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Sensitivity of Quantitative Metrics Derived from DCE MRI and a Pharmacokinetic Model to Image Quality and Acquisition Parameters

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Abstract

Rationale and Objectives—This study aims to investigate the sensitivity of quantitative metrics derived from dynamic contrast-enhanced (DCE) magnetic resonance imaging and a pharmacokinetic (PK) model to image quality and acquisition parameters.

Materials and Methods—A computer-synthesized DCE model that consisted of a large range of values of K^{trans} (transfer constant of a paramagnetic contrast agent from blood to tissue), v_p (fractional plasma volume), and k_{ep} (back flux rate) was created to test the reliability of quantitative metrics derived from a standard PK model. Effects of the contrast-to-noise ratio (CNR), total acquisition time, and sampling interval on the stability and bias of the derived metrics were investigated.

Results—The instability and bias of the estimated K^{trans} , v_p , and k_{ep} values increased with sampling interval and decreased with increasing CNR. Total acquisition times had limited influence on the estimations of K^{trans} and v_p values, but increasing the total acquisition time improved the stability of the estimation of k_{ep} values. However, for small k_{ep} values, the stability was still poor even with a total acquisition time of 8 minutes. Also, the stability and bias of the estimated values of K^{trans} , v_p , and k_{ep} are interrelated.

Conclusions—Our synthesized DCE model represents perfectly reproduced data except for the presence of Gaussian-distributed random noise. Our analysis suggests minimum changes that may be considered potentially significant in longitudinal therapy assessment studies. Our data are complementary to experimental data from human subjects and phantoms, and provide guidance for the design of image acquisition strategies.

Keywords

DCE MRI; pharmacokinetic model; imaging biomarker; stability; therapy assessment

Dynamic contrast-enhanced (DCE) magnetic resonance (MRI) is emerging as a biomarker for assessment of cancer therapy and normal tissue toxicity(1–6). Quantitative metrics obtained by applying a pharmacokinetic (PK) model to DCE MRI have been related to underlying physiological parameters such as vascular permeability, vascular volume, perfusion, and extravascular extracellular space. Previous studies have investigated factors influencing accuracy and precision of quantitative metrics derived from DCE MRI and the

PK models. Most attention has been given to the factors that impact measurement of the arterial input function, such as the amplitude, sampling rate, temporal jitter, dispersion, partial volume, and inflow effect, as well as the propagation of these measurement errors on the derived quantitative metrics (7–11). However, few studies address reproducibility of DCE MRI measures and stability of the PK model, both of which affect reliability of subsequently derived quantitative metrics and validity of the metrics as a biomarker for therapy assessment.

Recently, efforts have been made to standardize DCE MRI acquisition protocols, establish quality assurance procedures for multicenter clinical trials, and assess reproducibility of test and retest measures. Although the importance of reproducibility of DCE MRI measures as well as the derived quantitative metrics is well recognized, there are few published data to provide guidelines for investigators (12–15). Furthermore, reproducibility of the quantitative metrics derived from a PK model and DCE MRI depends on many interconnected factors, including stability of scanner hardware, physiological conditions, image acquisition parameters, image quality, and the analysis method used. Therefore, it is important to understand the impact of physiological-related, measurement-related, as well as quantification method-related effects on reproducibility of the quantitative metrics, and to develop strategies to improve reproducibility while considering these effects. Few studies to date have investigated the stability of the PK model and associated computational algorithms under the influence of image acquisition parameters and noise (16).

This study aims to analyze the sensitivity of quantitative metrics derived from DCE imaging data and the standard model that was published in a review article in 1999 (17) to image quality and acquisition parameters. First, we created a synthesized dynamic model to mimic the DCE data from brain normal tissue after irradiation to neovascular tumors. The physiological conditions investigated involve a mildly leaky blood-brain barrier with low blood volume density, and a severely leaky vasculature with various blood vessel densities. This synthesized model was investigated with different image acquisition parameters and contrast-to-noise ratios (CNRs). We analyzed the stability and bias of estimation of quantitative DCE metrics as well as their dependence on image quality and acquisition parameters. Our data provide suggestions for DCE image acquisition parameters, and minimum changes of quantitative DCE metrics that might be considered significant in longitudinal therapy assessment studies. Most importantly, our findings suggest areas for caution in the interpretation of the results as well as for improvement of quantification of DCE imaging data.

