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The effects of *intra*-voxel contrast agent diffusion on the analysis of DCE-MRI data in realistic tissue domains

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Abstract

Purpose—Quantitative evaluation of dynamic contrast enhanced MRI (DCE-MRI) allows for estimating perfusion, vessel permeability, and tissue volume fractions by fitting signal intensity curves to pharmacokinetic models. These compartmental models assume rapid equilibration of contrast agent within each voxel. However, there is increasing evidence that this assumption is violated for small molecular weight Gadolinium chelates. To evaluate the error introduced by this invalid assumption, we simulated DCE-MRI experiments with volume fractions computed from entire histological tumor cross-sections obtained from murine studies.

Methods—A 2D finite element model of a diffusion-compensated Tofts-Kety model was developed to simulate dynamic T_1 signal intensity data. Digitized histology slices were segmented into vascular (v_p), cellular, and extravascular extracellular (v_e) volume fractions. Within this domain, K^{trans} (the volume transfer constant) was assigned values from 0 to 0.5 min^{-1} . A representative signal enhancement curve was then calculated for each imaging voxel, and the resulting simulated DCE-MRI data analyzed by the extended Tofts-Kety model.

Results—Results indicated parameterization errors of $-19.1\% \pm 10.6\%$ in K^{trans} , $-4.92\% \pm 3.86\%$ in v_e , and $79.5\% \pm 16.8\%$ in v_p for use of Gd-DTPA over 4 tumor domains.

Conclusion—These results indicate a need for revising the standard model of DCE-MRI to incorporate a correction for slow diffusion of contrast agent.

Keywords

DCE-MRI; tumor; cancer; kinetics; modeling; diffusion

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is performed by acquiring sequential T_1 -weighted images before, during, and after the intravenous injection of a Gadolinium-based contrast agent. As the contrast agent is delivered into a tissue of interest, it decreases the native T_1 relaxation time, thereby increasing the measured signal intensity. As the contrast agent leaves the tissue, relaxation time returns to baseline, resulting in a return to baseline in signal intensity. Thus, each voxel within the image series yields a signal intensity time course that can then be analyzed with a pharmacokinetic model to return estimates of parameters of physiological interest related to (for example) vessel perfusion and permeability and tissue volume fractions (1). These parameters, which can be obtained on a region-of-interest or individual voxel scale, find application in both diagnostic (2–5) and prognostic (6–9) settings in various cancers. Due to leaky and fragile tumor-associated vasculature, DCE-MRI has a well-established presence in the quantitative imaging of cancer (10–13).

The standard approach to analyzing DCE-MRI data is the two-compartment Tofts-Kety model, which describes the exchange of contrast agent between the vascular and extravascular-extracellular spaces (14). The utility of the parameters returned from a model is fundamentally limited by the ability of the model to sufficiently and realistically capture the in vivo behavior. A fundamental assumption of most DCE-MRI models is that contrast agent is actively delivered throughout each voxel *via* blood vessels, and not through passive *inter*-voxel diffusion. There is an increasing body of evidence indicating that this assumption can lead to significant estimation errors of the desired pharmacokinetic parameters, and extended models accounting for both active delivery and *inter*-voxel diffusion have been proposed (3,15–18). These methods show promise in improving the accuracy of many dynamic contrast-enhanced imaging modalities, particularly those using fast-diffusing contrast agents.

A second limitation of the standard model is the assumption of instantaneous and uniform filling of the extravascular extracellular space (EES). In its original implementation, the Kety model was used to measure the concentration of solvated gasses in the two compartments of interest, and as such, assumes a high molecular diffusivity of the solvate (19). However, in DCE-MRI, the contrast agent is many times larger than a gaseous molecule and therefore has a lower characteristic diffusivity, D . In fact, the range of D for gadolinium chelates has been measured to be $1\text{--}4 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$ (20,21), which is multiple orders of magnitude less than that of the typical gases dissolved in tissue ($17\text{--}1,010 \text{ mm}^2 \text{ s}^{-1}$) (22,23). Assuming unhindered 3D diffusion in water, the mean displacement of gaseous particles is on the order of 10 mm in 1 second, compared to roughly 0.04 mm for Gd-DTPA. For comparison, the apparent diffusion coefficient of water in cancerous tissue is approximately $0.01\text{--}3 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (6), equivalent to a mean displacement of 0.13 mm in 1 second. In tissues like the heart, the above assumption may be valid, due to a combination of high flow and high capillary density (24). In cancers with limited perfusion, the assumption that the domain is uniformly filled may be incorrect, thereby introducing a systematic parameterization error. To account for this possibility, Larson *et al.* proposed models which incorporate the possibility of non-uniform contrast agent distribution, making

use of virtual compartments (25). However, these models are complex and require high-temporal resolution and high signal-to-noise data to accurately fit parameters (26). Further, validation of models utilizing virtual compartments is challenging. Owing to its relative simplicity, the extended Tofts-Kety model has become standard for quantitative DCE-MRI analysis (27).

