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A Model-Constrained Monte Carlo Method for Blind Arterial Input Function Estimation in Dynamic Contrast-Enhanced MRI: I) Simulations

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Abstract

Widespread adoption of quantitative pharmacokinetic modeling methods in conjunction with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has led to increased recognition of the importance of obtaining accurate patient-specific arterial input function (AIF) measurements. Ideally, DCE-MRI studies use an AIF directly measured in an artery local to the tissue of interest, along with measured tissue concentration curves, to quantitatively determine pharmacokinetic parameters. However, the numerous technical and practical difficulties associated with AIF measurement have made the use of population-averaged AIF data a popular, if suboptimal, alternative to AIF measurement. In this work, we present and characterize a new algorithm for determining the AIF solely from the measured tissue concentration curves. This Monte Carlo Blind Estimation (MCBE) algorithm estimates the AIF from subsets of D concentration-time curves drawn from a larger pool of M candidate curves via nonlinear optimization, doing so for multiple (Q) subsets and statistically averaging these repeated estimates. The MCBE algorithm can be viewed as a generalization of previously published methods that employ clustering of concentration-time curves and only estimate the AIF once. Extensive computer simulations were performed over physiologically- and experimentally-realistic ranges of imaging and tissue parameters, and the impact of choosing different values of D and Q was investigated. We found the algorithm to be robust, computationally-efficient, and capable of accurately estimating the AIF even for relatively high noise levels, long sampling intervals, and low diversity of tissue curves. With the incorporation of bootstrapping initialization, we further demonstrated the ability to blindly estimate AIFs that deviate substantially in shape from the population-averaged initial guess. Pharmacokinetic parameter estimates for K^{trans} , k_{ep} , v_p , and v_e all showed relative biases and uncertainties of less than 10% for measurements having a temporal sampling rate of 4 seconds and a concentration measurement noise level of $\sigma = 0.04$ mM. A companion paper discusses the application of the MCBE algorithm to DCE-MRI data acquired in eight patients with malignant brain tumors.

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 a widely-used method with applications in a number of areas including oncology (Evelhoch (1999); Hylton (2006); Padhani & Husband (2001)), cerebral and cardiac perfusion (Batchelor *et al.* (2007); Elkington *et al.* (2005); Harrer *et al.* (2004); Jerosch-Herold & Muehling (2008); Lee & Johnson (2009); Lüdemann

et al. (2009); Pack *et al.* (2008); Sourbron *et al.* (2009)), drug development (Batchelor *et al.* (2007); Gossmann *et al.* (2002); Liu *et al.* (2005); O'Connor *et al.* (2007); Wilmes *et al.* (2007)), and musculoskeletal radiology (Hodgson *et al.* (2007); Workie & Dardzinski (2005); Workie *et al.* (2004); Zierhut *et al.* (2007)). Quantitative analysis of DCE-MRI data involves numerical solution of a model representing the time dependence of contrast concentration on pharmacokinetic model parameters. The Extended Tofts-Kety model (ETKM) is one of the most popular of a number of models that have been applied to 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 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. Conventionally, both $C_p(t)$ and $C_t(t)$ are measured, and the pharmacokinetic parameters K^{trans} , k_{ep} , and v_p are determined by nonlinear regression. A fourth parameter, v_e , representing the extracellular extravascular volume fraction, is defined as $v_e = K^{trans}/k_{ep}$.

Solution of Equation (1) involves fitting the model to the measured tissue concentration curves, assuming an accurately measured AIF. This conventional approach to pharmacokinetic modeling is well-understood and commonly-used. However, the requirement for simultaneous, accurate estimates of blood plasma and tissue contrast concentrations poses a number of practical difficulties. First is the need for a major artery in the imaging field of view (FOV). In many situations, it is difficult to find a suitable artery near the tissue of interest, so either an extended FOV must be used, compromising spatial and/or temporal resolution, or an assumed functional form must be used in lieu of a measured AIF, neglecting physiologic variation in the distribution and elimination of contrast in the blood pool and causing errors in the fitted pharmacokinetic parameters (Ahearn *et al.* (2004)). Second, the dynamic range of the imaging pulse sequence must be sufficiently large to allow accurate quantification of both the large first-pass bolus peak concentration and the much smaller tissue concentrations. Unfortunately, pulse sequences with high sensitivity to low contrast concentrations suffer from significant nonlinearity and signal saturation at high concentrations. Conversely, sequences that are tuned to high concentrations compromise sensitivity at low concentration levels (Schabel & Parker (2008)). Third, image acquisition must be sufficiently rapid to adequately sample the first pass of the contrast bolus. Insufficiently rapid imaging can result in inaccurate measurement of the AIF and vascular component in tissue (v_p) by missing the bolus peak. The rapid temporal variation of contrast concentration in the blood pool with bolus contrast injection necessitates higher sampling rates for AIF characterization than are generally necessary to accurately characterize tissue concentration (Cheng (2008); Henderson *et al.* (1998)). Fourth, partial volume effects, pulsatility, and inflow artifacts can further reduce the accuracy with which the AIF can be experimentally determined (Cheng (2007); Kjølby *et al.* (2009); Kotys *et al.* (2007); van Osch *et al.* (2001, 2003, 2005)). Finally, even if the AIF can be accurately measured in an artery near the tissue of interest, a growing body of evidence suggests that the incoming contrast bolus is often significantly delayed and/or dispersed by the time it has passed through the vascular network and reached the capillary bed through which contrast molecules are exchanged with the tissues of interest (Calamante *et al.* (2006); Ko *et al.* (2007)). For these reasons, accurate quantification of the true tissue AIF remains a major challenge to pharmacokinetic modeling using DCE-MRI data.

Recently, methods have been proposed in the literature that eliminate the need to directly measure the AIF, including reference region models (Yang *et al.* (2004, 2009); Yankeelov *et al.* (2005, 2007)) and blind estimation (DiBella *et al.* (1999); Fluckiger *et al.* (2009); Riabkov & DiBella (2002, 2004)). While the reference region methods have shown some promise, they are fundamentally limited by the need for inclusion of a region of normal tissue within the FOV, by the assumption that the pharmacokinetic parameters of this normal tissue are well known, and by the assumption that the AIF in the tissue of interest is identical to the AIF in the reference tissue. Methods that operate without assuming any knowledge of reference regions can be divided into unconstrained (DiBella *et al.* (1999); Riabkov & DiBella (2004)) and constrained (Fluckiger *et al.* (2009); Yang *et al.* (2004, 2009)) blind estimation approaches. Unconstrained blind estimation was shown to have relatively high noise sensitivity compared to the use of a parameterized arterial input function (Riabkov & DiBella (2002)). Previous approaches have relied on unsupervised clustering of the measured tissue curves to reduce noise and provide reasonable AIF estimates.

