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On the advancement and software support of decision making in focused ultrasound therapy

Berichte des Fraunhofer ITWM, Nr. 247 (2015)

ISSN 1434-9973

Bericht 247 (2015)

Die Veröffentlichungen in der Berichtsreihe des Fraunhofer ITWM können bezogen werden über:

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Vorwort

Das Tätigkeitsfeld des Fraunhofer-Instituts für Techno- und Wirtschaftsmathematik ITWM umfasst anwendungsnahe Grundlagenforschung, angewandte Forschung sowie Beratung und kundenspezifische Lösungen auf allen Gebieten, die für Techno- und Wirtschaftsmathematik bedeutsam sind.

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

On the advancement and software support of decision making in focused ultrasound therapy

Alexander Scherrer* Stefan Jakobsson† Karl-Heinz Küfer‡

September 29, 2015

Abstract

Focused ultrasound therapy (FUS) is a modern and promising way for minimally invasive cancer treatment. Recent advances in treatment technology, bio-physical models and numerical simulation methods gave rise to a significant curative potential. However, clinical routine of FUS still features classical planning approaches, which widely fail in exploiting these possibilities. In contrast, the structure of FUS planning problems strongly suggests interactive multi-criteria decision making (MCDM) concepts in order to improve treatment efficiency and quality. This research work introduces an MCDM approach to FUS planning and explains how to bridge the conceptual gap between the clinical state of the art and this new planning paradigm from a practitioner's perspective.

Keywords: Focused ultrasound, Multi-criteria optimization, Decision support systems

Mathematics Subject Classification: 90B50, 90C29, 92C50

1 Introduction

1.1 Focused ultrasound therapy overview

Focused ultrasound is a modern and promising therapy modality, [38, 19], which allows for minimally invasive treatment of various kinds of cancer, see for example [47, 63, 44]. It relies on energy transfer into the tissue with acoustic waves emitted by some ultrasound transducer, which induce a pressure field in the sonicated volume and thereby cause some heating of the tissue leading to

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its coagulation [34, 55, 33]. Although history of therapeutic ultrasound started in the 1960s, [4, 25], the major innovation steps have taken place in the recent past:

- *Increased degrees of freedom* were achieved with independently controllable transducer elements, [65, 40]. This technological advance over the former technology of transducers with fixed focus increased the curative potential of FUS considerably.
- *Mathematical models for plan quality* from the closely related medical field of hyperthermia quantify the cell-biological impact of temperature on tissue by means of the Arrhenius model, [57, 17]. These models underwent a conceptual transfer into FUS, [15, 29], but their further development is a topic of ongoing fundamental research and wide establishing and acceptance still needs to grow.
- *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, [30, 18, 31]. Furthermore, the aspect of tissue motion and deformation caused by respiration also requires consideration in FUS planning, [39, 56, 42]. The concrete formulation of goals, which are widely accepted, is still up to come.
- *Efficient plan computation methods* are required for an adequate handling of the many degrees of freedom, the complex structure of the underlying physics, a sufficient achievement of the planning goals and a suitable balancing between their conflicting character. The development of such optimization routines started with [16, 67, 3] and has been a major research topic since then.
- *FUS planning in clinical routine* has partly adopted some of these innovations as features of certified planning software tools, [41, 45]. However, the average stage of development is still far below the state of the art in FUS research, mainly because of an inadequate software support of the FUS planning process. One resulting major problem is the time consumption required for plan search as well as validation of results during plan application.

The specification of several planning goals to be considered followed by the stepwise search for suitable technical parameters in order to compromise the goals suitably in the resulting therapy plan gives clinical FUS planning the typical flavor of a multi-criteria optimization (MCO) problem respectively. Discussions with FUS practitioners have revealed strong need for an advance of clinical FUS therapy planning to the desirable level of supported multi-criteria decision making (MCDM). However, these discussions also indicated considerable scepticism how to conduct such a major shift of planning paradigms in a smooth and intuitive way. It is actually another concept in cancer therapy that depicts a path for such a conceptual leap: intensity-modulated radiation therapy (IMRT).

1.2 Radiation therapy overview

Radiation therapy (RT) is a well-established and the most common cancer therapy besides clinical surgery and chemotherapy, [69, 70]. It relies on energy transfer into the tissue by means of photons and electrons, sometimes also heavier charged particles, which cause an ionization and thus destruction of the molecular cell structure. There are strong analogies to FUS, which suggest closer examination in this context. First of all, RT is another application from medicine, which widely lacks precise mathematical descriptions to exploit when approaching the planning problem. It also features physicians as main protagonists, who typically have only moderate knowledge on sophisticated mathematical algorithms and concepts of mathematical decision making. The transition of planning paradigms in RT may thus provide valuable insight how to proceed in FUS. The major innovation steps of RT also show striking analogies:

- *Increased degrees of freedom* were achieved with multi-leaf collimators, [10, 9, 68], which allowed for intensity modulation (IM) and thereby a significant improvement of the curative potential over the classical open field, wedge and compensator technology originating from [66, 26].
- *Mathematical models for plan quality* were first established in [8, 7, 53], rely on physical or cell-biological principles and are the topic of ongoing research since then.
- *Planning goals* are mostly the therapy success by means of widely covering the cancerous tissue with sufficiently high doses and the wide avoidance of complications in the health tissue entities, which turns RT planning into a multi-criteria decision making problem [71, 32, 11].
- *Efficient plan computation methods* are required for an adequate handling of the many degrees of freedom, the complex structure of the underlying physics, the sufficient achievement of considered planning goals and a suitable balancing between the multiple conflicting planning goals. IMRT plan optimization routines were first introduced in [6, 36, 35].
- *IMRT planning* based on mathematical optimization routines has been clinical standard for quite some time, [7]. However, practitioners requested more time-efficient software solutions especially for the balancing of several planning goals.
- *Interactive multi-criteria IMRT planning* was therefore the natural next innovation step, which allowed for a planning process directly conducted by the physician with improved plan quality and reduced time consumption [46, 64, 13].

1.3 Contents

This research work introduces a FUS planning concept, which exploits the analogies between FUS and IMRT in order to provide practitioners with a smooth

and intuitive way for transposing from the FUS state of the art to the advantageous level of interactive multi-criteria planning. Section 2 introduces the basic facts about FUS plans and then addresses the stages of FUS planning as shown in Figure 1 with their underlying processes: the formulation of planning criteria and their balancing in the modeling stage, the numerical plan optimization stage and the stage of interactive plan search, which features the overview of planning options, the selection and recombination of optimized plans and the comprehensible visualization of a plan. Section 3 presents the whole concept as part of the software demonstrator *Ultrasound Therapist* developed by Fraunhofer ITWM, [23], in the Fraunhofer internal project *MAVO Extracorporeal focused Ultrasound Therapy*, grant no. MAVO 821012, [24].