Barnes *et al.* investigated the effect of *intra*-voxel diffusion on the accuracy of the standard model *in silico*, using simulated domains generated by means of a pseudo-random algorithm for the placement of cells and vessels (28). It was determined that intra-voxel diffusion, within the range of standard gadolinium chelates, introduces significant parameterization error into the analysis of typical DCE-MRI data. They also demonstrated that this parameterization error was eliminated as the contrast agent diffusivity was increased into the gaseous range (28).

The present study aims to rigorously investigate the effects of intra-voxel diffusion of contrast agent, within realistic tissue domains derived from *in vivo* tumors, on the accuracy of the pharmacokinetic parameters derived from the extended Tofts-Kety model. We hypothesize that parameterization error due to diffusivity will increase as the coefficient of diffusion of the contrast agent decreases. We predict that this occurs due to slow diffusion away from vasculature, resulting in non-uniform filling of the domain. This is in contrast to the assumption of uniform filling of the extra-cellular compartment. In particular, we predict that there will be significant parameterization errors seen in DCE-MRI analysis when using common gadolinium-based contrast agents. These hypotheses will be tested by developing a finite element method (FEM) model of segmented histological slices, obtained from BT474 tumors grown in mice.

Methods

Figure 1 provides a visual guide through each component of the experiments and data analysis.

Histological Analysis

While details are presented in Sorace *et al.* 2016, the salient features are as presented here (29). Representative histologically-stained images are demonstrated by Figure 1a, and the resulting segmentation shown in Figure 1b. All procedures were approved by the Institutional Animal Care and Use Committee. BT474 (invasive ductal carcinoma) mammary gland cells (10^7) were grafted into the hind-flank of adult female *fox nu/nu* mice (Charles River Laboratories, Wilmington, MA), and tumors were allowed to grow for 4–6 weeks, until the size of the tumor exceeded 200 mm^3 . Animals were humanely sacrificed and tumors were immediately excised and fixed in 10% formalin. Tumors were then stored in 70% ethanol for further processing. Serial slices of the tumor ($5 \mu\text{m}$ thickness) were taken at the center cross-section of the tumor. Hematoxylin and eosin (H&E, for cell identification) and anti-CD31 (ab28364, Abcam Cambridge, MA, for endothelial cell and vascularity identification) stains were performed on consecutive histological slices. Slides were digitally scanned at $20\times$ resolution ($0.5 \mu\text{m}$ lateral resolution) with bright-field microscopy using a Leica SCN400 Slide Scanner (Leica Microsystems Inc, Ariol, Buffalo

Grove, IL) (29). Digitized CD31 and H&E stains from corresponding mice were then registered by intensity-based rigid transformation (MATLAB Image Processing Toolbox, Natick, MA). H&E images were then segmented into cellular and extra-cellular regions using color thresholding in Hue-Saturation-Value (*HSV*) space. Nuclei were first segmented by thresholding the dark blue stain in H&E, while the cytoplasm was segmented from the background by thresholding purple stained H&E regions. To create an initial mask of cellular space, which was later refined, the masks for nuclei and cytoplasm were combined. The distance transform was performed on the inverse of the cellularity mask (equivalent to a mask of extracellular space), and the resulting image was watershed-transformed to obtain the edges between cytoplasm and extra-cellular space. Likewise, the distance transform was performed on the mask of nuclei, and watershed-transformed to identify the boundary between nuclei and cytoplasm. Finally, each segmented nuclei was morphologically dilated until reaching the boundary between cytoplasm and extra-cellular space, filling in any small holes in the initial mask of cellularity.

CD31 stains were segmented into vascular and non-vascular space using color thresholding to identify epithelial tissue, and a closing operation (dilation followed by erosion) to fill in open space within blood vessels. Red-colored regions were selected using the *HSV* color space, and then converted into a rough mask of vascularity. This rough mask was then refined by morphological closing, closing the lumen of the blood vessels in the vascular mask and removing small holes within vascular regions. Objects smaller than 2 μm in diameter were excluded from the vascular mask to accurately represent the segmentation at the lower finite element resolution.

Registered masks of cellularity and vascularity were then down-sampled from 0.5 μm to 2 μm lateral resolution to achieve a reasonable solve time for the finite element model (FEM; see below). Finally, the mask of extracellular space was modified such each blood vessel has a region of extracellular space 2 μm thick surrounding it. This was done to ensure each vessel could distribute contrast agent to the extravascular extracellular space in all directions, and was not hindered by cellularity directly adjacent to the vasculature. All morphological operations were performed on histological images using a 3×3 pixel sliding window. An example of the resulting segmentation is presented in Figure 1b. All image processing was performed using the MATLAB Image Processing Toolbox (2016a, Natick, MA).

