Photothermal Impact of Terahertz Radiation for Brain Therapy: Applications in Neuromodulation and Hyperthermia

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ABSTRACT

Recent advancements in brain therapy techniques, including neuromodulation, optogenetics, and brain-computer interfaces, have revolutionized the treatment landscape for neurological disorders. One emerging area of interest in neuroscience research is the exploration of terahertz radiation due to its unique properties and potential therapeutic applications. Terahertz radiation is capable of being absorbed by biological tissues, and its frequency range coincides with the vibrational levels and resonance of biological molecules and proteins. In this study, we investigate the photothermal effect of terahertz radiation on brain tissue using 2D computational models developed in COMSOL Multiphysics® Software. One model focuses on healthy brain tissue, while the other examines the targeted heating of tumor tissue with minimal impact on adjacent healthy brain tissue. Various terahertz frequencies, power levels, and exposure times are considered to establish application-based safety limits for this technology. Our findings pave the way for the safe utilization of terahertz radiation in neuromodulation techniques, where tissue heating is undesired, as well as in thermogenetics and brain hyperthermia therapies, where controlled heating is essential for therapeutic efficacy.

CCS CONCEPTS

• **Computing methodologies** → **Model development and analysis**; **Modeling methodologies**.

KEYWORDS

Terahertz (THz), Brain, Tumor, Photothermal, Neuromodulation, Cancer treatment.

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1 INTRODUCTION

The field of neuroscience studies the brain and nervous system, employing a multi-scale approach that spans from molecules and cells to behavior and cognition. This expanding knowledge base has significantly propelled advancements in therapeutic strategies for complex neurological disorders in recent years. While traditional interventions like surgery, radiation, and medication offer some benefits, they often come with limitations and significant side effects. To address these shortcomings, researchers are actively exploring more targeted therapeutic approaches. With the continuous integration of novel technologies and a deeper understanding of brain physiology and pathophysiology, the field is being propelled forward, transforming previously untreatable conditions into manageable ones.

For instance, neuromodulation represents the manipulation of neural activity in specific brain regions or neural networks. This modulation can occur through various approaches, including chemical, optical, magnetic, electrical, and thermal stimulation. Chemical neuromodulation refers to using pharmaceutical substances to modulate the brain's neurotransmitter levels or receptor activation, which then tunes ion channels [14]. Optical stimulation, also known as optogenetics, delivers light to targeted light-sensitive proteins in specific brain areas to activate or inhibit particular neuronal populations [10]. Transcranial magnetic stimulation relies on the magnetic fields generated from an implanted coil in the skull that can depolarize neurons to modulate the neural activity of the brain [8]. Electrical stimulation, such as deep brain stimulation and transcranial electric stimulation, involves implanting electrodes to deliver electric pulses to specific areas in the brain [20]. Thermal neuromodulation, termed thermogenetics, is a technique that involves the use of heat to modulate neural activity in the nervous system. Focused ultrasound and radiofrequency ablation are the most common methods of thermogenetics, where they are used to generate heat on specific brain regions to either selectively stimulate neural activity or destroy targeted nerve tissue [1]. Radiofrequency ablation is usually performed by raising the brain tissue temperature of an awakened patient between 315.15 K and 318.15 K (42°C and 45°C) for less than 30 seconds, and it is considered tissue destructive when the brain tissue temperature is above 323.15 K (50°C). Thermal neuromodulation has been clinically used to treat chronic pain, movement disorders, epilepsy, psychiatric disorders, and even neurodegenerative diseases like Alzheimer's disease [11].

