NETI – Network Inference
Version 1.1
User Manual

NETI download page: http://bioinfo.curie.fr/projects/reverse-engineering/

Author: Eugene Novikov (Institute Curie)
E-mail: Eugene.Novikov@curie.fr

System Requirements

NETI is written in Java (interface) and C++ (algorithms). It runs on Windows platforms 95/98/Me/NT/2000/XP (may be used under Unix after recompiling C++ code) and needs the Java Runtime Environment (JRE) to be installed:
(http://www.java.com/en/download/)

Software has been tested on the following systems:
(I) Pentium® 4 CPU 3.00GHz and 1 GB of RAM
(II) Intel® Mobile Celeron® CPU 2.00GHz and 256 MB of RAM
No reasons why it should not work with the other configurations.

Installation

NETI can be downloaded from the NETI download page http://bioinfo.curie.fr/projects/reverse-engineering/

Click NETI 11 Setup.exe to start the NETI 1.1 installer and follow the instructions*.

NETI 1.1 installation creates a “Curie/NETI 1.1” folder in the list of Programs of the Windows Start menu. This new folder contains the following entries:

- NETI 1.1 starts Network inference software;
- User Manual is a user manual pdf file;
- Uninstall NETI will remove NETI from your computer.

Installation procedure may also create a “NETI 1.1” icon on your Desktop.

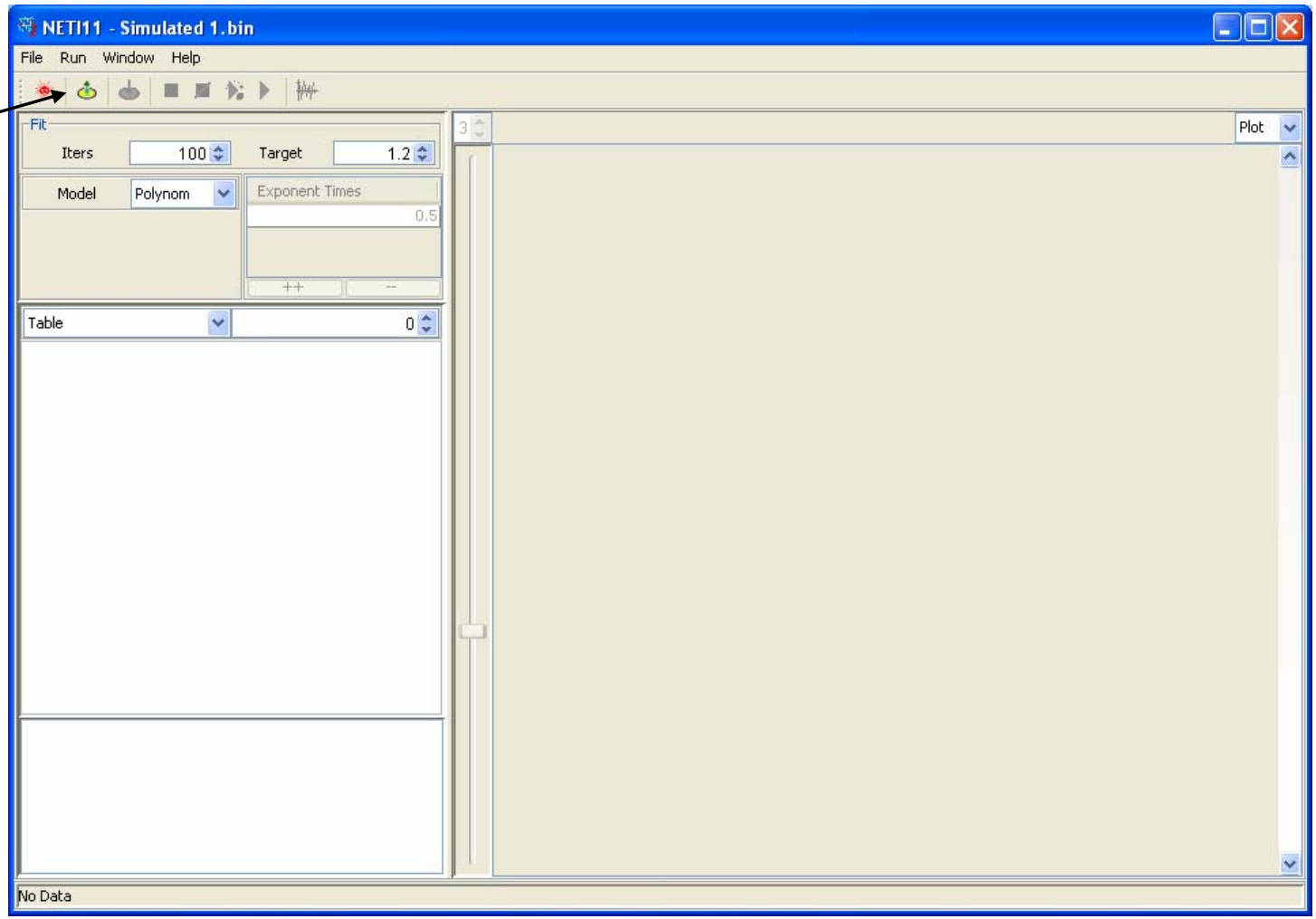
*) Installation procedure asks about the default size of the JVM (Java Virtual Machine) memory allocation pool. It is recommended to set it as large as possible, but not larger than the amount of available RAM.

Network Inference

Processing Window

Data can be downloaded using the “Load Data …” button from the Toolbar or the Menu Item “File|Load|Load Data …” (Ctrl+O).

See next page for examples of the input data formats.



Input Data Format

Without standard errors:

Header	Time	x0	x1	x2	x3	x4	x5	…
Sample	;	0	1.0101	2.0202	3.0303	4.0404	5.05051	…
E1	0	0.00003	0.00003	0.00003	0.00003	0.00003	0.00003	…
E2	1	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	…
KKK	2	0.003	0.00296	0.00291	0.00287	0.00284	0.0028	…
P_KKK	3	0	0.00001	0.00002	0.00003	0.00003	0.00004	…
KK	4	1.2	1.19743	1.1904	1.17974	1.16613	1.15009	…
P_KK	5	0	0.00253	0.00948	0.01994	0.03313	0.0484	…
PP_KK	6	0	0	0.00001	0.00004	0.00012	0.00026	…
K	7	1.2	1.19999	1.19985	1.19931	1.19795	1.19533	…
P_K	8	0	0.00001	0.00008	0.00038	0.00114	0.00259	…
PP_K	9	0	0	0	0	0	0.00001	…
KPase	10	0.12	0.12	0.11997	0.11985	0.11955	0.11897	…
P_KKK_KK	11	0	0.00003	0.00007	0.0001	0.00013	0.00015	…
PP_KK_KK	12	0	0	0.00003	0.00016	0.00046	0.00104	…
KPase_PP_KK	13	0	0	0	0	0	0	…
…	…	…	…	…	…	…	…	…

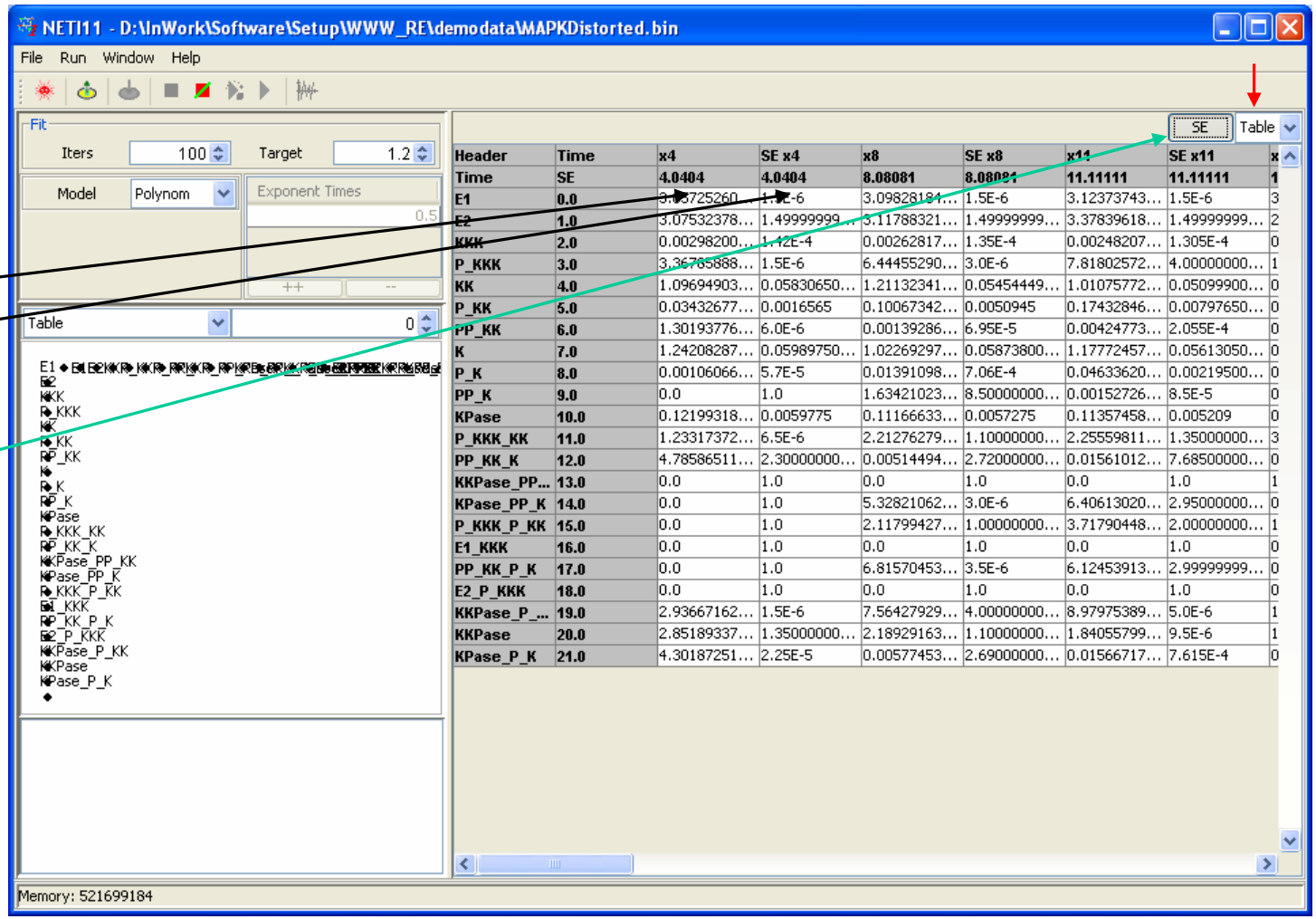
With standard errors (SE is indicated in the table cell [1;1]):

Header	Time	x2	SE x2	x10	SE x10	x13	SE x13	…
Sample	SE;	2.0202	2.0202	10.10101	10.10101	13.13131	13.13131	…
E1	0	3.02E-05	1.50E-06	3.00E-05	1.50E-06	3.15E-05	1.50E-06	…
E2	1	2.79E-04	1.50E-05	2.87E-04	1.50E-05	3.18E-04	1.50E-05	…
KKK	2	0.00286195	1.45E-04	0.00250212	1.32E-04	0.00260262	1.28E-04	…
P_KKK	3	2.14E-05	1.00E-06	6.97E-05	3.50E-06	9.56E-05	4.50E-06	…
KK	4	1.21922989	0.05952	1.06178469	0.052231	1.00851474	0.048417	…
P_KK	5	0.00993045	4.74E-04	0.13696104	0.007016	0.18396007	0.0098425	…
PP_KK	6	9.74E-06	5.00E-07	0.00265924	1.49E-04	0.00669657	3.58E-04	…
K	7	1.18169628	0.0599925	1.14199093	0.057234	1.0437543	0.0529535	…
P_K	8	8.16E-05	4.00E-06	0.03169311	0.0015605	0.08431202	0.0040365	…
PP_K	9	0	0.01	8.49E-04	4.20E-05	0.00607996	3.06E-04	…
KPase	10	0.11832766	0.0059985	0.11307701	0.0054215	0.08518873	0.004654	…
P_KKK_KK	11	7.16E-05	3.50E-06	2.27E-04	1.25E-05	2.92E-04	1.45E-05	…
PP_KK_KK	12	2.96E-05	1.50E-06	0.0103351	5.69E-04	0.02333924	0.0012625	…
KPase_PP_KK	13	0	0.01	0	0.01	0	0.01	…
…	…	…	…	…	…	…	…	…

Table View

Intensity values with the corresponding standard errors (*SE*).

