Automated modeling workflow in Pirana

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Background

An automated workflow alleviates the burden on modeling scientist by removing the repetitive task of running and evaluating many candidate models, standardizes the model development between modelers, and standardize the results reported from such an analysis ultimately leading to higher quality of PopPK analyses (*Schmidt et al. JPKPD 2014 Aug*). In Pirana (version >= 2.10), such a workflow is made available, and in this tutorial we will walk through an example of an automated population PK analysis.

Tutorial

For this tutorial, we will use the template model library that is provided with Pirana, and a (simulated) dataset of an iv-administered drug also provided with Pirana (`demo.csv`).

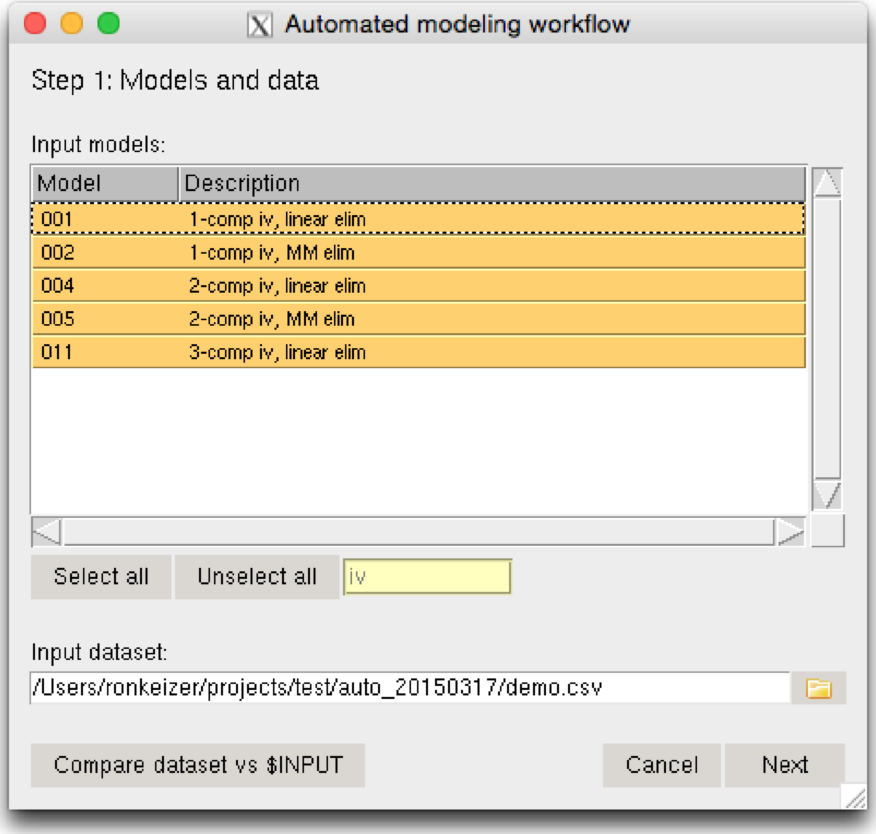
Start

Start Pirana Create a new project folder somewhere on your hard-drive (or cluster). Browse into this folder (with Pirana). In this folder, copy the file `demo.csv` that is included in the Pirana installation folder (`Pirana/automod_library/demo/demo.csv`). In Pirana, go to **Tools –> Automated modeling workflow**.

Screen 1: Models and dataset

This screen shows all models available in the library and which can be selected to be included in the analysis. Use the filter for conveniently selecting e.g. only *iv* or only *oral* models. The dataset should of course be specified as well before you can advance to the next step. By default, it will use the first `.csv` file in this folder (in alphabetic order).