2 Methodology

2.1 A FUS plan

A FUS plan is characterized by a configuration

$$\mathbf{X} = (\mathbf{x}(t))_{t\in[0,t_{\mathrm{end}})} \in \mathbb{X} \tag{1}$$

of time dependent and technically applicable plan parameters $\mathbf{x}(t)$. These parameters comprise the position of the transducer, the sonication schedule in terms of durations and subsequent cooling times of the single sonications and the control parameters of the transducer elements in each sonication. State of the art treatment devices have about 10^2 elements, see for example [41, 45]. Sonication of a volume $\mathbb{V}$ with a FUS transducer configured with these parameters induces a time-dependent temperature field

$$\mathbf{T} = (T(\mathbf{v},t))_{\mathbf{v}\in\mathbb{V},t\in[0,t_{\mathrm{end}})} \tag{2}$$

which is obtained by computing the Helmholtz equation of acoustics, [34], and the Pennes bio-heat equation, [55]. The numerics of this physical simulation can be found, for example, in [14, 37, 48, 49]. Suitable implementation of the computation methods allows for major speed up: for example, [27] mentions simulation times in the order of about 10^0 seconds for a volume with about 10^6 grid points and time discretization of about 10^2 time steps.

2.2 A notion of medical quality

The heating of a volume point $\mathbf{v}$ up to some point of time t accumulates to some cell-biological impact

$$\mathbf{d}(t) = (d(\mathbf{v},t))_{\mathbf{v}\in\mathbb{V}} \tag{3}$$

which originates from the Arrhenius model, see Section A, and whose specific formulation is up to the practitioner's personal taste. Averaging the cell-biological impact over the volume points of some tissue entity $\mathcal{V} \subseteq \mathbb{V}$ then yields

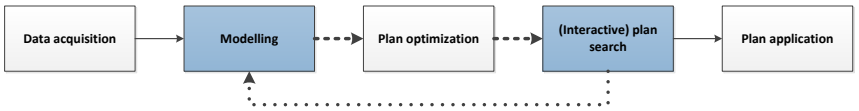

Figure 1: Basic FUS planning process: preliminary stage of data acquisition and terminal stage of plan application confine the (time) interval available for generating a FUS plan in the stages for modeling a FUS plan optimization problem followed (thick dashed arrow) by its computation in the plan optimization stage and the subsequent (thick dashed arrow) exploration of the computation results in the stage of (interactive) plan search. In case this stage does not provide the FUS planner with the desired result, he/she may return to the modelling stage (thick dotted arrow) in order to modify the problem accordingly.

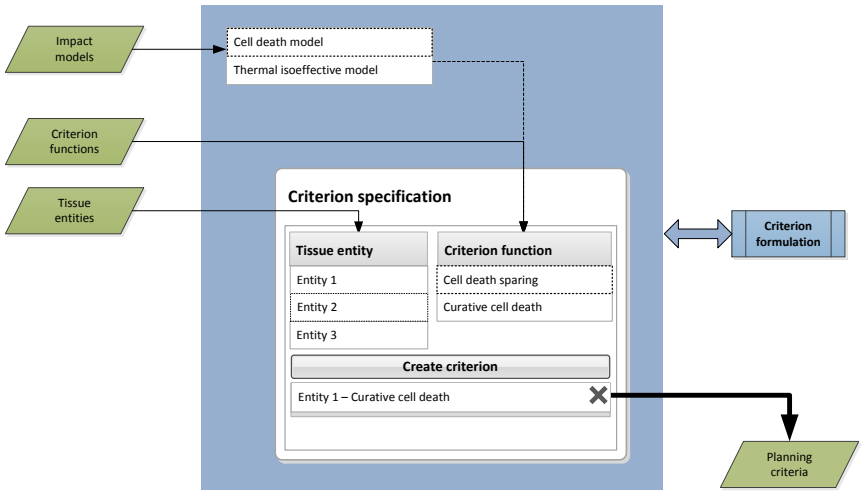

Figure 2: Criterion formulation: selection of the cell-biological impact model (top middle) from the underlying data of supported models (top left) and specification of the planning criteria as pairs of tissue entity and criterion function compatible to impact model (center). The graphical dialogs (middle) form the visualization of the underlying criterion formulation process, which yields the planning criteria to be used in the subsequent stages of FUS plan optimization and plan search.

the main notion of medical quality

$$f(\mathbf{d}(t_{\text{end}})) = \Phi\left(\int_{\mathbf{v}\in\mathcal{V}} \varphi(d(\mathbf{v}, t_{\text{end}}))d\mathbf{v}\right) \tag{4}$$

with examples provided in Section B. Other aspects of plan quality may consider the overall treatment time.

2.3 The multi-criteria planning problem

FUS planning requires the consideration of various tissue entities such as the cancerous tissue of the tumor, which shall receive a sufficiently high cell-biological impact, and nearby healthy tissue entities, which shall simultaneously be spared as much as possible. However, even the formulation of the cell-biological impact (3) in the tissue based on the Arrhenius model from Section A as well as the modelling of medical quality (4) with respect to tissue entities like in Section B may turn out a very tricky task for the planner. Suitable value assignment to the biological parameters requires a thorough knowledge of the underlying cell-biological processes and selection of an adequate criterion function with appropriate model parameter values requires a deeper understanding of the numerical characteristics of these functions. From the perspective of decision making, the typical FUS planner should not have to worry about these aspects, hence a decision support system for clinical FUS planning must provide a very intuitive functionality of the modeling task. The functionality proposed herein relies on the file-based import of configurations for the cell-biological impact model and the planning criterion functions, which are then offered to the FUS planner in simple graphical dialogs for selection without bothering the planner with sophisticated modeling tasks. Figure 2 shows the graphical dialog for choosing the cell-biological impact and the specification of planning criteria. This dialog consists of a drop-down menu with the unique names of contoured tissue entities extracted from the underlying medical image data and another drop-down menu with the criterion functions, which result from the acquired data of supported criterion functions and fit to the already selected cell-biological impact model. The FUS planner just needs to pair a tissue entity with some criterion function in order to specify a planning criterion of the form

$$g(\mathbf{X}) := (f \circ \mathbf{d}(t_{\text{end}}) \circ \mathbf{T})(\mathbf{X}) \tag{5}$$

for the upcoming plan computations. Note that only by choosing a criterion function like the ones from Section A, the planner also specifies implicitly classifies a tissue entity as cancerous entity, which must receive a curative impact, or healthy entity, which should be spared, an information of high relevance for configuring plan computation.

