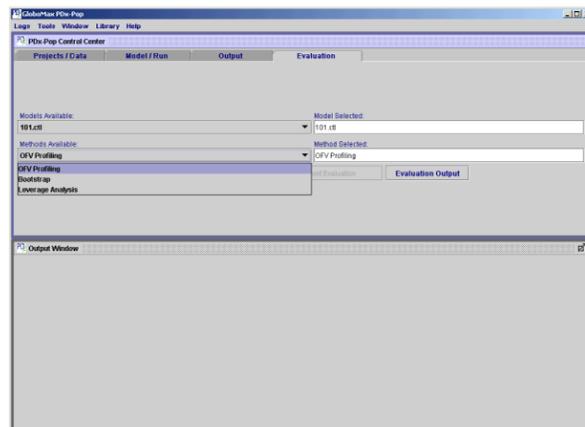


Purpose

Population PK-PD model evaluation is used to determine whether the model developed is adequate for its intended purpose and to generate informative diagnostics. The evaluation methods for non-linear mixed effect models generally involve relatively complicated and time consuming techniques that limit their implementation to more experienced modelers. However, these methods often employ methods that are suitable for automation via a graphical user interface (GUI) that allows selection of the model to evaluate and user-entered evaluation parameters at run-time and display of calculated results and diagnostic plots.

Methods

Figure 1. Screenshot of PDX-Pop showing new Model Evaluation Module.



Model Evaluation Methods:

1. Objective Function Value Profiling:

Confidence intervals of the parameter estimates based on the NONMEM estimates of standard errors are based on the assumption of normality of distributions of the parameters. NONMEM, though, only requires these distributions to be symmetric, not necessarily multivariate normal. In this case, confidence intervals based on standard errors may not reflect the true confidence limits. Moreover, actual confidence interval may not be symmetric. In this case, NONMEM standard error estimates cannot be used to estimate confidence intervals of the parameter estimates.

Another way to establish a confidence interval for an estimated parameter is by objective function profiling. The procedure consists of multiple runs of the final model with one of the parameters fixed at several different values in the vicinity of its final estimate. All the other parameters are then estimated. A set of minimum objective function values (OF) obtained in the runs is plotted against the value of the parameter that was fixed. Values of the parameter that correspond to a 3.84 OF increase compared to the OF at the final estimate of the parameter are the boundaries of the 95% confidence interval for that parameter.

The PDX-Pop Model Evaluation module automates the objective function profiling and asymmetric confidence interval calculation. The program calls NONMEM to calculate the minimum of the objective function and estimates of the parameters. It outputs result to a file that contains the fixed theta, estimate of other parameters and the value of the objective function. The program allows the user to specify the model to use, the theta intended to be profiled and whether more or less points in the profile are required by the user.

2. Leverage Analysis:

Leverage analysis evaluates the effect on the model parameters of repeatedly removing a portion of the data set representing a random segment of the patients. The mean parameter values obtained by repeatedly fitting the final population model to a fixed number of jackknife replicates are compared to the final population model parameter estimates obtained without jackknife replication.

Leverage analysis procedure consists of the following steps:

1. All patients are randomly divided into N groups, each consisting of roughly (100/N)% of the total number of patients. Excluding patients from one of N groups from the full data file created N new data files.
2. The model is fitted to each of the resulting data files, and the model parameters are compared with those obtained from the fit of the full data file.
3. The procedure is repeated several times (with different random selections of N groups and/or different values of N) to ensure a reliable comparison.
4. Estimates of the parameters obtained for each partial data set are plotted and visually analyzed for stability.
5. Following, Jackknife parameter estimates and confidence intervals are obtained using Student t approximations.

The PDX-Pop Model Evaluation module automates the Leverage analysis and computation of Jackknife estimates, variance, and confidence intervals, and plotting of leverage estimates. The program calls NONMEM to calculate the minimum of the objective function and estimates of the parameters. It outputs result to a file that contains the parameter estimates and the value of the objective function. The program allows the user to specify the model to use and a random seed (or auto seed) for generation of the data sets for the leverage analysis..

