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## **ANALYSIS OF THERMOTHERAPY WITH MAGNETIC Fe<sub>3</sub>O<sub>4</sub> NANOPARTICLES IN CANCER TISSUES AND COMPARISON WITH NiFe<sub>2</sub>O<sub>4</sub> AND CoFe<sub>2</sub>O<sub>4</sub>**

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### **Abstract**

Treatment of cancer, the most common and deadly disease worldwide, requires more targeted and effective methods due to the fact that conventional methods such as chemotherapy and radiotherapy also damage healthy tissues. Magnetic nanoparticles (MNPs) offer a promising approach for selective heating and destruction of tumor cells, especially in magnetic hyperthermia (thermotherapy) applications. In this study, researchers numerically investigated the thermo-therapy effects of magnetic iron hydroxide (Fe<sub>3</sub>O<sub>4</sub>) nanoparticles (NPs) on cancer tissues, comparing them with NiFe<sub>2</sub>O<sub>4</sub> and CoFe<sub>2</sub>O<sub>4</sub> NPs. The thermal behaviors, magnetic field parameters, and treatment efficacy of MNPs were evaluated. In the simulations, the time- and space-dependent temperature distributions of the NPs in the injection site were evaluated; temperature changes were recorded for a period of 70 seconds and for various radial distances and angular positions. In addition, the NP density formed 18 hours after injection was analyzed, and the capacity of the particles to spread in the tissue was observed. According to the findings, NiFe<sub>2</sub>O<sub>4</sub> provided the highest temperature increase (~39–40°C) and the most homogeneous thermal distribution, while CoFe<sub>2</sub>O<sub>4</sub> showed the medium level (~37–38°C) and Fe<sub>3</sub>O<sub>4</sub> the lowest (~34–35°C) thermal efficiency. Diffusion analyses revealed that NiFe<sub>2</sub>O<sub>4</sub> spread over a wider area in the tissue, whereas Fe<sub>3</sub>O<sub>4</sub> remained more localized. These results show that NiFe<sub>2</sub>O<sub>4</sub> is the most suitable candidate for thermo-therapy in terms of both its thermal efficiency and diffusion potential.

**Keywords:** Magnetic nanoparticles, iron hydroxide, thermo-therapy, cancer treatment, magnetic field

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## **1. Introduction**

Cancer remains one of the most common and deadly diseases worldwide. Traditionally, cancer treatment involves targeting tumor cells through chemotherapy and radiotherapy, which also damage healthy tissues and cause serious side effects. Therefore, the development of more effective and targeted treatment methods is of extreme importance. The revolutionary innovations from recent developments in nanotechnology have also been applied in cancer treatment. Thermotherapy, through magnetic hyperthermia in particular, has emerged as a promising modality for cancer treatment by taking advantage of the multifunctional capabilities of iron oxide nanoparticles (IONPs), notably Fe<sub>3</sub>O<sub>4</sub>. Magnetic nanoparticles (MNPs) stand out as a promising approach for selectively heating and destroying tumor cells, especially in magnetic hyperthermia (thermotherapy) applications [1].

While thermotherapy is an effective method for treating many types of tumors, it is severely hampered by the damage it causes [2, 3, 4]. For improving the effectiveness of this technique, several approaches were proposed. In recent studies, researchers have investigated various aspects of magnetic Fe<sub>3</sub>O<sub>4</sub> NPs, including their synthesis, biocompatibility, targeted delivery capabilities, and their enhanced thermal effects under alternating magnetic fields (AMF). One new method for using magnetic nanoparticles, like Fe<sub>3</sub>O<sub>4</sub>, NiFe<sub>2</sub>O<sub>4</sub>, and CoFe<sub>2</sub>O<sub>4</sub>, in cancer treatment called magnetic hyperthermia (MHT) involves putting these nanoparticles into tumors so they can heat up the surrounding tissue when exposed to alternating magnetic fields (AMF) [5, 6, 7].

MHT is defined as the localized application of heat to cancerous tissues via the excitation of MNPs under an AMF. MHT operates by generating thermal energy through the excitation of MNPs, which produce heat via relaxation mechanisms like Néel and Brownian relaxation when exposed to an AMF. This process effectively elevates the temperature of targeted tumors to cytotoxic and therapeutic levels, typically between 42°C and 46°C [8, 9], which leads to the death of cancer cells or sensitization to chemotherapy and radiotherapy. It is of prominent importance not to damage the surrounding healthy tissue; therefore, the need for “smart” NPs is also paramount. The localized hyperthermia induced by the use of such smart NPs selectively targets tumor cells while largely sparing healthy tissues by making use of the inherent thermal sensitivity of cancer cells to elevated temperatures. IONPs, especially those synthesized as superparamagnetic Fe<sub>3</sub>O<sub>4</sub>, represent a viable solution due to their favorable physical and chemical properties, including small size, high biocompatibility, and ease of functionalization for targeted therapies [10, 11].

Different properties and performance outcomes result from the methods used to synthesize IONPs. Coprecipitation method can yield NPs with effective heating capabilities crucial for hyperthermia applications [11], whereas green synthesis methods that utilize plant extracts enhance biocompatibility and reduce toxicity [12]. When characterized appropriately, synthesized NPs exhibit desirable properties for effective magnetothermal effects that can be further modulated by surface modifications such as surface coatings to improve hyperthermic properties [10].

MHT can also be coupled with other therapeutic modalities, such as chemotherapy and radiotherapy, to potentially incorporate drug delivery constructs with Fe<sub>3</sub>O<sub>4</sub> NPs, which can serve not only as heating agents but also as carriers for anticancer drugs [13]. This dual function integrates hyperthermia with traditional chemotherapy, aiding in targeting and eliminating

tumor cells, minimizing systemic toxicity, and enhancing chemotherapy efficacy through controlled heating [14, 15].

