Radio Frequency Thermal Treatment of Liver Tumours

-Influence of Blood Perfusion and Large Vessels

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Abstract

Radio frequency ablation (RFA) is a commonly used minimally invasive method of treating liver cancer tumours which utilises RF current for heating tumour tissue up to a lethal temperature. RF current is generated by a power generator and applied to the tumour by an electrode which is inserted into the tumour either during percutaneous or open surgery.

RFA is a method that has great advantages compared to traditional surgical resection of tumours due to minimal invasiveness, it can be used for a greater number of patients and enables repeated treatments. Even though there are many advantages coupled to RFA there are still some problems and difficulties associated with the method. One of these problems is the cooling effect from large vessel blood flow within the liver, the so called heat sink effect.

The aim of this master thesis work has been to develop a theoretical finite element model of RFA within Comsol Multiphysics software. This theoretical model has been used to simulate blood perfusion effects on resulting ablation volume. The effects from different large vessel blood flow parameters has been investigated, these parameters are: blood flow velocity, blood vessel diameter and distance between blood vessel and RF electrode. A factorial design has been utilised to setup parameter levels for the different simulations. A linear- and a second degree regression model has been calculated based on simulation results. The parameter with largest impact on simulative ablation volume and the interaction effects between the parameters were determined from the regression model coefficients. In addition to this has two simulations been performed, modelling perfused- and unperfused liver tissue, in order to investigate the effects resulting from microvascular perfusion.

The result shows that the parameter with largest impact on simulative ablation volume are the distance, it was also shown that there are a small interactional effects between diameter and distance, where a small distance increases the effect from a varying diameter. Modelled microvascular perfusion was shown to give a decrease in simulative ablation volume. A shortage of this master thesis work is the lack of experimental verification of the developed model.
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1 Introduction

This master thesis is a part of a larger research project carried out within the departments of Biomedical engineering (IMT), Management and engineering (IEI), both at Linköping’s university, and the surgical clinic at the University hospital, Linköping. The overall aim is to develop a patient specific simulator for Radiofrequency ablation (RFA) of liver tumours. The objective of the simulator is to optimize the RFA, accounting for the specific anatomy of every patient and tumour.

To achieve the aim, two main goals have to be fulfilled and thereafter integrated into one. The first goal is to develop a method for automatically segmentating the liver geometry from CT/MR data and to classify important structures such as tumours and large vessels. The second goal is to develop a heat transfer model for liver tissue that take cooling effects from blood perfusion including large vessels into account. This master thesis work is the first step forward achieving the second of these goals.

RFA treatment utilizes RF current to generate heat within liver tumours. The power of applied RF current is regulated so that tumour tissue reaches a temperature were cell death occurs. RFA has become a common method of choice since it offers a less invasive alternative compared to traditional surgical resection. In spite of the positive sides of RFA compared to traditional surgery there still are problems and difficulties related to the method that has to be investigated. One common problem when treating tumours in the highly perfused liver is the so called heat sink effect which is the result of blood flowing in sufficiently large vessels inside the treated area. Flowing blood enables heat to be transported within and out of the treated area. In homogenous tissue without large vessel blood flow the RFA treatment results in an ablation volume which is nearly spherical. This symmetrical shape might be altered when performing RFA close to larger blood vessels leading to an insufficient heating of tumour tissue close to the vessel.

1.1 Aim and problem

The aim of this master thesis is to theoretically model RFA in liver tissue and to give a better understanding of how ablation volume is affected by liver perfusion, especially from large vessels. The impact on ablation volume in the developed RFA model of three different large vessel blood flow parameters is investigated. The three parameters chosen for investigation are the distance between RFA electrode and vessel wall, velocity of the flowing blood and diameter of the vessel. These parameters are chosen since they all are considered to have impact on the heat sink effect. Which one of these three parameters has the greatest impact and are there any interactional effects between the parameters? A comparison between two different levels of microvascular perfusion will be investigated in order to enlighten the effects on ablation volume. A 3D Finite element model (FEM) will be built and solved in Comsol Multiphysics (CM) software. Different methods of modelling perfusion and heat sink effect will be compared in the development of the model. A full $2^3$ factorial design will be used for setup of the parameter level combinations used in the simulations.
1.2 Background

RFA is a widely accepted method for treating liver cancer tumours, as it offers a less invasive alternative compared to traditional surgical resection and is the method of choice for a large number of patients. Surgical resection involves a major surgical operation that isn’t suitable for all patients due to multifocal disease, tumour size and location of tumour in relation to key vessels [1]. RFA can be used for a greater number of patients and it has a greater potential in repeated treatment of tumour recurrences or new metastases compared to traditional surgical resection [2]. Although RFA is commonly used for many patients, surgical resection still is the method with highest long-term survival rates [3]. This fact might partially be a result of the high recurrence rates related to RFA which is a result of surviving tumour cells close to large vessels due to the heat sink effect [4].

The liver is an organ with very high blood perfusion; blood is supplied from two large vessels, the hepatic artery and the portal vein. Large veins branching from the portal vein can be found throughout the whole liver. Numerous both experimental and numerical modelling and simulation studies have been performed to investigate the nature of RFA in liver tissue, several of these studying the effects of blood perfusion. The numerical approach is a common and popular method of studying RFA. It is both fast and inexpensive compared to experimental studies; this makes it a powerful tool both for investigating difficulties related to RFA and for the tryouts of new approaches for improving the method. Some of these published works (both experimental and numerical) have been studied and act as a starting point for the current work, a summary of these studies will be presented below.

Different aspects of blood perfusion has been the target of several studies, it has been shown that both large vessel blood flow and microvascular perfusion affects the results of RFA treatment in the liver. The impact of large vessel diameter on the heat sink effect in liver tissue has been investigated by Lu et al. by in vivo RFA experiments on pigs. They measured the volume of ablated tissue both by postablation CT imaging and histopathological methods. A possible heat sink effect was defined by a layer of thermally unaffected tissue in the vicinity of the vessel. What they could show was a consistent heat sink effect for vessel diameters larger than 4 mm. Their study also showed a transition zone for diameters in-between 2 and 4 mm, were the heat sink effect was seen in some of the cases [5].

Experimental studies performed by Chang et al. investigated the relation between the heat sink effect and vascular flow. They compared RFA treated volume in pig livers for the following flow cases; normal flow, vascular inflow occlusion, vascular outflow occlusion and total occlusion. Their result showed that a complete vascular occlusion results in a significantly higher treated volume [6]. Kolios et al. showed by a numerical simulation study that microvascular perfusion of tissue plays a significant role in altering the amount of heat transferred to large vessels, where an increased perfusion decreases the cooling effect from large vessels [7].

Different approaches of decreasing blood perfusion in order to decrease the heat sink effect have been investigated; vascular occlusion due to clamping and pharmacological decrease of blood flow has both been shown to give an increase in ablation volume. According to Gilliam’s will a decreasing blood flow decrease the cooling effects of perfusion but also increase the risk of vessel injuries due to ablation [8].
An important issue for understanding and modelling RFA and the heat sink effect is knowledge about the physical properties of liver tissue. Exact values for physical properties are difficult to determine due to the complex non-homogenous structure of tissue and the often temperature dependent physical properties. Physical properties that affect RFA are electrical conductivity, thermal conductivity, density and specific heat capacity. Duck has in his work *Physical properties of tissue* contributed with a large collection of physical properties [9].

An investigation of RFA by modelling and simulation involves simplifying the modelled tissue with a continuum model which overlooks microscopic structures. Theoretical modelling involves creating a geometry resembling the current RFA case, the geometry is assigned with proper differential equations describing the coupled time-dependent thermal-electrical problem. Simulations are performed within the developed model to receive the numerical solution of the modelled case.

Tungjitkusolmun et al. [1], Chang [10] and Cosman et al. [11] has published numerical studies which all utilizes Pennes bio-heat equation (which take liver perfusion into account) for modelling heat transfer within liver tissue. Welp et al. investigated the effect from a large vessel on a fixed distance from the RF electrode within unperfused liver tissue. Their investigation was performed with a numerical FEM model, modelling a 12 minutes RFA treatment with a constant applied power of 25 W. They did more specifically investigate how ablation volume changed for different blood flow rates. Furthermore did Welp assume a thermally and hydrodynamically fully developed laminar blood flow with a constant vessel wall temperature. According to this were a constant heat transfer coefficient used to describe convective heat flux from the liver tissue to the large blood vessel. They could show that variations in blood flow rate didn’t significantly affect the size of the ablated volume for their chosen vessel diameters and flow rates [3].
2 Radio Frequency Ablation

RFA treatment is a common minimally invasive surgical technique for treatment of e.g. cardiac arrhythmias and cancer tumours in liver, kidney, lung, bone, prostate and breast [12]. In this work focus is solely on the treatment of liver cancers including: primary liver cancer (hepatocellular carcinoma) in cirrhotic patients, metastatic colorectal cancer, for patients not suitable for surgical resection, and symptomatic neuroendocrine tumours [13].

2.1 Equipment

Several different RFA equipments are available on the market today, and they differ both in power output and electrode design. Common for all equipments are a power generator delivering a RF current which flows between an electrode and a grounding pad. A selection of different existing electrode designs are: electrode shaped as an umbrella with several tines, which can be expanded inside the tumour in order to increase treated volume, micropore perfused electrodes where saline solution can be infused into the treated area in order to increase electrical conductivity of the tissue as well as cooling the electrode, multiple electrodes in a straight parallel setup and single straight, internally cooled electrodes. Maximum power output for different power generators lies between 60 and 250 W. The most common ways of controlling power output is by measuring tissue impedance or electrode temperature.

