ON THE OPTIMAL MATCHING MEDIUM AND THE WORKING FREQUENCY IN DEEP PELVIC HYPERTHERMIA

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***Abstract* -** A necessary step when designing electromagnetic-based medical devices is the choice of an optimal matching medium, standing between the patient and the phased array applicator, and the operating frequency. This is crucial to improve the efficiency both from a technical and clinical points of view. In this paper, we propose a new approach, based on the propagation theory, to support the selection of the matching medium properties and the working frequency in a robust way by accounting for patient body shape and properties variability. The case of adjuvant hyperthermia treatment administered to patient with tumors in the pelvic region has been used as a numerical assessment in both 2D and 3D patient specific models. For this case, the proposed approach suggests an optimal range of working frequencies (130MHz<f<500MHz) and of matching material properties (ε_b<20), wherein one can select the working conditions depending on the trade-off between penetration and focal spot dimensions as well as other specific requirements. Results have been compared to the working frequencies used by the commercial applicators and using demineralized water as matching material. In conclusion, this work assesses the proposed approach in its general-purpose mathematical formulation, thus, paving the way for its wide application.

***Keywords* —Electromagnetic Propagation Theory; Matching Material; Medical Device; Microwave Hyperthermia; Transmission Line Theory.**

I. INTRODUCTION

THE use of electromagnetic (EM) waves for medical device development is gaining a central role as from the EM versatility of serving different purposes ranging from diagnostics [1]-[3], (thermal) therapy [4]-[7] and monitoring [8]-[10]. Propagation and interaction of EM waves with biological media represents the common ground amongst all of these applications. Although it would be advisable to take advantage of EM propagation theory to optimally determine the working condition of medical devices, optimal design choices have been sometimes hampered by both technological and biocompatibility issues. Moreover, very few studies exist in which the matching media (positioned between the medical device and the patient body) and the working frequency are appropriately optimized.

The presence of the matching media aims both at reducing multi-path reflections and at maximizing the amount of EM waves transmitted inside the patient body. This directly impacts the scattered signal amplitude for diagnostic and monitoring purposes as well as it has a direct impact on the power deposition levels needed for therapy. Accordingly, the selection of the optimal matching media should be the result of a trade-off between mechanical and chemical properties (e.g., robustness, cooling capabilities, toxicity of the material), electromagnetic properties (e.g., electrical permittivity and conductivity) and actual feasibility. Generally, in thermal therapy applications, demineralized water is adopted as matching medium due to its biocompatibility [11]. Moreover, through circulation, such a matching media acts as a cooling agent preventing skin burns in therapeutic application. Also, demineralized water is generally used for its low electric conductivity (in the mS/m range) which is a mandatory requirement to reach the therapeutic field intensity and power deposition level into the tumor while not using oversized power amplifiers. However, only few studies investigated whether the above medium represents an optimal choice for EM thermal therapy.

Besides the matching media, the choice of the working frequency is essential in EM-based medical device development. The optimal working frequency is usually determined as a trade-off between penetration depth and either spatial resolution, when in diagnostic mode, or focus size, when in therapeutic mode. As a matter of fact, one would aim at a higher resolution when making a diagnosis and at a target conformal heating pattern when administering

This is the post-print version of the following article: G. G. Bellizzi, K. Sumser and M. T. Bevacqua, "On the Optimal Matching Medium and the Working Frequency in Deep Pelvic Hyperthermia," in IEEE Journal of Electromagnetics, RF and Microwaves in Medicine and Biology, vol. 5, no. 3, pp. 223-230, Sept. 2021, doi: 10.1109/JERM.2020.3047980. Article has been published in final form at: https://ieeexplore.ieee.org/document/9310292.

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a thermal treatment.

The selection of both frequency and matching media EM properties cannot be performed in an unrelated way and it has a direct impact on the performance of the EM-based medical device, which usually consists of a phased antenna array. In this respect, it would be advisable to address this issue starting from the EM propagation theory and then taking into consideration other specifications, such as mechanical and biocompatibility factors.

Different contributions have been proposed in the literature on the topic. Recently, Trefnà et al. [12] has proposed an innovative matching media manufacturing approach improving stability and reproducibility needed during treatments as well as for simulation purposes. However, water electrical properties have been used as matching medium. Earlier, an effective approach has been proposed to optimally determine the matching liquid electrical properties and operating frequencies for breast cancer imaging and brain strokes diagnostic purposes [13]-[15]. Although promising, generalization and application to the case of therapeutic purposes as well as actual feasibility have never been pursued. Other researchers have proposed intrinsically limited and biased trial-and-error procedures based on a posteriori observation and empirical experiences [16].

