The potential of constrained SAR focusing for hyperthermia treatment planning: analysis for the head & neck region

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Keywords: treatment planning, constrained optimization, convex programming, SAR

Abstract

Clinical trials have shown that hyperthermia is a potent adjuvant to conventional cancer treatments, but the temperatures currently achieved in the clinic are still suboptimal. Hyperthermia treatment planning simulations have potential to improve the heating profile of phased-array applicators. An important open challenge is the development of an effective optimization procedure that enables uniform heating of the target region while keeping temperature below a threshold in healthy tissues. In this work, we analyzed the effectiveness and efficiency of a recently proposed optimization approach, i.e. focusing via constrained power optimization (FOCO), using 3D simulations of twelve clinical patient specific models. FOCO performance was compared against a clinically used particle swarm based optimization approach. Evaluation metrics were target coverage at the 25% iso-SAR level, target hotspot quotient, median target temperature (T50) and computational requirements. Our results show that, on average, constrained power focusing performs slightly better than the clinical benchmark (ΔT50 = +0.05 °C), but outperforms this clinical benchmark for large target volumes (>40 cm³, ΔT50 = +0.39 °C). In addition, the results are achieved in a shorter time (~44%) and are repeatable because the approach is formulated as a convex optimization problem.

1. Introduction

During hyperthermia cancer treatments, the tumor temperature is elevated to a supra-physiologic temperature (40–44 °C) for 60–90 min. Clinical trials have demonstrated the therapeutic benefit of this treatment in combination with radio- and chemo-therapy (Franckena et al 2008, Cihoric et al 2015, Datta et al 2016, Issels et al 2016). Still, given the thermal dose-effect relations found in literature (Sherar et al 1997, Franckena et al 2008), increase of the temperature would further enhance this clinical effectiveness. Accurate pre-treatment optimization and real-time adaptations of the administered heating may be crucial steps for further progress and widespread clinical adoption of hyperthermia (Paulides et al 2016). Especially for challenging anatomical sites such as the head & neck (H&N) region (Paulides et al 2016) and in absence of real-time feedback control (Wust et al 2002, Stauffer 2005), maximization of the heating by phased array applicators relies on optimization of treatment settings in pre-treatment planning. Hyperthermia treatment planning (HTP) involves obtaining the optimal complex excitation coefficients of the signals feeding the applicator. The objective of this procedure is to induce a homogeneous temperature over a given target area, while avoiding high temperatures, i.e. ‘hot-spots’, in healthy tissues. Herefor, treatment quality surrogates based on the predicted specific absorption rate (SAR) and temperature distribution have been defined, and are being used to obtain the desired target conformal temperature increase (Paulides et al 2013, 2016).

Whether the SAR or temperature distribution should be optimized is still a topic of debate amongst hyperthermia researchers (Paulides et al 2013). Optimizing the temperature distribution would seem the most natural approach, since increasing temperature is of course the ultimate goal of a hyperthermia treatment (Kok et al...
However, although thermal optimization intuitively relates best to measured temperatures, a systematic study to assess the actual relation between the predicted temperature and the clinical outcomes is to the best of our knowledge not available yet. For SAR, a study by Lee et al (1998) demonstrated that a relation exists between SAR coverage indicators and clinical outcome of the hyperthermia treatments. In addition, temperature based optimization generally exploits global optimizers, which are affected by high computational cost, problem-specific parameters tuning and applicable only to limited-size problems, since optimization complexity rises exponentially with the number of unknowns (i.e. number of antennas) (Wolpert and Macready 1997). Since computation time is not unlimited and parameter tuning might be different for each clinical scenario, global optimizers may in practice not always deliver the optimal solution. While some efficient approaches have been proposed in the literature (Köhler et al 2001, Seebass et al 2001, Gellermann et al 2006), performances cannot be guaranteed for all possible cases. Here, Canters et al (2013) showed that, for the case of deep pelvic hyperthermia, the benefit of directly optimizing the temperature pattern is lost under the very large uncertainties of thermal modeling. Moreover, note that the more accurate thermal dependent model (Song 1984) further strongly impacts the overall computational burden. On the other side, SAR is directly related to the complex excitation coefficients via the Maxwell equations. Also, provided the model is adequate, SAR is principally correctly calculated by a planning system which is, on the other side, not the case for the temperature distribution because of the assumptions in thermal modelling, as outlined in this paper. Further, SAR can be experimentally validated within a QA procedure. Hence, SAR performance of a hyperthermia system can be computationally and metrologically controlled (Paulides et al 2016). However, while results in contrast with the one in Canters et al (2009) were found by De Greef et al (2010) and (2011), from a theoretical point of view, optimizing the SAR pattern is, in principle, faster than temperature optimization, since it does not imply solving the bio-heat equation as well.

