

Potential Thermal Effect of Stimulating Brain Tissue during Low Level Laser Therapy

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Abstract. Low level laser therapy (LLLT) is a promising and noninvasive technique in treating a multitude of medical conditions by activating healing and cell regeneration. It is also used to stimulate the brain function. The aim of this study is to investigate the Potential Thermal Effect of LLLT during stimulation. LLLT is characterized by low-intensity treatment. However, what is the dose of intensity required to stimulate the brain without a possible thermal effect. To address this, a simulation model was proposed and implemented using Finite Element Analysis within the COMSOL Multiphysics software package. This approach aims to determine the optimal combination of energy density and irradiation time that would yield the most effective enhancement of cell activity in the brain. The best power density is 166 mW/cm² (joule density 20 J/cm²) and 2 min exposure is enough to stimulate the brain when applying 808 nm with optic cap that gives a laser spot size of 3 cm². The determination of optimal parameters is imperative in the context of brain activation. It is crucial to ensure that the tissue temperature does not exceed 0.5 °C, which is the permissible temperature limit for effective stimulation. The findings will provide valuable insights into the optimization of LLLT protocols, thereby establishing a foundation for its safe and effective application in therapeutic settings. © 2023 Journal of Biomedical Photonics & Engineering.

Keywords: stimulation; Low Level Laser Therapy; COMSOL multiphysics; brain; thermal effect.

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1 Introduction

Low level laser therapy (LLLT) is a simple, safe, noninvasive treatment that uses low intensity of laser light to treat a multitude of conditions that require stimulation of healing or relief of pain [1] and inflammation [2], restoration of function [3], and rejuvenation and brain health disorders [4].

The basic concept of LLLT is the delivery of therapeutic doses of laser energy to affected tissues at an energy level that is much lower than the threshold required for thermal damage but sufficient to cause tissue reaction [5]. Where visible or near infrared (NIR) lasers (600–1064 nm) are typically used with an irradiation time

of a few seconds to minutes or sometimes even more, in the low power range of (1–500 mW) [5], and an increase in temperature up to 0.5 °C is enough to cause changes in cell function [6].

Despite many the positive results, still there is some controversy about the effectiveness of LLLT, this is because the mechanism of its interaction is not well understood, beside that the optimal parameters have not been systematically determined yet [7].

LLLT has been shown to increase blood flow and oxygenation in various parts of the body, including those areas where it was applied. This may help improve cellular function and increase energy production, which

is the adenosine triphosphate ATP within cells, and thus stimulate the activity of neurons [8].

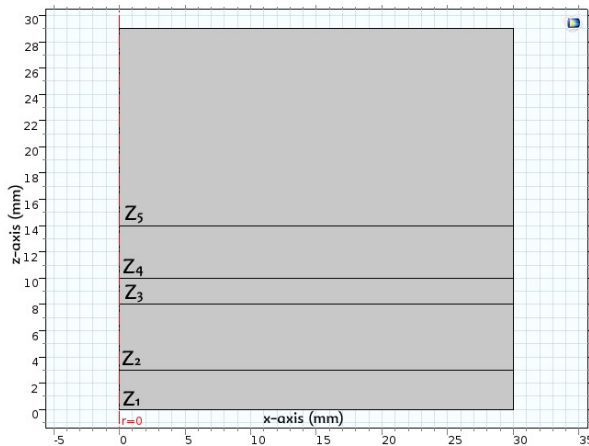


Fig. 1 Brain layers model, z_1 is a scalp, z_2 is a skull, z_3 is a cerebrospinal fluid (CSF), z_4 is a gray matter, and z_5 is a white matter.

Table 1 Typical thickness of brain tissue layers.

Tissue layers	Thickness (mm)	Refractive index n
Scalp	3	1.33
Skull	5	1.34
Cerebrospinal fluid (CSF)	2	1.37
Gray Matter	4	1.39
White matter	20	1.40

Lampl [9, 10] and Hashmi et al. [11] suggested that the utilization of transcranial laser stimulation with low-energy lasers within the near-infrared wavelengths has the potential to modulate brain functions and elicit neurotherapeutic effects. Barrett and Gonzalez-Lima [12] conducted the initial controlled study demonstrating that transcranial laser stimulation enhances cognitive and emotional brain functions in humans. The researches by Rojas and Gonzalez-Lima [13–15] and Chung et al. [16] have provided valuable insights into the historical progression of this field as well as the underlying principles and applications of LLLT in enhancing cortical metabolic capacity and memory retention even in individuals with Alzheimer's disease.

Table 2 Thermal properties of the simulation model.