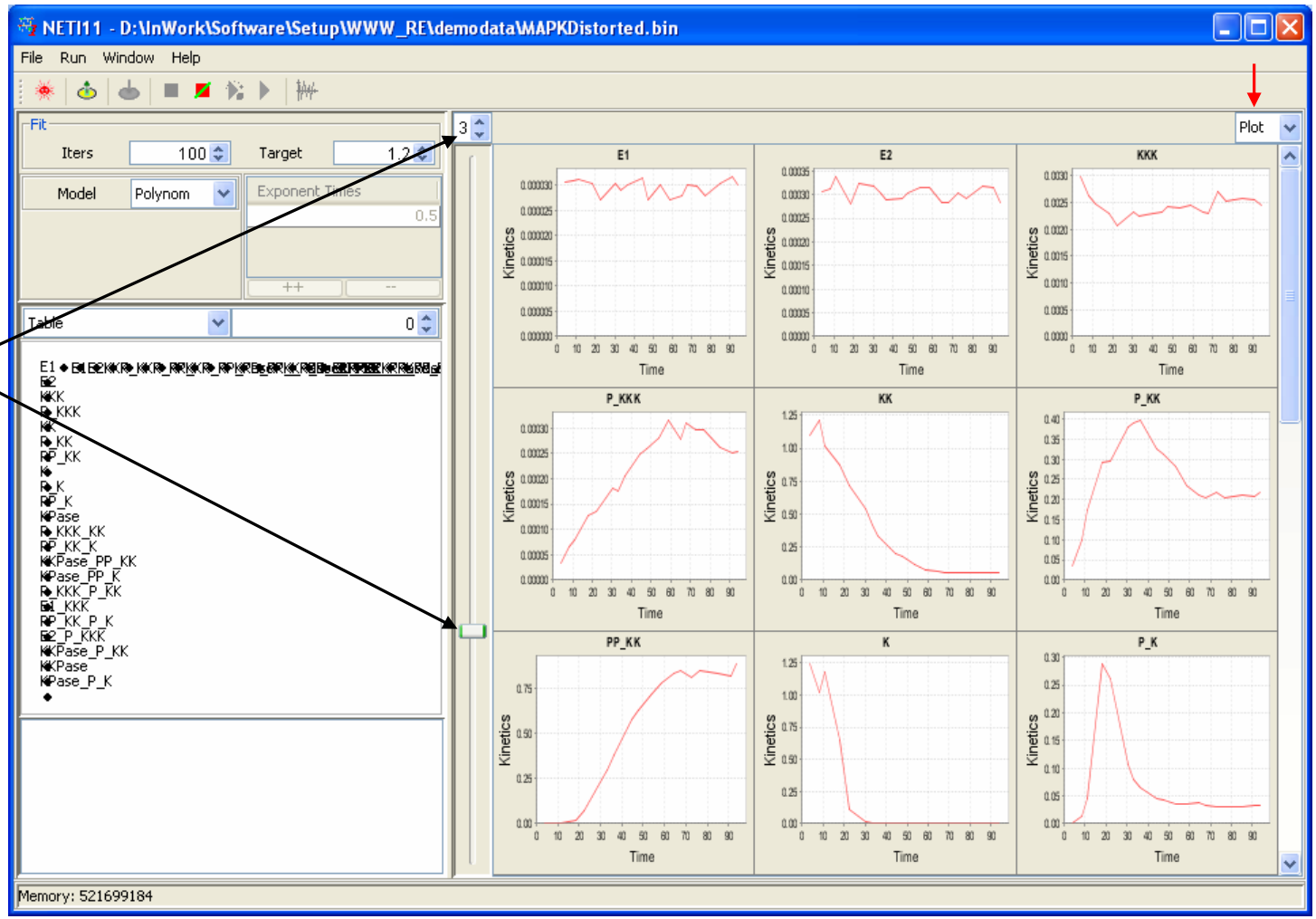
SE column can be hidden using the "*SE*" button from the local toolbar.



Header	Time	x4	SE x4	x8	SE x8	x11	SE x11	x
Time	SE	4.0404	4.0404	8.08081	8.08081	11.11111	11.11111	1
E1	0.0	3.36725260...	1.5E-6	3.09828184...	1.5E-6	3.12373743...	1.5E-6	3
E2	1.0	3.07532378...	1.49999999...	3.11788321...	1.49999999...	3.37839618...	1.49999999...	2
KKK	2.0	0.00298200...	1.42E-4	0.00262817...	1.35E-4	0.00248207...	1.305E-4	0
P_KKK	3.0	3.36765888...	1.5E-6	6.44455290...	3.0E-6	7.81802572...	4.00000000...	1
KK	4.0	1.09694903...	0.05830650...	1.21132341...	0.05454449...	1.01075772...	0.05099900...	0
P_KK	5.0	0.03432677...	0.0016565	0.10067342...	0.0050945	0.17432846...	0.00797650...	0
PP_KK	6.0	1.30193776...	6.0E-6	0.00139286...	6.95E-5	0.00424773...	2.055E-4	0
K	7.0	1.24208287...	0.05989750...	1.02269297...	0.05873800...	1.17772457...	0.05613050...	0
P_K	8.0	0.00106066...	5.7E-5	0.01391098...	7.06E-4	0.04633620...	0.00219500...	0
PP_K	9.0	0.0	1.0	1.63421023...	8.50000000...	0.00152726...	8.5E-5	0
KPase	10.0	0.12199318...	0.0059775	0.11166633...	0.0057275	0.11357458...	0.005209	0
P_KKK_KK	11.0	1.23317372...	6.5E-6	2.21276279...	1.10000000...	2.25559811...	1.35000000...	3
PP_KK_K	12.0	4.78586511...	2.30000000...	0.00514494...	2.72000000...	0.01561012...	7.68500000...	0
KKPase_PP...	13.0	0.0	1.0	0.0	1.0	0.0	1.0	1
KPase_PP_K	14.0	0.0	1.0	5.32821062...	3.0E-6	6.40613020...	2.95000000...	0
P_KKK_P_KK	15.0	0.0	1.0	2.11799427...	1.00000000...	3.71790448...	2.00000000...	1
E1_KKK	16.0	0.0	1.0	0.0	1.0	0.0	1.0	0
PP_KK_P_K	17.0	0.0	1.0	6.81570453...	3.5E-6	6.12453913...	2.99999999...	0
E2_P_KKK	18.0	0.0	1.0	0.0	1.0	0.0	1.0	0
KKPase_P_...	19.0	2.93667162...	1.5E-6	7.56427929...	4.00000000...	8.97975389...	5.0E-6	1
KKPase	20.0	2.85189337...	1.35000000...	2.18929163...	1.10000000...	1.84055799...	9.5E-6	1
KPase_P_K	21.0	4.30187251...	2.25E-5	0.00577453...	2.69000000...	0.01566717...	7.615E-4	0

Plot View

The number of the graph columns and the height of the graph rows can be adjusted using the corresponding controls.

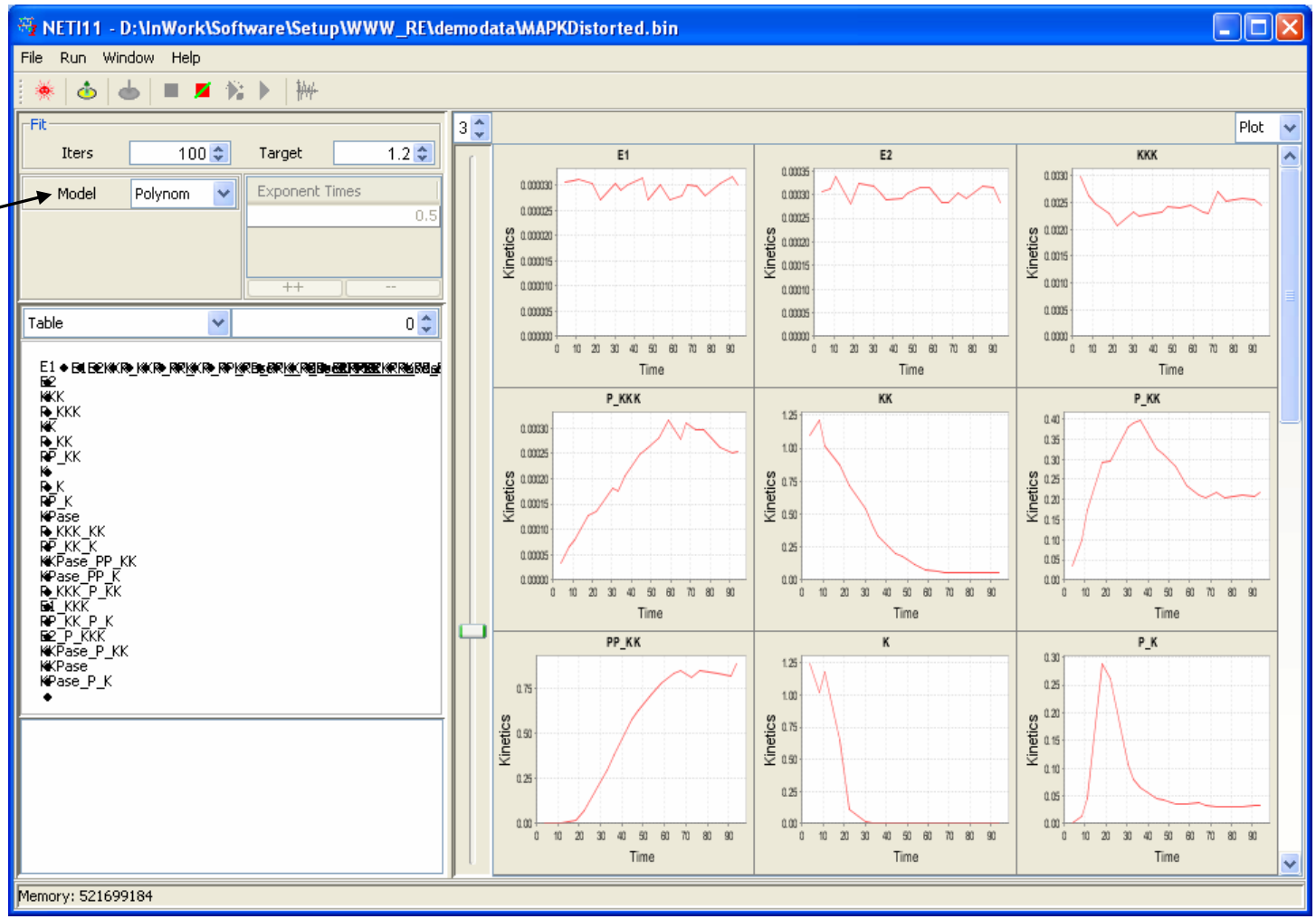


Inference Model Definition (I)

See the paper for more details.

