Determination of heterogeneous thermal parameters using ultrasound induced heating and MR thermal mapping

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Abstract. In this paper a method for the determination of spatially varying thermal conductivity and perfusion coefficients of tissue is proposed. The temperature evolution in tissue is modelled with the Pennes bioheat equation. The main motivation here is a model based optimal control for ultrasound surgery, in which the tissue properties are needed when the treatment is planned. The overview of the method is as follows. Same ultrasound transducers which are eventually used for the treatment, are used to inflict small temperature changes into tissue. This temperature evolution is monitored using MR thermal imaging and the tissue properties are then estimated based on these measurements. Furthermore, an approach to choose transducer excitations for the determination procedure is also considered.

The purpose of this paper is to introduce method and therefore simulations are used to verify method. Furthermore, computations are accomplished in a 2D spatial domain.

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1. Introduction

In this paper we propose a method which can be used to determine the thermal conductivity and perfusion coefficient of tissue by using ultrasound and MR temperature imaging. Generally speaking, the problem corresponds to the parameter identification problem of the heat equation from given measurements of the system. However, in this case the perfusion and the ultrasound absorption of tissue give additional terms to the heat equation which need further inspection.

The motivation of this study is closely related to ultrasound surgery. In ultrasound surgery high intensity focused ultrasound (HIFU) is used to heat the target tissue (e.g. tumor) so that the accumulated thermal dose causes necrosis. Ultrasound surgery has been clinically proven to be feasible in a number of different situations (Hynynen et al. 2001, Visioli et al. 1999, Sanghvi et al. 1999, Vallancien et al. 1996, Chapelon et al. 1999). Clinically, ultrasound surgery treatment is carried out so that sharply focused temperature elevation is produced into tissue by using focusing ultrasound transducers. By moving this focus the whole target tissue can be destroyed. However, this method has disadvantages. For example, since the focal spot
is small, it takes a long time to scan the whole target volume and therefore overall treatment time is long.

Ultrasound treatment can also be carried out by using a system of several transducers called a phased array. Using phased arrays the size of focal spots can be increased and the position of each spot can be moved electrically by changing the phase of an individual transducer element. The ultrasound surgery treatment planning can be done in several ways and the application of model based optimization methods have been recently studied (Malinen et al 2003, Erdmann et al 1998, Vanne and Hynynen 2003).

An MRI scanner can be used to measure temperature distributions in tissue (Ishihara et al 1995). Therefore, it can be used to ensure the correct location of a focus spot during treatment. Furthermore, this temperature data can be used as the system feedback for the model-based optimal stochastic control methods (for example, see Malinen et al (2005)). Furthermore, after treatment the MRI scanner can be used to ensure that the whole target tissue is ablated.

To implement model-based optimization algorithms, the acoustic and thermal properties of tissue must be known. Although the tissue properties have been widely studied and average values have been collected for different tissues, some properties depend on the physiological state of the tissue, especially on the water content. Therefore, it is possible that in some cases the actual physical values differ from the average values so much that the model based-algorithms in treatment planning may fail. Thus, it could be beneficial if the thermal and acoustic properties could be determined before the actual ultrasound treatment.


Methods for the determination of the thermal properties of biological tissue have also been developed. In these studies the Pennes bioheat equation has usually been used to model temperature evolution in tissue (Pennes 1948). The thermal pulse decay method, in which power pulses are induced and temperature elevation is measured using a small thermistor bead, can be used to determine local thermal conductivity
and blood perfusion (Arkin et al 1986). Methods to determine perfusion coefficients using parameter estimation technique and the steady-state Pennes bioheat equation have also been described in (Divrik et al 1984, Clegg and Roemer 1985). However, in vivo measurements using thermocouples or thermistors are out of question in clinical situations. The measurement of homogeneous thermal conductivity using infrared imaging technique is demonstrated by Telenkov et al (2001).

The determination of the thermal properties noninvasively using ultrasound induced heating and MR thermal imaging are studied recently (Cheng and Plewes 2002, Vanne and Hynynen 2003). In these studies tissue properties were determined by heating the target volume so that temperature elevation did not cause tissue damage. Produced temperature elevation was tracked using an MRI scanner, and the tissue properties were determined from the temperature measurements using specific fitting procedure. In those methods ultrasound field were produced using single transducer and produced field was approximated with Gaussian function. However, this assumption is only valid in the specific situation in which the target medium is homogeneous.

In the present paper, the above methods are extended so that thermal properties can be determined in a heterogeneous medium. The determination method is based on the use of a phased array. It is clear that the accuracy of the estimates depends on the used transducer excitations. We will also investigate a suboptimal choice for the excitations, that is, the amplitudes and phases of transducers. The construction of the excitations and the method itself require that the produced ultrasound field is known, and in the case of heterogeneous medium the computation of the ultrasound field is more complicated. In this paper the Helmholtz equation is used to model acoustic field and the subproblem is solved using the ultraweak variational formulation (UWVF). The discretization of the thermal forward problem is accomplished using the finite-element scheme. The target domain is assumed to contain several subdomains in which the tissue parameters are approximated to be constants. In practice, these homogeneous subregions can be constructed from MR images so that each subregion is composed of an organ or a part of it. Since only small temperature changes can be inflicted, the thermal and acoustic properties of tissue can be approximated to be constant (Waterman et al 1991, Anhalt et al 1995, Worthington et al 2002). This will also mean, that the coefficients can be obtained only at the ambient temperature and another model has to be employed for the temperature dependence of the coefficients.

The rest of this paper is organized as follows. The ultra weak variational formulation for the Helmholz equation is reviewed in section 2 (and in Appendix A). The semi-discrete FEM model for the bioheat equation is also reviewed in section 2. In section 3, the solution of the inverse problem is discussed and the construction of excitations is treated in section 4. Numerical simulations are carried out in section 5, and discussion is given in section 6.

2. Mathematical models

2.1. Helmholtz equation

Let $\Omega \subseteq \mathbb{R}^{2,3}$ be a bounded domain corresponding (a part of) the human body. In this paper we discuss only the two dimensional case. In the time-harmonic case ultrasound pressure $P$ can be expressed as $P(x,t) = p(x)e^{i\omega t}$, where $x \in \Omega$. In heterogeneous
medium the space dependent part \( p \) can be modeled using Helmholtz equation

\[
\nabla \cdot \left( \frac{1}{\rho} \nabla p \right) + \frac{k^2}{\rho} p = 0,
\]

(1)

where \( k \) is the wave number and \( \rho \) is the density of the medium. In an absorbing medium, the wave number is of the form \( k = 2\pi f/c + i\alpha \), where \( f \) is the frequency of the wave field, \( c \) is the speed of sound and \( \alpha \) is the absorption coefficient (Bhatia 1967).

