Internship in computational neuroscience @ INRIA Lyon

Partial differential equations to understand the pathological signatures of the astrocytic end-foot in Alzheimer's disease

Key-words: Neuroscience, Astrocytes, Alzheimer's disease, Computational Modeling, PDE, Numerical simulations

Location: Centre Inria de Lyon
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Team: **AIstroSight** - https://team.inria.fr/aistrosight/
The AIstroSight team develops innovative computational methods for neuropharmacology and the discovery of new drug candidates to treat brain diseases.

Duration: 6 months

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Background & rationale

Alzheimer's disease (AD), the most common cause of dementia, is a multifaceted neurodegenerative disease. Research has identified numerous cell types and pathological mechanisms involved in disease development. Yet, targets that would significantly hinder the progression of AD in patients remain to be identified. Historically, studies have focused on tau tangles and ß-amyloid (Aß) deposition, which were observed in postmortem AD brains[1]. Recently, blood vessel dysfunction has been reported as a feature of early stages of AD[2]. Understanding the cell-cell interactions that maintain brain vasculature and how they are altered in AD is thus crucial to address the effects of these vascular changes on disease progression.

The blood-brain barrier (BBB) is comprised of multiple cells including astrocytes[3], that are uniquely positioned to mediate interactions between neurons and blood vessels via a specialized compartment called the astrocyte endfoot. In addition to maintaining BBB integrity, astrocyte endfeet regulate the blood flow (neurovascular coupling), nutrient uptake, and waste clearance[4]. While astrocyte and vascular dysfunction are early features of AD, how these alterations relate to each other and contribute to disease progression is not known. The identification of these mechanisms could thus shed light on pathways that could be targeted to preserve brain health in AD.

Goal of the internship

The goal of this internship is to integrate structural and proteomics signatures of astrocyte endfeet at different stages of AD to evaluate the functional consequences of these alterations (Fig. 1). This *in silico* work will focus on neurovascular coupling which is in part mediated by astrocytes[5,6] and is altered in AD[7]. An initial model of neurovascular coupling at endfeet in control mice has been implemented in the lab (Dupeuble et al., *in prep*). The first goal of this internship is to spatialize this model to allow simulations in complex realistic geometries, ideally via variational formula for the reaction-diffusion equations. The second objective is to leverage endfoot proteomics data measured *in vivo* by the Díaz Castro lab (University of

Edinburgh, Scotland)[8] to investigate the impact of altered protein expression levels observed at different stages of AD progression (unpublished) on NVC.

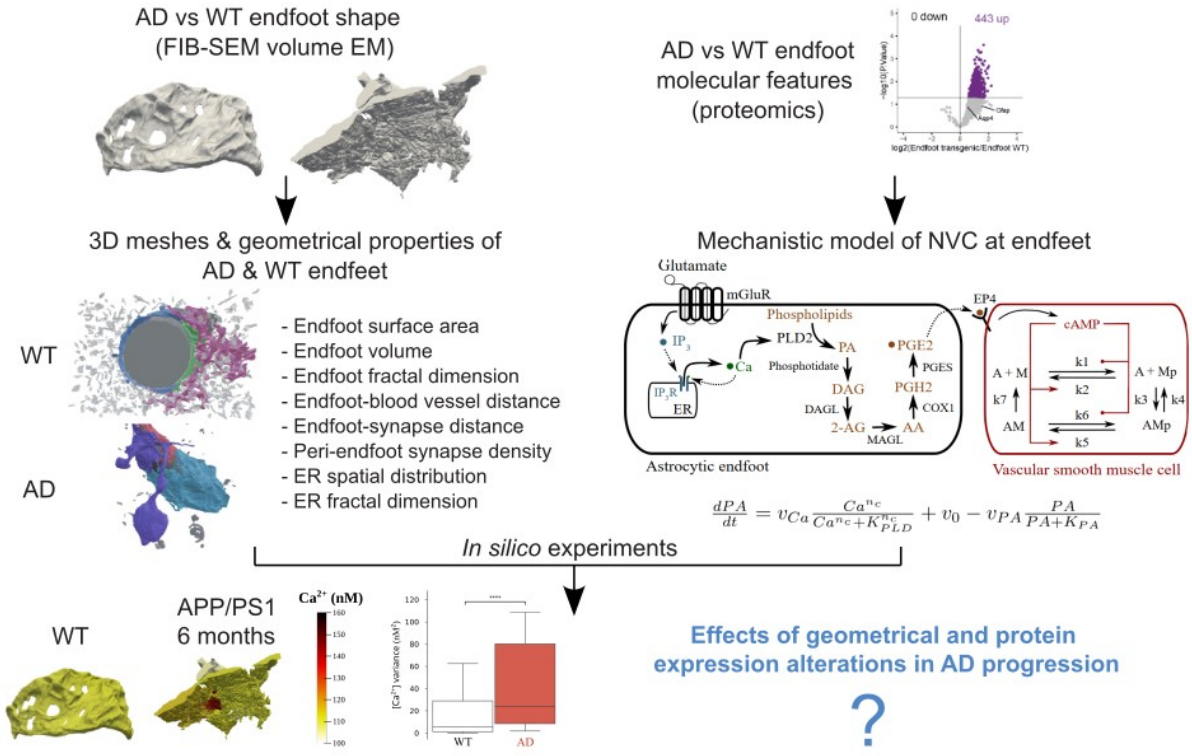

Figure 1*: Overview of the collaborative research project. 3D reconstructions of endfeet derived from FIB-SEM volume EM have been acquired by the Murai lab (McGill University, Canada) and have been used to quantify geometrical features of WT and AD endfeet. Protein expression levels in endfeet have also been quantified by the Diaz-Castro lab (Edinburgh university, Scotland) in WT and AD endfeet, which will help identify parameters that are altered in AD. Together, the data available will allow running in silico experiments to decipher the influence of geometrical and molecular features on NVC during AD progression.*

Simultaneously, simulations will consider structural alterations of endfeet in AD (unpublished) measured using the FIB-SEM volume EM method of the Murai Lab (McGill University, Canada)[9] to infer mechanistic links between endfoot structure and altered NVC in AD. The model will be developed using partial differential equations following the mass action law and Michaelis-Menten kinetics. *In silico* experiments will be performed using FEniCs software to allow simulations in volume EM 3D cell reconstructions. The model's output corresponds to radius variations of blood vessels following neuronal stimulation. The model will be validated with experimental data from the literature (e.g. from Institoris et al.[10] for control mice).
This computational work will be instrumental to propose functional consequences of structural and molecular endfoot changes in AD reported by our collaborators, and will set the foundation for future work to identify pathways that could be targeted to prevent AD progression.

In this context, the intern is expected to:

- conduct a literature review on finite element algorithms suited to simulations in complex geometries (e.g. SMART[11]) and astrocyte models, in particular spatial models
- develop a PDE model of calcium signaling based on the G-ChI model of astrocyte calcium signaling[12]
- calibrate the model with calcium recordings from the literature
- extend the model to neurovascular coupling, based on a model developed in the lab (Dupeuble et al., in prep.)
- adapt the model to protein expression changes reported during AD progression
- design and conduct *in silico* experiments to study NVC at endfeet in healthy and AD conditions

During this internship, the intern will participate to a joint meeting in Edinburgh with the collaborating teams.

Requirements

- Mathematical modeling
- Statistics
- Python
- Knowledge in cell biology and/or neuroscience will be appreciated but is not mandatory

References

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