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A. Scherrer, S. Jakobsson, A. Belyarev, A. Hoffmann, M. Bortz, X.-R. Reit, K.-H. Küfer

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Fraunhofer-Institut für Techno- und
Wirtschaftsmathematik ITWM
Fraunhofer-Platz 1

67663 Kaiserslautern
Germany

Telefon: +49(0)631/31600-4674
Telefax: +49(0)631/31600-5674
E-Mail: presse@itwm.fraunhofer.de
Internet: www.itwm.fraunhofer.de

Vorwort

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In der Reihe »Berichte des Fraunhofer ITWM« soll die Arbeit des Instituts kontinuierlich einer interessierten Öffentlichkeit in Industrie, Wirtschaft und Wissenschaft vorgestellt werden. Durch die enge Verzahnung mit dem Fachbereich Mathematik der Universität Kaiserslautern sowie durch zahlreiche Kooperationen mit internationalen Institutionen und Hochschulen in den Bereichen Ausbildung und Forschung ist ein großes Potenzial für Forschungsberichte vorhanden. In die Berichtreihe werden sowohl hervorragende Diplom- und Projektarbeiten und Dissertationen als auch Forschungsberichte der Institutsmitarbeiter und Institutsgäste zu aktuellen Fragen der Techno- und Wirtschaftsmathematik aufgenommen.

Darüber hinaus bietet die Reihe ein Forum für die Berichterstattung über die zahlreichen Kooperationsprojekte des Instituts mit Partnern aus Industrie und Wirtschaft.

Berichterstattung heißt hier Dokumentation des Transfers aktueller Ergebnisse aus mathematischer Forschungs- und Entwicklungsarbeit in industrielle Anwendungen und Softwareprodukte – und umgekehrt, denn Probleme der Praxis generieren neue interessante mathematische Fragestellungen.

Prof. Dr. Dieter Prätzel-Wolters
Institutsleiter

Kaiserslautern, im Juni 2001

A HYBRID OPTIMIZATION METHOD FOR FOCUSED ULTRASOUND PLAN COMPUTATION

A. SCHERRER[*], S. JAKOBSSON[†], A. BELYAEV[‡], A. HOFFMANN[*], M. BORTZ[*], X.-R. REIT[§], AND K.-H. KÜFER[*]

Abstract. Focused ultrasound therapy (FUS) is a modern and promising modality for minimally invasive cancer therapy. However, clinical routine still faces major problems in exploiting its full curative potential. The need for suitable mathematical concepts for FUS plan computation provides an urgent and important topic of current research. This work introduces a novel FUS plan computation method, which mimics the clinical planning workflow in form of a hybrid optimization method. This method combines practically sound heuristics with goal-oriented continuous optimization methods based on optimal control. It thereby provides a suitable compromise between the required numerical expense and the achieved plan quality.

Key words. Focused ultrasound therapy, partial differential equations, heuristic methods, nonlinear programming, optimal control

AMS subject classifications. 35J05, 35K20, 49J20, 90C06, 90C30, 90C59

1. Introduction.

1.1. Overview of focused ultrasound. Focused ultrasound is an emerging modality, [23, 11], for minimally invasive treatment of several kinds of cancer, see for example [28, 46, 25]. It relies on energy transfer into the sonicated tissue with acoustic waves emitted by some ultrasound transducer, which there induce a pressure field causing some tissue heating followed by cell coagulation [18, 37, 16]. The technological innovation of independently controllable transducer elements, [49, 24], increased the curative potential of FUS a lot compared with the former technology of transducers with fixed focus. The quality of a FUS plan primarily depends on the achieved cell-biological impact of temperature on tissue, which in the related field of hyperthermia was quantified with the Arrhenius model, see [16], and has led to FUS-specific mathematical models like in [8, 15]. Planning goals prominently comprise the therapy success by sufficiently high cell-biological impact in most of the cancerous tissue and acceptably low side effects by wide sparing of the healthy tissue entities, [47, 10, 48]. An adequate handling of the many degrees of freedom, the complex structure of the underlying physics and a sufficient achievement of the several planning goals requires efficient methods for FUS plan computation. Hence, a lot of effort is spent on the precise and efficient simulation of the underlying physical processes, see for example [7, 22, 28, 30, 51, 29, 13], and also the development of suitable numerical optimization routines is a major topic of research and development [9, 50, 2, 33, 31, 32, 34, 21, 36, 27].

1.2. Motivation and contents. The complex structure and high dimensionality of the FUS simulation component and planning problem turn FUS plan computation into a numerically very expensive task, see for example [32], and the above mentioned literature indicates various approaches for efficient optimization of FUS plans: Works like [7, 22, 28, 30, 51, 29] head for suitable physical models facilitating

[*]Fraunhofer Institute for Industrial Mathematics (ITWM), Kaiserslautern (Germany)
[†]Fraunhofer Chalmers Center (FCC), Göteborg (Sweden)
[‡]Google, München (Germany)
[§]Goethe-Universität, Frankfurt am Main (Germany)

efficient pressure simulation and approaches like [13] in addition exploit possibilities for speedup provided by the used hardware framework. The first publications on FUS plan computation use very simple optimization strategies like [9] or simulation surrogates, see for example [50]. The advanced approach of [33, 31, 32] uses optimal control in combination with a specific goal function for numerical optimization of FUS plan parameters. [21] addresses the incorporation of delivery aspects as additional planning goal into this approach. The delivery aspect contributes a lot to the complexity of the FUS planning problem and is thus addressed as separate subproblem in works like [36].

The research work presented herein tackles the complexity of FUS plan computation by adopting strategies of stepwise FUS planning widely used in clinical practice while retaining flexibility in terms of used simulation method and planning problem formulation. Clinical routine often features a decomposition of the FUS planning problem into the coupled subproblems of applicator positioning, sonication placement and sonication design and addresses these subproblems one after the other. The presented approach mimics this strategy by means of a hybrid FUS plan optimization method, which combines the algorithm concepts examined in the preliminary works of [40, 19], an optimal control approach analogous to [31] with a generalized connection to physical simulation and formulation of planning goals and the algorithmic studies of [4], a nonlinear programming method, see [42, 43] and the multi-criteria decision support concept invented in [41]. This approach allows for FUS plan optimization with high efficiency in terms of computation time as well as memory consumption. First, the general FUS planning problem is formulated and then decomposed into its subproblems. Then the approaches for solving the structurally simpler subproblems of applicator positioning and sonication placement are sketched. Main focus is put on the much more sophisticated problem of sonication parameter optimization, which in particular combines optimal control, nonlinear programming and connection to a simulation component.

2. Methodology.

2.1. The FUS planning problem. A FUS plan is characterized by a configuration of technically applicable and time dependent, but piecewise constant plan parameters $\boldsymbol{u}(t) \in \mathbb{R}^I$. Sonication of a volume $\mathcal{X} \in \mathbb{R}^3$ with a FUS therapy device configured with control parameters $\boldsymbol{u}(t)$ induces a pressure field $p(\boldsymbol{x}, \boldsymbol{u}(t))$ over the volume points $\boldsymbol{x}$, which follows from the Helmholtz equation, see [18]. Denoting for each space point $\boldsymbol{x}$ by $\rho(\boldsymbol{x})$, $v(\boldsymbol{x})$ and $\alpha(\boldsymbol{x})$ the tissue density, speed of sound and attenuation coefficient respectively and by f the frequency, this equation reads

$$\nabla_{\boldsymbol{x}} \cdot \left(\frac{1}{\rho(\boldsymbol{x})} \nabla_{\boldsymbol{x}} p(\boldsymbol{x}, \boldsymbol{u}) \right) + \left(\frac{2\pi f}{v(\boldsymbol{x})} + i\alpha(\boldsymbol{x}) \right)^2 \frac{1}{\rho(\boldsymbol{x})} p(\boldsymbol{x}, \boldsymbol{u}) = 0 \tag{2.1}$$