In this paper, we aim at 1) expanding and generalizing the approaches proposed in [13]-[15] for breast and brain medical diagnosis to both the case of therapeutic and diagnostic use of EM-based medical devices; 2) including patient body variability by means of a Monte-Carlo style approach which is completely missing in [13]-[15]. This is a crucial aspect that makes the selection of the working conditions much more robust and reliable. More in details, the approach does not presume to declare in absolute the optimal frequency and the matching medium combination. It aims instead at identifying convenient regions wherein one can select the working condition of the EM devices, by considering not only the good trade-off between penetration and resolution, but also other specifications (for instance, a liquid medium).

The proposed methodology is assessed for the case of adjuvant hyperthermia for patient with tumor in the pelvic region being treated with the BSD2000-3D/MR system (PYREXAR Medical, West Valley City, UT, USA) [17]. Hyperthermia treatment planning (HTP) is performed to 2D and 3D patient specific CAD models and the results compared to commercially available applicators and their corresponding working conditions.

II. The Proposed Approach

The proposed approach benefits from the interaction mechanism between EM waves and the patient body, as well as the propagation theory. In particular, three factors are taken into account: the reflection (or alternatively transmission) coefficient, the penetration depth and the spatial resolution. The reflection coefficient represents the amount of incident EM wave which is reflected by the biological tissues. The penetration depth is a measure of how deep the EM waves can penetrate into biological tissues, while the resolution influences the accuracy of the diagnosis and monitoring, as well as the EM field focus size in the therapy.

All of these factors have to be appropriately optimized in order to ensure a sufficient EM signal level within the tissues, which implies a precise and accurate diagnosis, monitoring or thermal treatment. To this end, in this paper, starting from the results in [13]-[15], we propose an approach composed of four different steps, as detailed in the following.

1) 1D planar layers model. The first step consists of schematizing the interaction between the EM waves and the patient tissues by means of a one-dimensional (1D) model [18]-[20]. This consists of a sequence of planar layers, representing the different tissues, and having the same electromagnetic properties and 1D dimension of the corresponding tissue. Although simple, this 1D model can be adopted to study the EM wave propagation through the biological tissue and provide some interesting guidelines for the selection of the optimal working conditions [13]-[15].

2) Transmission line model. By using the formalism of transmission line [18], each planar layer is seen as an equivalent transmission line with given characteristic impedance and length, depending on the EM properties and size of the layer. In particular, by denoting with ε_x, σ_x and Δ_x the relative permittivity, conductivity and size of the layer mimicking a generic tissue, respectively, the characteristic impedance is evaluated as:

$$Z_x(f, \varepsilon_x, \sigma_x) = \sqrt{\frac{\mu_0}{\varepsilon_0 \left[\varepsilon_x(f) - j\,\frac{\sigma_x(f)}{\omega\varepsilon_0}\right]}} \qquad (1)$$

while its propagation constant as:

$$k_x(f, \varepsilon_x, \sigma_x) = \omega \sqrt{\mu_0 \varepsilon_0 \left[\varepsilon_x(f) - j\,\frac{\sigma_x(f)}{\omega\varepsilon_0}\right]} \qquad (2)$$

wherein $\omega = 2\pi f$, being f the working frequency.

3) Estimation of the amount of reflected EM waves. Once the biological scenario at hand is schematized by means of subsequent transmission lines, the amount of incident EM waves which is reflected by the biological tissues is analytically estimated by using the Telegraphists' equations [18]. In particular, the amplitude of the reflection coefficient $|\Gamma|$ is evaluated as a function of frequency and of the electrical properties of the matching fluid, that is [18]:

$$|\Gamma|(f, \varepsilon_b, \sigma_b) = \left|\frac{Z_{eq}(f, \varepsilon_x, \sigma_x, \Delta_x) - Z_b(f, \varepsilon_b, \sigma_b)}{Z_{eq}(f, \varepsilon_x, \sigma_x, \Delta_x) + Z_b(f, \varepsilon_b, \sigma_b)}\right| \qquad (3)$$

wherein the subscript b is associated to the matching medium, Z_b is the characteristic impedance associated to the matching medium and Z_{eq} is the input (or equivalent) impedance at the first interface met by EM waves, that is the one between the matching medium and the outer biological tissue of the anatomical model. Note that Z_{eq} and Z_b must be evaluated by taking into account that both the matching medium and the tissue can be lossy. By changing the frequency f and the electromagnetic properties $(\varepsilon_b, \sigma_b)$ of the matching fluid, a design map $|\Gamma|$ can be obtained.