Here we present a new approach to blind estimation that directly estimates the AIF from many different sets of measured tissue curves in a Monte Carlo fashion. This method, which we refer to as Monte Carlo Blind Estimation (MCBE), requires neither normal reference tissue curves nor clustering methods to accurately estimate the true AIF, and can be considered a generalization of previous methods (see Discussion). The utility and accuracy of MCBE are demonstrated here using extensive computer simulations. We consider finite sampling rate, concentration measurement noise, quality of the initial AIF estimate, and convergence rate of the MCBE algorithm as it depends on various parameters. Both the fidelity of the blind estimates of the AIF and the accuracy of pharmacokinetic parameter estimates based on the resulting estimated AIFs are compared to truth, and the regime in which the MCBE algorithm is practical and useful is assessed. Results of application of the MCBE method to DCE-MRI data acquired in malignant human brain tumors are presented and discussed in a companion paper (Schabel *et al.* (2010)).

Methods

Input Function Model

We model AIFs with a flexible parameterized functional form (Schabel & Parker (2008)), essentially identical to the parameterization used for the alternating minimization with model (AMM) blind estimation method (Fluckiger *et al.* (2009)):

$$C_p(t) = \sum_{n=1}^3 a_n G(t - \Delta_n, \alpha_n, \tau_n) + a_4 S(t - \Delta_4, \alpha_4, \tau_4, T), \quad (2)$$

which is the sum of three normalized gamma variate curves:

$$G(t, \alpha, \tau) = \begin{cases} 0 & t < 0 \\ t^{\alpha-1} e^{-t/\tau} / N_G & t \geq 0, \end{cases} \quad (3)$$

and a sigmoid curve:

$$S(t, \alpha, \tau, T) = \begin{cases} 0 & t < 0 \\ e^{-t/T} \gamma(\alpha, (\frac{1}{\tau} - \frac{1}{T}) t) / N_S & t \geq 0, \end{cases} \quad (4)$$

where $t = 0$ corresponds to the actual bolus arrival time, $\Gamma(\alpha)$ is the gamma function, $\gamma(\alpha, x)$ is the lower incomplete gamma function, and the normalization factors are

$$N_G = \left(\frac{e}{\tau(\alpha-1)} \right)^{1-\alpha},$$

$$N_S = \Gamma(\alpha) \left(\frac{T-\tau}{T} \right) \left(\frac{\tau}{T} \right)^{\tau/(T-\tau)}. \quad (5)$$

Conceptually, the four terms in the AIF model can be associated with the first pass bolus ($n = 1$), the first and second recirculation peaks ($n = 2, 3$), and the well-mixed/washout phase ($n = 4$). The number of free AIF model parameters can be reduced from 17 to 11 without noticeable degradation of fit quality by applying the following constraints (based on correlations empirically observed in fitting measured AIF data): $\Delta_3 = \Delta_4$, $\alpha = \alpha_1 = \alpha_2 = \alpha_3 = \alpha_4$, and $\tau_2 = \tau_3 = \tau_4$. A physiologically-reasonable *a priori* set of AIF parameters was determined by fitting this 11-parameter model form for the AIF to the experimentally-derived population-averaged AIF measurement data reported by Parker, *et. al* (Parker *et al.* (2006)). Parameter values for this population AIF, C_p^{pop} , are given in Table 1, along with values for a different model AIF, C_p^{mod} , that we use to generate the “true” input functions used in the Monte Carlo simulations described below. Figure 1 plots C_p^{pop} (thin black curve) and C_p^{mod} (thick black curve).

The pharmacokinetic model described by Equation (1) is invariant under the simultaneous transformations $C_p(t) \rightarrow \gamma C_p(t)$, $K^{trans} \rightarrow K^{trans}/\gamma$, and $v_p \rightarrow v_p/\gamma$ for any scalar value γ (as holds true for the broader class of convolutional pharmacokinetic models). As a consequence, the single arbitrary global AIF scale factor, γ , remains indeterminate. This scale factor must be constrained by a secondary measurement of true blood pool contrast concentration or other means (Fluckiger *et al.* (2009)), as is discussed in more detail below. Because of this model scale invariance, the scale factor for the first-pass bolus in Equation (2) may be fixed at unity: $a_1 = 1$, further reducing the AIF model to 10 free parameters.

Blind AIF Estimation

Given an assumed functional form for the AIF such as the model of Equation (2), it is, in principle, possible to simultaneously determine the free parameters describing C_p along with the three free pharmacokinetic parameters, K^{trans} , k_{ep} , and v_p by nonlinear regression of Equation (1) to each individual measured C_t . Doing so provides an independent estimate of both the AIF and the PK parameters for every voxel, in our case a total of thirteen free parameters. In practice, however, this severely under-constrains C_p , which is expected to be similar for all tissue voxels within an imaging region of interest (ROI), as well as resulting in decreased confidence in PK parameter estimates due to model parameter covariances (over-fitting). Alternatively, all measured tissue curves could be simultaneously fit with a single model AIF. While this would enforce the constraint that all tissue voxels see an identical AIF, for an ROI with N voxels this method would result in an extremely large nonlinear minimization problem having $3N + 10$ free parameters. Given that an ROI in DCE-MRI easily may contain $N = 10^4 \times 10^6$ voxels, such an approach rapidly becomes computationally infeasible. The assumption of an identical AIF feeding all tissue voxels in the ROI may also be unrealistic, particularly for highly heterogeneous tissues such as tumors (Fluckiger *et al.* (2009)). Previous work in blind AIF estimation demonstrated that it is possible to unambiguously determine the AIF by simultaneous regression to only two tissue curves, provided that those curves have sufficient variation in their pharmacokinetic parameter values and sufficiently low measurement noise. In recent work with clustering and blind estimation (Fluckiger *et al.* (2009); Yang *et al.* (2004, 2007)) between 2 and 10 clusters were used, although the performance of these methods as a function of the number of reference curves has not been investigated in detail.

Here, we describe Monte Carlo Blind Estimation (MCBE), an alternative approach to blind estimation that determines the AIF directly from randomly-generated subsets of the measured tissue curves in a computationally-efficient manner. The MCBE algorithm proceeds as follows:

1. Select a pool of concentration-time curves from the tissue region of interest. The selected curves should show significant contrast enhancement. Visible blood vessels should be excluded as their large amplitude will tend to dominate the contribution of the more weakly-enhancing tissue curves. The total number of curves in the pool is denoted M .
2. Repeat the following steps Q times:
 - a. Randomly draw a subset of D curves from the pool of M , with replacement (allowing the same curve to appear more than once in a subset). The pool should be substantially larger than the subset size ($M \gg D$) to ensure that the likelihood of subsets having multiple identical curves is small. Denote these curves $C_t^{q,d}$, where q ($1 \leq q \leq Q$) represents the current curve subset and d ($1 \leq d \leq D$) represents the d -th curve in the current (q -th) subset.
 - b. Make an initial guess at the AIF, denoted $\widehat{C}_p^q$, that is ideally a reasonable prior estimate of the true AIF. Fit Equation (1) to each curve in the current subset separately, using $\widehat{C}_p^q$ to obtain initial estimates of the PK parameter values for each of the D curves: $\{\widehat{K}^{trans,q,d}, \widehat{k}_{ep}^{q,d}, \widehat{v}_p^{q,d}\}$.
 - c. Determine PK and AIF model parameters by simultaneously fitting Equation (1), with $C_p(t)$ parameterized using Equation (2), to all D curves of the current subset via nonlinear regression. The regression algorithm is initialized with the starting guesses from the previous step, and optimizes $10 + 3D$ free parameters (10 from the AIF model and $3D$ tissue PK parameters). The final AIF model parameters provide a blind estimate of the AIF for the current curve subset, which we denote $\tilde{C}_p^q$. The corresponding PK parameter estimates ($\{\tilde{K}^{trans,q,d}, \tilde{k}_{ep}^{q,d}, \tilde{v}_p^{q,d}\}$) are discarded. If the optimization algorithm fails to converge for the current subset, it is restarted at step (a).
3. Compute the final blind AIF estimate, $\tilde{C}_p$, by taking the median of all Q of the individual AIF estimates: $\tilde{C}_p = \text{median}\{\tilde{C}_p^q\}$ and scale the tail concentration of $\tilde{C}_p$ to match that of the true AIF.
4. Compute pharmacokinetic parameters by fitting Equation (1) to tissue curves using $\tilde{C}_p$ as the AIF.

