ISoP NEWS

June 2019

Message From the President

By Justin Wilkins

It's been a very busy couple of months for ISoP…

As I write this, we've just opened registration for ACoP10, to take place in Orlando, Florida, on 20-23 October. Response has been amazing so far, with more than 200 attendees signed up already! I hope you'll join us for this, our tenth meeting. In keeping with our theme this year, "Modeling Without Borders" – a topic quite close to my heart – I'm delighted that we've secured speakers from regions where pharmacometrics has traditionally been under-represented to address us. I for one am excited to see what our Conference Chair, Mirjam Trame, and her team will deliver – it's looking pretty good from where I'm sitting. Just as exciting, the topic of our preconference on the Sunday before ACoP kicks off is "Clinical Pharmacometrics: Bringing Models to Patients", and has been organized by Co-Chairs Navin Goyal and Liz Lakota with the support of ISoP's Clinical Pharmacometrics Special Interest Group (SIG) and the American College of Clinical Pharmacology (ACCP).

We hope you'll be able to join us for one of the pharmacometrics events of the year!

We've also launched our Five-Year Strategic Plan. Each of its five pillars and one very important foundation has a Working Group implementing it. *Scientific Expertise and Innovation*, led by Five-Year Strategy originator and Past President Jin Jin, will focus on encouraging research and innovation in pharmacometrics; *Influence*, led by Heather Vezina, will work on increasing the impact of pharmacometrics on decision-making during drug discovery, development and clinical practice; *Education*, led by President-Elect Brenda Cirincione, will improve the consistency, quality and availability of educational resources for pharmacometricians through every stage of their careers; *Tools and Resources*, led by myself, will facilitate development of and access to pharmacometric software tools, both open source and commercial and promote open science; *Internationalization*, led by Siv Jönsson, will work to expand ISoP's outreach to pharmacometric community members across the globe; and *Operational Effectiveness*, led by Pete Bonate, will ensure ISoP has the resources and staff to support and implement the plan. It's a hugely ambitious undertaking that will transform ISoP as it continues to grow and mature. We're going to need a bit of help!

The best way to volunteer is to follow the "Volunteer" link on our very pretty new website at www.go-isop.org. The result of almost a year of development, the new ISoP website is designed to be a one-stop shop for all things pharmacometrics. We'd love to hear your feedback!

Last but not least, we've launched our ISoPmx app. Available on both iOS and Android platforms, our new app will serve as a mobile hub for ISoP, year-round, and at certain times of the year, will host conference app services for ACoP and other meetings that request it – its debut was at PAGANZ earlier this year, and it was by all accounts a great success. You can find ISoPmx on your platform's app store – let us know what you think! This is by no means all we've been up to in 2019. There's so much more to come. Stay tuned!

Highlights In this Issue **Page**

Registration is now OPEN for ACoP10

to be held October 20th to 23rd, 2019, at the Rosen Shingle Creek Hotel in Orlando, Florida!

ACoP10 is shaping up to be a great meeting with exciting new events and features. You can find the most up-to-date information on our **conference website**, but here just a few highlights to pique your interest:

Main Conference (October 20th – 23rd, 2019 + free tutorials on October 24th, 2019):

The main conference agenda is now available! 18 exceptional scientific sessions are lined up. We bet it will be difficult for you to choose between the parallel sessions. Main conference attendees can also register for free tutorials to be held on Thursday morning, October 24th. Please plan your travel accordingly and register ASAP – several tutorial sessions are already full and waitlisted. Multiple events throughout the entire main conference are specially designed and targeted towards our growing student and trainee community.

New this year is our Sponsored-Investigator-Session. We have invited three international speakers from low- and middle-income countries to share their research, goals, and their unique scientific perspective with us.

There will be ample opportunities to network with colleagues and friends, and all with late morning poster session start times (8AM)!

Stay tuned for details on our much-anticipated evening patio social event on Monday, October 21st, and remember to bring your dancing shoes!

Awards:

Think about your colleagues and their outstanding achievements! There is still an opportunity to **nominate your colleagues for one of our seven ISoP Award categories through Sunday, June 30th 2019**.

Conference Abstracts:

The Call for Abstracts is now closed; decision notifications have been sent out and we are excited about the many outstanding contributions we received! This year's poster sessions are set up to be exceptional with many exciting cutting edge research. Soon all abstracts will be made available online on our conference website for the first time!

ACoP10 will offer two poster walks; one during the opening reception with special selected posters by the ACoP10 Abstract committee and one during the main conference to highlight and recognize outstanding scientific achievements in Mathematical and Computational Sciences (MCS).

Pre-conference (Sunday, October 20th, 2019):

The Pre-Conference on, "Clinical Pharmacometrics: Bringing Models to Patients" will feature 4 exciting sessions presented by a diverse group of scientific experts from academia, research institutes, regulatory agencies, and pharmaceutical and technology industries. Presentations will focus on the application of pharmacometrics to direct patient care. The planned program is intended to bring together pharmacometricians with clinical interests and clinicians with an interest in pharmacometrics.

Given the scope, this year's Preconference has been developed in close collaboration with the Clinical Pharmacometrics Special Interest Group.

Pre- and Post-Conference Workshops (October 19th – 20th and 24th – 25th, 2019):

ACoP10 provides many pre- and post-meeting workshops covering a range of topics for you to choose from. Space is limited and separate registration is required, so please be sure to secure your place at one or more training sessions.

Be sure to **register NOW** as ACoP10 registration will be **limited to 800 attendees** and pre-conference registration will be limited to 150 attendees. We look forward to seeing you in Orlando!

Mirjam N. Trame, ACoP10 Conference Chair

On Behalf of the ACoP10 Planning Committee

Spotlight on Dan Goldstein

Principal Researcher and Assistant Managing Director Microsoft Research, New York City

By Peter Bonate

You may remember that in the last newsletter we had a column "What's the Deal with Wind Chill?" That was written by Dan Goldstein, a decision scientist, who generously allowed ISoP to reprint it in our newsletter. So I thought it would be interesting to find out more about Decision Science and what a Decision Scientist does.

Tell us about yourself. What is your background?

My training is in computer science and cognitive psychology. I have a PhD from the University of Chicago and have taught or researched at Wharton, Columbia, Harvard, Stanford, and the Max Planck Institute.

What is decision science?

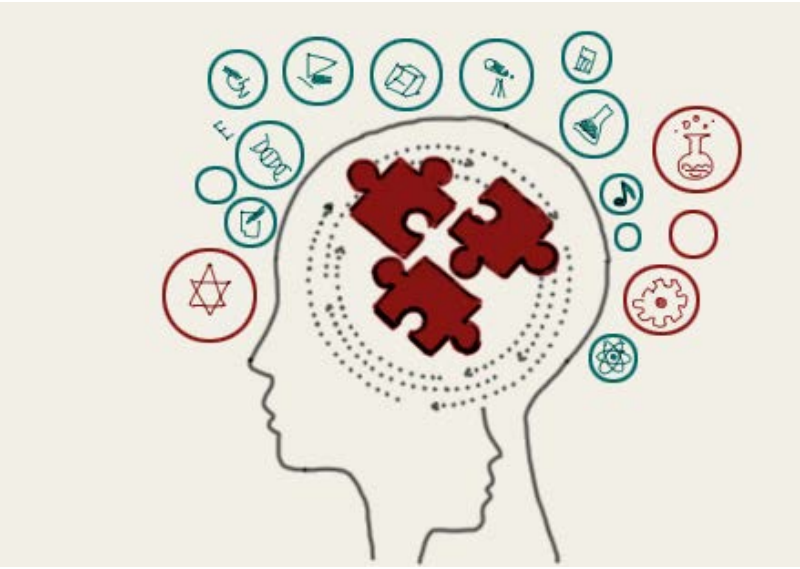
Decision Science is the study of decision making from normative and descriptive angles. Normative, also called prescriptive work concerns evaluating decision quality and proposing optimal decisions or procedures. Descriptive work focuses on how humans make decisions and how these decisions compare to prescriptive ones.

How did you get interested in it?

Like many life-shaping decisions we make, I stumbled onto it quite accidentally. I met my PhD advisor at a cocktail party and we hit it off and started working together.

