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A linear algorithm of the reference region model for DCE-MRI is robust and relaxes requirements for temporal resolution

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Abstract

Dynamic contrast enhanced MRI (DCE-MRI) has utility for improving clinical diagnoses of solid tumors, and for evaluating the early responses of anti-angiogenic chemotherapies. The Reference Region Model (RRM) can improve the clinical implementation of DCE-MRI by substituting the contrast enhancement of muscle for the Arterial Input Function that is used in traditional DCE-MRI methodologies. The RRM is typically fitted to experimental results with a non-linear least squares algorithm. This report demonstrates that this algorithm produces inaccurate and imprecise results when DCE-MRI results have low SNR or slow temporal resolution. To overcome this limitation, a linear least-squares algorithm has been derived for the Reference Region Model. This new algorithm improves accuracy and precision of fitting the Reference Region Model to DCE-MRI results, especially for voxel-wise analyses. This linear algorithm is insensitive to injection speeds, and has 300- to 8000-fold faster calculation speed relative to the non-linear algorithm. The linear algorithm produces more accurate results for over a wider range of permeabilities and blood volumes of tumor vasculature. This new algorithm, termed the Linear Reference Region Model, has strong potential to improve clinical DCE-MRI evaluations.

Keywords

Dynamic contrast enhanced MRI; Permeability; Reference region model; Pharmacokinetics; Linear models; Gd-DTPA

1. Introduction

Dynamic contrast enhanced MRI (DCE-MRI) involves the serial acquisition of MR images before, during and after the injection of a paramagnetic contrast agent (CA) that changes the T_1 relaxation of extracellular water. A concentration-time curve for a tissue of interest (TOI) is calculated by correlating the dynamic changes in signal amplitude with changes in the tissue's T_1 relaxation time caused by the extravasation of the CA. These experimental curves are analyzed by fitting them to an appropriate pharmacokinetic model to estimate physiological parameters, such as perfusion, permeability, and extracellular volume fraction

[1,2]. DCE-MRI has been used to assess the response to anti-angiogenic therapies in clinical [3] and preclinical [4] settings, and has shown some promise for differentiating malignant tumors from benign tumors [5].

DCE-MRI results are typically analyzed using the Tofts model or variations of this model [1,2,6]. These analyses require knowledge of the concentration of the CA in the blood plasma [7–9] also known as the arterial input function (AIF), or its indirect estimation by other means [10]. However, obtaining a reliable AIF is one of the major technical challenges in DCE-MRI [11,12]. In addition, the Tofts model and its variations typically require a temporal sampling of 5 s/image to accurately estimate the model parameters [13]. These difficulties have been overcome by using Reference Region Models (RRM), which use the concentration curve in a reference region (RR) as a surrogate for the AIF [14,15]. These new models for DCE-MRI also relax the requirements for fast temporal resolution to 30–40 s/image [16,17]. The RRM is used to estimate the volume transfer constant and extravascular extracellular volume fraction of the TOI, known as $K^{trans,TOI}$, and $v_{e,TOI}$, respectively, relative to the same parameters of the RR, $K^{trans,RR}$ and $v_{e,RR}$.

A Non-linear Least Squares (NLSQ) algorithm is used to fit the RRM to experimental concentration curves. Unfortunately, NLSQ fittings perform poorly under low SNR conditions that are typical in clinical DCE-MRI studies [18]. Additionally, results from NLSQ fittings of the Tofts model and RRM are highly dependent on the initial estimates of the constants to be calculated [19,20]. Because tumors are heterogeneous, the initial estimates may not apply to all regions of the tumor, which may lead to inaccurate fittings. Finally, the time required to obtain a parametric map through voxel-wise calculations that use a NLSQ algorithm to reach a sufficiently stringent fitting convergence can often exceed 1 h, which is impractical for most radiology clinics.

These limitations of the RRM may be overcome by formulating the model in terms of ratios of $K^{trans,TOI}$ to $K^{trans,RR}$ (known as $R^{K^{trans}}$), $K^{trans,TOI}$ to $v_{e,TOI}$ (known as $k_{ep,TOI}$) and $K^{trans,RR}$ to $v_{e,RR}$ (known as $k_{ep,RR}$) [20]. Initial estimates of these parameters are not required if the parameters are calculated using a Linear Least Squares (LLSQ) fitting algorithm [21,22]. LLSQ algorithms have shown better performance for typical DCE-MRI analysis with the Tofts model than NLSQ algorithms under low SNR and slow temporal resolution [23]. Additionally, LLSQ algorithms typically produce parametric maps within seconds, which can greatly facilitate the practical use of these algorithms.

In this report, we refer to the NLSQ analysis of the RRM as the NRRM, and we refer to the LLSQ analysis of the RRM as the LRRM. We present the derivation of the LRRM for DCE-MRI that relates the concentration-time curves of the TOI and RR in terms of $R^{K^{trans}}$, $k_{ep,TOI}$ and $k_{ep,RR}$. We used computer simulations to compare the accuracy and precision of the LRRM and NRRM as a function of injection speed, temporal resolution and signal-to-noise ratio (SNR). We also evaluated experimental DCE-MRI results of a mouse model of mammary carcinoma to compare the performance of the LRRM to the NRRM under practical conditions, and to experimentally evaluate the conclusions from the simulations.

2. Theory

In this work we employ the notation and symbolic conventions described by Tofts, et al., [24] and Yankeelov et al. [15]. According to the generalized kinetic model for DCE-MRI, the differential equation that describes the pharmacokinetic behavior of a contrast agent (CA) within a voxel is:

$$\frac{dC_{TOI}(t)}{dt} = K^{trans,TOI} \cdot C_p(t) - k_{ep,TOI} \cdot C_{TOI}(t) \quad (1)$$

where $C_p(t)$ and $C_{TOI}(t)$ are the concentrations of the CA at time t in plasma and the TOI, respectively; $K^{trans,TOI}$ is the transfer constant (min^{-1}) between plasma and the Extravascular Extracellular Space (EES) of the TOI; $k_{ep,TOI}$ is the rate constant (min^{-1}) between EES of the TOI and plasma, which is also equal to $K^{trans,TOI}$ divided by $v_{e,TOI}$ (the extravascular-extracellular fractional volume of TOI). As previously described [15], the dependence of Eq. (1) on $C_p(t)$ can be eliminated by using a second tissue (a RR) as a surrogate for the AIF in the TOI. This additional tissue is described by Eq. (2):

