Effective Diffusion and Tortuosity in Brain White Matter*

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***Abstract*— Patients affected by glioblastomas have a very low survival rate. Emerging techniques, such as convection enhanced delivery (CED), need complex numerical models to be effective; furthermore, the estimation of the main parameters to be used to instruct constitutive laws in simulations represents a major challenge. This work proposes a new method to compute tortuosity, a key parameter for drug diffusion in fibrous tissue, starting from a model which incorporates the main white matter geometrical features. It is shown that tortuosity increases from 1.35 to 1.85 as the extracellular space width decreases. The results are in good agreement with experimental data reported in the literature.**

I. Introduction

Patients affected by glioblastoma, which is the most common malignant tumor, suffer from a poor prognosis. Despite surgery, chemotherapy and radiation are aggressive techniques, the median survival time does not exceed 2 years [1], [2]. In this clinical scenario, convection enhanced delivery (CED) has shown encouraging results because it allows to overcome the blood-brain barrier (BBB) which is a major obstacle in reaching the parenchyma with therapeutics [3], [4]. Indeed, in CED, a pharmaceutical agent is injected directly into the brain by means of a catheter which is linked to an external pump that provides a defined flow rate. The ability to predict, in the operative phase, the distribution of the drug inside the tumor is one of the most important factors affecting CED efficacy as suggested in Refs. [5], [6]. Therefore, several numerical models aimed at predicting the efficacy of this treatment and the penetration of the drug have been developed in the last twenty years [7]–[9]. However, they are still affected by unsatisfactory predictive capabilities. One of the reasons for the lack of success in producing definitive answers and simulation tools for this problem is that most of the constitutive parameters involved vary significantly from one study to another. Indeed, the brain has proved to be a challenging medium to be studied because of the extreme difficulty to conduct either experimental campaigns or numerical studies [10].

One of the most important parameters affecting CED outcomes is tortuosity which mainly depends on the extracellular space (ECS) geometry [10]–[13]. Although the ECS plays a fundamental role in determining the CED performance, its characteristics are still largely unknown, especially since its width is quantified in the tens of nanometers. Several studies [12]–[15] have determined that the ECS occupies about 20% of the brain volume; the ECS is composed by narrow spaces between the cells of the central nervous system, which form an interconnected system of channels demarcated by cellular membranes. The gap between each membrane is filled with a fluid, whose characteristics resemble the cerebrospinal fluid, and the extracellular matrix consisting of proteoglycans, hyaluronan and other proteins [10], [15]. Although different important steps forward have been made in this area, linking the microscopic properties of the ECS to macroscopic parameters remains challenging [13]. Tortuosity, which expresses the geometrical complexity of the ECS, is defined as

$$\lambda=\sqrt{(D/D^*)}, \tag{1}$$

where D is the free diffusion coefficient determined in water or a very dilute gel and D^* is the effective diffusion coefficient due to the hindrance of the ECS. Two different approaches have been developed to determine the tortuosity. The experimental approach, that may be conducted *ex vivo* or *in vivo*, exploits molecules with a hydrodynamic diameter much smaller than the gap between cells, which are used as a probe to infer the ECS characteristics. Tortuosity values range from 1.44 to 3.50 depending on the animal used, the probe molecules and the physio-pathological conditions, as evidenced by the detailed studies reported in Refs. [10], [12], [16]. A value of about $\lambda=1.6$ has been assigned to normal brain in physiological condition. The second approach consists in the creation of geometrical models which undergo Monte Carlo simulations [13]–[15]. The first set of simulations reported in Refs. [13], [14] have shown that a maximum value of $\lambda=1.225$ can be attained by modelling the system as an assembly of regularly spaced convex cells (cubes and other objects); this value is remarkably lower than the values extracted from experiments. To fill the gap between experiments and simulations, the authors of Refs. [11], [15] have hypothesized the presence of dead-space microdomains that hinder the molecules diffusion. This approach produced results that are much closer to the experiments, but its geometry is based on cubes with cavities of different shapes and the authors could only speculate on the morphological basis for these assumptions. Therefore, this paper aims to shed light on tortuosity focusing, on the relationship with the ECS geometry. To do that, we propose a new geometry model for white matter with realistic features and that is able to match experimental data. Moreover, to the best of our knowledge, this is the first attempt to differentiate between gray and white matter.

II. Methods

A. Dataset

In this work, we used the axon diameter distribution (ADD) of the corpus callosum of a monkey which was

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provided by [17]. The authors used the measured inner diameter of myelinated axons and the average width of the myelin sheath to construct a realistic model.

