Dynamic Contrast Enhanced – Magnetic Resonance Imaging (DCE-MRI): insights about Arterial Input Function definition, model selection and the quantitative Signal Difference method

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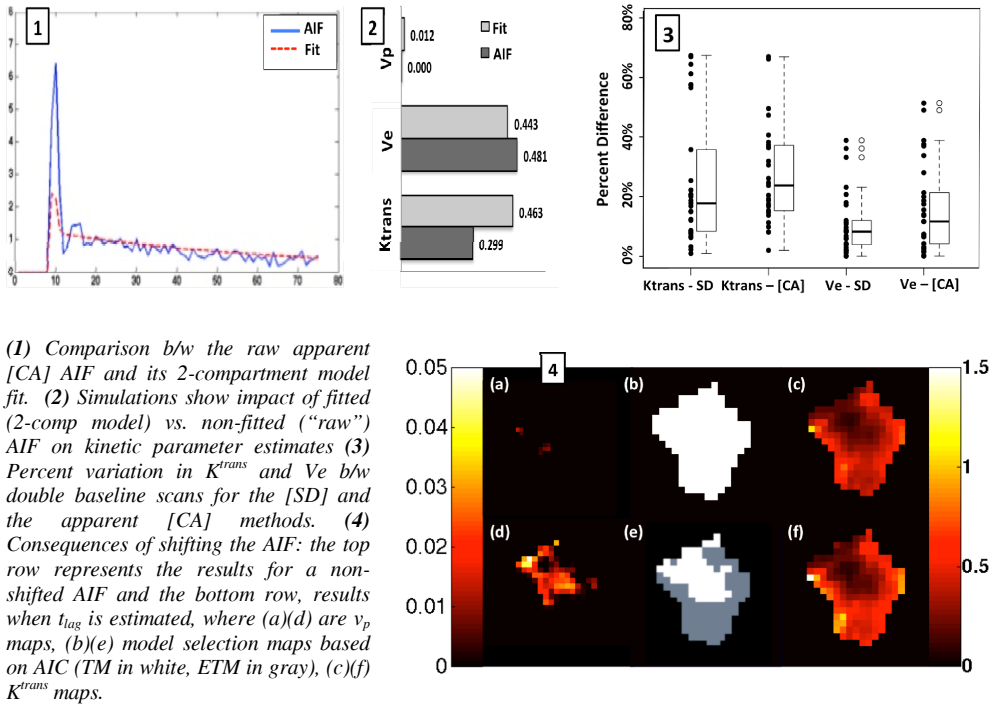
Introduction: Dynamic contrast enhanced MRI (DCE-MRI) is a useful tool that can help assess vascular changes and drug efficacy, particularly in drug angiogenesis targeted therapies. However, in order to employ DCE-MRI successfully in multicenter trials with longitudinal measures, data acquisition and processing needs to be streamlined and reproducibility of results must be emphasized. The goal of this work was to evaluate different approaches for the efficient processing of DCE-MRI data. We evaluated 1) the use of a "raw" arterial input function [AIF] as a forcing function in the kinetic model which was compared to a forcing function based on a 2-compartment model fitted to the same "raw" AIF data 2) the use of the signal difference [SD] method[1,2] which assumes linearity between signal intensity and concentration compared to the standard concentration-based [CA] approach which requires accurate T1 measurements, and 3) the effect of estimating t_{lag}, the time lag between the tissue and AIF uptake curves in the kinetic model, and its effect on estimates and interpretability of other model parameters, in particular the fractional blood plasma volume, v_p.

