QSP
UK

UK Quantitative Systems Pharmacology Network

Exchange Workshop 2

2nd to 4th July 2018

University of Reading, UK.

Welcome!

Welcome to the Second Exchange Workshop of the EPSRC/MRC co-funded UK Network on Quantitative Systems Pharmacology (QSP).

This three day workshop is structured around the five areas of drug absorption, clinical data & modelling, toxicology and adverse events, validation & uncertainty quantification, and future application areas for QSP.

We have an exciting line up of international speakers, new and established, working in QSP and its related fields in academia and industry. All bring their own distinctive approach to problems directly and indirectly related to QSP research in these areas, each of which provides an opportunity to see QSP in action as well as learn techniques which directly impact QSP research.

Experience shows that our Workshops work the best when everyone gets involved in the discussion and problem solving, so please do get involved in the discussions, regardless of your background and enjoy yourselves!

We are grateful to Ruth Harris for providing administrative support for this meeting, and gratefully acknowledge funding from the Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council UK as well as support from Pfizer, AstraZeneca and GlaxoSmithKline.

On behalf of the UK QSP Organising Committee we hope you enjoy this meeting and welcome your input and feedback.

Marcus Tindall (on behalf of the Organising Committee)

Organising Committee
Prof Leon Aarons (Manchester)
Prof Mike Chappell (Warwick)
Dr Lourdes Cucurull-Sanchez (GlaxoSmithKline)
Prof Gianne Derks (Surrey)
Dr Pinky Dua (Pfizer)
Dr Marcus Tindall (Reading)
Prof Ben Whalley (GW Pharmaceuticals)
Dr James Yates (AstraZeneca)

Meeting Venue
All activities will take place at the Henley Business School, University of Reading, Whiteknights Campus, Reading, RG6 6UD, UK (Please see the campus map on page 5 of this booklet). All lectures will be held in the G15 Lecture Theatre on the Ground Floor. All food, including morning and afternoons teas will be served in G03. We also have the use of room G04 for eating in. Rooms G03, G04, 101 and 102 will be used for breakout discussion at designated times during the Workshop.

A busy campus!
There is significant road and buildings work underway on the Whiteknights Campus the week of the Workshop as well as graduation ceremonies. The campus and Henley Business School are likely to be busy for the duration of the Workshop. We advise all delegates to plan trips accordingly and to not leave valuables lying around.

Registration desk & name badge
This can be found in room G04 of Henley Business School building. Your name badge serves as your unique identification for the meeting whilst on the Reading University Campus. Please do remember to have it with you at all times so University staff and the workshop organisers know who you are and can give you access to the areas you require for the duration of the workshop.

Meeting Programme
A copy of this programme can be downloaded from
www.qsp-uk.net/reading-2018.html.
Paper copies are available at the registration desk in room G03 of Henley Business School.

Morning/Afternoon tea and lunch
Morning and afternoon teas will be served in room G03 of the Henley Business School.

Accommodation
If you have requested accommodation then this has been reserved for you in Stenton Hall on the University Campus. You will be able to check in to your accommodation from 18hrs on Monday 2nd July (time in the Workshop programme has been allocated for this).

Please remember to check out of your accommodation by 10am on the morning of Wednesday 4th July, unless you have arranged additional accommodation with the Organisers. All rooms are pre-paid and participants, unless otherwise agreed with the conference organisers, will need to pay for any extra costs on their departure.

<u>If you have requested additional accommodation you will have been advised prior to the School regarding its availability. If you have not heard from the organisers regarding this, please get in touch with us as soon as possible.</u>

Accommodation reception
This can be found on the ground floor of Windsor Hall and is open Monday to Friday from 8.00 to 20.00hrs.

Breakfast
This will be served in Eat @ the Square from 07:30 until 09:00 hours (Building 7 on the Campus map on page 5).

Monday evening meal
This will be available in Eat at the Square from 19.00-20.45 hours (Building 7 on the Campus map on page 5).

Workshop Dinner
This will be held in the Meadow Suite, Park House on the evening of Tuesday 3rd July. It will be proceeded by a drinks reception in Park House.

Bar
A bar can be found in Park House (Building 8 on the Campus map on page 5) and is open each day from 12.00 to 23.00hrs.

Wifi Access
Wifi access is provided via separate login details for each Workshop delegate. Access details are available from the school registration desk.