B. Geometry creation

The geometry was created using an ad-hoc algorithm within the Matlab program (Mathworks, Nantick, MA). The main idea was to create a geometry that could resemble closely the white matter microstructure. Therefore, we modeled the axons as straight cylinders parallel to each other with a circular cross section according to the ADD and the myelin sheath width [18]. Moreover, ECS volume ratio and ECS width were made to vary within physiological values [12]. The algorithm to generate the geometry was based on the advancing front approach described in [19] but, instead of having tangential circles, we imposed the minimum distance between each of them to be the ECS width, as shown Fig. 1(a). Moreover, to keep the ECS volume fraction in the physiological range, we implemented a complementary algorithm which, respecting the ADD and ECS width constraints, adds a new circle in each void space which is suitable, as depicted in Fig. 1(b). This second part exploited the skeletonization algorithm described in [20]; indeed the skeleton branch points represent the location where the distance between close circles is maximized. Finally, the circles were extruded to form 3D cylinders whose length was designed according to the specification suggested in [14]; the result of the generation of the three-dimensional domain used for the numerical models reported in the next sub-section is shown in Fig. 1(c). We created five 3D geometries whose geometrical features are summarized in Table 1.

C. Numerical modeling

The numerical simulation were conducted using the software MCell [21]–[23] which allows measuring the effective diffusion coefficient and tortuosity reproducing the experimental point-source paradigm [10]. In each simulation, 5000 molecules were released in the center of the volume and let free to diffuse. We did not include any chemical reaction between molecules and axons membrane since we were only interested in the effect that geometry has on tortuosity. Therefore, each collision was modelled as perfectly elastic [13]. We set a free diffusion coefficient D=10^{-7} cm^2/s with a time step Δt=1 μs for a total simulation time of 10 seconds.

TABLE I. MAIN FEATURES OF THE BRAIN GEOMETRIES CREATED

ECS width [nm]	ECS Volume ratio	Number of axons	Dimension [μm]
5	0.18	7490	60.6 x 60.6 x 62.6
20	0.21	7204	60.5 x 60.5 x 62.5
40	0.25	6934	62.1 x 62.1 x 64.1
60	0.27	6754	63.4 x 63.4 x 65.4
80	0.32	6868	65.7 x 65.7 x 67.7

These parameters resulted in a mean linear step length:

$$L_{mean}=2\sqrt{(D\Delta t/\pi)}, \quad (2)$$

which is about six times smaller than the minimum space between axons. In this way, each molecule executed several Monte Carlo steps between consecutive interactions with axon surfaces [11]. The sampling box approach originally developed by Ref. [14], was used in the generalized version provided by Ref. [13] to take into account the anisotropic shape of our geometry. In this second method, each concentric box is defined by three dimensions a_x, a_y and a_z along each principal axis; however, since we want to compute the effective diffusion along each axis separately, we let two out of three dimensions become much larger so that the domain can be considered to be infinitely large along those axes. This allows us to examine the behavior of the system in the third remaining direction (e.g. to compute the effective diffusion along the x axis, with both a_y and $a_z \rightarrow \infty$). In this way, we set 8 sampling boxes along each principal direction. Being transparent at the molecules passage, their only function is to count the number of molecules inside them as a function of time. The number of molecules n in each box is described by the following equation:

$$n(t)=n_0\mathrm{erf}(a_x/4\sqrt{(D^*_x t)})\ \mathrm{erf}(a_y/4\sqrt{(D^*_y t)})\ \mathrm{erf}(a_z/4\sqrt{(D^*_z t)}) \quad (3)$$

where n_0 is the initial number of molecules, t is the time and D^*_x, D^*_y, D^*_z are the effective diffusion coefficients along the principal directions. Equation (3) was used to fit the simulation data by means of a Matlab based nonlinear fitting algorithm thus estimating D^* for each box. The final value of D^*_x, D^*_y, D^*_z and so λ_x, λ_y, λ_z was obtained averaging the results of each box along the principal axes.