Tissues	Heat Conductivity $W/(m \cdot K)$	Density kg/m^3	Specific Heat Capacity $J/(kg \cdot K)$	Metabolic Heat (W/m^3)
Scalp	0.342	1100	3391	363
Skull	1.15	1990	1313	70
CSF	0.64	1000	4096	0
Gray Matter	0.5	1080	3696	16700
White matter	0.5	1080	3583	4175

The temperature of biological tissue when subjected to laser stimulation is not only dependent on the laser parameters but also on the thermal attitude of the tissue towards the wavelength of applied laser as well. Consequently, the thermal response of the tissue tends to vary even when exposed to the same parameters of the laser.

Heating the scalp and skull also has a significant impact on the path and position of thermal propagation within the layers of brain tissue. Hence, it is essential to consider the limitations associated with LLLT applied on the human brain due to the possible thermal effects.

Many studies have attempted to model thermal changes in biological tissues under laser irradiation [17, 18]. Simulation are usually done by studying the light diffusion and temperature changes in biological tissue that occur after the absorption of the light energy of laser [19].

The Pennes' bio-heat equation to study the temperature distribution in biological tissues, is an important step in simulating laser-tissues interaction [20, 21]. It is the most famous equation, and it is considered good because it deals with the effects of blood perfusion and metabolism on the biological tissue, which is so important in stimulation, in addition to being simple and accurate, thus it was used to study the heat distribution in the brain layers in our simulation model [18, 21, 22].

The importance of the presented work lies in exploring the potential thermal effect that occurs during neural stimulation, which has not been reported previously, where the parameters used in LLLT has not determined as well. Laser 808 nm was chosen because it is the widely used in stimulation. This study can be used as a reference for other researchers who want to experiment with LLLT in their studies.

2 Modeling Method

The aim of this study was to analyze the temperature distribution of the human brain tissue under variable near-infrared laser irradiation in order to estimate the thermal range, which is related to the activation of neurons. The optimal LLLT parameters such as power density (energy density) and treatment time were investigated during applying laser 808 nm with spot size of 3 cm^2 . Using a model based on finite element method FEM implemented on COMSOL Multiphysics 5.0 software and Pennes' bio-heat transfer equation.

Table 3 Optical parameters of brain tissue.

Tissues	Absorption coefficient, μ_a (1/m)	Scattering coefficient, μ_s (1/m)
Scalp	18	11818
Skull	16	10909
CSF	1	66
Gray Matter	25	7700
White matter	5	36450

Table 4 Effect of power density and treatment time on the tissue temperature distribution.

Power (mW)	500	400	300	200	100
Laser spot size (cm ²)	3	3	3	3	3
Power density (mW/cm ²)	166	133	100	66	33
Irradiation time (min)	Tissue temperature (°C)				
1	37.39	37.33	37.27	37.25	37.22
2	37.59	37.48	37.38	37.29	37.29
4	37.84	37.70	37.55	37.39	37.35
5	37.94	37.77	37.61	37.44	37.37
10	38.22	38.00	37.79	37.58	37.42
15	38.32	38.09	37.86	37.63	37.44
20	38.39	38.14	37.90	37.65	37.45

2.1 Bioheat Transfer Equation

The heat transfer in tissue is a complex process and the main sources of heat transfer are via radiation, air conduction and convection. In addition, blood flow also affects heat transfer. Therefore, the Pennes' bioheat equation is used to calculate the temperature of the tissue irradiated by laser exposure [20, 23, 24]:

$$\delta_{ts} \rho C \frac{\partial T}{\partial t} + \nabla(-K \nabla T) = \rho_b C_b \omega_b (T_b - T) + Q_{met} + Q_{Laser}, \quad (1)$$

where δ_{ts} is a time ratio (the default value is 1), ρ is a density of tissue (kg/m³), C is a specific heat of tissue (J/(kg·K)), T is a temperature (°C), K is a thermal conductivity of tissue (W/(m·K)), ρ_b is a density of blood (kg/m), C_b is a specific heat of blood (J/(kg·K)), ω_b is a volumetric perfusion rate (kg/(s·m)), T_b is a temperature of arterial blood (°C), Q_{met} is a metabolic heat source (W/m³), Q_{Laser} is a laser heat source (W/m³).

2.2 LLLT Propagation Calculation

While a fraction of laser light is absorbed by the tissue, the remaining light will be scattered, reflected or refracted. Here, we suppose that the light source is Gaussian beam and we can define Q_{Laser} in Eq. (1) as follows [19, 22, 24]:

$$Q_{Laser} = \mu_a [(1-R) \frac{2P}{\pi \omega_0^2} \exp(\frac{-2r^2}{\omega_0^2}) \exp(-\mu_t z) f(t)], \quad (2)$$

where μ_a is an absorption coefficient (1/m), R is a reflectance at normal incidence, P is a laser power (W), ω_0 is a beam radius at irradiation surface (m), $\mu_t = \mu_a + \mu_s$ is an attenuation coefficient of tissue (1/m), μ_s is a scattering coefficient (1/m), $f(t)$ is a time function.

