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Numerical Study and Ex Vivo Assessment of HIFU Treatment Time Reduction through Optimization of Focal Point Trajectory

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Abstract. Treatment time reduction is a key issue to expand the use of high intensity focused ultrasound (HIFU) surgery, especially for benign pathologies. This study aims at quantitatively assessing the potential reduction of the treatment time arising from moving the focal point during long pulses. In this context, the optimization of the focal point trajectory is crucial to achieve a uniform thermal dose repartition and avoid boiling.

At first, a numerical optimization algorithm was used to generate efficient trajectories. Thermal conduction was simulated in 3D with a finite difference code and damages to the tissue were modeled using the thermal dose formula. Given an initial trajectory, the thermal dose field was first computed, then, making use of Pontryagin's maximum principle, the trajectory was iteratively refined. Several initial trajectories were tested.

Then, an *ex vivo* study was conducted in order to validate the efficiency of the resulting optimized strategies. Single pulses were performed at 3MHz on fresh veal liver samples with an Echopulse and the size of each unitary lesion was assessed by cutting each sample along three orthogonal planes and measuring the dimension of the whitened area based on photographs.

We propose a promising approach to significantly shorten HIFU treatment time: the numerical optimization algorithm was shown to provide a reliable insight on trajectories that can improve treatment strategies. The model must now be improved in order to take *in vivo* conditions into account and extensively validated.

Keywords: HIFU, ultrasound surgery, treatment time, optimization, optimal control

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INTRODUCTION

Treatment time reduction is a key point to expand the use of high intensity focused ultrasound (HIFU) surgery, especially for benign pathologies such as breast fibroadenomas and thyroid nodules. Several strategies have been reported to achieve this goal, based on MRI monitoring [1], optimization of pulse arrangement [2], optimization of the duty cycle [3] or multiple focusing with phased array [4]. These strategies aim at maximizing thermal build-up while maintaining pre-focal heating at an acceptable level and avoiding overtreatment, which, from our viewpoint, is a waste of energy.

This study aims at quantitatively assessing the potential time reduction arising from moving the focal point during unitary pulses of 24s, which is close to the limit of use of the transducer at the power levels used in clinical treatments. In this context, the optimization of the focal point trajectory is crucial to achieve a uniform thermal dose repartition and avoid boiling.

The system considered was Theraclion's Echopulse, comprising a single-element transducer moved by a 4-axis robot. At first, we conducted a numerical study to optimize the trajectory during a single pulse. Then, *ex vivo* experiments allowed to compare the performance of the resulting strategies.

MATERIALS AND METHODS

Numerical Model

The acoustical simulations were done using Sonesson's code [5] which solves the Khokhlov-Zabolotskaya-Kuznetsov equation (KZK) in an axisymmetric domain. The resulting axisymmetric heat source field was then expressed on a 3D cartesian grid.

We used Penne's bioheat equation [6] to compute the evolution of the temperature field:

$$\rho_t C_t \frac{\partial T(x,t)}{\partial t} = k_t \nabla^2 T(x,t) + \omega_b \rho_b C_b (T_b - T(x,t)) + Q_{ac}(x,t) \quad (1)$$

where T is the temperature field in the tissue, k_t , ρ_t and C_t are respectively the conductivity, the density and the specific heat of the tissue, ω_b , ρ_b , C_b and T_b are respectively the volumetric blood perfusion rate, the density, the specific heat and the equilibrium temperature of blood. Q_{ac} is the heat source term.

It was solved with Matlab with a finite difference method based on explicit Euler discretization in time and a centered scheme of order 2 in space. The discretized equation can be written in the form:

$$T^{n+1} = \mathbf{A}T^n + Q^n \quad (2)$$

where T and Q are vectors of size N^3 , with N the number of points in each direction, and \mathbf{A} is a sparse matrix of size $N^3 \times N^3$. Perfusion was not taken into account in this study but it does not change the formalism.

The initial temperature was set to $310K$ and Dirichlet boundary conditions were used. The properties of the medium were set to $k_t = 0.6W.m^{-1}.K^{-1}$, $\rho_t = 1000kg.m^{-3}$, $C_t = 3600J.kg^{-1}.K^{-1}$. In the acoustical simulations, the acoustic attenuation of the tissue was set to $\alpha_t = 0.8dB.cm^{-1}.MHz^{-1}$ and the speed of sound was set to $c_t = 1570m.s^{-1}$. The excitation frequency of the transducer was set to $3MHz$.

Finally, the thermal dose field $D(x,t)$ was computed in order to model the thermal damages to the tissue [7]:

$$D(x,t) = \int_0^t R(T)^{316-T(x,\tau)} d\tau \quad (3)$$

For sake of simplicity, we considered that $R = 0.5$ independently of the temperature. The tissue is considered to be dead where $D > 14400s$ at $43^\circ C$.

