Published in final edited form as:

Phys Med Biol. 2010 August 21; 55(16): 4807–4823. doi:10.1088/0031-9155/55/16/012.

A Model-Constrained Monte Carlo Method for Blind Arterial Input Function Estimation in Dynamic Contrast-Enhanced MRI: II) *In Vivo* Results

Matthias C. Schabel, Edward V. R. DiBella, Randy L. Jensen, and Karen L. Salzman
Utah Center for Advanced Imaging Research, Department of Radiology, University of Utah Health Sciences Center, 729 Arapleen Drive, Salt Lake City UT 84108-1218

Matthias C. Schabel: matthias.schabel@hsc.utah.edu

Abstract

Accurate quantification of pharmacokinetic model parameters in tracer kinetic imaging experiments requires correspondingly accurate determination of the arterial input function (AIF). Despite significant effort expended on methods of directly measuring patient-specific AIFs in modalities as diverse as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), dynamic positron emission tomography (PET), and perfusion computed tomography (CT), fundamental and technical difficulties have made consistent and reliable achievement of that goal elusive. Here, we validate a new algorithm for AIF determination, the Monte Carlo Blind Estimation (MCBE) method (which is described in detail and characterized by extensive simulations in a companion paper), by comparing AIFs measured in DCE-MRI studies of eight brain tumor patients with results of blind estimation. Blind AIFs calculated with the MCBE method using a pool of concentration-time curves from a region of normal brain tissue were found to be quite similar to the measured AIFs, with statistically significant decreases in fit residuals observed in six of eight patients. Biases between the blind and measured pharmacokinetic parameters were the dominant source of error. Averaged over all eight patients, the mean biases were +7% in K^{trans} , 0% in k_{ep} , -11% in v_p , and +10% in v_e . Corresponding uncertainties (median absolute deviation from best fit line) were 0.0043 min⁻¹ in K^{trans} , 0.0491 min⁻¹ in k_{ep} , 0.29% in v_p , and 0.45% in v_e . Use of a published population-averaged AIF resulted in larger mean biases in three of the four parameters (-23% in K^{trans} , -22% in k_{ep} , -63% in v_p), with the bias in v_e unchanged, and led to larger uncertainties in all four parameters (0.0083 min⁻¹ in K^{trans} , 0.1038 min⁻¹ in k_{ep} , 0.31% in v_p , and 0.95% in v_e). When blind AIFs were calculated from a region of tumor tissue, statistically significant decreases in fit residuals were observed in all eight patients despite larger deviations of these blind AIFs from the measured AIFs. The observed decrease in root-mean-square fit residuals between the normal brain and tumor tissue blind AIFs suggests that the local blood supply in tumors is measurably different from that in normal brain tissue and that the proposed method is able to discriminate between the two. We have shown the feasibility of applying the MCBE algorithm to DCE-MRI data acquired in brain, finding generally good agreement with measured AIFs and decreased biases and uncertainties relative to use of a population-averaged AIF. These results demonstrate that the MCBE algorithm is a useful alternative to direct AIF measurement in cases where acquisition of high-quality arterial input function data is difficult or impossible.

Keywords

Magnetic resonance imaging; dynamic contrast-enhanced; DCE-MRI; arterial input function

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), in conjunction with quantitative pharmacokinetic (PK) modeling, is becoming a standard method of acquiring non-invasive imaging biomarkers for longitudinal studies in oncology and drug development (Leach *et al.* (2005)). DCE-MRI experiments typically involve rapid, repeated acquisition of heavily T_1 -weighted images covering a tumor or other region of interest (ROI) before, during, and after bolus injection of a low molecular weight paramagnetic contrast agent (CA). Time courses of both blood and tissue contrast concentrations are determined from the measured signal changes (Schabel & Parker (2008)), and the resulting curves subjected to regression analysis with one of a variety of pharmacokinetic (PK) models intended to extract physiological parameters of the imaged tissues such as vascular permeability, blood flow, perfusion, interstitial volume, and microvessel density.

The Extended Tofts-Kety model (ETKM) is commonly used for pharmacokinetic analysis of DCE-MRI data (Kershaw & Buckley (2006); Tofts *et al.* (1999)). In this model, the time-dependent contrast concentration in a tissue voxel, $C_t(t)$, is described by:

$$C_t(t) = K^{trans} C_p(t) \star e^{-k_{ep}t} + v_p C_p(t), \quad (1)$$

where $C_p(t)$ is the contrast concentration in the capillary blood plasma (also known as the arterial input function or AIF), K^{trans} is the transfer rate constant, k_{ep} is the washout rate constant, v_p is the volume fraction of blood plasma, and the asterisk represents the convolution operator.

Conventional approaches to the solution of Equation (1) involve regression of the model function to the measured tissue concentration curves using a measured or population-averaged AIF. Regression provides estimates of the pharmacokinetic parameters K^{trans} , k_{ep} , and v_p , from which the extracellular extravascular volume, $v_e = K^{trans}/k_{ep}$, may be computed. While this approach is straightforward, for reasons discussed in detail in a companion paper (Schabel *et al.* (2010)) the need to measure both blood plasma and tissue contrast concentrations simultaneously and accurately is problematic. Furthermore, evidence in the literature suggests that the AIF can be significantly delayed and/or dispersed by passage through the vascular network between a large artery in which it is measured and the capillary bed through which contrast molecules exchange with the tissues of interest (Calamante *et al.* (2006); Ko *et al.* (2007)). As a result, limited ability to accurately determine the AIF is one of the major sources of uncertainty in DCE-MRI pharmacokinetic modeling (Port *et al.* (2001)).

