Diffusion Processes in the extracellular space of the brain

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Abstract

This is a project in computational neuroscience based on some 8 articles describing various aspects of diffusion in the extracellular space of the brain.

1 Background material

For all practical purposes, the brain of a rat is considered equal to the brain of a human in this project.

1.1 Basics of the brain

The human brain consists of two types of cells; the neurons and neuroglia. Neurons are tasked with signal processing and transport, while the glia are thought to have more janitoral tasks. The neurons are bathed in a salt solution that is mainly Na^+ and Cl^-. Inside the neurons, a highly regulated salt solution of mainly K^+ sets up a potential difference to the outside of around -65mV. The neurons are in constant communication with eachoter through action potentials, which are disturbances in the membrane potentials on neurons. Theese action potentials are generated in the body of the cell, called the soma, and then propagate down the axon without loss of amplitude. After propagating down the axon, the action potential reaches a synapse which is a gate to another neuron. If the action potential is of significant strength, vesicles carrying neurotransmitters merge with the synapse membrane, letting the neurotransmitters diffuse to the dendrite of the other neuron. If enough neurotransmitters reach the pos-synaptic side, the signal continues propagating to the soma of this neuron, and the entire process starts over again. The interest of this project lies, mainly, in the diffusion processes that take place in the space between theese types on cells, the so-called extracellular space (ECS). This is a narrow space ($\sim 10 - 100$ nm [1]) with a highly complicated geometry (figure 1). Surprisingly, the ECS adds up to a total of 20% of the total brain volume. We can understand this by realizing that every part of a cell must be separated from another cell by the ECS. Since the cells consists of axons and dendrites which are (somewhat) fractal, we see that this eventually means separating a vast ammount of surface area from other surface areas.

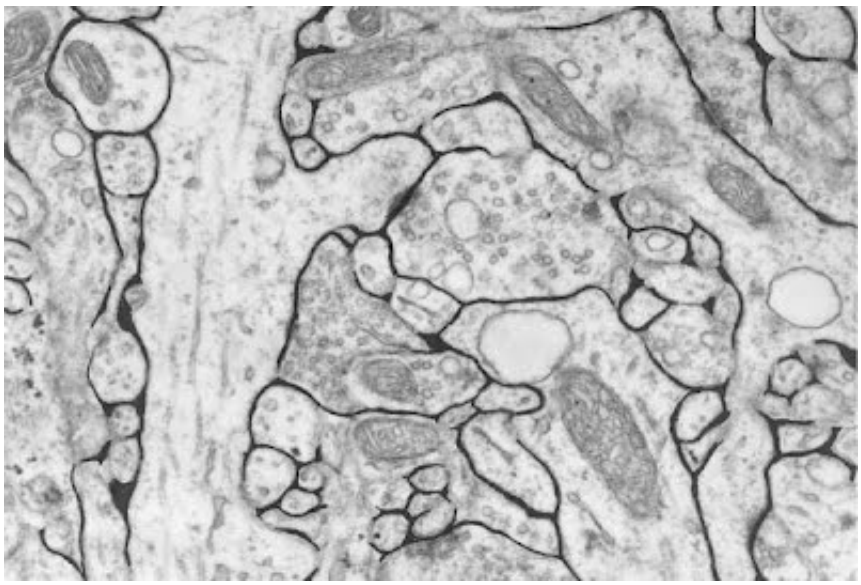

Figure 1: Electron micrograhp of a small region of the cerebral cortex of a rat with a prominent synapse. The black areas os the picture indicate the ECS, which may be reduced in size as a conequence of the processing. The asterix (*) indicates the postsynaptic side of a synapse on a dendrite. On the other side of the synaptic cleft one can make out the pre-synaptic terminal containing several small, round vesicles filled with neurotransmitter molecules. Figure taken from Nicholson.

The ECS is thought to support the diffusion of oxygen and nutrients to the neurons and glia, and diffusion of carbon dioxide and other waste from theese cells through the blood - brain barrier and into the bloodflow.

