

Nonlinear mixed effects model (NLMEM)

List of learning resources

Basic concepts of NLMEM

□ Introduction of NLMEM

Basic concepts in population modeling: part 1- overview. [Mould D R, CPT:PSP, 2012.](#)

Basic concepts in population modeling: part 2- PK modeling. [Mould D R, CPT:PSP, 2013.](#)

Basic concepts in population modeling: part 3- PD modeling. [Upton R N, CPT:PSP, 2014.](#)

□ Introduction of NONMEM system

NONMEM tutorial part 1: commands and options. [Bauer R J, CPT:PSP, 2019a.](#)

NONMEM tutorial part 2: estimation methods. [Bauer R J, CPT:PSP, 2019b.](#)

Get started with NLMEM

□ Pirana workbench for NONMEM

Tutorial on [Pirana](#). [Keizer R J, CPT:PSP, 2013.](#)

Pirana guides (...\\Pirana\\doc).

□ Aiding tools for NONMEM

Instructions for [Perl-speaks-NONMEM \(PsN\)](#): performing advanced M&S with NONMEM ([Introduction 1](#) and [Introduction 2](#))

Instructions for [Xpose 4](#): plotting and analyzing NONMEM output

Instructions for [xpose](#) ([ggplot2](#)-based): plotting and analyzing NONMEM output

□ How to develop a PopPK model: a case study with tobramycin

[Nonlinear Mixed Effects Models: Case Studies](#) (Data clean-up, model building, and model evaluation). Bonate P L, Springer, 2011.

[Tobramycin dataset](#) in NONMEM format (download the Datxplere project files)

□ Model diagnostics

Tutorial on metrics and graphics for NLMEM with continuous data. [Nguyen T H T, CPT:PSP, 2017.](#)

Guides and handbooks for NLMEM

Introductory handbook for NLMEM with a focus on NONMEM system. [Owen J S, John Wiley & Sons, 2014.](#)

NONMEM guides in pdf (...\\nm73g64\\guides).

NONMEM guides in html (...\\nm73g64\\html).

Leading handbook of the NLMEM theory for PKPD analysis. [Bonate P L, Springer, 2011.](#)

Handbook for the principles, applications and examples with NLMEM. [Ene I. Ette, John Wiley & Sons, 2007.](#)

Model evaluations (VPC and parameter uncertainty)

□ Visual predictive check (VPC)

Tutorials on VPC: [PAGE 17 \(2008\) Abstr 1434](#) and [Holford at Auckland](#)

VPC for censored and categorical data. [PAGE 18 \(2009\) Abstr 1604.](#)

Introduction of [pcVPC](#)

□ Parameter uncertainty

Covariance matrix (multivariate normal distribution):...\\nm73g64\\html\\covarian.htm

Bootstrap ([light reading](#) and [deep reading](#))

Log-likelihood profiling ([basic concept](#))

Sampling importance resampling (SIR): [concept](#) and [automation](#)

Estimation methods

Conditional methods

Derivation of FO, FOCE, FOCEI, and Laplacian. [Wang Y, JPKPD, 2007](#) and Chapter 7 ([theory of NLMEM](#), p225-231) NONMEM Users Guide - Part VII. R-based reproduction of [FO](#) and [FOCE](#)

EM methods

Theory of EM algorithm (deep reading). [Dempster A P, 1977](#). Iterative two stage (ITS). [Mentré F, 1995](#). Importance sampling (IMP). [Bauer R J, 2004](#). SAEM. [Delyon B, 1999](#).

M3 method for censored data

Handling censored data. [Ahn J E, JPKPD, 2008](#) and [Bergstrand M, AAPS J, 2009](#).

Handling Missing and Censored Data. Chapter 8 ([practical issue of missing and censored data](#), p339-344) Tutorial on censored observations with NONMEM. [Holford at Auckland](#).

Shrinkage

Importance of shrinkage in EBEs for diagnostics. [Savic R M, AAPS J, 2009](#). Tutorial on shrinkage. [PAGE 16 \(2007\) Abstr 1087](#). Shrinkage (quantification, influencing factors, and impact). [Xu X S, AAPS J, 2012](#).

Log-normal distribution

Variability in the log-domain. [Elassaiss-Schaap J, CPT:PSP, 2020](#). Derivation of variability for log-normal distribution. [PAGE 18 \(2009\) Abstr 1508](#).

Transformations

Data and parameter transformations. [Pascal Girard, PAGE meeting, 2002](#). Semiparametric distributions (logit and box-cox transformations). [Pettersson K J F, Pharm res, 2009](#).

Common NONMEM error messages and solutions

NONMEM errors and solutions. Bonate P L, Springer, 2011 ([chapter 8](#), p345-348). NONMEM Users Guide Part V - Introductory Guide - Chapter 13 (Errors in NONMEM Runs): [.../nm73g64/html/V/13.html](#) NONMEM error messages: interpretation and resolution. Owen J S, John Wiley & Sons, 2014 ([chapter 6](#), p188-193).

PKPD modeling strategies

Simultaneous vs. sequential PKPD analysis: alternatives. [Lacroix B D, JPKPD, 2012](#). Simultaneous vs. sequential PKPD analysis: best-case performance. [Zhang L, JPKPD, 2003a](#). Simultaneous vs. sequential PKPD analysis: robustness of methods. [Zhang L, JPKPD, 2003b](#).

Miscellaneous

Models for time-varying covariates. [Wählby U, BJCP, 2004](#). Linearization for speeding up the covariates testing. [Khandelwal A, AAPS J, 2011](#). Calculation of CWRES. [Hooker A C, Pharm res, 2007](#). finedata: [.../nm73g64/html/finedata.htm](#) [NONMEM User Archive](#)