QSP Quantitative Systems Pharmacology

ISoP SPECIAL INTEREST GROUP

QSP SIG Newsletter Winter 2021/2022

IN THIS ISSUE

Introduction

by Benjamin, QSP SIG Chair

Dear reader,

Thank you for taking the time to read this early 2022 newsletter from the Quantitative Systems Pharmacology (QSP) special interest group (SIG) of the International Society of Pharmacometrics. The Leadership Team of the SIG puts together this newsletter to update you on recent developments in our scientific community and to share with you SIG's activities towards our mission to advance the development and utilization of safe and efficacious medicines through the application of QSP.

As every year, the American Conference of Pharmacometrics (ACOP) means, for our SIG, a rotation in responsibilities. During ACOP 12, and three new members have joined the team at this occasion: Lourdes Cucurull-Sanchez as our new Vice Chair, Neha Murad our communication director and Jingqi Gong our secretary.

During ACOP12, we ran our annual "Meet the SIG" session with 60 attendees. During this meeting, we came back on the past year achievements providing a quick overview of the QSP SIG Student Symposium organized in April 2021 as well as the Virtual QSP Week organized in August. An update from the current Working Groups was also shared at this occasion. Finally, we started sharing and discussing 2022 plans and objectives. We are very much grateful for the feedback received during that session. These feedbacks, together with the ones we received by meeting our SIG steering committee on November 15, 2021, helped us move forward in planning 2022. While the team is currently finalizing the 2022 plans, we are happy to share that we will again organize the student symposium as well as the virtual QSP week in 2022 (stay tuned for more information on these events in the near future). This is aligned with our wish to continue in 2022 the SIG's action towards our educational purpose. In addition, we aim to support our working groups delivering on science, strengthen engagement with our members and promote inclusive culture in all of our actions. We are still looking forward to feedback from the whole community as unique opportunities to steer our action towards making the most meaningful impact to our scientific community.

Contents

As of our last official membership count for ACoP12, we are glad to share that the SIG has 186 members; and there are still plenty of opportunities to join the SIG, or get more involved if you are already a member. If you happen to be reading this but are not a member of the SIG, you can join through the QSP SIG page of the official ISoP website. There is no added cost for ISoP members. If any of the Working Groups appeal to your interests, please reach out to a chair! If you have any general questions about the SIG, general suggestions or feedback on activities, or are interested in launching a new Working Group, please reach out to a member of the Leadership Team.

Finally, we hope you will enjoy the content of this newsletter and are looking forward to interacting with you during upcoming events.

Sincerely,

Benjamin Ribba and the QSP SIG Leadership Team






Top left: Benjamin Ribba – Chair, Ioannis Androulakis – Chair-Elect, Lourdes Cucurull-Sanchez– Vice-Chair. Bottom Left: Neha Murad – Communications Director, Christina Friedrich – Past Chair, and Jingqi Gong – Secretary.

Past Events

by QSP SIG Leadership Team

ACoP12

Meet The QSP SIG Event

After the great success last year, the "*Meet the QSP SIG*" event was conducted virtually and was very well attended (with over 60 attendees at one point). The event kickstart with the introduction of the new leadership team, updates from both the SIG and working groups, and poster recommendations from all the working groups. We also announced the 2021 QSP SIG Student Award Winner, Catherine Weathered a Ph.D. candidate from Purdue University. Catherine presented a short talk about her work entitled "Prophylactic Targeting of Bacterial Biofilms: An Agent-Based Model to Assess the Efficacy of Targeting Biofilms in Mycobacterium avium Reinfection". Congratulations, Catherine!

ACoP12 QSP Programming

There were several QSP related sessions on the ACoP11 program, some of which have been briefly summarized below:

1. *Towards a standardized assessment framework of mechanistically detailed models including QSP and PBPK: Zooming in on model validation. (Chair: Anna Sher and Pras Pathmanathan)*

   This session took a deep dive into the model validation of mechanistically detailed models in QSP and PBPK. Dr. Piet Van Der Graaf provided a very interesting talk about the current and impending challenges looking at simple vs. complex models' validation with an case example for COVID-19 vaccine trials. Many discussions were involved around the terminology for different QSP models and bottleneck of model reproducibility. Dr. Hao Zhu from the FDA also touched on the recently 2020 FDA proposed standardized model credibility assessment framework of mechanistically detailed models including PBPK and QSP, with specific focus on a standardized approach to model validation. Dr. Mark Transtrum and Dr. Gary Mirams provides insights on the benefits of model reduction techniques for validated PBPK and QSP models with case examples from cardiac modeling validation for complex QSP models. The panel Q&A discussion with the audience was very engaging and interactive to explore opportunities and challenges on the standardization, assessment and ways on how to enhance consistency and quality of model validations.

