MURPA Seminar, Friday 26 March 2010 at 10am

Title: Mathematical models of cardiac muscle cells: Predicting drug-induced arrhythmias

Presenter: Dr Ania Sher, Oxford University

Location: Seminar Room 135, Building 26 Clayton

Abstract

Many drugs fail to reach the market because of side effects on the heart. Cardiac toxicity (in particular, whether a new drug will have undesirable side effects by causing dangerous changes in heart rhythm – 'arrhythmias') is a principal factor leading to abandonment of otherwise promising drug candidates. For instance, the level of inhibition of the hERG channel is one of the preclinical markers commonly used to predict the risk of a drug causing Torsade-de-Pointes (TdP) arrhythmia. While it has been suggested to avoid the use of drugs with a maximum therapeutic concentration within 30-fold of the hERG IC50 value, there are many drugs which are exceptions to this rule: hERG inhibitors which do not cause TdP, and drugs which cause TdP but are not hERG inhibitors. Moreover, performing in vivo experiments and measurements is often difficult (e.g. for humans, sometimes very dangerous or even impossible) while mathematical modelling of the heart can provide insights into the physiological processes and potential biomarkers without any harm. In this talk, I will review the existing approaches of modelling drug interactions at the sub-cellular and cellular levels in ventricular myocytes. In order to improve the model fit to the experimental data and to identify the key parameters responsible for drug action at different frequencies, such tools as the Nimrod parameter sweep and optimization toolkit developed in Prof Abramson's group could be used. Further, I will discuss how computational models of heart muscle cells are being used to predict the effect of multi-channel drug action on a cardiac cell dynamics, as well as on the risk of TdP development. I will also present how modeling can suggest improved (as compared to hERG IC50 value) marker(s) for TdP risk assessment.