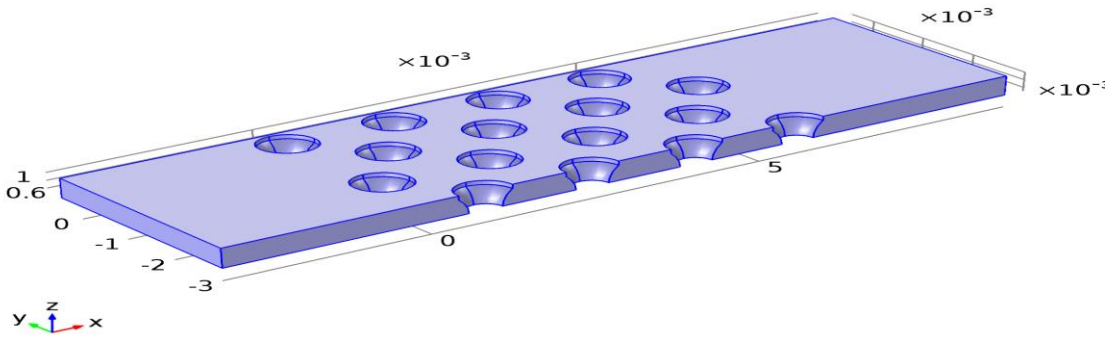


Figure (4.2): The 3-D Biosensor Design

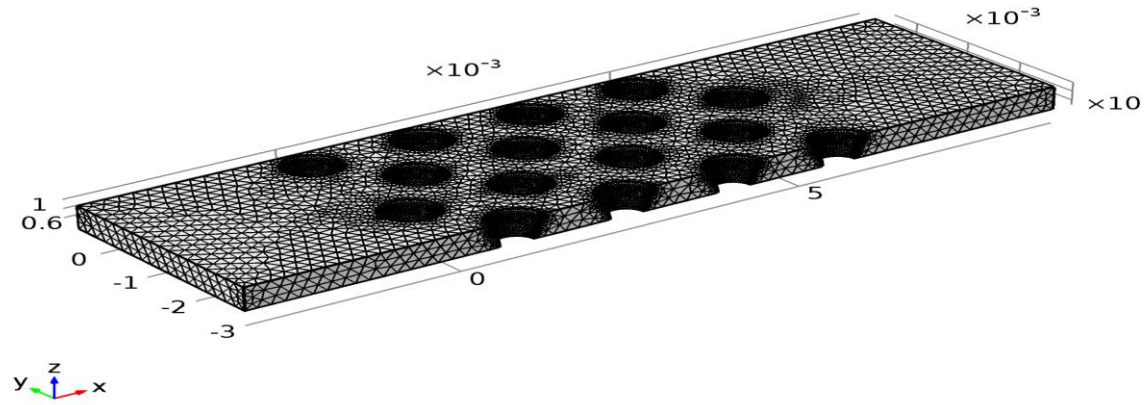


Figure (4.3): The Biosensor Mesh

4 .2 Phase Two:

4.2.1 Optical Scattering Off a Gold Nano-sphere

This model demonstrates the calculation of the scattering of a plane wave of light off of a gold nanoparticles. The scattering is computed for the optical frequency range, over which gold can be modeled as a material with negative complex-valued permittivity.

4.2.2 Model Definition

A gold sphere of radius r = 100 nm is illuminated by a plane wave, The free space wavelength range from 400 nm to 700 nm is simulated. As shown in **Figure (4.4)** The complex refractive index of gold is taken from

the Optical Materials Database, where interpolation functions for a large number of commonly used optical materials are found.

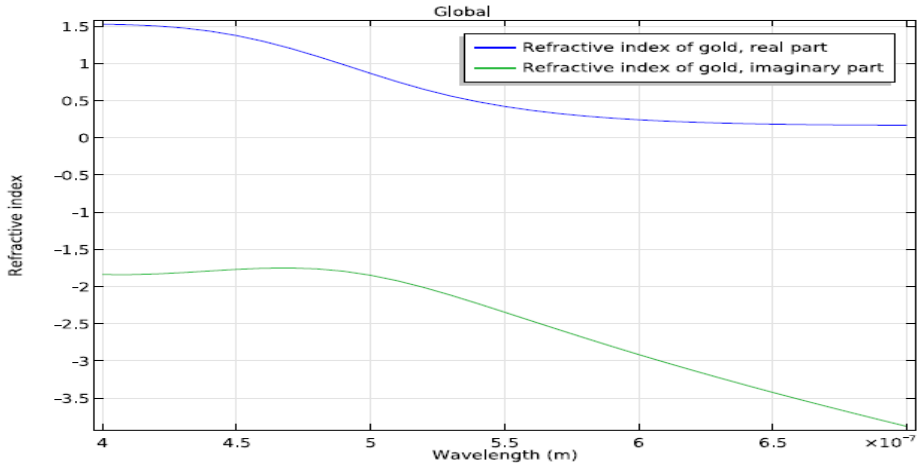


Figure (4.4): Refractive index of gold.

From the refractive index, the relative permittivity as shown in **Figure (4.5)** was found from the relation

$$\varepsilon_r = \varepsilon' - j\varepsilon'' = (n' - jn'')^2 \qquad (10)$$

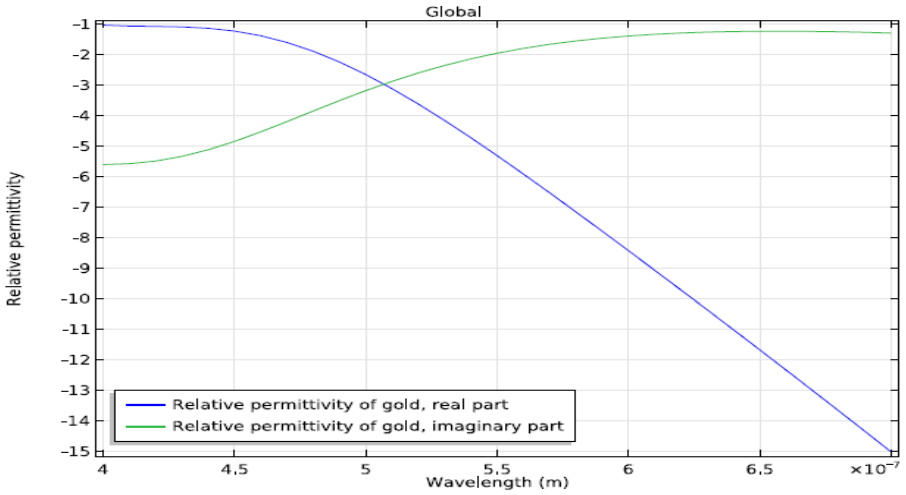


Figure (4.5): Relative permittivity of gold.

Over the wavelength range of interest, it is possible to compute the skin depth as shown in **Figure (4.6)** via next relation

$$\delta = \frac{1}{\mathrm{Re}\sqrt{-k_{0\varepsilon_r}^2}} \qquad (11)$$

where k0 is the free space wavenumber, and εr is the complex-valued relative permittivity.

