

preDiCT

(Computational Prediction of Drug Cardiac Toxicity) Predicting Drug Interactions

The preDiCT project will model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation. Using this information, the project hopes to identify new biomarkers which will provide more reliable indication of harmful drug side effects.

Objectives of the Project

Problem or Context

Current best practice in pharmaceutical development relies on the Q-T interval (the spacing of two points on an electrocardiogram) as a proxy for potentially dangerous side effects. However, it is known that some drugs which fail this test do not lead to arrhythmia (e.g. Ranolazine, whose safety was demonstrated by researchers at the University of Oxford). We hope to be able to develop more accurate gauges of potential cardiotoxicity.

A significant and growing number of drug candidates fail to reach market due to adverse effects on heart rhythm which only show up during clinical trials. We hope to achieve a better understanding of the underlying mechanisms, which may lead to refinement of the drug development process to avoid these side effects.

Project

The preDiCT project will model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation.

This will require advances beyond the current state-of-the-art in:

- Mathematical models of individual ion channels, which control the electrical activation of each heart cell;
- Tissue models, which encapsulate chemical processes and physical relationships between millions of individual muscle cells in the heart; and
- The computer code, which must compute these relationships as a series of complex equations, to enable faster than real-time simulation of a beating heart.

Project Progress

In the first 18 months of the project the currently available mathematical models of cells have been checked, their limitations identified and strategies for refinement developed. In order to test these models, they had to be built from and validated against experimental data from the scientific literature and provided by preDiCT academic and pharmaceutical partners. Significant work has been required to 'normalise' these data with respect to the experimental protocols used to acquire them, in order to make them directly comparable. A database for publications, protocols and tested compounds has been developed and populated with an initial list of drugs and selected publications.

Sensitivity Analysis using software developed by preDiCT has determined that most of the existing models must be refined in order to be predictive. Effort is now being concentrated on improving the models, to enable fast, reliable simulation of normal and altered cardiac electrophysiology.

A better understanding of the factors determining species-dependent drug interactions, combined with analysis of ECG signals and the assessment of arrhythmogenic factors, enables the investigation of new and better biomarkers to complement current drug-safety metrics.

As of January 2010, we have developed models of the action of two drugs, lidocaine and dofetilide, on ionic channels, and computationally efficient models of rabbit and human cardiac electrophysiology. We have also evaluated new biomarkers of arrhythmic risk and reviewed ionic and cellular biomarkers of arrhythmic risk.

In order to compute drug effects on human ventricles, the project has begun to develop highly efficient numerical algorithms and implement them on

SCENARIO

Given that most of the costs of bringing a new drug to market are incurred during the clinical trial phases, there would be a huge economic and clinical impact for being able more accurately to predict which drugs are likely to cause arrhythmias. Even when drugs do make it through to clinical trials, the statistical power of those trials is often insufficient to predict adverse effects which may (recently in the cases of Vioxx and Celebrex) appear only when the drug is given to large numbers of patients over long periods of time.

A more predictive approach utilising advanced mathematical and computational modelling holds out hope of being able to spot and pre-empt these very low-probability effects.

massively parallel computers. The consortium is making use of extensive high-performance computing facilities in the UK (DEISA), Italy, Germany and Japan.

All the tools will be integrated into a Virtual Research Environment: an integrative portal to the complex set of tools and information needed to conduct *in silico* experiments. The VRE will be designed for everyday use by academic researchers and pharmaceutical industry scientists, to facilitate more extensive use of *in silico* methods in the drug discovery and development process.

The traceability of the complete project will be ensured by storing all the results and simulations, including the metadata describing the *in silico* experiments, and the models developed will be provided to the wider community via the CellML repository.

The key to the success of the project is the cooperation with the pharmaceutical industry. Our initial consortium involved key pharmaceutical companies to assist with steering the project. Over the first 18 months, we have deepened these relationships and extended the number of pharmaceutical companies involved. At our pharma workshop in October 2009, this engagement extended to defining projects to work on with each of these companies.

Expected Results & Impacts

The preDiCT project aims to improve our understanding of the mechanisms of negative drug actions on the heart, which will:

- Improve safety testing for new drugs;
- Help speed up and streamline the drug discovery process by identifying likely profiles of 'good' and 'risky' compounds (the pharmaceutical industry currently spends nearly €3bn per new approved drug);
- Help pave the way to patient-specific healthcare through simulation; and
- Push the boundaries of simulation and high-performance computing, enabling progress in scientific research in many areas.

Furthermore, by extending the frontiers of *in silico* experimentation, our project will enable future researchers to refine, replace and ultimately reduce the use of animals in pharmaceutical and other cardiac research.



preDiCT

Computational Prediction of
Drug Cardiac Toxicity

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- GlaxoSmithKline Research and Development (United Kingdom)
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KEYWORDS

Cardiac, Physiological modelling, Drug safety, Ventricle, Electrophysiology