PhD position, Institut de Mécanique des Fluides de Toulouse (IMFT)

Modeling and simulation of transport within the brain: does blood vessel pulsatility drive metabolic waste clearance ?

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Subject description: Waste produced by the activity of neural cells in the brain, including amyloid, are cleared by two distinct physiological systems (Fig. 1): the microvascular system, a multi-scale network of small blood vessels, which ensures the distribution of blood throughout the brain tissue, and the cerebrospinal fluid/interstitial fluid (CSF/ISF) system, which can be considered as a lymphatic system for the brain. The CSF fills the large spaces within and around the brain (cerebral ventricles and subarachnoid space, respectively), while the ISF fills the microscopic spaces between brain cells and around blood vessels (interstitium and perivascular spaces, respectively). These two systems, which have been the object of intense research [Sec17, Kel23, Boh22], are coupled through mechanical interactions. For example, the periodic increases of blood pressure induced by cardiac contractions drive periodic vessel dilations, not only at the brain surface (in the SAS), but also within the brain tissue. Crucially, recent *in vivo* experiments have demonstrated that these vessel dilations induce a narrowing of perivascular spaces (PVS), a phenomenon that is exacerbated in sleep versus wakefulness [Boj23]. Simple axisymmetric models of ISF flow and solute transport in PVS at the micro-scale suggested that this difference in pulsatility contributes to the observed enhancement of waste clearance in sleep compared to wakefulness [Boj23]. However, such models typically consider a single vessel/PVS unit, which makes it difficult to integrate the heterogeneity of transport regimes inherent to network structures [Ber20,Goi21]. Moreover, such models also overlook the couplings with solute transport in the brain interstitium and in the blood vessels. This limits our ability to understand the interplay between reduced clearance and disease progression in diseases which involve the accumulation of toxic waste within the brain tissue (Alzheimer's disease) or the walls of blood vessels (Cerebral Amyloid Angiopathy, CAA) [Gre20].

Therefore, the objective of this PhD is to investigate how the couplings between solute transport in blood and in CSF/ISF impact overall brain clearance. Getting inspiration from [Boj23], we will enrich our anatomically realistic network model for intravascular clearance, which couples intravascular transport [Ber20] with reactive transport in the interstitium [Pas24]. For that purpose, getting inspiration from [Ber20, Mar19], we will derive a 1D model for dispersive perivascular transport that considers an annular domain surrounding the blood vessels, the effect of periodic forcing (imposed vessel wall motion) and exchanges

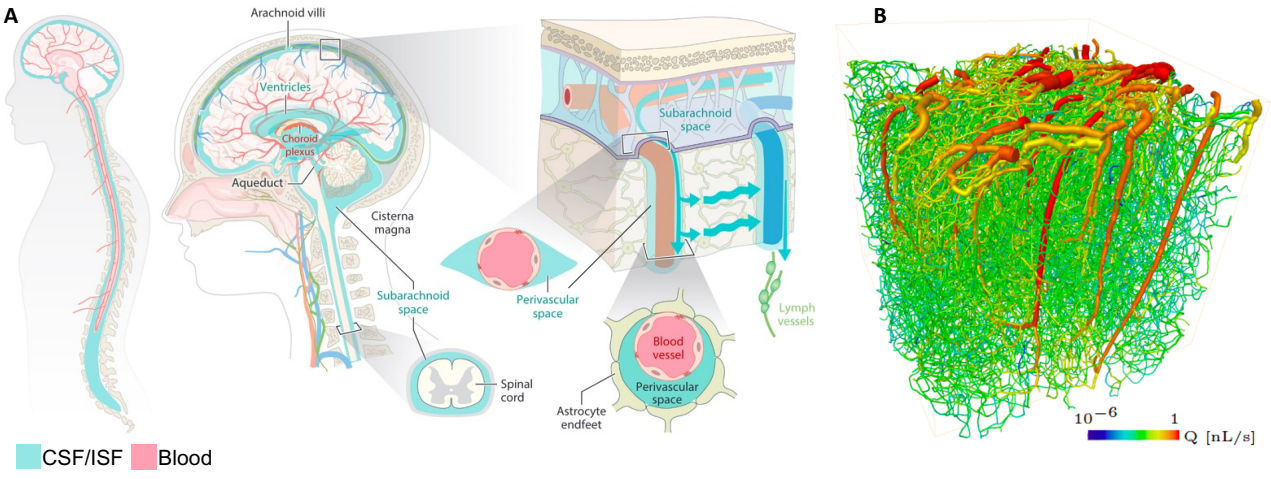

Figure 1: Fluid systems involved in the clearance of metabolic waste from the brain. A: Schematic representation from microscopic (bottom right) to macroscopic scale (left) from [Kel23]. B: Heterogeneity of blood flow in an anatomically realistic microvessel network at the mesoscale (~1 mm3 of tissue), from [Goi21].

with blood and interstitium (Robin boundary conditions). We will also perform a parametric analysis to determine the transport regimes in which intravascular dispersion induced by blood pulsatility should also be considered. We will then integrate these 1D models at network scale (treatment of bifurcations, coupling with transport and reaction in tissue). Validation will be considered by comparison with steady-state chronic infusion of tracers in baseline conditions and under controlled manipulation of pulsatility in healthy or CAA rodents. Depending on the candidate profile, she/he may also participate to the exploitation of these models for parametric analyses aiming at understanding how abnormalities observed in the brain of CAA rodents may affect brain clearance and disease progression.

Academic context : This PhD project is funded by the Leducq Foundation as a part of the Leducq Foundation Transatlantic Network of Excellence on Brain Clearance, an interdisciplinary consortium involving 11 research groups with top level expertise on brain clearance systems [Van24]. Among these, the Porous and Biological Media group of IMFT is a pioneer in the multiscale modeling of brain microvascular networks, based on mixed-dimensional Eulerian descriptions [Ber20,Pey18,Pas24], and in the use of such modeling for physio-pathological interpretations [Cru19,Goi21]. The Vascular Dysfunction & Hemostasis group of Sainbiose develops models of the coupling between blood vessels and CSF dynamics at the global scale of the brain down to the microscale of a single PVS, in order to interpret both animal models and clinical data in the context of neurodegenerative diseases [Boj23,Val20]. The successful candidate will benefit from training and support throughout the Early Carrier Investigators Scheme of the Leducq network, including regular in-person and virtual meetings, and preferential access to relevant experimental results.

Profile: Strong background in theoretical and numerical fluid mechanics. Experience with advanced C++ will be welcomed. Demonstrated motivation for work at the interface between disciplines, in a collaborative environment. A Master Degree in Physics, Fluid Mechanics or related disciplines is required, as well as fluency in English.

Administrative aspects: The employer is *Toulouse National Polytechnique Institute*. This PhD project is funded for 3 years, starting on September/October 2024 (Gross salary: ~ 27 600 €/year; Net salary, including social security: ~ 22 300 €/year).

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