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Simulation Studies on Blood Flow, Temperature and Oxygen Transport due to Laser Irradiation of Breast Tumor Vascular

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Abstract

It has been shown that tumor cells are resistant to radiation and that increasing tumor oxygen levels via laser-mediated hyperthermia treatment increases tumor cell radio sensitivity. Hence, studies of the effects of laser irradiation on tumor oxygen levels are of great interest, as they allow for the optimization of hyperthermia treatment.

Accordingly, in this study is to develop a finite element model to simulate the heat transfer due to laser irradiation of tumor tissue, the blood flow through a tumor capillary, and the effect of changing temperature on blood flow rates and oxygen delivery to tumor tissue and. This can be achieved by using finite element models using COMSOL Multiphysics software (FEM lab).

1- Introduction:

Laser irradiation works best for cancers that are rapidly or actively dividing, and recent research suggests that it enhances radio sensitivity of dividing cells by enhancing oxygenation of the tumor tissues. This oxygenation is thought to be caused by increased blood perfusion coupled with a decreased oxygen consumption rate due to mild hyperthermia [1].

However, further investigation on the use of hyperthermia in conjunction with radiotherapy is necessary to study the effects of this technique on normal tissues as well as to quantify the vessels due to the increase in temperature. The effect of hyperthermia is not limited to tumor cells but is also observed on the microvasculature. The effect of hyperthermia on tumor vasculature is of considerable interest since controlling the tumor blood flow can improve the efficiency of tumor treatment. For example, in radiotherapy, improving the blood flow can increase the tumor oxygenation; similarly in chemotherapy, increasing the blood flow helps increase the delivery of appropriate pharmacological agents.

The relationship between the changes in oxygen partial pressure (PO_2) and blood flow in heated tumors was investigated by animal experiments [2].

The result showed that tumor oxygenation or PO_2 increases immediately after mild temperature hyperthermia. In another study by Song and coworkers [3], the damage caused to a tumor when an anti tumor drug was used alone and when it was used in combination with hyperthermia was investigated, and it was observed that there was a longer growth delay when an anti tumor drug was used in combination with mild hyperthermia.

In summary, exploring the hyperthermia-blood flow-oxygenation relationship is essential for the realization of targeted drug delivery. Modeling the hyperthermia-blood flow-tissue interaction may be beneficial for the analysis and optimization of the parameters governing planned hyperthermia treatment procedures.

Accordingly, the focus of this study is the development of a finite element model to simulate the blood flow through a tumor capillary, and resulting changes in flow rates and oxygen delivery to tumor tissue as a result of the heat transfer due to laser irradiation of tumor cells.

2- Geometrical Description of the Capillary / Tumor Tissue Model:

The tumor vessels are different from the vessels in normal tissues, which are permeable, fragile, and larger. Less et al., [4], found that the mean values of the diameter and the length of capillaries in a mammary adenocarcinoma are 10 and 67µm, respectively [4]. On the other hand, the mean values of diameter and the length of capillaries in normal tissues are 5 and 500µm, respectively [4].

The tumor vascular beds are different from the vascular beds in the normal tissues, which are parallel, in series, or in a combination type. Figure (1) shows the modeled blood vessel network in a breast tumor [5]. Here, we consider that the tumor vascular beds are parallel to the normal vascular beds

In order to model blood vessel network in a breast tumor described in Figure (1), a classical Krogh cylinder approach, [6], was used to analyze the oxygen distribution in a tissue.

