In depth understanding of dementia-associated changes to neuronal signalling

Theme: Neuroscience & Mental Health
Reference: MRC19NMHBa Nogaret

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The function of neurons within cortical networks and their response to external stimulation depend critically on the type of ionic channels present in the neuron membrane. These ionic channels behave as molecular transistors which control the passage of ionic currents through the neuron membrane. The kinetics and response thresholds of ion channels determine the spiking or bursting nature of voltage oscillations and the specific response of a neuron to current stimulation. Different categories of neurons host different types of ion channels whose functional role is not well understood at present and disease states can substantially alter electrical behaviour by modifying ion channel complements. In addition, the proteins making up ion channels that determine intrinsic excitability are encoded by a relatively small fraction of the genome. The voltage response of a neuron to current stimulation therefore contains all information on the hidden kinetic parameters and voltage thresholds which characterize individual protein molecules. Combining observations of the neuron membrane voltage with powerful inference methods would open a route for sequencing ion channels and explain the specialization of brain cells.

This project builds on sophisticated mathematical techniques developed at Bath to extract the parameters of multichannel conductance models. The completed models so far have been very successful in making quantitative predictions of neuron behaviour to arbitrary current protocols. The Bath team has further improved the efficiency and accuracy of parameter extraction to the extent where the method has become sufficiently accurate for single valued parameter solutions to be obtained and ion channels to be sequenced. Electrophysiologists at Exeter will support the student in performing patch clamp recording in hippocampal brain slices using sophisticated current protocols designed in Bath.

The PhD student will design complex current protocols which will be injected into individual neurons and build on existing nonlinear inference methods to obtain quantitative models of CA1 pyramidal neurons. The recorded neurons will be categorized according to their electrical properties which will be reconstructed by forward integration of the completed models, and we will attempt to reconcile these classifications with the emerging theme of functional diversity within single pyramidal cell classes.

Work in by the Exeter team over the last decade has revealed changes in the intrinsic properties of these same pyramidal cells in multiple models of Alzheimer's disease-associated pathology although the specific conductance changes underpinning these finding are still poorly understood. The methods developed in Bath will be applied to this question with the goal of better understanding how these cognitively important cells are impacted by dementia.

IMPORTANT: In order to apply for this project, you should apply using the DTP's online application form: https://cardiff.onlinesurveys.ac.uk/gw4-biomed-mrc-dtp-student-2019

More information on the application process may be found here:
http://www.gw4biomed.ac.uk/doctoral-students/

APPLICATIONS OPEN ON 24 SEPTEMBER AND CLOSE ON 23 NOVEMBER 2018.

You do NOT need to apply to the University of Bath at this stage – only those applicants who are successful in obtaining an offer of funding form the DTP will be required to submit an application to study at Bath.