EXAMINATION OF IDEAL PHYSICAL PARAMETER CHOICES FOR EFFICACIOUS HYPERTHERMIC TREATMENT OF CANCER

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PHYSICS

ABSTRACT

This dissertation presents results on the computational modeling of electromagnetic and thermal effects during the hyperthermic treatment of cancer using magnetic nanoparticles. Magnetic nanoparticle hyperthermia can be used for direct targeting and destruction of tumors through heat treatment or as a complement to chemotherapy. This method of treatment would be much less invasive than many current treatment options. Additionally, since these are nanoscale devices, the hyperthermic treatment of the cancer cells would be extremely localized. This would cause very minimal damage to surrounding tissue, making these systems superior to traditional hyperthermic treatment.

The use of ferrofluids for cancer treatment requires that appreciable volumetric heating power be generated, while maintaining safe values of frequency and magnetic field strength and reducing the risk of spot heating healthy tissue. In order to implement this treatment in the clinical setting, it is therefore necessary to determine an ideal range of input parameters. These include the complex magnetic susceptibility of the ferrofluid, the magnitude of the driving magnetic field, and and frequencies of oscillation.

It is also necessary to study the impact of variation in biological parameters within the patient population on treatment effectiveness. These parameters include the rates of blood perfusion and the electrical and thermal properties of each of the tissue layers. The determination of the ideal set of parameters for magnetic nanoparticle hyperthermia is accomplished by the coupling of the solution of Maxwell’s equations in a model of the tumor and surrounding tissue as input to the
Pennes Bioheat Equation (PBE). Both sets of equations are solved via the Finite Difference Time Domain (FDTD) Method.

It is found, based on the models used in this research, that for tumor tissue perfusion rates and/or brain tissue perfusion rates which are low, that magnetic nanoparticle hyperthermic therapy is able to safely and thoroughly heat a tumor region of diameter 3 cm to steady-state temperatures which lead to apoptotic cell death. Additionally, it is also found that for these parameter values, the tumor border is also heated to apoptotic temperatures. However, for larger values of tumor/healthy tissue perfusion rates, even for field strengths and frequencies above the regime deemed safe, apoptotic heating is not achieved for nanoparticle volume fractions deemed to be safe. However, temperatures for these parameter values are large enough to possibly amplify the effects of chemotherapy drugs or radiotherapy.
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LIST OF ABBREVIATIONS

AC  Alternating Current
FMR  Ferromagnetic Resonance
PBE  Pennes Bioheat Equation
SAR  Specific Absorption Rate
SLP  Specific Loss Power
ECM  Extracellular Matrix
BBB  Blood-Brain-Barrier
BBTB  Blood-Brain-Tumor-Barrier
IONP  Iron Oxide Nanoparticle
GBM  Glioblastoma Multiforme
MFH  Magnetic Fluid Hyperthermia
MQS  Magneto-Quasistatic
BTE  Boltzmann Transport Equation
FDTD  Finite Difference Time Domain
PDE  Partial Differential Equation
CHAPTER I
INTRODUCTION

1.1 Overview

Hyperthermia therapy for cancer is a medical treatment in which tissue temperatures are elevated, usually to a value of at least 41ºC, for the purpose of damaging or destroying cancer cells. Magnetic nanoparticles under the influence of an AC magnetic field are increasingly attracting attention in medicine and pharmacology as promising materials for use as functional colloidal mediators for hyperthermic cancer treatment and drug-delivery agents. This research examines the electromagnetic and thermal behavior of magnetic nanoparticle systems during the hyperthermic treatment of cancer. This is done through computational modeling of these systems in vivo, under the influence of an AC magnetic field. This research will focus on modeling of ferrofluid hyperthermic treatment of brain cancer, as this is one of the most difficult forms of cancer to treat, and there are currently fewer treatment options with only very limited efficacy. The goal of these calculations is to determine a therapeutic range of operational parameters for treatment, including magnetic field strengths and frequencies, and magnetic susceptibilities for the ferrofluid, based on published clinical standards.

1.2 Magnetic Nanoparticle Hyperthermia as a Novel Cancer Treatment

1.2.1 Hyperthermia as a Route to Apoptotic Cancer Cell Death

Tumor growth depends not only on the rate of cell proliferation, but also on the rate of cell death. Additionally, alterations in genes that control the pathways
to preprogrammed cell death, known as apoptosis, are implicated in tumorigenesis. Deficiencies in apoptosis lead to a protracted cell lifetime, resulting in abnormal cell growth independent of the cell division process. These deficiencies also may create an environment which leads to an accumulation of genetic mutations which spur the development of cancerous tissue [1]. Novel treatments which would induce or increase the rate of apoptosis of cancer cells therefore are both a promising alternative to traditional treatments, such as chemotherapy and radiation, and a viable adjuvant to these treatments.

A sustained temperature above 41\(^\circ\)C can cause irreversible damage to cell function which may lead to cell death as well as heat-induced sensitization of cells to radiation and some cytotoxic drugs. Sustained temperatures between 41\(^\circ\)C and 45\(^\circ\)C predominantly lead to apoptosis. As was previously mentioned, apoptosis is a form of intentional cell death based on a genetic mechanism. Cells undergoing this process rapidly shrink, lose inter-cellular contact, undergo condensation of chromatin and irregular bulging of the cytoplasm, and finally break up into smaller apoptotic bodies. These bodies are then digested by neighboring cells or macrophages. Apoptosis is favorable as the dominant mechanism for cell death induced by hyperthermic cancer treatment as it is considered less likely to lead to inflammatory responses and lysis of cells, which damage the overall health of the organism [2][3]. A sustained temperature above 45\(^\circ\)C causes other forms of cell death, commonly referred to as necrosis, the general term for the path to cell death [4][5][2]. Cells that die due as a result of necrosis do not send the same chemical signals to the immune system as cells undergoing apoptosis. Nearby macrophages are then unable to locate, engulf, and digest the dead cells. This leads to a build-up of dead tissue and cell debris, and likely an inflammatory response [2][3].

Localized hyperthermia should ideally heat cancerous tissue to temperatures
between 41\(^\circ\)C and 45\(^\circ\)C, in order to induce apoptosis in cancer cells, while maintaining temperatures below 41\(^\circ\)C within the healthy tissue, in order to insure survival of the healthy cells. Hyperthermic cancer treatment is advantageous due to fewer side effects than traditional chemotherapy or radiotherapy, particularly when these temperature constraints are maintained [6][7][8].

Magnetic materials under the influence of an AC magnetic field are particularly convenient for hyperthermic applications. Magnetic nanoparticle systems can be utilized both as drug delivery agents for chemotherapy and for direct targeting and destruction of tumors through heat treatment. Additionally, since these are nanoscale materials, the energy deposition in the cancer cells would be extremely localized. Surrounding tissue would therefore incur minimal damage, making these systems superior to traditional hyperthermic treatment.

1.2.2 Challenges Presented in the Treatment of Brain Cancer

1.2.2.1 Current Statistics and Prognosis

Brain tumors are among the most difficult forms of cancer to treat. As many advances have been made in chemotherapy, radiation, and surgery, improving survival rates for many other forms of cancer, the prognosis for patients with malignant gliomas (the most common type of brain cancer, which forms from glial cells) remains quite poor. The most common form of primary intracranial malignant tumor is the glioma, which accounts for 30% of adult cases. The estimated incidence of malignant gliomas in the United States is 14.7 per 100 thousand; approximately 5000 new cases annually [9]. Glioblastoma multiforme, a particularly aggressive form of glioma, has a median prognosis of approximately 14 months. Only a four month improvement in the median survival time for glioblastoma multiforme has been seen over the past 30 years [1][7][9]. Additionally, only 3 - 5% of patients are referred to as “long term survivors” as they survive for longer than 3
years [10]. Traditional therapies are therefore inadequate and novel treatments, including magnetic fluid hyperthermia, are called for in order to make significant advances in long term patient survival statistics.

1.2.2.2 Morphology and Pathology

Both low and high grade gliomas have very irregular borders which tend to grow in a diffuse manner, and become highly entangled with healthy brain tissue. Individual glioma cells or small groups of cells can easily detach from the primary tumor mass and then, following routes determined by the anatomical structure of the brain and Extracellular Matrix (ECM), travel significant distances. Glioma cells seem to have evolved unique mechanisms for invasion of the surrounding tissue that are specifically evolved for the brain ECM [7]. The ability of glioma cells to pervade throughout healthy brain structures creates a troublesome clinical challenge, as these cells are widely believed to be responsible for tumor recurrence after surgery, radiation, and chemotherapy. Surgical resection is, however, an important component of treatment for gliomas and other brain tumors for diagnostic purposes, as well as debulking and alleviation of symptoms due the mass effect of the tumor and edema. Figure 1.1 displays an example of astrocytoma morphology. (Astrocytoma is the most common type of glioma, of which glioblastoma multiforme is a subtype.) Figure 1.1 also is an example of the aggressively recurrent nature of the glioma, even when treated with surgery, radiation, and chemotherapy.

Gliomas are often deep-seated in the brain, and occur in or invade the white matter, which has a lower rate of blood perfusion than grey matter. The deep-seated nature of these tumors and lower perfusion rate provide an additional treatment challenge which is not adequately met by traditional therapies [12]. The small particle size and the possibility of guidance with a magnetic field render ferrofluids advantageous for surmounting this problem. For example, in one study,
Figure 1.1: From “Effectiveness of Interferon-Beta and Temozolomide Combination Therapy Against Temozolomide-Refractory Recurrent Anaplastic Astrocytoma” by Fujimaki et al., 2007, World Journal of Surgical Oncology, Vol. 5, number1, p. 89. Copyright 2007 by Creative Commons. Reprinted with permission.

MRI of brain with recurrent anaplastic astrocytoma: (A) MRI on February 16, 2005. The figure displays a tumor in the right and left frontal lobe as well as the right thalamus. (B) MRI after surgery, radiation and chemotherapy is shown. According to Fujimaki et al, “The tumor has completely disappeared except for slight enhancement adjacent to the surgical border.” (C) Recurrence of the thalamic tumor in spite of maintenance chemotherapy on November 16, 2005. (D) Increase in size of the thalamic tumor; months after radiotherapy treatment. (E) After 6 cycles of therapy with a relatively novel chemotherapeutic agent, temozolomide, the thalamic lesion increased in size, and the patient developed dysarthria and hemiparesis. (F) After 2 courses of treatment with interferon-beta and temozolomide, the tumor shows only a partial response [11].
magnetic nanoparticles were entrapped in nanosized liposomes and then guided by magnetic force to a solid tumor in a mouse model [13].

Gliomas, especially high grade tumors, are highly vascularized. Tumor vasculature is more permeable than the vasculature of healthy brain tissue. Whereas the gaps between the endothelial cells in the brain, which create the BBB are around 3nm, the gaps that form the BBTB are around 12nm [12]. The small size of both the BBB and the BBTB presents a challenge for delivery of chemotherapy drugs to the tumor site. However, the difference in size between the BBB and BBTB provides another advantage for delivery to the tumor site. Particles could be injected or guided with a magnetic field, then passively delivered preferentially to the tumor site via the leaky tumor vasculature [12].

Analysis of observations of both living and dead glioma patients has shown that, although the ranges are wide, gliomas are detectable on enhanced CT at an average diameter of 3 cm. This diameter is based on a sphere of equal volume to the tumor volume [14]. Tumor sizes modeled in this study will be based on this average tumor diameter. It is of critical importance for the development of a magnetic nanoparticle hyperthermia treatment to determine if it is possible to heat the tumor border to apoptotic temperatures in order to destroy stray tumor portions and cells which are enmeshed with healthy tissue.

1.2.3 Magnetic Nanoparticles for Hyperthermic Cancer Treatment

Since investigation of the applications of magnetic materials for hyperthermia began in 1957, a wide variety of magnetic materials, field strengths, and frequencies have been used in these experiments [15]. Human clinical trials have recently begun as a result of the increased safety and efficacy of magnetic nanomaterials for hyperthermia [16]. The subject of this research is the computational modeling of electromagnetic and thermal effects during the hyperthermic treatment of cancer.
using magnetic nanoparticles systems, particularly ferrofluids.

1.2.3.1 Advantages of Magnetic Nanoparticles for Cancer Treatment

The primary disadvantage of most forms of chemotherapy and radiotherapy is that they aren’t targeted for a particular type of cell or tissue. Traditional chemotherapy drugs are administered intravenously, leading to a broad systemic distribution. This leads to a general attack on healthy and cancerous cells alike, leading to adverse reactions. Functionalized magnetic nanoparticles could be delivered to a specific tumor site, thereby reducing systemic distribution of the drug and reducing the amount of the drug necessary for treatment [17]. A magnetically targeted therapy could work in the following way: A cytotoxic drug would be attached magnetic nanoparticle carrier which is biocompatible. The resulting biocompatible ferrofluid would be injected into patient via the circulatory system. Once the drug-coated nanoparticles entered the bloodstream, an external magnetic field would be used to drive the particles to the tumor site. Once the drug/nanoparticle complex is concentrated in the tumor region, the drug would be released either via enzymatic activity or changes in physiological conditions such as pH, osmolality, or temperature, and be taken up by the cancer cells [17]. Figure 1.2 is a schematic representation of such a delivery system.

1.2.3.2 Magnetic Nanoparticle Size and Concentration: Toxicity and Efficacy

A critical issue for therapeutic use of magnetic nanoparticles is the length of time that particles remain in the bloodstream, and their path to elimination from the body. This is an issue important for both safety and efficacy of the treatment. Particles must remain in the tumor tissue long enough for effective treatment, but be safely eliminated from the body, so that toxic concentrations of iron are not reached.

Magnetic nanoparticles are typically seen by the immune system as invaders,
Driving

Figure 1.2: Magnetic nanoparticles may be used for hyperthermic cancer therapies alone, or as a delivery system for chemotherapeutic drugs. A simplified schematic representation of a magnetic nanoparticle drug delivery system shown in cross-section: an external magnetic field is used to drive magnetic carriers flowing in the circulatory system in order to cross the BBB (ordinarily 3 nm, but may be increased by certain drugs) or BBTB (about 12 nm).

and the body will try to remove them from circulation using various pathways which depend on the hydrodynamic radius (a.k.a. Stokes’ radius, the radius of a hard sphere that diffuses at the same rate as the particle) of the particles. A particle size of 10 nm to 200 nm is thought to be optimal for intravenous injection. Outside of this range, the magnetic nanoparticles lack enough circulation time to reach the tumor site as larger particles are rapidly taken up by the spleen and smaller particles are too easily subject to renal clearance [18].

Chronic iron toxicity is known to develop only after the liver iron
concentration exceeds 4 mg Fe/g of liver tissue. This is about 20 times the amount typically seen in the liver. For an average liver mass of 1800g [19], this means a maximum of 7.2 g of iron in the liver at a given time before there is a significant risk for chronic iron toxicity. The typical dosage reported in clinical studies is 10mg of Fe/g of tumor tissue. The tumor mass treated with this dosage would have to exceed 720 g (about half the mass of the entire average-sized human brain [19]) in order to reach an amount of 7.2 g of iron in the bloodstream. Injections with this small concentration of 10mg/g tumor tissue have been shown clinically to be safe and nontoxic [18][20]. Additionally, studies have been done for targeted thermotherapy via Iron Oxide Nanoparticle (IONP)s to induce apoptosis of human glioblastoma cells in mouse and rat models which show no toxicity to human astrocytes (characteristic star-shaped glial cells in the brain from which astrocytoma cancer cells originate). In this study, human astrocyte cells were treated with control vehicle (serum-free medium) or IONPs (with a concentration of 0.3 mg/mL) for 1 hour. No significant toxicity found with human astrocytes 3 days after treatment with the IONPs [21].

1.2.3.3 Clinical Studies Using Magnetic Nanoparticles

A wide variety of clinical studies have been performed for magnetic nanoparticle fluid hyperthermic cancer treatment on animal subjects, for example, [22], and since 2001 human studies have been performed [23]. Magnetic fluid hyperthermia is generally well tolerated and improves patient outcome for a variety of cancers [16].