Another brain therapeutic technique similar to thermal neuromodulation is hyperthermia, which involves raising the brain tissue temperature above normal levels to achieve medical therapeutic

purposes, including cancer treatment and managing infectious diseases. External hyperthermia involves applying heat to the scalp or head region from an outside heat source. In contrast, interstitial hyperthermia involves implanting focused heat sources, such as microwave antennas or electrical electrodes, near the targeted tissue to raise its temperature [19]. For cancer therapy, hyperthermia can be employed alongside chemotherapy or radiotherapy to enhance their effectiveness by denaturing proteins, making cancerous cells more susceptible to cell death or damaging tumor tissue. During such treatment, the temperature of the tumor is raised to 313.15 K - 318.15 K (40°C - 45°C) for destructing cancer cells. This technique was previously studied using a 915 MHz antenna as a heat source, and it was feasible for raising the brain tumor temperature within 30 minutes of exposure to electromagnetic radiation [21].

The interaction of terahertz (THz) waves with biological tissue differs from that of optical frequencies and lower frequencies, like radio frequencies and millimeter waves. At the terahertz frequency band, the radiation energy matches the vibrational energy levels of molecules in the tissue, causing high absorption coefficients. Additionally, water molecules exhibit high absorption in the terahertz band due to the vibrations of the hydrogen bonds, and the water content in the brain tissue is relatively high compared to other tissues. Hence, the absorption coefficient of brain tissue tends to be relatively high compared to other frequency bands [16]. The absorbed radiation within the tissue will then be transferred to thermal energy, enabling the use of terahertz radiation for thermoneurotherapy methods like thermal neuromodulation and hyperthermia for the treatment of brain diseases. This photothermal effect of the terahertz radiation was previously studied on proteins [2], red blood cells[3], corneal tissue [6], and human skin [4, 18]. The photothermal effect of a 1 THz electromagnetic wave on the breast and brain tissues was investigated in [7]. In this work, the brain was modeled as an organ composed of white matter and gray matter, each with its own unique properties. Modeling the brain as a whole organ is valuable for studying large-scale neural networks and global brain dynamics. In contrast, focusing on a small-scale tissue enables a thorough analysis of the functional and microstructural characteristics of that specific region. This approach is useful for analyzing localized instances, understanding certain brain diseases, or determining the effects of targeted therapy on particular brain regions. This approach helps researchers acquire high-resolution insights from tissue models that whole-organ models could have overlooked. On the other hand, the non-thermal impact of terahertz radiation is gaining growing interest within neuroscience research to promote neuronal growth and development, potentially aiding treatment for neurodevelopmental disorders or nerve damage [12].

This paper investigates the photothermal effect within a specific range of the THz frequency band (0.8 THz - 1.5 THz) on brain tissue. We employ two 2D COMSOL Multiphysics® models to analyze the distribution of power and subsequent heat transfer within both healthy and tumor brain tissue. Additionally, our analysis incorporates the influence of blood perfusion on temperature regulation. In these models, we explore the effects of various radiation power levels and exposure durations on brain tissue to gain a comprehensive understanding of the impact of terahertz radiation. Our findings demonstrate that terahertz radiation induces thermal changes in brain tissue, which can be precisely controlled through adjustments in frequency, power, and exposure time. This research paves the way for the potential use of terahertz electromagnetic radiation in short-duration, targeted brain radiation therapies. Applications include neuromodulation, where tissue heating is not required, as well as thermal neuromodulation and hyperthermia, where controlled heating is necessary. Further research is needed to explore how this technology can be used to treat a variety of brain diseases, including chronic pain, movement disorders, epilepsy, psychiatric disorders, neurodegenerative diseases such as Alzheimer's disease, cancer, and infectious diseases.

The paper is structured as follows: Sec.2 describes the methodology used in our study, including the development of the 2D COMSOL Multiphysics® models, the scenarios considered, and the parameters defining the tissues. Sec.3 presents the simulation results, highlighting the thermal effects of various radiation power levels and exposure durations on brain tissue, setting application-based limits, and demonstrating the heating impact of the radiation on targeted tumor tissue. Finally, Sec. 4 concludes the paper by summarizing the outcomes, discussing limitations, and suggesting future research work.

