Published in final edited form as:

Phys Med Biol. 2013 March 21; 58(6): 1983–1998. doi:10.1088/0031-9155/58/6/1983.

A diffusion-compensated model for the analysis of DCE-MRI data: theory, simulations, and experimental results

Jacob U Fluckiger¹, Mary E Loveless², Stephanie L Barnes³, Martin Lepage⁴, and Thomas E Yankeelov^{3,5,6,7,8}

Jacob U Fluckiger: Jacob.fluckiger@northwestern.edu

¹Department of Radiology, Northwestern University Chicago, Illinois 60611

²School for Science and Math, Vanderbilt University Nashville, Tennessee 37212

³Institute of Imaging Science, Vanderbilt University Nashville, Tennessee 37212

⁴Department of Nuclear Medicine & Radiobiology and Centre d'imagerie moléculaire de Sherbrooke, Université de Sherbrooke Sherbrooke, Quebec, Canada, J1H 5N4

⁵Department of Radiology and Radiological Sciences, Vanderbilt University Nashville, Tennessee 37212

⁶Department of Biomedical Engineering, Vanderbilt University Nashville, Tennessee 37212

⁷Department of Physics, Vanderbilt University Nashville, Tennessee 37212

⁸Department of Cancer Biology, Vanderbilt University Nashville, Tennessee 37212

Abstract

Accurate quantification of pharmacokinetic parameters in dynamic contrast-enhanced (DCE) MRI may be affected by the passive diffusion of contrast agent (CA) within the tissue. By introducing an additional term into the standard Tofts-Kety (STK) model, we correct for the effects of CA diffusion. We first develop the theory describing a CA diffusion corrected STK model (DTK). The model is then tested in simulation with simple models of diffusion. The DTK model is also fit to 18 *in vivo* DCE-MRI acquisitions from murine models of cancer and results are compared to those from the STK model. The DTK model returned estimates with significantly lower error than the STK model ($p < 0.001$). In poorly-perfused (i.e., $K^{trans} < 0.05 \text{ min}^{-1}$) regions the STK model returned unphysical v_e values, while the DTK model estimated v_e with less than 7% error in noise-free simulations. Results *in vivo* data revealed similar trends. For voxels with low K^{trans} values and late peak concentration times the STK model returned v_e estimates > 1.0 in 40% of the voxels as compared to only 16% for the DTK model. The DTK model presented here shows promise in estimating accurate kinetic parameters in the presence of passive contrast agent diffusion.

Keywords

DCE-MRI; contrast agent diffusion; cancer

1. Introduction

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) requires the acquisition of a series of T_1 -weighted images before and after the injection of a paramagnetic contrast agent (CA), so that the variation of MR signal intensity with time can be recorded for each image voxel or region of interest (ROI). As the agent enters into a tissue, it changes the native relaxation properties and, therefore, the measured MR signal intensity. Similarly, as the agent is transported out of the tissue, the relaxation parameters

and associated MR signal intensity return to their baseline values. In the quantitative analysis of such data, the signal intensity time courses are analyzed using an appropriate model, and physiological parameters related to (for example) blood flow, vessel permeability, and tissue volume fractions can be extracted for each voxel or ROI (Alonzi et al., 2007, Tofts et al., 1999, Turnbull, 2009, Yankeelov and Gore, 2009). These parameters have been shown to provide insight into tumor growth and treatment response (Drew et al., 2001, Muller-Brusselbach et al., 2007, Pickles et al., 2005, Yankeelov et al., 2007).

One commonly used model in quantitative DCE-MRI in cancer, the so-called Tofts-Kety (here referred to as the standard Tofts-Kety or STK) model (Kety, 1951, Tofts and Kermode, 1991), describes the tissue as two well-mixed compartments (i.e., intravascular and extravascular-extracellular space) between which CA can flow. The STK model assumes that the arrival of the CA within a particular region of interest (ROI) is the result of active perfusion from the blood supply, while passive diffusion of the CA within the tumor is not considered. This assumption may prove to be problematic in regions where the diffusion of CA between well-perfused and poorly perfused, or necrotic, regions may be significant. As it was originally developed, the STK model was never intended for use in regions where contrast agent could diffuse from capillaries distant to the voxel of interest, or where CA could diffuse out of a voxel of interest (Tofts, 1997). There is an increasing body of evidence in the literature that ignoring the effects of CA diffusion within the necrotic regions of a tumor can lead to erroneous or unphysical values in the parameters returned by the STK model (Barnes et al., 2011, Egeland et al., 2008, Egeland et al., 2011, Cho et al., 2009, Egeland et al., 2012).

Several methods have been developed to account for contrast agent diffusion within tumors. Pellerin et al. (Pellerin et al., 2007) proposed a combined diffusion-perfusion (DP) model that corrects for the effects of diffusion by incorporating CA diffusion between neighboring voxels into the Tofts-Kety model. This method requires solving for all model parameters within the ROI simultaneously, which can be computationally expensive for larger numbers of voxels. A second method, by Jia et al. (Jia et al., 2008), proposed a layered ROI approach based on the gradient of the signal intensity to solve for contrast agent diffusion within tumors. More recently, Koh et al. (Koh et al., 2012) accounted for gadolinium diffusivity directly by solving the diffusion equations in tumors with both well-perfused and necrotic regions. While the methods developed by Jia et al. and Koh et al. provide quantitative information on the enhancement heterogeneity in tumors, they do not incorporate physiological parameters such as those found in the STK model.

In this study we propose a straightforward modification of the STK model that accounts for diffusion of the CA within the tumor by incorporating the salient features of the DP (Pellerin et al., 2007) and Koh (Koh et al., 2012) models. A fundamental difference in this implementation is the voxel-wise approach to solving for CA diffusion, thereby greatly reducing the overall computational load while still accounting for the effects of CA diffusion. We first develop the theory behind this model, and then test the proposed method in simulations based on *in vivo* data. To experimentally test the predictions of the simulations, we also present *in vivo* results of the proposed model as applied to a murine model of breast cancer.

