NONMEM

ICON

What is NONMEM?

NONMEM stands for NONlinear Mixed Effects Modeling. NONMEM is a computer program that is implemented in Fortran90/95. It solves pharmaceutical statistical problems in which within subject and between subjects variability is taken into account when fitting a pharmacokinetic and/or pharmacodynamic (PK/PD) model to data. The appropriate statistical analysis using the appropriate model helps pharmaceutical companies determine appropriate dosing strategies for their products, and increases their understanding of drug mechanisms and interactions.

NONMEM software was originally developed by Lewis Sheiner and Stuart Beal and the NONMEM Project Group at the University of California, and has been used for over 30 years for population analysis by many pharmaceutical companies and the PK/PD modeling community. Its continued development and improvement by ICON Development Solutions assures pharmaceutical companies that they may continue to use the analysis tool with which they are familiar for present day pharmaceutical development.

PK/PD are data typically collected from clinical studies of pharmaceutics agents, involving the administration of a drug to individuals and the subsequent observation of drug, metabolite, and/or biomarker levels (most often in the blood, plasma, or urine), as well as clinical outcome measures. Proper modeling of these data involves accounting for both unexplainable inter- and intra-subject effects (random effects), as well as measured concomitant effects (fixed effects). NONMEM allows this mixed effect modeling. Such modeling is especially useful when there are only a few measurements from each individual sampled in the population, or when the data collection design varies considerably between these individuals. However, NONMEM is a general program which can be used to fit models to a wide variety of data.

History of NONMEM Development

Date	**Version**	**Sponsor/ Medium/ Language**	**Components Added**	**Documentation Added** (NONMEM Users Guide Series)	**Description**
1980	I	UCSF Fortran IV source code IBM specific binaries Magnetic tape	NONMEM (LS, SB): FO	Part I Users Basic (SB) Part II Users Supplemental (SB)	FO: Simultaneously discern variability of measured levels of drug or drug response (residual variance) within a subject (intra-subject effects), and variability of PK/PD parameters between subjects (inter-subject effects). Method could determine how population PK/PD parameters related to patient characteristics, even when there were few data points per subject.
1984	II	Fortran 77 source code All platforms (AB)	PREDPP I (SB, LS, AB): ADVAN1-6	Part VI PREDPP (SB)	PREDPP: library of routines for specific PK models, designed by Stuart Beal and implemented by Alison Boeckmann. Reduced the mathematical barrier which users had to overcome.

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1989	III		PREDPP II (SB, LS, AB): ADVAN7-9 NM-TRAN I (AB)	Part IV NM-TRAN (SB) Part V Introductory (AB,LB)	NM-TRAN: Data preprocessor and model translator, made it much easier for PK/PD models to be developed.
1992	IV	Floppy disks	NONMEM (SB): FOCE/Laplace Interaction Mixture models PREDPP III: ALAG (AB), ADVAN10 (SB) NM-TRAN II (AB)	Part III Installation (AB) Instructions for Installation on DOS (WB) Part VII Conditional Estimation Methods (SB)	FOCE: FO was fast, but very approximate. Sometimes inaccurate assessments occurred if residual error and/or inter-subject variability were large. Conditional method (FOCE), while also approximate, was more accurate for a larger variety of problems.
1994			NONMEM Users Network Internet		
1996				On-line help (AB,LB,SB) Part VIII Help (AB,LB,SB)	
1998	V	SETUP,SETUP.bat (AB) NMFE (AB) NSIZES,PSIZES, TSIZES (SB,AB)	NONMEM (SB): LIKELIHOOD (Non-normal Likelihood such as Discrete/ non-continuous observations; logistic regression) Superproblems Centering Hybrid methods Raw-data and Marginal Data Items PREDPP IV (SB): ADVAN11-12 NM-TRAN III (AB): $MIX LAST20 (for Year 2000) TRANSLATE	NONMEM V Supplemental (SB)	
2000-2001		Globomax: Licensing distribution, additional platforms, support CDROM, CDSETUP, CDSETUP.BAT (WB, AB)		Readme (AB,WB)	
2006	VI 1.0	Icon Development Solutions acquires Globomax, NONMEM Commented code SIZES	NONMEM (SB): PRIOR post-processing nonparametric estimation Stieltjes method in NONMEM PREDPP V (AB): MTIME NM-TRAN IV (AB): $INFN recursive abbreviated code abbreviated functions INCLUDE record	Introduction to Version VI (SB,TL,AB) HTML On-line Help (TL, AB) PDF versions of guides (TL, AB)	For many problems the speed and stability of the FOCE/ FOCE-INTERACTION method was improved over previous versions (SB).

