Published in final edited form as:

NMR Biomed. 2017 September ; 30(9): . doi:10.1002/nbm.3737.

Simultaneous measurement of T_1/B_1 and pharmacokinetic model parameters using Active Contrast Encoding (ACE) MRI

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Abstract

Purpose—To assess the feasibility to combine dynamic contrast enhanced (DCE) MRI with measurement of RF transmit field B_1 and pre-contrast longitudinal relaxation time T_{10} .

Methods—A novel approach has been proposed to simultaneously estimate B_1 and T_{10} from a modified DCE-MRI scan that actively encodes the wash-out phase of the curve with different amount of T_1 and B_1 weighting using multiple flip angles and repetition times, hence referred to as active contrast encoding (ACE) MRI. ACE-MRI aims to simultaneously measure B_1 and T_{10} together with contrast kinetic parameters, such as transfer constant K^{trans} , interstitial space volume fraction v_e , and vascular space volume fraction v_p . The proposed method was tested using numerical simulations and in vivo studies with mouse models of breast cancer implanted in the flank and mammary fat pad, and glioma in the brain.

Results—In the numerical simulation study with signal-to-noise ratio of 10, both B_1 and T_{10} were estimated accurately with error of $5.1 \pm 3.5\%$ and $12.3 \pm 8.8\%$, and coefficient-of-variance (CV) of $14.9 \pm 8.6\%$ and $15.0 \pm 5.0\%$, respectively. Using the same ACE-MRI data, the kinetic parameters, K^{trans} , v_e , and v_p , were also estimated with error of $14.2\% \pm 8.3\%$ ($\text{CV} = 13.5 \pm 4.6\%$), $14.7 \pm 9.9\%$ ($13.3 \pm 4.5\%$), and $14.0 \pm 9.3\%$ ($14.0 \pm 4.5\%$), respectively. For the in vivo tumor data from eleven mice, voxel-wise comparisons between ACE-MRI and DCE-MRI methods showed that the mean differences for the five parameters are: $K^{\text{trans}} = 0.006$ (/min), $v_e = 0.016$, $v_p = 0.000$, $B_1 = -0.014$ and $T_1 = -0.085$ (s), which suggests a good agreement of the two methods. When compared to separately measured B_1 and T_{10} , and DCE-MRI estimated kinetic parameters as reference, the mean relative errors of ACE-MRI estimation are $B_1 = -0.3\%$, $T_{10} = -8.5\%$, $K^{\text{trans}} = 11.4\%$, $v_e = 14.5\%$ and $v_p = 4.5\%$ respectively.

Conclusion—This proof-of-concept study demonstrates that the proposed ACE-MRI method can be used to estimate B_1 and T_{10} along with contrast kinetic model parameters.

Graphical Abstract

Pre-contrast T_1 and flip angle correction factor B_1 were estimated using the post-contrast dynamic measurement in order to save the extra scan time required to measure B_1 and T_1 for quantitative DCE-MRI data analysis. The proposed method actively encodes the wash-out phase of DCE-MRI curve with different amount of T_1 and B_1 weighting using multiple flip angles and repetition times. The results demonstrate the feasibility of measuring T_{10} , B_1 , and contrast kinetic parameters simultaneously from the actively-encoded dynamic enhancement data.

Keywords

Dynamic contrast enhanced MRI; T_1 mapping; B_1 mapping; active contrast encoding; contrast kinetic model

INTRODUCTION

T_1 -weighted dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is a powerful tool for diagnosis and assessing treatment response of cancer (1–4) as well as various inflammatory diseases, such as multiple sclerosis (5), rheumatoid arthritis (6), and inflammatory bowel diseases (7,8). Time-intensity curves of DCE-MRI contain rich information about the tissue microcirculation environment and can be analyzed using contrast kinetic models to estimate physiologically relevant parameters, such as transfer constant (K^{trans}), plasma volume fraction (v_p), and extravascular extracellular space volume fraction (v_e) (9,10). However, accurate estimation of contrast kinetic model parameters remains challenging, particularly due to the need to separately measure the pre-contrast longitudinal relaxation time constant (T_{10}) of the tissue (9) and actual flip-angles (FA) used for T_1 measurement and the dynamic scan (11–13).

The degree of contrast enhancement in a tissue varies with the tissue relaxation time T_{10} , such that analyses of DCE-MRI data based on time-intensity curves without taking into account of potential T_{10} variability in lesions could result in a limited diagnostic accuracy (14). For contrast kinetic model analysis, DCE-MRI time-intensity curves are converted to contrast agent concentration curves. Such signal-to-concentration conversion process requires T_{10} values which can be measured using various methods, such as inversion recovery (15,16) and variable flip angle methods (17), at a cost of extra scan time. In addition, accurate T_1 mapping typically requires correction for the inhomogeneous radiofrequency (RF) transmit field (B_1) which determines the actual FA (11,18–20). The

acquisition of a separate B_1 field map can also be used to correct for the B_1 inhomogeneity effect in the T_1 -weighted DCE-MRI data itself. Various B_1 mapping methods have been developed based on either magnitude (18,21,22) or phase (23–25) images made sensitive to the B_1 field. Most of these B_1 mapping methods require either a long repetition time (TR) to minimize the influence of T_1 or an extra measurement of the B_0 field to minimize the off-resonance effect, leading to further increase of scan time. Furthermore, other factors also affect the actual FA, such as slice profile (26,27) and RF amplifier nonlinearity (28). Hence, the scan time required for these additional measurements of T_{10} and B_1 can often be similar to or longer than the actual DCE-MRI scan itself (11,29), particularly when the target imaging volume is large as in body imaging and breast imaging. Given a limited scan time in most clinical scans, it is not trivial to conduct a quantitative DCE-MRI experiment with appropriate B_1 and T_{10} measurements.

In this study, we introduce a novel approach to simultaneously measure both B_1 and T_{10} values along with kinetic model parameters from dynamic scan data without having to run additional sequences for separate measurement of B_1 and T_{10} . While conventional DCE-MRI scans use one FA and one TR during the whole time course of the dynamic scan for about 5–10 min (2,3,9), our proposed method use multiple sets of FA and TR parameters to encode the washout part of DCE-MRI time-intensity curves with different T_1 - and B_1 -weighted contrasts. The basic idea of this method, namely Active Contrast Encoding (ACE) MRI, is that both B_1 and T_{10} can be treated as additional parameters to determine the MRI time-intensity curves, and can be estimated together with tissue contrast kinetic model parameters, using the constraint that the contrast agent concentration curve is continuous. A proof-of-concept study was conducted to demonstrate and evaluate the proposed method using numerical simulations as well as in vivo studies with mouse models of breast cancer in flank and mammary fat pad, and glioma in the brain.