MATERIALS AND METHODS

Standard PK Model

The standard PK model for quantification of parameters associated with DCE MRI and with diffusible and extracellular paramagnetic contrast agents was presented in a 1999 review article (17) as:

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) e^{-K_{ep}(t-\tau)} d\tau + v_p C_p(t) \quad (1)$$

where C_t and C_p are the contrast concentrations in tissue and arterial plasma, respectively, K^{trans} is the transfer constant of a paramagnetic contrast agent from intravascular space to extravascular space, v_p is the fractional plasma volume, $k_{ep} = K^{trans}/v_e$ depicts the back flux rate of the contrast agent from tissue to plasma, and v_e is the fractional volume of extravascular extracellular space. Given a set of DCE MRI data, three parameters, K^{trans} , v_p , and v_e , can be estimated from Equation 1. The precise relationship of these quantitative

metrics (K^{trans} , v_p , and k_{ep} [or v_e]) to true underlying physiological parameters is hardly validated histopathologically (18). The utility of the measurements depends on physiological conditions under study (17), and interpretation of extracted quantitative metrics should be handled with caution. In this project, we investigated the sensitivity of K^{trans} , v_p , and k_{ep} (or v_e) as derived from DCE imaging data using Equation 1 with the CNR, sampling interval, and total acquisition time.

Synthesized DCE Phantom

A synthesized DCE phantom was developed to include a large range of values of K^{trans} , v_p , and k_{ep} , and to satisfy Equation 1. The theoretical contrast-concentration time curve of blood plasma (C_p) was obtained from arterial DCE data of a human subject, after cleaning and smoothing, and corrected by a factor of $1/(1-Hct)$, where Hct is a small vessel hematocrit of 0.45. The tested K^{trans} values were 0.0, 0.001, 0.005, 0.01, 0.05, 0.1, and 0.5 minute^{-1} , in which the values of 0.0–0.01 minute^{-1} mimic brain tissue from normal to mildly leaky blood-brain barrier, and 0.05–0.5 minute^{-1} depict leaky neovascular tumors. The v_p values of 0.01, 0.02, 0.05, and 0.1, corresponding to blood volume of 1.8, 3.6, 9.1, and 18.0 mL/100 g, respectively, were considered, in which the low range covers microvasculature volumes in normal to mildly abnormal brain tissue, and the high range depicts neovascular tumors. The k_{ep} values were 0.0, 0.0067, 0.0333, 0.0667, 0.3333, 0.6667, and 3.3333 minute^{-1} , which corresponded to K^{trans} values of 0.0, 0.001, 0.005, 0.01, 0.05, 0.1, and 0.5 minute^{-1} and a v_e value of 0.15. The theoretical contrast-concentration time-curve of tissue or tumor (C_t) was created using Equation 1 with combinations of the described parameters. The temporal sampling interval, Δt , of the C_t time-curve was 1 second. The synthesized DCE phantom was subsequently subsampled with temporal sampling intervals of 2, 4, and 6 seconds to test different sampling paradigms. The total DCE series acquisition time (T) lasted 274 or 480 seconds.

To investigate the effect of noise on the derived quantitative metrics, Gaussian-distributed random noise was added to the theoretical C_t time curves to obtain a CNR of 10, 20, 50, or 100. Here, the CNR was defined as the ratio of the peak contrast enhancement to the standard deviation of signal intensities at the baseline before contrast injection. In typical brain and head and neck tumors of experimental DCE MRI data, the CNR is estimated to be 10–20. For each combination of tested parameters (eg, $K^{trans} = 0.005 \text{ minute}^{-1}$, $v_p = 0.02$, and $k_{ep} = 0.03 \text{ minute}^{-1}$, T = 274 seconds, and $\Delta t = 1 \text{ second}$), the simulated data were generated 2500 times for each CNR level using a Gaussian-distributed random noise generator to test stability and bias of each of the derived quantitative metrics.

Testing of the Synthesized Phantom

The synthesized dynamic model was fitted to Equation 1 using nonlinear least squares fitting and a Simplex optimizer, which was developed in-house as part of a package of functional imaging analysis tools (19). First, we tested the ability to reproduce “true” values of K^{trans} , v_p , and k_{ep} from the synthesized DCE data without adding noise using our software tool. Next, we applied our validated quantification tool to the synthesized DCE phantom with various CNRs to derive quantitative metrics of K^{trans} , v_p , and k_{ep} . The mean of the estimates, bias of the estimates from the true value, root mean squared error (RMSE) between the estimates and the true value of each of the metrics for each CNR, under each of combinations of tested metrics, and under each combination of imaging acquisition parameters (sampling interval and total acquisition time) were determined. The stability of the estimates was determined by the RMSE of 2500 estimations, and the bias was measured by the discrepancy between the mean of the 2500 estimations and the true value. A 95% confidence interval (CI) suggests a minimum change of each metric under each condition to

be considered potentially significant in the study of an imaging biomarker for therapy assessment.

RESULTS

Validation of PK Modeling Software

First, we evaluated our PK modeling software tool that was based upon nonlinear least squares fitting and Simplex optimization, for estimation of values of K^{trans} , v_p , and k_{ep} from the standard model (Equation 1) using the synthesized DCE phantom without noise, sampling interval $\Delta t = 1$ second, and total acquisition time of 274 seconds. Without noise, nonlinear least squares fitting resulted in estimated values of K^{trans} and v_p perfectly down to 10^{-8} , and values of k_{ep} down to 10^{-6} , which suggests excellent reliability of our PK modeling software tool for evaluation of the derived quantitative metrics from the synthesized DCE model with Gaussian noise as well as with other acquisition parameters.

