The potential of terahertz sensing for cancer diagnosis

Zohreh Vafapour a,b,⁎, Afsaneh Keshavarz c, Hossain Ghahraloud d,e

a Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, 60607, USA
b Department of Electrical and Computer Engineering, University of Illinois at Chicago, Chicago, IL, USA
c Department of Physics, College of Science, Shiraz University, Shiraz, 71946, Fars, Iran
d Department of Chemical Engineering, Shiraz University, Shiraz, 71345, Fars, Iran
e Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, 21218, MD, USA

A R T I C L E   I N F O

Keywords:
Biomedical engineering
Biophysics
Optics
Photonics
Terahertz sensing
Cancer detection
Terahertz pulse detecting method
Complex refractive index sensing
Finite difference time domain (FDTD) method
Semiconductor devices

A B S T R A C T

The terahertz (THz) region lies between the microwave and infrared regions of the electromagnetic (EM) spectrum such that it is strongly attenuated by water and very sensitive to water content. Here, we numerically present the terahertz sensing/imaging (Vafapour et al., 2018a, b) approaches. The terahertz sensing is non-ionizing and has numerous potential applications (Vafapour et al., 2018a, b; Pickwell and Wallace, 2006; Keshavarz et al., 2019a, b; Keshavarz et al., 2019a, b; Tao et al., 2010; O’Hara et al., 2008; Ghafari et al., 2019; Emami Nejad et al., 2019; Vafapour, 2019; Chen et al., 2011b; Vafapour and Ghahraloud, 2018), detecting (Keshavarz et al., 2019a, b; Park et al., 2014; Yan et al., 2019; Sadeghzadeh Lari et al., 2020) and imaging (Zhang, 2002; Carranza et al., 2015; Zhou et al., 2018) approaches.

Terahertz technology has been advancing rapidly because of its tremendous potential applications (Vafapour et al., 2018a, b; Pickwell and Wallace, 2006; Keshavarz et al., 2019a, b; Keshavarz et al., 2019a, b; Tonouchi, 2007; Mittleman et al., 1996; Ferguson and Zhang, 2002; Kawase et al., 2003; Wang and Mittleman, 2004; Withayachumnankul et al., 2007; Farmani et al., 2018; Vafapour et al., 2018; Chen et al., 2012; Zhu et al., 2014; Vafapour et al., 2018; Ma et al., 2019; Vafapour et al., 2018). Among them, THz cancer diagnosis is drawing much attention as THz electromagnetic (EM) waves can detect the variation of cells caused by cancer.
by cancer, thereby rendering a new modality of medical imaging (Fitzgerald et al., 2006; Pickwell and Wallace, 2006; Yin et al., 2007; Nakajima et al., 2007; Ji et al., 2019). First published results on cancer tissue imaging using THz pulsed radiation is in Ref. (Woodward et al., 2003), later confirmed by studies on various cancer types and organs in Ref. (Fitzgerald et al., 2006), suggest that THz imaging can be used for macroscopic visualization of tumor margins in fresh tissues. The THz cancer detection application is published by Keshavarz et al. (Keshavarz et al., 2019a, b) which demonstrated the possibility of using THz sensing technology in a water-based metamaterial (MM) for in vivo skin cancer detection. Emami Nejad et al. (Emami Nejad et al., 2019) proposed a supersensitive nano biosensor which demonstrated the enhancement of the capability of measurement and detection of cancer cells by THz sensing technology.