Recently there have been several studies for the safety and effectiveness of such treatments on human gliomas using xenografts implanted into mouse and rat models, including the aggressive form Glioblastoma Multiforme (GBM) [24][21]. These studies have shown that magnetic nanoparticle hyperthermia is very effective.
in treating GBM. For example, Jordan et al 2006 [24] measured different intratumoral temperatures in a Magnetic Fluid Hyperthermia (MFH) study between 43°C and 47°C. A gain of survival was correlated with the intratumoral temperatures, and the group reported a 4.5 fold prolongation in life compared to the baseline after treatment at 47°C. In their study, Jordan et al. used an alternating magnetic field applicator system (MFH 12-TS, MagForce Nanotechnologies, from Berlin, Germany) operating at a frequency of 100 kHz and variable field strengths of $0 \leq H_0 \leq 18 \text{kA/m}$. These results are displayed in table 1.1 and figure 1.3.

| Prolonged Survival Times With Magnetic Nanoparticle Hyperthermia Treatment |
|-----------------------------|--------------------------|--------------------------|
| Treatment Group            | Mean Survival (days) ± s.d. | Survival Factor |
| C - 0                       | 8.9 ± 3.1                | 1                       |
| C - A                       | 8.0 ± 1.6                | 0.9                     |
| C - B                       | 7.6 ± 0.7                | 0.9                     |
| C - F                       | 10.1 ± 1.1               | 1.1                     |
| T - DDM128 P6 39°C          | 10.3 ± 2.1               | 1.2                     |
| T - MFL AS 43°C             | 15.4 ± 6.3               | 1.7                     |
| T - MFL AS 44°C             | 28.3 ± 7.4               | 3.2                     |
| T - MFL AS 45°C             | 34.7 ± 6.8               | 3.6                     |
| T - MFL AS 46°C             | 37.8 ± 2.2               | 4.3                     |
| T - MFL AS 47°C             | 39.7 ± 3.5               | 4.5                     |

Table 1.1: Data from Jordan et al 2006: “Factor describes prolongation of survival in correlation to group C-0=tumor growth control; C-A=application of magnetic fluid DDM128 P6, no magnetic field treatment; C-B=application of magnetic fluid MFL AS, no magnetic field treatment; C-F=application of normal saline and magnetic field treatment; T-DDM128 P6=application of dextran-coated nanoparticles, treatment temperature 39°C; T-MFL AS=application of aminosilane-coated nanoparticles, treatment temperature 43° - 47°C.” [24]

A study by Maier-Hauff et al. was done in 2007, in which 14 human GBM patients were injected with aminosilane coated iron oxide nanoparticles (tumor injections were performed using 3-D image guiding). The patients were then exposed to an external alternating magnetic field to induce hyperthermic heating of the nanoparticle/tumor region. All patients in the study initially had tumors less than 5cm radius and life expectancy of at least 3 months [6]. With the alternating
magnetic field applicator operating at a frequency of 100 kHz and variable field strengths of $2.5 \leq H_0 \leq 18$ kA/m. All patients also received radiotherapy. After the therapy sessions were completed, patients were monitored by clinical examination and CT scans at 3 month intervals. No side effects due to nanoparticle injection such as headache, nausea, vomiting or allergic reactions were observed. Additionally, there were no neurological deficits, infection, or serious trauma such as bleeding in the area, and swelling was easily controlled. Magnetic field strengths of
3.8 \leq H_0 \leq 13.5 \text{kA/m} were used for thermotherapy, and, according to the study, were well tolerated by the patients with only minor side-effects [6]. In this study, the ferrofluid was injected in order to achieve a homogeneous distribution.

Patients in this study had a survival prognosis of 2.7 to 11.5 months, and the treatment outcome resulted in a median survival of 14.5 months [6]. This is a promising result, yet modest when compared to the rat model results. Calculations in this research will attempt to provide a guide in order to improve results for future clinical studies. Deficiencies in the clinical study by Maier-Hoff et al. are likely attributable to several factors, which will also be an issue for other clinical studies without the aid of preliminary computational and/or analytical modeling. These issues include problems in calculating the appropriate magnitude of the AC magnetic field in order to produce the optimal thermal dose and difficulties in heating the entire tumor region to sufficient temperatures in order to achieve cell death. Optimal values for magnetic field strength and nanoparticle concentration must be found, and future studies in order to better understand ferrofluid diffusion would also be useful in optimizing heating patterns. As previously stated, it is of critical importance in reducing the likelihood of a recurrence not only to heat the bulk of the tumor to apoptotic temperatures, but to heat stray cancer cells, including those on the diffuse border of brain tumors, to apoptotic temperatures.

1.2.3.4 Safety Considerations for Operational Parameters

The safe and useful range of magnetic field strengths and frequencies for these applications are considered to be \(0 < H < 15 \text{kA/m}\) and \(0.05 < f < 1.2 \text{MHz}\). Higher field strengths can lead to problems including aggregation of magnetic materials, leading to embolisms. Lower frequencies can cause stimulation of the skeletal or peripheral muscles, or even stimulation of the cardiac muscles and arrhythmias. It has also been established that exposure to fields where the product
$H_0 \cdot f$ is less than $4.85 \cdot 10^8 \text{ Am}^{-1} \text{s}^{-1}$ (where $H_0$ is the magnitude of the applied magnetic field) is safe for use in humans [25]. This restriction limits tissue heating power and may be relaxed depending on the diameter of the region being treated and the severity of the illness. We assume a weaker criterion $H_0 \cdot f < 5 \cdot 10^9 \text{ Am}^{-1} \text{s}^{-1}$ in our calculations [25][26].

In addition to the restrictions on these input parameters mentioned in previous sections, one must also consider the delivery of the magnetic nanoparticles to the tumor region. This is of particular concern for the treatment of deep-seated brain tumors, where direct injection of the magnetic material to the tumor site is impractical. Magnetic nanoparticles must in this case be able to cross the BBTB in order to be of use for treatment.

In order to determine a safe range of parameters where the risk of spot heating of the healthy tissue is minimized, yet appreciable volumetric heating power is generated, it is necessary to determine a therapeutic set of input parameters, including $H_0$, $f$, and material properties of the ferrofluid.

1.2.4 Goals

The following research objectives and results are outlined in this dissertation:

1) A multilayer model of the tumor and surrounding tissue will be constructed. The solution of Maxwells equations in this model will be coupled with the Pennes Bioheat Equation (PBE) as input for power deposition.

2) Both sets of equations are solved for a multilayer model of the human head via the Finite Difference Time Domain (FDTD) Method.

3) A set of ideal input parameters will be found, including $H_0$, $f$, and material properties of the ferrofluid, that are able to heat the model brain tumor region to temperatures between $41^\circ\text{C}$ and $45^\circ\text{C}$, in order to achieve apoptotic heating of the cancerous tissue. This will be achieved while maintaining safety restrictions for the
upper and lower bounds on $H_0$ and $f$ ($< H < 15 \text{ kA/m}$ and $0.05 < f < 1.2 \text{ MHz}$), the product ($H_0 \cdot f \leq 4.85 \cdot 10^8 \text{ Am}^{-1}\text{s}^{-1}$), clinically relevant ferrofluid concentrations, and empirical thermal and dielectric properties of both healthy and tumor tissue.

4) It will be demonstrated that at ferrofluid concentrations currently shown to be safe in clinical trials, magnetic nanoparticles small enough to cross the BBB are capable of enough thermal deposition to cause apoptotic death of cancer cells.

5) It will be determined if it is possible to find a set of operational parameters that lead to apoptotic heating of the model tumor boundary region. This is of vital importance for the development of a magnetic nanoparticle hyperthermia treatment for brain cancer that is able to reduce the risk of tumor regeneration after surgical resection of the tumor mass.

6) Uniform magnetic fields will be achieved for the simulated AC magnetic field in order to minimize artifacts in the calculation results, and because clinically a uniform magnetic field in the cranial region is of use in order to reduce the risk of nanoparticle aggregation in regions with higher magnetic field gradients.

7) Calculations will be performed for various model geometries in order to determine the effect of the tumor location and ferrofluid distribution.

8) Uniform heating patterns will be achieved in order to reduce the risk of spot-heating of healthy tissue.

9) The sensitivity of model tumor temperature to variation in blood perfusion rates during magnetic nanoparticle hyperthermia therapy will be determined.

10) Recommendations for future computational work on ferrofluid hyperthermia will be made. This includes continual refinement of the model in order to more realistically determine the effect of the asymmetry of the glioma border and rigorous determination of sensitivity of the thermal behavior of the system to all of the relevant input parameters. Ultimately, multiscale modeling would be the best possible option for a realistic simulation of the thermal transport for the magnetic
nanomaterial/human body system under the influence of the exciting AC magnetic field. The model should include electromagnetic and thermodynamic behavior on the nanoscale, the effects of the tissue and blood vessels on the mesoscale, and macroscopic thermal effects. This includes, for example, convective heat transfer at the boundary tissue layers.

11) Recommendations for future magnetic nanoparticle hyperthermia treatments will be made. This includes the design of functionalized magnetic nanomaterials for use as an adjuvant to chemotherapy, and for tumor imaging in order to aid both the diagnostic and treatment process.

1.2.5 Synopsis

Determining the ideal parameters, including as the necessary values for \( H_0 \), \( f \), and the material properties for a ferrofluid, especially the imaginary susceptibility \( \chi'' \) capable in tumor tissue temperatures between \( 41^\circ \text{C} \) and \( 45^\circ \text{C} \), while maintaining safe values for the magnetic field and frequency, will be the central thrust of this research. These calculations will also be performed for a variety of blood perfusion rates, as this is an important parameter for the calculations, to which tissue temperature is extremely sensitive. The effect of model geometry, especially tumor location and ferrofluid distribution, will be investigated. Finally, recommendations will be made for refinement of future calculations and additional computational work which should be done, as well as design of functional magnetic nanoparticles and treatment protocols for hyperthermic treatment of brain cancer.
CHAPTER II

THEORY

2.1 Heating Mechanisms for Magnetic Nanoparticle Materials

2.1.1 Overview

The determination of a set of input parameters, such as the electromagnetic excitation field amplitude and frequency and magnetic nanomaterial properties, which produce a clinically desirable tissue temperature profile for ferrofluid hyperthermia is a multiscale non-equilibrium heat transfer problem. Heat transfer is the transport of energy from one location and/or form to another by energy carriers. Examples of these carriers are photons, phonons, or electrons in solids or atoms or molecules via diffusion in gases and liquids. Consider a distribution function $f(\mathbf{r}, \mathbf{p}, t)d\mathbf{r}d\mathbf{p}$, which represents the number of carriers in a statistical ensemble of particles with momentum $\mathbf{p}$ within the volume $d^3r$ about a position, $\mathbf{r}$. The non-equilibrium Boltzmann Transport Equation (BTE) relates the time evolution of the distribution function to factors which influence the distribution, including any external forces, diffusion, and scattering [27][28]:

$$\frac{\partial f(\mathbf{r}, \mathbf{p}, t)}{\partial t} + \frac{\mathbf{p}}{m} \cdot \nabla f(\mathbf{r}, \mathbf{p}, t) + \mathbf{F}(\mathbf{r}, t) \cdot \frac{\partial f(\mathbf{r}, \mathbf{p}, t)}{\partial \mathbf{p}} = \left( \frac{\partial f(\mathbf{r}, \mathbf{p}, t)}{\partial t} \right)_{\text{scatt}} \tag{2.1}$$

Where $m$ is mass of a particle in the statistical ensemble and $\mathbf{F}$ is the net force acting on a particle in the ensemble. Inspection of the BTE in its most general form such as in (2.1), demonstrates the manner in which energy may be delivered to
carrier particles via a force, such as an electric or magnetic field, and then transferred via carrier particles through diffusion processes or scattering. In the case of magnetic nanoparticle hyperthermia, energy is delivered to electrons in the magnetic nanomaterial via an external AC magnetic field. Then, through thermal relaxation processes (such as hysteresis and Néel Relaxation, which will be discussed in this chapter and in Appendices D and E) and due to coupling with the crystal lattice, the energy is converted to thermal energy and transport occurs via phonons and/or magnons [29]. So, conduction is one manner in which thermal energy is transported within the magnetic nanoparticle material and the surrounding tissue.

If magnetic nanoparticles are in solution, or shortly after delivery to the tumor, before adsorption of the magnetic nanoparticles into tumor tissue occurs, the particles may rotate in the fluid suspension in response to the applied AC magnetic field. Then, the energy delivered by the applied field is converted to mechanical energy to drive Brownian rotation of the particles. In the Brownian rotation process energy is dissipated through friction, and thermal energy transport occurs via scattering and diffusion in the fluid. Additionally, as particles are delivered to the site, ferrofluid diffusion occurs. Thermal energy is then, in addition to conduction, transferred to the surrounding tissue by diffusion processes.

The relaxation process which dominates depends largely on the magnetic nanoparticle size. However, in practice, ferrofluids are polydisperse and soon after delivery to the site and application of the electromagnetic excitation source, these relaxation and heat transfer processes happen concurrently. As was previously mentioned, after adsorption into tissue hysteresis and Néel Relaxation relaxation processes dominate. It is clear that in order to calculate the appropriate operational parameters for ferrofluid hyperthermia, it is necessary to create a model which takes into account the contribution of the various relaxation process and energy transport processes which occur in the magnetic material, the fluid suspension, and
surrounding tissue.

Appreciable magnetic losses due to an alternating magnetic field to be utilized for heating arise due to several processes of magnetization reversal in the nanoparticle system. These include Néel Relaxation, Brownian Relaxation, and hysteresis. Eddy current induced heating of small magnetic particles is negligibly small in comparison to magnetic losses. The term “inductive heating” sometimes used for magnetic particle heating in biomedical literature is therefore misleading [30]. The approximation in the next section for inductive heating for magnetic nanoparticle materials and comparison to magnetic losses at similar field strengths and frequencies will serve to demonstrate this.

2.1.2 Power Loss Due to Inductive Heating

An electrically conductive body subject to an Alternating Current (AC) magnetic field will have induced electrical currents that give rise to heating due to the resistance of the material. Smythe found an analytical expression for the time averaged power dissipation of an inductively heated sphere [31]. If it is assumed that the particles are smaller than the domain size, then \( \mu = \mu_0 \) (we use SI units throughout), the Smythe formula simplifies. The subsequent power series expansion (after multiplication by the number of spheres in a sample, \( n = \frac{3\phi_v}{4\pi R^3} \), where here \( \phi_v \) is the volume fraction of nanoparticles in the fluid and \( R \) is the radius of a single particle, which is assumed to be the same for all particles in the sample) then yields the time-averaged power dissipation per unit volume:

\[
P = \phi_v \sigma \left( \pi RBf \right)^2 \frac{2}{5} \tag{2.2}
\]

(2.2) applies to small particles and is valid for frequencies much less than the
critical frequency, \( f_c \) (at \( f = f_c \) the radius of the sphere is equal to the skin depth), where:

\[
f_c = \frac{1}{\pi R^2 \mu_0 \sigma}
\]  

\( \sigma \equiv \text{electrical conductivity} = 200 \ \Omega^{-1} \text{cm}^{-1} \) for magnetite, so \( f_c = 5 \cdot 10^{17} \) Hz for \( R = 5 \) nm, then if \( B = 0.06 \) T and \( \phi_v = 0.071 \) (typical values for clinical hyperthermia with a ferrofluid), \( P = 2.5 \cdot 10^{-10} \text{Wcm}^{-3} \). If instead, \( \sigma = 9.3 \cdot 10^4 \ \Omega^{-1} \text{cm}^{-1} \) (for iron), \( P = 1.2 \cdot 10^{-7} \text{Wcm}^{-3} \). Since appreciable heating occurs due to magnetic nanoparticle fluid hyperthermia, there must be some heating mechanism other than induction for these materials [32][17][33].

An analytical derivation of the power dissipation in an ensemble of conducting spheres subject to an alternating magnetic field is detailed in Appendix A.

