An Extended Matrix Method for Analysis of Restricted Diffusion in Multi-Compartment Tissue

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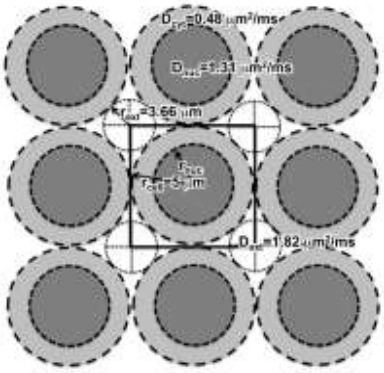
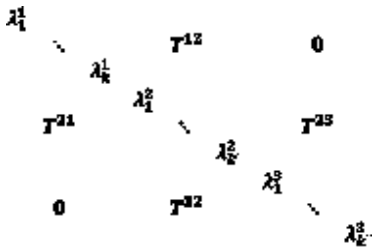
Introduction: Diffraction patterns found in q-space analysis of diffusion in a restricted geometry have offered hope of being able to infer nucleus size directly from the locations of signal minima. Nucleus size can be the sole indicator of cancer in its earliest stages. The impulse-propagator (matrix) formalism allows one to extend diffraction results with simple delta functions to realistic PGSE and OGSE sequences, but has not heretofore been applied to realistic cell geometries defined by semi-permeable membranes. Here we extend the matrix method to an idealized representation of nucleus, cytoplasm, and extracellular fluid in a random array of identical cells, with nuclear membrane permeability.

Methods: We consider a collection of spherical cells containing concentric spherical nuclei. Our models of the extracellular region range from free diffusion to flow in a collection of spheres fitted to the interstitial spaces. In the impulse-propagator formalism[1], the normalized signal from each compartment is approximated as a series of delta-function impulses, with q-values $\mathbf{q}_1,\mathbf{q}_2,\ldots\mathbf{q}_N$. The normalized signal is:

$$S/S_0=S(\mathbf{q}_1)RA(\mathbf{q}_2)RA(\mathbf{q}_3)\ldots..RS^T*(-\mathbf{q}_N)$$

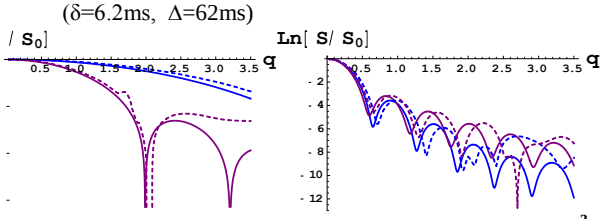


where the A's are matrices expressing the effects of the individual impulses, the S's are vectors representing the first and last impulses, and R is a diagonal matrix representing diffusion between impulses. The elements of the A's, S's, and R are derived using a basis of eigenfunctions of the diffusion operator $D\nabla^2$ with boundary conditions appropriate for the compartments. For spherical compartments, these eigenfunctions are of the form $u_{klm}(r,\theta,\varphi)= F^l(c_{kl}\, r)\, Y^l_m(\theta,\varphi)$, where F^l is a linear combination of spherical Bessel functions of the first and second kind, both of order l, the constants c_{kl} are chosen so as to satisfy reflecting boundary conditions at the membranes, and Y^l_m is a spherical harmonic[2]. About 1000 modes u_{klm} are needed for adequate spatial resolution, defining matrices of dimension 1000x1000. For a configuration of 3 compartments with semi-permeable membranes, the matrices A generalize to block-diagonal matrices composed from the A-matrices for the separate compartments, while the new R matrices are of the form:

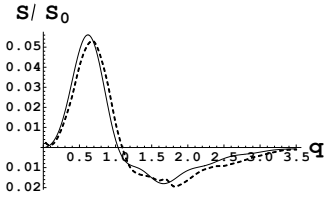


where the λ's are the eigenvalues of the diffusion operator for compartments 1,2, 3, and the T matrices, giving transitions between adjacent compartments, are formed from integrals of products of modes along the membranes. To compensate for the inter-compartment transition probabilities, intra-compartment propagators are crudely "renormalized", giving an adjustment of the A matrices for the separate compartments. For the case of impermeable membranes, with T=0, results were verified by comparing with those of a Monte Carlo simulation for the same geometry.