2. Theory

The diffusion compensated Tofts-Kety (DTK) model proposed here is an extension of the standard Tofts-Kety (STK) model commonly used in quantitative DCE-MRI analysis (Tofts et al., 1999). The STK model represents the time rate of change of the concentration of CA,

$C_t(t)$, as a linear, ordinary, first-order differential equation that describes the movement of the CA between the intravascular and extravascular compartments:

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

where K^{trans} is the volume transfer constant, v_e is the extravascular extracellular volume fraction, and $C_p(t)$ represents the concentration of CA in the blood plasma, also known as the arterial input function (AIF).

The STK model described in Eq. (1) can be readily amended to include the diffusion of CA caused by concentration gradients between adjacent voxels. In this case, we assume that the CA diffusion between two adjacent voxels will depend on the average diffusion coefficient between the two voxels, and the difference in the concentration of the CA in the extravascular, extracellular space. For any particular voxel, the total change in CA concentration due to diffusion can be found by summing the contributions from diffusion over the neighborhood of that voxel. Following the derivation outlined by Pellerin et al. we write the diffusion-perfusion model as:

$$\frac{d}{dt}C_{ii}(t) = K_i^{trans}C_p(t) - K_i^{trans}\frac{C_{ii}(t)}{v_{ei}} + \sum_N \left(\frac{D_i + D_N}{2} \right) \alpha \left(\frac{C_N(t)}{v_{eN}} - \frac{C_i(t)}{v_{ei}} \right), \quad (2)$$

where D_i is the diffusion coefficient for each voxel, α is a constant relating to the size of the voxel (equal to $1/a^2$ where a is the in-plane voxel length), the subscript i refers to the voxel of interest, and the subscript N refers to the neighborhood of adjacent voxels surrounding the i^{th} voxel through which CA can diffuse (see Eq. (3) in (Pellerin et al., 2007)). Because the parameters for each voxel are explicitly dependent on those from each of its neighbors, the model in Eq. (2) requires solving for model parameters in all voxels within the entire region simultaneously. Previous efforts (Pellerin et al., 2007) applying Eq. (2) employed a simulated annealing algorithm to converge to the optimal solution. The computational effort needed to find this solution is super-linearly related to the number of voxels in the solution space; a point we return to in the Results section.

We now modify the diffusion-perfusion model given in Eq. (2) to remove the interdependence of the voxel fitting. This is done by making the assumption that the difference in the extravascular, extracellular volume fraction (v_e) between adjacent voxels is small, and can therefore be neglected. Thus, we set $v_{eN} = v_{ei}$ to combine the two fractions in the last term on the right hand side of Eq. (2) into a single term. Additionally, we assume that the difference in the diffusion coefficient (D) between adjacent voxels is also small.

This allows us to replace the average term $\left(\frac{D_i + D_N}{2} \right)$ in Eq. (2) with a single parameter, D_i . The validity of these assumptions will depend on both the voxel size in the image as well as the heterogeneity of the tumor (see Discussion section for more on this important point). These assumptions allow each voxel within the ROI to be fit independently of its neighbors. In the implementation of Pellerin et al. (Pellerin et al., 2007) the neighborhood was defined as the in-plane voxels immediately above, below, left and right of the voxel being fit. Using these assumptions we obtain the following, simplified version of Eq. (2):

$$\frac{d}{dt}C_{ii}(t) = K_i^{trans}C_p(t) - K_i^{trans}\frac{C_{ii}(t)}{v_{ei}} + \sum_N D_i \alpha \left(\frac{C_i(t) - C_N(t)}{v_{ei}} \right), \quad (3)$$

where all parameters are as in Eq. (2). Eq. (3) depends only on the parameters for a particular voxel and the concentration time courses of that voxel and its nearest neighbors, which are measured in the DCE-MRI scan.

3. Methods

3.1 Simulations

The ability of the DTK model to accurately return kinetic parameters in the presence of CA diffusion was tested in computer simulations. The K^{trans} , v_e , and D values selected for the simulations were based on *in vivo* DCE-MRI data from previous animal experiments (described below). Because the complex physical properties of CA diffusion in a biological system such as a tumor make a complete simulation unfeasible by current methods, we used the diffusion-perfusion simulation method described in (Pellerin et al., 2007) to generate CA time courses. Using this framework, we simulated a single slice from three circular, radially symmetric, “tumors” with an in plane spatial resolution of 0.27 mm. A single slice was used for the simulations as the slice thickness in the DCE-MRI experiments outlined below was several times the in-plane resolution (i.e., 2 mm through plane resolution vs. 0.27 mm in plane resolution) so that the effects of inter-plane diffusion of CA are taken to be negligible compared to in-plane diffusion. In simulation 1, K^{trans} was set to 0.3 min^{-1} in the rim and 0.05 min^{-1} in the core while v_e was set to a uniform value of 0.5 in both the rim and core. This simplified geometry, representing a tumor with a well-perfused rim and necrotic core, was selected to maximize the effect of diffusion within the core of the tumor. Simulation 2 used a wider variation of parameters. K^{trans} was set to 0.3 min^{-1} in the rim and then decreased linearly over 1 mm to 0.05 min^{-1} in the core and v_e increased linearly from 0.4 at the rim to 0.6 in the core, and was then held constant throughout the core. Simulation 3 used the same distribution for K^{trans} as simulation 2, while v_e increased linearly from 0.4 at the rim to 0.6 in the center of the tumor. Figures 1 – 3 show the distribution of K^{trans} and v_e for a line profile taken across each of the simulated, radially symmetric tumors. A population AIF, as seen in figure 4 was used to implement the model for each simulated tumor (Loveless et al., 2012). For each voxel, the K^{trans} and v_e values were used to generate simulated tissue CA concentration curves. In all the tumors simulated here, a CA diffusion value of $2.6 \times 10^{-4} \text{ mm}^2/\text{s}$ was used to generate the curves, which is consistent with previous efforts to measure the diffusivity of the CA in tumors (Gordon et al., 1999, Koh et al., 2012).