Stability and Bias of Derived Quantitative Metrics

CNR—The relative RMSEs and biases of K^{trans} , v_p , and k_{ep} generally increased with a decrease in CNR. Examples of relative RMSEs and biases of estimated values of K^{trans} , v_p , and k_{ep} as a function of CNR with a sampling interval of 1 second and total acquisition time of 274 seconds are given in Figure 1. The relative RMSEs of the estimates increased markedly as CNR fell below 20 (Fig 1), suggesting PK model fitting is less stable when CNR is low. The effects of noise on the estimated values of K^{trans} , v_p , and k_{ep} were different, because the relative RMSEs were small for v_p , modest for K^{trans} , and large for k_{ep} given the same CNR (Fig 1). For CNR of 20 or greater, the relative RMSEs were ~4 % or lower for v_p , and 12% or smaller for K^{trans} , and 25% or lower for k_{ep} , except the smallest k_{ep} value of 0.0067 minute⁻¹. The relative biases in the estimated values of K^{trans} and v_p were <6% for CNRs from 10 to 100, which are small enough to not be a concern. However, the relative RMSE and bias for estimation of k_{ep} were much greater than for K^{trans} and v_p . For the smallest k_{ep} values of 0.0067 minute⁻¹, the relative bias of the estimation was 30% and the relative RMSE was 165% for CNR = 100, and even greater for lower CNRs, suggesting unreliable estimation of the k_{ep} value as small as 0.0067 minute⁻¹ even with a sampling interval of 1 second.

Sampling interval—The relative RMSEs and biases of the estimates of K^{trans} , v_p , and k_{ep} generally increased with sampling intervals. Examples of the effect of sampling intervals on the estimations of K^{trans} , v_p , and k_{ep} with CNR of 20 and total acquisition time of 274 seconds are given in Figure 2. For a sampling interval of 6 seconds, the relative RMSEs of estimates of the three metrics were two to three times greater than those obtained for 1 second. Similar to the effect of CNR, given the same sampling interval, the relative RMSEs were smallest for v_p , modest for K^{trans} , and largest for k_{ep} . Furthermore, for the estimations of the large value of $v_p = 0.1$ the relative RMSEs and biases were more sensitive to the sampling interval than for the small values (Fig 2). However, for the estimations of the large or small values of K^{trans} (eg, K^{trans} of 0.5 or 0.001 minute⁻¹), the relative RMSEs and biases were more sensitive to the sampling interval than for the intermediate values (Fig 2). For the estimation of the small value of k_{ep} (eg, 0.007 minute⁻¹), the relative RMSEs and biases were so large as 300% or greater, regardless of the sampling intervals. For the estimation of the k_{ep} value of 0.07 minute⁻¹, the relative RMSEs were more sensitive to the sampling interval than for the large values. For tested sampling intervals of 1–6 seconds, the relative biases were ~6% or smaller for all metrics except for small values of K^{trans} of 0.001 minute⁻¹ and k_{ep} of 0.007 minute⁻¹, and large values of K^{trans} of 0.5 minute⁻¹ (Fig 2).

Total acquisition time—Effects of total acquisition time on the stability and bias of the estimations of K^{trans} , v_p , and k_{ep} were very different. Examples of the relative RMSEs and biases of the estimations of K^{trans} , v_p , and k_{ep} as a function of total acquisition time with a sampling interval of 1 second and CNR of 20 are shown in Figure 3. For estimation of v_p , both the relative RMSEs and biases were insensitive to total acquisition time. For estimation of K^{trans} values $>0.005 \text{ minute}^{-1}$, the relative RMSEs and biases were also insensitive to total acquisition time, whereas for small values of $K^{trans} < 0.005 \text{ minute}^{-1}$ doubling the total acquisition time from 274 seconds to 480 seconds improved the relative RMSE and bias by at least a factor of 2 (Fig 3). The improvement for the estimation of k_{ep} was qualitatively similar to that for K^{trans} , but the extent was greater than for K^{trans} . For instance, for the estimations of k_{ep} values $<0.07 \text{ minute}^{-1}$ in the combination of the v_p values 0.05, the relative RMSEs were reduced by a factor from 4 to 56 and the relative biases by a factor from 3 to 14 when total acquisition time was increased from 274 seconds to 480 seconds. Although there was a large extent of improvement with the long acquisition time of 480 seconds, the relative RMSEs were still $>200\%$ for the estimation of the k_{ep} value of $0.007 \text{ minute}^{-1}$ and 18–105% for the k_{ep} value of 0.03 minute^{-1} in all combinations of v_p values, suggesting unreliability in the estimations of the k_{ep} value as small as $0.007 \text{ minute}^{-1}$, even with a acquisition time as long as 8 minutes.

