Loco-regional hyperthermia treatment planning: optimisation under uncertainty

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Chapter 2

Hyperthermia treatment planning: current status and application in the Academic Medical Center Amsterdam
2.1 Introduction

Hyperthermia treatment planning (HTP) is the process of modelling and optimization of the power- and/or temperature distribution prior to or during hyperthermia treatment. This chapter discusses the different steps and the challenges of the process, figure 2.1 provides a schematic overview.

2.2 Imaging

The first step in the simulation process is the imaging of the patient. The acquired images are used to formulate the dielectric and thermal patient model that are needed to compute the power- and temperature distribution later on in the process. At the AMC, the imaging modality used for hyperthermia treatment planning is computerized tomography (CT). In order to image the patient in a posture as similar as possible to that during the hyperthermia treatments, the patient is laying on a water bolus and the same mattresses as used during treatment. An example of such an image, represented by three cross-sections, is given by figure 2.2. The images show that there is a good contrast between fat-like, muscle-like and bone tissue.

2.3 Segmentation

Segmentation is the classifications of volume elements in the acquired image into different tissues or tissue categories. A plethora of segmentation techniques exist ranging from manual (delineation) to semi-automated and automated techniques (21). Important for hyperthermia is that tissues are correctly classified based on thermal and dielectric properties. In our department we use an automated segmentation procedure that is based on the Hounsfield units (HUs) of the CT image. In this way inner air, muscle-, fat-like- and bone tissue can be distinguished. A manual step in the segmentation process is the definition of the target. The target is delineated by a radiation oncologist. Figure 2.3 shows a labelled CT image that is the result of the segmentation including the target definition.
Figure 2.1: Schematic overview of the different steps HTP consists of.
Figure 2.2: Three slices through an image acquired with CT. The patient is laying on the water bolus and the mattresses (not visible). The cross-hair indicates the relative position of the three orthogonal slices.

Figure 2.3: An example of a segmented CT scan based on multiple thresholds. Yellow indicates a fat-like tissue, light blue inner-air, red a muscle-like tissue, green the bony anatomy and the ochre indicates the target volume.
2.4 Formulating the dielectric patient model

Assuming a one-to-one mapping of tissue types to dielectric properties, a dielectric model of the patient can be formulated. The properties of interest are the electrical permittivity and the electrical conductivity. These properties are assigned by using literature values \(^{(22)}\) at the relevant frequency. Important to note is the high contrast between fat-like/bone and muscle tissue, this high contrast can give rise to resonant dielectric structures leading to hot-spots in the tissue.

2.5 Downscaling

In order to limit computational costs, the patient model is re-sampled on a grid with a lower resolution. In our simulation procedure we use the winner-takes-all method meaning that the tissue type of a low resolution voxel is determined by the type that makes up the largest fraction of its volume \(^{(23)}\). The advantages of this method are that the dielectric contrast between tissues is preserved and that it is a very fast method. In addition, a discrete set of media can be used and this set is preserved after re-sampling.

Alternatively an anisotropic method can be used \(^{(24)}\). Here the admittance in the three principle directions is computed so that the information on the orientation of a dielectric interface is preserved. The admittance is computed by solving Laplace’s equation setting the potential to unity at the top and zero at bottom face of a voxel (in the relevant direction). This will result in a potential distribution with a corresponding current distribution. From these distributions an effective admittance and therefore the effective electrical conductivity and permittivity can be computed. Similarly the effective thermal conductivity can be computed from the heat flux within a voxel when applying a temperature difference in the three principle directions. A disadvantage of this approach is that it comes at the cost of a more time consuming and memory expensive procedure.

