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OPTIMAL CONSTRAINED FIELD FOCUSING FOR HYPERTHERMIA CANCER THERAPY: A FEASIBILITY ASSESSMENT ON REALISTIC PHANTOMS

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Abstract—Microwave hyperthermia is a non-invasive treatment for cancer which exploits a selective heating of tissues induced through focused electromagnetic fields. In order to improve the treatment's efficiency, while minimizing side effects, it is necessary to achieve a constrained focusing of the field radiated by the sources. To address this issue, in this paper we present an innovative and computationally effective approach to the field focusing for hyperthermia. The proposed method, after establishing the number of sources to be used, determines the excitations of the given set of sources such to produce a maximum field in a given region of space, subject to a completely arbitrary mask for the field amplitude in all other regions. As the approach relies on a formulation of the problem in terms of convex programming, it is able to achieve the globally optimal solution without the adoption of computationally intensive global optimization procedures. A preliminary assessment of feasibility is given on hyperthermia therapy of breast cancer by means of numerical examples run on realistic 2D phantoms of female breast.

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1. INTRODUCTION

Oncological hyperthermia, also called cancer thermal therapy or thermotherapy is a non-invasive treatment which is cooperatively exploited in cancer therapy and consists in exposing the body tissues to high temperatures for a sufficient period of time, in order to damage and kill cancer cells, while not significantly affecting healthy tissues. The treatment is based on the general principle stating that the properties of a cell population which characterize it as malignant also render that cell population more sensitive to an increase of the temperature than normal cells [1]. Hence, it is possible to selectively raise the temperature to the therapeutic range (42°C to 45°C) within the tumor and keep it below 42°C in the surrounding tissues, so to avoid side effects [2]. Notably, the adoption of hyperthermia has been shown to increase the effectiveness of radio and chemio-therapy treatments [3, 4].

Microwaves can provide an effective means to induce the selective heating in hyperthermia treatment [5]. Hence, in the last years, several efforts have been done to design effective applicators able to transfer microwave energy to the treatment area. In particular, the challenging requirements for these devices (e.g., the ability to focus the field and modify the absorbed power distributions during use, while being light and compact) have addressed the efforts towards the design of array configurations, where a suitable choice of the amplitude and phase of the excitations makes it possible the realization of desired radiation patterns. Hence, applicators based on different kind of linear [6, 7], planar [8], hexagonal [9], circular [10, 11], cylindrical [12], spherical [13], elliptically bent [14] and annular arrays [15] have been considered in the literature. More recently, other solutions have been considered, such as the use of left-handed metamaterials to improve focusing capabilities in shallow tumors treatments [16], or the adoption of deformable mirrors [17] or ultra-wide-band beamformers [19, 20] in breast cancer therapy.

Regardless of the specific solution implemented, the crucial issue is the capability of the applicator of guaranteeing the desired focusing of the field within the "target region" (i.e., where the tumor is located), without increasing the temperature elsewhere. Such a task is made even more difficult by the complex and heterogeneous nature of the biological structures at hand, which makes it possible the presence of *hot spots* located in regions different from the target area. Hence, to ensure the treatment effectiveness and reliability, the focusing procedure has to be properly constrained in order to avoid these detrimental effects.

In order to deal with such an issue, in this paper we propose and test a focusing strategy which is able to keep under control the maximum allowed power deposition in each single pixel of the scenario at hand other than the tumor region. Such a goal is reached by generalizing a recently introduced method for the synthesis of "pencil beams" by means of fixed-geometry arrays [21, 22]. This methodology determines the excitation of each element of the applicator in such a way that the overall device radiates the maximum field within a given region of space, subject to completely arbitrary upper bounds for the field values elsewhere. A remarkable feature of the approach is that it relies on a formulation of the problem in terms of convex programming (CP) [18], so that the adoption of computationally intensive global optimization procedures is not necessary. The adopted synthesis approach is also different from the one proposed in [19], where the excitations are determined by exploiting the "back-propagation" of the sought field within the biological structure at hand, rather than pursuing a constrained optimization task as done here.

