Bioheat Transfer: Hyperthermia for Cancer Treatment

G. Goudarzi, H. Sadrhosseini, M. Bijarchi

Abstract**—**This numerical study focuses on using magnetic nanoparticles (MNPs) under an external magnetic field for localized heating of cancerous tissues to minimize damage to healthy tissues by simulating the thermal effects of MNPs in cancerous tissue. The numerical analysis provides detailed insights into temperature distribution and tissue damage, demonstrating the potential effectiveness of this method. In this study, a cancerous tissue thickness of 50 μm and a magnetic field frequency of 1 MHz has been used. This confirms the potential of MNPs for precise, localized hyperthermia in cancer therapy.

Keywords**—** Bioheat Transfer, Cancer Treatment, Hyperthermia, Magnetic Nanoparticles.

I. Introduction

Heat transfer occurs when two objects at different temperatures exchange energy. The human body transfers heat internally (bioheat transfer) and externally. Understanding this requires considering various factors, such as the specific body parts involved, the environment, and additional factors. The effects of temperature on biochemical processes are categorized into hyperthermia (increased temperature), hypothermia (decreased temperature), and cryobiology (subfreezing temperature), all of which can be used in medical treatments, particularly hyperthermia. Hyperthermia heats cancerous tissue using microwave probes, lasers, or magnetic fields, each with its pros and cons. The study of bioheat transfer, particularly in hyperthermia for cancer treatment, has gained significant attention for its potential to improve therapeutic outcomes.

Smith J. defines Hyperthermia as an elevated body temperature due to failed thermoregulation that occurs when the body produces or absorbs more heat than it dissipates.[1] Unlike fever, where the hypothalamus increases the body's set-point temperature to fight off infection, hyperthermia involves a rise in body temperature above the hypothalamus-controlled set point.[2] Hyperthermia can be a medical technique that uses heat to destroy or weaken a small volume of cells.**Error! Reference source not found.** Recent studies have shown that hyperthermia can also boost local and systemic immune responses.[4] As a treatment for cancer, hyperthermia involves exposing target tissues to high temperatures to either destroy the tissues directly (thermal ablation with temperatures above 47°C) or make cancer cells more susceptible to other treatment modalities (thermal sensitization in the temperature range of 41-45°C). This elevation in temperature changes vascular permeability increases blood flow and leads to tumor oxygenation.[5] Depending on the tumor type and its position, different hyperthermia techniques can be chosen, such as whole-body, interstitial (nanoparticle-based), regional, and external hyperthermia.**Error! Reference source not found.**[6] National Cancer Institute indicates that various techniques are employed to generate heat for hyperthermia treatment, including probes that use microwaves or radio waves, ultrasound, heating fluids, heated chambers or blankets, lasers, and the injection of magnetic nanoparticles under the influence of an external magnetic field. Each technique has its advantages and limitations.[7] For instance, Dario B Rodrigues, et al. used Radio Frequency (RF)/ Microwave (MW) technology is commonly used to treat cancer patients with hyperthermia, where electromagnetic energy is absorbed by tissues and converted into heat**Error! Reference source not found.**. Ultrasound provides an alternative by generating heat through mechanical friction**Error! Reference source not found.** while lasers offer precise control over heating**Error! Reference source not found.**. Magnetic nanoparticles, excited under an alternating magnetic field, can induce localized heating, making them promising for treating small or deep-seated tumors**Error! Reference source not found.**.

This research aims to provide a comprehensive understanding of the heat transfer dynamics in biological tissues subjected to hyperthermia. It evaluates the effectiveness of various hyperthermia techniques, highlighting their advantages and limitations. Specifically, it focuses on the magnetic nanoparticle method, where nanoparticles are introduced into the tumor and subjected to an alternating magnetic field to generate heat.

