Chapter 5

Uncertainty in hyperthermia treatment planning: the need for robust system design

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Abstract

**Purpose:** Hyperthermia treatment planning (HTP) is an important tool to improve the quality of hyperthermia treatment. It is a practical way of designing new hyperthermia systems and can be used to optimize the phase and amplitude settings to achieve optimal heating. One of the main challenges to be dealt with however is the uncertainty in the modeling parameters.

**Methods:** The role of dielectric and combined dielectric and perfusion uncertainty on optimization was investigated by means of HTP for six different systems: the 70MHz AMC-4 (AMC: Academic Medical Center) and AMC-8 system, a 130MHz version of the AMC-8 system, a three ring AMC-12 system operating at 130MHz, the BSD SigmaEye applicator and a dipole applicator with 3 rings each containing 6 dipole pairs operated at 150MHz. For 5 patients with cervix uteri carcinoma a patient model was created based on a hyperthermia planning CT. Variation of tissue parameters resulted in 16 dielectric models for every patient. In addition 4 thermal models were created to study the combined effect of perfusion and dielectric uncertainty.

**Results:** The impact of dielectric uncertainty on optimization is found to be clearly dependent on the number of channels and increased from 0.5°C for 4 channels to 1.5°C for the 18 channels system. As a result the potential gain relative to the AMC-4 system for the 70MHz AMC-8 system was found to be largely compromised while for the remaining systems a robust improvement in $T_{90}$ was observed. The dipole applicator showed the best target heating for two out of five patients while for three others heating efficacy was comparable to the 130MHz AMC-12 system or the 130MHz AMC-8 system (1 patient).

**Conclusions:** Considering the increase in complexity when the number of channels is increased from 12 to 18, the AMC-12 system is considered as a good compromise between heating efficacy and robustness while still being a manageable heating system in clinical practice.
5.1 Introduction

Hyperthermia is a potent radio- and chemo-sensitizer for which in several randomized phase III trials substantial improvements in tumour response and/or overall survival have been demonstrated (10; 12; 13). Hyperthermia treatment aims at elevating the temperature of the tumour to 40 – 45°C without inducing overheating in the normal tissues. Since this is a technically challenging task, numerical simulation is commonly suggested as a way to increase treatment quality.

Over the last two decades, the models that describe the process of heating in hyperthermia have greatly improved regarding detail and conceptual complexity. High resolution simulation has become feasible within practical time frames. The availability of hardware acceleration, e.g. the use of graphical processing units (GPUs), has made an important contribution to this (60; 70). Different studies investigated the correctness of Pennes’ bio-heat equation and/or proposed adaptations to incorporate vessel – tissue heat transfer in a physically more accurate way (25; 71; 34). In addition attempts were made to incorporate the thermo-regulatory response to heating (42; 48; 72).

Validation of hyperthermia treatment planning (HTP) and proving its added value to experience-based hyperthermia treatment remains a difficult task. Sreenivas et al. (39) reported on the qualitative agreement between simulations and clinical observations for the HyperPlan treatment planning system. They were able to discriminate between easy-to-heat and difficult-to-heat patients and to qualitatively correlate the predicted temperature- and power distribution to reported complaints. These distributions however were not predictive for the occurrence of these complaints. A quantitative study by Franckena et al. showed that HTP guided steering i.e. the combination of simulation and on-line feed-back by the patient could approach but not improve the empirically established treatment protocol (73). A study by our group showed that HTP for treatment of oesophagus carcinoma can enhance the local power absorption level when empirically optimized phase settings resulting from electric field measurements are combined with numerically optimized amplitudes (74). A validation study for cervix patients by our group showed a good correlation of intra-luminal ΔT measurements with calculated SAR profiles provided that good thermal contact could be achieved (75).

One of the reasons why HTP still plays a limited role in the clinic is the fact that dielectric and thermal modeling parameters are needed as an input for the models. If these parameters are only known with limited precision, predictions based
on simulation are fundamentally uncertain since the uncertainty of the parameters propagates in the power- and temperature calculations.

In a previous study we investigated the role of perfusion uncertainty on the robustness of optimization (62). This study showed that under perfusion uncertainty the achieved target temperature, can be up to 1°C lower than the optimal temperature if the perfusion is known.

