Overview of Modeling Tools in Drug Development

Rada Savic

Webinar series “Impact of Modeling & Simulation in Drug Development” hosted by Rosa & Co. LLC.

Dept of Pharmaceutical Biosciences, Uppsala University, Sweden
Overview of Modeling Tools in Drug Development

Pharmacometrics

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Software landscape

Type of modeling

Stage of drug development

Modeling process

Environment, experience

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Today’s focus

Modeling process

- Nonlinear mixed effects
- Preclinical/Clinical
Exploratory analysis, DATA

**Aim:** To easily explore data features:
- Time profiles
- Subsets (dose groups, covariates)
- Statistical Summaries (# of samples, subjects)
- Covariate profiles

**SOFTWARE:**
- any software which modeler is familiar with
  - R, S-plus, SAS
  - Any diagnostics software: Xpose, PLT Tools, Mango Solution
- modelling software with built-in graphical functions:
  - Monolix
  - Phoenix
(I) Exploratory analysis, MODEL STRUCTURES

Aim: To understand properties of the model
- Relationship between parameters and the time profile
- Parameter ranges
- Stiffness of the differential equation system

SOFTWARE:
- Berkeley Madonna
  - sliders (explore easily parameter space)
  - batch runs (several runs in parallel)
  - interactive & visual
  - easy to use

- Monolix (“check initial values” function)
Pulse Check?
II. Modelling & simulation tools

- Statistical theory
  - Frequentist
    - Parametric
  - Bayesian
    - Nonparametric
    - Both (Parametric)
NONLINEAR MIXED EFFECTS MODELS

● Increasingly used
  – in all phases of drug development for analysis of PKPD data
  – in clinical pharmacology for analysis of PK variability and for therapeutic drug monitoring
  – for analysis of response in clinical trials and cohorts

● Relies on several assumptions
  – structural model (model nonlinear with respect to parameters)
  – model for between-subject variability (assumption on random effects)
  – model for residual error

➢ Research in estimation methods, covariate testing, optimal design, model evaluation
Development of estimation methods

1970
- Nonlinear regression in PK and PD
- NONMEM FO

1980
- Linear mixed-effects models
- EM - algorithm
- NPML
- FOCE
- Bayesian methods using MCMC

1990
- Laplacian
- Gaussian Quadrature
- ITBS/P-PHARM
- NPEM
- POPKAN
- PKBUGS

2000
- Limitations of FOCE
- New ML algorithm based on Stochastic EM

## Software for estimation in NLMEM

<table>
<thead>
<tr>
<th></th>
<th>Maximum likelihood</th>
<th>Bayesian estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parametric</strong></td>
<td><strong>NONMEM</strong> (FO, FOCE, Laplace, <strong>SAEM</strong>)</td>
<td><strong>PK BUGS</strong></td>
</tr>
<tr>
<td></td>
<td>WinNonMix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R: nlme (FOCE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SAS</strong>: Proc <strong>NLMIXED</strong> (FO, FOCE, AGQ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ppharm (ITS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>MONOLIX</strong> (<strong>SAEM</strong>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S-ADAPT (MCPEM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDX-MCPEM</td>
<td></td>
</tr>
<tr>
<td><strong>Nonparametric</strong></td>
<td><strong>NPML</strong></td>
<td><strong>Dirichlet process</strong></td>
</tr>
<tr>
<td></td>
<td>NPEM (USC*PACK)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NONMEM</td>
<td></td>
</tr>
</tbody>
</table>
Parametric software

- The major software group
- Parameter distribution have defined parametric shape
- Maximum likelihood principle
- **Range of estimation algorithms:**
  - FO
  - FOCE
  - LAPLACE
  - SAEM
  - MCPEM
  - ITS

- **Available software:**
  - NONMEM, MONOLIX, PHOENIX
  - S-ADAPT, SAAM, NLME (R, S, SAS)
NONMEM

- Developed by Stuart L. Beal and Lewis B. Sheiner in the late 1970s at UCSF
- Versions up to VI are properties of UC
- Version 7 is the current version (ICON development solutions)
- Gold standard software used in academia and industry

The software consist of 3 parts:

1. Program itself – general regression program
2. PREDPP
   - Predictions computing
3. NM-TRAN
   - Pre-processor
   - Allows inputs to be specified in a user friendly manner
NONMEM7 advancements

- New estimation methods
- New residuals
- FORTRAN 95
- Other improvements
New Estimation methods

• Traditional methods: FO, FOCE, Laplace
• Expectation Maximization (EM) methods:
  - Iterative two stage EM (ITS)
  - Monte Carlo importance sampling EM (IMP)
  - Monte Carlo Importance Sampling EM Assisted by Mode *a Posteriori* estimation (IMPMAP)
  - Stochastic Approximation EM (SAEM)
• Markov Chain Monte Carlo Bayesian Analysis (BAYES)
Running the new methods in NONMEM

$EST METHOD=ITS INTERACTION NITER=50
$EST METHOD=IMP INTERACTION
$EST METHOD=IMPMAP INTERACTION
$EST METHOD=SAEM INTERACTION
$EST METHOD=BAYES INTERACTION
NONMEM 7 accepts multiple estimation lines

Useful for:

- Comparing results from different methods
- Getting initial estimates for a method which is sensitive to them
- Speed improvements
- Testing different methods
NONMEM 7 accepts multiple estimation lines (2)

$EST METHOD=ITS INTER FILE=ex1.ext NITER=500 PRINT=5 NOABORT SIGL=4
   CTYPE=3 CITER=10 CALPHA=0.05 NOPRIOR=1 NSIG=2

$EST METHOD=SAEM INTER NBURN=3000 NITER=500 PRINT=100
   SEED=1556678 ISAMPLE=2

$EST METHOD=IMP INTER EONLY=1 NITER=5 ISAMPLE=3000 PRINT=1 SIGL=8
   NOPRIOR=1

• Each method passes final estimates on to next method
• Any setting specified in one $EST will carry over to the next $EST, unless a new value is specified.
Execution control of multiple runs

- Each estimation step can be stopped at any time (Ctrl-K), and NONMEM will begin the new methods from stop point.
- (Ctrl-E) exits the NONMEM run completely.
## NONMEM7, New residuals

<table>
<thead>
<tr>
<th>Approximation</th>
<th>Prediction</th>
<th>Residual</th>
<th>Weighted residual</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FO</td>
<td>NPRED</td>
<td>NRES</td>
<td>NWRES</td>
<td></td>
</tr>
<tr>
<td>FO INTER</td>
<td>PREDI</td>
<td>RESI</td>
<td>WRESI</td>
<td>As in NM 6</td>
</tr>
<tr>
<td>FOCE</td>
<td>CPRED</td>
<td>CRES</td>
<td>CWRES</td>
<td>As in [1]. Some interaction included.</td>
</tr>
<tr>
<td>FOCE INTER</td>
<td>CPREDI</td>
<td>CRESI</td>
<td>CWRESI</td>
<td></td>
</tr>
<tr>
<td>MC based</td>
<td>EPRED</td>
<td>ERES</td>
<td>ECWRES</td>
<td>Monte Carlo version of CWRES</td>
</tr>
<tr>
<td>MC based INTER</td>
<td>EPRED</td>
<td>ERES</td>
<td>EWRES</td>
<td>Monte Carlo version of CWRESI</td>
</tr>
<tr>
<td>MC based</td>
<td></td>
<td>NPDE</td>
<td></td>
<td>As in [2]</td>
</tr>
</tbody>
</table>

NONMEM 7: Fortran 95

• NONMEM has been rewritten in Fortran 95

• Lots of limitations from previous versions reduced or eliminated
  – Improved error processing
  – Variable name lengths, data formats can all be adjusted
  – More object oriented (easier to change things and update)
F95 – user visible changes

- Different compiler – new installation
- ‘==, >, /=, >=’ instead of ‘EQ, GT, NE, GE’
- Data labels and variables may be 20 characters long
- 50 columns allowed in dataset
- Continuation character: ‘&’

\[ CL = \text{THETA}(1) \times \text{AGE} + \& \& \text{THETA}(2) \times \text{WT} \]
NONMEM7: Other improvements