The efficacy of MHT can be significantly influenced by the cancer cells' endocytosis of NPs. Electrical stimulation can facilitate precise regulation of endocytosis to enhance the uptake of IONPs by cancer cells, thereby increasing their therapeutic effects [16]. Enhanced cellular internalization leads to higher local concentrations of these NPs within tumor sites, which consequently improves the heating efficiency of the localized therapy. Also affirmed by El-Kholany and Gebreel [17], MNPs can be systematically administered to enhance targeted delivery and localized heating.

The rise in temperature of cancer cells not only recruits cell apoptosis via heat shock proteins but also may initiate a range of cellular signaling pathways that can affect tumor aggressiveness and treatment response [18]. Investigation of differential thermal responses of various cancer cell lines to hyperthermia using Fe<sub>3</sub>O<sub>4</sub> NPs revealed dual photothermal applications in complex NP systems [19]. Furthermore, the degradation of cancerous tissues post-hyperthermic treatment has prompted investigations into NP biocompatibility and clearance from the body [20, 21, 22]. Elucidating the degradability and biosafety of synthesized Fe<sub>3</sub>O<sub>4</sub> NPs is crucial, which indicates how iron oxide's interactions could modulate responses and enhance anticancer strategies [23]. The biocompatibility of these NPs is paramount, especially when used in conjunction with other therapeutic agents. The ideal size ranges and other properties of IONPs, such as morphology and surface charge, which maximize heat generation, are among the important parameters affected by the synthesis routes [24, 11].

As the quick literature survey reveals, the exploration of Fe<sub>3</sub>O<sub>4</sub> NPs in thermotherapy offers several research areas ranging from synthesis and characterization to applications in targeted therapies. In this regard, the integration of MNPs in hyperthermia represents a promising field of study in cancer treatment. However, the versatility of MNPs extends beyond iron oxides. NiFe<sub>2</sub>O<sub>4</sub> and CoFe<sub>2</sub>O<sub>4</sub> nanoparticles possess favorable magnetic properties, with research indicating distinct saturation magnetization values and coercive forces that may influence their efficacy in hyperthermia applications [25]. For instance, studies show that CoFe<sub>2</sub>O<sub>4</sub> nanoparticles exhibit advantageous magnetic behaviors that can enhance their heating capabilities in therapeutic applications [25]. Moreover, these nanoparticles have exhibited compatibility in combinatory treatments aimed at overcoming the limitations presented by standalone therapeutic modalities, such as chemotherapy and radiotherapy [26, 22].

Recently, the potential of magnetic nanoparticles (MNPs), especially IONPs, for biomedical applications has increased significantly. Liu et al. [27] presented a comprehensive study that thoroughly explored the synthesis, surface functionalization, and application areas of Fe<sub>3</sub>O<sub>4</sub> MNPs. While emphasizing the role of surface modifications on biocompatibility and stability, it was shown that these particles can be used in many areas, such as magnetic separation, drug delivery, biosensors, and environmental purification. The local heat production of IONPs by directly targeting tumor cells has increased the effectiveness of thermotherapy methods. Tay et al. [28] argued that magnetic particle imaging (MPI)-guided MHT could increase its efficacy and reduce damage to healthy tissues; supporting this method with *in vivo* experiments, it has shown strong potential for clinical applications. This approach is furthered by the studies proposed by Espinosa et al. [29], based on the combination of MHT and photothermal therapy. Studies with IONPs, whose physicochemical properties have been carefully characterized, have shown that these two therapeutic methods provide a more

homogeneous and localized thermal effect when used together. The results obtained both in vitro and in vivo clearly demonstrate the synergistic effect of these two methods.

Mustafa et al. [30] studied the effects of MNP-based radiofrequency thermotherapy on human breast adenocarcinoma cells and showed that this method effectively triggered cell death. The study provides important data for optimizing treatment parameters, thus providing a bridge to clinical applications. Similarly, Jordan et al. [31] evaluated the efficacy of hyperthermia with MNPs in the treatment of malignant glioma in rats. The study shows that MHT suppresses tumor growth by providing selective and controlled heat increase in tumor cells, thus increasing treatment efficacy. These findings provide important contributions to innovative treatment strategies integrating nanotechnology into oncology. Similar successes have been observed in clinical studies on human subjects. Maier-Hauff et al. [32] evaluated the safety and efficacy of radiotherapy combined with magnetic IONPs injected directly into the tumor in patients with recurrent glioblastoma multiforme. The data obtained showed that hyperthermia can increase the efficacy of radiotherapy and demonstrated the potential of NP-based therapies in personalized medicine.

The study by Johannsen et al. [3], which was conducted specifically for prostate cancer, comprehensively examined the feasibility, imaging possibilities, and three-dimensional temperature distribution of MNP-assisted hyperthermia. This approach, which provides controlled and homogeneous heat distribution increases treatment efficacy and offers significant advantages in terms of safety. Soetaert et al. [33] addressed the potential of IONPs not only in heat therapy but also in immunotherapy. In this respect, the study constitutes a valuable resource for the development of versatile and more effective cancer treatment approaches. Espinosa et al. [34] comparatively evaluated the thermal effects in his study, in which the effectiveness of MHT and photothermal therapies was analyzed by comparing the heating behaviors of iron oxide and gold nanoparticles in water, cells, and living organisms. The findings contribute to a better understanding of the therapeutic activities and heating mechanisms of these nanomaterials. Finally, Purushotham et al. [35] discussed the potential of thermosensitive core-shell MNPs for combined therapy by combining drug delivery and magnetic heating properties. This innovative approach highlights the importance of multidisciplinary strategies in cancer treatment and sheds light on future clinical applications.