Besides the attractive features recalled above, many SAR based optimization approaches have been proposed in the literature. Among the others, a relatively recently proposed approach is the so-called focusing via constrained power optimization (FOCO). FOCO is formulated such that it focuses the power deposition onto a target location ‘properly’ set within the target volume, while constraining it to predisposed levels in the healthy tissues to prevent treatment limiting hot spots. From the physical point of view, FOCO pursues the focusing of the electromagnetic field pattern, and consequently it could in principle allow an accurate control of the SAR distribution by exploiting the additional degree of freedom on the control point selection. FOCO is formulated in terms a convex programming problem so that it is effective and relatively insensitive to reconstruction and parameter uncertainties (both thermal and electromagnetic) as shown in Iero et al (2013a, 2013b), (2014) and Bellizzi et al (2018). FOCO can effectively solve the required multi-objective problem is expected to be faster than temperature optimizers and other global search algorithms. Moreover, it ensures the global optimality of the solution regardless of problem size (i.e. number of unknowns/antennas) or parameters tuning, as global search algorithms are circumvented (Cappiello et al 2017). In addition, through constrained (convex) optimization, FOCO allows controlling the occurrence of hot-spots, which is impossible with time-reversal (Tanter et al 2001, Takook et al 2017) or beam-forming (Zastrow et al 2011) methods. However, the performance of FOCO in a realistic clinical scenario is unknown.

In this work, we assessed the capabilities of FOCO in a very challenging clinical scenario: HTP for patients with H&N cancer treated with the HYPERcollar3D (Togni et al 2013). This scenario presents a very good case for assessment of the benefit of FOCO since: target conformal heating is possible and therefore HTP is pivotal and routinely used (Paulides et al 2016) and temperature simulations have been extensively validated and a dedicated set of tissue properties are available (Verhaart et al 2015). Therefore, this scenario is highly suited for testing FOCO in terms of predicted treatment quality (SAR and temperature) and computational costs. For benchmarking, we used the clinic adopted optimization routine, as presented in Rijnen et al (2013). This approach is aimed at maximizing the separation between the average SAR induced in the target volume and the highest SAR in normal tissue. This optimization problem is non-convex and a global optimization algorithm is required. However, it has a proven robustness to thermal tissue properties (Canters et al 2013) and a strong relation with the predicted temperature (Canters et al 2009).

2. Materials & methods

In this section we summarize the two approaches we compare (sections 2.1 and 2.2, respectively) and illustrate the evaluation setup and data set (section 2.3).

2.1. Hyperthermia treatment planning in VEDO

Patient specific 3D models and simulation results were obtained using the clinical HTP procedure. Hereto, computerized tomography (CT) scans were segmented into various tissues using an atlas based auto segmentation routine followed by a manual adjustment in software tool iSeg (v.3.8 Zurich Medtech, Zurich, Switzerland) (Fortunati et al 2013). This patient specific model, together with the applicator model, were
imported into Sim4Life (v.3.4 Zurich MedTech AG, Zurich, Switzerland). For each antenna, the total field was computed when excited using a 1 V sinusoidal signal at the operating frequency of 434 MHz. The SAR pattern is optimized using the in-house developed visualization tool for electromagnetic dosimetry and optimization, i.e. VEDO (Rijnen et al 2013), which also provides visualization and statistics of the SAR patterns.