3. Bootstrap Analysis:

Bootstrapping is a data re-sampling method for estimating sampling variances, confidence intervals, and stability of regression models. Bootstrapping can be especially useful for evaluating the performance of a population model where ethical and medical concerns limit sample size. Using the bootstrap approach, the mean parameter values obtained by repeatedly fitting the final population model to a reasonable number of bootstrap replicates are compared to the final population model parameter estimates obtained without bootstrap replication.

Bootstrap analysis procedure consists of the following steps:

1. The new replication of the data file is obtained by random draw (with replacements) from the original data file.
2. The model is fitted to the resulting data file, and the model parameters are saved for the final analysis.
3. Steps 1 and 2 are repeated 100-1000 times (with the different random draws).
4. Distributions of the parameter estimates are plotted and visually analyzed.
5. Bootstrap parameter estimates, standard errors and confidence intervals are obtained.

The PDX-Pop Model Evaluation module automates the bootstrap analysis, computation of bootstrap estimates, variance, and confidence intervals and plotting of histogram of the parameter estimates. The program controls creation of bootstrap data files and calls NONMEM to calculate the minimum of the objective function and estimates of the parameters. It outputs results to a file that contains all parameter estimates and the value of the objective function. The program allows the user to specify the model to use, the random seed (or automatic seed), and the number of bootstrap replications.

Results

1. Objective Function Value Profiling:

Confidence intervals of each of the fixed effect parameters of the final model can be estimated by profiling of the objective function. Because variances of the random effects and error parameters can be expressed through fixed effect parameters, the program can also be used for profiling of the variances of random effects and error terms. The confidence intervals obtained through profiling can be compared with the NONMEM confidence intervals. In the following example, interindividual and residual variances were reparameterized as thetas to allow them to be profiled.

Figure 2. Objective function profile and confidence interval for Omega11 (obtained by reparameterization as Theta3).

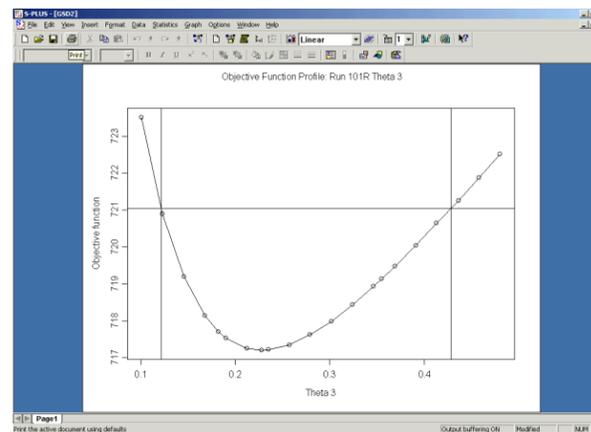


Figure 3. Output from objective function profiling of Omega11.

```
PDX-Pop OFV Profiling Report for Run 101R
profiling.ssc [14OCT2004]
[1] "Confidence interval(3.84 level) for the
[2] parameter Theta 3* is from 0.1217 to 0.4281"

* Omega11 was reparameterized as Theta 3
```

2. Leverage Analysis:

Results of the leverage analysis are the plots of the parameter estimates versus leverage run number. Output of the program is the confidence interval of the parameter as determined by the leverage estimates.

Figure 4. Leverage analysis of model 101.ctl. (Plot for thetas shown, similar plots for omegas and sigmas.)

