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## Summary

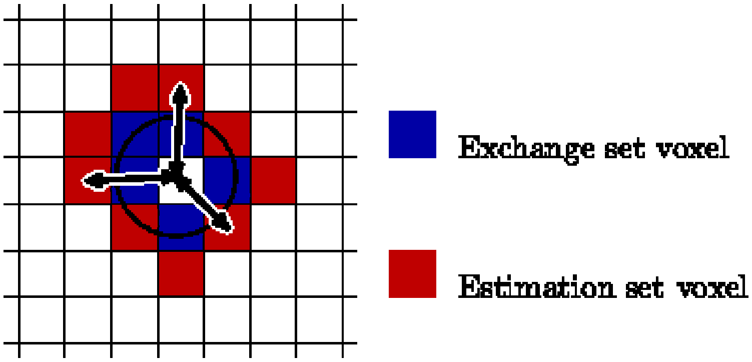
The major treatment modalities for cancer are surgery, radiotherapy and chemotherapy. The effect of the last two treatment modalities can be enhanced by using hyperthermia as an adjuvant therapy. A hyperthermia treatment consists of a temperature elevation above 41$^\circ\mathrm{C}$ in the tumour. During a treatment the resulting temperature profile can be sampled and statistical representations such as the lowest or mean temperature can be obtained. These statistical measures need not correspond to those of the true three-dimensional temperature field. The correspondence can be enhanced by increasing the number of sample points or by calculating the total temperature profile based on the treatment temperature samples. In order to calculate the temperature profile resulting from a hyperthermia treatment, the heating apparatus needs to be modelled to obtain a corresponding power deposition. This power deposition can then be used to calculate the complete temperature profile. The development of a computer model capable of calculating the temperature profile given a power deposition is the subject of this thesis.

For a long time it has been recognised that the blood flow has a major influence on the heat transport in tissue. All kinds of continuum models have been proposed taking the collective thermal behaviour of the total vasculature including the perfusion into account by changing the governing differential equation. The implementation of one of the suggested differential equations is described in Chapter 2.

$$\rho_{\mathrm{tis}} c_{\mathrm{tis}} \frac{\partial T}{\partial t} = \nabla \cdot \left( k_{\mathrm{eff}} \nabla T \right) + c_{\mathrm{b}} W_{\mathrm{b}} \left( T_{\mathrm{art}} - T \right) + P \qquad \left[ \mathrm{W\,m^{-3}} \right]$$

This model uses a `heat sink term' combined with an `effective conductivity' to describe the thermal influence of blood flow. The heat sink term is correlated with the thermal equilibration of the blood while the effective conductivity is linked to the heat transport due to the blood flow. The differential equation is transformed into a two and a three level finite difference representation. The two level finite difference scheme suffers from a time step limitation which is not present in the three level scheme. The three level scheme has the disadvantage of being non-dissipative.

A continuum model, such as the one described in Chapter 2, cannot account for the local thermal impact of the vasculature. For this phenomenon we need to take the vasculature, down to a certain diameter, into account discretely: we must describe every vessel with a diameter larger than a given limit individually. The resulting DIscrete VAsculature (DIVA) thermal model combines the continuum formulation with discrete vasculature. In Chapter 3 the implementation of a single discrete vessel segment is described. The tissue grid and the vessel segment share the same coordinate system but the vessel segment definition is independent of the calculation resolution the tissue is modelled on. The thermal interaction of a vessel segment with its surrounding tissue is calculated using an analytical expression for the interaction of a vessel embedded in a coaxial homogeneous tissue cylinder. The vessel segment is split into several `buckets', each holding one blood temperature sample. For the analytical interaction expression between a bucket and its surrounding tissue, temperature samples in the direct vicinity of the bucket are needed. Every bucket calculates its own interaction with the surrounding tissue using tissue temperature samples found in the `estimation set'. The calculated heat exchange is imposed on the tissue in the `exchange set': voxels located inside the vessel in the global coordinate system.