What kinds of problems do you solve? What was the most interesting problem you had to solve.

My colleagues and I have been working on how people solve optimal stopping problems. One classic problem is called the "secretary problem". Suppose you are trying to hire the best secretary in town. You can interview candidates one at a time. After each interview, you have to decide to make an offer or not. If you don't offer, you will certainly lose the candidate to another employer. Now suppose there is a line of 100 secretaries in your waiting room. How do you proceed if you want to hire the best one? It's on old problem with a simple solution, but a solution that is too hard for most mere mortals to derive. Nonetheless, untrained people do pretty well at this problem in realistic environments. We want to understand how they do it.



What is a typical day like for you?

I have a number of research projects going and each day at work consists of hopping from meeting to meeting advancing each project a little bit. Brain storming, white-boarding, programming, data analysis, writing are the major activities, and I tend to do all of them side by side with other people--even programming and writing. It's a pretty social job.

What kind of background does one need to do decision science?

It helps to have experience with behavioral experiments, in particular how to design and run experiments that are sound and efficient. You also need to understand the normative theories of decision making and the prerequisites there are probability, statistics, logic, and mathematical economics.

Who employs decision scientists and what skills do you need to be successful?

Outside of academia, decision scientists find work in companies, governments and consultancies that run experiments. "Behavioral economist" is code for decision scientist. Many "data science" job postings are filled by people with a background in decision science.

Where does one go for more information on decision sciences?

I run a website called Decision Science News which sends one email a week and posts the latest on decision science conferences and research news. It can be found online at http://www.decisionsciencenews.com/

People can subscribe at this link https://feedburner.google.com/fb/a/mailverify?uri=DecisionScienceNews

Also of interest is the Society for Judgment and Decision Making http://www.sjdm.org/ which is the largest academic society on decision science.

Papers Worth Reading

by The ISoP Publications Committee
(Angela Birnbaum, Peter Bonate, David D'Argenio, Ashwin Karanam, Shaun Kumar, Jin Niu, Ana Ruiz, & Catherine Sherwin)

K. Jorga, B. Reigner, C. Chavanne, G. Alvaro and N. Frey. Pediatric Dosing of Ganciclovir and Valganciclovir: How Model-Based Simulations Can Prevent Underexposure and Potential Treatment Failure. *CPT: Pharmacometrics Syst. Pharmacol.* 8:167–176, 2019. (Suggested by David D'Argenio)

The theoretical framework underlying the application of pharmacokinetic models to the design dosage regimens was formalized by Krüger-Thiemer in the mid 1960s. The use of model-based dosing incorporating patient-specific information was introduced by Jelliffe in the late 1960s. In his work, Jelliffe applied a model for digoxin's kinetics that incorporated the relation between digoxin's half-life and CrCL to determine patient-specific loading and maintenance doses of digoxin for achieving effective plasma concentrations.

Now we fast-forward 50 years to this recent paper by Jorga et al., appearing in one of ISoP's affiliated journals, in which the authors evaluate dosing algorithms for intravenous ganciclovir and oral valganciclovir for use in the prevention and treatment of pediatric cytomegalovirus (CMV) infection. Using a validated population model and extensive demographic data representing a diverse pediatric patient population, the authors demonstrate that the commonly used BW-based dosing algorithm for valganciclovir and ganciclovir may lead to underexposure of ganciclovir in very young patients. Based on their modeling and simulation framework, the authors then propose and evaluate a dosing algorithm based on both BSA and CrCL (via the Schwarz formula) to provide adequate exposure for the prevention of CMV in pediatric patients across all ages. This work provides an elegant illustration of how population models coupled with a rigorous simulation framework can lead to improved prescribing guidelines, one of the goals of the early pioneers of pharmacokinetics.

Chaturvedula A., Calad-Thomson S., Liu C., Sale M., Gattu N., Goyal N. Artificial Intelligence (AI) and Pharmacometrics: Time to Embrace, Capitalize and Advance? CPT Pharmacometrics Syst Pharmacol. 2019 Apr 21. doi: 10.1002/psp4.12418. (Suggested by Angela Birnbaum and Ashwin Karanam)

With recent advances in data science, artificial intelligence (AI), deep learning (DL) and machine learning (ML) have been adopted by almost every industry in some form. This piece by Chaturvedula et al. examines the current state of AI/DL/ML in the drug development process and discuss how such technologies can be further incorporated into the overarching pharmacometrics framework. The authors discuss how ML has been applied to pharmacometrics using the global search method 'Genetic Algorithm.' Unlike the regularly used greedy search algorithms the Genetic Algorithm can provide a more robust way of optimal model identifications.

The paper also examines examples of using AI/DL in improving the drug selection process by merging DL/AI with chemoinformatics such as screening candidates for Burton's Tyrosine Kinase inhibition. Also discussed is the need for cross-industry partnerships such as Accelerating Therapeutics for Opportunities in Medicine (ATOM) which can help derive more information from existing datasets and models. The authors conclude with a discussion of the current state of the regulatory perspective on applications of AI/ML/DL and how these might be a much needed tool for pharmacometricians moving forward.

Did You Know?

Old versions of the newsletter are posted on the ISoP Website:

http://go-isop.org/newsletters/

If you've read an interesting paper tell us why and send it to the ISoP Newsletter for publication. Items can be emailed to: peter. bonate@astellas.com.

Update from the Statistics and Pharmaco-metrics (SxP) SIG

By France Mentré and Mike Smith

The SxP SIG was created in 2016 and is under the umbrella of ISOP and ASA (American Statistical Association). Its goal is to promote collaboration between Statisticians and Pharmacometricians, to enable each discipline to learn and grow from the other and to develop innovative approaches to model informed drug development.

Since 2019, the SxP has a new steering committee. France Mentré (University of Paris) and Mike Smith (Pfizer) are the two co-chairs. The other members are: Malidi Ahamadi (Merck), Alfred Balch (University of Utah), Robert Bies (University of Buffalo), Erin Dombrowsky (BMS), Jonathan French (Metrum), Luke Fostvedt (Pfizer), Vijay Ivaturi (University of Maryland), Siv Jönsson (University of Upssala), Efthymios Manolis (EMA), Bret Musser (Regeneron), Lei Nie (FDA), Gary Rosner (Johns Hopkins), Stacey Tannenbaum (Astellas), Tim Waterhouse (Metrum), Jingtao Wu (Takeda), Hao Zhu (FDA), Matt Zierhut (J&J), Alice Zong (J&J).

The SIG has a complete website with all our activities, event, a blog, a general discussion forum, and a PKPD programmer discussion forum (https://community.amstat.org/sxp/home). There are currently ~250 members, and it is free to join (no need to be member of ISOP or ASA) using the website.

In 2019, SxP SIG got sessions accepted in each of our two main conferences, please attend:

- At JSM19 (Joint Statistical Meeting, Denver, August): Effective application of modelling, simulation and knowledge sharing in drug development, Chair: Bret Musser
- At ACOP10 (Orlando, October): "You say to-mah-to, I say to-may-to…" – What statisticians and pharmacometricians wished each other understood better, Chair: Stacey Tannenbaum and Jonathan French.

The SxP Sig has co-signed the following comment on Jaki et al. article and we encourage all of you to read the original article, our comment, and the authors' answer.

- Krause A, Kloft C, Huisinga W, Karlsson M, Pinheiro J, Bies R, Rogers J, Mentré F, Musser BJ and the ASA/ ISoP Special Interest Group of Statistics and Pharmacometrics (SIG SxP). Comment on Jaki et al., A proposal for a new PhD level curriculum on quantitative methods for drug development. Pharmaceutical Statistics 17 (5):593-606, Sep/Oct 2018, DOI: 10.1002/pst.1873.
- Pharm Stat. 2019 May;18(3):278-281. doi: 10.1002/pst.1940. Epub 2019 Apr 1.

Please join the SxP SIG, it is free to join (no need to be member of ISOP or ASA): https://community.amstat.org/sxp/home.

