Multi-objective Optimization and Stochastic Analysis in Focused Ultrasonic Therapy Simulation

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Abstract: We present new results in stochastic multi-objective optimization applied to focused ultrasonic therapy planning. This type of non-invasive therapy uses focused ultrasound for the destruction of tumor cells and magnetic resonance tomography for identification of tumor volume and healthy organs. During the therapy planning the treatment parameters, such as frequency and intensity of ultrasound, are adjusted to achieve maximal tumor destruction and minimal influence to the healthy organs. For this purpose multi-objective optimization is used. RBF metamodeling is employed for continuous representation of discretely sampled results of numerical simulation and for evaluation of inherent uncertainties. We apply two algorithms for multi-objective optimization capable of non-convex Pareto front detection in the considered problem. Cross-validation procedure and sensitivity analysis are used for estimation of uncertainties. A realistic application case demonstrates the efficiency of the approach.

1 INTRODUCTION

Due to the non-invasive nature of the focused ultrasonic therapy its control is often limited to imaging methods, e.g. MRT. Numerical simulation becomes an important step for the therapy planning. Efficient methods for the focused ultrasonic simulation have been presented in paper (Georgii et al., 2011). It uses a combination of Rayleigh-Sommerfeld integral for near field and angular spectrum method for far field computations, which allows determining the pressure field in heterogeneous tissue. The bioheat transfer equation is used to determine the temperature increase in therapy region. Thermal dose is defined according to CEM model or Arrhenius model (Nandlall et al., 2009); (Pearce, 2009) as a functional of temperature-time dependence in every spatial point in therapy region. The simulation is considerably accelerated by GPU based parallelization.

The purpose of therapy planning is a maximization of thermal dose inside the target zone (TDin) and minimization of thermal dose outside (TDout). As usual in multi-objective optimization (Ehrgott AND Gandibleux, 2002), the optimum is not an isolated point but a hypersurface (Pareto front) composed of points satisfying a tradeoff property, i.e. none of the criteria can be improved without simultaneous degradation of at least one other criterion. Thus, for a two-objective problem, the Pareto front is a curve on the plot (TDin, TDout) bounding the region of possible solutions, see Fig.2. Efficient methods have been developed for determining the Pareto front.

The simplest way is to convert multi-objective optimization to single objective one, by linearly combining all objectives into a single target function $t(x)= \sum w_i f_i(x)$ with user-defined constant weights w_i. Maximization of the target function gives one point on Pareto front, while varying the weights allows to cover the whole Pareto front. In this way only convex Pareto fronts can be detected, because non-convex Pareto fronts produce not maxima but saddle points of the target function. There are methods applicable also for non-convex Pareto fronts.

Non-dominated set algorithm (NDSA) finds a discrete analogue of Pareto front in a finite set of points. For two points f and g in optimization criteria space the first one is said to be dominated by the second one if $f_i \leq g_i$ holds for all i=1..Ncrit. A point f belongs to non-dominated set if there does not exist another point g dominating f. (Kung et al., 1975) implements a fast recursive procedure to find all non-dominated points in a given finite set.

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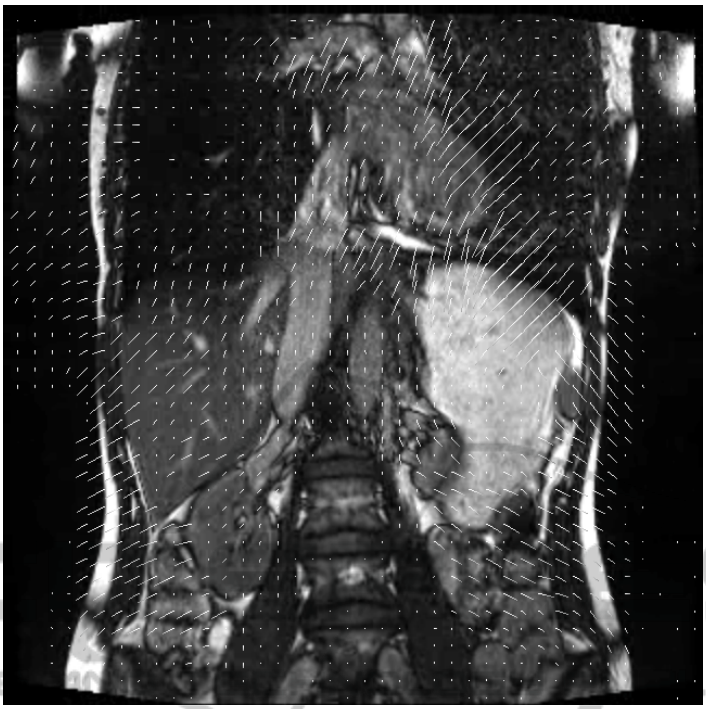

Figure 1: MRT slices are used as a basis for volumetric material model.

