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Effects of Flip Angle Uncertainty and Noise on the Accuracy of DCE-MRI Metrics: Comparison Between Standard Concentration-Based and Signal Difference Methods

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Abstract

Dynamic contrast-enhanced MRI is becoming an increasingly important tool to assess tumors and their response to treatment. In the most common method of computing tumor perfusion parameters, the concentration of the injected contrast agent is first computed in both tumor and blood which is subsequently fit to a perfusion model, typically the Tofts two compartment model. However, this strategy can be highly sensitive to errors in the excitation flip angle and noise. More recently, a simpler method of determining perfusion was developed in which the difference signal, obtained by subtracting the measured time course signal by the signal prior to bolus arrival, is utilized in lieu of the concentration values. The goal of this work is to compare the performance of these two strategies with simulation experiments in the presence of flip angle errors and different levels of image signal to noise ratios (SNRs). Results show that with the conventional method, if assumed pre-contrast T_1 of blood is used, large errors in perfusion (exceeding 400% and 200% for K^{trans} and v_e , respectively) can occur in the presence of flip angle deviations typically observed *in vivo*. However, when baseline T_1 values are measured for both tumor and blood, the errors become a function of flip angle difference between the two locations, with nearly no error if the flip angle errors are identical at both locations. The errors are substantially smaller with the signal difference strategy (less than 100% for both K^{trans} and v_e). The latter method also yields more consistent perfusion values at varying SNR levels. The results suggest that measuring the actual flip angle may be critical for obtaining absolute perfusion values, but in studies in which relative changes in perfusion is of primary interest or if true flip angles are not known, the signal difference strategy may be preferred over the standard concentration-based method.

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Keywords

dynamic contrast-enhanced MRI (DCE-MRI); perfusion; signal difference method

1. Introduction

Dynamic contrast enhanced (DCE-) MRI is a quantitative imaging technique that has been widely used in the assessment of pathological process in various tumors, such as lesions of the brain, breast, and prostate [1–6]. In DCE-MRI, an exogenous contrast agent (CA) distributes into tissue and causes the reduction of tissue longitudinal relaxation time T_1 , which leads to enhanced signal intensities. T_1 -weighted images are acquired rapidly and continuously before, during, and after the injection of the contrast agent, and the acquired time series is analyzed and fit to the commonly-used Tofts (Kety) model [7–9], which provides pharmacokinetic parameters reflecting the pathological condition. The Tofts model consists of two compartments, blood plasma and extravascular extracellular space (EES), which are separated by the endothelium, and assumes that the contrast agent washes into EES from the plasma compartment with a rate K^{trans} that represents tumor perfusion and vascular permeability. Other quantitative parameters in DCE-MRI include fractional volume of EES (v_e), the gadolinium washout rate $k_{\text{ep}} (= K^{\text{trans}}/v_e)$, and blood plasma volume (v_p) within the tumor tissue.

The standard method of computing tumor perfusion parameters from the DCE-MRI time series requires first computing the concentration of the contrast agent in both blood plasma (C_p) and tumor (C_t). With this strategy, the intrinsic pre-contrast T_1 values of tumor and blood are required, although assumed values for each have also been used [10,11]. While an inversion recovery method is sometimes used for baseline T_1 measurement, long scan times can prohibit its use in routine applications, and other strategies, such as the variable flip angle (VFA) [12–14] technique, are often employed for this purpose.

In addition to baseline T_1 , the excitation flip angle must also be known, and the prescribed flip angle is typically used to compute the concentrations. However, it is known that the transmit RF field could vary substantially throughout the body due to imperfect hardware and dielectric effects causing the actual flip angles in tissues to be different from the prescribed (nominal) values. For example, it has been observed *in vivo* that the flip angle variability can be on the order of $\pm 40\%$ throughout the body in a large imaging FOV ($\approx 40\text{cm}$) [15]. Incorrect flip angles can yield errors in measuring the intrinsic T_1 using the variable flip angle method. For instance, it was shown previously that a -15% calibration error of the flip angle will lead to a -28% error in T_1 estimation [14]. Further, since both the incorrect flip angle and the erroneously computed T_1 are used in computing concentrations from the dynamic series [16,17], these errors potentially have compounding effects. Because the flip angle can vary spatially, one may be required to acquire a flip angle map for accurate quantification of tissue gadolinium concentrations [15].

