QSP
UK

UK Quantitative Systems Pharmacology Network

Exchange Workshop 3

9th to 10th September 2019

University of Reading, UK.

Welcome!

Welcome to the Third Exchange Workshop of the UK Quantitative Systems Pharmacology (QSP) Network.

This workshop is an opportunity to explore advances in the use of artificial intelligence and mechanistic mathematical modelling in advancing the discovery and development of pharmaceuticals. Even more so, it represents the exciting opportunity of exploring how the use of such methods can complement each other in seeking to tackle questions and problems in the area.

I am sure there will be many different thoughts on how the two fields can be brought together and at which stage of the drug discovery and development process they can be used. We want to hear them!

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 Mrs Ruth Harris for providing administrative support for this meeting.

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)
Dr James Yates (AstraZeneca)

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, UK (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 Slingo Lecture Theatre which can be found on the ground floor of the JJ Thomson building. Rooms 100 and 113 on the first floor of the Department of Mathematics & Statistics will be used for breakout discussion. The two buildings are connected so there is no need to go outside to move between the spaces.

Registration desk & name badge
This is located near the Slingo Lecture Theatre. 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-2019.html,
during the course of the meeting. Paper copies are available at the Workshop Registration Desk.

Morning/Afternoon tea and lunch
Morning and afternoon teas will be served either near the Slingo Lecture Theatre or in the Common Room (1st floor) of the Department of Mathematics & Statistics (please see the Programme on page 6 for location details throughout the meeting). All lunches will be served in the Common Room of the Department of Mathematics & Statistics.

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 9th September (time in the Workshop programme has been allocated for this).

Please remember to check out of your accommodation by 10am on the morning of Tuesday 10th September, 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.

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.

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).

Workshop Dinner
This will be held in Eat @ the Square on the evening of Monday 9th September. It will be proceeded by a drinks reception in Park House Bar.

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 workshop registration desk.

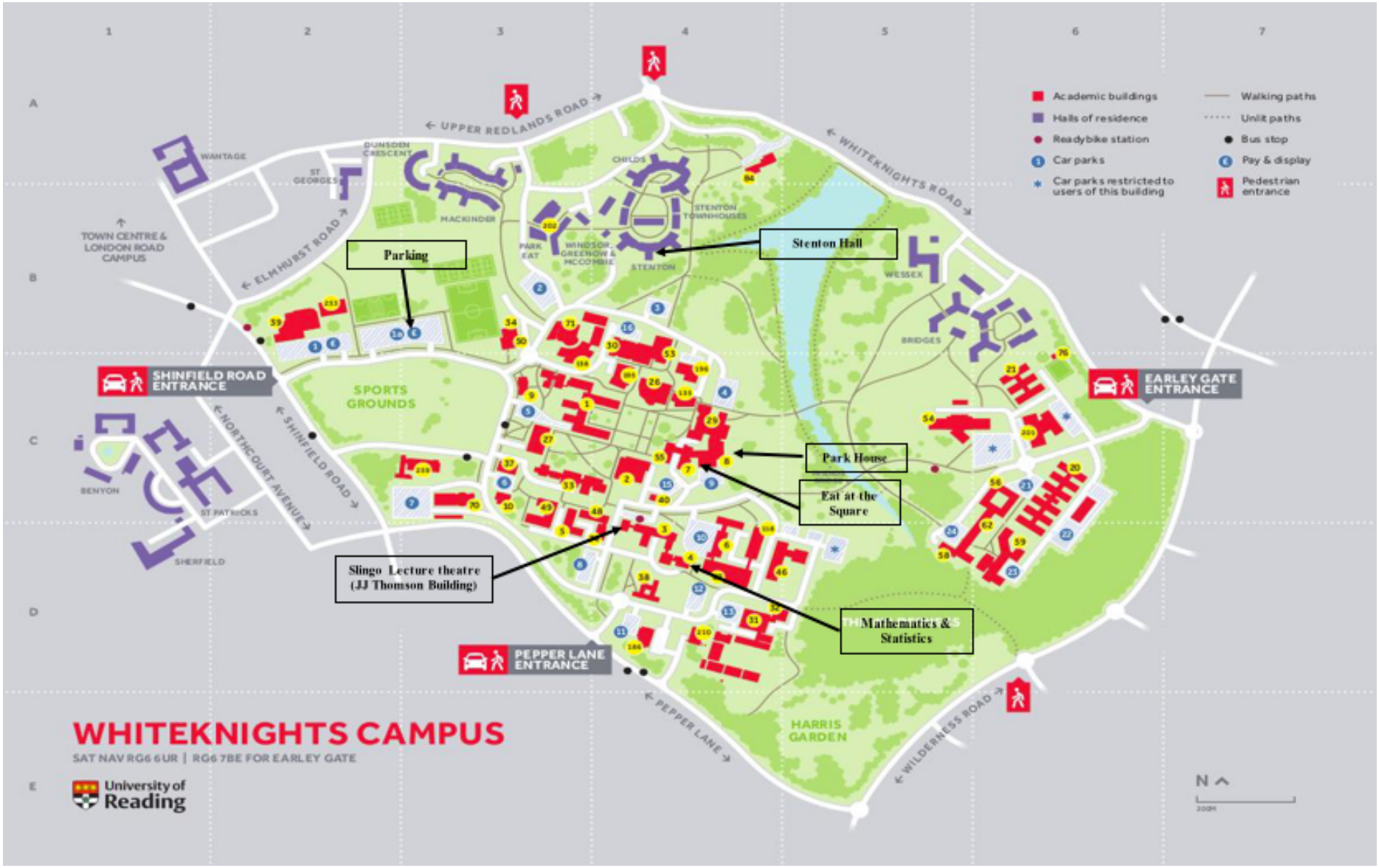
Parking & parking permits
All participants who have cars with them should park in the main visitor car park (Car Park 1a) near the Shinfield Road entrance of the University (please see the map on page 5 of this booklet). Parking is free for the duration of the Workshop, but you will need to display the 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 Monday and Tuesday 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 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.