A natural next step in multi-criteria optimization would be the encoding of strict requirements on the desired FUS plans in form of constraining value bounds for some planning criteria. However, clinical routine of FUS regularly

faces situations with requirements that are unfulfilled for various reasons. Skeletal structures may shield parts of the tumor volume and cause insufficient coverage, unfavorably located healthy structures may receive major heating causing complications or insufficiently incorporated respiratory tissue motion may deteriorate plan quality, see for example [1, 5, 19, 43]. A constrained FUS plan optimization problem may therefore easily turn out infeasible during the computations. Furthermore, specification of suitable constraint values for averaging criterion functions of type (4) would require a descent knowledge in mathematical optimization from the FUS planner and thus again lead to problems similar to the above mentioned ones. Hence, a more suitable approach as presented herein is to incorporate all planning criteria into the objective function of the multi-criteria FUS plan optimization problem

$$\begin{aligned} &\text{minimize} && \mathbf{g}(\mathbf{X}) := (g_j(\mathbf{X}))_{j=1,\ldots,J} \\ &\text{subject to} && \mathbf{X} \in \mathbb{X} \end{aligned} \tag{6}$$

and address the individual importance of planning goals by their suitable balancing.

2.4 Balancing of planning criteria

A good FUS plan features a suitable compromise between the various considered planning goals, which from the perspective of multi-criteria decision making requires preference information about the criteria, see for example [51, Chapters II.1-2]. Analogous to IMRT planning, the spectrum of FUS treatment options is individual for every single patient case and a priori unknown. Hence, a good FUS plan featuring a suitable compromise between the criteria has to be found for each planning case individually and methods relying on a priori preference information, see [51, Chapter II.4], do not apply. A major difference to IMRT planning lies in the clinical workflow, which comprises the three consecutive major steps of medical imaging, the generation of a FUS plan and its immediate application with an overall time consumption of a few hours, see [21, 50]. This implies an acceptable time interval for plan generation of much less than one hour, hence FUS planning does not allow for a posteriori preference methods, see [51, Chapter II.3], with costly Pareto approximation and later exploration. These limiting aspects leave interactive methods, see [51, Chapter II.5], which incorporate preference information flexibly during the decision making process, as the only feasible option.

This implies the question which method from multi-criteria optimization and decision making to actually use for interactive multi-criteria FUS planning. Like in IMRT, a FUS plan with overall high medical quality must compromise suitably between all major planning criteria. Nonscalarizing methods, see for example [20, Chapter 5], which consider the criteria in a specific order, bear the risk that the potential for improvement is mostly spent on the first few considered criteria and inadequate handling of the criteria considered later on. Hence scalarization techniques, see [20, Chapter 4], which allow for a simultaneous consideration of all criteria, are much more adequate. The practice of multi-criteria

IMRT planning also gives proof to these approaches, see [71, 32, 11]. IMRT planning benefits from well-established models for plan quality, see [8, 7, 53], which is, however, not the case in FUS planning. While numerical comparability of criterion values can be somehow achieved by appropriate transformation of the pre-configured criterion functions, see Section B, their interpretation in terms of absolute plan quality is difficult. All kinds of ε-constraint, reference point and reference direction methods as well as other methods related to them, which rely on the specification of values with clear meaning, can thus not be smoothly applied to the FUS plan optimization problem.

A natural option is therefore the Tchebycheff method, which was first invented in [61, Chapters 13-15] and designed as a user-friendly method not requiring any sophisticated information from the decision maker. Denote by $\mathbf{g}^* = (g_j^*)_{j=1,\dots,J}$ a utopian objective vector and by $\mathbf{w} = (w_j)_{j=1,\dots,J}$ a weight vector with $w_j \geq 0$ and $\sum_{j=1,\dots,J} w_j = 1$. Then applying the method of weighted metrics to problem (6) yields

$$\begin{aligned} &\text{minimize} && \left\| (w_i \cdot |g_j(\mathbf{X}) - g_j^*|)_{j=1,\dots,J} \right\|_p \\ &\text{subject to} && \mathbf{X} \in \mathbb{X} \end{aligned} \tag{7}$$

which is for $1 \leq p < \infty$ called the weighted L_p-problem and for $p = \infty$ the weighted Tchebycheff-problem, see [51, Chapter II.3]. In case of criterion functions with an image normalized to the interval $[0, 1]$ like in Section B, the utopian vector can be set to zero and the absolute value can be also omitted. The only remaining parameters for the balancing of planning criteria are the weights w_i. Experience from IMRT is that balancing mainly takes place between just a few antagonistic criteria such as tumor volumes and healthy risks located nearby, and FUS as another minimally invasive therapy from a clinical perspective features the same situation. planners in IMRT are used to a balancing of multiple planning criteria with various functional elements of a graphical user interface for long time, see [7], FUS planners are not. This indicates the need to provide the FUS planner with a very simple and intuitively usable software feature, which allows for an easy balancing of planning criteria, the triggering of a FUS plan computation and also the subsequent exploration of already existing planning options in the actual therapy decision making. The concept presented herein addresses these aspects with the software feature shown in Figure 3. This triangular planning screen allows for assignment of the two most important planning criteria to two upper corners. all other criteria are mapped to the lower corner. It contains a single functional element in form of a button, which can be moved inside the triangle. In case of only one criterion, the functional element is restricted to the upper corner carrying the criterion. In case of two criteria, the functional element is confined to the triangle edge connecting the two upper corners. Its relative position with respect to the corners in terms of barycentric coordinates, see [12, 22], determines the criterion weights, where the coordinate with respect to the lower corner equals the sum of weights for the criteria assigned to this corner. The method of weighted metrics thus combines most naturally with this functional element. Moving the button within the tri-