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2008	VI 2.0		NONMEM (TL,AB): Default boundary test is user selectable More items in a table file PREDPP (AB) Initial steady-state feature NMTRAN(AB): Eta partial derivatives G and H variables can be tabled $PRIOR to replace user PRIOR subroutine. Abbreviated code for implementing the PHI function (integral of normal density). Abbreviated code for tabling each individual's contribution to the objective function value (TL, AB).		
2009	7.1.0	Fortran 95, centralized global variable definitions (Nous Infosystems). double precision throughout, including input data record (Nous Infosystems). Encrypted source code (AB). License file (RB).	NONMEM (RB): ITS: Iterative Two Stage SAEM: Markov Chain Monte Carlo (MCMC) Stochastic Approximation Expectation Maximization (EM) IMP: Monte Carlo importance sampling EM BAYES: MCMC Bayesian Analysis Additional output files for easy post-processing Improved incidence of success with FOCE Improved SuperProblem robustness (Nous) Diagnostics CWRES, NPDE SIGL: Better control of gradients in FOCE/ Laplace $COV: Reactivation of UNCONDITIONAL PREDPP (RB): ADVAN13, Sequential application of estimation methods. NM-TRAN (AB, Nous): Increased flexibility such as 50 data items per record, more digits and E-field numeric notation allowed, 20 character data item names.	Introduction to NONMEM Version 7 (RB)	FOCE performance was further improved with converting all computations to double precision, and supplying additional user control (SIGL). Advanced Monte Carlo estimation methods allow exact maximum likelihood estimation, removing bias often observed with FOCE in very sparse data (fewer observations per subject than parameters to be fitted), and with non-normally distributed data.
2010	7.1.2		Minor bugs fixed: NONMEM (RB): band symmetric matrices properly processed. SLOW option automatically applied with single subject problems. INTERACTION option more flexible with SAEM or MCMC. MSF system transfers information properly. Multiple sub-problems with simulation and estimation work correctly. PREDPP (AB,TL) When SS=2, model is correctly evaluated. NMTRAN (RB, AB) $COV properly interpreted regardless of position in control stream file.	Introduction to NONMEM Version 7.1.2. (RB)	

