Message from the President
By Brenda Cirincione

I cannot speak for everyone but for ISoP this is an insanely busy time. The Board of Directors started out this year with the intent of transforming a lot of our processes and procedures as well as increasing the opportunities for, and benefits to, our membership. All of this with the intent to position the society to allow for even more growth and success in the future. Then the pandemic occurred. We continue to hope that everyone is doing well and staying safe as we progress into the autumn-winter season in the Northern Hemisphere. But for ISoP, things have proceeded and in fact, we have even more challenges than before. I want to take a moment to thank all our members for their continued support for the initiatives for the Society during this incredibly challenging time. I would like to highlight a few of these activities:

Virtual ACoP. We have just launched the registration for our virtual ACoP meeting. While on paper this might seem like a relatively simple task, it has been a huge lift for many members of our society. We would like to thank Navin Goyal, Heather Vezina, C. J. Musante and the ACoP planning committee for all their ongoing efforts in converting ACoP to a virtual meeting. They are working tirelessly to provide a virtual conference with the look and feel of the ACoP that we are accustomed to. Thank you to our session chairs, speakers, poster presenters for their patience as we work through the details of virtual and going the extra step of recording their sessions and to thank Sponsors and Exhibitors for continuing to support our community and ISoP's mission.

The platform we have chosen to host the virtual conference should provide us all with a mix of live presentations and recorded options, poster sessions and even the opportunities to meet up with missed friends and colleagues. You can also network at alumni receptions and the social event. Please also visit the exhibitors and take advantage of the virtual environment to learn even more, maybe, than you would have in person! For more up to date information, please keep an eye on the [https://www.go-acop.org](https://www.go-acop.org) website. We are looking forward to “seeing” all of you in November.

We want to thank you all for nominating so many members for awards, and as future Fellows of ISoP. The Awards Committee is working hard to review the material and will soon vote to select the recipients. We look forward to congratulating the new award winners at our upcoming virtual Awards Ceremony at ACoP.

We are also actively working on the election of the new Board members. I would like to thank you all for the largest voting turnout in ISoP history! It is inspiring to know that so many of you took the time to help shape the Society’s future, and hope you’ll continue to do so. We look forward to congratulating the 2021 board members at the ACoP meeting.

In addition, we are excited about the applications we received for the chair of the Inclusion and Equity Committee. We are in the process of interviewing candidates as I write this. The role of this new committee is extremely important to this society and we look forward to sharing their vision and plans with the broader membership in the near future.
Message from the President (continued)

In addition, it is important to highlight that our progress with the initiatives in the 5 Year Strategic Plan. This is a critical part of the growth and development of ISoP over the next few years, and I want to thank everyone for their continuing efforts on moving them forward.

Lastly, we thought we would take advantage of the newsletter and virtual environment to issue a Special Edition at the end of the year. This bumper edition will provide an update on our committees, the Five-Year Strategy initiatives, SIGs, new board members, and much more. Please keep an eye out for this special summary of our society and its ongoing activities.

Thank you to all of our members, who continue to impress me with their visions, creativity, motivation and the ability to be flexible in a challenging environment.

Mathematical Oncology Newsletter

There is an interesting new newsletter that is published by mathematical.oncology.org. The newsletter curates’ articles related to mathematical oncology, both recent publications and preprints. They also discuss recent topics in the news. Go to their website to sign up.

Mark your calendars for ACoP11 – hosted virtually from 9-13 November 2020. While we would have loved to see everyone in person in Colorado, we will ensure that you are still able to connect with friends and colleagues in addition to learning and sharing research. You can find the most up-to-date information and timelines on our website, but here just a few highlights to pique your interest:

- 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.
- The main conference brings a slate of exceptional and interactive scientific sessions making it difficult for you to choose between which sessions to attend.
- The daily schedule is designed to allow colleagues across several time zones to attend the multitude of events and interact with other attendees across the globe.
- 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.
- The poster sessions will provide opportunities for interactions with poster presenters including our winners for the Quality and Trainee Abstract Awards, MCS, QSP, ClinPMx and SxP SIG poster awards.
- There will be ample opportunities to connect 1:1 and network with colleagues and friends. Stay tuned and watch out for networking and social event announcements!

Registration is open now! Secure yourself a spot at ACoP11 by registering early.

We look forward to seeing you soon (virtually)!

On behalf of the ACoP11 Planning Committee,
Navin Goyal – ACoP Conference Chair
[https://www.go-acop.org/](https://www.go-acop.org/)
Volunteer Spotlight on Michelle Johnson

Chief Operating Officer
Metrum Research Group

By Peter Bonate

Tell us about yourself.

I am currently enjoying life as the Chief Operating Officer at Metrum Research Group. I am a marketer by trade and joining MetrumRG has been my first foray into the wild world of life sciences. Prior to MetrumRG, I held marketing and business management roles in several industries including professional athletics, entertainment, higher education, and non-profit. I live in the Boston area with my husband (an introverted software engineer… opposites attract!), 18 year old son, and 15 year old daughter.

What do you do at Metrum?

As COO, I am accountable for the strategy and implementation of the business side of the company. This includes functions like HR, IT, Quality, Resource and Project Management, and Finance. My days are filled with a constant toggle from big picture thinking to tactical implementation. I am deeply blessed to work with an amazing group of people, who are humble, smart, and innovative. (For more about life as a COO, check out this podcast.)

How did you get involved with ISoP and what do you do?

The first time I attended ACoP (in 2016), I was overwhelmed by such a close-knit community of scientists. I felt like I was at a high school reunion, but I went to a different school and spoke a different language! But I have to say, so many people in the ISoP community have welcomed me (even though I am not a scientist!).

Sometimes it’s hard to keep up with the vernacular and the pace and depth of the intense scientific discussions (even those that happen over coffee or cocktails). And though I am surrounded by incredibly smart and capable quantitative scientists, time and again I have been encouraged to offer my perspective. It’s been a pleasure to help out with the planning and logistics of several ISoP events at the local level and also to serve on the ACoP planning committee for the last few years.

What’s the best experience you’ve had at ACoP?

The game show format of the 2019 Innovation in Communication session was a blast. I was definitely in the hot seat helping Brenda Cirincione judge the contestants’ responses.

Why do you think it’s important to volunteer for ISoP?

For someone like me, it’s important to give back and contribute to the communities to which I am part. With ISoP, I struggled at first to find a place where I could contribute (I am not qualified to review scientific abstracts or to design innovative and cutting edge scientific programming) but I was hopeful there would be a place for me to plug in. Serving on the ACoP committee has been a great fit for my skills and experience. And you know what? If I can provide value to this amazing community, YOU CAN TOO!

At this point in your life, what motivates you?

I am driven by having laser focus on my “why”. It’s so easy to get lost in the details of WHAT I am doing and HOW I am doing it. I need to step back and remember WHY I am doing it. This drastically increases creativity, performance, and satisfaction.

What is something people don’t know about you?

I lived in Central China (Henan, Zhengzhou) for two years teaching a marketing course to college students. This was an amazing time for me and my family and we learned a lot about empathy and compassion and most importantly about having a heart of gratitude.