While the brain consists of multiple layers, each one has a different optical parameter value. The depth coordinates of each layer are defined as z_1, z_2, z_3, z_4 , and z_5 , which represents scalp, skull, cerebrospinal fluid (CSF), gray matter (adipose tissue), white matter (granular tissue) respectively as demonstrated in Fig. 1. Thus the heat source for the first and second layers as follows:

The heat source of the Scalp layer (first one) is:

$$Q_{Scalp} = \mu_{a1} \cdot [(1-R) \frac{2P}{\pi \omega_0^2} \exp(\frac{-2r^2}{\omega_0^2}) \cdot \exp(-\mu_{s1} z - \mu_{a1} z) \cdot f(t)], \quad (3)$$

The heat source of the skull layer (second one) is:

$$Q_{Skull} = \mu_{a2} \cdot [\frac{2P}{\pi \omega_0^2} \exp(\frac{-2r^2}{\omega_0^2}) \cdot \exp(-\mu_{s1} z_1 - \mu_{s2}(z - z_1) - \mu_{a1} z_1 - \mu_{a2}(z - z_1)) \cdot f(t)], \quad (4)$$

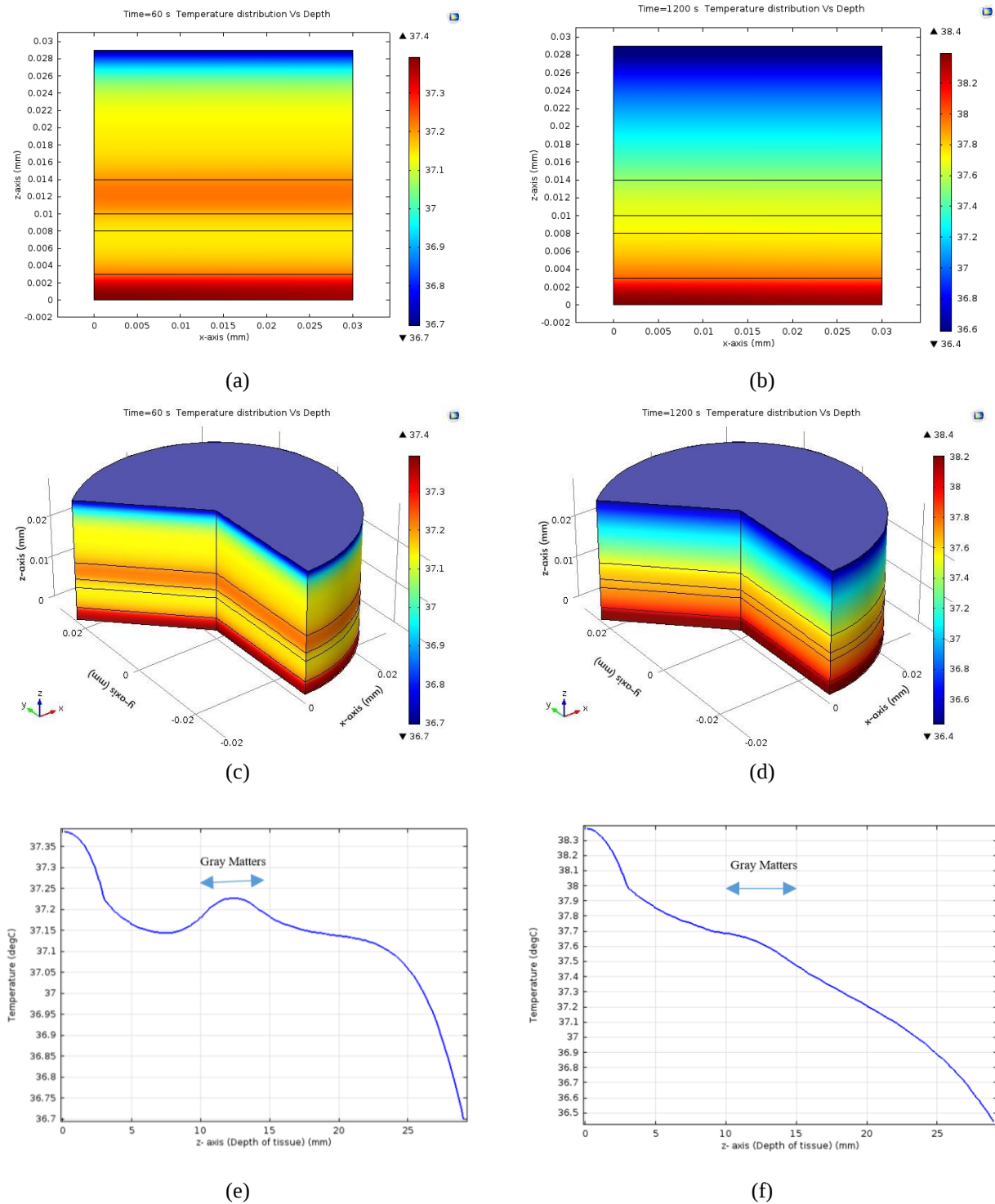


Fig. 2 2D temperature distribution for power density 166 mW/cm^2 at (a) $t = 60 \text{ s}$ and (b) 1200 s ; temperature distribution in a cylinder model at (c) 60 s and (d) 1200 s ; temperature versus depth of tissue (e) at 60 s , and (f) 1200 s .