2.6 Treatment set-up

With the dielectric patient model formulated, the heating system can be defined. Patients are heated with a single ring or both rings of the AMC-8 system. The position of the waveguides is adjusted to the dimensions of the patient. By default, patients
are positioned with the center-of-gravity of the target volume in the center of the heating system. In the direction normal to the waveguide aperture, a 5cm gap is left between the patient and the waveguide. During treatment superficial cooling takes place by means of circulated water boluses. These boluses prevent overheating of normal tissues within the first centimeters measured from the patient’s surface. Not only do the boluses provide cooling, they also are needed to couple the incident electromagnetic fields into the patient since with air between the waveguides and the patient the incident field would largely reflect at the surface of the patient.

2.7 Electric field calculations

After the formulation of a dielectric model of the patient and a model of the heating system, the electromagnetic (EM) fields imposed by the different sources can be computed. Two commonly applied techniques in numerical electromagnetics are the finite-element method (FEM) and the finite-difference time-domain method (FDTD). FEM is a conformal technique (generally formulated in the frequency domain) that is efficient in terms of number of cells. However, generating a mesh is time-consuming and the quality of the mesh has an impact on the quality of the solution.

FDTD is, in its original formulation, a non-conformal voxel based technique. It is, in contrast to FEM, matrix free. Generating the mesh is a straightforward task as it maps naturally from 3D images such as CT images\textsuperscript{1}. An additional advantage is that it is an explicit method (as opposed to implicit for matrix based methods) that is parallel by nature and is well suited for GPU acceleration. FDTD is the technique used in our department.

The FDTD method simulates the evolution of the electric and magnetic field at the points of a regular grid. The simulated signal is processed by taking the discrete Fourier transform (DFT) at the frequency of interest.

2.8 Power-density based optimization

When the electric fields are calculated, a first type is optimization is possible: power-density based or SAR (specific absorption rate)-based optimization. The phases and amplitudes of the sources can be computed such that the power density distribution

\textsuperscript{1}Although the same mesh would also be suitable for FEM calculations, two of its major advantages i.e. conformity and efficiency in terms of number of cells would not apply to that situation
is optimal according to a certain criterion. Such a criterion can for example be the amount of power delivered to the target relative to the total power. It is instructive to consider a simple, 1D, example to understand how the power distribution can be steered.

Consider two plane waves described by fields $E_z^1$ and $E_z^2$. Without loss of generality, we define the amplitudes ($A_1$ and $A_2$) and phases of the fields ($\phi_1$ and $\phi_2$) at $x = \pm L/2$. If field 1 propagates in the $+x$ direction and field 2 propagates in the $-x$ direction then

$$E_z(x) = E_z^1 + E_z^2 = A_1 e^{j(-k(x+L/2)+\phi_1)} + A_2 e^{j(k(x-L/2)+\phi_2)}$$ (2.1)

where $A_1$ and $A_2$ are the amplitudes of the plane waves at $-L/2$ and $L/2$, respectively, $k = 2\pi/\lambda - \delta j (m^{-1})$ is the wavenumber, $\lambda$ (m) is the wavelength and $\delta$ (m$^{-1}$) is modelling the attenuation of the propagating waves. The power density as a function of position is then given by

$$P(x) = \sigma \frac{\sqrt{2}}{2} E_z^*(x) E_z(x)$$ (2.2)

and hence

$$P(x) = \sigma \left( A_1^2 e^{2\delta(x+\frac{L}{2})} + A_2^2 e^{2\delta(x-\frac{L}{2})} + 2A_1 A_2 e^{-\delta L} \cos \left( \frac{4\pi}{\lambda} x + \phi_2 - \phi_1 \right) \right).$$ (2.3)

Here $\sigma$ (S/m) is the electric conductivity of the medium in which the waves propagate and $\ast$ denotes the complex-conjugate.