Several methods have recently appeared in the literature that attempt to infer the AIF from measured tissue concentration curves, obviating the need to measure it directly (DiBella *et al.* (1999); Fluckiger *et al.* (2009); Riabkov & DiBella (2002, 2004); Walker-Samuel *et al.* (2007); Yang *et al.* (2004, 2009); Yankeelov *et al.* (2005, 2007)). In a companion paper we describe a new blind AIF estimation algorithm, called Monte Carlo Blind Estimation (MCBE), and characterize it with extensive computer simulations (Schabel *et al.* (2010)). This algorithm directly estimates the AIF from a set of measured tissue curves using a parameterized model function to constrain the functional form of the AIF, and requires neither normal reference tissue curves nor clustering methods to accurately estimate the shape of the true AIF over a wide range of image acquisition parameters. Here we apply the MCBE algorithm to *in vivo* DCE-MRI data acquired in a group of eight patients with histopathologically-confirmed brain tumors in which high-quality measured AIFs were available and compare the performance of the MCBE method to the use of a measured AIF.

Methods

DCE-MRI Measurements

In vivo T_1 -weighted DCE-MRI data was acquired in eight brain cancer patients from whom informed consent was obtained under an Institutional Review Board (IRB)-approved protocol. All eight patients were scanned during standard stereotactic imaging prior to surgery. Patient 7 had a clinical history of antero-septal cardiac infarct, while patient 8 had a clinical history of myocardial infarction, coronary artery disease, diabetes, and transient ischemic attack. Clinical histories of the remaining six patients showed no significant cardiovascular pathologies. After standard non-contrast imaging for pre-operative planning was completed, the lesion of interest was identified and maps of pre-contrast longitudinal relaxation time ($T_{1,0}$) were measured using the variable flip angle (VFA) spoiled gradient echo (SPGR) method with flip angles of $\alpha = 3^\circ$ and 20° (Schabel & Morrell (2009)). DCE-MRI measurements were then made using a fast three-dimensional SPGR sequence (f3d) on a 1.5 T Siemens TIM Avanto scanner (four patients) or a 3 T Siemens TIM Trio and Verio scanners (four patients), with the same field of view used for the VFA $T_{1,0}$ measurements. Pulse sequence parameters chosen to maximize sampling rate within constraints of adequate signal-to-noise ratio (SNR) and coverage of the lesion of interest are given in Table 1 along with other relevant imaging and contrast injection data. Because DCE-MRI data were acquired as add-on measurements to clinically-indicated stereotactic imaging prior to brain surgery, imaging protocols varied slightly to accommodate different scanner hardware and SAR limits. Additional information including patient age, body mass, lesion location, clinical diagnosis, and location of the measured AIF is given in Table 2.

A standard (~ 0.1 mmol/kg) dose of low molecular weight gadolinium chelate contrast agent (Omniscan, GE Healthcare, or Multihance, Bracco Diagnostics) was injected into the antecubital vein through an 18–22 gauge IV followed by a saline flush using a power injector (Medrad Spectra Solaris), with volumes and injection rates as specified in Table 1. Contrast injection was timed to coincide with the end of acquisition of frame N_B of the dynamic data. A twelve-channel transmit/receive head coil was used. Flip angle variation along the slab encoding direction was estimated using a homogeneous phantom of known $T_{1,0}$, and, in three study patients, by assuming a constant $T_{1,0}$ value of 240 ms for subcutaneous fat. These experiments indicated that the impact of flip angle variation near the slab boundaries was small except for roughly the outer 10% of slices at each boundary. To minimize the potential for bias in conversion of signal to contrast concentration (Schabel & Parker (2008)), these slices were excluded from our analysis.

Pre-contrast signal intensity, S_0 , was determined by averaging the N_B baseline images prior to injection and SNR was computed from the ratio of the baseline signal to its standard deviation. Time curves of relative enhancement were generated from the time-dependent DCE-MRI signal, $S(t)$, as $\Xi(t) = (S(t) - S_0)/S_0$. Tissue concentration-time curves, $C(t)$, were then computed by numerical solution of the full nonlinear concentration-dependence of the SPGR signal in the fast exchange limit (Schabel & Parker (2008)), with voxelwise tissue $T_{1,0}$ values determined using the VFA method discussed above. Literature values for the T_1 and T_2^* relaxivities appropriate to the administered contrast agent at the imaging field strength were used (Rohrer *et al.* (2005)). Concentration measurement uncertainties were computed as described in Schabel & Parker (2008). The direct effect of $T_{2,0}^*$ on concentration measurements is eliminated by the use of relative enhancement, and the very short T_E values used in imaging should result in minimal susceptibility-induced signal loss. A $T_{2,0}^*$ value of 50 ms was assumed in calculations of contrast concentration uncertainty.

AIFs were obtained from the middle cerebral arteries in seven of the eight study patients. In patient 6 the middle cerebral arteries were not visible within the imaging field-of-view, so the AIF was measured in the posterior superior sagittal sinus instead. A method similar to that described in (Rijpkema *et al.* (2001)) was used to measure the AIF: curves of relative enhancement within a manually-selected cuboidal ROI that reached their maximum value within 30 seconds of initial bolus arrival and had a maximum enhancement corresponding to a concentration of at least 1 mM were identified. From among this set of curves, those with peak Ξ values in the top 10% were selected and the median relative enhancement of the resulting curves was computed. This time curve of relative enhancement was then converted to concentration in the same way as described for tissue curves (above) to obtain an estimate of the true AIF. A fixed pre-contrast longitudinal relaxation time for whole blood of $T_{1,0} = 1441$ ms was assumed at 1.5T and 1932 ms at 3T (Stanisz *et al.* (2005)). We have attempted to determine measured AIFs as accurately as possible, but, in the absence of a viable and independent “gold standard” method for computing the true AIF *in vivo*, it must be assumed that these measured AIFs are close to truth.