Some of the most recent studies that address and evaluate the potential of Fe<sub>3</sub>O<sub>4</sub>, NiFe<sub>2</sub>O<sub>4</sub>, and CoFe<sub>2</sub>O<sub>4</sub> IONPs in biomedical applications in various fields such as diagnosis, targeted drug delivery, imaging, and thermal therapy in detail by experimental and computational methods are summarized in Table 1 to provide a concise but comprehensive context to evaluate the original contribution of the present work.

**Table 1.** Recent studies on the use of IONPs in cancer treatment

Study	Material	Method	Aim
Jiang et al. [36]	Gold Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Experimental (in-vitro)	Tumor diagnosis by ultra-sensitive biomarker detection. Treatment of cancer using innovative nanodrugs and targeted drug delivery systems. Early warning and monitoring of tumor progression.
Shekhar et al. [37]	Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Experimental and Numerical	Enhance sensitivity and selectivity in cancer detection. Improve the therapeutic efficiency of anticancer

			agents. Improve stability, solubility, half-life, and tumor aggregation of drugs.
Zulfiqar et al. [38]	Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Experimental (in-vitro)	Treatment efficacy through precise localization of magnetic properties. Minimally invasive therapeutic applications.
Sharma et al. [39]	Fe <sub>2</sub> O <sub>3</sub>	Experimental (in-vitro)	Targeted drug delivery for antibacterial treatment. Enhanced therapeutic efficacy of antibiotics through encapsulation. Overcoming limitations of traditional drugs. Efficient drug binding and loading.
Chatterjee and Dhibar [40]	Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Experimental (in-vitro)	Targeted cancer treatment using nanomaterial-based drug delivery systems to enhance drug efficacy and minimize side effects in cancer treatment.
Liu et al. [41]	Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Experimental (noninvasive imaging techniques).	Differentiation between cancerous and normal tissue. Noninvasive monitoring of tumor growth. Identification of changes in tumor and microenvironment in response to treatment.
Subtawewasin and Pijitrojana [42]	Fe <sub>3</sub> O <sub>4</sub>	Experimental (in-vitro)	Use of MNPs in cancer treatment Enhancing therapeutic efficacy and enabling targeted therapies.
This study	Fe <sub>3</sub> O <sub>4</sub> NiFe <sub>2</sub> O <sub>4</sub> CoFe <sub>2</sub> O <sub>4</sub>	Numerical	Evaluate and compare the thermal behavior and diffusion characteristics of Fe <sub>3</sub> O <sub>4</sub> , NiFe <sub>2</sub> O <sub>4</sub> , and CoFe <sub>2</sub> O <sub>4</sub> MNPs Determine their suitability for achieving therapeutic temperature ranges, assess spatial heat distribution, and examine long-term nanoparticle dispersion patterns for optimized, localized cancer treatment applications.

Magnetic iron hydroxide (Fe<sub>3</sub>O<sub>4</sub>) NPs have significant potential in cancer treatment due to their biocompatibility, magnetic properties, and controlled release capabilities. When an external magnetic field is applied, these NPs can trigger apoptotic processes in cancer cells by generating localized heat at the tumor site and increase treatment efficacy without damaging healthy tissues. This study aims to analyze the thermotherapy effects of magnetic iron hydroxide NPs on cancer tissues. This analysis includes modeling of the thermal behavior of NPs, optimization of magnetic field parameters, and experimental evaluation of treatment efficacy. This introduction emphasizes the importance of MNP-based thermotherapy in cancer treatment and clearly outlines the purpose and scope of the study. The use of magnetic iron hydroxide NPs can contribute to the development of a less invasive and more effective treatment method by providing a new perspective in cancer treatment. This study is considered an important step in the intersection of nanotechnology and medical sciences.

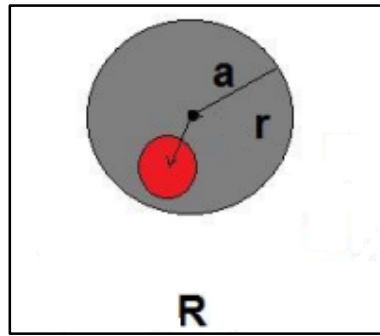
## 2. Materials and methods

The origin of the biothermal heat transfer equation dates back 60 years, when it was first proposed by Pennes [43], who modeled the heat transfer in a stationary human forearm and concluded that heat is generated by metabolism in the tissue and that heat is also transferred between the blood and adjacent tissues. Among the main limitations of laboratory models is the absence of physiological states of tumors and the body. Several electro-physical properties of biological mediators, such as thermal and electrical conductivity, specific heat, bulk density, and dielectric constant, should be included in the models. Furthermore, as blood perfusion is

largely influential on heat transfer and it acts differently in tumor or normal tissue, and as the spaces in the vessels affect the cooling of the blood, vascularization should always be considered. Finally, heat sources, namely MNPs, should be included in thermotherapy to complete the original tumor model. Body tissue consists of many cells. Therefore, the intercellular space has to be considered in cancer tissue modeling. The general form of the Pennes equation is as follows:

$$\rho c \frac{\partial T}{\partial t} + \nabla \cdot (k \nabla T) = \rho_b C_b \omega_b (T_b - T) + Q_{met} + Q_{ext} \quad (1)$$

where  $\omega_b$  is the intravenous injection rate,  $T_b$  is the arterial temperature,  $Q_{met}$  and  $Q_{ext}$  denote the metabolic and external heat sources. Tumors are usually defined by a geometric shape. These geometries are usually spherical or cylindrical. Thus, they are surrounded by a region of measurement  $R$  or a layer of healthy tissue of radius ( $\infty$ ) (Figure 1).