As far as the EM properties $(\varepsilon_x, \sigma_x)$ of the biological tissues, different databases, arising from ex-vivo measurements, are available in literature [21]. Moreover, effective methods have been introduced for an accurate and patient specific estimation of the in-vivo EM tissue parameters [22]-[25]. On the other hand, no systematic databases or methods exist for the estimation of the thickness Δ_x which is associated to each layer mimicking biological tissues. However, tissue's extensions variability cannot be neglected as in [13]-[15]. Indeed, the design map $|\Gamma|$ depends on Δ_x through the input impedance Z_{eq}, hence, different design maps $|\Gamma|$ can be obtained by varying the extension of the tissues Δ_x.

4) Accounting for tissues size variability. A Monte-Carlo-based analysis is included to take into account for thickness Δ_x variability [26]. First, a domain of possible and admissible values for each tissue has been defined [27]-[30]. Second, some values are generated as uniformly distributed random numbers over the defined domain, thus generating different vectors of possible realizations, that is $\underline{\Delta}_i = \{\Delta_b, \Delta_1, \ldots, \Delta_n \ldots, \Delta_N\}$, wherein the subscripts n and i identify, respectively, the n-th tissue and the i-th realization, and N is the total number of tissues adopted in the adopted anatomical model. Then, for each i-th realization, a deterministic computation of the $|\Gamma|$ map is performed, thus generating the i-th map $|\Gamma_i|(f, \varepsilon_b, \sigma_b, \underline{\Delta}_i)$. The results are finally combined by evaluating the mean $|\Gamma|_m(f, \varepsilon_b, \sigma_b)$ and the standard deviation $|\Gamma|_{std}(f, \varepsilon_b, \sigma_b)$ of the overall maps.

Note that step 4) aims at a robust and reliable selection of the working conditions. Indeed, one can consider that low standard deviation $|\Gamma|_{std}$ indicates that the working condition is more robust with respect to tissue extension variability, as the reflection coefficient values $|\Gamma_i|$ tend to be close to the mean $|\Gamma|_m$. On the other hand, a high standard deviation $|\Gamma|_{std}$ indicates that the reflection coefficient values $|\Gamma_i|$ are spread out over a wider range and the variability of the tissue extension can have a significant impact in the actual reflection coefficient.

As a final concern, once the $|\Gamma|_m$ map is obtained for any given application, it is then possible to select the optimal relative permittivity ε_b, conductivity σ_b and the frequency. Obviously, the choice has to take into account for the application-specific trade-off between penetration depth and spatial resolution (both in therapy and diagnostics). Then, the optimal working condition can be selected as the one that minimizes both the mean map $|\Gamma|_m$ and the standard deviation $|\Gamma|_{std}$. Moreover, in a practical scenario, the availability of a matching medium with optimal dielectric properties at a specific frequency need to be considered.

III. Optimal Working conditions in Deep Pelvic Hyperthermia

Oncologic adjuvant hyperthermia takes place when the tumor temperature is elevated to 40-44°C for 60-90 min [30] -[36]. Therapeutic benefit of adjuvant hyperthermia in combination with radiotherapy and chemotherapy has been demonstrated by clinical trials [37]-[40]. In this framework, selecting the operating frequency and the electrical properties of the matching medium represents a way towards that would enable target conformal heating, higher temperatures and the possibility to undersize the power amplifiers with direct effect on costs. In conclusion, hyperthermia is a well-suited case study to prove the feasibility of our method.

