Thermal modelling for hyperthermia

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Thermal modelling for hyperthermia

Thermisch modelleren ten behoeve van hyperthermie
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Het beschreven werk werd verricht op de afdeling Radiotherapie van het Universitair Medisch Centrum Utrecht, participerend in het Image Sciences Institute en de onderzoekschool voor biomédische beeldwetenschappen, ImagO, in een door de Nederlandse Kankerbestrijding gefinancierd project. Deze uitgave is tot stand gekomen met financiële steun van de Nederlandse Kankerbestrijding en het ImagO.
Hey ho let's go
Ramones, Blitzkrieg Bop.


## Contents

1 General introduction
   1.1 Hyperthermia techniques ................................. 1
   1.2 Thermal dose ............................................ 2
   1.3 Calculating a temperature distribution ..................... 4
       1.3.1 Power deposition .................................. 4
       1.3.2 Thermal modelling ................................. 5
   1.4 This thesis ............................................. 8

2 Comparison of temperature distributions in interstitial hyperthermia: experiments in bovine tongues versus generic simulations
   2.1 Introduction ............................................ 11
   2.2 Methods ................................................ 12
       2.2.1 Hyperthermia treatments on isolated bovine tongues with
             the MECS HIT system ................................ 13
       2.2.2 Simulations ....................................... 16
   2.3 Results ................................................ 19
       2.3.1 Measurements on isolated bovine tongues ............ 19
       2.3.2 Simulations ....................................... 21
   2.4 Discussion ............................................. 25
       2.4.1 Temperature profiles along tracks .................. 25
       2.4.2 Temperature plane and volume distributions ......... 28
   2.5 Conclusions ............................................ 29

3 Modelling individual temperature profiles from an isolated perfused bovine tongue
   3.1 Introduction ............................................ 31
   3.2 Agar-agar phantom ....................................... 33
       3.2.1 Measurements agar-agar phantom ................... 35
       3.2.2 Simulations of the agar-agar phantom .............. 37
       3.2.3 Results from agar-agar phantom experiment ......... 37
3.3 Isolated bovine tongue .............................. 38
  3.3.1 Measurements in isolated bovine tongue .... 38
  3.3.2 Reconstruction ............................... 39
  3.3.3 Simulation set up ............................. 40
  3.3.4 Results from isolated bovine tongue experiments 42
3.4 Discussion ........................................ 46
  3.4.1 Agar-agar phantom .......................... 46
  3.4.2 Isolated bovine tongue ....................... 47
3.5 Conclusions ....................................... 51

4 How to apply a discrete vessel model in thermal simulations when only incomplete vessel data is available 53
  4.1 Introduction ..................................... 54
  4.2 Methods ......................................... 58
    4.2.1 Bleed-off in stripped vasculature ......... 60
    4.2.2 Modelling blood that left the discrete vasculature 62
    4.2.3 Evaluation of the temperature distributions 64
  4.3 Results .......................................... 64
    4.3.1 Full tree .................................... 64
    4.3.2 Qualitative comparison between DIVA and the heat sink model 64
    4.3.3 Simulation with incomplete discrete vessel trees 65
    4.3.4 Continuum models and choosing the optimal continuum parameters 68
    4.3.5 Summary of results .......................... 69
  4.4 Discussion ....................................... 71
  4.5 Conclusions ..................................... 74

5 Determination and validation of the actual 3D temperature distribution during interstitial hyperthermia of prostate carcinoma 77
  5.1 Introduction ..................................... 79
  5.2 Methods ......................................... 81
    5.2.1 Patient inclusion and implantation ......... 81
    5.2.2 Reconstruction of the treatment set-up ...... 82
    5.2.3 Electrode temperatures ....................... 83
    5.2.4 Perfusion level and power deposition ...... 84
    5.2.5 Validating the calculated temperature distribution 84
    5.2.6 Agar-agar phantom .......................... 85
  5.3 Results .......................................... 86
    5.3.1 Measured temperature distribution ......... 86
    5.3.2 Simulated temperature distribution and perfusion estimations 86
    5.3.3 Validating in agar-agar phantom ............. 87
    5.3.4 Validating in individual patients .......... 88
Contents ix

5.4 Discussion ......................................................... 90
5.5 Conclusion ......................................................... 94

6 Summary and general discussion .............................. 97
   6.1 Summary of this thesis ......................................... 97
   6.2 General discussion ........................................... 99
   6.3 Prospects of thermal modelling .............................. 102
     6.3.1 Non hyperthermia applications ......................... 104

7 Samenvatting ....................................................... 107

References .......................................................... 111

Publications ......................................................... 120

Dankwoord .......................................................... 123

Curriculum vitae ................................................. 126
Chapter 1

General introduction

Hyperthermia aims at increasing the temperature of malignant tissues to the range of 40-44 °C. It is used adjuvantly to radiation therapy in order to enhance tumour control and survival as was recently demonstrated for pelvic tumours by Van der Zee et al. (2000). A major problem in quality assurance of hyperthermia is the quantification of treatments. Both the duration and the level of the temperature elevation contribute to the applied dose of a hyperthermia treatment (Sapareto and Dewey, 1984; Oleson et al., 1993; Rau et al., 2000). A first requirement to quantify this dose is a description of the full 3D temperature distribution. Measuring by means of invasive thermometry does generally not yield a representative sampling (Corry et al., 1988). An alternative for assessing the full 3D distribution is the use of thermal modelling. To model heat transfer in solids only conduction has to be taken into account. In vivo temperature calculations also have to cope with convective heat transport by blood (Lagendijk, 1990; Roemer, 1990). Cold blood enters the locally heated volume, applies cooling, removes heat and by doing so can severely affect the temperature distribution. Modelling the thermal impact of blood can be done in several fashions as will be discussed in more detail later on. Ideally all blood vessels are taken into account individually (Lagendijk, 2000). However in clinical applications not all vessels needed for thermal modelling can be reconstructed due to limited data acquisition. This thesis addresses the problem of thermal modelling with incomplete angiographic data and also the experimental validation of discrete vessel simulations.

1.1 Hyperthermia techniques

There are various techniques available to heat tissue. The preferred method of heating depends on the location of the tumour and the volume to be treated. Whole body hyperthermia using infra-red heating is used to suppress meta-static
disease (Robins et al., 1997; Berry et al., 1997). Local regional hyperthermia heats large but localized deep seated volumes with electromagnetic radiation in the radio-frequency range (Wust et al., 1995). Higher frequency radiation in the microwave range (Lee, 1995) or ultrasound (Corry et al., 1982) is used for heating superficially located tumours. Small tumours which are accessible for implanting needles can be treated with interstitial hyperthermia, a technique that uses small heating devices implanted in the target volume. Various devices can be used such as ultrasound (Hynynen, 1992; Diederich, 1996), hot water tubes (Brezovich et al., 1989; Schreier et al., 1990) or ferro-magnetic seeds (Mack et al., 1993; Væ Wieringen et al., 1997). A complete overview of the various interstitial techniques can be found in Stauffer et al. (1995). At our department electrodes at 27 MHz operating from within plastic catheters are used (Lagendijk et al., 1995); the so called Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS IHT) system.

In this thesis, phantoms and actual patients are interstitially heated with our MECS IHT system. The MECS IHT system uses capacitively coupled electrodes at 27 MHz (Visser et al., 1989) and is developed at our department in collaboration with the Daniel den Hoed Cancer Center, Rotterdam, the Netherlands (Lagendijk et al., 1995; Van der Koij, 1997; Kaatee, 2000). Figure 1.1 shows the system in operation and the heating applicators used. The electrodes operate from within plastic catheters and are therefore capacitively coupled with the surrounding tissue and behave like current sources (Deurloo et al., 1991). Multiple electrodes (typically 2) per catheter (Kaatee et al., 1997a; Crezee et al., 1999) and multiple catheters (typically 15) facilitate the 3D control of the power deposition at centimeter scale. This is necessary to compensate local cooling due to blood flow (Crezee and Lagendijk, 1992; Van der Koij et al., 1997b; Kaatee et al., 1997b) and tissue heterogeneities (Van der Koij et al., 1996). Originally the system had 64 independent channels, 32 with positive polarity and 32 of negative polarity. From clinical phase I experience (see chapter 5) we learned that the power per electrode was too low. By reducing the number of channels to 32, 16 with positive and 16 with negative polarity the power per electrode was tripled. The system is temperature controlled using 7 sensor thermocouple strings integrated with the heating applicators (De Leeuw et al., 1993; Crezee et al., 1997; Kaatee et al., 1999).

1.2 Thermal dose

To allow comparison of hyperthermia treatments that yield different heterogeneous temperature distributions for different periods of time, these treatments need to be quantified. This can be done by calculating the applied thermal dose. Several definitions of thermal dose are found in the literature (Sapareto and Dewey, 1984; Oleson et al., 1993; Rau et al., 2000). They all obey the intuition that higher temperatures for a longer period of time imply a higher thermal dose. For calculating
1.2. Thermal dose

Figure 1.1: MECS-IHT in operation and exploded view of a two electrode heating applicator.

the thermal dose a reliable 3D temperature distribution is necessary, all the cold and the hot spots need to be taken into account.

Ideally the full 3D temperature distribution is non-invasively measured on-line, for instance by MR thermometry (Nelson and Tung, 1987; Samulski et al., 1992; Wlodarczyk et al., 1998; De Zwart, 2000). However absolute temperature measurements are very hard due to patient movements (De Zwart, 2000) and the temperature resolution is low (De Zwart et al., 1996). Furthermore not all hyperthermia techniques and certainly not our MECS-IHT system are easily integrated with MRI.

In clinical practice temperature distributions are quantified using a limited set of temperature samples. A simple measures is the minimum temperature (Dewhirst et al., 1984; Shimm et al., 1990; Cox and Kapp, 1992; Sneed et al., 1992) or the percentage of samples from the tumour volume above the target temperature (Paulsen et al., 1984; Strobbein, 1994). A step further is to use the samples to produce temperature volume histograms. From the histograms statistical parameters such as \( T_{10} \), \( T_{50} \) and \( T_{90} \) can be derived which indicate the temperature that is...
reached by 10, 50 and 90% respectively of the temperature measurements. These parameters quantify the achieved temperature distribution (Ryan et al., 1994; Stea et al., 1994). This only yields accurate results when the temperature distribution is sampled at representative locations which in general is not the case (Corry et al., 1988).

The full 3D temperature distribution can be obtained from thermal modelling. To do this, the applied power deposition as well as the heat transport have to be calculated. For each hyperthermia technique a dedicated model to calculate the power deposition is needed. For our MECS HTT system (see section 1.1) the model by De Bree et al. (1996) is used. To calculate the temperature distribution the impact of blood flow has to be accounted for because cold blood enters the locally heated volume, applies cooling, removes heat and thus can affect the temperature distribution (Lagendijk, 1990; Roemer, 1990). There are various models to choose from. Basically two approaches can be distinguished, the continuum models and the discrete vessel models, as will be discussed in section 1.3. The first approach models the thermal impact of all blood vessels with a single, global parameter, the latter models the thermal impact of each vessel individually. At our department a Discrete VAsculation (DIVA) thermal model is developed (Kotte et al., 1996, 1999) which is used for calculation of clinical temperature distributions, see chapter 5.

1.3 Calculating a temperature distribution

Calculating the temperature distribution in a patient is basically a two-step process. Unless a hot source (conductive) heating device is used, first the power deposition in the patient has to be calculated, usually presented as the Specific Absorption Rate (SAR) in (W kg\(^{-1}\)). The calculated SAR distribution is then used in a thermal model for calculating the temperature distribution.

1.3.1 Power deposition

Each heating modality needs a dedicated power deposition model. Calculation of the SAR by ultrasound is cumbersome and only recently some investigations started to model the acoustic propagation in actual anatomies (Moros et al., 1999, 2000; Salomir et al., 2000; Mahoney et al., 2001).

To calculate the power deposition from electromagnetic radiation Maxwell’s equations have to be solved. Various methods can be used to calculate the resulting power deposition; Sullivan (1992); Berntsen and Homsleth (1994); Van de Kamer et al. (2001a) use a finite difference time domain approach, Zwamborn et al. (1992) uses a conjugate gradient method, Paulsen et al. (1993) a finite element method.
1.3. Calculating a temperature distribution

For interstitial hyperthermia at 27 MHz the volume of interest (typical dimension 10 cm) is small compared to the wavelength in muscle (approximately 1 m) (Johnson and Guy, 1972). In this case the quasi-static approximation can be used (Dirks, 1988; Hand et al., 1991). De Bree et al. (1996) used this approximation in the power deposition model for the MECS IHT applicators.

1.3.2 Thermal modelling

After the power deposition is calculated, the temperature distribution can be calculated. Basically two approaches can be distinguished, the continuum models and the discrete vessel models as will be discussed below. For a review of heat transfer in hyperthermia see for instance Lagendijk (1990); Chato (1990) or more recently Lagendijk (2000).

Bio-heat model The continuum model used most often is the Pennes bio-heat or heat-sink model (Pennes, 1948). The thermal impact of blood is described by introducing an energy drain which is proportional with the volumetric perfusion level and the elevation of the local tissue temperature. Equation 1.1 states the local heat balance for this model.

\[
\rho_{\text{tis}} c_{\text{tis}} \frac{\partial T}{\partial t} = \nabla \cdot (k_{\text{tis}} \nabla T) - c_{\text{b}} W_{\text{b}} (T - T_{\text{art}}) + P \tag{1.1}
\]

In this equation \( T \) (K) is the local tissue temperature and \( t \) (s) is the time, \( \rho_{\text{tis}}, c_{\text{tis}} \) and \( k_{\text{tis}} \) are the tissue density (kgm\(^{-3}\)), specific heat (JK\(^{-1}\)kg\(^{-1}\)) and thermal conductivity (WK\(^{-1}\)m\(^{-1}\)) respectively, \( c_{\text{b}} \) is the specific heat of blood, \( W_{\text{b}} \) the volumetric perfusion rate (kgm\(^{-3}\)s\(^{-1}\)), \( T_{\text{art}} \) the arterial blood temperature (K) and \( P \) is the sum of the absorbed power and metabolic heat production (Wm\(^{-3}\)).

The term on the left hand side of the equal sign describes the temperature evolution in time, the first term on the right hand side of the equal sign describes the heat transfer due to conduction, as occurs in solid materials. The second term is the actual contribution of blood to the heat transfer, the assumption is that arterial blood with temperature \( T_{\text{art}} \) is heated in the capillaries to the local tissue temperature \( T \) without any pre-heating.

Equilibration length In reality blood is pre-heated by the interaction with the heated surrounding tissue. The rate at which a vessel is heated can be quantified by the equilibration length (Chen and Holmes, 1980), characterizing the distance it takes for the blood in a vessel to thermally equilibrate to the temperature of the surrounding tissue. Main arteries typically have a high flow and large equilibration length in the order of meters (Crezee and Lagendijk, 1992). Capillaries have low flow, very short equilibration lengths (0.1 \( \mu \)m (Crezee and Lagendijk, 1992)) and are therefore always in thermal equilibrium with the surrounding tissue. Chen and
Holmes (1980) and Van Leeuwen et al. (2000b) showed that vessels with a diameter between 0.2 and 0.5 mm take care of a major part of the thermal equilibration of the arterial blood and are therefore thermally significant.

**Sophistication of the bio-heat model and the effective conductivity model** The bio-heat model by Pennes (1948) uses a very basic method to incorporate blood flow in thermal simulations. Wulff (1974) presented a sophistication of the bio-heat model by replacing the non-directional perfusion term $W_b$ by a directed flow. The problem with this model is that when the net mass flow is zero, the impact of blood is assumed non-existing while for instance 2 counter current vessels with equal flow will certainly affect the heat transport. Furthermore, also this model does not take into account the pre-heating of blood. Chen and Holmes (1980) investigated the equilibration length and thus the pre-heating of blood vessels. They concluded that all large, thermally significant, vessels should be modelled individually and the remaining, not-discretely modelled vessels should be taken into account by a conventional heat sink combined with a directional flow term as presented by Wulff (1974). Additionally they introduced a term which describes the enhanced thermal conductivity due to vasculature. Weinbaum and Jiji (1985) demonstrated that incomplete counter-current heat exchange is the primary mechanism of heat transfer and they proposed a limited $k_{ef}$ model which describes the thermal impact of blood solely by an enhanced thermal conductivity tensor.

Whether to use a heat-sink model or an enhanced thermal conductivity model depends on the equilibration length of the vessels to be modelled collectively (Baish et al., 1986). Charny et al. (1990) showed that for hyperthermic conditions the vessels with diameters smaller than 200 µm should be modelled with the limited $k_{ef}$ model. The COMAC workshop on treatment planning and modelling (ESHO Taskgroup Committee, 1992) recommended the use of a mixed heat-sink and $k_{ef}$ model in cases where no discrete vessels are available. However a continuum model can never predict the thermal impact of individual vessels and a discrete vessel model is preferred above continuum modelling (Lagendijk, 1982; Crezee and Lagendijk, 1992; Lagendijk et al., 1994; Rawnsley et al., 1994; Kolios et al., 1995; Van Leeuwen et al., 2000b; Raaymakers et al., 2000b).

**Discrete vasculature modelling** In a discrete vessel model the thermal impact of many vessel segments within a complex vasculature have to be taken into account individually. The impact on the temperature distribution can be calculated analytically only for very basic vessel configurations as done for single vessels by Chen and Holmes (1980); Crezee and Lagendijk (1992); Huang et al. (1994) and for counter-current vessels by Weinbaum et al. (1984); Baish et al. (1986); Wissler (1988); Zhu et al. (1988, 1990); Zhu and Weinbaum (1995). Therefore modelling
the thermal impact of a complex, detailed, discrete vasculature has to be done numerically.

The first numerical models could only cope with straight vessels (Lagendijk et al., 1984; Chen and Roemer, 1992; Rawnsley et al., 1994; Chan, 1992) or branching networks with only perpendicular vessel connections (Huang et al., 1996). Mooibroek and Lagendijk (1991) presented a more versatile model which could cope with curved vessel networks. However the vessel description is directly coupled with the resolution of the discretized tissue, which makes describing extensive and curved vasculature cumbersome.

At our department a very flexible and versatile Discrete VAsculature (DIVA) model has been developed (Kotte et al., 1996, 1999). The vessel description is done geometrically and is fully independent of the tissue description. It can calculate the thermal impact of very detailed vessel networks as demonstrated for instance in Van Leeuwen et al. (1999, 2000b) and in chapter 4 of this thesis.

**DIVA thermal model** The conductive heat transport in tissue is modelled using a finite difference scheme. For the calculations the anatomy is discretized on a rectangular grid into tissue voxels and the tissue properties of each voxel can be set. The vessels are described as geometrical, curved tracks in 3D with an associated diameter and blood flow. This way the vessel definition is fully independent of the tissue discretization. Vessel networks, both arterial and venous, are constructed by connecting the individual vessel segments.

The axial temperature profile along a vessel segment is discretized one dimensionally. The interaction with the tissue is calculated using tissue temperature samples, a blood temperature sample and the distance between the center of the vessel and the location of the tissue temperature sample. The heat flow across the vessel wall is calculated using an analytical expression that describes the heat flow from a central tube (the vessel) inside a larger cylinder (the surrounding tissue), see Kotte et al. (1996, 1999) for details.

The blood flow is defined per segment and flow conservation at junctions is not mandatory. If at a branching point blood flow is not conserved a bleed-off is created. This bleed-off can be used to incorporate the loss of blood along a vessel segment by not-discretely modelled small vessels and micro-vasculature branching of that vessel segment. The blood leaving the discrete vasculature, at these bleed-off locations or at the end of the network, is not per se in thermal equilibrium with the surrounding tissue. DIVA offers various methods to complete the thermal equilibration of this out-flowing blood. In chapter 4 five strategies to do this are investigated.
Validating DIVA and incomplete discrete vasculature. For simple vessel geometries DIVA has been theoretically validated by comparing simulated temperatures with analytic results (Van Leeuwen et al., 1997b,a). Validating simulations of volumes with complex vessel networks requires experimental validation. This thesis presents a experimental validation in realistically perfused phantoms and in patients.

Validation was first performed on isolated, perfused, bovine tongues. This allows full control over the perfusion and very precise anatomical and angiographic reconstruction with a cryo-microtome (see chapter 3). Obviously this procedure can not be applied to patients. For real patients data acquisition is done using ultrasound (chapter 5) or MRI (Raaymakers et al., 2000c). The anatomy and the heating implant can be reconstructed relatively easy. However, the discrete vessels, especially the small ones, are hard to reconstruct individually. Current clinical MR (Börjesson and Stöcker, 1997) and ultrasound techniques (Kruger Hagen et al., 2001) do not reveal all thermally significant discrete vessels. Using these incomplete vessel data means that the thermal interaction of the blood with the tissue is not completed. Several methods are available to complete this thermal interaction (Kotte et al., 1999; Van Leeuwen et al., 2000b; Raaymakers et al., 2000b). Five different strategies to do this are investigated in chapter 4.

1.4 This thesis

Summarized in one sentence, the aim of this thesis is experimental validation of thermal simulations that include discrete vessels and investigating the impact of incomplete angiographic data on thermal simulations. This is done first on isolated, perfused, bovine tongues with very extensive data acquisition. Secondly in a clinical setting while calculating the temperature distribution in prostates during interstitial hyperthermia. Before conducting the clinical validation a study has been performed aiming at compensating the thermal impact of limited angiographic data. The reason is that in a clinical situation not all thermally significant vessels can be reconstructed individually.

In chapter 2 the measured temperature distributions from isolated, perfused bovine tongues heated with the MECS IHT system are presented at various perfusion levels. The results are compared with simulations of a generic bovine tongue to see if a generic description suffices to predict the temperature distribution accurately.

In chapter 3 a more thorough validation is done by comparing temperature profiles from an isolated, perfused bovine tongue with simulations of the reconstruction of that particular tongue. A one-on-one comparison between measured and simulated temperature profiles is conducted. The power deposition model (De Bree et al., 1996) is left out of the validation by using hot water sources for heating. These
apply steady, well-defined thermal boundary conditions which can be used directly in DIVA and thus no power deposition has to be calculated.

In chapter 4 five different strategies are presented for modelling the thermal impact of not discretely modelled vessels in addition to a limited discretely modelled vessel network. A volume with a full, artificially generated but realistic, counter current vessel network and a power deposition is defined and the temperature distribution is calculated. To mimic incomplete discrete vasculature the full tree is gradually stripped, that is, the number of discretely described vessels is reduced in four steps until no discrete vessels are left. For each strip-level the temperature distribution is calculated for the five different compensation strategies. The resulting temperature distributions are compared with the full tree simulation.

In chapter 5 DIVA is used to calculate the temperature distribution in the prostate during interstitial hyperthermia with the MECS IHT system. No discrete vasculature could be reconstructed. The perfusion level is estimated from the thermal simulations combined with the thermal wash-out at the end of the treatment. The calculated temperature distribution is validated by comparing individual thermosensors from the measurements and from the simulations. The thermometry integrated with the heating applicators was used, as well as dedicated additional thermometry catheters and thermometry from within applicators that were switched-off for a certain period of time.

In chapter 6 this thesis is summarized and the prospects of thermal modelling are discussed.
Chapter 2

Comparison of temperature distributions in interstitial hyperthermia: experiments in bovine tongues versus generic simulations

This chapter has been published as

Abstract

Temperature distributions resulting from hyperthermia treatments on isolated perfused bovine tongues were compared to simulations by a treatment planning system. The aim was to test whether the discrete vessel model used for the treatment planning is able to predict correct generic temperature distributions.

Tongues were heated with the Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS IHT) system, while the steady state temperature distribution was mapped by scanning 10 thermocouples along paths perpendicular to the interstitial implant. For simulations a tongue was defined with generic discrete vasculature and an electrode implant analogue to the experiments. To model vascular generations not described discretely, a local heat-sink was implemented at the end of each terminating branch.

The discretely modelled vasculature showed itself on the temperature distributions in two ways. Individual vessels caused very local, sharp wells in the tracked temperature profiles. In the presence of large vessels a collective behaviour was also seen, i.e. a regional lowering of temperature. Both phenomena can be recognized in the experimentally obtained temperature distributions too. Predicting correct generic temperature distributions is feasible with the discrete vessel model used.
2.1 Introduction

Clinical hyperthermia is the application of elevated tissue temperatures. For an adequate hyperthermia treatment, a homogeneous tumour temperature distribution as well as a sufficiently high temperature is needed. Tissue heterogeneities (Van der Koij et al., 1996) and especially large blood vessels (Lagendijk, 1990; Roemer, 1990) affect the temperature homogeneity. Treatment planning can help to diminish these temperature heterogeneities, requiring modelling of the thermal behaviour of the vasculature (Lagendijk et al., 1993).

