Metamaterial Biosensor on THz Regime for Early Detection and Quantitative Analysis of Skin Cancer

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Abstract—Terahertz imaging exhibits significant potential in the early detection of skin cancer. This work introduces a metamaterial unit cell that operates in the terahertz (THz) band for non-invasive contact-based detection of skin cancer. The sensor relies solely on the reflection coefficient response, offering high sensitivity to subtle changes in tissue properties without complex signal processing, making it potentially cost-effective and simpler to implement for early cancer detection. The simulations utilised 3D models representing normal skin, basal cell carcinoma (BCC), and melanoma skin types. The dielectric characteristics of the samples were determined using the Double Debye model. The simulation demonstrated that the metamaterial design exhibited properties of a double negative material at the specific frequency of 1.15 THz. Following skin contact and malignancy, the reflectance coefficient exhibited a shift towards lower frequencies. The melanoma sample exhibited the most significant shift in resonance towards lower frequencies, indicating a more severe form of cancer compared to BCC. Furthermore, it was observed that the disparity in resonance frequencies between normal skin and malignant skin increased as the thickness of the sample increased. The sensor's sensitivity in identifying cancer thickness was measured at 9.25 GHz/µm for basal cell carcinoma (BCC) and 10.2 GHz/µm for melanoma. In addition, the linear regression analysis demonstrated a strong correlation between the resonance frequency and the variation in cancer thickness, as indicated by the R^2 values of 0.9948 and 0.9947 for BCC and melanoma, respectively. These findings demonstrate that the sensor can detect skin cancer of any severity at the initial stages of its development.

Keywords-Metamaterial; THz; cancer; sensor

I. INTRODUCTION

Modern lifestyles make individuals susceptible to highly harmful diseases, necessitating prompt detection. Cancer is a prevalent illness in Malaysia. In Malaysia, there are more than 200 different types of cancer, and more than 50 per cent of patients are diagnosed during the advanced stages [1]. Delayed cancer treatment is correlated with costly and difficult treatment [2]. Skin cancer is a malignancy characterised by the abnormal growth of skin cells, typically caused by prolonged exposure to ultraviolet (UV) radiation [3]. There are three primary categories of skin cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCS), and cutaneous malignant melanoma (CMM). To diagnose skin cancer, a biopsy is performed. This involves using an anaesthetic to numb the skin, and then surgically removing a suspected portion of tissue. The tissue sample is then sent to a laboratory for testing [4]. Nevertheless, this technique is intrusive and requires a significant amount of time. In the discipline of Systems Biology, numerous mechanistic models have been recently suggested to identify and manage the biochemical and biophysical properties of skin cancer [5]. On the other hand, biosensors are small, user-friendly, and portable