2.1.3 Dielectric Losses

Magnetic nanomaterials such as magnetite and maghemite nanoparticle fluids have a dielectric function with real and imaginary components which are nonzero. Thus, they can exhibit measurable dielectric losses which depend on both the carrier fluid and magnetic material used, the size and shape of the nanoparticles, and the frequency of the applied field. For example, for some ferrofluids and an applied electromagnetic field with frequencies below the 500 kHz range, which is preferred for magnetic fluid hyperthermia, counterion polarization effects which fit the Schwarz model result in dielectric losses [34][35]. (The Schwarz model suggested that polarization of the counterion layer around colloidal particles by an external electric field was responsible for dielectric dispersion effects observed
for colloidal particles in some fluid suspensions [36][37].

Additionally, tumor tissue and healthy tissue layers also have both real and imaginary permittivity components, and therefore exhibit dielectric losses. Values for the real and imaginary components of the permittivity for the tumor/ferrofluid composite region, as well as the other tissue layers are included in the model presented in this dissertation, and the power loss associated with these values is given by:

\[
P_{\text{dielectric}} = \frac{1}{2} \int_V \sigma |E|^2 dV
\]  \hspace{1cm} (2.4)

Where \( \sigma \) is the conductivity and of course,

\[
\tilde{\epsilon} = \epsilon_r \epsilon_0 + \frac{\sigma}{i\omega}
\]  \hspace{1cm} (2.5)

Where \( \tilde{\epsilon} \) is the the complex permittivity, \( \epsilon_0 \) is the free space permittivity, \( \omega \) is the angular frequency, and \( \epsilon_r \) is the relative permittivity. So, knowledge of the conductivity, or the complex dielectric function (2.5), or given that we know only a single component, in some cases the Kramers-Kronig relations (see Appendix C) allow for calculation of the other component and thus, the conductivity for (2.4).

Further details on the manner in which the composite tumor tissue/ferrofluid region dielectric properties are calculated and included in the model may be found in III.

However, in the frequency regime of interest for ferrofluid hyperthermia (\( \sim 200kHz - 1MHz \)), the imaginary permittivity component for magnetic nanoparticle fluids is small. For example for the highest concentration of magnetite nanoparticles (volume fraction of .19) in an oil (Isopar -m) in a study by Pelster et al., for a temperature of 293 Kelvin and frequency between 10 kHz and 1 MHz, .1
\[ \varepsilon'' \leq 1 (\varepsilon' \text{ is about 5.5 for this entire frequency range}) \] [38].

Additionally, the concentration of magnetic nanoparticles used for hyperthermia are relatively low (a volume fraction of .003 corresponding to 10mg of Fe per gram of tumor is typical [22]), and the permittivity of the ferrofluid/tumor composite depends on the concentration of nanoparticles in the surrounding medium. The Hanai - Bruggeman equation for the effective complex permittivities of a dielectric material with spherical inclusions is given by [39][40]:

\[
\frac{\varepsilon_i - \varepsilon}{\varepsilon_i - \varepsilon_m} \left( \frac{\varepsilon_m}{\varepsilon} \right)^{\frac{1}{3}} = 1 - \nu
\]

(2.6)

Where \( \nu \) is the volume filling factor. \( \varepsilon_m \) and \( \varepsilon_i \) are the complex dielectric permittivity of the surrounding matrix and inclusion, respectively. \( \varepsilon \) is the complex dielectric permittivity of the mixture. Equation (2.6) is in good agreement with measured values for low concentration ferrofluids in the frequency range appropriate for hyperthermia [40][41]. Since \( \nu \) for magnetic nanoparticles in the tumor/ferrofluid composite region is small, the electrical conductivity and real part of the permittivity of the region used in these calculations are nearly the same values as tumor tissue alone.

Additionally, the magnitude of the electrical field in the region of interest (inside the head region) is small and therefore for the frequency range used in these calculations, dielectric losses are minimal in comparison to magnetic losses. See Chapter IV for benchmarking calculations supporting this assertion.

2.1.4 Power Loss Due Brownian and Néel Relaxation Processes

The heating processes for magnetic nanoparticle fluids were first detailed by Rosensweig, using the same formulation as the Debye model for dielectric dispersion
An alternating magnetic field of the form:

\[ H(t) = H_0 \cos \omega t = Re[H_0 e^{i\omega t}] \] (2.7)

The magnetization of the ferrofluid can then be expressed in terms of its complex susceptibility \( \chi = \chi' - i\chi'' \). The volumetric heating power \( P \) of a ferrofluid due to the phase lag between the applied field and the magnetization (and therefore a nonzero value for \( \chi'' \)) is given by [32]:

\[ P = f \Delta U = \mu_0 \pi \chi'' f H_0^2 \] (2.8)

Further details of the calculation of (2.8) are found in Appendix E. It should be kept in mind that this expression is for a monodispersion. Rotation of the particles in the viscous medium (Brownian relaxation) and rotation of the magnetic moments of or within the crystal (Néel relaxation and hysteresis) both result in power dissipation. High heating rates are achieved in the regime of particle size where the Néel mechanism does not dominate the relaxation processes. \( \chi'' \) depends upon many material properties of the ferrofluid, including the the nanoparticle size and size distribution, the volume fraction of nanoparticles in the fluid, the domain magnetization of the suspended particles, the viscosity of the fluid, and the frequency of the applied magnetic field [32]. This formula is restricted to small amplitudes of the magnetic field since the typical magnetic saturation is not included. [42].

Measurements of the heat generation from magnetic particles are most often
quoted in terms of the Specific Absorption Rate (SAR), which has units of W/g. Since (2.8) gives the volumetric heating power of a ferrofluid, the SAR is given by:

\[ SAR = \frac{P}{\rho_m} \]  \hspace{1cm} (2.9)

where \( \rho_m \) is the mass density of the ferrofluid. The SAR is also referred to as the Specific Loss Power (SLP) in the literature [42]. Ferromagnetic materials have a hysteretic magnetic response curve, and require extremely high field strengths (\( \approx 100 \text{ kAm}^{-1} \)) in order to reach their maximum magnetic response, called magnetic saturation. As such, for field strengths below the safety constraint of 15 kAm\(^{-1}\), only minor hysteresis loops are utilized for heating. This leads to low SAR values, as power loss is related to the area inside the hysteresis curve. For a more detailed explanation of the magnetic hysteresis phenomenon and magnetic response curves of different materials, including the nonlinear and anhysteretic response of superparamagnetic materials, see Appendix E and Appendix D Further details about how power losses are related to the hysteresis curve are also included in Appendix D.

As magnetic nanoparticle fluids have a square dependence on the applied magnetic field (see Appendix E for details), they are capable of generating higher heating power at lower field strengths than ferromagnetic materials. The ferrofluid reported by Hergt et al [43] with the highest heat generation has a SAR of 45Wg\(^{-1}\) at 6.5kAm\(^{-1}\) and 300 kHz which extrapolates to 209 W g\(^{-1}\) for 14 kA m\(^{-1}\), compared to 75 W g\(^{-1}\) at 14 kA m\(^{-1}\) for the ferromagnetic magnetite sample with the greatest heat generation [17][43]. Ferrofluids are evidently capable of appreciable heat generation within the safety constraints for \( H_0 \) and \( f \) and for reasonably small
sample sizes. Increasing the SAR of the ferrofluid is of particular interest when designing magnetic nanoparticle hyperthermia treatments [30], as this is an important factor in the production of significant heating while maintaining safe values of $H_0$ and $f$.

In this dissertation, calculations will only implicitly include material properties of the ferrofluid. They enter the calculations through inclusion of the $\chi''$ parameter. In order to determine an ideal ferrofluid for hyperthermic applications, it is important to have a viable model for ferrofluid heating in the magnetic field and frequency regime appropriate for hyperthermia. The ideal $\chi''$ parameter range found in these calculations may then be accurately related to these material properties for design of functional nanoparticles for hyperthermic cancer treatment.

Simple relaxation models for ferrofluids often outlined in the literature combine (2.8) with the assumption that the magnetization decays exponentially with relaxation time $\tau_R$ [42].

\[
\frac{\partial M(t)}{\partial \tau_R} = \frac{1}{\tau} (M_0(t) - M(t)) \tag{2.10}
\]

where $M_0$, given by

\[
M_0 = \chi_0 H_0 \cos(\omega t) = Re\chi_0 (H_0 e^{i\omega t}) \tag{2.11}
\]

is the equilibrium magnetization in the applied magnetic field of the form

\[
H(t) = H_0 \cos(\omega t) \tag{2.12}
\]

and
\[ M(t) = \text{Re}[\chi H_0 e^{i\omega t}] = H_0[\chi' \cos(\omega t) + \chi'' \sin(\omega t)] \]

Substituting (2.13) and (2.11) into equation (2.10) yields the following form for the imaginary susceptibility:

\[ \chi''(f) = \frac{\chi_0 2\pi f \tau_R}{1 + (2\pi f \tau_r)^2} \] (2.14)

This relation is useful for some materials and some input parameter values.

A rigorous theory for the dynamic susceptibility of magnetic fluids was presented by Shliomis and Stepanov [44] for a broad range of frequencies, including Ferromagnetic Resonance (FMR). Those models are based on the Landau - Lifshitz equation [45], and are restricted to the small amplitude Larmor precession regime and low damping. They are therefore not appropriate for describing hysteresis losses of interest for magnetic nanoparticle heating for hyperthermia [42].

\[ \frac{\partial M}{\partial t} = -\gamma M \times H_{\text{eff}} - \alpha \gamma \frac{M}{M} \times (M \times H_{\text{eff}}) \] (2.15)

One mechanism present in ferrofluid relaxation processes is the aforementioned Néel mechanism, where the giant magnetic moment of the nanoparticle rotates as it aligns with the applied magnetic field, and then attempts to realign to its easy axis orientation. The relaxation times found commonly in the current literature may be derived based on a simple magnetic two-level model [42]. According to Néel, it is given in terms of thermal activation across the energy barrier KV (where K is the anisotropy energy density) separating the two levels [46].
\[ \tau_N = \tau_0 e^{\frac{KV}{\kappa T}} \] (2.16)

For a derivation of the Néel relaxation time, based on the original 1949 derivation by Néel for the magnetic two-level model, see Appendix B.

The Brownian relaxation mechanism, due to re-orientation of particles in the fluid suspension of viscosity \( \eta \) is given by the relaxation time \( \tau_B \):

\[ \tau_B = \frac{\pi \eta d_h^3}{2kT} \] (2.17)

\( d_h \) is the hydrodynamic diameter, rather than the diameter of the magnetic core of a particle.

As can be seen in Figure 2.1 and Figure 2.1, Néel relaxation generally dominates at higher frequencies and smaller particle sizes and vice versa for Brownian relaxation [42].

<table>
<thead>
<tr>
<th>Ferrofluid Type</th>
<th>critical diameter (nm)</th>
<th>critical frequency (kHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maghemite and Water</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Maghemite and Ester Oil</td>
<td>24</td>
<td>0.1</td>
</tr>
<tr>
<td>Ba-Hexaferrite and Water</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Co-ferrite and Water</td>
<td>7</td>
<td>1 \cdot 10^4</td>
</tr>
<tr>
<td>Co-ferrite and Glycerin</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2.1: From Rosensweig 2002 [32], parameters separating Brown and Néel spectral regions.

Much of the current literature on hyperthermia states that for hyperthermia, the Brownian mechanism must dominate in order to produce significant
heating \[32\][42]. However, Brownian relaxation is actually of little relevance for hyperthermic applications, as mobility of magnetic particles is highly suppressed in biological tissue \[42\]. Therefore magnetic losses for hyperthermia applications are mainly due to Néel relaxation processes and magnetic hysteresis processes for multidomain particles.

The Néel relaxation model is appropriate for a certain range of particle sizes, field strengths, and frequencies. Additionally, there is a restriction on particle diameter for superparamagnetic relaxation. If in the absence of an applied magnetic field, the time used to measure the magnetization of the nanoparticle ensemble, \(\tau_M\), is much larger than the Néel relaxation time, \(\tau_N\), the average magnetization of the
nanoparticle system appears to be close to zero (i.e. the system has negligible magnetic coercivity, $H_C$). Then, the system is said to be superparamagnetic.

Figure 2.2 illustrates for a frequency of 400 kHz (an appropriate frequency for hyperthermia) the magnetic field strength and particle size regimes where the Néel relaxation models and superparamagnetic relaxation models apply, and the regime where quasi-stable magnetic hysteresis should be considered as part of the thermal model.

In this research, power deposition is calculated based on the linear model. This assumption is reasonable for design of ferrofluid hyperthermia treatments for brain cancer as only very small particles are able to cross the blood-brain-tumor-barrier ($\approx 12\text{nm}$ core size is the approximate upper limit on magnetic core size for crossing the blood-brain-tumor-barrier [12]). Additionally, as Brownian heating is not a consideration for magnetic fluid hyperthermia, heating does not depend on whether particles have an inter- or extra-cellular location [42]. Spatial distribution and diffusion of the nanoparticle ensemble does of course play a critical role in the determination of the heating pattern.

2.2 The Pennes Bioheat Equation

In 1948, Pennes developed an equation to model macroscopic heat transfer in perfused tissue [47][48]. Pennes’ equation was based on the Fourier equation (also known as the heat equation) for macroscopic heat transfer with internal heat generation and isotropic tissue thermal conductivity, $k$. The Fourier equation is given by:

$$\rho C \frac{\partial T}{\partial t} = k \nabla^2 T + h_{int} \quad (2.18)$$
Where $h_{int}$ is the internal heat generation rate per unit volume, and $\rho$ and $C$ are the density and specific heat of the conducting medium. Pennes based his equation on the following form of (2.18) for blood-perfused tissue with metabolic heat generation:

$$\rho C \frac{\partial T}{\partial t} = k \nabla^2 T + h_b + h_m$$

(2.19)

Where $h_b$ and $h_m$ are heat generation rate per unit volume for blood perfusion and metabolic heating, respectively, and $\rho$, $C$, and $k$ are the tissue density, specific heat, and thermal conductivity. The metabolic heating was assumed by Pennes to be homogeneous.

Pennes then suggested that the rate of heat transfer between blood and tissue is proportional to the product of the volumetric perfusion rate and the difference between the arterial blood temperature and the local tissue temperature [47][48] :

$$h_b = w \rho_b C_b (1 - \kappa)(T_a - T)$$

(2.20)

Where $\rho_b$ is the blood density, $C_b$ is the specific heat of blood, $w$ is the blood perfusion rate per unit volume, $T_a = \text{arterial blood temperature}$, and $T$ is the local tissue temperature [47]. $\kappa$ is a factor between 0 and 1 that accounts for the lack of thermal equilibrium between blood and tissue. Blood is assumed to enter the tissue volume at $T_a$ and then the heat transfer processes bring the blood to the temperature, $T$. Pennes set $\kappa = 0$ in his theoretical calculations, as do the majority of researchers today [48]. Pennes assumed that the blood perfusion effect is homogeneous and isotropic.

Combining (2.19) and (2.20), the Pennes Bioheat Equation (PBE) is:
\[ \rho C \frac{\partial T}{\partial t} = k \nabla^2 T + w \rho_b C_b (1 - \kappa) (T_a - T) + h_m \]

(2.21)

In the case of magnetic fluid hyperthermia, the Pennes equation may then be modified to include heat generation due to the heating of the ferrofluid in an AC magnetic field, \( h_F \). With the assumption that \( \kappa = 0 \), and the modification to include \( h_F \), we have:

\[ \rho C \frac{\partial T}{\partial t} = k \nabla^2 T + w \rho_b C_b (T_a - T) + h_m + h_F \]

(2.22)

The heating power that determines \( h_F \) can be approximated by (2.8), which is the result of Rosensweig’s derivation [32] for rotational relaxation of single domain magnetic particles dispersed in a fluid. (See Appendix E.) Further details specific to the calculation of \( h_F \) and the method used in this dissertation for solving equation (2.22) may be found in III.
Figure 2.2: From “Validity limits of the Néel relaxation model of magnetic nanoparticles for hyperthermia” by Hergt et al, 2010, Nanotechnology, Vol. 21, number1, p. 015706.3. Copyright 2002 by Elsevier. Reprinted with permission [32] [42], for magnetic particles of effective anisotropy of 10kJm$^{-3}$ and applied field frequency 400kHz, the graph gives critical particle diameter where linear theory ceases dependent on magnetic field amplitude.
3.1 Model

3.1.1 Overview

In this research, the program Semcad X [49] will be used to solve the PBE, for a model of the human head with a cancerous region with embedded magnetic nanoparticles using the Finite Difference Time Domain (FDTD) method.

