

UK Quantitative Systems Pharmacology Network



Training Workshop

8th to 10th July 2026

University of Warwick, UK.

Welcome!

Welcome to the UK QSP Network July 2026 Training Workshop!

We are excited to bring together a range of researchers working on QSP in academia and industry. It is now some 11 years since we as a collective of enthusiastic researchers in QSP and it's related fields started our series of meetings. We are very pleased to have made it this far thanks to the support of people such as yourselves.

The future of QSP research looks bright and we hope from both the invited and submitted talks along with the poster presentations and the interactive training events, you will gain an insight into the current state of QSP research.

We are grateful to our colleagues in Warwick 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.

Organising Committee

Prof Mike Chappell (Warwick)
Dr Lourdes Cucurull-Sanchez (Pharmetheus)
Prof Marcus Tindall (Reading, Lead)
Dr James Yates (AstraZeneca)
Dr Mark Penney (AstraZeneca)
Dr Cristina Santini (Roche)

Meeting Venue

All activities will take place in Scarman Conference Centre, with simulations sessions happening in the School of Engineering, University of Warwick.

Registration desk & name badge

This can be found in the main foyer of the Scarman Conference Centre building. Your name badge serves as your unique identification for the meeting whilst on the Warwick 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/warwick-2026.html

A few paper copies are available at the registration desk.

Morning/Afternoon tea and lunch

Morning and afternoon teas will be served in Scarman Conference Centre lounge, right of the main reception desk.

Accommodation

If you are a full delegate then an ensuite room has been reserved for you in the University of Warwick Conference Centre accommodation entitled "Jack Martin". Keys for those delegates staying on campus can be collected from 15.00hrs. Time to check into accommodation has been allocated for between 15.00hrs and 19.00hrs on the evening of 8th July. Evening dinner for those attending on the 8th starts at 19.00hrs.

Please remember to check out of your accommodation by 9.30hrs on the morning of Friday 10th July. All rooms are pre-paid and delegates, unless otherwise agreed with the conference organisers, will need to pay for any extra costs on their departure. This includes drinks during the evening meals.

Breakfast

For those delegates staying on campus breakfast will be available each morning from 7.30hrs to 9.00hrs in the Scarman Restaurant.

Wednesday and Thursday evening meals

For full delegates this is included in your registration fee and will be served in the Scarman Restaurant.

Reception and Workshop dinner

The Workshop Dinner will be held on the evening of Thursday 9th July from 19.00 to 21.00 hrs in Scarman Restaurant. If delegates wish to purchase drinks during the meal, then they will need to meet the cost of this.

Bar

The Scarman bar is open each night of the week until 22.00 hrs. Alternative venues include The Dirty Duck in the Student's Union and Varsity just behind the Security Gatehouse.

Wifi access and Computing facilities

Wifi access is via eduroam. Computing facilities are available in rooms F211 and F215 of the School of Engineering Building and during your stay at the Conference Centre.

Parking permits

Parking permits for delegates staying on campus need to be obtained by entering your details at

These allow delegates to park in the car parks adjacent to their conference accommodation. For day delegates, parking permits can be obtained from the workshop registration desk in the IDL Building.

Posters

If you are displaying a poster please ensure this is placed on the poster display boards at the reception on the evening of Wednesday 8th July.

Library access

Delegates are welcome to use the University of Warwick Central Library. Access can be obtained by presenting photo ID and completing a short form at the Library helpdesk. Delegates will then be given a Reference Only day pass. Alternatively, for longer access you can complete a form for a full library card which is valid for a year.

Sport Centre Access

As a full delegate, you also get access to the facilities at the Warwick Sports Centre. If interested, please speak to a member of the conference centre reception team.

Luggage store

A secure luggage store is available in the Conference Reception.

Delegate attendance list

A delegate attendance list has not been included in this programme given it will appear on the Internet. A separate delegate 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 (Reading), Mike Chapell (Warwick) or any other member of the Organising Committee.

Meeting queries

If you have any queries during the meeting please contact Miss Chloe Smith or Prof Mike Chappell in the first instance. We will do our utmost to accommodate any requests.

Arriving at the University of Warwick

Location: Scarman | Warwick Conferences, University of Warwick, Scarman, Scarman Rd, Coventry CV4 7SH. Find on [Google Maps](#).

Please find information for traveling to the University of Warwick here: <https://warwick.ac.uk/fac/sci/eng/research/grouplist/biomedicaleng/qsp-uk/travelingtotheuniversityofwarwickforqspuk/>

This postcode will direct you to Gibbet Hill Road, the main road through the University. Follow signs for Lakeside Village, which will direct you to additional signposts for Scarman and Radcliffe.

Travelling by car?

Car parks for Scarman can be found at the rear of the centre. Follow the signposts once in Lakeside Village.

Register for attendee parking:

Click on the link: [Car Parking Conferences](#)

- Fill out all fields with your personal details (please enter dates for when your event is taking place)
- Enter the promotional code ***MOCZW*** (please ensure there are no spaces before the code as the system may recognise this as an additional character)

Traveling by train?

From Coventry Train Station

Coventry sits on the West Coast Mainline and is served by trains from London Euston, Birmingham (New Street and International) and Leicester, with frequent services running seven days a week. It is the recommended station for most visitors.

From the station:

- Taxi: A taxi rank operates outside the station. The journey takes roughly 10-15 minutes and costs approximately £10-15, depending on traffic.
- Bus: Take the number 11 or 12X bus, both of which stop at the Rail Station Bridge stop on Warwick Road, a one-minute walk from the station. Journey time is around 12–25 minutes depending on the service. A single fare is around £3.00 (correct at time of writing; please check current fares), and contactless/cash payment is accepted on board (note: some international cards may not work).

From Birmingham International Station

Birmingham International (which also serves Birmingham Airport) has a direct rail link to Coventry. During weekdays, trains depart from Birmingham International to Coventry on average every 10 minutes, with the journey taking between 10-15 minutes. This makes it a convenient option for delegates flying in via Birmingham Airport, simply take the train to Coventry and then follow the taxi/bus directions above.

From Birmingham New Street

Birmingham New Street also has regular direct services to Coventry. During weekdays, trains depart on average every 10 minutes, with the journey taking between 20-30 minutes depending on the specific service used. From Coventry station, follow the taxi/bus directions above to reach Scarman.

From London

Direct trains run from London Euston to Coventry on the West Coast Mainline, operated by Avanti West Coast and London Northwestern Railway, this is the most direct route and is recommended for delegates arriving from London. The journey typically takes around one hour to Coventry, plus onward transfer time to campus.

Alternatively, services from London Marylebone run to Leamington Spa, a nearby station also served by Warwick Conferences transport links from there, the U1 or U2 bus serves the campus, stopping at Parish Church Stand B, a seven-minute walk from the station. Note that Leamington Spa does not have a taxi rank, so pre-booking a taxi is advised if you'd prefer not to take the bus.



The UK QSP Leadership Team

	Prof Mike Chappell is a Professor within the School of Engineering at the University of Warwick where he leads the Biomedical and Biotechnology Research Cluster and co-leads the School's Biomedical Engineering Institute (the BMEI). He is also a Co-Lead for the University's Research Spotlight for Health, Technologies in Healthcare theme. He has research expertise in the systems modelling and data analysis of biomedical, pharmacokinetic/pharmacodynamic, biological and Quantitative and Systems Pharmacology (QSP) processes. Much of his work relates to the application to these fields of techniques in system dynamics, non-linear systems, data analytics, control and system identification with application to effective drug design and development, metabolic systems, cancer, diabetes, motion capture, orthotics and prosthetics. He also has specific expertise in structural identifiability and indistinguishability analyses that are important prerequisites to experiment design, model parameter estimation and model validation. He has had close research collaborations with the pharma industry for over 30 years. He led the Marie Curie funded European Industrial Doctorate training network in QSP on Innovative Modelling for Pharmaceutical Advances through Collaborative Training (IMPACT) in collaboration with AstraZeneca. He is also a partner in the current EU funded ERAMET (Ecosystem for RAPid adoption of modelling and simulation METHods to address regulatory needs in the development of orphan and paediatric medicines) project. He is a member of the Management Committee for the QSP-UK network, a member of the organising committee for the annual PKUK conference and is also a member of the International Federation for Automatic Control (IFAC) Technical Committee 8.2 on Biological and Medical Systems.
	Dr Lourdes Cucurull-Sanchez, PhD MPhil is a Principal Director MIDD consultant and QSP Scientific Lead at Pharmetheus AB. She has 20+ years of experience in the pharmaceutical industry, with 15+ years in Quantitative Systems Pharmacology and 8+ years in Machine Learning. She has held leadership positions at GSK and Pfizer, and a postdoc at the University of Cambridge. She is an elected trustee of the ISoP Board, Chair of ACoP 2026, former Chair of the ISoP QSP SIG, former IQ Consortium member, founder of the UK QSP Network, and member of ASCPT. Lourdes has a PhD and an MPhil in Chemistry (Universitat Autònoma de Barcelona & University of Newcastle upon Tyne). She is a proud champion of equity principles, active scientific conference speaker (+30 invited communications) and author (H-index = 21). She serves as reviewer for several scientific journals and events, and as editorial board member for the Quantitative Medicine journal.
	Dr Mark Penney is a Director of Translational PKPD and DMPK in Oncology, AstraZeneca. He has over 20 years of experience in applying mathematical modelling in the pharma industry, from early in discovery through to late-phase clinical trials and therapeutic areas. He much prefers early discovery, believing that mechanistic modelling here can bring unique insights and more optimal drugs through to clinical testing.