Inference models:

- *Integral model with the zero-degree polynomial kernel;*
- *Integral model with single-exponential kernel;*
- *Differential model;*

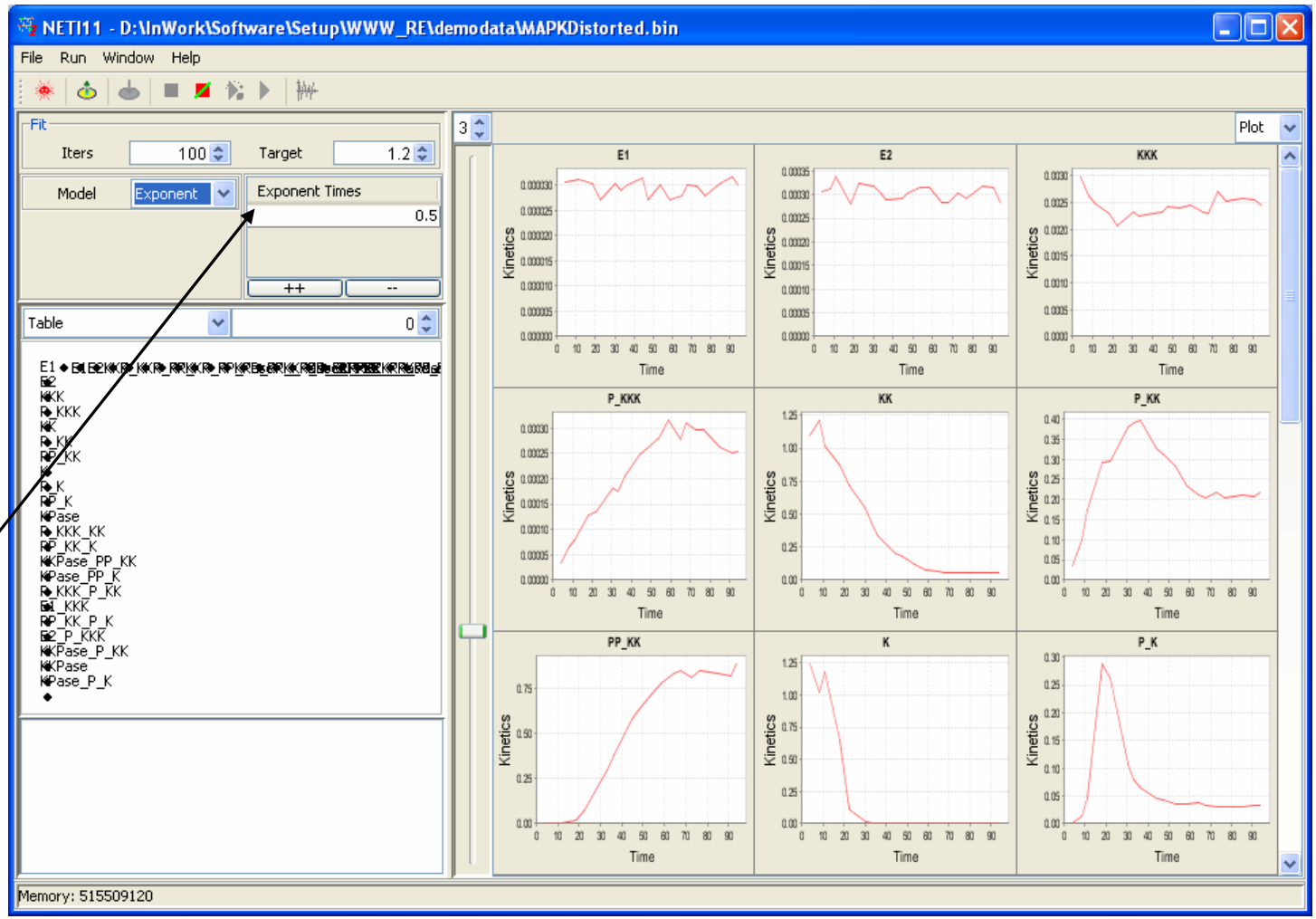


Novikov E, Barillot E: *Regulatory network reconstruction using an integral additive model with flexible kernel functions*, submitted to BMC Systems Biology

Inference Model Definition (II)

For the single-exponential kernel, the decay times are defined as $\tau = \alpha T$, where T is the last time point in a time series and α is the user-defined range scaling factor taken from the *Exponent Times* table.

If several values for α are given (several lines in the *Exponent Times* table), they will be tested, one by one, to ensure the best fitting quality.

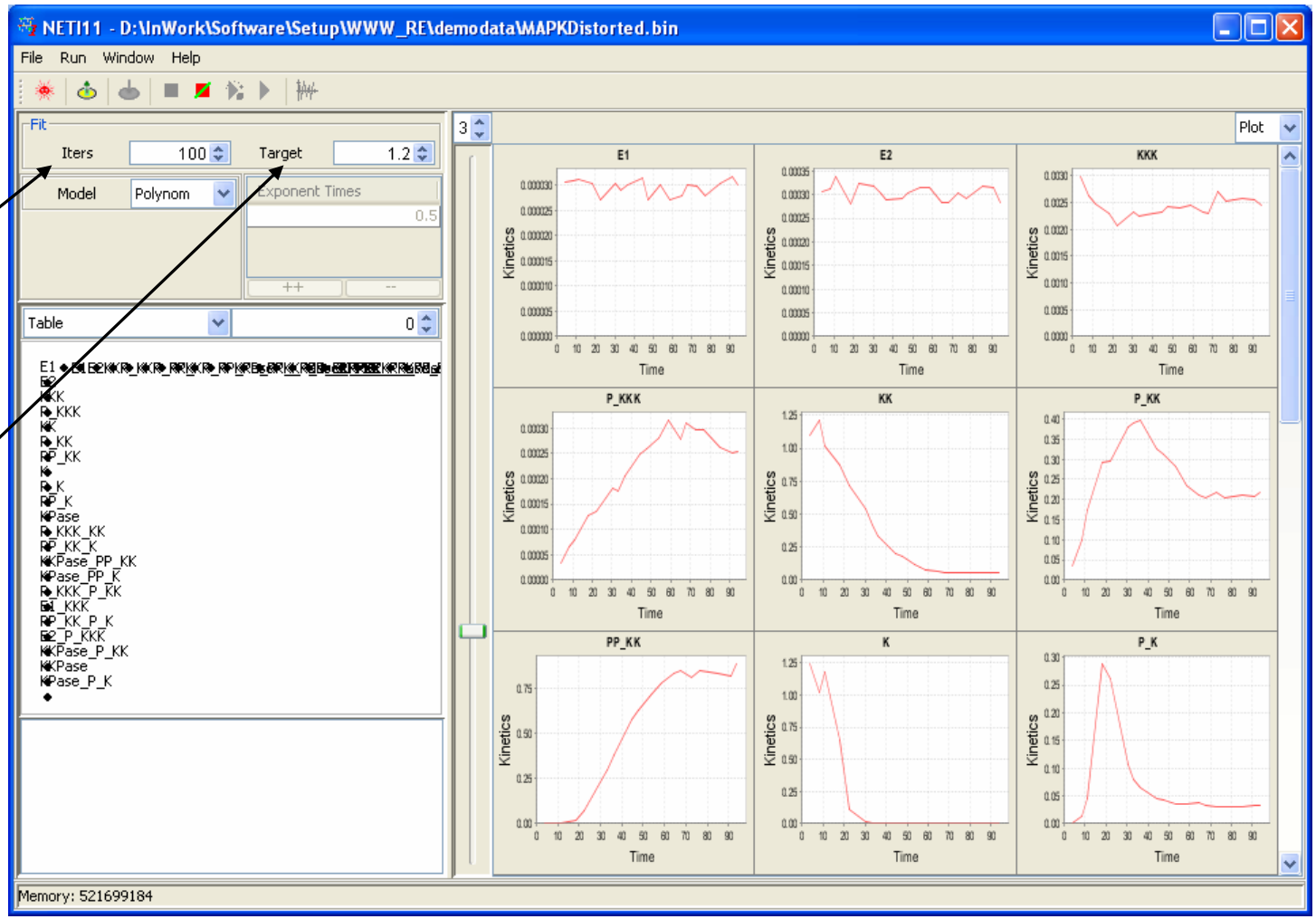


Inference Model Definition (III)

See the paper for more details.

Iters is the stopping criterion: maximal number of links that can be created.

Target is the stopping criterion: minimal limit for the χ^2 overall fitness criterion.



