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Rigorous Investigation of Ring Resonator Nanostructure for Biosensors applications in breast cancer detection

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Abstract

Here, several ring resonator nanostructure for biosensors are proposed. To evaluate the results, finite difference time domain (FDTD) method is applied. Also, several main parameters including transmission spectrum is analyzed to obtain of sensitivity and figure of merit. As the technology goes on, using sensors and biosensors are more attracted by many researchers in various fields such as medicine. Biosensors are devices, in them biological elements and analytes have interacted and the reaction between them is measured then would be expressed as understandably in output. Biosensors have various components such as analyte, bioreceptor, transformer, electronics and display and are in different groups based on their mechanisms. Biosensors could be used to detect and diagnose bacteria, viruses, and early detect of breast cancer. Various methods such as X-ray mammography, ultrasound scan, DBT, ultrasonography of breast, and so on have been provided, but they have some disadvantages. In the biosensors field, various methods are introduced for early detection of breast cancer. In this study some researches and experienced have been investigated.

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1. INTRODUCTION

Biosensors are a way to reach the smart city from the analog world. Biosensor is a device, in which specific biochemical responses are used to detect chemical compounds using thermal, optical, and electrical signals. Meanwhile, isolated enzymes, immune system, tissues, organs or whole cells will be used. Sensors are divided to various groups including physical sensors, chemical sensors, and biosensors, that have been used in different fields such as food safety, health care, environmental monitoring, and biosecurity [1,2]. Biosensors have several components and parts among analyte, bioreceptor, transducer, electronics and display and are divided to optical, electrochemical or piezoelectric groups based on their mechanisms. Bacteria and virus could be detected by biosensors [5]. If you want to detect analyte, it should be immobilized on the transducer surface, then they have interaction together and some physical changes will occur on the transducer surface, which are diagnosed by transducer, amplified and would be delivered to the processor to be shown at the in output [6]. Since the biosensors have many properties, have been utilized in many fields including food safety, environmental, agriculture, medicine, etc. [7]. Some parameters such as selectivity, reproducibility, stability, sensitivity, and linearity have to in account in using biosensors [8]. Breast Cancer (BC) is one of the common malignant-tumor disease. Moreover, the last CA cancer magazine shows it has a growing rate. Based on population growth, it would be predicted that something around 3.2 Million new patients will have been in the world by 2025. More important, not only the diseases numbers increases, but also the patients age decreases. Many factors such as age, family health history, the environment, etc. cause these conditions. This disease has an unavoidable high rate, but dying of it could be controlled and decreased. Fast and early detection of this disease is important to therapy, because it will be metastasizing at the middle or last stages, so that it is vital to detect it at the first steps to help the patients stay alive [9]. Microwave Imaging (MWI) is one of the detection ways in medicine to diagnose cancerous tumors [10]. The other imaging and clinical methods such as mammography with X-ray, Magnetic Resonance Imaging (MRI), Ultrasound Scan, Digital Breast Tomosynthesis (DBT), breast Ultrasonography, image breast with the Wavelia device, Microwave Imaging of the Breast, Biopsy, etc. have been used to detect breast cancer [11].

Table1. The comparison of some methods in cancer detection [12].

No.	Method	Adv and disadv
1	Biopsy-based methods	High cost/ trained experts are needed
2	Biosensor-based methods	High biological sample distribution/ High power/ Low sample requirement/ Short analysis time/ and multiple detection
3	Biomarkers-based methods	High sensitivity/ Expensive/ Complicated/ Need trained individuals
4	Screening-based methods	Costly/ Limited imaging resolution. It is standard for breast cancer, but not effective for dense and small tumors

Tumors are divided as benign and malignant, in which malignant could be metastasized, grow fast, make harmful substances, and be a threat for human health. Malignant tumors, called cancer, make genetic mechanism to be adopted with the environment where live and grow and escape from the body's immune systems. When normal cells are changing to tumors, there are proteins or small molecules that are used as tumor marker on the cells surface or serum, which could be a good sign in early diagnosis and tumors treatment of cancer [13]. Using biosensors is a method to detect cancers. Biosensors can detect and manage cancer by diagnosing biological analyte such as protein, DNA, RNA, etc. and convert to an electrical signal. Since biosensors are fast and accurate, would be used in processes such as live cell imaging, mass metastasis, chemotherapy effect evaluation [14]. Many researches have been published about different biosensors in medicine and breast cancer detection, which some are introduced in continue.

