UK Quantitative Systems Pharmacology Network

Exchange Workshop 2

2nd to 4th July 2018 - University of Reading, UK.

Draft Programme

(Please see page 4 for abstracts)

Monday 2nd July

10.30-11.10 Registration & coffee – Henley Business School (G03)
11.10-11.20 Welcome (G15 Lecture Theatre)
Drug Absorption
11.20-12.10 ***Over 30 years of mechanistic modelling of drug dissolution, absorption, the gut wall and oral bioavailability: A good time to pause for reflection?*** Adam Darwich (University of Manchester)
12.10-12.40 ***P-glycoprotein (Abcb1) expression and activity are sex-, feeding- and circadian time dependent, implications for mechanistic modelling*** Annabelle Ballesta (INSERM & Paris Sud University/University of Manchester)
12.40-13.10 ***TBA***
13.10-14.00 Lunch (G03 & G04)
14.00-14.30 ***TBA***
14.30-15.00 ***The dynamics of a dimerization model*** Philip Aston (University of Surrey)
Clinical Data & Modelling
15.00-15.50 ***The Mastermind Research approaches- on the use of mathematical modelling to predict human CNS PK and PKPD*** Elizabeth CM de Lange (Leiden)
15.50-16.30 Afternoon tea (G03 & G04)
16.30-17.45 Breakout group discussion (G04, 101 & 102)
17.45-18.00 Summary of Day 1
18.00-19.00 Accommodation check-in (Windsor Hall)
19.00-20.30 Dinner (Eat @ The Square)

Tuesday 3rd July (Poster day)

Toxicology and Adverse Events
9.00-9.50 ***Maths and stats in toxicological risk assessment*** John Paul Gosling
9.50-10.20 ***Multiscale modelling of drug transport in Systems Pharmacology*** Joseph Leedale (Liverpool John Moores University)
10.20-10.50 ***Blood flow and solute transfer in the human placenta*** Igor Chernyavsky (University of Manchester)
10.50-11.20 Morning tea with posters (G03 & G04)
Validation & Uncertainty Quantification

11.20-12.10 ***TBA*** Douglas Ferguson (AstraZeneca)
12.10-13.00 ***Calibrating cardiac cell models using Bayesian history matching*** Richard Clayton (University of Sheffield)
13.00-14.00 Morning tea with posters (G03 & G04)
14.00-14.30 ***Comparing parameter estimation methods for cardiac ion current models*** Michael Clerx (University of Oxford)
14.30-15.00 ***Variance based global sensitivity analysis of a mechanistic physiological absorption model for BCS I-IV compounds*** Nicola Melillo (University of Pavia/University of Manchester)
Toxicology and Adverse Events (cont …)
15.00-15.50 ***TBA*** Richard Currie (Syngenta)
15.50-16.30 Afternoon tea with posters (G03 & G04)
16.30-18.00 Breakout discussion (G04, 101 & 102)
18.00-18.15 Summary of Day 2 (G15 Lecture Theatre)
18.15-19.05 Break
18.45-19.30 Reception (Meadow Suite, Park House)
19.30-21.00 Workshop dinner (Meadow Suite, Park House)

Wednesday 4th July

9.00-9.30 Network update
Data and Clinical Modelling
9.30-10.20 ***Modelling Anthracycline Cardiac Toxicity*** Steven Niederer (Kings College London)
10.20-10.50 ***Improving the prediction of local brain drug distribution profiles with a new mathematical model*** Esmeé Vendel (Leiden University)
11.50-11.20 Morning tea (G03 & G04)
11.20-11.50 ***Towards multiscale PBPK/PD modelling: Integrating Systems Biology models of interferon alpha in a whole body*** Priyata Kalra (University of Heidelberg)
11.50-12.20 ***Case study of enhancement of a Quantitative Systems Pharmacology model of hypertension and applications to novel drug development*** Maithreye Rengaswamy (Vantage Research)
12.20-13.30 Lunch (Entrance to HBS)
13.30-13.50 ***Multi-scale modelling of anthracycline cardiotoxicity in heart contraction*** Alexandre Lewalle (Kings College London)
Future Applications of QSP
13.50-14.40 ***Adaptation and homeostasis in the immune system*** Deborah Dunn-Walters (University of Surrey)
14.40-15.30 ***TBA*** Andrew White (Unilever)

15.30-15.45 Close of Meeting
15.45-16.15 Afternoon tea
16.15 Departure

ABSTRACTS

INVITED TALKS

Over 30 years of mechanistic modelling of drug dissolution, absorption, the gut wall and oral bioavailability: A good time to pause for reflection?