	Dr. Cristina Santini is a Senior Principal Scientist at Roche (Basel), working as a Disease Modeler on the Pharmaceutical Sciences department. The Disease Modeling team develops quantitative models of disease using preclinical/clinical data. These models then inform clinical outcomes and individualized drug predictions for optimal patient treatment through model simulation. Dr. Santini is a Computer Engineer, with an MSc in Artificial Intelligence and a PhD in Electronics from the University of York, UK.
	Prof Marcus Tindall (Lead, UK QSP Network) is Professor of Mathematical Biology in the Department of Mathematics and Statistics at the University of Reading, UK. He started his academic career in 1993 with a parallel BA (Mathematics/German) and BSc (Physics), followed by a 1st class BSc honours degree in Mathematics at the University of Queensland, Brisbane, Australia. This was followed by a 4 year UK Overseas Research Council PhD Fellowship in Applied Mathematics in The Department of Mathematics at the University of Southampton, the work focused on avascular tumour growth. He then headed on to the University of Oxford for postdoctoral work in the Mathematical Institute where for the first two years he focused on research and developing new interdisciplinary collaborations between mathematicians and life scientists, leading to the funding of numerous research grants. This was followed by a three year BBSRC funded grant focused on modelling bacterial chemotaxis with Profs Judy Armitage (Biochemistry) FRS and Philip Maini (Mathematics) FRS. His career at Reading commenced in 2008 with a five year RCUK Fellowship, to establish Systems Biology and Mathematical Biology at the University of Reading. He became a Professor in 2022. Marcus' research covers a wide range of application in the biological, medical, pharmacological and food systems sciences. He has worked in the areas of tumour growth, bacterial cell regulation, platelet regulation, cholesterol regulation, antibiotics, multi-scale crop growth, model parameterisation, systems toxicology, wound healing and more recently the development of high fibre white bread and the resilience of UK fruit and vegetable supply chains. Forthcoming work is focused on modelling adrenal gland function and disruption. His work uses a range of mathematical approaches including dynamical systems theory, numerical and asymptotic analysis and agent based modelling. He has developed undergraduate courses in Systems Biology, Mathematical Biology and Pharmacology and works closely with researchers in academia and industry. He initiated the UK QSP Network in 2015 with funding from the EPSRC and MRC in collaboration with academic and industry colleagues, many of which now for 11 years of yearly activities he is proud to write that we have developed a close working community in QSP research.
	Dr James Yates, MMath, PhD, is currently Head of Translational and Clinical Pharmacology at Khanda Therapeutics. He also holds an honorary Professorship at the University of Warwick, UK. He has over 20 year's experience of applying mathematical modelling in drug discovery and development, across oncology, infectious disease and immunology. In this time he has worked with a broad range of modalities, including NCEs, biopharm and oligonucleotides. He has a deep interest in the development of translational modelling approaches to optimise drug R&D. He has published over 100 peer review papers on this topic.

Programme

<i>Wednesday 8th July 2026</i>	
18.00-21.00	Registration, posters and dinner.
15.00-21.00	Check into accommodation (Residential attendees)

<i>Thursday 9th July 2026</i>	
	Breakfast for residential attendees
9.00-9.05.	Introduction
9.05-9.45	Best Practices on QSP Model Reporting for Regulatory Use: perspectives from ISoP QSP SIG Working Group with spotlight on Virtual Populations and AI <i>Alexander Kulesza</i> ESQ Labs
9.45-10.25	Target mediated drug disposition (TMDD) <i>Dave Fairman</i> GSK
10.25-11.05	From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modelling <i>Alberto Ippolito</i> Merck
11.05-11.30	Break and posters
11.30-12.10	Mechanistic models of respiratory viral dynamics to quantify antiviral effects in vivo <i>Joesph F Standing</i> UCL
12.10-12.40	Finding the Minimum Requirement for a Capecitabine Hand-foot Syndrome Trial through Ordinal Modelling <i>Zijn Lin</i> University of Liverpool
12.45-13.45	Lunch
13.45-14.25	Industrial and regulatory use of mechanistic mathematical models: lessons from cardiac safety assessment <i>Gary Mirams</i> Nottingham
14.25-15.05	Can Large Language Models Support QSP Modelling? Insights from Building QSP-Copilot <i>Anuraag Saini</i> Boehringer-Ingelheim
15.05-15.45	Can mechanistic models improve dose scheduling? <i>Carina Dunlop</i> UCL
15.45-16.00	Break and posters
16.00-16.30	Assessing Practical Identifiability and Predictability in Quantitative Systems Pharmacology Models <i>Ivan Borisov</i> (InSysBio CY)
16.30-18.15	Interactive training event: Introduction to Julia (InSysBio) & Simbiology <i>Ivan Borisov (InSysBio CY), and Jérémy Huard (MathWorks)</i>
18.15-19.00	Break
19.00-21.00	Workshop Dinner

<i>Friday 10th July 2026</i>	
	Breakfast for residential attendees
9.00-9.40	Mechanistic PK/PD framework for T cell engager-induced peripheral B cell depletion

	<i>Pieter Van Brantegem</i> Johnson & Johnson
9.40-10.10	Maternal–foetal PBPK modelling of daily oral versus long-acting injectable aripiprazole and olanzapine during pregnancy <i>Philip Bediako – Kakari</i> University of Liverpool
10.10-10.50	Quantitative Systems Toxicology for Crop Protection: A HPPD Herbicide Case Study <i>Steve Webb</i> Syngenta
10.50-11.20	Break
11.20-11.50	No One-Size-Fits-All: A Multi-Model Evaluation of Optimization-Based and Surrogate-Assisted Virtual Population Generation in QSP <i>Federico Reali</i> University of Trento
11.50-12.20	Quantitative parameter free methods for toxicokinetics <i>Inzish Sajid</i> University of Reading
12.20-13.15	Lunch
13.15-14.15	Actual intelligence, thoughtfully integrated: Computation-in-the-Loop as a Paradigm for Agentic QSP <i>Priyata Kalra</i> Simulation Plus
14.15-14.45	Feedback, discussion, thanks and close.

Abstracts

INVITED TALK ABSTRACTS



Best Practices on QSP Model Reporting for Regulatory Use: perspectives from ISoP QSP SIG Working Group with spotlight on Virtual Populations and AI

Alexander Kulesza (ESQlabs GmbH, Germany)

Quantitative Systems Pharmacology (QSP) has matured into a mainstream and regulatory grade component of Model-Informed Drug Development (MIDD). Yet the field continues to lack overarching standards for this intrinsically diverse family of modeling tools, especially with regards to model development, assessment and application reporting. In 2024, the ISoP QSP SIG Working Group on Credibility Assessment was launched to draw on the community experience of QSP practitioners for addressing this gap. The resulting white paper ([\[2604.07811\] Best Practices on QSP Model Reporting for Regulatory Use: perspectives from ISoP QSP SIG Working Group](#)) proposes consensus best practices for QSP model reporting and credibility assessment for regulatory use, with a particular focus on Context of Use, reproducibility, and structured documentation requirements, of which key elements will be outlined. A central theme is the credibility of Virtual Populations (Vpops). As virtual trial simulations become more prevalent in regulatory submissions, evaluating Vpop performance is as critical as validating the underlying model. The talk therefore touches on "traditional" Vpops versus emerging digital twin approaches and proposes context-dependent evaluation and workflows for uncertainty assessment. Looking ahead, the integration of AI into QSP workflows introduces both opportunity and new credibility challenges. We will discuss the implications of QSP-AI hybrid models for reporting standards and regulatory expectations and outline the key unmet needs and guidance gaps that the field must address as these approaches move toward submission readiness.