Interaction among metrics selves—The stability and bias of estimations of one metric also depended on the values of other metrics or combinations of the other metrics. Examples of the relative RMSEs and biases of the estimations of v_p , K^{trans} , and of k_{ep} under the influence of the other metrics and with acquisition parameters of CNR = 20, sampling interval $\Delta t = 1$ second, and total acquisition time of 8 minutes are shown in Figure 4.

For estimation of v_p , the relative RMSE was influenced by the value of K^{trans} , whereas the relative bias was not. Note that the relative bias was small, $<0.5\%$ for all combinations. The relative RMSEs were less than 10% for all but two exceptions, in which the relative RMSEs were 23.4% for $v_p = 0.01$ and 12.3% for $v_p = 0.02$ when they were combined with a large K^{trans} value of 0.5 minute^{-1} (Fig 4). Note that the stability of the estimation for the small values of v_p is affected much more by large K^{trans} than for the large values of v_p .

For estimation of K^{trans} , the relative bias and RMSE were affected by the value of v_p as well as the value of K^{trans} itself. The relative biases were less than 6% and relative RMSEs were less than 15% for all but two combinations, in which $K^{trans} = 0.001 \text{ minute}^{-1}$ in combination with $v_p = 0.1$ or 0.05 . For the estimation of the K^{trans} value of $0.001 \text{ minute}^{-1}$, the relative biases were 1.7%, 5.4%, 16.1%, and 49.0%, and the relative RMSEs were 5.7%, 12.5%, 33.9%, and 142.5% when $v_p = 0.01, 0.02, 0.05$, and 0.1 , respectively, suggesting that the estimation of the small K^{trans} value is strongly influenced by the values of v_p , as the K^{trans} estimation worsens with an increase in the v_p value.

For estimation of k_{ep} , the relative RMSE and bias were affected by the value of v_p as well as the value of k_{ep} itself, which is similar to that for estimation of K^{trans} (Fig 4). The relative RMSE and bias increased with a decrease in the value of k_{ep} . For estimation of $k_{ep} = 0.007 \text{ minute}^{-1}$, the relative bias was greater than 62% and the RMSE was greater than 203%, regardless of the values of v_p and K^{trans} , suggesting it is unreliable to estimate k_{ep} values as small as $0.007 \text{ minute}^{-1}$, even when extending the total acquisition time to 8 minutes. For estimation of $k_{ep} = 0.033 \text{ minute}^{-1}$, the relative bias was $<1\%$ as long as v_p was <0.1 , which is not a concern. However, when in a combination with $v_p = 0.1$ or greater, the relative bias increased to 15%. The relative RMSEs for estimation of $k_{ep} = 0.033 \text{ minute}^{-1}$ ranged from 18% to 105% when the v_p values varied from 0.01 to 0.1, respectively, suggesting that estimation of k_{ep} values of 0.03 minute^{-1} is unstable. For estimation of $k_{ep} = 0.067 \text{ minute}^{-1}$, the relative bias was not a concern, $<1\%$ for all v_p values, whereas the relative

RMSEs were <18% for $v_p < 0.1$, and >35% for $v_p > 0.1$. For estimation of k_{ep} values of 0.33–3.33 minute^{-1} , the relative biases were <0.1% and the relative RMSEs were <4% for all tested v_p values, suggesting a range of k_{ep} values in which the estimations are stable.

95% confidence intervals—Using the RMSE from 2500 estimations of each of the metrics under each combination of the three metrics, acquisition parameters and CNRs, we calculated 95% confidence intervals (CI) of single estimation (eg, single voxel) of the metric of interest, which suggest a minimum change to be considered as potentially significant in longitudinal therapy assessment studies because of the influence of the noise in DCE images and the uncertainty in the activity time curves with given acquisition parameters. Tables 1 and 2 list 95% CIs of each of the metrics for single estimation (eg, single voxel) at CNR of 20, total acquisition time of 274 seconds, and sampling intervals of 1 second and 4 seconds, respectively. Table 3 shows 95% CIs at CNR of 20, total acquisition time of 480 seconds, and sampling intervals of 1 second. Similarly, 95% CI for comparison of means in repeated measures were calculated. Additional 95% CIs in other combinations of CNRs, total acquisition times and sampling intervals are not shown because of the limitation of the length of this article, but can be provided for online access.

