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EARLY DIAGNOSIS OF MYOCARDIAL INFARCTION

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***Abstract* - Myocardial infarction (MI) is caused when the blood flow to a segment of the myocardium is disrupted .It can be diagnosed earlier by the excess release of a protein named troponin in the blood. Tests for cardiac biomarker (Troponin I) can also be used to help determine a person's risk of having these conditions or to help monitor and manage someone with suspected MI. The main aim of this thesis is to develop a point-of-care device for rapid detection of Myocardial Infarction by means of protein named troponin I (cTnI).MI is characterized by damage to the cardiac myocytes, which causes the troponins to enter the circulation, where they can be detected using biosensor (Surface Plasmon Resonance). SPR technique measures the refractive index of very thin layers of material absorbed on metal. Antibodies have been immobilized on the surface of a thin metal film, deposited on the reflecting surface of the glass prism, When interactions between antigen and immobilized antibodies occur change in the refractive index occurs, Variation in light intensity reflecting from the back of the film will be detected. This led to the development of bedside troponin I testing methods**

Index Terms – Myocardial infarction,Biomarker, Biosensor, SPR, Troponin I, Cardiac myocytes.

I. INTRODUCTION

Recently Cardiovascular Diseases are the leading cause of death among the individuals in developing countries.There are about 37 million Indians are affected by Myocardial Infarction every year.Out of that 72% are Silent Ischemic Heart Diseases.Myocardial Infarction is caused by occlusion of coronary arteries by cholesterol deposits.This leads to decreased flow of blood through the heart's muscle.Therefore heart's muscles got damaged.

Early diagnosis of Myocardial Infarction(MI) is very important.The oldest test is the ECG test which checks the heart's electrical activity.Early diagnosis using ECG test is very difficult .Biomedical engineering is the application of engineering principles and design concepts to medicine and biology.It can be used to combine the technical and problem solving skills of engineering with the clinical knowledge. Biomedical engineering can be applied to all stages of health care, from diagnosis through treatment.

The thesis includes a brief introduction to the anatomy and physiology of human heart and the abnormalities which happens when Myocardial infarction occurs .It introduces the concept of troponin testing and the change in reflectance by means of Surface plasmon resonance biosensor

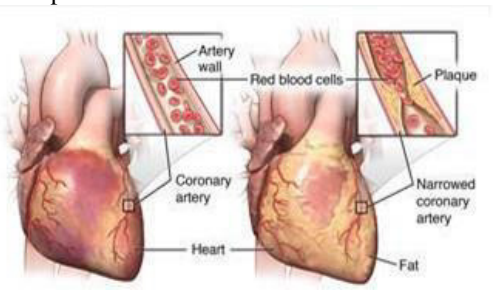

Figure 1 Normal heart Vs Heart with myocardial Infarction

II. METHODOLOGY

In a basic SPR biosensor, one wall of the glass prism is immobilized with the biomolecule (antibody, ligand, etc.) and the target analyte flows across it. As the antigen–antibody binding interaction occurs, the intensity of light changes and quantifies the concentration of the target analyte. As it uses simple apparatus for detection, SPR is useful for rapid detection which does not require tedious labeling processes as in other optical techniques.

SPR-based sensors work on the principle of changes in resonance on irradiating the substrate with light waves. The shifts in the resonance curves reflect the movement of valence electrons when stimulated with light. Figure 3.1 shows the block diagram using SPR as a biosensor.

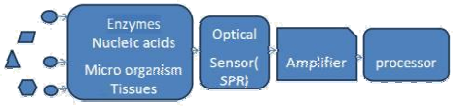

Figure 2 Block diagram using SPR as a biosensor

A biosensor is a biological detection system consists of a biological component combined with a transducer to perform measurement of a biochemical quantity. A typical biosensor includes a bioelement such as an enzyme, antibody, or a cell receptor, and a sensing element or a transducer.