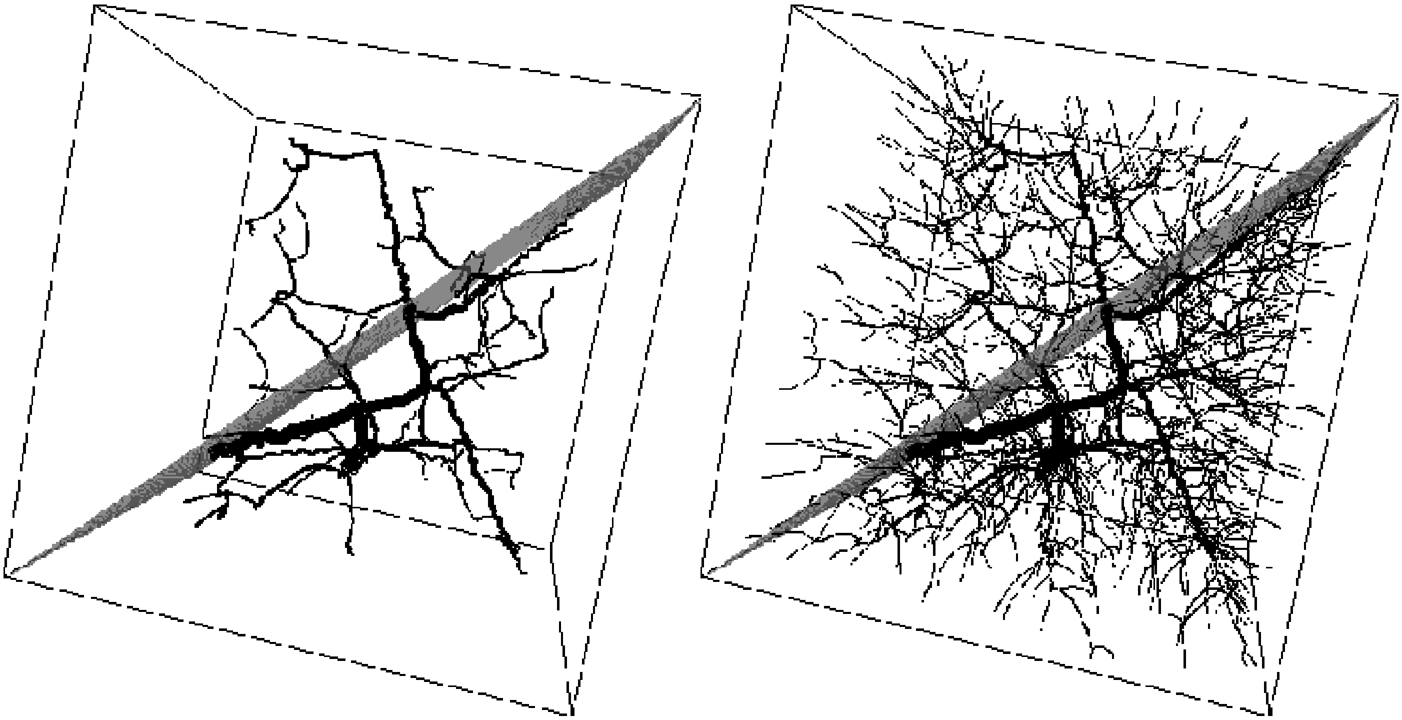


Projection of a vessel onto the tissue grid together with the two associated voxel sets. The interaction is calculated based on the distances between the temperature samples and the centre of the vessel.

The blood (bucket) temperatures are shifted along the vessel after an interpolation of the calculated heat flows resulting in an accurate inclusion of the blood flow during a time step. This new modelling technique has been evaluated by modelling situations for which analytical solutions could be found, showing excellent results. Single vessel segments or collections of single vessel segments can be used to model fully artificial situations, needed to test the behaviour of the model (Van Leeuwen et al.,1997b). The model has also been tested for counter current vessel segment pairs as this situation plays an important role in the thermal behaviour of vascularised tissue and analytical solutions can be found in the literature. The results of these calculations are influenced by the tissue resolution, as anticipated, and generally show good correspondence with the theoretically obtained results (Van Leeuwen et al.,1997a).

In order to model vasculature found in tissue, the single segments are incorporated in a tree topology mimicking a genuine vessel tree. The modelling of the the thermal influence of such a vessel tree is described in Chapter 4, together with a technique to account for vasculature connected to modelled vessel segments but too small to be modelled discretely. Blood leaving an arterial vessel tree inside the modelled volume, in general, is not equilibrated with its surrounding tissue. The heat needed for this equilibration process is extracted from the `sink set': a set of voxels being thermally influenced by the blood leaving the vasculature. Blood entering a venous vessel tree needs an inflow temperature which is obtained by averaging the tissue temperature found in the `sample set'. These sink/sample sets need to be defined by the user and offer a huge model parameter space requiring automated set creation. These sets govern the effective simulation perfusion of the enclosed region. When the spatial distribution of (limited) terminal vessel segment endpoints is not in accordance with the original perfusion, effective perfusion artifacts occur.

