QSP
UK

UK Quantitative Systems Pharmacology Network

Exchange Workshop 4

12th & 13th July 2023

University of Reading, UK.

Welcome!

It is a great pleasure to welcome you to the Fourth Exchange Workshop of the UK Quantitative Systems Pharmacology (QSP) Network.

Over the next two days we will be looking back at what QSP has achieved to date, where things perhaps could have been different, QSP in the context of AI and what challenges and opportunities lie ahead for QSP and its communities.

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! There will be the opportunity to discuss things both in-person as well as online.

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)
Dr Giovanni Di Veroli (AstraZeneca)
Prof Patrick Lewis (Royal Veterinary College)
Dr Mark Penney (AstraZeneca)
Dr Cristina Santini (Roche)
Prof Marcus Tindall (Reading)
Dr James Yates (GlaxoSmithKline)

Meeting Venue
All events will take place in the JJ Thomson or Department of Mathematics & Statistics buildings on the Whiteknights Campus of the University of Reading (Please see the campus map on page 5 and programme on page 6 of this booklet for further details).

All lectures will be held in the Ditchburn Lecture Theatre which can be found on the ground floor of the JJ Thomson building.
Room 113 on the first floor of the Department of Mathematics & Statistics and the Mathematics & Statistics Common Room (Room 112) will be used for discussion groups.

The JJ Thomson and Mathematics & Statistics buildings are connected so there is no need to go outside to move between them. Signs have been placed around the buildings to help you find your way. If in doubt, please ask.

Registration desk & name badge
This is located near the Ditchburn Lecture Theatre. Your name badge serves as your unique identifier whilst on the University of Reading Whiteknights 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.

Online participation
If you have registered to attend the meeting online you will be sent relevant Teams links. If you have not received these, please contact Marcus Tindall (m.tindall@reading.ac.uk).

Meeting Programme
A copy of this programme can be downloaded from
www.qsp-uk.net/reading-2023.html

Morning/Afternoon tea and lunch
Morning and afternoon teas will be served either near the Ditchburn Lecture Theatre or in the Common Room of the Department of Mathematics & Statistics (1st floor, room 112) – please see the meeting programme for the location of all meals. All lunches will be served in the Common Room of the Mathematics & Statistics Department.

Accommodation
If you have requested accommodation then this has been reserved for you on the University Campus. You will be able to check in to your accommodation from 14hrs on 12th July (time on the evening of 12th has been allocated for this).

Please remember to check out of your accommodation by 10am on the morning of Thursday 13th 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.

Accommodation reception
This can be found on the ground floor of Windsor Hall and is open Monday to Friday from 8.30 to 17.30hrs. Please see the accommodation information for further information on contact numbers for out of hours access.

Breakfast
This will be served in Park Eat from 7:30 until 09:00 hours. Park Eat is located near the accommodation.

Workshop Dinner
This will be held in Eat @ the Square (Building 7 on the attached map) on the evening of Wednesday 12th July from 20.00hrs. It will be proceeded by a drinks reception in Park House Bar (Building 8 on the Campus map on page 5) from 19.00hrs.

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 by clicking on the 'Guest' network option.

