Long-time behaviour of a coupled PDE model of high intensity focused ultrasound heating of biological tissue

by
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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The work in chapter 2 was performed by June Murley at the University of Waterloo under the supervision of Dr. Sivabal Sivaloganathan. Assistance was provided by the HIFU research group of the Sick Kids Hospital of Toronto, lead by Adam Waspe and Dr. James Drake, in the form of clinical knowledge and access to some results of their clinical trials.

The work in chapters 3 and 4 was performed by June Murley under the supervision and guidance of Dr. Sivabal Sivaloganathan and Dr. Messoud Efendiev. The work has been published in *Advances in Mathematical Sciences and Applications* [21].

The work in chapter 5 was performed by June Murley under the supervision and guidance of Dr. Sivabal Sivaloganathan and Dr. Messoud Efendiev. The work has been published in the *Bulletin of Mathematical Biology*.

Abstract

High Intensity Focused Ultrasound (HIFU) has emerged as a novel therapeutic modality, for the treatment of various cancers, that is gaining significant traction in clinical oncology. It is a cancer therapy that avoids many of the associated negative side effects of other more well-established therapies (such as surgery, chemotherapy and radiotherapy), and does not lead to the longer recuperation times necessary in these cases. However, the mathematical modeling of this treatment for the sake of treatment planning and non-clinical study requires further development. In this thesis, popular models for the propagation of ultrasound and temperature, as well as the biological effects caused by these, are discussed. We introduce a coupled PDE model of the bioheat propagation caused by HIFU and establish that the solution exists and is unique. We further study the long-term dynamics of the solution under quasi-periodic external forcing, which corresponds to the periodic (or quasi-periodic) pulsing of the ultrasound under conditions where a patient is treated clinically with HIFU threapy. In this case, we are able to prove the existence of uniform attractors to the corresponding evolutionary processes generated by our model and to estimate the Hausdorff dimension of the attractors, in terms of the physical parameters of the system.

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Dedication

To Dr. Nasser Saad, without whom I would not be here.

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Chapter 1: Introduction

History records the constant struggles of mankind with cancer over many millenia. In fact, the earliest documented evidence of cancer has been found in the fossilized bone tumours of mummies of ancient Egypt, Chile, and Peru (see David et al [3]).

The term cancer is used generically to describe many different diseases that arise as a result of the uncontrolled proliferation and accumulation of mutated cells in multicellular organisms. At the cellular level, carcinogenesis is understood to be a multistep process involving mutation and selection for cells with increasing capacity for proliferation, survival, invasion, and metastasis. The first step in the process, tumour initiation, is believed to arise as a result of genetic alterations leading to abnormal proliferation of a single cell. Cell proliferation then leads to the outgrowth of a population of clonally derived tumour cells. Tumour progression continues, as additional mutations occur within cells of the tumour population - some of these mutations confer a selective advantage to cells (e.g. more rapid growth) and the offspring of cells bearing such mutations will consequently become dominant within a tumour population. This process is known as clonal selection, since a new clone of tumour cells has evolved with properties (such as survival, invasion, or metastasis) that confer a selective advantage. Clonal selection continues throughout tumour development, so that tumours are continuously evolving, becoming more rapid-growing and increasingly malignant.

A 2013 survey carried out by the American Medical Association showed that cancer is poised to overtake cardiovascular diseases as the leading cause of mortality in industrialized countries. Over the course of a year, roughly 15 million new individuals will be diagnosed with cancer, and at least a further 8 million people will lose their battle with cancer, and the numbers are increasing. Cancer continues to pose a major threat to public health worldwide, and the rates of cancer incidences have increased in most countries since 1990. As research continues to reveal more about the complex multiscale nature of cancer, new treatments, like High Intensity Focused Ultrasound (HIFU), are emerging in an attempt to develop non-invasive therapies that have minimal side effects but increased efficacy (see Bailey et al [2] and references therein).

In the context of cancer therapies, HIFU is a relatively new development which has yet to gain widespread acceptance in a clinical setting. While HIFU was conceptually developed in the mid-1950s and was used (to various degrees of success) in treating some neurological conditions, its uses remained few and far between. Two or three decades of technological advances were necessary before the true potential of this technology became apparent for clinical applications (Hindley et al [5]). In recent years, HIFU has gained significant traction as a therapeutic modality and is now routinely used in a number of clinical applications (ranging from painless removal of uterine fibroids [5] to non-invasive destruction of solid tumours [2]). HIFU is a minimally-invasive surgical technique that can be used to thermally ablate both malignant and benign tumours, as well as to cauterize injured vessels and organs (to staunch internal bleeding), with minimal damage to surrounding tissue. HIFU has been proposed as an alternative to surgery for treatment of cancer and various tumour types, including prostate, breast, brain, and renal cancer, amongst others. Currently, it is also used for palliative care, for example, to alleviate the pain resulting from the metastasis of malignant tumours to bone tissue.

The emergence of HIFU as a powerful new therapeutic modality in the treatment of cancers, promises to revolutionize cancer care worldwide. The use of mathematical modelling to predict the effects of HIFU for thermal ablation has facilitated the effective implementation of this therapeutic modality for certain disorders such as osteoid osteomas, essential tremors and prostate ablation. Figure 1 illustrates a typical set-up for clinical administration of HIFU to treat uterine fibroids. The further development and generalization of mathematical models for soft tissue lesions, cavitation and disruption of the blood brain barrier, suggest significant opportunities for mathematics to contribute to the development of HIFU as the "gold standard" for cancer therapy.

Over the past 50 years, High Intensity Focused Ultrasound has become a subject of increasing interest among medical researchers. HIFU causes selective tissue necrosis in a very well defined volume, at a variable distance from the transducer, through heating or cavitation. For the past two to three decades, the use of HIFU has been investigated in many clinical settings. The most abundant clinical trial data comes from studies on the

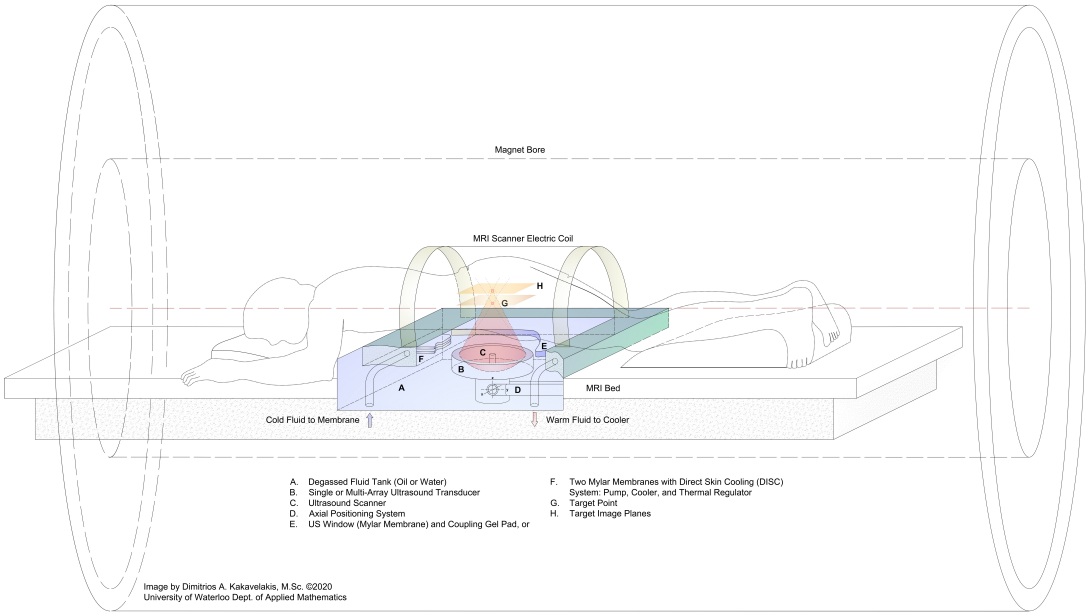

Figure 1: An MRI-guided HIFU apparatus.
(Figure by D. Kakavelakis, PhD candidate, University of Waterloo.)

treatment of prostatic disease, although early research did examine its potential applications in neurosurgery. More recently horizons have been considerably broadened, and the potential of HIFU as a non-invasive surgical tool has been demonstrated in many settings including the treatment of tumours of the liver, kidney, breast, bone, uterus and pancreas, in addition to its successful use in rectifying conduction defects in the heart, as well as to perform surgical haemostasis, and for the relief of chronic pain of malignant origin. Further clinical evaluation and developments will undoubtedly follow, but recent technological advances suggest that HIFU is likely to play an increasingly significant role in future surgical practice.

While the quest continues for a reliable and minimally-invasive alternative to open surgery, the endoscopic revolution is well underway and there is much research activity in other relevant fields such as laser, radiofrequency, cryo-, thermo- and brachytherapies. Lithotripsy is now an established treatment for kidney stones and gallstones, but currently, the only pervasive, non-invasive modalities used in mainstream clinical oncology are chemotherapy and radiotherapy, and while effective in many instances, they both have significant, associated negative side-effects. High intensity focused ul-

trasound has the potential to provide clinicians with another truly non-invasive, targeted treatment option. Its scope is not, however, limited to the treatment of only malignant cancers, but can also be used in a palliative setting for relief of chronic pain, for haemostasis, or even for the treatment of cardiac conduction or congenital anomalies.

In this thesis, we present a mathematical analysis of a class of models of High Intensity Focussed Ultrasound. In chapter 2, we discuss the modelling assumptions, challenges and possible generalizations. We conclude with a presentation of the system of partial differential equations that will be analyzed in subsequent chapters. In chapter 4, we analyze this coupled system of partial differential equations used to model the interaction of HIFU with biological tissue. The mathematical model takes into account the effects of both diffusive and convective transport on the temperature field, when acoustic (ultrasound) energy is deposited at a particular location (focal point) in the biological tissue. This model poses significant challenges in establishing existence and uniqueness of solutions, which we consider to be a crucial first step in any realistic, applied mathematical study of HIFU therapy. In this chapter, we establish well-posedness of our model, using the Leray-Schauder principle, together with a-priori estimates. In chapter 4, we take the next natural step of studying the long-time dynamics of solutions to this model, in the case where the external forcing is quasi-periodic. This is particularly relevant, since it corresponds to the periodic (or quasi-periodic) pulsing of high intensity focussed ultrasound, when HIFU therapy is administered clinically, to a patient. In this case, we are able to prove the existence of uniform attractors to the corresponding evolutionary processes generated by our model and to estimate the Hausdorff dimension of the attractors, in terms of the physical parameters of the system. Finally, in chapter 5, we review the work carried out in this thesis and discuss possible future research building on this work.

The content in chapter 3 and chapter 4 has appeared in Advances in Mathematical Sciences and Applications [21] and the content in chapter 5 has appeared in a paper submitted to the Bulletin of Mathematical Biology.

Chapter 2: Mathematical Modelling of High Intensity Focussed Ultrasound (HIFU)

Ultrasound is a subset of the mechanical compression waves known as acoustic waves, which also includes audible sound. Ultrasound waves are distinguished from audible sound waves by vibrating at higher frequencies, but have the same underlying physical processes [52]. This relation between ultrasound and audible sound is analogous to the relation between ultraviolet light and visible light, as ultraviolet light is a higher frequency form of electromagnetic wave than visible light [43]. In the case of electromagnetic waves, the relation is often expressed in terms of wavelength, but since higher frequencies result in shorter wavelengths, both ultrasound and ultraviolet light can be considered higher frequency and lower wavelength versions of audible sound and visible light.

An acoustic wave is a mechanical wave that results through the back-and-forth vibrations of the particles of the medium through which the wave is passing. Due to frictional effects, some of the energy from this acoustic vibration is absorbed as it passes through the tissue and some of that energy is converted into heat [52]. In diagnostic ultrasound, the waves passing through the tissue deposit insufficient energy to heat up the tissue to the point of having a significant effect on the physiological and structural properties of the tissues. However, it is possible to heat the tissue to affect these properties of the tissue by increasing the acoustic intensity and this effect may be localized by focusing the ultrasound in a cone. This is the idea behind high-intensity focused ultrasound [2].

Acoustic intensity is a measure of acoustic power, or energy emitted per unit time, per unit area [2]. This intensity is proportional to the energy absorbed by the tissue, so the use of ultrasound of higher intensity increases the heat produced. In order to efficiently use this heating effect, the ultrasound waves are focused through the use of a convex transducer, which causes the ultrasound waves to all pass through a single point known as the focal point of the transducer. When it is properly calibrated, this results in relatively diffuse ultrasound effects away from the focal point with negligible heating of the peripheral tissue and increasing deposition of thermal energy in the neighbourhood

of the focal point, with maximal energy deposition at the focus. It is possible to calibrate this transducer such that tissue ablation only occurs around the focal point. In this manner, it is possible to cause only a small region around this focal point to thermally necrose - that is, cell death through heat - while the rest of the tissue is not heated to the point of causing irreversible damage. This method may then be used to eliminate, for example, tumour cells, without causing damage to the intervening tissue as would be the case with other therapeutic modulaities [61].

The development of high-intensity focused ultrasound is comparatively recent. While there was some success in treatment of certain neurological conditions in the 1950s, the therapeutic effects were temporary and problems in focusing the ultrasound accurately required surgery to access the right areas of the brain [35]. These issues in focusing the ultrasound accurately also plagued other theoretical applications, so the technique saw little clinical testing until the end of the 20^{th} century [32], where it attracted attention as a potential form of non-invasive, non-radioactive intervention. HIFU has been used in a number of clinical applications, such as stopping internal bleeding (*hemostasis*) and enhancing the body's immune response (*immunotherapy*). However, for the sake of clarity, descriptions of the methodology will focus on its application in tissue ablation at a focal point used in order to destroy cancerous tumours [2].

An *ultrasound transducer* is used to produce the focused ultrasound with a curved shape manufactured in such a way that the propagating wave will eventually converge at a point, known as the *focal point*, as illustrated in Figure 1. This transducer is placed in water in order to reduce reflection and refraction. Acoustic waves, like ultrasound, transmit more faithfully between different media when the media have similar physical properties. If there is a large difference between the media, most of the wave is reflected rather than transmitted, which results in significant energy dissipation at the interface and should be avoided. Since much of the body is made of water, it is a closer match to the body than air, particularly in soft tissues, and thus reduces the effects of reflection [40]. The ultrasound then passes through a gel pad placed against the body, which is even closer to the soft tissues in terms of its mchanical properties, making the transmission even smoother [22].

When cells remain at a sufficiently elevated temperature for a long enough time, the heat begins to denature the proteins inside it [2]. That is, the structure of these proteins is lost and they lose their normal function [62], which results in cell death [2]. Denaturation of proteins is similar to the process that causes a cooked egg to have different physical properties from a raw egg [16].

In Figure 1, a cylindrical magnet included in the equipment is used in a magnetic resonance guidance system. In soft tissues, magnetic resonance imaging (MRI) may be used to measure the temperature of the tissue. As such, MRI-guided HIFU uses this for feedback on the heating of tissues by the ultrasound [32]. MRI-guided HIFU is a fairly recent development; until 2005, the only clinical applications for MRI-guided HIFU that had gained any traction were the treatment of uterine fibroids and breast neoplasms [35]. However, further applications are under development [22] and HIFU has been used in many other applications under other imaging methods [35].

One very successful application of MRI-guided HIFU in clinical applications has been in the treatment of uterine fibroids, which are benign tumours in the uterus [61]. Despite their benign status as tumours, they can have negative side-effects [59], so they still may need to be removed. MRI-guided focused ultrasound is one treatment method, which causes heat-induced cell ablation to decrease the size of the tumour until side-effects are relieved and, in fact, causes further decrease in tumour size over subsequent months [32]. Compared to other treatments, MRI-guided focused ultrasound has fewer restrictions than laparoscopic and hysteroscopic myomectomy [60] and has fewer post-surgical complications [32], in part due to the non-invasive method of application [35]. The particular form of HIFU therapy that this proposal is focused on is a completely local treatment [22] in a similar manner to the use of local surgery for tumours that have not metastasized [46]. However, there are other methods, such as immunotherapy, which provide a systemic treatment of cancer [35] and could be studied using some of the same modeling techniques with the HIFU being considered here and should be studied at a later time.

Cancer is fundamentally a genetic disease since it is initiated through the mutation of genes that code for the synthesis of proteins regulating cell differentiation and growth

(proto-oncogenes). These mutated genes (known as oncogenes) do not lead to the synthesis of proteins that regulate mitosis and the cells begin to divide in an uncontrolled fashion. Cancer cells have evaded the normal control checkpoints that regulate growth and proliferation, growing and proliferating in an uncontrolled fashion. Furthermore, as the cancer progresses, cancer cells use the circulatory system to start new colonies of cancer cells throughout the body (metastases) [4].