2 MODEL DEVELOPMENT METHODOLOGY

A 2D numerical model of the brain tissue has been developed on COMSOL Multiphysics® to simulate the interaction between terahertz radiation and the brain tissue to understand the photothermal impact of the terahertz electromagnetic wave on the exposed tissue.

2.1 Model Framework

This model incorporates two different physics, as first described in [17]. First, it evaluates the power intensity distribution within the brain tissue according to the diffusion approximation of the Radiative Transfer Equation [13]. This equation is used to describe photon propagation in an absorbing and scattering medium, as is the case in biological tissues, as follows:

$$\frac{1}{v}\frac{\partial \Phi(\mathbf{r},t)}{\partial t} = D\nabla^2\Phi(\mathbf{r},t) - \mu_a\Phi(\mathbf{r},t) + S(\mathbf{r},t), \tag{1}$$

where v is the velocity of light, $\Phi(\mathbf{r},t)$ is the photon fluence rate at position $\mathbf{r}$ and time t, D is the diffusion coefficient, μ_a is the absorption coefficient, and $S(\mathbf{r},t)$ is the source term representing the photon emission. The radiation source is considered to be a Gaussian beam with a parametric maximum power density. Then, the power at each point in the model is calculated depending on the power density distribution and the mesh area.

The diffusion coefficient D is related to the scattering and absorption properties of the medium and is calculated according to the following equation:

$$D = \frac{1}{3(\mu_a + \mu_s')}, \tag{2}$$

where μ_s' is the reduced scattering coefficient, which is neglected as it is less dominant in the case of terahertz interaction of biological tissue [5].

After determining the power density distribution in the modeled medium, the model evaluates the corresponding medium heat change based on the radiation intensity and the medium absorption coefficient. This step utilizes Penne's Bioheat Equation to describe

Table 1: The Model Parameters

Tissue	Parameter	Unit	Value	Ref.
Healthy	Specific Heat Capacity	$J/(kg.K)$	3630	[9]
	Thermal Conductivity	$W/(m.K)$	0.51	
	Density	kg/m^3	1046	
	Absorption Coefficient	cm^{-1}	194 - 266	[22]
	Refractive Index	-	2.08 - 1.98	
Tumor	Specific Heat Capacity	$J/(kg.K)$	3621	[21]
	Thermal Conductivity	$W/(m.K)$	0.5	
	Density	kg/m^3	1043	
	Absorption Coefficient	cm^{-1}	204 - 290	[22]
	Refractive Index	-	2.18 - 2.01	

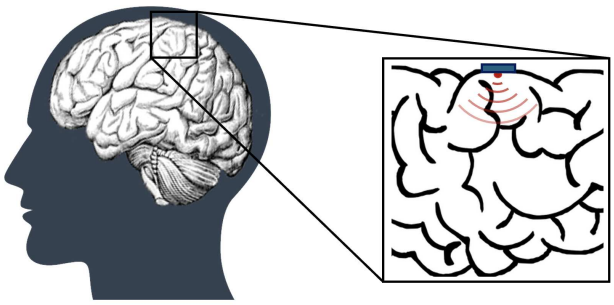


Figure 1: Implanted terahertz electromagnetic radiation source in the brain tissue.

the heat transfer in the brain tissue [15], including the blood perfusion effect, which is responsible for regulating the tissue temperature, as follows:

$$\rho C \frac{\partial T}{\partial t} = k\nabla^2 T + \rho_b C_b \omega_b (T_b - T) + Q_{met}, \tag{3}$$

where ρ is the density of the tissue, C is the specific heat capacity of the tissue, T is the temperature of the tissue, t is time, k is the thermal conductivity of the tissue, ρ_b is the density of blood, C_b is the specific heat capacity of blood, ω_b is the blood perfusion rate, T_b is the arterial blood temperature, and Q_{met} is the metabolic heat generation per unit volume.