**Figure 1.** Coordinate modeling of healthy tissue and cancerous tissue. The white area shows healthy tissue, the gray area shows cancerous tissue, and the red area shows NP distribution.

Here we will examine the equations used to study heat transfer within the tissue. Generally, we base the introduced equations on observations from experiments where temperature sensors measure the temperature according to the heat source. The same temperature source is then included in the heat transfer equation. Today, they have become research tools for heat transfer applications in living tissues. In the thermotherapy process, the aim is to destroy cancer cells by increasing the temperature of biological tissues using heat sources such as electromagnetic waves, ultrasound, and radio waves. Therefore, modeling the heat transfer process is of great importance to correctly evaluate the heat and temperature distribution during treatment and to examine the extent of damage to tumors and healthy tissues. Heat exchange in biological tissues is a function of many parameters, such as heat transfer coefficients in tissue and blood, blood flow rate, and heat rate produced by body metabolism. This complex process includes conduction, convection, and radiation; metabolic heat; and evaporation (phase change) mechanisms. It is worth noting that the effect of blood flow on all these heat transfer modes is undeniable. The rate of blood penetration into the body tissue can fluctuate over a wide range depending on various physiological, physical, environmental, pharmaceutical, and chemical conditions. The numerical solution of the Pennes equation in the cylindrical coordinate system is obtained as follows:

$$\rho_t c_t \frac{\partial T_t}{\partial t} = \nabla (k \nabla T_t) + W_b \rho_b C_b (T_a - T_t) + q_m \quad (2)$$

In this relationship, the b index represents the blood, and the t index represents the tissue.  $Q_m$  is the amount of heat produced by the body's metabolism (in  $[W/m^3]$ ).  $T_a$  is blood temperature in the arteries, and  $W_b [m^3/s]$  is the blood penetration rate into the tissue. It is worth noting that studies on patients have shown that every 0.5 degrees Celsius of fever increases the body's metabolic heat by approximately 0.7%. The Pennes heat transfer equation is based on the thermal equilibrium of blood and tissue; accordingly, blood enters the tissue with  $T_a$  at arterial temperature according to the blood diffusion rate coefficient and exits through the veins after reaching thermal equilibrium with the tissue. Therefore, in this model, the blood penetration rate into the tissue is homogeneous and isotropic. In addition, there is a thermal equilibrium between blood and tissue in the capillary structure of biological tissues. This coefficient is shown in the table below for various biological tissues. As can be seen, these values vary significantly depending on different physiological and pharmacological conditions. Our primary objective in this study is to treat cancerous tissue with heat therapy as a last resort. To do this, the temperature of the target tissue should be increased to  $48^\circ\text{C}$  without causing significant damage to the tissue surrounding the tumor. The volume fraction of the nanofluid is obtained using the following equation 2:

$$\Phi = \frac{\left(\frac{m_p}{\rho_p}\right)}{\left(\frac{m_p}{\rho_p} + \frac{m_{bf}}{\rho_{bf}}\right)} \times 100 \quad (3)$$

In the above formula, the molar mass of the NP and the base liquid are  $m_p = 231.54$  (gr/mol) and  $m_{bf} = 114.23$  (gr/mol), respectively. By substituting all the values, the volume fraction value ( $\Phi$ ) is obtained as 0.2127. The density also affects the heat transfer performance; as the NP concentration increases, the density also increases.  $m_{nf} = 345.77$  (gr/mol) The molar mass and effective density of the nanofluid are obtained as follows:

$$\rho_{nf} = \Phi \rho_{nP} + \rho_{bf}(1 - \Phi) \quad (4)$$

The effective heat capacity, then, is obtained by

$$c_{nf} = \frac{\Phi \rho_{nP} C_p + (1 - \Phi) \rho_{bf} c_{bf}}{\rho_{nf}} \quad (5)$$

We obtain the thermal conductivity using the following equation:

$$k_{nf} = k_{bf} \left[ \frac{k_{nP} + (n - 1)k_{bf} - (n - 1)\Phi(k_{bf} - k_{nP})}{k_{nP} + (n - 1)k_{bf} + \Phi(k_{bf} - k_{nP})} \right] \quad (6)$$

Since magnetic iron oxide NPs are 3-dimensional,  $n = 3$ .

Viscosity of nanofluid is obtained from the following equation:

$$\mu_{nf} = \frac{\mu_{bf}}{(1 - \Phi)^{2.5}} \quad (7)$$

**Table 2.** Blood penetration rate coefficient in different tissues of the human body [17]

Tissue	Typical penetration coefficient	Maximum penetration coefficient
Bone	2.5	60
Liver	29	176
Heart	70	400
Kidney	400	466
Protein	8	30
Skin	200	479

The Pennes model is the first bioheat study to define the blood penetration parameter into biological tissue, and it's easy to use. In this model, it is assumed that the blood reaches all points of the tissue at arterial temperature  $T_a$ , and the temperature effects caused by large blood vessels are ignored.

### 3. Results and discussions

The MNPs, such as  $Fe_3O_4$ ,  $NiFe_2O_4$ , and  $CoFe_2O_4$  in thermotherapy each exhibit distinct physicochemical properties that determine their performance, therapeutic efficacy, and safety profile in cancer treatment.