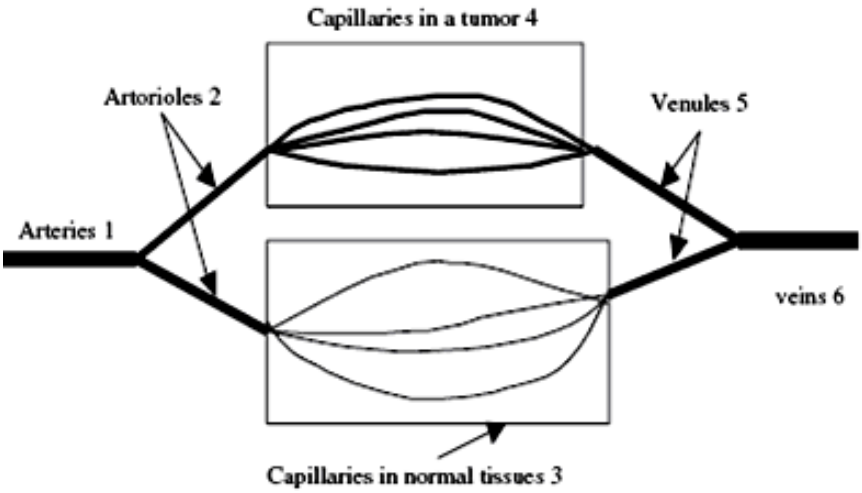


Fig. 1. The blood circulation network in normal tissues and in tumor

In the Krogh model, it is assumed that the tissue can be subdivided into parallel and evenly spaced cylindrical tissue. The schematic of the computed domain is shown in Figure (2) where the model is divided into two regions: the capillary and the tumor tissue.

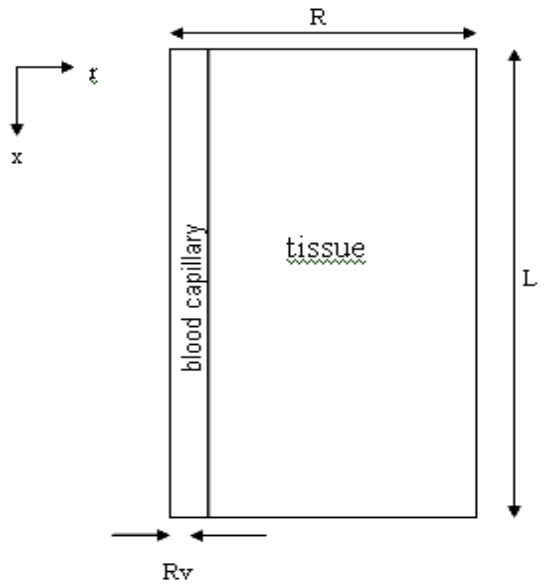


Fig. 2. The Capillary / tumor tissue model schematic adopted from He et al [7].

In which the Dimensions (taken from He et al. [7]) Rv (radius of blood capillary) = 6 μm, R (radius of tumor tissue) = 60μm, L (total length of tumor tissue) = 100μm.

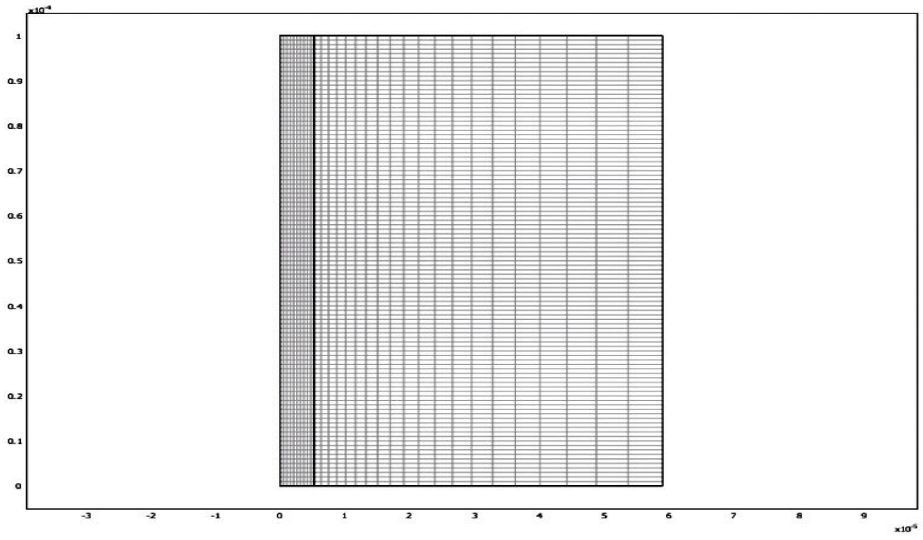


Fig. 3. Capillary / tumor tissue mesh

As shown in Figure (3), the breast model mesh was divided into two regions: the capillary and the tumor tissue. For this model, quadrilateral elements were mapped with an increasing mesh density near the blood vessel, the region of highest flux. The total number of elements used is 3000.