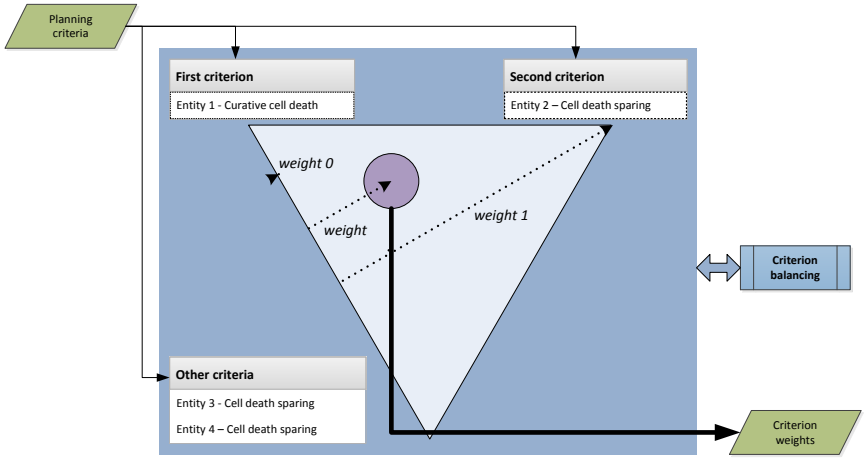

Figure 3: Balancing of planning criteria: assignment of specified planning criteria to the triangle corners (top middle and bottom middle) and placement of circular functional element (center) for the specification of criterion weights as output (right bottom) of the criterion balancing process (right). Its position with respect to the upper right corner and opposite triangle edge determines the weight with respect to the second criterion (dotted arrows).

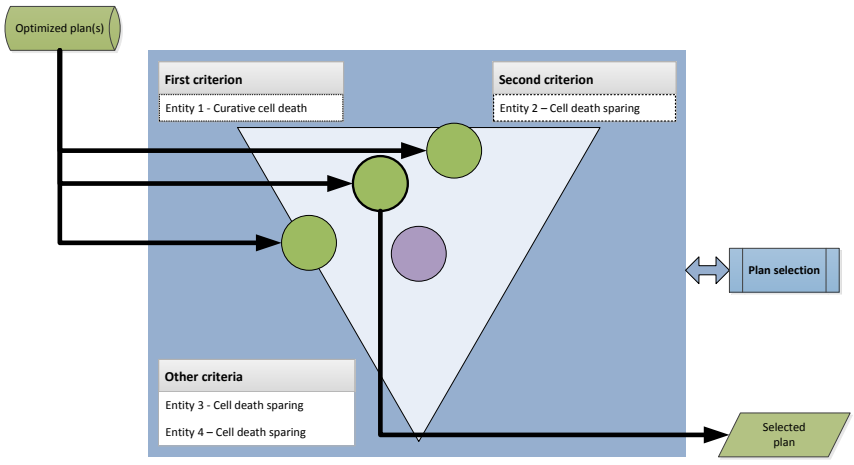

Figure 4: Overview of planning options: depiction of optimized plans (left) with immovable buttons positioned according to the individual criterion weights (center) and selection of one plan as output of plan selection process (right).

angle causes an update of weights according to the element's current position, where the weights of the criteria assigned to the lower corner are equally scaled. In order to give one of these criteria a specific weight, the planner switches this criterion in the planning screen with a criterion assigned to one of the two upper corners.

2.5 Plan optimization

A click on this button triggers a computation of the FUS plan optimization problem (7) with the criterion weights determined by the button's current position. Each iteration of an optimization run requires a simulation for the current parameter configuration, see Section 2, which gives rise to overall computation times of several minutes. Details on the numerical optimization algorithm used in this context and a general overview of FUS plan computation methods are given in [58].

2.6 An overview of planning options

After a successful optimization run, a new immovable button is added to the planning screen at the position of the functional element representing the computed FUS plan. The main functional element is reset to some default position within the triangle, see Figure 4. Such immovable buttons provide the planner with an overview of the existing planning options in form of already computed FUS plans. Hence, also existing FUS plans are characterized by the specific criterion weights, which circumvents the above mentioned problems in this context how to refer to a plan without any speaking values available. The planner can access one of these FUS plans just by clicking the corresponding button, which is a usability concept analogous to the triggering of a plan computation. The access of a computed plan implies the question of a suitable plan visualization for multi-criteria FUS planning.

2.7 The visualization of results

The description of a FUS plan in terms of the underlying plan parameters (1), the resulting temperature field (2) or the cell-biological impact (3) already offer several possibilities for plan visualization. However, these very detailed plan descriptions on many volume points and possibly time steps are impossible to comprehend in a quick exploration of existing planning options. On the other hand side, visualization of only the criterion values (5) provides too few information about a plan, which furthermore is difficult to interpret in view of the already mentioned problems. The situation in IMRT planning is analogous: a view on the technical parameters does not allow for a direct interpretation in terms of results, the highly refined dose distribution on some volume is impossible to comprehend in short time and the criterion values indicating plan quality with respect to some tissue entity offer only course information about a plan. However, IMRT features the cumulative dose-volume histogram, see [60, 28],

which allows for comprehensible plan visualization with still sufficient detail. The approach proposed herein transfers this concept to FUS by mapping the total cell-biological impact $\mathbf{d}(t_{\text{end}})$ for a tissue entity $\mathcal{V}$ to a histogram curve

$$\mathbf{h}(\mathbf{d}(t_{\text{end}})) = (h(d, \mathbf{d}(t_{\text{end}})))_{d\in[0,\infty)} \tag{8}$$

which depicts for each cell-biological impact value d the volume percentage

$$h(d, \mathbf{d}(t_{\text{end}})) = \frac{1}{|\mathcal{V}|} \int_{\mathbf{v}\in\mathcal{V}} 1_{[d,\infty)}(d(t_{\text{end}}))d\mathbf{v} \tag{9}$$

of the entity receiving at least this impact as shown in Figure 5. The value of a criterion function (4) for some tissue entity can be considered as some average of the corresponding histogram curve according to Section C, which in turn provide a more refined view on medical quality than the criterion values themselves. By clicking one of the buttons representing the already computed FUS plans, a FUS planner also obtains the histogram visualization of the corresponding plan as a first detailed overview based on which he can decide how to proceed. Note that the graphical functional concept for plan computation or plan selection is identical.

2.8 An interactive planning method

As previously mentioned, FUS planning in the clinical workflow is confined to a time interval of much less than one hour and each plan optimization requires several minutes of computation time. Hence, the planner can trigger only a few optimization runs in order to find a suitable FUS plan. This restriction bears the risk, that the planner considers none of the few computed plans entirely satisfactory with respect to all planning criteria with the feeling, that a suitable mixture of these plans located "in between" might do best, but without enough time to find this plan with a few more optimization runs. In IMRT planning, this problem is adequately met with an recombination of existing plans, see [52, 62, 59], which does not require further optimization runs and can thus be conducted interactively.

