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ORIGINAL ARTICLE

Optical and analytical investigations on dengue virus rapid diagnostic test for IgM antibody detection

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Abstract Evaluation of binding between analytes and its relevant ligands on surface plasmon resonance (SPR) biosensor is of considerable importance for accurate determination and screening of an interference in immunosensors. Dengue virus serotype 2 was used as a case study in this investigation. This research work compares and interprets the results obtained from analytical analysis with the experimental ones. Both the theoretical calculations and experimental results are verified with one sample from each category of dengue serotypes 2 (low, mid, and high positive), which have been examined in the database of established laboratorial diagnosis. In order to perform this investigation, the SPR angle variations are calculated, analyzed, and then validated via experimental SPR angle variations. Accordingly, the error ratios of 5.35, 6.54, and 3.72 % were obtained for the low-, mid-, and high-positive-specific immune globulins of patient serums, respectively. In addition, the magnetic fields of the biosensor are numerically simulated to show the effect of different binding mediums.

Keywords Surface plasmon resonance · Biosensors · Analytical analysis · Numerical model · Dengue rapid diagnostic test

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1 Introduction

The enzyme-linked immunosorbent assay (ELISA) technique is the typical method that has been used to quantify the antigen–antibody (Ag–Ab) interaction in biological samples for laboratory diagnosis [2, 12, 22, 26, 31, 41]. In these reported works [13, 29, 35], common ELISA method is a slow process due to the required incubation times (for a few hours to 2 days) and does not provide sensitive detection in non-laboratory settings typical of the point of care (POC) [44]. The automated ELISA system requires high-level expertise and expensive bulky equipment. Also, it is not available in many hospitals and consumes considerable amounts of chemicals. The polymerase chain reaction (PCR) technique [21, 25, 45] is another biochemical-based diagnosis that can be useful as long as the antigen is contained in the blood and cannot be applied once the viral genome has degraded. The rapid immune chromatography method [8] is another option for the detection of dengue infection. It takes only a few minutes and easy to use. This method needs one drop of blood for diagnosis. Therefore, the rapid immune chromatography method is only suitable for screening. This method is also not able to provide high sensitivity and specificity results.

Surface plasmon resonance (SPR) is an optical technique with applications in a variety of disciplines, especially in sensing devices. Its wide popularity can be attributed to the cross-disciplinary philosophy of present day researches [6, 34, 37, 43]. The SPR can be applied to probe changes in refractive index, which often occur within the immediate vicinity of the sensor surface. Previously, SPR was used for the investigation of inherent optical properties of thin metal films. Its usage has subsequently been expanded to a variety of applications including absorbance measurements, bio-kinetics, biosensing techniques, bulk liquid measurements, immune sensing, blood protein

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detection, gas detection, light modulation, process analytics, spectrometers, microscopy, refractive index measurements, polarization fibers, and thin film characterization [3, 5, 27, 28, 30, 36, 42].

In sensors, the surface plasmon (SP) mode is stimulated at the interface of a thin metal film and a small dielectric layer using a light wave. A refractive index change of the dielectric medium results in a change in propagation constant of the SP mode waveguide. Therefore, this alters the condition of coupling among the propagated light wave with specific incident angle and the SP wave and can be seen as changing one of the optical wave characteristics interacting with the SP mode. Based on their optical characteristics, these sensors can be categorized into polarization, phase, intensity, wavelength, and angular modulation. In this work, angular modulation was used for detection [15, 16, 32].

A commercial system which is based on the SPR technique has been applied to measure the wide range of real-time biomolecular interactions. It is possible to characterize the ligand–analyte binding reactions without the labeling requirements. The incident laser light is reflected from the inner face of the prism, which has its outer face coated by a layer of thin noble metal film, i.e., gold in common SPR setup. The intensity of reflected light will be lost to produce a resonance in electrons at the thin metal film at a unique angle [1]. Since the unique angle is dependent on the refractive index of the material on the thin metal surface, this phenomenon has therefore been applied to demonstrate molecular interactions in solid–liquid interfaces. One reactant (ligand) is immobilized on the gold surface, and another reactant (analyte) is flowed on the gold surface. When antibodies (Abs) as the analyte and antigens (Ags) as the ligand interact to bind each other, the response is produced and monitored in real time. The SPR biosensors measure the refractive index changes in the vicinity of the immobilized surface ligands [38].