3- Analysis of the Blood Flow in the Human Breast:

In order to make the model adaptable to individual shapes of segmented vessels, we considered the geometry of a vessel as a volume in which an incompressible fluid (blood) flows. The direction of the blood flow and the initial speed profile are implemented as boundary conditions.

The incompressible Navier-Stokes equation for the blood (Newtonian fluid) is expressed by [8] as:

$$\rho\frac{\partial u}{\partial t}+\rho(u.\nabla)u=\nabla[-\rho I+\eta(\nabla u+(\nabla u)^{T})-(2\eta/3-K)(\nabla.u)I]+F \qquad (1)$$

Where: η is the dynamic viscosity (kg m^{-1} s^{-1}), K is the dilatational viscosity (W K^{-1} m^{-1}), ρ is the density (kg m^{-3}), u is the velocity field (m s^{-1}), p is the pressure (pa), F is a volume force field such as gravity, I is the identity matrix or unit diagonal matrix. The parameters used in modeling the blood flow rate among the model and the boundary conditions are described in table (1) and table (2)

Table (1) Subdomain properties (taken from He et al. [7] and Yoshida et al. [9]):

Properties		blood
Density	kg/m^3	1100(7)
Dynamic Viscosity	Pa.s	0.0044 [7]
Diffusion Coefficient	m^2/s	1.86E-09 [9]

Table (2) Fluid flow Properties:

Property		Inlet	outlet
Pressure	pa	2306	1160

4- Analysis of oxygen distribution in blood vessels and tissue:

The classical Krogh cylinder approach [6] was used to analyze the oxygen distribution in a tissue. In the Krogh model, it is assumed that the tissue can be subdivided into parallel and evenly spaced cylindrical tissue units, and that each of the units has a capillary which supplies oxygen to the tissue region surrounding it. Thus, a normal and tumor tissue unit were extracted in order to analyze the oxygen distribution in the vessels and the tissue ,The equation governing oxygen transport in the vessels and the tissue can be expressed as follows[7]:

$$\alpha \frac{\partial P_{o_2}}{\partial t} = D\alpha \left(\frac{\partial^2 p_{o_2}}{\partial r^2} + \frac{\partial^2 p_{o_2}}{\partial z^2} \right) - u\alpha \frac{\partial^2 p_{o_2}}{\partial r^2} - M \quad (2)$$

Where: p_{o_2} is the partial pressure of oxygen, α is the oxygen solubility, *D* is the oxygen diffusivity, and *M* is the oxygen consumption rate. The oxygen diffusion properties used in modeling oxygen distribution in blood vessels and tissue are taken from table (3) and table (4):

Table (3) Boundary properties (taken from He et al. [7])

Property		Inlet
Oxygen Partial Pressure	mm Hg	50

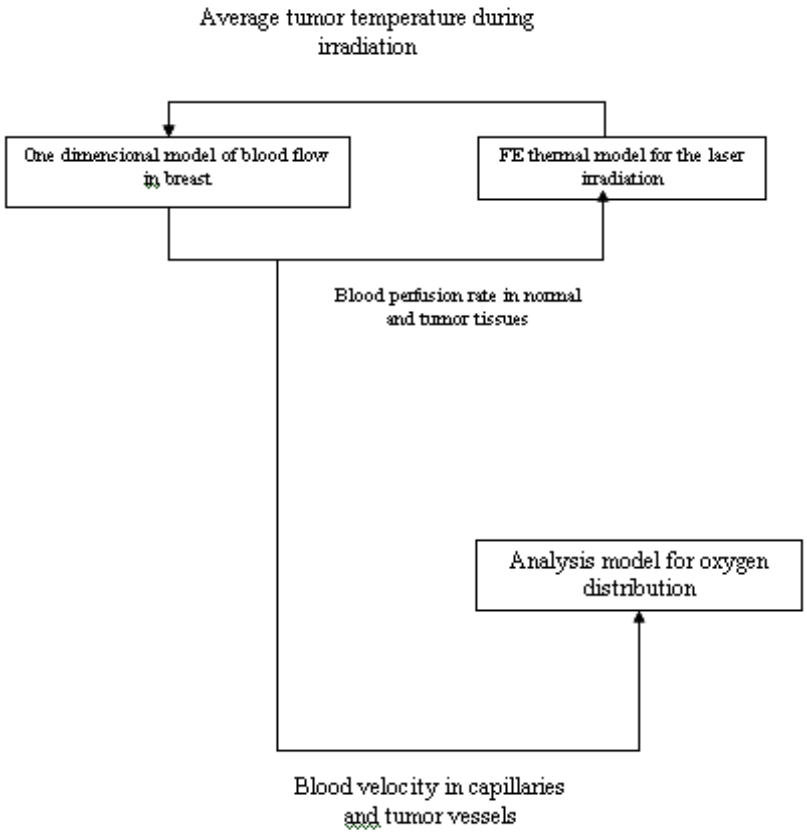
Table (4) Sub domain properties (taken from He et al. [7] and Yoshida et al[9]):