$$\frac{dC_{RR}(t)}{dt} = K^{trans,RR} \cdot C_p(t) - k_{ep,RR} \cdot C_{RR}(t) \quad (2)$$

where $C_{RR}(t)$ is the concentration of the CA in the RR at time t , $K^{trans,RR}$ is the transfer constant for the RR, and $k_{ep,RR}$ is the rate constant for the RR. Assuming that $C_p(t)$ is the same for both tissues, it is possible to solve Eq. (2) for $C_p(t)$ yielding:

$$C_p(t) = \frac{1}{K^{trans,RR}} \cdot \frac{dC_{RR}(t)}{dt} + \frac{1}{v_{e,RR}} \cdot C_{RR}(t) \quad (3)$$

substituting Eq. (3) into Eq. (1) eliminates the dependence of Eq. (1) on $C_p(t)$ and yields Eq. (4):

$$\frac{dC_{TOI}(t)}{dt} = \frac{K^{trans,TOI}}{K^{trans,RR}} \cdot \frac{dC_{RR}(t)}{dt} + \frac{K^{trans,TOI}}{v_{e,RR}} \cdot C_{RR}(t) - k_{ep,TOI} \cdot C_{TOI}(t) \quad (4)$$

As previously reported [15], the solution to Eq. (4) is:

$$C_{TOI}(t) = \frac{K^{trans,TOI}}{K^{trans,RR}} \cdot C_{RR}(T) + \frac{K^{trans,TOI}}{K^{trans,RR}} \cdot [k_{ep,RR} - k_{ep,TOI}] \cdot \int_0^T C_{RR}(t) \cdot e^{(-k_{ep,TOI})(T-t)} dt \quad (5)$$

Eq. (5) is the NRRM developed by Yankeelov et al. [15], and it can be used to estimate the relative transfer constant of the TOI compared to the RR ($R^{Ktrans} = K^{trans,TOI}/K^{trans,RR}$). An alternative is to derive the LRRM by integrating both sides of Eq. (4) and assuming that the initial concentration of the CA in both tissues is equal to zero (Eq. (6)).

$$C_{TOI}(T) = R^{Ktrans} \cdot C_{RR}(T) - \frac{K^{trans,TOI}}{v_{e,RR}} \cdot \int_0^T C_{RR}(t) dt + k_{ep,TOI} \cdot \int_0^T C_{TOI}(t) dt \quad (6)$$

Expressed in matrix form, Eq. (6) is equal to Eq. (7).

$$\vec{A} = \vec{M} \cdot \vec{b} \quad (7)$$

where

$$\vec{A} = \begin{pmatrix} C_{RR}(T1) \\ C_{RR}(T2) \\ \vdots \\ C_{RR}(Tn) \end{pmatrix}; \vec{b} = \begin{pmatrix} R^{Ktrans} \\ K^{trans,TOI} \\ \frac{v_{e,RR}}{k_{ep,TOI}} \end{pmatrix}; \quad (8)$$

$$\vec{M} = \begin{pmatrix} C_{RR}(T1) & \int_0^{T1} C_{RR}(t)dt & -\int_0^{T1} C_{TOI}(t)dt \\ C_{RR}(T2) & \int_0^{T1} C_{RR}(t)dt & -\int_0^{T1} C_{TOI}(t)dt \\ \vdots & \vdots & \vdots \\ C_{RR}(Tn) & \int_0^{T1} C_{RR}(t)dt & -\int_0^{T1} C_{TOI}(t)dt \end{pmatrix} \quad (8)$$

If the elements of columns two and three of vector $\vec{M}$ are approximated by numerical integration, Eq. (7) can be solved for the elements of $\vec{b}$ using LLSQ.

$C_{TOI}(T)$ and $C_{RR}(T)$ are not measured directly in a DCE-MRI experiment, and instead the change in the longitudinal relaxation rate (ΔR_1) of each tissue is transformed to concentration via Eqs. (9) and (10).

$$\Delta R_{1,TOI} = R_{1,TOI}(t) - R_{1,TOI}(0) = r_1 \cdot C_{TOI} \quad (9)$$

$$\Delta R_{1,RR} = R_{1,RR}(t) - R_{1,RR}(0) = r_1 \cdot C_{RR} \quad (10)$$

where r_1 is the CA longitudinal relaxivity ($\text{mM}^{-1} \text{s}^{-1}$), and $R_{1,TOI}(0)$ and $R_{1,RR}(0)$ are the R_1 of the TOI and RR before injection of the CA. The working equations for the NRRM (Eq. (11)) and LRRM (Eq. (12)) can be obtained by solving for the concentration of each tissue in Eqs. (9) and (10), substituting into Eqs. (5) and (6), and multiplying by r_1 to obtain Eqs. (11) and (12). Eq. (11) is the NRRM that is fitted to the ΔR_1 of each tissue using a NLSQ method, and Eq. (12) is the LRRM that is fitted to the ΔR_1 using a LLSQ method.

$$\Delta R_{1,TOI}(T) = R^{Ktrans} \cdot \Delta R_{1,RR}(T) + R^{Ktrans} [k_{ep,RR} - k_{ep,TOI}] \cdot \int_0^T \Delta R_{1,RR}(t) \cdot e^{(-k_{ep,TOI}) \cdot (T-t)} dt \quad (11)$$

$$\Delta R_{1,TOI}(T) = R^{Ktrans} \cdot \Delta R_{1,RR}(T) + \frac{K^{trans,TOI}}{e,RR} \cdot \int_0^T \Delta R_{1,RR}(t) dt - k_{ep,TOI} \cdot \int_0^T \Delta R_{1,TOI}(t) dt \quad (12)$$

3. Methods

3.1. Simulations

Computer simulations were used to study the effect of injection speed, temporal resolution, a wide range pharmacokinetic constants, and statistical noise on the accuracy and precision of estimating R^{Ktrans} and $k_{ep,TOI}$ with the LRRM and NRRM. These simulations were conducted using a MacBook Pro notebook computer with a 2.4 GHz Intel Core 2 Duo processor and 4 GB of 667 MHz memory (Apple, Inc., Cupertino, CA). The *trust-region-reflective* algorithm was used for NRRM fitting, as implemented in the *lsqcurvefit* routine of Matlab v. 7.12 (Mathworks Inc., Natick, MA). The termination tolerance of the least squares objective function was set to 10^{-15} , and was set to a maximum of 1000 iterations. The upper bound was set to $100 \text{ min}^{-1}/\text{min}^{-1}$ for R^{Ktrans} , and 10 min^{-1} for $k_{ep,TOI}$ and $k_{ep,RR}$. The lower bound was set to 10^{-4} for all parameters. The Matlab function *mldivide* was used to estimate the parameters with the LRRM. No bounds or initial estimated were used for this method.