II. Methods of Hyperthermia in Cancer Treatment

A. Radiofrequency

RF/MW technology applicators are commonly used for hyperthermia (HT) in cancer treatment. These applicators use antennas operating in the near field zone to irradiate tissue with high-frequency electromagnetic (EM) fields. In the human body, tissues act as lossy dielectrics, poorly insulating and conducting electricity. As EM waves propagate through biological tissues, their energy is absorbed and converted into

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G. Goudarzi, H. Sadrhosseini, M. Bijarchi, Sharif University of Science and Technology, Department of Engineering and Science, Iran

heat, raising the temperature of the irradiated area. The heating mechanisms vary with the frequency of the EM wave.**Error! Reference source not found.** At RF frequencies below approximately 10 MHz, Joule heating occurs as free electrons create an electric current, converting energy into heat through resistive losses due to microscale friction. Above 10 MHz, oscillations are too rapid for charged particles to generate a current, so heating results from the kinetic energy of rotating polar molecules like water.**Error! Reference source not found.** RF/MW hyperthermia (HT) treatments are divided into local and regional HT. Local HT targets superficial and deep-seated tumors using external, intraluminal, or interstitial MW methods. Regional HT uses RF-based applicators for deep-seated pelvic or abdominal tumors. Localized heating is achieved with MW (>300 MHz), while deep regional heating uses RF (300 MHz). Common clinical HT frequencies are 70-100, 434, and 915 MHz.**Error! Reference source not found.**. Overall, RF/MW hyperthermia is effective for both superficial and deep-seated tumors, but it involves complex tissue interactions and varying heating mechanisms depending on frequency, which can limit the specificity of treatment.

B. Ultrasound

Ultrasound is one of the hyperthermia methods usually used for external hyperthermia. As a mechanical wave, ultrasound provides an alternative technology for generating heat through mechanical friction, which has the unique advantage of adequate tissue penetration at wavelengths that permit beam shaping and focusing. The penetration depth of the ultrasound can be adjusted from less than 1 cm up to about 20 cm. The disadvantages of ultrasound include high bone absorption and the inability to penetrate through tissues that contain air. Different generations of ultrasound devices exist, each with its advantages and disadvantages.**Error! Reference source not found.** In summary, ultrasound hyperthermia offers good tissue penetration and focusing capabilities, but it is limited by high bone absorption and difficulty in penetrating air-containing tissues, reducing the precision of the treatment.

C. Perfusion

Perfusion hyperthermia involves a procedure in which a warmed solution containing anticancer drugs is used to bathe or is passed through the blood vessels of the tissue or organ containing the tumor. This technique is often combined with chemotherapy to enhance the treatment's effectiveness.[16] American cancer society define another approach, known as regional perfusion or isolation perfusion, involves removing some of the patient's blood, heating it, and then returning it to the tissues or organs containing the tumor. This method allows for targeted treatment of the cancerous area while minimizing damage to surrounding healthy tissues.**Error! Reference source not found.** To conclude, perfusion hyperthermia effectively targets cancerous tissues and can be combined with chemotherapy, but it requires complex procedures involving heated solutions or blood, which can limit precision and control over the treatment.

D. Whole body hyperthermia

Whole-body hyperthermia involves placing the entire body in a heated chamber or hot water bath or wrapping it with heated blankets. The patient lies down in a hyperthermia machine – a dome-shaped bed. The head area is kept outside the chamber, protecting it from the heat, and oxygen is delivered to the patient through a nasal cannula. The machine is set to a temperature that will raise the patient's body heat to simulate a fever, usually between 102º-104º Fahrenheit.[18] In essence, whole-body hyperthermia effectively raises body heat to simulate a fever and protects the head area, but it involves the entire body being placed in a heated environment, which can lead to non-specific heating and potential side effects.

E. Lasers

Hyperthermia using lasers involves emitting high-intensity, directional, monochromatic, and coherent light. From visible to infrared light (400 to 900 nm), tissue penetrability increases with wavelength. Near-infrared lasers, with good penetrability, are used to treat deep lesions. The laser heats the tissue surface first, then spreads to surrounding areas, allowing continuous tumor heating. The temperature can be easily controlled by adjusting the laser's output power, making near-infrared lasers ideal for tumor hyperthermia due to their simplicity and low cost. With advancements in nanotechnology, lasers are now combined with nanoparticles. Nanoparticles have higher energy absorption efficiency than normal tissues, enhancing heating effectiveness.**Error! Reference source not found.** Ultimately, laser hyperthermia offers high intensity and directionality with good tissue penetrability and controllable temperature, but the initial heat is applied to the surface before spreading to surrounding tissues, which can limit the specificity and precision of the treatment.