For the rest of the layers, the heat source equations will be written in the same way, taking into account the optical parameters and thickness of each layer.

Since the heat source changes with time, it should be multiplied by a time function

$$f(t) = \exp\left(-4 \cdot \frac{(t - \tau)^2}{\tau^2}\right), \quad (5)$$

where t is the calculation time (s), and τ is the irradiation time (s).

2.3 Simulation Model

The simulation is based on 2D model mimic the human brain using FEM software COMSOL Multiphysics 5.0.

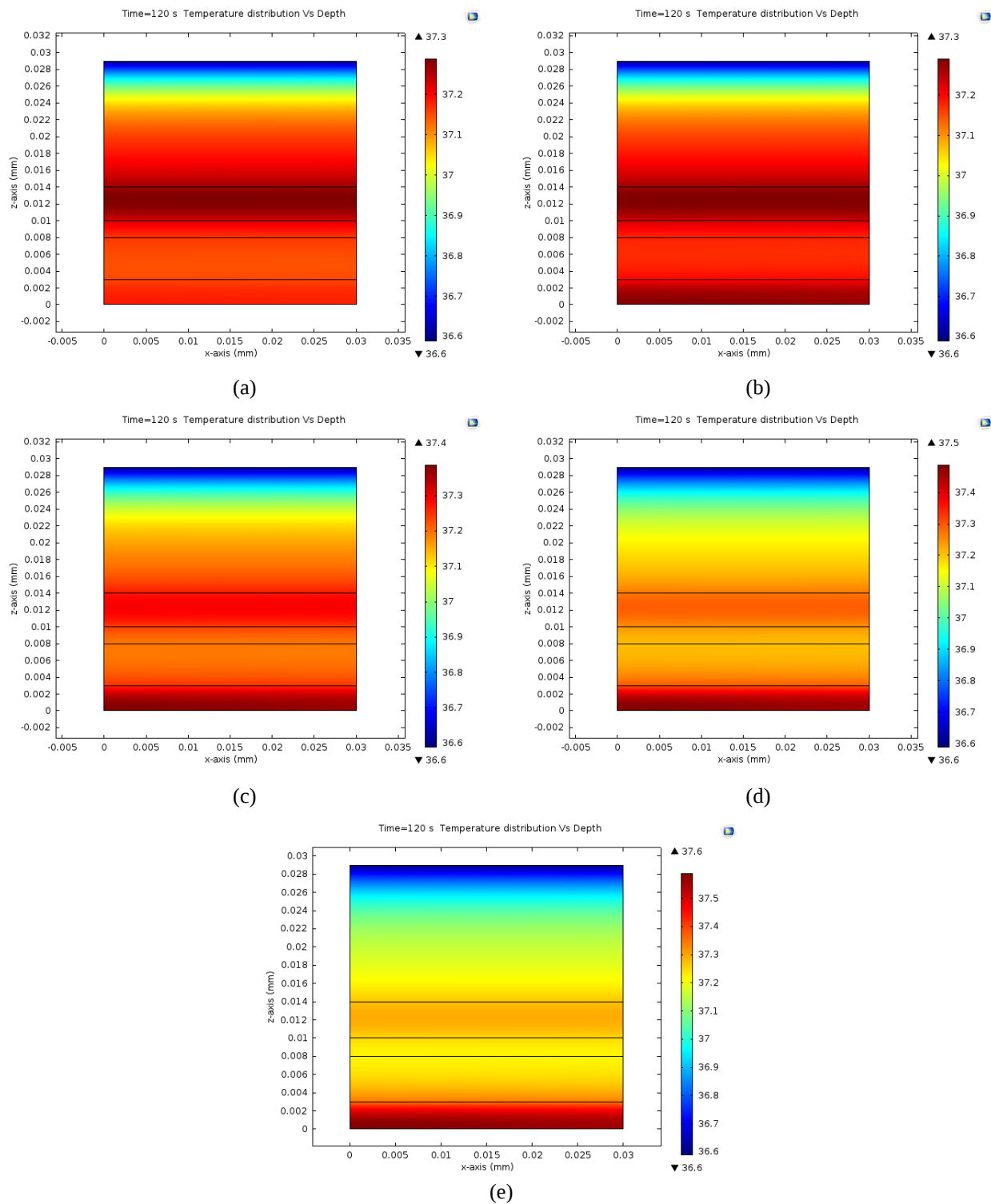


Fig. 3 2D temperature distribution at $t = 120$ s for different power density: (a) 33 mW/cm², (b) 66 mW/cm², (c) 100 mW/cm², (d) 133 mW/cm², and (e) 166 mW/cm².