In the 20th and 21st centuries, multiple therapeutic modalities have emerged, including chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, stem cell therapy, and gene therapy, yet no definitive cure for cancer exists. The various treatments can be administered separately or in combination for greater efficacy. For example, radiotherapy is often administered with chemotherapy to improve the effects of radiation. All of these treatments have shown some effectiveness in treating particular cancers, but also have their own limitations [4]. For example, radiation therapy is a cancer treatment where cancerous cells are killed by ionizing radiation and different types of radiation therapies have been developed to administer the radiation to different regions of the body. These include Three-Dimensional Conformal Radiotherapy, conformal proton beam radiation therapy, Intensity Modulated Radiotherapy, and Image Guided Radiotherapy, amongst others [4]. The challenge in radiation therapy is to ensure that radiation is administered in such a manner that the cell kill is maximized for cancer cells and minimized for normal cells. Another difficulty is that different tumours show different radio sensitivities; that is, the effectiveness of radiation therapy varies from case to case making it difficult for doctors to predict whether the treatment will be effective for particular cases. In addition, radiation therapy results in several adverse side effects, ranging from skin reactions, mouth dryness, hair loss, nausea, vomiting, fatigue, to loss of appetite [4].

Chemotherapy is another therapeutic modality often used to shrink the size of a tumour, increase the effectiveness of radiotherapy, and treat cancers like leukemia and lymphoma. Despite the breadth of its uses, chemotherapy often compromises the immune systems of patients, leaving them vulnerable to opportunistic diseases and infections. Side effects include fatigue, shortness of breath, dizziness, easy bruising,

bleeding of the gums, hair loss, dryness of hair and skin, nausea, loss of appetite, constipation, and diarrhea. Also, certain alkylating agents, inhibitors, and antimetabolites can result in neurotoxic effects on the central nervous system [4].

In comparison, properly administered HIFU has minimal side-effects. In studies on the removal of uterine fibroids by HIFU, it was noted that recovery was substantially faster than using previous techniques of local surgery and had no side-effects which could be directly linked to the treatment [61]. While HIFU is not a panacea for all cancers - for example, it is unable to deal with non-localized forms of cancer [22] that radiochemotherapy can sometimes alleviate [7] - its minimal side-effects make it a good candidate in cases where it is effective. By improving the methods and predictive modeling of HIFU, the range of cases where HIFU is effective will increase, allowing for more conditions to be treated with minimal adverse reactions.

Modeling challenges

Many challenges arise when attempting to model HIFU. Some of them are more physiological and treatment-planning-oriented than mathematical, but even these challenges often give rise to mathematical challenges as it becomes necessary to account for them in the models and to use the models to provide insights and propose solutions.

The review paper written by Bailey *et al.* [2] provides a list of some of the current major challenges facing HIFU if it is to be accepted into standard clinical practice. The problems considered are mostly physiological in nature, but they can demonstrate the interconnectedness of physiological and mathematical issues. Some of these are beyond the scope of this thesis. For example, the monitoring of the treatment through forms of real-time imaging such as magnetic resonance imaging is important to properly guide the treatment process and is only possible through a strong mathematical understanding of the imaging methods, but the focus of this thesis is on the mechanics of treatment rather than the monitoring of its effects.

However, other physiological challenges noted in Bailey *et al.* have a more direct impact on this work. The first of these is the unintended absorption of ultrasound. The

intent in HIFU is to only cause significant physical effects on the tissue at the focal point of the ultrasound. In a homogeneous material, this happens naturally, as the most energy is absorbed at the focal point where the ultrasound is concentrated, as previously described. However, the tissue is not homogeneous and different parts of the tissue absorb ultrasound energy at different rates, particularly skin and bone. In the case of skin, the rate is several times higher than other soft tissues and so will react more strongly to HIFU. Since it is necessary for the ultrasound to pass through skin first, care must be taken to minimize energy absorption from the ultrasound waves passing through the skin to avoid burns, which are the most common side-effect of transcutaneous HIFU treatment [2]. Bone is even more effective at absorbing ultrasound than skin and, in many applications, it is preferrable to avoid bone entirely in the path of the ultrasound, even to the point of removing ribs in the way of the ultrasound beam [12]. In cases where the HIFU target is in bone, the ultrasound has almost no penetrative power, as it is absorbed almost immediately. These effects must be taken into consideration in treatment planning, which is the second challenge considered by Bailey *et al.* and the most mathematically-focused challenge. This restricts us from considering only the effects at the focal point, as it is necessary to ascertain the effects of this early attenuation.

Treatment planning covers a number of considerations requiring proper mathematical modeling. One aspect of particular importance is identifying the evolution of the tissue properties over the treatment. The focal point is typically about the size of a rice kernel and the treatment region for the removal of many tumours is significantly larger [2]. In order to destroy the entire tumour, it becomes necessary to make several individual lesions from different passes of the ultrasound. However, the tissue properties change as the tissue is heated and as it goes through thermally-induced necrosis [26, 27], making later passes dependent upon previous passes. It is necessary to have models which reflect these changes to the tissue in order to avoid unpredictable behaviour in later passes. Some of this unpredictability can be lessened by allowing the tissue to cool completely between passes, but this method becomes prohibitively time-consuming [2]. In order to properly predict these changes, it is necessary to calibrate the parameters in the models, which can be a challenge, as experimental measurements can be difficult to obtain, particularly for abnormal states such as high temperature

states, and the differences between patients have to be estimated on sometimes limited information.

This lack of information is partially a result of technical limitations. Mathematically interesting but clinically infeasible results have their uses, especially as advancing technology makes some previously clinically infeasible methods viable. However, in the short term, it is preferrable to consider clinically applicable results. To be applicable, certain non-theoretical considerations must be considered, such as ease of use, portability, and affordability. However, theoretical modeling can greatly assist in dealing with these technical limitations. Clinical trials and targeted engineering, which are important in the continued development of HIFU treatments, are expensive and are not undertaken lightly. Through theoretical modeling, it is possible to predict likely outcomes and weed out unnecessary tests. The predictive power of the models also increases the reliability of the treatment methods, which is an important technical consideration [2].

Beyond the physiological challenges, the models themselves provide significant mathematical challenges whose resolution can then have important impact upon the resultant treatment methods. As previously noted, the tissue parameters change over the course of the treatment, but the equations most commonly used in HIFU modeling treat these parameters as constant values. Changing these parameters into functions dependent on the tissue's time-dependent properties, such as temperature, requires an alternative derivation of the models and even using a simple piecewise function for the parameters complicates the use of the equations in the model. The typical model of HIFU treatment considers three equations where each equation is only reliant upon the equations coming before it. However, the inclusion of temperature effects on acoustic properties, for example, results in a cyclical coupling of the acoustic equation and the heat equation. In contrast, previous models have only included a source term in the heat equation which depends on the solution of the acoustic equation, whilst the solution of the acoustic wave equation is independent of the solution of the heat equation.

It is also necessary to consider what properties and characteristics are crucial aspects to be captured in in the model. As an example, some clinical studies use an equation known as the Rayleigh-Sommerfeld integral to model the propagation of the

ultrasound waves, which is a linear model, but many mathematical papers prefer the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation, which, amongst other things, includes nonlinear interaction of the ultrasound waves. This nonlinear interaction can result in significant deviation from the predictions of a linear model, as shown in Figure 2 [2], but it is much less significant in many circumstances. The choice of which terms are significant is important, as excluding significant terms will result in inaccurate results, but including unnecessary terms will complicate the understanding of the effects of the interactions and decrease the speed and ease of use of the model.

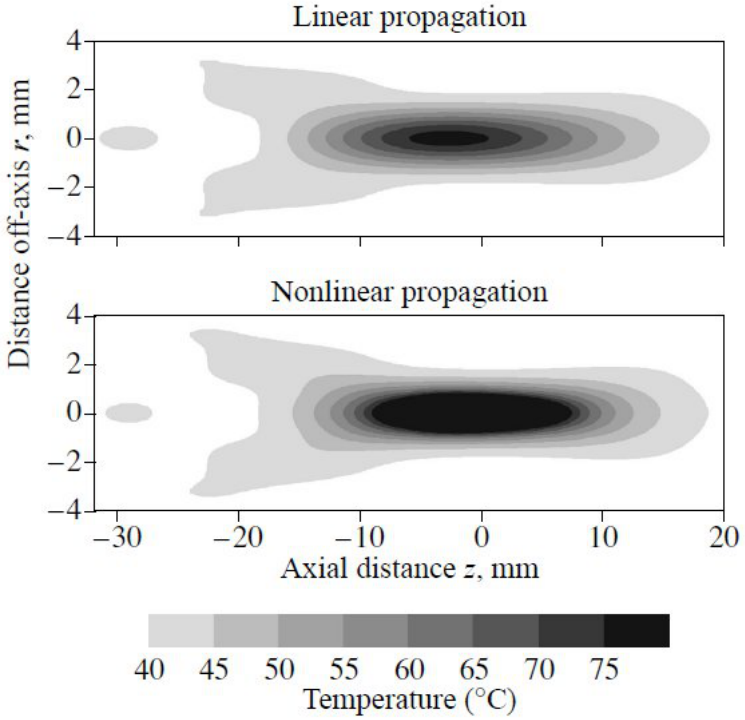

Figure 2: Potential effect of nonlinear ultrasound modeling [2].

This choice of terms is further complicated by the available information limiting an exact description by the model. For example, it is known that bloodflow through a region of tissue heated by HIFU has an effect on the temperature distribution throughout the tissue [51]. However, an exact distribution of the blood vessels in the treatment region is unavailable, requiring a hypothetical blood vessel network to be used as an approximation. Similar shortcomings in our knowledge of the exact distribution of the

heterogeneous nature of the tissue complicate the relevance and applicability of the homogenized approximations used in the model.

Preliminary models

While there is some variation in the specific equations used in the model, the overall form of the model has become largely standardized as a system of three equations. As a first approximation, these equations may be presented in an order such that each relies only on the previous equation in the set.

The first equation is an acoustic equation, which describes the propagation of the ultrasound waves. This equation is often either based on the Helmholtz equation, such as the Rayleigh-Sommerfeld integral that results from a Green's function solution to the Helmholtz equation, or derived from similar equations of acoustic wave motion, such as the KZK equation that follows a similar derivation with nonlinear equations. The Helmholtz equation itself may be written in the form,

$$(\nabla^2 + k_w^2)p = 0 \tag{2.1.1}$$

where p is the acoustic pressure and k_w is the wave number. This equation is also sometimes written in terms of the velocity potential ϕ, but under the assumptions of the Helmholtz equation, the acoustic pressure and the velocity potential are proportional to each other by a constant factor [40].

This acoustic pressure results in a heat term from the attenuation of the wave as it passes through the tissue, q_m, which for a constant absorption term α may be written as

$$q_m = 2\alpha I = \frac{2\alpha < p^2 >}{c_0 \rho_0} \tag{2.1.2}$$

where I is the acoustic intensity, c_0 is the speed of sound in the medium, ρ_0 is the density of the medium at constant pressure, and the brackets $< \cdot >$ denote time-averaging. [2].

This q_m is used as a heat source term in the heat equation. While a number of variations have been proposed [5], a commonly used heat equation is the Pennes bio-

heat equation [3]. This equation was developed in the middle of the 20th century in the study of temperature distribution in the resting forearm at room temperature conditions [51], but it has since also been used to describe temperature distribution under abnormal temperature conditions, like the high temperatures of HIFU treatment, due to its relative accuracy and simplicity. The heat source term that was originally used for metabolic heat production is replaced by the heat source term from the HIFU treatment, q_m, resulting in the equation for temperature T,

$$\rho_0 c_p \frac{\partial T}{\partial t} = \nabla \cdot k\nabla T + c_{p_b} W_b (T_a - T) + \frac{2\alpha < p^2 >}{c_0 \rho_0} \tag{2.1.3}$$

where c_p and c_{p_b} are the specific heat capacities for tissue and blood, respectively, k is the thermal conductivity, W_b is the blood perfusion rate, and T_a is the arterial blood temperature. The blood perfusion rate is not directly related to a measureable property of the tissue, but is instead a fitting constant to approximate the way heat is removed from the HIFU-heated tissue through the flow of blood in the region. This term and its criticisms will be discussed in more detail below.

While the bioheat equation gives a good description of the temperature distribution in the tissue as a result of the HIFU, the effect on the tissue is more important in applications that aim to thermally necrose tissue such as cancerous tumours than simply the temperature distribution. This is accomplished through an equation for equivalent thermal dose or thermal damage. In HIFU applications, a thermal dose equation, which converts the temperature distribution to the equivalent amount of time to cause the same effect at a constant temperature of $43^\circ C$, is used. The equation takes the form,

$$TD_{43^\circ C} = \int_0^t R^{43^\circ C - T(t')} dt' \tag{2.1.4}$$

where $TD_{43^\circ C}$ is the equivalent time at $43^\circ C$ and R is a piecewise constant such that [2]

$$R = \begin{cases} 0.25 & : T(t) < 43^\circ \\ 0.5 & : T(t) \geq 43^\circ \end{cases} \tag{2.1.5}$$

Both this equation and the thermal damage model used in applications such as skin

burns and laser hyperthermia are derived from the Arrhenius equation. The Arrhenius equation is a logarithmic fit which relates the reaction rates of chemical processes at different temperatures. This Arrhenius fit is only accurate for certain ranges of temperatures [18], which is the reason for the change in R in different temperature ranges. The thermal damage model and the derivation of both Arrhenius equation-derived equations will be discussed below.

Acoustic equations

In the study of the propagation of ultrasound in biological tissues, most work in the field begins with the theory of acoustic waves in fluids. In soft tissues, this is a reasonable assumption, as much of the tissue is made up of fluid. This assumption is less reasonable in bone, which is more solid, and thus requires alterations to the usual equations to take into account nonlinear effects which may be significant.

In the case of both the Helmholtz and the Khokholov-Zabolotskaya-Kuznetsov (KZK) equations, the derivation of the acoustic model begins with conservation equations. Following Landau and Lifshitz's derivation of the Helmholtz equation [40], since a sound wave in a medium is physically expressed through the oscillatory motion of the medium, conservation equations are chosen to consider three properties: the velocity $\vec{v}$ (of the oscillatory motion which makes up the acoustic wave), density ρ (as the wave compresses and decompresses the medium as it passes through), and pressure p (as the compression and decompression causes a change in local pressure). In a fluid, these properties may be related through the Euler's equations of fluid dynamics for an inviscid fluid,

$$\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v} = -\frac{1}{\rho}\nabla p \tag{2.2.1}$$

and a continuity equation

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v}) = 0 \tag{2.2.2}$$

For the derivation of the classical wave equation, it is assumed that the sound wave causes small oscillations in the medium where the velocity of the particles in the medium,

$\vec{v}$, is small compared to the speed of sound c. Since these are small oscillations, this causes only small changes in pressure and density in the medium. We can represent this by expressing the pressure p and density ρ as

$$p = p_0 + p'; \quad \rho = \rho_0 + \rho' \tag{2.2.3}$$

where p_0, ρ_0 are the unperturbed, equilibrium pressure and density and p', ρ' are the changes in these equilibria, which are assumed to be much smaller than the equilibrium values. Since these changes and the velocity are all assumed to be small, any terms with two or more of these perturbation terms multiplied together will be even smaller and may be neglected. Also, the equilibrium values are assumed to be constant, so any derivatives of them are zero. Thus, placing the terms which may be dropped within square brackets, equation (2.2.1) becomes

$$\begin{aligned}
\frac{\partial \vec{v}}{\partial t} + \big[(\vec{v}\cdot\nabla)\vec{v}\big] &= -\frac{1}{\rho_0+\rho'}\nabla(p_0+p') \\
(\rho_0+\rho')\frac{\partial \vec{v}}{\partial t} &= -\big[\nabla(p_0)\big] - \nabla(p') \\
\rho_0\frac{\partial \vec{v}}{\partial t} + \big[\rho'\frac{\partial \vec{v}}{\partial t}\big] &= -\nabla(p') \\
\frac{\partial \vec{v}}{\partial t} &= -\frac{1}{\rho_0}\nabla(p')
\end{aligned} \tag{2.2.4}$$

and equation (2.2.2) becomes

$$\begin{aligned}
\frac{\partial}{\partial t}(\big[\rho_0\big] + \rho') + \nabla\cdot\big((\rho_0+\rho')\vec{v}\big) &= 0 \\
\frac{\partial \rho'}{\partial t} + \rho_0\nabla\cdot\vec{v} + \big[\nabla\cdot(\rho'\vec{v})\big] &= 0 \\
\frac{\partial \rho'}{\partial t} + \rho_0\nabla\cdot\vec{v} &= 0
\end{aligned} \tag{2.2.5}$$

However, since this is a system of two equations in three variables, we eliminate the small change in density by assuming the medium is *adiabatic* – that is, heat does not enter or leave the system – which allows us to relate the change in pressure to the change

in density by

$$p' = \Big(\frac{\partial p_0}{\partial \rho_0}\Big)\rho' \tag{2.2.6}$$

where the derivative with respect to the equilibrium density is taken for constant entropy. It should be noted that the assumption that the medium is adiabatic does not appear in the derivation of the KZK equation [37], as this may not be a reasonable assumption in medical practice.

