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ORIGINAL RESEARCH

A novel computation method for detection of Malaria in RBC using Photonic biosensor

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Abstract Initial stage detection of malaria is very helpful in reducing the human death rate. Generally manual diagnosis is used for detection of malaria using 100 × to 600 × microscope but time required for this process is very large and false report chances are more, which results in death of a person. A high speed, low cost and result accurate biosensor plays a key role in diagnosis of malaria. When malaria parasite's infects RBC's, its mechanical, physical and biochemical structure will get modified results in change of refractive index of RBC. Therefore, refractive index varies from normal RBC to infected RBC. This factor is utilized to design the photonic biosensor for detection of malaria in humans and it is label free detection method. The proposed photonic crystal sensor has 10 μm × 10 μm dimension. The extracted sample is placed in the sensor holes and light beam with a wavelength of 1.85–1.95 μm is fed inside the bio sensor. If the malaria parasites are present then there will be variation in RI from normal sample results in the wavelength shift. FDTD technique is used for the simulation of this model. Quality factor achieved for this design is 214 and the sensitivity for change in refractive index is 225 nm/RIU.

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Keywords Biosensor · RBC-red blood cells · Malaria · FDTD- frequency division time domain · RI-Refractive index · Photonic Crystal

1 Introduction

Malaria is one of the deadly diseases transmitted by the female mosquito bite Anopheles. In 2019 December, World health organization has reported that there are 228 million malaria cases out of that 405,000 are death cases [1]. African countries are badly affected by the malaria parasites and it shares the maximum percentage of malaria cases in the world wide. Children are also more severely affected group by malaria disease, around 67% of malaria deaths are children under the age group of 5.

Malaria parasites that can infect humans are been classified as plasmodium falciparum, P. Ovale, P. Vivax and P. Malarial. In this types P. falciparum is most deadly parasite, persons who encounters this type of parasite having high risk of death. When infected mosquito bites humans its symptoms appear usually from 10 to 15 days, it has to be treated at the initial stage only if not it progresses more and more causing severe illness which leads to death. The complications of malaria are swelling of brain blood vessels, breathing problem due to accumulation of fluids in lungs. Kidney, spleen and liver failure, damages to RBC causes Anemia.

Places with longer life span of mosquitoes there will be intense transmission of malaria. The African species of mosquitoes has longer life span therefore it shares 90% of malaria cases. Transmission will also depend on the climatic conditions of the regions such as rainfall, humidity and temperature. Spreading of malaria will also depends on the immunity of the person. Regions with less immunity

are more prone to malaria epidemic, therefore malaria is more in African countries.

The proposed model is novel in approach because it is designed using low cost, faster result, label free photonic crystal biosensor and diagnosis of malaria is done using RBC at different stages of the disease such as Ring stage in the period of 24 h, Trophozoite stage period of 24–36 h, Schizont stage period of 36–48 h in the human body, it plays a significant role to find the current condition of the person.

Arslan Khalid et al. have proposed malaria detection using automated image processing technique for microscopic images. The generated images are zoomed to 800X by microscope. The sample is Giemsa stained to acquire the images [4]. Octave Iradukunda et al. have modelled Machine Learning based Malaria Prediction, they used dataset of National Institute of Health in USA, which contained total of 27,560 RBC. It is a intense learning technique and results depends on the data set provided from old results [9]. Bhaiyya D. Ghanmode et al. have done work to find the malaria concentration using digital image processing techniques [5]. Salih Bayar et al. has designed the FPGA based CNN algorithm for malaria detection [10]. Image process techniques are not label free method, so the chances of error are more due to initial stain preparation for the sample. Also, parasite's structure and physical bonding are not same in all regions, it depends on climatic condition of that region. FPGA method is too complex and algorithm efficiency will also matter in detection of parasites. So, the proposed model is label free, cost and computation time is less.

The proposed work is systemized in paper as follows. Section-A gives brief summary of malaria and previous works done on detection of malaria. The section-B defines basics of the photonic crystal with the help of maxwells equation and its working mechanism. Section-C gives the steps to design biosensor and its workflow. Section-D shows results with transmission spectrum in each stage of malaria and discussion on quality factor and sensitivity. And finally, Section-E gives conclusion about the sensor work.

2 B Photonics

Photonics is an emerging field in biosensor and has wide range of applications. Photonics is a branch of science deals with the study of light and its properties. In this work photonic crystal structure is used to design the sensor, in Photonic crystals the structure is periodic in arrangement. In this periodic structure when a light is passed it forbids certain wave length of light to pass straight-through the structure which forms bandgap in the frequency spectrum [3]. This bandgap in wavelength based mainly on refractive index of that material, the periodic structure refractive index and the lattice constant between the structure holes of crystal. It is related by Bragg's law:

$$2d.\sin\theta = n\lambda \tag{1}$$

where 'd' is lattice constant, θ is the angle of incidence of light to the structure, λ is the wavelength.

