Summary and discussion

Bio heat transfer

Hyperthermia is the application of high temperatures, above 41°C, to tumour tissue. Clinical applications are discussed in the general introduction. The main goal of this study was verification of the validity of bio heat models used in hyperthermia treatment planning to predict the three-dimensional temperature distribution during the application of hyperthermia. For this purpose a number of thermal model tests were designed and executed in isolated perfused bovine kidney and tongue. The theoretical background of the main bio heat models is given in chapter 1, chapter 2 discusses methods to test these models, describing among others a method for isolated perfusion of muscle tissue developed at our department (Bos et al. 1991). The actual thermal model tests are described and discussed in chapters 3 to 6. The validity of thermal models is now confirmed for both extreme cases, the continuum description of the collective flow by small vessels using an enhanced effective tissue conductivity k_{eff} and the discrete description of flow in large, thermally significant vessels. Medium and small vessel heat transfer, vessel diameter smaller than 0.5 mm, is best described with an enhanced k_{eff}. This was shown in chapters 3 and 4 for both the transient and steady state temperature distribution, especially in comparison with predictions by the conventional bioheat transfer equation. Simple methods to obtain an estimate for k_{eff}, compatible with most clinical heating techniques, are discussed in chapters 2, 3 and 4. The most direct method is based on measurement of the heat diffusion rate, this method can be applied when the power deposition is very localised and is suitable for most forms of interstitial heating. Estimates for k_{eff} obtained using these methods suggest k_{eff} increases linearly with increasing tissue blood flow, reaching a value twice the intrinsic tissue conductivity at a blood flow of 1.7 $\mathrm{kgm^{-3}s^{-1}}$ in bovine kidney and tongue tissue. This result applies to a relatively small volume, higher values of k_{eff} can be expected in larger volumes containing relatively larger vessels.

Large, thermally unequilibrated vessels can be modelled either discretely or with the heatsink model, where the heatsink term represents the heat escaping from the heated volume through the large, thermally unequilibrated veins without further interaction with the surrounding tissue. A modification factor f is introduced in chapter 6 denoting the fraction of heat escaping without further interaction. The modified heatsink model will correctly predict the mean temperature rise if the heated volume is large and the large vessel distribution uniform. The advantage of the heatsink model is its simplicity, but for treatment planning a discrete description is preferable in order to correctly predict local temperature inhomogeneities, especially those found near large vessels. This was confirmed by the experiments in chapter 4 where just a small volume was heated by 2x2 hot water tubes; only the presence of a large vessel in the heated volume caused heatsink like heat removal, in all other cases the heatsink model prediction was incorrect. A first attempt to simulate the hot water tube experiments using the discrete vessel model is described in chapter 5 and was partially successful; the inclusion of smaller vessels, with diameters down to 0.5 mm, is required to improve the accuracy.

Applications in clinical hyperthermia

Some applications of bioheat models in clinical hyperthermia were discussed, especially regarding large, thermally unequilibrated blood vessels which have a significant impact on the temperature distribution and cause serious temperature inhomogeneities (Lagendijk 1982). Practical consequences for treatment planning and applicator design in general were discussed in chapter 7. One of the results, supported by experimental data in chapter 3, was that the effective tissue conductivity of the tissue around a large, thermally unequilibrated vessel is of great interest for the micro temperature distribution near the vessel. High $\mathrm{k}_{\mathrm{eff}}$ corresponds to a low tissue heat resistance and comparatively less temperature inhomogeneity in tissue near large vessels, but also to a higher heat removal; more power is required to raise the local tumour temperature to therapeutic levels than for low k_{eff}.

