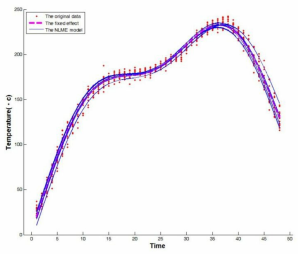

Icon 7.5 Nonmem Nonlinear Mixed Effects Modelling User Guide

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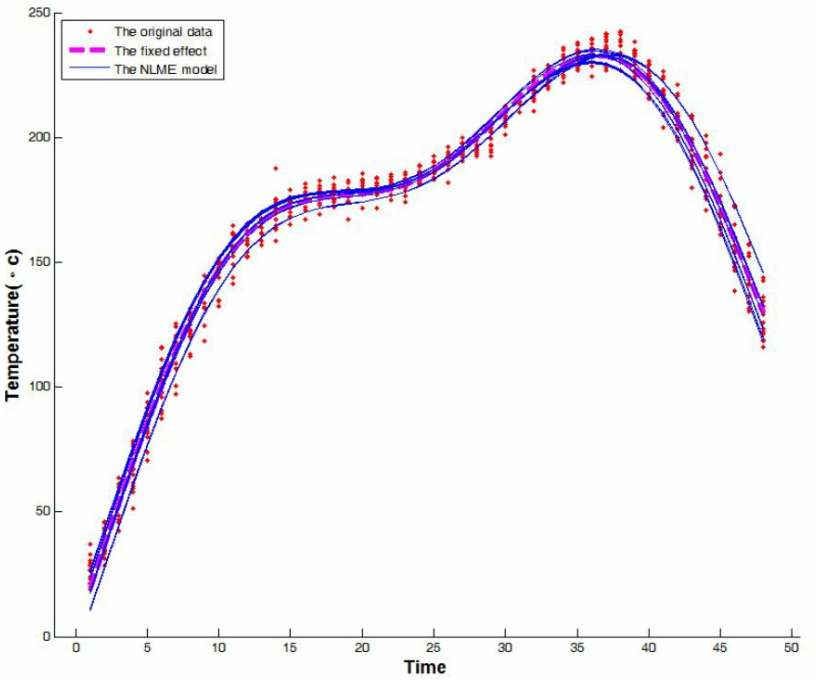


NONMEM® is a nonlinear mixed effects modelling tool used in population pharmacokinetic — pharmacodynamic

(PK/PD) analysis. The software was developed by the NONMEM® Project Group at the University of California, San Francisco. The PK/PD modelling community has relied on the use of the NONMEM® statistical software for over 30 years. Drug level PK data and drug response PD data are typically collected from clinical studies of pharmaceutic agents. Proper modelling of these data involves accounting for both unexplainable between and within subject effects (random effects), as well as measured concomitant effects (fixed effects).

Such modelling is especially useful when there are only a few PK or PD measurements from each individual sampled in the population, or when the data collection design varies considerably between these individuals. The appropriate statistical analysis with NONMEM using the appropriate model helps pharmaceutical companies determine appropriate dosing strategies for their products, and increase their understanding of drug mechanisms and interactions. NONMEM can also simulate data for a variety of these population PK/PD problems.

The continued development of NONMEM is important to our customers. The changes that are incorporated into new versions is in response to customer requests, and from understanding by our developers of some improvements that are needed, such as increased incidence of success in solving problems, greater speed, smaller memory usage, and parallel computing of a single problem.

The Software
NONMEM is an evolving programme, reflecting tested methodological and programming improvements. NONMEM has been developed in accordance with a robust software development life cycle (SDLC) process with supporting documentation according to industry level quality standards. The software has been fully tested, is functioning as expected, is scientifically sound and fit for use for statistical analysis, and acceptable for release to customers. The software consists of three parts:

- NONMEM itself, the basic and very general nonlinear regression programme
- PREDPP, a very powerful package of subroutines handling population PK data as well as general linear and nonlinear models, which can free the user from coding standard kinetic type equations m/herself while simultaneously allowing complicated patient-type data to be easily analysed
- NM-TRAN, a preprocessor allowing control and other needed inputs to be specified in a user-friendly manner. Both NONMEM and NM-TRAN are batch type programmes.