Parking
Stenton Hall
Park House
Eat at the Square
Slingo Lecture theatre (JJ Thomson Building)
Mathematics & Statistics
SHINFIELD ROAD ENTRANCE
EARLEY GATE ENTRANCE
PEPPER LANE ENTRANCE
SPORTS GROUNDS
HARRIS GARDEN
WHITEKNIGHTS CAMPUS
SAT NAV RG6 6UR | RG6 7BE FOR EARLEY GATE
University of Reading
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
UPPER REDLANDS ROAD
WHITEKNIGHTS ROAD
ELMHURST ROAD
SHINFIELD ROAD
NORTHCOURT AVENUE
PEPPER LANE
WILDERNESS ROAD
TOWN CENTRE & LONDON ROAD CAMPUS
WANTAGE
DUNSDEN CRESCENT
ST GEORGES
MACKINDER
CHILDS
STENTON TOWNHOUSES
PARK EAT
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STENTON
WESSEX
BRIDGES
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Programme

Monday 9th September

10.00-11.00 Registration & coffee (Slingo Lecture Theatre)
11.00-11.10 Welcome (Slingo Lecture Theatre)
11.10-12.00 ***Mapping biology from mouse to man using transfer learning*** Prof Ben Macarthur (University of Southampton)
12.00-12.50 ***Exploring the role of mechanistic mathematical modelling to support understanding of transdermal drug delivery and drug monitoring*** Dr Jane White (University of Bath)
12.50-13.50 Lunch (Mathematics & Statistics Common Room)
13.50-14.20 ***Application of protein-protein interaction network analysis in Hereditary Spastic Paraplegias*** Ms Nikoleta Vavouraki (University of Reading)
14.20-15.10 ***Identifying biological signals differentiating responders and non-responders to cancer immunotherapy using machine learning analysis of virtual populations*** Dr Vincent Lemaire (GenenTech)
15.10-15.40 ***BioModels Parameters: A resource to search and access parameters from published systems models*** Dr Krishna Tiwari (European Bioinformatics Institute)
15.40-16.00 Breakout group discussion (Slingo Lecture Theatre, Rooms 100 and 113 of Mathematics & Statistics)
16.00-16.30 Afternoon tea (Common Room)
16.30-17.40 Breakout group discussion
17.40-18.00 Breakout group discussion summary (Slingo Lecture Theatre)
18.00-18.45 Accommodation check-in (Stenton Hall)
18.45-19.30 Reception (Park House Bar)
19.30-21.00 Dinner (Meadow Suite, Park House)

Tuesday 10th September

9.00-9.50 ***Mechanistic modelling for the prediction of nanobiomaterial distribution to enhance drug delivery*** Dr Marco Siccardi (University of Liverpool)
9.50-10.20 ***Predicting rat heart left ventricular function by means of Gaussian process emulation*** Dr Stefano Longobardi (King's College London)
10.20-11.00 Morning tea with posters (near Slingo Lecture Theatre)
11.00-11.50 ***Regulatory networks for drug discovery*** Dr Ben Sidders (AstraZeneca)
11.50-12.20 ***Multiscale modelling approaches to describe drug-induced gut toxicity*** Dr Carmen Pin (AstraZeneca)
12.20-12.50 ***QSP/AI/ML a match made in heaven or hell?*** Dr James Yates (AstraZeneca)
12.50-14.00 Lunch with posters (Mathematics & Statistics Common Room)
14.00-14.50 ***Natural language processing to interpret pharmacokinetic literature*** Dr Joe Standing and Mr Ferran Gonzalez Hernandez (University College London)
14.50-16.00 Group discussion (Slingo Lecture Theatre, Rooms 100 and 113 of Mathematics & Statistics)
16.00-16.30 Afternoon tea with posters (Mathematics & Statistics Common Room)
16.30-17.00 Summary of discussion, network activities and further funding
17.00 Close of meeting

