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INFLUENCE OF VASCULAR STASIS BASED BLOOD PERFUSION ON MAGNETIC NANOPARTICLES MIGRATION USING MODIFIED THERMAL DAMAGE MODEL: AN ILLUSTRATION OF THERMAL BY-STANDER EFFECT

Manpreet Singh

Department of Mechanical Engineering,
University of Maryland Baltimore County,
Baltimore, MD, USA

INTRODUCTION

MicroCT imaging assisted *in-vivo* animal studies have suggested possible change in nanoparticle distribution after heating[1]. The redistribution of nanoparticles from the region of higher concentration to the region of lower concentration is described as *"Thermal By-Stander Effect"*[1,6].

One hypothesis[7] suggests the possibility of continuous regeneration of living human tissues due to meeting of oxygen demands through arterial blood. Hence, due to this regeneration process, the biological tissues shows an accelerated tissue repair and recovery with an evident rise in blood perfusion levels. Previous studies[2-3] implemented regeneration term into Arrhenius formulation; however, effect of hyperemic region through vascular stasis (non-linear perfusion change[4-5]) is missing for such regeneration based model.

This study incorporates vascular stasis based blood perfusion for magnetic nanoparticle assisted thermal therapy to model the thermal by-stander effect using modified thermal damage model with regeneration.

METHODS

Pennes Bioheat Transfer Equation[6] (PBHTE) is used to compute the temperature field distribution in both the healthy, *h* and cancerous, *c* tissue domains respectively as per equations (1a) and (1b);

$$\rho_h c_h \frac{\partial \mathrm{T}_h}{\partial \mathrm{t}} = k_h \nabla^2 \mathrm{T}_h + \omega_{h,0} \rho_b c_b (\mathrm{T}_b - \mathrm{T}_h) + Q'''_{met,h} \quad (1a)$$

$$\rho_c c_c \frac{\partial \mathrm{T}_c}{\partial \mathrm{t}} = k_c \nabla^2 \mathrm{T}_c + \omega_{c,0} \rho_b c_b (\mathrm{T}_b - \mathrm{T}_c) + Q'''_{met,c} + Q'''_{source} \quad (1b)$$

Here, the subscripts *b* and *met* represents blood and metabolic heat generation respectively. The thermophysical properties for biological tissue domains are shown in Table-II. Contribution of heterogeneously distributed magnetic nanoparticles are extracted from MicroCT images from pixel value information known as Specific Absorption Rate (SAR) mapped at different tumour locations. This source term[6] is coupled with Concentration as $Q'''_{source}(x,y,z,t) = 2266.67 \times C(x,y,z,t)$. The governing equation for nanoparticle diffusion is given as;

$$\frac{\partial C(x,y,z,t)}{\partial t} = \nabla \cdot \left[\phi D_n \nabla \left(\frac{C(x,y,z,t)}{\phi} \right) \right] \quad (2)$$

where, the diffusion coefficient (D_n) relates to interstitial space (ϕ) and diffusion coefficient in unbound interstitial fluid ($D_{n,f}$) as;

$$D_n = D_{n,f} \left[\frac{2\phi}{3-\phi} \right] \quad (3)$$

The interstitial space tends to increase with the cell-necrosis as;

$$\phi = \phi_o + (80\% - \phi_o)\left(1 - e^{-\Omega(\mathrm{x,y,z,t})}\right) \quad (4)$$

Spatio-temporal thermal cell-death, Ω(dimensionless) can be computed as per first-order traditional Arrhenius equation;

$$\Omega(x,y,z,\tau) = \int_0^\tau A e^{-E_a/R_u T(x,y,z,t)}\, dt \quad (5)$$

The Arrhenius kinetic rate equation is recently modified[1-3] to account for regeneration of healthy cells. The modified thermal damage is;

$$\frac{d\Omega(\mathrm{x,y,z,t})}{d\mathrm{t}} = A\left(1 - \Omega(x,y,z,t)\right) \exp\left(\frac{-E_a}{R_u T(x,y,z,t)}\right) - B\omega_{c,0}\Omega(x,y,z,t) \quad (6)$$

where, R_u is the universal gas constant 8.314 J/(mol·K), τ is the duration of exposure(s), T is the temperature (K), B is a dimensionless coefficient[2] (9×10^{-3}). The thermal damage parameter, $\Omega = 1$ represents 63.21% of denaturation of proteins sufficient to initiate coagulation. It should be noted that the induced thermal damage is zero before the onset of nanoparticle assisted heating.