Alexander is a Chemist with a PhD focusing on theoretical and computational methods for structural and optical property predictions. He then spent several years in academia (U. of Lyon) working on molecular dynamics simulation and free energy methods dedicated to protein structure and aggregation. Alex moved to systems pharmacology applying large-scale disease and quantitative systems pharmacology models integrated into clinical trial simulations, across a number of disease areas. Alex is now leading the QSP team within ESQlabs with the aim to promote widespread application of integrated PBPK and QSP modeling. He is also currently affiliated at the pharmacy Department of University of Namur, working towards better qualifying PBPK/QSP for regulatory decision making. In line with these two activities, he joined the International Society of Pharmacometrics (ISoP) QSP Special Interest Group Working Group on Credibility Assessment of QSP for Regulatory Use, proposing best practices for QSP model reporting in regulatory settings.



Target mediated drug disposition

Dave Fairman (GSK)

Target-mediated drug disposition (TMDD) is commonly observed with monoclonal antibodies because high-affinity binding to high-abundance and/or rapidly eliminated targets can strongly influence both pharmacokinetics and lead to complexity in interpreting effects on free target levels. This presentation will utilise examples of mAbs binding to soluble targets to illustrate the complexities of interpretation, challenges and best practise with bioassay strategies, and common challenges with data analysis including addressing identifiability.

Dave is currently Respiratory and Immunology CPMS Translational head and is accountable for Clinical Pharmacology input into preclinical projects plus oversight and guidance of the Clinical pharmacology aspects of early phase clinical studies. His background is in translational pharmacology with a specialisation in biologics including TMDD modelling and biologics assay selection best practise.

Previous experience includes the Clinical Pharmacology and Drug Metabolism and Pharmacokinetics department at MedImmune (AZ). His portfolio included preclinical and clinical biologics projects spanning the Oncology and Cardiovascular Therapy Areas with a focus on diabetes. Immediately prior to this position he led the Allergy & Respiratory preclinical modelling team at Pfizer and was responsible for the delivery of multiple small molecule candidate PKPD/dose prediction packages for compounds progressing to human clinical studies.



From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modelling

Alberto Ippolito (Merck)

Virtual patients and digital patients/twins are two similar concepts gaining increasing attention in health care with goals to accelerate drug development and improve patients' survival, but with their own limitations. Although methods have been proposed to generate virtual patient populations using mechanistic models, there are limited number of applications in immuno-oncology research. Furthermore, due to the stricter requirements of digital twins, they are often generated in a study-specific manner with models customized to particular clinical settings (e.g., treatment, cancer, and data types). Here, we discuss the challenges for virtual patient generation in immuno-oncology with our most recent experiences, initiatives to develop digital twins, and how research on these two concepts can inform each other.

Alberto Ippolito is an Associate Director of Translational Quantitative Pharmacology (TQP) for Merck Serono, part of Merck KGaA. He began QSP modelling during his postdoctoral fellowship at the Johns Hopkins School of Medicine and then continued his training when he joined the Early Oncology DMPK modelling and simulations team at AstraZeneca. At Merck, Alberto constructs QSP models for a range of modalities in oncology, autoimmune disorders and infertility.



Mechanistic models of respiratory viral dynamics to quantify antiviral effects in vivo

Joseph F Standing^{1,2,3}

1. School of Pharmacy, University College London, London, UK.
2. Department of Pharmacy, Great Ormond Street Hospital for Children, London, UK.
3. Department of Clinical Pharmacology, University of Stellenbosch, Stellenbosch, SA.

Antivirals have a potentially crucial role to play in the early treatment of respiratory viral infections in cases where vaccine prevention is unavailable or limited, and in particular in immunocompromised patients and neonates/young infants, in whom usually self-limiting infections can cause serious illness. In order to replicate, viruses need to enter host cells, in this case usually in the respiratory epithelium, meaning models which account for both host and viral dynamics may be required to capture antiviral effect. These models consist of ordinary differential equations describing the time course of virus and immune components and parameters estimated using nonlinear mixed effects. In this talk, using the target cell limited model as a basis, simplifications and extensions will be discussed to show the inferences that can be made on antiviral effects in clinical antiviral trials, and how these models can be used to predict optimal dosing, timing and treatment duration. In addition in vitro antiviral screening methods will be discussed and initial ideas on extrapolating models built on in vitro data to human challenge viral dynamics will be presented.

References: Agyeman AA 2022 Br J Clin Pharmacol. 88(12):5428-5433. Gastine S 2021 Clin Pharmacol Ther. 110(2):321-333. Kamal MA 2015 AAC 2015:59;5388. Lowe DM 2022 PLoS Med. 2022 19(10):e1004120. Nguyen TB 2025 JID 2025. Standing JF 2023 Lancet Infect Dis. 23(2):132-133. Standing JF 2024 Nat Commun. 2024 Feb 23;15(1):1652. Zhang S 2023 CPT:PSP 12(10):1450-1460.

Prof Standing is an academic and hospital pharmacist who holds a PhD in clinical pharmacology, and MSc in Statistics. Prior to becoming a professor he held two UK Medical Research Council academic fellowships (Methodology 2011-2015, Clinician Scientist 2015-2020) which led to the development of a paediatric pharmacometrics research group at the UCL Great Ormond Street Institute of Child Health. The main research interests of the group are in undertaking clinical and pre-clinical pharmacokinetic-pharmacodynamic (PKPD) with the aim to improve the evidence base of medicines for children. Therapeutic areas include infectious diseases, oncology, critical care and neurology. The group is funded from research council and European agencies, charities/non-profit, and pharmaceutical industry collaborations. In addition, Prof Standing Leads a MSc module and short-course entitled "Pharmacometrics", where students gain theoretical and practical computational knowledge on population PKPD.



Industrial and regulatory use of mechanistic mathematical models: lessons from cardiac safety assessment

Gary Mirams (University of Nottingham)

Mechanistic mathematical models of cardiac electrophysiology, developed over seven decades from the Hodgkin-Huxley equations to multi-scale descriptions of the human ventricular action potential, have recently entered international regulatory guidance through the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative. CiPA was motivated by the high false-positive rate of QT prolongation as a cardiac safety marker, and replaces it with a multi-ion-channel assay coupled to in silico simulation, producing a quantitative Torsade risk score calibrated against a reference set of marketed compounds with consensus risk classifications. We examine what CiPA's partial regulatory success reveals about the conditions under which mechanistic models gain

	regulatory acceptance: the importance of separating training from validation data, the need to quantify and propagate uncertainty from ion channel screening through to risk predictions, and the difficulty of demonstrating statistically that incremental model improvements translate to better risk classification. The talk closes with open questions in uncertainty quantification and model complexity that remain to be addressed.
Gary is a Professor of Mathematical Physiology at the University of Nottingham Centre for Mathematical Medicine & Biology. His team works in electrophysiology and uses mathematical models to understand how drugs interact with multiple cardiac ion channels and the consequences of this. He is working with a number of pharmaceutical companies and the US Food & Drug Administration to embed modelling in drug safety assessment, and develops free open source software to perform the simulations.	

	Can Large Language Models Support QSP Modelling? Insights from Building QSP-Copilot <i>Anuraag Saini (Boehringer-Ingelheim)</i> QSP workflows in pharmaceutical R&D are severely bottlenecked by manual knowledge integration, labor-intensive coding, and inconsistent reproducibility. To address these scalability challenges, we present a novel architectural framework that integrates Large Language Models (LLMs) within a modular, multi-agentic system. This approach orchestrates autonomous agents to handle the end-to-end modeling lifecycle, from automated literature mining and knowledge graph construction to mathematical formulation and code generation. By embedding "human-in-the-loop" validation and strict provenance tracking, the architecture automates routine tasks, reducing development timelines by 40% while ensuring the scientific rigor and transparency required for regulatory decision-making.
	Anuraag Saini is a Quantitative Systems Pharmacology Scientist at Boehringer Ingelheim with a decade of experience in developing mechanistic modeling frameworks across inflammation and oncology. He co-developed QSP-Copilot methodology that integrates agentic workflows into QSP. Trained as a mechanical engineer at IIT Madras, he brings a rigorous quantitative foundation from his diverse experience which continues to inform his approach to mechanistic modelling.