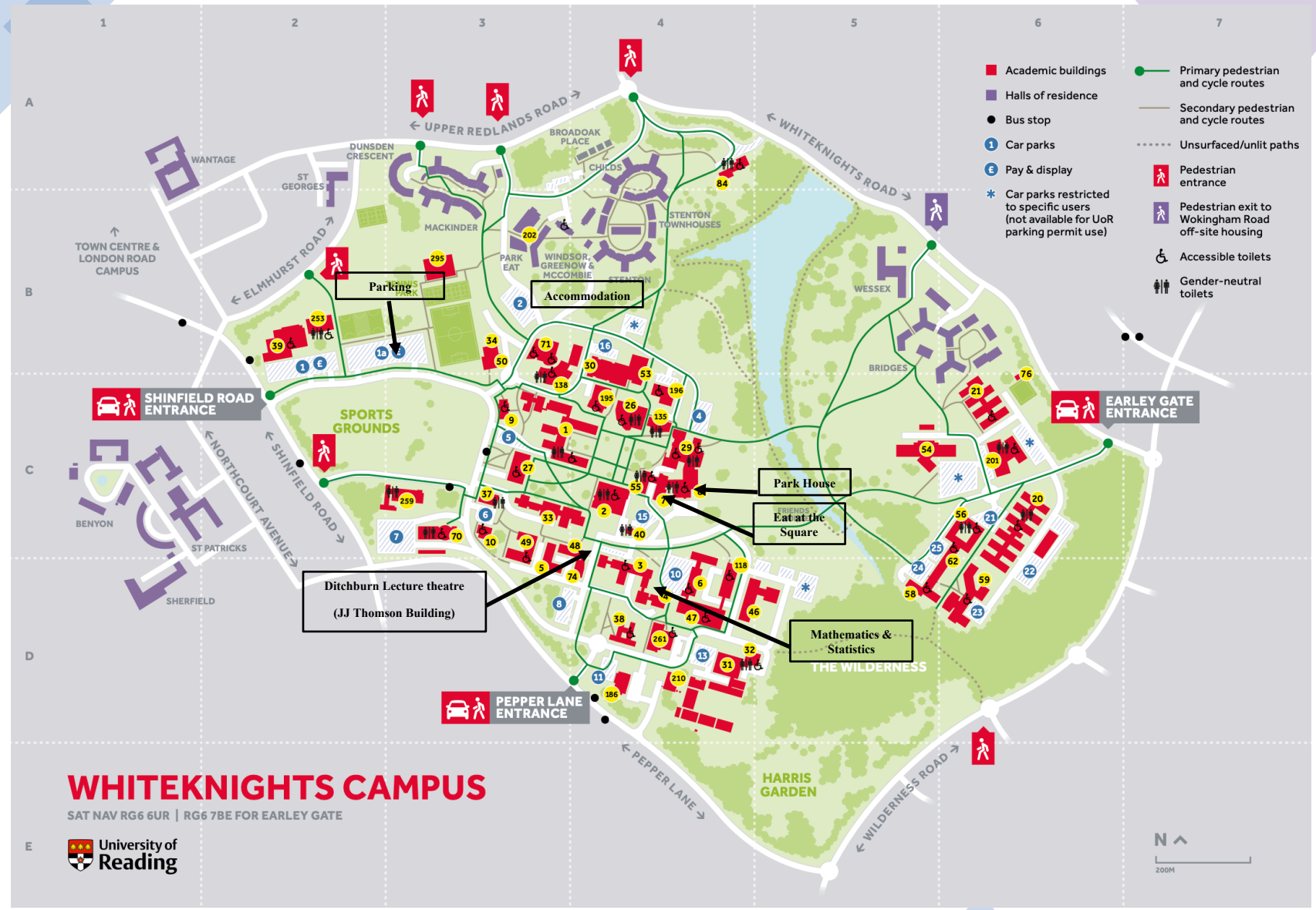
Parking & parking permits
All participants who have cars with them should park in the main visitor car park (Car Park 1a) near the Shinfield Road entrance of the University (please see the map on page 5 of this booklet). Parking is free for the duration of the Workshop, but you will need to display the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

Luggage store
A secure luggage store will be available to all workshop participants on the afternoon of the Wednesday and Thursday morning of the meeting. Please ask for details.

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 will be made available on Day 2 of the meeting. If delegates would not like their details shared (name, affiliation and e-mail address) with other delegates, please let Marcus Tindall (m.tindall@reading.ac.uk) know by the close of the 12th July.

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.


Academic buildings
Halls of residence
Bus stop
Car parks
Pay & display
Car parks restricted to specific users (not available for UoR parking permit use)
Primary pedestrian and cycle routes
Secondary pedestrian and cycle routes
Unsurfaced/unlit paths
Pedestrian entrance
Pedestrian exit to Wokingham Road off-site housing
Accessible toilets
Gender-neutral toilets
Parking
Accommodation
Park House
Eat at the Square
Ditchburn Lecture theatre (JJ Thomson Building)
Mathematics & Statistics
SHINFIELD ROAD ENTRANCE
EARLEY GATE ENTRANCE
PEPPER LANE ENTRANCE
SPORTS GROUNDS
THE WILDERNESS
HARRIS GARDEN
UPPER REDLANDS ROAD
WHITEKNIGHTS ROAD
ELMHURST ROAD
SHINFIELD ROAD
NORTHCOURT AVENUE
PEPPER LANE
WILDERNESS ROAD
TOWN CENTRE & LONDON ROAD CAMPUS
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DUNSDEN CRESCENT
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Programme