As an alternative to first computing the gadolinium concentrations to derive the perfusion parameters, it was recently shown that the parameters could be calculated more directly from MR images using the absolute signal difference between the post-contrast DCE-MRI

time series and the pre-contrast baseline signal [18–20]. This technique is based on the observation that under certain conditions, the signal difference is proportional to the concentration of contrast agent, and therefore conversion from signal intensity to concentration may be unnecessary. In addition, measurement of the baseline T_1 values would not be necessary for perfusion calculations with the signal difference strategy.

Image noise is another important factor that can affect perfusion parameter estimation. Since high temporal resolution and high spatial resolution are both desired in DCE-MRI studies, the SNR of pre-contrast baseline images can often be low, sometimes near the level of the background noise. In the conventional method of computing perfusion, the dynamic time series is normalized to the pre-contrast signal by division, therefore noisy baseline image can potentially lead to large measurement errors. On the other hand, the signal difference method simply subtracts the baseline value, often leading to smaller errors. For example, if the true baseline signal intensity is one unit, but image noise artifactually raises that level to two, then the normalized dynamic signal will be lowered by 50% upon division by the noisy baseline signal. However, if the baseline is instead subtracted, the normalized signal is off by only one unit, which is the difference between the measured and true baseline levels. Thus, as long as the post-contrast tissue SNR is above ~ 3 (which is almost always the case, as evidenced by bright post-contrast signal in most tumors relative to background), the method of signal difference will be less sensitive to varying noise levels.

The goal of this work is to systematically compare the performance of the conventional concentration-based method for DCE-MRI perfusion parameter calculations with that of the signal difference method, taking into account the spatial variations in flip angles and in the presence of varying levels of image noise.

2. Theory

2.1. Conventional concentration-based method

The two-compartment Tofts model describes the dynamic time course of contrast agent concentrations in tissue (C_t) and blood plasma (C_p):

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

where v_e is the EES volume fraction and K^{trans} is the volume transfer constant between vascular space and EES [8,21]. The above equation can be solved for C_t :

$$C_t(t) = K^{trans} \int_0^t C_p(t') \cdot \exp \left[\frac{-K^{trans}(t - t')}{v_e} \right] dt'. \quad [2]$$

Equation [2] ignores the blood volume within the tissue, and a modified version of Tofts model includes a second term to account for the within-tissue vascular plasma volume [9]:

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(t') \cdot \exp \left[\frac{-K^{trans}(t - t')}{v_e} \right] dt'. \quad [3]$$

The relationship between C_p and the whole-blood CA concentration (C_b) is $C_p = \frac{C_b}{1 - Hct}$, where Hct is the hematocrit level.

The typical MR sequence utilized in DCE-MRI is the T_1 -weighted 3D spoiled gradient echo sequence. Ignoring the effects of T_2^* decay (appropriate for short TE imaging), the signal intensity has the following form:

$$S = K \cdot \sin\theta \cdot \frac{1 - \exp[-TR(1/T_{10} + r \cdot [CA])]}{1 - \cos\theta \cdot \exp[-TR(1/T_{10} + r \cdot [CA])]} = K \cdot \sin\theta \cdot \frac{1 - \exp(-TR \cdot R_1)}{1 - \cos\theta \cdot \exp(-TR \cdot R_1)}, \quad [4]$$

where S is the time-dependent DCE-MRI signal intensity, r is the relaxivity of the contrast agent, and K is a factor dependent on the spin density and receiver gain of the imaging system. T_{10} is the native pre-contrast T_1 value of the tissue or blood, $R_1 = 1/T_1$ is the time-dependent relaxation rate, θ is the flip angle, and TR the repetition time.