NONMEM
provides an extensive set of output files with results placed in table format for easy incorporation into post-processing statistical and graphical software.

NONMEM 7.5 includes the following features

1. The following population analysis methods are available for handling a variety of PK/PD population analysis problems:
    - First Order Conditional Estimation (FOCE)
    - Laplace Conditional Estimation
    - Iterative Two Stage (ITS)
    - Importance Sampling Expectation-Maximization (IMP)
    - Stochastic Approximation Expectation-Maximization (SAEM)
    - Markov-Chain Monte Carlo Bayesian Analysis (BAYES, NUTS)
2. Parallel computing of a single problem over multiple cores or computers, for estimation, covariance assessment, simulation, nonparametric analysis, and posthoc parameter and weighted residual diagnostic evaluation, significantly reducing completion time
3. Increased efficiency of dynamic memory allocation to handle very large problems, eliminating the need to

recompile the NONMEM program for unusually large problems

4. Techniques to improve performance of FOCEI, including increased incidence of success, specifying gradient precision, increased incidence of reaching global minimum, and a FAST algorithm that significantly speeds up estimation
5. Automatic optimisation of settings for easier usage of Monte Carlo analysis methods
6. New ODE solvers CVODES and IDAS with customized control for efficient analysis of differential and algebraic differential (equilibrium) equations
7. Delay Differential Equation solver algorithms, such as ADVAN16, which uses RADAR5 by Guglielmi and Hairer, an implicit 4th order Runge-Kutta method, for stiff delay equations, and ADVAN17 for stiff delay differential algebraic equations.
8. Evaluation and optimal design for clinical trials
9. Automatic stabilization of problems against numerical exceptions
10. Multiple mixed effects levels, with random effects across groups of individuals such as clinical site, may be modelled. Sites themselves may be additionally grouped, such as by country, etc.
11. MCMC Bayesian Analysis by method of Gibbs and standard Metropilis-Hastings sampling (BAYES), as well as Hamiltonian no U-turn sampling (NUTS). Also, average of phi() values are collected throughout the stationary distribution (positive iterations) phase, with conditional variances. Individual parameter samples during BAYES analysis can be conveniently collected without additional user code required.
12. User-defined parameters may have reported their standard errors and variance-covariances associated with etas as well as those associated with thetas (or omegas and sigmas).
13. Variance-covariance matrix information can be imported from previous runs, and used to evaluate total standard errors of user defined items in tables, or to bring in variance-covariance matrices from alternative sources (IMP,SAEM,BAYES,SIR), as priors for TNPRI problems.
14. Complete control of which records are outputted for user-defined tables, including first-only within individual, last-only within individual, first-last-only within individual, and specific exclusion of records by abbreviated code logic.
15. Improved incidence of completion when using the “Super Problem” feature
16. An empirical method of modeling steady state dosing is available that can handle any complexity of repeated dosing regimen.
17. You may increase the number of significant digits displayed for population parameter results in the NONMEM report file.
18. Additional result files, with number of significant digits selectable by the user, and which can be easily read by post-processing programs
19. Control stream files may be written in mixed case, for more aesthetically readable code, there may be any number of data items per data file, and record label names may be as large as 30 characters.
20. Easier to code Inter-occasion Variability
21. Symbolic reference to thetas, etas, and epsilons
22. improve code readability. Thetas may also be symbolically named at the $THETA record, in conjunction with the initial values specified.
23. Subscripted variables may be used in abbreviated code, for use in DO loops.
24. Variance matrix parameters output in covariance and correlation format
25. Variance matrix parameters may be input in covariance, correlation, or Cholesky format
26. XML markup version of the report file
27. Boot-strap simulations may be performed within NONMEM.