We also eliminate reliance on the change in pressure p' by expressing the velocity of the fluid particles, $\vec{v}$, in terms of a scalar function, the velocity potential ϕ, which always exists in the case of irrotational flow. Since $\vec{v} = \nabla\phi$, then equation (2.2.4) gives us that

$$\begin{aligned} \frac{\partial}{\partial t}\nabla\phi &= -\frac{1}{\rho_0}\nabla(p') \\ \nabla\Big(\frac{\partial \phi}{\partial t} + \frac{1}{\rho_0}p'\Big) &= 0 \end{aligned} \tag{2.2.7}$$

Since the gradient is zero, then the expression inside is equal to a constant. For our purposes, it may be assumed that this constant is zero, as this expression will be later used in a derivative. Thus,

$$p' = -\rho_0 \frac{\partial \phi}{\partial t} \tag{2.2.8}$$

Combining equations (2.2.6) and (2.2.8), we obtain

$$\rho' = -\frac{\rho_0}{\partial p_0 / \partial \rho_0}\frac{\partial \phi}{\partial t} \tag{2.2.9}$$

Thus, substituting this into equation (2.2.5) and replacing the velocity with the velocity potential, it is straightforward to show that this gives rise to the wave equation:

$$\frac{\partial^2 \phi}{\partial^2 t} - c^2 \Delta\phi = 0 \tag{2.2.10}$$

for $c = \sqrt{\frac{\partial p_0}{\partial \rho_0}}$ for constant entropy.

As mentioned above, a similar process is used for deriving the KZK equation, which

is commonly used in the literature for high-intensity focused ultrasound, under different initial equations but similar assumptions for the size of fluid particle velocity and pressure and density variations. The standard form used in this application was derived by Kuznetsov [37] for approximately planar waves – that is, sound waves that do not change as much perpendicular to the direction that the sound wave is moving as they do parallel to this direction.

In Kuznetsov's derivation, he expressed the equation in terms of the velocity potential, but it is currently used in the literature in terms of the pressure, through a relation like (2.2.8). The reason for this focus on acoustic pressure comes from the fact that the heat produced by the ultrasound is usually given in terms of the pressure, as will be discussed in the following section. Using the notation of Bailey et al. [2], the KZK equation describing the pressure in the medium that the sound wave passes through is given by

$$\frac{\partial p}{\partial z} - \frac{\beta}{{c_0}^3 \rho_0} p \frac{\partial p}{\partial \tau} - \frac{b}{2{c_0}^3 \rho_0} - \frac{b}{2{c_0}^3 \rho_0} \frac{\partial^2 p}{\partial \tau^2} = \frac{c_0}{2} \int_{-\infty}^{\tau} \Delta_{\perp} p(\tau') d\tau' \tag{2.2.11}$$

where z is the coordinate along the direction of the sound wave propagation and τ is a delayed time variable for sound wave propagation along the axis of motion such that $\tau = t - \frac{z}{c_0}$. This form of the KZK equation has four terms, which are, in order: the change in pressure along the direction of the main sound wave movement; a nonlinear term, where β is a nonlinear coefficient; a term for attenuation (the loss of intensity as the wave passes through the medium), where b is a dissipative coefficient; and a term for diffraction (the bending of sound waves due to obstacles), where $\Delta_{\perp}$ is a Laplacian operator only for coordinates perpendicular to z.

Another model used in practice is the Rayleigh integral, which considers a wave propagating from an area on an infinite rigid plane, which may be derived from the Helmholtz equation through the use of Green's functions. The Green's function for the Helmholtz equation of a wave propagating from a point source on a rigid flat surface at $z = 0$ is

$$G_k(x_s|x) = {R_1}^{-1} e^{ikR_1} + {R_2}^{-1} e^{ikR_2} \tag{2.2.12}$$

for

$$R_{1,2} = \left[(x_S - x)^2 + (y_S - y)^2 + (z_S \mp z)^2\right]^{\frac{1}{2}} \tag{2.2.13}$$

where R_1 and R_2 take different values for the $\mp$. The equation may be written

$$p(x) = \frac{1}{4\pi}\int\int_S \left[p(x_S)\nabla_S G_k(x_S|x) - G_k(x_S|x)\nabla_S p(x_s)\right]_{z_S=0} \cdot e_z dx_S dy_S \tag{2.2.14}$$

Since the subset of the rigid surface we are integrating over is at $z = 0$, then $z_S = 0$. At $z_S = 0$,

$$\begin{aligned} \nabla_S G_k(x_S|x) \cdot e_z &= 0 \\ G_k(x_S|x) &= 2R^{-1}e^{ikR} \\ \nabla_S p(x_S) \cdot e_Z &= i\omega\rho v_n(x_S, y_S) \end{aligned} \tag{2.2.15}$$

and thus (2.2.14) reduces to the Rayleigh integral, [52]

$$p(x) = -\frac{i\omega\rho}{2\pi}\int\int v_n(x_S, y_S)R^{-1}e^{ikR}dx_S dy_S \tag{2.2.16}$$

Bioheat equations

Since the main desired effects of HIFU on biological tissue – specifically, the cauterization of tissue – are achieved as a result of the heat produced, it is important to understand how this heat flows and redistributes through the body. To do this, most researchers rely on the bioheat equation derived by Pennes in the 1940s for a resting human forearm [51].

The experiment was run on men with normal blood pressure and no evidence of disease in the muscles or nervous system. The subjects lay on a hospital bed from between 8 and 9 AM until four to six hours had passed, nude save for a small sheet over their hips. Conditions in the lab, such as temperature, were kept as consistent as possible, though they encountered issues in keeping humidity consistent. During this time, the temperature in the forearms of the subjects were measured by passing a wire with ther-

mocouples attached through a section of the forearm where it wouldn't pierce either nerves or arteries. These thermocouples measured the temperature at their location in the forearm, giving an approximate distribution of temperature within the tissue. It is approximate, as it gave a number of discrete points rather than a continuous spectrum and there was a chance that the thermocouples would shift in position within the tissue, though the latter issue was minimized by holding the wire taut. There was also the issue that heat would be conducted by the wires of thermocouples and the alcohol swab prior to insertion lowered the local temperature, but it was assumed that this effect would be negligible after giving an hour for the system to return to equilibrium. This data was used to then fit the parameters in his derived bioheat equation [51].

The actual derivation of the bioheat equation required a few assumptions about the form of the forearm for the sake of fitting this data, but these particular assumptions are not required for understanding the equation in general applications and so will not be reported here. However, some assumptions are relevant to all applications. First, the vasculature is not specifically modeled. Every point in space is assumed to contain both tissue and blood vessels, with the blood flow uniform throughout. Second, the thermal conductivity, k, is assumed to be constant throughout the tissue being modeled; in cases where there are multiple layers of tissue, it is assumed to be constant within any specific layer.

The equation is, in essence, the classical heat equation [24] with specific assumptions for the heat source term. Specifically, it is assumed that heating in the tissue is from the movement of heat due to blood flow through the tissue and from tissue metabolism [51]. The rate of heating from these effects are, respectively, h_b and h_m, though modern sources (such as Bailey *et al.* [2] and Khaled and Vafai [36]) refer to the latter as q_m. Using the notation of Khaled and Vafai, while referencing Bailey *et al.* for the form of the equation in three dimensions, the heat equation under this heat source $h_b + q_m$ may be expressed as

$$\rho c_p \frac{\partial T}{\partial t} = k\nabla^2 T + h_b + q_m \tag{2.3.1}$$

where ρ is the tissue density, c_p is the tissue specific heat, T is the tissue temperature, and k is the tissue thermal conductivity [36]. A function for the rate of heat generation

from the tissue metabolism is not given. In HIFU, this term is usually replaced by a function for the heat generated by the ultrasound. This replacement is done without explanation, but it reflects an unstated assumption that the metabolic heat generation occurs over too long a time period to be relevant.

The heat transfer between blood and tissue, by contrast, is considered to be proportional to the difference between the temperature of blood flowing into a point in the tissue or the "arterial blood temperature," T_a, and the temperature of blood flowing out of that point in the tissue or the "venous blood temperature," T_v [51]. Specifically, using the notation of Khaled and Vafai [36],

$$h_b = c_{p_b} W_b (T_a - T_v) \tag{2.3.2}$$

where c_{p_b} is the specific heat of blood and W_b is the volumetric rate of blood flow through tissue. In order for this function to be useful, it is necessary to consider these blood temperatures as constants or as functions of time, space, and/or temperature. In Pennes's derivation, the incoming arterial blood temperature T_a is assumed to be constant [51], though some alternate derivations of temperature models in biological tissues have included a separate equation for the blood temperature [57].

As for the outgoing blood temperature, Pennes assumed that the venous blood temperature came to an equilibrium value somewhere between the temperature of the tissue T and the incoming arterial blood temperature T_a so that

$$T_v = T + k'(T_a - T) \;\; ; \quad 0 \leq k' \leq 1 \tag{2.3.3}$$

where k' is an equilibrium constant, so that equation (2.3.2) becomes

$$h_b = c_{p_b} W_b (k' - 1)(T - T_a) \tag{2.3.4}$$

Pennes notes that finding the actual equilibrium value of the venous blood temperature would require experimental validation. However, he hypothesized that the blood would reach complete equilibrium with the tissue as it left, so that $k' = 0$ and thus the outgoing

blood temperature T_v is equal to the tissue temperature T. This means that the rate of heat transfer between blood and tissue is

$$h_b = c_{p_b} W_b (T_a - T) \tag{2.3.5}$$

He incorrectly identified this as occurring at $k' = 1$ [51], where $T_v = T_a$, but this would mean that the blood does not lose or gain any heat as it passes through the tissue. In such a case, there would be no heat transfer between blood and tissue.

Taking this into account, we arrive at the Pennes bioheat equation as used in the literature,

$$\rho c_p \frac{\partial T}{\partial t} = k\nabla^2 T + c_{p_b} W_b (T_a - T) + q_m \tag{2.3.6}$$

Thermal dose equations

Although the two thermal dose equations considered in this thesis have different forms, they both are essentially derived from the Arrhenius equation [18, 68]. The Arrhenius equation is an empirical relation used in theoretical chemistry to describe the change in the reaction rates of chemical reactions with regards to temperature. This was initially used by Arrhenius in the study of sugars breaking down in the presence of various acids. He found that the effect of temperature on this reaction's rate was too large to be accounted for merely through the change in kinetic energy of the molecules or dissociation of the acids from the temperature. The change between the reaction rates at different temperature was found to be [34]

$$k_{T_1} = k_{T_0} e^{\mu (T_1 - T_0)/2T_0 T_1} \tag{2.4.1}$$

where T_i is the temperature in $^\circ K$, k_{T_i} is the reaction rate at temperature T_i, and μ is a constant related to the energy of activation (or, in this case, inactivation [18]). This relation has been found to be considerably accurate in describing the change in reaction rates of chemical processes over limited temperature ranges, with especially limited temperature ranges in biological reactions like inactivation of proteins [34]. In the case

of the thermal dose and thermal damage equations, this temperature range has not been studied in great depth. The thermal dose equation was developed specifically in the range of $37°C$ to $46°C$ for Chinese hamster ovary cells, with a parameter change at $43°C$ [18]. The resultant equation is considered to give a decent approximation for lesion formation at higher temperatures due to necrosis occuring so rapidly at these higher temperatures [2], but the parameter values and critical temperature of $43°C$ were chosen arbitrarily, and are known to vary under various circumstances [55]. Studies in pig skin burn models support this idea, suggesting another change in parameter values somewhere in the $50°C$ range and that parameter values may depend on cell type, but different studies do not all agree on the exact values [68]. This does suggest that current parameter values should be considered with caution outside the studied $37°C$ to $46°C$ range.

Within the appropriate temperature ranges, this exponential relation in (2.4.1) allows for a linear fit to the relation between the logarithm of the reaction rate and the inverse of the temperature in degrees Kelvin. From this, the Arrhenius equation is thus also sometimes written in the form [34]

$$v(T) = Ae^{-E/RT} = Ae^{-\Delta H/2T} \tag{2.4.2}$$

where v is the velocity of the reaction, E is the activation energy, R is the gas constant, T is the temperature in degrees Kelvin, and ΔH is the inactivation energy of molecules proposed by Dewey *et al.* [18] to be the most ciritcal in the reaction causing cell death in cal/mole. The parameter A is most accurately a temperature-dependent function, which in the case of thermal necrosis takes the form

$$A(T) = 2.05(10^{10})e^{\Delta s/2}T \tag{2.4.3}$$

where Δs is the entropy of inactivation in cal/degree Kelvin/mole, but A is typically treated as a constant as the change in the linear $A(T)$ due to temperature is much smaller than the change due to the exponential part of $v(T)$ [18]. It should be noted that the units for ΔH, Δs, and T will result in the units in the exponential terms in $v(T)$ to cancel

out.

This version of the Arrhenius equation is used to derive both the most well-known[33] model for the macroscale effect of heat on tissue in HIFU, the thermal dose model[55], as well as the thermal damage model used in skin burn and laser irradiation models [68]. To derive the thermal dose model, we define $\frac{1}{\tilde{D}_0} = v(T)$ as exponential slope of the heat inactivation survival curve. Then the change in the slope per degree change in the temperature, R, is[18]

$$R = \frac{\tilde{D}_0 \ \ at \ \ T+1}{\tilde{D}_0 \ \ at \ \ T} = e^{-\Delta H/2T(T+1)} \tag{2.4.4}$$

where ΔH and T retain their values as per the units expressed above, but are unitless. This results from the ratio of $\tilde{D}_0$ to itself will cancel all units. In a similar form to the relation between reaction rates in (2.2.1), the time required to have the same effect at different constant temperatures can be related by

$$t_1 = t_2 R^{T_1 - T_2} \tag{2.4.5}$$

for constant temperatures T_1, T_2 and elapsed times t_1, t_2 [55]. A variable temperature may be written as an integral by approximating it as a Riemann sum and taking the limit as $\Delta t \to 0$. Using $43°C$ as a reference temperature, the thermal dose at $43°C$

$$TD_{43^\circ} = \int_0^t R^{43°C - T(t')} dt' \tag{2.4.6}$$

where the thermal dose $TD_{43°C}$ is the time taken to cause an equivalent reaction in the tissue at $43°C$ to the temperature profile T over time t [55]. Irreversible thermal damage to the tissue is considered to have taken place at 240 equivalent minutes at $43°C$ [2].

The parameters for the Arrhenius equation are determined by taking the natural log of $v(T)$ and linearly fitting $\ln v(T)$ to $\frac{1}{T}$ (see [18]). However, the Arrhenius equation only provides a good fit as long as the range of temperatures is not too large [34]. In the case of the thermal dose model, this is demonstrated by taking two sets of parameter values: one below $43°C$ and one above it [18]. For these parameter values, the value of

R does not change significantly and so may be approximated by[55]

$$R = \begin{cases} 0.25 & : T(t) < 43^\circ \\ 0.5 & : T(t) \geq 43^\circ \end{cases} \tag{2.4.7}$$

These parameters fit the survival curves of the studied Chinese hamster ovary cells, but they consider only the range of temperatures between $37^\circ C$ and $46^\circ C$,[18].

To derive the thermal damage model, the reaction velocity $v(T)$ is used as the reaction rate of the chemical reaction of protein P to denatured protein D,

$$P \xrightarrow{v(T)} D$$

as the main process behind thermal necrosis is the denaturation of proteins [2]. Thus, the changes in concentrations of the reactants C_i may be modeled as

$$\frac{dC_D}{dt} = v(T)C_P = v(T)(C_T - C_D) \tag{2.4.8}$$

where C_T is the total concentration of proteins, both denatured and not denatured. This may be rearranged and integrated to give

$$\begin{aligned} \frac{dC_D}{C_T - C_D} &= v(T)dt \\ \ln(C_T) - \ln(C_T - C_D) &= \int_0^t v(T)dt \\ \ln\left(\frac{C_T}{C_T - C_D}\right) &= \int_0^t v(T)dt' \end{aligned} \tag{2.4.9}$$

This logarithm, which represents the fraction of denatured proteins, is defined as the thermal damage parameter $\Omega = \ln\left(\frac{C_T}{C_T - C_D}\right)$. Thus, the thermal damage equation is[73]

$$\Omega(t) = A\int_0^t e^{E/RT(t')}dt' \tag{2.4.10}$$

This thermal damage parameter allows for judging various levels of damage based on the percentage of proteins which have been denatured by thermal necrosis. As the equa-

tion was initially developed for burn models, this has been used to determine different severities of burns [68], but in the case of thermal necrosis, the second-degree burn level of $\Omega \geq 1$ is used to represent irreversible damage [73].

Due to the fact that both the thermal dose and thermal damage models are derived from the Arrhenius equation, it is simple to convert fitted parameters of the thermal damage model into the thermal dose model. An approximate constant R can be developed through

$$R \approx e^{-E/R_{gas}T(T+1)} \tag{2.4.11}$$

for temperatures T within the range where the thermal damage parameters are valid. The inverse problem of converting thermal dose parameters into thermal damage parameters is not possible, as the thermal dose model only has one parameter R which combines two parameters A and E of the thermal damage model. However, work on the thermal dose model has only considered the values of R noted above and thus such conversions are unecessary.

Chapter 3: System of bioheat equations

The third term in (2.3.6), the blood perfusion term can be heuristically justified on the basis of Newton's Law of cooling. The Pennes bioheat equation has been the subject of criticism, as it is less justified physically, and we refer the reader to Wissler[66] for further discussion of more physically justifiable extensions of this equation. Thus, using a common approximation to treat the soft tissue as an incompressible fluid, we may use a more standard term that takes fluid flow into account in the heat source term.