In this paper, we consider a simplified scenario based on a $2D$ geometry and TM polarization, so that the proposed approach is partially limited to the case wherein the field to be maximized is scalar. Nevertheless, the approach is able to deal with the overall power deposition inasmuch constraints are concerned, and it can be somehow generalized to the case wherein all the three field components have to be maximized by means, for instance, of a multiobjective optimization strategy (see conclusions for more details). Notably, the fact that the approach is able to reach the global optimum under given power deposition constraints allows to state that the achieved Specific Absorption Rate (SAR) [23] distribution can assess the ultimate performances one can achieve (but for the subsequent thermal analysis, which is outside of the scope of the present paper).

To give an assessment of the proposed procedure, we have considered the application of microwave hyperthermia for breast cancer treatment. In particular, in order to perform such an analysis under realistic conditions from both the anatomical and electromagnetic point of views, we have exploited some numerical phantoms based on experimentally assessed dispersion relationship [24, 25] and 3D MRI images [26]. In particular, taking advantage of this resource, we have generated "realistic" 2D scenarios to perform a preliminary feasibility study for breast tumors in different locations and at different operating frequencies. The evaluation of SAR in the simulated scenarios has confirmed the capability of the proposed procedure to achieve a focused SAR deposition, thus showing its effectiveness in depositing as much energy as possible within the region of interest of the considered

biological models.

2. THE PROPOSED APPROACH AND ITS EQUIVALENCE TO A CP PROBLEM

To artificially increase tumor temperature to a desired peak value, hyperthermia cancer therapy exposes tumor tissues to electromagnetic radiations for an extended period of time [5]. In order to induce a heating of the target inclusion(s) without affecting the surrounding healthy tissues, the applicator has to induce a field having a maximum amplitude in the target region, while being limited by a suitable upper bound mask elsewhere [5].

Since the operating frequency must be such to guarantee a sufficient penetration of the wave, the targeted area (the tumor) is in the order of the probing wavelength or even smaller[†] (see also below). Then, the kind of pattern needed to produce the local temperature increase can be thought as a kind of "pencil beam". This kind of field can be synthesized in a very fast and effective fashion via fixed-geometry arrays (wherein the elements excitations are the degrees of freedom) by taking inspiration from the approach given in [21, 22]. According to this point of view, the problem underlying hyperthermia can be recast as the constrained synthesis of a focused field, which corresponds to a total field distribution having its maximum into the tumor region and being as low as desired elsewhere.

In the following, we reformulate the approach [21, 22] for the present field focusing problem by assuming the simple case of scalar fields, which corresponds to assume that the biological region which has to be heated is two dimensional, i.e., invariant along the direction of the field. A schematic view of the scenario is given in Figure 1.

Let us denote with $\underline{r}$ the coordinate spanning the observation space (in our simplified scenario a portion of a plane) and express as

$$E(\underline{r}) = \sum_{n=1}^{N} I_n \Phi_n(\underline{r}) \tag{1}$$

the component of interest of the total field arising in the treated region when the source is a N-elements arbitrary (fixed-geometry) array. In Eq. (1), $\Phi_n(\underline{r})$ represents the corresponding component of the total field arising in the scenario at hand when only the n-th antenna is fed (by a unitary excitation) and I_n is the actual complex excitation of the n-th antenna.

[†] Note that even in cases where the target region is larger, it may be anyway convenient to focus the field at the center of the region.

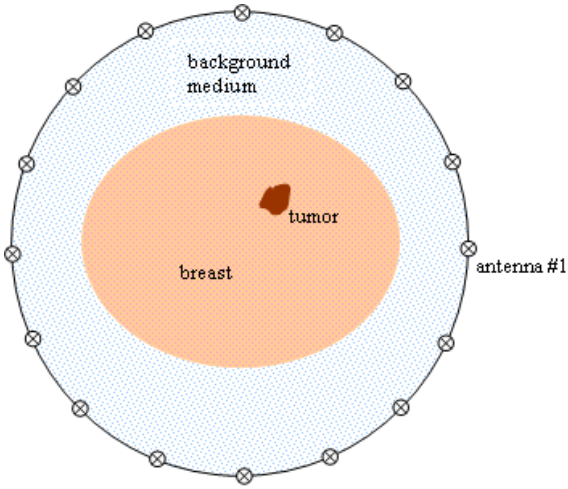

Figure 1. The considered 2D field-focusing problem. The applicator consists of a circular array of (infinitely extended) filamentary currents numbered in counterclockwise order. The breast and the antennas are immersed in a background medium.