For each of the three simulated tumors, the STK model was fit to each pixel’s time course throughout the tumor to obtain estimates for K^{trans} and v_e . The proposed DTK model was also fit to each pixel to obtain a second set of parameter estimates for K^{trans} , v_e , and D . In the model defined by Eq. (3), the concentration time course of each voxel depends on the concentration of CA in the neighboring voxels. In the implementation used here, the neighborhood of contributing voxels consisted of a four-connected in-plane neighborhood centered on the pixel being fit. To test the proposed DTK model against the DP model developed by Pellerin *et al*, the DP model was also fit to each of the simulated tumors. The simulated annealing approach outlined in (Pellerin et al., 2007) was used, with the cooling schedule parameter (ϵ) set to 0.95. The error in K^{trans} and v_e was then calculated for each pixel and model. Parameter errors were reported as mean $\pm$ standard deviation, and paired t-tests were used to determine statistically significant differences between each model’s output parameters and those used to generate the tumors. Differences were considered significant for $p < 0.05$.

To assess the effects of measurement noise on the DTK model, zero-mean, Gaussian noise with a standard deviation equal to 2.5% and 10% of the peak concentration in each tumor was added to each of the simulated concentration time curves. The STK and DTK models were fit to each of the noisy tumors and the errors in the resultant parameters were

calculated. The noise experiments were repeated for 100 noise realizations, and the mean parameter results along with the 95% confidence interval (CI) were calculated.

To assess the effect of the low K^{trans} value in the simulated necrotic core of the tumor on the DTK model, the parameters from simulation 1 were repeated five times with the K^{trans} value in the core set to 0.02, 0.06, and 0.10 min^{-1} , respectively. As the DTK model returned parameters with zero error with noise-free curves, zero-mean, Gaussian noise with a standard deviation equal to 5% and 10% of the peak concentration in each simulation was added independently, to each simulated tumor. One hundred noise realizations were performed at each noise level and the mean parameter values were calculated along with the 95% CI.

3.2 Experimental Data

The DTK model was also tested *in vivo* in 13 mice from which 18 datasets were acquired. Prior to imaging, each mouse was injected with calu-6 human lung carcinoma cells that were developed using a previously published protocol (Wedge et al., 2002). The tumors were allowed to grow 15 to 20 days before imaging, with tumor size ranging from 200–250 mm^3 . All imaging was performed on a 9.4T scanner (Varian, Palo Alto, CA). Pre-contrast (axial) T_1 maps were obtained using a fast low-angle shot (FLASH) gradient echo sequence with nine inversion times ranging from 20–10,000 ms, with $\text{TR}/\text{TE}/\alpha = 12100 \text{ ms}/3.44 \text{ ms}/15^\circ$, number of excitations (NEX) = 4, and field of view (FOV) = 35 mm^2 . An ECG gated gradient echo sequence was then used to obtain the dynamic images with $\text{TR}/\text{TE}/\alpha = 100 \text{ ms}/2.83 \text{ ms}/25^\circ$, NEX = 2, slice thickness = 2 mm, and the same FOV as the T_1 maps. A 128×128 acquisition matrix was used for both the T_1 maps and the dynamic imaging; resulting in an in-plane resolution of 0.27 mm. A 0.1 mmol/kg bolus of Gd-DTPA (Magnevist, Bayer Healthcare Pharmaceuticals, Wayne, New Jersey) was injected over 2.5 seconds following the acquisition of the fifth frame.

Following data acquisition, the central slice through each tumor was identified, and each voxel within the tumor was fit independently with both the STK and DTK models. A previously evaluated population-average AIF (Loveless et al., 2012), measured from a similar population of animals and using an identical injection protocol, was used to fit the two models to the DCE-MRI data. Literature values were used to initialize the curve fitting (Pellerin et al., 2007) and the diffusion coefficient for the DTK model was initialized to $2.6 \times 10^{-4} \text{ mm}^2/\text{s}$. Time to peak (TTP) maps were also generated for each mouse. Each voxel was assigned a value from one to four to identify in which quartile of the dynamic time series the peak concentration value for that voxel was reached. This was done to test the hypothesis that voxels which slowly accumulate CA, due to passive rather than active delivery (i.e., CA diffusion from neighboring voxels, rather than CA perfusion from a feeding vessel within the voxel), will exhibit the most error in the STK model fitting. The correlation between the parameters calculated with the STK and DTK models were evaluated with both the Pearson and concordance correlation coefficients (PCC and CCC respectively). The CCC tests the strength of the correlation, as well as the deviation of the correlation from the line of unity. A Wilcoxon rank-sum test was used to evaluate whether the parameters returned by the two models within each group were significantly different.