THEORY - Active Contrast Encoding (ACE)-MRI

The main concept of ACE-MRI is illustrated in Figure 1. Conventional DCE-MRI studies for quantitative contrast kinetic analyses require extra scan time for B_1 and T_{10} measurements in addition to the actual dynamic scan. In ACE-MRI, the B_1 and T_{10} mapping procedures are embedded within the dynamic scan such that there is no extra scan time dedicated to the measurement of B_1 and T_{10} maps. The actual FA achieved in a DCE-MRI scan can be affected by various factors, such as B_1 field inhomogeneity (18), RF pulse profile (26), nonlinearity of RF amplifier (28), tissue properties (19), and imperfect spoiling in steady-state imaging (13). In this study, we assume that the actual FA is scaled by B_1 for simplicity, although this scaling factor could be a combination of multiple factors mentioned above.

When a spoiled gradient echo sequence is used for ACE-MRI, the signal intensity $S(t)$ is expressed as the following:

$$S(t) = S_0 \frac{(1 - e^{-R_1(t)TR(t)}) \sin(B_1 \alpha(t))}{(1 - \cos(B_1 \alpha(t))) e^{-R_1(t)TR(t)}} e^{-TE/T_2^*} \quad [1]$$

where S_0 represents the fully relaxed signal for a 90° pulse when $TR \gg 1/R_1(t)$. When $TE \ll T_2^*$, the exponential term for T_2^* decay can be approximated as 1. $R_1(t) = 1/T_{10} + r_1 C(t)$ where r_1 is contrast agent longitudinal relaxivity and $C(t)$ is tissue concentration. $\alpha(t)$ is flip angle. In this study, B_1 is defined as the ratio of actual flip angle to the nominal flip angle which could be affected by the RF transmit field strength as well as other factors including slice profile. It may not be adequate to simplify these effects into one parameter since they can produce non-linear errors in signal. Modeling them using more than one parameter should be more accurate. In this study, a linear model using one parameter B_1 was used for simplicity.

In ACE-MRI, both FA (α) and TR are not fixed constants, but functions of time for active contrast encoding;

$$\alpha(t) = \begin{cases} \alpha_1, & 0 \leq t < t_1 \\ \alpha_2, & t_1 \leq t < t_2 \\ \vdots \\ \alpha_i, & t_{i-1} \leq t < t_i \\ \vdots \\ \alpha_N, & t_{N-1} \leq t \leq t_N \end{cases} \quad \left(i=1, \dots, N \right), \text{ and} \quad [2]$$

$$TR(t) = \begin{cases} TR_1, & 0 \leq t < t_1 \\ TR_2, & t_1 \leq t < t_2 \\ \vdots \\ TR_i, & t_{i-1} \leq t < t_i \\ \vdots \\ TR_N, & t_{N-1} \leq t \leq t_N \end{cases} \quad \left(i=1, \dots, N \right), \quad [3]$$

where N is the number of segments with different T_1/B_1 -weighted contrasts. Simulated ACE-MRI curves in Figure 2a show examples with $N=7$, $t_f = \{267, 294, 321, 348, 383, 496, 529\}$ s, $\alpha_f = \{10^\circ, 12^\circ, 8^\circ, 5^\circ, 2^\circ, 90^\circ, 10^\circ\}$, and $TR_f = \{12, 12, 12, 12, 12, 100, 12\}$ ms. The baseline protocol (FA= 10° and TR=12 ms) is repeated at the end of the encoding to allow interpolation of the time intensity curve between the data with the baseline protocol. This encoding scheme was arbitrary selected to have multiple small flip angles around the Ernst angle with the TR of the baseline protocol and an approximate range of T_1 values (1.5–2.5s) expected in this proof of concept study at 7T.

The concept of ACE-MRI experiment is further illustrated in Figure 2a which shows ACE-MRI time-intensity curves with different B_1 and T_{10} values as well as different kinetic model parameter values shown in Table 1. Each plot in Figure 2a shows the effect of one parameter change in the time-intensity curve pattern. Variation in B_1 or T_{10} induces a shift of time-intensity curve in a way which is not seen in the changes induced by one of the contrast kinetic model parameters. However, it could be difficult to differentiate the effect of

B_1 or T_{10} if only one scan protocol, such as in the baseline, is used. ACE-MRI provides an opportunity to measure the effect of B_1 and/or T_{10} or the actual value themselves from a time-intensity curve.

Each combination of FA and TR is played out for a short period of time to achieve the steady state for a given condition, as opposed to continuous changing these sequence parameters in Magnetic Resonance Fingerprinting (MRF) (30). This scheme allows us to use the steady state portion of each combination without the need to consider the transient state influenced by both spin dynamics and contrast agent concentration change. With the data acquisition method in this study, each frame has 450 excitations. When TR=12ms with the Ernst angle for FA, it takes about 384 excitations until the relative error between the measured and steady state becomes less than 1%. For TR=100ms, it takes 46 excitations. Hence, for simplicity, we used only the steady state portion of data (typically without the first measurement in each combination of FA and TR) in this study. This approach can be generalized to use the entire time course by modeling the transient response.

The time intensity curve with multiple jump discontinuities can be predicted by using a contrast kinetic model if B_1 and T_{10} are known. For instance, tissue contrast concentration, $C(t)$, can be modeled using the extended generalized kinetic model (GKM) with a vascular compartment (9,31),

$$C(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(u) \exp\left(-\frac{K^{trans}}{v_e}(t-u)\right) du \quad [4]$$

where $C_p(t)$ is the contrast concentration in the plasma and $C(t)$ is tissue contrast concentration. K^{trans} , v_e and v_p are transfer constant, interstitial space volume fraction, and vascular space volume fraction respectively. In fast exchange limit, $R_1(t) = 1/T_{10} + r_1 C(t)$. When the water exchange is not in fast exchange limit, $R_1(t)$ is not linearly proportional to $C(t)$, but still remains as a piecewise continuous function naturally and can be related to $C(t)$ using additional parameters for water exchange. Hence, regardless of the water exchange regime, the $R_1(t)$ can be used to predict time-intensity curve, $S_p(t)$, with multiple jump discontinuities using Equations [1–4]. In this study, fast exchange limit is assumed for simplicity.

Estimation of the contrast kinetic parameters as well as B_1 and T_{10} can be conducted in two ways; (i) model-based approach and (ii) model-free approach. The model-based approach can be applied when the AIF is known and the contrast kinetic model is adequate for all the voxels. This approach is to estimate all parameters including T_{10} and B_1 together during the model fit process. Alternatively, in the model-free approach, estimation of T_{10} and B_1 maps from ACE-MRI data can be performed first without using AIF, followed by contrast kinetic model analysis including estimation of AIF using the estimated T_{10} and B_1 maps. These two approaches are described further in the following.

