Primary Focus: General Pharmacometrics **Session Format:** Tutorials: 180 mins

Tutorial Title:

Know a Good Model When You See It, See a Good Model When you Find It: Effective Visualizations for Developing and Qualifying popPK/PKPD, MBMA, and other Pharmacometric Models.

Chairs: Jeffrey R. Sachs and Jos Lommerse

Session Description:
The proposed workshop will provide background and novel techniques (along with R code), enabling three essential pharmacometric tasks:

1. Identification of a model and its covariates,
2. Visualization of models with complex covariate structures, and
3. Visual checks of model quality.

It will provide sufficient background to allow novice participants (with experience in R) to benefit yet contains sufficient new material for more advanced users. It will also help advance the field by providing opportunities specifically aimed at encouraging debate about how to build and check the trustworthiness (i.e. utility) of a model.

The workshop will focus on the application of novel visualization methods. Session 1 will review modeling of subject- and summary-level data (popPK/PKPD and MBMA, resp.) and the importance of visualization in identifying and qualifying models. Sessions 2 and 3 will cover V^2ACHER and V^3PC (respectively)*. These methods harmonize models, data and covariates, enabling intuitive and effective interpretation of model results and quality. Session 4 will allow participants to get support on applying the methods to their own examples (or more advanced examples that we will supply), and will give an overview and examples of VACHETTE (a newer, not-yet-published extension of V^2ACHER), a method enabling the same capabilities for time-dependent (e.g. compartmental, QSP, or other ODE-based) models.

In order to have time for both background and practice, the proposed workshop will be run as four sessions of 45 minutes each. In Sessions 1-3, participants will run each step hands-on on the provided practice examples using partially completed code templates. Session 1 will start the hands-on work with a simple example, Sessions 2 and 3 will build on that example. This will ensure that the steps in the process are clear, and that participants can successfully complete a realistic example end-to-end during the workshop. Installation requirements and optional preparation of participants' problems will be shared prior to the workshop along with required input data formats for software other than nlme R package. Training material will be made available after the workshop.

Learning Objectives:

1. Awareness of differences between subject- and summary-level analyses and the role of intuitive visualizations in efficient and effective model building;
2. How to create effective visualizations using standard open-source code (based on output from CRAN packages like nlme or other software such as NONMEM);
3. How to use V^2ACHER visualizations to more rapidly and easily gain insight by harmonizing model and data plotting across covariate groups/values;
4. Basics of the tidyvpc R package (on CRAN), and the V^2ACHER code (to be provided) to help identify appropriate models and visualize the consistency and reliability of predictions that include covariates;
5. Advantages and disadvantages of VPC, pcVPC, and V^3PC diagnostic plots;
6. Introduction to VACHETTE (next generation of V^2ACHER) to ODE-based and other more complex models;
7. How to apply the methodology to the participants' own models; and,
8. How to use these intuitive visualizations to increase impact through improved communication with non-modelers.

* Lommerse, J, Plock, N, Cheung, SYA, Sachs, JR. V^2ACHER: Visualization of complex trial data in pharmacometric analyses with covariates. CPT Pharmacometrics Syst Pharmacol. 2021; 10: 1092– 1106. https://doi.org/10.1002/psp4.12679

Session 1 Speakers: Nathan Teuscher and S. Y. Amy Cheung

Refresher on Non-Linear Mixed Effect Models (NLME) Development and Considerations: Basics of Base and Covariate Models for Subject- and Summary-Level Data

Non-Linear Mixed-Effect (NLME) modeling is the standard pharmacometrics approach to support decision making in R&D. In this session we will review the basics of NLME software and model development including NONMEM and nlme in R. We will re-enforce the need to understand the key questions, underlying pharmacology, pharmacokinetic processes, and assays that provide the data. We will then focus on the key concepts of model development and incorporation of covariates to explain observed variability. This session will include hands-on practice in R with a provided example.

Session 2 Speakers: Jeffrey R. Sachs and Jos Lommerse

V^2ACHER for Intuitive, Clear Visual Overlay of Data for MBMA or Other NLME Models

The application of the novel visualization method V^2ACHER* will be presented using examples with increasing complexity, from simple single-covariate exposure-response models up to more complicated, multi-covariate models. Comparison of various traditional visualization techniques will be compared against V^2ACHER visualization and pros and cons will be discussed. V^2ACHER visualization examples will be implemented in R. Several simple examples will be prepared so that participants can implement V^2ACHER in template code to visualize with and without V^2ACHER scaling of observations and simulations. This session will include hands-on practice with a provided example building on the example from Session 1.

Session 3 Speaker: Nele Mueller-Plock

Knowing Quality and Qualifying Knowing: VPC, pcVPC, and V3PC

In this section we give an overview of basic diagnostic plots and their advantages and disadvantages under various conditions. The focus will be on assessing differences between standard visual predictive check (VPC) and how modifications of this method (pcVPC, V^3PC) can help interpreting results when confronted with sparse data along with models including covariate relationships. We will show that pcVPC – while already improving on many aspects compared to VPC – may be limited by binning across important covariates. We will introduce how V^3PC can lessen this limitation by scaling observed and simulated data to a selected reference curve prior to plotting. Differences between the diagnostic tools will be demonstrated and practiced using an example with subject-level data. This session will include hands-on practice with a provided example building on the example from Session 2.

Session 4 Speakers: Jos Lommerse and Anna Largajolli

Advanced Examples and Consultation on Examples Provided by Participants

Advanced examples discussed here will include applications of VACHETTE (a newer, not-yet-published extension of V^2ACHER), a method enabling the same capabilities for time-dependent (e.g. compartmental, QSP, or other ODE-based) models.

Participants will have the option of using their own data at all stages of this workshop; this will be an opportunity for hands-on exploration of their specific examples with help from the experts. Users can bring their own anonymized/non-proprietary examples (of E_{max} or other static models for V^2ACHER, or other models for discussion).