Wednesday 12th July

10.30-11.00	Registration & coffee (Ditchburn Lecture Theatre)
11.00-11.05	Welcome (Ditchburn Lecture Theatre)
11.05-11.45	***Quantitative Systems Pharmacology: Past, Present and Future*** Prof Piet van der Graaf (Certara QSP & The University of Leiden)
11.45-12.25	**How Do I Fix Thee, QSP? Let Me Count the Ways** Dr Helen Moore (University of Florida)
12.25-12.50	***Integrating mechanistic cancer models into pre-clinical drug trials: a spatially resolved model to predict tumour growing fractions*** Dr Carina Dunlop (University of Surrey)
12.50-13.15	***Studying targeted protein degradation using a QSP approach for proteolysis targeting chimeras (PROTACs)*** Dr Folguera-Blasco (AstraZeneca)
13.15-14.00	Lunch & Posters (Mathematics & Statistics Common Room & Room 113)
14.00-14.25	***Agent-based modelling of drug-induced injuries of the intestinal crypt*** Dr Louis Gall (AstraZeneca)
14.25-15.05	***Quantitative Systems Pharmacology in the Age of Artificial Intelligence*** Dr Ben Ribba (Roche)
15.05-15.30	***Building FAIR and reproducible collection of machine learning and systems biology models in BioModels repository*** Dr Rahuman Sheriff (EMBL's European Bioinformatics Institute)
15.30-15.55	***Leveraging Open Systems Biology Standards for Improved Reusability and Reproducibility of Pharmacological Models*** Dr Paul Lang (JuliaHub)
15.55-16.30	Afternoon Tea & Posters (Mathematics & Statistics Common Room & Room 113)
16.30-17.40	**Group discussion -** ***What have we achieved as a community and what problems/issues remain to be tackled?*** (Mathematics & Statistics Common Room, Room 113 & Online Teams Groups)
17.40-18.00	Summary (Ditchburn Lecture Theatre)
18.00-19.00	Break and accommodation check-in (Main accommodation reception)
19.00-20.00	Drinks Reception (Park House Bar)
20.00-21.30	Dinner (Eat @ The Square)

Thursday 13th July

8.30-9.00	Arrival coffee (Ditchburn Lecture Theatre)
9.00-9.40	***Opportunities and Challenges for the Application of Quantitative Systems Toxicology in Drug Discovery and Development*** Dr Kylie Beattie (GlaxoSmithKline)
9.40-10.20	***Is Quantitative Systems Toxicology the big brother of QSP?*** Dr Giovanni Di Veroli (AstraZeneca)
10.20-10.45	***QSP/QST modelling using pre-clinical and clinical data reveals potential mechanisms of drug-induced liver signals observed during an AZD first in human study*** Dr Aydar Uatay (AstraZeneca)
10.45-11.15	Morning coffee (Ditchburn Lecture Theatre)
11.15-12.45	**Group discussion –** ***What are the future application areas for QSP?*** (Mathematics & Statistics Common Room, Room 113 & Online Teams Groups)
12.45-13.15	**Discussion summary and close** (Ditchburn Lecture Theatre)
13.15-14.00	Lunch (Mathematics & Statistics Common Room)
14.00	Departures

ABSTRACTS

INVITED TALKS

Quantitative Systems Pharmacology: Past, Present and Future
Piet van der Graaf (Certara QSP & The University of Leiden)

The significant potential impact of model-informed drug development (MIDD) on cost and efficiency of late-stage pharmaceutical R&D was already reported nearly 2 decades ago[2]. However, despite adoption across industry and regulatory agencies, the attrition during earlier stages of drug development and discovery remains high, with Phase 2 success rate running well below 30% for most portfolios[3]. More than a decade ago, this issue was recognized by the US National Institute of Health (NIH) who organized two workshops in response, which brought together leaders from academia, industry, and government in the field of systems biology and pharmacology/pharmacometrics. The white paper that arose from this initiative can be considered as one of the early milestones that defined quantitative systems pharmacology (QSP) as a sub-discipline within MIDD.