ACE-MRI: Model-Based Approach

In case the AIF function is known or a population based AIF function is used, the model-based approach can be used. The contrast kinetic model parameters can be estimated together with B_1 and T_{10} by minimizing the difference between the measurement and predicted data from the model parameters, B_1 and T_{10} :

$$\{\hat{B}_1, \hat{T}_{10}, \hat{K}^{trans}, \hat{v}_e, \hat{v}_p\} = \arg \min \sum_t \left(\frac{S_m(t)}{S_m(0)} - \frac{S_p(t)}{S_p(0)} \right)_{B_1, T_{10}}^2 \quad [5]$$

where $S_m(t)$ is the measured time-intensity curve and $S_p(t)$ is the predicted time-intensity curve, $S_m(0)$ and $S_p(0)$ are their baseline signal intensity respectively. In this study, we assessed whether the estimated parameters, $\{\hat{B}_1, \hat{T}_{10}, \hat{K}^{trans}, \hat{v}_e, \hat{v}_p\}$, approach the true values and quantified the uncertainties of the estimated parameters in comparison with a conventional DCE-MRI approach assuming B_1 and T_{10} values were known.

Figure 2b shows the DCE-MRI curve and ACE-MRI curve simulated with the nominal values shown in Table 1 and the AIF shown in Figure 2a. Rician noise with signal to noise ratio (SNR) of 10 was added to the curves. SNR was defined as the ratio of the baseline signal to the standard deviation of the Gaussian noise added to the imaginary and real parts of the complex data while assuming the simulated MRI signal was only in the real part of complex MRI data. In both cases, it was attempted to estimate all 5 parameters using Eq.[5]. The results in the third plot show that the conventional DCE-MRI data cannot be used to estimate all five parameters reliably as the relative errors are close to 100%. In contrast, the variability of estimated parameters is substantially smaller with the ACE-MRI (relative errors < 10%), suggesting that ACE-MRI data have enough information to support estimation of all 5 parameters.

ACE-MRI: Model-Free Approach

In case the AIF function is to be measured from the data, the model-free approach can be used. The model-free approach is used to separate the parameter estimation process into two steps; estimation of B_1 and T_{10} first using only the slow washout portion of an ACE-MRI curve, followed by a conventional contrast kinetic model analysis with the estimated B_1 and T_{10} . For the slow wash-out portion of an ACE-MRI curve, even though the signal intensity is discontinuous due to the encoding, the contrast concentration curve remains continuous and can be approximated by a line between data points acquired using the base line protocol (FA=10° in this study). The interpolated tissue concentration curve can be converted to signal intensity curve using given B_1 and T_{10} values and compare with the measured signal intensity curve to see if the active contrast encoding patterns match with each other. In this way, pre-contrast B_1 and T_{10} can be estimated without using a pharmacokinetic model. Another advantage of model-free approach is that it divides the estimation of five parameters into two steps; estimation of two parameters (B_1/T_{10}) and estimation of contrast kinetic parameters ($K^{trans}/v_e/v_p$) using the estimated B_1/T_{10} . For the model-free approach, only the washout portion of ACE-MRI curve is used in the estimation of B_1 and T_{10} :

$$\{\hat{B}_1, \hat{T}_{10}\} = \arg \min \sum_t \left(\frac{S_{m_washout}(t)}{S_m(0)} - \frac{S_{p_washout}(t)}{S_p(0)} \right)_{B_1, T_{10}}^2 \quad [6]$$

where $S_{m_washout}(t)$ and $S_{p_washout}(t)$ are the corresponding washout portion of $S_m(t)$ and $S_p(t)$. Once $\hat{B}_1$ and $\hat{T}_{10}$ are obtained, $\hat{K}^{trans}$, $\hat{v}_e$, $\hat{v}_p$ can be estimated using the whole ACE-MRI curve for the fit as in conventional contrast kinetic model analysis.

In both model-based and model-free approaches, the reason that T_{10} can be estimated from the ACE encoding of the washout period is that T_{10} is used in the conversion of concentration-to-signal in the washout period. If only one combination of TR and FA is used for the washout period (i.e. ACE is not used), there is a large uncertainty in T_{10} estimation as demonstrated in Fig. 2b. However, when multiple combinations of TR and FA are used for the washout period (i.e. ACE is used), T_{10} and B_1 are critical factors to determine the conversion of a “continuous” concentration curve to a “step-like” signal curve. It is because the step-jumps in the signal between different combinations of TR and FA depend on T_{10} and B_1 which are two important parameters in the signal equation (Eq.[1]). The model-free approach is only different from the model-based approach in terms of how the continuity of the concentration curve is modeled; a linear interpolation between two measurements for the model-free approach vs. a pharmacokinetic model for the model-based approach.

Estimation of B_1 Field Map in Model-Free Method

One of the advantages of using the model-free ACE-MRI method is that it is flexible to include a regularization procedure for B_1 map. For instance, this can be achieved by using a simulated annealing method to enforce smoothness in B_1 map iteratively. The procedure of the simulated annealing method used in this study is as follows:

- let temperature $T=0.2$ and cooling factor $c=0.7$
- *estimate B_1 and T_{10} using equation [6] for all voxels*
- smooth B_1 field
- for $k=0$ through $k_{\max}$
 - *add thermal random noise to the smoothed B_1 field, $B_1=B_1(1+T \times \text{random noise})$*
 - *estimate T_{10} of all voxels with B_1 from last step using equation [6]*
 - *estimate B_1 of all voxels with T_{10} from last step using equation [6]*
 - *reduce the noise temperature ($T=T \times c$)*
 - smooth B_1 field
- Output: the final B_1 field

One way to smooth the B_1 field is to use a locally weighted linear regression as demonstrated in this study using *lowess* filter in Matlab (MathWorks, Natick, MA, USA) with maximum iteration of 6 that resulted in about 3% of final noise level for B_1 .

METHODS

In this study, the model-based approach was used to assess the parameter estimation uncertainty in ACE-MRI using numerical simulation. Then, for numerical phantom images and in vivo studies, the model-free approach was used to incorporate regularization of B_1 field.

Uncertainty in Parameter Estimation (Model-Based Method)

A numerical simulation study was conducted to assess the feasibility of using ACE-MRI to estimate B_1 and T_{10} along with contrast kinetic parameters and to measure the uncertainty in the estimated parameters. The model-based approach (Eq.[5]) was used for this simulation study to assess the uncertainty in parameter estimation since it is more challenging to estimate all parameters at once than the model-free approach (Eq.[6]) that estimates parameters in two groups; first round for B_1 and T_{10} and second round for the kinetic parameters. Both DCE-MRI and ACE-MRI data were generated using the extended generalized kinetic model (Eq.[4]) with an AIF, $C_p(t)$, obtained from a previous 7T mouse study (32). It was assumed that the actual FA was affected by a scaling factor B_1 for all flip angles. For the conventional DCE-MRI data, fixed TR (12 ms) and FA (10°) were used to generate the data. For the ACE-MRI data generation, both FA and TR were varied to encode various T_1 weighting contrasts as defined in the previous section for Figure 2. Rician noise SNR=20 or 10 was added to $S(t)$. Temporal resolution was 5.4 s/frame for small flip angles and 45 s/frame when FA = 90° .

