

## Comparison of cellular- and tissue-scale models of dynamic contrast-enhanced MRI

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**Introduction:** Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a temporal imaging technique used to evaluate vascular and cellular properties of tissue in a variety of cancers. During rapid acquisition of  $T_1$ -weighted MR images, a paramagnetic contrast agent is introduced intravenously in a controlled manner. The resulting signal intensity time-course for each voxel within the imaging matrix can then be fit to a pharmacokinetic model [1], which allows for the determination of local tumor tissue properties, including, for example, vascular volume fraction ( $v_p$ ), extravascular extracellular volume fraction ( $v_e$ ), and the volume transfer constant ( $K^{trans}$ ; related to vessel perfusion and permeability). Standard pharmacokinetic models assume active delivery and equilibration of the contrast agent within each voxel, but slow diffusion of contrast agent is not currently incorporated. This effort aims to evaluate the error associated with the standard model due to contrast agent diffusion, using biological tissue samples.

**Methods:** Nude mice ( $n=3$ ) were subcutaneously injected with BT474 breast cancer cells, and allowed to grow into tumors of approximately 250 mm<sup>3</sup>. Tumors were excised, and sequential histological sections were taken and stained for cellularity (H&E) and vascularity (CD31)<sup>2</sup>. This data was digitized and segmented to identify cellular, vascular, and extravascular extracellular regions within the tumor (MATLAB Image Processing Toolbox, Natick, MA). The resulting segmented image was meshed for transient finite element method (FEM) implementation of the standard model, simulating perfusion and diffusion of the contrast agent at the cellular scale<sup>3</sup>. This is performed using the 2D diffusion equation within the extracellular space, and active delivery of contrast agent at vessel boundaries. Simulations were performed for a physiological range of diffusivities,  $D$ , [ $1 - 4 \times 10^{-4}$  mm<sup>2</sup> s<sup>-1</sup>]. The resulting maps of contrast agent concentration were partitioned into MR-voxel sized regions (438  $\mu$ m  $\times$  438  $\mu$ m), and signal intensity was calculated. Signal intensity time courses for each region were fit to the standard model (tissue-scale) to obtain parameters analogous to those obtained from *in vivo* imaging.

**Results:** Using a well-perfused voxel, and increasing  $D$  from  $1 \times 10^{-4}$  to  $4 \times 10^{-4}$  mm<sup>2</sup> min<sup>-1</sup>, the absolute parameterization error of  $v_e$  is reduced from 13.0% to 2.1%, and  $K^{trans}$  is reduced from 68.3% to 37.7%. Artificially reducing the cellularity of the domain by morphological erosion further improved parameterization error;  $v_e$  was reduced to 1% (from 13%), and  $K^{trans}$  was reduced to 5% (from 22%) ( $D = 4 \times 10^{-4}$  mm<sup>2</sup> s<sup>-1</sup>). Using entire tumor domains from mice ( $n=3$ ), it was determined that the percent error of  $v_p$  is minimized with a short signal intensity time-to-peak, while  $v_p$  error is maximized in voxels with a long time-to-peak.

**Conclusion:** Error in the standard analysis of DCE-MRI data can be attributed to the slow diffusion of contrast agent within the tissue domain, and the tortuous network of the extracellular space, which contribute to the uneven distribution of contrast agent within the tumor domain. In order to improve the accuracy of the standard model, we propose the inclusion of a diffusion term which corrects for physiological levels of contrast agent diffusivity.

**References:** [1] Tofts *et al.*, *Magn Reson Med*, 1991; 17 (2) : 357-67. [2] Sorace *et al.*, *Breast Cancer Red Treat*, 2016; 155 (5) : 273-83. [3] Barnes *et al.*, *PlosOne*. 2014; 9 (9)