The equipment modelled in this work is the Cool-tip™ RFA system (Valleylab, Boulder, CO, USA) (see Figure 1). The power generator of this equipment delivers a RF-current at 480 kHz and a maximum power output of 250 W [12]. The Cool-tip RF-electrode has a needle-like internally cooled geometry. The cooling fluid is pumped into the electrode by an external pump. The electrode has an outer diameter of 1.5 mm and an active part that constitutes of the electrode’s outer 2 cm (see Figure 2). The remaining electrode length is covered with a thin electrically insulating cover. In order to examine the inner geometry of the electrode, one electrode was split along its axial direction. Photos from this examination can be seen below (see Figure 3). The outer electrode pipe surrounds a hollow inner space with a diameter of 1.2 mm which ends ~2.25 mm from the electrode tip. Positioned inside this cavity is a thin inner pipe which makes up the inlet of the cooling fluid. Outlet of the cooling fluid is made up by the cavity in between inner and outer pipe.

2.2 Procedure

The aim of RFA treatment is to heat tumour tissue to lethal cell temperature, while at the same time minimizing surrounding tissue damage. Tissue coagulation resulting in cell death occurs when temperature exceeds 50 °C [14]. In RFA this is accomplished by the delivery of RF current into the tumour of interest, which results in so called resistive heating. RF current is generated by the power generator and applied by the RF electrode which is inserted into the tumour. Current flows from the electrode to a grounding pad placed on the patient’s skin.
RFA treatment of liver tumours can be performed either during open surgery or by an image guided percutaneous operation. Percutaneous RFA treatment is performed under image guidance where ultrasound and CT are the most widely used modalities. Ultrasound and CT can be used during RFA to approximate the ablated zone. Agents used in combination with CT or Ultrasound can be an aid for visualization and approximation of the ablation volume. Treatment time and power level has to be adjusted in order to reach necessary ablation volume for each individual case but also in order to minimize the risks of damaging healthy liver tissue. To achieve a successful treatment of large tumours overlapping of several ablation volumes might be necessary [13]. Cooling of the electrode makes it possible to deploy more power into the whole tissue compared to a non-cooled electrode since it prevents tissue from charring close to the electrode [3].

![Image of RFA equipment and electrodes](image)

**Figure 1** Cool-tip™ RF generator (upper left), cooling fluid pump (right) and three cool-tip single straight electrodes [15].
Figure 2 Cool-tip electrode with the inner pipe placed aside at its axial position. The inner pipe is the inlet for the cooling fluid while the inner space between inner and outer pipe act as cooling fluid outlet.

Figure 3 Cross section of the outer electrode pipe and electrode tip.
3 Principles of RF tissue heating

RF tissue heating is based on the principle of inducing an ion current into tissue by the application of a RF field between an electrode and a grounding pad. The friction that ion movement in the tissue causes results in so-called joule heating (resistive heating).

Biological tissues can be treated as quasi-static in the RF range (300kHz – 1Mhz), this means that they can be described as purely resistive, neglecting the small part of impedance that dielectric permittivity constitutes. Electric field, $E$ [V m$^{-1}$], applied to a tissue can be described by Laplace’s equation:

$$\nabla \cdot (\sigma \nabla V) = -\nabla \cdot \sigma \mathbf{E} = 0 \quad \text{eq. 3.1}$$

Where $V$ [V] is the potential, $\sigma$ [S m$^{-1}$] is the electrical conductivity and $\nabla = \left( \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right)^T$ is the gradient operator. Electrical conductivity of a medium is the reciprocal of the medium’s resistivity i.e. conductivity is a value that describes how easily an electric current flow within the medium. Solved ions stands for the electrical current flow in biological tissues when an external electric field is applied, therefore is the electrical conductivity dependent on ion concentration. In addition is the electrical conductivity dependent on temperature of the tissue and frequency of the applied electric field [10]. Exact behaviour of the electrical conductivity dependency of temperature in tissues is unknown. For temperature ranges around normal body temperature, electrical conductivity is measured to increase linearly with a temperature coefficient [9]. When tissue temperature reaches 100°C, boiling and vaporization will occur which will lead to a decrease in electrical conductivity due to insulating effects of gas bubbles and a raise of tissue impedance [16].

An applied electric field in the RF range induces a current density $J$ [A m$^{-2}$] in the tissue. The size of $J$ in any point of the tissue is given by ohm’s law:

$$\mathbf{J} = -\sigma \nabla V = \sigma \mathbf{E} \quad \text{eq. 3.2}$$

To model current sources equation 3.2 can be extended with two additional terms, one describing externally generated current density $\mathbf{J}^e$ and one describing internal current sources, $Q_i$, which results in equation 3.3 [17].

$$-\nabla \cdot (\sigma \nabla V - \mathbf{J}^e) = Q_i \quad \text{eq. 3.3}$$

Joule’s law describes resistive heating, $Q$ [W m$^{-3}$], in every point of the tissue:

$$Q = \frac{J^2}{\sigma} = \mathbf{JE} \quad \text{eq. 3.4}$$

When describing the electric field for a region with Laplace’s equation, appropriate boundary conditions has to be assigned to inner and outer boundaries of the region. These boundary
conditions can be of two types; either fixed value condition, where the potential is defined, or fixed flow condition, where the current $J$ over the boundary is defined.

Spherically spreading current density, $J$, will result in a decrease inversely proportional to the radial distance from the electrode to the power of two, which results in a decreasing joule heating, inversely proportional to the radial distance to the power of four, according to equation 3.4 [18].
4 Principles of heat transfer

Heat transfer is the transfer of energy resulting from differences in temperature. Heat is transferred by three different mechanisms: conduction, convection and radiation. Radiation will not be described in this chapter since it can be ignored in this work [18].

4.1 Conduction

Conduction is described by *Fourier’s law*, equation 4.1, which couples heat flux, \( q \) [W m\(^{-2}\)], within a medium, to the temperature gradient.

\[
q = -k \frac{\partial T}{\partial x}
\]

Where \( x \) is the direction of temperature gradient and \( k \) [W m\(^{-1}\) K\(^{-1}\)] is the thermal conductivity of the medium. Microscopic structures of tissue will not be modelled in this work; instead will a thermal conductivity which reflects the *continuum* of the tissue be used i.e. average macroscopic effect of tissue structure. *Fourier’s law* (eq. 4.1) together with the First Law of Thermodynamics gives the *General Heat conduction equation* (eq. 4.2) which describes both spatial and time dependent changes of the temperature field in a heat transferring medium.

\[
\rho C \frac{\partial T}{\partial t} + \nabla \cdot (-k \nabla T) = Q
\]

Where \( \rho \) [kg m\(^{-3}\)] is the medium’s density, \( C \) [J kg\(^{-1}\) K\(^{-1}\)] is the medium’s heat capacity and \( Q \) [W m\(^{-3}\)] is either a heat source or sink [19].

To solve the general heat conduction equation (eq 4.2) for a region, appropriate boundary conditions has to be assigned to the outer and inner boundaries of the region. In this work two different boundary conditions are used, the Dirichlet condition which assigns a fixed temperature to a boundary and the Neumann boundary condition in which a fixed heat flux condition is assigned to a boundary.

4.2 Convection

Heat transfer by convection can be divided into two groups: natural convection and forced convection. Common for both types of convection are heat transfer between a solid medium and a fluid or in-between fluids. Natural convection is convective heat transfer where the fluid motion only results from inner temperature differences i.e. density differences. Forced convection is dominated by external pressure forces and will be in this work’s focus, since it constitutes the main part of heat transfer between tissue and flowing blood. Convective heat transfer within a flowing medium can be described by the addition of a convective term to the general heat conduction equation (eq 4.2).
\[ \rho C \frac{\partial T}{\partial t} + \nabla \cdot (-k \nabla T + \rho C \mathbf{u} T) = Q \]  

**eq. 4.3**

Where \( \mathbf{u} \) [m s\(^{-1}\)] denotes the velocity field vector of the fluid flow. Equation 4.3 is valid under the approximation of incompressible fluid [19].

Convective heat flux from a surface of a medium to a fluid can be described by *Newton’s law of cooling*.

\[ q_s = h(T_s - T_\infty) \]  

**eq. 4.4**

Equation 4.4 describes the proportionality between surface heat flux and temperature difference, between surface and fluid bulk temperature (fluid temperature far away from the surface). \( h \) [W m\(^{-2}\) K\(^{-1}\)] is the *heat transfer coefficient*, which not only is a material property; it depends both on geometry and motion of the fluid flow and on the fluid properties.

The *Nusselt* number is the dimensionless description of convective heat transfer from a surface for a certain fluid, flow condition and geometry. It couples several dimensionless numbers and local geometry to the heat transfer coefficient \( h \). The Nusselt number is under certain approximations only dependent on the *Reynolds number, Re*, (dimensionless number describing flow condition), the *Prandtl number, Pr*, (dimensionless number describing fluid properties) and local geometry. For example, a definition of the Nusselt number for a circular pipe with diameter \( D \) containing a flowing fluid with thermal conductivity \( k \) is [20]:

\[ Nu = \frac{hD}{k} \]  

**eq. 4.5**

The heat transfer coefficient, \( h \), can be determined analytically or empirically. Analytical determination of \( h \) can be done by combining Fourier’s law of heat conduction (eq. 4.1) with Newton’s law of surface cooling (eq. 4.4) this requires that the fluid temperature distribution is known [21]. Empirical determination of \( h \) is done by measuring \( q_s, T_s \) and \( T_\infty \) and correlating the results to the dimensionless numbers [20].