Although this assumption of incompressibility may appear unjustified in the context of ultrasound, as a truly incompressible fluid would be acoustically inert, this model focuses only on the transmission of heat in biological tissue and the evolution of the temperature field. In such a model, the assumption of incompressibility may be justified [42]. The methods used in this thesis may be used with some adjustments in the case of a slightly compressible fluid ($\nabla_x \cdot \vec{v}(t,x) = \varepsilon$). Further research is required to move to assumptions which are valid in every part of the larger problem, but this first step provides a baseline.

Let Ω be a bounded domain of x in $\mathbb{R}^d$. In our application, $d = 3$, but the following proofs work in general. As a consequence of the assumption that the soft tissue behaves like an incompressible fluid, we have

$$\nabla_x \cdot \vec{v}(t,x) = 0 \tag{3.1}$$

for fluid velocity of the biological tissue, $\vec{v}$ and for $t \geq \tau$ for some $\tau \in \mathbb{R}$. The velocity and temperature are related by Darcy's Law in the following manner:

$$\vec{v}(t,x) = \nabla_x \cdot P(t,x) - \vec{\gamma} \cdot T(t,x) \tag{3.2}$$

where P is the fluid pressure in the biological tissue and $\vec{\gamma}$ is a constant parameter to match the scalar temperature with the other vector terms. Finally, using this fluid velocity, we arrive at a modified heat equation where the ad hoc blood perfusion term

is replaced with a more theoretically sound convection term,

$$\frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \vec{v}(t,x)\nabla_x \cdot T(t,x) + h(t,x) \tag{3.3}$$

In the case where $\vec{v}(t,x)$ and $h(t,x)$ are known, then (3.3) is an advection-diffusion equation with a known proof of well-posedness. However, in real application, the velocity term will not generally be measurable due to the complexities of biological tissue, so we cannot rely on this. The system of nonautonomous equations (3.1-3.3) defines the fluid velocity in terms of tissue temperature and fluid pressure, which means that, to solve this system of nonautonomous equations, we need to find (P,T). We assume that we know the initial distribution of the functions in Ω and that we may define non-homogeneous boundary conditions such that

$$P(t=\tau,x) = P_\tau(x); \qquad P(t,x')|_{x'\in\partial\Omega} = P_{bd}(x') \tag{3.4}$$

$$T(t=\tau,x) = T_\tau(x); \qquad T(t,x')|_{x'\in\partial\Omega} = T_{bd}(x') \tag{3.5}$$

The following compatability conditions need to be imposed:

$$P_\tau(x')|_{x'\in\partial\Omega} = P_{bd}(x') \qquad T_\tau(x')|_{x'\in\partial\Omega} = T_{bd}(x') \tag{3.6}$$

Without loss of generality, we assume $P_{bd}(x') = 0$.

However, it is possible to define the fluid pressure P in terms of the temperature T by applying the gradient operator to equation 3.3. Using equation 3.2, we obtain

$$\Delta_x P(t,x) = \vec{\gamma}\nabla_x \cdot T(t,x) \tag{3.7}$$

This leads to the full system of nonautonomous equations which constitute our model,

and take the form

$$\Delta_x P(t,x) = \vec{\gamma}\nabla_x \cdot T(t,x) \tag{3.8}$$

$$\vec{v}(t,x) = \left(\nabla_x \cdot (-\Delta_x)^{-1}\vec{\gamma}\cdot(\nabla_x T) + T\right) \tag{3.9}$$

$$\frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \vec{v}(t,x)\nabla_x \cdot T(t,x) + h(t,x) \tag{3.10}$$

$$P(t=\tau,x) = P_\tau(x); \qquad P(t,x')|_{x'\in\partial\Omega} = P_{bd}(x') \tag{3.11}$$

$$T(t=\tau,x) = T_\tau(x); \qquad T(t,x')|_{x'\in\partial\Omega} = T_{bd}(x') \tag{3.12}$$

We seek a solution of (3.8-3.12) as a pair

$$\big(T(t,x),P(t,x)\big) \in W^{(1,2),p}\big([\tau,\eta]\times\Omega\big) \times W^{(1,3),p}\big([\tau,\eta]\times\Omega\big) \tag{3.13}$$

for $t \geq \tau$, which satisfy the equations in the sense of distributions. Note that $u \in W^{(1,2),p}\big([\tau,\eta]\times\Omega\big)$, by definition, means that

$$u \in L^p([\tau,\eta]\times\Omega)), \;\; \partial_t u \in L^p\big([\tau,\eta]\times\Omega\big), \;\; D^\alpha u \in L^p\big([\tau,\eta]\times\Omega\big) \tag{3.14}$$

for $0 \leq |\alpha| \leq 2$. The value of $p = p(n)$ (where n is the dimension of the space $\Omega \in \mathbb{R}^n$) can be chosen "a posteriori" to guarantee compact embedding[58].

$W^{(1,2),p}\big([\tau,\eta]\times\Omega\big) \subset C\big([\tau,\eta],C^\varepsilon(\Omega)\big)$ for some $\varepsilon \in (0,\frac{3}{2}]$. It is known that for sufficiently large $p = p(n) >> 1$, dependent on dimension n, this compact embedding holds (see Simon[58]). From (3.13), it follows

$$\begin{aligned} T_\tau(x) &\in W^{2(1-\frac{1}{p}),p}(\Omega), \qquad P_\tau(x) \in W^{3-\frac{2}{p},p}(\Omega) \\ T_{bd}(x') &\in W^{2-\frac{1}{p},p}(\Omega), \qquad P_{bd}(x') \in W^{3-\frac{1}{p},p}(\Omega) \end{aligned} \tag{3.15}$$

As already indicated, we seek a solution

$$\big(T(t,x),P(t,x)\big) \in W^{(1,2),p}\big([\tau,\eta]\times\Omega\big) \times W^{(1,3),p}\big([\tau,\eta]\times\Omega\big) \tag{3.16}$$

that satisfies (3.8-3.10) in a weak sense. To that end, we will assume the following

compatibility conditions are satisfied:

$$T_\tau(x) = T_{bd}(x), \qquad P_\tau(x) = P_{bd}(x) \tag{3.17}$$

Lemma 2.1. *Let $\big(P(t,x),\ T(t,x)\big)$ be a solution of (3.8-3.10), with $P_{bd}(x^{'}) := 0$. Then for every fixed $t \geq 0$ and for every $1 < p < \infty$, we have*

$$||P(t,x)||_{W^{3-\frac{2}{p},p}(\Omega)} \leq C||T(t,x)||_{W^{2-\frac{2}{p},p}(\Omega)} \tag{3.18}$$

Proof Indeed, this implies that $P(t,x)$ satisfies

$$\begin{cases} \Delta_x P(t,x) = \vec{\gamma}\nabla_x T, \qquad x \in \Omega \\ P|_{\partial\Omega} = 0 \end{cases} \tag{3.19}$$

From assumptions of Lemma 2.1, it follows that $\vec{\gamma}\nabla_x T \in W^{1-\frac{2}{p},p}(\Omega)$. Then, by elliptic regularity theory (which studies the behaviour of weak solutions of elliptic partial differential equations; see Renardy & Rogers[53]), the assertion of Lemma 2.1 follows.

Corollary 2.1. *Let $\big(P(t,x), T(t,x)\big)$ be a solution of (3.8-3.12). Then the following holds:*

$$||P(t,x)||_{W^{(1,3),p}([\tau,\eta]\times\Omega)} \leq C||T(t,x)||_{W^{(1,2),p}([\tau,\eta]\times\Omega)} \tag{3.20}$$

Thus, it is sufficient to prove all "a priori" estimates for the temperature component of $\big(P(t,x), T(t,x)\big)$ of the solution to (3.8-3.12).

The following Corollary 2.2 will be used in the proof of uniqueness of solutions. However, to formulate Corollary 2.2, some preliminary work is necessary. From

$$\begin{cases} \Delta_x P(t,x) = \vec{\gamma}\cdot\nabla_x T \\ P(t,x)|_{\partial\Omega} = 0 \\ \vec{v} = \nabla_x P - \vec{\gamma}T \end{cases} \tag{3.21}$$

It follows that

$$\vec{v} = -\big(\vec{\gamma} + \nabla_x(-\Delta_x)^{-1}\vec{\gamma}\cdot\nabla_x\big)T(t,x) \tag{3.22}$$

where the inverse $(-\Delta_x)^{-1}$ is taken with homogeneous Dirichlet boundary conditions. We denote by

$$\Psi(x,D)T(t,x) := -\big(\vec{\gamma} + \nabla_x(-\Delta_x)^{-1}\vec{\gamma}\cdot\nabla_x\big)T(t,x) \tag{3.23}$$

Corollary 2.2. *The operator $\Psi(x,D)$ defined by (3.23) acts from $L^2(\Omega)$ to $L^2(\Omega)$ and satisfies for each fixed $t \geq 0$*

$$||\Psi(x,D)\xi(x)||_{L^2(\Omega)} \leq C||\xi(x)||_{L^2(\Omega)} \tag{3.24}$$

for all $\xi(x) \in L^2(\Omega)$.

Indeed, the linear pseudodifferential operator $\Psi(x,D)$ defined by (3.23) is order zero and, as a consequence, satisfies (3.24). Thus, $\vec{v}(t,x) = \Psi(x,D)T(t,x)$ and we rewrite the equation for T(t,x), (3.10), as follows:

$$\partial_t T(t,x) - \Delta_x T = -\nabla T \cdot \Psi(x,D)T(t,x) + h(t,x) \tag{3.25}$$

with

$$T(t,x)|_{t=\tau} = T_\tau(x), \qquad T(t,x')|_{\partial\Omega} = T_{bd}(x') \tag{3.26}$$

In the next chapter, we establish existence and uniqueness of solutions in $W^{(1,2),p}\big([\tau,\eta]\times\Omega\big)$. This is an important step in establishing a rigorous mathematical foundation for a model. Some PDEs admit no solutions and some boundary value problems produce multiple solutions, and numerical simulations will not always demonstrate this. Neither of these results will properly model a real, physical reaction, as any physical reaction above the molecular scale will occur in exactly one way, so it is necessary to first prove that the boundary value problem will also have exactly one possible solution.

Chapter 4: Existence and Uniqueness of Solutions to the HIFU Model

We work in the L^p space of the domain of this family of equations with $p = p(n) >> 1$ (we will choose a concrete value for p later). Let $Q_{\tau,\eta}$ be

$$Q_{\tau,\eta} := [\tau,\eta] \times \Omega \tag{4.1}$$

where η is sufficiently large to include the time interval of interest.

We assume that the heat source term, $h(t,x)$ is known a priori and that $h \in L^p(Q_{\tau,\eta})$. Then our problem can be stated as follows:

Find $T \in W^{(1,2),p}(Q_{\tau,\eta})$ such that

$$\frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \Psi(x,D)T(t,x) \cdot \nabla_x T(t,x) + h(t,x) \tag{4.2}$$

where

$$T_\tau(x) \in W^{2(1-\frac{1}{p}),p}(\Omega); \qquad T_{bd}(x') \in W^{2-\frac{1}{p},p}(\partial\Omega) \tag{4.3}$$

To prove the existence of a solution under these conditions, we connect equation (5.4) to a simpler linear equation using the Leray-Schauder principle (see Section 1).

In this case, if for $\lambda = 0$, $\phi(0;x) = 0$ has at least one solution, say x_0^*, then by the Leray-Schauder principle, it follows that for $\lambda = 1$, $\phi(1;x) = 0$ has a solution x_1^*. In this manner, we establish existence of a weak solution to (5.4-5.5).

In order to apply the Leray-Schauder principle to equations (3.8-3.12), we form a family of equations where the velocity, $\vec{v}(t,x)$ in equation (3.2) is replaced by $\vec{v}(\lambda;t,x)$, where

$$\vec{v}(\lambda;t,x) = \nabla_x \cdot P(\lambda;t,x) - \vec{\gamma} \cdot \lambda T(\lambda;t,x) \tag{4.4}$$

By the same methods used in the derivation of (3.8-3.9), it is possible to show that

$$\vec{v}(\lambda;t,x) = \lambda\vec{v}(t,x) \tag{4.5}$$

which in turn makes the family of equations, equivalent to equation (3.10), take the form

$$\begin{aligned}\frac{\partial T}{\partial t}(\lambda;t,x) &= \Delta_x T(\lambda;t,x) - \lambda\vec{v}(t,x)\nabla_x \cdot T(\lambda;t,x) + h(t,x)\\ \frac{\partial T}{\partial t}(\lambda;t,x) &= \Delta_x T(\lambda;t,x) - \lambda\Psi(t,x)T(\lambda;t,x)\cdot\nabla_x T(\lambda;t,x) + h(t,x)\end{aligned} \tag{4.6}$$

For $\lambda = 0$, the equation in the family (5.6) becomes

$$\frac{\partial T}{\partial t}(0;t,x) = \Delta_x T(0;t,x) + h(t,x) \tag{4.7}$$

$$T(0;\tau,x) = T_\tau(x) \in W^{2(1-\frac{1}{p}),p}(\Omega); \tag{4.8}$$

$$T((0;t,x')|_{x'\in\partial\Omega} = T_{bd}(x') \in W^{2-\frac{1}{p},p}(\partial\Omega) \tag{4.9}$$

It is well known (see Ladyženskaja, Solonnikov, & Ural'ceva[38]) that the initial boundary value problem (eqns (5.6)-(5.8)) has a unique solution. When $\lambda = 1$, the equation is the same as equation (3.10). Therefore, it remains to bring the initial boundary value problem (eqns (5.5)-(5.8)) to the form (5.6) and prove the uniform a priori estimates with respect to λ in the space $W^{(1,2),p}(Q_{\tau,\eta})$.

Reduction of our model to Leray-Schauder form

Let $\tilde{T}$ be a solution to (5.6) with the given initial and boundary conditions (3.12). Because of our choice of spaces for these conditions, (5.5), it is possible to show that $\tilde{T}$ exists and that $\tilde{T} \in W^{(1,2),p}(Q_{\tau,\eta})$ (see Ladyženskaja *et al.*[38]). Then we can choose the family of solutions $T(\lambda;\cdot)$ from (5.7) as the sum of $\tilde{T}$ and an unknown function $T^*(\lambda;\cdot)$: $T(\lambda;\cdot) = T^*(\lambda;\cdot) + \tilde{T}(\cdot)$. From equations (5.7) and (5.8), it follows that if

$T^*(\lambda;\cdot)$ exists, it will satisfy the family of equations

$$\begin{aligned}\frac{\partial T^*}{\partial t}(\lambda;t,x) &= \Delta_x T^*(\lambda;t,x)\\ &\quad -\lambda\Psi(x,D)(T^*(\lambda;t,x)+\tilde{T}(t,x))\cdot\nabla_x(T^*(\lambda;t,x)+\tilde{T}(t,x))\\ &\quad T^*(\lambda;\tau,t)=0; \qquad T^*(\lambda;t,x')|_{x'\in\partial\Omega}=0\end{aligned} \tag{4.10}$$

As a result of the homogeneous initial and boundary conditions, $H := (\partial_t - \Delta_x)^{-1}$, $H : L^p(Q_{\tau,\eta}) \to W^{(1,2),p}(Q_{\tau,\eta})$[38], which in turn leads to

$$\begin{aligned}T^*(\lambda;t,x) &= -H\big(\lambda\Psi(x,D)(T^*(\lambda;t,x)+\tilde{T}(t,x))\cdot\nabla_x(T^*(\lambda;t,x)+\tilde{T}(t,x))\big)\\ T^*(\lambda;t,x)+\lambda H\big(\Psi(x,D)(T^*(\lambda;t,x)+\tilde{T}(t,x))\cdot\nabla_x(T^*(\lambda;t,x)+\tilde{T}(t,x))\big) &= 0\\ T^*(\lambda;t,x)+\lambda K(T^*(\lambda;t,x)) &= 0\end{aligned} \tag{4.11}$$

where K is defined as

$$K(u(t,x)) = H\big(\Psi(x,D)(u(t,x)+\tilde{T}(t,x))\cdot\nabla_x(u(t,x)+\tilde{T}(t,x))\big) \tag{4.12}$$

To apply the Leray-Schauder principle, we have to show that:
a) the operator K is a compact operator in $W^{(1,2),p}(Q_{\tau,\eta})$ and
b) $T^*(\lambda;t,x)$ satisfies the uniform a priori estimate $||T^*(\lambda;t,x)||_{W^{(1,2),p}(Q_{\tau,\eta})} \leq C^*$.

If a) and b) are satisfied, the Leray-Schauder principle may be used to prove that $T^*(1;t,x)$ and hence $T(t,x) = T^*(1;t,x) + \tilde{T}(t,x)$ exist. The proof of the existence of a solution for component T of our model is based on the dissipative estimates in $W^{(1,2),p}$-spaces.