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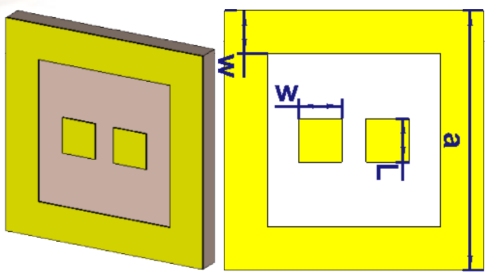
devices that can be used to detect skin cancer. Biosensors provide convenient and efficient techniques for real-time and quick monitoring without the need for labelling. Specifically, biosensors that function at terahertz (THz) frequencies have demonstrated significant advancements in the advancement of high-performance sensing technologies. The frequency range spanning from 0.1 THz to 10 THz provides a low energy level for individual photons and a high level of penetration [6]. Furthermore, this spectrum of frequencies corresponds to the vibrational energy levels of different biomacromolecules. The unique properties of THz waves have created opportunities for researchers to propose in-vivo medical imaging and diagnostics. However, the detection of trace-level compounds in direct sensing at THz frequencies is challenging due to the strong attraction of water molecules [6]. To address this difficulty, metamaterials (MMs) can be employed to amplify the electromagnetic field [7], [8]. The ionization harms living cells and the human body, which is not caused by THz frequencies, as they possess a low energy level. Moreover, the THz band encompasses the rotational and vibrational energy levels of numerous polar compounds and macromolecules found in biological systems. This characteristic can be employed to analyse and identify biological tissues [9]. Tumours generally have a larger water content compared to healthy tissues, resulting in a substantial absorption of THz waves. This leads to the identification of tumours through the detection of a distinct THz absorption spectrum [10]. In recent times, many sensors based on metamaterials have been suggested to detect cancer [11]–[14]. In reference [15], a Terahertz (THz) Metamaterial (MM) was suggested, demonstrating an absorption rate of 99% at a frequency of 3.71 THz. A different sensor, with two hexagonal gold layers arranged in loops, was suggested in reference [16]. The sensor exhibited significant field confinement inside the sensing zone at a frequency of 3.15 THz, resulting in an absorption rate of 99.9%. A triple-band metamaterial-based biosensor with great sensitivity was proposed in [17] for several types of cancer detection . The sensor was constructed with a dielectric layer of polyimide, featuring a gold patch and complete grounding on its lower surface. The analyte sample completely occupied the metallic patch, resulting in the emergence of numerous resonances. A novel method for detecting skin cancer was proposed in [18], which utilised a semiconductor film and water-based terahertz MM to achieve high sensitivity. Terahertz pulse imaging was utilised in a reflection geometry to identify skin-related malignancies. Azizi et al. [19] suggested a simplified technique for early detection of skin cancer. They incorporated a pair of split ring resonators (SRRs) at the centre of the T-shaped prototype line. The SRR resulted in an intensified electric field, whereas the gaps mostly contributed to the capacitance and clustering of the electric field. However, most of the past research primarily concentrates on set sample sizes or constant volumes of the sample, which, in practice, vary. Hence, our research has developed a novel resonator utilising THz metamaterial to detect the two prevalent forms of skin cancer in their first phases. The characteristics of basal cell cancer (BCC) and melanoma are represented using second-order Debye dielectric properties. Significantly, the analysis also considers the impact of tumour thickness and position, aiding in the identification of tumour location and the assessment of cancer severity. This sensor design utilises a direct-contact mechanism with the sample to minimise reflections and impedance mismatches between the sensor and the skin. The metamaterial sensor demonstrated operates within the THz frequency band and can detect skin cancer during its initial stages. The innovative metamaterial sensor is anticipated to possess great lateral sensitivity in the THz frequency band, enabling it to differentiate between the characteristics of healthy and malignant skin.

II. METHOD

The key contribution of this work is in the designing of a highly sensitive THz sensor which can detect different types of skin cancer cells (e.g., BCC, CMM) at different thicknesses of skin tumours. The system relies on the near field Electromagnetic (EM) waves. The generated THz waves illuminate the sample under test (skin) through the sensor design and some percentage of signal passes through the skin with the remaining power being reflected through the design. The reflected signal possesses significant information regarding the severity of tumour spreading through skin in form of resonance frequency and its amplitude. The variation of the resonance frequency in the case of normal skin sample in studied in this research in the case of BCC and CMM cancerous cells.

Figure 1 shows the metamaterial proposed design. The schematic was modelled and simulated in CST Microwave Studio. The metamaterial unit cell design consists of a hollow square-shaped patch with a couple of strips at the centre modelled on a 150×150 μm^2 substrate. As seen in layered view, the sensor consists of two layers. Gold is used as a metallic part and polyimide with a dielectric constant (ε) of 3.5 is used as the dielectric part. The thickness of the polyimide substrate, (h) and gold patch, (t), is 15 µm and 1 µm, respectively. The hollow square-shaped has a thickness (w) of 25 µm and the length (l) of metallic strips is 25 µm. Figure 2 shows the MM design's reflection coefficient response where the design shows dip at 1.15 THz with amplitude of -15 dB. It can also be seen from Figure 1 in layered view that the metamaterial does not have a ground plane with a metallic material. In this method, cancerous skin cells can be detected non-invasively by using only one port so that the changes in reflection coefficient can be detected with higher sensitivity and without any second port. The simulation setup with the skin sample is shown in Figure 1 (d). Since this is the metamaterial unit cell it is expected that the design satisfies the conditions of a metamaterial which is to represent negative permittivity (ε) and negative permeability (μ). The Numerical Robust Method (NRM) was used to extract the permittivity and permeability of the unit cell [20]. As shown in Figure 3, the constitutive parameters of MM are seen as negative at the resonance frequency of 1.15 THz, thus the unit cell exhibits double negative MM characteristics.



