High-sensitivity biosensor for simultaneous detection of cancer and diabetes using photonic crystal microstructure

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Received: 21 April 2021 / Accepted: 6 November 2021 / Published online: 24 November 2021 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

Abstract
In this study, we propose a refractive index-based sensor to detect skin cancer (Basal, HeLa, MDA-MB-231) through human blood. It also can detect diabetes through human tear fluid based on photonic crystals (PhC) at the same time. The proposed PhC composed of silicon rods in the air bed arranged in a hexagonal lattice, forms the fundamental structure, and two tubes are used to place the cancerous or diabetic samples for measurement. The sensor’s transmission characteristics are simulated and analyzed by solving Maxwell’s electromagnetic equations using the finite-difference time-domain method for samples under study. The diagnosis of three types of cancer and diabetes is based on changing the samples’ refractive index by applying the laser source centered at 1550 nm. Our results demonstrate that the proposed structure’s quality factor and sensitivity can be adjusted by changing the sensor’s geometry. They reveal that the transmission power is between 91–100%, depending on the sample. The sensitivity range is also between 1294 and 3080 nm/RIU. The maximum figure of merit is about 1550.11 RIU−1 with a detection range of 31 × 10−6 RIU. The small biosensor area of 61.56 μm² makes it suitable for various applications in compact photonic integrated circuits.

Keywords Photonic crystal biosensor · High sensitivity · Skin cancer · Human blood · Tears fluid

1 Introduction

Integrated optical circuits (IOCs) have significant advantages over electronic integrated circuits (EICs). IOCs have a much higher propagation speed, very low loss, low data transmission error, and very high security compared to electrons in EICs. In recent years, photonic
crystals (PhCs) have played an important role in designing all-optical circuits due to their unique properties. One of these features is their photonic bandgap (PBG) that prevents lights of certain wavelengths from propagating in one, two, or any number of polarization directions within the PhC structure. PhCs are designed in one, two, and three-dimensional structures, whose two-dimensional structure has been considered by researchers due to its greater applications and fabrication simplicity. Research groups designed a variety of structures using two-dimensional PhCs such as optical filters (Guo et al. 2019; Alipour-Banaei et al. 2014; Rakhashani and Mansouri-Birjandi 2013; Naghizade and Saghaei 2020a; Foroughifar et al. 2021), logic gates (Younis et al. 2014; Andalib and Granpayeh 2009; Hussein et al. 2018), encoders and decoders (Naghizade and Khoshima 2018; Moniem 2016; Naghizade and Saghaei 2020b; Naghizade et al. 2018), comparators (Fakouri-Farid and Andalib 2018; Jile 2020), multiplexers and demultiplexers (Naghizade and Mohammadi 2020; Naghizade and Sattari-Esfahan 2017), adders and subtractors (Hosseinzadeh Sani et al. 2020; Moradi 2019; Sani et al. 2020a; Maleki et al. 2021a, b; Sami et al. 2020; Naghizade and Saghaei 2021a), registers (Pahari and Guchhait 2012; Martinez-Dorantes et al. 2017), memories (Kuramochi et al. 2014; Alexoudi et al. 2020; Uda et al. 2018), splitters (Naghizade and Mohammadi 2019; Parandin et al. 2018; Saghaei et al. 2017), analog-to-digital converters (Naghizade and Saghaei 2021b; Sani et al. 2020b, c), optical fibers (Ghanbari et al. 2017, 2018; Saghaei et al. 2015, 2016a, b; Aliie et al. 2020; Diouf et al. 2017; Saghaei 2017), sensors (Tavakoli et al. 2019; Tabrizi et al. 2021; Alden Mostaan and Saghaei 2021; Kowsari and Saghaei 2018; Sani et al. 2020d; Qing and Mojtaba 2021; Sani and Khosroabadi 2020), PhC fibers (Saghaei et al. 2015; Diouf et al. 2017; Saghaei 2018; Ebnali-Heidari et al. 2012, 2014; Rcae et al. 2018; Saghaei and Van 2019; Saghaei and Ghanbari 2017; Ghanbari et al. 2019; Kalantari et al. 2018), switches (Mehdizadeh et al. 2017; Chen et al. 2006; Alipour-Banaei et al. 2015; Danaee and Kaatuzian 2011), interferometers (Gu et al. 2007; Saghaei et al. 2019; Danaee et al. 2019), as well as all-optical clocked sequential circuits including flip-flops (Rao et al. 2020; Zamanian-Dehkordi et al. 2018), synchronous and asynchronous counters (Poustie et al. 2000; Kaur and Kaler 2014).