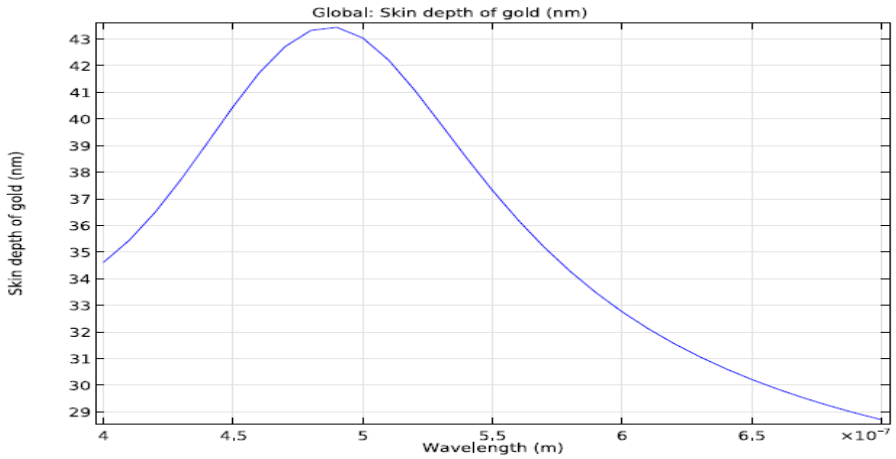


Figure (4.6): Skin depth of gold.

Table (4.1)and Table(4.2)show the parameters and variables of gold nanosphere model obtained from COMSOL Multiphysics which contain the abbrivation,expression,value and description of input .

Table (4.3): Parameter of GNPs model.

Name	Expression	Value	Description
r0	100[nm]	1E-7 m	Sphere radius
lda	400[nm]	4E-7 m	Wavelength
t_air	lda/2	2E-7 m	Thickness of air around S...
t_pml	lda/2	2E-7 m	Thickness of PML
h_max	lda/6	6.6667E-8 m	Maximum element size,air

Table (4.4): Variable of GNPs model.

Name	Expression	Unit	Description
l_gold	int_L(ewfd.Qrh)	W	Heat losses
n_gold	int_L(ewfd.nxxj*ewfd.kixx)/(pi*r 0^3/3)		Refractive index of gold
epsilon_gold	n_gold^2		Refractive permittivity of gold
deltaS_gold	1/real(sqrt(-(ewfd.k0*n_gold)^2))	m	Skin depth of gold

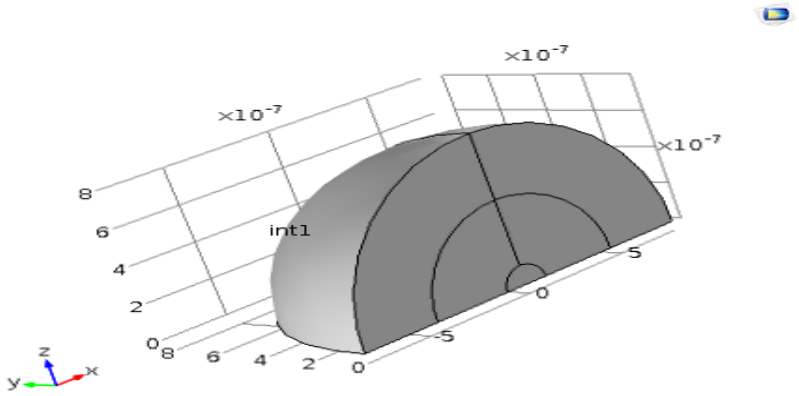


Figure (4.7): 3D model of GNPs

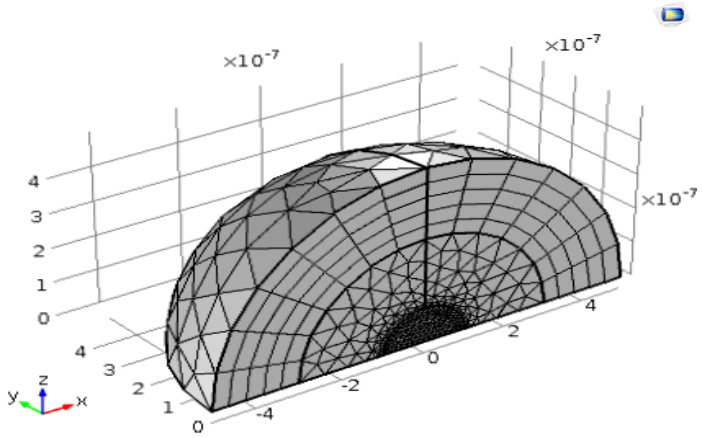


Figure (4.8): GNPs mesh.

4 .3 Phase Three:

4.3.1 Introduction Protein Ion-Exchange

The binding of proteins to ion exchangers can be described within the steric mass action approximation (SMA). This approach assumes that the adsorption of a protein can be considered as an exchange reaction of the protein with a given number of adsorbed ions. The fluid phase contains four components: two proteins, solvent, and one salt. The adsorption/ desorption kinetics is described by two equilibrium reactions where proteins displace ions adsorbed at the surface and vice versa.

The equilibrium describing the adsorption/desorption reactions is

$$S(ads)+P \Leftrightarrow P(ads)+S \qquad (12)$$

Here, S denotes the salt ion, P stands for either protein A and B. Once P is adsorbed, P(ads), salt ions are displaced, reducing the concentration of adsorbed salt ions, S(ads).

4.3.2 Model Definition

The system is modeled both in 0D and in 3D. The former model setup is adequate to investigate the kinetics of the equilibrium reactions . The latter makes it possible to study the surface of the ion-exchange beads that make up the porous structure of the ion-exchange mass.The reaction kinetics are described by Equation 13 and 14 for proteins A and B are entered directly into the interface as equilibrium surface reactions. The equilibrium constants for reaction 1, adsorption of A, is $K1eq = 2$ and for reaction 2, adsorption of B, is $K2eq = 5$. These are entered as well, relating the concentrations as followed

$$K_1^{eq} = \frac{c_s c_{A(ads)}}{c_A c_{s(ads)}} \tag{13}$$

$$K_2^{eq} = \frac{c_s\, c_{B(ads)}}{c_B c_{s(ads)}} \tag{14}$$

In order to compute the concentrations, both protein surface concentrations need to be set as dependent in the Equilibrium Species Vector section. The proteins enter the biosensor with a Feed Inlet with concentrations that vary in accordance to a 10 s Gaussian pulse with a maximum of 0.05 mol/m3. The outlet flow rate regulates so that the volume of the biosensor is constant. Initially, no protein is available in the column and the ion-exchange mass is set to be completely adsorbed with salt, i.e. the initial site density, $\gamma 0$, is equal to the initial surface concentration of S, S(ads).

The reaction kinetics are taken directly from the 0D model with the Generate Space-Dependent Model feature and are collected in a Chemistry interface that also supplies computed diffusion coefficients

and fluid density for the 3D setup. The mass balances describing the species mass transport in the pores of the column are set up with the Transport of Diluted Species interface with diffusion and convection accounted for

$$\frac{\partial c_i}{\partial t} + \nabla.(-D_i \nabla c_i) + u \,.\nabla c_i = 0 \qquad (15)$$

On the right hand side of Equation 4 no reaction source is present for the bulk. However, the surface of the ion-exchange beads produces a reaction source that needs to be coupled to this equation. This is simply done with a Surface Reaction interface. Such an interface is always automatically generated with the use of the Generate Space-Dependent Model feature if surface reactions are present. The 3D model also computes the convective velocity, u, with a Free and Porous Media Flow interface. The velocity is based on the assumption that the velocity, U, within the biosensor is 0.1 mm/s and that the inlet is open to the surroundings, i.e. exposed to the atmospheric pressure.