When estimating the AIF for subset q , the previous $q - 1$ AIF estimates, $\{\tilde{C}_p^1, \dots, \tilde{C}_p^{q-1}\}$, are available as a source of additional prior information. We consider two methods for the AIF initialization in step 2b above. The first method, which we term **fixed initialization**,

assumes that the *a priori* guess, $\widehat{C}_p^q$, is independent of previous AIF estimates. A simple choice is to use a fixed guess based on AIF parameters derived from fitting a population-averaged AIF. In the simulations described below, the $\widehat{C}_p^q$ for fixed initialization are generated starting from the parameters for C_p^{pop} given in Table 1. Each parameter except Δ_1 and α is then multiplied by a uniform random number in the range [0.5, 1.5]. We keep Δ_1

fixed because the bolus arrival time can be relatively accurately estimated from the tissue curves themselves, and α is kept fixed because covariance in curve width between α and τ makes it unnecessary to vary both. While not strictly necessary, this randomization serves to minimize the potential for biasing the blind AIF estimate toward a fixed initial guess and expands the AIF parameter space that is explored by the MCBE algorithm.

The second method, which we term **bootstrapping initialization**, allows $\widehat{C}_p^q$ to be a function of the previous AIF estimates: $\widehat{C}_p^q = f(\tilde{C}_p^1, \dots, \tilde{C}_p^{q-1})$. In bootstrapping simulations, a number of subsets (Q) with fixed initialization are run, allowing the AIF estimate to partially converge toward a better AIF estimate than the starting guess. Once these initial subsets with fixed initialization are completed, $\widehat{C}_p^q$ is computed for subsequent bootstrapping subsets by restarting the algorithm using the median of the previous $q-1$ estimates so that the starting guess for the AIF tracks the current best estimate, running an additional Q^* subsets. In the bootstrapping method, the initial AIF estimates using fixed initialization are only intended to provide an improved starting guess, so they are ignored in the final AIF computation. The final blind AIF estimate, $\tilde{C}_p$, is computed as the median of these Q^* estimates of $\tilde{C}_p^q$. Because the MCBE algorithm generates multiple AIF estimates, bounds on the variability in the final AIF estimate may be computed from quantiles other than the median.

All simulations and analysis presented in this paper were performed using custom-written MATLAB code (The Mathworks, Natick MA). Nonlinear regression was implemented using a large-scale trust-region reflective Newton algorithm with the following optimization parameters: termination tolerance for changes in AIF/PK parameter values = 10^{-3} , termination tolerance for changes in $\chi^2 = 10^{-4}$, maximum number of function evaluations = 2000, maximum number of iterations = 20. The following AIF parameter constraints were applied in the nonlinear regression algorithm: $\Delta_1 \in [-0.5, 0.5]$, $\alpha \in [1, \infty)$, $\tau_1 \in [0, \infty)$, $\Delta_2 \in [\Delta_1, \Delta_1 + 1]$, $a_2 \in [0, 1]$, $\tau_2 \in [0, \infty)$, $a_3 \in [0, 1]$, $\Delta_3 \in [\Delta_2, \Delta_2 + 1]$, $a_4 \in [0, 1]$, $T \in [0, \infty)$. Other than positivity constraints ($\tilde{K}^{trans,q,d} \in [0, \infty)$, $\tilde{k}_{ep}^{q,d} \in [0, \infty)$, $\tilde{v}_p^{q,d} \in [0, \infty)$), we do not constrain pharmacokinetic parameters in our regressions.

Computer Simulations

To validate and test the performance of the MCBE algorithm, we performed a number of simulations under various conditions. For each individual simulation, a new pool of $M = 50000$ random sets of pharmacokinetic parameters was generated. These parameters were drawn from uniform random distributions covering physiologically-reasonable ranges of values: $K^{trans} \in [0, 1]$, $v_e \in [0.15, 1]$, and $v_p \in [0, 0.2]$ (Cheng (2008)), with $k_{ep} = K^{trans}/v_e$. The true AIF, C_p , was computed from the C_p^{mod} parameters in Table 2 and was discretized at time points ranging from 0 to 5 minutes with a temporal sampling interval of 0.1 s. C_p^{mod} is shown in Figure 1. In some simulations the true AIF was broadened with a gaussian kernel of standard deviation S , to test robustness of convergence for true AIFs that differ substantially from the initial guess. The contrast bolus arrival time was fixed at one minute.

For the q -th curve subset, D sets of PK parameters were selected from the pool of M random candidates. The D true tissue curves for this subset, $C_t^{q,d}$ ($1 \leq q \leq Q$, $1 \leq d \leq D$), were generated at a temporal resolution of 0.1 second (consistent with the true AIF) from Equation (1) by numerical convolution using the selected PK parameters. All convolutions were performed using a fast Fourier transform (FFT) zero-padded to avoid aliasing.

Measured plasma, $\tilde{C}_p$, and tissue curves, $\tilde{C}_t^{q,d}$, were then generated from the corresponding true curves by linearly downsampling to the simulated Δt value. Uncorrelated, gaussian-

distributed random noise with a standard deviation of σ was added to each of the tissue curves and the MCBE algorithm described in the previous section was run on the resulting simulated data. The specific parameters used for each of the various Monte Carlo simulations are given in Table 2. Where multiple values of parameters are listed, all combinations of parameter values were simulated.

Simulations A_1 through A_4 were performed to assess the effect of changing Q , the number of random subsets, and D , the number of tissue curves per subset, on the accuracy and precision of blind AIF estimation and to establish reasonable values for these parameters in subsequent simulations. Simulations A_1 and A_3 used the unbroadened C_p^{mod} shown by the thick black line in Figure 1, while simulations A_2 and A_4 used C_p^{mod} broadened by convolution with a gaussian of $S=0.15$ minute width. The sampling time ($\Delta t = 4$ s) and concentration measurement noise ($\sigma = 0.04$ mM) were chosen to be realistically-achievable in *in vivo* DCE-MRI experiments on modern MRI scanner hardware. The fixed initialization method was used for A_1 and A_2 and bootstrapping for A_3 and A_4 . A total of 256 subsets of curves were fit for each $D \in \{2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 32\}$, with 50 fixed iterations used in the bootstrapping simulations.

