On the Problem of Diffusivity in Heterogeneous Biological Materials with Random Structure

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Abstract Biological tissues are multicompartmental heterogeneous media composed of cellular and subcellular domains. Randomly walking water molecules may have different diffusion coefficients and densities (concentrations) in different domains, namely within cells and within the outer medium. Results of the proposed effective media scale-averaging iterative scheme are used to explore the effects of a large range of microstructural and compositional parameters on the apparent (effective) diffusion coefficient. A self-consistent modelling framework for predicting the steady-state effective diffusion coefficient is presented; the framework reveals the strong dependence of the apparent diffusion coefficient on the ratio of the microscopic diffusion coefficients of the comprising phases, permeability of the cells, and their volume fractions.

Keywords Diffusion · Renormalisation group method · Heterogeneous biological tissue · Magnetic resonance

1 Introduction

Estimation of the effective diffusion properties of fluids in random heterogeneous materials is a frequent task in materials physics. With the advent and widespread use of magnetic resonance imaging (MRI), the problem also arises in medical and biological physics [1, 2]. The task can be formulated as follows: using the methods of MRI, it is possible to evaluate the apparent (effective) diffusion coefficient (D_{eff}) in biological tissue? Further, the sensitivity of the diffusion coefficient to the disordered geometry of the tissue, the

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volume fraction of the comprising phases, the ratio of the microscopic diffusion coefficients within the cells and outside, and the permeability coefficient of the cells may be evaluated. The understanding of the latter is important for clinical applications since changes in cell permeability are often an indicator of pathology. Thus, measurement of changes in cell membrane permeability using diffusion experiments could become an indispensable tool in early diagnosis and treatment of many diseases [3].

In MRI experiments, diffusion is measured as a part of the attenuating signal due to the loss of the coherence of water molecules brought about by random motion in the presence of the external linear magnetic field (as can be assumed from a perfect gradient coil system) and compensated local magnetic inhomogeneities (susceptibility effects). However, in the process of signal decay, the relaxation of magnetisation is characterised with both longitudinal T_1 and transverse T_2 times. Relaxation can be different for different regions due to variation of the local magnetisation. Nevertheless, at long diffusion times, signal attenuation can be described with single exponential curve with a specific D_{eff} :

$$S/S_0 = \exp(-b \times D_{\text{eff}}), \quad (1)$$

where $b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$ is a factor defined according Stjeskal–Tanner formula [1] (γ is a gyromagnetic constant, Δ is a diffusion time, and G is a magnetic field gradient with duration δ). The diffusion properties of biological tissues have been described by a number of authors [4–9]. In these works, it has been shown that the anisotropic properties of the diffusion coefficient are in good agreement with hindered and restricted models of diffusion, especially in the long-time scale regime. The diffusion model is quite meaningful for the description of anisotropy and fibre tracking in the white matter of brain tissue, for example. The usual approach taken to investigate the heterogeneous nature of brain tissue is to study fibres of packed cylinders arranged in different types of symmetrical arrays such as a square or a hexagon and use the *Maxwell–Garnett effective media approximation* [10] or depict tissue as a set of parallel cylinders and use the *series-parallel approximation* [6]. In such models, it is difficult to introduce a highly randomised structure which is very natural in biological materials but is quite the opposite of the case in solid-state crystals. Using the approach to diffusion proposed in this article, it is possible to study disordered biological materials and take into account the influence of the complex geometry and topology on the effective transport (diffusive) properties of the tissue.

Based on the following description of the physical process, it is reasonable to guess that the effective medium theory is applicable. The typical diffusion-weighted echo planar imaging MRI sequence allows one to acquire information about dephasing of water molecule spins with durations ranging from $T_d = 20 - 300$ ms. The self-diffusion coefficient of pure water at the temperature 36.6°C is $2.94 \cdot 10^{-9} \text{ m}^2/\text{s}$. We believe that the presence of glia cells in the extracellular space is consistent with a hindered diffusion coefficient that is lower than 30% that of free water at the body temperature and is around $2 \cdot 10^{-9} \text{ m}^2/\text{s}$. Besides, intracellular diffusion is strongly influenced by neurofilaments and microtubules and thus the intracellular diffusion constant is less than 75% that of free water and is estimated as $0.75 \cdot 10^{-9} \text{ m}^2/\text{s}$. Using Einstein's diffusion equation ($\langle x^2 \rangle = 2DT_d$), it is possible to calculate the average translation $\langle x^2 \rangle$ of a water molecule, which is around $8 - 35 \text{ }\mu\text{m}$. The diameter of the fibres varies by about $6 \text{ }\mu\text{m}$. The average distance between fibres is around $12 - 18 \text{ }\mu\text{m}$. It is easy to understand that the water molecule probes all tissue compartments, and the MRI signal gives an averaged or homogenised

effect of attenuation. In particular, the effective properties appear at the long diffusion time limit where $T_d = 100 - 300$ ms. Numerical simulation of the dephasing process is rather challenging and demands significant computational power. Indeed, if the density of free water is 0.995 g/cm^3 at a temperature of 36.6°C , and molar mass is 18.01524 g/mol , then in a 2 mm^3 voxel, there are around $270 \cdot 10^{18}$ molecules or $4.441 \cdot 10^{-4} \text{ mol}$. Water molecules of size $3.2 \text{ \AA}$ experience more than 10^6 collisions during the travelling distance of $15 \text{ }\mu\text{m}$. The huge number of colliding molecules together with the highly inhomogeneous structure of the environment hampers seriously the direct modelling of the discrete random walk. In these circumstances, the mean diffusion can be estimated either by the conventional effective media schemes [11, 12], assuming superposition principles (Maxwell–Garnett approximation), or nonlinear scale averaging iterative methods [13, 14].