Table (4.5):show the parameters of protein model obtained from COMSOL Multiphysics which contain the abbrivation,expression,value and description of input .

Table (4.5): Parameter of protein model.

Name	**Expression**	**Value**	**Description**
Arsurf	$2e^4$[m^2]	$20000m^2$	Surface reaction area
vfp	1[m^3]/s]	$1m^3/s$	Volumetric feed to the inlet
Keq01	2	2	Equilibrium constant reaction
Keq02	5	5	Equilibrium constant reaction
CAmax_in...	5e-2[mol/m^3]	$0.05mol/m^3$	Maximum concentration of A
CBmax_in…	5e-2[mol/m^3]	$0.05mol/m^3$	Maximum concentration of B
CS0surf	0.99e-5[mol/m^2]	$9.9E\text{-}6mol/m^2$	Initial surface concentration S
CH2O	55600[mol/m^3]	$55600mol/m^3$	Concentration solvent (W..

G0	1e-5[mol/m^2]	1E-5mol/m^2	Initial site density of react…
MA	0.2[kg/mol]	0.2kg/mol	Molar mass of protein A
MB	0.15[kg/mol]	0.15kg/mol	Molar mass of protein B
MS	0.058[kg/mol]	0.058kg/mol	Molar mass S
MH2O	0.018[kg/mol]	0.018kg/mol	Molar mass water
rho_ H2O	100[kg/m^3]	1000kg/m^3	Density water
rho_ p	1400[kg/m^3]	1400kg/m^3	Density protein
rho_ S	1000[kg/m^3]	1000kg/m^3	Density S
myH2O	1e-3[pa*s]	0.001pa.s	Kinetic viscosity water
U_column	1e-4[m/s]	1E-4m/s	Average fluid velocity wit….

Figure (4.8), Figure (4.9) show the 3-dimension model of protein and protein meshing respectively.

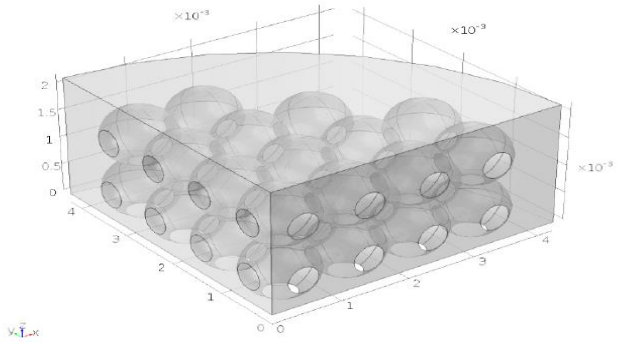


Figure (4.8):3D model of protein.

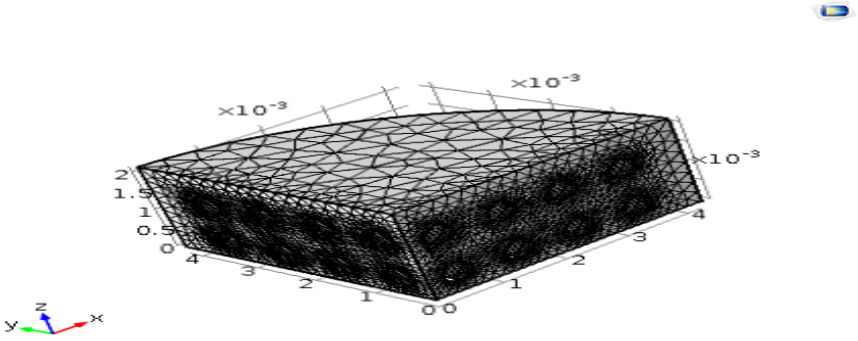


Figure (4.9): Protein mesh.

CHAPTER FIVE

Results and Discussion

5.1 Results

5.1.1 Biosensor Model based on GNPs

As shown in chapter four the following results were obtain using COMSOL Multiphysics .

5.1.1.1The magnitude of the laminar velocity field in the flow cell:

Figure (5.1): show the velocity magnitude which is very higher around the active surface(pillars) than the rest and walls of the field.

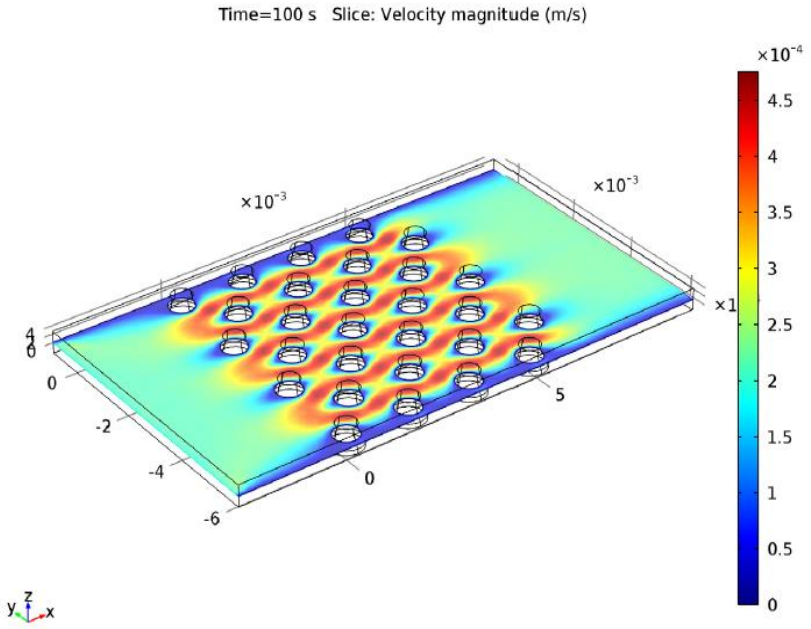


Figure (5.1): The magnitude of the laminar velocity field in the flow cell.

5.1.1.2 Concentration distribution in the analyte stream and surface coverage of adsorbed species :

Figure (5.2) through Figure (5.5) show the concentration of the species, *P*, in the stream as well the relative coverage of surface adsorbed species, *PS*, as the analyte pulse passes through the flow cell.

The velocity distribution of the flow field causes pillars near the wall to reach their maximum adsorption level at a later time compared to pillars in the center of the stream. Pillars near the wall also take longer to release adsorbed analyte. The position of a pillar in a row also has an effect on the maximum adsorption level and the time at which it is reached.