The optimization strategy implemented in VEDO is based on the notion that planning in hyperthermia treatment is a multi-objective optimization problem with a twofold aim: (1) maximizing the SAR within the target volume (TV) and (2) minimizing the SAR in hotspots. Starting from this consideration, the cost function is the so-called target to hotspot SAR quotient (THQ), expressed as:

\[
\text{THQ} = \frac{\langle \text{SAR} \rangle_{\text{HTV}}}{\langle \text{SAR} \rangle_{\text{HS}}} \tag{1}
\]

THQ is defined as the ratio between the mean SAR in the target area (\(\langle \text{SAR} \rangle_{\text{HTV}}\)) and the average SAR in hotspots (\(\langle \text{SAR} \rangle_{\text{HS}}\)) defined as the 1% volume of healthy tissue volume with the highest SAR occurs (Rijnen et al 2013). This optimization problem is non-convex so it is tackled by a global optimizer. Hereto, the well-known particle swarm optimization (PSO) (Chen 2016), with settings customized to the specific case is used (Cappiello et al 2017).

2.2. Focusing via constrained power optimization

The FOCO approach is inserted in the optimization routine as follows. Considering \(x \in \Omega\) a generic point of the 3D region of interest, say \(\Omega\), the SAR can be expressed as:

\[
\text{SAR}(x) = \frac{\sigma(x) |E(x)|^2}{2 \rho(x)} \tag{2}
\]

Where \(\sigma\) is the conductivity (S m\(^{-1}\)), \(\rho\) is the mass density (kg m\(^{-1}\)) and \(|E(x)|^2\) is the squared amplitude of the total electric field generated by the ‘weighted’ N monochromatic sources surrounding \(\Omega\).

Assuming \(\Phi_n = \Phi_{x,n} i_x + \Phi_{y,n} i_y + \Phi_{z,n} i_z\) the total electric field induced by the unitary excited \(n\text{th}\) antenna in \(\Omega\) when all the other antennas are off, the overall electric field, i.e. \(E = E_x i_x + E_y i_y + E_z i_z\), in a generic point in the domain of interest can be expressed as:

\[
E(x) = \sum_{n=1}^{N} I_n \Phi_n(x) \tag{3}
\]

where \(I_n(n = 1, 2, ..., N)\) represent the complex excitation coefficients of the signals fed into the antenna array.

Considering a target point properly set within the target area, say \(r \in \Omega\), the constrained focusing problem can be generically stated as:

Determine the set of the array’s complex excitations coefficients such to maximize the squared amplitude of the field in the target point, i.e. \(|E(r)|^2\), while enforcing arbitrary upper bounds in the rest of the domain of interest.

This maximization problem is non-linear and belongs to the class of NP-hard problems (Wolpert and Macready 1997), since the considered cost functional \(|E(r)|^2\) is a non-negative quadratic polynomial with respect to the unknowns \(I_n\). As such, the global optimality of the solution is not ensured and global optimization procedures are needed.

On the other hand, when one of the field components, \(E_i(r)\), can be considered to be dominant above the other ones, FOCO circumvents the above difficulty by exploiting the degree of freedom on the field phase reference, assuming that the field in the target point is real (Isernia and Panariello 1998, Iero et al 2014).

Under such a circumstance, the problem can then be stated as:

Find \(I_n(n = 1, ..., N)\) such to:

\[
\max \{ \Re \{ E_i(r) \} \} \tag{4a}
\]

subject to:

\[
\Im \{ E_i(r) \} = 0 \tag{4b}
\]

\[
|E(x)|^2 \leq \mathcal{M}(r) \quad x \in \Omega \setminus \Pi(r) \tag{4c}
\]

where \(\Re \{ \cdot \}, \Im \{ \cdot \}\) and \(\Pi(r)\) represent the real part, the imaginary part and the target volume, respectively.

As constraints (4b) and (4c) define a convex set of unknowns (Isernia and Panariello 1998), and considering that cost function (4a) is a linear function of the unknowns, the overall constrained focusing problem can be now conveniently cast as a convex programming problem. As such, the globally optimal solution can be efficiently determined via local optimization procedures.
2.3. Mask function & target point

The ‘mask’ function, i.e. \( M.F(\mathbf{r}) \), is a non-negative arbitrary function that allows enforcing patient-specific constraints on the power deposition outside the chosen target area. Higher weights can be applied to tissues exhibiting higher power losses to counteract undesired heating.