Parking & parking permits
All participants who have cars with them should park in the main visitor car park (Car Park 1a) near the Shinfield Road entrance of the University (please see the map on page 5 of this booklet). Parking is free for the duration of the Workshop, but you will need to display the appropriate permit. These can be obtained from the registration desk or by e-mailing the Organisers.

Luggage store
A secure luggage store will be available to all Workshop participants on the Wednesday of the Workshop.

Participant e-mail addresses
Participant e-mails have not been included in this programme given it will appear on the Internet. A separate participant e-mail list is available from the registration desk.

QSP website
Please see www.qsp-uk.net for all details on the UK QSP Network. If you have any suggestions or queries, please contact Marcus Tindall or a member of the Organising Committee.

Workshop queries
If you have any queries during the Workshop please contact Marcus Tindall in the first instance. We will do our utmost to accommodate any requests.


Accommodation Reception (Windsor Hall)
Parking
Stenton Hall
Henley Business School
Park House
Eat at the Square
SHINFIELD ROAD ENTRANCE
EARLEY GATE ENTRANCE
PEPPER LANE ENTRANCE
SPORTS GROUNDS
THE WILDERNESS
HARRIS GARDEN
TOWN CENTRE & LONDON ROAD CAMPUS
ELMHURST ROAD
WHITEKNIGHTS ROAD
NORTHCOURT AVENUE
SHINFIELD ROAD
PEPPER LANE
WILDERNESS ROAD
Academic buildings
Halls of residence
Readybike station
Car parks
Car parks restricted to users of this building
Walking paths
Unlit paths
Bus stop
Pay & display
Pedestrian entrance
WHITEKNIGHTS CAMPUS
SAT NAV RG6 6UR | RG6 7BE FOR EARLEY GATE
University of Reading

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Programme

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 ***Variance based global sensitivity analysis of a mechanistic physiological absorption model for BCS I-IV compounds*** Nicola Melillo (University of Pavia/University of Manchester)
12.40-13.10 ***BioModels: A resource for curated biological and biomedical models*** Rahuman Sheriff (European Bioinformatics Institute, EMBL-EBI)
13.10-14.00 Lunch (G03 & G04)
14.00-14.30 **Use of the Oral Minimal Model Method to Quantify the Effect of Sotagliflozin on Gastrointestinal Glucose Absorption in Subjects with Type 2 Diabetes** Michela Riz (Sanofi-Aventis Deutschland GmbH)
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 (G15 Lecture Theatre)
18.00-19.00 Accommodation check-in (Reception, Windsor Hall Ground Floor for Stenton 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 (University of Liverpool)

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)
<u>Validation & Uncertainty Quantification</u>
11.20-12.10 **Quantifying and Communicating Uncertainty in Human PK and Dose Prediction** Douglas Ferguson (AstraZeneca)
12.10-13.00 ***Calibrating cardiac cell models using Bayesian history matching*** Richard Clayton (University of Sheffield)
13.00-14.00 Lunch with posters (G03 & G04)
14.00-14.30 ***Comparing parameter estimation methods for cardiac ion current models*** Michael Clerx (University of Oxford)
<u>Toxicology and Adverse Events (cont …)</u>
14.30-15.20 **Opportunities and Challenges in identifying and modelling effects on the "DARTable genome" to enable prediction of Developmental and Reproductive Toxicity** Richard Currie (Syngenta)
15.20-15.50 **Extended Reaction Schemes and Drug Targeting** Markus Kirkilionis (University of Warwick)
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)
18.15-18.45 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 UK QSP Network update
<u>Data and Clinical Modelling</u>
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)
10.50-11.20 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
Centre for Applied Pharmacokinetic Research, School of Health Sciences, The University of Manchester, Manchester, UK.

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.

BioModels: A resource for curated biological and biomedical models

Rahuman Sheriff
European Bioinformatics Institute, European Molecular Biology Laboratory (EMBL-EBI)

BioModels (http://www.ebi.ac.uk/biomodels/) is a repository of mathematical models representing biological and biomedical processes. BioModels database offers a platform to share mathematical models easily with systems modelling community and thereby supports model reuse and repurposing. Since its inception in 2005, BioModels has seen a steady growth in the number of models that it hosts. The last content release (June 2017) of BioModels included 1640 models from literature, including kinetic, logical and contain-based models and 143,070 models automatically generated from pathway resources. Last year BioModels had its first ever largest submission of patient derived genome scale metabolic models. These are 6753 patient specific in-silico models representing tumor metabolism across 21 different types of cancer.