This article presents a theoretical model for water diffusion in biological tissue on the basis of the iterative effective medium scale-averaging algorithm and describes its application to the two different problems: (1) the influence of the volume fraction of extracellular water on the apparent diffusion coefficient and (2) the influence of the permeability of the cells and importance of the ratio of the extracellular and intracellular diffusivity on the apparent diffusion coefficient. This article starts with the presentation of a short review of the *classical theory* of diffusion in effective media. This is followed by the presentation of a *geometrical model* of a random heterogeneous material and numerical results of the apparent diffusion coefficient obtained by the *recursive effective media approach*.

2 Theory (Classical Approach)

Biological tissue contains structures and complex geometries that impede the free diffusion of water and other molecules. Due to environmental effects, the diffusion coefficient measured by MRI is usually smaller than the bulk value and is, thus, termed the apparent diffusion coefficient. Specifically, the “apparent” descriptor refers to the fact that the diffusion coefficient is measured in presence of structural barriers that interfere with the free translation of molecules (it is important to note that additional factors such as bulk motion, micro motion, and background nonlinear magnetic field and magnetic susceptibility also affect the measured apparent diffusion coefficient value). Restricted diffusion alters the linearity of the Einstein equation and the measured apparent diffusion coefficient is a function of the diffusion time and the geometry of the restrictive space.

In general, in biological tissue, it is possible to outline two types of regions. One region possesses many restrictions and obstacles, and the other region exhibits relatively free translation of water molecules. As a consequence, the two regions are characterised with different diffusivities. Let the restricted region be characterised with a diffusion coefficient D_2 , and let it occupy a volume fraction $(1 - p)$. The second region, which exhibits free translation of water molecules, is described by a diffusion coefficient D_1 of extracellular water with a volume fraction p . The Maxwell–Garnett approximation [11] (sometimes termed the *effective-medium approximation*) is valid for such a two compartment heterogeneous system and is given by the following formula:

$$\frac{D_{\text{eff}}c_{\text{eff}} - D_1c_1}{D_{\text{eff}}c_{\text{eff}} + (d - 1)D_1c_1} = p \frac{D_2c_2 - D_1c_1}{D_2c_2 + (d - 1)D_1c_1}, \quad (2)$$

where the extracellular water density is c_1 and the intracellular water density is c_2 , and d is a dimension of the space (in our particular case $d = 2$). The effective concentration of water molecules is then

$$c_{\text{eff}} = c_1 p + c_2 (1 - p) \quad (3)$$

and D_{eff} is the effective diffusion coefficient of the composite biological tissue.

The permeability of the spatially arranged membranes is an important factor in biological systems. A simple model of a restricted diffusion is the Crick model [15], which describes molecular diffusion in the space between two parallel barriers. In this model, molecules diffuse perpendicular to the orientation of the restricted barriers with permeability k located at distance a . At very short diffusion times (i.e., $t < ka$), the majority of molecules do not experience the effects of barriers; thus, the measured diffusion coefficient is nearly equal to the bulk value. At longer diffusion times, the molecules are allowed to randomly translate throughout the space during which they may reflect from or diffuse through the barriers, in both cases experiencing some change in the free translational displacement that could not have occurred in the absence of the barriers. In this case, the measured intracellular diffusion coefficient is the effective diffusion coefficient, D_2 , given by [16]:

$$D_2 c_2 = \frac{ka D_{\text{int}} c_2}{ka + D_{\text{int}} c_2}, \quad (4)$$

which includes the contributions of distinct intracellular diffusion D_{int} , and the restrictions to diffusion arising from k and a . Equation 4 is a modified version of Crick's formula which takes account of the spaces between cell membranes and other molecules, such as proteins, that have a fractional concentration $(1 - c_2)$. The restrictions reduce the displacement of the diffusing molecules predicted by the Einstein equation. In these circumstances, the measured diffusion coefficient is an apparent value of the self-diffusion value and can be treated as an apparent diffusion coefficient.

The Maxwell–Garnett approach is well-suited for the case of small concentrations of cells provided that they are well separated from each other, and it is possible to utilise the principles of superposition. Additionally, the intermediate regime of the cell volume fraction needs to be described. Besides, the natural distribution of the size of the intracellular region is also not taken into account in the Maxwell–Garnett theory. We extend the existing approach and propose the use of a geometrical model of the highly randomised structure; this is described in the next section.

3 Geometrical Model: The Iterative Lattice

In electron-microscope images of the histological cross-section of biological tissue (white matter of the brain), it is possible to recognise two subsets of the structure distinctly: myelinated axons and the extracellular free water matrix (Lübke, J.H.R., private communication) [17–19]. Thus, the white matter (such as the corpus callosum) is represented as a bundle of cylinders (myelinated axons) randomly embedded in free water matrix and can be treated as a two-phase medium, where one of the phases (fibres) has composite properties (Fig. 1a).