Theorem 4.1. *Let $T^*(\lambda;t,x)$ be a solution of the family of equations*

$$\begin{aligned}\frac{\partial T^*}{\partial t}(\lambda;t,x) &= \Delta_x T^*(\lambda;t,x)\\ &\quad - \lambda\Psi(x,D)(T^*(\lambda;t,x)+\tilde{T}(t,x))\cdot\nabla_x(T^*(\lambda;t,x)+\tilde{T}(t,x)) \qquad (4.13)\\ &\quad T^*(\lambda;\tau,t)=0; \qquad T^*(\lambda;t,x')|_{x'\in\partial\Omega}=0\end{aligned}$$

where $t\geq\tau$, $t,\ \tau\in\mathbb{R}$, and $p=p(n)>>1$ is sufficiently large to guarantee compactness of embedding

$$W^{(1,2),p}(Q_{\tau,\eta})\subset\subset C\big([\tau,\eta],C^{\varepsilon}(\Omega)\big) \qquad (4.14)$$

for some $\varepsilon\in(0,\frac{3}{2}]$. Then the following estimate holds:

$$\begin{aligned}&||T^*(\lambda;t,x)||_{W^{(1,2),p}([\tau,\tau+1]\times\Omega)}+||P^*(\lambda(t,x)||_{W^{(1,3),p}([\tau,\tau+1]\times\Omega)}\\ &\quad\leq C^*\big(||T_\tau(x)||_{W^{2(1-\frac{1}{p}),p}(\Omega)}\big)e^{-\alpha(t-\tau)}\\ &\quad\quad + C^*\big(||T_{bd}(x')||_{W^{2-\frac{1}{p},p}(\partial\Omega)}+||P_{bd}(x')||_{W^{3-\frac{1}{p},p}(\partial\Omega)}\big) \qquad (4.15)\end{aligned}$$

where $t\geq\tau$, $\tau\in\mathbb{R}$, $\alpha>0$, and C^* is a constant that is independent of λ.

Proof: A proof of Theorem 4.1 is based on the following lemma.

Lemma 4.2. Let $u(t,x)$ be a solution of

$$\begin{cases}\partial_t u(t,x)-\Delta_x u(t,x)=h(t,x)\\ u(t,x)|_{t=0}=u_o(x); \qquad u(t,x')|_{\partial\Omega}=u_{bd}(x')\end{cases} \qquad (4.16)$$

where $\Omega\subset\subset\mathbb{R}^n$. We set $R_\eta=[\eta,\eta+1]\times\Omega$ for every $\eta>0$. Let $h\in L^p(R_\eta)$, $u_o(x)\in W^{2(1-\frac{1}{p}),p}(\Omega)$, and $u_{bd}\in W^{2-\frac{1}{p},p}(\partial\Omega)$, assuming the compatibility condition

$u_o(x^{'})|_{x^{'}\in\partial\Omega} = u_{bd}(x^{'})$ as in (3.6). Then,

$$\int_{\eta}^{\eta+1} \big(||\partial_t u(t,x)||^p_{L^p(\Omega)} + ||u(t,x)||_{W^{2,p}(\Omega)}\big)dt$$
$$\leq C\big(||u_o(x)||_{W^{2(1-\frac{1}{p}),p}(\Omega)} e^{-\alpha\eta} + ||u_{bd}(x^{'})||_{W^{2-\frac{1}{p},p}(\partial\Omega)}\big)$$
$$+ C\int_0^{\eta+1} e^{-\alpha(\eta-t)}||h(t,x)||_{L^p(\Omega)}dt \tag{4.17}$$

Here, $\alpha > 0$ and depends on the first eigenvalue of the Laplacian on Ω. This is called the dissipative version of the parabolic maximal regularity ($\alpha = 0$ is the classical parabolic maximal regularity, see LSU [38], page 342). Due to the trace theorem, it is sufficient to prove (4.16) only for $u_o(x) = 0$, $u_{bd}(x^{'}) = 0$, as the general case can be reduced to this case (see Remark 4.3 below).

For a proof of (4.17), we recall the *classical interior estimate* for the case $u_o(x) \equiv 0$ in Ω and $u_{bd}(x^{'}) \equiv 0$ on $\partial\Omega$. It reads as follows:

$$||u||_{W^{(1,2),p}(R_\eta)} \leq C\big(||h(t,x)||_{L^p(R^{'}_\eta)} + ||u(t,x)||_{L^2(R^{'}_\eta)}\big) \tag{4.18}$$

where $R^{'}_\eta = [max\{\eta-1,0\},\eta+1]\times\Omega$ and the constant C is independent of η.

Assume for a moment that (4.18) holds. Multiplying (4.16) by u and integrating by parts we obtain

$$\frac{1}{2}\frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + ||\nabla_x u||^2_{L^2(\Omega)} = \int_\Omega h(t,x)u(t,x)dx \tag{4.19}$$

From the Poincare inequality

$$\frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + 2\alpha||u||^2_{L^2(\Omega)} = 2\int_\Omega h(t,x)u(t,x)dx \tag{4.20}$$

$$\Rightarrow \frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + \alpha||u||^2_{L^2(\Omega)} \leq C||h(t,x)||_{L^2(\Omega)}e^{\alpha\eta}\int_0^\eta \frac{\partial}{\partial t}\big(e^{\alpha t}||u||^2_{L^2(\Omega)}\big)$$
$$\leq Ce^{\alpha t}||h(t,x)||^2_{L^2(\Omega)} \tag{4.21}$$

Integrating (4.20) over $[0,\eta]$, we obtain

$$e^{\alpha\eta}||u||^2_{L^2(\Omega)} \leq ||u_o(x)||^2_{L^2(\Omega)} + C\int_0^\eta e^{\alpha t}||h(t,x)||^2_{L^2(\Omega)}dt$$

$$||u(t,x)||^2_{L^2(\Omega)} \leq ||u_o(x)||^2_{L^2(\Omega)}e^{-\alpha\eta} + C\int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||^2_{L^2(\Omega)}dt \tag{4.22}$$

Inserting (4.22) into (4.18) we obtain

$$||u||_{W^{(1,2),p}(R_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)}e^{-\alpha\eta} + \int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||^2_{L^2(\Omega)}dt\big); \qquad \alpha > 0 \tag{4.23}$$

$$||u||_{W^{(1,2),p}(R_\eta)} := \int_0^\eta\int_\Omega |\partial_t u|^p dxdt + \int_0^\eta ||u||^p_{W^{2,p}(Q_T)}dt \tag{4.24}$$

Hence, it remains to prove (4.18). To this end, we recall that we have

$$||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} \tag{4.25}$$

for the solution $s(t,x)$ of

$$\begin{cases} \partial_t s(t,x) = \Delta_x s(t,x) + h(t,x) \\ s(t,x)|_{t=max\{\eta-1,0\}} = 0, \qquad s(t,x)|_{\partial\Omega} = 0 \end{cases} \tag{4.26}$$

(5.31-5.32) can be found in Ladyzhenskaja *et al.* [38], pages 342-355.

For $\eta \leq 1$, we have

$$\begin{cases} \partial_t s(t,x) = \Delta_x s(t,x) + h(t,x) \\ s(0,x) = 0; \quad s|_{\partial\Omega} = 0 \end{cases} \tag{4.27}$$

and from (5.31), we have

$$||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} \tag{4.28}$$

$$\Rightarrow ||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + ||s(t,x)||_{L^p(R'_\eta)}\big) \tag{4.29}$$

$$\Rightarrow ||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + \int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||_{L^p(R'_\eta)}dt \tag{4.30}$$

It remains to prove (4.18) for $\eta \geq 1$, where $R'_\eta := [\eta-1,\eta+1]\times\Omega$. In order to deduce (4.18) for $\eta \geq 1$, consider

$$r(t,x) := \big(t-(\eta-1)\big)^N u(t,x), \tag{4.31}$$

where N can be chosen later in connection with p. Obviously $r(t,x)$ satisfies

$$\begin{aligned} \partial_t r(t,x) &= \Delta_x r(t,x) + \tilde{h}(t,x), \\ r|_{t=\eta-1} = 0, &\quad v|_{\partial\Omega} = 0 \end{aligned} \tag{4.32}$$

where

$$\tilde{h}(t,x) := \big(t-(\eta-1)\big)^N h(t,x) + N\big(t-(\eta-1)\big)^{N-1}u(t,x) \tag{4.33}$$

Consequently,

$$||r(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||\tilde{h}(t,x)||_{L^p(R'_\eta)} \tag{4.34}$$

From (5.26), it follows that

$$||\tilde{h}(t,x)||_{L^p(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} + C'||\big(t-(\eta-1)\big)^N u(t,x)||_{L^p(R'_\eta)} \tag{4.35}$$

It remains to estimate the last term in (5.33). To this end, we will also use the following embedding:

$$W^{(1,2),p}(R'_\eta) \subset\subset L^\infty(R'_\eta) \tag{4.36}$$

for sufficiently large $p = p(n) >> 1$. Indeed,

$$\int_{R'_\eta} |\big(t-(\eta-1)\big)^{N-1} u(t,x)|^p dxdt = \int_{R'_\eta} |\big(t-(\eta-1)\big)^{N} u(t,x)|^{\frac{p(N-1)}{N}} |u(t,x)|^{\frac{p}{N}} dxdt$$
$$\leq \int_{R'_\eta} |u(t,x)|^{\frac{p}{N}} dxdt \cdot ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)}$$
$$\leq ||u(t,x)||^{\frac{p}{N}}_{L^{\frac{p}{N}}(\Omega)} \cdot ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)} \tag{4.37}$$

From (5.37), it follows that

$$\int_{R'_\eta} \Big(\big(t-(\eta-1)\big)^{N-1} |u(t,x)|\Big)^p dxdt \leq ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)} \cdot ||u(t,x)||^{\frac{p}{N}}_{L^{\frac{p}{N}}(\Omega)} \tag{4.38}$$
$$\leq \big(||r(t,x)||^{\frac{N-1}{N}}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\frac{1}{N}}_{L^{\frac{p}{N}}(\Omega)}\big)^p$$

$$\Rightarrow ||\big(t-(\eta-1)\big)^{p-1} u(t,x)||_{L^p(R'_\eta)} \leq C_1 ||r(t,x)||^{\frac{N-1}{N}}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\frac{1}{N}}_{L^{\frac{p}{N}}(R'_\eta)} \tag{4.39}$$

Choosing $p = 2N$ ($N >> 1$) and $\alpha := \frac{1}{N}$, we obtain

$$||\big(t-(\eta-1)\big)^{N-1} u(t,x)||_{L^p(R'_\eta)} \leq C_1 ||r(t,x)||^{1-\alpha}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\alpha}_{L^2(R'_\eta)}$$
$$\leq \varepsilon ||r(t,x)||_{W^{(1,2),p}(R'_\eta)} + C_\varepsilon ||u(t,x)||_{L^2(R'_\eta)} \tag{4.40}$$

Here we have used the inequality $x^{1-\alpha} y^\alpha \leq \varepsilon x + C_\varepsilon y$ for each $\varepsilon > 0$ and for every $x > 0$, $y > 0$. Thus we obtain from (5.26).

$$||r(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + ||u(t,x)||_{L^2(R'_\eta)}\big) \tag{4.41}$$

In order to finish the proof of (4.18), it remains to note that

$$||u(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C_2\big(||h(t,x)||_{L^p(R'_\eta)} + ||u(t,x)||_{L^2(R'_\eta)}\big), \tag{4.42}$$

where C_2 does not depend on η. Q.E.D.

Remark 4.3. The general case, that is $T(t,x)|_{t=\tau} = T_\tau(x)$ and $T(t,x)|_{\partial\Omega} = T_{bd}(x^{'})$ can be reduced to the case of

$$T_\tau(x) = T_{bd}(x^{'}) \equiv 0 \tag{4.43}$$

in the following way: let $\big(T_\tau(x), T_{bd}(x^{'})\big) \neq 0$ and $T_*(x)$ be a solution of

$$\begin{cases} \Delta_x T_*(x) = 0, & x \in \Omega \\ T_*|_{\partial\Omega} = T_{bd}(x^{'}) \in W^{2-\frac{1}{p},p}(\partial\Omega) \end{cases} \tag{4.44}$$

It is well-known that $T_* \in W^{(1,2),p}\big([\tau,t]\times\Omega\big)$. Let

$$\tilde{T}_*(t,x) = (t-\tau)\big(T(t,x) - T_*(x)\big) \tag{4.45}$$

Obviously, $\tilde{T}_*(t,x)$ satisfies

$$\begin{cases} \frac{\partial \tilde{T}_*(t,x)}{\partial t} = \Delta_x \tilde{T}_*(t,x) + (t-\tau)\big(h(t,x) + \vec{v}(t,x)\cdot\nabla_x T(t,x)\big) \\ \tilde{T}_*(t,x)|_{t=\tau} = 0; \qquad \tilde{T}_*(t,x)|_{\partial\Omega} = 0 \end{cases} \tag{4.46}$$

As a corollary of Lemma 4.2 with standard L^p-estimates (see Ladyženskaja[38]), we obtain the assertion of Theorem 4.1.

Uniqueness

Now that we have established existence of a solution to (3.10), it remains to prove that this solution is unique.

Theorem 5.1. *Let $\big(T(t,x), P(t,x)\big)$ be a solution of (3.8 - 3.12) belonging to $W^{(1,2),p}(Q_{\tau,\eta}) \times W^{(1,3),p}(Q_{\tau,\eta})$, as shown to exist via the Leray-Schauder method. Then such a solution is unique.*

Proof: Let $\big(T_1(t,x), P_1(t,x)\big)$ and $\big(T_2(t,x), P_2(t,x)\big)$ be two solutions of (3.8 - 3.12)

belonging to $W^{(1,2),p}(Q_{\tau,\eta}) \times W^{(1,3),p}(Q_{\tau,\eta})$ respectively and $w(t,x) = T_1(t,x) - T_2(t,x)$, then

$$\begin{cases} \partial_t w = \Delta_x w + \big(\nabla_x T_1(t,x)\big)\Psi(x,D)w(t,x) + \big(\nabla_x w(t,x)\big)\Psi(x,D)T_2(t,x) \\ w(t,x)|_{\partial\Omega} = w(t,x)|_{t=\tau} = 0 \end{cases} \tag{4.47}$$

Note that, due to the embedding (4.14), we have $||\nabla_x T_1(t,x)||_{L^\infty(\Omega)} \leq C_*$ and $||\Psi(x,D)T_2(t,x)||_{L^\infty(\Omega)} = ||v_2(t,x)||_{L^\infty(\Omega)} \leq C_*$. Multiplying (4.47) by $w(t,x)$ and integrating over $x \in \Omega$ we obtain

$$\begin{aligned} &\frac{1}{2}\partial_t ||w(t,x)||^2_{L^2(\Omega)} + ||\nabla_x w(t,x)||^2_{L^2(\Omega)} \\ &\qquad \leq C_* ||\nabla_x w(t,x)||_{L^2(\Omega)} + C_* ||\Psi(x,D)w(t,x)||_{L^2(\Omega)} \cdot ||w(t,x)||_{L^2(\Omega)} \\ &\qquad \leq C_1 ||w(t,x)||^2_{L^2(\Omega)} + \frac{1}{2}||\nabla_x w(t,x)||^2_{L^2(\Omega)} \end{aligned} \tag{4.48}$$

Here we used Corollary 2.2, that is

$$||\Psi(x,D)w(t,x)||_{L^2(\Omega)} \leq C||w(t,x)||_{L^2(\Omega)} \tag{4.49}$$

Integrating the last line of (4.48) over $[\tau,t]$ and using Gronwall's inequality [53], we obtain $w(t,x) \equiv 0$. This establishes the uniqueness of the solution.

Chapter 5: Existence of Uniform Attractors for our HIFU model

We will follow Chepyzhov & Vishik (1994) [10] and Chepyzhov & Efendiev (2000) [11]. We begin with some preliminaries. Let E be a Banach space. In E we consider the nonautonomous Cauchy problem

$$\begin{cases} \partial_t u = A(u,t) \\ u|_{t=\tau} = u_\tau, \ \ u \in E, \ \ \tau \in \mathbb{R}, \ \ t \geq \tau, \end{cases} \tag{5.1}$$

where $A(u,t) : E_1$ x $\mathbb{R} \to E_0$ is a family of nonliear operators and E_1 and E_0 are Banach spaces. We assume that the embeddings $E_1 \subset E \subset E_0$ are everywhere dense.

We always assume that the initial value problem (3.8-3.12) has a unique solution $u(t) \in E \ \forall t \geq \tau$ and $\forall \tau \in \mathbb{R}$ and $u_\tau \in E$.