Update From the Clinical PMx Sig

By Marc Scheetz and the Leadership Team

The Clinical Pharmacometrics SIG continues to be active. At present, we have 115 members engaged in the mission to synergize collaborations between pharmacometricians and clinicians. Dr. Luning Zhuang was elected as the Scientific Secretary, and Dr. Sean Avedissian was appointed as the Junior Secretary. The SIG will sponsor upcoming sessions at 1) ACoP 10: Pre-Conference meeting on "Clinical Pharmacometrics: From Equations to Patients" 2) American College of Clinical Pharmacology Annual Meeting: "Pediatric Therapeutic Drug Monitoring and Drug Development in the Age of Pharmacometrics".

Events are scheduled to *Meet the SIG* at both ACoP 10 and ACCP. At ACoP 10, the Clinical Pharmacometrics SIG will be co-hosting a social with the MCS and SxP SIGs. The event is planned for Tuesday October 22 from 5:30 – 7 pm. Further details to be released prior to ACoP. Please join us at these meetings! People with interest are encouraged to contact the SIG at clinical.pmx.sig@go-isop.org.

Update from the Pharmaco-metrics Network Benelux (PNB) Meeting

By Wilbert deWitte

The Pharmacometrics Network Benelux meeting is organised twice a year and aims to bring together the pharmacometrics community from both industry and academia in Belgium, the Netherlands and Luxembourg and is supported by ISoP. The meetings last for half a day and are organized at various locations. On the 9th of May, around 65 attendees gathered for the 14th meeting in Niel, Belgium, organised with the support of Thomas Bouillon and Pieter Annaert from the KU Leuven.

The theme of this meeting, 'Applied PKPD modelling: from prediction to prescription', was rather broad and the meeting was focused on PKPD modelling applications anywhere in the chain from drug discovery to the clinic. The first half of the meeting was focused on Therapeutic Drug Monitoring (TDM) and the associated challenges and opportunities for Modelling & Simulation. Ruben Faelens (KU Leuven) opened this session with the keynote lecture. He introduced the topic, highlighted the future perspective on the needs for dose optimisation and discussed the challenges of model development and evaluation towards prediction of the future of each patient, rather than data fitting and extrapolation on population level.

The challenges in TDM were further discussed by Sebastian Wicha (University of Hamburg), who demonstrated the consequences of uncertainty in sampling times and the difficulties in selecting the best model from literature options. The session was completed by two dose optimisation examples; isoniazid and beta-lactam antibiotics by Stijn van Beek (Radboud UMC) and Sofie Dhaese (Ghent University), respectively.

After the break, Bas Goulooze (Leiden University) talked about Item Response Theory for iatrogenic withdrawal in children and he showed how adding supervision and multidimensionality could influence the result to obtain the most meaningful model.

Secondly, Feifan Xie (Ghent University) discussed Markov modelling for cisplatin-induced nephrotoxicity and leukopenia and how this could be used to optimise cisplatin dosing. The session was followed by Erwin Dreesen and Wannee Kantasiripitak (KU Leuven), who shared their results on dose optimisation for Vedolizumab and Golimumab in inflammatory bowel diseases. Finally, Gilbert Koch (University of Basel) discussed how optimal control theory could be used to optimize drug dosing schemes to obtain a desired pharmacodynamic time profile. The discussion was continued over drinks after which this successful meeting was concluded.

RedIF – ISoP Montevideo Local Event

By Dr. Manuel Ibarra
Profesor Adj. Área de Biofarmacia y Terapéutica
Centro de Evaluación de Biodisponibilidad y Bioequivalencia de Medicamentos (CEBIOBE)
Departamento de Ciencias Farmacéuticas.
Facultad de Química, Universidad de la República – Uruguay

As part of RedIF's and ISoP's mission, the 1st RedIF-ISoP Local Event was held in Montevideo, Uruguay, on April 26th 2019, hosted by the *Universidad de la República* (UDELAR).

RedIF (Iberoamerican Pharmacometrics Network, www.redifar.org) was founded in 2017 as the natural association across research groups from Argentina, Brazil, Chile, Colombia, Cuba, Mexico, Panama, Spain and Uruguay. The main interest of this network is the promotion and advancement of Pharmacometrics in Latin America. As part of ISoP's mission to offer a central organization for the integration of national and international Pharmacometrics communities, initiatives, consortia and educational activities, the Society has supported RedIF activities including the 1st Latin American Pharmacometrics Symposium in 2017 (Montevideo, Uruguay) as well as the 2nd RedIF annual meeting held in Guadalajara, Mexico in November 2018 [1].

This RedIF-ISoP Local Event aimed to advance the discussion around how Modeling and Simulation can push forward the development of drugs, therapeutic strategies, and basic research in pharmacology and pharmaceutical innovation in Latin America. Four focused talks given by Manuel Ibarra (UDELAR), Mirjam Trame (Novartis), Wenping Wang (Novartis) and Lawrence Lesko (UF) were directed to a broad audience of 50 attendees which covered an important spectrum including the local Pharmaceutical Industry, regulators from Uruguay's Ministry of Health, professionals from the clinical setting and researchers from Universities of Argentina, Brazil and Uruguay.

Manuel Ibarra introduced the audience to the event with a talk on "Pharmacometrics in Uruguay, advances and perspectives", showing part of the research and applications conducted in the country and addressing the challenges and opportunities of bringing the discipline into play at a national and regional level.

In the group picture, from left to right: Juan Francisco Morales (UNLP, La Plata University, Argentina), Bibiana Verlindo de Araújo (UFRGS, Federal University of Rio Grande do Sul, Brazil), Wenping Wang (Novartis), Prof. Marta Vázquez (Head of the Pharmaceutical Sciences Department, Universidad de la República, Uruguay), Manuel Ibarra (Prof. of Biopharmaceutics and Therapeutics, Universidad de la República, Uruguay), Mirjam Trame (Novartis), Prof. Pietro Fagiolino (Director of the Bioavailability and Bioequivalence Centre for Medicine Evaluation, Universidad de la República, Uruguay), Lawrence Lesko (Emeritus Prof. University of Florida).

Mirjam Trame, through the talk entitled "Dose Finding in Drug Development: How Can Pharmacometrics Help?" showed several successful examples of applying Modeling and Simulation in dose finding at different phases of Drug Development in Novartis.

Wenping Wang gave an illustrative example applying Time to Event modeling for dose justification within Ilaris® (Novartis) regulatory submission ("Regulatory dose-justification for Ilaris in the treatment of SJIA.").

Finally, Larry Lesko resumed the evolution of pharmacometrics with focus on the regulatory science, its impact in Drug Development and regulatory decisions, and the current and future opportunities for the discipline in diverse areas of application, emphasizing the importance of keeping the focus on the patient ("Pharmacometrics to Guide Regulatory Decisions on Drug Approvals and Therapeutics").

The event was very well received by the participants and considered highly successful by the organizers. These activities are a fundamental contribution to the promotion of Pharmacometrics in the developing world.

In addition, 8 posters were presented in a "Recycle your poster" modality. PhD students from research groups of Brazil (Federal University of Rio Grande do Sul and University of Maringá) and Uruguay (UDELAR) presented and discussed their works to the attendees.

References:

1. Ibarra M, Dalla Costa T, Schaiquevich P, et al. Iberoamerican Pharmacometrics Network Congress 2018 Report: Fostering Modeling and Simulation Approaches for Drug Development and Regulatory and Clinical Applications in Latin America. CPT:PSP (2019) 8, 197-200.

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- At ACOP10 the SxP SIG will be hosting a lunch meet up for members and anyone interested in joining the SIG. Come along and meet other members of the SIG and hear the steering committee's plans for 2019 and beyond. We will also be joining the Clinical Pharmacometrics and Mathematics and Computational Sciences SIGs for a social event.

The SxP Sig has co-signed the following comment on Jaki et al. article and we encourage all of you to read the original article, our comment, and the authors' answer.

> Krause A, Kloft C, Huisinga W, Karlsson M, Pinheiro J, Bies R, Rogers J, Mentré F, Musser BJ and the ASA/ ISoP Special Interest Group of Statistics and Pharmacometrics (SIG SxP). Comment on Jaki et al., A proposal for a new PhD level curriculum on quantitative methods for drug development. Pharmaceutical Statistics 17 (5):593-606, Sep/Oct 2018, DOI: 10.1002/pst.1873.
> Pharm Stat. 2019 May;18(3):278-281. doi: 10.1002/pst.1940. Epub 2019 Apr 1.