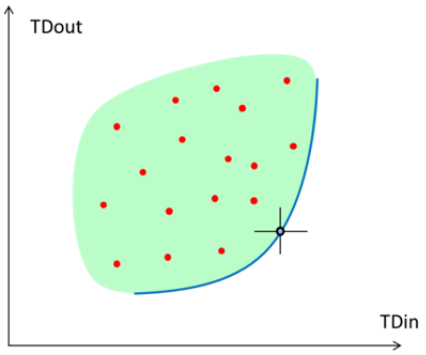

Figure 2: Robust multi-objective optimization using metamodeling of simulation results. Red points denote simulation results, the continuous green region indicates a metamodel of simulation results, the blue curve the Pareto front, the black point with error bars an optimal representative with confidence limits.

A continuous method is LP-based local improvement algorithm (LIA). It produces a trajectory towards the Pareto front starting from an initial design. Each step solves a linear program (Hornung et al., 2010)

maximize ε;
where $(\nabla f_i, \Delta x) \geq \varepsilon \geq 0$ and $-\delta \leq \Delta x^j \leq \delta$

w.r.t. the threshold ε and the step Δx, for the given gradients of objectives ∇f_i and the size of trust region [-δ,δ]. Here i=1..Ncrit, j=1..Npar. The approach ensures that all criteria have an improvement at least ε, maximally possible within the given trust region. The algorithm terminates at Pareto front, where no further improvements are possible.

In the case when only a restricted number of simulations is available metamodeling of simulation results becomes useful. The objectives are interpolated continuously in between simulation results, and optimization algorithms are applied to interpolated functions. In particular, RBF metamodeling (Buhmann, 2003) has the advantage of generic non-degeneracy in arbitrary dimensions and the availability of a tolerance predictor. The interpolated function f(x) is represented as a linear combination of special functions Φ() depending only on the distance to the sample points x_k:

$$f(x) = \sum_{k=1..Nexp} c_k \, \Phi(|x-x_k|) \qquad (1)$$

The coefficients c_k can be found from known function values in sample points $f(x_k)$ by solving a moderately sized linear system with a matrix $\Phi_{kn} = \Phi(|x_k-x_n|)$.

In practical problems, different sources of uncertainty should be considered. Uncertainties of metamodeling are related with the quality of sampling in parameter space. These uncertainties are reduced with the increasing density of sampling, i.e.

when more simulations are included into analysis. This type of uncertainty can be estimated by a cross-validation procedure, measuring a sensitivity of the function value to the removal of sample points. With the usage of Sherman-Morrison-Woodbury formula it can be found analytically (Nikitin et al, 2012):

$$\varepsilon_k = f(x_k) - f(x_k)|_{xk\ removed} = c_k / (\Phi^{-1})_{kk} \quad (2)$$

Another type of uncertainties comes from physical model. In addition to optimization parameters x, the objectives also depend on a number of model parameters p, such as physical properties of biomaterials. These parameters are measured imprecisely. The corresponding variation of results can be estimated by means of the first order reliability method FORM (Clees et al., 2012):

$$\sigma(f) = (\sum_{j=1..Npar} (\partial f/\partial p^j\ \sigma(p^j))^2)^{1/2} \quad (3)$$

where non-correlated variations of parameters p^j are assumed, and $\sigma()$ denotes standard deviation. Finally, these two sources of scatter can be combined into a single measure:

$$err = (\varepsilon^2+\sigma^2)^{1/2}. \quad (4)$$

In further sections we apply the above described methodology for the multi-objective optimization and stochastic analysis of focused ultrasonic therapy simulation.

2 MODELING

A generic workflow for modeling of the focused ultrasonic therapy has been described in our paper (Borsotto et al., 2012). Numerical simulation uses FUSimlib software (http://www.simfus.de) on 512 x 512 x 256 voxel grid. Ultrasound has been focused in the center of the target zone for the neutral breath state. The computational model includes angular spectrum method with heterogeneous tissue and reflections. CEM model is used for determination of thermal dose. The result after 10 seconds of exposure time has a form of spatial distributions of pressure amplitude, temperature and thermal dose. Fig.3 shows a typical result for thermal dose on slice 97/256 near the focal point.