In recent years, the refractive index sensor based on Fano resonance has become an active research topic (Wen et al. 2015). Fano resonance is formed by the interference between discrete-state energy levels (narrow non-radiative dark mode) and continuous-state energy bands (broad radiant, bright mode), and it results in an asymmetrical and sharp linear graph (Luk’yanchuk et al. 2010). Therefore, they are widely used in optical switches, nonlinearity, slow-optical devices, and biosensors (Butet and Martin 2014; Klimov et al. 2017; Peng et al. 2018). Liu et al. proposed a planar meta-material sensor with electromagnetic induction transparency with a sensitivity of 588 nm/RIU (Liu et al. 2010). Guo Yuan et al. studied a new type of symmetrical plasma structure composed of a metal–insulator-metal (MIM) waveguide and a semi-ring short tube to control the asymmetric linear shape resonance wavelength, and it had a sensitivity of 575 nm/RIU (Yuan et al. 2018). Zhou Jinli et al. designed a sensor with a trapezoidal structure to study the refractive index’s sensitivity by filling a half-wavelength waveguide and a refractive index medium with a sensitivity of approximately 750 nm/RIU (Zhou et al. 2018). Zhou Jinli et al. also designed a sensor with a trapezoidal structure to study the refractive index’s sensitivity by filling a half-wavelength waveguide and a refractive index medium with a sensitivity of approximately 750 nm/RIU (Zhou et al. 2017). Zafar et al. proposed a double elliptical ring-shaped resonator that can be used to detect the concentration of hemoglobin in the blood, with a sensitivity of 1100 nm/RIU (Zafar et al. 2018). Wang Mengmeng et al. developed a nano sensor with a baffle and a circular resonant cavity to achieve a double Fano resonance with a sensitivity of 1114.3 nm/RIU (Wang et al. 2019).

There are two main methods used to identify biological cells. In the conventional method, labels are used to identify the characteristics of biological cells, which is a traditional and invasive method, and in the second method, non-invasive and unlabeled tools are
used to diagnose cell conditions that there are no markers required to identify the analytes. Since no labels are attached to the molecules, their true information and nature remain intact. Biosensors can also be used in cancer research to analyze target cell lines or protein changes in the cell. All-optical biosensors are suitable structures for fast detection. The main function of PhC-based biosensors is based on changing the refractive indices of the samples. The structure designed in this work can simultaneously detect three types of cancer and diabetes, improving the structure’s performance from existing sensors. On the other hand, it is possible to detect their disease by simultaneously having samples of two people. The proposed device can be used as an appropriate method to accelerate cancer diagnosis and diabetes in critical situations and crowded hospitals.

1.1 Cancer (blood sample)

Skin cancer is the most common malignancy and accounts for about half of all cancers in the United States. More than 1 million cases of skin cancer are diagnosed in this country every year. In 2009, there were approximately 11,590 deaths from skin cancer (American Cancer Society 2009). Risk factors for skin cancer include exposure to ultraviolet light, age, male gender, genetic susceptibility, and structural factors, such as hair color, number of moles, skin color, and skin reaction to sunlight (Naldi et al. 2005). There are three types of skin cancer: Hela, Basal cell, and MDA-MB-231 cell, which originates from three main types of epidermal cells.