Because of the stochastic nature of the blind estimation algorithm, different realizations of the Q subsets of tissue curves will produce different AIF estimates. In order to assess the sensitivity of $\hat{C}_p$ to random variation in the Q subsets of D curves, for each D we computed $\hat{C}_p$ for 4000 different random subsets containing each $Q \in \{2, 10, 100\}$ from the 256 blind AIF estimates. The 5th, 50th, and 95th percentiles of these 4000 subsets were then calculated to give the median and range of blind AIF estimates for each Q and D . The median (connected black points) and 5th and 95th percentiles (black lines) are shown in Figure 2 for all values of D for $Q = 2, 10$, and 100 (left, middle, and right columns, respectively). The true AIF is shown by the red curves. In this figure, $\hat{C}_p$ for parameter set A_1 is plotted in the top row and for parameter set A_2 in the bottom row. Simulations A_3 and A_4 were identical except for the use of Q iterations of bootstrapping following 50 initial iterations of fixed blind estimation. The corresponding blind AIF estimates are plotted in Figure 3 for simulations A_3 (top row) and A_4 (bottom row). For all four sets of simulations, both the mean difference between $\hat{C}_p$ and C_p and the root-mean-square (RMS) difference between the 95th and 5th percentiles of $\hat{C}_p$ were computed from these 4000 random sets.

To test the sensitivity of blind AIF estimation to the initial guess, $\hat{C}_p$, two sets of simulations (B_1 and B_2) were performed for true AIFs of varying widths: $S \in \{0.0, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30\}$ minutes. These simulations were performed with $D = 12$, and used the same sampling interval and noise level as in simulations A_1 through A_4 . The B_1 simulations were performed using $Q = 50$ iterations of fixed initialization, while the B_2 simulations used 50 iterations of fixed initialization with an additional 50 iterations of bootstrapping ($Q = 50 + 50^*$). In addition to the seven different values of S tested, a simulation was run for both B_1 and B_2 that was identical to the $S=0.0$ simulation with the exception that the median initial AIF guess was broadened by increasing the value of τ for C_p^{pop} from $\tau = 0.0442$ (see Table 1) to $\tau = 0.12$.

Two simulation parameter sets (C_1 and C_2) were used to evaluate the impact of finite sampling interval ($\Delta t \in \{1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 25, 30\}$ s) and concentration measurement noise level ($\sigma \in \{0.001, 0.01, 0.02, 0.04, 0.08, 0.16\}$ mM) on blind AIF and pharmacokinetic parameter estimates. The sampling intervals and noise levels were chosen to span the range of values that are potentially relevant to DCE-MRI. $D = 12$ curves were fit per realization, unbroadened (C_1) and broadened (C_2) AIFs were used as before, and fifty bootstrapping iterations were performed after fifty initial fixed iterations ($Q = 50 + 50^*$) to

determine the final blind AIF estimate. To assess the sensitivity of the MCBE algorithm to the diversity of tissue curves (essentially the range of pharmacokinetic parameter values for the measured tissue curves), simulations C_3 and C_4 were run using a greatly restricted pharmacokinetic parameter space with decreased v_p : $K^{trans} \in [0.25, 0.50]$, $v_e \in [0.4, 0.6]$, and $v_p \in [0.01, 0.05]$.

Joint probability density functions (JPDFs) of pharmacokinetic parameter estimates were computed as follows: 1) 10000 values of each parameter were randomly drawn from the simulation PK parameter distributions and used to compute a corresponding set of tissue curves to which random concentration noise was added at the appropriate level. 2) The blind AIF estimate for the simulation, $\tilde{C}_p$, was used to fit the simulated tissue curves with

Equation (1) to obtain a set of blind pharmacokinetic parameter estimates: $\tilde{K}^{trans,k}$, $\tilde{k}_{ep}^k$, $\tilde{v}_p^k$, and $\tilde{v}_e^k$. 3) The blind pharmacokinetic parameter estimates were then binned in a two-dimensional histogram against the true parameter values, with K^{trans} ranging from 0.0 to 1.0 with a bin size of 0.02, k_{ep} ranging from 0.0 to 2.0 with a bin size of 0.04, v_p ranging from 0.0 to 0.2 with a bin size of 0.002, and v_e ranging from 0.0 to 1.0 with a bin size of 0.02.

To address the potential impact of allowing the tissue bolus arrival time to vary from voxel to voxel, simulation D_1 was run. In this simulation, each tissue curve was delayed by up to 15 seconds relative to the injection time by a random delay time chosen from a uniform distribution: $\delta t \in [0, 15]$ s. Initial guesses for the delay time for all tissue curves were set to zero ($\delta t = 0$), and the pharmacokinetic model used to perform the regression in step 2c of the MCBE algorithm described above was modified to incorporate a separate delay time for each curve within a subset.

Finally, simulation E_1 was performed to assess the relative contribution of concentration measurement noise to overall variability in blind AIF estimates. This was done by rerunning the MCBE algorithm on a single fixed set of $QD = 100 \times 12$ tissue curves for $R = 100$ different random noise realizations at each of six noise levels: $\sigma \in \{0.001, 0.01, 0.02, 0.04, 0.08, 0.16\}$ mM. The variability in blind AIF estimates stemming purely from concentration noise (statistical uncertainty) was estimated by taking the blind AIF estimates for each noise realization and computing the 25th and 75th percentiles of those AIF estimates across noise realizations. The variability in blind AIF estimates stemming from variation in both curve sets and concentration noise was determined by taking the 25th and 75th percentiles of the blind AIF estimates for all noise realizations and computing their medians. The relative contribution of concentration noise to overall variability in the blind AIF estimate (explained variance) was then approximated by taking the ratio of the mean square differences of these two quantities.

Results

Figures 2 and 3 compare blind AIF estimates with truth over wide ranges of Q (number of random realizations) and D (number of tissue curves per realization). The $\tilde{C}_p$ curves shown in Figure 2 (simulations A_1 and A_2) use fixed initialization, while those shown in Figure 3 (simulations A_3 and A_4) use bootstrapping initialization. In all four cases, it is apparent that increasing either Q or D results in decreased variability of the AIF estimates. For the AIFs determined using fixed initialization, a noticeable bias is also apparent in $\tilde{C}_p$ for small values of D that is essentially independent of Q . This bias is dramatically decreased in the simulations utilizing bootstrapping initialization.

We further investigated the Q and D dependence of the mean bias and RMS variability (e_{RMS}) in the blind AIF estimates, computed as the mean and RMS of $\tilde{C}_p - \bar{C}_p$. Mean bias was essentially independent of Q and decreased exponentially with increasing D . The use of

bootstrapping led to a median decrease in bias of 114% (interquartile range: -99% to -136%) going from simulation A_1 to A_3 and of 122% (interquartile range: -98% to -190%) going from simulation A_2 to A_4 . RMS variability was found to decrease exponentially with both Q and D . We found that a simple log-linear model, $\log \varepsilon_{RMS} = b_0 + b_1 \log Q + b_2 \log P$ mM, fit the variability data with less than 5% error for all four simulation parameter sets. The use of bootstrapping decreased median variability by 22% (interquartile range: -15% to -29%) for simulations A_1 and A_3 and by 51% (interquartile range: -37% to -57%) for simulations A_2 and A_4 .