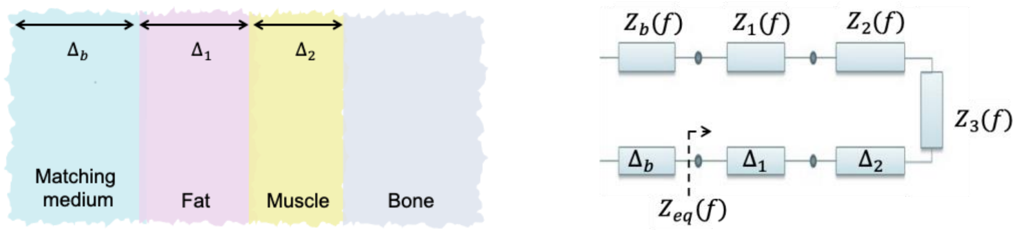
Nowadays several clinical and pre-clinical phased array applicators for deep pelvic hyperthermia have been proposed. However, generally demineralized water is used as matching medium and operating frequencies are selected in the range 70 to 120MHz [40]-[42]. However, while some evidences have shown that higher frequencies would be beneficial [43], no investigation on both matching medium and operating frequency has been proposed.

A. Design map for the selection of the optimal working condition

According to Section II, the pelvis has been modelled by using $N = 3$ layers (see Fig. 1), fat, muscle and bone, respectively, and by neglecting the skin layer, as generally done in HTP [41],[44],[45]. In particular, the bone has been considered to be indefinitely extended, being the inner tissue. In order to take into account for frequency dispersion of biological tissues, their EM properties ε_x, σ_x (at room temperature) have been modelled according to the fourth-order Cole-Cole model [46],[47]. Note that the use of planar multi-layer and transmission line models for the selection of the optimal working conditions of HTP applicators is completely new. From the best of authors' knowledge, no intelligent selection procedure based on both planar multi-layer and transmission line models has been proposed in literature earlier.

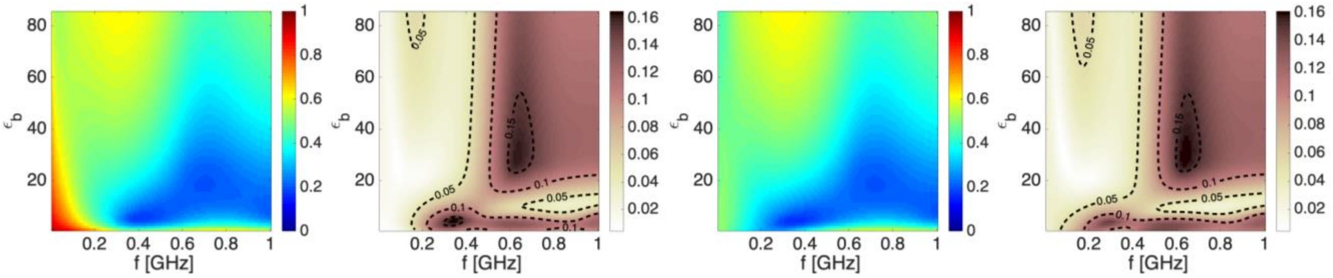
The relative permittivity ε_b of the matching medium have been assumed to range, respectively, between 1-85, whereas the investigated frequency range has been fixed from 10MHz, which is in the order of the working frequency of commercial applicators, to 1GHz. Higher frequencies are possible but not convenient due to the low penetration depth in the inspected tissues. Note that not every frequency in such a range can be used for medical purposes. As far as electric conductivity of matching medium, it is highly dependent on the frequency and is correlated to the relative permittivity. However, a lossless matching would be of interest in order to reach the therapeutic field intensity and power deposition level into the tumor while not using oversized power amplifiers. To account for a realistic matching medium, in the following, both 0 S/m and 0.04S/m have been considered.

Figure 2 depicts the results of this analysis obtained by considering 400 possible realizations of $\underline{\Delta}_i$. In particular,



(a) (b)

Figure 1. 1D models of the pelvic region. Planar layers model (a) and transmission line model (b).



(a) (b) (c) (d)

Figure 2. Optimal working conditions for deep hyperthermia. $|\Gamma|_m$ and $|\Gamma|_{std}$ maps as a function of frequency f and relative permittivity ε_b of the matching medium, in case of $\sigma_b = 0\ S/m$ (a)-(b) and $\sigma_b = 0.04\ S/m$ (c)-(d), respectively. As the amplitude of $|\Gamma|_m$ assumes values in the interval [0,1], the scale has been set up consequently. In (b) it is not possible to see a maximum red region, as there is no region with $|\Gamma|_m$ equal to 1.