Bandgap of the structure will also depend on crystal rod radius and the wavelength of the incident light from the source. Photonic crystal is been classified based on the structural composition as 1-dimenstion, 2-dimenstion, 3-dimenstion structures. 3D structures are very complex to design and error free fabrication is difficult to attain. In the present work 2d structure is used, it also gives better light confinement inside the structure and steps to fabricate is also not too complex. To obtain required sensing characteristics defects are done in the crystal structure, by removing certain holes or changing the size of the holes [6]. When defects are introduced a pilot wavelength can occur in the bandgap, this gives the reference arm or point in the sensor design. Photonic bandgap depends on number of factors, but fine tuning can be done by introduction of defects by changing physical characteristics.

The time varying EM fields obey Maxwell's equations which in differential form are as follows:

$$\nabla.H(r,\ t) = 0 \tag{2}$$

$$\nabla \times E(r,\ t) = -\mu(r)H(r,\ t)/\partial t \tag{3}$$

$$\nabla \times H(r,\ t) = \sigma(r)\mathrm{E}(r,\ t) + \varepsilon(r)\partial\mathrm{E}(r,\ t) \tag{4}$$

$$\nabla.E(r,\ t) = \rho(r,\ t)/\varepsilon(r)(r,\ t) \tag{5}$$

where, E (r, t) and H (r, t) are time varying electric and magnetic fields ε(r), μ(r) and σ(r) are permittivity, permeability and conductivity of the medium respectively. Equations 2, 3, 4, 5 gives relationship of permittivity and permeability in terms of electric and magnetic fields wave propagation through the crystal.

The refractive index η and dielectric function ε are related by $\varepsilon = \eta^2$. Based on the Refractive index only sensor working can be characterized. Variation in the refractive index will results in the shift in the bandgap wavelength.

To simulate the structure using perfectly matched layer condition Finite Difference Time Domain method is used. In this structure space is divided into small cells and simulation is done in X, Y and Z axis. In this simulation is done using Maxwell's electromagnetic equations.

3 C Biosensor design

A two-dimensional structure is used to design the sensor. It is a two layered structure, a base layer to give support to sensor and the top layer is sensing part. Base material is silicon dioxide with refractive index of 1.48 and the sensing part has 3.45 refractive index with holes made in the silicon layer. Defects is created by absence of holes in Z shape in the sensor array from input side end to output side end. A point defect is made in the middle line to tune the resonance point. Holes radius is 150 nm and it is same for all holes in the entire structure. The lattice constant is 520 nm both in x-axis and y-axis. A gaussian source with input wavelength of 1.85 μm–1.95 μm is placed at the input side end of the line waveguide. A power monitor is used at the output side end to record the output intensity having 500 simulation points at the curve. In the monitor setting PML is selected to observe the outside radiated energy from the structure. Mesh condition is set to the entire structure to avoid the external factors like temperature, humidity, dust etc. in varying the output curve. 2D FDTD simulation is done covering the entire structure in X and Y plane of the structure. The FDTD method is time-tested and stable, and can efficiently handle material dispersion and nonlinearities. It is based on the time-domain, it can cover a wide range of frequency in a single simulation run. In the Z-axis it is placed at the middle of the sensor part aligned to the source and the monitor to record the more accurate result. To design the structure and run the simulation Lumerical software is used.

Figure 1 shows X–Z axis view of the biosensor, underlying structure is made of base material silicon dioxide and the upper sensor layer is configured as holes in slab.

Table 1 gives the main design specifications in constructing the sensor and its corresponding values. Figure 2 depicts the X–Y image of the 2-dimensional structure of the proposed malaria biosensor. The thickness from base material to top is 20 nm, in this pipe hole structure extracted sample is placed. In this Z shaped Line defects is made by the absence of some holes in the input side waveguide and output end waveguide. A point defect is done at centre line by removing one hole. The radius of sensor array holes is all kept constant and the RBC samples are filled in the sensor holes of the slab. The sensor is placed in air, therefore the background index in the simulation environment is set 1, indicating the refractive index of air. The beam width of the source is adjusted based on the width of the defect created. Sensor holes are one of the tunning factors in achieving the quality factor. The ring surrounding the holes are varied in small steps to achieve the maximum Q-factor of the sensor.