Resonators to detect breast cancer

Biopsy is a method to detect disease with some side effects such as pain and bleeding. Some other methods such as MRI and Endoscopy are expensive. In a study to detect unhealthy cells, the transmitted spectrum intensity of healthy and cancerous cells has been compared, and their refractive index, due to protein changes, has been shifted and a significant shift has occurred in the frequency, which is a sensor to diagnose cancer and normal cells. Since ring resonators are sensitive to refractive index, they are widely used in photonic chips. In such studies, analyte molecules are attached to sample on top of the resonator, the analyte existence causes refractive index changes in external environment of ring resonator, as a result, the refractive index of coating near the ring surface would changes. This refractive index changing causes causes transferring the cavity resonance wavelength, which is proportional to the total molecules mass of the surface directly. In this work, linear and point defense have been used to control light inside crystal photonic. In it, light collisions the cell through the photonic crystal and from the other side it is read and being cancerous or normal of cell is diagnosed. In sensor Fig (1), a waveguide is used on top as bus and another one is at bottom as drop.

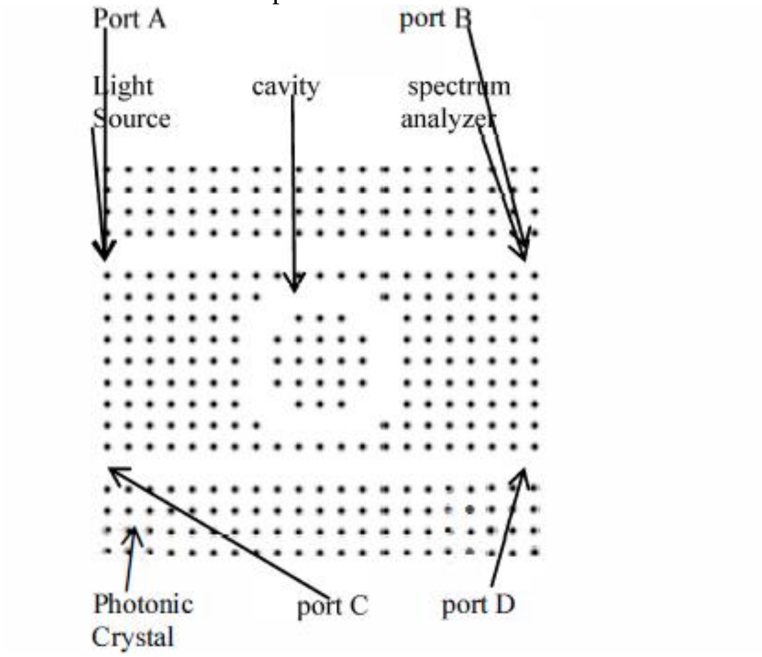

Fig1. Design of photonic crystal resonator ring

In which, the input is A, the bus waveguide output is B, and drop waveguide ports are C and D. The resonant modes central cavity has interaction with photonic crystal resonator ring. When the input wave does not return to part A, the transmission power reaches its maximum value. The dielectric constant differs in photonic crystal cavities based on being healthy or cancerous of the cell. Therefore, the frequency would be changed and their refractive index is compared.

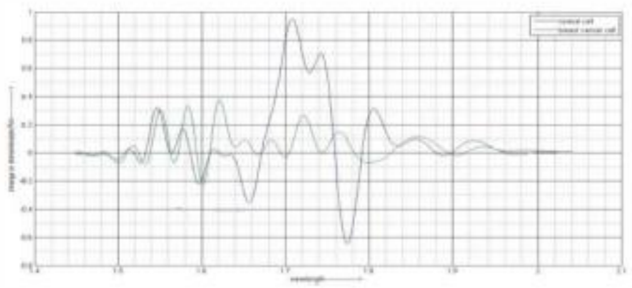

Fig2. Shift in peak wavelength for normal and breast cancer cell

The Gaussian wave is radiated to part A as input, due to occured resonance in cavity, so coupling occurs on both sides of the buses and output will be shown in B. The shift in normal and cancerous cells are shown in Fig (2). [15,16].

In another work, the biosensor sensitivity to detect cancer cell is increased significantly, using optimizing ring resonator parameters. As expected, when the refractive index of the modes changes on the ring resonator surface, the resonance wavelength of the ring resonator so does. In optical resonator, light moves in a closed loop. Microsphere is a kind of optical ring resonator with a high quality factor, it is made of SiO2 or polymer, which is a cavity for energy accumulation in a specific wavelength. Since optical fiber has a small diameter, so light coupling in it is difficult. Therefore, integrated waveguide with a larger layer core is used.The ring resonator can be made by connecting two single waveguides together as a circular structure. In this work (Fig3), light is entered to optical fiber by laser, and the light is coupled to the waveguide using grating couplers due to size dissimilation of optical fiber and the waveguide. After passing light through the ring resonator, it couples to optical fiber again and is detected by detector. A normal and a healthy person has refractive index 1.35, while the blood refractive index with cancer cells differs. The light emission in ring resonator with various blood is different cause different blood has different refractive index (Fig. 4) [17].

