

HeCaToS Newsletter

Hepatic and Cardiac Toxicity Systems modelling (HeCaToS)

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Editorial Note

Welcome to the third issue of the HeCaToS Newsletter!

HeCaToS project has just completed its fourth year and is now entering at the final year. HeCaToS aims to establish *in silico* prediction models for human heart and liver toxicity, and after four consecutive years of fruitful collaboration between fourteen partners across Europe, interesting results have been obtained and published in high impact journals. During these four past years, we designed assays using 3D human cardiac and hepatic cell models to mimic drug exposure to cardiac and liver toxicants based on *in vivo* PK profiles. Data generated by cross-omics approaches and functional analytical techniques were utilized to retrieve information on key cellular toxic events. Both *in vitro* and clinical data from biopsies of drug induced liver and heart injury provided a framework to build up *in silico* prediction models.

From 15-18th of November, all partners will meet again in Valencia for the 4th Annual Meeting to present and discuss results of the project. We are looking forward to this key event!



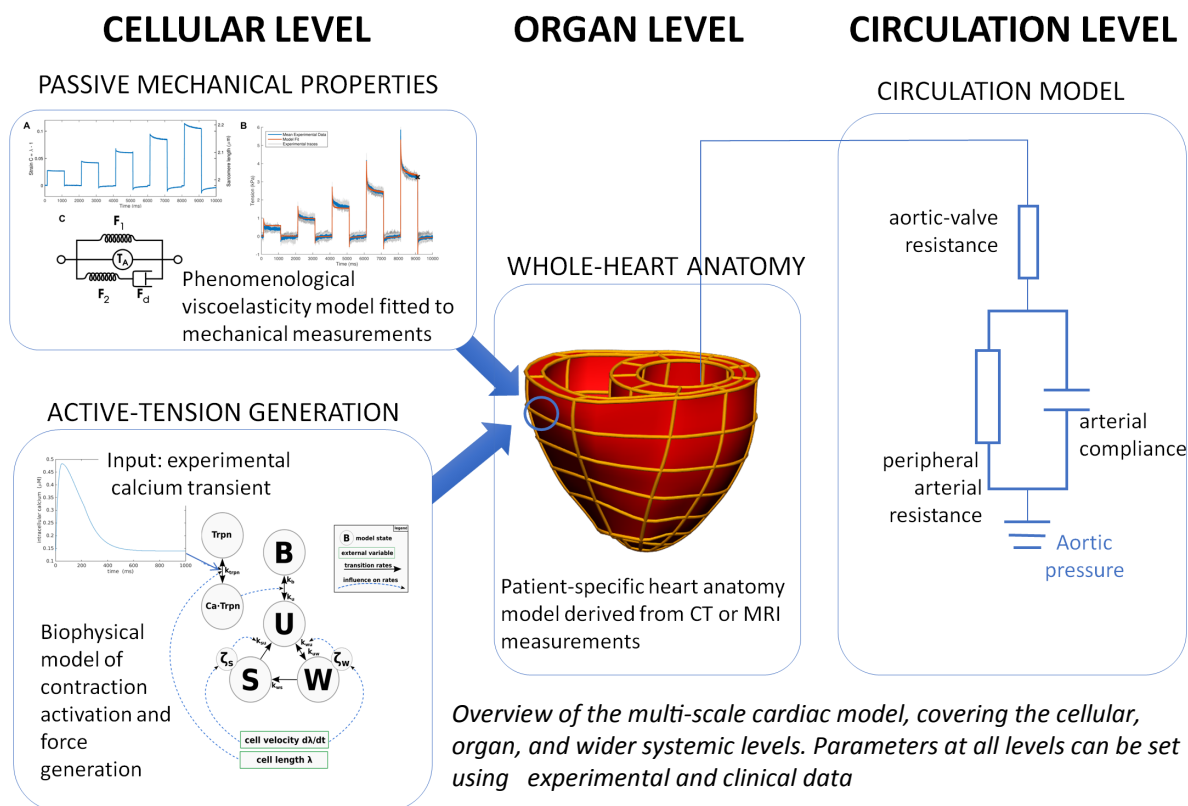
4th HeCaToS Annual Consortium Meeting

Valencia - Spain
November 15-17, 2017

Multiscale modelling of doxorubicin cardiotoxicity

By Dr. Alexandre Lewalle, Dr. Steven Niederer (King's College London)

The impact of the anthracyclines on cardiac function has been extensively documented over decades, but experimental and clinical studies have yielded mostly a piece-wise picture of cardiotoxicity that remains to be integrated. The response to a drug is often multi-faceted, potentially involving multiple subsystems within the heart, and therefore a better understanding of drug-induced heart failure hinges on an estimation of the relative contributions and interactions of the different underlying mechanisms following drug exposure. This objective is unfortunately beyond the reach of experiments. However, data-driven computational modelling provides a framework for simulating and analysing the mechanisms that collectively govern cardiac function *in silico*, using available experimental and clinical data to reproduce the behaviour of the real system with maximum consistency.



