

HYPERTHERMIA EFFECTS ON MACROSCOPIC FLUID TRANSPORT IN TUMORS

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ABSTRACT Combining the effects of transvascular and interstitial fluid movement with the structural mechanics of a tissue is important to accurately describe processes such as nutrient transport in a tumor cell. Further, hyperthermia can have a role; for example, temperature variations can be induced in order to treat some kinds of tumors, like liver tumor. Recently, the study of the effects of hyperthermia on fluid flow and mass transport in biological systems by considering the fluid-structure interaction has gained researchers attention. In the present paper, fluid flow in a tumor mass is analyzed at a macroscopic scale by considering the effects of both solid tissue deformation and hyperthermia. Governing equations are averaged over a Representative Elementary Volume (REV) of the living tissue, and written by means of the thermo-poroelasticity theory. Darcy's law is used to describe fluid flow through the interstitial space, while transvascular transport is described with a generalized Starling's law. The effects of hyperthermia on the living tissue are included with a source term in the tissue momentum equation that considers the thermal expansion. Governing equations with the appropriate boundary conditions are solved with the finite element commercial code COMSOL Multiphysics in steady state regime. The numerical model is validated with analytical results from Netti *et al.* [1997] for an isothermal case. Results are presented in terms of pressure, velocity and temperature fields, for various thermal loads and the effect of hyperthermia on various physical parameters is analyzed.

NOMENCLATURE

Latin symbols

C_p	Heat capacity at constant pressure (J/kg·K)
e^*	Volumetric strain
k	Thermal conductivity (W/m·K)
K_h	Average tissue hydraulic conductivity (m ² /Pa·s)
L	Average hydraulic conductivity coefficient (m/Pa·s)
p	Interstitial fluid pressure (Pa)
p_v	Vascular pressure (Pa)
Q_{gen}	Hyperthermia heat source (W/m ³)
Q_{met}	Metabolic heat source (W/m ³)
r	Radial coordinate (m)
r^*	Dimensionless radial coordinate
R	Cell radius (m)
S/V	Surface to volume ratio (1/m)

T	Temperature (K)
\mathbf{u}	Velocity vector (m/s)
u, v	Velocity components (m/s)
\mathbf{x}	Solid displacement vector (m)

Greek symbols

α	Thermal expansion coefficient (1/K)
μ	Lamé parameter (Pa)
λ	Lamé parameter (Pa)
ρ	Density (kg/m ³)
ϕ	Porosity

Subscript

in	Initial
ref	Reference value

Superscript

*	Scaled
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INTRODUCTION

A biological tissue consists of a microvascular bed with blood flow through many vessels. As such it is quite natural to treat the living tissue as a porous medium [e.g., Khaled and Vafai 2003; Khanafer and Vafai 2006; Zhang 2009]. Thus, then porous media theory can be utilized for bioheat transfer analysis, in which fewer assumptions are needed as compared to the established bioheat transfer models [e.g., Khaled and Vafai 2003; Khanafer and Vafai 2006; Khanafer and Vafai 2009]. Hyperthermia occurs when the body produces or absorbs more heat than it can dissipate. This is usually due to excessive exposure to heat. Hyperthermia can also be produced artificially by medical devices and it may be used as a therapeutic method to bring about an artificial rise in temperature in certain types of cancer tissues [e.g., Jain 1987a], such as skin cancer [e.g., Wang *et al.* 2007], or vascular stent delivery [e.g., Stoeckel *et al.* 2004]. Up to now, various heating methods allowing hyperthermia to be produced, such as resistive heating with external electrodes [e.g., Lv *et al.* 2005; Tsuda and Kuroda 1996], microwaves [e.g., Zhu *et al.* 1998; Martin *et al.* 1992], ultrasound [e.g., Marmor *et al.* 1979] and lasers [e.g., Kim *et al.* 1996], have been used. The heat has to be applied directly to the tumor in order to prevent the damage to healthy tissue surrounding the tumor. The knowledge of the entire temperature field in the treatment region allows us to control the tumor heating. Understanding thermal transport and temperature distribution within biological organs is important for therapeutic aspects related to hyperthermia treatments [e.g., Keangin and Rattanadecho 2013] and cryogenics [e.g., Rabin and Plitz 2005; Rios and Rabin 2006]. Majchrzak *et al.* [2008] carried out the modelling of biological tissue heating by external electromagnetic field. To analyse the problem a simplified 2D mathematical model based on the Pennes equation supplemented with an equation determining the electric field produced by the external electrodes was built; at the same time, different values of electric field parameters were taken into account. The model was subjected to the numerical investigations using the boundary element method. It was underlined that the temperature differences and temperature gradients in the domain considered were rather small. Varon *et al.* [2015] carried out a numerical study under uncertainties of the treatment of cancer based on hyperthermia induced by radiofrequency electromagnetic waves, where the tumor is supposed to be loaded with nanoparticles. The focus of the paper is on the solution of the inverse problem dealing with the estimation of state variables, like the temperature distribution in the tissues.