The synthesis procedure requires that a suitable number of antennas is exploited. In particular, by taking into account the finite dimensional nature of electromagnetic fields, it is possible to show that the required number of antennas is related to the radius a of the minimum circle covering the "target" (in our case, the breast) and is given by $N \approx 2\beta a$, β being the wavenumber in the medium where the antennas are hosted [27, 28].

The optimal focusing of scalar fields for hyperthermia cancer therapies can be then stated as follows:

$$\text{maximize} \quad |E(\underline{r}_{tumour})|^2, \tag{2}$$

while

$$|E(\underline{r})|^2 \leq UB(\underline{r}) \quad \underline{r} \in \Omega, \tag{3}$$

wherein $\underline{r}_{tumor}$ denotes the tumor location, $UB(\underline{r})$ is a non-negative function corresponding to field amplitudes not-inducing injurious temperature increases into healthy tissues and Ω represents the region wherein cancer inclusions are not present.

Following [21, 22], it is possible to find globally optimal solutions to such a "power pattern" synthesis problem in a simple manner and with little computational effort.

In fact the phase reference in the direction $\underline{r}_{tumor}$ is a degree of freedom. Then, without any lack of generality, a convenient choice is to assume that the field in this direction is purely real, so that the optimization task (2) can be recast as the maximization of the real part of the field. Accordingly, the problem can be now formulated as the determination of the real and imaginary parts of the excitation coefficients $\Re(I_n)$, $\Im(I_n)$ $(n = 1, \ldots, N)$ such that:

$$\Psi(\underline{I}) = -\Re[E(\underline{r}_{tumor})] \quad \text{is minimum,} \tag{4}$$

subject to:

$$\Im[E(\underline{r}_{tumor})] = 0, \tag{5}$$

$$|E(\underline{r}_t)|^2 \leq UB(\underline{r}_t) \quad \forall t = 1, 2, \ldots, T, \tag{6}$$

wherein $\underline{I} = I_1, \ldots, I_N$ is the vector of the excitation coefficients and $\underline{r}_1, \ldots, \underline{r}_T$ is a suitable discretization of the domain Ω. Notably, as conductivity and density of the different organs are known, a proper choice of the UB function allows to deal with constraints on the SAR, which are definitely the actual constraints of interest.

As a crucial circumstance, the generic $|E(\underline{r}_t)|^2$, $(t = 1, \ldots, T)$ is a positive semidefinite quadratic form (as a function of the elements excitations), so that it can be shown that the constraints (6) define a *convex set* in the space of the unknowns [21]. Moreover, constraint (5) is linear in terms of the excitations, so that it also defines a *convex set* in the space of the unknowns. As the intersection of convex sets is still convex, constraints (5), (6) define a convex set. Finally, in (4) $\Re[E(\underline{r}_{tumor})]$ is a linear function of the real and imaginary parts of the excitation coefficients, so that the whole problem can be formulated as the minimization of a linear function in a convex set, i.e., a CP problem [18], and can be solved in a globally optimal fashion without recurring to global optimization techniques.

3. NUMERICAL ASSESSMENT IN BREAST TUMOR TREATMENT

Breast tumor is one of the most common form of cancer in women. While prevention through early diagnosis is understood as the main way to defeat this disease, the development of effective and accurate treatments is crucial as well. Also due to the fact that the development of diagnostic set-ups for breast cancer is presently a very relevant research argument in electromagnetics, and that one can think of set-ups able to operate in both the diagnostics and therapeutic modes, in the following we test the interest and effectiveness of the proposed approach in a set of numerical simulations concerned with

the problem of focusing the field onto a tumor located in the breast. In particular, in order to ensure both the electromagnetic and the anatomic reliability of the considered simulations, we have taken advantage of the numerical phantoms provided by the researchers at Wisconsin University [26]. These phantoms have been obtained from 3D MRI images of breast converted into images of dielectric permittivity and electric conductivity by adopting suitable dispersion models, based on Debye and Cole-Cole models whose parameters have been assessed through extensive measurement campaigns [24, 25].

