INTERNATIONAL SOCIETY OF PHARMACOMETRICS

ISoP NEWS

May 2020

Message from the President

By Brenda Cirincione

It goes without saying that this quarter's newsletter comes at a time when we have all had major changes in our day-to-day life routine. Currently, we are all facing different types of challenges for many of us it is this work from home environment. As the discipline of pharmacometrics, we can successfully work from home, if the access to the necessary computing environments is in place. This doesn't make it easy, though, as we expand from trying figure out unique ways to explain complex models across zoom environments to making sure the Wi-Fi is still able to keep up. For many, the challenges also come from the adaptation of our home life and our work life to the same physical space. You realize that your exercise tracker is not incorrect when informing you that, due to the exciting models being developed or challenging problems occupying your mind, you have walked less than 100 steps the entire day (likely in a small repetitive path between the coffee table serving as a make shift office to the kitchen). Hopefully with the transition to summer weather we can improve on that!

Over the last two decades we have watched the field of pharmacometrics mature and expand in both scope and complexity. As ISoP we are in the unique position to shape the next steps for our discipline and what we would like to accomplish. Many of the initiatives we have started with our five-year strategic plan are about to launch in the 2nd half of this year and will provide us with a foundation to write the next chapter in the pharmacometrics path. Please watch for the announcement of new opportunities to shape the future of ISoP – we need your input!

With respect to the COVID-19 pandemic, there are many working on great things to accelerate the path to answers. Along with others, ISoP is positioned to help connect some of these great efforts. Brian Corrigan and Matt Rizk at ASCPT have put together a COVID-19 related clinical pharmacology taskforce (http://discuss.go-isop.org/t/covid-19-related-clinical-pharmacology-or-pharmacometrics-taskforce-s/1388) – have a look if you'd like to contribute or volunteer. Please see the discuss.go-isop.org site (http://discuss.go-isop.org/t/covid-19-resources/1397) as a place to indicate if you are working on an COVID-19 initiative that you would like to share or get some help with from our community, or if you have any new ideas for areas that pharmacometrics or ISoP could contribute to this cause. There are many activities ongoing, some of which have been shared on Facebook, LinkedIn and Twitter, and it would be great if we could pull them together in a single place.

There are two exciting ways to contribute and recognize our colleagues currently ongoing. The call for nominations for the ISoP Board of Directors is now open. Although being a member of the Board involves a significant commitment of time and effort, it's a great deal of fun, and a socially and professionally rewarding experience. Please consider nominating yourself or a colleague who you believe will be able to contribute to the growth and evolution of ISoP. Please see the website (http://go-isop.org/2021-isop-board-of-directors-nominations/) or contact ISoP President-Elect and Nominations Committee chair C J Musante for additional information.

The 2020 call for ISoP Award nomination is also open. ISoP recognizes innovative science and outstanding leadership in the field of pharmacometrics and related scientific areas. Every year, we present the Lewis B. Sheiner Lecturer Award, the Innovation Award, the Leadership Award, the Outstanding Research Manuscript Award (for publications *in 2019*), the Emerging Scientist Award and the Unsung Hero Award. Now is the time to recognize colleagues and peers! See the website for more information about each award and how the nomination process works (http://go-isop.org/awards/), or contact Awards Committee chair Chris Penland for more information. The submission deadline is May 31, 2020.

I hope everyone is safe and well. I look forward to when we can all be together discussing exciting science and catching up on current activities! In the meantime, even separated, our greatest strength is our close-knit community. Let's stay in touch and support one another in these challenging times.

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ACoP11 is shaping up to be a great meeting with exciting new events and features. The ACoP planning committee is working tirelessly to put together an excellent program for ISoP's annual meeting. Registration for ACoP11 will open soon. ISoP members will receive 100% refund of their registration costs should the event be cancelled due to COVID-19. Secure yourself a spot at ACoP11 by registering early. You can find the most up-to-date information and timelines on our website, but here just a few highlights to pique your interest:

Main Conference (October 4-7, 2020 + free tutorials on October 8, 2020):

- The main conference agenda is now available! We bet the exceptional scientific sessions will make it difficult for you to choose between which sessions to attend.
- Main conference attendees can also register for free tutorials to be held on Thursday morning, October 8th Please plan your travel accordingly.
- The **Communication Challenge** is a new session being introduced to the existing multiple events specially designed and targeted towards our growing student and trainee community.
- There will be ample opportunities to network with colleagues and friends.
- Stay tuned for details on our much-anticipated evening social event on Monday, October 5th.

Conference Abstracts:

- The Call for Abstracts is open until May 15th. Don't delay, submit your abstracts now.
- There are multiple opportunities to win awards and recognition for your abstracts that include the Quality and Trainee Abstract Awards, MCS, QSP, ClinPmx and SxP SIG poster awards and poster walks. See website for more details.

Pre-conference (Sunday, October 4, 2020):

- The Pre-Conference on, "**The Rising Role of Modeling in Oncology - From Translation to Confirmation**" will feature exciting sessions presented by a diverse group of scientific experts from academia, research institutes, regulatory agencies, and pharmaceutical and technology industries.

Workshops:

- As every year, ACoP will host several pre- and post-meeting workshops covering a wide array of topics. Please visit the website for more details including pricing. Remember to plan your travels accordingly if you register for any of these workshops.

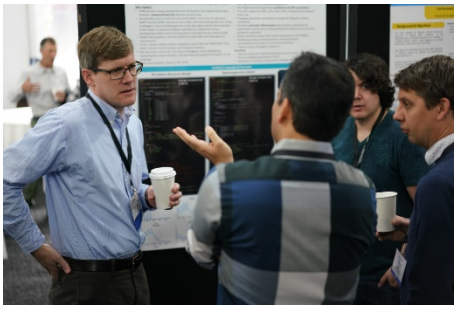
We look forward to seeing you in Colorado!

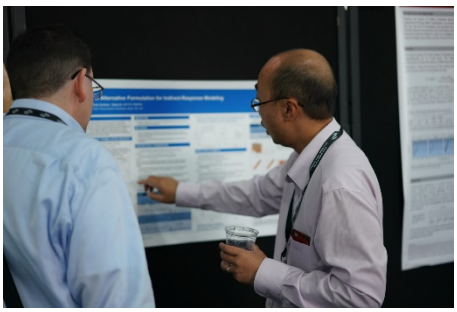
On behalf of the ACoP11 Planning Committee,

Navin Goyal – ACoP11 Conference Chair

https://www.go-acop.org/

Photos from Past ACoPs:

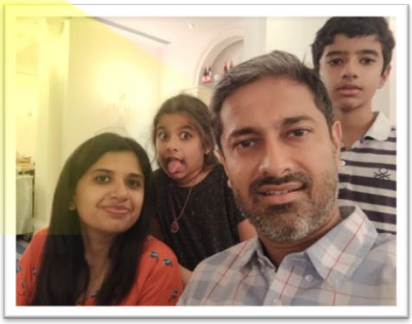




Spotlight on Rukmini and Vikram Kumar

Vantage Research

By Peter Bonate



Tell us about yourselves:

Rukmini: I started life as a physicist and then moved on to physiological modeling in my PhD. Then and now, I love the integrative, inter-disciplinary and applied nature of modeling of biological systems. Apart from work, I am a homebody - reading, family and friends keep me occupied.

Vikram: I started my career as a computer engineer and spent many years as a techie in Networking technologies, then moved into the business side of things after a Berkeley MBA. I was always keen on starting something, ultimately leading to founding Vantage – and have been enjoying the journey at Vantage!

What got you both into pharmacometrics?

Rukmini: I don't do pharmacometrics - I enjoy working with pharmacometricians though! I work on QSP, PBPK and other physiology-based modeling and analysis approaches. Having to craft the problem statement clearly, coming up with a robust solution while taking care of uncertainties - that is what I find most exciting. I also appreciate the opportunity to work on real-life problems and have impact on high-value decisions. Modeling in pharma is a sweet spot if you want to be a scientist and have a practical streak.

Vikram: I married into pharmacometrics (more specifically systems pharmacology)! For several years, while I was a proper techie (writing code and building networks), I knew little about modeling biology and drug development. After returning to India, and sizing up business opportunities, one such opportunity was to partner with my wife and start a CRO. We dived in!

So what do you do in your job? What's a typical day like for you?

Rukmini: These days it's all about managing the overall direction of each of the research teams at Vantage and trying to stay on top of the literature on the various threads we are working on. I also immensely enjoy working with the scientists at Vantage on both the methods of QSP as well as the skills to be a consultant, putting the client's problems front and center.

Vikram: I'm the CEO. I'm also the HR guy, the Ops guy, the Finance guy, and the buyer of the coffee machine! What I am most focused on these days is process development – building an efficient, robust, value-driven process, that allows us to function as an extension of the client's team.

What's it like to work together (although I guess most of are all working together now at home)?

Rukmini: Working with a spouse takes some getting used to in the beginning, especially drawing clear lines between work and home life requires deft navigation! We have been working together now for 6 years, so I'd say we've got the hang of it. We have complimentary approaches to problem solving and that helps us manage a company well together.

Vikram: You're seeing each other a *lot*. It takes some getting used to. The trick is to draw a line at some point and "stop the work talk". Once you figure that out, it is a good balance. On the plus side, the trust level and alignment in decision making is unbeatable.

What are doing to stay engaged and sane during this pandemic? What has been the biggest challenge?

Rukmini: Online gym and sticking to a routine for the win! We live in India where the lockdown is quite severe. We are grateful that we can work through this at all, as many businesses just cannot manage the logistics. All our collaborators are also working from home, so they understand the challenges. To be honest, so far it has been more efficient work-

wise than I had anticipated. In the meanwhile, allowing us to glimpse different aspects of our colleagues' lives - their pets, kids, homes and increasingly unruly manes.