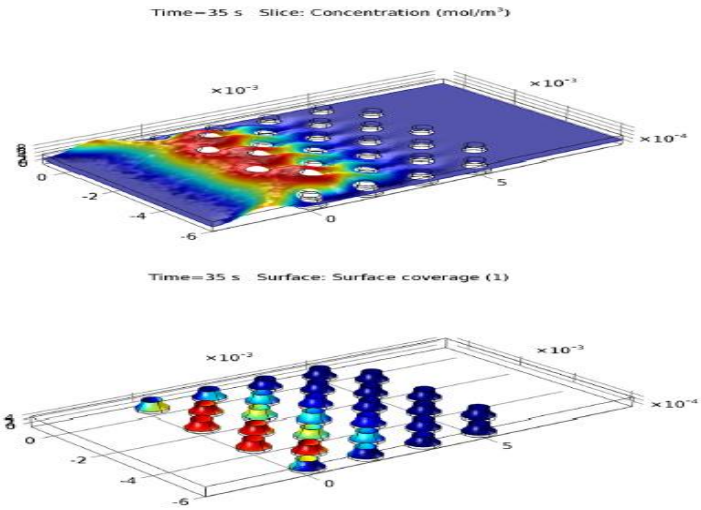


Figure (5.2): Concentration distribution in the analyte stream and surface coverage of adsorbed species at t = 35 s.

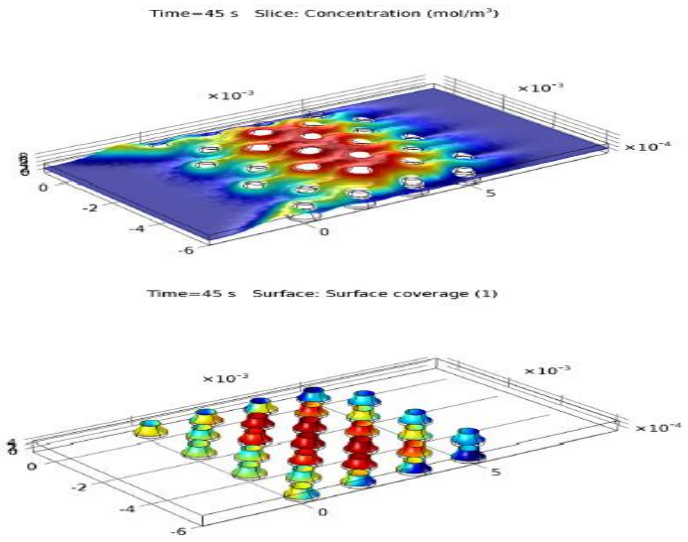


Figure (5.3): Concentration distribution in the analyte stream and surface coverage of adsorbed species at t = 45 s.

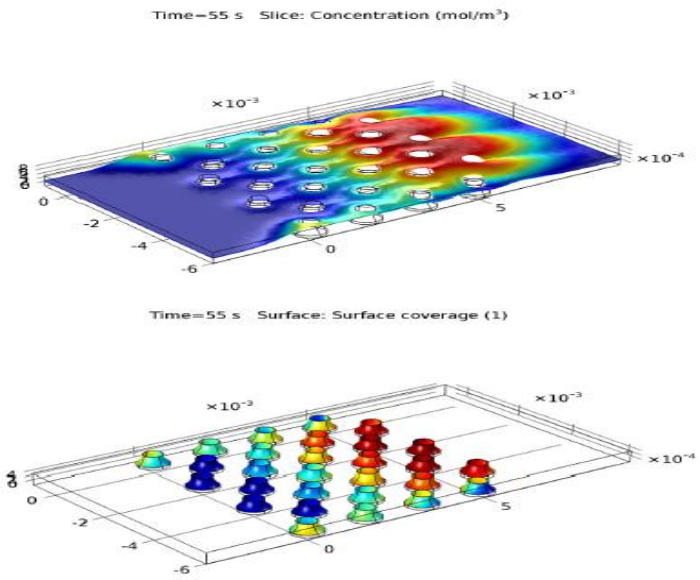


Figure (5.4): Concentration distribution in the analyte stream and surface coverage of adsorbed species at t = 55 s.

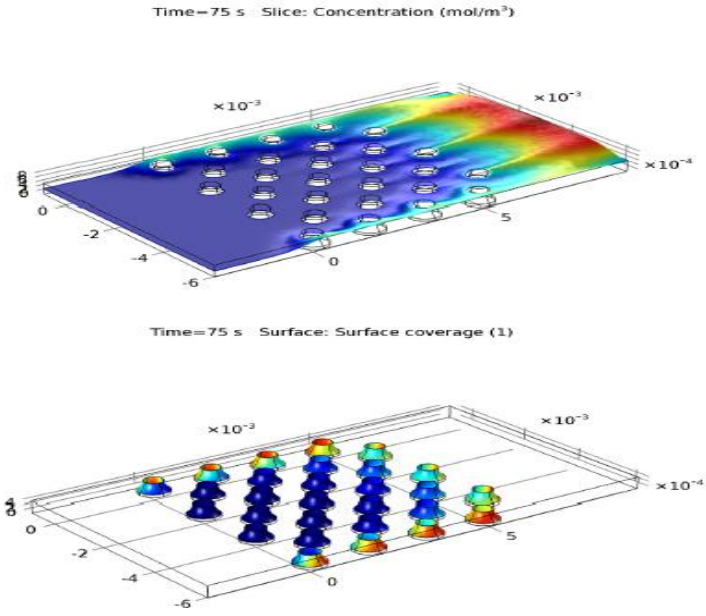


Figure (5.5): Concentration distribution in the analyte stream and surface coverage of adsorbed species at t = 75 s.

5.1.1.3 Average fractional surface coverage of adsorbed analyte PS:

geometrical effects (effect on maximum absorption level) cause the sensor signal to become relatively diffuse as shown in **Figure (5.6)**.

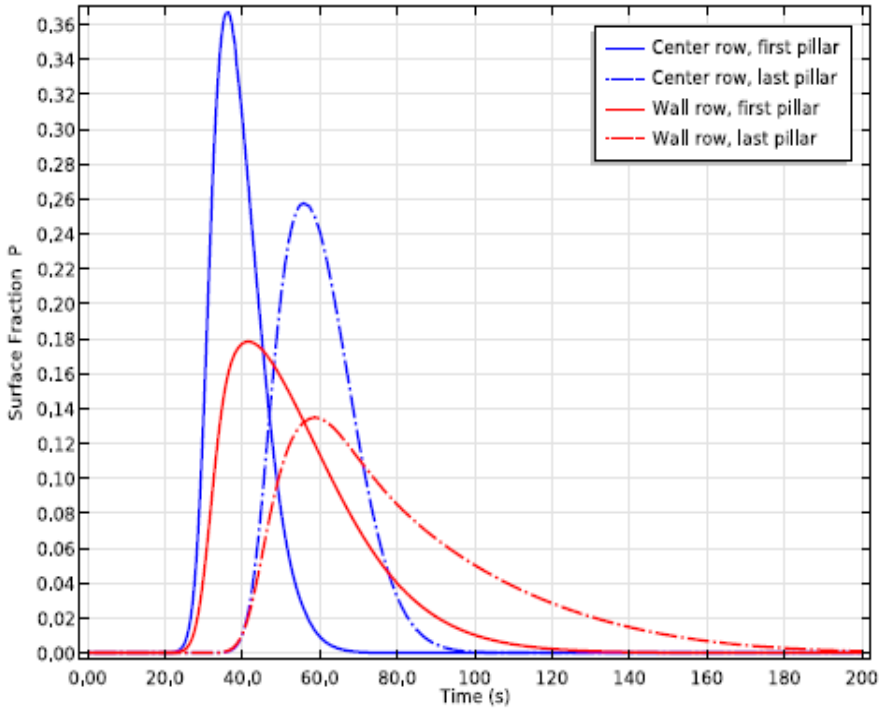


Figure (5.6): Average fractional surface coverage of adsorbed analyte PS.

