

# HeCaToS Newsletter

Hepatic and Cardiac Toxicity Systems modelling (HeCaToS)

European Commission Research  
and Innovation FP7 programme

Project number: 602156

Issue Number 1

October 2016

## In This Issue

- Welcome from our Editor
- The chemistry of simulating cell membrane
- Who's who?
- Recent publications

## Editorial Note

Welcome to the first issue of the HeCaToS Newsletter. The HeCaToS Newsletter will be a biannual publication featuring the latest project related information, keeping you up to date with recent project developments as well as the details of any forthcoming events and training opportunities.

HeCaToS project is a partnership between private funders and public institutions across the European Union aiming to bring about scientific and technological advances in the chemicals and the consumer health industry, and it is in this collaborative spirit that we also hope the Newsletter can be used as a platform for HeCaToS staff across the consortium to share their knowledge and interests with colleagues at other project partner institutions.

The 3<sup>rd</sup> HeCaToS Annual Meeting will be held in Valencia, Spain, from the 2<sup>nd</sup> - 4<sup>th</sup> November 2016. We look forward to seeing you there.



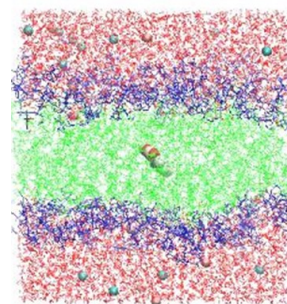
# The chemistry of simulating cell membrane

By Dr. ChungHo Lau, Imperial College London

Computational chemistry plays a key role in providing us mechanistic insight into drug toxicity at the molecular level. Dr. Ian Gould (Imperial College London) is one of the pioneers of AMBER force field, and I interviewed Dr. Gould and his team member working on the project, Dr. Dimitrios Toroz, to learn more about their work:

## Why is it important to simulate the behaviour of cell membrane?

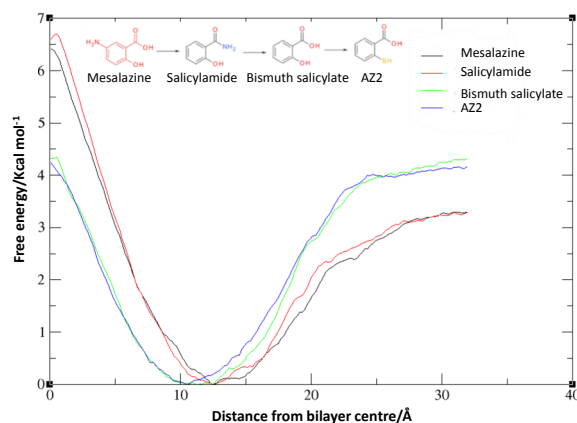
This can provide useful information on the spatial organization and the dynamics of the different constituent parts of the membrane at the atomic level. Also, we can track the drug molecules and their kinetics as they travel across the cell membrane. This is very important because this allows us to make prediction on drug toxicity and the binding of small molecules to receptors, accurately discriminating between toxic with non-toxic analogues.



*Molecule travelling across the lipid bilayer*

## What methods and techniques do you use to model the cell membrane?

We typically model the cell membrane as lipid bilayers using a simulation method called molecular dynamics. This powerful technique can be applied in the fields of chemical physics, material science, as well as the modelling of biomolecules, to study the movements of all the atoms and molecules in a given system. We and others have shown that this approach to be useful in predicting drug toxicity.



*Free energy profiles for four drug molecules*

## What are you currently working on?

We have recently been working on lipid14 force field which allows us to carry out tensionless simulation of a different number of lipid types using various combinations of head and tail groups. This also allow the free energy profile for the transfer of any particular molecule across the lipid bilayer, such as a drug, to be calculated. We can also predict the passive diffusion of toxicants from this information.



*Dr. Ian Gould (left) and his team member working on the project, Dr. Dimitrios Toroz (right)*

## Who's who?



Dr. Ralf Herwig is currently based at the Max Planck Institute for Molecular Genetics in Berlin. Having started off as a mathematician with an interest in non-parametric statistics and clustering algorithms, throughout his career, he has developed numerous statistical methods and algorithms for analysing high-throughput genomic data. His current work includes developing and applying statistical methods for integrating and analysing omics datasets. And more recently his research focus includes modelling biological processes such as metabolic pathways and signal transduction pathways.