Figure 2.4 shows for $L = 0.5\text{m}$, $\lambda = 0.5\text{m}$ and $1/\delta = 0.25\text{m}$ the power density distribution as a function of position for two different phase settings: $0^\circ$ and $70^\circ$ phase difference. This example demonstrates a number of important phenomena. First of all, the size of the focus (measured by the full-width half-maximum) is given by $\lambda/4$. Furthermore the location of the optimum is determined by the phases of the two sources independent of the chosen amplitudes. The location of the optimum is given by

$$x_{\text{opt}} = -\frac{\lambda(\phi_2 - \phi_1)}{4\pi}.$$ (2.4)

This also demonstrates that the focus is steered away from the ‘sources’ at $x = \pm L/2$ if the phase of the relevant source is increased while decreasing the phase brings the optimum towards the source. This basic principle is a useful rule-of-thumb in the
Figure 2.4: Electromagnetic interference between two plane waves according to equation 2.3 for two different phase settings: $\phi_2 - \phi_1 = 0^\circ$ and $\phi_2 - \phi_1 = 70^\circ$ ($L = 0.5\text{ m}$, $\lambda = 0.5\text{ m}$ and $1/\delta = 0.25\text{ m}$).
Hyperthermia treatment planning

Finally, the sensitivity of the focus to the phase can be estimated from

$$\frac{\partial x_{\text{opt}}}{\partial \phi_2} = -\frac{\lambda}{4\pi}.$$ 

At 70MHz, the wavelength is approximately 0.5m in water so that the sensitivity is ≈4cm/rad. This means that the phase difference $\phi_2 - \phi_1$ should be changed by approximately 14 degrees to shift the focus with 1cm.

The size of the focus ($\lambda/4$) gives an estimate of the upper limit of the frequency based on target coverage. A target with a representative diameter of 5cm is covered if the wavelength in water equals 20cm which corresponds to a frequency of 175 MHz. This is a very coarse estimation, however it gives an idea in what kind of frequency range loco-regional hyperthermia devices operate. If the frequency is significantly higher the wavelength gets too short and it will no longer be possible to cover the target.

2.9 The thermal patient model and temperature calculations

To translate the calculated power density distribution into a temperature distribution, a model is needed to describe how the absorption of power leads to a rise in temperature. Heat transfer in the human body is characterized by the heat exchange between the tissues and the tissue vasculature. Vessels can be characterized thermally by their the equilibration length ($L_{\text{eq}}$)

$$L_{\text{eq}} = \frac{m_{\text{ves}} c_b}{\pi} \left( \frac{1}{2k_{\text{tis}}} \ln \left( \frac{r_{\text{tis}}}{r_{\text{ves}}} \right) + \frac{1}{\text{Nu} k_b} \right),$$

where $m_{\text{ves}}$ is the mass flow (kg/s), $c_b$ (J/(kg K)) the heat capacity of the blood, $k_{\text{tis}}$ (W/(m K)) the thermal conductivity of the tissue that the vessel is embedded in, $r_{\text{tis}}$ (m) the radius of a cylinder at which a constant temperature boundary condition was applied, $r_{\text{ves}}$ (m) the radius of vessel, Nu (-) a dimensionless number expressing the ratio of conductive and convective heat transfer within the blood and $k_b$ (W/(m K)) is the thermal conductivity of the blood. The equilibration length is a typical length scale over which the blood temperature is affected by heat transfer from the

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2 One of the most important simplifications made here is that broadening of the focus due to thermal conduction is ignored which in practice will improve the coverage.
Figure 2.5: Equilibration length – vessel length ratio as a function of vessel diameter. Vessels for which $L_{eq}/L << 1$ show instant thermal equilibration with their surroundings while vessels for which $L_{eq}/L >> 1$ can be considered volumes of constant temperature. The latter type of vessels give rise to so-called cold-tracks. Data taken from (26).

tissues to the blood. Mathematically, the difference between the inlet and the tissue temperature at radius $r_{tis}$ is reduced by a factor $e^{-1}$ over the equilibration length.

Vessels with a large $L_{eq}$ compared to their length $L$ can be considered as volumes of constant temperature since it takes $10 – 100$ vessel lengths before the blood has travelled one equilibration length.