	Can mechanistic models improve dose scheduling? <i>Carina Dunlop (UCL)</i> At the centre of mathematical models of tumour treatment as used in pre-clinical drug discovery work are empirical growth laws. These are well-suited for fitting to the data available, mostly longitudinal studies of tumour volume, however, beyond these short time windows predictive power can be compromised. In contrast, in the academic mathematical biology community mechanism-based models form a key focus of research. However, can these complex models ever be fit-for-purpose in the real-world context of use? I will address the challenges and benefits of integrating spatial mechanistic models into preclinical trials. I will present how spatially resolved models can be reduced to a growth law of a similar form to those currently widely adopted and will show how incorporating mechanistic and nonlinear tumour dynamics could improve the design of dosing schedules.
	Dr Carina Dunlop is Associate Professor in Applied Mathematics in the Dept. of Mathematics, University College London. She obtained her undergraduate degree in Mathematics and a PhD (DPhil) in Applied Mathematics from the University of Oxford. She then moved into working on biological systems for her postdoctoral research first in Oxford at the Centre for Mathematical Biology and then as a BIOMS research fellow at Heidelberg University, Heidelberg, Germany. Her laboratory works at the interface of mathematics, physics and computer science generating advanced computational models that incorporate physical forces and a spatial perspective. In early cancer modelling work, she investigated mechanisms underlying the lag times observed in colorectal cancer progression and the formation of colorectal polyps. Currently, her lab is working on spatially averaged growth models for preclinical drug trials and the investigation of optimal dosing protocols.



Assessing Practical Identifiability and Predictability in Quantitative Systems

Pharmacology Models

Ivan Borisov (InSysBio CY)

Background: Virtual Populations (VPops) are widely used in quantitative systems pharmacology (QSP) to predict the variability in patient responses observed in clinical trials. Several approaches for VPop generation have been proposed [1,2]. However, their practical application in real-world QSP projects is often challenged by endpoint-specific requirements, limited availability of individual patient data, and computational complexity.

Assessing Practical Identifiability and Predictability in Quantitative Systems Pharmacology Models Practical identifiability addresses the crucial question of how well a mechanistic model is constrained by the available experimental data. In a typical model calibration workflow, practical identifiability analysis typically assumes that structural identifiability has already been established. However, profile likelihood-based practical identifiability analysis is often used as a surrogate for structural identifiability assessment when the complexity of QSP models limits the applicability of structural methods. Furthermore, the same profile likelihood framework can be extended beyond parameter analysis to quantify uncertainty in model states and predictions. As a result, practical identifiability and predictability analyses play a crucial role in the development of QSP models. This talk will introduce the concepts of practical identifiability and predictability using representative models from the Benchmark Initiative repository. Through these examples, we will demonstrate how profile likelihood analysis can be used to assess parameter uncertainty, detect non-identifiable parameters, and quantify uncertainty in model predictions using LikelihoodProfiler.jl, an open-source Julia package for profile likelihood-based uncertainty analysis. The strengths and limitations of profile likelihood methods will be discussed in comparison with alternative identifiability approaches, including Fisher Information Matrix-based analyses. Different profiling strategies and their practical application to QSP models will be illustrated. The presentation will also address several open challenges in identifiability analysis, particularly in the context of large-scale mechanistic models. Finally, we will discuss how identifiability and predictability analyses can inform other model development activities, including optimal experimental design and model reduction.

Ivan received his Master's degree in Mechanical Engineering from the Department of Mathematics and Mechanics of Lomonosov Moscow State University in 2011. After graduation, he worked at IBM East Europe/Asia as technical specialist in IBM Software products.

In 2017, he joined InSysBio, a Systems Biology and QSP company, where he works as a mathematician and software developer. He contributes to the development of key software tools for QSP model simulation and analysis, including the practical identifiability toolkit LikelihoodProfiler.jl and packages for virtual patients generation. In addition to software development, his research focuses on advancing mathematical and computational methods for QSP modelling, with particular interests in practical identifiability, model predictability, virtual populations, and optimal experimental design. Ivan is the author and co-author of InSysBio scientific publications and his works are annually presented at international conferences including PAGE and ACoP.



Scalable parameter prioritization in large QSP models: Feature ranking methods as a complement to GSA (Interactive session)

Jérémy Huard (MathWorks)

Global Sensitivity Analysis (GSA) is a key tool of Quantitative Systems Pharmacology (QSP) for identifying influential parameters and understanding model behaviour. Variance-based methods such as Sobol indices provide comprehensive insights into parameter effects and interactions. However, their computational cost scales poorly with model size and parameter dimensionality, often requiring large numbers of model evaluations. This poses a practical limitation for routine application in large-scale QSP models.

In this work, we investigate the use of feature ranking and selection methods from data science as a computationally efficient pre-screening step for parameter prioritization. Techniques including Minimum Redundancy Maximum Relevance (mRMR), F-test-based ranking, ReliefF, and Shapley value-based approaches are applied to simulation datasets generated from QSP models using space-filling sampling designs. These methods estimate parameter importance with substantially fewer model evaluations than traditional GSA.

Although both feature ranking methods and variance-based GSA rely on simulation datasets derived from space-filling sampling, the number of required model evaluations differs substantially. Feature ranking techniques can provide robust parameter prioritization from relatively small sample sizes, whereas Sobol-based GSA typically requires orders of magnitude more simulations to accurately quantify main and interaction effects.

We propose a workflow in which feature-based rankings provide an efficient first-pass prioritization, reducing the parameter space prior to applying variance-based GSA for detailed quantification. This combined strategy enables a more targeted and tractable sensitivity analysis while preserving the strengths of established GSA methods.

This one-hour session will be conducted as a hands-on workshop. Participants will be guided through the different methods presented, with explanations of their underlying principles and practical implementation. An example QSP workflow will be run interactively, allowing attendees to apply feature ranking techniques on a published QSP model.

Jérémy Huard is a Principal Application Engineer for Quantitative Systems Pharmacology at MathWorks, the maker of MATLAB and SimBiology. He supports pharmaceutical companies in their modelling efforts by presenting workflows, delivering training, and performing proof-of-concepts. Before joining MathWorks in 2013, Jérémy worked in the field of Systems Biology, specifically on integrating the effects of proliferative signalling pathways with the hepatocyte cell cycle at the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, Germany. He holds a M.Eng. (Dipl-Ing) with a major in Biomedical Engineering from Télécom Physique Strasbourg, France.



Mechanistic PK/PD framework for T cell engager-induced peripheral B cell depletion

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Background: B cell dysregulation and autoantibody production drive many autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (1). B cell depletion has shown clinical efficacy. T cell engagers (TCEs) link B and T cells, forming a complex that activates T cells and induces B-cell killing (2). This approach is expected to achieve deep B cell depletion and potentially enable durable, drug-free remission.

Aim: To explore the relationship between receptor-level TBE kinetics, measured in vitro, and B cell depletion in patients.

Methods: A mechanistic PK/PD framework was developed based on an existing pharmacodynamics-mediated drug disposition framework (3). B and T cell dynamics were described using a zero-first order turnover model. B cell depletion was captured by an additional first-order elimination pathway driven by TBE complex concentrations via a sigmoidal E_{max} model. T cells were activated by the TBE complex and replenished through first-order kinetics. At the receptor level, CD20 and CD3 synthesis and degradation were modeled on B and T cells, respectively, with drug-bound receptors undergoing internalization and degradation. TBE complexes were formed upon simultaneous binding of the drug to CD20 and CD3. A scaling factor was introduced to link receptor- and cell-level models, representing the hypothetical microenvironment volume per B and T cell (ξ_B and ξ_T , respectively). Digitized data from the mosunetuzumab Phase 1 first-in-human study presented at EULAR 2025 was used (4). Population PK and K-PD models were fitted in NONMEM to characterize drug kinetics and B cell dynamics and to estimate the required parameters.