ABSTRACTS

INVITED TALKS

Mapping biology from mouse to man using transfer learning
Prof Ben Macarthur (University of Southampton)

During the early stages of the drug development process the biological mode of action of a compound is investigated using experiments in vitro and in vivo in model organisms. If these experiments are successful, and there is evidence that a drug is effective for a desired purpose, then there is then a need to determine if the biology learnt in the pre-clinical models will transfer to the human and ultimately the clinic. The ultimate success of the development pipeline is therefore dependent upon effective transfer of information from one phase of the development process to the next. There is a branch of machine learning – known as transfer learning, representation learning, or *learning to learn* – that takes information learnt from one setting and passes it to another, and so is ideally suited to problems like this. Here, I will discuss how ideas from transfer learning can be used to improve the biomedical research and development pipeline. As an example, I will show how transfer learning can be used to determine when biology learnt from one organism (the mouse) can be effectively transferred be to another (the human) and when it cannot.

Exploring the role of mechanistic mathematical modelling to support understanding of transdermal drug delivery and drug monitoring
Dr Jane White (University of Bath)

The main purpose of our largest organ, the skin, is to provide a barrier function, protecting the body from harmful external substances whilst preventing excessive water loss from it. So when it comes to thinking about delivering or monitoring drugs across the skin, it is clearly challenging to understand how that might be possible. However, since the skin is large and accessible, there is a real interest in exploring the potential to exploit it for pharmaceutical purposes.

In this talk, I will present a selection of projects that I have worked on that use mechanistic mathematical models to explore and to understand the processes that underpin the results of empirical studies. I will demonstrate the capacity of this modelling approach to contribute to hypothesis testing and will discuss how mechanistic modelling is an important addition to the theoretical toolbox for colleagues working in the pharmaceutical sciences.

Natural language processing to interpret pharmacokinetic literature
Dr Joe Standing and Mr Ferran Gonzalez Hernandez (University College London)

Predictions of pharmacokinetic (PK) properties of newly discovered drugs are largely based on prior knowledge from other compounds, but much of this potentially important data is currently locked in the format of scientific papers. Existing pharmacology databases are maintained through costly and time-consuming manual curation, which limits their ability to exploit the extensive PK literature. On the other hand, text-mining approaches have begun to emerge as an alternative, aiming to automatically retrieve and structure this information. In this talk, we will present our current work on information retrieval of PK articles using Natural Language Processing. Specifically, Machine Learning approaches to identify relevant articles will be presented together with Named Entity Recognition algorithms for further characterization of the studies.

Mechanistic modelling for the prediction of nanobiomaterial distribution to enhance drug delivery
Dr Marco Siccardi (University of Liverpool)

Nanomedicine strategies have emerged as an advanced approach to enhance drug delivery and improve the treatment of several diseases. The processes that underpin nanobiomaterial (NBM) pharmacokinetics and pharmacodynamics are not as fully characterised as conventional medicines and consequently the development of novel NBM is complicated by extensive development and optimisation processes based on experimental and pre-clinical models. Mechanistic and physiologically based pharmacokinetic (PBPK) modelling combines mathematical equations to describe the anatomical, physiological and molecular processes regulating pharmacokinetics, with *in vitro* data to simulate and predict ADME of conventional and nano-enabled medicines. PBPK simulations could find valuable applications in multiple steps of the nanobiomaterial development and regulatory framework, supporting a better understanding of the mechanisms defining distribution and a rational optimisation of applications in humans.

Identifying biological signals differentiating responders and non-responders to cancer immunotherapy using machine learning analysis of virtual populations
Dr Vincent Lemaire (GenenTech)

The ability of biomarkers to predict which patient respond to immune checkpoint inhibitors has been inconsistent. For example, while PDL1 expression is positively correlated with a favorable outcome to treatment by anti-PDL1 in some solid tumors, it cannot clearly separate responders and non-responders in most situations. Here we use QSP modeling and machine learning to identify biological signals that could differentiate responders and non-responders to MPDL3280A (anti-PDL1 antibody) in non-small cell lung cancer (NSCLC).

We developed a QSP model of cancer immunity in human, including interactions of immune cells, and modulation by the PD1, CTLA4 and TIGIT pathways. The model was calibrated using knockout and cell depletion mouse data, as well as human IHC and FACS data. We generated a population of >8000 virtual patients with high diversity in biology and patient phenotypes. The statistics of response was calibrated to match the response data of MPDL3280A in NSCLC from the BIRCH phase 2 trial. We then used Support Vector Machine analysis of the model parameters in the virtual population to identify differences in biology separating responders and non-responders.

Model predictions for the objective response rate as a function of PDL1 expression and of CD8+ T cell number match clinical data, providing confidence in the use of the model. Our analysis indicates that 7 biological processes related to NK cells, CTLs, tumor, Th1/IL2, PDL1 expression and drug PK can predict response with sufficient accuracy, when considered together. The predictive relationship is given by the machine learning model.