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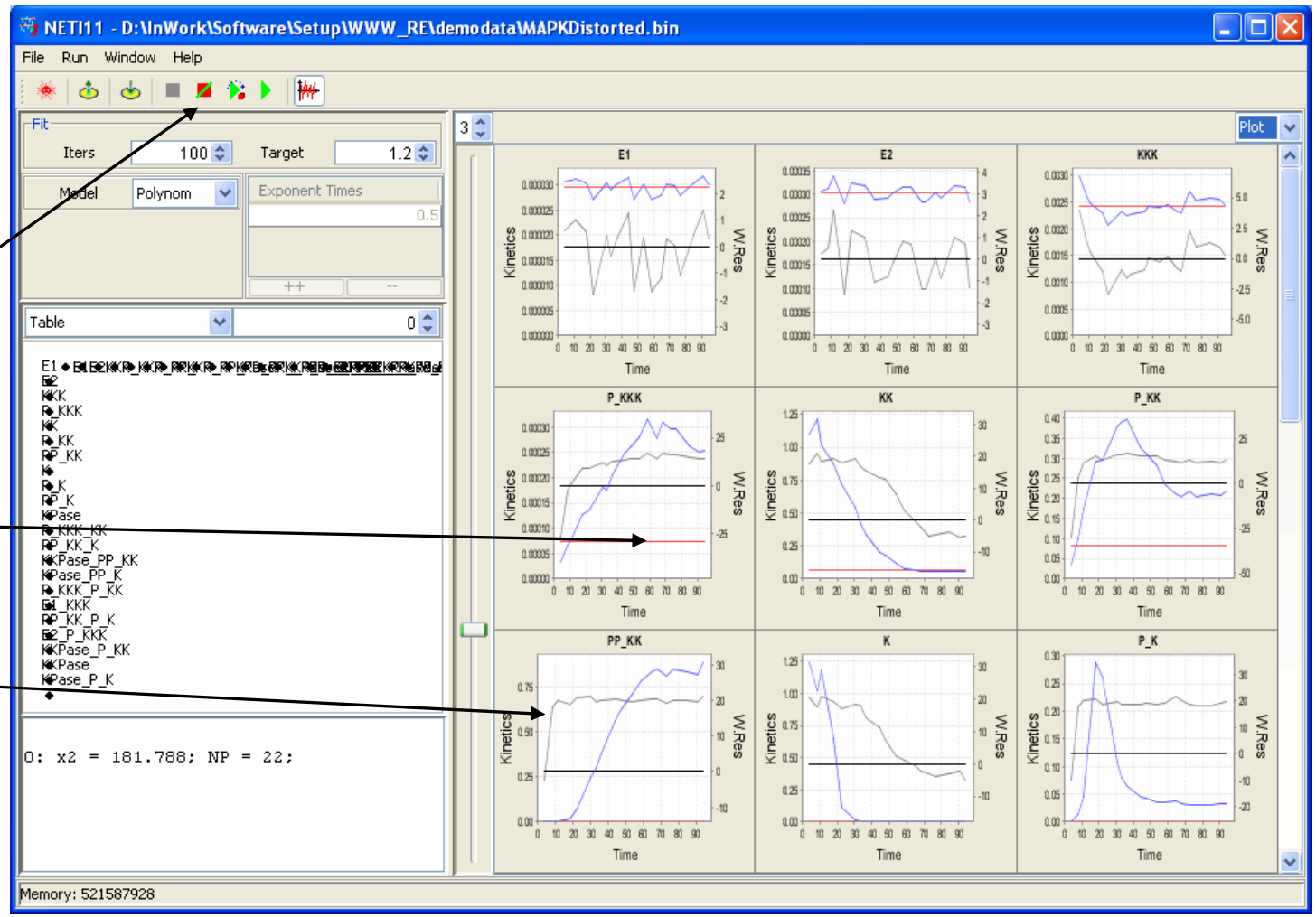
Initialization (I)

Press the “Init” button from the Toolbar or select the Menu Item “Run|Init” (F3) to initialize the inference.

The default (background) behavior will be assigned to each node (red line).

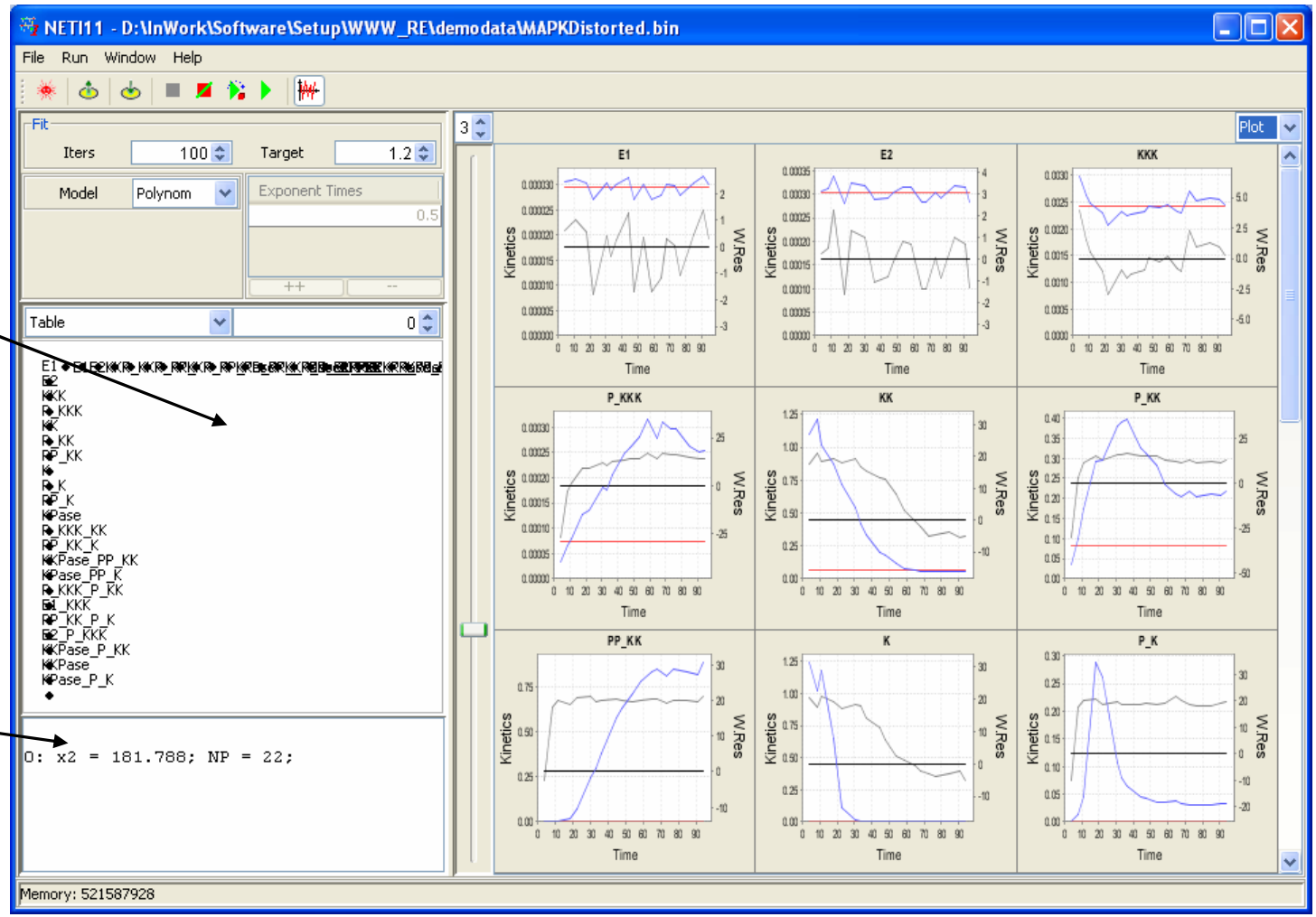
Gray line is the residuals: the differences between the experimental and reconstructed time series.



Initialization (II)

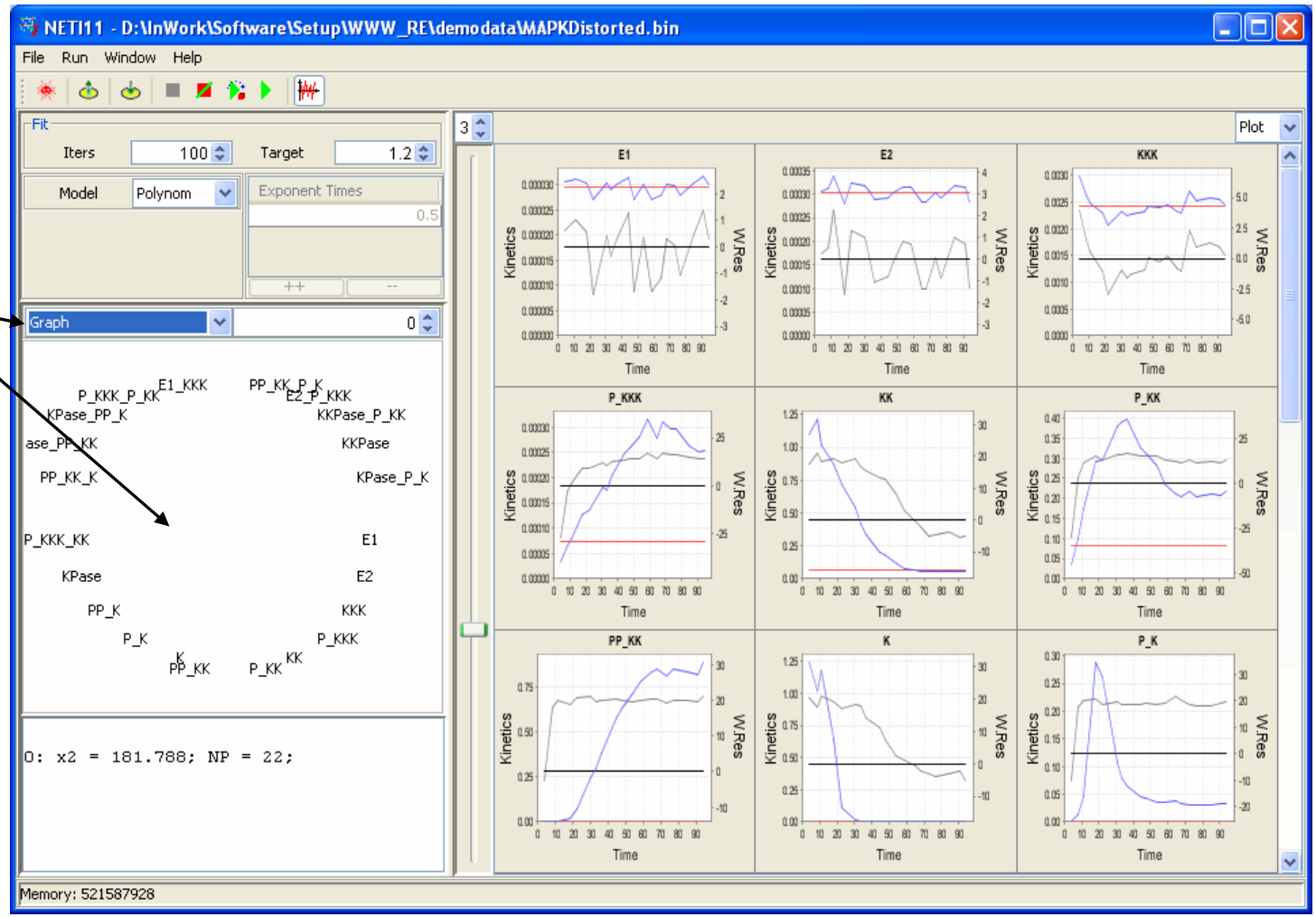
The interaction table is empty as there are no interacting nodes so far.

The number of iterations (links) and the fitness criterion are shown in the log window.