### 4.3 Fluid flow, velocity- and temperature profiles

The nature of fluid flow is one factor influencing convective heat transfer. Flow can be classified into two different types: *turbulent* and *laminar*. The characteristics of turbulent flow are random fluctuations in velocity, whereas the situation when these fluctuations don’t occur is laminar flow [21]. Flow condition is described by the Reynolds number, Re. Equation 4.6 couples Re, for flow in pipes, with the mean velocity, \( \bar{u} \), pipe diameter, \( D \), and kinematic viscosity, \( \nu \).

\[ \text{Re} = \frac{\bar{u}D}{\nu} \]  

**eq. 4.6**

To distinguish between turbulent and laminar flow a transitional Reynolds number, Re\(_t\), can be calculated. Flow in pipes has a transitional Reynolds number around 2300, where values over the transitional value is classified as turbulent flow and lower values is classified as
laminar flow [21]. The velocity profile for laminar flow in pipes will develop from the entrance until it reaches a fully developed state. The velocity in a circular pipe where the laminar flow profile is fully developed increases with a parabolic function (eq. 4.7) from zero at the pipe wall to a maximum value, $V_c$, at the centreline (see Figure 4).

$$V(r) = V_c \left( 1 - \left( \frac{r}{R} \right)^2 \right) \quad \text{eq. 4.7}$$

In the same manner is a thermal profile of varying temperature developed in a flowing fluid when the fluid’s temperature differs from the pipe wall temperature. A fully developed thermal profile will be reached in the two cases of either constant surface heat flux or constant surface temperature. A fully developed thermal profile doesn’t imply that the temperature of the fluid doesn’t change; it only implies that the relation in between the temperatures at the pipe wall and the pipe’s centreline are constant [20].

4.4 Convection from large vessels

When RFA is performed in the close vicinity of a large vessel, convective heat transfer will occur between heated tissue and flowing blood. The blood flow will transport heat out of the heated region and thereby result in a cooling effect which is described as the heat sink effect. A correlation to calculate the Nusselt number and thereby the heat transfer coefficient for pipes with fully developed laminar flow and constant surface temperature is equation 4.8, where, $D$, is the diameter and $L$ is the pipe length [4].

$$Nu = 4 + 0.48624 \ln \left( \frac{Re \cdot Pr \cdot D}{18 \cdot L} \right) \quad \text{eq. 4.8}$$

4.5 Bio-heat transfer

Blood perfusion is a factor which has a great impact on heat transfer in tissue, convective heat transfer occurs between flowing blood and solid tissue for blood vessels of all sizes. Total convective transfer between tissue and blood is affected by vessel size, flow velocities and number of vessels in the volume of interest. These factors together and their non-steady behaviour have lead to big difficulties describing and modelling thermal behaviour of blood perfused tissue. Several approaches of describing heat transfer in blood perfused tissue has been presented, this work presents and compares two of these approaches; Pennes bio heat equation and the Effective conductivity equation ($k_{eff}$-equation) [22].
Pennes Bio-heat equation (eq. 4.9) is a modification of the general heat conduction equation (eq. 4.2) with two additional terms, one describing the effect of blood perfusion and the other describing the effect of generated metabolic heat.

$$\rho C \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - m_b C_b (T - T_b) + Q_m$$  

\text{eq. 4.9}

Where $m_b, C_b$, and $T_b$ is mass flow rate, specific heat and temperature of the blood respectively [9]. $Q_m$ describes heat generated from metabolic processes in tissues, this term is negligible compared to the RF power deposition [14]. Pennes bio-heat equation assumes that all heat exchange between tissue and blood occurs in the capillary bed; this implies that the capillary blood flow act as a heat sink [18].
5 Finite Element Method

Physical phenomena are often described by differential equations which only for very simple cases can be solved by classical analytical methods. The finite element method (FEM) offers a method to approximate the solution for arbitrary differential equations. This chapter will give an overview and basic introduction to the FEM concept.

5.1 Meshing – Division of the interesting region

The principal concept of FEM is to divide a region (1D, 2D or 3D), over which a certain physical behaviour and differential equation is valid, into smaller elements. A region divided into elements is called mesh. The mesh element for a 1D-region constitutes of linear segments where the end points constitute the nodes of the mesh. For 2D, triangular shaped mesh elements can be used where the three corners constitute the nodal points (see Figure 5). For 3D, tetrahedrons can be used as mesh elements where the four corner points constitute the nodes [23]. Both for 2D and 3D cases other geometries than the above mentioned can be used as mesh elements, such as rectangular- and box like geometries. The number of elements that the region of interest is divided into will partly steer the accuracy of the solution, where more mesh elements offers a more accurate approximation. An increase in the number of mesh elements also increases the size of the equation system that has to be solved.

![Mesh element and Nodal point](image)

**Figure 5** 2D triangular mesh.

5.2 Approximating functions

Instead of approximating a solution for the whole region, which could involve unknown variables with a highly non-linear behaviour, the solution is approximated for every single mesh element. This approximation is done by assigning an approximating function to each mesh element. For 1D the approximation function describes the unknown variable’s value over the linear element, between the two end points, where for 2D it approximates the
unknown variable’s value for the surface between the corner points of the element. Sought nodal variable values make up the unknowns of the problem and the number of nodes is the degree of freedom (d.o.f.). An approximating function can be linear or of higher order, where higher order functions add extra d.o.f. For simplicity reasons are the rest of this chapter describing a one dimensional stationary heat transfer case within a bar of length $L$ and with the temperature $T$, as unknown variable.

Next step is to rewrite the approximating functions assigned to each and every element to shape functions, $N_i$, which describes the temperature, $T$, over the whole region.

$$T = Na$$  \hspace{1cm} \text{eq. 5.1}

Where $N = [N_1 \ldots N_k]$ is a matrix containing all shape functions $N_i$ and $a = [T_1 \ldots T_k]$ is a vector containing the $k$ nodes’ unknown temperatures. Shape function $N_i$ equals one for nodal point $i$ and zero for all other nodes. Spatial differentiation of $T$, which is used in the FEM formulation, can be described in terms of shape functions as:

$$\frac{dT}{dx} = Ba \quad \text{where} \quad B = \frac{dN}{dx}$$  \hspace{1cm} \text{eq. 5.2}

### 5.3 Strong- and weak formulation

Time independent heat transfer within the one dimensional bar is described by the following reformulation of the general heat conduction equation (eq. 4.2):

$$\frac{d}{dx} \left( k \frac{dT}{dx} \right) + Q = 0; \quad 0 \leq x \leq L$$  \hspace{1cm} \text{eq. 5.3}

Solving equation 5.3 requires two boundary conditions, one for each end of the bar i.e. $x = 0$ & $x = L$. These two boundary conditions can be assigned with either a Dirichlet- or a Neuman boundary condition (see chapter 4). The so called strong form of the heat equation is constituted by equation 5.3 together with the following boundary conditions.

$$k \frac{dT}{dx} = h; \quad x = 0$$  \hspace{1cm} \text{eq. 5.4}

$$T = g; \quad x = L$$

When considering the strong form of the heat equation it can be seen that temperature is twice differentiated. From this follows that an approximation function which can be at least twice differentated has to be chosen. The so called weak formulation of the heat equation is utilized to avoid this requirement. The weak equation is formulated with the general heat conduction equation (eq. 4.2) as a starting point. The whole equation are thereafter multiplied with an arbitrary weight function, $v$, and integrated over the bar’s length i.e. from $x = 0$ to $x = L$. By rewriting the resulting equation and by utilizing the integration by parts rule, equation 5.5 is formulated as:
\[
\int_0^L \frac{dv}{dx} k \frac{dT}{dx} dx = \left[ vk \frac{dT}{dx} \right]_0^L + \int_0^L vq dx \tag{eq. 5.5}
\]

Equation 5.5 together with appropriate boundary conditions makes up the weak formulation of one dimensional heat flow and is the base for the FEM formulation.

5.4 FEM formulation

The weight function, \( v \), in the weak formulation of the heat equation can be chosen according to the Galerkin method which give: \( v = Ne \), where \( e \) is an arbitrary matrix, \( v = v^T \) and \( v = e^T N^T \).

This gives:
\[
\frac{dv}{dx} = c^T B^T \tag{eq. 5.6}
\]

where
\[
B^T = \frac{dN^T}{dx} \tag{eq. 5.7}
\]

The approximating functions (eq. 5.6) and (eq. 5.7) are inserted into the weak formulation of heat equation (eq. 5.5) to form equation 5.8, where \( c^T \) is independent of \( x \) and therefore placed outside the brackets.

\[
c^T \left[ \left( \int_0^L B^T k B dx \right) a + \left[ N^T k \frac{dT}{dx} \right]_0^L - \int_0^L N^T Q dx \right] = 0 \tag{eq. 5.8}
\]

Equation 5.8’s second term, \( \frac{dT}{dx} \), is not substituted with \( Ba \) (eq. 5.2) since this term must be specified with the appropriate boundary conditions. Since \( c^T \) is an arbitrary matrix, equation 5.8 can be rewritten as:

\[
\left( \int_0^L B^T k B dx \right) a = \left[ N^T k \frac{dT}{dx} \right]_0^L + \int_0^L N^T Q dx \tag{eq. 5.9}
\]

Equation 5.9 makes up the equation system which is solved in order to get the approximate FEM solution of the heat transfer problem for the bar. The equation system can be reformulated into a more compact formulation:

\[
Ka = f \tag{eq. 5.10}
\]

where
\[
K = \left( \int_0^L B^T k B dx \right) \tag{eq. 5.11}
\]

and
\[
f = f_h + f_l = \left[ N^T k \frac{dT}{dx} \right]_0^L + \int_0^L N^T Q dx \tag{eq. 5.12}
\]
\( \mathbf{K} \) is the system’s \textit{stiffness matrix}, \( \mathbf{f}_b \) and \( \mathbf{f}_l \) are the system’s \textit{boundary vector} and \textit{load vector} respectively. The principles used here for the one dimensional case is general and can be applied to cases with higher dimensional order [23].
6 RF liver ablation model

6.1 Software

Modelling and simulations in this work were carried out in the FEM software Comsol Multiphysics 3.3 (CM). CM constitutes of several predefined application modes that cover different physical phenomena such as heat, electricity and flow. These different application modes contain predefined model setups with appropriate differential equations. The development of a model in CM consists of choosing appropriate application modes for the problem, creating a geometry and assigning proper physical properties and boundary conditions to the application modes. In CM it’s possible to couple several different application modes to one model a so called multiphysics model.