Biosensors are operated based on the principle of signal transduction. These components include a bio-recognition element, a biotransducer and an electronic system composed of a display, processor and amplifier.The bio-recognition element, essentially a bioreceptor, is allowed to interact with a specific analyte (Troponin I). The transducer measures this interaction and outputs a signal. The intensity of the signal output is proportional to the concentration of the analyte (Troponin I). The signal is then amplified and processed by the electronic system.

Biosensor is mainly divided into three sections. (i) Sensor: a sensitive biological element (biological material (eg. tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, etc), (ii) Transducer: it is the detector element (works in optical) that transforms the signal resulting from the interaction of the analyte with the biological responsible for the display of the results in a user-friendly way, (iii) third section is the associated electronics, which comprises of signal conditioning circuit (amplifier), processor and a display unit.

The electrical signal from the transducer is often low and superimposed upon a relatively high and noisy (i.e. containing a high frequency signal component of an apparently random nature, due to electrical interference or generated within the electronic components of the transducer) baseline. The signal processing normally involves subtracting a 'reference' baseline signal, derived from a similar transducer without any biocatalyst membrane, from the sample signal, amplifying the resultant.

A.SYSTEM ARCHITECTURE

In a basic SPR biosensor, one wall of the glass prism is immobilized with the biomolecule (antibody, ligand, etc.) and the target analyte flows across it. As the antigen–antibody binding interaction occurs, the intensity of light changes and quantifies the concentration of the target analyte. As it uses simple apparatus for detection, SPR is useful for rapid detection which does not require tedious labeling processes as in other optical techniques.

SPR-based sensors work on the principle of changes in resonance on irradiating the substrate with light waves. The shifts in the resonance curves reflect the movement of valence electrons when stimulated with light.Fig shows the principle and angle shift of SPR sensor. Fig 3 shows the principle of SPR sensor.

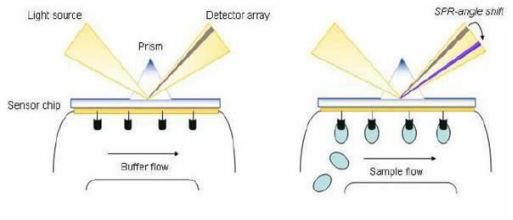

Figure 3 Principle of SPR sensor

Surface plasmon resonance (SPR) is a phenomenon that occurs when polarized light hits a metal film at the interface of media with different refractive indices.

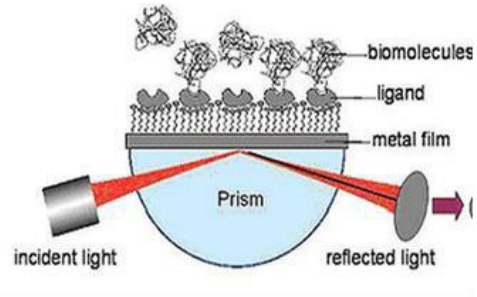

Figure 4. SPR Experimental Setup

Figure 4 shows the Basic components of an instrument for SPR bio sensing: A glass slide with a thin gold coating is mounted on a prism. Light passes through the prism and slide, reflects off the gold and passes back through the prism to a detector. Changes in reflectivity versus angle or wavelength give a signal that is proportional to the volume of biopolymer bound near the surface. A flow cell allows solutions above the gold surface to be rapidly changed. SPR technique measures the refractive index of very thin layers of material absorbed on metal.

Antibodies have been immobilized on the surface of a thin metal film,deposited on the reflecting surface of the glass prism,When interactions between antigen and immobilized antibodies occur change in the refractive index occurs ,Variation in light intensity reflecting from the back of the film will be detected. In a typical SPR bio sensing experiment, one interactant in the interactant pair (i.e., a ligand or biomolecule) is immobilized on an SPR-active gold-coated glass slide which forms one wall of a thin flow-cell, and the other interactant in an aqueous buffer solution is induced to flow across this surface, by injecting it through this flow-cell . When light (visible or near infrared) is shined through the glass slide and onto the gold surface at angles and wavelengths near the so-called "surface plasmon resonance" condition, the optical reflectivity of the gold changes very sensitively with the presence of biomolecules on the gold surface or in a thin coating on the gold. The high sensitivity of the optical response is due to the fact that it is a very efficient, collective excitation of conduction electrons near the gold

