Diffusivity in the Brain White Matter: Application of the Recursive Effective Medium Approximation

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1. Introduction: Estimation of the effective diffusion properties of a random heterogeneous biomaterial is a frequent task in biophysics. With the advent and widespread use of the *MRI* technique, the problem also arises in neuroscience [1]. It can be formulated as follows: using the methods of *MRI*, it is possible to evaluate the effective apparent diffusion coefficient (ADC_{eff}) in brain white matter. Then, in the context of the modelling framework, the sensitive of the diffusion coefficient to the disordered geometry of the brain tissue, the volume fraction of the comprising phases, the ratio of the microscopic diffusion coefficients within the cells and outside, the cell size and the permeability coefficient of the cells may be estimated. In fact, measurement of the changes in cell membrane permeability using diffusion could become an indispensable tool in early diagnosis and progression of many diseases [2] and the quantitative sensitivity of diffusivity to this microparameter can be established only within an appropriate theoretical framework. The diffusion properties of biological tissues have been described in the literature [3,4,5]. In these works it has been shown that the anisotropic properties of the ADC_{eff} are in good agreement with *hindered models* of the diffusion in the *long time* mono-exponential regime (Eq. 1). We model such behaviour of water molecules in brain white matter to explore a bridge between local and effective global diffusive transport properties.

2. Methods: Defining the effective ADC_{eff} of a brain white matter with randomly distributed properties is a rather complicated task. Here, we introduce some assumptions to simplify the problem. Myelinated axons can be treated as cylinders that are statistically homogeneously and isotropicaly distributed in the extracellular water basin. The symmetry of the problem allows us to suppose that the transverse space is orthogonal to the longitudinal axes of axons. Then, for the mathematical evaluation of the transversal diffusivity, $D_{eff,T}$, the tissue can be mapped on a square lattice (Fig. 1). Spatial micro-inhomogeneities (i.e. tissue components) are modelled by the lattice junctions, and the interjunction bonds simulate their contacts with neighbours. We supposed that heavy bonds describe properties of the myelinated axons and thin bonds belong to the extracellular water bath. Locally, for the heterogeneous tissue-averaged upper and low (subscriptions U and L in notations) bounds of the strongly fluctuating diffusion coefficient can be estimated with the help of the Maxwell-Garnett principles [6] and modified Crick's formula [3]. The effective transverse diffusion coefficient then can be evaluated by the iterative coarse-graining procedure (Fig. 2) with the scale averaging recursive algorithm (Eq. 2a-e) of the square lattice [7, 8]. The convergence of the iterations to the stable point is presented in the Fig.3, which results in the calculation of the $D_{eff,T}$ as a function of the broad range of the extracellular water volume fraction p and permeability coefficient k. At the same time the *longitudinal* diffusion, $D_{eff,L}$, can be estimated by using the Eq. 3.

$$S/S_0 = \mathrm{e}^{\left(-b\cdot ADC_{eff}\right)};\quad ADC_{eff} = \left(D_{eff,L} + 2\cdot D_{eff,T}\right)/3 \tag{1}$$

$$\begin{cases} p_{j+1} = 2p_j^5 - 5p_j^4 + 2p_j^3 + 2p_j^2 & (2a)\\ D_{eff,T}^{(U,\,j+1)} = D_{eff,T}^{(U,\,j)} c_{ext}\left(2R_j p_j + \left(3-2p_j\right)\right)\cdot\left(\left(R_j\left(3-p_j\right)+p_j\right)c_{eff}^{(j)}\right)^{-1} & (2b)\\ D_{eff,T}^{(L,\,j+1)} = D_{eff,T}^{(L,\,j)} c_{\mathrm{int}}\left(\left(1+2p_j\right)+2R_j^{-1}\left(1-p_j\right)\right)\cdot\left(\left(\left(1-p_j\right)+R_j^{-1}\left(2+p_j\right)\right)c_{eff}^{(j)}\right)^{-1} & (2c)\\ R_j = \left(c_{ext}D_{eff}^{(U,\,j)}\right)\Big/\left(c_{\mathrm{int}}D_{eff}^{(L,\,j)}\right) & (2d)\\ c_{eff}^{(j)} = c_{ext}\,p_j + c_{inr}\left(1-p_j\right) & (2e) \end{cases}$$

$$D_{eff,L}c_{eff} = p\,D_{ext}c_{ext} + \left(1-p\right)D_{\mathrm{int}}c_{\mathrm{int}} \tag{3}$$

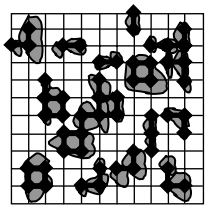


Fig.1

Fig.1. Mapping of the brain white matter structure on the square lattice (transverse view). Heavy bonds represent axons immersed in the extracellular water basin.

