Mathematical Modelling of Microglia and the Neuroimmune System

PhD Studentship

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Experimental and theoretical investigations aiming to understand the human brain typically focus on neurons, with relatively little attention being paid to glial cells. However, once deemed mere support cells, microglia are now widely recognised as prominent contributors to neurodegeneration and neuroinflammation. Microglia perform many tasks while interacting with neurons, astrocytes, and oligodendrocytes. Biologically realistic computational models of microglia will facilitate an understanding of their physiology for drug development. Microglia involve a myriad of membrane-coupled receptors, which enable them to sense concentration changes in their environment to begin either process extension or whole-cell chemotaxis. Previously, we built a basic mathematical model of microglia for studying some cellular aspects involved in directed motility [1-3].

Microglial activation is a normal response to various challenges, such as infection, injury, or neurodegenerative diseases like Alzheimer's and Parkinson's. Activated microglia release pro-inflammatory molecules such as cytokines and chemokines to recruit other immune cells and clear the site of damage or infection. This PhD project aims to extend the basic mathematical model by taking the regulation of microglial migration and inflammatory responses into account. Crosstalk between several receptor systems, which involves complex interactions at the molecular and cellular levels, will be investigated through computational modelling to shed light on the electrophysiological complexity of microglial cells in neuroinflammation. Growing evidence shows that chemokine receptors (found on the surface of microglia cells that interact with a type of cytokine called a chemokine) actively take part in calcium (Ca^{2+}) signalling in tandem with purinergic receptors (microglia surface receptors activated by extracellular purines like adenosine and ATP that influence many microglial functions). More importantly, the activation of specific purinergic receptors regulates chemokine pathways involved in microglial migration and directs neuroinflammation. The research will help us understand how the migration of microglia is regulated by a very complex machinery of cytosolic Ca^{2+} and how microglial cells talk to each other and other immune cells for a cascaded inflammatory response. Understanding these interactions is crucial for deciphering the regulatory mechanisms that govern neuroimmune responses, cell migration, and inflammatory processes, with potential implications for therapeutic interventions in diseases associated with neuroimmune dysregulation involved in neurodegeneration.

Applicants should have a passion for discovery and a background in computational neuroscience, computer science, medical science, mathematics, biology, chemistry, physics, engineering, or related fields. You will have the opportunity to work with a diverse team of world-leading experts in computational and experimental neuroscience at several research institutions in the UK and abroad.

Please contact **Dr Alireza Poshtkohi** (a.poshtkohi@herts.ac.uk) or **Prof Volker Steuber** (v.steuber@herts.ac.uk) directly if you are interested in this project.

References

1. A. Poshtkohi, J. Wade, L. McDaid, J. Liu, M. Dallas, A. Bithell, *Mathematical Modelling of PI3k/Akt Pathway in Microglia*, Neural Computation, 36:4 (2024). doi: 10.1162/neco_a_01643
2. A. Poshtkohi, *Computational Modelling of Plasma Membrane Electrophysiology and Calcium Dynamics in Microglia*, PhD Thesis, University of Ulster, 2023.
3. A. Poshtkohi, J. Wade, L. McDaid, J. Liu, M. Dallas, A. Bithell, *Mathematical Modelling of Human P2X-mediated Plasma Membrane Electrophysiology and Calcium Dynamics in Microglia*, PLoS Computational Biology, 17:11 (2021). doi: 10.1371/journal.pcbi.1009520