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surface. The extent of binding between the solution-phase interactant and the immobilized interactant is easily observed and quantified by monitoring this reflectivity change .An advantage of SPR is its high sensitivity without any fluorescent or other labeling of the interactants

III RESULT AND DISCUSSION

Winspall is the software for the simulation of surface plasmon resonance reflectivity curve based on Fresnal formalism. Dielectric constants and thickness of prism, air, gold, protein(Troponin) are placed in the layer system table. Based on the amount of protein reflectivity curve is shown.As an analyte binds to the ligand the accumulation of protein on the surface results in an increase in the refractive index. This change in refractive index is measured in real time and the result is plotted as a response or resonance units verses time (sensor gram).Table 1 represents the the thickness and dielectric constants of Prism, Air, Gold and Troponin protein.

Table 4.1 Thickness and dielectric constants of prism,Air,gold and troponin protein.

components	Thickness	Dielectric constant	
		(real)	
Prism	0	2.29	0
Air	0	1	0
Gold	50nm	-12.45	1.3
Protein(Troponin)	3nm	1.4	0

"Thickness" and "Eps-X" are to be filled in the layer system table. The latter describes the real and imaginary part of the dielectric constants of all materials and media involved.

A laser beam is reflected from the base of a prism and the reflected light is collected as a function of the angle of incidence (taken against the surface normal). Optical constants of the prism and air needs to be filled in the layer system table. Optical components: No. 1 is the prism, Not a layer so "0" for the thickness is chosen. The real part of the dielectric constant is ' = 2.29 (corresponding to a refractive index of n=1.51). There is no adsorption in the glass and hence, the imaginary part is zero. The next component (No. 2) is air with "no thickness", and'=1 (n=1) and "=0 (no absorption).Figure 4.2 shows the layer system table with dielectric constants for prism and air is shown below.

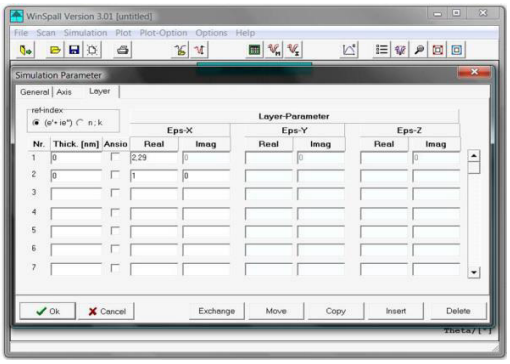

Figure 5 Layer system table

Figure 5 shows the typical curve describing total internal reflection. Light is reflected from an interface separating high index from low index material.

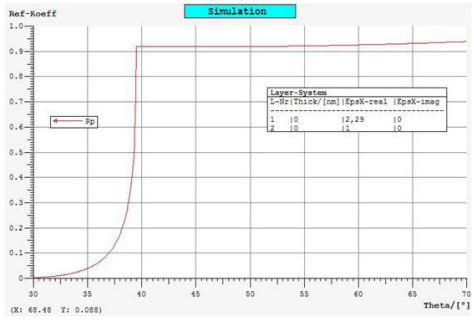

Figure 5 Total internal reflection

Fig 6 shows the reflection which occurs in the prism. At low angles basically all light passes through the interface without any reflection. Just below about 39° more and more light is reflected until total internal reflection is reached.

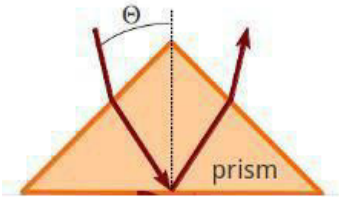

Figure 6 Reflection in prism

The figure 6 shows the addition of gold in the setup. The reflection varies with respect to the type of material.