As we are considering a simplified 2D scenario, the phantom herein exploited has been obtained by extracting a slice from the 3D original phantom. Then, since the available images are related to healthy patients, a circular inclusion having the features of a tumor has been artificially inserted in the model. In particular, a tumor of 4 mm radius displaced in two different positions (close to the breast surface and in the fibroglandular region) have been considered, see Figure 2. It is worth to note that the performances of the method depend on the size of area onto which the beam has to be focused, so that they are expected to improve when larger tumors are dealt with. As such, this example, which is representative of an ablation therapy as applied to a tumor detected in its early stage, can be considered as a kind of *worst-case* study.

The applicator is a circular array of radius of 20 cm and the breast is positioned at the center of the reference system. The synthesis procedure has been carried out at two frequencies, 2 GHz and 2.25 GHz. In order to improve the penetration of the wave in the breast, as well as possibly achieve a better focusing, the breast and the overall scenario including the sources are immersed into a matching liquid. Such a medium, which also may help in keeping the temperature of the skin and of the non tumoral region in the prescribed limits, is chosen by exploiting the criteria given in [29] and taking into account that, the size of the region to be focused must be not smaller than $\lambda/4$, where λ is the wavelength in the host medium, in order to avoid *superdirective* sources [30] or poor focusing. By trading off the different requirements, the relative permittivity of the background medium (i.e., the matching liquid) has been fixed equal to 36. Since a feasibility assessment is our aim, we have assumed that the medium is lossless. Although this is certainly not exactly achievable in actual situations, it is worth to note that similar features can be indeed realized by means of suitable mixtures [31]. Once the background medium is fixed, we exploit the results recalled in Section 2 to fix the number of sources. Considering $a = 6.3$ cm, it follows that a suitable number of antennas at both 2 GHz and 2.25 GHz is $N \approx 30$. Note that such a number depends on