Vikram: At first it felt bizarre. Now, after several weeks, there's a sameness to every day that I have to remind myself what day of the week it is. But it's been philosophically interesting - you realize you need very few things to get on with life.

We're very fortunate to be able to continue working - work gives you something to focus on amidst all the uncertainty. As a group, we've managed to work from home and across geographies, for 7 weeks straight - and we've been remarkably productive. It's certainly changed my notions about how teams can successfully interact and collaborate.

And to add some variety, we use Google Meet for work, Zoom for workouts, and WebEx to chat with friends over the weekend!

What are some reasons you would say to someone to join ISoP?

Rukmini: I've been going to ACOP almost continuously from 2011 (in San Diego?). In this decade or so, I have seen increasing acceptance of QSP community and leadership from ISOP in emphasizing the role of modeling in drug development. It is also clear that the organization started as a group of friends and that seed of camaraderie and fun still is at the center of ISOP.

Vikram: The network – it's global, it's friendly, it is focused on the science, and it is full of people with strong opinions. I like that ISoP is expanding its scope to accommodate new areas that are coming up. The more you participate, the more you get out of it. And it's a fun group!

My last question is always fun. What's your favorite food?

Rukmini: This *is* fun. While I'm happy to try many things, comfort/favorite foods are often what you grow up with. So like many South Indians, I need a strong cup of milky coffee in the morning and a cup of tangy yoghurt and rice to end the day (Ellen gets introduced to Yoghurt and Rice by Padmalakshmi).

Vikram: A crispy taco, with guacamole, rice and beans, a little bit of hot sauce! Crispy Okra. Any kind of Chaat (Pani puri, Bhel Puri). And chocolate. Sorry, did you say only 1?

ACoP11 Abstract Submission Deadline - May 15

Deadline for ACoP11 abstract submission is approaching soon - May 15th! Submit your work and be part of the exciting science at the conference. Please go to the following link to find guidelines and further details for submitting your abstract (https://www.go-acop.org/call-for-abstracts).

There are several opportunities to win recognitions for your abstracts that include the Quality and Trainee Abstract Awards, MCS, QSP, ClinPmx and SxP SIG poster awards and poster walks, as well as the new session "Communicating your Research" for our Student and Trainee attendees.

Authors of accepted abstracts will be notified between July 7 – July 10. Authors can withdraw their submission if they are unable to register for ACoP11 due to COVID-19. Please refer to the earlier email blast and the ACoP11 website (www.go-acop.org) for more details, including reimbursement policy on registration fees.

Please reach out to us at abstracts@go-acop.org if you have any questions. Thank you in advance for supporting ACoP, and we look forward to seeing you in Aurora, Colorado!

Best regards,

Kenta Yoshida, ACoP11 Abstracts Committee Chair
On Behalf of the ACoP11 Planning Committee

From The Director's Desk

The ACoP11 planning committee is working hard to develop a conference program on par with ACoP meetings of the past. ACoP will feature:

- 1-day pre-conference
- 11 vendor sponsored workshops
- Daily poster sessions
- 4 free tutorials

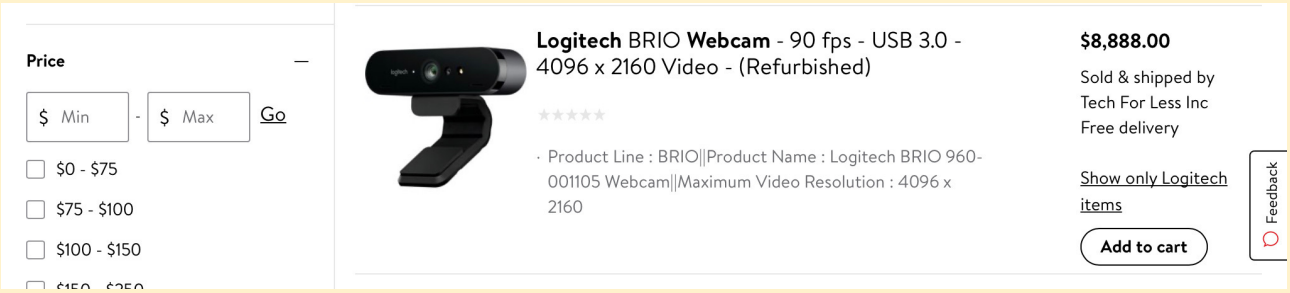
Early Bird registration will begin June 1st. With this year's registration form, attendees will be able to renew their ISoP membership for the current or upcoming membership year. Non-member attendees who become members by completing the membership section of the form, will be able to take advantage of discount pricing immediately. That's an instant savings of $400.

It is important to note, that once you have submitted your registration selections, you will not be able to modify your choices. Attendees will not be able to add workshops or change tutorial selections later. Please visit www.go-acop.org to review the entire slate of workshops and programming choices prior to the opening of registration.

I look forward to seeing you in Aurora.

Enrico Smith

As Seen on Walmart.com



I needed a new webcam and came across this great deal

Papers Worth Reading

by The ISoP Publications Committee (Angela Birnbaum, David D'Argenio, Ashwin Karanam, Peter Bonate, and Ana Ruiz)

Mihaila R et al. Modeling the Kinetics of Lipid-Nanoparticle-Mediated Delivery of Multiple siRNAs to Evaluate the Effect on Competition for Ago2., *Molecular Therapy: Nucleic Acids*, 16:367-377, 2019. doi.org/10.1016/j.omtn.2019.03.004 (suggested by David D'Argenio)

Small interfering RNAs (siRNAs) have been used to selectively silence targets of interest in coupled signaling pathways. Advances in RNAi formulation and delivery have led to the recent approval of the first siRNA therapeutic. While siRNAs hold promise as combination therapies aimed at multiple targets, the degree of competition between siRNAs may prove problematic.

This paper by Mihailia et al., uses a mechanistic model in an effort to better understand the factors that govern siRNA competition, and then uses the model to investigate strategies aimed at mitigating competitive interactions. Building on the previous modeling work by the group on lipid-nanoparticle (LNP)-formulated siRNAs, this report proposes a model-based explanation for the differences observed *in vitro* in the degree of competition between siRNAs, when delivered by the commonly used transfection reagent RNAiMax and LNPs. This work may serve to guide the development and application of translatable models to optimize delivery of siRNA combinations.

Andersen KG et al., The proximal origin of SARS-CoV-2. Nature Medicine 26; 450-452, 2020.

There are a lot of crazy theories out there regarding how the Covid-19 pandemic started, one of them being that is was genetic manipulation of a coronavirus by the Chinese that was then (accidentally) released into the population. In what may be the most downloaded paper in history (4.34 Million downloads), Andersen and colleagues performed a genetic analysis of the viral genome of the Covid-19 virus and conclusively showed it was natural in origin and NOT man-made.

It is impossible not to include a few COVID19 papers, more or less related to our field (as chosen by Ana Ruiz):

Bonate PL. COVID-19: opportunity arises from a world health crisis. *J Pharmacokinet Pharmacodyn* 47, 119–120 (2020). https://doi.org/10.1007/s10928-020-09681-5

Xiang F, Wang X, He X, et al. Antibody Detection and Dynamic Characteristics in Patients with COVID-19 [published online ahead of print, 2020 Apr 19]. *Clin Infect Dis*. 2020; ciaa461. doi:10.1093/cid/ciaa461

Other non-COVID19 Papers:

Zuccaro V, Lombardi A, Asperges E, Sacchi P, Bruno R. PK/PD and antiviral activity of anti-HCV therapy: is there still a role in the choice of treatment? *Expert Opin Drug Metab Toxicol*. 2020;16(2):97–101. doi:10.1080/17425255.2020.172145 (suggested by Ana Ruiz)

A review article discussing that PK and PD relationship should be integrated into the management of anti-hepatitis C virus (HCV) treatment.

Davies M, Jones RDO, Grime K, et al. Improving the accuracy of predicted human pharmacokinetics: lessons learned from the AstraZeneca drug pipeline over two decades. Trends Pharmacological Sci, Available online 28 April 2020. https://doi.org/10.1016/j.tips.2020.03.004 (suggested by Peter Bonate)

Scientists at AstraZeneca compared the human pharmacokinetic predictions of 116 compounds using its 5-dimensional framework launched in 2011, which was based on a series of papers published starting in that year by PhRMA on best practices in human pharmacokinetic prediction. A total of 83% of candidates reached the clinic with no pharmacokinetic issues and 71% of exposure predictions (64% for AUC, 78% for Cmax, and 70% for half-life) were within a 2-fold error margin.

Desnoyer A, Broutin S, Delahousse J, et al. Pharmacokinetic/pharmacodynamic relationship of therapeutic monoclonal antibodies used in oncology: Part 2, immune checkpoint inhibitor antibodies [published online ahead of print, 2020 Feb 6]. *Eur J Cancer*. 2020;S0959-8049(20)30005-8. doi:10.1016/j.ejca.2020.01.003 (suggested by Ana Ruiz)

This review summarizes the PK characteristics of immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 agents) and the exposure-response relation reported for both efficacy and toxicity endpoints and explores possible interactions with PD considerations

Pappalardo F, Russo G, Pennisi M, et al. The Potential of Computational Modeling to Predict Disease Course and Treatment Response in Patients with Relapsing Multiple Sclerosis. *Cells*. 2020;9(3):586 (suggested by Ana Ruiz)

The choice of disease-modifying drugs (DMDs) approved for the treatment of relapsing multiple sclerosis (MS) mostly relies on the judgment and experience of neurologists and the evaluation of the therapeutic response can only be obtained by monitoring the clinical and magnetic resonance imaging (MRI) status during follow up.

A computational modeling infrastructure named Universal Immune System Simulator (UISS), has been developed. This modeling infrastructure could simulate the main features and dynamics of the immune system activities. Simulations based on the health history and demographic characteristics of patients can be performed and match clinical and MRI patient records having the potential to run the time course of the disease, relapse and response with the different available therapies.