1.2 Diffusion in general

Diffusion is a transport process which in it's well known macroscopic form has been attributed to Adolf Fick. In 1855, building on the earlier experimental work of Graham, Fick formulated the macroscopic law later known as Fick's law

$$\text{flux} = -D \times \text{concentration gradient} \tag{1}$$

Where $[D] = \frac{m^2}{s}$ is the diffusion constant. Fick's law leads to the well known partial differential equation in the concentration.

$$\frac{\partial C}{\partial t} = D\nabla^2 C \tag{2}$$

Einstein later (1905) proposed the most usefull relation between the diffusion constant and a fluid viscosity

$$D = \frac{k_B T}{6\pi\eta r} \tag{3}$$

. There are several relations on this form, relating the diffusion constant to various other easily measurable quantities. The most relevant for the study of diffusion in the ECS would be

$$\langle r^2 \rangle = 2dDt \tag{4}$$

in the limit of large t (that is in steady state). Equation 4 relates the root-mean-square displacement of a particle after a time t (t is large) in a d dimensional space. There are two good reasons to consider the transport mechanisms in the ECS as diffusion processes. First of all, diffusion goes seamlessly from micro to macro scale. In our case, this is perfect since the channels of the ECS are very narrow, but not nececarily narrow enough to consider all the microscopical effects. Second, the geometry of the problem is somewhat similar to diffusion in porous media. TO DO!!!

1.3 Why diffusion in ECS

Though there are several reasons to study diffusion processes in the ECS this project has a specific goal in mind. The einstein relation 3 relates the diffusion constant to the viscosity of the medium in which the diffusion is taking place. From the definition of viscosity we have $v_d = \mu F$ where $F = qE$. We can also define the current from the drift velocity of the particles as $j = cqv_d = \sigma E$ where $\sigma = c\mu q^2$ is the electrical conductance, in this case, of the ECS. Inserting this in the einstein relation 3 lets us express the conductivity in terms of the diffusion constant $\sigma = \frac{cq}{k_B T} D$. We are interrested in the extracellular conductance for measurment purposes. TO DO!! SAY SOMETHING ABOUT NETWORK MODELS?

2 Mathematical models

There diffusion in the ECS is, of course, modelled by a diffusion equation, but rather a modified one than the basic diffusion equation 2. Since the geometry of the ECS is very narrow, molecules diffusing in this space will not be subject to free diffusion, as the normal diffusion equation assumes. The diffusing molecules will bounce off cell membranes (we are now considering macromolecules on such a scale that speaking off a cell membrane makes sense) and other molecules. There may even be molecules absorbed by cells, getting stuck onto membranes or going through similar processes. We therefore see it fit to introduce a modified version of the diffusion equation which is more similar to the diffusion equation governing diffusion in porous media.

$$\frac{\partial C}{\partial t} = D^* \nabla^2 C + \frac{s}{\alpha} - k'C \tag{5}$$

Where we have introduced an effective diffusion constant D^* defined from the tortuosity, $\lambda = \sqrt{\frac{D}{D^*}}$, which is a parameter saying something about the reduction in the diffusion constant compared to free diffusion (usually measured in a low percentage agar solution in water). The tortuosity can also be interpreted as a measure of the "twistyness" of the media in which the diffusion is taking place. α is defined as the relative volume fraction the ECS accounts for, s is a source term, and the $k'C$ term models the uptake of the diffusing molecules by cell membranes etc. Note that equation 5 is only one of several possible equations used to model this kind of diffusion, and that terms accounting for the (now assumed absent []) bulk flow in the ECS, and other possibly contributing terms, are not included. The model does, however, illustrate the general idea behind the modelling of diffusion in the ECS.

3 Measurment techniques for brain diffusion characteristics

Measurment of the diffusion constant in the ECS can be done in 4 different ways, where one has the obvious advantage of not having to remove the brain from the scull. For in vitro measurments there main types of measurment are optical, and ionsensitive microprobes.

3.1 Optical measurments

3.2 TMA^+ measurments

3.3 Radiotracer methods

The radiotracer methods are perhaps the most intuitive methods for measuring diffusion characteristics in the ECS, and were also the first methods applied quantitatively (1962 []).

3.4 Diffusion Tensor Imaging

This is a non-invasive measurment which has its obvious advantages in it's ability to be used on living humans. Diffusion tensor magnetic resonance imaging (DTI) is, as the name suggests, a type of magnetic resonance imaging. It measures the selfdiffusion tensor of water molecules in the ECS using six or more gradients.

References

[1] Charles Nicholson. "Diffusion and related transport mechanisms in brain tissue". In: *Reports on progress in Physics* 64.7 (2001), p. 815.