PhD position:
Simulation of reactive transport dynamics in the brain microcirculation: how does the vascular architecture control the emergence of critical regions?

Subject description : Blood microcirculation supplies neurons with oxygen and clears their neurotoxic waste through a dense capillary network connected to tree-like network of larger vessels (arterioles and venules, Fig. 1). This microvascular architecture results in highly heterogeneous blood flow and travel time distributions [Jes12,Sak14], whose consequences on brain pathophysiology begin to be uncovered. To explore this question, the Toulouse Institute of Fluid Mechanics (IMFT) and Geosciences Rennes (GR) have bridged together their expertise on cerebrovascular structure/function relationships, e.g. [Lor11], and on the physics of transport in disordered media, e.g. [LeB08]. This has led to the first physics-based upscaling framework describing the dynamics of solute transport in brain microvascular networks [Goi21]. This new representation uses random network and dipole flow theories to derive a stochastic model for solute transport in microvascular networks. It predicts the appearance of critical regions under reduced perfusion, i.e. blood vessels with insufficient oxygen or excessive waste, which may play a key role in the onset of Alzheimer' disease. This advance opens new opportunities for understanding the physics of solute transport in the brain and its impact on neurovascular diseases.

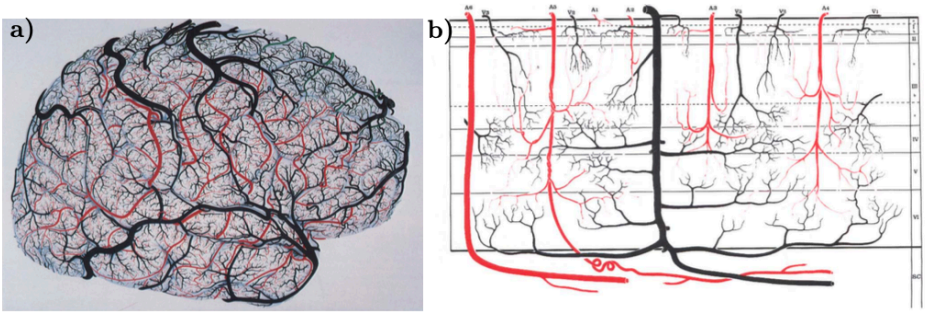

Figure 1: spatial organization of the arterial and venous systems in the cortical layer of the human brain [Duv81]: a. lateral view of the arterial and venous systems running over the cortical surface **b.** arteriolar and venular sub-branches in depth of the cortical layer. Arterioles are shown in red, venules in black. The deepest region correponds to sub-cortical white matter.

To inform and enrich this new upscaling framework, the objective of this PhD project is to investigate how the spatial organization of arterioles/venules controls the overall rates of oxygen delivery and waste clearance, the appearance and preferential localization of critical regions for oxygen and wastes in the brain tissue (i.e. outside vessels), and their growth under reduced perfusion. To this end, we will leverage the High-Performance Computing tools developed at IMFT for the simulation of blood flow and transport in large microvascular networks [Pey18,Ber20], which now integrate a realistic representation of transport and reaction within the tissue [Pas24]. The work program will include:

- We will first simulate blood flow and solute transport/reaction in the tissue in different brain microvascular architectures for available vascular architectures ($1mm^3$ from the rodent cortex) and pathophysiological ranges of parameters (blood flow, transport and reaction properties in blood and tissue). For that purpose, the intravascular transport solver will need to be optimized to improve stability for high flow vessels. We will use the result to analyse the concentration statistics in tissue and the spatial relationships between the arterioles/venules and the local extrema of the concentration fields.
- We will then focus on the impact of these larges vessels by manipulating their architecture as follows: A. Axploiting experimental imaging data across various brain areas, from public repositories or shared by collaborators. This will require careful pre-processing (data curation and annotation, generation of boundary conditions). B. develop synthetic biomimetic networks whose structure can be modified (eg. following [Lin19], Fig. 2), to reproduce and generalize the link between network structure and transport properties.
- We will make the associated simulations available to the scientific community by creating an open database.

Depending on the candidate profile, she/he may also participate to the development of the novel theoretical framework that is needed for the interpretation of the results.