The baseline contrast kinetic parameters for simulation were $K^{\text{trans}}=0.2505/(\text{min})$, $v_e=0.45$, and $v_p=0.06$ (33). The baseline B_1 and T_{10} were 1 and 2.3 s, respectively. To evaluate the performance of the proposed ACE-MRI method in a wide range of conditions, the simulation study was repeated by changing one parameter at a time as shown in Table 1. Simulation was also conducted to assess the influence of different FA and TR on the estimation result, in order to determine the range of FA and TR values to be used for ACE-MRI experiments. Parameter estimation with noisy data can be sensitive to initial values. For that reason, approaches using multiple initial guesses have been used in previous studies (34–36). In this study, fifty randomly selected initial guesses were used for each noisy time-intensity curve in model-based method. The result with the minimum sum of squares of the differences was selected as the final result. Accuracy of the estimated parameters was measured by the difference between the mean estimated value and the true value used for data simulation. Precision was assessed in terms of coefficient of variation (CV = standard deviation/mean). The average of accuracy and precision measures was used as measure of uncertainty.

The simulation data was also used to assess the effect of the large flip angle used for the active contrast encoding on the uncertainty in estimation of B_1 . The largest flip angle α_6 was varied from 30° to 90° while all the other scan parameters were kept same and the baseline

kinetic parameters were used. Contrast encoding with a large flip angle for B_1 estimation would require a longer TR, not to exceed the specific absorption rate (SAR) and/or RF amplifier duty cycle limit. The effect of TR on the parameter uncertainty was evaluated by changing TR from 33 ms to 100 ms for $\alpha_6 = 90^\circ$. All parameter estimations were conducted using the Simplex (37) method provided in Matlab (MathWorks, Natick, MA).

Numerical Phantom Simulation using the model-free method

In order to demonstrate the proposed simulated annealing approach to estimate the ACE-MRI parameters, we generated a numerical phantom with different tissue properties (five different areas for tumors embedded in a larger area for the muscle tissue) and T_{10} values as shown in Table 2. The B_1 field was assumed as a spherical cap with its minimum (0.9) at the center and the maximum (1.1) at the lateral sides of the phantom as shown in Figure 3d. The extended GKM equation (Eq.[4]) with an AIF same as in Figure 2a was used with the ACE-MRI protocol described above in order to generate ACE-MRI data with noise at SNR of 10. The proposed ACE-MRI method with the simulated annealing approach was implemented to estimate B_1/T_{10} and compared with the true B_1/T_{10} .

In Vivo ACE-MRI Experiment using the model-free method

The ACE-MRI technique was tested using in vivo mouse experiments. Six eight-week-old BALB/c mice were given 1×10^5 4T1 murine breast cancer cells suspended in 0.1mL of PBS in the flank (n=2) and mammary fat pad (n=4) regions. Five eight-week-old C57BL6 mice were given 1×10^5 GL261 mouse glioma cells suspended in 4 μ L of PBS using a Hamilton syringe for stereotatic intracranial injection. Those mice were scanned between post-injection day 8 and day 28 when tumors were observed. The mice were treated in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and this study was approved by the Institutional Animal Care and Use Committee.

MRI experiments were performed on a 7T micro-MRI system, consisting of a Biospec Avance II console (Bruker Biospin MRI, Ettlingen, Germany) interfaced to a 200-mm horizontal bore magnet (MagneX Scientific, Yarnton, Kidlington, Oxfordshire, UK) with an actively shielded gradient coil (Bruker, BGA-95; gradient strength, 750 mT/m). A quadrature Litz body coil (inner diameter 32mm) (Doty Scientific, Columbia, SC, USA) was used to image the animals with 4T1 tumors either on the flank or the mammary fat pad. An in-house built quadrature Litz brain coil (inner diameter 21mm) was used for brain imaging of the animals with GL261 tumors. For MRI scans, general anesthesia was induced by 1.5% isoflurane in air. The animal body temperature was maintained at $34 \pm 2^\circ\text{C}$ during the scan.

Prior to the dynamic study, T_1 measurement was performed using a RARE-VTR (Rapid Acquisition with Relaxation Enhancement - Variable TR) pulse sequence available in Bruker systems to compare with T_{10} measured from ACE-MRI. B_1 field was measured using the signal null method (18) with three large flip angles of 140° , 150° and 160° ($TR=1s$). A 3D FLASH sequence was used for dynamic scans using the ACE-MRI method. Scan parameters were $TR/TE=12/2.6$ ms ($TR=100$ ms when $FA=90^\circ$), image matrix = $50 \times 80 \times 9$ for 4T1 tumor ($100 \times 100 \times 9$ for GL261 tumor), and resolution = $0.4 \times 0.4 \times 2$ mm for 4T1 tumor ($0.15 \times 0.15 \times 1$ mm for GL261 tumor). This sequence was run to acquire 78 frames for

about 9 min with multiple flip angles (10°, 12°, 8°, 5°, 2°, 90° and 10°) and different number of frames (50, 5, 5, 5, 5, 3, and 5, respectively). Temporal resolution was 5.4 s/frame for small FAs and 45 s/frame when FA=90°. A bolus of Gd-DTPA in saline at the standard dose of 0.1 mmol/kg was injected through a tail vein catheter, starting 1 min after the acquisition of pre-contrast images.

Reference Tissue AIF

AIF was obtained from a reference region in the muscle (38) using only parts of the data with the baseline scan protocol (i.e., FA=10° and TR=12ms). B_1 and T_{10} values of the reference tissue, which are used for AIF generation, were obtained from ACE measurement for ACE-MRI. The Gd concentration in the plasma, $C_p(t)$, was estimated from that of a reference tissue, $C_{tis}(t)$, using the following equation: $C_p(t) = C_{tis}(t)/V_e + (1/K^{trans})dC_{tis}(t)/dt$. K^{trans} and v_e of the muscle were assumed to be 0.11 min⁻¹ and 0.15, respectively (38). In order to minimize the effect of noise, a multiple layer neural network with 3 by 2 neurons in each hidden layer was used to fit the tissue concentration curve (39) owing to the good curve approximation ability of neural networks (40). The obtained AIF was used to estimate 3 free parameters (K^{trans} , v_e , v_p) per each voxel using the B_1 and T_{10} obtained from the first step of the model-free approach of ACE-MRI. Conventional DCE-MRI data analysis was conducted using separately measured B_1 and T_{10} . Voxel wise comparison of the five parameters was carried out for the contrast enhancing regions of the tumors. It should be noted that for model-free ACE-MRI, T_{10}/B_1 used for reference tissue AIF were obtained from the method itself; however, for model-based ACE-MRI, T_{10}/B_1 used for reference tissue should be known in advance if a reference tissue AIF is to be used. For DCE-MRI, T_{10} and B_1 for a reference tissue AIF were obtained from separate RARE-VTR measurement and signal null method measurement.