To initiate the simulations, three AIFs with three different injection speeds were simulated using Eq. (13).

$$C_p(t) = A \cdot t^B \cdot e^{(-t \cdot C)} + D \cdot \left[1 - e^{(-t \cdot E)} \right] \cdot e^{(-t \cdot F)} \quad (13)$$

The following parameters were used to simulate each speed: AIF1) Fast 10-s injection speed, $A=30.0$ mM, $B=1.0$, $C=4.00$ min⁻¹, $D=0.65$ mM, $E=5.0$ min⁻¹, $F=0.04$ min⁻¹; AIF2) Moderate 40-s injection speed, $A=120.0$ mM, $B=3.0$, $C=4.34$ min⁻¹, $D=0.80$ mM, $E=1.0$ min⁻¹, $F=0.07$ min⁻¹; AIF3) Slow 80-s injection speed, $A=55.0$ mM, $B=5.5$, $C=3.98$ min⁻¹, $D=0.80$ mM, $E=1.0$ min⁻¹, $F=0.07$ min⁻¹ [13]. As with other published simulations, these AIFs did not include a transit delay from the injection site to the tumor or bolus dispersion during the transit delay [13,16]. However, the Reference Region Model has been shown to be insensitive to these effects for injection speeds as fast as 10 s [25]. All of the AIFs were calculated from $t=0$ to $t=35$ min at a temporal resolution of 1.0 s. A series of $C_{TOI}(t)$ and $C_{RR}(t)$ curves were then calculated using each AIF and Eq. (14), with $K^{trans}=0.25$ min⁻¹ and $k_{ep}=0.62$ min⁻¹ for the TOI curve, and $K^{trans}=0.10$ min⁻¹ and $k_{ep}=1.00$ min⁻¹ for the RR curve (Fig. 1).

$$C_t(T) = K^{trans} \int_0^T C_p(t) \cdot e^{[-k_{ep}(T-t)]} dt \quad (14)$$

The values assigned for the TOI are characteristic of various human tumors [26], while the RR values are reasonable for muscle tissue [27]. Two sources of systematic error were explored using simulated data that did not include noise. First, all the AIFs, $C_{TOI}(t)$ and $C_{RR}(t)$ were downsampled from their initial temporal resolution (Δt) of one second to $\Delta t=60$ s in intervals of 1 s, and all parameters were estimated with the LRRM and NRRM for each new Δt . Second, the effect of extreme pharmacokinetic constants was studied by estimating K^{trans} and $k_{ep,TOI}$ using the LRRM and NRRM as $K^{trans,TOI}$ was changed from 0.1 to 0.7 min⁻¹ in steps of 5×10^{-3} min⁻¹, $v_{e,TOI}$ was changed from 0.10 to 0.7 (mL/mL) in steps of 5×10^{-3} (mL/mL), while $K^{trans,RR}$ and $k_{ep,TOI}$ were fixed at 0.1 and 1.0 min⁻¹, respectively.

The AIF with the best performance in the systematic error analysis was used to study the combined effect of SNR and Δt on the accuracy and precision of the LRRM and NRRM. First, all simulated data were recalculated with $\Delta t=1, 10, 30$, and 60 s. Second, Gaussian noise was added to produce SNRs from 5 to 50. The SNR was defined as $SNR = S_{max}/\sigma$, where S_{max} represents the maximum signal of each curve and σ is the standard deviation of the noise (SD). Third, each simulation was repeated 1000 times for each condition of SNR and Δt . The accuracies of parameter estimations were evaluated in terms of the mean percentage error (Eq. (15)), and the precision was evaluated using the standard deviation of the percentage error (Eq. (16)), where $\hat{P}_{ij}$ is the estimated value of the j th data of the i th parameter, P_i is the true value of the i th parameter, and N is the number of data points (1000 for this study).

$$\mu_{error} = 100 \cdot \frac{1}{N} \left(\sum_{j=1}^N \left[(\hat{P}_{ij} - P_i) / P_i \right] \right) \quad (15)$$

$$\sigma_{error} = 100 \cdot \sqrt{\frac{1}{N} \sum_{j=1}^N (\hat{P}_{ij} - \mu_{error})^2} \quad (16)$$

3.2. Mouse model

Twenty-one female SCID mice weighting 21–23 g were housed and maintained under specific pathogen-free conditions in accordance with the guidelines of the American Association for Laboratory Animal Care. All experiments met the current regulations and standards of the U.S. Department of Agriculture, the U.S. Department of Health and Human Services, the National Institutes of Health, and the University of Arizona Animal Care Facility. Each mouse was injected subcutaneously in the right flank with 10×10^6 MDA-231 cells in 0.1 mL of saline. The tumor was measured every 2 to 3 days using electronic calipers and allowed to grow for 22–23 days to a volume of 250 mm^3 before initiating MRI studies.

3.3. DCE-MRI protocol

Each mouse was scanned 22–23 days after tumor implantation using a Biospec 7.0 T scanner (Bruker Biospin Inc., that was equipped with a 72 mm birdcage coil (Bruker Biospin, GmbH, Karlsruhe, Germany)). Before the imaging scan, the mouse was anesthetized with 1.5–2% isoflurane in O_2 carrier gas, a 27 G catheter was inserted in the tail vein and physiological monitoring leads were connected to monitor respiration rate and core body temperature during the MRI session. The mouse was kept at $37.0 \pm 0.2^\circ \text{C}$ during the MRI studies using warmed air that is controlled by an automated temperature-feedback system (SA Instruments, Inc., Stony Brook, NY).

