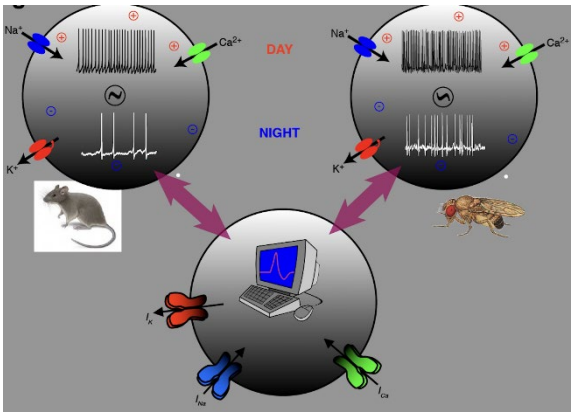
Modelling the effect of ageing in silico and on Drosophila and mouse clock neurons



Supervisory team:
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Host institution: University of Bristol

Project description:
All organisms are subject to daily environmental changes caused by the earth's rotation leading to the evolution of circadian clock mechanisms that regulate changes in behaviour, physiology and metabolism across the day to ensure their timely occurrence and allowing environmental adaption. The central circadian clock maintains a ~24-hour rhythm and consists of clock neurons that express a molecular oscillator that cycles every 24-hours by a mechanism conserved from Drosophila to mammals including humans. Circadian rhythms are important for health, with misalignment resulting in sleep disorders, depression and cancer. With ever-increasing human lifespans, understanding how circadian rhythms change during ageing is of growing interest and health relevance, with the population aged over 60 years old set to more than double by 2050. 40-70% of old people experience chronic circadian and sleep disturbances with Parkinson and Alzheimer's disease causing more pronounced circadian and sleep deficits, with poor sleep contributing to disease pathology. We have shown clock neurons show activity rhythms with higher firing rates and more depolarized membrane potentials during the day in both flies and mice. However, the mechanisms driving day/night differences clock excitability are not understood. We have shown that ageing disrupts circadian rhythms, sleep and clock neuron excitability in flies with similar effects in aged mice, again by unknown mechanisms.

In this collaborative, interdisciplinary and strategically relevant PhD project, the candidate will be trained to perform a combination of electrophysiology, pharmacology, genetics, imaging, behaviour and computational modelling, to identify which clock neuron expressed potassium channels underlie the day/night differences in membrane excitability and how these are changed by ageing. The overall aim of this collaborative studentship is to test the hypothesis that ageing changes the potassium channel mediated membrane properties of clock neurons, which will be investigated through the following objectives:

1. To determine which potassium channels underlie the clock neuron membrane properties changed by ageing
    a. Determine the potassium channel mediated changes that switch clock neurons between day/night activity
    b. Develop a model of day/night differences in clock neuron excitability and test if the proposed potassium channel changes switch the neurons between day/night

2a. Determine how ageing affects potassium channel mediated changes in clock neuron excitability

2b. Develop a model of the effect of ageing on clock neuron excitability and test if the proposed potassium channel mediated change can switch the neurons between young and old 2C: Compare Drosophila and mammalian models of day/night differences in clock neuron excitability and ageing.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.