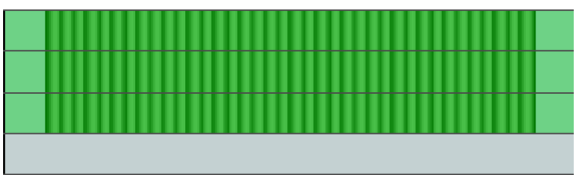

Fig. 1 Photonic biosensor front view

Table1 Design specifications

SL. No	Parameters	Values
1	Radius of sensor holes	150 nm
2	Lattice constant of sensor holes	520 nm
3	Base (SiO_2) refractive index	1.48
4	Sensor (Si) Refractive index	3.45
5	Normal red blood cell	1.402
6	Infected cell at ring stage	1.395
7	Infected red blood trophozoites stage	1.383
8	Infected red blood schizont stage	1.37
9	Wavelength of Gaussian light source	1.85–1.95 μm

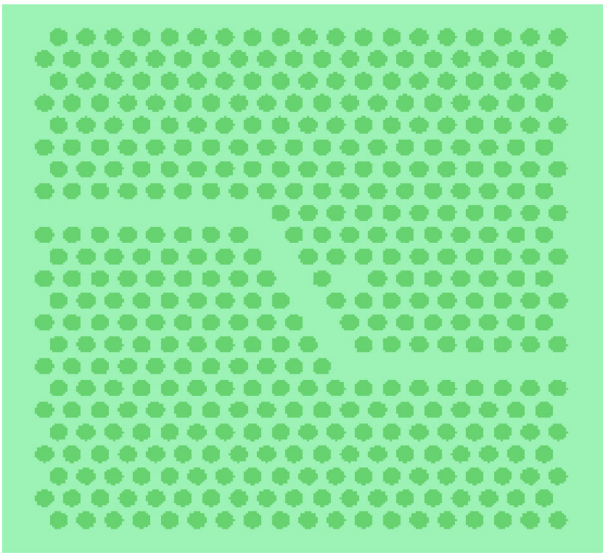

Fig. 2 top view of the PhC sensor

(Fig. 3) illustrates the process in malaria detection using the extracted sample. It uses the spectrum comparison for detection process using RI of sample.

Array code:

```
z_span = %z span%;
n_rows = 20;
n_cols = 24;
even_flag = 0;
for(i = -20/2:n_20/2) {
for(j = -24/2:24/2) {
addcircle;
```

```
set("140 nm",radius);
if( even_flag = = 0) {
set("x",(j)xa + a/2);
} else {
set("x",(j)xa);
}.
set("y",(i)xaxsqrt(3)/2);
set("z",0);
set("0.2 μm ",z_span);
set("material",material);
if(get("material") = = "silicon").
{ set("3.45",index);}
}.
if(even_flag = = 0) {
even_flag = 1;
} else {
even_flag = 0;
}
}
```

4 D Simulation results

This section consists of transmission spectra of normal RBC and infected RBC. The size of the hole radius is 150 nm, for the analysis two iterations is done. First Gaussian light with wavelength of 1.85–1.95 μm is injected to the structure by filling the holes with sample of normal RBC analyte having refractive index of 1.402, next the obtained transmission spectrum is been noted down. In the second iteration holes are filled by malaria parasite infected RBC into the Holes. At the end results of the both the iterations are compared to compute the presence of malaria parasite. In this sensor, analysis can be done on two ways, one is wavelength shift and the intensity shift.

