Towards the optimisation of acoustic fields for ablative therapies of tumours in the upper abdomen

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Abstract. The efficacy of high intensity focused ultrasound (HIFU) for the non-invasive treatment of cancer has been demonstrated for a range of different cancers including those of the liver, kidney, prostate and breast. As a non-invasive focused therapy, HIFU offers considerable advantages over other techniques such as chemotherapy and surgical resection, in terms of its non-invasiveness and low risk of harmful side effects. There is, however, a number of significant challenges which currently hinder its widespread clinical application. One of these challenges is the need to transmit sufficient energy through the ribcage to induce tissue necrosis at the required foci whilst minimising the formation of side lobes and sparing healthy tissue. Ribs both absorb and reflect ultrasound strongly. As such, a common side effect of focusing ultrasound in regions located behind the rib cage is the overheating of bone and surrounding tissue, which can lead to skin burns. Successful treatment of a patient with tumours in the upper abdomen therefore requires a thorough understanding of the way acoustic and thermal energy are deposited. This is likely to rely on a treatment planning procedure in which optimal source velocity distributions are obtained so as to maximise a dose quantity at the treatment sites, whilst ensuring that this quantity does not exceed a specified threshold at other field locations, particularly on the surface of the ribs. Previously, a boundary element approach based on a Generalised Minimal Residual (GMRES) implementation of the Burton-Miller formulation was developed to predict the field of a multi-element HIFU array scattered by human ribs, the topology of which was obtained from CT scan data [1]. This work describes the reformulation of the boundary element equations as a least-squares minimisation problem with non-linear constraints. The methodology was subsequently tested at an excitation frequency of 100 kHz on a spherical multi-element array in the presence of a perfectly rigid cylindrical scatterer with hemi-spherical end-caps. Reduction of side lobes in the exterior domain and of acoustic pressure magnitudes on the surface of the cylinder were achieved whilst preserving a local maximum in the focal region.

1. Background

High intensity focused ultrasound (HIFU) enables highly localised, non-invasive tissue ablation and its efficacy has been demonstrated for treating a range of cancers, including abdominal tumours [2].
There are nevertheless a number of significant challenges currently limiting its more widespread clinical application. In the cases of liver, kidney and pancreatic cancers, ribs may act as reflectors and aberrators. In addition to this, bone is a highly attenuating medium. As such, a common side effect of focusing ultrasound in regions located behind the rib cage is the overheating of bone and surrounding tissue, which can lead to skin burns over the location of the ribs [3], [4]. Hence, care must be taken so that sufficient energy is delivered through the rib cage to ablate tissue at the required location whilst also minimising the formation of side lobes. With the advent of piezoelectric multi-element transducer arrays used in conjunction with multi-channel electronics, there is an opportunity to address these challenges, as the magnitude and phase of each transducer element may be adjusted to create an optimal beam profile.

Botros et al [5] describe a method in which the design of a HIFU array was optimised using the pseudo-inverse technique (minimum norm least-squares solution) and by enforcing a constrained preconditioned pseudo-inverse method. The procedure calculates the required primary sources on the array while maintaining minimal power deposition over solid obstacles such as the ribs. Although the methodology endeavours to tackle the inverse problem described above, it suffers from the following limitation that the forward propagation model is 2D and relies on high frequency simplifications, and that the shape of the rib contours is idealised.

Liu et al [6] carried out a numerical study based on a modified Rayleigh-Sommerfeld integral approach where the feasibility of using a spherical ultrasound phased array for trans-rib liver tumour thermal ablation was investigated. Based on the feedback from anatomical imaging, array elements obstructed by the ribs were deactivated in an effort to minimise heat deposition on the ribs.

An approach based on adaptive optimisation has been discussed by Cauchard et al [7]. This was based on the analysis of signals backscattered from ex vivo ribs immersed in water, towards the HIFU array functioning in transmit/receive mode, in order to identify which elements required deactivation for minimisation of the reflected acoustic signal. Although this approach could be incorporated as part of a pre-operative procedure using a suitable forward model, it will not guarantee that the acoustic pressure on the surface of the ribs will not exceed a given threshold, since this condition is not a constraint.