We generated a high diversity virtual population based on a QSP model of cancer immunity. A machine learning analysis of the population led to a relationship predicting response to MPDL3280A in NSCLC. We now aim to translate this relationship into clinically measurable biomarkers.

Regulatory networks for drug discovery
Dr Ben Sidders (AstraZeneca)

Inference over causal graphs has proven useful for the study of dynamic biological systems in the context of drug discovery. We have created a causal graph from gene & protein regulatory interactions derived using natural language processing (NLP) applied to the primary scientific literature. We use the graph to study disease related systems and here will describe examples related to the characterisation of a drug's mechanism of action, as well as to the definition of cancer subtypes with active subnetworks that influence their response to immunotherapy.

CONTRIBUTED TALKS
(Underlined names are those presenting)

Application of protein-protein interaction network analysis in Hereditary Spastic Paraplegias

Nikoleta Vavouraki[1], Dr Patrick Lewis[1,2], Dr Marcus Tindall[3], and Dr Claudia Manzoni[1,2]
1: Department of Pharmacy, University of Reading, RG6 6AH
2: UCL Institute of Neurology, University College London, WC1N 3BG
3: Department of Mathematics and Statistics, University of Reading, RG6 6AH

Background: Protein-protein interactions (PPIs) are fundamental to allow protein functionality in the context of complexes and pathways. Therefore, the study of PPI networks (PPIN) formulated around sets of proteins coded by genes implicated in disease could unveil the functional pathways involved in disease mechanism(s). PPIN analysis is ideal for the identification of drug targets in complex diseases, such as the Hereditary Spastic Paraplegias (HSPs), a group of neurodegenerative and neurodevelopmental diseases that lead to weakness and stiffness (i.e. spasticity) in the lower limbs. Although more than 70 genetic types have been reported, the underlying molecular mechanisms remain elusive and no drugs are available.
Methodology / Results: The HSP-PPIN was generated with PPI data for all the associated disease-genes, as produced by PINOT, a novel online bioinformatic tool that provides a list of unique and scored PPIs for the all genes of interest. The analysis of the HSP-PPIN was based on functional enrichment and topological node clustering. The former unveiled functions and pathways highly enriched in the network, which could hint for the disease mechanism(s). The latter focused on dividing the network based on pure topological/mathematical properties and then assigning clinical features to the obtained clusters to verify whether the network connectivity could be used as an unbiased tool to group clinical subtypes of HSPs.
Conclusion: A combination of bioinformatic tools was used to formulate a semi-automated pipeline identifying potential disease pathways and mechanisms, and prioritizing novel candidate genes to be associated with HSPs. Such an approach could aid rare disease gene discovery, drug development and can be potentially applied to the study of complex diseases in general.

BioModels Parameters: A resource to search and access parameters from published systems models

Chinmay Arankalle, Mihai Glont, Tung Nguyen, Krishna Tiwari, Henning Hermjakob, Rahuman S. Malik-Sheriff
European Bioinformatics Institute, Cambridge, UK.

Systems biology models of cell signalling, metabolic and gene regulatory networks have been shown to divulge mechanistic insight into cellular regulation. One of the major bottlenecks in building systems models is identification of model parameters. Searching for model parameters from published literature and models is essential, yet laborious task. To address this, we have developed a new resource, BioModels Parameters, that can facilitate easy search and retrieval of parameters values from models stored in BioModels (Chelliah et al. 2015; Glont et al. 2018). BioModels is a world's largest repository of curated models and is the third most used data resource after PubMed and Google Scholar among the scientists who use modelling in their research (Stanford et al. 2015; Szigeti et al. 2018). Using BioModels Parameters, modellers can now directly search for a model entity (e.g. a protein or drug) to retrieve the rate equations describing it; the associated parameter values (e.g.

degradation rate, production rate, Kcat, Michaelis-Menten constant, etc) and the initial concentrations, which are crucial for building model. Modellers can benefit by retrieving a range of a previously used parameter values to perform parameter scan and to set initial parameter values for model fitting. Currently, BioModels Parameters contains over 63,000 entries with data from 14,000 reactions and 60 different organisms.These data are directly extracted from the curated SBML models and presented in a table for easy access and visualization. The table provides cross-references to the original model and publication which can be referred to understand the complete context of the parameter usage. Furthermore, model entities are cross-linked to standard resources such as UniProt, ChEBI, GeneOntology, Reactome, SABIO-RK, etc. Thus, BioModels Parameters, publicly available at https://www.ebi.ac.uk/biomodels/parameterSearch/index, will be a valuable resource for systems biology modellers.

Predicting rat heart left ventricular function by means of Gaussian process emulation

Stefano Longobardi[1], Alexandre Lewalle[1], Sander Land[1], William E. Louch[2], Anna Sher[3], and Steven Niederer[1]

[1]Biomedical Engineering Department, King's College London, London, City of Westminster, United Kingdom.