DCE-MRI studies were conducted by acquiring a set of 3 contiguous axial image slices through the xenograft flank tumor, and 3 axial image slices through the femoral artery. The orientation of these image slices were determined by acquiring T_2 -weighted MR images with a RARE MRI protocol that used the following parameters: $\text{TR}=1.0 \text{ s}$, $\text{TE}=8.2 \text{ msec}$, slice thickness=0.5 mm; matrix=128×128, $\text{FOV}=3.5 \text{ cm}^2$, in-plane resolution=273 μm^2 ; NEX=1, and RARE=4.

A parametric map of endogenous T_1 relaxation rate, $R_1(t)$, with the same geometry as the T_2 -weighted images, was obtained by acquiring a series of single-echo images with the following parameters: $\text{TR}=0.375, 0.75, 1.5, 3.0, \text{ and } 6.0 \text{ s}$, $\text{TE}=9.07 \text{ msec}$, NEX=1. Eq. (17) was used to analyze these results, where α is the flip angle (90° for this study), and A is a constant that includes the proton density and scanner gain. We assumed that $\text{TE} \ll T_2^*$.

$$S = A \cdot \left[\frac{\sin \sigma \cdot (1 - e^{(-TR \cdot R_1)})}{1 - e^{(-TR \cdot R_1)} \cdot \cos \sigma} \right] \quad (17)$$

A series of T_1 -weighted images were acquired for DCE-MRI analysis using a RARE MRI protocol with the same geometry as the $R_1(t)$ maps, and the following parameters were used: $\text{TR}=250 \text{ msec}$, $\text{TE}=8.2 \text{ msec}$, NEX=2, and RARE factor=2. A total of 65 image sets were acquired for a total acquisition time of 34.66 min which equated to a temporal resolution of 32 s/image. After the fifth image set was acquired, 0.2 mmol/Kg Gd-DTPA (Magnevist™, Bayer Healthcare Inc., Leverkusen, Germany) was injected through the tail vein catheter in a total volume of 0.25 mL during 60 s. Finally, the $R_1(t)$ maps and Eq. (18) were used to estimate $\Delta R_1(t)$ for each voxel within TOI and the average $\Delta R_1(t)$ of RR.

$$R_1(t) = \frac{1}{-TR} \cdot \ln \left[1 - \frac{S(t)}{S(0)} (1 - e^{(-TR \cdot R_1(0))}) \right] \quad (18)$$

The $\Delta R_I(t)$ curves for RR and TOI were fitted to Eq. (11) (NRRM) and Eq. (12) (LRRM) to generate tumor parametric maps of R^{Ktrans} and $k_{ep,TOI}$. The goodness of fit for each voxel was evaluated in terms of the root mean square error (RMSE):

$$RMSE = \sqrt{\frac{N}{N-1} \sum_{j=1}^N (y_j - \hat{y}_j)^2} \quad (19)$$

where $\hat{y}_j$ is the estimated value of the j^{th} data point of the $\Delta R_{I,TOI}(T)$ curve, y_j is the observed value of the j^{th} data point of the $\Delta R_{I,TOI}(T)$ curve, and N is the number of data points in the $\Delta R_{I,TOI}(T)$ curve.

3.4. Downsampling of experimental data

The temporal resolution (Δt) of the $\Delta R_{I,TOI}(T)$ and $\Delta R_{I,RR}(T)$ curves were increased from their initial Δt of 32 s to $\Delta t=64, 96$ and 128 s by taking only every 2nd, 3rd and 4th point of the original curves. R^{Ktrans} and $k_{ep,TOI}$ were estimated at each new Δt and their Pearson's correlation coefficient with their value at $\Delta t=32$ s was calculated.

3.5. Statistical analysis

The differences in the values of the estimated parameters by LRRM and NRRM were evaluated at the 5% confidence level using Friedman's test, which is the non-parametric equivalent of a two-sided paired t-test. All the reported p-values are adjusted for multiple comparisons.

4. Results

The LRRM and NRRM algorithms were straightforward to implement in Matlab. The $C_A(T)$ curves simulated for this analysis were noise-free, and at a temporal resolution of 1 s for a total of 35 min. The termination tolerance of the NRRM fitting was set to a low level of 10^{-15} because higher tolerance levels produced less precise results, and comparing the precisions of the LRRM and NRRM methods was a goal of our study. The time to calculate a parametric map of R^{Ktrans} for a 128×128 image matrix was approximately 8.54 s using LRRM and 43.69 min using NRRM. Therefore, the LRRM produced results 306.98 times faster than NRRM under this best-case scenario. The speed of LRRM and NRRM as a function of SNR ranging from 5 to 50 was also tested. The time required to fitting curves using the NRRM increased exponentially as the SNR decreased. The average speed for one NRRM fitting was 1.35, 6.7 and 8.2 s when the SNR was 50, 10, and 5, respectively. The LRRM speed showed no dependence on the SNR, being 1.0×10^{-3} for one fitting for all studied SNR values. This result demonstrates that the iterative process of fitting the NRRM requires more calculation time relative to the simple one-time process of fitting a linear function, especially for noisy data, so that the LRRM is 1350–8200 times faster than NRRM (depending on the SNR).

4.1. Simulations

The LRRM and NRRM were used to evaluate simulated data that varied in temporal resolution and injection speeds (Fig. 2). The estimated values of R^{Ktrans} and $k_{ep,TOI}$ from these evaluations were compared to their initial values used to create the simulated data (Fig. 1). These results showed that NRRM systematically underestimated R^{Ktrans} at a temporal sampling >5.0 s and overestimated $k_{ep,TOI}$ at a temporal sampling >12.0 s. Although the injection speeds tested in our studies had only a minor influence on these systematic errors when the temporal sampling was <30 s, the injection speeds had a moderate effect on the magnitudes of systematic errors when the temporal sampling was >30 s.

For comparison, the LRRM showed almost no systematic error in determining R^{Ktrans} and $k_{ep,TOI}$ for all temporal sampling rates when a fast or moderate injection speed was used. When a slow injection speed and temporal sampling >30 s were used, R^{Ktrans} and $k_{ep,TOI}$ were systematically overestimated using the LRRM, but these systematic errors were less than or equal to the errors produced by the NRRM. These results indicated that DCE-MRI with LRRM can produce accurate results with a moderate or fast injection speed, while DCE-MRI with NRRM cannot produce accurate results unless the temporal sampling is fast (<5 s).

