

# The System for Population Kinetics

An Open Source Web Service for  
Population Analysis

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# Our Approach

- The System for Population Kinetics (SPK) employs a distributed architecture and web services to eventually deliver population analysis results rapidly and consistently
- The project builds on the availability of open source libraries and programs that minimize the need for completely new modules
- It is being built with a cluster architecture in mind

# The System for Population Kinetics

- Funding from NIH/NCRR and NIH/NIBIB
- Research resource
  - R&D, Collaboration, Service, Training, Dissemination
- Various incarnations:
  - A standalone executable
  - A portable software library in C++
  - **A web service with open source distribution**

# The Open Source Paradigm

- Source code is not secret
- Source code must be available
- The source can be redistributed
- If an open source software is modified and the enhancements are distributed, they also have to be covered under an open source license
  - (there can be exceptions)

# Open Source Advantages

- **SPK leverages the existence of other open source software products whenever possible**
  - *MySQL* relational database management system
  - *Tomcat* web server
  - *NetBeans* interactive development environment
  - *GNU RCS* revision control system
  - *Atlas* (Automatically Tuned Linear Algebra Software)
  - *CppAd* C++ automatic differentiation library
  - *GNU Operating System*
  - *Bugzilla* for bug and enhancement tracking

# Open Source Licenses

- Even a small product like SPK contains software released under a variety of open source licenses:
  - *Apache License*
  - *Artistic License*
  - *BSD License*
  - *GNU General Public License*
  - *GNU Library or Lesser General Public License*
  - *Mozilla & Netscape Public Licenses*
  - *Sun Microsystems Public Software License Agreement*

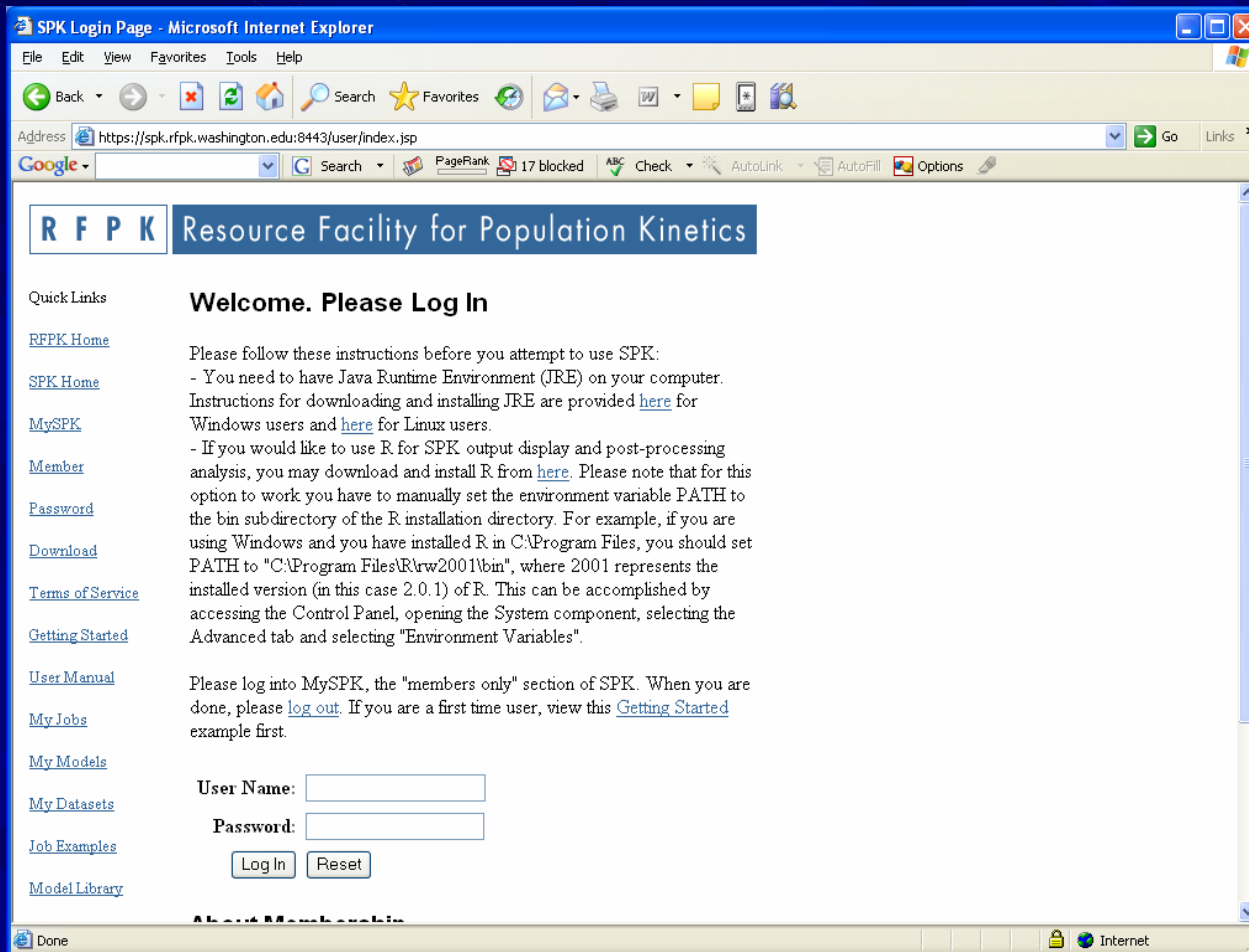
# The SPK Architecture



# Current SPK Capabilities

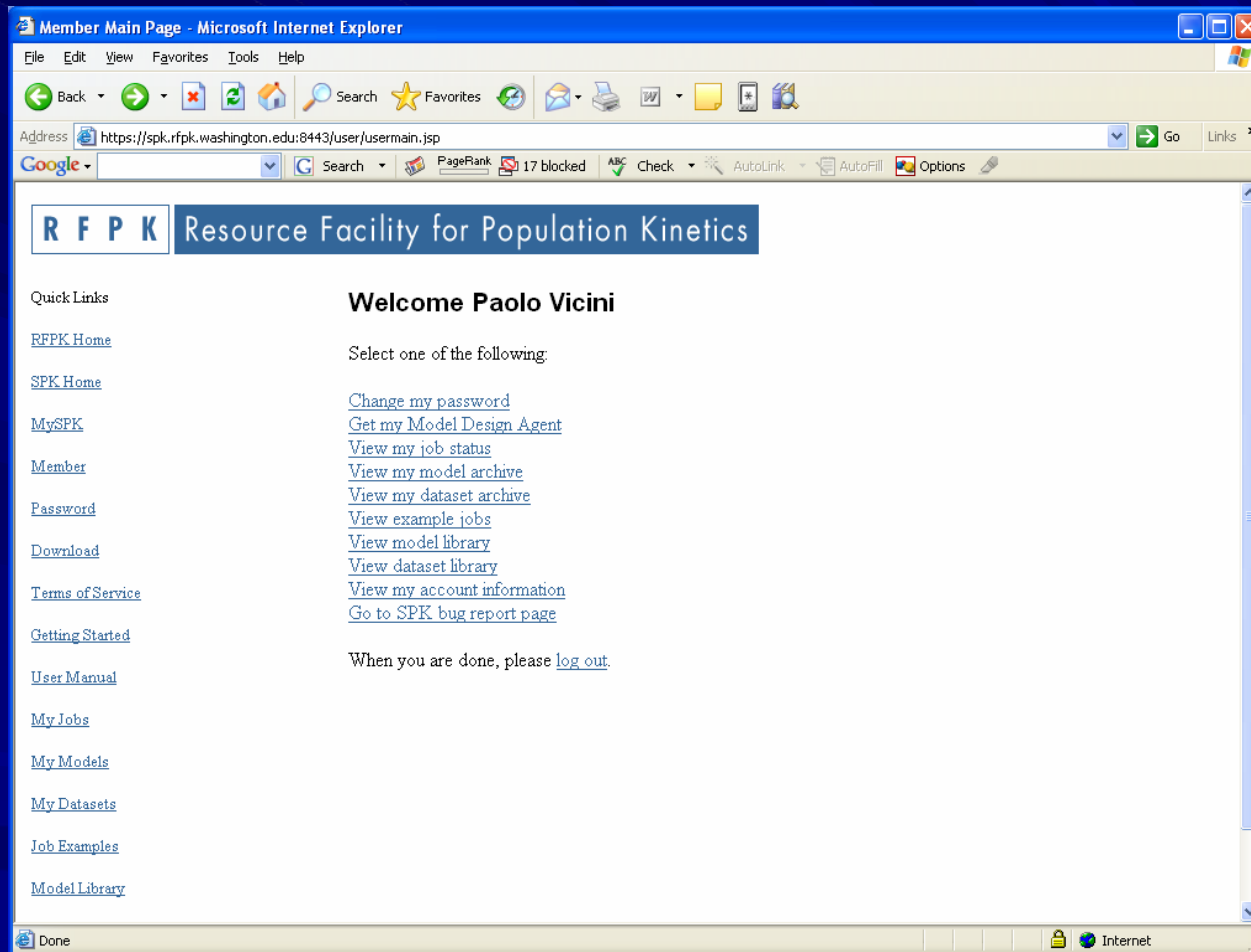
- Nonlinear mixed effects models defined with algebraic and differential equations
- Likelihood approximations for MLE
  - First Order
  - Expected Hessian
  - Laplace
  - Monte Carlo (or Grid) Likelihood at the estimate
- Standard Two Stage and Simulation capabilities are also available