This result led to some conclusions concerning the expected performance of different heating techniques in tissue volumes with varying k_{eff} and vessel density: An optimal temperature uniformity in the treatment volume requires a spatial SAR control with a resolution of 1 cm or better, if possible combined with preheating of large vessels in a large margin of normal tissue around the tumour. Few heating techniques satisfy both these requirements: Regional heating techniques do provide preheating of surrounding normal tissue, but SAR steering is crude. Scanned focussed ultrasound and some interstitial heating methods offer a good spatial SAR control, but the heated volume is usually small: no preheating. The potential of scanned focussed ultrasound in eliminating local temperature imhomogeneities due to the presence of large vessels is demonstrated by simulations by Lagendijk et al. (1993a,b). Recently a project was started at our department (in cooperation with the Daniël den Hoed Cancer Center in Rotterdam) to develop a segmented 'dual' interstitial heating electrode which is expected to provide better spatial SAR control than other techniques, especially in the longitudinal direction (Lagendijk 1990, 1991, Kaatee et al. 1993).

Another means of improving temperature uniformity during hyperthermia is raising the core temperature. If for instance the core temperature is 40°C the blood in a large vessel entering the tumour has to be raised just a further 2°C to reach therapeutic levels. This principle is presently used during regional heating.

Good spatial SAR control can only be fully exploited when either extensive thermometry or reliable treatment planning based on discretely modelled large vessels is used. A discrete vessel model has become available (Mooibroek and Lagendijk 1991), its successful application in the clinic depends on the ability to supply the relevant vessel data like size, density, flow velocity and direction. A promising technique for obtaining large vessel data is magnetic resonance angiography (MRA), which in principle enables a three-dimensional reconstruction of both the arterial and the venous network (Edelman et al. 1989, Kim and Cho 1990).

Future research

The work on thermal model tests should continue as model verification is not yet completed. The remaining problems include:

The dependence of k_{eff} on blood flow, especially in more complex geometries and vessel networks with counter-current flow.

The incorporation of unidirectional flow in the continuum models.
The transition between the discrete vessel and the continuum description.
The presented results show the validity of the k_{eff} model, further research is required to determine the dependence of k_{eff} on vessel size and blood flow in a realistic vascular network. Theoretical expressions for k_{eff}, e.g. equation (1.5) in chapter 1, all apply to a single generation of vessels in a homogeneous medium. The properties of k_{eff} must be investigated for realistic vessel networks, using both vessel data of individual patients and idealised standard vessel networks.

Although the experimental transient and steady state temperature profiles in chapter 3 were successfully interpreted using the limited k_{eff} model, the steady state profile presented in figure 6 did display a slight shift, suggesting the presence of a net flow in one direction. Apparently blood flow in the opposite directions was nearly, but not quite equal. A similar distortion is visible in the temperature profile computed for directed perfusion by Baish et al. (1986). At some anatomical sites a significant net flow may occur, for such sites a comparison should be made between describing small vessel convective heat transfer with an enhanced effective conductivity k_{eff} and with unidirectional flow vectors, as discussed in chapter 1; equation (1.3).

An important practical problem is the transition between the discretely described large vessels and the continuum description of medium size vessels. No problem occurs if the smallest vessel modelled discretely reaches thermal equilibrium with the surrounding tissue before ending. This requires the inclusion of sufficiently small vessels in the discrete model description, down to 0.5 mm diameter. However, reconstruction of very small vessels is not yet possible clinically, 2 mm diameter is about the minimum at present for MRA. This means the transition from the discrete vessel towards the continuum description of convection becomes a problem, because a 2 mm diameter artery or vein will generally not be in complete thermal equilibrium with the surrounding tissue. If its branches are not modelled discretely the heat flow remaining at the end of the discrete vessel must somehow be transferred to the surrounding tissue. A local heatsink or source seems a logical substitute for the discrete description of these branches, possibly combined with a radially directed, enhanced k_{eff}. Together these local sinks or sources may form a global heatsink if the 0.5-2 mm vessels are distributed isotropically.

An alternative solution is replacement of the missing 0.5-2 mm discrete vessels by some representative standard vessel network based on literature or dissection data. The exact location of any temperature inhomogeneity would then be unknown, but for systems with limited spatial SAR control the magnitude of the temperature inhomogeneity is more important than the location. With either method an error will be made in the prediction of the local temperature, the magnitude of this error should be assessed.

These three problems are adressed in a new research project at our department funded by the Dutch Cancer Society (IKMN 92-60).

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