A Monte Carlo study of the effects of cell membrane permeability on DWI-MRI contrast with oscillating diffusion gradients

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Introduction: Recent interest in the use of oscillating diffusion gradients in diffusion-weighted magnetic resonance imaging (DWI-MRI) stems from simulated and experimental results indicating that, for given gradient performance parameters (max. amplitude, slew rate), an oscillating gradient spin echo (OGSE) sequence is capable of sampling shorter diffusion times than conventional pulsed gradient spin echo (PGSE) sequences. The result is that, for a given b-value, OGSE’s generate contrast based on apparent diffusion coefficients (ADC’s) that are more likely to reflect changes in intracellular morphology, such as nucleus-to-cell volume ratio, associated with malignancy than PGSE’s. In order to assess the potential for OGSE’s in the early diagnosis of cancer, it is important to understand the effects of such cell parameters as membrane permeability on contrast. Up until now, analytical treatment of OGSE’s even in relatively simple cell-like geometries was unavailable, although there are some promising recent developments based on Callaghan’s impulse propagator theory (1). In this study, Monte Carlo simulations are used to assess the effects of membrane permeability on contrast between healthy and malignant cells when OGSE’s are used.

Fig 1: Simulation geometry

Methods: The Monte Carlo simulation used was an extension of the Camino DWI Java-based simulation toolkit (2). For this study, a new nested sphere geometry was programmed and implemented as a simplified cell model. In addition, the ability to simulate spatially varying diffusion step lengths, necessary to simulate the different diffusion environments, was implemented. The inner sphere represented the nucleus and the outer sphere the cytoplasm. Cells were packed in rectilinear voxels in a face centred cubic manner (intracellular volume ~ 74% of total volume) as shown in Fig. 1. Default cell parameters were taken from Xu et al (3): cell radius = 5 μm, diffusion coefficient (D) inside nucleus = 1.31 μm²/ms, D in cytoplasm = 0.48 μm²/ms, D in extracellular fluid = 1.82 μm²/ms. The nucleus-to-cell volume ratios (N/C) used were 6.2% and 22%, values indicated (3) for healthy and malignant cells, respectively. Prior to simulating an OGSE scan, diffusing particles were allowed to reach a non-uniform equilibrium distribution based on infinite mixing time with fully permeable membranes between compartments in the simulation geometry. A typical OGSE sequence is shown in Fig 2. Symmetric oscillating gradients are applied on either side of the 180° refocusing pulse. OGSE sequences simulated all had TE = 40 ms and sinusoidal gradient waves were simulated with 100 points/cycle. T2 relaxation effects were ignored. Simulations comprising 1x10⁶ particles and 10,000 time steps of 0.004 ms were carried out on two quad-core Intel Xeon CPU’s, and each required ~ 12 hrs to complete.

Results: Fig 3 shows relative signal difference (contrast) between cell systems with N/C=6.2% (healthy) and N/C=22% (malignant) as a function of OGSE frequency for cases where the probability of particles crossing the outer cell wall was held at zero (P_{cell}=0). The gradient amplitude at all frequencies was 1000 mT/m. Curves are shown for four different probabilities of particles crossing the nuclear membrane, P_{nuc}. P_{nuc}=0.036 corresponds to the physiological nuclear membrane permeability of 0.024 μm/ms (3), while P_{nuc}=0.013 is the value given by Xu et al (4) in an earlier paper. Fig 4 shows healthy-malignant contrast as a function of OGSE frequency for four different probabilities of crossing the cell outer wall, P_{cell}, with P_{nuc}, held at 0.036. P_{cell}=0.126 corresponds to the physiological cell membrane permeability of 0.024 μm/ms (3).

Discussion: The effect of increasing nuclear membrane permeability is to increase the maximum possible contrast achievable with an OGSE and shift this peak to lower frequencies. For example, peak contrast with P_{nuc}=0.1 occurs at ~200 Hz and is 1.75 times that with P_{nuc}=0.013 at 300 Hz. The effect of changing cell wall permeability, meanwhile, is minimal. The increasing contrast with increasing P_{nuc} can be explained as being due to the increased rate of movement from the relatively slow diffusion environment of the cytoplasm (D=0.48 μm²/ms) into the relatively fast diffusion environment of the nucleus (D=1.31 μm²/ms). These results indicate the importance of nuclear membrane permeability as a potential source of contrast in DWI-MRI and also the importance of including its effects in any modeling of DWI-MRI in cell systems.