(a) (b)

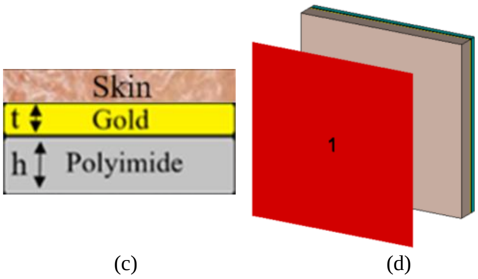


Figure 1. Metamaterial design and simulation setup (a) perspective view of unit cell, (b) front view of unit cell, (c) layered view from top with skin sample and (d) the simulation setup

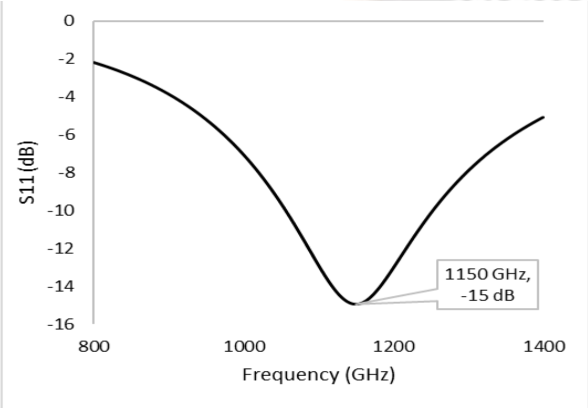


Figure 2. Resonance frequency of the MM design

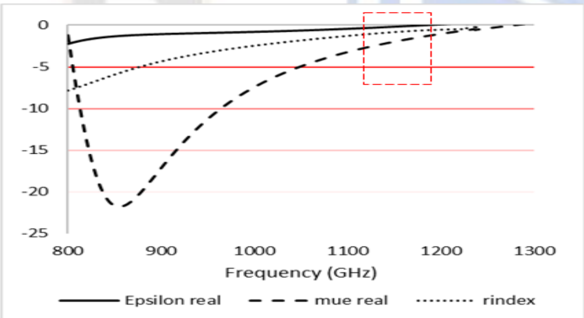


Figure 3. Extracted constitutive parameters of the designed unit cell

Subsequently, an examination is conducted on the metamaterial surface and its contact with the skin sample. The electric and magnetic fields distribution is depicted in Figure 4 and Figure 5, respectively, both with and without the presence of a skin sample. Figure 4 (a) displays the electric field strength, which measures approximately 3.82105 V/m when not in contact with the skin. In contrast, Figure 4 (b) illustrates that when in contact with the skin, the electric field strength decreases to 3.13105 V/m. The E-field distributions primarily localise in the upper and lower gaps between the two square patches of the sensor. Figure 5 (a) displays the H-field distributions, revealing that the highest strength of the magnetic field is located on the edges of square patches, measuring at 1071 A/m. Nevertheless, the H-field decreases to a maximum value of 969 A/m when the skin comes into contact with the surface of the sensor.

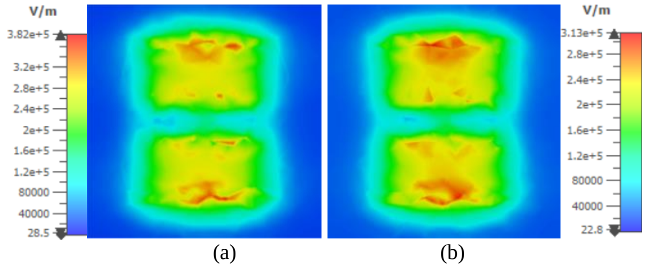


Figure 4. E-field distributions (a) without skin and (b) with skin

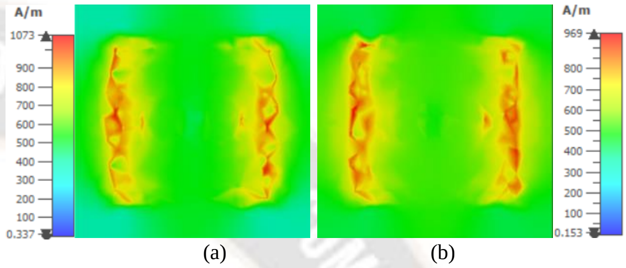


Figure 5. H-field distributions (a) without skin and (b) with skin

III. SKIN CANCER DETECTION

Electromagnetic simulations in the CST software are unable to utilise complex electric permittivity functions that exhibit dispersion. Nevertheless, in order to accurately represent the characteristics of any substance, it is necessary to utilise complex measures of permittivity or conductivity[21]. The study in reference [22] confirms the viability of employing the double Debye model for predicting the dielectric behaviour of human skin in the THz frequency range. The Double Debye model features two Debye relaxation processes that demonstrate the effect of an applied electric field on water molecules [23]. This study focuses on the phenomena of the interface between water molecules in the skin and terahertz radiation. The complex frequency in the THz band can be characterised by the Double Debye model, as specified in (1).

