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Pulsed-gradient spin-echo monitoring of restricted diffusion in multilayered structures

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ABSTRACT

A general mathematical basis is developed for computation of the pulsed-gradient spin-echo signal attenuated due to restricted diffusion in multilayered structures (e.g., multiple slabs, cylindrical or spherical shells). Individual layers are characterized by (different) diffusion coefficients and relaxation times, while boundaries between adjacent layers are characterized by (different) permeabilities. Arbitrary temporal profile of the applied magnetic field can be incorporated. The signal is represented in a compact matrix form and the explicit analytical formulas for the elements of the underlying matrices are derived. The implemented algorithm is faster and much more accurate than classical techniques such as Monte Carlo simulations or numerical resolutions of the Bloch–Torrey equation. The algorithm can be applied for studying restricted diffusion in biological systems which exhibit a multilayered structure such as composite tissues, axons and living cells.

1. Introduction

A pulsed-gradient spin-echo (PGSE) technique is a non-invasive experimental tool for studying diffusive processes in mineral porous media and biological systems [1–4]. The past decade is marked by a significant increase in spatial resolution, image quality and acquisition rapidity that resulted in numerous clinical applications such as brain or lung imaging [5–10]. In turn, the progress in theoretical understanding of restricted diffusion in such complex systems is less spectacular. Although the theory is well established for few simple confining shapes (such as slab, cylinder and sphere) [11], its extension to heterogeneous media is essentially an open problem. Several phenomenological formulas (e.g., bi-exponential fit, stretched-exponential fit, etc.) are therefore used for fitting and interpreting measured signals in biological systems [12–18]. Physical and geometrical interpretation of fitting parameters, as well as the respective roles of various attenuation mechanisms (bulk and surface relaxation, permeation through boundaries, etc.), are still poorly understood in general.

We propose a general mathematical description of restricted diffusion in multilayered structures (Fig. 1), in which the Laplace operator eigenfunctions are known in a closed analytical form:

- multiple slabs separated by parallel planes (e.g., a model of composite or multilayered tissues);
- multiple cylindrical shells (e.g., a model of axons); and
- multiple spherical shells (e.g., a rough model of a living cell in which layers represent a nucleus, a cytoplasm, and an extracellular space).

Pulsed-gradient encoding of any temporal profile, individual bulk relaxivity and diffusivity for each layer, different permeabilities between adjacent layers, and exchange with an exterior space are rigorously included in this treatment. An efficient, accurate and rapid numerical tool for computing the signal attenuation is designed and implemented in Matlab. Since most computations are performed analytically, this matrix formalism significantly outperforms classical numerical methods such as Monte Carlo simulations.

The paper is organized as follows. Section 2 describes the mathematical basis of the spectral approach to restricted diffusion in multilayered structures. Although the formulas may look cumbersome and sophisticated, their practical implementation is straightforward. After all, restricted diffusion in multilayered structures is a complex phenomenon which needs an adequate description. In Section 2.1, the Bloch–Torrey equation is formulated for multilayered structures and its physical interpretation is recalled. Section 2.2 introduces the Laplace operator eigenfunctions. In Section 2.3, the computation of the Laplace operator eigenvalues is detailed. Section 2.4 summarizes the main steps of the matrix formalism. A practical implementation for multiple slabs, cylindrical and spherical shells is explained in Section 2.5. In Section 3, a practical use of the matrix formalism is illustrated by several examples. In particular, the role of the permeability of intermediate boundaries is investigated. Appendices describe the explicit

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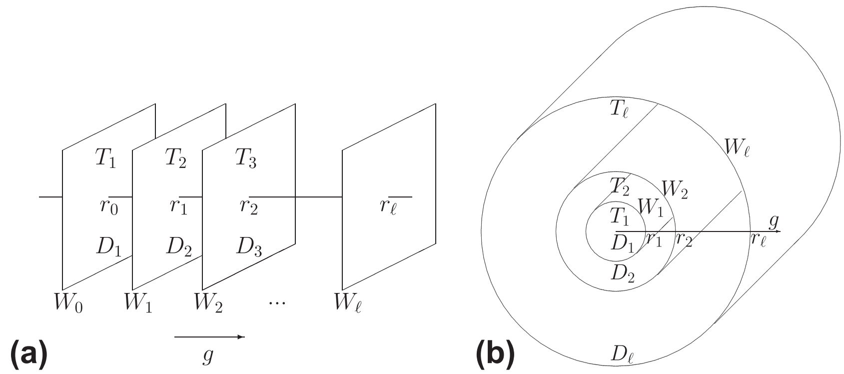

Fig. 1. Two examples of multilayered structures: (a) multiple slabs ($d = 1$) and (b) multiple cylindrical shells ($d = 2$).

formulas for the elements of the governing matrices. This is the key point for the performance of the matrix formalism.

