A theoretical framework to model diffusion MRI signals taking into account cell membranes

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Introduction

We want to investigate the relationship between physiological parameters and the observed diffusion MRI signal. Using a method based on heat layer potentials derived from the relevant Green's function, coupled with appropriate interface and boundary conditions, we model diffusion in biological tissue and simulate MRI signal attenuation. The input parameters to our model are the diffusion coefficients in the intra-cellular compartment, the extra-cellular compartment, and an interface ('membrane') compartment linking the two, the dimensions of the compartments, and continuity conditions on the interior and exterior of the 'membrane' compartment.

Method

For simplicity, as a first test case for our proposed method, we use the narrow pulse approximation:

$$S(\mathbf{q},\Delta) = \int_{\mathbf{z}_0}\int_{\mathbf{z}} e^{i\mathbf{q}(\mathbf{z}-\mathbf{z}_0)} P(\mathbf{z},\mathbf{z}_0,\Delta)\ \rho(\mathbf{z}_0)\ d\mathbf{z}\ d\mathbf{z}_0, \quad \mathbf{q} = \gamma\,\mathbf{g}\,\delta,$$

where ρ(z0) is the density distribution of the initial positions and P (z, z0, Δ) is the conditional probability of a spin initially at z0 being at z at time t = Δ. We will use the following diffusion model for P :

$$\left.\begin{aligned} P(\mathbf{z},\mathbf{z}_0,t) &= P^i(\mathbf{z},\mathbf{z}_0,t) \\ \frac{\partial P^i(\mathbf{z},\mathbf{z}_0,t)}{\partial t} &= D^i\nabla^2 P^i(\mathbf{z},\mathbf{z}_0,t) \end{aligned}\right\} \quad \mathbf{z}\in\Omega^i,\ i=\{\text{' intra', 'extra', 'mem'}\},$$

$$\left.\begin{aligned} D^i\frac{\partial P^i(\mathbf{z},\mathbf{z}_0,t)}{\partial \mathbf{n}} &= D^j\frac{\partial P^j(\mathbf{z},\mathbf{z}_0,t)}{\partial \mathbf{n}} \\ C^{ij}P^i(\mathbf{z},\mathbf{z}_0,t) &= P^j(\mathbf{z},\mathbf{z}_0,t) \end{aligned}\right\} \quad \mathbf{z}\in\Gamma^{ij},\ i,j=\{\text{' intra', 'extra', 'mem'}\},$$

where Ω^i, i = {' intra', 'extra', 'mem'} are the intracellular domain, the extracellular domain, and an interface domain around the membrane separating the two, respectively. The boundary separating domains i and j is denoted by Γ^{ij}. We use the layer potential representation for each P [i]:

$$P^i(\mathbf{z},\mathbf{z}_0,t) = w^i G(D^i,\mathbf{z},\mathbf{z}_0,t) + \sum_j\int_0^t\int_{\Gamma^{ij}} G(D^i,\mathbf{z}-\mathbf{y},t-\tau)\ \sigma^{ij}(\mathbf{y},\tau)ds_{\mathbf{y}}d\tau + \sum_j\int_0^t\int_{\Gamma^{ij}} \frac{\partial G}{\partial n_{\mathbf{y}}}(D^i,\mathbf{z}-\mathbf{y},t-\tau)\ \mu^{ij}(\mathbf{y},\tau)ds_{\mathbf{y}}d\tau,$$

where G(D^i, z, z0,t) is the free space Green's function for the diffusion coefficient D^i, and w^i =1 if z0 is in Ω^i and w^i = 0 otherwise. The first term in the above equation gives the correct initial condition, and second and third terms, called the single layer potential and the double layer potential, respectively, give the correct boundary conditions on Γ^{ij}. All three terms satisfy the diffusion equation with coefficient D^i, by construction. The densities σ^{ij} and μ^{ij} are unknowns and are discretized on the boundaries Γ^{ij}, i.e., the interface between the interior and the membrane regions and the interface between the membrane and the exterior regions. In fact, by slightly modifying the representation above, we suppose an infinite periodic lattice of point sources (with spacing L) and compute in each solve the quantity:

$$P^{periodic}(\mathbf{z},\mathbf{z}_0,t,\mathbf{q}) = \sum_{m\in\mathbb{Z}} e^{i\mathbf{q}(-(\mathbf{z}_0+2m\mathbf{L}))}P(\mathbf{z},\mathbf{z}_0+2m\mathbf{L},t).$$

