COMSOL CONFERENCE BOSTON 2012

Lowering of the Interstitial Fluid Pressure as a Result of Tissue Compliance Changes during High Intensity Focused Ultrasound Exposure: Insights from a Numerical Model

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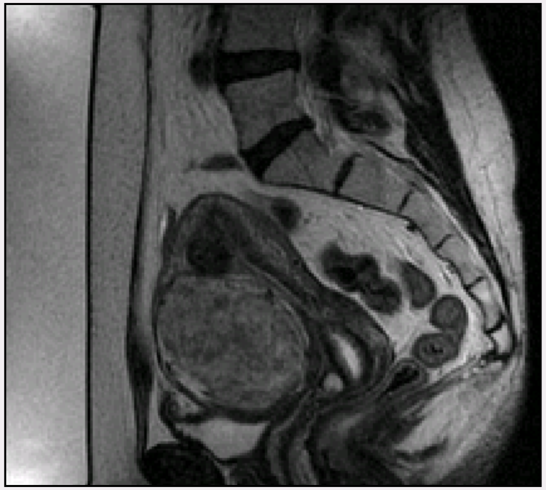
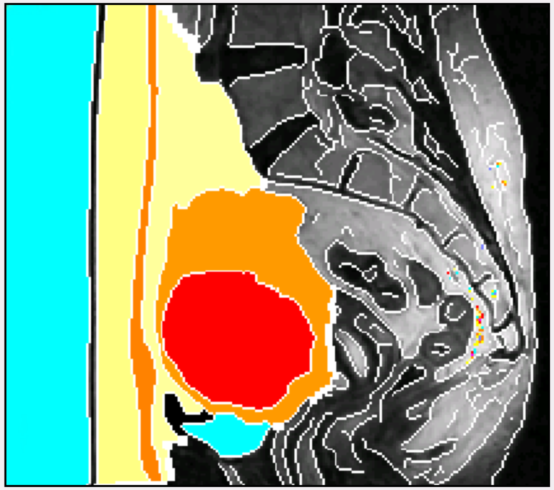
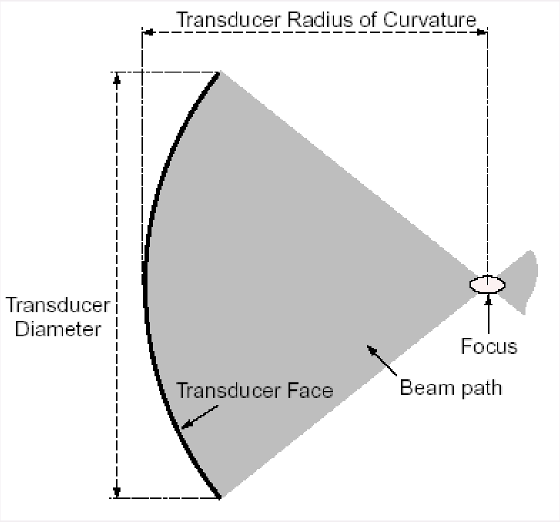
Excerpt from the Proceedings of the 2012 COMSOL Conference in Boston

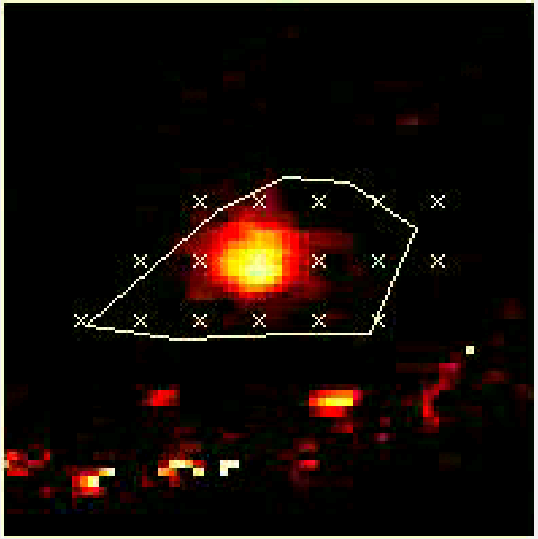
OUTLINE

MRI guided Focused Ultrasound is under investigation for thermal ablation of tumors



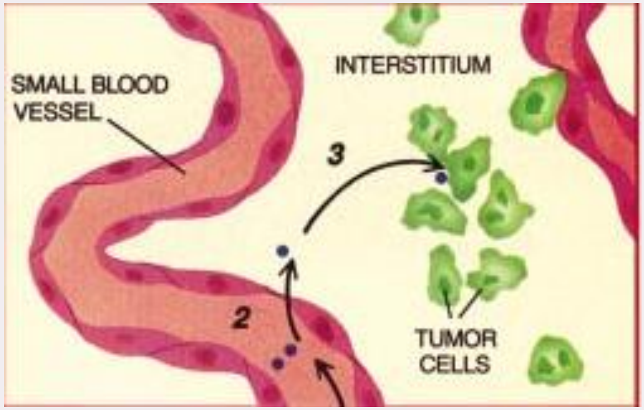


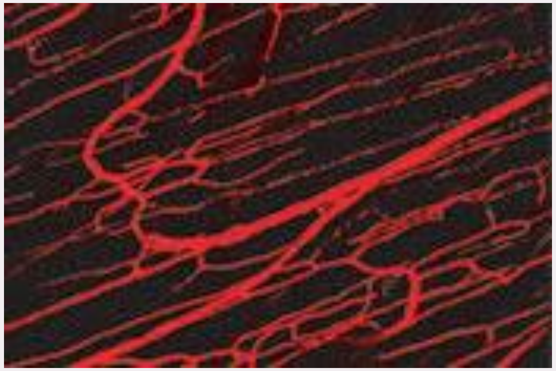




OUTLINE

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





Figures taken from R. K. Jain, Barriers to Drug Delivery in Solid Tumors, Scientific American, 1994