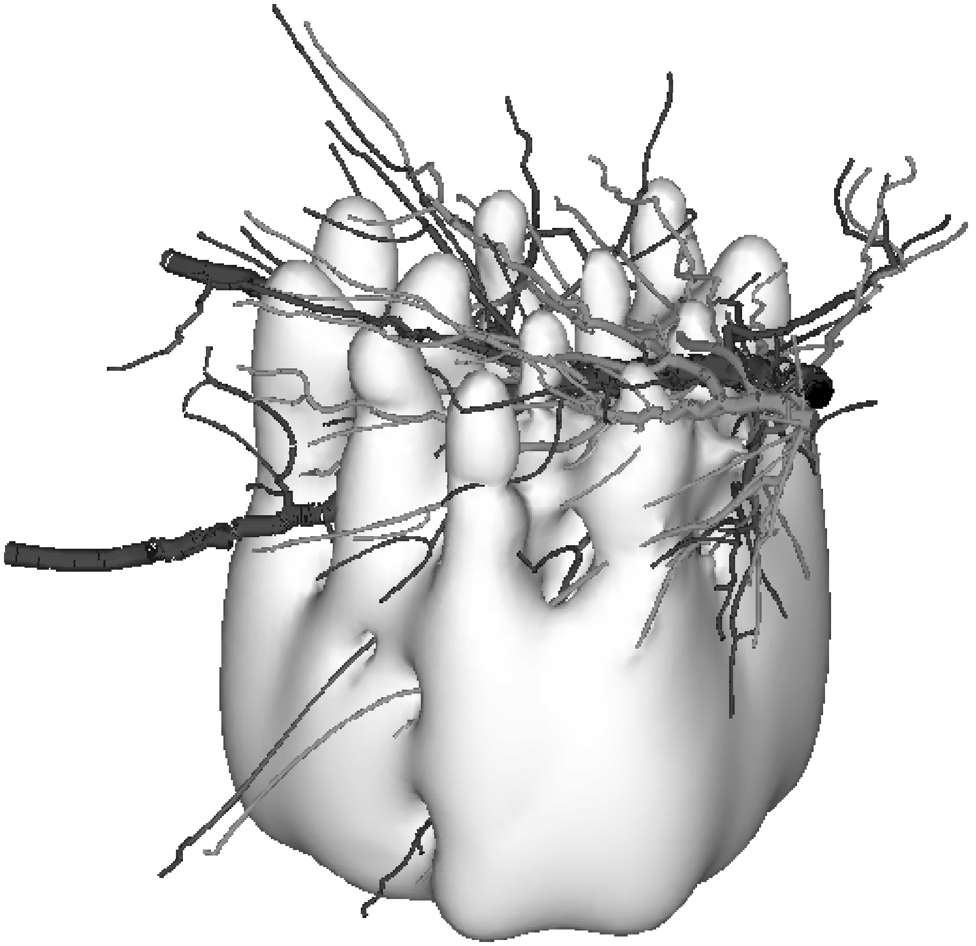
The thermal impact of eleborate vasculature on its surrounding tissue can be calculated and compared to the impact of limited vasculature



From clinical data sets only limited vasculature can be reconstructed. In Chapter 4 we show the capabilities of the model to deal with 'incomplete' vasculature.

Another option for modelling the `missing vasculature' is the extension of the reconstructed vessel tree with a number of artificial segments. This procedure is expected to produce vessel networks having a similar thermal influence on the surrounding tissue as the genuine vasculature: all the thermal effects of the vasculature are included elegantly. The tissue perfusion is defined by the distribution of terminal segment endpoints together with the blood flow in these terminal segments. Artificial vasculature can be produced with the program VAMP (Vasculature Assembly through Modifiable Potential), described by Van Leeuwen et al. (1998).

Hyperthermia treatment with ferromagnetic seeds is fully dependent on treatment planning calculations: after implantation, during treatment there is no feedback and no adjustment possibility. The choice of seeds and the implantation geometry must be established prior to the treatment. This hyperthermia modality is of conductive nature and therefore does not demand a power deposition calculation. The modelling of the thermal impact of ferromagnetic seeds is described in Chapter 5. The seed modelling technique is very similar to the technique used for vessel segments. The seed structures are also independent of the tissue grid resolution and defined geometrically in the global coordinate space. Again, buckets are used as the smallest functional part but with a (different) interaction calculation function compatible with the modelled seeds. In a vessel segment the axial heat transfer is governed by blood flow, in a thermo-seed the axial heat transfer is controlled by axial conduction in the seed implying a one-dimensional seed iteration scheme. The time step constraint found for the tissue iteration scheme is also valid for the seed iteration scheme demanding the use of small time steps. If the global (tissue) time step would yield an unstable seed time step, several sub time steps are taken adding up to the global time step.



This thermo-seed implementation can be used in combination with our DIVA model resulting in a flexible treatment planning system for hyperthermia using ferromagnetic seeds. Shown is a result from the simulation described by van Wieringen et al. (1998) All the previously described components are implemented in C++ using object oriented techniques. The classes used as building blocks for our model are described in Chapter 6. The chosen software development scheme facilitates the reuse of code at two levels. The shared functionality of classes can be put in a separate base class (e.g. a vessel bucket and a seed bucket are both derived from the base class bucket). The produced classes can be included in other programs needing the modelled structures. The described computer model is tested in situations for which analytical solutions are known. These are well defined situations; the computer model parameters are taken equal to the analytical model parameters, allowing us to test the capability of the model to include certain thermal phenomena. A true experimental verification has not been done. Such a test poses the interesting challenge of finding the optimal parameter set for a given (clinical) situation. This validation is currently undertaken using heating experiments in bovine tongues. Optimal data acquisition can be employed in this test site to reconstruct as much as possible of the thermally significant vasculature and tissue perfusion. These experiments should also result in strategies for finding the optimal parameter settings for situations where the clinical data is sub-optimal.