Forward Model

Figure 1c visually depicts the forward model. The extended Tofts-Kety model of DCE-MRI is described by the following ordinary, linear, differential equation with constant coefficients:

$$\frac{dC_t(t)}{dt} = K^{trans} C_p(t) - \frac{K^{trans}}{v_e} C_t(t), \quad [1]$$

where $C_t(t)$ and $C_p(t)$ are the concentration of contrast agent within the tissue and blood plasma compartments at time t , respectively. K^{trans} is the volume transfer rate of the contrast agent from the plasma to the extravascular compartment, and v_e is the extravascular

extracellular volume fraction (30,31). Solving Eq. [1] and including a correction factor for a non-negligible plasma volume fraction, v_p (4,31), yields the extended, two-compartment Tofts-Kety model:

$$C_t(t) = K^{trans} \int_0^t C_p(u) \exp\left(\frac{K^{trans}}{v_e}(t-u)\right) du + v_p C_p(t). \quad [2]$$

If $C_p(t)$ can be measured (or estimated), Eq. [2] can be fit to measured DCE-MRI data to estimate K^{trans} , v_e , and v_p on a voxel-wise basis.

To determine the accuracy of Eq. [2] in tissue, we extend the FEM methodology developed in Barnes *et al.* (28). The diffusion equation in two dimensions,

$$\frac{dC(x, y, t)}{dt} = \nabla \cdot D \nabla C(x, y, t), \quad [3]$$

is used to disperse contrast agent throughout the extravascular extracellular space, where $C(x, y, t)$ is the 2D spatial and temporal distribution of contrast agent within the domain. D is the coefficient of diffusion, or diffusivity (in units of mm^2s^{-1}) of the contrast agent, and is assigned values within the experimentally measured range ($1 \times 10^{-4} < D < 4 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$) (20,21). The vessel boundary conditions are set such that the flux of contrast agent is determined by an assigned K^{trans} . Further details on the FEM implementation and domain may be found in the Supporting Information (a).

To implement boundary conditions between the plasma and extravascular extracellular spaces, we write

$$\nabla C \cdot \hat{n} = P(C_p(t) - C(t)), \quad [4]$$

where P is the permeability, defined as $(K^{trans} V)/S$, with S as the total surface area of the vasculature within the voxel, $\hat{n}$ is the unit normal vector to the boundary, and V as the volume of tissue within the voxel. $C_p(t)$ is assigned as a constant at each time step, according to a population AIF (32,33). Because our simulation is in 2D, S is measured as vessel perimeter (mm), and V is measured in units of area (mm^2). For simplicity, $P(\text{mm} \cdot \text{min}^{-1})$ is assigned as a constant value for all vessel boundaries within the entire tumor domain, such that the voxel containing the maximum S will have a K^{trans} value of 0.5 min^{-1} , and voxels with no vasculature (i.e., $S = 0$) have a K^{trans} of 0 min^{-1} . This is equivalent to scaling K^{trans} from 0 to 0.5 min^{-1} as S scales from 0 to S_{max} . Further details on FEM mesh development and model implementation can be found in the Supporting Information (b).

These methods constitute the forward model which is used to simulate the spatio-temporal evolution of contrast agent within the histological FEM domain (Figure 1c). By changing the

model parameters (K^{trans} , v_e , v_p , D , tissue geometry), the model output (i.e., $C(x,y,t)$) is determined. The forward model output is then analyzed using the methodology outlined below in the *Simulations* section to systematically and quantitatively assess the error in the extended Tofts-Kety model on a voxel-wise basis, when the assumption of instantaneous and uniform filling of the contrast agent in the extravascular extracellular space is not satisfied. This model was designed such that all the extended Tofts-Kety parameters could be directly measured or assigned. It is not intended to be an exact representation of tumor biology and contrast agent delivery, but an investigational tool which allows fine parametric control in a large variety of biologically relevant geometries under best-case imaging conditions.

Simulations

For implementing the forward model, a range of diffusivities, D , for the common, clinically-approved Gadolinium-based contrast agents were chosen as 1.0, 2.0, 2.6 and $4.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ (20); in particular, $2.6 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ was chosen to simulate Gd-DTPA (Magnevist, Bayer, Berlin, Germany) (21). Each tumor ($n = 4$) was excised, stained, digitized, segmented, meshed, and evaluated using the forward model with the prescribed values of D . Resulting contrast agent distributions are used to calculate $R_{1, \text{voxel}}^k$ for each voxel at each time point k . $R_{1, \text{voxel}}^k$, along with the flip angle α , baseline signal intensity S_0 and TR , are used to calculate the signal intensity, SI_{voxel}^k , in each voxel:

$$SI_{\text{voxel}}^k = S_0 \cdot \frac{\sin \alpha (1 - \exp(-TR \cdot R_{1, \text{voxel}}^k))}{1 - \cos \alpha \cdot \exp(-TR \cdot R_{1, \text{voxel}}^k)}, \quad [5]$$

where we have assumed the echo time, $TE \ll T_2^*$. Further information on DCE-MRI simulation can be found in the Supporting Information (c), as can a comparison of simulated and in vivo DCE-MRI results (d) (Supporting Figure S7).