Properties		Blood	Tumor
Diffusion Coefficient	m^2/s	$1.86x10^{-9}$ [9]	$1.50x10^{-9}$ [7]
Reaction Rate	mol/m^3*s	0	-1.1 [7]

5- Coupling Equation:

In order to solve the above-mentioned hyperthermia-tissue–blood flow interaction problem formulated above, the weak coupling method was employed.

Fig. 4 The data transfer between the models



As shown in Figure (4) first, the blood pressure and the flow rate in different vessels are computed through the blood circulation model of the breast.

It has been observed that heating a tumor at 41–42^{o}C for a duration can induce an approximately two-fold increase in the tumor blood flow. Therefore, the response of the blood vessels to the tumor temperature is assumed to be [7]:

$$A = A_0 e^{b(T-T0)} \qquad (3)$$

Where A_0 and T_0 are the cross-sectional area and blood temperature before heating, respectively, and b is the variation coefficient.

Based on the experimental results, the value of b may be expressed as follows [7]:

$b = 0.1$ $T = 39.42\ ^{o}C$,

$b = -0.1$ $T > 42\ ^{o}C$,

Since the cross-sectional area of the blood vessels in the heating area under different tumor average temperatures is computable according to [9], the new blood perfusion due to a change in the blood vessel dimensions can be obtained by the one-dimensional blood circulation

model and may be transferred to the FE model instead of the old values. Simultaneously, the new blood velocities are input to the oxygen analysis model for the computation of oxygen partial pressure in the normal and tumor tissue units.

After initializing the tumor blood flow simulation with steady-state solutions of the flow and diffusion governing equations, transient flow and diffusion analysis was performed in which the time-varying capillary radius was implemented as a moving boundary in the capillary/tissue geometry. The resulting oxygen concentration surface plot Figure 5(a) showed significantly increased tissue oxygen concentration relative to the steady-state solution Figure 5(b).

