Loco-regional hyperthermia treatment planning: optimisation under uncertainty

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Citation for published version (APA):
Chapter 4

Optimization in hyperthermia treatment planning: the impact of tissue perfusion uncertainty

This chapter was published as:

**Purpose:** Hyperthermia treatment planning (HTP) potentially provides a valuable tool for monitoring and optimization of treatment. However, one of the major problems in HTP is that different sources of uncertainty degrade its reliability. Perfusion uncertainty is one of the largest uncertainties and hence there is an ongoing debate whether optimization should be limited to power-based strategies. In this study a systematic analysis is carried out addressing this question.

**Methods:** The influence of perfusion uncertainty on optimization was analyzed for five patients with cervix uteri carcinoma heated with the AMC-8 70 MHz phased-array wave-guide system. The effect of variations (up to ±50%) in both the muscle- and tumor perfusion level was investigated. For every patient, reference solutions were calculated using constrained temperature-based optimization for 25 different and known perfusion distributions. Reference solutions were compared to those found by temperature-based optimization using standard perfusion values and four SAR-based optimization methods. The effect of heterogeneity was investigated by creating $5 \times 100$ perfusion distributions for different levels of local variation ($\pm 25\%$, $\pm 50\%$) and scale (1cm, 2cm). Here the performance of the temperature-based optimization method was compared to a SAR-based method that showed good performance in the previous analysis.

**Results:** Solutions found with temperature-based optimization using a deviating perfusion distribution during optimization were found within 1.0°C from the true optimum. For the SAR-based methods deviations up to 2.9°C were found. The spread found in these deviations was comparable, typically 0.5-1.0°C. When applying intra-muscle variation to the perfusion, temperature-based optimization proved to be the best strategy in 95% of the evaluated cases applying $\pm 50\%$ local variation.

**Conclusions:** Temperature-based optimization proves to be superior to SAR-based optimization both under variation of perfusion level as well as under the application of intra-tissue variation. The spread in achieved temperatures is comparable. These results are valid under the assumption of constant perfusion at hyperthermic levels. Although similar results are expected from models including thermo-regulation, additional analysis is required to confirm this. In view of uncertainty in tissue perfusion and other modelling uncertainties, we propose feed-back guided temperature-based optimization as the best candidate to improve thermal dose delivery during hyperthermia treatment.
4.1 Introduction

Hyperthermia is the application of elevated temperatures in the range of 41 – 45°C to tumors. Its combination with radio- and/or chemotherapy has proven to improve clinical response in various randomized trials (12; 10; 13).

In loco-regional hyperthermia, applied to deep seated tumors such as pelvic tumors and oesophagus carcinoma (12; 68), heating is generally applied using phased array systems (53; 54). In our department the AMC-8 phased-array waveguide system is used for this purpose (53). This eight channel system operating at 70 MHz allows phase and amplitude steering in 3D due to electromagnetic (EM) interference between the fields that are imposed by the individual waveguides.

Since temperature during treatment is generally only measured along a limited number of invasive (intra-luminal) tracks, simulating the heating process, often referred to as hyperthermia treatment planning (HTP), is a valuable addition to monitor the treatment. Moreover, HTP can be used to determine the amplitude and phase of every individual antenna such that the power density distribution or the temperature distribution is optimal. Optimal here means that the highest thermal dose possible is delivered to the target within normal tissue limits (46; 28; 47; 49).

One of the major limitations of HTP however is that the generated patient model suffers from different sources of uncertainty. Van de Kamer et al (32) showed that intra-tissue variation of dielectric properties can result in errors in the order of 20% in power absorption. This result was found for a single antenna system and the inaccuracy is expected to increase even further with an increasing number of antennas.

Whereas uncertainty in the dielectric model of the patient might be resolved with better pre-treatment data acquisition (33), the perfusion distribution during treatment is a source of uncertainty which is more difficult to resolve. The perfusion distribution is crucial input data in the estimation of the temperature distribution which follows after calculation of the power absorption.