ELEVATED INTERSTITIAL FLUID PRESSURE

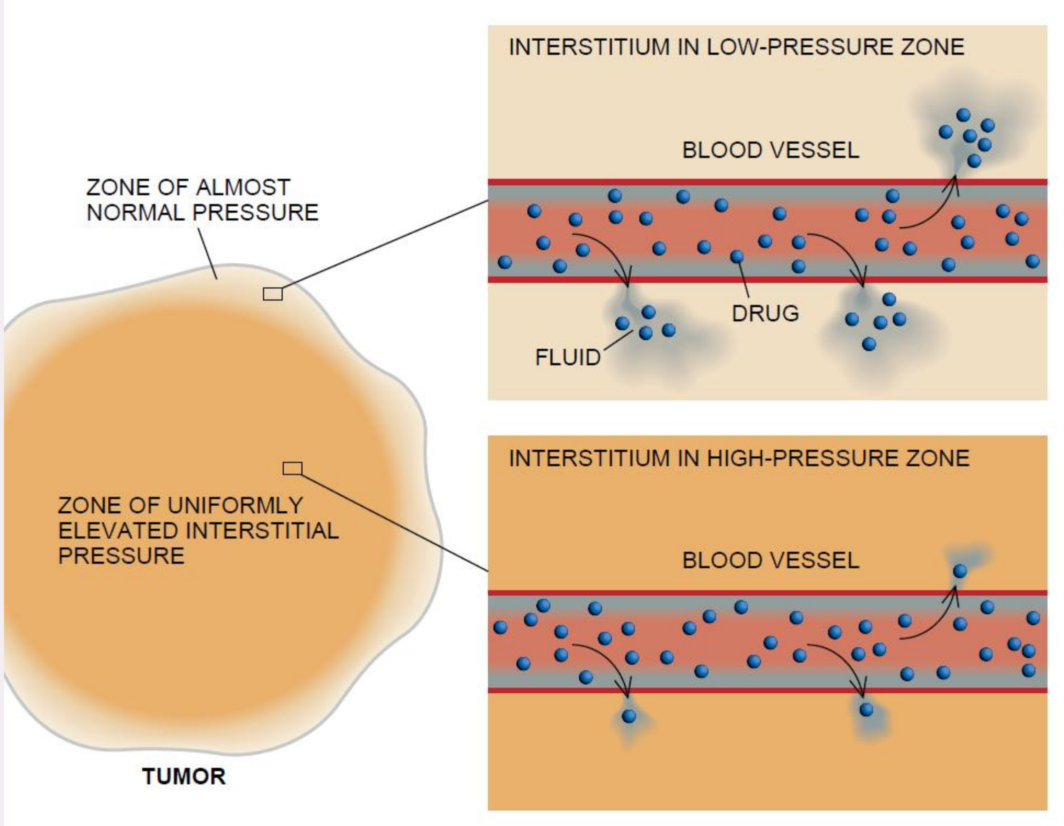
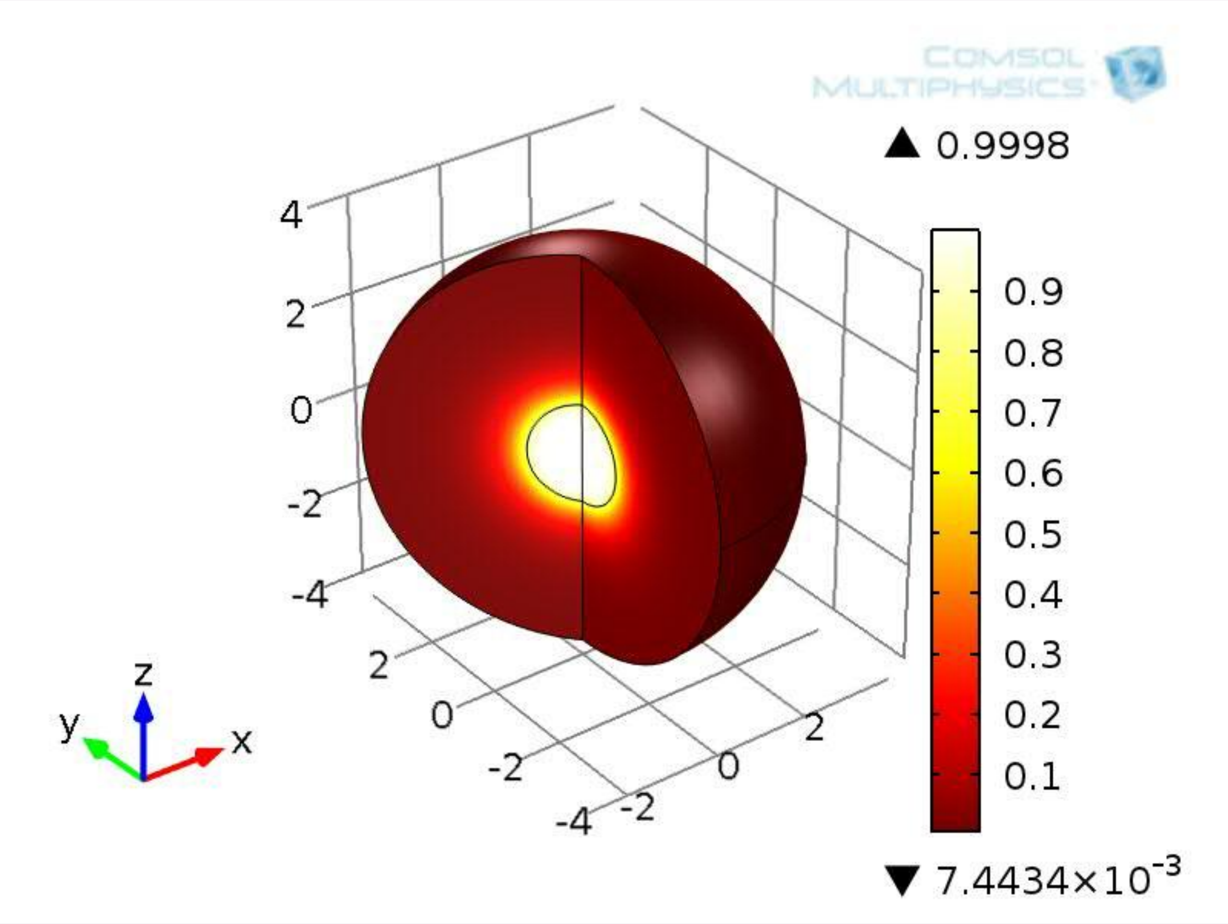


Figure taken from RK Jain, Barriers to Drug Delivery in Solid Tumors, Scientific American, 1994

FE simulations can predict this elevated pressure and its effect on drug delivery

