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Sensitivity Analysis of an Image-Based Solid Tumor Computational Model with Heterogeneous Vasculature and Porosity

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Abstract

An MR image-based computational model of a murine KHT sarcoma is presented that allows the calculation of plasma fluid and solute transport within tissue. Such image-based models of solid tumors may be used to optimize patient-specific therapies. This model incorporates heterogeneous vasculature and tissue porosity to account for non-uniform perfusion of an MR-visible tracer, Gd-DTPA. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was conducted following intravenous infusion of Gd-DTPA to provide 1 h of tracer-concentration distribution data within tissue. Early time points (19 min) were used to construct 3D K^{trans} and porosity maps using a two-compartment model; tracer transport was predicted at later time points using a 3D porous media model. Model development involved selecting an arterial input function (AIF) and conducting a sensitivity analysis of model parameters (tissue, vascular, and initial estimation of solute concentration in plasma) to investigate the effects on transport for a specific tumor. The developed model was then used to predict transport in two additional tumors. The sensitivity analysis suggests that plasma fluid transport is more sensitive to parameter changes than solute transport due to the dominance of transvascular exchange. Gd-DTPA distribution was similar to experimental patterns, but differences in Gd-DTPA magnitude at later time points may result from inaccurate selection of AIF. Thus, accurate AIF estimation is important for later time point prediction of low molecular weight tracer or drug transport in smaller tumors.

Key Terms

DCE-MRI; drug transport model; extracellular transport; arterial input function; two-compartment model; contrast agent extravasation

Introduction

Solid tumors are understood to have transport obstacles that hinder systemic delivery of drugs and can stymie the overall effectiveness of treatment, since it is difficult to deliver drugs to all cells in a tumor.⁴⁵ The inherent uniqueness and heterogeneity of each tumor vascular network, created in part by tumor angiogenesis, compound treatment difficulties. Tumor angiogenesis is responsible for the creation of vessel networks that are abnormal when compared to networks in healthy tissue. The abnormalities are marked by a

disorganized vessel network, as well as non-uniform microvascular permeability or vessel leakiness.¹² These abnormalities along with impaired lymphatic function are partly responsible for creating an elevated interstitial tumor pressure. Elevated tumor pressures can work against drugs exiting blood vessels and entering into the parenchyma en route to destroy cancer cells. Furthermore, each tumor has unique microvascular blood flow, interstitial hydraulic conductivity, and interstitial matrix elasticity, which contribute additionally to variations of intratumoral pressures and flows.³³ The net result is heterogeneous extravasation and distribution of therapeutic agents into tissue, dependent upon specific tumor environments, following systemic injection.

Early mathematical tumor models have provided the groundwork by which transvascular exchange, transport of interstitial fluid (extracellular plasma fluid), and transport of macromolecules can be noninvasively investigated. For example, tumor models have been used to understand the role of interstitial pressure on the transport of a systemically delivered solute.^{3,4} Baxter and Jain (1989) used a continuum porous media approach to tumor tissue to solve interstitial and solute transport (IgG, F(ab')₂, and Fab). Solving for an idealized spherical tumor, they found elevated interstitial fluid pressure (IFP) to be a significant barrier: (1) elevated IFP reduced the driving force for extravasation of fluid and macromolecules in tumors; (2) spatially-varying IFP resulted in non-uniform filtration of fluid and macromolecules from blood vessels; (3) elevated IFP lead to an experimentally verifiable, radially outward interstitial fluid velocity (IFV) which opposes the inward diffusion of interstitial solute such as tracers, macromolecules, or drugs.^{3,26}

Other researchers have further investigated tumor models using a continuum approach. El-Kareh and Secomb studied the effects of uniformly increased vessel permeability on transport of macromolecules within a spherical tumor geometry.¹⁴ In later studies, Baxter and Jain expanded upon their own spherical tumor model by including a necrotic core without functioning vessels.⁴ The goal was to establish a more realistic case of a non-uniformly perfused tumor by including the concept of heterogeneous tissue properties. They found that the necrotic core did not reduce the central interstitial pressure in the tumor and had an effect on solute distribution of large, slow-diffusing molecules.

Mathematical descriptions of tumor transport have been adapted to numerous treatment situations and have shown the potential to impact clinical practices. Eikenberry modeled delivery of doxorubicin to a solid tumor comprised of multiple tumor cords and showed the potential for predictability of dose efficacy and cardiotoxicity.¹³ Smith and Humphrey elucidated the role of transvascular exchange during the administration of drug via intratumoral convective-enhanced delivery (CED).⁴³ Their model suggested that transvascular exchange reduction procedures would increase convective flow thereby aiding infusion therapies.

Recent computational fluid dynamics (CFD) approaches to tumor drug delivery, by integrating more patient specificity with the aid of medical imaging data, have created a new realm of personalized clinical possibilities. Tan, et al. used patient MRI data to reconstruct the 3D geometry of a resected brain region where the main part of the tumor was removed.⁴⁷ In this simulation, the resected region was implanted with poly (lactide-co-glycolide) (PLGA) wafers loaded with 1% Etanidazole. Elevated pressure was predicted in the resected region, as well as in the remaining tumor tissue. Our group has also presented an image-based model, which includes *in vivo* heterogeneous vasculature data since the extent of vessel non-uniformity can vary from patient to patient.⁵³ This current study has two aims: (1) to expand upon the CFD modeling approach by incorporating spatially variable tissue porosity (volume fraction of extracellular extravascular space (EES) over

total tissue volume) in addition to variable vessel permeability and (2) to compare simulated tracer distribution to experimental concentration data derived from MRI.

In this study, heterogeneous tissue and vascular properties are modeled by incorporating spatially-varying porosity and vascular permeability maps created from two-compartment analysis of early-time point (19 min) dynamic contrast-enhanced (DCE) -MRI data. DCE-MRI allows signal enhancement measurements of MR contrast agent (CA) uptake and washout in the KHT sarcoma-bearing hind limbs of mice ($n = 3$). Signal enhancement was measured following the systemic delivery of the low molecular weight, extracellular CA, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and was used to quantify concentration of Gd-DTPA in tumor and healthy tissue in each voxel of MR data on a voxel-by-voxel basis. Porosity and permeability maps, derived from these data, were incorporated into a 3D porous media model to predict interstitial fluid and tracer transport in tumor and host tissue at later time points. A sensitivity analysis was conducted based on a range of literature values using the data of one mouse: (1) to select an arterial input function (AIF) (the time-dependent CA concentration in arterial blood plasma) based on consistency of the first 19 min of experimental and simulated tracer transport and (2) to investigate the effects of baseline tissue and vascular transport properties on interstitial fluid and tracer transport. The optimal AIF and baseline transport properties were used to simulate interstitial fluid and tracer transport for two additional KHT sarcomas. Magnitude and distribution of experimental and simulated tracer concentration in tumor was compared for all three tumors.

An image-based solid tumor model may be used to optimize and evaluate treatment strategies for patient-specific therapies. The computational model presented here provides the necessary first steps toward that application. First, the simulation of CA uptake and washout in the tumor environment provides a foundation from which the model can be expanded to investigate transport of reactive drugs. Second, sensitivity analyses of these models provide a better understanding of the underlying transport processes and the effects of vascular and tissue properties within realistic tumor geometry. Third, by comparing simulations to experimental data, elements of the tumor model can be refined to create more accurate image-based models of drug delivery.