By using such models to perform virtual “experiments”, we can investigate the effect of drug exposure on specific physiological parameters in drug-induced heart failure. Within this approach, intracellular- and tissue-scale parameters can be varied independently or synchronously, in consideration of patient data, to assess their influence on global phenotypes.

Our work within the HeCaToS project has sought to elucidate the mechanistic basis for observed differences in cardiac phenotypes resulting from doxorubicin cardiotoxicity. We first developed a generic finite-element computational model of the heart, incorporating state-of-the-art knowledge of cardiac behaviour. This model is designed to solve the system of ordinary differential equations (ODEs) expressing mechanical balance of forces in the contracting heart tissue.

Next, using clinical measurements of the heart anatomy and blood-ejection characteristics (left-ventricular ejection fraction, maximum ejection pressure), we calibrated the phenomenological parameters of the generic model to reproduce the organ-scale behaviour observed in healthy humans (the “baseline” phenotype). We then investigated how these baseline parameters can be modified to yield the corresponding phenotypes of doxorubicin-treated patients. Using this approach, we identified two potential modes of doxorubicin-driven transformation of the heart, involving either the passive elastic properties or the active contraction mechanisms.

By considering measurements done on HeCaToS patient biopsies, we now seek to relate differences observed at the intracellular and tissue levels (e.g. collagen content, and protein abundances measured by mass spectrometry) to the phenomenological model parameters. Hence, we aim to elucidate which of these two modes, passive or active, is the most likely dominant contribution to heart-failure.

Integrating multiple scales of biological organization: Combining physiology-based pharmacokinetic (PBPK) and cellular response modeling

By Dr. Lars K pfer (RWTH Aachen University)

Multi-scale models simultaneously describe the distribution of a drug within the body as well as the resulting toxic effect at cellular and tissue scale. At the organism level, physiologically-based pharmacokinetic (PBPK) models are applied to simulate drug ADME (ADME: Absorption, distribution, metabolism and excretion) processes and to quantify drug exposure in target and off-target tissue. PBPK models describe the physiology of the human body at a large level of mechanistic detail and are based on curated collections of physiological parameters such as organ volumes, surface areas, and blood flow rates. In addition, PBPK models may furthermore be used to estimate tissue-plasma partition coefficients from drug specific physicochemical properties such as lipophilicity or molecular weight. Taken together, this information allows the quantification of drug concentration profiles in the interstitial environment of tissues and organs, which may in turn be used as input concentrations for dedicated response models at the cellular scale.

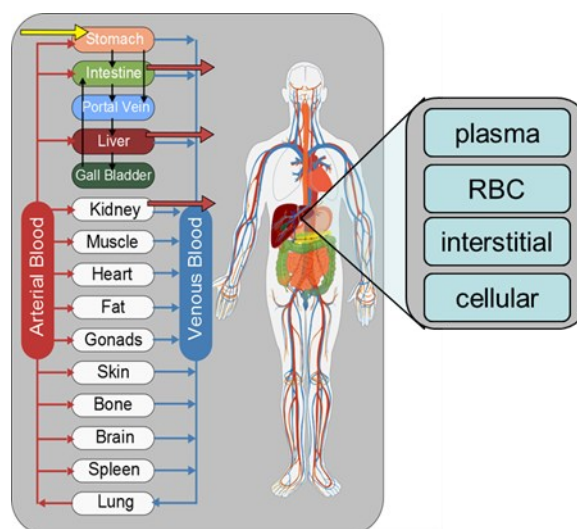


Figure 1: Physiologically-based pharmacokinetic (PBPK) modelling

Different modelling concepts from computational systems biology may be used, such as interaction graphs, stoichiometric, or dynamic models to describe responses at the cellular scale in the face of extracellular perturbations. The choice of a particular modelling formalism is largely driven by the toxic effect which needs to be investigated. For example, stoichiometric models may be used to describe depletion of endogenous metabolites and co-factors in the face of a drug-induced perturbation of cellular metabolism, while interaction graphs are rather suited to identify regulatory drug effects.

The group at the RWTH Aachen has developed several strategies for vertical model integration across different scales of biological organisation, to address different clinical manifestations of drug-induced liver injuries (DILI). The basic idea underlying all of these concepts is to apply the interstitial drug concentration profiles simulated with PBPK models to quantify extracellular tissue exposure. One of these concepts, termed PICD (PICD: PBPK-based *in vivo* contextualisation of *in vitro* gene expression data), allows for example the analysis of *in vitro* omics data within a whole-body context.