The target area \( \Pi_{FOCO} \) is defined as a non-isotropic volume expansion of the so-called hyperthermia target volume (HTV) which, following radiotherapy, generally corresponds to the clinical target volume (CTV) (Bur-nett et al 2004). Figure 1 schematically shows how \( \Pi_{FOCO} \) was defined. Starting from the CTV delineation, the margins used by \( \Pi_{FOCO} \) include the volume of a minimum focussing sphere, which we define as a ‘resolution sphere’ (RS). Considering the physical limitation of the focusing capability of any phased array applicator in tissue, as theoretically and experimentally shown in Bucci et al (1998), Paulides et al (2005), this RS is a sphere with a diameter of \( \approx \frac{\lambda_m}{3} \), being \( \lambda_m \) the wavelength in a medium with average dielectric tissue properties. The RS is centered at the HTV centre of mass, i.e. the ‘target point’ \( (\mathbf{r}_t) \).

Note that \( \Pi_{FOCO} \) is used only in the optimization phase. All distribution evaluations have been done using the HTV for a fair comparison.

2.4. Evaluation setup and dataset

The considered dataset consists of twelve 3D patient models generated during HTP for patients with H&N cancer that were planned for treatment with the HYPERcollar3D (Togni et al 2013). In total, twelve patient models were included, of which one was planned for treatment, but not treated due to insufficient TC25, and two patients were treated using a reduced HTV (table 2). The cases where specifically included to investigate if FOCO would not only improve the optimization of currently treated patients but also enable to expand the number of treated patients.

The HYPERcollar3D consists of a ring-shaped phased array of twenty patch antennas, equally divided over three rings, operating at 434 MHz. Using HTP, twelve out of the twenty antennas are selected, as only twelve amplifiers are available for the clinical treatment (Togni et al 2013). Note that the applicator design aims at constructive interference, so generally the \( z \)-component could be considered as dominant. A water bolus fills the space between the applicator and the patient to enhance electromagnetic coupling and to avoid undesired heating that may arise at the patients skin (Rijnen et al 2015).

The electromagnetic and thermal tissues parameters have been assigned after the segmentation procedure according to Verhaart et al (2015), as reported in table 1. Concerning the thermal analysis, the initial body temperature has been chosen according to the physiologic body temperature, i.e. approximately 37 °C. The water bolus boundary condition has been modelled as a mix of convective and Neumann boundary conditions with a heat transfer coefficient of 50 W m\(^{-2}\) kg°C\(^{-1}\) and a temperature of 37° whereas the internal air boundary condition has been modelled similarly with a heat transfer coefficient of 8 W m\(^{-2}\) kg°C\(^{-1}\) and a room temperature of 20° (Verhaart et al 2015). All simulations are run on a pc equipped with an Intel Core i7-3770 (3.4 GHz) CPU and 8 GB of RAM.

In this study, the planning results are ultimately evaluated using the temperature distribution, which is simulated using the Pennes bio-heat transfer equation (Pennes 1948). The temperature distribution was achieved by adjusting SAR to a maximum of 44 °C in normal tissue, i.e. outside the HTV.

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5 Considering this as the main axis of the body.
2.4.1. SAR evaluation metrics

The comparison carried out on the expected SAR distributions has been performed considering standard synthetic HTP parameters as reported in Canters et al. (2009), i.e. target coverage and THQ. The first indicates the coverage of SAR over the HTV, while the THQ provides an indication of hot-spots prominence relative to the average SAR in the HTV. Target coverage at 25% (TC25) was shown predictive for clinical outcome in superficial hyperthermia (Lee et al. 1998) and THQ was shown to highly correlate with simulated temperatures for deep hyperthermia in the pelvic region (Canters et al. 2009). As in this analysis THQ plays the role of a comparison parameter, the subscript PSO has been adopted for the clinical benchmark result.

Lastly, since optimization time is relevant in a real-time re-optimization scenario, also the computational time needed to determine the complex excitation coefficients has been monitored, and indicated as $t_{FOCO}$ and $t_{PSO}$.

2.4.2. Temperature evaluation metrics

The comparison has been conducted using the T50 prediction as standard hyperthermia treatment quality parameter, as it was shown to indicate a good outcome of a treatment (Canters et al. 2009). T50 is defined as the iso-temperature volume that covers at least 50% of the HTV when the maximum temperature reached in healthy tissues is $44 \, ^\circ C$. Similar to the SAR distribution analysis, the subscripts FOCO and PSO have been adopted to identify the two techniques.

3. Results

As an initial verification step, the Dice similarity coefficient (Dice 1945) between $H_{FOCO}$ and HTV was evaluated, obtaining a value of, i.e. $\approx 1$, which demonstrates their excellent overlap.