Dr. Lars Küpfer is based at Bayer and the RWTH Aachen University and his research group models the physiology in liver and is responsible for the vertical integration of computational models that follow different mathematical formalisms. Within the context of the project multiscale models will be developed to represent the complex cellular networks that exist in the surrounding organs/tissues; this would give us mechanistic understanding and more detailed descriptions about drug-related toxicity at the different organ sites. Importantly the computational models developed by Dr Küpfer would provide a highly flexible template for integrating and contextualising the various experimental data generated by the HeCaToS project partners.



Olivia Clayton obtained a BSc in Biochemistry and a Master's degree in Bioengineering from the Paul Sabatier University of Toulouse, France. Olivia joined the HeCaToS project in November 2015 as a Senior Associate, working in the mechanistic safety department headed by Dr Adrian Roth at Roche (Basel). Olivia performs the *in vitro* drug toxicity assays on the 3D cardiac and hepatic microtissues, and is responsible for generating valuable samples for subsequent omics analysis. Her cardio or hepato-toxicant assays include 3 daily concentration adjustments to closely mimic exposure *in vivo*. Olivia works closely with both up and down-stream partners to develop and improve the intensive 2-week long treatments she carries out on the 3D microtissues models. In her spare time Olivia enjoys musical theatre, graphic novels and cooking.

## Recent Project Publications

Project participants have worked hard to communicate what they have learnt in this project to the public through research publications.

### **Funding from the HeCaToS project has been acknowledged in the following publications:**

---

Dent et al., Imaging phase separation in model lipid membranes through the use of BODIPY based molecular rotors. *Physical Chemistry Chemical Physics* 17, 18393-18402 (2015).

Devaux et al., Long noncoding RNAs in cardiac development and ageing. *Nature Reviews Cardiology* 12, 415-425 (2015).

Hardt et al., ToxDB: pathway-level interpretation of drug-treatment data. *Database-the Journal of Biological Databases and Curation*, (2016).

Herwig et al., Analyzing and interpreting genome data at the network level with ConsensusPathDB. *Nat. Protocols* 11, 1889-1907 (2016).

Koufaris et al., Systematic integration of molecular profiles identifies miR-22 as a regulator of lipid and folate metabolism in breast cancer cells. *Oncogene* 35, 2766-2776 (2016).

Land, et al., A Spatially Detailed Model of Isometric Contraction Based on Competitive Binding of Troponin I Explains Cooperative Interactions between Tropomyosin and Crossbridges. *PLOS Computational Biology* 11, (2015).

Madej et al., A Parameterization of Cholesterol for Mixed Lipid Bilayer Simulation within the Amber Lipid14 Force Field. *Journal of Physical Chemistry B* 119, 12424-12435 (2015).

Piers et al., Myocardial scar predicts monomorphic ventricular tachycardia but not polymorphic ventricular tachycardia or ventricular fibrillation in nonischemic dilated cardiomyopathy. *Heart Rhythm* 12, 2106-2114 (2015).

Rasche, et al., ARH-seq: identification of differential splicing in RNA-seq data. *Nucleic Acids Research* 42, (2014).

Skjevik et al., All-atom lipid bilayer self-assembly with the AMBER and CHARMM lipid force fields. *Chemical Communications* 51, 4402-4405 (2015).

### **The HeCaToS project has been mentioned and cited in the following publications:**

---

Gocht et al., The SEURAT-1 Approach towards Animal Free Human Safety Assessment. *Altex-Alternatives to Animal Experimentation* 32, 9-24 (2015).

Hendrickx et al., diXa: a data infrastructure for chemical safety assessment. *Bioinformatics* 31, 1505-1507 (2015).

Krauskopf et al., Development and regulatory application of microRNA biomarkers. *Biomarkers in Medicine* 9, 1137-1151 (2015).