# Website Point of Entry



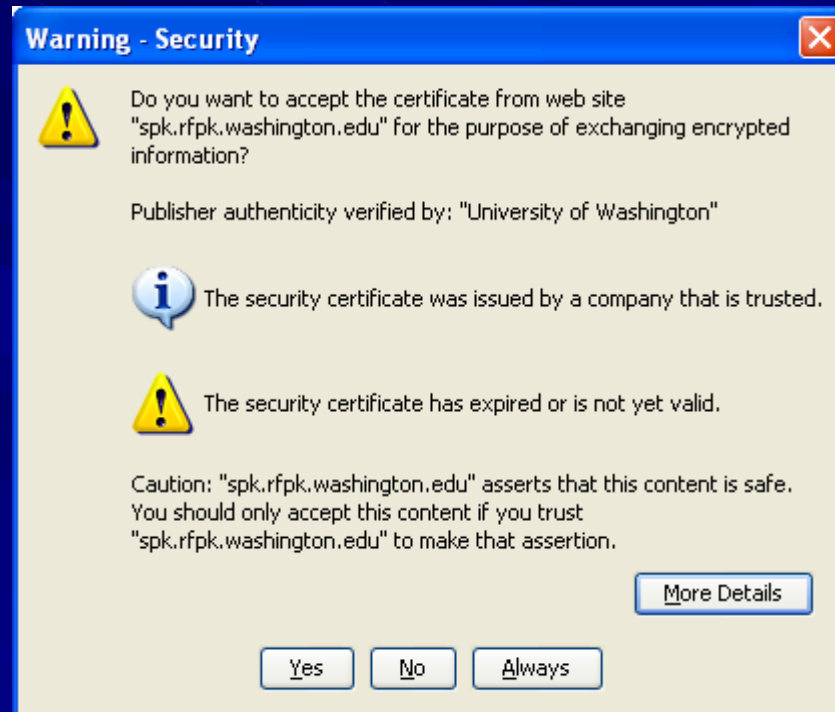
■ Access to SPK requires an account

# Login Screen



■ Accounts are available upon request

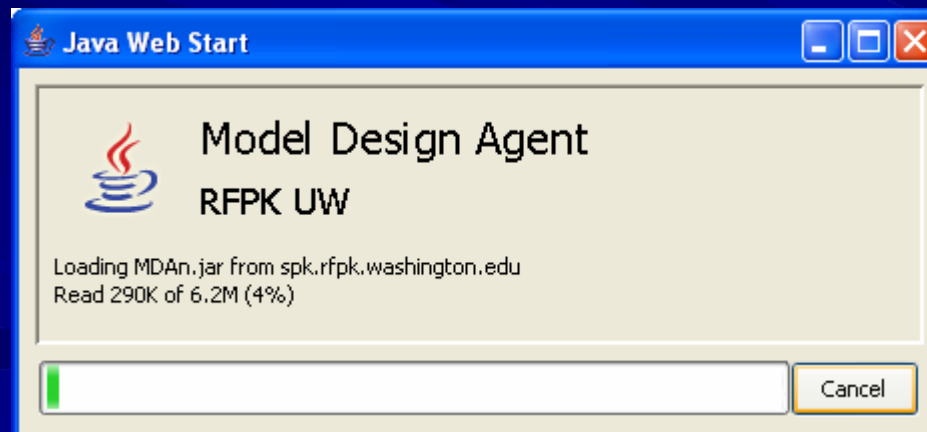
# Security Certificate



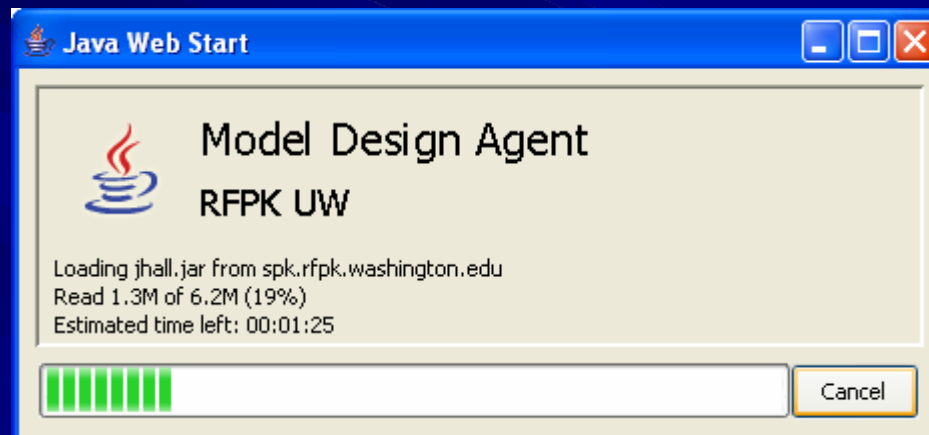
■ Dataset transactions are secure

# Download of the MDA

- The MDA is the client that runs on the user's machine
- The MDA is updated every time the user logs in
- New features are instantly available when deployed

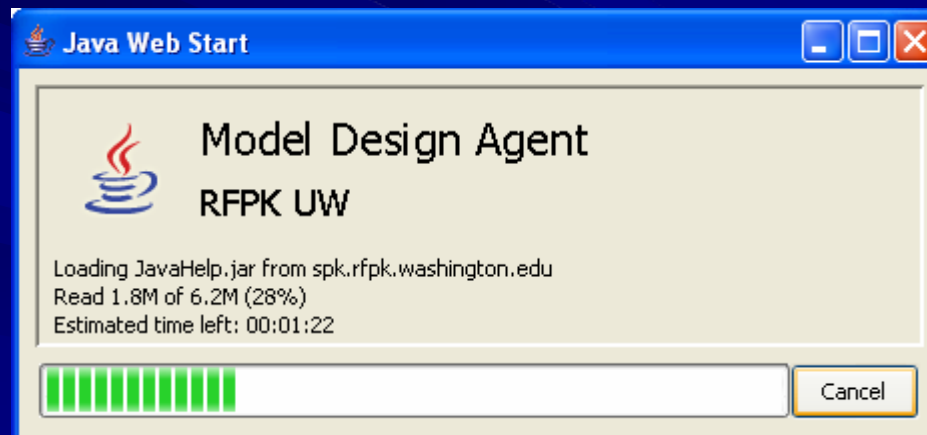


# Download of the MDA



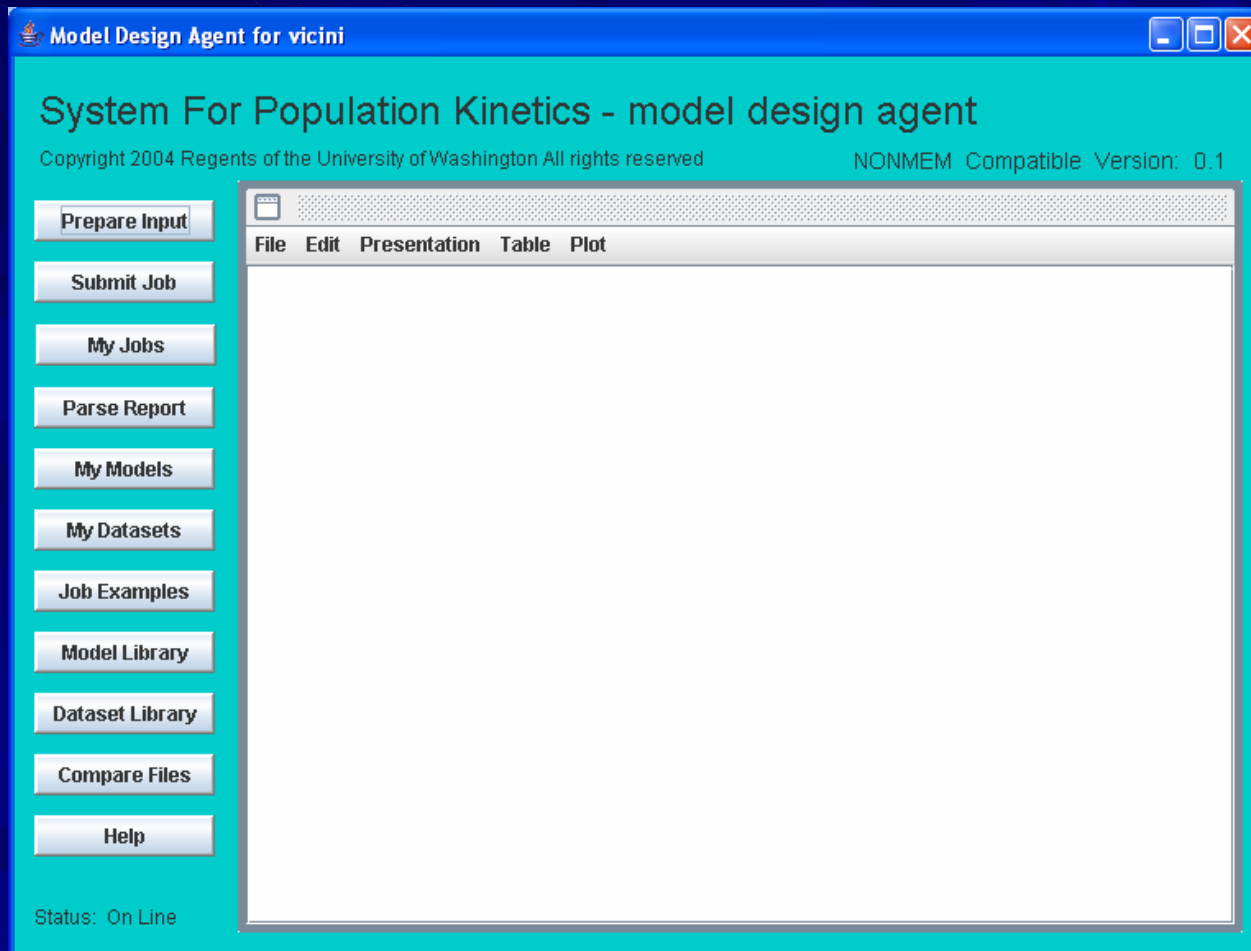
- The MDA is downloaded every time it changes

# Download of the MDA



- Help system and executable are both updated

# Model Design Agent Welcome Screen



- The MDA requires downloading the Java Runtime Environment, available from Sun Microsystems

