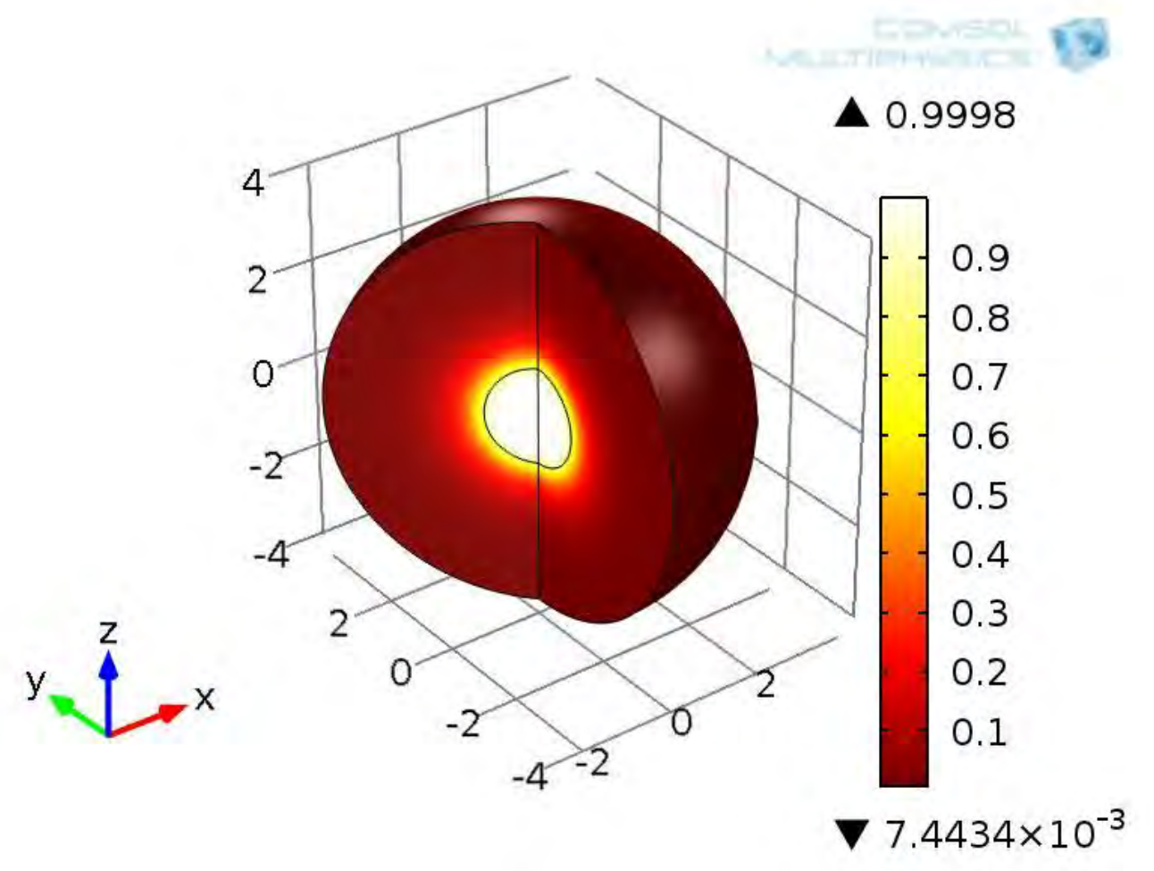
Lowering of the Interstitial Fluid Pressure in Tumors During High Intensity Focused Ultrasound Exposure

Elisabetta Sassaroli, Brian E. O'Neill
The Methodist Hospital Research Institute, Houston, TX, 77030, USA

Introduction: Interstitial fluid pressure (IFP) is elevated in tumors. Owing to this elevated IFP, the interstitial fluid velocity (IFV) is negligible throughout the tumor but significant near the tumor margin. Any therapeutic strategy that can lower the IFP will likely improve drug convection within the tumor and decrease convection of drugs from the tumor margin. High intensity focused ultrasound (HIFU) has been shown to reduce the IFP and to improve the penetration of therapeutics in tumors. We have used a mathematical model to simulate the effect of HIFU on the IFP and on the IFV. We have shown that a reduction of the IFP as a result of HIFU exposure facilitates fluid convection and macromolecule distribution within the HIFU exposed volume and reduces fluid convection and macromolecule wash out at its margin.