2.2 Investigated Case Scenarios

Several scenarios within our study are analyzed to investigate the photothermal impacts of terahertz radiation on the brain thoroughly. The first scenario involves studying the effect of different terahertz frequencies on healthy brain tissue, considering the variation of power levels and exposure time. This scenario is beneficial in understanding the radiation interaction with the brain and helps investigate its potential in different brain therapeutic techniques. This is then followed by the second scenario, which examines the photothermal effect of the terahertz radiation on brain tumors, giving us insights into how to utilize this photothermal effect to damage specific tissues while minimizing the impact on neighboring healthy brain tissue.

For healthy brain and tumor tissue, all the thermal and electrical parameters are required to model those two mediums. The thermal parameters, such as the specific heat capacity, thermal conductivity, and density, are frequency-independent. However, the electrical parameters, like the refractive index, absorption coefficient, and scattering coefficient, are frequency-dependent. Table 1 presents the parameters used to model the healthy and tumor brain tissues for frequencies between 0.8 THz and 1.5 THz. The initial temperature of the modeled healthy brain and tumor tissues is 310.15 K, equal to 37°C.

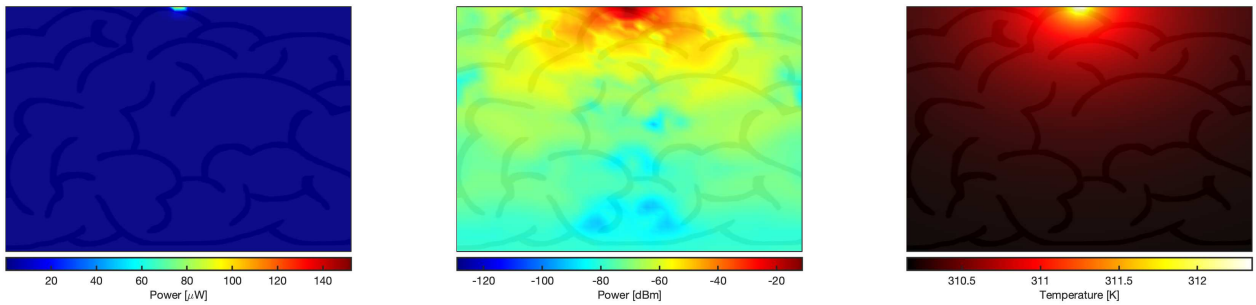
3 STUDY FINDINGS AND REFLECTIVE ANALYSIS

3.1 Terahertz Wave Interaction the Brain Tissue

Terahertz waves exhibit a low penetration depth in the range of hundreds of micrometers, which is advantageous for targeted brain therapy. The first study examines a scenario depicted in Fig. 1, where a terahertz radiation source emits continuous 1 THz electromagnetic waves into a 5 mm × 5 mm section of brain tissue. Fig. 2a illustrates the radiation power of 160 μW (approximately -8 dBm) as it penetrates the brain tissue. Due to the high absorption coefficient of the brain tissue, the power is entirely absorbed within less than 0.1 mm of tissue thickness. Thus, visualizing the power distribution on a logarithmic scale (i.e., dBm) is more effective, as shown in Fig. 2b. The initial tissue temperature before radiation exposure was set to 310.15 K. The temperature increase resulting from the absorbed electromagnetic field over 30 seconds raised the tissue temperature by approximately 2.4 K, as depicted in Fig. 2c.

The absorption coefficient of a material specifies the amount of energy being absorbed per unit distance as the energy propagates in this material. The higher the absorption coefficient, the more energy is absorbed by the medium; hence, the higher the temperature the material will experience. Since the absorption coefficient is frequency-dependent, the change in tissue temperature is frequency-dependent as well, as presented in Fig. 3. For 30 seconds of terahertz radiation exposure, the temperature of the tissue slightly changed with the change in frequency when the transmission power was relatively low. However, when the power transmitted from the antenna increased, the variation in the tissue temperature was more obvious when changing the radiation frequency. This shows the importance of choosing the frequency and required power for each application.