Semcad uses the FDTD solver with volume mesh techniques applied to a 3D model in order to solve Maxwell’s equations in Partial Differential Equation (PDE) form in the region of interest. The electromagnetic results are then used in the thermal simulation to solve the PBE and determine the heating. For more information on the FDTD method, see Appendix F.

3.1.2 AC Magnetic Excitation Source

The current version of the model uses square Helmholtz coils to provide the AC magnetic field excitation. Square Helmholtz coils are capable of producing a magnetic field more uniform than the more commonly seen circular Helmholtz coils [50]. For calculation results demonstrating the field uniformity, see chapter IV.

3.1.3 Material Properties of Tissue Layers

In order to perform the calculation, the user must provide dielectric, magnetic and thermal properties of all materials, the excitation for the coils (for example, the current or voltage), the AC frequency, and specify a solver (such as the
\eta = .003
\rho_{\text{composite}} = (1 - \eta)\rho_{\text{tumor}} + \eta\rho_{\text{ferrofluid}}
\frac{1}{C_{\text{composite}}} = \frac{1 - \eta}{C_{\text{tumor}}} + \frac{\eta}{C_{\text{ferrofluid}}}
\frac{1}{K_{\text{composite}}} = \frac{1 - \eta}{K_{\text{tumor}}} + \frac{\eta}{K_{\text{ferrofluid}}}
\sigma_{\text{composite}} = (1 - \eta)\sigma_{\text{tumor}} + \eta\sigma_{\text{ferrofluid}}

Figure 3.1: Square Helmholtz coils and multi-tissue layer model of human head, including a central composite region of tumor tissue and magnetic nanoparticle Fluid. In both examples, the tumor/ferrofluid composite material properties were mean values of the material properties of the tumor tissue and magnetite nanoparticles, assuming homogeneity of the region. \eta = .003, where \eta is the volume fraction magnetite nanoparticles in the tumor region. 10mg of Fe per g of tumor corresponds to a volume fraction of \eta = .003. This is the typical dosage reported in clinical studies [22].

FDTD solver). Densities and thermal properties of all tissue layers (skin, skull, and grey matter) and perfusion rates of the skin and skull layers were those detailed by Duck [19] and are similar to those found in the current literature [55].

3.1.3.1 Dielectric Properties of Tissue Layers

Conductivities and permittivities for the tissues at the various frequencies were obtained using the publicly available program atsf.exe [56] and are listed in table 3.2:
Table 3.1: Tissue layer thicknesses used in these calculations. Values for the healthy tissue layer thicknesses were obtained from several sources in the literature for average adult male and female subjects and compiled in [51]. The scalp thickness was obtained by [52] for a location slightly above and behind the upper tip of the ear. The skull thickness was based on temporal bone measurements of 20 year old male and female adults by [53] and the diameter of the entire head was based on the data by [54]. The radius of the brain region was then determined by subtraction of the scalp and skull thicknesses from the head diameter. The tumor radius was based on the average size of a glioma when first detectable on enhanced CT at an average diameter of 3 cm [14].

<table>
<thead>
<tr>
<th>Tissue Layer Dimensions for the Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue name</td>
</tr>
<tr>
<td>Brain Tissue Layer Radius</td>
</tr>
<tr>
<td>Skull Layer Thickness</td>
</tr>
<tr>
<td>Scalp Layer Thickness</td>
</tr>
<tr>
<td>Tumor Radius</td>
</tr>
</tbody>
</table>

Table 3.2: Dielectric properties for the various tissue layers included in the model, excluding the tumor layer properties which are a composite value obtained from the dielectric properties of the tumor tissue and the ferrofluid. This is discussed in further detail in section 3.1.3.4.
3.1.3.2 Perfusion Rates

The range for perfusion rates for the tumor region were those found in the literature for various grades of astrocytomas [57]. The perfusion rates for grey matter and white matter were also found in [57]. Table 3.3 lists the ranges of perfusion rates used in these calculations.

<table>
<thead>
<tr>
<th>Tissue name</th>
<th>Perfusion Rate $ml\cdot min^{-1}\cdot kg^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey Matter</td>
<td>250 - 780</td>
</tr>
<tr>
<td>White Matter</td>
<td>80 - 330</td>
</tr>
<tr>
<td>Bone</td>
<td>30</td>
</tr>
<tr>
<td>Skin</td>
<td>120</td>
</tr>
<tr>
<td>Astrocytoma (Grade I)</td>
<td>30 - 430</td>
</tr>
<tr>
<td>Astrocytoma (Grade II)</td>
<td>30 - 1010</td>
</tr>
<tr>
<td>Astrocytoma (Grade III)</td>
<td>260 - 980</td>
</tr>
<tr>
<td>Astrocytoma (Grade IV)</td>
<td>150 - 1020</td>
</tr>
<tr>
<td>Brain Metastases</td>
<td>30 - 720</td>
</tr>
</tbody>
</table>

Table 3.3: Perfusion rates for the various tissue layers included in the model. The perfusion rates in the tumor and brain tissue are varied in the calculations in order to determine the effectiveness of hyperthermic cancer treatment for different test subjects, types of brain tumors, and stages of cancer.

3.1.3.3 Thermal Properties and Densities of Tissue Layers

<table>
<thead>
<tr>
<th>Thermal Properties and Densities of Tissue Layers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue name</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Grey Matter</td>
</tr>
<tr>
<td>White Matter</td>
</tr>
<tr>
<td>Skull</td>
</tr>
<tr>
<td>Skin</td>
</tr>
</tbody>
</table>

Table 3.4: Thermal properties of various tissue layers, where $c$ is the Specific Heat Capacity in $J\cdot kg^{-1}\cdot K^{-1}$, $k$ is the thermal conductivity in $W\cdot m^{-1}\cdot K^{-1}$, and $\rho$ is the density in $kg\cdot m^{-3}$.  

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3.1.3.4 Tumor/Ferrofluid Composite Region

We assume homogeneity within the target region. Mean value of specific heat $c$, density $\rho$, and electrical conductivity $\sigma$, for cancerous tissue with embedded nanoparticles can be approximated by a serial arrangement of the two materials with the two volume proportions:

\begin{align*}
\nu &= .003 \\
\rho_{\text{composite}} &= (1 - \nu)\rho_{\text{tumor}} + \nu\rho_{\text{ferrofluid}} \\
c_{\text{composite}} &= (1 - \nu)c_{\text{tumor}} + \nu c_{\text{ferrofluid}} \\
\frac{1}{k_{\text{composite}}} &= \frac{1 - \nu}{k_{\text{tumor}}} + \frac{\nu}{k_{\text{ferrofluid}}}
\end{align*}

The tumor and ferrofluid material properties that are used in order to determine the composite values for the calculation are given in the following table, where a concentration of $\eta = .003$ is assumed in order to determine the composite value shown in the table:

| Material Properties for the Tumor/Ferrofluid Composite Region |
|---------------------------------|-----|------|--------|-----------------|
| Tissue name                     | $c$  | $k$  | $\rho$ | $\sigma$ (@500 kHz for example) |
| Tumor Tissue                    | 3500 | .55  | 1060.  | 0.15187         |
| Magnetic Nanoparticles          | 4000 | 40   | 5180.  | .15187          |
| Composite Region                | 3501.5 | .552 | 1072.36| 0.15187         |

Table 3.5: Material properties of various tissue layers, where again, $c$ is the Specific Heat Capacity in $J \cdot kg^{-1} \cdot K^{-1}$, $k$ is the thermal conductivity in $W \cdot m^{-1} \cdot K^{-1}$, $\rho$ is the density in $kg \cdot m^{-3}$, and $\sigma$ is the electrical conductivity in S/m. Thermal properties for the tumor tissue were obtained from [58][59][60], the density was obtained from [61] (tumor tissue is generally more dense than healthy tissue [61]) and the thermal properties and densities for magnetic nanoparticles were obtained from [62]. The permittivity and conductivity of the composite region is assumed to be the same as that of the surrounding grey matter as the concentration is low enough that the difference between the tumor tissue alone and tissue embedded with nanoparticles is negligible with respect to the dielectric constants (see section 2.1.3).
The imaginary magnetic susceptibility, $\chi''$ used in the calculations was based on values found in the literature which would be observed for magnetite or maghemite nanoparticle materials at a given frequency [43][30][63]. The values were obtained by averaging the value for ferrofluid solutions (the upper bound because more heating occurs when the Brownian relaxation mechanism is present) and the value for immobilized nanoparticles (the lower bound, where only hysteresis or the Néel mechanism give rise to heating). So then, for example at 500 kHz, the value used for $\chi''$ in SI units is $\chi'' = 10$. These are values that would typically be observed for nanoparticle concentrations currently preferred for clinical use ($\eta = .003$ [22]). Higher susceptibilities would be seen for similar ferrofluids with higher concentrations of nanoparticles (but too large a concentration may be toxic) or different magnetic materials (such as bacterial magnetosomes [63][30][42]). The magnetic susceptibility enters the calculation in terms of the magnetic conductivity (see Appendix F).

The model geometry, i.e. the positioning of the tumor region within the brain, was also varied in the calculations. The particular geometry and value used for $\chi''$ are indicated for a particular set of results in chapter V.

### 3.1.4 Boundary Values and Initial Values

The initial value for the tissue layers is set to 37$^\circ$ C

<table>
<thead>
<tr>
<th>Boundary Values</th>
<th>25$^\circ$C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature of the Surrounding Medium (Air)</td>
<td>25$^\circ$C</td>
</tr>
<tr>
<td>Heat transfer rate at scalp/background (air) boundary</td>
<td>5 W/m$^2$/K</td>
</tr>
<tr>
<td>Heat Flux</td>
<td>W/m$^2$</td>
</tr>
</tbody>
</table>

Table 3.6: Boundary values for the boundary layer (scalp).
4.1 Benchmarking Calculations

4.1.1 Magnetic Field Uniformity

Calculations were first performed in order to verify uniformity of the magnetic and electric field due to the square Helmholtz coils.

Figure 4.1: Square Helmholtz coils and central region with vacuum material properties. For the majority of the benchmarking calculations the alternating current in the coils is 200 Amps, which leads to a maximum applied field of $H = 447 \text{ A/m}$. Similar results for larger field strengths (10kA/m) are also shown.
Figure 4.2: Contour plot for $\text{RMS}|H|$ at 30 kHz and a maximum applied field magnitude of 447A/m, in order to illustrate field uniformity in the x-y plane in a central slice (see inset model diagram for coordinate system).

Figure 4.3: Above is shown $\text{RMS}|H|$ at 30 kHz and a maximum applied field magnitude of 447A/m along the x axis (see inset model diagram for coordinate system) at $y = 0, z = 0$ (blue line) and $y = 185$ mm, $z = 0$ (green line). It can be seen that $\text{RMS} - H -$ is uniform within 7% at 185mm from the origin along the y axis.
Figure 4.4: Contour plot for RMS$|H|$ at 100 kHz and a maximum applied field magnitude of 447A/m, in order to illustrate field uniformity in the x-y plane in a central slice.

Figure 4.5: Above is shown RMS$|H|$ at 100 kHz and a maximum applied field magnitude of 447A/m along the x axis at y = 0, z = 0 (blue line) and y = 185 mm, z = 0 (green line). It can be seen that RMS$—H—$ is uniform within 7% at 185mm from the origin along the y axis.
Figure 4.6: Contour plot for RMS$|H|$ at 1 MHz and a maximum applied field magnitude of 447 A/m, in order to illustrate field uniformity in the x-y plane in a central slice.

Figure 4.7: Above is shown RMS$|H|$ at 1 MHz and a maximum applied field magnitude of 447 A/m along the x axis at y = 0, z = 0 (blue line) and y = 185 mm, z = 0 (green line). It can be seen that RMS$|H|$ is uniform within 7% at 185 mm from the origin along the y axis.
Figure 4.8: Contour plot for RMS$|H|$ at 3 MHz and a maximum applied field magnitude of 447A/m, in order to illustrate field uniformity in the x-y plane in a central slice.

Figure 4.9: Above is shown RMS$|H|$ at 3 MHz and a maximum applied field magnitude of 447A/m along the x axis at $y = 0, z = 0$ (blue line) and $y = 185$ mm, $z = 0$ (green line). It can be seen that RMS$|H|$ is uniform within 7 % at 185mm from the origin along the y axis.
Figure 4.10: Contour plot for RMS$|H|$ at 1 MHz and a maximum applied field magnitude of 10 kA/m, in order to illustrate field uniformity in the x-y plane in a central slice.

Figure 4.11: Above is shown RMS$|H|$ at 1 MHz and a maximum applied field magnitude of 10 kA/m along the x axis at $y = 0$, $z = 0$ (blue line) and $y = 185$ mm, $z = 0$ (green line). It can be seen that RMS—$H$— is uniform within 10 % at 185mm from the origin along the y axis.
Figure 4.12: RMS|E| for 100 kHz for the square Helmholtz coils with and without loading of a dielectric sphere (the dielectric is water in this case). A slight decrease in RMS—E— field amplitude is seen in the region of interest. RMS—E— remains uniform in the region of interest. Similar results were obtained for frequencies between 100 kHz and 3 MHz.

Figure 4.13: RMS|E| for 1 MHz for the square Helmholtz coils with and without loading of a dielectric sphere (the dielectric is water in this case).
Figure 4.14: RMS|E| for 3 MHz for the square Helmholtz coils with and without loading of a dielectric sphere (the dielectric is water in this case).

Figure 4.15: Power factor vs. frequency results for loaded (water) versus unloaded (water) for square Helmholtz coils is shown in order to demonstrate the contribution of the “loading effect” in the frequency regime of interest for ferrofluid hyperthermia.
4.1.2 Conclusions

From the data contained in this section, it can be seen that the applied field is quite uniform within the region of interest for the field strengths and frequencies of use for magnetic fluid hyperthermia. Additionally, the loading effect is reasonably minimal within the region of interest so as not to produce artifacts within the results. This is important because the applied field in these calculations is meant to be a source of excitation for the tissue/ferrofluid system, rather than a source of investigation in its own right.
CHAPTER V

RESULTS

5.1 Results for Asymmetric Model Geometry: Tumor Location Near Brain Periphery

5.1.1 Overview

In the following calculations, the initial tissue temperature is set to 37°C for all tissue layers. Then, at 1800 seconds, the alternating magnetic field is applied until 6000s, after a steady state has been reached for the temperature.

![Asymmetric Model Image]

Figure 5.1: Asymmetric Model: The tumor/ferrofluid composite region is located close to the skull region, on the periphery of the brain tissue.

5.1.2 The Applied Magnetic Field Frequency Parameter and Its Effect on the Steady State Temperature

Calculations were performed for the field amplitude of 10kA/m, which is near the largest safe value for the applied magnetic field strength. At $f = 500$kHz, the product of $H_0 \cdot f < 5 \cdot 10^9$ Am$^{-1}$s$^{-1}$ is the extreme upper limit for safety, as it is an order of magnitude larger than the values deemed safe and comfortable in the
study by Brezovich et al [25]. \(H_0 \cdot f\) is less than \(4.85 \cdot 10^8\) Am\(^{-1}\)s\(^{-1}\). This restriction limits tissue heating power and may be relaxed depending on the diameter of the region being treated and the severity of the illness. We assume a weaker criterion \(H_0 \cdot f < 5 \cdot 10^9\) Am\(^{-1}\)s\(^{-1}\) in our calculations [25][26]. The goal of the calculations is to produce a steady state temperature between 41°C and 45°C (apoptotic heating) for the entire tumor region, including the edges, and to avoid overheating the surrounding healthy tissue.

![Temperature vs time for Center of Tumor region](image.png)

Figure 5.2: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for two different frequencies which are typical for ferrofluid hyperthermia, the lowest perfusion rate, and the largest field amplitude allowed by the restriction for patient comfort and safety. Here the perfusion rate is 30 ml/min/kg and the applied field amplitude is 10kA/m. Based on the steady state temperature in the calculations, heating in the apoptotic range occurs for \(f = 500\) kHz, but not for 200kHz. A 5.5 degree increase in temperature is seen for a 1.5-fold increase in frequency.

