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SIMULATION OF HEMOGLOBIN DETECTION USING SURFACE PLASMON RESONANCE BASED ON KRETSCHMANN CONFIGURATION

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Abstract

Researches on detecting haemoglobin have been intensively carried out as the number of anemia cases increases in both developed and developing countries. The haemoglobin concentration is influenced by some factors including gender, age, and environmental conditions of residence. As to this, the development of sensors to detect haemoglobin concentrations with high sensitivity, free labels, and high resolution is needed. In this study, sensor simulations were conducted and analyzed by varying the haemoglobin concentration using Lumerical Finite Difference Time Domain. The results of the simulations showed a different decrease in reflectance in each different haemoglobin concentration. The analysis of the simulations employed the graph method to determine the sensitivity value. The results showed that the sensitivity of the haemoglobin sensor was 0.2765 g/dL with a large Signal to noise ratio of 0.6875, the size of the sensor resolution obtained was $0.28 . 10^{-3}$ and the value of Full Width at Half Maximum was 5.11^{o}. The configuration and sensor materials are believed to be able to improve sensor performance in measuring haemoglobin concentration. Therefore, this sensor model can be used to detect haemoglobin in the concentration range of patients with anemia.

Keywords: Biosensing, FDTD, Haemoglobin, Kretschmann configuration, Surface plasmon resonance.

1. Introduction

Anemia has been one of the health problems suffered by many people in developed and developing countries [1]. Anemia is a serious health problem, particularly for pregnant women as it causes premature birth, babies with low weight, and even death [2]. In addition, anemia has a negative effect on up to 50% of patients with chronic heart failure (CHF). Even though the cause of anemia in CHF cannot be diagnosed with certainty, it is thought to be due to impaired function in the kidneys [3]. According to the World Health Organization (WHO), anemia is defined as a state of haemoglobin concentration in the body (Hb) < 12 g/dL for women and < 13 g/dL for men. The haemoglobin concentration is influenced by gender, age, and other factors like environmental conditions of residence [4]. Therefore, to overcome this problem, a sensor that can detect haemoglobin concentrations with high sensitivity, label-free, and high resolution needs to be developed.

Studies on haemoglobin detection have been widely conducted using different methods, such as multi-wavelength pulse oximetry method [5], spectrophotometric method and RBC number, resonant wavelength shift method [6] and others. The methods used to detect haemoglobin are also consistent with previous studies that detect glucose [7]. These methods have different parameters but they have the same general parameters, including the resolution or accuracy in measuring haemoglobin concentration. The Surface Plasmon Resonance (SPR) method is known to have a very far resolution that is 23 times better than other methods [5].

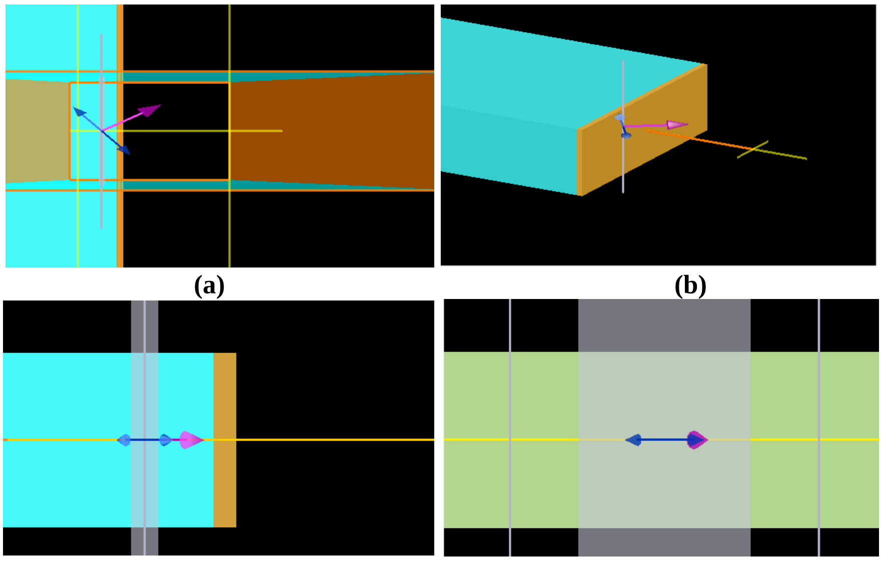
Plasmon surfaces are electrons that oscillate on the surface of conductor material so that the surface plasmon resonance is a plasmon that resonates on the metal surface [8, 9]. SPR supports sensors and biosensors so that they experience rapid development in various fields such as electrochemistry, medicine, and in the medical field [10, 11]. Currently, SPR is developed for biosensors because it can monitor real-time biomaterial interactions, such as growth factors, viruses, glycoprotein nucleic acids, and the amount of haemoglobin (concentration) [12]. There are several configurations on the plasmon resonance surface, such as lattice configuration, optical waveguide configuration, and Kretschmann configuration. The Kretschmann configuration is most widely used because of its inexpensive manufacturing process. It uses a prism allowing the light to pass through a material with a high refractive index. Evanescent waves are thus formed along the surface between metals and analytes. The waves are strongly influenced by refractive index changes that occur in the background or analyte, making it possible to investigate biochemical reactions that occur on metal surfaces [13]. Based on this, the SPR can be used as a haemoglobin detection sensor. SPR detects haemoglobin by firing gold with a laser beam from various angles. The presence of molecules on the metal surface shifts the refractive index of the analyte so that there is a shift in the minimum angle position of the SPR.