The approach presented herein transfers this concept of plan recombination to FUS planning in the following way: as soon as there is more than one plan displayed on the triangular planning screen, the convex hull between the corresponding immovable buttons is highlighted. By placing the functional element inside of this area, the planner can trigger a recombination of existing plans, see Figure 6. Again, the barycentric coordinates of the element's position with respect to the immovable buttons representing the existing plans determine the corresponding recombination coefficients. An exemplary recombination routine is given in Section D. The temperature field simulation for the recombined plan parameter configuration can be done quickly according to [27] and thus allows for interactive FUS planning based on the already computed plans. Note that this recombination feature supplements the existing functional concept in a most natural way.

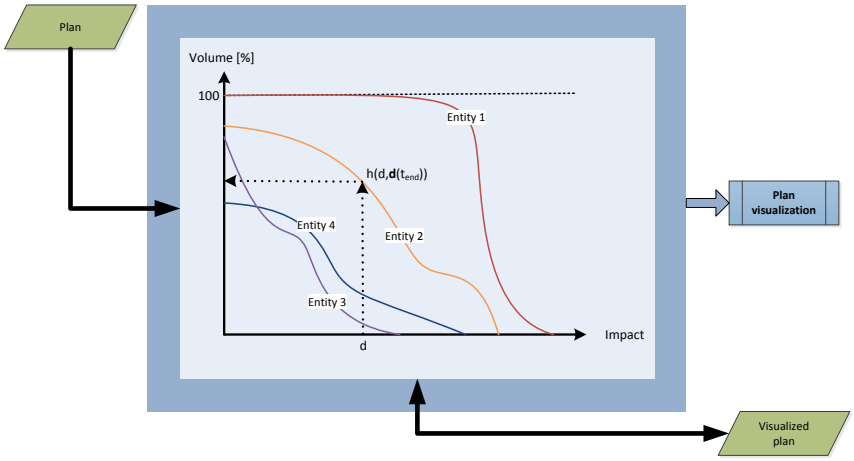

Figure 5: Visualization of a plan: mapping of a plan (left) to a histogram (center) with entity-specific curves, which show for some cell-biological impact d the volume percentage $h(d, \mathbf{d}(t_{\text{end}}))$ receiving at least this impact. The histogram display is one component of plan visualization (right).

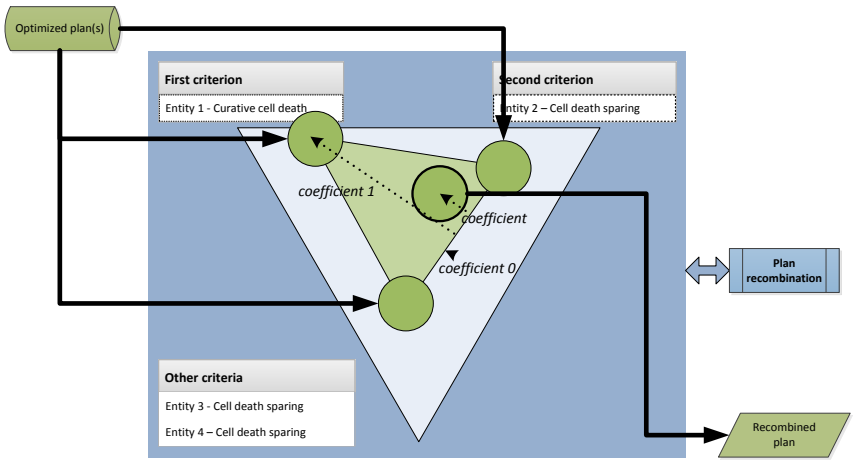

Figure 6: Recombination of plans: convex hull between the optimized plans (smaller triangle in center) with the functional element for recombination located inside. Its position with respect to the upper left plan button and opposite triangle edge determines the coefficient with respect to the plan (dotted arrows).

Figure 7 shows the planning process from Figure 1 in a more detailed form with all previous introduced work steps.

3 Results and discussion

Mathematical development of the previously introduced MCDM approach to FUS planning took place at Fraunhofer ITWM, [23], in the Fraunhofer internal project *MAVO Extracorporeal focused Ultrasound Therapy*, grant no. MAVO 821012, [24]. Implementation gave the ITWM software demonstrator *Ultrasound Therapist*, [23], whose functional concept is illustrated for the following artificial test case.

3.1 An exemplary test case

The transducer in use is of flat quadratic shape with a decomposition into 8×8 equally shaped quadratic elements of 10×10mm side length. It allows for a repositioning by means of lateral shifts into two orthogonal directions within a range of ± 20mm and angular inclinations into two orthogonal directions within a range of $\pm 15°$. The frequency interval ranges from 0.5 to 1.4MHz and the maximal total power of the transducer, which distributes equally over all elements, is 1000W. The transducer elements allow for acoustic emissions with phase shifts on the range of $\pm\pi$.

The considered volume is a $120 \times 120 \times 240$mm cuboid, which contains two ellipsoidal entities of healthy tissue with elliptic radii of $20 \times 20 \times 20$mm and $20 \times 30 \times 20$mm respectively and another ellipsoidal entity of cancerous tissue with elliptic radii of $20 \times 20 \times 40$mm located in between as illustrated in Figure 8. The cell-biological impact in a point was quantified with the Arrhenius model (10), the sparing of the healthy entities was modelled with the criterion function (13) and the main planning goal of a curative impact in the cancerous tissue was formulated with the criterion function (12) and the threshold value $d_{\text{cur}} = 0.95$. The location and geometry of entities in combination with the planning goals represents a pretty common situation of FUS planning indicating a strong need for MCDM. Viewed from the transducer's position along the sonication direction, a risk entity of health tissue, which should be widely spared in FUS plan application, partly shields the target entity, which requires extensive coverage with a curative impact. Furthermore, achievement of a sufficiently large impact in the target entity inevitably causes large impact in some parts of the other risk entity is located right next to the target.

Plan computation is done with the method described in [58], which features heuristic positioning of the transducer, heuristic placement of sonications in the tissue on a triangular grid (in this case with 2×5mm resolution), manual specification of the frequency (here to 1MHz) and analytic computation of optimal phase shifts. The remaining parameters of sonication times and element-specific powers are obtained by means of nonlinear programming based on numerical temperature simulation and optimal control.

