Advanced Designs for Dose-Time-Response Models

Ludger Sandig, Markus Lange, Jörg Rahnenführer, Katja Ickstadt

Dose-Time-Response Models are a flexible tool for modeling longitudinal observations, for example in dose-finding clinical trials. They are based on pharmacokinetic modeling ideas for an unobserved time-changing drug concentration which is mapped empirically to observable responses. These mathematical building blocks can be flexibly combined to model a variety of dosing regimens.

From the perspective of experimental design, a set of doses and a set of observation time points has to be selected. Previous results exist for selecting optimal single observation times for a given dose, as well as for selecting optimal doses for given observation times [1, 2]. Here, Bayesian D-optimal designs perform well while being more robust than locally D-optimal designs.

We extend these results by numerically investigating the following modifications:

1. Designs with dose-specific optimal observation intervals. A dose D is administered at time $t = 0$, and J observations are taken at $t = 0, \Delta t, 2\Delta t, ..., (J-1)\Delta t$. The design variables are D and Δt, i.e. an optimal design consists of a collection of pairs $\{(D, \Delta t)_k : k = 1, ...K\}$ and associated weights $w_1, ..., w_K$.

2. Designs for two-dose treatment regimens. A first dose D_1 is administered at $t = 0$, and a second dose D_2 at $t = \tau$. The design variables are D_1, D_2, and τ. Observation times are considered as fixed.

3. Two-stage adaptive designs accommodating interim posterior uncertainty. When observations are taken sequentially from two cohorts of subjects, the information-theoretic interpretation of Bayesian design naturally suggests an objective function for updating the design for the second cohort based on an interim analysis of the observations from the first.

Our simulations show that these strategies can, in some scenarios, greatly outperform the previously published designs.

References

[1] Holger Dette, Andrey Pepelyshev, and Weng K. Wong. *Optimal designs for composed models in pharmacokinetic-pharmacodynamic experiments*. Discussion Paper. Technische Universität Dortmund, 2009. DOI: 10.17877/DE290R-810.

[2] Markus R. Lange and Heinz Schmidli. "Optimal Design of Clinical Trials With Biologics Using Dose-Time-Response Models". In: *Statistics in Medicine* 33.30 (2014), pp. 5249–5264. DOI: 10.1002/sim.6299.