28. Initial individual ETAs may be introduced from an external source for improved incidence of success of analysis.
29. Expanded Prior distributions including inverse Wishart/Gamma and LKJ Correlation distributions for OMEGAS/SIGMAS, Normal/T-distribution for THETAS
30. Enhanced non-parametric analysis methods

System Requirements

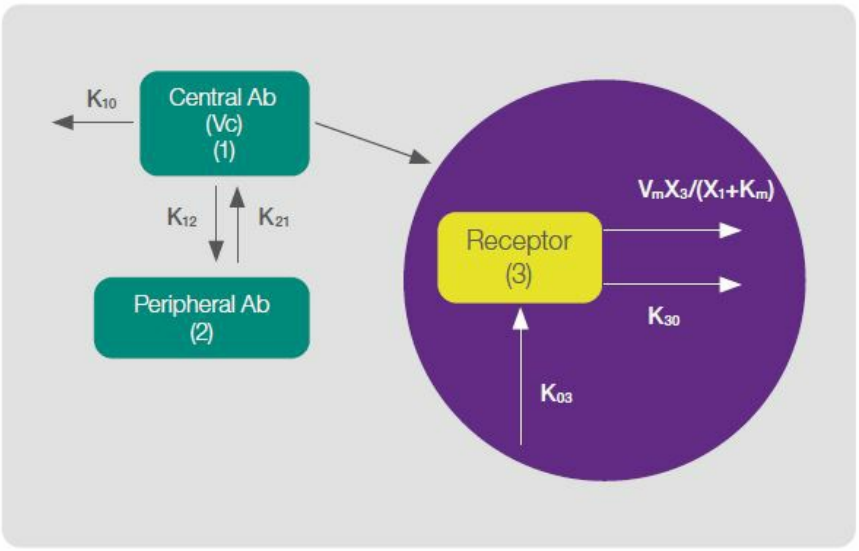
The NONMEM computer programme is written and distributed in ANSI FORTRAN 95 code, and therefore, can be used with most hardware and operating systems incorporating a Fortan 95 compiler adhering to the ANSI standard. It has been shown to operate with Intel Fortran Compiler 9.0 or greater for Windows or Linux, and gFortran for Windows or Linux. Since a NONMEM run can take considerable CPU time, perhaps many hours, depending on the speed of the computer and the size of the problem, it is advisable to use a fast machine. At least 1 and preferably 2 GB of memory should be available for exclusive use of NONMEM and NMTRAN programmes.

Licensing
The NONMEM programme is available for download, which together with the documentation and all updates and additions to the programme, will be delivered for a license subscription fee to be paid annually. This fee is subject to change from year to year, and at each anniversary the licensee at its option may choose not to renew the license. The following example demonstrates NONMEM's ability to perform an MCMC Bayesian analysis on a complex PK/PD problem.

We compare Bayesian analysis performed in NONMEM 7 with WinBUGS/Blackbox V1.4 for data simulated using receptor-mediated clearance and indirect response model typically used in antibody therapeutics. Data were simulated with 17 PK and 18 PD observations for each of 50 subjects receiving a bolus of drug, followed by short infusion a week later. The PK model has 2 compartments (Vc, k12, k21) with first-order (k10) and receptor-mediated clearance (Vm, Kmc). The PD model is indirect response, with receptors generated by zero order process (k03), and removed by first order process (k30) or via drug-receptor complex (Vm, Kmc).