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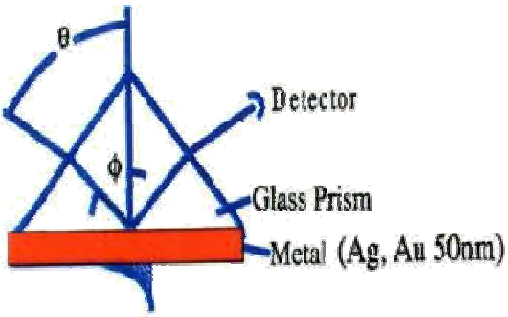

Figure 7 Addition of gold

Add an optical component between the glass and the air: a 50 nm thick typical values for gold but can vary to some extent due to slight differences in the evaporation process. Gold layer with the optical constants "Eps-X real"=-12.45 and "Eps-X imag"=1.3. The reflectivity curve looks totally different: First, the strong increase from 0 to almost 1 around the angle of total internal reflection is much more shallow due to the reflective properties of the gold. Secondly, a surface plasmon shows up as a strong dip in reflectivity at around 43°. The entire intensity or the laser beam is now bound in this plasmon and no part of the light is reflected. This curve now describes the optical properties of a typical "blank substrate" used for surface plasmon measurements.

Figure 8 shows the reflectivity curve when adding 50nm thick typical values for gold is shown below

Figure 8 Reflectivity Curve after adding 50nm thick gold layer

Now add 3 nm layer on top of the gold with a Dielectric constant of =1.4– Troponin protein. The plasmon resonance has shifted a little (angle gets shifted to 43.5 degree). Figure 9 shows the Reflectivity curve when adding the dielectric constant of the protein

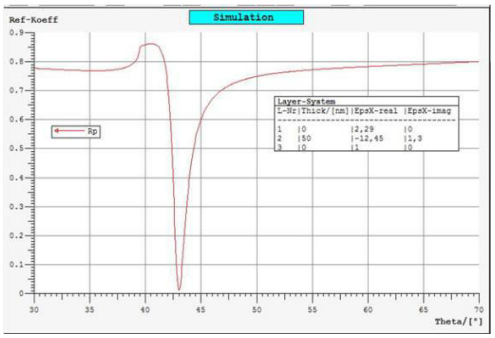

Figure 9 Reflectivity Curve after adding dielectric constant of protein(Troponin)

Thicker layer 30 nm leads to a stronger shift of the plasmon resonance at about 50 degree. Figure 10 shows the curve after adding 30nm thicker layer of protein.

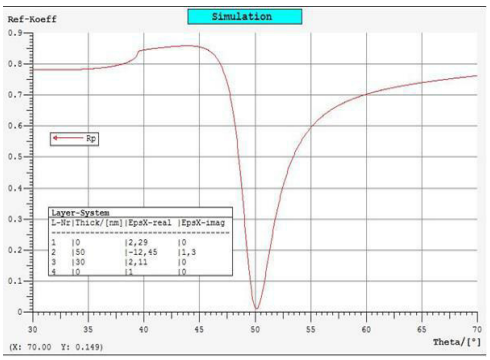

Figure 10 Reflectivity Curve after adding 30nm thicker layer of protein

Even thicker: 300 nm gets something new. A very sharp dip in the reflectivity curve but at a smaller angle(42 degree). This is not a plasmon, this is a waveguide mode. The first waveguide for this layer system.There are more to come as the layer gets thicker. Figure 11 shows sharp dip in reflectivity.

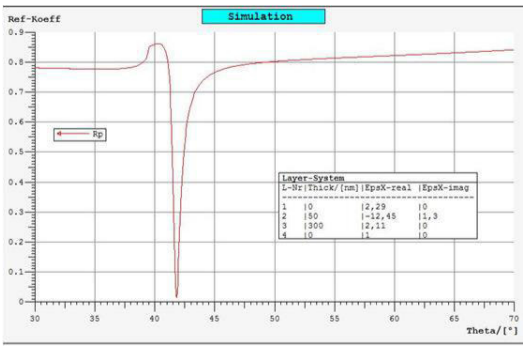

Figure 11 Sharp dip in reflectivity

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around 43°.