To increase the computational speed process, the 2D axisymmetric coordinate model was designed, and then revolved into a cylindrical shape, where r -axis represents the radius of the cylinder and z -axis represents the depth in brain tissue inhomogeneous multilayer. Fig. 1 indicates the geometry model, which consists of five layers z_1 , z_2 , z_3 , z_4 , and z_5 are scalp, skull, CSF, gray

matter (adipose tissue), and white matter (granular tissue) respectively [25, 26]. The bioheat equation, Eq. (1) was used to calculate the heat transfer from a continuous-wave laser, Gaussian beam with a wavelength 808 nm (Konftec Laser, Klas DX, for LLLT), and optical cap that gives a laser spot size of 3 cm². The thickness of each layer and refractive index n is given in Table 1 [26, 27].

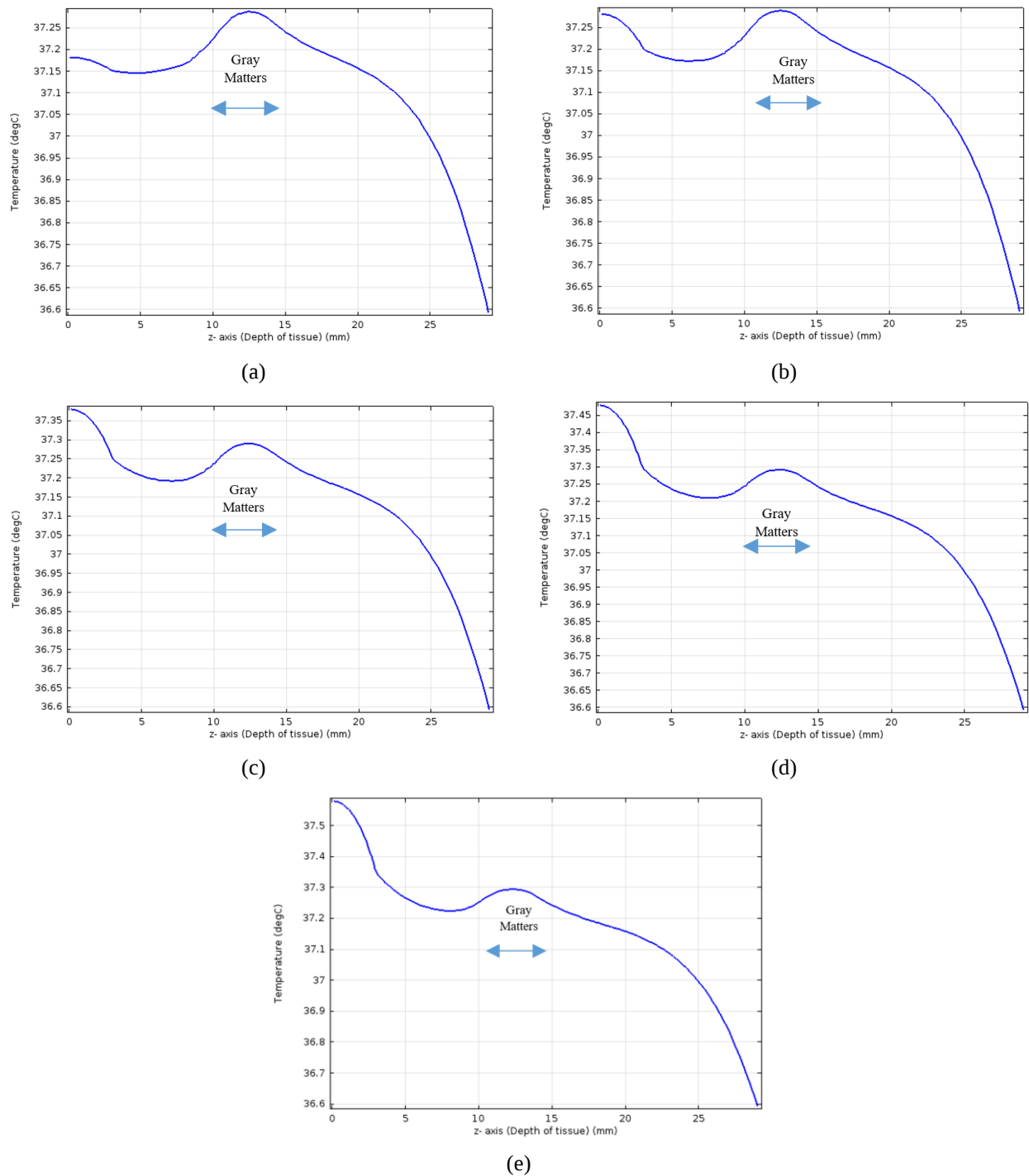


Fig. 4 Temperature versus depth of tissue (z) at $t = 120$ s for power density (a) $33 \text{ mW}/\text{cm}^2$, (b) $P = 66 \text{ mW}/\text{cm}^2$, (c) $100 \text{ mW}/\text{cm}^2$, (d) $133 \text{ mW}/\text{cm}^2$, and (e) $166 \text{ mW}/\text{cm}^2$.

The thermal properties and optical parameters which used are summarized in Table 2 [28–30] and Table 3 [31–35] respectively. The blood density is $1060 \text{ kg}/\text{m}$, the water content in blood is about 80% [31]. The blood heat capacity is $3770 \text{ J}/(\text{kg}\cdot\text{K})$ [32] and the arterial blood temperature is supposed to be 37°C .

In Eq. (2), the reflectance $R = \frac{(n-1)^2}{(n+1)^2}$, and n is the

refractive index of the tissue which are summarized in Table 1 [26, 27].

In this COMSOL model, the initial and four boundary conditions are defined as follows:

1) Line of axial symmetry is set to be thermally insulated;

Table 5 Best power density and irradiation time for treatment by low level laser therapy (LLLT).

Power (mW)	500	400	300	200	100
Laser spot size (cm ²)	3	3	3	3	3
Power density (mW/cm ²)	166	133	100	66	33
Irradiation time (min)	2	2	4	10	20
Joule density (J/cm ²)	20	16	24	40	40
Tissue Temperature (°C)	37.59	37.48	37.55	37.58	37.45

2) The scalp surface is set to be a natural convection boundary with the surrounding air $q_{conv} = h(T_{inf} - T)$ [36]. Where q_{conv} is the heat flux due to convection, and T is the surface scalp temperature, 37.1 °C; h is the heat transfer coefficient, 10 W/(m²·K) and T_{inf} is the external temperature, 25 °C;

3) Boundaries between inner layers are set to be continuity; and we supposed the initial temperature of other boundaries, 37.2 °C [36].

3 Results and Discussions