Materials and Methods

Animal Preparation

Animal models provide means to investigate *in vivo* systemic delivery of CA and create permeability and porosity maps. The patient-specific model was based on three C3H female mice (Jackson Laboratories, Bar Harbor, ME) that were each inoculated with 10^5 murine KHT sarcoma cells in the gastrocnemius muscle. Tumors were grown for 7 days to a hind limb diameter between 6.0–7.5 mm. During imaging, mice were anesthetized using a gas mixture of 98% oxygen, 2% isoflurane and given a $0.1\text{--}0.2\text{ mmol kg}^{-1}$ of body weight (bw) bolus tail vein injection of Gd-DTPA (Omniscan, GE Healthcare Inc., Princeton, NJ) CA at a constant rate ($\sim 0.4\text{ mL min}^{-1}$, 0.23 mL). Animal experiments were performed within the principles of the Guide for the Care and Use of Laboratory Animals and approved by the University of Florida Institutional Animal Care and Use Committee (IACUC).

MR Imaging

The MR experiment was performed using a Bruker Avance imaging console (Bruker NMR Instruments, Billerica, MA) connected to Magnex Scientific 11.1 T horizontal bore magnet system (Varian, Inc., Magnex Scientific Products, Walnut Creek California). Hind limbs of the mice were placed in a 1.5 cm inside diameter, transmit and receive, volume coil. Multiple T_2 -weighted spin echo (SE) scans ($TR = 2000\text{ ms}$, $TE = 15, 30, 45, 60$ and 75 ms)

were acquired for the calculation of T_2 values. Tumor boundaries could be manually segmented for each slice.¹⁰ Segmented images were used for geometric reconstruction of the tumor and host tissue volumes. A variable time for recovery (TR) SE sequence (TR = 5000, 2000, 1000, 500 and 250 ms, TE = 15 ms, field of view (FOV) = 2 cm × 1 cm × 1 cm, 9 slices, matrix size = 192 × 96, NA = 2), was acquired for calculation of native tissue T_1 values used in CA concentration calculations. Serial DCE-MR images, consisting of T_1 -weighted SE sequence (TR/TE = 330 ms/9.4 ms, FOV = 2 cm × 1 cm × 1 cm, 9 slices, matrix = 192 × 96, NA = 6, total acquisition time = 2 min 6 s) were collected before and after CA administration. T_1 -weighted SE sequence with a short TE was used to avoid noise in the measured signal that can occur under hypoxic conditions² with sequences sensitive to T_2 effects.

Vascular Permeability Maps

Vascular leakiness was described using endothelial transfer coefficient (K^{trans}) values. K^{trans} values were estimated using a two-compartment model approach, where the two compartments are the blood plasma and EES. From DCE-MRI data, K^{trans} values were quantified on a voxel-by-voxel basis by: (1) estimating CA concentration in tissue via the relationship between concentration and signal intensity⁹ and (2) using a Tofts and Kermode model to fit to the CA kinetics within the first 19 min. Previous DCE-MRI data showed that peak tissue concentration was reached within 5 min post-injection for fast enhancing breast tumor ($K^{\text{trans}} > 0.1 \text{ min}^{-1}$) and that this time window was acceptable to properly fit K^{trans} .³⁹ The 19-minute time window was chosen for our study because of slower enhancing peripheral tumor tissue (peak time at ~17 min). It was assumed that change in CA concentration in tissue is dominated by a fast transvascular exchange at early time points. Though, over longer time scales interstitial convection and diffusion may play an important role in the distribution of CA within the tumor space requiring a continuum approach to make accurate predictions.

A linear relationship between contrast agent concentration and T_1 was assumed. An average of the pre-contrast images was used to solve for baseline (pre-injection) signal values, and the transverse-relaxation contribution to signal was assumed to be unity. Then, concentrations of Gd-DTPA in tissue were solved at each time point using the standard spin-echo signal equation⁹

$$C_t = \frac{1}{R_1} \left[\frac{1}{\text{TR}} \ln \frac{S(0)}{S(0) - S(C_t) \cdot (1 - e^{-\text{TR}/T_{10}})} - \frac{1}{T_{10}} \right]. \quad (1)$$

C_t is the volume-averaged tissue concentration of Gd-DTPA determined by MRI; R_1 is the longitudinal relaxivity of the contrast agent; TR is the recovery time; T_{10} is the relaxation time without contrast agent; $S(C_t)$ and $S(0)$ are signal intensities at CA concentrations C_t and zero respectively; TR, T_{10} , $S(0)$, and $S(C_t)$ are known values; and R_1 was approximated as $2.7 \text{ L mmol}^{-1} \text{ s}^{-1}$ (based on Gd-DTPA relaxivity⁴⁰ in rat muscle at 6.3 T).

Tofts-Kermode two-compartment model⁴⁸ incorporates basic physiological phenomena to describe the transport of systemically injected contrast agents into tissue space. The two-compartment model can be described by

$$\frac{dC_t}{dt} = K^{\text{trans}} C_p - \frac{K^{\text{trans}}}{\phi} C_t \quad (2)$$

where t is time; C_p is the AIF that describes the time course of Gd-DTPA concentration in the blood plasma; ϕ is the volume fraction of EES or porosity (also referred to as v_e in tumor

perfusion studies). The volume fraction of plasma in each voxel was assumed small compared to ϕ . Transvascular transport of Gd-DTPA solely into the EES at early post-infusion times was assumed. C_p following a bolus injection was represented by a biexponential decay⁴⁸ that was normalized:

$$C_p(t) = d \left[a_1 e^{-m_1 t} + a_2 e^{-m_2 t} \right] \quad (3)$$

where a_1 and m_1 represent the amplitude and rate constant, respectively, of the fast equilibrium between plasma and extracellular space; a_2 and m_2 represent the amplitude and rate constant of the slow component of the clearance; d is the dose of the bolus injection. Solving Eq. (2) by substitution of Eq. (3) in terms of concentration of CA in tissue, C_t , produces

$$C_t(t) = K^{\text{trans}} d \left\{ \frac{a_1}{\frac{K^{\text{trans}}}{\phi} - m_1} e^{-m_1 t} + \frac{a_2}{\frac{K^{\text{trans}}}{\phi} - m_2} e^{-m_2 t} - \left(\frac{a_1}{\frac{K^{\text{trans}}}{\phi} - m_1} + \frac{a_2}{\frac{K^{\text{trans}}}{\phi} - m_2} \right) e^{-\frac{K^{\text{trans}}}{\phi} t} \right\} \quad (4)$$

MR experimental concentrations determined by Eq. (1) were used to fit Eq. (4) in order to solve K^{trans} and ϕ at each voxel within the tumor boundary to generate 3D maps. K^{trans} and ϕ parameters were fit using a nonlinear regression in MATLAB (MATLAB Version 7.1, The MathWorks, Inc., Natick, MA). Only physically relevant ranges were considered (K^{trans} 0 and 0 ϕ 1) where $R^2 > 0.5$. Values of K^{trans} were set to zero and $\phi = 0.3$ in voxels where the fit was poor ($R^2 < 0.5$). This occurred in <5% of voxels within all three tumors.

3D Porous Media Mathematical Model

The 3D porous media tumor model accounts for the CA-distribution time dependence on the underlying plasma flow and diffusion within the interstitial space of tissue. Each point in space in this porous media model contains a tissue and vascular component. The vascular components provide a source or sink for both plasma fluid and tracer per unit tissue volume. The filtration rate of plasma fluid per unit volume (J_v/V) across the vessel wall is described by Starling's law³

$$\frac{J_v}{V} = L_p \frac{S}{V} (p_v - p_i - \sigma_T (\pi_v - \pi_i)) \quad (5)$$

where L_p is the vessel permeability, S/V is microvascular surface area per unit volume, p_v is the microvascular pressure, p_i is the IFP, σ_T is the average osmotic reflection for plasma protein, π_v is osmotic pressure in microvasculature, and π_i is osmotic pressure in interstitial space. Since we were interested in capturing vascular heterogeneity, it was necessary to include vessels that were non-uniformly permeable to both plasma fluid and CA. K^{trans} values directly describe the leakiness of vessels to CA. In order to account for heterogeneous plasma fluid leakiness, K^{trans} values were normalized by the average K^{trans} within the tumor, $\bar{K}^{\text{trans}}$, and this normalized value was used to scale J_v/V in order account for plasma leakiness heterogeneities. This was done assuming that patterns of leakiness are similar for both tracer and plasma fluid.