Few researchers have successfully reported that the optical technique can detect the dengue virus. The SPR-based immunosensor for serological diagnosis [23], suitability of rapid diagnostic tests [39], increasing the sensitivity of acute dengue diagnosis using dengue NS1 antigen detection in combination with anti-glycoprotein E IgM and IgG serology [10], and early detection of all four dengue virus serotypes via SPR biosensor with high sensitivity and specificity [19] are examples of reported works on dengue diagnostics. However, the study of dengue virus is more complete if the mathematical assessments of binding between analytes and its relevant ligands on the SPR biosensor were done together with optical and clinical data analysis for biomolecular diagnosis of the dengue disease.

Finite element method (FEM), or finite element analysis (FEA), is a computation technique used to obtain approximate solutions of boundary value problems [4, 11]. Simply stated, a boundary value problem (BVP) is mathematical, whereby one or more dependent variables must satisfy a differential equation everywhere within a known domain of independent variables and satisfy specific conditions on the domain's boundary. The extensive use of FEM in solving the BVP of different disciplines has led to the production of lots of computational software such as COMSOL multiphysics. It is recognized for its flexibility and multidisciplinary modeling capability. COMSOL includes a powerful radio frequency module that is suitable for analyzing optical phenomena and has been accepted as one of the more dependable tool for simulating optical interactions [17, 18, 20, 46]. In this work, COMSOL is employed to study SPR.

Sunita Kumbhat et al. [23] have reported that the SPR technique can detect the dengue virus experimentally; however, they have not performed any analytical and numerical analysis in their study. In this manuscript, we compare and interpret the results obtained from analytical analysis with the experimental ones in the dengue virus diagnostics through biosensor. Moreover, according to our experiments, the patient specimens are classified into three types (low, mid, and high positive) of dengue serotypes 2, and only 1 μl volume of patient's serum is required to determine the SPR angle variation for each assay.

2 Materials and methods

2.1 Sample collection

Blood samples which were used in this work were collected from University Malaya Medical Centre, Hospital Ampang and Hospital Tengku Ampuan Rahimah (Klang). The approval of this study protocols was accepted by the institutional review board of the University of Malaya Medical Centre (Ethics no. 782.90) and from both Klang and Ampang Hospital (Ethics no. NMRR-10-683-6420). Written informed consent from patients was obtained prior to blood collection, and the study was conducted in accordance with the "Declaration of Helsinki."

Sera from symptomatic cases were collected and subjected to in-house IgM-Capture ELISA [24] for IgM detection, and hemagglutination inhibition (HI) test [7] for total dengue antibody detection. The evidence of infection has been defined through using the following criteria to transform the numeric positive/negative (*P*/*N*) ratio into four discrete categories: *P*/*N* ratio of <2 (definitive negative), *P*/*N* ratio of = 2 and <3 (low positive), *P*/*N* ratio of = 3 and <5 (mid positive), and *P*/*N* ratio of = 5 and >5 (high positive) [24]. These classified data were applied to the samples in this work. All samples used in this study were secondary

