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FloD: a new method to quantify bulk flow in brain extracellular space

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Brain can be viewed as a porous medium. From this point of view, brain cells form a "solid" phase while extracellular space (ECS) forms a "liquid" phase that fills the pores between them. The brain ECS has fundamental importance for brain function [1,2]. It serves as a reservoir for ions and a channel for transport of biologically significant molecules, including the clearance of harmful metabolites. Xie et al. [3] suggested that bulk flow of the interstitial fluid, rather than diffusion, is the dominant mechanism for the removal of harmful substances from the ECS. However, this idea has yet to be experimentally supported. An early attempt using radiotracers to measure bulk flow in a normal brain tissue found flow only in white matter and no flow in gray matter [4]. Here we propose a flow detection (FloD) method to directly evaluate the flow of interstitial fluid *in vivo*, which would allow us to quantify the respective contributions of the diffusion and the bulk flow to the transport of molecules in ECS.

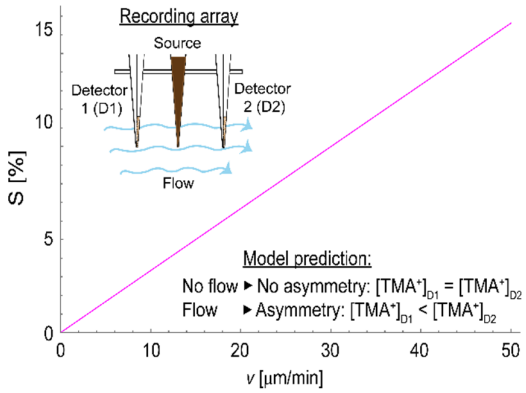

Figure 1. FloD method: recording setup and model prediction. We used the D typical for the tetramethylammonium (TMA) probe molecule. We expect to be able to reliably detect flow values of about 10 µm/min in the ECS. Such flow or higher would play a significant role in the clearance of harmful macromolecular metabolites. D1 are D2 are the detectors of tetramethylammonium.

The FloD method (Fig. 1) relies on asymmetry of the point-source diffusion pattern induced by the flow of interstitial fluid. While FloD can employ various time patterns of the source, the easiest to consider is a steady release rate of an extracellular probe molecule into the ECS. Without flow, it would produce a symmetrical diffusion pattern with the concentration $c(r)$ falling with distance $r = \sqrt{(x^2 + y^2 + z^2)}$: $c = A / (4 \pi D r)$, where A is a constant and D is an effective diffusion coefficient. This pattern changes in the presence of flow. Assuming the flow velocity v along the x-axis, diffusion pattern becomes asymmetrical along this axis: $c = (A / (4 \pi D r)) \exp((v x - |v| r) / (2 D))$. The degree of symmetry S can therefore be assessed with two detectors, e.g., ion-selective microelectrodes, placed at x and $-x$:

$$S = 2 (c(x) - c(-x)) / (c(x) + c(-x)) = 2 \tanh((x v) / (2 D)).$$

This experimentally accessible parameter (expressed as a percentage in Fig. 1) depends directly on the Péclet number $Pe = x v / D$ for the advective-diffusive ECS transport of a molecule over characteristic distance x. The Pe determines whether diffusion or flow dominates the transport. In combination with known values of D for many ECS molecules, the flow velocity v can be extracted.

In conclusion, we have developed a theoretical basis for the FloD method capable of measuring the bulk flow in brain neuropil. We plan to use this method to determine if the interstitial bulk flow significantly contributes to the clearance of harmful substances from the brain, which has not yet been determined.

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