IFP is elevated everywhere in a tumor and decays sharply at its boundary.

Figure 1. Relative IFP in a spherical tumor surrounded by normal tissue.

In a tumor, the IFV is negligible everywhere except at the tumor boundary and directed away from the tumor

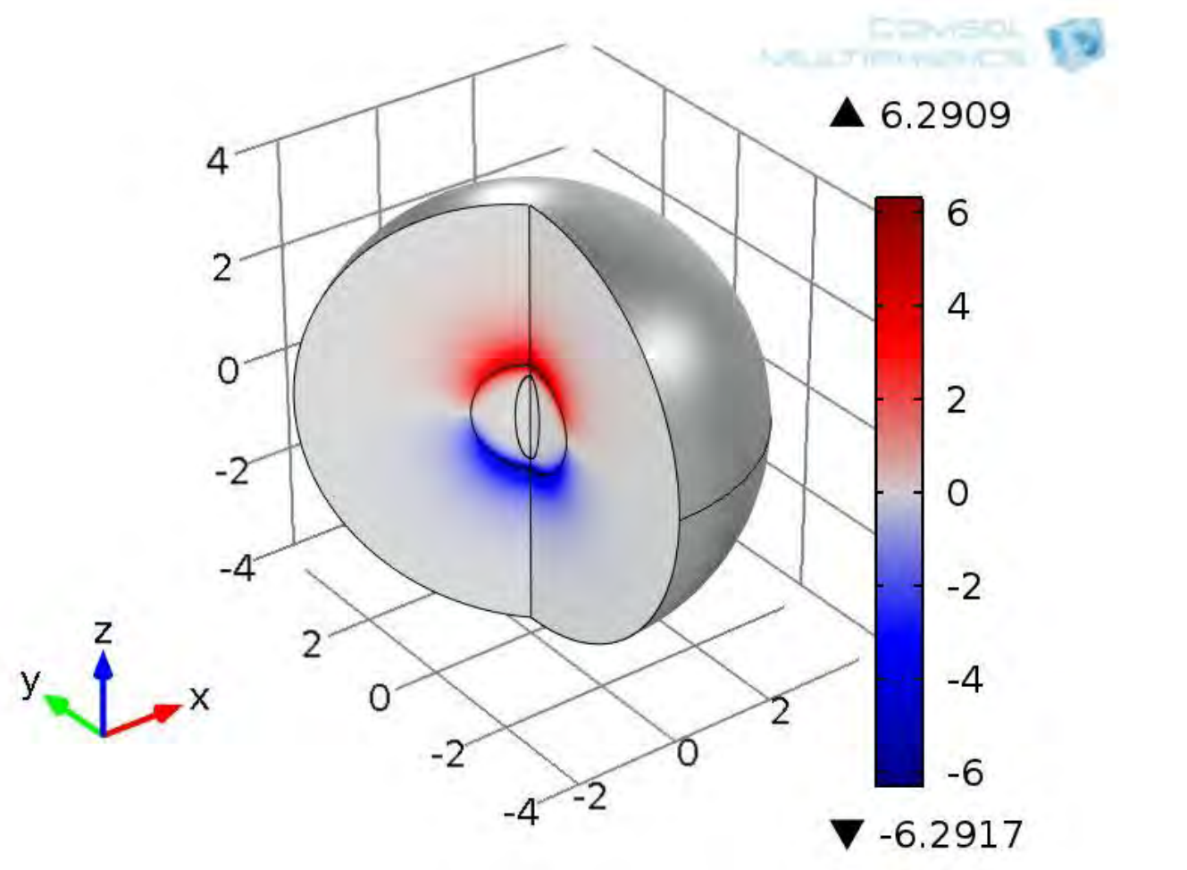


Figure 2. Relative axial IFV in a spherical tumor surrounded by normal tissue.