In this case the problem is to solve pressure field caused by the phased array of \( N_s \) separate transducers. The surface of the \( \ell \)th element of the array is denoted with \( \Gamma_\ell \) and the part of the boundary which is artificial, i.e. does not correspond to any actual boundary of the human body, is denoted by \( \Gamma_a \). Due to the superposition principle, the field can be computed for each transducer element separately as follows. Assume that \( \ell \)th element is oscillating with an uniform normal velocity \( v_n \) and the rest of elements are passive. The produced field \( p \) is obtained as the solution of problem

\[
\nabla \cdot \left( \frac{1}{\rho} \nabla p \right) + \frac{k^2}{\rho} p = 0 \quad \text{in } \Omega
\]

(2)

\[
\frac{\partial p}{\partial \nu} = i2\pi f \rho v_n \quad \text{on } \Gamma_\ell
\]

(3)

\[
\frac{\partial p}{\partial \nu} - ikp = 0 \quad \text{on } \Gamma_a
\]

(4)

\[
\frac{\partial p}{\partial \nu} = 0 \quad \text{on } \partial \Omega \setminus (\Gamma_\ell \cup \Gamma_a),
\]

(5)

where \( \nu \) is the outward unit normal on the boundary. The boundary condition (4) for the artificial boundary \( \Gamma_a \) corresponds to a zeroth-order absorbing boundary condition and the boundary condition (5) for the rest of the boundary of the domain corresponds to the rigid surface. The boundary conditions (3-5) can be rewritten as

\[
\frac{1}{\rho} \frac{\partial p}{\partial \nu} - i\sigma p = \tau \left( -\frac{1}{\rho} \frac{\partial p}{\partial \nu} - i\sigma p \right) + g \quad \text{on } \partial \Omega,
\]

(7)

where \( \sigma \) is a real positive parameter, \( \tau \in \mathbb{C} \) such that \(|\tau| \leq 1\) and \( g \) is a function on \( \partial \Omega \). The previous boundary conditions are obtained when we choose \( \tau = 1 \) and \( g = i4\pi f v_n \) on \( \Gamma_\ell \), \( \tau = 1 \) and \( g = 0 \) on \( \partial \Omega \setminus (\Gamma_\ell \cup \Gamma_a) \), and \( \tau = 0, g = 0 \) and \( \sigma = k/\rho \) on \( \Gamma_a \).

The solution of the problem (2)-(5) can be approximately found using several numerical methods. The finite difference method and finite element methods are commonly used. However, those methods usually requires from 10 to 15 discretization points or elements per wavelength, in the case of high ultrasound frequencies, the use of those methods leads to very large problems and causes too large computational burden. Ray approximations are usually used to avoid this problem (Fan and Hynynen 1992, Kühnicke 1996, Botros et al. 1997, Botros et al. 1998). However, this approach leads to accurate solution only when medium is almost homogeneous. An alternative approach is to use methods which allow to use already known prior information of the solutions. These methods include the partition of unity method (PUM) (Babuska and Melenk 1997), the least squares method (Monk and Wang 1999), and the ultra weak variational formulation (UWVF) (Cessenat and Despres 1998).

In this study the Helmholtz equation is solved by using the UWVF. The UWVF can also be used to compute the ultrasound field in optimal control problems for
ultrasound surgery (for example, see Malinen et al. (2003)). The UWVF of the problem and its discretation is briefly described in Appendix A. For more detailed derivation, reader is referred to (Cessenat 1996, Cessenat and Despres 1998, Huttunen et al. 2002).

2.2. Bioheat equation

Heat transfer in biological tissue is usually modeled with the Pennes’ bioheat equation (Pennes 1948)

\[ \rho C_T \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) - w_B C_B (T - T_A) + Q, \]  

where \( T \) is the temperature, \( \rho \) is the density of the medium, \( \kappa \) is the thermal conductivity, \( C_T \) and \( C_B \) are the heat capacity of the tissue and blood, respectively, \( w_B \) is the blood flow rate, \( T_A \) is the temperature of arterial blood and \( Q \) is a heat source. From now on we denote \( \beta = w_B C_B \) where \( \beta \) is called the perfusion coefficient.

For the boundary and initial conditions we have

\[ T(t, x) = T_A \quad \text{when } x \in \partial \Omega \quad (9) \]
\[ T(0, x) = T_A \quad \text{when } x \in \Omega. \quad (10) \]

These conditions are chosen since the temperature of arterial blood is assumed to be the same as body temperature. Furthermore, the temperature \( T_A \) can be considered as an ambient temperature.

There are some limitations included in the bioheat equation. The bioheat equation takes into account only the arterial blood flow, while the effects of the capillary network and veins are neglected. The effects of capillaries and large veins can be taken into account (Kotte et al. 1996, Lang et al. 1999a), but these models are more complicated and their usage will require detailed information from circulation. However, the bioheat equation has proven to be suitable to predict temperature evolution in tissue when the effect of perfusion is small (Damianou et al. 1995, Kolios et al. 1998, Moros et al. 1993).

The temperature elevation in tissue is caused mainly by ultrasound absorption and thus tissue metabolism can be neglected. Hence the heat source term for the time-harmonic acoustic pressure can be written as (Duck et al. 1998, Pierce 1991)

\[ Q = \frac{\alpha |p|^2}{pc}, \]  

where \( \alpha \) is the absorption coefficient and \( c \) is the speed of sound.

In this study the semi-discrete finite element method is used for the discretization of the bioheat equation as follows. The Galerkin scheme with piecewise linear basis functions is used for spatial discretization. The intensity \( |p|^2 \) is approximated in the same basis as the temperature. This method results in the system of ordinary differential equations

\[ M \frac{dT}{dt} = -(S + \bar{M})\bar{T} + (S + \bar{M})\bar{T}_A + \bar{M}\bar{d}, \]  

where \( \bar{T}, \bar{T}_A \) and \( \bar{d} \) are vectors consisting of temperature, arterial blood temperature and intensity \( |p|^2 \), respectively, and \( M, S, \bar{M} \) and \( \bar{M} \) are matrices whose elements are

\[ M_{ij} = \int_{\Omega} \rho C_T \phi_j \phi_i dx, \]
\[ S_{ij} = \int_{\Omega} (\kappa \nabla \phi_j, \nabla \phi_i) \, dx, \]
\[ \bar{M}_{ij} = \int_{\Omega} \beta \phi_j \phi_i \, dx \quad \text{and}, \]
\[ \bar{\bar{M}}_{ij} = \int_{\Omega} \frac{\alpha}{\rho c} \phi_j \phi_i \, dx, \]

where \( \phi_j \) is the \( j \)'th basis function. In this paper the material parameters are approximated to be constants in elements.

The equation (12) is solved using the implicit Euler method. Let \( \{t_1, \ldots, t_{N_t}\} \) be a partition of the time interval so that \( \Delta t = t_{j+1} - t_j \). By denoting the values of temperature and intensity at time \( t_j \) as \( \bar{T}_j \) and \( d_j \), the implicit Euler method results in an equation

\[ [M + (S + \bar{M}) \Delta t] \bar{T}_{j+1} = M \bar{T}_j + (S + \bar{M}) \bar{T}_a \Delta t + \bar{\bar{M}} \bar{d}_{j+1} \Delta t, \quad (13) \]

which with an initial condition \( \bar{T}_0 = \bar{T}_A \) can be used to compute the thermal evolution.

3. Solution of the inverse problem

In this paper the unknown parameters are assumed to be spatially varying and piecewise constant. It is clear that the discretization of the parameters has an impact on the stability of the problem. Computationally the most straightforward choice would be to use the same mesh for the both forward problem and parameter estimation problem. This choice would, however, lead to a very unstable problem. This kind of approach would require the explicit modelling of the spatial characteristics of the unknown parameters.