Models submitted to BioModels are curated to reproduce simulation results reported in the reference publication to ensure the quality and reproducibility. Furthermore, model components are semantically enriched using cross-references to external database resources and ontologies. We are actively involved in developing resources to support such model annotations. In order to enable the provision of the Minimal Information Required In the Annotation of Models (MIRIAM) we are maintaining a registry of data collections and Identifiers.org, a cross-reference resolving system [2], as well as a set of qualifiers to define the relationship between a model component and the resource used to annotate it. Systems Biology Ontology (SBO), a set of common systems modelling vocabularies used for annotation of models is developed through and for community collaboration [3]. The classic BioModels platform (http://www.ebi.ac.uk/biomodels-main/) primarily supported SBML models whereas the beta release of our current platform based on JUMMP infrastructure supports models encoded in diverse formats including PharmML, mathematica, matlab, COMBINE Archive, etc. Thus, BioModels benefit modelers by providing access to reliable and semantically enriched published models in standard formats that are easy to share, reproduce and reuse.

References

[1] Vijayalakshmi Chelliah, Nick Juty, Ishan Ajmera, Raza Ali, Marine Dumousseau, Mihai Glont, Michael Hucka, Gaël Jalowicki, Sarah Keating, Vincent Knight-Schrijver, Audald Lloret-Villas, Kedar Nath Natarajan, Jean-Baptiste Pettit, Nicolas Rodriguez, Michael Schubert, Sarala M. Wimalaratne, Yangyang Zhao, Henning Hermjakob, Nicolas Le Novère and Camille Laibe (2015) BioModels: ten-year anniversary. Nucleic Acids Research 43 (D1): D542-D548.

[2] Juty N., Le Novère N., Laibe C. (2012) Identifiers.org and MIRIAM Registry: community resources to provide persistent identification. Nucleic Acids Research, 40: D580-D586

[3] Courtot M., Juty N., Knüpfer C., Waltemath D., Zhukova A., Dräger A., Dumontier M., Finney A., Golebiewski M., Hastings J., Hoops S., Keating S., Kell D.B., Kerrien S., Lawson J., Lister A., Lu J., Machne R., Mendes P., Pocock M., Rodriguez N., Villeger A., Wilkinson D.J., Wimalaratne S., Laibe C., Hucka M., Le Novère N. (2011) Controlled vocabularies and semantics in systems biology. Molecular Systems Biology. 7: 543

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, Leiden 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.

Quantifying and Communicating Uncertainty in Human PK and Dose Prediction

Douglas Ferguson
AstraZaseneca

In drug discovery, prospective prediction of human pharmacokinetics facilitates the differentiation of possible clinical candidates and is a key step in the prediction of efficacious clinical dose, optimal dosing regimen and therapeutic index. Of equal importance to the prediction of point estimates for each human PK parameter, is the accurate quantitation and communication of the uncertainty in the point estimates. This presentation describes a

'Monte-Carlo' based approach to estimating prediction intervals for both primary PK parameters (such as Cl and V_{ss}) and key secondary parameters such as C_{max}, half-life & clinical dose.

A number of PK parameter prediction methods (both IVIVe and allometry based) were investigated, using established test sets of clinical drugs, in order to characterize the distribution of measured (population mean) clinical PK parameter values relative to the point estimate predictions. For each method, the distribution of Log(measured/predicted) was characterized (in terms of shape, standard deviation σ and average bias) and used as an estimate of the prediction error distribution associated with that method.

For prospective PK prediction for new clinical candidates, a Monte-Carlo approach was utilized to provide random samples to build posterior distributions of *possible* 'true' values for the population mean of each primary parameter. Each possible 'true' value, resulting from the application of a particular PK parameter prediction method, was obtained by combining the point estimate prediction with a random sample from the associated prediction error distribution. The posterior distributions of possible 'true' values for key secondary parameters (such as efficacious dose and C_{max}) were obtained by repeated random sampling of sets of primary parameter estimates from the respective posterior distributions. Each set of primary parameters was then used in the PK function of a relevant PKPD/efficacy model and the dose required to result in a specific extent of predicted clinical efficacy was determined.

Cumulative probability plots were created using the predicted distribution of possible 'true' values and used to provide estimated prediction intervals for each primary and secondary parameter.

This approach has broad utility within drug discovery for the quantitation of risk associated with the inherent uncertainty in prospective PK prediction. Illustrative examples include quantifying the probability that the required clinically efficacious dose will exceed the maximum absorbable dose or that the population mean C_{max} will exceed a defined threshold.

