



## ICON: Symbol of Excellence Providing Standard of Excellence in Population Analysis Software

ICON is committed to providing the most advanced analysis methods and tools for the pharmaceutical industry through continued enhancements to the NONMEM<sup>®</sup> software, the industry standard for population pharmacokinetic/pharmacodynamics analysis; ensuring pharmaceutical companies may continue to use this trusted analysis tool, incorporating classical as well as new analysis algorithms for present day pharmaceutical development. In addition, PDx-Pop<sup>™</sup>, a graphical interface working in concert with NONMEM<sup>®</sup>, integrates with existing tools and its own automated methods to expedite population modeling and analysis, providing optimal flexibility, increased efficiency and functionality

### New Features of NONMEM<sup>®</sup> 7.4, Planned Release Date April 2017

#### PARALLELIZATION EXTENDED TO MORE TASKS

The evaluation of weighted residuals for the \$TABLE step. This can take a long time for Monte Carlo assessed EWRES and NPDE, so these would benefit from parallelization. To turn off parallelization:

**\$TABLE ... PARAFILE=OFF**

Evaluation of final empirical Bayes estimates of etas (EBE's) after the estimation step (when FNLETA=1). To turn off parallelization during the FNLETA step,

**\$EST ... FPARAFILE=OFF**

Simulation can now be parallelized. Only on occasion is simulation so slow that it needs to be parallelized. So it is off by default. To turn it on:

**\$SIM ... FPARAFILE=ON**

Permit constant seed patterns regardless of whether you choose parallelization or not with

**\$SIML ... PARAFILE=ON RANMETHOD=P**

Nonparametric analysis can be parallelized. To turn it off,

**\$NONP PARAFILE=OFF**

#### ADDITIONAL TABLE OUTPUT CONTROL

Specific table records may be excluded from being printed. A data item or defined variable may be identified on a \$TABLE record as an EXCLUDE\_BY variable, which if not 0, will exclude the record. For example:

**\$PK**

...

**EXCL=0**

**IF(ID.GE.45.AND.ID.LE.53) EXCL=1**

...

**\$TABLE ID TIME DV IPRED CL V1 Q V2 ETAS(1:LAST)**  
**EXCLUDE\_BY EXCL NOAPPEND FILE=exctable.par NOPRINT**

The table exctable.par will not list records from subjects 45 to 53. If more than one exclusion variable is listed, then if any of these have a non-zero value, the record will be excluded.

#### IMPROVED SPEED FOR FOCE/ITS ANALYSES

The FAST option has been added to FOCE/ITS analysis, which can increase the speed of these analyses by up to 3-4 fold during the estimation of differential equation models, as well as speed up the covariance step by the same factor. The FAST method takes advantage of mapping analytical eta derivatives via MU referencing to evaluate theta analytical derivatives. This increases the speed and accuracy of derivatives required for FOCE assessment. For thetas that should not have inter-subject variability, provide a Mu-reference equation, and set OMEGA to 0. For example:

**\$PK**

**MU\_1=THETA(1)+THETA(2)\*LOG(AGE)**

**MU\_2=THETA(3)**

**MU\_3=THETA(4)**

...