Initialization (III)

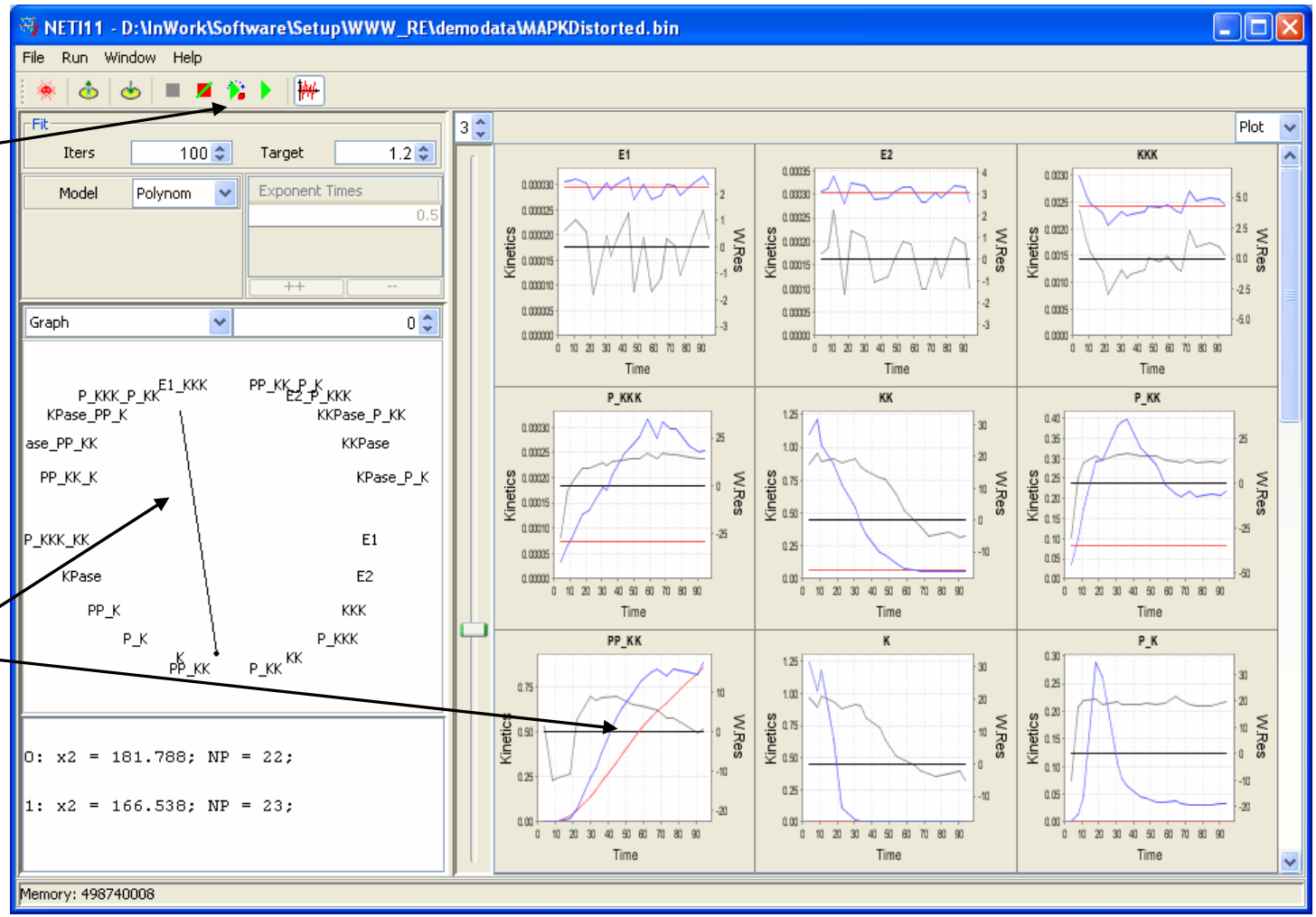
The interaction table can also be presented as a network graph.



Step-by-Step Inference

Network inference can be performed in the "step-by-step" mode, using the "Step" button from the Toolbar or the Menu Item "Run|Step" (F4).

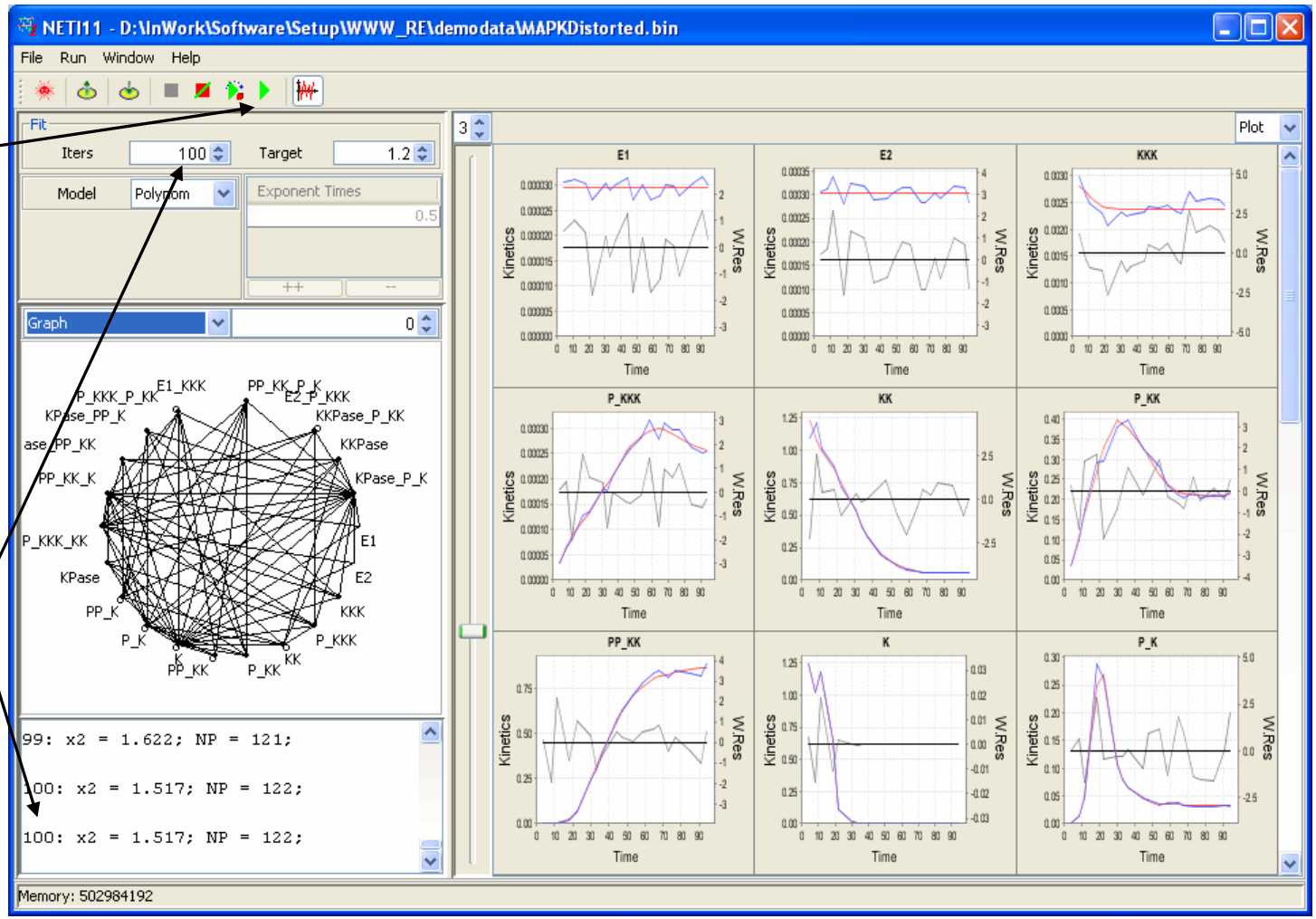
At each step, the procedure selects the node with lowest fitness and finds another node, which can explain the behavior of the given node in the best way (ensuring the lowest χ^2 criterion value for the given node).



Automatic Inference

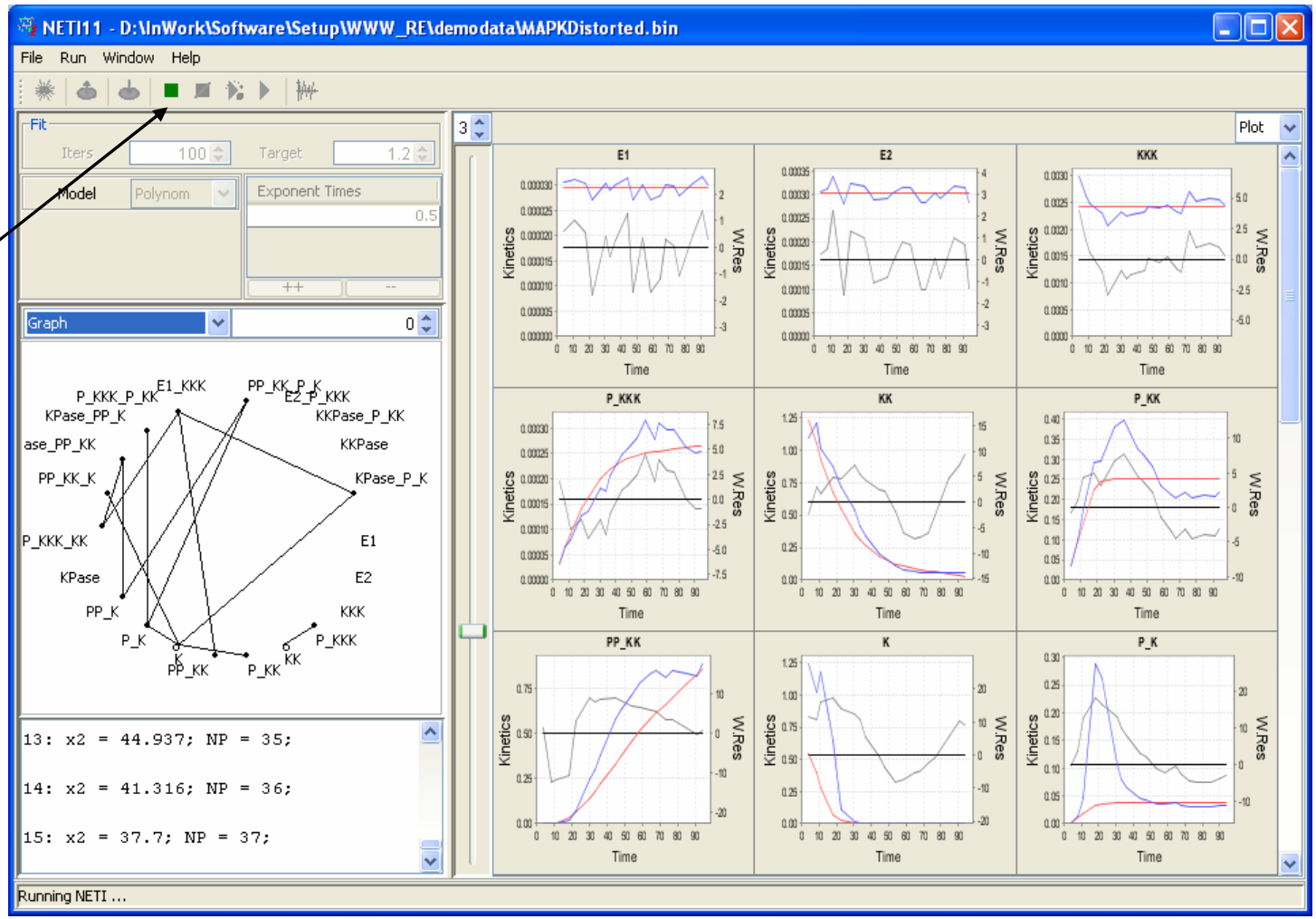
Network inference can be performed in the automatic mode, using the “Run” button from the Toolbar or the Menu Item “Run|Run” (F5).