Thus, it can be argued that a main objective of QSP (at least from an industry perspective) was to contribute to the improvement of Phase 2 success and recent examples suggest that this has indeed been achievable[3]. The focus on early development, where typically there is a high degree of biological uncertainty (in particular for novel therapeutic approaches or mechanisms of action), implies that a key objective of QSP is to extrapolate to untested clinical scenario's, such as Phase 2 outcomes in the first cohort of patients based on (limited) preclinical and healthy volunteer data.

This often results in QSP models being associated with a significant degree of "uncertainty" and explains why it may not be suitable to directly apply well-established validation approaches from pharmacometrics (PMx) to QSP. The former usually relies on the availability of rich datasets, and the model validation focuses on statistical evaluation of how well the model captured the existing data, not on the ability to extrapolate and predict untested scenarios. The distinction between PMx and QSP lies in the nature of the questions they aim to address and the data available to answer them. A simple way to put it is: "When the answer to the question is in the dataset, use pharmacometrics. When the answer to the question not in the dataset, use QSP". In this regard, QSP and pharmacometrics should be considered as complementary rather than competing approaches within the wider MIDD context. In fact, in the context of drug development the boundaries between various modeling disciplines will continue to blur and in the next decade we will see an increased focus on integration, for example between QSP and physiologically-based pharmacokinetics (PBPK) and the linking of QSP models to clinical endpoints using AI/ML approaches, which is arguably the most exciting development in our discipline.

1. Based on Lemaire, V., Hu, C., van der Graaf, P.H., Chang, S. and Wang, W. (2023). No recipe for QSP model validation, but a balancing act between risk and cost, submitted
2. Lalonde RL *et al.* (2007). Model-based drug development. Clin Pharmacol Ther. doi: 10.1038/sj.clpt.6100235.
3. Fernando K, *et al.* (2022). Achieving end-to-end success in the clinic: Pfizer's learnings on R&D productivity. Drug Discov Today. doi: 10.1016/j.drudis.2021.12.010.

How Do I Fix Thee, QSP? Let Me Count the Ways
Helen Moore (University of Florida)

Quantitative systems pharmacology (QSP) modeling has been used widely since the NIH Quantitative and Systems Pharmacology Workshop held in 2008. As with most new or developing fields, there are numerous issues with QSP and related concepts that we can point to. I will highlight some of these from a mathematician's point of view, and suggest ways to solve or mitigate them.

Quantitative Systems Pharmacology in the Age of Artificial Intelligence
Ben Ribba (Roche)

While quantitative systems pharmacology (QSP) comes with the promise to provide mechanistic insights into pathophysiology and treatment effects, it suffers from inherent limitations when it faces big data; limitations on which machine learning and artificial intelligence (ML/AI) approaches excel, while generally suffering from a lack of interpretability. It is then natural to think of ways to get the best of the two "worlds"; and the literature over the last 2 years indicates that our scientific community has taken that opportunity seriously.

We will first review the state-of-the-art in the application of ML/AI approaches for QSP in particular, for model development, identification of biomarkers, quantification of drug-response variability and precision dosing, and will be primary focusing on non-communicable diseases, an area in which QSP is associated with significant challenges such as the lack of validated biomarkers or the subjective nature of clinical endpoints. Then, because the "S" of QSP stands for "systems", we will discuss the opportunity for QSP to embrace a more "systems view" on some of these indications through extending its data integration capability from the biological and pharmacological remits alone to cognitive, behavioral and functional data, in particular through methods such as reinforcement learning.

Opportunities and Challenges for the Application of Quantitative Systems Toxicology in Drug Discovery and Development
Kylie Beattie (GlaxoSmithKline)

This presentation will provide an overview of how Quantitative Systems Toxicology is used to support decision making in drug discovery and development. Through example applications, opportunities and impacts of Quantitative Systems Toxicology are highlighted. Existing challenges associated with embedding Quantitative Systems Toxicology approaches within pharmaceutical companies as well as future directions and opportunities are described.