When models and dataset have been selected, you should check whether the `$INPUT` record in the models matches with the headers in the dataset. For this,



Step 1: Models and data

Input models:

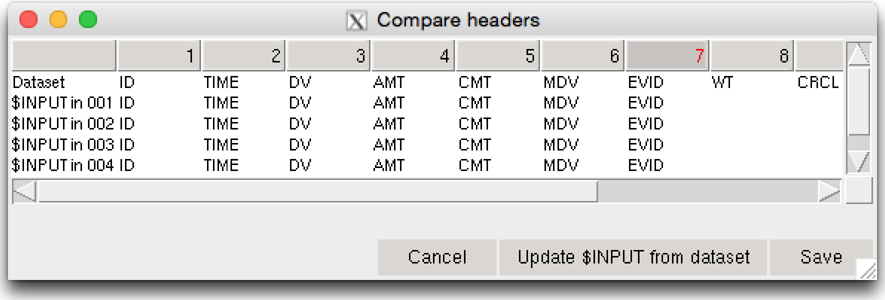
Model	Description
001	1-comp iv, linear elim
002	1-comp iv, MM elim
004	2-comp iv, linear elim
005	2-comp iv, MM elim
011	3-comp iv, linear elim

iv

Input dataset:

/Users/ronkeizer/projects/test/auto_20150317/demo.csv

Figure 1: Screen 1: Models and dataset



	1	2	3	4	5	6	7	8	
Dataset	ID	TIME	DV	AMT	CMT	MDV	EVID	WT	CRCL
$INPUT in 001	ID	TIME	DV	AMT	CMT	MDV	EVID		
$INPUT in 002	ID	TIME	DV	AMT	CMT	MDV	EVID		
$INPUT in 003	ID	TIME	DV	AMT	CMT	MDV	EVID		
$INPUT in 004	ID	TIME	DV	AMT	CMT	MDV	EVID		

Figure 2: Compare/set input headers

click the button `Compare dataset vs`$INPUT'. This will bring up screen shown in figure 2:

If the `$INPUT` in the models (shown in rows 2-. . .) does not match up with the dataset (shown in row 1), you can click the button `Update $INPUT from dataset`. This will create a new $INPUT record for all models. After clicking **Save**, when the models will be written (in step 3 of the automated analysis), the $INPUT records in all models will be changed to the new one. It is left to the user to make sure that the variables used in the model are still included in $INPUT, as there is no extra check in place for that.

For our current analysis, we will select all *iv* models, so filter on *iv*, and select the remaining models. Update the `$INPUT` records, click *Save* and then *Next* to advance to the next step.

Screen 2: Setting initial parameter estimates

In the second screen, we can set initial parameter estimates, as well as lower and upper bounds. All parameters are read from the models that were selected in step 1. The parameter descriptions are defined in the models as comments to `$THETA`, `$OMEGA`, and `$SIGMA` blocks, like e.g.