The MR signal intensities can be converted to contrast agent concentrations in tissue and blood (C_t and C_b) as follows [22]:

$$C = \frac{\ln \left(\frac{e^{-2TR/T_{10}} \cdot \cos\theta \cdot (1 - S_{rel}) + e^{-TR/T_{10}} \cdot (S_{rel} \cdot \cos\theta - 1)}{e^{-TR/T_{10}} \cdot (\cos\theta - S_{rel}) + S_{rel} - 1} \right)}{TR \cdot r}, \quad [5]$$

where $S_{rel} = \frac{S}{S_{baseline}}$ is the relative signal intensity and is equal to the time series S normalized to its pre-contrast (baseline) signal $S_{baseline}$, and C refers to either C_t or C_b . To compute the concentration, the native pre-contrast T_{10} value is required, which can be computed from additional data acquired prior to the dynamic series. The VFA technique is often utilized [13], in which several spoiled gradient echo images are acquired with various flip angles. The acquired signal can be transformed to a linearized form:

$$\frac{S_i}{\sin\alpha_i} = E_1 \cdot \frac{S_i}{\tan\alpha_i} + M_0 \cdot (1 - E_1), \quad [6]$$

where S_i represents the signal intensity at flip angle α_i , $E_1 = \exp(-TR/T_1)$, and M_0 the equilibrium magnetization. The native T_{10} can be extracted from the slope (E_1) since $T_{10} = -TR/\ln(E_1)$. The perfusion parameters can subsequently be obtained by fitting the calculated concentrations to Eq. [2] or [3].

2.2. Signal difference method

The signal difference method [18,19] uses the absolute signal difference between the dynamic time series and its pre-contrast baseline to fit the perfusion parameters directly without the need for T_{10} and $[CA]$. In this method, signal intensity curve S is subtracted by its baseline $S_{baseline}$, resulting in the following:

$$\Delta S = S - S_{baseline} = K \cdot \sin\theta \cdot \left[\frac{1 - \exp(-TR \cdot R_1)}{1 - \cos\theta \cdot \exp(-TR \cdot R_1)} - \frac{1 - \exp(-TR \cdot R_{10})}{1 - \cos\theta \cdot \exp(-TR \cdot R_{10})} \right], \quad [7]$$

where $R_{10} = 1/T_{10}$. Under the assumption of $TR \ll T_1$ (and thus $TR \ll T_{10}$), the above equation could be simplified [19]:

$$\Delta S \approx K \cdot \sin\theta \cdot TR \cdot \left[\frac{R_1}{1 - \cos\theta \cdot (1 - TR \cdot R_1)} - \frac{R_{10}}{1 - \cos\theta \cdot (1 - TR \cdot R_{10})} \right] \approx K \cdot \frac{\sin\theta \cdot TR}{1 - \cos\theta} \cdot \Delta R_1(t) = K \cdot \frac{\sin\theta \cdot TR}{1 - \cos\theta} \cdot r \cdot [CA], \quad [8]$$

Equation [8] indicates that the signal difference is approximately proportional to [CA]. This allows one to substitute signal differences for plasma and tumor gadolinium concentrations in Eq. [2] or [3] in lieu of having to first derive the concentrations [19]. Equation [8] also shows that the signal difference is independent of intrinsic T_{10} . The relationship between concentration and signal difference is shown in Fig. 1 for three different flip angles and a range of baseline T_1 values. The figure shows that the relationship becomes increasingly linear and independent of T_{10} at higher flip angles, indicating larger flip angles may yield more accurate results with the signal difference method, as the cosine terms in Eq. [8] approach zero. In the typical range of gadolinium concentrations observed in tissues, good linearity is achieved at all three flip angles.

With the conventional technique, accurate flip angles are needed both for the T_{10} measurement and for computing concentration from the dynamic series (Eqs. 5 and 6). For the signal difference method, although knowledge of an exact flip angle is not required, similar flip angles at the locations of the AIF and tumor is typically assumed, noting the presence of the flip angle (θ) in the proportionality constant in Eq. [8]. Thus, flip angle differences between the locations of the tumor and AIF can also lead to errors in perfusion estimations.