Besides the effect of the radiation frequency and power, the duration of tissue exposure to radiation is also a crucial parameter to investigate in this study. As depicted in Fig. 4, the longer the exposure time, the greater the amount of radiation absorbed by the tissue, and consequently, the higher the temperature rises. As previously mentioned, this variation is less pronounced at lower radiation power levels compared to higher power levels. Due to



(a) (b) (c)

Figure 2: (a) Power distribution in μW, (b) Power distribution in dBm, and (c) the temperature profile in K of the modeled 5 mm × 5 mm brain tissue after 30 seconds of exposure to 1 THz electromagnetic radiation.

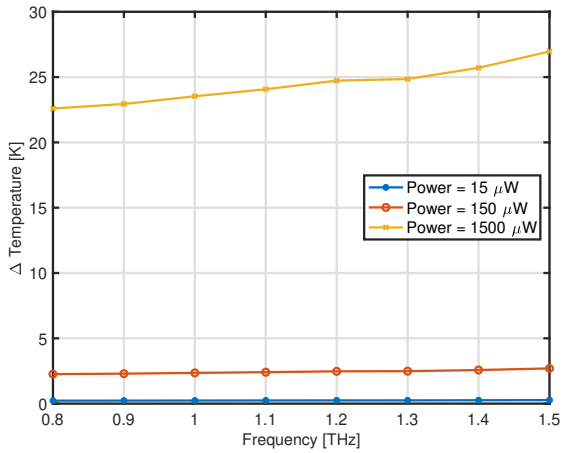


Figure 3: The maximum change in the brain tissue temperature after 30 seconds of exposure to radiation of varying frequencies and power.

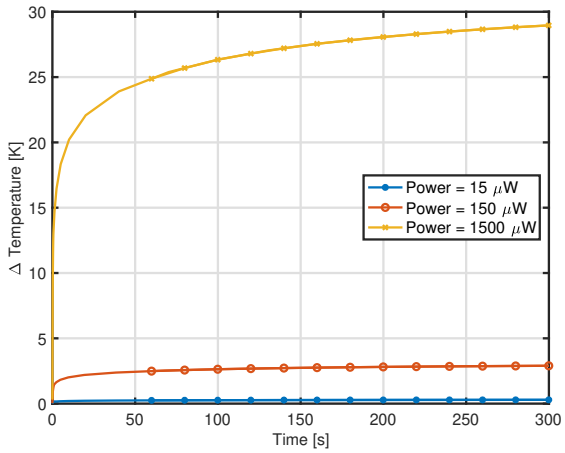


Figure 4: The change in the brain tissue temperature after exposure to 1 THz electromagnetic wave with different power levels.

blood perfusion in the brain, which is responsible for regulating tissue temperature, the temperature of the tissue increases but tends to stabilize and reach equilibrium over time. This emphasizes the significance of considering exposure time for each specific application, as understanding and optimizing exposure time is essential for achieving desired outcomes while mitigating potential risks.

For most localized brain treatments, it's recommended to keep the radiation exposure duration relatively short, typically less than a minute, to achieve the desired effects while minimizing the risk of adverse reactions. Focusing specifically on a low radiation duration of 30 seconds, Fig. 5 illustrates how different power levels of 1 THz electromagnetic radiation can be applied across various applications. In Power Zone 1, corresponding to radiation levels below -15 dBm (approximately 31.6 μW), the thermal impact on brain tissue is minimal, resulting in less than a 1 K increase in tissue temperature. This power range is suitable for applications such as brain-computer interfaces (BCIs), deep brain stimulation systems (DBS), and neuro-monitoring or neuromodulation, where tissue heating is not necessary. For thermal neuromodulation (thermogenetics) or hyperthermia, where tissue heating is desired, Power Zone 2, ranging between -15 dBm and -3 dBm (From approximately 31.6 μW to 501 μm), is appropriate. Within this range, tissue temperatures elevate to levels between 311.15 K and 317.15 K. This level of heating should still be below the threshold for causing significant tissue damage, however, it could cause micro- or nano-scale changes such as protein denaturation. Power Zone 3, corresponding to radiation power that is higher than -3 dBm (501 μW), represents radiation levels where brain tissue may incur damage, potentially leading to cellular death due to the pronounced thermal effects.