In this paper we use simple anatomical prior information for the parameters. In other words, the domain is divided into smaller subdomains in which tissue properties are assumed to be constants. This division can be done, for example, by using MRI images. The parameters are assumed to be mutually independent. As we shall see, this choice leads to a numerically stable problem. If the parameters cannot be assumed to be constants within the subregions and are assumed to exhibit jumps across the subregion boundaries, more elaborate prior models for the parameters can be used (Kaipio et al 1999).

Let \( \kappa^{(r)} \) and \( \beta^{(r)} \) be the thermal conductivity and perfusion coefficient for the \( r \)'th subdomain. Let \( f \) be a vector consisting of the unknown parameters, that is, \( f = (\kappa^{(1)}, \ldots, \kappa^{(N_r)}, \beta^{(1)}, \ldots, \beta^{(N_r)})^T \), where \( N_r \) is the number of subdomains. The observation model can be written as

\[ g = A(f) + \epsilon, \quad (14) \]

where \( g \) and \( \epsilon \) are observations and observation noise, respectively, and \( A \) is the mapping for the forward problem. Let \( m \) be a mapping so that \( t_{m(j)} \) is a time when the \( j \)'th observation is obtained. Furthermore, let \( N_z \) be the number of locations from which measurements are available and \( P \in \mathbb{R}^{N_z \times N_m} \) be a projection matrix from computational mesh to the measurement mesh. Then \( g \) and \( A \) are of the form

\[ g = \begin{pmatrix} g_1 \\ \vdots \\ g_{N_m} \end{pmatrix} \in \mathbb{R}^{N_z \times N_m}, \quad A = \begin{pmatrix} P\bar{T}_{m(1)} \\ \vdots \\ P\bar{T}_{m(N_m)} \end{pmatrix} \in \mathbb{R}^{N_z \times N_m}, \quad (15) \]
where $g_j$ is a vector containing observations at time $t_{m(j)}$, $\bar{T}_j$ is a vector containing temperatures computed from the equation (13) and $N_m$ is the number of times when measurements are taken.

The general framework for the estimation problem is Bayesian statistics and statistical inverse problems. For a recent text on the theory, see Kaipio and Somersalo (2005). In this framework, the unknown parameters $f$, the observations $g$ and the noise $n$ are assumed to be random variables. Due to the additive observation model (14), the likelihood density $p_{g|f}$ can be written as

$$p_{g|f}(g|f) = p_e(g - A(f)),$$

where $p_e$ is the probability density of noise. The noise is assumed to be Gaussian with zero expectation. Therefore, we have

$$p_{g|f}(g|f) \propto \exp \left\{ -\frac{1}{2} (g - A(f))^T \Sigma_e^{-1} (g - A(f)) \right\},$$

where $\Sigma_e$ is the covariance matrix of the noise.

The posterior density exhibits all information of the unknowns given the observations. For the posterior density $p_{f|g}$ we obtain

$$p_{f|g}(f|g) \propto p_{g|f}(g|f)p_f(f),$$

where $p_f$ is the prior density which is a statistical model for the unknowns. Several different kinds of inference can be drawn from the posterior density including point estimates such as maximum a posteriori and conditional mean estimates; as well as interval estimates and marginal densities.

Due to the small number of unknowns we can pose an uninformative prior model for the unknowns and to assume that the parameters are mutually independent. Thus we set $p_f(f) = p_+(f)$, where the latter is unity for all $f$ for which every element is positive and zero otherwise. Thus we have

$$p_{f|g}(f|g) \propto p_{g|f}(g|f)p_+(f).$$

In this paper we consider only maximum a posteriori (MAP) estimates and approximations for the marginal densities for the unknowns. Due to the simple prior model the MAP estimates correspond superficially (in this case only) to constrained maximum likelihood estimates. It should be noted that if more elaborate prior models are used, the maximum likelihood estimates turn unstable, see Kaipio and Somersalo (2005).

Assume that the components of the noise are independent and equally distributed. In this case the MAP estimate corresponds to a minimum of functional $\ell_g$ defined as

$$\ell_g(f) = ||g - A(f)||^2.$$

Since $A$ is non-linear with respect to parameters $f$, the solution of minimization problem is computed iteratively as follows

$$\hat{f}_{j+1} = \hat{f}_j + \lambda_j d_j,$$

where $\lambda_j$ is a step size and $d_j$ is the search direction. In this study the standard Gauss-Newton method with line search is used (Dennis and Schnabel 1983). Therefore, the search direction can be written as

$$d_j = (J_j^T J_j)^{-1} J_j^T (g - A(\hat{f}_j)).$$
where $J_j$ is the Jacobian matrix of $A$ computed in the point $\hat{f}_j$. The step size is chosen using a line search method i.e. $\lambda_j$ is a point which minimizes a functional $\Phi$ defined as
\begin{equation}
\Phi(\lambda) = \ell_z(\hat{f}_j + \lambda d_j) = \|g - A(\hat{f}_j + \lambda d_j)\|^2.
\end{equation}
The step size is computed by using repeated quadratic interpolation.

The Jacobian matrix of $A$ is of the form
\[ J_j = \begin{pmatrix}
    P \frac{\partial T_{m(1)}}{\partial \kappa^{(1)}} & \ldots & P \frac{\partial T_{m(1)}}{\partial \kappa^{(N_{R})}} \\
    \vdots & \ddots & \vdots \\
    P \frac{\partial T_{m(N_{M})}}{\partial \kappa^{(1)}} & \ldots & P \frac{\partial T_{m(N_{M})}}{\partial \kappa^{(N_{R})}}
\end{pmatrix}, \]
and it is computed at $f = \hat{f}_j$. The partial derivatives can be computed as follows. By differentiating both sides of (13) we obtain
\begin{align*}
\frac{\partial S}{\partial \kappa^{(i)}} \hat{T}_{j+1} \Delta t + [M + (S + \hat{M}) \Delta t] \frac{\partial \hat{T}_{j+1}}{\partial \kappa^{(i)}} & = M \frac{\partial \hat{T}_{j}}{\partial \kappa^{(i)}} + \frac{\partial S}{\partial \kappa^{(i)}} \hat{T}_{a} \Delta t \\
\frac{\partial M}{\partial \beta^{(i)}} \hat{T}_{j+1} \Delta t + [M + (S + \hat{M}) \Delta t] \frac{\partial \hat{T}_{j+1}}{\partial \beta^{(i)}} & = M \frac{\partial \hat{T}_{j}}{\partial \beta^{(i)}} + \frac{\partial M}{\partial \beta^{(i)}} \hat{T}_{a} \Delta t.
\end{align*}
By grouping terms we obtain
\begin{align}
\frac{\partial \hat{T}_{j+1}}{\partial \kappa^{(i)}} = A^{-1} \left[ - \frac{\partial S}{\partial \kappa^{(i)}} (\hat{T}_{j+1} - \hat{T}_{a}) \Delta t + M \frac{\partial \hat{T}_{j}}{\partial \kappa^{(i)}} \right] \quad \text{and} \quad (24) \\
\frac{\partial \hat{T}_{j+1}}{\partial \beta^{(i)}} = A^{-1} \left[ - \frac{\partial M}{\partial \beta^{(i)}} (\hat{T}_{j+1} - \hat{T}_{a}) \Delta t + M \frac{\partial \hat{T}_{j}}{\partial \beta^{(i)}} \right].
\end{align}
where $A = M + (S + \hat{M}) \Delta t_j$. Hence the partial derivatives can be computed recursively using (24) and (25) since $\frac{\partial \hat{T}_{0}}{\partial \kappa^{(i)}}$ and $\frac{\partial \hat{T}_{0}}{\partial \beta^{(i)}}$ are zero.