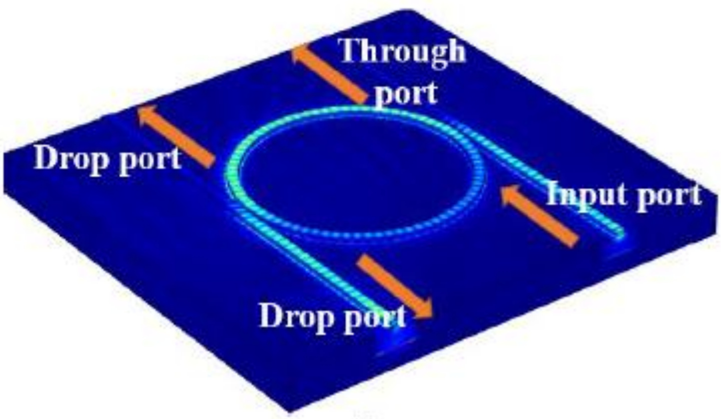

Fig3. Ring resonator circuit in which light is being coupled from linear waveguide to ring waveguide [17].

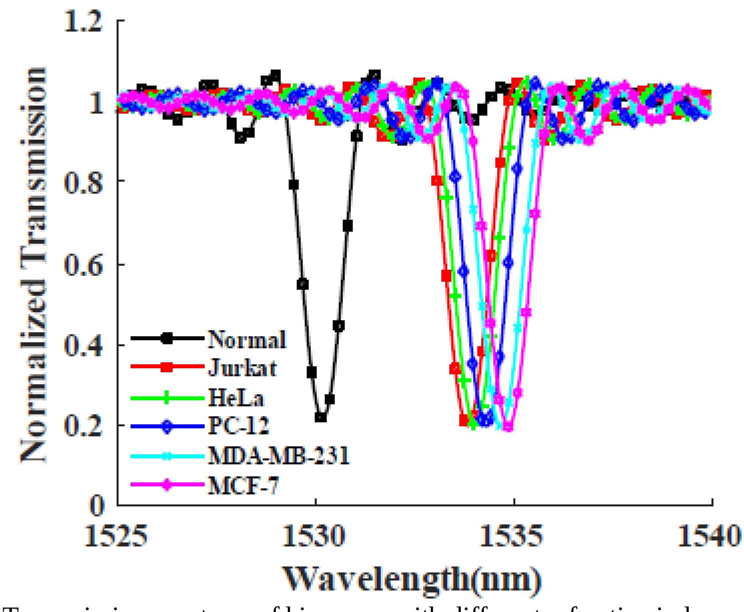

Fig4. Transmission spectrum of biosensor with different refractive index and different cells [17].

Another optical biosensor is a silicon-based micro-ring resonator including two optical free-label biosensors. First structure has a resonator with a micro-radius disk 1.6 micrometer with a curved waveguide; the second structure has a ring resonator with outer radius 2.3 micrometers. Some curved waveguides are wrapped around micro-resonator to increase coupling length and structural parameters. There is a high-quality cavity to detect a small shift in the resonance peak. The bending loss can be reduced by increasing the radius of resonator and increasing the coupling length between bus waveguide and micro-cavity. In this work, the tat is on micro-disk and causes its refractive index changing, then, resonance wavelength changes are shown (Fig. 5) [18].