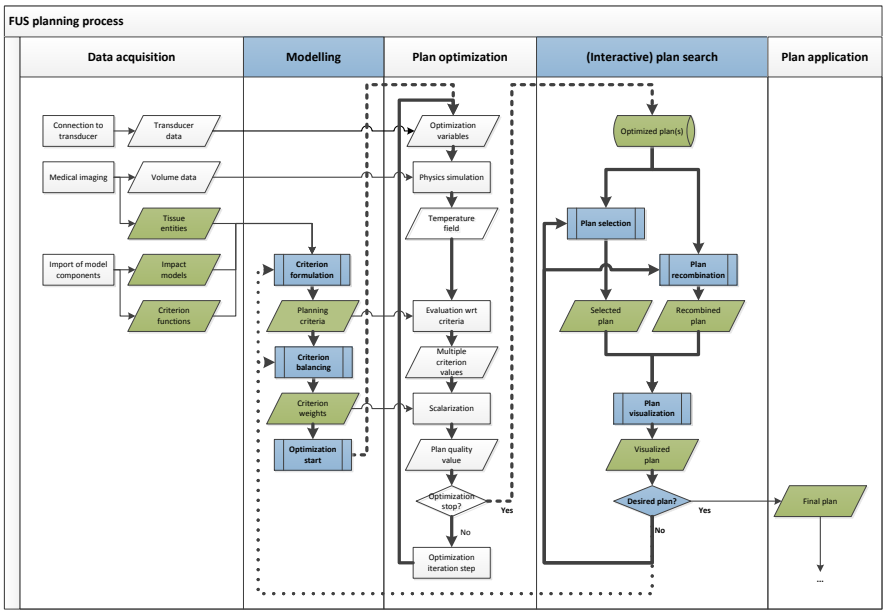

Figure 7: Detailed FUS planning process: the modelling stage contains the workflow for formulating a single-objective plan optimization problem (thick solid arrows) based on acquired data about the planning case. The FUS planner then moves on (thick dashed arrow) to the subsequent plan optimization stage, which contains the iterative workflow for numerically solving this problem (thick solid arrows). In case of success, this workflow stops with an optimized plan, which is transferred (thick dashed arrow) to the stage of plan search, where the set of all optimized plans is explored. this stage provides the FUS planner with the two workflow options of simple plan selection and advanced plan recombination in order to find the desired FUS plan (thick solid arrows). In case of a success search, this final plan enters the terminal stage of plan application. Otherwise, the FUS planner switches back to the modelling stage for a modification of planning criteria or criterion weights (thick dotted arrows).

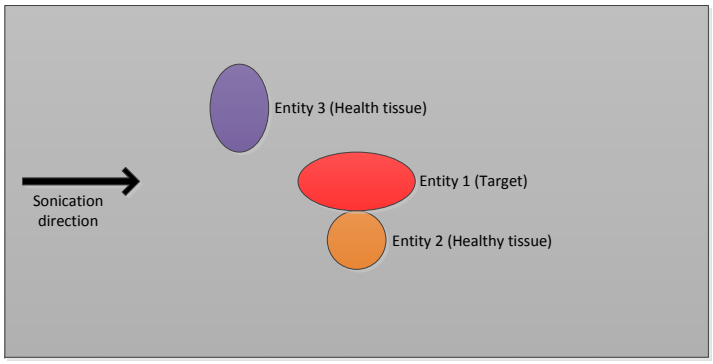

Figure 8: Test case: the target entity of cancerous tissue is located between two nearby risk entities of health tissue.

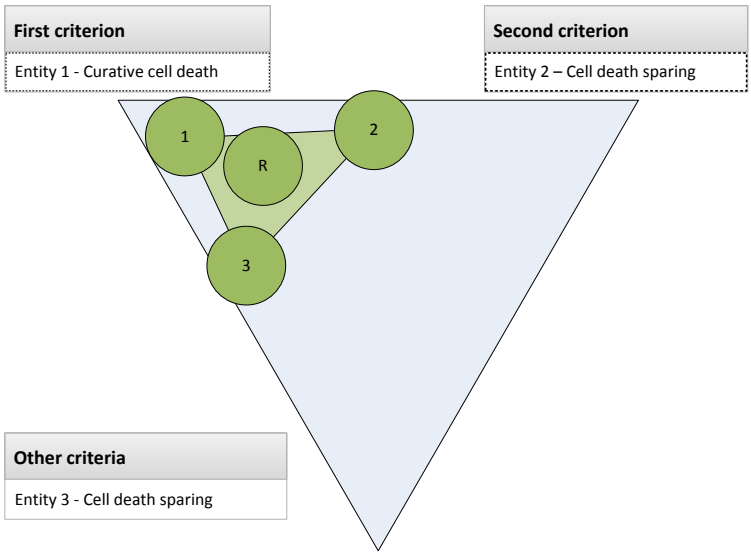

Figure 9: Criterion balancing, plan computation and plan recombination in the planning screen: Depiction of three optimized plans with the corresponding buttons enumerated from 1 to 3 and of the convex hull spanned by them with the recombination button R.

3.2 Plan optimization and recombination results

The three planning criteria on the target entity and the two healthy entities then enter the balancing process on the planning screen as shown in Figure 9 after three plan computations.

For the first plan computation, the button is placed close to the upper left corner representing the curative cell death on target entity 1 in order to assign a high weight to this planning goal. Figure 10 shows the histogram of the resulting plan. A high percentage of the target volume receives a cell death percentage of at least the threshold value $d_{\text{cur}} = 0.95$ and lower cell death percentages occur only in a small part of the target entity. However, the histogram curves of the healthy tissue entities show the downside of this prioritization. The good coverage of the target entity implies rather poor conformality of the volume with high cell death rates, which spreads out into the adjacent healthy tissue entity 2 and hence its histogram curve extends far to the right. Also entity 3, which shields the target entity along the sonication direction, attains moderately low cell death rates in a major part of its volume as indicated by a characteristic kink in the left part of the histogram curve.

An alternative plan, which reduces the first criterion weight and assigns a higher weight to the second criterion on the adjacent healthy tissue entity 2, see the corresponding button position in the middle of the two upper triangle corners, is shown in Figure 11. This plan features a better sparing of entity 2 from high cell-biological impact, which is indicated by a corresponding histogram curve shifted towards the left and downwards. The weight of the third planning criterion measuring the impact on healthy entity 3 is almost the same, which is also reflected by only minor changes of the corresponding histogram curve, which still features the kink for lower impact values. However, the coverage of the target entity worsened in form of lower volume percentages for the cell death rates slightly below the threshold value.