In this paper, we conducted an SPR-based sensor simulation using the Kretschmann configuration to detect haemoglobin. The solution of haemoglobin with a concentration of 0, 65, 87, 173, and 261 g/L was analysed by measuring the changes in the refractive index at a wavelength of 670 nm. The thickness of the gold layer used is 50 nm because it can produce a narrow width of Full Width at Half Maximum (FWHM) [14]. Sensor simulation uses the Finite Difference Time Domain (FDTD) method with the FDTD Solution Lumerical software. FDTD is a method for solving an equation using an approach to obtain an estimate as the endresult. FDTD method is commonly used to solve equations related to electromagnetic waves and Maxwell equation on a problem [15].

2. Model and Method

The proposed sensor design using FDTD method was developed. A simulation system was created in several stages, including 1) determining the software used, 2) designing the system model with the application, 3) analyzing variables affecting the system, 4) testing the simulation system by comparing the simulation results with the data of other studies, 5) conducting the simulation data processing, and 6) analysing the data obtained.

The sensor was simulated using the Kretschmann configuration. Three-dimensional sensor construction was made with 50 nm thick prism coated with nano-laminated gold to detect haemoglobin concentrations. This design is illustrated in Fig. 1. The gold layer was irradiated on a laser with a wavelength of 670 nm with a sweeping angle of 36-80 degrees. Reflectance was then analysed on each dielectric and gold surface by calculating the magnetic field and electric field using the FDTD method. Meanwhile, haemoglobin detection was simulated with the concentrations of 0; 6.5; 8.7; 17.3; and 26.0 g/dL. The haemoglobin sample that we simulated was Hb in pure water.


(a) (b)

(c) (d)

Fig. 1. Construction of a thin gold-plated haemoglobin sensor based on a Kretschmann configuration: (a) construction of a three-dimensional view, (b) display of the XY axis, (c) Display of the XZ axis, and (d) Display of the YZ axis.

The simulation time was 1000 fs, mesh accuracy was 6, the boundary condition like perfectly matched layer (PML) was set so that the profile of gold can be similar to the original characterization. Transmittance in the simulation is obtained by making a set of commands (coding) on the system.

The parameters to be analysed were sensitivity, FWHM, and signal to noise ratio (SNR). These parameters are known through the reflectance graph versus the interrogation angle. Sensitivity was analysed by calculating the angle shift when the SPR occurred at a different refractive index. Angle shift and haemoglobin concentration were plotted into the graph. The graph gradient was the sensor sensitivity. FWHM was analysed by measuring the curve width as shown in Fig. 2. The Signal to noise ratio (SNR) was analysed by calculating the sensitivity and width of FWHM. The sensitivity divided by FWHM was SNR. The modelled sensor performance was verified by comparing the results of the simulation with the results of the simulations carried out by Menon et al. [16].