5.1.2 gold nanoparticles'(GNPs) model in Multiphysics

5.1.2.1 The far-field radiation pattern:

Figure (5.7)show that at short wavelengths, a single gold sphere scatters light forward, in the direction of propagation of the incident light. At longer wavelengths, the scattered fields from the sphere look more as the radiation pattern of a dipole antenna.

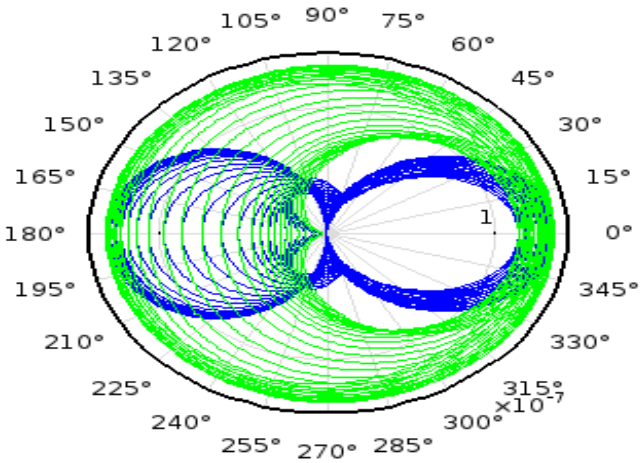


Figure (5.7): The far-field radiation pattern in the E-plane (blue) and H-plane (green) when wavelength is 700 nm**.**

5.1.2.2 The heat losses in gold nanoparticles:

Figure(5.8) and **Figure(5.9)** show that the particle preferentially absorbs the shorter wavelengths. The radius of the sphere can also be varied to see how the absorption depends upon the geometry, according to optical properties of gold nanoparticles the decrease of heat losses start from 500nm.

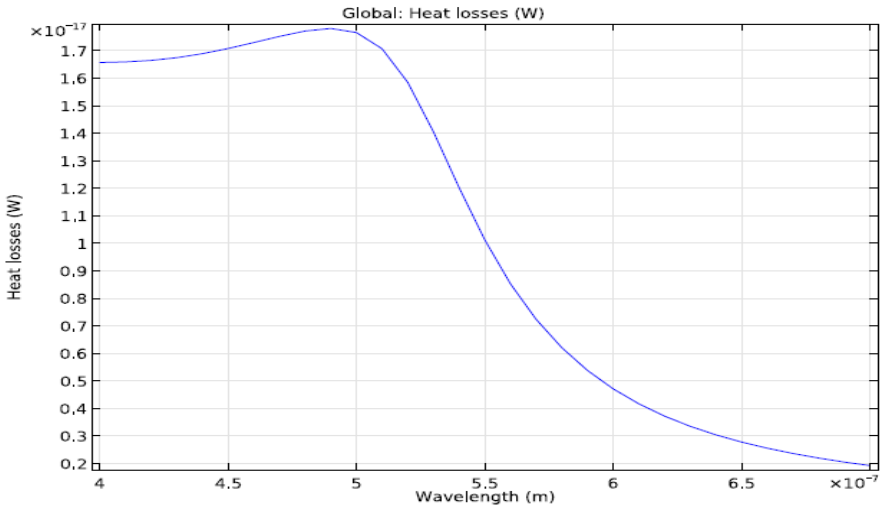


Figure (5.8): The resistive heating losses in the gold sphere.

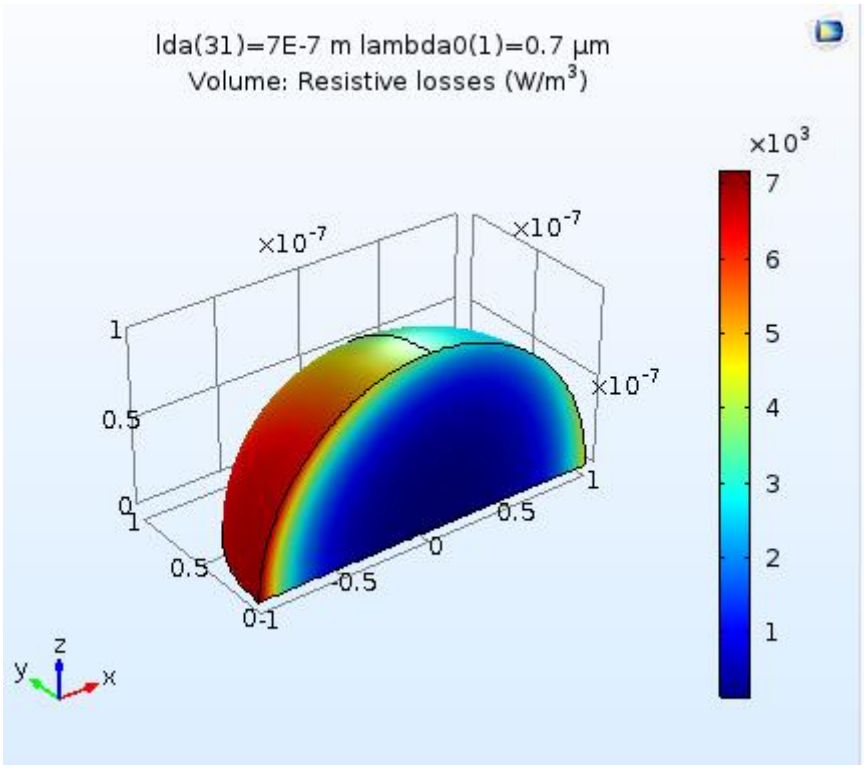


Figure (5.9): Resistive losses (w/m3).

5.1.3 Protein Adsorption model

5.1.3.1 The concentrations of the reacting species change with the time:

Figure (5.10)show Concentrations of the reacting species as functions of time Initially, only adsorbed salt species are present in the column. The concentrations of proteins A and B are seen to change with the Gaussian concentration pulse feed inlet. A stronger adsorption affinity of protein B compared to protein A is readily observed, also the concentration of bulk salt species S increases as the proteins adsorb at the surface. Towards the end of the pulse, most proteins have been adsorbed in the column and the bulk salt species have exited the system.