F. Magnetic nanoparticles

Magnetic nanoparticle hyperthermia is an advanced cancer treatment method that utilizes the unique properties of magnetic nanoparticles to target and destroy cancer cells. As described in the study "Comparative Study on The Effects of Increase in Injection Sites on The Magnetic Nanoparticles Hyperthermia" by Ali Dehghan et el., this technique involves injecting magnetic nanoparticles directly into a tumor. Following the injection, an external magnetic field is applied, causing the nanoparticles to oscillate and generate heat, selectively raises the temperature of the tumor cells. The localized heating effect induced by the magnetic nanoparticles can lead to thermal ablation, where the elevated temperatures cause irreversible damage and death of the cancer cells. This method is advantageous as it minimizes damage to surrounding healthy tissue, reducing the side effects commonly associated with conventional cancer treatments such as chemotherapy and radiation therapy. The referenced study highlights that the distribution and concentration of nanoparticles within the tumor are critical factors influencing the treatment's efficacy. By

optimizing the number of injection sites, the study found that a more uniform distribution of nanoparticles could be achieved, thereby enhancing the overall effectiveness of the hyperthermia treatment. This targeted approach improves the precision of cancer therapy and offers new possibilities for treating tumors resistant to traditional treatments. The ability to control the heating process externally allows for real-time adjustments and monitoring, providing a highly adaptable and personalized treatment option.[20] Since the main purpose of this research is the application of magnetic nanoparticles, it will be discussed in detail.

III. MAGNETIC NANOPARTICLES IN HYPERTHERMIA

As previously discussed, various hyperthermia techniques exist, each with limitations that prevent mainstream use. Among these, microwave hyperthermia has been relatively successful but is limited to treating superficial tumors. However, recent advancements in nanoscience have introduced a promising new method: magnetic field hyperthermia. Nanotechnology, particularly in biomedical science, focuses on objects with at least one dimension on the nanometer scale, allowing nanoparticles (NPs) to penetrate organs, tissues, and even cells due to their small size. Additionally, their high surface-to-volume ratio makes NPs highly reactive, endowing them with unique properties compared to bulk materials. These characteristics open new possibilities for biomedical applications, including hyperthermia cancer therapy.

Magnetic Nanoparticles (MNPs), in particular, can be excited under an alternating magnetic field to generate heat, making them a focal point in hyperthermia research. It can be utilized to directly damage and eliminate cancerous cells, enhance mass transfer for drug delivery, serve as a trigger for thermosensitive drugs, or complement other treatments to improve overall outcomes. This method shows promise for treating small or deep-seated tumors.[21]

Conventional hyperthermia techniques often create a temperature gradient with a maximum at the body's surface, which rapidly decreases with distance from the external source. This results in significant energy dissipation in healthy tissues along the radiation path, leading to non-selective tissue heating and potential side effects. In contrast, MNPs focus the energy from the external source on the tumor, inducing localized thermal destruction while minimizing adverse effects on surrounding healthy tissues.[22]

The concept of using MNPs for hyperthermia dates back to 1957, when maghemite nanoparticles (γ-Fe_2O_3) were employed due to their low toxicity and known metabolic pathways.**Error! Reference source not found.** This technique is based on the observation that tumor cells can be destroyed by maintaining a temperature between 43 and 46 °C for a certain period, while healthy cells remain less affected. The heating process is facilitated by applying an alternating magnetic field of appropriate amplitude and frequency.

One major challenge in magnetic hyperthermia is reducing the quantity of MNPs required for effective treatment in living tissues. To address this, enhancing the power dissipation or heating efficiency of MNPs is crucial. Several factors influence heating efficiency, including the amplitude and frequency of the external alternating magnetic field, magnetic anisotropy, magnetization, particle-particle interactions, and the size and size distribution of the MNPs.[24]

This study focuses on magnetic field hyperthermia due to its potential for targeted tumor treatment with minimal impact on healthy tissues. To better understand and optimize this technique, a precise simulation of temperature distribution within tissues is done. This approach provides valuable insights into the thermal behavior of magnetic nanoparticles, facilitating the advancement of this promising cancer treatment method.