Combining the effects of transvascular and interstitial fluid movement with the structural mechanics of a tissue is important to accurately describe processes such as nutrient transport in a tumor cell and hyperthermia can have an important role.

Recently, the study of the effects of hyperthermia on fluid flow and mass transport in biological systems by considering the fluid-structure interaction has gained researchers attention. Chung and Vafai [2014] analyzed LDL accumulation in an arterial wall by considering the thermal expansion of the wall caused by external and internal thermal loads. In their model, Ludwig-Soret and Dufour effects were also taken into account. The authors analyzed the effect of thermal expansion on changing the behavior of flow, mass transport, and elastic structure while incorporating the variations in the effective LDL diffusivity and consumption rate, as well as other dominating parameters. AlAmiri *et al.* [2014] analyzed pulsatile turbulent flow and heat loads effects on tumor tissues under hyperthermia.

To capture the experimental behavior of tumors in the computational studies, appropriate constitutive models have to be considered [*e.g.*, Unnikrishnan *et al.* 2010]. The inherent spatial heterogeneity, hierarchical tissue structure, and active nature of the tumor provide significant hurdles in the development of an accurate constitutive model of tumor. These difficulties lead to the development of approximate models for specific events of tumor tissue mechanics. In the computational studies, tumors were considered as, linear/nonlinear, elastic/viscoelastic, multiphase, and poroelastic materials.

In the present work, fluid flow in a tumor mass is analyzed at a macroscopic scale by considering the effects of both solid tissue deformation and hyperthermia. Governing equations are averaged over a Representative Elementary Volume (REV) of the living tissue, and written by means of the thermoporoelasticity theory. Darcy's law is used to describe fluid flow through the interstitial space, while transvascular transport is described with a generalized Starling's law. The effects of hyperthermia on the living tissue are included with a source term in the tissue momentum equation that considers the thermal expansion. Governing equations with the appropriate boundary conditions are solved with the finite element commercial code COMSOL Multiphysics in steady state regime, and the numerical model is validated with analytical results from Netti *et al.* [1997] for an isothermal case, in which poroelastic theory was employed to describe the time dependent behavior of interstitial fluid pressure in a deformable porous tumor. Results are presented in terms of pressure, velocity and temperature fields, for various thermal loads and the effect of hyperthermia on various physical parameters is analyzed. This contribution can be helpful to analyse phenomena such as interstitial fluid movement when hyperthermia occurs in a living tissue.

MATHEMATICAL MODEL

Volume-averaged governing equations In order to solve the physical problem, the whole tumor tissue is modeled as a spherical macroscopic porous media. The whole porous media is made up by cellular, vascular and interstitial-lymphatic spaces [*e.g.* Fung 1990]. The vascular space is only a small percentage of the total volume. Two phases of the porous media are identified: the first is formed by the interstitial phase, in which the interstitial flow with water and macromolecules passes through at a certain velocity, while the second phase is made up by the cellular volumes. Following porous media theory, governing equations are written by considering the variables to be averaged over a Representative Elementary Volume (REV) [*e.g.*, Vafai 2015]. This REV has linear dimensions that are at least one order of magnitude more than the intercapillary distance [*e.g.*, Netti *et al.* 1997], in order to make statistically meaningful the averaging process.

Governing equations are written by means of the thermoporoelasticity theory, in which thermal effects are included together with the mutual coupling between the fluid flow and the porous matrix deformation.