Computation of the pressure field by means of numerical solution of the Helmholtz equation may happen in several different ways, see for example [7, 22, 28, 30, 51, 29, 13]. The research work presented herein uses the simulation approach presented in Section A. The pressure field induces a time-dependent temperature field in the tissue

$$T(\boldsymbol{x}, t) \quad \text{in} \quad \mathcal{X} \times [0, t_{\text{end}}] \tag{2.2}$$

which is implicitly described by the Pennes bio-heat equation, see [37]. Denoting for each space point $\boldsymbol{x}$ by $\lambda(\boldsymbol{x})$, $c(\boldsymbol{x})$, $w_{\text{b}}(\boldsymbol{x})$, $\alpha(\boldsymbol{x})$ and $v(\boldsymbol{x})$ the thermal conductivity, heat capacity, perfusion rate, attenuation coefficient and speed of sound respectively and by T_b, c_b and ρ_b the temperature, heat capacity and density of the blood, this equation reads

$$c(\boldsymbol{x})\rho(\boldsymbol{x})\frac{\partial T(\boldsymbol{x},t)}{\partial t} = \nabla\cdot(\lambda(\boldsymbol{x})\nabla T(\boldsymbol{x},t)) + c_\mathrm{b}\rho_\mathrm{b}w_\mathrm{b}(\boldsymbol{x})(T_\mathrm{b}-T(\boldsymbol{x},t)) + \frac{\alpha(\boldsymbol{x})|p(\boldsymbol{x},\boldsymbol{u}(t))|^2}{\rho(\boldsymbol{x})v(\boldsymbol{x})} \tag{2.3}$$

Eq. (2.3) can be written in operator form as

$$\frac{\partial T(\boldsymbol{x},t)}{\partial t} = \mathcal{L}(\boldsymbol{x})T(\boldsymbol{x},t) + Q(\boldsymbol{x},\boldsymbol{u}(t)) \tag{2.4}$$

where $\mathcal{L}$ is a linear differential operator and the term Q includes the effects of the generated ultrasound field,

$$\mathcal{L}(\boldsymbol{x}) = \frac{\nabla\cdot(\lambda(\boldsymbol{x})\nabla) - c_\mathrm{b}\rho_\mathrm{b}w_\mathrm{b}(\boldsymbol{x})}{c(\boldsymbol{x})\rho(\boldsymbol{x})}, \qquad Q(\boldsymbol{x},\boldsymbol{u}(t)) = \frac{c_\mathrm{b}\rho_\mathrm{b}w_\mathrm{b}(\boldsymbol{x})T_b}{c(\boldsymbol{x})\rho(\boldsymbol{x})} + \frac{\alpha(\boldsymbol{x})|p(\boldsymbol{x},\boldsymbol{u}(t))|^2}{c(\boldsymbol{x})\rho^2(\boldsymbol{x})v(\boldsymbol{x})} \tag{2.5}$$

Computation of the temperature field by numerically solving the Pennes equation can be done with methods from [6]. The temperature field T up to some point of time t has a cell-biological impact at the tissue point $\boldsymbol{x}$, which follows from the Arrhenius model [16] in a logarithmic form as

$$D(\boldsymbol{x},t) = \int_0^t d(T(\boldsymbol{x},t'))dt' := -\int_0^t A(T(\boldsymbol{x},t'))\exp\left(-\frac{E_\mathrm{a}(T(\boldsymbol{x},\tau))}{RT(\boldsymbol{x},\tau)}\right)dt' \tag{2.6}$$

$A(T)$ denotes the temperature-dependent reaction rate, which is 0 for body temperature implying $d(T_\mathrm{body}) = 0$, $E_\mathrm{a}(T)$ the activation energy and R the ideal gas constant. Alternative models for the cell-biological impact are provided in [8, 15]. Accumulation of the cell-biological impact up to some t_end over all points of some planning volume in $\mathcal{X}$ yields a notion of FUS plan quality with respect to this specific planning volume. In case of a tumor structure, one may evaluate plan quality with the function

$$f(D(\boldsymbol{x},t_\mathrm{end})_{\boldsymbol{x}\in\mathcal{X}}) = \left[\frac{1}{|\mathcal{X}_\mathrm{tumor}|}\int_{\boldsymbol{x}\in\mathcal{X}_\mathrm{tumor}}\left(\max\{D_\mathrm{cur} - e^{D(\boldsymbol{x},t_\mathrm{end})}, 0\}\right)^2 d\boldsymbol{x}\right]^{\frac{1}{2}} \tag{2.7}$$

This function averages the undershooting of some curative and thus desirable cell-biological impact D_cur over the planning volume $\mathcal{X}_\mathrm{tumor}$. In case of a healthy organ at risk, one may use a function like

$$f(D(\boldsymbol{x},t_\mathrm{end})_{\boldsymbol{x}\in\mathcal{X}}) = \left[\frac{1}{|\mathcal{X}_\mathrm{risk}|}\int_{\boldsymbol{x}\in\mathcal{X}_\mathrm{risk}}\left(e^{D(\boldsymbol{x},t_\mathrm{end})}\right)^2 d\boldsymbol{x}\right]^{\frac{1}{2}} \tag{2.8}$$

The presence of multiple planning volumes in consideration yields a FUS planning problem with a vector valued objective function $(f_j)_{j=1,\ldots,J}$, hence plan computation for the resulting multi-objective FUS plan optimization problem requires some (continuously differentiable) scalarization function like the Tchebycheff method, [45],

$$F(D(\boldsymbol{x},t_\mathrm{end})_{\boldsymbol{x}\in\mathcal{X}}) := \|(w_j\cdot f_j(D(\boldsymbol{x},t_\mathrm{end})_{\boldsymbol{x}\in\mathcal{X}}))_{j=1,\ldots,J}\|_p \tag{2.9}$$

with $1 \le p < \infty$ and objective-specific weights $w_j \ge 0$ fulfilling $\sum_{j=1,\ldots,J} w_j = 1$ in order to obtain a single-objective optimization problems discussed in [41]. More information on multi-criteria optimization and decision making can be found, for example, in [45, 35, 12]. The single-objective FUS plan optimization problem reads

$$
\begin{aligned}
&\min_{\boldsymbol{u}(t)} F(D(\boldsymbol{x}, t_{\text{end}})_{\boldsymbol{x}\in\mathcal{X}}) \quad \text{subject to} \\
&\frac{\partial}{\partial t}\begin{bmatrix} T(\boldsymbol{x},t) \\ D(\boldsymbol{x},t) \end{bmatrix} = \begin{bmatrix} \mathcal{L}(\boldsymbol{x})T(\boldsymbol{x},t) + Q(\boldsymbol{x},\boldsymbol{u}(t)) \\ d(T(\boldsymbol{x},t)) \end{bmatrix} \quad \text{in} \quad \mathcal{X}\times[0,t_{\text{end}}] \\
&\begin{bmatrix} T(\boldsymbol{x},0) \\ D(\boldsymbol{x},0) \end{bmatrix} = \begin{bmatrix} T_{\text{body}} \\ 0 \end{bmatrix} \quad \text{in} \quad \mathcal{X}
\end{aligned}
\tag{2.10}
$$

This problem is supplemented with boundary conditions for T of Neumann (insulated boundary) or Dirichlet (prescribed temperature) type.

