Methods for adaptive optimal design using nonlinear mixed effect models.

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Many drugs exhibit major variability in both how a drug goes through a patient (the pharmacokinetics or PK) and what a drug does to a patient (the pharmacodynamics or PD), with variability occurring both between patients as well as within patients over time. Further, patients may experience shifts in body function or disease status over time causing changes in the PK and PD of a drug. Thus, in drugs with a narrow therapeutic range, dose selection may require individual adaptation both before and after drug administration. For example, Warfarin (the most widely prescribed anticoagulant for the prevention and treatment of thromboembolic events) is a highly effective treatment after thromboembolic events but is limited by a narrow therapeutic range combined with a large variation in the dose required to achieve that therapeutic target. Thus, an optimal dose that leads to a favourable balance between the wanted antithrombotic effect and the risk of bleeding must be found for each patient. In such cases, measurements of drug concentrations and/or disease biomarkers from patients as well as population nonlinear mixed-effect (pharmacometric) models can be valuable for dose individualisation. Through the use of these population pharmacometric models and patient observations one can use Bayesian forecasting to predict the PK and PD for a given dose of a drug, or to adjust and optimize the dose given to a patient. The accuracy of this Bayesian forecasting depends on the model used as well as the number of patient observations of a variable and when those observations occur.

This project proposes to investigate the use of Brownian motion terms in population pharmacometric models (PKPD models) to describe random parameter variation, parameter drift and change points in parameter values. We will then use these models to optimize the process of Bayesian forecasting in a number of example systems including Warfarin.