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

Where ε_∞ is permittivity at maximum frequency, ε_s is static permittivity, ε_2 is intermediate frequency limit, τ_1 is slow relaxation frequency and τ_2 is fast relaxation frequency [18]. In this study, we used the well-renown Double Debye characteristics of BCC as described by Pickwell [24]. The parameters for Melanoma were acquired from [25] , while those for normal skin were obtained from [21]. Table 1 presents the summary of Double Debye parameters modelled in CST Microwave Studio software for normal skin, BCC, and melanoma.

TABLE I. DOUBLE DEBYE PARAMETERS OF NORMAL SKIN, BCC AND MELANOMA

Sample	ε_∞	ε_s	ε_2	τ_1(PS)	τ_2 (ps)
Normal Skin	3.4	25	5	7	1
BCC	4.2	40	6.2	10	1
Melanoma	4.3	58	4.6	5	0.49

The 3D representation depicted in Figure 6 provides a thorough representation of different types of cancer, exposing the hidden progression of cancer under the skin, especially during its initial phases when observable symptoms are not apparent. In order to tackle this difficulty, our study presents a skin model that includes a hidden layer of cancer at different levels. Following that, simulations are performed to aid in early detection of cancer, specifically targeting a 5 µm layer of skin with different thicknesses of cancer. Figure 7 illustrates the results of the simulation for the development of basal cell carcinoma (BCC) at a depth of 5 µm within healthy skin. The results for BCC are depicted by solid lines, while situations without BCC, which display normal skin of the same thickness, are represented by dotted lines. A comparative study is conducted to examine the differences between healthy and malignant skin. Significantly, the change in resonance towards lower frequencies becomes apparent as the thickness of the BCC layer grows. In addition, the change in resonance becomes larger as the thickness of BCC increases. This is demonstrated by a shift in frequency from 943 GHz to 758 GHz when the BCC thickness varies from 5 µm to 25 µm.

Figure 8 exhibits a more prominent change in resonance frequency in the context of melanoma, as compared to BCC. The figure employs a consistent representation, using solid lines to indicate melanoma findings and dotted lines to depict normal skin outcomes. An increase in melanoma thickness from 5 µm to 25 µm results in a change of resonance towards lower frequencies. The increased change is ascribed to the disruptive influence of melanoma on the dielectric characteristics of the skin. Increased dielectric disruptions from melanoma directly trigger amplified resonance shifts in double Debye analysis. In addition, a persistent shift in the frequency of resonance, similar to what is observed in basal cell carcinoma (BCC), is detected in melanoma. The decrease in frequency resonance becomes more pronounced as the sample thickness increases, highlighting the capability of our sensor to accurately detect and measure the severity of skin cancer via detailed THz imaging.

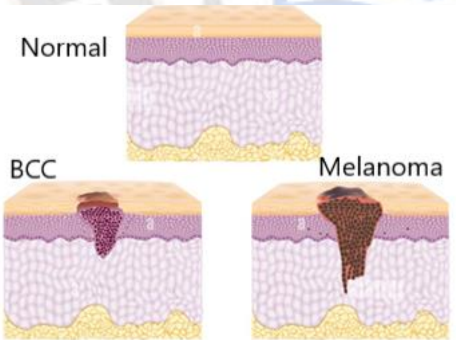


Figure 6. Types of skin cancers [26]

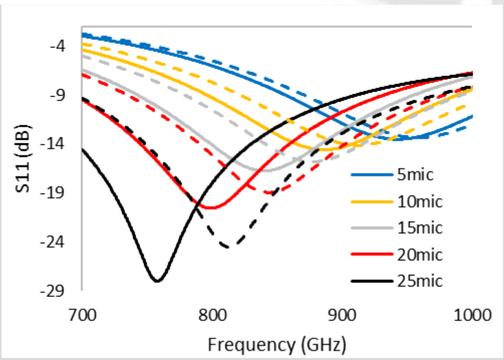


Figure 7. S_{11} at different thicknesses of BCC (___) and normal skin (---)

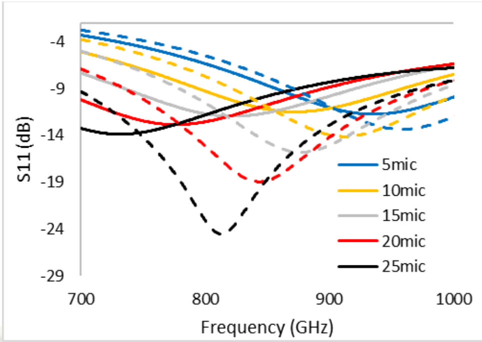


Figure 8. S_{11} at different thicknesses of melanoma (__) and normal skin (---)