The tissue continuum was modeled as a porous media. In tissue, the continuity equation³ and Darcy's law were used to solve IFP and tissue-averaged IFV ($\mathbf{v}$) and were given by

$$\nabla \cdot \mathbf{v} = \frac{K^{\text{trans}}}{\bar{K}^{\text{trans}}} \frac{J_v}{V} - \frac{L_p S_L}{V} (p_i - p_L) \quad (6)$$

and

$$\mathbf{v} = -K \nabla p_i, \quad (7)$$

respectively. The first term on the right hand side of Eq. (6) describes a volumetric source due to the vasculature; the second term on the right hand side is a sink due to lymphatic vessels. $L_{pL}S_L/V$ is the lymphatic filtration coefficient, p_L is pressure in the lymphatic vessels, and K is the tissue hydraulic conductivity. Lymphatic function was assumed in host tissue only with $p_L = 0$ kPa. Darcy's law is commonly applied to tumors, perfused muscle tissues, and flow in soft connective tissues.²⁷ K is small in these types of tissues such that the role of viscosity is more important at the fluid-solid interface of the porous media than within the fluid.

Transport of interstitial Gd-DTPA was solved using the convection and diffusion equation for porous media⁴⁹:

$$\frac{\partial C_t}{\partial t} + \frac{\mathbf{v}}{\phi} \cdot \nabla C_t - D_{\text{eff}} \nabla^2 C_t = K^{\text{trans}} \left(C_p - \frac{C_t}{\phi} \right) - \frac{L_{pL}S_L}{V} (p_i - p_L) \frac{C_t}{\phi} \quad (8)$$

where D_{eff} is the effective diffusion coefficient for Gd-DTPA in tissue. The second and third term on the left describe convective flux and diffusive flux, respectively. The transvascular source term on the right is a modified form of the Kedem-Katchalsky equation where diffusion dominates the transfer of solute across the microvessel wall; the sink term on the right accounts for lymphatic drainage of solute in normal tissue. A block diagram shows the flow of the mathematical methodology and experimental comparison (Fig. 1).

Computational Model

From MR slices, tumor and hind limb geometries were manually segmented (MATLAB v.7, Natick, MA) based on contrast differences in T_2 values (Fig. 2a). Triangulated mesh surfaces were generated to create tumor and host tissue boundaries (Amira 4.1.1, San Diego, CA) and were converted to parametric representation, non-uniform rational B-spline surfaces (NURBS) (Geomagic Studio, Research Triangle Park, NC). Meshes for the volumes of host tissue and tumor were created (Gambit, Fluent, Lebanon, NH; Fig. 2b). Meshes were composed of ~2,700,000 4-node tetrahedral elements. The large number of elements aided the porous media solver with convergence for solutions with steep pressure gradients at the tumor boundary in the CFD software package (FLUENT 6.3, Fluent, Lebanon, NH).

Prediction of tumor tracer distribution was a two-step process. First, steady-state interstitial plasma fluid flow was solved (Eq. (6)). Then, tracer transport (Eq. (8)) was solved over 1 h. Boundary conditions were such that the solute was assumed to exit at the cut ends at the same rate as the interstitial plasma fluid. Additionally, the skin boundary was assumed to be impermeable to tracer and plasma while the cut ends of the leg were considered far enough away from the tumor boundary and therefore set to a normal tissue pressure^{19,26}, $p_i = 0$ kPa. Initial tissue concentration was zero for the tracer solution.

Sensitivity Analysis

The model was dependent on vascular and tissue transport parameters as well as AIF. Values in Table 1a were used for all simulations. Some of these values were selected based on the model presented by Baxter and Jain (1989); these particular parameters are not well-measured in literature and are often used by other models of interstitial flow within tumors.^{38,47,53} Table 1b contains the nominal baseline values for the sensitivity analysis that were selected based on or near the ranges obtained from literature.

Three AIFs were considered in order to estimate the time course of CA concentration in blood plasma: a fast decay²³ where $a_1 = 9.2 \text{ kg bw L}^{-1}$, $a_2 = 4.2 \text{ kg bw L}^{-1}$, $m_1 = 0.004 \text{ s}^{-1}$, and $m_2 = 0.0008 \text{ s}^{-1}$; an intermediate decay¹ where $a_1 = 13.0 \text{ kg bw L}^{-1}$, $a_2 = 16.0 \text{ kg bw L}^{-1}$, $m_1 = 0.005 \text{ s}^{-1}$, and $m_2 = 0.00043 \text{ s}^{-1}$; a slow decay^{48,51} where $a_1 = 4.0 \text{ kg bw L}^{-1}$, $a_2 = 4.8 \text{ kg bw L}^{-1}$, $m_1 = 0.002 \text{ s}^{-1}$, and $m_2 = 0.0002 \text{ s}^{-1}$. Given that dose was 0.2 mmol kg^{-1} , a_1 and a_2 were scaled so that $C_p(t=0)$, C_{p0} , was 2.0 mM based on the dilution calculation (from the measured concentration of the bolus injection of Gd-DTPA and the estimated blood volume of the mouse based on body weight).¹¹ K^{trans} and ϕ maps were created for each AIF and used to simulate interstitial fluid flow and the first 19 min of tracer transport. The slow AIF was selected for the sensitivity analysis because the average Gd-DTPA concentration in tumor tissue, $C_{t,\text{avg}}$, behavior was most similar to the experimental data (Fig. 3). K^{trans} and ϕ maps created based on the slow AIF were used for sensitivity analysis (Fig 4).

Other parameters of interest in this sensitivity analysis were as follows: tumor vessel permeability ($L_{p,t}$), normal tissue permeability ($L_{p,n}$), $L_{pL}S_L/V$, D_{eff} , and ratio of tumor hydraulic conductivity to normal tissue hydraulic conductivity (K_t/K_n). K_t/K_n was chosen to account for the relative difference in hydraulic conductivity of normal and tumor tissue as measured experimentally. C_{p0} was also analyzed to observe the effects of over- or under-estimating this value. Sensitivity analysis was conducted by using high and low values with respect to the baseline values. Permeability, $L_{pL}S_L/V$, and K_t/K_n values were set such that the high case was $2 \times$ baseline and the low case was $0.5 \times$ baseline. D_{eff} were set such that high case $10^1 \times$ baseline and low case was $10^{-1} \times$ baseline. The high case for C_{p0} was 2.5 mM and low case was 1.5 mM .

Results

Interstitial Fluid Transport

For the baseline simulation of interstitial fluid transport, pressure was predicted to be higher within the tumor than outside the tumor. The pressure contour in Fig. 5a shows higher IFP ($P_{t,\text{max}} = 1.4 \text{ kPa}$) within the tumor than the surrounding host tissue for the baseline simulation. Pressure varied within the tumor from 0.86 kPa at the boundary to 1.4 kPa in the tumor core (slightly skewed towards the left from mid-tumor in Fig. 5a). The pressure fell sharply ($|\Delta P_{t,\text{max}}| = 0.79 \text{ kPa mm}^{-1}$) at the tumor boundaries Fig. 5b. Outward flow of interstitial fluid from the tumor was observed (Fig 6a). The magnitude of volume-averaged fluid velocity was predicted to be highest at or near the boundary of the tumor $0.59 \mu\text{m s}^{-1}$ and $0.41 \mu\text{m s}^{-1}$ at both ends of the bisecting line (Fig. 6a & Fig 6b). Approximately 1 mm into the host tissue, fluid velocity was reduced by 75% to $0.1 \mu\text{m s}^{-1}$ and continued to decrease to the cut ends ($\sim 0.03 \mu\text{m s}^{-1}$).