The superparamagnetic properties and biocompatibility of  $Fe_3O_4$  make it suitable for MH, and it has been widely studied [11]. Further, it is synthesized into nanoparticles typically ranging from 10 to 100 nm, which falls in the optimal size range for therapeutic applications [44, 11]. Conversely,  $CoFe_2O_4$  nanoparticles demonstrate even higher magnetic saturation levels and exhibit robust hysteresis properties, which are critical for effective heating under an AMF [45].  $NiFe_2O_4$  is characterized by a combination of advantageous magnetic properties and lower toxicity, but its heating efficiency under AMF has been reported to be somewhat inferior compared to  $Fe_3O_4$  and  $CoFe_2O_4$  [45].

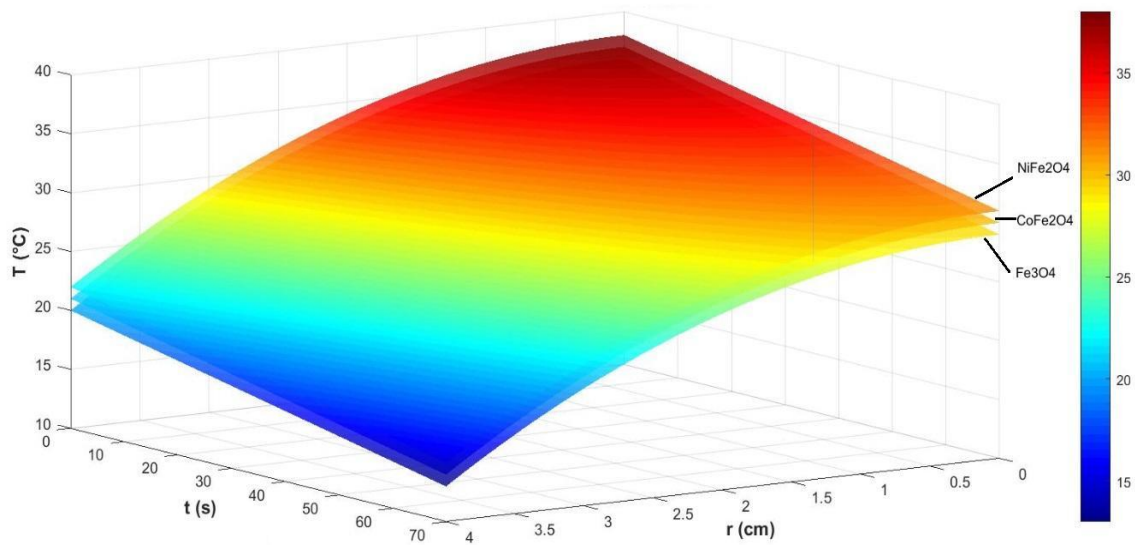
Research by Alkhayal et al. [46] found that  $Fe_3O_4$  NPs could be useful for targeting tumors with heat treatment and highlighted the need to improve MNP features, like size and coating, to ensure they absorb heat effectively for successful hyperthermic treatment. Their study showed that doses of  $Fe_3O_4$  NPs could significantly reduce tumor viability in vivo without adversely affecting surrounding healthy tissues.

$CoFe_2O_4$  nanoparticles are effective at generating heat owing to the fact that they exhibit superior specific loss power (SLP) when subjected to AMF. Optimal heating occurs at smaller particle diameters, typically around 5-7 nm, which supports the idea that decreased particle size enhances thermal responses [45]. In contrast, studies on  $Fe_3O_4$  nanoparticles show a broader operational temperature range for effective hyperthermia, typically achieving tumor temperatures of 42-46 °C, which is essential for inducing apoptosis in cancer cells [11].  $NiFe_2O_4$  presents a middle-ground scenario, with adequate thermal properties, albeit less optimal than  $CoFe_2O_4$  for inducing hyperthermia. The biocompatibility of these NPs is critical to minimize adverse effects in medical applications.  $Fe_3O_4$  nanoparticles modified with surfactants such as citric and oleic acids have been shown to significantly enhance biocompatibility, facilitating their use as drug delivery systems or for therapeutic heating [47, 48]. Despite its higher heating

efficiency,  $\text{CoFe}_2\text{O}_4$  raises concerns regarding safety and long-term biocompatibility because its cobalt content may increase cytotoxicity [45]. To improve therapeutic applications while preserving superior biocompatibility,  $\text{NiFe}_2\text{O}_4$  nanoparticles can be functionalized by hybridizing with biodegradable polymers [49].