Is Quantitative Systems Toxicology the big brother of QSP?
Giovanni Di Veroli (AstraZeneca)

CONTRIBUTED TALKS
(Underlined names are those presenting)

Integrating mechanistic cancer models into pre-clinical drug trials: a spatially resolved model to predict tumour growing fractions
A Nasim[1], J. Yates[1], G. Derks[2] and C. Dunlop[3]
[1] DMPK modelling, GSK, Stevenage, UK. [2] Mathematics Institute, University of Leiden, Netherlands.
[3] School of Mathematics and Physics, University of Surrey, UK.

Mathematical models of tumour growth for pre-clinical drug discovery tend to be empirical growth laws. These are well-suited to the data available, mostly longitudinal studies of tumour volume, however, they typically ignore the mechanistic processes of growth potentially restricting their flexibility and inhibiting their translation across studies. Within mathematical oncology modelling in contrast focuses on descriptive mechanistic models founded on a consideration of spatial effects. There is now a great opportunity to better use spatial modelling to improve translational drug development. This talk will address the challenges and benefits of integrating spatial mechanistic models into preclinical trials and developing models that are fit-for-purpose in an industrial context. We present a diffusion-limited model of tumour growth and demonstrate how this spatial model can be reduced to a growth law of a similar form to those currently widely adopted. We show that this model can be integrated into pre-clincial work flows and can be extended to models of drug action and dosing. We validate this approach for both cell-derived xenograft (CDX) and patient-derived xenograft (PDX) data. We show that this approach can add significant value to preclinical drug development allowing for the dynamic prediction of tumour growing fraction and drug availability.

Studying targeted protein degradation using a QSP approach for proteolysis targeting chimeras (PROTACs)

Nuria Folguera-Blasco[(1)], Cesar Pichardo-Almarza[(1)], Linda Irons[(2)], Holly Kimko[(3)]
AstraZeneca, Systems Medicine, Clinical Pharmacology and Quantitative Pharmacology ; (1) Cambridge, UK; (2) Waltham, US ; (3) Gaithersburg, US.

Targeted protein degradation is showing promising results for the treatment of various diseases, in particular cancer [1], mainly through the development of new therapies based on Proteolysis Targeting Chimeras (PROTACs) [2]. This work, based on experimental data, presents a computational framework for simulation of mechanistic models (QSP) describing the dynamics of PROTACs and their impact on ubiquitination and protein degradation [3]. The QSP approach provides an efficient and convenient way to evaluate specific dosing scenarios allowing to find optimal administration schedules for different PROTAC molecules. The modularity of the QSP model allows to describe further relevant mechanisms (e.g. tumour growth, toxicity), increasing its utility and impact in the drug development process. Overall, simulation results evaluating the mode of action of PROTACs and their effect on targeted protein degradation are encouraging, as they highlight the potential use of computational tools to aid with the development and understanding of new therapeutic modalities.

References:
[1] S. Khan et al., 'PROteolysis TArgeting Chimeras (PROTACs) as emerging anticancer therapeutics', Oncogene, vol. 39, no. 26, pp. 4909–4924, Jun. 2020
[2] K. Li and C. M. Crews, 'PROTACs: past, present and future', Chem Soc Rev, vol. 51, no. 12, pp. 5214–5236, Jun. 2022
[3] D. W. Bartlett and A. M. Gilbert, 'A kinetic proofreading model for bispecific protein degraders', J Pharmacokinet Pharmacodyn, vol. 48, no. 1, pp. 149–163, Feb. 2021

Agent-based modelling of drug-induced injuries of the intestinal crypt

Louis Gall
Systems Medicine, CPQP, CPSS, Biopharmaceutical R&D, AstraZeneca, Cambridge, UK

Abstract: We have built a multi-scale agent-based model (ABM), with individual cells interacting in the crypt geometry, that reproduces the dynamic, self-organising behaviour of the intestinal crypt. Tissue homeostasis, and its restoration following drug-induced injury, is achieved through multiple signalling pathways, namely the Wnt, Notch, BMP and RNF43/ZNRF3 pathways, and contact inhibition. This dynamic signalling network interacts with the main cell cycle proteins, governing the progression of each cell across the division stages. Each of these signalling networks can be perturbed to mechanistically simulate drug-induced injury in the intestinal crypt, for true multi-scale modelling of disruptions of the intestinal epithelium from protein to tissue level.