IV. NUMERICAL ANALYSIS OF HYPERTHERMIA

This study focuses on the numerical analysis of magnetic heat sources and their effects on prostate cancer tissue. The governing equations of continuity, momentum, concentration, energy, and Arrhenius tissue destruction are solved, considering the non-Newtonian and temperature-dependent properties of blood flow inside the cancerous capillary. The geometric model includes the capillary and surrounding cancerous tissue, simulated in three dimensions.

A. Geometry of the Problem

The geometry of the figure includes the capillary and the cancerous tissue around it and , with a magnetic field which is concentric with the tissue positioned at 10 mm from the upper wall of the capillary.Utilizing the data from Table I, the three-dimensional geometry can be illustrated as depicted in Fig. 1. It is important to note that the dimensions in this figure are not to scale. The important point to consider about magnets is that the north magnet has to be up and the south be down, so when the magnetic field is applied (from S to N), it would cause nanoparticles to move upward. (the simulation geometry is shown in Fig. 1)

TABLE I VALUES RELATED TO THE GEOMETRY OF THE PROBLEM

Parameter	value (unit)
Capillary length (L)	1 (mm)
Cancerous capillary diameter (Dc)	40 (μm)
Cancerous tissue thickness (Dt)	50 ((μm)
Magnet diameter (Dm)	4 (mm)
Magnetic field distance from upper part of tissue (h)	10 (mm)
Magnetic field frequency (f)	1 (MHz)

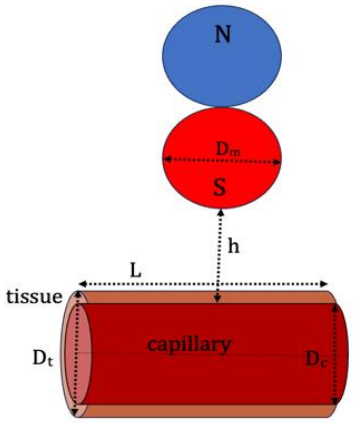

Fig. 1 Geometry of The Problem

TABLE II BLOOD PROPERTIES

Parameter	value (unit)
Zero shear rate viscosity (μ_0)	0.056 (Pa.s)
Infinite shear rate viscosity (μ_∞)	0.0034 5(Pa.s)
Relaxation time (Γ)	3.313 (s)
Power index (n)	0.3568
Density (ρ)	1056.2 (kg/m^3)

Additionally, the other material used is the prostate tissue. The properties of the prostate tissue are in Table III below:

TABLE III PROSTATE PROPERTIES

Parameter	value (unit)
Heat capacity at constant pressure (C_p)	3760 J/(kg·K)
Density (ρ)	1045 kg/m³
Thermal conductivity (k)	0.51 W/(m·K)
Frequency factor (A)	1e91 1/s
Activation energy (E_a)	5.6e5 J/mol

B. Materials of the problem

The base fluid for magnetic nanoparticles is blood, which exhibits non-Newtonian behavior in capillaries. Scientists commonly use the Cross and Carreau-Yasuda models to characterize pseudoplastic fluid behavior. Here Carreau model is used for the simulation where μ is defined as: [25]

$$\mu = \mu_\infty + (\mu_0 - \mu_\infty)[1 + (\Gamma\dot{\gamma})^2]^{\frac{n-1}{2}} \quad (1)$$

The symbols μ_0 and μ_∞represent the zero-shear rate and infinite shear rate viscosities, respectively [25]. The parameter n denotes the power law index, which characterizes the rheological behavior of the fluid. For Newtonian fluids, n=1, whereas for non-Newtonian fluids, n≠1.[26] Additionally Γ is a material time constant and γ is defined as:

$$\dot{\gamma} = \sqrt{\frac{1}{2}\Pi} \quad (2)$$

where $\dot{\gamma}$ is the shear rate, and Π is the scalar quantity defined as the trace of the squared first Rivlin-Ericksen tensor. The scalar quantity Π is given by[27]:

$$\Pi = trace(A_1^2) \quad (3)$$

The first Rivlin-Ericksen tensor A_1 is defined as:

$$A_1 = \nabla v + (\nabla v)^T \quad (4)$$

where A_1 is the first Rivlin-Ericksen tensor, ∇v is the velocity gradient tensor, and $(\nabla v)^T$ is its transpose.[28]

For the simulation, the properties of blood were used as they are mentioned in Table II and assumed it to be a non-Newtonian fluid. The Carreau model was employed to describe its rheological behavior.[25]

The simulation uses magnetic nanoparticles based on Iron (Fe) injected into the bloodstream. Typically, Alloy powder core ferrite, and 1006 (both in nano size) are used together when there are no more specific details available. This combination ensures effective magnetic properties required for the simulation.