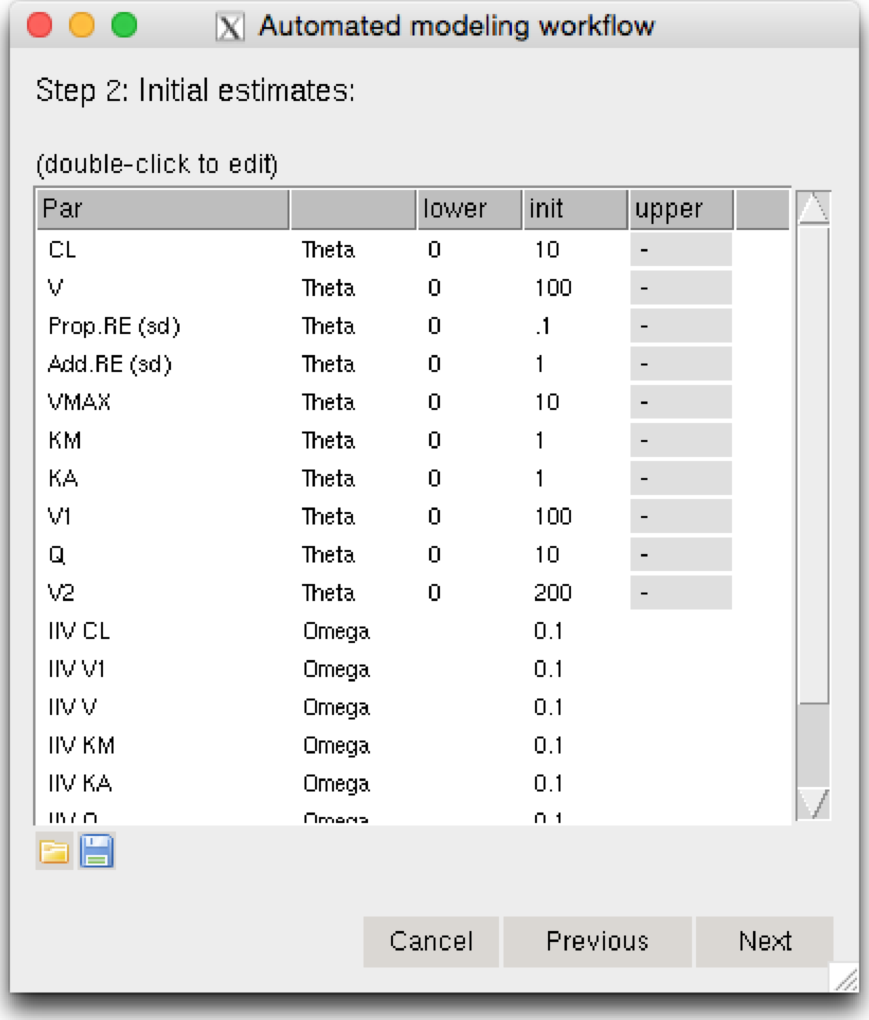
```
$THETA
(0, 5, 100); CL
(0, 5, 100); V

$OMEGA
(0.1); CL
(0.1); V

$SIGMA
0.05 ; proportional error
```

Note: At current, correlations in $OMEGA and $SIGMA cannot be specified for an automated analysis. I.e. only the diagonal elements of $OMEGA and $SIGMA can be specified in the template models if you want to update them in this step. You can still include models that have full $OMEGA or $SIGMA blocks as template model, however you cannot provide descriptions (as comments) to the parameters in the block, and you cannot update them in this step of the analysis.

The two buttons below the parameter grid can be used to save and (re-)load parameter definitions to file.



Automated modeling workflow

Step 2: Initial estimates:

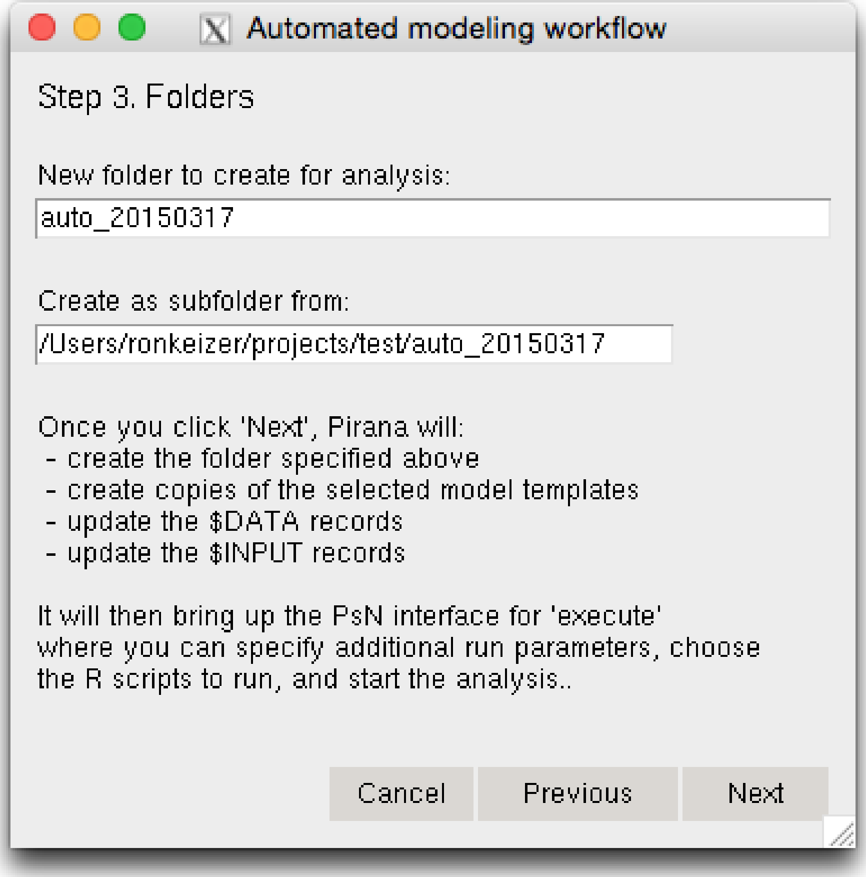
(double-click to edit)