III. RESULTS

The geometry was designed to be axisymmetric with respect to two principal directions: the first runs parallel to

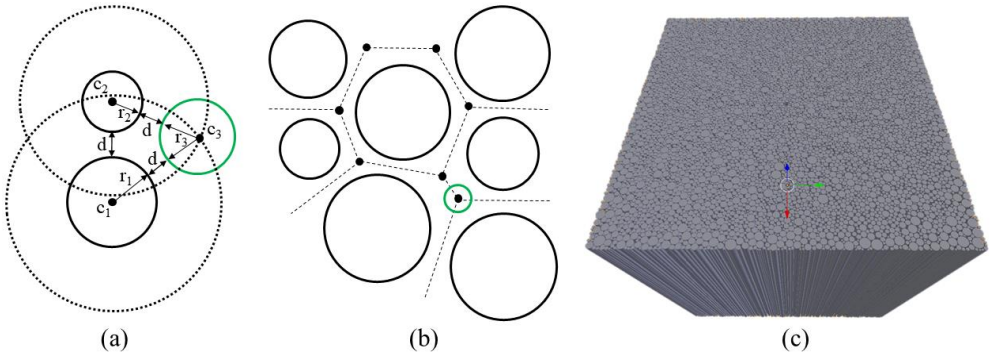

Figure 1. Circles generation algorithm: (a) given two circles with radius r_1 and r_2 and centered at c_1 and c_2 respectively, the center c_3 of the new circle (green) with radius r_3 is given by one of the two intersections of the dotted circles with radius r_1+r_3+d and r_2+r_3+d centered at c_1 and c_2 respectively; (b) in the second part of the algorithm, new circles are added at the skeleton branchpoints (black dot) if they respect the ADD and the ECS width; (c) each circle is extruded in a straight cylinder to produce the final three-dimensional geometry.

the axons and the second is perpendicular to them. We verified this statement comparing the results obtained along the x and the y axis which showed negligible differences. Fig. 2 gives a graphical idea of the axisymmetric behavior of the system: in Fig. 2(a) the molecules spread radially in a uniform way whereas in Fig. 2(b), the molecules move preferentially in the z direction. Therefore, only the results obtained along the x and z axes, namely the radial and longitudinal directions, will be shown. In Fig. 3, it is possible to notice that λ_z (longitudinal tortuosity) is constant and equal to 1. This behavior was expected because the axons are parallel to each other and so they do not offer any obstacles to the diffusion of molecules along this direction. In other words, the longitudinal component of the random displacement performed during the simulation is never affected. In contrast, λ_x (radial tortuosity) is always higher than 1 because the axons geometry hinders the molecules movement. Furthermore, Fig. 3 shows that λ_x is inversely proportional to both ECS volume ratio and ECS width, meaning that the effective diffusion varies from 29 to 54% of the free diffusion. Finally, Fig. 3 compares λ_x with the convex cell model presented in Ref. [14] and experimental data of similar brain structures reported in Ref. [12].

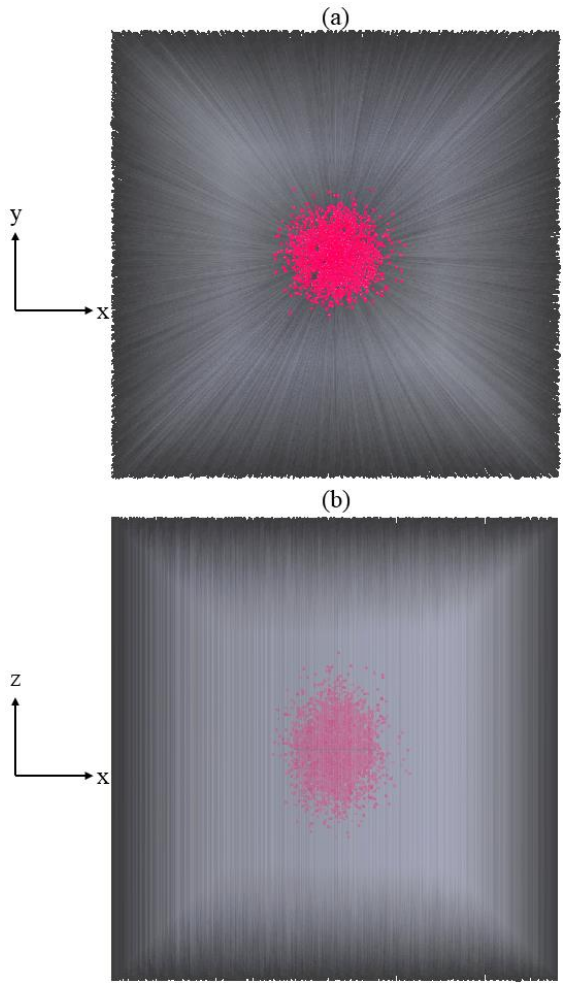

Figure 2. (a) Top view and (b) frontal view of one of the five volumes studied in our simulations, showing the diffusing molecules after 1.8 seconds. The anisotropic behavior of the system is highlighted by the ellipsoidal shape of the molecules cloud in (b).