Thus, it is determined that for 500 kHz, 10 kA/m, and a low perfusion rate, the entire tumor of the given geometry is heated to temperatures in the apoptotic heating range.
Figure 5.3: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for two different frequencies which are typical for ferrofluid hyperthermia, the lowest perfusion rate, and the largest field amplitude allowed by the restriction for patient comfort and safety. Here the perfusion rate is 30 ml/min/kg and the applied field amplitude is 10kA/m. Based on the steady state temperature in the calculations, heating of the tumor edges in the apoptotic range occurs for \( f = 500 \text{ kHz} \), but not for 200kHz. A 3.7 degree increase in temperature is seen for a 1.5-fold increase in frequency.
Figure 5.4: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for two different frequencies which are typical for ferrofluid hyperthermia, the lowest perfusion rate, and the largest field amplitude allowed by the restriction for patient comfort and safety. Here the perfusion rate is 497.882 ml/min/kg and the applied field amplitude is 10kA/m. Based on the steady state temperature in the calculations, heating does not reach the apoptotic range for either frequency. A 1.25 degree increase is seen for a 1.5-fold increase in frequency.
Figure 5.5: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for two different frequencies which are typical for ferrofluid hyperthermia, the lowest perfusion rate, and the largest field amplitude allowed by the restriction for patient comfort and safety. Here the perfusion rate is 497.882 ml/min/kg and the applied field amplitude is 10kA/m. Based on the steady state temperature in the calculations, heating does not reach the apoptotic range for either frequency. A 1.2 degree increase in temperature is seen for a 1.5-fold increase in frequency.
5.1.3 The Applied Magnetic Field Amplitude Parameter and Its Effect on the Steady State Temperature

Figure 5.6: Explicit temperature versus time calculations for temperature sensors placed in the center of the tumor region. Calculations here were performed for $f = 500\,\text{kHz}$ and various applied magnetic field amplitudes. Here the perfusion rate is 497.882 ml/min/kg, the same as the surrounding healthy brain tissue. Based on the steady state temperature in the calculations, heating in the apoptotic range occurs for applied field amplitudes at or above 15 kA/m.

Based on the calculations for various applied field strengths and a perfusion rate of 497.882 ml/min/kg, apoptotic heating does not occur for field strengths within the safe range for the product $H_0 \cdot f$. 

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Figure 5.7: Explicit temperature versus time calculations for temperature sensors placed on the edge of the tumor region. Calculations here were performed for $f = 500\text{kHz}$ and various applied magnetic field amplitudes. Here the perfusion rate is $497.882 \text{ ml/min/kg}$, the same as the surrounding healthy brain tissue. Based on the steady state temperature in the calculations, heating in the apoptotic range occurs only for applied field amplitudes above $15 \text{kA/m}$. 

Temperature vs time for the Edge of Tumor Region

- $f = 500\text{kHz}$
- $T(t)$: /Thermo: $H=15\text{kA/m}$ $f=500\text{kHz}$ perfusion $= 497.882\text{ml/min/kg}$ Thermo Point Sensor 1
- $T(t)$: /Thermo: $H=10\text{kA/m}$ $f=500\text{kHz}$ perfusion $= 497.882\text{ml/min/kg}$ Thermo Point Sensor 1
- $T(t)$: /Thermo: $H=5\text{kA/m}$ $f=500\text{kHz}$ perfusion $= 497.882\text{ml/min/kg}$ Thermo Point Sensor 1

![Graph showing temperature vs time for various field amplitudes](image-url)
Figure 5.8: Graph of applied field strength versus the maximum steady state temperature. The expected quadratic dependence on the applied field strength is found, as expected. Thus the sensitivity of the steady state temperature calculation to the applied field strength, approximated by $\frac{\partial T}{\partial H_0}$ is given by 0.02892$H_0$ for the particular regime (note that $f$ is set to 500kHz and the perfusion is set to 497.882 ml/min/kg.) This then leads to, for comparison to the frequency sensitivity calculations, a 1.9 degree change in steady - state temperature for a 1.5 - fold change in the applied field if the initial field strength is 5 kA/m. If the field is increased 1.5 - fold from 6 kA/m, the change in the steady-state temperature is 2.75 degrees.
5.1.4 The Perfusion Rate Parameter and Its Effect on the Steady State Temperature

![Diagram](image.png)

Figure 5.9: Variation of tumor perfusion rates: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for \( f = 500\,\text{kHz} \), an applied field strength of 10kA/m, and various tumor perfusion rates. Apoptotic heating occurs for the given field strength and frequency for tumor perfusion rates at 200 ml/min/kg or below and a healthy brain tissue perfusion rate of 497.882 (an average value for healthy brain tissue).

Based on the slopes of the temperature-perfusion rate curves in figure 5.13, the steady state temperature (both at the center of the tumor and on the tumor/brain tissue border) is more sensitive to the tumor tissue perfusion rate than the surrounding brain tissue perfusion rate. If the curves in 5.13 for temperature versus tumor perfusion rate are approximated as exponentially decreasing, then in the regime of interest a 1.5-fold increase in the tumor perfusion rate leads to a 2 degree decrease in the steady-state temperature for the center of the tumor region and a 1 degree decrease in the steady state temperature for the edge of the tumor region. For a 1.5-fold increase in the brain tissue perfusion rate, there is only .8 degree decrease in the steady-state temperature for the center of the tumor region and a .4 degree decrease in the steady state temperature for the edge of the tumor region.
Figure 5.10: Variation of tumor perfusion rates: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for $f = 500\text{kHz}$, an applied field strength of 10kA/m, and various tumor perfusion rates. Near-apoptotic heating occurs for the given field strength and frequency for tumor perfusion rates at 200 ml/min/kg or below and a healthy brain tissue perfusion rate of 497.882 (an average value for healthy brain tissue).

Figure 5.11: Variation of brain tissue perfusion rates: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for $f = 500\text{kHz}$, an applied field strength of 10kA/m, and various tumor perfusion rates. Near-apoptotic heating occurs for the given field strength and frequency for brain tissue perfusion rates at 80 ml/min/kg or below and a tumor tissue perfusion rate of 497.882 (an average value for healthy brain tissue).
Figure 5.12: Variation of brain tissue perfusion rates: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for $f = 500$ kHz, an applied field strength of $10$ kA/m, and various tumor perfusion rates. Near-apoptotic heating occurs for the given field strength and frequency for brain tissue perfusion rates at $80$ ml/min/kg or below and a tumor tissue perfusion rate of $497.882$ (an average value for healthy brain tissue).

Figure 5.13: Perfusion rates for tumor tissue and healthy tumor tissue values versus the steady state temperature value in the center and at the edge of the tumor region.
Figure 5.14: Contour plot for the asymmetrical model geometry for an applied field strength of 10kA/m and frequency of 500 kHz (slice is taken through the center of the tumor region, where $z = 0$). It can be seen that the tumor tissue is thoroughly heated to the apoptotic regime, while the surrounding healthy tissue remains below this range and is thus preserved.
5.2 Results for Symmetric Model Geometry: Deep-Seated Tumor Location

5.2.1 Overview

Calculations were performed in order to determine the effect of variation in model geometry on the temperature profile of the tissue layers. The following results are for the symmetrical model seen in 5.15, with the tumor in the central location. This model, in addition to demonstrating the effects of variation in model geometry for the system, represents the case of a deep-seated tumor. This is important because treatment of these tumors is extremely challenging and magnetic fluid hyperthermic treatments should be designed as a viable alternative to more traditional treatments for this type of cancer.

![Figure 5.15: Symmetric Model: The tumor/ferrofluid composite region is centrally located.](image)

5.2.2 The Applied Magnetic Field Amplitude Parameter and Its Effect on the Steady State Temperature
Figure 5.16: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for $f = 500\text{kHz}$ and various applied magnetic field amplitudes. Here the perfusion rate is $497.882 \text{ ml/min/kg}$, the same as the surrounding healthy brain tissue. Based on the steady state temperature in the calculations, heating in the apoptotic range occurs for applied field amplitudes at a value above $10 \text{ kA/m}$. The temperature values are quite similar to 5.6. A 0.85 degree increase in temperature is seen for a 1.54-fold increase in field amplitude.
Figure 5.17: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for $f = 500\text{kHz}$ and various applied magnetic field amplitudes. Here the perfusion rate is $497.882\text{ ml/min/kg}$, the same as the surrounding healthy brain tissue. Based on the steady state temperature in the calculations, heating in the apoptotic range occurs for applied field amplitudes at a value above $10\text{ kA/m}$. The temperature values are quite similar to 5.7. A 0.8 degree increase in temperature is seen for a 1.54-fold increase in field amplitude.
5.2.3 The Perfusion Rate Parameter and Its Effect on the Steady State Temperature

Figure 5.18: Variation of tumor perfusion rates: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for $f = 500\, \text{kHz}$, an applied field strength of $10\, \text{kA/m}$, and two different extreme values for tumor perfusion rates. Apoptotic heating occurs for the given field strength and frequency for a tumor perfusion rate of $30\, \text{ml/min/kg}$ or below and a healthy brain tissue perfusion rate of $497.882$ (an average value for healthy brain tissue).

Based on the slopes of the temperature-perfusion rate curves in figure 5.22, the steady state temperature (at the center of the tumor and on the tumor/brain tissue border) is more sensitive to the tumor tissue perfusion rate than the surrounding brain tissue perfusion rate. If the curves for temperature versus tumor perfusion rate in 5.22 are approximated as exponentially decreasing, then in the regime of interest a 1.5-fold increase in the tumor perfusion rate leads to a 2 degree decrease in the steady-state temperature for the center of the tumor region and a 1.4 degree decrease in the steady state temperature for the edge of the tumor region. For a 1.5-fold increase in the brain tissue perfusion rate, there is only a .9 degree decrease in the steady-state temperature for the center of the tumor region and .6 degree decrease in the steady state temperature for the edge of the tumor region.
Figure 5.19: Variation of tumor perfusion rates: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for \( f = 500 \text{kHz} \), an applied field strength of 10kA/m, and two different extreme values for tumor perfusion rates. Apoptotic heating occurs for the given field strength and frequency for a tumor perfusion rate of 30 ml/min/kg or below and a healthy brain tissue perfusion rate of 497.882 (an average value for healthy brain tissue).

Figure 5.20: Variation of brain tissue perfusion rates: Explicit temperature versus time calculations for the center of the tumor region. Calculations here were performed for \( f = 500 \text{kHz} \), an applied field strength of 10kA/m, and various tumor perfusion rates. Near-apoptotic heating occurs for the given field strength and frequency for brain tissue perfusion rates at 80 ml/min/kg or below and a tumor tissue perfusion rate of 497.882 (an average value for healthy brain tissue).
Figure 5.21: Variation of brain tissue perfusion rates: Explicit temperature versus time calculations for the edge of the tumor region. Calculations here were performed for $f = 500$ kHz, an applied field strength of 10 kA/m, and various tumor perfusion rates. Near-apoptotic heating occurs for the given field strength and frequency for brain tissue perfusion rates at 80 ml/min/kg or below and a tumor tissue perfusion rate of 497.882 (an average value for healthy brain tissue).

Figure 5.22: Perfusion rates for tumor tissue and healthy tumor tissue values versus the steady state temperature value in the center and at the edge of the tumor region.
Figure 5.23: Contour plot for the symmetrical model geometry for an applied field strength of 10kA/m, frequency of 500 kHz (slice is taken through the center of the tumor region, where z = 0), and perfusion of 30 ml/min/kg. It can be seen that the tumor tissue is thoroughly heated to the apoptotic regime, while the surrounding healthy tissue is on the lower bound of this range. It can be seen that the temperature profile is slightly elevated for this model geometry when compared to the asymmetrical model shown in the previous section. Thus, for a more centrally located tumor, and a very low perfusion rate, the applied field frequency or amplitude should be decreased.
Thus, based on these calculations, it appears that the steady state temperature has a square dependence on the applied field frequency parameter (this is due to the frequency dependence of the imaginary susceptibility parameter - if this parameter was fixed for all frequencies, the steady state temperature would go up linearly with frequency). The steady state temperature increases proportionally to the square of the applied field, and displays exponential sensitivity to the tumor blood perfusion rate.
6.1 Conclusions

It was shown that for $f = 500\text{kHz}$, $H_0 = 10\text{kA/m}$, low tumor perfusion rates (below 200 ml/min/kg), average rates of blood perfusion for the other tissue layers (497.882 ml/min/kg for the brain tissue layer, 120 ml/min/kg for the skin tissue layer, and 30 ml/min/kg for the skull layer) or lower, for two different tumor locations (one deep-seated, and one near the brain periphery) tumor tissue is heated to the apoptotic regime ($41^\circ\text{C}$ and $45^\circ\text{C}$). It was also demonstrated that for the same field amplitude and frequency, lower healthy brain tissue perfusion rates (80 ml/min/kg), tumor tissue perfusion rates set to the value which would be average for healthy brain tissue (497.882 ml/min/kg – with 120 ml/min/kg for the skin tissue layer, and 30 ml/min/kg for the skull layer) that tumor temperatures reach near apoptotic temperatures (see section 5.1.4 and 5.2.3). Then, it may be inferred for tumor temperatures slightly below 497.882 ml/min/kg and healthy brain tissue perfusion rates on the low side of normal (below 80 ml/min/kg), that the tumor would be heated to apoptotic temperatures. This heating occurs for $H_0 \cdot f < 5 \cdot 10^9 \text{Am}^{-1}\text{s}^{-1}$, the upper limit having been imposed as a safety restriction. Additionally, this is for the nanoparticle volume fraction of .003 corresponding to 10mg of Fe per gram of tumor, the value preferred for safe clinical use [22]. The complex permittivity of the ferrofluid/tumor composite, and therefore the heating depends, on the concentration of nanoparticles.

It is then concluded, based on the models used in this research, that for tumor tissue perfusion rates and/or brain tissue perfusion rates which are low, that
magnetic nanoparticle hyperthermic therapy is able to thoroughly heat a tumor region of diameter 3cm to steady-state temperatures which lead to apoptotic cell death. Additionally, for these parameter values, the tumor border is also heated to apoptotic temperatures. However, for larger values of tumor/healthy tissue perfusion rates, even for field strengths and frequencies above the regime deemed safe, apoptotic heating is not achieved for nanoparticle volume fractions deemed to be safe. However, temperatures for these parameter values are large enough to possibly amplify the effects of chemotherapy drugs (see table 1.1 and figure 1.3).

The following recommendations are then made for clinical trials: Blood perfusion rates for both healthy brain tissue and cancerous tissue should be obtained before treatment. Given that either perfusion rates is low, or that both are simultaneously moderate to low, magnetic nanoparticle hyperthermia alone may be deemed an appropriate treatment, capable of safely achieving apoptotic cell death for the entire volume of a tumor of the size seen in this study or smaller. Given that the perfusion rates of either the normal brain tissue or the tumor tissue are larger, or both are simultaneously moderate to high, magnetic nanoparticle hyperthermia may be effective when used in tandem with chemotherapy drugs.

Whether magnetic nanoparticle hyperthermia is used alone, or as an adjuvant to chemotherapy or radiotherapy, the volume fraction of .003 corresponding to 10mg of Fe per gram of tumor typically seen in clinical trials may be used. Applied field strengths between 6.5 kA/m and 10 kA/m and frequencies between 200 MHz and 500 MHz should be used. The field strengths and frequencies may be increased or decreased depending on the size of the tumor or the given perfusion rates.

Additionally, the future development of biocompatible magnetic nanoparticle materials with higher values for imaginary susceptibilities would make magnetic nanoparticle hyperthermia alone (rather than as a chemotherapy adjuvant) appropriate for average or larger tumor tissue and/or brain tissue perfusion rates.
An example of such a material would be a synthetic magnetic nanomaterial with a narrow size distribution, such as is seen in materials produced by bacterial magnetosomes [63][42].
CHAPTER VII

FUTURE WORK

7.1 Calculations

7.1.1 Rigorous Parameter Sensitivity Studies

In order to very precisely design treatment protocols based on measured values of blood perfusion rates for each patient, it is important to perform a rigorous parameter sensitivity study. These calculations may be done, for example, using a program such as Matlab for distributed computing, in order to optimize the parameter values in the PBE.