# The User Database

Job ID	Submission Time	Status Code	Model.Version	Dataset.Version	Job Abstract
547	Mon 2005-08-01 16:27:25	PDT Compiler Error	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
546	Mon 2005-08-01 16:24:45	PDT Compiler Error	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
545	Mon 2005-08-01 16:05:31	PDT Successful Run	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
526	Thu 2005-07-28 14:46:39	PDT Successful Run	One compartment C...	cadralazine.txt.1	CADRALAZINE 1_EXP
490	Fri 2005-07-22 14:15:21	PDT Successful Run	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
489	Fri 2005-07-22 13:55:45	PDT Successful Run	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
488	Fri 2005-07-22 13:53:38	PDT Compiler Error	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
464	Thu 2005-07-21 14:43:22	PDT Successful Run	One compartment C...	cadralazine.txt.1	CADRALAZINE 1_EXP
463	Thu 2005-07-21 14:38:22	PDT Successful Run	One compartment C...	cadralazine.txt.1	CADRALAZINE 1_EXP
462	Thu 2005-07-21 14:32:08	PDT Successful Run	One compartment C...	cadralazine.txt.1	CADRALAZINE 1_EXP
460	Thu 2005-07-21 12:57:19	PDT Compiler Error	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO
459	Thu 2005-07-21 12:56:21	PDT Compiler Error	TwoExponential In...	study0.txt.1	TWO EXPONENTIAL MODEL STUDYO

Search Jobs      Group member: vicini      Total found: 62      < Previous Page      Next Page >

- The **Model** contains all analysis details (e.g. model equations, chosen likelihood approximation, number of iterations)
- The **Dataset** contains all experimental information
- **Dataset + Model = Job**
- The output of the job is the Model informed on the Data (Estimation) or a new, simulated Dataset (Simulation)
- All this is stored in a read-only database

# A Job Example

- A Job is described by its Model and Dataset (note the version number)
- A Job has an Input and an Output
- A Job could have a Parent (e.g. using First Order output to start a conditional estimation)
- Warm Start feature

The screenshot shows a software window titled "Job Information - vicini". It contains the following fields and buttons:

- Job Owner:** vicini
- Job ID:** 526
- Method:** First Order
- Model:** One compartment CL,V
- Dataset:** cadralazine.txt
- Abstract:** CADRALAZINE 1\_EXP
- Version:** 24
- Buttons:** Abort Job, Change It

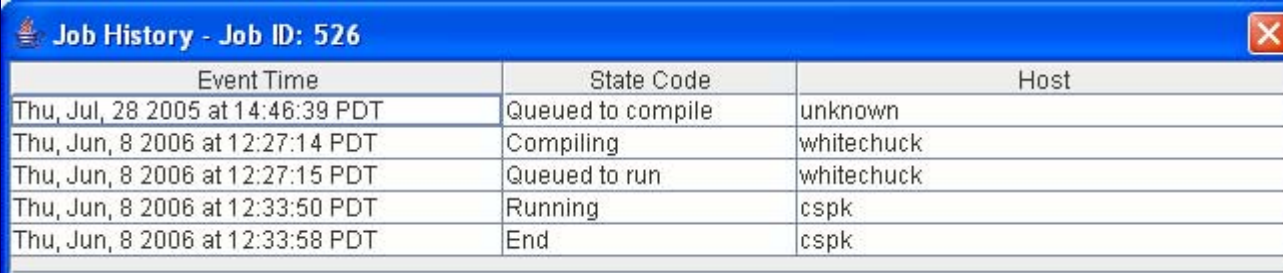
**View Current Job:**

- Buttons: Model, Dataset, Input, Output, Job History, Job Parent, Job Report

**Create New Job:**

- Set the current job as the parent job of the new job.
- Initialize parameters from current job input. **From Input**
- Initialize parameters from current job output. **From Output**
- Warm Start**
- Likelihood**
- Population**

# Job History



The screenshot shows a window titled "Job History - Job ID: 526". The window contains a table with three columns: "Event Time", "State Code", and "Host". The table lists five events:

Event Time	State Code	Host
Thu, Jul, 28 2005 at 14:46:39 PDT	Queued to compile	unknown
Thu, Jun, 8 2006 at 12:27:14 PDT	Compiling	whitechuck
Thu, Jun, 8 2006 at 12:27:15 PDT	Queued to run	whitechuck
Thu, Jun, 8 2006 at 12:33:50 PDT	Running	cspk
Thu, Jun, 8 2006 at 12:33:58 PDT	End	cspk

- A job history allows to track machine usage

# Report Parsing: Job Data

The screenshot displays the 'Model Design Agent for vicini' software interface. The main window title is 'System For Population Kinetics - model design agent'. Below the title, it states 'Copyright 2004 Regents of the University of Washington All rights reserved' and 'NONMEM Compatible Version: 0.1'. On the left side, there is a vertical menu with buttons for 'Prepare Input', 'Submit Job', 'My Jobs', 'Parse Report', 'My Models', 'My Datasets', 'Job Examples', 'Model Library', 'Dataset Library', 'Compare Files', and 'Help'. The main area shows a 'Summary Report: Job-526' window with a menu bar (File, Edit, Presentation, Table, Plot) and the following text:

```
Summary Report
Job Identification number: 526
Job Description: CADRALAZINE 1_EXP
Time of Job Submission: Thu, Jul, 28 2005 at 14:46:39 PDT
Time of Job Completion: Thu, Jun, 8 2006 at 12:33:58 PDT
SPK Computing Time: 3.0 s
Analysis Type: population
Sub-problem Number:      N/A
Seed for Simulation:     N/A
Analysis Method: First Order
Model Name: One compartment CL,V   Model Version: 24
Model Description: Single compartment model with clearance parametrization
Model Version Log: FO, full covariance, additive error, revised bounds on THETA
Dataset Name: cadralazine.txt      Dataset Version: 1
Dataset Description: CADRALAZINE DATA SET FROM WAKEFIELD ET AL. 1996
```

At the bottom left of the interface, the status is 'Status: On Line'.

■ The Summary Report contains version info

# Report Parsing: Estimate Results

Model Design Agent for vicini

System For Population Kinetics - model design agent

Copyright 2004 Regents of the University of Washington All rights reserved NONMEM Compatible Version: 0.1

Summary Report: Job-526

File Edit Presentation Table Plot

Minimum Value of Objective Function: -55.0261

Parameter Estimation Result:

=====

Parameter	Estimate	Std. Error	Coef. of Var.	95% Confidence Interval		Variability
				L-bound	U-bound	
THETA						
1	2.64E+00	3.87E-01	1.46E+01	1.87E+00	3.42E+00	
2	1.50E+01	5.36E-01	3.57E+00	1.39E+01	1.61E+01	
OMEGA						
1,1	1.25E-01	4.70E-02	3.75E+01	3.11E-02	2.19E-01	3.54E-01
1,2	1.96E-02	1.87E-02	9.54E+01	-1.79E-02	5.71E-02	
2,2	6.59E-03	4.53E-03	6.88E+01	-2.49E-03	1.57E-02	8.12E-02
SIGMA						
1,1	5.19E-03	2.45E-03	4.73E+01	2.79E-04	1.01E-02	7.20E-02

\*For OMEGA, this column indicates BSV in standard deviation units.  
For SIGMA, this column indicates RUV in standard deviation units.

Status: On Line

■ Parameter estimates are shown with SEs

# Report Parsing: Display Options

The screenshot shows the 'Model Design Agent for vicini' software interface. The main window title is 'System For Population Kinetics - model design agent'. Below the title, it says 'Copyright 2004 Regents of the University of Washington All rights reserved' and 'NONMEM Compatible Version: 0.1'. On the left side, there is a vertical toolbar with buttons: 'Prepare Input', 'Submit Job', 'My Jobs', 'Parse Report', 'My Models', 'My Datasets', 'Job Examples', 'Model Library', 'Dataset Library', 'Compare Files', and 'Help'. The main area displays a 'Summary Report: Job-526' window. This window has a menu bar with 'File', 'Edit', 'Presentation', 'Table', and 'Plot'. The 'Presentation' menu is open, showing options: 'Error Message' (Ctrl-R), 'Warning Message' (Ctrl-W), 'Objective/Likelihood' (Ctrl-J), 'Parameters' (with a right-pointing arrow), 'Statistics' (with a right-pointing arrow), 'Tables' (Ctrl-B), 'Scatterplots' (Ctrl-C), 'Summary' (Ctrl-M), 'Optimization Trace' (Ctrl-Z), and 'Individual IDs' (Ctrl-I). The background of the report window shows a table with columns for parameters and their associated statistics. The table data is as follows:

Parameter	Coef. of Var.	95% Confidence Interval	Variability	
		L-bound	U-bound	
THETA				
1	1.46E+01	1.87E+00	3.42E+00	
2	3.57E+00	1.39E+01	1.61E+01	
OMEGA				
1,1	1.25E-01	4.70E-02	3.75E+01	3.11E-02
1,2	1.96E-02	1.87E-02	9.54E+01	-1.79E-02
2,2	6.59E-03	4.53E-03	6.88E+01	-2.49E-03
SIGMA				
1,1	5.19E-03	2.45E-03	4.73E+01	2.79E-04

\*For OMEGA, this column indicates BSV in standard deviation units.  
For SIGMA, this column indicates RUV in standard deviation units.