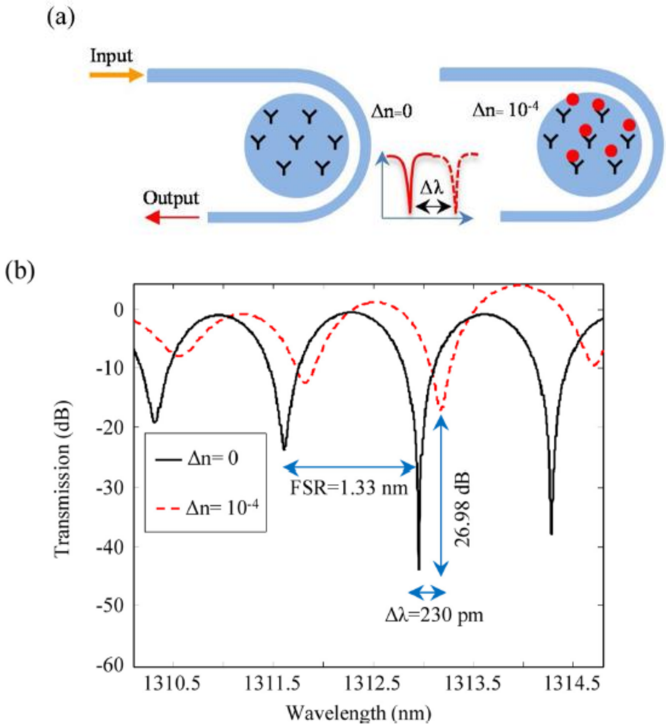

Fig5. (a) A biosensor schematic with resonance spectrum (b) Transmission resonance changes due to effective coefficient changes [18]

A 2D photonic crystal based biosensor with circular tubes in a square grid to detect cancer and glucose in urine has been presented. Blood glucose is 165 to 180 mg/dL normally. In this work, a 2D photonic crystal ring resonator- based resonator with two inverse waveguides and a ring resonator are used. If the urine concentration be different, the urine refractive index will be changed, that this causes changes in sensor output response. There are some photonic crystals in the structure controlled by defects and used for sensing. In this work, the input is a Gaussian wave coupled to ring resonator by input waveguide and reached to output waveguide by ring resonator. Now, if Bilirubin, Albumin, Urea, and Glucose concentration increase, the refractive index increases, too and sensor

output power decreases. By having sensor output power, the corresponding concentration could be measured, which is used for sensing applications [19].
To detect breast cancer an optical optofluidic meta-surface has been presented. Optical resonators that use Surface Plasmon Resonance or photonic crystal, are used in free-label sensors, cause can bound resonance fields and be sensitive to biomarkers by their surface. In the presented work, 2D periodic array of silicon Nano-posts (SNPs) is used and the structure is made on the upper thin silicon layer with SOI substrate and covered by graphene oxide Nano-sheets and has interacted by antibody molecules. Also, a polydimethylsiloxane (PDMS) slab with an input and output is stuck to upper surface of SNPs, that causes liquid analytes flow between PDMS and the buried oxide layer of the SOI substrate be restricted. In the work, the combination of silicon-on-insulator (SOI) Nano-photonic and Nano-fluids is used for detection. The meta-surface is formed of periodic array with silicon Nano-posts placed on the SOI surface and are connected to specific molecular receptors. This sensor overcomes the restriction caused by diffusion. This device resonance wavelength is about 1550 Nano-meter. ErbB2 protein biomarker, used for breast cancer detection, has been used in this work, and the refractive index changing caused by ErbB2 molecules are measured in it, when these molecules are on the sensor surface. The measured reflectance spectrum is shown in Fig (6.a), in which SNP is black, it is red when covered by GO layer, and is blue when mixed with cancer molecules. When samples containing 2ErbB are injected to Nano-fluidic channel, there is a reflection spectrum shown in Fig (6.b). More increasing the samples, the higher shift to higher wavelength in the reflection spectrum [20].

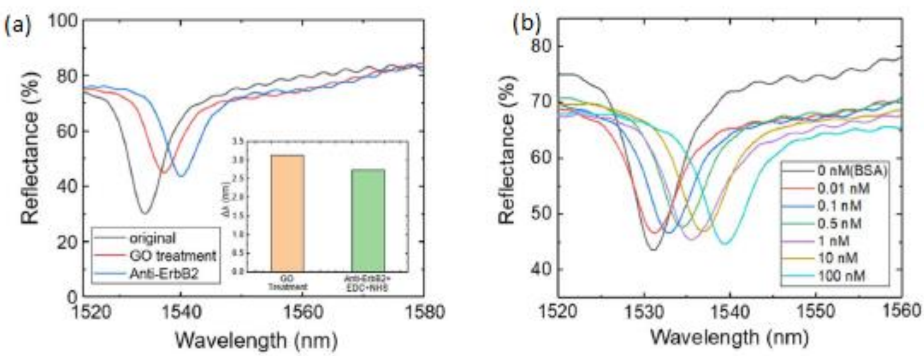

Fig 6. (a). Reflectance spectrum of pure sensor, GO layer, and anti-ErbB2 antibody coating. (b). Reflection spectra with ErbB2 in different concentrations [20].