Van de Kamer et al. (32) studied the sensitivity of the temperature and specific absorption rate (SAR) distribution for different applications of hyperthermia. For the coaxial TEM applicator (76), they concluded that the differences in SAR or temperature due to different electric conductivity and permittivity are negligible in comparison to the differences resulting from other uncertainties such as found in the tissue perfusion. However the authors also suggested that the effect of limited accuracy may become more important in the optimization of phase and amplitude settings of multi-antenna phased-array hyperthermia systems as hot-spots are sensitive to dielectric uncertainties in particular.

Another important application of HTP, besides simulations for individual patients, is the design of new systems. It is not feasible from a practical point of view to evaluate every system concept in an experimental let alone clinical setting. Hence, simulation is the best available option to design new hyperthermia systems. However, a comparison between systems has to be made taking parameter uncertainty into consideration.

As hyperthermia systems evolve, the steering capabilities improve by increasing the number of degrees-of-freedom available for phase/amplitude steering. Different simulation studies (47; 46; 55) have shown that the SAR- and/or temperature-distribution of single ring systems, capable of 2D phase/amplitude steering, can be improved by moving to multiple ring 3D systems operating at frequencies around 150 – 200 MHz. However, it is important to investigate whether this gain is robust since, as indicated before, HTP is subject to a number of sources of uncertainty. This was acknowledged in (47) when determining the optimal antenna configuration. The optimal number of channels per ring and the frequency were the result of a compromise between optimal heating and sensitivity of the thermal dose with respect to positioning and phase and amplitude errors.

To reflect the relevance of parameter uncertainty in hyperthermia treatment planning, this study focusses on the impact on optimization. Different systems that have varying operating frequencies and numbers of channels available for phase/amplitude steering will be compared and differences in sensitivity will be related to the problem
Robust system design with HTP

<table>
<thead>
<tr>
<th>System</th>
<th>active element</th>
<th>f (MHz)</th>
<th>#rings</th>
<th>#channels</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC-4</td>
<td>waveguide</td>
<td>70</td>
<td>1</td>
<td>4</td>
<td>AMC-4</td>
</tr>
<tr>
<td>AMC-8</td>
<td>waveguide</td>
<td>70</td>
<td>2</td>
<td>8</td>
<td>AMC-8-70</td>
</tr>
<tr>
<td>AMC-12</td>
<td>waveguide</td>
<td>130</td>
<td>3</td>
<td>12</td>
<td>AMC-12</td>
</tr>
<tr>
<td>BSD SigmaEye</td>
<td>dipole pair</td>
<td>100</td>
<td>3</td>
<td>12</td>
<td>SigmaEye</td>
</tr>
<tr>
<td>3 × 6 dipole pair applicator (47)</td>
<td>dipole pair</td>
<td>150</td>
<td>3</td>
<td>18</td>
<td>DP18</td>
</tr>
</tbody>
</table>

Table 5.1: Overview of the studied systems together with their basic characteristics of designing an effective but robust loco-regional hyperthermia system.

5.2 Methods & Materials

5.2.1 Applicator systems

In this study six loco-regional hyperthermia systems were considered with a varying number of channels and different operating frequencies. The first two are the AMC-4 and AMC-8 phased-array waveguide system operating at 70MHz. The waveguides of these systems are organized in a single ring for the AMC-4 system, enabling 2D steering (56), whereas the eight waveguides of the AMC-8 system are organized in two rings, allowing phase and amplitude steering in 3D (53). In addition treatment was simulated for a virtual 130MHz version of the AMC-8 system and a virtual 130MHz AMC-12 system, a three ring waveguide system. In a previous study, assuming parameter certainty, 130MHz was found to be the optimal frequency for the 8 and 12 channel system (77).