Blind AIF Estimation

The details of the MCBE algorithm are presented in a companion paper (Schabel *et al.* (2010)). For each patient, blind estimation was performed on two distinct pools of tissue curves. The first pool of curves was selected from a cuboidal region of interest (ROI) placed in normal, non-pathologic tissue on the side of the brain contralateral to the known tumor, while the second pool was selected from an ROI covering the enhancing lesion. Images of these ROIs were assessed visually for early enhancement after contrast injection and the ROIs adjusted as necessary to exclude any voxels showing enhancement patterns and morphology obviously characteristic of arterial and/or venous voxels. Tissue curves having a mean post-injection contrast concentration greater than or equal to 0.05 mM were then selected from the curves within the specified ROI. This threshold value, roughly twice the average concentration measurement noise in these data sets, was empirically chosen to produce a reasonable number of curves in the pool (M) with adequate signal-to-noise ratio (SNR). Provided there are sufficiently many curves for the algorithm to choose from (M much greater than the number of curves per subset, $D: M \gg D$), the specific method of curve selection appears to have relatively little impact on the performance of the blind estimation algorithm. The initial bolus arrival time (as opposed to the known contrast injection time) was estimated from the median of the selected time curves by inspection.

When running the MCBE algorithm, we set the number of curves per subset to $D = 12$ and used 50 fixed iterations followed by 50 bootstrapping iterations ($Q = 50 + 50^*$, Schabel *et al.* (2010)). Based on the simulations presented in the companion paper, these settings should be sufficient to obtain good quality blind estimates, but we have not attempted to optimize them for performance. Because measured tissue concentration curves are occasionally affected by artifacts arising from motion, poor estimates of $T_{1,0}$, or other unmodeled effects, in our *in vivo* analysis we apply an auxiliary convergence check at each iteration. This check consists of comparing the median absolute deviation (MAD) of the fit residuals using the starting AIF guess with the MAD using the blind AIF estimate, where:

$$\text{MAD} = \text{median} \left\{ \left| C_t^{\text{meas}}(t_i) - C_t^{\text{fit}}(t_i) \right| \right\}. \quad (2)$$

This estimator is different from the χ^2 estimator that is minimized by the nonlinear regression algorithm, so it serves as a means of identifying robust convergence; curve sets for which χ^2 decreases but MAD does not are rejected and a new curve set drawn. The final blind AIF is normalized to the mean of the last ten measurements of the AIF. Variability in

blind AIF estimates was assessed by computing the 5th and 95th percentiles of the 50 bootstrapping iterations, giving low and high bounds on blind AIFs at the 95% confidence level.

The performance of the MCBE algorithm was assessed in three ways: first by directly comparing the blind and measured AIFs, second by comparing the root-mean-square (RMS) compartment model fit residuals of the tissue curves for the two AIFs, and third by generating joint probability density functions (JPDFs) of pharmacokinetic parameter values derived using the two AIFs. Model fit parameters were also computed using a population AIF (Parker *et al.* (2006)) for comparison, with the arrival time of the population AIF set to the arrival time of the blind AIF for consistency.

Statistical significance of changes in RMS fit residuals was computed, compensating for the presence of additional free model parameters in the blind estimate, using the Bayes Information Criterion (BIC, Schwarz (1978)):

$$\text{BIC} = \ln \frac{1}{nv} \sum_{j=1}^v \sum_{i=1}^n \left(C_t^{\text{meas},j}(t_i) - C_t^{\text{fit},j}(t_i) \right)^2 + \frac{k}{nv} \ln nv, \quad (3)$$

where the first term is the logarithm of the mean squared error, n is the number of measurement time points, v is the number of voxels being compared, and k is the total number of free parameters ($3v$ for the measured AIF and $3v+10$ for the blind AIF). A smaller value of BIC indicates a statistically-significant improvement in quality of fit.

Biases and uncertainties in pharmacokinetic parameter values were determined using a robust linear regression algorithm (MATLAB's robustfit function) to fit blind parameter estimates versus parameters computed using the measured AIF. Bias was computed from the linear slope of the best fit line, while uncertainty was computed as the median absolute deviation (a robust estimator of statistical dispersion) of the fit residuals (Huber (1990)). For normally-distributed data, standard deviation is related to MAD by $\sigma \sim 1.48 \text{ MAD}$. Similar fits were performed on parameter estimates using the population AIF versus the measured AIF.

Results

Figure 1 shows ROIs (white rectangles) and selected voxels for normal brain tissue (aqua), tumor tissue (yellow), and AIF (red) for eight slices of data from patient 5. Representative sets of $D = 12$ randomly-selected tissue time-concentration curves from one iteration of the MCBE algorithm in this patient are shown in Figure 2 for both normal brain tissue (left panel) and tumor tissue (right panel). Corresponding nonlinear regressions are shown by the smooth black curves. Note the difference in concentration scale between the two panels. For clarity, curves are sorted from low to high peak concentration and the baseline concentration of each successive curve is offset vertically by 0.1 mM. Differences in curve shape, diversity, and level of contrast uptake between normal brain tissue and tumor tissue are clearly apparent.

Plots of the measured AIF (blue lines) and the blind AIF estimate derived from normal brain tissue using the MCBE method (dashed red lines) are shown in Figure 3 for all eight study patients. Low (5th percentile) and high (95th percentile) bounds on blind AIF estimates, computed as described above, are shown by the thin red lines. Table 3 gives the pool size (M), and median change (along with the 25th/75th percentile range) in root-mean-square (RMS) fit residuals between fits using the measured and blind AIFs for all eight patients for normal tissue voxels (left columns) and tumor tissue voxels (right columns). Cases where

the change in RMS residuals was significant based on decreased value of BIC for all voxels within the curve pool, computed from Equation (3), are indicated by an asterisk.