2.2. Problem decomposition. The configuration $\boldsymbol{u}(t)$ consists of FUS plan parameters of different semantic type. The placement of the FUS applicator is described by its origin and alignment in form of coordinate values, shifts and angles. The sonication points in the tissue, whose number L is typically of the order 10^1, are characterized by their coordinates and corresponding phase shifts of the FUS applicator elements, whose number M is of the order 10^2, the sonication schedule contains the starting times and durations of the sonications and each single sonication is characterized by the powers of the FUS applicator elements. The large number of plan parameters in combination with the dimensions of time and spatial discretization and the numerical expense for solving the Pennes equation (2.4) gives the FUS planning problem (2.10) an intractable computational complexity. However, the different semantics of the plan parameters and their individual handling in FUS practice imply a natural decomposition of problem (2.10) into a sequence of tractable subproblems with moderate coupling:

1. In general, practitioners position the FUS applicator according to the location and geometrical shape of planning structures such as tumor volume and organs at risk without taking into account details of FUS propagation and tissue interaction as described by Pennes equation (2.4) and Arrhenius model (2.6). They also prefer to position the applicator once before FUS treatment starts and not to change this setting between or during the sonications for technical reasons. The corresponding subproblem of applicator positioning is the topic of Section 2.3.
2. Clinical FUS routine employs empirically validated strategies for placing the sonication points in the tissue, which rely on fundamental knowledge about the resulting cell-biological impact and the circumvention of certain problematic physical effects without dealing with details of FUS propagation and tissue interaction. Section 2.4 addresses the corresponding subproblem of sonication placement with a suitable heuristic.
3. After positioning the FUS applicator and placing the sonications, each single sonication has to be designed in terms of its parameters. The selection of suitable values requires detailed and numerically expensive FUS simulations on volume and time discretization. The corresponding subproblem of sonication design and its computation with mathematical optimization based on optimal control is the topic of Section 2.5.

The real challenge of FUS plan computation lies in the third subproblem of sonication design. The subsequent considerations therefore address the first two simple subproblems only on a illustrative conceptual level and then focus on the algorithmically challenging third subproblem.

2.3. Applicator positioning. The subproblem for the positioning of the FUS applicator strongly depends on the specific technical degrees of freedom. The subsequent considerations will thus stay on the conceptual level and provide an illustrative example. The FUS applicator origin $\boldsymbol{a}_{\text{origin}}$ may be placed inside some set $\mathcal{A}_{\text{origin}}$, which follows from the technical degrees of freedom for its alignment in terms of translations or rotations out of some initial applicator position. The integral type of criterion functions with respect to the tumor like (2.7) motivates an alignment of the FUS applicator that provides a good average for all points of the tumor volume and thus with respect to the tumor barycenter

$$\boldsymbol{x}_{\text{tumor}} = \frac{1}{|\mathcal{X}_{\text{tumor}}|} \int_{\boldsymbol{x} \in \mathcal{X}_{\text{tumor}}} \boldsymbol{x} \, d\boldsymbol{x} \tag{2.11}$$

Without regard to the FUS modulation, the shape of the sonication cone basically follows from the shape of the FUS applicator's geometric cross section $\mathcal{A}(\boldsymbol{a}_{\text{origin}})$ and thus reads

$$\mathcal{X}_{\text{FUS}}(\mathcal{A}(\boldsymbol{a}_{\text{origin}})) = \{\boldsymbol{x}_{\text{tumor}} + \alpha(\boldsymbol{a} - \boldsymbol{x}_{\text{tumor}}) : \ \alpha \geq 0, \ \boldsymbol{a} \in \mathcal{A}(\boldsymbol{a}_{\text{origin}})\} \tag{2.12}$$

The major tradeoff in the FUS planning problem (2.10)) takes place between the sufficient coverage of the tumor volume and the maximal sparing of the healthy organs at risk $\mathcal{X}_{\text{risks}}$, which requires maximal degrees of freedom in terms of FUS modulation and thus a sonication cone of maximal size. The FUS applicator alignment problem then reads

$$\begin{aligned} \max_{\boldsymbol{a}_{\text{origin}} \in \mathcal{A}_{\text{origin}}} \ & |\mathcal{A}(\boldsymbol{a}_{\text{origin}})| \quad \text{subject to} \\ & \mathcal{X}_{\text{FUS}}(\mathcal{A}(\boldsymbol{a}_{\text{origin}})) \cap \mathcal{X}_{\text{risks}} = \emptyset \end{aligned} \tag{2.13}$$

see also Figure 1.

A suitable formulation for $\mathcal{X}_{\text{risks}}$ depends on the individual form of problem (2.13).

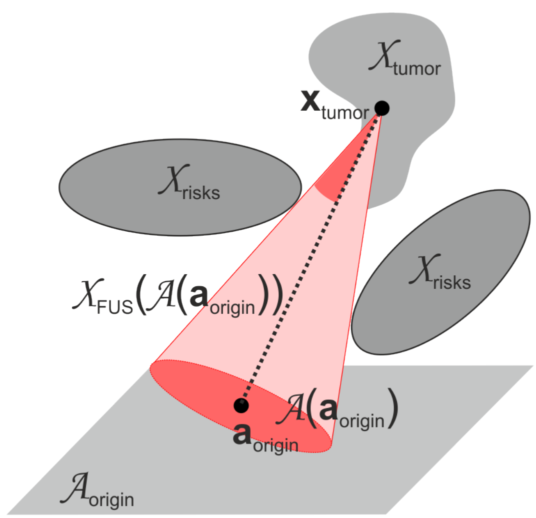

Fig. 1: Schematic view on the FUS applicator alignment problem

The most suitable formulation of this problem depends on the description of the organs at risk and the geometry of the FUS applicator. For example, [40] considers a flat FUS applicator of circular shape, which implies a circular cone, and covers the organs at risk with ellipsoids and derives an analytic formulation of the boundary points of cone and ellipsoids. The objective function of problem (2.13) then essentially reduces to the opening angle of the cone as illustrated in Figure 1. This concrete formulation allows for a computation with nonlinear programming methods, see [3]. From a general point of view, (2.13) belongs to the class of semi-infinite programming problems [20], which in many cases allow for a reduction to nonlinear programming problems, see for example [39].

2.4. Sonication placement. The subproblem for the placement of FUS sonications essentially features the coverage of the tumor volume with areas of tissue coagulation due to major cell-biological impact (2.6) around the sonication points. These areas basically have some uniform ellipsoidal shape oriented along the main direction of FUS propagation and a maximal size defined by the properties of heat diffusion in the tissue. Using the ellipsoid main axes $\boldsymbol{e}_1$, $\boldsymbol{e}_2$ and a third vector $\boldsymbol{e}_3$ with

$$\|\boldsymbol{e}_3\|_2 = \|\boldsymbol{e}_2\|_2, \qquad \boldsymbol{e}_1 \perp \boldsymbol{e}_3, \qquad \angle(\boldsymbol{e}_2, \boldsymbol{e}_3) = 60^\circ$$

one can define a triangular sonication grid around the tumor barycenter with

$$\mathcal{S} = \{\boldsymbol{x}_{\text{tumor}} + s_1 \cdot \boldsymbol{e}_1 + s_2 \cdot \boldsymbol{e}_2 + s_3 \cdot \boldsymbol{e}_3 : \; s_1, s_2, s_3 \in \mathbb{Z}\} \tag{2.14}$$

as shown in Figure 2 and obtain the relevant sonication points as

$$\mathcal{S}_{\text{FUS}} = \mathcal{S} \cap \mathcal{X}_{\text{tumor}} \tag{2.15}$$

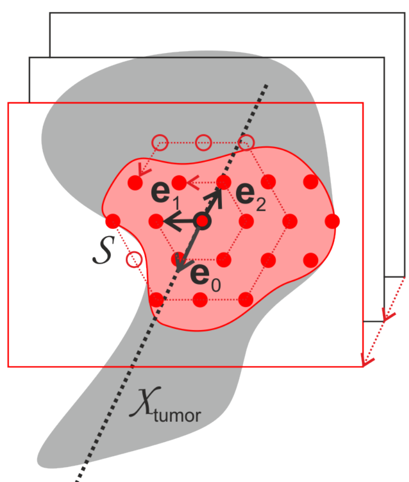

Fig. 2: Schematic view of the FUS sonication placement problem

Major cell-biological impact (2.6) causes changes in the tissue parameters in the Pennes equation (2.10), which are difficult to predict. Clinical routine circumvents the resulting uncertainties of FUS propagation and tissue interaction by a "from back to forth" approach, which first addresses the sonication points of maximal distance to the FUS applicator and then successively makes its way towards the points of minimal distance. Different approaches for ordering the sonication points of the same distance were examined in [19] with the conclusion, that a "circular from inner to outer" approach benefits most from the heat diffusion in the tissue in terms of the obtained cell-biological impact. This implies a total ordering relation on the grid (2.14), which ranks the sonication points first according to their layers from back to forth, then according to the circles in a layer and then in their (counter-)clockwise order on a circle, see Figure 2.