RESULTS

Evaluation uncertainty in parameter estimation using model-based method

A series of numerical simulation studies with SNR = 10 were conducted to assess the uncertainty in estimated ACE-MRI parameters by changing one parameter at a time in the range shown in Table 1. It was found that the variation in the contrast kinetic parameters does not have any noticeable effect on the measurement of B_1 (median: 1.00, IQR: 0.95–1.03) and T_{10} (median: 2.31, IQR: 2.14–2.54). The worst case to estimate B_1 and T_{10} in terms of the uncertainty was when B_1 was 0.8, the lowest value in this study, as the median B_1 = 0.80 (IQR: 0.67–0.88) and median T_{10} = 2.30 (IQR: 1.79–3.48) (Supplemental Figure 1).

The influence of FA on B_1 estimation from the ACE-MRI data was also investigated using a range of FA values for α_6 (Eq.[2]). When α_6 = 30°, the inter-quartile range (IRQ) of B_1 was 0.52 (0.72 – 1.24). The IRQ of B_1 decreased substantially to 0.04 (0.98 – 1.02) as α_6 increased to 90°. Similar patterns were observed with other parameters, suggesting that accurate estimation of B_1 is crucial as it affects the estimation of all the other parameters (Supplemental Figure 2). The IRQ of B_1 remains within 0.085 over the range of TR values investigated, suggesting that the selection of TR does not noticeably change the uncertainty

of the parameter estimation (Supplemental Figure 3). Based on these data, $\alpha_6 = 90^\circ$ and $TR = 100$ ms were used for the rest of study including both numerical simulation studies and in vivo experiments.

The coefficient of variation estimated with the quartiles of parameters ($CV_q = IQR/median$) increased up to 46% when B_1 decreased from 1.2 to 0.8. In terms of CV_q , the variation of the true K^{trans} , v_e , v_p , and T_{10} also did not have any noticeable effect on the estimation accuracy of other parameters (Supplemental Figure 4).

The uncertainties of ACE-MRI parameters measured with the simulated data were compared with those of DCE-MRI data using B_1 and T_{10} containing no error or 10% error. The range of parameters shown in Table 1 was used to generate data for this simulation study. Table 3 summarizes the accuracy and precision of parameters estimated using ACE-MRI (when $SNR = 10$) in comparison with those from DCE-MRI. The errors of ACE-MRI kinetic parameters were bigger than the errors of DCE-MRI kinetic parameters using accurate B_1 and T_{10} with no error, but smaller than the errors of DCE-MRI kinetic parameters with 10% error in either B_1 or T_{10} .

Estimation of B_1 field map and numerical phantom study in model-free method

Figure 3 shows the model-free ACE-MRI procedure with the simulated annealing method described above. The numerical phantom had five different tumors in a muscle tissue as described in Table 2. Figure 3b shows an example tumor signal enhancement curve with a model fit to the washout portion. Figure 3c demonstrates the tissue concentration data converted from the data in Figure 3b with the baseline protocol and a linear approximation of tissue concentration for the ACE part. Figure 3d and 3e shows comparison of parameter color maps between DCE-MRI and ACE-MRI methods. The mean and standard deviation of the parameters estimated using the model-free ACE-MRI and DCE-MRI are summarized in Table 2 for the five tumors and muscle region.

In Vivo Mouse Imaging

The proposed model-free ACE-MRI method was tested for in vivo mouse imaging and compared with a conventional DCE-MRI approach with separate T_1 and B_1 mappings. Figure 4a shows representative images of a mouse with 4T1 flank tumor scanned with the ACE-MRI method. Figure 4b shows the reference tissue AIFs obtained from ACE-MRI and DCE-MRI methods are close to each other as they overlap almost perfectly. The ACE-MRI model fits well to the measured signal enhancement ratio curves as demonstrated in Figure 4c. Figure 4d and 4e showed DCE-MRI and ACE-MRI parameter color maps. The pixel maps of the kinetic model parameters based on the ACE-MRI data appear to be well regularized despite additional free parameters, which suggests that the parameter estimation was robust. The estimated B_1 map was in good agreement with the B_1 map measured with the signal null method. The estimated T_{10} map matches well with the T_1 map obtained from the RARE-VTR method. The v_p estimates from both DCE-MRI and ACE-MRI are smaller than the vascular volume fraction usually expected for tumors. This may be related to the AIF and the relatively simple contrast kinetic model used in this study, which appears to be affecting both DCE-MRI and ACE-MRI results. The Bland-Altman plots of the estimated

five parameters (Figure 4f) show good agreement between the two methods: DCE-MRI with T_1/B_1 mapping and ACE-MRI. Similar results are also shown for representative examples of 4T1 in mammary fat pad (Figure 5a) and GL261 in the brain (Figure 5b). In theory, we expected that the proposed method would work regardless of the contrast agent extravasation. However, in practice, the areas without extravasation, such as brain regions with intact blood-brain barrier (Figure 5b), had low SNR and remained challenging to estimate B_1 and T_1 . Hence, we excluded those areas without contrast agent extravasation.

Figure 6 shows Bland-Altman plots of five parameters estimated by DCE-MRI and ACE-MRI methods for all tumor voxels pooled from the eleven animals. The mean differences are close to zero and there is no noticeable trend, indicating a good agreement between the two methods. Using DCE-MRI estimated parameters as reference, the mean relative errors of ACE-MRI estimation are $B_1 = -0.3\%$, $T_{10} = -8.5\%$, $K^{\text{trans}} = 11.4\%$, $v_e = 14.5\%$ and $v_p = 4.5\%$ respectively. The noticeable patterns in B_1 and T_{10} plots in Figure 6 are due to the libraries with discrete step sizes used for B_1 and T_{10} estimation in the model-free method. T_{10} and B_1 have similar effects on DCE curves, but still different depending on flip angles and TR as shown in Figure 2a. The correlation between B_1 and T_{10} is -0.32 for ACE and -0.55 for DCE, which are in line with the effect of T_{10} and B_1 shown in Figure 2a.

Figure 7 shows comparisons of estimated five parameters between ACE-MRI and DCE-MRI in terms of the median values of individual tumors. The Pearson correlation coefficients of K^{trans} , v_e , v_p , B_1 , and T_{10} were 0.95, 0.92, 0.89, 0.63, and 0.83 (with one outlier excluded), respectively.

DISCUSSION

In this proof-of-concept study, we demonstrated that the ACE-MRI method could be used to estimate the flip angle correction factor B_1 and T_{10} simultaneously along with the contrast kinetic model parameters, without using any additional scan dedicated to measure B_1 and T_{10} . Numerical simulation data were used to show that the proposed active contrast encoding during the wash-out phase of a dynamic scan enables estimation of B_1 and T_{10} . The proposed ACE-MRI method was also demonstrated for imaging mouse models of breast cancer and brain tumor at 7T. The estimated contrast kinetic parameters are in line with literature (41–43) and their parameter maps appear well regularized while clearly delineating the lesion, indicating that the contrast kinetic model fitting to the ACE-MRI data was robust. The B_1 and T_{10} estimated from the ACE-MRI data matched well with the B_1 and T_1 measured using the dedicated pulse sequences. Data presented in this work attest that the proposed ACE-MRI is a plausible alternative way to a conventional combination approach of DCE-MRI and separate B_1/T_1 measurement for quantitative assessment of tissue microcirculation environmental parameters.

