Stochastic differential equations in NONMEM: implementation, application, and comparison with ordinary differential equations - DTU Orbit (14/08/2019)

Stochastic differential equations in NONMEM: implementation, application, and comparison with ordinary differential equations

Purpose. The objective of the present analysis was to explore the use of stochastic differential equations (SDEs) in population pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Methods. The intra-individual variability in nonlinear mixed-effects models based on SDEs is decomposed into two types of noise: a measurement and a system noise term. The measurement noise represents uncorrelated error due to, for example, assay error while the system noise accounts for structural misspecifications, approximations of the dynamical model, and true random physiological fluctuations. Since the system noise accounts for model misspecifications, the SDEs provide a diagnostic tool for model appropriateness. The focus of the article is on the implementation of the Extended Kalman Filter (EKF) in NONMEM for parameter estimation in SDE models.

Results. Various applications of SDEs in population PK/PD modeling are illustrated through a systematic model development example using clinical PK data of the gonadotropin releasing hormone (GnRH) antagonist degarelix. The dynamic noise estimates were used to track variations in model parameters and systematically build an absorption model for subcutaneously administered degarelix.

Conclusions. The EKF-based algorithm was successfully implemented in NONMEM for parameter estimation in population PK/PD models described by systems of SDEs. The example indicated that it was possible to pinpoint structural model deficiencies, and that valuable information may be obtained by tracking unexplained variations in parameters.

General information
Publication status: Published
Organisations: Department of Informatics and Mathematical Modeling, Mathematical Statistics
Contributors: Tornøe, C. W., Overgaard, R. V., Agerso, H., Nielsen, H. A., Madsen, H., Jonsson, E. N.
Pages: 1247-1258
Publication date: 2005
Peer-reviewed: Yes

Publication information
Journal: Pharmaceutical Research
Volume: 22
Issue number: 8
ISSN (Print): 0724-8741
Ratings:
Scopus rating (2005): SJR 1.233 SNIP 1.175
Web of Science (2005): Indexed yes
Original language: English
DOIs:
10.1007/s11095-005-5269-5
URLs:
http://www2.imm.dtu.dk/pubdb/p.php?4202
Source: orbit
Source-ID: 185637
Research output: Contribution to journal › Journal article – Annual report year: 2005 › Research › peer-review