SB^{3}C2019
Summer Biomechanics, Bioengineering and Biotransport Conference
June 25 -28, Seven Springs, PA, USA

THEORETICAL EVALUATION OF TEMPERATURE ELEVATION, THERMAL DAMAGE, TRANSPORT POROSITY ENHANCEMENT, AND MAGNETIC NANOPARTICLE MIGRATION IN TUMORS DURING LOCAL HEATING

Manpreet Singh, Ronghui Ma, Liang Zhu

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

INTRODUCTION

Recent microCT imaging study[1] has demonstrated different patterns of nanoparticle distribution by local heating. A much larger nanoparticle distribution volume in tumors after heating was observed than that in tumors without localized heating, suggesting possible nanoparticle redistribution/migration during heating. It is unclear what kinds of mechanisms resulted in the nanoparticle migration from high concentration region to low concentration region. It has been speculated that an increase in nanoparticle diffusion coefficient may play an important role here. It is possible that the intracellular solution is released from the dead cells after cell membrane raptures. The relationship between diffusion coefficient and porosity of tumors suggest a 3.5 fold increase in nanoparticle diffusion coefficient if the porosity is elevated from 20% to 60%.

In this study, we develop a 1-D model to evaluate to what extent the enhanced nanoparticle diffusion coefficient leads to an increase in the nanoparticle distribution volume in tumors after local heating. The Pennes bioheat equation is used to simulate temperature elevations in a tumor with magnetic nanoparticle deposition, when it is subject to an alternating magnetic field. The blood perfusion rate and metabolism in tumors, and local tumor porosity are coupled with local thermal damage using the Arrhenius integral. Finally, the diffusion equation is implemented to simulate possible spreading of nanoparticle, providing a dynamic volumetric heat generation rate distribution in the heat transfer simulation. Results from the 1-D model may be extended to 3-D situations of nanoparticle redistribution in magnetic nanoparticle hyperthermia based on realistic microCT scans of tumors.

METHODS

A spherical tumor (10 mm in radius, initial porosity φ_0=0.2) is proposed for this study. The tumor is exposed to a convection environment (h=10 W/m^{2}K, T_{air}=25°C), and magnetic nanoparticles originally injected occupy a smaller spherical region (4 mm in radius) at the tumor center. The volumetric heat generation rate distribution Q'''_{MNH} was initially uniformly distributed in the small spherical region as 1.38*10^6 W/m^3. The Pennes bioheat equation[2] in 1-D spherical coordinates used to simulate the transient temperature field during magnetic nanoparticle hyperthermia:

$$\rho c\frac{\partial T}{\partial t}=\frac{k}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right)+\frac{\omega_0}{e^{\Omega}}\rho_b c_b(37-T)+\frac{Q'''_{m,0}}{e^{\Omega}}+Q'''_{MNH} \quad (1)$$

All the thermal properties in Eq. 1 such as density ρ (1000 kg/m^3), specific heat c (3500 J/kgK), thermal conductivity k (0.64W/mK), blood perfusion rate ω_0 (0.00083 1/s) and metabolism $Q'''_{m,0}$ (2708 W/m^3) are the same as that in Lebrun et al.[3] In Eq. 1, both the blood perfusion rate and metabolism decrease as the increase in the local thermal damage, defined by the Arrhenius integral Ω:

$$\Omega(r,t)=A\int_0^t \exp\left[-E_a/R_u T(r,\tau)\right]d\tau \quad (2)$$

Q'''_{MNH} in Eq. 1 is directly proportional to the local volume-averaged nanoparticle concentration C (mol per unit volume of tissue) as:

$$Q'''_{MNH}(r,t)=2266.67*C(r,t) \quad (3)$$

Thermal damage to tissue also results in an increase in the porosity φ from its original value φ_0 as:[4]

$$\varphi(r,t)=\varphi_0+(100\%-\varphi_0)(1-e^{-\Omega(r,t)}) \quad (4)$$

The governing equation for nanoparticle diffusion is written as

$$\frac{\partial C}{\partial t}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(\varphi D_n r^2\frac{\partial(C/\varphi)}{\partial r}\right) \quad (5)$$

where the diffusion coefficient D_n is a function of the interstitial space fraction (porosity) φ:[4]

$$D_n=D_{n,f}\left[2\varphi/(3-\varphi)\right] \quad (6)$$

where $D_{n,f}$ is the nanoparticle diffusion coefficient in interstitial fluid.

The initial temperature field in the tumor is assumed uniform as 37°C, and the initial nanoparticle concentration C_0 in the small sphere is 608.899 mol/m^3. Heating duration is set as 25 minutes (1500 seconds). The coupled equations (Eqs. 1-6) are solved simultaneously using COMSOL software.

RESULTS

Figure 1 shows temperature and thermal damage contours at various time instants during heating. The maximal temperature occurs at the tumor center and reaches 57°C after heating of 25 minutes. The thermal damage defined as $\Omega \geq 4$ with the dark red color. Thermal damage region occupies a sphere with a radius of 3.3 mm after 1000 seconds of heating. At the end of 1500 seconds of heating, tumor cell within a spherical region with a radius of 4.8 mm are permanently damaged.