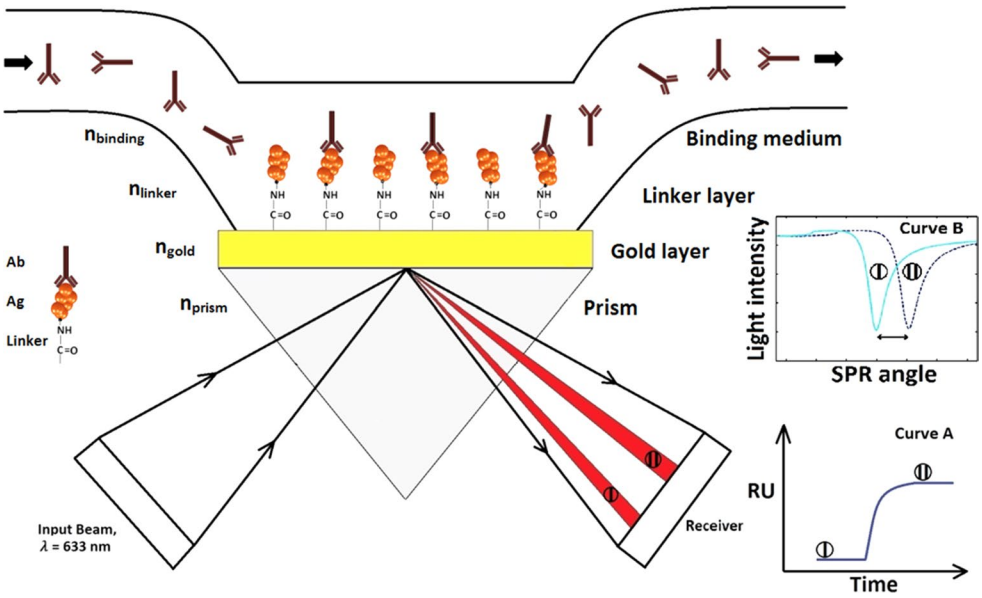

Fig. 1 The detection approach of SPR setup. The SPR reaction is correlated with refractive index changes at the surface of biosensor, caused by changing concentration of the binding medium when the antibodies as a target bind to the immobilized antigens as a probe

infection samples, and these criteria were done using the HI on the paired sample [7].

2.2 Equipment and reagents

The Biacore 3000 system is used to implement the experiments in this dengue research, and all protocols described and used materials herein are based on this device. One of the most widely used chips of the system for various detections in microbiological fields is CM5. Its operating principle is based on SPR technique and is a good choice for the experiments in this study. The approach is capable of assessing the deviation of SPR angle following detection of anti-dengue virus immunoglobulin M antibodies (IgM) in human serum samples. The distinction of dengue-specific IgM from cross-reactive IgM and the IgM reactions against the infection of serotypes, which are higher than other serotypes of the most major dengue virus infection, are the primary causes of using dengue-specific IgM [33]. The serotype-specific IgM was provided by the University of Malaya Medical Center (UMMC).

N-hydroxysuccinimide (NHS) and *N*-ethyl-*N*-(dimethylaminopropyl) carbodiimide (EDC) solutions (from amine coupling kit) are used to activate the surface of biosensor before the injection of the ligand. Deactivation and further washing away of loosely associated ligands are performed with ethanolamine solution with pH 8.5. The 10 mM sodium acetate buffer with a pH 4.5 is used to dilute the analyte to have sufficient concentration for the assay process.

For repeated use of the same sensor chip, the surface should be regenerated by the removal of analyte and any other non-covalently bound material. However, the ligand should be kept intact and should not be inactivated or denatured during the regeneration phase. A low pH buffer 10 mM glycine–HCl (pH 2.0) is used as a solution for regeneration of the chip surface.

2.3 SPR chip construction and Biacore instrument setup

According to CM5 biosensor structure [14], the chip is a glass surface covered with a thin layer (~50 nm) of gold, providing the physical conditions for generating the SPR signal. A coating on the gold layer provides a means for attachment of the ligand. In the case of the CM5 chip, this is a 100-nm-thick carboxymethyl-dextran matrix as a linker layer. This matrix provides a relatively inert hydrophilic environment suitable for most biomolecular interactions. This allows efficient immobilization from dilute solutions as well (Fig. 1).

Each angle of the reflected beam strikes the instrument's detector at a different point, and thus, the detector continuously records the position of reduced light intensity and calculates the SPR angle. The optical device has no moving parts, and the fixed geometry enhances stability and allows binding to be monitored in the real time.

A baseline SPR angle is first determined by washing buffer over the surface with a fixed amount of ligand attached. To this flow of buffer, some analyte is then added. The binding of analyte to immobilized ligand causes an increase in the refractive index at the surface; thereby, changing the SPR angle is directly proportional to the amount of bound analyte. The SPR angle change is reported as resonance units (RU) as shown in Fig. 1-curve A, where 1000 RU correspond to an angle change of ~0.1°,

and 1 RU corresponds to a refractive index change of ~1×10^{-6}. If the added molecule does not bind to a target or receptor, the SPR angle change (Fig. 1-curve B) in the sample and reference flow cells will be the same, and after subtraction, will give a zero net RU response that indicates no binding occurred. Only bound protein generates a positive SPR signal, and that signal, recorded over time, produces a sensorgram.

2.4 Analytical and numerical modeling of plasmons on the sensor surface

FEM is a general variational method, which finds a variational function whose minimum/maximum/stationary point corresponds to the solution of the partial differential equations (PDE) subject to certain boundary conditions. Its application to EM problems can be done through the Maxwell's equations in the frequency domain. FEM analysis of a problem consists of few general steps in this study, which are as follows: defining the required global parameters, modeling the proposed SPR configuration in design environment, meshing the model domain so that the simulated material is homogeneous on each element, deriving the governing equation for an element, assembly of all elements into a system of equations, and the solution of the system of equations based on electric/magnetic field and power flow of the structure.