C. Physics of the problem

1) Heat transfer in fluids

Heat transfer in fluids within this simulation is driven by magnetic nanoparticles. Without them, only bioheat transfer is considered. Their movement under an external magnetic field causes localized heating, significantly enhancing overall heat transfer. To accurately calculate it, we consider a physical model for the fluid, which in this case is blood. The properties required for this are detailed in Table IV.

TABLE IV BLOOD PROPERTIES CONSIDERED IN FLUIDS HEAT TRANSFER

Parameter	value (unit)
Reference temperature (T_R)	37 (°C) = 310.15 (K)
Velocity in x direction (V)	0.0002 (m/s)
Thermal conductivity (k)	0.51 W/(m·K)
Density (ρ)	1056.2 (kg/m³)
Heat capacity at constant pressure (c_p)	3770 J/(kg·K)
Initial temperature (T_0)	310.15 K

2) Bio heat transfer

Bioheat transfer studies heat distribution and its effects in biological tissues, crucial for applications such as hyperthermia treatment for cancer, where controlled heating is used to damage or destroy cancerous cells; thus, thermal damage was added to the equations and Arrhenius kinetics model was used.

For calculation the amount of bio heat transfers in the Table V and Table VI were considered.

TABLE V TISSUE PROPERTIES CONSIDERED IN BIOHEAT TRANSFER

Parameter	value (unit)
Thermal conductivity(k)	0.57 (W/m.K)
Density (ρ)	1045 (kg/m^3)
Heat capacity at constant pressure (c_p)	3760 (J/kg.K)
Blood perfusion rate ($\dot{Q}$)	10e-9 (1/s)
Metabolic heat source (Q_m)	31872.5 (W/m^3)
Frequency factor (A)	1.80e32 (1/s)
Activation energy (E_a)	2.36e5 (J/mol)

TABLE VI BLOOD PROPERTIES CONSIDERED IN BIOHEAT TRANSFER

Parameter	value (unit)
Thermal conductivity (k)	0.51 (W/m.K)
Density (ρ)	1056.2 (kg/m^3)
Heat capacity at constant pressure (c_p)	3770 (J/kg.K)
Blood perfusion rate ($\dot{Q}$)	10e-9 (1/s)
Metabolic heat source (Q_m)	31872.5 (W/m^3)
Frequency factor (A)	1.80e32 (1/s)
Activation energy (E_a)	2.36e5 (J/mol)

Arrhenius kinetics model is used to calculate damage done to tissue by a thermal source [29]:

$$\alpha(t) = \alpha_0 + \int_0^t (1-\alpha)^n A e^{\frac{-\Delta E}{RT}} dt \qquad (5)$$

where ΔE is he activation energy, R is the gas constant and T is the temperature. α_0 as the initial degree of injury. And α is the amount of tissue damage.

3) Magnetic field with no current

Two magnets (north and south) are added as a magnetic field with no current, and for their remanent flux direction, south is considered -1 in *y*-direction and north as +1 in *y*-direction. To investigate the effect of magnetic field on nanoparticles and their effect on blood flow Eq. (6) is used :

$$H = \left(\frac{B}{\mu_0}\right)\left(\frac{D_m}{2}\right)^2 \frac{1}{(x-x_{MAG})^2+(z-z_{MAG})^2} \qquad (6)$$

This equation describes a magnetic field H in terms of various parameters, including the magnetic flux density B, the permeability of free space μ_0 a distance parameter D_m and spatial coordinates (x,z) relative to the position of a magnetic source (x_{MAG}, z_{MAG}).

V. RESULT AND DISCUSSION

Simulations indicate a uniform temperature of 37°C across the surface. The visualization includes contour lines that represent the magnetic potential distribution. Seven representative points were selected for the calculations to ensure comprehensive analysis. Using the primary simulation data, following diagrams are generated: Fig. 2 illustrates the blood capillary temperature which increases logarithmically to around 52°C before stabilizing. Fig. 3 shows the tissue temperature starting from approximately 49°C and rising to its maximum at the part closes to the center of the vein. Fig. 4 depicts the thermal damage to the blood vessel, increasing over time and ranging between 0 and 1, calculated using Equation 5. Lastly, Fig. 5 presents the thermal damage to the prostate tissue, also ranging between 0 and 1 and increasing with time and temperature, reaching a maximum value of 1.