Adam S. Darwich
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The first mechanistic models of drug absorption were academically led research efforts aimed at developing early screening tools to inform compound selection in pharmaceutical research and development (R&D) (Dressman and Fleisher, 1986). Current physiologically-based pharmacokinetic (PBPK) absorption models share many aspects of their early predecessors, yet much progress have been made on extending these to include advanced formulation and dissolution behaviour, luminal fluid dynamics, transporter effects, gut wall metabolism and more (Kostewicz *et al*., 2014).

Today, PBPK absorption modelling is applied throughout pharmaceutical R&D, from candidate selection to preclinical drug development, prediction of biopharmaceutics effects, post-approval formulation development and bioequivalence. As a consequence there has been considerable effort to extend the use of PBPK absorption modelling in the context of regulatory submissions (Margolskee *et al*., 2017). Yet, many challenges still remain, not least because of the difficulty in directly verifying the many stages of the absorption process through clinical validation.
Here the current state of the science, future outlook, and the challenges that are being faced in model development and validation are highlighted. Further, we reflect on how quantitative systems pharmacology can be integrated with PBPK absorption modelling to gain further insight into some of the underlying mechanisms that govern oral bioavailability in healthy and gut disease.

References

Dressman, J. B. & Fleisher, D. 1986. Mixing-tank model for predicting dissolution rate control or oral absorption. *J Pharm Sci,* 75**,** 109-16.
Kostewicz, E. S., Aarons, L., et al. 2014. PBPK models for the prediction of in vivo performance of oral dosage forms. *Eur J Pharm Sci,* 57**,** 300-21.
Margolskee, A., Darwich, A. S., et al. 2017. IMI - Oral biopharmaceutics tools project - Evaluation of bottom-up PBPK prediction success part 2: An introduction to the simulation exercise and overview of results. *Eur J Pharm Sci,* 96**,** 610-625.

The Mastermind Research approaches- on the use of mathematical modelling to predict human CNS PK and PKPD

Elizabeth CM de Lange
Leiden Academic Centre for Drug Research, Leidien University, The Netherlands.

CNS drug development and adequate CNS disease treatment has been hampered by inadequate consideration of CNS pharmacokinetic (PK), pharmacodynamics (PD) and disease complexity (reductionist approach). We have to improve by using integrative model-based approaches to understand the time- and condition dependent interrelationships between CNS PK and PD processes to be able to predict PK and PD in other conditions (Mastermind Research approaches).

Here, a few examples with increasing complexity will be given on 1) blood-brain barrier transport and effects of L-DOPA in a unilateral rat model of Parkinsons's disease; 2) the development and validation of a translational model to predict remoxipride PKPD in human; and 3) the

development and validation of a generic physiologically-based CNS drug distribution model to predict human CNS PK in multiple physiologically relevant compartments.

Maths and stats in toxicological risk assessment

John Paul Gosling
School of Mathematics, University of Leeds, UK.

There has been increasing pressure to end the overreliance on animal experiments and to consider non-animal approaches when making decisions about human safety. Mathematical models are becoming a viable alternative. The costs of running mathematical models are considerably less than the costs of laboratory experimentation. However, just as mice and rats are not humans, a mathematical model is not a human, but such models can be thought to be representative of a human's response to chemical exposure.

There has yet to be a general acceptance of the value of mathematical models in the context of safety assessment. The difficulty is in bringing the results from complicated mathematical models into risk assessments that have been historically driven by animal data. Understanding of biological systems, as laid out in adverse outcome pathways, can be harnessed to make mathematical models more accessible to risk assessors. In this talk, I will highlight some key principles of using mathematical models within an adverse outcome pathway framework that could greatly increase the acceptance of mathematical models by risk assessors. The presentation will give an overview of mathematical models to characterise and quantify uncertainty, covering the different types of uncertainty faced, tiered approaches to handling uncertainty in toxicology and how to deal with the gaps between models (both in vitro and in silico) and reality.