A given problem is divided into many subproblems that are easier to solve, via a process called meshing. The problem is said to be divided into a finite number of elements. Different shapes may be used for elements depending on the geometry to be resolved and the computational resources available. Throughout our numerical studies in this thesis, triangular and rectangular mesh elements (selection based on different structures) are considered.

The SPR optical unit consists of a source for a light beam with free space wavelength 633 nm that passes through a prism (fused silica with refractive index 1.457) and strikes the surface of sensor at an angle such that the beam is totally reflected. Under these conditions, an electromagnetic component of the beam, the evanescent wave, propagates into the binding medium and can interact with mobile electrons in the gold film at the surface of the glass. At this particular wavelength and incident angle, a SP wave of excited electrons (the plasmon resonance) is produced at the gold layer (thickness ~50 nm) and is detected as a reduced intensity of the reflected light beam. The carboxymethyl-dextran matrix (thickness ~100 nm) and binding medium layers are located on the gold layer, respectively.

Figure 2 shows the configuration of the proposed carboxymethyl-dextran matrix-on-gold SPR biosensor, where the gold surface is covered with a fused silica prism. A light wave (of vacuum wavelength λ_0) passes through the

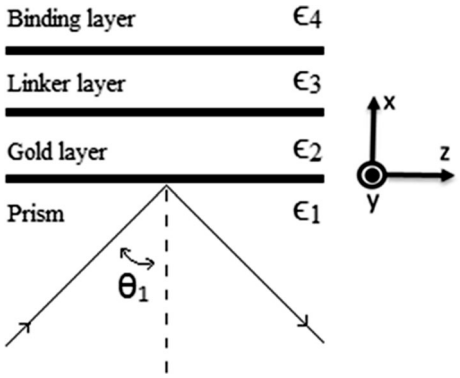

Fig. 2 The waveguide structure for mathematical and numerical modeling of SPR biosensor

prism and is totally reflected at the prism–metal interface, generating an evanescent wave. This evanescent wave can penetrate the thin gold layer and propagate along the x direction with propagation constant $k_x = n_{\text{prism}}\left(\frac{2\pi}{\lambda_0}\right)\sin\theta_1$, where θ_1 is the light incident angle in the first medium (prism) and n_{prism} is refractive index of the prism. The propagation constant k_x can be adjusted to match that of the surface plasmon polariton (SPP) by controlling the angle of incidence. The theoretical angle change can be calculated using complex Fresnel equations [9, 40]. The interaction of the light wave and the SPP can change the characteristics of light wave, such as the totally reflected intensity r_p is:

$$r_p = \frac{(M_{11} + M_{12}q_N) \times q_1 - (M_{21} + M_{22}q_N)}{(M_{11} + M_{12}q_N) \times q_1 + (M_{21} + M_{22}q_N)} \tag{1}$$

where

$$M_{ij} = \left(\prod_{k=2}^{N-1} M_k\right)_{ij}; \quad i,j = 1,2 \tag{2}$$

M is the characteristic matrix of this structure, which is given by

$$M_k = \begin{bmatrix} \cos\beta_k & -i\sin\beta_k/q_k \\ -iq_k\sin\beta_k & \cos\beta_k \end{bmatrix} \tag{3}$$

and where q_k is defined as:

$$q_k \cong \frac{\sqrt{\varepsilon_k - n_1^2\sin^2\theta_1}}{\varepsilon_k} \tag{4}$$

and the phase factor is expressed by

$$\beta_k = d_k\left(\frac{2\pi}{\lambda_0}\right)\sqrt{\varepsilon_k - n_1^2\sin^2\theta_1} \tag{5}$$

in which case, the design is considered by defining the arbitrary layer as thickness ($d_k = x_k – x_{k-1}$), dielectric constant