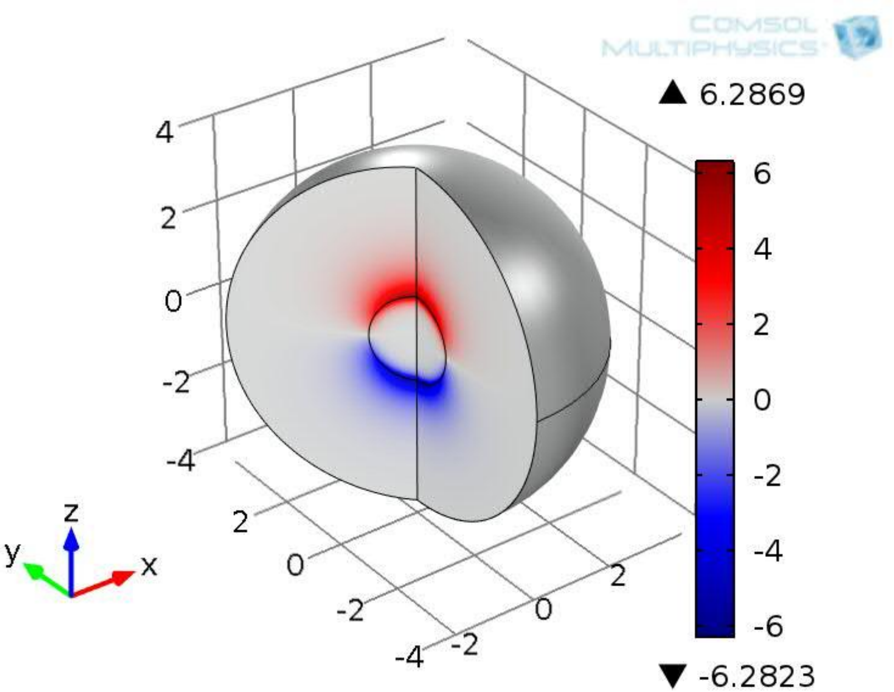
BAXTER AND JAIN MODEL

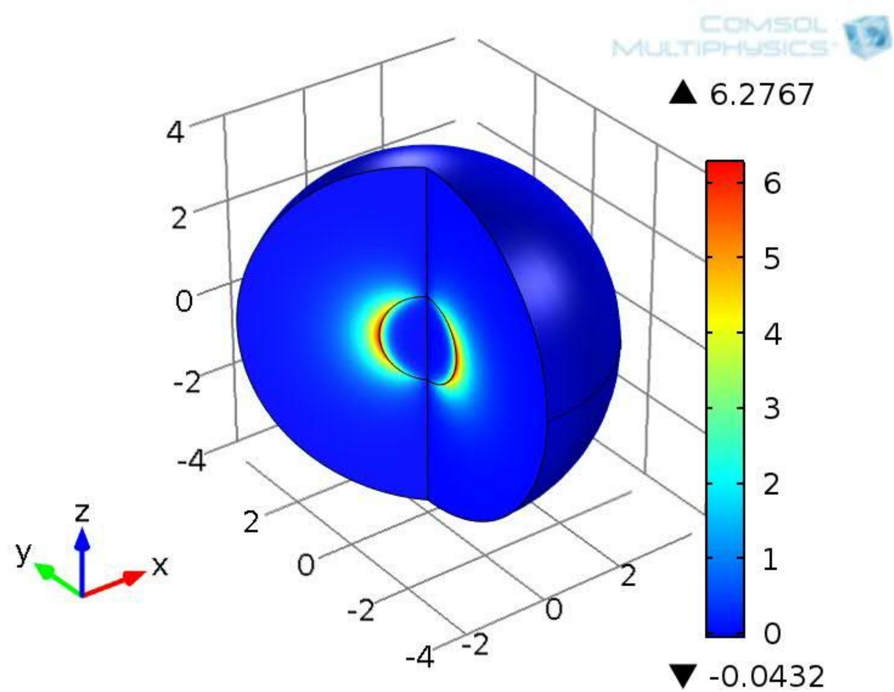
Interstitial Fluid Pressure is elevated everywhere in a tumor and decays sharply at its boundary



BAXTER AND JAIN MODEL

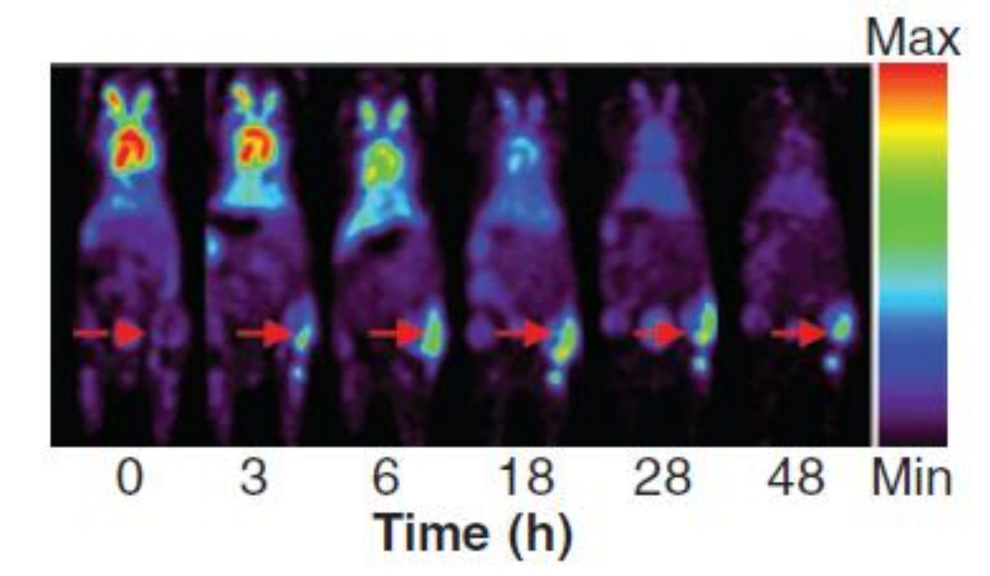
In a tumor, the interstitial fluid velocity is negligible everywhere except at the tumor boundary and directed away from the tumor

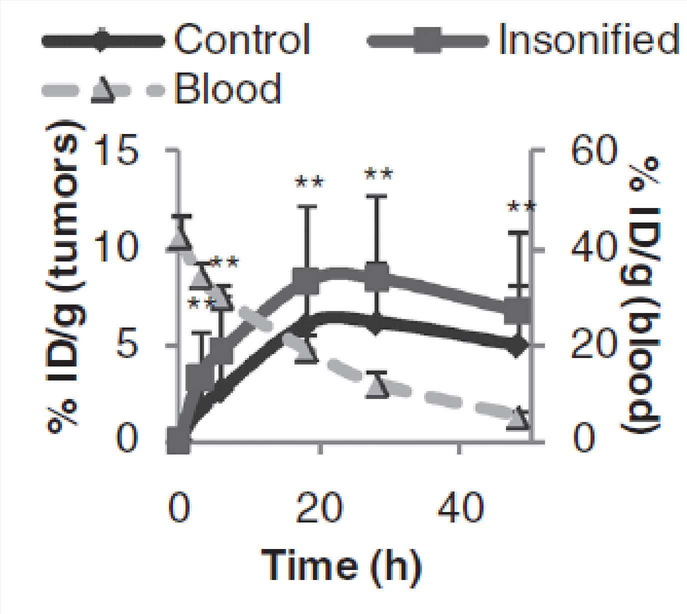




HIFU EFFECT

High intensity focused ultrasound (HIFU) has been shown to improve the penetration of therapeutics in tumors in animal models

