Advances in Mathematical Sciences and Applications
Vol. 29, No. 1 (2020), pp. 231–246

GAKKOTOSHO
TOKYO JAPAN

A COUPLED PDE MODEL OF HIGH INTENSITY ULTRASOUND HEATING OF BIOLOGICAL TISSUE, PART I: WELL-POSEDNESS

M.A. Efendiev
Institute of Computational Biology, Helmholtz Center Munich, Neuherberg, Germany
(E-mail: messoud.efendiyev@gmail.com)

J. Murley
Department of Applied Mathematics, University of Waterloo, Waterloo, ON N2L 3G1, Canada
(E-mail: jmurley@uwaterloo.ca)

and

S. Sivaloganathan
Department of Applied Mathematics, University of Waterloo, Waterloo, ON N2L 3G1, Canada
&
Centre for Math Medicine, The Fields Institute, Toronto, ON M5T 3J1, Canada
(E-mail: ssivaloganathan@uwaterloo.ca)

Abstract. Over the past decade, High Intensity Focused Ultrasound (HIFU) has emerged as an important novel therapeutic modality in the treatment of cancers, that avoids many of the associated negative side effects of more well-established cancer therapies (eg chemotherapy and radiotherapy). In this paper, a coupled system of partial differential equations is 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. The 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 paper, we establish well-posedness of our model, using the Leray-Schauder principle, together with a-priori estimates.

Communicated by Editors; Received July 7, 2020
This work is supported by NSERC.
AMS Subject Classification: 35A01, 35A02, 35A16, 35K20, 35K55, 35Q92.
Keywords: HIFU, heating of biological tissue, oncology, maximal Lp-regularity, Leray-Schauder principle, pseudodifferential operator, a priori estimates, coupled PDE model.

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 multi-scale 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])

In this paper, we study a mathematical model developed to capture the evolution of the temperature field under HIFU heating at a focal point in a medium. The model takes into consideration both the convective and diffusive transport of heat, together with inhomogeneous initial and boundary conditions. The main purpose of this paper is to establish the well-posedness of the system of coupled partial differential equations that constitute our model. The proof of the existence and uniqueness of the solution is based on the Leray-Schauder principle and the use of a priori estimates. In section 1, we briefly

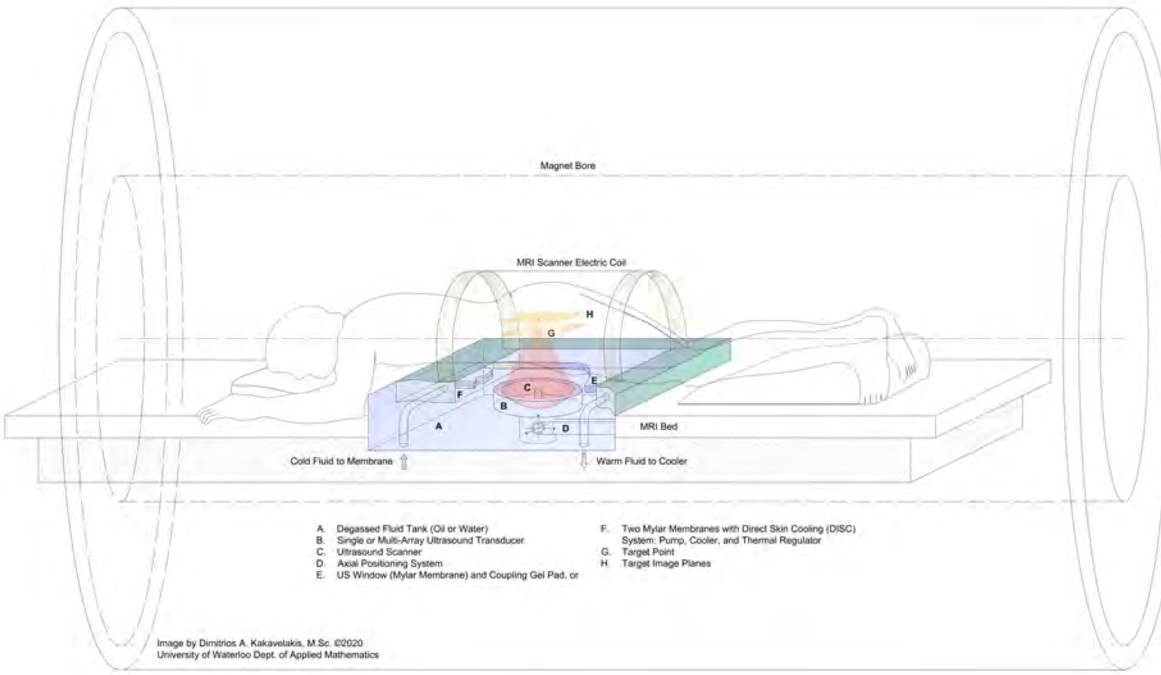

Figure 1: An MRI-guided HIFU apparatus.