There are two major merits in cancer diagnosis: First, it covers a wider area compared to the optical microscopy measurements, and second, once the systematic analysis is established, it can provide an objective judgment which is independent of the skill of medical professionals. The tissue hydration studies were proposed as an initial medical application (Avinone et al., 1999; Mittleman et al., 1999). It has also been tested in skin, lung, pancreas, and breast cancer applications (Woodward et al., 2003; Fitzgerald et al., 2006; Joseph et al., 2011; Brun et al., 2010). The THz imaging, sensing and detecting approaches, which utilizes the EM radiation spectrum between 0.1 and 10 THz, have been investigated to assess their potential to diagnose cancers by measuring the water content change and cell deformation of malignant tumors (Globus et al., 2003; Fitzgerald et al., 2006; Son, 2009; Sy et al., 2010; Park et al., 2011) or by sensing the nanoparticle probes targeted at cancerous tumors (Oh et al., 2009; Oh et al., 2011; Park et al., 2012; Son, 2013) and/or by analyzing the spectral responses EM THz wave (such as reflected, transmitted and absorbed spectra) from the sample (Keshavarz et al., 2019a, b; Emami Nejad et al., 2019) due to changes in the optical properties of the samples.

This article describes the use of various intelligent analysis approaches to choose relevant sensing parameters and optimize the processing of THz reflectance spectral responses data in the diagnosis of in vivo and ex vivo of basal cell carcinoma (BCC) skin cancer, and detect breast and colon cancer samples. We discuss the current state-of-the-art in terms of THz sensing/detecting systems; describe current applications, future potential, and our own approaches to harnessing this novel technology.

2. THz bio detector design investigation

The response of a THz sensor can be very fast, but it is noisy. A further reduction of noise is possible by using sensors with smaller active area. We proposed the optical sensor in micro-size which describe as a small device. The unit cell of the proposed THz bio sensor design which consists of double-layer dielectric material in cross shape, a glass substrate and a quartz layer as a dielectric spacer (or buffer layer) and an H-shaped semiconductor (Indium antimonide, InSb) antenna depicted schematically in Figure 1. The ground plane of quartz, with a dielectric layer spaced in between of the H-shaped semiconductor antenna and the substrate. The space between the semiconductor antenna and the glass substrate (the lowest layer in the structure) is filled by quartz as the dielectric spacer with thickness of 5 μm. Dimensions of the cross (in microns) are: 400 μm as the length and width in the x- and y-direction. The thickness of both cross-shape materials is 5 μm and thickness of the H-shaped semiconductor element is 4 μm. The other geometrical parameters are presented in Figure 1b. This two-layer dielectric and the semiconductor element couple to both the electric and magnetic components of incident THz EM waves and allows for maximization of the reflectance at a certain THz frequency. The dielectric ground plane is designed to be thick enough to prevent light transmission and therefore guarantees a narrow band reflectance with high reflectivity to be more appropriate for fabrication process.

For numerical calculations, we used the finite time constraint (FDTD) method and used the CST Microwave Studio simulator software. For the calculations, we used a single cell, in which the lateral boundaries x and y were used as periodic boundaries, and perfectly matched layers in the z direction were considered to eliminate non-physical boundary reflections. When the wave of the plane THz EM lands vertically on the structure with polarization along the z-axis, the connection resonance must be created between the dual dielectric layer and the H-shaped semiconductor antenna. The light transmission from the whole structure is very close to zero and the resonance peak is more visible in the reflection spectrum.

3. Cancer detection potentials

Early detection of cancer greatly improves prognosis, treatment opportunities, and the chances of survival. Early detection of cancer increases treatment chances and greatly increases the chances of survival. (Alexandrov et al., 2010; Mingaleev et al., 2002; Titova et al., 2013; Bogomazova et al., 2015; Demidova et al., 2013; Saffarian and Tzeng, 2016, 2017bib - Saffarian and Tzeng_2017bib_Saffarian and Tzeng 2016). Although current screening protocols may be replaced in the future by more up-to-date and efficient technologies, developing a clear and systematic approach to early detection of cancer will lead to greater use of advanced technologies and further advances in cancer diagnosis and control. Be. Here, we present a new and practical method using a bio-detector structure in the THz range to detect three different types of cancer (skin, breast and colon cancers) as in vivo and ex vivo detection by analyzing THz reflected waves from the cell samples suspected of cancer. First, we investigate the complex refractive index (CRI) sensing of the THz designed by calculating the THz frequency shift of the reflected spectrum and optical sensing properties of the
This research focuses on improving the performance of CRI bio detectors/sensors for medical, chemical, and biological detection applications. Additionally, it leads to design strategies for performance improvement of CRI bio detectors/sensors for medical, chemical, and biological detection applications.