3. Methods

Numerical simulations were performed to systematically compare the accuracy of perfusion parameters between conventional and signal difference methods in the presence of flip angle errors and various levels of noise. For the arterial input function (AIF), an experimentally derived population-averaged function form [23], slightly modified to match the arterial input curves observed in our protocols (slightly broader with peak $C_b \approx 4.3$ mM) was employed. The following parameters were used: precontrast blood $T_1 = 1200$ ms, pre-contrast tumor $T_1 = 800$ ms, $TR = 3.2$ ms, CA relaxivity = $4.0s^{-1}/mM$. Four different K^{trans} values (0.1, 0.4, 0.8, and 1.2 min^{-1}) along with $v_e = 0.4$ and $v_p = 0.02$ were used to generate the tumor signal.

For the conventional method, two different scenarios were simulated regarding the use of intrinsic T_{10} values. In the first case, the intrinsic T_{10} values of both the blood and tumor were assumed to be measured with the VFA technique. In the second, tumor T_{10} was assumed to be measured by the VFA technique, while true blood T_{10} was assumed to be known (1200 ms). Given the challenges in measuring T_1 in moving blood, this is often done in DCE-MRI studies [10,11]. For computing the intrinsic T_{10} values using VFA, nominal flip angles of 2° , 5° , 10° , 15° , and 20° were used, while a nominal flip angle of 25° was

assumed for DCE-MRI. For the flip angle deviations, a range of error of -40% to $+40\%$ from the prescribed flip angle was utilized. After the MR signals for VFA and DCE-MRI data were generated using the actual (i.e. not prescribed) flip angles, perfusion parameters were subsequently computed assuming the nominal prescribed flip angles. For the signal difference method, the difference signal S was used in lieu of concentration values for computing the perfusion parameters.

To compare the performance with respect to noise, varying amounts of normally distributed zero-mean complex noise were added to the tumor and AIF time series. Subsequently, for the AIF, a 25-pixel averaging of the magnitude blood signal was performed simulating an ROI measurement of blood signal, while the tumor signal was processed on a pixel-wise basis with no averaging. Since the linearity between S and $[CA]$ varies with flip angle, comparisons between standard and signal difference methods were performed at each noise level for a range of flip angles for the dynamic data (15° , 25° , 35° , 45° , and 55°). At each combination of noise level and flip angle, the simulation was repeated 100 times and the resulting mean $\pm$ SD (standard deviation) were compared. For this comparison in evaluating noise effects, it was assumed that there were no flip angle errors.

4. Results

Figure 2 compares the errors in the perfusion parameters in the presence of flip angle errors at the locations of the AIF and tumor for $K^{\text{trans}} = 0.4 \text{ min}^{-1}$. The horizontal axes indicate the flip angle errors in blood and tumor, while the vertical axis represents the perfusion parameter error. Note that errors are much greater for the conventional methods (top two rows) compared to that of the signal difference method. For example, the maximum error in K^{trans} exceeds 400% for the former, while it is below 100% for the latter. Interestingly, for the case in which both blood and tumor intrinsic T_1 s are measured (top row), when flip angle errors are identical at the locations of the tumor and AIF, the errors are close to zero (indicated by the points that run from $[-40, -40]$ to $[40, 40]$ flip angle error), and the error increases sharply as the flip angles at the two locations increasingly differ. This is more clearly seen in Fig. 3 where the errors are displayed with respect to flip angle differences.

Figure 3 shows that for the conventional method when the intrinsic T_1 s of both blood and tumor are measured using VFA, the errors in perfusion parameters are nearly zero when the flip angle difference between AIF and tumor is zero regardless of whether the actual angles are accurate. Thus, when both blood and tumor T_1 s are measured, the *difference* in absolute flip angle between the two locations is more important than the actual values. However, when blood T_1 is assumed, this no longer the case. This dependence on the flip angle difference also seems to be true for the v_e error of the signal difference method, while those of K^{trans} and v_p are somewhat dependent on the actual flip angles. A key observation to be made from Figs. 2 and 3 is that the range of errors is much smaller for K^{trans} and v_e for the signal difference method compared to the conventional method (maximum error of $\sim 80\%$ vs. $\sim 250 - 450\%$), although there tends to be a small positive bias for K^{trans} (around 20%) even in the absence of flip angle errors.