Application of Agent-Based Modeling to COVID-19 Predictions

By Mary Choules

Agent-based modeling (ABM), first developed in the 1940's, is style of predictive modeling that has become a common tool for social and epidemiology sciences. ABM takes a mechanistic approach to computational modeling; however, in lieu of ordinary differential equations, ABM uses autonomous "agents." Each agent class is assigned rules by which their behavior is governed. The simulation occurs over a designated period of time and factors affecting the outcome are analyzed. For example, in an infection disease model, factors that are commonly analyzed include: population density, initial infectious burden, and isolation precautions. Other factors such as latency period, infection time, and mortality rate are usually based on literature data. Another benefit of ABM, the simulated populations are easily stratified and randomized by factors such as age, gender, and infection status (susceptible, infectious, and resistant) (Miksch F, *et al.* 2019). An example result of this type of modeling is shown in **Figure 1.**

Since the emergence and discovery of the infectious respiratory disease designated COVID-19, several research groups have released publications utilizing ABM to predict the potential burden of COVID-19 on the world's resources. At the time of writing, four such articles have been published from several collaborating groups spearheaded by Alison P. Galvani, PhD. These publications have contributing members from groups across the United States (US) as well members from Canada, China, and multiple European countries. Demonstrating that this type of research is a global effort, highlighting the importance of open science, information sharing, and collaborative multi-functional projects.

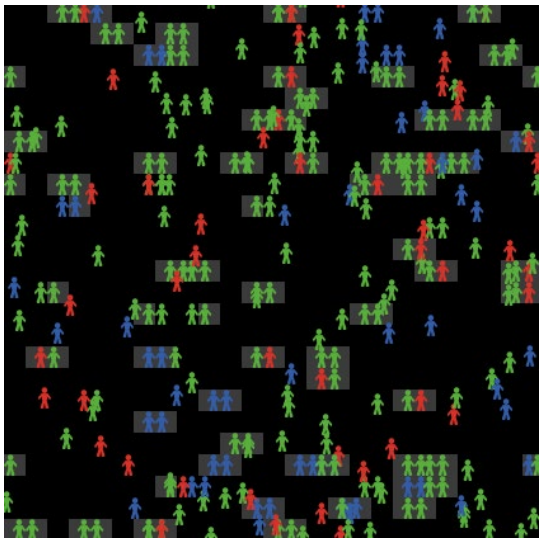


Figure 1. Example output from Netlogo HIV infection model where a population of people are analyzed for HIV status based on average coupling tendency, average commitment, average condom use, and average test frequency. Red (HIV positive), blue (HIV status unknown), green (HIV negative).

Briefly, two of the publications projected the ICU or hospital bed requirements during the potential peak of infection in the US (Moghadas SM, *et al*. 2020) and Canada (Shoukat A, *et al*. 2020). Both papers explored the effect of isolation on healthcare burden during the peak of infection. Moghadas, *et al*. determined that 20% self-isolation would reduce the number of ICU beds required at the peak by 48.4% in the US. In addition, when the basic reproduction number (R_0) is lowered from 2.5 to 2.0, the required number of ICU beds is reduced by 73.5%. Shoukat A, *et al*. reported that with 20% isolation (R_0 = 2.5), the peak of infection would be delayed by 2-4 weeks and ICU bed requirements would be reduced by 23.5% in Canada. When self-isolation was increased to 40%, ICU bed requirements were reduced by 53.6% and the peak of infection was still only delayed by 2-4 weeks. However, both papers reported that despite self-isolation (20% or 40%), demand would still exceed available capacity in both US and Canada, which is an alarming result.

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The remaining two publications, both with the primary author Chad R. Wells, PhD, addressed the effect of travel bands and the demand for ventilators in the US, respectively. The first paper specifically explored the beneficial impact of the control measures implemented by China. They utilized international flight patterns coupled with daily COVID-19 incidence outbreak data within China. The simulations determined that the implemented control measures effectively decreased the daily rate of exportation of COVID-19 by 81.3% on average. The final paper was an expansion on the Moghadas SM, *et al* publication, by simulating ventilator demand within the US during the peak of COVID-19 infection. The simulations predicted that at the peak of infection, 115,001 invasive ventilators and 89,788 non-invasive ventilators would be needed, on average. Based on current availability and normal continued usage, the simulations predicted an additional requirement of at least 45,341 invasive and 77,289 non-invasive ventilators would be required at the peak of infection. Another daunting foreshadowing.

The four publications briefly summarized herein describe the real-world application of ABM to the current COVID-19 crisis. Although, the simulations are somber reflections of the lack of preparedness, they provide valuable insight to the potential havoc this epidemic could wreak on our healthcare systems. Predictions using ABM grant time to prepare additional resources, increase self-isolation efforts, and be more adequately prepared for the worse-case scenario. Although predictions can over or underestimate the observed effect, it is better to be over prepared than underprepared when disaster strikes.

References:

Miksch F, *et al.* PLoS ONE. 2019;14(8):e0221464.

Moghadas SM, *et al*. Proc Natl Acad Sci USA. 2020;117(16):9122-9126.

Shoukat A, *et al.* CMAJ. 2020;cmaj.2000457.

Wells CR, *et al*. Proc Natl Acad Sci USA. 2020;117(13):7504-7509.

Wells CR, *et al*. Lancet Infect Dis. 2020; S1473-3099(20)30315-7.

Did You Know?

Old versions of the newsletter are posted on the ISoP Web site:

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

The ISoP Newsletter Needs Contributors

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

Register Now for ISoP's LinkedIn Group and Stay Up to Date on Everything ISoP

https://www.linkedin.com/groups/4544242/

Springer has released over 500 books to download for free until the end of July for educators, students, and academics.

The link can be found here: https://www.springernature.com/gp/librarians/news-events/all-news-articles/industry-news-initiatives/free-access-to-textbooks-for-institutions-affected-by-coronaviru/17855960

Update from the QSP SIG

By Brian Schmidt and the leadership team

The last month has led to a dramatic shift in all of our lives. Our QSP SIG began the year with goals of driving scientific engagement for our community and fostering more engagement for our QSP scientists, and made good progress. The pandemic rapidly created a number of issues for the QSP scientific community's plans and also more broadly for ISoP. For example, Quantitative Systems Pharmacology Congress 2020 is delayed until 2021, SUNY Buffalo's 2020 QSP Symposium is also delayed until 2021, and QSP Summit 2020 is now delayed until November. Even WCOP, which was in planning for years, has been affected. All of that being said, we are working to adapt our strategy over the next several months. Since our last update, QSP SIG has also been shifting focus to planning virtual events to make the most of the current situation. We will have announcements as these efforts are more mature.

We wanted to use this forum to say that, at the moment, we feel proud of our colleagues and more generally the efforts of our industry for several reasons. First, many are making contributions and driving innovation to bring new vaccines and repurpose medicines to fight the pandemic. Second, many of our colleagues are ensuring the supply of all the other medicines patients need is minimally disrupted and we continue to make progress toward developing new treatments as much as possible. Third, our industry has done well in ensuring many of our colleagues are still employed, working, and productively contributing to manufacture and development of new medicines. Of course, there are other maladies many are still working to combat. For example, the American Cancer Society projected there will be 606,520 deaths from cancer for the US alone in 2020 (ref. 1). COVID-19 has also led to a number of restrictions that have professional and personal implications. Even for modelers that can work fully remotely, there are many challenges with such extended social distancing policies, even if they are needed. We are thankful to all that have continued to contribute to the QSP SIG in spite of personal hardship and challenges, and in some cases sick family and friends.

On a much more positive note, the QSP SIG has played an active role in contributing to the development of programming for ACoP11. For everyone that requested feedback from the QSP SIG leadership team on their programming submissions, we hope we were able to provide good feedback and also, in some cases, connect you with additional community members with similar research interests. We also want to thank the ACoP11 scientific programming committee, led by Craig Comisar, early this year. They have done an excellent job engaging more community experts early in the scientific session review process, which we believe is creating an even higher quality program for ACoP11 and increasing the transparency for many in the Society. Christina Friedrich from the QSP SIG leadership team has invested much effort ensuring we can provide timely feedback on QSP programming. Also: there will again be a SIG student award and invited QSP poster encore presentations at an evening ACoP QSP working group introduction and poster event! Students, please submit your high quality QSP research to ACoP by the deadline, May 15, to be eligible for the QSP SIG Student Award! Everyone that submits a QSP-related poster abstract will be considered for an invitation for a highly visible encore presentation to engage with the QSP SIG working groups at the evening event! Of course, the higher quality of the work and the closer the focus is to a working group's focus areas, the better the chance your presentation will be invited.

We also would like to acknowledge the continued efforts of our working groups and their chairs. Of note, the working group focused on uncertainty, variability, and error in QSP models held their kickoff meeting recently. There was a diverse gathering of academicians, QSP scientists, and other pharmaco-metricians that joined the inaugural meeting. We look forward to exciting developments from this group, currently chaired by Joshua Apgar of Applied BioMath and Michael Weis of Rosa & Co.

1.) Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2020. CA. Cancer J. Clin. 70, 7–30 (2020).

Updates from the MCS SIG

By Gilbert Koch

After having two excellent speakers in the past MCS luncheons at ACoP, we are currently finalizing our plans with another excellent speaker for our third luncheon at ACoP11. An announcement of the next luncheon speaker will be made in June 2020. We are promoting a tutorial that will take place at the 2020 ACoP, titled "Model Analysis Boot Camp for Pharmacometricians". This tutorial is organized by Helen Moore and Craig Thalhauser, and will focus on sensitivity and identifiability for models that require estimation of parameter values (including models such as QSP and PKPD models).