Consider the two-parameter family of maps $\{U(t,\tau), t \geq \tau\}, \qquad U(t,\tau) : E \to E,$ such that

$$U(t,\tau) : u_\tau \to u(t). \tag{5.2}$$

DEFINITION 3.1 A family of maps $\{U(t,\tau)\}$ is called a *process* if

- $U(\tau,\tau) = Id$ (identity) and
- $U(t,s) \odot U(s,\tau) = U(t,\tau)$ for all $t \geq s \geq \tau$, $\tau \in \mathbb{R}$

In this chapter, we are mainly interested in processes generated by nonautonomous evolution equations such as (3.8-3.12). It's clear that a process is a natural generalization of a semigroup $S_t : E \to E$, which corresponds to autonomous evolution equations; that is, $A(u,t) \equiv A_0(u)$. Note that in this case, it is easy to see that

$$U(t,\tau) = U_0(t-\tau) \tag{5.3}$$

Our main goal is to study the large-time asymptotics of a process $\{U(t,\tau)\}$ generated

by equation (5.1): that is, the behaviour of trajectories $u(t) = U(t,\tau)u_\tau$ of (5.1) when $t-\tau$ tends to infinity. As we will see below, the large-time dynamics of a process can be described in terms of attractors (we give a precise definition of *attractor* later). We follow Chepyzhov and Vishik (1994) [10]. As was shown in the paper, an adequate theory of attractors for nonautonomous equations is obtained by considering a family of processes $\{U(t,\tau)\}$ instead of a single process where $g \in \Sigma$ is a functional parameter. For the convenience of the reader, we recall basic definitions from Chepyzhov and Vishik (1994) [10]. Indeed, consider the family of Cauchy equations

$$\partial_t u = A_{g(t)}(u), \tag{5.4}$$

$$u|_{t=\tau} = u_\tau, \qquad u_\tau \in E \tag{5.5}$$

where for any fixed $t \in \mathbb{R}$, $A_{g(t)}(u)$ is, in general, a nonlinear operator acting from a Banach space E_1 to a Banach space E_0 and $E_1 \subset E \subset E_0$ (everywhere dense). We assume that a functional parameter $g(t)$ belongs to a certain closed set Σ in $C_b(\mathbb{R},W)$, where $\{C_b(\mathbb{R},W)$ denotes the space of bounded continous functions on $\mathbb{R}$ with values in a certain metric space W, with $T(h)\Sigma = \Sigma$, where

$$T(h)g(t) := g(t+h), \qquad h \in \mathbb{R} \tag{5.6}$$

We suppose that the problem (5.4)-(5.5) is well-posed for any symbol $g(t) \in \Sigma$ so that any solution $u(t) \in E$ (we specify in each case what we mean by "solution") can be represented as

$$\begin{aligned} u(t) &= U_g(t,\tau)u_\tau, \\ g &= g(t) \in \Sigma,\ u_\tau \in E,\ \tau \in \mathbb{R},\ t \geq \tau \end{aligned} \tag{5.7}$$

Due to the uniqueness theorem for (5.4)-(5.5), operators defined by (5.7) define a process and satisfy the following translation identity:

$$U_{T(h)g}(t,\tau) = U_g(t+h,\tau+h), \qquad \forall h \geq 0,\ t \geq \tau,\ \tau \in \mathbb{R} \tag{5.8}$$

Let $S(t) : E \times \Sigma \to E \times \Sigma$ be the family of operators defined by

$$S(t)(u,g) = (U_g(t,0)u, T(t)g), \qquad t \geq 0, \ \ (u,g) \in E \times \Sigma \tag{5.9}$$

It is not difficult to see that the family of operators $\{S(t)\}$ defined by (5.9) forms a semigroup on the extended phase space $E \times \Sigma$. We use this fact throughout this chapter.

Before formulating the main result for a family of processes $\{U_g(t,\tau)\}$ from a dynamical viewpoint, we recall some definitions [10, 30]. Let E be the Banach space as before, and denote by $\beta(E)$ the set of all bounded subsets E.

DEFINITION 3.2 A set $B_0 \subset E$ is called a *uniformly* (with respect to Σ) *absorbing* (or *attracting*) set for the family of processes $\{U_g(t,\tau)\}$ if for any $\tau \mathbb{R}$ and any $B \subset \beta(E)$ there exists $T = T(\tau, B) \geq \tau$ such that

$$\bigcup_{g\in\Sigma} U_g(t,\tau)B \subset B_0, \qquad \forall t \geq T \text{ (absorbing property)}, \tag{5.10}$$

and

$$\lim_{t\to+\infty} \sup_{g\in\Sigma} \operatorname{dist}_E\big(U_g(t,\tau)B, P\big) = 0, \qquad \forall \tau \in \mathbb{R}, \ \ B \subset \beta(E) \text{ (attracting property)}. \tag{5.11}$$

DEFINITION 3.3 A closed set $\mathbb{A}_\Sigma \neq \varnothing$ is called a *uniform* (with respect to Σ) *attractor* of the $\{U_g(t,\tau)\}$ if it is uniformly attracting and is contained in any closed uniformly attracting set $\tilde{\mathbb{A}}$ (minimality property).

Following Haraux (1991) [31], a family of processes possessing a compact, uniformly absorbing (uniformly attracting) set are called uniformly compact (or uniformly asymptotically compact) processes. Now we are in position to formulate the main result on the existence of attractors for a family of processes. Let $\Pi_1 : E \times \Sigma \to E$ be the projector defined by $\Pi_1(u,g) = u$.

THEOREM 3.4 *Let a family of processes* $\{U(t,\tau)\}$, $g \in \Sigma$, *acting in the Banach space E be uniformly compact and* $(E \times \Sigma, E)$ *continuous. Then the semigroup* $\{S(t)\} : E \times \Sigma \to E \times \Sigma$ *defined by* (5.9) *possesses the global attractor* $\mathscr{A}$. *Moreover,* $\mathbb{A} = \Pi_1 \mathscr{A}$ *is the uniform attractor of the family of processes* $\{U_g\}$.

For a proof, see Chepyzhov and Vishik (1994) [10].

In the following section, we will apply Theorem 3.4 to our hyperthermia model with external forces which are quasiperiodic in t. Let $\bar{h}(t,x) \in \mathscr{H}\big(h(t,x)\big)$, where by $\mathscr{H}\big(h(t,x)\big)$ we denote the hull of a given quasiperiodic function $h(t,x)$ of t. Note that, by definition,

$$\mathscr{H}(h(t,x)) := \overline{\{T(\theta)h(t,x) : \theta \in \mathbb{R}\}}^{C_b(\mathbb{R},W)} \tag{5.12}$$

that is, the closure in $C_b(\mathbb{R},W)$ of the set of all translations of the given quasiperiodic function h. Depending on the context, we will take $W = L_p(\Omega)$ or $W = L_\infty(\Omega)$. On the other hand, a quasiperiodic (in t) function $h(t,x)$ can be represented as

$$h(t,x) = \tilde{h}(\alpha_1 t, \ldots, \alpha_k t, x) \tag{5.13}$$

where $\tilde{h}(\omega_1, \ldots, \omega_j + 2\pi, \ldots, \omega_k, x) = \tilde{h}(\omega_1, \ldots, \omega_k, x)$ and the numbers $\alpha_1, \ldots, \alpha_k$ are rationally independent. When $\tilde{h}(\omega_1, \ldots, \omega_k, x)$ is a continuous function on $\mathbb{T}^k$ (k-dimensional torus), one can easily see that the hull $\mathscr{H}(h)$ is a set

$$\begin{aligned}\mathscr{H}\big(h(t,x)\big) = \{&\tilde{h}(\alpha_1 t + \omega_{10}, \ldots, \alpha_k t + \omega_{k0}, x); \\ &\omega_0 = (\omega_{10}, \ldots, \omega_{k0}) \in \mathbb{T}^k\}\end{aligned} \tag{5.14}$$

Thus, due to (5.14), it is reasonable to consider the torus $\mathbb{T}^k$ as the symbol space through the map

$$\begin{aligned}\mathbb{T}^k \ni \omega_0 \to h(\alpha t + \omega_0, x) \\ := \tilde{h}(\alpha_1 t + \omega_{10}, \ldots, \alpha_k t + \omega_{k0}, x) \in C_b(\mathbb{R}, W).\end{aligned} \tag{5.15}$$

We set

$$T(\theta)\omega_0 = [\omega_0 + \alpha\theta] := \omega_0 + \alpha\theta \ (\mathrm{mod}\ \mathbb{T}^k) \tag{5.16}$$

Obviously, $T(\theta)\mathbb{T}^k = \mathbb{T}^k$.

We will apply Theorem 3.4 to the family of processes generated by (3.8-3.12).

Long-time dynamics of solutions for hyperthermia model

In this section, we will prove the existence of a uniform attractor of our model equations (3.1-3.5).

$$\begin{cases} \nabla_x \cdot \vec{v}(t,x) = 0, & x \in \Omega, t \geq \tau \\ \vec{v}(t,x) = \nabla_x P(t,x) - \vec{\gamma} T(t,x), & x \in \Omega, t \geq \tau \\ \frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \vec{v}(t,x)\nabla_x \cdot T(t,x) + h(t,x) & x \in \Omega, t \geq \tau \\ P(t,x)|_{x \in \partial\Omega} = P_{bd}(x) & x \in \Omega \\ T(0,x) = T_o(x); \quad T(t,x')|_{x' \in \partial\Omega} = T_{bd}(x') & x \in \Omega \end{cases} \tag{5.17}$$

where $h(t,x)$ is a quasi-periodic external source, Ω is a bounded domain in $\mathbb{R}^n$ with a sufficiently smooth boundary, $\big(T(t,x), P(t,x)\big)$ are unknown functions (temperature and pressure, respectively), $\vec{\gamma} = (\gamma_1, \ldots, \gamma_N)$ is a given constant vector, say $|\vec{\gamma}| = 1$.

As already indicated above, we will apply Theorem 3.4 to the family of Cauchy problems

$$\begin{cases} \nabla_x \cdot \vec{v}(t,x) = 0 & x \in \Omega, t \geq \tau \\ \vec{v}(t,x) = \nabla_x P(t,x) - \vec{\gamma} T(t,x), & x \in \Omega, t \geq \tau \\ \frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \vec{v}(t,x)\nabla_x \cdot T(t,x) + \bar{h}(t,x) & x \in \Omega, t \geq \tau \\ P(t,x)|_{x \in \partial\Omega} = P_{bd}(x), & x \in \Omega \\ T(0,x) = T_o(x); \quad T(t,x')|_{x' \in \partial\Omega} = T_{Bd}(x') & x \in \Omega \end{cases} \tag{5.18}$$

with $\bar{h}(t,x) \subset \mathscr{H}\text{ull}(h(t,x))$.

To apply Theorem 3.4 in our cases, we have to prove the existence of a uniformly

absorbing (uniformly attracting) set. To this end, let us recall that our problem (3.19, 3.12) generates a a family of processes $\{\mathbb{U}_{\omega_o}(t,\tau)|t \geq \tau\}$, $\omega_o \in \mathbb{T}^k$ in the space $\mathbb{V}_0 = W^{2-\frac{1}{p},p}(\Omega) \cap \{T(t,x)|_{x\in\partial\Omega} = T_{bd}(x)\}$. Specifically,

$$\begin{aligned} &\mathbb{U}_{\omega_o}(t,\tau):\ \mathbb{V}_0 \to \mathbb{V}_0 \qquad\qquad t \geq \tau \\ &\mathbb{U}_{\omega_o}(t,\tau):\ T_\tau(x) \to T(t,x) \end{aligned} \tag{5.19}$$

where $T(t,x)$ is a solution of (5.18) with the h term in the form of $\tilde{h}(\alpha t + \omega_0, x) = \tilde{h}(\alpha_1 t + \omega_{10}, \ldots, \alpha_k t + \omega_{k0}, x)$.

Proposition 4.1: *The family of processes constructed above for our model (5.18), that is,* $\{\mathbb{U}_{\omega_o}(t,\tau) \mid t \geq \tau,\ \tau \in \mathbb{R},\ \omega_o \in \mathbb{T}^k\}$, $\mathbb{U}_{\omega_o}(t,\tau) : \mathbb{V}_0 \to \mathbb{V}_0$ – *is uniformly bounded and uniformly compact in* $\mathbb{V}_0$.

Proof: In the previous chapter, we obtained the following dissipative estimate:

$$\begin{aligned} &||T(t,x)||_{W^{(1,2),p}(Q_{\tau,\eta})} + ||P(t,x)||_{W^{(1,3),p}(Q_{\tau,\eta})} \\ &\qquad \leq Q\Big(||T_\tau(x)||_{\mathbb{V}_0}\Big) e^{-\alpha(t-\tau)} + Q(||T_{bd}(x')||_{W^{2-\frac{1}{p},p}(\partial\Omega)} \\ &\qquad\qquad + ||P_{bd}(x')||_{W^{3-\frac{1}{p},p}(\partial\Omega)} + C||\bar{h}(t,x)||_{C\left(\mathbb{T}^k, L^p(\Omega)\right)}, \qquad \alpha > 0 \end{aligned} \tag{5.20}$$

where constant C, $\alpha > 0$, and the monotonic function Q are independent of $T_\tau(x)$. From this dissipative estimate, it follows that

$$||\mathbb{U}_{\omega_o}(t,\tau)T_\tau(x)||_{\mathbb{V}_0} \leq C_3\big(||T_\tau(x)||_{\mathbb{V}_0}\big) \tag{5.21}$$

where constant C_3 depends on initial data $||T_\tau(x)||_{\mathbb{V}_0}$. This proves uniform boundedness of the process $\mathbb{U}_{\omega_o}(t,\tau)$ with respect to $\omega_o \in \mathbb{T}^k$. Moreover, the same dissipative estimate also implies that the set

$$\mathbb{B}_1 = \{\psi(x) \in \mathbb{V}_0 \mid ||\psi(x)||_{\mathbb{V}_0} \leq C_*\} \tag{5.22}$$

where C_* is a sufficiently large constant depending on $||T_{bd}(x)||_{W^{2-\frac{1}{p},p}(\Omega)}$ and $\sup_{\omega_o\in\mathbb{T}^k}||\tilde{h}([\omega_o+\alpha t],x)||_{L^p(\Omega)}$, but independent of $\omega_o\in\mathbb{T}^k$ is uniformly absorbing set for the family $\{\mathbb{U}_{\omega_o}\}\in\mathbb{V}_0$.

To apply Theorem 3.4, we need to show existence of a compact absorbing set in $\mathbb{V}_0$. However, the set $\mathbb{B}_1$ is not compact in $\mathbb{V}_0$. To obtain a compact absorbing set, consider the new set

$$\mathbb{B}_{abs} := \bigcup_{\omega_o\in\mathbb{T}^k}\bigcup_{\tau\in\mathbb{R}}\mathbb{U}_{\omega_o}(\tau+1,\tau)\mathbb{B}_1 \tag{5.23}$$

Proposition 4.2: The set $\mathbb{B}_{abs}\subset\mathbb{V}_0$ defined by equation (5.23) is a compact set in $\mathbb{V}_0$.

Proof: To show this, we consider

$$\hat{T}(t,x) = (t-\tau)\big[T(t,x)-T^*(x)\big] \tag{5.24}$$

where $T^*(x)$ is a solution of

$$\begin{cases}\Delta_x T^*(x)=0, & x\in\Omega\\ T^*(x')|_{x'\in\partial\Omega}=T_{bd}(x')\in W^{2-\frac{1}{p},p}(\partial\Omega)\end{cases} \tag{5.25}$$

From elliptic regularity theory [20, 47, 53], it follows that $T^*(x)\in W^{2,p}(\Omega)$. Obviously,

$$\begin{cases}\frac{\partial\hat{T}}{\partial t}=\Delta_x\hat{T}+(t-\tau)\nabla_x T(t,x)\cdot\Psi(x,D)T(t,x)-T^*(x)-\bar{h}(t,x)\\ \hat{T}(t=\tau,x)=0, \qquad \hat{T}(t,x')|_{x'\in\partial\Omega}=0\end{cases} \tag{5.26}$$

Here, we use the fact that that $T(t,x)$ is a solution of

$$\begin{cases}\partial_t T(t,x)-\Delta_x T(t,x)=-\nabla T(t,x)\cdot\Psi(x,D)T(t,x)+\bar{h}(t,x)\\ T(t=\tau,x)=T_\tau(x)\in\mathbb{B}_1\\ T(t,x')|_{x'\in\partial\Omega}=T_{bd}(x')\in W^{2-\frac{1}{p},p}(\partial\Omega)\end{cases} \tag{5.27}$$

Remark 4.3: Here, we impose additional requirements on on the right hand side of

(5.27). namely $\bar{h}(t,x) \in L^{\infty}(Q_{\tau,\eta})$.

Let $h^*(t,x) := (t-\tau)\nabla_x T(t,x)\Psi(x,D)T(t,x) - T^*(x) - \bar{h}(t,x)$ and $T_\tau(x) \in \mathbb{B}_1$. Then due to $||\nabla_x T||_{L^{\infty}(Q_{\tau,\eta})} \leq C$, $||v(t,x)||_{L^{\infty}(Q_{\tau,\eta})} \leq C$, we obtain $h^*(t,x) \in L^{\infty}(Q_{\tau,\eta})$. Consequently, for any $q > p$, since $\bar{h}(t,x) \in L^{\infty}(Q_{\tau,\eta}) \subset L^{q}(Q_{\tau,\eta})$, we obtain that $h^*(t,x) \in L^{q}(Q_{\tau,\eta})$.

$$||\hat{T}(t,x)||_{W^{(1,2),q}(Q_{\tau,\eta})} \leq Q_2(||T_{bd}(x')||_{W^{2-\frac{1}{q},q}(\partial\Omega)} + ||P_{bd}(x')||_{W^{3-\frac{1}{q},q}(\partial\Omega)}) \tag{5.28}$$

where Q_2 is a monotonicity function. Consequently the set $\mathbb{U}_{\omega_o}(t,\tau)\mathbb{B}_1 - T^*(x)$ is bounded in $\mathbb{V}_0$. Since $T^*(x) \in W^{2,p}(\Omega)$ where $p >> 1$ and $q > p$, then $\mathbb{B}_{abs} = \mathbb{U}_{\omega_o}(t,\tau)(t,\tau)\mathbb{B}_1$ is compact in $\mathbb{V}_0$. Here we use our new assumption $\bar{h}(t,x) \in L^{\infty}(Q_{\eta,\tau})$ for the first time. Hence Proposition 4.3 is proved and as a consequence, we obtain that the family of processes $\{\mathbb{U}_{\omega_o}(t,\tau)|t \geq \tau\}$ poseesses a uniform attractor in $\mathbb{V}_0$.