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.

Opportunities and Challenges in identifying and modelling effects on the "DARTable genome" to enable prediction of Developmental and Reproductive Toxicity

Richard Currie
Product Safety Syngenta Jealott's Hill International Research Centre, Bracknell, UK.

Historically the identification of chemical substances with developmental and reproductive toxicity (DART) was achieved by *in vivo* DART testing in the rat and rabbit. However this is resource intensive, slow and does not adequately inform subsequent chemical design should a DART effect be observed. More rapid approaches to assess or predict DART and consequently enable chemical design are therefore highly desirable. However DART effects are difficult to predict given the diversity of biological mechanisms used during ontogenesis. In an attempt to address this Wu *et al.* (2013) developed a decision tree to identify potential for DART based on chemical domains and a small number of receptor binding molecular initiating events (MIEs). Unfortunately, when applied to agrochemical (and consequently also pharmaceutical and veterinary medicine) chemical space, this approach is overly conservative. The use of surrogate tests (mouse embryonic stem cells, Zebrafish (ZF), C elegans, D discoidium) has been proposed. However, our evaluation of a subset of crop protection chemicals demonstrates that these assays are useful for identifying a potential chemical class specific liability, but poor concordance of individual compound results between these surrogates and the mammalian studies makes them unsuitable for replacement of pivotal mammalian DART tests. Consequently, we have developed an approach to generating a tiered testing strategy for DART effects informed by a discovery toxicology programme aimed at developing quantitative adverse outcome pathway (AOP) knowledge of DART effects and the consequent elucidation of the "DARTable genome". The key limitation in prediction for most of these MIEs is a lack of quantitative knowledge of the biological processes alterations required to move the system into an adverse phenotype. As an example we show for one Syngenta CP research project that the use of a combination of *in vitro* assays and *in vivo* pharmacokinetic studies can predict when a target-induced DART (e.g. omphalocele, body wall closure defects) occurs. However, this approach is limited by the need to build experimental knowledge of the relationship between target site substance concentration and toxicity. Exploring whether the approaches used in quantitative systems pharmacology can also be applied to predict toxic doses by the DARTable genome is an area of current research.

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

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

Nicola Melillo[1,2], Leon Aarons[2], Paolo Magni[1] and Adam S. Darwich[2]
[1]Laboratory of Bioinformatics, Mathematical Modelling and Synthetic Biology, Department of Electrical, Computer and Biomedical Engineering, Università degli Studi di Pavia, Pavia, Italy.
[2]Centre for Applied Pharmacokinetic Research, Division of Pharmacy & Optometry, The University of Manchester, Manchester, UK.

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.

Use of the Oral Minimal Model Method to Quantify the Effect of Sotagliflozin on Gastrointestinal Glucose Absorption in Subjects with Type 2 Diabetes

Hans-Christoph Schneider, Ashley Strougo, Britta Göbel, Thomas Klabunde, Raphael Dahmen, Michela Riz
Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

The "oral minimal model method" allows assessing the regulation of postprandial glucose metabolism, extracting valuable and quantitative information at individual level from mixed-meal or oral glucose tolerance test. This approach is extensively used in pathophysiology to

evaluate the capability in controlling glucose levels in different populations and under different medications. Here, we investigated how to extend the oral glucose minimal model by including Urinary Glucose Excretion (UGE), in order to assess the effect of sotagliflozin on the oral glucose absorption in type-2-diabetic (T2D). Sotagliflozin is a dual SGLT1 and 2 inhibitor that reduces plasma glucose by blocking renal SGLT2 and by inhibiting intestinal SGLT1, thus increasing urinary glucose excretion and protracting gastrointestinal glucose absorption. The sotagliflozin effect was quantified in terms of renal threshold for glucose excretion (RTg) and gastrointestinal glucose absorption rate.

In a Phase IIa study, after a 14-day washout period from metformin, T2D patients were randomized to receive placebo or 150 mg or 300 mg QD sotagliflozin in an oral liquid formulation for 4 weeks. Oral glucose tolerance tests (OGTT) were performed in each arm before the treatment period (Day -2) and at the end of treatment (Day 27).

A first modeling step was required to quantify for each subject the effect on RTg using the total amount of glucose excreted over 24h via urine and 8-point self-measured blood glucose. It showed that both sotagliflozin doses significantly lowered RTg from 212.4 ± 44.4 to 108.8 ± 26.3 mg/dL (mean ± SD) under 150 mg QD and from 226.5 ± 27.6 to 96.2 ± 24.0 mg/dL under 300 mg QD.