Additionally, we are discussing topics to form relevant working groups within the MCS SIG. More information about these working groups will be published soon on our website https://sites.google.com/view/mcssig/mcs-sig . Want to get updates about all of these topics and opportunities to participate in MCS SIG activities? We are a very welcoming SIG, and you can join us by using the link at the bottom of this page: https://go-isop.org/special-interest-groups-sigs-and-communities/mathematical-and-computational-sciences-sig/

Update from the Clinical Pharmacometrics Sig

By Nikolas Onufrak

The Clinical Pharmacometrics SIG is pleased to recognize a renewed Memorandum of Understanding between our co-sponsoring organizations, the American College of Clinical Pharmacology and the International Society of Pharmacometrics. As acknowledged by the societies' Presidents Dr. Vikram Arya and Dr. Brenda Cirincione, this strategic partnership provides the foundation to deliver on the SIG's goals of fostering collaboration between clinicians and pharmacometricians and advancing precision medicine.

The SIG is equally pleased to announce the sponsorship of two scientific sessions at the ACCP annual meeting this September, both held on Monday, September 21st. The first, Assessing the Feasibility of Model-Informed Precision Dosing: A Point-Counterpoint Debate (10:00 – 11:30 AM), features perspectives from multiple stakeholders on the opportunities as well as the challenges of achieving MIPD. The second, Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice (3:30 – 5:30 PM), will provide evidence and approaches for the dose-individualization of this therapeutic modality, with a focus on antipsychotics. Consistent with the aforementioned societal partnership, we hope you can join us for these sessions in Bethesda this fall!

Stimulated by last summer's FDA workshop on precision dosing, the SIG is actively contributing to a white paper examining the current status of dose individualization within drug labels, areas where precision dosing is clinically championed, and the path towards a more tailored and informative drug label. Further, the SIG is currently in the planning stages for a series of webinars aimed at demonstrating cross-functional use of pharmacometric approaches to ensure drug safety.

Finally, with ACoP11 abstracts due May 15th, the SIG would like to remind the student and postdoc community of our annual Clinical Pharmacometrics Abstract Award. Any abstract consistent with the SIG's mission will be considered for official recognition, with the winner receiving a commemorative plaque and the opportunity to showcase their work at the annual Meet-the-SIG Luncheon in the form of a short podium presentation.

EMA Issues Regulatory Roadmap 2025

By Peter Bonate

The EMA has issued a plan to advance regulatory science over the next 5 to 10 years for human and veterinary medicine. Their EMA Regulatory Science 2025: Strategic Reflection can be found at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.

Within the human medicine section, the document consist of 6 overarching goals: catalyzing the integration of science and technology in medicines' development, driving collaborative evidence generation – improving the scientific quality of evaluations, advancing patient-centered access to medicines in partnership with healthcare systems, addressing emerging health threats and availability/therapeutic challenges, and enabling and leveraging research and innovation in regulatory science.

The role of modeling and simulation figures prominently throughout the document and one of the subgoals is to optimize their capability for modeling, simulation, and extrapolation. Expect in the years ahead guidance's related PKPD requirements and use of artificial intelligence in modeling and simulation.

WCoP Update

Due to the coronavirus pandemic, the WCoP committee took the difficult decision of postponing this year's conference. The new dates for WCoP 2021 in Cape Town will be Sunday Feb 7th to Wednesday Feb 10th. Thanks to those who registered and planned to attend WCoP 2020 for bearing with us, and we hope that even more of you can join us in Cape Town next year!

Visit our website at https://wcop2020.org/ (yes, we need to change our URL ☺) for more information.

Updates from the ISoP Student Community

By Ashwin Karanam

The ISoP student community seeks to foster the interest in pharmacometrics by promoting communication among trainees from various disciplines aiming for efficient drug development and rational drug treatment in patients. The focus of this community is to create a dynamic platform for educational and scientific events that allows trainees to exchange and broaden their knowledge in this field. Furthermore, peers from all over the world have the opportunity to interact and support each other's personal and professional development. Our mission is to give trainees the opportunity to voice and lead the future of pharmacometrics with ISoP.

The new student leadership team consists of Ashwin Karanam (University of Minnesota) serving as the chair, Brian Cicali (University of Florida) serving as the Chair-Elect and Patrick Hanafin (University of North Carolina, Chapel Hill) serving as the Secretary. We also have Yi Ting (Kayla) Lien (University of Florida) in the advisory role of Past-Chair. Additionally, Dr. Vijay Ivaturi is assuming the role of ISoP Board Liaison for the Student Community. The ISoP Student community would like to thank the past Board Liaison, Dr. Mirjam Trame and all the past Student Leadership Team members who have helped our community grow and flourish.

L-R(top): Ashwin Karanam, Chair; Brian Cicali, Chair-Elect; (bottom) Patrick Hanafin, Secretary; Yi Ting (Kayla) Lien, Past-Chair.

How to get involved with the committee

The Student Community is composed of trainee members from academic institutes across the globe. Whoever is interested is strongly encouraged to join by becoming a member of ISoP and applying to be a committee representative. To find out more, feel free to contact the leadership team (please email karan040@umn.edu) or the respective representative from your University/country/region on the steering committee. You can find details about our community here. We highly encourage you to check out our website created and maintained by the student community. We also have an ISoP Student-specific Category for student discussion can be found on the discuss.go-isop.org forum. We highly encourage trainees to visit and post any discussion topics.

(continued on page 22)

Don't Forget to Visit ISoP's Career Center!

https://go-isop.careerwebsite.com/

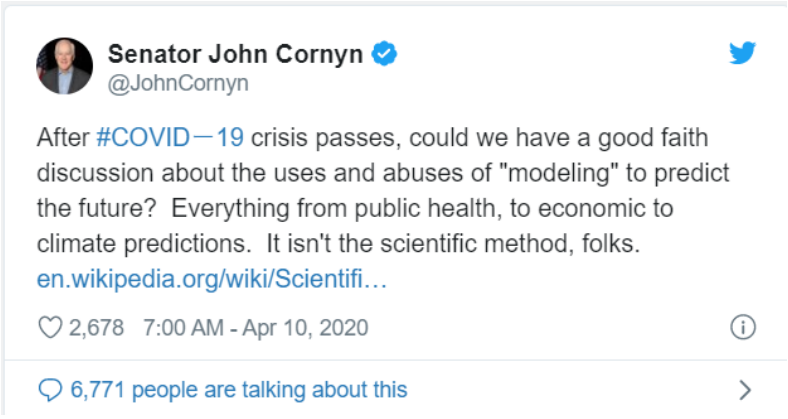
No, Senator, Science Can't Do Away with Models

Here's why Senator John Cornyn's critique of modeling is misguided

By Scott K Johnson

The following article was originally published by ARS Technica (https://arstechnica.com/science/2020/04/no-senator-science-cant-do-away-with-models/).

On Friday, Texas Senator John Cornyn took to Twitter with some advice for scientists: models aren't part of the scientific method. Scientists have responded with a mix of bafflement and exasperation. And Cornyn's misconception is common enough—and important enough—that it's worth exploring.



Cornyn's beef with models echoes a talking point often brought up by people who want to reject inconvenient conclusions of systems sciences. In reality, "you can make a model say anything you want" is about as potent an argument as "all swans are white." The latter is either a disingenuous argument, or you have an embarrassingly limited familiarity with swans.

Models aren't perfect. They can generate inaccurate predictions. They can generate highly uncertain predictions when the science is uncertain. And some models can be genuinely bad, producing useless and poorly supported predictions. But the idea that models aren't central to science is deeply and profoundly wrong. It's true that the criticism is usually centered on mathematical simulations, but these are just one type of model on a spectrum—and there is no science without models.

What's a model to do?

There's something fundamental to scientific thinking—and indeed most of the things we navigate in daily life: the conceptual model. This is the image that exists in your head of how a thing works.

Whether studying a bacterium or microwaving a burrito, you refer to your conceptual model to get what you're looking for. Conceptual models can be extremely simplistic (turn key, engine starts) or extremely detailed (working knowledge of every component in your car's ignition system), but they're useful either way.

As science is a knowledge—seeking endeavor, it revolves around building ever-better conceptual models. While the interplay between model and data can take many forms, most of us learn a sort of laboratory-focused scientific method that consists of hypothesis, experiment, data, and revised hypothesis.

In a now-famous lecture, quantum physicist Richard Feynman similarly described to his students the process of discovering a new law of physics: "First, we guess it. Then we compute the consequences of the guess to see what… it would imply. And then we compare those computation results to nature… If it disagrees with experiment, it's wrong. In that simple statement is the key to science."

In order to "compute the consequences of the guess," one needs a model. For some phenomena, a good conceptual model will suffice. For example, one of the bedrock principles taught to young geologists is T.C. Chamberlin's "method of multiple working hypotheses." He advised all geologists in the field to keep more than one hypothesis—built out into full conceptual models—in mind when walking around making observations.

That way, instead of simply tallying up all the observations that are consistent with your favored hypothesis, the data can more objectively highlight the one that is closer to reality. The more detailed your conceptual model, the easier it is for an observation to show that it is incorrect. If you know where you expect a certain rock layer to appear and it's not there, there's a problem with your hypothesis.

There is math involved

But at some point, the system being studied becomes too complex for a human to "compute the consequences" in their own head. Enter the mathematical model. This can be as simple as a single equation solved in a spreadsheet or as complex as a multi-layered global simulation requiring supercomputer time to run.

And this is where the modeler's adage, coined by George E.P. Box, comes in: "All models are wrong, but some are useful." Any mathematical model is necessarily a simplification of reality and is thus unlikely to be complete and perfect in every possible way. But perfection is not its job. Its job is to be more useful than no model.

Consider an example from a science that generates few partisan arguments: hydrogeology. Imagine that a leak has been discovered in a storage tank below a gas station. The water table is close enough to the surface here that gasoline has contamin-

ated the groundwater. That contamination needs to be mapped out to see how far it has traveled and (ideally) to facilitate a cleanup.