For the fluid flow, mass and momentum equations are written in the following:

$$\nabla \cdot (\phi \mathbf{u}) = L \frac{S}{V} (p_v - p) \quad (1)$$

$$\nabla p = -\frac{\phi}{K_h} \mathbf{u} \quad (2)$$

where ϕ is the porosity, \mathbf{u} the fluid velocity vector, L the average hydraulic conductivity coefficient of the capillary wall, S/V the surface to volume ratio, p_v the vascular pressure, p the interstitial fluid pressure and K_h the average tissue hydraulic conductivity. The source term on the right in the mass equation is referred to the Starling equation without considering the lymphatic drainage. It represents the effect of hydrostatic pressure on the interstitial flow movement. Equation (2) is also known as the Darcy's law. It can be derived from the momentum equation in steady-state under the hypothesis of negligible macro-inertial and viscous (Brinkman) effects, and micro-inertial (Forchheimer) effects. Macroscopic inertial effects can be significant only for lengths over than $K_h \phi \mathbf{u} / \rho$ that rarely occur for significant applications [e.g., Vafai and Tien 1981 and Khakpour and Vafai 2008]. Macroscopic viscous effects can be assumed to be negligible for low permeability, since the pressure gradient is balanced by the micro-inertial term instead of the viscous term [Brinkman 1949]. Such effects become important only in regions near the boundaries, with thicknesses of the order of the square root of the permeability (Brinkman screening distance). In this study, this thickness is of the order of about 10^{-14} m that is pretty small when compared to the computational domain dimensions. Further, Nield and Bejan [2006] reported that Brinkman effects are negligible in most of the practical applications. Micro-inertial effects, also known as Forchheimer effects, can be neglected since they occur only for relatively high Reynolds numbers. Indeed, Nield and Bejan [2006] reported that the transition from Darcy's law to Darcy-Forchheimer's law occurs for about 10^2 square root permeability-based Reynolds number. In the present study, this number is fairly lower than transition values (velocities are of the order of micrometers, while Brinkman screening distance is of the order of about 10^{-14} m), so Forchheimer effects can be neglected. Finally, it has to be observed that the reliability of the aforementioned equations has been demonstrated for filtration problems through arterial walls by founding good agreement with experimental results [e.g., Yang and Vafai 2008, Wang and Vafai 2013 and Iasiello *et al.* 2016].

For the solid matrix, momentum equation is reported in the following, under the hypothesis of a linear elastic material:

$$\mu \nabla^2 \mathbf{x} + (\mu + \lambda) \nabla (\nabla \cdot \mathbf{x}) - (2\mu + 3\lambda) \alpha \nabla (T - T_{ref}) - \nabla p = 0 \quad (3)$$

where μ and λ are Lamé parameters, \mathbf{x} the solid displacement vector, α the thermal expansion coefficient and T the temperature. This equation is written from the equilibrium condition, considering a source term ∇p that couples the effects of fluid flow on the solid matrix [e.g., Netti *et al.* 1997], and a temperature term that considers the thermal effects on the solid matrix. Temperature is always calculated here with reference to the temperature T_{ref} of 37 °C that is typical of the human body. It is noticed that the temperature gradients, that change the displacement field, affect the flow field since thermo physical properties are changing.

Finally, energy equation is written under the assumption of Local Thermal Equilibrium (LTE) between the two phases [e.g., Amiri and Vafai 1994; Alazmi and Vafai 2001].

$$\rho C_p \mathbf{u} \cdot \nabla T = k \nabla^2 T + (1 - \phi) Q_{met} + Q_{gen} \quad (4)$$

where ρ is the density, C_p the heat capacity at constant pressure, k the thermal conductivity, Q_{met} the metabolic heat source and Q_{gen} the heat generated by hyperthermia. The second term on the right side represents the heat source due to metabolic reactions [e.g., Rabin and Shitzer 1998; Lienhard 2005]; its value is $Q_{met} = 33,800 \text{ W/m}^3$. The third one is a term referred to the heat generation

induced by hyperthermia. Its value is a function of the electric field, and it can be obtained from Maxwell equations [e.g., Keangin and Rattanadecho 2013]. In this paper, only a sensitivity analysis with mean values of heat generation is employed, in order to simplify the model without solving the electrical field problem.