Building FAIR and reproducible collection of machine learning and systems biology models in BioModels repository

Divyang Deep Tiwari, Nils Hoffmann, Kieran Didi, Sumukh Deshpande, Sucheta Ghosh, Tung V. N. Nguyen, Karthik Raman, Henning Hermjakob, Rahuman Sheriff

BioModels is a leading repository of curated mathematical models of biological systems. With increasing use of Machine learning (ML) models in life sciences and medicine, BioModels is extended to support FAIReR (Findable, Accessible, Interoperable, Reusable, and Reproducible) sharing of ML models. Similar to systems biology models, ML models are also scattered across various platforms and there are several challenges that hinder their accessibility, reproducibility and reuse. We developed community protocol to disseminate FAIReR ML models through BioModel. The protocol consists of eight steps, including sharing model training code, dataset information, reproduced figures, model evaluation metrics, trained models, Dockerfiles, model metadata, and FAIR dissemination. Comparable to ODE, logic and constraint-based model collections in BioModels repository, we aim to build and share a comprehensive public collection of FAIR ML models through incentivized community curation. In this talk, I will discuss about our pilot implementation where we curated diverse ML models to demonstrate the feasibility of our approach and the emerging challenges. Building a FAIReR collection of ML and systems biology models will directly enhance the reproducibility and reusability, minimising the effort needed to reimplement models, maximising the

impact on their application to understand the complex interactions between drugs, diseases, and patients, drug development and personalized medicine.

Leveraging Open Systems Biology Standards for Improved Reusability and Reproducibility of Pharmacological Models

Paul F Lang(1), Sebastian Micluța-Câmpeanu(1), Elisabeth Roesch(1), Chris Rackauckas(1,2,3)
JuliaHub (1), PumasAI (2), MIT (3)

Background and Objectives: In systems biology, open standards facilitate model exchange and storage, reusability and reproducibility. Here, we set out to identify where these standards can help in the development process of pharmacological models. In particular, we focus on the ability of open standards to (1) describe biology with a mathematical model, (2) specify experimental readouts, (3) define dosing schemes and trials, (4) specify QSP and (5) NLME optimization problems.

Methodology: We used the quantitative systems pharmacology tool PumasQSP, which has import capability for open standards such as BioNetGen, SBML, CellML, and PEtab. To illustrate the potential and limitations of these standards, we took a breast cancer model through the PumasQSP modeling workflow.

Results:

1. The breast cancer model was specified in BioNetGen, which can be exported to SBML and used for both deterministic and stochastic simulations.
2. The PE tab format allows for the independent specification of experimental readouts in tabular form.
3. PEtab lacks a dosing table, but its extensibility allowed us to import a PumasQSP dosing table.
4. PEtab defines likelihood or posterior probabilities as optimisation objectives from which we generate a virtual population.
5. NLME models are only supported in PharmML.

Conclusion and Impact: Open standards have the potential to facilitate QSP modeling pipelines. We believe their uptake can positively influence model reproducibility and reusability across computing platforms and research teams.

QSP/QST modelling using pre-clinical and clinical data reveals potential mechanisms of drug-induced liver signals observed during an AZD first in human study

Aydar Uatay[1], Dominic Williams[2], Anna Fettiplace[3], John Meissen[4], Michelle Hsueh[5],Jennifer Tan[6], Sherri Matis-Mitchell[7], Holly Kimko[1], Giovanni Di Veroli[1]
Systems Medicine[1], Hepatic Safety[2], Patient Safety Science[3], Integrated Bioanalysis[4], Translational Medicine[5], Computational Biology[6], Patient Safety Analytics[7]

AZD is a small molecule targeting cancer and involved in gene transcription. During the first in human study significant synchronous elevations of ALT and bilirubin were detected consistent with potential Hy's Law cases. The absence of clinically apparent liver injury required clarification of the underlying mechanisms. To that extent we performed integrated analysis of *in vitro* and *in vivo* omics and clinical biomarkers data via QSP/QST modelling. Leveraging on all this data, we modelled down-modulation of a bile acid transporter to simulate plasma bile acid levels consistent with clinical findings (including metabolomics). Simulations showed that significant intrahepatic accumulation of bile acids and subsequent hepatocyte apoptosis (but not necrosis), was a likely mechanism for ALT elevation. This work exemplifies how the combination of clinical, *in vitro* omics data and modelling can help in deriving mechanisms explaining observed enzymes elevations and therefore de-risk a drug program.