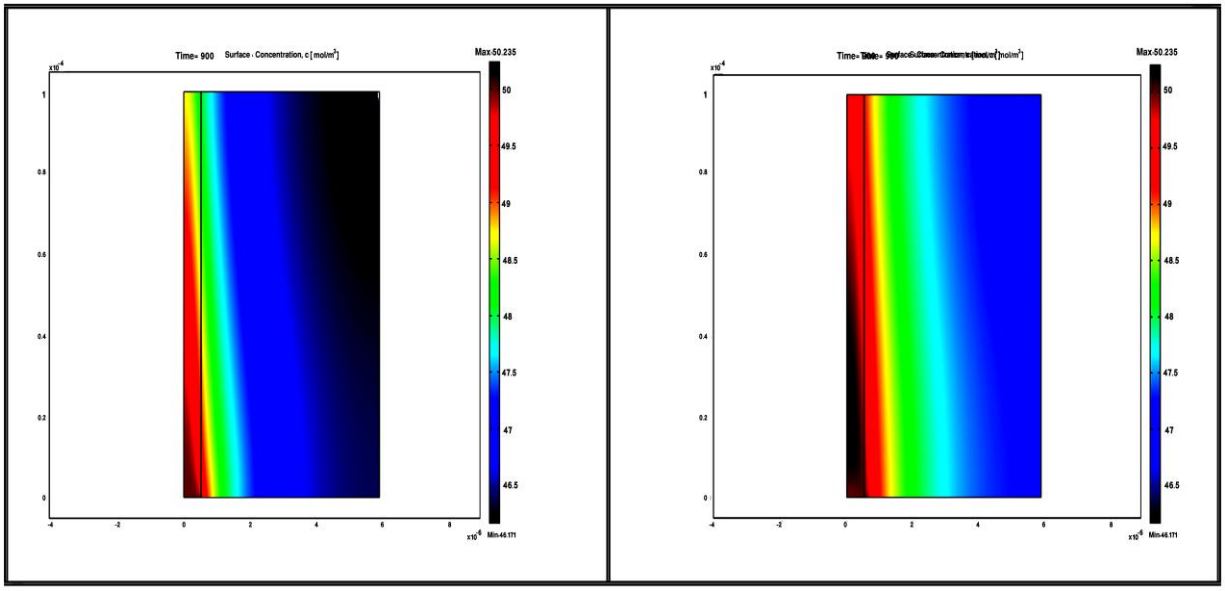


Fig. 5 The oxygen concentration surface plot in the tumor capillary and tissue a) at steady state and b) following 900s of laser heating.

This result follows intuition, since increasing capillary radius while maintaining a constant pressure drop across the capillary increases volumetric blood flow through the capillary and thus total oxygen flux into the capillary, which leads to increased oxygen delivered to the tissue.

By plotting partial pressure of oxygen as a function of radius r at three different points in the tissue Figure (6), we observed that the oxygen concentration was greatest near the inlet and lowest near the outlet (as expected), and that at all three sections of the tissue, heating increased the tissue oxygen concentration to about the same extent. These plots were again found to be in close agreement with data reported by He et al. [7], confirming the validity of our model.

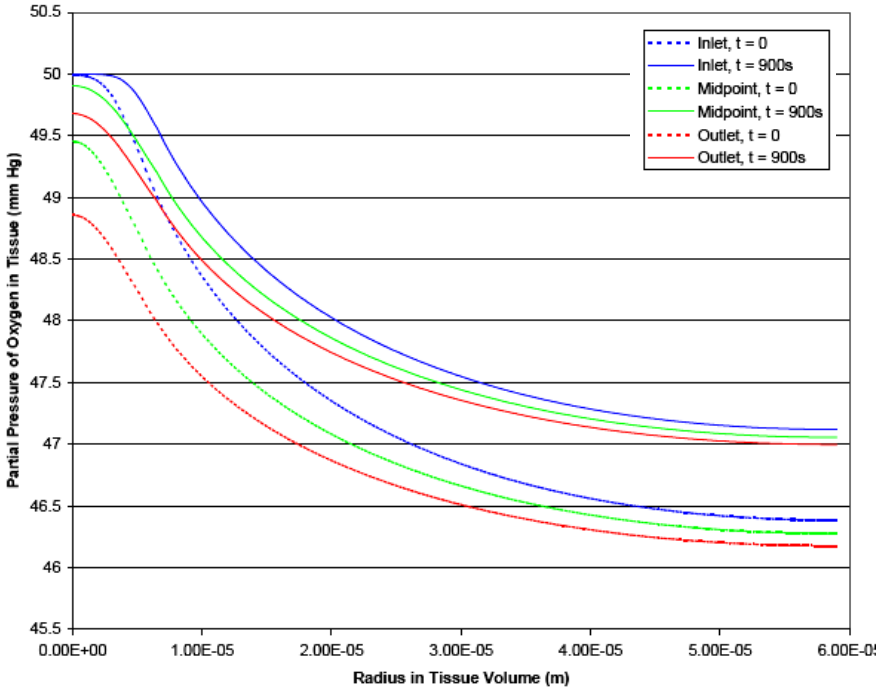


Fig. 6. Partial pressure of oxygen as a function of radius in tissue at a) "inlet": x = 0.01 mm b) "midpoint": x = 0.05 mm c) "outlet": x = 0.09 mm.

6- Sensitivity Analysis of the Models

1.1 Heating Time:

We tested heating times of 0, 150, 300, 600, and 900 seconds and plotted the partial pressure of oxygen as a function of radius r at x = 0.05 mm (tissue midpoint). From the plots Figure (7), we saw that laser heating increased tissue oxygen concentration significantly (relative to before heating, shown as the blue dashed line) after only 150s, and after 600s of treatment, the oxygen concentration profile in the tissue reached a near-steady state.