The idea of combining multiple flip angles with DCE-MRI has been used in previous studies to assess the effect of water exchange using multiple flip angles in the washout phase (44) and to improve the accuracy and precision in estimation of T_1 and pharmacokinetic model analysis using multiple flip angles in the baseline acquisition (45). However, to our knowledge, it has not been reported that multiple flip angles after the contrast injection can

be used to measure B_1 and T_{10} simultaneously along with the contrast kinetic model parameters. The results in this study substantiate this somewhat counter-intuitive concept that the post-contrast data can be used to estimate some pre-contrast tissue properties. The present study demonstrates that the step-like signal curve generated using multiple flip angles and TRs can provide a unique opportunity to estimate the T_1 of tissue before the contrast injection along with B_1 and also suggests a feasibility of extending the utility of the contrast enhanced dynamic data to assessment of the tissue properties that have not been measured by conventional DCE-MRI experiments.

Measurement of B_1 map

Fast B_1 mapping has been a subject of interest for many quantitative MRI measurements, including DCE-MRI, as B_1 non-uniformity is one of the main causes of difference between the nominal flip angle and actual flip angle. In order to reduce the scan time, fast imaging methods with extended echo-train-length (46,47) or echo-planar imaging (48,49) have been used, in addition to employing a means to minimize the effect of not-fully recovered longitudinal magnetization by playing out special radiofrequency (RF) pulses at the end of the sequence (49,50). In case of phase-based methods, the influence from the B_0 inhomogeneity brings a need for additional B_0 field mapping at the cost of additional scan time or careful advanced design of RF pulse. For the Bloch-Siegert Shift method, RF power deposition in the tissue is another constraint as the measurement accuracy improves with the Bloch-Siegert Shift pulse power (24,25). While these recent developments in B_1 mapping offer a number of different ways to measure B_1 field map, acquiring B_1 map during clinical scans still remains technically challenging and an extra burden of scan time. In ACE-MRI, a large flip angle (90°) needs to be included to estimate B_1 more accurately which in turn helps to estimate T_1 and other contrast kinetic parameters accurately. Nevertheless, it was feasible to estimate the B_1 map from the dynamic data without using an additional B_1 mapping sequence. In this proof-of-concept study, we selected $TR=100ms$ for the limited scan time for the large flip angle. However, further study is warranted to investigate the optimal choices of flip angles and TR for a given scan time in different applications.

Simultaneous measurement of B_1 and T_1

While B_1 and T_1 can be measured separately, they are often measured simultaneously as measurement of one parameter is closely related with the other. Deoni (20) has shown that variable flip angle data and inversion recovery data can be used together to estimate B_1 and T_1 by fitting the signal models of two experiments that include the B_1 and T_1 parameters. This approach, known as DESPOT1-HIFI (Driven Equilibrium Single Pulse Observation of T_1 with High-speed Incorporation of RF field Inhomogeneities). The ACE-MRI method introduced in the current study are based on a similar idea; both T_1 and B_1 can be estimated when the data are sufficiently encoded with various T_1 and B_1 weighted contrasts. While DESPOT1-HIFI uses an inversion recovery pulse sequence as an additional one, the ACE-MRI protocol in this study uses the data with 90° flip angle and a longer TR. Deoni (51) also showed that this concept can be further extended to estimate multi-component T_1 and T_2 as well as B_0 and B_1 by using an array of different contrast images; gradient echo imaging data with 9 different flip angles, inversion recovery imaging data with one inversion time, and balanced steady-state imaging data with 9 flip angles which took about 16 min for the whole

brain. In a similar way, the proposed ACE-MRI method can also be extended to estimate other parameters simultaneously. Recently, Ma et al (30) introduced a new technique, namely MR fingerprinting (MRF), in which multiple MR properties of a tissue can be simultaneously measured by using a pseudo-randomized acquisition that measures data with unique signal evolutions of different tissues. For instance, it was demonstrated that an inversion-recovery balanced steady state free-precession sequence with randomized flip angles and TRs for readout could be used to simultaneously estimate T_1 , T_2 , proton density, and off-resonance frequency values. This idea of randomized “contrast encoding” used in MRF can also be applied to ACE-MRI for further optimization of the protocol to reduce uncertainty in parameter estimation. It may not be a trivial task though to incorporate such randomized encoding in a contrast enhanced MRI experiment since T_1 and T_2/T_2^* are time varying parameters depending on the contrast agent concentration. Optimization of the contrast encoding scheme for ACE-MRI is an important subject that needs to be investigated in future studies.

Potential clinical applications

ACE-MRI has a high potential to simplify and shorten MRI exam time as it can provide comprehensive information about tissue MR properties from a single scan. Breast cancer imaging can be one of the areas suitable to apply ACE-MRI. Previous studies have shown that MRI is the most accurate diagnostic imaging modality to date, particularly for mammographically occult malignancies in young women with high lifetime risk for breast cancer (52). However, current breast MRI protocols are time consuming and costly, such that screening MRI is not available to all women at high risk for breast cancer. It is therefore necessary to improve diagnostic accuracy while shortening exam time, in order to allow more women to benefit from breast MRI. ACE-MRI can be a good candidate for such an abbreviated exam of the breast since it can be used to extract multiple tissue properties simultaneously. The specific contrast to be encoded in the ACE-MRI protocol can be tailored to meet the need of a specific application. As described in the method section, the encoding scheme used in this study was arbitrary chosen to have small flip angles around the Ernst angle based on the selected TR and expected T_1 values at 7T. This encoding scheme can be further optimized in future studies and for specific applications depending on the availability of scan time and field strength. Future studies are warranted to optimize ACE-MRI protocol and to investigate the feasibility of using ACE-MRI for an accelerated exam of the breast and for other clinical applications.

Possible confounding effects

In this study, reference-tissue AIF was used for in vivo data analysis. For the reference region selected, our model-free ACE-MRI method estimated T_{10} and B_1 are quite close to separately measured reference region T_{10} and B_1 , which resulted in quite close AIFs for each animal. The estimated parameters using the ACE-MRI and DCE-MRI are in good agreement. Limited by the spatial resolution in this study, direct measurement of AIF from an artery was not feasible as the influence of inflow effect and partial volume effects also needs to be considered. Population based AIF might be an alternative AIF for the analysis.

T_2^* effect can play an important role in T_1 -weighted DCE-MRI studies, particularly at high magnetic field, such as 7T used in this study. It has been shown in previous study (53) that T_2^* is not constant across the duration of the DCE-MRI experiment such that it can have substantial influence on the contrast kinetic parameter estimation at 7T. In the present study, we compared the proposed ACE-MRI with conventional DCE-MRI without correction for the T_2^* effect in both methods. We expect that the agreement between the two methods would be improved by correcting for the T_2^* effect, which will be investigated in future studies using either a multiple gradient echo sequence or ultra-short echo time sequence.