It is well known that during heating, the blood perfusion rate, $\omega_{c,0}(t)$ first increases at hyperthermic temperature due to vasodilation of vessels and then starts decreasing due to total collapse of vasculature[5]. This phenomenon is known as "*degree of vascular stasis*" or "*vascular collapse*" or "*fractional injury*" or "*vascular stasis*". The functional dependence of $\omega_{c,0}(t)$ on VS is shown in fig. 2 and Eq. 7 as;

$$\omega_{c,0}(t) = \begin{cases} \omega_{b,o}(1 + 30 \cdot \mathrm{VS}); & for\ 0 < \mathrm{VS} \le 0.02 \\ \omega_{b,o}(1.86 - 13 \cdot \mathrm{VS}); & for\ 0.02 < \mathrm{VS} \le 0.08 \\ \omega_{b,o}(0.884 - 0.79 \cdot \mathrm{VS}); & for\ 0.08 < \mathrm{VS} \le 0.97 \\ \omega_{b,o}(3.87 - 3.87 \cdot \mathrm{VS}); & for\ 0.97 < \mathrm{VS} \le 1.00 \\ 0; & for\ \mathrm{VS} > 1.00 \end{cases} \quad (7)$$

VS can be mathematically expressed as

$$\mathrm{VS}(x, y, z, t) = 1 - \exp(-\Omega(x, y, z, t)) \quad (8)$$

Here, the baseline value of blood perfusion, $\omega_{b,o}$ is extracted from the thermal infrared imaging by adjusting the metabolic heat generation rates and blood perfusion values using inverse heat transfer analysis[6]. The Arrhenius kinetic coefficients used to evaluate the vascular stasis (VS) and thermal damage (Ω) are summarized in Table-I.

Table-I: Arrhenius coefficients considered in this study[1-5].

Parameters	Symbol [Units]	Vascular Stasis	Thermal damage
Frequency factor	A [s^{-1}]	1.98×10^{106}	3.1×10^{98}
Activation Energy	E_a [$Jmol^{-1}$]	6.67×10^5	6.28×10^5

#bulk tissue consideration.

Table-II: Thermophysical properties[6].

Property	Symbol [Units]	Healthy Tissue	Cancerous Tissue	Blood
Thermal conductivity	k [W/(mK)]	0.5	0.5	0.55
Density	ρ [kg/m^3]	1060	1060	1060
Specific heat capacity	c [J/(kgK)]	3780	3780	3780
Baseline blood perfusion	ω_b [m^3/(sm^3)]	0.00285#	0.00111#	–
Metabolic heat generation	Q_{met} [W/m^3]	9265#	3602#	–
Porosity	ϕ [-]	–	20%	–
Diffusion coefficient in unbound interstitial fluid	$D_{n,f}$ [m^2/s]	–	9.57×10^{-12}	

#extracted from thermal imaging using inverse heat transfer analysis.

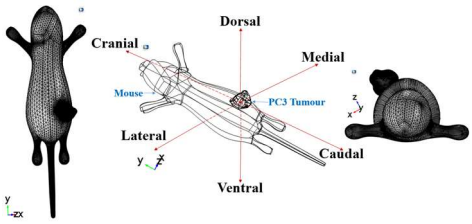
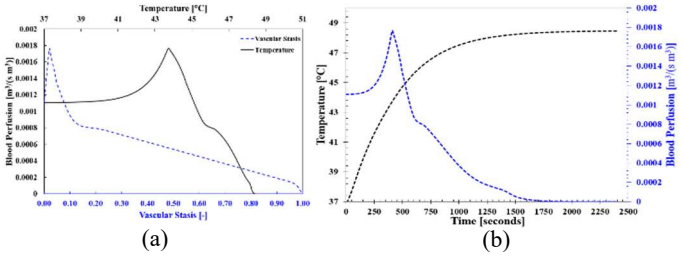


Figure 1. Wireframe and meshed model of mouse and PC3 tumour.