TBA

Ferguson
AstraZaseneca

Calibrating cardiac cell models using Bayesian history matching

Richard H. Clayton
Department of Computer Science, University of Sheffield

Calibrating cardiac cell models against experimental action potential measurements can be difficult because experimental action potentials are variable, and the number of model parameters is often large. History matching is an approach to this problem where the cardiac cell model is replaced by a fast running statistical model, or emulator, enabling parameter space to be explored efficiently. The model parameter space is reduced iteratively. At each iteration, the emulator is evaluated at a large number (up to 3 million) of locations in parameter space, and the outputs are compared with experimental observations, taking into account the variance of experimental observations and the variance of the emulator. In the talk I will describe this approach, and discuss the benefits and challenges around using it with cardiac cell models.

TBA

Richard Currie
Syngenta

Modelling Anthracycline Cardiac Toxicity

Steven Niederer
Biomedical Engineering Department, Kings College London

The clinical use of the anthracycline doxorubicin is limited by its cardiotoxicity. Doxorubicin cardiac toxicity occurs both acutely when the compound is present and chronically years after the drug was last delivered. There are direct effects of the drug binding to specific proteins and secondary effects caused by protein remodelling in response to the drug. We have used computational models to investigate the most important pathways explaining the toxic phenotypes in cardiac myocyte calcium handling, electrophysiology and metabolism. Here we show how we can use detailed biophysical models to integrate disparate experimental data into a common framework and test hypothesised mechanisms.

Adaptation and homeostasis in the immune system

Deborah Dunn-Walters
Faculty of Health & Medical Sciences, University of Surrey

Some immune receptors are invariant, and help the innate arm of the immune system to provide immediate general help in an emergency. However, this protection is not able to provide sterilising immunity in the longer term. To completely defeat a pathogen the adaptive immune system is shaped to provide specificity against individual antigens, and the memory of this specificity is retained in memory immune cells that can respond more quickly upon secondary challenge. This is the basis of vaccination, which remains the most effective preventative measure we have for human health. The diversity of human T cell receptors, and B cell receptors (which are also secreted as antibodies), is huge. There are theoretically over 1018 different antibodies that can be made by gene rearrangement/combinatorial assortment/somatic hypermutation processes. Hence in theory we could have receptors to bind every binding site on every pathogen. When we are challenged, the repertoire is changed to increase representation of the useful antibodies. There is a flip side to this huge diversity, in that we must avoid self-binding. So, tolerance mechanisms exist to delete self-reactive cells. Recent developments in high throughput sequencing and single cell technologies are producing large datasets to help in our understanding of immune repertoires. Understanding the trade-offs in adaptive immune repertoire development, and the likely binding specificities of immune receptors, can help in antibody discovery projects and is important in order to understand vaccine efficacy, autoimmunity, allergy/hypersensitivity, immunodeficiency, diseases of chronic inflammation and cancer immunity.

TBA

Andrew White
Unilever

CONTRIBUTED TALKS

P-glycoprotein (Abcb1) expression and activity are sex-, feeding-, and circadian time-dependent, implications for mechanistic pharmacokinetics modeling.

Alper Okyar[1], Elisabeth Filipski[2], Enza Piccolo[3], Narin Ozturk[1], Helena Xandri-Monje[4], Zeliha Pala[1], Kristin Abraham[4], Ana Rita Gato de Jesus Gomes[4], Mehmet N. Orman[7], Xiao-Mei Li[2], Robert Dallmann[4], Francis Lévi[2,4,6], Annabelle Ballesta[2,4,5].

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[4]Division of Biomedical Sciences, Warwick Medical School, University of Warwick, UK.
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[7] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ege University, Bornova, Turkey.