Boundary conditions Even if a one-dimensional coordinate system is sufficient to solve the problem, a two-dimensional cylindrical coordinate system is herein employed by studying a half circle with symmetry axis. This happens in order to easily manipulate the finite element code here employed. At the symmetry axis, symmetry conditions are employed for all the equations. At the boundaries of the computational domain, the pressure is set equal to 0 mmHg with no viscous stress; an antisymmetry boundary condition with tangential displacement equal to zero is set for the displacement and a Dirichlet boundary condition of 37 °C is employed for the energy equation. The first two boundary conditions are used since there are no contact forces at the boundaries, while the third in order to simulate that the boundaries of the tumor cells are as far as to be reached from the thermal dose. Reference is made to the computational domain, shown in Fig.1.

Porous media properties Governing equations (1) – (4) are solved only if thermo physical properties are known. In the flow field equations, it is noticed that both porosity and hydraulic conductivity [e.g., Lai and Mow 1980] are taken as a function of the displacement field:

$$\begin{cases} \phi = \frac{e^* + \phi_{in}}{1 + e^*} \\ K_h = K_{h,in} e^{\beta e^*} \end{cases} \quad (5)$$

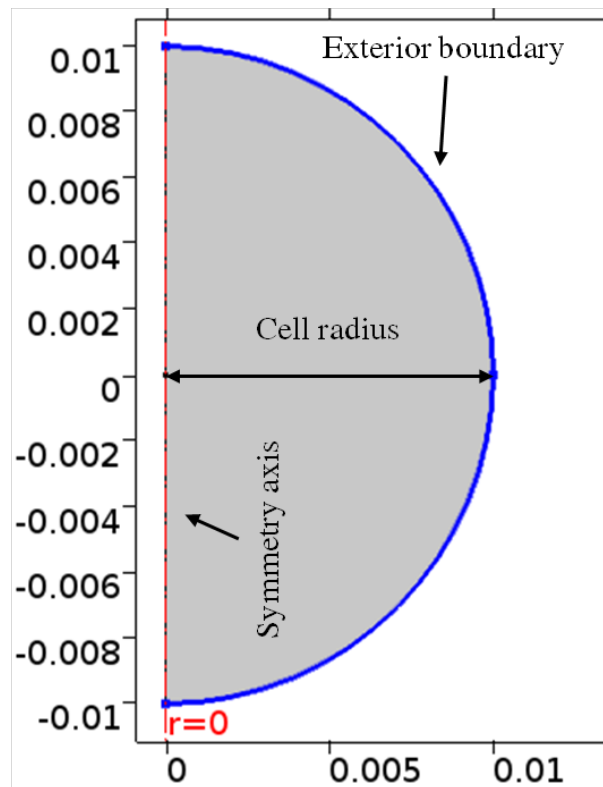


Figure 1 – Computational domain.

where e^* is the volumetric strain and the subscript in stands for porosity and hydraulic conductivity without displacement fields effects, *i.e.* $\phi_{in} = 0.20$ [*e.g.*, Jain 1987b] and $K_{h,in} = 4.13 \cdot 10^{-8}$ cm²/mmHg·s [*e.g.*, Swabb *et al.* 1974]. In the hydraulic conductivity equation, $\beta = 2$ [*e.g.*, Støverud *et al.* 2012]. The employed porous media properties are summarized in Table 1.

Numerical solution Governing equations are solved by using the finite element code COMSOL Multiphysics. A boundary-layer triangular mesh is used, with about 100,000 elements. Grid convergence has been verified with Richardson extrapolation on both velocity and pressure field averaged values, with a criterion of less than 1%. A RMS convergence criterion of 10^{-4} is used without any significant changes in the solution.

Table 1
Porous media properties

Property	Value	Reference
ϕ_{in}	0.20	Jain [1987b]
$K_{h,in}$	$4.13 \cdot 10^{-8}$ (cm ² /mmHg·s)	Swabb <i>et al.</i> [1974]
L	$3.6 \cdot 10^{-7}$ (cm/mmHg·s)	Baxter and Jain [1989]
S/V	200 (1/cm)	Hilmas and Gilette [1974]
λ	684 (mmHg)	Nicholson and Phillips [1981]
μ	15.2 (mmHg)	Nicholson and Phillips [1981]
α	$6.376 \cdot 10^{-5}$ (1/K)	Rabin and Plitz [2005], Rios and Rabin [2006]
ρ	1000 (kg/m ³)	Duck [1990], Kolios <i>et al.</i> [1995]
C_p	4180 (kg/m ³)	Duck [1990], Kolios <i>et al.</i> [1995]
k	0.6 (W/m·K)	Duck [1990], Kolios <i>et al.</i> [1995]

RESULTS

Comparisons with the analytical solution from Netti *et al.* [1997] are presented in the following.