Joint probability density functions comparing pharmacokinetic model parameters determined using the measured AIFs with those determined using the normal brain blind AIFs are shown in Figure 4. The JPFDs shown include all tissue voxels within the imaging FOV. Figures 5 and 6 present eight slices of data from Patients 4 and 5, respectively. Mean post-contrast signal is shown in the top panel, with the lesion location indicated by yellow ellipses. Pharmacokinetic parameter maps for K^{trans} , v_e , and v_p computed using the blind AIF from normal brain are shown in the middle panel and those computed using the measured AIF in the bottom panel.

Biases between the pharmacokinetic parameters determined from robust linear regression to the JPFD data plotted in Figure 4, averaged over all eight patients, were +7% (range -8% to +32%) in K^{trans} , 0% (range -9% to +16%) in k_{ep} , -11% (range -33% to +6%) in v_p , and +10% (range -3% to +40%) in v_e . Corresponding uncertainties were 0.0043 min⁻¹ in K^{trans} (range 0.0008 min⁻¹ to 0.0085 min⁻¹), 0.0491 min⁻¹ in k_{ep} (range 0.0187 min⁻¹ to 0.0938 min⁻¹), 0.29% in v_p (range 0.05% to 1.22%), and 0.45% in v_e (range 0.12% to 0.80%). Use of the population-averaged AIF proposed by Parker *et al.* (2006) gave biases of: -23% (range -41% to -6%) in K^{trans} , -22% (range -42% to +2%) in k_{ep} , -63% (range -87% to -39%) in v_p , and +10% (range +3% to +22%) in v_e , and uncertainties of: 0.0083 min⁻¹ in K^{trans} (range 0.0032 min⁻¹ to 0.0150 min⁻¹), 0.1038 min⁻¹ in k_{ep} (range 0.0515 min⁻¹ to 0.1854 min⁻¹), 0.31% in v_p (range 0.08% to 1.15%), and 0.95% in v_e (range 0.30% to 2.11%). Robust linear regression to JPFD data comparing the measured AIF to the blind tumor tissue AIF for tumor voxels alone, averaged over all eight patients, showed mean biases of +7% (range -22% to +73%) in K^{trans} , -13% (range -39% to +27%) in k_{ep} , -5% (range -36% to +41%) in v_p , and +16% (range +3% to +27%) in v_e . Corresponding uncertainties were 0.0053 min⁻¹ in K^{trans} (range 0.0014 min⁻¹ to 0.0095 min⁻¹), 0.0323 min⁻¹ in k_{ep} (range 0.0107 min⁻¹ to 0.0719 min⁻¹), 0.21% in v_p (range 0.07% to 0.36%), and 0.59% in v_e (range 0.08% to 1.07%).

The left panel of Figure 7 compares the measured AIF (blue) with the blind AIFs estimated from normal brain tissue (dashed red line) and tumor tissue (dot-dashed black line) in patient 4, in whom the greatest discrepancy between normal and tumor blind AIFs was observed. Maps of pharmacokinetic parameters for a single slice through the tumor are shown in the right panel, with K^{trans} in the top row, k_{ep} in the second row, v_p in the third row, and percent change in RMS fit residuals between measured and blind AIFs in the fourth row. The maps computed using the measured AIF are plotted in the first column, with the normal tissue blind AIF in the second column, and with the tumor tissue blind AIF in the third column. Median parameter values derived from the normal tissue blind AIF, averaged over all tumor voxels, were: $K^{trans} = 0.089$ min⁻¹, $k_{ep} = 0.55$ min⁻¹, $v_p = 3.6\%$, and $v_e = 15.5\%$. These values showed a 15% increase in K^{trans} relative to the measured AIF, an increase of 6% in k_{ep} , an increase of 1% in v_p , and an increase of 8% in v_e , with a median decrease in RMS fit residuals of 2.1%. In contrast, use of the tumor AIF resulted in a 73% increase in K^{trans} , an increase of 27% in k_{ep} , an increase of 41% in v_p , an increase of 22% in v_e , and a decrease in RMS fit residuals of 8.2% in this patient.

Discussion

Application of the Monte Carlo Blind Estimation algorithm to *in vivo* DCE-MRI data acquired in eight brain tumor patients demonstrates that it is possible to accurately reproduce measured arterial input functions using only concentration-time curves from normal brain tissue. The blind AIFs shown in Figure 3 show good agreement with the measured AIFs, and

result in relatively small errors in pharmacokinetic parameter estimates that predominantly manifest as linear biases (Figure 4). Statistically-significant decreases in the RMS model fit residuals (Table 3) were observed in six of the eight patients using the blind AIF derived from normal brain tissue, with residuals being comparable (within $\pm 0.5\%$) to those from the measured AIFs in the other two patients. These results suggest that the MCBE algorithm is capable of extracting AIFs directly from tissue curves without inclusion of arterial voxels. The resulting model fits are at least as good as, and generally better than, those obtained by direct measurement.

Our analysis of the MCBE method *in vivo* has two principal limitations. First, while we assume that the measured AIF is the reference “truth”, the reality is somewhat more complex due to the difficulty of making accurate measurements of arterial blood concentration *in vivo* (Cheng (2007)) as well as the further difficulty of assessing the uncertainty in those measurements. While we have attempted to minimize the effects of the numerous difficulties associated with direct measurement of the arterial input function (discussed at length in the Introduction of the companion paper), the lack of an independent “gold-standard” measurement of the true AIF makes it difficult to determine the source and significance of discrepancies between measured and blind AIFs in this study.