P-glycoprotein (*P-gp*) is a main efflux transporter that mediates the detoxification of many anticancer drugs and other xenobiotics. Both *P-gp* expression and toxicities of *P-gp* substrates may largely vary according to the patient's sex, feeding status, and circadian timing system that rhythmically regulates the organism over 24h. A molecular understanding of inter- and intra-patient variations of *P-gp* activity would allow for optimizing drug exposure though personalized administration schedules. A systems pharmacology approach enabled us to simultaneously study the effect of sex, feeding status and circadian time on *P-gp* activity in the gastro-intestinal system of mice. Robust circadian changes in *P-gp* mRNA and protein levels were demonstrated in the ileum of mice of both sexes, with larger amplitudes and earlier phases in females as compared to males. In the colon, no circadian rhythm was found in *P-gp* mRNA amounts whereas protein levels only displayed time-dependent variations in females. Similarly, liver *P-gp* protein expression showed 24h-rhythm in females, but not in males. *P-gp* activity was assessed through multi-factorial PK studies of talinolol, a pure *P-gp* substrate. Statistically significant differences were found in plasma, ileum and liver talinolol PK profiles according to sex, feeding status and circadian timing. Physiologically-based modelling revealed that *P-gp* activity circadian mean was higher in males compared to females in both ileum and liver, for all feeding conditions. *P-gp* activity circadian amplitudes were consistently higher in females than in males. *P-gp* activity circadian maxima significantly varied with respect to sex by up to 10h. Fasting increased *P-gp* activity in both liver and ileum of male mice, and only in ileum of females, and decreased *P-gp* activity circadian amplitudes. The mathematical model of P-gp circadian activity that was developed in the gastro-intestinal system provided parameter estimates according to sex and feeding status. It can further be incorporated into physiologically based PK models of any *P-gp* substrates for personalizing their circadian administration.

The dynamics of a dimerisation model

Philip J. Aston, Gianne Derks and Christine Gavin
Department of Mathematics, University of Surrey, UK.

We consider a dimerisation model in which a receptor can bind to two ligand molecules which is an extension of the well studied target mediated drug disposition (TMDD) model where the receptor binds to only one ligand molecule. The binding is assumed to be the fastest process which gives a separation of time scales. When a single ligand dose is administered, there is a short (fast) phase in which the concentration of the monomer (receptor bound to one ligand molecule) rapidly increases and then decreases again as it is formed and then converted to the dimer (receptor bound to two ligand molecules). After this fast initial phase, the concentration of the monomer is observed to be very small for a relatively long time period. However, once the concentration of the ligand is sufficiently small, there is another rapid increase in the monomer concentration before it eventually

settles back to its final zero value. We consider the mechanism behind this second increase in the monomer.

In phase space, it is found that the increase in the monomer concentration is associated with an intersection of two components of the slow manifold in which an incoming one-dimensional manifold intersects an outgoing two-dimensional manifold. In order to understand this transition, the crucial question is to determine the direction on the two- dimensional outgoing manifold that the incoming trajectory transitions to. We use geometric desingularisation (the blow-up method) to analyse this transition. This enables us to derive an estimate for the peak value of the monomer in terms of the model parameters.

Multiscale modelling of drug transport in Systems Pharmacology

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New drugs are tested for toxic side effects in the laboratory using isolated cells. These toxicity tests traditionally involve cells cultured in a flat, 2D environment. However, emerging experiments where cells are cultured in 3D have been shown to more closely resemble the functionality of cells within the body. While the increasing usage of 3D experiments represent more realistic biology, the underlying physical processes of what happens to the drug in these environments is not fully understood. Our research shows how mathematical models can be used to simulate the activity and transport of drugs in 3D, informing experimentalists on how best to use these systems to test for toxicity.

A multiscale mathematical modelling framework to describe the temporal and spatial dynamics of drugs in multicellular environments will be presented. The model combines information relating to the diffusion, transport and metabolism of chemical species (drugs) in 3D environments. A simplified 3D microscale single-cell model was analysed to study different transport mechanisms by varying boundary conditions on the cell membrane. A more complex multicellular model has been developed to study the effects of cellular arrangement and density on the transport and penetration of drugs to simulate the problem for *in vitro* microtissue environments. Following the preliminary theoretical work, integration of experimental data is incorporated to develop realistic geometries and parameterise the model for a range of pharmacologically realistic scenarios.

Blood Flow and Solute Transfer in the Human Placenta

Alexander Erlich[1], Philip Pearce[2], Gareth Nye[3], Paul Brownbill[3], Romina Plitman Mayo[4], Rohan Lewis[5], Ed Johnstone[3], Oliver Jensen[1], Igor Chernyavsky[1,3]
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[3]Maternal and Fetal Health Research Centre, St Mary's Hospital, Manchester;
[4]Department of Engineering, University of Cambridge; [5]Faculty of Medicine, University of Southampton.

