Synthesizing Distributions of Magnetic Nanoparticles for Clinical Hyperthermia

P. Di Barba[1], F. Dughiero[2], E. Sieni[2]
[1]University of Pavia, Department of Electrical Engineering, via Ferrata, 1 - 27100 Pavia, Italy
[2]University of Padova, Department of Electrical Engineering, via Gradenigo 6/a - 35131 Padova, Italy
paolo.dibarba@unipv.it, {fabrizio.dughiero,elisabetta.sieni}@unipd.it

Abstract — An automated procedure based on evolutionary computation and Finite Element Analysis (FEA) is proposed to synthesize the optimal distribution of nanoparticles (NPs) in multi-site injection for a Magnetic Fluid Hyperthermia (MFH) therapy.

I. Introduction

In clinical hyperthermia based on magnetic fluids, the tumor region temperature depends among others on the concentration and distribution of NPs [1], [2]. Then, even if the magnetic field is maximally uniform in the treatment region, the thermal field might not have the same uniformity degree due to the non uniform-distribution of NPs in the tissues. In [3] a thermal problem was solved considering a non uniform distribution of the NPs power density evaluated experimentally [3],[4]. The relevant power density was used in [4] to optimize the position of NPs injections, in order to fulfill some therapeutically important constraints on the tumor temperature. However, in [4] the distribution of magnetic field was disregarded. Moreover, a gradient-based, local-search oriented algorithm was used for optimization. In this paper, an automated procedure of optimization, based on evolutionary computing and FEA [5], is proposed in order to find the position of multiple NPs injections determining a tumor temperature close to the therapeutic value. A realistic NPs distribution [1] is considered to compute the power density, while the direct problem models both magnetic and thermal fields.

II. Physical Model and Optimization Problem

The magnetic field source is a winding composed of four concentric coils, J_m and Jc, as in Figure 1(a) [6]. The target region Ω_T, *i.e.* the tumor, which must be appropriately heated, exhibits an elongated shape like that in Figure 1(b) because the tumor shape generally has an irregural form. In fact, the aim of the paper is synthesizing the NPs injections in order to increases the temperature up to a terapeuthic value in a real tumor. The surrounding volume, Ω_L and Ω_B, are target and control regions, respectively, in which the temperature must be limited in order not to damage healthy tissues. The Ω_F region is healthy tissue around, Ω_L. Reference is made to a liver tumor in the abdominal cavity.
The aim of the design problem is to identify the optimal position of a few NPs injections in order to have a uniform distribution of the temperature field taking into account the distribution of the magnetic NPs in the tumor, and also limit the diffusion of the NPs in the healthy tissue. Therefore, a bi-objective optimization problem is originated; the optimal placement of two NPs distributions with the same initial concentration is considered as the basic case.

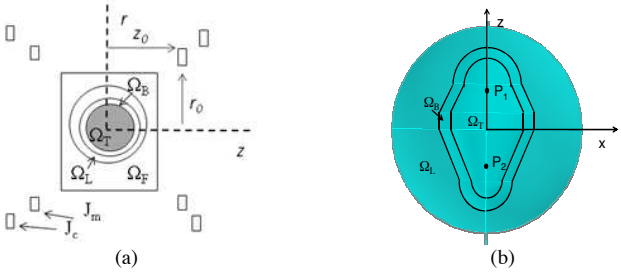

Figure 1: Geometry of (a) MFH winding and (b) shape of the target volume Ω_T.

The optimization variables are the positions of two NPs injections (*x, y* and *z* coordinates), and the dispersion, σ, i.e. the standard deviation of a Gaussian function used to describe the NPs distribution in the tissues. As a consequence, the numerical solution of the direct problem is based on a FEA tool [5], [6] for three-dimensional transient thermal analysis. The governing equation is the Fourier one equipped with the blood perfusion term [2], [7]:

$$c_p \gamma \frac{\partial T}{\partial t} = \lambda \nabla^2 T - c_b w_b (T - T_a) + P \qquad (1)$$

in a time interval of 300 s. In (1) λ is the thermal conductivity, c_p the specific heat, γ the density of the tissue and T the temperature. Moreover, T_a is the basal body temperature (at 37°C), w_b is the mass flow rate which depends on tissue and temperature, c_b is the blood specific heat [7]. The term P is the NPs power density considering NPs concentration, ϕ:

$$P(x,y,z,T,H,\phi) = \mu_o \pi \chi''(x,y,z,T,H,\phi) f H^2(x,y,z) \qquad (2)$$

in which H is the intensity of the magnetic field, f the frequency of the field and χ'' the imaginary part of the magnetic susceptivity that depends on the local concentration of NPs, ϕ:

$$\chi'' = \phi(x,y,z,\sigma) f_1(T) f_2(\xi(H,T)) f_3(\omega,\tau) \qquad (3)$$

In (3), σ is the standard deviation that describes the NPs dispersion from the injection center. In particular, function f_2 depends on the Langevin parameter, ξ, which in turn depends on field intensity, H, and temperature, T, while function f_3 depends on field pulsation, ω, and NPs relaxation time, τ [1] and f_1 on temperature only. Let a spatial function of the NPs concentration, ϕ, with a Gaussian shape be assumed. For an injection point *j* it is:

$$\phi_j(x,y,z,\sigma) = \phi_0 e^{-\frac{1}{2}\left(\frac{(x-\eta_{j,x})^2}{\sigma^2}+\frac{(y-\eta_{j,y})^2}{\sigma^2}+\frac{(z-\eta_{j,z})^2}{\sigma^2}\right)} \qquad (4)$$