The ISoP Newsletter Needs Contributors

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

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


By David D’Argenio

One of the early applications of modeling in physiological systems is Bolle’s 1961 model of insulin control of glucose. As our understanding of the complexities involved in metabolic regulation in health and disease has evolved, including in type 2 diabetes mellitus (T2DM), QSP models have been proposed and applied to better direct therapeutic approaches to treat T2DM. While these QSP approaches have mostly involved dynamic system models, the recent Boolean network model by Pritha Dutta et al. broadens this conventional perspective. (See the work by Mager and his group in JPKPD 45:159–180, 2018 for an insightful review of Boolean network modeling in systems pharmacology.)

In this paper by Pritha Dutta et al., a Boolean network model for T2DM is presented that integrates the insulin resistance pathway with the pancreatic β-cell apoptosis pathway implicated in T2DM. The model was used to simulate the dynamics of gene expression induced by different combinations of five input signals, ER stress, oxidative stress, and the cytokines TNFα, FasL and IL-6, all of which serve as triggers for insulin resistance and β-cell apoptosis. Proposed future applications of the model include virtual gene knockout experiments to determine genes that play pivotal roles in insulin resistance, β-cell apoptosis, or both.

Kiersten Utsey et al. Quantification of the Impact of Partition Coefficient Prediction Methods on PBPK Model Output Using a Standardized Tissue Composition Drug Metabolism and Disposition July 14, 2020, dmd.120.090498; DOI: https://doi.org/10.1124/dmd.120.090498

By Angela Birnbaum and Ashwin Kanaram

Physiologically-based pharmacokinetic (PBPK) models have become increasingly commonplace in predicting drug disposition in various tissues and/or in various target populations. One of the key drug-related parameters for building a PBPK model are tissue-to-plasma partition coefficients – an organ specific parameter controlling the disposition of drug in organs/tissues. In-vivo quantification of partition coefficients is difficult, hence multiple equation-based methods for calculating these coefficients are available and should be considered. Comparison between the various methods is limited due to differences in input parameters used (e.g. availability of tissue compositions in humans) in predicting partition coefficients.

This manuscript compared five available partition coefficient prediction methods and their effect on model predictions (Poulin and Theil method, Berezhkovskiy method, Rodgers and Rowland method, Schmitt method and PK-Sim Standard method) using a standardized tissue composition database for 11 compounds representing different drug classes: strong bases, weak bases, acids, neutrals, or zwitterions. Predictions were compared to observed concentrations digitized from literature and predicted drug half-lives from clinical studies. Evaluation of the impact of the standardized versus available literature-based tissue composition values for calculated partition coefficients shows the Poulin and Theil, Berezhkovskiy and Schmitt methods were most adversely affected and the PK-Sim method was remarkably robust. Interestingly, none of the five methods included in the study produced better model predictions than the others for the various drug classes. Evaluation should be done on a case by case basis by looking at sensitivity of predictions to the various methods available. Optimization of partition coefficients should be considered during model development.


This white paper written by the Translational and ADME Sciences Leadership Group, the Clinical Pharmacology Leadership Group, and DruSafe within the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) Working Group describes the use of minimum anticipated biological effect level (MABEL) calculation methods and how they impact dose selection in early clinical trials. It provides recommendations for first in human (FIH) starting dose selection based on the views of the working group and the IQ consortium. The concept of MABEL was introduced by the European Medicines Agency’s Committee for Medicinal Products for Human Use after the FIH trial TGN1412 (TeGenero AG, Würzburg, Germany) to provide a FIH method for novel therapies to minimize biological activity and theoretically providing safety in FIH volunteers. However, the authors suggest that MABEL is being commonly used as a default as opposed to data-driven and risk-based approaches in both industry and by health authorities leading to FIH starting doses far smaller than an appropriate therapeutic dose. The authors provide an overview of the various FIH dose selection methods including both toxicology- and pharmacology-based approaches. Results from a survey sent to IQ member companies on the use of MABEL in various therapeutic areas are presented. Although MABEL is used differently across companies, it is commonly used to calculate and determine the MABEL-based starting dose, PKPD modeling of in vitro and in vivo data was used in 34% of 88 molecules. It was noted that an increase in modeling of all available data was being seen over time with most submissions being in the latter year time group (2015-2017). Through case studies that used decision tree and risk factor tables in deciding appropriateness of using a MABEL approach for FIH doses, the authors propose that use of such tools would help identify FIH doses that balance safety while providing therapeutic levels to FIH patients and volunteers.
News from the Mathematical & Computational Sciences (MCS) SIG

By Gilbert Koch

A new webinar series from the MCS SIG

The MCS SIG is hosting a webinar series this coming fall and spring. Each webinar will cover an exciting topic on mathematical and computational modeling in medicine. All webinars will be at 11 AM Eastern Time and presented via Zoom. The schedule is as follows:

- March 8, 2021: Bree Aldridge, Ph.D., Tufts University. The Long and The Short of it: Paths to Engineering TB Treatment.

For registration and further details please see the MCS SIG website (#mcs_isop): https://sites.google.com/view/mcssig/mcs-sig

Newly-established MCS SIG Working Groups

The MCS SIG has established three new Working Groups with the topics (i) optimal control, (ii) combining pharmacometrics, machine learning, and dynamical theory, and (iii) sensitivity analysis and uncertainty quantification. If you are interested in one of these working groups and want to volunteer, send an email to the corresponding chair or co-chair (see below for contact info).

**Optimal Control Working Group**

Optimal control has been used extensively in fields such as aerospace and economics. However, it has only seen limited application in the biomedical field. For example, while there have been numerous theoretical studies applying optimal control to cancer treatment, the concepts seldom translate to preclinical or clinical studies. This has been partly due to issues including the complexity of the methods and the lack of accessible software tools.

**Goals and objectives:**

The MCS SIG Working Group on Optimal Control will help address these issues by providing resources including annotated summaries of analytical and numerical methods, reviews of software tools, and suggested best practices for implementing optimal control approaches.

**Chair:** Carl Panetta (Carl.Panetta@STJUDE.ORG), St. Jude Children’s Research Hospital Memphis, TN, USA. Member of MCS SIG steering committee.

**Co-chair:** open

**Combining Pharmacometrics, Machine Learning, and Dynamical Theory Working Group**

Computationally-efficient methods, such as machine learning (ML) are becoming increasingly important in medicine. In addition, artificial intelligence (AI) methods such as neural networks are useful to map complex mathematical algorithms. A fundamental challenge for the biomedical community to fully embrace the power of modeling and ML/AI could arise from their lack of causality. Dynamical theory has been proven to be a useful tool to provide such causal reasoning and bridges quantitative thinking of modelers and semi-qualitative reasoning that prevails in biology. Hence, incorporating dynamical reasoning could help to reduce the risk of data-driven modeling.
Goals and objectives:
To maximize knowledge from available data by combining pharmacometrics, ML/AI, and dynamical theory, and to integrate the three methods to rigorously extract the mechanistic essence that are embedded in models and to reveal the overall picture from the potentially confusing data.

Chair: Tongli Zhang (zhangtl@ucmail.uc.edu), University of Cincinnati. Member of MCS SIG steering committee.

Co-chair: Gilbert Koch (gilbert.koch@ukbb.ch), University Children’s Hospital Basel, Switzerland. Member of MCS SIG steering committee.