Status: On Line

■ There are other output visualization options

# Default Plots

The screenshot shows the 'Model Design Agent for vicini' software interface. The main window title is 'System For Population Kinetics - model design agent'. Below the title bar, there is a copyright notice: 'Copyright 2004 Regents of the University of Washington All rights reserved' and 'NONMEM Compatible Version: 0.1'. On the left side, there is a vertical toolbar with buttons for 'Prepare Input', 'Submit Job', 'My Jobs', 'Parse Report', 'My Models', 'My Datasets', 'Job Examples', 'Model Library', 'Dataset Library', 'Compare Files', and 'Help'. The main area displays a 'Summary Report: Job-526' with a menu open over the 'Plot' option. The menu lists several plot types: 'Default Plots', 'Entire Report Data', 'Use MDA Plotter', and 'Use R Language'. The 'Default Plots' sub-menu is expanded, showing options like 'PRED vs DV', 'PRED vs DV by ID', 'DV PRED vs TIME', 'DV PRED vs TIME by ID', 'IPRED vs DV', 'IPRED vs DV by ID', 'DV IPRED vs TIME', and 'DV IPRED vs TIME by ID'. The background of the report window shows a table with columns for 'Parameter', 'Estimate', 'Std. Error', 'Coef. of Var.', and 'Variability'. The table is partially visible, showing parameters THETA, OMEGA, and SIGMA.

Model Design Agent for vicini

System For Population Kinetics - model design agent

Copyright 2004 Regents of the University of Washington All rights reserved NONMEM Compatible Version: 0.1

Summary Report: Job-526

File Edit Presentation Table Plot

Minimum Value of Objective

Parameter Estimation Result

Parameter Estimate Std. Error Coef. of Var. Variability

THETA

Parameter	Estimate	Std. Error	Coef. of Var.	Variability
1	2.64E+00	3.87E-01	1.46E+01	
2	1.50E+01	5.36E-01	3.57E+00	

OMEGA

Parameter	Estimate	Std. Error	Coef. of Var.	Variability
1,1	1.25E-01	4.70E-02	3.75E+01	3.11E-02
1,2	1.96E-02	1.87E-02	9.54E+01	-1.79E-02
2,2	6.59E-03	4.53E-03	6.88E+01	-2.49E-03

SIGMA

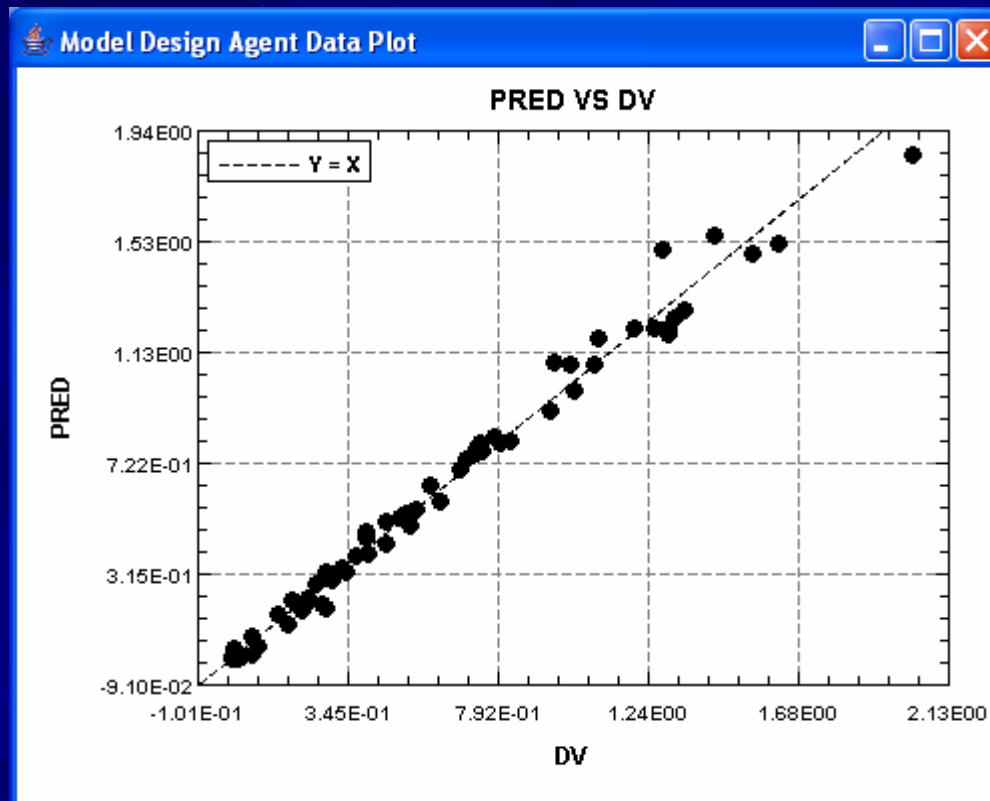
Parameter	Estimate	Std. Error	Coef. of Var.	Variability
1,1	5.19E-03	2.45E-03	4.73E+01	2.79E-04

\*For OMEGA, this column indicates BSV in standard deviation units.  
For SIGMA, this column indicates RUV in standard deviation units.

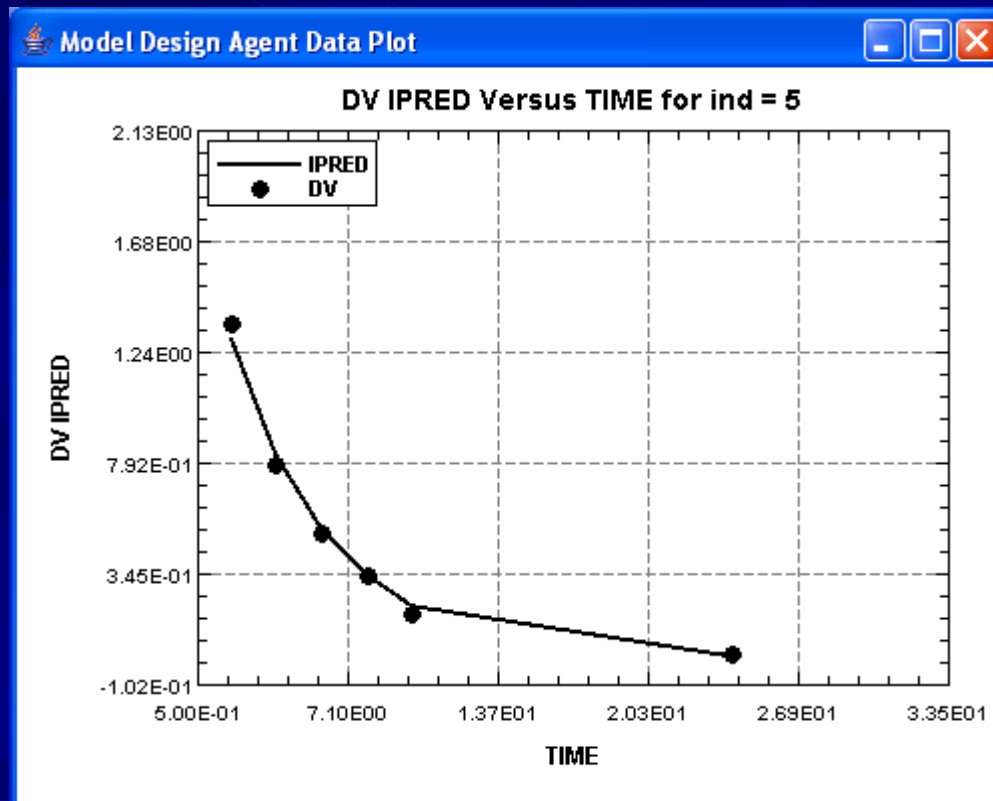
Status: On Line

■ Default plots are easily accessible

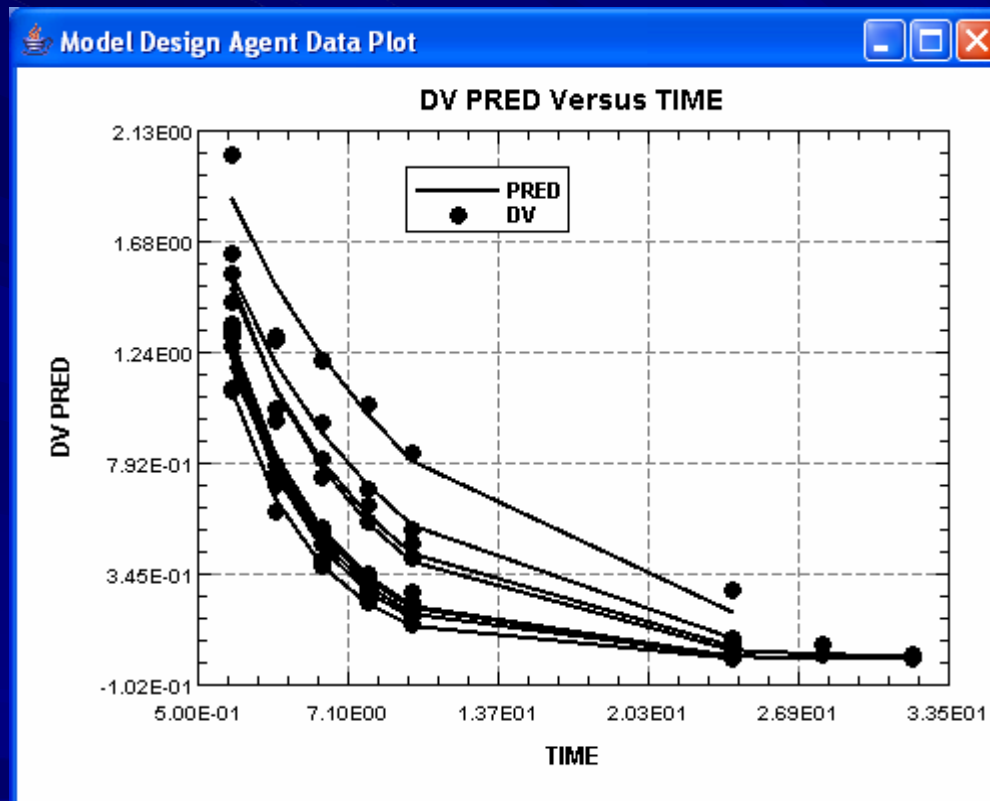
# Example Plots



# Example Plots



# Example Plots



# Model and Analysis Definition

- The model is entered and linked to data through a modeling wizard available through the MDA
- The user is walked through the various steps and on-line help is available at each step
- Online help is updated constantly and instantly available on the user's machine through MDA updates
- Jobs can be cloned – the output of one can become the input for another, e.g. using first order results to seed a conditional estimation run

# Creating A Run: Analysis Selection

**Model Design Agent Input File Generation Tool**

**Steps:**

- 1. Analysis Selection**
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. ....