4. Results

4.1 Computer Simulations

Results from the first set of simulated tumors are shown in figures 1 through 3. In each figure, the mean parameter value through a cross-section of the radially symmetric tumor returned by the modeling is shown by a solid line and the 95% CI is shown by the shaded

region. In cases where the returned parameter from the model differs from “truth”, the true parameter values are shown in black. The errors in the parameters calculated by each model for each of these simulations are summarized in Table 1. For all three simulated tumors at all levels of noise the errors in the parameters returned from the STK model are significantly higher than the errors returned by the DTK model ($p = 0.0017$). This is expected, as the geometry and parameter values of the simulations were selected to maximize the effects of CA diffusion. It should also be noted that the DTK model reduces to the STK model in regions where diffusion of CA can be neglected, as seen in Figures 1–3 in pixels where the K^{trans} value and that of its neighbors are all above 0.05 min^{-1} . In each of the three simulated tumors, the largest errors in the STK and DTK estimates for v_e occurred in the center of the simulated tumors, where K^{trans} is small and the delivery of CA is dominated by diffusion. In addition, in voxels with low K^{trans} , the overall concentration level is low and the influence of noise on the model fitting is proportionally larger. The errors in v_e increased with increasing simulation noise for both the STK and DTK models. In addition, the 95% CI for the STK and DTK estimates for v_e increased as the noise in the tissue curves increased. Errors in K^{trans} for the STK model remained fairly constant (an increase of approximately 0–3%) with increasing simulation noise, while errors in K^{trans} for the DTK model increased with noise, though the overall error remained significantly lower than that in the STK model at all noise levels. Qualitatively, fitting the simulated time courses with the STK model resulted in K^{trans} values that appear to be averaged between the rim and the core of the tumor and an overestimation of v_e in the core of the tumor. Fitting the time courses with the DTK model resulted in K^{trans} values with low overall error, while the v_e error was highest in regions where the gradient of the ‘true’ v_e varied the most. Representative model fits from two voxels in simulation 1 are highlighted in Figure 4.

The results of fitting each of the three simulated tumors with the DP model using a simulated annealing approach are shown in Figure 5. Due to computational constraints, each of these tumors was fit without the addition of noise to the simulated tumor curves. The DP model results from the first simulated tumor had an error of 14.5% $\pm$ 11.1% (absolute error: $0.012 \pm 0.007 \text{ min}^{-1}$) (the analogous values for the DTK and STK models can be found in Table 1 and are not repeated in the text) for K^{trans} and 11.3% $\pm$ 4.5% (absolute error: 0.057 ± 0.023) for v_e . For the second tumor the errors from the DP model were: 11.2% $\pm$ 6.2% (absolute error: $0.016 \pm 0.009 \text{ min}^{-1}$) for K^{trans} and 5.9% $\pm$ 5.3% (absolute error: 0.031 ± 0.025) for v_e . The third tumor had errors of 10.6% $\pm$ 7.0% (absolute error: $0.015 \pm 0.009 \text{ min}^{-1}$) for K^{trans} and 14.2% $\pm$ 7.1% (absolute error: 0.070 ± 0.029) for v_e . In each case, the errors in K^{trans} were similar to those from the STK model, while the errors in v_e were similar to those from the DTK model. It should be noted that the simulated annealing approach had a smaller variation in v_e error than either of the voxel-wise approaches, particularly in the tumor cores. This is due, in part, to the nature of the simulated annealing algorithm which only allows incremental changes in the parameter values during the estimation process.

The effect of the minimum K^{trans} value on the DTK model is illustrated in figure 6. Each panel shows the mean and 95% CI of 100 noise realizations with 5% and 10% noise. The mean error in v_e increases exponentially with decreasing K^{trans} values in the core of the tumor. In particular, when the core K^{trans} value is equal to 0.02 min^{-1} the mean error for v_e is 30.4% $\pm$ 26.7% (absolute error: 0.152 ± 0.133), but when the core K^{trans} value increases to 0.1 min^{-1} the v_e error decreases to 1.9% $\pm$ 1.2% (absolute error: 0.010 ± 0.006).

As noted above, the simulated annealing approach originally outlined in (Pellerin et al., 2007) is indeed computationally prohibitive. Using a desktop computer (Intel i7-2640M CPU, 2.80 GHz, 4 GB RAM), fitting a single 22×22 pixel slice from the simulated tumor

took an average of 70 hours to complete. In comparison, fitting the same tumor slice with the STK model took an average of 11 seconds, and with the DTK model the calculations took an average of 52 seconds. All calculations were done using custom software written for Matlab (the MathWorks, Natick, MA).

4.2 Experimental Data

Representative results from fitting the STK and DTK models to an *in vivo* mouse dataset are shown in figure 7. For reference, this tumor was also fit with the DP model using the simulated annealing approach with the cooling schedule parameter (ϵ) set to 0.97. A diffusion value of $2.6 \times 10^{-4} \text{ mm}^2/\text{s}$ was assumed for this tumor, and the K^{trans} and v_e parameters were estimated in approximately 72 hours (as compared to approximately 90 seconds for the DTK model and 15 seconds for the STK model). The tumor shown in figure 7 has a well-perfused rim and a poorly perfused core, which is reflected in both the DTK and STK model fits for K^{trans} . As expected from the simulation results, the fits from the DTK and STK models for K^{trans} have a similar range and distribution. The K^{trans} values in the transition region between the rim and core of the tumor fit with the STK model appear to be spatially ‘smoothed’ as compared to those from the DTK model. This is consistent with the spatial smoothing seen in the simulations outlined above (see, e.g., the top row of Figure 3). In contrast, the DP approach returned K^{trans} values an average of 0.14 min^{-1} lower than the values for the STK or DTK models. The STK model fits for v_e show a large region in the core of the tumor with v_e values greater than 0.9, largely in a region where K^{trans} was less than 0.1 min^{-1} . The DTK and DP approaches return average values of 0.45 and 0.40, respectively, in this same region. Again, these values are consistent with the large v_e values returned by the STK model in the cores of each of the simulated tumors. This region is also marked clearly on the TTP map (see figure 7.g), with voxels in the core of the tumor showing a steady increase in CA concentration throughout the imaging session.