Quesson et al [8] describe a method for selecting the elements of a HIFU transducer array to deactivate based on the relative location of the focal point and the ribs, identified from anatomical MR data. This method was implemented both ex vivo and in vivo in pig liver and was compared against the case in which all elements were activated. Temperature variations near the focus and ribs were monitored, demonstrating the benefit of deactivating selected array elements for sparing the ribs from excessive heating whilst still ensuring high enough temperatures for tissue ablation at the focus.

A similar approach was adopted by Marquet et al [9] where experiments investigating trans-rib HIFU using both ex vivo human ribs immersed in water and in vivo on pigs with 3D movement detection and compensation included.

The deactivation of transducer elements obstructed by ribs, or so-called binarised apodisation, described in [6], [7], [8] and [9], whilst practical in a clinical setting, is suboptimal, as acknowledged by Quesson et al [8]. This approach does not directly address the inverse problem of optimising the magnitudes and phases of the transducer element drive voltage to transmit sufficient energy through the ribcage to induce tissue necrosis at the required foci, whilst keeping the pressure on the ribs below a given threshold and ensuring minimal formation of side-lobes. Furthermore, binarised apodisation may hamper the treatment of deep-seated abdominal tumours in humans, where deactivating any number of elements may significantly reduce the ultrasonic intensities delivered at the focus.
Additionally, in order to reach the required temperature rise for tissue necrosis, an increase in treatment times may occur as a result of deactivating transducer elements. There is therefore a requirement to solve this inverse problem using a suitable forward model capable of addressing the effects of scattering and diffraction on 3D anatomical data. In the work described in this paper, the boundary element approach proposed by Gélat et al [1] was used, after implementation of dissipative mechanisms in the medium surrounding the ribs, in the form of a complex wave number. From the discretised form of the Helmholtz surface integral equation applied to locations on the surface of the scatterer and in the exterior domain, the inverse problem was formulated in which the unknowns were the complex velocities of each element on a transducer array.

Effects of nonlinear propagation were not considered as part of this work. It is however well known that HIFU fields can result in highly nonlinear behaviour in the focal region (Wu et al, 2004) leading to distortion of the acoustic waveform and transfer of energy from the fundamental frequency towards higher order harmonics. From the point of view of treatment planning, it has been suggested that correcting for aberrations introduced by the presence of bone need not require nonlinear propagation models and that linear approaches may generally suffice [10]. Furthermore, nonlinear behaviour is likely to be mainly confined to the central focal lobe. Hence, although a more rigorous treatment of the focal region may be required, useful information can be obtained from linear models when investigating energy depositions at the surface of the ribs.

The reformulation of the boundary element approach was tested on a reduced-complexity problem involving a 256 element spherical phased array with pseudo-random distribution of the elements on its surface. Each element was vibrating at a frequency of 100 kHz, and a perfectly rigid cylindrical scatterer was placed between the array and its geometric focus. Using a Numerical Algorithms Group (NAG) Numerical Library [11] routine which calculates the minimum of a sum of squares for a set of nonlinear constraints, optimal values for the real and imaginary parts of the element velocities were obtained so that the acoustic pressures at specified locations in the exterior domain best fitted a required field distribution in a least-squares sense. Implementation of the constraints ensured that the acoustic pressure magnitudes on the surface of the cylinder did not exceed a specified threshold and that the element velocity magnitudes were kept within the specified dynamic range.

2. Theory
Consider an exterior domain $V_{ext}$ bounded by a surface $\Lambda$ and by a closed smooth surface $S$. Let $\Lambda$ be at a sufficiently large distance from the acoustic sources and from the surface $S$. Let the boundary condition on $\Lambda$ satisfy Sommerfeld’s acoustic radiation condition. The propagation of time-harmonic acoustic waves in a homogeneous isotropic inviscid medium is described by the Helmholtz equation:

$$\nabla^2 p(\vec{r}) + k^2 p(\vec{r}) = 0, \forall \vec{r} \in V_{ext}$$  \hspace{1cm} (1)

where $p$ is the acoustic pressure, $k^* = \omega / c^*$ is the acoustic wave number where $\omega$ is the angular frequency, $c^*$ the complex sound speed in the external medium and $\vec{r}$ is the position vector. A time harmonic dependence is implicitly assumed, so that the acoustic pressure is given by the real part of $p(\vec{r})e^{\int \omega t}$. A source term may be included in the right hand side of (1) (incident pressure wave), but it is convenient to split the total pressure $p(\vec{r})$ as the sum of the incident pressure $p_i(\vec{r})$ and the pressure scattered by the surface $S$, $\forall \vec{r} \in V_{ext}$.