Statistical Analysis

After computing the signal intensity for each simulated voxel, the time course for each voxel is fit to Eq. [2], using least-squares error minimization in MATLAB (MathWorks, Natick, MA) to provide estimates of K^{trans} , v_e , and v_p (akin to what would be calculated on a voxel-wise basis in a standard, in vivo DCE-MRI study). Estimates of v_e and v_p are bounded between 0 and 1, and K^{trans} is bounded between 0 and 5 min^{-1} . This process is represented by the curve-fitting shown in Figure 1c, and the estimated parameters shown in Figure 1f. Finally, these parameters are then compared to the histological (v_e , v_p) and assigned (K^{trans}) parameters, and a percent error is calculated for each simulated voxel (Figure 1e):

$$\% \text{ Error}_{\text{voxel}} = \left(\frac{\text{Param}_{\text{voxel}}^{\text{fit}} - \text{Param}_{\text{voxel}}^{\text{histology}}}{\text{Param}_{\text{voxel}}^{\text{histology}}} \right), \quad [6]$$

where, $Param_{voxel}^{fit}$ represents one of the parameters (i.e., K^{trans} , v_e , or v_p) obtained from curve-fitting the SI time-course, and $Param_{voxel}^{histology}$ is the same parameter either measured histologically or assigned in the forward model. $\%Error_{voxel}$ values are then used to determine the accuracy of the standard model. These results are reported as mean $\pm$ the 95% confidence interval, at each simulated D (Table 1). Note that voxels with a histological $v_p = 0$ will result in an undefined $\%Error$ in v_p and K^{trans} , due to a zero denominator, and are omitted from the summary of results in Table 1. It is important to note that, in all Figures, the error in v_e has been corrected to reflect the fraction of EES which is accessible to contrast agent and connected to a vascular source. Any EES which is not accessible to the contrast agent is not included in the calculation of the error in v_e , except where it is explicitly reported in Table 1.

Domain Size Analysis

To determine the effect of domain size on the accuracy of the standard model, three different domains were considered. These domains consisted of a single 10 μm diameter vessel in empty EES, a single 10 μm diameter vessel surrounded by uniformly spaced (6 μm in all directions) 10 μm diameter cells, and a single vessel surrounded by cells measured using the methods described above in *Histological Analysis*. In each of these domains, we set zero-flux boundary conditions, and evaluated the forward model. Initially, the domain consisted of only the blood vessel and the domain resulting from a single morphological dilation (i.e., addition of a single layer of white pixels around the white region of a binary mask) of the vessel. The domain size was then incrementally increased by further dilating the previous domain four times, and then the model was again run to compare fit and true volume fractions as a function of increasing domain size. Each domain was grown until morphological dilation was performed a total of 60 times. Each simulation was repeated for values of $D = 1.0, 2.0$, and $4.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$. Error analysis for each domain was performed according to the methods described in the *Statistical Analysis* section.

Results

Using a poorly perfused tumor domain (Figure 2a, $K^{trans} = 0.05 \text{ min}^{-1}$, $v_e = 0.93$, $v_p = 0.003$), three values of D were used to determine the effects of diffusion. The resulting signal intensity time-courses for these simulated scans are depicted in Figure 2b. As D is increased from 1.0 to $4.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$, the total amount of contrast agent within the EES increases, corresponding to an increase in total signal enhancement. The results of the FEM simulation for this domain are shown in Figure 2c and Supporting Figure S1. Initially, at $t = 1 \text{ min}$, the distribution of contrast agent within the voxel is extremely uneven. For $D = 1.0, 2.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$, the voxel does not equilibrate until near the end of the simulated experiment. As D is further increased to $4.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$, the concentration of the contrast agent within the domain takes less time to equilibrate. Increasing D corresponds with an improvement in parameterization error from -31.8% to -15.5% in K^{trans} , and from -23.7% to -0.2% in v_e . Similar results were observed in a well-perfused voxel ($K^{trans} = 0.18 \text{ min}^{-1}$, $v_e = 0.66$, $v_p = 0.009$) in Figure 3a, with increasing total signal enhancement correlating with increasing D (Figure 3b). The well-perfused voxel equilibrates much sooner, and with a lower D than the

poorly perfused voxel (Figure 3c, Supporting Figure S2). Parameterization error of K^{trans} improves from -30.3% to 11.7% , error in v_e improves from -5.7% to 3.1% , and error in v_p improves from 49.9% to 4.3% . Absolute error in v_e is notably lower for all values of D in the well perfused voxel (Figure 3c), when compared to the necrotic voxel (Figure 2c, Supporting Figure S1). Errors in K^{trans} are similar between the two sampled voxels, while the error in v_p is more sensitive to changes in D for the well-perfused voxel. The necrotic domain demonstrates a characteristic slow wash-in and lack of notable wash-out (Figure 2b), while the well-perfused domain demonstrates both wash-in and wash-out (Figure 3b) (27).