Results: The PK data was best described by a two-compartment model with linear elimination. The parameter estimates were: k_a (first-order, after subcutaneous administration) 0.23 1/day (RSE 31.19%); CL 1.11 L/day (8.7%); $V_{central}$ 10.45 L (45.2%); $V_{peripheral}$ 8.82 L (25.0%); and Q 0.53 L/day (21.4%). IIV was implemented on $V_{central}$ and was 45.2% (19.0%) with residual variability (additive on the log scale) 0.51 (12.0%). In the PK/PD model, implementation of the scaling parameters ξ_B and ξ_T proved to be effective. The parameter estimates were: death rate of B cells 8.51×10^{-4} 1/day (3.5%); baseline B cells 596 cells/ μ L (8.1%); ξ_B 0.995 mL/cell (25.3%); ξ_T 4.5 pL/cell (0.5%); killing due to TBE complex formation 3971.9 microL/cell/day (53.6%); EC50 0.13 nM (47.7%). IIV on CL, implemented in the K-PD model a priori to account for differences in individual PK profiles, was 104.9% (17.3%). IIV on baseline B cells was 52.7% (15.7%). Residual variability (additive on the log scale) was 1.09 (11.2%).

Conclusions: In the absence of T cell data, a PK/PD model incorporating a prespecified T cell compartment, along with scaling factors ξ_B and ξ_T adequately described the observed B cell depletion.

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	subcutaneously administered mosunetuzumab in participants with systemic lupus erythematosus. In. Barcelona, Spain [Poster]: EULAR 2025; 2025.
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Pieter Van Brantegem is a pharmacist and Principal Scientist at the department of Clinical Pharmacology and Pharmacometrics at Johnson & Johnson. He earned his PhD at KU Leuven, Belgium, where he investigated liver transporters. He completed a postdoctoral fellowship at the University of California, San Francisco, focusing on optimizing tuberculosis treatment regimens through modeling and simulation. His current work centers on drug development in the immunology space, integrating pharmacometric approaches to advance therapeutic innovation.

	Quantitative Systems Toxicology for Crop Protection: A HPPD Herbicide Case Study <i>Steve Webb (Syngenta)</i> Quantitative Systems Toxicology (QST) integrates mechanistic biology with mathematical modelling to support human health risk assessment and inform regulatory decision-making. This introductory talk outlines how QST approaches can be applied in agricultural chemistry to strengthen safety evaluations while reducing reliance on animal testing. As an example, we focus on herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD) - an enzyme essential in plants and also present in mammals. In mammals, HPPD inhibition can elevate circulating tyrosine, which may lead to downstream biological effects. Inter-species differences in tyrosine handling and response add complexity to translating animal findings to human relevance. We present a mechanistic model of tyrosine homeostasis that links exposure to predicted blood tyrosine dynamics. Parameterised and evaluated using data from more than 100 HPPD-inhibiting molecules, the model supports quantitative translation from laboratory species to humans and enables estimation of safety-relevant thresholds. The talk concludes with a discussion of practical considerations for deploying QST in crop protection - data needs, uncertainty, and validation - and highlights opportunities for industry-academia collaboration to advance predictive, fit-for-purpose QST tools.
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Steve joined Syngenta in February 2020, bringing more than 20 years of academic experience in researching and teaching mathematical modelling, with a focus on toxicokinetics, physiologically based kinetic (PBK) modelling, and toxicodynamics. He has authored 97 peer-reviewed journal publications, cited over 2,000 times. Steve is now a Science & Technology Fellow at Syngenta, contributing to the company's global science strategy. He also serves on several expert groups within Crop Life Europe and the Health and Environmental Sciences Institute focused on PBK/PD modelling and quantitative in vitro-to-in vivo extrapolation.

	Actual intelligence, thoughtfully integrated: Computation-in-the-Loop as a Paradigm for Agentic QSP <i>Priyata Kalra (Simulations Plus)</i> Mechanistic models in quantitative systems pharmacology (QSP) provide a principled framework for integrating biological knowledge with data, yet their development remains largely bespoke, manual, and time-intensive. Translating a scientific hypothesis into validated, decision-ready insight typically demands months of iterative model execution, scenario testing, parameter sourcing, and documentation, the majority of which is translational work rather than mechanism development: mapping clinical datasets to model inputs, reconciling study-design details, extracting and unit-converting literature parameters with traceable provenance, editing configurations, and assembling results into reporting-grade outputs. This session introduces and demonstrates a Computation-in-the-Loop framework that couples large language models (LLMs) with a deterministic mechanistic QSP engine to enable natural-language-driven
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	execution, interrogation, and interpretation of QSP models; while leaving the biology, the equations, and the numerics firmly under human control. The central architectural commitment, and the one most relevant to a methodologically rigorous audience, is the inversion of the usual trust relationship. The mechanistic engine remains the sole source of numerical truth; the LLM acts only as an orchestration and reasoning layer within a multi-agent system. Stochastic AI reasoning is thereby anchored in validated mechanistic computation: intent expressed in natural language is routed only to deterministic, validated procedures and never to improvised numerics. This anchoring is what mitigates hallucination risk and preserves auditability; every action is logged, and every result traces back to the request and the source prompt and data that produced it. Working through a representative disease case study, participants will engage with three coordinating agents that interact through standardized Model Context Protocols (MCP). A Data agent performs reproducible preparation - ingesting raw trial deliverables and analysis plans, surfacing missing values and design assumptions rather than hiding them, and enforcing formatting rules as reusable, version-controlled tests so that bad data fails before it reaches the engine. A Modeling agent drives deterministic execution and structured scenario exploration - composing combination and population scenarios with validity enforced before evaluation, running virtual cohorts, and returning outputs with appropriate uncertainty and reference comparators. A Reporting agent captures the exploratory session as a transparent, auditable record and re-expresses models into standard formats (with explicit acknowledgement that solver and hardware differences require human intervention). The session is framed honestly around its limits. We will distinguish where agents add genuine value, schema-validated extraction, free-text-to-parameter mapping grounded in literature-informed decisions, model construction and reasoning from where human judgement remains non-negotiable: mechanistic structure, governance of ambiguous parameter assignments, and scientific interpretation. By the end, participants will be able to run a complete curation-to-report cycle through an agentic workflow, critically evaluate a trust-by-construction architecture and learn concepts useful against the fast moving AI for QSP definition, and articulate for their own work the boundary between what should be automated and what must stay human. Familiarity with QSP or population modeling is assumed; no prior agentic-AI experience is required.
	Dr. Priyata Kalra is a mechanistic-modeling and computational biologist turned product leader, specializing in QSP, PBPK, IVIVE, and AI-integrated models. She holds an M.Sc. in Systems Biology (University of Heidelberg) and a Ph.D. (with Bayer Pharmaceuticals) focused on QSP models for biologics. After a postdoc in computational toxicology at BASF, she developed a hybrid AI-PBPK plant bioavailability model at Bayer Crop Science and supported an FDA Oral cavity PBPK-IVIVE project at Simulations Plus. As a Product Manager, she now oversees AI solutions across all product lines, and she serves as an expert contributor to the European Commission's Designathon NAMs roadmap.

SUBMITTED TALK ABSTRACTS

Finding the Minimum Requirement for a Capecitabine Hand-foot Syndrome Trial through Ordinal Modelling

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Background: Capecitabine is the most frequently used oral chemotherapy drug. It has an unpredictable absorption profile and consequently large inter-individual variability (IIV) in systemic exposure and causes hand-foot syndrome (HFS) in some patients, which requires dose reduction or discontinuation.

Aim: Our aim is to study the minimum number of patients and observation duration to construct a quantitative model which relates capecitabine dosing and adverse drug reactions.

Method: A previous established proportional odds logistic regression model (ordinal model) with Markov process was used in this work (Hénin et al., 2009). We simulated this ordinal model to generate training data using approved dosing regimen. To test the effect of sample size, we selected different sample size of 1600, 400, 100 and 20. To evaluate how observation duration affected parameter uncertainty, we curtailed the observation duration from the end in 3-week cycles, from 30-week to 18-week. Then, the model was refitted to these training datasets to examine whether we may recover the true parameters. We assessed the goodness of fit, relative standard error of the fixed effects (%RSE) and shrinkage for random effects. The evaluation criteria were %RSE < 20% for fixed-effect parameters and shrinkage of IIV < 30% for random effects. We further validated the model by comparing the probability of a transition in the training data with that in the model simulation. R package rxode2 was used for simulation and nlmixr2 First-Order Conditional Estimation with Interaction (FOCEI) was used for fitting.