Let us give a mathematical description of this two-compartment system. The ensemble of all possible realisations of a random medium can be described by the probability space $(\Omega, \mathcal{F}, P)$, where Ω is a sample space, $\mathcal{F}$ is a σ -algebra of subsets of Ω , and P is a probability measure. Let each point $\omega \in \Omega$ from sample space Ω correspond to a realisation

Fig. 1 **a** Diffusing molecules probe biological tissue in different compartments. **b** Mapping of the random and heterogeneous tissue onto a square lattice. Every bond of the lattice represents the tissue compartment in the local area. The lattice consists of two types of bonds assigned to the free water matrix (thin bonds) and myelinated axons (heavy bonds). **c** The rules of mapping of the deformed Wigner–Seitz cell onto the set of bonds

of the random medium that occupies some subset V of d -dimensional Euclidean space, i.e. $V \in R^d$. Each realisation ω of the two-phase random heterogeneous material occupies the region of space $V \in R^d$ of volume V that is partitioned into two disjoint random sets: phase 1, a region $V_1(\omega)$ of volume fraction p , and phase 2, a region $V_2(\omega)$ of volume fraction $(1 - p)$. Since the random sets $V_1(\omega)$ and $V_2(\omega)$ are the complements of one another, $V_1(\omega) \cup V_2(\omega) = V$ and $V_1(\omega) \cap V_2(\omega) = \emptyset$. For a given realisation ω of the two-phase random medium, the structure function $I^{(i)}(\vec{r}; \omega)$ for phase $i = \{1, 2\}$, is given for $\vec{r} \in V$ by

$$I^{(i)}(\vec{r}; \omega) = \begin{cases} 1, & \vec{r} \in V_i(\omega) \\ 0, & \vec{r} \notin V_i(\omega) \end{cases}, \quad (5)$$

with

$$I^{(1)}(\vec{r}; \omega) + I^{(2)}(\vec{r}; \omega) = 1. \quad (6)$$

For simplicity, we will drop ω from the later notation and write $I^{(i)}(\vec{r})$ for $I^{(i)}(\vec{r}; \omega)$. Note that local average of any function $f[I^{(i)}(\vec{r})]$ is

$$\langle f[I^{(i)}(\vec{r})] \rangle = p\{I^{(i)}(\vec{r}) = 1\} f(1) + p\{I^{(i)}(\vec{r}) = 0\} f(0), \quad (7)$$

and particularly

$$\langle I^{(i)}(\vec{r}) \rangle = p\{I^{(i)}(\vec{r}) = 1\}. \quad (8)$$

Suppose for the realisation $V_i(\omega)$ all $I^{(i)}(\vec{r})$ from Eqs. 5 and 6 are known for any $\vec{r} \in V$, and the probability law of $V_i(\omega)$ is given by the joint finite n -dimensional distribution

$$P\{I^{(i)}(\vec{r}_1) = j_1, I^{(i)}(\vec{r}_2) = j_2, \dots, I^{(i)}(\vec{r}_n) = j_n\} = \left\langle \prod_{k \in K} I^{(i)}(\vec{r}_k) \prod_{l \in L} [1 - I^{(i)}(\vec{r}_l)] \right\rangle, \quad (9)$$

where $K = \{k \leq n; j_k = 1\}$ and $L = \{l \leq n; j_l = 0\}$, and Eq. 8 is taken into account.

Defining structural and effective physical (diffusion) parameters of a material with randomly distributed local properties is a rather complicated task. Hence, we introduce some simplifying assumptions. Myelinated axons can be treated as cylinders which are statistically homogeneously and isotropically distributed in a water basin. The symmetry of the problem allows us to split the system into $1d$ and $2d$ subspaces. Let the $2d$ transversal space be orthogonal to the $1d$ longitudinal axes of the axons. Then, for the mathematical evaluation of the orthogonal features, the tissue can be mapped on a square lattice (Fig. 1b). Spatial micro-inhomogeneities (i.e., tissue components) are modeled by the lattice junctions, and the interjunction bonds simulate their contacts with neighbours. We supposed that the heavy bonds describe properties of the myelinated axon, and the thin bonds belong to the water matrix. Mapping rules described in Fig. 1c include variation in size, shape, and volume fraction of the complex structure of the biological tissue.

A very effective real space renormalisation group for calculation of the structural properties of the random lattice of bonds was introduced by Reynolds et al. [20, 21]. The procedure is shown in Fig. 2a for a square network. In the left part of the figure, we have a section of the original lattice, and on the right, we have the same section of the renormalised lattice. As a renormalisation cell, we chose a simple eight-bond cell with linear size $b = 2$. If the cell can be traversed horizontally, then the heavy (renormalised) horizontal bond is present and similar for the vertical direction. This is depicted in Fig. 2b with some more details. Bonds labeled ABCDEFGH are replaced by the two “Wheatstone” bridges. After this transformation, the initial square lattice is converted to another (self-dual) square lattice, with the distance between sites twice as large and with each bond between the two nearest neighbouring sites being the “Wheatstone” bridge. The connectedness of bond A' is, thus, determined by those of bonds ABDEF as shown in the middle part of Fig. 2b. The connectedness of bond C' is found from the original connectivity bonds CDEGH. If we repeat renormalisation recursively, then the mapping is equivalent to replacing the original lattice by a hierarchical structure in which each bond has an internal structure which is the same as that of the original. On such a lattice, the Migdal–Kadanoff transformation is exact [22]; thus, we build different levels of the hierarchical lattice.