Figure 4 depicts the means and 95% confidence intervals of the parameterization errors for a single mouse tumor (histology and segmentation of tumor shown in Figures 5d–f), using the full range of values of D within the physiological range. Mean error in all parameters approaches zero with increasing D . K^{trans} is most often underestimated, with its mean value below zero at all diffusivities simulated in this study. The confidence interval for K^{trans} error begins to contain positive values at $D = 2 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ (Figure 4a). Likewise, mean error in v_e is negative for all simulated diffusivities, but Eq. [2] begins to overestimate v_e at values of $D = 2.0 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ (Figure 4b). Error in v_p is by far the most widely varied, although the estimation of v_p improves steadily as D increases (Figure 4c). A map of parameterization error in all parameters for $D = 2.6 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ is shown in Figures 5a–c. Areas of high necrosis near the center of the tumor demonstrate high error in K^{trans} . This simulation predicts that DCE-MRI, using the imaging parameters in the *Methods* section, will contain inherent parameterization error of K^{trans} between -32.0 and 8.8% , v_e error between -10.0% and 2.4% , and v_p between 95.6% and 149.9% . Voxels with a histological $v_p = 0$ are marked with an “X”, and are not included in the 95% confidence intervals displayed in Figure 4, as division by zero is undefined (see Eq. [12]). Undefined parameterization error most frequently occurs for voxels on the edge of the tumor domain, where the voxel is not completely occupied by tissue, or in regions of necrosis. 95% confidence intervals for each individual mouse are provided in Supporting Figures S4–S6.

The 95% confidence intervals of the errors demonstrated in Figures 4 and 5, as well as those found in the remaining subjects, can be seen in Table 1. This table summarizes our complete results for each specimen ($n = 4$), at each of the four assigned values of D . In aggregate, the mean error of each parameter improves with increasing D . For $D = 2.6 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$, the K^{trans} is most often underestimated, while the number of voxels over-estimated increases with D . The same trend is true of v_e . The parameter v_p is nearly always over estimated, with error reduced with increasing diffusivity. Note that Table 1 also reports v_e error uncorrected for regions without contrast agent accessibility. On average, there is a difference of 20% between values corrected for contrast agent accessibility and raw values without this correction. This difference in error is discussed in detail in the *Discussion* section.

Figure 6 illustrates the effect of domain size on K^{trans} error by examining the domain immediately surrounding a single vessel. As the domain surrounding the vessel becomes larger, the parameterization error worsens. Figure 6a depicts this phenomenon in a voxel containing no cells (i.e. composed solely of the vessel and extravascular extracellular space) to demonstrate this effect with smooth curves. Error in K^{trans} is most sensitive to lower diffusivity, while higher diffusivity continues to result in the best parameter estimation.

Figure 6b depicts the same phenomenon with a domain of evenly distributed cells around a central circular blood vessel. The addition of cells increases the rate of error accumulation in K^{trans} as the domain size is increased. Figure 6c depicts the process using a domain generated from actual histology; the same trend of accumulating error with increasing window size is apparent with all parameters. Due to the pseudo-random distribution of cells, the spikes in error are more present than in the domain with evenly distributed cellularity (Figure 6b). In general, all parameters are most accurately estimated with a contrast agent of higher diffusivity, and the Eq. [2] estimation of each parameter worsens as the domain increases in size, thereby increasing the distance the contrast agent must travel to fill the domain. This process was performed on a number of other tissue domains and blood vessels, and the same general trend of increasing error with increasing window size was found to hold (results not shown). It should be noted that when v_p is reduced below 0.01 (shown with a dashed vertical line in Supporting Figure S3), the extended Tofts-Kety model no longer holds (1,14), introducing a high parameterization error in v_p .

Discussion

The results above are intended to demonstrate the error due to diffusion in the extended Tofts-Kety model, for values of K^{trans} , v_e , and v_p within tumor domains derived from entire histology slices. These methods enable us to examine situations which arise in biological tissues that might not occur in contrived or overly-simplistic models of cell density. Of particular note is the presence of regions within the tumors which, due to the distribution of cells, do not allow for any contrast agent to reach them. Such regions were evident in all four tumors studied, suggesting that there could be pockets of tissue in vivo which will not contribute to contrast agent-mediated signal enhancement. In our calculation of error, regions of extravascular extracellular space with no possible enhancement were counted in the v_{eis} fraction, and only regions accessible to contrast agent were counted in v_e . When non-accessible regions are accounted for, the extended Tofts-Kety model is 20% more accurate in all cases. Volume fractions with isolated regions of extravascular extracellular space can never be quantified using a model of perfusion, and may be better measured *via* diffusion weighted MRI (34). However, this effect may be mitigated in real tissue, given that there will be more physical pathways for the contrast agent to diffuse through in three dimensions.