6.2 Geometry

A 3D geometry was created in CM’s own CAD environment using a Cartesian coordinate system (see Figure 6). A cylinder with height 0.1 m and radius 0.05 m was drawn to model liver tissue; a cylinder modelling the blood vessel was embedded into the liver cylinder. The orientation of the blood vessel cylinder is along the x-axis with the vessel axis parallel to the liver cylinder axis. The diameter and exact location of this vessel is varied due to simulation case. Modelled electrode geometry (see Figure 7) constitutes only of the outer part of the real electrode geometry (see chapter 2, figure 2 & 3); this simplification is due to the complexity of modelling the electrode’s thin structures. The electrode geometry is embedded into the liver cylinder so that the tip of the electrode is situated in the centre of the cylinder i.e. the origin of the Cartesian coordinate system. An efficient way of decreasing the number of d.o.f. for a FEM model is to use symmetries in the model’s geometry. In the current geometry the xz-plane acts as a symmetry plane which is used to cut the geometry in half. The geometry is divided into so called subdomains (see Table 1) which are defined regions of a medium, subdomains are separated by boundaries (see Table 2).

| Table 1 Subdomains with labels referring to figure 6 and figure 7. |
|-----------------|-----------------|
| Subdomains     | Description     |
| 1               | Liver tissue    |
| 2               | Blood           |
| 3               | Electrode       |

| Table 2 Boundaries with labels referring to figure 6 and figure 7. |
|-----------------|-----------------|-----------------|
| Boundaries      | Description     | Boundaries      | Description     |
| 4               | Outer boundary  | 9               | Active electrode surface |
| 5               | Symmetry plane  | 10              | Insulated electrode surface |
| 6               | Blood vessel inlet | 11           | Electrode cooling channel |
| 7               | Blood vessel outlet |
| 8               | Blood vessel wall |
Figure 6 Model geometry with notations referring to table 1 & 2.
6.3 Modelling electric field and current

Modelling electric field and current in tissue (subdomains 1 and 2) is done with equation 3.3 where internal and external current sources, $Q_j$ and $J^e$, both are set to zero.

\[ - \nabla \cdot (\sigma \nabla V - J^e) = Q_j \]

\[ \text{eq } 3.3 \]

The modelled electrode (subdomain 3) has a high conductivity, which leads to low resistive heating compared to liver tissue; this makes it possible to inactivate the electrode subdomain in the electrical field and current model [24]. The anisotropy of $\sigma$ for radio frequencies is not significant and the value is therefore considered to be isotropic [16]. Electrical conductivity for the modelled blood is set to a static value since changes in blood temperature is assumed to be low. Electrical conductivity for liver tissue is set to increase linearly with temperatures up to 100°C and to drop rapidly for temperatures over 100°C. This behaviour is set to resemble the decrease in electrical conductivity due to vaporisation, described in chapter 3.

The expression for the used temperature dependent electrical conductivity is:

\[ \sigma_{T, Liver} = \left( \sigma_{Liver} \left( 1 + \alpha_{Liver} (T - T_{body}) \right) \right) \cdot \text{sgn} \]

\[ \text{eq. } 6.1 \]
Where $\text{sigm}$ denotes a sigmoid logistic function decreasing rapidly from one to zero when temperature exceeds 100°C (see appendix 1). $\alpha_{\text{liver}}$ [°C⁻¹] is the temperature coefficient which describes the linear increase of equation 6.1. Equation 6.1 is used for modelling the electrical conductivity for liver tissue in all simulation cases except the two cases comparing microvascular perfusion, for which the $\text{sigm}$ function is removed due to complexity reasons. Table 4 shows values of the used conductivities and temperature coefficients.

To resemble the rapid decrease in potential with increasing radial distance from the electrode, the model’s initial potential distribution is set to decrease exponentially with increased radial distance.

Power is supplied to the model by applying a potential to the modelled electrode’s active surface (boundary 9) according to a fixed value boundary condition (eq 6.2).

$$V = V_0 \quad \text{eq. 6.2}$$

The electrode potential value is adapted so that the total amount of developed power (by resistive heating) in the modelled liver tissue stays at a constant predefined value of 12.5 W. Modelled electrode potential is coupled to resistive heating by CM’s integrated coupling function (see appendix 2). The remainder of the electrode surface (boundary 10) and the planes of symmetry (boundary 5) are both set to be electrically insulated i.e. boundary current flux is set to zero according to equation 6.3 where $\mathbf{n}$ denotes the normal vector of the boundary surface [25].

$$\mathbf{n} \cdot \mathbf{J} = 0 \quad \text{eq. 6.3}$$

Outer boundary (boundary 4) of the model together with the inlet and outlet of the blood vessel (boundaries 6 and 7) are set to a fixed value condition (eq. 6.2) which sets the potential to zero. The validity of this boundary condition can be strengthened by the fact that the potential decreases very fast with increasing distance from the electrode. The boundary which makes up the modelled vessel wall (boundary 8) is set to a current flux continuity condition according to equation 6.4.

$$\mathbf{n}_1 \cdot \mathbf{J}_1 = \mathbf{n}_2 \cdot \mathbf{J}_2 \quad \text{eq. 6.4}$$

### 6.4 Modelling heat transfer

According to Wren [22] are the fundamental differences between the two bio-heat transfer equations described in chapter 4, the following: “Pennes’ equation extracts heat from tissue, but the heat flux within the model is unaffected. For the $k_{\text{eff}}$ equation, the heat flux within the model is increased, but the heat remains in the modelled area until it has been conducted to the model boundary.” The aim of this work is to study heat sink effect from large vessels in the liver. The $k_{\text{eff}}$ equation assumes that thermal equilibration occurs in the higher levels of vessel size and is therefore the model of choice for modelling heat transfer in tissue and electrode (subdomains 1,2, and 3) in this work. The $k_{\text{eff}}$ equation (eq. 6.5) is formulated by inserting an effective thermal conductivity into equation 4.3. The velocity vector $\mathbf{u}$ is set to zero for all subdomains except for the blood vessel (subdomain 2).
\[ \rho C \frac{\partial T}{\partial t} + \nabla \cdot \left( -k_{\text{eff}} \nabla T + \rho C u T \right) = Q \]  

\text{eq. 6.5}

Effective thermal conductivity, \( k_{\text{eff}} \), is measured by Bhattacharya and Mahajan by in vivo measurements on pig liver [26]. One simulation case is performed with a tabulated thermal conductivity value for non-perfused liver tissue; this simulation is done in order to compare microvascular effect on heat transfer. Table 6 shows values of the used thermal properties, all thermal properties are set to be isotropic and non temperature dependent.

Initial temperatures for the entire model are set to body temperature, 37 °C.

The thin electrical insulating cover (boundary 10) of the non active part of the electrode is modelled according to equation 6.6. Equation 6.6 is a predefined function which enables heat transfer over thin structures without the need of meshing its geometry. \( d_c \, [\text{m}] \) is the thickness of the modelled structure.

\[ -n(-k_1 \nabla T_1) - n(-k_2 \nabla T_2) = 0 - d_c \rho c \frac{\partial T}{\partial t} - \nabla_i (-d_c k_c \nabla_i T) \]  

\text{eq. 6.6}

The outer boundary (boundary 4) besides the planes of symmetry and the outlet of blood vessel are modelled with a Dirichlet condition (eq. 6.7) of 37 °C.

\[ T = T_0 \]  

\text{eq. 6.7}

Outer electrode boundary (boundaries 9) is modelled as continuity with the Neumann condition according to equation 6.8, describing pure conductive heat transfer.

\[ -n_1(-k_1 \nabla T_1) - n_2(-k_2 \nabla T_2) = 0 \]  

\text{eq. 6.8}

The symmetry plane is modelled with a Neumann condition of zero heat flux according to equation 6.9.

\[ -n(-k \nabla T) = 0 \]  

\text{eq. 6.9}

The cooling channel of the electrode is inactivated in the heat transfer application mode. This is done in order to decrease the d.o.f. of the model.

Two alternatives of modelling the cooling inner boundary (boundary 11) of the electrode were compared before deciding which one to implement. The first alternative investigated was applying a Neumann condition and the second condition was applying a Dirichlet condition. Modelling according to the Neumann condition utilizes equation 4.4 for the definition of a convective heat flux over the cooling channel surface. To model convective heat flux in an appropriate manner it requires an approximate value of the convective heat transfer coefficient, \( h \). This approximation can be done according to the different approaches described in chapter 4. The inner flow geometry of the electrode contains a 180 degree turn which will induce turbulence; this fact leads to difficulties approximating the heat transfer coefficient with the described analytical approaches. Experimental measurements would have been necessary to give an appropriate approximation of the heat transfer coefficient value.
Modelling according to the Dirichlet condition is based on the assumption that convective cooling by fluid flow is high enough to ensure a constant surface temperature all over the cooling channel surface. Measurements done by Welp et al., in ex vivo experiments on non-perfused liver with a cool-tip 2 mm electrode, showed that the temperature at the electrode tip were nearly constant at 10 °C for the whole 12 min ablation time [3]. This result strengthens the assumption of a constant inner surface temperature and act as the base for choosing to model electrode cooling with a Dirichlet condition of \( T = 10 \degree C \) (eq. 6.7).

Two alternative methods of modelling large blood vessel and resulting convective heat transfer were examined and compared before one of the methods was chosen for this model. The first investigated alternative was to model the vessel wall as a heat sink, with a Neumann condition and an approximated heat transfer coefficient, \( h \), according to equation 4.8. When modelling with the Neumann condition, blood within the vessel is not part of the heat transfer model. The second investigated alternative is to model the actual flow and heat transfer of the blood within the vessel. When using this method the velocity field vector, \( \mathbf{u} \), in the general heat equation (eq. 4.3) is assigned with the value from the laminar velocity profile according to equation 4.7.