The overall shapes of the error curves are similar for the other K^{trans} values that were simulated, although the ranges of errors differ to some degree. The results for all four K^{trans} values are summarized in Table 1. When blood and tumor pre-contrast T_1 s are both measured, the perfusion parameter errors for the conventional method are nearly identical between the high and low K^{trans} values. When blood T_1 is assumed, the range of errors is a function of true K^{trans} , with larger true K^{trans} and v_e values resulting in greater errors. For the signal difference method, errors in K^{trans} and v_e are relatively stable across all simulated K^{trans} values.

Figure 4 compares the effects of noise between conventional and signal difference methods at various flip angles ($K^{\text{trans}} = 0.4 \text{ min}^{-1}$). As expected, the accuracy of the conventional method improves as SNR increases, as evidenced by decreasing mean error and SD. For the signal difference method, the figures indicate that the parameters K^{trans} and v_e are generally less sensitive to varying noise levels compared to the conventional technique, indicated by flatter curves. While there is a bias in the average K^{trans} value at lower flip angles with the signal difference technique, the average values are more consistent across the SNRs. Our results also indicate that at a flip angle of around $35^\circ - 45^\circ$, the bias in K^{trans} becomes small, on the order of 10%. Accurate average v_e values ($<5\%$) and relatively low SDs ($<10\%$) are achieved with the signal difference method at all SNRs. For v_p , while the SDs are generally similar for the two methods, the conventional method yields more accurate mean values.

As before, the results for the other simulated K^{trans} values ($= 0.1, 0.8, 1.2 \text{ min}^{-1}$) show similar trends as those for $K^{\text{trans}} = 0.4 \text{ min}^{-1}$ and the results are summarized in Table 2. Table 2 shows that over a wide range of SNRs we had considered ($\text{SNR} = 1$ to 10), the signal difference method yields more consistent perfusion values, demonstrated by smaller ranges of errors (second row of each cell of the table). However, similar to what is observed in Fig. 4, biases in the measured K^{trans} values exist for the signal difference method. These offsets, however, diminish at higher excitation flip angles.

5. Discussion

Our simulations show that when flip angle errors are identical at the locations of AIF and tumor, accurate perfusion parameter values can be obtained with the conventional method as long as both blood and tumor T_{10} s are measured. Thus, if the AIF is located close to the tumor, flip angle errors may not have a large impact on measurement accuracy. However, when flip angles between AIF and tumor locations are different, the measurement errors could become very high. In the range of flip angle errors observed *in vivo*, the DCE-MRI parameter errors can approach several hundred percent.

For the signal difference method, the range of errors in the presence of flip angle errors is substantially smaller for K^{trans} and v_e , compared to that of the conventional method. The smaller error range indicates that this method is less sensitive to flip angle deviations and may be more suitable to detect changes in follow-up examinations, e.g. following treatment. The bias in K^{trans} for the signal difference method is in part due to the fact that the method assumes a linear relationship between signal difference and $[CA]$, which is not strictly true, particularly at lower flip angles. As this bias is expected to be similar between scans

utilizing similar flip angles, it should not substantially influence the measurement of relative changes in the perfusion parameters between two scans, which may be particularly useful in treatment effect studies where relative changes may be more important than absolute values.

At lower SNRs the errors in the average perfusion values expectedly increase with the conventional method due to the positive bias in estimating the baseline signal. When the dynamic curve is divided by the biased baseline, substantial errors in the perfusion parameters could thus occur. With the signal difference strategy, however, the baseline is subtracted from the signal curve, which is generally less sensitive to these biases. While the signal difference method is overall less sensitive to differing noise levels, there is a bias (offset) in the computed perfusion parameters. However, for K^{trans} , the offset appears to decrease with the increase of flip angle. As the S -[CA] relationship is increasingly linear at higher flip angles (Fig. 1), one would expect that these biases will diminish at higher flip angles. At the same time, however, increasing the flip angle reduces the baseline signal due to signal saturation, subsequently increasing the measurement error beyond an optimum flip angle value. For v_e , the signal difference method is superior to the conventional method at all SNR levels. Due to the low plasma volume fraction in tissues, the relative errors for v_p are generally larger and more variable (higher SD).