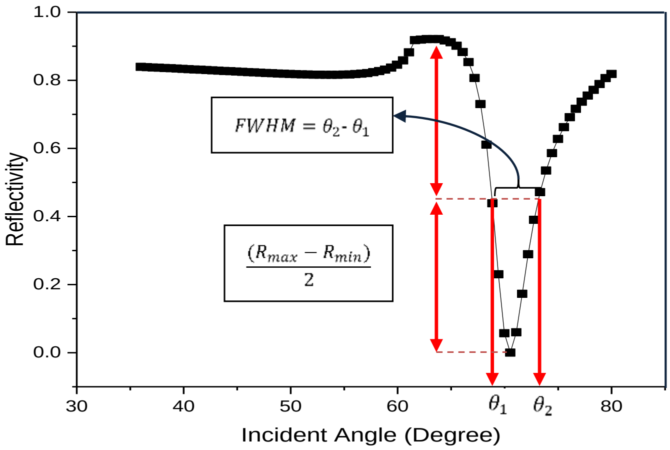


Fig. 2. Simulation analysis method for calculating FWHM values.

3. Results and Discussion

Kretschmann configuration is based on surface plasmon excitation events when Magnetic Transverse (TM) *k* passes through a nanofilm (εM) metal that has a refractive index lower than the refractive index of an analyte (nP> nD) at a certain angle [17].

The resonance conditions in the Kretschmann configuration can be explained by assuming the laser beam is polarized by the Prism-Metal-Layer sensor layer. Thus, based on the three-layer Fresnel equation, the reflectance is [14, 18]:

$$R = \left| \frac{r_{pm} + r_{ms} \exp(2ik_{mz}d)}{1 + r_{pm} r_{ms} \exp(2ik_{mz}d)} \right|^2 \tag{1}$$

$$R_{min} = 1 - \frac{4\eta}{(1+\eta)^2} \tag{2}$$

$$\eta \cong \frac{\epsilon_m''}{4|\epsilon_m'| \sin \emptyset} \left(1 + \frac{2\epsilon'^{\,2}_m}{{n_s}^3 \epsilon_m''} \kappa_s\right) exp\left[\frac{4\pi d}{\lambda} \sqrt{|\epsilon_m'|} \left(1 + \frac{{n_s}^2}{2|\epsilon_m'|}\right)\right] \tag{3}$$

Sensor simulations were carried out by the FDTD method. The sensitivity of haemoglobin sensors was based on gold-plated thin-film SPR, and the reflectivity was plotted against the angle of incidence in the SPR response curve as obtained from FDTD analysis in Fig. 3.

Figure 3 is the result of an FDTD analysis at a wavelength of 670 nm with water as an analytic medium or a haemoglobin concentration of 0 g/L. As shown in Fig.4, in the reflectance within the range of 36º-60º there was no resonance between the metal surface plasmon and the laser. A resonance event occurs at an angle of 70.53º. This is indicated by a large decrease in reflectance on the curve or a weakened total reflection (ATR) [19]. ATR is caused by the frequency of laser electromagnetic waves on the metal surface equal to the frequency of plasmon oscillations. The event can be formulated by equation (1). The resonance angle at 0 g/L of haemoglobin was used as a reference in calculating the resonance angle shift.

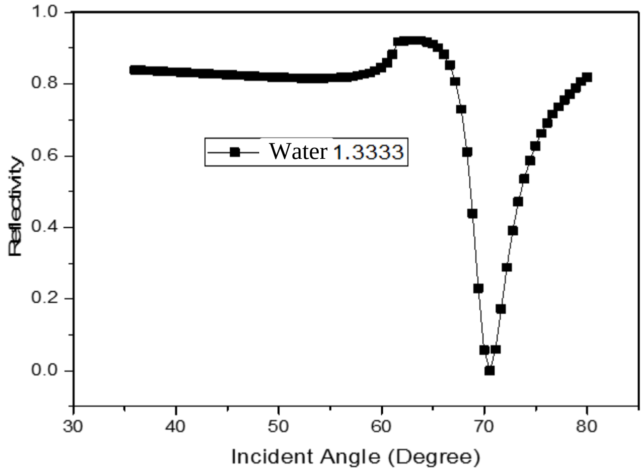


Fig. 3. The reflectivity curve for the resonance angle at 0 g/L of haemoglobin.