4. Construction of transducer excitations

For the estimation of the thermal parameters of tissue, transducer excitations (amplitudes and phases) could be chosen arbitrarily in principle, as long as the maximum temperature stays below the critical level. However, the choice of the excitations clearly has an effect on the quality of estimates and accuracy of the estimates can be very poor if random excitations are used.

On the other hand, the optimal excitations could be obtained based on proper statistical formulation of the problem as an optimal measurement problem. In the related methods the estimate error norm is typically minimized over all feasible measurement parameters, which in this case are the excitations. For example, the excitations could be chosen such that the trace of the covariance of estimation error $\Sigma_j = E\{(f - \hat{f})(f - \hat{f})^T\}$ is minimized. However, this kind of approach leads to very large problems which are very difficult to solve in practice, see Kaipio et al. (2004).

To overcome the computational problems related to the more exact approaches, we employ some physical intuition on how changes in the temperature distribution carry information on the parameters. Initially, we concentrate on how to choose excitations that provide good thermal conductivity estimates. Based on intuition, we aim for such excitations that induce localized temperature elevations (high gradients of the temperature) in some point of the target volume. It is clear that the high gradients further induce major changes in the temperature in the neighborhood, with
the speed depending on the local thermal conductivity. In principle, the method is one generalization of a method in which focused transducer is used to produce localized temperature elevation and by moving transducer some chosen points are heated. However, the presented method is based on the use of phased array and therefore we can change the location of focus spot without that we physically move the transducer.

A short account on how to create localized temperature elevation is as follows. Denote $\hat{u} = (\hat{u}_1, \ldots, \hat{u}_N)$ where $\hat{u}_j$ is the excitation of the $j$'th transducer ($\hat{u}_j = A_j e^{i\phi_j}$, where $A_j$ is the amplitude and $\phi_j$ is the phase of transducer). Let $D$ be a region where localized spatial fluctuation should occur. Furthermore, in some cases it is possible that the temperature elevation in some other regions should be avoided. For example, if the region $D$ is near a region consisting of highly absorbing medium, such as bone or skin, produced acoustic field usually causes high temperature elevation also into this region. Let $D'$ be such a region, or the empty set if this kind of a region is not needed. We will choose $\hat{u}$ such that it minimizes a functional $\tilde{F}$ defined as

$$
\tilde{F}(\hat{u}) = -\int_D \|\nabla Q_\hat{u}(x)\|^2 dx + \alpha \int_{D'} Q_\hat{u}(x) dx + \beta \|\hat{u}\|^8,
$$

where $\|\cdot\|$ is the Euclidean norm, $\alpha$ and $\beta$ are positive coefficients and $Q_\hat{u}$ is the source term of the bioheat equation defined in (11). The first term in the functional causes that the gradient of the source term is large. This leads to localized temperature elevation into the region $D$. The second term provides that the ultrasound absorption in the region $D'$ is small. The third term ensures that the solution of the minimization problem exists by restricting the maximum amplitude. The detailed description of the minimization process is in Appendix B.

To construct excitations for parameter estimation, we do following steps for $r = 1, \ldots, N_r$:

(i) Choose a region $D_r$ where localized spatial fluctuation should occur. Set $D = D_r$ and $D' = \emptyset$.

(ii) Choose $\beta$ to be small number and compute $\hat{u}$. If the optimization algorithm did not converge, increase the value of $\beta$ and repeat the algorithm until the optimal $\hat{u}$ is found.

(iii) Compute the pressure field corresponding $\hat{u}$. If the produced acoustic field causes high temperature elevation into some other region, choose $D'$ to cover that region and compute $\hat{u}$ again ($\alpha$ is chosen experimentally so that obtained field is adequate).

(iv) Set $\hat{u}^{(r)} = \hat{u}$.

The time-dependent excitation $\hat{u}(t)$ is constructed from excitations $\hat{u}^{(r)}$ so that each transducer element is turned on equally long time. More precisely, we set

$$
\hat{u}(t_k) = \alpha^{(r)} u^{(r)} \quad \text{when } (r-1)N_s < k \leq rN_s,
$$

where $\{t_0, \ldots, t_R\}$ is a partition of a time interval so that $t_{j+1} - t_j = \Delta t$ and $N_s$ is an integer. Furthermore, $\alpha^{(r)}$ is a constant which is chosen so that the maximum temperature in the domain will not rise over the critical level. At time between $t_k$ and $t_{k+1}$ the excitation $\hat{u}(t)$ is chosen so that the amplitude and the phase are linearly interpolated.

It is possible that during this heating process overall temperature reaches its maximum value (e.g. 4°C above the ambient temperature) and further heating is not
Table 1. Acoustic parameters used in the simulations.

<table>
<thead>
<tr>
<th>Subdomain</th>
<th>$\alpha$ (Nep/m)</th>
<th>$c$ (m/s)</th>
<th>$\rho$ (kg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Omega_I$</td>
<td>$0^a,d$</td>
<td>1500$^a$</td>
<td>1000</td>
</tr>
<tr>
<td>$\Omega_{II}$</td>
<td>$12^a$</td>
<td>1610$^a$</td>
<td>1200$^{b,d}$</td>
</tr>
<tr>
<td>$\Omega_{III}$</td>
<td>$5^a,c$</td>
<td>1485$^a$</td>
<td>1020$^a$</td>
</tr>
<tr>
<td>$\Omega_{IV}$</td>
<td>$5^c$</td>
<td>1547$^a$</td>
<td>1050$^b$</td>
</tr>
</tbody>
</table>

$a$ (Duck et al 1998)
$b$ (Gautherie 1990)
$c$ (Goss et al 1980)
$d$ (Mahoney et al 2001)
$e$ (Skinner et al 1998)

possible. If this occurs, the cooling period is added i.e. $\hat{u}_{ts}$ is chosen to be zero. In the two dimensional case the perfusion rate is so low that cooling time should be long. However, those cooling periods provide good information about perfusion in tissue and provides that the perfusion coefficient estimates are more accurate. Therefore cooling period is also added to the end of the measurement procedure.

5. Numerical results

The computations were carried out in a two-dimensional spatial domain based on an actual X-ray image from a cross section of a cancerous breast. The domain is shown in figure 1. The domain is divided into four subdomains: $\Omega_I$ is the water layer, $\Omega_{II}$ is skin, $\Omega_{III}$ is the breast tissue and $\Omega_{IV}$ is the cancerous tissue. The acoustic and thermal parameters of the tissues were set to correspond to the average values reported in (Duck et al 1998, Gautherie 1990) (acoustic parameters) and (Mahoney et al 2001, Skinner et al 1998, Lang et al 1999$^b$) (thermal parameters). The acoustic parameters are given in table 1 and the thermal parameters are given in table 2. Furthermore, the heat capacity of blood $C_B$ was set to 3770 J/kgK (Mahoney et al 2001) and the ambient temperature was set to 37$^\circ$ C.