Besides for these waveguide systems, heating was simulated for two phased-array dipole systems. The first one is a three ring, four dipole pairs per ring, system that resembles the BSD SigmaEye applicator (78). The operating frequency of the system is set to 100MHz. Finally, the effect of parameter uncertainty for a system with a very large number of independent channels was evaluated. In (47) a system of 3 rings with 6 pairs of dipole antennas each, operating at 150MHz, was considered as the optimal loco-regional system. Figure 5.1 shows an applicator model according to these specifications used in our study. A summary of all studied systems is provided by table 5.1.
5.2.2 Patient model and electric field calculations

For five patients with a cervix uteri carcinoma (target volume: 27–139cm³) hyperthermia treatment was simulated. Patient models were derived from a hyperthermia treatment planning CT scan. This scan is made while the patient is laying on the same mattresses and water bolus as used during treatment to emulate the treatment set-up as close as possible. The in-plane voxel size of the scan is $0.9375 \times 0.9375 \text{mm}^2$ and the slice thickness is 5mm.

Segmentation of the tissues into bone, fat, inner-air and muscle was based on thresholding by Hounsfield units. The target was manually delineated by a radiation oncologist. The segmented model was re-sampled on a $5.0 \times 5.0 \times 5.0 \text{mm}^3$ grid using the winner-takes-all method i.e. the tissue with the largest volume fraction determines the low-resolution voxel type.

Patients were positioned with the center-of-gravity of the target volume in the center of the heating system. The distance between the rings of the AMC-8 systems and the AMC-12 system was set to 1.5cm.

Electric field calculations were based on the finite-difference time-domain (FDTD) method (37) implemented for GPU execution. The computational domain was truncated with perfectly matched layers (59; 79).
Table 5.2: Range of dielectric properties of fat/bone and muscle tissue (32). Here $\sigma$ is the electric conductivity and $\varepsilon_r$ the relative electric permittivity. The same dielectric parameters were used for all frequencies given that the deviations in this frequency range are small with respect to the studied parameter variation.

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
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<td>$\sigma_{\text{mus}}$</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</tr>
<tr>
<td>$\varepsilon_{r,\text{mus}}$</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$\sigma_{\text{fb}}$</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$\varepsilon_{r,\text{fb}}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3: Enumeration of the 16 dielectric cases. The “-” and “+” symbols in the table refer to the low and high values as reported in table 5.2.

### 5.2.3 Optimization

The optimization method used in this study is a constrained temperature-based method. Temperature-based optimization methods provide a natural way of constraining heating of normal tissue by imposing a maximum tolerable temperature. For this reason, this method was preferred here over SAR-based methods (62).

With the electric fields computed, Pennes’ bio-heat equation with temperature-independent perfusion was used to establish the relation between phase/amplitude and local temperature (27; 28). With this relation known it becomes possible to optimize a thermal dose parameter under normal tissue constraints in a constrained nonlinear optimization procedure. In this study the CFSQP package (65) was used to find the solutions to this optimization problem. The objective for optimization was maximization of the $T_{90}$ under the constraint that the normal tissue temperature does not exceed 45°C. To prevent extreme differences in the contribution of the antennas to the total power, which is not considered acceptable, constraints were applied to the relative amplitudes. Antennas were required to contribute at least 10% and no more than 40% of the total power for the AMC-4 and at least 5% and no more than 25% for the AMC-8 systems. For the AMC-12 and the SigmaEye system these limits were set to 3% and 15% and for the DP18 system to 2% and 10%. In order to reduce the chance of convergence to a local minimum, 10 different runs...


<table>
<thead>
<tr>
<th>Tissue type</th>
<th>$\sigma$ (S/m)</th>
<th>$\epsilon_r$ (-)</th>
<th>$\rho$ (kg/m$^3$)</th>
<th>$c$ (J/(kg K))</th>
<th>$k$ (W/(m K))</th>
<th>$w_b$ (kg/(m$^3$ s))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner-air</td>
<td>0.0</td>
<td>1.0</td>
<td>1.29</td>
<td>10000$^*$</td>
<td>0.024</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>0.05</td>
<td>10</td>
<td>1595</td>
<td>1420</td>
<td>0.65</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatty</td>
<td>0.06</td>
<td>10</td>
<td>888</td>
<td>2387</td>
<td>0.217</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle-like</td>
<td>0.75</td>
<td>75</td>
<td>1050</td>
<td>3639</td>
<td>0.56</td>
<td>3.6</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.74</td>
<td>65</td>
<td>1050</td>
<td>3639</td>
<td>0.56</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 5.4: Default thermal and dielectric parameters. Here $\rho$ is the density, $c$ the specific heat, $k$ the thermal conductivity and $w_b$ the volumetric perfusion rate. The perfusion values are assumed to be representative for patients under hyperthermic conditions. *The heat-capacity of air was set to be ten times higher than its actual value to allow a larger time-step. The effect of this on the temperature distribution is negligible.

