Project Details	
Project Code	MRCNMH24Ba Nogaret
Title	Single-shot diagnosis of ion channel dysfunction in neurological disease from data assimilation of cell membrane dynamics
Research Theme	Neuroscience & Mental Health
Summary	Ion channel mutations play an increasingly recognised role in Epilepsy and Alzheimer's disease. This project will apply inverse computational methods to infer ion channel dysfunction from time series analysis of electrophysiological recordings. The link between anomalous electrical activity in the brain and channelopathies that will be established by this studentship will identify new therapeutic targets for neurological disease.
Description	Many neurological diseases originate in the dysfunction of cellular ion channels. Their diagnosis presents a challenge especially when alterations in the complement of ion channels are a priori unknown. Current approaches based on voltage clamps lack the throughput necessary to identify the mutations causing changes in electrical activity. Here, we introduce a single-shot method for diagnosing changes in the complement of ion channels from changes in the electrical activity of a cell. We developed data assimilation to estimate the parameters of individual ion channels and from these parameters reconstruct the ionic currents of hippocampal CA1 neurons to within +/-11% of their actual value. DA correctly predicts which ionic current is altered and by how much after we blocked the BK, SK, A and HCN channels with selective antagonists of known potency. We now aim with this studentship to identify the alterations in ion channels induced by genetic mutations in neurological disease. This is critically important to correctly diagnose channelopathies, improve drug screening and help design optimal treatment strategies. The work programme aims to estimate the ion channel parameters that govern gate kinetics, activation thresholds and ionic conductances and their alteration by neurological disease: epilepsy and Alzheimer disease. At Bath, the student will learn to use powerful data assimilation computational techniques to infer the full complement of ion channels by synchronizing a multichannel conductance model to time series current clamp recordings (Nogaret et al., Sci. Rep. 6, (2016) 32749, Abu-Hassan et al., Nature Comm. 10 (2019) 5309). The method has proven its success in transferring information from biological data to conductance models by predicting neuronal dynamics and by estimating the selectivity and potency of ion channel antagonists in hippocampal neurons. The breakthrough this studentship will make will be to adapt data assimilation to diagnosing neurological disease and establishing a quantitative link between electrical anomalies and the underlying ion channel alterations. The PhD student will learn to collect electrophysiological recordings from epileptic neurons at the University of Bristol. Dr Hodge's team has expertise in patch clamping transgenic epileptic fruit flies and has gained access to human epileptic neurons within the GW4 Community project (2022). They have already synthesized electrophysiological recordings on Drosophila with mutated sodium channels (SCN1A/Nav1.1, SCN2A/Nav1.2), calcium channels (CACNA1A Cav2.1, P/Q-type), and potassium channels (KCNQ2, KCNQ3, KCNT2). These recordings are immediately available for the student to

	analyse with the data assimilation algorithm developed in Bath. At the University of Exeter, the student will learn to prepare brain slices of transgenic mouse models of Alzheimer's disease and obtain electrophysiological recordings of both diseased and control neurons. 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/epilepsy, single cell RNA sequencing will be performed on the same cells from which recordings were taken. Parameter estimates provided by the mathematical framework will be compared to RNA expression levels following qPCR analysis. Once validated, the quantitative model will be used to optimise drugs to restore normal function in Alzheimer/Epileptic neurons. The data assimilation method will help identify the channelopathies which are relevant to the anomalous electrical activity. Unlike bottom-up methods such as transcriptomics or proteomics, which identify all mutations but are unable to tell which ones are functionally relevant, data assimilation only infers those mutations that are functionally relevant. This provides unique insight in the causes of disease and will identify therapeutic targets.
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