Current approaches assessing reproductive safety of chemical substances in humans are expensive and time consuming and may be of limited relevance as a predictor of adverse effects. The human placenta is a critical life-support system that nourishes and protects a rapidly growing fetus. The human placenta is also a unique organ, with a complex network of fetal vessels packed into thin shells in direct contact with maternal blood. It also differs significantly from placentas of other species both in structure and in function, making it very hard to choose a suitable animal model.

We aim to address a pressing challenge of characterising human placental structure-function relationship and providing better advice on the transfer and potential toxicity of various solutes in pregnancy. This challenge can only be met by a combination of *ex vivo* and *in silico* approaches.

Ex vivo, we employed a versatile perfusion model [1, 2] that maintains the human placenta after birth in near-*in vivo* condition and allows to assess multiple physiological parameters, such as net solute transfer, tissue oxygenation and metabolism. *In silico*, we developed and validated a set of microscopy imaging-based 3D computational and reduced mathematical models [3, 4] that predict key structural and physical determinants for the transport of a wide class of lipophilic and some hydrophilic solutes.

The developed framework captures key features of a complex multi-scale system and may contribute to future placenta-on-the-chip technology that has the potential to transform regulatory, industrial and clinical practice.

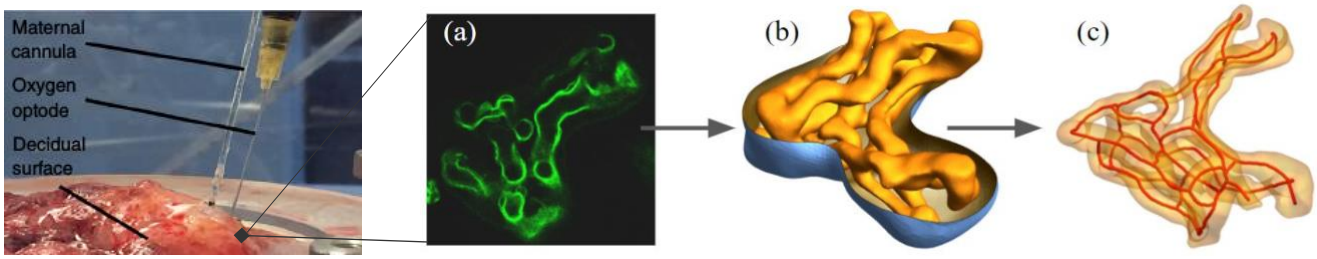

Figure 1. (Left) A close-up look at the *ex vivo* placental perfusion setup [1, 2]. (Right) A pipeline from 3D confocal microscopy to 1D network [3, 4]: (a) a micrograph of feto-placental vascular endothelium; (b) segmented 3D confocal image, with fetal capillary surface shown in yellow and villous shell surface in blue; (c) vascular centrelines used for spatial statistics and reduced 1D network model.

References

[1] Nye G, et al. (2018) *J Physiol* (*in press*; doi.org/10.1113/JP275633).
[2] Nye G, et al. (2017) *Placenta* 57: 328.
[3] Pearce P, et al. (2016) *PLoS ONE* 11: e0165369.
[4] Plitman Mayo R, et al. (2016) *J Biomech* 49: 3780-87.

Comparing parameter estimation methods for cardiac ion current models

Michael Clerx
University of Oxford

Blocking or modulating cardiac ion channels is an important target for anti-arrhythmic drugs, and a major risk factor in general pharmacology. Models of ionic currents, combined into models of the cellular action potential, can be joined together to form multiscale systems physiology models, in which the effects of channel-modulating drugs can be studied. Despite its size (roughly that of a human fist), the heart can be remarkably sensitive to minute changes in ion channel kinetics, which are sometimes accommodated but other times cause lethal disruptions. To make confident predictions about such a system, it is vital that the underlying ion currents are well characterised.

