Project title: In silico modelling of monocyte and macrophage molecular regulation in ageing and chronic disease

Project reference: DT4H_09_2023

Co 1st supervisor: Dr David Watson – Department of Informatics

Co 1st supervisor: Dr Robert Knight - Centre for Craniofacial and Regenerative Biology

Aim of the project

Monocytes and macrophages are a critical cell population for fighting infection and for repair of tissue after injury, but show impaired function in ageing. Although several key molecules associated with inflammation and immune cell function are known to be affected by ageing, it is unclear how these correspond to age-associated changes to monocyte/ macrophage function. This project therefore aims to create a digital twin of the ageing monocyte and macrophage to i) predict which molecules are affected by ageing, and ii) to make predictions about functionally important molecules which may be affected by ageing. Using causal machine learning techniques, we will design synthetic intervention models for policy evaluation and optimisation. These data-driven algorithms will allow researchers to run in silico experiments that are safer and more efficient than randomised control trials, giving clinicians the tools to design new treatment regimes for this important health associated issue.

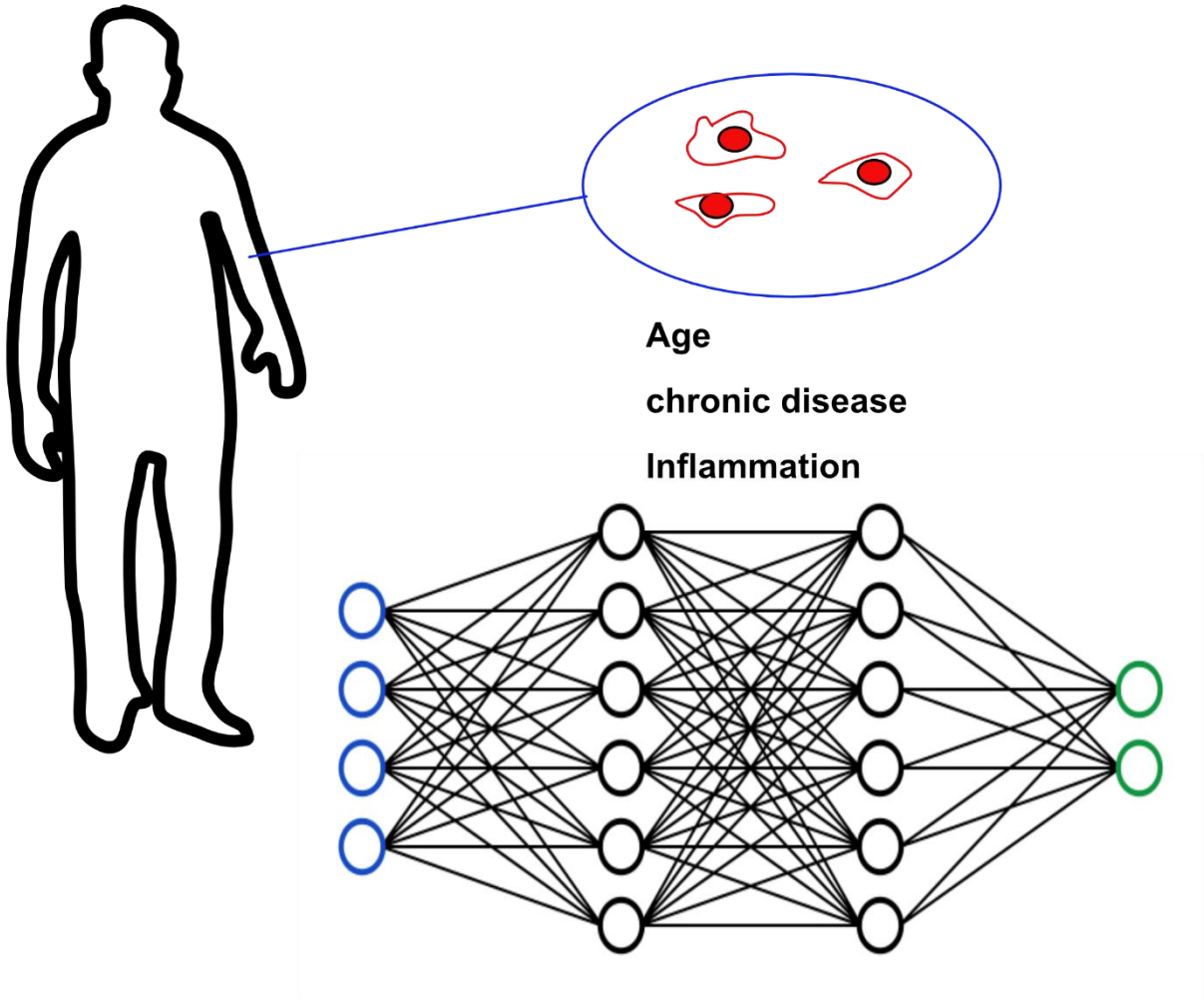
Project description

Changes to the immune system underlie a number of frailties and diseases in human ageing. Monocytes and macrophages are phagocytic cells essential for protection against disease and for repairing body tissues. In ageing and a number of chronic diseases, these cells show altered programs that impair their effectiveness. Although a number of changes have been documented, the plasticity and complex behaviour of these cells has prohibited the generation of a comprehensive model that can explain how they are affected by ageing. Monocytes are circulatory cells derived from stem cells in the bone marrow. They are recruited to sites of tissue injury, such as infections, where they often differentiate into macrophages. Both monocytes and macrophages can engulf pathogens and damaged tissues as well as secrete cytokines and chemokines to regulate other immune and resident cells. They are crucial for both promoting inflammation, by activating key signalling pathways such as NF-kB and TLR receptors, but also for resolving inflammation at later stages. Dysregulation of this switch has profound consequences for repair of injured tissue or clearance of pathogens and a common feature of chronic disease and ageing.

Despite the importance of monocytes and macrophages in regulating organismal health, there is little understanding of the molecular changes that affect their function. Specifically, there is no predictive model that can explain the consequences of the molecular changes occurring in these cells as a consequence of ageing or disease. This project therefore aims to generate a digital twin of ageing monocytes and macrophages for predicting how these conditions can alter their molecular function.

Standard machine learning algorithms prioritise correlation over causation and are therefore ill-suited to the task of modelling interventions in complex systems. However, recent advances in causal inference have paved the way for a new class of synthetic intervention models, which can predict treatment effects for various subpopulations given a combination of (potentially sparse) training data and some structural assumptions. We will combine these approaches to create a data-driven digital twin of ageing monocytes and macrophages, pooling data from different environments using deep neural networks with graphical constraints. Model performance will be tested on a combination of synthetic and real-world data on unseen treatment levels. A successful digital twin will vastly speed up the process of drug discovery and repositioning, as in silico experiments can be run safely and cheaply.

Ideal applicants will have an academic background in biology and programming experience in Python. Knowledge of probability theory and/or information theory a plus.



A digital twin for monocytes and macrophages in ageing and people with chronic disease will be developed using models for causal inference to predict molecular causes for impaired cell function.