DISCUSSION

In this study, we analyzed the effects of image quality and acquisition parameters on the quantitative metrics derived from synthesized DCE data and the standard model. Particularly, we analyzed the effects of the CNR, sampling interval, and total acquisition time on the stability and bias of the estimations of K^{trans} , v_p , and k_{ep} . We evaluated the values of K^{trans} , v_p , and k_{ep} over a large range and tested the stability and bias of the estimations more than 2500 times for each of expectation value, CNR level, and combination of image acquisition parameters. Our analyses provide information on how reliable the quantitative metrics derived from a PK model plus the involved numerical algorithms and a synthesized DCE data under an experimental condition (acquisition parameters, image quality, and physiological conditions) are. These synthesized DCE data represent perfectly reproduced DCE MRI measures except for the presence of Gaussian-distributed random noise, which are complementary to experimental data from human subjects and phantoms. Our results suggest strategies in acquisition and analysis of DCE imaging to improve reproducibility. Finally, our findings reveal that some of the metrics as well as combination of the metrics cannot be estimated reliably with given image quality and acquisition parameters. Our results of the analysis and the synthesized dynamic model can be made available for public access for other users to test their software.

We demonstrate a CNR dependency of the stability and bias in the estimation of the values of K^{trans} , v_p , and k_{ep} . Both the stability and bias of the estimations are worsened markedly when the CNR falls below 20. The sensitivity of the three metrics of K^{trans} , v_p , and k_{ep} to noise is different and in the ascending order of v_p , K^{trans} , and k_{ep} . The reliability of estimated k_{ep} values is quite worse than the values of K^{trans} and v_p , suggesting caution when it is used for therapy assessment. Our experimental DCE MRI data from human brain and HN tumors acquired on a 1.5 T or 3.0 T scanner with a single dose of Gd-DTPA injection indicate that the CNR is in the range of 10–20. Our findings in this analysis suggest that it is important to have a CNR close to 20 to have stable estimates of K^{trans} and v_p . The improvement of CNR in DCE MRI can be achieved by optimizing image acquisition (eg, reducing voxel size, optimizing contrast by repetition time, echo time, and flip angle, and using a high-field magnet and high-quality coil).

We characterize dependency of the stability and bias of estimating K^{trans} , v_p , and k_{ep} on the sampling interval. The bias of estimation of the three metrics is less sensitive to the

sampling interval, except for large values of K^{trans} and v_p and small values of k_{ep} . The stability of estimations is two to three times worse for the sampling interval of 6 seconds than 1 second. Therefore, it is important to choose an adequate sampling rate. To do so, the first choice in optimization of the acquisition parameter is to reduce spatial resolution, by which both the CNR and the sampling rate can be improved, as long as the spatial resolution is acceptable for imaging heterogeneous contrast uptake. Parallel imaging acquisition can also improve the sampling rate, but with a tradeoff in CNR. Precaution needs to be taken for parallel imaging in dynamic acquisition with unexpected artifacts.

We show that prolonging the total acquisition time from 4 to 8 minutes affects the estimations of the v_p values very little and the estimations of the K^{trans} values minimum. The major gain of prolonging the acquisition time is to improve the reliability of the estimations of the k_{ep} values. Even with the total acquisition time of 8 minutes, the reliability of the estimations of the small values of k_{ep} is unsatisfactory. It should be caution when using k_{ep} in therapy assessment.

We reveal the interaction among the metrics or combinations of the metrics on the stability and bias of the estimations of the individual metrics. Although overall the reliability of the estimates of small K^{trans} values (eg, $0.001 \text{ minute}^{-1}$) is worse than for the large values, the values of v_p affect the estimates of K^{trans} , as the large v_p values result in worsening estimates of K^{trans} . On the other hand, the reliability of the estimates of small v_p values (eg, 0.01) is worse than the large ones, but the values of K^{trans} have influence on the estimates of v_p , in which the large K^{trans} values lead to worse estimates of the small v_p values. It is worthwhile to point out that for these two discussed combinations, the reliabilities of the estimates of K^{trans} and v_p are not similar. Some efforts that aim to improve the estimates in these ranges or combinations could be beneficial for certain applications of therapy assessment.

In this study, we did not analyze the influence of the errors in arterial input function on the derived quantitative metrics. There is no need to reiterate the importance of the arterial input function. The factors that influence the arterial input function as well as derived quantitative metrics from DCE MRI and the PK models, including the amplitude, sampling rate, temporal jitter, and partial volume averaging, have been addressed and tested intensively in previous studies (7–11). The previous studies indicate that the uncertainty in the arterial input function has greater impact on the estimation of v_p values than the K^{trans} and k_{ep} values. Therefore, in our study, we focus on other factors that impact the reliability of the derived quantitative metrics.

The findings in our study suggest that it is worthwhile to test the software tool that is used for therapy assessment studies using the synthesized dynamic model, thereby to understand the performance of the software tool and the PK model. The findings of our study also indicate that some efforts can be used to improve the estimation of some metrics. Our data in this study suggest some strategies for DCE image analysis to improve the reliability of the data. For example, a better CNR can be obtained by estimating quantitative imaging metrics from a volume of interest than in a single voxel. This strategy requires predefining the volume of interest, which may not be suitable to evaluate heterogeneity of tumors. Comparison of the 95% CIs for a single voxel and means suggests another strategy. In this strategy, quantitative metrics are still estimated from DCE data voxel by voxel. Then, the mean values in each of the heterogeneous volumes (if they can be delineated independently) are used to assess therapy effects on each of the heterogeneous volumes, by comparing the changes of the mean values after and before therapy, which has more statistical power than assessing a single voxel.