This work focuses on a range of diffusivities D which represents those common for gadolinium based contrast agents. Barnes *et al.* demonstrated that as D increases into the gaseous range, the domain equilibrates within the time-resolution of a typical DCE-MRI experiment, and approaches instantaneous equilibration of contrast agent within the extravascular extracellular space (28). In particular, with high diffusivity, overestimation of K^{trans} indicates that more contrast agent is present in the voxel than would be indicated by perfusion and permeability alone. Likewise, overestimation of v_e indicates that the washout of contrast agent from the voxel is slower than expected, and that the voxel is leaking into neighboring voxels (27). While we do show that for some voxels, K^{trans} and v_e are overestimated, our results (Table 1, and Figures 2, 3, 5) indicate that K^{trans} and v_e are most often underestimated for gadolinium chelate MRI contrast agents.

Figure 2c clearly demonstrates an unequal distribution of contrast agent within the imaging voxel, and a clear relationship between the total concentration, signal intensity, and contrast agent diffusion. With low D , the rate at which the voxel can fill with contrast agent is limited by the bottleneck of high-concentration at the vessel boundary. The extended Tofts-Kety model dictates that the rate of exchange between the plasma and extravascular extracellular compartments is governed by the concentration gradient between those two compartments (Eq. [4]). Therefore, if contrast agent is unable to quickly diffuse away from the vessel to fill empty portions of the extravascular extracellular space, the amount of contrast agent entering the domain will be limited due to a small gradient between compartments. Figure 5 demonstrates the same phenomenon in terms of distance instead of time. Faster-diffusing contrast agents are able to equilibrate a larger region of the extravascular extracellular space in a shorter time period, and therefore will more accurately represent the entire voxel on the time scale of a DCE-MRI experiment. Contrast agents which diffuse more slowly will not be able to evenly fill a large region of extravascular extracellular space, and therefore decreases the accuracy of the model.

An example of the error commonly encountered when performing a DCE-MRI experiment, using a temporal resolution of 1.6 seconds, and Gd-DTPA, is depicted in Figure 4. The large error in K^{trans} is particularly of note due to its common application in diagnosing (2–5) and evaluating response in cancer (6–8,29). Thus, an accurate estimate of perfusion is necessary to provide accurate predictions of tumor growth and response to therapeutics. By correcting for the error introduced by diffusion, we hypothesize that accurately estimated parameters will have even more predictive power for diagnosis and prognosis. This will require modification of the extended Tofts-Kety model to account for both inter- and intra- voxel diffusion.

Previous efforts have investigated methods to improve the accuracy of the extended Tofts-Kety model by treating the tumor as a continuum, while accounting for *inter*-voxel diffusion between boundaries (3,15–18). These models are applicable for using fast-diffusing contrast agents, or for correcting for necrotic regions of the tumor where the only source of signal enhancement is from the diffusion of contrast agent from neighboring voxels. They do not, however, account for the underestimation of K^{trans} and v_e resulting from *intra*-voxel diffusion as demonstrated in the routine pre-clinical DCE-MRI procedures using common gadolinium chelates described in this manuscript.

Our study of intra-voxel diffusion was limited due to stability requirements (Eq. [12]); evaluating the forward model for an entire tumor domain at $D > 4 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ was prohibitively long. By taking advantage of mesh partitioning and parallelization, we could potentially extend our model to analyze contrast agents with diffusivities in the gaseous range ($0.17\text{--}10.1 \text{ cm}^2 \text{ s}^{-1}$) (6,7), although CA in this range of diffusivity would likely not be delivered through injection. Decreasing the simulation time would also allow for simulations of the Tofts-Kety model within the flow-limited regime, as increased contrast agent velocity would require finer time-steps. For the same reasons, the spatial resolution of our model is limited to $2 \text{ }\mu\text{m}$ in the imaging plane, and it is assumed that each blood vessel is surrounded by at least $2 \text{ }\mu\text{m}$ of extracellular space. This was a necessary assumption to allow contrast agent to enter the domain from all directions from any given vessel. In real tissue, even with

cells directly adjacent to the vasculature, we expect gaps which are smaller than $2\text{ }\mu\text{m}$, or paths which are accessible *via* the third spatial dimension. These small gaps would allow contrast agent to travel more freely within the tumor as compared to the forward model we have presented. However, as gaps become smaller, diffusion becomes restricted, and the rate of contrast agent dispersion is decreased. Our ability to model the domain is limited to structures above $2\text{ }\mu\text{m}$, potentially limiting the accuracy of our simulations in regions with high cellularity. Our model is also limited in that the concentration within the plasma compartment is constant in space, and varies temporally with the given population AIF (32). This means our analysis is limited to the permeability-limited case of the Tofts-Kety model (30). This analysis does not accurately reflect tissues in the flow-limited regime of the extended Tofts-Kety model. Any significant flow could more effectively deliver contrast agent to the tissue, potentially leading to greater distribution of the agent throughout the extravascular extracellular space, thereby helping to reduce the error demonstrated by the above results. Implementation of a similar analysis for flow-limited perfusion would most likely require the characterization of volumetric flow (we note that others have implemented flow in 2D (16)). As K^{trans} in many types of cancer is thought to depend on both permeability and flow, the permeability-limited extreme may not represent the majority of tissue physiologies. For this reason, we limit the applicability of this analysis to solid tumors with poor vascularization and perfusion (see, e.g., (35) and (36)). BT474 tumors were selected for the present study as they provide a range of physiologies from well-perfused to necrotic. While we anticipate that the general trends observed in this study would also be observed in other tumor types, the degree to which they are achieved would be dependent upon their specific vascular features.

