Understanding the cellular processes that support pattern separation in the hippocampal dentate gyrus and how ageing affects memory

Supervisory team:
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Project description:
We all know that ageing can affect our memory, particularly our ability to discriminate between similar events. For example, our ability to remember 'where I put my car keys today' as opposed to 'where I put them yesterday' becomes increasingly difficult as we get older. Pattern separation refers to the process of representing highly similar memories in distinct ways so they can coexist without interference; it is one of the first memory processes affected by ageing. Pattern separation is a function of the hippocampal dentate gyrus that comprises granule cells, mossy cells, and different classes of interneurons. The question we want to ask is how these different cell types control the dynamics of dentate gyrus circuitry to bring about pattern separation?

Mossy cells are known to be key regulators of circuit dynamics in the dentate gyrus and essential to pattern separation because they influence the balance between excitation and inhibition in the circuitry at different frequencies. Because each class of interneuron has very different intrinsic firing properties, our theory is that mossy cells regulate the dynamics of the circuitry across a range of frequencies by recruiting different interneuron classes at different frequencies.

This project will involve recording and manipulating the dynamic responses of mossy cells, granule cells and different classes of interneurons in the dentate gyrus using optogenetics and in vitro electrophysiology. Crucially, we will also manipulate the activity of these cell populations using optogenetics during behavioural tasks that measure memory formation and recall. The results of these experiments will be used to further refine our computational biophysical model of DG circuitry and pattern separation. The model includes the intrinsic properties of known cell types of the dentate gyrus, and will include their ion channels, receptors, and dendritic morphologies to recapitulate the spatiotemporal dynamics of the circuitry as closely as possible. Simulations will be implemented in Python or Julia and run on the University of Bristol's Blue Crystal supercomputer. The model will then be used to predict the effect of different pharmacological agents that target specific cell types, ion channels or receptors in the dentate gyrus. These predictions will be tested experimentally, as above, to prove the model.

The results from this project will advance our understanding of pattern separation and could well lead to novel strategies and drug therapies to tackle the decline of pattern separation and memory that can occur with age.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.