The LRRM and NRRM were also used to evaluate simulated data that varied in $K^{trans,TOI}$ and $v_{e,TOI}$. The values of $K^{trans,RR}$ and $k_{ep,TOI}$ were held constant for these simulations. The simulated data used the moderate injection speed, because the initial simulations described above showed excellent performance with AIF2, and this moderate injection speed matched our experimental conditions. The systematic error in estimated R^{Ktrans} was lower for LRRM than NRRM for each combination of $K^{trans,TOI}$ and $v_{e,TOI}$ (Figs. 3A, B). The greatest errors with each analysis method were observed for high $K^{trans,TOI}$ and low $v_{e,TOI}$. This result was expected, because the DCE-MRI curve has a low initial signal that is rapidly changing under these conditions, which is more difficult to fit than a high initial signal that is changing slowly. These systematic errors in estimated R^{Ktrans} for both LRRM and NRRM were independent of R^{Ktrans} , but scale with $k_{ep,TOI}$ (Figs. 3C, D). Again, LRRM showed lower systematic errors than NRRM, with only 8.5% error at the maximum $k_{ep,TOI}$ relative to 21.2% error for NRRM. These results demonstrated that DCE-MRI with LRRM can provide accurate estimates of R^{Ktrans} over a wider range of tumor vascular conditions than NRRM.

The LRRM and NRRM were then used to evaluate simulated data that varied in SNR and injection speeds. A temporal resolution of 1 s was used for this simulation. The average errors, and the standard deviations of these fitting errors, were determined for the estimated R^{Ktrans} and $k_{ep,TOI}$ values of 1000 simulations relative to the R^{Ktrans} and $k_{ep,TOI}$ values used to create the simulated data (Fig. 4). Both the LRRM and the NRRM showed greater average errors in estimated R^{Ktrans} and $k_{ep,TOI}$ as the SNR decreased. Yet the errors with LRRM were smaller than the errors with NRRM for all SNRs. For example, for a SNR of 5, the estimated R^{Ktrans} reached a maximum error of $-62.45 (\pm 6.14)\%$ with LRRM relative to $-98.5 (\pm 6.14)\%$ with NRRM, and the estimated $k_{ep,TOI}$ reached a maximum error of $101.44 (\pm 37.31)\%$ with LRRM relative to $>230\%$ with NRRM. The errors when using NRRM were comparable to the errors with LRRM only at the highest SNR of 50. The standard deviations of these results were also smaller when using LRRM relative to NRRM at SNR >10 . Importantly, for a SNR of 50 these standard deviations were negligible for LRRM while these standard deviations were substantial for NRRM, which indicated that LRRM provided more precise fittings to the data. For a SNR of 5, the NRRM showed negligible standard deviations for estimates of R^{Ktrans} and showed lower errors for $k_{ep,TOI}$ than at a SNR of 10, which indicated that these fittings had failed to adequately fit the noisy data. In addition, the errors in estimated R^{Ktrans} and $k_{ep,TOI}$ were independent of the injection speeds tested in our study when LRRM was used, while estimates with NRRM showed errors that were dependent on injection speed. These results showed that DCE-MRI with LRRM can produce more precise results than the NRRM, especially at low SNRs, and regardless of injection speeds between 10 and 60 s.

The LRRM and NRRM were then used to evaluate simulated data that varied in SNR and temporal resolutions ($\Delta t=5, 10, 30$, and 60 s). AIF2 was used to simulate a moderate injection speed. The average error, and the standard deviation of this average, was determined for the estimated R^{Ktrans} and $k_{ep,TOI}$ values of 1000 simulations relative to the R^{Ktrans} and $k_{ep,TOI}$ values used to create the simulated data (Figs. 5, 6). As with the previous simulations, the errors in estimating R^{Ktrans} increased as the SNR decreased for both LRRM

and NRRM. Yet the errors in estimated R^{Ktrans} with LRRM were smaller than the errors with NRRM for all SNRs. Also, the errors in estimated R^{Ktrans} with NRRM were strongly dependent on temporal resolution, even at high SNR of 50, while the estimates with LRRM were relatively insensitive to the temporal resolution. Importantly, the worst-case conditions of 60 s temporal resolution and SNR of 5 produced a relatively small error of $-5.98 (\pm 16.03)\%$ with LRRM. These results demonstrated that DCE-MRI with LRRM can produce more precise results for estimated R^{Ktrans} than the NRRM, especially at low SNRs, and regardless of injection speeds between 10 and 60 s.

Similarly, the errors in estimating $k_{ep,TOI}$ increased as the SNR decreased in these simulations (Fig. 6). The errors in estimated $k_{ep,TOI}$ with LRRM were also smaller than errors with NRRM for fast temporal resolutions of 5 and 10 s, but the errors with LRRM were larger than errors with NRRM for slower temporal resolutions. Both the LRRM and NRRM produced errors in estimated $k_{ep,TOI}$ that were dependent on temporal resolution. These results demonstrated that DCE-MRI with LRRM can produce more precise results for estimated $k_{ep,TOI}$ than the NRRM at fast temporal resolutions, but not at slow temporal resolutions.

5. Experimental

An experimental DCE-MRI study was performed with 21 mice that had a subcutaneous tumor of MDA-MB-231 mammary carcinoma. A representative example of one mouse of this study showed an increase in the MR signals in the tumor after the injection of contrast agent, with more signal enhancement observed in the tumor's periphery than the core (Fig. 7). The average SNR of a single voxel within the tumor was approximately 5, while the SNR for the average signal for the entire tumor was about 102, and the tumor region was comprised of 221 voxels. This difference in SNR between the tumor voxels and the tumor ROI provided the opportunity to test the conclusion from the simulations that the LRRM has advantages relative to the NRRM under low SNR conditions but not high SNR conditions, as described below. MR signals also increased in the muscle near the tumor, including the selected reference region that consisted of a 3×3 -voxel region with a total SNR of 52 for the 9 voxels. The eventual decrease in MR signals occurred sooner and faster for the reference region relative to the tumor.

