Tumor Arterial Input Function (AIF) estimation in DCE-MRI studies using a multiple reference tissue method

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Introduction: Accurate estimation of the arterial input function (AIF) is essential for quantitative analysis of DCE-MRI data. We have previously demonstrated that a common AIF can be estimated from the contrast agent concentration versus time curves ($C_t(t)$) in two reference tissues with different enhancement patterns (1). This double reference tissue method (DRTM) is based on the two assumptions that (**a**) each tissue's AIF has the same shape, but may have a different arrival time; (**b**) we know *a priori* what kinetic model can adequately describe the $C_t(t)$. Assumption (**b**) of the DRTM has limited its applications. For a particular tumor, it is usually unknown what kinetic model is adequate (2). This makes the tumors generally unfit as the reference tissues in the DRTM. Now we generalize the DRTM to a multiple reference tissue method (MRTM).

Materials and Methods: In the MRTM, which uses two or more reference tissues with *unknown* kinetic parameters to estimate the AIF, we use an automatic model selection scheme to drop Assumption (**b**) in the DRTM. We start from a simple kinetic model, for example a two-compartment model (3) without inclusion of the blood plasma volume parameter, v_p. With the simple model, we estimate the AIF and obtain the goodness of the fit to the data. Then we increase the model complexity for example by including the parameter v_p. Using the new model, we will estimate the AIF again and obtain the goodness of the fit by the new AIF. We will stop increasing the model complexity when the improvement in the goodness of the fit is statistically insignificant. With this scheme, the adequate kinetic model for the reference tissues is determined from the data themselves. By using a non-parametric smoothing method (4) and modifying a Fast Fourier Transform algorithm (5), we are able to significantly increase the accuracy of the algorithm.

We apply the MRTM to the DCE-MRI data of 8 renal cell cancer patients from an on-going clinical trial on the cancer drug Sorafenib. T1 weighted images of bone metastases in the pelvic region were scanned with 2 second resolution for about 7 minutes pre and post bolus injection of Gd-DTPA. Using a cluster analysis (6), voxels in the tumor ROI are divided into subsets such that all voxels within each subset have similar $C_t(t)$. The tumor heterogeneity leads to many subsets having a significantly different mean $C_t(t)$ (Fig. 1**a**) so that each subset can be considered as a reference tissue. Selecting 3-8 subsets as the "multiple reference tissues", the AIF was then estimated with the MRTM using the two-compartment model. For each tumor the automatic model selection scheme was used to determine whether the inclusion of the blood plasma volume parameter was necessary. The adjusted Chi-square, defined as the sum of squared errors divided by the variance of the measurement noise and the degree of freedom, is used to indicate the goodness of the fit. For comparison, we also used a fixed bi-exponential AIF (3) to fit the tumor data.

Results: One representative example is shown in Fig. 1. In 5 out of 8 patients, the contribution of the blood plasma to the measured contrast agent concentration in tumors was found significant. The AIFs estimated by the MRTM generally demonstrate both a first pass peak and a washout phase. Even the second pass of the contrast agent bolus can be shown with striking details due to the high signal to noise ratio (SNR) of the fitted AIF (Fig. 1**b**). The AIFs estimated by the MRTM all closely resemble published AIFs determined by blood sampling (7). The adjusted chi-square of the fit by the AIFs estimated with the MRTM is usually over 10 times less than that by the fixed bi-exponential AIF. Due to the improved fit by the estimated AIF, the kinetic parameters of the tumor estimated on a voxel-by-voxel basis were found to have high SNR (Fig 1**c**-1**e**).

Discussions and Conclusions: The MRTM can be generally applied in DCE-MRI studies to estimate the local AIF of tumors using the heterogeneous tumor itself as a source of "multiple reference tissues". The estimated local AIFs closely resembled published AIFs and significantly improved the goodness of the fit. Further studies are needed to investigate whether this method can provide more reproducible quantitative DCE-MRI parameters to assess tumor perfusion and permeability, hence improving DCE-MRI based cancer diagnostics and therapeutic monitoring.