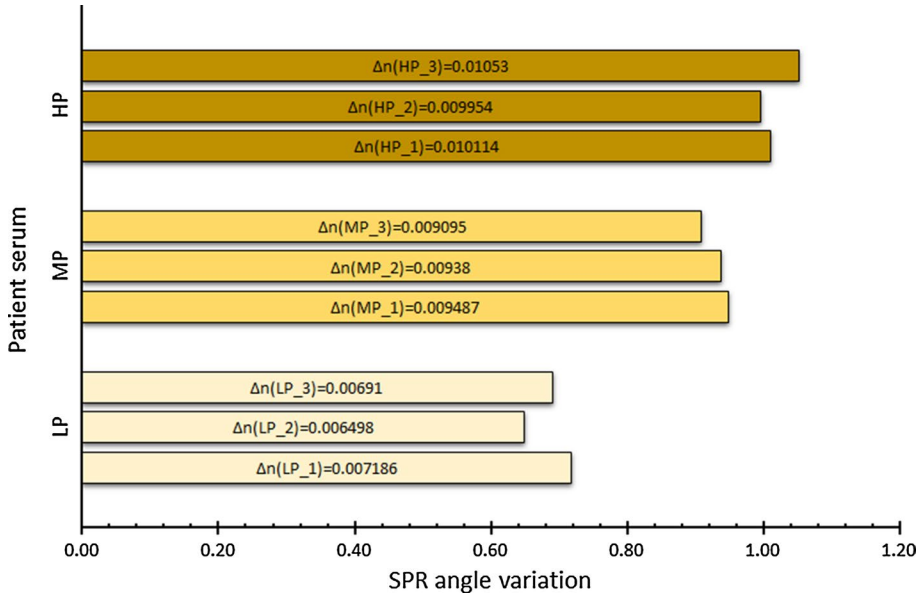

Fig. 3 Patients' serum via SPR angle variation and their refractive index changes

ε_k, and refractive index n_k. Finally, the reflectance R for the TM-polarized light of the complete multilayer structure is described by

$$R = \left|r_p\right|^2 \tag{6}$$

Besides the experimental results, this study deals with the optical properties of biosensor structure through analytical and numerical analysis.

3 Results and discussions

The SPR measurements as applied in biosensors are used to monitor the changes in thickness or refractive index of thin films at metal surfaces. In this study, the change in refractive index was proposed for the rapid detection of anti-dengue virus in human serum samples experimentally, analytically, and numerically.

3.1 Sensor characterization

The binding interaction between target and probe molecules is monitored by changing the SPR angle in real time. In the current case study, the dengue antigens are immobilized to the top surface of biosensor through carboxymethyl-dextran matrix (NHS/EDC solutions for activation of surface and ethanolamine for completion of immobilization procedure are used). The 1 µl of patients' samples, which diluted in sodium acetate with pH 4.5, are injected on the sensor surface one by one.

Since the sensitivity of Biacore system is each 1000 RU corresponds to an angle change of ~0.1°, and 1 RU corresponds to a refractive index change of ~1×10^{-6} of proteinous material [14], the SPR angle variations are calculated for all low-, mid-, and high-positive categories of dengue virus serotype 2. The SPR angle variations in each category are presented in Fig. 3.

According to the SPR angle variation obtained from each category, the refractive index change (Δn) of binding medium for different serums was calculated and depicted in Fig. 3. Based on sample table, the SPR angle variations were 0.6910°, 0.9095°, and 1.0532° for low-, mid-, and high-positive patients' serums with changing refractive index 6.910×10^{-3}, 9.095×10^{-3}, and 10.532×10^{-3}, respectively.

3.2 Analytical analysis for surface binding affinity

Based on analytical investigation, the plot of totally reflected intensity versus angle of incidence termed SPR curve was shown in the left side of Fig. 4. To generate a SPR curve, we used a generalized four-layer model. The first layer is prism with refractive index $n_1 = n_{\text{prism}}$. The kth layer (k: 2, 3) has a thickness of d_k and the local dielectric function $\varepsilon_k(\lambda_0)$ or the refractive index $n_k(\lambda_0)$. In $\lambda_0 = 633$ nm, there are the prism ($n_1 = 1.457$) | gold ($d_2 = 50$ nm, $n_2 = 0.2 + i3.32$) | linker ($d_3 = 100$ nm, $n_3 = 1.515$) | binding medium, where n_4 was found from experimental results.