Summary results from all 18 DCE-MRI acquisitions are shown in figure 8. For each dataset, the time-to-peak (TTP) concentration was grouped into two bins, each representing half of the total acquisition time. As seen in figure 7, these halves correspond to the tumor rim (quartiles 1 and 2 from figure 7.g) and the tumor core (quartiles 3 and 4 from figure 7.g). The median parameter values for the voxels in each bin were calculated. For voxels with a TTP in the first half, the correlation between the DTK and STK models’ estimate of K^{trans} is high, with a PCC and CCC of 0.868 and 0.699, respectively. For voxels with a TTP in the second half of the data, the correlation between the models’ estimate of K^{trans} decreases (PCC = 0.826, CCC = 0.584), though the parameter values from the two models are not significantly different ($p = 0.30$). It is also apparent from panel 7.b that later TTP concentrations represent voxels with smaller K^{trans} values.

The correlation between the v_e values calculated with the STK and DTK models is also dependent on which data is included. For voxels with a TTP concentration in the first half, the correlation between the two models is high (PCC = 0.811, CCC = 0.585). These voxels are largely within the rim of the tumor, and the results from the two models are not significantly different ($p = 0.33$). The Pearson correlation coefficient in v_e values estimated with the STK and DTK models remains high for voxels with TTP concentrations in the final half of the data (PCC = 0.853), indicating a high linear relationship between the values returned by the two models. However, the CCC for this portion of the data decreases significantly (CCC = 0.148), which indicates that the agreement between the two models is biased. Overall, 40% of the individual voxels with a TTP concentration in the second half of the data return v_e values greater than or equal to the theoretical limit of 1.0 when fit with the STK model. In contrast, only 16% of the voxels with a TTP concentration in the second half of the data return unphysical v_e values when the DTK model is used. These voxels are located within the tumor core, and the results from the two models are significantly different

at the 5% level ($p \ll 0.05$). These results are expected based on the results of the simulations above, where voxels with late time-to-peak concentration (TTP), or continuously rising concentration, in combination with low K^{trans} values, are those most affected by CA diffusion.

5. Discussion

As a tumor begins to grow larger than a few mm^3 it can no longer sustain itself through passive diffusion of nutrients from the surrounding tissue. At this point, the tumor begins to recruit new vascularization to sustain further growth (Folkman, 2002). The high permeability resulting from tumor-induced angiogenesis makes cancer a good application for quantitative DCE-MRI. However, the CA is not delivered actively to regions with significant necrosis or where there is no significant vascularization, such as in the tumor core (Jain, 1987). It has been hypothesized that CA in these regions is likely delivered *via* passive diffusion from neighboring tissues that achieved a higher concentration (Netti et al., 2000, Jain, 1987, Koh et al., 2012, Pellerin et al., 2007). The presence of CA diffusion through the extravascular extracellular space would render the Tofts-Kety model invalid (Tofts, 1997). It has been shown previously in simulation that, in the presence of diffusion, the Tofts-Kety model, without any corrections, returns erroneous or unphysical parameter values (Pellerin et al., 2007, Barnes et al., 2011).

The proposed DTK model apparently corrects for diffusion as evidenced by the simulations and experimental data. The simulations showed that, in regions where K^{trans} is less than 0.1 min^{-1} , the TK model overestimates v_e . Also in simulation, both the DTK and STK model were able to estimate K^{trans} over a wide range of values and configurations with errors approximately equal to 23% for the STK model and on the order of 1–3% for the DTK model. The results from the simulations led us to predict that our experimental data would show that the STK model would have a systematic overestimation of v_e in poorly-perfused regions of the *in vivo* tumors, and a good agreement in K^{trans} estimates between the DTK and STK models. These patterns were, in fact, subsequently observed in the experimental data.

The distribution of the kinetic parameters returned by the STK model fits to the experimental data presented here is consistent with previous results investigating DCE-MRI in mouse models of cancer (Su et al., 2003, Cha et al., 2003). These studies show a clear distinction between the rim and core of the tumors. The results from the experimental data presented here show that voxels with late time-to-peak values are more likely to result in unphysically large values for v_e as fit by the STK model. In addition, the voxels with time-to-peak concentration in the third and fourth quartiles of the data tended to be those with K^{trans} values near 0. This was expected, as voxels with late time-to-peak concentration are likely poorly-perfused and receive contrast agent largely through passive diffusion from neighboring voxels; results that are consistent with those previously reported (Jia et al., 2008, Pellerin et al., 2007, Marchal et al., 1992). The results from the experimental data show that the DTK model returns lower values for v_e in the regions of the tumor with continuous and late delivery of CA. At the same time, the K^{trans} and v_e values estimated with the DTK model for tissues with early time-to-peak concentration correlated well with those estimated with the STK model. This suggests that use of the DTK model in well-perfused regions would not significantly change the quantitative results.

It is important to point out that errors in DCE-MRI parameters may impact the utility of the method in a number of applications which use DCE-MRI – such as diagnosis, and treatment planning and monitoring. Though many clinical management decisions with DCE-MRI rely on relative signal enhancement, recent studies have shown that quantitative models show

higher sensitivity to therapy response than semi-quantitative or qualitative analyses (Marinovich et al., 2012, Ah-See et al., 2008, Ovrebo et al., 2011). The spatial “smoothing” of the K^{trans} maps caused by diffusion that is evident in our simulations (see, e.g., figures 1–3), could limit the resolution of the DCE-MRI parameters beyond the native imaging resolution. Correcting for the effects of diffusion has the potential to impact clinical decisions using quantitative DCE-MRI modeling.