Please join the SxP SIG, it is free to join and there is no need to be member of ISOP or ASA. The URL is:
https://community.amstat.org/sxp/home

So come and join us at the interface between pharmacometrics and statistics – it's the best of both worlds!

Update from the Mathematical and Computational Sciences (MCS) SIG

By Helen Moore, MCS Chair

The MCS SIG has been working hard to plan interesting and fun activities for this year.

Plans for the 2019 American Conference on Pharmacometrics (ACoP):

At our luncheon on Wednesday October 23, we will make announcements about the MCS SIG, and then present our 2019 MCS poster award. The poster award winner will give a short talk on the work in their poster. We will also have a longer talk by our featured speaker. We are excited to announce that Tom Banks, PhD, Distinguished University Professor of Mathematics at North Carolina State University will be this year's featured speaker. His current research interests include the areas of optimal control, parameter estimation, and inverse problems.

In addition to the MCS poster award, we will also highlight three additional posters with significant mathematical and computational content during a poster walk, which will take place during the Monday afternoon poster session.

For the first time, we will be participating in an additional event, jointly sponsored by the Clinical Pharmacometrics and the Statistics and Pharmacometrics SIGs. After two full days of conference programming, we will host a social the evening of Tuesday, October 22, that promotes ties between the SIGs. We have engineered some fun into this event, and you won't want to miss it!

Additional information:

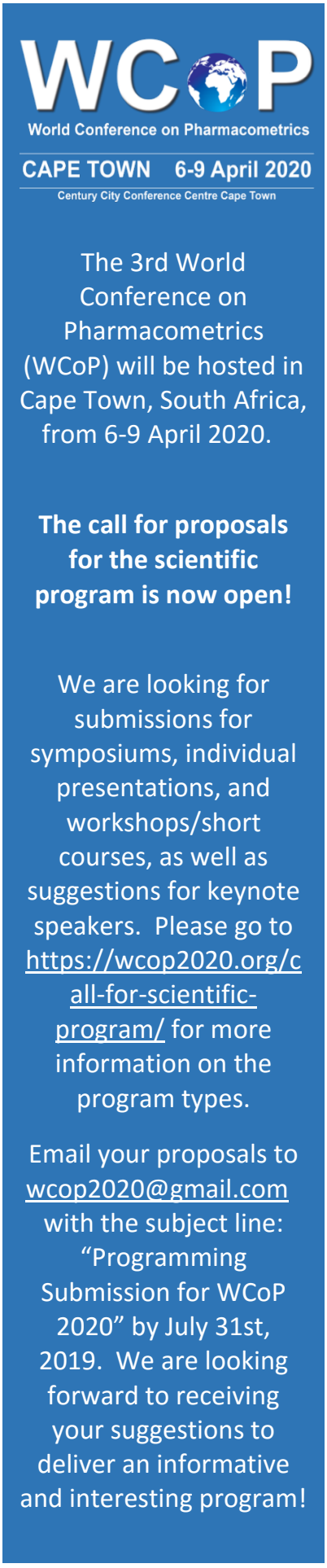
The Society for Mathematical Biology Annual Meeting will be held in Montreal, Canada July 21-26, 2019. There will be sessions that will likely be interesting to modelers in drug development, including sessions with talks by ISoP members. Registration and other information can be found here: http://www.smb2019.org/index_e.php

We thank our outgoing Steering Committee members Coen van Hasselt and Yuan Xiong for their time on the committee.

We are seeking candidates to run for Secretary in our September elections. The secretary position will be open to MCS members who are interested in getting more involved. The candidate elected to this position will serve one year as Secretary, then one year as Vice Chair, followed by a year as Chair.

Join the MCS SIG to get advance notice of these and other opportunities. Click here for more information (membership link at the bottom of the page): http://go-isop.org/special-interest-groups-sigs-and-communities/mathematical-and-computational-sciences-sig/

Want to get more involved with the MCS SIG? Have questions or ideas? Contact the Chair, Helen Moore, at dr.helen.moore@gmail.com .



News from CPT: Pharmacometrics & Systems Pharmacology (PSP)

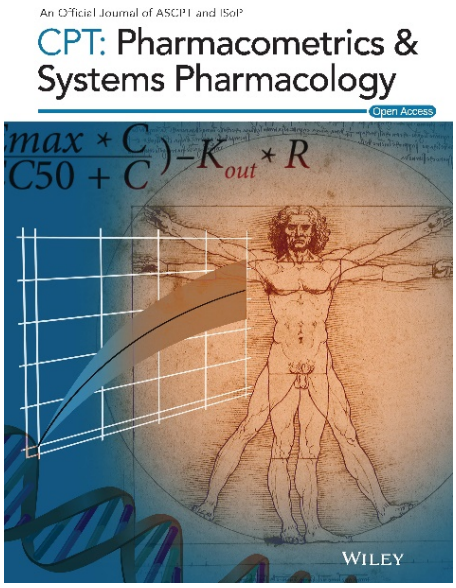
by France Mentré, Vikram Sinha and Ping Zhao

In this newsletter we emphasize the 'System Pharmacology' component of our journal with two events that happened during the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2019 Annual Meeting:

1. The *PSP* Award given to the author of a review paper on the reproducibility of quantitative system pharmacology (QSP) models.
2. The special June issue of *PSP* on PBPK and QSP features papers developed from these two ASCPT 2019 Pre-conferences.

1. Reproducibility of Quantitative Systems Pharmacology Models

Each year during the ASCPT Annual Meeting the *PSP* Award is given. For 2019, the *PSP* editorial team decided to give the award to Daniel Kirouac, PhD, from Applied BioMath, LLC (see photo taken during ASCPT award ceremony in March 2019). The award was given for his Review paper with Brian Cicali, BS, MS, a PhD student at University of Florida, and Stephan Schmidt, PhD, University of Florida: "Reproducibility of Quantitative Systems Pharmacology Models: Current Challenges and Future Opportunities."



As the use of QSP models is seeing widespread models, this publication raises the issue of reproducibility. The authors conducted a survey of published models and found that after evaluating 12 models only 4 were executable, in that figures from the associated manuscript could be reproduced. The authors point to the diversity of modeling platforms that are in use and diversity of "code" files. While *PSP* requires that the model code be submitted as part of any manuscript that is considered for publication, many journals do not, and the diversity in the modeling platforms and submitted code is a reality. The authors propose a few ideas to enable model sharing going forward, including annotated, standardized model scripts and files.

To realize continued use and acceptability of QSP models, reproducibility and ease of access of previously established models are critical. To a major extent, the more established approaches of population based approaches and physiologically-based PK models have standardized the "code" with these models; this has resulted in consistent training and broader use in their application. Indeed, as QSP models become more public, the debate should reside with the implications of the biology rather than questions about the output due to an inability to reproduce models.

By nature, the development and use of QSP models are highly technical and practitioners of QSP study extremely complex, biological systems where data sources are varied, and models tend to be assumption rich.

While descriptions of methods and data sources are included in published papers, these sections often lack enough detail. As *PSP* does, journals should include policies on data availability and encourage the use of reusable model code as part of manuscript submissions and publications. If practitioners can agree to standards for the submission of model code, wider uptake and impact would be accelerated.

→ Please submit good articles, reviews, tutorials, commentary to *PSP* to compete for the annual award!

1. Special June issue of *PSP* on PBPK and QSP

Two Pre-Conferences, "PBPK (Physiologically-based Pharmacokinetic) Modeling for the Development and Approval of Locally Acting Drug Products" and "Advancing QSP (Quantitative Systems Pharmacology) Toward Predictive Drug Development: From Targets to Treatments," were held at the ASCPT 2019 Annual Meeting. A special issue of *PSP* is dedicated to articles contributed by Pre-Conference speakers and organizers and will be available in June 2019. Speakers and panelists of both Pre-Conference reviewed state of sciences of each approach, discussed roles to support regulatory decision making, and identified gaps and new opportunities to successful applications of each approach.