This work focuses on the effect of flip angle uncertainty and inhomogeneity within the imaging volume and the effects of noise in the measurement of perfusion parameters. It should be noted that unlike the conventional technique in which the signals are normalized to the baseline, the signal difference method can be susceptible to receiver coil sensitivity since absolute signal intensities are utilized. In the present work variations in receiver coil sensitivity was not considered, and in order to realize the potential benefits of the signal difference method as described in this work, body coil receive mode, or an array coil sensitivity map would need to be included in the protocol and be used to scale the signal intensities. However, similar to that of the conventional method, if the AIF and tumor locations are in close proximity, errors due to varying receive coil sensitivities are expected to be small. When using the conventional technique, our results suggest that a flip angle map, e.g. using AFI (Actual Flip-Angle Imaging [24]), may be required to accurately measure the perfusion parameters.

In conclusion, our results show that although there may be small offsets in computed perfusion values with the signal difference strategy, it is generally less sensitive to flip angle errors and varying noise levels, and may be a more precise technique compared to the standard method. The signal difference strategy for measuring tumor perfusion may thus prove to be a useful method for detecting changes in follow-up studies.

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Fig. 1.

Relationship between signal difference and [CA] in terms of various intrinsic T_1 values (T_{10}) and flip angles (FA). For each of the three flip angles (15° , 25° , and 50°), a range of T_{10} values (from 500 to 2500 ms in 100 ms increments) was used to generate the separate curves. For the largest flip angle, the curves for different T_{10} s essentially overlap. The magnified region of the plot shows the typical range of gadolinium concentration in tumor tissues.

Fig. 2.

3D surface plots comparing perfusion parameter measurement errors. Horizontal axes correspond to the relative flip angle (FA) errors at the locations of the tumor and AIF, vertical axes of the 1st and 2nd columns correspond to relative K^{trans} and v_e errors, while that of the 3rd column denotes absolute v_p error. As v_p values are typically very small, absolute error may be more informative for its evaluation. All flip angle errors (%) are relative to the nominal flip angle of 25° . The first row shows the results for the conventional method when both intrinsic T_1 s are measured, the second row is with assumed blood T_1 ($= 1200$ ms) and measured tumor T_1 , while the third row depicts the results for the signal difference method. True perfusion parameters: $[K^{\text{trans}}, v_e, v_p] = [0.4 \text{ min}^{-1}, 0.4, 0.02]$.

Fig. 3.

Perfusion parameter measurement errors as a function of flip angle differences between the locations of the tumor and AIF (%Error in tumor – %Error in AIF). The first row shows the results for the conventional method when both intrinsic T₁s are measured, the second row shows the results of the conventional method with assumed blood T₁ (= 1200 ms) and measured tumor T₁, while the third row shows the results of the signal difference method. The horizontal axis represents the flip angle difference between tumor and blood (in percent relative to nominal 25°), while the three columns correspond to the measurement errors for

K^{trans} , v_e , and v_p respectively. True perfusion parameters: $[K^{\text{trans}}, v_e, v_p] = [0.4 \text{ min}^{-1}, 0.4, 0.02]$.

Fig. 4.

Measurement errors (mean and SD) of K^{trans} , v_e , and v_p for conventional and signal difference methods. SNR is defined as baseline AIF signal intensity divided by the noise standard deviation. Flip angle of 25° was used, and true perfusion parameters were $[K^{\text{trans}}, v_e, v_p] = [0.4 \text{ min}^{-1}, 0.4, 0.02]$.

Table 1

Ranges of errors of the perfusion parameters in the presence of flip angle errors (−40% − +40%) for different K^{trans} values. Values for v_e and v_p were held constant at 0.4 and 0.02 respectively, throughout the simulations.