2. *A VUE on the use of QSP models as digital evidence: A Report from the QSP SIG Working Group on Variability, Uncertainty, and Error in QSP Models. (Chairs: Joshua F. Apgar and Michael Weis)*

   The Variability, Uncertainty, and Error in QSP Models Working Group for the QSP SIG developed a session to communicate the group's goals and provide some initial results for the community. The working group co-chairs, Dr. Joshua Apgar and Dr. Michael Weis, provided an introduction for the session, emphasizing the group's focus on sets of methods, theory, and best practices for establishing prediction reliability that are appropriate for QSP models. They also communicated a vision for the future outputs of the group, including the development of white papers, workshops, and more. Dr. Pegy Foteinou and Dr. Jared Weddell presented on behalf of the communications subteam, "When the stakes are high: helping key stakeholders understand quantitative predictions by QSP models." Their presentation also touched on definitions of terms used in QSP modeling, which sparked much discussion in the session. Dr. Jessica Brady and Dr. Justin Feigelman presented on behalf of the technical methods subteam, "Taming of the zoo: understanding the menagerie of

computational methods in QSP virtual patient population development and calibration, sensitivity analysis, and uncertainty quantification." Their presentation compared several sensitivity analysis methods, described common strategies and tools for the development of virtual populations and applying them to generate predictions, and touched on some known methods that can be used to assess uncertainty in not just model parameters but especially model predictions. Finally, Cibele Falkenberg presented on behalf of the data subteam, "Odds are your biggest source of uncertainty is not statistical: transparently dealing with data challenges in QSP models." Their presentation included an initial framework for better describing how quantitative information being used to inform model pathways and parameters was being gathered and the associated degree of confidence. Overall, the session was informative, helped to communicate some of the challenges and associated strategies for QSP modeling, and demonstrated progress from this cross-industry team.

3. *Development and Applications of Agent-Based Modeling: Spatial Quantitative Systems Pharmacology/Toxicology. (Chairs: Holly Kimko and Aleksander S. Popel)*

The presentation by C. Gong focuses on the development of a coupled QSP+ABM model for the visualization of a tumor microenvironment, where the ABM framework explored spatial QSP simulations. The work demonstrated how such an integrated model can be used to assist in simulating clinical trials by developing in silico virtual cohorts of patients and quantifying the effects of immunotherapies. The framework enabled the integration of complex imaging and pathology data as well.
The presentation by C. Pin explored the development of a QST (toxicology) framework coupled with a microphysiological system. An ABM model was used to describe the intestinal epithelium in order to: a) assess the impact of various intestinal injuries fb) integrate mechanisms of toxicity and cell proliferation and mechanisms diving division cycles; and c) model in vivo (mouse) data.
Finally, the paper by P. Macklin focused on the "PhysiCell", an open source multicellular simulation framework to emphasize the importance of emerging behaviors stemming from complex cell-cell interactions. The framework was demonstrated with simulations on large numbers of cells (10^5) in 2- and 3-structures. Extensions to modeling complex PKPD were also discussed, as well as the emergence of opportunities for coupling high performance computing and machine learning for improving efficiency.

4. *Quantitative Clinical Pharmacology Modeling and Simulation: A Critical Tool in Addressing the COVID-19 Pandemic. (Chairs: Hao Zhu and Jianghong Fan)*

This session presents the applications of different modeling approaches to address COVID-19.
The presentation by Dr Rohit Rao from Pfizer described a QSP model to link COVID-19 viral dynamics, immune response, tissue damage and various biomarkers. IL-6 was used as the linker to disease severity. This model recapitulated the viral dynamics for intervention with different mechanisms of action, including neutralizing antibodies and anti-virals. It was shown to match viral load response and severity improvement in various trials. Simulations from this model suggested early intervention was more effective for attenuating both viral and immune biomarkers than later treatment, stressing the importance of early intervention of the disease.
Mannie Chigutsa from Eli Lilly presented two case studies where modeling and simulations were used to support dose range selection in First-In-Human study, and dose justification for emergency use authorization. In the first case, two independent modeling methods were used to select the FIH doses: an integrated PKPD model to select the dose resulting in greatest viral load reduction and fastest viral clearance, and a PBPK to predict the dose to yield lung exposure that provided 90% protection over four weeks. The PBPK model was then shown in good agreement with the observed data. In the second case, PK/PD modeling approaches were used to describe the clinical data, and simulations were used to justify the clinical dose based on probability of target attainment. In addition, this presentation also concluded earlier treatment was associated with greater viral reduction.
In Jinghong Fan's talk from FDA, a case study of using whole body PBPK modeling to predict the impact of organ dysfunction on remdesivir and its active metabolites PK was presented. Lung and liver were the two