Sensitivity Analysis and Uncertainty Quantification Working Group

Sensitivity analysis (SA) and uncertainty quantification (UQ) are important for understanding properties of mathematical models and their impact on fits to data or predictions. For example, SA can be used to determine which model parameters are most influential for model responses. UQ focuses on quantifying uncertainties inherent to model parameters, experimental data, and model responses. SA/UQ techniques can be used to prioritize data collection in order to better estimate key parameters, and thus improve predictions. They can also be used to help inform appropriate levels of confidence for the use of model predictions when data are not available.

Goals and objectives:
Disseminate research on quantifying sensitivities and uncertainties in math models. Connect ISoP members to academics developing state-of-the-art SA/UQ theory, methods, tools. Provide training opportunities for students and professionals

Chair: Helen Moore (dr.helen.moore@gmail.com) Applied BioMath. Member of MCS SIG steering committee

Co-chair: Ralph Smith, NC State University. Academic researcher, ACoP11 tutorial presenter

Update from the Clinical PMx SIG

By Nikolas Onufрак

The Clinical Pharmacometrics SIG is pleased to announce its 2020 ACCP Student Abstract Award winner, Dr. Mu’taz Jaber, PharmD, who will be formally recognized and present his work, HydroC-Precision: An Integrated Hydrocortisone Dosing and Biomarker Platform for Treating Children with Congenital Adrenal Hyperplasia, during the virtual ACCP 2020 meeting held September 21st-23rd. Along with the SIG-sponsored session, Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice, we hope you were able to remote in for these excellent topics.

Mu’taz Jaber, PharmD
University of Minnesota

Finally, the SIG is seeking nominations for the position of Scientific Secretary. Nominees will be elected via member vote, serving a one-year term starting September 2021 with the opportunity to progress through the SIG’s Leadership Team in subsequent years. If you are interested in becoming a member of the SIG Leadership, please email the SIG Leadership at clinical.pmx.sig@go-isop.org.

The New Kid in Town - Population Approach Group of Malaysia (PAGMAS)

By Qing Xi Ooi, on behalf of PAGMAS

Introduction to PAGMAS

PAGMAS was founded by a group of pharmacometricians from the academia, industry, consultancy sector, and government sector in Malaysia and was officially approved by the Registrar of Societies (ROS), Malaysia, as a registered, non-profit national society on 22nd February 2019. To date, PAGMAS has 19 active members. The objectives of PAGMAS are to:

Mu’taz Jaber, PharmD
University of Minnesota

Zachary Taylor, MS
Cincinnati Children’s Hospital
• promote the development and application of pharmacometrics in clinical, regulatory, industrial, and experimental settings in Malaysia.

• offer a dynamic platform for the integration of the pharmacometrics community in Malaysia and to bridge the community to the international communities with shared interests in pharmacometrics.

• provide pharmacometrics resources, mentoring, a platform for events, collaborative opportunities, and educational assistance to the local and international pharmacometrics communities.

Pharmacometrics Analysis using NONMEM Workshop 2020

PAGMAS organized its very first activity, Pharmacometrics Analysis using NONMEM Workshop, on 10th - 11th February 2020 at the University of Malaya in Kuala Lumpur, Malaysia. A total of six pharmacometricians led and facilitated the hands-on workshop, as well as presented works that showcase the unique application of the population approach in different pharmacologic and therapeutic settings. The workshop was attended by 22 participants from the academia (academics and postgraduate students), hospitals (healthcare professionals), and clinical research centers (clinical researchers). The workshop received overwhelmingly positive feedback from the participants who found the workshop enjoyable and the materials easy to understand; and most importantly, had their interest piqued to learn more about pharmacometrics.

Looking into the future

PAGMAS is in the process of working out an official partnership with the International Society of Pharmacometrics (ISoP) to foster integration and innovation and to enhance collaboration within the pharmacometrics field. We look forward to the partnership and are excited to meet pharmacometrics enthusiasts from different parts of the world and to give back to the community.

In addition, PAGMAS has a few webinars in the pipeline. In these webinars, students from different countries will be invited to share their experience in pursuing a PhD in pharmacometrics. Key focus of subsequent webinars will be to showcase life as a pharmacometrician in various settings (academia, regulatory agency, pharmaceutical company, and consultancy firm). The goal of these webinars is to facilitate discussion in a collegial and friendly environment between seasoned PhD students/pharmacometricians and individuals who are considering pursuing postgraduate studies in pharmacometrics or a career as a pharmacometrician.

Contact us

PAGMAS is actively looking to get connected with the local and international pharmacometrics community. Whether you are looking for an opportunity to collaborate, to pursue pharmacometrics postgraduate study in Malaysia, to share your experience in establishing a pharmacometrics society, or if you just need someone to talk to about pharmacometrics, please reach out to PAGMAS (pagmas.sec@gmail.com). We are in the process of updating our official website (www.pagmas.com). Bookmark us and stay tuned for more updates of PAGMAS activities and events!

Did You Know?

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

http://go-isop.org/newsletters/
Systems Modeling with Academic and Biopharma Industry Applications at a Math Conference

By Mahua Roy and Helen Moore

The Society for Industrial and Applied Mathematics (SIAM), founded in 1952, is a society with more than 14,000 members. Like ISoP, it is international and non-profit, with members from both academia and industry. The main aims of SIAM are to “advance the application of mathematics and computational science”, to support development of new theory needed for these applications, and to provide media for the exchange of such information and ideas. This aligns well with the aims of ISoP, and in particular, of the Mathematical and Computational Sciences (MCS) Special Interest Group (SIG).

SIAM holds an annual conference that typically draws more than 1,500 attendees; this year’s conference, which was virtual and free, had 4,200 registrants. With encouragement and support from the MCS SIG, which is working to increase ties to applied mathematics researchers and societies, we organized a SIAM session of eight speakers to share their mathematical modeling work applied to drug development with this audience. When one of our speakers cancelled two days before the event, we organized several of our other speakers into a panel on “Math Modeling Careers in Biopharma Industry” for that time slot.

By organizing this session with SIAM, we achieved several goals on behalf of the MCS SIG. First, we were able to showcase the modeling and analysis methods being used in the biopharma industry. Second, the speakers shared information about the questions and types of problems of interest in drug development. And third, the panel discussion about math modeling careers in biopharma provided insights to academic researchers who were interested in learning more about these careers and information on how to get a job in this industry.

We provide titles and descriptions below, and the full abstracts for this session are available at these links:

https://meetings.siam.org/sess/dsp_program sess.cfm?SESSIONCODE=69249
https://meetings.siam.org/sess/dsp_program sess.cfm?SESSIONCODE=69250

**Targeting Metabolic Pathways in Cancer using a Discrete Cell-Based Modeling Approach**, Mahua Roy, Pfizer: a math model to predict potential targets against tumor growth.


**DEs, DCs and Doses: Mathematical Approaches to Designing Cancer Vaccines**, Arni Radunskaya, Pomona College: sensitivity analysis identified patients more likely to respond to a dendritic cell vaccine.


**Panel Discussion: Math Modeling Careers in the Biopharma Industry**, Lyndsey F. Meyer, Peiying Zuo, Peter Bloomingdale, Sietse T. Braakman, Helen Moore; Mahua Roy, moderator

**Systems Modeling for Ursodeoxycholic Acid Metabolism in Healthy and Patients with Primary Biliary Cirrhosis**, Peiying Zuo, Astellas Pharma: prediction of interactions of a therapeutic drug in this patient population.
Update from the QSP SIG

By Brian Schmidt and the Leadership Team

There have been many developments and events in the QSP community over the last several months, and members of our ISoP QSP SIG have helped to drive several.