References: **1**. Yang C *et al*, MRM 2004; 52:1110. **2**. Port RE *et al*, MRM 1999; 10:233. **3**. Tofts PS *et al*, MRM 1991; 17:357. **4**. Fan J and Gijbel I, Local polynomial modeling and its applications, 1996. **5**. Riabkov DY and Di Bella EV, IEEE Trans Biomed Eng 2002; 49:1318. **6**. Everitt BS, Cluster analysis, 1993. **7**. Fritz-Hansen T *et al*, MRM 1996; 36:225.

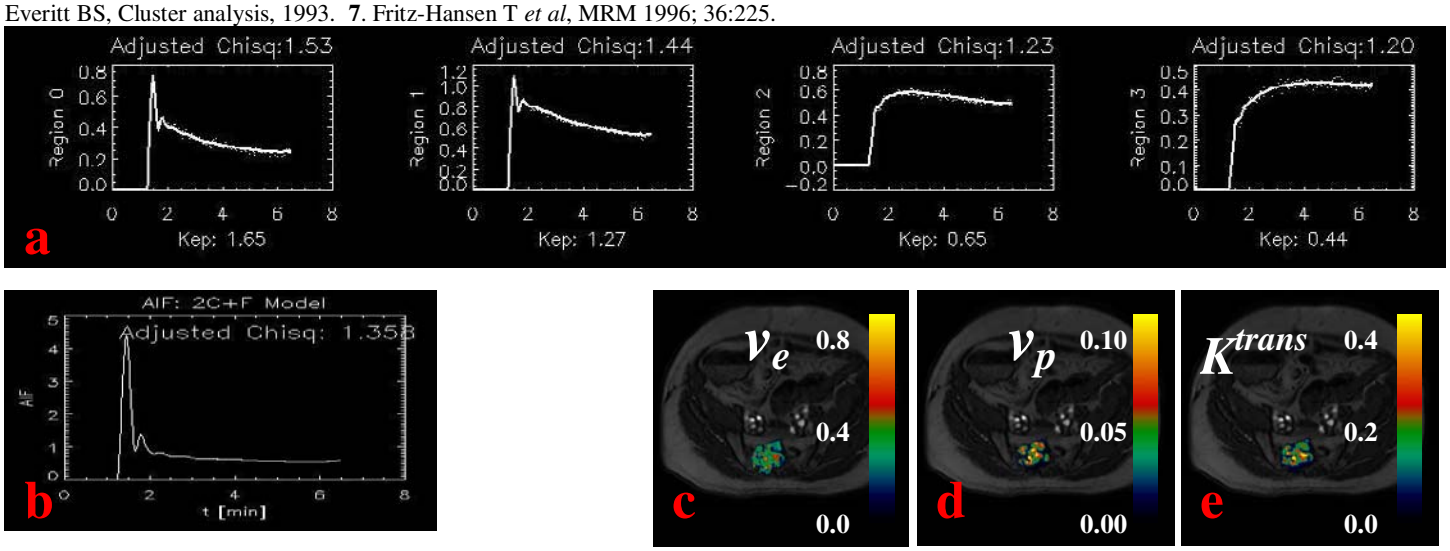

Figure 1: Application of the MRTM to a renal cell cancer patient. The kinetic model is determined to be a two-compartment model with significant blood plasma contribution. (**a**) Mean $C_t(t)$ of some subsets from the tumor ROI. X coordinate is the time in minute, Y coordinate is the concentration. The estimated AIF shown in (**b**) gives excellent fit (solid lines) to the measured data (dots). (**c**) extravascular extracellular space fractional volume (v_e) map of the tumor, (**d**) blood plasma contribution (v_p) map, (**e**) contrast agent transfer constant (K^{trans} [min^{-1}]) map.