Figure 4 shows the SPR angle variations based on the mathematical model of SPR structure. For this purpose, the obtained experimental changes in refractive index for each sample were applied in the analytical model. These changes have been schematically illustrated with corresponding sensorgrams in right side of Fig. 4. The SPR

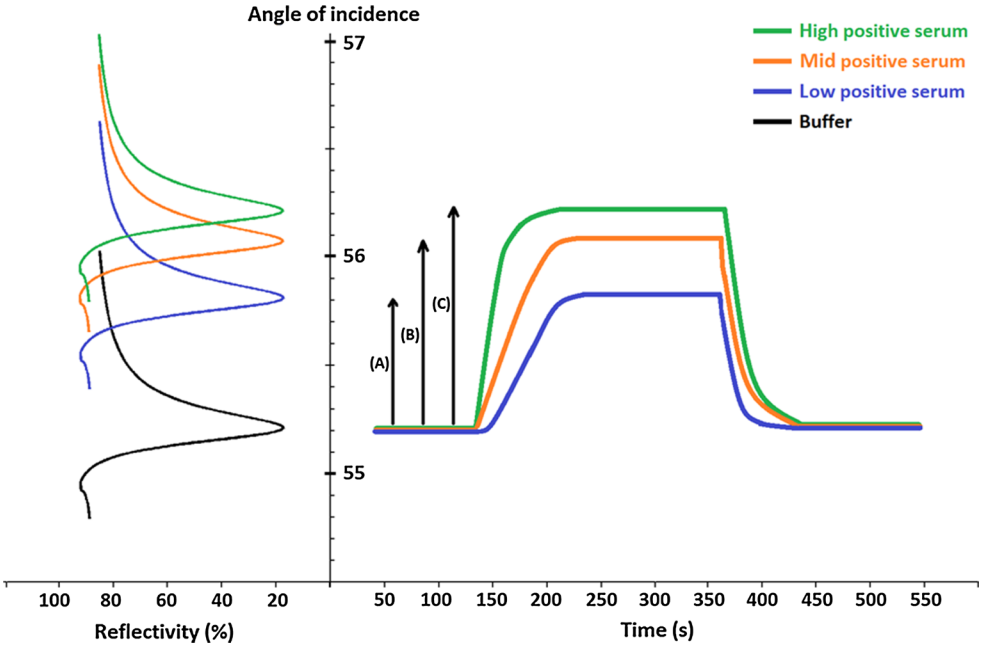

Fig. 4 The rotated presentation of the SPR dip (*left section*) that forms directly the pointer of the each sensorgram (*right section*) from clinical analysis

Table 1 The experimental data of ELISA test and the SPR biosensor using low-, mid- and high-positive patient serums

Type of sample (HI)	Patient serum	Results			
		ELISA method			SPR method
		P/N ratio	NS1	IgM	Serotype II ($\Delta\theta_{SPR}$)
Low positive (Ab titer 10–160)	LP_1	2.67	–	+	0.7186
	LP_2	2.47	+	+	0.6498
	LP_3	2.79	+	+	0.691
Mid positive (Ab titer 160–640)	MP_1	4.5	+	+	0.9487
	MP_2	3.75	+	+	0.938
	MP_3	3.93	+	+	0.9095
High positive (Ab titer 1280–10240)	HP_1	5.25	+	+	1.0114
	HP_2	6.06	+	+	0.9954
	HP_3	7.02	–	+	1.0532

angle variations in low- (A), mid- (B), and high (C)-positive dengue patient serums were calculated 0.654°, 0.85°, and 1.014°, respectively.

3.3 Validating simulation based on experimental results

Here, the experimental results are compared with theoretical results from mathematical analysis. According to the Sect. 3.1, the change in SPR angle was measured for rapid detection of anti-dengue virus in human serum samples experimentally. Based on the relationship of SPR angle and refractive index, the refractive index changes of binding medium for different serums can be acquired. In order to show the accuracy of theoretical analysis, the obtained refractive index of samples is applied to the mathematical model of SPR biosensor, which has been presented in the methodology section. Since there are about a large number of samples, only one sample from each category of dengue serotypes 2 (low, mid, and high positive) is selected and examined for verification of the analytical analysis. With respect to the sample table (Table 1), the SPR angle variation of sample LP_3, MP_3, and HP_3, which are as

Table 2 The SPR variations of three categorized serums analytically and experimentally and their mathematical error

Serum no.	SPR angle variation		Error (%)
	Mathematical	Experimental	
LP_3	0.654	0.6910	5.35
MP_3	0.850	0.9095	6.54
HP_3	1.014	1.0532	3.72