7.1.2 Multiscale Models

A realistic model which would include the properties of the magnetic material at the nanoscale, the cell properties and vasculature at the mesoscale, and the macroscopic thermal transport properties, and a realistic geometry for the boundary layers (especially the tumor/ferrofluid composite region boundary) is also an important component in designing ferrofluid hyperthermia treatments with extreme precision. Calculations of this type are quite expensive and may also be performed with the aid of distributed computing.

7.2 Experimental

7.2.1 Novel Materials

Novel materials tailored for use in magnetic nanoparticle hyperthermia may also be developed with the aid of optimized multiscale calculations. In order to use
lower field strengths and frequencies, or to apply ferrofluid hyperthermia as a stand-alone treatment in subjects with normal or higher blood perfusion rates, materials with larger imaginary susceptibilities in the frequency range of use for hyperthermia should be developed. Bacterial magnetosomes produce magnetic nanoparticle materials with extremely large imaginary susceptibilities in the regime of interest for hyperthermia. This is due, in part, to the narrow size distribution of nanoparticles produced [63]. However, these materials may not be biocompatible for use in the brain [63]. Synthetic ferrofluids may be produced with similar features with the aid of optimized multiscale models of these materials.
LIST OF REFERENCES


APPENDIX A

POWER LOSSES DUE TO INDUCTION FOR AN ENSEMBLE OF NANO-SIZED CONDUCTING SPHERES
A.1 Power Dissipation in a Conducting Material Due to an Applied Field

The power dissipation due to magnetic induction can be found through the use of the Magneto-Quasistatic (MQS) form of Maxwell’s equations given by [33][64]:

\[
\nabla \times \mathbf{H} \approx \mathbf{J} = \sigma \mathbf{E}
\]

\[
\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} = -\mu \frac{\partial \mathbf{H}}{\partial t}
\]

\[
\nabla \cdot \mathbf{B} = 0
\]

(A.1)

Where \( \mu \) and \( \sigma \) are the permeability and conductivity of the material, and \( \mathbf{J} \) is the current density. \( \mu \) and \( \sigma \) are both assumed to be constant.

The time-averaged power deposition per unit volume \( dV \) is given by

\[
\langle P \rangle dV = \langle \mathbf{J} \cdot \mathbf{E} \rangle ; \quad [33][64], \text{ so:}
\]

\[
\langle P \rangle = \frac{1}{2} Re \left\{ \int (\mathbf{E} \cdot \mathbf{J}^*) dV \right\}
\]

(A.3)

We must find \( \mathbf{E} \) and \( \mathbf{J} \) in order to solve for the power dissipated due to induction.

In terms of the magnetic vector potential \( \mathbf{A} \),

\[
\mathbf{E} = -\frac{\partial \mathbf{A}}{\partial t}
\]

(A.4)

With Ohm’s law (for an isotropic medium), Faraday’s law (A.1) and (A.6) can be written as:

\[
\nabla \times \mathbf{J} = -\sigma \frac{\partial \mathbf{B}}{\partial t}
\]

\[
\mathbf{J} = -\sigma \frac{\partial \mathbf{A}}{\partial t}
\]

(A.5)

Then, in finding the magnetic vector potential \( \mathbf{A} \) and the current density \( \mathbf{J} \) we can solve for the power dissipated due to eddy currents for a single sphere, and
then extend that solution to an ensemble of nano-sized spheres, in order to demonstrate that this power deposition is minimal in comparison to the power dissipated via magnetic losses.

(The following is largely based on the Smythe [31] derivation for an electrically conducting sphere in a magnetic field, which varies sinusoidally in time, but is spatially uniform.)

The current flowing in the conducting material produces a magnetic field (and vector potential) given by:

\[
\nabla \times \mathbf{B} = \mu \mathbf{J} \quad (A.6)
\]
\[
\nabla^2 \mathbf{A} = -\mu \mathbf{J} \quad (A.7)
\]

Taking the time derivative of \( \mathbf{B} \), given in (A.4), and from (A.5) and Gauss’ Law, which gives \( \nabla \cdot \mathbf{J} = 0 \),

\[
\sigma \mu \frac{\partial \mathbf{J}}{\partial t} = -[\nabla \times (\nabla \times \mathbf{J})] = \nabla^2 \mathbf{J} \quad (A.8)
\]

Similarly,

\[
\sigma \mu \frac{\partial \mathbf{A}}{\partial t} = -[\nabla \times (\nabla \times \mathbf{A})] = \nabla^2 \mathbf{A} \quad (A.9)
\]

\[
\sigma \mu \frac{\partial \mathbf{B}}{\partial t} = -[\nabla \times (\nabla \times \mathbf{B})] = \nabla^2 \mathbf{B} \quad (A.10)
\]

(A.8), (A.9), and (A.10) are the diffusion equations for \( \mathbf{J} \), \( \mathbf{A} \), and \( \mathbf{B} \). We seek the steady-state solution to (A.9) for a spherical conductor with
conductivity $\sigma$, permeability, $\mu$, and radius $R$, in a spatially uniform (in the $z$-direction) alternating magnetic field, $B e^{i\omega t}$, with boundary conditions such that $A$ remains finite as the radius $r$ goes to zero, and $A$ approaches zero as the radius $r$ approaches infinity.

Since we have that the magnetic field producing the eddy currents in this case is uniform, and our material is spherical, we have axial symmetry and can assume that the field $B$ has no $\phi$ component (where $\hat{\phi} = -\hat{i}\sin(\phi) + \hat{j}\cos(\phi)$. The vector potential then only has a $\phi$ component and can be written:

$$A = A_\phi(r, \theta, t) \hat{\phi}$$

(A.11)

Then, from (A.9), taking the Laplacian of (A.11),

$$\mu \sigma \frac{\partial A_\phi}{\partial t} = \nabla^2 A = (\nabla^2 A_\phi + A_\phi \nabla^2) \hat{\phi}$$

(A.12)

then, letting $u = \cos(\theta)$

$$\mu \sigma \frac{\partial A_\phi}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial A_\phi}{\partial r} \right) + \frac{(1 - u^2)^{1/2}}{r^2} \frac{\partial^2 [(1 - u^2)^{1/2} A_\phi]}{\partial u^2}$$

(A.13)

Solutions to Laplace’s equation for $A_\phi$ (A.13), with steady state eddy currents and external excitation from a uniform magnetic field of frequency $\omega$ are of the form $A_\phi(r, \theta) = \text{Re}[\Theta r^{-1/2} e^{i\omega t}]$. Putting $A(r, \theta)$ into (A.13) and using the separation of variables technique [31][64][65], we have:

$$(1 - u^2) \frac{\partial^2 \Theta_n}{\partial u^2} - 2u \frac{\partial \Theta_n}{\partial u} - \frac{\Theta_n}{1 - u^2} + n(n + 1) \Theta_n = 0$$

(A.14)
\[ \frac{\partial^2 R_n}{\partial r^2} + \frac{1}{r} \frac{\partial R_n}{\partial r} - \left[ ip + \frac{n(n + 1) + \frac{1}{4}}{r^2} \right] R_n \]  

(A.15)

Where \( p = \sigma \mu \omega = \frac{2}{\delta^2} \), and \( \delta = \sqrt{\frac{2}{\sigma \mu \omega}} \equiv \) the skin depth of the conductor [31]. (A.14) has solutions given by the associated Legendre functions of the first kind [65]:

\[ \Theta(\theta) = P_1^n(u^2 - 1)^{\frac{1}{2}} \frac{d P_n(u)}{du} \]
\[ \Theta(\theta) = Q_1^n(u^2 - 1)^{\frac{1}{2}} \frac{d Q_n(u)}{du} \]  

(A.16)

and (A.15) has solutions which are the modified Bessel functions with argument \( x \), where \( x = \sqrt{ipr} \). Then \( A_\phi \) is:

\[ \text{Re} \left[ r^{-\frac{1}{2}} [C_n P_n^1(u) + D_n Q_n^1(u)] \left\{ E_n I_{n+\frac{1}{2}}(\sqrt{ipr}) + F_n K_{n+\frac{1}{2}}(\sqrt{ipr}) \right\} e^{i\omega t} \right] \]  

(A.17)

In regions where the conductivity is zero, the solutions to (A.13) are given by:

\[ R' = Ar^n + Br^{-n-1} \]  

(A.18)

For a conducting sphere in a uniform (in the z-direction) alternating magnetic field, \( B e^{i\omega t} \), with conductivity \( \sigma \), permeability, \( \mu \), and radius \( R \), the solution to (A.13) is given by:

\[ A = \frac{Br \sin(\theta)}{2} \hat{\phi} = \frac{Br P_1^1 \cos(\theta)}{2} \hat{\phi} \]  

(A.19)

Therefore, all terms in (A.18) and (A.17) except \( n = 1 \) vanish, and the magnetic vector potential must vanish at infinity and remain finite inside the sphere, so from (A.17):
\( \mathbf{A}_{\text{out}} = \frac{1}{2} B(r + Fr^{-2}) \sin(\theta) \hat{\phi} \quad R < r < \infty \) 
(A.20)

\( \mathbf{A}_{\text{in}} = \frac{1}{2} BEr^{-\frac{3}{2}} I_{3/2} \left[ \sqrt{i\rho r} \sin(\theta) \right] \hat{\phi} \quad 0 < r < R \) 
(A.21)

Applying the boundary conditions at \( r = a \) (Continuity of \( \mathbf{A} \) at the boundary and Neumann boundary condition),

\[ A_{\text{out}} = A_{\text{in}} \quad (A.22) \]

\[ \mu_0 \frac{\partial}{\partial r} (r \sin(\theta) A_{\text{in}}) = \mu \frac{\partial}{\partial r} (r \sin(\theta) A_{\text{out}}) \quad (A.23) \]

gives:

\[ E = \frac{3\mu_0 R^2 \xi}{(\mu - \mu_0)\xi I_{-\frac{1}{2}}[x] + [\mu_0(1 + \xi^2) - \mu]I_{\frac{1}{2}}[x]} \quad (A.24) \]

\[ F = \frac{(2\mu + \mu_0)\xi I_{-\frac{1}{2}}[x] - [\mu_0(1 + \xi^2) + 2\mu]I_{\frac{1}{2}}[x] R^3}{(\mu - \mu_0)\xi I_{-\frac{1}{2}}[x] + [\mu_0(1 + \xi^2) - \mu]I_{\frac{1}{2}}[x]} \quad (A.25) \]

Where \( \xi = \sqrt{i\rho a} \)

Then from (A.5),

\[ \mathbf{J} = -i\omega \sigma \mathbf{A}_i = \frac{ip}{\mu} \mathbf{A}_i \quad (A.26) \]

Then, substituting \( \mathbf{A}_{\text{in}} \) from (A.20) and \( \mathbf{J} \) from (A.26) into (A.3), after integration
from we have: $\theta = 0$ to $\theta = \pi$

$$\langle P_{\text{diss}} \rangle = \frac{\pi \sigma \omega^2 B^2}{3} E^* E \int_0^R I_{\frac{3}{2}}[(ip)^{\frac{1}{2}}] I_{\frac{3}{2}}[(-ip)^{\frac{1}{2}}] r dr \quad (A.27)$$

Where

$$I_{\frac{3}{2}}[(\pm ip)^{\frac{1}{2}}] = \left[ \frac{\pi}{2} (\pm ip)^{\frac{1}{2}} R \right]^{\pm \frac{3}{2}} + \sinh \left[ \frac{1}{2} (2p)^{\frac{1}{2}} (1 \pm i) R \right]$$

$$I_{-\frac{3}{2}}[(\pm ip)^{\frac{1}{2}}] = \left[ \frac{\pi}{2} (\pm ip)^{\frac{1}{2}} R \right]^{-\frac{3}{2}} + \cosh \left[ \frac{1}{2} (2p)^{\frac{1}{2}} (1 \pm i) R \right]$$

and

$$I_{\frac{1}{2}}[\zeta] = \left( I_{-\frac{1}{2}}[\zeta] - \frac{1}{\zeta} I_{\frac{1}{2}}[\zeta] \right) \quad (A.28)$$

In (A.28), $\zeta = (\pm ip)^{\frac{1}{2}} R$

$$\langle P_{\text{diss}} \rangle = \frac{\pi \sigma \omega^2 B^2}{3} E^* E (\pi p^\frac{3}{2} R)^{-1} \left[ \frac{1}{2} (2pR^2)^{\frac{1}{2}} \left( \sinh(2pR^2)^{\frac{1}{2}} + \sin(2pR^2)^{\frac{1}{2}} - \cosh(2pR^2)^{\frac{1}{2}} + \cos(2pR^2)^{\frac{1}{2}} \right) \right] \quad (A.29)$$

Then, plugging in $E^*E$, from (A.24):

$$\langle P_{\text{diss}} \rangle = \left\{ 3\pi R^5 \omega^2 \mu^2 B^2 \left[ \frac{u}{2} (S + s) - C + c \right] \right\} /$$

$$\left\{ U^2 \left[ (pR^2 + 1) C + (pR^2 - 1) c - u(S + s) \right] + U \mu_0 p R^2 u(S - s) + \mu_0^2 p^2 R^4 (C - c) \right\} \quad (A.30)$$

Where $u = (2p)^{\frac{1}{2}} R = \frac{2a}{\delta}$, $p = \frac{2}{\delta^2}$, $C = \cosh(u)$, $c = \cos(u)$, $S = \sinh(u)$, $s = \sin(u)$,
and $U = \mu - \mu_0$

If we assume the magnetic nanoparticles are smaller than the domain size, and allow $\mu = \mu_0$,

$$\langle P_{\text{diss}} \rangle = \frac{3\pi RB^2}{\sigma\mu^2(C - c)} \left[ \frac{u}{2}(S + s) - C + c \right]$$

$$= \frac{3\pi RB^2}{\sigma\mu^2(cosh(u) - cos(u))} \left[ \frac{u}{2}(sinh(u) + sin(u)) - cosh(u) + cos(u) \right]$$

(A.31)

Since we have that the frequency $f = 2\pi*\omega \ll f_{\text{crit}} = \frac{1}{\pi R^2 \mu_0 \sigma}$ (at $f = f_c$ the radius of the sphere, $R$ is equal to the skin depth, $\delta$), and $p = \sigma \mu \omega$, so

$$u = (2p)^{\frac{1}{2}} = (2\sigma \mu \omega)^{\frac{1}{2}} R$$

we take the low frequency limit in (A.31) and perform a power series expansion of (A.31) about $u = 0$

$$\left[ \frac{u}{2}(sinh(u) + sin(u)) - cosh(u) + cos(u) \right] \left[ cosh(u) - cos(u) \right] = \frac{u^4}{180} + O[u]^8 + ...$$

(A.32)

Truncating the series in (A.32) above $O[u]^7$, and plugging the result into (A.31) gives:

$$\langle P_{\text{diss}} \rangle \approx \frac{3\pi RB^2}{\sigma\mu^2} \frac{u^4}{180}$$

$$= \frac{3\pi R^5 B^2 \sigma \omega^2}{15}$$

$$= \frac{4\pi R^5 B^2 \sigma f^2}{15}$$

(A.33)

The power dissipated per unit volume, where $V$ is the total volume of the sample, and $n$ is the number nanoparticles in the sample, and keeping in mind that the
volume fraction of nanoparticles in the solution is given by \( \phi_v = \frac{n_{Vnp}}{V} \) (\( V_{np} \) is the volume of a single nanoparticle, assumed to be the same for all particles in the sample), is given by:

\[
\langle P_{diss} \rangle_n = \frac{\langle P_{diss} \rangle_3 \phi_v}{V} = \frac{\langle P_{diss} \rangle_3 \phi_v}{4\pi R^3} = \left[ \frac{4\pi R^5 B^2 \sigma f^2}{15} \right] \left[ \frac{3\phi_v}{4\pi R^3} \right] = \frac{\pi \phi_v \sigma (RBf)^2}{5}
\]

(A.34)

Similarly, Thompson [33] found an expression for \( \langle P_{diss} \rangle \) by eddy currents, using a semi-infinite cylindrical model with an axial magnetic field and \( f \ll f_{crit} \). The expression for a single cylinder is:

\[
\langle P_{diss} \rangle = \frac{|H_0|^2 \pi R \ell_{sample}}{\sigma \delta}
\]

(A.35)

It is also apparent from (A.35) that when the cylinder is on the order of 100nm or less, the power dissipation due to eddy currents is negligible.
APPENDIX B

NÉEL’S MAGNETIC TWO - LEVEL MODEL
B.1 Magnetic Two-Level Model

The following is based on the original 1949 derivation of the relaxation time of very small ferromagnetic particles in an applied magnetic field by Louis Néel [46]. The full derivation may also be found in English in a more recent compilation of Néel’s work [66].