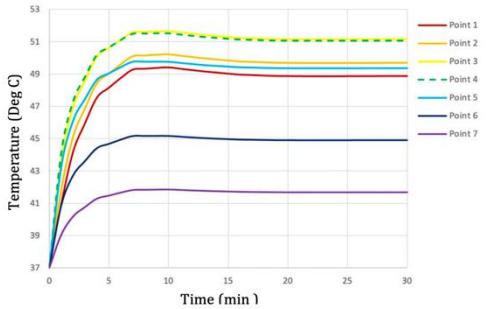

Fig. 2 Capillary temperature Vs time at various points

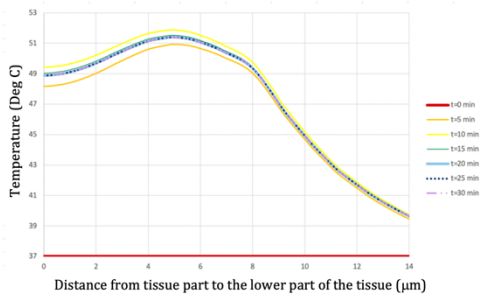

Fig. 3 Tissue temperature versus distance from the lower part of the tissue at various times.

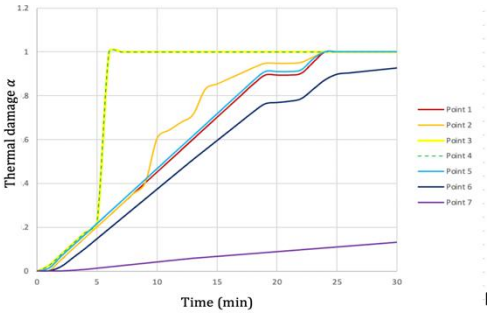

Fig. 4 Thermal damage to the capillary versus time studied in different parts

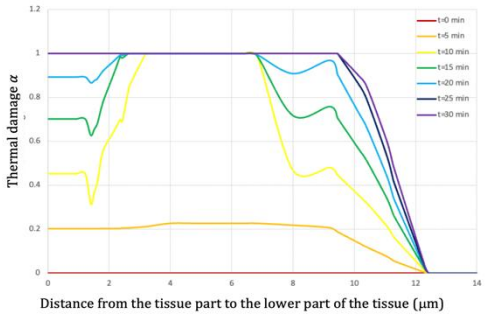

Fig. 5 Thermal damage to the tissue versus the distance in different parts of the tissue at various times

VI. VALIDATION

To validate the simulation, is compared with the reference paper.**Error! Reference source not found.** As can be seen in Fig. 6, the temperature of the tissue reaches approximately 325 Kelvin. Based on the simulation, the temperature of the center of the tissue reaches 52°C, which is 325.15 K in Kelvin. The error is approximately 1.14%, indicating that this is validated work.

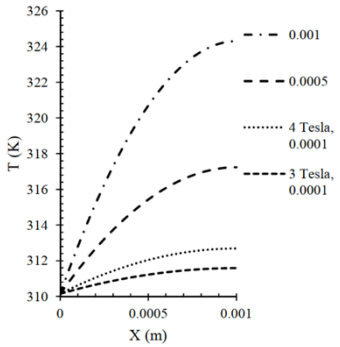

Fig. 6 Temperature of the center of tissue along the x-axis

VII. CONCLUSION

In this study, a simulation of cancerous prostate tissue and its vein under a thermal heat source was conducted. The heat source, a magnetic field positioned 10 mm from the tissue, induced the movement of injected magnetic nanoparticles within the vein, generating heat and facilitating hyperthermia treatment. Key findings include both vein and tissue temperatures increased to nearly 52°C, the required heat for hyperthermia, and then stabilized which can be seen in Fig. 2 and Fig. 3 .The tissue temperature is highest near the vein's center and decreases with distance from both the vein and the magnetic field. Thermal damage ranged from 0 to 1, starting at zero, peaking to one, and then slightly decreasing before stabilizing that is indicated in Fig. 4 and Fig. 5. The capillary temperature also increased logarithmically to about 52°C before stabilizing, indicating that beyond this threshold, additional heating does not cause further damage. These findings are crucial for optimizing therapeutic heating applications, ensuring effective treatment while minimizing damage.