Figures 2(a) and (c) depict the $|\Gamma|_m$ for 0 S/m and for 0.04S/m, respectively. Both maps show the existence of *forbidden* regions (in red and green), wherein the reflection coefficient assumes values higher than 0.5. This means that a significant amount of the EM waves is reflected by the interface between the matching medium and the first biological tissue. On the other hand, regions corresponding to minimum values of $|\Gamma|_m$ exist lower than 0.4 (the ones in blue and light blue), in the following referred as *convenient* or *optimal* one. In figures 2(b) and (d) the $|\Gamma|_{std}$ maps are reported. These maps show that the maximum error that can be made is equal to 0.16, while it can be also lower than 0.05.

Once the convenient regions are identified through the maps, the optimal working condition can be selected as the (f, ε_b) pair which corresponds to a minimum value of $|\Gamma|_m$ and $|\Gamma|_{std}$, as well as which ensures a good trade-off between penetration and resolution. Possibly, other specifications can be taken into account.

Figure 2(c) identifies optimal frequency range [130–500] MHz and optimal relative permittivity ε_b lower than 20. Also, this range is optimal from the point of view of reliability and robustness with respect to Δ_x variability (see Fig. 2(d)). It is worth noting that the working conditions identified by the proposed approach are sensibly different to the one commonly used by the commercially available applicators. These latter rely on demineralized water (with relative permittivity about 80) as matching material and an operating frequency in the range [70-120] MHz.

Finally, it is important to stress that the thus obtained design maps represent a useful tool for the selection of the optimal working conditions. They allow to identify forbidden and convenient regions, but they do not declare in absolute the optimal (f, ε_b) pair. Indeed, its selection can also depend on other specifications. For instance, a liquid medium can be of interest in order to fill the entire space between body and the applicator. Then, among the different pairs (f, ε_b) belonging to the convenient region, one can select the one that allows to implement a liquid medium.

B. 2D Proof-of-Concept Analysis

A 2D proof-of-concept analysis has been carried out by using an in-house developed MoM considering a slice of a patient with a tumor in the pelvis region. The 2D model [22] has been considered to be placed in front of a line source with a distance of 0.38 m from the center of the model.

The aim of these numerical analysis is to solve the forward problem and compute the induced current distributions, when different working conditions are considered. First, the state-of-the-art case of demineralized water as matching medium using 70MHz, 100MHz, 120MHz has been considered. Second, these latter have been benchmarked to the working conditions as determined from the proposed approach. For instance, three different frequencies belonging to the convenient regions have been considered, that are 128MHz, 250 MHz and 434 MHz. Each frequency has been tested by using a matching media having ε_b higher as well as lower than 20.

Figure 3 depicts the amplitudes of the currents induced in the pelvis in different working conditions. In particular, as the frequency is different for each working condition, in order to have a fair comparison, the current have been normalized with respect to the energy of the corresponding incident field. In the following, this quantity is referred as $\widehat{W}$. As long as the frequency is lower than 130 MHz, the penetration depth is sufficiently large, so that the EM wave can penetrate the tissues. However, the induced currents have a very low amplitude, unless the right matching fluid is

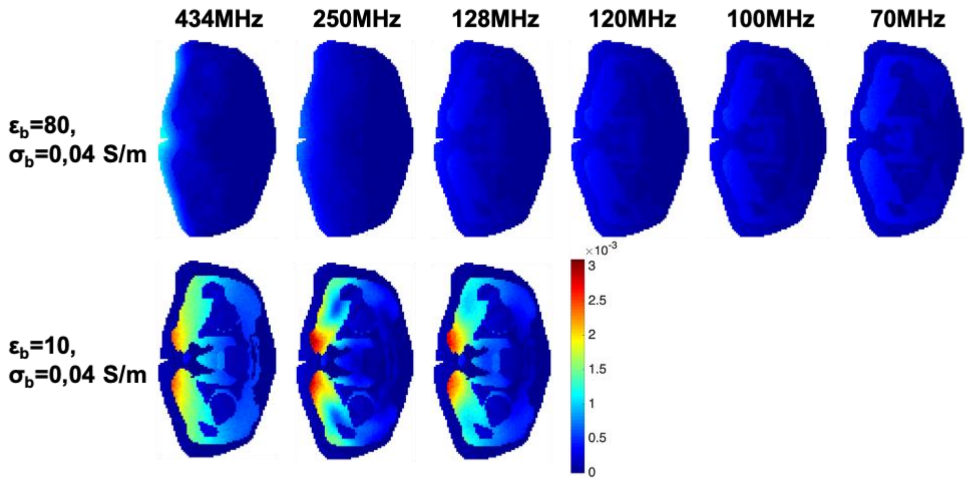


Figure 3. 2D assessment of the optimal working conditions for deep HTP. Amplitudes of induced currents normalized with respect to the energy (l_2-norm) of the incident fields, as a function of the working frequency and the properties of the matching medium. The line source is located at the left side of the pelvis.