**Analysis Selection**

Select Model and Analysis Options:

**Parameter estimation**  **Parametric model**  **Nonparametric model**  
 **Parameter identifiability analysis**  **Data simulation**

Select Analysis Type:

**Population analysis**  **Individual analysis**  **Two-stage analysis**

Select Model Type:

**Creating an analytic/algebraic model**  
 **Using the RFPK model library**  
 **Using the RFPK graphical model editor**

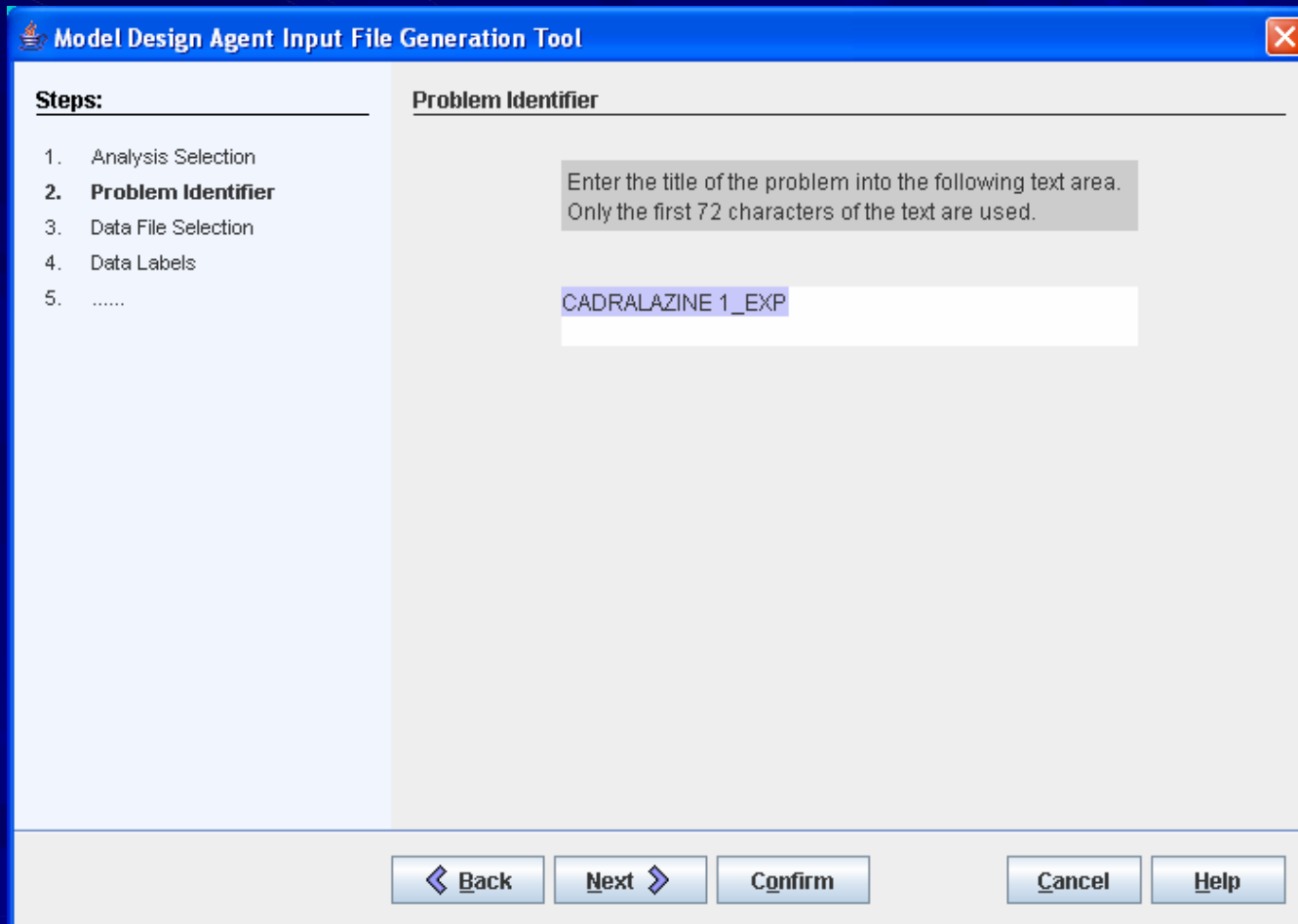
Select Statistics Option:

**Computing statistics of parameter estimates**

Optional NONMEM Compatible Output:  **Tables**  **Scatterplots**

Reload Previous SPK Model or Input:

# Creating A Run: Problem Identifier



The screenshot shows a software window titled "Model Design Agent Input File Generation Tool". The window is divided into two main sections. On the left, under the heading "Steps:", there is a list of five steps: 1. Analysis Selection, 2. **Problem Identifier**, 3. Data File Selection, 4. Data Labels, and 5. .... The second step, "Problem Identifier", is currently selected and highlighted. The right section of the window is titled "Problem Identifier" and contains a text area with the instruction: "Enter the title of the problem into the following text area. Only the first 72 characters of the text are used." Below this instruction, the text "CADRALAZINE 1\_EXP" is entered into the text area. At the bottom of the window, there are five buttons: "Back" (with a left arrow), "Next" (with a right arrow), "Confirm", "Cancel", and "Help".

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
- 2. Problem Identifier**
3. Data File Selection
4. Data Labels
5. ....

**Problem Identifier**

Enter the title of the problem into the following text area.  
Only the first 72 characters of the text are used.

CADRALAZINE 1\_EXP

◀ Back   Next ▶   Confirm   Cancel   Help

# Creating A Run: Data File

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
- 3. Data File Selection**
4. Data Labels
5. ....

**Data File Selection**

**Use data file previously loaded from parent job.**

Data file name:

**Load in dataset from My Datasets**

**Load in dataset from Dataset Library**

**Load in data file from local file system**

Enter data file name (including full path) or browse.

Click "Read File" button to load data file.

There are 3 columns in the data file.

# Creating A Run: Data Labels

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
- 4. Data Labels**
5. ....

**Data Labels**

Click data column and choose data item name:  
- ID (if used) item must be in first column  
- DV (dependent variable) item is required  
- Item name and alias must be uppercase and unique

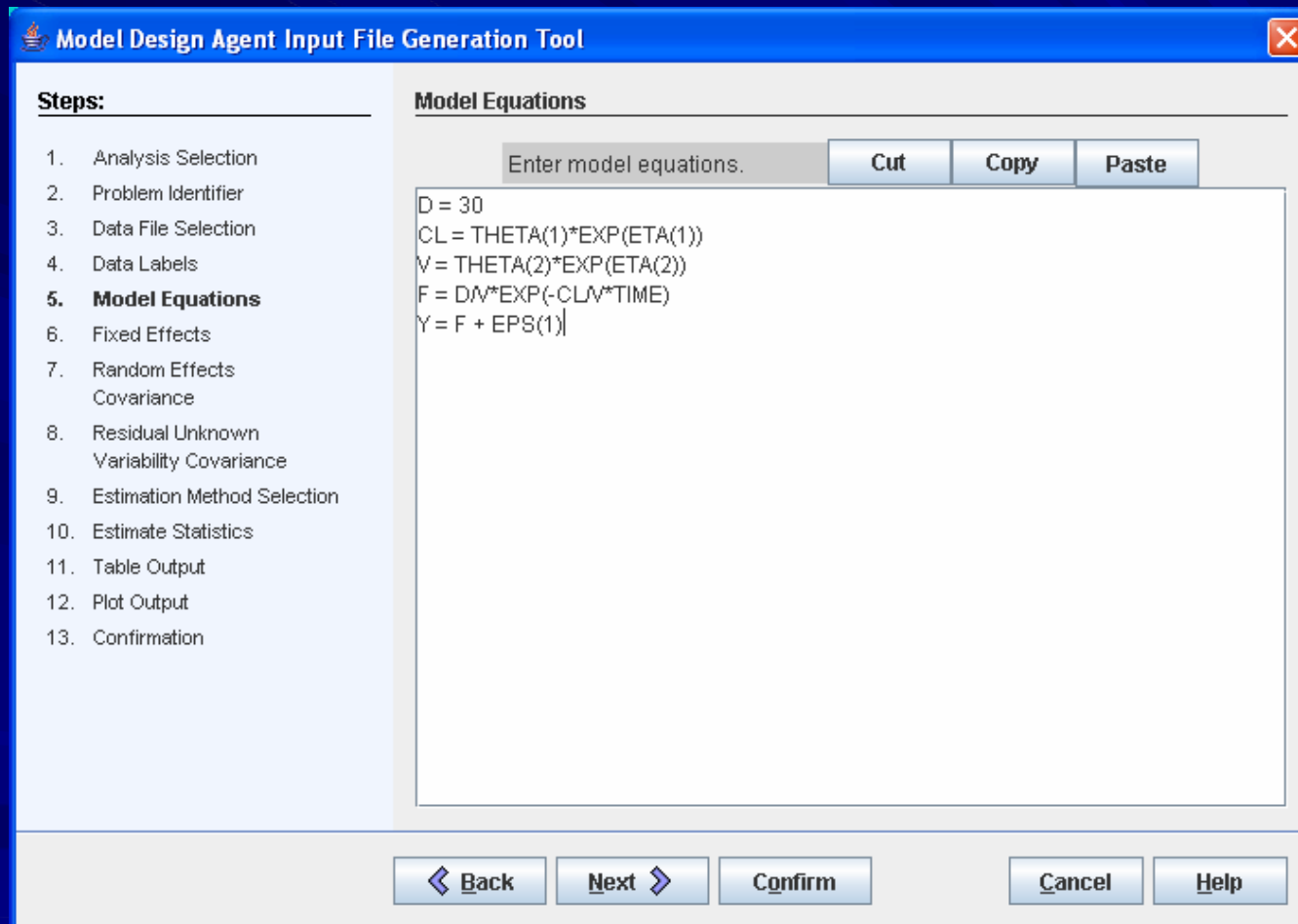
**Standard item**    DV    Alias

**User-defined item**        Centered

**Drop data column**       

Column 1	Column 2	Column 3
ID	TIME	DV
1	2	1.09
1	4	0.75
1	6	0.53
1	8	0.34
1	10	0.23