The LRRM and NRRM were used to estimate R^{Ktrans} , $k_{ep,TOI}$, and $k_{ep,RR}$ from the average $\Delta R_{I,TOI}(T)$ and the average $\Delta R_{I,RR}(T)$, for each mouse (Table 1). The estimates obtained using LRRM were not statistically different from those obtained with NRRM, because the confidence intervals of the fittings overlapped. Both algorithms showed an equal RMSE, which showed equal precision of fitting the experimental data. The estimated parameters were comparable to reported values for other tumor types and muscle [24,28,29]. These experimental results showed that the LRRM and NRRM performed similarly when fitting data with high SNR, moderate temporal resolution and moderate injection speed, which agreed with conclusions from the simulations.

A voxel-wise analysis was then performed to construct parametric maps of R^{Ktrans} , $k_{ep,TOI}$ and RMSE with LRRM and NRRM for each mouse. Representative maps of R^{Ktrans} for the central imaging slice for one mouse are shown in Figs. 7D and E. All maps for the 21 mice showed a tumor core with $R^{Ktrans} < 1.0$ and a tumor periphery with R^{Ktrans} that ranged from 1.5 to $5.0 \text{ min}^{-1}/\text{min}^{-1}$. However, as shown by the cumulative histograms for these two maps, the median R^{Ktrans} of all tumor voxels using LRRM was 0.18 while the median value using NRRM was 0.03 (Fig. 8A). A Friedman test produced a value of $p < 0.001$, which demonstrated that the two maps were statistically different.

The cumulative histograms showed that only ~10% of the voxels of the R^{Ktrans} map obtained with NRRM had values between 0.12 and 1.0, while 50% of the voxels of the map obtained with LRRM had values between 0.12 and 1.0 (Fig. 8A). The cumulative histogram for the ratio of R^{Ktrans} estimated with each algorithm showed that this ratio is less than 1.0 for almost all of the voxels, further demonstrating that values estimated with NRRM were lower than estimates with LRRM (Fig. 8B). Therefore, under experimental conditions of low SNR that are typical of single-voxel analyses, the NRRM systematically underestimated R^{Ktrans} for many voxels of the tumor region relative to the value of R^{Ktrans} determined with LRRM, which agreed with conclusions from the simulations.

A similar analysis was performed to evaluate the voxel-wise distribution of the parametric maps of $k_{ep,TOI}$. Both maps exhibited a similar median $k_{ep,TOI}$ (Table 1). However, the cumulative distributions of the voxel values indicated that ~10% of the voxels determined using NRRM had extremely high values (Fig. 3.8C). The comparisons of results with LRRM vs. NRRM were also visualized in the cumulative histograms for the ratio of $k_{ep,TOI}$ and $k_{ep,RR}$ estimated with each algorithm, which showed that this ratio is greater than 1.0 for 30% and 70% of the voxels for each measurement, respectively (Fig. 8B). Therefore, NRRM systematically overestimated the experimental $k_{ep,TOI}$ for some voxels of the tumor region relative to the value of $k_{ep,TOI}$ determined with LRRM, which agreed with conclusions from the simulations.

Finally, the effect of temporal resolution (Δt) on the estimated R^{Ktrans} and $k_{ep,TOI}$ with the LRRM and NRRM was studied. The ΔR_1 curves for each voxel of each mouse and the reference region were downsampled from their initial values of 32 s, to values of 64, 96 and 128 s. R^{Ktrans} and $k_{ep,TOI}$ were estimated with the LRRM and NRRM at each temporal resolution. The values estimated at the slower temporal resolutions were compared with values estimated at 32 s using scatter plots (Fig. 9). When the LRRM was used, R^{Ktrans} and $k_{ep,TOI}$ estimated with slower Δt were highly correlated with $R^{Ktrans-32}$ and $k_{ep,TOI-32}$, while the NRRM estimated different R^{Ktrans} and $k_{ep,TOI}$ at each temporal resolution. These trends are confirmed by the Pearson's correlation coefficient (r , Table 2). $R^{Ktrans-32}$ was highly correlated with $R^{Ktrans-128}$ when the LRRM was used to estimate the parameters ($r=0.80$), while the $R^{Ktrans-32}$ and $R^{Ktrans-128}$ estimated with the NRRM showed a lower correlation ($r=0.29$). As further evidence, the RMSE of the fittings with the NRRM were compared with the RMSE of the LRRM at each temporal resolution (Fig. 9G,H). Although the distributions of RMSEs for the NRRM and LRRM were comparable for a temporal resolution of 32 s, the NRRM showed greater RSME relative to LRRM at slower temporal resolutions. These experimental results confirmed that the LRRM is relatively insensitive to temporal resolution, while NRRM is more sensitive to temporal resolution, which agreed with conclusions from the simulations.

6. Discussion

Although the Reference Region Model addresses some of the challenges of DCE-MRI analyses, the NRRM may be impractical for many pre-clinical and clinical studies. Our simulations confirm that the NRRM can only produce accurate and precise results when the temporal resolution is fast. Also, NRRM produces inaccurate results especially when $K^{trans,TOI}$ and v_e,TOI are both high, which typically occurs for angiogenic tumors that are intended to be studied by DCE-MRI, which decreases the value of DCE-MRI for clinical evaluations. We attribute these problems to the fitting of a non-linear function, especially for rapidly changing functions that are sampled with insufficiently slow temporal resolution. Furthermore, our simulations and experimental results show that NRRM estimates inaccurate and imprecise R^{Ktrans} values when DCE-MRI curves have low SNR, which is especially detrimental for experimental voxel-wise analyses. The slow calculation speed of

the NLSQ algorithm for the NRRM is impractical for most clinical studies, and also problematic for pre-clinical studies.