In both the high and low cases of the sensitivity analysis, interstitial hypertension was observed within the tumor with a decrease in pressure at the tumor-tissue interface (Fig. 5b). The high $L_{p,t}$, $L_{p,n}$, and low $L_{pL}S_L/V$, K_t/K_n cases all resulted in intratumoral pressures that were greater than the baseline simulation. Percentage increase in intratumoral pressures from the baseline was highest for the high $L_{p,t}$ case. Decreases in the pressure gradient at the tumor-tissue interface from the baseline simulation were observed in the low K_t/K_n , $L_{pL}S_L/V$, $L_{p,t}$ and high $L_{p,n}$ cases. The low $L_{p,t}$ and high K_t/K_n resulted in a flattening of intratumoral IFP profile. Percent difference in intratumoral pressure and pressure gradient at the tumor-tissue interface for all cases with respect to the baseline deviations are calculated in Table 2.

Volume-averaged velocity of interstitial fluid was predicted to be highest near the boundary of the tumor in all cases of the sensitivity analysis (Fig 6b). Volume-averaged velocity at the

boundary was reduced by $> 100\%$ near the cut ends in all cases. High $L_{p,t}$, K_t/K_n and $L_{p,n}$, and low $L_{p,n}$ and K_t/K_n cases all resulted in tumor boundary tissue-averaged IFVs that were greater than the baseline simulation. The highest increase in velocity was witnessed for the high $L_{p,t}$ case, which corresponded to a peak volume-averaged velocity of $\sim 0.8 \mu\text{m s}^{-1}$ at the tumor-tissue interface. $L_{p,n}$ had little effect on the velocity at the tumor boundary ($< 2\%$ difference from baseline).

Tumor vessel permeability, $L_{p,t}$, had the greatest impact on the interstitial fluid solution. Changes in $L_{p,t}$ resulted in a $> 30\%$ difference from the baseline when looking at three behaviors: intratumoral pressure, tumor-tissue pressure gradient, and magnitude of velocity at the tumor-tissue interface. Normal vessel permeability, $L_{p,n}$, was the least sensitive parameter in terms of impact on the interstitial fluid solution. Though the low and high C_{p0} cases resulted in respectively higher and lower K^{trans} values than the baseline (within the tumor), interstitial fluid transport for the low and high C_{p0} cases was identical to the baseline.

Baseline simulations for the two additional KHT sarcomas resulted in lower interstitial peak pressures (0.50–0.75 kPa) and boundary pressure gradients ($|\Delta p_{1,\text{max}}| = 0.15 \text{ kPa mm}^{-1}$) than the data set used for the sensitivity analysis; however, the pressure distribution pattern was similar. Subsequently, outward flow of interstitial fluid was observed with the highest magnitude of volume-averaged fluid velocity near the boundary of the tumor ($0.35 \mu\text{m s}^{-1}$).

Tracer Transport

The effect of AIF upon average Gd-DTPA concentration, $C_{t,\text{avg}}(t)$, in tumor tissue was examined and compared to experimental data obtained from MRI for the first 19 min (Fig. 3). Three simulations of tracer transport were conducted which corresponded to three AIFs. The aim was to determine the best AIF based on agreement between experimental and simulated $C_{t,\text{avg}}(t)$ behavior at early time points. The simulated curves showed higher peak concentration than the MR measured concentration. Peak concentrations were 11%, 30%, and 30% higher than the experimental peak for slow, intermediate, and fast respectively. Assuming monoexponential decay for the tumor volume-averaged washout behavior, decay rates were as follows: -0.029 min^{-1} (experimental), -0.050 min^{-1} (fast), -0.034 min^{-1} (slow), and -0.045 min^{-1} (intermediate). The slow AIF produced peak concentration and washout behavior in tumor similar to experimental observation.

The baseline simulation showed increased Gd-DTPA deposition on the left half of the tumor (Fig. 7), which corresponded to the leakier, left side of the tumor (Fig. 4a). Clearance of Gd-DTPA due to transvascular exchange was observed in the tumor from 5 to 60 min. Tracer transport simulations showed qualitative spatial distribution and transient behavior similar to that of the experimental data. Also, tracer transport was less sensitive than interstitial fluid transport to changes in model parameters in Table 1b (Fig. 8). However, tracer transport was sensitive to changes in C_{p0} .

Considerable overlap along the bisecting tumor line was observed for the baseline simulation and simulations of high and low model parameters from Table 1b (Fig. 8). The consistency of the distribution pattern along the tumor line resulted in a high Pearson product-moment correlation coefficient (PMCC), r , for all simulated cases ($r > 0.99$ for $t = 5, 30, 60 \text{ min}$). Concentration deviations from the baseline within the tumor were estimated; root mean squared (RMS) errors, ϵ , were found to be small for all cases ($0.03 \times 10^{-5} \text{ mM} < \epsilon < 4.4 \times 10^{-5} \text{ mM}$), but for the high and low C_{p0} cases ($80 \times 10^{-5} \text{ mM} < \epsilon < 260 \times 10^{-5} \text{ mM}$) over the 1 hr simulation (Table 3). The high and low C_{p0} cases along the tumor line resulted in C_t lower and higher than the baseline case at $t = 5 \text{ min}$, respectively. High and low $L_{p,t}$, $L_{p,n}$, $L_{pL}S_L/V$, K_t/K_n and D_{eff} cases exhibited a similar washout behavior to

$C_{t,avg}(t)$ of the baseline case ($\sim -0.03 \text{ min}^{-1}$). Variations in experimental and numerical error made it difficult to correlate the small changes in ϵ to relative sensitivity for the tissue and vascular parameters.

The results of the sensitivity analysis showed agreement between simulated and experimental C_t for the first 30 min ($\epsilon = 0.46 \times 10^{-3} \text{ mM}$ at $t = 5 \text{ min}$; $\epsilon = 0.58 \times 10^{-3} \text{ mM}$ at $t = 30 \text{ min}$) for all cases but high and low C_{p0} ($1.8 \times 10^{-3} \text{ mM} < \epsilon < 3.9 \times 10^{-3} \text{ mM}$). At $t = 60 \text{ min}$, all cases over-predicted C_t ($0.5 \times 10^{-3} \text{ mM} < \epsilon < 1.8 \times 10^{-3} \text{ mM}$) within the tumor (Fig. 8c). Even though C_t was over-predicted, sensitivity analysis simulations showed similar patterns of Gd-DTPA concentration distribution to experimental patterns ($r > 0.89$) within the tumor. Including the host tissue in the correlation reduced $r = 0.42$ at $t = 60 \text{ min}$. This was due to later peak C_t ($> 17 \text{ min}$) in the experimental data observed at two regions of the host tissue (2–3 mm and 16–20 mm; Fig 8).