Plasmon to detect breast cancer

Surface Plasmon Resonance is an optical method in which little changes refractive index are detected. In a work, light source, prism, gold film, and detector are used as Kretschmann configuration with a thin gold film coating as a sensor chip in the prism, in where the light hit the gold surface solution and if the radiation angle be more than critical angle, Total Internal Reflection (TIR) occurs and a wave is created. In a specific angle greater than the critical angle, the wave destroys localized electrons or gold film plasmons and the reflected light is decreased at this point strongly. The plasmon creates an electric field between the metal surface and the solution, and when smallness changes occur in the refractive index, plasmon occurs as another way and wave raises due to light total reflection and such wave decays exponentially by keeping out of surface. When there is no cancer cell, the angular shift is different for total internal reflection than there are some cancer cells [21].

One of the presented work, is one that in gold nanorods (GNR) in plasmonic are used to diagnose breast cancer cells. As we know, copper is an essential element in the body to control homeostasis, but beeing too much causes cancer. CA15-3 protein marker currents in the blood, that is related to cancer, so CA15-3 breast cancer antigen can be mixed by copper in breast cancer serum, and GNR-based plasmonic-biosensor-based plasmonic biosensor can be used to detect cancer. In this solution, CA15-3 with various concentrations is added and when the concentration raises, red shift occurs and the spectrum is recorded. If the concentration becomes too high or low, there is no interaction between antibody and the antigen and the sensitivity decreases. It should be noted that, this work has been compared with hospital results and shows high accuracy [22].

The biosensors can be installed and used on smart mobile phones, in which sensing results are shown on the screen. A smartphone biosensor system with the multi-testing-unit (SBSM) based on Surface Plasmon Resonance and with microfluidics is presented, that works base on LSPR and detecting wavelength shift and three lasers are used to calibrate the spectrum. Two cancer-related biomarkers CA125 and CA15-3 are considered as target proteins. Then, these two proteins various concentrations are tested and each sensor absorption spectrum is measured to measure wavelength shift. By considering the obtained results, these two proteins concentration is low in serum of patients with breast cancer bur, the monitoring must be continuously for a long time [23].

To detect extracellular vesicles of breast cancer cells, curved Nano-plasmonic sensor has been used. Extracellular vesicles (EVs), micro-nano lipid packets are in all body fluids and are used liquid biopsy targets to detect breast cancer, cause their structure reflects cell data. Their detection needs a device with high sensitivity, since diseased EVs are less than normal EVs. To overcome this problem, curved surface enhanced Raman spectroscopy (SERS) method has been used. Enhanced Raman scattering is a method of Raman scattering works by plasmonic resonance on the substrate surface, increases the light intensity, and improves the Raman signal, in addition uses extracellular vesicles as liquid biopsy marker and enhanced Raman spectroscopy to diagnose cancer. Gradient index materials in addition normal plasmonic waveguide can increase light coupling from radiating laser to the plasmonic surface and be propagated to further distances by plasmon waves distribution of near gradient. Certainly, all gradients materials are not placed on around of SERS surface directly, as this prevents the investigated analyte to reach surface, where maximum electromagnetic wave confinement and also maximum Raman enhancement exist. To solve it, optical conversion in used, in which the material slope curves without changing in their electric field behavior. Namely, using Nanoparticles on curved substrate, the resonance field is enhanced more and analyte reaches the nanoparticles surface easily. Using the results, it could be shown that, the electric field around Nanoparticles increases in both flat and curved states, while the size of hot-spot for the curved substrate is clearly significantly bigger. By attention to the result of Fig (7), it could be seen that six algorithms by having high-concentration samples have been used. That all of them, detect all EVs spectra including BT-20 cancer cell with low concentration [24].

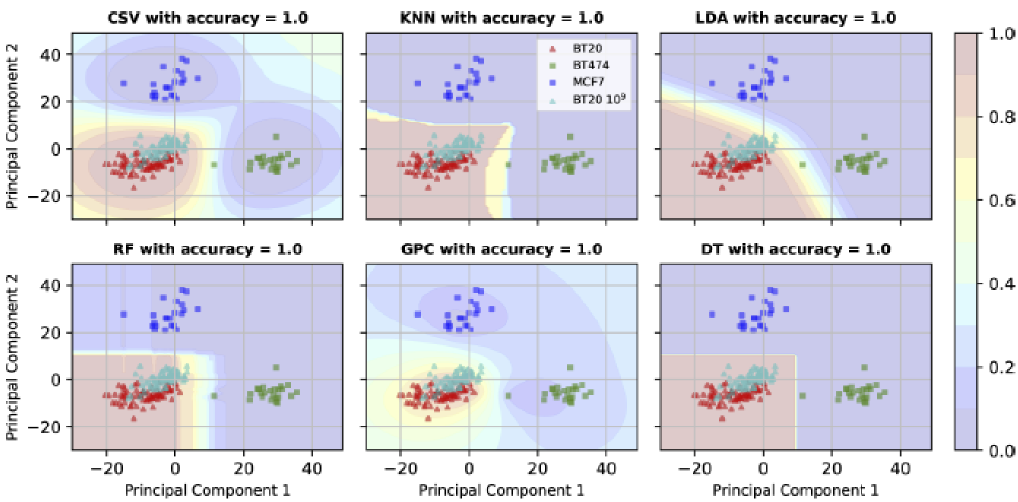

Fig (7). Obtained probability distribution using six given algorithms [24].