**\$OMEGA BLOCK(2)**

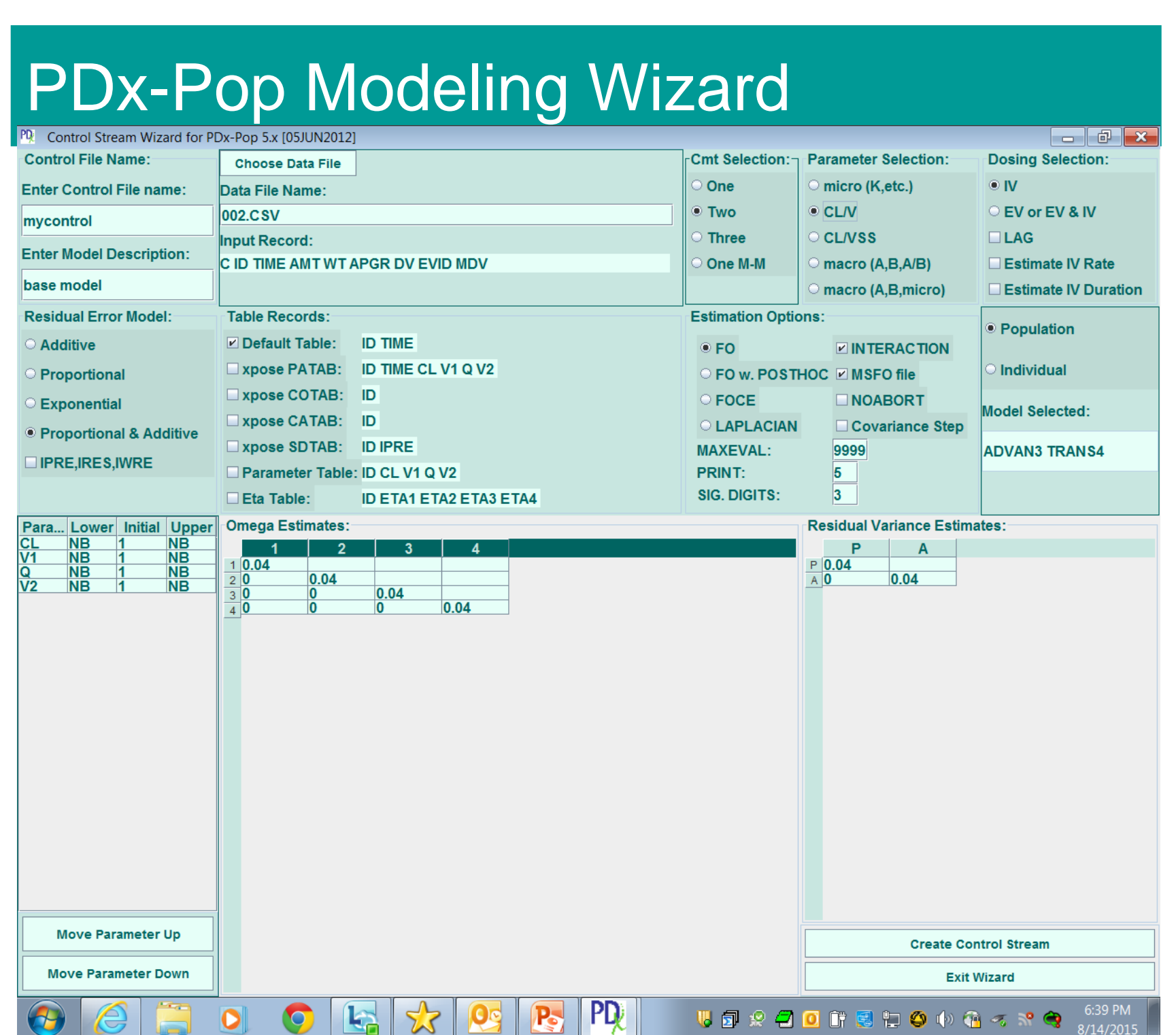
**0.2**

**0.01 0.2**

**\$OMEGA (0.0 FIXED)**

...

**\$EST METHOD=1 INTERACTION FAST ...**



#### PDx-Pop Extended Summary Output

FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL	DESCRIPTION/ VARIABILITY		
THETA 1	1.69	2.50%	1.61	1.77	LN(CL)
2	1.61	2.97%	1.52	1.70	LN(V1)
3	0.820	8.63%	0.681	0.959	LN(Q)
4	2.39	2.17%	2.29	2.49	LN(V2)