Pennes (1948) proposed a heat-sink model, Chen and Holmes (1980) and Weinbaum and Jiji (1985) an enhanced effective tissue conductivity to describe convective heat transfer by vasculature. Experiments were performed in isolated perfused organs (Crezee et al., 1991; Kolios et al., 1996) and in vivo (Schreier et al., 1990; Moros et al., 1993) to test the validity of these models. The results show these models give a rough approximation of bio-heat transfer. The problem with these models is that they give a continuum description of basically discrete vasculature, they cannot predict the local temperature near discrete vessels and are therefore not suitable for hyperthermia treatment planning (Lagendijk et al., 1993). Recent bio-heat models incorporate a real physical description of individual vessels (Moolbroek and Lagendijk, 1991; Rawnsley et al., 1994; Kotte et al., 1996) instead of a continuum parameter.

The model developed by Kotte et al. (1996) is the first that allows thermal modelling of patient specific discrete vasculature. This paper is a first test whether this model is able to predict general characteristics in the temperature distributions in perfused tissue. To this end simulations of a generic bovine tongue with a generic vessel structure are compared to steady state temperature distributions measured in isolated perfused bovine tongues. Validation by modelling individual tongues is the topic of current research and not included in this paper. This requires a geometrical description of the tongue specific vasculature on a scale that is not available yet.

The tongues were heated interstitially by a current source system (Lagendijk et al., 1995) and temperature distributions were mapped at various perfusion rates up to 7 ml (100 gr)−1 min−1. For simulations a tongue model was used with a generic vasculature based on Crezee et al. (1991) and elaborated with a network constructing program by Van Leerwen et al. (1995). The temperature distribution was computed using a discrete vessel model (Kotte et al., 1996). To settle for vessel generations not taken into account discretely local heat-sinks/sources were introduced the end of the terminating segments. At terminating arteries the outgoing blood is equilibrated instantaneously to the local tissue temperature (determined in a spherical volume centered around the end of the vessel), the required energy is extracted from the surrounding tissue. Veins start at the local tissue tem-
2.2 Methods

2.2.1 Hyperthermia treatments on isolated bovine tongues with the MECS IHT system

Hyperthermia equipment   The 27 MHz Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS IHT) system (Lagendijk et al., 1995) heats tissue by electrodes, which are capacitively coupled (Visser et al., 1993) with the tissue via the plastic catheter wall (see Figure 2.1(b)). An array of electrodes is implanted to control the transversal power steering, the probes are segmented to provide longitudinal control of the power deposition. There are two groups of 32 channels with opposite polarity, so dipole fields can be generated. In Figure 2.1 tissue heating with a dual electrode is depicted schematically. A 7 point thermocou-

![Diagram](image.png)

(a) Electrode in tissue.

(b) Schematic of capacitive coupling.

**Figure 2.1:** Diagram of tissue heating by a dual electrode.

ple string (constantan manganin) is included in the electrode (Crezee et al., 1997). The duty cycle steering of each electrode is controlled by a reference temperature of the corresponding thermocouple. The combination of short (1 cm) electrodes with treatment planning provides an excellent way of compensating local cooling heterogeneities (Van der Koij et al., 1996, 1997b), e.g. due to presence of cold vessels. In this study 2 cm dual electrodes are used, furthermore their position is not optimized with respect to the vasculature, thus temperature homogeneity is not optimal. This is not necessary as our main goal is comparing experiments with simulations.
Chapter 2. Validation in generic bovine tongues

Experimental setup  Measurements were performed in isolated bovine tongues at various perfusion levels, and also in a no flow phantom tongue (a cylindrical plastic bag filled with homogeneous, at 27 MHz muscle-like tissue). A bovine tongue is a suitable clinical phantom for hyperthermia treatments. The vasculature (shown in Figure 2.4(b)) is similar to that of humans and the tissue consists primarily of homogeneous muscle. Therefore local cooling heterogeneities will be due to the cooling effects of vessels mainly, and not to tissue heterogeneity. To control the perfusion in bovine tongues, the arteries are connected to a perfusion circuit (Bos et al., 1991) and the flow is controlled using a roller pump (Watson-Marlow 505S/RL). The perfusion is determined by dividing the total inflow rate by the tongue weight. Perfusion levels between 0 and 7 ml (100 gr) min⁻¹ were used. In vivo the perfusion varies between 3 and 80 ml (100 gr) min⁻¹ (Guyton, 1981).

A diagram of the experimental setup is shown in Figure 2.2(a). The whole setup is kept at room temperature. The bovine tongues (the first 20 cm) were suspended with their tip down and perfused with a blood replacing medium (serum free Minimal Essential Medium (S-MEM), Life Technologies, Breda, the Netherlands). An artificial lung (Baxter Univox oxygenator) was used for oxygenation with Carbo-gene (95% O₂, 5% CO₂). To prevent dehydration of the skin the tongues were rubbed with an aqueous ointment (per gram: 300 mg H₂O, 70 mg wool fat, 30 mg wax, 40 mg mono-oleine, 560 mg vaseline). With this setup the tongue is a useful phantom for about 10 hours, after that edema occurs. Figure 2.2(b) shows the

![Diagram of the experimental setup](image1)

**Figure 2.2:** Schematic setup of the experiment and of the isolated bovine tongue with the position of the electrodes and the thermocouple tracks relative to each other.
plane of thermocouples and the electrode configuration relative to each other. The hexagonal implant consisted of 7 nylon catheters with 16 mm spacing, loaded with dual electrodes (5 mm gap) of 20 mm length per segment and 1.2 mm diameter. The target temperature was set to 30 degrees Celsius (approximately 8 degrees above room temperature). The temperature distribution was mapped in a plane perpendicular to the electrodes by scanning a row of 10 parallel bare constantan manganin thermocouples (diameter 100 \( \mu \)m) in 1 mm steps by means of a micro manipulator (Prior, precision 0.1 mm accuracy 0.1 mm). The spacing of the tracks was 5 mm, the scanned area extends 15 mm around the implant. Three tracks were meant to skim the electrodes in order to register the local temperature maximum. The plane was located approximately 1 cm from the middle plane of the implant, i.e. 1 cm from the point in between two electrodes in one catheter. (In one case two planes were scanned simultaneously, the second plane was located at about 2 cm from the middle.) The plane is also shown schematically in Figure 2.4, the tracks run parallel with the \( x \)-axis, i.e. in vivo they would run caudally, towards the largest vessels (arteries profunda linguae and corresponding veins). The experiments were carried out on five bovine tongues, in which altogether six planes of 10 thermocouple tracks each were scanned at various perfusion levels.

In the phantom tongue experiments a simple household ventilator (30 W) was used to apply more stable boundary conditions. This was not done when using bovine tongues, the convected air would enhance the vapourisation of perfusion fluid running down the skin, yielding less stable boundary conditions.

Data acquisition The temperature measurements are performed during power off of the MECS IHT system to overcome interactions of the generated current field with the thermocouples. The thermometry system was specially designed to get rid of electrical interactions within 1 s, all channels are read within 320 ms and the precision is 0.005 K, described in detail by De Loouw et al. (1993). Temperature profiles are obtained by measuring the temperatures as a function of length along the thermocouple tracks and the data are considered in two ways: 1) individual temperature profiles, 2) temperature plane distributions by combining profiles.

The procedure of analyzing the temperature plane data is shown using an example. In Figure 2.3(a) a temperature plane distribution is shown consisting of \( 10 \times 60 \) data points. The hexagon indicates the region of interest of the plane, the cross section of the plane of thermocouples with the convex hull around the electrodes.

The (linearly) interpolated data of Figure 2.3(a) result in a 2D temperature distribution (Figure 2.6). This gives a qualitative impression of the homogeneity of the temperature distribution. For a quantitative impression \( T_{10} - T_{90} \) is used, a parameter extracted from the cumulative temperature volume histogram (CTVH) depicted in Figure 2.3(b). A CTVH shows the volume fraction (\( y \)-axis) above a
certain temperature ($x$-axis) (Ryan et al., 1994; Stea et al., 1994). The temperature of the target volume before treatment is the origin. $T_{10}$ is the temperature above which 10 percent of the volume samples lies. The definition of $T_{50}$ and $T_{90}$ is similar. The $T_{10}$-$T_{90}$ is an indication of the heterogeneity of the target volume. In Figure 2.3(b) the $T_{10}$-$T_{90}$ of the histogram is projected on the $x$-axis. The calculation of $T_{10}$-$T_{90}$ (of a plane instead of a volume) is done with the non-interpolated data.

2.2.2 Simulations

The experiments performed with bovine tongues as described in section 2.2.1 are simulated by a treatment planning system. The bovine tongue is approximated by a cylindrical muscle containing a generic vessel network, surrounded by air at a fixed temperature. This allows a comparison between trends in the experiments and simulations. The perfusion levels in the simulations vary between 0 and 12.5 ml (100 gr$^{-1}$) min$^{-1}$, a larger range than used in the experiments because generic simulations are made, i.e. the perfusion levels can not be compared exactly to the experimental ones.

The treatment planning system A finite difference model is used to describe conductive and convective heat transport in a volume heated by interstitial current
sources. A volume with vasculature can be defined together with an electrode implant. Simulation of the treatment consists of two steps. The power deposition at a certain current injection by the electrodes on the grid is calculated by solving the Maxwell equations using a finite difference method (De Bree et al., 1996). Successively the temperature distribution is calculated (Kotte et al., 1996). Both models are fully 3–dimensional. The vessel description is geometrical, independent of the grid size of the volume.

For simulating an actual treatment a control program is used which sequentially calculates the power deposition and the temperature distribution. The reference temperature of each electrode can be given and after each temperature calculation the injected currents are evaluated until a stable temperature distribution is reached (Van der Koijk et al., 1996). The maximum (reference) temperature allowed on the electrodes was 8 K. The initial and boundary temperature were set to 0 K as was the inflow temperature of vessels entering the modelled volume.

Table 2.1: Media properties used in the simulations.

<table>
<thead>
<tr>
<th>medium</th>
<th>$\sigma$ [S m$^{-1}$]</th>
<th>$\epsilon_r$</th>
<th>$\rho$ [kg m$^{-3}$]</th>
<th>$c_p$ [J kg$^{-1}$ K$^{-1}$]</th>
<th>$k$ [W m$^{-1}$ K$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>'air'</td>
<td>0.7</td>
<td>80</td>
<td>1000</td>
<td>4000</td>
<td>0.1</td>
</tr>
<tr>
<td>muscle</td>
<td>0.6</td>
<td>113</td>
<td>1000</td>
<td>4200</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Volume modelled The simulated volume is depicted in Figure 2.4(a) together with the electrode implant. The size is 6.6 cm by 6.6 cm by 5.0 cm and is divided in voxels of 1 cubic millimeter. Each voxel contains an index to represent its media properties, shown in Table 2.1. The volume is of medium type 'air', and contains a cylinder of medium type 'muscle' with a radius of 3.2 cm and a height of 5.0 cm. Only the part of the tongue with the implant is modelled, at the top and bottom plane of the cylinder no heat can be exchanged, i.e. adiabatic boundary conditions are applied. On the air-tongue boundary heat is exchanged conductively, the temperature of 'air' is fixed to 0 K. The 'air' can absorb heat without an increase of its temperature, hence its density has no effect on heat transport; using an extended density allows the simulations to run faster. The thermal conductivity of 'air' is set in accordance with the effects of forced convection, as in the case with a phantom tongue.

In Table 2.1, $\sigma$ is the electric conductivity, $\epsilon_r$ the relative permittivity, $\rho$ the mass density, $c_p$ the specific heat capacity and $k$ the thermal conductivity. The electrode implant is similar to the one used in the experiments, described in section 2.2.1 (see Figure 2.2(b) and 2.4(a)).
Chapter 2. Validation in generic bovine tongues

(a) Modeled tongue with electrodes, the vasculature used and a plane of which the temperature distribution is determined, extracted temperature profiles lie in this plane, in the direction of the negative $x$-axis.

(b) Generic vasculature.

Figure 2.4: Simulated volume and the vessel network used (scale is in meters).

Vasculature The vessel network (Figure 2.4(b)), is based on anatomic information and elaborated by a network constructing program. The main arteries (the inner two structures) and their first branches form the basis together with the accompanying veins (the outer ones) (Crezee et al., 1991). Further generations of branches are created by a network constructing program (Van Leeuwen et al., 1995). The diameter of the first arterial and venous segments is 2 and 3 mm, the diameter of the smallest terminating branches is 0.26 and 0.44 mm respectively. The diameters of the remaining segments are set such to obtain the same flow in branches of one generation. The vessel network used is implemented with conservation of blood flow, i.e., when the total inflow rate is doubled the flow rate through individual vessels is doubled. The equilibrium length (Chen and Holmes, 1980) for the terminating segments is approximately 1 cm at 3.13 ml (100 g) $^{-1}$ min $^{-1}$. Further elaboration of the discrete vasculature is too time consuming at present, smaller vessels are settled for by a local heat-sink in a spherical volume centered around the end of the vessel. The energy needed to equilibrate the blood in the terminating segment to the local tissue temperature is withdrawn from this volume. Such a distributed heat-sink dependent on the local tissue temperature was
2.3. Results

2.3.1 Measurements on isolated bovine tongues

*Individual temperature tracks*  Figure 2.5 shows temperature profiles along four typical tracks, in Figure 2.5(a) from the phantom tongue, in Figure 2.5(b) and 2.5(c) from a bovine tongue at no flow and at 6 ml (100 gr)⁻¹ min⁻¹. All tracks show higher temperatures on the left hand side due to the presence of a thermally insulating template for inserting the thermocouples. In the phantom tongue the temperature profiles are very smooth, only the electrodes and boundaries are distinct features. When using the same configuration of tracks in bovine tongue with no perfusion the signature of the electrodes on the temperature profile is less pronounced, because positioning thermocouples and electrodes accurately is hard in fresh bovine tongues due to the tough skin around the soft muscle. When flow is applied the profile of two tracks is not affected very much while the others are lowered and two clear local minima ('wells') are seen, in track 56 and 57.

*Temperature plane distributions*  A typical interpolated temperature plane distribution (constructed from 10 tracks with 60 temperature samples each) is shown
Chapter 2. Validation in generic bovine tongues

(a) Temperature profile in the phantom tongue.

(b) Temperature profiles in bovine tongue at no flow.

(c) Temperature profiles in bovine tongue at 6 ml (100 gr)\(^{-1}\) min\(^{-1}\).

Figure 2.5: Temperature profiles for individual tracks (experimental data).
in Figure 2.6 for a flow of 0 and of 7 ml (100 gr)\(^{-1}\) min\(^{-1}\). The electrodes are visible as hot spots, especially in the flow situation. The temperature distribution is quite uniform in the no flow situation. At increasing flow, the entire temperature distribution is lowered. Again the left hand side remains warmer in both panels due to the presence of the template.

![Graphs](image.png)

(a) No flow.  
(b) 7 ml (100 gr)\(^{-1}\) min\(^{-1}\).

**Figure 2.6:** Interpolated transversal planes (experimental data).

**Cumulative temperature plane histograms** The cumulative temperature plane histograms (CTPH's), corresponding with the panels of Figure 2.6 are shown in Figure 2.7(a). The tilted histogram of the flow situation points to increased heterogeneity. Figure 2.7(b) shows CTPH's of no flow situations in various tongues, including the phantom tongue. Although the planes in the various tongues are located within a range of 2 mm around the center of either one of the electrodes, \(T_{50}\) varies clearly.

Figure 2.8(a) shows \(T_{10}-T_{90}\) and Figure 2.8(b) shows \(T_{50}\) as function of the perfusion. Figure 2.8(a) shows planes reacting with differing sensitivity on flow and Figure 2.8(b) shows a decreasing \(T_{50}\) as function of the flow. (The data shown in Figure 2.6 Figure 2.7(a) and can be found in Figure 2.8 as tongue 21-03-96.)

**2.3.2 Simulations**

**Iso-temperature surfaces** The resulting temperature distributions are visualized in Figure 2.9 by iso-temperature surfaces at 4 and 5 K (flow 3.13 ml (100 gr)\(^{-1}\) min\(^{-1}\)).
Figure 2.7: Cumulative temperature plane histograms (experimental data).

Figure 2.8: $T_{10}-T_{90}$ and $T_{50}$ versus perfusion, for all tongues (experimental data).
2.3. Results

Only the large vessels are included to clarify the orientation. Vessels clearly penetrate the iso-temperature surfaces.

\[ \text{Figure 2.9: Iso-temperature surfaces at } 3.13 \text{ ml (100 gr)}^{-1} \text{ min}^{-1} \]

with a dual electrode implant, a simplified vasculature is shown for sake of clarity (simulated data, scale is [m]).

Cumulative temperature volume and plane histograms In Figure 2.10 the CTVH of the no flow, the 0.39, 0.78, 1.56, 3.13, 6.25 and the 12.5 ml (100 gr)\(^{-1}\) min\(^{-1}\) flow situation are shown. The histograms shift to the lower temperatures at higher perfusion rates. In Figure 2.11(a), CTPH's of the no flow situation are shown. Because of the symmetry, only planes of one half of the implant are shown. In Figure 2.11(b) the \(T_{50}\) (upper graph) and the \(T_{10}-T_{90}\) (lower graph) of the CTPH's are plotted as a function of the plane shift, relative to the middle plane. The planes from Figure 2.11(a) are denoted by the black squares. The heterogeneity is 0.6 K for all planes, but \(T_{50}\) increases towards the middle; planes near the middle have higher temperatures than planes near the border. The local minimum around the middle plane is due to the gap between the electrodes.

Figure 2.12(a) shows the CTPH's at 6.25 ml (100 gr)\(^{-1}\) min\(^{-1}\) of the planes of Figure 2.11(a). Heterogeneity varies strongly per plane. Figure 2.12(b) shows \(T_{50}\) (upper graph) and \(T_{10}-T_{90}\) (lower graph) as a function of the plane shift. The planes from Figure 2.12(a) are denoted by the black squares. \(T_{10}-T_{90}\) is increasing towards the middle, whereas \(T_{50}\) is decreasing.
Figure 2.10: Cumulative temperature volume histograms for various flow rates (simulated data).

Figure 2.11: Cumulative temperature plane histograms and the $T_{50}$ and $T_{10}-T_{90}$ versus the plane shift in the no flow situation (simulated data).
2.4 Discussion

2.4.1 Temperature profiles along tracks

The tracks for the simulated no flow simulation (Figure 2.14) and for the phantom tongue (Figure 2.5(a)) show qualitative agreement, bearing in mind no attempt was
Chapter 2. Validation in generic bovine tongues

(a) $T_{10} - T_{90}$ per plane as function of the perfusion.

(b) $T_{50}$ per plane as function of the perfusion.

Figure 2.13: $T_{10} - T_{90}$ and $T_{50}$ per plane and of the whole volume, as function of the perfusion (simulated data).

(a) 4 Temperature profiles in the no flow situation.

(b) The 4 temperature profiles of Figure 2.14(a) all shifted 2 mm.

Figure 2.14: Temperature profile along tracks from the no flow simulation, the tracks are shifted 2 mm in the second panel (simulated data).
2.4. Discussion

Figure 2.15: Temperature profiles along tracks from the 625 ml (100 gr)\(^{-1}\) min\(^{-1}\) simulation, the tracks are shifted 2 mm in the second panel (simulated data).

(a) 4 Temperature profiles at 625 ml (100 gr)\(^{-1}\) min\(^{-1}\).

(b) The 4 Temperature profiles of Figure 2.15(a) all shifted 2 mm.

made to reproduce the thermally insulating effect of the template. The measured no flow bovine tongue tracks (Figure 2.5(b)) are affected by the less controlled insertion of the thermocouples and electrodes (section 2.3.1). The tracks in the flow experiments (Figure 2.5) and simulations (Figure 2.14 and 2.15) have the same position relative to the electrodes but not relative to the vasculature which varies between the tongues.

In the flow situation both in experiment and simulation a few sharp wells are seen. Simulations show that these are caused by large vessels running close to a track. However the dominating effect of blood flow is the lower temperature of a region, especially at the side of the large vessels (Figure 2.15). As explained in section 2.2.1 the tracks leave the tongue at the caudal side where the profunda linguae arteries run. The regional lowering of the temperature in the simulations is fully due to the collective behaviour of discretely modelled vasculature since blood flow is only modelled by discrete vasculature (for similar results see Lagendijk et al. (1994)). More vessels are present at the side of the large vessels, here the lowering is stronger. This behaviour seems to be confirmed in the experimental setup, few vessels can be distinguished individually in the temperature profiles and also the regional lowering, particularly at the side of the large vessels can be seen (Figure 2.5(c)). Apparently discrete vasculature displays collective behaviour, with the number of discrete vessels per volume defining the resulting temperature distribution.

In the simulations the peaks from the electrodes are sharpened when flow is ap-
plied, which is typical heat-sink behaviour (Strohbehn, 1983; Schreier et al., 1990; Crezee et al., 1991; DeFord et al., 1991). The sharpest peaks around the electrodes are on the right hand side where the large vessels run, compare the peaks in track 24 in Figure 2.15(b). This heat-sink-like behaviour is fully due to the discrete vessels; at 3.13 ml (100 gr)\(^{-1}\) min\(^{-1}\) the heat transfer in the local heat-sinks/sources at the end of terminating vessels accounts for less than 10% of total convective heat transfer (this ratio was computed by comparing the absolute heat-flux through the heat-sinks/sources and the absolute heat-flux over the vessel walls, both arterial and venous). This was expected since the equilibrium length for the terminating segment was approximately 1 cm, this percentage will rise for higher blood flow rates.

Application of the discrete vessel model with generic vasculature shows a collective behaviour of discrete vasculature. Correct trends in the temperature distributions in perfused bovine tongues were predicted (compare Figure 2.8 with 2.13) as well as the regional lowering due to the presence of large vessels (see Figure 2.5(c) and 2.15). A priori vascular information is necessary for predicting temperature distributions in individual patients. These data are not yet available. Rawnsley et al. (1994) applied a discrete vessel model for computing the temperature distribution in dog thigh, but included discrete vessels retrospectively, not guided by angiographic data but adding vessels at locations so that the simulated temperature distribution matched the experimental data. A major disadvantage of this approach is that thus a large vessel is only modelled discretely if it happens to cross a thermocouple track (a matter of coincidence, in Figure 2.15 a 2 mm track shift causes a vessel signature to disappear completely), otherwise a heat-sink is used. Obviously hyperthermia treatment planning is intended for reconstructing temperature gradients at locations not covered by thermometry.

### 2.4.2 Temperature plane and volume distributions

**No flow situation**  In the simulations even slight variations in the plane position cause the \(T_{50}\) to change (Figure 2.11), explaining the variation of the \(T_{50}\) in the no flow experiments (Figure 2.7(b) and 2.8(b)). As seen from Figure 2.11(b) at approximately 1 cm from the middle plane (the plane position in the experiments) \(T_{50}\) starts decreasing rapidly towards the borders. This heterogeneity is caused by the heterogeneous cooling field; only the borders are cooled. Furthermore tissue heterogeneities and slight differences in boundary conditions cause \(T_{10}-T_{50}\) and \(T_{50}\) to vary more in bovine tongues than in simulations.

**Flow situation**  In the simulations the temperature volume distribution can be examined from Figure 2.10 and 2.13. The \(T_{10}-T_{50}\) of the volume is roughly stable as function of perfusion. At a closer look, the \(T_{10}-T_{50}\) first decreases and later
increases. When low flow (2 ml (100 gr)\(^{-1}\) min\(^{-1}\)) is applied, no longer only the
borders but also the core of the volume is cooled. The maximum temperature on
the electrodes is located more towards the borders (not shown), causing better
compensated boundaries (compare Figure 2.11(b) and 2.12(b)). When the flow
increases further, heterogeneity increases until finally most vessels are unequilibrated and the blood mainly equilibrates in the local heat-sinks/sources at the
end of terminating vessels. At this point the model behaves much like a distributed
heat-sink. Although the borders are better compensated for, higher perfusion cools
the entire volume and thus lowers the \(T_{50}\) (see Figure 2.10).

