Received: 29 March 2021 | Revised: 29 March 2021 | Accepted: 29 March 2021

DOI: 10.1002/psp4.12625

EDITORIAL

Welcome to the statistics and pharmacometrics themed issue

Pharmacometrics and Statistics have a long, common history, as many of the methods and software tools used in pharmacometrics were developed by statisticians from the theory of mixed effect models. However, the intersection between these two disciplines is still limited both in academia and in drug development.

In 2016, the "Statistics and Pharmacometrics" (SxP) special interest group (SIG) (https://community.amstat.org/sxp/home) was launched under the umbrella of both the American Statistical Association and the International Society of Pharmacometrics. Both Jonathan French (Associate Editor, *CPT: Pharmacometrics and Systems Pharmacology* [*CPT:PSP*]) and France Mentré (Editor-in-Chief, *CPT:PSP*) were members of the steering committee of this SIG at its launch, and Dr. Mentré was the co-chair in 2018 and 2019. The goal of the SIG is to promote collaboration between statisticians and pharmacometricians, enabling each discipline to learn and grow from interactions with each other and to develop innovative approaches to model-informed drug development.

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) family of journals has a rich history of themed issues. This issue marks the inaugural themed issue for *CPT:PSP*. Because of the close ties between Statistics and Pharmacometrics, it seemed fitting that the theme cover topics at the intersection of these two disciplines. Our goal is that *CPT:PSP* becomes the leading journal for the publication of original research articles, tutorials, and perspectives that enhance the interaction between pharmacometrics and statistical scientists as they promote model-informed drug development and use. To that end, this issue contains articles on a range of topics, including modeling effects of covariates, statistical power, handling missing and problematic data, modeling toolsets, and the relevance of estimands in pharmacometrics.

Understanding the factors driving interindividual variability in pharmacokinetics and pharmacodynamics is a goal of many population analyses. In this issue, Ayral et al.[1] present a novel stepwise covariate modeling method that makes use of the information contained in the model at one step to choose which parameter-covariate relationship to fit in the next. Hartung et al.[2] derive and evaluate nonparametric goodness-of-fit tests for parametric covariate models, transferring concepts from statistical learning to the pharmacological setting. Smania and Jonsson[3] compare methods for simulating baseline covariates for the purpose of clinical trial simulation and advocate for using a flexible method based on conditional distributions.

A traditional area where statisticians play a role is in power and sample size calculations. Two articles demonstrate that pharmacometric methods can contribute substantially to this field. Chen et al.[4] analyze data from clinical trials to treat Parkinson's disease, comparing item-response theory (IRT) models to more traditional longitudinal models for a total score derived from the items. They demonstrate that IRT models make better use of the data and are able to detect drug effects with markedly reduced sample sizes. Couffignal et al.[5] demonstrate the power of using crossover studies to detect a treatment effect in the presence of a gene-treatment interaction.

Two articles touch on the theme of missing data. In their Tutorial, Irby et al.[6] provide a literature review and guidance for dealing with missing or erroneous pharmacokinetic data, focusing on issues with concentration versus time, dosing, and covariate data. Jaber et al.[7] provide a perspective on evaluating models using weighted residuals when the data include censored observations.

In recent years, one of the most discussed statistical concepts in clinical trials is the concept of estimands and the importance of clearly distinguishing between the scientific question and the modeling approach. Akacha et al.[8] provide an introduction to estimands in the context of clinical drug development and share their perspective on why estimands are helpful for the practicing pharmacometrician. Lastly, Fidler et al.[9] describe the benefits of statisticians and pharmacometricians using a common tool, such as R, enabling us all to "speak the same language."

We would also like to take this opportunity to recognize three scientists whose work was fundamental to both statistics and pharmacometrics: George Box, Nan Laird, and Lew Sheiner. Although professors Box and Sheiner are well known to the readers of *CPT:PSP*, Professor Laird may not

be. She is the Harvey V. Fineberg Professor of Biostatistics (Emerita) in the Harvard School of Public Health. Dr. Laird received the 2021 International Prize in Statistics in recognition of "her work on powerful methods that have made possible the analysis of complex longitudinal studies." Her two pioneering articles on the expectation-maximization algorithm[10] and analysis of longitudinal data[11] are foundational for the statistical modeling of pharmacometric data. Finally, we would be remiss if we did not take the time to thank the reviewers, whose thoughtful and timely comments on the articles included in this issue were invaluable.

Jonathan French[1]
France Mentré[2]

[1]*Metrum Research Group, Tariffville, Connecticut, USA*
[2]*Université de Paris, INSERM, IAME, Paris, France*

Correspondence
Jonathan French, Metrum Research Group, Tariffville, Connecticut, USA.
Email: jonathanf@metrumrg.com

REFERENCES

1. Ayral G, Si Abdallah J-F, Magnard C, Chauvin J. A novel method based on unbiased correlations tests for covariate selection in nonlinear mixed effects models–the COSSAC approach. *CPT: Pharm Syst Pharmacol*. 2021;10:318-329.
2. Hartung N, Wahl M, Rastogi A, Huisinga W. Nonparametric goodness-of-fit testing for parametric covariate models in pharmacometric analyses. *CPT: Pharm Syst Pharmacol*. 021 Mar 23. https://doi.org/10.1002/psp4.12614. Online ahead of print.
3. Smania G, Jonsson EN. Conditional distribution modeling as an alternative method for covariates simulation: comparison with joint multivariate normal and bootstrap techniques. *CPT: Pharm Syst Pharmacol*. 2021;10:330-339.
4. Chen C, Jönsson S, Yang S, Plan EL, Karlsson MO. Detecting placebo and drug effects on Parkinson's disease symptoms by longitudinal item-score models. *CPT Pharm Syst Pharmacol.* 2021;10:309-317.
5. Couffignal C, Mentré F, Bertrand J. Impact of study design and statistical model in pharmacogenetic studies with gene-treatment interaction. *CPT Pharm Syst Pharmacol.* 2021;10:340-349.
6. Irby DJ, Ibrahim ME, Dauki AM, et al. Approaches to handling missing or "problematic" pharmacology data: Pharmacokinetics. *CPT: Pharm Syst Pharmacol* 2021;10:291-308.
7. Jaber MM, Cheng S, Brundage RC. Evaluation of bias in weighted residual calculations when handling BLQ data using Beal's M3 method. *CPT Pharm Syst Pharmacol.* 2021;10:275-278.
8. Akacha M, Bartels C, Bornkamp B, et al. Estimands–what they are and why they are important for pharmacometricians. *CPT Pharmacometrics Syst Pharmacol.* 2021;10:279-282.
9. Fidler M, Hooijmaijers R, Schoemaker R, Wilkins JJ, Xiong Y, Wang W. R and nlmixr as a gateway between statistics and pharmacometrics. *CPT Pharmacometrics Syst Pharmacol.* 2021;10:283-285.
10. Dempster A, Laird N, Rubin D. Maximum likelihood from incomplete data via the EM algorithm. *J R Stat Soc Series B*. 1977;39(1):1-38.
11. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.