In Fig. 2, pressure and volumetric strain along the dimensionless radial coordinate $r^* = r/R$ are presented for two values of vascular pressure, $p_v=3$ mmHg and $p_v=10$ mmHg. It is reminded that the volumetric strain, for Cartesian systems, is equal to the divergence of the displacement field. It is shown that for both the pressure and the volumetric strain the values are uniform in the first part of the domain, with a rapid decrease in the last part. This means that the fluid tends to move from the core of the domain to the external parts. A good agreement with the analytical solution is exhibited.

In Fig. 3, the velocity vs. the dimensionless coordinate is reported for $p_v=3$ mmHg and $p_v=10$ mmHg. It is shown that the velocity increases around the domain boundaries, since the pressure difference, that is the driving force, increases.

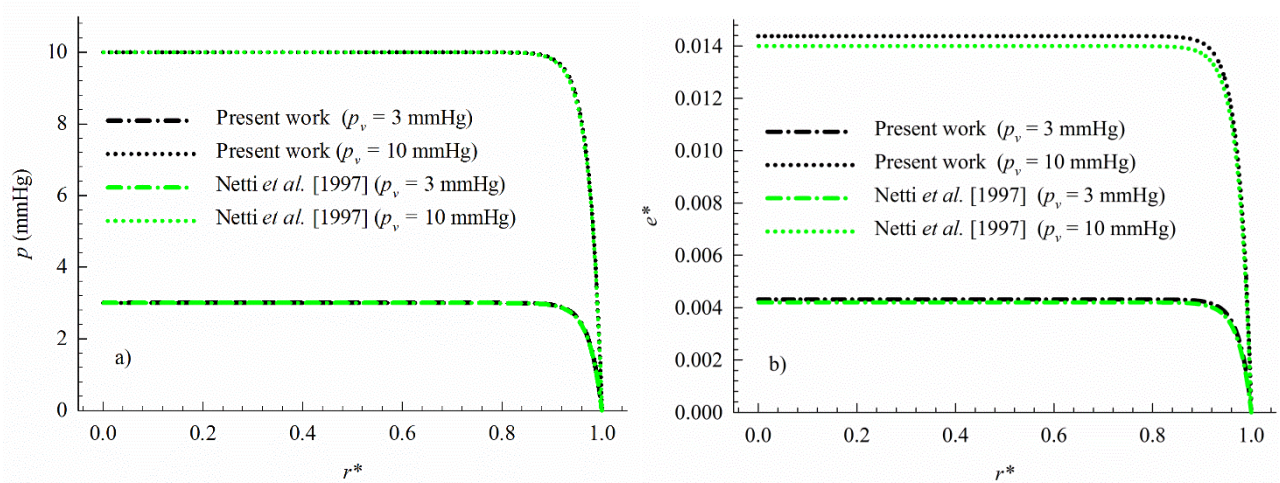


Figure 2 – Comparisons with analytical results from Netti *et al.* [1997] for different values of vascular pressure p_v : a) pressure and b) volumetric strain.

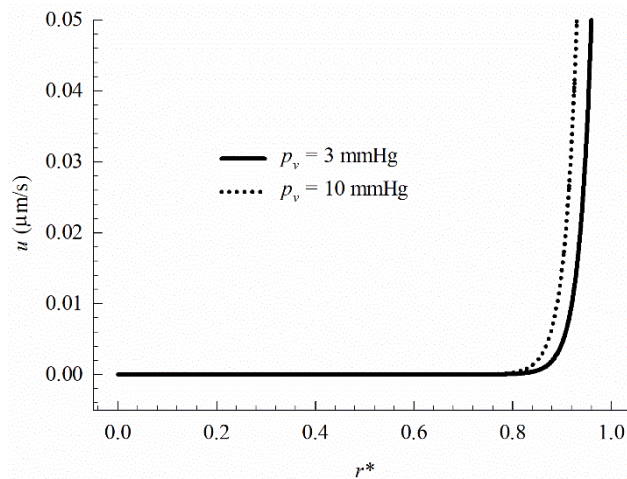


Figure 3 – Velocity fields for different values of vascular pressure p_v .

