Estimation of Population Pharmacokinetic Measures and Selection of Sampling Times

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ABSTRACT

Objectives: In many pharmaceutical studies multiple blood samples are taken for each enrolled patient, and various population pharmacokinetic (PK) measures, such as area under the curve (AUC), maximal concentration (Cmax) and time to maximal concentration (Tmax) are of interest. The objectives of this presentation are:

1. Comparison of a model-based approach, when a compartmental model is fitted and the explicit formulae for PK measures are used, and a nonparametric approach, when numerical integration is used for estimating AUC and sample values - for Cmax and Tmax. Since regulatory agencies usually require the model-independent estimation of PK measures, we focus on the nonparametric approach while using the model-based approach as a benchmark.
2. Recommendation of how to "split" a single sampling grid into two (or more) subsets which substantially reduces the number of samples taken for each patient but often has little effect on the precision of estimation in terms of mean squared error (MSE).
3. Introduction of costs, in particular costs of patient's enrollment and costs of analyzing samples, and comparison of sampling grids under cost constraints.

Methods: We exploit ideas from the earlier work on the selection of sampling schemes for parametric compartmental models which was based on optimal model-design methods; see [1-3]. Three types of population PK measures and methods of their estimation are introduced. The discussed methods involve calculating PK measures and averaging over the population yet differ in the order of the two operations; for details, see [4]. Special attention is given to a specific nonparametric method when one starts with averaging responses at each time point over all patients and then gets population estimates of PK measures for the "averaged" curve. This method is applicable in the case of sparse sampling which is often encountered in population PK studies.

Results/Conclusions: We present simulation results for nonlinear regression model generated by a one-compartment PK model, and closed-form solutions for the MSE of the empirical estimator of AUC for a simple quadratic regression model with random intercept.

1. When the model is correctly specified, the model-based approach outperforms the nonparametric one in terms of precision of PK measures' estimation, but often not by much.
2. Using split grids has little effect on the precision of estimation and has negligible effect on the bias term and terms associated with population variability for AUC estimation.

3. If costs of analyzing samples and costs of patient's enrollment are taken into account, then sampling schemes with split grids may become optimal.

References:

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