introduce the function spaces, the Leray-Schauder principle and a priori estimates that will subsequently be used to establish existence and uniqueness of solutions to our model. In section 2, we formulate the problem that will be studied analytically. In section 3, we use Leray-Schauder degree theory and a priori estimates to establish well-posedness of our model. We conclude, in section 4, with some remarks and briefly discuss forthcoming work (by us) on the existence of non-autonomous attractors, under suitable conditions, for our problem, as well suggestions for future work.

Function Spaces and Leray-Schauder Principle

In this section, we recall some theoretical concepts used in the formulation of our abstract problem. This will include the definition of the Sobolev spaces which will be required in addition to trace spaces, the Leray-Schauder principle, and embedding theorems used in section 3 to establish existence and uniqueness of weak solutions to our model (see section 2 for the formulation of the model). We begin with the definition of the required function spaces.

Definition 1.1. Let Ω be a domain in $\mathbb{R}^n$ and let p be a positive real number. Then $L^p(\Omega)$ is a metric space $< X, ||\cdot||_{L^p(\Omega)} >$ where the metric $||\cdot||_{L^p(\Omega)}$ is defined

$$||u(x)||_{L^p(\Omega)} = \int_{\Omega} |u(x)|^p dx \tag{1.1}$$

For functions where $||u(x)||_{L^p(\Omega)} < \infty$ for all $x \in \Omega$, the elements of set X are the equivalence classes of these measurable functions, where two functions are equivalent if they are equal almost everywhere in Ω (see Adams[1]).

Definition 1.2. Let Ω be a domain in $\mathbb{R}^n$, let p be a positive real number, and let m be a nonnegative integer. Then we define $|| \cdot ||_{W^{m,p}(\Omega)}$ (see Adams[1]) such that, for the weak partial derivative D^α,

- $||u||_{W^{m,p}(\Omega)} = \left\{ \sum_{0\le|\alpha|\le m} ||D^\alpha u||^p_{L^p(\Omega)} \right\}^{1/p}$ if $1 \le p < \infty$;

- $||u||_{W^{m,\infty}(\Omega)} = \max_{0\le|\alpha|\le m} ||D^\alpha u||_{L^\infty(\Omega)}$.

Then a **Sobolev space** $W^{m,p}(\Omega)$ is the metric space $< X, || \cdot ||_{W^{m,p}(\Omega)} >$ such that

$$X = \{u \in L^p(\Omega) : D^\alpha u \in L^p(\Omega) \text{ for } 0 \le |\alpha| \le m.\} \tag{1.2}$$

To study the equations of our model, we will also need Sobolev spaces with fractional derivatives $m \in \mathbb{R}_+$ rather than only $\mathbb{Z}_+$.

Definition 1.3. Let Ω be a bounded domain in $\mathbb{R}^n$ and let s and $p > 1$ be positive real numbers. Then the norm in the fractional Sobolev space $W^{s,p}(\Omega)$ can be defined as (Triebel [11]).

$$||u||_{W^{s,p}(\Omega)} = ||u||^p_{W^{[s],p}(\Omega)} + \sum_{|\alpha|=[s]} \int_\Omega \int_\Omega \frac{|D^\alpha u(x) - D^\alpha u(y)|}{|x-y|^{n+\{s\}p}} dxdy \tag{1.3}$$

where $[s]$ is the integer part of s and $\{s\}$ is the decimal part of s.

Additionally, we will make use of parabolic Sobolev spaces, $W^{(1,2),p}([\tau,\eta] \times \Omega)$, where $(t,x) \in [\tau,\eta] \times \Omega$, which are defined as

$$\begin{aligned} W^{(1,2),p}([\tau,\eta] \times \Omega) = \\ \{T(t,x) \in & L^p([\tau,\eta] \times \Omega) : \frac{\partial T}{\partial t}(t,x) \in L^p([\tau,\eta] \times \Omega), \\ & \Delta_x T(t,x) \in L^p([\tau,\eta] \times \Omega)\} \end{aligned} \tag{1.4}$$

with metric

$$\begin{aligned} ||u||_{W^{(1,2),p}([\tau,\eta]\times\Omega)} &= ||\partial_t u||_{L^p} + ||\Delta_x u||_{L^p([\tau,\eta]\times\Omega)} \\ &= \Big(\int_{([\tau,\eta]\times\Omega)} |\partial_t u|^p \Big)^{1/p} + \Big(\int_{([\tau,\eta]\times\Omega)} |\Delta_x u|^p \Big)^{1/p} \end{aligned} \tag{1.5}$$

for $1 \le p < \infty$.

