A double bolus injection protocol improves the precision of K^{trans} in clinical DCE-MRI analysis

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Introduction The use of an individually-measured AIF is generally assumed to increase the precision with which the dynamic contrast-enhanced MRI (DCE-MRI) endothelial transfer constant K^{trans} and other kinetic parameters can be obtained relative to the use of an assumed AIF. However, the accurate measurement of an AIF is itself subject to errors, which can lead to degraded parameter accuracy and reproducibility, especially if the AIF and tissue time course are "mis-sampled" relative to their true shape(1) (Fig. 1) – a likely scenario if a low temporal resolution DCE-MRI protocol is utilized. There is scope for alternative injection protocols designed to reduce the impact of AIF mis-sampling and we investigate the possible advantage in extending the number of peaks (i.e. the number of contrast agent boluses) from one to two. Our hypothesis is that in a scenario where the first bolus peak is mis-sampled, a second bolus, if appropriately administered, may then compensate for a mis-sampled first peak and subsequently improve the overall accuracy and reproducibility of K^{trans} and other parameters. We demonstrate using simulations that this is indeed the case at temporal resolutions typically employed in clinical DCE-MRI studies.

Methods Two forms of contrast agent injection were simulated, based on a pre-determined high temporal resolution population AIF(2), to produce high temporal resolution one (AIF_1) and two (AIF_2) peak AIFs, with a sampling interval of 0.23s. 39 tissue uptake (C_t) curves with different physiological parameters were simulated using the adiabatic approximation to the tissue homogeneity model(3) to provide a realistic set of test data. Both AIF forms and all C_t curves were down-sampled to form four data sets per AIF with sampling intervals (temporal resolution) of 2.3s, 4.6s, 9.2s and 18.4s. Within each down-sampled AIF_1 data set, AIF and C_t curves were generated at 10 different offset times of the curves relative to the sampling interval to mimic the effect of mis-sampling the 'true' AIF and C_t curves. The AIF and C_t curves were assumed to be synchronized in time. Within each down-sampled AIF_2 data set, the same conditions were applied, but the second bolus was administered with an additional offset of ½ sampling interval delay relative to the sampling of the first peak. Both $AIF_{1,2}$ were designed to use the same total amount of contrast agent, with the injection rate for AIF_2 halved relative to AIF_1 to generate a comparable bolus width. For each data set, the AIF and C_t curves were converted to signal intensity units and Gaussian noise was added to achieve 100 instances of each curve at each of a range of SNR levels. Once converted back to concentration units, each C_t curve was fitted using the extended Kety model(4) to generate K^{trans}, v_p (blood plasma volume), and v_e (extravascular extracellular space) estimates. The median parameter estimates at each SNR were compared with the true simulation values and absolute % error was calculated.

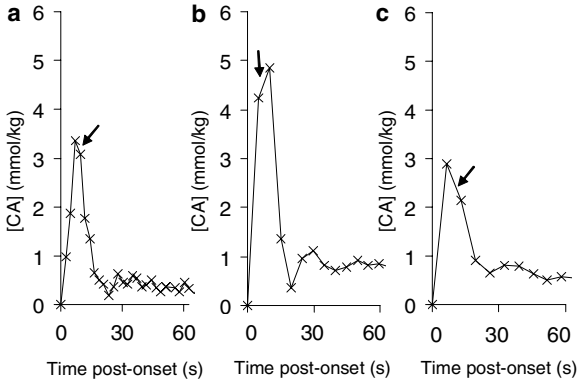

Figure 1: Poorly sampled AIFs measured *in-vivo*. (a) AIF calculated from iliac artery with 2.3 s sampling time, (b) aorta with 4.5 s sampling time and (c) from the external carotid artery with 5.9 s sampling time. Mis-sampling, indicated by an arrow, is manifest by a "shoulder" on the first-pass peak.

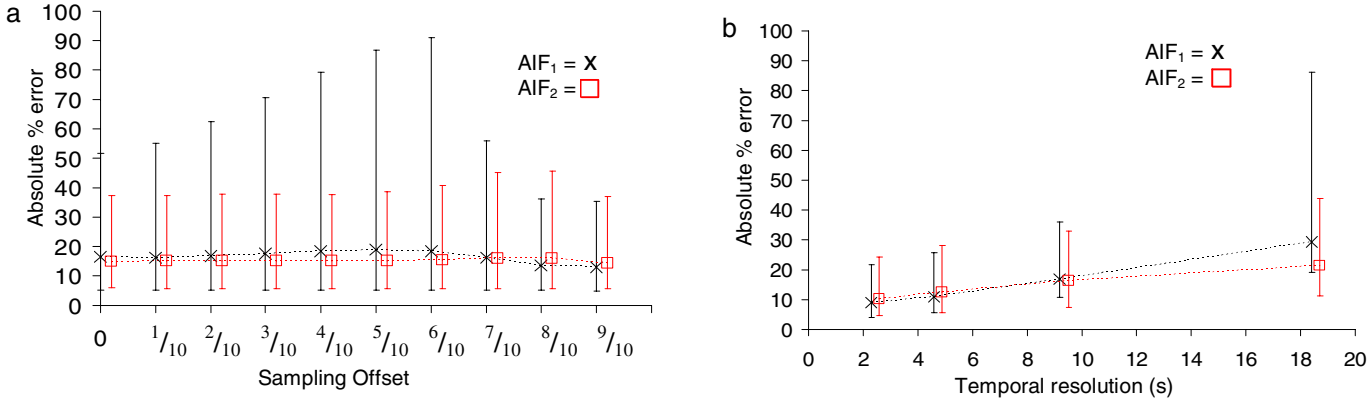

Figure 2: Examples of the performance of AIF_1 and AIF_2. (a) Error in K^{trans} as a function of offset of the arrival of the first bolus peak as a fraction of the temporal resolution. Crosses and squares show mean abs. error and bars show range over all C_t curves and all temporal resolutions investigated. (b) Error in K^{trans} as a function of temporal resolution over all sampling offsets. Crosses and squares show mean abs. error and bars show range over all C_t curves and all peak offsets investigated. SNR = 13 (typical of clinical DCE-MRI studies).

Results When the dynamic time series is most severely mis-sampled (i.e. when the bolus peak arrival falls at the centre of the sampling interval) the absolute % error for AIF_1 is generally larger than for AIF_2, particularly at longer sampling intervals (Fig. 2a). In contrast, the error performance of AIF_2 is largely constant across the sampling offset range. At shorter sampling intervals the average and range of error is slightly lower when using AIF_1, irrespective of peak offset. However, at longer sampling intervals the overall error performance of AIF_2 is better than that of AIF_1 (Fig. 2b). Similar patterns are observed in the errors associated with v_p measurement (data not shown).

Conclusion For greatest precision in kinetic parameter evaluation it is necessary to sample the AIF and subsequent tissue time course (C_t) with high definition. However, given that mis-sampling of data exists in clinical studies, as demonstrated in Fig.1, and given that we have no knowledge of the degree of bolus offset relative to sampling points that may occur, our results suggest that at temporal resolutions in excess of 9 seconds a double bolus AIF protocol would be beneficial. At these longer sampling intervals AIF_2 successfully compensates for information lost in the first-pass of contrast agent by having an offset second bolus. Many clinical DCE-MRI studies are carried out with relatively low temporal resolution, indicating the potential benefits of using a double (fractionated) AIF protocol such as we propose, without an increase in dose of contrast agent.

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