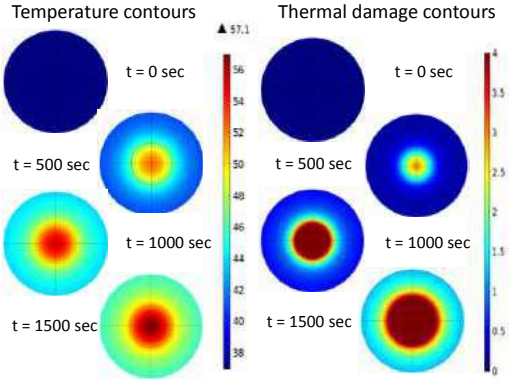

Figure 1: Temperature distribution (left) and thermal damage region (right) in the tumor during heating

The results of the spatially and temporally varying porosity and nanoparticle diffusion coefficient are updated during the heating, shown in Figure 2. Initially, the porosity is uniform everywhere as 20%, and it gradually increases as thermal damage spreads from the tumor center to its periphery. After 1000 seconds of heating, the porosity at the center increases to 93%. At the end of the heating session the porosity of most tumor region is 100%, suggesting permanent thermal damage. The change of the effective nanoparticle diffusion coefficient due to increase in porosity follows a similar trend (Figure 3) and the diffusivity at center increases from its initial value of $9.57*10^{-12}$ to $6.59*10^{-11}$ (m^2/s) after 1500 seconds of heating.

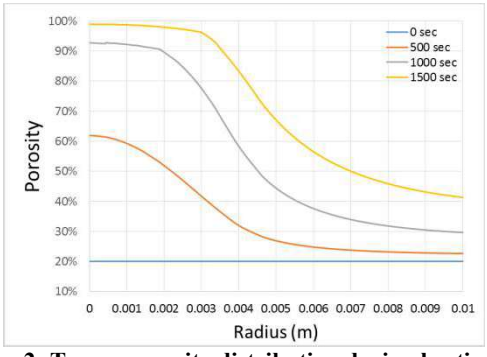

Figure 2: Tumor porosity distribution during heating

The nanoparticle distribution has been re-simulated based on the updated porosity and nanoparticle diffusion coefficient and the results are shown in Figure 4. The initial nanoparticle concentration profile is assumed as a quasi-step function. Once the thermal damage spreads towards the tumor periphery, significant nanoparticle diffusion occurs in the region with the maximum concentration gradient. As a result, it is observed that nanoparticles have diffused to the tumor periphery, expanding the tumor region containing nanoparticles from a spherical regions with a radius of 4 mm (t=0) to that with a radius of 4.7 mm at the end of the heating session. If one defines the nanoparticle distribution volume as a region containing a nanoparticle concentration ≥5% of the maximal nanoparticle concentration, a heating of 1500 seconds results in a nanoparticle distribution volume increase by approximately 62%.

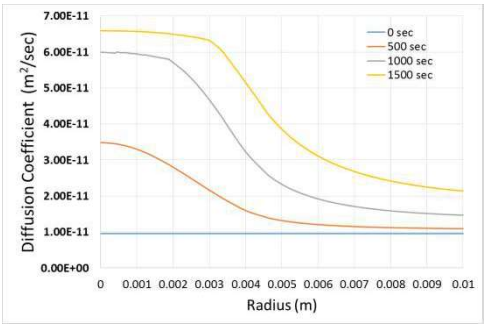

Figure 3: Distribution of the enhanced nanoparticle diffusion coefficient during heating

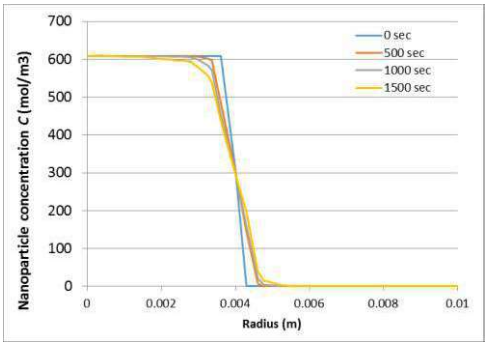

Figure 4: Nanoparticle concentration redistribution due to change in the tumor structure during heating

SUMMARY

In this study, a theoretical framework is developed, consisting of a nanoparticle diffusion model and a heat transfer model to address possible nanoparticle redistribution. Their dynamic interactions during magnetic nanoparticle hyperthermia treatment are evaluated via modified tumor porosity and diffusion diffusivity of nanoparticle concentration in porous tumors. The simulation results have shown that thermal damage induced nanoparticle redistribution has increased the tumor volume containing nanoparticles by 62%. This study demonstrates the feasibility of enhancing nanoparticle dispersion from injection sites using targeted thermal damage.

ACKNOWLEDGEMENTS

This research was supported by an NSF research grant (CBET-1705538). The research was performed in partial fulfilment of the requirements for the PhD degree by Manpreet Singh from the University of Maryland Baltimore County, Baltimore, Maryland, USA.

REFERENCES

[1] Gu et al., ASME *J Heat Transfer*, in press, 2019.
[2] Pennes, *Journal of Applied Physiology*, 1:93–122, 1948.
[3] Lebrun et al., *Journal of Thermal Biology*, 62:129-137, 2016.
[4] Zhang et al., ASME *J Heat Transfer*, 131(4):043209, 2009.