Second, while the MCBE algorithm accurately reproduces the shape of measured AIFs in our study population, it cannot determine the global scale factor. This limitation arises from the fundamental invariance of Equation (1) to simultaneous rescaling of $C_p(t)$, K^{trans} , and v_p (Schabel *et al.* (2010)). As a consequence, a single reference measurement of blood plasma contrast concentration is needed to obtain quantitative pharmacokinetic parameter estimates. Here we have used the tails of the measured AIFs to provide the needed scale factor, which reintroduces a dependence on blood pool measurements. In practice, however, this limitation is not severe. Because the needed measurement is obtained from the tail of the AIF, when the bolus is well-mixed in the blood pool, it is much less affected by saturation effects, arrival time, and limited temporal resolution than first-pass measurements. Furthermore, this scale factor can be obtained, for example, by imaging a major artery or vein with a pulse sequence specifically tailored for quantitative blood pool concentration measurement (such as one of the numerous quantitative T_1 sequences) at the end of the data acquisition period. Nevertheless, a well-characterized, accurate, and thoroughly-validated MRI method for absolute blood pool concentration measurement is needed for the MCBE algorithm to make true, quantitative estimates of the AIF and pharmacokinetic parameter values.

Another potential limitation of this study is the heterogeneity of acquisition parameters used during data collection, including contrast agent, scanner field strength, and imaging pulse sequence parameters. Since the processing and analysis methods used here compensated for known differences in contrast agent relaxivities and imaging parameters, the primary sources of potential biases have been addressed. The absence of any obvious systematic differences in either AIF estimates or kinetic parameter values between the 1.5T and 3T studies, lends support to this contention.

In patients 3, 4, and 7 the measured and normal tissue blind AIFs show consistency between the first-pass peak amplitude and width, recirculation peak, and tail height and slope. Patient 6 shows very similar scale and shape, but a delay is clearly visible between the blind and measured AIFs; this delay presumably stems from the fact that the measured AIF was determined from the venous sinuses in this patient rather than from the arterial blood, and provides evidence that the MCBE algorithm is able to correctly determine the tissue bolus arrival time. Discrepancies are visible in the recirculation phase of the data from patients 1 and 5, but otherwise the blind and measured AIFs show good agreement. In the former, the observed discrepancy in the recirculation peak height lies outside the confidence bounds for

the blind AIF estimates, suggesting a systematic discrepancy, while the latter is mostly consistent with the upper variability bound of the blind estimates. The blind estimate of the first-pass peak height in patient 2 is approximately 20% greater than in the measured AIF, but the measured AIF still lies within the confidence bounds. Because most sources of systematic error in AIF measurement will tend to lead to underestimates in bolus peak height (in particular saturation, finite sampling rate, and partial volume effects), this may indicate the impact of one or more of these issues in the measured AIF in this patient. Finally, the width of the blind AIF in patient 8 is substantially different than measured, though the upslope and tail are in reasonable agreement and the upper blind confidence bound is consistent with the measured AIF. The visibly higher noise level in the measured AIF in this patient indicates that it was of lower quality than those in the other seven patients. It is worth noting that the confidence bounds tend to be broadest in the first pass peak of the AIF, and narrowest in the tail region. Also notable is the presence of inter-patient variability in the tightness of the confidence bounds stemming from differences in the signal-to-noise ratio (SNR), diversity, and size of the tissue curve pool used to generate the blind AIF estimates.

The principal metric of concern for characterization of blind AIFs relative to measured AIFs is the accuracy with which pharmacokinetic model parameters can be estimated. Figure 4 shows joint probability distribution functions for all eight study patients comparing values of K^{trans} , k_{ep} , v_e , and v_p determined using the measured AIFs (x-axes) with values determined using the blind AIFs from normal brain tissue (y-axes). A white line drawn along the diagonals indicates the line of perfect agreement that would be achieved if there were exact correspondence between the two sets of parameter values. In all eight patients, there is strong linear correlation between measured and blind parameter estimates of K^{trans} , k_{ep} , and v_e and somewhat weaker correlation between v_p values. Robust linear regression to JPFD data shows that blind AIF estimates from normal tissue provide pharmacokinetic parameter estimates that generally have lower bias and uncertainty in the patient data than those obtained using a population-averaged AIF.

The presence of voxels with sufficient post-contrast enhancement to allow blind AIF estimation in both tumor and normal brain tissues is shown for patient 4 in Figure 1. While nearly all tumor voxels show enhancement reaching our chosen threshold value of post-contrast concentration, as indicated by the yellow voxels, fewer of those in the normal brain, shown in aqua, do so. This behavior is consistent with what is expected in the presence of an intact blood-brain barrier (BBB): enhancement of normal brain tissue stems primarily from the vascular contribution, with essentially no leakage of contrast into healthy brain tissue. In contrast, brain tumors, particularly those with high tumor grade, demonstrate disruption of the BBB through elevated vascular permeability, an effect that is responsible for generally higher contrast concentration levels observed within tumors. Thus, the most strongly-enhancing voxels in intact brain tissue are generally those with a high vascular volume, while strongly-enhancing tumor voxels may arise from regions with either high vascular volume or high vascular permeability, with disruption of the BBB enhancing transendothelial contrast transport.