We compare three methods of fitting ion current models to data. First, a traditional `disjoint' method, in which a separate protocol is used to bring out each relevant aspect of channel behaviour. The measured currents are not used directly, but transformed into summary statistics (e.g. plots of peak current against voltage) to which model equations can directly be t. Secondly, the `whole-trace fitting' method, in which the same protocols are used, but instead of deriving summary statistics an

error is defined between the measured and predicted current, and this is minimised by adjusting all model parameters simultaneously. Finally, whole-trace fitting to novel protocols, designed to provide maximum information in a minimal time frame
(Beattie et al. J Physiol, 2018). For each type of fitting, we investigate (1) how well the method constrains the parameters, (2) how the methods perform in the presence of different types of noise, and (3) how the methods fare in unexpected regions of the parameter space, e.g. when channel behaviour has been modified by pharmacological intervention. Our results show how modern parameter estimation techniques can yield models with greater predictive power, while being more robust against unexpected (and more interesting) results.

Variance based Global Sensitivity Analysis of a Mechanistic Physiological Absorption model for BCS I-IV compounds

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There is a strong regulatory interest in the use of sensitivity analysis to evaluate the physiologically-based pharmacokinetic models exploited in pharmaceutical research & drug development [1]. One possible application is the prediction of fraction absorbed and bioavailability for orally administered drugs. The OrBiTo project (Innovative Medicines Initiative) executed an evaluation of various physiological models for drug absorption. Results showed a very highly variability in the prediction [2].

In this context, we performed a variance based global sensitivity analysis (GSA) on a compartmental mechanistic physiological model for drug absorption, based on the CAT model [3], with the aim of identifying key parameters that influence the fraction absorbed (f_a) and the bioavailability (F_{oral}). This analysis was done for each of the four Biopharmaceutical Classification System (BCS) classes: class I (highly permeable, highly soluble); class II (highly permeable, lowly soluble); class III (lowly permeable, highly soluble); and class IV (lowly permeable, lowly soluble). Variance based GSA aims to quantify the importance of each model parameter with respect to a model output *Y*, considering all the parameters in their whole range of variation. The importance of a parameter is related with the fraction of the variance (*V*) of *Y* explained by the variation in that parameter: the higher the $V(Y)$ fraction is, the more important the parameter is [4, 5].

The parameters variability that mainly explain f_a and F_{oral} variances were different for each BCS class and were in accordance with the definition of the classes themselves. For class I compounds, the parameters that mainly explain $V(f_a)$ were related to the formulation properties, for class II compounds to the dissolution process, for class III to both absorption process and formulation properties and for class IV to both absorption and dissolution processes. Considering F_{oral}, the results were similar to those for f_a, with the addition that parameters related to gut wall and liver clearances were important as well in determining $V(F_{oral})$.

This work aimed to identify the importance of different parameters for varied types of drugs, to improve the knowledge of the model and inform the choice of what parameters that need to be more carefully considered.

Improving the prediction of local brain drug distribution profiles with a new mathematical model

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A better understanding is needed of the complex processes that govern the concentration-time profile of a drug in the brain. The brain is not a homogeneous tissue and there are many local differences in tissue characteristics, such as cerebral blood flow, brain cell types, binding sites and brain fluid flow

dynamics. These local differences may influence the local distribution of a drug within the brain. A better understanding of local drug distribution improves the prediction of drug effects. As access to the brain is highly limited, mathematical models provide a helpful tool. These should be based on the physiological processes of drug distribution into and within the brain. The brain is highly perfused by a large network of blood capillaries. Following intravenous or oral administration and subsequent intestinal absorption, the drug circulates in this brain capillary network before entering the brain. To enter the brain, a drug has to cross the blood-brain barrier (BBB), which highly limits transport into the brain. Once a drug has passed the BBB, it is distributed in the brain fluids, including the brain extracellular fluid (ECF). Within the brain ECF, a drug binds to both specific binding sites, which makes the drug exert its effect, and non-specific binding sites, which prevents the drug from exerting its effect and may cause side-effects. To get a better insight into the distribution of drugs within the brain, we create a new 3D spatial model. This model describes a 3D brain tissue unit that represents a part of the brain tissue and consists of the blood capillaries surrounding the brain extracellular fluid (ECF) that includes drug binding sites. This unit could be considered the smallest building block of the brain in terms of drug distribution. We explicitly describe blood flow, BBB transport, distribution within the brain ECF and drug binding in one model, which has not been done before. We model how a drug is transported through the blood by the cerebral blood flow and exchanges with the brain ECF by passive and active transport across the BBB. We describe the change in the concentration of free and bound drug in the brain ECF by a system of partial differential equations. For this we take into account diffusion, the unidirectional brain ECF bulk flow and the kinetics of drug binding to specific as well as non-specific binding sites.