3.2 Heating Targeted Brain Tumor

Tumor tissue exhibits slightly different thermal and electrical properties compared to healthy brain tissue, as detailed in Table 1. Notably, tumors possess a higher absorption coefficient, resulting in

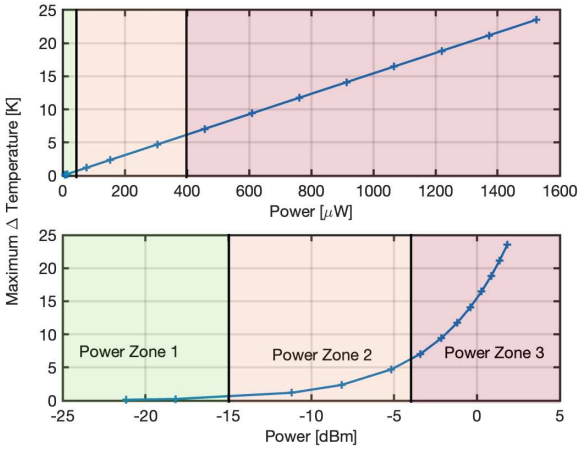


Figure 5: The maximum change in the brain tissue temperature after exposure to 1 THz electromagnetic wave for 30 seconds with different power levels.

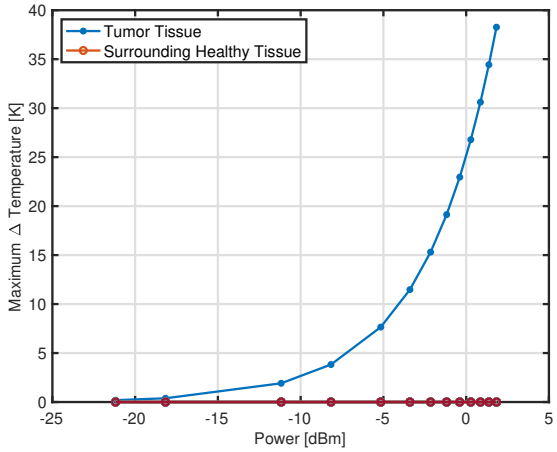


Figure 7: The maximum change in the brain tumor tissue temperature after exposure to 1 THz electromagnetic wave for 30 seconds with different power levels compared to the surrounding healthy tissue maximum temperature rise.

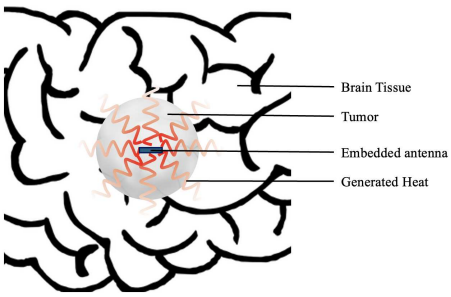


Figure 6: Placement of terahertz radiation source at the center of a brain tumor for localized heating.

increased absorption of electromagnetic radiation and elevated temperatures within the tumor compared to healthy tissue. To gain insight into the photothermal effects of terahertz radiation on tumors, we developed a model representing a 5 cm × 5 cm section of healthy brain tissue with a centrally located tumor measuring 2 cm in diameter, as depicted in Fig. 6. In this model, a 1 THz radiation source is positioned at the center of the tumor to enable targeted heating.

The absorbed electromagnetic energy within the tumor is converted into thermal energy, leading to an increase in its temperature, with the maximum temperature observed at the tumor's center. One notable advantage of using terahertz radiation in this case is its low penetration depth, which limits its reach to the surrounding healthy tissue, thereby preventing an increase in its temperature. This advantageous property is illustrated in Fig. 7, where the maximum temperature within the tumor tissue (at the center) exponentially increases with higher radiation power, while the surrounding healthy brain tissue remains unaffected. Exposure to a 1 THz radiation source with power exceeding -5 dBm for 30 seconds can elevate the tissue temperature more than 7 K. Such temperature elevations induce various cellular effects within the tumor, including protein denaturation, DNA damage, and disruption of cellular membranes, ultimately leading to cell death and tissue damage.