The registration of tissue deformation on the basis of MRT images is used for proper characterization of the breathing process. It has been shown in (Borsotto et al., 2012) that the breathing process is one of the major sources of uncertainties in focused ultrasonic therapy simulation. For characterizing the breathing process two image sequences have been processed, each containing 104 z-slices with 320 x 320 xy-resolution. One sequence corresponds to the breath-in state, another one to the neutral breath state. Point-to-point correspondence between images has been determined using a block-matching method. Fig.1 shows the resulting field of motion vectors for slice 51/104 of the neutral breath sequence.

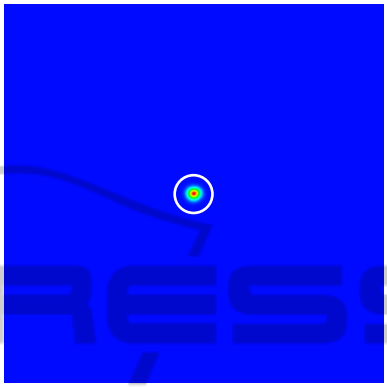

Figure 3: Typical simulation result, thermal dose (range: 0eq.min/blue to 0.6eq.min/red). The target zone in the neutral breath state is marked by the white circle.

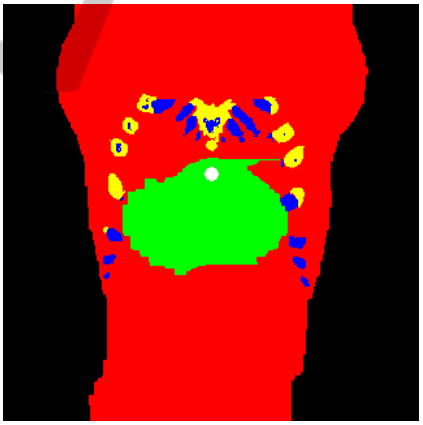

Figure 4: Spatial material distribution: gel (black), liver (green), other soft tissue (red), cartilage (blue), bones (yellow). White color marks the target zone.

Segmentation procedure defines spatial distribution of biomechanical characteristics on the voxelized model. 5 types of materials are introduced shown with different colors on Fig.4, for the slice 21/104. A target zone has been modeled as a ball of 1cm diameter located on the upper part of the liver. Its motion according to breathing process is evaluated on the basis of the motion vector field found in the registration procedure and controlled by a single parameter (t=0…1) for the transition from neutral to breath-in state. A finer 512 x 512 x 256 voxel grid

has been used for simulation, where the distribution of material has been subsampled into, using proper positioning transformations.

3 OPTIMIZATION

Optimization is performed with respect to the following parameters.

Table 1: Optimization parameters and their variations.

frequency	0.25…0.75 MHz
initial particle speed	0.23...0.282 m/s

The frequency of transducer is an important parameter controlling focused ultrasonic therapy simulation. The other one, initial particle speed, is proportional to an acoustic intensity emitted by the transducer (Georgii et al., 2011). As optimization objectives the thermal dose inside and outside the target zone have been defined as sums of the thermal dose over corresponding voxels, ∑TDin / ∑TDout. The variation range of optimization parameters was regularly sampled with 25 simulations, from which 19 fall in the region of interest, shown on Fig.5. RBF metamodel constructed on simulation results shows Pareto front of non-convex type, for which NDSA and LIA Pareto front detectors have been applied.

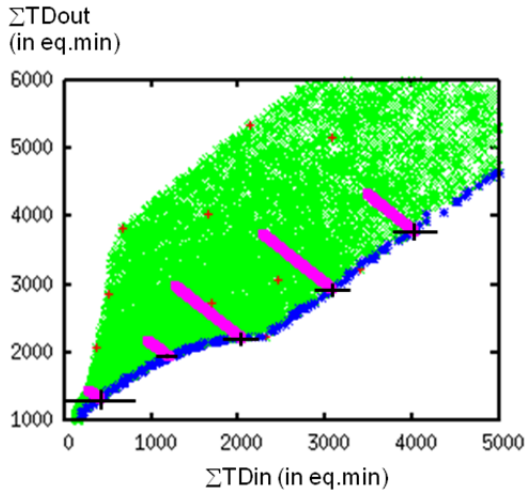

Figure 5: Results of multi-objective optimization. Red points denote simulation results, the green points indicate a metamodel of simulation results, the blue points indicate the Pareto front detected by NDSA, the magenta points show trajectories of interior points towards Pareto front found with LIA. Black crosses show the tolerances of the metamodel found with cross-validation procedure.

For convenience of the therapy planning it is advisable to use a special tool for design parameter optimization, DesParO (Clees et al., 2012), see Fig.6. It allows to change interactively optimization parameters and to see immediately the variation of optimization criteria. Constraints can be set e.g. maximizing one objective and minimizing the other, in this way the Pareto front can be explored. Graphical representation of interdependencies between parameters and criteria allows to find most influencing parameters and most sensitive criteria. Also, the uncertainties of metamodeling found with cross-validation procedure are shown (the red bars under criteria sliders).