Taking into account the spatial discretization of $\mathcal{X}$ in form of the nodes $\boldsymbol{x}_n$ for $n = 1, \dots, N$, where N is typically of the order 10^6, the set of sonication points (2.15) is basically obtained by assigning the tumor volume points $\boldsymbol{x}_n \in \mathcal{X}_{\text{tumor}}$ to the vicinal sonication grid points.

2.5. Sonication design. After positioning the FUS applicator and placing the sonication points, the remaining FUS planning problem (2.10) in terms of plan parameters $\boldsymbol{u}$ reduces to the search for best possible starting times and durations oof the sonications and the powers for the FUS applicator elements, [49, 24], for each sonication based on a numerical FUS simulation and accumulation of the cell-biological impact based on the Pennes equation (2.4) and the Arrhenius model (2.6). Therefore, this is a PDE-constrained optimal control problem. In this section the discretize-then-optimize approach [5] is used to formulate the costate equation and calculate the gradient with respect to the control parameters.

Denote by $\boldsymbol{T}(t), \boldsymbol{D}(t), \boldsymbol{d}(\boldsymbol{T}(t)), \boldsymbol{Q}(\boldsymbol{u}(t)) \in \mathbb{R}^N$ the temperature, cell-biological impact and ultrasound source term respectively on the spatial discretization at time t and approximate the differential operator $\mathcal{L}$ in Eq. (2.10) by the matrix $\boldsymbol{\mathcal{L}} \in \mathbb{R}^{N\times N}$. The FUS planning problem (2.10) then reads

$$\begin{aligned} &\min_{\boldsymbol{u}(t)} F(\boldsymbol{D}(t_{\text{end}})) \quad \text{subject to} \\ \frac{d}{dt}\begin{bmatrix} \boldsymbol{T}(t) \\ \boldsymbol{D}(t) \end{bmatrix} &= \begin{bmatrix} \boldsymbol{\mathcal{L}}\boldsymbol{T}(t) + \boldsymbol{Q}(\boldsymbol{u}(t)) \\ \boldsymbol{d}(\boldsymbol{T}(t)) \end{bmatrix} \quad \text{in} \quad (0, t_{\text{end}}) \\ \begin{bmatrix} \boldsymbol{T}(0) \\ \boldsymbol{D}(0) \end{bmatrix} &= \begin{bmatrix} \boldsymbol{T}_{\text{body}} \\ \boldsymbol{0} \end{bmatrix} \end{aligned} \tag{2.16}$$

LEMMA 2.1. *Let $\boldsymbol{u}^* : [0, t_{\text{end}}] \mapsto \mathbb{R}^M$ be the optimum of problem (2.16) with the corresponding state $\boldsymbol{z}^*(t) := (\boldsymbol{T}^*(t), \boldsymbol{D}^*(t)) \in \mathbb{R}^{2N}$. Then there exists a costate $\boldsymbol{\lambda}^*(t) = (\boldsymbol{\lambda}^*_T(t), \boldsymbol{\lambda}^*_D(t)) \in \mathbb{R}^{2N}$ that satisfies the equation*

$$\frac{d}{dt}\boldsymbol{\lambda}_T(t) = -\boldsymbol{\mathcal{L}}^t \boldsymbol{\lambda}_T(t) + \nabla \boldsymbol{d}(\boldsymbol{T})^t \nabla F(\boldsymbol{D}(t_{\text{end}})) \tag{2.17}$$

with the terminal condition $\boldsymbol{\lambda}_T(t_{\text{end}}) = \boldsymbol{0}$.

Proof. According to the formula (B.2) the Hamiltonian takes the form

$$H(\boldsymbol{z}, \boldsymbol{\lambda}, \boldsymbol{u}) = (\boldsymbol{\mathcal{L}}\boldsymbol{T} + \boldsymbol{Q}(\boldsymbol{u}))^t \boldsymbol{\lambda}_T + \boldsymbol{d}(\boldsymbol{T})^t \boldsymbol{\lambda}_D \tag{2.18}$$

where the costate vector $\boldsymbol{\lambda}_T$ corresponds to the temperature and $\boldsymbol{\lambda}_D$ corresponds to the Pontryagin minimum principle, see Theorem B.1, provides for the costate vectors the equations

$$\frac{d}{dt}\boldsymbol{\lambda}_T(t) = -\nabla_{\boldsymbol{T}} H = -\boldsymbol{\mathcal{L}}^t \boldsymbol{\lambda}_T(t) - \nabla \boldsymbol{d}(\boldsymbol{T})^t \boldsymbol{\lambda}_D(t) \tag{2.19}$$

$$\frac{d}{dt}\boldsymbol{\lambda}_D(t) = -\nabla_{\boldsymbol{D}} H = \boldsymbol{0} \tag{2.20}$$

The terminal conditions are

$$\boldsymbol{\lambda}_T(t_{\text{end}}) = \mathbf{0} \tag{2.21}$$

$$\boldsymbol{\lambda}_D(t_{\text{end}}) = -\nabla F(\boldsymbol{D}(t_{\text{end}})) \tag{2.22}$$

From the equation (2.20) it follows that $\boldsymbol{\lambda}_D(t) \equiv \text{const}$. Hence, Eq. (2.22) implies that

$$\boldsymbol{\lambda}_D(t) \equiv \boldsymbol{\lambda}_D(t_{\text{end}}) = -\nabla F(\boldsymbol{D}(t_{\text{end}})) \tag{2.23}$$

and, therefore, the statement follows from Eqs. (2.19) and (2.23). Since the costate vector $\boldsymbol{\lambda}_D(t)$ is not affecting any of the other variables, we can omit it in the solution process. □

The considered time range is discretized

$$0 = t_0 < \ldots < t_{K+1} = t_{\text{end}} \tag{2.24}$$

into intervals of suitable length $\tau_k = t_k - t_{k-1}$ for $k = 1, \ldots, K+1$. These intervals make up for the sonication time intervals $[t_{k_{l-1}}, t_{k_l})$ for $l = 1, \ldots, L$, where k_l increase monotonously from $k_0 = 0$ to $k_L = K$. Each sonication is defined by a vector $\boldsymbol{u}_l \in \mathbb{R}^I$, where

$$\boldsymbol{u}(t) \equiv \boldsymbol{u}_k \equiv \boldsymbol{u}_l \quad (t \in [t_{k-1}, t_k),\ k_{l-1} < k \leq k_l) \tag{2.25}$$

with the sonication time $\sigma_l = t_{k_l} - t_{k_{l-1}}$, which is typically of the order of 10^1 seconds. Computation of problem (2.16) on the time discretization (2.24) comprises a numerical solution of the Pennes equation (2.4) in order to obtain the temperatures (2.2) and the accumulation of their cell-biological impact (2.6). In order to make the integration stable, the time steps τ_k have to be small, hence K is typically of the order 10^3. The vectors $\boldsymbol{u} = (\boldsymbol{u}_1, \ldots, \boldsymbol{u}_L) \in \mathbb{R}^{IL}$ and $\boldsymbol{\sigma} = (\sigma_1, \ldots, \sigma_L) \in \mathbb{R}^L$ summarize the sonication parameters and sonication times respectively.