This first step allowed including subject-specific information on UGE into the oral glucose minimal model. The modified version of the model was then applied to the OGTT data to evaluate the rate of oral glucose appearance in T2D subjects. The model could well describe the glucose profile for each subject and the rate of glucose appearance could be estimated with good precision. In particular, it showed that both sotagliflozin doses reduced the amount of glucose absorbed during the first hour after glucose intake. The area under the curve (AUC) for the rate of oral glucose appearance in the first hour was reduced from Day -2 to Day 27 by 33.3% under 150 mg QD sotagliflozin and by 42.3% under 300 mg QD sotagliflozin. No difference was found in AUC between 0 and 3 hours from Day -2 to Day 27 indicating that sotagliflozin mediated inhibition of intestinal SGLT1 protracts but does not generally block glucose absorption.

The oral glucose minimal model represents a powerful tool to extract quantitative information from clinical data. Here, it could be extended to analyze the rate of oral glucose appearance under sotagliflozin treatment from OGTT data in T2D subjects without the need for complex tracer studies. In particular, the model based analysis could quantify for sotagliflozin the protraction in the time course of oral glucose absorption. This additional effect is attributed to the inhibition of gastrointestinal SGLT1 and is expected to add beneficial effects of this dual SGLT1 and 2 inhibitor in the post-prandial phase.

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

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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.

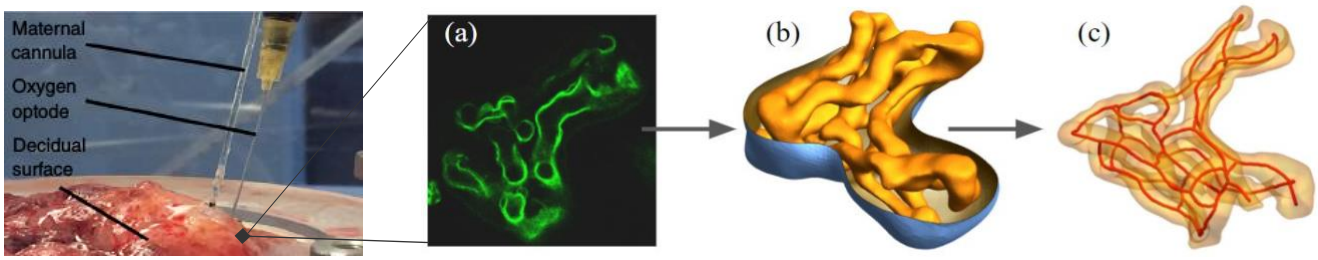

Figure 1. (Left) A close-up look at the *ex vivo* placental perfusion setup [1, 2]. (Right) A pipeline from 3D confocal microscopy to 1D network [3, 4]: (a) a micrograph of feto-placental vascular endothelium; (b) segmented 3D confocal image, with fetal capillary surface shown in yellow and villous shell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

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Comparing parameter estimation methods for cardiac ion current models

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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 fitted. 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.

Extended Reaction Schemes and Drug Targeting

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Reaction schemes are essential in the mathematical modelling of biochemical systems. They describe biochemical reactions on the micro-level, and with the knowledge of molecular copy numbers, the mathematical description can be lifted to the system state by introducing the chemical master equation. In cases particle numbers are very high for all molecular types involved, there is a shortcut description called mass-action kinetics, giving rise to a deterministic dynamical system. In this talk we introduce a fundamental new idea, the extended reaction system, which in contrast to classical reaction schemes allows molecules to have several discrete states, for example molecular conformations. As an application we discuss classical and extended reaction schemes associated to the cell cycle, which is important to understand for many cancer related drug target problems.

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.

Case study of enhancement of a Quantitative Systems Pharmacology model of hypertension and applications to novel drug development

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Hypertension is a prevalent disease worldwide that leads to various complications such as kidney disease and cardiac arrest. Efficacy (measured by reduction of blood pressure) and safety (many adverse events, including unsafe increases in plasma potassium) are the key considerations in development of drugs in this therapeutic area. Quantitative Systems Pharmacology (QSP) models that capture the complex physiology and pharmacology of novel agents allow for hypothesis generation, simulation of virtual patients and support systematic decision making in drug development.