# Creating A Run: Model Equations



The screenshot shows a software window titled "Model Design Agent Input File Generation Tool". The window is divided into two main sections. On the left, a "Steps:" list contains 13 numbered items, with the fifth item, "5. Model Equations", highlighted in bold. On the right, the "Model Equations" section features a text input area with a placeholder "Enter model equations." and three buttons: "Cut", "Copy", and "Paste". The text area contains the following equations:  
 $D = 30$   
 $CL = \text{THETA}(1) * \text{EXP}(\text{ETA}(1))$   
 $V = \text{THETA}(2) * \text{EXP}(\text{ETA}(2))$   
 $F = D/V * \text{EXP}(-CL/V * \text{TIME})$   
 $Y = F + \text{EPS}(1)$

At the bottom of the window, there are five buttons: "Back" (with a left arrow), "Next" (with a right arrow), "Confirm", "Cancel", and "Help".

# Creating A Run: Fixed Effects

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
- 6. Fixed Effects**
7. Random Effects Covariance
8. Residual Unknown Variability Covariance
9. Estimation Method Selection
10. Estimate Statistics
11. Table Output
12. Plot Output
13. Confirmation

**Fixed Effects**

Enter initial estimates and bounds (except that FIXED is selected)  
- To get default bounds, press ENTER after entering initial estimate  
- Bounds influence stopping criteria (INF bounds not recommended)  
- Note: exponential expression may not be NONMEM compatible

Initial Estimate   FIXED

Lower Bound   -INF

Upper Bound   INF

List of fixed effect values and limits you have entered in NONMEM Syntax

(0.3,3,30)
(0.5,5,50.0)

# Creating A Run: BSV

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
6. Fixed Effects
- 7. Random Effects Covariance**
8. Residual Unknown Variability Covariance
9. Estimation Method Selection
10. Estimate Statistics
11. Table Output
12. Plot Output
13. Confirmation

**Random Effects Covariance**

Enter random effects covariance initial estimate.  
Bounds on random effects covariance and individual random effects set internally by SPK.

New block    Diagonal    Full matrix

Block size:

Constrained to be equal to preceding block

Covariance blocks and initial estimates in NONMEM syntax

```
$OMEGA BLOCK(2) 0.09 0.02 0.01
```

# Creating A Run: RUV

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
6. Fixed Effects
7. Random Effects Covariance
- 8. Residual Unknown Variability Covariance**
9. Estimation Method Selection
10. Estimate Statistics
11. Table Output
12. Plot Output
13. Confirmation

**Residual Unknown Variability Covariance**

Enter residual unknown variability covariance initial estimate.  
Bounds on residual unknown variability covariance set internally by SPK.

New block     Diagonal     Full matrix

Dimension

Constrained to be equal to preceding block

Covariance blocks and initial estimates in NONMEM syntax

```
$SIGMA DIAGONAL(1) 0.03
```

# Creating A Run: Method Selection

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
6. Fixed Effects
7. Random Effects Covariance
8. Residual Unknown Variability Covariance
- 9. Estimation Method Selection**
10. Estimate Statistics
11. Table Output
12. Plot Output
13. Confirmation

**Estimation Method Selection**

Select an estimation method and available option(s) on the right.

**First Order**

**Expected Hessian**

**Laplace Approximation**

**Standard Two-Stage**

**Iterative Two-Stage**

**Global Two-Stage**

**Obtain individual estimates**

RUV depends on random effects

Center random effects

Make automatic error recovery

Use MAP Bayesian Objective

Enter Cov for THETA

Enter or select values for the following options.

**Significant digits (stopping criterion)** 3

**Maximum number of iterations** 450

**Summary print iteration interval** 5

Method and options expressed in NONMEM syntax

```
IMATION METHOD=0 POSTHOC SIGDIGITS=3 MAXEVALS=450 PRINT=5
```

◀ | | ▶

◀ Back Next ▶ Confirm Cancel Help

# Creating A Run: Estimate Covariance

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
6. Fixed Effects
7. Random Effects Covariance
8. Residual Unknown Variability Covariance
9. Estimation Method Selection
- 10. Estimate Statistics**
11. Table Output
12. Plot Output
13. Confirmation

**Estimator Covariance Method Selection**

Select method  
Note: the H and HSH options apply only to individual analysis.

R -- The Hessian Matrix

S -- The Cross-Product Matrix

**Default -- The Sandwich Matrix**

H -- The Expected Hessian Matrix

HSH -- The Expected Hessian Cross-Product Matrix

---

Selection expressed in NONMEM syntax

\$COVARIANCE

◀ Back   Next ▶   Confirm   Cancel   Help

# NONMEM Control File

**Model Design Agent Input File Generation Tool**

**Steps:**

1. Analysis Selection
2. Problem Identifier
3. Data File Selection
4. Data Labels
5. Model Equations
6. Fixed Effects
7. Random Effects  
Covariance
8. Residual Unknown  
Variability Covariance
9. Estimation Method Selection
10. Estimate Statistics
11. Table Output
12. Plot Output
- 13. Confirmation**

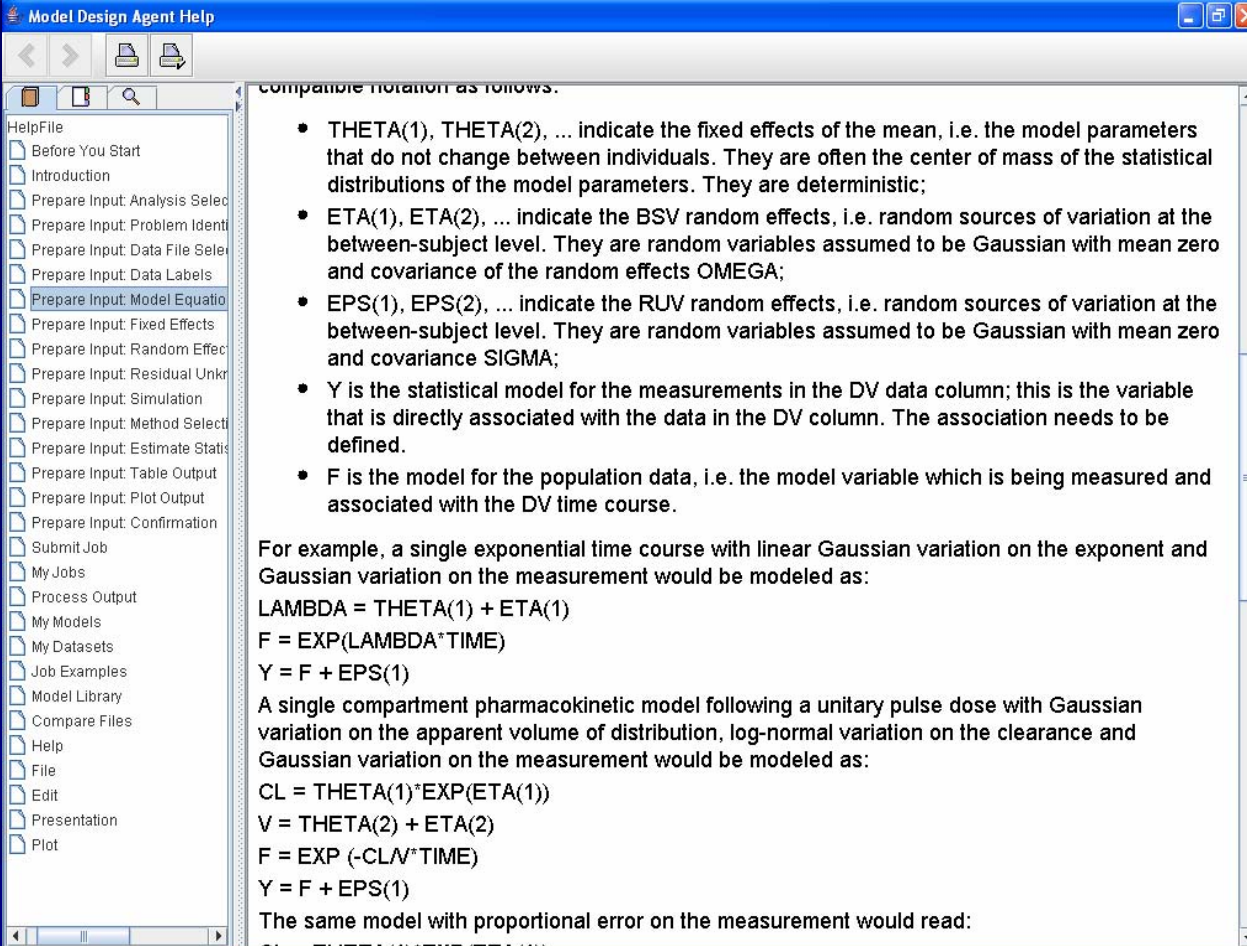
**Confirmation**

Control file in NONMEM syntax:

```
$PROBLEM CADRALAZINE 1_EXP
$DATA cadralazine.bt
$INPUT ID TIME DV
$PRED
D = 30
CL = THETA(1)*EXP(ETA(1))
V = THETA(2)*EXP(ETA(2))
F = DV*EXP(-CLV*TIME)
Y = F + EPS(1)
$THETA
(0.3,3,30)
(0.5,5,50.0)
$OMEGA BLOCK(2) 0.09 0.02 0.01
$SIGMA DIAGONAL(1) 0.03
$ESTIMATION METHOD=0 POSTHOC SIGDIGITS=3 MAXEVALS=450 PRINT=5
$COVARIANCE
$TABLE Y FILE=cadralazine.out
$SCATTERPLOT DV VS PRED FROM 1 TO 64 NOABS0 NOORD0
```

**Back** **Next** **Finish** **Cancel** **Help**

# Online Help System (JavaHelp)



The screenshot shows a JavaHelp window titled "Model Design Agent Help". The left pane contains a tree view of help topics, with "Prepare Input: Model Equatio" selected. The right pane displays the following content:

compatible notation as follows.

