R/NONMEM Toolbox for Simulation from Posterior Parameter (Uncertainty) Distributions

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Abstract

Background: Model-based simulations are a necessary part of the drug development process. Model parameters are always known with some level of imprecision (uncertainty). Uncertainty in the current state of knowledge can be incorporated into the simulation framework quantitatively and explicitly as posterior probability distributions. This also enables assessment of global sensitivity of simulation (trial) outcomes to underlying assumptions about model parameters (and even the model itself). The application of these methods to models developed in NONMEM (GloboMax/ICON, Ellicott City, MD) has been limited due to the lack of the off-the-shelf software that would allow easy and efficient implementation.

Methods: Parameter uncertainty was implemented as an additional level in the non-linear mixed effects model hierarchy. Simulations from posterior probability distributions across all parameters were implemented using R (R Development Core Team; www.r-project.org), with the system model simulation implemented in NONMEM.

Results: A toolbox of several R scripts that allow for an easy adaptation to a particular project was created. Simulations from posterior distributions were implemented in three steps. First, posterior parameter distributions were simulated. Fixed-effect parameters were simulated from a multivariate normal distribution. Inter-subject and residual variance parameters were simulated from inverse Wishart or inverse Chi-square distributions. Modes of these distributions reflected the expected values of the population parameters while the variance-covariance matrix (for the multivariate normal distribution) and degrees of freedom (for the inverse Wishart or inverse Chi-square distributions) reflected uncertainty of these expectations. Results of the parameter simulations were saved as ASCII parameter files. Alternatively, parameter files could be created outside of the toolbox by sampling from posterior distributions created by MCMC or bootstrap methods. Second, for each set of parameters from the parameter file, a NONMEM simulation control stream was created and run. Finally, simulation results were either output to text files for future data analysis, or summarized using custom R functions.

Conclusions: A flexible and relatively easy to use R/NONMEM package for simulating from posterior distributions has been developed (code available from http://MetrumInstitute.org/downloads/index.shtml).

How Simulations are Used in Drug Development?

- Evaluate and optimize the study design (e.g., dosing, sampling, sample size)
- Evaluate the possible range of study outcomes (e.g., percent of responders) under various dosing regimens
- Evaluate power of the study and probability of success

What is Clinical Trial Simulation (CTS)?

- Simulation of the individual concentration-time and/or effect-time courses of the future study participants under various dosing regimens
- Necessary component of the successful simulation project: predictive PK and PK/PD models
- Things to remember: model parameters (and models) are known with some precision (uncertainty)

CTS with Uncertainty: Basic Idea

- Uncertainly of prior knowledge is incorporated into the simulation framework quantitatively and explicitly

Why Include Uncertainty?

- When uncertainty is not included, simulation results are only valid if the model and parameters are true.
- Including uncertainty allows for a quantitative evaluation of the current state of knowledge
  e.g. What is the probable range of outcomes, given what you know now?

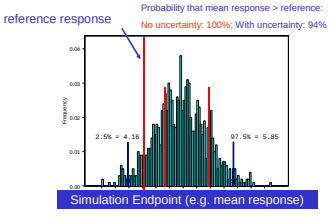
Questions Addressed by Different CTS Approaches

- Conventional CTS (without uncertainty):
  - What is the expected outcome, if my choices of model and parameter values are good descriptions of the truth?
- CTS with uncertainty:
  - Given my current state of knowledge, what is the range of probable outcomes?

Simulation Plan

- CTS with uncertainty:
  - Select model and distribution of model parameters
  - Simulate study 1000 times (each time with different values of population parameters drawn from parameter distributions)
  - Investigate range of possible outcomes (given our current knowledge)
  - Investigate sensitivity of the results to assumptions (does not require additional simulations)

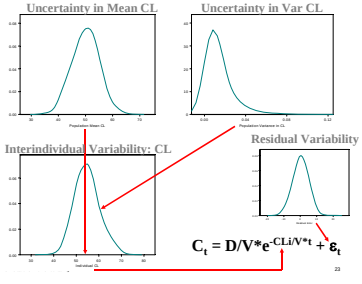
Simulation with Uncertainty Results



Obtaining Measures of Uncertainty

- Standard errors or confidence intervals of parameters from prior modeling exercise (bootstrap, likelihood profile)
- Posterior distributions from Bayesian modeling results
- Review of literature for ranges of plausible values
- Poll experts for their opinions (everyone's view can be part of the simulation)

Simulations: Mixed-Effects Modeling Framework



Example: Optimal Design of the Trial Using Simulations with Uncertainty

Attend Oral Presentation by John Mondick, Applications section, Friday, June 16, 2006, 13:45-14:05

John Mondick, Leonid Gibiansky, Marc R. Gastonguay, Gareth J. Veal, Jeffrey S. Barrett, Acknowledging Parameter Uncertainty in the Simulation-Based Design of an Actinomycin-D Pharmacokinetic Study in Pediatric Patients with Wilms' Tumor or Rhabdomyosarcoma