The PBPK Pre-Conference was cosponsored by ASCPT and the Office of Generic Drugs at the US Food and Drug Administration. The scope of the Pre-Conference was the use of PBPK to asses bioequivalence (BE) for locally acting drug products. For locally acting drug products, a PK-based paradigm is extremely challenging. On one hand, plasma drug exposures can be low or undetectable; on the other hand, measuring drug concentrations over time at the site of action in humans is neither feasible nor ethical. These challenges often default BE assessment of generics of such drug products to pharmacodynamic or comparative clinical end-point BE studies, which are costly and often insensitive to potential formulation or dose differences. The ability of PBPK to simulate local drug concentrations make it possible to assess BE of generics of a locally acting drug product.

Discussions focused on three types of locally acting drug products: orally inhaled and nasal drug products, topical dermatological drug products, and ophthalmic drug products.

Gaps and inconsistencies in QSP modeling practices eluted to in the previous section stimulated convening of the QSP Pre-Conference. This Pre-Conference was co-sponsored by ASCPT, International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), the International Society of Pharmacometrics (ISoP), and the US Food and Drug Administration. In the past seven years, the number of regulatory QSP submissions has increased every year, as observed in "Quantitative Systems Pharmacology: A Regulatory Perspective on Translation," by Zineh. Topp and colleagues, in "Industrialization of Quantitative Systems Pharmacology," highlighted that best practices, training, education, and a clear understanding of regulatory expectations are key to the success of QSP. Wang *et al.,* identified specific challenges in QSP, which include modeling placebo effect, in their Perspective, "Incorporating placebo response in quantitative systems pharmacology models."

Both Pre-Conferences were successful in reviewing the progress made in each field and identified challenges and gaps that should be addressed.

→ Please have a look at the dedicated June 2019 issue of *PSP*!

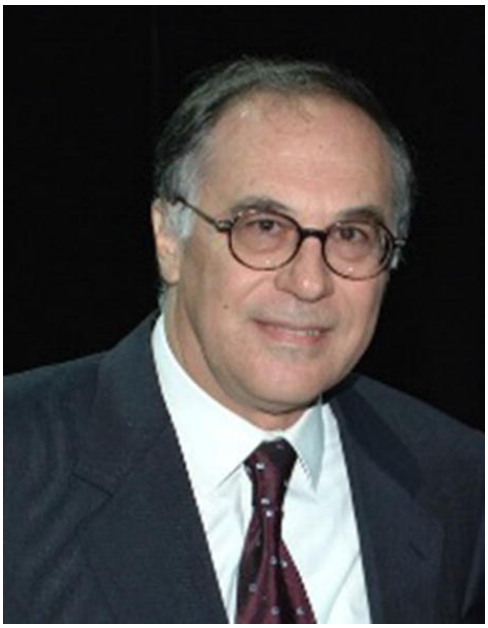
The ISoP Newsletter Needs Contributors

Please contact
Peter Bonate at
peter.bonate@astellas.com
if you are interested.

News from the Journal of Pharmacokinetics and Pharmacodynamics

William Jusko, Editor-in-Chief

The *Journal of Pharmacokinetics and Pharmacodynamics* Honors Panos Macheras



The April 2019 publication of *JPKPD* (https://rd.springer.com/article/10.1007/s10928-019-09628-5) was a Special Issue that served to highlight the scientific accomplishments of Panos Macheras, Professor Emeritus in the Department of Pharmacy of the National and Kapodistrian University of Athens, on the occasion of his 75th birthday. Compiled and guest edited by Laszlo Endrenyi and Robert R. Bies, published were a Macheras biography plus 8 articles that included two reviews, one tutorial, and five original papers. These articles included original contributions that complemented and descended from the Macheras innovations in the fields of bioequivalence, drug dissolution and absorption, biopharmaceutics classification, drug-milk interactions, heterogeneous kinetics, and nonlinear dynamics. JPKPD was pleased to honor a pioneering and multi-talented contributor to the field of pharmaceutical sciences.

The DDMoRe Foundation

By Stefano Zamuner

What is the DDMoRe Foundation?

The DDMoRe Foundation was founded in April 2016 with the aim to promote, maintain and enhance the open-source DDMoRe standards and tools emanating from the DDMoRe Consortium (European-IMI project 2011-2016). The DDMoRe Foundation objectives are to deliver and improve the quality, efficiency and cost effectiveness of Model-Informed Drug Development (MIDD) and Therapeutic Use. The Foundations current partners consist of Pharmaceutical Companies and Academic Institutions sharing the belief that MIDD will benefit greatly from model standardization and tool integration. By elaborating on principles of model sharing and tool interoperability based on these standards, the foundation can support and enhance the community at large.

The objectives of the DDMoRe Foundation are:

- Maintain and enhance public domain content from the DDMoRe Consortium (**www.ddmore.eu**);
- Provide specific DDMoRe Foundation Partner benefits;
- Increase DDMoRe utilization and global awareness; and
- Expand DDMoRe functionally according to the wishes of the DDMoRe Foundation Partners.

Foundation membership and community

The DDMoRe foundation includes partners from both academia (Uppsala University, University of Pavia and University of Leiden) and industry (Servier, GSK, Merck Serono).

The current DDMoRe Foundation board members are:

- Paolo Magni, University of Pavia,
- Katy Wolstencroft, Leiden University,
- Mats Karlsson, Uppsala University,
- Marylore Chenel, Servier,
- Stefano Zamuner, GSK,
- Pascal Girard Merck Serono, and
- Peter Milligan, Pharmetheus.

There are also three community groups relying on the support of volunteers:

- Model Repository Community Group
- Thoughtflow Community Group
- Language Community Group

One of the core principles of the DDMoRe Foundation is model sharing. Sharing models among scientists from different institutions (academic institutions, pharmaceutical companies, SME, hospitals, agencies) enhance the robustness of a model since it has been tested in different conditions (i.e., different patient population, inclusion of new covariates etc.).

Model sharing is a "patient centric" initiative since it allows a more efficient drug development and helps to rationalize the therapeutic use of drugs (i.e., pharmacometricians from hospitals can access to models developed by pharma companies).