3.1. Complex refractive index THz sensing/detecting

To examine in more detail the performance of the THz bio detector/sensor which is shown in Figure 2, we survey the changes of the optical influential parameters and materials used in the proposed optical sensor device, such as the real and imaginary parts of the complex refractive index (CRI) of the surrounding medium/material.

The THz bio detector/sensor based on reflected EM optical responses techniques are receiving a high degree of attention because of the need to develop simple, low-cost, high-throughput detection technologies for several applications such as cancers diagnosis and virus’s detection. Here, we use a THz MM design for the detection limit of resonant CRI sensors/detectors that consider all optical parameters that affect the sensing/detecting performance (Jakišić et al., 2011; Vafapour and Zakery, 2016; Vafapour and Zakery, 2015; Le et al., 2016; Vafapour et al., 2017). This research is a common method that provides the conditions for quantifying and comparing the performance of optical biosensors based on optical resonance/detectors. Additionally, it leads to design strategies for performance improvement of CRI bio sensors/detectors for medical, chemical, and biological detection applications.

Figures 3 and 4 display the sensing performance by using the reflected spectra, where the real and imaginary parts of the CRI of surrounding medium are changed. By increasing the amount of real part of the CRI from 1.05 to 1.35, the resonant reflected THz frequency shows an apparently large red shift as shown in Figure 3, where the imaginary parts are considered as a fixed amount of 0.002. To clearly show the shifting properties of the reflection spectrum, the frequency of the peak reflected spectra and other optical sensing properties of the design at four different values of the real parts of CRI are presented in Table 1 with the corresponding resonant wavelengths and full width at half-maximum (FWHM) values. It is shown that increasing the real part value by the step of 0.1, the resonant frequency can be red-shifted by more than 0.07 THz, i.e., the wavelength has blue-shifted by more than 167 μm. As shown in Figure 3 and Table 1. The resonance peak frequency (RP) varies, but the maximum reflected coefficients for different CRI cases are almost unchanged. So, we defined the sensitivity (SR) as follows (Vafapour et al., 2018a, b)

\[ SR = \frac{\Delta f}{\Delta n} \]  

where \( \Delta f \) defined as frequency shift of the maximum reflectance coefficient and \( \Delta n \) is the changes in real part of the CRI. So, we can define the figure of merit (FOM) as

\[ FOM = \frac{SR}{FWHM} \]  

which can reach to 1.5 where the reflection coefficient is about 92.8%.

Table 1 indicates that the sensitivity and FOM are 264 GHz/RIU and 1.5, respectively. Compared to the big changes in frequency shift, the reflection coefficient is nearly unchanged.

Figure 4 shows the reflectivity spectra of the proposed THz bio detector by changing the imaginary part of the CRI of the surrounding materials. Here, the reflectivity, R(ω) is defined as

\[ R(\omega) = 1 - T(\omega) - A(\omega) \]  

where T(ω) is the transmission and A(ω) is the absorption. From Figure 4, we can see that the reflectivity undergoes a small amount of decreasing when the imaginary part of the CRI increases from 0.002 to 0.063. It is noted that the reflected resonance peak is totally unchanged when the imaginary part of the CRI of sensing medium vary from 0.002 to 0.0063, but the reflectance coefficient decreases by increasing the imaginary part of the CRI. Therefore, we can detect the CRI change by observing the decreasing trend of the reflectance percentage of the spectra. However, the bio sensor/detector discussed here is from a different perspective. Here, we investigate the CRI sensing/detecting reflected spectra for the first time as a THz bio sensor/detector (using the CRI and changes both parts separately). It should be noted that the resonance peak frequency has not changed, but the maximum reflected coefficients for the different

Figure 2. Schematic drawing of the THz bio detector device when the sample is investigating/testing using illumination of the THz EM wave.