The temperature $\boldsymbol{T}$ is computed with the explicit Euler scheme, [6], and the cell-biological impact $\boldsymbol{D}$ is accumulated with the trapezoidal integration rule, [1]. Hence, the FUS planning problem (2.16) reads

$$\min_{\boldsymbol{u},\boldsymbol{\sigma}} F(\boldsymbol{D}_K) \quad \text{subject to} \tag{2.26}$$

$$\boldsymbol{T}_k = \boldsymbol{T}_{k-1} + \tau_k(\boldsymbol{\mathcal{L}}\boldsymbol{T}_{k-1} + \boldsymbol{Q}(\boldsymbol{u}_k)) \quad (k = 1, \ldots, K) \tag{2.27}$$

$$\boldsymbol{D}_k = \boldsymbol{D}_{k-1} + \frac{\tau_k + \tau_{k+1}}{2}\boldsymbol{d}(\boldsymbol{T}_k) \qquad (k = 1, \ldots, K) \tag{2.28}$$

$$\boldsymbol{T}_0 = \boldsymbol{T}_{\text{body}} \tag{2.29}$$

$$\boldsymbol{D}_0 = \mathbf{0} \tag{2.30}$$

In this section the formulas for computing the value and in particular the gradient of the target function $F(\boldsymbol{D}_K)$ with respect to the plan parameters $\boldsymbol{u}$ and $\boldsymbol{\sigma}$ are provided. They are required for numerical solution of problem (2.26)–(2.27) with nonlinear optimization methods.

The statement of the lemma below follows immediately from Eq. (2.27).

Lemma 2.2. *Infinitesimal variation of $\boldsymbol{T}_k$ with respect to the parameters $\boldsymbol{u}_k$ and τ_k can be written as*

$$\Delta\boldsymbol{T}_k = \Theta_k^{\boldsymbol{T}}\Delta\boldsymbol{T}_{k-1} + \Theta_k^{\tau}\Delta\tau_k + \Theta_k^{\boldsymbol{Q}}\nabla\boldsymbol{Q}(\boldsymbol{u}_k)\Delta\boldsymbol{u}_k, \tag{2.31}$$

where

$$\Theta_k^{\boldsymbol{T}} = I + \tau_k \boldsymbol{\mathcal{L}} \in \mathbb{R}^{N\times N}, \qquad \Theta_k^{\tau} = \boldsymbol{\mathcal{L}} \boldsymbol{T}_{k-1} + \boldsymbol{Q}(\boldsymbol{u}_k) \in \mathbb{R}^N, \quad \Theta_k^{\boldsymbol{Q}} = \tau_k \in \mathbb{R} \tag{2.32}$$

For the subsequent considerations, we use the conventions $\Theta_{K+1}^{\boldsymbol{T}} = \boldsymbol{0}$, $\Delta \boldsymbol{T}_0 = 0$ and $\Delta\tau_{K+1} = 0$.

LEMMA 2.3. *Infinitesimal variation of $F(\boldsymbol{D}_K)$ with respect to the parameters $\boldsymbol{T}_k$ and τ_k can be written as*

$$\Delta F(\boldsymbol{D}_K) = \sum_{k=1}^{K} \left(\Psi_k^{\boldsymbol{T}} \Delta \boldsymbol{T}_k + \Psi_k^{\tau} \Delta\tau_k \right) \tag{2.33}$$

where

$$\begin{aligned} \Psi_k^{\boldsymbol{T}} &= \frac{\tau_k + \tau_{k+1}}{2} \nabla F(\boldsymbol{D}_K)^t \nabla \boldsymbol{d}(\boldsymbol{T}_k) \in \mathbb{R}^{1\times N} \\ \Psi_k^{\tau} &= \frac{1}{2} \nabla F(\boldsymbol{D}_K)^t \left(\boldsymbol{d}(\boldsymbol{T}_k) + \boldsymbol{d}(\boldsymbol{T}_{k-1}) \right) \in \mathbb{R} \end{aligned} \tag{2.34}$$

Proof. Infinitesimal variation of the target functional $F(\boldsymbol{D}_K)$ and $\boldsymbol{D}_K$ from Eqns. (2.26), (2.28) reads

$$\begin{aligned} \Delta F(\boldsymbol{D}_K) = \nabla F(\boldsymbol{D}_K)^t \Delta \boldsymbol{D}_K &= \nabla F(\boldsymbol{D}_K)^t \sum_{k=1}^{K} \frac{\tau_k + \tau_{k+1}}{2} \nabla \boldsymbol{d}(\boldsymbol{T}_k) \Delta \boldsymbol{T}_k \\ &+ \nabla F(\boldsymbol{D}_K)^t \sum_{k=1}^{K} \frac{1}{2} \boldsymbol{d}(\boldsymbol{T}_k) \Delta\tau_k + \nabla F(\boldsymbol{D}_K)^t \sum_{k=2}^{K+1} \frac{1}{2} \boldsymbol{d}(\boldsymbol{T}_{k-1}) \Delta\tau_k \end{aligned}$$

and the claim follows with $\boldsymbol{d}(\boldsymbol{T}_0) = \boldsymbol{0}$ and the above conventions. ∎

COROLLARY 2.4. *Under the assumption of similar time steps $\tau_k \approx \tau_{k+1}$ for $k = 1, \ldots, K$, computation of the costate with the implicit Euler method reads*

$$\begin{aligned} \boldsymbol{\lambda}_{K+1} &= \boldsymbol{0} \\ \boldsymbol{\lambda}_k &= (\Theta_{k+1}^{\boldsymbol{T}})^t \boldsymbol{\lambda}_{k+1} - (\Psi_k^{\boldsymbol{T}})^t \quad (k = 1, \ldots, K) \end{aligned} \tag{2.35}$$

Proof. Discretized costate equation in Lemma 2.1 with the implicit Euler scheme reads

$$\begin{aligned} \boldsymbol{\lambda}_k &= \boldsymbol{\lambda}_{k+1} - \tau_{k+1} \left(-\boldsymbol{\mathcal{L}}^t \boldsymbol{\lambda}_{k+1} + \nabla \boldsymbol{d}(\boldsymbol{T}_k)^t \nabla F(\boldsymbol{D}_K) \right) \\ &= (I + \tau_{k+1} \boldsymbol{\mathcal{L}})^t \boldsymbol{\lambda}_{k+1} - \left(\tau_{k+1} \nabla F(\boldsymbol{D}_K)^t \nabla \boldsymbol{d}(\boldsymbol{T}_k) \right)^t \end{aligned}$$

and substitution of $\Theta_k^{\boldsymbol{T}}$ and $\Psi_k^{\boldsymbol{T}}$ yields the claim. ∎

THEOREM 2.5. *Under the sound assumption of almost equally scaling time steps*

$$\Delta\sigma_l \approx (k_{l+1} - k_l - 1) \Delta\tau_k \quad (k_l < k \leq k_{l+1})$$

the partial derivatives of the target functional $F(\boldsymbol{D}_K)$ have the form

$$\begin{aligned} \nabla_{\boldsymbol{u}_l} F(\boldsymbol{D}_K) &= - \sum_{k=k_l}^{k_{l+1}-1} \boldsymbol{\lambda}_k^t \nabla \Theta_k^{\boldsymbol{Q}} \boldsymbol{Q}(\boldsymbol{u}_l) \\ \frac{\partial}{\partial \sigma_l} F(\boldsymbol{D}_K) &= \frac{1}{k_{l+1} - k_l - 1} \sum_{k=k_l}^{k_{l+1}-1} \left(\Psi_k^{\tau} - \boldsymbol{\lambda}_k^t \Theta_k^{\tau} \right) \end{aligned} \tag{2.36}$$