The DP model originally proposed by Pellerin *et al.* (Pellerin et al., 2007) also attempts to correct for diffusion in a tumor. This model uses a simulated annealing approach to simultaneously solve for the pharmacokinetic parameters across an entire region of interest, given an experimentally determined diffusion coefficient map (as determined by diffusion measurements of interstitial water). This method has been shown in simulation to return accurate model parameters at the cost of a high computational load. In contrast, the DTK model proposed here solves each voxel or region-averaged tissue concentration curve independently, greatly simplifying the optimization process. In practice, the time required to fit the DTK model to the data scaled linearly with the number of voxels to be fit, and took, on average, five times longer to fit than the STK model per voxel, which represents a speed up of several orders of magnitude over the simulated annealing approach previously described (Pellerin et al., 2007). One potential limitation of the voxel-wise implementation of the DTK model presented here is that it removes global control over the conservation of contrast agent. In the simulations and experimental results presented here, the total amount of contrast passed laterally between voxels is not forced to be zero. Future implementations of the DTK model should incorporate a conservation term to the model fitting.

One potential drawback of the proposed method is the introduction of an extra parameter, D , into the model minimization. Care must be taken in the model fitting to avoid convergence to local minima. This problem can be reduced by providing the model-fitting algorithm with a good initial guess. It is important to note that this limitation is not unique to Eq. (3). Indeed, any nonlinear curve-fitting approach must avoid local minima in the optimization problem, an issue that is only compounded as the number of free model parameters is increased; this includes the extended TK model which includes a plasma volume (v_p) term. In our implementation, we used literature values for the pharmacokinetic model parameters to initialize a least-squares fitting routine when estimating parameters for the simulated and experimental data.

As noted above, the DTK model assumes that the local (i.e., adjacent voxel) spatial variance in the extravascular, extracellular volume fraction is small. As seen in the simulation results, the error in the DTK fit for v_e depends on the local changes in v_e in the diffusion neighborhood. In practice, the validity of this assumption, and the degree to which the DTK model can be used, will depend on both the heterogeneity of the tumor being imaged as well as the spatial resolution of the acquired images. In regions of tissue where the vascular and cellular density vary significantly voxel to voxel, the simplifying assumption that v_e is constant between neighboring voxels will not be valid. Future work with the DTK model will include quantifying the effects of v_e heterogeneity on the model accuracy and precision. However, the results from the simulations and *in vivo* data presented here suggest that the DTK model will perform at least as well as the STK model in poorly-perfused regions of tumors under conditions similar to what was tested here. In addition, the K^{trans} values in the core of the majority of the tumors test in this experiment as returned by either the STK or DTK model were approximately equal to 0.05 min^{-1} ; results from the simulations presented here suggest that the error in v_e returned by the DTK model will be less than 10% given this minimum value for K^{trans} and moderate measurement noise.

The DTK model proposed in this work is a practical approach that is able to correct for CA diffusion within a tumor. The difference in the parameters returned by the DTK model and the Tofts-Kety model are near zero when the region is well-perfused and uniform. Future work with this model will include validating the v_e values returned by the DTK model with histological staining to identify the extracellular space.

Acknowledgments

We thank the National Institute of Health through funding mechanisms NCI 5P50CA128323, NCI R01CA138599, NCI 1U01CA142565, and NCI P30 CA068485. M.E.L. was supported on an AstraZeneca predoctoral training grant. We thank Dr. David Smith, Ph.D. who provided valuable technical assistance. We thank Drs. Daniel Colvin, Ph.D., Zou Xu, M.D., and Mr. Jarrod True, and the Mouse Metabolic Phenotyping Core for assistance with technical MRI and animal care issues. M.L. is the Canada Research Chair in Magnetic Resonance Imaging and member of the FRQ-S – funded Centre de recherche clinique Étienne – Le Bel.

References

- Ah-See ML, Makris A, Taylor NJ, Harrison M, Richman PI, Burcombe RJ, Stirling JJ, D'arcy JA, Collins DJ, Pittam MR, Ravichandran D, Padhani AR. Early changes in functional dynamic magnetic resonance imaging predict for pathologic response to neoadjuvant chemotherapy in primary breast cancer. *Clin Cancer Res*. 2008; 14:6580–6589. [PubMed: 18927299]
- Alonzi R, Padhani AR, Allen C. Dynamic contrast enhanced MRI in prostate cancer. *Eur J Radiol*. 2007; 63:335–350. [PubMed: 17689907]
- Barnes, SL.; Gore, JC.; Yankeelov, TE. Proc 19th Annual Meeting ISMRM. Montreal: ISMRM; 2011. Modeling the Effect of Diffusion on the Assessment of Ktrans and ve in DCE-MRI.
- Cha S, Johnson G, Wadghiri YZ, Jin O, Babb J, Zagzag D, Turnbull DH. Dynamic, contrast-enhanced perfusion MRI in mouse gliomas: correlation with histopathology. *Magn Reson Med*. 2003; 49:848–855. [PubMed: 12704767]
- Cho H, Ackerstaff E, Carlin S, Lupu ME, Wang Y, Rizwan A, O'donoghue J, Ling CC, Humm JL, Zanzonico PB, Koutcher JA. Noninvasive multimodality imaging of the tumor microenvironment: registered dynamic magnetic resonance imaging and positron emission tomography studies of a preclinical tumor model of tumor hypoxia. *Neoplasia*. 2009; 11:247–259. 2p following 259. [PubMed: 19242606]
- Drew PJ, Kerin MJ, Mahapatra T, Malone C, Monson JR, Turnbull LW, Fox JN. Evaluation of response to neoadjuvant chemoradiotherapy for locally advanced breast cancer with dynamic contrast-enhanced MRI of the breast. *Eur J Surg Oncol*. 2001; 27:617–620. [PubMed: 11669587]
- Egeland TA, Gaustad JV, Benjaminsen IC, Hedalen K, Mathiesen B, Rofstad EK. Assessment of fraction of hypoxic cells in human tumor xenografts with necrotic regions by dynamic contrast-enhanced MRI. *Radiat Res*. 2008; 169:689–699. [PubMed: 18494552]
- Egeland TA, Gaustad JV, Galappathi K, Rofstad EK. Magnetic resonance imaging of tumor necrosis. *Acta Oncol*. 2011; 50:427–434. [PubMed: 20950229]
- Egeland TA, Gulliksrud K, Gaustad JV, Mathiesen B, Rofstad EK. Dynamic contrast-enhanced-MRI of tumor hypoxia. *Magn Reson Med*. 2012; 67:519–530. [PubMed: 21661044]
- Folkman J. Role of angiogenesis in tumor growth and metastasis. *Semin Oncol*. 2002; 29:15–18. [PubMed: 12516034]
- Gordon M, Chu K, Margaritis A, Martin A, Ethier C, Rutt B. Measurement of Gd-DTPA diffusion through PVA hydrogel using a novel magnetic resonance imaging method. *Biotechnology and Bioengineering*. 1999; 65:459–467. [PubMed: 10506421]
- Jain RK. Transport of molecules in the tumor interstitium: a review. *Cancer Res*. 1987; 47:3039–3051. [PubMed: 3555767]
- Jia G, O'dell C, Heverhagen JT, Yang X, Liang J, Jacko RV, Sammet S, Pellas T, Cole P, Knopp MV. Colorectal liver metastases: contrast agent diffusion coefficient for quantification of contrast enhancement heterogeneity at MR imaging. *Radiology*. 2008; 248:901–909. [PubMed: 18710983]
- Kety SS. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev*. 1951; 3:1–41. [PubMed: 14833874]