Par		lower	init	upper	
CL	Theta	0	10	-	
V	Theta	0	100	-	
Prop.RE (sd)	Theta	0	.1	-	
Add.RE (sd)	Theta	0	1	-	
VMAX	Theta	0	10	-	
KM	Theta	0	1	-	
KA	Theta	0	1	-	
V1	Theta	0	100	-	
Q	Theta	0	10	-	
V2	Theta	0	200	-	
IIV CL	Omega		0.1		
IIV V1	Omega		0.1		
IIV V	Omega		0.1		
IIV KM	Omega		0.1		
IIV KA	Omega		0.1		
IIV Q	Omega		0.1		

Figure 3: Screen 2: Initial parameter estimates

For our analysis, let's leave the parameters as they are. Click **Next** to advance to the next step.

Screen 3: Folders



Automated modeling workflow

Step 3. Folders

New folder to create for analysis:
auto_20150317

Create as subfolder from:
/Users/ronkeizer/projects/test/auto_20150317

Once you click 'Next', Pirana will:
- create the folder specified above
- create copies of the selected model templates
- update the $DATA records
- update the $INPUT records

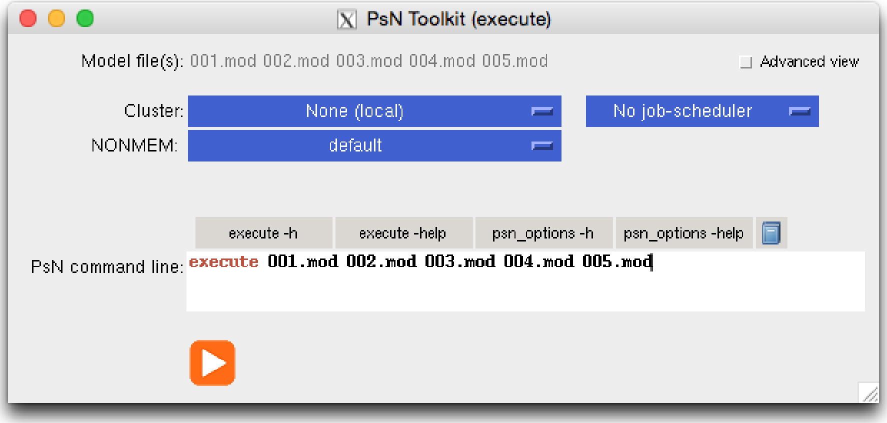
It will then bring up the PsN interface for 'execute' where you can specify additional run parameters, choose the R scripts to run, and start the analysis..

Figure 4: Screen 3: Folders

In this screen we can specify where to create the new models and run the analysis. By default it will generate a new folder name based on the current date, and as a subfolder from the current folder in Pirana. This screen also lists the actions that Pirana will perform once you click *Next*.