From Figure 2.7(a) and 2.8(a) and Figure 2.13(a) a trend can be seen of increasing
temperature heterogeneity (\(T_{10} - T_{90}\)) and decreasing \(T_{50}\) at higher perfusion rates.
Heterogeneity varies per plane; the number and kind of vessels running near a
plane, i.e. their location, determine the sensitivity for changes in the perfusion.
In Figure 2.12(b) the location of the vessels is clearly reflected in the graphs. At
5 mm from the middle plane the main arteries and their first branches run parallel
with the planes (giving rise to a maximum in the heterogeneity and a minimum
in \(T_{50}\), at 15 mm the main veins run (here the \(T_{50}\) stops increasing contrary to
the no flow situation, see Figure 2.11(b)). Due to the local heating (typical size
4 cm), even small arteries remain cold (diameters from 0.5 mm up have relatively
long equilibrium lengths from 7 cm up (Crezee, 1993)). The effect of perfusion can
be seen clearly when comparing Figure 2.11 and 2.12 for the simulations and from
Figure 2.8 for the experiments. Again slight changes of the plane location severely
affect its temperature distribution.

2.5 Conclusions

The experiments and simulations roughly agree when a generic comparison is
made. In both experiments and simulations the temperature heterogeneity per
plane increases when flow is applied, whereas the \(T_{50}\) decreases. The vasculature
causes large variations in the \(T_{10} - T_{90}\) and \(T_{50}\) per plane, the location of the sampled
plane with respect to the vasculature determines the sensitivity for flow changes.

Individual tracks from experiments and simulations showed similar temperature
heterogeneities along the tracks. The phantom tongue (no flow) agreed very well
with the simulations. In flow situations only few large vessels can be distinguished
individually whereas the majority of vessels was reflected by the regional lowering
of temperature.

The discrete vessel model together with a distributed heat-sink is able to predict
temperature distributions, including under-dosed areas near vessels. The collective
behaviour of the vasculature is described by modelling discrete vessels together
with a distributed heat-sink.
Chapter 2. Validation in generic bovine tongues

Further investigation will be done on extensive data acquisition for modelling specific tongues to compare experiments and simulations on a more individual base. For example a specific track from the experiments with the corresponding track from the simulations. For that, the vasculature of an individual tongue has to be modelled, as well as the exact tissue properties and the position of the electrodes and scanning thermocouples, relative to each other and to the vasculature.

The ultimate goal is patient specific treatment planning within clinically acceptable computation time. This will yield prospective and interactive optimization of the treatment. Such specific planning will also reduce the need for extensive invasive thermometry in the clinic. Currently the treatment planning system can only be applied retrospectively, as computation times are of the order of 20 hours on a workstation (Silicon Graphics, R5000). Promising acceleration techniques are under investigation.
Chapter 3

Modelling individual temperature profiles from an isolated perfused bovine tongue

This chapter has been published as

Abstract To predict the temperature distribution during hyperthermia treatments a thermal model that accounts for the thermal effect of blood flow is mandatory. The Discrete VAsculature (DIVA) thermal model developed at our department is able to do so; geometrically described vessels are handled individually and the remaining vasculature is modelled collectively. The goal of this paper is to experimentally validate the DIVA model by comparing measured to modelled temperature profiles on an individual basis.

Temperature profiles in an isolated bovine tongue heated with 3 hot water tubes were measured at 3 controlled perfusion levels, 0, 6 and 24 ml (100 gr)⁻¹ min⁻¹. The geometry of the tongue, the hot water tubes, thermo couples and discrete vasculature down to 0.5 mm diameter were reconstructed by using cryo-microtome slices at 0.1 mm cubic resolution. This reconstruction of the experimental set up is used for the modelling of individual profiles.

In a no flow agar-agar phantom DIVA showed nearly perfect correspondence between measurements and simulations. In the isolated bovine tongue the correspondence at no flow was slightly disturbed due to geometrical distortion in the reconstruction of the experimental set up. Measurements showed decreasing temperature profiles with increasing perfusion. DIVA correctly predicted this decrease in temperature as well as the thermal impact of a large vessel close to a thermocouple. Blood flow was modelled using discrete vasculature and using a heat sink model. Although at 24 ml (100 gr)⁻¹ min⁻¹ correspondence between heat sink simulations and measurements was reasonable, modelling discrete vasculature yielded the best correspondence at both 6 and 24 ml (100 gr)⁻¹ min⁻¹.
Chapter 3. Validation in an individual bovine tongue

The results strongly suggest that with accurate data acquisition DIVA can predict temperature profiles on an individual basis. For this kind of patient specific treatment planning in the clinic geometrical reconstruction of the anatomy, vasculature and the heating implant is necessary. MRI is capable to provide these data. Further research will be done on thermal simulations of actual clinical hyperthermia treatments.
3.1 Introduction

Hyperthermia treatment planning aims to give prospective information about the temperature distribution during a hyperthermia treatment. The elevated temperature distribution is affected by blood flow which need to be accounted for (Lagendijk, 1990; Roemer, 1990). To do so adequately, the modelling of discrete vessels is mandatory (Lagendijk, 1982; Crezee and Lagendijk, 1992; Lagendijk et al., 1994; Rawnsley et al., 1994; Kolos et al., 1995; Raaymakers et al., 1998; Van Leeuwen et al., 2000b). The Discrete VAsole model presented by Kotte et al. (1996) takes into account the thermal effects of individual vessels. However, not all vessels can be modelled individually since data on position and volume flow of the smallest vessels is lacking with current data acquisition techniques. DIVA therefore also offers methods to account for the not individually modelled vessels (Kotte et al., 1999). This paper aims to test DIVA experimentally, including the validity of these alternative methods for the not-individually modelled vessels.

When modelling a discrete vessel tree, not all branches will have the same thermal impact. A vessel tree consists of a main vessel that branches into smaller vessels which branch on their turn and so on until the capillary level is reached. At each branching point the cross section will increase causing decreasing flow in the child branches (Murray, 1926). The out-flowing blood of a large vessel with high blood flow will not be in thermal equilibrium with the surrounding tissue. This can be seen when the equilibration length (Chen and Holmes, 1980) is regarded, characterizing the distance it takes for the blood in a vessel to equilibrate to the temperature of the surrounding tissue. The main arteries typically have a high flow and large equilibration length in the order of meters (Creeze and Lagendijk, 1992), whereas the capillaries have low flow, very short equilibration lengths (0.1 \( \mu \text{m} \) (Creeze and Lagendijk, 1992)) and are therefore always in thermal equilibrium with the surrounding. Pennes (1948) assumed that the thermal equilibration of blood takes place instantaneously in the capillaries. Chen and Holmes (1980) and Van Leeuwen et al. (2000b) showed that a significant part of the thermal equilibration already takes place earlier in the vessel tree in vessels with a diameter between 0.2 and 0.5 mm.

In principle DIVA can model all vessels discretely down to the individual capillaries. Technical limitations, i.e. computer performance and detection of the numerous tracks of for instance the capillaries, lead to modelling of partial vessel trees. Van Leeuwen et al. (2000b) used DIVA to theoretically investigate the thermal effects of incompletely modelled vessel trees. The thermal effect of a very detailed, fully equilibrated, artificial discrete vessel tree (main artery 2.4 mm diameter, 712 terminating branches with 0.27 mm diameter) in a simple homogeneously perfused tissue geometry was simulated. The resulting steady-state temperature distribution was used as a reference for simulations with gradually stripped trees.
That is, repeatedly removing the smallest branches, until the most sparse tree had terminating branches of 1 mm diameter. Terminating vessels of these incomplete trees are not in thermal equilibrium with the surrounding. Ideally the out-flowing blood from a vessel would be forced to equilibrate in the anatomical territory perfused by this vessel. In practice it is very hard to determine these territories and two alternative strategies were used to compensate for the missing vessels in the stripped trees:

local sink sets tries to compensate the missing branches locally. Each terminating artery gets assigned a sub-volume, i.e. a sink set and the energy required to equilibrate the out-flowing blood to the mean temperature of the sink set is taken from that sink set volume, thus implementing local heat sinks using the local arterial temperatures as was originally proposed by Pennes (1948). Local sink sets are allowed to overlap. Then the blood of multiple terminating vessels has to be equilibrated in the same volume, effectively causing a higher local volumetric perfusion. Overlapping sink sets caused large heterogeneities in the perfusion distribution. In this case the local sink sets were spheres with a size defined by the entire volume divided by the number of terminating branches.

cubel in this case the associated sub-volume is the entire volume. The compensation is done globally. The energy required to equilibrate blood from terminating arteries to the mean temperature of the volume is evenly withdrawn from the entire volume, thus implementing a global heat sink using the global arterial blood temperature in addition to the discretely modelled vasculature.

For sparse vessel trees the cubel yielded best correspondence with the full tree, for very dense trees the local sink sets. The dense tree will have small terminating vessels and therefore typically small equilibration lengths. If so, the local sink set method is valid since the blood from terminating vessels is likely to have equilibrated within the volume of the local sink set. This is not the case with larger equilibration lengths for the terminating vessels, associated with higher blood flow or with sparse trees with larger terminating branches. Now the heterogeneous perfusion distribution will cause severe deviations in the temperature distribution. Cubel uses the correct perfusion distribution and offers better results. This will also be discussed in section 3.3.3.

As mentioned, the above findings are from theoretical analyses. The aim of this paper is to experimentally validate the DIVA model. Raaymakers et al. (1998) validated the DIVA model in a generic fashion and found that DIVA was able to predict generic temperature distributions in isolated perfused bovine tongues. The aim of this paper is to investigate if DIVA is able to predict temperature profiles on an individual basis. To do so, a one-on-one comparison was made between measured and modelled temperature profiles from an isolated perfused bovine
tongue heated with hot water tubes. Temperature profiles were measured along 11 parallel thermocouple tracks in steps of 1 mm at 0, 6 and 24 ml (100 gr)⁻¹ min⁻¹.

For such individual modelling, anatomy, vasculature, thermocouples and hot water tubes of this specific tongue were reconstructed with a cryo-microtome technique (0.1 mm cubic resolution) and incorporated in DIVA (at 0.5 mm cubic resolution). The arterial tree was reconstructed down to approximately 0.5 mm diameter, yielding 111 terminating arteries. The reconstructed venous tree was limited to only the main veins and some of their branches. The most accurate method to model the missing vasculature is dependent on the equilibration length of the terminating arteries which in turn is dependent on the perfusion. The results of Van Leeuwen et al. (2000b) predict that at 6 ml (100 gr)⁻¹ min⁻¹ this reconstructed vasculature will approximately thermally equilibrate in or before the terminating vessels. The local sink set method is expected to handle the equilibration of the out-flowing blood acceptably. At 24 ml (100 gr)⁻¹ min⁻¹ this is not the case and the cubel method is expected to be preferable. In this paper both methods are used in combination with the reconstructed tree. Also the limiting case of stripping all discrete vasculature was simulated, i.e. no discrete vessels which is effectively the conventional heat sink model (Pennes, 1948).

The validation on an actual patient is cumbersome since the reconstruction with the cryo-microtome technique is not applicable and current imaging modalities do not yield 0.5 mm cubic resolution without distortion. An isolated perfused bovine tongue is a suitable phantom for validating DIVA because its vasculature is similar to that of humans. Furthermore reconstruction of anatomy and angiography is relatively easy. The comparison between temperature measurements and simulations was performed first on a no-flow agar-agar phantom. This way the correspondence in a geometrically well defined situation could be studied.

3.2.2 Agar-agar phantom

3.2.2.1 Measurements agar-agar phantom

A rectangular block of homogeneous muscle-like tissue, Agar-agar, 58 by 63 by 94 mm was placed on a metal grid. 4 Steel hot water tubes (outer diameter 2.5 mm, inner diameter 2.0 mm) with 2 cm spacing were introduced horizontally, each flushing 8 ml s⁻¹ water of 38.3°C. This high flow of 2.5 ms⁻¹ causes turbulent flow within the hot water tube. The outer wall temperature of each tube was measured. The agar block was rinsed with water of 21.3°C to apply stable boundary conditions. Temperature profiles of the steady-state temperature distribution were obtained by scanning 10 constantan manganin thermo couples (diameter 100 μm) through the block in steps of 1 mm in a vertical plane perpendicular to the hot
water tubes. Their mutual spacing was approximately 5 mm. Because the thermocouples did not run exactly in 1 plane and parallel to each other, both entrance and exit position were determined with a marking gauge relative to origin of the agar-agar phantom (was also done for the hot water tubes). See Figure 3.1. The scanning was done by means of a micro-manipulator (Prior, precision 0.1 mm accuracy 0.1 mm).

![Schematic drawing of agar-agar phantom](image1)

**(a) Schematic drawing of agar-agar phantom**

![Thermocouples projected on a slice through the simulated temperature distribution, with the hot water tubes drawn as black circles](image2)

**(b) Thermocouples projected on a slice through the simulated temperature distribution, with the hot water tubes drawn as black circles**

**Figure 3.1:** Schematic drawing of the agar-agar phantom and the slice through the simulated temperature distribution in which the thermocouples are located (since the thermocouples are not exactly in 1 plane they are projected on a representative slice).
3.2.2 Simulations of the agar-agar phantom

The agar-agar phantom was geometrically reconstructed (see Figure 3.1(a)) and modelled with our thermal model to obtain the temperature profiles for comparison with the measured profiles. Table 3.1 shows the media properties used. A rectangular block of 58 by 63 by 94 mm was defined with 118 by 128 by 190 voxels, this includes a one voxel layer on all sides to model the boundary conditions, i.e. the flowing water. The flowing cooling water was modelled by assigning those voxels an increased thermal conductivity of 3.0 W m$^{-1}$ K$^{-1}$ (Lagendijk, 1990) and a fixed temperature. At the bottom the metal grid was modelled by a layer of voxels with a thermal conductivity of 75 W m$^{-1}$ K$^{-1}$ and a fixed temperature. The thermocouple tracks and hot water tubes were assumed straight lines between begin and end point. The steel hot water tubes were modelled as vessels of 2.5 mm diameter with an infinite flow, i.e. the temperature of the water remains constant along the tube. The Nusselt number, the tube-tissue heat transfer coefficient was set to 7.2 because the flow profile was turbulent due to the high flow. The mixing cup hot water temperature was set to 38.3 °C. When the steady-state temperature was reached in the model, temperature profiles along the same tracks as in the experiments were extracted.

<table>
<thead>
<tr>
<th>medium</th>
<th>density [kg m$^{-3}$]</th>
<th>specific heat [J kg$^{-1}$ K$^{-1}$]</th>
<th>conductivity [W m$^{-1}$ K$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>agar</td>
<td>1000</td>
<td>4000</td>
<td>0.5</td>
</tr>
<tr>
<td>hot water</td>
<td>1000</td>
<td>4000</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 3.1: Media properties used in the simulation of the agar-agar phantom.

3.2.3 Results from agar-agar phantom experiment

Figure 3.1(b) shows a slice from the simulated temperature distribution, which is approximately the plane scanned by the thermocouples. The position of the hot water tubes is indicated with black circles.

In Figure 3.2, 4 measured temperature profiles and their corresponding simulations are plotted. Profile 2 grazes a hot water tube and encounters the steepest gradients. Profile 3 is parallel to profile 2 but approximately 5 mm downwards, number 6 and 8 are approximately 30 and 38 mm downwards from profile 2. The modelled profiles show very good correspondence with the measurements and will be discussed in section 3.4.1.
3.3 Isolated bovine tongue

3.3.1 Measurements in isolated bovine tongue

The procedure of measuring steady-state temperature profiles in an isolated bovine tongue is basically the same as the procedure described in section 3.2.1. Isolated bovine tongues offer the advantage of various controlled perfusion levels and a human-sized vasculature. The tongue (0.3 kg) was obtained from the slaughter house. Within one hour after death its 2 arteries were cannulated and connected to a perfusion circuit (Bos et al., 1991). An isolated bovine tongue in this set up is a useful flow phantom for at least 6 hours (Bos et al., 1991). The tongue was suspended with its tip down and an implant of 3 horizontal hot water tubes was introduced. Perpendicularly a vertical plane of 11 thermo couples with a mutual spacing of 5 mm was placed for measuring steady-state temperature profiles in steps of 1 mm. The surface of the tongue was rinsed with water of approximately 20 °C to apply stable boundary conditions. The venous out-flow also ran freely.

Figure 3.2: 4 Temperature profiles from measurements (thick lines) in agar-agar phantom together with the modelled profiles (thin lines).
over the tongue however its quantity is negligible relative to the amount of cooling water. In Figure 3.3 the set up is shown. Temperature profiles were measured in steps of 1 mm at perfusion level 0, 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\). A roller pump (Watson-Marlow 505S/RL) controlled the perfusion of the blood-replacing medium (serum free minimal essential medium (S-MEM), Life Technologies, Breda, The Netherlands) with a fixed temperature of 22.6 °C.

![Image](image1.png)

(a) Overview of bovine tongue, hot water tubes are indicated with hw, scanning thermocouples with t (running from plate to tongue, unfortunately hardly visible in the photograph) and water sprinkler.

![Image](image2.png)

(b) Close up of water sprinkler.

**Figure 3.3:** Photographs of the bovine tongue during measurements.

### 3.3.2 Reconstruction

For correct one-on-one simulations the set up as described in section 3.3.1 need to be reconstructed precisely. Therefore after the experiments were performed the
hot water tubes were replaced with graphite sticks of 2.5 mm diameter, the thermocouples were replaced with white linen thread of 0.5 mm diameter and the arterial vasculature was filled with liquid plastic (Araldite F) which hardens in a few hours. This procedure yields good geometrical reconstruction of the vasculature (Van der Zwan, 1991). Unfortunately the veins have valves that prevent flow reversal and thus prevent injecting the plastic. Subsequently the tongue was frozen to -20 °C and sliced using a cryo-microtome. After each slicing of 0.1 mm a photograph of the tongue was made, yielding images with 0.1 mm² resolution. These images were stacked and formed thus a 3D reconstruction of the tongue. The data set was resampled to 0.5 mm cubic to obtain a manageable sized set (4.5 Mega byte), only for reconstruction of the veins the 0.1 mm cubic data set was used. The boundary of the tongue was drawn manually, the position of the hot water tubes and scanning thermocouples were determined and the geometry of the arterial vasculature was reconstructed down to branches of approximately 0.5 mm diameter, yielding 111 terminating branches. The mean length of the terminating branches was 6 mm. Because of the high contrast between green Araldite F and the tissue the arteries were easier to reconstruct than the veins. The main veins and some of their branches could be found from the original 0.1 mm resolution data set. See Figure 3.4 for the reconstruction of vasculature, hot water tubes and scanning thermocouple tracks. In the reconstruction process, especially before the freezing, the geometry of the tongue has changed slightly compared to its suspended position during measurements. The consequences will be discussed when comparing the measurements with the simulations 3.4.

3.3.3 Simulation set up

The tissue was assumed to be homogeneous muscle, density 1000 kg m⁻³, specific heat capacity 4000 J kg⁻¹ K⁻¹, thermal conductivity 0.6 W m⁻¹ K⁻¹, these values are based on ESHO Taskgroup Committee (1992). The steel hot water tubes were modelled as vessels with a Nusselt number 7.2 and an infinite water flow, i.e. the temperature of the water remains constant along the tube (similar as described in section 3.2.2). The blood vessels had laminar flow and therefore a Nusselt number of 3.6. The mixing cup temperature for the hot water tubes and the in-flow blood temperature were set according to the temperature in the corresponding experiment (the hot water temperature varied slightly between experiments with different perfusion levels). Around the tongue a layer of voxels with the properties of flowing water was modelled, see section 3.2.2. Temperature profiles from the steady-state distribution were taken at 0, 6 and 24 ml (100 gr)⁻¹ min⁻¹ for comparison with the measured profiles.
3.3. *Isolated bovine tongue*  

![Diagram of blood vessels](image)

(a) Side view.  
(b) Axial view.

**Figure 3.4:** Reconstructed arteries (dark grey), veins (light grey), hot water tubes and scanning thermocouples (black) from cryo-microtome data set.

*Modelling the thermal impact of blood flow*  In the no-flow simulation a thermal model only needs to take into account conduction of heat. However to model blood flow, i.e. the 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\) simulation, the reconstructed vessel tree is incorporated in DIVA. The perfusion distribution in the tongue is assumed to be homogeneous. Since the reconstruction is limited to vessels of approximately 0.5 mm diameter, the blood from terminating vessels does not have to be in thermal equilibrium with the surrounding tissue. As mentioned in section 3.1 DIVA offers methods to compensate for the missing branches:

**Local sink sets**  In this case the local sink sets are spheres of 2.8\(\cdot\)10\(^{-6}\) m\(^3\) (radius of 8.7 mm), i.e. the volume of the tongue, 0.31\(\cdot\)10\(^{-3}\) m\(^3\), divided by the number of terminating branches (111). Thus the combined volume of the local sink sets equals the volume of the tongue. The spheres are allowed to overlap. This overlap corrupts the perfusion distribution (see section 3.1), however the out-flow blood temperatures are correct. The corrupt heterogeneous perfusion distribution causes more severe errors in the temperature distribution when the out-flowing blood is far from equilibrated. So this method is valid when blood from the terminating vessels is nearly in thermal equilibrium with the tissue and will only locally affect the temperature distribution. Kotte *et al.* (1999) showed this is preferable above the situation in which the original perfusion map is used to set the blood flows in
discrete vasculature. Then the correct perfusion distribution is used but the equilibrium lengths and out-flow temperatures are altered. Only the largest veins are modelled which collect largely unheated blood from the entire volume. Therefore the in-flow temperature of veins is set to the boundary temperature.

**Cubel** Actually a special case of local sink sets. Here the volume attached to each terminating vessel is the entire volume instead of a local sub-volume. The perfusion distribution is not corrupted by overlapping sets and the blood flows in the limited discrete vessel tree are also correct. The cubel can be seen as a heat sink using the global arterial blood temperature in addition to the limited discrete vessel tree.

Only the complete reconstructed tree was used in this study and, for comparison, the limiting case of no discrete vessel at all was simulated with the conventional heat sink model (Pennes, 1948).

### 3.3.4 Results from isolated bovine tongue experiments

The effect of perfusion can be seen clearly from the measurements. Figure 3.5 shows the measured temperature profiles along track 2 for 0, 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\). With increasing perfusion the profiles becomes lower and also the shape of the profile changes. Each profile is measured twice and good reproducibility of the measurement is seen, most temperature differences between the two measurements occur at 24 ml (100 gr)\(^{-1}\) min\(^{-1}\), they do not exceed 1 K.

![Figure 3.5: Measured temperature profile 2 at 0, 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\), each profile is measured twice.](image)

The accuracy of the reconstruction of the experimental set up can be seen best from the comparison between no-flow measurements and simulations since only
heat conduction is involved. Figure 3.6 shows 4 temperature profiles from the no-flow measurements and the corresponding profiles from the simulations. These profiles are representative for the 11 profiles measured. Profile 3 grazes 2 hot water tubes, however the peaks in the simulations are closer to each other than in the measurement leading to a higher plateau in between the tubes. The simulated profiles 5 and 6 are very similar to the measured profiles but are consistently higher. Finally profile 10, this track is far away from the heated area, the maximum temperature elevation is low and approximately the same for measurements and simulations. The measured profile is a little smoother than the simulated one. The deviations between measurements and simulations are larger than for the no-flow experiments in agar-agar, see Figure 3.2.

Simulations were also performed at 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\). The same tracks as in the no-flow comparison are used (see Figure 3.6). The 6 ml (100 gr)\(^{-1}\) min\(^{-1}\)
and 24 ml (100 gr $^{-1}$ min $^{-1}$) measurements are plotted together with the cubel simulations, in Figure 3.7 and Figure 3.8. It turned out that cubel yielded the best correspondence at both perfusion levels. In Figure 3.10 the differences between the various simulations will be discussed.

![Figure 3.7: 4 Temperature profiles at 6 ml (100 gr $^{-1}$ min $^{-1}$) from measurements (thick lines) in isolated bovine tongue and the corresponding profiles from the cubel simulations (thin lines).](image)

The correspondence between measurements and simulations in Figure 3.7 and 3.8 is comparable to the no-flow situation (Figure 3.6), i.e. simulated profiles have approximately the same shape and decrease similarly in amplitude as the measurements with increasing perfusion. The plateau of profile 3 is still too high for 6 (only a little) and 24 ml (100 gr $^{-1}$ min $^{-1}$). The simulations show a larger decrease of the second peak. The simulated profile 5 shows for both perfusion levels more signature of the hot water tubes and slightly too high temperatures in the 24 ml (100 gr $^{-1}$ min $^{-1}$) simulation. In profile 6 both measurements and simulations show a local minimum at about 33 mm at 6 and 24 ml (100 gr $^{-1}$ min $^{-1}$).
Figure 3.8: 4 Temperature profiles at 24 ml (100 gr)−1 min−1
from measurements (thick lines) in isolated bovine tongue
and the corresponding profiles from the cubel simulations
(thin lines).