Case Study: Enhancement of a QSP Hypertension Model to simulate a novel therapeutic agent for Hypertension: Vantage Research was required to adapt an existing QSP model of Hypertension (originally created by Entelos Inc (Hallow et al, 2014), to simulate a novel therapeutic agent acts by manipulating signalling in the Renin-Angiotensin-Aldosterone system (RAAS) that is critical to regulation of blood pressure. However, by reasonably well understood feedback mechanisms, this also may cause a pathological increase in plasma potassium in some patients. Of specific interest to the client was the question: Can we predict efficacy and safety measures in hypertensives with diverse pathophysiology for a new therapeutic agent? This talk will present the process of developing, enhancing and applying a multi scale QSP model in collaboration with a Pharmaceutical client to address such questions in clinical development (Nakada et al, 2017).

QSP Methods, Challenges and Approach to Solutions: The talk will be structured based on the key stages of the QSP process (Gadkar et al, 2016).

(1) Add physiology (for potassium regulation) to an existing QSP model requires identification of "top-down" clinical data and "bottom-up" data from public literature.
(2) Create Virtual Patients with variability in newly created physiology are created.
(3) PK/PD properties of the novel compound are added to simulate the trial of interest, and research questions are addressed.

Challenges relating to data availability and quality will be explored in detail: identifying model parameters when data is sparse, resolving conflicts between information, and quantifying the uncertainty in model predictions based on uncertainty in data will be discussed. The need for deep interdisciplinary collaboration between biologists and mathematicians/engineers for effective model building and interpretation of results will be emphasized.

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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.

POSTERS

Stochastic effects and Fractal Kinetics in the Pharmacokinetics of drug transport

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Pharmacokinetics (PK) attempts to model the progression and time evolution of a drug in the human body from administration to the elimination stage. It is the primary quantitative approach used in drug discovery/development (in the pharma industry). The overwhelming majority of PK models are based on equilibrium kinetics with all the reaction kinetics occurring in a well-mixed, homogeneous environment. Of course as is well known, the human body is comprised of heterogeneous media with non-equilibrium chemical kinetics. As a result, the transport processes and reaction mechanisms are often atypical. In this study, we apply ideas from stochastic processes and fractal kinetics in order to better capture the time course of a drug through the body when there is spatial and temporal heterogeneity. We discuss the limitations of the Langevin equation and Bourret's approximation and apply Van Kampen's approach to the random differential equations arising from the stochastic formulation of a standard one compartmental pk model. Although one compartment models can produce good fits if a drug disperses rapidly so that equilibrium is achieved (in all tissues) swiftly, in general they are oversimplifications of a complex process. Thus we also extend the two compartmental model Kearns et al., to incorporate fractal Michaelis Menten kinetics and compare with experimental data from the literature for paclitaxel.

A Mathematical Model and Numerical Results for the Bio-glass (SiO_2-CaO-P_2O_5)

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The development of porous bioactive glasses is part of a multidisciplinary approach. This family of substitutes is particularly adapted to regenerative medicine and suitable for many applications such as prolonged-release drug. For example, in contact with living tissue, bioactive glasses produce a series of physicochemical reactions at the material/bone tissue interface that lead to the formation of a layer of calcium phosphate. The evolution of this layer exhibits the ability to form a stable chemical bond with the adjacent living bone tissue. It is this bond which characterizes the bioactivity of a material. In pharmacology, the developments of bioactive systems have shown that the release of drugs from the synthesized porous bio-glasses is controlled by a diffusion mechanism, such as a dissolution-precipitation process, due to the porosity criteria. In this work we develop a mathematical model to analyze the dissolution and bioactivity for the bio-glass **(**SiO_2-CaO-P_2O_5). A numerical framework using a finite element scheme is detailed to show useful results in tissue engineering applications.

Using QSP to evaluate monoclonal antibody targets within the IL-6 signalling pathway in rheumatoid arthritis