Contrast concentration-time curves shown in Figure 2 for normal brain tissue (left panel) and tumor tissue (right panel) clearly demonstrate the differences between the characteristic uptake in these two tissues. Peak and mean concentrations in normal brain tissue are both significantly lower than those in tumor, curve shape is generally more similar to a purely vascular signal (with an early rise to peak followed by a decreasing tail), and diversity in curve shape is generally lower. Nevertheless, in both normal and tumor tissues, the MCBE algorithm converges robustly, consistent with the simulation results presented in the companion paper. Blind AIF estimates derived from tumor tissues show statistically-

significant decreases in fit residuals for tumor voxels in all eight patients, and some characteristic differences are seen when comparing to the measured AIFs. In particular, in a number of blind tumor AIFs the recirculation and washout phases appear to be suppressed relative to those in normal tissue blind AIFs, and there is a perceptible lag in the leading edge of contrast arrival in the blood pool.

Our observation that blind AIFs estimated directly from tumor tissue curves deviate from those estimated from normal tissues in the same patients is consistent with results in sarcomas (Fluckiger *et al.* (2009)), where it was found that blind AIF estimates from tumor tissue ROIs manifested delay and dispersion relative to the AIF measured in arterial blood. The idea of a local AIF is also supported by observation of delay and dispersion of the AIF in dynamic susceptibility contrast (DSC) studies in the brain (Calamante *et al.* (2006); Ko *et al.* (2007)). Despite this, the inability to directly validate predicted discrepancies between the AIF in normal brain tissue and the AIF in tumor tissue remains a limitation of the work described here. Some support can be inferred from changes in RMS fit residuals. Observed changes in fit residuals using the normal brain blind AIF are smaller, and are relatively uniform and consistent throughout the brain. In contrast, the tumor blind AIFs generally show large decreases in RMS residuals in the tumor itself, but minimal changes or increases in unaffected brain tissues.

The discussion here has focused on the ETKM, but the methods described are easily extended to subsume different types of pharmacokinetic models such as those that account for spatial variation in bolus arrival time (Orton *et al.* (2007)), finite capillary filling times (Koh *et al.* (2006); St. Lawrence & Lee (1998)), or deviation of water exchange from the fast exchange limit (Li *et al.* (2005)). Indeed, while our analysis emphasizes tissue concentration curves derived from DCE-MRI measurements, data from any quantitative imaging modality (such as CT, PET, and SPECT) could be used instead. The MCBE method appears to be a practical and effective algorithm for blind AIF estimation that generalizes earlier algorithms relying on clustering of tissue curves.

Acknowledgments

M. C. S. and E. V. R. D. would like to thank the Ben and Iris Margolis Foundation and the Benning Foundation for their support of this work. M. C. S. also gratefully acknowledges the National Institute for Biomedical Imaging and Bioengineering for its support of this work through the K25 Career Development Award #K25EB005077.

References

- Calamante, Fernando; Willats, Lisa; Gadian, David G.; Connelly, Alan. Bolus delay and dispersion in perfusion MRI: implications for tissue predictor models in stroke. *Magn Reson Med.* 2006; 55(5): 1180–5. [PubMed: 16598717]
- Cheng, Hai-Ling Margaret. T1 measurement of flowing blood and arterial input function determination for quantitative 3D T1-weighted DCE-MRI. *J Magn Reson Imaging.* 2007; 25(5):1073–8. [PubMed: 17410576]
- DiBella EV, Clackdoyle R, Gullberg GT. Blind estimation of compartmental model parameters. *Phys Med Biol.* 1999; 44(3):765–80. [PubMed: 10211809]
- Fluckiger J, Schabel MC, DiBella EVR. Model-based blind estimation of kinetic parameters in dynamic contrast enhanced (DCE)-MRI. *Magn Reson Med.* 2009; 62(6):1477–1486. [PubMed: 19859949]
- Huber, PJ. *Robust Statistics.* John Wiley and Sons; New York: 1981.
- Kershaw, Lucy E.; Buckley, David L. Precision in measurements of perfusion and microvascular permeability with T1-weighted dynamic contrast-enhanced MRI. *Magn Reson Med.* 2006; 56(5): 986–92. [PubMed: 16986107]