The finite element simulation results give temperature distribution of the brain tissue during stimulation process at different laser power density (energy density) and time irradiation, are displayed in Table 4, Fig. 2, Fig. 3, Fig. 4, and Fig. 5.

Table 4 shows that the higher laser power density and the longer time irradiation, the temperature of brain tissue increased, this rise could reach more than 0.5 °C for a long time, so we should be careful even when we are dealing with LLLT. The appropriate stimulation time for brain tissue should not exceed two minutes (120 s) at 166 mW/cm², 20 J/cm², but we can apply a maximum power density of 100 mW/cm², 24 J/cm² so the stimulation time can be increased to 4 min (240 s) without happening any undesired heat effect. It also appears, when laser power density is increased by keeping the irradiation time constant, the upper temperature of the brain is increasing linearly, this is consistent with Vitkaya's simulation outcome [18].

Table 5 summarizes the best power density, joule density, and irradiation time for treatment by LLLT safely.

Fig. 2, demonstrates overheating in all layers of the brain, while the red color gradations express where the most heating occurs. Fig. 2(a) represents two dimensions, and Fig. 2(b) illustrates after revolved in a cylindrical shape, the greatest rise appears when applying laser power density of 166 mW/cm² (20 J/cm²) and the stimulation time 60 and 1200 s, the temperature of the scalp, reaches 37.39 °C and 38.39 °C, respectively. Fig. 2(c) represents the changes in temperature within the tissue depth (z).

Fig. 3 shows that although the cerebrospinal fluid is located before the gray matter, the temperature of CSF is quite lower than the temperature of the gray matter, as it

is shown in the simulation how the temperature of the scalp increases during stimulation and then decreases in the area of the skull and CSF and returns to collect energy again in the gray area, a small amount of laser energy can be scattered in the white matter, and this is clearly visible when a small amount of time and power density, such as 33 and 66 mW/cm² at 60 and 120 s respectively. This happens because gray matter has a higher absorption of the 808 nm laser compared to CSF and white matter. We also note that when the intensity (power density) increases, most of the heat will accumulate in the first scalp layer, thus if we want to stimulate the inner layers, we should apply low intensity and time such as (33 and 66 mW/cm²) at (60 and 120 s).

Fig. 4 illustrates the temperature versus the irradiation time, and another peak is visibly in the gray matter, especially in 33 and 66 mW/cm² at 60 and 120 s as we mentioned that before.