Because tracer transport was less sensitive to changes in transport parameters, baseline values were used to predict transport in the two additional KHT sarcomas (Fig. 9). Similar simulated and experimental distribution patterns of Gd-DTPA concentration were observed at $t = 5$ and 30 min ($r > 0.78$) within the tumor (Fig. 9a–9d); however, the correlation in the tumor was not as strong ($r > 0.58$) at $t = 60 \text{ min}$ (Fig. 9e–f). Magnitude of simulated Gd-DTPA concentration along the bisecting line through a tumor was greater than experimental magnitudes at $t = 60 \text{ min}$ ($0.5 \times 10^{-3} < \epsilon < 2.1 \times 10^{-3} \text{ mM}$; Fig. 9e–9f). Furthermore, the average Gd-DTPA concentration within the entire tumor volume for the simulations were greater than experiments at $t = 60 \text{ min}$ for all three tumors. The largest percent difference of average Gd-DTPA concentration within the tumor volume (700%) occurred in the tumor shown in Fig. 9b–9f. Relative concentration error was $< 38\%$ in the other two tumors.

Discussion

This study presents the first image-based tumor model, with both heterogeneous vasculature and tissue porosity, which predicts interstitial fluid and solute transport within tissue. The model exhibits two important interstitial transport characteristics: it predicts interstitial hypertension, and increased velocities at the host tissue-tumor interface. A high correlation was observed ($r > 0.89$) between predicted and experimental spatial deposition of Gd-DTPA along a bisecting line within the tumor at 1 h in the tumor used to develop the model. Also, transient behavior (washout rates) of Gd-DTPA in the tumor showed good agreement between the simulation and experiment. The two additional KHT sarcomas used to test the developed model showed varied outcomes in terms of predicting the average concentration of Gd-DTPA at 1 h. Namely, experimental and simulated concentration distribution and magnitude correlated well for one modeled tumor while errors were significant in the other. The mismatches in late time point transient behavior emphasizes acquisition of personalized AIFs for further optimization to provide better estimates of concentration at 1 h in transvascular exchange dominated tumors.

In previous studies, intratumoral IFP has been investigated and hypertension has been simulated^{3,37,47,53} and measured.^{5,7,19,34,52} IFP values have been shown to vary within a tumor line and to be proportional to tumor volume by Gutmann et al.¹⁹ In their study, a pressure range of 0.5 – 4.4 kPa for squamous cell carcinomas was observed. The baseline intratumoral pressures simulated in this image-based model fell within the low end of this range. This could be in part due to tumor size. The tumor volumes in the current study were smaller ($\sim 95\%$) than the non-metastatic smallest tumors investigated by Gutmann's group. In our model, a smaller tumor would be expected to have a lower intratumoral IFP. Smaller tumors have fewer vessels than larger tumors so they have fewer available fluid sources. Previous models of idealized tumors predicted increased velocities at the tumor boundary.²⁵

For an isolated tumor with a diameter of 2 cm, fluid velocity at the boundary was approximately $0.1\text{--}0.2\ \mu\text{m s}^{-1}$. In the presented model, velocity at tumor boundary in the baseline simulation was predicted to be higher ($0.35\text{--}0.60\ \mu\text{m s}^{-1}$).

It should be noted that solute transport in this study was limited to a low molecular weight MR visible tracer, Gd-DTPA. The transport of low molecular weight tracers is less likely to be convective when compared to macromolecular tracers or therapeutic agents. Despite these limitations, image-based models using Gd-DTPA as an interstitial tracer offers a few advantages: (1) DCE-MRI using Gd-DTPA is well understood, documented, and it is a clinically used approach to understand the tumor environment; (2) DCE-MRI using Gd-DTPA provides qualitative and quantitative (e.g., vascular leakiness maps) data; (3) Gd-DTPA is similar molecular weight to some chemotherapeutic drugs (e.g. doxorubicin = $543\ \text{g mol}^{-1}$); (4) Gd-DTPA extravasates more effectively than macromolecules and does not bind, hence it provides a best case scenario for the evaluation of smaller macromolecular drug transport.

For solute transport simulations, the model presented in this study exhibited a similar extent of heterogeneity (70–80% difference in maximum and minimum concentrations) at early time points (5–6 min) along a bisecting tumor line as a previous Gd-DTPA transport model from our group.⁵³ However, there are two markedly different tracer transport behaviors between our two studies. In the previous study, along the entire extent of the bisecting tumor line, Gd-DTPA concentration increased and the concentration profile flattened over the course of 30 min. The current study observed an overall decrease across the bisecting line for this same time course and a less dramatic flattening. These differences are likely due to three factors in our model: (1) a faster decaying AIF than the previous model provided for transvascular sink terms during the first 30 min of the simulation; (2) the incorporation of both spatially varying porosity and K^{trans} allowed for more finely tuned kinetic behavior than the previous fixed porosity model; (3) lower effective diffusivity contributed to less dramatic flattening of the tracer concentration profile.

The sensitivity analysis pointed out aspects of the model—parameters, source terms, and measurements—that most effect transport. This knowledge can be used to simplify the model by reducing the number of input parameters. Also, the sensitivity analysis was conducted with *a priori* knowledge of the experimental data. This allowed the investigation of changes in model parameters to provide a best fit to the experimental concentration data.

Interstitial fluid flow was most sensitive to vessel permeability with $L_{p,t}$ having the most profound impact on IFP and boundary fluid velocity. These permeability values scale pressure differences that exist across vessel walls and directly affect volumetric source and sink terms of the continuity equation. Non-invasive, patient-specific measurements of $L_{p,t}$ might be necessary in order to make more accurate predictions of intratumoral pressure and tumor boundary convection using an image-based modeling approach. Alternatively, non-invasive measurements of IFP distribution in tumors²² could be imported into this model to better estimate transport parameters such as $L_{p,t}$ and calculate transport. With the validation of predicted intratumoral IFP, these models could be used to predict disease progression after radiotherapy in patients with cervix cancer.³² Long-term studies of cervical cancer have reported that intratumoral pressures have greater impact on predicting survival than tumor hypoxia.¹⁷

Gd-DTPA tracer transport was relatively insensitive to changes in vascular and tissue transport parameters. When modeling low molecular weight tracers or drugs in smaller tumors (~6–7 days for KHT sarcoma cells), it is likely that tracer transport is dominated by transvascular exchange, rather than convection or diffusion, at the simulated time scale. In

the case of transvascular exchange-dominated tumors, accurate AIF and C_{p0} measurements are the most important parameters for accurate prediction of concentration in tissue at later time points. For larger tumors, this may not be the case due to the increase of tumor tissue heterogeneity, which will occur as the tumor develops necrotic regions. Because the transvascular exchange term is dominant, due to the frequency of high K^{trans} (0.1 min^{-1}) values in the tumor, it might not be important to have a continuum porous media approach which accounts for convection and diffusion in the interstitial space of smaller tumors at the simulated time scale; a two-compartment model may suffice. However, it should be noted that the low average porosity in all three tumors (~ 0.1) could have masked the role of convection and diffusion. It has been suggested by other researchers that low porosity values (< 0.2) in the tumor obtained from DCE-MRI may be indicative of convective tracer clearance and not physiologically low extracellular volume fraction.²² A continuum porous media approach is likely necessary to model cases of lower leakiness where the transvascular exchange term is less dominant and porosity values less obtainable using early DCE-MRI time points. In these cases diffusion and convection can have greater impact on interstitial molecules and porosity values would have to be obtained DCE-MRI independent methods or fixed. Moreover, the continuum model would be necessary to model transport of macromolecular agents that require convective transport over smaller time scales.