Figure 3. The simulated results of reflectance spectrum for different real parts of the CRI of the surrounding medium.

Figure 4. The simulated results of reflectance spectrum for different imaginary parts of the CRI of the surrounding medium.
CRIs in the table have changed (see Figure 4 and Table 2). Therefore, we defined the sensitivity \( S \) as:

\[ S = \frac{\Delta R}{\Delta k} \quad (4) \]

where \( \Delta R \) defined as shift of reflectivity and \( \Delta k \) is the changes in imaginary part of the CRI.

### 3.2. Skin cancer diagnosis

Excessive exposure of skin tissue to ionizing UV radiation can cause DNA damage and mutations, which leads to transformation and uncontrolled proliferation of basal cells, creating tumors known as basal cell carcinoma (BCC) (Yu et al., 2012). Early diagnosis of this type of tumor accelerates the recovery process, and treatment becomes easier and less costly.

Since basal cells form the deepest layer of epidermis (outermost layer of skin), they are not visible, making the early diagnosis of BCC difficult.

Today, many articles have examined the differences in water content and water binding status in normal and cancerous tissues (Pickwell et al., 2004a, b). Because the THz EM wave is very sensitive to polar materials, including water, and reacts clearly to polar material, we recommended using THz EM wave imaging to detect BCCs. Many researchers have modelled healthy skin and the BCC with the double Debye model (Pickwell et al., 2004a, b).

\[
\varepsilon(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_2}{1 + i\omega\tau_1} + \frac{\varepsilon_2 - \varepsilon_\infty}{1 + i\omega\tau_2} \quad (5)
\]

where \( \varepsilon_\infty, \varepsilon_s, \varepsilon_2, \tau_1 \) and \( \tau_2 \) are temperature dependent of high frequency permittivity, static dielectric constant, intermediate frequency limit, slow relaxation time, and fast relaxation time, respectively. As we know, the tissues of the human body are examined in two types of \( \text{ex vivo} \) and \( \text{in vivo} \) situations. \( \text{Ex vivo} \) refers to experiments and measurements in which the tissue is examined in an environment outside of the living creature with minimal change of conditions. \( \text{In vivo} \) refers to experiments and measurements that the tissue is examined inside the living organism.

![Figure 5](image_url). The reflected spectra THz EM wave of the design came from normal skin (solid-curves) and BCC (dashed-curves) cell samples into different situations: \( \text{in vivo} \) and \( \text{ex vivo} \).

Undoubtedly, experiments in \( \text{in vivo} \) are realistic and provide more accurate results, but the experimental conditions are more difficult in this case. Here, we investigate to detect the normal and cancerous samples in both cases. The optical constants and parameters in the double Debye model (Equation 5) for healthy skin and BCC for \( \text{ex vivo} \) and \( \text{in vivo} \) (Pickwell et al., 2005) are presented in Table 3.
the difference between normal and cancerous skin (BCC) for in vivo case is greater than ex vivo. The reflection spectrum of BCC sample for ex vivo case is about 50.76% at $\omega_0 = 0.345$ THz which is slightly red shifted in compression with normal skin tissue sample with high reflection coefficient of 53.26% at $\omega_2 = 0.35$ THz. Also, the reflection spectrum for BCC sample for in vivo case is approximately 61.2% at $\omega_3 = 0.361$ THz which is red shifted in compression with normal skin tissue sample with high reflection coefficient of 62.81% at $\omega_4 = 0.368$ THz. Therefore, it can be concluded that examining skin suspected of having cancer gives clearer results for in vivo than the ex vivo method.