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Gita Goudarzi was born in Tehran, Iran, on January 16, 2000. She received a Bachelor of Science degree in mechanical engineering from Sharif University of Technology, Tehran, Iran, in 2023. Her major field of study was bio heat transfer, and her BSc reserach Project focused on heat transfer in the human body under supervision of Dr. Bijarchi and Dr. Sadrhosseini.

She has gained valuable work experience as a member of Iran's National Elites Foundation at Iran University of Science and Technology, where she was involved in designing and building pressure sensors. She also interned as a Mechanical Engineer at Ahansan Company, contributing to the design and construction of pressure tanks and their equipment. Gita has served as a Heat Transfer Teaching Assistant at Sharif University of Technology. Her current research interests include bio heat transfer and thermal systems.

She won first place in student projects at the TEBIYAN ceremony at Shahid Beheshti University in 2015. She has demonstrated excellent teamwork and leadership abilities throughout her career.

Hani Sadrhosseini (Member, IAE) was born in Tehran, Iran, on December 10, 1977. She received the Ph.D. degree in mechanical engineering from Eastern Mediterranean University, Famagusta, Turkey, in 2010. Her Ph.D. dissertation was titled "Use of Magnetic Fields in Damping Convection and Controlling Dopant Segregation in Semiconductor Melts." She also received the M.Sc. degree in mechanical engineering from Eastern Mediterranean University, Famagusta, Turkey, in 2005, with a Master thesis titled "Experimental Study of Fluid Flow in a Duct Filled with Porous Media." She earned her B.Sc. degree in physics from the Faculty of Science, Department of Physics, Shahid Beheshti University, Tehran, Iran, in 2000. Her major field of study was thermodynamics and heat transfer.
She currently works at Sharif University of Technology - International Campus. She has authored/co-authored several publications, including "Examination of a novel solar still equipped with evacuated tube collectors and thermoelectric modules" (Desalination, 2016), "Multi-objective optimization of regenerative ORC system integrated with thermoelectric generators for low-temperature waste heat recovery" (Energy Reports, 2021), and "Filtration of aerosol particles by cylindrical fibers within a parallel and staggered array" (Microsystem Technologies, 2016). Her current and previous research interests include thermodynamics, heat transfer, and the study of fluid dynamics in porous media.
Dr. Sadrhosseini has received several awards and has worked for various committees and publications**.**

Mohammad Ali Bijarchi received his Ph.D. degree and completed his postdoctoral program in mechanical engineering from Sharif University of Technology, Tehran, Iran, in 2020 and 2021. He is currently an assistant professor in the Department of Mechanical Engineering at Sharif University of Technology.

He has also worked as a visiting scholar at Harvard University, Cambridge, MA, USA, from 2017 to 2018 with Dr. Hadi Shafiee and Dr. David Weitz. His educational background includes a BSc and MSc in Mechanical Engineering from the University of Tehran, Iran, completed in 2012 and 2014, respectively.
He is currently an Assistant Professor at Sharif University of Technology, Tehran, Iran. His research interests include AI in fluid mechanics and heat transfer, specifically physics-informed neural networks (PINNs), renewable energies such as energy harvesting and solar desalination, heat transfer including battery thermal management, heat transfer enhancement, and inverse heat transfer, and ferrohydrodynamics focusing on the dynamics of ferrofluid droplets and microfluidics. Among his notable publications are "Experimental investigation of the thermal management of flat-plate closed-loop pulsating heat pipes with interconnecting channels" (Applied Thermal Engineering, 2015), "Ferrofluid droplet manipulation using an adjustable alternating magnetic field" (Sensors and Actuators A: Physical, 2020), and "Hybrid paper–plastic microchip for flexible and high-performance point-of-care diagnostics" (Advanced Functional Materials, 2018).
Dr. Bijarchi has been recognized for his contributions to the field with several awards and honors. He has also served on various committees and editorial boards, contributing to the advancement of knowledge and research in his areas of expertise.