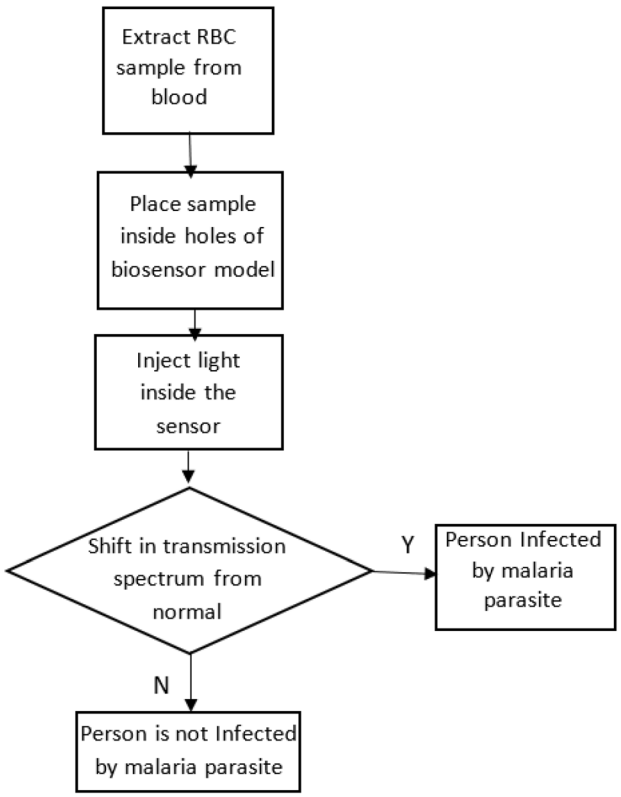

Fig. 3 Malaria detection process

The malaria computation efficiency of sensor is determined using biosensors quality factor (Q) and the sensitivity. Q-factor of sensor is defined as resonant wavelength to the difference between the wavelength at full width half maximum (FWHM).

$$Q = \frac{\lambda\gamma}{FWHM} \tag{6}$$

where 'λr' is maximum resonating wavelength and FWHM is difference between the maximum power to half power wavelength. The achieved Quality factor for the proposed sensor = 214.

Sensitivity of biosensor is stated as the relative change in the resonating wavelength (Δλ) to the corresponding change in the refractive index (Δn).

$$s = \frac{\Delta\lambda}{\Delta n} \tag{7}$$

The limit of detection (LOD) indicates the minimum change detectable for the change in refractive index, which is a function of FWHM and sensitivity and is calculated using equation (Table 2), (Fig. 4)

$$LD = \frac{FWHM}{S} \tag{8}$$

(Figs. 5a, b) initial stage of disease occurs within 24 h of infection. In the first iteration holes are packed with the normal extracted sample having refractive index of 1.40 is processed using simulator, its obtained transmission plot with resonant wavelength of 1921 nm is kept as reference for further comparison. In the second iteration holes sample with ring stage is placed in the sensor with refractive index of 1.39 is simulated and the obtained resonance peak at

Table 2 Quality factor for different hole array size

Size of holes (nm)	λr	FWHM	Q-factor
140	1912	10	191
145	1917	9.8	195
150	1921	9	214
155	1928	9.6	200
160	1932	9.4	194

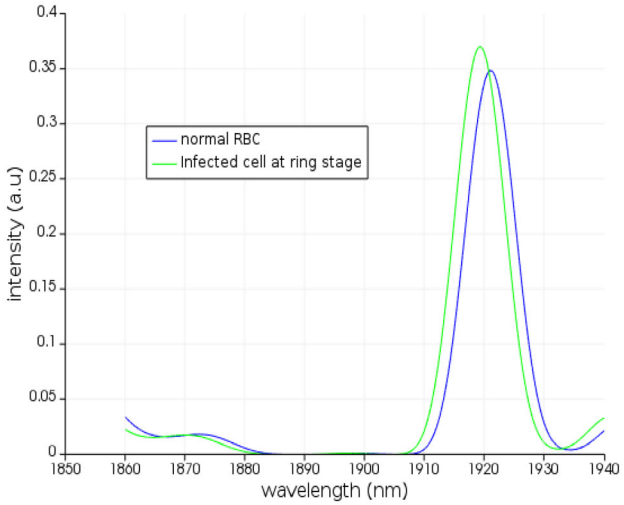

Fig. 4 Transmission spectra in ring stage

1919 nm. Comparing these two iterations, wavelength shift noted is 02 nm and intensity shift is 0.02 a.u.

Figure 4 shows the transmission plot for trophozoites stage of malaria. The resonating wavelength got is 1917 nm, shift of 04 nm wavelength and change in intensity is 0.04 a.u with respect to the normal sample. Figure 5 is the schizont stage and it is the last stage of malaria disease, having the large shift of wavelength of 06 nm and intensity change in peak curve is 0.06 a.u. For the hole radius of 150 nm the resulted quality factor is 214 and the computed sensitivity is 225 nm/RIU.

Figure 6 shows the electric field intensity inside the sensor in the simulation process. flow elites light propagating in the waveguide of the top sensor layer (Table 3).

5 E Conclusion

Manual microscopy, image processing and machine learning is time consuming and each has its own challenges. The designed biosensor is cost effective and highly efficient to compute the malaria-parasite infected-RBC. The proposed biosensor is novel approach in immediate processing gives good result in matters of accuracy and detection using RBC. Since this computation is label free the error probability is very less. The dimension of the biosensor is 10 µm × 10 µm, by changing the various sensing parameters the quality factor is improved and the sensitivity is also made sharp for computation. The normal RBC's and malaria-parasite infected RBC's refractive index is used to compute the malaria in humans. The proposed photonic biosensor computation efficiency is better than the microscopy, image processing techniques. The sensor is modelled using Lumerical software suit and simulation is done by 2D-FDTD method.