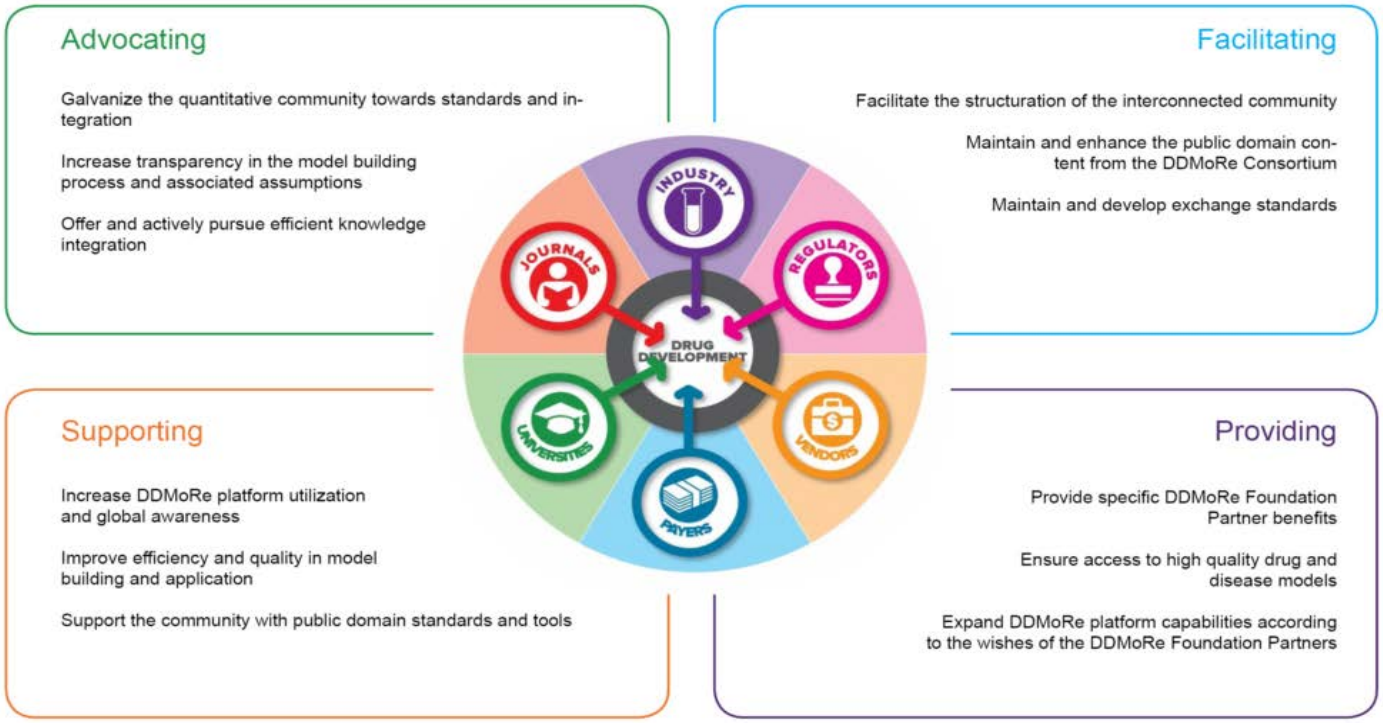
DDMoRe Repository

The DDMORE Model Repository http://repository.ddmore.foundation is an open, publicly-available, free-to-use platform for storing pharmacometric PK/PD and drug-disease models. It is indexed, fully searchable and supported by peer-review. Currently the foundation is considering a major upgrade of the model repository to improve the system architecture of the current database, including additional features aimed to enhance the user interface, and facilitate the upload of new models. Scientists submitting their abstracts to pharmacometric meetings (e.g. PAGE, ACOP, PAGANZ…) or peer-reviewed journals are encouraged to upload their models in the library for sharing them with the very active community who offers a price for the best contributors, creating the largest freely available population PK/PD library.

While it may seem that this can be achieved by the publication of models in scientific papers, in practise extracting a model from a paper is often not straightforward. Models are complex to report and papers can only give an approximate description (sometimes erroneously) of the models that make them difficult, if not impossible, to reproduce.

By providing a public on-line resource of good quality models the DDMoRe Repository overcomes these problems. The repository allows to search for and download models that cover a wide range of diseases and equally importantly everyone can add his own models to the repository and share with colleagues. We would encourage authors to do this when they submit a paper for publication. The repository provides a persistent identifier that authors can reference in their papers facilitating the access to the model code.

Drug Disease Model Resources
ddmore



The content of the repository is supported by a group of volunteers led by Celine Sarr/Pharmetheus, that work to increase and improve the content of the repository and provide help to new users. More about their work can be found here: https://www.ddmore.foundation/model-repository-community/.

Periodically the Foundation and Model Repository community group run the DDMoRe repository challenge where the best newly submitted model is rewarded with a cash prize. The last challenge was run at the end of 2018 and the winner was Thierry Buclin, of CHUV [1]. His model on colistin in patients receiving continuous renal replacement therapy (CRRT), is now available online (http://repository.ddmore.foundation/model/DDMODEL00000295).

The repository continues to grow. As of May 2019, the repository has 135 models. Many of these models were provided by the publicly funded DDMoRe project that preceded the creation of the foundation, but 30 models have been shared by volunteer efforts in the last 2 years. Over the last year the repository has been used by 914 users from 32 countries, with many outside of Europe and North America, and from all continents. During the same period 1575 models were downloaded.

Over the next year to 18 months we hope to improve the software running the repository. At the moment we use a bespoke software platform called JUMMP that was developed as part of the publicly funded DDMoRe research project. This is proving expensive to maintain, and now that we have been using the repository for several years our users have suggested many ways that we can improve the software. Rather than try and fund a software development project to do this, we are exploring the option of customising an *off the shelf* solution.

We expect that a detailed technical evaluation of potential software platforms will begin later this year. With improvements to the repository software and a committed and growing user community we are optimistic for the future of the DDMoRe repository.

Interoperability framework in R

The other main project of the foundation is the upgrade of the interoperability framework in R (IOR), aiming to take advantage of the interoperability tools developed and maintained by DDMoRe Foundation. This later feature basically allows a pharmacometrician to store a model developed for one software (e.g. NONMEM), translate it to another software (e.g., PFIM, software (e.g. Monolix, WinBugs, POPED, …), run it and store a Standard Output (SO) that can be re-used by the IOR for a future run [2]. The suite of software (Library + IOR) should facilitate the exchange and the re-usability of models across academia and industry in the spirit of MIDD.

References

[1] https://www.chuv.ch/fr/chuv-home/formation/offre-de-formation/offre-de-formation-detail/formation/pharmacologie-et-toxicologie-cliniques-medecin/

[2] Terranova N, Smith MK, Nordgren R, Comets E, Lavielle M, Harling K, Hooker AC, Sarr C, Mentré F, Yvon F, Swat MJ. The Standard Output: A Tool-Agnostic Modeling Storage Format. CPT Pharmacometrics Syst Pharmacol. 2018 Sep;7(9):543-546.

The Future of Modelling and Simulation in Pharmacometrics with Julia

By Vijay Ivaturi, Chris Rackauckas, Viral B. Shah

Pharmacometricians have been early adopters of mathematical programming tools. We use tools that allow us to solve real problems. However, given the diversity of problems that we solve, our field has seen a split in the languages that we use due to the problems they are tailored to solve. R has become a staple in the community due to its strong statistics, data manipulation and plotting libraries. MATLAB and its ODE solvers have been the basis for many QSP models. The NLME community is still very much rooted in more traditional tools like FORTRAN, while machine learning is leading some researchers to explore Python.

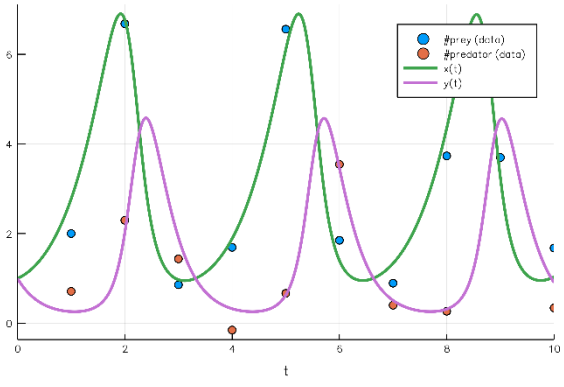
While having a Swiss army knife helps, an alarming trend in this field is the language split between the package developers and users. Pharmacometrics is a discipline where we need to know that the code we are running is doing what the mathematics says, and we need to validate everything. However, the libraries that we are calling are generally written in other languages and treated as an undebuggable black-box.

If you're interested in adding a hook in R's deSolve ODE solvers for some new QSP model, or want to dig in and find out why Stan's Bayesian estimation is missing a peak, you will not find R code. Instead, you will find that the core of these libraries are written in FORTRAN 77/90 and C++, and investigating what they are doing requires using opaque and non-interactive languages.

This is a requirement because writing low-level code was a traditional requirement for higher speed. Smart programmers who know how to work with SIMD vectorizers, stack-allocation of volatile structs (and how they are sometimes miscompiled), and pointer tricks on mutable buffers compile a binary that the interactive language calls and the details of the algorithm are intertwined with a computer science degree. This is done because the performance difference is not small, and one can easily get performance increases of 10x-1000x by utilizing these "close to the metal" features to optimize the implementation of their underlying loops.