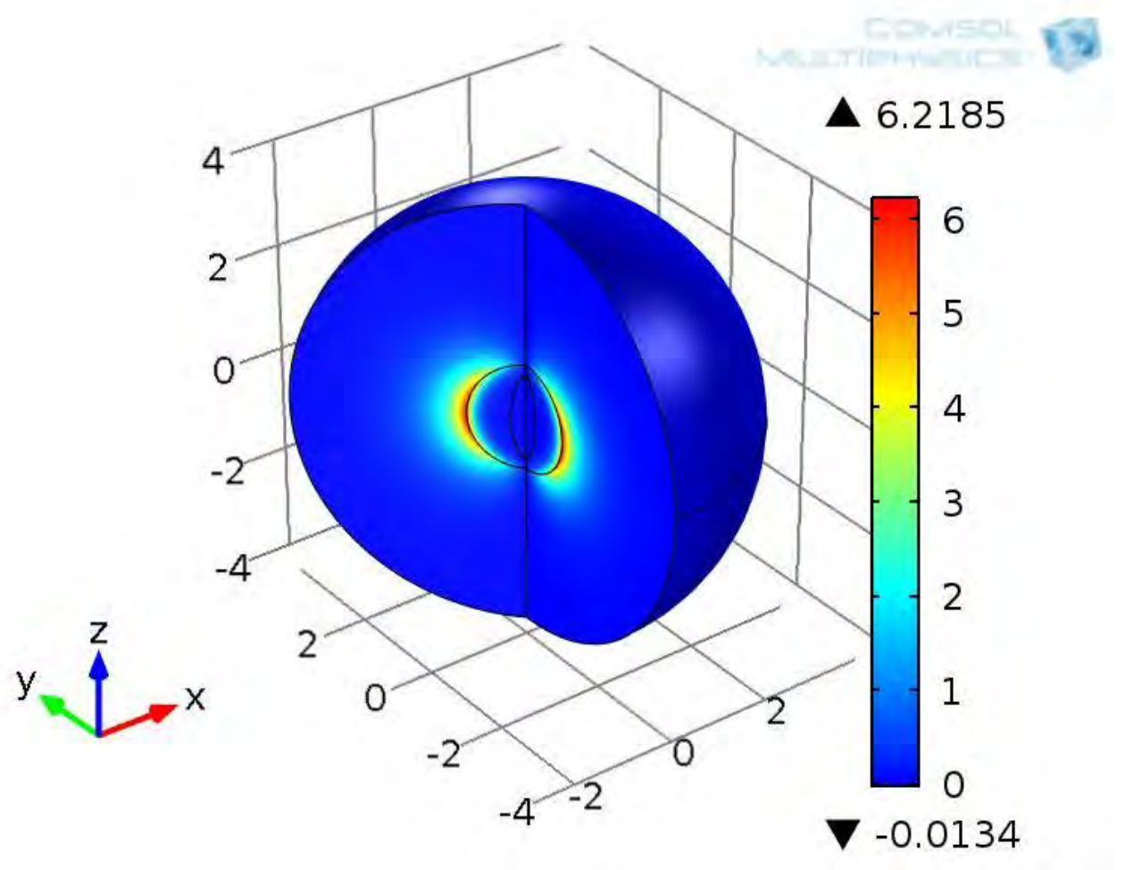


Figure 3. Relative radial IFV in a spherical tumor surrounded by normal tissue.

Computational Methods: The linear biphasic model of tumor tissue developed by Netti et al. [1] has been employed in this work. The model allows to determine

- the tissue dilation e: $\frac{\partial e}{\partial t} - KH\nabla^2 e + HL_p \frac{S}{V} e = L_p \frac{S}{V} P_e$

K tissue hydraulic conductivity; *H* = 2μ+λ aggregate modulus of interstitium
L_p hydraulic conductivity of capillary; *S/V* surface area of vessel wall per unit volume of tissue; P_e effective vascular pressure

- the interstitial fluid pressure P_i: $\nabla \boldsymbol{e} = \frac{\nabla \boldsymbol{P_i}}{2\mu + \lambda}$
- the tissue displacement ***u***: $e = \nabla \cdot \boldsymbol{u}$
- the interstitial fluid velocity ***v***: $\phi \left[\boldsymbol{v} - \frac{\partial \boldsymbol{u}}{\partial t} \right] = -K \nabla P_i$ ϕ volume fluid fraction