Tables 2 and 3 report TC25, THQ, T50 and computational time, as well as patient details including target volume size. The target volumes ranged from 19.1 to 287.1 cm$^3$. As expected, THQ for FOCO is on average $\approx 20\%$ lower than THQ_{PSO}, THQ is the optimization parameter in the clinical PSO-based strategy. Conversely, on average, target coverage and T50 were found to be approximately equal, with a slight improvement with FOCO, since $\Delta TC25$ was $3\%$ greater and $\Delta T50$ increased by $0.05 \, ^\circ C$. Moreover, the computational time required by FOCO was $0.36 \pm 0.14$ min, which is $44\%$ lower than $(0.61 \pm 0.53$ min).

Figure 2 depicts the normalized SAR distribution and the inherent temperature distribution obtained by means of FOCO and THQ PSO optimized for patient IDs A and N. This figure shows that the optimization results for FOCO and THQ PSO are indeed very similar in small tumours, but differs greatly in large tumours. Specifically, FOCO provides a much higher SAR coverage in large target volumes, while reducing SAR in normal tissue. Table 2 shows that FOCO indeed performs much better for these patients, i.e. $\Delta TC25 = +5\%$ and $\Delta T50 = +0.39 \, ^\circ C$ on average for patients A-C, N and M. Note that the target volumes of this group are all larger than $40 \, cm^3$, with an average volume size of $145.4 \pm 111.6 \, cm^3$. 

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Table 1. Electromagnetic and thermal tissue parameters at 434 MHz accordingly to Verhaart et al (2015).

|                | $\epsilon_r$ | $\sigma$ (S m$^{-1}$) | $\rho$ (kg m$^{-3}$) | $c$ (J kg$^{-1}$ $^\circ C^{-1}$) | $k$ (W m$^{-1}$ $^\circ C^{-1}$) | $Q$ (W kg$^{-1}$) | $\omega$ (ml min$^{-1}$ kg$^{-1}$) |
|----------------|--------------|-------------------|---------------------|---------------------------------|---------------------------------|-----------------|----------------------------------|
| Internal air   | 1.0          | 0.0               | 1.2                 | —                               | —                               | —               | —                                |
| Lung           | 23.6         | 0.38              | 284                 | —                               | —                               | —               | —                                |
| Muscle         | 56.9         | 0.81              | 1090                | 3421                            | 0.40                            | 0.96            | 442.8                            |
| Fat            | 11.6         | 0.08              | 911                 | 2348                            | 0.50                            | 0.51            | 255.0                            |
| Bone           | 13.1         | 0.09              | 1908                | 1313                            | 0.32                            | 0.15            | 10.0                             |
| Cerebrum       | 56.8         | 0.75              | 1045                | 3696                            | 0.55                            | 15.5            | 763.3                            |
| Cerebellum     | 55.1         | 1.05              | 1045                | 3635                            | 0.51                            | 15.7            | 770.0                            |
| Brain stem     | 41.7         | 0.45              | 1046                | 3630                            | 0.51                            | 11.4            | 5586                             |
| Myelam         | 35.0         | 0.46              | 1075                | 3630                            | 0.51                            | 2.48            | 160.3                            |
| Sclera         | 57.4         | 1.01              | 1032                | 4200                            | 0.58                            | 5.89            | 380.0                            |
| Lens           | 37.3         | 0.38              | 1076                | 3133                            | 0.43                            | —               | —                                |
| Vitreous humor | 69.0         | 1.53              | 1005                | 4047                            | 0.59                            | —               | —                                |
| Optical nerve  | 35.0         | 0.46              | 1075                | 3613                            | 0.49                            | 2.48            | 160.3                            |
| Cartilage      | 45.1         | 0.60              | 1100                | 3568                            | 0.49                            | 0.54            | 35.0                             |
| Thyroid        | 61.3         | 0.89              | 1050                | 3609                            | 0.52                            | 87.1            | 5624.3                           |
| Tumor          | 59.0         | 0.89              | 1050                | 3950                            | 1.5                             | —               | 848.0                            |
Figure 3 depicts the SAR and temperature comparison parameters for PSO and FOCO. PSO was better in terms of THQ and the metrics were equal in terms of TC25. In this figure, green circles have been added to mark the large TV cases.