If money and effort was no object, you could drill a thousand monitoring wells in a grid to find out where it went. Obviously, no one does this. Instead, you could drill three wells close to the tank, determining the characteristics of the soil or bedrock, the direction of groundwater flow, and the concentration of contaminants near the source. That information can be plugged into a groundwater model simple enough to run on your laptop, simulating likely flow rates, chemical reactions, and microbial activity breaking down the contaminants and so on, spitting out the probable location and extent of contamination. That's simply too much math to do all in your head, but we can quantify the relevant physics and chemistry and let the computer do the heavy lifting.

A truly perfect model prediction would more or less require knowing the position of every sand grain and every rock fracture beneath the station. But a simplified model can generate a helpful hypothesis that can easily be tested with just a few more monitoring wells—certainly more effective than drilling on a hunch.

Don't shoot the modeler

Of course, Senator Cornyn probably didn't have groundwater models in mind. The tweet was prompted by work with epidemiological models projecting the effects of COVID-19 in the United States. Recent modeling incorporating the social distancing, testing, and treatment measures so far employed is projecting fewer deaths than earlier projections did. Instead of welcoming this sign of progress, some have inexplicably attacked the models, claiming these downward revisions show earlier warnings exaggerated the threat and led to excessive economic impacts.

There is a blindingly obvious fact being ignored in that argument: earlier projections showed what would happen if we didn't adopt a strong response (as well as other scenarios), while new projections show where our current path sends us. The downward revision doesn't mean the models were bad; it means we did something.

Often, the societal value of scientific "what if?" models is that we might want to change the "if." If you calculate how soon your bank account will hit zero if you buy a new pair of pants every day, it might lead to a change in your overly ambitious wardrobe procurement plan. That's why you crunched the numbers in the first place.

Yet complaints about "exaggerating models" are sadly predictable. All that fuss about a hole in the ozone layer, and it turns out it stopped growing! (Because we banned production of the pollutants responsible.) Acid rain was supposed to be some catastrophe, but I haven't heard about it in years! (Because we required pollution controls on sulfur-emitting smokestacks.) The worst-case climate change scenario used to be over 4°C warming by 2100, and now they're projecting closer to 3°C! (Because we've taken halting steps to reduce emissions.)

These complaints seem to view models as crystal balls or psychic visions of a future event. But they're not. Models just take a scenario or hypothesis you're interested in and "compute the consequences of the guess." The result can be used to further the scientific understanding of how things work or to inform important decisions.

What, after all, is the alternative? Could science spurn models in favor of some other method? Imagine what would happen if NASA eyeballed Mars in a telescope, pointed the rocket, pushed the launch button, and hoped for the best. Or perhaps humanity could base its response to climate change on someone who waves their hands at the atmosphere and says, "I don't know, 600 parts per million of carbon dioxide doesn't sound like much."

Obviously these aren't alternatives that any reasonable individual should be seriously considering.

The spread of COVID-19 is an incredibly complex process and difficult to predict. It depends on some things that are well studied (like how pathogens can spread between people), some that are partly understood (like the characteristics of the SARS-CoV-2 virus and its lethality), and some that are unknowable (like the precise movements and actions of every single American). And it has to be simulated at fairly fine scale around the country if we want to understand the ability of hospitals to meet the local demand for care.

Without computer models, we'd be reduced to back-of-the-envelope spit-balling—and even that would require conceptual and mathematical models for individual variables. The reality is that big science requires big models. Those who pretend otherwise aren't defending some "pure" scientific method. They just don't understand science.

We can't strip science of models any more than we can strip it of knowledge.

ISoP would like to thank Scott K. Johnson and ARS Technica for allowing us to reprint this article.

How Would You Define Pharmacometrics?

The Influence Working Group is looking to update the ISoP web page and make it more user friendly for people wanting to learn more about pharmacometrics and what pharmacometricians do. We realized that no where on the website is pharmacometrics defined. This caused the Working Group to define pharmacometrics and in the process realized just how hard this is to do today. The old definitions just do not apply today.

The Working Group is seeking your input. How would you define pharmacometrics? Go to

https://www.surveymonkey.com/r/NN2QYJ7

and give us your definition of pharmacometrics. Yours could be the one we use on the website.

A Staggering Case of Editorial Misconduct

By Peter Bonate

Recently an article appeared in the Journal of Theoretical Biology (JTB) that blew my mind and I thought I would share it with you. The editorial appeared 7 March 2020 (https://www.sciencedirect.com/science/article/pii/S0022519320300278?via%3Dihub). The original story starts with Jonathan Wren, a researcher from the Oklahoma Medical Research Foundation. His story can be found here: https://academic.oup.com/bioinformatics/article/35/18/3217/5304360. Wren submitted a paper to the journal Bioinformatics. When he got the reviews back, one of the reviewers requested that some references be added. This is not uncommon. What makes it uncommon is that 35 references were requested, 90% of which were from the reviewer, and the remainder of which were from reviews that heavily cited the reviewer. This request artificially inflates the reviewer's h-index and other citation benefits. As a result, the reviewer was banned from future reviews and Bioinformatics underwent a systematic examination of their review policies to make sure this does not happen again.

The story takes a twist when JTB announced in March, after becoming aware of the issue at Bioinformatics, they discovered that the same individual banned from Bioinformatics was also a reviewer and handling editor for their journal. They undertook an audit of the work done by this individual and found the following:

1.) In the role of editor, they handled papers from their own institution. After further review, it was found that on some papers the identity or existence of the submitting authors could not be confirmed.

2.) In the role of editor, they assigned papers to reviewers whose existence could not be confirmed and, in some cases, were the editor acting as a reviewer under a pseudonym.

3.) The reviews had a pattern of comments. Titles were frequently requested to be changed to include reference to methods the editor invented; the introduction and discussion sections were requested to include methods the editor invented; requests were made for references to papers published by the editor; and in some cases, the handling editor was the co-author on the publication.

As a result of their audit, the editorial board immediately removed the handling editor and all complicit reviewers from the reviewer database.

While horrifying this does not appear to be an isolated incident. Wren has developed an algorithm to detect such fraud and claims there is another case that is even more egregious than the one here, but that has not been reported yet.

I applaud the co-chief editors of JTB for their openness and honesty. Without this notice to the readers, this type of dishonesty would continue unabated. As editor-in-chief of the Journal of Pharmacokinetics and Pharmaco-dynamics, I was especially interested in how this might affect JPKPD. I passed along these articles to the Associate Editors, who were as shocked as I was when I first read them. I can say that we are aware of no such incidents at our journal, perhaps because we are a smaller journal in terms of yearly published papers and that we are a relatively tight knit group of Associate Editors and reviewers.

This idea of reviewer-coerced citations is not new (Thombes et al. reviewed this previously in the Journal of Journal of Psychosomatic Research 78; 1-6; 2015) but to what level it exists in other journals is not clear. What surprises me about this case is that when the reviewer suggested including many new references is that the authors did not complain to the editor(s). I think had they done so this dishonesty might have been caught earlier. Nevertheless, cases like this damage the reputation of scientists and scientific journals everywhere. Hopefully by making everyone aware of the issue is the first step to guarding against it in the future.

R Hints

Suppose you have a dataframe Z and you want to test whether column X is contained within Z. exists() is a general R function that tests whether a variable exists or not; it returns a Boolean, TRUE or FALSE. You would think exists("Z$X") would work. In this case, you would be wrong.

Let's create a dataframe Z with a variable X that has 1 row with a value of 5:

```
〉 Z <- data.frame(X=5)
〉 Z
  X
[1] 5
〉 exists("Z")
[1] TRUE            # so far so good
〉 exists("Z$X")
[1] FALSE           # wrong!
```

Clearly there is a dataframe Z that has a variable X in it. But the exists() function says FALSE. What gives?

For this to work you must include recode this using the where option.

```
〉 exists("X", where = Z )
[1] TRUE
```

Now it works!!

As an alternative, you could use:

```
〉 "X" %in% colnames(Z)
[1] TRUE
```

This will give you the same result, but this only works for dataframes. The exist() trick with the where option also works for lists.

A Primer on Understanding Software Licensing

By Devin Pastoor

Licensing is a pervasive component in any ecosystem. The rapid adoption of free and open source software to build tools and perform analyses has brought with it the challenge of navigating a maze of licensing considerations. Freely available code without an explicitly declared license is, by default, copyrighted by the author. As such, you can't just publicly upload a bunch of source code without a license and walk away, hoping others will start using it. Similarly, when creating software, it is important to understand the limitations or conditions associated with using other code or libraries you find. This article is a primer to major licensing considerations present with software you may encounter in the pharmacometrics discipline.

Generally, a license will fall under one of a couple primary categories: proprietary/commercial, copyleft, permissive, and public domain (see Table 1).

Proprietary software is owned and controlled by the creator. Software such as MATLAB, SAS, NONMEM, and Monolix fall into this category. Such software is often, but not exclusively, closed source. As mentioned above, just because a software's code is available to see does not make it open to use without restriction. Copyleft, permissive, and public domain licenses provide options so the creator can make their creation open and available for others to use and extend, while also providing some measure of control (or not). On one end, public domain licenses essentially provide no rules or guidance beyond including attribution. On the other end, copyleft licenses help enforce a philosophy that open source software must stay open. In particular, if your intent is to make and distribute changes or software built on top (derivative works) to others, copyleft licenses prevent keeping the source code closed (private). It is important to note - the act of distribution is a key trigger to the necessity to make the source open. Per the GNU site: "The GPL does not require you to release your modified version, or any part of it. You are free to make modifications and use them privately, without ever releasing them.

This applies to organizations (including companies), too; an organization can make a modified version and use it internally without ever releasing it outside the organization. But if you release the modified version to the public in some way, the GPL requires you to make the modified source code available to the program's users, under the GPL." In the middle are permissive licenses, which focus more on providing software for anyone to use with minimal restrictions yet providing some legal language around certain well-trodden points of legal discussion. A high-level summary of the most well-established FOSS licenses are is shown in Table 2.