Water exchange effects (2,54,55) is another factor that can influence parameter estimations. It has been known that different combinations of TR and flip angle have different strengths of the water exchange effect. In this study, we assumed that the water exchange effect is negligible for simplicity. However, this assumption needs to be assessed more carefully in future studies. A combination of different water exchange effects in the ACE-MRI protocol may provide a unique opportunity to estimate the transvascular or transcytolemmal water exchanges rates more accurately. Further study is warranted to assess this potential application of the ACE-MRI method.

Limitations

While ACE-MRI was successfully used for this study, there are several limitations of the method that need to be considered in future studies. First of all, the current study did not attempt to estimate all possible factors affecting the actual flip angle beyond a scaling factor noted as B_1 . A possible nonlinearity of RF power amplifier could be one of those factors and could be measured in advance for calibration. This RF calibration measurement may need to be done at each site before performing ACE-MRI. It is generally expected that clinical scanners have better performance than research scanners for small animals, but it could still be necessary to calibrate the power amplifier of a clinical scanner as shown by Balezeau et al (28). Further development is warranted to extend the ACE-MRI protocol to estimate this kind of additional hardware factors. Similar concept of calibration as well as extension of ACE-MRI methods can be considered for RF slice profile and imperfect spoilers.

Another limitation of this study was that the contrast kinetic model was fixed to the extended GKM model. We chose this model as it is most commonly used. ACE-MRI data can be analyzed with any contrast kinetic model, just like conventional DCE-MRI data. Estimation of two additional parameters of B_1 and T_{10} included in ACE-MRI can be an extra burden in parameter estimation. Nevertheless, the results in our simulation study suggested that the uncertainty of contrast kinetic model parameters did not increase substantially by having two additional parameters in ACE-MRI and the parameter maps of mouse ACE-MRI data showed well regularized patterns. These observations support the feasibility of using ACE-MRI with more complex contrast kinetic models, such as the adiabatic approximation of tissue homogeneity model or kinetic models with water exchange terms (56).

The proposed active contrast encoding method is supposed to be applied to the washout phase that is available in most DCE-MRI protocols. In this study, we focused on demonstrating the main idea of utilizing the washout phase for the ACE technique with a 9-min DCE-MRI protocol including the baseline acquisition for 1 min. Such a 9-min scan

length is not the shortest among DCE-MRI studies, but certainly well within the range of scan times used for published clinical DCE-MRI studies (33,44,57,58). The proposed ACE method can be further optimized for shorter scan times. In this study, we assumed a linear washout tissue concentration curve. With the actual data and numerical simulation, we found a linear approximation is as good as any other model for the concentration curve at a later washout phase. However, in theory, a log-linear is a better model than a linear model. Furthermore, a piece-wise linear approximation can also be used to apply the proposed method in the earlier washout part of the DCE curve in order to shorten the scan time if necessary.

Conclusions

Both simulation and in vivo results in this study suggest that the proposed ACE-MRI method can be used to estimate B_1 and T_{10} along with contrast kinetic model parameters. It was found that estimation of kinetic parameters was remarkably robust, which can be substantiated by the good quality parametric maps and data obtained from the in vivo ACE-MRI. Data presented in this proof-of-concept study suggest that ACE-MRI can be used to shorten the scan time by eliminating the need to have separate B_1 and T_{10} mapping procedures. Future study is warranted to further optimize the ACE-MRI protocol for specific clinical and research applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant sponsor: National Institutes of Health; Grant number: R01CA160620

Abbreviations

DCE-MRI	dynamic contrast enhanced MRI
ACE-MRI	Active Contrast Encoding MRI
CV	coefficient-of-variance (=standard deviation/mean)
FA	flip angle
TR	repetition time
MRF	Magnetic Resonance Fingerprinting
GKM	generalized kinetic model
AIF	arterial input function
SNR	signal to noise ratio
SAR	specific absorption rate
RARE-VTR	Rapid Acquisition with Relaxation Enhancement - Variable TR

IQR	inter-quartile range
CVq	coefficient-of-variance with quartiles (=IQR/median)
RF	radiofrequency

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Figure 1.

Block diagrams of conventional DCE-MRI and proposed ACE-MRI methods. In DCE-MRI, measurement of T_{10} and B_1 is performed prior to injection of contrast agent. In contrast, the proposed ACE-MRI can measure T_{10} and B_1 from the dynamic data encoded with multiple FA and TR values.

Figure 2.

Feasibility of measuring T_{10} and B_1 from ACE-MRI data. (a) ACE-MRI data were generated using the extended generalized kinetic model with the baseline parameters shown in Table 1. For each plot, one kinetic parameter was varied as shown in Table 1, while all the other parameters were kept constant. As described in the text, the baseline FA was 10° followed by active contrast encodings with 12° , 8° , 5° , 2° , 90° and 10° again. TR was 12 ms except when FA= 90° where TR=100ms. It is demonstrated that the changes induced by T_{10} or B_1 are different from those induced by contrast kinetic parameters, indicating the feasibility of estimating T_{10} and B_1 from the ACE-MRI data. (b) The feasibility of measuring B_1 and T_{10} from a contrast enhancement curve is demonstrated. Simulated DCE-MRI enhancement curve with Rician noise of SNR=10 (black crosses) and the GKM fit (blue solid line) and ACE-MRI enhancement curve with Rician noise of SNR=10 (black crosses) and the model fit (blue solid line). It is demonstrated that inclusion of B_1 and T_{10} in the kinetic parameter estimation with only one T_1/B_1 -weighting resulted in large relative errors around 100% in all estimated parameters (blue boxes). By using ACE-MRI protocol, T_1 and B_1 can be estimated together with pharmacokinetic parameters K^{trans} , v_e and v_p and with substantially smaller relative errors around 10% or less. Boxplots show relative errors in the estimated five parameters, estimated using 50 different Rician noises added to both DCE-MRI and ACE-MRI curves. (blue boxplot: DCE-MRI results with SNR=20; red box plot and green box plot: ACE-MRI results with SNR=20 and SNR=10 respectively).

Figure 3.

Demonstration of model-free ACE-MRI with a numerical phantom. (a) Simulated T₁ weighted image before the contrast injection. (b) Signal enhancement curve (black crosses, SNR=20) from lesion 1 in (a) and a fit to the washout part (red solid line). (c) Base line tissue concentration curve (blue crosses) converted from signal enhancement curve in (b) and a linear approximation of the washout part (red solid line). (d) & (e) Comparison of parameter color maps between ACE-MRI and DCE-MRI methods.

Figure 4.