Let's use the defaults and click *Next*.

Screen 4: PsN dialog



Model file(s): 001.mod 002.mod 003.mod 004.mod 005.mod

Cluster: None (local) No job-scheduler

NONMEM: default

PsN command line:

```
execute 001.mod 002.mod 003.mod 004.mod 005.mod
```

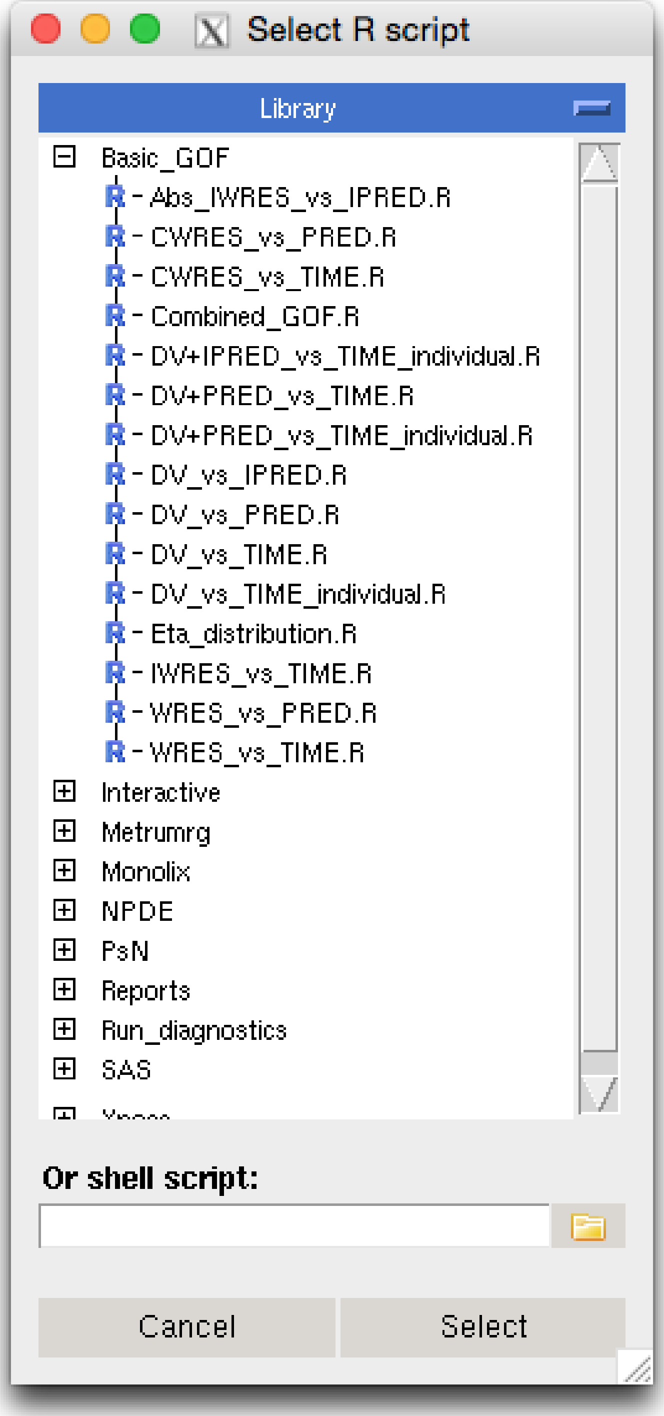
Figure 5: Screen 4: PsN

Pirana should now have switched automatically to the new folder where you will see the newly generated models. Pirana will also automatically bring up the PsN `execute` dialog. In this dialog, if you switch to **Advanced view**, you can select which R script(s) to run after all runs have been completed to generate goodness-of-fit plots. Click the *folder* icons next to the R scripts textboxes to select R scripts (or batch files) to run after (or before) the analysis (figure 6).