Results: At the approved dose, at least 400 patients were needed for good parametric inference, with 8 out of 12 parameters achieving an RSE below 10% and 2 additional parameters achieving an RSE below 30%. Only $B_{0 \leftarrow 1}$, the parameter associated with transition from grade 1 hand-foot syndrome (HFS) to 0, has %RSE > 20% even sample size increased to 1600, due to lower probability of this transition. Shrinkage of the elimination rate constant K and Logit-transformed probabilities are between 20%-60% across all sample sizes. For a 30-week dataset with n = 400, we fitted the model and simulated this trial 400 times. The observed transition probabilities in the training data are within the 5th–95th predicted percentiles. Sample sizes of 100 or less resulted in unsatisfactory parameter inference, with 7 parameters exceeding 20% RSE at a sample size of 100 and all parameters exceeding 20% RSE at a sample size of 20. Similarly, a 30-week observation period were recommended.

Conclusion: These findings define the minimum requirements of 400 and observation duration of 30 weeks needed to reliably apply ordinal model for model-informed clinical trial design and individualised dosing regimen modifications.

Reference - Hénin, E., et al. (2009). A Dynamic Model of Hand-and-Foot Syndrome in Patients Receiving Capecitabine. *Clinical Pharmacology & Therapeutics* 85(4) 418-425.

Maternal–foetal PBPK modelling of daily oral versus long-acting injectable aripiprazole and olanzapine during pregnancy

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Background: Pregnancy is associated with substantial physiological and psychological changes that can exacerbate pre-existing psychiatric disorders, including psychosis. Antipsychotic treatment is often required to maintain maternal stability during pregnancy, yet it may also result in unintended foetal drug exposure. Discontinuation is frequently not a safe option, as relapse or clinical deterioration may compromise maternal wellbeing and pregnancy care. Both oral and long-acting injectable (LAI) antipsychotics are used clinically, but little is known about how formulation-dependent differences in maternal pharmacokinetics influence foetal exposure. Quantifying these differences may support safer prescribing strategies during pregnancy. We therefore developed maternal–foetal physiologically based pharmacokinetic (PBPK) models to compare predicted foetal exposure following daily oral and monthly LAI dosing of two widely prescribed second-generation antipsychotics, aripiprazole and olanzapine.

Methods: Full-body adult and pregnancy PBPK models were developed and implemented in MATLAB® SimBiology. The pregnancy model incorporated gestation-dependent anatomical, physiological and metabolic changes, including trimester-specific alterations in CYP enzyme activity. A multi-compartment materno-foetal PBPK sub-model was integrated to simulate bidirectional placental drug transfer via passive diffusion and predict foetal plasma concentrations during the second and third trimesters. Model predictions were qualified against clinical pharmacokinetic data from non-pregnant and pregnant populations, with all key outputs falling within a two-fold error threshold. Simulations were conducted in virtual pregnant populations (n = 100 per scenario) using clinically relevant oral and monthly LAI regimens: aripiprazole 15–20 mg orally versus 300–400 mg LAI monthly, and olanzapine 10–15 mg orally versus 300–405 mg LAI monthly. Steady-state outputs included cord-to-maternal plasma concentration ratios (C:M), foetal area under the concentration-time curve (fAUC), foetal maximum concentration (fCmax), and foetal-to-maternal AUC ratios.

Results: Predicted fCmax was 59–78% higher with LAI aripiprazole than with oral aripiprazole, and 68–181% higher with LAI olanzapine than with oral olanzapine. Predicted C:M ratios were 0.59–0.69 for oral aripiprazole and 0.61–0.66 for LAI aripiprazole, while oral olanzapine yielded values of 0.34–0.64 compared with 0.89–0.96 for LAI olanzapine. Cumulative 28-day foetal exposure was consistently lower with oral regimens than with the corresponding LAI regimens for both drugs. Predicted foetal exposure generally decreased with advancing gestational age for aripiprazole regimens, consistent with gestation-dependent increases in CYP3A4 and CYP2D6 activity, whereas olanzapine showed less consistent trimester-related variation.

Conclusions: Within this modelling framework, the evaluated monthly LAI regimens produced greater predicted foetal exposure than oral regimens for both aripiprazole and olanzapine. These findings highlight the importance of considering formulation-specific pharmacokinetics when prescribing antipsychotics during pregnancy. However, foetal pharmacokinetic exposure does not directly equate to clinical risk and should be interpreted within a broader maternal–foetal benefit–risk context. Further clinical and translational studies are needed to determine the safety implications of LAI versus oral antipsychotic use during pregnancy.

No One-Size-Fits-All: A Multi-Model Evaluation of Optimization-Based and Surrogate-Assisted Virtual Population Generation in QSP

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Background: Quantitative systems pharmacology (QSP) models increasingly support clinical decision-making, including dose selection and trial design, by integrating mechanistic knowledge with heterogeneous experimental data. Sparse population-level data and model non-identifiability often yield multiple plausible parameterizations, motivating the use of virtual populations (VPops) to represent uncertainty and inter-individual phenotypic variability [1,2]. Among VPop generation strategies [3-6], widely used approaches follow the Allen et al. framework [3], generating large plausible populations (PPops) and selecting VPops to match clinical distributions [3,4]. As model complexity increases and VPop generation becomes more computationally demanding, we benchmark classical optimization-based methods against surrogate-assisted alternatives across QSP models, focusing on total computational cost.

Methods: Two optimization-based VPop generation approaches—simulated annealing (SA) [3] and Metropolis–Hastings Monte Carlo (MH) [4]—were benchmarked against a surrogate-assisted method (SM) using random search [7]. All methods rely on the Allen et al. PPop-to-VPop acceptance–rejection scheme [3], differing only in PPop generation. Evaluations were performed on three QSP models of increasing complexity—plasma cholesterol regulation [8], colonic motility [9], and Gaucher’s disease type 1 [10]—implemented in MATLAB R2025b. VPop generation methods were compared by established metrics of efficiency, diversity, convergence to empirical target distributions (Kolmogorov–Smirnov (KS) distance on marginal distributions and multivariate energy distance), and computational cost [4]. Simulations ran on a MacBook Pro (Apple M2, 16 GB RAM).

Results: Generating 10000 plausible patients, performance varied by model and evaluation metric, revealing recurring trade-offs. In the plasma cholesterol model, MH showed the strongest convergence and highest efficiency, with the lowest runtime (~185 s) versus SM (~934 s) and SA (~2049 s); SM generated the most diverse VPops. In the colonic motility model, SM delivered a large runtime advantage (~1517 s vs ~10886–16521 s for SA/MH) and the best convergence by multivariate energy distance, whereas MH achieved the lowest KS distance and SA the highest diversity. In the Gaucher’s disease model, SM again reduced total computational time (~960 s; ~2.6x faster than MH at ~2478 s), produced the most diverse VPops, and achieved convergence close to the best method (KS: 1.36 vs 1.27 for MH; energy distance comparable to SA).

Conclusions: VPop generation in QSP is strongly context dependent: no single method consistently dominates across models of differing complexity, data characteristics, and outputs. However, the surrogate-assisted strategy—despite surrogate-training overhead—showed a clear benefit in the higher-complexity test cases, markedly reducing runtime and PPop generation time while maintaining competitive convergence and VPop diversity.

Quantitative parameter free methods for toxicokinetics

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Pharmacology and toxicology studies often use compartmental ordinary differential equation (ODE) mathematical models to understand how a chemical compound distributes and exerts its effects throughout the body. Such models require experimental data to inform parameterisation. However, such data is often costly and not always available and thus we need to identify new ways to parameterise such ODE models under data-limited conditions - the aim of this work is to address this challenge. In this talk, I will explain a novel methodology that can be effectively used to parameterise biologically based ODE models. It involves a stepwise approach, including: generating stochastic Petri net (SPN) qualitative data; scaling the qualitative SPN data into quantitative synthetic data; and using this synthetic data to obtain model parameters and their associated distributions. I will demonstrate this methodology against case examples to illustrate its feasibility and reliability, including a model for the regulation of thyroid hormone levels in the brain. I will also describe troubleshooting methods to improve accuracy of this approach, including: varying the number of initial Petri Net tokens; deploying a scaling approach; and how to flex according to the nature of the experimental data provided. Through this exploration, I will illustrate how you can enhance the robustness and precision of this methodology when applied to more complex systems.