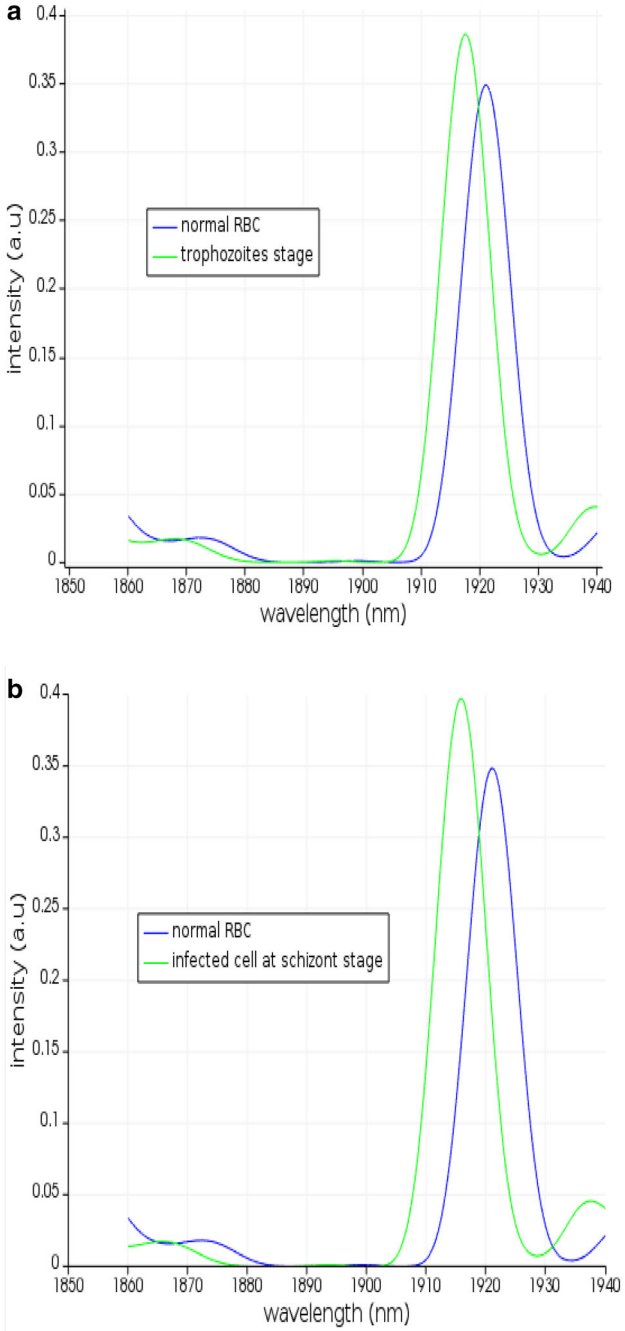

Fig. 5 **a** Transmission spectra in trophozoites stage, (**b**) Transmission spectra in schizont stage

6 F Future scope

Photonics is a most promising field in detection of disease for its label free detection method. Whole world is facing lot of challenge in detection of COVID-19. Photonics can be used for early detection of corona by using refraction index of the sample.

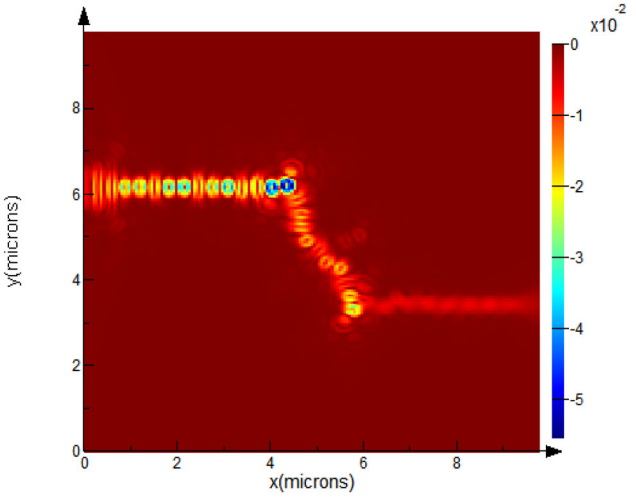

Fig. 6 Electric field intensity

Table 3 Wavelength shift and intensity shift

Type of cell	Resonant λ	λ shift	Intensity	Intensity shift
Normal	1921 nm	–	0.34	–
Ring stage	1919 nm	02 nm	0.36	0.02 a.u
Trophozoites stage	1917 nm	04 nm	0.38	0.04 a.u
Schizont stage	1915 nm	06 nm	0.40	0.06 a.u

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