(a) (b)

Figure 2. Blood perfusion variation on vascular stasis and temperature at minimal temperature location.

RESULTS AND DISCUSSION

Fig.1. shows the wireframe and meshed model of PC3 tumour attached to the flank position of mouse. In this problem formulation, the blood perfusion of cancerous lesion is defined as a piecewise function of vascular stasis as per equation 7 and pictorially represented in fig. 2(a). It can be inferred from fig. 2(a) that the maximum peak of perfusion is achieved at 43.5°C. From fig. 2(b), perfusion collapse occurs at minimal temperature location takes 1750 sec. Fig. 3 illustrates temperature (T_{max}=83.13°C, T_{min}=48.46°C, T_{avg}=67.23°C), modified thermal damage with healthy tissue regeneration ($\Omega_{modified}$=1), diffusion coefficient (4.87×10^{-11}m^2/s), vascular stasis (VS=1), and porosity (80%) after 2400 sec. The probe is located at minimum temperature location to monitor these parameters. It is noticeable from fig. 3 that there is 39.62% increase in redistribution volumes of nanoparticles and five-fold increase in diffusion coefficient after heating of 2400 sec. The implementation of equation 4 is verified through fig. 3(e) that maximum interstitial space of 80% inside PC3 tumour can be achieved after thermal cell-death of 63.2%. The physical interpretation of this regeneration term implies that thermal damage would not propagate deep inside the healthy tissue fringes. Thus, it can inferred that regeneration phenomenon prevents and suppress the collateral thermal damage spread at the interface within bounds of Ω≤1 which is in agreement with the findings of literature[3-5].The implication of this work would help design better heating protocol designs in future. However, more experimental exploration is needed in this context.

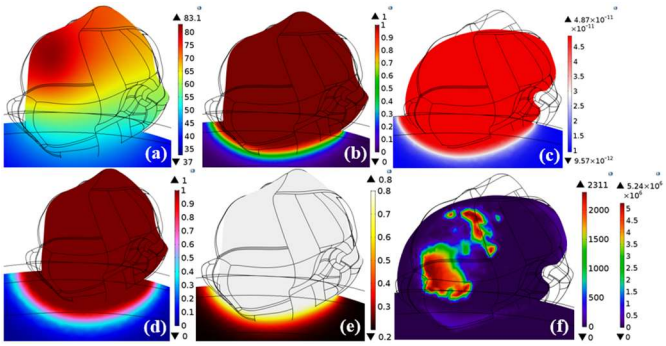


Figure 3. (a) Temperature [°C], (b) Modified thermal damage [-], (c) Diffusion coefficient [m^2/s], (d) Vascular stasis [-], (d) Porosity [-] at 2400 sec and (e) Initial concentration distribution [mol/m^3] and Nanoparticle heat generation rate [W/m^3].

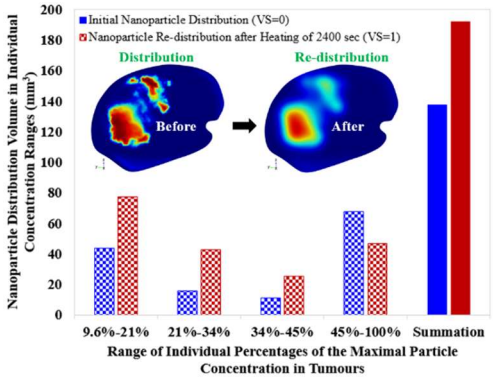


Figure 4. Nanoparticle distribution volumes in individual nanoparticle concentration ranges before heating-left patterned bars (VS=0) and after heating-right patterned bars (VS=1).

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