This minimum was not present in the no-flow situation and is most distinct in the
6 ml (100 gr)−1 min−1 measurements and simulations. Finally for profile 10 the
correspondence is similar to the no-flow comparison, same maximum temperature
and the measurement a little broader than the simulated profile.

To investigate their different behaviour, simulations with local sink sets, cubel and
heat sink alone are compared. In Figure 3.10 the results from these simulations are
plotted together with the measured temperature profile for track 6 at perfusion
level 6 and 24 ml (100 gr)−1 min−1. Profile 6 is chosen because this thermocouple
runs very close to a large vessel and lies close to the heated area, see Figure 3.9.

The measured profile 6 at 6 ml (100 gr)−1 min−1, Figure 3.10(a), clearly shows the
presence of the artery by the local cooling around 33 mm. The simulations which
include discrete vasculature, local sink sets and cubel, show the lower temperatures too. The heat sink simulations only show the lowering of the whole pro-
46  Chapter 3. Validation in an individual bovine tongue

Figure 3.9: Reconstructed slice of the bovine tongue. Artery, thermocouple 6 and a hot water tube can be seen.

file relative to the no-flow situation and no specific lowering around 33 mm. At 24 ml (100 gr)\(^{-1}\) min\(^{-1}\) the difference between the cubel and the heat sink model becomes smaller, see Figure 3.10(b). The simulations with local sink sets yield the lowest temperatures. For profiles outside the heated area the difference between the various simulations is very small for both 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\).

When all measured profiles are considered (including those not presented here) the cubel simulations yield the best correspondence with the measurements at both perfusion levels. At 6 ml (100 gr)\(^{-1}\) min\(^{-1}\) the cubel and local sink sets simulations perform better than the heat sink model. At 24 ml (100 gr)\(^{-1}\) min\(^{-1}\) the results from local sinks sets simulations becomes less accurate whereas the difference between cubel and heat sink becomes smaller.

3.4 Discussion

3.4.1 Agar-agar phantom

The experiments in agar-agar, Figure 3.2, show that in a geometrically well-defined set up with no perfusion the model can predict the temperature distribution accurately. The deviation in profile 2 can be explained with the fact that thermocouple tracks in the simulations are assumed straight lines between begin and endpoint. In the measurements track 2 is running just under the hot water tube and is bend there slightly (in Figure 3.1(b) only the reconstructed thermocouple tracks are plotted). So in the straight line reconstruction the profile will lie further from the tube and yield lower temperatures.
In fact the agar-agar phantom is a basic test for modelling discrete vasculature since the hot water tubes are represented as straight vessels. This way the cylindrical shape of the tubes is taken into account. Obviously these tubes can not be modelled with a continuum model considering the dimensions of the phantom. Also in all simulations modelling the bovine tongue, the hot water tubes are modelled discretely.

### 3.4.2 Isolated bovine tongue

The massive thermometry available in the bovine tongue gives detailed and reproducible temperature profiles at different perfusion levels, see Figure 3.5. The cause of the deviations in temperature at 24 ml (100 gr)\(^{-1}\) min\(^{-1}\) is not fully clear. There might have been changes in the geometry of the tongue in between the measurements or the steady-state temperature distribution was not reached completely. The differences between measurements and simulations in Figure 3.8, are however larger than can be explained by these artifacts alone.

*Profiles at no flow* The no-flow agar-agar phantom yields fairly good correspondence between measurements and simulations, see Figure 3.2. The no-flow experiments in the isolated bovine tongue (Figure 3.6) however yield larger deviations. This may be explained by the geometrical distortion of the tongue during prepa-
ration for the cryo-microtome slicing. The geometry of the tongue changes slightly
due to the onset of rigor mortis and the freezing. This cannot be corrected for
easily because the deformation is direction dependent. In the direction the tem-
perature profiles were taken the modelled tongue seems consistently smaller than
in the measurements, as can be seen in profile 3 in Figure 3.6 where the simulated
peaks are closer to each other than the measured peaks. And in profile 6 in Fig-
ure 3.7 where the simulated profile has the same shape as the measured profile but
is narrower. The agar-agar phantom was reconstructed by measuring all sizes with
a marking gauge. This causes no deformations during the reconstruction process
and better correspondence with the simulations.

Profiles at 6 and 24 ml (100 gr)\(^{-1}\) min\(^{-1}\). The causes of deviation between mea-
surements and simulation for the no-flow are clearly also affecting the 6 and
24 ml (100 gr)\(^{-1}\) min\(^{-1}\) experiments. Additionally deformed vasculature (and there-
fore perfusion distribution) will affect the temperature profiles. Still the profiles of
the cubel simulations in Figure 3.7 and 3.8 correspond well with measurements.
The overall decrease of the temperature profiles was predicted correctly. Devia-
tions already present in the no-flow comparison remained the same, e.g. the too
high plateau in the simulated profile 3 is also present in the 24 ml (100 gr)\(^{-1}\) min\(^{-1}\)
simulation and less prominent at 6 ml (100 gr)\(^{-1}\) min\(^{-1}\). The too large decrease of
the second peak can be explained by a small reconstruction error. A small change
in the distance between track and needle will cause relatively large temperature
differences since the temperature gradient near the hot water tube is very steep.
In Figure 3.7 approximately 1.5 K per mm and in Figure 3.8 approximately 1.8 K
per mm. The shape of profile 5 shows 2 local maxima in the simulations against 1
in the measurements. At close inspection, also in the no-flow simulation a hardly
noticeable minimum is present at approximately 27 mm. In simulations this local
minimum is enhanced with increasing perfusion. In the no-flow measurements it
is not present, this is again probably due to the distorted reconstruction of the
tongue. The measured profile 6 is close to a discrete vessel, see Figure 3.9, and
shows a local minimum around 33 mm especially at 6 ml (100 gr)\(^{-1}\) min\(^{-1}\) and
less prominent at 24 ml (100 gr)\(^{-1}\) min\(^{-1}\). The minimum is most likely due to that
vessel as will be discussed in the next paragraph. Cubel simulations predicted this
correctly. The location of the minimum varies a little between simulations and
measurements, again caused by reconstruction errors. Profile 10 is far (approx-
imately 2 cm) from the heated area. No steep gradients due to discrete vasculature
and the hot water tubes are expected since the temperature elevation is small (less
than 3 K). Also in this region the cubel simulations yield good correspondence
with the measurements.

Apparently the correspondence between measurements and simulations does not
suffer much from the fact that only the main veins were reconstructed. From theoretical studies Huang et al. (1996) found a very small, negative contribution to the heat removal by the venous network but indicated that the vasculature used was not very realistic. Van Leeuwen et al. (2000b) showed in a more realistic vessel network that heat removal by veins is small compared to the heat removal by the arterial network and that omission of the venous network results in a very small, approximately 5% increase of the mean temperature. Still large veins crossing the heated area are thermally significant and should be modelled discretely. However in this case the measured temperature profiles were from the middle of the tongue, i.e. in between the 2 main arteries, see Figure 3.4(b) and relatively far from large veins. The thermal impact of the venous network on that area is shielded off by the arterial vasculature.

Modelling missing branches in various fashions At 6 ml(100 gr)$^{-1}$ min$^{-1}$ the modelling of discrete vasculature is important and dominates the temperature distribution as can be seen from Figure 3.10(a). A temperature minimum is seen near a vessel around 33 mm. In local sink sets and cube1 simulations this minimum is also seen. When this vessel is not modelled individually this effect is absent, as can be seen from the heat sink simulations, see Figure 3.10(a). Therefore it most likely is the vessel that locally affects the temperature profile around 33 mm. A collective description for all vasculature is not suitable at this perfusion level and the heat sink model shows worst agreement with the measurements. The terminating vessels from the limited discretely modelled tree are nearly thermally equilibrated. At 6 ml(100 gr)$^{-1}$ min$^{-1}$ their equilibration length is 8 mm while their actual length is approximately 6 mm. The local sink sets simulation yielded good correspondence with the measurements. The cube1 simulation does not differ very much from the local sink sets simulation and yields even better correspondence with the measurements. Local sink sets use the local arterial out-flow temperature to compensate branches not modelled individually. Apparently the corrupt heterogeneous perfusion distribution caused by overlapping local sink sets does undo this advantage. The cube1 method uses the correct homogeneous perfusion distribution which compensates the shortcoming of using only the global arterial out-flow temperature. When the equilibration lengths of the terminating vessels are even shorter Van Leeuwen et al. (2000b) showed that the local sink sets will be preferable over the cube1 method.

At 24 ml(100 gr)$^{-1}$ min$^{-1}$ cube1 simulations again yield best correspondence with the measurements, followed by heat sink simulations. As predicted by Van Leeuwen et al. (2000b), see section 3.1, the local sink sets perform worse compared to the 6 ml(100 gr)$^{-1}$ min$^{-1}$ situation. The terminating vessels have larger equilibration lengths, around 30 mm, while their actual length is approximately 6 mm. They are far from equilibrated and relatively much of the thermal equilibration of the
Chapter 3. Validation in an individual bovine tongue

blood need to be accounted for collectively. Therefore a correct perfusion distribution is important. As mentioned previously cube1 simulations use the correct perfusion distribution and show the best results. The local sink sets cause an erroneous heterogeneous perfusion distribution and hence an erroneous temperature distribution. Because the thermal impact of the volumetric perfusion becomes more dominant relative to the impact of discrete vessels the heat sink model yields much better correspondence than at 6 ml (100 gr) \textsuperscript{\textminus1} \text{min} \textsuperscript{\textminus1}. Even though no discrete vessels are modelled the correspondence near a vessel is reasonable. This can be seen from Figure 3.10(b) where the thermocouple track runs close to a vessel. In the limiting case of infinite blood flow the temperature distribution is fully dominated by the volumetric perfusion: the cube1 and heat sink simulations then yield exactly the same result.

DIVA in clinical practice Predicting temperature distributions in actual patients is more complex than in isolated bovine tongues. Theoretical analyses by Chen and Holmes (1980) and Van Leeuwen \textit{et al.} (2000b) showed that vessels down to 0.2 mm diameter are thermally significant and contribute to the heat transfer due to blood flow. 3D Phase Contrast MRI in the clinic is typically at 0.8 mm cubic resolution and enables detailed reconstruction of anatomy, heating implant and vasculature. Obviously not all vessels down to 0.2 mm can be reconstructed this way. These missing branches will be modelled collectively as is described in section 3.1 and 3.3.3. Also the blood flow in the vessels and the perfusion distribution, probably heterogeneous and dynamic, are not easily quantified. Currently only 2D quantitative perfusion imaging is clinically feasible using MRI (vonken \textit{et al.}, 1999). The absolute 3D perfusion distribution is important for a reliable temperature simulation. To obtain an estimation of the 3D perfusion distribution temperature simulations in the correct geometrical description of a patient can be performed. Initially the perfusion level can be estimated from 2D perfusion imaging. By comparing the temperature decay at the end of a treatment with simulations a better estimation of the 3D perfusion distribution can be made (Lagendijk \textit{et al.}, 1999). As mentioned previously, it is now shown that DIVA can predict temperature profiles on an individual base under the condition of reliable data acquisition. With the above mentioned inaccuracies simulated temperature distributions will deviate from the actual temperatures. Future research will be done on optimizing the angiography in order to visualize smaller discrete vessels since Van Leeuwen \textit{et al.} (2000b) showed that modelling more vessels discretely will be rewarded with a more accurate prediction of the temperature distribution. DIVA is now being introduced in the clinic for evaluating interstitial hyperthermia treatments of brain and prostate tumours with our Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS-IHT) system (Lagendijk \textit{et al.}, 1995).
3.5 Conclusions

It was shown that DIVA is capable of predicting temperatures in an isolated perfused bovine tongue. The deviations between measurements and simulations are mainly due to errors in the reconstruction of the experimental set up, as with simple reconstruction methods in the agar-agar phantom better correspondence was found than in the no-flow comparison of bovine tongues. The cubel method to model blood flow predicts the effect of discrete vasculature correctly throughout the tongue at both 6 and 24 ml (100 gr) \(^{-1}\) min \(^{-1}\). As expected the local sink sets yielded only good results at low perfusion whereas the heat sink shows reasonable agreement with the measurements at high perfusion.

The results strongly suggest the accuracy of predicting temperatures is determined by the quality of the data acquisition. The reconstruction method of the bovine tongue as described in this paper is very detailed although obviously not clinically applicable. Similarly reliable data acquisition for clinical application of individual hyperthermia treatment planning is difficult but mandatory. MR is a promising candidate, it can yield anatomy, angiography and perfusion data.

From the current clinical data acquisition techniques only incomplete vessel trees can be reconstructed down to approximately 0.5 mm diameter. It depends on the perfusion level which method has to be used to compensate for the missing branches. As clinical relevant perfusion is typically in the range of 10 to 60 ml (100 gr) \(^{-1}\) min \(^{-1}\), out-flowing blood will not be thermally equilibrated at all. It is shown that in that case the local sink sets are not suitable for accurate predictions of the temperature distribution. In this specific case the cubel method is preferable to predict the temperature distribution up to 24 ml (100 gr) \(^{-1}\) min \(^{-1}\). Obviously the heat sink model is easier to implement than the cubel method, only the global perfusion distribution has to be obtained. Future research has to show whether and at what perfusion level the deviations between cubel and heat sink simulations are small enough to justify application of the heat sink model.
Chapter 4

How to apply a discrete vessel model in thermal simulations when only incomplete vessel data is available

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Abstract For accurate predictions of the temperature distribution during hyperthermia treatment a thermal model should incorporate the individual impact of discrete vessels. In clinical practice not all vessels can be reconstructed individually. This paper investigates five possible strategies to model the thermal impact of these missing vessels.

A tissue volume with a detailed, realistic, counter current discrete vasculature is heated and the steady-state temperature distribution is calculated using our Discrete Vasculature (DIVA) thermal model. To mimic incomplete discrete vasculatures the full tree is gradually stripped, that is, the number of discretely described vessels is reduced in four steps until no discrete vessels are left.

At each strip level the steady-state temperature distribution is calculated for five different strategies to model the missing vessels. The strategies all use a local or global heat sink model additional to the discrete vasculature. The resulting temperature distributions are compared with the full tree simulation.

With increasing strip level the correspondence with the full tree simulation deteriorated for all strategies. An optimal strategy was found to model the missing vessels depending on the available angiographic data. It was also found that simulations with a decreased number of discrete vessels or no vessels at all, yield temperatures which are too high. Theoretically this can be compensated by increasing the thermal conductivity, finding the optimal value is done empirically.
4.1 Introduction

Treatment planning can be used to predict and evaluate the 3D temperature distribution resulting from a hyperthermia treatment. For calculations of the temperature distribution in vivo blood flow contributes to heat transfer and need to be accounted for (Lagendijk, 1990; Roemer, 1990). To do so correctly a thermal model should incorporate the thermal impact of discrete vasculature (Lagendijk, 1982; Crezee and Lagendijk, 1992; Lagendijk et al., 1994; Rawnsley et al., 1994; Kolios et al., 1995; Raaymakers et al., 1998). Our Discrete VAsculature (DIVA) model (Kotte et al., 1996) accounts for these heat transport phenomena. It uses a grid-independent vessel description in which every modelled vessel segment is supplied to the model as a three-dimensional curve with associated diameter and blood flow. Van Leeuwen et al. (1997b,a) presented theoretical verification of DIVA. Experimental validation of DIVA is described by Raaymakers et al. (1998, 2000a) where temperature distributions were measured in an interstitially heated, isolated, perfused bovine tongue. The tongue, heating implant and vasculature were reconstructed. Thermal simulations yielded good correspondence with the measurements at various perfusion levels.

The number of discretely modelled vessels is only limited by practical limitations, e.g. computer performance or the laborious description of the three-dimensional curve of the numerous small vessels. The capabilities of DIVA are nicely demonstrated by Van Leeuwen et al. (1999), the temperature rise due to a mobile phone was simulated in a segmented head with a realistic, artificially generated, detailed discrete counter-current vasculature.

For clinical applications ideally all thermally significant vessels are taken into account in thermal simulations. I.e. all vessels that contribute to the heat transfer need to be modelled. To determine which are the smallest thermally significant vessels the equilibration length (Chen and Holmes, 1980) need to be regarded, characterizing the distance it takes for the blood in a vessel to thermally equilibrate to the temperature of the surrounding tissue. Main arteries typically have a high flow and large equilibration length of the order of meters (Crezee and Lagendijk, 1992). Capillaries have low flow, very short equilibration lengths (0.1 µm (Crezee and Lagendijk, 1992)) and are therefore always in thermal equilbrium with the surrounding tissue. Chen and Holmes (1980) and Van Leeuwen et al. (2000b) showed that vessels with a diameter between 0.2 and 0.5 mm take care of a major part of the thermal equilibration of the arterial blood and are therefore thermally significant.

With current data acquisition techniques the position and flow of the smallest vessels is not retrievable. In clinical practice 3D phase contrast MR angiography is used to reconstruct the patient specific vasculature (Raaymakers et al., 1999, 2000c) because this yields also a 3D anatomy in the same coordinate system.
4.1. Introduction

Typically the scan resolution is 0.8 mm³ and reconstruction of discrete vasculature is limited to vessels of 0.6 mm diameter (Börjesson and Stöcker, 1997). Therefore thermal simulations need a method for accurate modelling the thermal impact of these not-detected, i.e. not-discretely modelled, vessels.

Kotte et al. (1999) presented various methods to compensate for missing branches. These methods were presented by modelling a tissue volume (6×6×6 cm³), heated by a central cubic power deposition (4×4×4 cm³). A heterogeneous perfusion distribution was modelled by a realistic, computer-generated, detailed discrete vasculature (Van Leeuwen et al., 1998). The perfusion in the high perfused area was 21.0 ml (100 gr)⁻¹ min⁻¹ and in the low perfused area 10.5 ml (100 gr)⁻¹ min⁻¹ (see Figure 4.2). Then the smallest branches were removed from the vasculature, the various compensation methods were used and the resulting temperature distribution was compared to the full tree simulation.

Three methods were presented to compensate for the removed branches. Basically, blood from terminating arteries is forced to equilibrate to the tissue temperature of a sub-volume attached to each terminating vessel. This equilibration is done by a heat sink approach (Pennes, 1948) completing the thermal impact of the blood. This conventional heat sink is a collective means of accounting for the heat removal by the blood. Pennes (1948) stated that the amount of energy withdrawn from tissue with a temperature T_{is} [K] by blood with a temperature T_{b} [K] is c_{b}W_{b}(T_{is} - T_{b}) [W m⁻³]. With c_{b} [J kg⁻¹ K⁻¹] the specific heat capacity of blood and W_{b} [kg m⁻³ s⁻¹] the volumetric perfusion rate. In the conventional heat sink the temperature of the blood is equal to the body core temperature, the underlying assumption is that arterial blood of body core temperature only and instantaneously exchanges heat in capillaries. In this paper the thermal equilibration of the blood from the discrete vessels is completed in the attached sub-volumes using a heat sink. However here the local arterial out-flow temperature is used instead of a global body core temperature. Ideally these sub-volumes, so called local sink sets, would be the anatomical territory perfused by this vessel (Cormack and Lamberty, 1986). In practice it is very hard to determine these territories and an alternative strategy is used to approximate the ideal situation. First Kotte et al. (1999) divided the volume in 10×10×10 sub-volumes. The sub-volume in which an artery terminates is assigned as its local sink set. The remaining sub-volumes are added to the local sink set of the closest terminating vessel. This way the local sink sets will vary in size but the entire volume is covered. Figure 4.1(a) illustrates the formation of local sink sets for a simplified situation. Using 1000 sub-volumes yields acceptable computation times, increasing the number of sub-volumes will result in a more detailed delineation of the local sink sets but also in basically the same local sink sets.

The blood from a terminating artery is distributed over its local sink set, as shown
Chapter 4. Thermal modelling with incomplete vessel data

(a) Formation of local sink sets in a 2D situation. The tissue grid is divided in a coarser grid of sub-volumes of 10 by 10 tissue voxels. The gray sub-volumes form the local sink set of the left hand terminating artery, the white sub-volumes form the local sink set of the right hand terminating artery.

(b) Blood from a terminating vessel is distributed over its local sink set (represented as a sphere) determining the local perfusion.

Figure 4.1: Schematic illustrations of formation and perfusion of local sink sets.

schematically in figure 4.1(b). In fact the blood is distributed over the local sink set using a relative perfusion map, in this case the relative perfusion distribution as present in the full tree simulation. So the perfusion level in the local sink set is defined by the amount of out-flowing blood and the size of the local sink sets. (Kotte et al., 1999) presented two possible strategies to match the blood flow of the terminating vessels and the cumulative perfusion in their local sink sets:

Flow defined The blood flow in the incomplete vasculature is used to determine the perfusion distribution. The blood flow in the root segment of the limited vasculature is the same as for the full tree. Using flow conservation at junctions the flow in terminating segments is set. Approximately the correct blood flows are used but the sizes of the local sink sets may vary as mentioned previously. Therefore the resulting effective perfusion distribution will be different than the one used in the full tree simulation.

Perfusion defined Another way is using the correct perfusion distribution as used in the full tree situation. The blood flow in the terminating segments is altered in such way to yield the correct perfusion distribution when the out-flowing blood is distributed over their local sink sets. This is done by
determining the cumulative perfusion of a local sink set in case of the correct absolute perfusion map and using this as the blood flow in the terminating arteries. By using flow conservation at junctions the blood flow in the entire vasculature can be set. In this way the correct perfusion distribution is used but due to the variation in local sink set size now the blood flows in the terminating vessels vary. Note that the blood flow in the root segment will have the same value as the flow defined situation, only the flow distribution over all vessel segments has altered.

The third method presented by (Kotte et al., 1999) was referred to as Cubel. Cubel is in fact a special case of the flow defined method as described above. Now the simulated volume is not divided in 1000 sub-volumes which build up the local sink sets, instead the entire volume (that is: 1 cubic volume, hence the name Cubel) is the local sink set of each terminating vessel. The blood from the discrete vasculature is distributed over the entire volume. This way the effective perfusion distribution is exactly the same as in the full tree simulation. Effectively Cubel applies a heat sink which uses the mean arterial out-flow temperature additional to the discretely modelled vessels.

Kotte et al. (1999) found that Cubel yielded the best correspondence with the full tree simulation followed by the flow defined and the perfusion defined simulation. However it turned out that the software implementation of the formation of the local sink sets from the 1000 sub-volumes was incorrect. Therefore the conclusions about the performance of the compensation methods are not valid as will be shown in this paper. The paper of Kotte et al. (1999) must be seen merely as a demonstration of possible compensation methods, further research is necessary to find the optimal strategy.

The aim of this paper is to investigate various methods for modelling missing branches. The flow defined and perfusion defined method, the Cubel and two new strategies will be investigated. All methods will be studied at various strip levels. The simulation set-up is basically the same as used by Kotte et al. (1999). The various strategies will be compared to the full tree simulation and mutually. The number of branches removed from the full tree is increased in four steps. After the last step no discrete vasculature is left. At each stage the performance of the various strategies is studied. To model the situation without discrete vasculature a heat sink model (Pennes, 1948), an effective conductivity model Chen and Holmes (1980); Lagendijk et al. (1984); Weinbaum and Jiji (1985); Baish et al. (1986) and a combination of these models is used.

Van Leeuwen et al. (2000b) already compared two compensation methods offered by DIVA. That work focussed on the impact of different discrete vessel generations on the temperature distribution. To do so the thermal effect of a very detailed, fully equilibrated, artificial discrete vessel tree (main artery 2.4 mm diameter,
712 terminating branches with 0.27 mm diameter) in a simple homogeneously perfused tissue geometry was simulated. The resulting steady-state temperature distribution was used as a reference for simulations with gradually stripped trees. That is, repeatedly removing the smallest branches, until the most sparse tree had terminating branches of 1 mm diameter. This way the thermal impact of the different vessel generations was investigated. To compensate for the missing branches Cubel was used as well as a more intuitive strategy; all terminating arteries were assigned a spherical local sink set of the equal size. The size was determined by dividing the entire volume by the number of terminating branches. Overlapping local sink sets cause a heterogeneous, incorrect perfusion distribution, especially for very sparse vasculatures and Cubel yielded better correspondence with the full tree simulation. Therefore the strategy of spherical local sink sets is not taken into account in this study.

4.2 Methods

In summary, the simulations are basically the same as presented by Kotte et al. (1999). A tissue volume is modelled using DIVA. The heterogeneous perfusion is taken care of by a detailed, computer generated vasculature. The vasculature is gradually stripped, i.e. the smallest vessels are removed in four steps and the temperature distributions after each step are compared to the full tree simulations. The missing branches are compensated for in five different ways.