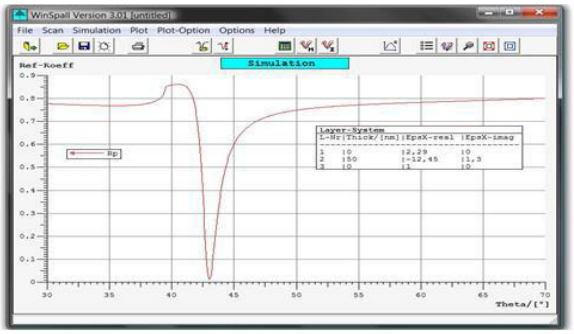
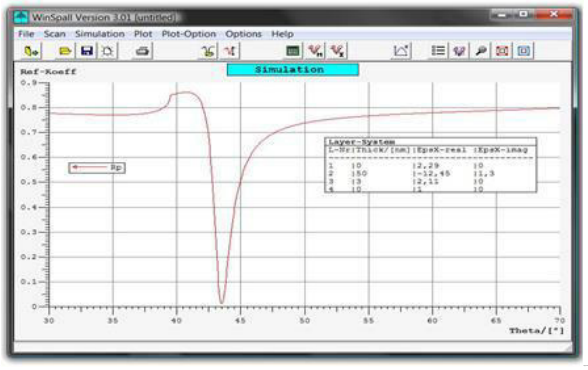


Figure 12(a) Reflectivity curve without protein



The top graph shows the SPR curve shift due to molecular binding at the SPR sensor. The dip in the curve (lowest light intensity),When plasmons are excited. Full SPR curves are used to obtain physical properties of the adsorbed sample.

As an analyte binds to the ligand the the accumulation of protein on the surface results in an increase in the refractive index. This change in refractive index is measured in real time and the result is plotted as a response or resonance units verses time (sensorgram).Figure 13 shows that light source should be monochromatic and p-polarized (polarized in the plan surface) to obtain a sharp dip.

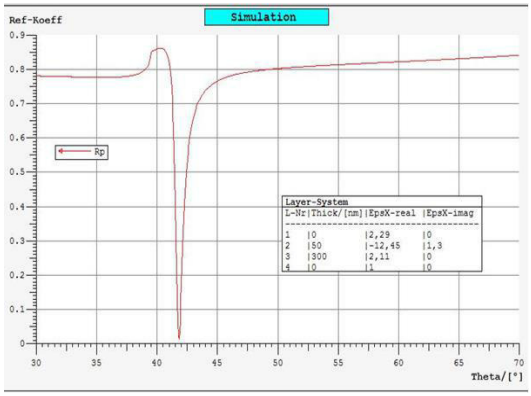


Figure 13 Reflectivity Curve due to monochromatic and polarized light source

Table 2 Shift in angle of resonance

Layer(protein)	**Shift in angle**
3nm	43.5 degree
30nm	50 degree
300nm	42 degree(Sharp dip)
3000nm	Upto 70 degree(5 modes)

The table 2 shows that according to the amount of protein ,shift in the angle occurs .Winspall is the software for the simulation of surface plasmon resonance reflectivity curve based on Fresnal formalism. Dielectric constants and thickness of prism, air, gold, protein(Troponin) are placed in the layer system table .Based on the amount of protein reflectivity curve is shown.As an analyte binds to the ligand the the accumulation of protein on the surface results in an increase in the refractive index. This change in refractive index is measured in real time and the result is plotted as a response or resonance units verses time (sensor gram)

This project presents an complete overview of different types of biosensors, their working principles, advantages, and applications of various biosensors are described. Because of various transduction technologies, most of the research is focused on improving sensitivity, selectivity, and stability. Most commercial biosensors developed till date is needed to focus in clinical applications. Among the various kinds of biosensors SPR biosensor is chosen because of its improved sensitivity, selectivity and stability. An ultrasensitive surface plasmon resonance (SPR) sensor was developed for the specific detection of human cardiac troponin I (cTnI), a principle diagnostic marker for myocardial damage. The thin gold film evaporated on a glass slate, which was employed as a SPR sensing film, was modified by hollow gold particles and then was immobilized with antibodies for specific recognition of target analyte.Due to high cost of the instrumentation, simulation can be done by Winspall software.

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