4. Discussion

4.1. Evaluation of the results

In this study, we have demonstrated the clinical capabilities of FOCO, a recently proposed method for hyperthermia treatment planning, based on constrained SAR optimization via convex programming. The assessment has been carried out in an actual clinical scenario and the outcomes compared to the clinically used benchmark, i.e. THQ PSO-optimized planning (Rijnen et al 2013). The results showed that, although FOCO overall performs comparably to the benchmark, there is a tendency to outperform this benchmark for target volumes above \( \approx 40 \text{ cm}^3 \) in terms of T50. In \( \approx 50\% \) of the analysed cases (i.e. patient D to L) a negligible average difference was found on TC25, corresponding to a \( \Delta T_C \) of \( 0.05 ^\circ C \) and to an average TV of \( 30 \pm 9 \text{ cm}^3 \). In the remaining cases, related to a bigger average TVs of approximately \( 145.4 \pm 111.6 \text{ cm}^3 \), a \( \Delta T_C \) equal to \( +5\% \) and a \( \Delta T_5 \) equal to \( +0.39 ^\circ C \) was found. This analysis suggests that similar performance can be achieved by the two planning approaches for the average target volume in all locally-advanced diseases, whereas FOCO delivers a higher average for the larger target volumes in this group compared to the THQ PSO optimized solution. On

| Patient ID | Tumor location | TV (cm³) | TC25 (%) PSO | THQ (—) PSO | T50 (°C) PSO | TC25 (%) FOCO | THQ (—) FOCO | T50 (°C) FOCO |
|------------|----------------|---------|--------------|-------------|--------------|--------------|-------------|--------------|
| A          | NNM            | 54.1    | 80 73        | 1.29 1.01   | 40.01 40.18  |              |             |              |
| B          | Oropharynx     | 239.4   | 72 78        | 0.94 0.99   | 40.01 40.41  |              |             |              |
| C          | Larynx         | 40.1    | 70 81        | 1.70 1.19   | 37.97 39.01  |              |             |              |
| D          | NNM            | 34.3    | 80 88        | 1.55 1.10   | 40.33 39.88  |              |             |              |
| E          | PG             | 36.6    | 98 98        | 0.89 0.91   | 40.71 41.46  |              |             |              |
| F          | Oropharynx     | 34.5    | 79 76        | 0.86 0.66   | 40.17 39.48  |              |             |              |
| G          | Oropharynx     | 28.0    | 100 100      | 1.27 1.21   | 40.77 40.47  |              |             |              |
| H          | Hypopharynx    | 43.4    | 97 98        | 1.54 1.38   | 41.43 41.03  |              |             |              |
| I          | Oropharynx     | 19.1    | 100 100      | 1.23 1.16   | 41.38 41.77  |              |             |              |
| L          | Oropharynx     | 21.8    | 98 94        | 1.10 0.88   | 42.17 41.39  |              |             |              |
| M          | Oropharynx     | 106.5   | 88 78        | 0.99 0.93   | 40.24 40.04  |              |             |              |
| Nb         | NNM            | 287.1   | 24 50        | 1.18 0.74   | 38.23 38.79  |              |             |              |

|               | mean         | 78.7 ± 89.7 | 82 ± 21 | 85 ± 15 | 1.21 ± 0.28 | 1.01 ± 0.21 | 40.28 ± 1.21 | 40.33 ± 0.96 |
| mean (TV > 40 cm³) | 145.4 ± 111.6 | 67 ± 25 | 72 ± 12 | 1.22 ± 0.30 | 0.97 ± 0.16 | 39.29 ± 1.10 | 39.64 ± 0.73 |

| Patient ID | PSO | FOCO |
|------------|-----|------|
| A          | 0.40 | 0.28 |
| B          | 0.49 | 0.41 |
| C          | 0.65 | 0.26 |
| D          | 0.30 | 0.40 |
| E          | 0.50 | 0.24 |
| F          | 0.42 | 0.33 |
| G          | 0.52 | 0.33 |
| H          | 0.43 | 0.25 |
| I          | 0.51 | 0.41 |
| L          | 0.49 | 0.38 |
| M          | 2.28 | 0.32 |
| Nb         | 0.39 | 0.77 |

|               | mean | 0.61 ± 0.53 | 0.36 ± 0.14 |

Table 2. Patient and treatment characteristics, i.e. tumor volume, location, TC25, THQ and T50 for the analyzed HTP approaches. The patient indicated with * was planned for treatment with the HYPERCollar3D, but not treated due to insufficient TC25. Patients indicated with b were treated using a reduced HTV, which was smaller than the radiotherapy treatment volume. NNM and PG stand for neck node metastasis and parotid gland, respectively.