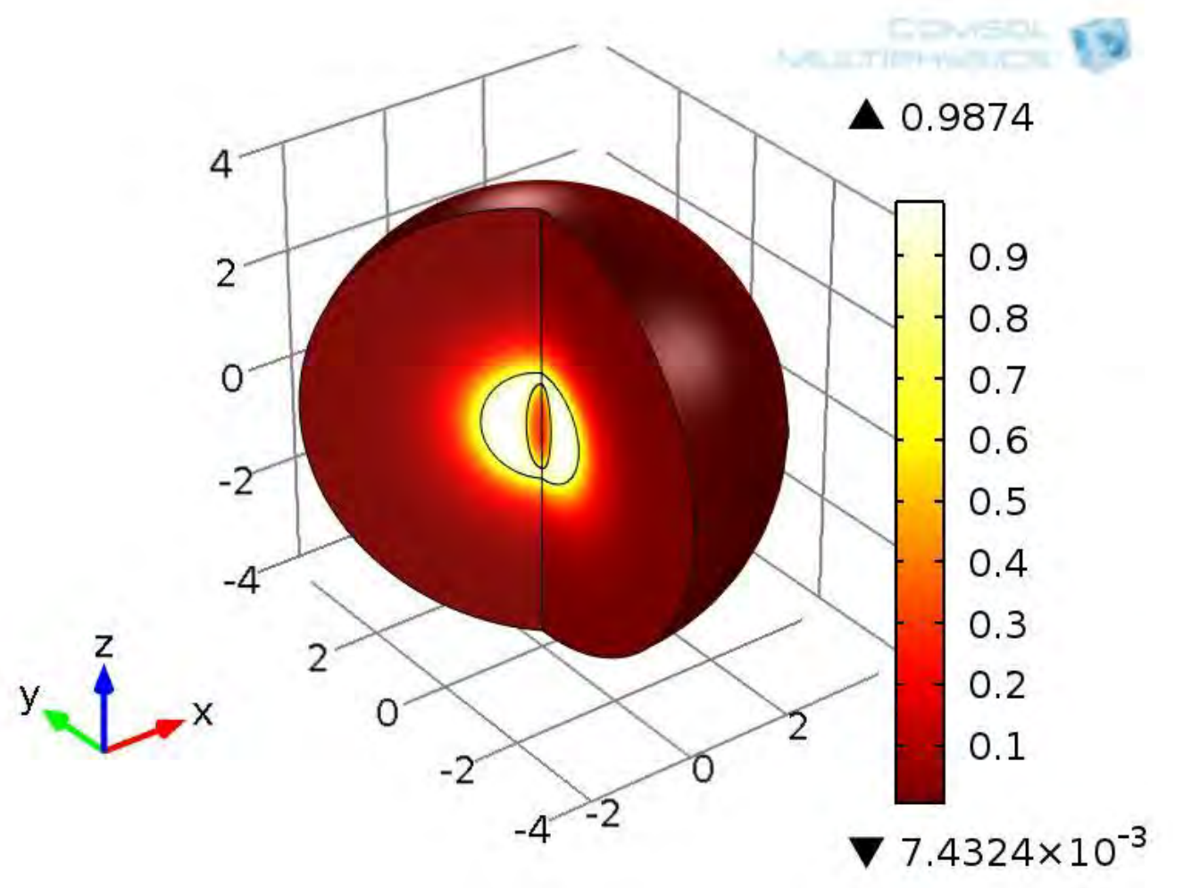
•The observed lowering of the Interstitial fluid pressure in the HIFU affected region [2] has been modeled as a result of a sudden change (increase) of the interstitium aggregate modulus H (inverse of tissue compliance) in the above equations.

• The Baxter and Jain model [3] for macroscopic solute transport in tumors has been employed to find the tumor tissue concentration C_i of a given macromolecule (a monoclonal antibody of molecular weight 50,000)

$$\frac{\partial C_i}{\partial t} + \nabla \cdot \left(-D \nabla C_i + \boldsymbol{v} C_i \right) = \frac{PS}{V} \left(C_p - C_i \right)$$

P vascular permeability coefficient; *D* diffusion coefficient
C_p plasma solute concentration $C_p = C_{op} \exp(-t/\tau_p)$

Results:



If the aggregate modulus of the interstitium is increased as a result of HIFU exposure, then the model predicts a lowering of the IFP at the focal region.

Figure 4. Relative IFP drop in a spherical tumor surrounded by normal tissue.

Normalized axial and radial IFV corresponding to the reduced IFP of Figure 4. The normalization is with respect to the IFV at the outer edge of the tumor shown in Figures 2 and 3. The lowering of the IFP facilitates fluid convection inside the HIFU affected volume and significant decrease fluid loss at the HIFU exposure boundary with the velocity directed towards the tumor center.