While the efforts of these impressive programs and their programmers are laudable, this split between "languages used to write packages" and "languages used to do science" is not a sustainable way to build a fast, usable, and verifiable scientific computing ecosystem. **This is the problem that Julia solves**. Code written in Julia is as fast as C or Fortran while being dynamic and interactive like R and MATLAB. Julia achieves this by reengineering what it is to be a high-level language from the ground up, using a type-based multiple-dispatch system that cannot easily be applied to fix languages like R, Python, or MATLAB. This means that a scientific computing ecosystem has been built from scratch to have Julia code all the way down without losing performance. There are thus three things that are gained by using Julia for scientific computing: its user-developer connection, it's the diverse ecosystem which has quickly grown due to the ease of development, and the speed of its packages. The user-developer connection is an invaluable asset when working in Julia. One could be just a researcher using packages developed by others, but can very easily, e.g. use @edit on a plot that would open up the Julia file in the library and add their own features in. Within hours one goes from a user to a "package developer." As this barrier between users and developers is so small, the developers are all there in the user communities. The support system that thus exists in the Julia Slack and Discourse is unparalleled due to the fact that many times your questions will be answered by people who not only know how to use the package but also know the code. The number of people verifying obscure edge cases is also increased when every user is one line away from checking a code that's in a language they know. This has allowed Julia to grow to have a very well-connected package ecosystem because it's easy to make packages talk to each other since we are all using the same underlying language: Julia.

The connectedness and ease of development have allowed Julia to grow to have one of the most diverse and feature-rich package ecosystems. Julia packages are some of the most advanced in differential equations, statistics, and machine learning. One of the central packages for pharmacometrics in Julia is DifferentialEquations.jl. This software ecosystem is undergoing continual advances in the areas of parallelism (multithreaded, distributed, and GPU), improved solver strategies like IMEX and exponential integrators, along with advancing the methodologies in new mathematical modeling areas like delay differential equations (DDEs), stochastic differential equations (SDEs), and jump equations (Gillespie). All of the tricks, like adjoint sensitivity analysis for parameter estimation, mixing differential equations into neural networks, automatic symbolic calculation of Jacobians, etc. are all supported by this one library, making it both faster than the traditional libraries while being easier to use for modern modeling practice.



Sample Julia Plot

In the statistical libraries, packages like DataFrames.jl, Distributions.jl, and MixedModels.jl are stunning counterparts to the R ecosystem. In fact, MixedModels.jl was developed by the same author as lme4 (Douglas Bates), who now requests users of lme4 to use JuliaCall to call MixedModels.jl from R since the Julia package has both better convergence properties and runs 30x faster. While on the machine learning side, machine learning libraries like Flux.jl and MLJ.jl give full-featured learning pipelines in ways that allow for GPUs and other acceleration opportunities.

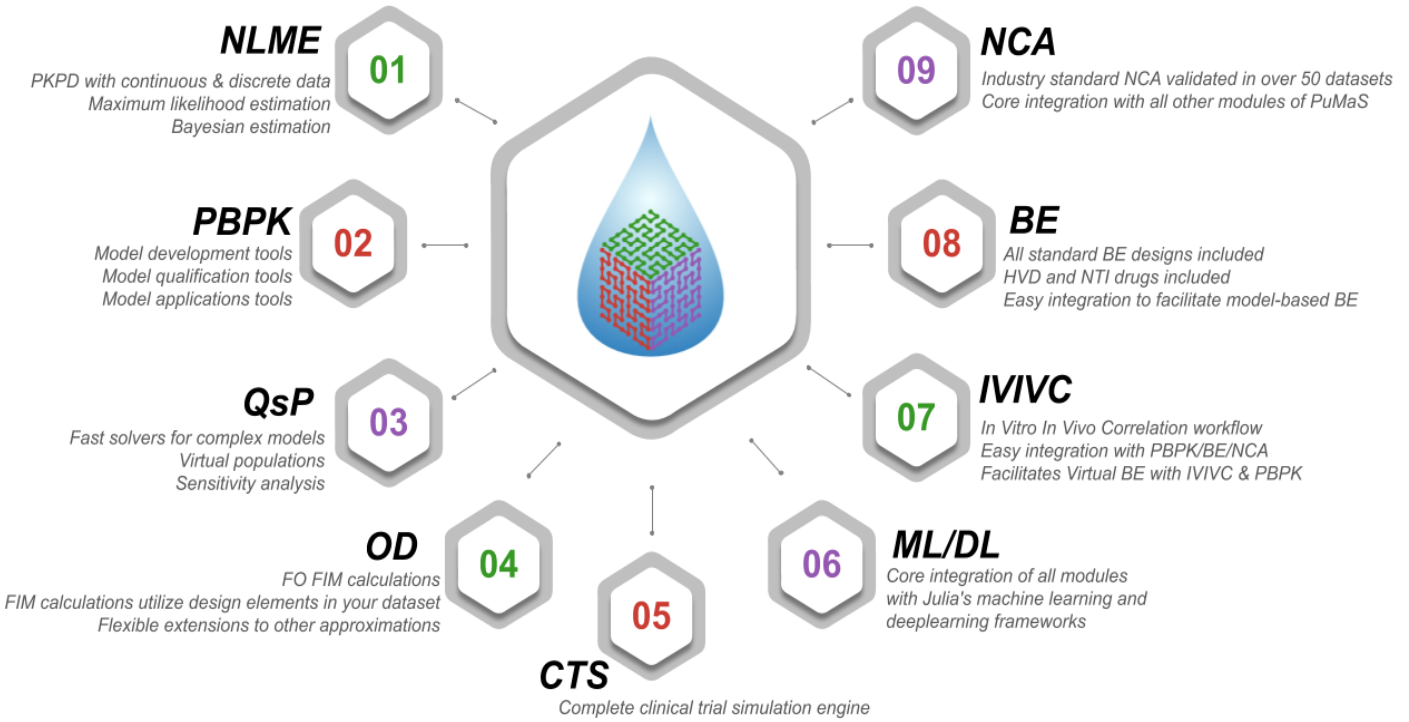
And the pivotal feature, in the end, is the speed. The differential equation solvers have the most comprehensive set of benchmarks found at DiffEqBenchmarks.jl and its unique algorithms routinely beat classic C++ and Fortran methods. Users coming from R, Python, and MATLAB routinely report speedups, averaging at around 30x before optimizing the code. For example, this was recently demonstrated on a cardiac QSP model from Pfizer (26x), on a battery efficiency differential-algebraic equation model at Carnegie Melon (30x), and on the test suite at MATLABDiffEq.jl. In cases where there are no similar algorithms in other packages, like high order adaptive stochastic differential equation integrators, the difference is

even more dramatic, with a stochastic epithelial-mesenchymal transition model (EMT) besting the standard methods by ~3000x.

Speed itself is a feature that enables models. By being faster and easily parallel, the size of the model can continue to increase and new domains can be explored. This is the central idea behind PuMaS.jl, which is a soon to be released pharmacometric modeling suite in Julia.

Building off of DifferentialEquations.jl, it allows for the large ODE models of PBPK and QSP models, while allowing nonlinear mixed effects (NLME) population models. The simulation methods can make use of these special GPU-accelerated high order ODE/SDE/DAE/DDE/etc. solvers to enable pharmacometricians to start exploring entirely new models. This is coupled with the ability to do parameter estimation through maximum likelihood and Bayesian methods (HMC and SAEM). A connected suite for bioequivalence and NCA allows one to integrate the whole simulation and estimation pipeline, and the connectedness to the existing Julia package ecosystem allows for one to swap in global optimizers, automatic differentiation, and uncertainty quantification.

Julia is written for scientific computing and its vibrant community involves mathematicians, statisticians, software engineers, and life-science majors. The Pharmacometrics community has mostly revolved around clinicians, pharmacists, life-science majors and consists of very few highly technical scientists from an engineering or mathematical background. Julia in pharmacometrics will provide an opportunity to make our community more inclusive and bring innovation and efficiency that is otherwise left at the mercy of the develop-user split. We are hopeful.



Communication Corner

By Peter Bonate

I Can't…um…Take It Anymore!

We've all sat through it - those meetings where the presenter says..um.. every..um....other..um..word. For me, I would rather listen to fingernails on a chalkboard than listen to half an hour of this kind of presentation. At times I want to stand up and scream "stop!", but more than likely I may just leave (it's hard to do this at work, but I definitely will do it at a conference. Life is too short). I am sure that the presenter doesn't realize what they are doing and that if they did, they would try not to do so.

What are filler words? These are the words we use to fill in-between sentences or pauses in our sentences where our mouth catches up with our brain so as to not leave an empty space in the air. They are words like "um", "ah", "you know", "so", etc. Academics have a special word (they have a special word for everything, right? Arghh. See it's hard to stop) for filler words, called dysfluencies.