- Koh TS, Hartono S, Thng CH, Lim TK, Martarello L, Ng QS. In vivo measurement of gadolinium diffusivity by dynamic contrast-enhanced MRI: A preclinical study of human xenografts. *Magn Reson Med*. 2012
- Loveless ME, Halliday J, Liess C, Xu L, Dortch RD, Whisenant J, Waterton JC, Gore JC, Yankeelov TE. A quantitative comparison of the influence of individual versus population-derived vascular input functions on dynamic contrast enhanced-MRI in small animals. *Magn Reson Med*. 2012; 67:226–236. [PubMed: 21688316]
- Marchal G, Ni Y, Van Damme B, Van Hecke P, Michiels J, Yu J, Zhang X, Baert AL. Role of contrast agent perfusion and of diffusion in the NMR signal enhancement of liver lesions. *J Comput Assist Tomogr*. 1992; 16:690–698. [PubMed: 1522258]
- Marinovich ML, Sardanelli F, Ciatto S, Mamounas E, Brennan M, Macaskill P, Irwig L, Von Minckwitz G, Houssami N. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: systematic review of the accuracy of MRI. *Breast*. 2012; 21:669–677. [PubMed: 22863284]
- Muller-Brusselbach S, Komhoff M, Rieck M, Meissner W, Kaddatz K, Adamkiewicz J, Keil B, Klose KJ, Moll R, Burdick AD, Peters JM, Muller R. Deregulation of tumor angiogenesis and blockage of tumor growth in PPARbeta-deficient mice. *EMBO J*. 2007; 26:3686–3698. [PubMed: 17641685]
- Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, Jain RK. Role of extracellular matrix assembly in interstitial transport in solid tumors. *Cancer Res*. 2000; 60:2497–2503. [PubMed: 10811131]
- Ovrebo KM, Gulliksrud K, Mathiesen B, Rofstad EK. Assessment of tumor radioresponsiveness and metastatic potential by dynamic contrast-enhanced magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 2011; 81:255–261. [PubMed: 21816291]
- Pellerin M, Yankeelov TE, Lepage M. Incorporating contrast agent diffusion into the analysis of DCE-MRI data. *Magn Reson Med*. 2007; 58:1124–1134. [PubMed: 17969007]
- Pickles MD, Lowry M, Manton DJ, Gibbs P, Turnbull LW. Role of dynamic contrast enhanced MRI in monitoring early response of locally advanced breast cancer to neoadjuvant chemotherapy. *Breast Cancer Res Treat*. 2005; 91:1–10. [PubMed: 15868426]
- Su MY, Cheung YC, Fruehauf JP, Yu H, Nalcioglu O, Mechetner E, Kyshtoobayeva A, Chen SC, Hsueh S, McLaren CE, Wan YL. Correlation of dynamic contrast enhancement MRI parameters with microvessel density and VEGF for assessment of angiogenesis in breast cancer. *J Magn Reson Imaging*. 2003; 18:467–477. [PubMed: 14508784]
- Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*. 1997; 7:91–101. [PubMed: 9039598]
- Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*. 1999; 10:223–232. [PubMed: 10508281]
- Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. *Magn Reson Med*. 1991; 17:357–367. [PubMed: 2062210]
- Turnbull LW. Dynamic contrast-enhanced MRI in the diagnosis and management of breast cancer. *NMR Biomed*. 2009; 22:28–39. [PubMed: 18654999]
- Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth Pf, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res*. 2002; 62:4645–4655. [PubMed: 12183421]
- Yankeelov TE, Gore JC. Dynamic Contrast Enhanced Magnetic Resonance Imaging in Oncology: Theory, Data Acquisition, Analysis, and Examples. *Curr Med Imaging Rev*. 2009; 3:91–107. [PubMed: 19829742]
- Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, Meszoely I, Mayer IA, Herman CR, Mcmanus K, Price RR, Gore Jc. Integration of quantitative DCE-MRI and

ADC mapping to monitor treatment response in human breast cancer: initial results. *Magn Reson Imaging*. 2007; 25:1–13. [PubMed: 17222711]

Figure 1.

Results from simulation 1. Each panel shows a cross-section through the tumor with the true (black) and estimated (color) parameter values. The first two rows correspond to the K^{trans} and v_e results from the STK model respectively and the final three rows correspond to the K^{trans} , v_e , and D results from the DTK model. The x-axis refers to the pixel number. The solid lines refer to the mean parameter values over 100 noise realizations, while the shaded regions contain the 95% confidence intervals for the parameter estimates.