The analysis of sensitivity of the derived DCE quantitative metrics to imaging acquisition parameters and image quality could provide guidance in the design of an image acquisition paradigm for therapy assessment of an organ of interest and in the interpretation of the data. Therefore, a computer-synthesized dynamic model with known values of physiological parameters, different levels of CNRs, and various acquisition parameters can provide information that are complementary to test and retest data from human subjects and phantoms. One of the advantages of the computer-synthesized data is to allow us to cover large of ranges of the physiological parameters and create a large number of simulations. However, the computer-synthesized DCE data are based on a model, and this model does not necessarily addresses all parameters that could affect actual DCE data in humans and in all diseases. It does provide an assessment of relevant and potentially important biases and possible errors that have to be considered if indeed the human system behaved perfectly according to the model, but this may not always be the case. To the extent that it does, these estimates should be quite reasonable, relevant, and complementary to the data that can be obtained from human subjects.

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Figure 1.

The relative root mean squared errors (RMSEs) and biases of the estimations of v_p (fractional plasma volume), K^{trans} (transfer constant of a paramagnetic contrast agent from blood to tissue), and k_{ep} (back flux rate) as a function of contrast-to-noise ratio (CNR) at total acquisition time of 274 seconds and sampling interval of 1 second. The relative RMSEs and biases of the estimations of the k_{ep} values of $0.007 \text{ minute}^{-1}$ were 165% or 30% or greater, and out of the scales in the plots on the bottom row.

Figure 2.

The relative root mean squared errors (RMSEs) and biases of estimations of v_p (fractional plasma volume), K^{trans} (transfer constant of a paramagnetic contrast agent from blood to tissue), and k_{ep} (back flux rate) as a function of sampling interval at contrast-to-noise ratio (CNR) = 20 and total acquisition time of 274 seconds. For the k_{ep} values of 0.007 minute⁻¹, the relative RMSEs and biases were larger than 300%, and out of the scales of the plots on the bottom row.

Figure 3.

The relative root mean squared errors (RMSEs) and biases of estimations of v_p (fractional plasma volume), K^{trans} (transfer constant of a paramagnetic contrast agent from blood to tissue), and k_{ep} (back flux rate) as a function of total acquisition time at contrast-to-noise ratio (CNR) = 20 and $\Delta t = 1$ second. For the estimations of the k_{ep} values of 0.007 minute⁻¹, the relative RMSEs and biases were large, and out of the scales in the plots on the bottom row.

Figure 4. The relative root mean squared errors (RMSEs) and biases of v_p (fractional plasma volume), K^{trans} (transfer constant of a paramagnetic contrast agent from blood to tissue), and k_{ep} (back flux rate) at contrast-to-noise ratio (CNR) = 20, total acquisition time = 480 seconds and $D\Delta t = 1$ second.

TABLE 1
95% Confidence Intervals at CNR = 20, $\Delta t = 1$ second, and Total Acquisition Time = 274 seconds