In previous years we held annual or biannual “QSP Day” events, which are small, one day, regional conferences where we invite notable speakers from the community to present their recent progress and where we also often hold a poster session. This year, we changed our QSP Day event to a virtual “QSP Week” event with alternating sessions and poster presentations. Using a combination of Zoom presentations and Slack channels, the event was highly successful with over 300 registrants. There were six main presentations spanning topics from examples of QSP disease platform model applications, detailed modeling of T cells, as well as presentations covering many therapeutic areas, including the immune response to COVID-19. In addition, six virtual poster sessions were run by QSP SIG Working Groups, each featuring 4 Virtual Poster presentations. We would like to again congratulate our two poster award winners: Roy Song of GlaxoSmithKline for his work, “Application of Quantitative Systems Pharmacology (QSP) platform for Immuno-Oncology for evaluating OX40 agonist, and anti-PD1+OX40 agonist therapies for advanced NSCLC” and Florence Véronneau-Veilleux from the University of Montreal for her work, “Mechanistic modeling of levodopa pharmacodynamics through the time course of Parkinson’s disease.”

Congratulations! We would also like to thank all of the Working Group leaders for the work that they put into organizing and moderating the Virtual Poster sessions. We are preparing a more complete write-up of this recent event. The Organizing Committee, which consisted of our Leadership Team as well as Valeriu Damian, did a great job organizing and moderating this event. We would also like to thank Enrico Smith for his contributions to the success of the event, as well as support from Steve Duffull and the ISoP Board.

Earlier in the summer, there was an FDA-industry scientific exchange where companies presented case studies and had in-depth discussions about how to assess QSP modeling efforts. Many ISoP QSP SIG members played a role on the organizing committee and as moderators, and this was a follow-up event to a preliminary QSP group discussion held at ACoP10. This was an important event and discussion for our community to have, as there is growing interest in applying QSP in later-stage clinical development and to support interactions with health authorities. I would like to thank my co-chairs, Jane Bai and Kapil Gadkar, for their efforts in developing the sessions as well as the follow-up. I would also like to thank the organizing committee, moderators, speakers, and assessment teams for their efforts. I also would like to thank Tarek Leil for his suggestions on the format and feedback on the assessment strategy. I believe this is the first event we have had with such an in-depth review of QSP case studies with assessment teams. Although the assessments entailed some additional work, they helped to better clarify the different approaches currently being employed.

Finally, please note that the voting for the QSP SIG Vice-Chair role is now open! We have two very well-qualified candidates running for the position this year: Ioannis Androulakis from Rutgers University and Sookyung Woo from State University of New York at Buffalo. Our 2020-2021 QSP SIG Leadership Team will be announced at our Meet the QSP SIG event at Virtual ACoP11, where we will also bid farewell to the team (keeping in mind that you can check out but you never really leave!). The event will also include the QSP SIG Student Award presentation, and we will have updates on the year and from our Working Groups and discussion of our plans for the year to come. Please join us!

Update from SxP Sig

By Mike K. Smith and Stacey Tannenbaum

Here we are in Fall 2020. It seems like no time since Spring, and yet time has bent, stretched, dragged and flown past simultaneously. We’re all experiencing a period of change – change in circumstances, in working environments, work priorities, life priorities. And so it is with the SxP SIG as well. In early Summer 2020 the SIG Steering Committee met and we handed over co-chair of the SIG from France Mentre to Stacey Tannenbaum. I’d like to thank France for her leadership of the SIG and welcome Stacey as the new co-chair. We also have a few Steering Committee members who have finished their term and stepped back, so there are some spaces available for the membership to fill – we will be getting in touch and asking for nominations and applications in the next few weeks. We have also had a change in curator of the SIG website – Malidi Ahamadi has volunteered to take over from Jingtao Wu. We will be looking at how best to serve the website, which is currently under the ASA Community pages, to make it more accessible and more easily updated. Currently the website is at: https://community.amstat.org/sxp/home.

As usual we have had students submit ACoP abstracts for the SxP SIG Student Award and we are very pleased to announce the winner of our prize this year is the abstract “Spatiotemporal Response Heterogeneity across Metastases in Metastatic Colorectal Cancer” by Jiawei Zhou and Yanguang Cao of UNC Chapel Hill. Congratulations!

As with previous ACoPs we’ll be bringing the SxP membership together during ACoP11. More details will be shared with you shortly.

With coronavirus severely constraining our ability to meet up and share experiences, we plan on having several virtual SxP events. The first of these will be a webinar by Drs Hao Zhu and Lei Nie from the FDA who will be reprising presentations from a recent DIA meeting on the topic of MIDD. They will discuss the efforts by industry and regulatory agencies to pilot and embed MIDD in drug development, areas where special attention is required within the MIDD framework and where biostatistics and clinical pharmacology functions can collaborate on MIDD topics. Watch out for notice of this webinar and make sure to tune in. Details will be shared shortly.
Choosing Fonts for Your Data Visualization

By Tiffany France

This article was previously posted on Medium (medium.com) and the author has graciously agreed to allow ISoP to republish it in its entirety. Please visit her website (https://www.tiffanyfrance.com/) for examples of data visualization.

The purpose of data visualization is to provide a layout that relays lots of information quickly. Good visualizations help the user understand complicated data without allowing the design to get in the way. Any text accompanying the graphics should be easy to read to the point that it almost disappears.

In this article, I will be explaining how to pick a highly readable and aesthetically pleasing typeface for your project. I will focus primarily on small text, that is, text in a data visualization that is meant to explain the layout, including labels, callouts, and sources. In order to serve a wider audience, I will only recommend free Google fonts, though there are many good paid options.

Highly Readable Fonts

Highly readable fonts take less brainpower to interpret. Visualizations with good typography have a consistent rhythm. They look like a cohesive unit. Good typography doesn’t grandstand—it explains the content without getting in the way of the user’s experience. Copy should be minimal, pared down to the essentials for comprehension of the graphical elements.

To understand how type is “highly readable” at small sizes, let’s look at a few elements of type.

### X-height

X-height is the height of the body of the lower-case letters minus any ascenders or descenders. Because lowercase letters sometimes have different heights, this height is measured using the letter “x”.

<table>
<thead>
<tr>
<th>Font</th>
<th>x-height</th>
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</thead>
<tbody>
<tr>
<td>Gill Sans</td>
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<td>Open Sans</td>
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<td>Noto Sans</td>
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<tr>
<td>Lato</td>
<td>10px</td>
</tr>
</tbody>
</table>

The x-height directly affects how readable fonts are at small sizes. For instance, take a look at the graphic above. All of these fonts are 10px. Which typeface do you find most readable? Gill Sans and Athelas have smaller x-heights, making the text more difficult to read. Open Sans, Noto Sans, and Lato have larger x-heights, lending to easier readability at small sizes. When choosing a font for data visualization, opt for a typeface with a large x-height.

Note also, Lato has a good x-height, but shorter line-length. If your visualization has an x-axis with limited space for ticks, you may want to consider a more condensed typeface like Lato.

### Counter

The counter is the empty space in letters such as “p” and “o”.