Ultrasound transducers (20 elements) were placed on the left side of the domain so that the geometrical focus of the transducer system was located in the center of the cancerous tissue. The frequency of ultrasound transducers was taken to be 500 kHz. The frequency is lower than with the treatment of breast cancer. However, this frequency is chosen, since the higher frequencies leads to the increase of computational task (the purpose of this work is to evaluate method). Furthermore, this frequency corresponds nearly to the feasible frequencies used with the brain cancer treatment (Sun and Hynynen 1999) which is an important application of ultrasound surgery.

The Helmholtz equation was solved separately for each transducer using the UWVF. The computations were done in a mesh consisting of 7113 elements and 3664 nodes. The accuracy of the UWVF solution was verified by comparing the UWVF solution to the analytical Rayleigh integral solution in the case of homogenized (averaged) material parameters (analytical solutions do not exist for an inhomogeneous target). The difference between these solutions were from 8 % to 15 % in the whole domain and from 1 % to 2.5 % on the central axis (i.e. when $x_2 = 0$).

The used excitations were computed using the method outlined in section 4. The regions $D_r$, where localized temperature elevations were produced, are shown in figure 2 (dark regions). An example of a region $D'$, where temperature elevation was
Figure 1. The domain used in computations. The domain is divided into four subdomains $\Omega_I-\Omega_{IV}$ in which physical parameters are assumed to be constant. Black lines on the left boundary represent ultrasound transducers (numbered 1,…,20).

Table 2. Thermal parameters used in the simulations. The perfusion of tumor varies enormously depending on tumor (Song et al. 1984). In this case perfusion is chosen to be higher than in the corresponding normal tissue.

<table>
<thead>
<tr>
<th>Subdomain</th>
<th>$\kappa$ (W/Km)</th>
<th>$C_T$ (J/kgK)</th>
<th>$w_B$ (kg/m$^3$s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Omega_I$</td>
<td>0.60$^a$</td>
<td>4190$^a$</td>
<td>0</td>
</tr>
<tr>
<td>$\Omega_{II}$</td>
<td>0.50$^b$</td>
<td>3770$^b$</td>
<td>1.0$^a$</td>
</tr>
<tr>
<td>$\Omega_{III}$</td>
<td>0.50$^b$</td>
<td>3550$^b$</td>
<td>0.7$^b$</td>
</tr>
<tr>
<td>$\Omega_{IV}$</td>
<td>0.65$^c$</td>
<td>3770$^c$</td>
<td>2.3</td>
</tr>
</tbody>
</table>

$^a$ (Mahoney et al. 2001)
$^b$ (Skinner et al. 1998)
$^c$ (Lang et al. 1999b)

avoided, is also shown (light gray region). Each excitation was turned on for 6 s. Since perfusion is low in the two dimensional case, three cooling periods are used. The first cooling period was set to be at between 72 s and 132 s, the second at between 162 s and 180 s and the third at between 204 s and 228 s. The excitations were computed using a mesh with 3784 elements and 1966 nodes and for the temporal discretation the time step was set to 0.6 s. The maximum temperature elevation caused by the constructed excitations was 3.24°C. The excitations for some ultrasound transducers are shown in figure 3. The pressure fields at several time periods are shown in figure 4.

Estimates were computed in a mesh consisting of 7818 elements and 3998 nodes. The computation mesh is shown in figure 5. For temporal discretization, a time step
Figure 2. Selected regions used to compute ultrasound excitations. The regions where localized temperature elevations were produced are colored black. The gray area is an example of a region $D^r$, where temperature elevation is avoided. The numbers indicate the index $r$ of excitation $\hat{u}^{(r)}$. The numbers 13, 19 and 24 are missing since these corresponds to cooling periods.

was taken to be $\Delta t = 0.15\, \text{s}$ which was found to be adequately accurate. To avoid over optimistic predictions of the method, the simulated data were computed using denser spatial and temporal discretization. This denser mesh contains 31272 elements and 15813 nodes, and the time step was $\Delta t = 0.03\, \text{s}$. The computed temperature evolution was interpolated to a grid consisting of 128x128 points. The standard deviation of Gaussian noise added to simulated data was $1^\circ\, \text{C}$. Acquisitions times for MRI temperature imaging of the breast are reported to be between 2.3 and 7.2 seconds (Hynynen et al 2001, Bohris et al 2001). In this case the time between measurements was set to 4.5 s, so that the number of temporal grid points between consecutive measurements was 50.

The thermal conductivity and the perfusion coefficient for water are known. Therefore, the unknown parameter vector $f$ can be written as $f = (\kappa^{(2)}, \kappa^{(3)}, \kappa^{(4)}, \beta^{(2)}, \beta^{(3)}, \beta^{(4)})^T$, where, for example, $\kappa^{(2)}$ and $\beta^{(2)}$ are the thermal conductivity and the perfusion coefficient for the subdomain $\Omega_2$. The starting point of the iteration was taken to be $f_0 = (0.1, 0.1, 0.1, 3800, 3800, 3800)^T$. The iterations were stopped when the relative change in parameters between two iterations was smaller than 0.1%.

The computed estimates are shown in table 3. The error of obtained thermal conductivity estimates is less than 7% and the maximum error of perfusion coefficients is less than 19%. This level of accuracy is adequate for the optimal control schemes (for example, see Malinen et al (2005)).
The amplitude of the transducer 1

The phase of the transducer 1

The amplitude of the transducer 10

The phase of the transducer 10

The amplitude of the transducer 17

The phase of the transducer 17

Figure 3. Excitation trajectories ($\hat{u}_j(t) = A_j(t)e^{i\omega_j(t)}$) for some ultrasound transducers. Numbers indicates to the index of excitation $\hat{u}^{(r)}$. The excitations are normalized such that a unity excitation causes 1 MPa pressure to the origin of the domain.

The error estimates shown in the table 3 are obtained from the approximate MAP error covariance estimate which can be written as

$$\Sigma_f = E\{(f - \hat{f})(f - \hat{f})^T\} \approx (J^T\Sigma_{\epsilon}^{-1}J)^{-1},$$

(28)

where $J$ is the Jacobian matrix of $A$ computed in the obtained estimate $\hat{f}$. Since the components of the measurement noise were assumed to be independent and equally distributed, we have $\Sigma_{\epsilon} = \sigma^2 I$, and

$$\Sigma_f \approx \sigma^2(J^TJ)^{-1}.$$  

(29)

The variance of noise $\sigma^2$ can be approximated as

$$\sigma^2 \approx \frac{\|g - A(\hat{f})\|^2}{N_zN_m - N_r}.$$  

(30)

The computed value of $\sigma^2$ was 1.0021, which corresponds to the standard deviation of noise added to simulated data.
Figure 4. Left column: the absolute value of computed pressure fields (MPa) for several time periods. Right column: black elements represent area $D_r$, where the gradient of the source term of the bioheat equation is optimized, and the area containing gray elements (over skin) represents region where temperature elevation is avoided. Numbered black lines represent ultrasound transducers.
Figure 5. The mesh used in the computations of estimates consisting of 7818 elements and 3998 nodes.

