Human *in Silico* Drug Trials in Population of Cardiac Cell Models

Elisa Passini[1], Oliver Britton[1], Alfonso Bueno-Orovio[1], Blanca Rodriguez[1]

[1] Computational Cardiovascular Science Group, Department of Computer Science, University of Oxford, Oxford (UK)

Description:

Early prediction of cardiotoxicity is critical for drug development. A key challenge is the large variability in drug responses across the population, also depending on underlying cardiac disorders and drug-drug interactions. Human-based computer models constitute an emerging technology to test and predict safety and efficacy of therapies in patients. They represent a fast and cheap alternative to animal experiments, also facilitating the translation to humans.

Experimentally-calibrated populations of *in silico* cardiac models are designed to tackle the variability challenge[1]. Each virtual cell has different electrophysiological properties, accounting for the variability observed across individuals, and also including diseases/mutations. This allows to predict drug cardiotoxicity at the population level, and identify sub-populations at higher risk of developing adverse events. Simulations are based on ion channel data, routinely measured during drug-development, and predict changes in cardiac biomarkers and drug-induced abnormalities associated with pro-arrhythmic risk in patients.

This methodology has been integrated into Virtual Assay, a user-friendly software to run human *in silico* drug trials, and it was used in validation studies on reference compounds[2,3], demonstrating higher accuracy than animal experiments. By providing early predictions of drug-induced adverse cardiac events, it has the potential to revolutionise the current drug cardiac safety testing pipelines.

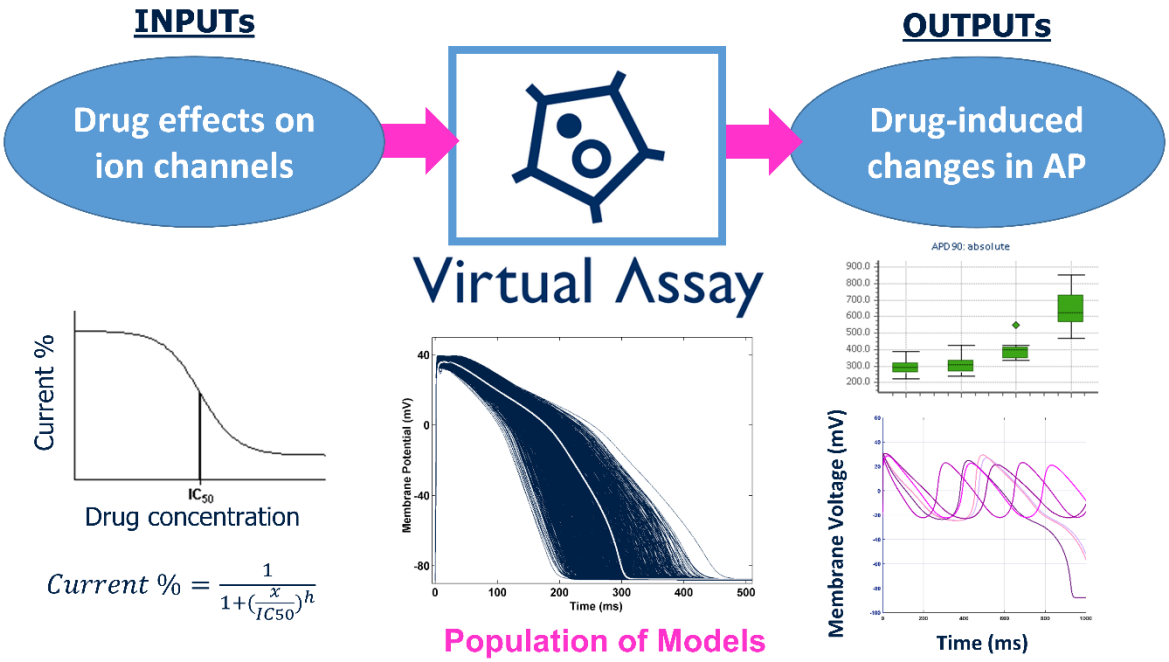

Figure 1: Schematic representation of human in silico drug trials in population of cardiac cell models. Simulation inputs are the drug effects on cardiac ion channels, measured experimentally and represented by IC_{50} and Hill coefficients. Simulation outputs are drug-induced changes on cardiac biomarkers and occurrence of repolarisation abnormalities, which have been associated with clinical risk of drug-induced arrhythmias.

Figure 2: From left to right – Alfonso Bueno-Orovio, Blanca Rodriguez, Elisa Passini and Oliver Britton is the team driving the work on human in silico drug trials using population of human cardiac cell models and the development of the Virtual Assay software.

Weblink:

http://www.cs.ox.ac.uk/ccs/virtual-assay

References:

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2. Passini E, Britton OJ, Lu HR, Rohrbacher J, Hermans AN, Gallacher DJ, Greig RJH, Bueno-Orovio A, Rodriguez B: Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity. Front Physiol. 2017, 8(668). doi: 10.3389/fphys.2017.00668.
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