As the text above says, the shape of the counter affects readability at small sizes. The eyes should roll easily over the letterforms. Your viewer should not have to spend time figuring out if the letter is an o or an e. Fonts with distorted counters render poorly in small sizes. Whimsical fonts such as Marker Felt should be avoided. Note how difficult it is to read dense fonts like League Gothic and Futura Condensed at small sizes. This is because the counters are elongated when the font is squished. When choosing a font for your visualization, look to use a font with a stable, open counter.

### Serifs

Serifs are the little swooshes or feet around a letter form.

Serifs are often avoided in labeling content because the extra flourishes sometimes muddle the view of the letterform. The first three lines above are serif fonts. Compare those to the last two typefaces which are sans-serif (without serifs). In these examples, the sans-serif words are easier to decipher. While some serif fonts are passable at smaller sizes, if you are unsure, then skip them and opt to use a sans-serif typeface.

### Using Numbers

Typeface numeric values are either proportional and tabular.

<table>
<thead>
<tr>
<th>Number</th>
<th>Font</th>
</tr>
</thead>
<tbody>
<tr>
<td>32154</td>
<td>Montserrat</td>
</tr>
<tr>
<td>32154</td>
<td>Open Sans</td>
</tr>
<tr>
<td>32154</td>
<td>Lato</td>
</tr>
</tbody>
</table>

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Choosing Fonts for Your Data Visualization (continued)

Open Sans is a tabular typeface that centers numbers within the column space. Lato, however, offsets the number in the column space. Why is this important? Because that little bit of awkward space requires your brain to work to understand that this is a continuous string of numbers. We can eliminate that work by choosing a typeface with tabular numbers and even spacing.

Watch out for old style numbers. Raleway is a beautiful typeface that is commonly used for text and logos, however, it doesn’t work well for labeling data visualizations. That’s because it uses old style numbers instead of lining numbers. Look how the 3, 5, and 4 descend below the baseline. This treatment is not only hard to read in a visualization, but it also looks somewhat jumbled outside of the text.

Typographic Design Systems

A typographic design system, as used below, is a declaration of font sizes, weights, and line heights to be used in a layout. Systems help to ensure visual consistency across a project. Here are five systems to try in your design. The suggested pairings below use open-source Google fonts. Please note that the screenshots are not true-to-life font sizes due to the rendering of images on this page.

Example 1: One font/One size

The “One font/One size” typographic system uses a single typeface with a continuous set size, resulting in a universal visual texture. This subtle approach is good for laying out dashboards or when adding graphs to a business report. Importance can be noted by using a heavier font weight or shades of gray.

Use in the wild: An example of this technique is the Google Trends dashboard. Google Trends uses Roboto typeface for both the header and the labels. The dashboard separates content by using a card-based layout. This card uses one typeface and one font size throughout the composition.

Example 2: One font/Big header

The “One font/Big header” typographic system uses a single font with a header that is larger and bolder than the rest of the content. A bigger header stands out, helping users quickly understand what the content is about.

Use in the wild: The Washington Post uses a “One font/Big header” system in the visualization below. The font is ITC Franklin Pro typeface (available for purchase). Note their use of all caps for the navigation. The designer keeps the font family and size consistent so that the navigation feels like it belongs with the rest of the layout.

Font used: Lato is a good data visualization typeface because it is highly readable at small sizes. The font has clean counters, a moderate x-height, and tight, but not distorted, letter spacing. The numeric values are tabular and evenly spaced for ease of reading. The bold weight can be distinguished easily from the regular weight, however, the semi-bold doesn’t have enough distinction from regular or bold and should be avoided. Lato was released on Google Fonts in 2015 and is currently the 3rd most popular font on their site.

Some states have turnout as low as 1 in 3 eligible voters

Average turnout for the voting eligible population in the 2008, 2010 and 2014 midterm elections.

Use of Lato typeface in the Google Trends dashboard.
Choosing Fonts for Your Data Visualization (continued)

The following is a use case of the “One font/Big header” system. This example uses Assistant typeface in 24px for the header, and 14px for the rest of the content.

Font used: Assistant is a crisp, modern typeface that works well in design because of its simple, open aesthetic, and rhythmic letter sizing. The numbers are well balanced and have no gaps or compromised letterforms. Assistant is an open-source font family that builds off Source Sans Pro. The project is open to collaboration and accepts contributions to the Github repository.

Example 3: Two fonts / Heavy & light

The “Two fonts/Heavy & light” typographic system uses two sans-serif fonts with complementary x-heights and letter spacing. The header is set to a heavy weight, the content is set to a light weight.

Use in the wild: Reuter’s “The Rohingya Crisis: Life in the camps” data visualization uses a heavy & light typeface combination. The designer used Reuter’s proprietary typeface “Knowledge” for the header. The data labels are Source Sans Pro available from the Google Fonts library. As a side note, notice how “Negative for E. Coli” is grayed out to draw attention to the first three metrics.

The content is set in Noto Sans, a clean font, with slightly condensed letter spacing, compensated by clear circular counters and a generous x height. The tabular numbers include a sturdy number “1” with a wide foot, giving a solid appearance to the number structure.

Noto Sans is part of a larger family of Noto typefaces. There are over 100 different typefaces in the group, with the purpose of providing “visual harmony” across multiple languages and script forms. This makes Noto Sans a particularly good option for multilingual visualizations.
Choosing Fonts for Your Data Visualization (continued)

Example 4: One serif / One sans-serif

The “One serif/One sans-serif” system uses two fonts — one serif and one sans-serif.

Use in the wild: Below is a screenshot from the New York Times article “Coronavirus in the US”. The title uses NYT Cheltenham and the data labels use NYT Franklin, both proprietary fonts created for the New York Times. The labels have two components: a larger, more prominent state name and a smaller, less prominent number. The use of these two styles creates a pattern that helps the viewer decode information quickly. Which catches your eye? The state name or the number?

Example 5: Serif for reading/Sans-serif for labeling

With the “Serif for reading/Sans-serif for labeling” system, the header, sub-header, and any article copy is should be set to a serif typeface. This thinking is based on a long-standing debate in design theory of whether serif fonts are easier to read for long passages of text. For maximum readability, keep line length to less than 60 characters.

Use in the wild: The New York Times does a particularly good job of mixing their NYT Cheltenham serif typeface for reading with a NYT Franklin sans-serif typeface for labeling data. Even though these are two categorically different typefaces, they work together because the letterforms have complementary counters, large x-heights, and similar stroke-widths at matching weights.
Choosing Fonts for Your Data Visualization (continued)

Fonts used: Lora is a Google font optimized for screen, but also works well for print projects. The chart text is Libre Franklin, a Franklin-based typeface, meaning it belongs to a group of fonts inspired by the original Franklin Gothic typeface designed around 1910.

Final Thoughts

The fonts and systems above are interchangeable. The following is a list of typefaces mentioned:

- Lato
- Assistant
- Noto Sans
- Source Sans Pro
- Libre Franklin

These are the fonts mentioned for headers and copy:

- PT Sans
- Merriweather
- Lora

Good typography practices start by understanding how the components of letterforms lend themselves to high readability. I hope this approach helps you find a type design system that works for you.

What are your favorite fonts to use in data visualization? Let me know below and thanks for reading!

Tiffany France

This article was originally published at: https://medium.com/nightingale/choosing-a-font-for-your-data-visualization-2ed37afea637

If you are interested in more about this topic and other topics related to data visualization, visit Nightingale, The Journal of the Data Visualization Society (https://medium.com/nightingale).