One of the most important take-aways is that people have built successful, well adopted languages, products, and tools under all of these licensing options. That said, the degree of difference between permissive vs copyleft is clearly visible around the restrictions for use, especially if the objective is to develop closed-source commercial software. In particular, differences between copyleft licenses leave much to interpretation. When considering the infectious nature of GPL licenses, it is unclear with dynamic languages (such as R/Python/Julia) how licenses of dependencies propagate. For example, if you are developing an R package, and decide to use an R package that is GPL licensed, is your package intrinsically GPL licensed or can you license your code base under any license? This may seem clear cut due to the infectious nature of the GPL being copyleft, that if you include a GPL licensed dependency, according to the letter of the licensing terms, your code must follow GPL and the source made available if you want to distribute it to others. Yet, many people argue that given dependencies are not embedded in your code, rather the user installs them independently, it would not trigger the infectious propagation of GPL. This rabbit hole goes deeper when you consider beyond even packages, R (and the Linux operating system) itself is GPL licensed. Unfortunately, there is no canonical answer.

Table 1

	Proprietary	Copyleft	Permissive	Public Domain
What can user do?	Controlled by creator	User controlled, with certain rules	May have some restrictions	No restrictions
Clause?	Controlled by creator	Derivative work must provide attribution, and licensed under CopyLeft license	Derivative work must provide attribution	Derivative work must provide attribution
Source Code	Controlled by creator	Must be made available	Does not have to be open	No rules
Re-Licensing	Controlled by creator	Derivative work cannot be proprietary.	Derivative work can be released under other license(s), including proprietarily	Derivative work can be released under other license(s), including proprietarily
Commercial Restrictions	Controlled by creator	Allowed	Allowed	Allowed

Table 2						
License Name	MIT	Apache	BSD	LGPL2/3	GPL2/3	AGPL2/3
Type	Permissive	Permissive	Permissive	Copyleft	Copyleft	Copyleft
Copyright protection	✓	✓	✓	✓	✓	✓
Can be used in propriety projects	✓	✓	✓	✓	✓	✓
Explicit Patent License	✗	✓	✗	✗	✗	✗
Source code can remain closed, when distributed to others	✓	✓	✓	✗	✗	✗ even on servers/ web without distribution
Examples	julia, dplyr, node.js	docker, spark, arrow, kubernetes	Stan, python	xpose, future	R, nlmixr, shiny, ggplot2, mrgsolve, redhat linux	Rstudio server, pknca

Though some suggest trying to avoid packages under copyleft licenses to bypass the need to take a stance, by looking at the top 5 license types specified by Package on CRAN (R's central package management repository), we can see over 90% of packages are GPL-derivatives (Table 3).

While on this tour of licensing options, an additional licensing structure to be aware of are dual/multiple licenses, where the software is made available under different licensing structures given certain conditions, as set by the creators. In many cases this is used to support the overarching funding objectives of the project and provide some security around IP protection. Take RStudio - which provides a robust open source version licensed under AGPL-3, while also including a commercial professional version with additional functionality, especially tailored towards large businesses and power users. The biggest risk as a consumer, of using software with a dual license is weighing the risk given you must abide by the more restrictive (often non-commercial) licensing option. Licenses with heavy restrictions outside of the commercial option run the risk that given the overall project velocity slows down or goes in an alternate direction, there is no way for the community to step in to make major contributions or influence the direction of the project without the blessing of the creators.

As a developer, if considering such a dual strategy, there are also some more creative licensing strategies being explored in the general technology community, such as licenses where the code starts with a particular (often more restrictive) license, however after a period of time - such as one year to 18 months from any release - converts to a general open source license such as BSD, GPL or MIT. This gives some nice safety the project longevity, as if it is ever abandoned by the driving company/individuals the overall community will ultimately have freedom to continue on with the project if they so choose.

To learn more about how you may choose a license for your projects, two useful links are:

https://opensource.guide/legal/

https://choosealicense.com/

As a parting thought, as a scientific community, in the same spirit as open science - scientific software should strive to be free and open. As a developer, if the goal is to commercialize a product that must be clear and a license chosen appropriately to protect your IP. However this should be weighed carefully against the possibility that choice will dramatically reduce the opportunity for community engagement and growth in favor of finding paying customers with no interest in contributing and growing the science. There are numerous success stories around building sustainable products and tools that also promote open science and collaboration. For those looking to develop, don't get too hung up on licenses, just get out and build!

Table 3

License	Type	Number of Packages
GPL (>= 2)	Copyleft	4164
GPL-3	Copyleft	3185
GPL-2	Copyleft	2510
MIT + file LICENSE	Permissive	2095
GPL (>= 3)	Copyleft	754

Announcing the New MBMA Sub-SIG (part of SxP SIG)!!

The new MBMA Sub-SIG has now been officially established within the SxP SIG. Its mission is to promote Model-Based Meta-Analysis and its application in drug development, to raise awareness and interest, and to support the development of new talent.

The MBMA Sub-SIG is in the process of developing a roadmap with five key workstreams. We are looking for volunteers to help lead the development of this Sub-SIG and to help promote awareness of this important topic. The main objectives of the MBMA Sub-SIG are:

- Create and maintain a forum for communication and collaboration between scientists interested in MBMA
    - Facilitate interactions between subject matter experts
    - Interact with software developers to create "fit-for-purpose" application/toolboxes
- Promote research and train practitioners
    - Develop courses to educate the Pharmacometrics and Statistics communities and raise awareness in Academia
    - Explore novel methodological research tools and applications (e.g., combining Individual Patient Data and Aggregate-level data, MBMA of survival data, etc.…)
    - Develop and publish a document for best practices in MBMA
- Increase awareness and promote MBMA to increase its utility and impact in drug development
    - Build bridges with pharmacometricians, statisticians, epidemiologists, clinicians, HEOR, Market Access, etc.
    - Interactions with regulatory agencies and academics

The current vision of the MBMA Sub-SIG roadmap consists of five key workstreams.

1. Software: Maintaining current documentation of available MBMA-related tools and developing specialized tools to streamline MBMA analyses.
2. Methodologies: Documenting wide range of MBMA methodologies in published literature and presentations, and preparation of a best practices document to guide future analysts.
3. Education: Develop, maintain, and promote training materials to educate pharmacometricians, statisticians, and senior leaders about MBMA methodologies and applications.
4. Awareness: Promoting the benefits of MBMA within and beyond Pharmacometricians and Statisticians by engaging in industry outreach and organizing regular discussions on MBMA-related topics.
5. Website: Developing and maintaining a website to facilitate the objectives of the MBMA Sub-SIG.

We are looking for individuals who would be interested in contributing to these workstreams or could even propose additional workstream topics.

Please join us if you are interested in contributing or learning more about MBMA! Just send us an email at: MBMAsig@gmail.com.

Co-Chairs:
Marion Bouillon-Pichault, Senior Principal Scientist, Quantitative Clinical Pharmacology, Bristol-Myers Squibb

Matt Zierhut, Scientific Director, Statistics & Decision Sciences, Janssen Pharmaceuticals

CPT:PSP News

By France Mentre, EIC

NEW AE:

CPT: Pharmacometrics & Systems Pharmacology (PSP) is pleased to welcome a new Associate Editor. Dr. Stefanie Hennig joined the *PSP* team in April. Stefanie is a consultant in PK and PK/PD modelling and simulation in various phases of drug development in a variety of population groups for Certara Strategic Consulting.

Stefanie obtained her Pharmacy and Master of Science degree in Germany and a PhD from the University of Queensland. She worked as a postdoc and researcher at Uppsala University in Sweden. Before joining Certara, she held a tenured academic position at the University of Queensland and was a senior fellow of the Humboldt Foundation, Germany. She holds honorary positions as visiting researcher with the Freie Universitaet Berlin, Germany and the Queensland University of Technology, Australia.

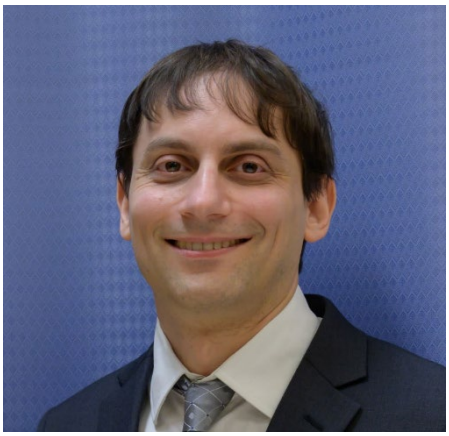
Stefanie is very active within the Pharmacometrics community worldwide, as the secretary of the Population Approach Group of Australia and New Zealand (PAGANZ), a member of the executive committee organizing the World Conference of Pharmacometrics (WCoP), and the Chair of the local organizing committee for WCoP2016. She has supported the Australian regulatory Therapeutic Goods Administration agency since 2014 as an advisor on the Pharmaceutical Subcommittee.

Her main research interests are around optimizing dosing in children and dose individualization using Bayesian forecasting. Her main therapeutic areas of interest are cystic fibrosis, anti-infective, respiratory, oncology, TB, and HIV.

The *PSP* team looks forward to availing itself of Stefanie's range of experience and expertise!

PSP AWARD:

Although the ASCPT Annual Meeting in March was cancelled, *PSP* still wishes to announce the winner of the 2020 *PSP* Award: Dr. Andrew Stein and co-authors for their paper "Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells." In this article, Dr. Stein and colleagues developed a model for the kinetics of tisagenlecleucel and the impact of therapies for treating cytokine release syndrome (tocilizumab and corticosteroids) on expansion. Data from two phase II studies in pediatric and young adult relapsed/refractory B cell acute lymphoblastic leukemia were pooled to evaluate this model and evaluate extrinsic and intrinsic factors that may impact the extent of tisagenlecleucel expansion. This work represents the first mixed-effect model-based analysis of CAR-T cell therapy. We thank Dr. Stein and his co-authors for their valuable contribution to the field.