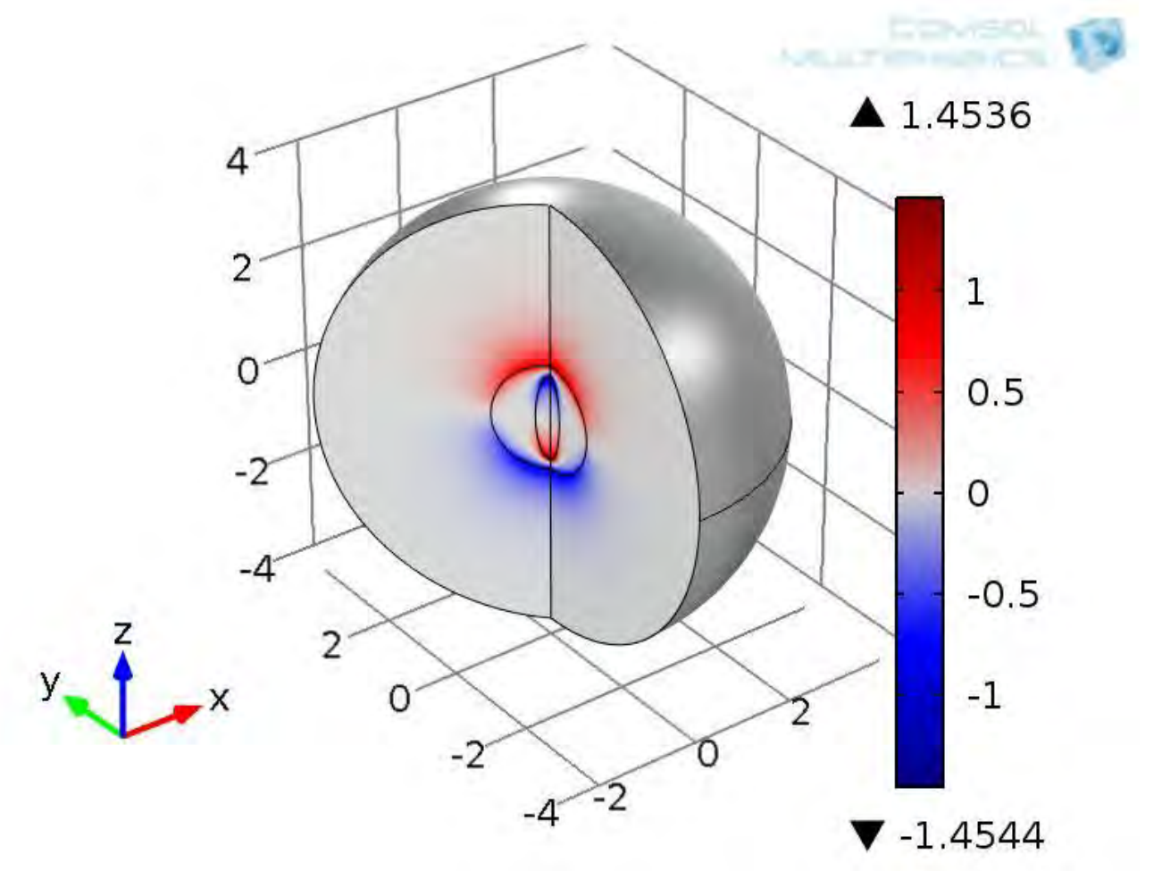


Figure 5. Normalized axial IFV in a spherical tumor surrounded by normal tissue.