News from the Journal of PK and PD

The August issue of the Journal is a themed issue entitled The Role of Pharmacometrics in Dosing During Pregnancy and Lactation. This themed issue is co-edited by Sara K. Quinney from Indiana University and Peter Bonate from Astellas. This issue contains the following articles:

- A pharmacometrician’s role in enhancing medication use in pregnancy and lactation: S.K. Quinney & P.L. Bonate
- Challenges in conducting clinical research studies in pregnant women: M. McKiever, H. Frey, and M.M. Costantine
- Clinical lactation studies and the role of pharmacokinetic modeling and simulation in predicting drug exposures in breastfed infants: P.O. Anderson & J.D. Momper
- Enabling pregnant women and their physicians to make informed medication decisions using artificial intelligence: L. Davidson & M.R. Boland
- Integration of physiological changes during the postpartum period into a PBPK framework and prediction of amoxicillin disposition before and shortly after delivery: A. Dallmann, A. Himstedt, J. Solodenko, I. Ince, G. Hempel, and T. Eissing
- Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy: K. Abduljalil, A. Pansari, and M. Jamei

The editors would like to thank all the contributors for making this issue a success.
How Does the Pipe Operator Actually Work?

By Thomas Neitmann

This is a new column for the newsletter. WhateveR will discuss R topics, programming tips, and other items of interest related to R. This column was originally published by Thomas Neitmann on his website (thomasadventure.blog) on 15 June 2020. Thomas has graciously agreed for ISoP to republish the post in its entirety. Thank you, Thomas! Please visit his blog.

Note that all R code is in courier font.

I think it’s fair to say that the pipe operator %>% from the {magrittr} package—made famous by its use in {dplyr}—revolutionized R. Using %>% you can chain together multiple functions to create pipelines for your data. That way you can write highly expressive code and mitigate the need to define intermediate variables for each step of your data processing. But how does %>% actually work? If you think about it, %>% does something quite astonishing: it applies the function on its right to the expression of its left. Achieving this is not really straightforward which is why I decided to write this post.

Before I start, though, a word of caution and a disclaimer. First, I will cover some advanced R in this post. If you are new to R then this probably isn’t for you. Second, in this post I will not look at the actual code of %>% as defined in {magrittr}. Why? Because {magrittr} does some fancy stuff to take care of edge cases that blur the essence of what %>% is all about. Instead I will use this minimal definition of %>% which really captures the essence of this operator and can replace the ‘real’ pipe operator in probably more than 95% of cases. Without further ado, here it is:

```
`%>%` <- function(lhs, rhs) {
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <- c(
    rhs[[1L]],
    lhs,
    as.list(rhs[-1L])
  )
  call <- as.call(building_blocks)
  eval(call, envir = parent.frame())
}
```

Take a deep breath. I understand that this might look frightening. But don’t worry, I will walk you through it step-by-step.

Let’s start with the very first line. lhs is short for left-hand side and rhs—as you might guess—stands for right-hand side. So, %>% is defined as a function of something to its left and something to its right. If you’ve ever used %>% this should make sense. But isn’t %>% an operator rather than a function? Yes and no. %>% is an operator but it also is a function. In fact, every operator in R be it *, + or %*% is a function. That’s why you can use %>% like any other function, e.g.

```
`%>%`("This actually works!",
  print())
[1] "This actually works!"

"Just like this!" %>% print()
[1] "Just like this!"
```

Granted this defies the purpose of %>% but just so you know.

Next, let’s move on to the function body, i.e. the code between { and }. What does substitute() do? Usually, if you pass an argument to a function it is evaluated.

```
identity <- function(x) {
  x
}
```

```
y <- 1
identity(y)
[1] 1

identity(mean(1:10))
[1] 5.5
```

Using substitute() you can infer the actual expression that was passed to an argument. Put differently, you bypass evaluating the expression but instead quote it.

```
identity2 <- function(x) {
  substitute(x)
}
```

```
identity2(y)
y
identity2(mean(1:10))
mean(1:10)
```

Why is this useful? Because you can actually modify this quoted expression which is exactly what %>% needs to do. Let’s move on to line 3 of %>% to see what I mean.
How Does the Pipe Operator Actually Work (Continued)?

```r
`%>%` <- function(lhs, rhs) {
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <- c(
    rhs[[1L]],
    lhs,
    as.list(rhs[-1L])
  )
  building_blocks
}

mtcars %>% subset(cyl == 4,
  select = c(hp, cyl))
```

This looks interesting. Apparently you can subset a quoted expression like a list using `[[`. When you have a quoted expression `expr` that involves a function, `expr[[1L]]` will get you the name of the function and `expr[-1L]` will get you the arguments of the function.

```r
expr <- identity2(mean(x = 1:10, na.rm = TRUE))

expr[[1L]]
mean
expr[-1L]
(1:10)(na.rm = TRUE)
```

But wait, `(1:10)(na.rm = TRUE)` looks almost like a function, doesn’t it? Indeed. R will always interpret the first element in a quoted expression as a function. To circumvent this I used `as.list()`.

```r
as.list(expr[-1L])
$x
1:10
$na.rm
[1] TRUE
```

Going back to the current definition of `%>%` we actually already have all we need.

```r
mtcars %>% subset(cyl == 4,
  select = c(hp, cyl))
```

The first element in the list is the function on the right-hand side that should be applied to the left-hand side. The left-hand side appears second in this list, i.e. as the first argument of rhs, just as needed. The next elements are the remaining argument to rhs in the order initially specified.

A list is not what we need, though. We somehow have to turn this list into a function call. This is where `as.call()` comes into play.

```r
`%>%` <- function(lhs, rhs) {
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <- c(
    rhs[[1L]],
    lhs,
    as.list(rhs[-1L])
  )
  call <- as.call(building_blocks)
  call
}

mtcars %>% subset(cyl == 4,
  select = c(hp, cyl))
```

At this point `%>%` returns the code we want to run. But this code is still quoted and not evaluated yet. We can manually run it using the `eval()` function.

```r
code <- mtcars %>%
  subset(cyl == 4,
    select = c(hp, cyl))

eval(code)
```

```
hp  cyl
Datsun 710  93 4
Merc 240D  62 4
Merc 230  95 4
Fiat 128  66 4
Honda Civic 52 4
Toyota Corolla 65 4
Toyota Corona 97 4
Fiat X1-9  66 4
Porsche 914-2 91 4
Lotus Europa 113 4
Volvo 142E 109 4
```

But that’s obviously cumbersome. Instead we will evaluate the quoted expression directly inside `%>%`.

```r
`%>%` <- function(lhs, rhs) {
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <-
    c(rhs[[1L]], lhs, as.list(rhs[-1L]))
  call <- as.call(building_blocks)
  eval(call)
}
```

This looks interesting. Apparently you can subset a quoted expression like a list using `[[`. When you have a quoted expression `expr` that involves a function, `expr[[1L]]` will get you the name of the function and `expr[-1L]` will get you the arguments of the function.

```
expr <- identity2(mean(x = 1:10, na.rm = TRUE))

expr[[1L]]
mean
expr[-1L]
(1:10)(na.rm = TRUE)
```

But wait, `(1:10)(na.rm = TRUE)` looks almost like a function, doesn’t it? Indeed. R will always interpret the first element in a quoted expression as a function. To circumvent this I used `as.list()`.

```
as.list(expr[-1L])
$x
1:10
$na.rm
[1] TRUE
```

Going back to the current definition of `%>%` we actually already have all we need.

```
mtcars %>% subset(cyl == 4,
  select = c(hp, cyl))
```
How Does the Pipe Operator Actually Work (Continued)?