One important factor to consider in this therapy is the exposure time. As previously discussed, as the exposure time increases, the temperature of the exposed tissue rises. Fig. 8 demonstrates that over extended periods of radiation, the temperature can propagate to the surrounding tissue, posing unintended risks. In these figures, the tumor location is highlighted by the blue circle. It can be observed that for exposure durations of 30 seconds, 5 minutes, and 10 minutes to 1 THz electromagnetic radiation, the surrounding tissue remains thermally unaffected by the radiation. However, after 1 hour of exposure, the temperature propagates and elevates the temperature of the healthy tissue, potentially causing adverse effects. This indicates that extended radiation time can be employed for larger tumors to cover a greater tumor area, or multiple targeted spots can be treated with shorter radiation duration. These findings underscore the potential of terahertz radiation for use in neuromodulation and for localized heating in hyperthermia-based cancer treatments, emphasizing the need to carefully manage exposure times, power, and frequency to avoid unintended thermal impacts on healthy tissue.

4 CONCLUSIONS

With advancements in neuroscience and brain therapeutic techniques, the potential use of terahertz radiation in brain therapies is being explored. This application can have both behavioral and thermal impacts. In this paper, we demonstrate how brain tissue interacts with terahertz radiation using a multiphysics model that employs the diffusion approximation of the radiative transfer equation and Penne's bioheat equation. We investigate the effects of various terahertz frequencies, radiation power levels, and exposure times on the tissue's overall temperature. Our findings allow us

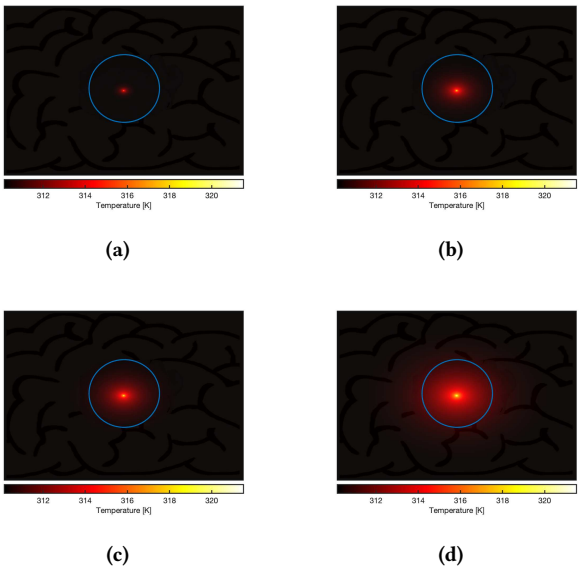


Figure 8: The photothermal impact of terahertz radiation on brain tumor after (a) 30 seconds, (b) 5 minutes, (c) 10 minutes, and (d) 1 hour of exposure.

to establish parameter limits based on the intended application. Additionally, we show that terahertz radiation can be utilized for short-duration targeted therapy, where induced heat in the tissue can cause cell death, making it a potential treatment for tumors in cancer therapy.

This study is limited to frequencies ranging from 0.8 THz to 1.5 THz, as these are the ranges for which tissue electrical properties are available in the literature for rat brain tissue. Future work should explore the entire terahertz frequency band on human brain tissue, considering that biological protein and molecule vibrational levels exist within this range. In vivo experiments will be necessary to verify the model's findings and to investigate the behavioral effects of the radiation on tissue, enhancing our understanding of its potential use in neuromodulation. Finally, the development of nano/microdevices that can be externally controlled while being placed in specific brain regions will bring this technology closer to real-world applications.

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