Suppose the geometry of extracellular water matrix allows one to travel from one side of the “H” cell to the opposite one without penetrating into the other phase. Then, if we apply such a condition on different realisations $\omega \in \Omega$ of two-component system, we can describe the spanned cluster ABDEF (or CDEGH) with a joint *conditional* finite-dimensional distribution $P(p)$ from Eqs. 8 and 9 (here, we have dropped awkward notation of the structure function). The probability $1 - P(p)$ is valid for the complementary case.

The connectedness function $P(p)$ for the “H” cell can be expressed by the “five-bond” polynomial equation

$$P(p) = p^5 + 5p^4(1 - p) + 8p^3(1 - p)^2 + 2p^2(1 - p)^3. \quad (10)$$

Fig. 2 **a** Rescaling a lattice by forming cells from a group of eight bonds. The rescaling factor $b = 2$. **b** The real space renormalisation scheme for vertical and horizontal “H” cells (“Wheatstone” bridges). **c** Generic parts of the original 2×2 “H” cell, which contribute to the horizontal spanning cluster

Equation 10 was constructed according to the following rules:

- The probability that five, four, three, and two heavy bonds are present in spanned cluster is p^5 , $p^4(1-p)$, $p^3(1-p)^2$, and $p^2(1-p)^3$, respectively.
- Only those configurations are available to represent the connectedness of the opposite sides to characterise the spanned cluster.
- The probability of the connectedness is, then, computed by: (a) multiplying the probability that n bonds are extant with the number of n bond configurations; (b) summing these products over all n bond configurations.

The whole procedure is depicted in Fig. 3c together with the conditional probability function weighting factors.

After simplification of the polynomial relation Eq. (10), the general equation becomes:

$$P(p) = 2p^5 - 5p^4 + 2p^3 + 2p^2. \quad (11)$$

If we take into account the renormalisation properties of the hierarchical lattice for the Migdal–Kadanoff transformation (see Figs. 2a, b), then

$$p_{j+1} = 2p_j^5 - 5p_j^4 + 2p_j^3 + 2p_j^2. \quad (12)$$

where j is a level of the hierarchical lattice. The roots (solutions) or fixed points of the algebraic Eq. 12 that belong to the physically meaningful range ($0 \leq p_* \leq 1$) are $p_* = \{0, 0.5, 1\}$. The first and third roots represent the pristine and vacant lattices (completely full or empty limits). These limits are referred to as being “stable” or “homogeneous” because the recursive procedure for solving Eq. (12) drives the configuration to those limits through

Fig. 3 **a** Connectedness function $P(p)$ (left arrow, heavy line) and its derivative $P'(p)$ (right arrow, dashed line). Maximum of $P'(p)$ is approached at the fixed point $p_* = 0.5$. Thin dashed lines connecting bisector and connectedness functions are the renormalisation of the volume fraction p_j according Eq. 12. **b** The divergence of the correlation length ξ on the hierarchical lattice near the point $p_* = 0.5$

successive reduction of the minority phase. At these points, the system exhibits translational symmetry and the “stable” fixed points represent “sinks.” The second fixed point $p_* = 0.5$ is labelled as being “unstable” or a “source” of the flux of the renormalisation parameter p_j . Bernasconi [13] had already shown that for bond renormalisation on the square lattice, the nontrivial root of the equation $P(p_c, b) = p_c$ is universal for any b and $p_c = 0.5$ due to self-duality.

The connectedness function $P(p)$ and its derivative $P'(p)$ are plotted in Fig. 3a. The maximum of $P'(p)$ is approached at the fixed point $p_* = 0.5$. Thin dashed lines connecting the bisector and the connectedness functions are the renormalisation of the volume fraction p_j according to Eq. 12. Within the vicinity of $p_c = 0.5$, the system yields scaling properties and can be treated as a stochastic fractal. Near the fixed point, the typical linear cluster dimension (or the correlation length) $\xi = b^l$ diverges as (Fig. 3b):

$$\xi \sim |p - p_c|^{-\nu}, \quad (13)$$

and the correlation function exponents may be estimated, with the help of Eq. 11, as

$$(P(p) - p_c) = b^{-\frac{1}{\nu}} (p - p_c) \quad (14)$$

if in the process of sequentially building the hierarchical lattice the rule

$$\left. \frac{\xi(P(p))}{\xi(p)} \right|_{p \rightarrow p_c} = b \quad (15)$$

is kept at every level j (for “H” cell, $\nu = 1.43$). Thus, the scaling range of the correlation length of the hierarchical lattice is within the bounds

$$b \leq \xi(p) \leq L, \quad (16)$$

where L is a macroscopic sample size. In Fig. 3b, in the region $p < p_*$ the correlation length is the typical linear size of a free water island, confined in surrounding fibre bundles, and, when $p > p_*$, the correlation length is the typical linear size of grouped fibre bundles embedded in the free water matrix.