The proposed sensor detects skin cancers by subcutaneous blood fluid. The refractive index of cells measures the main function of detection in the bloodstream. In the measurement method, according to the refractive index determined, we only checked the presence or absence of cancer cells in the blood, for example, if there is the lowest amount of basal cells in the blood, the refractive index changes and the output is shown. On the other hand, as a future work, this sensor can be upgraded to measure the concentration of cells. because the proposed biosensor measures human tear fluid in addition to measuring blood samples, it cannot focus on the concentration of cancer cells. In this article, only the presence or absence of Hela, Basal and MDA-MB-231 cells has been measured and analyzed.

1.2 Diabetes (tears fluid sample)

Diabetes is a metabolic disorder in the body. In this disease, the body’s ability to produce the first hormones is lost, or the body is resistant to insulin, so insulin production cannot function normally. The main role of insulin is to lower blood sugar by various mechanisms. There are two main types of diabetes: in type 1 diabetes, the degeneration of beta cells in the pancreas leads to a defect in insulin production, and in type 2, the body’s resistance to insulin increases, which may eventually lead to the destruction of beta pancreas cells and complete failure of insulin production. In type 2 diabetes, genetic factors, obesity, and dementia play a major role in the disease. Diagnosis, as well as screening for diabetes, can be done with a blood sugar test. The test for the presence or absence of diabetes is usually done with pain and bleeding. This article uses a tear fluid to distinguish a person with diabetes from a normal person (Makaram et al. 2014).

Common methods for monitoring diabetes are invasive methods, which include the analysis of glucose concentrations in blood, plasma, or serum samples collected by the needle method. Another method uses “test strips,” in which the color of the strip changes depending on the concentration of glucose in the urine, but the results can be due to air
or finger contamination or interference with the light source. Fluorescent signal detection methods are unlabeled and often require expensive photon detection equipment. The sensitivity of plasmon surface resonance (SPR) sensors is strongly influenced by the quality (thickness, roughness, and uniformity) of the deposited metal, and unless modified with a specific enzyme, they cannot measure samples with complex compounds (Diabetes Care-Blood Glucose Test Strips 2014). In this study, human tear fluid is used instead of using a blood sample for the presence or absence of diabetes cells to reduce pain and bleeding.

The paper is organized as follows: The mathematical background and physical structure of the biosensor are presented in Sect. 2. In Sect. 3, the numerical results achieved by solving Maxwell’s electromagnetic equations using the finite-difference time-domain (FDTD) method are discussed. The paper is closed by the conclusion in Sect. 4.

2 Mathematical background and physical structure

2.1 Mathematical background

In this study, the FDTD method is used to solve Maxwell’s equations. The desired biosensor has meshed with tiny grids. The grid size (Δx, Δy) is selected with different values in the FDTD solution. We set the boundary condition of the waveguide as a perfectly matched layer to absorb the electromagnetic waves. The propagation of light in a PhC structure is obtained by solving Maxwell’s electromagnetic equations as follows

\[ \nabla \times \left( \frac{1}{\varepsilon} \nabla \times H \right) = \left( \frac{\omega}{c} \right)^2 H \]  

(1)

where \( \varepsilon \) is the permittivity and \( \omega \) is the frequency. The quality factor is another key indicator used to measure the overall performance of the sensor. It is calculated as follows:

\[ Q_f = \frac{\lambda_0}{\text{FWHM}} \]  

(2)

where \( \lambda_0 \) is the output resonant wavelength, and FWHM represents the full width at half maximum (FWHM) of the optical signal related to the sensor’s resolution. The following equation expresses the biosensor sensitivity

\[ S = \frac{\Delta \lambda_0}{\Delta n} \left( \frac{\text{nm}}{RIU} \right) \]  

(3)

Here \( \Delta \lambda_0 \) is the amount of change in the wavelength in Fano resonance and \( \Delta n \) denotes the amount of change in the refractive index. The figure of merit (FOM) is positively correlated with the performance and capability of the sensor and can be expressed by the following formula

\[ FOM = \frac{S}{\text{FWHM}} \]  

(4)