4 Conclusions

Stimulation using LLLT in the field of red to near-infrared light energy has gained a great interest in recent years as a new and safety therapeutic application in neurology.

We found that the thermal effects are negligible (<0.5 °C) and below the human thermal pain threshold when we use very low power (100, 200 mW), power density (33, 66 mW/cm²), and low time (60, 120 s). Besides, low intensities tend to work better than higher intensities for the same wavelength, and it will affect the inner layers as well. However, doses delivered with an 808 nm laser (about 500 mW, Power density 166 mW/cm²) even it is rather low are able to significantly increase tissue temperature.

Therefore, there must be a mechanism to verify the correctness of the steps involved in determining the appropriate dose and time for stimulation before applying it clinically, and this is what the simulation achieves in this study.

Disclosures

The authors declare no conflict of interest.

References

1. J. T. Hopkins, T. A. McLoda, J. G. Seegmiller, and D. G. Baxter, "Low-level laser therapy facilitates superficial wound healing in humans: a triple-blind, sham-controlled study," *Journal of Athletic Training* 39(3), 223–229 (2004).
2. R. A. B. Lopes-Martins, R. Albertini, P. S. L. Martins, J. M. Bjordal, and H. C. C. F. Neto, "Spontaneous effects of low-level laser therapy (650 nm) in acute inflammatory mouse pleurisy induced by carrageenan," *Photomedicine and Laser Therapy* 23(4), 377–381 (2005).
3. R. T. Chow, G. Z. Heller, and L. Barnsley, "The effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomized, placebo-controlled study," *Pain* 124(1–2), 201–210 (2006).
4. D. Gigo-Benato, S. Geuna, A. de Castro Rodrigues, P. Tos, M. Fornaro, E. Boux, B. Battiston, and M. G. Giacobini-Robecchi, "Low power laser biostimulation enhances nerve repair after end-to-side neurorrhaphy: a double-blind randomized study in the rat median nerve model," *Lasers in Medical Science* 19, 57–65 (2004).
5. Y. Y. Huang, A. C. H. Chen, J. D. Carroll, and M. R. Hamblin, "Biphasic dose response in low level light therapy," *Dose-Response* 7(4), 358–383 (2009).
6. M. M. Christian, S. L. Firebaugh, and A. N. Smith, "COMSOL Thermal Model for a Heated Neural Micro-Probe," *Proceedings of the 2012 COMSOL Conference, Milan, Italy*, 10–12 (2012).
7. R. W. Waynant (Ed.), "Lasers in medicine," 1st ed., CRC Press, Boca Raton, USA (2011). ISBN: 9780429120541.
8. M. R. Hamblin, T. N. Demidova, "Mechanisms of low level light therapy," *Proceedings of SPIE* 6140, 614001 (2006).
9. Y. Lampl, "Laser treatment for stroke," *Expert Review of Neurotherapeutics* 7(8), 961–965 (2007).
10. Y. Lampl, J. A. Zivin, M. Fisher, R. Lew, L. Welin, B. Dahlof, P. Borenstein, B. Andersson, J. Perez, C. Caparo, S. Ilic, and U. Oron, "Infrared laser therapy for ischemic stroke: a new treatment strategy: results of the neurothera effectiveness and safety trial-1 (NEST-1)," *Stroke* 38(6), 1843–1849 (2007).
11. J. T. Hashmi, Y. Y. Huang, B. Z. Osmani, S. K. Sharma, M. A. Naeser, and M. R. Hamblin, "Role of low-level laser therapy in neurorehabilitation," *PM&R* 2(12S), S292–S305 (2010).
12. D. W. Barrett, F. Gonzalez-Lima, "Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans," *Neuroscience* 230, 13–23 (2013).
13. J. C. Rojas, A. K. Bruchey, and F. Gonzalez-Lima, "Low-level light therapy improves cortical metabolic capacity and memory retention," *Journal of Alzheimer's Disease* 32(3), 741–752 (2012).
14. J. C. Rojas, A. K. Bruchey, and F. Gonzalez-Lima, "Neurometabolic mechanisms for memory enhancement and neuroprotection of methylene blue," *Progress in Neurobiology* 96(1), 32–45 (2012).
15. J. C. Rojas, A. K. Bruchey, and F. Gonzalez-Lima, "Neurological and psychological applications of transcranial lasers and LEDs," *Biochemical Pharmacology* 86(4), 447–457 (2013).
16. H. Chung, T. Dai, S. K. Sharma, Y. Y. Huang, J. D. Carroll, and M. R. Hamblin, "The nuts and bolts of low-level laser (light) therapy," *Annals of Biomedical Engineering* 40, 516–533 (2012).
17. A. C. Thompson, S. A. Wade, W. G. Brown, and P. R. Stoddart, "Modeling of Light Absorption in Tissue during Infrared Neural Stimulation," *Journal of Biomedical Optics* 17(7), 075002 (2012).
18. A. Y. Vitkaya, S. S. Seker, "Study of Temperature Distribution in Light-Tissue Interaction Using the FEM," *Turkish Journal of Electrical Engineering and Computer Sciences* 24(3), 807–819 (2016).
19. S. Kim, S. Jeong, "Effects of temperature-dependent optical properties on the fluence rate and temperature of biological tissue during low-level laser therapy," *Lasers in Medical Science* 29, 637–644 (2014).
20. R. Ostadhosseini, S. Hoseinzadeh, "The solution of Pennes' bio-heat equation with a convection term and nonlinear specific heat capacity using Adomian decomposition," *Journal of Thermal Analysis and Calorimetry* 147(22), 12739–12747 (2022).
21. F. Fanjul-Velez, O. G. Romanov, and J. L. Arce-Diego, "Efficient 3D numerical Approach for Temperature Prediction in Laser Irradiated Biological Tissues," *Computers in Biology and Medicine* 39(9), 810–817 (2009).
22. R. Zhou, H. Chen, and Z. Mou, "FEM Model of the Temperature Distribution in the Brain during Enhanced Infrared Neural Stimulation Using Nanoparticles," *Journal of Applied Mathematics and Physics* 7(2), 381–393 (2019).
23. E. Kengne, A. Lakhssassi, R. Vaillancourt, and W. M. Liu, "Monitoring of temperature distribution in living biological tissues via blood perfusion," *The European Physical Journal Plus* 127, 89 (2012).
24. P. Hooshiar, A. Moradi, and B. Khezry, "Bioheat transfer analysis of biological tissues induced by laser irradiation," *International Journal of Thermal Sciences* 90, 214–223 (2015).
25. A. Ishimaru, "Wave propagation and scattering in random media," Academic Press (1978). ISBN: 978-0-12-374701-3.
26. M. S. Wrobel, A. P. Popov, A. V. Bykov, M. Kinnunen, M. Jedrzejewska-Szczerska, and V. V. Tuchin, "Multi-layered tissue head phantoms for noninvasive optical diag-onistics," *Journal of Innovative Optical Health Sciences* 8(3), 1541005 (2015).
27. K. Uma Maheswaria, S. Sathiyamoorthy, "Soft tissue optical property extraction for carcinoma cell detection indiffuse optical tomography system under boundary element condition," *Optik* 127(3), 1281–1290 (2016).