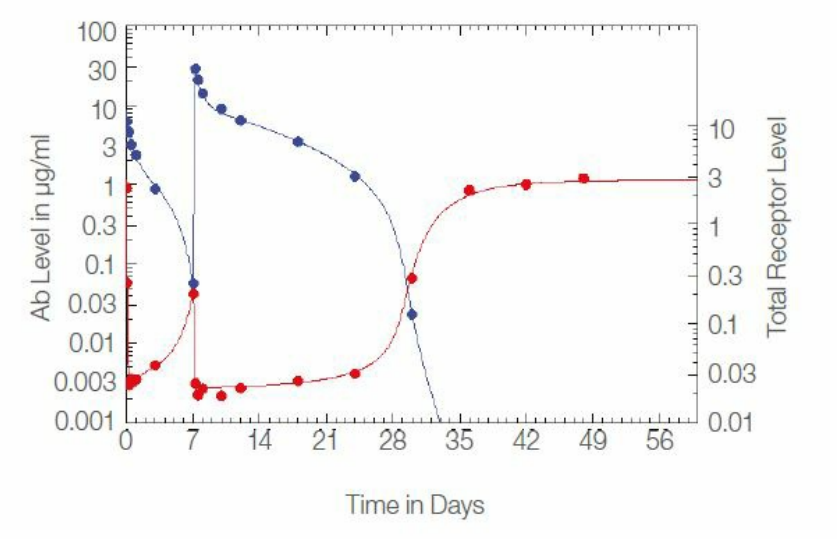
There are 46 population parameters, variances/co-variances,and intra-subject error coefficients. NM7 uses a Gibbs or Metropolis-Hastings algorithm to implement the MCMC procedure. Bayesian analysis consisted of 4000 burn-in followed by 30,000 sample iterations, and uninformative priors were supplied. Extensive random mixing occurred in the sampling history for all parameters. Mean differences between sorted samples from NM7 and WinBUGS were typically <1% of the sample means. Root mean square differences between sorted samples from NM7 versus WinBUGS were 2-20% of the standard errors of the estimates. NM7 provides convenient and accurate access to MCMC Bayesian methods for population PK/PD problems.

Diagram of Model
A data set was simulated using a typical PK/PD model often used in antibody therapeutics (antibody-receptor dynamics). The data set consisted of 50 patients each with a rich sampling of 17 PK and 18 PD observations per individual, sampled over a period of 50 days after receiving a bolus dose of 0.3 mg/kg antibody therapeutic followed by a 4 hour intravenous infusion of 1 mg/kg Ab one week later.