For our analysis, we will select the **Basic GOF plots as single doc** from the `Reports` folder to create GOF plots for all models. The graphical report will automatically be opened, but is also available from the *Reports* tab on the right.

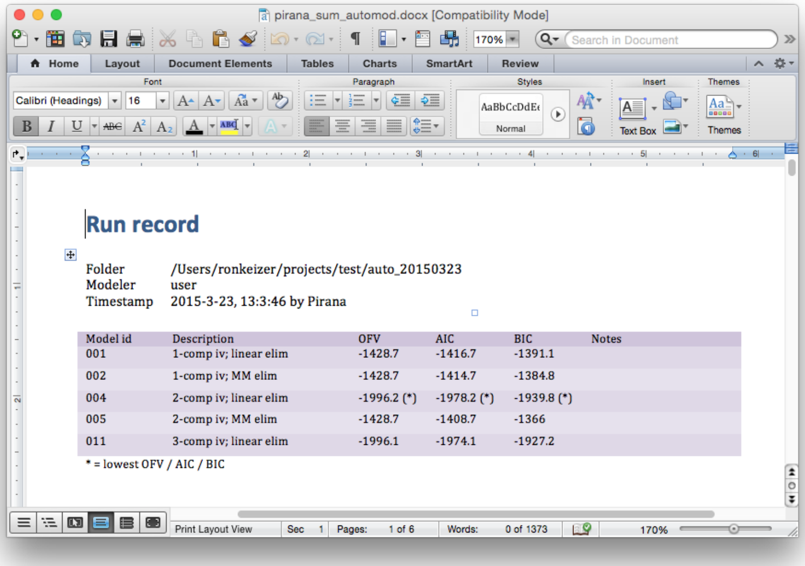
If you have not selected R scripts to be executed automatically after the analysis has completed, you can still create them afterwards by selecting the runs and running any R script from the **R** tab on the right side of the Pirana window.

Besides the graphical report, Pirana can generate a *numeric* report for the analysis, including e.g. OFVs, basic run information and parameter estimates. This document is not generated automatically but has to be requested manually after the analysis is complete: Make sure Pirana is still in the folder where the analysis was run, and then go to **Tools** –> **Automated modeling workflow** –> **Report**. On the first page you will see an overview of all models included in the analysis and their respective OFV, AIC and BIC (figure 7). The subsequent pages includes information on each individual run in the analysis.



- Basic_GOF
  - Abs_IWRES_vs_IPRED.R
  - CWRES_vs_PRED.R
  - CWRES_vs_TIME.R
  - Combined_GOF.R
  - DV+IPRED_vs_TIME_individual.R
  - DV+PRED_vs_TIME.R
  - DV+PRED_vs_TIME_individual.R
  - DV_vs_IPRED.R
  - DV_vs_PRED.R
  - DV_vs_TIME.R
  - DV_vs_TIME_individual.R
  - Eta_distribution.R
  - IWRES_vs_TIME.R
  - WRES_vs_PRED.R
  - WRES_vs_TIME.R
- Interactive
- Metrumrg
- Monolix
- NPDE
- PsN
- Reports
- Run_diagnostics
- SAS
- Xpose

Figure 6: Select R script



Run record

Folder /Users/ronkeizer/projects/test/auto_20150323
Modeler user
Timestamp 2015-3-23, 13:3:46 by Pirana

Model id	Description	OFV	AIC	BIC	Notes
001	1-comp iv; linear elim	-1428.7	-1416.7	-1391.1	
002	1-comp iv; MM elim	-1428.7	-1414.7	-1384.8	
004	2-comp iv; linear elim	-1996.2 (*)	-1978.2 (*)	-1939.8 (*)	
005	2-comp iv; MM elim	-1428.7	-1408.7	-1366	
011	3-comp iv; linear elim	-1996.1	-1974.1	-1927.2	

* = lowest OFV / AIC / BIC

Figure 7: Report in Word