- Ko, Linda; Salluzzi, Marina; Frayne, Richard; Smith, Michael. Reexamining the quantification of perfusion MRI data in the presence of bolus dispersion. *J Magn Reson Imaging*. 2007; 25(3):639–43. [PubMed: 17326085]
- Koh TS, Cheong LH, Tan CK, Lim CC. A distributed parameter model of cerebral blood-tissue exchange with account of capillary transit time distribution. *Neuroimage*. 2006; 30(2):426–35. [PubMed: 16246589]
- Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, Jayson GC, Judson IR, Knopp MV, Maxwell RJ, McIntyre D, Padhani AR, Price P, Rathbone R, Rustin GJ, Tofts PS, Tozer GM, Vennart W, Waterton JC, Williams SR, Workman P. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. *Br J Cancer*. 2005; 92(9):1599–610. [PubMed: 15870830]
- Li, Xin; Rooney, William D.; Springer, Charles S. A unified magnetic resonance imaging pharmacokinetic theory: intravascular and extracellular contrast reagents. *Magn Reson Med*. 2005; 54(6):1351–9. [PubMed: 16247739]
- Orton MR, Collins DJ, Walker-Samuel S, d’Arcy JA, Hawkes DJ, Atkinson D, Leach MO. Bayesian estimation of pharmacokinetic parameters for DCE-MRI with a robust treatment of enhancement onset time. *Phys Med Biol*. 2007; 52(9):2393–408. [PubMed: 17440242]
- Parker, Geoff JM.; Roberts, Caleb; Macdonald, Andrew; Buonaccorsi, Giovanni A.; Cheung, Sue; Buckley, David L.; Jackson, Alan; Watson, Yvonne; Davies, Karen; Jayson, Gordon C. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magn Reson Med*. 2006; 56(5):993–1000. [PubMed: 17036301]
- Port RE, Knopp MV, Brix G. Dynamic contrast-enhanced MRI using Gd-DTPA: Interindividual variability of the arterial input function and consequences for the assessment of kinetics in tumors. *Magn Reson Med*. 2001; 45:1030–1038. [PubMed: 11378881]
- Riabkov, Dmitri Y.; DiBella, Edward VR. Estimation of kinetic parameters without input functions: analysis of three methods for multichannel blind identification. *IEEE Trans on Biomed Eng*. 2002; 49(11):1318–27.
- Riabkov, Dmitri Y.; DiBella, Edward VR. Blind identification of the kinetic parameters in three-compartment models. *Phys Med Biol*. 2004; 49(5):639–64. [PubMed: 15070194]
- Rijpkema M, Kaanders JH, Joosten FB, van der Kogel AJ, Heerschap A. Method for quantitative mapping of dynamic MRI contrast agent uptake in human tumors. *J Magn Reson Imaging*. 2001; 14(4):457–63. [PubMed: 11599071]
- Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. *Invest Radiol*. 2005; 40(11):715–24. [PubMed: 16230904]
- Schabel, Matthias C.; Fluckiger, Jacob U.; DiBella, Edward VR. A Model-Constrained Monte Carlo Method for Blind Arterial Input Function Estimation in Dynamic Contrast-Enhanced MRI : I) Simulations. *Phys Med Biol*. 2010; XX(X):XX–XX.
- Schabel, Matthias C.; Morrell, Glen R. Uncertainty in T(1) mapping using the variable flip angle method with two flip angles. *Phys Med Biol*. 2009; 54(1):N1–8. [PubMed: 19060359]
- Schabel, Matthias C.; Parker, Dennis L. Uncertainty and bias in contrast concentration measurements using spoiled gradient echo pulse sequences. *Phys Med Biol*. 2008; 53(9):2345–73. [PubMed: 18421121]
- Schwarz G. Estimating the dimension of a model. *The Annals of Statistics*. 1978; 6(2):461–464.
- StLawrence KS, Lee TY. An adiabatic approximation to the tissue homogeneity model for water exchange in the brain : I. theoretical derivation. *J Cereb Blood Flow Metab*. 1998; 18:1365–1377. [PubMed: 9850149]
- Stanisz, Greg J.; Odobina, Ewa E.; Pun, Joseph; Escaravage, Michael; Graham, Simon J.; Bronskill, Michael J.; Henkelman, R Mark. T1, T2 relaxation and magnetization transfer in tissue at 3T. *Magn Reson Med*. 2005; 54(3):507–512. [PubMed: 16086319]
- Tofts PS, Brix G, Buckley David L, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from

- dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*. 1999; 10(3):223–32. [PubMed: 10508281]
- Walker-Samuel S, Parker CC, Leach MO, Collins DJ. Reproducibility of reference tissue quantification of dynamic contrast-enhanced data: comparison with a fixed vascular input function. *Phys Med Biol*. 2007; 52(1):75–89. [PubMed: 17183129]
- Yang, Cheng; Karczmar, Gregory S.; Medved, Milica; Stadler, Walter M. Estimating the arterial input function using two reference tissues in dynamic contrast-enhanced MRI studies: fundamental concepts and simulations. *Magn Reson Med*. 2004; 52(5):1110–7. [PubMed: 15508148]
- Yang, Cheng; Karczmar, Gregory S.; Medved, Milica; Oto, Aytekin; Zamora, Marta; Stadler, Walter M. Reproducibility assessment of a multiple reference tissue method for quantitative dynamic contrast enhanced-MRI analysis. *Magn Reson Med*. 2009; 61(4):851–9. [PubMed: 19185002]
- Yankeelov, Thomas E.; Luci, Jeffrey J.; Lepage, Martin Li; Rui, Debusk; Laura, Lin; Charles, P.; Price, Ronald R.; Gore, John C. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. *Magn Reson Imaging*. 2005; 23(4):519–29. [PubMed: 15919597]
- Yankeelov, Thomas E.; Cron, Greg O.; Addison, Christina L.; Wallace, Julia C.; Wilkins, Ruth C.; Pappas, Bruce A.; Santyr, Giles E.; Gore, John C. Comparison of a reference region model with direct measurement of an AIF in the analysis of DCE-MRI data. *Magn Reson Med*. 2007; 57(2): 353–61. [PubMed: 17260371]

Figure 1. Regions of interest (white rectangles) and corresponding tumor (yellow), normal tissue (aqua), and AIF (red) voxels for eight slices of data from patient 5.

Figure 2. Twelve tissue curves (gray lines) and corresponding nonlinear regressions (black lines) for a single MCBE subset ($D = 12$) of normal brain tissue (left panel) and tumor tissue (right panel) from patient 5 are shown. Successive curves are offset vertically by 0.1 mM for visual clarity.

Figure 3.

Plots comparing the measured AIF (solid blue lines) and the blind AIF derived from normal brain tissue (dashed red lines) for all eight study patients. 5th and 95th percentile confidence bounds on the blind AIF estimates are shown by the thin red lines.

Figure 4.

Joint probability density functions (JPDFs) for the estimated pharmacokinetic parameters K^{trans} (top row), k_{ep} (second row), v_e (third row), and v_p (fourth row) in all eight study patients, computed using the measured AIF (horizontal axis) versus the same parameters computed using the blind AIF derived from normal brain tissue (vertical axis). All tissue voxels within the imaging FOV were included.

Figure 5. Comparison of pharmacokinetic model fitting in patient 4, using the measured AIF and the blind AIF derived from normal brain tissue. Eight slices are shown, with mean post-contrast signal in the upper panel. A yellow ellipse is used to indicate the lesion location on the mean signal images. The middle panel shows K^{trans} (min^{-1}), v_e , and v_p computed using the blind AIF in the first, second, and third rows, respectively. The lower panel shows the same parameters computed using the measured AIF.