Table 3. Computational times related to the analysis reported in table 2.
the other side, the discordant results found for patient D and M indicate that further investigations are needed to better evaluate the large target volume threshold.

In alignment with the study of Wust et al (1996), we found that performance of THQ based optimization is worse for larger and more complex HTVs. Notably, a crucial aspect of SAR optimization is the proper choice of the cost function, as the problem is multi-objective. In the case defocusing is needed, as required for a relatively small wavelength relative to the target region area, optimizing the THQ yields sub-optimal solutions, see figure 2. Interestingly, the possibility of achieving a tighter control on the spatial distribution of SAR, by properly positioning the target point exploited by the FOCO procedure, would allow to overcome such a limitation.

In the current study, we used SAR optimization and exploited temperature simulations for relative assessment of optimization performance. The reason for this approach is that current temperature simulations are prone to severe uncertainties due to uncertainties in tissue cooling parameters, which can vary in time, within tissues, between tissues and between patients. The impact of tissue cooling uncertainties for H&N hyperthermia are unknown. For deep pelvic hyperthermia, Canters et al (2009) have shown that large uncertainties of thermal properties negates the benefit of optimizing the temperature distribution. Also, Drizdal et al (2018) found large differences between predicted target coverage for different thermal tissue property models, but a strong correlation between the coverage derived from SAR and H&N specific constant tissue cooling base temperature predictions (Chen 2016), as also used in the current study. These results shed a different light on the ongoing debate on SAR or temperature optimization. They also stress the crucial importance of more research on the validation of thermal modelling and on the assessment of dynamic, temperature dependent, tissue cooling properties. In future, with increasing knowledge on temperature dependent and transient tissue cooling properties, temper-

Figure 2. Temperature and normalized SAR distribution related to case A on a sagittal view, and N on a coronal view obtained by means of THQ PSO optimized and FOCO.

Figure 3. SAR and temperature distribution performances comparison on TC25 (a) and THQ (b) and T50 (c). Note that the group of large targets contains untreated cases to analyze if FOCO would enable treating these patients. Large target volumes have been marked with additional green circles. Note, in (a) two cases are overlapped—see figure 1.
Evaluation of the method

In this work, we faced the common inability to define optimal treatment quality. In the clinic, thermal dose effect relations advocate the use of CEM43°CT90 (Thrall et al 2000) and/or T50 (Franckena et al 2009). In contrast to measurements, which are often from a limited number of locations, thermal modelling holds the advantage that techniques can be compared using the full 3D distribution. Unfortunately, thermal modelling is prone to severe thermal tissue property inaccuracies and hence temperature simulation accuracy is limited (Bruggmoser et al 2012). Current thermal modelling ignores the considerable impact of the temperature dependence of the tissue properties (Verhaart et al 2015), which can seriously hamper technology comparisons (Drizdal et al 2018). In this work, we analyzed both temperature (T50) and SAR (THQ, TC25) quantifiers. Power was increased in the temperature simulations until the maximum temperature in normal tissue reached 44 °C, to match the clinical procedure in patients are treated up to feedback by complaints. As such, we focussed our attention to relative differences rather than absolute values. Note that, for the particular case of H&N hyperthermia, Verhaart et al (2015) showed that T50 can be predicted with a median accuracy of 0.8 °C, even when ignoring thermoregulation. Hence, our simulations are expected to be sufficiently predictive since the tissue cooling values have been specifically optimized for the case at hand. By exploiting both SAR and temperature indicators, we assume that our analysis provides the optimal combination of relative metrics to compare optimization performance from a clinical point of view.