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New monoclonal antibody (mAb)-based therapeutics for treating rheumatoid arthritis (RA) inhibit the activity of cytokines, such as interleukin-6 (IL-6). Treatment with tocilizumab (TCZ) shows that binding to the IL-6 receptor alpha mIL-6R is an effective strategy for treating RA with high remission rates in clinical use. Alternatives have been proposed with mAbs such as sirukumab (SRK) and olokizumab that bind to IL-6 itself. To explore the merits and caveats of IL-6 or mIL-6R as targets in RA we built a quantitative systems pharmacology (QSP) model. An existing ordinary differential equation model of IL-6 signalling in Crohn's disease was modified to include elements present in RA and then fitted and validated using clinical data. Model simulations of treatment with TCZ and SRK suggested that the targets were responsible for key differences in a patient's pharmacokinetic and pharmacodynamics responses. On the one hand, targeting mIL-6R resulted in an effective but comparatively short-lived response explained by the pool of soluble mIL-6R and target-mediated elimination routes. On the other hand, targeting IL-6 resulted in a longer duration of response which could allow for a reduced strength of current proposed doses. Our model also predicted a rebound of serum IL-6 and soluble IL-6R:IL-6 trans-signalling complex towards the end of the SRK treatment, unlike the TCZ treatment. Monitoring this rebound may be relevant to evaluating efficacy and safety in future clinical studies of anti-IL-6 therapies. This research presents a suitable case for using QSP to inform early go or no-go decisions in drug discovery such as commitment to target, biomarker selection at clinical trials, or the launch and design of exploratory experiments to further understand the disease mechanisms.

Computational modelling of placental xenobiotics transfer as an integrated system

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The placenta controls the materno-fetal transfer of both endogenous substrates and xenobiotics, with important implications for health and disease. In particular, the placenta determines the fetal exposure to drugs taken by the mother, which is a safety critical area where currently large uncertainties exist. Transfer from mother to fetus requires transport across the two plasma membranes of the placental syncytiotrophoblast, each of which contains a distinct complement of different transporter proteins with overlapping substrate specificity. Due to this inherent complexity it is currently not fully understood how the different transporters on both membranes work together to mediate net flux across the placenta.

Informed by ex-vivo perfused placenta experiments, the aim of this work was to develop computational models to describe how human placental transfer functions as an integrated system. Based on our previous work, a compartmental modelling approach was combined with a carrier based modelling framework to represent the kinetics of the individual classes of transporters on each plasma membrane. Preliminary modelling work captured the principal features of transplacental transfer and demonstrated how modulating individual transporter activity can affect overall transfer.

Initial ex-vivo human placental perfusion experiments focussed on the fetal to maternal transfer of the antidiabetic drug glibenclamide as a model substrate. Results demonstrated increased glibenclamide clearance from the fetal circulation in the presence of the OATP/MRP substrate BSP, suggesting interactions between uptake and efflux transporters at the fetal facing basal membrane. Based on these results, this computational-experimental approach is now being taken forward to enable a more mechanistic understanding of placental transfer of xenobiotics and drug-drug interactions.

Bayesian models for target variables and accuracy of time-to-event prediction for anti-cancer agents with specific applications to novel subtypes of breast cancer.

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Introduction: Recently, the study of the METABRIC cohort [1] via integrative clustering confirmed that there are at least 10 subtypes of breast cancer, which have different clinical outcomes. Moreover, it was established that the integrative cluster-2 (iC-2), currently classified as ER+, has poor prognosis. The aim here is to develop new tailored therapies by mapping genomic features associated with survival outcome in iC-2. As clinical trials for specific gene signatures are needed, the application of methods that work with small datasets are becoming ever more important. Bayesian models in conjunction with weakly informative priors offer a method to tackle the over-fitting/under-fitting dilemma by avoiding power issues and biased hazard ratio estimates.

The model: We filtered a dataset of iC-2 patients (n = 72) from the METABRIC cohort [1], which included clinical and genomic covariates. In addition, treatment effects were also considered such as, chemotherapy, radio-therapy, hormone-therapy or surgery (mastectomy or breast conservation). We propose a Poisson generalised additive mixed likelihood to model the event occurrence, δi. This model has a log link that relates the hazard rate (hi) to a linear combination of the log-hazard ratios, or β parameters, and X the n*p matrix of covariates; the logartithm of the differential time τi as an off-set variable; and a low-rank thin-plate splines function $f(\cdot)$, where the fixed knots kk are shrinked towards a first degree polynomial to avoid over-fitting.

$$\delta_i \sim \text{Poisson}(h_i)$$

$$\log(h_i) = \alpha + \mathbf{X}\beta + \log\tau_i + f(t_i) \qquad \beta \sim N(0,1), \quad \alpha \sim N(0,10^2)$$

$$f(t_{ij}) = b_0 + b_1 t_i + \sum_{k=1}^{K} b_k \left|t_{ij} - k_k\right|^3 \qquad b_k \sim N(0,\sigma_b^2)$$

Methods: Model performance was measured via the survival Brier score (BS) [2], which is defined as the squared distance between the predicted and observed survival outcomes. Three covariate models were compared: clinical (C), clinico-genomic (CG) and clinico-genomic with treatment effects (CGwT). A Bayesian hierarchical model was built on the Monte Carlo cross-validation results by assuming the BS measures, xi , to be jointly multivariate normal with average difference, $\mu 0$, the quantity of interest.