The procedure performs until the number of created links is higher than the *Iters* value, or until the χ^2 value is lower that the *Target* value.



Terminate Processing

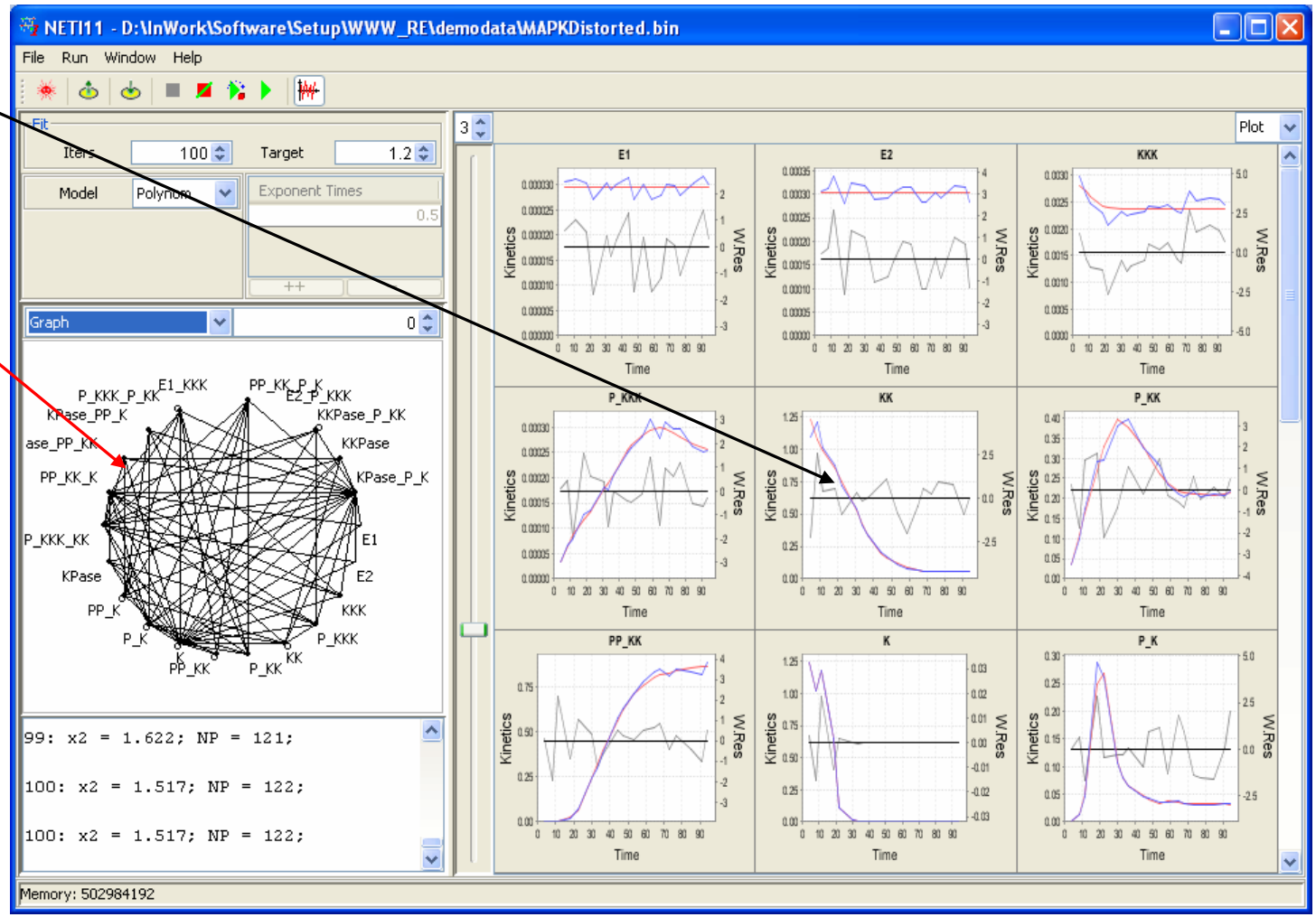
Processing can be stopped by pressing the "Stop" button on the Toolbar or selecting the Menu Item "Run|Stop".



Results

The quality of fit can be visually appreciated.

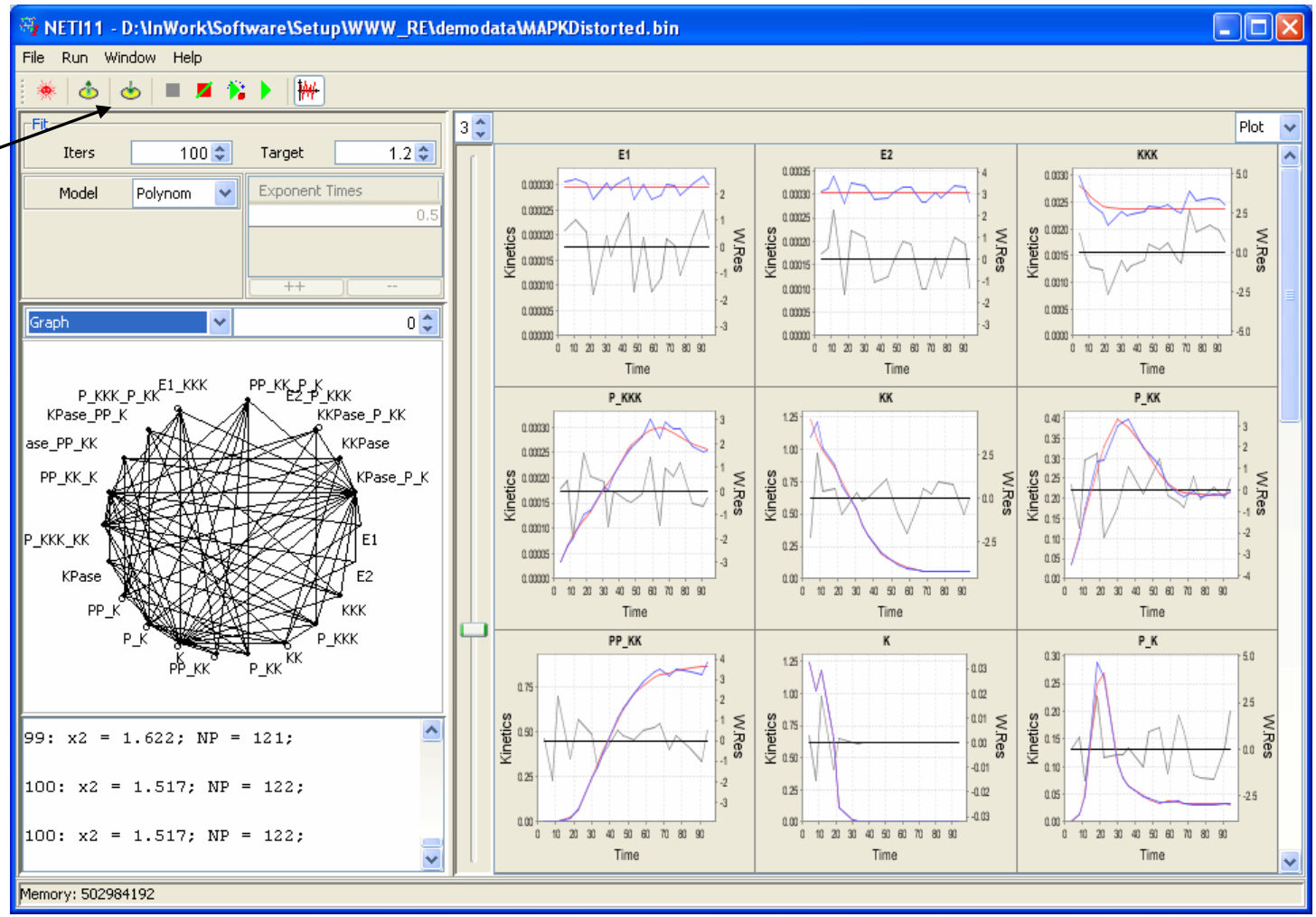
The resulting network graph.



Save Results

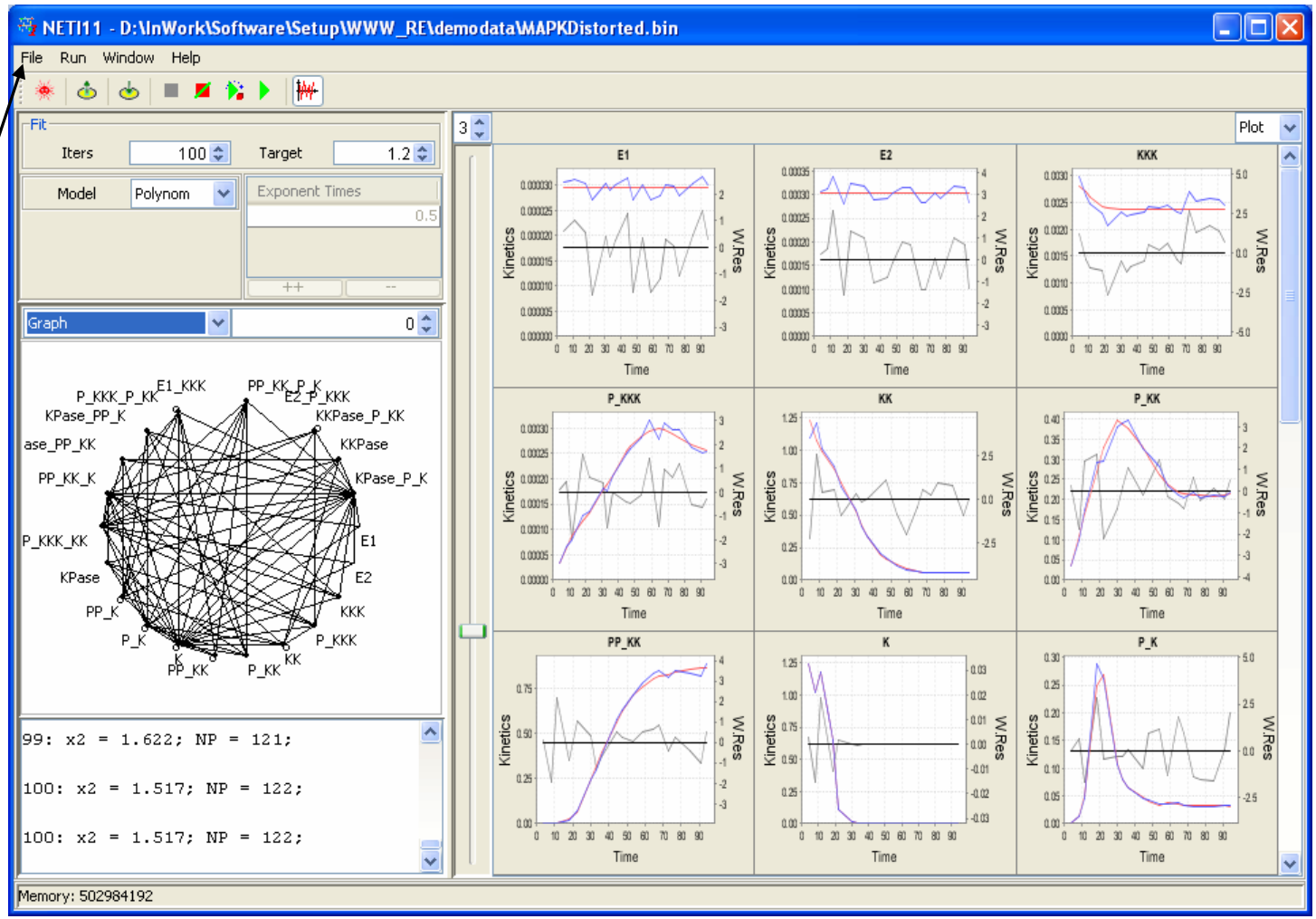
To save the results use the “Save Analysis ...” button from the Toolbar or the Menu Item “File|Save|Save Analysis …” (Ctrl+S).