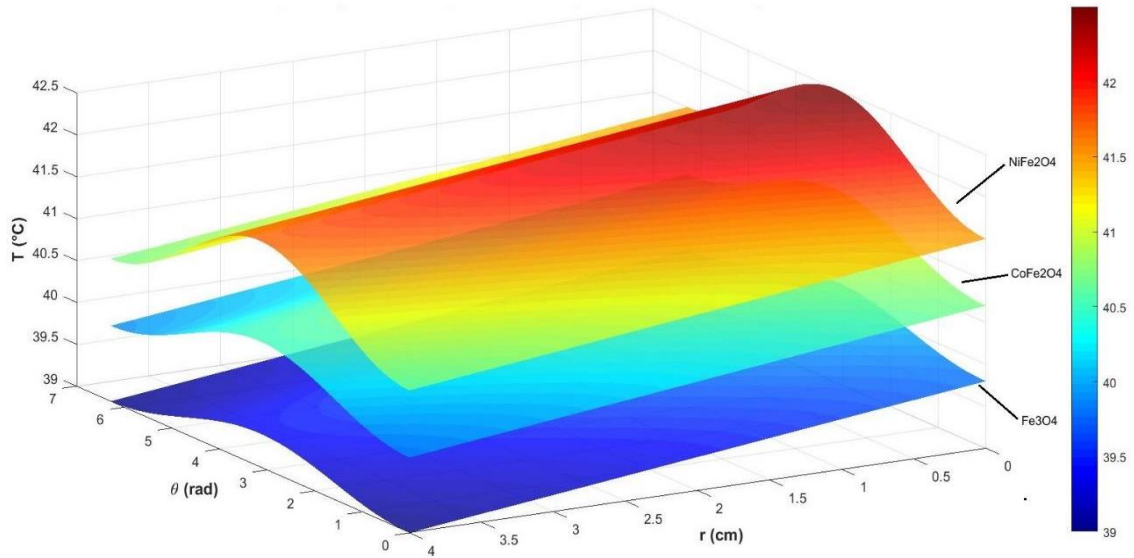
Studies investigating the synergistic effects of these nanoparticles in combination therapies demonstrate varying levels of efficacy. For example, the integration of  $\text{Fe}_3\text{O}_4$  nanoparticles with chemotherapeutic agents (e.g., lapatinib) has demonstrated significant antitumor effects while simultaneously increasing treatment precision [49, 50]. Conversely,  $\text{CoFe}_2\text{O}_4$ 's higher saturation magnetization allows for more effective heat generation, which has shown potential for enhanced efficacy when combined with known cytotoxic agents, although its cytotoxic profiles complicate safe therapeutic use [45]. Research on  $\text{NiFe}_2\text{O}_4$  in combination treatments appears promising but tends to yield comparatively mixed results concerning therapeutic advancements, indicating a need for further exploration into its utility in synergistic applications compared to the more established  $\text{Fe}_3\text{O}_4$  systems [45, 51]. While studies indicate that  $\text{Fe}_3\text{O}_4$  nanoparticles can achieve effective tumor ablation and penetration into cellular structures [50, 48], the unique heating characteristics of  $\text{CoFe}_2\text{O}_4$  may encourage shifts in research focus toward its applications in more resistant tumor types or settings that require higher thermal outputs [45].

Figure 2 shows the three-dimensional diagram of spatiotemporal distribution of temperature for the three NPs ( $\text{NiFe}_2\text{O}_4$ ,  $\text{CoFe}_2\text{O}_4$  and  $\text{Fe}_3\text{O}_4$ ) subjected to zero-angle heat treatment. Such analyses are critical for evaluating the thermal performance of NPs used in MHT and optimizing the treatment process. The graphs follow a decreasing trend; that is, the temperature transfer reaches the maximum level in the areas close to the cancerous tissue, and as we can see in the graphs, the transfer temperature reaches 38.5 degrees Celsius. Then the temperature decreases and reaches its lowest value close to the skin. In addition,  $\text{NiFe}_2\text{O}_4$  NP has the highest temperature distribution in the cancerous tissue, while  $\text{CoFe}_2\text{O}_4$  has the lowest temperature distribution. Although the temperature of ( $\text{NiFe}_2\text{O}_4$ ) decreases faster, the temperature decrease of ( $\text{CoFe}_2\text{O}_4$ ) NP occurs later than all other NPs.



**Figure 2.** Spatiotemporal temperature distribution at a zero-degree angle by injection of three MNPs ( $\text{NiFe}_2\text{O}_4$ ,  $\text{CoFe}_2\text{O}_4$ , and  $\text{Fe}_3\text{O}_4$ ) in thermotherapy for brain tissue.

The data clearly demonstrate that  $\text{NiFe}_2\text{O}_4$  generates the highest peak temperatures, followed by  $\text{CoFe}_2\text{O}_4$  and  $\text{Fe}_3\text{O}_4$ . The curve of  $\text{NiFe}_2\text{O}_4$  reaches approximately 39–40°C, while  $\text{Fe}_3\text{O}_4$  lags behind with a maximum of about 35°C, confirming its comparatively lower heating efficiency. This behavior can be attributed to the magnetic properties and specific absorption rate (SAR) of the particles.  $\text{NiFe}_2\text{O}_4$ , having higher coercivity and anisotropy, yields more efficient heat conversion under the same magnetic field conditions. The spatial profile shows that the temperature decreases with an increase in radial distance from the injection point, creating a heat gradient that supports localized thermal ablation. The change in the temperature distribution over time depends on the magnetic properties of the NPs, which helps to manage the treatment process in a controlled manner. The temperature distribution in the image clearly reveals the local heating caused by MNPs in the brain tissue. This localized heating is crucial for targeting cancer cells while protecting surrounding healthy tissues.