These spaces are useful for examining parabolic equations of second order.

We also recall the Leray-Schauder theorem (used in section 3) in the following (working) form:

Let X be a Banach space and, for any $\lambda \in [0,1]$, $\phi_\lambda : X \to X$ be a family of nonlinear operators of the form

$$\phi_\lambda(x) = x + K(\lambda, x) \tag{1.6}$$

where for each $\lambda \in [0,1]$, $K_\lambda : X \to X$ is a compact operator. (K is usually, but not always, a nonlinear operator.)

Moreover, assume that the solutions x_λ of $\phi_\lambda(x_\lambda) = 0$ are uniformly bounded (that is, $||x_\lambda||_X \leq C_*$).
Then if for $\lambda = 0$, $\phi_0(x) = 0$ has at least one solution, say x_0^*, then for $\lambda = 1$, $\phi_1(x) = 0$ has a solution x_1^*. A rigorous formulation of the Leray-Schauder theorem is provided below (see Nirenberg[7]):

Theorem 1.4 (Leray-Schauder principle). *Let Q be a bounded domain in a Banach space X and let $F : \bar{Q} \to X$ be a continuous and compact operator. Furthermore, let $q \in Q$ be a point and let*

$$x + \lambda F(x) \neq p$$

hold for all $p \in \partial Q$ and $\lambda \in [0,1]$. Then the equation

$$x + F(x) = q \tag{1.7}$$

has at least one solution in Q.[4, 7]

Model and Problem Formulation

The use of mathematical modelling to predict the effects of HIFU for thermal ablation has facilitated the implementation of this therapeutic modality for certain disorders such as osteoid osteomas, essential tremors and prostate ablation. 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" treatment modality for cancer therapy. One approach to modelling the effects of HIFU (see Bailey *et al.*[2] and references therein) has been through a system of coupled partial differential equations: a linear wave equation for the propagation of the ultrasound through the tissue, coupled to the Pennes bio-heat equation (a linear heat equation with a source term for the the acoustic energy deposition obtained from the solution to the wave equation), and a thermal dose model (to control the acoustic energy deposition of ultrasound exposure). The acoustic pressure derived from the acoustic wave model, $q(t,x)$, is used to determine the heat source term, $h(t,x)$in the Pennes bio-heat equation. The heating caused by focused ultrasound is a result of the energy absorption from the acoustic wave passing through the tissue. This is reflected in the heat source term by defining an absorption coefficient, α, for each tissue to correlate the tissue heat with the acoustic intensity. It is possible to show that

$$\tilde{h}(t,x) = \alpha I = \frac{\alpha q^2(t,x)}{\rho c_0} \tag{2.1}$$

where I is the acoustic intensity, ρ is the tissue density, and c_0 is the speed of the acoustic wave in the tissue.[2]

The tissue temperature, $T(t,x)$, resulting from HIFU heating is determined from the Pennes bioheat equation, with source term given by (1.1),

$$\rho c_p \frac{\partial T(t,x)}{\partial t} = \nabla \cdot (k \nabla T(t,x)) + \omega_b c_{p,b}(T_a - T(t,x)) + \tilde{h}(t,x) \tag{2.2}$$

The third term in (1.2), the blood perfusion term can be heuristically justified on the basis of Newton's Law of cooling (see Pennes[8] for a more detailed discussion of the Pennes bioheat equation). The Pennes bioheat equation has been the subject of criticism, as it is less justified physically, and we refer the reader to Wissler[12] 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.

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

$$\nabla_x \cdot \vec{v}(t,x) = 0 \tag{2.3}$$

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:

$$\vec{v}(t,x) = \nabla_x \cdot P(t,x) - \vec{\gamma} \cdot T(t,x) \tag{2.4}$$

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,

$$\frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \vec{v}(t,x) \nabla_x \cdot T(t,x) + h(t,x) \tag{2.5}$$

The system of nonautonomous equations (2.3-2.5) 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 nonhomogeneous boundary conditions such that

$$P(t=\tau,x) = P_\tau(x); \qquad P(t,x')|_{x' \in \partial\Omega} = P_{bd}(x') \tag{2.6}$$

$$T(t=\tau,x) = T_\tau(x); \qquad T(t,x')|_{x' \in \partial\Omega} = T_{bd}(x') \tag{2.7}$$