The results are saved as a list of links in the text file (importable into Microsoft Excel).



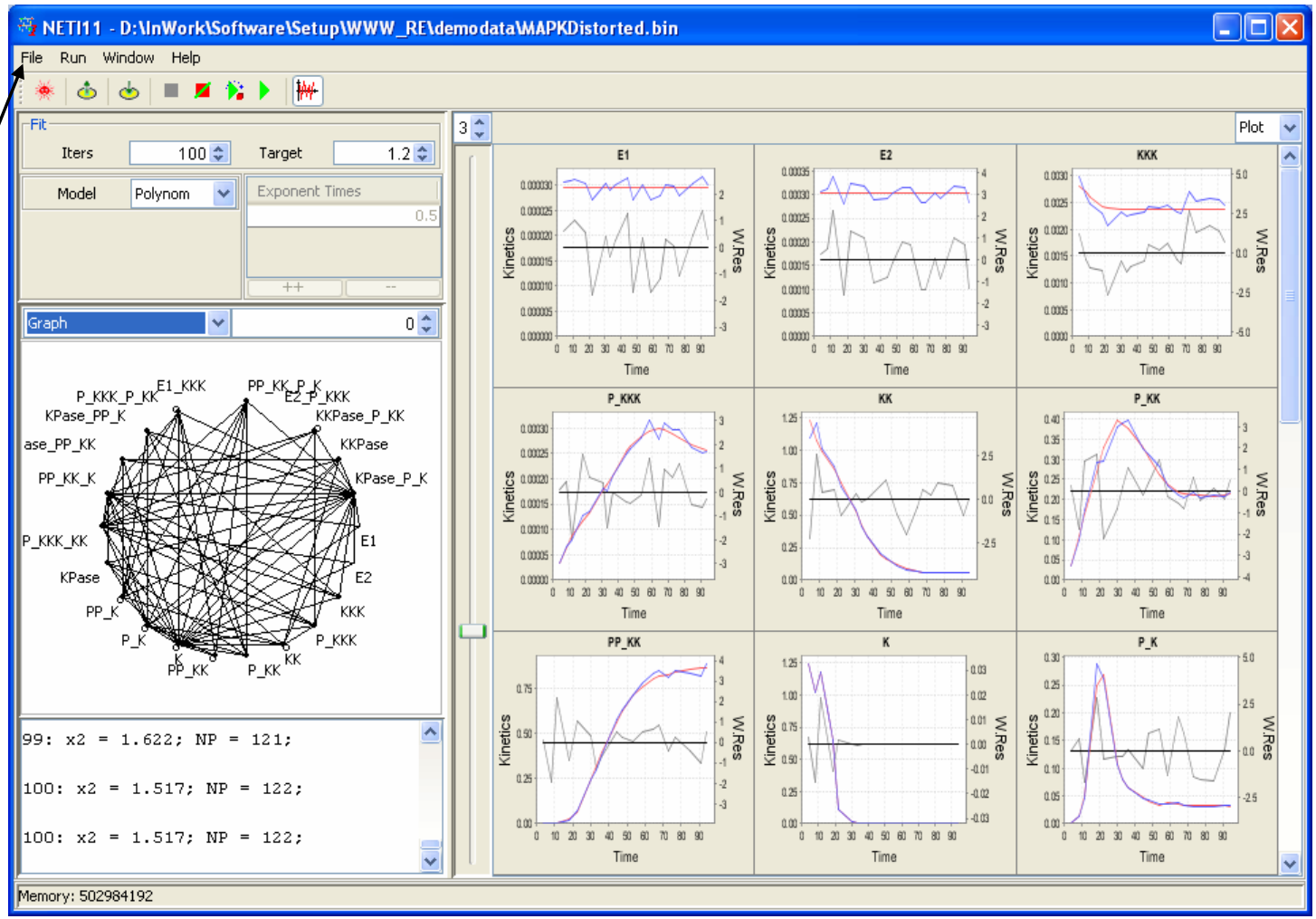
Save Experiments

The whole experiment (results, parameters, other settings) can be saved (using the Menu Item "File|Save|Save Experiment …" (Ctrl+W)) in the internal (binary) format to be able to restore it (using the Menu Item "File|Load|Load Experiment …" (Ctrl+R)) in the future to reanalyze the data.



Set Batch Options

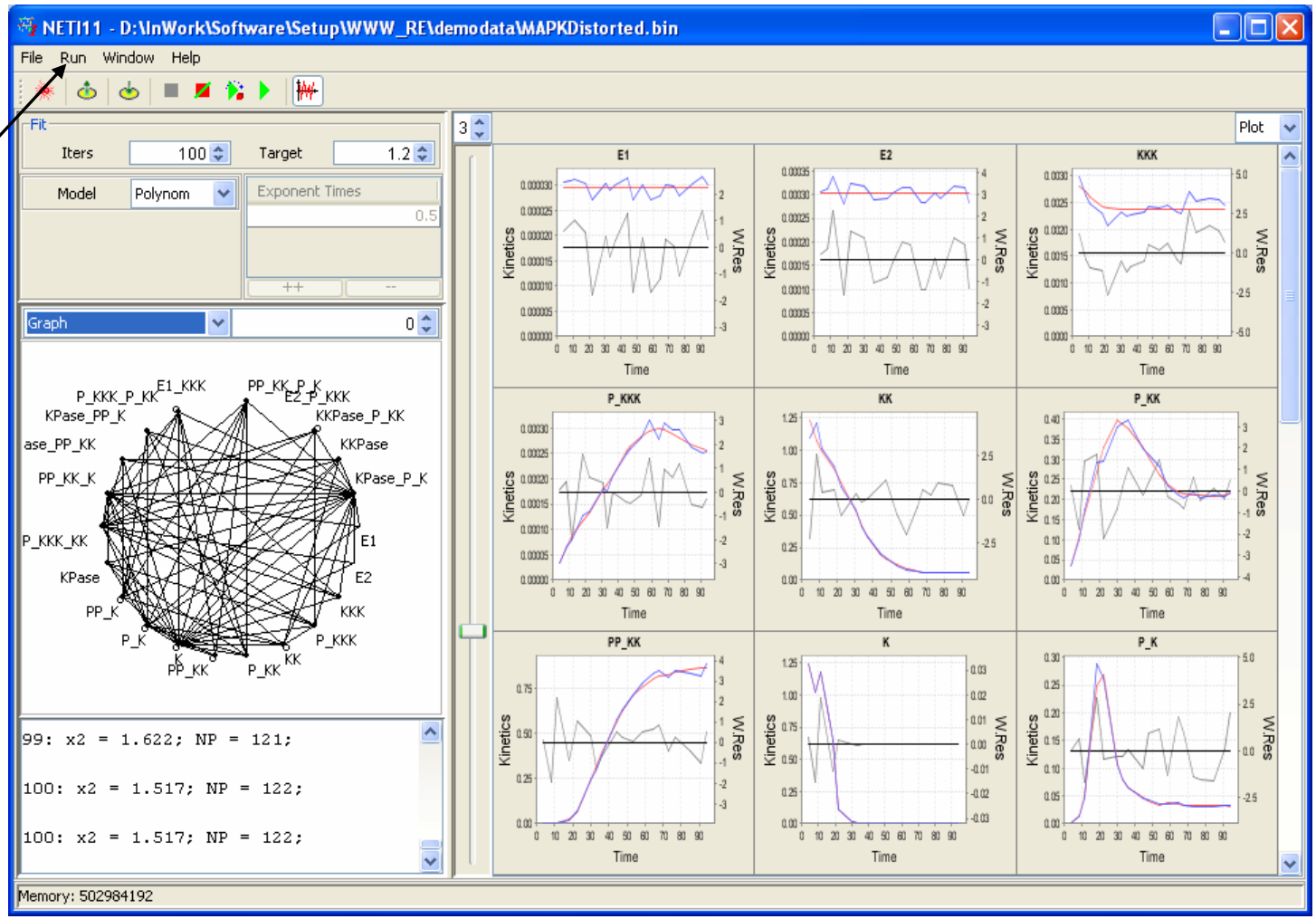
Using the Menu Item “File|Set Batch Options”, all settings can be saved to be applied to other data sets.