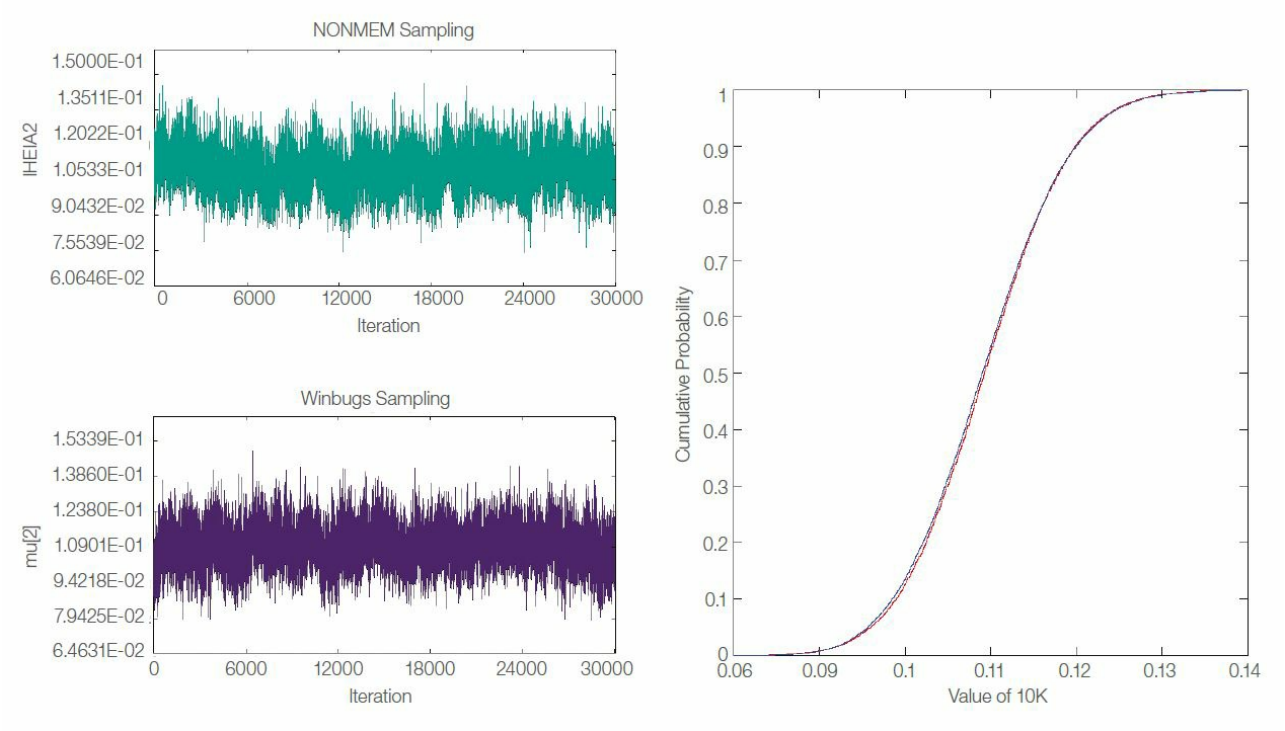


Typical PK/PD Profile

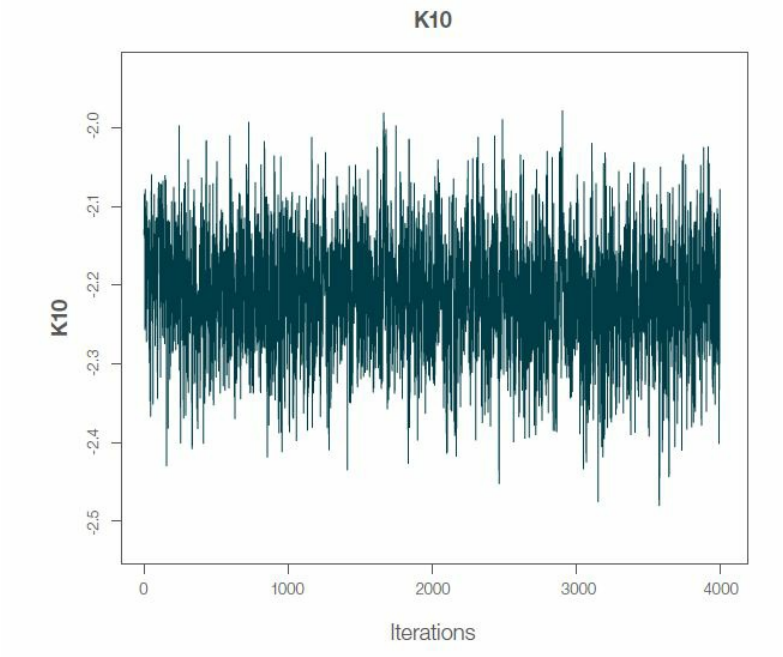
Individual parameters were generated from a multivariate log-normal distribution of population parameters. Serum antibody and total receptor levels were simulated at selected times from a univariate normal distribution with mean about the individual predictive value, and with variance that was proportional to the square of the predictive value. A typical PK/PD profile is shown.



Example of Bayesian History Plot and Cumulative Distribution for Parameter k10



Improved Algorithms in NONMEM 7.5 such as Enhanced Gibbs Sampling and Hamiltonian no U-turn Sampling (NUTS) Generate Decorrelated Samples More Efficiently, Requiring Fewer Total Samples to Properly Represent the Posterior Distribution 2020 ICON plc. All rights reserved. ICONplc.com/nonmem



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