Initially, Néel assumes that there is no applied field, and that a single domain magnetic particle has two equivalent ground states with magnetizations pointing in opposite directions, which are separated by an energy barrier which is the result of shape and magnetocrystalline anisotropies. It is assumed that as the system approaches the steady state, that the thermal energy of the system will allow the system to surmount the barrier transition from one state to the other [46][66]. Néel further simplifies the calculation that allows for a discrete orientation approximation in assuming the thermal energy is small compared to the height of the energy barrier [66][67]. Néel then extends the calculation to include the effect of an applied AC magnetic field on the relaxation time.

Consider a particle of volume $V_{np}$, which is sufficiently small the spins of the individual atoms that make up the particle are rigidly coupled to one another, and thus the particle can be assumed to have a single magnetic domain. The single magnetic moment of the entire particle is referred to as the “giant magnetic moment” of the particle. The giant magnetic moment $M$ has magnitude $M$ given by [46][66]:

$$M = V_{np}M_s(T)$$ \hspace{1cm} (B.1)

$M_s(T)$ is the spontaneous magnetization, a quantity which is a function of the temperature, $T$, and is determined by the material properties of the particle. $M_s(T)$
is a quantity used when describing a spin-ordered state for certain materials (ferromagnetic or ferrimagnetic materials) in the absence of an applied magnetic field at temperatures below a critical temperature called the Curie temperature, $T_c$. At $T_c$ the spontaneous magnetization is zero, and above $T_c$ the material is paramagnetic [65]. Since for these particles, the demagnetizing field is shape-dependent, and as a result of the coupling forces between $\mathbf{m}$ and the particle crystal lattice, the material under consideration is anisotropic, so we may define an "easy axis" orientation for the particle. In the absence of an applied magnetic field, this easy axis orientation is the preferred direction for the magnetization of the particle, i.e. it is the direction corresponding to the minimum energy.

B.1.1 The System Without an Externally Applied Field

If there are no thermal fluctuations and in the absence of an applied field, then $\mathbf{M}$ is aligned along the easy axis. We will designate this orientation in the rectangular coordinate system $Oxyz$ as $Ox$ or $Ox'$, where $Ox$ and $Ox'$ point in opposite directions, and both correspond to the minimal energy orientation. The energy of the system, in terms of the orientation of $\mathbf{M}$ with respect to $Ox$ is given by [46][65]:

$$E_A = \frac{1}{2} M_s H \sin^2 \theta$$  \hspace{1cm} (B.2)

where the demagnetizing field $H$ is positive and constant, and depends upon the magnetocrystalline and shape anisotropies [46]. Once thermodynamic equilibrium is attained at a temperature, $T$, and in the absence of external forces, the probability of finding the direction of $\mathbf{M}$ at an angle between $\theta$ and $\theta + d\theta$ with respect to $Ox$ is given by the Boltzmann formula [46]:

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\[ g(\theta)d\theta = C \exp\left\{ -\frac{V_{np}M_s H \sin^2 \theta}{2kT} \right\} \sin(\theta) \]
\[ = \frac{V_{np}M_s H}{2kT} \exp\left\{ -\frac{V_{np}M_s H \sin^2 \theta}{2kT} \right\} \sin(\theta) \]  

(B.3)

where \( k \) is the Boltzmann constant, and \( C \) was by setting the probability of finding \( \theta \) between 0 and \( \pi \) to 1. \( \text{Néel} \) also assumes that thermal fluctuations are small enough that \( M \) remains in the neighborhood of \( O_x \) or \( O_x' \) and \( \sin(\theta) \approx \theta \). The probability for finding \( M \) in the neighborhood of either \( O_x \) or \( O_x' \) is 1/2. It should also be noted in this case, that should, for example a magnetic field be applied along \( O_x \) and then turned off, that as \( M \) would not be able to surmount the potential barrier at \( \pi/2 \) and the probability of finding \( M \) in the region between 0 and \( \pi/2 \) is almost 1. A significant thermal fluctuation or applied field is needed to surmount the barrier.

If we instead, for statistical purposes, consider a system of \( N \) identical particles. At time \( t \), \( N \) particles have \( M \) aligned in the neighborhood of \( O_x \), and \( N-P \) have \( M \) aligned in the neighborhood of \( O_x' \). Then the number of particles with \( M \) between \( \theta \) and \( \theta + d\theta \) is given by [66]:

\[ dN = 2Pg(\theta)d\theta \quad 0 \leq \theta \leq \pi/2 \]
\[ dN = 2(N-P)g(\theta)d\theta \quad \pi/2 \leq \theta \leq \pi \]  

(B.4)

Since the number of particles crossing from either the region of \( O_x \) to \( O_x' \) or \( O_x' \) to \( O_x \) during time \( dt \) is proportional to \( dt \), then the number of particles gained or lost to the \( O_x \) region is:
\[ dP = \frac{(N - P)}{2\tau_0} dt - \frac{P}{2\tau_0} \]  

(B.5)

According to Néel since the macroscopic magnetization of the system is proportional \( S = 2P - N \), the solution of which may be found by solving the differential equation (B.5), we have for this macroscopic magnetization, the following form:

\[ S = S_0 e^{-\frac{t}{\tau_0}} \]  

(B.6)

Where \( \tau \) is the relaxation time. As energy is transferred to the system of coupled spins via thermal energy of the crystalline lattice, the forces of coupling with the lattice must be determined. This is equivalent to a couple \( \mathbf{\Gamma} \) which acts perpendicularly to \( \mathbf{M} \), in the equatorial plane. Then, we have:

\[ \frac{d\sigma}{dt} = \mathbf{\Gamma} = -\frac{\partial E_A}{\partial \theta} = -M_s H \sin(\theta) \cos(\theta) \]  

(B.7)

Where \( \sigma \) is the angular momentum of a gyroscope, as the coupled spins are analogous and mathematically equivalent to such a system. The perturbing couples, associated with the thermal deformation of the crystal lattice are then related to the angular velocity of the magnetic moments in the neighborhood of the equatorial plane by:

\[ \left| \frac{d\theta}{dt} \right| = \frac{e}{mM_s \left| \mathbf{\Gamma} \right|} \]  

(B.8)
Where e and m are the electron charge and mass. Néel then reasons that the
number of particles with magnetic moments crossing the equatorial plane, dP, with
positive velocity, in time dt is equal to the number of particles whose moments at
time t are between that plane and the cone of \( \pi/2 = \left| \frac{\theta}{dt} \right| dt \) [66].

Then,

\[
\frac{P}{2\tau_0} \, dt = P g \left( \frac{\pi}{2} \right) \left| \frac{d\theta}{dt} \right| dt
\]  

(B.9)

and

\[
\tau_0 = \left( \frac{m k T}{e V_{np} H T} \right) exp \left\{ \frac{2 k T}{M_s V_{np} H} \right\}
\]  

(B.10)

Then, in order to determine \( \tau_0 \), one must find \( |\Gamma| \), the average value of the
perturbing couples, due to anisotropy.

B.1.2 The System With an Externally Applied Field

With the application of an external field \( H_{app} \), which points along the
positive x axis, Ox, parallel to one of the easy axis positions, the energy of the
system becomes:

\[
E'_A = \frac{1}{2} M_s V_{np} H \cos^2(\theta) - V_{np} M_s H_{app} \cos(\theta)
\]  

(B.11)

Then if \( H_{app} \) is less than H, the equilibrium positions are still at \( \theta = 0 \) and \( \theta = 2\pi \),
however since the applied field introduces an asymmetry to the system, the height
of the energy barrier depends on the direction of rotation of $\mathbf{M}$

$$\begin{align*}
E(0, \pi) &= \frac{M_s V_{np} (H + H_{app})^2}{2H} \\
E(\pi, 0) &= \frac{M_s V_{np} (H - H_{app})^2}{2H}
\end{align*}$$

(B.12)

Also as a result of this asymmetry introduced by the applied field, we have, instead of (B.5):

$$dP = \frac{(N - P)}{\tau(\pi, 0)} dt - \frac{P}{\tau(0, \pi)}$$

(B.13)

$\tau(\pi, 0)$ and $\tau(0, \pi)$ is determined via steps similar to (B.6) - (B.10), and we must find $|\mathbf{\Gamma}|$ in order to find the exact form of the relaxation constants.

In order to find the perturbing couples $|\mathbf{\Gamma}|$, Néel notes that we must consider the changes of the demagnetizing field, and the magnetocrystalline and magnetoelastic forces of coupling with the crystal lattice. In the event that all of the vibrational modes of the particle are not known, an approximation is made through only taking into account homogeneous deformations, which are characterized by a tensor $A_{ij}$ with 6 components, in the y-z plane. If the elastic deformations are assumed isotropic, the elastic deformation energy of a particle is given by [66]:

$$E_d = \frac{V_{np}}{2G} (A_{22} - A_{33})^2 + 2GV_{np}A_{23} + ...$$

(B.14)

$G$ is the shear modulus. Since each term has average value $kT/2$, 

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\[ (A_{22} - A_{33})^2 = \frac{kT}{V_{np}G} \]
\[ (A_{23})^2 = \frac{kT}{4V_{np}G} \]  
(B.15)

Then for the magnetoelastic energy, assuming that the material has
magnetostriction which is isotropic and has spontaneous magnetization in the y-z
plane at angle \( \phi \) relative to the y axis, and since only two terms from (C.12) give
rise to a couple [66]:

\[
E_e = -3G\lambda[(A_{22} - A_{33})\cos^2(\phi) + 2A_{23}\cos(\phi)\sin(\phi)]
\]  
(B.16)

Where \( \lambda \) is the saturation value for the longitudinal magnetostriction. \textit{Néel} finds
from (B.7), and the fact that the values \( \Gamma \) have a Gaussian distribution [66]:

\[
|\Gamma| = 3\lambda(\frac{2kT}{\pi V_{np}G})^{\frac{1}{2}}
\]  
(B.17)

Similarly, the couples due to the demagnetizing field are found (in units of energy
per cm\(^3\)):

\[
E_f = E_d = -DM_s^2[(A_{22} - A_{33})\cos^2(\phi) + 2A_{23}\cos(\phi)\sin(\phi)]
\]  
(B.18)

D is a number related to the geometry of the particle, which varies from \( \frac{4\pi}{5} \) for a
sphere to \( \pi \) for a cylinder. \textit{Néel} takes D = 3 as the average value. Then, for \( |\Gamma| \) for
both (B.17) and (B.18) we have [66]:

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\[ |\Gamma| = |3G\lambda - DM_s^2| \left( \frac{2kT}{\pi V_{np}G} \right)^{\frac{1}{2}} \]  

(B.19)

We then have, from (B.13), (B.19): and

\[
\frac{1}{\tau(0, \pi)} = C \left( 1 + \frac{H_{app}}{H} \right) \left( 1 - \frac{H_{app}^2}{H^2} \right)^{\frac{1}{2}} \exp \left\{ \frac{-V_{np}M_s(H + H_{app})^2}{2HkT} \right\}
\]

\[
\frac{1}{\tau(\pi, 0)} = C \left( 1 - \frac{H_{app}}{H} \right) \left( 1 - \frac{H_{app}^2}{H^2} \right)^{\frac{1}{2}} \exp \left\{ \frac{-V_{np}M_s(H - H_{app})^2}{2HkT} \right\}
\]

(B.20)

Where C is given by [46][66]:

\[
C = \frac{eH}{2m} |3G\lambda - DM_s^2| \left( \frac{2V_{np}}{\pi GkT} \right)^{\frac{1}{2}}
\]

(B.21)

It should be noted that (B.6) now has the following form, obtained from (B.13) as there is a shift in the macroscopic magnetic moment due to the asymmetry introduced by the applied field [46][66]:

\[
S = S_1 + (S_0 - S_1)e^{-\frac{t}{\tau_1}}
\]

(B.22)

Where \( \tau_1 \) is determined by (B.20). The results of (B.20) and (B.6), though obtained from a relatively simple model, are quite accurate in certain circumstances. These results do break down, however, if the applied field is weak and varies with time [66].
APPENDIX C

THE COMPLEX MAGNETIC SUSCEPTIBILITY
C.1 Overview

This section outlines the physical meaning of the complex magnetic susceptibility, $\chi''$, and its relationship to the magnetic response of a material to a time-varying magnetic field. The applied magnetic field in this case is weak enough that there is a delay in time between a change in the applied field and the resultant change in magnetization.

C.2 Isotropic Complex Susceptibility

First we will consider the simple case where the magnetization of a material is colinear with the applied field which produces it. As will be demonstrated, this implies an isotropic complex susceptibility function. The applied field is given by [68]:

$$H = A \cos(\omega t) = Re\left[Ae^{i\omega t}\right] \quad (C.1)$$

Then, the response is also sinusoidal (this is a general property of any linear system):

$$M = B \cos(\omega t + \phi) = Re\left[Be^{i\omega t + \phi}\right] \quad (C.2)$$

Let $\tilde{H}$ and $\tilde{M}$ are the complex amplitudes of (C.1) and (C.2), respectively. The complex susceptibility $\chi$ is defined as:

$$\frac{\tilde{H}}{\tilde{M}} = \frac{B}{A} e^{i\omega t} \quad (C.3)$$
$\frac{B}{A}$ and $\phi$ depend on the angular frequency $\omega$, for a given material and fixed conditions, including temperature. Then $\chi$ is also a function of frequency and characterizes a particular material [68]. We can write $\chi$ as:

$$\chi = \chi' - i\chi'' \quad (C.4)$$

The complex relative permeability is then:

$$\mu = 1 + \chi = \mu' - i\mu''$$
$$\mu' = 1 + \chi'$$
$$\mu'' = \chi'' \quad (C.5)$$

All terms in (C.4) and (C.5) are also individually frequency dependent. Then,

$$M(t) = (\chi' - i\chi'')H(t) = Re\left[ (\chi' - i\chi'')A(cos(\omega t) + isin(\omega t)) \right]$$
$$= A\left[ \chi' cos(\omega t) + \chi'' sin(\omega t) \right] \quad (C.6)$$

It is apparent from (C.6) that $A\chi'$ gives the component of $M(t)$ that is in phase with $H(t)$ and $A\chi''$ gives the component that lags behind $H(t)$ by $\frac{\pi}{2}$. The instantaneous power delivered by the field to the material is then (see Appendix E):

$$\langle P \rangle = \frac{\mu_0}{2} \omega \chi'' A^2 \quad (C.7)$$

So, $\chi''$ is characterizes the magnetic losses for a material.
Given that we are still in the regime where a linear approximation is appropriate, and given the complex magnetic susceptibility function or complex permeability function, we can predict the response to a given time-dependent applied field. \( H(t) \) is the applied field and \( H' \) is the Fourier transform of \( H(t) \):

\[
H'(\omega) = \frac{2}{\pi} \int_0^\infty H(t) \cos(\omega t) dt
\]

(C.8)

Each term in (C.8) can be thought of as an excitation which produces a response \( dM(\omega) \) (again, a property of linear systems).

\[
dM(\omega) = H'(\omega) d\omega \left[ \chi' \cos(\omega t) + \chi'' \sin(\omega t) \right]
\]

(C.9)

Then with our assumption of a linear system, \( \chi \) or \( \mu \) give a complete description of the magnetic response of a material (at a given temperature) [68].

\[
M(t) = \int_0^\infty H'(\omega) d\omega \left[ \chi' \cos(\omega t) + \chi'' \sin(\omega t) \right]
\]

(C.10)

If we also take the causality principle as an axiom [68], then the real and imaginary parts of \( \chi \) or \( \mu \) are not independent functions. Then a single component of either function is a complete description of the magnetic response of a material (at a given temperature). The Kramers - Kronig relations give [68]:

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\[ \chi' = 2 \pi \int_{0}^{\infty} \frac{\chi''(\omega)}{\omega^2 - \omega^2} \omega d\omega \]
\[ \chi'' = -\frac{2}{\pi} \int_{0}^{\infty} \frac{\chi'(\omega)}{\omega^2 - \omega^2} \omega d\omega \]  
(C.11)

We must however, know one of the components of \( \chi \) or \( \mu \) over then entire spectrum in order to make use of (C.11).