Discrete VAsculature (DIVA) model  DIVA models the heat transfer in perfused tissue. The thermal impact of each discrete vessel is taken into account individually (Kotte et al., 1996). Vessel segments can be coupled to build an entire vessel network (Kotte et al., 1999). Both arterial and venous vessel trees can be modelled. The tissue is discretized on a 3D grid and thermal interaction between tissue voxels is modelled using a finite difference time domain approach. Vessel segments are supplied as 3D geometric curves with an associated diameter. The vessel description is independent of the grid resolution. The temperature profile along a segment is discretized one dimensionally. The interaction with the tissue is calculated using tissue temperature samples, a blood temperature sample and the distance between the center of the vessel and the location of the tissue temperature sample. The heat flow across the vessel wall is calculated using an analytical expression that describes the heat flow from a central tube (the vessel) inside a larger cylinder (the surrounding tissue).

The blood flow is defined per segment. Therefore flow conservation at junctions is not mandatory. This enables the modelling of bleed-off along the vessel tree. DIVA
4.2. Methods

offers various strategies to model the thermal impact of the out-flowing blood from these bleed-off locations or from terminating vessels. Exactly these strategies will be studied in this paper and are described in detail below.

Volume A tissue volume of $0.06 \times 0.06 \times 0.06$ m$^3$ is heated by a central power deposition of $0.04 \times 0.04 \times 0.04$ m$^3$. The volume boundary is kept at a constant temperature of 0 K. A heterogeneous perfusion distribution is applied as shown in Figure 4.2. Two values occur, 10.5 and 21.0 ml $(100 \text{ gr})^{-1} \text{ min}^{-1}$ for respectively the low and high perfused half. Table 4.1 shows the tissue properties used.

![Figure 4.2: The simulation volume is split into two differently perfused regions. The lower half of the volume is uniformly perfused with 21.0 ml $(100 \text{ gr})^{-1} \text{ min}^{-1}$; the perfusion value of the upper half amounts 10.5 ml $(100 \text{ gr})^{-1} \text{ min}^{-1}$. The dot indicates the entrance point of the vessel tree.](image)

Vasculature The perfusion is handled by a realistic, detailed, counter-current vasculature generated using the Vasculature Assembly through Modifiable Potential (VAMP) program (Van Leeuwen et al., 1998). The root segment of the arterial tree had a diameter of 1.5 mm, the 960 terminating segments are 0.15 mm in diameter. The venous tree consists of 938 terminating segments of 0.3 mm diameter with a root segment of 3 mm diameter. The distribution of the endpoints is according to the relative perfusion distribution, see Figure 4.3(a). The arterial inflow temperature is equal to the volume boundary temperature, 0 K.

To simulate the use of incomplete vessel trees the vasculature was gradually stripped, as shown in Figure 4.3. The first stripping removed all arterial branches
Table 4.1: Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue conductivity $k_{\text{tn}}$</td>
<td>0.6 W m(^{-1}) K(^{-1})</td>
</tr>
<tr>
<td>Tissue specific heat $c_{\text{tn}}$</td>
<td>4000 J kg(^{-1}) K(^{-1})</td>
</tr>
<tr>
<td>Tissue density $\rho_{\text{tn}}$</td>
<td>1000 kg m(^{-3})</td>
</tr>
<tr>
<td>Blood conductivity $k_b$</td>
<td>0.6 W m(^{-1}) K(^{-1})</td>
</tr>
<tr>
<td>Blood specific heat $c_b$</td>
<td>3840 J kg(^{-1}) K(^{-1})</td>
</tr>
<tr>
<td>Blood density $\rho_b$</td>
<td>1060 kg m(^{-3})</td>
</tr>
<tr>
<td>Nusselt number</td>
<td>4.0</td>
</tr>
<tr>
<td>Power density $P$</td>
<td>76000 W m(^{-3})</td>
</tr>
<tr>
<td>Number of grid voxels</td>
<td>$100 \times 100 \times 100$</td>
</tr>
<tr>
<td>Volume dimensions</td>
<td>$0.06 \times 0.06 \times 0.06$ m(^3)</td>
</tr>
</tbody>
</table>

with a diameter smaller than 0.3 mm and venous branches smaller than 0.6 mm diameter. This results in an arterial tree with 50 terminating branches of 0.3 mm diameter and a venous tree with 47 terminating branches of 0.6 mm. This tree is referred to as strip 0.3, see Figure 4.3(b). In the second strip level all arterial branches with a diameter smaller than 0.6 mm and all venous branches smaller than 1.2 mm diameter are removed. Both the arterial as the venous tree have 8 terminating branches. This vasculature is referred to as strip 0.6, see Figure 4.3(c). In the strip 1.2 vasculature all arterial branches with a diameter smaller than 1.2 mm and all venous branches smaller than 2.4 mm diameter are removed. Resulting in a single terminating artery and vein, see Figure 4.3(d). The fourth and last strip level leaves no discrete vasculature.

4.2.1 Bleed-off in stripped vasculature

In the full tree the blood flow in the root segment is set and flow conservation at junctions is applied to set the flow in all other branches. By stripping the tree, junctions will disappear and the blood flow in the remaining segments is not altered. Flow conservation along the remaining segment is not automatically the case. By not adapting the flow in the remaining vasculature in fact a bleed-off is modelled.

The exact blood flow in all remaining segments of a stripped vasculature is only known because it is build using the full tree. For each strip level also the situation without bleed-off is modelled. By using the blood flow rate in the root segment and applying flow conservation at all junctions a stripped tree without bleed-off can be constructed.

Note that both vasculature with or without bleed-off have the same blood flow in their root segment. The same amount of blood is used to perfuse the volume. The
4.2. Methods

(a) Full arterial tree.

(b) Strip 0.3 tree.

(c) Strip 0.6 tree.

(d) Strip 1.2 tree.

Figure 4.3: Full arterial tree and the arterial tree at various strip levels. The counter-current venous tree is omitted for the sake of clarity.
difference is the location where the blood leaves the discrete vasculature. Without bleed-off all blood leaves the discrete vasculature from terminating branches. With bleed-off the blood leaves the discrete vasculature along the entire tree (at former junctions) and at the terminating branches.

The formation of local sink sets from the 1000 sub-volumes in case of bleed-off is basically the same as described in section 4.1 for trees without bleed-off. All locations where blood leaves the discrete vasculature are treated similarly. So in case of bleed-off, all bleed-off locations plus terminating branches get a local sink set. First the sub-volume they are located in is assigned as their local sink set. Then all remaining sub-volumes are added to the local sink set of the closest bleed-off location or terminating branch.

4.2.2 Modelling blood that left the discrete vasculature

The aim of this study is to compare the performance of various strategies to complete the thermal equilibration of blood at various strip levels in addition to the discrete vessel model. In section 4.1 the Cubel, flow-defined and perfusion-defined method were introduced. The two other possible strategies to compensate the thermal effect of missing vessels are absolute-perfusion and vessels-plus-heat-sink.

Flow defined As described in section 4.1 the perfusion in each local sink set is defined by the amount of blood flowing into that local sink set. The blood is thermally equilibrated to the temperature of the tissue in the local sink set. This way an additional heat sink is applied in which the local arterial temperature and a locally defined perfusion are used. The use of bleed-off will change the number and size of the local sink sets and therefore the effective perfusion distribution. Terminating veins use the average tissue temperature of a local sink set as their inflow temperature. At bleed-off locations, for veins rather bleed-in locations, the blood temperature is determined by (flow weighted) averaging of the temperature of the blood from the local sink set and from the supplying vessel segment.

Perfusion defined Here also the perfusion in each local sink set is defined by the amount of blood flowing into that local sink set. Only now the blood flows in the vasculature are altered to yield the correct perfusion distribution as explained in section 4.1. The blood flow of veins is set in the same way as arteries, the venous in-flow temperature is determined in the same way as in the flow defined strategy. This again applies an additional heat sink in which the local arterial temperature and a locally defined perfusion are used. The difference with the flow defined situation is that the blood flows in the vasculature and therefore the effective perfusion distribution are different.
4.2. Methods  63

**Absolute perfusion** In this strategy the perfusion in the local sink set is not defined by the amount of blood coming from the corresponding vessel but from an absolute perfusion map as defined by the full tree situation. The blood flows in the vasculature are the same as for the flow defined situation. Also the local arterial temperature of each terminating vessel is used for the additional heat sink. Veins are treated as described for the flow defined strategy. In this strategy the cumulative perfusion of a local sink set not necessarily equals the blood flow from the corresponding vessel.

**Vessels plus heat sink** This strategy resembles the absolute perfusion strategy. Only here not the local arterial out-flow temperatures are used for the additional heat sink but instead a global (0 K) temperature is used. In fact a fully conventional heat sink is added to the discrete description of the vasculature. The veins are treated as described for the flow defined strategy.

**Vessels defined sink** This strategy was introduced by Kotte et al. (1999) as Cubel, see section 4.1. Like the vessels plus heat sink strategy, vessels defined sinking also uses the correct absolute perfusion map. Only here the global blood temperature used in the additional heat sink is defined by the vessels rather than setting it to a default of 0 K. Instead the average arterial out-flow temperature is used. The veins use the average tissue temperature of the entire volume as their in-flow temperature. Vessels defined sinking was introduced by Kotte et al. (1999) to solve the incorrect perfusion map in the flow defined strategy.

**No discrete vasculature / continuum models** After the final stripping no discrete vasculature is left. To model the thermal impact of blood flow continuum models are used. Both the conventional heat sink model (Pennes, 1948) and a thermal conductivity model (Chen and Holmes, 1980; Lagendijk, 1984; Weinbaum and Jiji, 1985; Baish et al., 1986) are applied as well as a combination model. Chen and Holmes (1980); Weinbaum and Jiji (1985); Baish et al. (1986) present analytically deduced formulas to describe the thermal conductivity of a specific generation of vessels. The result is amongst others dependent on the thermal equilibration length of the vessels, the actual length and their orientation towards the temperature gradient present. Van Leeuwen et al. (2000b) determined the contribution of the various vessel generations in a vasculature similar to the one used here. For small vessels a very small contribution to the thermal conductivity was found. For larger vessels the value could not be determined accurately. The computation of the effective thermal conductivity contribution of multiple generations together or the entire vasculature is currently not feasible using the theoretical formulas. Empirically Crezee et al. (1994) found that the thermal conductivity of the entire vasculature is determined by the volumetric perfusion, see also section 4.3.4. In
this paper the optimal value for the thermal conductivity is found empirically, as done in section 4.3.4.

4.2.3 Evaluation of the temperature distributions

The results from simulations with incomplete vessel trees are compared to the full tree simulation. The temperature distributions are subtracted from the full tree distribution. Both the absolute temperature difference and the plain temperature difference distribution are determined. Only the heated volume of $4 \times 4 \times 4 \text{ cm}^3$ is evaluated. The absolute temperature difference distributions are presented in cumulative temperature difference histograms, the fraction of voxels is plotted against the absolute temperature difference, e.g. Figure 4.7(a). A steep decreasing graph indicates good correspondence with the full tree simulations. This way the various methods can be compared easily. A drawback of absolute temperature differences is that distinction between positive and negative temperature differences is not possible.

Therefore also plain temperature differences are used, presented as histograms, the percentage of voxels of the $4 \times 4 \times 4 \text{ cm}^3$ heated volume is plotted against the temperature difference, e.g. Figure 4.7(b). The best correspondence with the full tree is when the histogram is a small peak centered around 0 K difference. If the temperatures are consistently higher respectively lower than in the full tree simulation the histogram shows mainly negative respectively positive temperature differences.

4.3 Results

4.3.1 Full tree

Figure 4.4 shows the 3 K iso-temperature surface of the full tree simulation. The temperature distribution is clearly affected by the discrete vasculature, penetrating the iso-temperature surface. The maximum temperature reached in the full tree simulation was 7.6 K.

4.3.2 Qualitative comparison between DIVA and the heat sink model

Figure 4.5 shows slices through the temperature distribution as obtained from the full tree, the strip 0.3 vessels defined sink with bleed-off and the heat sink simulation. The full tree simulation yields high heterogeneity caused by the discrete vasculature and the heterogeneous perfusion map. The remaining vasculature in the strip 0.3 vessel defined sinking with bleed-off shows roughly the same pattern. The heat sink shows only heterogeneity due to the heterogeneous perfusion map.
4.3. Results

Figure 4.4: The 3 K iso-temperature surface in the full tree simulation, together with the arterial vasculature.

The results will be discussed in a more quantitative manner in section 4.3.3 and 4.3.4.

Figure 4.6 shows the cumulative temperature volume histogram of the full tree simulation, the strip 0.3 vessels defined sink with bleed-off, the strip 0.3 flow defined with bleed-off and the heat sink simulation. The histograms of the vessels defined sink and the flow defined simulations resemble the histogram of the full tree simulation best. A more quantitative comparison is made below.

4.3.3 Simulation with incomplete discrete vessel trees

As explained in section 4.2, our DIVA model offers various strategies to cope with the out-flowing blood from terminating vessels or at bleed-off locations. Each strategy is compared to the full tree simulation and per strategy the strip level is increased from 0.3 mm to 1.2 mm. This is done both with and without bleed-off.

Flow defined In Figure 4.7(a) and Table 4.2 a deterioration with increasing strip level is shown. Only for the strip 0.3 a bleed-off results in better correspondence. Note that the strip 1.2 without bleed-off coincides with the heat sink simulation. When the strip level is increased as well as when bleed-off is introduced, the histograms are shifted towards the negative temperatures, i.e. yield higher temperatures, see Figure 4.7(b) and Table 4.3.

The quantitative information of these histograms is well captured in Table 4.2
Figure 4.5: Slice through the temperature distribution of the full tree, the strip 0.3 bleed-off vessels defined sink and the heat sink simulation. White is 7.6 K, black is 0 K. The projection of the perfusion division plane runs from the lower left corner to the upper right.

Figure 4.6: Cumulative temperature volume histogram of the full tree simulation, the strip 0.3 bleed-off vessels defined sink, the strip 0.3 bleed-off flow defined and the heat sink. Only the heated sub-volume is included in the histograms.
4.3. Results

Figure 4.7: Cumulative and normal histograms of the (absolute) temperature differences with the full tree simulations. The flow defined simulations with and without bleed-off tree at strip level 0.3, 0.6 and 1.2 mm are shown.

and 4.3. Therefore for convenience of comparison the results of the remaining four strategies are only presented in Table 4.2 and 4.3.

Perfusion defined The results show a similar picture as the flow defined simulations. With increasing strip level the correspondence with the full tree deteriorates, see Table 4.2 and the temperatures rise as shown in Table 4.3. Bleed-off also deteriorates the correspondence with the full tree simulation for all strip levels. Also here, when the strip level is increased as well as when bleed-off is introduced, higher temperatures are reached in the simulations, see Table 4.3.

Absolute perfusion The strip 0.3 simulation improves dramatically by using a bleed-off whereas the strip 0.6 and 1.2 deteriorate by a bleed-off as shown in Table 4.2. The strip 1.2 deteriorates by the bleed-off and becomes worse than the heat sink simulation. These simulations show that the use of a vessel tree with more branches (strip 0.3 without bleed-off) yields worse correspondence than strip 0.6 without bleed-off). Table 4.3 shows that as well increasing the strip level as the use of bleed-off causes higher temperatures.
**Chapter 4. Thermal modelling with incomplete vessel data**

**Vessels plus heat sink**  The use of bleed-off hardly affects the temperature distribution, see Table 4.2 and 4.3. The strip 0.6 without bleed-off coincides with the strip 0.6 with bleed-off and the strip 1.2 simulations with and without bleed-off coincide with the heat sink simulation. The strip 0.6 yields better correspondence than the strip 0.3 simulations which show too low temperatures. Also here increasing the strip level yields higher temperatures.

**Vessels defined sink**  Also in the last compensation strategy increasing the strip level yields higher temperatures, see Table 4.2. For the strip 0.6 and 1.2 the results with bleed-off are worse than the heat sink simulation as shown in Table 4.3 and bleed-off causes lower temperatures (Table 4.3) but also a slightly better correspondence with the full tree simulation (Table 4.2).

**4.3.4 Continuum models and choosing the optimal continuum parameters**

Continuously stripping the discrete vasculature will result in thermal simulations without any discrete vessels, i.e. using a continuum model. In Figure 4.8(a) the heat sink simulation is plotted together with the strip 0.3 vessels defined sink without bleed-off simulation, the latter performs better. From Figure 4.8(b) can be seen that the heat sink yields too high temperatures, i.e. the histogram is not centered around 0 K but shifted towards negative temperatures. The heat sink simulation can be improved by adding an increased thermal conductivity (Chen and Holmes, 1980). The optimal correspondence with the full tree simulation is obtained when the histogram of the plain temperature differences is centered around 0 K and is determined empirically. By increasing the value in the low perfused half from 0.6 to 0.75 W m\(^{-1}\) K\(^{-1}\) and in the high perfused half to 0.9 W m\(^{-1}\) K\(^{-1}\) the histogram becomes centered around 0 K, see Figure 4.8(b) and Table 4.3. When the blood flow is modelled by an increased thermal conductivity alone the optimal values are higher, 1.65 and 2.7 for the respectively low and high perfused half. Coincidentally the optimal values for the thermal conductivity are predicted by a linear dependency of the perfusion as found by Crezee et al. (1994), \(K_{\text{eff}} = K(1 + W_b)\), with \(W_b\) the volumetric perfusion in kg m\(^{-3}\) s\(^{-1}\).

Adding an increased thermal conductivity as described above is also applied on the flow defined simulations for strip 0.6 without bleed-off and strip 1.2 with bleed-off. The enhancement is largest for the strip 1.2 simulation as shown in Figure 4.9(a). Figure 4.9(b) shows that it is possible to center the histograms around 0 K by adapting the thermal conductivity, see also Table 4.3. For the strip 1.2 simulation the thermal conductivity was increased to 0.9 and 1.2 W m\(^{-1}\) K\(^{-1}\) for respectively the low and high perfused half of the volume. For the strip 0.6 simulation
4.3. Results

(a) Cumulative histogram of absolute temperature differences.
(b) Normal histogram of the temperature differences.

Figure 4.8: Cumulative and normal histograms of the (absolute) temperature differences with the full tree simulations. The histogram of respectively strip 0.3 vessels defined sink without bleed-off, heat sink, thermal conductivity alone and the combined heat sink and thermal conductivity simulations are shown.

the optimal correspondence was found for 0.675 and 0.75 W m$^{-1}$ K$^{-1}$ for respectively the low and high perfused half of the volume.

Choosing and optimization of the thermal conductivity is only possible by comparing the results with the full tree simulation. If the normal histogram of the plain temperature differences is centered around 0 K temperature difference the optimal match is found. Obviously in clinical practice this can not be done since information about the full tree is lacking. This illustrates the limitations of thermal simulations with incomplete discrete vasculature.

4.3.5 Summary of results

Table 4.2 summarizes the results of the cumulative histograms. Each simulation is characterized by a single temperature: the temperature difference under which 90% of the heated volume lies, or in other words the temperature difference that is exceeded by only 10% of the heated volume. Perhaps unnecessarily, the lower the indicated temperature difference the better the correspondence with the full tree simulation. As noted in section 4.3.1 the maximum temperature reached in the full tree simulations was 7.6 K.
Figure 4.9: Cumulative and normal histograms of the (absolute) temperature differences with the full tree simulations. The histograms show the flow defined simulations. For both the strip 0.6 without bleed-off and the strip 1.2 with bleed-off the thermal conductivity is varied in order to optimize the correspondence with the full tree simulation.

Table 4.2: The temperature difference with the full tree simulations that is only exceeded by 10% of the heated volume. (The bleed-off simulations are referred to as bOf)

<table>
<thead>
<tr>
<th>Simulation</th>
<th>strip 0.3</th>
<th>strip 0.6</th>
<th>strip 1.2</th>
<th>no vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>flow def</td>
<td>0.74</td>
<td>1.28</td>
<td>1.83</td>
<td>-</td>
</tr>
<tr>
<td>idem optimized Keff</td>
<td>-</td>
<td>1.17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>bOf flow def</td>
<td>0.52</td>
<td>1.51</td>
<td>2.57</td>
<td>-</td>
</tr>
<tr>
<td>idem optimized Keff</td>
<td>-</td>
<td>-</td>
<td>1.53</td>
<td>-</td>
</tr>
<tr>
<td>perf def</td>
<td>0.70</td>
<td>1.49</td>
<td>1.83</td>
<td>-</td>
</tr>
<tr>
<td>bOf perf def</td>
<td>0.82</td>
<td>1.64</td>
<td>1.89</td>
<td>-</td>
</tr>
<tr>
<td>abs perf</td>
<td>1.36</td>
<td>1.33</td>
<td>1.82</td>
<td>-</td>
</tr>
<tr>
<td>bOf abs perf</td>
<td>0.78</td>
<td>1.45</td>
<td>1.95</td>
<td>-</td>
</tr>
<tr>
<td>vessels + sink</td>
<td>1.40</td>
<td>1.27</td>
<td>1.82</td>
<td>-</td>
</tr>
<tr>
<td>bOf vessels + sink</td>
<td>1.47</td>
<td>1.28</td>
<td>1.82</td>
<td>-</td>
</tr>
<tr>
<td>Vessels defined sink</td>
<td>0.94</td>
<td>1.43</td>
<td>1.85</td>
<td>-</td>
</tr>
<tr>
<td>bOf Yes def sink</td>
<td>0.74</td>
<td>1.84</td>
<td>2.02</td>
<td>-</td>
</tr>
</tbody>
</table>

sink only - - - 1.83
sink optimized Keff - - - 1.38
4.4. Discussion

Table 4.3: The mean temperature difference and variance with the full tree simulation. (The bleed-off simulations are referred to as biof)

<table>
<thead>
<tr>
<th>Simulation</th>
<th>strip 0.3</th>
<th>strip 0.6</th>
<th>strip 1.2</th>
<th>no vessels</th>
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<td>-0.74 ± 0.62</td>
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<tr>
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<td>-0.20 ± 0.45</td>
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<tr>
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<td>-0.62 ± 0.47</td>
<td>-1.24 ± 1.05</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>-0.25 ± 0.74</td>
<td>-</td>
</tr>
<tr>
<td>perf def</td>
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<td>-0.59 ± 0.50</td>
<td>-0.74 ± 0.62</td>
<td>-</td>
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<tr>
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<td>-0.70 ± 0.52</td>
<td>-0.83 ± 0.58</td>
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<tr>
<td>abs perf</td>
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<td>-0.34 ± 0.55</td>
<td>-0.73 ± 0.62</td>
<td>-</td>
</tr>
<tr>
<td>biof abs perf</td>
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<td>-0.55 ± 0.49</td>
<td>-0.93 ± 0.58</td>
<td>-</td>
</tr>
<tr>
<td>vessels + sink</td>
<td>0.64 ± 0.28</td>
<td>-0.39 ± 0.47</td>
<td>-0.73 ± 0.62</td>
<td>-</td>
</tr>
<tr>
<td>biof vessels + sink</td>
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<td>-0.36 ± 0.49</td>
<td>-0.73 ± 0.62</td>
<td>-</td>
</tr>
<tr>
<td>Vessel defined sink</td>
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<td>-0.55 ± 0.48</td>
<td>-0.76 ± 0.62</td>
<td>-</td>
</tr>
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<td>-0.90 ± 0.64</td>
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<tr>
<td>sink</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-0.28 ± 0.72</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-0.30 ± 0.60</td>
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Table 4.3 shows the mean temperature difference and the variance with the full tree simulation. Since the normal histograms are approximately symmetric around the maximum, the mean temperature difference indicates the position of the peak, see Figure 4.7(b). A positive respectively negative mean temperature difference means that the temperature distribution is higher respectively lower than the full tree temperature distribution. The variance is a measure for the width of the peak.

The flow defined simulation with bleed-off yields the best correspondence with the full tree simulation. Increasing the strip level deteriorates the correspondence for all simulations except for absolute perfusion without bleed-off and the vessels plus heat sink, with and without bleed-off. For all strip 0.6 and strip 1.2 simulations the use of a bleed-off deteriorates the correspondence. For the strip 0.3 simulations (still using a quite detailed discrete vasculature) the use of a bleed-off yields varying results. The vessels defined sink, flow defined and the absolute perfusion simulations benefit from a bleed-off. The perfusion defined and vessels plus heat sink show worse results when using a bleed-off.

4.4 Discussion

Increasing the strip level deteriorates the correspondence with the full tree simulation in two ways. Firstly, the temperature heterogeneity due to discrete vessels dis-
appears as illustrated in Figure 4.5. Secondly the temperature distribution yields higher temperatures for reduced vasculatures, see Figure 4.7(b) and Table 4.3. This is irrespective of the compensation method used and is also valid for a pure heat sink simulation, see Figure 4.8(b).