Timing measurements on the workstation used to perform these simulations (Apple Mac Pro 2×3 GHz Quad-Core Intel Xeon, 9GB RAM) demonstrated that algorithm execution time scales linearly with Q for fixed initialization, as expected. Use of bootstrapping leads to slightly sub-linear execution time dependence on Q because each iteration is initialized with a better starting guess, thereby improving convergence rate. In contrast, execution time (t_{ex}) shows an exponential dependence on D . Empirically, we found that the execution time for a single set of D tissue curves for simulation A_1 scales as $\log t_{ex} = p_1 D + p_2$ where $p_1 = 0.0572$ and $p_2 = 0.7535$. For $D = 6$, $\Delta t = 4$ s, and $\sigma = 0.04$ mM, an iteration took 3.0 s, while $D = 12$ took 4.2 s, and $D = 32$ took 13.2 s.

Bootstrapping initialization results in improved robustness to deviation of the starting guess, $\hat{C}_p$, from the true AIF. Figure 4 plots the results of simulations B_1 and B_2 , showing the performance of the MCBE algorithm for a series of broadened AIFs deviating progressively farther from the population-averaged starting guess. AIF estimates are shown by the connected black points, with the true AIF shown by the thick red line and the starting guess by the thin blue line. Results from the B_1 simulations are shown in the left panel and from the B_2 simulations in the right. The simulations without bootstrapping, shown in the left panel, show good agreement with truth for $0.00 \leq S \leq 0.15$. However, for $S \geq 0.20$, the blind AIF estimates with fixed initialization show progressively worse agreement with truth. The addition of 50 iterations of bootstrapping, shown in the right panel, results in robust blind AIF estimates that remain accurate over the entire range of S values tested. Simulations for the case of a very broad initial guess (bottommost curves in each panel) show similar behavior, demonstrating that the MCBE algorithm with bootstrapping functions equally well when the true AIF is narrower than the initial guess.

From the standpoint of practical applications of blind estimation, the primary endpoint of interest is the accuracy and precision with which the model pharmacokinetic parameters may be estimated. Figure 5 compares the relative biases and uncertainties for simulation C_1 , computed as median (connected circles) and 25th/75th percentiles (shaded) of the percent relative difference between PK parameter estimates made using $\hat{C}_p$ and truth (black curves) and between $\tilde{C}_p$ and truth (red curves), for a wide range of Δt (sampling interval) and σ (tissue concentration noise) values. The Δt dependence of $(\tilde{K}^{trans} - K^{trans})/K^{trans}$ (black) and $(\tilde{K}^{trans} - K^{trans})/K^{trans}$ (red) is plotted in the first row, $(\tilde{k}_{ep} - k_{ep})/k_{ep}$ (black) and $(\tilde{k}_{ep} - k_{ep})/k_{ep}$ (red) in the second row, $(\tilde{v}_p - v_p)/v_p$ (black) and $(\tilde{v}_p - v_p)/v_p$ (red) in the third row, and $(\tilde{v}_e - v_e)/v_e$ (black) and $(\tilde{v}_e - v_e)/v_e$ (red) in the fourth row. Plots in the first column are for simulations with a tissue curve noise level of $\sigma = 0.01$ mM, the second for $\sigma = 0.02$ mM, the third for $\sigma = 0.04$ mM, the fourth for $\sigma = 0.08$ mM, and the fifth for $\sigma = 0.16$ mM. By using a noiseless AIF that accurately represents the true AIF sampled at the appropriate rate, the curves for bias and uncertainty using $\tilde{C}_p$ represent a best case scenario that neglects the presence of concentration noise as well as the numerous potential sources of bias such as partial volume, pulsatility and inflow artifacts, signal saturation, etc... in the measured AIF. In reality, use of a measured AIF will suffer to some extent from most of these in a way that is difficult to quantify and that will further degrade the fidelity with which the pharmacokinetic parameters may be estimated.

Considering first the top row of Figure 5, we see that $\tilde{K}^{trans}$ shows both minimal bias and uncertainty for $\Delta t = 12$ s and $\sigma = 0.04$ mM. At low noise, both bias and uncertainty become abruptly larger for $\Delta t = 14$ s. At higher noise levels, the bias and uncertainty both increase more consistently with Δt . While the curves for K^{trans} show similar behavior, the bias is smaller and more variable with Δt , while the uncertainty is more variable and becomes larger for the longest Δt values. The curves for k_{ep} (second row) show broadly similar behavior. In both cases, the blind parameter estimates are of comparable accuracy to the measured estimates for $\Delta t = 12$ s and $\sigma = 0.04$ mM, and show increasing negative bias and comparable uncertainty for $\sigma = 0.08$ mM. We can qualitatively understand this behavior by considering the full width at half-maximum (FWHM) of the first-pass bolus peak of the true AIF, which is 12.6 s for this set of simulations. Sampling intervals that are longer than this will generally lead to undersampling of the leading edge of the tissue contrast uptake curve, resulting in an underestimation of K^{trans} . Similarly, undersampling of the trailing edge of the bolus will lead to overestimation of the blood plasma washout rate and a corresponding underestimation of k_{ep} . Estimates of the blood plasma volume fraction, v_p , are shown in the third row. Here $\tilde{v}_p$ and $\bar{v}_p$ show rapidly degrading accuracy with increased Δt , with large, fluctuating biases and uncertainties for $\Delta t = 8$ s for both estimates. This is consistent with our expectation that this parameter will be most sensitive to sampling rate when rapid contrast boluses are injected. Finally, v_e estimates are shown in the fourth row. Due to the presence of correlated biases in K^{trans} and k_{ep} , estimates of v_e are relatively stable for $\Delta t = 16$ s.

Figure 6 plots representative sets of simulated tissue curves (blue circles) along with model regressions (black lines) and fit residuals (green points) for simulations $C_1 - C_4$ in the left column. Corresponding $\tilde{C}_p$ curves are plotted (black connected circles) along with the true AIF (red lines) and AIF residuals ($\tilde{C}_p - \bar{C}_p$, green points) in the right column. Results for the full PK parameter ranges, C_1 and C_2 , are plotted in the first two rows, while the results for the restricted PK parameter ranges, C_3 and C_4 , are plotted in the bottom two rows.

Joint probability density functions were generated as described above for simulations $C_1 - C_4$ and D_1 for all four pharmacokinetic parameters at each sampling interval, Δt , and noise level, σ . The JPDFs for simulation C_1 are shown in Figure 7, with K^{trans} plotted in the top panel, k_{ep} in the second panel, v_p in the third panel, and v_e in the fourth panel. Values of Δt increase from left to right and values of σ from top to bottom within each panel. A logarithmic color scale is used to emphasize the presence of outliers. Superimposed on each JPDF is a colored star representing the overall accuracy and precision of the parameter estimation. Joint PDFs with relative bias and uncertainty that are both less than 5% are labeled with a green star, those with the largest of the two lying between 5% and 10% with a yellow star, those with the largest of the two lying between 10% and 20% with an orange star, and those with either exceeding 20% with a red star.