The insensitivity of vascular and tissue transport parameters resulted in no considerable spatial changes in time, yet temporal and spatial distribution of baseline simulation and experiment Gd-DTPA in tissue was comparable. This underscores the importance of spatially heterogeneous leakiness and porosity in the transvascular exchange mechanism for solute transport in patient-specific tumor models as well as proper estimation of baseline C_{p0} . The low and high C_{p0} case illustrated the importance of proper dose measurement. There are two potential sources of error, which can lead to incorrect estimation of original values of C_{p0} . First, Omniscan Gd-DTPA is highly concentrated (287 mg mL^{-1}) and requires a ~ 30 -fold dilution for one dose. Second, the mouse blood volume per weight requires estimations based on the mean literature value from a range of values ($63\text{--}80 \text{ mL kg}^{-1}$). For example, the combination of these two factors could lead to an over-estimation of C_{p0} if Gd-DTPA is over-diluted and/or the actual mouse blood volume per weight is greater than the estimated mean value. When comparing predicted concentrations with MR data, it should be noted that sources of error also exist in the MRI-derived *in vivo* concentration values. R_1 , which inversely scales the concentration estimated from MRI, was based a literature value that was measured in rat muscle at 6.3 T. This could be a direct source of error when comparing magnitudes of simulated (baseline) and experimental concentration, if the actual R_1 varies from implemented literature value. Also, concentration measurements are dependent upon T_{10} maps that were created by fitting a monoexponential curve to 5 data points measured from a variable TR SE sequence. Errors can occur from the fit as well as motion between TRs. Motion was minimal since movement was not observed between scans. Additionally, there is background noise that comes from all of the electrical components used for imaging. The background noise can lead to less accurate measurements of low concentrations ($< 0.01 \text{ mM}$). Furthermore, the noise has the potential to reduce the number of properly K^{trans} fitted voxels, which happened infrequently ($< 5\%$ of tumor voxels).

Another limitation of the model was the use of an AIF based on literature values. This potentially lowers the patient specificity of the model. In this study, AIF was selected from a range of literature values based on a comparison of simulated and experimental transient behavior of $C_{t,\text{avg}}(t)$ in tumor tissue at early time points. Though the slow AIF resulted in an acceptable correlation for one data set, it may not have been the experimental AIF for all data sets. This fact was likely the cause of the large simulated and experimental concentration discrepancies at later time points seen in Fig. 9b–9f. K^{trans} magnitudes and

patterns, to a lesser degree, can be altered based on the type of AIF used. This could lead to variations of tracer deposition, since K^{trans} is essentially a kinetic parameter that drives the tracer transport source term. In the future, more accurate models can be obtained by measuring patient-specific AIFs to create more accurate 3D K^{trans} and ϕ maps, as well as source terms in tracer transport which include a C_p term.

The image-based patient-specific framework of this study offers opportunities to fine-tune the model for a variety of applications. The model can be adjusted to incorporate a wider variety of tumor environments. For example, the image-based model can be expanded to include necrotic regions. A larger range of uptake and washout behaviors can be observed in larger necrotic tumors which cannot be characterized by K^{trans} and ϕ used in the standard two-compartment model.¹⁶ In addition, diffusion-weighted imaging could be used to detect regions of increased diffusion, which have been shown to be correlated with regions of necrosis.^{24,30,31} These regions can be modeled as avascular and highly diffusive porous regions within the framework of the presented computational model. Additional patient-specificity can be captured with tensorial descriptions of K and D_{eff} to account for preferential interstitial fluid and tracer transport. This method has been employed to predict transport in central nervous system tissue with the aid of diffusion tensor imaging.^{28,29,41} The prediction of patient-specific interstitial fluid flow could also be incorporated into a multiscale model to predict shear stresses on tumor cells within the extracellular matrix. Brinkman's equation can be used instead of Darcy's law to solve momentum in the tumor microenvironment because it allows for a no-slip boundary condition.⁴⁶ Since shear stresses on tumor cells have been found to induce a G₂/M cell cycle arrest and inhibit cell differentiation, tissue remodeling could potentially be predicted with this type of multiscale model.⁸ In order to predict transport of a therapeutic drug, the model could also be expanded to account for binding and degradation of drug by including a rate of binding term in the tracer transport equation. The model presented in this study could account for binding or degradation of extravasated solute with the knowledge of its degradation constant in tissue, β .⁴⁷ For example, a first-order elimination term, βC_t , can be subtracted from the right-hand side of Eq (8).

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References

1. Aref M, Brechbiel M, Wiener EC. Identifying tumor vascular permeability heterogeneity with magnetic resonance imaging contrast agents. *Invest Radiol.* 2002; 37:178–192. [PubMed: 11923640]
2. Baudalet C, Ansiaux R, Jordan BF, Havaux X, Macq B, Gallez B. Physiological noise in murine solid tumours using T2*-weighted gradient-echo imaging: a marker of tumour acute hypoxia? *Phys Med Biol.* 2004; 49:3389–3411. [PubMed: 15379021]
3. Baxter LT, Jain RK. Transport of Fluid and Macromolecules in Tumors .1. Role of Interstitial Pressure and Convection. *Microvascular Research.* 1989; 37:77–104. [PubMed: 2646512]
4. Baxter LT, Jain RK. Transport of Fluid and Macromolecules in Tumors .2. Role of Heterogeneous Perfusion and Lymphatics. *Microvascular Research.* 1990; 40:246–263. [PubMed: 2250603]
5. Boucher Y, Baxter LT, Jain RK. Interstitial Pressure-Gradients in Tissue-Isolated and Subcutaneous Tumors - Implications for Therapy. *Cancer Research.* 1990; 50:4478–4484. [PubMed: 2369726]

6. Boucher Y, Jain RK. Microvascular pressure is the principal driving force for interstitial hypertension in solid tumors: implications for vascular collapse. *Cancer Res.* 1992; 52:5110–5114. [PubMed: 1516068]
7. Boucher Y, Kirkwood JM, Opacic D, Desantis M, Jain RK. Interstitial Hypertension in Superficial Metastatic Melanomas in Humans. *Cancer Research.* 1991; 51:6691–6694. [PubMed: 1742743]
8. Chang SF, Chang CA, Lee DY, Lee PL, Yeh YM, Yeh CR, Cheng CK, Chien S, Chiu JJ. Tumor cell cycle arrest induced by shear stress: Roles of integrins and Smad. *Proc Natl Acad Sci U S A.* 2008; 105:3927–3932. [PubMed: 18310319]
9. Chen XM, Astarly GW, Sepulveda H, Mareci TH, Sarntinoranont M. Quantitative assessment of macromolecular concentration during direct infusion into an agarose hydrogel phantom using contrast-enhanced MRI. *Magn Reson Imaging.* 2008; 26:1433–1441. [PubMed: 18583082]
10. Deng J, Rhee TK, Sato KT, Salem R, Haines K, Paunesku T, Mulcahy MF, Miller FH, Omary RA, Larson AC. In vivo diffusion-weighted imaging of liver tumor necrosis in the VX2 rabbit model at 1.5 Tesla. *Invest Radiol.* 2006; 41:410–414. [PubMed: 16523024]
11. Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C. A good practice guide to the administration of substances and removal of blood, including routes and volumes. *Journal of Applied Toxicology.* 2001; 21:15–23. [PubMed: 11180276]
12. Dreher MR, Liu WG, Michelich CR, Dewhirst MW, Yuan F, Chilkoti A. Tumor vascular permeability, accumulation, and penetration of macromolecular drug carriers. *J Natl Cancer I.* 2006; 98:335–344.
13. Eikenberry S. A tumor cord model for Doxorubicin delivery and dose optimization in solid tumors. *Theor Biol Med Model.* 2009; 6:-.
14. Elkareh AW, Secomb TW. Effect of Increasing Vascular Hydraulic Conductivity on Delivery of Macromolecular Drugs to Tumor-Cells. *International Journal of Radiation Oncology Biology Physics.* 1995; 32:1419–1423.
15. Foy BD, Blake J. Diffusion of paramagnetically labeled proteins in cartilage: Enhancement of the 1-D NMR imaging technique. *Journal of Magnetic Resonance.* 2001; 148:126–134. [PubMed: 11133285]
16. Furman-Haran E, Grobgeld D, Degani H. Dynamic contrast-enhanced imaging and analysis at high spatial resolution of MCF7 human breast tumors. *J Magn Reson.* 1997; 128:161–171. [PubMed: 9356271]
17. Fyles A, Milosevic M, Pintilie M, Hill RP. Long-term performance of hypoxia and IFP as prognostic factors in cervix cancer. *Radiother Oncol.* 2006; 78:S67–S67.
18. Gordon MJ, Chu KC, Margaritis A, Martin AJ, Ethier CR, Rutt BK. Measurement of Gd-DTPA diffusion through PVA hydrogel using a novel magnetic resonance imaging method. *Biotechnol Bioeng.* 1999; 65:459–467. [PubMed: 10506421]
19. Gutmann R, Leunig M, Feyh J, Goetz AE, Messmer K, Kastenbauer E, Jain RK. Interstitial Hypertension in Head and Neck Tumors in Patients - Correlation with Tumor Size. *Cancer Research.* 1992; 52:1993–1995. [PubMed: 1551128]
20. Guyton AC, Granger HJ, Taylor AE. Interstitial fluid pressure. *Physiol Rev.* 1971; 51:527–563. [PubMed: 4950077]
21. Guyton AC, Scheel K, Murphree D. Interstitial Fluid Pressure .3. Its Effect on Resistance to Tissue Fluid Mobility. *Circ Res.* 1966; 19:412-&. [PubMed: 5914853]
22. Hassid Y, Furman-Haran E, Margalit R, Eilam R, Degani H. Noninvasive magnetic resonance imaging of transport and interstitial fluid pressure in ectopic human lung tumors. *Cancer Research.* 2006; 66:4159-+. [PubMed: 16618737]
23. Heilmann M, Walczak C, Vautier J, Dimicoli JL, Thomas CD, Lupu M, Mispelter J, Volk A. Simultaneous dynamic T1 and T2* measurement for AIF assessment combined with DCE MRI in a mouse tumor model. *MAGMA.* 2007; 20:193–203. [PubMed: 17929067]
24. Herneth AM, Guccione S, Bednarski M. Apparent Diffusion Coefficient: a quantitative parameter for in vivo tumor characterization. *Eur J Radiol.* 2003; 45:208–213. [PubMed: 12595105]
25. Jain RK. Transport of molecules across tumor vasculature. *Cancer Metastasis Rev.* 1987; 6:559–593. [PubMed: 3327633]