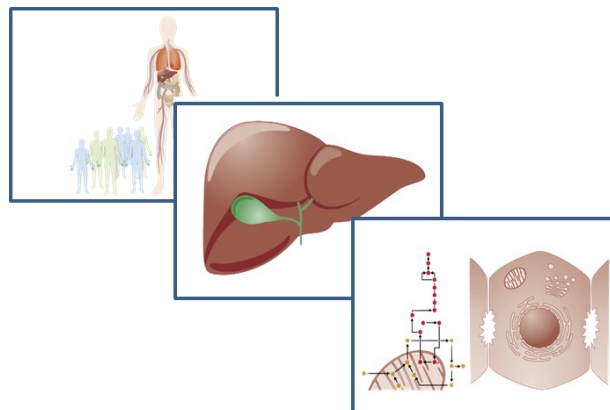


Figure 2: Vertical integration and multiscale modelling

The basic idea of PICD is to identify drug doses through reverse dosimetry which had to be given *in vivo* at the patient level to achieve the same drug exposure as applied in an *in vitro* cell culture experiment. Dose–response curves can thus be generated for all *in vitro* time points by mapping *in vitro* toxicity data to the identified *in vivo* doses. PICD has so far been applied in three studies using published omics data from the Open TG-GATEs library (Igarashi et al. 2015). The approach has amongst others been used (1) to analyse cases of acute azathioprine-induced DILI (Thiel et al. 2017b), (2) to compare patterns of pathway activation in a set of 15 marketed hepatotoxicants (Thiel et al. 2017c), and (3) to investigate cellular expression responses during the co-administration of caffeine and acetaminophen (Thiel et al. 2017a). These efforts will be substantially facilitated in the future with HeCaToS data being generated with a model-based assay design that mimics *in vivo* drug concentrations in human patients (Kuepfer et al. 2017).

Further concepts applying physiologically-based modelling to analyse further manifestations of DILI such as hepatocellular toxicity or cholestasis are currently developed at Aachen. In each case, PBPK models are used to account for distribution of compounds at the whole-body level to quantify inducing drug exposure at tissue level. This makes PBPK an important building block for any approach aiming for vertical integration of models up to an organism scale.

References

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Who's who?



Prof. Dr. Pilar Sepúlveda is an Associated Professor of Histology at CEU-Cardenal Herrera University of Valencia. In 2009, she joined the Hospital La Fe Research Centre (Valencia, Spain) as research fellow and in 2014 she was integrated in the Regenerative Medicine and Heart Transplantation Unit where she is currently Head of this unit. Her research interests focus on cardiovascular cell therapy with adult stem cells and exosomes. Particular focus is on the screening of cardio-protective compounds using iPSC derived cardiomyocytes. Within HeCaToS, she seeks to elucidate the role of miRNA as predictive tools of cardiac induced toxicity in anthracycline treated patients.



Dr. Nathalie Selevsek is a senior scientist at the Functional Genomics Centre, a joint core facility of the ETH Zurich and the University of Zurich. After completing her PhD in biology at the Biochemical Engineering Department in Saarbrücken (Germany), in 2008, she joined Prof. Ruedi Aebersold's lab for a Postdoc at ETH Zurich, where she worked on the development and application of mass spectrometry-based proteomics technologies in systems biology and biomedical research. Within HeCaToS, she is applying proteomics to investigate human liver and heart toxicity using 3D microtissues as *in vitro* models.



Dr. Ugis Sarkans is a technical team leader at the European Bioinformatics Institute (EBI), a part of the European Molecular Biology Laboratory. He completed his PhD in computer science at the University of Latvia, and joined EBI in August 2000. Ugis has been involved in developing community standards for life sciences, as well as establishing and running several data resources, most notably, ArrayExpress and the BioStudies database. His main professional interest is building infrastructures for scientific data and knowledge management. In the context of HeCaToS project, he is responsible for creating the data management infrastructure, for data curation and data warehousing in the BioStudies database.

Recent Project Publications

Below you will find all research articles published since the previous issue of the HeCaToS Newsletter in April 2017, demonstrating the progress of the scientific work and the high impact in the scientific community.

Kuepfer, L., O. Clayton, C. Thiel, H. Cordes, R. Nudischer, L. M. Blank, V. Baier, S. Heymans, F. Caiment, A. Roth, D. A. Fluri, J. M. Kelm, J. Castell, N. Selevsek, R. Schlapbach, H. Keun, J. Hynes, U. Sarkans, H. Gmuender, R. Herwig, S. Niederer, J. Schuchhardt, M. Segall and J. Kleinjans (2017). "A model-based assay design to reproduce in vivo patterns of acute drug-induced toxicity." *Archives of Toxicology*.

Niederer, S. A., B. L. de Oliveira and M. J. Curtis (2017). "The opportunities and challenges for biophysical modeling of beneficial and adverse drug actions on the heart." *Current Opinion in Systems Biology* 4(Supplement C): 29-34.

Lewalle, A., S. Land and S. Niederer (2017). "Development of a Patient-Based Computational Modeling Framework for Analyzing the Mechanisms of Doxorubicin Cardiotoxicity." *The FASEB Journal* 31(1 Supplement): lb713-lb713.

Sarkans, U., M. Gostev, A. Athar, E. Behrangi, O. Melnichuk, A. Ali, J. Minguet, J. C. Rada, C. Snow, A. Tikhonov, A. Brazma and J. McEntyre (2017). "The BioStudies database—one stop shop for all data supporting a life sciences study." *Nucleic Acids Research*: gkx965-gkx965.

Thiel, C., H. Cordes, I. Conde, J. V. Castell, L. M. Blank and L. Kuepfer (2017). "Model-based contextualization of in vitro toxicity data quantitatively predicts in vivo drug response in patients." *Archives of Toxicology* 91(2): 865-883.

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