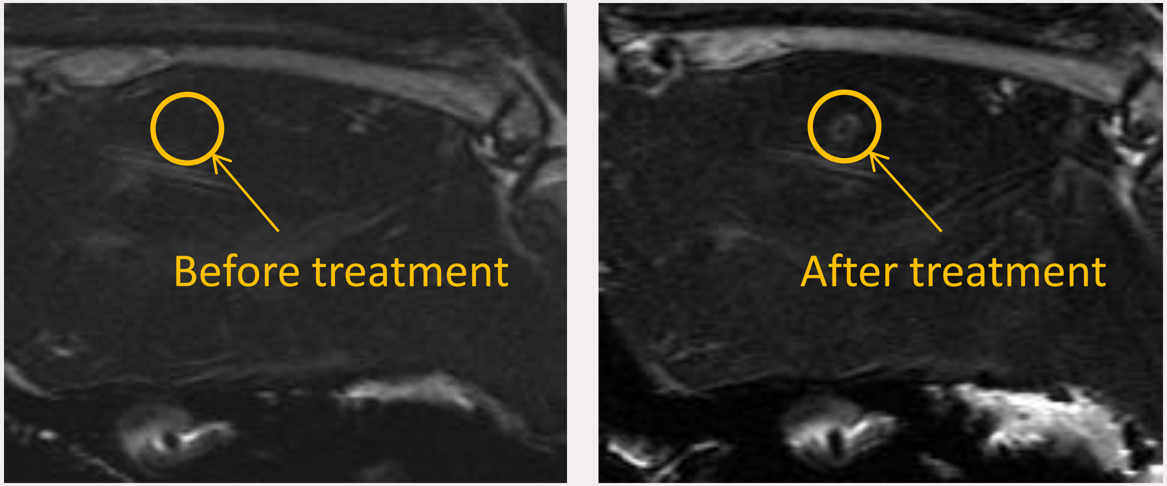




Watson *et al.* Cancer Research, 2012

HIFU EFFECT

- There is a rapid edema formation with associated increased uptake of macromolecules by tissue as a result of focused ultrasound exposure



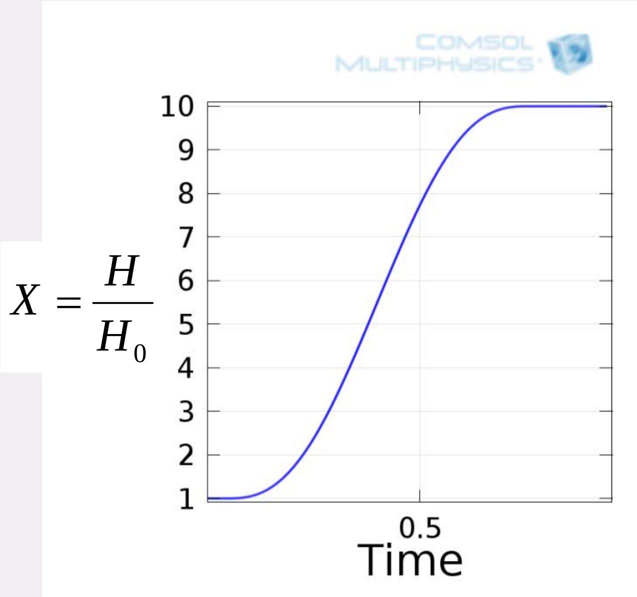
- During edema formation due to tissue thermal injury several studies have shown that the interstitial fluid pressure decreases quickly to negative values associated with a rapid formation of edema (Wiig *et al.* Acta Anaesthesiol. Scand. 2003)

MODELING OF HIFU EFFECT

- Physiology parameters that control fluid transport in tissue:

  hydraulic permeability of the vascular wall: L_p
  hydraulic conductivity of the interstitium: K
  aggregate modulus of the interstitium: $H = 2\mu+\lambda$

- Initial fall of the IFP observed in the HIFU experiments
- In the region affected by the HIFU, the aggregate modulus of the interstitium is suddenly increased (compliance C=1/H is reduced)



GOVERNING EQUATIONS

The linear biphasic model of tumor tissue developed by Netti *et al.* Cancer Res, 1995 has been employed in this work:

Tissue considered as a porous medium

$$\nabla \cdot \left[\phi \mathbf{v} + (1-\phi)\frac{\partial \mathbf{u}}{\partial t} \right] = \Omega(\mathbf{r},t)$$

ϕ volume fluid fraction

u tissue displacement

v interstitial fluid velocity

Ω fluid source term given by Starling's Law

$$\Omega(\mathbf{r},t) = \frac{L_p S}{V}\left(P_e - P_i\right)$$

L_p capillary hydraulic conductivity

S/V surface area of vessel wall per unit volume of tissue

P_e effective vascular pressure

P_i interstitial fluid pressure

GOVERNING EQUATIONS

- Generalized form of Darcy's Law

$$\phi\left[\mathbf{v}-\frac{\partial \mathbf{u}}{\partial t}\right]=-K\nabla P_i$$

K is the average tissue hydraulic conductivity

Effective Tissue : $T=-P_i I+\tau$ $\quad \tau=\lambda eI+2\mu\varepsilon$

e *dilatation*
λ, μ Lame' constants
ε strain tensor

Momentum Balance: $\nabla\cdot T=0$

- The above equations allow to determine: P_i, ***v***

- Convective-diffusion equation for the macroscopic solute transport

$$\frac{\partial C_i}{\partial t}+\nabla\cdot\left[-D\nabla C_i+\mathbf{v}C_i\right]=\frac{\xi S}{V}\left(C_p-C_i\right)$$

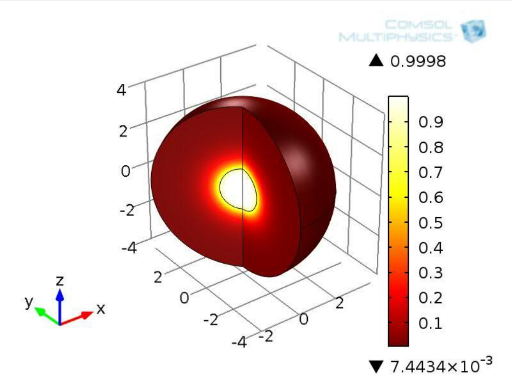
D diffusion coefficient
ξ vascular permeability coefficient