The following compatability conditions need to be imposed:

$$P_\tau(x^{'})|_{x^{'} \in \partial\Omega} = P_{bd}(x^{'}) \qquad T_\tau(x^{'})|_{x^{'} \in \partial\Omega} = T_{bd}(x^{'}) \tag{2.8}$$

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 2.5. Using equation 2.4, we obtain

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

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

$$\begin{aligned}
\Delta_x P(t,x) &= \vec{\gamma}\nabla_x \cdot T(t,x) && (2.9)\\
\vec{v}(t,x) &= \big(\nabla_x \cdot (-\Delta_x)^{-1}\vec{\gamma}\cdot(\nabla_x T) + T\big) && (2.10)\\
\frac{\partial T}{\partial t}(t,x) &= \Delta_x T(t,x) - \vec{v}(t,x)\nabla_x \cdot T(t,x) + h(t,x) && (2.11)\\
P(t=\tau,x) &= P_\tau(x); \qquad P(t,x')|_{x'\in\partial\Omega} = P_{bd}(x') && (2.12)\\
T(t=\tau,x) &= T_\tau(x); \qquad T(t,x')|_{x'\in\partial\Omega} = T_{bd}(x') && (2.13)
\end{aligned}$$

We seek a solution of (2.9-2.13) as a pair

$$\big(T(t,x),P(t,x)\big) \in W^{(1,2),p}\big([\tau,\eta]\times\Omega\big) \times W^{(1,3),p}\big([\tau,\eta]\times\Omega\big) \qquad (2.14)$$

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

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

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[10].

$W^{(1,2),p}\big([\tau,\eta]\times\Omega\big) \subset C\big([\tau,\eta],C^\epsilon(\Omega)\big)$ for some $\epsilon \in (0,\frac{3}{2}]$. It is known that for sufficiently large $p = p(n) >> 1$, dependent on dimension n, this compact embedding holds (see Simon[10]). From (2.14), it follows

$$\begin{aligned}
T_\tau(x) &\in W^{2(1-\frac{1}{p}),p}(\Omega), \qquad P_\tau(x) \in W^{3-\frac{2}{p},p}(\Omega)\\
T_{bd}(x^{'}) &\in W^{2-\frac{1}{p},p}(\Omega), \qquad P_{bd}(x^{'}) \in W^{3-\frac{1}{p},p}(\Omega) && (2.15)
\end{aligned}$$

As already indicated, we seek a solution

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

that satisfies (2.9-2.11) in a weak sense. To that end, we will assume the following compatibility conditions are satisfied:

$$T_\tau(x) = T_{bd}(x), \qquad P_\tau(x) = P_{bd}(x) \qquad (2.16)$$

Lemma 2.1. *Let $\big(P(t,x),\ T(t,x)\big)$ be a solution of (2.9-2.11), with $P_{bd}(x^{'}) := 0$. Then for every fixed $t \geq 0$ and for every $1 < p < \infty$, we have*

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

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

$$\begin{cases} \Delta_x P(t,x) = \vec{\gamma}\nabla_x T, & x \in \Omega \\ P|_{\partial\Omega} = 0 \end{cases} \tag{2.17}$$

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 (see Renardy & Rogers[9]), the assertion of Lemma 2.1 follows.

Corollary 2.1. *Let $\big(P(t,x), T(t,x)\big)$ be a solution of (2.9-2.13). Then the following holds:*

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

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 (2.9-2.13).

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

$$\begin{cases} \Delta_x P(t,x) = \vec{\gamma}\cdot\nabla_x T \\ P(t,x)|_{\partial\Omega} = 0 \\ \vec{v} = \nabla_x P - \vec{\gamma}T \end{cases} \tag{2.18}$$

It follows that

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

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

$$\Psi(x,D)T(t,x) := -\big(\vec{\gamma} + \nabla_x(-\Delta_x)^{-1}\vec{\gamma}\cdot\nabla_x\big)T(t,x) \tag{2.19}$$

Corollary 2.2. *The operator $\Psi(x,D)$ defined by (2.19) acts from $L^2(\Omega)$ to $L^2(\Omega)$ and satisfies for each fixed $t \geq 0$*

$$||\Psi(x,D)\xi(x)||_{L^2(\Omega)} \leq C||\xi(x)||_{L^2(\Omega)} \tag{2.20}$$

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

Indeed, the linear pseudodifferential operator $\Psi(x,D)$ defined by (2.19) is order zero and, as a consequence, satisfies (2.20). Thus, $\vec{v}(t,x) = \Psi(x,D)T(t,x)$ and we rewrite the equation for T(t,x), (2.11), as follows:

$$\partial_t T(t,x) - \Delta_x T = -\nabla T\cdot\Psi(x,D)T(t,x) + h(t,x) \tag{2.21}$$

with

$$T(t,x)|_{t=\tau} = T_\tau(x), \qquad T(t,x')|_{\partial\Omega} = T_{bd}(x') \tag{2.22}$$

In the next section, we establish existence and uniqueness of solutions in $W^{(1,2),p}\big([\tau,\eta]\times\Omega\big)$.