As the vessels become smaller in length and diameter, $L_{eq}/L$ also reduces. Based on figure 2.5, if the vessel diameter is 0.5mm or smaller it takes 1 vessel length or less to reach the tissue temperature at radius $r_{tis}$. The constant temperature approximation as could be used for the larger vessels is therefore no longer valid.

Following the blood from aorta downstream it will be observed that its temperature does not change until it arrives at the vessels with a diameter of 1mm or smaller. Then, before arriving at the capillaries, the blood will experience some heating, often referred to as pre-heating, whereas in the capillaries instantaneous equilibration with the environment may be assumed. Based on this assumption Pennes in 1948 formulated a continuum approach to model tissue – vasculature heat transfer (27).
Pennes’ bioheat equation is given by

$$\rho_{tis} c_{tis} \frac{\partial T}{\partial t} = \nabla \cdot (k_{tis} \nabla T) - w_b c_b (T - T_a) + P. \tag{2.7}$$

Here $\rho_{tis}$ (kg/m$^3$) is the density of the tissue, $c_{tis}$ (J/(kg K)) the tissue’s heat capacity and $w_b$ (kg/(m$^3$ s)) the tissue perfusion. This equation relates a change in temperature to thermal conduction, cooling by perfusion and heating due to an external source of power. The arterial inflow temperature $T_a$ that appears in the perfusion term of the equation is in general assumed to be constant throughout the patient and as well constant in time. This is one of the limitations of Pennes’ model since it does not naturally incorporate pre-heating.

An example of a calculated temperature distribution is shown in figure 2.6 together with the segmented anatomy and the power density distribution. Although certain features of the power density distribution are found in the temperature distribution as well, external cooling and smoothing by conduction cause clear differences between the power density and the temperature distribution.

### 2.10 Temperature-based optimization

Since temperature is clinically the most relevant parameter (disregarding biological dose or thermal enhancement for now), an optimization method based on temperature is preferred over the previously mentioned power density- or SAR-based optimization method (for a more in-depth discussion see chapter 4). Such a method can be formulated by defining what the optimal temperature distribution is for the target in a mathematical way, an object function, and providing constraints to protect the normal tissue. As a limiting temperature for normal tissues, 45°C will be used in
Since the power distribution can be steered through the phases and amplitudes of the sources, it is computationally beneficial to express the temperature at a certain position in the patient as a function of these phases and amplitudes in an analytical way. If the perfusion is assumed to be constant, Pennes’ bio-heat equation is a linear equation and it can be shown that temperature is given by

$$T(\vec{x}) = \sum_{i=1}^{N} \sum_{j=1}^{N} v_i^* T_{ij} v_j + T_{00}$$  \hspace{1cm} (2.8)

where $v_{i,j}$ is the complex amplitude of the $i$-th or $j$-th source and $T_{ij}$ is the contribution to the temperature due to EM interference between sources $i$ and $j$ (28). The kernel elements follow from calculation of the temperature distribution with the power distribution as a result of sources $i$ and $j$. The temperature at the boundary of the domain is set to zero in this step. The contribution of the boundary conditions to the temperature is given by $T_{00}$ which follows from a temperature calculation applying no power and the actual boundary conditions.

### 2.11 Thermometry and validation of treatment planning

To validate treatment planning, a number of approaches are available. In patients intraluminal measurement probes and in some cases limited invasive probes are available for measurement. These probes are used to monitor the temperature during treatment but can also be used for differential measurements, so called ‘$\Delta T$’ measurements. The initial response to heating is dominated by the power term in Pennes’ equation. Conductive effects are expected to be small as the temperature gradients are still building up. Similarly, the difference between the arterial temperature $T_a$ and the tissue temperature $T$ is relatively small. Hence, the initial change in tissue temperature may be approximated by

$$\rho c_p \frac{\partial T}{\partial t} \approx P,$$  \hspace{1cm} (2.9)

stating that the power density is proportional to the measured temperature rise.