v_p			K^{trans}			k_{ep}					
True Value	95% CI	1.96 RMSE/M (%)	True Value	95% CI	1.96 RMSE/M (%)	True Value	95% CI	1.96 RMSE/M (%)			
0.01	0.0097	0.0102	2.6	0.001	0.0008	0.0013	22.8	0.0067	-0.0669	0.1297	313.0
0.01	0.0097	0.0103	3.1	0.005	0.0047	0.0054	7.0	0.0333	0.0004	0.0660	98.8
0.01	0.0095	0.0105	5.3	0.010	0.0094	0.0106	6.2	0.0667	0.0374	0.0962	44.0
0.01	0.0085	0.0114	14.5	0.050	0.0478	0.0523	4.5	0.3333	0.3079	0.3591	7.7
0.01	0.0081	0.0119	19.3	0.100	0.0960	0.1042	4.1	0.6667	0.6374	0.6967	4.4
0.01	0.0054	0.0146	45.7	0.500	0.4632	0.5372	7.4	3.3333	3.1538	3.5156	5.4
0.02	0.0194	0.0204	2.5	0.001	0.0006	0.0016	45.3	0.0067	-0.1347	0.2552	323.7
0.02	0.0194	0.0205	2.8	0.005	0.0044	0.0056	11.9	0.0333	-0.0177	0.0905	148.6
0.02	0.0194	0.0206	3.1	0.010	0.0093	0.0107	7.4	0.0667	0.0319	0.1017	52.2
0.02	0.0184	0.0215	7.8	0.050	0.0476	0.0524	4.8	0.3333	0.3065	0.3606	8.1
0.02	0.0180	0.0220	10.1	0.100	0.0958	0.1043	4.3	0.6667	0.6357	0.6978	4.7
0.02	0.0151	0.0248	24.2	0.500	0.4609	0.5398	7.9	3.3333	3.1408	3.5281	5.8
0.05	0.0485	0.0511	2.7	0.001	-0.0006	0.0035	144.0	0.0067	-0.4604	0.7826	385.8
0.05	0.0486	0.0512	2.6	0.005	0.0039	0.0066	25.9	0.0333	-0.0641	0.1650	227.0
0.05	0.0485	0.0515	2.9	0.010	0.0084	0.0117	16.6	0.0667	-0.0102	0.1468	114.9
0.05	0.0482	0.0518	3.6	0.050	0.0471	0.0529	5.7	0.3333	0.3001	0.3662	9.9
0.05	0.0475	0.0524	4.9	0.100	0.0947	0.1053	5.3	0.6667	0.6282	0.7049	5.8
0.05	0.0441	0.0561	12.0	0.500	0.4502	0.5486	9.9	3.3333	3.0863	3.5724	7.3
0.10	0.0939	0.1046	5.4	0.001	-0.3580	0.3746	4394.8	0.0067	-5.3816	6.5883	992.0
0.10	0.0970	0.1023	2.7	0.005	0.0027	0.0085	51.1	0.0333	-0.1424	0.3048	275.4
0.10	0.0972	0.1026	2.7	0.010	0.0073	0.0132	29.1	0.0667	-0.0573	0.2085	175.9
0.10	0.0966	0.1033	3.4	0.050	0.0448	0.0552	10.4	0.3333	0.2729	0.3926	18.0
0.10	0.0961	0.1039	3.9	0.100	0.0916	0.1086	8.5	0.6667	0.6053	0.7295	9.3
0.10	0.0910	0.1086	8.8	0.500	0.4306	0.5738	14.3	3.3333	2.9952	3.6863	10.3

CNR, contrast-to-noise ratio; k_{ep} , back flux rate; K^{trans} , transfer constant of a paramagnetic contrast agent from blood to tissue; RMSE, root mean squared error/mean; v_p , fractional plasma volume.
95% CI: mean $\pm$ 1.96*RMSE for single estimation (eg, single voxel estimation); 1.96 RMSE/M (%): 100*1.96*RMSE/mean.

TABLE 2
95% Confidence Intervals at CNR = 20, $\Delta t = 4$ seconds, and Total Acquisition Time = 274 seconds

v_p			K_{trans}			k_{ep}			
True Value	95% CI	1.96 RMSE/M (%)	True Value	95% CI	1.96 RMSE/M (%)	True Value	95% CI	1.96 RMSE/M (%)	
0.01	0.009	0.010	5.3	0.001	0.0006	0.0017	-0.1416	0.2628	333.6
0.01	0.009	0.011	5.9	0.005	0.0044	0.0057	-0.0216	0.0942	159.6
0.01	0.009	0.011	10.4	0.010	0.0088	0.0112	0.0114	0.1243	83.2
0.01	0.007	0.013	29.3	0.050	0.0458	0.0548	0.3333	0.3865	15.0
0.01	0.006	0.014	41.2	0.100	0.0920	0.1094	0.6667	0.7325	9.2
0.01	-0.003	0.018	141.3	0.500	0.4342	0.6034	3.3333	3.8116	11.8
0.02	0.019	0.021	5.4	0.001	0.0000	0.0027	102.2	0.0067	352.4
0.02	0.019	0.021	5.6	0.005	0.0040	0.0063	22.3	0.0333	211.8
0.02	0.019	0.021	6.2	0.010	0.0086	0.0115	14.4	0.0667	98.8
0.02	0.017	0.023	15.6	0.050	0.0454	0.0550	9.6	0.3333	16.1
0.02	0.016	0.024	21.0	0.100	0.0916	0.1097	9.0	0.6667	9.6
0.02	0.005	0.029	68.4	0.500	0.4266	0.6155	18.1	3.3333	12.8
0.05	0.043	0.056	12.8	0.001	-0.1372	0.1528	1848.7	0.0067	815.9
0.05	0.047	0.052	5.4	0.005	0.0026	0.0087	53.8	0.0333	275.1
0.05	0.047	0.053	5.7	0.010	0.0073	0.0134	29.7	0.0667	171.7
0.05	0.046	0.054	7.3	0.050	0.0445	0.0561	11.6	0.3333	19.6
0.05	0.045	0.055	9.6	0.100	0.0901	0.1114	10.6	0.6667	11.5
0.05	0.033	0.061	29.6	0.500	0.4049	0.6343	22.1	3.3333	15.8
0.10	0.077	0.118	20.8	0.001	-0.4600	0.5258	1498.0	0.0067	771.6
0.10	0.094	0.105	5.4	0.005	-0.0023	0.0157	134.1	0.0333	353.7
0.10	0.094	0.105	5.3	0.010	0.0049	0.0170	55.3	0.0667	234.5
0.10	0.093	0.107	6.8	0.050	0.0394	0.0611	21.5	0.3333	36.4
0.10	0.092	0.108	7.9	0.100	0.0840	0.1178	16.7	0.6667	17.9
0.10	0.077	0.117	20.3	0.500	0.3615	0.6871	31.1	3.3333	22.0