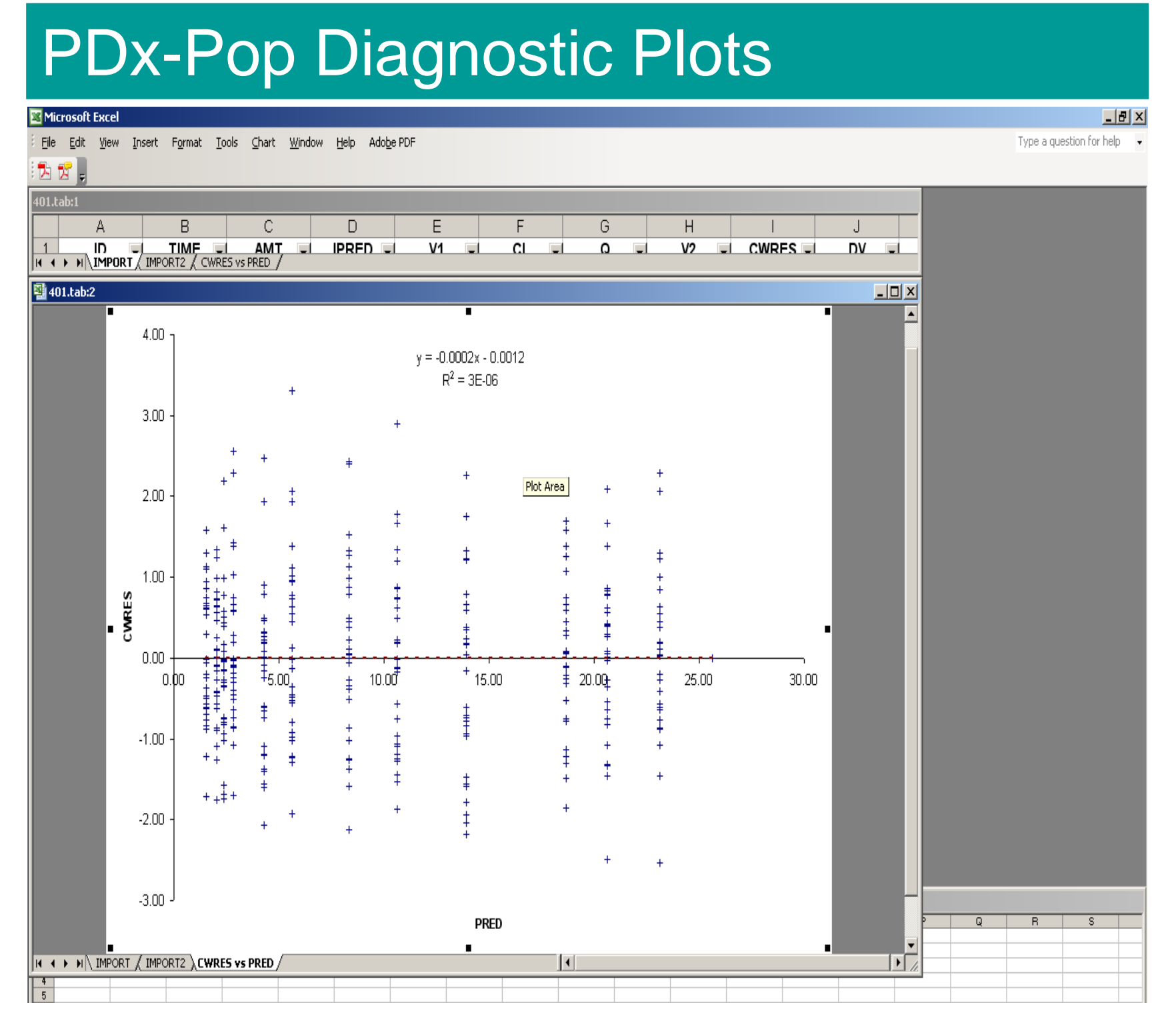
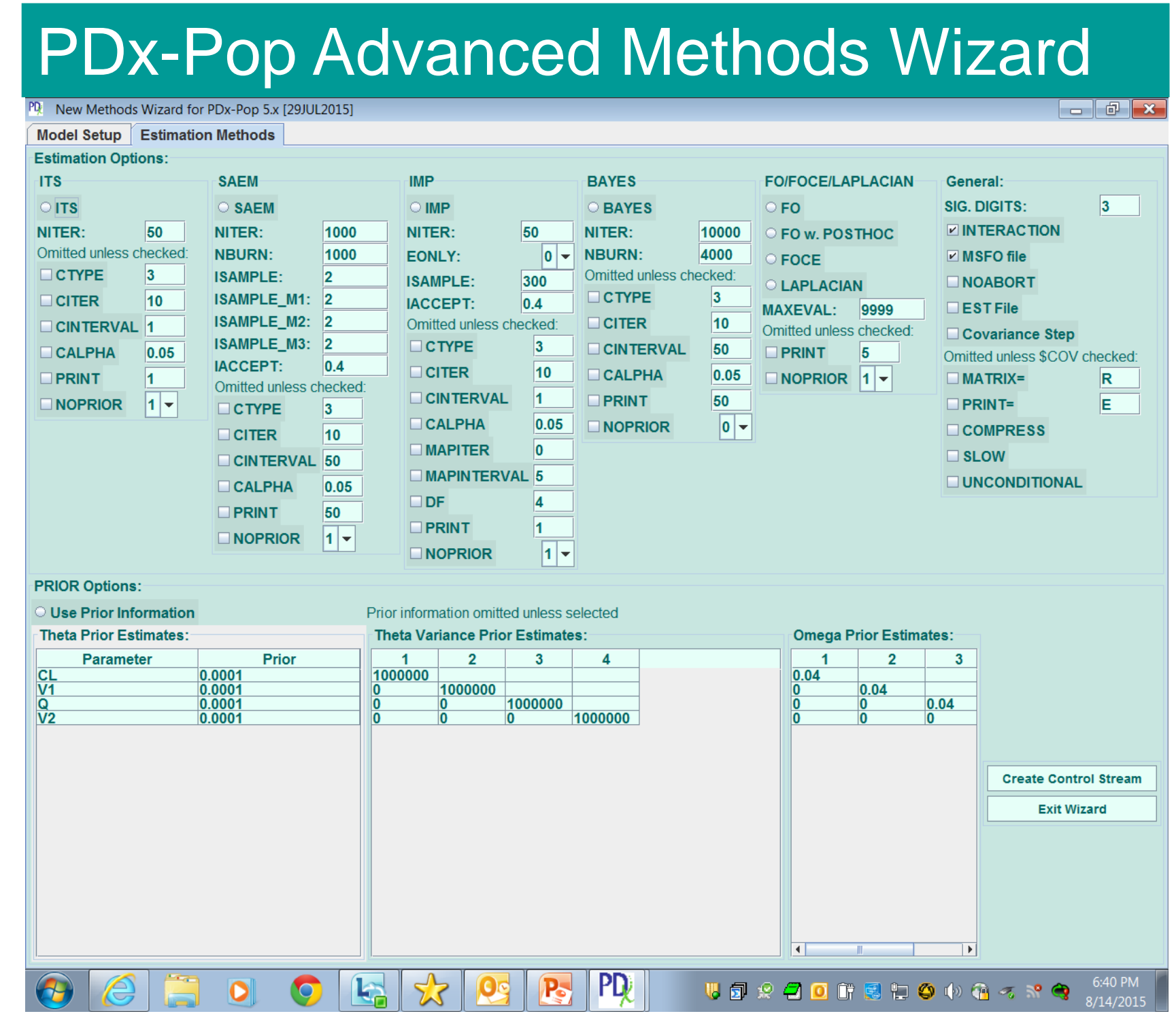
  