- THETA(1), THETA(2), ... indicate the fixed effects of the mean, i.e. the model parameters that do not change between individuals. They are often the center of mass of the statistical distributions of the model parameters. They are deterministic;
- ETA(1), ETA(2), ... indicate the BSV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance of the random effects OMEGA;
- EPS(1), EPS(2), ... indicate the RUV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance SIGMA;
- Y is the statistical model for the measurements in the DV data column; this is the variable that is directly associated with the data in the DV column. The association needs to be defined.
- F is the model for the population data, i.e. the model variable which is being measured and associated with the DV time course.

For example, a single exponential time course with linear Gaussian variation on the exponent and Gaussian variation on the measurement would be modeled as:

$$\text{LAMBDA} = \text{THETA}(1) + \text{ETA}(1)$$
$$\text{F} = \text{EXP}(\text{LAMBDA} * \text{TIME})$$
$$\text{Y} = \text{F} + \text{EPS}(1)$$

A single compartment pharmacokinetic model following a unitary pulse dose with Gaussian variation on the apparent volume of distribution, log-normal variation on the clearance and Gaussian variation on the measurement would be modeled as:

$$\text{CL} = \text{THETA}(1) * \text{EXP}(\text{ETA}(1))$$
$$\text{V} = \text{THETA}(2) + \text{ETA}(2)$$
$$\text{F} = \text{EXP}(-\text{CL}/\text{V} * \text{TIME})$$
$$\text{Y} = \text{F} + \text{EPS}(1)$$

The same model with proportional error on the measurement would read:

$$\text{CL} = \text{THETA}(1) * \text{EXP}(\text{ETA}(1))$$

# Job Submission

**Job Submission Dialog**

**Model** | Dataset | Job

New model (NONMEM control file)

New version of an existing model

Existing version of an existing model

model name (<=20 characters)

One compartment CLV

model description (<= 100characters)

Single compartment model with clearance par ametrization

version

24

version log

unds on THETA

OK Cancel

- Upon submission of the job to the computational servers, the user is asked for version information
- If this is a previously developed model, the system recognizes it

# Job Submission

**Job Submission Dialog**

**Model** **Dataset** **Job**

New dataset

New version of an existing dataset

Existing version of an existing dataset

dataset name (<=20 characters )

cadralazine.txt

dataset description (<=100 characters )

CADRALAZINE DATA SET FROM WAKEFIELD  
ET AL. 1996

version

1

version log

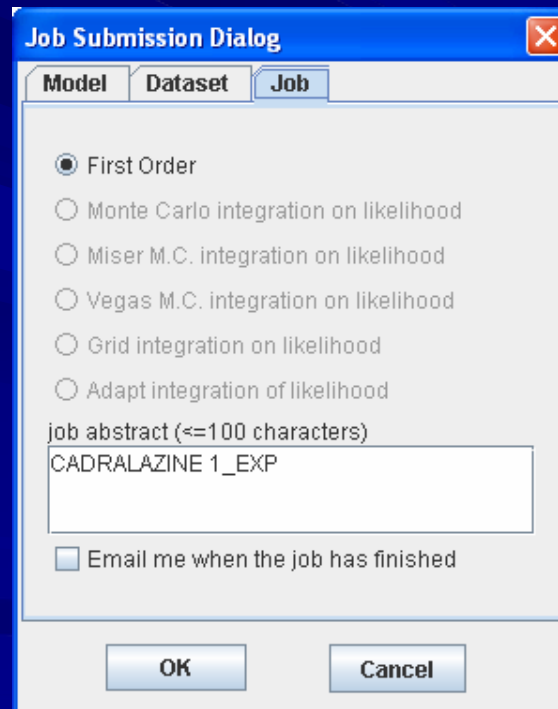
efield et al. 1996

OK Cancel

- The dataset version is also reconciled within the job as it is submitted
- Again, if the version is a previous one, the system recognizes it

# Job Submission

- At this point the user can enter a job abstract and verify the estimation method



The screenshot shows a dialog box titled "Job Submission Dialog" with three tabs: "Model", "Dataset", and "Job". The "Job" tab is selected. It contains a list of radio buttons for estimation methods: "First Order" (selected), "Monte Carlo integration on likelihood", "Miser M.C. integration on likelihood", "Vegas M.C. integration on likelihood", "Grid integration on likelihood", and "Adapt integration of likelihood". Below this is a text field labeled "job abstract (<=100 characters)" containing the text "CADRALAZINE 1\_EXP". At the bottom, there is a checkbox labeled "Email me when the job has finished" which is unchecked. The dialog has "OK" and "Cancel" buttons at the bottom.

# User Model List

- The user can access his/her models and data separately from the jobs
- Version control is built in the system

The screenshot displays a software interface with two main windows. The 'Model List - vicini' window shows a table of models, with Model ID 91, '20 COMPARTMENT DELAY', selected. The 'Version List - Model ID: 91' window shows a detailed view of the selected model's history, including revision numbers, authors, revised times, and log messages.

Model ID	Model Name
147	VLDL
141	Linear model
91	20 COMPARTMENT DELAY
89	Rise and washout mod
87	Two Compartment Mode
86	NIST BOXBOD
85	NIST BENNETT5
82	ECKERLE4
79	MGH09
75	Algebraic SCFO
73	Single Plasma C0mpar
52	DANWOOD NIST MODEL

Revision	Author	Revised Time	Log Message
1	vicini	PST 2005.08.24.16.52.13	ALGEBRAIC 20 COMPARTMENT DELAY FIRST TRY
2	vicini	PST 2005.08.24.16.53.36	DEFINED T=TIME
3	vicini	PST 2005.08.24.17.00.01	MAXEVAL = 0 for debugging
4	vicini	PST 2005.08.24.17.04.27	fixed long equations
5	vicini	PST 2005.08.24.17.09.29	removed spaces
6	vicini	PST 2005.08.24.17.20.08	changed SIGDIGITS
7	vicini	PST 2005.08.25.14.43.53	made the factorials DOUBLE instead of INT
8	vicini	PST 2005.08.25.14.52.18	Individual estimation with roundoff factorial problem fixed
9	vicini	PST 2005.08.25.15.07.54	AMOXICILLIN POPULATION ANALYSIS
10	vicini	PST 2005.08.31.16.28.02	@added an additive error component EPS(2)
11	vicini	PST 2005.08.31.16.49.10	@\$error purely additive
12	vicini	PST 2005.09.02.14.17.13	@Model for amoxicillin data - third trimester
13	vicini	PST 2005.09.02.15.17.57	@Additive error model for amoxicillin PK
14	vicini	PST 2005.09.02.15.30.19	@Changed initial conditions for Ka and Ke
15	vicini	PST 2005.09.02.15.36.01	@changed again initial conditions to avoid PK flip-flop
16	vicini	PST 2005.09.02.15.44.54	@changed initial conditions again
17	vicini	PST 2005.09.02.15.55.46	@yet another set of initial conditions
18	vicini	PST 2005.09.02.16.45.06	@changed initial estimates for OMEGA
19	vicini	PST 2005.09.02.16.48.18	@changed OMEGA initial estimates to 0.7

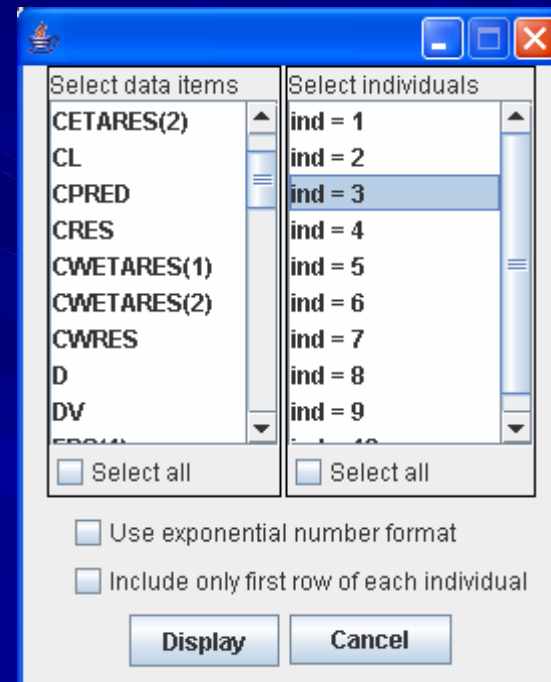
MGH09 model from the NIST website <http://...>

DANWOOD MODEL FROM NIST DATABASE <http://w...>

List  Versions  Jobs Group member vicini Total found 37 Previous Page Next Page

# Table Builder

- Tabular output can be defined ad hoc depending on the purpose
- Any model variable can be included
- Only selected individuals may be displayed



# Default Tables

Model Design Agent for vicini

System For Population Kinetics - model design agent

Copyright 2004 Regents of the University of Washington All rights reserved NONMEM Compatible Version: 0.1

