The effect of tissue hydraulic conductivity on interstitial fluid pressure (IFP) as measured by DCE-MRI in human prostate

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Abstract
Previous studies have described models for transport of molecules for different sizes by diffusion or convection (1). Interstitial fluid pressure (IFP) has been identified as a major obstacle in the uptake and distribution of different macromolecular agents used in *in vivo* anti-tumor therapies in solid tumors (2). Here we present modeling of the IFP and demonstrate the correlation between different physiological properties of solid tumor and IFP. Based on our model, we show that the hydraulic conductivity of the tissue has an important role on the IFP. This suggests that effective therapy of solid tumors requires a mechanism to exploit the hydraulic conductivity of the tumor and the surrounding tissue.

THEORY
Based on Starling's hypothesis of volume flow of fluid, transvascular transport of fluid (filtration rate of plasma) is described by:

$J = L_{\mathrm{p}} A_{\mathrm{c}}(p_{\mathrm{v}} - p_i - \sigma_T[\pi_{\mathrm{v}} - \pi_{\mathrm{i}}])$

Where J is the volume flow across a vessel wall (m^3/s), L_p the hydraulic conductivity of the microvascular wall (m^2 s/kg), A_c the surface area of the vessel wall (m^2), p_v the vascular fluid pressure (Pa), p_i represents IFP (Pa), σ_T the osmotic reflection coefficient, π_i the colloid-osmotic pressure of interstitial fluid (Pa), and π_v is the colloid-osmotic pressure of plasma (Pa) (2). Transport of fluid in an interstitial compartment steady laminar flow in a porous medium was modeled using Darcy's Law and conservation of mass:

$\vec{u} = -K\nabla\vec{p}, \qquad \nabla\cdot\vec{u} = L_{\mathrm{p}}A_{\mathrm{c}}(p_{\mathrm{v}} - p_i - \sigma_T[\pi_{\mathrm{v}} - \pi_{\mathrm{i}}]) - L_{\mathrm{pL}}A_{\mathrm{c}}(p_i - p_{\mathrm{L}}), \qquad \frac{\partial C}{\partial t} + \frac{1}{\varphi}u\cdot\nabla C = D\nabla^2 + P\frac{S}{V}(C_p - C) + \frac{J_v}{V}(1-\sigma)C_p$

Where $\vec{u}$ is the velocity vector (m/s) in $\nabla\vec{p}$ the gradient of the pressure (Pa), K the tissue hydraulic conductivity of, A the surface area of the material through which fluid flows (m^2), and μ is the viscosity of fluid (kg/m s) and L_{pL} is the lymphatic hydraulic conductivity, and p_L is the lymphatic pressure. C is the interstitial concentration, C_p is the arterial input function, and φ is the porosity of the tissue.

MATERIALS AND METHODS
Prostate cancer patient was scanned at 3-T (GE, Waukesha WI, USA) before surgery. DCE-MRI was performed with 7 seconds temporal resolution using a T1-weighted 2D fast spoiled gradient echo (FSPGR) sequence (TR/TE/α = 3.3 msec /1.6 msec /12°). Dynamic images were acquired for over 5.8 minutes after the Gd-DTPA bolus injection (0.2 mmol/kg). Using the Tofts' model, T1-weighted MR signal samples were fitted (3). Maps of K^{trans} and v_e were generated (Fig. 1A). Similar to Zhao et al, a 2D finite volume implementation of the SIMPLE (Semi-Implicit Method for Pressure Linked Equations) algorithm was developed in Matlab and was used to simultaneously solve Darcy's Law for the pressure, velocity, and conservation of mass for transient interstitial concentration (4). Boundary conditions: $\frac{\partial P}{\partial n} = 0$, $\frac{\partial C}{\partial n} = 0$; Initial Condition: $C(x, y, t_o) = 0$. A preconditioned conjugate gradient method was used in order to resolve the resulting linear system of equations. Two tissue hydraulic conductivity cases were considered: 1) our system consists of a homogenous slab of tumor tissue surrounded by normal tissue as a system boundary with a constant hydraulic conductivity profile (Fig 1B); 2) our system consists of a slab of tumor (segmented using the pathology map) with a gradient (Gaussian shaped) scalar isotropic tissue hydraulic conductivity profile (Fig. 1C).

