

NONMEM®

NONMEM® is a nonlinear mixed effects modeling 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 modeling 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 pharmaceutical agents. Proper modeling of these data involves accounting for both unexplainable between- and within-subject effects (random effects), as well as measured concomitant effects (fixed effects). Such modeling 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, and smaller memory usage.

The Software

NONMEM® is an evolving program, reflecting tested methodological and programming improvements. The software consists of three parts:

- (i) NONMEM® itself, the basic and very general nonlinear regression program
- (ii) 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 him/herself

while simultaneously allowing complicated patient-type data to be easily analyzed

- (iii) 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 programs.

NONMEM® 7.1.2 can perform the following the following statistical analyses:

1. First order nonlinear mixed effects (FO)
2. First order conditional estimation (FOCE)
3. Second order conditional estimation (Laplace)
4. Non-parametric estimation of individual parameters
5. Iterative two stage, an approximate first order expectation-maximization method (ITS)
6. Monte Carlo importance sampling expectation-maximization (IMP)
7. Markov Chain Monte Carlo stochastic approximation EM (SAEM).
8. Three stage hierarchical Markov Chain Monte Carlo (MCMC) Bayesian estimation.

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® 7.2 will include the following enhancements:

1. Parallel computing of a single problem over multiple cores or computers. The computation of a single problem that can take many hours or days may be distributed over two or more cores and/or computers to complete in a shorter time.
2. 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.
3. Control stream files may be written in mixed case.
4. Variance matrix parameters output in covariance and correlation format.
5. Variance matrix parameters may be input in covariance, correlation, or Cholesky format.
6. XML markup version of the NONMEM® report file.
7. Features to facilitate stochastic differential equations (SDE).

System Requirements

The NONMEM® computer program is written and distributed in ANSI FORTRAN 95 code, and therefore, can be used with most hardware and operating systems incorporating a Fortran 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 (Intel Fortran compiler is preferred). 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 programs.

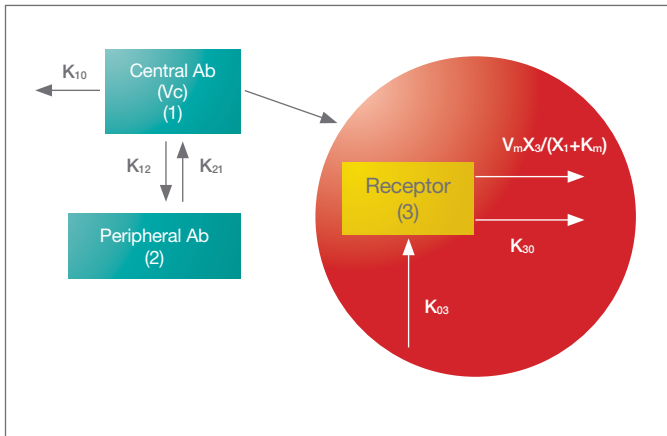
Licensing

The NONMEM® program is available on a CD ROM, which together with the documentation and all updates and additions to the program, will be delivered for a license royalty 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.

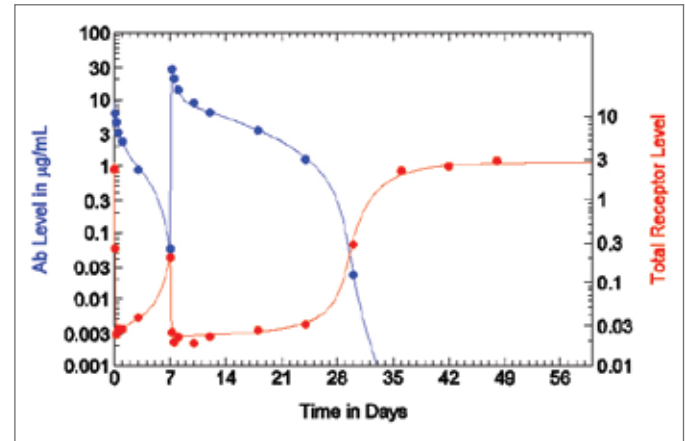
The following example demonstrates NONMEM's ability to perform an MCMC Bayesian analysis on a complex PK/PD problem.

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 (V_c , k_{12} , k_{21}) with first-order (k_{10}) and receptor-mediated clearance (V_m , K_{mc}). The PD model is indirect response, with receptors generated by zero order process (k_{03}), and removed by first order process (k_{30}) or via drug-receptor complex (V_m , K_{mc}). There are 46 population parameters, variances/co-variances, and intra-subject error coefficients. NM7b 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 NM7b and WinBUGS were typically <1% of the sample means. Root mean square differences between sorted samples from NM7b 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:



Typical PK/PD Profile



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.