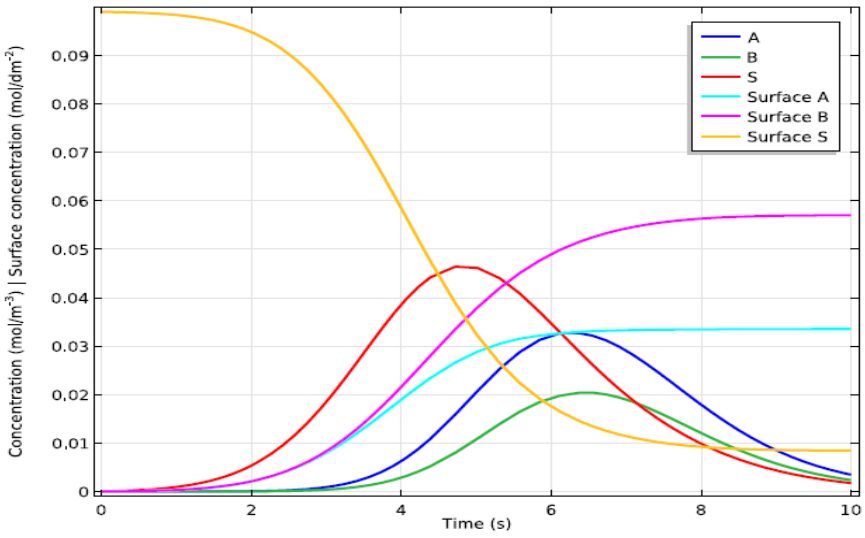
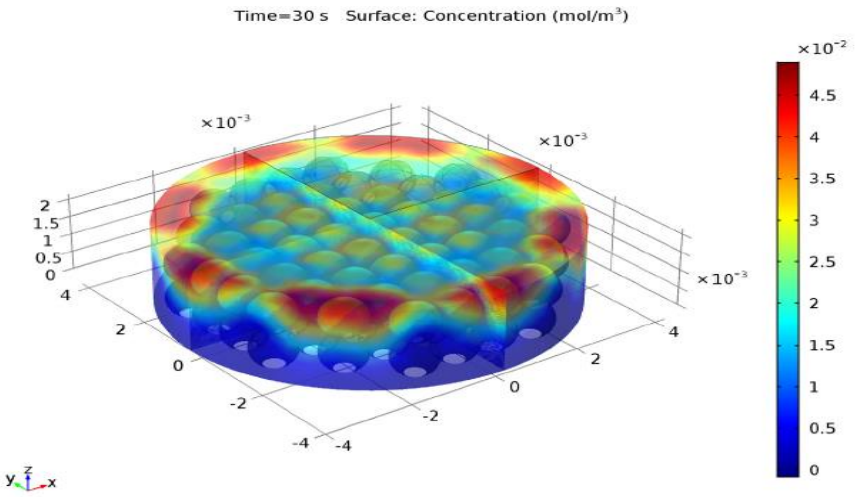


Figure (5.10): Concentrations of the reacting species as functions of time (s).

5.1.3.2 Behavior of protein B after 5 sec and 30 sec:

A comparison between **Figure (5.10) and Figure (5.11)**, in which the bulk concentration is shown, indicate that the beads at the center of the column are less accessible for adsorption or that the protein is more rapidly adsorbed at the center, both phenomena lowering the bulk concentration there.



Figure(5.11): Bulk concentration of B at 5 s.

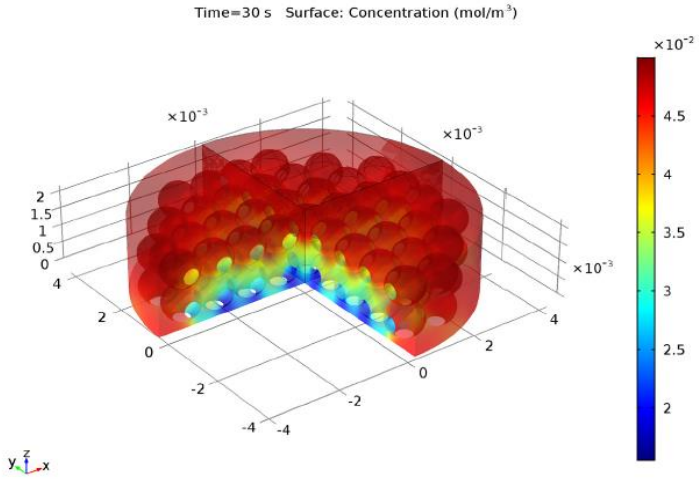


Figure (5.12): Bulk concentration of B at 30 s.

To get a proper understanding of the ion-exchange beads, a comparison of the adsorbed B surface concentration at the two times is also made with the results in **Figure(5.12)and Figure(5.13)**. The lower surface concentration of B in the center suggests that less B is adsorbed there and that the porous structure obstructs the species transport.

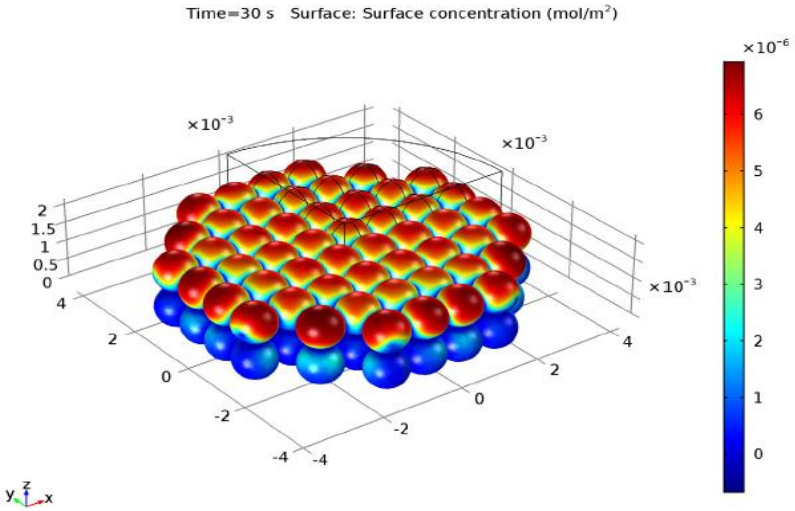


Figure (5.13) : Surface concentration of B at 5 s.

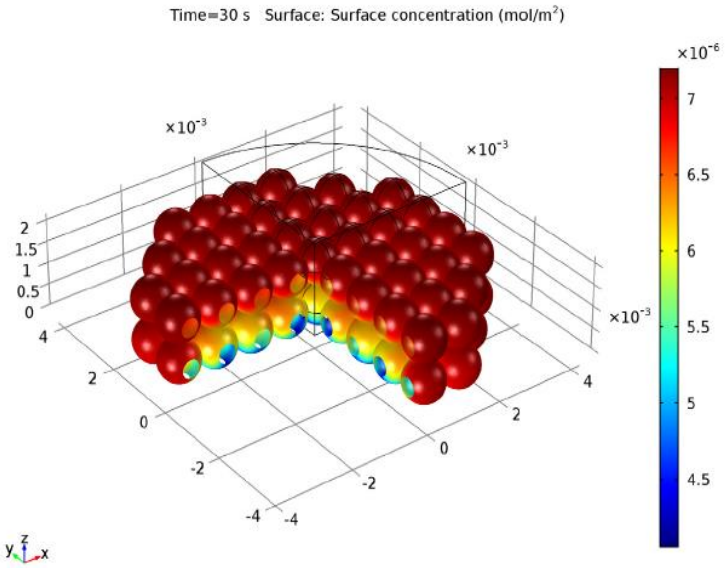


Figure (5.14): Surface concentration of B at 30 s.