were carried out with 10 different randomly selected feed vectors. Mathematically the optimization problem is summarized as follows

$$
\text{maximize } T_{90}(\vec{v})
$$

subject to

$$
T(\vec{x}; \vec{v}) \leq T_{\text{constraint}}(\vec{x})
$$

and

$$
f_{\text{min}} \leq P_i(\vec{v}) / P_{\text{tot}}(\vec{v}) \leq f_{\text{max}},
$$

where $\vec{v}$ holds the amplitudes and phases of the systems, $P_{\text{tot}}$ is the total power, $P_i$ the power delivered by the $i$-th channel and $f_{\text{min}}$ and $f_{\text{max}}$ are the lower and upper limit for the relative power, respectively.

### 5.2.4 Uncertainty

To study the effect of uncertainty in the dielectric parameters on the quality of temperature based optimization, electric field calculations were performed for all combinations of the low and high conductivity and low and high permittivity values for both tissue types (table 5.2) as presented in table 5.3. Every combination was used as a scenario, with corresponding optimal phase/amplitude settings. By taking the difference of the $T_{90}$ resulting from these optimal settings and the $T_{90}$ resulting from phase/amplitude settings that were computed with standard dielectric parameters (according to table 5.4), the impact of uncertainty was measured. Standard settings were applied at a power level for which the normal tissue temperature constraints are still respected for the considered scenario (62). The same dielectric parameters were used for all frequencies as the differences in this frequency range are small compared to the studied parameter variation as presented in table 5.2.
The combined effect of dielectric and thermal uncertainty was analysed in a similar way as for the dielectric uncertainty alone. We choose to vary fat and muscle perfusion with $\pm 25\%$ independently, leading to 4 possible combinations. Combined variation of dielectric properties and tissue perfusion then gives rise to $16 \times 4 = 64$ combinations.

To limit the required computation time, in this study a tissue specific but temperature independent perfusion level was used in the thermal modelling step. This assumption makes Pennes’ equation linear and optimization can hence be performed efficiently. To illustrate the effect of this assumption, the phase/amplitude settings that were found for the five patients and the six hyperthermia systems with the standard dielectric and also thermal parameters were evaluated using a temperature-dependent perfusion model (80)

$$w_b = \begin{cases} (w_b)_{\text{baseline}} + (w_b)_{\text{max incr}} \exp \left( \frac{-(T-T_{\text{crit}})^2}{s} \right) & T \leq T_{\text{crit}} \\ (w_b)_{\text{baseline}} + (w_b)_{\text{max incr}} & T > T_{\text{crit}} \end{cases}$$

(5.2)

Here $(w_b)_{\text{baseline}}$ (kg/(m$^3$s)) is the perfusion value under normo-thermic conditions, $(w_b)_{\text{max incr}}$ (kg/(m$^3$s)) the maximum increment as a result of thermo-regulation, $T_{\text{crit}}$ ($^\circ$C) is a critical temperature level above which the maximum perfusion level is reached and $s$ ($^\circ$C$^2$) is a scaling parameter that determines the shape of the half-Gaussian. The choice of parameters for the temperature-dependent perfusion model are presented in table 5.5. As in the previous analysis, standard settings were applied at a power level for which the normal tissue temperature constraints are still respected.