**Figure 3.** Temperature distribution of three IONPs against angle and radial distance.

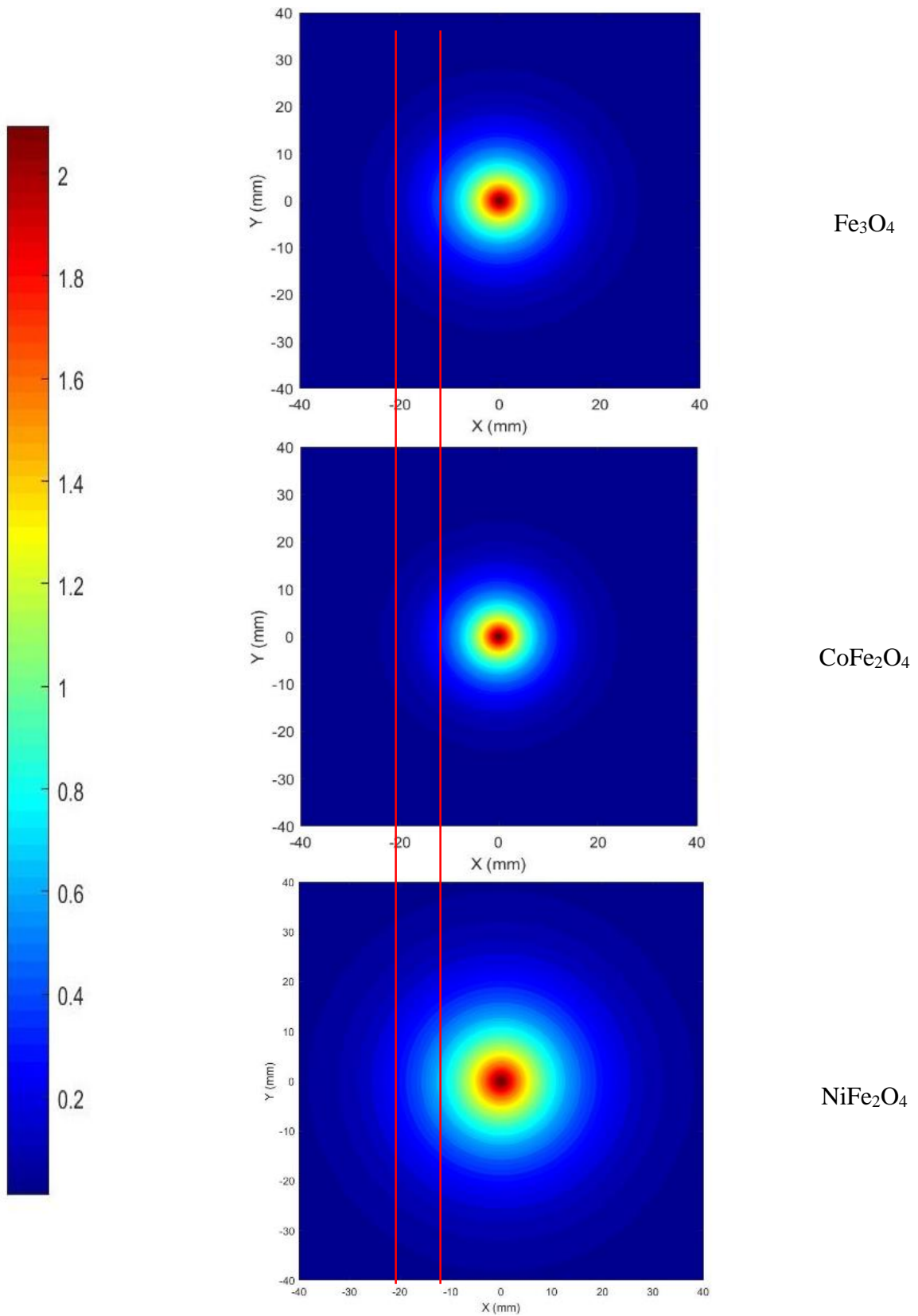
Figure 3 displays the steady-state temperature distribution of  $\text{NiFe}_2\text{O}_4$ ,  $\text{CoFe}_2\text{O}_4$ , and  $\text{Fe}_3\text{O}_4$  NPs against angle ( $\theta$ ) and radial distance ( $r$ ) from the injection site. The visual provides a detailed view of the temperature profiles of different NPs during MH, allowing the thermal performance of each material to be evaluated. Such analyses play a critical role in the selection of NPs to be used in the treatment process and in the optimization of treatment protocols. The graph presented in Figure 3 confirms the superior thermal response of  $\text{NiFe}_2\text{O}_4$ , maintaining a temperature above 41.5°C, followed by  $\text{CoFe}_2\text{O}_4$  (~41°C) and  $\text{Fe}_3\text{O}_4$  (~40°C). Interestingly, the angular symmetry is mostly preserved, indicating isotropic heating behavior — critical for uniform therapy. The thermal plateau exhibited by  $\text{NiFe}_2\text{O}_4$  suggests its suitability in sustaining therapeutic temperatures throughout a wider spatial range, reducing the risk of insufficient heating at tumor margins. In contrast,  $\text{Fe}_3\text{O}_4$  shows a steeper decline with both angle and radius, underscoring its limited thermal reach.

In Figure 4, nanofluid diffusion patterns are shown 18 hours post-injection, visualized in XY-plane heatmaps. The concentration peaks at the center ( $X = 0$ ,  $Y = 0$ ) and gradually declines outward in all three cases. However, clear differences in diffusion characteristics are evident:

- $\text{NiFe}_2\text{O}_4$  displays the widest dispersion, suggesting superior diffusion and distribution

through the tissue matrix.

- $\text{CoFe}_2\text{O}_4$  shows a moderate profile.
- $\text{Fe}_3\text{O}_4$  retains the most localized profile with a sharper concentration gradient.



**Figure 4.** Nanofluid concentration in target tissue after 18 h diffusion period

The concentration distribution of Fe<sub>3</sub>O<sub>4</sub>, CoFe<sub>2</sub>O<sub>4</sub>, and NiFe<sub>2</sub>O<sub>4</sub> NPs in the target tissue provides a comparative view of how each NP spreads and concentrates in the tissue, which is of great importance in understanding the distribution and adhesion properties of NPs in the tissue. In particular, Fe<sub>3</sub>O<sub>4</sub> NPs are seen to have a more homogeneous and limited distribution in the tissue, which clearly reveals why this material is frequently preferred in therapeutic applications. The distribution of CoFe<sub>2</sub>O<sub>4</sub> NPs exhibits a more localized structure compared to Fe<sub>3</sub>O<sub>4</sub>. This shows that CoFe<sub>2</sub>O<sub>4</sub> is concentrated in more specific areas in the tissue and therefore may be more effective in targeted treatment areas. However, this localized distribution may require more precise control during the treatment process. NiFe<sub>2</sub>O<sub>4</sub>'s better spread enhances therapeutic coverage but also poses challenges for containment in sensitive tissues. The distribution of NiFe<sub>2</sub>O<sub>4</sub> NPs appears to be more irregular than the other two materials, which shows that this material spreads and adheres less homogeneously in the tissue.