Proof. In order to calculate the partial derivatives of the target function $F(\boldsymbol{D}_K)$ with respect to the parameters $\boldsymbol{u}_k$ and τ_k for $k = 1, \dots, K$, the term $\sum \Psi_k^{\boldsymbol{T}} \Delta \boldsymbol{T}_k$ has to be removed from Eq. (2.33) using the discrete costate equation (2.35)

$$\begin{aligned}
\sum_{k=1}^{K} \Psi_k^{\boldsymbol{T}} \Delta \boldsymbol{T}_k &= \sum_{k=1}^{K-1} \boldsymbol{\lambda}_{k+1}^t \Theta_{k+1}^{\boldsymbol{T}} \Delta \boldsymbol{T}_k - \sum_{k=1}^{K} \boldsymbol{\lambda}_k^t \Delta \boldsymbol{T}_k \\
&= \sum_{k=2}^{K} \boldsymbol{\lambda}_k^t \left(\Delta \boldsymbol{T}_k - \Theta_k^{\tau} \Delta \tau_k - \Theta_k^{\boldsymbol{Q}} \nabla \boldsymbol{Q}(\boldsymbol{u}_k) \Delta \boldsymbol{u}_k \right) - \sum_{k=1}^{K} \boldsymbol{\lambda}_k^t \Delta \boldsymbol{T}_k \\
&= - \sum_{k=2}^{K} \boldsymbol{\lambda}_k^t \left(\Theta_k^{\tau} \Delta \tau_k + \Theta_k^{\boldsymbol{Q}} \nabla \boldsymbol{Q}(\boldsymbol{u}_k) \Delta \boldsymbol{u}_k \right) - \boldsymbol{\lambda}_1^t \Delta \boldsymbol{T}_1 \\
&= - \sum_{k=1}^{K} \boldsymbol{\lambda}_k^t \left(\Theta_k^{\tau} \Delta \tau_k + \Theta_k^{\boldsymbol{Q}} \nabla \boldsymbol{Q}(\boldsymbol{u}_k) \Delta \boldsymbol{u}_k \right) \qquad (2.37)
\end{aligned}$$

Now we substitute the result (2.37) in the target functional variation (2.33),

$$\begin{aligned}
\Delta F(\boldsymbol{D}_K) &= \sum_{k=1}^{K} \left(\boldsymbol{\Psi}_k^{\boldsymbol{T}} \Delta \boldsymbol{T}_k + \Psi_k^{\tau} \Delta \tau_k \right) \\
&= \sum_{k=1}^{K} \left(\left(\Psi_k^{\tau} - \boldsymbol{\lambda}_k^t \Theta_k^{\tau} \right) \Delta \tau_k - \boldsymbol{\lambda}_k^t \Theta_k^{\boldsymbol{Q}} \nabla \boldsymbol{Q}(\boldsymbol{u}_k) \Delta \boldsymbol{u}_k \right) \qquad (2.38)
\end{aligned}$$

The statement of the theorem follows from Eqs.(2.25), (2.38) combined with the assumption of almost equally varying scaling steps. ∎

All previous considerations combine to Algorithms 1 and 2 for computing the objective function value and gradient. Alternatives concerning the time stepping method, the numerical integration rule and also the algorithmic exploitation of the Pontryagin maximum principle of Theorem B.1 are discussed in [4].

Algorithm 1 Objective value computation - forward iterations

Initialize plan parameters and times
Create time discretization (2.24)
Initialize $\boldsymbol{T}_0$ and $\boldsymbol{D}_0$ from initial condition of problem (2.10)
for $l = 1$ **up to** L **do**
  Get source term $\boldsymbol{Q}(\boldsymbol{u}_l)$ of Pennes equation (2.4)
  for $k = k_l + 1$ **up to** k_{l+1} **do**
    Compute $\boldsymbol{T}_k$ with time stepping method (2.27)
    Compute $\boldsymbol{D}_k$ with (2.28)
  end for
  Save $\boldsymbol{T}_{k_{l+1}}$
end for
Compute and store $\nabla F(\boldsymbol{D}_K)$
Compute and return $F(\boldsymbol{D}_K)$

Algorithm 1 takes the source term of the Pennes equation (2.4) for the L sonications as input, which can be efficiently computed with the method of [13]. The algorithm computes the temperature information $\boldsymbol{T}_k$ on the time discretization (2.24) with the time stepping method (2.27), the accumulative cell-biological impact $\boldsymbol{D}_k$ with (2.28) and returns the value and gradient of the objective function $F(\boldsymbol{D}_K)$. All these vectors are defined on the spatial discretization with N nodes. The time stepping method uses the current source term and the discretized differential operator $\mathcal{L}_h$ of the Pennes equation (2.4), which is a band matrix according to [6], and the previous temperature vector for obtaining the current temperature vector. An update of the accumulative cell-biological impact (2.28) requires only the current temperature vector. A computation run of Algorithm 1 thus happens with a numerical expense of $O(K \cdot N)$ floating point operations and in this particular formulation a memory consumption of $O(N)$ bytes.

Algorithm 2 Objective gradient computation - backward iterations

```
for l = L down to 1 do
    Get source term derivative ∇Q(u_l) of Pennes equation (2.4))
    for k = k_l + 1 up to k_{l+1} do
        Compute T_k with time stepping method (2.27))
    end for
    for k = k_{l+1} down to k_l + 1 do
        Compute Θ_k^T, Θ_k^τ, Θ_k^Q with (2.32)
        Compute Ψ_k^T, Ψ_k^τ with (2.34)
    end for
    Compute ∇_{u_l} F(D_K) and ∂/∂σ_l F(D_K) with (2.36)
    Delete T_{k_{l+1}}
end for
Return ∇_u F(D_K), ∇_σ F(D_K)
```

The saving of the temperature vector $\boldsymbol{T}_{k_{l+1}}$ at the start of the next sonication, which has a memory consumption of $O(L \cdot N)$ bytes, happens in view of Algorithm 2. This algorithm takes the source term derivatives of the Pennes equation (2.4) and the starting temperatures for the L sonications as input, performs backward iterations over the sonications and computes the temperature information $\boldsymbol{T}_k$ for each sonication with the time stepping method (2.27). The benefit of this second temperature simulation with an additional computational expense of $O(K \cdot N)$ flops lies on the memory side, where a saving of temperatures for the whole time discretization (2.24) in Algorithm 1 with a total memory consumption of $O(K \cdot N) \gg O(L \cdot N)$ bytes can be avoided. Algorithm 2 then computes the operators of the temperature update (2.31) and the objective function update (2.33) and then the objective function gradient with respect to the plan parameters (2.36) as final output. All these computations require $O(K \cdot N)$ flops and a total memory consumption of $O(L \cdot N)$ bytes. The obtained objective function values and gradients serve as input of some generic nonlinear programming method, see for example [42, 43].

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Appendix A. Pressure field simulation. Denote the transducer elements $\mathcal{X}_m$, $m = 1, \ldots, M$, with their powers P_m, phase shifts φ_m, densities ρ_m and speeds of sound v_m. The pressure field can be numerically obtained from Helmholtz equation

(2.1) by means of the Rayleigh-Sommerfeld integral, see [26, 18, 17], as

$$p(\mathbf{x},\mathbf{u}) = 2\pi i f \rho(\mathbf{x}) \cdot \sum_{m=1,\dots,M} e^{i\varphi_m} \cdot \phi_m(\mathbf{x})$$

with the velocity potential for the mth transducer element in the volume point $\mathbf{x}$

$$\phi_m(\mathbf{x}) = \frac{1}{2\pi}\sqrt{\frac{2\cdot P_m}{|\mathcal{X}_m|\cdot \rho_m \cdot v_m}} \cdot \int_{\mathbf{x}'\in\mathcal{X}_m} \exp\left(-\int_{\mathbf{x}''\in[\mathbf{x}',\mathbf{x}]}\left(\frac{2\pi i f}{v(\mathbf{x}'')} + a(\mathbf{x}'')\right) d\mathbf{x}'' \cdot ||\mathbf{x}'-\mathbf{x}||\right) \frac{1}{||\mathbf{x}'-\mathbf{x}||} d\mathbf{x}'$$