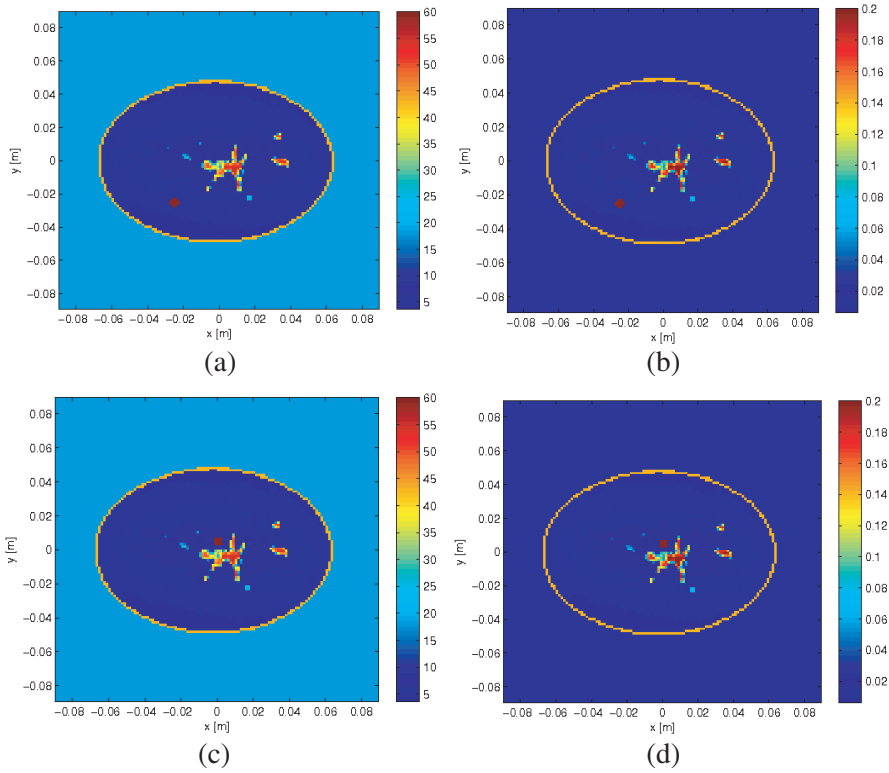

Figure 2. Spatial distribution of the electromagnetic parameters of 2D phantoms considered for the feasibility assessment. Top row: superficial breast tumor (a) permittivity, (b) conductivity. Bottom row: fibroglandular breast tumor (c) permittivity, (d) conductivity.

the electromagnetic features of the medium, as it would become lower if a medium with a lower permittivity is considered. On the other hand, according to the above discussion, this choice would worsen the performance of the approach in terms of spatial selectivity.

To obtain the total electromagnetic fields needed in the synthesis procedure, see Eq. (1), the electromagnetic scenario described above has been simulated using a full-wave method of moments (MoM) forward solver. According to the usual discretization criterion for MoM approaches [32], the suitable size of the cell is $\approx \lambda_{\min}/10$, wherein $\lambda_{\min}$ is the wavelength with respect to the maximum value of permittivity in the scenario. In our numerical simulations, we have considered a 128×128 grid, which is large enough to ensure the fulfillment of the criterion at all the considered frequencies. It is worth to note that the MRI images are given on a much finer grid, which is indeed redundant

as far as the electromagnetic simulation is concerned. Therefore, we have down-sampled the MRI images to obtain the permittivity and conductivity maps onto the 128×128 grid and avoid useless computational overhead.

While in actual clinical applications the upper bound mask UB has to be fixed on the basis of the specific properties of tissues and on the planned treatment [33], in the following, the upper bound mask UB is fixed in a rather simple fashion (which however again corresponds to a *worst-case* analysis. In particular, a constant value (which may be thought as determined from the worst case SAR constraint) is used for UB for regions other than tumors, while an arbitrary large level (i.e., no constraints) is allowed for the tumoral region and outside the breast (wherein some thermal refrigeration is possible). As the internal fields linearly depend on the excitations of the different antennas, fields will just be a scaled version of the present one when modifying the constant value of UB.

As a first example, let us consider the case of a tumor located close to the breast surface, which is simpler to handle in view of the lower penetration required and the lower selectivity which is needed (because of the difference existing among the conductivity properties of the tumor and those of the surrounding fat tissue). The results of the proposed constrained focusing procedure at the two considered frequencies are given in Figures 3(a), (b), where we have reported the SAR distribution resulting from the synthesized field. The SAR has been computed according to the formula [23]:

$$SAR = \frac{1}{2}\frac{\sigma}{\rho}|E|^2, \tag{7}$$

wherein σ and ρ denote the tissue's conductivity and density, respectively. The adopted values of density are those reported in [20], which are recalled for the reader's convenience in Table 1.

From these results, one can appraise the capability of the procedure of concentrating (at each frequency) the field's energy into the target area. Moreover, one can notice the increase of the maximum value of SAR in the tumor with the frequency, which is related to the increase of tumor conductivity with frequency (see [25]

Table 1. Density of breast, tumor [20] and background medium [kg/m^3].

mammary tissue	skin	tumor	background
1069	1085	1182	1000

for details), as well as to the fact that the target region is larger with respect to wavelength. Then, an obvious idea suggests that the procedure effectiveness can be enhanced by exploiting multi-frequency source excitations. Accordingly, we have simulated an applicator of this kind by adding the specific absorbed powers of the synthesized fields, to achieve the overall SAR distribution shown in Figure 3(c), which improves significantly that obtained through the single frequency experiments. Of course, consideration of more frequencies would further improve the results, but would also entail an increase in the applicator's complexity. Finally, the amplitude and the phase of the synthesized excitation coefficients are shown in Figures 4(a), (b), respectively.