The numerical simulations were performed with Matlab R2013b, on a Dell Precision T7500 workstation with 24GB RAM.

Optimal Control Algorithm

Definitions

We used the optimal control approach described in [1] but it was applied to the trajectory of the focal spot during a pulse. The algorithm is briefly summarized here for the considered equations.

We note u the control variable (the position of the focal spot). The objective is to minimize the cost function J , which is of the form:

$$J(u) = \int_{t_0}^{t_1} g(T(t), u(t), t) dt \quad (4)$$

with t_0 and t_1 delimiting the time interval considered for the optimization process; usually t_0 denotes the beginning of the pulse and $t_1 - t_0$ is greater than the pulse duration. Note that $T(t)$ is a vector of size N^3 containing the temperature in each point of the domain. It follows the equation 2.

In this context, the adjoint state p , which has the same size as T , is defined as the solution of:

$$\dot{p} = \mathbf{A}^T p(t) + \partial_T g(T, u, t) \quad (5)$$

with $p(t_1) = 0$ and with T denoting the matrix transposition operator.

We then define the Hamiltonian:

$$H(T, p, u, t) = p^T (\mathbf{A}T(t) + Q(u, t)) - g(T, u, t) \quad (6)$$

With these definitions, Pontryagin's maximum principle states that a necessary condition for u^* to minimize J is that:

$$\forall t \in [t_0, t_1], u^*(t) = \underset{u}{\operatorname{argmax}} H(T, p, u, t) \quad (7)$$

Hamiltonian maximization

The maximization of the Hamiltonian was performed with a modified gradient method. At the iteration it , the gradient of the hamiltonian with respect to u was computed at each time step n . Then, u_{it+1} was computed as:

$$\forall n \in 1, \dots, N_t, u_{it+1}^n = u_{it}^n + h \frac{\partial_u H_{it}^n}{\sum_{k=1}^{N_t} \|\partial_u H_{it}^k\|} \quad (8)$$

with N_t the number of time steps, h the step in the gradient method and the notation $\partial_u H_{it}^n = \partial_u H(T_{it}^n, p_{it}^n, u_{it}^n, t^n)$. With the standard gradient method, the expression would have been: $\forall n \in 1, \dots, N_t, u_{it+1}^n = u_{it}^n + h \partial_u H_{it}^n$.

Algorithm

Step 1: Initialization

- a) Set the parameters and choose an initial trajectory u_0 .

Step 2: While $it < N_{itmax}$ and $h > h_{min}$

- a) Compute the temperature field and $J(u_{it})$.
- b) If $J(u_{it}) < J(u_{it-1})$ or $it == 0$
 - i) Compute the adjoint state backwards in time.
 - ii) Compute the gradient of the Hamiltonian and u_{it+1} from equation 8.

Else

- i) $h = \frac{h}{2}$ and $u_{it+1} = u_{it-1} + \frac{u_{it} - u_{it-1}}{2}$

Cost Function

The design of the cost function is a crucial step in any optimization process and, indeed, the resulting trajectories are very sensitive to the cost function. In this study, the objective was to create the largest possible lesion in a given time. The most basic idea would be to minimize the untreated volume at the end of the pulse but the evaluation of the adjoint variable in equation 5 requires the derivative of g with respect to T . Therefore, a cost function was designed based on the following principles:

- zones where the dose is close to the threshold of 14400s must be favored.
- the cost of highly overtreated areas must be high. Slight overtreatment is however tolerated.
- the cost of untreated areas is high and begins to lower only close to the threshold of 14400s.

The results presented in this paper were obtained for the following expression of g (see Figure 1):

$$g(T, u, t) = \begin{cases} -7.6875L^2 + 46.025L - 61.649 & , L \leq 3.8 \\ 15.9991L^2 - 133.9935L + 280.3861 & , 3.8 < L \leq 4.1875 \\ 3.1033L^2 - 25.9899L + 54.2526 & , 4.1875 < L \leq 4.8 \\ 3.8014L - 17.2465 & , L > 4.8 \end{cases}$$

with $L(T) = \log_{10}(D(T) + 1000)$. $L = 4.1875$ corresponds to $D = 14400s$, the retained threshold for tissue killing.

It is also possible to penalize more strongly partially treated areas than untreated areas as they also correspond to a waste of energy; however, the more complex the cost function is, the more difficult it becomes to adjust its parameters. When the focal spot is moved with a robotic system, it is also possible to take into consideration the limits of the robot in terms of speed and acceleration. The easiest way is to penalize the first or second-order derivative of u in the cost function.