Hence, tissue oxygen concentration was found to be very sensitive to heating time initially, and then virtually insensitive to it after a certain threshold (~600s).

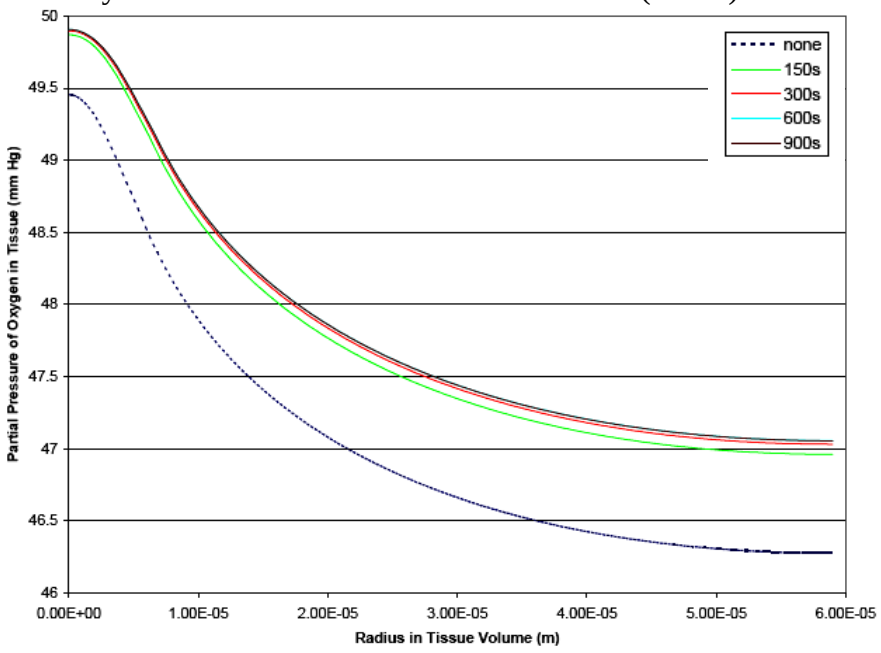


Fig. 7. Oxygen concentration profile at tissue midpoint following heating for various heating periods.

1.2 Diffusivity of Oxygen in Blood and Tissue:

In order to investigate the sensitivity of our model to diffusivity values for oxygen in blood and tissue, we varied the literature values (1.86×10^{-9} m^2/s and 1.50×10^{-9} m^2/s for blood [9] and tissue [7], respectively) by +/- 20% and observed the resulting oxygen concentration profiles at the tissue midpoint (Figure 8-9). We observed that varying the diffusivity of oxygen in blood had a very minor effect on our results: varying the parameter by +/- 20% resulted in only about +/- 0.1% difference in the average p_{o2} at the tissue midline after 900s of heating. Hence, our model showed little sensitivity to the diffusivity of oxygen in blood. However, varying the diffusivity of oxygen in tissue by +/- 20% resulted in about +/- 1% difference in the average p_{o2} at the tissue midline after 900s of heating. Hence, our model was found to be about one order of magnitude more sensitive to the diffusivity of oxygen in tissue than the diffusivity of oxygen in blood.