A suitable ray-tracing along the line segment connecting $\mathbf{x}'$ and $\mathbf{x}$ is an integral part of the simulation approaches, see for example [13]. Rewriting the velocity potential as

$$\phi_m(\mathbf{x}) = \frac{1}{2\pi}\sqrt{P_m} \cdot \tilde{\phi}_m(\mathbf{x})$$

where $\tilde{\phi}_m$ contains only the frequency f as the only plan parameter, which is considered predefined in this context, the source term (2.5) of the Pennes equation (2.4) reads

$$Q(\boldsymbol{x},\boldsymbol{u}(t)) = \frac{c_\mathrm{b}\rho_\mathrm{b} w_\mathrm{b}(\boldsymbol{x}) T_b}{c(\boldsymbol{x})\rho(\boldsymbol{x})} + \frac{\alpha(\boldsymbol{x})}{c(\boldsymbol{x})\rho^2(\boldsymbol{x})v(\boldsymbol{x})} \sum_m \sum_{m'} \sqrt{P_m P_{m'}} e^{i(\varphi_m - \varphi_{m'})} \tilde{\phi}_m(\mathbf{x}) \tilde{\phi}^*_{m'}(\mathbf{x}) \tag{A.1}$$

This term attains its maximal value in $\mathbf{x}$ for the phase shifts

$$\varphi_m = -\arg \tilde{\phi}_m(\mathbf{x}) \quad \Longleftrightarrow \quad e^{i\varphi_m} = \frac{|\tilde{\phi}_m(\mathbf{x})|}{\tilde{\phi}_m(\mathbf{x})} \tag{A.2}$$

which can thus be analytically found and excluded from the sonication design problem of Section 2.5. Equation (A.1) allows for a computation of the source term as well as its partial derivatives with respect to the plan parameters P_m, which serve as input of the Algorithms 1 and 2, based on precomputed $\tilde{\phi}_m$.

Appendix B. Fixed time, free endpoint problem. Consider the fixed time, free endpoint optimal control problem with the terminal payoff $F : \mathbb{R}^N \mapsto \mathbb{R}$, [38], which can be formulated as

$$\begin{aligned} &\min_{\boldsymbol{u}(t)} F[\boldsymbol{z}(t_\mathrm{end})] \quad \text{subject to} \\ &\frac{d}{dt}\boldsymbol{z}(t) = \boldsymbol{y}(\boldsymbol{z}(t),\boldsymbol{u}(t)) \qquad \text{for} \quad (0,t_\mathrm{end}), \\ &\boldsymbol{z}(0) = \boldsymbol{z}_0, \end{aligned} \tag{B.1}$$

where $\boldsymbol{y} : \mathbb{R}^N \times \mathbb{R}^M \mapsto \mathbb{R}$ is given, $\boldsymbol{u}(t) : \mathbb{R} \mapsto \mathbb{R}^M$ is a control vector and $\boldsymbol{z}, \boldsymbol{z}_0 \in \mathbb{R}^N$ are the state and initial state respectively.

The control theory Hamiltonian for the problem B.1 is the function

$$H(\boldsymbol{z}, \boldsymbol{\lambda}, \boldsymbol{u}) := \boldsymbol{y}(\boldsymbol{z}, \boldsymbol{u})^t \boldsymbol{\lambda}, \tag{B.2}$$

where the vector $\boldsymbol{\lambda}$ is called the costate vector.

THEOREM B.1 (Pontryagin minimum principle, [38]). *Let $\boldsymbol{u}^* : [0, t_{\text{end}}] \mapsto \mathbb{R}^M$ be the optimum of problem (B.1) with the corresponding state $\boldsymbol{z}^* : [0, t_{\text{end}}] \mapsto \mathbb{R}^N$. Then there exists a costate $\boldsymbol{\lambda}^* : [0, t_{\text{end}}] \mapsto \mathbb{R}^N$ with*

$$\frac{d}{dt}\boldsymbol{\lambda}^*(t) = -\nabla_{\boldsymbol{z}} H(\boldsymbol{z}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}^*(t)) \tag{B.3}$$

$$\frac{d}{dt}\boldsymbol{z}^*(t) = \nabla_{\boldsymbol{\lambda}} H(\boldsymbol{z}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}^*(t)) \tag{B.4}$$

and

$$H(\boldsymbol{z}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}^*(t)) = \min_{\boldsymbol{u}(t)} H(\boldsymbol{z}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}(t)) \quad (0 \leq t \leq t_{\text{end}})$$

In addition, the mapping $t \mapsto H(\boldsymbol{z}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}^*(t))$ is constant. Finally, there is a terminal condition

$$\boldsymbol{\lambda}^*(t_{\text{end}}) = -\nabla F(\boldsymbol{z}^*(t_{\text{end}})) \tag{B.5}$$

Appendix C. Impact-volume histogram. [41] introduce the impact-volume histogram (IVH) based on the DVH concept from radiation therapy, see [44, 14], which allows for a comprehensible overview on medical plan quality. The IVH maps the total cell-biological impact $D(\mathbf{x}, t_{\text{end}})$ for a tissue entity $\mathcal{X}'$ to a histogram curve

$$\mathbf{h}(D(\mathbf{x}, t_{\text{end}})_{\boldsymbol{x}\in\mathcal{X}'}) = (h(D', D(\mathbf{x}, t_{\text{end}})_{\boldsymbol{x}\in\mathcal{X}'}))_{D'\in[0,\infty)}$$

which depicts for each (non-logarithmic) cell-biological impact value D' the volume percentage

$$h(D', D(\mathbf{x}, t_{\text{end}})_{\boldsymbol{x}\in\mathcal{X}'}) = \frac{1}{|\mathcal{X}'|} \int_{\mathbf{x}\in\mathcal{X}'} 1_{[D',\infty)}(e^D(\mathbf{x}, t_{\text{end}}))d\mathbf{x}$$

of the entity receiving at least this impact. The value of a criterion function like (2.7, 2.8) for some tissue entity can be considered as some average of the corresponding histogram curve according to [41], which in turn provide a more refined view on medical quality than the criterion values themselves, but a more comprehensible view than a volume-based visualization of the time-dependent temperature field or accumulated cell-biological impact.

REFERENCES

[1] M ABRAMOWITZ AND IA STEGUN, *Handbook of Mathematical Functions with Formulae, Graphs, and Mathematical Tables*, Dover Publications, 1972.

[2] D ARORA, M SKLIAR, AND RB ROEMER, *Model-predictive control of hyperthermia treatments*, IEEE Transactions on Biomedical Engineering, 49 (2002), pp. 629–639.

[3] MS BAZARAA, HD SHERALI, AND CM SHETTY, *Nonlinear Programming: Theory and Algorithms*, Wiley, 2013.

[4] A Belyaev, *Optimal control in focused ultrasound therapy.* Master's thesis, Faculty of Mathematics - Technische Universität Kaiserslautern, 2011.

[5] JT Betts, *Practical Methods for Optimal Control and Estimation Using Nonlinear Programming: Second Edition*, Advances in Design and Control, Society for Industrial and Applied Mathematics, 2010.

[6] JC Butcher, *Numerical Methods for Ordinary Differential Equations*, John Wiley & Sons, 2003.

[7] FP Curra, PD Mourad, VA Khokhlova, RO Cleveland, and LA Crum, *Numerical simulations of heating patterns and tissue temperature response to high-intensity focused ultrasound*, 47 (2000), pp. 1077–1089.

[8] C Damianou and K Hynynen, *The effect of various physical parameters on the size and shape of necrosed tissue volume during ultrasound surgery*, Journal of the Acoustical Society of America, 95 (1994), pp. 1641–1649.

[9] DR Daum, MT Buchanan, T Fjield, and Kullervo Hynynen, *Design and evaluation of a feedback based phased array system for ultrasound surgery*, IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 45 (1998), pp. 431–438.

[10] MW Dewhirst, BL Viglianti, M Lora-Michiels, M Hanson, and PJ Hoopes, *Basic principles of thermal dosimetry and thermal thresholds for tissue damage in hyperthermia*, International Journal of Hyperthermia, 19 (2003), pp. 267–294.

[11] TJ Dubinsky, C Cuevas, MK Dighe, O Kolokythas, and JH Hwang, *High-intensity focused ultrasound: Current potential and oncologic applications*, American Journal of Roentgenology, 190 (2008), pp. 191–199.

[12] M Ehrgott, *Multicriteria Optimization*, Springer, Berlin, 2005.