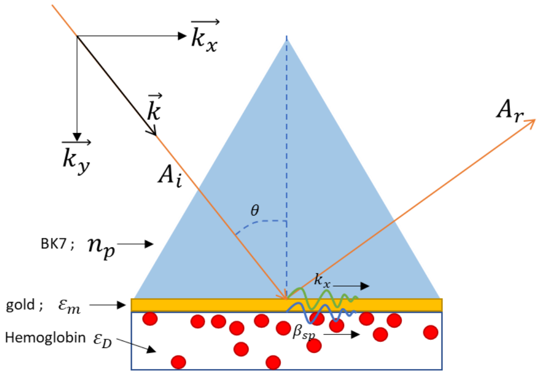


Fig. 4. SPR excitation used the couple prism with the Kretschmann configuration.

As shown in Fig. 5, variations in the concentration of Hb function to determine the performance of the sensor against changes in concentration in the analyte. The simulation results of haemoglobin at a concentration of 6.5; 8.7; 17.3; and 26 g/dL with a wavelength of 670 nm at 23°C showed a different ATR angle. ATR haemoglobin angle of high concentration was higher than that of low concentration. This is due to the concentration of Hb that changes the refractive index in the area near the thin gold layer. As shown in Eq. (2), when the haemoglobin concentration increases, the refractive index in the area near the gold layer also increases. This supports the research carried out by Prabowo et al. [17] which discusses the effect of the refractive index by shifting angles.

Figure 5 illustrates the different Hb concentrations that cause shifts at the resonance angle. When the haemoglobin concentration increases, the resonance angle also increases. Increased resonance angle of high concentration haemoglobin was higher than low haemoglobin concentration. The sensor also shows that it can respond quickly and continuously, showing the stability and ability of nano-laminated gold films to detect different concentrations of different haemoglobin concentrations. The sensitivity of the sensor can be calculated by plotting data like Fig. 6.

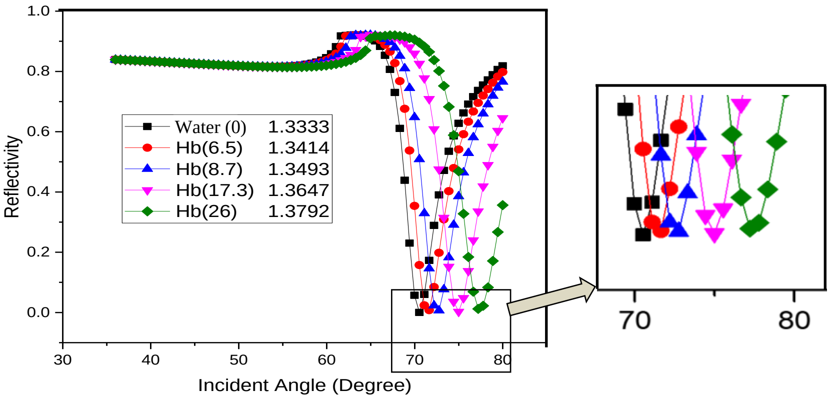


Fig. 5. Simulation results of haemoglobin with a concentration of 6.5; 8.7; 17.3; and 26 g/dL with a wavelength of 670 nm at 23°C.

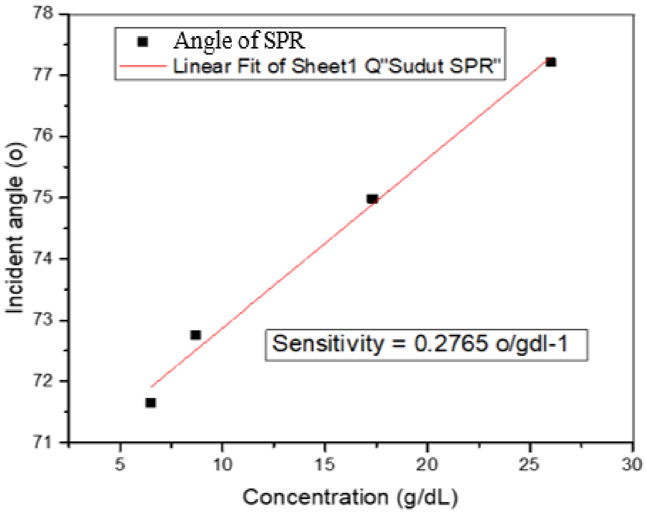


Fig. 6. A shift in resonance angles with different haemoglobin concentrations.