RESULTS AND DISCUSSION
Maps of the pressure field and velocity field were generated for the constant and gradient based scalar isotropic tissue hydraulic conductivity cases (Fig. 1). For both,

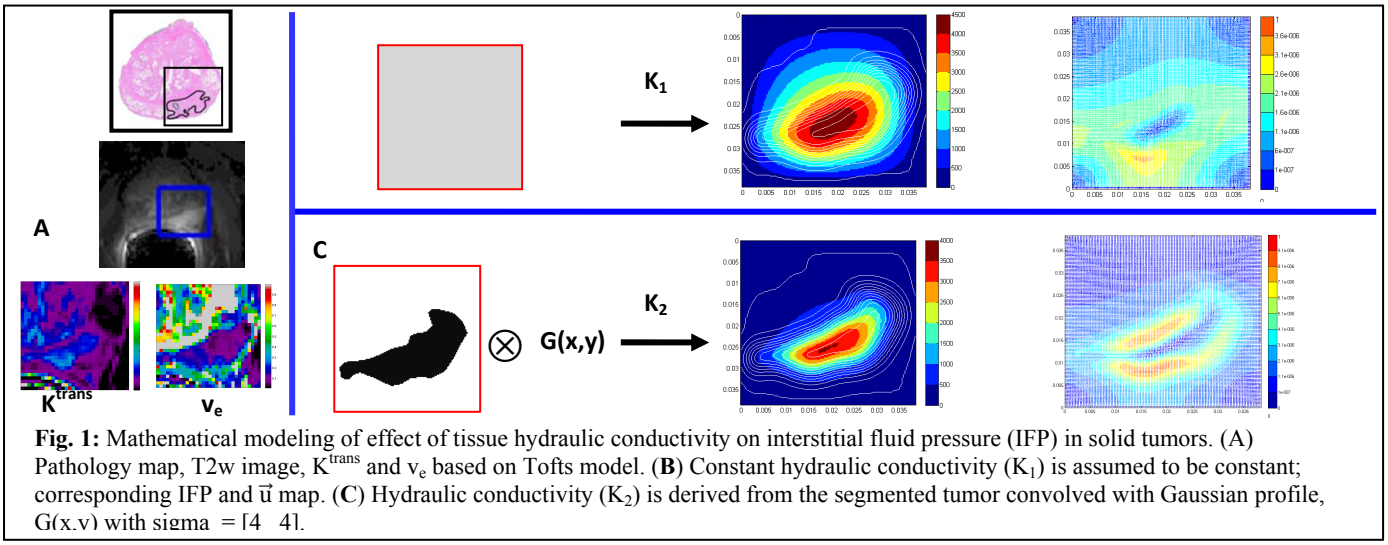

Fig. 1: Mathematical modeling of effect of tissue hydraulic conductivity on interstitial fluid pressure (IFP) in solid tumors. (A) Pathology map, T2w image, K^{trans} and v_e based on Tofts model. (**B**) Constant hydraulic conductivity (K_1) is assumed to be constant; corresponding IFP and $\vec{u}$ map. (**C**) Hydraulic conductivity (K_2) is derived from the segmented tumor convolved with Gaussian profile, G(x,y) with sigma = [4 4].

pressure maps indicate a high interstitial pressure within the tumor which generates an outwardly directed pressure source within the tumor core. This is due to the presence of a pressure source (lack of lymphatics and drainage). The magnitude of this source is inversely related to the tissue hydraulic conductivity. However, for the case with a tissue hydraulic conductivity gradient (lowest within tumor and outwardly increasing) the highest pressure region is more centrally located within the tumor and is outwardly decreasing. This indicates a need to further investigate tissue hydraulic conductivity anisotropy using a tensor approach. Corresponding velocity maps have the highest magnitude within the outer rim of the tumor where the pressure gradient is the highest. The model is simplified and assumes that neighboring tumor tissue is homogeneous. The porous media model will be refined and extended to account for realistic tissue heterogeneity using a stochastic partial differential equation approach.

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