We study the model with analytical methods and numerical simulations. This allows us to examine the effect of processes important to drug distribution and effect, such as passive and active transport across the BBB and drug binding kinetics, on the local concentration-time profiles of free and bound drug. Moreover, the model allows us to generate a local distribution profile of a drug within the brain.

The ultimate goal of our model is to represent (part of) the brain tissue by a network of brain tissue units, in which each brain tissue unit may be assigned different physiological properties to reflect the heterogeneity of the brain.

Towards multiscale PBPK/PD Modelling: Integrating Systems Biology Models of Interferon Alpha in a Whole Body

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Background: More recently, mechanistic Physiologically Based Pharmacokinetic (PBPK) Models have been successfully used as a tool for predicting dose recommendations and selecting drug candidates. Therapeutic proteins are an increasingly important class of drugs and compared to small molecules their pharmacokinetics and pharmacodynamics have characteristic difference due to their large molecule size and ubiquitous presence in the physiological environment.

Method: Using the case of IFN-α treatment in humans we here present a novel approach for the integration of molecular pathway models at the cellular level into physiology-based pharmacokinetic (PBPK) models at the organism scale.

Results: The multi scale model describes the whole-body distribution of IFN-α and the resulting cellular signalling response in the JAK/STAT pathway. It captures the non-linear pharmacokinetic behaviour of IFN-α within the body shedding light on the changes in signalling behaviour when considered an in-vivo context.

Conclusion: This work is a significant step towards quantitative systems pharmacology. The goal of this work is to understand the mutual dependencies of the tissue specific pharmacokinetic availability of IFN-α and the resulting therapeutic response at the cellular signaling level. Moreover, it provides generic workflow for the integration of cellular models based on in-vitro data within an in-vivo context.

Keywords : Quantitative Systems Pharmacology, Systems Biology, IFN-α Signalling Pathway, Modelling, Multicellular Systems Biology.

Rengaswamy - TBC

Multi-scale modelling of anthracycline cardiotoxicity in heart contraction

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The anthracycline family of chemotherapeutic drugs have well-known cardiotoxic side effects. However, decades of research have yielded a piece-wise picture of cardiotoxicity that remains to be integrated. Data-driven computational modelling provides a framework for simulating and analysing the mechanisms that collectively govern cardiac function, and hence for investigating the impact of drug exposure on specific physiological parameters in drug-induced heart failure. In effect, these modelling tools constitute a virtual *in-silico* laboratory for exploring physiological parameters in the light of clinical measurements, and hence for providing mechanistic insight into the causes of heart failure.

One issue of interest for understanding impaired cardiac function is the relative contribution of changes in the passive and active properties of the heart tissue, following drug exposure. To approach this question, we used a multi-scale computational model of the heart to simulate features of the cardiac cycle that are readily measured as part of the routine clinical treatment of cancer patients. The model implements mechanisms ranging from the cellular to the whole heart level, to reproduce cardiac behaviour under physiological conditions. In the simulations, an externally imposed calcium signal triggers contraction forces throughout the tissue, eliciting a viscoelastic deformation of the anatomy and the ejection of blood into the circulation. The model parameters are amenable to fitting using direct measurements and data available in the literature.

Using this modelling framework, we compared heart-failure patients receiving anthracycline treatment, with healthy controls. For both cohorts, cardiac anatomy (left-ventricular (LV) cavity dimensions, wall thickness) and LV ejection fraction were characterised using echocardiography measurements. Hemodynamic measurements yielded ejection pressures and heart rates. Biopsies taken from the heart-failure patients provided measurements of the collagen volume fraction and underwent a proteomic analysis by mass spectrometry. The model parameters were explored to reproduce the observed behaviour of each cohort phenomenologically. The resulting combination of measurements and simulations then provides a platform for critically discussing the cellular- and tissue-level mechanisms that potentially contribute to passive and active mechanical behaviour in the context of doxorubicin-induced heart failure.

----------OOO----------