Additional limitations of the present study are related to the fact that biological domains are 3D, thus any two-dimensional simplification will misrepresent reality. In 2D, the contrast agent within the vasculature may immediately leave the voxel, whereas $C_p(t)$ may vary along the length of a vessel in 3D. Regions in 2D which are inaccessible to the contrast agent may be accessible in the third dimension. As these issues are complicating factors in 3D, we investigated a 2D model specifically to probe the effects of slow contrast agent diffusion on DCE-MRI parameter accuracy, and decouple the analysis from (other) confounding factors. Finally, we offer no immediate solution to eliminate this error from the analysis of DCE-MRI. Potential methods for correcting this model may explicitly include the molecular diffusivity of the contrast agent, as well as including prior knowledge of the spatial distributions of vascular and cellular volume fractions obtained from other imaging techniques.

Future efforts will investigate the effect of the flow-limited case, requiring alternative treatment of the plasma compartment, K^{trans} , and inclusion of a perfusion term in the FEM. Investigating the problem in 3D may be explored *via* high-resolution 3D imaging techniques (e.g. confocal, multiphoton, or light-sheet microscopy) to establish experimentally-motivated computational domains (37). Future work may also include methods of parameterizing the spatial distribution of blood vessels within a voxel, as vessel proximity to a voxel boundary plays a central role in inter-voxel exchange of contrast agent. Additionally, future development of a diffusion-corrected inverse model for DCE-MRI is of interest.

Conclusion

The purpose of this study was to illustrate the effect of diffusion of contrast agent on parameterization error in the analysis of quantitative DCE-MRI data. By simulating the distribution of contrast agent within an entire tumor domain, we are able to highlight the sources of error which might be seen in a typical DCE-MRI experiment. More specifically, by using histological stains of cellularity and vascularity, highly realistic tumor domains were generated for FEM implementation of the extended Tofts-Kety model at sub-MRI-voxel resolution. From these simulations, we were able to perform simulated DCE-MRI experiments, compare assigned (K^{trans}) and histologically measured parameters (v_e and v_p) with those estimated by curve-fitting to the extended Tofts-Kety model, and produce a spatial map of parameterization error. Our results show that diffusion plays a measurable and significant role in determining the accuracy of the current widely used DCE-MRI model, and point towards the need for an improved model which accounts for the diffusion of contrast agent within and between voxels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Depiction of workflow for developing the simulation domain. Scale bar = $50 \mu\text{m}$. Panel a depicts the cellularity (H&E) and vascularity (CD31) stains of a whole tumor slice (along with magnified ROIs of a representative $438 \mu\text{m} \times 438 \mu\text{m}$ voxel region). Histological staining for two consecutive central slices was performed on four tumors, each from an individual mouse. Panel b depicts whole tumor segmentation after registration and image processing, (along with a magnified ROI of a $438 \mu\text{m} \times 438 \mu\text{m}$ voxel region). Extravascular extracellular space is represented in blue, cells are represented in green, and vessels are represented in red. A segmented image and FEM mesh was created for each of the four tumors studied. Panel c depicts FEM modeling and fitting done to produce a simulated DCE-MRI curve for a single voxel. Modeling was performed using values of $D = [1, 2, 2.6, 4] \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ for each of the four tumors studied. Panel d depicts the measurement of model parameters by calculation of volume fractions. Panel e shows the comparison of truth and simulated measurements from extended Tofts-Kety analysis. Panel f lists model parameters obtained from fitting to the simulated signal intensity time-course.

Figure 2.

Model results from simulations performed on a representative necrotic tissue domain. Panel a displays segmentation of the necrotic domain into the extravascular extracellular space, cells, and vasculature. The extravascular extracellular space is represented in blue, cells represented in green, and vessels represented in red. Note the large areas of extravascular extracellular space, and sparsely distributed cells and vasculature. Dimensions of the domain are $438 \mu\text{m} \times 438 \mu\text{m}$. Panel b presents signal intensity time-course, comparing signal enhancement with varying diffusivity. Vertical dashed lines indicate the time-points shown in Panel c. This voxel exhibits the characteristic slow enhancement and lack of wash-out typically associated with necrotic regions in the tumor. Panel c shows concentration distributions at sampled time points 1, 3.5, and 8 minutes into the simulated DCE-MRI scan ($D = 2 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$). The measured error at this diffusivity is -22.8% for K^{trans} , -8.0% for v_e , and -6.1% for v_p . Simulations at $D = 1, 4 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$ can be found in Supporting Figure S1.