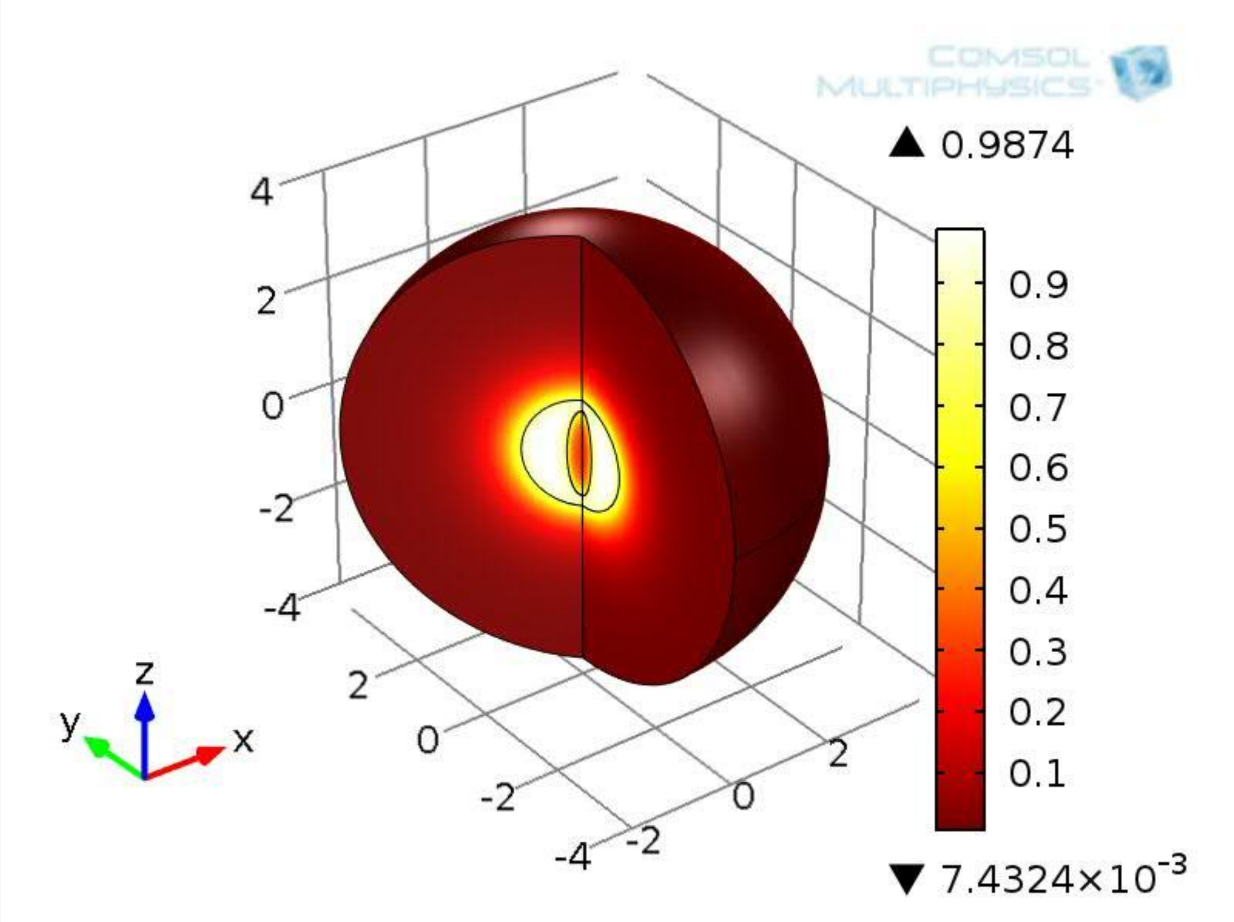
$$C_p=C_{0p}e^{-t/\tau_p}$$

C_p Plasma solute concentration:
Bolus injection

INTERSTITIAL FLUID PRESSSURE DROP

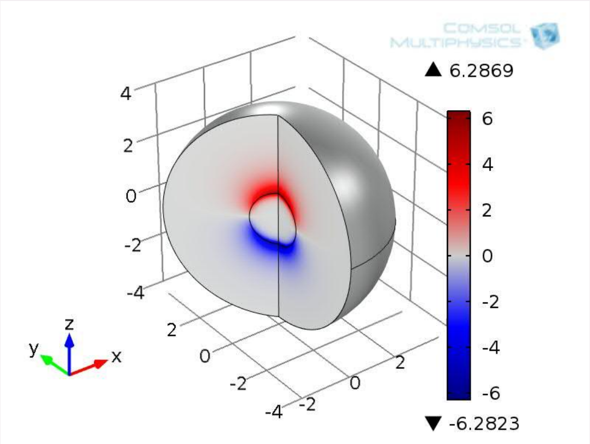
Relative interstitial fluid pressure drop in a spherical tumor surrounded by normal tissue