A microfluidic plasmonic biosensor has been used to detect breast cancer antigen, in which, the light is transmitted through sub-wavelength nanotubes made on gold and silver thin films, related to Surface Plasmon Resonance (SPR) and sensitive to refractive index changing on metal. In this work, a plasmonic biosensor based on Nanotube arrays made on gold film to transmit spectrum signal and to detect human epidermal receptor protein-2 (HER2), a breast cancer antigen has been used. When the signal radiates and hits the metal surface, an interactive measurable signal occurs. These two layers are attached using gold coating and a chrome layer. To obtain transmission spectrum, a halogen lamp with a broad emission band has been used, so that, light perpendicularly focuses on Nano-metal arrays surface, the transmitted light is gathered by fiber under the array and the spectrum is transferred to a computer. In this work, when refractive index changes, red shift occurs which is expected for plasmonic substrate. In this case, glass slides are more sensitive and red shift in glass band is higher in addition, changing in refractive index causes changing in SPR sensor response. By increasing refractive index, red shift arises and since sensor can detect refractive index in near metal surface, so that, it could be used to detect HER2 and since antigen molecules have a small mass and causes not large changes in the index, secondary antibody and sandwich mode have been used to increase sensitivity. The SPR substrate has high sensitivity and in compression of array-based plasmonic biosensors to analyze spectrum has a very good linear behavior [25].

Using optical fiber to detect breast cancer

Optical fiber interferometer and Fiber bragg grating could be used to diagnose breast cancer biomarker (HER2) as free-label. Fluorescent labels or chromosome methods are efficient methods in this way, but there are expensive and complex. In this work, sensor has a uniform waist region at the center and two transition regions on sides. The transition region excites the fundamental mode and high order modes, when it propagates along the central uniform waist region, at the other transition region the two modes are coupled. In this, the light is radiated to the optical spectrum analyzer through FBG sensor, and by increasing the refractive index red shift occurs and the temperature changes in sensor change with optical fiber interferometer and FBG response. The FBG temperature response is independent of taper interferometer temperature response, and FBG has been used as a thermometer to control the temperature at the process. When the antibody attaches, the the refractive index of the fiber surface increases. In a presented work, despite existing low concentration of biomarker, i.e. 2 Nano-grams per milliliter, the cancer sign is detected, which is useful for early detection of breast cancer [26].

Optical Fiber Aptasensor based on Plasmonic methods, is a method to detect breast cancer. In which, optical fiber has been used as a small SPR device based on the Kretschmann prism, that is appropriate for low-concentration samples. To diagnose, there is a gold-coated optical fiber with thiolated aptamers on it to detect mammaglobin proteins, breast cancer biomarkers. Such proteins flows in the blood and are targeted by the probe. gold-coated Tilted Fiber Bragg Tratings (TFBGs) have special spectral characteristics due to plasmonic excitation on coated metal external surface, that causes resonance weak in narrow spectral region, where plasmoic occurs, consequently, decreases amplitude. resonance further away from the SPR causes less sensitivity, up to a core-mode resonance at the so-called Bragg wavelength, located at the right end of the spectrum. Since, the medium permittivity is adjacent to the metal surface, so, high dispersion of the SPR existed, therefore, near-infrared (NIR) resonances located closest to the SPR attenuation show the highest sensitivity and others are less impacted by changing surrounding refractive index. The sensitive modes are located on the short wavelength side of the maximum SPR attenuation. This technique helps in positioning and automatic selection of the most sensitive mode for analyzing (Fig.8) [27].

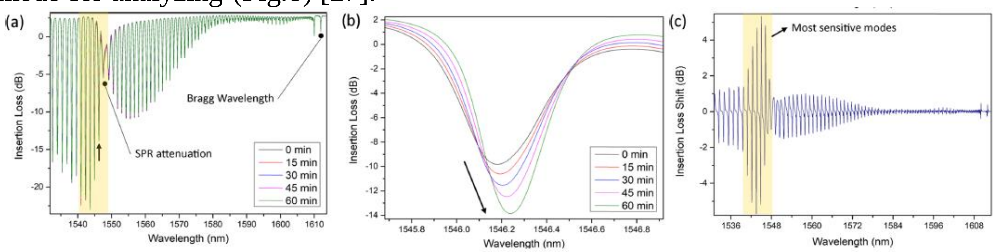

Fig (8). (a). overlap obtained spectra using gold-coated TFBG(s) in aptamer-containing solution during the process (b). Focusing on obtained sensitive mode resonance of part (a). (c). The differences between obtained spectrum before and after localization of the sensitive mode resonances [27].