[2]Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Ullevål, Kirkeveien 166, NO-0407 Oslo, Norway.

[3]Internal Medicine Research Unit, Pfizer, Cambridge, Massachussetts, United States.

In this study, we employ mathematical models to quantitatively characterise a healthy rat left ventricle's contractility function. In order to do this, we make use of a computational model of heart electrophysiology and calcium dynamics, sarcomere contraction and mechanics derived from real ventricles geometries. Fitting the arising multi-scale heart contraction model to experimental data remains a massive challenge. Bayesian history matching (HM) technique has been shown to be a valuable approach for global parameter inference when fitting models of high-dimensional parameter spaces. HM is an iterative process that reduces the model's input space by discarding regions that are unlikely to match experimental data. HM commonly makes use of Gaussian processes (GPs) which are computationally efficient surrogates of the model. Previously employed for fitting models of galaxy formation [1], infectious disease transmission [2], plant physiology [3] and lately human atrial cell [4], HM has never been applied (to our knowledge) in the context of whole organ cardiac models nor multi-physics problems. Here we employ HM technique to fit the mathematical multi-scale model, discerning physiologically meaningful regions of the inputs parameter space. By simulating all the points obtained in the last HM iteration, we show that the identified high-dimensional region is able to reproduce features experimentally observed in the reference rat and in agreement with literature values.

[1] Ian Vernon, Michael Goldstein, and Richard G. Bower. Galaxy formation: a Bayesian uncertainty analysis. Bayesian Anal. , 5(4):619–669, 12 2010.

[2] Ioannis Andrianakis, Ian Vernon, Nicky McCreesh, McKinley TJ, Jeremy Oakley, Rebecca Nsubuga, Michael Goldstein, and Richard White. Bayesian history matching of complex infectious disease models using emulation: A tutorial and a case study on hiv in uganda. PLoS Computational Biology , 11:e1003968, 01 2015.

[3] Elizabeth Vernon and Joann Tschanz. Dopamine , pages 1–2. Springer International Publishing, Cham, 2017.

[4] S. Coveney and R. H. Clayton. Fitting two human atrial cell models to experimental data using Bayesian history matching. Prog. Biophys. Mol.
Biol. , 139:43–58, 11 2018.

Multiscale modelling approaches to describe drug-induced gut toxicity

Carmen Pin
Clinical Pharmacology, ADME, & AI, Clinical Pharmacology & Safety Sciences, Biopharmaceuticals R&D, AstraZeneca, Cambridge, UK.

In instances where gastrointestinal tract (GI) toxicity is mediated by on-target mechanisms, such as oncology treatments, it is not feasible to mitigate the liability through compound screening or optimization during drug discovery. An alternative is to optimize clinical dose and schedule using mathematical models. Emerging multiscale models enable the prediction of toxicity and recovery at multiple spatial and temporal scales. They are instrumental to quantify how target organs respond to toxicological challenges as a whole and at each structural level. In this presentation, we will discuss modelling approaches able to describe the propagation of drug toxicity across scales in the gastrointestinal (GI) epithelium and how these approaches may enable quantitative predictions of GI clinical adverse effects based on the compound mechanism of action. We will use the data and models generated within TransQST project to illustrate the application of computational models to bridge scales and connect molecular toxicity with epithelial disruption in the gut.

QSP/AI/ML a match made in heaven or hell?

Hitesh Mistry[1] and James Yates[2]
[1]Division of Pharmacy/Cancer Sciences, University of Manchester.
[2]AstraZeneca.

AI/ML has become the new buzz phrase in academic science and has been plied to just about any daily prediction task from survival prognosis in Oncology through to predicting re-offending risk and making financial investment decisions. Many of the original studies have been argued to be biased as favouring ML/AI approaches. Indeed the examples presented will highlight in many fields AI/ML gave rise to a false dawn and the repercussions have been quite dramatic including a recent lawsuit. The examples presented should serve as a warning to others wanting to utilise AI/ML approaches especially in a field where the noise in the input data can be higher than the output and the bulk of the data is simply not reliable. Finally a presentation of a combined mechanistic modelling/ML example from the literature will be shown from the pharmaceutical industry which highlights how to perform a near perfect con.

POSTERS
(Underlined names are those presenting)

A Tool to Enable Best Practices in Quantitative and Systems Pharmacology Models
Paul Andrews[1,2], Jacob Busfield[1,2], Ed Clark[1,2], Becky Naylor[1,2], Adam Nellis[1,2] and Andy Turner[1,2]
[1] Simomics, IT Centre, Innovation Way, York, YO10 5NP, UK, https://www.simomics.com
[2] Department of Electronic Engineering, University of York, York, YO10 5DD, UK

Cucurull-Sanchez et al. [1] present a set of best practices for QSP practitioners in academia and industry aimed at maximising the impact of their models. Adhering to these best practices provides a framework for the development, testing and documentation of QSP models that should promote their reproducibility, reusability and application in new contexts.