Simulation Tool: Requirements

1. Monte Carlo simulation hierarchy with multiple levels of nested random effects (at least 3)
2. Ability to incorporate joint uncertainty distributions from other methods (e.g. bootstrap, Bayesian)
3. Simulation and estimation (ML) for typical population PK and PD systems in same tool
4. Programmable/extensible language with data manipulation and graphics capability
5. Platform neutral (Win, Unix, Linux, Mac OS X)

Current Simulation Tools

Some programs with Monte Carlo simulation capabilities at parameter uncertainty level are available, but not all requirements are met:

- WinBugs
- NONMEM PRIOR subroutine
- Trial Simulator
- Others...

NMSUDs R/NONMEM Package

1. Generates draws from the uncertainty distributions at inter-trial level, maintaining joint distribution (covariance) of parameters

   -OR-

1. Samples from previously determined uncertainty distributions (e.g. Bootstrap, Bayesian Posteriors)
2. Generates NONMEM control streams for simulation (estimation)
3. Runs NONMEM or R for simulation (and possibly estimation) of each trial
4. Summarizes the results of each trial and across all trials

Implementation

Table 1 describes distributions that are used to draw population parameters and the parameters of these distributions that need to be specified by the user.

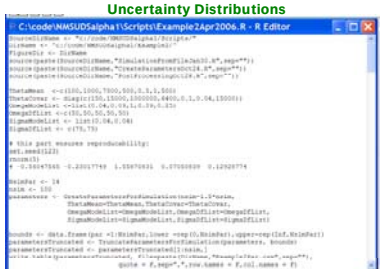
Table 1 Distributions that are used to draw population parameters.

Parameter type (NONMEM name)	Distribution	Parameters of the distribution	Implementation	How to assign distribution parameters based on NONMEM run
Single uncorrelated population parameter (THETA)	Normal	Mean μ, variance σ^2	Standard R function rnorm(., μ, σ)	μ: population parameter estimate; σ: standard error of the parameter estimate.
Set of correlated population parameters (THETA)	Multivariate normal	Vector of mean values M, variance-covariance matrix Σ	Standard R function mvrnorm(., M, Σ)	M: vector of population parameter estimate; Σ: variance-covariance matrix of the parameter estimates.
Variance of the random effect (OMEGA)	Scaled inverse χ^2	Number of degrees of freedom v, scale s^2.	Standard R function vs^2/rchisq(., v)	v: number of patients used to obtain the estimate; s^2: estimated variance of the random effect.
Variance-covariance matrix of the random effects (OMEGA)	Inverse Wishart	Number of degrees of freedom v, scale matrix S. Implicit parameter is the S matrix dimension k.	Proprietary R function myriwish(k, v, vS) based on the standard riwish() function	v: number of patients used to obtain the estimate; vS: estimated variance-covariance matrix of the random effect.
Variance of the error term (SIGMA)	Scaled inverse χ^2	Number of degrees of freedom v, scale s^2.	Standard R function vs^2/rchisq(., v)	v: number between the number of patients and the number of observations used to obtain the estimate; s^2: estimated variance of the error.

Constraining Simulated Parameters

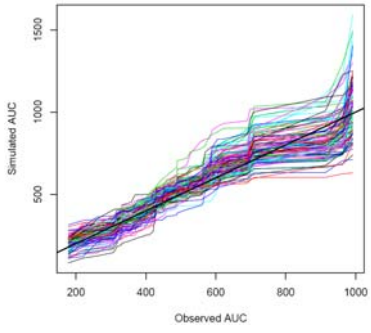
- When simulating from a multi-variate Normal covariance matrix, use caution about plausible values for population-level parameters.
- Constrain model so that plausible values are simulated, e.g.:
  LNCL=THETA
  CL=EXP(LNCL)
- Bootstrap distributions and Bayesian posteriors may already be constrained to plausible values

Generate Parameters by Sampling from Uncertainty Distributions

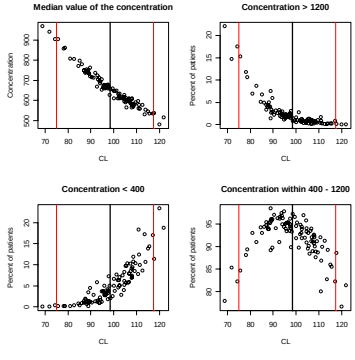


Simulate from Uncertainty Distributions using NONMEM Model Control Stream

Summaries of Simulations with Uncertainty: Quantile-Quantile Plot



Summaries of Simulations with Uncertainty: Sensitivity Analysis



NMSUDs R/NONMEM Package

Open-source tool, distributed under GPL.

Download alpha version of code from:
www.metruminstitute.org/downloads

Forward questions/comments to:
NMSUDs@metruminstitute.org