To describe the waveguide structure’s transmission characteristics more appropriately, we used the FDTD for quantitative analysis. The output power is defined as \( P_{out} \), and the input power is \( P_{in} \), and the transmittance ratio is \( T = \frac{P_{out}}{P_{in}} \).
2.2 PhC biosensor

The proposed structure is shown in Fig. 1. It has two linear tubes for cancer and diabetes cells’ simultaneous diagnosis in one or two people. A PhC composed of silicon rods in the air bed arranged in a hexagonal lattice with a lattice constant of $a = 600 \text{ nm}$ forms the fundamental structure, and two tubes are used to place the samples for measurement. The radii of the red and cyan tubes are $R_{C1} = 0.9a$, and $R_{C2} = 1.1a$.

Using the plane wave expansion (PWE) method, the fundamental structure’s photonic band diagram has been calculated. Our results demonstrates that there is a wide normalized bandgap in TM polarization mode at $0.276 < a/\lambda < 0.446$, which is equal to $1345 \text{ nm} < \lambda < 2173 \text{ nm}$ for $a = 600 \text{ nm}$. This bandwidth covers C and L optical transmission bands. The lowest optical fiber loss is in the C-band (1530–1565 nm) and is generally used in many transmission applications. The L-band (1565–1625 nm) is the second lowest-loss wavelength band and is a popular choice when using the C-band is not sufficient to meet the bandwidth demand. A sample of human blood is placed inside the red tube, and a cyan tube is filled with a sample of tear, and a tunable laser source centered at $\lambda = 1550 \text{ nm}$ is applied to the biosensor’s input waveguide. The resonance wavelength shifts due to the samples’ refractive indices and two resonant wavelengths are received simultaneously at the device output. All the parameters used in designing the proposed structure are listed in Table 1.
3 Result and discussion

In Fig. 2a, blood and tear samples of healthy people with refractive indices of 1.36 and 1.35 are placed inside the red and cyan tubes, respectively. As shown in the figure, two resonance wavelengths are received at the output; these resonance wavelengths represent healthy people. The light wave has been applied to the structure, and the shifted resonant wavelength for a healthy blood sample is equal to $\lambda_{s2} = 1.593 \, \mu m$, and also the shifted wavelength for a healthy tear sample is equal to $\lambda_{s1} = 1.562 \, \mu m$. If we get these two resonance wavelengths at the output of our structure, we will find that the person or people are healthy, and there are no cancer or diabetes cells in the samples. Important parameters in an optical biosensor are sensitivity, FOM, quality factor, FWHM, and detection limits (DL). As shown in Fig. 2, for the normal tear sample having a refractive index of 1.35, a resonance is centered at 1.562 $\mu m$. It has the $FWHM = 1.8 \, nm$ and $FWHM$ is 2.2 $nm$ for a normal blood sample with a refractive index of 1.36. In detecting a healthy person without cancer cells and diabetes cells, the sensitivity value is $S = 3080 \, nm/RIU$, and the figure of merit is $FOM = 1550.11 \pm 150.11 \, RIU^{-1}$. The transmission spectra are 95% for sample #1 and 100% for sample #2. Figure 2b shows the resonance wavelengths of normal blood and tear samples in dB scale.

Table 2 shows the refractive indices of the three types of normal and cancerous blood cells and normal and diabetic tear cells.

Table 2  Refractive indices of three types of normal and cancerous blood cells and normal and diabetic tear cells

| Analytic used | Refractive index | Analytic used | RI |
|---------------|-----------------|---------------|----|
| Blood sample #1 | RI | Tears sample #2 | |
| Basal cell (normal) | 1.360 | Normal cells of diabetes | 1.350 |
| Basal cell (cancerous) | 1.380 | Affected cells of diabetes | 1.410 |
| HeLa cell (normal) | 1.368 | | |
| HeLa cell (cancerous) | 1.392 | | |
| MDA-MB-231 cell (normal) | 1.385 | | |
| MDA-MB-231 cell (cancerous) | 1.399 | | |

Fig. 2  Resonance wavelengths of normal blood and tear samples, a Normalized resonance power, b Normalized resonance power in dB scale
According to these refractive indices, we study their resonant wavelength to identify the disease.

