Cell Density and Spacing Influence DSC-MRI Data Acquired in Brain Tumors

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Introduction: In DSC-MRI studies, the leakage of contrast agent (CA) into the extravascular extracellular space (EES) creates magnetic field differences ($\Delta\chi$) between cells and the EES, which can result in additional extravascular T_2* effects well after the initial bolus of CA passes through the tissue. These effects have been clinically assessed using such metrics as the percent signal recovery [1]. We recently proposed that such DSC-MRI signals are influenced by the extravascular compartmentalization of CA and could potentially be used to extract information about the underlying spatial distribution of tumor cells within tissue (e.g. cell density, intercellular distance) [2]. The goals of this computational study were to 1) identify physically and physiologically relevant cell phantoms for simulating DSC-MRI data and 2) further investigate the relationship between the extravascular T_2* effects and tumor cellularity.

Methods: Simulated 3D cellular phantoms were created using packed spheres and ellipsoids. To achieve packing densities that approximate those found *in vivo* we created phantoms consisting of randomly distributed overlapping and non-overlapping spheres, face centered cubic (FCC) arranged spheres and ellipsoids with various aspect ratios [3]. For each phantom we varied the sphere or ellipsoid volume fraction, size and spacing. Magnetic field perturbations induced by susceptibility variations between the simulated intra- and extra-cellular compartments, and the associated gradient echo transverse relaxation rates, were computed using a computational approach that combines the finite perturber method (FPM) [4] with the finite difference method (FDM) [5], which we term the Finite Perturber Finite Difference Method (FPFDM) [6]. The susceptibility variations were computed for physiologically relevant CA concentrations.

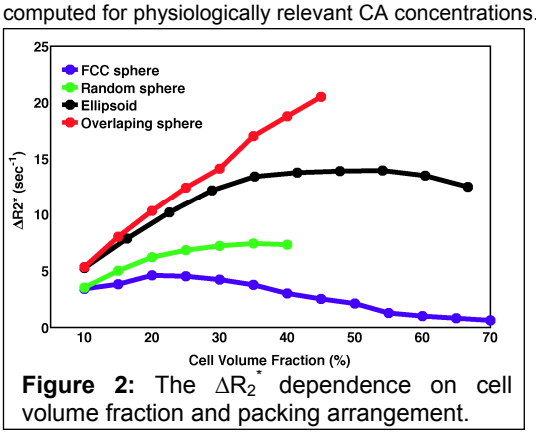

Figure 2: The ΔR_2^* dependence on cell volume fraction and packing arrangement.

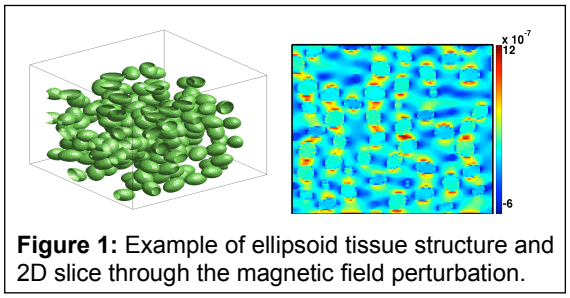

Figure 1: Example of ellipsoid tissue structure and 2D slice through the magnetic field perturbation.

Results: **Figure 1** shows an example phantom consisting of packed ellipsoids and a 2D plane of the computed magnetic field perturbations. As noted by Pathak et al, the advantage of the FPM is that field perturbations can be computed for arbitrarily shaped structures such as that shown here [4]. **Figure 2** shows the influence of four different packing arrangements on the computed ΔR_2^* values. Phantoms consisting of overlapping, randomly distributed spheres created the largest ($\Delta\chi$) values and exhibited a linear relationship with packing (or cell volume) fraction. Since the field perturbations for overlapping spheres are computed as if the perturbers do not overlap this approach likely overestimates the true ΔR_2^*. Conversely, the highly ordered FCC sphere phantoms resulted in the smallest ΔR_2^*, reflecting the relative homogeneity of the induced magnetic fields. Randomly oriented non-overlapping spheres yielded slightly greater ΔR_2^* changes and a non-linear relationship with packing fraction. Computationally, it is difficult to achieve high volume fractions using this approach making it difficult to adjust the features of interest (e.g. cell spacing). Finally, the packed ellipsoids, which better approximate cell shape, enable higher packing fractions (> 70%) and are less ordered, and also yielded a non-linear relationship between ΔR_2^* and cell volume fraction whose values were greater in magnitude than those found with non-overlapping spheres. Taken together these results demonstrate that ΔR_2^* values are highly dependent on the cell volume fraction and shape. For non-overlapping objects these effects become more pronounced for cell volume fractions ranging from 40 – 60%. For a fixed cell volume fraction of 30% and different $\Delta\chi$ values, the ΔR_2^* values also depend on the distance between cells as shown in **Figure 3**, where the minimum cell separation is the smallest distance between two ellipsoids in a given phantom. For comparison, the length of the longest semi major axis of the ellipsoids in this simulation was 10 μm. Thus, for a given cell volume fraction, cells that are closer together, such as may occur when cells are regionally localized within a voxel, will yield greater ΔR_2^* variations as compared to those that are more homogenously distributed throughout a voxel.

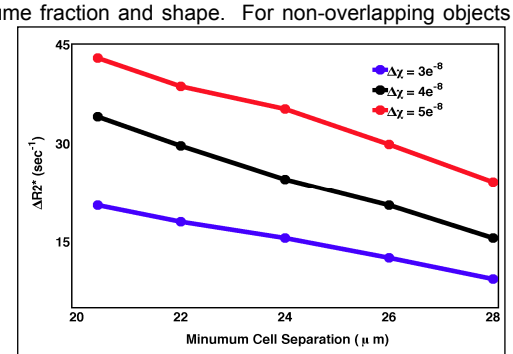

Figure 3: ΔR2* values depend on cell spacing.

Conclusion: The computational results presented herein support the hypothesis that DSC-MRI data acquired in the presence of contrast agent leakage are highly sensitive to variations in cell density, distribution and geometry.

References: [1] R. Mangla, et al, AJNR Am J Neuroradiol, 2010. [2] Quarles CC, et al, Phys Med Biol, 2009. [3] G. W. Delaney, *et al*, Phys Rev Lett, 2010. [4] Pathak A P, et al. NeuroImage, 2008. [5] Junzhong Xu, et al. Phys Med Biol. 2007.[6] Natenael S, et al. ISMRM 2011.

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