For simulation C_1 at $\sigma = 0.04$ mM, K^{trans} may be estimated to better than 10% for $\Delta t = 7$ s and better than 20% for $\Delta t = 12$ s, k_{ep} to better than 10% for $\Delta t = 7$ s and better than 20% for $\Delta t = 14$ s, v_p to better than 10% for $\Delta t = 4$ s and better than 20% for $\Delta t = 8$ s, and v_e to better than 10% for $\Delta t = 10$ s and better than 20% for $\Delta t = 16$ s. Use of the broadened AIF in simulation C_2 leads to somewhat decreased estimation accuracy: for $\sigma = 0.04$ mM, K^{trans} may be estimated to better than 10% for $\Delta t = 5$ s and better than 20% for $\Delta t = 7$ s, k_{ep} to better than 10% for $\Delta t = 5$ s and better than 20% for $\Delta t = 7$ s, v_p to better than 10% for $\Delta t = 2$ s and better than 20% for $\Delta t = 4$ s, and v_e to better than 10% for $\Delta t = 7$ s and better than 20% for $\Delta t = 10$ s.

Figure 8 shows JPDFs of blind AIF estimates for simulation C_3 , plotted as in Figure 7. As expected, the accuracy of PK parameter estimates is degraded, particularly at higher noise

levels and sampling intervals. In this low-diversity case, with $\sigma = 0.04$ mM, K^{trans} may be estimated to better than 10% for $\Delta t = 4$ s and better than 20% for $\Delta t = 7$ s, k_{ep} to better than 10% for $\Delta t = 4$ s and better than 20% for $\Delta t = 6$ s, v_p to better than 10% for $\Delta t = 2$ s and better than 20% for $\Delta t = 5$ s, and v_e to better than 10% for $\Delta t = 6$ s and better than 20% for $\Delta t = 8$ s. In simulation C_4 , with both low curve diversity and a broadened AIF and for $\sigma = 0.04$ mM, K^{trans} may be estimated to better than 20% for $\Delta t = 4$ s, k_{ep} to better than 20% for $\Delta t = 4$ s, v_p to better than 20% for $\Delta t = 3$ s, and v_e to better than 20% for $\Delta t = 8$ s. These results demonstrate that, while the accuracy of AIF estimation is decreased with lower curve diversity, it remains possible to obtain results of reasonable accuracy even when all tissue curves are quite similar.

Introduction of a delay time term to each tissue curve, as we have done in simulation D_1 , leads to some degradation in the accuracy of PK parameter estimation. Nevertheless, for $\sigma = 0.04$ mM, it remains possible to estimate K^{trans} to better than 10% for $\Delta t = 5$ s and better than 20% for $\Delta t = 8$ s, k_{ep} to better than 10% for $\Delta t = 3$ s and better than 20% for $\Delta t = 5$ s, v_p to better than 10% for $\Delta t = 2$ s and better than 20% for $\Delta t = 5$ s, and v_e to better than 10% for $\Delta t = 5$ s and better than 20% for $\Delta t = 8$ s.

Simulation E_1 finds a maximum contribution (explained variance) of concentration measurement noise to the total mean square variability in blind AIF estimates of 9.6% for $\sigma = 0.016$ mM, decreasing to 5.8% at $\sigma = 0.08$ mM, 4.0% at $\sigma = 0.04$ mM, 2.6% at $\sigma = 0.02$ mM, 1.2% at $\sigma = 0.01$ mM, and 0.2% at $\sigma = 0.001$ mM. This demonstrates that the major source of variability in the blind AIFs, for the noise levels considered here, is the stochastic variation between subsets of curves rather than concentration measurement noise.

Discussion

Extensive Monte Carlo simulations demonstrate that it is possible to accurately estimate the true AIF over a broad range of physically-reasonable imaging and pharmacokinetic parameters, using only measured tissue concentration curves. The MCBE blind AIF estimation algorithm described here is straightforward to implement, and, because it operates directly on measured tissue concentration curves rather than requiring clustering or identification of a region of normal reference tissue, its application is simple and efficient. Two primary parameters, the number of random subsets of tissue curves (Q) and the number of tissue curves per subset (D) characterize the algorithm. Although uncertainty in blind AIF estimates decreases exponentially with both Q and D , the supralinear increase in execution time with D , compared to the linear dependence on Q , implies that the smallest D value that provides adequate fidelity of AIF estimation should be used. The primary concern is to select a value of D that is sufficiently large to avoid biases in $\tilde{C}_p$. In general, for the AIFs and parameter ranges considered here, values of D in the range 6–12 appear to provide accurate AIF estimates with acceptable performance. Minimization of bias in the blind AIF and improvement in convergence for AIFs that deviate substantially from the initial guess make bootstrapping initialization the preferred method. Bootstrapping appears to provide good convergence of the blind AIF estimate to the true AIF even in cases where the true AIF is much broader than the initial AIF guess or vice-versa.

Depending on the noise level of the tissue curves, use of 50 iterations of fixed initialization followed by 50 iterations of bootstrapping ($Q = 50 + 50^*$) appears to provide reasonable performance for the scenarios considered here. Noisier data sets or those having restricted diversity of pharmacokinetic parameters may benefit from increased Q . Convergence failure rate is dependent on the specific parameters of the simulation, but is generally quite low (less than one percent of curve subsets for sampling intervals and noise levels that are typical of clinical DCE-MRI measurements). While we have not considered it here,

improved execution time could likely be achieved by monitoring the change in $\tilde{C}_p$ from iteration to iteration and using a convergence criterion to terminate the algorithm. However, in general the total execution time for blind AIF estimation is on the order of hundreds of seconds on modern workstation hardware, a performance level that should be quite acceptable for most practical applications.

Negative biases appear in estimates of K^{trans} and k_{ep} at high noise levels. It should be possible to mitigate these biases by acquiring data at slightly lower spatial resolution or by averaging together tissue curves in postprocessing. The curves could be averaged by simply spatially downsampling measurements or by a hybrid method that employs, for example, some of the clustering methods used in other blind estimation work. However, it is important to note that concentration noise levels of $\sigma = 0.02 - 0.04$ mM are easily achievable in *in vivo* DCE-MRI measurements in the brain with isotropic spatial resolutions in the range of 1.5–2 mm (Schabel *et al.* (2010)), and data acquired at a noise level of $\sigma = 0.16$ mM would be considered of extremely poor quality. We have found that similar noise levels can be achieved in sarcoma and prostate DCE-MRI. In more challenging situations such as abdominal imaging, higher noise levels are to be expected, and the suitability of the MCBE algorithm in these cases remains to be demonstrated. Another potential concern, not treated in the current work, are artifacts and other systematic sources of error arising, for example, from patient motion, breathing, or other sources, or inclusion of voxels for which Equation (1) poorly represents the time course of enhancement. In such situations our assumption of normally-distributed noise may no longer be reasonable, and caution is advised in extrapolating our results to these cases.

Simulations performed with very low diversity of tissue curve PK parameters (simulations C_3 and C_4) show degradation in the performance of the MCBE algorithm and the accuracy of pharmacokinetic parameter estimation, but even in this more difficult case it remains feasible to recover parameter values with reasonable accuracy for experimentally-feasible sampling intervals and measurement noise levels. While malignant tumors typically manifest a wide range of parameter values, these results suggest that the MCBE method may also be applicable to situations such as quantitative cardiac or cerebral perfusion where the tissue curves are primarily either normal or ischemic tissue, and consequently have a lower level of diversity.