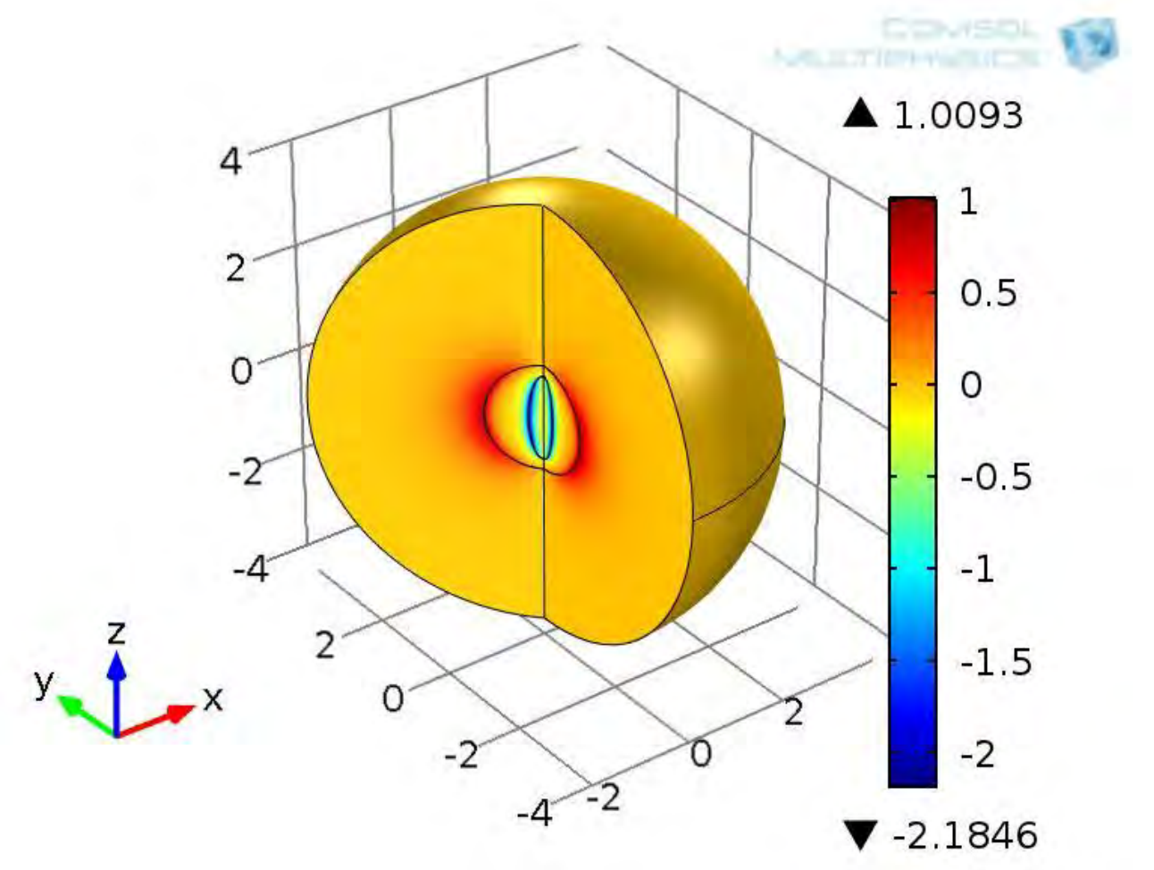


Figure 6. Normalized radial IFV in a spherical tumor surrounded by normal tissue.

Normalized IFV along two specific directions as a function of dimensionless time. Relative distance <1 represents region within the tumor, whereas >1 represents region outside of the tumor

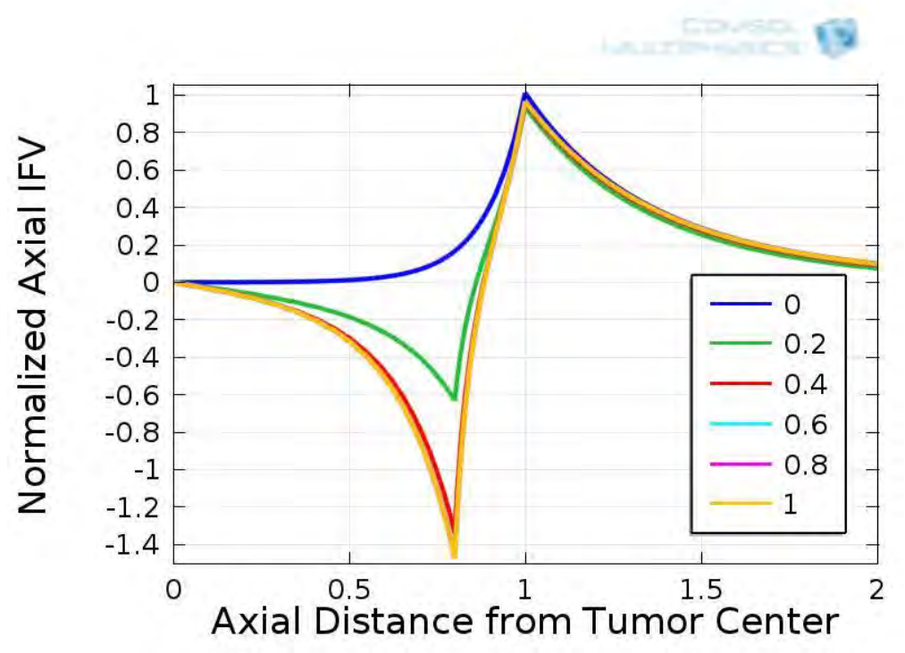


Figure 7. Normalized IFV along the axial direction. The HIFU affected area is for a axial distance less than 0.8.