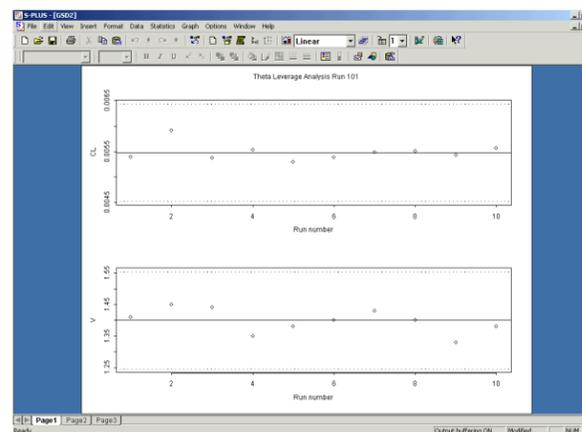


Figure 5. Output from leverage analysis of model 101.ctl.

```
PDX-Pop Leverage Analysis Report for Run 101

$theta.summary:
      Leverage Leverage      Leverage      Leverage      Leverage
Names  .est  .var      .RSE      .lower      .upper
1 CL  0.00558  2.993333e-007  9.804904  0.004342343  0.006817657
2 V   1.37000  1.467778e-002  8.843203  1.095935409  1.644064591

      NONMEM.se  NONMEM.RSE  NONMEM.est  NONMEM.lower  NONMEM.upper
1  0.000486    8.868613    0.00548    0.00452744    0.00643256
2  0.078600    5.614286    1.40000    1.24594400    1.55405600
```

Similar output generated for omegas and sigmas

3. Bootstrap Analysis:

Results of the bootstrap analysis are the histograms of the parameter estimates. These histograms also contain the NONMEM estimate (the solid vertical line) and NONMEM 95% confidence interval (the dashed vertical lines). Output of the program is the list with NONMEM and bootstrap estimates and standard errors.

Figure 6. Bootstrap parameter plots for model 101.ctl. (Plot for omegas shown, similar plots for thetas and sigmas.)

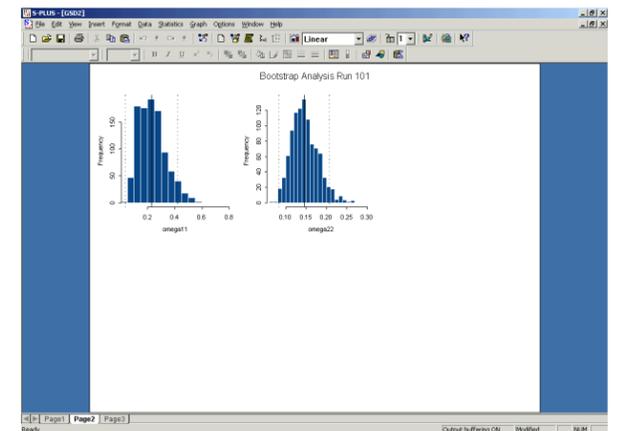


Figure 7. Output from bootstrap analysis of model 101.ctl.

```
Comparison of NONMEM Bootstrap Analysis Results for Omega Parameters:
$runNumber:
[1] "boot-101"

$NONMEM.param:
      est      se  lowerCI  upperCI
1  0.228  0.0982  0.035528  0.420472
2  0.146  0.0317  0.083868  0.208132

$Bootstrap.param:
      est      se  lowerCI  upperCI
1  0.2383117  0.10503453  0.0883  0.482
2  0.1474781  0.03340831  0.0907  0.219

$Success.Rate:[1] 100

Similar output generated for thetas and sigmas
```

Conclusions

Objective function profiling, leverage analysis, and bootstrapping were implemented as the initial set of a larger group of model evaluation methods to be implemented within PDX-Pop, a Java-based GUI designed to facilitate NONMEM analyses. The three methods were incorporated into a new model evaluation module.

The implementation generates S-Plus® scripts that constitute documentation of the methods, summary tables where appropriate, and report-ready graphs suitable for inclusion in reports. Methods requiring re-sampling or data splitting automatically generate the required data subsets and tabulate random seeds thus allowing replication of the methods.

Incorporating model evaluation features into a graphical environment that includes data and project management, model building and output evaluation provides a complete framework for efficient population modeling that is readily used by less-experienced users and is more time effective for proficient modelers. The new model evaluation framework facilitates extension of PDX-Pop to easily include new and innovative model evaluation methodologies. Future implementations will incorporate posterior predictive check, 95% confidence intervals of the predictions for a typical individual, and automated covariate searching.