The mutation of two BRCA-1and BRCA-2 genes in 75 to 80% is related to breast cancer. The numerical modeling of graphene-covered optical fiber is another work to detect breast cancer. In a work, a thin metal film is covered by fiber to separate sensing medium and dielectric, that biomolecules be absorbed better. The Attenuated Total Reflection (ATR) method, has been used to diagnose such genes. Graphene is used to improve system operation, which is sandwiched between gold film as a medium to absorb light. In it, various DNA(s) are added to graphene surface, so due to changing cancer biomarkers concentration, the refractive index has been changed and changing in refractive index, has a great effect on displacement of SRF and SPR curves to shift [28].
Using silicone microfibers is another method to detect breast cancer. HER2 is a well-documented biomarker known as cancer cell proliferation, found in body fluids. Optical fiber is very flexible with high sensitivity. In a work, fiber has

two transient regions with 3mm length, and a uniform region with a waist 8 μm and length 1.2 cm, in which the light is transferred using a controlled optical spectrum analyzer after radiating to it. If the optical fiber diameter reduces, the refractive index sensitivity increases. In this, antibodies are placed on the microfibers surface and HER2(s) are recognized that causes changing in refractive index, by increasing refractive index, a red shift are observed in the wavelength. On the other hand, by increasing in temperature, blue shift occurs. To avoid measurement errors, the room temperature keeps on 26 ◦C in all over the process [29].

In another work, HER2 biomarker of breast cancer with optical fiber-based surface plasmon resonance (OF-SPR) has been used. One centimeter of optical fibers is covered by a gold film that causes most sensitivity in device to surface refractive index changing, when gold film thickness changes, sensors are checked again. OF-SPR is a white light source with a spectrometer. The light enters the fiber tip then is reflected to the spectrometer. In this work, an anti-HER2 aptamer is connected to the gold layer on the optical fiber surface. The optical fiber is covered by a hard shield. By changing the refractive index and sensitivity according to the thickness of the gold film, changes are happened and shown in normalized spectrum [30].

Graphene to detect breast cancer

graphene is a usage material in this field. In a study, reduced graphene oxide has been used to detect BRCA1 gene, this gene mutation is related to breast cancer. Reduced graphene oxide is prepared by chemical or thermal reduction of graphene oxide (GO) and immobilizes the probe biomolecules. By comparing graphene oxide and reduced graphene oxide, it could be seen that he reduced one has more adhesion on the substrate. In the study, reduced graphene oxide and simple silver paint are assembled on silicon oxide, DNA with various concentrations is used and them with BRCA1 gene are detected [31].

Another work to detect it, is using a multilayer structure graphene-based terahertz absorber. Graphene has two internal and external conductivities, that sum of both is total conductivity. Using it causes high sensitivity and figure of merit (FOM). A multi-layer structure with a gold bottom layer as reflector is created, then a quartz substrate is placed on gold, the graphene ribbons with a width of 3 μm are located on top substrate, another quartz layer with a permittivity of 3.75 is put on graphene, and finally, graphene element is placed on the second substrate. Two absorbers as sensor have been proposed, in them the difference between the two structures is in the main absorber element. As we know, cancerous tissues have more permittivity in real and imaginary parts, which more frequency shift and loss is expected in results for cancerous cells. In a study, in constant thickness, by increasing distance, frequency shift increases one micrometer. When tissue is placed on the absorber surface, the operating frequency increases because of emerging the capacitive effect between the tissue and the absorber, so that cancer cells can be diagnosed [32,33].

A platform based on graphene and Herceptin is prepared, in which HER2 antibody is used to distinct single cell, and a graphene-based immunosensor on glassy carbon electrode is used to specify the amount of SK-BR-3 cancer cells on glassy carbon electrode surface, which is simple and low-cost. This sensing method is based on three glassy carbon electrodes; the herceptin-conjugated graphene is poured on the electrodes using ultrasonic method. The used Herceptin is dispersed in graphene and caused selectivity as a biological receptor. Herceptin-Graphene substrate causes transmission resistance reduction, conductivity and surface area increasing. The linear range in a biosensor indicates the analyte concentration, where biosensor exhibits an appropriate linear response, to reach the linear range, biographene electrode has been used. Graphene-Herceptin biosensor calibration graph at the range of one to eighty cells is shown in figure (9), where the results are successful for real samples, because cancer cells concentration in blood is very low [33]. Also several practical configuration are proposed recent years [34-39].