Temperature field for $Q_{gen} = 1 \cdot 10^6 \text{ W/m}^3$ and temperature profiles for different heat loads are reported in Fig. 4a and Fig.4b, respectively. It is shown that the maximum temperature value occurs at the center point of the spherical domain, with a rapid decrease along the radial coordinate, reaching the value of $37 \text{ }^\circ\text{C}$ on the periphery of the domain, Fig. 4a. In Fig. 4b, varying the heat load, temperature can reach about $65 \text{ }^\circ\text{C}$, that is typical of induced hyperthermia applications. The temperature rapid decrease along the radius is more marked when the heat induced by hyperthermia increases (Q_{gen}). The volumetric strain for different heat loads is presented in Fig. 5. The isothermal case is the one already presented in the validation part of the paper. It is shown that the more the heat load, the higher is the volumetric strain. This because, with references to Fig. 4b, the strain caused by the local temperature difference with the reference temperature becomes more pronounced.

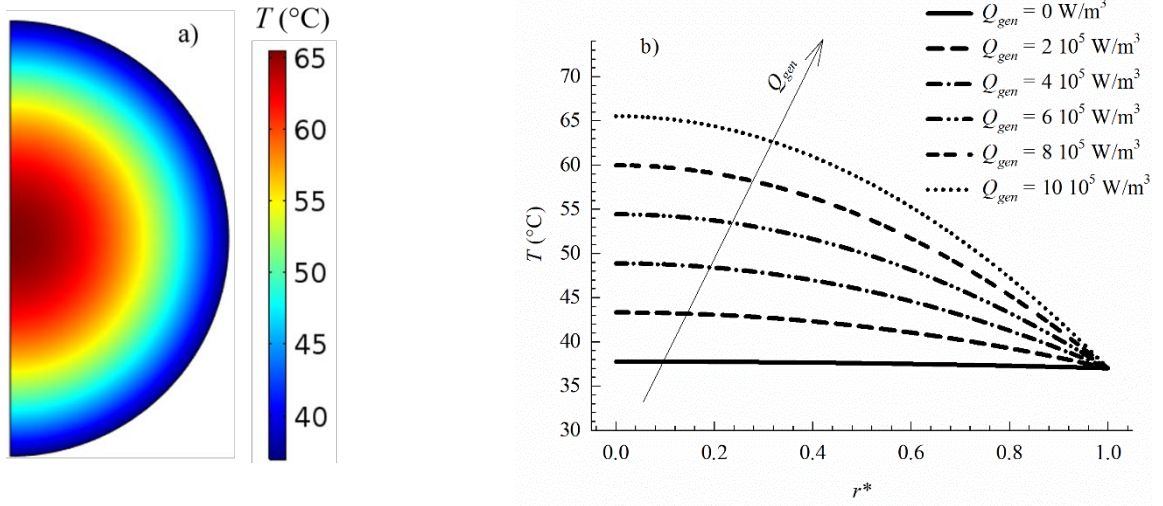


Figure 4 – a) Temperature field for $Q_{gen} = 1 \cdot 10^6 \text{ W/m}^3$ and b) temperature profiles for different heat loads.

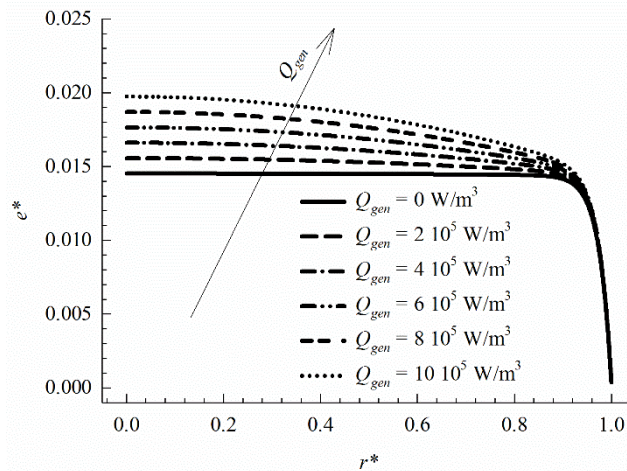


Figure 5 – Hyperthermia effects on volumetric strain e^* .

