

Project Details	
Project Code	MRC21NMBa Nogaret
Title	Predicting the dementia-induced changes to neuronal ion channels: a combined experimental and in silico approach
Research Theme	Neuroscience & Mental Health
Summary	The effect of neurodegenerative conditions, such as Alzheimer's disease, on neuronal ion channel properties is not well understood. This project will combine sophisticated inverse mathematical methods with brain slice electrophysiology to quantify changes to specific ion channels in dementia. This interdisciplinary approach will provide important insights into neurophysiological dysfunction.
Description	<p>Neurons display a wide range of electro-responsive properties which depend on the expression of a range of distinct voltage-gated ion channels. Estimating the microscopic parameters of these ion channels is critically important to build a quantitative understanding of the effects of neurodegenerative disease on neurons' electrical output and subsequently to design drugs with improved efficiency. We aim to estimate the parameters that govern ion channel kinetics, activation and inactivation thresholds and ionic conductances. They are responsible for the alterations in channel activity in Alzheimer disease (Chakroborty et al., Eur. J. Pharma. 739, (2014) 83; Brown et al., Neurobiol. of Aging 32.11 (2011) 2109-e1) and other neurological diseases such as Parkinson disease (Chan et al., Nature Neurosci. 14.1 (2011) 85), Rett syndrome (Oginsky et al., J. Cell. Physiol. 232.5 (2017) 1151), epilepsy (Lerche et al., J. Physiol. 591.4 (2010) 753), and autism (Schmunk et al., Front. Genetics 4 (2013) 222). Whilst knowledge of these parameters facilitates quantitative understanding of neural response, it is difficult to estimate them because many are hidden from observation. For example, voltage clamp measurements yield information on a single type of ion channel at a time. In recent years, powerful data assimilation methods have been developed to infer the full complement of ion channels from time series current-clamp recordings. The Bath group has spearheaded this effort by building quantitative models that predict the behaviour of songbird neurons (Sci. Rep. 6, (2016) 32749), of hippocampal and respiratory neurons (Nature Comm. 10 (2019) 5309) and by incorporating these models in chip implants that reverse the effects of heart failure (J. Physiol. 598 (2020) 455). This project will build on the recent advances of the Bath team and on the expertise of the Exeter team in patch-clamping small networks of healthy and diseased neurons. At Exeter, the PhD student will acquire electrophysiological recordings of CA1 in brain slices prepared from transgenic mouse models of Alzheimer's disease. Using specific current injection protocols designed to constrain all model parameters, the student will collect empirical data required for the computational aspect to the project. In Bath, the PhD student will compute ion channel parameters from the membrane voltage recordings of healthy and diseased neurons to quantify the changes introduced by Alzheimer's disease pathology at the level of individual ion channels. Models completed with the extracted parameters will allow us to predict the behaviour of diseased neurons and to understand the effect of drugs on them via simulation. To assess the performance of the data assimilation method in predicting how the expression levels of</p>

	<p>specific ion channels are altered in Alzheimer’s disease, single cell RNA sequencing will be performed on the same cells from which recordings were taken. Estimates of channel conductances provided by the mathematical framework will then be compared to RNA expression levels following qPCR analysis. To validate model predictions on the action of drugs, the PhD student will compare them to real cell recordings of brain slices before and after the action of channel blockers and agonists. Once validated, the quantitative model will be used to optimise drugs to restore normal function in Alzheimer neurons. Work 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.</p>
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Supervisory Team

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