Figure 2.

Results from simulation 2. Each panel shows a cross-section through the tumor with the true (black) and estimated (color) parameter values. The first two rows correspond to the K^{trans} and v_e results from the STK model respectively and the final three rows correspond to the K^{trans} , v_e , and D results from the DTK model. The x-axis refers to the pixel number. The solid lines refer to the mean parameter values over 100 noise realizations, while the shaded regions contain the 95% confidence intervals for the parameter estimates.

Figure 3.

Results from simulation 3. Each panel shows a cross-section through the tumor with the true (black) and estimated (color) parameter values. The first two rows correspond to the K^{trans} and v_e results from the STK model respectively and the final three rows correspond to the K^{trans} , v_e , and D results from the DTK model. The x-axis refers to the pixel number. The solid lines refer to the mean parameter values over 100 noise realizations, while the shaded regions contain the 95% confidence intervals for the parameter estimates.

Figure 4.

The population AIF used to generate the simulations (left) and representative tissue curves from the simulations along with the model fits (right). The true parameters for the two curves are ($[K^{trans} v_e]$): $[0.30 \text{ min}^{-1} 0.5]$, $[0.05 \text{ min}^{-1} 0.5]$. The parameters returned by the STK model are $[0.29 \text{ min}^{-1} 0.37]$ and $[0.049 \text{ min}^{-1} 0.67]$ while the parameters returned by the DTK model are $[0.30 \text{ min}^{-1} 0.48]$, and $[0.051 \text{ min}^{-1} 0.50]$.

Figure 5.

Results from the application of the DP model to the diffusion simulations shown in figures 1–3. In each panel, the black line refers to the true parameter value and the colored lines refer to the estimated parameter. Each simulation was done without any simulated measurement noise.

Figure 6.

Results from the diffusion simulation shown in figure 1 while varying the minimum K^{trans} value. The solid colored line in each panel represents the mean parameter value returned by the DTK model. The shaded regions represent the 95% confidence interval from 100 noise realizations done with 5% noise (red, blue) and 10% noise (magenta, cyan).

Figure 7.

Representative results from the experimental data showing the K^{trans} and v_e parametric maps obtained by the STK (panels a and d), DTK (panels b and e) and DP (panels c and f) models. The TTP map (panel g) displays the quartile of the data in which the peak concentration value for that voxel was reached. Panel h shows a map of the diffusion parameter (D) returned by the DTK model. The K^{trans} maps produced by the models reveal a well-perfused rim with a poorly-perfused core in the tumor. The v_e values from the STK model in the core were unphysically large. For reference, the central slice of the DCE-MRI scan through the tumor region is shown with the ROI shown in panels (a)-(f) highlighted. (The circular object on the left most portion of the image is a water phantom.)

Figure 8.

Summary of all *in vivo* results comparing mean model parameters from the STK and DTK fits. The columns represent voxels with a time to peak concentration occurring in different halves of the total data acquisition. The Pearson's correlation coefficient (PCC), concordance correlation coefficient (CCC), and p value are marked in each panel. Observe how the agreement between the STK and DTK's estimates of v_e decreases from the first to second half (bottom row). In each panel the line of unity is shown for reference.

Table 1

Summary of results from noise simulations. The results correspond to figures 1–3.

	STK Model						DTK Model					
	K^{trans}			v_e			K^{trans}			v_e		
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Tumor 1	22.6%	36.1%	30.9%	13.8%	0%	0%	0%	0%	0%	0%	0%	0%
	0.019	0.023	0.154	0.069	0	0	0	0	0	0	0	0
0% noise												
Tumor 2	10.7%	15.2%	93.1%	170.5%	0.5%	0.6%	6.7%	11.2%	25.7%	12.9%		
	0.012	0.014	0.545	1.029	0.001	0.002	0.035	0.064	6.67E-05	3.36E-05		
Tumor 3	12.4%	17.4%	76.7%	141.3%	0.6%	0.4%	9.0%	17.1%	19.3%	12.7%		
	0.012	0.013	0.439	0.852	0.001	0.001	0.050	0.103	5.03E-05	3.31E-05		
Tumor 1	22.6%	36.1%	30.9%	13.9%	0.5%	0.4%	5.6%	6.1%	15.0%	18.1%		
	0.019	0.023	0.155	0.070	0.000	0.000	0.028	0.031	3.89E-05	4.71E-05		
2.5% noise												
Tumor 2	10.7%	15.2%	93.6%	171.6%	0.8%	0.5%	6.3%	7.7%	29.9%	10.3%		
	0.012	0.014	0.548	1.035	0.002	0.002	0.032	0.041	7.77E-05	2.68E-05		
Tumor 3	12.4%	17.4%	77.5%	143.6%	0.8%	0.6%	9.3%	17.0%	18.2%	11.7%		
	0.012	0.013	0.444	0.866	0.001	0.001	0.051	0.103	4.74E-05	3.04E-05		
Tumor 1	22.6%	36.2%	31.6%	14.5%	2.7%	3.4%	16.9%	12.1%	36.1%	26.1%		
	0.019	0.023	0.158	0.072	0.002	0.002	0.085	0.061	9.38E-05	6.80E-05		
10% noise												
Tumor 2	10.8%	15.2%	94.7%	169.7%	2.1%	1.9%	11.9%	9.5%	47.2%	20.3%		
	0.012	0.014	0.554	1.024	0.004	0.003	0.063	0.051	1.23E-05	5.27E-05		
Tumor 3	12.4%	17.5%	80.6%	151.1%	2.1%	1.6%	14.3%	14.9%	36.7%	20.3%		
	0.012	0.013	0.462	0.911	0.003	0.002	0.076	0.090	9.54E-05	5.28E-05		