with ϕ_0 constant concentration and $\eta_{j,i}$, $i=x,y,z$, Cartesian coordinates of the injection point. Equation (4) is written

under the assumption that the diffusion speed is equal for the three orthogonal directions and uncorrelated with the one along the other directions. If multiple injection points, *N*, are considered, the concentration ϕ of NPs in a volume is nothing but the superposition of *N* Gaussian functions:

$$\phi(x,y,z,\sigma) = \sum_{i=1}^{N} \phi_i(x,y,z,\sigma) \quad (5)$$

Given the power source as in (2) and the NPs distribution as in (5), the two objective functions characterizing the design problem are: (a) the volume of the tumor region in which the temperature is higher than a given threshold (*e.g.* 42°C), to be maximized, and (b) the surface of the tumor region on which the temperature is very close to the given threshold, to be maximized. In practice, the distance between actual and prescribed temperature is minimized. The aforementioned volumes or surfaces are recovered after uniformly sampling the region in the FE model. In the Ω_T region the former objective function is evaluated as follows:

$$R_1(T) = 100 \cdot \frac{N_T(T > 42)}{N_{T\,tot}} \quad (6)$$

where N_T is the number of temperature samples in the tumor region Ω_T for which the temperature is higher than 42°C, whereas $N_{T,tot}$ is the number of temperature samples in the whole tumor region, Ω_T. The latter objective function is evaluated on the tumor surface, *S*, as follows:

$$E_1 = \frac{1}{(37 - T_n)^2} \sum_{j=1}^{M} (T_j - T_n)^2 \quad (7)$$

where *M* is the number of temperature samples, T_j, on the tumor surface, T_n is the temperature threshold (42°C). Moreover, the following constraints have been defined:

$$R_2(T) = 100 \cdot \frac{N_S(T > 41.5)}{N_{S\,tot}} \quad (8)$$

R_2 is evaluated on the surface of the tumor, *S*, and accounts for the points on the boundary at a temperature higher than 41.5°C. Therefore, the goal is to maximize (6) and minimize (7) with respect to the injection point coordinates, subject to R_2>50. The most general solution is given by the relevant Pareto front [5].

The magnetic problem is solved first in order to compute the magnetic field intensity in the whole domain. The input of the transient thermal problem is the power source (2) evaluated from the magnetic field intensity and the distribution of NPs (5). Then, (6), (7) and (8) are evaluated from the thermal solution at 300 s.

III. RESULTS

Fig. 2 shows the effect of the standard deviation value, σ, in (4), and so in the NPs distribution (5), and also the temperature distribution after 300 s of treatment.

In Table I the values of objective functions and constraint (6), (7) and (8) for different values of the standard deviation σ are reported. The R_1 values increases with σ increasing whereas R_2 has a minimum for σ= 35 mm.

Preliminary results have been obtained either maximizing the R_1 function subject to (8), or - alternatively - minimizing the E_1 function subject to (8); both single-objective (SO) procedures started from the same initial point. Results are reported in Fig. 3. For E_1 and R_1 based optimization, one obtains P_1=(9.5, -1.5, -29.9), P_2=(-11.2, 3.1, 37.8), and P_1=(-3.8, 1.1, 25.5), P_2=(5.2, -0.7, -31.5), respectively. The corresponding values of (6), (7) and (8) are in the last two lines of Table I. The assumption of conflicting objectives seems to be assessed, because the two (P_1,P_2) pairs found are different. In Fig. 3, an approximation of the 2D objective space is obtained after the SO optimizations. Seemingly, a weak Pareto front, with low sensitivity near the optimum, is detected. In the full-length paper, the bi-objective problem will be solved in a systematic way, and the effect of small perturbations on the NPs injection points will be considered.

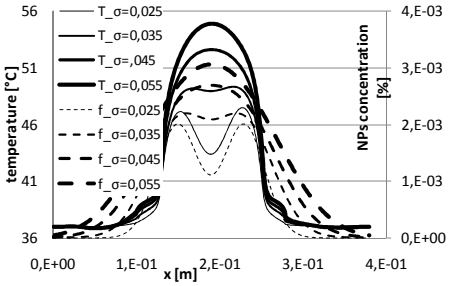

Figure 2: Effect of standard deviation, σ, in (4) on the tumor temperature, T (continous lines) and NPs concentration,f (dotted lines).

TABLE I
EFFECT OF STANDARD DEVIATION IN (4) ON (6),(7) AND (8), AND OPTIMIZATION RESULTS FOR TWO S-O PROBLEMS

σ[mm]	R_1 [%]	E_1	R_2 [%]
25	51,0	5357,27	3,0
35	89,0	467,69	62,0
45	99,0	1310,32	100,0
50	100,0	2999,98	100,0
E_1 minimization	91	397.8	70
R_1 maximization	95	705.7	83

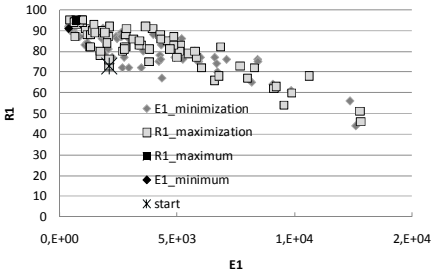

Figure 3: Objective space approximation.

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