POSTERS

Finding Safety Signals in Sparse Data: Zero-Inflated Models for Pharmacovigilance

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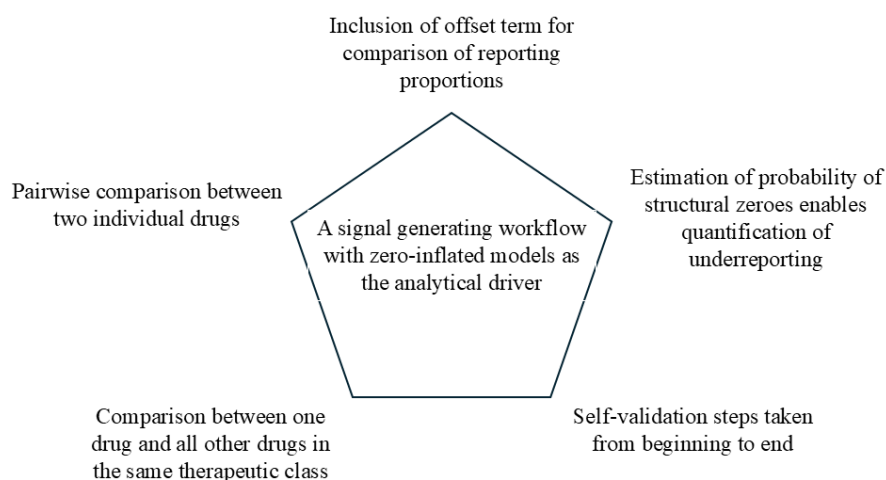


Figure 1: Diagram summarising the advantages of the proposed signal generating workflow with zero-inflated models as the primary analytical driver.

Background

Disproportionality analysis (DA) remains as the most commonly utilised signal detection method (SDM) in pharmacovigilance (PV) [1]. Despite its ubiquity, there are inherent limitations within spontaneous reporting systems (SRS) which yield sparse data, reflecting the rare nature of adverse drug reaction (ADRs) [2]. Such sparsity may hinder the quality of signals produced from DA, inevitably rendering the majority of signals as noise [3].

However, we believe there is utility within such sparsity, such as the extent of underreporting. Therefore, we suggest the application of zero-inflated (ZI) models: ZI Poisson (ZIP) and ZI negative binomial (ZINB) as potential additions to the current stable of SDMs. Furthermore, a common approach when conducting PV studies is to perform DA as the sole analytical driver [4]. Given that a signal is information on a new or known adverse event which may be associated with a medicine and warrants further investigation [5], we believe that through data-linking signals produced from DA, the fitting of ZI regression models and pharmacological data of off-target interactions of medicines, the resulting multi-faceted signal is of greater robustness and reliability.

Objective

The aim of this study is to present the framework for a signal generating workflow (SGW) with ZI models as the main analytical driver; DA will be performed for comparison. The produced signals would be data-linked with interactions between off-targets and the selective serotonin reuptake inhibitors (SSRIs). SSRIs serve as the drug class of choice due to the dynamic nature of its safety profile, increasing use and ongoing concerns [6].

Methods

Data from the Medicines and Healthcare products Regulatory Agency (MHRA) was obtained in December 2025. The raw data was transformed into two structures: the first one enabled sex-stratified DA to be performed whereas the second one enabled fitting of ZI models. Goodness-of-fit tests on system organ class (SOC) counts enabled determination of Poisson or negative binomial (NB) distribution prior to model fitting. During model fitting, an offset term was included during model construction. After model fitting, variance of Pearson residuals (VPRs) and weight of evidence were estimated to assess absolute and relative model fitting, respectively. For both DA and ZI-model fitting,

post-hoc analysis was performed; the Benjamini-Hochberg correction method was applied to the produced p-values. ZI models were fitted as the logistic component computed probability of structural zeroes.

Results and conclusion - Agreement was shown between signals produced from DPA and ZI models. Models where response variable (Y) was the SOC of metabolism and nutrition disorders (Metab) was determined to be significant as $VPR = 1.18$; $VPR > 1.00$ suggests that the model fitting was good due to excess variability beyond statistical noise. This comparative study between DA and ZI models showed potential for the application of ZI models due to the rare and sparse nature of ADRs. From a model diagnostic perspective, signals of greater robustness were produced when $Y = \text{Metab}$ as $VPR = 1.18$ suggested a signal which exceeded statistical noise. Subsequent steps would include the application of this SGW to a more informative dataset and data linking with off-target interactions and SSRIs.

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Towards optimal design of T-Cell Engagers by allowing for the variable distribution of the target antigen

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Background - T-Cell Engagers (TCEs) are multispecific molecules that bind a antigen on a target cell and an activating receptor on T-cells, leading to the activation of the T-cell and its destruction of the target cell. The complexity of the mechanism, disconnect between PK and the response and the disparity in conditions between the patient and the laboratory assays, make the rational design and dosing of TCEs difficult. Models attempting to elucidate these mechanisms and extrapolate from in vitro cytotoxicity data have been published (for example [1-3]) and have provided insights into the behaviour of these complex molecules. However, the design and dose-estimation of TCEs remains a largely empirical exercise.

One limitation is that the target cell population is treated as homogeneous, such that all cells will be killed for a given dose with sufficient time. However, as Liu et al. 2023 [4] showed, cells with lower target antigen expression are killed more slowly, or not at all, reflecting the issue of antigen escape as a factor in a lack or loss of response. A model that accounts for the distribution of antigen expression could ensure that TCEs are more-optimally designed to kill the target tumour cells, while sparing lower expressing healthy cells.

Methods - The target cell distribution is implemented as an array whose index denotes the target antigen expression and the element value the number of cells with that expression. Log-normal, normal and uniform antigen distributions are demonstrated here. Another array describes the distribution of T-cells with respect to the activating receptor CD3. Calculations are then performed independently on each target cell element. Target cell killing within an element is determined by its associated T-cell:TCE:target cell trimer level; the model presented here

adopts the simple trimer formulation of Jiang et al. 2018 [1]. The trimer-cell killing relationship is modelled as either a fixed threshold, a linear or a sigmoid function.

Results - The model recreates the observations in Liu et al. 2023 [4] on the preferential killing of higher expressing cells and antigen escape. We show this allows the design of a TCE tuned to eliminate tumour but not healthy cells. However, this is dependent on the antigen distribution and the cell killing function. Intriguingly, both of these determine the in vitro cytotoxicity profile, suggesting that the unknown killing function may be derived from cytotoxicity data.

Conclusions - Existing models of TCEs can be extended to allow for the dependency of target antigen distribution of cell killing. Implemented as part of a larger model correctly assessing trimer levels and the experimental versus indication cell lines, this begins to allow the more optimal design of TCEs.

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A mathematical model of cell state dynamics in melanoma

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Melanoma is a cancer of the melanocyte, known to have an ability to readily switch between distinct transcriptional cell states that convey different phenotypic properties (e.g. hyper-differentiated, neural crest-like). This phenotypic plasticity is believed to underpin intratumour heterogeneity and adaptation responses that contribute to therapy resistance and immune evasion of the tumour. Understanding the mechanisms underlying acquisition of transcriptional cell states and cell-state switching is therefore crucial for improving therapeutic strategies. These transitions are driven by dynamic and reversible changes in cellular transcriptional programs, a process that is governed by gene regulatory networks (GRNs), motivating the need for mechanistic models that connect network dynamics to cell-state behaviour. We model a minimal gene regulatory network comprising three key transcription factors (TFs), whose varying expression levels encode distinct melanoma cell states, and use deterministic spatiotemporal differential equation models to study gene expression dynamics. Our aim is to identify the network parameters governing state transitions and develop a predictive framework for melanoma cell-state behaviour.

While large scale GRNs are difficult to analyse, a reduced GRN can capture the core regulatory interactions while remaining analytically tractable. To facilitate analysis, we exploit a cooperative TF binding approximation in which the models are piecewise-linear, allowing analytical characterisation of stable and unstable gene expression states and a systematic exploration of the parameter regimes in which these states arise. This analysis identifies distinct monostable and bistable parameter regions and reveals state transitions arising from bifurcations as network parameters vary. The resulting parameter landscape motivates experimentally testable hypotheses, as state transitions emerge through biologically interpretable changes in TF regulation. For example, variations in effective activation and repression threshold may correspond to epigenetic regulation or changes in chromatin accessibility, which are implicated in melanoma progression and therapeutic response.

We then extend the framework to the tissue scale using a simplified representation of intercellular communication to demonstrate how local signalling interactions can generate coordinated population-level dynamics. The spatiotemporal model suggests that diffusive intercellular signalling may contribute to the emergence of coordinated expression behaviour in tumours. In simulations, stronger effective communication over longer ranges led to phenotypically homogeneous populations, whereas weaker signalling permits stable heterogeneous patterns of cell states.