Figure 3.

Model results from simulation performed on a representative well-perfused tissue domain. Edges of the domain have zero flux boundary conditions. Panel a displays segmentation of the well-perfused domain into the extravascular extracellular space, cells, and vasculature. The extravascular extracellular space is represented in blue, cells represented in green, and vessels represented in red. Cells and vasculature are more evenly distributed than in Panel a. Panel b presents signal intensity time-course, comparing signal enhancement with varying diffusivity. Vertical dashed lines indicate the time-points shown in Panel c. Note that this domain exhibits a rapid enhancement, and slow washout, typical of a well-perfused voxel. Panel c shows concentration distributions at sampled time points 1, 3.5, and 8 minutes into the simulated DCE-MRI scan ($D = 2 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$). The measured error at this diffusivity is -19.4% for K^{trans} , -3.8% for v_e , and 21.5% for v_p . Simulations at $D = 1, 4 \times 10^{-4} \text{ mm}^2\text{s}^{-1}$ can be found in Supporting Figure S2.

Figure 4.

Mean and 95% confidence intervals of the parameterization error in a single mouse specimen (see Figure 5) for a range of diffusivities. Panel a summarizes the parameterization error of K^{trans} as a function of diffusivity of the contrast agent. The mean of the measurement approaches 0 for each value of increasing D . As diffusivity increases, the standard model begins to over-estimate K^{trans} , shown with error bars extending above 0%. Panel b summarizes the parameterization error of v_e as a function of diffusivity. The model more accurately predicts v_e with increasing D , with over-prediction occurring more frequently with increasing D . Panel c summarizes the parameterization error of v_p as a function of diffusivity. The standard model nearly always overestimates v_p , but becomes more accurate with increasing diffusivity. Note that K^{trans} and v_e are most often underestimated at the D values used in this simulation.

Figure 5.

Depiction of parameterization error for a single tumor specimen, with $D = 2.6 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$ (appropriate for Magnevist). Regions marked with an “X” do not contain any detected vasculature, and thus result in an undefined parameterization error. Panel a displays the absolute percent error in K^{trans} . In general, K^{trans} is not accurately measured throughout the entire tumor, with regions of highest error occurring in necrotic regions. Panel b presents absolute percent error in v_e while Panel c shows absolute percent error in v_p . Note that the scale bar ranges from 0 to 500%; error in v_p is considerably higher than in K^{trans} or v_e . H&E and CD31 stains of the tumor are depicted in Panels d and e, respectively, while whole tumor segmentation is depicted in Panel f. Scale bar is the length of a voxel, 438 μm .

Figure 6.

Comparison of K^{trans} accuracy as a function of distance from blood vessel. Starting with the domain shown in Panel a, only the elements directly adjacent to the blood vessel are included in the simulated DCE-MRI scan. For each data point shown in the right-hand Panel, the initial domain is expanded in all directions using morphological dilation with an 8 pixel neighborhood. The window of elements used in the simulation continues to increase in size, up to 120 μm away from the nearest vessel boundary. Panel a depicts a simple domain containing a single 10 μm diameter vessel, and the associated error as the analysis window increases in size. Panel b presents results from the same procedure performed in Panel a, but includes evenly spaced cells, both with 10 μm diameter, spaced 6 μm apart. Note the similar trends in increasing error, with decreased smoothness caused by the addition of cells. Panel c shows a segmented domain from a section of tumor. Note similar trends to Panels a and b, with even further decreased smoothness due to the pseudo-random distribution of cells in the domain. In all cases, the fastest diffusing contrast agent allows for the best K^{trans} estimation with a large window size. At low window size, the model accurately measures K^{trans} , but begins accumulating error as the domain increases in size and the contrast agent must diffuse

further to fill the domain. Error for v_e and v_p are shown in Supporting Figure S3. Scale bar 20 μm .

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Table 1

Summary of parameterization errors over all four tumors

$D (\times 10^{-4} \text{ mm}^2\text{s}^{-1})$	% Error K^{trans}	% Error $v_e, \text{corrected}$	% Error $v_e, \text{un-corrected}$	%Error v_p
1	-36.9 ± 7.2	-11.3 ± 3.79	-30.1 ± 4.10	93.5 ± 16.1
2	-23.6 ± 9.5	-5.02 ± 3.76	-25.6 ± 4.07	85.2 ± 16.6
2.6	-19.1 ± 10.6	-4.92 ± 3.86	-26.1 ± 4.02	79.5 ± 16.8
4	-10.6 ± 12.3	-1.23 ± 5.22	-24.4 ± 4.03	74.9 ± 16.8