New and Advanced Features of NONMEM 7.4 Workshop

Date of Meeting: 05 June 2017

Location: PAGE 2017, Budapest, Hungary

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The objective of this course is to introduce advanced concepts of population pharmacokinetics in NONMEM. The course is targeted to individuals interested in solving population PK/PD problems using the new stochastic methods. The course is for those who are familiar with classic NONMEM methods (first order (FO)/first order conditional estimation (FOCE)/Laplace), and are familiar with constructing control stream files. Most of the course is instructional, with several hands-on examples for attendee participation. A thorough discussion of stochastic approximation expectation maximization (SAEM), Importance sampling (IMP), and Markov chain Monte Carlo Bayesian analysis (Gibbs BAYES sampling and new in NONMEM7.4: Hamiltonian no-U turn sampling) will be presented, along with hands-on exercises. In addition, the FAST algorithm for FOCE analysis, new in NONMEM 7.4, will be introduced. After attending this course, the participant will know how to use advanced stochastic methods for analyzing population PK/PD data; structure the models into a MU-referencing format that will greatly increase the efficiency of the analyses; apply prior information from previous analyses to the present data; create population mixture models; create models for categorical data; use new abbreviated code features for easier modeling of inter-occasion variability; model additional mixed effects levels for grouping individuals, such as inter-clinical site variability; use the DO loop feature in abbreviated code, such as for handling multiple bolus doses in transit compartment models that use the analytical absorption function. Additional topics covered are: parallel computing and dynamic memory allocation for efficient memory usage; symbolic referencing to thetas, etas, and sigmas; Monte Carlo search algorithms to improve FOCE estimation; built-in individual weighted residuals; bootstrap tools for simulation; and greater control in average eta shrinkage calculations; and automatic protection against numerical exceptions using NONMEM7.4's new $ABBR PROTECT feature.

	Agenda Items	
1.	**Introduction**	8:30 – 8:45 AM

.	**Modifications and Enhancements to NONMEM 7**
	- Conversion of Fortran 77 to Fortran 90/95
	- Centralized Error Processing
	- Improvements in Gradient Methods
	- Decreased Incidence of Estimation Failure Due to Numerical Problems
	- Added Option to Specify Step-Size for Gradient Calculation
	- Increased Number of Data Items and Label Lengths
	- Flexible Numerical Formats for Input and Output
	- Mixed case in control streams
	- Added Information in Standard Results File
	    - Identifier Tags for Certain Sections
	    - Shrinkage of Variance
	    - Complete Information Correlation Matrix output of OMEGA, SIGMA, and Variance-Covariance of estimates
		8:45 – 9:30 AM

	- Additional features of $TABLE Outputs (new in NM 7.4)
	      - Algorithmic control of which records to output
	      - In addition to FIRSTONLY, one can select LASTONLY or
	        FIRSTLASTONLY records of each subject.
	      - ONEHEADERPERILE option
	      - Output standard errors of individual parameters
	- Additional Weighted Residuals outputs (conditional, exact versions)
	- Additional Output Files Easily Readable by Post-Processing Software
	      - XML version of NONMEM report file
	      - Shrinkage information: shk file
	      - Conditional means and variances for mixture sub-populations:
	       .phm file
	      - FO/FOCE/LAPLACE gradients: .grd file
	      - Monte Carlo, EM, Bayesian convergence diagnostics: .cnv file	

3.	**New Methods Available in NONMEM 7, Theory, Overview** - Monte Carlo Importance Sampling Expectation Maximization (EM) (IMP) - Markov Chain Monte Carlo (MCMC) Stochastic Approximation EM (SAEM) - Iterative Two Stage (ITS)	9:30 – 10:00 AM
4.	**Break**	10:00 – 10:15 AM
5.	**Mu Modeling** - Model Modifications That Improve Efficiency of EM Methods (Mu Modeling)	10:15 – 11:00 AM
6.	**Examples for EM Methods (hands-on)** - Basic two compartment model problem, incorporate Mu Model	11:00 – 11:45 AM
7.	**Lunch**	11:45 – 12:45 PM
8.	**Examples for EM Methods (hands-on)** - Two compartment model with age and gender covariates	12:45 – 1:45 PM

9.	**Bayesian Analysis (hands-on)**
	- MCMC Bayesian Analysis (METHOD=BAYES)
	- Prior information for MCMC Bayesian Analysis, including
	  new NM 7.3 feature of adding priors to SIGMA
	  parameters
	- Revisit two compartment model, adding Bayesian analysis
	- Hamilton No U-Turn algorithm in NM 7.4 (METHOD=NUTS)
		1:45 – 2:45 PM

10.	**Break**	2:45 – 3:00 PM
11.	**More Examples with EM and Bayesian Analysis** -Population mixture model problem - Interoccasion variability problem using enhanced abbreviated code	3:00-4:00

	feature of NM 7.3
	- Inter-site variability example of NM 7.3
	- Modeling transit compartment problem with multiple doses, using DO loop
	  feature of abbreviated code in NM 7.3
	-Receptor Mediated Clearance (target-mediated drug disposition) using FAST
	  FOCEI algorithm of NM 7.4	

12.	**Additional Considerations for EM and Bayesian Analysis** - Termination Testing - Making Numerically Stable Models: Using the $ABBR PROTECT feature of NM 7.4 - Categorical data problem	4:00-4:15

13.	**Additional Features to NONMEM 7**
	- Dynamic Memory Allocation, use of $SIZES
	- Parallel Computing
	         - In addition to parallel computation for estimation and covariance
	           step, simulation, final estimation of table outputs and weighted
	           residuals, and nonparametric analysis are also parallelized (new in
	           NM 7.4)
	         - Control iteration printing to parallel log file (new in NM 7.4)
	- Increased number of mixed effects levels
	- Symbolic references to thetas, etas and epsilons for easier coding
	- DO loop usage and indexing of thetas, etas and epsilons in
	    abbreviated code
	- AUTO option and optimization of EM options
	- Additional prior distributions (new in NM7.4): Inverse Gamma and LKJ
	   Correlation distributions for OMEGAS/SIGMAS, T-distribution for
	   THETAS
	- Monte Carlo search algorithms to improve estimations in FOCE
	- Built-in conditional individual weighted residuals (CIWRES)
	- Greater control in assessing average eta shrinkage
	 - Bootstrap tools for simulation
	 - quasi-random Monte Carlo extended to simulations and all Monte
	   Carlo methods
	 - New ODE solvers CVODES (ADVAN14) and IDAS (ADVAN15) with
	   customized control for efficient analysis of differential and algebraic
	   differential (equilibrium) equations (new in NM 7.4)
		4:15 – 4:45 PM

15.	**PDx-Pop 5.2 Interface For NONMEM 7**
	- Real-Time Graphical Monitoring of Objective Function
	- Interaction with NONMEM Run
	         - Toggle Switch for Console Printing of Iterations
	         - Switch to End a Problem Gracefully
	         - Switch to End a NONMEM Gracefully
	- Extended Summary Output
	- Graphical Display of Parameter Sampling History (BAYES)
	- Setting Up and Running Multiple Analysis Chains Simultaneously
	- Graphical and Tabular Summary of Multiple Analysis Chains (BAYES)
	- Stratified Bootstrap
	- Visual predictive check
	- PDx-Pop on Linux and MAC OS X
		4:45 – 5:00 PM