Numerical Investigation of the Number of Design Points in Bayesian D-optimal Designs in Respect to Prior Uncertainty

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ABSTRACT

We study the number of unique design points that appear in Bayesian optimal designs for pharmacokinetic models (PK), in respect to the level of prior uncertainty. We consider API and ED designs, in fixed and mixed effects PK models, using additive, proportional and combined error weighting schemes. In order to assess the number of points we used 2 and 3 parameter PK structural models and the Fisher information matrix published in (Retout and Mentre 2003, J Pharmacokinet Pharmacodyn 30:417). For optimisation we used a sequential quadratic programming (SQP) method and a Simulated Annealing algorithm and for sampling from the prior distribution we used Monte Carlo and Latin hypercube sampling methods. Bayesian optimal design methods (both API and ED) may produce more unique points than the number of model parameters, however, this does not happen always, and depends on a lot of factors. In respect to the magnitude of the uncertainty, for API with additive error, for both fixed and mixed effects, the extra points appear gradually as the uncertainty increases. A considerable region of small uncertainty gives results almost identical to the local design and each extra point appears abruptly after a critical value of the uncertainty like a bifurcation. Proportional error does not seem to give the same behaviour and time points do not split, while the behaviour with combined error depends on the relation between additive and proportional. For the ED criterion, the splitting of time points occurs for higher uncertainty, but for additive error in fixed effects does not occur at all. Also, if elementary designs with weights are used to account for the number of subjects for each design, these weights where not found to change a lot with uncertainty. In the context of the number of unique optimal design points, we will also attempt to stimulate discussion on equivalence theorem for mixed effects models.