Further we focus on uncertainties coming from physical model.

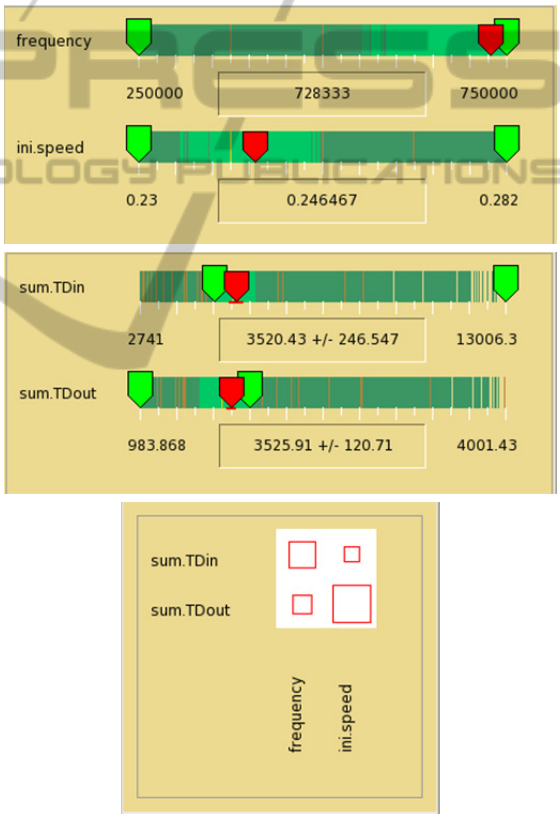

Figure 6: Optimization problem in DesParO Metamodel Explorer. On the top: sliders of parameters, in the center: sliders of criteria, on the bottom: a pattern of interdependencies between parameters and criteria.

4 SENSITIVITY ANALYSIS

In our previous paper (Borsotto et al, 2012) the sensitivity of the result to variation of 29 parameters has been evaluated, including 5 biomechanical

characteristics for 5 materials each, 3 blood characteristics and 1 breathing parameter. It has been shown that the parameters most influencing the result are the absorption coefficients for gel, soft tissue and liver as well as the breathing parameter.

For improving accuracy of the physical model a precise measurement of absorption coefficients as well as synchronization of transducer focal point with breathing process has been proposed.

Here we present a new estimation of sensitivity, based on improved measurements of critical parameters given in (Peters, 2007).

For estimation of sensitivity, the parameters have been varied in ±σ interval according to Table 2 below, then a central difference scheme has been used to estimate entries of the Jacobian matrix:

$$J_{ij} = \partial\, crit_i / \partial\, par_j \quad (5)$$

The sensitivity matrix is defined as

$$S_{ij} = J_{ij}\, \sigma_j \quad (6)$$

and presented in Table 3. Then total r.m.s. of two criteria is evaluated:

$$\sigma(crit_i) = (\sum_{j=1..Npar} S_{ij}^2)^{1/2} \quad (7)$$

and presented in Table 4 together with the mean values of the criteria.

Comparing with the previous result, we see significant improvement of precision, especially if breathing influence is compensated. These uncertainties should be taken into account during the therapy planning.

Table 2: Standard deviations of absorption coefficient (in 1/m), from (Peters, 2007).

gel	0.001
liver	1.2
soft tissue	0.7

Table 3: Sensitivity matrix for objectives ∑TDin / ∑TDout (in eq.min).

	gel	soft tissue	liver
absorption	-0.2 / -0.3	-183.6 / 277.3	709 / 378.5

breath	-505.2 / 546.6

Table 4: Standard deviations and mean values for ∑TDin / ∑TDout (in eq.min).

	∑TDin	∑TDout
r.m.s. total	889.5	720.4
r.m.s. breath compens.	732.1	469.2
mean	2273.7	3743.8

5 CONCLUSIONS

A generic approach for focused ultrasonic therapy planning on the basis of numerical simulation has been presented including multi-objective optimization and stochastic analysis. Its application to a realistic test case has been demonstrated. RBF metamodeling of simulation results has been performed for continuous representation of two optimization objectives. Non-convex Pareto front of the objectives has been determined by means of non-dominated set and local improvement algorithms. Uncertainties of metamodeling have been estimated by means of cross-validation procedure. These uncertainties can be reduced with the increasing density of sampling, i.e. including more simulations into analysis. Uncertainties of physical model have been estimated by means of sensitivity analysis. Improved accuracy of the physical model and compensation of the influence of the breathing process provide better precision of the result.

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