28. G. H. Lu, T. Mackawa, and H. Kimura, "[An Integrated Model of Thermodynamic-Hemodynamic-Pharmacokinetic System and Its Application on Decoupling Control of Intracranial Temperature and Pressure in Brain Hypothermia Treatment](#)," *Journal of Theoretical Biology* 242(1), 16–31 (2006).
29. D. A. Nelon, S. A. Nunneley, "[Brain Temperature and Limits on Transcranial Cooling in Humans Quantitative Modeling Results](#)," *European Journal of Applied Physiology and Occupational Physiology* 78, 353–359 (1998).
30. A. Datta, V. Bansal, J. Diaz, J. Patel, D. Reato, and M. Bikson, "[Gyri-precise head model of transcranial directcurrent stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad](#)," *Brain Stimulation* 2(4), 201–207 (2009).
31. F. A. Duck, "Physical Properties of Tissues: A Comprehensive Reference Book," Academic Press (1990). ISBN: 9780122228001.
32. D. A. Torvi, J. D. Dale, "[A Finite Element Model of Skin Subjected to a Flash Fire](#)," *Journal of Biomechanical Engineering* 116(3), 250–255 (1994).
33. P. Sawosz, S. Wojtkiewicz, M. Kacprzak, W. Weigl, and A. Borowska-Solonyko, "[Human skull translucency: post mortem studies](#)," *Biomedical Optics Express* 7(12), 5010–5020 (2016).
34. M. Bhattacharya, A. Dutta, "[Computational Modeling of the Photon Transport, Tissue Heating, and Cytochrome C Oxidase Absorption during Transcranial Near-Infrared Stimulation](#)," *Brain Sciences* 9(8), 179 (2019).
35. J. L. Sandell, T. C. Zhu, "[A Review of in-vivo optical properties of human tissues and its impact on PDT](#)," *Journal of Biophotonics* 4(11–12), 773–787 (2011).
36. G. H. Lu, T. Mackawa, and H. Kimura, "[An Integrated Model of Thermodynamic-Hemodynamic-Pharmacokinetic System and Its Application on Decoupling Control of Intracranial Temperature and pressure in Brain Hypothermia Treatment](#)," *Journal of Theoretical Biology* 242(1), 16–31 (2006).