

# NEWSLETTER

In silico human-based methodologies for evaluation of drug safety and efficacy

## “In Silico Human drug safety and efficacy” project.



The project “In silico human-based methodologies for evaluation of drug safety and efficacy” officially started on 1<sup>st</sup> October 2016. The main goal of this initiative is to accelerate the use of *in silico* methodologies for the evaluation of drug safety and efficacy in academic, industrial, regulatory and clinical settings. The coordinated action of these four sectors aims to improve the efficiency of drug testing through the use of human-based computer models, refined and evaluated, using experimental and clinical recordings. Through this project we will work towards the refinement, reduction and replacement of animals in the drug development process, and the development of a more reliable and accurate process for drug testing. The team is formed by a partnership across industry, academia, hospitals and regulatory agencies from 14 countries.

The webpage of this project <http://www.cs.ox.ac.uk/insilicocardiotox/home> is an open space to share knowledge, papers and models and a reference for experts on in silico methodologies for drug safety and efficacy.

We would like to encourage all partners to get involved and send news, papers and models related to in silico drug safety and efficacy to [patricia.benito@cs.ox.ac.uk](mailto:patricia.benito@cs.ox.ac.uk) to keep the website alive.

## News and Events

### Success of the “In Silico Drug Safety and Efficacy” Symposium

On 21<sup>st</sup>-22<sup>nd</sup> September 2017, the “*In Silico Drug Safety and Efficacy Symposium*” was hosted by the Computational Cardiovascular Science team at the Department of Computer Science, University of Oxford. The event was organised in the context of the “*In Silico human-based methodologies for evaluation of drug safety and efficacy*” project, funded by the National Centre for the Replacement, Refinement & Reduction of Animals in Research, and additionally supported by the UK QSP Network, the Wellcome Trust and the University of Oxford.

The number of delegates reached almost 100, a perfect size that allowed both an easy networking with key experts on the field and a good overview of current trends on scientific disciplines, experimental approaches and regulatory perspectives involved on drug safety and efficacy. The programme covered one day and a half of presentations and discussions, meals and a social dinner event, which allowed the attendees to discuss ideas and collaborative alliances with the key stakeholders.

The symposium demonstrated the significant development and uptake that *in silico* methodologies are experiencing in their application to drug safety and efficacy. All key players in the field, including representatives from industry, academia, hospitals and regulatory agencies, presented their latest advances and perspectives on the use of *in silico* modelling to investigate cardiotoxicity, cardiac contractility or drug safety.

You can check the program of the event <http://www.cs.ox.ac.uk/insilicocardiotox/symposium>.



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## Personalised In-Silico Cardiology



A new collaborative initiative has been launched to establish a European Innovative Training Network (ITN) for the development of Personalised in-silico Cardiology (PIC).

The PIC is a 4 year project that will train 15 innovation leaders in the vision of a healthcare supported by *in-silico* and computational technologies. Recent scientific progress has created an exceptional capacity to simulate the heart and its interaction with the circulatory system *in-silico*. Patient-specific *in-silico* models enable comprehensive integration and interpretation of clinical data. These models provide the pathway for developing personalised and preventive management strategies for cardiovascular diseases that are tailored to each patient. In addition, recent advances in data science, such as machine learning and data mining enable the extraction of novel insights and knowledge from the large repositories of clinical data from health information systems. Further information at: <http://picnet.eu> and on twitter: [@PICnetEU](https://twitter.com/PICnetEU)

## Heart Attack Simulation

Researchers from the University of Auckland show what a live beating heart looks like when it's having a heart attack. Using computational biomechanics and medical imaging, researchers at the Auckland Bioengineering Institute (ABI) have built a dynamic 3D computer model of the two main pumping chambers (ventricles) of the heart. The interactive model shows how the motion of the ventricles is affected by the three most common heart disease scenarios – heart attack, arrhythmia and heart failure.