Material and Methods: This analysis makes use of simulated data in additional to data from 10 patients with liver metastases from colorectal cancer[3]. MRI scans were performed twice at baseline (within 48 hours) to establish parameter repeatability. 75 axial volumes were consecutively acquired every 4.97 s on a 1.5T Philips Intera system (Philips Medical Systems), using a 3D SPGR sequence (TR, 4.0ms; TE, 0.82ms; $\alpha = 20^{\circ}$), and a 0.1 mmol/kg bolus IV injection of Omniscan (Amersham Health). Apparent concentration was derived from T1 maps[4]. Kinetic analysis was performed using an in-house DCE-MRI R-package[5]. AIFs were defined for each patient in the aorta according to the method presented by Roberts et al.[6]. A non-fitted AIF was used as a forcing function in each kinetic model used, and for comparison, a conventional two-compartment model was fitted to the AIF. The signal difference time curves were obtained voxel-wise by subtracting the mean voxel pre-contrast signal intensity (SI) to the corresponding SI time curve. Data were normalized for each patient using the first baseline, in which the peak of the first-pass bolus was scaled to 1mM. The resulting scaling factor was then applied to the rest of the dynamic time curves (both tissue and AIF) and used to normalize the dynamic data of the second baseline scan. The time lag between the tissue and AIF uptake curves was estimated on a per slice basis, using the median lesion signal. Coefficient of Variation (%CV) and the Akaike Information Criterion (AIC) were calculated for each voxel to quantify parameter identifiability and goodness of fit, and to enable comparison between the Tofts Model (TM) and the extended Tofts model (ETM). Model parameters were derived only from tumor voxels that were defined as enhancing (more than 75% of the voxel's concentration or signal-difference values were above zero).



***(1)** Comparison b/w the raw apparent [CA] AIF and its 2-compartment model fit. **(2)** Simulations show impact of fitted (2-comp model) vs. non-fitted ("raw") AIF on kinetic parameter estimates **(3)** Percent variation in K^{trans} and Ve b/w double baseline scans for the [SD] and the apparent [CA] methods. **(4)** Consequences of shifting the AIF: the top row represents the results for a non-shifted AIF and the bottom row, results when t_{lag} is estimated, where (a)(d) are v_p maps, (b)(e) model selection maps based on AIC (TM in white, ETM in gray), (c)(f) K^{trans} maps.*

Results: Fitting the AIF with a 2-compartment model may result in the underestimation of the AIF's peak *(Fig.1)*. As shown by simulations, this can lead to errors in model parameter estimates as compared to the use of a forcing function *(Fig.2)*.

In this study, the [SD] method resulted in less variability (lower % difference) in model parameter estimates using double baseline scans, when compared to the [CA] method *(Fig.3)*. The outliers in *Fig.3* are largely based on lesions located at the edge of the FOV, and are likely affected by non-linearity between signal intensity and concentration at those locations.

Estimating t_{lag} increases mean v_p estimates and the number of voxels in tumors where the ETM better fits the data compared to the TM based on AIC. However, this shift has no significant influence on K^{trans} and Ve estimates *(Fig.4)*, and %CVs for kinetic parameters unchanged when estimating the lag. Based on our simulations, if the time lag is not accounted for, v_p values will be either zero or under-estimated. If the true $v_p>0$, then the ETM gives more accurate estimates than the TM. If the true $v_p=0$, both TM and ETM models converge to the same results, even for high levels of noise. This is true, however, only if time lags are taken into account; if not, the ETM may produce non-zero (erroneous) v_p estimates.

Conclusion: For future multi-center clinical trials including the use of longitudinal DCE-MRI measurements, we suggest using the [SD] method with a shifted data-derived non-fitted AIF, as these techniques reduce the requirements for both data acquisition and modeling. As found in other studies[1,7], repeatability of model parameter estimates with these methods is close, if not better than conventional methods. The tradeoff is some loss of precision, which is less of a concern when evaluating treatment effects over time. For the SD method, changes in coil placement may lead to differential scaling of AIF and tumor curves due to sensitivity (B1) variation that will bias quantitative measures over time. Consistency of coil placement should be emphasized in site training and may be later evaluated with the use of coil sensitivity maps. While K^{trans} and Ve values do not seem to be greatly influenced by the time lag between tissue and AIF uptake, estimating this parameter appears to be key for v_p estimates. Evaluating different model fits on a per-voxel basis requires additional computational time, but provides some insights on the robustness of parameter estimates. For voxels where the TM fits the data as well as the ETM, Vp estimates may be driven primarily by noise, and should be interpreted with caution.

References: [1] Ashton, ISMRM 2007, 2813 [2] Walker-Samuel et al., Phys. Med. Biol., 2007 [3] O'Connor et al., Clin. Cancer Res., 2009 [4] Do RK et al., Magn. Reson. Imag. Clin., 2009 [5] Ferl 2012, KATforDCEMRI, unpublished R-package [6] Roberts et al., MRM, 2010 [7] Zhao et al, ISMRM 2012, 1968.

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