Fig.2. The procedure of coarse-graining of the square lattice from Fig.1. Every bond from the corner *ABCDEFGH* can be occupied either by the extracellular water bath with the probability p or represent the fibre with probability (1-p). The transition of probability p after coarsening *ABCDEFGH - A'C'* is described by Eq. 2a.

Fig.3. Convergence of the upper (U) and lower (L) bounds of the fluctuating transverse diffusivity to the stable point after i iterations of recursion (Eq. 2b-e).

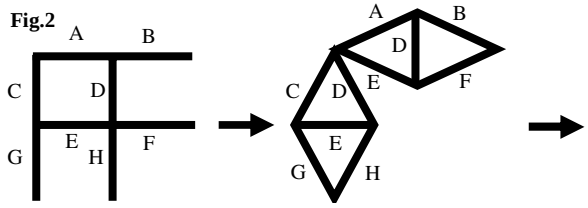


Fig.2

Fig.4a.

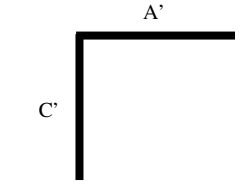


Fig.4a. Dependence of longitudinal normalized diffusivity versus extracellular volume fraction p and axon permeability k (Eq. 3).

Fig.4b. Dependence of the transverse normalized diffusivity versus extracellular volume fraction p and axon permeability k (Eq. 2a-e). Every point in this curve is a result of the recursive scale averaging procedure after approaching the stable point.

Fig.5. ADC_{eff} as a function of parameters p and k (Eq. 1).

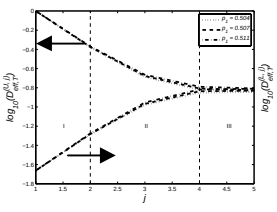


Fig.4b.

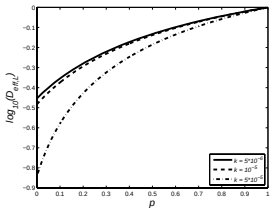
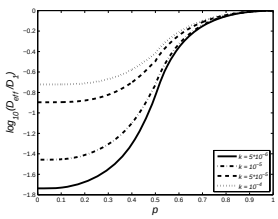
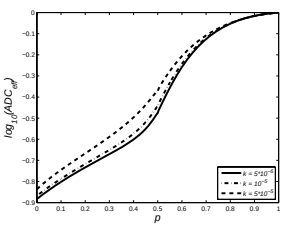


Fig.5.

Table 1. Sensitivity test of ADC_{eff} to the variation of the microscopic parameters X, $S_X = \partial log(ADC_{eff}) / \partial log(X)$. $D_{ext/int}$ – extra/intracellular diffusivity; k – axon permeability; a – cell size; p – extracellular volume fraction; $c_{ext/int}$ – extra/intracellular proton density.

	$D_{ext}[m^2/s]$	$D_{int}[m^2/s]$	p	c_{int}	c_{ext}	$a[m]$	$k[m/s]$
X	$2\ *10^{-9}$	$0.75*10^{-9}$	0.15	0.65	0.95	$6*10^{-6}$	$0.19*10^{-5}$
S_X	0.57	0.51	0.42	0.24	0.25	0.3	0.15





3. Results: Using the recursive procedure (Eq. 2) for the evaluation of the $D_{eff,T}$ together with $D_{eff,L}$ (Eq. 3) it is possible to estimate effective ADC_{eff} (Eq. 1) and check the sensitivity of this macro-parameter due to the microscopic changes. In the Fig. 5 the dependence of the effective ADC_{eff} upon the several micro-parameters are presented. The sensitivities of the ADC_{eff} to the full set of the parameters are collected in Table 1.

4. Discussion: The results of the proposed recursive effective media scale averaging iterative scheme were used to explore the effects of a large range of micro-structural and compositional parameters on the apparent (effective) diffusion coefficient. The proposed scheme can be used as a test of the various hypotheses of disease development on microscopical level as well as explanation of diffusion-based neuroimaging studies [9].

References: [1] Le Bihan D, Magnetic Resonance Imaging of Diffusion and Perfusion (Lippincott-Raven Press, New-York), 1995. [2] Horsfield M, Jones D, *NMR in Biomed*. **15** (7-8) (2002) 570. [3] Latour L, Svoboda K, Mitra P, Sotak C, *PNAS* **91**(1994) 1229. [4] Sen P, Basser P, *Biophys. J.*, **89** (2005) 2927. [5] Szafer A, Zhong J, Gore J, *Magn. Reson. Med.*, **33** (1995) 697. [6] Crank J, The mathematics of diffusion (Clarendon Press, Oxford) 1955. [7] Poznansky O, Novikov V, *J. Polym. Eng.* **19** (1999) 223. [8] Bernasconi J, *Phys. Rev. B* **18** (1978) 2185. [9] Darquie A, Poline J, Poupon C, *et al. PNAS* **98** (16) (2001) 9391.