Perfusion is easily determined under normo-thermic conditions (34), it increases however considerably in response to temperature elevation (4; 69). This change in perfusion is due to thermo-regulation, a process that is difficult to capture in a reliable quantitative model. Such a model should not only cover the relation between temperature and perfusion but also the scale on which the perfusion is regulated in reaction to a local temperature increase. In absence of such a model, or with missing information on its parameters, the perfusion distribution under hyperthermic conditions is not known and can only be estimated. As a result the computed temperature
distribution is also an approximation of the actual distribution during treatment.

In view of the uncertainty in tissue perfusion, it is important to investigate to what extent the result of optimization, e.g. a set of phases and amplitudes, is affected by this uncertainty. This is what could be called the robustness of the optimization method. It is argued, e.g. by Canters and co-workers (45), that because of tissue perfusion uncertainty the optimization procedure is better to be restricted to optimization of the power distribution. However, for such a conclusion to be drawn, a systematic analysis of the influence of uncertainty on different strategies of optimization is required and this is the subject of this study.

### 4.2 Materials and Methods

#### 4.2.1 Modelling of loco-regional hyperthermia treatment

At our department HTP input data are based on a CT scan in treatment position prior to treatment. This scan is segmented automatically based on the Hounsfield units in musclelike, fatlike tissues and bone tissue. The tumor is manually delineated by a radiation oncologist. The patient model is inserted in a model of the AMC-8 system where the patient is surrounded by water boluses kept at 12°C. The boluses provide superficial cooling and EM coupling. An example of the created patient- and system model for one of the five patients is shown in figure 4.1.

The electric fields imposed by the different waveguides of the AMC-8 system are calculated using the finite-difference time-domain (FDTD) method (37). After
calculation of the electric fields the power density distribution is calculated. The relation between field and power density is given by

\[ P_D = \frac{\sigma}{2} \vec{E}^* \cdot \vec{E} \]  

(4.1)

where \( P_D \) (W/m\(^3\)) is the power density, \( \sigma \) (S/m) the electric conductivity and \( \vec{E} \) (with complex-conjugate \( \vec{E}^* \)) the total electric field. The total field is composed of the fields imposed by the different sources and is given by

\[ \vec{E} = \sum_{i=1}^{N} \vec{E}^i \]  

(4.2)

with \( N \) the number of antennas. The complex valued vector \( \vec{E}^i \) is the electric field imposed by the \( i \)th source. Alternatively, the power absorption can be specified per unit of mass instead of volume and is then called the specific absorption rate (SAR). Mathematically,

\[ \text{SAR} = \frac{P_D}{\rho} \]  

(4.3)

where \( \rho \) (kg/m\(^3\)) is the tissue density.

The power density distribution serves as input to calculate the (steady-state) temperature distribution. Thermal modelling in this study is based on Pennes’ bio-heat equation given by

\[ \rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + P_D - w_b c_b (T - T_{\text{art}}). \]  

(4.4)

where \( c \) (J/(kg K)) is the heat capacity, \( k \) (W/(m K)) the thermal conductivity, \( w_b \) the volumetric perfusion kg/(m\(^3\) s), \( c_b \) (J/(kg K)) is the heat capacity of the (arterial) blood and \( T_{\text{art}} \) the temperature of the ‘feeding’ arterial blood (27). Under the assumption of constant perfusion (\( w_b \)) equation 4.4 is linear.

Thermal and dielectric parameters used in the modelling procedure are listed in table 4.1 (22; 58). The presented perfusion values are assumed to be representative under hyperthermic conditions. All simulations are based on a patient model defined at a resolution of \( 2.5 \times 2.5 \times 5.0 \) mm. This model results from downscaling the original segmented CT scan using the winner-takes-all method meaning that the tissue type of a voxel is determined by the tissue that takes up the largest fraction of the volume of that voxel.
Tissue type  $\sigma$ (S/m)  $\epsilon_r$ (-)  $\rho$ (kg/m$^3$)  $c$ (J/(kg K))  $k$ (W/(m K))  $w_b$ kg/(m$^3$ s)  
---
Inner-air  0.0  1.0  1.29  10000*  0.024  0
Bone  0.05  10  1595  1420  0.65  0.12
Fatty  0.06  10  888  2387  0.217  1.1
Muscle-like  0.75  75  1050  3639  0.56  3.6
Tumor  0.74  65  1050  3639  0.56  1.8

Table 4.1: Tissue properties as used in the simulations. The perfusion values are assumed to be representative for patients under hyperthermic conditions. *The heat capacity of air is 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.

4.2.2 Optimization techniques

In this study different HTP optimization techniques are compared in the presence of tissue perfusion uncertainty. This section describes the different objective functions that can be divided in temperature-based and SAR/power-based functions. A summary of the methods is given in table 4.2.

Constrained temperature-based optimization

Constrained temperature-based optimization maximizes the thermal dose delivered to the target within normal tissue limits. In absence of any uncertainties it is guaranteed to give the best temperature distribution achievable and is therefore considered as the method of reference. As a measure of thermal dose $T_{90}$ is taken, which represents a temperature that is achieved or exceeded in 90% of the target volume. Mathematically the optimization problem is given by

$$\max T_{90}(\vec{v}), \quad \text{subject to } T(\vec{x}) \leq T_{\text{constraint}}(\vec{x}), \quad f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}. \quad (4.5)$$

The constraint temperature $T_{\text{constraint}}$ is a function of position since for different tissue types/regions different constraint temperatures may be applied. Within this study $T_{\text{constraint}}$ is set to 45°C for all normal tissue types. The vector $\vec{v}$ is a complex-valued vector holding the amplitudes and phases of the different sources and $P_{\text{total}}$ and $P_i$ are the total power and the contribution to the power by the $i$th source respectively. The fractions $f_{P,\text{min}}$ and $f_{P,\text{max}}$ are safety limits that specify the minimum and maximum contribution of a source to the total power, respectively. For all optimization methods these fractions are set to 0.05 and 0.25, respectively. The optimization
procedure was implemented using CFSQP (65) and is based on the principles as published by Das and co-workers (28). To avoid convergence to a local maximum, the algorithm was initialized with 10 random starting points.

Since as a measure of thermal dose we consider $T_{90}$, it is sufficient to optimize for this dose parameter. For this reason other possible temperature-based objective functions are not investigated.

**SAR-based optimization**

In addition to the temperature-based objective function, four SAR-based objective functions were selected based on their relatively good performance (45) (table 4.2). Multiple SAR-based objective functions were selected to prevent a bias in the results that could be introduced by selecting only one SAR-based objective function. They are extensively explained and compared by Canters and co-workers (45) and are briefly described here.

The simplest SAR based objective to be optimized is the ratio of target and normal tissue SAR (or power density). In physical terms, the conformity of the SAR distribution is optimized. Mathematically it is given by

$$f(\vec{v}) = \frac{\int_{V_{\text{target}}} \text{SAR} dV}{\int_{V_{\text{normal}}} \text{SAR} dV} \quad \text{subject to } f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}. \quad (4.6)$$

While the previously mentioned objective only evaluates how much of the total power is delivered to the target, an objective acknowledging that local high SAR brings the risk of overheating, is given by the ratio of average target power and the integral of normal tissue SAR$^2$, mathematically expressed as

$$f(\vec{v}) = \frac{\int_{V_{\text{target}}} P D dV}{\left[\int_{V_{\text{normal}}} \text{SAR}^2 dV\right]^{1/2}} \quad \text{subject to } f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}. \quad (4.7)$$

An adaption to this method is made by weighing the SAR by the local perfusion value, rendering the objective function to

$$f(\vec{v}) = \frac{\int_{V_{\text{target}}} P D dV}{\left[\int_{V_{\text{normal}}} (\text{SAR}/w_b)^2 dV\right]^{1/2}} \quad \text{subject to } f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}. \quad (4.8)$$

This method is in between a SAR- and a temperature-based method since it partially includes thermal effects. External cooling and conduction are however not taken
Table 4.2: Summary of the considered objective functions with the corresponding constraints and a short-hand notation. The fractions $f_{P,\text{min}}$ and $f_{P,\text{max}}$ are 0.05 and 0.25, respectively. The normal tissue constraint temperature, $T_{\text{constraint}}(\vec{x})$, is set to 45°C.

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<th>Label</th>
<th>Object Function</th>
<th>Constraints</th>
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<td>T-1</td>
<td>$T_{90}(\vec{v})$</td>
<td>$T(\vec{x}) \leq T_{\text{constraint}}(\vec{x})$ and $f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}$</td>
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<td>SAR-1</td>
<td>$\frac{\int_{V_{\text{target}}} \text{SAR}dV}{\int_{V_{\text{normal}}} \text{SAR}dV}$</td>
<td>$f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}$</td>
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<td>SAR-2</td>
<td>$\frac{\int_{V_{\text{target}}} PDdV}{\left[\int_{V_{\text{normal}}} \text{SAR}^2dV\right]^{1/2}}$</td>
<td>$f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}$</td>
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<tr>
<td>SAR-3</td>
<td>$\frac{\int_{V_{\text{target}}} PDdV}{\left[\int_{V_{\text{normal}}} (\text{SAR}/w_k)^2dV\right]^{1/2}}$</td>
<td>$f_{P,\text{min}} \leq \frac{P_i}{P_{\text{total}}} \leq f_{P,\text{max}}$</td>
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<td>SAR-4</td>
<td>$\frac{\int_{V_{\text{normal}}</td>
<td>\text{SAR}&gt;SAR_{1%}} \text{SAR}dV}{\int_{V_{\text{normal}}</td>
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The maximum value of the SAR-based objective functions was calculated using a standard steepest-ascent implementation.

4.2.3 Tissue perfusion uncertainty

Table 4.3 is a schematic illustration of the effect of uncertainty on optimization and different approaches of analysis. It is based on the simplified case that there are two possible models of a patient, $A$ and $B$, and that it is unknown which one represents the actual patient correctly. If the optimization method uses model $B$ and model $B$ is a correct representation, then temperature $T_B(\vec{v}_B)$ is achieved, where $\vec{v}_B$ is the control vector, holding the optimized phases and amplitudes of the heating system. However, if the patient is in reality correctly represented by model $A$, then applying
Table 4.3: Schematic illustration of the method of analysis comparing different settings for the same patient model (horizontal) or the same settings for a different patient model (vertical). The term ‘model’ here applies to a certain perfusion distribution. However, the same analyses can be applied to different sources of inaccuracy, hence the term ‘model’.

<table>
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<tr>
<th>Actual patient model</th>
<th>Patient model in optimization</th>
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<tr>
<td>A</td>
<td>$T_A(\vec{v}_A)$ $T_A(\vec{v}_B)$</td>
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<tr>
<td>B</td>
<td>$T_B(\vec{v}_A)$ $T_B(\vec{v}_B)$</td>
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The same control vector $\vec{v}_B$ results in a temperature $T_A(\vec{v}_B)$. A comparison of $T_B(\vec{v}_B)$ and $T_A(\vec{v}_B)$ tells how sensitive the delivered thermal dose is to variations in the patient model under the same control vector ($\vec{v}_B$). E.g. suppose that $T_B(\vec{v}_B) = 42.0^\circ\text{C}$ and the perfusion distribution according to model $A$ is such that $T_A(\vec{v}_B) = 41.0^\circ\text{C}$ can be realized, then the difference in predicted and realized temperature equals $1.0^\circ\text{C}$ for those specific settings ($\vec{v}_B$).

On the other hand, a comparison of $T_B(\vec{v}_B)$ and $T_A(\vec{v}_B)$ does not tell how sensitive the optimization method is to uncertainty in the patient model. To answer that question the optimizer should be supplied with the correct patient model, model $A$, resulting in $T_A(\vec{v}_A)$ where $\vec{v}_A$ is the control vector resulting from optimization. Subsequently $T_A(\vec{v}_A)$ can be compared to $T_A(\vec{v}_B)$ measuring the temperature difference that results from supplying an incorrect patient model relative to supplying the correct patient model to an optimization method. Elaborating the previous example, if $T_A(\vec{v}_A) = 41.2^\circ\text{C}$, then the influence of assuming the wrong patient model, model $B$, only affected the optimization result by $0.2^\circ\text{C}$. This number is much more relevant than the previously mentioned $1.0^\circ\text{C}$ since it relates to the best achievable result under the actual circumstances i.e. model $A$.

The robustness of optimization under perfusion uncertainty was studied for five patients with cervix uteri carcinoma treated with hyperthermia. A set of perfusion distributions was generated by variation of standard perfusion values of muscle and tumor by -50%, -25%, 0%, 25% or 50%, in total leading to $5 \times 5 = 25$ possible distributions. For every one of these perfusion distributions, the optimal temperature distribution was computed by temperature-based optimization. These distributions serve as a reference since they represent the best possible temperature distribution in the case that this perfusion distribution represents reality.