organs in focus. Model was validated against plasma, urine and intracellular PK data of remdesivir and its metabolites. The exploratory analysis indicated that in subjects with hepatic impairment, intracellular concentration of metabolites increased in the liver and decreased in the lung. In subjects with renal impairment, metabolite exposure slightly increased in the liver but stayed unchanged in the lung. These results highlighted the impact of organ dysfunction on exposure of remdesivir metabolites in the liver and lung, providing guidance to dose adjustment of remedesivir in these sub-populations.
Finally, the presentation given by Rita Humeniuk from Gilead took us through the journey of remdesivir clinical development, emphasizing the critical role of quantitative pharmacology methods in supporting key decisions, which included adult and pediatric dose selection, DDI assessment, and TQT evaluation. Specially, PBPK was applied to predict DDI potential of remdesivir, which informed clinical DDI programs. It was also applied to predict dose for young children, which enabled rapid initiation of ph2b/3 pediatric trials.

5. *Specialized PBPK Models for Target Tissue Dynamics of Protein Therapeutics.*
(Chairs: Seshasai Pallikonda Chakravarthy and Kapil Gadkar)

Session 5a focused on PBPK modeling for novel biotherapeutics. Dr. Dhaval Shah (SUNY Buffalo) reported on the development of a translational PBPK model to characterize brain disposition of protein therapeutics. The research utilized microdialysis to provide data that moves beyond CSF levels to give insight into disposition within the brain. His team has also been able to characterize species-specific antibody trafficking.
Next Dr. Isha Taneja (Janssen) reported on an avidity-based binding model for a biparatopic anti-HER2 antibody for brain metastasis within a minimal PBPK framework. Inclusion of avidity considerations clarifies disposition. The model predicts differences between monovalent vs. biparatopic at lower receptor densities and suggested that low affinity biparatopic is as efficacious as high affinity at low receptor densities.
Dr. Gregory Ferl (Genentech) then reported on a physiologically based ocular model to support preclinical and clinical drug development. The goal was to infer target suppression from clinical observations. The model was used to explore the impact of physiological attributes on target and drug kinetics, and the relationship between aqueous (measurements), vitreous (dosing), and retina (site of action).
Finally, Joga Gobburu (U. of Maryland) presented a vision for an integrated framework leveraging mechanistic and AI approaches to gain deeper insights into target engagement. The goal is to predict efficacy given prognostic factors by employing DeepData to connect ML to mechanistic equations.

6. *2021 Cardiac Physiome Quantitative Systems Pharmacology (QSP) & Quantitative Systems Toxicology (QST) Special Session (Graciously written by Dr. Anna Sher)*

On November 9 2021, ACOP12 and Cardiac Physiome 2021 (co-organized by Dr Anna Sher, Pfizer) co-hosted a session on QSP & QST under the joint auspices. The session was moderated by Dr Kylie Beatie (GSK) and the keynote talk on "The When and why of cardiovascular QST & QST: An Industry perspective" was given by Dr CJ Musante (ISoP President & Pfizer), followed by a panel discussion with diverse points of view from Dr Limei Cheng (BMS), Dr Valeriu Damian (GSK), Dr Amy Pointon (AstraZeneca), Dr Christopher Pollard (Certara) and Dr Scott Siler (DILIsym, Simulations Plus). Panel members shared their perspectives and experience on a number of highly pertinent questions including how cardiovascular models currently (or have in the past) help make decisions on drug safety and/or made an impact in drug discovery or development projects within the companies. Panelists highlighted the challenges associated with cardiac QSP and QST models currently embedded within pharma companies, addressed model validation issues, and reflected on the opportunities for the future including the need for modelling inter-connected organ systems moving towards being able to simulate virtual human. Finally, the presenters shared advice for trainees who may be interested in collaborating with or pursuing a career in industry including mentorships and internships for undergraduate and graduate students, industrial postdoctoral positions, relevant summer schools and workshops (e.g. a list of resources for young trainees can be found on ISOP website)

Virtual QSP Week 2021

Last year the QSP SIG organized a week-long virtual QSP week in place of our regional QSP days. This year we built on the success of last year's event with another great program and interesting discussions, spread over 5 hour-long lunchtime (EDT) sessions over the course of one week, August 16th - 20th. The program included 6 speakers in 3 sessions, a poster session, and a lively hour of open discussion.

