The importance of cardiac ion channels on the electrocardiogram - partial least squares regression as a new tool in computational biology

S.A. Mann, A. Sadrieh, J.I. Vandenberg and A.P. Hill, Mark Cowley Lidwill Research Programme in Cardiac Electrophysiology, Victor Chang Cardiac Research Institute, Lowy Packer Building, 405 Liverpool St, Darlinghurst, NSW, 2010, Australia.

Abnormal heart rhythms, especially ventricular fibrillation, cause 10-15% of adult deaths in the developed world. A loss of function mutation in just one of the cardiac ion channels that underlie electrical signalling in the heart is sufficient to significantly increase the risk of sudden death, and often at a young age. Recent genome wide association studies and whole exome sequencing projects have identified hundreds of genetic variants in cardiac ion channel genes. Many of these are undoubtedly benign, but many are also likely to result in small alterations of function. The challenge is the interpretation of cumulative effects of multiple small perturbations on a multi variable nonlinear dynamic system. Our first foray into this area was restricted by computational constraints and therefore focused on single (atrial) cells (see Mann *et al.*, 2012). Utilising the computational power of graphics processing units, we have now developed an implementation of the electrocardiogram (ECG), based on the model of the human cardiac action potential by O'Hara *et al.*, (2011). We then used a partial least squares regression analysis approach, pioneered in this field by Sobie (2009), to interrogate how each of the models components contribute to the ECG signals at pacing rates that vary between 0.5 and 2 Hz. In addition to reproducing the well described relationships between repolarisation durations and delayed rectifier potassium currents our analysis can explain many previously unexplained clinical observations including the basis of altered T-wave amplitude and duration in the inherited arrhythmia syndromes SQTS and Anderson-Tiwali syndrome.

Mann SA, Otway R, Guo G, Soka M, Karlsdotter L, Trivedi G, Ohanian M, Zodgekar P, Smith RA, Wouters MA, Subbiah R, Walker B, Kuchar D, Sanders P, Griffiths L, Vandenberg JI, Fatkin D. (2012) Epistatic effects of potassium channel variation on cardiac repolarization and atrial fibrillation risk. *Journal of the American College of Cardiology* **59**, 1017–1025.

O'Hara T, Virag L, Varro A, & Rudy Y. (2011) Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Computational Biology* **7**, e1002061.

Sobie EA. (2009) Parameter sensitivity analysis in electrophysiological models using multivariable regression. *Biophysical Journal* **96**, 1264–1274.