<table>
<thead>
<tr>
<th>Tissue-type</th>
<th>$(w_b)<em>{\text{baseline}}/(w_b)</em>{\text{const}}$</th>
<th>$(w_b)<em>{\text{max incr}}/(w_b)</em>{\text{const}}$</th>
<th>$T_{\text{crit}}$</th>
<th>$s$</th>
<th>$(w_b)_{\text{const}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty</td>
<td>0.7</td>
<td>0.6</td>
<td>45</td>
<td>12</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle-like</td>
<td>0.3</td>
<td>1.4</td>
<td>45</td>
<td>12</td>
<td>3.6</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.5</td>
<td>1.0</td>
<td>43</td>
<td>12</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 5.5: Parameter choices for the different tissues of the temperature-dependent perfusion model (equation 5.2). Data were taken from (80). The constant perfusion values ($(w_b)_{\text{const}}$) correspond to those in table 5.4.

### 5.2.5 Acceleration of the optimization procedure

In view of the large number of cases to be optimized ($5 \times 6 \times 16 \times 4 + 1 = 2400$), a strategy was developed to
largely under-sample the number of tissue points so that the optimization can be done efficiently.

The optimization algorithm is likely to be accelerable since the computational costs are associated with the number of normal tissue constraints and only a very small fraction of the total normal tissue volume has a temperature close to the constraint temperature. It is a priori unknown however which voxels are part of this small fraction.

As a solution we under-sample the temperature grid e.g. by $4 \times 4 \times 4$ such that a normal tissue constraint is applied to only one voxel in every cube of $2 \times 2 \times 2\text{cm}^3$ (figure 5.2(b)). As a result, in some of the disregarded points, the constraint temperature will be exceeded when optimizing with this under-sampled set of normal tissue constraints (figure 5.2(c)). These points are added to the constraint set, followed by re-optimization (figure 5.2(d)). After a number of iterations the constraint set will be complete meaning that the constraints are satisfied for all normal tissue points.

In order to test the accelerated optimization procedure, optimization was performed for the DP18 system for all five patients assuming standard thermal and dielectric parameters. Standard optimization was compared to optimization with initial under-sampling to validate the method and to determine the level of acceleration.

5.3 Results

5.3.1 Acceleration of the optimization procedure

The achieved $T_{90}$ and timing results of the accelerated optimization method and the standard optimization method are presented for the 5 patients in table 5.6. The constraint set was complete within 3 to 7 iterations. Note that every iteration consists of 10 runs of the optimization procedure and that adding points to the constraint set is based on the best solution of those runs. Since the number of constraints is strongly reduced the overall time needed for optimization is reduced by a factor of 2.7 to 15 compared to the standard optimization method. As an example, figure 5.3 shows the maximum temperature in all normal tissue points and the number of normal tissue constraints as a function of the iteration number for patient 1 (case I in table 5.6). It was observed that the under-sampling and the standard optimization method converged to different solutions. This can be understood from the fact that the feasible trajectories through phase/amplitude space are different and for this reason
Figure 5.2: Illustration of the under-sampling procedure. A constraint temperature is applied to a sub-set of all normal tissue voxels according to a specified sample density (b). This under-sampling gives rise to temperatures above the constraint temperature in voxels not considered in the optimization procedure (c). These voxels are added to the constraint set followed by re-optimization (d). This procedure is repeated until the temperature constraints are satisfied for all normal tissue voxels.

Table 5.6: Evaluation of the under-sampling strategy. Reported times are for the complete optimization. The five cases are optimizations for the $3 \times 6$ dipole pairs system applying standard dielectric and thermal properties. In the case of under-sampling the number of constraints is the maximum number (the number in the last iteration). The number of constraints in the standard algorithm is based on a $\lambda = 500$ threshold to discard voxels that show negligible heating (28). (cnstr = constraint, iter = iteration, cnstr. red. = constraint reduction factor and SU = speed-up)
Figure 5.3: Example of the maximum normal tissue temperature and constraint number as a function of the iteration number for case I in table 5.6. Every iteration consists of 10 runs of the optimization algorithm with different starting points in phase/amplitude space.
convergence to a different solution can occur. As the comparison in table 5.6 shows however, these solutions result in equally good heating.