The need for a single, independently-determined overall AIF scale factor (common to all blind AIF estimation methods) is a limitation of this approach, but this limitation is less severe than might be assumed. Because the tail concentration long after contrast injection can be used to fix the AIF scale, there are a number of possibilities for determining this quantity. The most accurate means of doing so would be direct blood sampling and *ex vivo* analysis to measure the true plasma contrast concentration. Despite the added complexity of blood sampling, the relatively slow elimination of contrast in the washout phase makes doing so much more feasible than directly sampling concentrations at high temporal resolution throughout the bolus passage. A second possibility is to use an MRI imaging pulse sequence that has been specifically optimized for measurement of blood contrast concentration. Because the blood pool concentration is well mixed in the tail, an FOV encompassing any large vessel (potentially distant from the primary imaging site) can be chosen, and the relatively slow elimination of contrast makes the use of more accurate quantitative imaging methods feasible. Nevertheless, it is important to note that any inaccuracies in the scaling of the AIF will result in biases in estimates of the pharmacokinetic parameters.

In most of our simulations, we have assumed that the contrast bolus arrives simultaneously in all tissue voxels. While this assumption appears to be reasonable in data acquired in the

brain (Schabel *et al.* (2010)), this may not be the case in other tissues. We have investigated the behavior of the MCBE algorithm in the case where there is significant variation in bolus arrival time from voxel to voxel through simulation D_1 , allowing each tissue curve to have a different bolus arrival time drawn from a uniform random distribution ($\delta t \in [0, 15]$ s). Despite the addition of δt as a fourth effective PK parameter in this case, the MCBE blind AIFs show only a modest decrease in the accuracy of parameter estimation, which would be expected simply as a result of introducing an additional free parameter, suggesting that inclusion of a per-voxel delay time term does not pose a fundamental challenge for the MCBE algorithm.

The results of simulation E_1 demonstrate that, for realistic noise levels, variability in AIF estimated provided by the MCBE algorithm is dominated by variation between curve subsets rather than by concentration measurement noise. We can understand this heuristically by considering the limiting case in which there is very low diversity in the curve subsets (or very high noise levels). In this case, each subset will be quite similar to the others, with most of the variation between them, and the corresponding variability in blind AIF estimates, arising from noise. However, if we now begin to introduce more diversity between curve subsets, the individual estimates will not only vary due to noise, but also as a result of the presence of subsets with more or less diversity than the overall mean diversity of the pool. This additional source of AIF uncertainty exists because we are effectively solving a large inverse problem (inversion of Equation (1) for all voxels in the tissue curve pool) by repeatedly solving smaller, more ill-conditioned, inverse problems (inversion for the D curves in a subset). Thus, while the variability observed between individual AIF estimates is not strictly a statistical uncertainty, the dominance of this term over the direct noise contribution in the scenarios considered here make it a reasonable proxy for overall uncertainty in blind AIF estimates.

We have not yet systematically investigated the effect of the size of the pool of available tissue curves, M . If M is on the order of QD , the likelihood of any significant fraction of the curve subsets being the same is quite low. Since $QD = 100 \times 12$ corresponds to a cube $\sqrt[3]{1200} = 10.6$ voxels on a side, it is relatively easy to achieve large pool sizes and this issue is probably of little practical importance for most DCE-MRI applications. Preliminary simulations using the C_1 parameter set with $\Delta t = 4$ s, $\sigma = 0.04$ mM also show minimal degradation in the performance of the algorithm even for pools containing as few as 100 curves, suggesting that the large degree of combinatorial variety in curve subsets allows accurate AIF estimation with small pool sizes. For example, the number of combinations

with replacement is given by: $\binom{M+D-1}{D}$. For a pool of 100 curves, this results in $\binom{100+12-1}{12} = 4 \times 10^{15}$ possible distinct subsets of $D = 12$ curves. Future work will investigate the asymptotic behavior of this algorithm and the interplay of pool size and diversity in the limit of small pool sizes to evaluate the potential to accurately estimate local AIFs at sub-ROI spatial resolution (Calamante *et al.* (2004); Grüner *et al.* (2006)).

Other published blind estimation approaches either employ reference regions and bypass estimation of the AIF or estimate the kinetic parameters and the AIF alternately. These methods use relatively few curves as input, with k -means clustering used as a pre-processing step to decrease noise in the input tissue curves. Clustering is typically the most time-consuming step, and requires a decision about the number of clusters to be made either for a class of data or for each set of curves. Here, we directly generate multiple independent estimates of the AIF, without pre-processing. This is made feasible by the use of a constrained AIF model that limits the number of additional parameters that must be

estimated. An additional benefit of the MCBE algorithm described here is that it can provide confidence intervals for the estimated AIF that reflect the variability of the AIF estimates derived from different subsets of curves.

In the limiting case of $\lim_{Q \rightarrow 1}$, the MCBE algorithm is similar to the algorithms of Yang (Yang *et al.* (2004)) and Fluckiger (Fluckiger *et al.* (2009)), and can therefore be viewed as a generalization of blind AIF estimation algorithms that use clustering. The primary difference between the method described here in $\lim_{Q \rightarrow 1}$ and that of Yang is the different model used to constrain the blind AIF estimate. Aside from the use of direct rather than alternating optimization and the use of clustering, the MCBE algorithm is also essentially identical to the AMM (Fluckiger *et al.* (2009)) in this limit.

The pharmacokinetic model considered here is relatively simple. However, the MCBE algorithm is flexible and can be easily adapted to accommodate different AIF (Kim *et al.* (2008); Parker *et al.* (2006); Schabel & Parker (2008)) and pharmacokinetic (Koh *et al.* (2001, 2003); Lawrence & Lee (1998a,b); Li *et al.* (2005)) models. Finally, it is important to note that, while we have focused on DCE-MRI, the basic MCBE algorithm, with appropriate modification of the chosen pharmacokinetic model, should be equally applicable to time-resolved pharmacokinetic imaging data from other modalities such as perfusion CT, PET, and SPECT (DiBella *et al.* (1999); Feng *et al.* (1997); Kim *et al.* (2008); Koh *et al.* (2001); Wong *et al.* (2001)). Here we have comprehensively evaluated the MCBE method with extensive computer simulations. Application of MCBE to DCE-MRI data measured in eight patients with malignant brain tumors is presented in a companion paper (Schabel *et al.* (2010)).

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Figure 1.

Plots of the population-averaged AIF (C_p^{pop} , thin black curve) and model AIF (C_p^{mod} , thick black curve). Model parameters for C_p^{pop} and C_p^{mod} are given in Table 1.

Figure 2.

Dependence of blind AIF estimates on Q (number of random subsets) and D (number of tissue curves per subset) with $\Delta t = 4$ s and $s = 0.04$ mM. The top row shows blind estimates using simulation A_1 and the bottom row using simulation A_2 (Table 2). The first column shows results for $Q = 2$, the second for $Q = 10$, and the third for $Q = 100$. The true AIFs are shown by the red lines, the blind AIF estimate by the black connected points, and the 5th and 95th percentiles of the blind AIF estimates by the black lines. Median AIF and percentiles were computed as described in the text.