News from the Journal of PK & PD

By Peter Bonate, EIC

The Journal of Pharmacokinetics and Pharmacodynamics has recently announced changes to its Aims and Scope. The new Aims and Scope are:

Broadly speaking, JPKPD covers the area of pharmacometrics. The journal is devoted to illustrating the importance of pharmacokinetics, pharmacodynamics, and pharmacometrics in drug development, clinical care, and the understanding of drug action. The journal publishes on a variety of topics related to pharmacometrics, including, but not limited to, clinical, experimental, and theoretical papers examining the kinetics of drug disposition and effects of drug action in humans, animals, in vitro, or in silico; modeling and simulation methodology, including optimal design; precision medicine; systems pharmacology; and mathematical pharmacology (including computational biology, bioengineering, and biophysics related to pharmacology, pharmacokinetics, or pharmaco-dynamics). Clinical papers that include population pharmacokinetic-pharmaco-dynamic relationships are welcome. The journal actively invites and promotes up-and-coming areas of pharmacometric research, such as real-world evidence, quality of life analyses, and artificial intelligence (AI). JPKPD is an official journal of the International Society of Pharmacometrics.

With these changes we hope to more reflect the current state of activities in pharmacometrics, and to bring to light new and exciting research areas, like machine learning and real-world evidence.

For other news, look for a themed issue related to the Role of Pharmacometrics in Pregnancy. Invited papers will include reviews on physiologic changes during pregnancy, AI as a research tool, PBPK during pregnancy, population-methods, and challenges in conducing trials during pregnancy.

ISoP QSP SIG I-O Working Group Webinar Series

Pharmacometrics and Systems Pharmacology Approaches towards Preclinical and Clinical Development of CAR-T Cell Therapies

Dr. Aman P. Singh, MS, PhD, Senior Scientist Janssen Biotherapeutics, Spring House, PA, USA

May 26th, 2020 12:00 – 1:00 PM Eastern Time (US and Canada)

The Quantitative Systems Pharmacology (QSP) Special Interest Group within ISoP would like to invite you to the Immuno-Oncology (I-O) Working Group Webinar Series!

Register in advance for this webinar (open to nonmembers) here (Webinar link)

Abstract: Chimeric Antigen Receptors (CAR) T-cells have revolutionized the current cancer treatment. With the initial FDA approval Kymriah® and Yescarta®, the current landscape for CAR-T cells is burgeoning, with >90 candidates in the clinical development. The initial efforts were limited to hematological malignancies, but the field is quickly transitioning towards treatment of solid tumors. Although promising, the basic concepts of starting dose, PK and PD of these agents are distinct from conventional small/large molecules, and PK-PD relationships are not completely understood. At the preclinical setting, it is imperative to understand and quantitatively characterize the impact of CAR-specific (e.g. affinity, CAR density) and system-specific parameters (tumor burden) influencing the efficacy and in vivo expansion of CAR-T cells. It is also paramount to utilize translational systems PK-PD modeling approaches towards identifying the factors and different immune-subtypes, which influence the unique multiphasic PK profile in the clinic, which is often characterized by rapid distribution, expansion, contraction and persistence phases. Within the clinical setting, a model-based metanalysis of CAR-T kinetics is required to understand how different phases of cellular PK gets influenced across different CAR-constructs, disease targets, antigen expression and patient population.

Learning objectives: 1) To understand unique features, current challenges, and recent development in clinical pharmacology and pharmacometrics of cell-based therapies, 2) To mechanistically comprehend the unique CAR-T cell PK profile, comprising of rapid distribution, expansion, contraction and persistence phases and identify the drug- and system specific parameters influencing this multiphasic kinetic behavior in clinic, 3) To identify potential covariates influencing PK and PD behavior of cell-based therapies within the clinic, using model-based meta-analysis.

Speaker: Aman received his Master's in Pharmacometrics from Department of Pharmaceutical Sciences, University at Buffalo in 2012 working on translational PK-PD models for monoclonal antibodies. He joined Dr. Dhaval Shah's lab in 2013 working on different aspects of Antibody-Drug Conjugates (ADCs). He is currently working in the Biologics Development Sciences Department of Janssen Biotherapeutics, focusing on different antibody platforms in oncology and immuno-oncology such as CD3-bispecifics, Antibody drug conjugates, Radioimmunotherapy and CAR-Ts.

Visit ISoP QSP SIG Online!… and on LinkedIn!

Let's Stick with QSP

In a recent commentary, entitled "Let's Get Rid of the Q in QSP," Pete Bonate advocates for dropping a "Q" from the name of the special interest group (SIG) focused on quantitative systems pharmacology (QSP).

We think that the "Q" should stay. First, because the rationale for the current name is clear, and second because changing the name could generate confusion about the group's main mission.

The commentary argues that the term quantitative is superfluous because other fields, like systems biology, are quantitative, but do not use "quantitative" as they describe themselves. However, systems biology approaches have been developed that, while having a quantitative foundation, do not seek to provide a strictly quantitative understanding of disease or physiology. Some systems biology approaches have therefore been deemed "qualitative" by many scientists. For example, systems biology methods rooted in graph theory rely on knowledge of network topology and have been used to integrate molecular datasets to give additional qualitative insights from the data. Strategies such as reporter metabolites and network propagation are two examples of such "qualitative" systems biology approaches. Additional methods employed by systems biologists, such as Petri nets and logic-based network models, can yield general insights into network behavior without quantitative prediction of measurable physiologic endpoints.

The original commentary author refers to the 2011 white paper, "Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms." Although written nearly ten years ago, the white paper integrates a variety of still relevant sources when developing a broad definition for quantitative and systems pharmacology. The description that previous members and leaders of the QSP SIG have generally referenced as being most closely related to quantitative systems pharmacology is the one "rooted in engineering and pharmacological principles" that focuses on "the quantitative analysis of the dynamic interactions between drug(s) and a biological system… [that] aims to understand the behavior of the system as a whole, as opposed to the behavior of its individual constituents." That is, QSP models mechanistically describe physiological and pathophysiological processes and predict how to modify disease, or biomarker, trajectories through a pharmacological intervention, while providing time-varying, quantitative physiologic readouts. Predictions from QSP models often can be directly compared not just to subsystem-focused horizontal data sets, but to additional vertically integrated clinical datasets such as concentrations of molecular mediators, densities of cells, and other clinical endpoints reflective of health and disease. QSP models generally accomplish a substantial degree of vertical integration in addition to horizontal integration. This goal of dynamic and vertical integration is a primary focus for our practice, and contributes to the reasoning behind the importance of the "Q."

In a second argument, the author indicates that, because the white paper is focused on QSP and the original name for the field was "quantitative and systems pharmacology," since it is not feasible to put the "and" back in, we should drop the "quantitative" term all together as well, to avoid having to deal with QSP and "systems pharmacology" as two separate entities. This supposition and aim seem also problematic, at least to us. It is worth noting industry adopted the term "QSP" quickly after the white paper was published, and the formation of "quantitative and systems pharmacology" groups in industry did not outnumber or greatly precede the formation of QSP groups. Adoption of QSP as a name is not a change that has recently arisen simply due to unintentional dropping of an "and." There can be utility for qualitative systems approaches or in expanding strategies to implement additional omics datasets to inform mechanistic QSP model development and calibration. The formation of "quantitative and systems pharmacology" groups may have utility for some R&D organizations. However, due to the precedence and wide adoption of "QSP," we believe that the name shouldn't simply be changed where it is largely consistent with a community's existing primary practice.

In addition, the author references other SIGs in the International Society of Pharmacometrics, and suggests it is an inconsistent practice, and therefore not desirable, to have "quantitative" in the title of one individual SIG, given that the Society's contributions are all intrinsically quantitative. We don't believe it is appropriate to apply this kind of comparison between the names for the SIGs. Our community of QSP practitioners selected the name for the SIG based on the field they wanted the SIG to represent, and one that was fairly clear for the practitioners as to the main focus for the SIG. Indeed, to avoid confusion for current members and additional

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Communication Corner

By Stacey Tannenbaum

Smile, You're on Conference Call Camera!

It's almost Monday, which means there another week of Skype, WebEx, and Zoom meetings to look forward to- YAY. While the novelty of the remote meeting may have worn off (haven't all those early Zoom happy hours moved from blast to blasé?), understanding VC technology and etiquette can make a huge difference to help these meetings be productive, professional, and positive!

First, and most importantly, explore the options/settings of your conferencing app(s). Do this outside of a meeting, so you don't have the pressure of trying to change settings or figure out technology while others are (im)patiently waiting to get started. For each app, you can select and test your audio and video devices and choose the appropriate settings for meeting initiation. Even if you run meetings often, if you are the presenter/host for a meeting, you should dial in early to prepare, and you may want to ask a trusted colleague to also join you, so you can confirm that your mic, speakers, and camera are working properly, and that they can see your screen if you are sharing. Technology can be fickle.

Meeting participants should also get comfortable with the controls of the conferencing app – they should know how to quickly and seamlessly mute/unmute the mic, turn on/off the camera, share/unshare the screen, change their view, and message with other participants. We've all played conference call bingo where people have been speaking with the mute button on (or worse, being unmuted when they should NOT be), or when changing presenters becomes an awkward dance. The host may consider taking the first few minutes of a meeting to walk people through the conferencing app settings, so that everyone gains some comfort with the important features of the tool and can help the meeting to run smoothly. The host should also cover the expectations for participants (staying on mute when not speaking, etc.). Most conferencing apps allow a participant to change how they view the meeting content and other participants – for example, you may choose to see a gallery view of all participants, to spotlight the speaker so their video comes to the forefront, or to show only the shared screen. Unfortunately every conferencing app is different, but get to know the one(s) you use the most and you'll get a lot more out of a meeting when you're not distracted by trying to figure out the settings.