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2011	7.2.0	Enhanced nmfe72 execution scripts to accommodate parallel computing and building executable to fit size of problem	NONMEM: Dynamic memory allocation (Nous), Parallel computing estimation methods (Sale, Thomsen, RB), OMEGA and SIGMA additionally outputted in correlation format (RB) OMEGA and SIGMA may be inputted in correlation or Cholesky format (AB,RB) XML markup version of the standard results output file (RB) Features to facilitate stochastic differential equations (SDE) problems (RB) additional improvements in Monte Carlo EM methods (RB) MSF allows accurate resumption of advanced methods (RB) $CHAIN record to allow initial parameter setting from a raw output file (RB) Intermediate output from the Estimation Step for classical methods incudes native parameters (RB) Alternative convergence criterion for FO/FOCE/Laplace (RB) NM-TRAN (AB, Nous): Mixed case command and option entries allowed	Introduction to NONMEM Version 7.2.0 (RB) Part V updated for NONMEM 7.2.0 (AB)	Memory dynamically allocated according to problem size. No need to recompile the NONMEM program for unusually large problems. Memory is automatically sized according to the number of parameters and number of subjects. User may override program generated suggested values using a statement in the control stream. Often for moderate sized problems, this results in much smaller memory usage, compared to the standard memory usage in NONMEM 7.1.2 and earlier. Particularly helpful for parallel computing when using multiple cores on a single computer.
2013	7.3.0	Enhanced nmfe73 execution scripts to accommodate enhanced sizing options, and compiler location.	NONMEM (RB, Nous): More efficient memory allocation for sizing problems, particularly for huge models with many parameters to be estimated. More mixed effects levels, with random effects across groups of individuals such as clinical site, may now be modeled. Sites themselves may be additionally grouped, such as by country, etc. Algorithms to assess optimal settings for Monte Carlo estimation methods. Algorithms to aid in global optimization of classical estimation methods. Enhanced non-parametric analysis methods. NMTRAN (AB, Nous): Expanded language facilities for the control stream file, such as handling repetitive code, symbolic references to indexed parameters, extending code across lines, up to 67000 characters.	Introduction to NONMEM Version 7.3.0 (RB) Part V, VIII updated for NONMEM 7.3.0 (AB) Part III installation for NONMEM 7.3 (RB) Enhanced electronic version of Part II (RB)	More efficient memory allocation for sizing problems, particularly for huge models with many parameters to be estimated. More mixed effects levels, with random effects across groups of individuals such as clinical site, may now be modeled. Sites themselves may be additionally grouped, such as by country, etc. Easy to code inter-occasion variability. ETA's can be referenced by an index variable related to the inter-occasion data item. Symbolic reference to thetas, etas, and epsilons. Priors for SIGMA matrix may be added. Enhanced annealing feature for SAEM to facilitate estimation of fixed effect parameters (THETAs) that do not have associated inter-subject variance (ETA's). Boot-strap simulations.

Date	Version	Sponsor/ Medium/ Language	Components Added	Documentation Added (NONMEM Users Guide Series)	Description
2017	7.4.0	Enhanced nmfe72 execution scripts to accommodate parallel computing and building executable to fit size of problem.	NONMEM (RB): Expanded parallelization to weighted residual and other diagnostic evaluations and empirical Bayes estimation of etas for $TABLE step, parallelization of $SIML step, parallelization of $NONP step. Improved speed for FOCE and ITS by the FAST option, additional table output control allowing selection of specific records to be outputted, added new kernel in individual parameter sampling for SAEM and BAYES for more efficient sampling, added features for IMP sampling, added Hamiltonian no U-Turn sampling for BAYES analysis, allows T distribution priors for Thetas, Gamma distribution priors for Omegas and Sigmas, standard errors of user-defined and PREDPP parameters list in $TABLE records can be outputted, saddle reset for FOCE/Laplace estimation to avoid local minima and saddle points, preconditioning variance of estimation to improve robustness and accuracy in $COV step, added ADVAN14 (CVODES), and ADVAN15 (IDAS) differential equation solvers. NMTRAN(RB, AB, Nous): Expanded indexing to 3 digits for many internal arrays, expanded abilities to use OTHER user defined subroutines, enhanced symbolic index code processing.	Introduction to NONMEM Version 7.4.0 (RB) Part IV, V, VI, VIII updated for NONMEM 7.4.0 (AB) Part III installation for NONMEM 7.4 (RB) Documentation to CVODES and IDAS differential equation solvers	Improved speed for FOCE and ITS implemented through the FAST option, which performs analytical derivative assessments for Thetas. New kernel for Metropolis-Hastings uses an importance-sampling like sampler to increase sampling efficiency. No U-turn sampler useful for efficient sampling of parameters that are highly correlated. ADVAN14 (CVODES) is an enhancement of ADVAN13 (LSODA), and ADVAN15 (IDAS) is an enhancement of ADVAN9 (LSODI1), from Lawrence Livermore National Laboratory. OTHER routines may be utilized with any name, any number of input arguments, and any number of calls.

SB=Stuart Beal; LS=Lewis Sheiner; AB=Alison Boeckmann; TL=Thomas Ludden; WB=William Bachman; RB=Robert Bauer; Nous=Nous Infosystems, Inc.