Simomics develops cloud-deployed software tools to facilitate model evidencing and curation, with the aim of improving model transparency and confidence. These tools are used to expose model design decisions, reveal supporting data, and facilitate communication of model outputs.

We present here a new tool to facilitate "Team Science" projects based around mathematical and computational models. The tool couples model evidencing with configurable workflows to enable a team of modellers and clinical scientists to work effectively and collaboratively. It can be configured to support modelling projects that follow the six QSP workflow steps proposed in Table 2 of Cucurull-Sanchez et al. [1]. The six workflow steps map to the following functionalities of the tool: "1. Purpose and context of the model" -- stating project aims including their status (open, resolved) and impact, inclusion of key stakeholders (see user model described below), and describing the overall model context; "2. Model structure and modeling methodology" -- uploading model source code files and attach supporting evidence statement (with sources) to individual code concepts, identification and evidencing of model parameters; "3. Input data, knowledge and assumptions going into the model" -- recording the model scope, assumptions and limitations (with supporting evidence), uploading data files; "4. Model verification", "5. Model validation" and "6. Model results, application, and impact" -- recording sets of experiments run with the model, linking to model code files used, uploading and visualising model outputs (plots, result data files etc), and linking experiment outputs back to project aims.

The tool incorporates a flexible user model to allow groups of users to work on different aspects of projects and to raise potential issues with other users on elements of model evidencing, data and results within the tool. The tool is populated with exemplar QSP (and other systems biology) models to demonstrate how it can be used to facilitate maximising model impact.

[1] Cucurull-Sanchez, L., Chappell, M.J., Chelliah, V., Cheung, S.Y.A., Derks, G., Penney, M., Phipps, A., Malik-Sheriff, R.S., Timmis, J., Tindall M.J., van der Graaf, P.H., Vicini, P., and Yates, J.W.T., "Best Practices to Maximize the Use and Reuse of Quantitative and Systems Pharmacology Models: Recommendations From the United Kingdom Quantitative and Systems

Multiscale Modelling of Drug Transport and Metabolism in Liver Spheroids

Rachel Bearon[1], Joseph Leedale[2] and Steven Webb[2].
[1]Department of Mathematics, University of Liverpool.
[2]Department of Mathematics, Liverpool John Moores University.

In early preclinical drug development, potential candidates are tested in the laboratory using isolated cells. These *in-vitro* experiments traditionally involve cells cultured in a two-dimensional monolayer environment. However, cells cultured in three-dimensional spheroid systems have been shown to more closely resemble the functionality and morphology of cells *in-vivo*. While the increasing usage of hepatic spheroid cultures allows for more relevant experimentation in a more realistic biological environment, the underlying physical processes of drug transport, uptake and metabolism contributing to the spatial distribution of drugs in these spheroids remain poorly understood. The development of a multiscale mathematical modelling framework describing the spatiotemporal dynamics of drugs in multicellular environments enables mechanistic insight into the behaviour of these systems. Here, our analysis of cell membrane permeation and porosity throughout the spheroid reveals the impact of these properties on drug penetration, with maximal disparity between zonal metabolism rates occurring for drugs of intermediate lipophilicity. Our research shows how mathematical models can be used to simulate the activity and transport of drugs in hepatic spheroids, and in principle any organoid, with the ultimate aim of better informing experimentalists on how to regulate dosing and culture conditions to more effectively optimise drug delivery.

Ligand binding dynamics and the effects of cooperativity: linear and nonlinear models for dimerised receptors

Carla White[1] Lloyd Bridge[2]
[1]Swansea University
[2]University of West England

It is now widely accepted that consideration of binding and signalling dynamics is an important factor in the drug discovery process. Furthermore, there is widespread acknowledgement that many receptors, such as G protein-coupled receptors (GPCRs), may exist as dimers, whilst others dimerise in response to ligand binding. As classical receptor theory is built around monomeric receptor assumptions, an extension of this to include dimers is required in order to classify, quantify and simulate ligand-receptor interactions and their signalling outcomes. A key factor in developing theoretical models of dimer signalling is cooperativity, whereby the binding of a ligand to one receptor aects the binding of another receptor. We present and analyse two models for ligand binding dynamics as an essential building block in the development of dimerised receptor theory. Our rst model, a linear model for dimerised GPCRs, assumes that all receptors are pre-dimerised, where each of these are able to bind a single drug molecule. Our second model focuses on a vascular endothelial growth factor (VEGF) system. These receptors exist as monomers, and dimerisation is triggered upon ligand binding. Once a ligand molecule is bound to a receptor the ligand reversibly binds a second ligand, instantaneously dimerising the two receptors. The resulting ODE system for this model is nonlinear so we use both numerical and perturbation methods to analyse the intricacies of the time-course dynamics