Research has shown that a typical public speaker may use as many as 5 filler words per minute. That's a lot of "ums". This is bad because an audience wants to remain engaged. Too many filler words distract from your message and disengage the audience. It takes an audience more cognitive effort to filter out the filler words and get to the actual message.

Being able to remove filler words has beneficial effects. First, it makes you appear more professional. Think of politicians – you rarely hear a filler word. Or think of TED talks. You never hear a filler word there because the speakers have been trained so as to not use them. Although filler words give a chance for your brain to figure out what you are going to say next, a pause makes you appear more confident and in control of your speech. It's calming. Most pauses are short, about a second in length, but some of the best public speakers will often pause for 2 to 3 seconds, maybe even longer, because the pause can emphasize a point, build suspense, or give the audience time to absorb what has been said.

How can you stop using these words? First, you have to be aware of it. I remember the first time I became aware of my use of "um" was after seeing a video of myself giving a presentation. I was horrified at how bad I was and realized I needed to make a change in my speaking patterns. Today, with smart phones, it's easy to video or just simply do a voice recording of your yourself presenting. Listening to yourself speak can be a mind-blowing, self-awareness experience.

Stopping the use of filler words is like learning to break any bad habit. You have to make a conscious effort to not use them. It can be a bit disconcerting at first to pause between sentences and leave that empty space in the air. But in doing so, you actually give more weight to each sentence as it allows your message the time to sink in with the listener. You could use more conditioned avoidance techniques if you are having a really hard time not using them. For instance, during practices, have someone in the audience use a clicker or snap a rubber band every time you use a filler word. As you get better and better there will be fewer and fewer clicks. If you don't have someone to help you, you could do something yourself like tap your foot or tap your leg with your hand every time you use a filler work. This will serve as negative reinforcement for using too many filler words.

Then you need to practice. Practice, practice, practice at it. Stand in front of a mirror. Record yourself. Practice in the car. Practice at home. Practice. Over time you will get better and better at not using them. Trust me, once you make an effort to stop using filler words you become acutely aware of them, even, maybe especially, when other people use them.

You have to be careful though. Our filler words tend to become personal and they become our go-to words over and over. For instance, someone might say "like" for what seems like a million times in a presentation. Once you train yourself not to use that filler word, you must be careful that you don't start to use another filler word. Over time I have trained myself not to say "um", but I recently listened to myself give a presentation at a local ISoP event and was shocked to discover that I started using another filler word, a different filler word – "right". I was starting to end my sentences with the word "right." Being diligent on the use of filler words should never stop. You should always try to remain cognizant of their use.

Maybe We Could Use Electric Fence Dog Collars to Get Rid of Filler Words (or windbag politicians)

Every time a filler word is used … zap

The occasional use of filler words is to be expected. About 1 per minute is ok. It's human. It makes you relatable to the audience. It's the over-reliance of filler words to the point where they become crutch words that causes problems. So do me a favor, if you see me in the audience with rubber band, don't panic, but stop using filler words. Use pauses. Become a more polished public speaker. Me and the rest of the audience will thank you.

Meeting Announcement:

Pharmacometrics in the Developing World: Translational M&S and Virtual Bioequivalence

The Iberoamerican Pharmacometrics Network (RedIF, www.redifar.org) is announcing the celebration of its 2019 Congress in Havana, Cuba, on October 27 to 30: "Pharmacometrics in the Developing World: Translational M&S and Virtual Bioequivalence".

The Congress will be held in Tryp Havana Libre Melia Hotel, the most cosmopolitan and centric Melia hotel in Havana. Congress will feature keynote lectures, focused seminars, oral student session and poster session.

Confirmed keynote speakers:

- Lena Friberg, PhD. Uppsala University: "Pharmacometrics to combat antimicrobial drug resistance".
- Donald E. Mager, PhD. University at Buffalo: "Translational Pharmacometrics and system pharmacology models in oncology".
- Lawrence Lesko, PhD. University of Florida: "Physiologically Based Pharmacokinetic Modeling (PBPK) in Drug Development and Regulatory Science: From Bench to Bedside".

Focused seminars: Therapeutic Drug monitoring, Virtual Bioequivalence, PK/PD modeling, PBPK/PD & QSP and Internal Dosimetry in Radiopharmaceutical Development.

Also, several pre-congress and post-congress workshops will be held on MONOLIX (Lixoft), NONMEM (ICON plc), nlmixr and PK-Sim (Open Suites Pharmacology).

Abstract submission period is already open for both oral and poster presentation. Abstracts should be sent by e-mail to redif.cuba2019@gmail.com.

Authors should provide their abstract in English, in Word format (Arial, 12 pt., single space), including: Title: In Bold and capital letter; Authors and affiliations: Last name and first letter of the name using comas between every author (in black). The name of the author who will present the work should be underlined. Abstracts should be clear and precise, containing in no more than 300 words: Introduction, Materials and Methods, Results and Discussion and Conclusions. Deadline for submission: July 15.

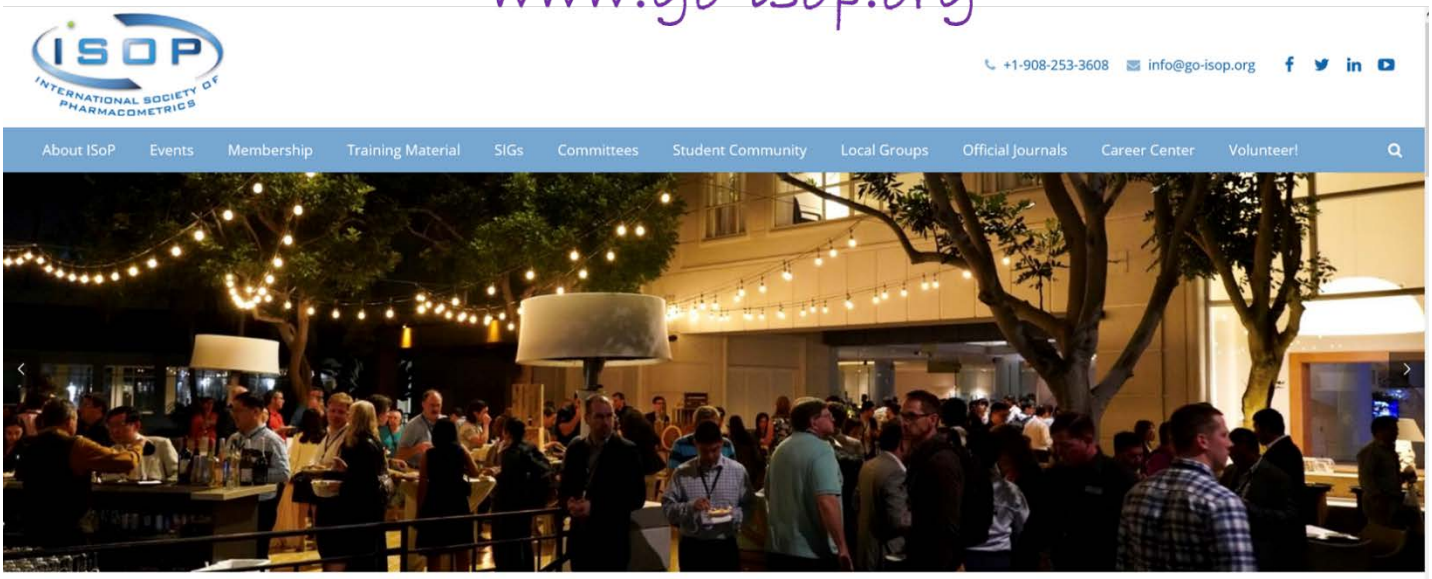
Information regarding registration fees and accommodations will be available soon.

Your participation will provide you the opportunity of sharing results and expertise with the most prominent specialist in Latin-America and other colleagues from all around the world as invited speaker/participant. In addition, incorporation of student sessions provides an excellent education framework for our future specialist in the field.

So please mark your calendars to join us in promoting the development of pharmacometrics in Latin America.

Have You Checked Out Our New Website?

www.go-isop.org

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