CNR, contrast-to-noise ratio; k_{ep} , back flux rate; K_{trans} , transfer constant of a paramagnetic contrast agent from blood to tissue; RMSE, root mean squared error/mean; v_p , fractional plasma volume.
95% CI: mean $\pm$ 1.96*RMSE for single estimation (eg, single voxel estimation); 1.96 RMSE/M (%): 100*1.96*RMSE/mean.

TABLE 3
95% Confidence Intervals at CNR = 20, Δt = 1second, and Total Acquisition Time = 480 seconds

v_p			K_{trans}			k_{ep}				
True value	95% CI	1.96 RMSE/M (%)	True value	95% CI	1.96 RMSE/M (%)	True value	95% CI	1.96 RMSE/M (%)		
0.01	0.0098	0.0102	2.2	0.001	0.0009	0.0011	-0.0157	0.0373	244.8	
0.01	0.0096	0.0104	3.7	0.005	0.0048	0.0052	0.0213	0.0455	36.2	
0.01	0.0094	0.0106	5.9	0.010	0.0096	0.0104	0.0555	0.0778	16.7	
0.01	0.0087	0.0113	13.2	0.050	0.0485	0.0515	0.3217	0.3451	3.5	
0.01	0.0082	0.0118	17.6	0.100	0.0968	0.1033	0.6667	0.6857	2.9	
0.01	0.0055	0.0145	45.4	0.500	0.4622	0.5379	3.3333	3.5138	5.5	
0.02	0.0195	0.0204	2.2	0.001	0.0008	0.0013	0.0067	-0.0362	0.0762	280.7
0.02	0.0195	0.0205	2.4	0.005	0.0047	0.0053	0.0333	0.0169	0.0500	49.5
0.02	0.0193	0.0207	3.3	0.010	0.0095	0.0105	0.0667	0.0540	0.0795	19.1
0.02	0.0186	0.0214	7.1	0.050	0.0484	0.0516	0.3333	0.3210	0.3455	3.7
0.02	0.0181	0.0219	9.6	0.100	0.0965	0.1036	0.6667	0.6465	0.6872	3.1
0.02	0.0151	0.0248	24.4	0.500	0.4613	0.5396	3.3333	3.1453	3.5221	5.7
0.05	0.0487	0.0510	2.2	0.001	0.0005	0.0018	0.0067	-0.0949	0.1806	321.4
0.05	0.0488	0.0512	2.4	0.005	0.0043	0.0058	0.0333	-0.0053	0.0726	115.9
0.05	0.0487	0.0513	2.6	0.010	0.0091	0.0109	0.0667	0.0425	0.0905	36.1
0.05	0.0483	0.0517	3.4	0.050	0.0481	0.0519	0.3333	0.3185	0.3480	4.4
0.05	0.0477	0.0523	4.5	0.100	0.0958	0.1042	0.6667	0.6422	0.6911	3.7
0.05	0.0437	0.0561	12.5	0.500	0.4514	0.5504	3.3333	3.1026	3.5693	7.0
0.10	0.0973	0.1020	2.4	0.001	-0.0013	0.0043	0.0067	-0.3164	0.5093	428.0
0.10	0.0976	0.1022	2.3	0.005	0.0037	0.0065	0.0333	-0.0305	0.1073	179.3
0.10	0.0976	0.1025	2.5	0.010	0.0083	0.0117	0.0667	0.0198	0.1125	70.1
0.10	0.0970	0.1030	3.0	0.050	0.0466	0.0535	0.3333	0.3074	0.3599	7.9
0.10	0.0963	0.1037	3.7	0.100	0.0931	0.1069	0.6667	0.6261	0.7065	6.0
0.10	0.0912	0.1087	8.7	0.500	0.4305	0.5716	3.3333	3.0002	3.6728	10.1

CNR, contrast-to-noise ratio; k_{ep} , back flux rate; K_{trans} , transfer constant of a paramagnetic contrast agent from blood to tissue; RMSE, root mean squared error/mean; v_p , fractional plasma volume.
95% CI: mean $\pm$ 1.96*RMSE for single estimation (eg, single voxel estimation); 1.96 RMSE/M (%): 100*1.96*RMSE/mean that defines a relative 95% confidence interval.