[13] J Georgii, C Dresky, A Meier, D Demedts, C Schumann, and T Preusser, *Focussed ultrasound - efficient GPU simulation methods for therapy planning*, in Workshop on Virtual Reality Interaction and Physical Simulation, VRIPHYS Proceedings 119-128, 2011.

[14] M Goitein and T Miller, *Planning proton therapy of the eye*, Medical Physics, 10 (1983), pp. 275–283.

[15] SJ Graham, L Chen, M Leitch, RD Peters, MJ Bronskill, FS Foster, RM Henkelman, and DB Plewes, *Quantifying tissue damage due to focussed ultrasound heating observed by mri*, Magnetic Resonance in Medicine, 41 (1999), pp. 321–328.

[16] X He and JC Bischof, *Quantification of temperature and injury response in thermal therapy and cryosurgery*, Critical Reviews in Biomedical Engineering, 31 (1948), pp. 355–422.

[17] J Heikkila, L Curiel, and K Hynynen, *Local harmonic motion monitoring of focused ultrasound surgery - a simulation model*, IEEE Transactions on Biomedical Engineering, 57 (2010), pp. 185–193.

[18] KR Hill, JC Bamber, and GR ter Haar, *Physical Principles of Medical Ultrasonics*, Wiley, 2005.

[19] A Hoffmann, *Physikalische und mathematische Modellbildung in der fokussierten Ultraschalltherapie (Physical and mathematical modeling in focused ultrasound therapy)*. Bachelor's thesis, Faculty of Mathematics - Technische Universität Kaiserslautern, 2011.

[20] H Hu, *Semi-infinite programming*, Technical report (Stanford University. Systems Optimization Laboratory), Stanford University, 1989.

[21] T Huttunen, JP Kaipio, and M Malinen, *Optimal control in high intensity focused ultrasound surgery*, in Optimization in Medicine, CJS Alves, PM Pardalos, and LN Vicente, eds., vol. 12 of Springer Optimization and Its Applications, 2008, pp. 169–195.

[22] T Huttunen, M Malinen, JP Kaipio, PJ White, and K Hynynen, *A full-wave Helmholtz model for continuous-wave ultrasound transmission*, 52 (2005), pp. 397–409.

[23] K Hynynen and G Clement, *Clinical applications of focused ultrasound the brain*, International Journal of Hyperthermia, 23 (2007), pp. 193–202.

[24] K Hynynen and FA Jolesz, *Demonstration of noninvasive ultrasound brain therapy through an intact skull*, Ultrasound in Medicine & Biology, 24 (1998), pp. 275–283.

[25] Y Kim, H Rhim, MJ Choi, HK Lim, and D Choi, *High-intensity focused ultrasound therapy: an overview for radiologists*, Korean Journal of Radiology, 8 (2008), pp. 291–302.

[26] LE Kinsler, AR Frey, AB Coppens, and JV Sanders, *Fundamentals of acoustics*, Wiley, 2000.

[27] Koninklijke Philips N.V., *Philips sonalleve.* http://www.healthcare.philips.com/main/products/mri/therapy/hifu/index.html (web page).

[28] TA Leslie and JE Kennedy, *High intensity focused ultrasound in the treatment of abdominal and gynaecological diseases*, International Journal of Hyperthermia, 23 (2007), pp. 173–182.

[29] H-L Li, C-L Liu, S-M Huang, and Y-W Hsi, *Focal beam distortion and treatment planning for transrib focused ultrasound thermal therapy: a feasibility study using a two-dimensional*

ultrasound phased array, Medical Physics, 37 (2010), pp. 848–860.

[30] J-L Li, X-Z Liu, D Zhang, and X-F Gong, *Influence of ribs on the nonlinear sound field of therapeutic ultrasound*, Ultrasound in Medicine and Biology, 33 (2007), pp. 1413–1420.

[31] M Malinen, *Computational Methods for Optimal Control in Ultrasound Therapy*, PhD thesis, University of Kuopio, 2004. Doctoral dissertation.

[32] M Malinen, T Huttunen, K Hynynen, and JP Kaipio, *Simulation study for thermal dose optimization in ultrasound surgery of the breast*, Medical Physics, 31 (2004), pp. 1296–1307.

[33] M Malinen, T Huttunen, and JP Kaipio, *Thermal dose optimization method for ultrasound surgery*, Physics in Medicine and Biology, 48 (2003), pp. 745–762.

[34] M Malinen, T Huttunen, JP Kaipio, and K Hynynen, *Scanning path optimization for ultrasound surgery*, Physics in Medicine and Biology, 50 (2005), pp. 3473–3490.

[35] K Miettinen, *Nonlinear Multiobjective Optimization*, Kluwer, Dordrecht, 1999.

[36] C Mougenot, B Quesson, BD de Senneville, PL de Oliveira, S Sprinkhuizen, F Palussière, N Grenier, and CTW Moonen, *Three-dimensional spatial and temporal temperature control with mr thermometry-guided focused ultrasound (mrghifu)*, Magnetic Resonance in Medicine, 61 (2009), pp. 603–614.

[37] HH Pennes, *Analysis of tissue and arterial blood temperatures in the resting human forearm*, Journal of Applied Physiology, 1 (1948), pp. 93–122.

[38] DA Pierre, *Optimization Theory with Applications*, Dover Books on Mathematics Series, Dover Publications, 1986.

[39] R Reemtsen and JJ Rückmann, *Semi-Infinite Programming*, Nonconvex Optimization and Its Applications, Springer, 1998.

[40] X-R Reit, *Positioning and thermal effect of the ultrasonic field in the extracorporeal focused ultrasound therapy.* Diploma thesis, Faculty of Mathematics - Technische Universität Kaiserslautern, 2011.

[41] A Scherrer, S Jakobsson, and KH Küfer, *On the advancement and software support of decision making in focused ultrasound therapy*, Revised version submitted to Journal of Multi-Criteria Decision Analysis, (2016).

[42] K Schittkowski, *NLPQL: A FORTRAN subroutine solving constrained nonlinear programming problems*, Annals of Operations Research, 5 (1986), pp. 485–500.

[43] ———, *NLPQLP: A Fortran implementation of a sequential quadratic programming algorithm with distributed and non-monotone line search - user's guide, version 3.11*, tech. report, Department of Computer Science, University of Bayreuth, 2009.

[44] WU Shipley, JE Tepper, GR Prout, LJ Verhey, OA Mendiondo, M Goitein, AM Koehler, and HD Suit, *Proton radiation as boost therapy for localized prostatic carcinoma*, Journal of the American Medical Association, 241 (1979), pp. 1912–1915.

[45] RE Steuer, *Multiple Criteria Optimization: Theory, Computation, and Applications*, John Wiley & Sons, Inc., 1986.

[46] M Tanter, M Pernot, J-F Aubry, G Montaldo, F Marquet, and M Fink, *Compensating for bone interfaces and respiratory motion in high-intensity focused ultrasound*, International Journal of Hyperthermia, 23 (2007), pp. 141–151.

[47] G ter Haar, *Ultrasound focal beam surgery*, Ultrasound in Medicine and Biology, 21 (1995), pp. 1089–1100.

[48] ———, *Therapeutic applications of ultrasound*, Progress in Biophysics and Molecular Biology, 93 (2007), pp. 111–129.

[49] J-L Thomas and MA Fink, *Ultrasonic beam focusing through tissue inhomogeneities with a time reversal mirror*, IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control, 43 (1996), pp. 1122–1129.

[50] H Wan, J Aarsvold, M O'Donnel, and C Cain, *?thermal dose optimization for ultrasound tissue ablation*, IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control, 46 (1999), pp. 913–928.

[51] X Zeng and RJ McGough, *Optimal simulations of ultrasonic fields produced by large thermal therapy arrays using the angular spectrum approach*, The Journal of the Acoustical Society of America, 125, pp. 2967–2977.

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Keywords: focused ultrasound therapy, partial differential equations, heuristic methods, nonlinear programming, optimal control
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