1. Unconditional covariance step
   \$COV\ UNCONDITIONAL$

2. New output files
   - XXX.cov  covariance matrix
   - XXX.cor  correlation matrix
   - XXX.coi  inverse of covariance matrix (Fisher information matrix)
   - XXX.ext  iteration information
     - Parameter values, OFV, SE of parameters (final iteration only)
     - Eigen values and condition number (final iteration only)

3. New ADVAN (13)

4. Improved control of precision in calculations

5. Shrinkage
MONOLIX software

- Free Matlab-based software implementing SAEM
- Developed under supervision of Pr Marc Lavielle at INRIA
- www.monolix.org
- Stand-alone version using MCR
- C++ code for ODE models (fast)
- Extensive PKPD library
- MLXTRAN for user defined models
- v1.1 available since Feb 2005
- v3.1 released in October 2009
- v4.0 commercial, available in September 2011
Success of MONOLIX

- Success of MONOLIX
  - Team of 4 development engineers from INRIA
  - Grant from ANR (2005-2008)
  - Use in academia and drug companies
  - Monolix project: Support from drug companies

- Success of SAEM
  - Now implemented in NONMEM 7
  - Soon available in MATLAB
Estimation & Outputs
(as in MONOLIX): without linearization

- Estimation of all variability components (even small) and their standard errors
- Estimation of individual random effects
  - From simulated posterior/conditional distribution
  - Mean, Var and Mode without approximation
- Likelihood estimated by importance sampling
- Population and Individual residuals
  From simulated marginal and posterior distributions
- No real importance of shrinkage (for population parameter estimation)
Extensions of the SAEM algorithm (as available and evaluated in MONOLIX)

- **Correct handling of BQL data**
  

- **Models defined by ODE**
  

- **Inter-occasion variability**
  

- **Discrete repeated data**
  


- **Count repeated data**
  
Extensions of the SAEM algorithm, evaluated and to be available in MONOLIX

- **Models defined by SDE**
  
  
  Marcellin, Del Moral, Lavielle. The SAEM algorithm for nonlinear mixed effect models with stochastic differential equations. *PAGE 2010*

- **Hidden Markov models**
  
  Delattre, Savic, Miller, Karlsson, Lavielle. Estimation of mixed Hidden Markov model with MONOLIX. Application to daily seizures data. *ACOP 2009 and PAGE 2010*

- **Mixture distribution, mixture of models**
  
  Lavielle, Mesa, Chatel, Vermeulen. Mixture models and model mixtures in MONOLIX. *PAGE 2010*

- **Time to event data**
  
  joint model and repeated time to event data

- **REML Estimation**
  
PHARSIGHT’S PHOENIX® NLME™
What is Phoenix?

Answer: Pharsight's new desktop software **platform**

An integrated environment for analysis, modeling and simulation in drug development, from the lab to the clinic

**Products on the Phoenix Platform have:**

- Engineering to adhere to modernized standards
- New tools to enhance the power and efficiency of analyses
- An easy-to-use GUI, with drop-down menus and radio buttons
- Traceability to facilitate 21CFR11 compliance
- Visual workflows for organization and easy re-use
- Easy export to report format (entire projects or pieces)
- Seamless movement from one Phoenix product to another
Pharsight’s Products on the Phoenix Platform

Phoenix WinNonlin:
Noncompartmental analysis, individual compartmental PK/PD modeling, bioequivalence tests, and specified handling of BQL data

IVIVC Toolbox for Phoenix WinNonlin:
In vitro-in vivo correlation analysis, deconvolution, convolution, Levy plots

Phoenix Connect:
Core Phoenix Platform functionality (data management, graphics, workflows, tables, etc.) as well as support for S-Plus, NONMEM, R, SAS, and Sigma Plot; import/export of CDISC SDTM datasets

Phoenix NLME:
Population PK/PD, simulation, covariate selection, bootstrap, predictive checks
What is Phoenix NLME?
Answer: a state of the art population modeling software system for both expert and novice PK/PD scientists who need powerful modeling capabilities in a system that is easy to learn, use, and support.
Alternatives to built-in model building

Graphical model builder:

Textual model builder:

def test():
    deriv(A1 = - (Cl + C))
    urineclt(A0 = (Cl + C))
    C = A1 / V
    dosepoint(A1, idosevar = AllDose, mrdosevar = AllInfDose, intracvar = AllInfRate)
    error(EPSs = 1)
    observe(C0obs = C + CSEs)
    stparm(Y = tvU * exp(nU))
    stparm(C1 = tvC1 * exp(nC1))
    covariate(Weight)
    covariate(Age)
    fixef(tvP = c(1, 1.0, ))
    llik(tvP1 = c(1, 0.0, 0, ))
    ravel(diag(nW, nC1) = c(1, 1))
Sample Screenshots

Some tables and plots available after a PopPK model fit

Initial estimates graphical tool
### Table comparing requested values

<table>
<thead>
<tr>
<th>Name</th>
<th>Method</th>
<th>-2(1L)</th>
<th>AIC</th>
<th>BIC</th>
<th>-2(1L)Delta</th>
<th>AIC Delta</th>
<th>BIC Delta</th>
<th>#Obs</th>
<th>#Subj</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Covariate Selection Stepwise, cstep01</td>
<td>FOCEL-B</td>
<td>1010.8265</td>
<td>1020.8265</td>
<td>1036.0493</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>0.00006</td>
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<tr>
<td>2</td>
<td>Covariate Selection Stepwise, cstep01, Cl-Weight</td>
<td>FOCEL-B</td>
<td>957.44318</td>
<td>965.44318</td>
<td>997.7037</td>
<td>55.38332</td>
<td>51.38332</td>
<td>48.393895</td>
<td>6</td>
<td>155</td>
</tr>
<tr>
<td>3</td>
<td>Covariate Selection Stepwise, cstep02, Y-Weight</td>
<td>FOCEL-B</td>
<td>914.76612</td>
<td>924.76642</td>
<td>945.0149</td>
<td>95.0149</td>
<td>94.0149</td>
<td>90.997985</td>
<td>6</td>
<td>155</td>
</tr>
<tr>
<td>4</td>
<td>Covariate Selection Stepwise, cstep02, Y-Weight</td>
<td>FOCEL-B</td>
<td>872.00989</td>
<td>882.00989</td>
<td>912.0574</td>
<td>0</td>
<td>0</td>
<td>100.8714</td>
<td>7</td>
<td>155</td>
</tr>
<tr>
<td>5</td>
<td>Covariate Selection Stepwise, cstep01, Cl-Weight</td>
<td>FOCEL-B</td>
<td>1010.897</td>
<td>1022.897</td>
<td>1040.393</td>
<td>0.13676</td>
<td>-1.883241</td>
<td>-4.9966651</td>
<td>6</td>
<td>155</td>
</tr>
<tr>
<td>6</td>
<td>Covariate Selection Stepwise, cstep04, Y-Weight, Cl-Weight</td>
<td>FOCEL-B</td>
<td>914.02998</td>
<td>923.02998</td>
<td>949.3193</td>
<td>96.31932</td>
<td>95.31932</td>
<td>93.84682</td>
<td>7</td>
<td>155</td>
</tr>
<tr>
<td>7</td>
<td>Covariate Selection Stepwise, cstep07, Cl-Weight, Y-Weight, Cl-Weight</td>
<td>FOCEL-B</td>
<td>873.35704</td>
<td>889.35704</td>
<td>919.7052</td>
<td>137.7052</td>
<td>131.7052</td>
<td>122.3030</td>
<td>8</td>
<td>155</td>
</tr>
<tr>
<td>8</td>
<td>Covariate Selection Stepwise, cstep01, Y-Weight</td>
<td>FOCEL-B</td>
<td>1000.6392</td>
<td>1010.6392</td>
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<td>155</td>
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<tr>
<td>9</td>
<td>Covariate Selection Stepwise, cstep01, Y-Weight, Y-Weight, Cl-Weight</td>
<td>FOCEL-B</td>
<td>912.29412</td>
<td>926.29412</td>
<td>947.5381</td>
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<td>91.50053</td>
<td>7</td>
<td>155</td>
</tr>
<tr>
<td>10</td>
<td>Covariate Selection Stepwise, cstep1, Cl-Weight, Y-Weight</td>
<td>FOCEL-B</td>
<td>873.68868</td>
<td>891.68868</td>
<td>919.9983</td>
<td>137.9983</td>
<td>131.9983</td>
<td>122.0626</td>
<td>8</td>
<td>155</td>
</tr>
</tbody>
</table>
Model comparer output