POSTERS
(Underlined names are those presenting)

Scientific Machine Learning (SciML) based Automatic Model Discovery in Systems Pharmacology

Sebastian Micluţa-Câmpeanu[(1)], Elisabeth Roesch[(1)], Paul Lang[(1)], Chris Rackauckas[(1,2,3)]
(1) JuliaHub, (2) Pumas-AI, (3) MIT CSAIL

Objectives: With the automated model discovery feature in PumasQSP, we not only aim to mix neural networks with the differential equations, but also to symbolically interpret the function learned by the neural network part.

Methods:
- Starting with the Lotka-Volterra system, we remove interaction terms.
- To recover missing dynamics, we add a neural network term to the system in place of the removed terms, yielding a system of UDEs.
- Using SINDy we extract symbolic equations from the function the neural network part of the UDE has learned.

Results:
- We show that simulation of the trained UDE system accurately matched the data, indicating that the neural network part has learned a function that is similar to the missing terms.
- We demonstrate that the recovered symbolic terms contain the missing terms from the function learned by the neural network part of the UDEs.

Conclusions and impact:
- In summary, we found that SciML techniques, such as UDEs and SINDy can be combined to automatically discover missing biology from data.

Systems level logic modelling of neuroinflammation in G93A SOD1 mouse model of ALS

Alex Foster-Powell[1], Guy Meno-Tetang[2], Donald E Mager[3], Amin Rostami[1] and Kayode Ogungbenro[1]
1: University of Manchester Centre for Applied Pharmacokinetics Research (CAPKR), 2: AstraZeneca, 3: University at Buffalo.

Background to the work undertaken: Neuroinflammation is a common feature in many neurodegenerative diseases, including ALS. Currently, we have a poor understanding of this response at the systems level in addition to a lack of longitudinal data.

Objectives: To develop a Boolean logic-based systems model to capture cell:cell communication in neuroinflammation during the late stages of the G93A SOD1 mouse model of ALS.

Methodology: A cell:cell communication network was constructed guided by the literature, with Boolean logic manually assigned to each node. In *vivo* RNA data was extracted from the literature relating to cell or protein level in G93A SOD1 mice as fold change from control (under various treatment conditions). Simulations were performed in MaBoSS, with asynchronous model updating from random initial conditions.

Results: 48-node, 152 edge network capture well late stage inflammation in SOD1 mice. 50% reduction in healthy motor neurons observed between healthy and SOD1 and SOD1/IL6-KO mice. Model describes the differentiation of oligodendrocytes, T-cells, microglia (into disease associated, RIPK1 regulated inflammatory and homeostatic) and reduction of the blood brain barrier.

Conclusions: The model successfully captured the data of the neuroimmune response in late stage G93A SOD1 mice.

Impact of the work: Model provides a platform, to confirm biological observations in addition to testing the impact that drug perturbations have on the system.

Structural Identifiability Analysis of Belantamab Mafodotin Pharmacokinetic Model for the treatment of relapsed/refractory multiple myeloma

Patrick Joyce [1], James Yates [2], Mike Chappell [1]
[1] School of Engineering, University of Warwick, Coventry, UK.
[2] GSK, Stevenage, UK.

A nested compartmental model has been developed to characterise the population pharmacokinetics of antibody-drug conjugate, total monoclonal antibody, and cysteine-maleimidocaproyl-MMAF in patients with relapsed / refractory multiple myeloma (Figure 1). The analysis of this model included the generation of parameter estimates, but no structural identifiability analysis.

Structural identifiability analysis determines whether the unknown parameters of a model can be uniquely identified (or otherwise) by the model's input-output behaviour.