4 Recursive Effective Media Approach

The physical model referred to in this study is described below. Anatomical sections of biological tissue (corpus callosum) reveal that myelinated axons can be modeled as cylinders embedded in the water matrix. Because we consider diffusion $\hat{D}(\vec{r})$ in the stationary (long-time scale) regime with no sources, then locally, at every point of the heterogeneous medium, the Laplace law (conservative and potential)

$$\vec{\nabla} \hat{D}(\vec{r}) \vec{\nabla} c(\vec{r}) = 0 \quad (17)$$

and Fick's law (linear constitutive relation)

$$\vec{J}(\vec{r}) = -\hat{D}(\vec{r}) \vec{\nabla} c(\vec{r}) \quad (18)$$

hold, together with the continuity Cauchy conditions at the two phase interfaces $\partial\Gamma_1$ and $\partial\Gamma_2$ for completeness [12]. The normal to surface component of the mass flux $\vec{J}_{\vec{n}}(\vec{r})$ at the different phases is

$$\vec{J}_{\vec{n}}(\vec{r}) \Big|_{\partial\Gamma_1} = \vec{J}_{\vec{n}}(\vec{r}) \Big|_{\partial\Gamma_2}, \quad (19)$$

and the concentration $c(\vec{r})$ is

$$c(\vec{r}) \Big|_{\partial\Gamma_1} = c(\vec{r}) \Big|_{\partial\Gamma_2}. \quad (20)$$

Here, we assumed that temperature and chemical activity are uniform throughout the object, and the driving force of mass transport is only a function of concentration. In the real case, the axons are covered with myelin sheath interrupted by nodes of Ranvier. Both of them play role in electrical properties of the axon and the transmission of neuronal signals. Myelin has a very dense structure, which leads to the small diffusivity (0.3 m²/s) compared to those of extra- or intraaxonal fluid. Due to this, the “weight” of myelinated diffusion is negligible and can be “screened out.” That is why we use a special case of thin, permeable myelin.

According to Eq. (7), the *locally averaged* diffusion tensor $\langle \hat{D}(\vec{r}) \rangle$ yields

$$\langle \hat{D}(\vec{r}) \rangle = p \hat{D}_1(\vec{r}) + (1 - p) \hat{D}_2(\vec{r}), \quad (21)$$

and the generalised local probability density distribution function is expressed as

$$\varphi(\hat{D}(\vec{r})) = p \delta(\hat{D}(\vec{r}) - \hat{D}_1) + (1 - p) \delta(\hat{D}(\vec{r}) - \hat{D}_2), \quad (22)$$

where $\delta(\hat{D})$ is the Dirac function.

Diffusion in the extracellular matrix is hindered due to the presence of glia cells and other tissues and is lower than the diffusivity of free water. We believe that the presence of glia in the extracellular space is consistent with an isotropic medium. The extracellular matrix then can be characterised with a spherical tensor:

$$\hat{D}_1(\vec{r}) = \begin{bmatrix} D_{11}^1(\vec{r}) & 0 & 0 \\ 0 & D_{11}^1(\vec{r}) & 0 \\ 0 & 0 & D_{11}^1(\vec{r}) \end{bmatrix}. \quad (23)$$

Cylindrical fibres possess transverse anisotropy, which is expressed in tensor form as:

$$\hat{D}_2(\vec{r}) = \begin{bmatrix} D_{11}^2(\vec{r}) & 0 & 0 \\ 0 & D_{11}^2(\vec{r}) & 0 \\ 0 & 0 & D_{33}^2(\vec{r}) \end{bmatrix}. \quad (24)$$

After the homogenisation procedure, Fick's law is defined as

$$\langle \vec{J}(\vec{r}) \rangle = -\hat{D}_{\text{eff}} \langle \vec{\nabla} c(\vec{r}) \rangle, \quad (25)$$

where the *volume averaged* mass flux and concentration, respectively, are:

$$\langle \vec{J}(\vec{r}) \rangle = \frac{1}{V} \int_V \vec{J}(\vec{r}) dV, \quad \langle \vec{\nabla} c(\vec{r}) \rangle = \frac{1}{V} \int_V \vec{\nabla} c(\vec{r}) dV. \quad (26)$$

For symmetry with respect to rotation about one axis, say the z-axis, it can be shown that the effective diffusion tensor has two independent components:

$$\hat{D}_{\text{eff}}(c_1, c_2, p, \hat{D}_1, \hat{D}_2) = \begin{bmatrix} D_{11}^{\text{eff}} & 0 & 0 \\ 0 & D_{11}^{\text{eff}} & 0 \\ 0 & 0 & D_{33}^{\text{eff}} \end{bmatrix}. \quad (27)$$

This is referred to as *transverse isotropic symmetry* and describes the geometry of cylindrical fibres embedded in the free water matrix.

The longitudinal component of the diffusion tensor can be calculated as a volume average:

$$D_{33}^{\text{eff}}(p, D_{11}^1, D_{11}^2) c_{\text{eff}} = p D_{11}^1 c_1 + (1 - p) D_{11}^2 c_2. \quad (28)$$

In the case of a small fraction of the fibres for the transverse component $D_{11}^{\text{eff}}(p, D_{11}^1, D_{11}^2)$, we could use the Maxwell–Garnett approximation Eq. 2. The specificity of this approximation is as follows: (1) the volume fraction of the water should be very small; (2) the solution should adhere to the principles of superposition; and (3) the model is naturally two-scale and does not describe multiscale fluctuations. However, in the transient region of a large number of fibres with fluctuating size, shape, and volume fraction, the transverse diffusivity needs to be estimated in a specific averaging scheme as described below.

In biological tissue, it is possible to recognise singular fibres, small groups of isolated fibres, and large bangles of fibres confining free water islands. It is difficult to treat such a system with two distinct scales, where diffusive properties vary either fast or slowly. Instead, the system exhibits all ranges of characteristic sizes of heterogeneities, ξ , and they are within a certain range (Eq. 16). Then, by the virtue of the “H”-cell model described in the previous section, the diversity of diffusivity on all scales can be derived and used to estimate the effective transverse diffusion coefficient.