For scattering problems, the integral representation of the solution to (1) is given by the Helmholtz integral equation:
where the Green’s function in a three-dimensional space is given by:

\[ G(\vec{r} | \vec{r}_q) = \frac{1}{4\pi\|\vec{r} - \vec{r}_q\|} e^{-ik\|\vec{r} - \vec{r}_q\|} \]  

and \( p(\vec{r}_q) \) is the pressure on the surface \( S \) at point \( \vec{r}_q \) and \( \vec{n}_q \) is the outward normal.

The problem described by the integral equation (2) suffers from non-uniqueness at frequencies of excitation approaching an eigenvalue of one of the (fictitious) modes of the cavity inside the scatterer. In cases where the dimensions of the scatterer are large compared with the wavelength in the propagating medium, such as in HIFU applications, this is likely to occur. The matrix formed by discretising equation (2) then becomes close to singular. When the wave number is purely real, the method which appears to offer the best compromise in terms of application of the Helmholtz integral equation to exterior acoustic problems involving scatterers of arbitrary shape remains the Burton-Miller formulation [12], which solves for a linear combination of equation (2) and its derivative with respect to the outward normal vector on \( S \) at \( \vec{r} \). However, for a wave number whose imaginary part is non-zero, solving the discretised form of equation (2) may be sufficient, as the fictitious modes of the cavity inside the scatterer are likely to be dampened out. For the problem investigated in this paper, it will be demonstrated in Section 3 that a discretisation of the Helmholtz integral equation is indeed sufficient and that the coupling term involving the normal derivative formulation need not be considered. The methodology described below for solving the inverse problem may nevertheless be generalised to the Burton-Miller formulation.

By discretising equation (2), for all position vectors \( \vec{r} \) on \( S \) corresponding to each node on the mesh of the surface, a linear system of equations may be generated. For a perfectly rigid scatterer, the normal derivative terms in equation (2) are zero.

\[
[H][p_{surf}] = -\{p_i\} \quad \text{(5)}
\]

where the acoustic pressures on the surface \( S \) have been relabelled \( \{p_{surf}\} \).

Let the incident field be a linear combination of plane circular pistons. The incident field on \( S \) is a linear combination of the source velocities of each piston. Equation (5) may therefore be re-written as:

\[
[H][p_{surf}] = -[\beta]\{U\} \quad \text{(6)}
\]

where the elements of \([\beta]\) may be obtained analytically in the far-field or by solving the Rayleigh integral in the near-field. \([\beta]\) is of dimension \( M \times N \), where \( M \) is the number of nodes on the surface \( S \) after its discretisation and \( N \) is the number of plane pistons.

Consider equation (3), where the position vectors are located in the exterior volume \( V_{ext} \). Again, the term on the left hand side involving the normal derivative of the acoustic pressure on \( S \) is zero for a perfectly rigid surface. When evaluated numerically, the integral may be expressed as a weighted sum
of the pressures on $S$. Additionally, the incident pressure at any given field location is a linear combination of the source velocities. Hence, for a specified number of locations in the exterior volume, we have:

$$ [Q][p_{surf}] = [p_{ext}] - [\gamma][U] $$

where the acoustic pressures in the exterior volume $V_{ext}$ have been relabelled $\{p_{ext}\}$. The coefficients in $[\gamma]$ may be obtained from the Rayleigh integrals relating each plane piston on the multi-element array to each location in $V_{ext}$.