Modelling the temperature heterogeneities due the missing vasculature is hard. Very local compensating methods are necessary which will require more knowledge about the missing vasculature than mostly available. An approximation is done by using local sink sets and local out-flow temperatures such as flow defined and perfusion defined simulations, rather than a global compensation method as vessels defined sink or a pure heat sink simulation. The various methods are discussed below.

Compensating the second effect, i.e. the temperature rise for increasingly stripped trees, can be done globally. Increasing the thermal conductivity improves the results both for the heat sink simulation, see Figure 4.8, and the simulations with discrete vessels, see Figure 4.9. This shows that the missing vasculature contributes to the thermal conductivity as already stated by Chen and Holmes (1980). The problem is that these optimizations can only be done when information about the full tree is available for comparison and are therefore not useful in clinical applications. This is a fundamental limitation of compensating limited discrete vasculatures in thermal simulations as long as reliable, prospective knowledge about the increase of the thermal conductivity due to a specific generation of vessels is lacking.

Flow defined The strip 0.3 simulation with bleed-off yields the best correspondence with the full tree simulation of all simulations, see Table 4.2. 90% of the evaluated volume differs less than 0.52 K from the full tree simulation. Without bleed-off the temperatures are too low, see Table 4.3 and Figure 4.7(b). In Figure 4.7(b) the strip 0.6 both with and without bleed-off is located around approximately the same temperature as the heat sink simulation. However the correspondence with the full tree is better because of the correctly modelled temperature heterogeneity by the remaining vasculature. When the number of vessels is further reduced as done in strip 1.2 without bleed-off only a single local sink set remains and thus the correct perfusion distribution is used. This is in fact the same situation as the strip 1.2 perfusion defined, absolute perfusion and vessels defined sink simulation. These all approach the heat sink simulation, see Table 4.2.

Introduction of bleed-off for the strip 1.2 yields the worst results of all simulations. Bleed-off causes the number of local sink sets to be increased, the 1000 sub-volumes are added to the local sink set of the closest terminating point or bleed-off location. The terminating point of the artery gets assigned the major part of the volume. However only a small part of the blood flow is left at the end of the vessel and the
major part of the volume will get a too low effective perfusion. The local sink sets near the beginning of the artery are smaller and get a too high effective perfusion. However these local sink sets are mainly located outside the heated area, this explains the too high temperature distribution.

**Perfusion defined** Here the correct perfusion distribution is used. The use of a bleed-off affects the arterial out-flow temperature but does not affect the effective perfusion distribution. The effect of using a bleed-off is small, see Table 4.2 and 4.3. For the strip 0.3 tree the performance is slightly worse than the flow defined simulation. For this strip level the correct blood flow is more important than using the exactly correct perfusion map. The correspondence between the strip 0.6 simulation with the full tree simulation is comparable with correspondence of the strip 0.6 flow defined simulation, see Table 4.2. The errors in the blood flow and arterial out-flow (perfusion defined) cause similar errors as using an incorrect perfusion distribution (flow defined). Also for the perfusion defined simulation the strip 1.2 simulation almost equals the heat sink simulation. Altering the blood flow by introducing a bleed-off shows no effect, using the correct perfusion distribution is more important than using the correct blood flow in the single remaining vessel.

**Absolute perfusion** For the strip 0.6 and 1.2 tree the results are comparable to the flow defined (except for the strip 1.2 with bleed-off) and perfusion defined simulations, see Table 4.2. Absolute perfusion simulations use the same blood flows as the flow defined simulation together with perfusion distribution as used by the perfusion defined simulations. The flow defined and perfusion defined simulations are mutually comparable for these strip levels and so is the absolute perfusion simulation.

For the strip 0.3 tree the performance is worse than the flow defined and perfusion defined simulations. The amount of out-flowing blood from a specific vessel or bleed-off location is not corresponding with the amount of blood that is thermally equilibrated in its local sink set, since the local perfusion level is determined by an absolute perfusion map and not by the amount of out-flowing blood. Cumulatively over all local sink sets the correct amount of blood is used however locally the incorrect arterial temperatures are used in the additional heat sink.

The effect of a bleed-off is clearest noticeable for the strip 0.3 simulation, see Table 4.2. The bleed-off increases the number of local sink sets. This increases the correspondence between arterial out-flow and the perfusion in the local sink set. This situation approaches the perfusion defined simulation.
Vessels plus heat sink  The conventional heat sink (Pennes, 1948) is added to a
discrete description of the vasculature. For the strip 0.3 simulation this causes
too high cooling since both the vasculature and the full heat sink are present, see
Table 4.3. The strip 0.6 performs better than the strip 0.3 simulation because the
erroneous high cooling is reduced by reducing the number of discrete vessels. The
strip 1.2 simulation has only a single vessel left and is nearly equal to the heat
sink simulation.

The presence of bleed-off hardly influences the temperature distribution. The arte-

terial out-flow temperatures are not used, nor is the effective perfusion distribution
affected by a bleed-off. The only difference is the blood flow inside the vessels and
therefore the temperature of the vasculature. The difference is only visible for the
strip 0.3 simulation. For the strip 0.6 and 1.2 only large vessels with high blood
flow are left. They will have low blood temperatures irrespective of a bleed-off.

Vessels defined sink  Adding a full heat sink as done in the vessels plus heat sink
caus e d too high cooling. The vessels defined sink strategy adds a heat sink which
uses a blood temperature defined by the global average out-flow temperature of
the vessels. Thus the impact of the additional heat sink is decreased by using the
temperature of the pre-heated blood. For the strip 0.3 this improves the results
as shown in Table 4.3. Because the global arterial out-flow temperature is used
instead of the local arterial out-flow temperature the results are not as good as flow
defined or perfusion defined simulations. Using a bleed-off yields a more realistic
average out-flow temperature and improves the results.

Without bleed-off the strip 0.6 tree yields comparable results as the vessels plus
heat sink simulation. Using a bleed-off causes lower blood flows and therefore
higher out-flow temperatures. This again decreases the cooling by the additional
heat sink and causes too high temperatures, see Table 4.3.

4.5 Conclusions

Various strategies were used to compensate incomplete vessel trees. Irrespective
of the method used, the more vessels available, the better the correspondence
with the full tree simulation. Using a bleed-off in an incomplete vessel tree yields
more realistic blood flows in the vasculature but can cause an erroneous effective
perfusion distribution if too few discrete vessels are present. The strip 0.3 flow
defined simulation with bleed-off yielded the best correspondence.

In these simulations determination of the bleed-off was done using information
from the full tree. In clinical practice determination of the correct bleed-off in a
incomplete vessel tree is not feasible yet since then the blood flow in each individual vessel has to be measured. Without bleed-off the flow defined and perfusion defined simulations yield the best results at all strip levels. It depends on the available angiographic data which method is most useful. If a perfusion distribution is available from e.g. MRI (Vonken et al., 1999) the perfusion defined method is the first choice. If the blood flow in the root segment of the vasculature can be measured, e.g. with ultrasound (Aaslid, 1986) or quantitative flow MRI (Bakker et al., 1999), the flow defined strategy is preferred.

When no discrete vessels are available a heat sink simulation yield an overestimation of the temperature distribution, i.e. too high temperatures. Theoretically this can be compensated by increasing the thermal conductivity. This can also be done for incomplete discrete vasculatures. In practice this optimization is not possible yet. The necessary reliable, prognostic knowledge about the contribution to the thermal conductivity or effective perfusion level of the missing branches is lacking.
Chapter 5

Determination and validation of the actual 3D temperature distribution during interstitial hyperthermia of prostate carcinoma

This chapter is accepted for publication as

Abstract To determine the thermal dose of a hyperthermia treatment knowledge of the 3D temperature distribution is mandatory. The aim of this paper is to validate an interstitial hyperthermia treatment planning system with which the full 3D temperature distribution can be obtained in individual patients.

Within a phase 1 study 12 patients with prostate cancer were treated with interstitial hyperthermia using our Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS IHT) system. The temperature distribution has been measured from within the heating devices and by additional thermometry.

The perfusion level has been estimated and the heating implant was reconstructed. The steady-state temperature distribution is calculated using our interstitial hyperthermia treatment planning system.

The simulated temperature distribution is validated by individually comparing the measured and simulated thermo-sensors, both for the thermometry integrated with the heating applicators and the additional thermometry. The entire procedure was also performed on a no-flow agar-agar phantom.

It was shown that the calculated temperature distribution of an individual patient during MECS interstitial hyperthermia is very heterogeneous. The validation indicates that the calculated temperature elevations match the measurements within approximately 1 °C.
Possible improvements are more precise reconstruction, incorporation of discrete vasculature and using a temperature dependent, heterogeneous perfusion distribution. Further technical improvements of the MECS-IHT system may also result in better temperature calculations.
5.1 Introduction

Hyperthermia, elevation of tissue temperatures to the range of 39-45 °C, is used as an effective boost technique to increase local tumour control and survival as shown recently again by Van der Zee et al. (2000). To define the thermal dose applied to a patient knowledge of the actual 3D temperature distribution is a necessity (Sapareto and Dewey, 1984). In literature, achieved temperature distributions are quantified by their estimated minimum temperature, or by limited sampling from invasive thermometry (Sneed et al., 1992; Ryan et al., 1994; Stea et al., 1994). The aim of this paper is to validate an interstitial hyperthermia treatment planning system with which the full 3D temperature distribution can be obtained in individual patients.

In a phase I study 12 patients with prostate cancer were treated with combined interstitial hyperthermia (IHT) and external beam irradiation (Van Vulpen et al., 2001). Our Multi Electrode Current Source Interstitial Hyperthermia Treatment (MECS IHT) system (Visser et al., 1989; Lagendijk et al., 1995) was used for heating. Dual electrodes per catheter and multiple catheters ensure 3D controlled power deposition in the target volume (Van der Koijk, 1997). On-line temperature measurements from within the applicators are used to control the 3D temperature distribution (Crezee et al., 1997; Kaate et al., 1999).

This integrated thermometry provides a 3D sampling of the temperature from within the heating applicators and can not be considered the full 3D temperature distribution. They are mainly effective for controlling the maximum temperature in the implanted volume. The minimum temperature in the implant can be estimated by successively switching-off heating applicators (Kaatte et al., 2001). Ideally the full 3D temperature distribution is non-invasively measured on-line, for instance by MR thermometry (Nelson and Tung, 1987; Samulski et al., 1992; Włodarczyk et al., 1998; De Zwart, 2000). However absolute small scale temperature measurements with MRI are very hard and the temperature resolution is sparse (De Zwart et al., 1996; De Zwart, 2000). Furthermore not all hyperthermia techniques and certainly not our MECS-IHT system are easily integrated with MRI.

In this paper thermal modelling is used to reconstruct the full 3D temperature distribution. This can be used for quality assurance of MECS interstitial hyperthermia according to Emami et al. (1991). Besides modelling heat transfer by conduction a thermal model has to incorporate the thermal impact of blood flow (Lagendijk, 1990; Roemer, 1990). The model used most often is the Pennes bioheat or heat-sink model (Pennes, 1948). The thermal impact of blood is described by introducing an energy drain which is proportional with the volumetric perfusion level and the elevation of the local tissue temperature. This and the enhanced thermal conductivity model (Chen and Holmes, 1980; Weinbaum and Jiji, 1985) are both continuum models and cannot predict the thermal impact of an individ-
ual vessel. Incorporation of individual vessels clearly improves the calculation of the temperature distribution (Lagendijk, 2000).

Which thermal model is used depends on the available data for patient specific reconstruction. The prostate and the implant cannot be reconstructed with MR given the patient position (see figure 5.1(a)) during implantation (Battermann, 2000). Altering the patient's position can cause movement of the implant. Therefore reconstruction is done using trans-rectal ultrasound and the patient is treated in the implantation position. However trans-rectal ultrasound reveals no discrete vasculature. Recent developments in power Doppler angiography shows vascular densities rather than individual vessels (Bogers et al., 1999), combination with contrast agents reveals some discrete vasculature (Kruger Hagen et al., 2001), this technique was not available for this study. Because the prostate is so deep seated post-treatment MR angiography presently cannot visualize the 3D vascular geometry.

As no angiographic data are available the bio-heat model has to be used for simulating the temperature distribution. Our Discrete VAsculature model (DIVA) (Kotte et al., 1996, 1999) originally has been designed to cope with individual vessels but can also run as a bio-heat model. DIVA has been validated theoretically by Van Leeuwen et al. (1997b,a) and experimentally by Raaymakers et al. (1998, 2000a).

Essential for the bio-heat model is using the correct volumetric perfusion level. Per patient perfusion data can be determined from the measured thermal decay at the end of the treatment. The rate of thermal decay correlates with the volumetric perfusion and can be quantified by fitting with a single exponential function, as done by Waterman et al. (1980) and many others, see Roemer et al. (1985). Since heat is not only removed by perfusion but also by conduction this estimation will be too high (Roemer et al., 1985) and is referred to as the effective perfusion. The contribution of conduction can be corrected for if information about heating geometry, thermal boundary conditions and initial conditions are taken into account in the estimation procedure (Newman et al., 1990). This way the volumetric perfusion can be estimated from the thermal decay, see section 5.2.4.

Another necessity for calculating the temperature distribution is the power deposition as administered during treatment. The power deposition by current source electrodes can be calculated using a quasi-static power deposition model (DeBree et al., 1996). The model also has to take care of the power absorption in the catheters. During treatment electrode powers are controlled using the electrode temperatures (Cresce et al., 1997; Kaatee et al., 2001), the exact absolute power output of individual electrodes can not be determined in a complex patient implant. Therefore also the simulations are temperature controlled and the measured temperature of each individual electrode is needed in the calculations.
When determining the measured electrode temperature the problem of self-heating arises. Electrode temperatures are measured by the 7 sensor thermo-couple string in each applicator during power-off intervals (De Leeuw et al., 1993). Directly after power-off the temperature read-out is erroneous as the nylon catheters absorb approximately 34% of the emitted energy (Van der Koij et al., 1997a). During treatment a power-off interval of 5 or 6 seconds is used, after this period the thermo-sensor yield the tissue temperature at the moment of switching-off the power (Kaatee et al., 1999). Of course the exact relation is dependent on the perfusion level and the power level of the electrode. The temperatures as used in the simulations are taken after 15 seconds power-off as explained in section 5.2.3 to yield the real tissue temperatures.

So finally the 3D temperature distribution can be calculated by using a patient specific reconstruction, perfusion estimation and the correct electrode temperatures. The temperatures are linked directly to the anatomy facilitating histograms of volumes of interest. This paper will not evaluate the achieved temperature distribution in detail, this will be done in future communications. The focus of this paper is the validation of the simulated temperature distribution. The thermometry inside the heating applicators, additional thermometry and switching-off an applicator all yield means to validate the simulations. The entire procedure is first tested on a no-flow agar-agar phantom.

5.2 Methods

5.2.1 Patient inclusion and implantation

In a phase I study 12 patients with prostate cancer were treated with combined interstitial hyperthermia (IHT) and external beam irradiation (Van Vulpen et al., 2001). All patients had stage III (T3N,M0), the average age was 65 years (45-74), the average prostate volume was approximately 40 cubic cm. For 7 patients the volumetric perfusion level was estimated and the 3D temperature distribution has been calculated. The other patients could not be evaluated because no thermal decay was measured or reconstruction from ultrasound was not possible. An average of 12 (7-16) catheters was implanted per patient. The low-loss nylon catheters with an inner diameter of 1.2 mm and outer diameter of 1.5 mm were implanted under trans-rectal ultrasound guidance as done routinely for brachy-therapy at our department (Battermann, 2000).

First 15 Gauge steel needles were implanted. After they were loaded with the plastic catheters, the needles were retracted. During the implantation and during the entire treatment the patient stayed in the position as shown in figure 5.1(a) to prevent movement of the implant. The catheters are filled with distilled water
and then loaded with dual-electrode (20-5-20 mm) MECS-IHT applicators. For all evaluated patients thermometry in the urethra was present. For all except 1 a catheter dedicated for thermometry was available. For 5 patients an applicator was switched-off during steady-state, thus mimicking an extra thermometry catheter, see section 5.2.5.

![Patient in treatment position, with MECS-IHT heating applicators in place.](image1)

![Transversal ultrasound image showing the contour of the prostate and the catheter positions. The urethra is visible in the circle, the extra thermo-string in the ellipse.](image2)

**Figure 5.1:** Patient during treatment and an ultrasound slice with catheters.

### 5.2.2 Reconstruction of the treatment set-up

After implantation a series of transversal ultrasound images with a mutual spacing of 5 mm was made, see figure 5.1(b). These slices are used for 3D reconstruction of the catheters and the urethra. The electrode and thermo-sensor positions can be reconstructed because their location inside the catheters is known. Post-treatment MRI is used to delineate the prostate volume (without catheters). The reconstructed implant can be matched with MR as shown in figure 5.5(a) using the urethra catheter. The urethra was only visible in MR when it was catheterized.

In the simulations the anatomy is defined as a homogeneous tissue grid with $2 \times 2 \times 2$ mm$^3$ resolution. The tissue properties used are stated in table 5.1. Vessels inside the prostate could not be visualized, a homogeneous perfusion level is assumed. The level of the perfusion is estimated as explained in section 5.2.4.
5.2. Methods

<table>
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<td>4000</td>
<td>-</td>
</tr>
</tbody>
</table>

5.2.3 Electrode temperatures

In the simulations the individual electrode temperatures during treatment are needed. They are defined by the average of all sensors inside a particular electrode. Directly after power-off the temperature read-out is erroneous due to self-heating. At approximately 15 seconds after power-off undisturbed temperatures can be obtained. The length of this period was determined by placing an applicator in a well-stirred water bath of fixed temperature and measuring both the inner and outer applicator temperature. Figure 5.2 shows that after 15 seconds power-off the thermo-sensors yield the correct tissue temperature outside the catheter. From the thermal decay at the end of the treatment the temperatures after 15 seconds power-off are determined. This 15 second decay is taken into account in the simulations as explained in the next paragraph.

![Figure 5.2: Normalized temperature difference as measured between inside and outside an applicator loaded in a low loss nylon catheter in a well-stirred water bath.](image-url)
5.2.4 Perfusion level and power deposition

Both the perfusion level and the power deposition by the electrodes are determined by iterative simulations. In summary, the power deposition is calculated by adjusting the power to each electrode until the measured and simulated temperature coincide and the perfusion level in the simulations is adjusted until the measured and simulated effective perfusion (as introduced in section 5.1) match. Both loops are schematically shown in figure 5.3.

For an arbitrary perfusion level the power deposition by the electrodes has been calculated (De Bree et al., 1996). Subsequently the steady-state temperature distribution and the following 15 second thermal decay were calculated. Then the electrode temperatures are determined and compared with the measurements. The power of each electrode is adjusted until the measured and simulated electrode temperatures coincide (Van der Koijk et al., 1996). The dielectric properties used are shown in table 5.1, the use of literature values suffices (Van de Kamer et al., 2001d). Figure 5.3(b) shows a diagram of the loop used to accomplish this.

A second iterative loop is used to estimate the perfusion level. From the measured temperature decay at the end of the treatment the effective perfusion of each thermo-sensor is determined, see section 5.1. This is done for the period from 20 to 320 seconds after power-off and yields the average measured effective perfusion for all thermo-sensors. The simulated effective perfusion is determined by calculating a similar thermal decay for the corresponding thermo-sensor locations. After comparing the effective perfusion estimation from measurements and simulations, the volumetric perfusion level in the simulations is adjusted and the calculation is performed again. This is repeated until a volumetric perfusion level is found for which a fair match for the effective perfusion is reached. Because the contribution of thermal conduction is accounted for the correct volumetric perfusion can be estimated. The optimization loop used is schematically shown in figure 5.3(a).

5.2.5 Validating the calculated temperature distribution

The calculated temperature distribution is validated by comparing measured and simulated temperatures at corresponding locations. This is done for the thermo-sensors integrated with the heating applicators and for additional thermometry. The integrated thermometry samples the high temperature area of the implant. All sensors which decay to the body core temperature after treatment are included in the comparison. The comparison is made 15 seconds after power-off to eliminate effects of self-heating in the measurements. The additional thermo-sensor strings sample from the low temperature area in the implant. Additional thermometry was available in the urethra and in dedicated catheters, both reconstructed from ultrasound, see figure 5.1(b). Also thermometry in a switched-off applicator can be
Figure 5.3: Diagram of simulating a hyperthermia treatment, figure 5.3(b) is the detailed diagram of the dashed block in figure 5.3(a).

regarded as additional thermometry. The number of sensors used for comparison may vary because of defect sensors or because only part of a thermometry catheter could be reconstructed from ultrasound images.

The comparison is quantified by the averaged temperature difference, and the averaged absolute temperature difference.

5.2.6 Agar-agar phantom

For validation purposes the treatment and evaluation procedure were also applied on an agar-agar phantom. A rectangular block of agar-agar (40 g l⁻¹ agar-agar and 3 g l⁻¹ NaCl dissolved in boiling distilled water) of 60×60×85 mm (xyz) was implanted with 7 catheters in a hexagonal implant along the z-axis, see figure 5.4(a), loaded with dual electrode (20-5-20 mm) applicators. All electrodes were controlled to yield a maximum temperature of 30 °C at 6 s after power-off. The phantom was submerged in a well-stirred water bath of fixed temperature of 19.7 °C to apply constant and well-defined boundary conditions. The 3D tracks of
5.3 Results

5.3.1 Measured temperature distribution

The temperature distribution is sampled by 7 thermo-sensors per catheter. These temperature data (approximately 90 samples) can be used to determine measured statistics about the achieved temperature distribution. The $T_{50}$ from these samples, indicating the temperature which is reached by 50 % of the temperature measurements, is presented as a reference to the simulated temperatures in Table 5.2.

5.3.2 Simulated temperature distribution and perfusion estimations

The simulated temperature distribution is registered with the anatomy. Thus the actual temperature within the anatomy can be investigated. Figure 5.5(a) shows a...
5.3. Results

MR slice with the iso-temperature lines from the corresponding temperature distribution for patient 11. This facilitates cumulative temperature volume histograms of the prostate. The simulated $T_{50}$ is defined for the entire prostate and not from a limited sampling at the thermo-sensor positions. The cumulative temperature volume histograms in figure 5.5(b) show an increase in temperature in the last 4 patients. This can also be seen from Table 5.2 for both the measured and simulated temperatures. The simulated $T_{50}$ is consistently lower than the measured $T_{50}$. The difference between the simulated $T_{10}$ and $T_{50}$ (indicating the temperature reached by 10 respectively 90 % of the temperature samples) show the heterogeneity in the temperature distributions. Furthermore, for the patients who could be evaluated the estimated perfusion values are presented.

(a) MR anatomy slice of patient 11 with the reconstructed electrodes (vertical white structures) and the iso-temperature lines. 37°C is the outer contour, the temperature increase is 2°C per iso-temperature line.

(b) Cumulative temperature volume histogram of the simulated temperature distribution for the prostate volume of the last 4 patients.

Figure 5.5: Anatomy with iso-temperature lines and cumulative temperature volume histograms.

5.3.3 Validating in agar-agar phantom

Figure 5.4(b) shows the simulated 28.7 °C (9 °C elevation) iso-temperature surface. Figure 5.6(a) and figure 5.6(b) show the temperature difference between measurements and simulations for the extra thermo-sensor strings respectively the switched-off applicator. The extra thermometry string 1 (located in the periphery
of the implant, see figure 5.4(a) matches closely for the first 3 cm, the last part shows larger differences. String 2 (located in the center of the implant) shows a close match along the entire catheter. For the switched-off applicator only the first sensor shows a large deviation with the simulated profile, the second sensor was defect. Table 5.3 shows the validation results quantitatively. The integrated thermometry matches within 1 °C. The extra string 2 shows approximately the same results as does the switched-off applicator. String 1 shows slightly worse results.

5.3.4 Validating in individual patients

Thermometry inside heating applicators Table 5.4 shows the temperature differences for all patients. The average differences are just below 0, i.e. the simulations yield slightly higher temperatures than the measurements. The absolute differences are in the range from 1 to 2 °C.