Since the real perfusion distribution is not known in practice, standard perfusion
Figure 4.2: Illustration of the concept of sub-optimality versus sensitivity. The administered dose depends on the perfusion distribution assumed during optimization and the real perfusion. If these two do not match this will lead to a different thermal dose than predicted. Only a part of this difference can be attributed to the fact that the incorrect information was provided to the optimizer. This is the sub-optimality. The difference between the sensitivity and sub-optimality is inherent and imposed by the circumstances.
values are used which are estimates. Using these perfusion values in optimization results in settings that are sub-optimal if the perfusion distribution is different during treatment.

To measure this sub-optimality, the settings found with standard perfusion values (standard settings) were evaluated for each of the 25 perfusion distributions. This results in 25 temperature distributions with corresponding $T_{90}$ that are compared to their reference $T_{90}$.

These values can however not be compared directly. The standard settings can give rise to normal tissue temperatures that exceed the constraint temperature since the tolerable power level was determined under other circumstances. On the other hand, if the maximum temperature is below the maximum tolerable normal tissue temperature the power level can be increased to use the standard settings to their full potential. For this reason the power level is adjusted so that the maximum temperature in the normal tissue equals the constraint temperature (section 4.2.4). This conforms to the actions taken in clinical practice.

After scaling, the difference of the $T_{90}$ of the reference solution and the $T_{90}$ following from standard settings gives the sub-optimality: the impact of incorrect perfusion data on optimization.

Figure 4.2 illustrates the applied concept: due to a mismatch of assumed and real perfusion values, the achieved thermal dose will differ from the predicted thermal dose (sensitivity). In this case, only part of this difference can be attributed to providing incorrect information to the optimizer (sub-optimality). The difference between sensitivity and sub-optimality is an inherent difference.

A similar analysis is carried out for the SAR-based techniques: the optimal settings according to the objective functions are evaluated at the limiting power level for the 25 perfusion distributions and compared to their reference.

**Heterogeneity**

The previous method of analysis was concerned with variation in perfusion level for a specific tissue. In reality, intra-tissue perfusion variations are expected as well. To investigate the sensitivity of optimization to intra-tissue variation of the perfusion, the following strategy was followed. On a specified spatial scale, 1cm or 2cm, random variation was applied to the perfusion of muscle tissue (figure 4.3). This variation is uniformly distributed over three discrete levels, either (-25, 0, 25%) or (-50, 0, 50%) and 100 random distributions were considered. For practical reasons, no reference
solutions were calculated since this would involve $5 \times 100$ optimizations per combination of spatial scale and level of variation. Instead the optimal solution according to the temperature-based objective (T-1) under standard perfusion values was compared to the optimal solution according to one of the SAR-based objective functions selected based on performance in the previously described analysis.

### 4.2.4 Power scaling

To evaluate the result of any of the optimization methods under a specific configuration in a clinically relevant way, the total power level should be adjusted such that the normal tissue constraint temperature is still respected. Since solutions resulting from optimization can be retrieved under incorrect input data or by a method that does not incorporate the normal tissue constraints, settings can generally not be applied directly. E.g., if the temperature in the normal tissues is below the constraint temperature in the entire patient, the applied settings are not used to their full potential and the power level can be increased. On the other hand, if the constraint temperature is exceeded, the settings found by optimization should be applied at a lower power level in order for them to be clinically feasible.

Given the linearity of Pennes’ bio-heat equation, the temperature distribution can be split into the temperature distribution that is the result of the actual boundary conditions with zero power and the distribution that results from the imposed power absorption distribution, setting the boundary temperature to zero (28). Math-
Mathematically, 
\[ T(\vec{x}) = T'(\vec{x}) + T_{00}(\vec{x}) \]  
(4.10)

where \( T'(\vec{x}) \) is the temperature at position \( \vec{x} \) due to heating and setting the boundary temperature to zero and \( T_{00}(\vec{x}) \) the temperature due to the actual boundary conditions with zero power. If the power level is \( P \) then applying a power level \( \alpha^2 P \) will change the temperature \( T'(\vec{x}) \) to \( \alpha^2 T'(\vec{x}) \). This can be used to determine the scaling factor
\[
\alpha(\vec{x}) = \sqrt{\frac{T_{\text{constraint}}(\vec{x}) - T_{00}(\vec{x})}{T(\vec{x}) - T_{00}(\vec{x})}}. 
\]  
(4.11) 