IV. Analysis and Discussion

An analysis of the sensor's sensitivity is carried out in this section. The MM sensor sensitivity is an important factor to analyse the sensor's capacity in predicting the existence of cancerous cells in the skin. The sensitivity was calculated using (2).

$$S = \Delta f / \Delta t \quad (2)$$

The sensor's sensitivity (S) is defined by the ratio of the shift in frequency (Δf) to the change in thickness (Δt) of the cancerous cell, expressed as S = Δf/Δt. In our study, the sensor exhibits a sensitivity of 9.25 GHz per micron for basal cell carcinoma (BCC) and 10.2 GHz per micron for melanoma. Notably, the sensor demonstrates a higher intensity in detecting melanoma compared to BCC. Despite considering a maximum cancerous cell thickness of 25 µm (subject to practical variations), the sensor remains capable of detecting elevated thicknesses of skin cancer samples.

To further analyse the obtained results, linear regression analyses were applied, treating the resonance frequency as the independent variable and the thickness of the skin cancer as the dependent variable. This analytical approach aids practitioners in estimating cancer growth into the depth of the skin. Figure 8 illustrates that the linear regression model accurately predicts BCC thickness with an R^2 value of 0.9948. Similarly, Figure 9 demonstrates the predictive capability of the proposed sensor for melanoma thickness, yielding an R2 value of 0.9947. The notably high R^2 values affirm the linearity of the resonance shift concerning changes in the thickness of cancerous cells, underscoring the sensor's exceptional performance in detecting cancer at its early stages.

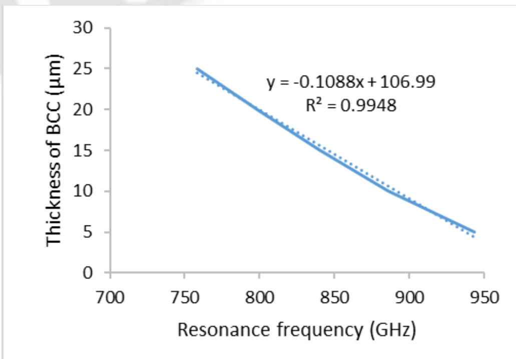


Figure 8: Linear regression applied to the results obtained from sensor in case of BCC.

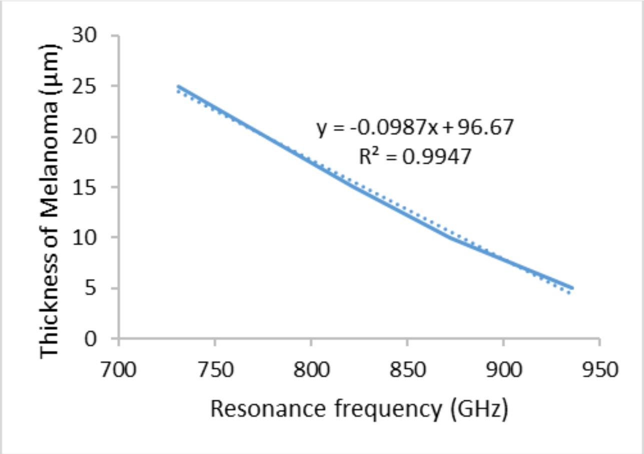


Figure 9. Linear regression applied to the results obtained from sensor in case of melanoma.

V. Conclusion

In conclusion, we present a novel micro biosensor that operates in the THz frequency range, demonstrating exceptional promise for the early detection of skin cancer. Our simulation of the interaction between THz radiation and both healthy and malignant skin tissues is an important milestone in understanding the use of THz imaging for detecting skin cancer. The sensor's exceptional sensitivity to polar molecules, specifically water, makes it an excellent option for cancer detection, considering the association between cancer progression and elevated water molecules in the skin.

The proposed sensor due to its unique single-port design, enables the non-invasive examination of skin samples in contact with the sensor. The scope of our research centres on two common forms of skin cancer, specifically basal cell carcinoma and melanoma, highlighting significant differences between normal and malignant skin. The sensor demonstrates a proportional reaction in resonance shifts with respect to sample thickness, indicating its suitability for measuring larger thicknesses outside the scope of this investigation.

The application of the linear regression method is valuable for determining the intensity of cancer, providing a reliable analytical tool. Our sensor exhibits exceptional efficacy in identifying the range of cancer severity, encompassing both mild cases and more advanced illnesses, by analysing the varied thicknesses of malignant cells. The results emphasise the sensor's capacity to transform the early detection and tracking of skin cancer, providing a hopeful pathway for boosting medical analysis and enhancing patient results.

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