If you've paid close attention to the definition of `%>%` I displayed in the beginning of this post, you will realize that this one here is a bit different. Let's try to run it.

```r
mtcars %>% subset(cyl == 4,
                   select = c(hp, cyl))
```

hp
cyl
Datsun 710 93 4
Merc 240D 62 4
Merc 230 95 4
Fiat 128 66 4
Honda Civic 52 4
Toyota Corolla 65 4
Toyota Corona 97 4
Fiat X1-9 66 4
Porsche 914-2 91 4
Lotus Europa 113 4
Volvo 142E 109 4

This seems to work just fine. However, let me make a little change to make you aware of a subtle bug in this function.

```r`
`%>%` `<- function(lhs, rhs) {
  mtcars <- NULL
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <-
    c(rhs[[1L]], lhs, as.list(rhs[-1L]))
  call <- as.call(building_blocks)
  eval(call, envir = parent.frame())
}
mtcars %>% subset(cyl == 4,
                   select = c(hp, cyl))
```

Error in subset.default(mtcars, cyl == 4, select = c(hp, cyl)): object 'cyl' not found

By default, eval() looks for the variables inside the expression given to it in the current environment. In this case that’s the environment of `%>%`. Only if the variable is not defined in the current environment it will go up one environment and look in the environment where the function was called. In this case that’s the global environment. Since I defined mtcars locally it will never look in the global environment, though. If you think about it, if we use the `%>%` operator in the global environment it should always start to look there not inside its own environment. To do so, I will make a little change to the definition of `%>%`.

```r`
`%>%` `<- function(lhs, rhs) {
  mtcars <- NULL
  lhs <- substitute(lhs)
  rhs <- substitute(rhs)
  building_blocks <-
    c(rhs[[1L]], lhs, as.list(rhs[-1L]))
  call <- as.call(building_blocks)
  eval(call, envir = parent.frame())
}
```

As stated initially, this is not the same as `%>%` in `{magrittr}`. The following code would work with the real `%>%` but doesn’t with the definition I presented here.

```r
"error_message" %>%
  gsub(pattern = "_*", replacement = " ", x = .)
```

Error in gsub("error_message", pattern = "_*", replacement = " ", x = .): object '.' not found

For `{magrittr}`’s `%>%`, . is a special symbol that acts as a placeholder for lhs. This is useful when a function takes the data not as its first argument as is the case with gsub(). The pipe I wrote in this post is not that ‘smart’ and always places its lhs as the first argument of rhs. Nevertheless, the `%>%` presented here is functional. `{dplyr}` could use this pipe operator and everything would work just fine. In fact, the `{poorman}` package—a base R clone of `{dplyr}`—uses more-or-less this definition for `%>%`.

If you have any questions please ask them in the comments [section of the blog]. I did my best to explain the concepts I presented in an understandable way but I’m sure my explanations lack in some points. And don’t be shy. Certainly someone else has the same question as you and will benefit from you asking it (and me providing a hopefully helpful answer).
News from CPT: PSP

CPT: Pharmacometrics & Systems Pharmacology: New research Collections on Pregnancy, COVID-19, or Oncology, and call for a SxP Issue

CPT: Pharmacometrics & Systems Pharmacology (PSP) has gathered published research articles from PSP on pregnancy into one new virtual collection launched in August 2020, available here.

PSP has gathered published research articles from PSP on pregnancy into one new virtual collection launched in August 2020, available here.

Since 2012, the journal has published more than a dozen articles describing the development and application of pharmacometrics and physiologically-based pharmacokinetic (PBPK) models for pregnant and lactating women. Contributed by a full range of researchers in academic, industry, and regulatory agencies, these works seek to address the historical, cultural, and regulatory barriers that contribute to the imbalance between the high prevalence of medication used by pregnant and lactating women and the scarcity/absence of clinical information on the effectiveness and safety of medications in these populations.

Recognizing the role that clinical pharmacology and translational science will play in combating the COVID-19 pandemic, all research published in PSP as has been gathered here. The joint virtual issue will continue to be updated as new papers on repurposing existing (approved) drugs to treat the virus in the short-term, the development of vaccines, and the discovery of new mechanisms of action and development novel drugs are accepted.

ASCPT’s family of journals has also launched joint-journal virtual issues that give readers access to published works on COVID-19 and oncology.

PSP publications on Oncology are gathered in the new joint virtual issue Oncology Innovations. This virtual issue provides a tour of select innovations in precision medicine, model-informed drug discovery and development frameworks, and the evolving clinical trial and regulatory landscape that nurture patient-focused oncology research. It also includes papers focusing on evolving clinical trials and the regulatory landscape.

Also of note, PSP has issued a Call for Papers to be published in a “Statistics and Pharmacometrics” themed issue launching in March 2021. The issue will focus on the intersection of statistical modeling, decision-making, and pharmacometrics and provide multi-stakeholder perspectives on topics of interest to statisticians and pharmacometricians building models to support decision-making in drug development and patient care. To be considered for publication in this high-profile themed issue, manuscripts should be submitted via the online submission and tracking system by November 15, 2020.

CPT: Pharmacometrics & Systems Pharmacology (PSP) has been accepted into Clarivate Analytics’ SCIE (Science Citation Index Expanded) and will receive its first Impact Factor in June 2021!

Please consider submitting your new, exciting research results on any of these topics to PSP!
Pharmacometrics and Covid-19 Modeling: Quo Vadis?
By France Mentre and Jeremie Guedj

The Covid-19 crisis has put modelers under unprecedented spotlights. This is particularly true for computational epidemiologists, who played a major role by advising governments to take radical decisions such as national lockdowns to preserve hospital capabilities. This also applies to pharmacometricians, for which the Covid-19 represents a “defining moment” to quote Piet van der Graaf. Nine months after the beginning of this crisis, what can we say about the role of pharmacometrics to rationalize and accelerate drug therapy?

Until now most clinical studies have focused on repurposed (i.e., already existing) drugs. In these times where decisions need to be done extremely rapidly, the temptation for investigators has often been to align on dosing regimens used in other indications. Yet, repurposed drugs have most often a lower antiviral activity against SARS-CoV-2 than against the virus they were originally designed for, and moreover do not necessarily have an advantageous pharmacokinetic profile in the respiratory tract, where most of the virus replicates. Consequently, many clinical pharmacologists and pharmacometricians have alerted on the risks to use drug dosing regimens that were unlikely to generate sufficient (if any…) exposure (non-exhaustively, lopinavir, hydroxychloroquine, ivermectine). Yet, at this day, the need to take rapid decisions (and the force of the conformism?) have led to ignoring many of these calls.

Relying on the in vitro antiviral activity and the pharmacokinetics of the drug is nonetheless not sufficient to anticipate its clinical efficacy. Exactly like public health intervention, one paradigm of antiviral treatment is to “flatten the viral curve” to avoid excessive cell damage, which in turn may decrease the risk of hyperinflammation and “cytokine storm”. This can be studied by models of viral dynamics. Because antiviral drugs typically block viral production or de novo cell infection, their effects are much more dramatic when they are given before all susceptible cells are infected (i.e., before peak viremia). However, an important feature of COVID-19 is that the peak of infection coincides with symptom onset. Therefore, many patients enrolled in clinical trials initiate treatment several days after the “window of opportunity”, when the viral load is already naturally declining.