Phantoms provide the possibility to perform measurements more extensively and without the time constraints present in a clinical setting. Phantom measurements also play an important role in the quality assurance of hyperthermia systems.
Ideally, a temperature monitoring system would be non-invasive and provide accurate volumetric temperature data. To date, the imaging modality that approaches this goal the closest is magnetic resonance imaging.

2.12 Feed-back guided steering

Traditionally, HTP is used to calculate how the SAR or temperature distribution depends on amplitude and phase settings. This information is used in a numerical optimization method to calculate optimal phases and amplitudes. However, with reliable volumetric thermometry this dependency can be reconstructed from a series of measurements in which the phases and amplitudes are varied (29; 30). This does not make HTP redundant however, as can be illustrated by a brief analysis of this reconstruction problem.

The power density $P(\vec{x})$ at location $\vec{x}$ in the patient can be expressed in the following way

$$ P(\vec{x}) = \frac{\sigma}{2} \vec{v}^H \mathbf{E}^H \mathbf{E} \vec{v} $$

(2.10)

here $\vec{v} = [A_1 e^{-i\phi_1}, \ldots, A_N e^{-i\phi_N}]^T$ with $N$ the number of independent channels of the phased array system and $\mathbf{E} = [\vec{E}_1, \ldots, \vec{E}_N]$. If $P(\vec{x})$ can be measured for a given steering vector $\vec{v}$, then the following reconstruction problem can be formulated

$$ r^k(E; \vec{x}) = P(\vec{x})^{k,M} - \frac{\sigma}{2} \vec{v}_k^H \mathbf{E}^H \mathbf{E} \vec{v}_k $$

(2.11)

here $r^k$ is the residual function that measures how well the matrix $\mathbf{E}$ describes the $k$-th measurement. Here $P(\vec{x})^{k,M}$ is the power density as measured at position $\vec{x}$ in the $k$-th measurement as indicated by the superscript $k, M$. A set of $6N$ measurements completely describes the antenna profiles (29; 31) as contained in matrix $\mathbf{E}$. The following minimization problem can be formulated

$$ \mathbf{E}^{rec} = \arg \min_{\mathbf{E}} \| \vec{r} \|_2^2 $$

(2.12)

where $\vec{r} = [r^1, \ldots, r^{6N}]$.

There are a number of challenges in this reconstruction problem. First of all the residual functions depend in a non-linear way on the electric field amplitudes and phases. Due to this non-linearity, reconstruction will be based on an iterative method that requires a reasonable estimate for the matrix $\mathbf{E}$ as a starting point for successful
reconstruction. Simulation is the best available option to provide this starting point for complex geometries.

Furthermore it should be noted that a complete reconstruction based on $6N$ measurements is rather time consuming. As an example, suppose that the total time needed for a single measurement consisting of a power pulse, data acquisition and cooling down of the patient equals 2 minutes. This would mean that for a 12 channel system the time needed for reconstruction equals $6 \times 12 \times 2 = 144$ minutes. As the measurements required for reconstruction are performed before the start of treatment, this time would add to the standard treatment time. This is clearly not acceptable in clinical practice and therefore alternative means have to be investigated. A potential solution would be partial reconstruction (30). Partial reconstruction is based on $K < 6N$ measurements so that the reconstruction problem is under-determined, i.e. there are more unknowns in the system than there are equations (or residual functions). To overcome this problem a regularization term has to be added to 2.12, e.g.

$$E_{rec} = \arg\min_E \| \vec{r} \|^2 + W \| E - E^{sim} \|$$

(2.13)

where $W$ is a weight factor (the choice of an appropriate norm to be used in the second term is out of the scope of this example). This regularization penalizes solutions that show large deviations with respect to the electric fields as predicted by simulations. This shows an additional need for simulations even if successful measurements of the power- or temperature distribution can be made.

### 2.13 Topics of research

After a general outline of the simulation procedure, this section will point out a number of topics that are still open to research. A summary is provided in tabular form in table 2.12.