Auckland Bioengineering Institute's Cardiac Mechanics Research team is led by Professor Martyn Nash, who is Professor of Biomedical Engineering at ABI and in Engineering Science. For the research programme funded by the Health Research Council, Martyn collaborates with co-leader Professor Alistair Young, a medical imaging expert, and National Heart Foundation Professor of Heart Health, Rob Doughty – both from the Faculty of Medical and Health Sciences (FMHS). The other collaborators on the programme are: Professor Peter Ruygrok, Associate Professor Malcolm Legget and Dr Kat Gilbert (FMHS), and Ms Jenny Wang and Dr Vicky Wang (Heart Foundation Research Fellow) from the ABI.

You can find the simulation at: <http://sites.bioeng.auckland.ac.nz/medtech/heart/>

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## Publications & Journals

### Call for Papers: Quantitative Systems Pharmacology (QSP)

UK

**Quantitative  
Systems  
Pharmacology  
NETWORK**

The Journal of Progress in Biophysics and Molecular Biology (PBMB) are requesting articles for a special issue on 'Quantitative Systems Pharmacology (QSP): Methods and Tools'. Articles must be submitted by 31st December 2017 for a planned publication date of July 2018. Articles must follow the PBMB submission guidelines, and can be original research or a review article. Specific topics of interest include parameter estimation, identifiability analysis, model reduction techniques, sensitivity analysis, virtual population studies in application to drug discovery, design and development.

For more information visit: the [website](#)

### Special Issue, Safety Pharmacology 2018, JPTM.

The Journal of Pharmacological and Toxicological Methods (JPTM) submission portal is now open for submission of papers for the special issue, [Safety Pharmacology 2018](#). Please ensure that you choose the article type: "SI:SafePharmacology18" for this special issue. The submission portal can be accessed from the following link: <http://www.evise.com/evise/jrnl/JPM>.

The Journal of Pharmacological and Toxicological Methods (JPTM) publishes original articles on current methods of investigation used in pharmacology and toxicology. Pharmacology and toxicology are defined in the broadest sense, referring to actions of drugs and chemicals on all living systems. Please see the [Guide for Authors](#) for



information on article submission.



### Special issue on Safety Pharmacology, Frontiers.

Frontiers has launched a special issue on "Safety Pharmacology, Risk Assessment QT Interval Prolongation and Beyond at Frontiers". Please visit the website to check all the publications: <http://journal.frontiersin.org/researchtopic/5662/safety-pharmacology-risk-assessment-qt-interval-prolongation-and-beyond>

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## Published Papers

In addition, the following papers have been recently published in several journals:

- ◆ [Identification of ion currents components generating field potential recorded in MEA from hiPSC-CM](#) F. Raphel, et al. IEEE Transactions on Biomedical Engineering.
- ◆ [In silico assessment of the effects of various compounds in MEA/hiPSC-CM assays: Modeling and numerical simulations](#), E. Abbate et al. Journal of Pharmacological and Toxicological Methods.
- ◆ [MRI-based heart and torso personalization for computer modeling and simulation of cardiac electrophysiology](#). E. Zacur, et al. Lecture Notes in Computer Science.
- ◆ [Modelling variability in cardiac electrophysiology: a moment-matching approach](#). E. Tixier, et al. Journal of the Royal Society Interface.
- ◆ [Phenotypic variability in LQT3 human induced pluripotent stem cell-derived cardiomyocytes and their response to antiarrhythmic pharmacologic therapy: An \*in silico\* approach](#). M. Paci, et al. Heart Rhythm.
- ◆ [Experimental and Computational Insight into Human Mesenchymal Stem Cell Paracrine Signaling and Heterocellular Coupling Effects on Cardiac Contractility and Arrhythmogenicity](#). J. Mayourian et al. Circulation Research.
- ◆ [A multiscale computational modelling approach predicts mechanisms of female sex risk in the setting of arousal-induced arrhythmias](#), P.C. Yang, et al. The Journal of Physiology.