The vector of surface pressures may be eliminated by combining equations (6) and (7).

$$ ([\gamma] - [Q][H]^{-1}[\beta])\{U\} = \{p_{ext}\} $$

Equation (6) may be re-written as follows.

$$ -[H]^{-1}[\beta]\{U\} = \{p_{surf}\} $$

or

$$ [A]\{U\} = \{p_{surf}\} $$

Equations (8) may be re-written as follows.

$$ [C]\{U\} = \{p_{ext}\} $$

All quantities in equation (11) will generally be complex. When investigating an inverse problem, it is often convenient to deal with an objective function of real variables. As such, equation (11) is rewritten as follows,

$$ \begin{bmatrix} \text{Re}[C] & -\text{Im}[C] \\ \text{Im}[C] & \text{Re}[C] \end{bmatrix} \begin{bmatrix} \text{Re}\{U\} \\ \text{Im}\{U\} \end{bmatrix} = \begin{bmatrix} \text{Re}\{p_{ext}\} \\ \text{Im}\{p_{ext}\} \end{bmatrix} $$

or

$$ [\hat{C}]\{\hat{U}\} = \{\hat{p}_{ext}\} $$

We wish to obtain a set of real and imaginary parts of source velocities which best fit a prescribed field pressure distribution in a least-squares sense such that:

- the acoustic pressure magnitudes on $S$ do not exceed a threshold defined by $p_{surf, max}$
- the source velocity magnitudes do not exceed the upper bound of the dynamic range of each element $U_{max}$.

This may be expressed as a least-squares minimisation problem with nonlinear constraints:

$$ \min \| [\hat{C}]\{\hat{U}\} - \{\hat{p}_{ext}\} \|^2_2 \text{ such that } \begin{cases} \{p_{surf}\} \leq p_{surf, max} \\ |U| \leq U_{max} \end{cases} $$
The HIFU transducer modelled as part of the underlying work was assumed to be a spherically shaped bowl and populated with \( N = 256 \) plane circular elements mounted onto its surface. The elements were each of \( a = 1 \text{ cm} \) radius. A radius of curvature of \( D = 50 \text{ cm} \) was used. The outer diameter of the HIFU transducer was chosen as 60 cm. The elements were pseudo-randomly spatially distributed on the surface of the array. The excitation frequency was assumed to be 100 kHz. A frontal view of the array is shown in figure 1.

![Figure 1. Frontal view of HIFU random phased array configuration. 1 cm element diameter, 60 cm array diameter, 50 cm focal length, 100 kHz frequency of operation.](image)

It is acknowledged that both the frequency of operation of the array and its dimensions do not conform to what is commonly used for transcostal HIFU [13]. Investigating a reduced-size problem such as this one is nevertheless both relevant and beneficial prior to applying the methodology to transcostal HIFU frequencies and dimensions, which will involve much greater computational resources.

3. Results

The Helmholtz integral equation boundary element approach was implemented on a dedicated computer cluster. The approach used here differs from that described in [1] as follows.

- The coupling coefficient in the Burton-Miller (normal derivative) formulation was set to zero.
- The speed of sound in the exterior was specified as a complex number.
- Operations were vectorised to solve equation (5) for multiple right hand sides simultaneously, thus enabling the coefficients of \([A]\) to be obtained more efficiently.

The routines employed to generate the boundary element matrices were obtained from the PAFEC (Program for Automatic Finite Element Calculations) VibroAcoustics software with permission from PACSYS Ltd.

A validation on a simple scatterer was carried out to justify setting the coupling coefficient in the Burton-Miller formulation to zero. The results displayed here are for a 100 kHz unit amplitude plane
wave scattered by a perfectly rigid cylinder with hemi-spherical end-caps. The cylinder was 22 cm in length and 1 cm in diameter. These were compared against the analytical solution for a cylinder of infinite length provided in [14] in the shadow zone between 1.2 cm and 50.0 cm (see figure 2).

![Helmholtz integral equation implementation of BE formulation on a cylindrical scatterer of 2 cm diameter and 22 cm length, with hemispherical end-caps. Incident field: unit amplitude 100 kHz plane wave travelling in positive z direction. Comparison against analytical solution involving infinite cylinder.](image)

**Figure 2.** Helmholtz integral equation implementation of BE formulation on a cylindrical scatterer of 2 cm diameter and 22 cm length, with hemispherical end-caps. Incident field: unit amplitude 100 kHz plane wave travelling in positive z direction. Comparison against analytical solution involving infinite cylinder.