The comparison were carried out in a pre-model conceptually similar to the real simulation model but with a thermal conductivity representing the unperfused case. Simulations were performed for two different velocities and two different vessel diameters, while the other simulating parameters were held constant, resulting in eight different simulation cases. An evaluation of the simulation results was done by calculating a total heat flux in a point close to the vessel wall and by comparing the appearances of the simulation results.

Comparison between the total heat fluxes showed that the difference in between the two cases were small (<15%). This result implies that the choice between the two methods doesn’t influence the heat flux in the chosen point in any large manner. The appearance of heat distribution in the simulation results from the flow case shows that heat spreads along the direction of the vessel. This behaviour is not seen in the simulation results from the heat transfer coefficient case. The difference in heat distribution appearance between the two choices of model shows that heating of the blood can’t be neglected. Due to this reason is the model with flowing blood considered more valid and chosen to be used in this work.

The vessel boundary (boundary 8) is set to a Neumann continuity condition according to equation 6.11 describing both conductive and convective heat flux.

\[
- \mathbf{n}_1 \left( - k_1 \nabla T_1 + \rho_1 C_{p1} \mathbf{u}_1 T_1 \right) - \mathbf{n}_2 \left( - k_2 \nabla T_2 + \rho_2 C_{p2} \mathbf{u}_2 T_2 \right) = 0 \quad \text{eq. 6.11}
\]

The velocity of blood flow is varied between the simulation cases. The boundary that makes up the outlet of the blood vessel (boundary 7) is assumed to be dominated by convective heat flux and is therefore modelled with a Neumann condition describing pure convective flux. The boundary that makes up the inlet of the blood vessel (boundary 6) is modelled with a Dirichlet condition of 37 °C (eq. 6.10).
6.5 Physical properties

**Table 3** Electrical conductivities of tissue

<table>
<thead>
<tr>
<th>Tissue/medium</th>
<th>Electrical conductivity, $\sigma$ [S m$^{-1}$] $37$ °C</th>
<th>Temperature coeff. [% °C$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.184 $^{(1)}$</td>
<td>0.95 $^{(2)}$</td>
</tr>
<tr>
<td>Blood</td>
<td>0.74 $^{(3)}$</td>
<td>--</td>
</tr>
</tbody>
</table>

$^{1}$ Value interpolated for 500 kHz from table 6.10, Duck [9].
$^{2}$ Values interpolated for 500 kHz (20-40°C) from table 6.18, Duck [9].
$^{3}$ Table 6.1, Duck [9].

**Table 4** Thermal properties of modelled materials

<table>
<thead>
<tr>
<th>Tissue/medium</th>
<th>$k$ [W m$^{-1}$ K$^{-1}$] $37$ °C</th>
<th>$C_p$ [J kg$^{-1}$ K$^{-1}$]</th>
<th>$\rho$ [kg m$^{-3}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, perfused</td>
<td>2.18 $^{(1)}$</td>
<td>3600 $^{(2)}$</td>
<td>1050 $^{(2)}$</td>
</tr>
<tr>
<td>Liver, unperfused $^{(2)}$</td>
<td>0.52</td>
<td>3600</td>
<td>1050</td>
</tr>
<tr>
<td>Blood $^{(2)}$</td>
<td>0.484</td>
<td>3840</td>
<td>1060</td>
</tr>
<tr>
<td>Electrode, stainless steel $^{(3)}$</td>
<td>15</td>
<td>500</td>
<td>7900</td>
</tr>
<tr>
<td>Electrode, insulating cover $^{(3)}$</td>
<td>0.01</td>
<td>3400</td>
<td>800</td>
</tr>
</tbody>
</table>

$^{(1)}$[26], $^{(2)}$[9], $^{(3)}$[11]
7 Simulation settings

7.1 Choice of appropriate mesh

A new mesh has to be established for all simulation cases that lead to a new geometry. The meshes are created by setting CM’s free mesh parameters (see Appendix 3). To create a mesh that is sufficiently fine, for trustworthy solutions, a stepwise refinement process has to be performed. In this stepwise process the simulation results from two simulations of neighbouring grade of mesh refinement is compared. If the simulation results deviates more than a predefined threshold value, a finer mesh has to be created. When the threshold value between two simulations isn’t exceeded the solution is said to have converged and the mesh is considered to be sufficiently fine. The measure used for comparing two refinement grades of a mesh in this work is the max/min temperature and the temperature profile along a specific line through the geometry. The used threshold value is 1°C.

7.2 Simulation settings

The choice of solver is based on the complexity of the model, i.e. the numbers of d.o.f. CM has direct and iterative solvers, where the direct solvers solve the problems faster compared to the iterative solvers, but at the same time less memory efficient. In this work a direct solver is used, which is due to the time gain compared to using an iterative solver.

Simulated treatment times are 12 min. Time steps taken by the solver in between time iterations are regulated by the solver itself. Initial and maximum time step can however be specified which is done in this work. Initial time step is set to 0.5 s and maximum time step is set to 15 s. Output time interval is set to 5 s and specifies for which time-points the solver returns a solution.

Relative and absolute tolerances control the error in between each time step. The tolerance setting controls both the accuracy of the solution and the simulation time. Relative tolerance controls the relative error for large solutions while the absolute tolerance controls the absolute error for small solutions. There is no accuracy of a solution if its value is less than the absolute tolerance [28]. Relative tolerance is set to 0.01, which is the default setting and absolute tolerance is set to 1 for all solved variables. The choice of absolute tolerance was validated by comparing simulation results from different tolerance settings.
8 Trial setup

8.1 Result measure

The measure used for analysing the simulation results is the volume of tissue that exceeds 50°C, this temperature is sufficiently high for tissue damage to occur and is therefore resembling ablated tissue [1]. Calculation of the ablation volumes are done for the final 12 min simulation result (see Appendix 4 for details around volume calculations). One simulation is performed for the case with no blood vessel present in the model; the resulting ablation volume from this simulation is used as a reference volume. An adjustment of the reference volume is done for each simulation case. The adjustment means that the reference volume is corrected by subtracting the part of the reference volume that the vessel geometry of each simulation case constitutes. All calculated ablation volumes are divided by their adjusted reference volumes. The resulting ratio makes up a measure of the heat sink effect on the current ablation volume, where a ratio of one represents no effect and a low ratio represents a large heat sink effect.

8.2 Parameter levels

Blood vessel diameter, distance between RF electrode and vessel, and velocity of the flowing blood are the three parameters chosen for investigation. The investigated interval of the parameter values are presented below.

The liver’s portal vein and its blood flow are chosen to act as a model for the high levels of vessel diameter and blood flow velocity. Typical size of the liver’s portal vein is 10 mm and average blood flow velocity is 22.9 cm s⁻¹ [4]. Low level of blood velocity is chosen to resemble a total occlusion of the portal vein and is therefore set to a value close to zero. Low level of vessel diameter is set to 1 mm. Low and high level of distance are chosen according to a prediction of which magnitude of distance that will affect the heat sink.

<table>
<thead>
<tr>
<th>Level</th>
<th>Average flow velocity [cm s⁻¹]</th>
<th>Diameter [mm]</th>
<th>Distance [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (+1)</td>
<td>23</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Semi high (+0.5)</td>
<td>17.5</td>
<td>7.75</td>
<td>12</td>
</tr>
<tr>
<td>Mean (0)</td>
<td>12</td>
<td>5.5</td>
<td>9</td>
</tr>
<tr>
<td>Semi low (-0.5)</td>
<td>6.5</td>
<td>3.25</td>
<td>6</td>
</tr>
<tr>
<td>Low(-1)</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

In addition, to the investigation of the large blood vessel’s effect on heat transfer, is a comparison between two different liver tissue perfusion settings performed. This comparison is performed between a simulation for a model with an effective thermal conductivity, modelling perfused liver tissue, and a simulation for a model with a thermal conductivity modelling unperfused liver tissue.
8.3 Statistical method

The effect of the three blood flow parameters is analysed using a full $2^3$ factorial design with one replication. This experimental design is chosen for the ability to distinguish which effect that has the largest impact and if there are any interaction effects. All three parameters are varied between a high- and a low level (Table 5). A linear regression model (eq. 8.1) is calculated in Matlab according to $\mathbf{k} = (\mathbf{C}^T \mathbf{C})^{-1} \mathbf{C}^T \mathbf{y}$. Where $\mathbf{C}$ is the so called design matrix containing the parameter levels for the full $2^3$ factorial design (see Appendix 5), $\mathbf{y}$ is a vector containing the calculated ratios from the simulations and the result $\mathbf{k}$ is a vector containing estimated coefficients for the regression model.

\[
\hat{y} = \bar{y}_{\text{measured}} + k_1 x_1 + k_2 x_2 + k_{12} x_1 x_2 + k_3 x_3 + k_{13} x_1 x_3 + k_{23} x_2 x_3 + k_{123} x_1 x_2 x_3 \quad \text{eq. 8.1}
\]

Estimated response (ratio), estimated coefficients and mean value of the simulation ratios are represented by $\hat{y}$, $k_i$ and $\bar{y}$ respectively. The subscript 1-3 represents the parameters; flow, diameter and distance respectively. $x_i$ represents the parameter levels in units coded according to equation 8.2, where $P$ represents the uncoded parameter value:

\[
x_i = \frac{P - (P_{\text{high}} + P_{\text{low}})/2}{(P_{\text{low}} - P_{\text{high}})/2} \quad \text{eq. 8.2}
\]

A normal probability plot is performed for the estimated coefficients; this is done in order to distinguish which effects that have large impact on estimated ratio. Estimated parameters that lie close to zero in the normal probability plot is considered unimportant and therefore omitted in the regression model. A centre point simulation (all parameters at zero level) is carried out in order to validate the estimated linear model. The centre point simulation ratio is compared with the estimated ratio from the regression model i.e. $x_i = 0$ for $i = 1,2,3 \Rightarrow \hat{y} = \bar{y}$. A large difference between these two implies that the linear model is insufficient and that it might be necessary to add quadratic terms in order to get a better fit [27], equation 8.3 shows a quadratic regression model.

\[
\hat{y} = \bar{y}_{\text{measured}} + k_1 x_1 + k_2 x_2 + k_{12} x_1 x_2 + k_3 x_3 + k_{13} x_1 x_3 + k_{23} x_2 x_3 + k_{11} x_1^2 + k_{22} x_2^2 + k_{33} x_3^2 \quad \text{eq. 8.3}
\]

If fitting a quadratic model (eq. 8.3) is shown necessary, additional measure points (simulations) has to be added. A face-centred design will then be combined with the addition of measure points at semi high/low levels. This extended design will totally consist of $12 + 2^3 = 20$ measure points. The estimation of the quadratic regression model coefficients will be done with Matlab’s stepwise regression function, which removes non-significant coefficients stepwise until all coefficients are significant at $p = 0.05$. The input to this function is the design matrix $\mathbf{C}$, for the extended experiment design (see Appendix 5), and a vector $\mathbf{y}$ containing all simulation ratios. A root mean square error, $s$, and an adjusted $R^2$ value is calculated where the adjusted $R^2$ value represents the proportion of total variability explained by the estimated regression model [29].
9 Results

9.1 Results $2^3$ design

Table 6 below shows the result from the first $2^3$ simulations, reference simulation and centre point simulation. The calculated ablation volumes and adjusted reference volumes are presented as well as the resulting ratios.