K^{trans} (min^{-1})	K^{trans} Error Range (%)			v_e Error Range (%)			v_p Absolute Error Range ($\times 10^{-2}$)		
	Conventional (T_1 meas)	Conventional (T_1 assumed)	Signal Difference	Conventional (T_1 meas)	Conventional (T_1 assumed)	Signal Difference	Conventional (T_1 meas)	Conventional (T_1 assumed)	Signal Difference
0.1	−81.7 ~ 449.1	−56.7 ~ 289.0	−32.4 ~ 96.7	−81.8 ~ 449.8	−50.6 ~ 214.9	−49.0 ~ 72.3	−1.6 ~ 9.0	−1.3 ~ 10.0	0.2 ~ 3.0
0.4	−81.6 ~ 446.6	−60.5 ~ 406.6	−8.9 ~ 80.1	−81.8 ~ 449.1	−52.9 ~ 243.8	−42.8 ~ 71.7	−1.6 ~ 9.0	−1.3 ~ 7.4	−0.3 ~ 3.5
0.8	−81.4 ~ 443.9	−64.0 ~ 561.9	7.1 ~ 82.5	−81.7 ~ 448.4	−53.9 ~ 276.3	−35.0 ~ 68.2	−1.6 ~ 9.2	−3.9 ~ 3.7	−3.2 ~ 4.0
1.2	−81.3 ~ 441.5	−66.2 ~ 694.9	13.5 ~ 92.0	−81.7 ~ 447.7	−54.9 ~ 312.3	−27.7 ~ 64.2	−1.7 ~ 9.4	−18.8 ~ 5.0	−7.1 ~ 5.1

Table 2

Ranges of errors (max - min) of the perfusion parameters throughout different SNR levels (1 to 10) for different K^{trans} values. Values for v_e and v_p were held constant at 0.4 and 0.02 respectively, throughout the simulations. Results are shown for several excitation flip angles. The numbers in each cell correspond to: Conventional method (top) and signal difference method (bottom). While the error approaches zero for the conventional method at the highest SNR, an offset exists with the signal difference method and is shown in parentheses (offset values taken at SNR=10).

K^{trans} (min^{-1})	K^{trans} Error Range (%)					v_e Error Range (%)					v_p Absolute Error Range ($\times 10^{-2}$)				
	15°	25°	35°	45°	55°	15°	25°	35°	45°	55°	15°	25°	35°	45°	55°
0.1	24.5 1.1 (23.1)	29.1 3.6 (12.3)	26.0 9.8 (7.2)	19.0 22.3 (4.6)	19.9 28.9 (2.2)	20.6 4.5 (-9.9)	42.9 19.1 (-4.5)	60.0 21.3 (-2.8)	72.1 40.3 (-1.7)	85.3 56.7 (-0.7)	0.8 0.4 (2.7)	0.5 0.8 (1.1)	0.4 0.8 (0.5)	0.2 0.7 (0.3)	0.5 1.1 (0.2)
0.4	34.0 3.4 (51.0)	34.6 2.4 (22.7)	33.5 8.9 (12.1)	29.3 11.8 (7.0)	23.7 17.9 (4.3)	20.4 2.2 (-3.1)	30.0 3.9 (-0.7)	43.5 3.4 (0.0)	46.8 4.7 (0.0)	45.8 3.8 (0.2)	0.6 0.4 (2.1)	0.4 0.6 (0.9)	0.5 0.7 (0.5)	1.2 1.5 (0.3)	0.6 1.6 (0.2)
0.8	42.9 2.8 (82.2)	37.7 5.3 (33.5)	38.5 6.8 (17.4)	35.7 11.8 (10.5)	32.2 15.2 (6.4)	22.7 2.9 (3.7)	32.4 3.0 (2.0)	42.3 3.9 (1.3)	44.3 4.8 (0.8)	48.1 2.6 (0.4)	0.4 0.4 (-0.7)	0.9 0.5 (0.0)	0.7 0.5 (0.0)	0.3 1.0 (0.0)	2.1 1.1 (0.0)
1.2	42.9 6.5 (92.1)	42.7 5.9 (37.0)	40.1 6.2 (18.7)	36.0 9.1 (11.4)	36.2 10.2 (7.0)	21.9 1.3 (8.4)	33.8 3.4 (3.8)	41.6 4.0 (2.1)	43.7 4.2 (1.2)	45.3 3.2 (0.9)	0.6 0.5 (-3.0)	0.3 0.5 (-0.9)	0.4 0.5 (-0.4)	0.6 0.8 (-0.2)	1.3 1.0 (-0.1)