We denote by $\mathbb{A}_{HT}^{un} \subset \mathbb{V}_0$ (hyperthermia) a uniform attractor for a family of processes $\{\mathbb{U}_{\omega_o}(t,\tau), t \geq \tau\}$, $\omega_o \in \mathbb{T}^k$. In the next section, we will prove an estimate of the Hausdorff dimension of $\mathbb{A}_{HT}^{un}$ in $\mathbb{V}_0$.

Definition 4.4: *Let E be a Banach space, let $Y \subset E$ be a compact subset of E, and let d, $\varepsilon \in \mathbb{R}_+$. Let the sets $\{B_{r_i}(y_i)$ be all coverings of Y for $r_i \leq \varepsilon$ and $y_i \in Y$. The d-dimensional Hausdorff measure of Y, $\mu(Y,d)$, is defined as*

$$\mu(Y,d) = \lim_{\varepsilon \to 0^+} \inf_{\{B_{r_i}(y_i)\}} \sum_i r_i^d = \sup_{\varepsilon \to 0^+} \inf_{\{B_{r_i}(y_i)\}} \sum_i r_i^d \tag{5.29}$$

Then the number

$$\dim_{Haus}(Y,E) = \inf\{d \mid \mu(Y,d) = 0\} \tag{5.30}$$

is called the Hausdorff dimension of Y in E [63].

Note that $\mathbb{U}_{\omega_o}(t,\tau) : \mathbb{V}_0 \to \mathbb{V}_0$ generates the semigroup

$$
\begin{aligned}
&S(t) : \mathbb{V}_0 \times \mathbb{T}^k \to \mathbb{V}_0 \times \mathbb{T}^k \\
&S(t)(T_o(x), \omega_o) = \big(\mathbb{U}_{\omega_o}(t,0)T_o(x), [\alpha t + \omega_o]\big) \\
&T_o(x) \in \mathbb{V}_0, \;\; \omega_o \in \mathbb{T}^k, t \geq 0
\end{aligned} \tag{5.31}
$$

which in turn corresponds to the following autonomous dynamical system

$$
\begin{cases}
\partial_t T(t,x) = \Delta_x T(t,x) - \nabla T(t,x) \cdot \Psi(x,D) T(t,x) + \bar{h}(t,x) \\
\partial_t \omega(t) = \alpha \\
T(0,x) = T_o(x), \qquad \omega(0) = \omega_o, \qquad T(t,x')|_{x' \in \partial\Omega} = T_{bd}(x')
\end{cases} \tag{5.32}
$$

where $T_\tau(x) \in \mathbb{V}_0$, $T_{bd}(x) \in W^{2-\frac{1}{p},p}(\partial\Omega)$, $\omega_o \in \mathbb{T}^k$, and $\Psi(x,D)$ is defined as in (3.17), or

$$
\begin{cases}
\partial_t y(t) = My(t), \qquad y(t)|_{t=0} = y_o \\
y(t) := \big(T(t,x), \omega(t)\big) \in \mathbb{V}_0 \times \mathbb{T}^k \\
M(y(t)) := (\Delta_x T(t,x) - \nabla T(t,x) \cdot \Psi(x,D) T(t,x) + \bar{h}(\omega(t),x), \alpha)
\end{cases} \tag{5.33}
$$

where $\omega(t) = [\alpha t + \omega_o]$, $\omega_o \in \mathbb{T}^k$ is a transformation of ω_0 on the torus $\mathbb{T}^k$ and $M : \mathbb{V}_0 \times \mathbb{T}^k \to \mathbb{V}_0 \times \mathbb{T}^k$. Since the process $\{\mathbb{U}_{\omega_o}(t,\tau),\ t \geq \tau\}$ defined by (5.19) is uniformly compact, then due to Theorem 3.4 the semigroup $S(t)$ defined by

$$
S(t)(T_o(x), \omega_o) = (\mathbb{U}_{\omega_o}(t,0)T_o(x), [\alpha t + \omega_o]) \tag{5.34}
$$

possesses a global attractor $\mathscr{A}_{HT}$ in $\mathbb{V}_0 \times \mathbb{T}^k$. Moreover, the projection $\Pi_1 \mathscr{A}_{HT}$ is the uniform attractor of the processes $\mathbb{U}_{\omega_o}(t,\tau) : \mathbb{V}_0 \to \mathbb{V}_0$ defined by $\mathbb{U}_{\omega_o}(t,\tau)T_\tau(x) = T(t,x)$, where $T(t,x)$ is a solution of (5.18) and $\Pi_1 : \mathbb{V}_0 \times \mathbb{T}^k \to \mathbb{V}_0$, $\Pi_1\big(\xi(x), \nu\big) = (\xi(x), 0)$. We denote by $\mathbb{A}^{un}_{HT} = \Pi_1 \mathscr{A}_{HT}$.

Obviously, $\dim_{\text{Haus}}(\mathbb{A}^{un}_{HT}, L^2(\Omega)) \leq \dim_{\text{Haus}}(\mathscr{A}_{HT}, L^2(\Omega) \times \mathbb{T}^k)$, where $\dim_{\text{Haus}}(\cdot,\cdot)$ denotes the Hausdorff dimension as defined in Definition 4.5. Hence to obtain an esti-

mate for $\dim_{\mathrm{Haus}}(\mathbb{A}^{un}_{HT}, L^2(\Omega))$, it is sufficient to obtain an upper bound for $\dim_{\mathrm{Haus}}(\mathscr{A}_{HT}$, $L^2(\Omega)\times\mathbb{T}^k)$. Note that $\mathscr{A}_{HT}\subset\mathbb{V}_0\times\mathbb{T}^k = W^{2(1-\frac{1}{p}),p}(\Omega)\times\mathbb{T}^k\subset L^2(\Omega)\times\mathbb{T}^k$. To this end, we will assume that $\tilde{h}\in C^1\left(\mathbb{T}^k, L^\infty(\Omega)\right)$, as well as using a well-known formula of Constantin, Foias, and Temam [63].

Let $\mathbb{E}_d$ be any d-dimensional subspace in the Hilbert space $L^2(\Omega)\times\mathbb{R}^k$ containing some orthonormal family in $L^2(\Omega)\times\mathbb{R}^k$, $z_j\in\mathbb{E}_d$, $j=1,2,\ldots,d$, belonging to $H^2(\Omega)\times\mathbb{R}^k$ such that $\big(z_i(x),z_j(x)\big)_{L^2(\Omega)\times\mathbb{R}^k}=\delta_{ij}$, $i,j=1,\ldots,d$, where $z_j(x)=(\theta_j(x),\nu_j)\in L^2(\Omega)\times\mathbb{R}^k$ and $\theta_j(x)|_{\partial\Omega}=0$. Let $y(t)=\big(T(t,x),\omega(t)\big)$ where $T(t,x)=\mathbb{U}_{\omega_o}(t,0)T_o(x)$ is a solution of (5.18) and $\omega(t)=[\alpha t+\omega_o]$, $y(0)\in\mathscr{A}_{HT}$. If

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t\sup_{\mathbb{E}_d}\sum_{j=1}^{d}\Big(M'\big(y(\tau)\big)z_j,z_j\Big)d\tau<0 \tag{5.35}$$

holds, then due to the aforementioned formula of Constantin, Foias, and Temam,

$$\dim_{\mathrm{Haus}}(\mathscr{A}_{HT},L^2(\Omega))\le d \tag{5.36}$$

By $M'\big(y(t)\big)$, we denote a quasidifferential of the mapping M defined by (5.33)

$$\begin{cases} M'\big(y(t)\big)z(x)=\Delta_x\theta(x)-\nabla_xT(t,x)\cdot\Psi(x,D)\theta(x)\\ \qquad\qquad -\nabla_x\theta(x)\cdot\Psi(x,D)T(t,x)+\tilde{h}'\big(\omega(t),x\big)\nu\\ z(x)=\big(\theta(x),\nu\big)\in L^2(\Omega)\times\mathbb{R}^k\\ \tilde{h}'\big(\omega(t),x\big):=\Big(\frac{\partial\tilde{h}}{\partial\omega_1},\ldots,\frac{\partial\tilde{h}}{\partial\omega_k}\Big) \end{cases} \tag{5.37}$$

with $\theta(x)|_{\partial\Omega}=0$. In (5.35), we take this quasidifferential of M at the point $y(\tau)\in\mathscr{A}_{HT}$.

Hence,

$$
\begin{aligned}
&\Big(M'\big(y(t)\big)z(x),z(x)\Big)\\
=&-||\nabla_x\theta(x)||^2-\big(\nabla_xT(t,x)\cdot\Psi(x,D)\theta(x),\theta(x)\big)-\big(\nabla_x\theta(x)\cdot\Psi(x,D)T(t,x),\theta(x)\big)\\
&\qquad+\int_\Omega\Big(\tilde{h}'\big(\omega(t),x\big),\nu\Big)_{\mathbb{R}^k}\cdot\theta(x)dx\\
=&-||\nabla_x\theta(x)||^2+\big(T(t,x),\Psi(x,D)\theta(x)\nabla_x\theta(x)\big)+\int_\Omega\Big(\tilde{h}'\big(\omega(t),x\big),\nu\Big)_{\mathbb{R}^k}\cdot\theta(x)dx\\
=&-||\nabla_x\theta(x)||^2+\big(T(t,x),\nabla_xP(t,x)\cdot\theta(x)\nabla_x\theta(x)\big)-\big(T(t,x),\gamma\theta(x)\nabla_x\theta(x)\big)\\
&\qquad+\int_\Omega\Big(\tilde{h}'\big(\omega(t),x\big),\nu\Big)_{\mathbb{R}^k}\cdot\theta(x)dx\\
\leq&-\frac{1}{2}||\nabla_x\theta(x)||^2\\
&\quad+C^{**}||\theta(x)||^2+\int_\Omega|\tilde{h}'\big(\omega(t),x\big)|^{\frac{1-\delta}{2}}\cdot|\tilde{h}'\big(\omega(t),x\big)|^{\frac{1+\delta}{2}}\cdot|\nu|\cdot|\theta(x)|dx\\
\leq&-\frac{1}{2}||\nabla_x\theta(x)||^2+C^{**}||\theta(x)||^2+\frac{b}{2}\int_\Omega|\tilde{h}'(\omega(t),x)|^{1-\delta}|\theta(x)|^2dx\\
&\qquad+\frac{|\nu|^2_{\mathbb{R}^k}}{2b}\int_\Omega|\tilde{h}'(\omega(t),x)|^{1+\delta}dx
\end{aligned}
\tag{5.38}
$$

where $0<\delta<1$, b is an arbitrary positive number, and C^{**} is a constant dependant on $||T_{bd}(x')||$ but independent of ω_o.

Let $G_1:=\max\limits_{\omega\in\mathbb{T}^k}\int_\Omega|\tilde{h}'(\omega(t),x)|^{1+\delta}dx$. Hence, for any $z=(\theta(x),\nu)\in L^2(\Omega)\times\mathbb{R}^k$ where $\theta(x)|_{x\in\partial\Omega}=0$.

$$
\begin{aligned}
&(Az,z):=(A_1\theta,\ \theta)+(A_2\nu,\ \nu)\leq\\
\leq&-\frac{1}{2}||\nabla_x\theta(x)||^2+C^{**}||\theta(x)||^2+\frac{b}{2}\int_\Omega|\tilde{h}'(\omega(t),x)|^{1-\delta}|\theta(x)|^2dx+|\nu|^2_{\mathbb{R}^k}\frac{G_1}{2b}
\end{aligned}
\tag{5.39}
$$

where A_j, $j=1,2$, are quadratic forms defined by

$$
\begin{cases}
(A_1\theta,\theta)=-\frac{1}{2}||\nabla_x\theta(x)||^2+C^{**}||\theta(x)||^2+\frac{b}{2}\int_\Omega|\tilde{h}'(\omega(t),x)|^{1-\delta}|\theta(x)|^2dx\\
(A_2\nu,\nu)=\frac{G_1}{2b}(\nu,\nu)
\end{cases}
\tag{5.40}
$$

Let us recall that our basic task is to estimate the expression

$$\sum_{j=1}^{d} \Big(M'\big(y(t)\big) z_j, z_j \Big)_{L^2(\Omega)\times\mathbb{R}^k} \tag{5.41}$$

where $z_j = (\theta_j(x), \nu_k) \in L^2(\Omega) \times \mathbb{R}^k$ with $(z_i, z_j) = \delta_{ij}$, $i, j = 1, 2, \ldots, d$.

Proposition 4.5 *Let $z_j = \big(\theta_j(x), \nu_j\big)$, $j = 1, 2, \ldots, d$, be any orthonormal system in $L^2(\Omega) \times \mathbb{R}^k$. Then there exists some integer k_1 such that $0 \le k_1 \le k$, some orthonormal (in $L^2(\Omega)$) vectors, $\bar{\theta}_1, \ \ldots, \ \bar{\theta}_{d-k_1}$, and some orthonormal (in $\mathbb{R}^k$) vectors, $\bar{\nu}_1, \ \ldots, \ \bar{\nu}_{k_1}$, such that*

$$\sum_{j=1}^{d} (Az_j, z_j) \le \sum_{i=1}^{d-k_1} (A_1 \bar{\theta}_i, \bar{\theta}_i) + \sum_{m=1}^{k_1} (A_2 \bar{\nu}_m, \bar{\nu}_m) \tag{5.42}$$

Proof: Let $\mathbb{E} \subset \mathbb{L}^2(\Omega) \times R^k$ be the subspace of the form

$$\mathbb{E} = \{\beta_1 \theta_1(x) + \cdots + \beta_d \theta_d(x)\} \times \mathbb{R}^k \tag{5.43}$$

where $\beta_j \in \mathbb{R}^1$, $j = 1, 2, \ldots, d$. In $\mathbb{E}$, there is a scalar product induced from $L^2(\Omega) \times \mathbb{R}^k$. Consider the restriction of (Az, z) to $\mathbb{E}$. Note that $z_j = \big(\theta_j(x), \nu_j\big) \in \mathbb{E}$ and is orthonormal in $\mathbb{E}$. Then

$$\begin{aligned}
&\big(A(\beta_1\theta_1 + \cdots + \beta_d\theta_d, \nu), (\beta_1\theta_1 + \cdots + \beta_d\theta_d, \nu)\big) \\
=&A_1(\beta_1\theta_1 + \cdots + \beta_d\theta_d, \beta_1\theta_1 + \cdots + \beta_d\theta_d) + (A_2\nu, \nu) \\
=&\sum_{i,j=1}^{d} \big(A_1\theta_i(x), \theta_j(x)\big) \cdot \beta_i\beta_j + (A_2\nu, \nu) \\
=&(\mathbb{B}\beta, \beta) + (A_1\theta, \theta)
\end{aligned} \tag{5.44}$$

From (5.44), it follows that the operator A is block diagonal, that is,

$$A = \begin{pmatrix} \mathbb{B} & 0 \\ 0 & A_2 \end{pmatrix} \tag{5.45}$$

and it is known that A can be transformed into diagonal form

$$A = \begin{pmatrix} \lambda_1 & & & & & \\ & \ddots & & & 0 & \\ & & \lambda_d & & & \\ & & & \nu_1 & & \\ & 0 & & & \ddots & \\ & & & & & \nu_k \end{pmatrix} \tag{5.46}$$

by orthogonal transformations in $L^2(\Omega)$ and $\mathbb{R}^k$ respectively. Let $\bar{\theta}_1(x), \ldots, \bar{\theta}_d(x)$ and $\bar{\nu}_1, \ldots, \bar{\nu}_k$ be orthonormal in $L^2(\Omega)$ and $\mathbb{R}^k$ eigenvectors of $\mathbb{B}$ and A_2 respectively. Obviously, orthonormal eigenvectors of $A : L^2(\Omega) \times \mathbb{R}^k \to L^2(\Omega) \times \mathbb{R}^k$ have the form $(\bar{\theta}_i, 0)$ and $(0, \bar{\nu}_m)$, $i = 1, \ldots, d$, $m = 1, \ldots, k$. We denote $\zeta_i(x) = (\bar{\theta}_i, 0)$, $\zeta_m = (0, \bar{\nu}_m)$. Then due to Courant's principle [11], we have

$$\sum_{j=1}^{d} (Az_j, z_j) \leq \sum_{j=1}^{d} (A\zeta_j, \zeta_j) \tag{5.47}$$

where $\{\zeta_j(x)\}$, $j = 1, \ldots, d$ are eigenvectors of the matrix A in $\mathbb{E}$ corresponding to the greater eigenvalues of the block operator A. Without loss of generality, we assume that (due to the block structure A) eigenvectors of A are $(\bar{\theta}_1, 0)$, $\ldots$, $(\bar{\theta}_{d-k_1}, 0)$, $(0, \bar{\nu}_1)$, $\ldots$, $(0, \bar{\nu}_{k_1})$, where $0 \leq k_1 \leq k$, $k_1 \in \mathbb{N}$.

