Reproducibility of the Reference Region Method for the Analysis of DCE-MRI Data

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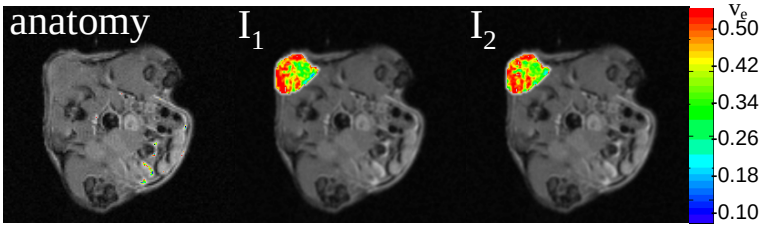
INTRODUCTION We have recently introduced a reference region model for the analysis of dynamic contrast enhanced MRI (DCE-MRI) data (1). The model relies on calibrating the signal intensity changes in the tissue of interest (TOI), e.g., a tumor, to that of a well characterized reference region (RR). The main result of the theory is given by Eq. [1]:

$$R_1^{TOI}(T)-R_{10}^{TOI} = R\bullet(R_1^{RR}(T)-R_{10}^{RR}) + R\bullet[(K^{trans,RR}/v_{e,RR}) - (K^{trans,TOI}/v_{e,TOI})]\bullet\int_0^T (R_1^{RR}(t)-R_{10}^{RR})\cdot\exp(-K^{Trans,TOI}/v_{e,TOI})\cdot(T-t))dt\,, \quad [1]$$

where R_1^{RR} and R_1^{TOI} are the longitudinal relaxation rate constants in the RR and the TOI, respectively, $K^{trans,RR}$ and $K^{trans,TOI}$ are the CR extravasation rate constants for the RR and TOI, respectively, and $v_{e,RR}$ and $v_{e,TOI}$ are the extravascular extracellular volume fractions for the RR and TOI, respectively, R_{10} is the pre-contrast R_1, and $R = K^{trans,TOI}/K^{trans,RR}$. Eq. [1] can be employed in a curve-fitting routine to extract $K^{trans,TOI}$ and $v_{e,TOI}$ if $R_{1,TOI}$ and $R_{1,RR}$ can be measured. By assigning a value to $v_{e,RR}$ fittings can be performed to extract $K^{trans,RR}$ and $K^{trans,TOI}$ and $v_{e,TOI}$. Similar methods have been presented by other groups (2,3). The purpose of these experiments is to test the reproducibility of this method. As DCE-MRI techniques find increasingly wide application in, e.g., assessment of tumor pharmacokinetics, it is important to know that the approach is reproducible and that variation from one imaging session to the next is due to physiological changes and not merely model imprecision.



	mouse #	1	2	3	4	5
	$K^{trans,RR}$	0.02	0.02	0.07	0.08	0.08
Inj. 1	$K^{trans,TOI}$	0.09	0.08	0.06	0.01	0.06
	$v_{e,TOI}$	0.28	0.12	0.14	0.05	0.16
	$K^{trans,RR}$	0.02	0.02	0.06	0.11	0.07
Inj. 2	$K^{trans,TOI}$	0.07	0.09	0.05	0.01	0.05
	$v_{e,TOI}$	0.25	0.10	0.13	0.06	0.12

METHODS Five female mice were injected subcutaneously in the hind limb with 10^6 4T1 mammary carcinoma cells and imaged using a Varian 7.0 T scanner equipped with a 38 mm quadrature birdcage coil one week post injection. A variable flip angle gradient echo approach was employed to produce a R_{10} ($\equiv 1/T_1$) map. The DCE-MRI protocol employed a standard T_1-weighted, GRE sequence to obtain 80 serial images for each of 8 axial oriented planes in 60 min of imaging. The parameters were: TR = 100 ms, TE = 3.1 ms, flip angle = 30°, FOV = $(30\text{ mm})^2$, slice thickness = 1.0 mm, matrix = 128^2, NEX = 4. A bolus of 0.2 mmol/kg Magnevist was delivered within 30 s *via* a tail vein catheter. Five Magnevist half-lives (~2.5 hours) were allowed to elapse (without removing the animal from the magnet) and the imaging procedure was repeated. Images were taken every 10 minutes between the two DCE studies so that all images could be spatially co-registered to the first image. In each mouse thirty voxels within the perivertebral muscle were selected as the RR. Both ROI and voxel-by-voxel analysis was performed; the large ROI was a 40 voxel region with the tumor. In each case, $v_{e,RR}$ was set to 0.08 (4) and $K^{trans,RR}$, $K^{trans,TOI}$, and $v_{e,TOI}$ were varied. $v_{e,RR}$ was fixed because it is well-characterized, while $K^{trans,RR}$ is less well characterized

RESULTS The **Figure** displays an axial view of a tumor from a central slice of mouse 1. The left panel is an anatomical image, while the middle and left panels are the $v_{e,TOI}$ parametric maps calculated for the first and second injections, respectively. Globally, there is little variation from the first to the second injection while local variations are small; there was less than 25% variation in over 70% of the voxels. ROI analysis was conducted on all mice and the **Table** summarizes those results. The difference in $K^{trans,RR}$ values from the first to second injections ranged from 15 % (mouse 2) to 38% (mouse 4). The difference in $K^{trans,TOI}$ values from the first to second injections ranged from 12 % (mouse 4) to 29% (mouse 1). The difference in $v_{e,TOI}$ values from the first to second injections ranged from 8% (mouse 4) to 33% (mouse 4). Overall, the variation in $K^{trans,TOI}$ and $v_{e,TOI}$ (from the first to second injection) averaged over all mice was 20% and 18%, respectively. Comparing the first injection to the second injection, all parameters test for correlation (r^2 = 0.92, 0.93, 0.98 for $K^{trans,RR}$, $K^{trans,TOI}$, $v_{e,TOI}$, respectively) and significance (all $P<0.01$).

DISCUSSION It was generally found that the $K^{trans,TOI}$ and $K^{Trans,RR}$ values had the most variation, while the $v_{e,TOI}$ value had the most stability. This is reasonable tissue volume fractions are not expected to change significantly during these five hour experiments, whereas some variation in vessel perfusion is reasonable on such a time scale. Standard power analysis suggests that, given a sample set of seven animals, the reference region model can significantly assess (with 90% power) longitudinal changes in tumors (due to growth or treatment response) as quantified by $K^{trans,TOI}$ and $v_{e,TOI}$, provided these parameters change by approximately 30%.

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