The scatterer was meshed using isoparametric eight-noded quadratic patches ensuring at least three elements per wavelength for a wavespeed of $1500+4.405i$ m s$^{-1}$, corresponding to an absorption coefficient of 47.2 Np per metre at 1 MHz (assuming a power law with a linear dependence on frequency). The density of the medium was assumed to be 1000 kg m$^{-3}$. Figure 2 shows agreement within 1.9% of the analytical solution in the shadow zone, at 0.2 cm from the surface of the cylinder along the z-axis. Oscillations about the analytical solution are observed, which are due to constructive and destructive interference from the waves diffracted by the end-caps of the cylinder.

After completing this validation, the incident field was replaced with that of the array shown in figure 1. A simulation solving equation (4) for multiple right hand sides was launched so that the product $[\mathbf{H}]^{-1}[\mathbf{B}]$ could be obtained in a single run. The axis of symmetry of the cylindrical scatterer was chosen to be parallel to the x-axis and located -5 cm away from the geometric focus of the array in the z-direction (towards the array). This arrangement is illustrated in figure 3.
From a knowledge of $[H]^{-1}[\beta]$, the acoustic pressure on the surface of the cylinder may be obtained using equation (6) for a given distribution of source velocities. In order to formulate the objective function and the constraints, the case of all elements vibrating in phase and with unit velocity amplitude was investigated. The acoustic pressure magnitudes at selected locations in the $y$-$z$ plane are shown in figure 4. The corresponding incident pressure field (i.e. in absence of the scatterer) is shown in figure 5.

The resulting acoustic pressure magnitude on the surface of the cylinder is shown in figure 6.
Figures 4 and 5 show that inserting the cylindrical scatterer between the array and the focus causes the acoustic pressure magnitude at the focus to drop from 9 MPa to 6 MPa. Figure 6 shows that the maximum pressure amplitude on the surface of the cylinder is 6 MPa for all elements of the array vibrating at an amplitude of 1 m s$^{-1}$ and with uniform phase. Based on these results, the value $p_{\text{surf}}^\text{max}$ in equation (14) was chosen as 4 MPa. $U_{\text{max}}$ was taken as 1 m s$^{-1}$. The vector of pressures in the exterior volume in the objective function (i.e. the “desired” field pressure distribution) was generated from incident pressure field values at 5192 equally spaced locations in the $y$-$z$ plane such that $-3 \text{ cm} \leq y \leq 3 \text{ cm}$ and $-3 \text{ cm} \leq z \leq 3 \text{ cm}$, the focus of the array being at the global origin. Locations inside a 1.5 cm radius around the axis of the scatterer were removed.

The NAG Numerical Library e04us routine was used to carry out the constrained minimisation [11]. It is designed to minimise an arbitrary smooth sum of squares function subject to constraints, which may include simple bounds on the variables, linear constraints and smooth nonlinear constraints. It employs a sequential quadratic programming method [15]. The partial derivatives of the constraints and of the objective function with respect to the minimisation variables were supplied. According to [11], scaling of the problem is likely to reduce the number of iterations required and make the problem less sensitive to perturbations in the data, thus improving the condition of the problem. It is suggested that, in the absence of better information it is sensible to make the Euclidean lengths of each constraint of comparable magnitude. The problem was therefore scaled by a factor of $10^{-6}$ and the constraints involving the source velocities were scaled by a factor of $10^{6}$ so that they were of the same order of magnitude as the surface pressure magnitude constraints. Initial values of the minimisation variables were all specified as $1/\sqrt{2}$ m s$^{-1}$ so that the magnitudes of the source velocities were initially at the upper end of the specified dynamic range. This generated a solution for the optimisation variables where both sets of constraints were satisfied. Were the rescaling not carried out prior to the minimisation, the NAG solver either became unstable or returned results which did not satisfy the constraints.

The real and imaginary parts of the velocities were subsequently rescaled and the surface and field pressures calculated. Figures 7 and 8 respectively display the magnitudes and phases of the element velocities of the array resulting from the constrained minimisation. It was verified that the velocity magnitudes did not exceed 1 m s$^{-1}$. 

**Figure 6.** Acoustic pressure magnitude on surface of cylinder resulting from field of 100 kHz multi-element array. Uniform unit amplitude velocity and zero phase.
Figure 7. Source velocity magnitudes resulting from constrained minimisation.  

Figure 8. Source velocity phases resulting from constrained minimisation.  