2. Mathematical basis

2.1. Bloch–Torrey equation

We consider a multilayered domain $\Omega = \Omega_1 \cup \cdots \cup \Omega_\ell$, composed of ℓ layers $\Omega_i = \{\mathbf{r} \in \mathbb{R}^d : r_{i-1} < |\mathbf{r}| < r_i\}$, with $r_0 < r_1 < \cdots < r_\ell = R$ (Fig. 1). Each layer Ω_i is characterized by diffusion coefficient D_i and relaxation time T_i (representing transverse spin-spin relaxation). The inner, outer and each intermediate boundary, $\Gamma_i = \{\mathbf{r} \in \mathbb{R}^d : |\mathbf{r}| = r_i\}$ $(i = 0 \ldots \ell)$, is characterized by permeability W_i. For such a composite system, the classical Bloch–Torrey equation becomes:

$$\begin{aligned}
&\left(\frac{\partial}{\partial t} - D_i\Delta + i\omega f(t)B(\mathbf{r}) + T_i^{-1}\right) m_i(\mathbf{r},t) = 0 \quad (\mathbf{r} \in \Omega_i, i = 1 \ldots \ell),\\
&D_i \frac{\partial}{\partial n} m_i(\mathbf{r},t) = -D_{i+1}\frac{\partial}{\partial n} m_{i+1}(\mathbf{r},t) \quad (\mathbf{r} \in \Gamma_i, i = 1 \ldots \ell - 1),\\
&D_i \frac{\partial}{\partial n} m_i(\mathbf{r},t) = W_i[m_{i+1}(\mathbf{r},t) - m_i(\mathbf{r},t)] \quad (\mathbf{r} \in \Gamma_i, i = 1 \ldots \ell - 1),\\
&D_\ell \frac{\partial}{\partial n} m_\ell(\mathbf{r},t) = -W_\ell m_\ell(\mathbf{r},t) \quad (\mathbf{r} \in \Gamma_\ell),\\
&D_1 \frac{\partial}{\partial n} m_1(\mathbf{r},t) = -W_0 m_1(\mathbf{r},t) \quad (\mathbf{r} \in \Gamma_0),
\end{aligned} \tag{1}$$

where $m_i(\mathbf{r},t)$ is the transverse magnetization inside the ith layer, $\Delta = \partial^2/\partial x_1^2 + \cdots + \partial^2/\partial x_d^2$ is the d-dimensional Laplace operator acting on $\mathbf{r} = (x_1,\ldots,x_d)$,$\partial/\partial n$ is the normal derivative on the boundary pointing to the exterior of the domain, and ω is the Larmor frequency associated with an applied magnetic field of a given (dimensionless) temporal profile $f(t)$ and of spatial variation $B(\mathbf{r})$.

The first equation states that the time evolution of the magnetization is caused by

- local random displacements of the spin-bearing particles, i.e., diffusion which is governed by the Laplace operator,
- encoding through the applied magnetic field, and
- bulk relaxations.

The second equation describes the conservation of the flux of magnetization between adjacent layers (the sign minus accounts for the opposite directions of two normal derivatives at the intermediate boundary Γ_i). The third equation accounts for the transfer properties (permeabilities W_i) of intermediate boundaries. It states that the diffusive flux is created by the drop in magnetization between two layers. For biological samples, typical water permeabilities are in the order of 10^{-5} m/s (e.g., for axons [19,20]). Finally, the last two equations describe the flux conservation at the outer and inner boundaries Γ_ℓ and Γ_0, respectively. If there is no inner boundary (Fig. 1b), the last equation is replaced by the condition of a regularity of $m(\mathbf{r},t)$ at the origin.

The above mathematical description is approximate. The underlying assumptions are:

- All the intermediate boundaries are infinitely thin. When such an approximation is not adequate, the frontier between two layers (e.g., a cellular membrane) can be modeled itself as an intermediate layer, with an effective diffusion coefficient and appropriate relaxation time.
- Although surface relaxation is formally neglected, it can be easily taken into account. For the outer and inner boundaries, the transport coefficients W_ℓ and W_0 represent the losses of the spin-bearing particles which leave the multilayered structure. But the very same constants W_ℓ and W_0 may also account for surface relaxation on the outer and inner boundaries. If surface relaxation at intermediate boundaries is also relevant, these infinitely thin boundaries can be replaced by additional intermediate layers for which surface relaxation can be effectively incorporated through the corresponding bulk relaxation times.
- The third equation relates the diffusive flux to the drop of magnetization between two layers. This is an effective model for describing transfer properties of a membrane. Another model relates the magnetizations at the edges of two layers by a linear relation, namely, $m_i(\mathbf{r},t) = w_i m_{i+1}(\mathbf{r},t)$ (as $\mathbf{r} \in \Gamma_i$), with a dimensionless constant w_i. The approach we present can be easily adapted to this model. At the same time, it is known that cellular membranes transfer species via different mechanisms (e.g., active transfer of some macromolecules [21,22]) which may result in more sophisticated equations. This paper is focused only on linear boundary conditions in Eq. (1).
- The Brownian dynamics of the spin-bearing particles is not always valid for biological systems. For instance, the dynamics of proteins and other macromolecules inside living cells is often anomalous [23–26]. Anomalous diffusion or other intricate dynamics are beyond the scope of the paper.

In what follows, we assume that a PGSE experiment is accurately described by Eq. (1).

2.2. Laplace operator eigenfunctions

A solution of the Bloch–Torrey Eq. (1) can be written in terms of the Laplace operator eigenfunctions [11,27,28]. For multilayered structures, each eigenfunction $u(\mathbf{r})$ satisfies the following equations: