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Diffusion and tissue microstructure

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Abstract

Diffusion of molecules in brain and other tissues is important in a wide range of biological processes, such as the delivery of drugs, and for measurements, such as diffusion-weighted magnetic resonance imaging. The time-dependent diffusion coefficient $D(t)$ of mobile molecules confined in pores or cells carries information about the confining geometry. At early times, $D(t)$ gives, irrespective of details, the pore surface to volume ratio (S/V_p), and the cell-wall permeability κ. At long times, $D(t)$ reaches a limiting value D_0/α, where tortuosity α is a characteristic of the geometry of the medium.

1. Introduction

According to the National Institute of Health[1], 50 million people in the USA alone suffer from damage to the nervous system, such as Parkinson's disease, Alzheimer's disease, stroke, vascular dementia, spinal cord and head injury and brain tumour. Needless to say, exploring functional brain architecture is an important problem. The purpose of this paper is to outline several techniques from the physics of diffusion in porous media that can help in studying brain and other tissue structures. The problem of diffusion of various chemicals through the complex porous structure of brain and other tissues is an important problem [1] for understanding drug delivery, and intra- and inter-cellular signalling. Recently, diffusion weighted nuclear magnetic resonance based techniques (NMR) have emerged [2–6] as premier non-invasive techniques for studying brain and its disorders. Magnetic resonance diffusion imaging permits visualizing ischemic regions promptly. By contrast, conventional MR images take up to 24 h before the infarcted region can be seen. The diffusion coefficient of water in brain decreases quickly following stroke and other brain injuries by about 30%–40% in both gray and white matter. Although the mechanism is not known, some believe it is that the decrease results from cell swelling and net movement of water molecules [4–7].

The rapid increase in the use of diffusion-weighted magnetic resonance imaging (MRI) has raised the need for a better understanding of diffusion in tissues. The exact relationship

[1] 'Know your Brain', National Institute of Health, PO Box 5801, Bethesda, MD 20824, USA.

between the apparent diffusion coefficient (a tensor in general) and tissue microstructure and composition is not known, but could benefit a great deal from studying diffusion as a function of diffusion length, i.e. the time of diffusion. Because the diffusion length in NMR can be tailored between micron to millimetre range, NMR is perfectly suited for studying biological structures in this range. The recognition of this unique capability of diffusion NMR has generated a great deal of interest, see for example, the references cited in [4].

Diffusion is widely used to probe structures and fluid dynamics in porous media, including such diverse materials such as cheese, chocolate, cement, rocks for oil exploration (see references cited in [8]). When molecules are contained in interstices or pores or blocked by tissue walls, their motion is hindered by the restricting geometry. The local geometry leaves a fingerprint, so to say, on the diffusion coefficient; changing it from the putative bulk time independent value D_0 to a time dependent $D(t)$. Water diffusion is highly sensitive to geometric features, such as cell size or fibre orientation (diffusion anisotropy in white matter). NMR measurements give us an unprecedented opportunity to obtain detailed information about the nature of the selective pathways, the relative permeability (flow channels of specific fluids). The dynamics of molecules involving relatively large displacements through diffusion and flow are particularly suited for probing time and space correlations in porous media.

In this paper we describe the inverse problem of deducing information about the confining geometry from the time-dependent diffusion coefficient $D(t)$ of mobile molecules confined in cells. We will point out that there are robust ways of deducing surface-to-volume ratio and cell-wall permeability.

2. Tortuosity in porous media with impermeable walls

In a well connected porous medium $D(t)$ approaches, at long times, a non-zero finite value, reduced by a geometrical factor known as the tortuosity α,

$$D(t \to \infty) \to \frac{D_0}{\alpha}. \tag{1}$$

The coefficient α is a dimensionless number that defines the dc limit of diffusion and conductivity, equation (2). There are a vast number of porous media where the pores are interconnected and displacement is restricted only by pore walls. Most biological tissues and sedimentary rocks fall into this category. The geometrical parameter [9] 'tortuosity' α plays an important role in various transport processes in porous media-ranging from conductivity of rocks [10] to the velocity of the fourth sound in super-leaks [9]. This factor plays an important role in diffusion in brain [1] as well. Nicholson and colleagues [1] treat diffusion in brain tissues as diffusion within a porous medium with impermeable walls. Obviously, extracellular diffusion with impermeable cells can be likened to diffusion in porous rocks where the grains are impermeable and fluid resides in the interstices. According to Nicholson, signalling between neurons in the brain takes place principally via the passive movement of substances in the extracellular space.

In porous rocks made of insulating grains, the conductivity of rock σ is proportional to the conductivity of the interstitial fluid σ_w through a geometrical factor F, which also relates to $\alpha = F\phi$, where ϕ is the porosity, i.e. the volume fraction of fluid,

$$\sigma = \frac{\sigma_w}{F}$$
$$D(t \to \infty) = \frac{D_0}{F\phi}. \tag{2}$$

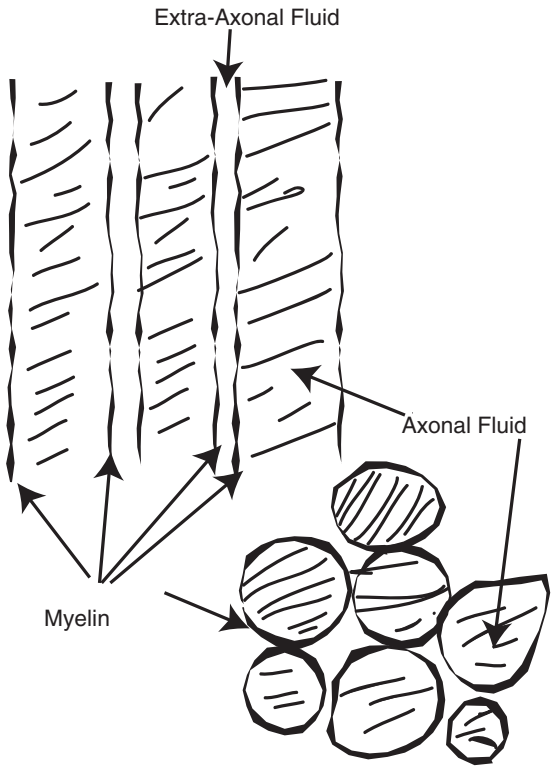

Figure 1. Schematics of white matter showing axons and the cross-section of the bundle (lower right). The gaps in the myelin sheath, known as nodes of Ranvier, are not shown. Water diffuses faster parallel to the fibres, than perpendicular to them.

So, at long times we expect that the mean square displacement grows linearly in time but with an effective diffusion constant D_0/α. The electrical conductivity measurements have been compared successfully to a diffusion derived long-time limit in many cases [8].

A large amount of literature on the theory of transport in complex porous media is devoted to computation of conductivity and hence of F and α. These results depend on the specific model chosen, however model independent bounds are known. Often these bounds are too wide to be useful. Exact results for some periodic structures can be obtained, see, for example, references in [7]. Only very few analytical results for random geometry are known. These again are generally based on the assumed shape of grains and uncontrolled approximations. For example, in packs of spherical beads, $\alpha = \sqrt{\phi}$ [10], a value that compares well with data [8]. If one uses the so called Archie relation [10], $\sigma = \sigma_w \phi^2$, which holds in a wide variety of rocks, one has $\alpha = \phi$. Numerical simulations using the histology of brain as geometric input gives a value [11] $\alpha = \phi^{0.82}$, somewhat intermediate between these two limits. However, white matter is highly anisotropic and for that new results are being developed. Exact results for tortuosity in model systems with permeable walls has been considered in Sen and Basser [7], where white matter (see figure 1) is modelled as an ordered pack of cylinders. Pioneering results for tortuosity that depends on wall permeability were first obtained by Latour *et al* [12] albeit using an approximate iterated dilute limit method [10].

The magnetic resonance imaging (MRI) can spatially resolve different types of biological tissue from contrasts in signals. MRI can detect gross structural changes, such as tissue

shrinkage and its reversal. Diffusion tensor imaging (DTI) is a powerful non-invasive tool to assess developing, normal and pathological white matter in the brain *in vivo* [2]. DTI is beginning to reveal microstructural abnormalities in white matter that are consistent with post mortem observations of white matter damage, such as myelin loss and enlargement of cells. DTI is capable of detecting these changes even when region investigated appears normal in standard MRI [2].

White matter, figure 1, has an underlying fibrous structure giving rise to an observed anisotropy in the diffusion coefficient, i.e. different diffusion coefficients parallel and perpendicular to the fibres. We [7] model diffusion in white matter fascicles as a problem of diffusion in an array of identical thick-walled cylindrical tubes immersed in an outer medium and arranged periodically in a regular lattice. The diffusing molecules have different diffusion coefficients and concentrations (or densities) within the tubes' inner core, membrane and myelin sheath, and within the outer medium. For an impermeable myelin sheath, diffusing molecules within the inner core are completely restricted, while molecules in the outer medium are hindered due to the tortuosity of the array of impenetrable tubes [7].

3. S/V_p with permeable walls

Transport of different molecules, especially of water, the fundamental solvent, entry of metabolite and exit of waste from cells across the membranes play key roles in all of biology. Diffusion across membranes is equally important in numerous physical and chemical systems especially in molecular sieves and nanoporous structures, with examples ranging from desalination, kidney dialysis to catalysis. Membrane permeability κ determines the rate of transport of chemicals between two compartments. With a permeable membrane, molecules diffuse across the wall, figure 2. Measurement of permeability of membranes is a difficult and challenging problem. There is a large literature on this subject, which is beyond the scope of this paper (see references in [8]). In a recent paper [13] an exact, universal, short-time asymptotic formula for the dependence of $D(t)$ on the permeability has been given. This can be used to estimate the permeability *in vivo* in a non-invasive measurement. The NMR data on erythrocytes [12] show that the effect of permeability can be significant on the observed $D(t)$ within the timescales of measurement and hence κ is deducible from the data.

At short-time limit, the surface appears flat. We use uppercase to denote propagators in 3D, for example, $G^{\mathrm{R}}(\mathbf{r}, \mathbf{r_1}, t)$ is the Green function for particles released to the right (within the cell) of the permeable wall at a point $\mathbf{r_1} \equiv \{x_1 > 0, y_1, z_1\}$ and ending up in another point $\mathbf{r} \equiv \{x, y, z\}$, at a time t later; we reserve the lowercase $g^{\mathrm{R}}(x, x_1, t)$ for the one dimensional problem considered in [13]. We take x to be direction normal to the surface. $G^{\mathrm{R}}(\mathbf{r}, \mathbf{r_1}, t) = G^{\mathrm{RR}}(\mathbf{r}, \mathbf{r_1}, t), x > 0$ and $G^{\mathrm{R}}(\mathbf{r}, \mathbf{r_1}, t) = G^{\mathrm{LR}}(\mathbf{r}, \mathbf{r_1}, t), x < 0$. To be explicit, $G^{\mathrm{RR}}(\mathbf{r}, \mathbf{r_1}, t)$ is the propagator for particles released to the right (within the cell) of the permeable wall at a point $\mathbf{r_1} \equiv \{x_1 > 0, y_1, z_1\}$ and ending up at another point $\mathbf{r} \equiv \{x > 0, y, z\}$, still within the cell, at a time t later. The superscripts RR denote particles released to the right and observed to the right of the membrane. Similarly, $G^{\mathrm{LR}}(\mathbf{r}, \mathbf{r_1}, t)$ denotes the propagator for the initial position to the right and the final position to the left of the membrane. The equations of motion for the propagators are:

$$\begin{aligned} D_{\mathrm{R}}\nabla^2 G^{\mathrm{RR}}(\mathbf{r}, \mathbf{r_1}, t) &= \frac{\partial G^{\mathrm{RR}}(\mathbf{r}, \mathbf{r_1}, t)}{\partial t}, \qquad x > 0, \quad x_1 > 0 \\ D_{\mathrm{L}}\nabla^2 G^{\mathrm{LR}}(\mathbf{r}, \mathbf{r_1}, t) &= \frac{\partial G^{\mathrm{LR}}(\mathbf{r}, \mathbf{r_1}, t)}{\partial t}, \qquad x < 0, \quad x_1 > 0 \end{aligned} \tag{3}$$

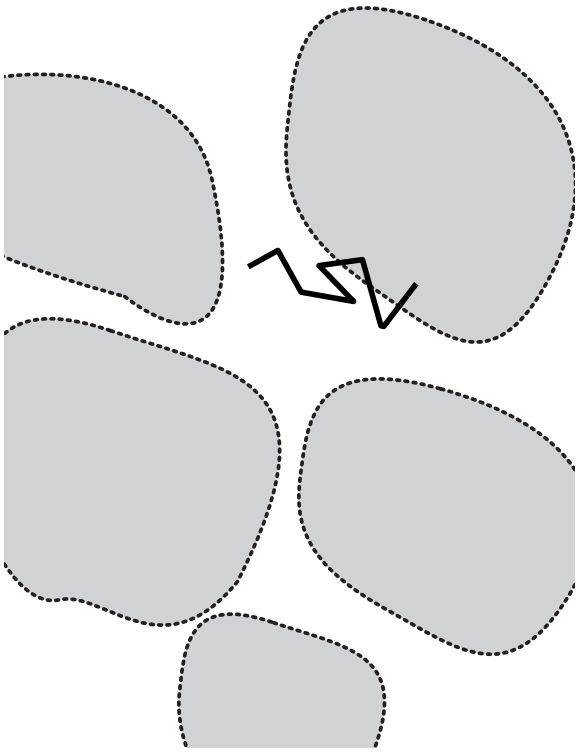

Figure 2. A cartoon of a random walk crossing a cell membrane. The diffusion coefficients, both parallel and perpendicular to membrane, are altered by the permeability factor κ.

with boundary conditions

$$D_{\mathrm{R}}\frac{\partial G^{\mathrm{RR}}(\mathbf{r},\mathbf{r_1},t)}{\partial x} = D_{\mathrm{L}}\frac{\partial G^{\mathrm{LR}}(\mathbf{r},\mathbf{r_1},t)}{\partial x}$$
$$= \kappa[G^{\mathrm{RR}}(\mathbf{r},\mathbf{r_1},t) - G^{\mathrm{LR}}(\mathbf{r},\mathbf{r_1},t)] \qquad \mathbf{r} \text{ on wall } \Sigma. \tag{4}$$

Here D_{R} and D_{L} are free (i.e. bulk) diffusion coefficients inside and outside of the cell respectively.

Diffusion parallel to the membrane is obtained by considering the time derivatives of the mean square displacements parallel to the wall and using the above equations of motions. For particles released to the right (within the cell) of the permeable wall at a point $\mathbf{r_1} \equiv \{x_1 > 0, y_1, z_1\}$ and ending up in another point $\mathbf{r} \equiv \{x > 0, y, z\}$, still within the cell,

$$\frac{\partial\langle(y-y_1)^2_{\mathrm{RR}}\rangle}{\partial t} = \frac{1}{V_{\mathrm{R}}}\int_{V_{\mathrm{R}}} \mathrm{d}^3 r_1 \int_{V_{\mathrm{R}}} \mathrm{d}^3 r\,(y-y_1)^2 \frac{\partial G^{\mathrm{RR}}(\mathbf{r},\mathbf{r_1},t)}{\partial t}. \tag{5}$$

Using equation (3) in equation (5), and integrating by parts repeatedly using Green theorem and adding a corresponding term for walkers released to the right of the membrane and ending up at the left, and using the boundary conditions equation (4) to cancel certain surface terms, we find for the walkers released inside the cell,

$$\frac{\partial\langle(y-y_1)^2_{\mathrm{R}}\rangle}{\partial t} = \frac{\partial\langle(y-y_1)^2_{\mathrm{RR}}\rangle}{\partial t} + \frac{\partial\langle(y-y_1)^2_{\mathrm{LR}}\rangle}{\partial t}$$
$$= \frac{1}{V_{\mathrm{R}}}\int_{V_{\mathrm{R}}} \mathrm{d}^3 r_1 \int_{V_{\mathrm{R}}} \mathrm{d}^3 r\,(y-y_1)^2 \frac{\partial G^{\mathrm{RR}}(\mathbf{r},\mathbf{r_1},t)}{\partial t}$$

$$+\frac{1}{V_{\rm R}}\int_{V_{\rm R}} {\rm d}^3 r_1 \int_{V_{\rm L}} {\rm d}^3 r\,(y-y_1)^2 \frac{\partial G^{\rm LR}(\mathbf{r},\mathbf{r_1},t)}{\partial t}$$
$$= 2D_{\rm R} M_0^{\rm RR}(t) + 2D_{\rm L} M_0^{\rm LR}(t). \tag{6}$$

Here

$$M_0^{\rm RR}(t) = \frac{1}{V_{\rm R}}\int_{V_{\rm R}} {\rm d}^3 r_1 \int_{V_{\rm R}} {\rm d}^3 r\, G^{\rm RR}(\mathbf{r},\mathbf{r_1},t),$$
$$M_0^{\rm LR}(t) = \frac{1}{V_{\rm R}}\int_{V_{\rm R}} {\rm d}^3 r_1 \int_{V_{\rm L}} {\rm d}^3 r\, G^{\rm LR}(\mathbf{r},\mathbf{r_1},t), \tag{7}$$

denote, respectively, the fraction of walkers ending up at time t on the right and on the left of the membrane, having been released at time $t = 0$ on the right.

This equation (6) has a simple interpretation. The rate of change of the mean square displacement for walkers released inside (right of the wall) has two contributions, first from fraction of walkers $M_0^{\rm RR}(t)$ that remains inside the cell with diffusion coefficient $D_{\rm R}$ and the fraction that oozes out to the left $M_0^{\rm LR}(t)$, where they diffuse with an effective diffusion coefficient $D_{\rm L}$.

We find at short-times:

$$\frac{\partial \langle (y-y_1)^2_{\rm R}\rangle}{\partial t} = 2D_{\rm R}\left(1-\kappa t\frac{S}{V_{\rm R}}\right) + 2D_{\rm L}\kappa t\frac{S}{V_{\rm R}} + \mathcal{O}(t^{3/2}), \tag{8}$$

for the walkers released on the right of the membrane. At short-times, a fraction $\kappa t\frac{S}{V_{\rm R}}$ of walkers leak out from right to left and have different diffusion coefficients. S is the total surface area. The result for diffusion perpendicular to the membrane is obtained by considering the time derivatives of the mean square displacements in the direction normal to the membrane, and using the above equations of motions,

$$\langle (x-x_1)^2\rangle_{\rm R} = 2D_{\rm R}t - \frac{S_{\rm R}}{V_{\rm R}}\left(\frac{8D_{\rm R}^{\frac{3}{2}}t^{\frac{3}{2}}}{3\sqrt{\pi}} - \sqrt{D_{\rm L}}\big(\sqrt{D_{\rm L}}+\sqrt{D_{\rm R}}\big)\kappa t^2\right) + \cdots. \tag{9}$$

Here $V_{\rm R}$ denotes the total volume within the cells and $V_{\rm L}$ is the total volume outside; $S_{\rm R}/V_{\rm R}$ is the total internal surface divided by the total internal cell volume. At short-times, a fraction $\kappa t\frac{S}{V_{\rm R}}$ of walkers leak out from right to left and have different diffusion coefficients. S is the total surface area. Computation of $M_0^{\rm RR}(t)$, $M_0^{\rm LR}(t)$ is expedited again by considering their time derivatives, such as,

$$\frac{\partial M_0^{\rm RR}(t)}{\partial t} = \frac{1}{V_{\rm R}}\int_{V_{\rm R}} {\rm d}^3 r_1 \int_{V_{\rm R}} {\rm d}^3 r\, \frac{\partial G^{\rm RR}(\mathbf{r},\mathbf{r_1},t)}{\partial t} \tag{10}$$

and using the equations of motion and using Green theorem and the exact form of the propagators [13].

Similar results can be found for particles released outside the cell, by swapping $L \leftrightarrow R$.

Previously Latour *et al* [12] analysed the long-time behaviour using a specific model of packed spherical cells with permeable walls. In their model, the most important result is that the tortuosity factor $\alpha(\kappa)$ depends on permeability [7]. However, as noted before, their pioneering result is based on an uncontrolled approximation of the iterated dilute limit [10]. The short-time correction that includes the term linear in $\kappa t S/V_{\rm p}$, independent of model geometry, would give a far more robust estimation.

4. Inverse problems and Kac's ideas

The common strategy for deducing geometry from diffusion results relies on the solution of the diffusion equation in bounded regions—such as the interior of a sphere. The diffusion equation

for bounded regions is amenable to 'spectral decomposition' in terms of eigenmodes and eigen frequencies. The strategy involves fitting observed data to results of 'forward modelling', i.e. to responses that are worked out numerically or analytically for specific model systems. Although analytical and numerical solutions exist only for simple geometries, this strategy works extremely well in many cases—for example in extracting diameters of spherical or cylindrical cells in mono disperse samples.

In biological systems, the shapes of cells are complex, connecting passages are tortuous, connectivity is random and, above all, many length scales come into play. For well connected systems, there is a continuum of eigen-modes. Inversion by the above techniques thus becomes impossible. For complex systems, even the forward problem becomes unsolvable, let alone the inverse problem. There are additional problems of non-uniqueness. Even for the case of objects having discrete spectra, it is not possible to identify shapes. Relatively simple but different shapes can give rise to same set of frequencies. For complex systems a set of different strategies are needed. One alternate robust strategy emerges from the study by Kac in his celebrated paper 'Can one hear the shape of a drum?' [14]. The connection to 'drums' derives from the well known fact in mathematical physics that the vibrations of membranes obey the diffusion equation [14].

Kac started out asking (roughly speaking) whether one can infer the geometric shape of a drum from knowing the drum's frequencies of vibrations (eigenfrequencies). Kac was unable to answer this question, and recently it has been proven that the answer is 'no' [15]. However, Kac showed that both the area of a drum's membrane and the length of its perimeter affect the short-time behaviour of certain functions of a drum's spectrum of normal modes. In other words, one can 'hear' a drum's area and perimeter. These results are *universal*—i.e. do *not* depend on the solution of forward problem for specific shape.

Computation of macroscopic transport coefficients, such as α, depends on the specific model chosen, although model independent bounds are known, and exact results for some periodic structures can be obtained, see, for example, in [7]. Although tortuosity α contains information about geometry, many different geometries can give rise to same α.

Kac's insights have prompted a new analysis of time dependent diffusion coefficients of more complex systems in terms of a few geometrical parameters, such as surface-to-pore-volume ratio S/V_p, average curvature, etc [8]. In systems where surface drives chemistry, e.g., biology, catalysis, colloidal sciences, as well as in transport in porous rocks, S/V_p is a key parameter which is directly analogous the perimeter of a drum. The importance of S/V_p is particularly paramount for systems with characteristic sizes in the micron range where NMR is unsurpassed as a tool. For example, NMR is unique in detecting changes in S/V_p of cells in ischemia, a fact that can be used for early detection, and, hence, for damage control. The short-time asymptotic form that we discuss above is more than a scaling law, it has all the constants needed to extract the geometrical parameter. At short times, $D(t)$ of *all* smooth porous media can be expressed by a single simple *universal* equation with the characteristic lengths of the system expressed in units of the diffusion length $\sqrt{2D_0t}$ the *scale parameter*. A *universal feature* in $D(t)$ determines the measured S/V_p, κ in a robust manner [8].

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