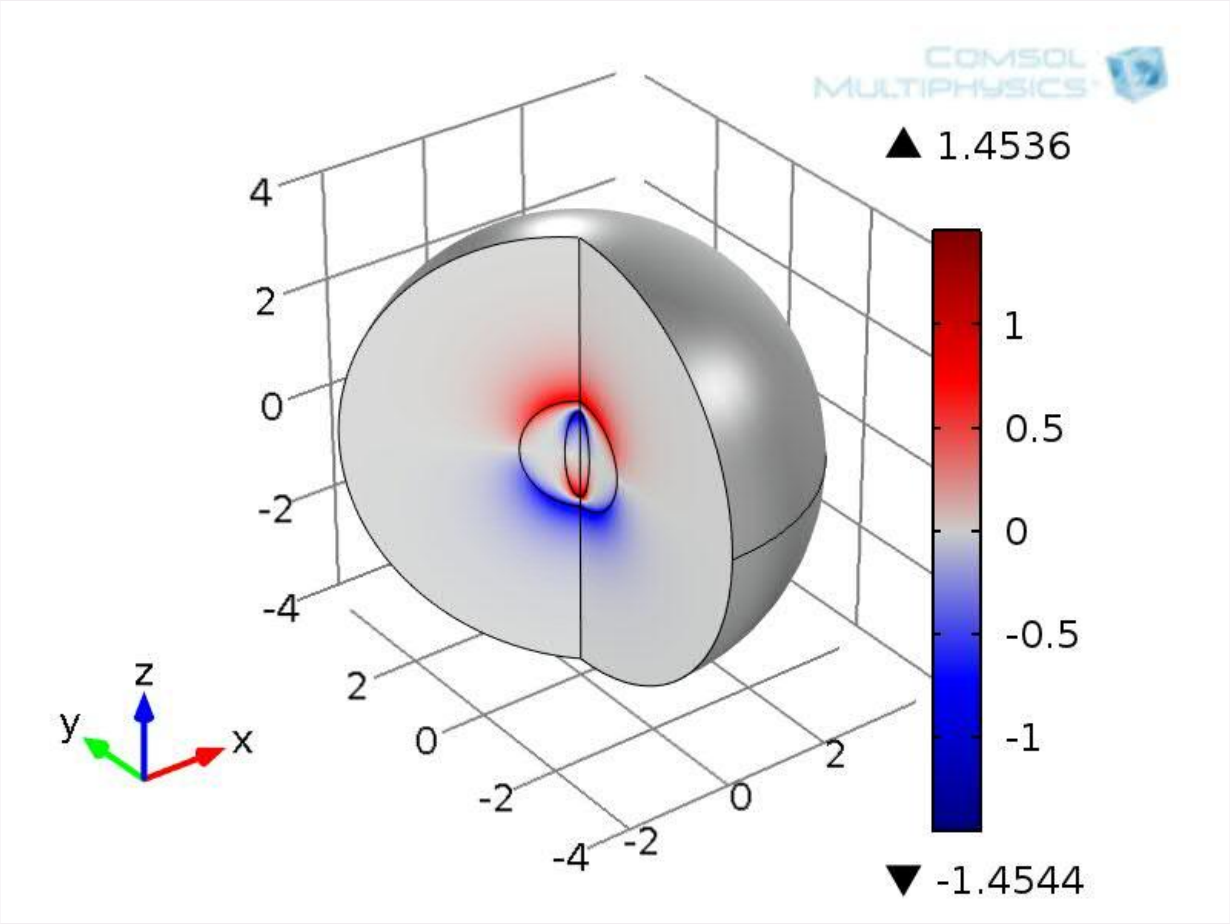




INTERSTITIAL FLUID VELOCITY

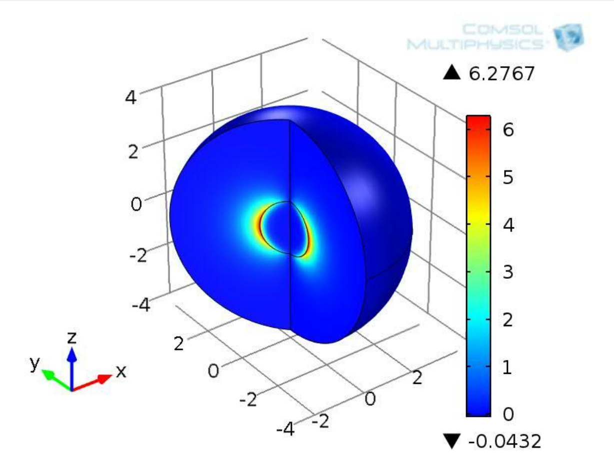
Normalized axial interstitial fluid velocity in a spherical tumor surrounded by normal tissue