Results: Figure 1 shows that the combination of breast conservation with hormone-therapy might offers a potentially better treatment than mastectomy without hormone-therapy. Figure 2 shows the posterior of BS for each model. Although CGwT performs

better than C and null (no covariates), CG and CGwT overlap (practically equivalent at 0.983, ± 0.01), indicating that CGwT might be over-fitting when taking into account the genomic covariates.

Conclusion and future work: This study indicates that breast conservation and hormone-therapy may potentially be the better available therapeutic option for iC-2. Our results show that the CGwT and CG covariate models yield superior predictions of survival outcome for iC-2 than the CG or null models. Future work will focus on the identification of genomic features that can be targeted allied to application of Bayesian models combined with weakly informative and shrinkage priors. Computations with Bayesian models were performed by Hamiltonian Monte Carlo sampling using the Stan software [3] and all relevant code can be found at https://github.com/csetraynor/survbayes2.

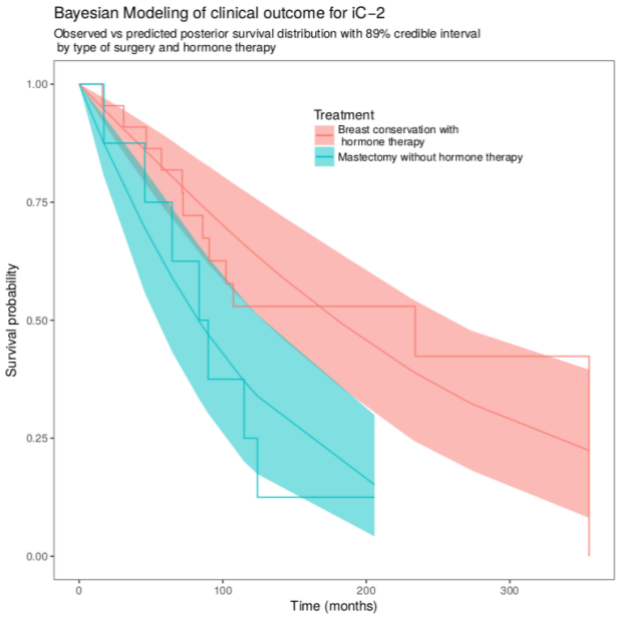

Figure 1: Kaplan-Meier estimate (step function), posterior mean (line) and 89% credible intervals (shaded area).

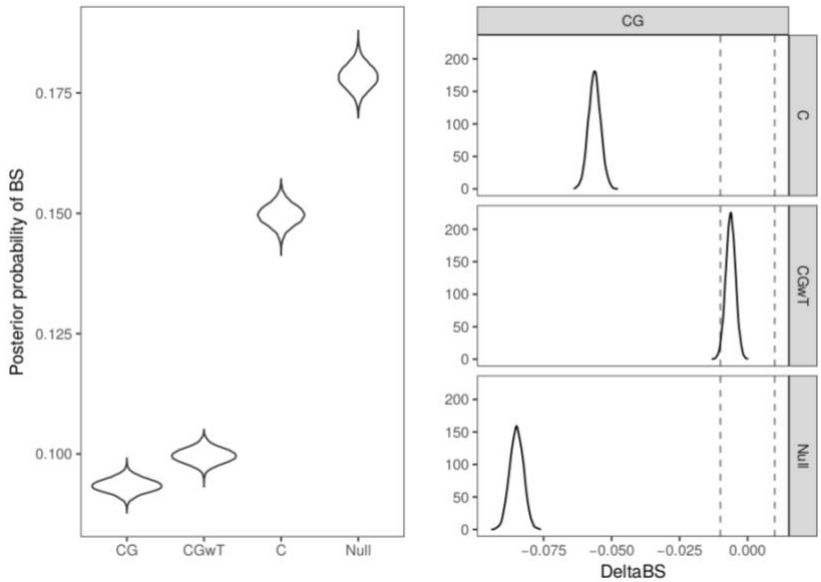

Figure 2: Posterior distribution of BS for null, clinical (C), clinico-genomic (CG) and clinico-genomic with treatment effects (CGwT) models.

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