Conversely, our simulations demonstrate that LRRM can produce accurate and precise results at slow temporal resolutions that are typical in most pre-clinical imaging centers and radiology clinics. Also, LRRM produces more accurate results than NRRM for angiogenic tumors that have high $K^{trans,TOI}$ and $v_{e,TOI}$. Furthermore, our simulations and experimental results show that LRRM estimates accurate and precise R^{Ktrans} values when DCE-MRI curves have low SNR, which is especially beneficial for voxel-wise analyses. We attribute these advantages of the LRRM to the fitting of a linear function that is insensitive to slow temporal resolution. Furthermore, the fitting of the LRRM's linear function to experimental data considers each data point to be equally important to the fitting process, while fitting the NRRM's non-linear function necessarily places more importance on data points that are changing more rapidly. Because the NRRM more heavily relies on a subset of data points, this method is more sensitive to noise. The fast calculation speed of the LLSQ algorithm for the LRRM is a tremendous benefit for pre-clinical and clinical DCE-MRI studies. Relaxing the requirements for temporal resolution and SNR may be especially helpful when comparing DCE-MRI results between radiology clinics. This advantage may accelerate the clinical evaluations of new anti-angiogenic chemotherapies, because standardizing the DCE-MRI protocols among multiple clinics that are participating in a single clinical trial is very challenging.

The LRRM algorithm is insensitive to injection speeds between 10 and 60 s that were tested in our simulations, while the NRRM shows a mild dependence on injection speed. Injection speeds are typically fast during clinical DCE-MRI studies, so injection speed should not be critically important when selecting NRRM or LRRM for clinical DCE-MRI analyses. Injection speeds are more variable when performing DCE-MRI studies with mouse models of human cancers. The type of vessel used for i.v. injection (e.g., tail vein, femoral vein, jugular vein) can dictate the size of the catheter or injection needle, which can influence injection speed. Fast i.v. injections can be more difficult to perform by researchers with limited expertise. Automated or manual injections of solutions with experimental contrast agents can vary in viscosity and volume, which may also dictate injection speed to avoid "catheter blow-out" from the mouse tail vein. Therefore, the LRRM may improve the analyses of pre-clinical DCE-MRI studies that are performed with slow injection speeds.

Although the experimental results of this study confirmed some of the conclusions of the simulations, additional experimental studies are warranted to test variations and other characteristics of the RRM. For example, the transit delay and dispersion of the initial bolus injection have been evaluated for the NRRM, which showed that the NRRM is insensitive to these effects [25]. A similar analysis could be performed with the LRRM. Our study used subsets of experimental images to test the effects of temporal resolution, yet k-space downsampling of the experimental results could be performed as an alternative method. Experimental studies with different injection speeds should be conducted to validate the effects of injection speeds that were demonstrated by our simulations. Testing a variety of mouse models that differ in tumor vascular permeabilities and/or blood volumes could be conducted to validate that the LRRM can accurately evaluate a wider range of tumor vascular characteristics than the NRRM as shown in our simulations. Our simulations are based on a two-compartment pharmacokinetic model, which is commonly employed when assessing new DCE-MRI methods. Yet a two-compartment model may not be appropriate for all tumor regions, so that expanding the LRRM to evaluate a multicompartment model may have merits. The NRRM has been extended to include consideration for the fractional plasma volume and transcytolemmal water exchange [30,31]. Extending the LRRM to include these effects may further improve the utility of this new algorithm. The NRRM has

been applied to analysis of DCE results obtained with SPECT, which suggests that the LRRM may have merits for DCE analyses with other imaging modalities [32]. This report establishes the LRRM for these additional studies.

7. Conclusions

The Linear Reference Region Model can estimate R^{Ktrans} and $k_{ep,TOI}$ with improved accuracy and precision relative to the NRRM. The LRRM is especially useful for DCE-MRI studies with low SNR and slow temporal resolution, and DCE-MRI evaluations that are performed on a voxel-wise basis. The LRRM is insensitive to injection speeds between 10 and 60 s while the NRRM has moderate sensitivity to injection speed. These advantages indicate that the LRRM has strong potential to improve clinical DCE-MRI evaluations.

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Fig. 1.

The simulated concentration-time curves for the simulations of LRRM and NRRM. A) Three arterial input functions (AIFs) were simulated using Eq. (13), which represented the consequences of fast, moderate, and slow injection speeds. B) The pharmacokinetics of a contrast agent in the Tissue of Interest (TOI) were determined using each AIF and kinetics that are characteristic of a solid tumor ($K^{trans}=0.25 \text{ min}^{-1}$ and $v_e=0.40 \text{ (mL/mL)}$). C) The pharmacokinetics of a contrast agent in the Reference Region were determined using each AIF and kinetics that are characteristic of muscle ($K^{trans}=0.10 \text{ min}^{-1}$ and $v_e=0.10 \text{ (mL/mL)}$). Each curve was calculated using intervals of 1 s from 0 to 35 min, but only the first 5 min are shown.

Fig. 2. Systematic errors as a function of temporal resolution and injection speed A) for estimated R^{Ktrans} and B) for estimated $k_{ep,TOI}$. Open symbols represent the LRRM and closed symbols represent the NRRM. circle, square and diamond symbols represent AIFs with injection speeds of 10, 40, and 80 s; AIF1, AIF2, and AIF3, respectively. The pharmacokinetics of the contrast agent in the Tissue of Interest (TOI) and Reference Region (RR) are described in the caption of Fig. 1.

Fig. 3. Systematic errors of the estimated R^{Ktrans} . The percent errors of the estimated R^{Ktrans} are shown as a function of $v_{e,TOI}$ and $K^{trans,TOI}$ a) when the LRRM is used, and B) when the NRRM is used. The percent errors of the estimated $k_{ep,TOI}$ are shown as a function of R^{Ktrans} and $k_{ep,TOI}$ A) when the LRRM is used, and D) when the NRRM is used. These systematic errors were evaluated using a temporal resolution of 6 s, an AIF with injection speed of 40 s (AIF2).

Fig. 4. Random errors as a function SNR and injection speed. Percent errors are shown when the LRRM (open symbols) and NRRM (closed symbols) were used to estimate A) R^{Ktrans} , and B) $k_{ep,TOI}$. Error bars represent the standard deviation of the error for a 1000 simulations. The SNR was set to the same value for the Tissue of Interest and Reference Region. The temporal resolution was set to 1 s and an AIF with an injection speed of 40 s was used (AIF2).