Let every bond of the lattice (Fig. 2a) represent the effective microscopic diffusion coefficient in the local area. The structured lattice consists of two types of bonds with diffusion coefficients, D_{11}^1 (heavy bond) and diffusion coefficients, D_{11}^2 (thin bond), respectively. The occurrence probability of a heavy bond is p and the occurrence probability of a thin bond is $(1 - p)$. The distribution of the phases with two distinct properties is described by the generalised probability density function Eq. 23.

Suppose that random biological tissue can be modeled according the scheme depicted in Fig. 2a–c. If j is an iterative step in the building of the hierarchical lattice, then for every iterative step, the probability density distribution function (Eq. 22) takes the form:

$$\varphi_j(D_{\text{eff}}^{\text{eff}}) = p_j \delta(D - D_{\text{eff}}^{(U,j)}) + (1 - p_j) \delta(D - D_{\text{eff}}^{(L,j)}). \quad (29)$$

The value $D_{\text{eff}}^{(U,j)}$ is an averaged effective diffusion coefficient calculated for the case when the myelinated axon is embedded in the free water matrix. Such an effective diffusion coefficient is regarded as an upper bound for the diffusion coefficient. For the initial step, $j=1$, the effective diffusion coefficient is given by $D_{\text{eff}}^{(U,1)} = D_{11}^1$ and D_{11}^1 is the free extracellular water diffusion coefficient. The coefficient $D_{\text{eff}}^{(L,j)}$ represents the inverse of the situation above and, therefore, $D_{\text{eff}}^{(L,1)} = D_{11}^2$ where D_{11}^2 is diffusion in the axons.

Locally, for heterogeneous tissue, averaged upper and lower bounds of the diffusion coefficient can be estimated with the help of the Maxwell–Garnett principles (Eq. 2). The upper and lower bounds could be represented by the heavy and thin bonds in the building of the “H” cell. The effective diffusion coefficient then can be estimated on the hierarchical lattice with the recursive algorithm. This algorithm has been previously used for the solution of the degradation problem in the solid-state and polymer materials with the help of Monte-Carlo methods [14]. After rearrangement of Eq. 2, the upper bound of the effective diffusion coefficient is evaluated as [23]

$$D_{11}^{(j+1,U)} c_{\text{eff}} = p_j c_1 D_{11}^{(j,U)} + (1 - p_j) c_2 D_{11}^{(j,L)} - \frac{p_j (1 - p_j) (c_1 D_{11}^{(j,U)} - c_2 D_{11}^{(j,L)})^2}{p_j c_2 D_{11}^{(j,L)} + (1 - p_j) c_1 D_{11}^{(j,U)} + c_1 D_{11}^{(j,U)}}. \quad (30)$$

If the following substitution for the phase volume fraction and effective diffusion coefficients in Eq. 30 is performed,

$$(1 - p_j) \rightarrow p_j, p_j \rightarrow (1 - p_j), D_{\text{eff}}^{(U,j)} \rightarrow D_{\text{eff}}^{(L,j)}, \text{ and } D_{\text{eff}}^{(L,j)} \rightarrow D_{\text{eff}}^{(U,j)}, \quad (31)$$

then the lower bound takes the form:

$$D_{11}^{(j+1,L)} c_{\text{eff}} = p_j c_1 D_{11}^{(j,U)} + (1 - p_j) c_2 D_{11}^{(j,L)} - \frac{p_j (1 - p_j) (c_1 D_{11}^{(j,U)} - c_2 D_{11}^{(j,L)})^2}{p_j c_2 D_{11}^{(j,L)} + (1 - p_j) c_1 D_{11}^{(j,U)} + c_2 D_{11}^{(j,L)}}. \quad (32)$$

In general the recursive algorithm consists of the following steps:

1. Initialise the upper and lower bounds of the diffusion coefficients, namely, $D_{\text{eff}}^{(U,j)}$ and $D_{\text{eff}}^{(L,j)}$.
2. Initialise the probability p_j to find the heavy bond on the “H” cell.
3. Evaluate the upper, $D_{\text{eff}}^{(U,j+1)}$ (Eq. 30) and lower, $D_{\text{eff}}^{(L,j+1)}$ (Eq. 32) bounds of the diffusion coefficients of the whole “H” cell according to the Maxwell–Garnett principles.
4. Evaluate the probability $P(p_j)$ of the connectedness of the heavy bonds (Eqs. 11, 12).
5. Return to step 1 if the norms $|D_{\text{eff}}^{(U,j+1)} - D_{\text{eff}}^{(U,j)}|$ and $|D_{\text{eff}}^{(L,j+1)} - D_{\text{eff}}^{(L,j)}|$ between the effective diffusion coefficients of the current $(j+1)$ th and the previous j th iterations are more then the prescribed error.

6. Stop the procedure if the norms $\left| D_{\text{eff}}^{(U, j+1)} - D_{\text{eff}}^{(U, j)} \right|$ and $\left| D_{\text{eff}}^{(L, i+1)} - D_{\text{eff}}^{(L, i)} \right|$ between the effective diffusion coefficients of the current and previous iteration are less than the prescribed error. The resulting coefficient corresponds to the effective diffusion, $D_{\text{eff}}^{(U(L), j+1)} = D_{\text{eff}}(p)$, of the highly randomised structure with $p = p_1$. Thus, the calculated transverse diffusivity is $D_{11}^{\text{eff}} = D_{\text{eff}}(p)$.