According to the data obtained from the numerical study results, the comparison table of the three tested IONPs is presented in Table 2.

**Table 2.** Comparison of performances of MNPs

MNP	Max Temp	Temp Uniformity	Thermal Spread (r & θ)	Diffusion Area	Overall Suitability
NiFe <sub>2</sub> O <sub>4</sub>	~39–40°C	High	Broad and uniform	Widest	Excellent
CoFe <sub>2</sub> O <sub>4</sub>	~37–38°C	Moderate	Slightly narrower than NiFe <sub>2</sub> O <sub>4</sub>	Moderate	Good
Fe <sub>3</sub> O <sub>4</sub>	~34–35°C	Low	Steep decline with radius	Most localized	Moderate

Accordingly, overall, NiFe<sub>2</sub>O<sub>4</sub> emerges as the most effective agent in terms of both heating performance and spatial coverage, making it a promising candidate for magnetic thermotherapy in brain tumors. CoFe<sub>2</sub>O<sub>4</sub> serves as a balanced alternative with moderate efficiency and diffusion. Although Fe<sub>3</sub>O<sub>4</sub> has been widely studied due to its biocompatibility and FDA approval, its lower thermal and diffusion performance may limit its application to more localized or superficial tumors unless further optimized. Different diffusion characteristics of MNPs reflect their varying hydrodynamic diameters and surface chemistry, which influence how they interact with extracellular matrix components and interstitial fluid pressures. These findings reveal important factors to consider when using MNPs in therapeutic applications. The distribution and adhesion properties of NPs in the tissue are critical for the efficacy and safety of the treatment.

## 4. Conclusion

The results obtained in this study, which investigated the thermal behaviors and diffusion properties of Fe<sub>3</sub>O<sub>4</sub>, NiFe<sub>2</sub>O<sub>4</sub>, and CoFe<sub>2</sub>O<sub>4</sub> MNPs on thermotherapy of cancer tissues, showed that MNPs trigger apoptotic processes of cancer cells by producing localized heat in the tumor region and can increase the treatment efficacy without damaging healthy tissues.

The main findings of the study can be listed as follows:

- Fe<sub>3</sub>O<sub>4</sub> showed limited effect with lower temperature increase and mostly localized diffusion. 18-hour diffusion period revealed that Fe<sub>3</sub>O<sub>4</sub> NPs showed a more homogeneous distribution in the tissue.
- CoFe<sub>2</sub>O<sub>4</sub> provided moderate heat production and distribution. CoFe<sub>2</sub>O<sub>4</sub> exhibited the most localized diffusion structure among the three MNPs. Therefore, CoFe<sub>2</sub>O<sub>4</sub> may be more

effective in targeted treatment areas but may require more precise control during the treatment process.

- NiFe<sub>2</sub>O<sub>4</sub> was found to be more effective therapeutically than other nanoparticles, with both higher heat production and a wider diffusion profile. Spatiotemporal analyses and radial temperature distribution graphs confirm that NiFe<sub>2</sub>O<sub>4</sub> provides a more homogeneous and sustainable heat profile within the target tissue. But the distribution of NiFe<sub>2</sub>O<sub>4</sub> NPs was found to be more irregular compared to the other two MNPs.

This comparative evaluation of Fe<sub>3</sub>O<sub>4</sub>, NiFe<sub>2</sub>O<sub>4</sub>, and CoFe<sub>2</sub>O<sub>4</sub> nanoparticles highlights the need for targeted applications. As already known, although CoFe<sub>2</sub>O<sub>4</sub> demonstrates superior heating capabilities, Fe<sub>3</sub>O<sub>4</sub> is the most widely accepted and implemented MNP in MHT due to its established safety and versatility and the fact that CoFe<sub>2</sub>O<sub>4</sub> has potential toxicity issues. On the other hand, NiFe<sub>2</sub>O<sub>4</sub> can be said to offer a balance that incorporates effective biocompatibility and flexibility in hybridization.

MNPs in cancer treatment have enormous potential in terms of targeting tumor cells and protecting healthy tissues. But the results of this study clearly suggest that several other parameters and properties of different MNPs, besides the thermal performances, should be taken into account during the treatment process.

### **Limitations and future research**

The main limitation of this study is that the model used is based entirely on numerical simulations and does not include experimental validation. Although the physical and biological parameters used are generally accepted values taken from the literature, many variables such as heterogeneity of real tissues, blood flow, immune system responses, and biochemical interactions remain outside the scope of such simulations. In addition, important biomedical factors such as surface coatings, biocompatibility, and long-term safety profiles of nanoparticles were not directly evaluated. Therefore, the results obtained are for preliminary evaluation purposes and should not be directly generalized to clinical applications.

In the future, it is of extreme importance to proceed to in vitro and in vivo experimental validation processes based on this study. In particular, testing the thermal and biological effects of NiFe<sub>2</sub>O<sub>4</sub> in an experimental environment will contribute to the evaluation of its clinical suitability. In addition, extended simulation models can be developed in which the effects of parameters such as different injection angles, multiple injection strategies, and variable magnetic field frequencies are analyzed. Surface functionalization strategies to increase the biocompatibility of nanoparticles should also be among the priority areas of future research. All these studies will contribute to the integration of MNP-based thermotherapy into clinical applications.

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