5.1.3.3 The velocity field

Figure (5.15):shows that the porous structure causes a quite distorted velocity field. The exception is at the walls where the flow is less obstructed due to the relatively large gap between beads and wall.

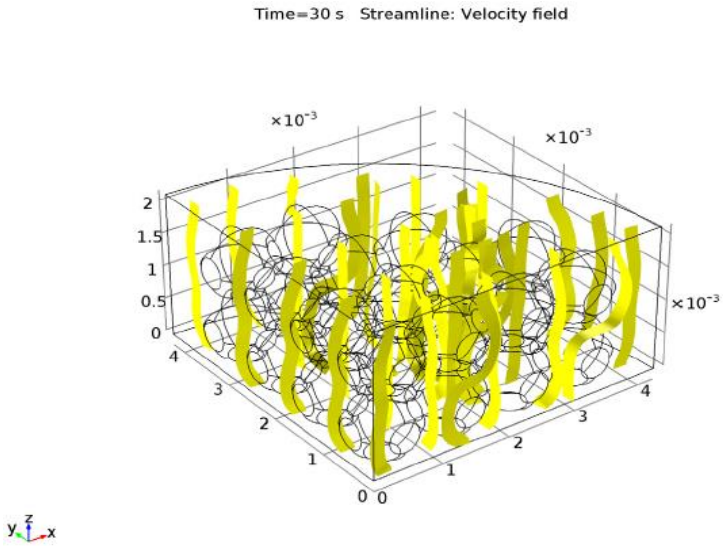


Figure (5.15): Velocity field in the pores of the column section.

5.2Discussion

In the biosensor model The velocity distribution of the flow field causes pillars near the wall to reach their maximum adsorption level at a later time compared to pillars in the center of the stream and geometrical effects cause the sensor signal to become relatively diffuse.

In the gold nanoparticles model short wavelengths, a single gold sphere scatters light forward, in the direction of propagation of the incident light. At longer wavelengths, the scattered fields from the sphere look more as the radiation pattern of a dipole antenna, and the particle preferentially absorbs the shorter wavelengths, according to optical properties of gold nanoparticles the decrease of heat losses start from 500nm.

In the protein model the concentration of bulk salt species S increases as the proteins adsorb at the surface, and the beads at the center of the column are less accessible for adsorption or that the protein is more rapidly adsorbed at the center, both phenomena lowering the bulk concentration, the walls where the flow is less obstructed due to the relatively large gap between beads and wall

CHAPTER SIX

Conclusion and recommendation

6.1 Conclusion:

Design and model of biosensor based on gold nanoparticles were performed using finite element analysis which was solver software package via simulator COMSOL Multiphysics. The biosensor was useful tool used to characterized the thermodynamics and kinetics interaction od biomolecules so biosensor provide advantages in low cost, simplicity, rapidity, stability and portability.

Three step of methodology were suggested. The first step was modeled biosensor based gold nanoparticles as materials with size 5.75 nm, while the second step was modeled of gold nanoparticles in Multiphysics to measure far-field radiation pattern which show that at short wavelengths, a single gold sphere scatters light forward, in the direction of propagation of the incident light. At longer wavelengths, the scattered fields from the sphere look more as the radiation pattern of a dipole antenna. and the heat losses in gold nanoparticles via the refractive index ,relative permittivity and skin depth of gold and that indicate the particle preferentially absorbs the shorter wavelengths.

The third step was modeled of protein adsorption to study the concentrations of the reacting species change with the time while The concentrations of proteins A and B are seen to change with the Gaussian concentration pulse feed inlet, also the behavior of protein in which the bulk concentration is shown, indicate that the beads at the center of the column are less accessible for adsorption or that the protein is more rapidly adsorbed at the center, both phenomena lowering the bulk concentration there. and the velocity field that the porous structure causes a quite distorted velocity field. The exception is at the walls where the

flow is less obstructed due to the relatively large gap between beads and wall all of above to increase the accuracy of magnitude of the laminar velocity field in the flow cell , concentration distribution in the analyte stream and surface coverage of adsorbed species and Average fractional surface coverage of adsorbed analyte concerned in biosensor model based on gold nanoparticles GNPS in Multiphysics .

6.2 Recommendations:

- Model of GNPs conjugate with protein in Multiphysics.
- Model and Study the functionalized GNPs immobilized in biosensor design in Multiphysics.
- Functionalize GNPs by conjugated to antigen/antibody instead of protein, and study the behavior of functionalized GNPs conjugated with antigen/antibody in biosensor model based in Multiphysics
- Comparison between biosensor based GNPs conjugated with antigen/antibody with other biosensor model.
- Specializes the biosensor model(Lateral flow immunoassay test strip) in certain diseases.

References

[1] M. Galindo, E, Institute of Biotechnology, National University of Mexico, Cuernavaca, "BIOSENSORS," vol. II, no. BIOTECHNOLOGY – Vol. II-Biosensors.

[2] S. Horikoshi and N. Serpone, "Introduction to Nanoparticles," pp. 1–24, 2013.

[3] H. N. Verma, P. Singh, and R. M. Chavan, "Gold nanoparticle : synthesis and characterization," vol. 7, 2014.

[4] R. Rashid, G. Murtaza, and A. Zahra, "Gold Nanoparticles : Synthesis and Applications in Drug," vol. 13, no. July, pp. 1169–1177, 2014.

[5] U. K. Parida and P. L. Nayak, "Biomedical Applications of Gold Nanoparticles : Opportunity and Challenges," vol. 1, no. 2, pp. 10–25, 2012.

[6] C. Jayaseelan, R. Ramkumar, A. Abdul, and P. Perumal, "Green synthesis of gold nanoparticles using seed aqueous extract of Abelmoschus esculentus and its antifungal activity," *Ind. Crop. Prod.*, vol. 45, pp. 423–429, 2013.

[7] A. Tomar and G. Garg, "Short review on application of gold nanoparticles," *Glob. J. Pharmacol.*, vol. 7, no. 1, pp. 34–38, 2013.

[8] C. L. L. C.Clark Jr., "Electrode Systems For Continuous Monitoring In Cardiovascular Surgery," *Ann. new york Acad. Sci. 102(1)29–45, 1962. doi 10.1111/j.*

[9] D. Newman, S. J. Setford. Enzymatic biosensors. Molecular biotechnology, "No Title," vol. 1385/MB:32.

[10] V. Ašeris, "COMPUTATIONAL MODELLING OF BIOSENSORS UTILIZING INTERMEDIATE SUBSTANCES ,Doctoral dissertation Physical sciences, informatics (09 P)," 2013.

[11] M. F. C. E. of biosensor con-struction J. Davis, D. H. Vaughan, "Elements of biosensor con- struction," *Enzyme Microb. Technol.*, no. 17(12):1030–1035.

[12] B. Advances, "Nanotechnology and biosensors. Biotechnol Adv," no. OCTOBER 2004, 2016.

[13] Q. W. Thesis, "Mathematical Methods for Biosensor Models

Mathematical Methods for Biosensor Models," 2011.

[14] M. W. Al-mufti, U. Hashim, and T. Adam, "Simulation of Nano lab on chip devices by using COMSOL Multiphysics," vol. 9, no. 2, pp. 1056–1061, 2013.