While FOCO delivers the globally optimal solution of its optimization functional, in practice THQFOCO values were lower than THQPSO. Of course, THQ represents the cost function in PSO in the current clinical procedure, whereas FOCO incorporates a different cost function. Hence, THQ would be a biased quantifier for comparisons between THQ PSO-optimized and FOCO. Moreover, looking at the relation between THQ and T50 in H&N hyperthermia, it is questionable whether higher THQ values are necessarily related to a higher performance in terms of T50. Our data is conflicting with Caners et al (2009), in which THQ was associated with a higher T50, since FOCO performed worse in terms of THQ but better in terms of T50. Consequently, the correlation between THQ (and alternative metrics) against simulated temperature parameters, extensively investigated for deep hyperthermia in Caners et al (2009), still need to be studied for the H&N region. In conclusion, while THQ unquestionably is a relevant optimization function and predictive for T50 (in deep pelvic hyperthermia), our investigation suggests that a work similar to the one in Caners et al (2009) needs to be carried out for the case at hand. Additionally, the conflicting results between the SAR and temperature metrics related to case A, depicted in figure 2, suggested a possible hybrid FOCO optimization procedure that exploit the fast SAR optimization with a mask function created on the basis of the temperature field hot-spots. Concerning the results of case A, it is possible to state that while FOCO is outperformed on TC25, this does not hold true on the temperature quantifier, T50.

Techniques comparison

From a computational point of view, FOCO is approximately 44% faster than THQ PSO. Since FOCO is cast as a convex programming problem, it does not exploit global optimizers that may suffer from larger computational times. In addition, global iterative optimizers may also suffer from sub-optimal solutions which, depending on the optimization space, could lead to a lower reproducibility. On the other side, FOCO is able to reduce computational time and ensure a less operator-dependent solution. From a clinical prospective, the improvement of the computational time goes towards the real-time adaptation of the administered heating, e.g. in case of patients complains. Moreover, in such a case an additional constraint on the sensitive area would be enforced. Assuming that the new constraints would not deliver an optimization result far from the previous one, FOCO can take profit from such a circumstance (using the first optimization solution as an improved initial guess) and further reducing computational time. The same approach is impossible using global optimizer.

Moreover, accordingly to the clinic practice, in the present work a voxel size equal to 5 × 5 × 5 mm has been adopted to keep the computational time of THQ PSO-optimized curbed. On the other side, FOCO would allow to increase the resolution (i.e. using a smaller voxel size) as well as an higher number of antennas at a limited increase of the computational time. Such a feature is of particular interest in magnetic resonance compatible applicators with PCB type antennas (Paulides et al 2017). In this case higher requirement in terms of resolution for the treatment planning are needed (Numan et al 2014). Here also the inevitable impact of electromagnetic and thermal uncertainty of tissue parameters on both FOCO and THQ PSO must be taken into account, to better

*6*Printed circuit board.
understand the combined impact. Finally, note that GPU\textsuperscript{2} implementation is feasible also for FOCO, and future plans are aimed at comparing optimization time improvement against THQ PSO.

Another improvement in FOCO could be the extension to all three components of the field. FOCO, indeed, is assuming that the axial component of the electric field was dominant above the others. Hence, even though the amplitude of the z-component was on average $3 \pm 0.8$ times greater than the x- and the y-component in the FOCO target point, FOCO performance versus PSO optimization could be improved when applied on three components of the field. This could, for example, affect the analysis of patients A and N, where the polarization may play a relevant role. Hence, we can conclude that further improvements could be achieved by exploiting the full vector nature of the field, determining the field intensity polarization in the target point leading to an improved power deposition distribution (iero \textit{et al} 2015).

5. Conclusion

In this work, we analyzed the recently proposed optimization approach FOCO in a clinical scenario, and benchmarked the results against the PSO approach used in the clinic (Rijken \textit{et al} 2013). The analysis has been conducted using 3D models generated for HTP of patients with H\&N cancer treated with the HYPERcollar3D (Togni \textit{et al} 2013). The results show that FOCO performs comparable to the clinical benchmark overall ($\Delta T_{50} = +0.05 \degree C$), but outperform the benchmark on average for target volumes above approximately $40 \text{ cm}^3$ ($\Delta T_{50} = +0.39 \degree C$). In addition, since FOCO is formulated as a convex optimization problem, the results are repeatable and achieved sensibly faster ($–44\%$).

Funding

This work has been supported by the Italian Ministry of Research under PRIN ‘Field and Temperature Shaping for Microwave Hyperthermia’ (FAT SAMMY), granted by COST Action MiMed TD1301 and supported by Sim4Life (Zurich MedTech AG, Switzerland).

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