During the building of the structure described in Fig. 2b and c, the following three parameters were renormalised [24]:

$$\begin{cases} (33a) : & D_{11}^{(j+1, U)} = p_j D_{11}^{(j, U)} + (1 - p_j) D_{11}^{(j, L)} - \frac{p_j (1 - p_j) \left(D_{11}^{(j, U)} - D_{11}^{(j, L)} \right)^2}{p_j D_{11}^{(j, L)} + (1 - p_j) D_{11}^{(j, U)} + D_{11}^{(j, U)}}, \\ (33b) : & D_{11}^{(j+1, L)} = p_j D_{11}^{(j, U)} + (1 - p_j) D_{11}^{(j, L)} - \frac{p_j (1 - p_j) \left(D_{11}^{(j, U)} - D_{11}^{(j, L)} \right)^2}{p_j D_{11}^{(j, L)} + (1 - p_j) D_{11}^{(j, U)} + D_{11}^{(j, L)}}, \\ (33c) : & p_{j+1} = 2p_j^5 - 5p_j^4 + 2p_j^3 + 2p_j^2. \end{cases} \quad (33)$$

System (33) is a system of nonlinear equations representing the flux of parameters in a six-dimensional parametric space.

In order to obtain a real picture of diffusivity in biological tissue, we input the parameters experimentally measured in [16, 25–28]. These parameters are collected in Table 1. The initial value for the upper bound was normalised to $D_{\text{eff}}^{(U, 1)} / D_{11}^1 = 1$ (where D_{11}^1 is extracellular water diffusion), and the lower bound was normalised to $D_{\text{eff}}^{(L, 1)} / D_{11}^1$ at the initial iterative step ($j = 1$). The value $D_{\text{eff}}^{(L, 1)}$ was calculated according to the modified Crick formula (Eq. 4, composite intracellular diffusion coefficient denoted as $D_2 = D_{11}^2$).

In Fig. 5a, the evolution of the renormalised transverse effective diffusion coefficient D_{11}^{eff} during j steps of the recursive procedure in decimal semi-logarithmic scales is depicted. The upper and lower bounds of the effective diffusion correspond to the left and right axes (as indicated with arrows). The real diffusion coefficient fluctuates between bounds. In the small scale, $\xi > b$, the fluctuations are gigantic, but when $\xi \gg b$ and $\xi \rightarrow L$, the system exhibits statistically homogenised properties. This phenomenon clearly appears in Fig. 5a, b and comprises the convergence of the upper and lower bounds from the left to the right with a growing scale ξ . It can be seen that there are three distinct parts in the evolution of the parameters: I linear; II nonlinear; and III stable. Regime I is a region of instability (demonstrating scaling symmetry); during the iteration process, the recursive value moves toward the attraction area III (region with translational symmetry). Regime II can be treated as a separatrix area.

In Fig. 4a, the initial fractions of the extracellular water were $p_1 = 0.504$ (dotted line), $p_1 = 0.507$ (dashed line), and $p_1 = 0.511$ (dashed and dotted line). It is evident that the upper and lower bounds for the diffusion coefficient converge to a certain value (attractor) which depends on the initial fraction of the extracellular water. As can be

Table 1 Parameters of the model

$D_{11}^1 [m^2/s]$	$D_{\text{int}} [m^2/s]$	$a [m]$	$k [m/s]$	p value	c_1	c_2
2.0×10^{-9}	0.75×10^{-9}	6.0×10^{-6}	$10^{-12}/10^{-4}$	$[0, 1]$	0.95	0.65

Fig. 4 **a** Evolution of the upper $D_{\text{eff}}^{(U, j)}$ and lower $D_{\text{eff}}^{(L, j)}$ bounds of the diffusion coefficient. The *right* and *left* arrows indicate the axes corresponding the lower and upper bound of the effective diffusion coefficient. Regions are: *I* non-stable; *II* separatrix; *III* attractor. A zoomed view of the area enclosed by the box on the right side of the figure is shown in **(b)**. **b** Zoomed view of approach of the attractor points for different volume fractions as shown in **(a)**. **c** The flux of the renormalising diffusion coefficients in diffusion parametric space $(D_{\text{eff}}^{(U, j)}, D_{\text{eff}}^{(L, j)})$. The scale is chosen as decimal logarithmic. The direction of the parametric flux is indicated with *arrows*. The movement of the parametric flux stops at the bisector line (*black dashed*)

observed in Fig. 4a, b, the larger value of the effective diffusion coefficient corresponds to the larger value of the initial fraction of the phase. For the case where $p_1 = 0.504$, the number of iterations is $j = 11$; this builds a lattice consisting of $\sim 8^{11}$ bonds. Such a

Fig. 5 Normalised transverse diffusion coefficient D_{11}^{eff} versus volume fraction p of the extracellular water in decimal semi-logarithmic scales. Every point of the curves corresponds to the attractor point after j iterations

number of bonds are enough to obtain a physical description of the highly randomised heterogeneous biological tissue. The procedure of iteration of the parameters was stopped in accordance with the condition, $\max \left\{ \left| D_{\text{eff}}^{(U, j+1)} - D_{\text{eff}}^{(U, j)} \right|, \left| D_{\text{eff}}^{(L, j+1)} - D_{\text{eff}}^{(L, j)} \right| \right\} < \varepsilon$, where the acceptable norm $\varepsilon = 10^{-3}$ was chosen.