#### 2.13.1 Imaging

A hyperthermia CT scan is typically acquired one week before the first treatment. As a consequence, day-to-day variation of the anatomy that is largely present in the abdomen will cause deviations between the actual anatomy at the time of treatment and the anatomy as encountered during the hyperthermia treatment.
2.13.2 Segmentation

Automatic segmentation by thresholding is an effective and efficient way of segmenting in general. A number of anatomical structures are not correctly classified by this method. One clear example of this is the sacrum. Parts of the bone (the marrow) are incorrectly segmented as muscle or fat tissue. In addition, arteries and veins are neglected by the method. An example of this is found in figure 2.7. Highly perfused organs such as the liver and kidneys are classified as muscle tissue with much lower perfusion. However, those organs are assumed to be sufficiently far away from the target area and hot-spots to not influence their heating.

2.13.3 Dielectric model

Dielectric parameters show large variation ($\pm 50\%$) and for this reason van de Kamer and co-workers (32) investigated the impact of this uncertainty. They concluded that the impact was small on average compared to other uncertain parameters that have to be known for simulation. For hot-spots larger differences were found in power absorption and temperature. However, their analysis was carried out for the co-axial TEM system, a single source system. It is unclear whether these uncertainties become more important for systems with more sources i.e phased-array systems. Furthermore van de Kamer et al. considered the impact of this type uncertainty on the quality of temperature- and power distribution predictions, but not on the quality of optimization.

In order to reduce uncertainty, dielectric properties can be determined by means
of non-invasive (indirect) measurements using MRI. Farace et al. (33) developed a method that images the water content of the different tissues. The dielectric properties are calculated based on a mixture model. By using this method, uncertainty for high water content tissues is expected to be reduced. Uncertainty in low water content tissues remains a problem.

Other methods exploit the similarities between MRI and hyperthermia. In both modalities time-varying fields are encountered that satisfy Helmholtz equation. Formulated in terms of the magnetic field this equation is given by

$$\nabla^2 \vec{B} = -k \vec{B}$$

(2.14)

were $k = \sigma \omega j - \omega^2 \mu e$. As the transverse circularly polarised component of the magnetic field can be measured with MRI (50; 51), the dielectric properties can be reconstructed from this equation. Two major challenges are present in this reconstruction problem. First, due to the presence of the second derivative, noise in the measurement data is amplified. Second, in the derivation of equation 2.14 $k$ is assumed to be constant. For this reason, successful reconstruction requires $k$ to satisfy a piecewise constant function and special care should be taken when handling dielectric interfaces.

### 2.13.4 Definition of the heating set-up

Since the patient is laying on a water bolus, control of position and posture is limited. The scale of the interference pattern at the frequency of 70 MHz is however sufficiently large to allow small shifts in the patient position. The ability of the system to correct for positioning errors depends on the antenna configuration.

By assuming that the patient is surrounded by water, the bolus – patient contact is largely over-estimated. A transition from contact to no-contact, e.g. at the caudal and cranial ends of the water bolus, can lead to a hot-spot due to local strong fields. In addition the plastic layer that is in between the water and the patient is ignored. This layer forms two interfaces with high dielectric contrast, from water to plastic and from plastic to skin. In addition to the electromagnetic effects, the amount of contact will have an impact on the superficial cooling.
2.13.5 EM Calculations

FDTD is a computationally expensive method. Since small dielectric structures can still be relevant, a high level of discretization is required.

A disadvantage of the FDTD method is that the number of time steps that are needed for numerical convergence has to be determined in a representative experiment for the type of simulation problems the FDTD method is used for. Testing for every problem how many time-steps suffice is too time-consuming. A robust implementation of a convergence criterion is therefore preferred. In several studies convergence is tested by probing the electric field in a selective number of points space. However, the choice of the points proves to be critical and easily leads to underestimation of the required number of time steps.