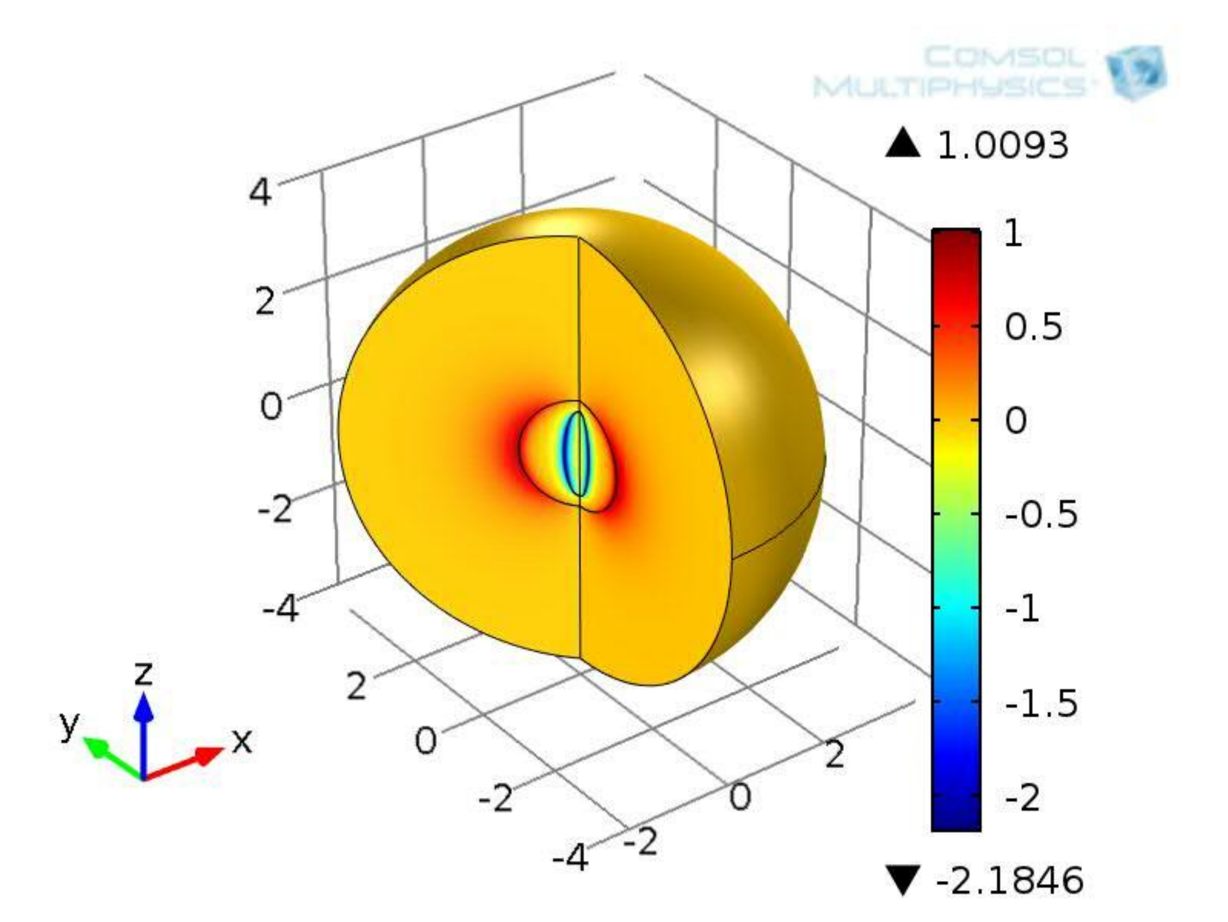




INTERSTITIAL FLUID VELOCITY

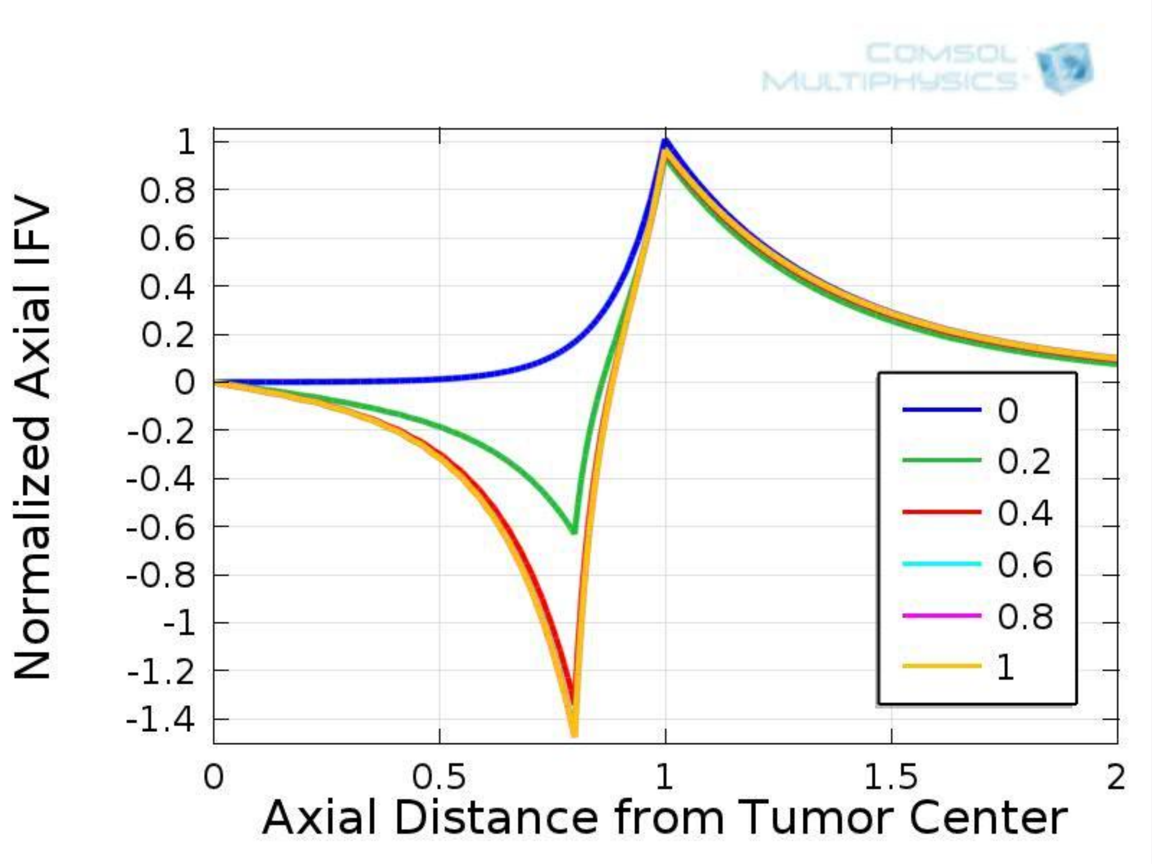
Normalized radial IFV in a spherical tumor surrounded by normal tissue