Well-posedness of the Model (2.9-2.13)

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

$$Q_{\tau,\eta} := [\tau, \eta] \times \Omega \tag{3.1}$$

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

$$\frac{\partial T}{\partial t}(t,x) = \Delta_x T(t,x) - \Psi(x,D)T(t,x) \cdot \nabla_x T(t,x) + h(t,x) \tag{3.2}$$

where

$$T_\tau(x) \in W^{2(1-\frac{1}{p}),p}(\Omega); \qquad T_{bd}(x') \in W^{2-\frac{1}{p},p}(\partial\Omega) \tag{3.3}$$

To prove the existence of a solution under these conditions, we connect equation (3.2) 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 (3.2-3.3).

In order to apply the Leray-Schauder principle to equations (2.9-2.13), we form a family of equations where the velocity, $\vec{v}(t,x)$ in equation (2.4) is replaced by $\vec{v}(\lambda;t,x)$, where

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

By the same methods used in the derivation of (2.9-2.10), it is possible to show that

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

which in turn makes the family of equations, equivalent to equation (2.11), take the form

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

$$\frac{\partial T}{\partial t}(\lambda;t,x) = \Delta_x T(\lambda;t,x) - \lambda \Psi(t,x) T(\lambda;t,x) \cdot \nabla_x T(\lambda;t,x) + h(t,x) \tag{3.4}$$

For $\lambda = 0$, the equation in the family (3.4) becomes

$$\frac{\partial T}{\partial t}(0;t,x) = \Delta_x T(0;t,x) + h(t,x) \tag{3.5}$$

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

$$T((0;t,x')|_{x' \in \partial\Omega} = T_{bd}(x') \in W^{2-\frac{1}{p},p}(\partial\Omega) \tag{3.6}$$

It is well known (see Ladyženskaja, Solonnikov, & Ural'ceva[6]) that the initial boundary value problem (eqns (3.4)-(3.6)) has a unique solution. When $\lambda = 1$, the equation is the same as equation (2.11). Therefore, it remains to bring the initial boundary value problem (eqns (3.3)-(3.6)) to the form (3.4) 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 (3.4) with the given initial and boundary conditions (2.13). Because of our choice of spaces for these conditions, (3.3), 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.*[6]). Then we can choose the family of solutions $T(\lambda;\cdot)$ from (3.5) as the sum of $\tilde{T}$ and an unknown function $T^*(\lambda;\cdot)$: $T(\lambda;\cdot) = T^*(\lambda;\cdot) + \tilde{T}(\cdot)$. From equations (3.5) and (3.6), it follows that if $T^*(\lambda;\cdot)$ exists, it will satisfy the family of equations

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

As a result of the homogeneous initial and boundary conditions, $H := (\partial_t - \Delta_x)^{-1}$, $H : L^p(Q_{\tau,\eta}) \to W^{(1,2),p}(Q_{\tau,\eta})$[6], which in turn leads to

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

where K is defined as

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

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 $||T^*(\lambda;t,x)||_{W^{(1,2),p}(Q_{\tau,\eta})} \le C^*$.

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*

$$\begin{aligned}\frac{\partial T^*}{\partial t}(\lambda;t,x) &= \Delta_x T^*(\lambda;t,x)\\ &\quad - \lambda\Psi(x,D)(T^*(\lambda;t,x)+\tilde{T}(t,x))\cdot\nabla_x(T^*(\lambda;t,x)+\tilde{T}(t,x))\\ &\quad T^*(\lambda;\tau,t)=0; \qquad T^*(\lambda;t,x')|_{x'\in\partial\Omega}=0\end{aligned} \tag{4.1}$$

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

$$W^{(1,2),p}(Q_{\tau,\eta}) \subset\subset C\big([\tau,\eta], C^{\epsilon}(\Omega)\big) \tag{4.2}$$

