AIF Induced Limits of Parameter Uncertainty in Pharmakokinetic Models of Pre-Clinical DCE-MRI

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Target audience: Investigators using DCE-MRI in preclinical models who are interested in optimizing the achievable parameter uncertainty through choice of appropriate contrast-agent injection protocols.

Introduction: Knowledge and control of the temporal evolution of contrast agent concentration in the blood plasma (arterial input function, AIF) is of crucial importance for the determination of physiological parameters from pharmakokinetic modeling of dynamic contrast-enhanced resonance imaging (DCE-MRI)[1,2]. More fundamentally the functional form of the AIF places an inherent limitation on the achievable parameter accuracy. This study explores the requirements an AIF has to fulfill so that a desired accuracy in the fit parameters can be achieved. This question has been previously explored in clinical DCE-MRI protocols[3] but has been largely ignored for the very challenging situation of small-animal DCE-MRI. One reason lies in the much greater difficulty of determining an AIF in rodents (high heart rate, limits in physiologically feasible injection rates). Typically, models such as the ones based on the Kety-Tofts compartmental approach[4] are used. They can be conveniently described in the impulse response formalism $C(t) = AIF(t) * IRF(t, [K^{trans}, ...])$, where * represents the convolution operation, C(t) is the (measured) total tissue contrast agent concentration, AIF(t) is the contrast agent concentration in the blood plasma and IRF(t) is the impulse response function, which is defined by the tissue properties. The transfer constant for contrast agent between blood plasma and the extracellular extravascular space, K^{trans}, is a tissue parameter of major interest and is particularly addressed in this study.

Methods: The reproducibility of pharmakokinetic parameters is examined by use of a bootstrapping procedure. Typical tissue concentration curves from dynamic measurements of T1 relaxation times in tumor tissue in a mouse tail are obtained on a Biospec 70/30 7.0 T MRI system. A population averaged AIF is derived from the signal phase of projection profiles at a temporal resolution of 100ms[5]. By applying the Kety-Tofts model, a typical set of tissue parameters is obtained. These parameters yield an impulse response function, used throughout this study. The subsequent procedure consists of four steps: (i) The AIFs peak width is varied while keeping the total amount of contrast agent (i.e. the area under the AIF curve) and the final concentration constant as shown in Fig.1. This corresponds to a variation of the bolus injection speed while maintaining the administered dose. (ii) The corresponding tissue concentration curves C(t) are derived by convolution of the various AIFs with the impulse response function (Fig.2). (iii) Gaussian noise of a constant magnitude is added to the tissue concentration curves. (iv) Tissue parameters are obtained by fitting the Kety-Tofts model to the noisy concentration curves. (v) Repetition of steps (iii)-(iv) yields a probability density distribution for K^{trans} (and other fit parameters – not shown). Gaussian fits, as shown in Fig.3, quantify its standard deviation. **Results:** As shown in the parameter uncertainty curve in Fig.4 the relative K^{trans} standard deviation grows monotonically with the AIF's peak width. **Discussion/Conclusion:** As expected, a slower contrast agent admission intrinsically impairs the accuracy of K^{trans}. The vertical offset of the parameter uncertainty curve depends on the magnitude of the Gaussian noise, which is added to the tissue concentration curves and which can be understood as a surrogate for actual noise in an experimental setup. The proposed procedure is applicable to virtually all models that rely on an arterial input function. To determine the desired duration of contrast agent injection in small-animal DCE-MRI, an investigator has to determine typical levels of signal-to-noise in the chosen DCE-MRI protocol. With a known level of noise of the measured contrast agent concentration one can predict, using the methodology presented in this study, the corresponding intrinsic parameter uncertainty. E. g. a typical SNR of about 3.2 and the population averaged AIF (peak width factor = 1) yield a relative K^{trans} accuracy of 8 per mil. Moreover, given a desired parameter accuracy, a maximum AIF width and thus a limit for possible contrast agent administration protocols can be derived.

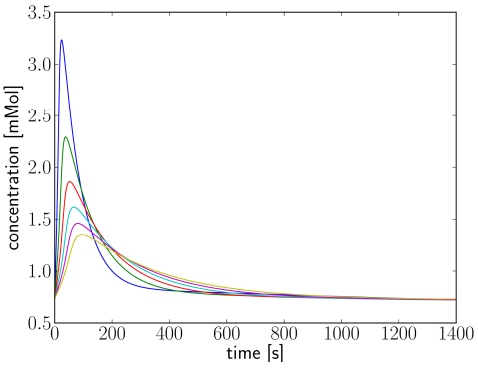

Figure 1: AIFs scaled with a peak width factor between 0.5 (narrow) and 2 (wide)

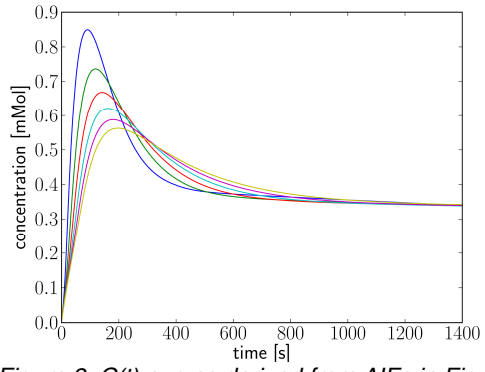

Figure 2: C(t) curves derived from AIFs in Fig.1 with corresponding colors

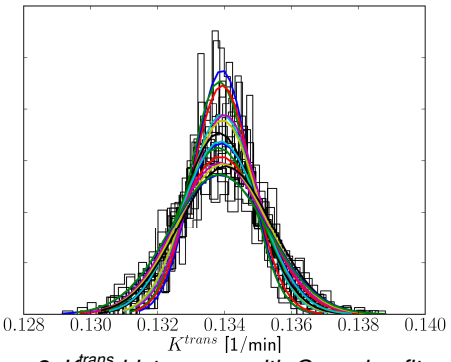

Figure 3: K^{trans} histograms with Gaussian fits

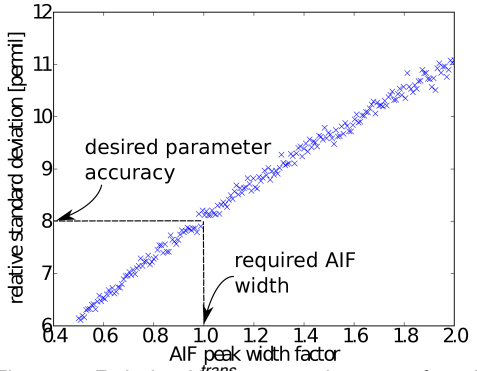

Figure 4: Relative K^{trans} uncertainty as a function of AIF peak width

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