Simulation of the effect of sodium and potassium blockers on the electrical activity of the heart: Modelling from ion-channels to the body surface.

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ABSTRACT

Prediction of drug-induced cardiotoxicity is a major concern for regulatory agencies, pharmaceutical industry and society. A number of preclinical and clinical methods and biomarkers have been proposed to detect possible drug cardio-toxic effects as early as possible during drug development. However, approval of drug compounds is decided based on evaluation of the QT interval in the Electrocardiogram (ECG), as conducted thorough QT studies. Therefore, early and improved prediction of potential drug-induced prolongation of QT interval from preclinical assays is one of the major goals in safety pharmacology. In the present work, we describe novel tools based on advanced computational techniques "Chaste" (www.cs.ox.ac.uk/chaste) allowing simulation of alterations in the human ECG induced by drug-induced effects on specific ionic currents. Chaste is a parallel finite element library, containing a bidomain solver. Chaste's parallelisation is based on the message-passing standard Message Passing Interface (MPI) and it uses ParMETIS to ensure optimal domain decomposition. A shared-memory aware MPI implementation was used to improve intra-node communications.

A 3D anatomically-based model of the whole human body is presented with biophysically-detailed representation of human membrane kinetics, realistic cardiac geometry, fibre orientation and heterogeneity in electrophysiological properties of cardiac ventricles. The 3D multiscale model is used to simulate the effect of specific drug concentrations of fast sodium and hERG current blocker on the action potential at the cell level, on activation and repolarization maps at the heart level, and on the Qt interval at the body surface level. The simulation of drugs effect is also shown on different biomarkers.