Table 6 Parameter levels (coded units) and results from the first $2^3$ simulations, reference simulation $(1)$ and centre point simulation $(2)$. Volume is actual ablation volume of current simulation $\#$, reference volume is adjusted reference volume for each simulation $\#$ and ratio is the ratio between volume and reference volume.

<table>
<thead>
<tr>
<th>Simulation $#$</th>
<th>Flow</th>
<th>Diameter</th>
<th>Distance</th>
<th>Volume $[\text{cm}^3]$</th>
<th>Reference volume $[\text{cm}^3]$</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{(1)}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.51</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>4.2478</td>
<td>4.4947</td>
<td>0.9438</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>2.5012</td>
<td>4.4947</td>
<td>0.5565</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
<td>1</td>
<td>-1</td>
<td>1.5117</td>
<td>3.4623</td>
<td>0.4382</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>-1</td>
<td>0.8123</td>
<td>3.4623</td>
<td>0.2346</td>
</tr>
<tr>
<td>6</td>
<td>-1</td>
<td>-1</td>
<td>1</td>
<td>4.5866</td>
<td>4.5100</td>
<td>1.01670</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>4.1401</td>
<td>4.5100</td>
<td>0.9180</td>
</tr>
<tr>
<td>8</td>
<td>-1</td>
<td>1</td>
<td>1</td>
<td>4.1694</td>
<td>4.5100</td>
<td>0.9245</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3.6602</td>
<td>4.5100</td>
<td>0.8116</td>
</tr>
<tr>
<td>10$^{(2)}$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.9176</td>
<td>4.4011</td>
<td>0.6629</td>
</tr>
</tbody>
</table>

Table 7 Estimated linear regression model coefficients.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.7306</td>
</tr>
<tr>
<td>Flow</td>
<td>-0.1002</td>
</tr>
<tr>
<td>Diameter</td>
<td>-0.1282</td>
</tr>
<tr>
<td>Flow * Diameter</td>
<td>0.0213</td>
</tr>
<tr>
<td>Distance</td>
<td>0.1871</td>
</tr>
<tr>
<td>Flow * Distance</td>
<td>0.0473</td>
</tr>
<tr>
<td>Diameter * Distance</td>
<td>0.0785</td>
</tr>
<tr>
<td>Flow * Diameter * Distance</td>
<td>-0.0248</td>
</tr>
</tbody>
</table>

The estimated coefficients in Table 7 show that flow and diameter decreases the ratio whereas distance and interaction between diameter and distance increases the ratio. A normal probability plot (see Appendix 6) of all the estimated linear model coefficients except for the constant, shows that the three main effects, flow, diameter and distance as well as the interaction between diameter and distance have an estimated coefficient larger than 0.05. The rest of the estimated effects are omitted in the estimated linear regression model equation 9.1, where $X_{\text{Flow}}$, $X_{\text{Dia}}$ and $X_{\text{Dist}}$ are the coded parameter variables.
estimated ratio = 0.7306 − 0.1002 X_{Flow} − 0.1282 X_{Dia} + 0.1871 X_{Dia} + 0.0785 X_{Dia} X_{Dist} \quad \text{eq. 9.1}

\begin{align*}
\text{Figure 8} & \text{ Plot of the linear regression model varying the three parameters one at a time while the other two are fixed at their mean levels (0). a) Varying flow b) Varying diameter c) Varying distance. All parameter values at their coded levels.} \\
& \\
\text{Estimated linear regression model is plotted in Figure 8; each parameter is plotted one at a time while the other two are held at a fixed level. It can be seen that flow and diameter both have slopes which represents a decreasing ratio for increasing parameter value while the opposite are seen in the distance plot. The slopes of the lines in plot a, b and c represents the estimated coefficients in the linear regression model. The steepest slope is found in plot c representing distance.} \\
& \\
\text{The constant value, of 0.7306, in the linear regression model represents the centre point value and should be compared to the centre point simulation ratio of 0.6629. The relative large difference of 0.0677 between these two values implies that a regression fit of higher degree might approximate the result better. In order to fit a second degree regression model to the result is additional simulations performed.}
\end{align*}
9.2 Results $2^3 +$ additional simulations

Table 8 Parameter levels (coded units) and results from all simulations, Reference simulation (1), Centre point simulation (2). Volume is actual ablation volume of current simulation #, reference volume is adjusted reference volume for each simulation # and ratio is the ratio between volume and reference volume.

<table>
<thead>
<tr>
<th>Simulation #</th>
<th>Flow</th>
<th>Diameter</th>
<th>Distance</th>
<th>Volume [cm$^3$]</th>
<th>Reference volume [cm$^3$]</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.51</td>
<td>-</td>
<td>0.9438</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>4.2420</td>
<td>4.4947</td>
<td>0.9106</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>2.5012</td>
<td>4.4947</td>
<td>0.5565</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
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<td>-1</td>
<td>1.5174</td>
<td>3.4623</td>
<td>0.4382</td>
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<tr>
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<td>1</td>
<td>1</td>
<td>-1</td>
<td>0.81529</td>
<td>3.4623</td>
<td>0.2346</td>
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<td>-1</td>
<td>1</td>
<td>4.5866</td>
<td>4.5100</td>
<td>1.01670</td>
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<td>7</td>
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<td>4.5100</td>
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</tr>
<tr>
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<td>1</td>
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<td>4.5100</td>
<td>0.9245</td>
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<td>0.6629</td>
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<td>3.4831</td>
<td>4.4011</td>
<td>0.7914</td>
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<tr>
<td>12</td>
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<td>0</td>
<td>2.8223</td>
<td>4.4011</td>
<td>0.6413</td>
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<tr>
<td>13</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>3.6392</td>
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<td>0.8097</td>
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<tr>
<td>14</td>
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<td>2.5348</td>
<td>4.2847</td>
<td>0.5916</td>
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<td>0</td>
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<td>-1</td>
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<td>4.0560</td>
<td>0.3025</td>
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<td>0</td>
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<td>1</td>
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<td>4.5100</td>
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<td>0</td>
<td>2.8989</td>
<td>4.4011</td>
<td>0.6587</td>
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<td>2.7445</td>
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<td>0.6236</td>
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<td>0</td>
<td>3.0884</td>
<td>4.4330</td>
<td>0.6967</td>
</tr>
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<td>20</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>2.6708</td>
<td>4.3535</td>
<td>0.6135</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
<td>-0.5</td>
<td>2.0311</td>
<td>4.1750</td>
<td>0.4865</td>
</tr>
<tr>
<td>22 (2)</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>3.4138</td>
<td>4.5100</td>
<td>0.7569</td>
</tr>
</tbody>
</table>

The ratios in Table 8 are used in Matlab’s stepwise regression function which results in an estimated quadratic regression model, equation 9.2, with $s = 0.057$, $R_{adj}^2 = 92.4$ and 95% confidence intervals for all coefficients.

estimated ratio $= 0.639(\pm 0.05) - 0.0926(\pm 0.038)X_{Flow} -$
$- 0.1226(\pm 0.038)X_{Dist} + 0.208(\pm 0.038)X_{Dist}^2 +$
$+ 0.0787(\pm 0.043)X_{Dist}X_{Dist} + 0.0881(\pm 0.055)X_{Flow}^2$

Equation 9.2 strengthens the effects seen in the linear regression model, the distance parameter has the largest coefficient and thereby the largest impact on ratio. Figure 9 shows the quadratic regression model for three different cases, holding one of the parameters fixed at mean level in each plot. The quadratic effect for the flow parameter in equation 9.2 is seen in Figure 9 a) and b) by the quadratic shaped surfaces.
Figure 9 Plot of the quadratic regression model varying two parameters at a time while the third is fixed at its mean value (0). a) Varying flow and diameter. b) Varying distance and flow. c) Varying diameter and distance.

9.3 Microvascular perfusion comparison

Table 9 Results from the comparative simulations between perfused and unperfused liver tissue, both cases are performed with all three blood flow parameters at their mean level (0).

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Volume [cm$^3$]</th>
<th>Reference Volume [cm$^3$]</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfused</td>
<td>2.9951</td>
<td>4.4011</td>
<td>0.6805</td>
</tr>
<tr>
<td>Unperfused</td>
<td>19.389</td>
<td>4.4011</td>
<td>4.405</td>
</tr>
</tbody>
</table>

The result from the two simulations comparing microvascular perfusion effects shows a very large increase in ratio for the unperfused case.
9.4  Graphical simulation results

Figure 10 Centre point simulation, simulation 10, all parameters at their mean levels (0).

a) Temperature isosurfaces, 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
Figure 11 Reference simulation no blood vessel simulation 1, temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

Figure 11 shows the unaffected symmetrical ablation volume which is created when no large blood vessel is present in the model.
Figure 12 Simulation 2 all parameters at their low levels (-1).
a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.
b) Cross section (xz-plane) of the blood vessel showing temperature for the 12 min simulation result.