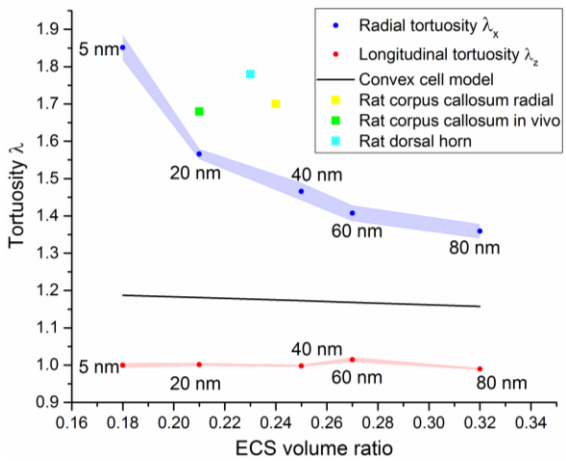

Figure 3. Radial tortuosity (blue) and longitudinal tortuosity (red) obtained with our simulations. The radial tortuosity decreases as both the ECS volume fraction and the ECS width increase. In contrast, the longitudinal tortuosity is constant and equal to 1. The radial tortuosity is compared with the convex cell model (black) [12], and experimental data obtained on different rat white matter fibre tracts [15].

IV. Discussion

The simulation of physiological models can follow two main approaches: finite element method (FEM) or Monte Carlo [24]. Both methods have advantages and drawbacks, but whereas in the first the accuracy is guaranteed by the solution convergence, in the second, this passage is not straightforward. Therefore, in Monte Carlo simulation, it is fundamental to assess the accuracy comparing numerical and theoretical results. In our model, the soundness of the method is proved by λ_z which is equal to 1 in all the simulations with a negligible standard deviation (Fig. 3). This result is in complete agreement with what was expected theoretically since the geometry was designed to offer no resistance in the longitudinal direction.

Moreover, the results depicted in Fig. 2 show that the geometrical anisotropy has a fundamental role in determining the molecules diffusion path. Since it has been demonstrated that the white matter is highly anisotropic [12], this factor should be taken into account to shed light on the diffusion process mechanism. Existing models [11], [15] have attempted to find a specific correlation between a certain geometrical feature, namely ECS volume fraction and dead-space microdomains, and the outcomes in term of tortuosity. However, it has been hard to find a morphological justification for the existence of the dead-space microdomains. In contrast with this, the geometrical model proposed in this paper matches most of the main histological white matter characteristics in terms of ADD, ECS volume ratio and width. The latter could have a prevalent responsibility as suggested by the results showed in Fig. 3. Indeed, the circular axonal cross sections facilitates the formation of bottlenecks followed by large cavities. While the bottlenecks provide a very small passage for the molecules to freely move across the matter, the cavities may be described as pockets [11] or lakes [25] where the molecules remain trapped. Finally, in Fig. 3, it is possible to note that the model produces a trend of λ_x that correlates well with the experimental values extrapolated from results

obtained from similar brain regions either *in vivo* or *ex vivo*. This suggests that our geometry has succeeded in including the main parameters responsible for this behavior. It should be noted that there is not a perfect agreement between the simulation and the experimental data. This could be easily explained by the fact that we aimed to understand the role of the geometry whereas the experimental tortuosity is a composite parameter, which depends on other factors such as extracellular matrix and hydrodynamic diameter of the diffusing molecules [10]. Nevertheless, understanding the relationship between geometry and tortuosity is fundamental to integrate this parameter with imaging techniques such as diffusion tensor imaging, used in CED interventions, which provides statistical information on the microstructure.

V. Conclusion

We presented a new model that incorporates the main geometrical features of the white matter. The model cannot be considered exhaustive since some assumptions had to be made to simplify the geometry along the z axis. Therefore, future improvements will incorporate characteristics concerning the longitudinal axonal development, such as curvature and cross-sectional area variation. Nevertheless, our model outcomes are in good agreement with the experimental data and represent a significant improvement with respect to previous works, whose failure to accurately predict tortuosity is probably due to their attempt to describe the whole brain. This suggests that a zone-wise approach which differentiates at least between white and gray matter could be more reliable in inferring the diffusion properties which are essential to determine the evolution of many biological and drug delivery process.

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