Requested side-by-side plots

<table>
<thead>
<tr>
<th>Covariate Selection Stepwise</th>
<th>Covariate Selection Stepwise</th>
<th>Covariate Selection Stepwise</th>
</tr>
</thead>
<tbody>
<tr>
<td>cstep00, CObs(µg/mL)</td>
<td>cstep01 CI-Weight, CObs(µg/mL)</td>
<td>cstep02 V-Weight, CObs(µg/mL)</td>
</tr>
<tr>
<td>Weighted Residuals</td>
<td>Weighted Residuals</td>
<td>Weighted Residuals</td>
</tr>
<tr>
<td>Standard Normal Quantiles</td>
<td>Standard Normal Quantiles</td>
<td>Standard Normal Quantiles</td>
</tr>
</tbody>
</table>

Pop 0.0
Cw/RES

Pop DV vs IPRED
Nonparametric software

Key difference:
- parameter distribution are not assumed to have predefined normal shape
- distributions shape is estimated from the data

Software:
- NPAG
- NPML
- NONMEM: VI & 7
- Phoenix
Bayesian analysis & software

- Philosophical differences in the statistical approach compared to frequentist analysis

<table>
<thead>
<tr>
<th></th>
<th>Bayesian</th>
<th>Frequentist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Random variables that arise from a distribution</td>
<td>Have a single true value</td>
</tr>
<tr>
<td>Prior</td>
<td>Data always combined with prior (although priors can be minimally informative)</td>
<td>Data is seldom combined with priors (formally)</td>
</tr>
<tr>
<td>Parameter uncertainty</td>
<td>Directly described as probabilities</td>
<td>The true parameter is within the 95% CI on 95% of the occasions if a study is repeated many times using samples from the same population</td>
</tr>
</tbody>
</table>
NONMEM vs. WinBUGS for Bayesian analysis

- **NONMEM environment**
  - Environment familiar
    - Data set
    - Model file
  - Easy switch between estimation methods
  - Multiple dosing handled for all models (PREDPP)

- **WinBUGS**
  - A variety of built-in distribution functions
  - No restrictions on levels of random effects
  - Runtimes shorter for some problems
  - More users experienced with Bayesian analyses
Pulse Check?
Model Diagnostics and Evaluation

- There are a range of tools that can aid in producing model diagnostics

- Model diagnostics:
  1. Numerical: PsN, Phoenix, Monolix
     - Numerical predictive check
     - Log-likelihood profiling
     - Nonparametric bootstrap, etc.
  2. Visual: Xpose, PLT Tools, Phoenix, Monolix, Mango solutions
     - Wide range of diagnostic graphs
     - Visual & Posterior predictive checks
What can PsN do?

- Assist modellers in different aspects of pharmacometric analysis:
  1. NONMEM run control
  2. Automatic computation of important model diagnostics
  3. Computer-intensive statistical methods
NONMEM run control with PsN

Main features:

- Executing NONMEM jobs with extended control
  - Automatic rerunning of models using perturbed initial estimates (to find/avoid local minima)

- Parallel execution of multiple NONMEM jobs

- Summary of main diagnostics of a NONMEM run
Computer-intensive statistical methods with PsN

1. Numerical and visual predictive checks \((\text{npc}, \text{vpc})\)
2. Nonparametric bootstrap \((\text{bootstrap})\)
3. Case-deletion Diagnostics \((\text{cdd})\)
   - Cross-Validation and Jackknife
4. Log-likelihood Profiling \((\text{llp})\)
5. Stepwise Covariate Model Building \((\text{scm})\)
6. Stochastic simulation and estimation \((\text{sse})\)
   - Randomization tests, Bias, RMSE, ...
What is Xpose?

- An population PK/PD model building aid for NONMEM.

- Xpose tries to make it easier for a modeler to use diagnostics in an intelligent manner.
What can Xpose do?