In Fig. 4c, the flux of effective diffusivities $D_{\text{eff}}^{(U, j)}$ and $D_{\text{eff}}^{(L, j)}$ in the parametric space with different initial conditions is depicted. The direction of the flux is indicated with arrows. The movement of the parametric flux stops at the bisector line (black dashed line). The initial fractions of the extracellular water were $p_1 = 0.504$, $p_1 = 0.507$, and $p_1 = 0.511$. The permeability varied from normal ($k = 5 \cdot 10^{-5}$ m/s), to low ($k = 10^{-12}$ m/s). The trajectory of the flux splits into different pathways, but all are eventually attracted by the bisector line (black dashed line) where equality $D_{\text{eff}}^{(U, j)} = D_{\text{eff}}^{(L, j)}$ occurs. The value of the curvature of the split trajectories depends on the initial concentration of extracellular water p_1 . If the initial concentration p_1 is closer to 1, then the curvature is higher and the effective diffusion is larger. This is correlated with the situation of the approach to the attractor zone in Fig. 4a and b where the point of the convergence, $D_{\text{eff}}^{(U, j)} \rightarrow D_{\text{eff}}^{(L, j)}$, strongly depends on the volume fraction. The dependence of the extent of the curvature as a function of permeability can be explained as follows. Once the difference in diffusion decreases (or the ratio $D_{11}^1/D_{11}^2 \rightarrow 1$), then the separatrix area II narrows, and the travelling trajectory in Fig. 4c straightens to a line for the case of high permeability. The stirring effect dominates for high extracellular–intracellular water molecule exchange. For this situation, it is difficult to recognise fraction dependence.

In Fig. 5, the dependence of the normalised transverse effective diffusion coefficient $D_{11}^{\text{eff}}/D_{11}^1 = D_{\text{eff}}^{(U, j)} \Big|_{j \rightarrow \infty}$ versus the fraction p of extracellular water is presented. The fraction of the cells is $(1 - p)$. Every point of the curve corresponds to the attractor point after j recursion procedures. The value of the permeability coefficient, k , is indicated in the legend of Fig. 5. The right and left asymptotes ($p \rightarrow \{0, 1\}$) converge to the upper and lower bounds of the effective media approximation, respectively.

The intermediate asymptote is located between the upper and lower bounds of the effective diffusion coefficient and demonstrates a characteristic jump. The jump disappears in the very high permeability coefficient limit, where intermittence dominates over the

Fig. 6 Dependence of the apparent diffusion coefficient D_{eff} (labeled on the vertical axis as ADC_{eff}) versus extracellular volume fraction and permeability coefficient)

localisation effects. The jump is usual for many diffusive (transport) processes and often is depicted with a logarithmic ratio [22]. The jump is in the vicinity of the threshold concentration $p_* = 0.5$ for two-dimensional case. In the realistic case, the volume fraction of the extracellular water varies from 0.1 to 0.4. As can be recognised from the modelling, in such a range of the variance of the volume fraction, the effective transverse diffusive coefficient is more sensitive to the permeability change rather than to the volume fraction of the extracellular water. Besides, the transverse case gives an inverse dependence on the permeability. Larger permeability contributes in lower transverse effective diffusivity which can lead to the point where the two compartments cannot be distinguished anymore.

For practical importance, it is useful to know the sensitivity of the apparent diffusion coefficient calculated as a trace of effective diffusion tensor in Eq. 27:

$$D_{\text{eff}} = (2D_{11}^{\text{eff}} + D_{33}^{\text{eff}})/3. \quad (34)$$

It can be calculated using Eqs. 27 and 33. Initial values are taken from the literature, where they were experimentally obtained and collected in Table 1. The results are presented in Fig. 6. Analysis of the sensitivity gives an indication of how they are associated with brain development and disease states. A similar problem is considered in [29] where the direct Brownian random walk Monte-Carlo numerical experiments were used. In both cases, the nonlinear behaviour of effective diffusion versus extracellular volume fraction is confirmed. The reason for such a pronounced nonlinear behaviour is in the increase in the probability of blocking of water molecules with a decrease of the extracellular volume fraction. Nonetheless, neuronal cells can exhibit degradation effects leading to the enhancing of permeability; such an effect reduces the blocking of water molecules. This is clearly demonstrated in Fig. 6.

The design of diffusion imaging experiments which can validate the proposed theory is reported in [30]. The essential point of such experiments is to vary the time scale as an argument of diffusion associated with probing the spatial scale. At short range, strong fluctuation is expected due to the heterogeneity of brain white matter. Such fluctuations

decrease on large length scales, leading to the estimation of effective apparent diffusion coefficient.

5 Conclusions

In summary, we have described a scale-averaging effective media iterative algorithm for the diffusion problem in random heterogeneous biological tissue. The diffusive (transport) properties were studied in the broad range of microscopic and composite parameters for biological multicompartmental heterogeneous tissue composed of cellular and subcellular domains. In these domains, the diffusing molecules may have different diffusion coefficients and densities (concentrations), namely within cells and within the outer medium. The results of the proposed effective media scale-averaging iterative scheme were used to explore the effects of a large range of microstructural and compositional parameters on the apparent (effective) diffusion coefficient on the iterative lattice composed of $\sim 8^{11}$ bonds. A self-consistent modelling framework for predicting the long-time scale effective diffusion coefficient was presented. This framework revealed the strong dependence of the apparent diffusion coefficient on the ratio of the microscopic diffusion coefficients of the comprising phases, their concentrations, and the permeability of the cells.

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