A comparison between the results in Figure 12 and Figure 13 (simulation 2 and 4) shows the impact of diameter, on ablation volume, for the case when flow and distance are kept on low levels. The vessel cross section in Figure 12 shows a very clear heating of the blood.
Figure 13 Simulation 4, flow (-1), diameter (1) and distance (-1).

a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.

b) Cross section (xz-plane) of the blood vessel showing temperature for the 12 min simulation result.
Figure 14  Simulation 5, flow (1), diameter (1) and distance (-1).

a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
Figure 15 Simulation 9, flow (1), diameter (1) and distance (1).

a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.
b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
A comparison between the results in Figure 16 and Figure 17 (simulation 11 & 12) shows that there’s only a small impact of blood flow velocity, on ablation volume, for the case with diameter and distance on mean levels. What can be seen by looking at the vessel cross sections in the same figures is that blood temperature is clearly affected by varying flow. The vessel cross section in Figure 16, which represents the simulation case with lower flow velocity, shows a clear heating of the blood up to temperatures close to 50°C.
Figure 17 Simulation 12, flow (1), diameter (0) and distance (0).

a) Temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
Figure 18 Simulation 13, flow (0), diameter (-1) and distance (0).

a) Temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.

The impact of vessel diameter, on ablation volume, is enlightened by comparing the graphical results in Figure 18 and Figure 19 (simulation 13 & 14), where flow and distance both are kept on mean level. A clear heating of the blood are seen in the vessel cross section of Figure 18.
Figure 19 Simulation 14, flow (0), diameter (1) and distance (0).
a) Temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.
b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
**Figure 20** Simulation 15, flow (0), diameter (0) and distance (-1).

a) Temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.

The impact of distance, on ablation volume, is enlightened by comparing the graphical results in Figure 20 and Figure 21 (simulation 15 & 16), where flow and diameter parameters both are kept on mean level. A clearly affected and asymmetric ablation volume is seen in the case with low distance level (Figure 20). The vessel cross section of Figure 20 shows a distinct heating of the blood, while Figure 21 shows that the blood has an almost unaffected and isotropic temperature of 37°C.
Figure 21 Simulation 16, flow (0), diameter (0) and distance (1).

a) Temperature isosurfaces for the 12 min simulation result, red = 50° C, light blue = 40° C and blue = 38° C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
Figure 22 Perfused liver tissue, flow (0), diameter (0) and distance (0).

a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.
b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.

A comparison between Figure 22 and Figure 23 shows the effect of liver perfusion on heat transfer.
Figure 23 Unperfused liver tissue, flow (0), diameter (0) and distance (0).

a) Temperature isosurfaces for the 12 min simulation result, red = 50°C, light blue = 40°C and blue = 38°C.

b) Cross section (xz-plane) of the blood vessel showing blood temperature for the 12 min simulation result.
Discussion

10.1 Method discussion

When considering the results of this work we have to be aware of the large uncertainties and approximations which are associated with modelling complex biological situations with bio heat transfer models. It has to be emphasised that the results of this report only work as a prediction of the used model; the results can’t in any way be extrapolated to the real in vivo situation without performing any verifying in vivo experiments. In spite of this the work can be seen as guiding in a qualitative manner when considering RF heating and heat transfer in the vicinity of large vessels. Strengthening for the developed model is the attempt to bring together a tissue perfusion model with modelling of blood flow within large vessels. Some aspects of the approximations and uncertainties coupled to the developed model will be discussed further in this chapter.

The used effective thermal conductivity value is taken from experimental measurements performed in vivo on pigs by Bhattacharya and Mahajan [26]. Effective thermal conductivity of tissues is largely dependent on tissue perfusion which is regulated by several factors. This results in a great difficulty to perform representative measurements of thermal conductivity since every intervention into the tissue of interest will affect perfusion and thereby affect effective thermal conductivity. The complexity of measuring \( k_{\text{eff}} \) has resulted in that a majority of published works uses Pennes’ bio heat equation rather than the \( k_{\text{eff}} \) equation.

The validity of the in vivo measured \( k_{\text{eff}} \) value of 2.18 \( \text{W m}^{-1} \text{K}^{-1} \), used in this work, can be strengthened by comparing it to a theoretically estimated \( k_{\text{eff}} \) value. A theoretical estimation is done with Crezee & Lagendijk’s expression for correlating effective thermal conductivity and volumetric tissue perfusion [7].

\[
k_{\text{eff}} = k (1 + a' w_{\text{blood}}) \tag{10.1}
\]

Where \( a' \) is an empirical parameter which equals 0.12 (ml min\(^{-1}\) 100g\(^{-1}\))\(^{-1}\). Equation 10.1 is used together with an approximated volumetric liver perfusion of 69.44 ml min\(^{-1}\) 100g\(^{-1}\) which results in a theoretical \( k_{\text{eff}} \) value of 4.78 W m\(^{-1}\) K\(^{-1}\) (for a more detailed calculation see appendix 7). A comparison between the two effective thermal conductivity values shows that they are of the same magnitude, which strengthens the used value.

A shortcoming of the developed model is the lack of temperature dependant thermal conductivity. It is very likely that thermal conductivity of tissue depends on temperature, either by changes in blood perfusion or by changes in other tissue properties. It is likely to believe that thermal conductivity increases for relatively small increases in tissue temperature due to increasing tissue perfusion. In addition is it possible to believe that thermal conductivity decreases, to a value lower than that for 37\(^\circ\)C, for high temperatures due to coagulation of blood in the microvascular blood flow. This behaviour makes it difficult to model thermal conductivity of tissues in a reliable manner. A possible effect of temperature dependent thermal conductivity on the ablation result is a lowering of the heat sink effect for high temperatures, due to decreasing thermal conductivity. At the same time is it possible to
believe that a decrease in thermal conductivity results in a heating more centralised around the electrode, resulting in a smaller ablation volume.

The developed model’s electrode cooling channel temperature of 10°C is based on Welp’s result from ex vivo experiment in unperfused liver tissue using the cool-tip RFA equipment [3]. The fact that Welp’s experiment was performed on unperfused liver tissue is important to consider since the current work’s aim is to model perfused liver tissue.

Used parameter levels are all considered to be representative for the modelled situation with exception for the velocity parameter. Blood flow within the human cardiovascular system has a velocity which is closely coupled to blood vessel diameter where flow velocity decreases with decreasing vessel diameter. This situation isn’t resembled in the developed model since this would make the comparison between the results difficult. This fact has to be considered when looking at the results from the simulation cases with low level diameter and high level flow velocities.

As a result measure the 50°C isotherm is an easily implemented measure. A discussion of the reliability of this measure is motivated, especially regarding its lack of time dependency. It is reasonable to believe that ablation volume is affected by the time for which tissue exceeds a certain critical temperature; this fact is not considered in the 50°C isotherm measure. A measure of ablation volume that includes the time as a parameter might have been an improved choice. Further on is the 50°C isotherm only a measure of ablated volume and not a measure of the actual heat sink effect occurring in the simulation case. An additional, or alternative measure, could have been the amount of power transported out of the model by the blood flow.

Time required for performing each simulation (0.5 -1.5 h) could have been reduced by a better choice of function modelling temperature dependent electrical conductivity (eq. 6.1). A better choice would have been a sigm function with a softer decrease, would have resulted in a less complex numerical problem and thereby a shortening of the time necessary for solving the problem. An improvement of the sigm function might also have enabled the comparative investigation to have been performed with the entire equation 6.1 instead of the shortened version used in this work.

The used statistical method has a theoretical advantage in that it gives an opportunity to investigate which factor that has the largest impact on the result and whether there exist any large interaction effects between parameters. One shortage of the statistical method is that it’s primarily made for investigating experiments where there is a natural source of randomness between the results. The simulation results of this study doesn’t involve any randomness since a simulation in one model, with a fixed mesh, results in the same solution no matter how many simulations you perform. This lack of randomness makes it difficult to say something about the statistical uncertainty of the result.

To increase the accuracy of the second degree regression model a larger number of simulations would have been necessary; this was not possible to perform due to the limited time frame of this work.
10.2 Result discussion

The resulting ratios are all considered to be within reason. The ratio of simulation 6 has a value exceeding one even though a blood vessel is modelled. This result might be explained by the fact that the heat sink effect is so small, that mesh differences, between simulation 6 and the reference simulation, brings a difference when calculating the volume large enough to make the ratio exceed one.

Estimated linear and second degree regression model (eq. 9.1 and 9.2) both shows that distance between electrode and blood vessel are the parameter with strongest impact on simulative ablation volume. This result implies that an increasing distance results in less heat transported out of the model by the blood flow and thereby in a ratio closer to one, i.e. a decrease of the heat sink effect and a larger simulative ablation volume. A look at the second degree regression model coefficients (eq. 9.2) shows that the impact on ratio from distance is almost twice as large as the impact from flow and diameter. The vessel cross section in Figure 20 shows that an electrode - blood vessel distance of only three millimetres makes it possible for blood close to the vessel wall to heat significantly in spite of the constant flow.

The quadratic regression model shows that there’s only a small impact by flow velocity on ablation volume. The result in Figure 16 and Figure 17 shows a large impact on blood heating within the vessel; this implies that flow might have an important role as protecting vessels from being damaged during tissue heating.

Interaction between diameter and distance is visualised by the twisted surface in figure 9 c). It shows that a varying diameter has a much larger impact on simulative ablation volume for cases where the distance parameter are small. The estimated coefficient for interaction effect between flow and distance, in the quadratic regression model (eq 9.2), is of the same magnitude as the estimated error, $s$, and therefore not considered significant.

