

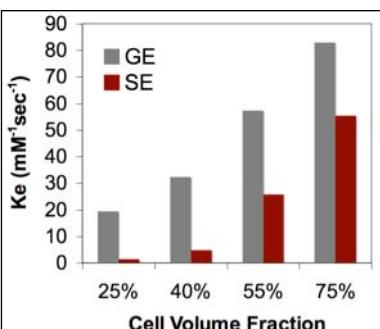
## The Assessment of Tumor Cellularity using DSC-MRI

N. B. Semmineh<sup>1</sup>, J. Xu<sup>1</sup>, J. C. Gore<sup>1</sup>, and C. C. Quarles<sup>1</sup>

<sup>1</sup>Radiology and Radiological Sciences, Vanderbilt University Institute of Imaging Science, Nashville, TN, United States

**Introduction:** The use of DSC-MRI for the assessment of tumor perfusion can be complicated when the blood-brain barrier is leaky, which can result in additional extravascular  $T_2^*$  effects well after the contrast agent (CA) initial bolus has passed through tissue [1]. The resulting DSC-MRI signals are then influenced by the extravascular compartmentalization of CA. We propose that such signals can be analyzed to extract imaging metrics sensitive to the spatial distribution of tumor cells within tissue (e.g. cell density, intercellular distance). The goal of this study was to investigate the relationship between the extravascular  $T_2^*$  effects and tumor cellularity using simulations as well as *in vitro* and *in vivo* studies.

**Methods:** To evaluate the magnetic field perturbations induced by susceptibility variations between arbitrarily shaped intra- and extra-cellular compartments, and the associated gradient echo (GE) and spin echo (SE) transverse relaxation rates, we used an efficient computational approach that combines the finite perturber method (FPM) [2] with the finite difference method (FDM) [3], which we term the Finite Perturber Finite Difference Method (FPFDM). A simulated 3D cellular phantom designed to reflect varying extravascular features (i.e. volume fraction, cell diameter, cell spacing) along with a range of CA concentrations was used as input for the FPFDM. The computed relaxation rates were used to determine the relationship between the extravascular susceptibility calibration factor ( $K_e = [CA]/R_2^*$ ) and cellularity. This relationship was also explored using *in vitro* cell phantoms. Cultured 9L cells were suspended in Matrigel, with varying density (25 – 80%) and doped with physiologically relevant concentrations of Gd-DTPA. Multi-echo gradient and spin echo images were



**Figure 2:** For a constant CA concentration, GE and SE  $K_e$  values depend on cell density.

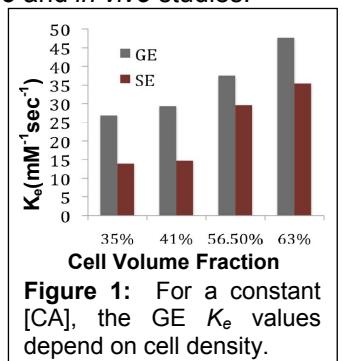
measure the transverse relaxation rates and calibration factors. Finally, *in vivo* studies were also performed in order to compare dual echo DSC-MRI derived  $K_e$  values [1,4] to DCE-MRI derived values of the extravascular extracellular volume fraction,  $v_e$  in a rat 9L gliomasarcoma model.

**Results:** Figure 1 shows that for a given CA concentration, the FPFDM predicts that the transverse relaxation rates, and the associated calibration factor, are highly dependent on the cell volume fraction. As cell volume fraction increases, or mean intercellular distance decreases, these effects become more pronounced. We are currently optimizing simulation conditions to include higher cell volume fractions. Similar results were found for the *in vitro* studies shown in Figure 2, which include a higher range of cell volume fractions. Consistent with the simulations and *in vitro* studies, an inverse correlation was found between the DCE-MRI parameter,  $v_e$ , and the dual-echo DSC-MRI derived  $K_e$  parameter, as illustrated in Figure 3.

**Discussion:** These preliminary results support the hypothesis that transverse relaxation rates that affect DSC measurements are highly sensitive to variations in cell density and distribution. They also confirm that DSC methods that assume the transverse relaxivity of agents is constant are prone to error. The effects described above will affect DSC-MRI signal time courses acquired in tissues with leaky vasculature but also suggest a new method for the assessment of tumor cellular features. Given the influence of CA distribution geometry on DSC-MRI it is expected that the spatial arrangement of cells (e.g intercellular distance) within tissue primarily determine these effects. Further, it is plausible that a combined GE and SE DSC-MRI approach, not unlike that used for vessel size imaging, could potentially be used to interrogate mean intercellular distance. Studies are currently underway to further characterize these effects.

**References:** [1] Quarles CC, et al, Phys Med Biol, 2009. [2] Pathak A P, et al. NeuroImage, 2008. [3] Junzhong Xu, et al. Phys Med Biol. 2007. [4] Quarles CC, et al, ISMRM 2007.

**Acknowledgements:** NCI R00 CA127599, NCI P30 CA068485, NCI U24 CA126588



**Figure 1:** For a constant [CA], the GE  $K_e$  values depend on cell density.



**Figure 3:** A comparison of DCE-MRI  $v_e$  and DSC-MRI  $K_e$  values reveals that  $v_e$  and  $K_e$  are inversely correlated, where low  $v_e$  regions (yellow, high cell density) correspond to regions with high  $K_e$  (red) and vice versa.