Additional thermometry and switched-off applicators Figure 5.7 shows a typical example of the measured and simulated profile along the urethra and dedicated thermometry string in patient 11. The measured samples along the urethra lack the sharp maximum as found from the simulations. For the additional string especially the fourth sensor show a large deviation with the simulations. The quantitative differences for all patients are summarized in table 5.5, on average the

Table 5.2: Estimated volumetric perfusion (ml (100g)/min), the effective perfusion from the treatments and the simulations are shown too. Also the simulated T10, T50 and T90 of the entire prostate volume is given together with the measured T50 as determined from the thermo-sensors approximately 3 seconds after power-off. Units of perfusion is ml(100g)/min and is indicated by an *.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eff.</td>
<td>perf(*)</td>
<td></td>
<td>eff.</td>
<td>perf(*)</td>
<td>T50 (°C)</td>
<td>T50 (°C)</td>
</tr>
<tr>
<td></td>
<td>vol.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sensor</td>
<td>volume</td>
</tr>
<tr>
<td>5</td>
<td>77±26</td>
<td>50</td>
<td>77±21</td>
<td>44.2</td>
<td>39.8</td>
<td>41.6</td>
<td>38.7</td>
</tr>
<tr>
<td>7</td>
<td>74±33</td>
<td>55</td>
<td>76±24</td>
<td>40.3</td>
<td>38.5</td>
<td>40.4</td>
<td>37.4</td>
</tr>
<tr>
<td>8</td>
<td>63±31</td>
<td>35</td>
<td>65±18</td>
<td>45.5</td>
<td>39.0</td>
<td>40.4</td>
<td>36.8</td>
</tr>
<tr>
<td>9</td>
<td>75±40</td>
<td>50</td>
<td>75±18</td>
<td>46.6</td>
<td>40.1</td>
<td>42.9</td>
<td>38.5</td>
</tr>
<tr>
<td>10</td>
<td>55±20</td>
<td>30</td>
<td>52±17</td>
<td>47.2</td>
<td>41.4</td>
<td>43.2</td>
<td>39.4</td>
</tr>
<tr>
<td>11</td>
<td>86±40</td>
<td>65</td>
<td>89±16</td>
<td>47.4</td>
<td>42.1</td>
<td>45.5</td>
<td>39.7</td>
</tr>
<tr>
<td>12</td>
<td>70±20</td>
<td>55</td>
<td>70±14</td>
<td>47.4</td>
<td>42.4</td>
<td>47.2</td>
<td>39.2</td>
</tr>
<tr>
<td>Agar</td>
<td>21±11</td>
<td>0</td>
<td>19±12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Chapter 5. Validation in prostate patients
5.3. Results

![Graphs showing temperature profiles](image)

(a) Additional thermometry.  
(b) Switched-off applicator.

**Figure 5.6:** Measured and simulated profile along 2 additional thermometry catheters and along a switched-off applicator in an agar-agar phantom.

<table>
<thead>
<tr>
<th>Agar-agar</th>
<th>number</th>
<th>average difference (°C)</th>
<th>average absolute difference (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>inside</td>
<td>41</td>
<td>0.7±1.3</td>
<td>1.0±1.1</td>
</tr>
<tr>
<td>extra1</td>
<td>7</td>
<td>1.1±1.2</td>
<td>1.1±1.2</td>
</tr>
<tr>
<td>extra2</td>
<td>7</td>
<td>0.1±0.6</td>
<td>0.5±0.3</td>
</tr>
<tr>
<td>switch-off</td>
<td>6</td>
<td>0.0±1.1</td>
<td>0.7±0.8</td>
</tr>
</tbody>
</table>

**Table 5.3:** Temperature differences in °C for the agar-agar phantom between measured and simulated temperature elevation of thermo-sensors inside heating applicators, for the additional thermometry and for the switched-off applicator. The average differences and the average absolute differences are shown.
absolute temperature difference is 1 °C. The urethra thermocouple string shows better matches than the sensors from the dedicated thermometry catheter.

The results for the switched-off applicators are shown in Table 5.6. The averaged absolute difference is 0.8 °C, slightly better than the results from dedicated thermometry catheters as presented above.

![Figure 5.7](image)

**Figure 5.7** The eleventh patient yields a typical example for the measured and simulated temperature profile along urethra and additional thermometry string. The symbols are the measurements, the lines are the simulated profiles.

## 5.4 Discussion

*Full 3D temperature distribution* In the literature temperature distributions are quantified using a limited set of temperature samples (Ryan et al., 1994; Stea
### Table 5.5: Temperature differences in °C between measured and simulated temperature increase of additional thermometry strings. The average differences and the average absolute differences are shown.

<table>
<thead>
<tr>
<th>Patient</th>
<th>number sensors</th>
<th>average difference (°C)</th>
<th>average absolute difference (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>urethra</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>-0.5±0.4</td>
<td>0.5±0.4</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>-0.7±0.8</td>
<td>0.8±0.7</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>-0.3±0.9</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>0.3±0.8</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0.2±0.7</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>-0.5±0.7</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>-0.1±2.0</td>
<td>1.5±0.8</td>
</tr>
<tr>
<td>all urethra</td>
<td>39</td>
<td>-0.3±0.8</td>
<td>0.7±0.5</td>
</tr>
<tr>
<td>extra</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>1.1±0.6</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>1.8±1.5</td>
<td>1.8±1.5</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>-1.2±2.4</td>
<td>1.2±2.4</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>-0.6±0.8</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>-0.4±1.5</td>
<td>1.0±1.0</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>-2.5±3.0</td>
<td>2.5±3.0</td>
</tr>
<tr>
<td>all extra</td>
<td>36</td>
<td>-0.1±1.5</td>
<td>1.3±1.4</td>
</tr>
<tr>
<td>all ur + extra</td>
<td>75</td>
<td>-0.2±1.2</td>
<td>1.0±1.0</td>
</tr>
</tbody>
</table>

### Table 5.6: Temperature differences in °C between measured and simulated temperature increase of switched-off applicators at approximately 2 minutes after switch-off. The average differences and the average absolute differences are shown.

<table>
<thead>
<tr>
<th>Patient</th>
<th>number sensors</th>
<th>average difference (°C)</th>
<th>average absolute difference (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>6</td>
<td>0.5±0.7</td>
<td>0.6±0.6</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>0.4±0.8</td>
<td>0.7±0.4</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>0.8±0.5</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>0.0±0.8</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>-0.3±2.0</td>
<td>1.5±1.3</td>
</tr>
<tr>
<td>all</td>
<td>30</td>
<td>0.3±1.0</td>
<td>0.8±0.7</td>
</tr>
</tbody>
</table>
et al., 1994; Dewhirst et al., 1984; Shimm et al., 1990; Cox and Kapp, 1992; Sneed et al., 1992). This only yields accurate results when the temperature distribution is sampled at representative locations which in general is not the case (Corry et al., 1988). Reconstructing the full 3D temperature distribution from discrete temperature samples as necessary for thermal dose calculations is nearly impossible.

In this paper for the first time the full 3D temperature distribution for individual patients is calculated, matched with anatomical imaging (figure 5.5(a)) and verified. This facilitates cumulative temperature volume histograms of the entire tumour volume which can be used for treatment optimization and quality assurance as proposed by Emami et al. (1991). Emami et al. (1991) stated that thermometry inside applicators cannot be used for quality assurance, additional thermometry should be used. However additional thermometry generally do not yield a representative sampling of the temperature distribution (Corry et al., 1988). Simulations in combination with corrected applicator temperatures are able to yield the full 3D temperature distribution. As expected, the simulated temperatures, representing the entire prostate, are much lower than found from the thermometry integrated in the applicators as shown in Table 5.2. The reason is that when evaluating the simulated temperature distribution also the low temperature regions in between the electrodes are taken into account.

Validation in agar-agar phantom  The question to be answered is: how accurate are the calculated temperatures? In the well-defined setting of an agar-agar phantom the temperatures are approximately within 1 °C see table 5.3. The perfusion is 0 ml(100g)^{-1} min^{-1} and is estimated correctly as shown in Table 5.2. The effective perfusion of 21 or 19 for the measurements respectively simulations is fully determined by conduction since heat transfer is due to and can be modelled by conduction only. A similar set-up is investigated previously by Raaymakers et al. (2000a), hot water tubes were used for heating and a nearly perfect match between measured and simulated temperatures was found.

It is shown that even in a homogeneous agar-agar phantom with well-defined boundary conditions the very heterogeneous temperature distribution during interstitial hyperthermia can not be predicted perfectly at individual locations, see string 1 in figure 5.6(a) or figure 5.6(b). The deviations found are mainly due to two errors, the geometrical reconstruction and the electrode temperatures. A temperature distribution during interstitial hyperthermia is characterized by steep temperature gradients, especially in the periphery of the heating implant, see figure 5.4(b) and 5.5(a). Very small reconstruction errors result in relatively large errors of the predicted temperature. Another cause for the deviation are the electrode temperatures used. From the measurements maximally 3 temperature samples are obtained per electrode which yield the mean electrode temperature. When the
5.4. Discussion

Sampling is not representative, the mean electrode temperature used in the simulations differs from the measurements. Using a single sensor to define the electrode temperature in the simulations is not a good alternative. In a homogeneous situation this should work provided that the sensor location is exactly known which is not the case. Furthermore in a real patient the temperature along an electrode varies due to passing blood vessels and tissue heterogeneities. Thus the use of the average electrode temperature is preferred to diminish the dependency of the sensor location.

Another problem with the electrode temperatures is the modelling of the self-heating. Undisturbed electrode temperatures are obtained 15 seconds after poweroff. To calculate the steady-state temperature distribution also this 15 second decay is simulated after which the results are compared with the measured electrode temperatures. Self-heating is incorporated in the model, however individual applicators show deviations from the idealized applicator description in the model (Van der Koijck et al., 1998). This way the simulated steady-state temperatures can be erroneous.

Validation in individual patients The same procedure is applied on patient data and validation is done in both high and low temperature areas of the implant. The thermometry inside the applicators is an indication of the differences between the measured and simulated temperatures in the highest temperature areas. However it is not a really independent validation since the average electrode temperatures are used for controlling the simulations. It yields an average error of 1.3 °C, see table 5.4. The additional thermometry and switched-off applicators are located in between heating applicators and sample the low temperature areas in the implant. They yield an average error of approximately 1 °C, see table 5.5 and 5.6.

The deviations as discussed above for the agar-agar phantom also hamper simulations of individual patients. To make things worse the heterogeneity of the simulated temperature distribution as shown in table 5.2 is only an under-estimation of the actual heterogeneity. The simulated anatomy is assumed homogeneous, tissue heterogeneity by for instance the capsule is not taken into account and no discrete vasculature are included in the modelling. Both phenomena can yield temperature heterogeneity in MECS interstitial hyperthermia as shown by Van der Koijck et al. (1996, 1997b). Furthermore the perfusion level in the simulations is assumed homogeneous. This introduces an error as in a patient this is not the case (Kruger Hagen et al., 2001). Thus predicting the temperature at a particular location is fundamentally limited by the coarse data acquisition and even harder than in an agar-agar phantom.

The presented procedure also yields an estimated perfusion for each patient. The average level was 49 ml(100g)^{-1} min^{-1}. From literature a whole range of perfusion
levels can be found from 8 to 64 ml(100g)^−1 min^−1 (Venn et al., 1996; Torna et al., 1988; Inaba, 1992) as determined with various techniques for various categories of subjects. A comparison is difficult because the values in this paper are determined immediately after the hyperthermia treatment. The preceding hyperthermia can affect the perfusion severely (Sekins et al., 1984; Xu et al., 1998; Waterman et al., 1998; Song et al., 2001) but the effect is poorly quantified. However in this paper the estimated perfusion was assumed constant in time but was estimated at approximately the same moment for which the steady-state temperature distribution was calculated.

Errors in the reconstruction of the geometry can be reduced for example by using the SPOT system, Nucletron BV, Veenendaal, the Netherlands, which provides 3D ultrasound imaging. 3D Power Doppler with contrast agents can reveal angiographic and perfusion data and is currently investigated by Bogers et al. (1999); Floratos et al. (2001b); Kruger Hagen et al. (2001). The effective perfusion level as measured by each thermo-sensor can also be used to estimate a 3D heterogeneous perfusion map. However this needs still a gold standard for validation and calibrations, for instance for brain, MRI can provide these data (Vonken et al., 1999). Using such a heterogeneous perfusion map can improve thermal simulations as shown by Craciunescu et al. (2001). Note that the large spread in the measured effective perfusion, see table 5.2, is not reflecting perfusion heterogeneities alone. Also for the no-flow agar-agar phantom large deviations in the effective perfusion are found. The contribution of conduction to the heat removal is dependent on the position. This way the effective perfusion can vary for locations that have the same volumetric perfusion.

5.5 Conclusion

The full 3D temperature distribution during MECS interstitial hyperthermia of an individual patient can be calculated and is very heterogeneous, stressing the importance of patient specific modelling. The absolute temperature differences for all evaluated thermo-sensors together show that the calculated temperature elevations match the measurements within approximately 1 °C. The average temperature difference for all patients together is negligible, approximately 0 °C.

Maybe the temperature distribution of the entire volume is calculated with higher accuracy as found from comparing measured and simulated temperatures in this study. Part of the inaccuracy is due to errors in the geometric reconstruction of the thermo sensors. Because of this measured and simulated temperature are compared at slightly different locations. However this can not be concluded from the presented data.
In summary, the average temperature level is fairly well predicted whereas the predicted heterogeneity is too low. The latter can seriously alter the calculated thermal dose as locally under-dosed volumes determine the treatment response (Dewhirst et al., 1984).

Possible improvements are more precise reconstruction, incorporation of discrete vasculature and using a temperature dependent, heterogeneous perfusion distribution. These improvements are hampered by current data-acquisition limitations but can be integrated with the presented procedure as it is. Part of the heterogeneity comes from the characteristics of the MECS-IHT system. Further technical improvements of the system, like lowering electrode self-heating and standardizing electrode characteristics, may also result in better temperature calculations.
Chapter 6

Summary and general discussion

6.1 Summary of this thesis

The aim of this thesis was experimental validation of thermal simulations which include discrete vessels and investigating the impact of incomplete angiographic data on thermal simulations. In chapter 2 perfused isolated bovine tongues were heated with our MECS IHT system, the steady state temperature distribution was mapped by scanning 10 thermo-couples along paths perpendicular to the interstitial implant. To avoid the angiographic reconstruction, a generic vasculature has been used in the simulations. The discretely modelled vasculature showed itself on the temperature distributions in two ways. Individual vessels caused very local, sharp wells in the tracked temperature profiles. In the presence of large vessels a collective behaviour was also seen, i.e. a regional lowering of temperature. Both phenomena can be recognized in the experimentally obtained temperature distributions too. However a generic vasculature is not suitable for a one-on-one comparison.

In chapter 3 such a one-on-one comparison is performed. Temperature profiles in an isolated bovine tongue heated by 3 hot water tubes were measured at 3 controlled perfusion levels. The geometry of the tongue, the hot water tubes, thermo-couples and discrete vasculature down to 0.5 mm diameter were reconstructed by using cryo-microtome slices at 0.1 mm cubic resolution. This reconstruction of the experimental set up is used for the modelling of individual profiles with DIVA. The same procedure was applied on a no-flow agar-agar phantom.

In the latter, reconstruction was simple and reliable and DIVA showed nearly perfect correspondence between measurements and simulations. This is in fact a basic test for modelling discrete vessels since the tubes are modelled as straight discrete vessels. Obviously the heating pattern by the tubes cannot be described adequately using a continuum model. In the isolated bovine tongue, even at no
flow, the correspondence was slightly disturbed due to geometrical distortion in the reconstruction of the experimental set up. The situation with perfusion present was modelled using the reconstructed discrete vasculature and also by a heat sink model. The discrete vasculature simulations performed a little better than the heat sink simulations by predicting a local cold spot near a large vessel. The predicted temperature profiles were affected by reconstruction errors but still the results sufficed to conclude that DIVA can predict temperature profiles on an individual basis.

Often information about the vasculature will not be available. Chapter 4 addresses the problem of thermal modelling when only incomplete vessel data are provided. DIVA offers the option to operate in a hybrid mode, some vessels are modelled discretely while the missing, i.e. not discretely modelled, vessels are accounted for collectively. This chapter investigates five possible strategies to model the thermal impact of these missing vessels. The strategies all use a local or global heat sink model additional to the discrete vasculature. Various stages of missing vasculature are studied. A realistic, counter current discrete vasculature is gradually stripped, that is, the number of discretely described vessels is reduced in four steps until no discrete vessels are left. Subsequently for each strip level the steady-state temperature distribution is calculated using the five different strategies. The results are compared with the full tree simulation. As could be expected, with increasing strip level the correspondence with the full tree simulation deteriorated for all strategies. An optimal strategy, depending on the available angiographic data, was found to model the missing vessels.

In chapter 5 the temperature distribution in individual patients with prostate cancer during interstitial hyperthermia was calculated. The heating implant was reconstructed from ultrasound images, ultrasound nor post treatment MRI revealed discrete vessels. Thermal modelling was done with the conventional bio-heat model. The perfusion level was assumed homogeneous and estimated by comparing the measured and simulated thermal decay at the end of treatment for approximately 90 locations in each patient. The calculated full 3D temperature distribution is matched with post-treatment MR facilitating cumulative volume histograms of delineated volumes, for instance the prostate. The entire procedure was also performed on a no-flow agar-agar phantom.

It was shown that the calculated temperature distribution during MECS interstitial hyperthermia of an individual patient is very heterogeneous. The results are validated by individually comparing measured and simulated temperatures. This is done for the thermometry integrated with the heating applicators and for additional thermometry. The calculated temperature elevations match the measurements within approximately 1 °C. The overall average temperature level is fairly well predicted whereas the predicted heterogeneity is too low. The latter
can seriously alter the calculated thermal dose as locally under-dosed volumes determine the treatment response (Dewhirst et al., 1984).

In conclusion, DIVA has been validated experimentally. The accuracy of temperature predictions in clinical situations is restricted by coarse data acquisition.

6.2 General discussion

The 3D temperature distribution during interstitial hyperthermia is defined by the combined action of the power deposition and the existing heat removal. For calculation of the temperature distribution both factors need to be accounted for. In this thesis the power deposition was applied by either hot water tubes or by MECS IHT applicators. The heat transfer has been modelled using DIVA. Correct reconstruction has been shown to be crucial for experimentally validating DIVA. The problem is that with increasing complexity of the treatment setting the reconstruction becomes more difficult and less accurate.

In case of a rectangular homogeneous agar-agar phantom the reconstruction is relatively straightforward, see chapter 3. Also the power deposition can be modelled easily if the heating is applied by hot water tubes. Hot water tubes simply imply a thermal boundary condition and all heat transfer can be modelled by conduction alone. Actually this yields a basic test for experimental verification of DIVA because the hot water tubes are modelled as straight vessels. DIVA showed nearly perfect correspondence with the measurements, see chapter 3. The use of MECS IHT applicators for heating complicates calculation of the temperature distribution, the resulting temperature predictions are slightly deteriorated, see chapter 5. The deterioration can be explained by errors in the measured electrode temperatures. The electrode temperatures are required in the iterative simulations to calculate the power deposition. They are determined 15 seconds after power-off to avoid the effect of self-heating. However the exact electrode temperature is hard to define, the 2 or 3 temperature samples per electrode are assumed to yield a representative average electrode temperature. The assumption is reasonably valid as introducing the procedure to calculate the power deposition deteriorates the results only slightly.

In an isolated bovine tongue the modelling of heat transfer is further complicated by the introduction of blood flow. For experimental validation of DIVA the discrete vessels have to be reconstructed. The advantage of an isolated bovine tongue is that reconstruction of the heating implant and a large part of the discrete vasculature can be done by extensive, destructive, data acquisition techniques. Even with these techniques the results at no flow are not as good as in a no-flow agar-agar phantom. As can be expected, reconstruction of an irregular bovine tongue yields
larger errors than for a rectangular agar-agar phantom. Still the case of a perfused isolated bovine tongue enabled experimental validating of DIVA.

In actual patients the repertoire of data acquisition techniques is confined. Most problems were expected in reconstructing the patient specific vasculature. It was anticipated that not all thermally significant vessels would be retrieved and various strategies to compensate for these missing vessels were investigated. However from MRI and ultrasound imaging no individual vessels at all could be found when the prostates were reconstructed. Therefore the conventional bio-heat model was used. The use of the heat sink model with the reconstructed patient specific heating implant, electrode temperatures and perfusion level is the most patient specific planning as currently feasible. It allows a fairly well prediction of the overall average temperature level, the heterogeneity present is fully due to the heating implant. Preferably also the discrete vasculature and a heterogeneous perfusion map are included in the thermal simulations. A first approximation to describe the perfusion heterogeneity can be the use of a generic prostate. The generic perfusion distribution can be used as a relative perfusion map which is scaled with the estimated average perfusion level for each individual patient.

Angiographic reconstruction of the prostate can be improved using power Doppler. Recent developments in power Doppler angiography shows vascular densities rather than individual vessels (Bojers et al., 1999). The density might be correlated with the perfusion distribution. In combination with contrast agents some discrete vasculature can be revealed (Kruger Hagen et al., 2001). Power Doppler can relatively easy be fitted in the interstitial hyperthermia implantation procedure, as this is already done under ultrasound guidance (Van Vulpen et al., 2001).

The use of MRI can improve the reconstruction, and thus the temperature predictions. MRI can visualize the anatomy and can also supply angiographic data registered with the anatomy. Furthermore it can provided quantitative perfusion data (Vonken et al., 1999). MRI was used for reconstruction of glioblastoma patients treated with interstitial hyperthermia (Raaymakers et al., 2000c). These patients kept their catheter implant for approximately a week and underwent MRI with the implant in situ. This facilitated easy and accurate reconstruction of the catheter tracks. Vessels down to 0.6 mm diameter could be detected (Börjesson and Stöcker, 1997) but no discrete vessels in the tumour volume were found, only in the surrounding tissue. However there must have been vasculature present in the tumour as perfusion values up to 55 ml/(100g) •min •¹ were measured both with MR (Vonken et al., 1999) and with the thermal wash-out technique presented in chapter 5. It has to be noted that the perfusion values found from both modalities could not be matched quantitatively. This can partly be explained by the fact the thermal wash-out determines the perfusion immediately after hyperthermia, whereas MRI was applied under normo-thermic conditions. Furthermore MRI
yielded only 2D data whereas the wash-out technique yielded an average perfusion over the 3D target volume. The simulations from these patients were not used for experimental validation because there was no additional thermometry present.

Even with improved angiographic reconstruction not all thermally significant vessels are likely to be found. Chapter 4 presents 5 strategies to model the missing vessels collectively. All strategies are based on a heat-sink approach. The compensation strategies can be improved by also including an enhanced thermal conductivity. Chen and Holmes (1980); Weimbaum and Jiji (1985) argue that an increase of the thermal conductivity is necessary to model the missing vasculature adequately. In chapter 4 it is shown that an increase of the scalar thermal conductivity improves the temperature predictions. The ultimate challenge is to determine the increment of the tensorial thermal conductivity prognostically for various gradations of incomplete vasculature. Thermal simulations in generic situations, similar to chapter 4, can be used to investigate this relation. Insight in the thermal conductivity behaviour of missing vasculature can further improve thermal modelling in clinical applications.

Modelling perfusion is complicated by the fact that perfusion is severely affected by hyperthermia (Sekins et al., 1984; Xu et al., 1998; Waterman et al., 1998; Song et al., 2001). From a technical point of view a temperature dependent perfusion can simply be built into DIVA, as is done for the bio-heat model by Lang et al. (1999). However, the required physiologic relation between perfusion and temperature is only poorly quantified. It seems more feasible to measure the perfusion at the same moment for which the temperature distribution is calculated, for instance by using the thermal wash-out data as done in chapter 5. This method can be improved by using the estimated effective perfusion of individual thermo-sensors to assess a 3D perfusion distribution. To do this reliably, the local heat transfer around individual thermo-sensors should be realistically modelled. This urges inclusion of discrete vasculature in the simulations otherwise the temperature heterogeneity is under-estimated and the effective perfusion is judged incorrectly.

There are other (physiologic) reactions on temperature elevations which theoretically can be built into DIVA. For instance to model tissue coagulation, a threshold temperature above which tissue characteristics change can be incorporated. Again, this further complicates data-acquisition as then also this threshold temperature should be determined for the various tissue types. Incorporation of this phenomenon is of interest for modelling ablation treatments of prostates (Diederich et al., 2000; Sokka and Hynynen, 2000; Floratos et al., 2001a), breasts (Hynynen et al., 2001) or liver meta-stases (Cioni et al., 2001; Livraghi et al., 2001). Another phenomenon that affects the local heat transfer is re-distribution of the blood pool. A re-distribution of the blood pool, also known as the steal effect, will alter the local perfusion. It can be induced by changes in the temperature of the surroundings
without changes in the local temperature. This can only be modelled adequately by including the entire body and the interaction with its surroundings. Given the problems of quantifying local physiologic reactions the description of whole body physiology is quite a challenge. Although prognostic knowledge about temperature dependent physiology is lacking, the impact of for instance a perfusion change or the induction of coagulated tissue can be studied with the DIVA as it is. This way the need of including such phenomena in thermal simulations can be investigated.