adopted. When a frequency higher than 128 MHz is considered, the selection of the matching fluid plays a key role. Indeed, in the case of 250Mz and 434 MHz, and $\varepsilon_b = 80$, the EM wave cannot penetrate the tissues, as the working conditions correspond to the forbidden region in Figure 2(c). On the other hand, when the right matching fluid is adopted, currents with larger amplitude are induced in the tissues.

Table I reports the energy (ℓ_2-norm) of $\widehat{W}$ over the investigation domain of the normalized currents, thus further confirming a higher energy level is reached if the working conditions are selected according to Subsection III.A.

Freq [MHz]	**70**	**100**	**120**	**128**	**128**	**250**	**250**	**434**	**434**
ε_b	80	80	80	80	10	70	10	80	10
$\|\widehat{W}\|$ [10^{-4}]	2.3	2.0	1.9	2	**32**	2.4	**26**	3.8	**28**

Table I. Energy of the normalized currents $\widehat{W}$ as a function of the working frequency and the properties of the matching medium ($\sigma_b = 0.04\ S/m$).

IV. Impact on Deep Pelvic HTP

A. *The Patient Model*

The 3D patient model having a solid tumor in pelvis region has been created using the clinical segmentation procedure. This procedure is based on delineation of computerized tomography (CT) scans into normal tissues and the target volume using a semi-automatic segmentation routine followed by a manual adjustment in software tool iSeg (Zurich Medtech, Zurich, Switzerland). The CT scans have been taken when the patient is lying in a tailored sling (PYREXAR Medical, West Valley City, Utah) matching patient positioning and body shape during treatment [33]. A trained clinician has identified the hyperthermia target volume (HTV) starting from the clinical target volume (CTV) for radiotherapy treatment, and adding certain margins depending on the specific case [48]-[50].

B. *The HTP Workflow*

The first step for HTP has included importing the segmented 3D patient model into Sim4Life (Zurich MedTech AG, Zurich, Switzerland) along with a 3D applicator model, the Pyrexar BSD2000 3D/MRI (Sigma Eye) applicator (PYREXAR Medical, West Valley City, UT, USA). Electromagnetic tissues properties for these frequencies have been assigned to each of the segmented tissues [21]. The total field has been computed for a 1V sinusoidal signal excitation and 20 periods of harmonic signal for each antenna at the operating frequency. The electric field per antenna has been normalized to 1W radiated power and the cubic filtered SAR (cf-SAR) pattern optimized using our *Visualisation Tool for Electromagnetic Dosimetry and Optimisation* (VEDO) software [50].

The adopted optimization strategy aims at maximizing the Target to Hotspot Quotient (THQ) defined as the ration between the average SAR within the target volume and the average SAR at the hot-spot, which is defined as the cumulative 1% volume in all healthy tissues with the highest SAR [51]. The Particle Swarm Optimization scheme has been used to maximize the THQ cost function.

C. *Comparative Assessment*

In order to assess the finding of the proposed approach, we have compared the outcome of HTP, on the same patient model, under different working conditions mimicking actual design choice performed by different applicators meant to treat tumor in the pelvic area [17],[40],[52]. To this end, we have considered five different cases. First, the case of demineralized water as matching media and operating frequency equal to 70MHz, 100MHz and 120MHz have been simulated. In this case, relative permittivity has been set equal to 79.08 and conductivity equal to 0.001 S/m. Second, being the system optimized to work in that range of frequencies, we have considered 128MHz and the relative permittivity equal to 10, according to the convenient region as in Section III.A. Lastly, we have considered the case of

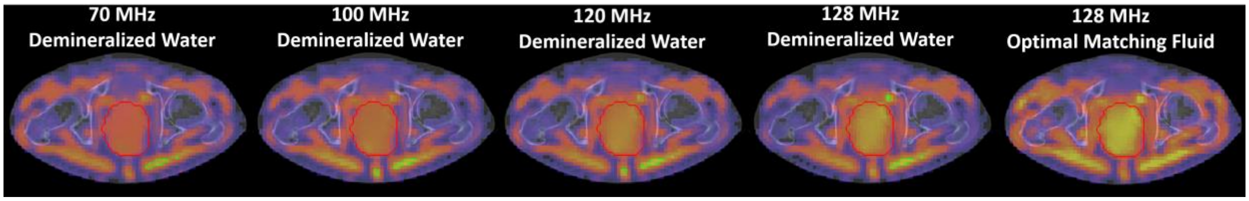


Figure 4. 3D assessment of the optimal working conditions for deep HTP. Predicted SAR distributions within the patient model as a function of the working frequency and the properties of the matching medium.