26. Jain RK, Baxter LT. Mechanisms of Heterogeneous Distribution of Monoclonal-Antibodies and Other Macromolecules in Tumors - Significance of Elevated Interstitial Pressure. *Cancer Research*. 1988; 48:7022–7032. [PubMed: 3191477]
27. Khaled ARA, Vafai K. The role of porous media in modeling flow and heat transfer in biological tissues. *Int J Heat Mass Tran*. 2003; 46:4989–5003.
28. Kim JH, Astarly GW, Chen X, Mareci TH, Sarntinoranont M. Voxelized model of interstitial transport in the rat spinal cord following direct infusion into white matter. *J Biomech Eng*. 2009; 131 071007.
29. Linninger AA, Somayaji MR, Erickson T, Guo X, Penn RD. Computational methods for predicting drug transport in anisotropic and heterogeneous brain tissue. *J Biomech*. 2008; 41:2176–2187. [PubMed: 18550067]
30. Lyng H, Haraldseth O, Rofstad EK. Measurement of cell density and necrotic fraction in human melanoma xenografts by diffusion weighted magnetic resonance imaging. *Magn Reson Med*. 2000; 43:828–836. [PubMed: 10861877]
31. Maier CF, Paran Y, Bendel P, Rutt BK, Degani H. Quantitative diffusion imaging in implanted human breast tumors. *Magn Reson Med*. 1997; 37:576–581. [PubMed: 9094080]
32. Milosevic M, Fyles A, Hedley D, Pintilie M, Levin W, Manchul L, Hill R. Interstitial fluid pressure predicts survival in patients with cervix cancer independent of clinical prognostic factors and tumor oxygen measurements. *Cancer Res*. 2001; 61:6400–6405. [PubMed: 11522633]
33. Milosevic MF, Fyles AW, Hill RP. The relationship between elevated interstitial fluid pressure and blood flow in tumors: A bioengineering analysis. *International Journal of Radiation Oncology Biology Physics*. 1999; 43:1111–1123.
34. Nathanson SD, Nelson L. Interstitial Fluid Pressure in Breast-Cancer, Benign Breast Conditions, and Breast Parenchyma. *Annals of Surgical Oncology*. 1994; 1:333–338. [PubMed: 7850532]
35. Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, Jain RK. Role of extracellular matrix assembly in interstitial transport in solid tumors. *Cancer Research*. 2000; 60:2497–2503. [PubMed: 10811131]
36. Paulson OB, Hertz MM, Bolwig TG, Lassen NA. Filtration and diffusion of water across the blood-brain barrier in man. *Microvasc Res*. 1977; 13:113–124. [PubMed: 859448]
37. Pozrikidis C, Farrow DA. A model of fluid flow in solid tumors. *Ann Biomed Eng*. 2003; 31:181–194. [PubMed: 12627826]
38. Pusenjak J, Miklavcic D. Modeling of interstitial fluid pressure in solid tumor. *Simulation Practice and Theory*. 2000; 8:17–24.
39. Radjenovic A, Ridgway JP, Smith MA. A method for pharmacokinetic modelling of dynamic contrast enhanced MRI studies of rapidly enhancing lesions acquired in a clinical setting. *Phys Med Biol*. 2006; 51:N187–N197. [PubMed: 16625029]
40. Rozijn TH, van der Sanden BP, Heerschap A, Creyghton JH, Bovee WM. Determination of in vivo rat muscle Gd-DTPA relaxivity at 6.3 T. *MAGMA*. 1999; 9:65–71. [PubMed: 10555175]
41. Sarntinoranont M, Chen XM, Zhao JB, Mareci TH. Computational model of interstitial transport in the spinal cord using diffusion tensor imaging. *Ann Biomed Eng*. 2006; 34:1304–1321. [PubMed: 16832605]
42. Sevic EM, Jain RK. Measurement of Capillary Filtration Coefficient in a Solid Tumor. *Cancer Research*. 1991; 51:1352–1355. [PubMed: 1997172]
43. Smith JH, Humphrey JAC. Interstitial transport and transvascular fluid exchange during infusion into brain and tumor tissue. *Microvascular Research*. 2007; 73:58–73. [PubMed: 17069863]
44. Stohrer M, Boucher Y, Stangassinger M, Jain RK. Oncotic pressure in solid tumors is elevated. *Cancer Res*. 2000; 60:4251–4255. [PubMed: 10945638]
45. Swabb EA, Wei J, Gullino PM. Diffusion and Convection in Normal and Neoplastic Tissues. *Cancer Research*. 1974; 34:2814–2822. [PubMed: 4369924]
46. Swartz MA, Fleury ME. Interstitial flow and its effects in soft tissues. *Annu Rev Biomed Eng*. 2007; 9:229–256. [PubMed: 17459001]
47. Tan WHK, Wang FJ, Lee T, Wang CH. Computer simulation of the delivery of Etanidazole to brain tumor from PLGA wafers: Comparison between linear and double burst release systems. *Biotechnology and Bioengineering*. 2003; 82:278–288. [PubMed: 12599254]

