Postdoctoral position:
Dynamic network adaption in brain micro-circulation

Context : Blood microcirculation supplies neurons with oxygen and clears their neurotoxic waste through a dense capillary network connected to tree-like networks 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 laboratory (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. This model predicts the appearance of anomalous transport, leading to critical regions, 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. In addition, it opens a range of new questions related to the simplifications of the model, including the idealization of the spatial organization of arterioles and venules and the static vessel diameters.

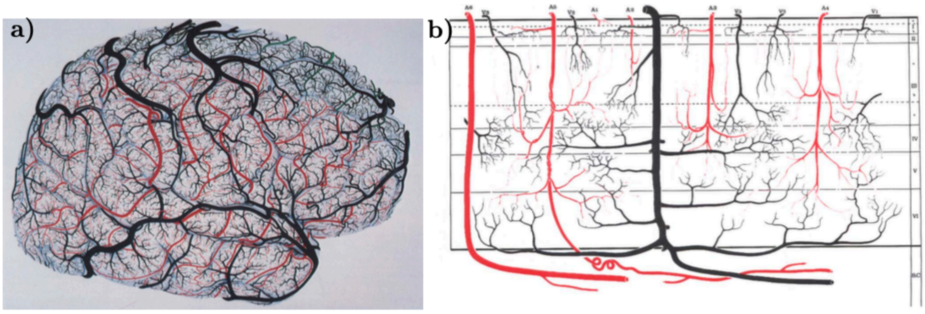

Figure 1: spatial organization of the arterial and venous systems in the cortical layer of the human brain [Duv81]: a. lateral view of the arterial and venous systems running over the cortical surface **b.** arteriolar and venular sub-branches in depth of the cortical layer. Arterioles are shown in red,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

Objectives and subject description : Our objective is to study whether dynamic adaptations of the microvascular network in response to neuronal activity and/or physiological stresses may mitigate the detrimental effect of anomalous transport in brain perfusion and clearance. While the current version of our model is based on static passive networks, vascular networks are indeed continuously-adapting. On the short term (milliseconds), vascular networks can dynamically adapt the diameters of their arterioles and capillaries in the range of about 80-120% to adjust blood flow to the local metabolic needs of the neurons which are active in the ongoing cognitive tasks [Dre22]. This phenomenon is known as neurovascular coupling. It is believed to be mediated by the release of vasolidatory molecules, coupled to electric signaling, originating from the active neurons [Sha21,Dre22]. On the longer term (years), vessel remodeling is driven, among other factors, by the intensity of shear forces on the vessel walls, with higher stresses leading to long term enlargement [*Alk08], and by the concentration of oxygen, with diameter adaptations and/or vessel growth driven by tissue hypoxia [Alb21]. The work program will include :

- **Neuro-vascular coupling :** we will consider the effect of changes in the arteriolar trees induced by neuro-vascular coupling on transport dynamics. Our past results have demonstrated that localized vasodilation of arterioles lead to macro scale changes in pressure, flow and red blood cell volume fractions [Lor11b]. Using simulation tools developed at IMFT, we will compute how these changes affect the statistics of flow rates, travel times, and concentrations of oxygen and metabolic waste. We will interpret these changes using a Lagrangian framework. We will further analyze the data to relate the overall, upscaled dynamics, with the spatial heterogeneity of flows and concentrations at network scale.

- **Hypoperfusion and hypoxia-induced remodeling :** we will investigate networks of evolving conductances, where the conductances will be updated to minimize the probabilities of flow rates below a threshold [Bha2] or to homogenize oxygen supply [Mei18]. The key question will be to test wether such permanent remodeling can counteract the inherent flow variability produced by the random network connections and the dipolar structure of flow induced by the boundary conditions. We will then study how the statistics of capillary flows can be tuned by the network structure and heterogeneity to optimize the distribution of resources. Following [*Alk08,Alb21], we will change vessel diameters with simple rules depending on local hemodynamic parameters, such as the intensity of shear forces acting on the vessel walls or the local concentration of oxygen, with higher stresses or hypoxia leading to long term vessel enlargement.

Academic context : This postdoctoral 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.

Profile: Strong background in flow, transport and reaction in heterogeneous media. Previous experience in the physics of dynamical biological networks will be highly welcomed. Demonstrated motivation for work at the interface between disciplines, in a collaborative environment. A PhD 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 *Rennes University*. This postdoctoral project is funded for 2 years, renewable, starting from February 2025.

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: tanguy.le-borgne@univ-rennes.fr and sylvie.lorthois@imft.fr, with Reference [PDRA Innermost] in the message subject.