Project Details	
Project Code	MRC22NMHBa Nogaret
Title	Predicting the dementia-induced changes to neuronal ion channels: a combined experimental and in-silico approach
Research Theme	Neuroscience & Mental Health
Summary	Channelopathies in which certain ion channels are over-expressed or absent occur in many neurological diseases. Currently, changes in neuronal function cannot be linked to underlying mutations in ion channel proteins. This interdisciplinary project will combine sophisticated computational methods with brain slice electrophysiology to quantify changes in specific ion channels in Alzheimer's disease and provide important insights into neurophysiological dysfunction.
Description	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 gives 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 and Bristol teams 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 extract 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 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 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 our computational method 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 inform drug design in restoring normal function in Alzheimer neurons. Work by the Exeter and Bristol teams 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.
Supervisory Team	
Lead Supervisor	
Name	Professor Alain Nogaret
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Department of Physics
Email Address	A.R.Nogaret@bath.ac.uk
Co-Supervisor 1	
Name	Dr Jon Brown
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	IBCS
Co-Supervisor 2	
Name	Dr Kyle Wedgwood
Affiliation	Exeter
College/Faculty	College of Engineering, Mathematics and Physical Sciences
Department/School	Living systems institute
Co-Supervisor 3	
Name	Dr James Hodge
Affiliation	Bristol
College/Faculty	
Department/School	School of Physiology, Pharmacology and Neuroscience
Co-Supervisor 4	
Name	Dr Gerald Finnerty
Affiliation	Other
College/Faculty	Medicine
Department/School	King's College Hospital London