The second example is concerned with the case of a tumor located

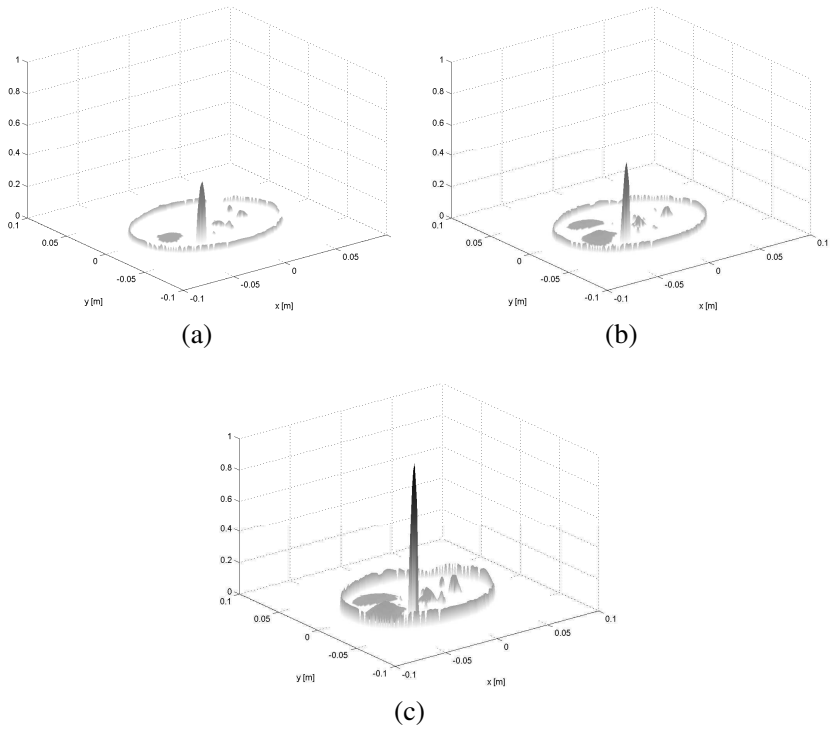

Figure 3. SAR distribution achieved with the adopted optimal focusing method, the case of a 8 mm tumor located close to the surface of a high-fat-content breast. (a) 2 GHz; (b) 2.25 GHz; (c) multifrequency source excitations.

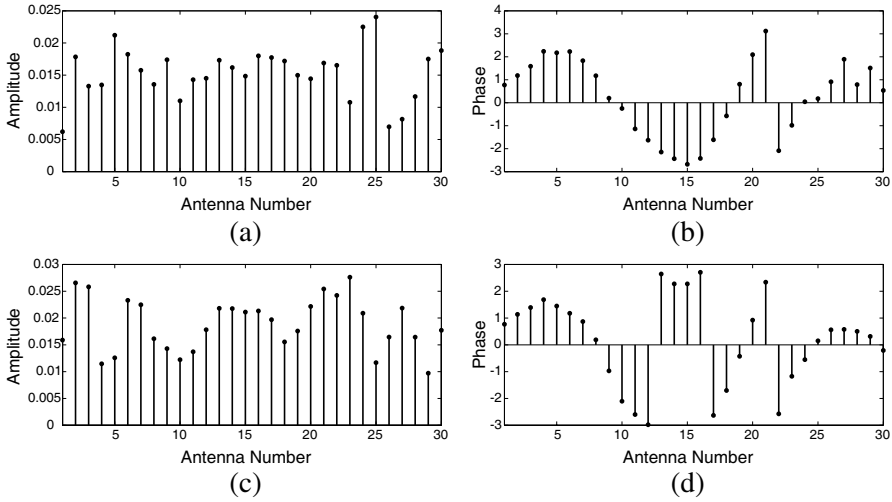

Figure 4. Excitation coefficients synthesized via the proposed focusing method for a 8 mm tumor located close to the surface of a high-fat-content breast. 2 GHz: (a) Amplitude, (b) Phase; 2.25 GHz: (c) Amplitude, (d) Phase.