Determining the necessary modelling resolution is another topic of research. The spatial discretization is generally sufficiently fine ($\Delta << \lambda/10$, where $\Delta$ is the grid spacing) to describe the wave propagation however since the dielectric anatomy is characterized by geometrically small structures, sampling should be fine enough to capture these. Resolution however should be carefully chosen since by doubling the number of cells in the three directions, taking the stability limit into account, calculation time increases with a factor of 16. An appropriate downsampling technique can be selected by analysing the convergence of the settings resulting from optimization.

Whether the fact that FDTD is non-conformal is relevant for this application is debatable. The surface reconstruction that is done after segmentation of the different tissues derives from a voxel-based image and is therefore already an approximation. On the other hand an approximation of a surface including its modelling errors might be more precise than a stair-case approximation.

2.13.6 Thermal modelling and temperature-based optimization

In Pennes’ model, large vessels can be defined as volumes of constant temperature and small vessels can be modelled with the perfusion term. The intermediate category is much harder to handle. In these vessels the temperature (during hyperthermia) gradually increases so the approach used for larger vessels can no longer be used. In addition, this ‘pre-heating’ will change the temperature of the blood ‘feeding’ the smaller vessels ($T_a$), reducing the cooling effect of the blood flow. If the transition from large to small scale vessels takes place on a length scale that is sufficiently small, conductive effects will give rise to smoothening and Pennes’ approximation may still be valid. If the length scale is too large for conduction to be
Figure 2.8: Perfusion - temperature relations for fat, muscle and tumor tissue according to (48).

effective, the model is likely to over-estimate cooling by perfusion.

The perfusion parameter in Pennes’ bio-heat equation determines to a large extent the accuracy of the temperature calculations. This parameter can be measured under normothermic conditions, but largely changes under hyperthermia. Unless the hyperthermia device is integrated with a measurement device (e.g. MRI), it is not possible to measure the perfusion distribution under hyperthermic conditions. As a result, the perfusion levels have to be estimated and therefore the temperature distribution is also an estimation.

Thermo-regulation (see for an example figure 2.8) makes the bio-heat equation non-linear, increasing the computational costs of optimization. In addition, whereas the constant perfusion model depends on a single parameter, thermo-regulation is typically described by a 4 parameter model (base-line perfusion, maximum perfusion, a temperature scaling parameter and a critical temperature (48)). Not only can
these parameters be patient specific, they are not said to be homogeneous. More complexity is added by the fact that it is not known on which spatial scale thermo-regulation takes place and this is expected to be of major importance. When perfusion depends on local temperature only, the size of hot-spots is likely to be underestimated by the constant perfusion model. A lower temperature at the boundary of a hot-spot according to the constant perfusion model corresponds to a lower perfusion in the thermo-regulated model and hence the temperature is expected to rise, causing the hot-spot to grow. On the other hand, if the thermo-regulation depends on the maximum temperature in the vicinity of a point, in the limiting case, the thermo-regulated model can be replaced by a model with the constant perfusion at the peak levels.

It is questionable whether knowledge of the perfusion would be enough given the limitations of the bio-heat equation. However, reducing the perfusion uncertainty is an important step to enable reliable quantitative HTP.

Another issue is the modeling of the external cooling by the water boluses. The heat transfer will depend on the flow pattern and the free-stream temperature of the water in the bolus. Since it is complex to recover or predict the flow pattern, a fixed boundary condition is applied. The currently applied boundary condition largely over-estimates the heat transfer and optimization could therefore allow superficial power levels which are not tolerated in practice.

Finally it should be noted that there is only limited basis to prescribe a maximum tolerable temperature (disregarding exceptions such as the spinal cord) to normal tissue. These levels might prove to be tissue dependent and maybe vary from patient to patient. Something similar holds for the acceptable total power level, which can be experienced differently by different patients or in different treatment sessions (due to training effects).
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<td>5</td>
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<td></td>
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<td>-</td>
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Table 2.1: Schematic overview of the steps in the numerical simulation of hyperthermia treatment.