Modeling Relaxation Effects during Bolus Passage through Leaky Vasculature using the Finite Perturber Method

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INTRODUCTION: Dynamic susceptibility contrast MRI (DSC-MRI) is a novel tool that has shown promise to increase the predictive power of diagnostic imaging, for example in the assessment of brain tumor grade [1]. Alterations in microvascular parameters such as blood volume and vascular permeability induced by pathological angiogenesis are detectable with DSC-MRI. However, the basic assumptions of DSC-MRI analysis are violated by contrast agent extravasation and recirculation, making it challenging to reliably quantify microvascular parameters in common brain pathologies such as brain tumors, stroke, and infection [2]. While analytical expressions for correcting contrast agent extravasation effects have been proposed, they are limited by computational approximations and assumptions regarding the underlying pathological vasculature [2]. Since microvessel geometry is a significant determinant of DSC-MRI contrast [3], we recently developed a novel computational platform called the *finite perturber method* (FPM), with which we can quantify susceptibility-induced contrast arising from *arbitrary* microvascular geometries [4]. In this preliminary work, we extended the FPM by incorporating a compartmental model to simulate arterial bolus passage and contrast agent extravasation. This allowed us to quantify the effects of contrast agent extravasation on the measured gradient-echo (GE) and spin-echo (SE) DSC-MRI signals, providing a powerful framework for assessing the complex dependence of the DSC-signal on the underlying microvasculature.

METHODS: In the FPM approach, the underlying vessel geometry is divided into minute "perturbers". To calculate the field shift at a given point, the shift due to each perturber is calculated independently. The total field shift is then calculated as the sum of the field shifts from all the perturbers. The field shift arising from the entire vascular structure is computed in the Fourier domain, details of which can be found in [4]. The FPM was extended to include an analytical model for the arterial input function [5]. An ensemble of randomly oriented cylinders was used to model the spatial and temporal distribution of microvascular susceptibility gradients that occur during contrast bolus passage. Contrast extravasation was modeled using a 2-compartment model [6]: $dC_T(t)/dt=K^{Trans}(C_a(t)-C_T(t)/v_e)$. C_T is the tissue concentration, K^{Trans} the influx constant, $k_{ep}=K^{Trans}/v_e$ the efflux constant, v_e the leakage space and C_a the microvascular contrast concentration. Both, effects of contrast leakage on T1: ΔT_1= 1-exp(-TR/T_1)exp(-TR•R_1•C_T•v_e), and on ΔR2 and ΔR2* due to reduction of the susceptibility gradient (Δχ) across the vessel walls: $\Delta\chi=\chi_a-\chi_T$ were considered. R_1 is the relaxivity of the contrast material, TR the repetition time. The biophysical parameters for the simulations were: B_0=1.5T, $\Delta\chi(max)=2\times10^{-6}$ (~72mM Gd-DTPA), fractional volume (FV)=0.003, TE_{GE}=60ms, TE_{SE}=60ms, dt=0.2ms, unrestricted diffusion coefficient=1.0 μm^2/ms, with 10000 protons randomly placed in the simulation universe, TR=1000 ms, T1=500 ms, $R_1=1.35\times10^4$ s^{-1}M^{-1}. Different tracer kinetic parameters were used (see figure legend) to simulate microvasculature in different angiogenic states ranging from highly permeable to low permeability.

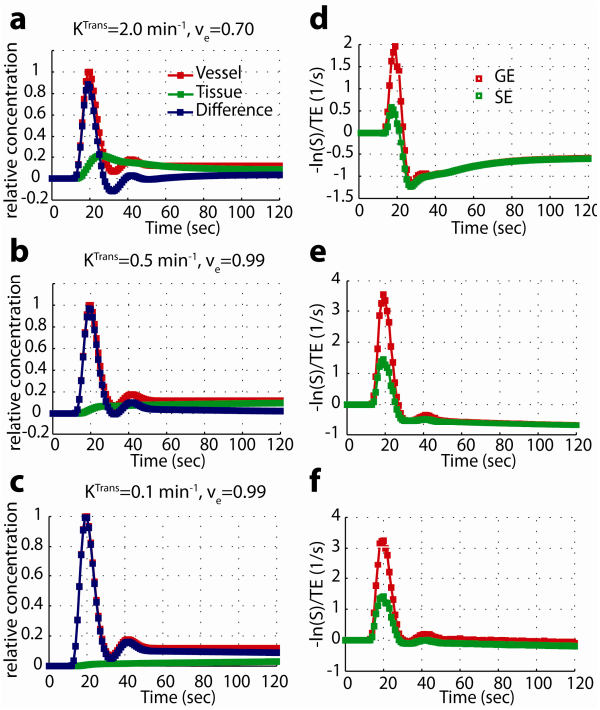

Figure 1: Diagrams depicting the simulated arterial contrast agent concentration, tissue concentration and concentration gradient as a function of time (a-c), and the simulated ΔR2 (SE) and ΔR2* (GE) as a function of time during bolus passage (d-f). Variation of K^{Trans} and v_e leads to significant differences in the observed DSC-MRI signal.

RESULTS: **Fig. 1a-c** show the relative microvascular contrast agent concentrations in a blood vessel, the tissue and the difference between the two, while **Fig.1d-f** show the resulting concentration-time ($\Delta R2^*(t)$ or ΔR2(t)) curves, respectively. One can clearly see that contrast extravasation leads to an increase in the tissue concentration (**Fig. 1a-c**, green traces). The concentration difference between the intravascular and the extravascular compartments (**Fig. 1a-c**, blue traces) determines the susceptibility gradient (Δχ) responsible for spin dephasing. In the case of highly permeable vessels with high vascular volume (**Fig. 1a,d**) contrast extravasation occurred quickly, producing significant undershoot for GE and SE signals. For the case of intermediate to low vascular permeabilities (**Fig.1b,e and c,f**), the previously described undershoot of the DSC-MRI signal was less pronounced.

DISCUSSION: The data presented in **Fig. 1** demonstrate that the effect of contrast agent extravasation on the DSC-MRI signal can be successfully modeled with the FPM. The complex relationship of multiple vascular (geometric, permeability, perfusion) and contrast-agent related parameters, as well as MR sequence-dependent parameters (TE and TR, GE or SE acquisition), can be examined with this approach. The presented preliminary data demonstrate that known characteristics of DSC-MRI signal curves can be modeled [4, 7]. However, further simulations are warranted to explore the dependence of the relaxation rates (ΔR2, ΔR2*) on the vascular geometry, contrast agent leakage, and the relative vessel distribution. Comparison with findings reported in the literature in various pathologies, such as stroke and brain tumors are currently being addressed in our laboratory. Such approaches will help determine the optimal acquisition parameters for clinical DSC-MRI protocols.

CONCLUSIONS: These simulations demonstrate the successful extension of the FPM to include vascular permeability and bolus tracking experiments. This new modeling approach provides a powerful framework to optimize imaging sequences and to examine the complicated interaction of pathological, physiological and biophysical phenomena that result in the observed DSC-MRI signal.

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