Project: Comparison of uncertainty methods in pharmacokinetic and pharmacodynamic modeling

Xiaomei Chen, Andrew C. Hooker

Background: Pharmacometrics[1] is an emerging science that combines statistics models and biology-based mechanistic or semi-mechanistic models to describe the movement of drugs through the body (pharmacokinetics, PK)[2] and body's biological response to drugs (pharmacodynamics, PD)[3]. Simply put, PK studies what the body does to the drug and PD studies what the drug does to the body. Both aspects play an important role during drug development and regulatory evaluation. Pharmacometric analysis commonly utilizes nonlinear mixed-effect (NLME) models (population models) to describe the PK and/or PD, which allows for effective data analysis of clinical trials, realistic clinical trial simulations and improved decision making. During pharmacometric modeling, assessment of uncertainty of model parameters (i.e. precision of parameter estimates) is a critical part of the process since evaluated uncertainty is utilized in a variety of aspects, including model selection, inference tests, power calculations, clinical trial simulation, etc. There are several ways to calculate model uncertainty including (1) a sandwich variance estimator; (2) the observed fisher information matrix; (3) a cross-product gradient matrix; (4) a parametric or non-parametric bootstrap; (5) sampling importance resampling; (6) Bayesian posterior distributions; etc. Although these different uncertainty methods have been widely studied in other types of statistical models, few publications have reported their performance in the setting of PKPD using NLME modeling.

The aims of the proposed project are:

(1) Literature search on the performance of different uncertainty methods;
(2) To compare different uncertainty methods through a simulated PK analysis;
(3) To compare the results from several uncertainty methods based on analysis of a series of real-life PK or PK/PD data;
(4) Write a project report summarizing the study results.

Prerequisite:

(1) Students are expected to have a good understanding of linear algebra
(2) The software that will be used during the project are: (no experience required)
    a. NONMEM (a tool for NLME modeling of PKPD data)
    b. R

The project will be co-supervised by

- Andrew C. Hooker, professor in Pharmacometrics Group, Dept of Pharmacy, UU. andrew.hooker@farmaci.uu.se
- Xiaomei Chen, postdoc in in Pharmacometrics Group, Dept of Pharmacy, UU. Xiaomei.chen@farmaci.uu.se

References

(1) Mould, D. R.; Upton, R. N. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. *CPT Pharmacometrics Syst Pharmacol* **2012**, *1*, e6. https://doi.org/10.1038/psp.2012.4.

(2) Mould, D. R.; Upton, R. N. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development-Part 2: Introduction to Pharmacokinetic Modeling Methods. *CPT Pharmacometrics Syst Pharmacol* **2013**, *2*, e38. https://doi.org/10.1038/psp.2013.14.

(3) Upton, R. N.; Mould, D. R. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3-Introduction to Pharmacodynamic Modeling Methods. *CPT Pharmacometrics Syst Pharmacol* **2014**, *3*, e88. https://doi.org/10.1038/psp.2013.71.