- Data exploration
- Run summaries
- Goodness-of-fit plots
- Individual plots
- IIV investigations
- Model comparisons
- Covariate model building (GAM, tree, etc)
- Customized/automatic plot creation after every NONMEM run
- Publication quality (customizable) plots
- Visual Predictive Checks (raw data, diagnostics)
- Mirror plots
Pulse Check?
RUN RECORD MANAGERS
PIRANA
The flexible modeling environment for NONMEM
PIRANA: Main features

- Model / run manager
  - Structure models (parent / reference models)
  - Keep notebook / use coloring

- Graphical user interface for PsN / nmfe
  - Connect to cluster(s) or run locally

- Built-in functionality for data-inspection
  - Create run reports with parameter estimates and run info
  - Connection with R / Xpose for advanced graphics
  - Extensible with custom R scripts / wizards

- Works on Windows / Linux / Mac OSX
<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Description</th>
<th>Method</th>
<th>Dataset</th>
<th>OPV</th>
<th>UOF</th>
<th>S</th>
<th>C</th>
<th>B</th>
<th>Slg</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>example1</td>
<td>Two compartment Model, Using ADVAN3, FOCEi</td>
<td>example1.csv</td>
<td>-1211.028</td>
<td>S</td>
<td>C</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>example10</td>
<td>F_FLAG04est2a.cf</td>
<td>example10.csv</td>
<td>10035.073</td>
<td>S</td>
<td>M</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>example10i</td>
<td>F_FLAG04est2a.cf</td>
<td>example10i.csv</td>
<td>10036.105</td>
<td>S</td>
<td>M</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>example2</td>
<td>Two compartment Model, Using ADVAN3, FOCEi</td>
<td>example2.csv</td>
<td>-10772.143</td>
<td>S</td>
<td>C</td>
<td>2.5</td>
<td>Use for sim</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>example3</td>
<td>Population Mixture Problem in 1 Compartment, FOCEi</td>
<td>example3.csv</td>
<td>-9961.746</td>
<td>S</td>
<td>C</td>
<td>3.3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>example4</td>
<td>Population Mixture Problem in 1 Compartment, FOCEi</td>
<td>example4.csv</td>
<td>-9961.055</td>
<td>S</td>
<td>C</td>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>example5</td>
<td>Population Mixture Problem in 1 Compartment, FOCEi</td>
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Development continues

- New version (June 2011):
  - Compatible with NM 7.2 (e.g. parallelization)
  - Wizards for e.g. model creation.
  - Compare parameter estimates multiple runs
  - Full PsN support

- More info:
  - [www.pirana-software.com](http://www.pirana-software.com)
Census, overview

- Census, first released in 2002, is a free, open-source Windows-based project management tool for NONMEM V, VI and 7

- Key features:
  - A fully-integrated overview of all the available NONMEM runs in a given project, arranged to facilitate easy viewing of all relevant information with a minimum of mouse clicks
  - Full Xpose 4/R integration, facilitating rapid generation of publication-quality, fully-customizable goodness-of-fit plots in PDF, BMP, JPEG, PNG, Postscript, TIFF and XFig formats
  - HTML run reports, summarizing key run data
  - Export of all project run data to CSV format (including covariance matrices)
  - Audit trailing
Census

Full, automatic Xpose integration
Census
Status, limitations and future

- Used extensively in pharmacometrics community (academia, regulatory, industry, SMEs)
- [http://census.sourceforge.net](http://census.sourceforge.net)
- Key drawback: Microsoft Windows only (although works well within Parallel/VMware virtual machines on Mac OS X and Linux)
- Next release: 1.2b3, imminent – complete NONMEM 7 integration
- Upcoming features:
  - PsN integration
  - Cross-platform migration
Pulse Check?
Conclusions

- We now have many tools to choose from to achieve our intended mission of fostering model-based drug development
- Our mission is to advocate change and innovation and evolution of the qualitative drug-development mindset
- Familiar and favorite tools should not get in the way of our mission
- Apply the best tool for the job, as all tools have strengths and weaknesses
- Keep learning!
Acknowledgements

- Dr. Helen Moore
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- Dr. Justin Wilkins
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