The value of \( \alpha(\vec{x}) \) can be computed for every normal tissue point and the minimum value determines the scaling factor that should be applied to make the temperature satisfy the constraint temperature everywhere. It should be noted that the linearity of Pennes’ bio-heat equation under the assumption of constant perfusion is crucial here. 

### 4.3 Results

#### 4.3.1 Variation of level

The effect of tissue perfusion uncertainty on temperature-based optimization for the five patients is shown in figure 4.4 and table 4.4. Every point in the scatter plot represents the \( T_{90} \) after optimizing for one of the 25 perfusion distributions. The reference values are found along the horizontal axis and every point corresponds to a single perfusion distribution. The corresponding value on the vertical axis is the \( T_{90} \) applying the optimization result found with temperature-based optimization using standard perfusion values to that particular distribution. The vertical distance of every point to the line ‘\( y = x \)’ is the sub-optimality. The distribution of the sub-optimality is depicted in the box-plot incorporated in the figures. For all patients, the points that correspond to ‘matching’ muscle perfusion and five different tumor perfusion levels are found on the line ‘\( y = x \)’. This shows that the applied changes in tumor perfusion in those cases do not affect the optimization result.

For the five optimization schemes the distribution of the sub-optimality is shown in figure 4.5. Again, as for the analysis of the temperature-based objective function, the \( T_{90} \) found applying the correct perfusion distribution is the reference value. For all patients, the temperature-based objective function evaluates to be the best
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Table 4.4: Optimal versus realized $T_{90}$ for patients 1 – 5 (top to bottom). The entries formatted as $(\cdot, \cdot)$ give the perfusion variation by $(\Delta \omega_{\text{target}}, \Delta \omega_{\text{muscle}})$ in percentage relative to the standard value.
Figure 4.4: A comparison of the $T_{90}$ found after optimization with constrained temperature-based optimization with the correct perfusion distribution and the $T_{90}$ applying the optimization result found using standard perfusion values. The vertical distance from every point to the line is the sub-optimality. The box plot indicates how the sub-optimality is distributed (whiskers extend to the minimum or maximum value or 1.5 times the inter-quartile range if these limits are not found within that range).
method. The performance of the SAR-based methods relative to the temperature-based method differs from patient to patient and none of the methods proves to be the best for all patients. In addition, the SAR-based methods are not found to be more robust than the temperature-based objective function.

4.3.2 Heterogeneity

The effect of heterogeneity is illustrated in figure 4.6 for different levels of variation and different scale. Here constrained temperature-based optimization (T-1) is compared to optimization method SAR-4. Clearly the spread increased both with level and scale. The latter demonstrates the phenomenon that the thermal effect of perfusion variation on a small spatial scale is reduced by thermal conduction. Except for a small fraction of the total number of evaluated cases (< 5% under an uncertainty of 50%), applying the constrained temperature-based objective function results in the highest thermal dose delivered to the target. Figure 4.7 shows the effect of heterogeneity on the temperature distribution for the constrained temperature-based method for one of the five patients. This is quantified by the average and the standard-deviation of the temperature distribution. With increasing scale and uncertainty level the average is observed to decrease. This is the result of power scaling that is required to meet normal tissue constraints. The normal tissue constraints are exceeded by larger amounts due to the increased uncertainty resulting in larger reductions of the power level. The increased uncertainty is reflected as well in a increased standard deviation of the local temperature.

4.4 Discussion and Conclusions

This study investigated the role of uncertainty in tissue perfusion on the robustness of optimization in hyperthermia treatment planning. It was found that, inspite of large uncertainty in the perfusion distribution and hence in the calculated temperature distribution, constrained temperature-based optimization remains superior over SAR-based alternatives. This holds for uncertainty in perfusion level as well as intra-muscle perfusion variations. Temperature optimization however is largely affected by the studied uncertainty and sub-optimalities up to 1.0°C were found.