Academic context : This PhD project is part of a collaboration, funded by the French National Agency for Research (ANR Innermost) between two teams developing complementary approaches. 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]. The Geosciences Rennes laboratory develops stochastic models for transport and reaction in porous media [LeB08,LeB13,Aqu21]. The successful candidate is expected to spend a significant amount of time in both groups. International collaborations will be developed with the Seattle Children's Research Institute.

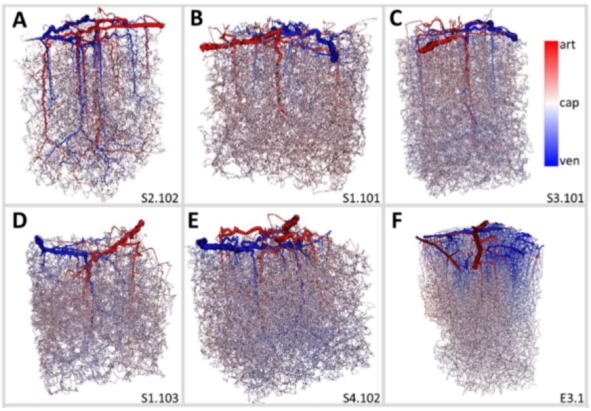

Figure 7: Synthetic biomimetic vascular networks from [Lin19], with tunable architecture. Arterioles and venues are represented in red and blue, respectively, while the capillary network is in grey.

Profile: Strong background in 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.

Academic supervisors: Sylvie Lorthois, Directrice de Recherche CNRS (IMFT), Tanguy Le Borgne, Professor (Observatoire des Sciences de l'Univers de Rennes).

Administrative aspects: The employer is *Toulouse National Polytechnique Institute*. This PhD project is funded for 3 years, starting on September/October 2024.

References:

[Aqu21] Aquino, T. & Le Borgne, T (2021). The chemical continuous time random walk framework for upscaling transport limitations in fluid–solid reactions, Advances in Water Resources, 154, 103981. **[Ber20]** Berg et al. Modelling solute transport in the brain microcirculation: is it really well mixed inside the blood vessels? *J. Fluid Mech*. (2020). **[Duv81]** Duvernoy, H. M., Delon, S. L. V. J., & Vannson, J. L. (1981). Cortical blood vessels of the human brain. Brain research bulletin, 7(5), 519-579. **[Goi21]** Goirand, F., Le Borgne, T., & Lorthois, S. (2021). Network-driven anomalous transport is a fundamental component of brain microvascular dysfunction. Nature communications, 12(1), 7295. **[Jes12]** Jespersen, S. N., & Østergaard, L. (2012). The roles of cerebral blood flow, capillary transit time heterogeneity, and oxygen tension in brain oxygenation and metabolism. Journal of cerebral blood flow & metabolism, 32(2), 264-277. **[Pey18]** Peyrounette et al. Multiscale modelling of blood flow in cerebral microcirculation: *PLOS ONE* (2018). **[Pas24]** Pastor-Alonso, D., Berg, M., Fomin- Thuneman, N., Boyer., F, Quintard, M., Davit, Y. & Lorthois, S. Modeling oxygen transport in the brain: An efficient coarse-grid approach to capture perivascular gradients in the parenchyma, PLOS Computational Biology, In press. **[Leb08]** Le Borgne, T., Dentz, M., & Carrera, J. (2008). Lagrangian statistical model for transport in highly heterogeneous velocity fields. Physical review letters, 101(9), 090601. **[Lor11]** Lorthois, S., Cassot, F., & Lauwers, F. (2011). Simulation study of brain blood flow regulation by intra-cortical arterioles in an anatomically accurate large human vascular network. Part II: flow variations induced by global or localized modifications of arteriolar diameters. Neuroimage, 54(4), 2840-2853. **[Sak14]** Sakadžić, S., Mandeville, E. T., Gagnon, L., Musacchia, J. J., Yaseen, M. A.,., ... & Boas, D. A. (2014). Large arteriolar component of oxygen delivery implies a safe margin of oxygen supply to cerebral tissue. Nature communications, 5(1), 5734.

For more information or to apply, please submit via email your curriculum vitae, copies of recent transcripts, a statement of your future career goals, and the names and email addresses of two references, to: sylvie.lorthois@imft.fr and tanguy.le-borgne@univ-rennes.fr, with Reference [Ph_D Innermost] in the message subject.