### 3.3. Breast cancer diagnosis

Breast cancer is the most common type of cancer for women around the world. Each year, the breast cancer has a high rate of female mortality (Bray et al., 2018). According to the studies, if diagnosis of breast cancer is faster, treatment is easier and less costly (Tayel et al., 2018). One of the most common imaging techniques for diagnosing breast cancer is x-ray mammography. However, this method is harmful to body tissues due to the use of ionizing X-rays and should not be used too many times (Nilavalan et al., 2007). In addition, this method requires the compression of the breast, which causes the person to suffer a lot (Sugitani et al., 2014).

Other methods, including magnetic resonance imaging (MRI) and ultrasound are also used to diagnose breast cancer; but they are so expensive (Nilavalan et al., 2007). One of the newest methods for detecting breast cancer is ultra-wideband (UWB) method (Wang et al., 2009). In this work, we propose a method for detecting a healthy breast tissue in compression with cancerous breast tissue by using a THz bio detector. In this method, we put the THz MM designed as the bio detector too close to the breast tissue; and by observing the reflectance spectrum of the biosensor, we can identify the tissue’s healthy or cancerous nature (see Figure 6). The reflectance spectrum of tumor breast sample is about 49.45% at $\omega_1 = 0.352$ THz which is red shifted in compression with normal breast tissue sample with high reflection coefficient of 50.78% at $\omega_2 = 0.365$ THz. In this section, we took an idea from the method presented in (Cassar et al., 2018) to simulate normal breast tissue and breast cancer tissue. In (Fitzgerald et al., 2014), Fitzgerald et al. used the Debye model (presented in Eq. 5) for healthy and cancerous breast tissues. Constants for this modelling are given in Table 4 and plotted in Figure 7.

### 3.4. Colon cancer diagnosis

Colon cancer is the third most common cancer in the world between men and women. Because the disease progresses slowly, early diagnosis of colon cancer has a tremendous effect on the treatment of the disease. So, early detection is very necessary. Optical methods are used to detect colon cancer using different frequencies. For example, Shmuel Argov et al., in 2002 (Argov et al., 2002) have proposed a method for the diagnosis of colon cancer using infrared radiation. Recently, THz imaging has been suggested for colon cancer imaging via an endoscope, and work is progressing in creating and testing endoscopic THz systems (Wang et al., 2014; Ji et al., 2009; Chen et al., 2011a). In other words, THz radiation is more useful than other frequencies for diagnosing colon cancer for a number of reasons, including non-ionization and high resolution (Wallace et al., 2008). Currently, the only previous published work on THz imaging of colon cancer is that of Reid et al. (2011), whose data was reanalyzed in the current research using our method by analyzing the reflected spectral responses. Their results are not listed here but full details can be found in their publication (Reid et al., 2011). Using their parameters, they reported the absorption coefficient and RI of the healthy and abnormal tissues (cancerous tissues). Using the formulas $\varepsilon = \varepsilon_1 + i\varepsilon_2$ for the permittivity of colon tissue, we can calculate the shift in reflection and absorption coefficient and RI relate to the real and imaginary part of the permittivity. The real and imaginary parts of permittivity are calculated as $\varepsilon_1 = \frac{\mu^2 - k^2}{\varepsilon_0}$ and $\varepsilon_2 = 2\varepsilon_0$ in which $\kappa = \frac{\omega}{\kappa}$, where $\kappa$, $\varepsilon$, $\alpha$ and $\omega$ respectively are the imaginary part of the RI, real part of the RI, speed of light in the vacuum, absorption coefficient, and $\omega = 2\pi f$ in which $f$ is the frequency of the light shining.