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

$$\begin{aligned}||T^*(\lambda;t,x)||_{W^{(1,2),p}([\tau,\tau+1]\times\Omega)} &+ ||P^*(\lambda(t,x)||_{W^{(1,3),p}([\tau,\tau+1]\times\Omega)}\\ &\le C^*\big(||T_\tau(x)||_{W^{2(1-\frac{1}{p}),p}(\Omega)}\big)e^{-\alpha(t-\tau)}\\ &\quad + C^*\big(||T_{bd}(x')||_{W^{2-\frac{1}{p},p}(\partial\Omega)} + ||P_{bd}(x')||_{W^{3-\frac{1}{p},p}(\partial\Omega)}\big)\end{aligned} \tag{4.3}$$

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

$$\begin{cases} \partial_t u(t,x) - \Delta_x u(t,x) = h(t,x) \\ u(t,x)|_{t=0} = u_o(x); \qquad u(t,x^{'})|_{\partial\Omega} = u_{bd}(x^{'}) \end{cases} \tag{4.4}$$

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 (2.8). Then,

$$\begin{aligned} \int_\eta^{\eta+1} \big(||\partial_t u(t,x)||^p_{L^p(\Omega)} + ||u(t,x)||_{W^{2,p}(\Omega)}\big) dt \\ \leq C\big(||u_o(x)||_{W^{2(1-\frac{1}{p}),p}(\Omega)} e^{-\alpha\eta} + ||u_{bd}(x^{'})||_{W^{2-\frac{1}{p},p}(\partial\Omega)}\big) \\ + C\int_0^{\eta+1} e^{-\alpha(\eta-t)}||h(t,x)||_{L^p(\Omega)} dt \end{aligned} \tag{4.5}$$

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 [6], page 342). Due to the trace theorem, it is sufficient to prove (4.4) 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 (4.5), 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:

$$||u||_{W^{(1,2),p}(R_\eta)} \leq C\big(||h(t,x)||_{L^p(R^{'}_\eta)} + ||u(t,x)||_{L^2(R^{'}_\eta)}\big) \tag{4.6}$$

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

Assume for a moment that (4.6) holds. Multiplying (4.4) by u and integrating by parts we obtain

$$\frac{1}{2}\frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + ||\nabla_x u||^2_{L^2(\Omega)} = \int_\Omega h(t,x)u(t,x)dx \tag{4.7}$$

From the Poincare inequality

$$\frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + 2\alpha||u||^2_{L^2(\Omega)} = 2\int_\Omega h(t,x)u(t,x)dx \tag{4.8}$$

$$\begin{aligned} \Rightarrow \frac{\partial}{\partial t}||u||^2_{L^2(\Omega)} + \alpha||u||^2_{L^2(\Omega)} &\leq C||h(t,x)||_{L^2(\Omega)} e^{\alpha\eta}\int_0^\eta \frac{\partial}{\partial t}\big(e^{\alpha t}||u||^2_{L^2(\Omega)}\big) \\ &\leq Ce^{\alpha t}||h(t,x)||^2_{L^2(\Omega)} \end{aligned} \tag{4.9}$$

Integrating (4.8) over $[0,\eta]$, we obtain

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

$$||u(t,x)||^2_{L^2(\Omega)} \leq ||u_o(x)||^2_{L^2(\Omega)}e^{-\alpha\eta} + C\int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||^2_{L^2(\Omega)}dt \tag{4.10}$$

Inserting (4.10) into (4.6) we obtain

$$||u||_{W^{(1,2),p}(R_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)}e^{-\alpha\eta} + \int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||^2_{L^2(\Omega)}dt\big); \qquad \alpha > 0 \tag{4.11}$$

$$||u||_{W^{(1,2),p}(R_\eta)} := \int_0^\eta \int_\Omega |\partial_t u|^p dxdt + \int_0^\eta ||u||^p_{W^{2,p}(Q_T)}dt \tag{4.12}$$

Hence, it remains to prove (4.6). To this end, we recall that we have

$$||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} \tag{4.13}$$

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

$$\begin{cases} \partial_t s(t,x) = \Delta_x s(t,x) + h(t,x) \\ s(t,x)|_{t=max\{\eta-1,0\}} = 0, \qquad s(t,x)|_{\partial\Omega} = 0 \end{cases} \tag{4.14}$$

(4.13-4.14) can be found in Ladyzhenskaja *et al.* [6], pages 342-355.

