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Optimal sampling times for pharmacokinetic modelling of a cocktail of phenotyping drugs

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"Cocktail" of drugs is of high interest to determine enzyme activity responsible for drug metabolism and pharmacokinetics. Phenotyping indexes can be derived from a few samples using nonlinear mixed effect models (NLMEM) for analyzing drug concentrations and maximum a posteriori estimation (MAP) of individual parameters. We proposed an informative design common to two molecules for a phenotyping study: midazolam (probe for CYP3A activity) and digoxin (P-glycoprotein).

Using data of a previous study, NLMEM for midazolam, its 1-OH-metabolite and digoxin were developed in software MONOLIX4.2. Based on these models, we proposed a common design using a compound optimality criterion which is a weighted sum of log determinants of population Fisher information matrix (FIM) for each compound. The resulting design was evaluated for MAP and predicted shrinkages were reported, based on Bayesian FIM, using R function PFIM 4.0. Finally, sampling windows were computed around the optimal times, satisfying an expected joint loss of efficacy (evaluated by Monte-Carlo simulation) < 5%.

The common design was composed of six samples (0.25, 1, 2.5, 5, 12, 48h post-administration) instead of ten samples if considering separately each molecule. Predicted relative standard errors of derived phenotyping indexes were < 30%, with shrinkages < 50%. The sampling windows provided more flexibility while maintaining 95%-efficacy, compared to the optimal design.

By combining NLMEM, compound design and sampling windows based on FIM, we were able to determine sparse samples allowing correct estimation of parameters for three compounds. This approach can be extended to efficiently design studies with cocktails including more drugs.