close to the breast duct and thus more in depth. As such, the focusing task is expected to be more difficult to be pursue. In addition, the required selectivity is also harder, as the electromagnetic properties of the tumor and of the duct are similar. The SAR distributions at the considered frequencies are shown in Figures 5(a), (b), which, as compared to the previous case, confirm the effect of the tighter constraints onto the procedure effectiveness. As a matter of fact, a (slightly) larger value of SAR is observed in the fibroglandular tissue surrounding the tumor, as well as in the skin layer. On the other hand, the increase with the frequency of the maximum SAR in the tumor is still observed, so that one can still take advantage of multi-frequency sources. The result achieved in this way is given in Figure 5(c), which shows that even in this case a satisfying focusing can be achieved. The amplitude and the phase of the synthesized excitation coefficients are reported in Figures 6(a), (b), respectively.

It is worth to note that the computational time needed to achieve the optimal distribution of the excitation coefficients is about 10 minutes on a standard laptop. Taking into account the quite large number of antennas, this is indeed an effective performance, as expected. On the other hand, the observed results, although satisfactory in terms of SAR, do not fully assess the safety and effectiveness of the proposed procedure, as a thermal analysis would

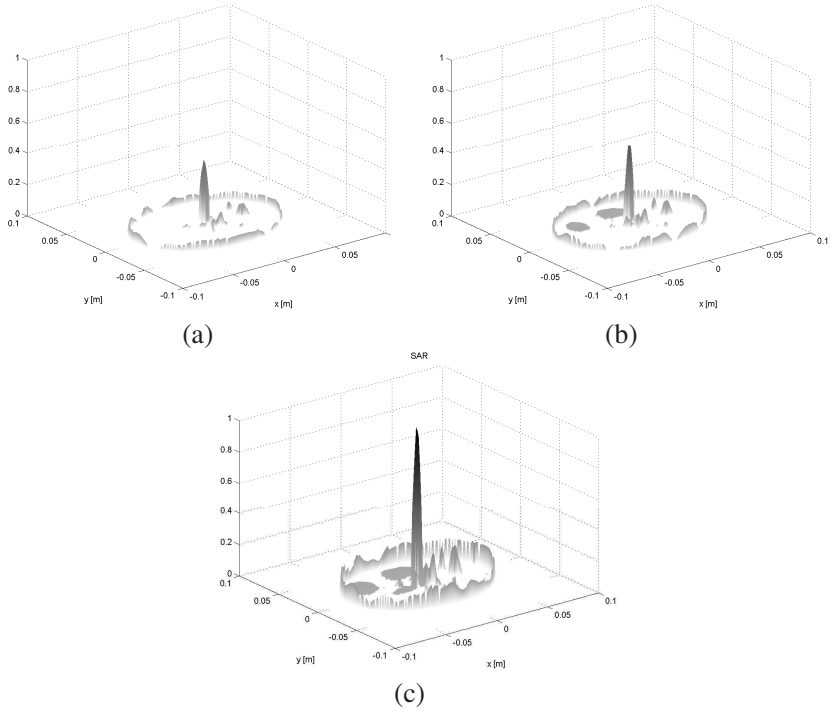

Figure 5. SAR distribution achieved with the adopted optimal focusing method, the case of a 8 mm tumor located in the fibroglandular region of a high-fat-content breast. (a) 2 GHz; (b) 2.25 GHz; (c) multifrequency source excitations.

be needed for a complete assessment. Nevertheless, the capability of ensuring in a deterministic fashion the achievement of a constrained focused field, as well as the possibility to eventually change (during the treatment) both the target region and the 'sidelobe' bounds allows to be optimistic about ultimate performances and therapeutic effectiveness.