The normal basal cells are placed in the red tube (sample #1) of the proposed biosensor shown in Fig. 1, and the basal cancer cells are placed in the cyan tube (sample #2). Due to intense sun exposure, basal cancer cells are formed in the skin’s outer layer (epidermis). These cells do not spread to other parts of the body. The cancer cells have a refractive index of 1.38, while the normal cells have a refractive index of 1.36. The sensor output spectrum has been plotted in Fig. 3a, where each case shows a specific resonance wavelength. The FWHM is about 2.2 nm for normal basal cells while it is 2 nm for basal cancer cells, and the FOM is $940.475 \pm 025$ RIU$^{-1}$ with a sensitivity of $S = 1893$ nm/RIU. Figure 3b shows the sensor output for detecting HeLa cancer cells. HeLa cells become cancerous due to infection with the human papillomavirus 18 (HPV18). The refractive index of these cells is 1.392, while the normal HeLa cell line has a refractive index of 1.368. The FWHM of the output signal is 2.2 nm for normal and FWHM = 1.9 nm for HeLa cell carcinoma, and the FOM = $940.475 \pm 025$ RIU$^{-1}$ and sensitivity are $S = 1642$ nm/RIU and transmissions power for normal, and cancer HeLa cells are $TE_N = 99\%$ and $TE_H = 95\%$. MDA-MB-231 is extracted from the human chest and isolated from the pleural disease from a breast cancer patient (Sami et al. 2020); the level of the FOM suitability shape value for $FOM = 6097$ RIU$^{-1}$ cancer cells. Figure 3c shows the resonance wavelengths for the MDA-MB-231 normal cell and MDA-MB-231 cancer cell.

![Fig. 3](image_url)  
**Fig. 3** Resonant wavelengths of normal and cancerous cells for a Basal cell, b HeLa cell, and c MDA-MB-231 cell and also d normal and diabetic tears.
The refractive index of this type of cancer is 1.399, and the breast’s normal cells have a refractive index of 1.385. As mentioned in the previous sections, the tear sample is used to diagnose diabetes, and normal cells have a refractive index of 1.35, while this coefficient for diabetics is about 1.41. Figure 3d shows the resonance wavelength for normal and diabetic cells at the sensor output. It demonstrates that the sensor sensitivity is $S = 1294$ nm/RIU, and normal and diabetic cell transmissions powers are $T_{EN} = 95\%$ and $T_{EH} = 100\%$, respectively. The FWHM = 1.8 nm for normal and FWHM = 1.9 nm for diabetic samples. This section studied the effects of physical parameters such as the radius of red and green tubes on the transmission power. Figure 4a shows the effect of red tube radius on transmission power, resonant wavelength, and FWHM.

The results were calculated for the sample of normal basal cells with the refractive index of 1.36. As shown in this figure, the power transmission in a radius of $R_{C1} = 540$ nm reaches 100%. From this case, it can be concluded that the best radius

![Graph A](image)

**Fig. 4** The resonant wavelengths, transmission power, and FWHM for different tube radius. a Normal cell. b Cancer cell
to reduce power losses to zero and pass 100% of the transmitted power is this radius. On the other hand, the FWHM in different radii has different values. However, it has less value for $R_{C1} = 540$ nm, representing the lowest bandwidth’s optical signal. Figure 4b shows the effects of green tube radius with a refractive index of 1.38 on the basal cancer cell on important structural parameters. In this case, by increasing the radius to $R_{C2}( < 660)$ nm, the amount of transmission power is almost constant, and by increasing the radius, the amount of transmission power decreases, and therefore in the radius of $R_{C2} = 660$ nm with 94% transmission power is the best choice. The amount of bandwidth has also reached the lowest value in this radius. Therefore, we selected the best radii of $R_{C1} = 540$ nm and $R_{C2} = 660$ nm by reviewing and analyzing the results. Our results are shown in Table 3. In this table, the sensitivity parameter, quality factor, transmission power, average bandwidth, and figure of merit are calculated for different refractive indices for sample #1 and sample #2. The maximum sensitivity in the red tube is equal to 2214 nm/RIU for the MDA-MB-231 Cell (Cancerous). Table 4 also compares the essential parameters of the structure proposed in this paper with other proposed articles. As shown in the table, our proposed structure is better than other structures in terms of detection sensitivity, transmission power, quality factor, the figure of merit, and simultaneous detection of two samples.