### 5.3.2 Dielectric uncertainty

Figure 5.4 shows the average $T_{90}$ for the six studied systems after temperature-based optimization for the 16 dielectric cases (Table 5.3). Every subplot shows the $T_{90}$ for the different systems in case of parameter certainty (solid line) and parameter uncertainty (dashed line) for one patient. In case of parameter certainty, optimization was performed for every dielectric case and the average $T_{90}$ over these cases is computed. In case of parameter uncertainty, optimization was performed only once assuming default dielectric parameters (Table 5.4). For the resulting settings, the $T_{90}$ was computed for all of the dielectric cases under scaling of the power to satisfy normal tissue constraints.

Both under parameter certainty as well as uncertainty, a significant increase in $T_{90}$ is predicted as the number of channels and the frequency increases. In the uncertain and hence more realistic case, for three out of five patients the 130MHz AMC-12 system showed comparable performance to the eighteen channel dipole applicator while for two others the dipole applicator showed better performance. The AMC-8-130 system showed to perform comparable to the SigmaEye system that has more channels but a lower frequency (100 MHz). The AMC-12 system performed better than the SigmaEye system for three patients and equally good for the remaining two patients.

As an example, the temperature distribution in the transversal mid-plane is shown for patient 1 in figure 5.5 for the different systems. This figure clearly shows the increased heating efficacy when the number of channels is increased together with the frequency.

The impact of uncertainty on the optimization of the temperature distribution is given by the difference in $T_{90}$ in case of certainty and uncertainty as observed in figure 5.4. This difference is plotted in figure 5.6 as a function of the number of channels and a trend is observed that the optimization becomes increasingly sensitive to dielectric uncertainty when the number of channels increases.

The results presented so far are based on the average $T_{90}$ that would be achieved. Figure 5.7 compares the $T_{90}$ for the individual patients for the DP18 system to the $T_{90}$ for the AMC-12 system since these systems were found to be competitive. The difference in $T_{90}$ between the two systems is plotted for patients 1 to 5 for the different
Figure 5.4: $T_{90}$ averaged over the different dielectric cases for the 6 systems and patients 1 to 5. In case of parameter certainty (solid line) optimization was performed for every dielectric case. In case of parameter uncertainty, standard dielectric tissue properties were assumed during optimization and the resulting settings were evaluated for the 16 different cases. To assure that the normal tissue constraints are respect to power level was scaled accordingly.
Figure 5.5: Transversal cross-section at mid-plane of the temperature distribution for the different systems for one of the dielectric cases. These results were found for patient 1 with the high permittivity and conductivity values as listed in table 5.2.
Figure 5.6: Average difference between optimal and realized \( T_{90} \) as a result of uncertainty in the dielectric parameters plotted as a function of the number of channels.
dielectric cases that are enumerated according to table 5.3. For individual patients large differences in the predicted gain were found. As an example, for patient 3 the gain varies between $-0.1$ and $1.3^\circ$C. Looking at the average gain (plotted as bars) the variation is largely reduced meaning that the selection of dielectric parameters is not likely to lead to a biased comparison of systems. Note that for certain dielectric cases it becomes slightly disadvantageous to use the DP18 system instead of the AMC-12 system.

5.3.3 Combined perfusion and dielectric uncertainty

Figure 5.8 shows the sub-optimality for all systems for perfusion uncertainty alone ($\pm 25\%$ in fat and muscle tissue). The sensitivity of the optimization result is, as holds for the dielectric uncertainty, dependent on the number of channels. Figure 5.9 shows the sub-optimality for all systems in case of combined dielectric and perfusion uncertainty. It is observed that on average the sub-optimality only changes slightly by adding perfusion uncertainty to dielectric uncertainty. This shows that the impact
of combined dielectric and perfusion uncertainty can not be treated as additive. In figure 5.10, the realized $T_{90}$ using the temperature-dependent perfusion model was compared to the $T_{90}$ predicted with the constant perfusion model. It is observed that ignoring the temperature dependency of the perfusion can lead to a significant overestimation of the thermal dose that can be delivered.

5.4 Discussion

This study investigated the impact of dielectric uncertainty and combined dielectric and perfusion uncertainty on optimization of hyperthermia treatment by means of treatment planning. In particular, this impact was compared between hyperthermia systems that are operated at different frequencies and have different numbers of channels for phase/amplitude steering. Patient heating was studied for the 70MHz AMC-4 and AMC-8 system, the virtual 130MHz AMC-8 and AMC-12 systems, the BSD SigmaEye applicator (3 rings with 4 pairs of dipoles each) and a 150 MHz $3 \times 6$ – dipole pairs system according to the specifications in (47).