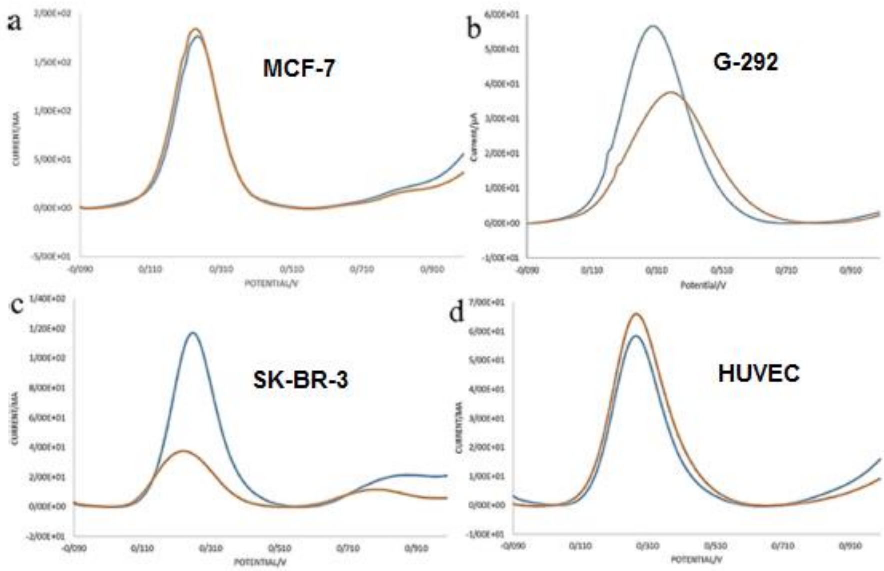

Fig (9). herceptin-graphene biosensor selectivity and comparison various cells in performance of bio-electrode sensing [33].

Some of these configuration are used two dimenssional materials with smart platforms[38-60].
Finally, the introduced method, publishing year, and methods to detect breast cancer using photonic and plasmonic methods are presented in Table [2].

Table2. Methods for early detection of breast cancer

No.	Author	Publishing year	Method
1	Fleming Dackson, et al	2014	hybrid photonic crystal ring resonator [15]
2	Chen, Shenna, et al.	2015	plasmonic sensor of gold nanorods. [22]
3	Johny Paulo, et al.	2016	Microfluidic and SPR [25]
4	Sun, Dandan	2017	fiber-optic interferometer and fiber Bragg grating [26]
5	Robinson	2017	Photonic crystal [19]
6	Wang, Yifei, et al.	2018	optofluidic metasurface [20]
7	Ali, Liaquat, et al	2018	optical ring resonator [16]
8	Firdous, S.	2018	surface plasmon resonance (SPR) [21]
9	Hossain, Biplob, et al	2019	Numerical modeling of graphene-coated optical fiber [28]
10	Filippidou, M. K., et al	2019	reduced graphene oxide [31]
11	Ali, Liaquat, et al.	2019	optical ring resonator [17]
12	Loyez, Médéric, et al	2020	optical fiber aptasensor with plasmonic [27]
13	Sun, Dandan, et al	2020	silica microfiber [29]
14	Malmir, Kiana	2020	Micro-resonators with bent waveguides [18]
15	Fan, Zhiyuan, et al.	2020	localized surface plasmon resonance with microfluid [23]
16	Rezazadeh, Afrooz	2021	Graphene-based THz absorber [32]
17	Loyez, Médéric, et al.	2021	sandwich optical fiber [30]
18	Kazemzadeh, , et al.	2021	curvature-inspired nanoplasmonic sensor [24]
19	Rahimzadeh, Zahra	2021	herceptin-conjugated graphene [33]

2. CONCLUSION

Breast cancer is the most common disease between women in all over the word. Annually many women lose their life due to it. To prevent these statistics incensement, various methods have been presented by researchers. Such methods are MWI, X-ray mammography, MRI, DBT, ultrasound, biopsy, etc., which each one has some advantages and disadvantages. Biosensors are an option that have been interested by researchers, these devices have special advantages that are used in different fields such as medical. They could be used for early detection of cancers, and breast cancer. Biosensors are made by various methods, in the presented work some of them have been introduced briefly.

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