@Health
Monthly Focus

preDiCT

Predicting Drug Cardiac Toxicity

European Commission
Information Society and Media

The preDiCT project began in June 2008, with a mission to model, simulate, and ultimately predict the impact of pharmacological compounds on the heart's rhythm using computer models.

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.

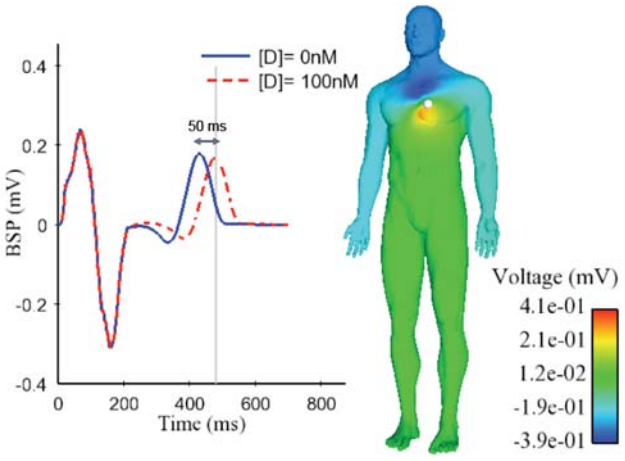
Real-world applications

One of the most dangerous cardiac side-effects, Torsades-de-Pointes (TdP), is linked to inhibition of an ion channel called hERG. The earliest stage of screening for TdP safety is currently a blunt instrument, automatically rejecting compounds that act strongly on this channel. However, there are many drugs which are hERG inhibitors and are safe, and others which cause TdP but are not hERG inhibitors.

We are working with partner GSK to improve the prediction of TdP risk in early stage compound development, using mathematical models to integrate experimental data on the activity of various commonly measured ion channels. Of the 31 drugs we studied with known TdP risk, we found that risk classification as 'safe' or 'dangerous' according to hERG inhibition alone misclassified nine drugs, while our methods correctly classified all but one. We are also conducting studies using data collected by Pfizer to evaluate new biomarkers based on the electrocardiogram for the assessment of drug-induced arrhythmic risk.

Understanding drug/ion channel interactions could also be key for the development of new arrhythmic therapies. We are working in collaboration with industrial partners to identify novel avenues for the treatment of atrial fibrillation. Simulation studies have identified the most significant ionic currents for the modulation of atrial arrhythmic activity in human for several conditions (short- versus long-term atrial fibrillation).

We are also working to refine our model of the drug ranolazine, and to study the role of the late sodium current in heart failure.



Drug-induced effects on the heart: from ion channel to surface body electrocardiogram (collaboration Oxford-Valencia-INRIA)

Expanding possibilities

Now in its final year, the project has produced the mathematical models and simulation tools required to simulate, for the first time, drug-induced effects on the heart from drug-ion channel interactions to the surface body Electrocardiogram (ECG). The ECG is still the main tool used clinically to detect potentially lethal drug-induced effects on the heart. Computer simulations using the state-of-the art technology developed within preDiCT can now be conducted to help in the identification of novel ECG-based biomarkers of drug cardiotoxicity and improve our understanding of drug-induced arrhythmias.

The simulations are only possible through the use of efficient and tested simulation software to run multiscale models thousands of times faster than could be done at the start of the project. Ultimately, all models will be made accessible through a Virtual Research Environment, which will record the modeller's activities at each stage in the process, allowing reproducible and more transparent results. The data used to build the models, as well as the simulation output files, will be accessible through the interface, allowing direct comparison of in silico experiments with real-world experimental results.

Making an impact

The ultimate aim of our research is to provide patients with safer drugs, and to help pharma companies test new compounds more quickly, accurately and cheaply. Continuous involvement with Pharma, alongside other dissemination activities, has expanded the outreach of our research, spreading the use of our tools and techniques by industrial and academic researchers.

The project has developed strong collaborative links between academic and industrial partners. We are now planning a workshop with members of regulatory agencies in February 2011, to showcase the exciting results of the project, and to explore how the technology and methodologies developed during the project could be adopted during the drug safety approval process.

All tools and models, including the Virtual Research Environment, will be made available open-source at the end of the project, in May 2011. We may be able to provide training or conduct additional case studies before then. If you are interested in using our models or software, or would like to propose an application for our research, please contact Katherine Fletcher.

Timetable: from 06/2008 – to 05/2011
Total cost: 5 545 692 €
EC funding: 4 100 000 €
Instrument: STREP
Project Identifier: FP7-2008-IST-224381

Important Links:

Project website: **www.vph-predict.eu**
Project factsheet: http://ec.europa.eu/information_society/activities/health/docs/projects/fp7/predict-factsheet.pdf

ICT for Health website: http://ec.europa.eu/information_society/ehealth

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