Figure 12 shows the histogram of the third optimized plan, whose underlying criterion priorization aims for an reduction of the kink in the histogram curve of entity 3 by placing the button somewhere between the upper left and the lower triangle corner. This criterion weighting smooths the kink in the third histogram curve with the downside effect of rather low cell death percentages occurring in a small volume part of the target entity, whose histogram curve leaves the horizontal 100%-line at a rather early stage.

Each of the three optimized plans features a desirable aspect in terms of plan quality, namely good target coverage (plan 1) or good healthy tissue sparing (plans 2 and 3). A FUS planner would therefore ask for a plan, which combines all these desirable features in a suitable way. The identical settings for transducer position, sonication placement, frequency and phase shifts for all three plans allow for their recombination (14) on the level of sonication times and powers, see Section D. Figure 13 shows the histogram of the recombined plan obtained by placing the recombination button somewhere inside the convex hull with a slight preference for plan 1. The corresponding histogram shows a target curve with a rounder shape for impact value slightly below the threshold

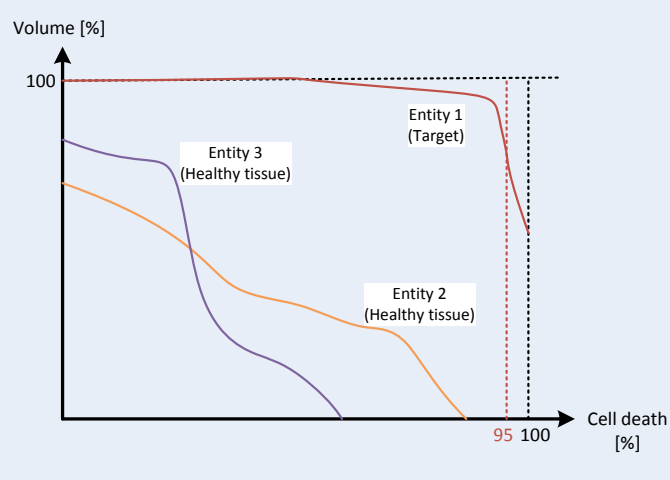

Figure 10: Histogram of the first plan: Good coverage of the target entity with high cell death percentages for the price of poor sparing of the two healthy tissue entities.

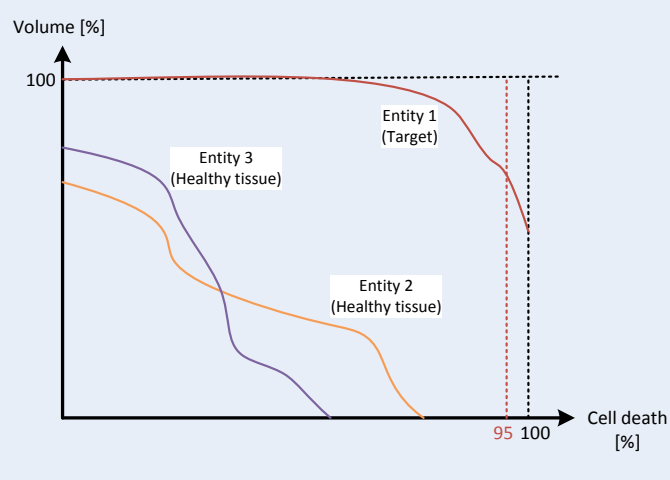

Figure 11: Histogram of the second plan: Improved sparing of healthy tissue entity 2 for the price of a worsened coverage of target entity 1.

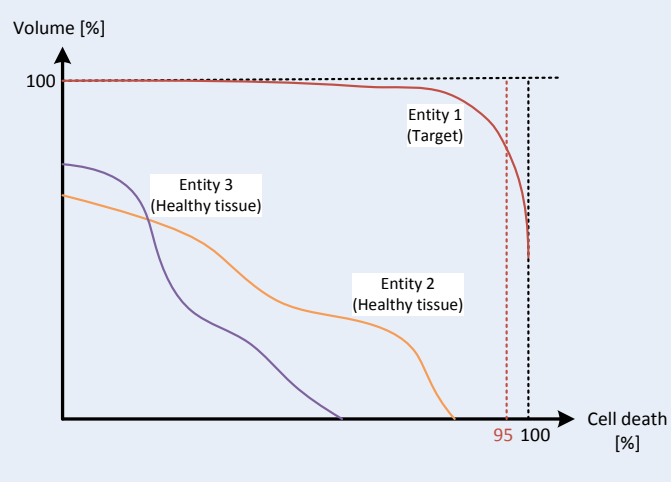

Figure 12: Histogram of the third plan: A smoother curve shape for entity 3, but worse coverage of the target entity 1 with rather a small minimal value of the cell death percentage.

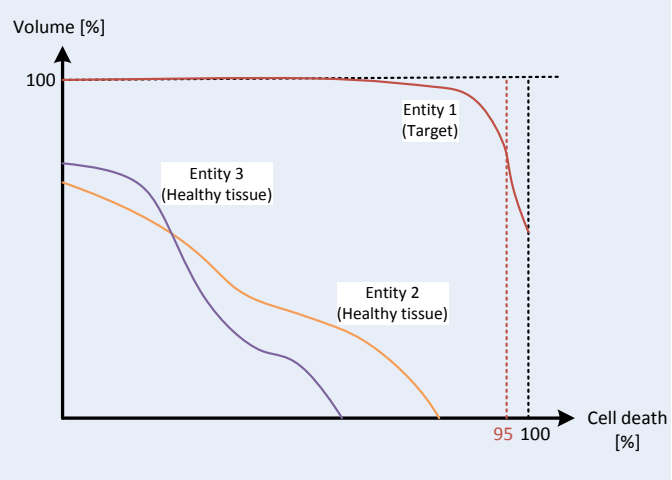

Figure 13: Histogram of the recombined plan: A suitable compromise between the the goals of covering the target entity and sparing the two health tissue entities.

and a still acceptable minimal cell death percentage, a better sparing of entity 2 indicated by a reduction of of volume percentages for higher cell death rates and a still visible, but smoothed kink in the curve for entity 3.