It has already discussed that volumetric strain induced by hyperthermia causes the porous media properties to be different, affecting the flow field. The porosity vs. the dimensionless radius is presented in Fig. 6a for different heat loads. It is shown that hyperthermia affects the porosity, especially for high heat loads. This because of the volumetric strain changes (Eq. 5). In Fig. 6b, the porosity scaled with the initial porosity ($\phi^* = \phi / \phi_{in}$) is presented, showing that the porosity can be enhanced of slightly less than about a 1.10 factor under hyperthermia conditions.

In Fig. 7a, the hydraulic conductivity vs. the dimensionless radius is presented for different heat loads. With reference to the isothermal case, the hydraulic conductivity is uniform in most of the computational domain. As for the porosity, it is shown that hydraulic conductivity is affected by hyperthermia. In particular, the heat-induced volumetric strains enhance it, making the flow to pass more easily through the pores (Eq. 5). Again, this is due to the temperature differences, that determine an enhance in terms of volumetric strain (Fig. 5). In Fig. 7b, the ratio between the hydraulic conductivity and its reference value ($K_h^* = K_h / K_{h,in}$) is presented. The hyperthermia can cause a very slight increase in terms of hydraulic conductivity.

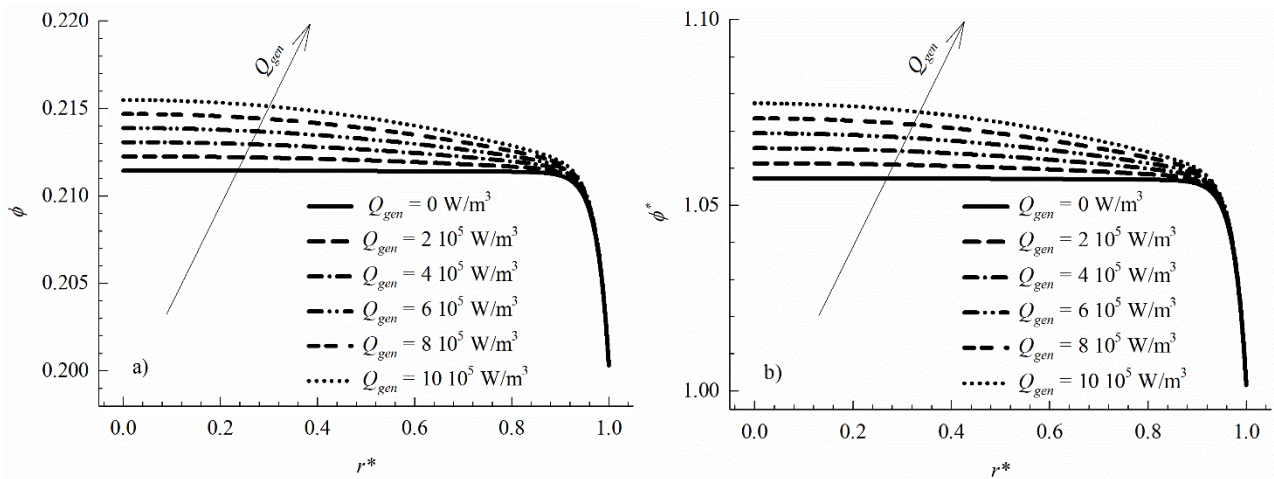


Figure 6 – Hyperthermia effects on a) porosity and b) on scaled porosity.