A method was developed to accelerate the optimization method considerably in
order to be able to evaluate a large number of variations reflecting the uncertainty in the default patient model. Initial under-sampling with correction proved to be an efficient optimization method for which the objective function shows only very small deviations in comparison to the standard method. Differences in phases and amplitudes were found between the two methods which can be attributed to convergence to different solutions. The small difference in the objective function however assures that equally good target heating is achieved. A comparable method was presented by Das and co-workers (28) where voxels (or elements) are grouped based on their heating potential and the correlation of the voxel specific optimal heating vector. Their method is more suitable in on-line procedures since the grouping of voxels can be performed in advance. This preparatory step is relatively time consuming but the actual optimization is fast. However, our method is more efficient when a large number of cases is to be evaluated.

Computational costs of parameter variation remain an issue to be addressed in future research. Although a temperature-dependent perfusion term and the inclusion of more accurate thermal modelling of the vasculature potentially describes bio-heat transfer better, the cost of optimization based on such models is currently relatively high. For the number of cases as considered in this study this would have lead
Figure 5.10: Realized $T_{90}$ for patients 1 to 5 for all systems if standard settings are evaluated using a temperature-dependent perfusion model and the predicted $T_{90}$ according to the constant perfusion model. This figure shows the difference in $T_{90}$ relative to the predicted value when ignoring thermo-regulation. The sub-optimality, the difference between the realized dose and the optimal thermal dose when including thermoregulation in the optimization procedure, cannot be derived from this figure (contrary to figure 5.4).
to unacceptably long computation times and for this reason a less complex model was used; Pennes’ bio-heat equation with constant perfusion specified per tissue type. Figure 5.10 illustrated the relevance of including the dependency of the perfusion level on temperature in the temperature model. Significant overestimation of the deliverable thermal dose can occur by ignoring this phenomenon.

Optimization for the multi-ring systems is clearly more sensitive to dielectric uncertainty than optimization for the single ring AMC-4 system. The sub-optimality increased, meaning that the difference between the achieved target temperature and the optimal temperature for the true dielectric tissue properties is larger. For the multi-ring systems this difference was on average 1-1.5°C while for the AMC-4 system this is typically 0.5°C (figure 5.6).

As a result of the increased sub-optimality, the gain predicted for the AMC-8-70 system relative to the AMC-4 system is expected to be largely compromised in practice if treatment is based on settings resulting from HTP. The potential gain, i.e. the gain that is predicted without parameter uncertainty, relative to the AMC-4 system, for the AMC-8-130, AMC-12, SigmaEye and DP18 systems is significantly higher than for AMC-8-70 system (0.5°C vs 1.5°C or larger) so that for 5 out of 5 patients increasing the operating frequency both with or without an increase in the number of channels is a robust improvement. Although the sensitivity to dielectric uncertainty is found to increase with an increasing number of channels, within the studied range, the heating efficacy shows a larger increase resulting in a net gain.

Our results agree with the conclusion of Seebass et al. (47), that the optimal system configuration for HTP-based loco-regional hyperthermia in the pelvic region is a set-up with three rings, each with 6 or 8 channels operating at 150MHz. The 130MHz AMC-12 system showed comparable performance to the DP18 system for 3 patients while for patients 3 and 5 the DP18 system performed better. The importance of choosing the optimal operating frequency is illustrated by the comparison of the AMC-8-130 and the SigmaEye system. While the SigmaEye system has more channels available, the AMC-8-130 system shows comparable performance. This is consistent with previous findings that the optimal frequency (depending on the precise configuration and the type of phased array elements) will be around 130 – 150 MHz (47; 77; 55). The AMC-12 system performed better than the SigmaEye system for three patients and equally good for the remaining two patients.