4 Conclusions

Focused ultrasound therapy still faces a major gap in development between the technical state of the art providing significant and the conceptual state of the art in the exploitation of this potential. A lot of effort is spent on the development of physical simulation and mathematical plan optimization. However, the FUS planning process lacks suitable concepts in particular in terms of goal-oriented and efficient multi-criteria decision making. This research work invents a novel approach, which allows for a smooth conceptual transfer from the current planning strategies used in clinical routine to the much desirable level of multi-criteria FUS plan optimization and interactive plan search. This approach is an integral part of software demonstrators implemented in a Fraunhofer internal project ready for introduction in research-oriented clinical routine of FUS planning.

A Arrhenius model

The Arrhenius model, [33], assumes thermally induced cell injury as a first order irreversible kinetic process and quantifies the cell death percentage in $\mathbf{v}$ at time t as

$$d(\mathbf{v},t) = 1 - \exp\left(-\int_0^t \frac{R_g T(\mathbf{v},t')}{Nh} \exp\left(1 - \frac{E_a - T(\mathbf{v},t')\Delta S}{R_g T(\mathbf{v},t')}\right) dt'\right) \tag{10}$$

see [54], with the ideal gas constant $R_g = 8.314\text{JK}^{-1}\text{mol}^{-1}$, Avogardo's number $N = 6.022 \cdot 10^{23}\text{mol}^{-1}$, Planck's constant $h = 6.626 \cdot 10^{-34}\text{Js}$, the activation energy E with $[E] = \text{Jmol}^{-1}$ and the entropy of activation ΔS with $[\Delta S] = \text{JK}^{-1}\text{mol}^{-1}$. The complex structure of this model as well as the value uncertainty of entering constants led to the use of various numerical approximations such as the thermal isoeffective dose (TID) model. This model converts the accumulated cell-biological impact of the original varying temperature into a duration

$$d(\mathbf{v},t) = \int_0^t R(T(t'))^{T_{\text{ref}} - T(t')} dt' \tag{11}$$

during which an artificial constant reference temperature T_{ref} achieves the same impact, [57, 17]. For example, [15] takes a reference temperature of $43°C$ and mentions 240min as a corresponding lethal duration. Literature lists various numerical fits to the function

$$R(T) = \exp\left(-\frac{E}{R_g T(T+1)}\right)$$

depending on the available experimental data, [17, 18, 2].

B Criterion functions

The main goal planning goal of FUS therapy planning is treatment success by sufficiently high cell-biological impact in most of the cancerous tissue. An exemplary criterion function of the general form (4) for formulating the planning goal is

$$f(\mathbf{d}(t_{\text{end}})) = \left(\frac{1}{|\mathcal{V}_{\text{tumor}}|} \int_{\mathbf{v} \in \mathcal{V}_{\text{tumor}}} \max\{d_{\text{cur}} - d(\mathbf{v}, t_{\text{end}}), 0\}^2 d\mathbf{v} \right)^{\frac{1}{2}} \tag{12}$$

which is inspired by the physical constraint function in IMRT introduced in [7]. Here $\mathcal{V}_{\text{tumor}}$ denotes the cancerous tissue entity of the tumor volume. d_{cur} denotes the aspired curative cell-biological impact, which in case of the Arrhenius model (10) could be some cell death percentage of, say, 95% or in case of the TID model (11) is the duration of 240min at some reference temperature. Another important goal is the wide sparing of a health tissue entity $\mathcal{V}_{\text{risk}}$ by preferably low cell-biological impact, which may in the form (4) be modeled as

$$f(\mathbf{d}(t_{\text{end}})) = \left(\frac{1}{|\mathcal{V}_{\text{risk}}|} \int_{\mathbf{v} \in \mathcal{V}_{\text{risk}}} d(\mathbf{v}, t_{\text{end}})^2 d\mathbf{v} \right)^{\frac{1}{2}} \tag{13}$$

for both Arrhenius and TID model. This criterion function resembles the EUD function from IMRT introduced in [53] for the exponent $a = 2$. Both criterion functions are formulated in such a way, that decreasing function values reflect improving plan quality. In case of the Arrhenius model, these criterion functions yield values from the interval $[0, 1]$. Such normalization can be also achieved in case of the TID model by means of suitable transformations.

C Criterion function and histogram curve

Rewriting of the histogram value (9) yields

$$h(d, \mathbf{d}(t_{\text{end}})) = \frac{1}{|\mathcal{V}|} \int_{d' \in [d, \infty)} \int_{\mathbf{v} \in \mathcal{V}} \delta(d(\mathbf{v}, t_{\text{end}}) - d') d\mathbf{v} dd'$$

where the inner integral with the Dirac δ can be considered as curve point of a differential histogram in d'. The general criterion function (4) can be rewritten as

$$f(\mathbf{d}(t_{\text{end}})) = \Phi \left(\int_{d' \in [0, \infty)} \varphi(d') \int_{\mathbf{v} \in \mathcal{V}} \delta(d(\mathbf{v}, t_{\text{end}}) - d') d\mathbf{v} \right)$$

which also relies on the differential histogram curve formulation. A criterion function can thus be alternatively considered as some averaging of a histogram curve.

D Plan recombination

Consider the case of FUS plans, which rely on the same grid of sonication points in the tissue sonicated in the same order from identical transducer positions. The specification of such plans in terms of the remaining plan parameters for the sonications enumerated by $l = 1, \ldots, L$ reads $\mathbf{X} = (\sigma_l, \mathbf{x}_l)_{l=1,\ldots,L}$ with the durations σ_l and the energies $\mathbf{x}_l$ for the transducer elements. The cooling periods between successive sonications can be encoded with σ_l as waiting times between them and zero energy vectors $\mathbf{x}_l = \mathbf{0}$. Recombination of plans $(\mathbf{X}_k)_{k=1,\ldots,K}$ with the coefficients $\mathbf{c} = (c_k)_{k=1,\ldots,K}$ with $c_k \geq 0$ and $\sum_{k=1,\ldots,K} c_k = 1$ then simply reads

$$\mathbf{X}(\mathbf{c}) = \sum_{k=1,\ldots,K} c_k \mathbf{X}_k = \left(\sum_{k=1,\ldots,K} c_k \sigma_{k,l}, \sum_{k=1,\ldots,K} c_k \mathbf{x}_{k,l} \right)_{l=1,\ldots,L} \tag{14}$$

Acknowledgments

This work was supported by the Fraunhofer Internal Programs under grant no. MAVO 821012. The authors would like to thank Christian Tönnes for implementation work on visualization and algorithmic backend.

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