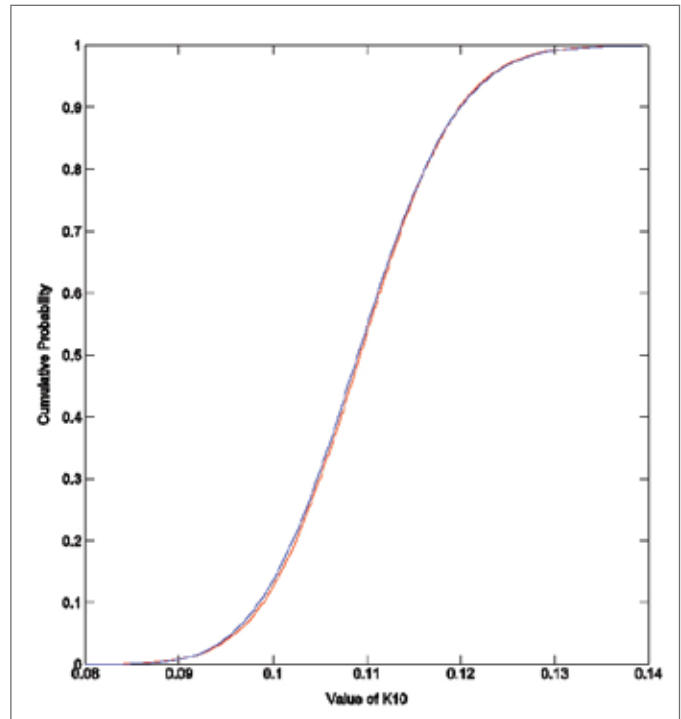
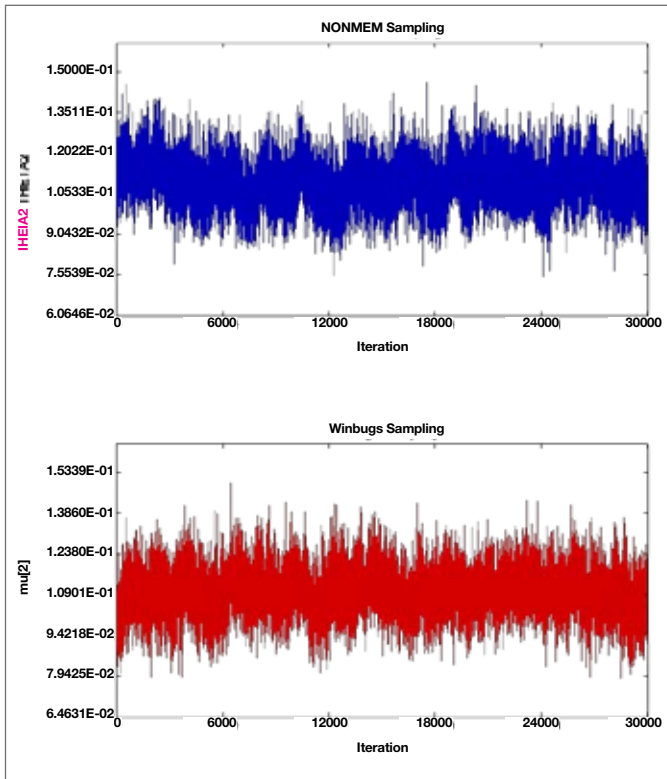
Individual parameters were generated from a multivariate log-normal distribution of population parameters. Serum antibody and total receptor levels were simulated at selected times from a univariate normal distribution with mean about the individual predictive value, and with variance that was proportional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

NONMEM® Versus WinBUGS Results

	Vc	K10	K12	K21	Vm	Kmc	K03	K30	SD1	SD2
Mean WinBUGS	49.939	0.109	1.739	0.835	9.688	1.275	40.926	0.495	0.097	0.150
Mean NONMEM	49.911	0.109	1.731	0.832	9.661	1.269	40.954	0.496	0.096	0.150
SE WinBUGS	3.822	0.008	0.104	0.063	0.645	0.099	2.934	0.035	0.003	0.004
SE NONMEM	3.838	0.008	0.107	0.062	0.640	0.096	2.943	0.035	0.003	0.004
Mean Diff/mean (%)	-0.06%	-0.16%	-0.43%	-0.36%	-0.28%	-0.52%	0.07%	0.23%	-0.05%	0.10%
RMS Diff/mean (%)	0.10%	0.24%	0.46%	0.39%	0.29%	0.57%	0.14%	0.25%	0.09%	0.11%
RMS Diff/SE (%)	1.29%	3.22%	7.72%	5.18%	4.40%	7.36%	2.02%	3.46%	2.55%	4.12%
	ΩVC	ΩK10	ΩK12	ΩK21	ΩVm	ΩKmc	ΩK03	ΩK30		
Mean WinBUGS	0.286	0.222	0.145	0.271	0.212	0.245	0.252	0.243		
Mean NONMEM	0.288	0.220	0.152	0.265	0.211	0.241	0.253	0.242		
SE WinBUGS	0.060	0.060	0.036	0.061	0.046	0.061	0.053	0.053		
SE NONMEM	0.061	0.056	0.038	0.060	0.046	0.058	0.054	0.053		
Mean Diff/mean (%)	0.53%	-1.29%	4.74%	-2.13%	-0.77%	-1.58%	0.52%	-0.41%		
RMS Diff/mean (%)	0.64%	2.32%	5.09%	2.22%	1.02%	1.87%	0.60%	0.67%		
RMS Diff/SE (%)	3.04%	8.59%	20.61%	9.86%	4.71%	7.54%	2.83%	3.09%		

SE=standard error; RMS=root mean square; Diff=difference; ΩVC =inter-subject variance of Vc, etc. SD1, SD2=coefficient of residual error for PK, PD samples, respectively.

Example of Bayesian History Plot and Cumulative Distribution for Parameter k10



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