A few other VC tips: if you want to look someone" in the eye", it may feel unnatural, but talk to the camera rather than looking at them on the screen! And remember… people can see the facial expressions you make (I am a world class eye roller), and can also see when you are typing, texting, playing Candy Crush on your phone, doing squats in your office, etc.; if you wouldn't do something during a face to face meeting, don't do it in your home office. Adjust your environment and behavior during VCs accordingly, because screenshots are forever! It should go without saying, too, that if the host and others in the meeting have their camera on, you should too- keeping it off is akin to going to a face to face meeting with a bag over your head!

Stacey on a zoom call with her other personalities

The 3 most important things for video calls are location (of your camera), location (your environment), location (of your light sources)! Your camera should be just about at eye-level, and should point straight at you rather than at an up or down angle. Adjust the distance from your face and upper body so that the camera is situated such that no one can tell you are not wearing pants (!!). Also, most cameras show a wide view of the room- so before you get on that call, check behind you; do you have some clutter or personal objects that should be out of frame or covered? Is there a window or bright lamp behind you that will make you look like a silhouette? Is the screen the only thing lighting your face, which makes you look sallow?

Of course, while it's nice to see faces, VCs are of little value without the audio component! If you are working in an open environment that you are sharing with others in your family, invest in a comfortable headset or earbuds with a mic. However, if you have a home office, most laptops have pretty decent speakers and mics which means you can converse a bit more normally. However, if you are using the built-in audio rather than a mic near your face, most noises in the room can be heard. It'll be very obvious if you start typing or clicking your mouse – not that you should be multitasking during meetings!

OPINIONS
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interested practitioners, it seems more desirable to continue to give each SIG independence in decisions such as how to name their group based on the focus of the science, activities, and of course their membership.

We would therefore also like to take this public opportunity to thank all of the members of the QSP SIG that contribute their expertise and drive to make our group the powerhouse both in scientific contributions and general activity in ISoP that it is today. We agree with the author on his points about the contributions of our SIG to the Society's mission!

This opinion piece is the consensus of the full QSP SIG leadership team and expressly approved by a near totality of the steering committee. QSP SIG leadership team: Brian Schmidt, Christina Friedrich, Benjamin Ribba, Eric Sobie, Abhishek Gulati, Peter Bloomingdale. QSP SIG steering committee in agreement: Jane Bai, John Burke, James Gallo, Rukmini Kumar, Tarek Leil, CJ Musante, Mark Peterson, Aleksander S. Popel, Saroja Ramanujan, Julio Saez-Rodriguez, Birgit Schoeberl, Iñaki F. Trocóniz, Piet van der Graaf, Paolo Vicini

Opinion is a column in the ISoP Newsletter that is meant to be like the Op-Ed section of the newspaper. Each piece expresses the views of the author(s) and do not reflect the opinion of the ISoP Board of Directors or the Communications Committee, which organizes the newsletter. These views are solely those of the author(s).

If you have an opinion piece you would like to submit, please send it to:

peter.bonate@astellas.com.

COMMUNICATION CORNER
(continued from previous page)

In the current environment, too, there will understandably be distractions and noises due to a shared space with families and pets, traffic noise or landscapers, etc. Do your best to minimize these by putting up a "do not disturb" sign on your home office door, or by warning your family that you'll be on a call if you work in a shared space. But generally people are patient with barking dogs and crying toddlers- this is real life, we're all in the same boat, and we're all doing our best!

And while meetings are there to serve a business purpose, it's ok to try to bring some levity to the virtual table. There's a time and place, of course, but when it's appropriate, play conference call bingo, have a dress theme (hats, sports jerseys, Hawaiian shirts), or have a "potluck" where everyone brings a favorite drink or snack. We all used to go for coffee or lunch and have non-work conversations with colleagues, so there's no reason to stop because we're working remotely- make the effort to keep connected during this time. VCs are a great way to get face time with your friends and colleagues, and can make for productive meetings, if done right!

I got several great tips that for this article from https://tier1performance.com/working-from-home/ and https://seed.co/blog/Video_Chat_Etiquette/. And Pete and I have contributed some advice to those making presentations over conference call formats with our Certara webinar (https://www.youtube.com/watch?v=JvRNWX48Dq0) and associated blog post: https://www.certara.com/2017/08/18/speaking-into-the-ether-challenges-of-the-virtual-pharma-workplace/. We hope you'll check it out.

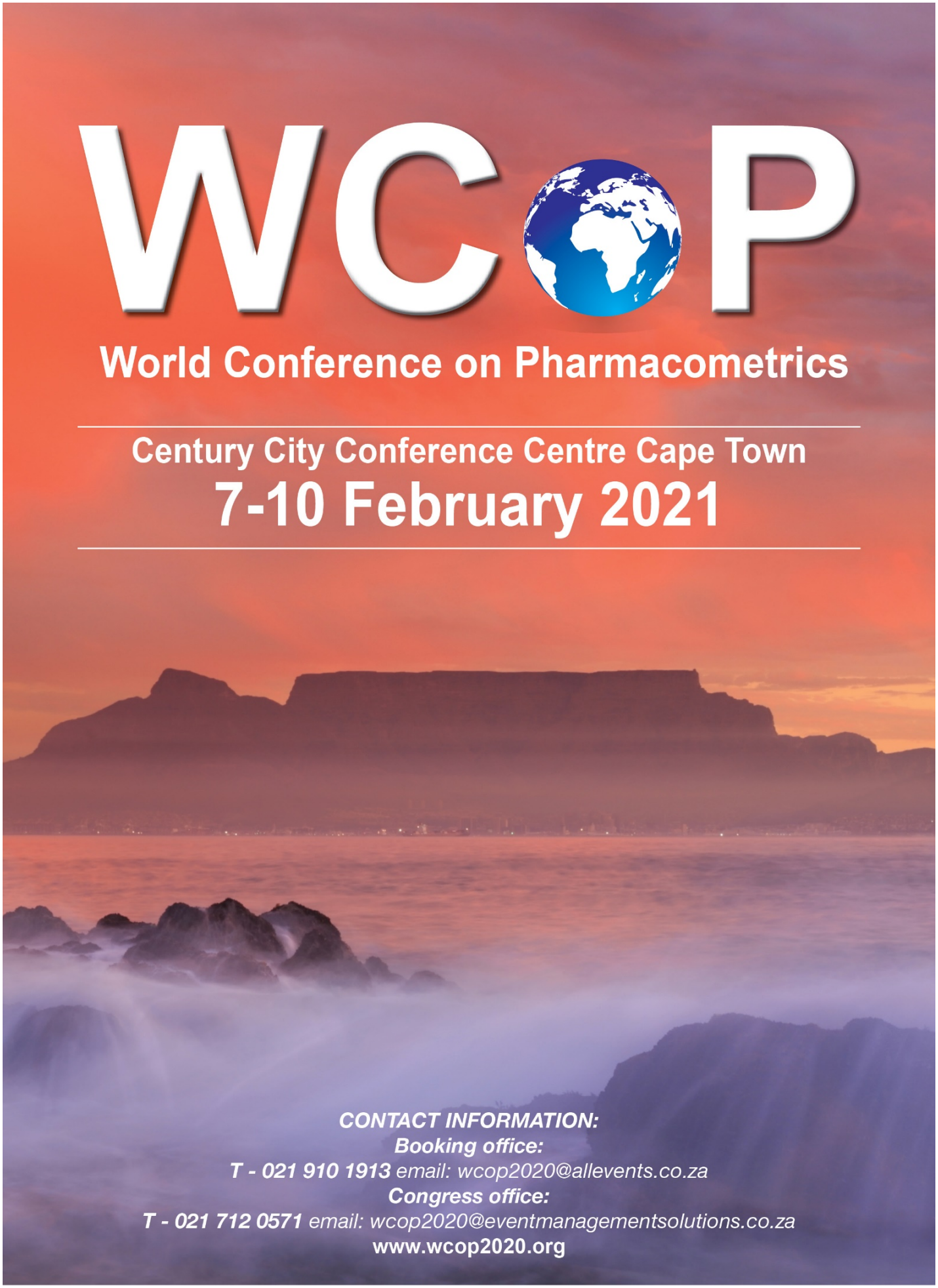
Do you have any great tips on making virtual meetings work or other remote working resources? Email them to Stacey.tannenbaum@astellas.com and your tips may be featured in an upcoming column!

UPDATES FROM THE ISoP STUDENT COMMUNITY
(continued from page 11)

Events to look forward to:

The Student Community is a permanent fixture at ACoP with trainee focused sessions. The ISoP Student Community works year round in collaboration with the ACoP Planning committee to create events which will help trainees from all over the world gain real-world understanding of using pharmacometrics in drug-development and allow for networking opportunities with established mentors from various specializations. For ACoP11, the events are being planned by ACoP11 Trainee Committee which is chaired by Brian Cicali and guided by the past-chair Ashwin Karanam and the ACoP11 Chair, Dr. Navin Goyal. Three fantastic events have been planned this year: 1) Trainee Mentoring Luncheon where the trainees can interact and network with established mentors from various disciplines and settings, 2) Trainee Tutorial Workshop with the intent of providing trainees with hands-on case-studies on how pharmacometrics is used in drug development. This year's student tutorial will be "Clinical Trial Design and Simulation: First in Human Dosing" and 3) Trainee Communication Challenge where approximately 10 student/trainee abstracts will be randomly selected via lottery from all accepted abstracts for a podium presentation. Each presenter will have 5 minutes (including Q&A) to present their abstract poster. The top 2 presenters will each win $500 courtesy of the Journal of Pharmacokinetics and Pharmacodynamics. Communicating your work in a fun, clear and succinct manner will help you win the Challenge!

The Student Community is also planning a webinar series for trainees with both early-stage and established speakers. The webinars are currently being planned with a tentative start in June, so please keep an eye out for our webinar series (to be announced on website our soon)!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World Conference on Pharmacometrics
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