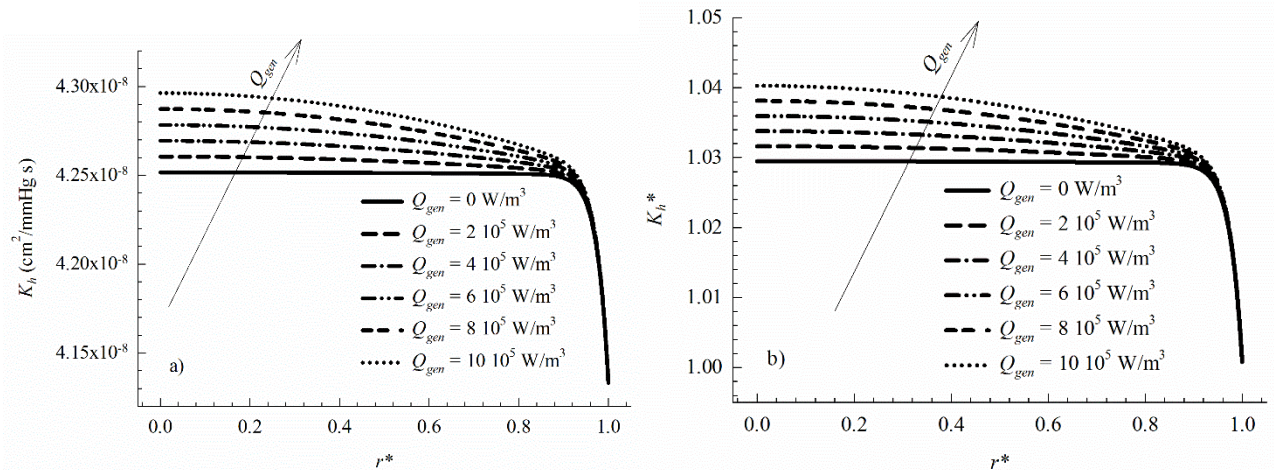


Figure 7 – Hyperthermia effects on a) hydraulic conductivity and b) scaled hydraulic conductivity.

The effects of hyperthermia on velocity and pressure fields along the dimensionless radius, caused by the changes in terms of porous media properties, are presented in Fig. 8. No substantial changes have been found. Similar results have been found in Chung and Vafai [2014] in their study on hyperthermia effects on low-density lipoprotein transport through a medium-size arterial wall. It is also noticed that, as also reported in their work, the change in terms of porous media properties can affect other physical problems such as chemical species transport.

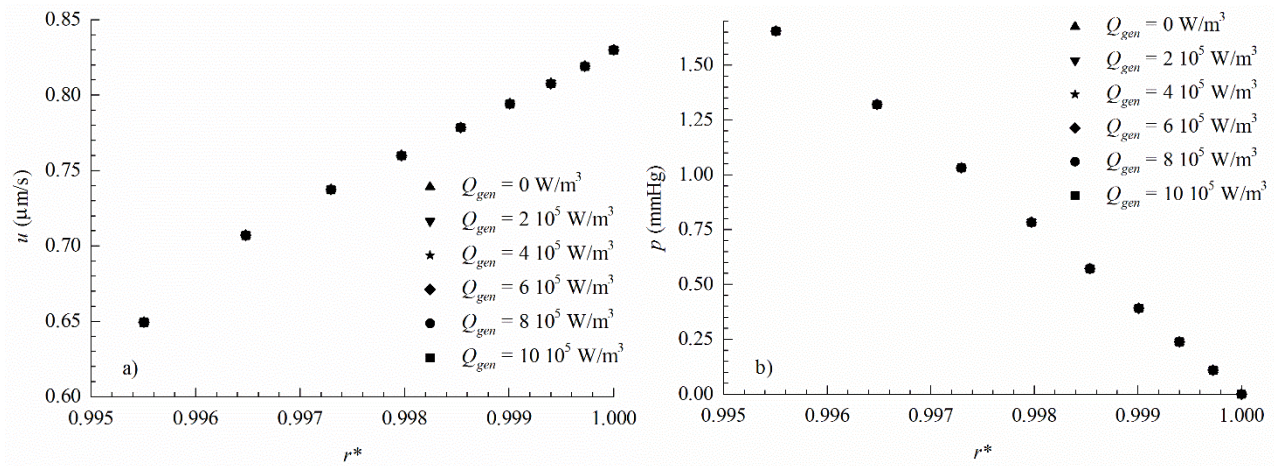


Figure 8 – Hyperthermia effects on a) velocity and b) pressure.

CONCLUSIONS

The objective of this preliminary study was to analyze the hyperthermia effects on macroscopic fluid transport in tumors, combining the effects of transvascular and interstitial fluid movement with the structural mechanics of the tissue. The fluid flow was analyzed at a macroscopic scale. Governing equations were averaged over a Representative Elementary Volume (REV) of the living tissue, and written by means of the thermo-poroelasticity theory, in steady state regime. The numerical simulations were carried out by means the commercial code COMSOL Multiphysics. Results were validated with analytical results from Netti *et al.* [1997] for an isothermal case. Simulations for various hyperthermia loads have been carried out. Such loads enhance porous media properties like porosity and permeability with a slightly less than 1.10 and 1.05 factor, respectively. These variations don't modify velocity and pressure fields in the tumor cell.

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