Results and discussion

We show the results of simulation for an infinite array of circular cells placed L=12 μm apart in x and y directions. Each intra-cellular compartment is a disk with a radius of 4 μm and D =10^{-3} $\mu m^2/\mu s$, each 'membrane' compartment (in fact the actual cell membrane and a slow diffusion domain extending on each side) is an annulus with an inner radius of 4 μm and an outer radius 5 μm, with D = 10^{-4} $\mu m^2/\mu s$, the exact-cellular compartment is the volume that remains and has D=10^{-3} $\mu m^2/\mu s$. We simulate up to Δ =10 ms. As a demonstration, we place a **single point source** in the interior of each intra-cellular compartment, at [-0.95,-1.29] μm from the center, and obtain the probability density distribution $P^{periodic}$ and the attenuation S for four values of **q,** using the orientation [1,1] and strengths 0, 0.1, 0.2, and 0.3 μm^{-1}. The computed $P^{periodic}$ at Δ=5ms and Δ=10ms is plotted in Figure 1, for one period of the lattice. We see that there is high probability of finding the particle in the interior compartment and the membrane compartment by the end of simulation time, but very little probability that it has entered the exterior compartment by that time. The attenuation S is plotted in Figure 2 at Δ= 0.5ms, 8ms, 10ms. The bottom line is a plot of $e^{-iq^2\Delta}$, D =10^{-3} $\mu m^2/\mu s$,the free diffusion attenuation with the larger D, the top line the free diffusion attenuation due to D = 10^{-4} $\mu m^2/\mu s$. The black line (diamond) is the volume weighted sum of the two free diffusion exponentials (no exchange case). The black line (circle) is free diffusion with a single weighted-averaged D = 8.23x10^{-4} $\mu m^2/\mu s$. The red line (x) is the computed attenuation, exhibiting a behaviour that changes from fast free diffusion at the short times (the particle not having seen the membrane) passing through intermediate values and exhibits slow diffusion for long times as the particle seems trapped by the slow diffusion compartment near the membrane. These results will be extended by integration over point sources placed everywhere in the domain to obtain a concentration weighted attenuation (actual MRI signal).

The time step we used in the present simulation was 100 μs, hence only 100 time steps were needed to compute the results discussed here.

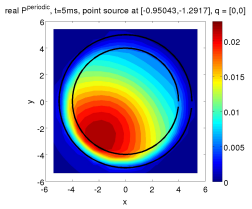

Figure 1a. t=5ms

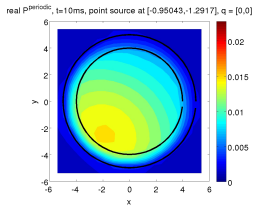

Figure 1b. t=10ms

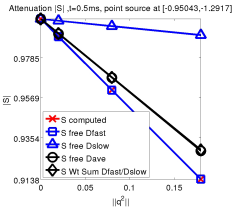

Figure 2a. t=0.5ms

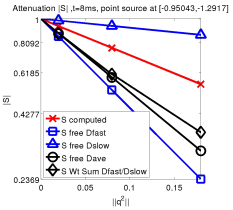

Figure 2b. t=8ms

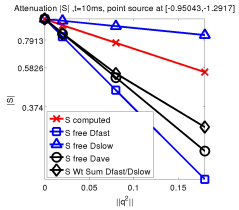

Figure 2c. t=10ms

Conclusion

This method is an alternative to Monte-Carlo or finite difference based simulation methods. An advantage is that much larger time steps can be used in simulation, while preserving accuracy and stability of the numerical method. This method should be faster/more accurate than Monte-Carlo or finite difference for the simulation of diffusion under simple interface conditions, and especially in simple geometries. It would be also promising as a part of an hybrid method, for example, in conjunction with Monte-Carlo, to treat complicated interface conditions and geometries. The method and results are presented for two dimensions. Future work in more accurate pulse approximations and extension to three dimensions is planned and poses no theoretical difficulties.