Project Details	
Project Code	MRCNMH26Ex Richards
Title	Using machine learning to classify microglia
Research Theme	NMH
Project Type	One of the chief advantages of this proposed project is that it intimately combines both theoretical work (including mathematics, programming, image analysis and machine learning) with wet-lab work (including cell culture and time-lapse imaging). This interdiciplinary combination is increasingly being used in both biological and biomedical research and will give the student an excellent, highly sought after skillset that will place them in a strong position for a broad range of career options.
Summary	During this exciting, fully-funded PhD, you will use machine learning to automatically classify the state of microglia (the brain's specialised immune cells). This will involve combining mathematics, computer programming and artificial intelligence with real experimental data to develop both supervised and unsupervised methods to predict microglial state. You will have the opportunity to collaborate with researchers in Exeter, Bristol, Newcastle and Leeds. This work has significant potential applications throughout biology and medicine, including in drug discovery, cancer and neurodegenerative conditions such as motor neuron disease, Parkinson's disease and Alzheimer's disease.
Description	**Background:** Microglia are the resident immune cells of the brain. They adopt a wide range of phenotypes to control the brain's immune response, including phagocytosing unwanted agents and releasing signalling chemicals to other cells in the brain. The scientific community has spent the last fifty years naively categorising microglial phenotype into just two types: M1 (inflammatory) and M2 (anti-inflammatory). However, recent work (including that by our collaborators) has led to the revolutionary idea that microglial state should instead be a "multidimensional concept", with a spectrum of states. Importance: Determining in how many states microglia can exist, whether these states form a continuum, and being able to predict microglial state is of fundamental medical importance. This is because microglia play a vital role in neurodegenerative disease (including motor neuron disease, Parkinson's disease and Alzheimer's disease) and cancer. Improved prediction of microglial state, particularly if this can be achieved from standard bright-field imaging, could revolutionise diagnosis of these conditions and provide a valuable tool in the search for treatments by, for example, aiding drug screening programmes. Machine learning: The vision is that microglial state could be predicted simply from cell shape. A human attempt to do this would be time-consuming and would be affected by unconscious bias and human error. Instead, what is needed is an automatic computational method. This is precisely what machine learning can achieve. Preliminary results in our group show that microglia can be classified with high accuracy (>93%) even using single cells. The aim of this PhD is to improve this. **Key research questions:** (1) What are the best machine learning techniques for automatically classifying microglial state? (2) How do these optimal techniques depend on image size, imaging conditions and imperfect training data?

	(3) Can the approach be optimised to run in real time and on multiple cells at the same time? **The approach**: This PhD will leverage the opportunity presented by our collaborations with Dr Kate Harris (University of Leeds) and Prof Ian Wood (University of Leeds). It will employ a truly multi-disciplinary approach to study possible states of microglia. The student will undertake a cross-disciplinary PhD, including machine learning, image analysis and time-lapse imaging experiments. This approach will allow the student to learn a highly-desirable combination of quantitative and experimental skills, leading to excellent future career prospects. Project plan and objectives: This cross-disciplinary studentship will be based within the Living Systems Institute at the University of Exeter. The student will also spend time at the University of Bristol and with our collaborators at the Universities of Newcastle and Leeds. Further, the student will join the Exeter Health Analytics network (which the first supervisor leads) to obtain a broad understanding of the role of mathematical modelling throughout human health, and will work with the Institute for Data Science and Artificial Intelligence at the University of Exeter. The project itself will include: Objective 1: Creation of novel machine learning approaches, in particular convolutional neural networks (CNNs), to automatically classify microglial state based on our existing large data set of over 20,000 microglia. This will involve exploring a number of different data sets and CNN architectures (LeNet-5, AlexNet, VGG-16, ResNet, Inception, Xception, Inception-ResNet, DenseNet and ResNeXt-50). Objective 2: Culturing and imaging of the human microglial HMC3 cell line to generate further data for training of CNNs and to test the accuracy of the machine learning models. Cells will be activated with either interferon (IFN alfa-2b) or lipopolysaccharide (LPS). Various stains will be used to aid identification of the cell shape, including wheat germ agglutinin (WGA), CellMask and Actin ReadyProbes. Objective 3: Design of image analysis software to automatically segment cells from raw microscopy images. This will be based on existing code in our groups. This will then be used to generate input data for the machine learning. Relevant techniques that will be considered include contrast adjustment, thresholding, morphological operations, edge detection, filtering, distance transforms and the watershed transformation. Objective 4: Application of the approach to microglia in the eye. This will involve working in the lab of Prof Andrew Dick at the Bristol Medical School (THS) in the University of Bristol. This group has a microglia reporter mouse model that will be used to generate new images of microglia in the eye. The CNNs will then be retrained on this new data and the differences and similarities to microglia in the brain investigated. We have designed the project so the student will have significant scope to take ownership. This particularly applies to Objective 1 (where there are several possible machine learning approaches) and Objective 3 (with several image analysis options). However, objectives 2 and 4 can also be tailored as required. Importantly, the proportion of time spent on each objective can be adjusted so that the student will be able to balance the project to best suits their needs.

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