![Figure 6](image.png)

**Figure 6.** The reflected spectra THz EM wave of the design came from normal breast and the tumor breast cell samples.

We introduce a method to distinguish between healthy and cancerous tissues samples. In this method, the difference of interaction between the healthy and cancerous colon tissues with THz radiation is due to the cancerous tissue contains more water than healthy tissue, and the polar molecules of the water absorb THz waves more, so, the reflection of the cancerous colon tissue is less than normal colon tissue sample (see Figure 8). Here, we insert the proposed THz MM in front of the colon tissue samples and shine the normal incidence of THz EM wave on it. By analyzing the reflectance spectrum of the optical bio detector device, we can identify the tissue’s healthy or cancerous nature (see Figure 8). As it is clearly shown in Figure 8, the reflection spectrum of the bio detector is different for healthy and cancerous tissue samples. The reflection spectrum of cancerous colon tissue is slightly red shifted in compression with normal colon tissue sample and the maximum peak reflection coefficient for the normal tissue sample is more than 50% (it is about 52.4% at $\omega_2 = 0.36$ THz), but for the cancerous tissue sample less than 50% (it is approximately 48.7% at $\omega_1 = 0.35$ THz). The reflected spectrum of the cancerous colon tissue is decreased because the more than 50% of the THz wave is absorbed by water in the cancerous colon tissue.

|          | $\varepsilon_1$ | $\varepsilon_2$ | $\tau_1$ [Ps] | $\tau_2$ [Ps] |
|----------|----------------|----------------|--------------|--------------|
| Normal breast | 2.1           | 76.5           | 3.9          | 10.3         | 0.07        |
| Tumor breast  | 2.5           | 77.9           | 4.3          | 9.1          | 0.08        |

Table 4. The optical parameters of normal breast and tumor breast samples for the double Debye model in which is presented in Eq. (5) (Fitzgerald et al., 2014).
4. Future directions and conclusions

Terahertz imaging, sensing, and detecting are still in the early stages of development. THz Pulsed Detecting (TPD) is a new opto-medical detecting modality for the detection of epithelial cancers. The presence of cancer often causes increased blood supply to affected tissues and a local increase in tissue water content may be observed. Furthermore, the structural changes that occur in affected tissues which causes changing the complex refractive index of the tissues have been used to contribute to THz detecting technology. By comparing/analyzing the reflected THz spectral responses from the tissue, the circumstances of the tissue sample can be detectable. This acts as so new and updated mechanism for THz detecting of cancer. Nowadays, this technique is improving to apply to the study of in vivo and ex vivo basal cell carcinoma (BCC) of skin cancer. This paper introduces THz technology and provides a recipe in the THz sensing and detecting techniques. Using time-domain analysis the contrast between diseased and normal tissue has been shown to be statistically significant, and regions of decreased THz reflection (increased THz absorption). Using the complex refractive index and reflection coefficient spectra of healthy and diseased cancerous tissue, we could detect three kinds of cancers (skin, breast and colon cancers). Comparisons of the differences between the spectra of different tissue types were made. Simulations were carried out to show the impulse responses from performing THz pulsed reflection to detect the kind of the tissue samples. A large difference was seen, as PREDICTED, between the impulse response of healthy and those of cancerous tissues. A difference in peak height and frequency shift of the reflected impulse responses between cancerous and healthy tissue is shown. Such difference encourages the development of opto-medical devices based on THz technology. This new technology will improve and enhance detecting techniques available to clinicians for improvement of cancer treatment and healthcare in general.

Declarations

Author contribution statement

Zohreh Vafapour: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Afsaneh Keshavarz: Performed the experiments; Analyzed and interpreted the data.
Hossain Ghahraloud: Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/referenced in article.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

The authors would like to express their special thanks to Dr. Reza Behrouzi from Department of Cell Biology, Harvard Medical School, professor Mitra Dutta from Physics, and Electrical and Computer Engineering departments of the University of Illinois at Chicago and Professor Michael A. Stroscio from Departments of Bioengineering, Physics, and Electrical and Computer Engineering departments of the University of Illinois at Chicago for their useful discussions.