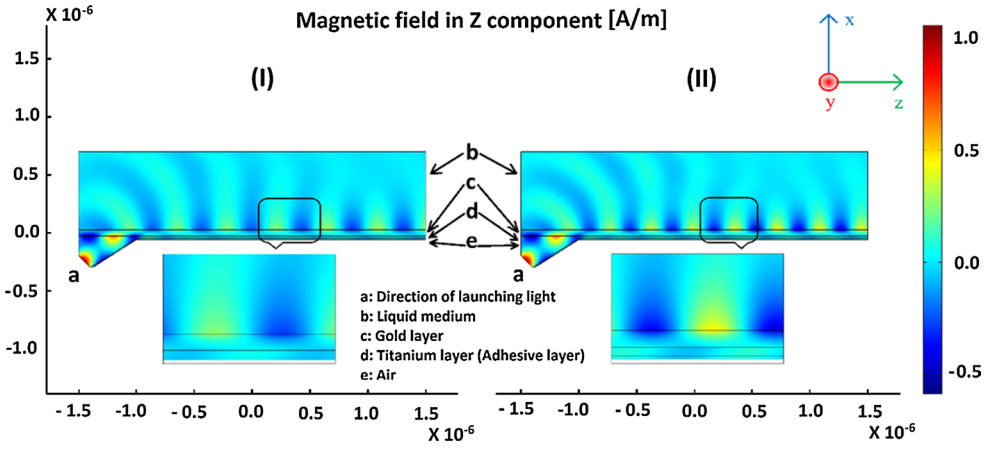

Fig. 5 The presence of magnetic field in z component by numerical modeling of biosensor structure (I) is with sample's refractive index of 1.33 and (II) is with sample's refractive index of 1.34

representative of low-, mid-, and high-positive dengue serotype 2, respectively, is presented along with their refractive index changes in Fig. 3.

Table 2 shows the mathematical error for dengue detection in low-, mid-, and high-positive patients' serums. According to this table, by experimental investigation on analyte–ligand binding quantity and then analytical analysis of the biosensor-based practical conditions, we found the error ratio of each category (~5.35, 6.54, and 3.72 %) compared with experimental results.

3.4 Numerical analysis for surface binding affinity

The SPR biosensor and its behavior are simulated by a numerical approach using FEM. The magnetic field in the z direction of plasmons on the gold film is simulated in Fig. 5. An increase in the z component of magnetic field (generated resonance on the gold surface) is observed when the refractive index of patient sample is increased. This increase is clearly shown in Fig. 6. This small change is due to the delicate sensitivity of SPR biosensor, showing the quantity of bound antibodies with the immobilized dengue antigens. The increasing of quantity raises the refractive index of binding medium, which are plotted in the magnetic field at the minimum as initial buffer (1.33) and maximum as a high-positive dengue serum (1.34). According to the quantity of bound Ag–Ab onto the sensor surface, the magnetic field varies between the two curves.

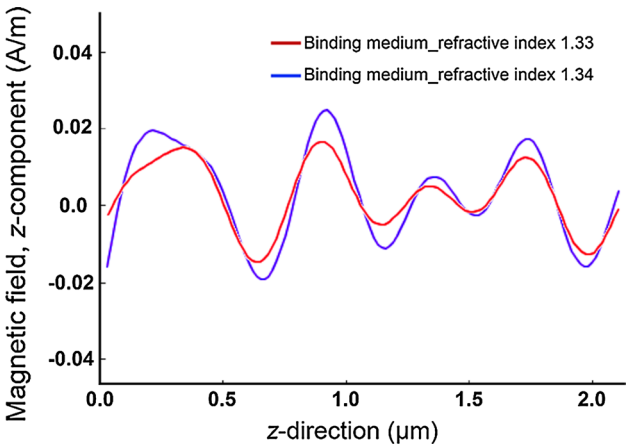

Fig. 6 Numerical analysis of biosensor structure with refractive index 1.33–1.34

4 Conclusion

We showed that the proposed SPR-based biosensor is satisfactory for the direct determination of dengue Ag–Ab binding interaction on the sensor surface. Experimental and computational investigations have been carried out in order to determine the dengue Ag–Ab interactions occurring on the surface of the SPR biosensor. This study indicated that the shifting of SPR angle in experimental and analytical results almost conforms to each other. The magnetic fields of the sensor surface were numerically simulated to show the effect of different binding mediums. This research work offers a promising analytical analysis of immunosensor interference in clinical diagnostics.

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