Table 3. Computed estimates $\hat{f}$ when computations were carried out in the mesh shown in figure 5. The error estimate $\hat{\sigma}_f$ is obtained from the approximate MAP error covariance estimate (29).

<table>
<thead>
<tr>
<th></th>
<th>Real</th>
<th>Estimate $\hat{f}$</th>
<th>Error estimate $\hat{\sigma}_f$</th>
<th>True Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\kappa^{(2)}$</td>
<td>0.5000</td>
<td>0.4659</td>
<td>0.0146</td>
<td>0.0342 (6.9%)</td>
</tr>
<tr>
<td>$\kappa^{(3)}$</td>
<td>0.5000</td>
<td>0.4725</td>
<td>0.0122</td>
<td>0.0276 (5.6%)</td>
</tr>
<tr>
<td>$\kappa^{(4)}$</td>
<td>0.6500</td>
<td>0.6188</td>
<td>0.0717</td>
<td>0.0313 (4.9%)</td>
</tr>
<tr>
<td>$\beta^{(2)}$</td>
<td>3770</td>
<td>4452</td>
<td>393</td>
<td>683 (18.1%)</td>
</tr>
<tr>
<td>$\beta^{(3)}$</td>
<td>2639</td>
<td>2534</td>
<td>58</td>
<td>105 (4.0%)</td>
</tr>
<tr>
<td>$\beta^{(4)}$</td>
<td>8671</td>
<td>9162</td>
<td>270</td>
<td>491 (5.7%)</td>
</tr>
</tbody>
</table>

Furthermore, the approximations of the marginal probability densities of the estimates are shown in figure 6. These marginal densities are Gaussian approximations based on linearizations around the estimates, that is, these density functions are of the form

$$p_{\hat{f}_i}(x) = \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp \left\{ \frac{1}{2} \frac{(x - \hat{f}_i)^2}{\sigma_i^2} \right\},$$

(31)

where $\hat{f}_i$ is the $i$'th component of the estimate and $\sigma_i$ is the standard deviation of the $i$'th component obtained from (29).

As it can be seen from table 3, the approximate estimation errors provide a reasonably good assessment of the errors. This is not always the case and statistical
procedures such as Markov chain Monte Carlo are sometimes needed to evaluate the accuracy of the estimates.

Several other tests were carried out, including coarsening the spatial mesh and time steps. These simulations with known parameter values have to be carried out to provide information on the computational requirements. It was also verified that the estimate errors as well as the slight discrepancy of the true errors and the estimated errors were due to the approximation error. The noise level did not have large effect on the accuracy of estimates. For example, when estimates were computed from noise free data, the relative error were 3-10% for the conductivity estimates and 3-15% for the perfusion estimates. Furthermore, in this case computed error estimates were very small and do not correspond to true error at all.

Recently, so-called approximation error methods have been proposed (Kaipio and Somersalo 2005). With these methods that rely heavily on the use of feasible prior models and extensive stochastic simulation for the construction of the error models, one can be able to reduce the computational models beyond conventional limits. This means that one can use significantly sparser meshes than without these extended observation models.

6. Conclusions and discussion

We have proposed a method which can be used to estimate thermal conductivity and perfusion in a heterogeneous tissue using ultrasound induced heating and MRI
thermal imaging. More precisely, we have presented a numerical method to compute tissue parameter estimates for subdomains of tissue from measured temperature data. The estimation method described in this paper was based on maximum a posteriori estimation and the forward model was constructed for Pennes’ bioheat equation using semi-discrete FEM scheme. The ultrasound fields were computed using the ultraweak variational formulation (UWVF).

Simulations were used to evaluate the estimation method. The simulations were carried out in a two-dimensional domain consisting of four separate subdomains. The results from simulations show that the maximum errors of thermal conductivity and perfusion estimates were near 7% and 18%, respectively. This accuracy is sufficient for the use in ultrasound treatment surgery planning. However, it seems that a significant part of this error is caused by approximation error in the observation model, and the estimates will be more accurate if denser discretization is used or approximation error methods are employed. The latter choice will eventually lead to computationally much more efficient schemes.

In this paper simulations were carried out in the two-dimensional domain, since the main purpose of this work was to evaluate method. However, the computations will eventually be carried out in three dimensional domains. Since the adequate mesh density is this high in 2D domains, the computational burden in three-dimensions is probably too high without parallel computing. Furthermore, it is probably imperative, that approximation error methods are applied to this problem before turning into 3D problems. In spite of all, there should not be any reason why the implementation of the method in 3D is not possible. For example, the UWVF for ultrasound field computation was implemented and verified in 3D (Huttunen et al 2005). In three-dimensions heat transfer due to conduction and perfusion is faster so it maybe possible that we should use denser temporal discretation. However, this also causes that information about temperature evolution is collected faster and overall treatment time can be shorter. Furthermore, cooling periods can be shorter, since less time is taken to transfer heat from tissue. On the other hand, in 3D the outer boundary is a two-dimensional surface instead of a one-dimensional arch. Therefore, more transducers can be used and transducers can be placed more versatility. This makes easier to produce desired ultrasound fields when transducer excitations are constructed.

Although the Pennes bioheat equation is proven to predict temperature fairly well in some cases (Damianou et al 1995, Kolios et al 1998, Moros et al 1993), it may fail if the target area contains large arteries or veins. However, there are modifications of the bioheat equations which takes into account the effects of large blood vessels (Kotte et al 1996, Lang et al 1999a). Furthermore, if the target domain contains elastic material such as bone, it is possible that Helmholtz equation is not a feasible model for the ultrasound wave propagation. An UWVF model for elastic wave equation has already been derived (Huttunen et al 2004). However, the model for linking of the fluid-solid models is still a topic for research (Huttunen et al 2006).

The absorption coefficient $\alpha$ should also be determined. However, this requires that ultrasound field must be computed several times at every iteration step, and this increases the computational burden significantly.

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Appendix A. The ultraweak variational problem and its discretation

For UWVF the computation domain is divided into \( N_e \) disjoint triangular elements \( \Omega_i \). Denote \( \nu_i \) as the outward unit normal for the \( i \)'th element and \( \Sigma_{ij} \) as the boundary between elements \( \Omega_i \) and \( \Omega_j \). Furthermore, we denote \( \Sigma_i = \partial \Omega_i \cap \partial \Omega_j \). The parameters \( k \) and \( \rho \) are approximated with piecewise constant functions, thus the problem (2)-(5) can be decomposed as

\[
\Delta p_i + k_i^2 p_i = 0 \quad \text{in } \Omega_i \text{ for all } i \quad (A.1)
\]
\[
p_i = p_j \quad \text{on } \Sigma_{ij} \text{ for all } i \text{ and } j \quad (A.2)
\]
\[
\frac{1}{\rho_i} \frac{\partial p_i}{\partial \nu_i} = \frac{1}{\rho_j} \frac{\partial p_j}{\partial \nu_j} \quad \text{on } \Sigma_{ij} \text{ for all } i \text{ and } j \quad (A.3)
\]
\[
\frac{1}{\rho_i} \frac{\partial p_i}{\partial \nu_i} - i\sigma p_i = \tau \left( -\frac{1}{\rho_i} \frac{\partial p_i}{\partial \nu_i} - i\sigma p_j \right) + g \quad \text{on } \Sigma_i \text{ for all } i, \quad (A.4)
\]

