Extracellular Diffusion in Brain: Distinct Diffusion Regimes at Different Spatial Scales

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1. Introduction

From biophysical perspective, brain is a porous medium. Brain cells are surrounded by a system of contiguous narrow pores called extracellular space (ECS, Fig. 1). The ECS occupies approximately 20% of the brain volume and it is filled with ionic solution and macromolecules of the extracellular matrix. The basic ECS structure is determined by a) the geometrical shape of cells, b) the width of the pores between the cells, and c) the macromolecules of the extracellular matrix (Fig. 1). These components dynamically change during brain cell activity and get altered, often irreversibly, in brain pathologies. Thus, unlike most porous media, brain is not static.

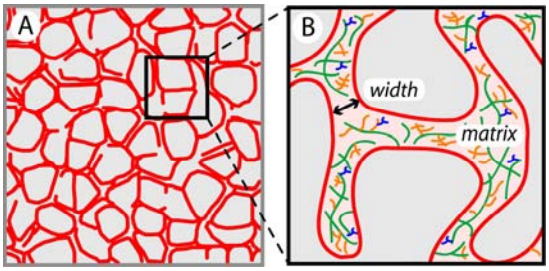

Fig. 1. A. Brain cells (*grey*) surrounded by the ECS (*red*). **B.** Cell geometries, pore width and matrix are key components of the ECS structure.

The ECS has fundamental importance for brain function. It exerts a direct influence on many essential processes in the brain, including the intercellular signaling and the transport of nutrients and metabolites [1, 2]. The ECS also forms the final segment of a delivery route for all drugs destined for the brain cells [3, 4]. Once introduced into the ECS, substances are transported predominantly by diffusion because the ECS lacks any active transport mechanism. Physiological effects of the substances diffusing in the ECS are governed by their concentrations and their arrival times, which in turn depend on the ECS structure affecting the diffusion. Biophysical parameters of the ECS have to be determined whenever quantitative understanding of any diffusion-mediated process is desired.

2. Diffusion analysis for the study of ECS

Diffusion can be exploited experimentally to quantify a) extracellular transport of molecules of interest (signaling molecules, nutrients and drug) but also b) structural properties of the ECS when an extracellular marker is employed [5, 6]. In a traditional diffusion experiment, molecules are released from a point source and their subsequent ECS concentration is analyzed as a function of position and time. Measurements, which involve diffusion over the distances of about 100 μm, yield an effective diffusion coefficient (D^*) (Fig. 2). When extracellular marker is employed, D^* is used to determine

how much the diffusion process in a complex ECS environment slows down in comparison to an obstacle-free medium. Tissue hindrance is expressed as a macroscopic ECS parameter tortuosity $\lambda = (D/D^*)^{0.5}$ [7] or diffusion permeability $\theta = D^*/D$ [8] (D is a free diffusion coefficient).

It has been taken for granted that D^* remains constant over all diffusion distances. However, we have recently discovered that diffusion in the brain is transiently anomalous over distances of a few tens of micrometers. This means that, over this distance, the rate of diffusion depends on time and generally is faster than currently believed. To explore the phenomenon of a transiently anomalous diffusion, we introduce the concept of a Dynamic Microdomain (DM), defined as the largest volume of the brain tissue in which the anomalous diffusion is observed (Fig. 2). Currently, we are developing a Fast Optical Tracking of Diffusion (FOTOD) method, which will characterize the time-dependent diffusion and it will enable estimation of DM size.

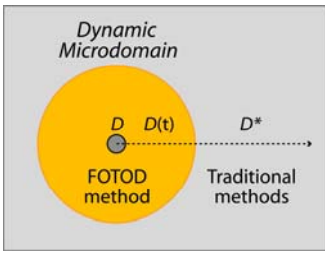

Fig. 2. Extracellular diffusion in three spatial regimes. D(t) denotes anomalous diffusion inside the DM.

3. New concepts and directions for ECS research

The long-term goal of our research is to construct and characterize a realistic three-dimensional model of the brain ECS, in order to predict the impact of microstructure on the transport of signaling molecules, nutrients and drugs. We propose that the ECS diffusion can be broken into three distinct spatial regimes (Fig. 2): 1) "fast normal" diffusion on a scale < ≈50 nm (e.g., the synaptic cleft), 2) "transiently anomalous" diffusion at a scale of about 0.05—50 μm (encompassing transport of signaling molecules, nutrients and drugs), and 3) "slow normal" diffusion on a scale > ≈50 μm (relevant for long distance transport, e.g., drugs injected into the ventricles). The focus of our current projects is an inquiry into the newly found second category (transiently anomalous diffusion), which is characterized by the DM. The new concept of the DM challenges current thinking on molecular diffusion in the brain, particularly over short and physiologically most relevant distances. Because many signaling molecules, nutrients and drugs do not diffuse beyond the DM, transiently anomalous diffusion within this domain is inherently important for the timing of diffusion-mediated processes.

References

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