Impact of vessel diameter on ablation volume is clearly seen in Figure 12 and Figure 14 (simulation 2 and 4) where diameter is varied between high and low level while the other two parameters are fixed. It should be emphasised that these figures represents the cases were distance are set on its low level, and therefore results in a situation where a varying diameter affects the results more strongly compared to the case when the distance is large due to interaction effect. The case for the low level of diameter (Figure 12) show a very small effect on simulative ablation volume but a significant effect on blood temperature which raises close to 60°C in the region nearby the RF electrode. The increase in blood temperature results in a 50°C isotherm which is stretched out along and within the vessel. The validity of this result can be discussed considering the non temperature dependant thermal conductivity. Since the blood temperature is close to 60°C it’s considered to be close to coagulation temperature, a possible coagulation would stop any further blood flow and thereby strongly affect the ablation result. Figure 14 shows that a larger vessel diameter gives a larger impact on simulative ablation volume and only a small heating of the blood within the vessel, which is probably due to the larger blood volume. This result can be compared to the experimental result by Lu et al. who showed heat sink effects for vessel diameters larger than 4 mm [5].

The two simulations comparing perfused and unperfused liver shows a clear increase in simulative ablation volume (Table 9) for the unperfused case compared to the perfused case, which is the same result as shown by Kolios et al. [7]. A decreased thermal conductivity,
resembling an unperfused liver, results in a large decrease of the heat sink effect which is due to the fact that less heat is transported to the large vessel boundary. The result from these two simulations can be discussed considering the used electrical conductivity for liver tissue. Electrical conductivity for liver tissue is described by equation 6.1 with the \textit{sigm} function removed. The removal of the \textit{sigm} function leads to an electrical conductivity which continues to increase linearly even though liver tissue reaches 100°C. This fact might result in an overestimation of the ablation volume and thereby an underestimation of the heat sink effect.

An interesting notation when looking at the graphical results of the simulations is the large extension of ablation volume in the electrode’s direction. This is probably due to the fact that electric current emitted from the tip of the electrode is much larger than the current emitted from the rest of the electrode surface. This unbalanced current distribution could be an interesting factor to consider when planning how to place the electrode in relation to large vessels.
11 Conclusion

The result of this work shows that distance is the parameter with largest impact on ablation volume compared to the diameter and flow velocity. The impact on the estimated ratio of the second degree regression model, resulting from distance is almost twice as large as the impact from the other two investigated parameters. An increasing distance between modelled RF electrode and large blood vessel decreases the heat sink effect and thereby increases the simulated model’s volume of ablation. An increasing blood flow velocity and vessel diameter is shown to increase the heat sink effect and thereby decrease the simulated model’s ablation volume. Interaction effect is shown to exist between diameter and distance, where a small distance increases the effect from a varying vessel diameter. A decrease in tissue perfusion, modelled by lowering the tissue thermal conductivity, is shown to result in a large increase of ablation volume.

12 Future work

Since a great shortcoming of the used method is the non existing experimental verification of the developed model, a coupling between practical experiments and simulation results would be of great interest in the future development of a more accurate model. A future validation of the model to an experimental in vivo RFA situation would hopefully enable an extrapolation of the results to the clinical situation.

It would also be interesting to investigate other parameters likely to affect RFA treatment result. These parameters could for example be the angle between RF electrode and blood vessel, treatment time and applied power.
References


17. COMSOL 3.3, User’s guide – electromagnetics, Comsol documentation.


25. COMSOL 3.3, General heat transfer - Adding highly conductive layers, Comsol documentation.


30. COMSOL 3.3, Meshing – Creating meshes, Comsol documentation.
Appendix 1

Sigmoid function

The following sigmoid function is used for modelling the sudden decrease in electrical conductivity of modelled liver tissue, reaching the vaporisation temperature of 100°C. The constant in front of the parenthesis in the exponent, of the expression, sets the steepness of the function and $T_{vap}$ defines the vaporisation temperature.

\[
sigm = \frac{1}{1 + e^{s(T - T_{vap})}}
\]

Figure 24 A plot of the temperature dependent electrical conductivity, equation 6.1.
Appendix 2

Integration coupled potential

Power developed in the simulations of this work is kept at a constant value throughout simulation time. In order to keep developed power constant, though tissue properties are changing with increasing temperature, the potential of the electrode has to continuously adapt to the current conditions. This can be done in CM by the help of integrated coupling variables. A stepwise description of how to create a control of the potential with aim to keep developed power constant is listed below.

- To assign a total resistive heating integration value to a variable, enter the following track in CM: Options > Integrated coupling variables > subdomain variables.

- Chose a subdomain of interest in the subdomain integration variables dialog box.

- Assign a variable name and an integrand, in this case $Q_{dc}$. The integration coupled variable will be updated in every time-iteration.

- Set up an ordinary differential equation (ODE) which connects total resistive heating to electrode potential, by entering the following track in CM: Physics > ODE settings.

- Assign a variable that you want to regulate, in this case $V_0$.

- Assign an equation for which the value of $V_0$ will be adapted to fulfil. In this case is the following equation assigned: $total\_power - power$ where the first term is the integration coupled variable for resistive heating and the second term is the wanted value of total resistive heating. CM will adapt $V_0$ so that $total\_power = power$.

- A good initial guess of regulated variable are required (not 0).

- In order to make the integration coupled variable control the potential and not vice versa, a non-ideal weak constraint setting has to be applied. This is done under the following track: Physics > Properties.
## Appendix 3

### Free mesh parameters

![Free Mesh Parameters dialog box](image)

_Tuning the mesh to the wanted refinement grade can be done by setting the parameters in the Free mesh parameters dialog box, see figure above. Either a predefined mesh size can be chosen, which automatically sets the parameters in the custom mesh size area. Predefined mesh size can be chosen between 9 different cases. When using the custom mesh size choice, mesh size parameters are defined manually by the user. Different custom mesh parameters will be described below [30]._

- **Maximum element size** – Optional parameter which specifies the maximum element size of the mesh, default value is a tenth of the maximum geometry distance.

- **Maximum element size scaling factor** – Parameter which is used when the maximum element size is not specified. The parameter specifies a factor which is multiplied to the default maximum element size. Default value of the parameter is one.

- **Element growth rate** – Specifies the rate of which the mesh elements can grow from a region of small elements to a region of larger elements.
• **Mesh curvature factor** – Couples the size of curved boundary elements to the curvature of the boundary. Curvature radius is multiplied with curvature factor and defines the maximum size of the boundary elements. Default value is 0.6 and a lower value results in finer boundary mesh elements.

• **Mesh curvature cutoff** – Prevents meshing of too small curved elements. When product between cutoff curvature and maximum geometry distance is larger than the boundary’s curvature the mesh generator considers the boundary to have a curvature with radius of the calculated product.

• **Resolution of narrow regions** – controls the number of created mesh layers in narrow regions, values less than 1 might result in anisotropy of mesh element size in the narrow region.
Appendix 4

Calculating ablation volume

CM’s integration tool is used for calculating ablation volumes, the integration is performed according to the following principal steps.

- Enter the following track in CM: Postprocessing > subdomain integration, choose which subdomain/s to integrate over.

- Define an expression to integrate; generally can this expression be one of CM’s predefined variables or a user defined logical expression. A combination of predefined variable and user defined logical expression can be used to delimit the volume over which the integration is performed over e.g. an expression such as \((x > 0) \cdot Q_{dc}\) will integrate total resistive heating over the chosen subdomain for which \(x > 0\).

Calculating ablation volume uses the following integrand: \((T > 50 + 273.15)\), which equals one where the expression is true and zero elsewhere.

- Choose for which solution time the ablation volume is going to be calculated and press ok.

- Resulting volume in cubic metres is calculated and presented by CM.
Appendix 5

Table 10 Design matrix for the $2^3$ factorial experiment setup. A constant column is necessary for calculation of the regression model constant. A, B and C represents flow, diameter and distance respectively.

<table>
<thead>
<tr>
<th>Constant</th>
<th>A</th>
<th>B</th>
<th>AB</th>
<th>C</th>
<th>AC</th>
<th>BC</th>
<th>ABC</th>
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</thead>
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Table 11 Design matrix for the extended design, the constant column is necessary for calculation of the regression model constant. A, B and C represents flow, diameter and distance respectively.

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Appendix 6

Figure 26 Normal probability plot for estimated linear regression model coefficients.
Appendix 7

Calculation of effective heat transfer coefficient

Effective heat transfer coefficient is calculated with the use of Crezee & Lagendijk’s expression for correlating effective conductivity and volumetric perfusion (eq. 10.1) where $a' = (0.12 \text{ ml min}^{-1} 100\text{g}^{-1})^{-1}$.

$$ k_{eff} = k(1 + a'w_{blood}) $$

Equation 10.1

Total liver perfusion is approximately 25 % of the total cardiac output (CO) of ~5 l/min at rest [31]. This perfusion value is used together with the average liver mass to calculate the volumetric perfusion rate, $w_{blood}$.

$m_{liver} \approx 1.8 \text{ kg}$ \(^{(1)}\)

$CO \approx 5 \text{ l/min}$ \(^{(2)}\)

$w_{liver} \approx 0.25 \cdot 5 = 1.25 \text{ l/min}$

Volumetric rate $= \frac{1250}{1.8} = 694.44 = 69.4 \text{ ml}\text{blood} \text{ min}^{-1} 100 \text{ g}\text{liver}^{-1}$

$k_{liver} = 0.512 \text{ W m}^{-1} \text{ K}^{-1}$ \(^{(1)}\)

Eq.10.1 $\Rightarrow k_{eff} = 0.512(1 + 0.12 \cdot 69.4) = 4.78 \text{ W m}^{-1} \text{ K}^{-1}$

\(^{(1)}[9], \quad ^{(2)}[31]\)