where \( p_i = p|_{\Omega_i} \). The boundary conditions (A.2) and (A.3) will ensure continuity of the pressure and the particle velocity. The boundary conditions (A.2) and (A.3) can be replaced with a boundary condition (Benamou and Despres 1997)

\[
\frac{1}{\rho_i} \frac{\partial p_i}{\partial \nu_i} - i\sigma p_i = \frac{1}{\rho_j} \frac{\partial p_j}{\partial \nu_j} - i\sigma p_j \quad \text{on } \Sigma_{ij} \text{ for all } i \text{ and } j, \quad (A.5)
\]
where a coupling parameter $\sigma$ is real positive parameter defined on $\Sigma_{ij}$. In this study the coupling parameter is chosen to be a mean value of the real part of $k/\rho$ over the boundary

$$\sigma = \frac{1}{2} \left( \frac{\Re(k_i)}{\rho_i} + \frac{\Re(k_j)}{\rho_j} \right) \quad \text{on } \Sigma_{ij}. \quad (A.6)$$

Assume that $p$ is in $H^1(\partial \Omega)$. Define a function $f$ on element boundaries as

$$f_i = \left( \left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) p_i \right)|_{\partial \Omega_i} \quad \text{for } i = 1, \ldots, N_e, \quad (A.7)$$

where $f_i$ is the restriction of $f$ to $\partial \Omega_i$. It can be shown (Cessenat and Despres 1998) that if $\frac{\partial p}{\partial v_i}$ is in $L^2(\partial \Omega_i)$ for all $j = 1, \ldots, N_e$, the function $f$ satisfies equation

$$\sum_{i=1}^{N_e} \int_{\partial \Omega_i} \frac{1}{\sigma} f_i \left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) q_i - \sum_{i=1}^{N_e} \sum_{j=1}^{N_e} \int_{\Sigma_{ij}} \frac{1}{\sigma} f_j \left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) q_i = \sum_{i=1}^{N_e} \int_{\Sigma_i} \frac{1}{\sigma} g \left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) q_i \quad (A.8)$$

for all sequences $(q_i)$ such that for all $i = 1, \ldots, N_e$ functions $q_i \in H^1(\Omega_i)$ satisfies

$$\Delta \bar{q}_i + k_i^2 \bar{q}_i = 0 \quad \text{(the adjoint Helmholtz equation) and} \quad (A.9)$$

$$\left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) q_i \in L^2(\partial \Omega_i), \quad (A.10)$$

where over bar denotes the complex conjugate. The equation (A.8) is called the ultraweak variational formulation of the Helmholtz problem.

The approximation space for the numerical solution is chosen as follows. For each $\Omega_i$ a family of functions $\{\varphi_{i,n}\}_{n=1}^{N_i}$ is chosen such that each $\varphi_{i,n}$ satisfies

$$\Delta \varphi_{i,n} + k_i^2 \varphi_{i,n} = 0 \quad \text{in } \Omega_i. \quad (A.11)$$

Functions $\varphi_{i,n}$ can be chosen in numerous ways. In this study the plane wave basis with support in $\Omega_i$ is chosen, i.e. we have

$$\varphi_{i,n} = \begin{cases} \exp(ik_i d_{i,n} \cdot x) & \text{in } \Omega_i \\ 0 & \text{in } \Omega \setminus \Omega_i \end{cases}, \quad (A.12)$$

where $d_{i,n}$ is a unit vector which defines the direction of the wave. The directions $d_{i,n}$ are chosen equally distributed, thus we have

$$d_{i,n} = \left( \cos \left( 2\pi \frac{n-1}{N_i} \right), \sin \left( 2\pi \frac{n-1}{N_i} \right) \right). \quad (A.13)$$

For the approximation of $f$ we have

$$f_i^n = \sum_{n=1}^{N_i} f_{i,n} \left( -\frac{1}{\rho_i} \frac{\partial}{\partial v_i} - i\sigma \right) \varphi_{i,n}, \quad (A.14)$$

where $f_{i,n}$ are constants to be determined.

In this study Galerkin scheme is used to discretization. This means that approximation space for the solution is chosen to be same as the space of test functions. By substituting (A.14) and $q_i \leftarrow \varphi_{i,n}, \ n = 1, \ldots, N_i$ to (A.8), the problem can be written in the form of matrix equation (Cessenat and Despres 1998)

$$(D - C)X = b, \quad (A.15)$$
from which unknowns $X = (f_{1,1}, \ldots, f_{1,N_1}, \ldots, f_{N_e,N_{N_e}})^T$ can be solved. Due to the compact support of basis functions, matrices $D$ and $C$ are sparse and $D$ is a Hermitian block diagonal matrix consisting $N_e$ blocks $D_i \in \mathbb{C}^{N_i \times N_i}$. It is proposed by Cessenat (1996) that matrix equation (A.15) is solved using the form

$$(I - D^{-1}C)X = D^{-1}b. \quad (A.16)$$

Due to the block diagonal structure of $D$, the inversion can be done block-wise for each $D_i$ separately. Furthermore, the number of basis functions can be chosen by charting the conditional number of matrix block $D_i$.

From equations (A.7) and (A.14) it can be seen that for the approximation of the pressure field $p$ we have

$$p^a = \sum_{i=1}^{N_i} f_{i,n} \varphi_{i,n} \quad \text{on } \partial \Omega_i. \quad (A.17)$$

This representation for $p^a$ is also approximately valid within the elements.

**Appendix B. Computing optimal ultrasound excitation**

Assume that the domain $\Omega$ is divided into elements and let $\mathcal{D}$ and $\mathcal{D}'$ be a subsets of $\Omega$ so that $\mathcal{D}$ contains elements $\Omega_e$, $e = 1, \ldots, E$ and $\mathcal{D}'$ contains elements $\Omega_{e'}$, $e = 1, \ldots, E'$. The problem is to found a minimum point of a functional $\mathcal{E}$ defined as

$$\mathcal{E}(\bar{u}) = - \sum_{e=1}^{E} \int_{\Omega_e} \| \nabla Q_{\bar{u}}(x) \|^2 \| x \| + \alpha \sum_{e=1}^{E'} \int_{\Omega_{e'}} Q_{\bar{u}}(x) \| x \|^2 + \beta \| \bar{u} \|^{8}. \quad (B.1)$$

The source term $Q_{\bar{u}}$ is assumed to be a piecewise linear, hence it can be written as $Q(x) = a_0 + a_1 x_1 + a_2 x_2$ where $x = (x_1, x_2) \in \Omega_e$. Let $x^{e,k} = (x^{e,k}_1, x^{e,k}_2)$ be the $k$'th node point of the element $\Omega_e$, thus we have $Q_{\bar{u}}(x^{e,i}) = a_0 + a_1 x^{e,1}_1 + a_2 x^{e,1}_2$ for $i = 1, 2, 3$. This can be written to the form of a matrix equation $Q_e = A_e a_e$ where $a = (a_0, a_1, a_2)^T$,

$$Q_e = \begin{pmatrix} Q_{\bar{u}}(x^{e,1}) \\ Q_{\bar{u}}(x^{e,2}) \\ Q_{\bar{u}}(x^{e,3}) \end{pmatrix} \quad \text{and} \quad A_e = \begin{pmatrix} 1 & x^{e,1}_1 & x^{e,1}_2 \\ 1 & x^{e,2}_1 & x^{e,2}_2 \\ 1 & x^{e,3}_1 & x^{e,3}_2 \end{pmatrix}. $$