Corollary 4.6 *There exist vectors orthonormal in* $L^2(\Omega)$ $\bar{\theta}_1, \ldots, \bar{\theta}_{d-k_1}$, $0 \le k_1 \le k$, *such that*

$$
\begin{aligned}
&\sum_{j=1}^{d}(Az_j,z_j) \le \\
&\le \sum_{j=1}^{d-k_1}\left(A_1\bar{\theta}_j,\bar{\theta}_j\right)+\sum_{m=1}^{k_1}\left(A_2\bar{v}_m,\bar{v}_m\right) \\
&\le -\frac{1}{2}\sum_{j=1}^{d-k_1}||\nabla_x\bar{\theta}_j(x)||^2+C^{**}\sum_{j=1}^{d-k_1}||\bar{\theta}_j(x)||^2 \\
&\qquad\qquad +\frac{b}{2}\sum_{j=1}^{d-k_1}\int_\Omega |h'(\omega(t),x)|^{1-\delta}|\theta_j(x)|^2dx+\frac{G_1}{2b}k_1 \\
&\le -\frac{1}{2}\sum_{j=1}^{d-k_1}||\nabla_x\bar{\theta}_j(x)||^2+C^{**}\sum_{j=1}^{d-k_1}||\bar{\theta}_j(x)||^2 \\
&\qquad\qquad +\frac{b}{2}\int_\Omega |\tilde{h}'(\omega(t),x)|^{1-\delta}\sum_{j=1}^{d-k_1}|\theta_j(x)|^2dx+\frac{G_1}{2b}k \\
&\le -\frac{1}{2}\sum_{j=1}^{d-k_1}||\nabla_x\bar{\theta}_j(x)||^2+C^{**}\sum_{j=1}^{d-k_1}||\bar{\theta}_j(x)||^2 \\
&\qquad\qquad +\frac{b}{2}\int_\Omega |\tilde{h}'(\omega(t),x)|^{1-\delta}\Big(\sum_{j=1}^{d-k_1}|\theta_j(x)|^2\Big)dx+\frac{G_1}{2b}k
\end{aligned}
$$

$$
\begin{aligned}
&\le -\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\bar{\theta}_j(x)||^2-\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\bar{\theta}_j(x)||^2+C^{**}\sum_{j=1}^{d-k_1}||\bar{\theta}_j(x)||^2 \\
&\qquad\qquad +\frac{b}{2}\int_\Omega |\tilde{h}'(\omega(t),x)|^{1-\delta}\rho(x)dx+\frac{G_1}{2b}k \qquad (5.48)
\end{aligned}
$$

where $\rho(x) := \sum_{j=1}^{d-k_1}|\theta_j(x)|^2$. On the other hand,

$$
\int_\Omega |h'(\omega(t),x)|^{1-\delta}\rho(x)dx=\int_\Omega\Big(\frac{1}{\varepsilon}|h'(\omega(t),x)|^{1-\delta}\Big)\Big(\varepsilon\rho(x)\Big)dx \qquad (5.49)
$$

Hence,

$$\int_\Omega |\tilde{h}'(\omega(t),x)|^{1-\delta}\rho(x)dx \leq \frac{n}{n+2}\int_\Omega \Big(\varepsilon\rho(x)\Big)^{1+\frac{2}{n}}dx + \frac{2}{n+2}\int_\Omega \Big(\frac{1}{\varepsilon}|\tilde{h}'(\omega(t),x)|^{1-\delta}\Big)^{1+\frac{n}{2}}dx$$
$$\leq \frac{n}{n+2}\varepsilon^{1+\frac{2}{n}}\int_\Omega \big(\rho(x)\big)^{1+\frac{2}{n}}dx + \frac{2}{n+2}\big(\frac{1}{\varepsilon}\big)^{1+\frac{n}{2}}G_2 \quad (5.50)$$

where $G_2 = \max_{\omega\in\mathbb{T}^k}\int_\Omega |\tilde{h}'(\omega(t),x)|^{(1-\delta)\frac{n+2}{2}}$. Hence, due to Proposition 4.4,

$$\sum_{j=1}^{d}\Big(M'\big(y(\tau)\big)z_j,z_j\Big) \leq$$
$$\leq -\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\theta_j||^2 + \frac{G_1}{2b}k + \int_\Omega C^{**}\rho(x)dx - \frac{1}{4}C_0\int_\Omega \big(\rho(x)\big)^{1+\frac{2}{n}}dx$$
$$+\frac{bn}{2(n+2)}\int_\Omega \varepsilon^{\frac{n+2}{n}}\big(\rho(x)\big)^{1+\frac{2}{n}}dx + \frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2$$
$$\leq -\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\theta_j||^2 + \int_\Omega\Big(\big(-\frac{C_0}{4}+\frac{bn}{2(n+2)}\varepsilon^{\frac{n+2}{n}}\big)\big(\rho(x)\big)^{1+\frac{2}{n}} + C^{**}\rho(x)\Big)dx$$
$$+\frac{G_1}{2b}k + \frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2 \quad (5.51)$$

where C_0 is a constant due to the Lieb Thirring inequality,

$$\int_\Omega \sum_{j=1}^{d-k_1}|\nabla_x w_j|^2dx \geq C_0\int_\Omega \big(\sum_{j=1}^{d-k_1}|w_j|^2\big)^{1+\frac{2}{n}}dx \quad (5.52)$$

Choosing $\varepsilon << 1$ such that

$$\frac{nb}{2(n+2)}\varepsilon^{\frac{n+2}{n}} = \frac{C_0}{8} \quad (5.53)$$

Then

$$\begin{aligned}
&\sum_{j=1}^{d}\Big(M'\big(y(\tau)\big)z_j,z_j\Big)\leq\\
&\leq-\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\theta_j||^2+\int_\Omega\Big(-\frac{C_0}{8}\big(\rho(x)\big)^{1+\frac{2}{n}}+C^{**}\rho(x)\Big)dx\\
&\qquad+\frac{G_1}{2b}k+\frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2
\end{aligned}\tag{5.54}$$

By using the extremum test on the variable $\xi=\rho(x)\geq 0$, it may be shown that the integrand in (5.54) $-\frac{C_0}{8}\big(\rho(x)\big)^{1+\frac{2}{n}}+C^{**}\rho(x)$ obtains its maximum value at

$$\rho(x)=(2C^{**})^{\frac{n}{2}}\Big(\frac{4n}{C_0(n+2)}\Big)^{\frac{n}{2}}=(2C^{**})^{\frac{n}{2}}C_4\tag{5.55}$$

Thus,

$$\begin{aligned}
&\sum_{j=1}^{d}\Big(M'\big(y(\tau)\big)z_j,z_j\Big)\leq\\
&\leq-\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\theta_j||^2+\int_\Omega(2C^{**})^{\frac{n}{2}}C_4dx+\frac{G_1}{2b}k+\frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2\\
&\leq-\frac{1}{4}\sum_{j=1}^{d-k_1}||\nabla_x\theta_j||^2+\frac{G_1}{2b}k+\frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2+|\Omega|(2C^{**})^{\frac{n}{2}}C_4\\
&\leq-\frac{\lambda_1}{4}(d-k_1)+\frac{G_1}{2b}k+\frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2+|\Omega|(2C^{**})^{\frac{n}{2}}C_4\\
&\leq-\frac{\lambda_1}{4}(d-k)+\frac{G_1}{2b}k+\frac{b}{n+2}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}G_2+|\Omega|(2C^{**})^{\frac{n}{2}}C_4\\
&<0
\end{aligned}\tag{5.56}$$

This implies that

$$\dim_{\text{Haus}}\mathscr{A}_{HT}\leq k+\frac{|\Omega|}{\lambda_1}(2C^{**})^{\frac{n}{2}}C_4+\frac{G_1}{2b\lambda_1}k+\frac{G_2b}{\lambda_1(n+2)}\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}}\tag{5.57}$$

Let us simplify this inequality. To this end, using (5.53),

$$\varepsilon^{\frac{n+2}{n}} = \frac{C_0 2(n+2)}{8nb} \tag{5.58}$$

$$\varepsilon = \Big(\frac{C_0(n+2)}{4n}\Big)^{\frac{n}{n+2}} \Big(\frac{1}{b}\Big)^{\frac{n}{n+2}} \tag{5.59}$$

$$\frac{1}{\varepsilon} = \Big(\frac{4n}{C_0(n+2)}\Big)^{\frac{n}{n+2}} b^{\frac{n}{n+2}} \tag{5.60}$$

$$\big(\frac{1}{\varepsilon}\big)^{\frac{n+2}{2}} = \Big(\frac{4n}{C_0(n+2)}\Big)^{\frac{n}{2}} b^{\frac{n}{2}} = C_4 b^{\frac{n}{2}} \tag{5.61}$$

and introducing a constant

$$C_4^{**} = |\Omega| C_4 \tag{5.62}$$

From (5.57), it follows that

$$\dim_{\text{Haus}}(\mathscr{A}_{HT}, L^2(\Omega)\times\mathbb{R}^k) \le k + \frac{C_4^{**}}{\lambda_1} + \frac{G_1}{2b\lambda_1}k + C_4\frac{G_2 b^{\frac{n+2}{2}}}{\lambda_1(n+2)} \tag{5.63}$$

Remember that b is an arbitrary positive number. We choose b such that the last two terms in (5.63) will be equal. This implies that

$$\begin{aligned} C_4\frac{G_2 b^{\frac{n+2}{2}}}{\lambda_1(n+2)} &= \frac{G_1}{2b\lambda_1}k \\ b^{\frac{n+4}{2}} &= \frac{G_1(n+2)}{2C_4G_2}k \\ b &= \Big(\frac{G_1(n+2)}{2C_4G_2}k\Big)^{\frac{2}{n+4}} \end{aligned} \tag{5.64}$$

Let $C_5 = \big(\frac{G_1}{2}\big)^{\frac{n+2}{n+4}}\big(\frac{C_4G_2}{n+2}\big)^{\frac{2}{n+4}}$. Substituting (5.64) into (5.63), we rewrite (5.63) as

$$\dim_{\text{Haus}}(\mathscr{A}_{HT}, L^2(\Omega)\times\mathbb{R}^k) \le k + \frac{C_4^{**}}{\lambda_1} + \frac{2}{\lambda_1}C_5 k^{\frac{n+2}{n+4}} \tag{5.65}$$

Now we are in a position to formulate our main result.

Theorem 4.7 *Let $\mathbb{A}_{HT}^{un}$ be the uniform attractor of $\{\mathbb{U}_{\omega_o}(t,\tau),\ t \geq \tau\}$ defined by (5.19). Then*

$$\dim_{Haus}(\mathbb{A}_{HT}^{un}, L^2(\Omega)) \leq k + \frac{C_4^{**}}{\lambda_1} + \frac{2}{\lambda_1} C_5 k^{\frac{n+2}{n+4}} \tag{5.66}$$

This provides the bound we were seeking to prove the existence of a uniformly absorbing (uniformly attracting) set in order to apply Theorem 3.4 to our results. In essence, we know that the asymptotic behaviour of our model will be well-behaved.

Chapter 6: Conclusion

While clinical applications of HIFU have greatly increased in the past decade, modelling and treatment planning for HIFU has lagged behind that of similar, more established treatment modalities (e.g. radiation therapy modelling is an example where clinical applications are guided by well-developed computer programs powered by mathematical models). Although much work remains to be done in these areas, work towards developing such mathematically guided programs and software for HIFU has started in earnest. Currently, while there is no unanimity as to which models should be used, the use of the models is unidirectional in the sense that a model of acoustic propagation is used to derive the acoustic pressure; this pressure term is used to calculate the ultrasound heat source for the model for tissue temperature distribution; and finally, this tissue temperature is used to calculate the thermal damage.

This view of the relation between the models is a simplification of the actual variation in tissue properties. It is known that the tissue parameters for both the acoustic and heat equations change in damaged tissue and, similarly, these tissue parameters' values will change under high pressures and temperatures [26, 27]. This suggests that a more accurate model would consider interrelations between the three equations rather than a simple unidirectional handing off of information to the equation preceding it. It is uncertain at this time how significant these dependencies are, as parameter values for biological tissues under even typical conditions are difficult to obtain [5].

There are also some questions regarding the accuracy of the thermal dose and thermal damage models. The thermal dose model in particular was derived for temperatures between 38°C and 46°C, but in HIFU treatments, the temperatures often rise as high as 70°C. It is generally considered that the thermal dose model remains accurate in this wider range [ref], but the Arrhenius model that underlies the derivation of both the thermal dose and thermal damage models is known to only be accurate in small temperature ranges for biological processes [2], which is the reason the value of R changes at 43°C [39]. No evidence has been provided that the parameters of the Arrhenius model does not change above 46C and a change in the parameters for the thermal damage model at

50C compared to the parameter values around 40C [50] suggest that this change should happen. Either R in the thermal dose equation may have more than two values to be accurate in the range of temperatures for HIFU or a new equation may be derived for a model like the Arrhenius model that is accurate in a wider range of temperatures.

As well, while heat is the dominant effect on tissue in HIFU treatments, acoustic pressure still has an effect on tissue, which is relevant in some applications [ref]. For example, certain frequencies and intensities of HIFU results in the formation of bubbles in bodily fluids like blood (cavitation), which have a variety of effects on both the body and the propagation of the ultrasound itself [48]. Some of these effects are desirable for certain applications and some can cause issues with other applications. However, modelling of these effects is not well defined and in some cases are too imprecise to give the necessary information, such as when attempting to temporarily open the blood-brain barrier in drug delivery [44].

In chapter 3, we considered a mathematical model that attempts to accurately model the effects of HIFU on biological tissue, and established existence and uniqueness of weak solutions to this model. We consider this to be the first step in the mathematical modelling continuum, and subsequent work will include the numerical exploration of the problem, which we consider to be an equally important step, since: (a) it can provide guidance as to where further development and refinement of mathematical tools and techniques (analytical and/or computational) are required, (b) it can identify shortcomings in existing models, and (c) it can shed light on the interplay of various subprocesses and therefore might provide important insight into a particular application.

Finally, in chapter 5, we study the asymptotic behaviour of dynamical systems which is a fundamental question in modern applied mathematics. One way to tackle this problem for dissipative dynamical systems is to consider its global attractors. A basic question then, is to study the existence of a global attractor, and once this is established, it is natural to study important properties of the global attractor, such as its dimension, dependence on parameters, regularity of the attractor etc.

In chapter 4, we answer many of these questions for a mathematical model developed to predict the interaction of HIFU with biological tissue. The model takes into consider-

ation both the convective and diffusive transport of heat, together with inhomogeneous initial and boundary conditions. One of the objectives of this chapter was to build on our earlier work in chapter 3 (which established well-posedness of the system of coupled partial differential equations that constitute our model), and prove the existence of a uniform attractor to this non-autonomous system of PDEs. In the work presented in Chapter 4, we study the long-time dynamics of solutions to our model equations, and establish the existence of a non-autonomous attractor. This puts the theoretical basis of our mathematical model on a firm foundation, and completes what we consider to be a fundamental first step in a truly applied mathematical approach to real-world problems.

The second (equally important) step in our modelling efforts (which will be the focus of future work) is the thorough numerical exploration of the HIFU problem and comparison with experimental data. This, we consider to be an equally important step for an applied mathematician, since: (a) it often highlights shortcomings of the model, where crucial underlying mechanisms (driving the underlying problem studied) may have been neglected. This, in turn, often leads to further developments and refinement of mathematical tools and techniques that result in a mathematical framework that (to a great extent) closely mirrors the physical problem it purports to model, (b) This application of "Ockham's razor" (which is a quintessentially applied mathematical approach to study real world problems) can often draw attention to shortcomings in existing models, and when appropriately applied, can lead to a model that provides a unique in silico approach to studying applications of HIFU (devoid of the ethical questions and challenges that face experimental, biomedical scientists when carrying out *in vivo* experiments). (c) Finally, a well developed mathematical model that provides a reliable framework to study a biomedical problem, can be used to generate hypotheses which can subsequently be investigated experimentally *in vivo*. In this manner, a good mathematical model can throw light on the interplay of various subprocesses, and lead to important insights into a particular therapeutic intervention or treatment strategy that can be confirmed by *in vivo* studies.

As evident from the enormous and growing interest in HIFU (both experimental and theoretical) over the past two decades, this novel, non-invasive, therapeutic modality

has emerged as an important, novel technology, with a myriad of potential applications. HIFU provides a non-invasive, non-ionizing, therapy that can be used to thermally ablate tissue at a target location, while minimally affecting the surrounding tissue. The use of mathematical modelling to predict the ef-fects of HIFU for thermal ablation has facilitated its use for certain disorders such as osteoid osteomas, essential tremors and prostate tumour ablation. The development of mathematical models for soft tissue lesions, cavitation and disruption of the blood brain barrier (to facilitate the delivery of high molecular drugs to treat brain tumours), suggest significant opportunities for mathematics to contribute to the development of HIFU as the "gold standard" for cancer therapy.

While there remain numerous unsolved problems in HIFU modelling and the field has not reached the point of predictive modelling and treatment planning seen in radiation therapy, these solutions are not out of reach. Mathematical models can provide a better understanding of the potential applications of HIFU and a better preparation for the differences in individual patients. It is possible and desirable to reach the point of treatment planning of HIFU as reached by radiation therapy in the present day.

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