Variations in the shift of resonance angles at different concentrations showed a linear increase. Thus, the sensitivity value can be determined by calculating the gradient of the curve that is sensitivity of 0.2765°/g dL^{-1}. Sensitivity of the sensor depends on a shift in resonance angle and haemoglobin concentration. The resonance angle shift is an important parameter in detecting haemoglobin. That is because the greater the displacement, the higher the sensitivity of the sensor. High sensitivity can detect small changes in concentration with large shifts as has been done by Abdulhalim [20]. Thus, changes in concentration can be detected.

Based on Fig. 6, it can be seen that the haemoglobin sensor can detect changes in haemoglobin concentration in the range 0-26 g/dL. This is consistent with research by Zafar et al. [21] who managed to detect haemoglobin concentrations with SPR-based sensors with Metal Insulator Metal (MIM) configurations. Therefore, according to Table 1, the sensor can be used to determine the concentration of Hb in anemia patients.

Table 1. Parameters for anemia and refractive index at certain concentrations.

Concentration Hb (g/dL)	Shift Angle of SPR	Category
0	0	-
< 6.5	1.113924051	Anemia
< 8.7	2.227848101	Anemia
13 - 17	4.455696203	Normal
>26	6.683544304	High

FWHM is a parameter that represents an error measuring the concentration of analyte [22]. According to Dwivedi et al. [23], the smaller FWHM value, the smaller the sensor error rate will be due to the uncertainty of the small gauge. Based on Fig. 6, FWHM the average obtained is 5.11°. Signal to noise ratio (SNR) is a parameter that represents all sensor parameters. SNR obtained based on analysis is 0.6875. This result is better than SPR-based sensors that have been done by Sharma [24], where we obtained an SNR of 0.2334.

Table 2 shows a comparison of sensor parameters. The haemoglobin sensor with BK7 50 nm Au shows a sensitivity of 553 times greater than the sensor with 40 nm silica Au. This is because many factors include the thickness of the gold, the amount of variation in haemoglobin and the dielectric material [25]. The width of 40 nm FWHM silica Au is 3 times smaller than the sensor we modelled. The resolution of BK & 50 nm Au shows 64 times smaller than 40 nm Silica Au. Before determining resolution, we determined the resolution of the interrogation angle of (0.001o) so that the SNR value of BK7 50 nm Au was obtained 0.28 . 10^{-3} g/dL and 40 nm Silica Au. 0.018 g/dL.

Table 2. Comparison of performance of haemoglobin sensor parameters using Kretschmann based SPR with haemoglobin sensor made by Sharma [5] with dielectric silica and thick 40 nm Au.

Performance Parameter	Silica Au 40 nm	BK7 Au 50 nm
Sensitivity (°/g.dL)	0.0005	0.2765
Avg. FWHM (°)	1.606	5.11
Resolution (g/dL)	0.018	0.28×10^{-3}
SNR	0.493	0.688

4. Conclusions

The modeling and simulation of surface plasmon resonance sensors was conducted to detect human haemoglobin based on the Kretschmann configuration. A variety of haemoglobin concentrations which can be an indicator of anemia was used in the study. The sensor parameters are sensitivity, FWHM, resolution, and signal to noise ratio have been investigated. The effect of gold thickness, dielectric material, and wavelength can improve sensor parameters. In this study, we reported that the sensitivity value was 0.2765 g/dL, FWHM was 5.11°, the sensor resolution was $0.28 \ . \ 10^{-3}$ and the signal to noise ratio was 0.688. Therefore, this sensor can be used to detect haemoglobin.

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