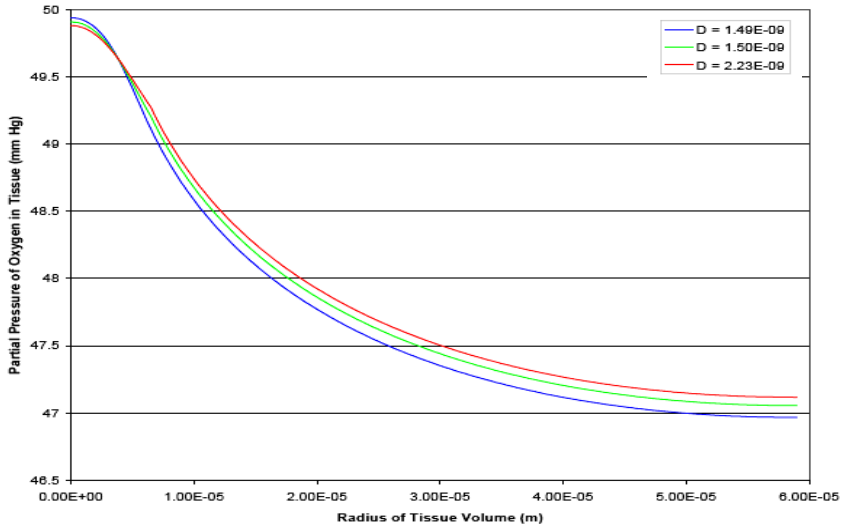


Fig. 8. Oxygen concentration profiles at the tissue midpoint for varying values of diffusivity of oxygen in blood.

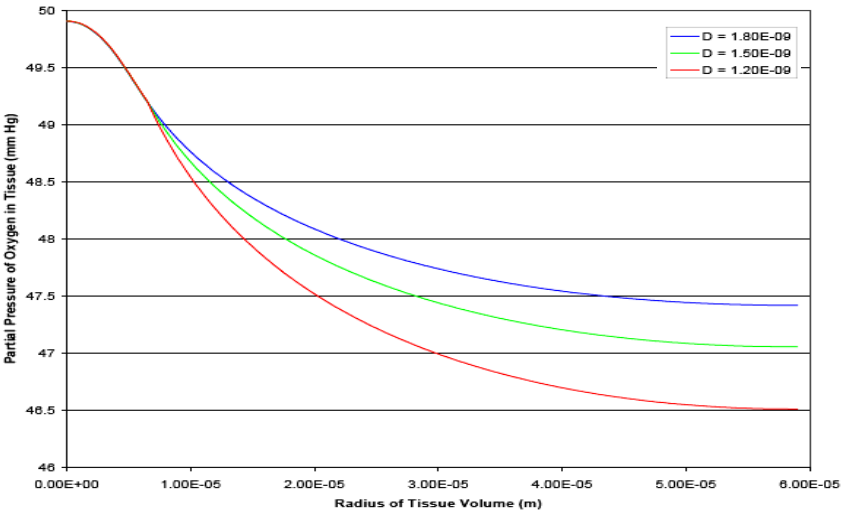


Fig . 9. Oxygen concentration profiles at the tissue midpoint for varying values of diffusivity of oxygen in tissue

6.3 Laser Intensity:

In order to both examine the sensitivity of our model to laser intensity and determine an optimal laser intensity to be used in hyperthermia treatment of breast tumors, we varied the laser intensity used (13000 W/m^2) by +/- 20% and 40% and examined the effect the blood flow and oxygen concentration in the tumor as a result of change of temperature.

In order to gauge the effect of treatment with laser intensity of 18000 W/m^2 on tissue oxygen concentration, we ran the moving mesh blood flow model for a simulation time of 900s using blood vessel radius values determined from the I = 18000 W/m^2 curve above. Results are shown below.

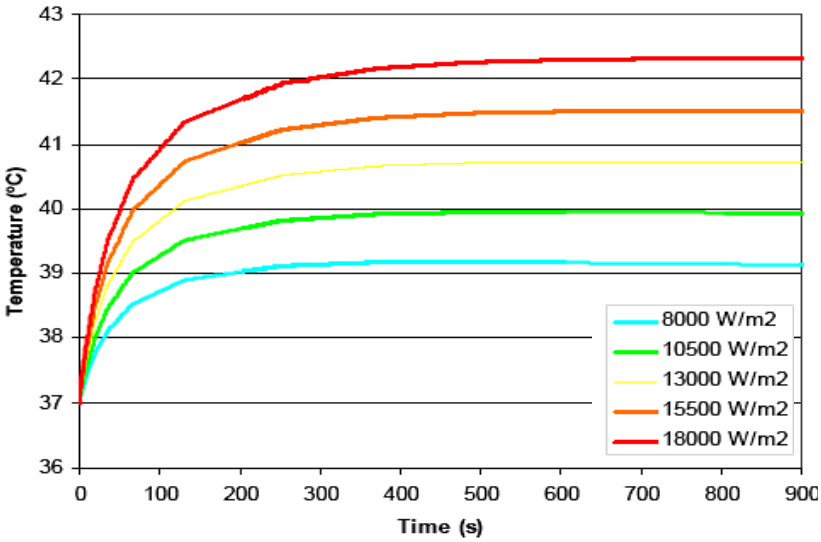


Fig. 10. Average tumor temperature over time during irradiation with laser of various intensities.