A representative example of 4T1 tumor on the flank to demonstrate parameter estimation using ACE-MRI. (a) Axial slice with ROIs for reference muscle (blue) and enhancing lesion rim (red). (b) AIF functions generated from ACE-MRI (red solid line) and DCE-MRI using the measured T_1/B_1 for the reference muscle region. Please note that for the AIF generation, ACE-MRI measured reference tissue T_1/B_1 and separately measured T_1/B_1 (RARE-VTR method and Signal Null Method) are used for corresponding method. (c) Lesion (black crosses) and muscle (blue crosses) enhancement curves and the corresponding fits (green solid lines). (d) and (e) Comparison of parameter color maps between DCE-MRI and ACE-MRI methods. For DCE-MRI method, T_{10} and B_1 were measured separately from RARE-VTR sequence and signal null method. (f) Bland-Altman plots show comparison between the estimated parameters from DCE-MRI and ACE-MRI for the enhancing voxels in the tumor.

Figure 5. Representative examples of DCE-MRI and ACE-MRI results for mouse 4T1 tumor in the mammary fat pad (a) and mouse GL261 glioma in the brain (b). ROIs in red indicate tumor enhancing rim and ROIs in blue indicate reference muscle region for AIF generation. For DCE-MRI method, T_{10} and B_1 were measured separately from RARE-VTR sequence and signal null method.

Figure 6.

Bland-Altman plots show voxel-wise comparisons between DCE-MRI and ACE-MRI methods for pooled pixels from all tumors of the 11 mice for K^{trans} (a); v_e (b); v_p (c); B_1 (d); and T_1 (e). Solid thin lines are mean difference (actual values are noted in each plot) and dash thin lines are mean ± 1.96 SD. The noticeable patterns in B_1 and T_1 plots in (d) and (e) are due to the libraries with discrete step sizes used for B_1 and T_1 estimation in the model-free method.

Figure 7.

Comparison of the median values between DCE-MRI and ACE-MRI (triangles: 4T1 flank tumor; circles: 4T1 mammary fat pad tumor; crosses: GL261 brain tumor) for K^{trans} (a); v_e (b); v_p (c); B_1 (d); and T_1 (e).

Table 1

Parameters used for assessment of the uncertainty in estimation of ACE-MRI parameters using numerical simulation studies.

Parameters	values
K^{trans} (/min)	0.05, 0.15, 0.25 , 0.35, 0.45
v_e	0.15, 0.25, 0.35, 0.45 , 0.55
v_p	0.03, 0.06 , 0.09, 0.12, 0.15
B_1	0.8, 0.9, 1.0 , 1.1, 1.2
T_{10} (s)	1.4, 1.7, 2.0, 2.3 , 2.6

* Numbers in bold are baseline values which were kept fixed while one of parameters was varied to different values shown in this table. The baseline values in this table are also used as the baseline values for flip angle and TR effect simulation in Supplemental Figures 2 and 3 and DCE simulation with assumed B_1/T_1 error in Table 3.

Table 2

Parameters used for the numerical phantom (true) and the parameters estimated by conventional DCE-MRI method using the true T_{10} and B_1 values and the model-free ACE-MRI.

		T_{10} (s)	B_1	$K^{trans} (min^{-1})$	v_e	v_p
Tumor #1	True	2.3	0.93 ± 0.02	0.25	0.45	0.06
	DCE			0.25 ± 0.02	0.45 ± 0.03	0.06 ± 0.01
	ACE	2.33 ± 0.07	0.93 ± 0.02	0.24 ± 0.02	0.43 ± 0.03	0.06 ± 0.01
Tumor #2	True	1.8	0.93 ± 0.01	0.10	0.30	0.09
	DCE			0.10 ± 0.01	0.30 ± 0.02	0.09 ± 0.01
	ACE	1.78 ± 0.06	0.94 ± 0.01	0.10 ± 0.01	0.30 ± 0.02	0.09 ± 0.01
Tumor #3	True	2.1	0.95 ± 0.02	0.15	0.25	0.12
	DCE			0.15 ± 0.01	0.25 ± 0.02	0.12 ± 0.01
	ACE	2.13 ± 0.07	0.96 ± 0.02	0.14 ± 0.01	0.24 ± 0.01	0.11 ± 0.01
Tumor #4	True	2.4	0.93 ± 0.01	0.20	0.35	0.15
	DCE			0.20 ± 0.02	0.35 ± 0.03	0.15 ± 0.02
	ACE	2.44 ± 0.08	0.93 ± 0.01	0.19 ± 0.02	0.33 ± 0.02	0.14 ± 0.01
Tumor #5	True	2.6	0.98 ± 0.01	0.30	0.50	0.10
	DCE			0.30 ± 0.03	0.50 ± 0.04	0.10 ± 0.01
	ACE	2.73 ± 0.08	0.98 ± 0.02	0.25 ± 0.02	0.43 ± 0.03	0.09 ± 0.01
Muscle #6	True	1.6	0.96 ± 0.03	0.11	0.15	0.01
	DCE			0.11 ± 0.01	0.15 ± 0.01	0.01 ± 0.00
	ACE	1.65 ± 0.09	0.97 ± 0.03	0.10 ± 0.01	0.14 ± 0.01	0.01 ± 0.00

* Numbers in bold are designed parameters for each tumor and muscle of the numerical phantom.

Table 3

Uncertainties of kinetic parameters estimated using conventional DCE-MRI data with 0% (first DCE-MRI column) or 10% (second DCE-MRI column) error in B_1 and T_{10} . The DCE-MRI with 10% error shows a summary of the cases with $\pm 10\%$ error in B_1 or T_{10} , not in both. These uncertainties in DCE-MRI are compared with those of model-based ACE-MRI in which B_1 and T_{10} are estimated together with the kinetic model parameters. For SNR=10, Rician noises were added to all the simulated DCE/ACE-MRI curves as described in text.

		<i>DCE-MRI</i>	<i>DCE-MRI</i>	<i>ACE-MRI</i>
B_1	Error (%)	0 *	10 *	5.1 $\pm$ 3.5
	CV (%)			14.9 $\pm$ 8.6
T_{10} (s)	Error (%)	0 *	10 *	12.3 $\pm$ 8.8
	CV (%)			15.0 $\pm$ 5.0
K^{trans} (min^{-1})	Error (%)	6.3 $\pm$ 5.0	60.4 $\pm$ 69.8	14.2 $\pm$ 8.3
	CV (%)	9.1 $\pm$ 4.3	11.0 $\pm$ 10.7	13.5 $\pm$ 4.6
v_e	Error (%)	4.0 $\pm$ 3.1	33.4 $\pm$ 31.0	14.7 $\pm$ 9.9
	CV (%)	9.0 $\pm$ 3.5	10.5 $\pm$ 6.2	13.3 $\pm$ 4.5
v_p	Error (%)	11.0 $\pm$ 8.5	17.8 $\pm$ 15.3	14.0 $\pm$ 9.3
	CV (%)	8.9 $\pm$ 3.8	10.8 $\pm$ 8.1	14.0 $\pm$ 4.5

* DCE-MRI data analysis was performed using the known B_1 and T_{10} values with either 0% or 10% error, in order to compare with the results from ACE-MRI that have about 10% errors in B_1 and T_{10} estimation.