Figure 9 shows the acoustic pressure magnitude on the surface of the cylinder, resulting from the source velocity distribution displayed in figures 7 and 8, which was verified not to exceed 4 MPa.  

Figure 9. Acoustic pressure magnitude on surface of cylinder resulting from field of 100 kHz multi-element array. Source velocity distribution obtained from constrained minimisation.  

Figure 10 shows the acoustic pressure magnitude in the $y$-$z$ plane resulting from the source velocity distribution displayed in figures 7 and 8.
This particular configuration makes it challenging for the majority of the acoustic energy to be transmitted in the vicinity of the focus, owing to the close proximity of the scatterer to the focal region of the array. This is further hindered by the cylinder’s large diameter compared with the beam of the array, as visualised in figure 3. The acoustic pressure magnitude at the focus shown in figure 10 is reduced by 14% compared with the case where all elements are vibrating in phase and with unit velocity amplitude. To investigate how side-lobes were affected by the constrained minimisation, the acoustic pressure magnitudes normalised to their value at the focus are displayed in figure 11, where all elements are vibrating with unit amplitude and uniform phase, and in figure 12, where the optimised velocity values are used.

![Figure 10](image10.png)

**Figure 10.** Acoustic pressure magnitude in y-z plane resulting from field of 100 kHz multi-element array. Source velocity distribution obtained from constrained minimisation.

![Figure 11](image11.png)

**Figure 11.** Normalised acoustic pressure magnitude in y-z plane resulting from field of 100 kHz multi-element array. Uniform unit amplitude velocity and zero phase.

![Figure 12](image12.png)

**Figure 12.** Normalised acoustic pressure magnitude in y-z plane resulting from field of 100 kHz multi-element array. Source velocity distribution obtained from constrained minimisation.
Figure 12 shows that a qualitative overall reduction in the side-lobes relative to the focus was achieved as a consequence of the constrained minimisation compared with the uniform amplitude and phase results displayed in figure 11.

4. Conclusions
An approach based on a GMRES implementation of the Helmholtz integral equation boundary element formulation was validated to model the scattering of the field of a multi-element random HIFU phased array by 3D objects of an arbitrary geometry under continuous wave excitation. The medium surrounding the scatterer featured a complex speed of sound thus allowing a phenomenological approach to modelling attenuation effects.

Using the discretised form of the Helmholtz integral equation for locations in the exterior volume and on the surface of the scatterer, the inverse problem of determining the complex velocities of a multi-element array which produces an acoustic pressure field that best fits a required acoustic pressure distribution in a least-squares sense was formulated such that:

- The pressure magnitude on the surface of the scatterer did not exceed a specified threshold.
- The amplitude of the velocity of each element on the array was bounded by maximum value defined by the dynamic range.

The approach was tested on a reduced-size problem involving a 100 kHz 256-element spherical array in presence of a cylindrical scatterer. Employing a NAG library solver, a least-squares minimisation with nonlinear constraints was carried out to solve the above problem, where the gradients of the objective function and of the constraints with respect to the optimisation variables were provided. The solver returned a set of real and imaginary parts for the source velocities which satisfied both sets of constraints, hence reducing side lobes and acoustic pressures on the surface of the scatterer compared with the case of all elements being driven with uniform phase and amplitude.

This technique shows promise in terms of providing an optimal solution to the transcostal HIFU problem of sparing the ribs from excessive ultrasound-induced heating whilst ensuring sufficient energy deposition at the treatment location and minimising side-lobes. Furthermore, the optimal velocity magnitude distribution suggests that only two to three elements come close to being deactivated, thus suggesting that binarised apodisation may be suboptimal. Simulations on human anatomical ribs at 1 MHz are currently being carried out and will form the basis of another paper. As part of this work, the scatterer was assumed to be perfectly rigid. In reality, it is known that both longitudinal and shear waves can be generated in bone [16], [17]. As bone is a highly attenuating medium compared to soft tissue, absorption of shear waves may play an important part of heating in the bone. A full elastodynamic boundary element formulation would be required to deal with this phenomenon accurately. It is acknowledged that this is a limitation of the method proposed in this paper. Nevertheless, a relatively simple extension of the proposed formulation could account for a locally reacting impedance boundary condition on the surface of the scatterer, which would represent a step beyond assuming that the ribs are acoustically hard surfaces.

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