Fig. 5. Random errors of the estimated R^{Ktrans} as a function of SNR and temporal resolutions. A) 60 s, B) 30 s, C) 10 s, and D) 5 s. Results using the LRRM (blue circles) and NRRM (red squares) are shown. The signal-to-noise ratio of the reference region was set to 50. Error bars represent the standard deviation of the error for a 1000 simulations. The pharmacokinetic parameters used are: $K^{trans,TOI}=0.25 \text{ min}^{-1}$, $v_{e,TOI}=0.40 \text{ (mL/mL)}$, $K^{trans,RR}=0.10 \text{ min}^{-1}$ and $v_{e,RR}=0.10 \text{ (mL/mL)}$.

Fig. 6. Random errors of the estimated $k_{ep,TOI}$ as a function of SNR and temporal resolutions of A) 60 s, B) 30 s, C) 10 s, and D) 5 s. Results using the LRRM (blue circles) and NRRM (red squares) are shown. The signal-to-noise ratio of the reference region was set to 50. Error bars represent the standard deviation of the error for a 1000 simulations. The pharmacokinetic parameters used are: $K^{trans,TOI}=0.25 \text{ min}^{-1}$, $v_{e,TOI}=0.40 \text{ (mL/mL)}$, $K^{trans,RR}=0.10 \text{ min}^{-1}$ and $v_{e,RR}=0.10 \text{ (mL/mL)}$.

Fig. 7.

Experimental evaluation of the Linear and Non-Linear Reference Region models: a representative example. A) The tissue of interest (TOI) representing a subcutaneous MDA-MB-231 tumor and the Reference Region (RR) representing muscle near the tumor are shown on an axial image of a mouse before injection. B) The same image as panel A at the point of maximum signal, 8 min after injection. C) Average ΔR_1 curves for the RR and TOI of the DCE-MRI study of the mouse, fitted to the LRRM and NRRM to estimate R^{Ktrans} , $k_{ep,TOI}$ and $k_{ep,RR}$. D) R^{Ktrans} parametric maps calculated with LRRM and NRRM. The analyses shown in panels C and D were repeated for all mice for which a DCE-MRI scan was successfully performed (21/24).

Fig. 8.

Voxel-wise determinations of experimental R^{Ktrans} , $k_{ep,TOI}$ and $k_{ep,RR}$ for 21 mice. A) Plots of the normalized cumulative distribution of $R^{Ktrans-32}$ estimated via the LRRM and NRRM. B) The normalized cumulative distribution of the ratio of R^{Ktrans} determined with NRRM vs. LRRM shows that NRRM calculates lower R^{Ktrans} values for ~95% of the voxels. The normalized cumulative distribution of the ratio of $k_{ep,TOI}$ determined from NRRM vs. LRRM shows that the distribution of voxel-wise $k_{ep,TOI}$ values is approximately the same for only ~20% of the voxels. The normalized cumulative distribution of the ratio of $k_{ep,RR}$ determined from NRRM vs. LRRM shows that NRRM calculates higher $k_{ep,RR}$ values for ~70% of the voxels, with more than a 2.5-fold higher value for 50% of the voxels. C) A plot of the normalized cumulative distribution of $k_{ep,TOI-32}$ with the LRRM and NRRM shows that the NRRM calculates more voxels with very high values ($>1.0 \text{ min}^{-1}$). D) The normalized cumulative distribution of the ratio of the root mean squared error (RMSE) of the fitting, shows that the error is similar for LRRM and NRRM at a temporal resolution of

32 while 50% of the voxels showed a higher error of fitting via NRRM at a temporal resolution of 128 s.

Fig. 9.

The effect of temporal resolution on the accuracy of the estimated pharmacokinetic constants via LRRM and NRRM. All scatter plots compare results with a temporal resolution of 32 s with temporal resolutions of 64, 96, and 128 s for all voxels of all mice in the TOI. Results are shown for A) R^{Ktrans} using the LRRM, B) R^{Ktrans} using the NRRM, C) $k_{ep,TOI}$ using the LRRM, D) $k_{ep,TOI}$ using the NRRM, E) $k_{ep,RR}$ using the LRRM, F) $k_{ep,RR}$ using the NRRM, G) $rmse$ using the LRRM, and H) $rmse$ using the NRRM. The total numbers of analyzed voxels is ~8200, for a total of 21 mice.

Table 1

The estimated parameters using LRRM and NRRM with average ΔR_1 curves.

Estimate	Median	Interquartile range		p-value*
		LRRM	NRRM	
R^{ktrans} ($\text{min}^{-1}/\text{min}^{-1}$)	0.01	0.01	0.36	0.26
$k_{ep,TOI}$ (min^{-1})	0.06	0.07	0.07	0.20
$k_{ep,kR}$ (min^{-1})	0.47	1.00	0.94	9.70
RMSE (mM)	0.01	0.01	0.01	0.01

* Friedman test performed at the 95% confidence level, N=21.

Table 2

The slope and Pearson correlation coefficient for all panels for Fig. 9.

Parameter	Model	Temporal resolution	Slope (CI)	r_{32} vs. T.R.
R_{Ktrans}	LRRM	64	1.02 (1.00,1.04)	0.94
		96	1.03 (1.00,1.05)	0.84
		128	1.17 (1.13,1.21)	0.80
	NRRM	64	0.84 (0.80,0.90)	0.27
		96	0.58 (0.50,0.64)	0.24
		128	0.41 (0.35,0.46)	0.29
$k_{ep,TOI}$	LRRM	64	0.86 (0.84,0.874)	0.92
		96	0.74 (0.73,0.77)	0.83
		128	0.68 (0.65,0.70)	0.76
	NRRM	64	0.62 (0.60,0.64)	0.70
		96	0.12 (0.11,0.13)	0.34
		128	0.40 (0.38,0.43)	0.55
$k_{ep,RR}$	LRRM	64	0.58 (0.56,0.61)	0.71
		96	0.36 (0.34,0.39)	0.55
		128	0.29 (0.25,0.32)	0.42
	NRRM	64	0.72 (0.70,0.75)	0.77
		96	0.47 (0.43,0.51)	0.43
		128	0.51 (0.49,0.54)	0.55
$rmse$	LRRM	64	0.86 (0.85,0.88)	0.92
		96	0.77 (0.76,0.80)	0.83
		128	0.73 (0.71,0.76)	0.81
	LRRM	64	0.89 (0.88,0.91)	0.91
		96	0.75 (0.72,0.78)	0.73
		128	0.88 (0.86,0.90)	0.85