Freq [MHz]	ε_b	σ_b [mS/m]	THQ	TC25 [%]	TC50 [%]	TC75 [%]
70	79,086	1,14	0.49	85	2	0
100	79,086	1,14	0.57	94	11	0
120	79,086	1,14	0.62	97	32	0
128	79,086	1,14	0.66	98	46	0
128	10	1,14	0.60	**99**	**62**	**1**

Table II. HTP SAR quality metrics as a function of the working frequency and the properties of the matching medium.

using demineralized water as matching media while still selecting the operating frequency deemed optimal.

D. *Evaluation Metrics*

The different performance has been quantitatively investigated using standard HTP SAR quality metrics: THQ and target coverage (TC). These metrics are currently used for clinical decision making as they were demonstrated to be predictive for median target temperature [53]. Specifically, the THQ is defined in the previous section. The TC is the volume percentage of the hyperthermia target volume covered by the 25% (TC25), 50% (TC50), and 75% (TC75) iso-SAR contour, with SAR being normalized to the maximum SAR in the patient. The higher the coverage, the better performance the matching fluid are provided.

E. *Results & Discussion*

Figure 4 depicts a cut view of the SAR distribution for each of these cases. Table II reports the SAR quality metrics as well as details for all the different investigated cases. The results show that changing the frequency (70, 100 and 120MHz) while using demineralized water as matching media has the larger impact on TC25 and TC50 with an average increase of 7 percentage points (range 2-14 percentage points) and 47 percentage points (range 30-60 percentage points), respectively. On the other hand, this has a smaller impact on the THQ and TC75 which remain on average unaltered. A similar trend is observed when comparing the case of 128MHz as operating frequency and demineralized water as matching media with the case deemed optimal according to Section III.A. However, a larger impact can be observed on TC50 with an increase of 26 %-points while TC25 and TC75 remain approximately unaltered.

By increasing the frequency, better performance is obtained, and a key role is played by the matching media. Indeed, when the relative permittivity is equal to 10, a higher SAR deposition is reached, as also shown in Figure 4.

In this preliminary work, we have posed our attention only on SAR quality metrics. However, our findings are consistent also in terms of predicted temperature [53]. Earlier, through simulation studies, the considered SAR quality metrics have been demonstrated to be optimal surrogate for the temperature distributions as well as highly correlated to median predicted target temperature (T50). Accordingly, differences in these SAR quality indicators would translate into a variation in predicted HTV temperature distribution. Hence, we have chosen not to include temperature simulation for two main reasons: SAR is usually the first step of technology development as it is the more straightforward indicator of the field propagation and, moreover, blood perfusion mechanisms are not fully known. Therefore, the open debate regarding thermal properties as well as the unknown impact on the clinical outcome could lead to different interpretations of these preliminary results.

V. Conclusion

An innovative approach for identifying convenient regions wherein one can select the working conditions of the EM medical devices is proposed based on propagation theory and starting from works [13]-[15]. In order to make their selection more robust and reliable, the patient body variability is considered via a Monte Carlo style analysis.

Even if general purpose, the proposed procedure is tested within the framework of hyperthermia. For this specific application, the proposed method identifies [130-500] MHz as optimal range of working frequencies and a material with relative permittivity lower than 20. This optimal region has been preliminary tested in 2D simplified scenario, by showing that the amplitude of the currents induced within the tissues is increased. Then, 3D simulations have been performed in the range of [70-128] MHz, in which the used clinical system has been optimized. Still, the 3D analysis is inline with the results of simplified 2D scenario.

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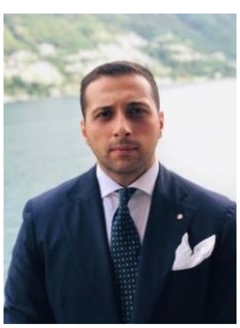

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