Finally, Fig. 5 shows the sensitivity based on the total refractive index of the samples. As can be seen in this figure, the highest sensitivity is related to the detection of blood samples (Blood S#1) of healthy person (Normal) from MDA-MB-231 cancer person (Unnormal). In addition, the lowest sensitivity is related to the detection of tears samples (Tears S#2) of a healthy person (Normal) from a diabetes person (Unnormal).
One of the most important advantages of the proposed sensor is the simultaneous measurement of two samples, which increases the functional range of the work. While measuring two different samples, it measures with the least error and high sensitivity. The reason that blood and tear fluid samples are used for measurement in the proposed sensor is also due to the proximity of the refractive index of these samples, which helps a lot in the process of measuring and reducing errors. The designed sensor can detect a person with cancer and diabetes from a healthy person by a human blood sample and a tears sample. One feature of the proposed structure is the simultaneous detection of two samples using two tubes. Due to the importance of the accuracy and sensitivity parameter in the sensors' design, the FWHM is 1.8 nm, and the FOM is about 1550.11 RIU$^{-1}$. The sensitivity is 3080 nm/RIU, and the resolution detection range is $31 \times 10^{-6}$ RIU.

Table 4: Comparison of detection sample #1 and sample #2, quality factor, transmission power, and sensitivity parameters of the proposed sensor with the reported sensors

| References                | Detection Sample | Quality factor | FOM (RIU$^{-1}$) | Transmission power (%) | Sensitivity (nm/RIU) |
|---------------------------|------------------|----------------|------------------|------------------------|----------------------|
| Tavousi et al. (2018)     | Blood            | 650 ± 50       | 1400 ± 200       | 80                     | 2500                 |
| Chopra et al. (2016)      | Blood and tears  | 1082           | –                | –                      | 6.5764               |
| Mohamed et al. (2016)     | Glucose          | –              | –                | 86                     | 422                  |
| Arafaa et al. (2017)      | Glucose          | $1.11 \times 10^5$ | 1117             | 92                     | 462                  |
| Arunkumar et al. (2018)   | Blood            | 262            | –                | 100                    | –                    |
| Almpanis and Papanicolaou (2016) | –              | –              | 88               | 98                     | 263                  |
| Lu et al. (2018)          | Blood, tears     | 1264           | 84               | 90                     | 840                  |
| This work                 | Blood, tears     | 946.50         | 1109.51 ± 55.235 | 100                    | 3080                 |

Fig. 5: The sensitivity of cancer cells and diabetes for different refractive indices

4 Conclusion

One of the most important advantages of the proposed sensor is the simultaneous measurement of two samples, which increases the functional range of the work. While measuring two different samples, it measures with the least error and high sensitivity. The reason that blood and tear fluid samples are used for measurement in the proposed sensor is also due to the proximity of the refractive index of these samples, which helps a lot in the process of measuring and reducing errors. The designed sensor can detect a person with cancer and diabetes from a healthy person by a human blood sample and a tears sample. One feature of the proposed structure is the simultaneous detection of two samples using two tubes. Due to the importance of the accuracy and sensitivity parameter in the sensors’ design, the FWHM is 1.8 nm, and the FOM is about 1550.11 RIU$^{-1}$. The sensitivity is 3080 nm/RIU, and the resolution detection range is $31 \times 10^{-6}$ RIU.
**Funding** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

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