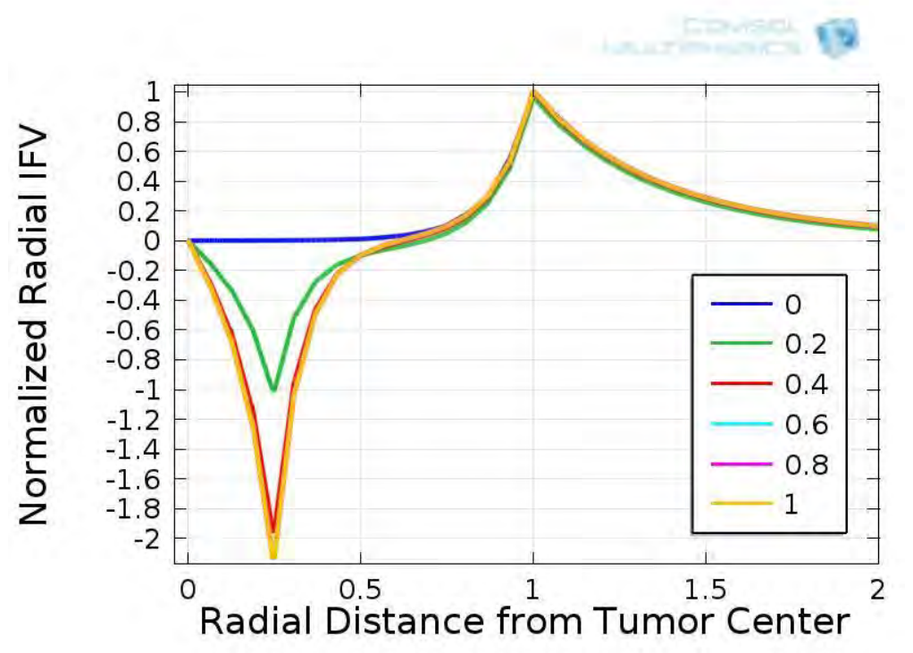


Figure 8. Normalized IFV along the radial direction. The HIFU affected area is for a radial distance less than 0.25.

Solutions of the macroscopic solute transport equation along the axial direction for a large macromolecule at different hours.

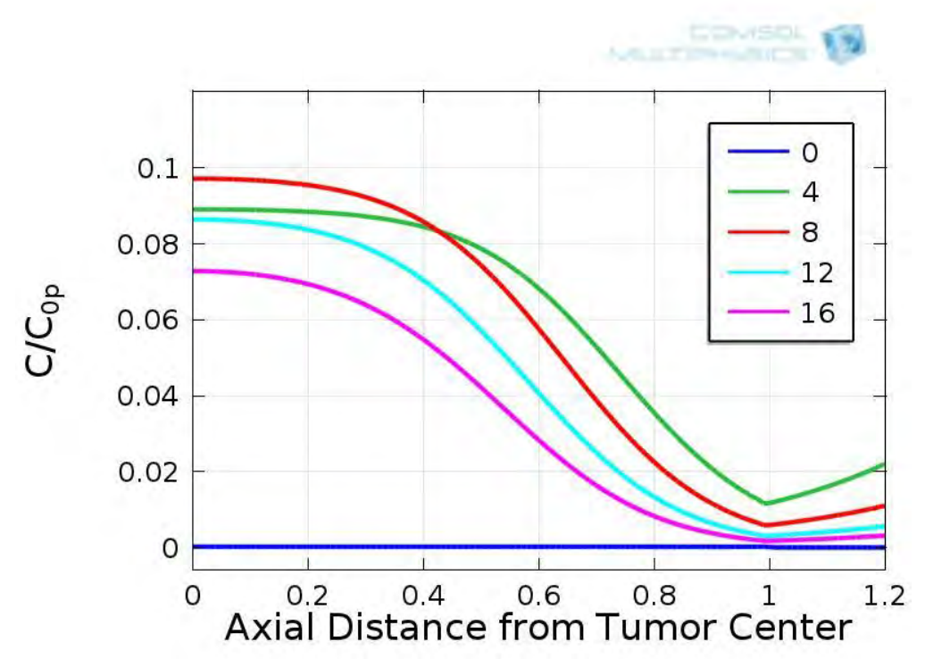


Figure 9. Solute concentration at different hours assuming the IFV to be the one at t=0 in Fig.7 which is typical of tumors.