48. Tofts PS, Kermode AG. Measurement of the Blood-Brain-Barrier Permeability and Leakage Space Using Dynamic Mr Imaging .1. Fundamental-Concepts. *Magnetic Resonance in Medicine*. 1991; 17:357–367. [PubMed: 2062210]
49. Truskey, GA.; Yuan, F.; Katz, DF. *Transport Phenomena in Biological Systems*. Upper Saddle River: Pearson Prentice Hall; 2004. p. 710
50. Victorino GP, Ramirez RM, Chong TJ, Curran B, Sadjadi J. Ischemia-reperfusion injury in rats affects hydraulic conductivity in two phases that are temporally and mechanistically separate. *Am J Physiol-Heart C*. 2008; 295:H2164–H2171.
51. Weinmann HJ, Laniado M, Mutzel W. Pharmacokinetics of Gddtpa Dimeglumine after Intravenous-Injection into Healthy-Volunteers. *Physiol Chem Phys*. 1984; 16:167–172.
52. Young JS, Lumsden CE, Stalker AL. The Significance of the Tissue Pressure of Normal Testicular and of Neoplastic (Brown-Pearce Carcinoma) Tissue in the Rabbit. *Journal of Pathology and Bacteriology*. 1950; 62:313–333. [PubMed: 14784896]
53. Zhao J, Salmon H, Sarntinoranont M. Effect of heterogeneous vasculature on interstitial transport within a solid tumor. *Microvascular Research*. 2007; 73:224–236. [PubMed: 17307203]

FIGURE 1.
Block diagram of the mathematical methodology and experimental verification.

FIGURE 2.

Geometric reconstruction of tumor and host tissue based on (a) T_2 maps (slice 5, middle of tumor of MR data set). Segmented tumor boundary is outlined in black. (b) CFD-compatible mesh of reconstructed hind limb that includes tumor (*light blue*), skin boundary (*green*), cut ends (*yellow*), and representation of slice 5 of the MR data (*dark blue*).

FIGURE 3.

Uptake and washout of average Gd-DTPA concentration, $C_{t,avg}(t)$, in tumor tissue at seven time points for the first 19 min. Comparison between $C_{t,avg}(t)$ based on experimental (*uptake rate* = $0.071 \text{ mM min}^{-1}$; *monoexponential washout rate* = -0.029 min^{-1}) and simulations implementing slow ($0.076 \text{ mM min}^{-1}$; -0.034 min^{-1}), intermediate ($0.089 \text{ mM min}^{-1}$; -0.045 min^{-1}), and fast ($0.089 \text{ mM min}^{-1}$; -0.050 min^{-1}) AIFs.

FIGURE 4.

Maps from slice 5 of MR data set of (a) K^{trans} and (b) ϕ with histograms. Maps were implemented in the CFD-compatible mesh based on the slow AIF. Areas of greatest leakiness and porosity, respectively, are in red.

FIGURE 5.

IFP sensitivity analysis for varying transport properties (Table 1b); (a) IFP contours for the baseline case; (b) IFP along the black line bisecting the tumor in Figure 5a (dashed lines indicates tumor boundary).

FIGURE 6.

Tissue-averaged IFV sensitivity analysis for varying transport properties (Table 1b); (a) Vector field for the baseline case; (b) IFV along the black line bisecting the tumor in Fig. 6a (dashed line indicates tumor boundary).

FIGURE 7.

Comparison of experimental and simulated Gd-DTPA distribution patterns in slice 5 for $t = 5, 30$, and 60 min for baseline transport values in Table 1b.

FIGURE 8.

Gd-DTPA distribution along bisecting line defined in Fig. 7. Simulation from sensitivity analysis of parameters in Table 1b and C_{p0} as compared with experimental distribution for (a) $t = 5$, (b) $t = 30$, and (c) $t = 60$ min (dashed line indicates tumor boundary).

FIGURE 9.

Gd-DTPA distribution along a bisecting line through two additional KHT sarcomas. Simulated Gd-DTPA distribution (*grey*) compared with experimental distribution (*black*) for two tumors at (a & b) $t = 5$, (c & d) $t = 30$, and (e & f) $t = 60$ min, respectively (dashed line indicates tumor boundary).

TABLE 1

a. Tissue and vascular parameters used in simulations.

Variable	Parameter	Value
$S/V (\text{m}^{-1})$	Microvascular surface area per unit volume	20000 ^t ; 7000 ⁿ [3,47]
$p_V (\text{Pa})$	Microvascular pressure	2300 [6]
$\pi_i (\text{Pa})$	Osmotic pressure in interstitial space	3230 ^t [44]; 1330 ⁿ [3,47]
$\pi_V (\text{Pa})$	Osmotic pressure in microvasculature	2670 [44]
σ_T	Average osmotic reflection coefficient for plasma	0.82 ^t ; 0.91 ⁿ [3,4]

b. Baseline tissue and vascular values used in sensitivity analysis.

Variable	Parameter	Value	Literature range
$L_p (\text{m Pa}^{-1} \text{ s}^{-1})$	Vessel permeability	2×10^{-11} ^t 3×10^{-12} ⁿ	t: 2.1×10^{-11} [3] – 3.5×10^{-10} [42] n: 7.3×10^{-14} [36] – 3.6×10^{-11} [50]
$L_{pL} S_L / V (\text{Pa}^{-1} \text{ s}^{-1})$	Lymphatic filtration coefficient	1×10^{-7}	8×10^{-8} – 2×10^{-6} [4]
$K (\text{m}^2 \text{ Pa}^{-1} \text{ s}^{-1})$	Hydraulic conductivity	1.9×10^{-12} ^t 3.8×10^{-13} ⁿ	t: 7.0×10^{-14} [35] – 1.8×10^{-12} [20] n: 6.4×10^{-15} [45] – 1.8×10^{-12} [21]
$D_{\text{eff}} (\text{m}^2 \text{ s}^{-1})$	Effective coefficient of diffusion	1×10^{-9}	6.9×10^{-9} [15] – 2.6×10^{-10} [18]

t: tumor tissue; n: normal host tissue

TABLE 2

Percent difference, from the baseline simulation (Table 1b), of peak intratumoral pressure, tumor-tissue interface pressure gradient, and boundary velocity in sensitivity analysis for range of tissue and vascular values (Table 1b).

Case	Change in intratumoral IFP (%)	Change in pressure gradient (%)	Change in boundary velocity (%)
High $L_{p,n}$	0.71	-1.8	-1.7
Low $L_{p,n}$	-0.71	1.5	1.9
High $L_{pL}S_L/V$	-14	0.38	5.1
Low $L_{pL}S_L/V$	14	-1.8	-4.7
High $L_{p,t}$	35	41	35
Low $L_{p,t}$	-34	-36	-35
High K_t/K_n	-6.4	10	17
Low K_t/K_n	27	-24	-41
High C_{po}	0.0	0.0	0.0
Low C_{po}	0.0	0.0	0.0

TABLE 3

Root mean square error, ϵ ($\times 10^{-5}$ mM), of Gd-DTPA distribution along bisecting tumor line within the tumor boundary shown in Fig. 7. Simulations were compared to baseline values listed in Table 1b.

Case	$t = 5 \text{ min}$	$t = 30 \text{ min}$	$t = 60 \text{ min}$
High $L_{p,n}$	0.16	0.083	0.056
Low $L_{p,n}$	0.09	0.044	0.030
High $L_{pL}S_L/V$	1.4	0.71	0.48
Low $L_{pL}S_L/V$	1.2	0.62	0.42
High $L_{p,t}$	3.0	1.5	1.0
Low $L_{p,t}$	3.6	1.8	1.2
High K_t/K_n	1.3	0.67	0.45
Low K_t/K_n	3.5	1.8	1.2
High D_{eff}	4.4	2.2	1.5
Low D_{eff}	0.6	0.31	0.21
High C_{p0}	160	81	260
Low C_{p0}	250	130	85