Figure 6. Comparison of pharmacokinetic model fitting in patient 5, using the measured AIF and the blind AIF derived from normal brain tissue, plotted as in Figure 5. Note that the upper range of K_{trans} extends to 1 min^{-1} in this figure.

Figure 7.

Comparison of the measured AIF (blue), blind AIF derived from normal tissue (dashed red line), and blind AIF derived from tumor tissue (dot-dashed black line) for patient 4 (left panel). Corresponding maps of the pharmacokinetic parameters for a single slice through the tumor, along with percent change in root-mean-square fit residuals for the normal blind and tumor blind AIFs relative to fitting with the measured AIF (ΔRMS), are shown in the right panel.

\$watermark-text

\$watermark-text

\$watermark-text

Table 1

MRI parameters for the DCE-MRI scans performed in 8 study patients. Repetition time (T_R) and echo time (T_E) are given in milliseconds, flip angle (α) in degrees, resolution in mm, length of dynamic scan (t_{max}) in minutes, sampling interval (Δt) in seconds, and total administered contrast dose in mmol/kg of body mass. Total number of scans (N_{meas}) is given along with number of scans prior to contrast injection (N_B). Contrast injection information is provided as V_C/R_C CA + V_G/R_G , where V_C represents the volume of contrast injected (ml), R_C the rate of contrast injection (ml/s), CA the contrast agent used (either Omniscan, OS, or Multihance, MH), V_G the volume of saline flush injected (ml), and R_G the rate of saline injection (ml/s).

Patient	Field	T_R	T_E	α	Matrix	Resolution	t_{max}	Δt	N_{meas}	N_B	Contrast injection	Dose
1	3T	2.80	1.02	17°	128 × 88 × 24	2.0 × 2.0 × 3.0	7.65	3.86	120	10	20/4 MH + 20/2	0.103
2	3T	2.82	1.04	17°	128 × 88 × 32	2.0 × 2.0 × 2.0	7.6	4.60	100	10	16/2 MH + 20/2	0.086
3	3T	2.73	0.88	19°	128 × 64 × 32	2.5 × 2.5 × 2.5	6.40	3.23	120	10	10/2.5 MH + 20/4	0.079
4	1.5T	3.08	1.18	20°	128 × 104 × 32	1.7 × 1.7 × 2.0	8.36	5.97	85	20	20/4 OS + 20/2	0.085
5	1.5T	3.08	1.19	20°	128 × 96 × 32	1.8 × 1.8 × 1.8	7.4	3.74	120	20	12/4 MH + 20/2	0.098
6	3T	2.91	1.08	18°	128 × 104 × 24	1.6 × 1.6 × 2.0	7.4	3.00	150	10	19/4 MH + 20/2	0.089
7	1.5T	2.92	1.09	25°	128 × 104 × 36	1.5 × 1.5 × 1.5	8.4	5.10	120	10	10/4 MH + 20/2	0.092
8	1.5T	3.45	1.38	15°	256 × 224 × 16	0.9 × 0.9 × 5.0	8.11	4.23	115	10	20/4 OS + 20/2	0.094

\$watermark-text

\$watermark-text

\$watermark-text

Table 2

Patient, lesion, and AIF measurement information for the eight study participants.

Patient	Age (yr)	Weight (kg)	Lesion location	Diagnosis	Measured AIF
1	64	97.5	R temporal lobe	glioblastoma multiforme	middle cerebral artery
2	43	92.5	L temporal lobe	glioblastoma multiforme	middle cerebral artery
3	49	63.5	R temporal lobe	glioblastoma multiforme	middle cerebral artery
4	51	117.9	R parietal lobe	glioblastoma multiforme	middle cerebral artery
5	22	60.9	R temporal lobe	pleomorphic xanthoastrocytoma	middle cerebral artery
6	20	106.6	L temporal lobe	glioblastoma multiforme	posterior superior sagittal sinus
7	70	54.4	R temporal lobe	meningioma	middle cerebral artery
8	68	106	L temporal lobe	glioblastoma multiforme	middle cerebral artery

\$watermark-text

\$watermark-text

\$watermark-text

Table 3

Pool size, M , and median and 25th/75th percentile changes in RMS fit residuals between measured and blind AIFs for voxels within the normal brain or tumor ROI where both K^{trans} and K_{ep} were significant at the 95% level. Asterisks indicate cases where fit quality (quantified by the Bayes Information Criterion) was significantly better for the blind AIF estimate than for the measured AIF.

Patient	normal brain ROI			tumor ROI		
	M	ΔRMS	25%/75%	M	ΔRMS	range
1	253	-1.5%*	(-5.0%/+0.5%)	321	-9.0%*	(-21.6%/-1.9%)
2	487	-0.4%	(-0.4%/+2.6%)	1117	-2.9%*	(-6.7%/+0.1%)
3	324	-3.2%*	(-8.4%/-0.8%)	890	-20.0%*	(-33.3%/-8.8%)
4	341	-0.3%*	(-1.1%/+0.1%)	919	-8.2%*	(-15.3%/-2.4%)
5	218	-1.0%*	(-3.8%/+0.0%)	850	-3.4%*	(-7.7%/-0.6%)
6	133	-1.7%*	(-5.6%/-0.3%)	974	-4.4%*	(-10.6%/-1.6%)
7	1038	-3.4%*	(-7.1%/-1.0%)	2333	-12.3%*	(-19.4%/-5.4%)
8	842	+0.3%	(-0.5%/+1.2%)	5167	-0.4%*	(-2.1%/+1.0%)