OMEGA	16.5%	0.112	0.218	CV =	40.6%	
1,1	16.5%	0.112	0.218	R =	-0.00503	
2,1	-0.00742	2.90e+003%	-0.0429	0.0414	R =	-0.00503
3,1	0.0124	244%	-0.0468	0.0716	R =	0.0704
3,2	0.0160	221%	-0.0534	0.0854	R =	0.1102
3,3	0.188	40.3%	0.0396	0.336	R =	43.4%
4,1	-0.0127	187%	-0.0593	0.0339	R =	-0.0807
4,2	0.0319	1.68%	-0.0318	0.0396	R =	0.0992
4,3	0.0333	137%	-0.0561	0.123	R =	0.198
4,4	0.150	26.7%	0.0714	0.229	CV =	38.7%

\*Indicates 95% confidence interval that includes zero  
 %RSE is percent relative standard error (100% x SE/EST)  
 Akaike Information Criterion = -1092.26  
 Schwarz Bayesian Criterion = -1033.26  
 CONDITION NUMBER = 26.7 (DOES NOT EXCEED 1000)

#### IMPROVEMENTS IN IMP, SAEM, BAYES ANALYSIS

- A new kernel has been added to the Bayesian sampling of individual parameters, that reduces the correlation between Metropolis-Hastings generated samples, for BAYES and SAEM methods.
- A Hamiltonian/No U-Turn Sampling (NUTS) algorithm has been implemented for BAYES analysis, similar to that in the software Stan. This algorithm increases the efficiency of Markov-Chain Monte Carlo Bayesian sampling among population and individual parameters, by reducing the statistical correlation between samples.
- New algorithms for creating multivariate samples for importance sampling are offered, such as mixed-normal and additional t-distribution methods.
- The GRDQ option provides faster importance sampling analysis when several thetas not mu-referenced need to be gradient assessed.



#### BUT WAIT, THERE'S MORE...

- \$SIM REWIND feature allows original data set to be used for all sub-problems.
- \$SIM NOSUPRESET feature allows simulation seeds not to be reset with each iteration of a super-problem.
- Read MSF files generated from earlier versions of NONMEM
- Omegas and Sigmas may have inverse Wishart or gamma distribution priors.
- Thetas may have normal or t-distribution priors.