For $\eta \leq 1$, we have

$$\begin{cases} \partial_t s(t,x) = \Delta_x s(t,x) + h(t,x) \\ s(0,x) = 0; \quad s|_{\partial\Omega} = 0 \end{cases} \tag{4.15}$$

and from (4.13), we have

$$||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} \tag{4.16}$$

$$\Rightarrow ||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + ||s(t,x)||_{L^p(R'_\eta)}\big) \tag{4.17}$$

$$\Rightarrow ||s(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + \int_0^\eta e^{-\alpha(\eta-t)}||h(t,x)||_{L^p(R'_\eta)}dt \tag{4.18}$$

It remains to prove (4.6) for $\eta \geq 1$, where $R'_\eta := [\eta-1,\eta+1]\times\Omega$. In order to deduce (4.6) for $\eta \geq 1$, consider

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

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

$$\begin{gathered} \partial_t r(t,x) = \Delta_x r(t,x) + \tilde{h}(t,x), \\ r|_{t=\eta-1} = 0, \quad v|_{\partial\Omega} = 0 \end{gathered} \tag{4.19}$$

where

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

Consequently,

$$||r(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C||\tilde{h}(t,x)||_{L^p(R'_\eta)} \tag{4.20}$$

From (4.20), it follows that

$$||\tilde{h}(t,x)||_{L^p(R'_\eta)} \leq C||h(t,x)||_{L^p(R'_\eta)} + C'||\big(t-(\eta-1)\big)^N u(t,x)||_{L^p(R'_\eta)} \tag{4.21}$$

It remains to estimate the last term in (4.21). To this end, we will also use the following embedding:

$$W^{(1,2),p}(R'_\eta) \subset\subset L^\infty(R'_\eta) \tag{4.22}$$

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

$$\begin{aligned} \int_{R'_\eta} |\big(t-(\eta-1)\big)^{N-1} u(t,x)|^p dxdt &= \int_{R'_\eta} |\big(t-(\eta-1)\big)^N u(t,x)|^{\frac{p(N-1)}{N}} |u(t,x)|^{\frac{p}{N}} dxdt \\ &\leq \int_{R'_\eta} |u(t,x)|^{\frac{p}{N}} dxdt \cdot ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)} \\ &\leq ||u(t,x)||^{\frac{p}{N}}_{L^{\frac{p}{N}}(\Omega)} \cdot ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)} \end{aligned} \tag{4.23}$$

From (4.23), it follows that

$$\begin{aligned} \int_{R'_\eta} \Big(\big(t-(\eta-1)\big)^{N-1} |u(t,x)|\Big)^p dxdt &\leq ||r(t,x)||^{\frac{p(N-1)}{N}}_{L^\infty(R'_\eta)} \cdot ||u(t,x)||^{\frac{p}{N}}_{L^{\frac{p}{N}}(\Omega)} \qquad (4.24) \\ &\leq \Big(||r(t,x)||^{\frac{N-1}{N}}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\frac{1}{N}}_{L^{\frac{p}{N}}(\Omega)}\Big)^p \end{aligned}$$

$$\Rightarrow ||\big(t-(\eta-1)\big)^{p-1} u(t,x)||_{L^p(R'_\eta)} \leq C_1 ||r(t,x)||^{\frac{N-1}{N}}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\frac{1}{N}}_{L^{\frac{p}{N}}(R'_\eta)} \tag{4.25}$$

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

$$\begin{aligned} ||\big(t-(\eta-1)\big)^{N-1} u(t,x)||_{L^p(R'_\eta)} &\leq C_1 ||r(t,x)||^{1-\alpha}_{W^{(1,2),p}(R'_\eta)} \cdot ||u(t,x)||^{\alpha}_{L^2(R'_\eta)} \\ &\leq \epsilon ||r(t,x)||_{W^{(1,2),p}(R'_\eta)} + C_\epsilon ||u(t,x)||_{L^2(R'_\eta)} \end{aligned} \tag{4.26}$$

Here we have used the inequality $x^{1-\alpha} y^\alpha \leq \epsilon x + C_\epsilon y$ for each $\epsilon > 0$ and for every $x > 0$, $y > 0$. Thus we obtain from (4.20).

$$||r(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C\big(||h(t,x)||_{L^p(R'_\eta)} + ||u(t,x)||_{L^2(R'_\eta)}\big) \tag{4.27}$$

In order to finish the proof of (4.6), it remains to note that

$$||u(t,x)||_{W^{(1,2),p}(R'_\eta)} \leq C_2\big(||h(t,x)||_{L^p(R'_\eta)} + ||u(t,x)||_{L^2(R'_\eta)}\big), \tag{4.28}$$

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

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

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

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

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

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

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

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

As a corollary of Lemma 4.2 with standard L^p-estimates (see Ladyženskaja[6]), we obtain the assertion of Theorem 4.1.