[15] J. W. Xueji Zhang, Huangxian Ju, "Electrochemical Sensors, Biosensors and Their Biomedical Applications," *Huangxian Ju, Joseph Wang, Acad. Press is an Impr. Elsevie*, 2008.

[16] R. M. Harsh Sharma, "Review of biosensors for foodborne pathogens and toxins," *Sensors Actuators B 183 535–549.*, 2013.

[17] K. M. Koczula and A. Gallotta, "Lateral flow assays," no. June, pp. 111–120, 2016.

[18] A. Parolo, C., de la Escosura-Muniz, A. and Merkoci, "Enhanced lateral flow immunoassay using gold nanoparticles loaded with enzymes," . *Biosens. Bioelectron. 40, 412–416 CrossRef PubMed*, 2013.

[19] L. Chen, J., Fang, Z., Lie, P. and Zeng, "Computational lateral flow biosensor for proteins and small molecules: a new class of strip logic gates.," *Chem. 84, 6321–6325 CrossRef PubMed*, 2012.

[20] T. B. Y. Comsol, "No Title," p. COMSOL AB (2009, April). [Online]. Available: http, 2009.

[21] I. Management, "APPLICATIONS OF COMSOL MULTIPHYSICS SOFTWARE TO," 2010.

[22] A. C. M. H. COMSOL AB (2009). COMSOL AB (2009, April). COMSOL Multiphysics Handbook, 2009.

[23] M. Hanke, "Short Introduction to Comsol Multiphysics Starting Comsol Multiphysics," pp. 1–6, 2006.

[24] Q. Li, K. Ito, Z. Wu, C. S. Lowry, and S. P. L. Ii, "COMSOL Multiphysics : A Novel Approach to Ground Water Modeling," vol. 47, no. 4, 2009.

[25] COMSOL AB., *M ultiphysics C OMSOL Q UICK S TART AND Q UICK R EFERENCE*. .

[26] J. O. Wilkes, "Introduction to COMSOL Multiphysics," p. 168.

[27] O. Š. M. Sapagovas, A. Štikonas, "Alternating direction method for the Poisson equation with variable weight coefficients in an integral

condition. Differential equations," *47(8)1176–1187, 2011*, no. .1134/S0012266111080118 (cit. on p. 22).

[28] M. S. F. Ivanauskas, T. Meškauskas, "Stability of differ- ence schemes for two-dimensional parabolic equations with non- local boundary conditions,Applied mathematics and computation," *215(7)2716–2732, 2009*, no. 1016/j.amc.2009.09.012 (cit. on p. 22).

[29] P. K. V. Skakauskas, "Numerical solving of coupled systems of parabolic and ordinary differential equations. Nonlinear analysis: modelling and control," *15(3):351–360,2010*, no. (cit. on p. 22).

[30] R. B. I. Tumasoniene, G. Kulvietis, D. Mazeika, "The eigen- value problem and its relevance to the optimal configuration of elec- trodes for ultrasound actuators," *J. sound Vib. 308(3-5)683–691, 2007*, no. 04.036 (cit. on p. 22).

[31] K. Balasubramanian and M. Burghard, "Biosensors based on carbon nanotubes," *Anal. Bioanal. Chem.*, vol. 385, 3, pp. 452–468, 2006.

[32] J. Ljungblad, "Antibody-conjugated Gold Nanoparticles integrated in a Fluorescence based Biochip,". June, 2009.

[33] X. Gao, L. Xu, S. Zhou, G. Liu, and X. Zhang, "Recent Advances in Nanoparticles-based Lateral Flow Biosensors," *Am. J. Biomed. Sci.*, vol. 6, no. 1, pp. 41–57, 2014.

[34] S. university sciences and technology department of biomedical engineering Eiman Mohamed, "Fabrication of an Immunochromatography Biosensor Using Green Synthesis Gold Nanoparticles." 2015.

[35] S. Qian, "A mathematical model of lateral flow bioreactions applied to sandwich assays," vol. 322. May, pp. 89–98, 2003.

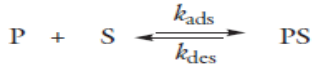
[36] Nianyin Zeng, Zidong Wang, Yurong Li, Min Du, and Xiaohui Liu, "Inference of Nonlinear State-Space Models for Sandwich-Type Lateral Flow Immunoassay Using Extended Kalman Filtering," *IEEE Trans. Biomed. Eng.*, vol. 58. 7, pp. 1959–1966, 2011.

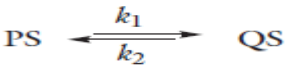
[37] S. Mackay, P. Hermansen, D. Wishart, and J. Chen, "Simulations of Interdigitated Electrode Interactions with Gold Nanoparticles for Impedance-Based Biosensing Applications," pp. 22192–22208, 2015.

Appendixes

Appendix(A)

Equations

(1) 

(2) 

(3) $r_{ads} = k_{ads} c_p$

(4) $r_{des} = k_{des} c_{ps}$

(5) $r_{quench} = k_1 c_{ps} + k_2 c_{Qs}$

(6) $\frac{\partial c_p}{\partial t} + \nabla.\left(-D_p \nabla c_p\right) + u \,.\nabla c_p = 0$

(7) $N_p = -r_{ads} + r_{des}$

(8) $\frac{dc_{s.p}}{dt} = r_{ads} - r_{des} - r_{quench}$

(9) $\frac{dc_{s.Q}}{dt} = r_{quench}$

(10) $\varepsilon_r = \varepsilon' - j\varepsilon'' = (n' - jn'')^2$

(11) $\delta = \frac{1}{Re\sqrt{-k_{0\varepsilon_r}^2}}$

(12) S(ads)+P⇔P(ads)+S

(13) $K_1^{eq} = \frac{c_s \, c_{A(ads)}}{c_A c_{s(ads)}}$

(14) $K_2^{eq} = \frac{c_s \, c_{B(ads)}}{c_B c_{s(ads)}}$

(15) $\frac{\partial c_i}{\partial t} + \nabla.(-D_i \nabla c_i) + u \,.\nabla c_i = 0$

Appendix(B)

Code and methods

```
if (!solution_state.equals("solutionexists")) {
  alert("Compute the solution before you animate.");
}
else {
  active_plot = "slice_and_height";
  model.result().export("anim1").set("target", "player");
  model.result().export("anim1").set("plotgroup", "pg11");
  model.result().export("anim1").set("maxframes", "10");
  model.result().export("anim1").set("showframe", 10);

  for (int ind = 0; ind < 11; ind++) {
    with(model.result().export("anim1"));
      set("showframe", ind);
      set("lastplaytime", 1.428520847054E12);
    endwith();
  }
  model.result().export("anim1").run();
}
```

```
if (model.sol("sol1").isInitialized()) {
  solution_state = "solutionexists";
}
else {
  solution_state = "nosolution";
  model.param().set("time_value", Math.round(model.param().evaluate("end_time")/7.1));
}

if (solution_state.equals("solutionexists")) {
  setFormObjectEnabled("/results/inputfield1", true);
  setFormObjectEnabled("/results/button1", true);
}
else {
  setFormObjectEnabled("/results/inputfield1", false);
  setFormObjectEnabled("/results/button1", false);
}
```