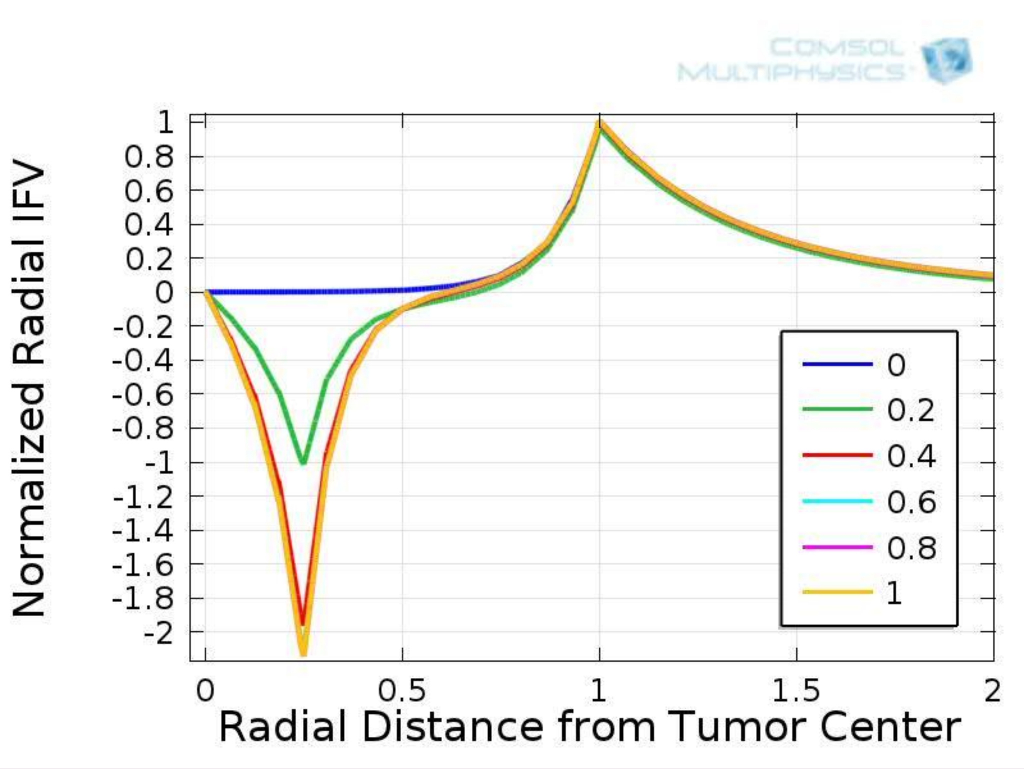
INTERSTITIAL FLUID VELOCITY

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



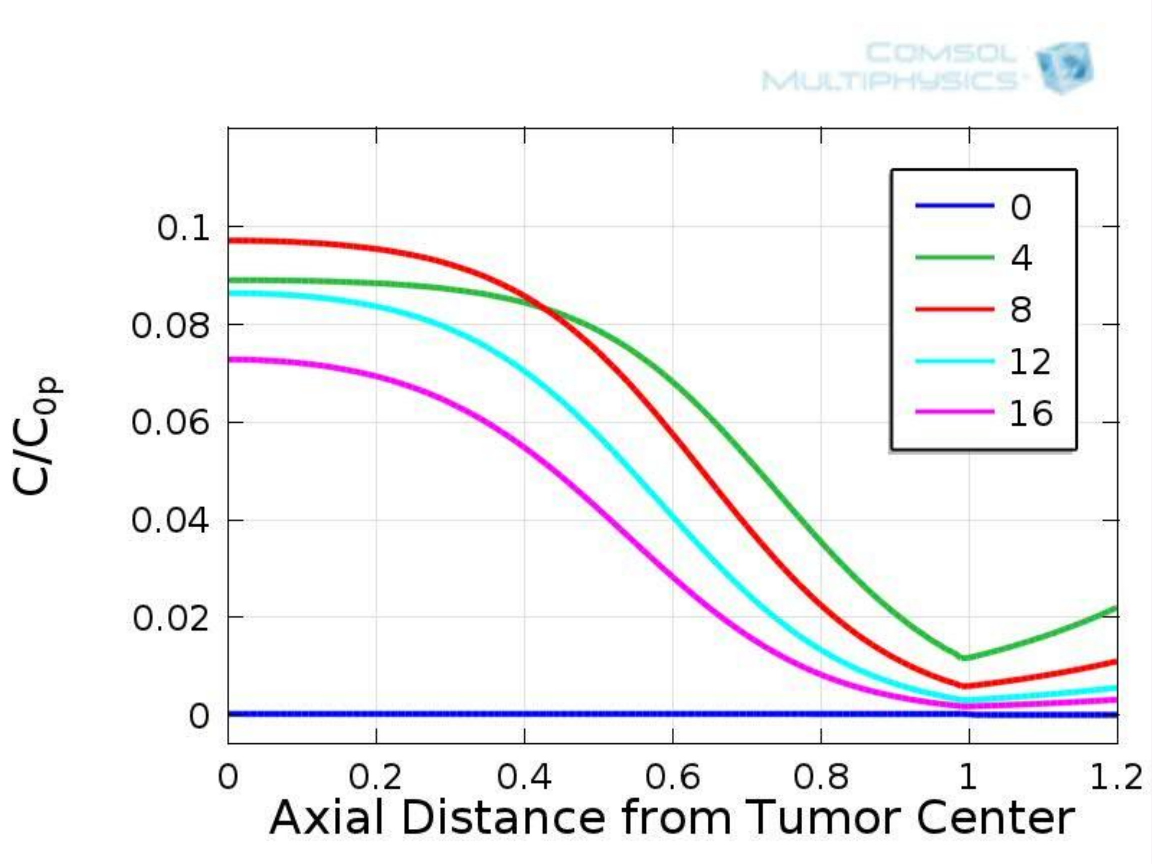
INTERSTITIAL FLUID VELOCITY

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



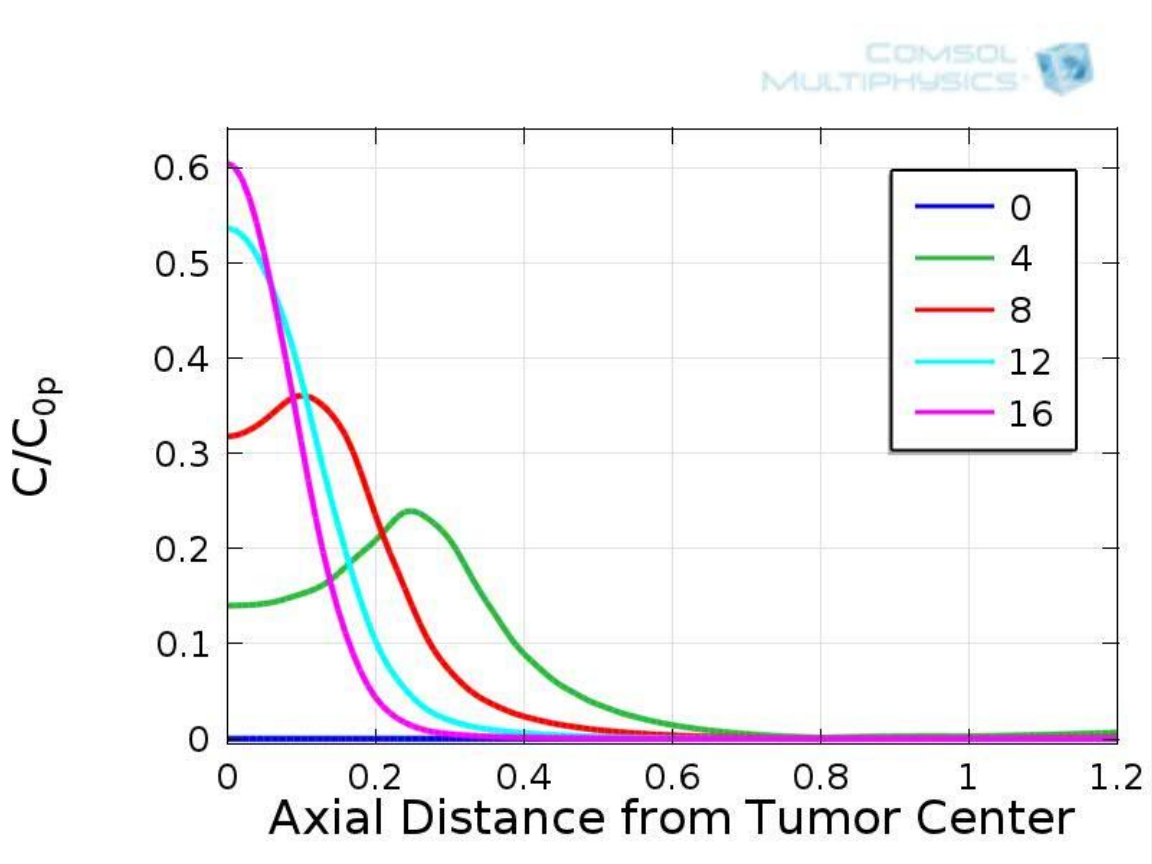
SOLUTE TRANSPORT EQUATION

Solutions of the macroscopic solute transport equation along the axial direction for a large macromolecule (MW: 50,000) at different hours according to the Baxter Jain Model



SOLUTE TRANSPORT EQUATION

Solute concentration at different hours after the drop of the interstitial fluid pressure



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

One possible mechanism is the temporary reduction of the interstitial fluid pressure

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