Finally, we derive a condition on system parameters determining the final state of a population of communicating cells, provided cell-cell signalling is sufficiently strong. This work provides an analytically tractable framework for studying a nonlinear regulatory network that is central to the development and

progression of melanoma, with potential applications in understanding tumour heterogeneity, therapy resistance and treatment response. The model provides a foundation for future studies that can incorporate more refined descriptions of the genetic pathways driving malignancy and the spatial organisation of tumour cell populations

Spatial Mechanistic Modelling of T-Cell Engagers with PhysiCell: Insights into Trimer dynamics and its relation to Cancer Killing

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The recent rapid expansion of immunotherapies in cancer treatment has increased the need for quantitative models provide insight into their mechanisms and limitations. T-cell engagers (TCEs) in particular are growing at a rapid pace with many new approvals and in clinical trials. This expansion has outpaced quantitative and mechanistic understanding, necessitating bespoke theoretical study. Furthermore, treatment limiting toxicities, T-cell exhaustion, and the hook effect are all factors which are constraining TCEs potential efficacy. Exploration of these process through mathematical and computational modelling may lead to unique insights to help further understand these processes and support the rational optimisation of TCE design. We present a PhysiCell based agent based model developed to investigate how binding kinetics, receptor expression, and spatial heterogeneity may influence TCE dynamics and cytotoxicities. By integrating mechanistic binding rules with spatially explicit cell-cell interactions, the model enables systematic exploration of trimer formation dynamics, the emergence of the hook effect, and their combined impact on tumour cell killing.

Model-Based Meta-Analysis of Paracetamol Dose-Response in Paediatric Tonsillectomy Pain

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Objectives: Model-Based Meta-Analysis (MBMA) is a quantitative method combining aggregated data from randomised clinical trials (RCTs) to improve statistical power and characterise dose-response, time course, and treatment effects across studies. Its application in paediatric extrapolation may support dose selection when paediatric data are sparse and RCTs are limited. The objectives were to: (1) identify a postoperative pain indication with both paediatric and adult studies reporting common efficacy endpoints and treatments; (2) curate a paediatric analysis database; and (3) develop an MBMA framework to characterise the selected postoperative pain indication in paediatric patients. This work supports modelling and quantitative systems pharmacology (QSP) approaches and was conducted within the Horizon EU-funded ERAMET project.

Methods: A systematic PubMed search of postoperative pain studies was performed according to a predefined protocol, following the relevant identification, screening, and eligibility assessment steps described in the Cochrane Handbook for Systemic Reviews of Interventions, and reported items in accordance with the PRISMA statement. The indication with the highest number of paediatric studies, also represented in adults with shared treatments and endpoints, was selected. A paediatric reference database was curated and variables standardised across studies. The modelling strategy proceeded in stages. First, studies with placebo and active arms were analysed to explore time and dose relationships. Subsequently, the model was extended to all eligible studies within the MBMA framework. Models were fitted in R using generalised least squares via the `gnls` function in the `nlme` package.

Results: The search identified 770 paediatric postoperative pain publications across several indications. Tonsillectomy was selected due to representation in both paediatric and adult populations and shared treatments and endpoints. In total, 36 paediatric and 35 adult tonsillectomy studies were identified. The most frequently reported

endpoint was the Visual Analogue Scale (VAS), and paracetamol was among the most studied drugs. Eight eligible paediatric studies were curated for the MBMA dataset, extracting age, weight, dosing regimen, time-course VAS pain scores, and key trial characteristics. Initial modelling used two studies containing placebo and active arms to explore time-course and dose–response relationships. Placebo response was modelled non-parametrically with study-specific time effects, while drug effect was modelled parametrically. An Emax relationship was identified, with stable estimates: Emax 1.23 logit units and ED50 23.23 mg/kg/day. The model described both placebo and treatment arms with good agreement. The same Emax model was applied to all eight studies (six without placebo arms). The parameter estimates obtained were: Emax 1.02 logit units and ED50 43.51 mg/kg/day. Model evaluation included goodness-of-fit diagnostics and assessment using information criteria (AIC/BIC), supporting adequate predictive performance. The Emax model consistently described the dose-response relationship across studies and provided robust fits across all treatment arms.

Conclusions: An MBMA framework was successfully developed to characterise the dose-response relationship of paracetamol in paediatric tonsillectomy pain. Future work will focus on expanding the curated tonsillectomy dataset by including adult references to investigate MBMA extrapolation, considering additional drug classes, combining different pain scales, and potentially including different indications.

Predicting clinical efficacy of HIV combination therapies from monotherapy data using QSP viral dynamics modelling

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The development of effective HIV therapies rests on the ability to predict long term efficacy of combination antiretroviral therapy (cART) from short duration monotherapy efficacy in treatment naïve individuals. This transition poses a formidable gap and challenge for forecasting optimal dosing regimens. We developed a Quantitative Systems Pharmacology (QSP) framework that leverages a mechanistic viral dynamics model to perform in silico trials using virtual patients, offering a promising method to accelerate cART HIV drug development. Key biological parameters in our framework were estimated with inter-individual variability from patient-level longitudinal clinical viral load data in untreated individuals and those undergoing treatment across major HIV drug classes. In silico trials of combination therapies were run using a large cohort of virtual patients and the predictive ability of the framework was validated by comparing clinical viral load responses with independent validation datasets for three different cART scenarios. Our results demonstrate that in silico trials consisting of virtual patients can quantitatively predict clinical responses to combinations of different HIV drug classes based on monotherapy data only. This workflow facilitates rapid and quantitative assessment of numerous cART regimens, using a QSP approach to transition between early and late phase clinical development and offering the possibility to reduce the number of unnecessary dosing regimens.

The Double-Edged Nature of Antibody Bivalency: Mathematical and Experimental Analysis of Cell Surface Antigen Occupancy and Opsonization

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Monoclonal antibodies are bivalent molecules and are thus able to engage two antigens concurrently, termed avidity. The therapeutic efficacy of an antibody drug can be broadly defined as a consequence of either antigen occupancy or target cell opsonisation. Therefore, depending on the intended mechanism of action, avid engagement of a therapeutic antibody may be desirable in order to attain high antigen occupancy and consequent antagonism. In some cases, such as target cell opsonisation and Fc-mediated cytotoxicity, avidity may limit efficacy when antigens are occupied with fewer antibodies per cell. We utilise a mathematical model of antibody-antigen binding to identify conditions under

which avidity hinders or enhances therapeutic potential. We calibrate the model with in vitro assays exploring the binding of a bivalent and monovalent panel of anti-PD-1 antibodies with a range of affinities, against cell lines with a range of target densities. In calibrating the model to the in vitro binding data, we observed an affinity-dependent discrepancy between experimentally observed and model-predicted cell binding that we hypothesize arises due to unavoidable assay limitations. The calibrated model is then reused to correct for the assay bias and to generate refined estimates for on-cell antibody binding. The predictions generated by this model for the influence of avidity on cell surface receptor engagement with therapeutic antibodies may guide strategies for their structural engineering and dosing.

Mixed-Integer Optimization for Virtual Population Selection in QSP

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Virtual Populations (VPops) are widely used in quantitative systems pharmacology (QSP) to predict the variability in patient responses observed in clinical trials. Several approaches for VPop generation have been proposed [1,2]. However, their practical application in real-world QSP projects is often challenged by endpoint-specific requirements, limited availability of individual patient data, and computational complexity.

Maximising the Life Expectancy of Cancer Patients Under Chemotherapy Using a Poisson Process Framework

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Cancer chemotherapy must balance between two competing objectives -treatment efficacy against the tumour and the risk of treatment related severe adverse events, including patient death. While optimal control theory (OCT) provides a principled framework for designing dosing protocols, most existing formulations rely on optimising heuristic cost functionals that lack direct clinical interpretability. In clinical practice treatment efficacy and patient tolerability are primarily assessed through survival metrics and adverse event rates. Here we introduce the Continuous Lifetime Payoff (CLP), a novel OCT objective functional that directly links treatment decisions to patient survival. It explicitly incorporates tumour dynamics, tumour eradication, and patient mortality from tumour progression, drug-related toxicity and age. Mortality is modelled as a Poisson processes, a framework that enables the patient's expected lifetime to be computed. The model and objective are biologically interpretable and can in principle be calibrated using clinical data. We demonstrate the approach for a logistic tumour growth model, illustrating the trade-offs between tumour control and toxicity. We fit age-related mortality from national life tables and demonstrate parameter inferability from overall survival curves using simulated data. The CLP offers a clinically grounded OCT objective and provides a foundation for data-driven optimisation of chemotherapy regimens.

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