Monday's session kicked off the week with an engaging introduction to integrating QSP and machine learning by Tongli Zhang (U. of Cincinnati). His talk was followed by a presentation by Hugo Geerts (Certara) about the use of a QSP model to understand clinical response variability in central nervous system diseases by examining the interactions between comedications, disease states and genotypes. Tuesday featured selected poster talks by Christina Battista (DILISym), Vaibhav Dixit (Pumas-AI), Haoyang Mi (Johns-Hopkins U.), Zackary Kenz (DILISym), and Rachel Rose (Certara).

We also have Wednesday focused on methodologies for model characterization by Gunnar Cedersund (Linköping University) discussed quantitative strategies for characterizing uncertainty in model predictions. Abhishek Gulati (Astellas) presented a perspective on data quality and strategies for visualizing model parameterizations in the context of sensitivity and data quality.

Something new this year was to have a dedicated day with open discussion forum. Dean Bottino (Takeda) who shared preliminary results of an industry-wide survey on the use of QSP in immuno-oncology that was recently conducted by the Immuno-Oncology QSP SIG Working Group. Survey findings stimulated a lively discussion about the real and perceived value of QSP. Carolyn Cho (Merck) also gave an update on the machine learning and QSP Working Group and discussed current topics of interest in the emerging discipline.

Finally, Friday's session was focused on QSP modeling of heart disease. Jeff Saucerman (U. of Virginia) discussed how high-throughput microscopy and -omic profiling of cardiac fibroblasts can be used to develop a computational model of large-scale regulatory networks. Limei Cheng (BMS) presented a physiological QSP model of heart failure developed to address the underlying mechanisms of heart failure and its various applications from preclinical to clinical, from evaluating dose selection and drug-drug-interactions to predicting continuous hemodynamics physiological processes in response to treatment.

The QSP SIG would like to thank all of the speakers, poster contributors, and all participants who made the 2nd annual vQSP Week a rousing success!

Future Events

Conferences

QSPC 2022: April 20-22, 2022, Leiden, The Netherlands
www.qspc.eu/qspc2022

The focus of Quantitative Systems Pharmacology Conference 2022 organized by the Leiden University and the Federation for the Advancement of Systems Pharmacology together with a Scientific Advisory Board of leading scientists in the field of QSP and physiological- and mechanism-based PKPD. The focus of QSPC2022 will be on emerging computational and experimental approaches in the field of quantitative systems pharmacology and mechanism-based or physiologically-based pharmacokinetics and pharmacodynamics. The meeting will include plenary lectures by both established and young scientists, poster presentations, and ample opportunities for networking.

QSP for Immuno-Oncology Workshop, 25th-26th April 2022, EMBL-EBI Cambridge, UK

Quantitative Systems Pharmacology (QSP) modelling and analysis is now a consolidated discipline and the UK QSP Network is leading in helping to shape best practice for QSP modelling in the UK. The EMBL-EBI is already involved in developing approaches to decipher systems biology in oncology, while in the pharmaceutical industry, immuno-oncology is a key area of therapeutic interest for drug discovery and development. This workshop therefore presents an opportunity for the EMBL-EBI, UK QSP Network and Pharma Industry to engage in cutting edge scientific discussions, with a view to identifying and developing pre-competitive research in the area of Immuno-Oncology QSP modelling. Membership to either the EMBL-EBI Industry programme or to the UK QSP Network is required to attend – for more details please check out the websites below:
Events | EMBL's European Bionformatics Institute (ebi.ac.uk)
UK Quantitative Systems Pharmacology Network (qsp-uk.net)

The 9th International Conference on the Foundation of Systems Biology in Engineering (FOSBE), August 28-31, 2022, Boston, MA
www.fosbe.org

Driven by the desire to push the envelope of systems biology towards addressing pressing health needs, the 2022 conference theme is Systems Biology for Life, and it will focus on challenges and opportunities for moving towards translational systems biology with emphasis on health as well as the phenomenal opportunities emerging from current advances in Quantitative Systems Pharmacology. For more information please see: www.fosbe.org

ASCPT 2022 : January 10, 2022 (QP community) & March 16-18, 2022 (main conference), Virtual
www.eventscribe.net//2022/ASCPT

Join this special rerun of the Quantitative Pharmacology (QP) Network Meeting content and take advantage of a new opportunity to participate in live chat and live Q&A with the panelists! ASCPT@night is ideal for attendees joining from Asia Pacific, working parents helping kids with virtual learning during the day, and anyone seeking alternative learning times. Drs. Karen Rowland Yeo (Certara) and Michael Tortorici (Aro Biotherapeutics) who are the QSP network and community chair will lead the session and will be join by Drs. Jin Y. Jin (Genentech) and Piet Van der Graaf from 8 pm – 9 pm ET.