Impermeable membranes: PGSE Results
(δ=6.2ms, Δ=62ms)



contrast in total signal:
S/S_0(N/C=22%) - S/S_0(N/C= 6.2%)

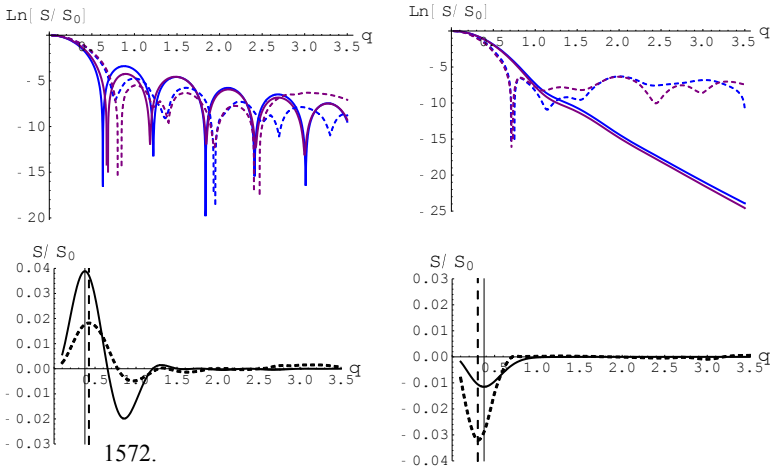


Results: Normalized signal vs. q (in units of $1/R_{cell}$) is shown for nucleus and cytoplasm, with results displayed for r_{nuc}=2μm (blue) and for r_{nuc}=3μm (purple). The contrast between the two cases is also shown. A strong diffraction pattern is observed with a PGSE sequence for both cytoplasm and nucleus. In the worst case, a diffraction pattern is absent in the total 3-compartment signal (not shown) but there is significant contrast between the two cases that can be traced to the first minimum in the cytoplasm pattern. Results compare favorably with those of corresponding Monte Carlo simulations[3] (dashed lines), especially for low q values. (On the other hand, a Gaussian Phase Distribution (GPD) approximation that uses the same eigenfunctions but gives a smooth drop off in signal as q increases[4], without a diffraction pattern, gives markedly different contrast results[3].) For membranes with biological permeability, signals for both PGSE and OGSE sequences differ in detail from the Monte Carlo results (dashed lines) based on a more exact treatment of intra-compartment propagation, but the contrast patterns in the bottom two panels are qualitatively similar, and agree in regard to optimal q values (vertical lines).

Discussion: 1) With a semi-permeable nuclear membrane, variations in a diffraction pattern that corresponds to the dimensions of the whole cell appear to be key to optimizing pulse sequences for sensitivity to nucleus size.

2) A method which represents inter-compartment propagation exactly, and adjusts intra-compartment propagation approximately, is sufficient for pulse-sequence optimization – an approach that is expected to generalize to other geometries and optimization scenarios.

Semi-permeable membranes: Signal from Nucleus + Cytoplasm
PGSE OGSE(f=80Hz, Δ=62ms)



References: **1**. Callaghan PT, J Mag Res 129: 74-84 (1997);
2.Codd SL, Callaghan PT, J Mag Res 137: 358-372 (1999);
3. Duane GS, Wang Y, Walters BR, Kim JK, J Mag Res (2013), available online: DOI 10.1016/j.jmr.2013.10.012;
4. Xu J, Does MG, Gore JC, J Mag Res 200:189-197 (2009)