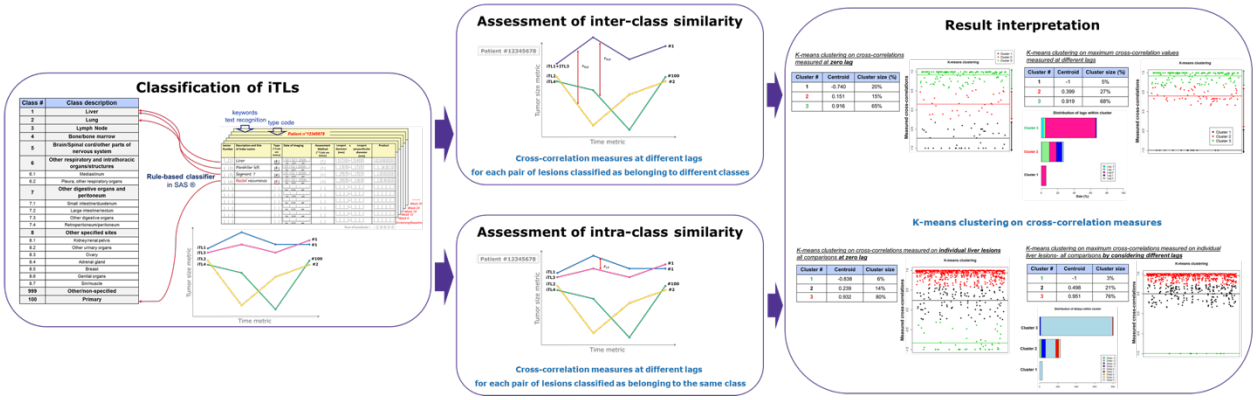
CICIL analysis of individual target lesions for tumor size models of drug resistance: a new methodology encompassing signal processing and machine learning

N. Terranova[1], P. Girard[1], A. Munafo[1]
[1]Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland.

Objectives: Developing a methodology to evaluate the gain in classifying individual tumor lesions (iTLs) into different tissues, to be used further in modelling of resistance to anticancer drugs, rather than the sum of tumor sizes.

Methods: A novel methodological approach for the non-parametric analysis of iTLs has been defined by integrating knowledge from signal processing and machine learning [1]. We called this new methodology ClassIfication Clustering of Individual Lesions (CICIL). The proposed workflow uses (i) a rule-based algorithm to classify iTLs based on functional and location criteria, (ii) the cross-correlation to estimate the similarity among classified TL dynamics by also considering potential delays, (iii) K-means clustering on cross-correlation measures to obtain a straightforward result interpretation. Thanks to the defined classification, the assessment of similarity of TL dynamics can be then performed both at the inter-class level (i.e., among TLs differently classified) and intra-class level (i.e., among iTLs similarly classified) (Figure 1).

Figure 1. Steps of the proposed methodology, simplified on one subject data, are shown for both inter-class and intra-class analyses. Classification of iTLs is automatically performed through a rule-based classifier based on keywords recognition in the lesion description and on the type code reported by physicians in the Case Report Form (CRF). Once iTLs have been classified, the similarity of their dynamics can be assessed by calculating cross-correlation measures for each pair of lesions classified in different classes in case of inter-class analysis, or within the same class in case of intra-class analysis. As cross-correlation measures are also calculated at different lags, maximum cross-correlation values can be used to assess at which delay the degree of similarity among lesion dynamics is maximized. Result interpretation is then facilitated by the adoption of the k-means algorithm for clustering cross-correlation measures at zero lag as well as maximum cross-correlations obtained by considering different lags.



Results: We have classified 2038 individual target lesions of 642 mCRC patients from two Phase II studies. Different dynamics of classified TLs were highlighted in 30% of patients involved in the inter-class analysis. In particular, 35% of cross-correlation measures computed without considering any delay indicated poor similarity. The degree of similarity substantially increased when considering delays between lesion dynamics. Similarity of iTLs dynamics was mainly indicated by results of the intra-class analysis.

Conclusions: The proposed approach, flexible enough to be applied to many cases and at different levels, provides a deeper understanding of available data and guides next modelling steps [2] by coupling the information on target TLs along with the lesion dynamics. A Java-based cross-platform implementation of the CICIL methodology was recently made available to the scientific community [1].

References:

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Modelling Anti-NGF activity in Quantitative Systems Pharmacology (QSP) Network: Tanezumab Case study

Pradeep Sharma[1], Peter Thornton[2], Michael Perkinton[2], Ian Gurrel [3]

1. Clinical Pharmacology, ADME, & AI (CPAA), Clinical Pharmacology & Safety Sciences, AstraZeneca, Cambridge, UK
2. Discovery Biology, Neuroscience, R&D BioPharmaceuticals, AstraZeneca, Cambridge, UK
3. DMPK, Neuroscience, R&D BioPharmaceuticals, AstraZeneca, Cambridge, UK

Nerve growth factor (NGF) is an important mediator of pain initiation and maintenance. Pharmacotherapies targeting this pathway have shown potential in the treatment of a variety of nociceptive and neuropathic pain conditions. Systems biology models for NGF signalling have been previously reported in literature [1]. We aim to apply these models in quantitative pharmacology by inclusion of drug pharmacokinetics, target engagement and clinical outcome. Tanezumab (anti-NGF monoclonal antibody) is used as a case study to be applied in this model.