With the progressive release of clinical trial data there will be a need for models that can capture the genuine impact of drugs on disease progression and propose better dosing regimens or relevant combinations. But it is also the time to show that models can go beyond the “one size fits all”, and to promote strategies that account for the clinical condition (outpatient/hospitalized), the characteristics at inclusion (age, co-morbidities, duration of symptoms) and the viral dynamics after initiation. Such strategies are not unfamiliar to infectious disease specialists, who use similar approaches in their management of patients with acute or chronic viral infections. We also know that clearing virus will not be sufficient to save severe patients, for which the viral “component” of the disease probably no longer plays a major role in disease progression. We therefore need systems pharmacology approaches to capture the complex interactions leading to dysregulation of the immune response, propose methods to evaluate the efficacy of immune-modulating agents and suggest relevant biomarkers.

We can hope that this crisis will see new ways of disseminating modeling predictions outside the community. Several initiatives have been made to share tools to visualize the effects of dosing regimens on drug pharmacokinetic and viral kinetics, and help clinicians or pharmacometricians that are not familiar with infectious disease modeling.

Modelers can also contribute by leveraging data from multiple sources, and models of meta-analyses can be a way to overcome the problem of multiple small studies and gain more insights on drug efficacy. But the most important is that academic researchers get out of their comfort zone. This crisis will not be a sprint, but a marathon in which just digesting the information and the data released on a daily basis is a Herculean task. More than ever, academic modelers need to share their work and their ideas and to trust each other. This holds at all times but is an absolute necessity during this crisis to avoid premature findings, redundancies and bring enough information such that reliable conclusions can be achieved.

Non-exhaustive reading list on pharmacometrics in Covid-19:

ISoP Logo Usage Policy

As a reminder to our members, we would like to re-post our logo usage policy.

The International Society of Pharmacometrics has copyrights and service mark registrations on its logo and the logo of the American Conference on Pharmacometrics, as well as use of “ISoP” and “ACoP,” the recognized abbreviations thereof, and regulates their use under the following guidelines:

Only the approved versions of the ISoP and ACoP logos (the latter with or without a numeric badge denoting meeting number) may be used.

The logos may not be distorted or altered in any way.

Logos must be used in their entirety; with the exception of affiliated Special Interest Groups (SIGs), Committees, and Communities, neither whole nor recognizable parts may be incorporated into another logo.

Logos must be printed in their original colors, or as greyscale versions: No other color combinations are allowed.

Active ISoP SIGs, committees, communities, local events and other groups affiliated to ISoP or ACoP are encouraged to use the logos, as long as guidelines are adhered to. Approved, high-resolution logos are available for download here.

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Logos may not be used in conjunction with claims that products conform to ISoP or ACoP standards.

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Requests to use any version of the ISoP or ACoP logos and for all new collateral images must be made in writing and directed to Enrico Smith (by email at admin@go-isop.org, or by post at Enrico Smith, International Society of Pharmacometrics, 1200 Rt 22E Suite 2000, Bridgewater, NJ 08807, USA).

Our logo usage policy is posted on the ISoP Website (http://go-isop.org/logo-usage-policies/).
Communication Corner
By Peter Bonate

Boundaries

Now more than ever, with most of us working from home, the line between our home life and work life is blurred. We juggle our work deadlines, teach our children, and still try to maintain some semblance of pre-COVID normality. But even before all this happened the line between work and home was already blurred. We are in touch with the office at all hours of the day, answering emails late at night, we have early morning and late evening meetings, and even answer emails while on vacation. In the United States more than half of Americans do not use all of their paid vacation time and I would hazard to guess that this year number will be higher. Is it any wonder then why most people are more stressed than ever?

One thing that I have been telling my employees over the years is that they need to set boundaries. I have started to write in big letters on their whiteboards “BOUNDARIES” to remind them of this – they are not their job. Setting boundaries is important psychologically because it defines within you where work ends, and you begin. There is an adage about “do you work to live, or do you live to work?” As our work-life boundaries become more and more blurred, we shift from working to live towards living to work. Now more than ever it is important for us to know where that line in the sand? Where is that boundary?

Setting boundaries is not just the responsibility of an employee; it’s also the responsibility of the company and the manager. I know from personal experience that some of my Japanese colleagues must never sleep because it doesn’t matter what time I send them an email, they promptly reply. Sending emails after-hours sends the message that you expect others around you to do the same, particularly if you are the manager.

Some companies, like Atos in France and Volkswagen in Germany, have taken the drastic step to turn off email servers after hours, or to delete all emails an employee receives while they are on holiday (Daimler, also in Germany). While this may work at companies that are predominantly in one geographic location, it may not work at companies that work in many countries. Nevertheless, if you have employees answering emails at 10 pm at night or on a Sunday afternoon when they should be enjoying their day off, you may want to see what is so important that they are doing that. That is something every manager can do.

What can you as an employee do to set boundaries? The first step is to know where your boundaries lie. Think about and set where your boundaries are. Maybe you are not going to answer emails on the weekend, calls after hours, or both while you are on holiday. Once you know where your line in the sand is, then you need to communicate this to your colleagues or clients. You can do this by setting up automatic messages, or by setting your office hours in your email signature line. Something like “I will be unavailable between 8 pm and 8 am CST to answering emails” clearly communicates your work hours.

Sometimes you will find that someone sends you an email in your dead zone hours and the next day says something snarky like “I tried to reach you last night, but you weren’t returning calls.” You can defuse this by calmly explaining that you are trying to be better about your work-life balance and that you are turning off all electronics between those hours. You will be surprised how many people say something like “That’s a good idea. I should do that.” Things get a little more tricky when it’s your boss that is calling or emailing. It helps to talk to your boss beforehand and set your working boundaries. That way if they do call, then you know it’s important, and you should respond. Of course, if you are really good, you are not checking your email or are turning off your phone to begin with.

In setting up your boundaries with your manager, conduct an audit and let them know how much time is spent working after hours. This often helps in justifying why you are wanting to set boundaries. If your boss refuses your request, perhaps it’s time to re-examine whether this place of employment is best for you. Fortunately, we work in a field where there are plenty of jobs to go around.

Now you may be asking yourself, if I don’t do this work after-hours how am I going to get it done during work hours? I am simply too busy. Stephen Covey published the 7 Habits of Highly Effective People. He talked about work quadrants setting up a 2 × 2 matrix with Urgent (yes/no) and Important (yes/no) as the marginals. You would be surprised how much time we spend on Quadrant IV: Not Urgent/Not Important. He recommends dropping Quadrant IV activities and focusing on Quadrant I activities. If you haven’t read that book yet, you should.

You are not always going to be able to keep your boundaries, nor should you. We all know there will be times when extra work is required, e.g., submission time. But is that extra work needed all the time? Rarely. Also recognize that setting boundaries is not going to make everyone happy. The heck with them. You can never make everyone happy, even if you work after-hours. You can only make yourself happy. Setting boundaries will make you happier and shows that you care about yourself. As a manager I respect people that set boundaries because it shows me that they know the importance of a good work-life balance and that lack of boundaries is a leading cause of burnout. So, do yourself a favor. Examine how you work, set your boundaries, and make your life happier.
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