PAGE 2022: June 28- July 1, 2022, Ljubljana, Slovenia
page-meeting.org

After a two-year hiatus owing to the ongoing COVID-19 pandemic, PAGE will resume face-to-face at the same venue as the cancelled 2020 meeting - Ljubljana, Slovenia - from 28 June to 1 July 2022! The PAGE meeting takes place in an informal atmosphere with vivid scientific discussion. PAGE 2022 will be held at the Cankarjev Dom. The meeting starts with a welcome reception on Tuesday evening 28 June. The scientific programme will start on Wednesday morning 29 June and will end at noon on Friday 1 July. Participants are encouraged to attend all conference days and present their work in the form of an oral presentation or poster.

ISoP QSP Events

QSP student event: Spring 2022, Virtual (more details to come)

A half-day symposium with speakers spanning from different sectors (industry, regulatory, academia, consultancy, and etc) which is then followed by lightning talks by students on similar topics. Students, trainees, and young professional can look forward to the QSP-specific career/soft-skill development session as well as virtual networking events! More information on the event and student abstract submission coming soon!

Virtual QSP Week, Summer 2022, Virtual

Back by popular demand! A third virtual QSP week will come to your way with various QSP sessions and poster sessions. Watch out for our emails to get more information!

ACoP13 Programming Proposals

The ACoP13 scientific programming are calling for proposals, submission opens on Feb 1st, 2022. ACoP13 will be held from October 30th to November 3rd, 2022, at the Gaylord Rockies Resort & Convention Center in Aurora, Colorado. If you have programming ideas or a proposal that falls within the scope of QSP SIG, please email us at isop_qsp_sig@go-isop.org. The SIG leadership team can give feedback or help find suitable speakers (if needed) for the proposals. This will help the SIG achieve its mission-to advance the development and utilization of safe and efficacious medicines through the application of QSP. We hope to work on ACoP proposals with you!

Want to get more involved with the SIG?

QSP SIG Working Groups

The QSP SIG working groups (WGs) allow small groups of scientists to focus on particular issues within the field. These can provide an excellent way to engage with other scientists, so please contact us at isop_qsp_sig@go-isop.org for information on WGs that might fit your interests. The QSP SIG's WGs that are currently active are:

- Variability, Uncertainty, and Error (VUE) in QSP Models
- Immuno-Oncology (IO)
- Integrating QSP and Machine Learning
- Neuroscience
- Drug Development Science

Working Group	Chairs	Goals and Objective
Variability, Uncertainty, and Error (VUE) in QSP Models	• **Joshua Apgar** • **Michael Weis**	Focus on the sources and impact of model uncertainty and biological variability within QSP
Immuno-Oncology	• **Samira Khalili** • **Iñaki F. Trocóniz**	Promote and share the QSP science in the Immuno-Oncology therapy area
Integrating QSP and Machine Learning	• **Carolyn Cho** • **Tongli Zhang**	Bring researchers together to critique, share and develop new approaches for integrating QSP models with multi-layer omics data as well as applying machine learning methods to better characterize QSP models.
Neuroscience	• **Peter Bloomingdale** • **Suruchi Bakshi (incoming)**	Promote and share the QSP science in the Neuroscience therapy area, Review and summarize published QSP models of neurodegenerative diseases
Drug Development Science	• **Brian Schmidt** • **Kapil Gadkar**	Assess and guide consistency in application for decision-making and scientific expectations. Two important focus areas identified are QSP model reporting and model assessment.

Join the SIG!

- ISoP QSP SIG webpage: http://go-isop.org/special-interest-groups-sigs-and-communities/quantitative-systems-pharmacology-qsp-sig/
- Send us an email: isop_qsp_sig@go-isop.org
- Participate in the Discussion Forum: http://discuss.go-isop.org/c/systems-pharmacology & https://isopqspsig.slack.com
- Follow us on Social Media:
  Twitter: https://twitter.com/QspSig &
  Linkedin: https://www.linkedin.com/groups/12072362
- Visit our website: https://sites.google.com/view/isopqspsig