SB³C2022
Summer Biomechanics, Bioengineering and Biotransport Conference
June 20-23, Eastern Shore, MD, USA

INCORPORATING VASCULAR STASIS BASED PERFUSION TO PREDICT THE THERMAL SIGNATURES OF CELL DEATH USING MODIFIED ARRHENIUS EQUATION WITH REGENERATION OF LIVING TISSUES

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INTRODUCTION

The thermal damage predictions by first-order Arrhenius kinetic rate equation gives us monotonic degradation of living tissues alongwith cancerous lesions. For low temperature hyperthermia (T≤41℃) i.e. at diathermic temperatures, biological tissues shows an accelerated tissue recovery and repair with an evident rise in blood perfusion levels and associated metabolic demands. At the temperature range of 40-42℃, some transformations and molecular-level changes in tumour cells might have been already initiated. According to the hypothesis of Dombrovsky et al., 2015 [1]; continuous regeneration of living human tissues due to the continuous supply of oxygen through arterial blood must be taken into account to counter balance the thermal degradation at quasi-static thermal conditions. However, previous studies [2-3] implemented regeneration term into Arrhenius formulation; however, to incorporate the effect of hyperemic region through vascular stasis (fractional injury) based non-linear perfusion change [4-5] is not addressed for such regeneration based model. This study aims to investigate this issue in the context of magnetic nanoparticle assisted thermal therapy.

METHODS

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

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

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

Here, the subscripts, *h* and *c* represents healthy and cancerous tissue domains respectively. Also, *met* represents metabolic *b* represents blood and *source,* is the heat source contribution of heterogeneously distributed magnetic nanoparticles [6] known as Specific Absorption Rate (SAR) mapped at different tumour locations (refer **fig.1**).

It is well known that during heating, the blood perfusion rate first increases at hyperthermic temperature due to vasodilation of vessels and then starts decreasing due to total collapse of vasculature due to thermal damage. This phenomenon is known as "*degree of stasis*" [5]. In this problem formulation, the blood perfusion of cancerous lesion is defined as a piecewise function of vascular stasis as per **equation 2** and **fig. 2**;

$$\omega_{c,0}(t) = \begin{cases} \omega_{b,o}(1 + 30 \cdot \Theta); & for\ 0 < \Theta \leq 0.02 \\ \omega_{b,o}(1.86 - 13 \cdot \Theta); & for\ 0.02 < \Theta \leq 0.08 \\ \omega_{b,o}(0.884 - 0.79 \cdot \Theta); & for\ 0.08 < \Theta \leq 0.97 \\ \omega_{b,o}(3.87 - 3.87 \cdot \Theta); & for\ 0.97 < \Theta \leq 1.00 \\ 0; & for \Theta > 1.00 \end{cases} \quad (2)$$

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 to match the thermal maps of infrared images [6]. The degree of vascular stasis (collapse of vasculature) can be calculated as per **equation (3)**;

$$\Theta(\mathrm{x}, \mathrm{y}, \mathrm{z}, \mathrm{t}) = 1 - \exp(-\Omega(\mathrm{x}, \mathrm{y}, \mathrm{z}, \mathrm{t})) \quad (3)$$

As per the traditional Arrhenius equation, the spatio-temporal thermal cell-death parameter, Ω (dimensionless), can be computed as per **equation (4)**;

$$\Omega(x, y, z, \tau) = \ln\left\{\frac{C(0)}{C(\tau)}\right\} = \int_0^{\tau} A e^{-E_a/R_g T(x,y,z,t)}\, dt \quad (4)$$

where, C represents concentration of cells, R_g is the universal gas constant ($8.314\ J/(mol \cdot K)$, τ is the duration of exposure(s), T is the temperature (K). 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. According to Rai and Srivastava, 2009 [7]; Ω=0 represents no burn, Ω=0.5 first degree burn, Ω=1 shows

approaching second degree burn and $\Omega=10^4$ represents third degree burn. The Arrhenius kinetic coefficients used to evaluate the degree of vascular stasis, Θ are summarized in **Table-I**. It is to note that these coefficients of vascular collapse or vascular shut-down are specific to perfusion changes and must not be compared with thermal damage coefficients reported in this context of work on thermal ablation [4-5].

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

The Arrhenius kinetic equation is recently modified by Dombrovsky and Timchenko, 2015 [1] and later revisted and implemented by Kumar and Rai, 2016 [2] and Liu and Chen, 2021 [3]. One additional term is introduced in Arrhenius equation to account for regeneration of the healthy cells. Thermophysical properties can be referred from **Table-II.**

$$\frac{d\Omega(x,y,z,t)}{dt} = A\big(1-\Omega(x,y,z,t)\big)\exp\left(\frac{-E_a}{R_g T(x,y,z,t)}\right) - B\omega_{c,o}\Omega(x,y,z,t) \qquad (5)$$

where, B is a dimensionless coefficient= 9×10^{-3}[2].

Table-II: Thermophysical properties [6].

Property	Symbol [Units]	Healthy Tissue	Cancerous Tissue	Blood
Thermal conductivity	k [W/(m K)]	0.5	0.5	0.55
Density	ρ [kg/m^3]	1060	1060	1060
Specific heat capacity	c [J/(kg K)]	3780	3780	3780
Baseline blood perfusion	ω_b [m^3/(s m^3)]	0.00285#	0.00111#	-
Metabolic heat generation	Q_{met} [W/m^3]	9265#	3602#	-

#extracted from thermal imaging using inverse heat transfer analysis.

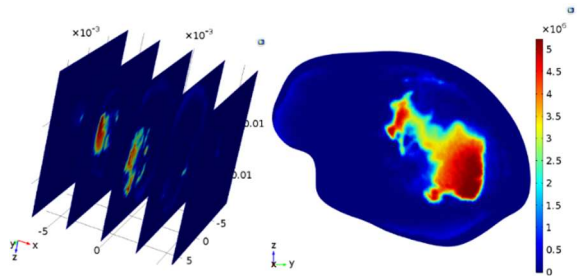

Figure 1. Heterogeneously distributed magnetic nanoparticles-SAR.

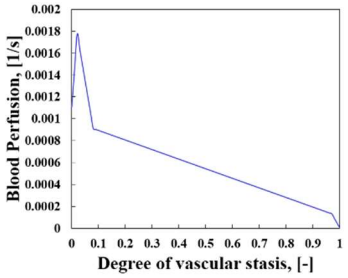

Figure 2. Perfusion dependence on stasis.

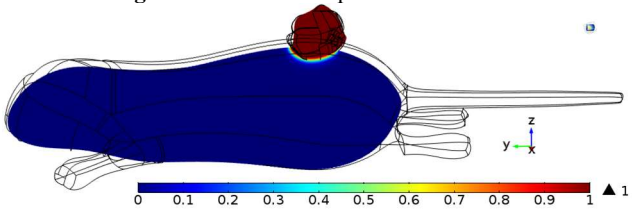

Figure 3. Modified thermal damage incorporating the effect of regeneration term thereby preserving healthy tissues at interface.

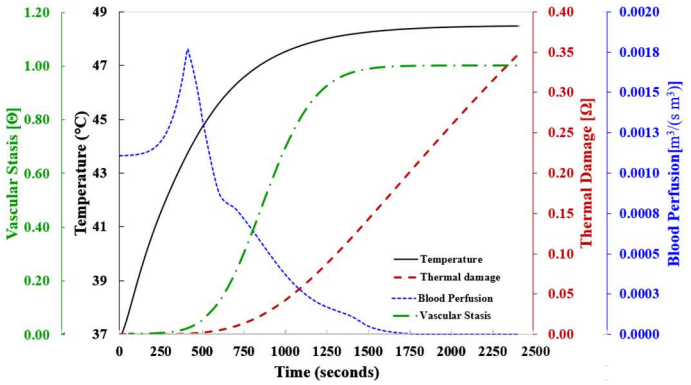

Figure 4. Perfusion, Vascular stasis, Thermal damage, Temperature variations at minimal temperature location of tumour.

RESULTS AND DISCUSSION

Perfusion mediated heat-sink impairs the efficacy of cancer treatment. Vascular stasis based perfusion variation is a predictive indicator of cancer response to the thermal treatment. **Fig. 4** demonstrates spatio-temporal variation of parameters: $\omega_{c,0}$, Θ, Ω and T at the minimum temperature location. Modified thermal damage is computed via **equation (5)** (shown in **fig. 3**) is in agreement with the results of Dombrovsky et al., 2015 [1]. The inclusion of regeneration of living tissues to compute the thermal signatures of cell-death suggests that the modified Arrhenius equation seems to restrict within the damage limits of $\Omega = 1$ (63.21% denaturation of protein). 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 which is in agreement with the findings of literature [3-5]. We speculate that for a tumour needs to be treated within the hyperthermic temperature range, it will not only predict accurate ablation volumes but also restricts the damage propagation front to cross the fringe layers at the interface of tumour and healthy tissue. Such a model based on vascular shunt-off is a real assessment of the thermal damage spread within bound of $\Omega = 1$. The implication of this work would help design better heating protocol designs in future. However, more experimental exploration is needed in this context. Similar simulation approach can be utilized by the physicians in clinical treatment planning to address the likelihood of achieving complete thermal ablation at cancerous lesion while sparing the critical surrounding organs. For the deadliest cancers like Glioblastomas, or chest wall recurrence (CWR) where the clinical margins are not enough to be sacrificed, these estimates will aid in better treatment planning.

ACKNOWLEDGEMENTS

The author would like to thank the Graduate School, UMBC for conferring the award of Dissertation Fellowship towards the progress of Doctorate degree and the Department of Mech. Engg. for the usage of computational facilities.

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