Obviously, without accurate (real-time) physiological data and models describing that data, hyperthermia treatment planning cannot provide quantitative information about the temperature distribution as induced during hyperthermia treat-
Figure 4.5: Comparison of different optimization techniques under uncertainty. The horizontal axis holds the different objectives where the SAR related objectives are as defined in table 4.2 (whiskers extend to the minimum or maximum value or 1.5 times the inter-quartile range if these limits are not found within that range).
Figure 4.6: $T_{90}$ evaluated for 100 different perfusion distributions resulting from local random variation of muscle perfusion by -25, 0 or 25% relative to the standard value or with -50, 0 or 50%. The latter level of variation was applied on both a 1cm and a 2cm scale. The applied phase/amplitude settings result from constrained temperature-based optimization (vertical axis) and the SAR-4 optimization method (horizontal axis).
Figure 4.7: The average and standard deviation of the 100 temperature distributions resulting from random variation of the perfusion distribution for one patient. The effect of level and scale of the applied variation is clearly visible.
ment. This hampers clinical application of hyperthermia treatment planning to date. However, in optimization the (exact) temperature distribution is of secondary interest. From the optimization point of view, uncertainty in the temperature distribution is only important when it leads to sub-optimal phase and amplitude settings. E.g., uncertainty in a vast amount of the normal tissue temperature distribution is irrelevant since the temperature is far from the constraint temperature. For this reason sub-optimality was analyzed instead of the error in temperature due to uncertainty.

When comparing different objective functions based on variation of muscle- and target perfusion level, optimization based on SAR (power) proves to be highly sub-optimal. In addition, there was no SAR-based objective function that systematically proved to be the best choice compared to the other SAR-based objective functions. This indicates that the adaptations made to SAR-1 e.g. considering $SAR^2$ instead of the SAR or weighing with the perfusion prove to be ineffective in resolving of what are known to be disadvantages of SAR-based optimization e.g. ignoring external cooling effects and conduction for which the local ‘scale’ of the absorption pattern is crucial.

The influence of heterogeneity on the delivered thermal dose depends on both the level and the scale of variation (figure 4.6). The SAR-4 method was compared to the temperature-based technique optimizing for $T_{90}$ (T-1). This SAR-based objective function performed above average for the different patients, compared to the other SAR-based objective functions, and was therefore selected. Although SAR-based optimization appears to be the best choice in a small fraction of the cases (< 5% for 50% local uncertainty), in the majority of the cases temperature-based optimization shows the best performance.

Apart from the perfusion uncertainty, all the remaining information required and the modelling itself were assumed to be exact. In reality this is not the case and other uncertainties will play a role as well. Examples are uncertainty in the dielectric properties, the actual anatomy of the patient during treatment and the EM and thermal modelling of the water boluses that are applied for reasons of EM coupling and superficial cooling. It is expected that the reliability of both SAR- and temperature-based is decreased by these uncertainties in a comparable amount on average.

Regarding the thermal modelling, one aspect that was not modelled in this study is thermo-regulation. Including any dependency of perfusion on temperature renders Pennes’ bio-heat equation to be non-linear. As a result, the optimization method as used here would no longer be applicable. This requires alternative methods to optimize (42; 48) and this is considered beyond the scope of this study. In addition, the
role of (large) vessels was not taken into account. It is expected that taking these phenomena into account would increase the difference between temperature- and SAR-based optimization even further since temperature-based optimization is capable of anticipating on them.

We demonstrated that the uncertainty in the temperature distribution as a result of uncertainty in the perfusion distribution does not imply that SAR-based methods would be superior to temperature-based methods. For this conclusion to be drawn, the sub-optimality of temperature-based optimization as a result of uncertainty should be larger than the difference in thermal dose comparing the true optimum and the solution according to SAR-based optimization. Based on our results this is not the case, regardless of the chosen SAR-based method. In addition, the SAR-based methods did not prove to be more robust under perfusion variation. The temperature-based method is however significantly affected by the studied uncertainty. In this view, also given the other sources of uncertainty, an adaptive temperature-based procedure anticipating on patient feedback is the best candidate to increase the thermal dose.

Acknowledgments The work described in this article was financially supported by the Dutch Cancer Society (grant UVA – 2006 – 3484).