Adding perfusion uncertainty to the dielectric uncertainty, it is observed that the sub-optimality shows on average only small differences with the sub-optimality originating from dielectric uncertainty alone. This can be understood by the con-
sidering the situation where dielectric uncertainty leads to a locally underestimated power density level causing an underestimation of the local temperature. If this coincides with an overestimation of the perfusion level, an even larger error in the local temperature will be the result. On the other hand if the perfusion level is underestimated the initial error due to the dielectric uncertainty will be reduced. The effect of combined sources of uncertainty will for this reason largely depend on the uncertainty range of the different parameters. In this view it should be noted that the uncertainty chosen for the perfusion of fat and muscle is modest and larger deviations maybe expected in practice. Regardless, our study emphasizes that uncertainties should, if possible, be studied in combination. The interaction between the uncertainties can be complex and cannot, for the studied example, be treated as additive.

The studied parameter uncertainty was limited here to dielectric and perfusion uncertainty. Other relevant sources of uncertainty are or may be found in patient position, posture and organ deformation (47; 35; 36; 81), or e.g. the parameters of the models that describe thermo-regulation (42; 48). Since the number of combinations to be evaluated rapidly becomes impractically large when various sources of uncertainty are combined, efficient sampling techniques (e.g. Monte Carlo) are needed to estimate the average impact of a larger set of uncertainties on the quality of optimization.

To reduce the impact of parameter uncertainty, future research could be focussing on robust optimization techniques that consider the model parameters as stochastic variables. Such an approach could for example focus on optimization of the expected value of \( T_{90} \) instead of optimizing for a specific case (82; 83; 84). Alternatively the level of uncertainty could be reduced if accurate non-invasive measurement of tissue properties would become available.

One of the key assumptions in the comparison of the systems described in this study is that treatment settings are based on HTP only. However, as the impact of the uncertainties on the quality of planning already indicates, there is a high likelihood of imminent hot-spots that were not forseen by treatment planning. The hyperthermician should be able to respond fast and adequately to these complaints. Adaptive on-line optimization methods (49) potentially provide a way to do so, but, these methods are still under development. Moreover, it is important that the system can also be operated based on intuitive understanding when treatment planning is not able to provide the hyperthermician with reliable advice. For the AMC-4 system the heating focus can be steered in 2D only, while for the two ring AMC-8 system the steering possibilities are already much more extensive. The focus can be steered in
3D but is also elongated or shortened in axial direction. Furthermore the focus can be tilted along the two remaining axes. For the DP18 system it becomes truly difficult to explain even basic steering actions. If reliable HTP is available this is exactly the strength of such a system since it provides the possibility to avoid hot-spots while effectively heating the target. In a situation where the operator has to rely on intuitive steering this becomes an important weakness of more sophisticated systems.

An additional argument to restrict the number of channels of a phased-array system in loco-regional hyperthermia comes from the reconstruction perspective (29; 31). The number of channels determines the number of experiments required to reconstruct the temperature – phase/amplitude relation in the patient. The time required for this reconstruction is a serious issue (31). Comparing a 18 to an 12 channel systems, the required amount of time for (full) reconstruction increases with a factor 1.5 for non-linear reconstruction and 2.25 for linear reconstruction (31).

5.5 Conclusions

Dielectric uncertainty has an important effect on optimization of phase and amplitude settings for optimal heating with multi-ring 3D loco-regional hyperthermia systems. As a trend it is observed that the sensitivity increases as the number of channels in the phased array systems increase. Combining dielectric uncertainties with perfusion uncertainty illustrates their interaction and the need to study them in combination. Despite of the increased sensitivity there is still a net gain when the frequency and the number of channels is increased. For all studied patients increasing the frequency of the AMC-8 system from 70MHz to 130MHz is a robust improvement. Heating with the DP18 system shows an additional improvement in \( T_{90} \) for some patients but not all taking uncertainty into account: for 3 out of 5 patients the AMC-12 system or AMC-8-130 system (1 patient) showed comparable heating efficacy. The AMC-8-130 system can be considered equivalent in terms of heating efficacy to the SigmaEye system whereas the AMC-12 system performed equally well or better than the AMC-8-130 system (for 2 and 3 patients respectively). Given the additional complexity associated with increasing the number of channels from 12 to 18 we consider the AMC-12 as the best compromise between heating efficacy and robustness.
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