Assume that the inverse matrix of $A_e$ exists (otherwise the area of the element is zero) thus $Q_{\bar{u}}$ and its gradient can be written as

$$Q_{\bar{u}}(x) = \begin{pmatrix} 1 & x_1 & x_2 \end{pmatrix} a_e = \begin{pmatrix} 1 & x_1 & x_2 \end{pmatrix} A_e^{-1} Q_e \quad \text{and} \quad \nabla Q_{\bar{u}}(x) = (a_1^e, a_2^e) = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} A_e^{-1} Q_e \quad \text{when } x \in \Omega_e. \quad (B.2)$$

Let $B$ be a matrix whose $ij$'th component $B_{ij}$ is the complex pressure in the $i$'th node point for the ultrasound field produced by the $j$'th transducer. Pressure in the $i$'th node $x_i \in G$ can be written as

$$p(x_i) = \sum_{j=1}^{N_e} \hat{u}_j B_{ij} = B^{(i)} \hat{u}, \quad (B.4)$$

where $B^{(i)}$ is the $i$'th row of $B$. Thus the vector $\bar{d}$ in (12) can be written as $\bar{d} = |B \hat{u}|^2$ (operation $\| \|^2$ for a vector is calculated point-wise). Let $B_e$ be a matrix containing those rows of matrix $B$ which corresponds to the nodes in the element $\Omega_e$, thus for
the vector $Q_e$ we have $Q_e = \gamma_e |B_e \hat{u}|^2$, where $\gamma_e$ is the value of $\alpha(\rho c)^{-1}$ in the element $\Omega_e$. Further, $\hat{\Xi}$ can be written as
\[
\hat{\Xi}(\hat{u}) = -\sum_{e=1}^{E} \gamma_e' ||D_e(B_e \hat{u})^2||^2 m(\Omega_e) + \alpha \sum_{e=1}^{E} \gamma_e S_e A_e^{-1} |B_e \hat{u}|^2 + \beta \|\hat{u}\|^8,
\]
where $m(\Omega_e)$ is the area of $\Omega_e$ and $\tilde{D}_e$ and $\tilde{S}_e$ are matrices of the form
\[
\tilde{D}_e = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} A_e^{-1}
\quad \text{and} \quad
\tilde{S}_e = \left( m(G_e'), \int_{G_e'} x_1 dx, \int_{G_e'} x_2 dx \right) = \frac{m(\Omega_e)}{3} \left( 3 \sum_{k=1}^{3} x_{1,k}, \sum_{k=1}^{3} x_{2,k} \right).
\]

The variable $\hat{u}$ is complex-valued. In order to use real arithmetic, we denote
\[
u = \begin{pmatrix} \Re(\hat{u}) \\ \Im(\hat{u}) \end{pmatrix}
\quad \text{and} \quad
C_e = \begin{pmatrix} \Re(B_e) & -\Im(B_e) \\ \Im(B_e) & \Re(B_e) \end{pmatrix},
\]
In this case we have $|B_e \hat{u}|^2 = (I I)(C_e u)^2$, where $I$ is an identity matrix. Define a functional $\Xi$ as
\[
\Xi(u) = -\sum_{e=1}^{E} \gamma'_e ||D_e(C_e u)^2||^2 + \alpha \sum_{e=1}^{E'} \gamma_e S_e (C_e u)^2 + \beta \|u\|^8,
\]
where $\gamma'_e = \gamma_2 m(G_e)$, $D_e = \tilde{D}_e(I I)$ and $S_e = \tilde{S}_e A_e^{-1}(I I)$. Since we have $\hat{\Xi}(\hat{u}) = \Xi(u)$, it is equivalent with the original problem to find a point $u$ which minimizes functional $\Xi$.

The minimum of $\Xi$ can be computed using the Newton-Raphson iteration
\[
u^{(k+1)} = \nu^{(k)} - \lambda^{(k)} d^{(k)},
\]
where $\lambda^{(k)}$ is a step size and $d^{(k)}$ is a search direction defined as
\[
d^{(k)} = \left( H_\Xi(\nu^{(k)}) \right)^{-1} \nabla \Xi(\nu^{(k)})^T,
\]
where $\nabla \Xi$ and $H_\Xi$ are the gradient and the Hessian matrix of $\Xi$, respectively. The gradient and the Hessian matrix of $\Xi$ can be written as
\[
\nabla \Xi(u) = -4 \sum_{e=1}^{E} \gamma'_e C_e^T \text{diag}(C_e u) E_e (C_e u)^2 + 2\alpha \sum_{e=1}^{E'} \gamma_e C_e^T \text{diag}(C_e u) S_e^T + 8\|u\|^6 u^T
\]
\[
H_\Xi(u) = -4 \sum_{e=1}^{E} \gamma'_e C_e^T \left[ \text{diag}(E_e (C_e u)^2) + 2\text{diag}(C_e u) E_e \text{diag}(C_e u) \right] C_e
\]
\[
+ 2\alpha \sum_{e=1}^{E'} \gamma_e C_e^T \text{diag}(D_e) C_e + 48\beta \|u\|^4 u u^T + 8\beta \|u\|^6 I,
\]
where $E_e = D_e^T D_e$.

In some cases the Hessian matrix can be ill-conditioned so that inverse does not exist or it is numerically unstable. In such a case one can toggle between the Newton-Raphson and steepest descent directions.

The step size $\lambda^{(k)}$ is chosen with the line search method, i.e. $\lambda^{(k)}$ is chosen to be a minimum of a functional $\Psi_k$ defined as
\[
\Psi_k(\lambda) = \Xi(\nu^{(k)}) - \lambda \nabla \hat{F}(\nu^{(k)})^T.
\]
The minimum of (B.7) can be solved with the modification of the Newton’s method

\[ \lambda^{(j+1)} = \lambda^{(j)} - \frac{d\Psi_k}{d\lambda}(\lambda^{(j)}) \frac{1}{\left| \frac{d^2\Psi_k}{d\lambda^2}(\lambda^{(j)}) \right|}. \]  

(B.8)

The first and second order derivatives of \( \Psi_k \) can be written as

\[ \frac{d\Psi_k}{d\lambda}(\lambda) = -\nabla \Xi(u^{(k)}) - \lambda \nabla \Xi(u^{(k)})^T \nabla \Xi(u^{(k)})^T \]

and

\[ \frac{d^2\Psi_k}{d\lambda^2}(\lambda) = \nabla \Xi(u^{(k)}) H_{\Xi}(u^{(k)}) \nabla \Xi(u^{(k)})^T \nabla \Xi(u^{(k)})^T. \]

For a general text of optimization, see (Dennis and Schnabel 1983).