Modelling of the role of glial cells in cerebral interstitial fluid movement

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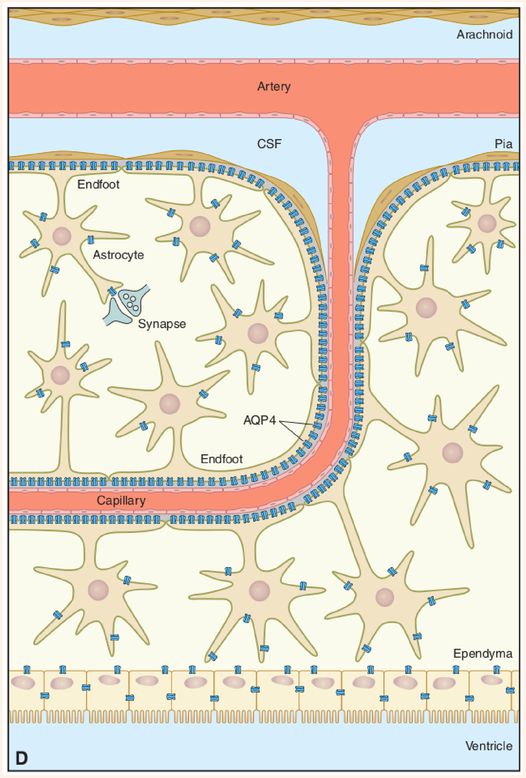
Physiology

Cerebral water homeostasis

There are still open questions related to how astrocyte water dynamics affect the overall water flow in the brain, removal of metabolic waste and solutes and the role AQP4 plays in pathological conditions such as cerebral oedema.

Within the endfoot barrier of astrocytes near the perivascular spaces surrounding the blood vessels, there is a high concentration of the channel membrane protein aquaporin-4. The AQP4 proteins form structures in the astrocytic membranes allowing for highly efficient water transport, and play an important role in mechanisms underlying volume and water homeostasis in the brain. The water transport through AQP4 is driven by osmotic pressure gradients, primarily regulated by movement of ions in the brain tissue.

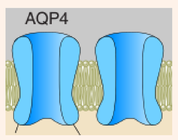
Traditional techniques, such as digital imaging and *in vivo* measurements, struggle to give insight due to both technical and ethical challenges. Mathematical and numerical modelling could give new insight.



[E. A. Nagelhus et al, 2013]

AQP4

Aquaporin–4 (AQP4) is a channel membrane protein and is the most prevalent aquaporin channel in the central nervous system. The AQP4 proteins form structures in the cell membranes allowing for highly efficient water transport.



Modelling

Mathematical models

Models for astrocyte dynamics at cellular level commonly takes the form of systems of ordinary differential equations and/or partial differential equations on the general form:

Find the ion concentration $[k]_n$ for ion specie $k \in K$, the electrical potential ϕ_n, the volume fraction α_n, the fluid velocity $\mathbf{u_n}$ and the hydrostatic pressure p_n for each compartment $n = I, E$ such that:

$$\begin{aligned}
\frac{\partial \alpha_n}{\partial t} &= F(\alpha_n, [k]_n, \mathbf{u}_n) \\
\frac{\partial (\alpha_n [k]_n)}{\partial t} &= G([k]_n, \phi_n, \mathbf{u}_n) \\
\phi_n &= H(\alpha_n, [k]_n) \\
\mathbf{u}_n &= I(\alpha_n, [k]_n, p_n) \\
p_n &= J(\alpha_n, [k]_n, \phi_n)
\end{aligned}$$

where F, G, H, I, J are subject to modelling, the ion species K notably includes K^+, Na^+, Cl^- and $n = I, E$ denotes the intra– and extracellular space, respectively.

Models addressing mechanical variables such as fluid velocity, hydrostatic pressure and compartment volume fractions, e.g. [Y. Mori, 2015], are not well explored numerically.

Numerical methods

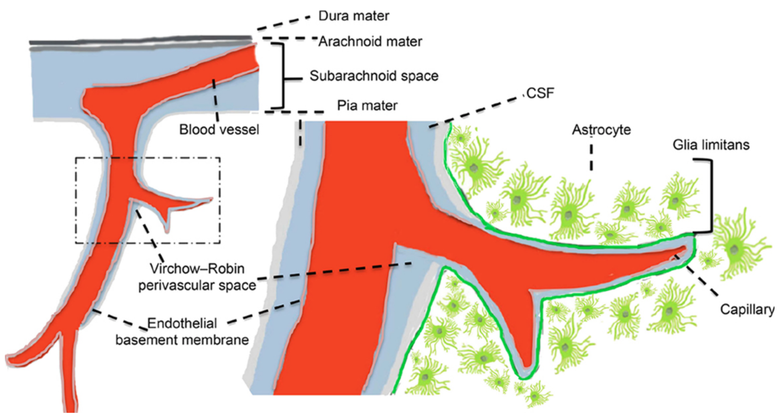
We aim to develop new mathematical and numerical models across scales to study the effects of osmotic pressure and microscopic fluid flow in brain water homeostasis.

- Design and analyze numerical schemes for existing mathematical models connecting mechanical and electrochemical variables at cellular level
- Extend model to couple glial dynamics at cellular level with fluid flow at vascular level and develop corresponding numerical schemes
- The finite element method (FEM) in space and an implicit scheme in time. The new schemes should ideally be robust, efficient and property preserving

FENICS PROJECT

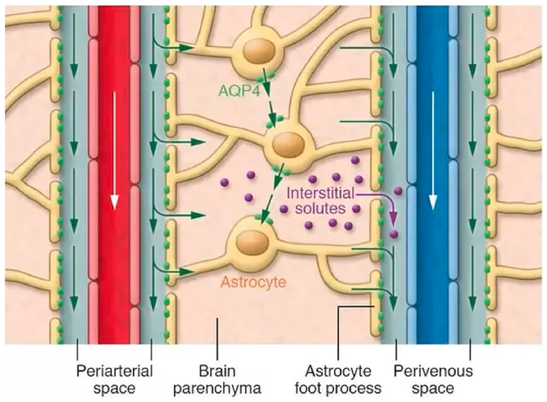
Computational studies

Could the osmotic pressure generated by ion concentration gradients be a driving force for flow in perivascular spaces?



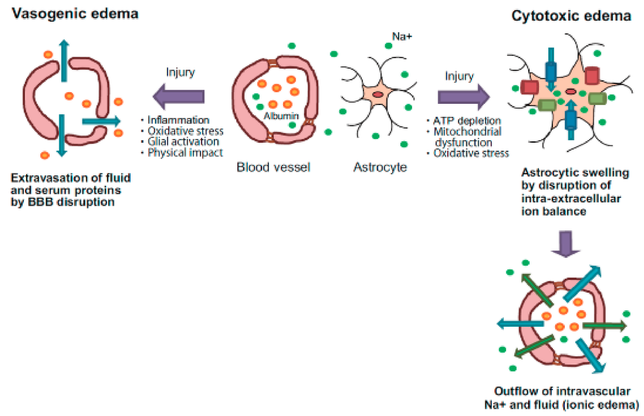
[R. Khorooshi et al, 2015]

How does astrocytic water dynamics affect the flow and transport of metabolic waste and solutes within the extracellular space?



[Quora, 2017]

What is the role of astrocytes and AQP4 in pathological conditions such as cytotoxic and vasogenic oedema?



[S. Michanga, 2015]