Population stochastic modelling (PSM)-An R package for mixed-effects models based on stochastic differential equations

The extension from ordinary to stochastic differential equations (SDEs) in pharmacokinetic and pharmacodynamic (PK/PD) modelling is an emerging field and has been motivated in a number of articles [N.R. Kristensen, H. Madsen, S.H. Ingwersen, Using stochastic differential equations for PK/PD model development, J. Pharmacokinet. Pharmacodyn. 32 (February(1)) (2005) 109-141; C.W. Tomoe, R.V Overgaard, H. Agero, H.A. Nielsen, H. Madsen, E.N. Jonsson, Stochastic differential equations in NONMEM: implementation, application, and comparison with ordinary differential equations, Pharm. Res. 22 (August(8)) (2005) 1247-1258; R.V. Overgaard, N. Jonsson, C.W. Tomoe, H. Madsen, Non-linear mixed-effects models with stochastic differential equations: implementation of an estimation algorithm, J. Pharmacokinet. Pharmacodyn. 32 (February(1)) (2005) 85-107; U. Picchini, S. Ditlevsen, A. De Gaetano, Maximum likelihood estimation of a time-inhomogeneous stochastic differential model of glucose dynamics, Math. Med. Biol. 25 (June(2)) (2008) 141-155]. PK/PD models are traditionally based ordinary differential equations (ODEs) with an observation link that incorporates noise. This state-space formulation only allows for observation noise and not for system noise. Extending to SDEs allows for a Wiener noise component in the system equations. This additional noise component enables handling of autocorrelated residuals originating from natural variation or systematic model error. Autocorrelated residuals are often partly ignored in PK/PD modelling although violating the hypothesis for many standard statistical tests. This article presents a package for the statistical program R that is able to handle SDEs in a mixed-effects setting. The estimation method implemented is the FOCE1 approximation to the population likelihood which is generated from the individual likelihoods that are approximated using the Extended Kalman Filter's one-step predictions.