Uniqueness

Now that we have established existence of a solution to (2.11), 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 (2.9 - 2.13) 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 (2.9 - 2.13) 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

$$\begin{cases} \partial_t w = \Delta_x w + \big(\nabla_x T_1(t,x)\big)\Psi(x,D)w(t,x) + \big(\nabla_x w(t,x)\big)\Psi(x,D)T_2(t,x) \\ w(t,x)|_{\partial\Omega} = w(t,x)|_{t=\tau} = 0 \end{cases} \tag{5.1}$$

Note that, due to the embedding (4.2), 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 (5.1) by $w(t,x)$ and integrating over $x \in \Omega$ we obtain

$$\begin{aligned} &\frac{1}{2}\partial_t ||w(t,x)||^2_{L^2(\Omega)} + ||\nabla_x w(t,x)||^2_{L^2(\Omega)} \\ &\qquad \leq C_*||\nabla_x w(t,x)||_{L^2(\Omega)} + C_*||\Psi(x,D)w(t,x)||_{L^2(\Omega)} \cdot ||w(t,x)||_{L^2(\Omega)} \\ &\qquad \leq C_1||w(t,x)||^2_{L^2(\Omega)} + \frac{1}{2}||\nabla_x w(t,x)||^2_{L^2(\Omega)} \end{aligned} \tag{5.2}$$

Here we used Corollary 2.2, that is

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

Integrating the last line of (5.2) over $[\tau,t]$ and using Gronwall's inequality [9], we obtain $w(t,x) \equiv 0$. This establishes the uniqueness of the solution.

Conclusion

In this paper, we have considered a mathematical model that attempts to accurately model the effects of HIFU on biological tissue, and have established existence and uniqueness of weak solutions to this model. In related forthcoming work, we also consider a dynamical approach to this non-autonomous HIFU model and prove existence of attractors to this non-autonomous system. We consider this to be the first step in the mathematical modelling continuum, to be shortly followed by the next step in our modelling efforts, 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.

As evident from the surge in interest in HIFU (both experimental and theoretical) over the past two decades, it has emerged as a novel, non-invasive, therapeutic modality with a myriad of potential applications. HIFU provides a non-invasive, non-ionizing, treatment modality 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 effects 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.

Acknowledgements

S. Sivaloganathan is grateful to NSERC for support of this research through an NSERC Discovery Grant; M.A. Efendiev is grateful to the University of Waterloo for the award of the James D. Murray Distinguished Visiting Professorship, during which time much of this research was carried out.

References

[1] Adams, Robert A. (1975) *Sobolev spaces.* Academic Press.

[2] Bailey, M.R.; Khokhlova, V.A.; Sapozhnikov, O.A.; Kargl, S.G.; & Crum, L.A. (2003) Physical Mechanisms of the Therapeutic Effect of Ultrasound (A Review). *Acoustical Physics* **49**(4): 369-388.

[3] David, A. R., & Zimmerman, M. R. (2010). Cancer: an old disease, a new disease or something in between?. *Nature Reviews Cancer*, **10**(10), 728-733.

[4] Efendiev, M.A. (2009). *Fredholm structures, topological invariants and applications.* American Institute of Mathematical Sciences.

[5] Hindley, Jonathan *et al.* (2004) MRI Guidance of Focused Ultrasound Therapy of Uterine Fibroids: Early Results. *American Journal of Roentgenology,* **183**(6), 1713-1719.

[6] Ladyženskaja, O. A., Solonnikov, V. A., & Ural'ceva, N. N. (1968). *Linear and quasi-linear equations of parabolic type.* American Mathematical Soc..

[7] Nirenberg, Louis (1974) *Topics in nonlinear functional analysis.* American Mathematical Soc..

[8] Pennes, H. H. (1948). Analysis of tissue and arterial blood temperatures in the resting human forearm. *Journal of applied physiology,* **1**(2), 93-122.

[9] Renardy, M., & Rogers, R. C. (2006). *An introduction to partial differential equations.* Springer Science & Business Media.

[10] Jacques, S. (1987). Compact sets in the space Lp (0, T; B). *Ann. Mat. Pura Appl.* **4**(146): 65-96.

[11] Triebel, H. (1978) Interpolation Theory, Function Space, Differential Operators, North-Holland, Amsterdam-New York.

[12] Wissler, E.H. (1987) Comments on Weinbaum and Jiji's discussion of their proposed bioheat equation. *Journal of biomechanical engineering,* **109**(4): 226-233.