The endpoint remains however the size of the lesion created for a given pulse duration. As the only movements allowed in this study were 2D (orthogonal to the main propagation axis), the performance of a trajectory was measured by the surface of the lesion in this plane. In order to get a significant measure of the efficiency of a pulse, we compute

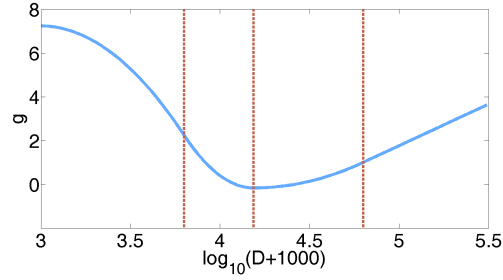


FIGURE 1. Representation of g as a function of thermal dose

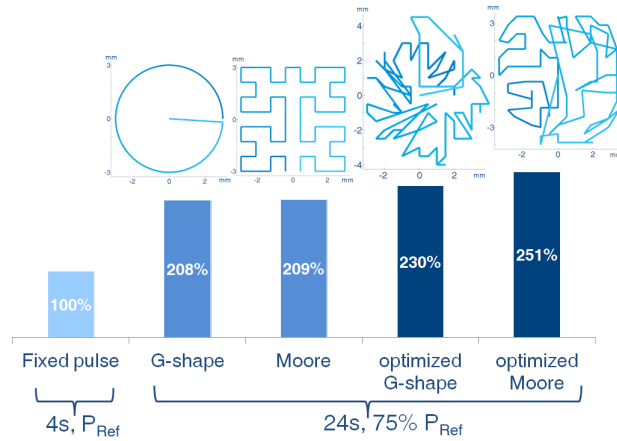


FIGURE 2. Comparison of the efficiency of different trajectories, P_{Ref} is a reference power.

the pause time, associated to a pulse according to Theraclion’s skin safety conditions. It depends on the depth of the target, the pulse duration and the power. Finally, the surfacic damage rate of a pulse is defined as the surface of a unitary lesion divided by the sum of the pulse duration and the pause time.

Ex Vivo Experiments

In order to assess the efficiency of the optimized trajectories, an *ex vivo* study was conducted: single pulses were performed at $3MHz$ on fresh veal liver samples with an Echopulse. The samples were formerly degased and maintained at an initial temperature of $37^{\circ}C$ in a salted water bath. The experiment was monitored with an ultrasound imaging probe. The size of each unitary lesion was assessed by cutting each sample along three orthogonal planes and measuring the dimension of the whitened area based on photographs.

RESULTS

The efficiency of two trajectories (G-shape and Moore) and their optimized versions are reported in Figure 2 and compared to Theraclion’s current procedure. They show that the optimization algorithm significantly improves the results of already intuitively good trajectories.

Another example is reported in Figure 3: according to the simulations, the optimized spiral was 57% more efficient than the initial spiral. Since this trajectory was impossible to realize robotically, it was smoothed. The smoothed version of the optimized spiral was 51% more efficient than the initial spiral. *Ex vivo*, the improvement was close to 40% . Therefore, the optimization algorithm proved its usefulness for modifying trajectories in order to increase the efficiency of the pulses. The numerical model allowed for a relatively good estimate of the gain; however, these results also highlight the importance of the precision of the model, which has to be improved.

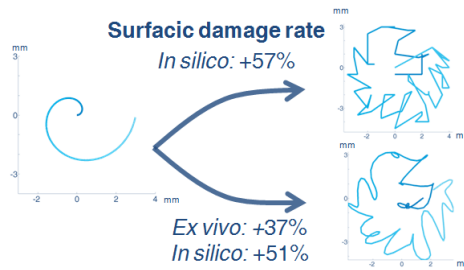


FIGURE 3. Comparison between simulation and *ex vivo* experiments

DISCUSSION

The approach presented in this paper shows promising results. Its major merit is to make complicated trajectories emerge with better performance compared to intuitively efficient trajectories such as spirals or circles. The resulting trajectories are highly dependent on the initialization, which is consistent with the fact the gradient method does not explore a large domain but rather converges to a local minimum around the initial guess. Moreover, the scores of the different resulting trajectories are very close which means that no class of trajectories seems to emerge with the cost function used in this study. Starting from a trajectory which has poor performances generally leads to a final solution that is close to the best scores, which proves the robustness of the algorithm.

For practical implementation, the algorithm can either be modified to take into account the specifications of the robot or the trajectories can simply be smoothed afterwards, even if this approach leads to a loss of efficiency. Solving the bioheat equation in the spectral domain also considerably smooths the trajectories compared to the FD method presented in this study. The extension of the results in 3D is straightforward although more computationally intensive as each movement of the focal spot along the main propagation axis requires a new simulation of the acoustical field.

In order to define clinically relevant trajectories, the perfusion must be taken into account, as it tends to limit the thermal build-up, and the defocusing due to the skin and the subcutaneous fat must also be modeled. The numerical model must be extensively validated over a wide range of trajectories: the comparison of the score of a given set of trajectories must give the same ranking as observed experimentally. Moreover, the domain of validity of the numerical model must be carefully checked: for example, the score obtained by a trajectory inducing a temperature over 100°C would not be significant as boiling is not taken into account in the model.

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