## Conferences & Events

### Comprehensive in-vitro Proarrhythmia Assay (CiPA) in-silico Working Group

The Comprehensive in-vitro Proarrhythmia Assay (CiPA) in-silico Working Group held a meeting on 9th November in Toronto alongside the Cardiac Physiome Workshop (7-8th November). The meeting discussed the US Food and Drug Administration (FDA) modelling group's work on the mathematical modelling aspects of the initiative, gathered feedback, heard new ideas and stimulated further collaborations.

CiPA is an international initiative, launched in 2013 by the US Food and Drug Administration, other drug regulatory agencies, industry and academic collaborators, to develop and validate a new mechanistic, in vitro and in silico paradigm for evaluating the proarrhythmic risk of new drugs. CiPA studies include ion channel effects in cell lines combined with mathematical action potential modelling to predict the effect of multiple ion channel block and associated pro-arrhythmic risk, and to check the integrated effect with stem-cell derived cardiomyocyte measurements. The CiPA project website is <http://cipaproject.org/>

### Gordon Research Conference, “Contemporary Advances and Challenges in Drug Safety Assessment”.



The Drug Safety GRC brings together basic and applied science focused on improving drug safety with a specific goal of creating interactions among drug safety scientists and experts from other disciplines. The opening sessions focus on computational approaches to modeling drug effect in complex systems and the challenges inherent in extrapolating safety signals across species to understand human risk. Applications for this meeting must be submitted by May 13, 2018 and the conference will be held June 10 - 15, 2018 in Easton, Massachusetts, US. <https://www.grc.org/drug-safety-conference/2018/>

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## Gordon Research Conference, “From Cardiac Mechanisms to Novel Therapeutic Approaches, Gordon Research Conference”.



The 2018 Gordon Research Conference (GRC) on Cardiac Regulatory Mechanisms, is the premier conference centred on the fundamental physiological mechanisms that control normal cardiac function and how they are altered by disease, with the goal of discovering novel mechanisms to protect or restore function of the failing, injured or arrhythmic heart. The subjects included in the program cover the latest advances in understanding cardiac function/dysfunction in the areas of heart failure, metabolic disease, cardiac signal transduction, cell or gene therapy, regulation by non-coding DNA/RNA, ion transport and myocyte/non-myocyte communication. The meeting will be held in New London, New Hampshire, US, June 3 - 8, 2018. Applications for this meeting must be submitted by May 6, 2018. For more information visit: <https://www.grc.org/cardiac-regulatory-mechanisms-conference/2018/>

## CompBioMed Webinar No. 1. HPC simulations of cardiac electrophysiology using patient specific models of the heart (using CHASTE and Alya).

This webinar provided an insight into the latest research of the Computational Cardiovascular Science group (the University of Oxford) on High Performance Computational (HPC) simulations of cardiac electrophysiology using patient specific models of the whole heart. The group has developed an image analysis and computational pipeline for the personalisation of anatomically-based human heart-torso models, from MRI data, generation of volumetric meshes, to patient-specific simulations of human heart function and ECG reconstruction. They focused on two well-known simulation software, Chaste and Alya.

You can find the video of webinar and all the complimentary material [here](#).

This webinar is part of a series of webinars of the CompBioMed project and is made in collaboration with the [VPH Institute](#). More information on future webinars can be found [here](#).



CompBioMed



## Awards

### The “Virtual Assay” software winner of the Safety Pharmacology Society Technological Innovation Award 2017



Elisa Passini received the Technological Innovation Award at the Safety Pharmacology Society Meeting 2017 for “Virtual Assay: a User-Friendly Framework for In Silico Drug Trials in Populations of Human Cardiomyocyte Models” .

The Computational Cardiovascular Science team at the University of Oxford supported by a EPSRC Impact Acceleration Award developed this user-friendly software for In Silico drug trials, using populations of human cardiac cellular models based on well-understood human cardiac physiology. The human cell populations are calibrated against experimental data and used to predict the effects of different pharmaceutical agents on human cellular response at the population level. Several major companies in the pharmaceutical industry are already using the software with promising results.

This award is a recognition to the importance of In Silico models in Safety Pharmacology.