In conclusion, it is also worth to remark that the operating conditions of the considered applicator (in terms of number of antennas, working frequency, matching fluid and so on) are also suitable to obtain a quantitative characterization of the breast via inverse scattering procedures [29], thus suggesting its dual (diagnostic and therapeutic) exploitation. In this respect, it is also worth mentioning the possibility of monitoring via inverse scattering the permittivity variation with temperature which was devised in some pioneering papers by Bolomey and co-workers [34, 35]. As a

matter of fact, would such a variation occur during treatment, the aforementioned reconstruction capability [29] and the fast nature of the proposed procedure suggest the interesting chance of an on-line reconstruction of the permittivity during treatment and a subsequent adaptive focusing.

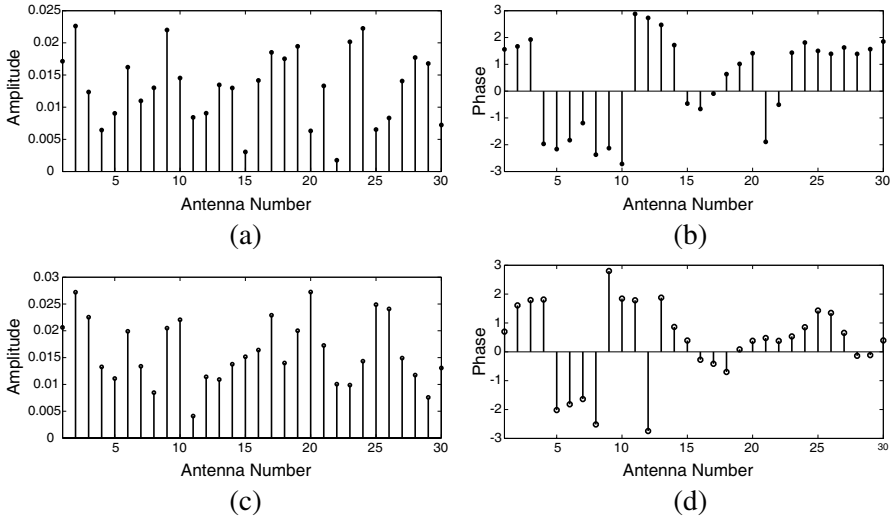

Figure 6. Excitation coefficients synthesized via the proposed focusing method for a 8 mm tumor located in the fibroglandular region of a high-fat-content breast. 2 GHz: (a) Amplitude, (b) Phase; 2.25 GHz: (c) Amplitude, (d) Phase.

4. CONCLUSIONS

In this paper, we have proposed a novel method to tackle the problem of focusing the electromagnetic field in hyperthermia applications. In particular, an approach based on an optimal constrained focusing method (which does not require global optimization tools) has been applied and its feasibility assessed through a numerical study in the case of breast cancer. Although such a study is based on a simple 2D scenario, it deals with realistic biological models, so that its promising results suggest to further proceed with the study.

The first future efforts will be devoted at extending the methodology to the actual 3D scenario. In this case, wherein a different kind of set up (such as for instance a cylindrical array) than the one herein considered has to be exploited, one can take advantage of the specific behavior of the adopted sources, which may give raise to a field having a dominant component with respect to the other ones.

Should this not be the case, one can still exploit the theory considered in this paper by solving three different focusing problems (one for each component) and then combine the results or use them as a starting information for solving a new focusing problem where the non convex optimization problem amounts to maximize the power density. Finally, a more general strategy would exploit a multi-criteria optimization framework [36], wherein the functions to be contemporarily optimized are the three field components. In such a framework, wherein optimal Pareto surfaces can be derived, the fact that each single problem can be reduced to a CP problem will be of help.

The issue of tissue's variability [37], as well as the study of the thermal effects of the synthesized fild will also be considered. While such analyses will make it possible to assess (but for a necessary clinical study) which is the field amplitude suitable for the treatment, the feasibility study herein reported suggests some considerations on the implications of the treatment. As a matter of fact, observing the examples, one can notice how SAR is mostly deposed in the tumor (as desired) and on the skin layer (owing to its conductivity). As such, one can argue that particular attention will be needed to control (possibly through cooling techniques) the temperature at the breast surface. In this respect, it is also worth noting that the computational effectiveness of the proposed approach can allow a rapid reconfiguration, if needed, of both the points to be focused and the constraints to be considered.

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