C.3 Anisotropic Complex Susceptibility

The relations found in the previous section were for an isotropic material. The more general relation between \( M(t) \) and \( H(t) \) in a rectangular coordinate system for an anisotropic material are given by [68]:

\[
\begin{pmatrix} M_1 \\ M_2 \\ M_3 \end{pmatrix} = \begin{pmatrix} \chi_{11} & \chi_{12} & \chi_{13} \\ \chi_{21} & \chi_{22} & \chi_{23} \\ \chi_{31} & \chi_{32} & \chi_{33} \end{pmatrix} \begin{pmatrix} H_1 \\ H_2 \\ H_3 \end{pmatrix}
\]

In any coordinate system, the relation between the excitation field, the magnetization, and the material magnetic susceptibility are given by the tensor relation:

\[ M = \chi H \]  
(C.12)

Where \( M, \chi, \) and \( H \) are tensors.
APPENDIX D

MAGNETIC HYSTERESIS AND SUPERPARAMAGNETISM
D.1 Overview

This section will review the various magnetic responses for different materials and their respective response curves. This will include a discussion of the phenomenon of magnetic hysteresis for ferromagnetic materials and the limiting case of superparamagnetism.

D.2 Magnetic Response of Different Classes of Magnetic Materials

D.2.1 Diamagnetism

The magnetic response of a particular material to an applied magnetic field depends on the properties of the individual atoms and molecules of the material and the interactions between those atoms and molecules [64]. Diamagnetic materials are made up of atoms and molecules with net angular momentum which is zero without the presence of an applied field. In the presence of an applied magnetic field, due to Lenz’s law [65], there is a small change in the orbital velocity of the electrons around the nuclei, and a very small bulk magnetization is produced in opposition to the applied field [64]. Diamagnetism is a very weak effect. The volumetric magnetic susceptibility, $\chi_v$ (which is given here in dimensionless SI units) for diamagnetic materials is in the range of approximately $-10^{-6}$ to $-10^{-3}$ [17]. In materials where the much stronger effect of paramagnetism is also present, i.e. materials with unpaired electrons, the diamagnetic effect still occurs, but it is not often observed as response curves are dominated by the paramagnetic effect.

D.2.2 Paramagnetism

If the atoms in a material have unpaired electrons, giving the atoms a net angular momentum, the material is paramagnetic [64]. The individual atoms or molecules that make up the substance have permanent dipole magnetic moments
Figure D.1: Response curve for diamagnetic materials. All atoms exhibit a diamagnetic response, due to Lenz’s law. This response is normally observed, however, in materials without unpaired electrons. This is because the paramagnetic response observed in materials with unpaired electrons is a significantly stronger effect, and acts positively in response to the applied field.

and these dipoles tend to align with the applied field. The net effect is that macroscopic magnetic moment of the material aligns with the applied field [64].

Like diamagnetic materials, paramagnetic materials don’t retain magnetization in the absence of an applied field. Thermal energy causes the spins to become randomly oriented and the net magnetic moment goes to zero without the influence of the applied field. $\chi_v$ for paramagnetic materials is in the range of approximately $10^{-6}$ to $10^{-1}$ [17].

Figure D.2: Response curve for paramagnetic materials.
D.2.3 Magnetic Hysteresis

Ferromagnetic materials exhibit a nonlinear magnetic response known as hysteresis. These materials are similar to paramagnetic materials, in that their magnetic response arises due to magnetic dipoles associated with unpaired electrons. [65].

However, the behavior of ferromagnetic materials under the influence of an applied field is extremely different than the linear response of paramagnetic materials seen in figure D.2. As is often the case when a system exhibits a highly nonlinear response to an external force, hysteresis is the result of collective behavior that arises due to coupling within the system. In this case, the coupling is due to interactions between the nearby magnetic dipoles. The individual dipole moments in these materials tend to align in the same direction as their nearest neighbors. This creates alignment in small patches, known as magnetic domains. Domains in ferromagnetic materials that are not permanent magnets are randomly oriented, and therefore the magnetic moments of the individual domains effectively cancel out one another, and the material is therefore not magnetized on the macroscopic scale [65].

The application of an magnetic field causes the magnetic moments of some domains to line up parallel to the field, yet the alignment of the magnetic moments of the individual domains is also influenced by the alignment of the moments of neighboring domains. At a domain boundary, the nearest neighbors compete for influence over the direction of the magnetic moment of the domain, and the neighbor most closely aligned with the applied field will tend to win out [65]. Domains aligned with the applied field grow, and as the magnetic field is increased, eventually the material will become "saturated" when all of the domain magnetic moments are aligned with the applied field. This process is depicted in figure D.3.

As was previously mentioned, energy is needed to overcome the barrier to domain wall motion imposed by magnetic anisotropy, microstructural impurities,
Figure D.3: Shown is an example magnetic hysteresis curve. If magnetized from a zero value, the bulk magnetization of the material follows a nonlinear curve as the applied field is increased. If the field is increased to a large enough value, the magnetization reaches the saturation point, $M_{sat}$. This process is not reversible. If the field is decreased, the material retains a large degree of magnetization. When the applied field is zero, the remaining value of magnetization is given by $M_r$, the magnetic remanence. A large negative magnetic field must then be applied in order to yield a bulk magnetization of zero. The value of this field is $H_c$, the coercivity.

and the grain boundaries in ferromagnetic materials [17]. This energy is delivered by the applied magnetic field, and is related to the area enclosed by the hysteresis loop. A time-varying magnetic field applied to a ferromagnetic material can then allow a continual deposition of energy into the system, which will be transferred into thermal energy. The power dissipation due to an AC magnetic field is proportional to the area of the hysteresis loop [17]:

$$P_{fm} = \mu_0 f \oint HdM$$  \hspace{1cm} (D.1)

Since the power dissipation due to an applied AC magnetic field is proportional to the area within the hysteresis loop, it follows that if the applied AC magnetic field
is not strong enough to reach the saturation point $M_s$, the minor loops generated (see figure D.4) have a smaller area than the major hysteresis curve, and thus the maximum power generation due to hysteresis losses is not attained.

Figure D.4: Hysteresis curve with minor loops

D.2.4 Superparamagnetism

Materials that exhibit superparamagnetic behavior, such as ferrofluids, have particles that are small enough that the magnetic moments of the particles are free to rotate in response to an applied magnetic field. These materials have an anhysteretic M-H curve, and the power losses due to these materials in an applied AC magnetic field have a square dependence on the applied field. This leads to higher heating powers at lower field strengths than ferromagnetic materials [17]. For further details on this, see Appendix E. The form of the magnetic response curve for a superparamagnetic material is shown in figure D.5.
Figure D.5: Magnetic response curve for a superparamagnetic material.
APPENDIX E

MAGNETIC LOSSES FOR FERROFLUIDS
E.1 Overview

Materials such as magnetic nanoparticle fluids (ferrofluids), have particles that are small enough that the magnetic moments of the particles are free to rotate in response to an applied magnetic field. Magnetic nanoparticles that are small enough to be single-domain have losses that are the result of Néel relaxation, while larger multidomain magnetic nanoparticles in a fluid suspension will exhibit losses due to friction through Brownian rotation in the fluid. It is also important to note that the Néel model is only appropriate for the smallest nanoparticles and low field strengths (\( \leq 15\text{kA/m} \)). Otherwise, ferrofluid losses may occur due to ensemble hysteresis losses [42]. In practice, ferrofluids are polydisperse and exhibit Néel, Brownian, and hysteresis losses in tandem [42]. Ferrofluids for hyperthermic cancer treatment are adsorbed into tumor tissues and as particles are no longer able to rotate freely, losses due to Brownian rotation are negligible.

The giant magnetic moments of the particles continually change direction in response to the applied field. Each time this change in direction occurs, there is an energy barrier which must be overcome due to the Néel process (see Appendix B), hysteresis, or Brownian losses due to friction. The change in direction of the magnetic moment of the particles then lags the changing applied field. This phase lag can be described in terms of its frequency dependent complex magnetic susceptibility \( \chi' - i\chi'' \) [17]. This appendix derives the heating power of ferrofluids due to an applied AC magnetic field. This is an approximation based on Rosensweig’s derivation [32] which applies to rotational relaxation of single domain magnetic particles dispersed in a fluid.

E.2 Details of the Calculation for Heating Power of Ferrofluids

The 1st Law of Thermodynamics for constant density system is given by:
\[ dU = dQ + dW \]  

(E.1)

Where \( U \) = internal energy, \( Q \) = heat added, and \( W \) = work done on the system.

Assuming adiabatic expansion, \( dQ = 0 \) and \( dW = H \cdot dB \). Then, \( dU = H \cdot dB \) = \( HdB \) and since \( B = \mu_0(H + M) \). The change in internal energy, \( \Delta U \) is:

\[ \Delta U = -\mu_0 f \int M dH \]  

(E.2)

The phase lag between the applied magnetic field and the alignment of the magnetic moments is represented in terms of the complex magnetic susceptibility of the material, and is given by \( \chi = \chi' - i\chi'' \). The time varying magnetic field is of the form: \( H(t) = H_0 \cos(\omega t) = Re[H_0 e^{i\omega t}] \). The magnetization is then given by:

\[ M(t) = Re[\chi H_0 e^{i\omega t}] = H_0[\chi' \cos \omega t + \chi'' \sin \omega t] \]  

(E.3)

The magnetic moments of the magnetic nanoparticles rotate to align with the changing applied field. As the magnetic field decreases, the magnetic moments rotate back to their equilibrium positions. A phase lag between the applied magnetic field and the rotation of the magnetic moments results in conversion of magnetic work into energy in the form of heat. So, from (E.2) and (E.3), this increase in internal energy can be written as:

\[ \Delta U = 2\mu_0 H_0^2 \chi'' \int_0^{\frac{2\pi}{\omega}} \sin^2 \omega t dt \]  

(E.4)
The volumetric heating power \( P \) is then:

\[
P = f \Delta U = \mu_0 \pi \chi'' f H_0^2
\]  
(E.5)
APPENDIX F

THE FINITE DIFFERENCE TIME DOMAIN METHOD
F.1 The Finite Difference Time Domain Method for Solving Maxwell’s Equations

F.1.1 Overview

The basic FDTD algorithm dates back to a 1966 paper by Kane Yee [69]. In this method, Maxwell’s curl equations are replaced by a set of finite difference equations and solved iteratively in the time domain. The basic procedure is as follows:

1) The time-dependent Maxwell’s equations (in partial differential form) are discretized using central-difference approximations to the time and space partial derivatives.

2) The finite-difference equations obtained in the first step are solved in the following leapfrog manner: the electric field vector components in a volume of space are solved at a given instant in time; then the magnetic field vector components in the same spatial volume are solved at the next instant in time.

3) The process is repeated over and over again until the desired transient or steady-state electromagnetic field behavior is fully realized.

For three dimensional models, calculating the curl numerically can become computationally challenging. Kane Yee’s 1966 paper suggested spatially staggering the vector components of the E-field and H-field about rectangular unit cells of a Cartesian grid so that each E-field vector component is located midway between a pair of H-field vector components, and vice versa [69]. This scheme, now known as a Yee lattice, has been shown to be quite a robust method for modeling the electromagnetic properties of a wide variety of systems, materials, and regimes.

F.1.2 Details of the Algorithm

Maxwell’s curl equations are discretized using a $2^{nd}$ order finite difference approximation both in space and in time in an equidistantly spaced mesh grid.
Figure F.1: Schematic representation of standard Cartesian Yee cell used for FDTD, about which electric and magnetic field vector components are distributed. This Yee cell is visualized here and in many FDTD software programs, such as SEMCAD [49], as a cubic voxel. Electric field vector components form the edges of the cube, and the magnetic field vector components form the normals to the faces of the cube. A three-dimensional space lattice (grid) consists of a multiplicity of such Yee cells. A mesh is assigned to a cad model in order to define the voxels, and then an electromagnetic wave interaction structure is mapped to the grid by assigning appropriate values of the complex permittivity to each electric field component, and the complex permeability to each magnetic field component.

From the first partial space and time derivatives:

$$\frac{\partial F(i, j, k, n)}{\partial x} = \frac{F^n(i + \frac{1}{2}, j, k) - F^n(i - \frac{1}{2}, j, k)}{\Delta x} + O[(\Delta x)^2]$$

$$\frac{\partial F(i, j, k, n)}{\partial t} = \frac{F^{n+\frac{1}{2}}(i, j, k) - F^{n-\frac{1}{2}}(i, j, k)}{\Delta t} + O[(\Delta t)^2] \quad (F.1)$$
Where $F^n$ is the electric (E) or magnetic (H) field at time $n \cdot \Delta t$ and i, j and k are the indices of the mesh, and $O[(\Delta x)^2]$ and $O[(\Delta t)^2]$ are error terms [49]. The equations (F.1) are applied to Maxwell’s curl equations in the following form:

\[
\nabla \times \mathbf{H} = \frac{\partial}{\partial t} \varepsilon \mathbf{E} + \sigma_E \mathbf{E} \\
\nabla \times \mathbf{E} = -\frac{\partial}{\partial t} \mu \mathbf{H} - \sigma_H \mathbf{H} \tag{F.2}
\]

Where $\sigma_E$ and $\sigma_H$ are the electrical conductivity and ”magnetic conductivity”, factors which represent the electrical and magnetic losses and depend on the material properties and frequency, $f$, of the applied field:

\[
\sigma_E = \omega \varepsilon_0 \varepsilon'' = 2\pi f \varepsilon_0 \varepsilon'' \\\n\sigma_H = \omega \mu_0 \mu'' = 2\pi f \mu_0 \mu'' \tag{F.3}
\]

Then, for example, the application of (F.1) to (F.1) gives for the $E_x$ component:

\[
\frac{E_x^{n+1}|_{i,j,k} - E_x^n|_{i,j,k}}{\Delta t} = \frac{1}{\varepsilon_{i,j,k}} \left( \frac{H_z^{n+1/2}|_{i,j+1/2,k} - H_z^n|_{i,j-1/2,k}}{\Delta y} - \frac{H_y^{n+1/2}|_{i,j,k+1/2} - H_y^n|_{i,j,k-1/2}}{\Delta z} - \sigma_{i,j,k} E_x^{n+1}|_{i,j,k} \right) \tag{F.4}
\]

then the following approximation is assumed [49]:

\[
E_x^{n+1/2}|_{i,j,k} = \frac{E_x^{n+1}|_{i,j,k} - E_x^n|_{i,j,k}}{2} \tag{F.5}
\]
and we find [49]:

\[
E_x |_{i,j,k}^{n+1/2} = \left(1 - \frac{\Delta t \sigma_{i,j,k}}{2 \epsilon_{i,j,k}}\right) E_x |_{i,j,k}^n + \left(1 + \frac{\Delta t \sigma_{i,j,k}}{2 \epsilon_{i,j,k}}\right) \left(\frac{\Delta t}{\epsilon_{i,j,k}}\right) \left(\frac{H_z |_{i,j+1/2,k}^{n+1/2} - H_z |_{i,j-1/2,k}^{n+1/2}}{\Delta y} - \frac{H_y |_{i,j,k+1/2}^{n+1/2} - H_y |_{i,j,k-1/2}^{n+1/2}}{\Delta z}\right)
\]

(F.6)