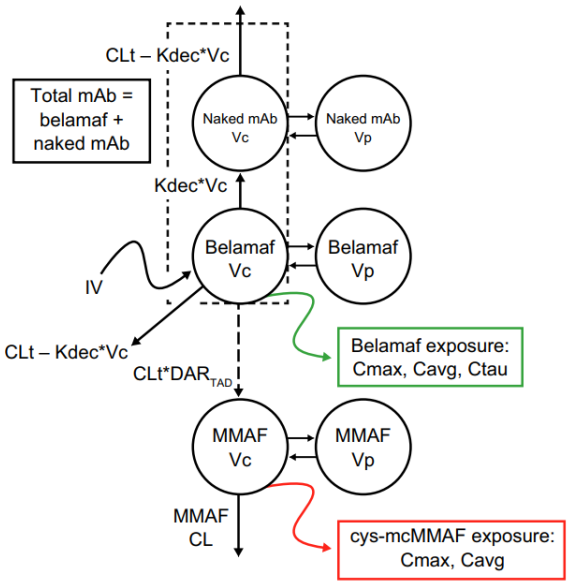

Figure 1: Population pharmacokinetic model for Belantamab Mafodotin. [1]

The original formulation for the clearance of this system, $CL_{ADC,Time}$, given in Equation 2

$$CL_{ADC,Time} = CL_{ADC,0} * exp\left(\frac{IMAX*Time^{\gamma}}{TI50^{\gamma}+Time^{\gamma}}\right) \qquad \text{(Equation 1)}$$

rendered structural identifiability analysis intractable. By adopting a mathematical reformulation of the clearance term, shown in Equation 3, and expressing the model with a reformulated clearance term, via application of the Taylor series approach it was possible to ascertain that the model was structurally identifiable.

$$CL_{ADC,Time} = CL_{ADC,0} * \left(1 + \left(\frac{IMAX*Time^{\gamma}}{TI50^{\gamma}+Time^{\gamma}}\right) + \left(\frac{IMAX*Time^{\gamma}}{TI50^{\gamma}+Time^{\gamma}}\right)^2 + \left(\frac{IMAX*Time^{\gamma}}{TI50^{\gamma}+Time^{\gamma}}\right)^3\right) \qquad \text{(Equation 2)}$$

Due to the time variant nature of the clearance expression, the model cannot be proven structurally identifiable at $t = 0$ in either model and instead was performed at some other time point $t > 0$.

The outcome of the analysis should enable the estimation of model parameters to be performed with greater confidence, to obtain more reliable estimates with narrower confidence intervals, in particular by also adopting a nonlinear mixed effects approach.

References

C. Rathi, J. Collins, H. Struemper, J. Opalinska, R. C. Jewell and G. Ferron-Brady, "Population pharmacokinetics of belantamab mafodotin, a BCMA-targeting agent in patients with relapsed/refractory multiple myeloma," *CPT: Pharmacometrics & Systems Pharmacology,* vol. 10, no. 8, pp. 851-863, 2021.

Developing a novel QST model for hemodynamic safety

Christopher Morris,[1] Amy Pointon[2], and Giovanni Di Veroli[1]
[1]Systems Medicine, Clinical Pharmacology & Quantitative Pharmacology, R&D BioPharmaceuticals, AstraZeneca, Cambridge.
[2]Cardiac Safety, Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Cambridge.

Background: Many pathways interact with hemodynamics including heart rate or blood pressure. While many targets are tested for secondary pharmacology (SecP), we lack quantitative understanding about SecP integration into overall functions. Assays give controlled results on molecular targets but not their interactions. *In vivo* studies give overall changes but cannot explain underlying mechanisms.

Objectives: Develop a QST platform providing mechanistic understanding of hemodynamic modulation from compounds' molecular interactions. The platform aims to improve translation across species and ultimately to humans.

Method: We designed a multi-scale model of hemodynamics integrating relevant molecular targets. Literature knowledge and data was used during the initial phase to build the structure and parametrize block interactions.

Results: The resulting "bottom-up" model relies on physiological data for dogs and rats. The model successfully captures various hemodynamic changes such as diurnal variations, nerve stimulation or vasoactive substances. It was designed such that most effects of SecP targets of relevance can be integrated into the final QST platform.

Conclusions: We built a mechanistic model for hemodynamic functions integrating 50 molecular targets and their interactions. The model will be further developed using *in vitro/in vivo* drugs datasets to generate a QST platform to improve translation and decision-making for hemodynamics.

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