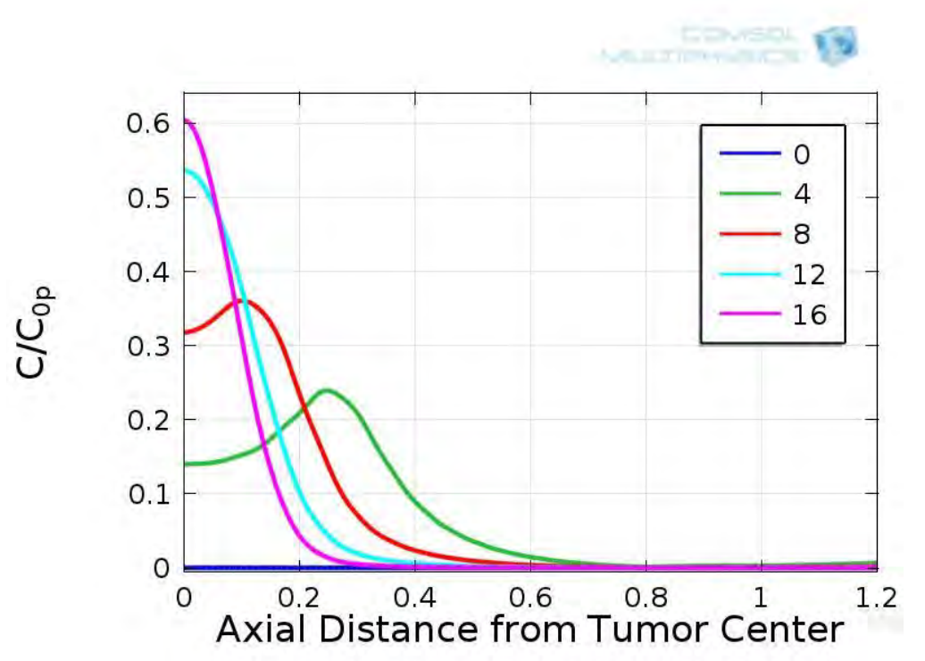


Figure 10. Solute concentration at different hours after the drop of IFP.

After the IFP drop, solute concentration inside the tumor is significantly increased and its escape from the tumor margin is significantly slowed down.

Conclusions: Efficient delivery of drugs in tumors still remains a big challenge in medicine. HIFU operated in thermal mode has been shown to improve drug delivery to tumors.

The interstitium, which is the space between the tissue cells and blood capillaries composed primarily by a gel of polysaccharides within a framework of collagen fibers and containing connective tissue cells named fibroblasts, has a natural tendency to swell. At equilibrium, the swelling pressure of the gel is counteracted by the fibroblasts which exert a contractive force on the collagen-fiber network via collagen-binding integrins [4]. HIFU exposure may release or reduce the tension from the fibroblasts on to the collagen fibers thus reducing the IFP and facilitating drug delivery as shown in this work.

This study presents a preliminary mathematical model upon which to build more complex models. It offers valuable guidance for experiments aimed at developing strategies that employ HIFU or any other means to lower IFP for improving drug delivery to solid tumors.

References:

1. Netti PA, Baxter LT, Boucher Y, Skalak R and Jain RK, Time-dependent behavior of interstitial fluid pressure in solid tumors: implications for drug delivery, *Cancer Res,* **55**, 5451–8 (1995)
2. Watson KD, Lai CY, Qin S, Kruse DE, Lin YC, Seo JW, Cardiff RD, Mahakian LM, Beegle J, Ingham ES, Reed RK and Ferrara KW, Ultrasound increases nanoparticle delivery by reducing intratumoral pressure and increasing transport in epithelial and epithelial-mesenchymal transition tumors, *Cancer Res,* **72**, 1485-93 (2012)
3. Baxter LT and Jain RK, Transport of fluid and macromolecules in tumors. I. Role of interstitial pressure and convection, *Microvasc Res*, **37**, 77–104 (1989)
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