PROPOSITION DE STAGE 2017-2018

Title: Modeling the transient adhesion of leucocytes into brain capillary vessels and its impact on cerebral blood flow in Alzheimer's disease.

Supervisors: Sylvie Lorthois (sylvie.lorthois@imft.fr, 0534322874) and Yohan Davit (yohan.davit@imft.fr)

Laboratory: Institut de Mécanique des Fluides de Toulouse (IMFT), together with the Department of Biomedical Engineering, Cornel University, USA (Professors Schaffer and Nishimura).

Project summary:

Context: this internship is part of the interdisciplinary Brain Micro Flow project (2014-2019) awarded to Sylvie Lorthois (http://brainmicroflow.inp-toulouse.fr) under the European Research Council Consolidator grant scheme (http://erc.europa.eu/consolidator-grants). Her group at IMFT focuses on modeling the structure and function of brain microcirculation at various scales. The Brain Micro Flow project also involves the Department of Biomedical Engineering of Cornell University, USA (https://snlab.bme.cornell.edu) for advanced in vivo optical imaging and manipulation of cerebral blood flow in healthy and Alzheimer's diseased (AD) mice.

Motivations: The cerebral microvascular system is essential to a large variety of physiological processes in the brain, including blood delivery and blood flow regulation as a function of neuronal activity (neuro-vascular coupling). It plays a major role in the associated processes leading to disease (stroke, neurodegenerative diseases) but the comprehension of the basic mechanisms involved is still largely incomplete. Cutting edge experimental technologies, including two-photon *in vivo* microscopy, have recently shown that a small percentage of brain capillary vessels, the smallest of all vessels, are transiently occluded by white blood cells, both in healthy and AD mice. The proportion of occluded vessels as well as their half-life seems however to be significantly higher in the diseased mice, suggesting that these capillary occlusions could be the long sought mechanism at the origin of the decrease of cerebral blood flow in AD.

Goal: Our objective is to test this hypothesis by modeling the dynamics of white blood adhesion to capillary vessel walls and its impact on global cerebral blood flow.

Methods: For that purpose, we will built up on a numerical analysis of cell adhesion in capillaries, whose diameter is comparable to or smaller than that of the cell, previously introduced by Takeishi [1]. In this analysis, the solid and fluid mechanics of a cell in tube flow was coupled with a slip bond model of bio-adhesive molecular interactions. The scaling laws extracted from this model will be coupled to our non-linear network model, which takes into account the complex blood rheology and enables to describe blood flow in large microvascular networks [2,3]. The global blood flow reduction will be studied as a function of various parameters, including the dissociation rate constant of the bio-adhesive bounds and their spring constant. These parameters will be adjusted to match the experimental dynamics experimentally observed at Cornell in both healthy and diseased mice.

Research program: Bibliographic study; Parametric study of the effect of single occlusions, as a function of their bio-adhesive properties and their position in the hierarchical structure of the capillary network; Generalization to weaker bio-adhesion properties, resulting in the slowing-down of white blood cells rather than their adhesion to the vessel walls ; Extension to multiple vessels.

References: [1] Takeishi et al. Am. J. Physiol. Heart Circulatory Physiol. 311, H395–H403, 2016. [2] Lorthois et al. NeuroImage 54, 1031–1042, 2011. [3] Lorthois et al. NeuroImage 54, 2840–2853, 2011.

Student profile: Strong background in numerical methods for fluid mechanics. Demonstrated motivation for work at the interface between disciplines, in close collaboration with researchers performing advanced in vivo experiments in live mice. Experience in C++ and high performance computing is welcomed. English, including good oral and writing skills.

Practical information: the candidate will receive the French standard Master's stipend (~550 €/month) for the duration of the internship, up to a maximum of 6 months.