Figure 3.

Dependence of blind AIF estimates on Q (number of random subsets) and D (number of tissue curves per subset) with $\Delta t = 4$ s and $s = 0.04$ mM. The top row shows blind estimates using simulation A_3 and the bottom row using simulation A_4 (Table 2). Other than the use of bootstrapping initialization all parameters are identical to those in Figure 2.

Figure 4.

Dependence of blind AIF estimates on starting guess is plotted for $Q = 50$, $D = 12$, $\Delta t = 4$ s, and $s = 0.04$ mM for seven true AIFs of varying widths (left panel, simulation B_1). The median initial guess, C_p^{pop} , is plotted with the thin blue line, the true AIF with the thick red line, and the final blind AIF estimate, $\tilde{C}_p$, by the connected black points. The right panel shows the result of performing identical simulations with the addition of 50 iterations of bootstrapping initialization, $Q = 50 + 50^*$ (simulation B_2). The bottommost curves in each panel were generated with simulation parameters identical to those of the topmost curves with the exception that a much broader starting guess was used.

Figure 5.

Plots of the median (connected circles) and 25th and 75th percentiles (shaded) of relative differences between estimated PK parameter values for simulation C_1 using the blind AIF estimate ($\tilde{C}_p$, black) and the temporally-downsampled true AIF ($\tilde{C}_p$, red). Curves for K^{trans} are plotted in the first row, k_{ep} in the second row, v_p in the third row, and v_e in the fourth row. The first column plots curves for a tissue concentration noise level of $\sigma = 0.01$ mM, the second for $\sigma = 0.02$ mM, the third for $\sigma = 0.04$ mM, the fourth for $\sigma = 0.08$ mM, and the fifth for $\sigma = 0.16$ mM.

Figure 6.

Plots of typical sets of simulated tissue curves (blue points), model regressions (black curves), and fit residuals (green points) for $Q = 50 + 50\star$ and $D = 12$ are shown for $\Delta t = 4$ s and $\sigma = 0.04$ mM in the first column. Corresponding blind AIF estimates are shown in the second column (black), along with the true AIFs (red) and the AIF residuals (blind minus true, green points). The simulations C_1 (first row) and C_2 (second row) provide relatively diverse tissue curves, while C_3 (third row) and C_4 (fourth row) provide relatively little curve diversity and low vascular signal (v_p) (see Table 2).

Figure 7.

Joint PDFs of the blind estimates vs. true values for the four pharmacokinetic parameters, plotted on a logarithmic color scale, for simulation C_1 . The true parameter value is plotted along the x -axis and the estimated value obtained by fitting Equation (1) using $\tilde{C}_p$ is plotted along the y -axis. K^{trans} is plotted over the range $[0, 1] \text{ min}^{-1}$, k_{ep} over $[0, 2] \text{ min}^{-1}$, v_p over $[0, 0.2]$, and v_e over $[0, 1]$. Green stars indicate cases where relative bias and uncertainty of the blind parameter estimates are both $\leq 5\%$, yellow stars where they are $\leq 10\%$, orange stars where they are $\leq 20\%$, and red stars where one or both are greater than 20% of the maximum plotted parameter value.

Figure 8. Joint PDFs for simulation C_3 (low tissue curve diversity), plotted as in Figure 7.

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Table 1

Parameters for Equation (2) for a fit of the model to the population-averaged AIF data of Parker *et al.*, C_p^{pop} , plotted by the thin black curve in Figure 1, and the base model AIF used for the Monte Carlo simulations described in this paper, C_p^{mod} , plotted by the thick black curve in the same figure.

AIF	a_1 (mM)	Δ_1 (min)	α	τ_1 (min)	a_2 (mM)	$\Delta_2 - \Delta_1$ (min)	τ_2 (min)	a_3 (mM)	$\Delta_3 - \Delta_1$ (min)	a_4 (mM)	T (min)
C_p^{pop}	6.0	1.0	2.92	0.0442	1.1208	0.2227	0.1430	0.3024	0.6083	0.7164	7.8940
C_p^{mod}	6.0	1.0	2.92	0.0633	1.6200	0.3000	0.0953	0.7164	0.6083	1.2732	14.7120

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Table 2

Parameters used in the various Monte Carlo simulations discussed in the paper. Q is the number of random subsets of curves and D the number of tissue curves per subset. An asterisk after Q is used to indicate that the bootstrapping method was used for the specified number of iterations. The pharmacokinetic parameters K^{trans} , v_e , and v_p were randomly chosen from uniform distributions over the ranges shown. The true AIF used for computation of tissue curves was determined by convolution of an AIF generated using the C_p^{mod} parameters from Table 1, broadened by convolution with a gaussian kernel of standard deviation S minutes. The sampling interval of temporal discretization is given by Δt . Gaussian-distributed random noise of standard deviation of σ mM was added to each tissue curve for each realization.

	Q	D	K^{trans} (min^{-1})	v_e	v_p	S (min)	Δt (s)	σ (mM)
A_1	256	$\dagger$	[0,1]	[0.15,1]	[0.0,2]	0.00	4	0.04
A_2	256	$\dagger$	[0,1]	[0.15,1]	[0.0,2]	0.15	4	0.04
A_3	50+256*	$\dagger$	[0,1]	[0.15,1]	[0.0,2]	0.00	4	0.04
A_4	50+256*	$\dagger$	[0,1]	[0.15,1]	[0.0,2]	0.15	4	0.04
B_1	50	12	[0,1]	[0.15,1]	[0.0,2]	$\mathcal{O}$	4	0.04
B_2	50+50*	12	[0,1]	[0.15,1]	[0.0,2]	$\mathcal{O}$	4	0.04
C_1	50+50*	12	[0,1]	[0.15,1]	[0.0,2]	0.00	$\dagger$	$\blacklozenge$
C_2	50+50*	12	[0,1]	[0.15,1]	[0.0,2]	0.15	$\dagger$	$\blacklozenge$
C_3	50+50*	12	[0.25,0.50]	[0.4,0.6]	[0.01,0.05]	0.00	$\dagger$	$\blacklozenge$
C_4	50+50*	12	[0.25,0.50]	[0.4,0.6]	[0.01,0.05]	0.15	$\dagger$	$\blacklozenge$
D_1	50+50*	12	[0,1]	[0.15,1]	[0.0,2]	0.00	$\dagger$	$\blacklozenge$
E_1	50+50*	12	[0,1]	[0.15,1]	[0.0,2]	0.00	4	$\blacklozenge$ 2

$\mathcal{O}$ $S \in \{0.00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30\}$ min

$\dagger$ $D \in \{2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 32\}$

$\dagger$ $\Delta t \in \{1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 25, 30\}$ s

$\blacklozenge$ $\sigma \in \{0.001, 0.01, 0.02, 0.04, 0.08, 0.16\}$ mM

$\dagger$ Each tissue curve had a random bolus arrival time chosen from a uniform distribution: $\delta t \in [0, 15]$ s.

² Each simulation was repeated with 100 different random noise realizations for an identical set of QD tissue curves.