The model comprised central plasma (3.8 L), interstitial fluid (12 L) and neuron (0.0001 L) compartments. The distribution of species networked with biological pathways of NGF interactions with receptors, was modelled by mass transfer and receptor binding kinetics. Plasma concentrations of tanezumab (dose 10 µg/kg) were simulated by accounting for targeted-mediated disposition (k_{int}=0.0427 day^{-1}) [2,3]. These data, together with receptor binding kinetics (k_{on}=16.2μM^{-1} min^{-1}, K_{off}= min^{-1}) were used to simulate changes in total NGF levels; output was compared with clinically observed levels. Predicted concentration profiles of tanezumab and total NGF were within 2-fold of clinically observed data. A sensitivity analysis was run on key uncertain parameters (e.g., baseline NGF levels) to understand implications on tanezumab-NGF binding. Further work is on-going to optimise and validate the model with available clinical PKPD data at different doses and routes of administration. The validated model will be a useful tool to inform design and development of future anti-NGF therapies.

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Quantitative cross species extrapolation of IFN-α administration and induced cellular responses in liver between human and mice

Bastian Kister[1], Priyata Kalra[2], Sabrina Wohlfart[3], Mario Koester[4], Walter Mier[3], Lars Kuepfer[5] and Ursula Kummer[1]
1 Department of Modeling of Biological Processes, COS/BIOQUANT, University of Heidelberg, Germany.
2 BASF SE, Ludwigshafen, Germany
3 Department of Nuclear Medicine, Heidelberg University Hospital, Heidelberg, Germany. 4 Department of Gene Regulation and Differentiation, Helmholtz Centre for Infection Research, Braunschweig, Germany.
5 Competence Center Systems Biology and Computational Solutions, Bayer Technology Services, Leverkusen, Germany.

Traditionally, IFN-alpha has been used in the treatment of hepatitis C virus (HCV) infected patients; however, its efficacy and tolerance is not optimal, highlighting the need for a deeper insight into its pharmacology and toxicology. Mice are important animal models for the corresponding characterisation of pharmaceuticals. However, there is a gap in understanding the mechanistic reasons of why mice respond differently to drugs than humans. In 1959, Russell and Burch introduced the principles of "3R": Reduction, Refinement and Replacement to animal testing. In this context, quantitative systems pharmacology (QSP) is a promising approach to estimate the effective dose-response concentrations and to conduct cross species extrapolation for the same.

This work is an endeavour to provide a novel quantitative cross species extrapolation approach based on mechanistically detailed multiscale physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models of intravenous IFN-alpha injection and the induced responses and activation of the biomarker Mx2 via the JAK/STAT signalling pathway. By doing so, we are then able to calculate effective concentrations of the cytokine arriving at the liver after the injection in both mouse and humans and its impact on the signalling behaviour of the hepatocyte. This also provides then an in-depth understanding of the factors associated with the variability in the IFN-alpha response. To our knowledge, this study demonstrates first a mechanistic quantitative systems pharmacology (QSP) framework anchored to internal drug and response concentrations at the target site of action: the liver. Furthermore, in this study we illustrate the unique possibility to elucidate causes of inter-species variability in IFN-α administration.

An *in silico* mechanistic representation of an *in vitro* neutropenia assay to explore dose and schedules

Cristina C. Santini[1], Carla Guarinos[1], Alicia Benitez[1], Estela G. Torano[1], Mark McConnell[2], Matthew Trotter[1], James Carmichael[1], Soraya Carrancio[3], Alex Ratushny[2]
[1]Celgene Institute for Translational Research Europe
[2]Celgene Corporation, Seattle
[3]Celgene Corporation, San Diego

Objectives: Lenalidomide, an immunomodulatory agent, is approved for the treatment of multiple myeloma, del 5q myelodysplastic syndrome and mantle cell lymphoma. Lenalidomide causes a reversible block in neutrophil maturation. To investigate the dose and schedule that allows for neutrophil recovery, we developed an *in silico* model based on an *in vitro* assay. This model is applied to explore dosing regimens.
Methods: A compartmental model was developed to represent the *in vitro* maturation assay [1]. Donor related parameters were fitted to DMSO treatment data and compound related parameters were fitted to the effect upon treatment with a concentration range of lenalidomide.

Results: The proposed model quantitatively represents the *in vitro* neutropenia maturation system and the block in neutrophil maturation caused by lenalidomide. *In silico* predictions for neutrophil recovery after off-drug period were validated experimentally (predicted vs experimental data R^2 = 0.985).

Conclusions: An *in silico* model that represents an *in vitro* neutropenia assay was developed. Good parameter fit and validated predictions support the applicability of the model to explore dose and schedule of lenalidomide *in silico* and propose regimens that could minimize a key clinical toxicity of this compound.

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