6.3 Prospects of thermal modelling

Progress of hyperthermia depends on understanding of the relation between the tumour control probability (TCP) and the thermal dose. The TCP defines the percentage of tumour cell kill by for instance hyperthermia. To determine the TCP the biological effect of a thermal dose on tumour tissue has to be known. For high temperature applications, for instance ablation of prostate tissue, this relation is trivial, ablation causes direct cell kill. For conventional hyperthermia applications this relation is not trivial and not known for clinical situations.

Thermal simulations can be used to determine the contribution of hyperthermia to the TCP in such clinical situations. From clinical follow-up the treatment response, i.e. TCP, can be measured. The applied thermal dose can not be measured due to limited thermometry, but can be supplied by thermal simulations. By combining these, a relation between thermal dose and TCP can be deduced. For instance the correlation between thermally under-dosed areas and the location of tumour re-growth can be investigated. Although the thermal dose calculations will not be flawless, this is the way to determine the impact of hyperthermia on the TCP. This knowledge is mandatory for optimization of hyperthermia technology and treatment strategies.

In regional hyperthermia, treatment optimization often consists of SAR optimization (Paulsen et al., 1999; Kroese et al., 2001). The power in the tumour volume is maximized while minimizing the treatment limiting SAR hot-spots. Recent developments allow accurate high resolution SAR computations (Van de Kamer et al., 2001a,b). However the significance of SAR hot spots can only be assessed after thermal simulations. Therefore several investigators included thermal simulations in the treatment optimization procedure, Wust et al. (1996); Das et al. (1999) used the bio-heat model, Seebass et al. (2001) used a bio-heat model in which the largest vessels (diameter larger than 0.8 cm diameter) were assigned a very high perfusion value. This way the vessel wall was kept at 37 °C but convective heat transfer by the blood was not modelled. Lang et al. (1999) presented an improved bio-heat model for regional hyperthermia treatment planning, the model can take into account a temperature dependent perfusion distribution. The problem in using this
model is finding the correct relation between perfusion and temperature. Discrete vessel simulations that take into account the convective heat transfer can be used to improve the temperature simulations in regional hyperthermia (Craciunescu et al., 2001). Which vessels are thermally significant and need to be accounted for individually depends on the heated site. In regional hyperthermia the heated volume has a typical length of 30 cm (De Leeuw et al., 1990; Van de Kamer et al., 2001a) against 5 cm for interstitial hyperthermia (chapter 5). Larger vessels such as the aorta and the iliacal vessels are certainly significant with equilibration lengths many times the typical length of the heated volume (Chen and Holmes, 1980; Crezee and Lagendijk, 1992). Vessels of 1 mm diameter have equilibration lengths of the same order of magnitude as the heated volume (Chen and Holmes, 1980; Crezee and Lagendijk, 1992) and will therefore also be thermally significant. The significance of the smaller vessels for thermal simulations depend on their suppling vessel. If supplied directly by large vessels, as is the case in for instance the kidney, no pre-heating of the blood is present besides a potential systemic temperature rise. Then also the smallest vessels will be thermally significant as they will cause temperature heterogeneity similar to what happens during interstitial hyperthermia. This requires extensive angiographic data acquisition for regional hyperthermia treatment planning.

Another complication in regional hyperthermia thermal modelling will be the systemic temperature elevation (Feldmann et al., 1993; Van Es et al., 1995). To predict this elevation correctly the impact of a loco-regional power deposition on the systemic temperature rise has to be incorporated. This requires physiologic data and inclusion of the entire body, its surroundings and their interaction in the model. Fortunately a more pragmatic solution is available by simulating only the treated volume and its direct surroundings and adding the systemic temperature rise up to the simulated temperature distribution. This only requires the measured systemic temperature rise, which should already be monitored for quality assurance purposes (Lagendijk et al., 1998), and the power input at the moment the temperature distribution has to be calculated.

In regional hyperthermia the perfusion level during steady-state can be estimated after the power input is determined from first pulse or thermal decay methods and by assuming a homogeneous temperature distribution at the location of measurement (Roemer et al., 1985; Lagendijk et al., 1988). Another way to estimate the perfusion is the use of the thermal decay from invasive thermometry in combination with thermal modelling as done for interstitial hyperthermia in chapter 5. In regional hyperthermia fewer and less sharp local temperature gradients are expected than in interstitial hyperthermia as the power deposition will be more homogeneous. This makes the effective perfusion as experienced by a thermo-sensor less sensitive for variations in its position, the impact of defects in reconstructing the thermo-sensor location will be decreased. The first method is easier and faster than
the second method where iterative thermal simulations are required. However the first method assumes a homogeneous temperature distribution and although the heterogeneity is less than for interstitial hyperthermia, the assumption is not fully valid. The latter method does take into account the contribution of conduction due to temperature heterogeneities and can be used to refine the estimations from the first method.

6.3.1 Non hyperthermia applications

The use of DIVA is not restricted to the hyperthermia field, also other applications can benefit from thermal simulations that include discrete vasculature. For instance the field of hypothermia, the application of cooling. Heat transfer in cooled volumes obeys the same physics as heat transfer in heated volumes. A nice example is given by Van Leeuwen et al. (2000a) where the temperature distribution in a neonatal head is modelled using DIVA. The head was cooled with a ice-cap in order to lower the risk of brain damage for neonatals. Another facet of hypothermia is cryo-surgery where tissue is frozen in order to apply direct cell kill. For evaluation of these treatments, phase change, more specific the freezing of tissue, has to be built into the model. Then DIVA can be used to calculate the extent of the frozen volume.

Also safety issues concerning possible local over-heating of the human can be investigated. An example is calculation of the change in brain temperature due to a mobile phone by DIVA (Van Leeuwen et al., 1999). This was done to investigate the possible over-heating of the brain, which was shown not to occur. Similarly possible over-heating of for example the eye due to mobile phone base stations or from looking into open fires or barbecues can be investigated. Another temperature related safety issue is patient heating in a MR scanner due the RF coils. Hand et al. (2000) presented a study in which the bio-heat model is used to calculate the temperature change in the leg.

Another application of heat in vivo is heat induced drug release (Kong and Dewhirst, 1999), here the heat itself is not therapeutic. A drug is administered systematically. The non-toxic drug releases a toxic compound when heated above a certain threshold. By localized heating high concentrations of the therapeutic agent can be administered without causing a systemic over-dosis. Thermal modelling can be used to determine which heating technique is suitable to yield the required temperature distribution. This technique is not yet applied in the clinic (Kong and Dewhirst, 1999), the thermo-sensitive liposomes need to be optimized. Another problem with this therapy is administering localized heating (Corry et al., 1988; Emami et al., 1996). For sites accessible for catheter implantation our MECS HIT system should be capable of supplying an adequate temperature distribution.
6.3. Prospects of thermal modelling

The easiest way to apply DIVA in the above mentioned applications is by using generic simulations. The impact of vasculature on freezing or on possible overheating of the eye can be investigated in artificial but realistically vascularized volumes. Van Leeuwen et al. (1998) presented an algorithm to generate detailed, realistic, counter-current vessel networks for thermal simulations with DIVA. Various cooling or heating procedures can be compared without the need and the errors of patient specific reconstruction. The gained insight in heating or cooling characteristics can be used to optimize the technology. Patient, or subject, specific thermal simulations require extensive data of the anatomy, angiography and power deposition on an individual basis as described in chapter 3 and 5. Then the model predictions will suffer from the same defects and shortcomings in the reconstruction and the modelling as hyperthermia applications do.
Chapter 7

Samenvatting

Hyperthermie als kankertherapie heeft het doel maligne weefsel te verwarmen tot een temperatuur van 40-44 ºC. Hyperthermie wordt toegepast in combinatie met radiotherapie om de tumorcontrole en de overleving van patiënten te verhogen. De effectiviteit van dergelijke behandeling is onlangs aangetoond voor tumoren in het bekkengebied in een studie door Van der Zee et al. (2000). Een groot probleem bij de kwantitatieve bewaking van hyperthermie is het kwantificeren van een behandeling. Zowel de duur als de grootte van de temperatuurverhoging dragen bij aan de dosis van een hyperthermiebehandeling. Om deze dosis te bepalen is in de eerste plaats een beschrijving van de volledige driedimensionale temperatuurverdeling nodig. Het meten met behulp van invasieve thermosensoren levert over het algemeen een niet-representatieve bemonstering van de temperatuurverdeling. Daarom zijn er modellen ontwikkeld om de driedimensionale temperatuurverdeling te berekenen. Deze modellen dienen rekeningen te houden met de convec-tieve warmtetransport door bloed. Immers, koud bloed dat een verwarmd gebied binnenstroomt zal warmte opnemen, dus lokaal koelen en eventueel verderop de opgenomen warmte weer afgeven. Er zijn verschillende modellen ontwikkeld om de effecten van bloed op de temperatuurverdeling te berekenen, idealiter worden alle bloedvaten individueel meegenomen in de berekening. Het doel van dit proefschrift is de experimentele validatie van temperatuurberekeningen waarbij de thermische impact van individuele bloedvaten is gemodelleerd. Daarnaast is onderzocht hoe de berekende temperatuurverdeling beïnvloed wordt wanneer niet alle bloedvaten individueel meegenomen worden omdat het in de klinische praktijk eigenlijk nooit mogelijk is alle bloedvaten in het verwarmde gebied te reconstrueren.

Een eerste poging tot validatie is beschreven in hoofdstuk 2. Vrij-geprepareerde rundertongen werden gebruikt als een realistisch patiënt fantoom. De twee arteriëlen van een tong waren aangesloten op een pomp, op deze manier was het mogelijk een gecontroleerde doorbloeding te bewerkstelligen. Verwarming vond plaats door middel van een tiental elektrodes die in plastic catheters in de tong geplaatst waren.
Vervolgens werd voor verschillende weefseldoorbloeding (ook wel perfusie) niveaus de temperatuurverdeling bemosten door langs 10 parallelle profielen in één vlak, thermostoppen te trekken in stapjes van 1 mm. De gemeten temperatuurprofielen werden vergeleken met de resultaten van generieke simulaties. Dat wil zeggen, in de simulaties werd een bloedvatnetwerk gebruikt dat gebaseerd was op informatie uit anatomische handboeken in plaats van de gereconstrueerde bloedvaten van een specifieke tong. Zowel de metingen als de simulaties lieten duidelijk het effect van de bloedvaten op de uiteindelijke temperatuurverdeling zien. Echter een één-op-één vergelijking voor een specifieke tong was niet mogelijk, daarvoor was het thermisch effect van het generieke bloedvatnetwerk en dat van de individuele tongen te verschillend.

In hoofdstuk 3 is wel een één-op-één vergelijking tussen meting en simulatie gedaan. Ook hier is een rundertong gebruikt waarvan de arteriën aangesloten zijn op een pomp. De interstitiële verwarming werd gedaan met behulp van warm-waterbuisjes, deze leveren een zeer stabiele en eenvoudig te modelleren warmteafgifte. Wederom werd de temperatuurverdeling voor verschillende perfusie-niveaus bemosten zoals hierboven beschreven. Nu echter werd in de berekeningen de zeer gedetailleerde reconstructie van de tong gebruikt in plaats van een generieke beschrijving. Zowel de vorm van de tong, het arterieel bloedvatnetwerk, de exacte positie van de 10 gemeten profielen en de positie van de warm-waterbuisjes werd bepaald. Op deze manier was het mogelijk om een één-op-één vergelijking tussen meting en simulatie te doen.

Om de bovenstaande procedure te testen is deze eerst toegepast op een rechthoekig blok weefsel-equivalent materiaal in plaats van een rundertong. Het reconstrueren van deze opstelling is veel simpeler en daarmee nauwkeuriger, echter er is geen doorbloeding wat het een niet erg realistisch fantoom maakt. Het is een soort basis test voor temperatuurberekeningen met individuele bloedvaten aangezien de warm-waterbuisjes als bloedvaten gemodelleerd worden. Deze test levert nagenoeg perfecte overeenkomst tussen de metingen en simulaties. Ook voor de rundertong zonder doorbloeding is een vergelijking gedaan tussen de gemeten en berekende temperatuurprofielen. De overeenkomst was iets minder goed dan voor het blok weefsel-equivalent materiaal, dit terwijl in beide gevallen geen doorbloeding aanwezig was. De reden is dat er kleine fouten optreden in de reconstructie van de tong, tussen het moment van meten en het moment van reconstructie kunnen kleine verschillen ontstaan in de positie van de warm-waterbuisjes en van de thermostoppen.

De tong met doorbloeding is op 2 manieren gemodelleerd. Eerst is het effect van de perfusie benaderd door een continuum model, het veel gebruikte heat-sink model van Pennes (1948). In dit model is het thermisch effect van bloed versimpeld door alle bloedvaten tezamen met één enkele parameter, namelijk de weefsendoorbloeding te beschrijven. Daarnaast is een berekening gedaan waarin alle gerecon-
struierde bloedvaten individueel meegenomen zijn, hiervoor is het DIVA model van Kotte et al. (1996, 1999) gebruikt. Beide modellen leveren globaal de correcte temperatuurverdeling. Echter met een continuüm model zoals het heat-sink model is het onmogelijk een lokale thermische onderdosering in de buurt van een bloedvat correct te voorspellen. De berekeningen met individuele bloedvaten deden dit wel. Hoewel de berekende temperatuurprofielen leden onder de genoemde fouten in de reconstructie waren de resultaten toch voldoende goed voor een één-op-eén experimentele validatie van DIVA.

In de praktijk zal vaak geen of slechts beperkte informatie van het bloedvatennetwerk voorhanden zijn. In hoofdstuk 4 is onderzocht hoe deze incomplete data het best gebruikt kunnen worden in thermische simulaties. DIVA biedt de mogelijkheid om bloedvaten individueel mee te nemen in een berekening, in combinatie met een continuüm model. De toevloeding van een continuüm model maakt het mogelijk het thermisch effect van de niet te reconstrueren bloedvaten toch te verdisconteren. In dit hoofdstuk zijn vijf verschillende methodes onderzocht, al deze methodes zijn gebaseerd op het eerder genoemde heat-sink model.

Als gouden standaard is een berekening genomen van de temperatuurverdeling in een stuk weefsel met een kunstmatig gegenereerd, realistisch, gedetailleerd bloedvatennetwerk en een eenvoudige warmtedepositie. Het effect van de verschillende methodes is onderzocht door ze toe te passen op een steeds beperkter wordend bloedvatennetwerk. De volledige boom, die voor de gouden standaard gebruikt werd, is in stapjes ontdaan van de kleinste bloedvaten. Dit is gedaan in vier stappen totdat uiteindelijk helemaal geen individuele bloedvaten beschikbaar waren (zie figuur 4.3). Zoals te verwachten was, werd het verschil van de berekende temperatuurverdeling met die van het volledige bloedvatennetwerk steeds groter naarmate het gebruikte bloedvatennetwerk meer en meer beperkt werd. De optimale methode om de niet te reconstrueren bloedvaten te verdisconteren hangt af van het soort bloedvat-informatie dat voorhanden is. Zo hangt de keus bijvoorbeeld af van het feit of de verdeling van de doorbloeding bekend is, zoals in principe te meten is met Magnetische Resonantie (MRI) technieken.

In hoofdstuk 5 is de temperatuurverdeling gedurende een interstitiële hyperthermiebehandeling van patiënten met prostaatkanker berekend en gevalideerd. Door de interstitiële wijze van verwarming zal er sprake zijn van een heterogene temperatuurverdeling met pieken rondom de verwarmingselektrodes. Met behulp van ultragehuid echografie werd de positie van de verwarmingselektrodes voor iedere patiënt bepaald. Deze techniek levert geen informatie over de doorbloeding, ook MRI na afloop van de behandeling geeft geen informatie over de doorbloeding of het aanwezige bloedvatennetwerk. Alle voorgaande bevindingen over berekeningen met individuele bloedvaten ten spijt werd alleen het heat-sink model gebruikt voor de berekening. Voor de simulaties werd een homogene doorbloeding van de pros-
Samenvatting

taat aangenomen. Deze doorbloeding werd per patiënt geschat door gebruikmaking van de temperatuurdaling aan het eind van de behandeling. De temperatuurdaling is immers gecorreleerd met de doorbloeding, hoe hoger de perfusie, hoe sneller de temperatuur van het verwarmde gebied zal dalen tot de lichaamstemperatuur. Per patiënt is op ongeveer 90 plaatsen in de prostaat de temperatuurdaling gemeten, deze is vergeleken met de temperatuurdaling uit de berekeningen, het perfusie niveau in de berekeningen werd vervolgens zo ingesteld dat de gemeten en berekende temperatuurdaling vergelijkbaar waren. Zodoende is het gemiddelde doorbloedingsniveau geschat.

De validatie is gedaan door het vergelijken van gemeten en berekendetemperaturen op overeenkomstige posities. Dit is gedaan voor de ongeveer 90 temperatuursensoren binnenin de verwarmingselektrodes, welke gebruikt worden voor de aansturing van het verwarmingssysteem, en voor temperatuursensoren die speciaal voor de validatie in de prostaat geplaatst zijn. De berekende temperatuurverhogingen komen met een marge van ongeveer 1 °C overeen met de gemeten temperatuurverhogingen. De berekening laat een heterogene verdeling zien ten gevolge van de geplekte temperatuur rondom de verwarmingselektrodes, echter de berekende temperatuurheterogeniteit is nog te laag aangezien er geen individuele bloedvaten meegenomen zijn. Deze laatste zijn wel degelijk belangrijk omdat juist lokale thermische onderdossen in de uiteindelijke effectiviteit van een hyperthermiebehandeling bepalen.

Samengevat, temperatuurberekeningen met DIVA waarbij individuele vaten meegenomen worden zijn experimenteel gevalideerd. De nauwkeurigheid van berekeningen voor klinische toepassingen wordt beperkt door de tekortkomingen in de data-acquisitie.
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“Mijn” eerste officiële post-doc was Nick van Wieringen, onze werkzaamheden zijn eigenlijk alleen op het basketbalveld geïntegreerd, maar dat was dan wel een echte hypertherme bezigheid. Alexis Kotte heeft me veel tijd bespaar met emacs commandos, linux truks en niet te vergeten een heuse sport-versie van zijn beroemde heatran, verder was het altijd prettig werkoverleg te voeren in de kadettilac op weg naar Beverwijk. Voor het betere netwerk, passes en set-ups is Ric Exterkate al jaren mijn steun en toeverlaat. Gerard van Leeuwen steunde me in de overtuiting dat niet-generiche programmaatjes best handig zijn, het mooiste voorbeeld vind ik xmgrBlackWhite.pl. John van der Koijk streefde naar generieke oplossingen, ik voelde me haast schuldig als ik weer eens (met mijn ad hoc mentaliteit) zijn code
aan het hacken was, wat dankzij de generieke opzet meestal een fluitje van een cent was. Jacob de Bree was op programmeergebied letterlijk mijn grote voorbeeld. De laatste paar maanden was Gijsbert Bol mijn kamergenoot en snelgroeiende computerheld, hij had de basTool1 klaar voor ik goed en wel de specificaties overdacht had, de basTool2 en basTool3 volgden snel.

Naast de interstitiële hyperthermie zijn er nog de grote jongens, waarmee tweewekelijks werkoverleg gevoerd werd. Hoewel Jeroen van Kamer net als ik A.I.O. was verdiende hij toch meer, naar voorbeeld van zijn verburen heeft hij mij van het verschil bijgevoerd. Hugo Kroese staat mij als parafras bij tijdens de verdeling, mocht ik ooit mee gaan doen aan Robot Wars dan hoop ik dat hij dat weer doet. Astrid de Leeuw is naast het grote werk tegenwoordig ook bij de interstitiële behandelingen betrokken, daarbij vervult ze tot nu toe de rol van secretaresse (meterve). Met Jaap Moolbroek heb ik helemaal in het begin nog een computer met legendarisch smerrig toetsenbord gedeeld.

Marco van Vulpen was de verantwoordelijk arts voor de interstitiële hyperthermie van prostaatpatiënten, de draft versies van zijn klinische artikel volgden elkaar sneller op dan ik kon lezen, onze besprekingen waren altijd in promptu, chaotisch en leuk. Een andere arts die genoemd moet worden in verband met interstitiële hyperthermie is Maarten Hulshof uit het AMC, hij coördineerde de studie voor glioblastoompatiënten. Aan de hand van deze patiënten groep is eigenlijk al het gereedschap ontwikkeld waarmee de prostaatbehandelingen geëvalueerd zijn. Ik heb uiteindelijk gekozen voor een artikel over de prostaatpatiënten, ik ben erg blij dat Maarten de berekenende temperaturen voor de glioblastoompatiënten in zijn artikel gaat gebruiken zodat alle moeite niet voor niets geweest is. Het scannen van deze patiënten was niet mogelijk geweest zonder de medewerking van Chris Bakker en de radioloog Ramos. Evert-Jan Vonken en Thijs van Osdi hebben prachtige perfusie-plaatjes gemaakt, helaas waren die niet te rijmen met mijn bevindingen van de perfusie, ze namen me dat gelukkig niet persoonlijk kwalijk. Een ander minder succesvol experiment betrof het afbeelden van kleine bloedvaten in een rontong, Chris Bakker en Romhild Hoogeveen hebben al hun kunstjes met MRI scanners aangewend maar het resultaat viel tegen, het waren wel leuke avondses-sies. Robert Stöcker en Pontus Börjesson hebben bepaald hoe klein die kleinste zichtbare vaatjes nu eigenlijk waren, als student hadden ze meer dan gemiddelde levenservaring en het was een waar plezier ze te begeleiden.

Wat met de MRI scanner niet lukte, lukte wel met behulp van Prof. Hillen van de afdeling Functionele Anatomie en zijn medewerkers. Met name Wilem van Wolfe-ren heeft talloze malen tongen geprepaveerd, hoewel dat precies werk is was hij altijd in staat tot uitgebreide discussies over uiteenlopende, maar meestal educatieve, onderwerpen. Ook Jan Doorn, Jan de Groot en Simon Plomp ben ik dankbaar voor hun hulp bij de gedetailleerde reconstructies van de tongen.
I also like to thank Oana Craciunescu from Duke University, NC, USA, our collaboration yielded the first calculations on real patient data with discrete vasculature in it. She really amazed me with the speed at which she included Cube6, perfDef and local sink sets in her daily vocabulary.

Als laatste wil ik Bram van Asselen bedanken die, met gevaar voor eigen lijf en leden, heeft geholpen de fysieke herinnering aan tong-experimenten te verwijderen.
Curriculum Vitae

Stellingen

behorend bij het proefschrift
‘Thermal modelling for hyperthermia’

1. Een homogene temperatuurverdeling in het doelgebied tijdens een interstitiële hyperthermiebehandeling is niet haalbaar,
2. De nauwkeurigheid van *in vivo* temperatuurberekeningen wordt beperkt door het tekortschieten van de huidige beeldvormende technieken,
3. Het is zinloos generieke simulaties te gebruiken voor een één-op-één experimentele validatie van thermische modellen voor hyperthermie (hoofdstuk 2 van dit proefschrift), generieke fantomen zijn juist wel bruikbaar (hoofdstuk 3 van dit proefschrift).
5. De bijdrage van een systemische temperatuurverhoging aan de gemiddelde temperatuur van een interstieel verwarmd gebied is veel meer dan een simpele optelling.
6. Het reconstrueren van het debiet in individuele bloedvaten aan de hand van een gemeten perfusieverdeling is eerder haalbaar dan het reconstrueren van de perfusieverdeling aan de hand van te meten stroomsnelheden in individuele bloedvaten.
7. Nadat MRI voor de dagelijkse en on line positieverificatie in de radiotherapie is geïntroduceerd zal deze gecombineerd worden met een rotatiebestraling met een continu geconformeerde collimator,
8. Overzichtsartikelen zijn erg handig voor de lezer maar duperen de originele auteurs.
9. Wetenschappelijke tijdschriften moeten genoegen nemen met een licentie voor het commercieel gebruik van een artikel en het copyright aan de auteur laten.
10. In het kader van Europese integratie moet Nederland zijn glastuinbouw opgeven.
11. Ter stimulering van bewuste vleesconsumptie moet een bezoek aan een slacht­­huis als programmaonderdeel in het middelbaar onderwijs opgenomen worden.
12. Elke studie naar de effectiviteit van een homeopathisch middel is placebo ge­­controleerd.