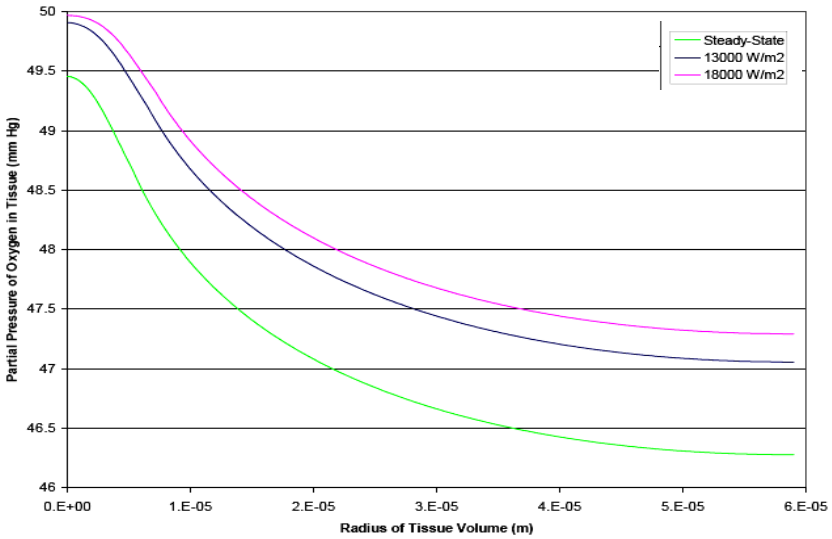


Fig. (11) Oxygen concentration profiles at the tissue midpoint before laser treatment (steady-state) and for 900s of laser irradiation at 13000 W/m^2 and 18000 W/m^2.

Relative to treatment with laser at 13000 W/m^2, only about 0.5% difference in average tissue partial pressure of oxygen was observed when a laser intensity of 18000 W/m^2 was used. Hence, our model is only moderately sensitive to laser intensity at the tissue oxygen concentration level, as a 40% increase in laser intensity brought about only a 0.5% increase in average tissue oxygen levels. It can also be seen that relative to steady-state conditions, treatment with 18000 W/m^2 laser for 900s resulted in ~1 mm Hg difference in tissue oxygen partial pressure far from the capillary. Since this is the difference in tissue oxygen levels associated with raising the average tumor temperature from 37ºC to about 42.5ºC (as has been shown to be effective for hyperthermia treatment), it can be concluded that, according to our model, a difference in tissue oxygen partial pressure of only about 1 mm Hg may be significant.

7- Conclusions and Discussions:

We have developed finite element models of a female breast with tumor and a plug of tumor tissue with a capillary whose radius varies with temperature in order to study the effects of laser irradiation on tissue oxygen levels in the tumor. Our model, which was validated primarily by comparison to a very similar albeit more complex model, clearly shows that laser irradiation of a breast tumor for over 600s can increase the partial pressure of oxygen in the tissue by 0.75 – 1 mm Hg. That is, with no treatment the P_{02} level is 0.75 – 1 mm Hg lower than in the case of any amount of laser irradiation. While such a slight change may seem unimportant, the impact of such a change is difficult to quantify without experimentation because of the complexity of coupling radiation therapy with our current model.

Indeed, in the literature there does not seem to be any specific percent decrease in tissue oxygen levels that correspond to increased radio sensitivity. However, experimental evidence shows that laser treatment for an hour at around 42.5ºC is ideal for hyperthermia treatment [10].

Again, while we were unable to use a target tissue oxygen level for treatment optimization purposes, we contend that the model we have developed may be useful for this purpose once adequate experimental data is available. In addition, a model of radiation therapy could be added to it in order to directly predict the effect of laser irradiation on radio sensitivity of tumor cells.

Hyperthermia treatment is attractive because it increases the sensitivity of tumor cells to radiation treatment and thus increases its efficacy.

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