Prepare Input

Submit Job

My Jobs

Parse Report

My Models

My Datasets

Job Examples

Model Library

Dataset Library

Compare Files

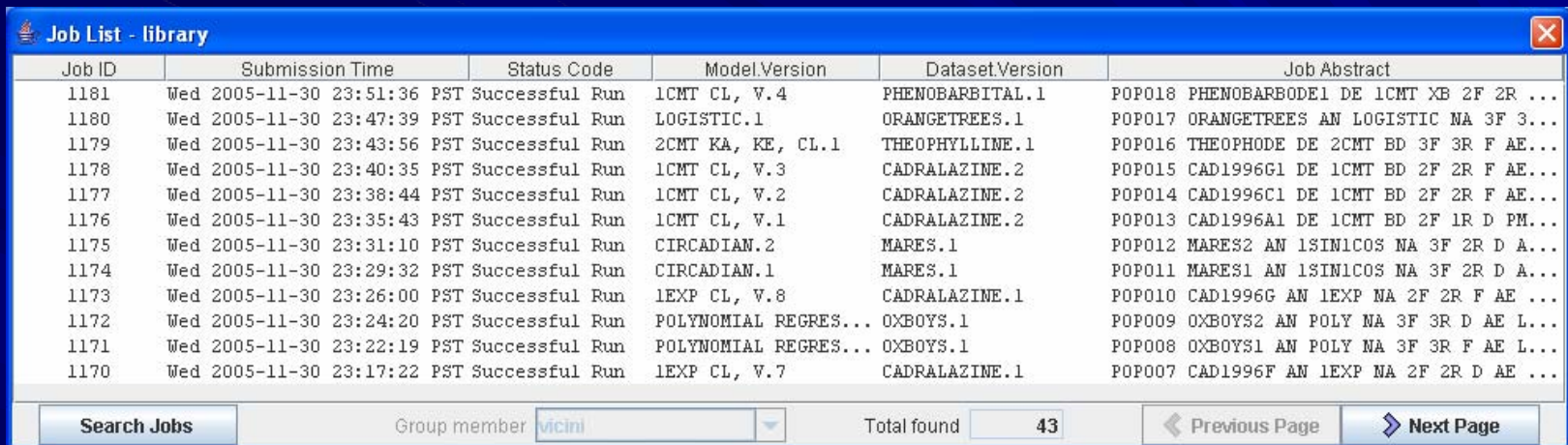
Help

Status: On Line

Table of default dataset

File	Edit	Presentation	Table	Plot
ID	TIME	DV	Default Table	ID TIME DV PRED (Free format)
1	2.0	1.09	First Row Only	ID TIME DV PRED (Exp. format)
1	4.0	0.75	Selected Dataset	ID TIME DV IPRED (Free format)
1	6.0	0.53		ID TIME DV IPRED (Exp. format)
1	8.0	0.34	0.318585	
1	10.0	0.23	0.206311	
1	24.0	0.02	0.00985383	
2	2.0	2.03	1.8487	
2	4.0	1.28	1.49893	
2	6.0	1.2	1.21534	
2	8.0	1.02	0.985402	
2	10.0	0.83	0.798968	
2	24.0	0.28	0.184052	
3	2.0	1.44	1.55098	
3	4.0	1.3	1.18923	
3	6.0	0.95	0.911863	
3	8.0	0.68	0.699185	
3	10.0	0.52	0.536111	
3	24.0	0.06	0.0835393	
4	2.0	1.55	1.48631	
4	4.0	0.96	1.08643	
4	6.0	0.8	0.794132	
4	8.0	0.62	0.580477	

# Job Library (Examples)



Job ID	Submission Time	Status Code	Model Version	Dataset Version	Job Abstract
1181	Wed 2005-11-30 23:51:36	PST Successful Run	1CMT CL, V.4	PHENOBARBITAL.1	POP018 PHENOBARBODE1 DE 1CMT XB 2F 2R ...
1180	Wed 2005-11-30 23:47:39	PST Successful Run	LOGISTIC.1	ORANGETREES.1	POP017 ORANGETREES AN LOGISTIC NA 3F 3...
1179	Wed 2005-11-30 23:43:56	PST Successful Run	2CMT KA, KE, CL.1	THEOPHYLLINE.1	POP016 THEOPHODE DE 2CMT BD 3F 3R F AE...
1178	Wed 2005-11-30 23:40:35	PST Successful Run	1CMT CL, V.3	CADRALAZINE.2	POP015 CAD1996G1 DE 1CMT BD 2F 2R F AE...
1177	Wed 2005-11-30 23:38:44	PST Successful Run	1CMT CL, V.2	CADRALAZINE.2	POP014 CAD1996C1 DE 1CMT BD 2F 2R F AE...
1176	Wed 2005-11-30 23:35:43	PST Successful Run	1CMT CL, V.1	CADRALAZINE.2	POP013 CAD1996A1 DE 1CMT BD 2F 1R D PM...
1175	Wed 2005-11-30 23:31:10	PST Successful Run	CIRCADIAN.2	MARES.1	POP012 MARES2 AN 1SINICOS NA 3F 2R D A...
1174	Wed 2005-11-30 23:29:32	PST Successful Run	CIRCADIAN.1	MARES.1	POP011 MARES1 AN 1SINICOS NA 3F 2R D A...
1173	Wed 2005-11-30 23:26:00	PST Successful Run	1EXP CL, V.8	CADRALAZINE.1	POP010 CAD1996G AN 1EXP NA 2F 2R F AE ...
1172	Wed 2005-11-30 23:24:20	PST Successful Run	POLYNOMIAL REGRES...	OXBOYS.1	POP009 OXBOYS2 AN POLY NA 3F 3R D AE L...
1171	Wed 2005-11-30 23:22:19	PST Successful Run	POLYNOMIAL REGRES...	OXBOYS.1	POP008 OXBOYS1 AN POLY NA 3F 3R F AE L...
1170	Wed 2005-11-30 23:17:22	PST Successful Run	1EXP CL, V.7	CADRALAZINE.1	POP007 CAD1996F AN 1EXP NA 2F 2R D AE ...

Search Jobs      Group member:       Total found:       < Previous Page      Next Page >

- The MDA has the ability to clone jobs
- Jobs from the Library can be modified by all users and used to start new jobs, perhaps with new datasets – this allows one to combine new data and previously developed models

# Model Library (Examples)

Dataset ID	Dataset Name	No. of Versions	Last Revised Time	Description
206	PHENOBARBITAL	1	PST 2005.11.30.23.51.35	Neonatal population pharmacokinetics of p...
205	ORANGETREES	1	PST 2005.11.30.23.47.39	Growth of orange trees
204	THEOPHYLLINE	1	PST 2005.11.30.23.43.56	Theophylline oral pharmacokinetics
203	MARES	1	PST 2005.11.30.23.29.32	Follicular population dynamics during the...
202	OXBOYS	1	PST 2005.11.30.23.22.19	Height data of a selection of boys from 0...
201	CADRALAZINE	2	PST 2005.11.30.23.35.43	Wakefield, Racine-Poon et al., Applied St...
200	RAIL	1	PST 2005.11.30.23.01.21	Pinheiro JC and Bates DM (2000), Mixed-Ef...
199	BENNETT5	1	PST 2005.11.30.22.31.11	NIST BENNETT5 <a href="http://www.itl.nist.gov/div...">http://www.itl.nist.gov/div...</a>
198	RAT43	1	PST 2005.11.30.22.29.10	NIST RAT43 <a href="http://www.itl.nist.gov/div898...">http://www.itl.nist.gov/div898...</a>
197	ECKERLE4	1	PST 2005.11.30.22.26.42	NIST ECKERLE4 <a href="http://www.itl.nist.gov/div...">http://www.itl.nist.gov/div...</a>
196	MGH10	1	PST 2005.11.30.22.24.40	NIST MGH10 <a href="http://www.itl.nist.gov/div898...">http://www.itl.nist.gov/div898...</a>
195	RAT42	1	PST 2005.11.30.22.21.46	NIST RAT42 <a href="http://www.itl.nist.gov/div898...">http://www.itl.nist.gov/div898...</a>

List  Versions  Jobs    Group member     Total found    

- Example jobs are available to help users get started
- Job = Data + Model
- The models can be used to start a new analysis

# General Plotting Capabilities

- A general plotting routine has been added to the MDA
- It allows to plot all model variables in various combinations
- It also displays histograms and features of the parameter distributions

**Plot Settings**

Select data columns      Symbol      Color

Y\_1 axis for: none      ●      ■

Y\_2 axis for: none      ●      ■

Y\_3 axis for: none      ●      ■

X axis for: none       Plot for each ID number

Plot the data in the Uniform Scales      Color

Add a vertical line along X = 0      ■

Add a horizontal line along Y = 0      ■

Add a unit slope line passing the origin Y = X      ■

Add linear regression line for      ■

Add regression percentiles of 99%      ■

Plot the data in the Log Scales       log( X )       log( Y )

Plot a histogram for the data X      Interval Size:     

Draw a vertical line at the 1st X data value, as True Value     

Plot Title:

X - Label:

Y - Label:

OK      Advanced      Cancel

# Planned SPK Capabilities

- Predefined library of common models
- Other population analysis methods
  - NPML – Nonparametric maximum likelihood
  - MCMC – Monte Carlo Markov chain
- Other resources can be integrated
  - Optimal experiment design
- Multilayered output
  - Population, conditional and individual estimates

# Software Development

- We have developed a novel mixed effects modeling tool to be released under an Open Source license
- The software has already been deployed over the Web as a web service
- We plan to add more capabilities to it as our user platform increases
- Other sites will be able to deploy their own installation and add to the code in keeping with the Open Source licensing spirit

# Interested?

- SPK accounts are granted upon request (pursuant to the SPK Terms of Use)
- Open source code release is forthcoming
- Computational hardware devoted to SPK should increase in the near future
- More information can be found at <http://www.rfpk.washington.edu>