Network Simulator

Run Network Simulator

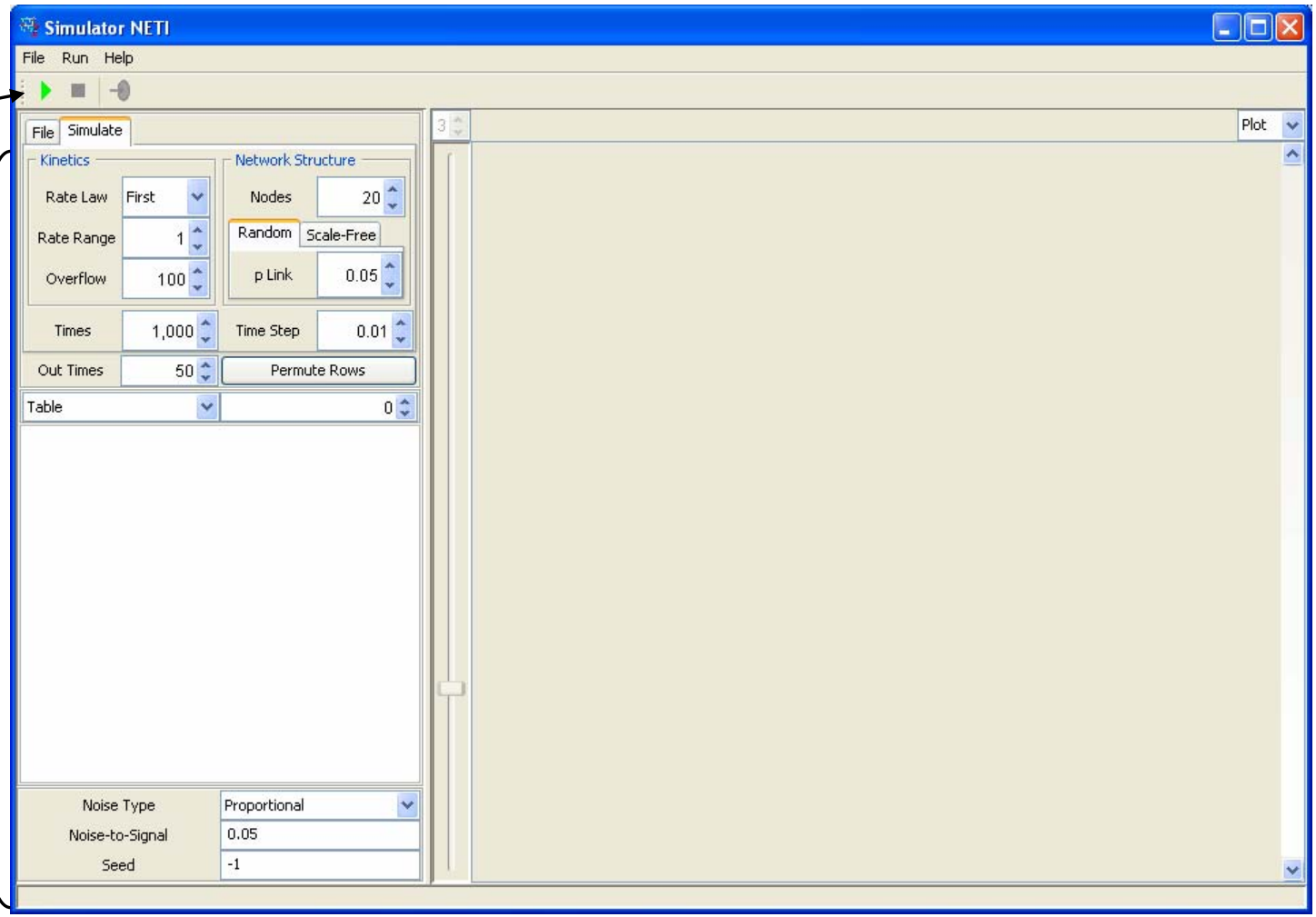
To open Network Simulator select the Menu Item "Run|Simulator".



Network Simulator Window

To start simulations press the “Run Simulations” button from the Toolbar or select the Menu Item “File|Run Simulations” (F5).

To simulate data the following parameters should be defined.

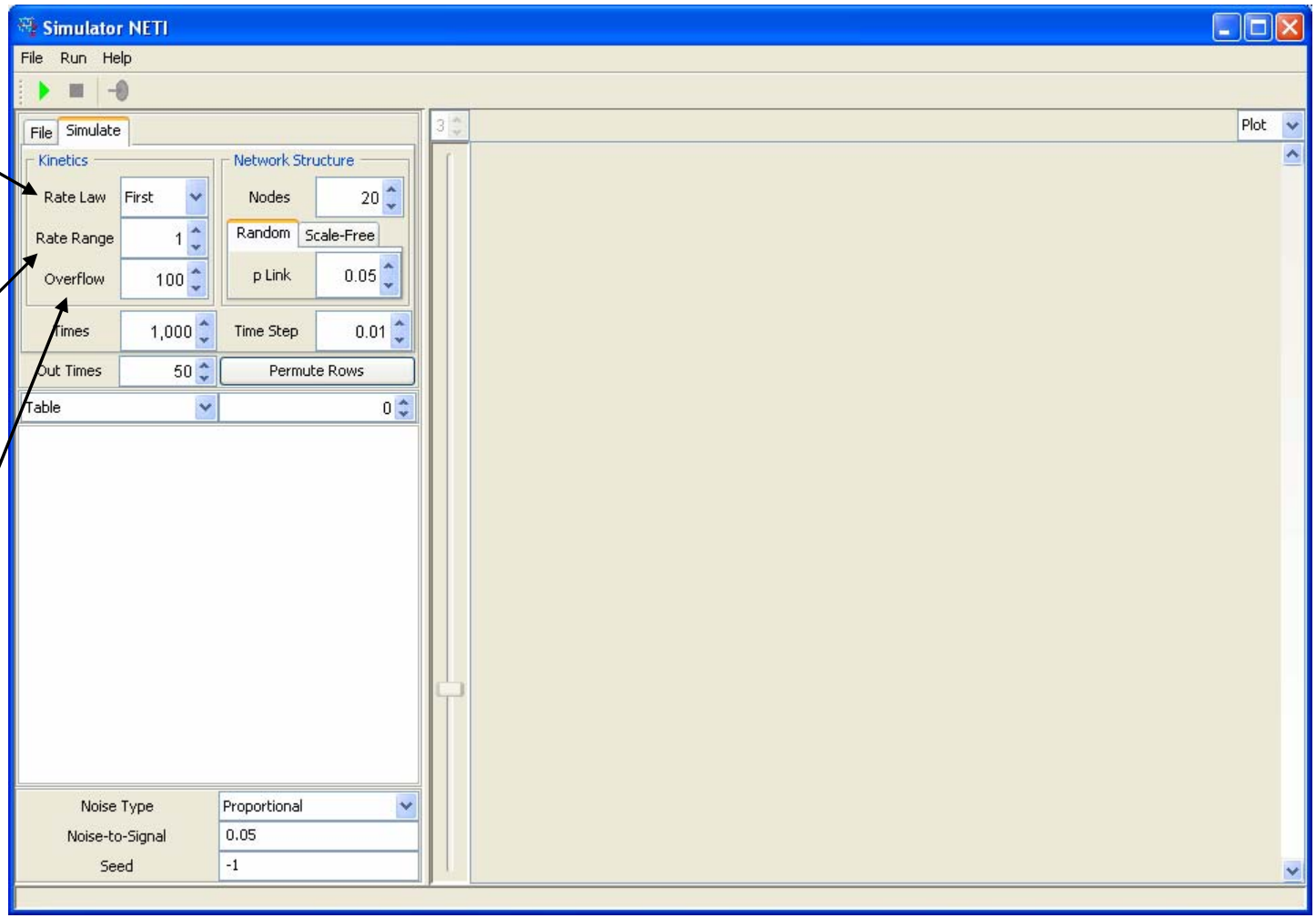


Artificial Networks (I)

Simulation model is defined by a set of ordinary differential equations with either *first*- or *second*-order kinetic *rate laws*.

The rates of kinetic equations are randomly selected from the interval: [-*Rate Range*; +*Rate Range*].

Generated time series is rejected, if it exceeds *Overflow*; procedure tries to find the structure and kinetic parameters without the overflow.



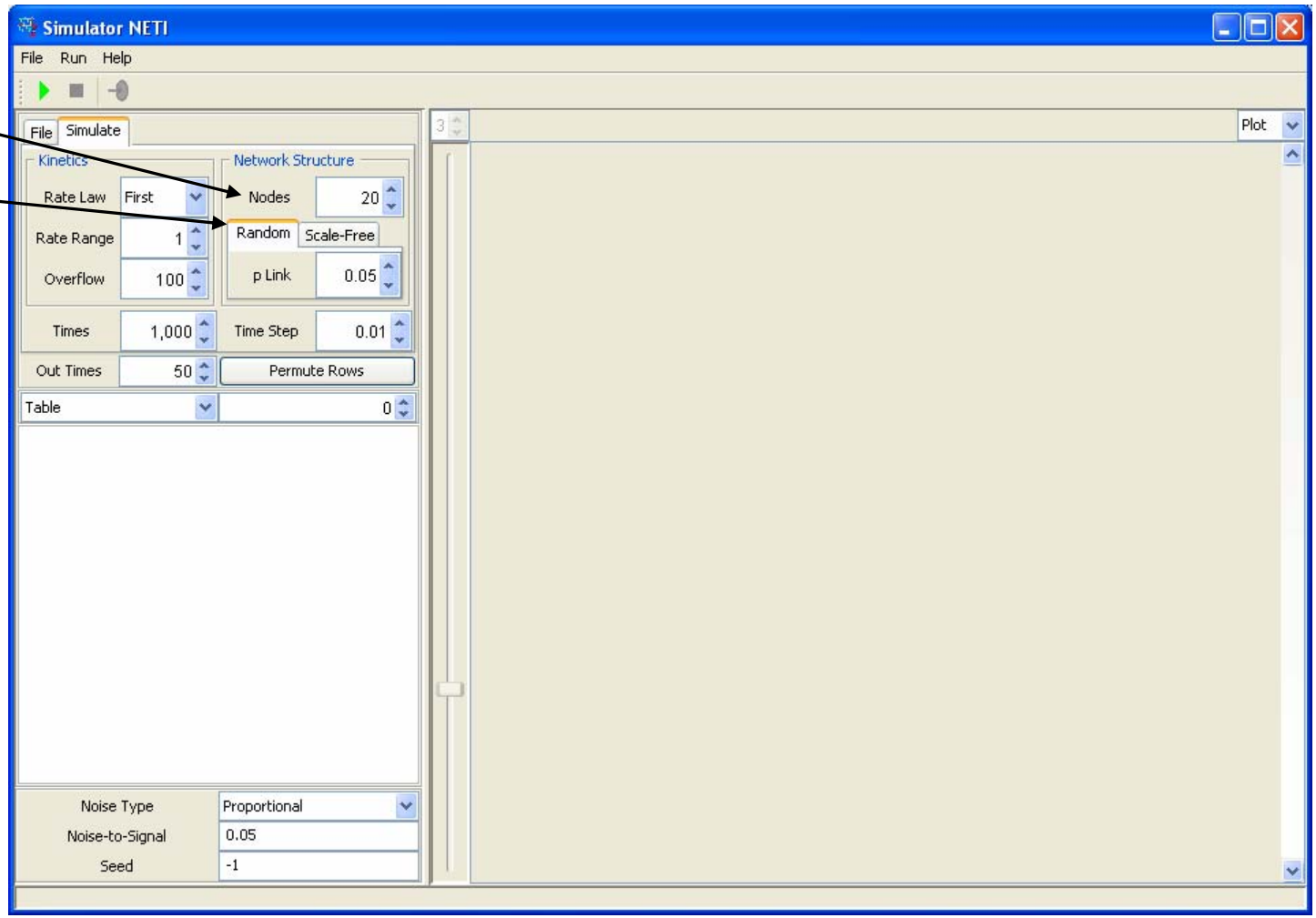
Artificial Networks (II)

See the paper for more details.

Number of Nodes.

Network Topology:
Random
Scale-Free

Random topology: any two nodes are connected with the probability p independently of the other connections.
Scale-free topology: the number of links at each node is approximated by a power-law distribution p(k) ~ k^{γ}.



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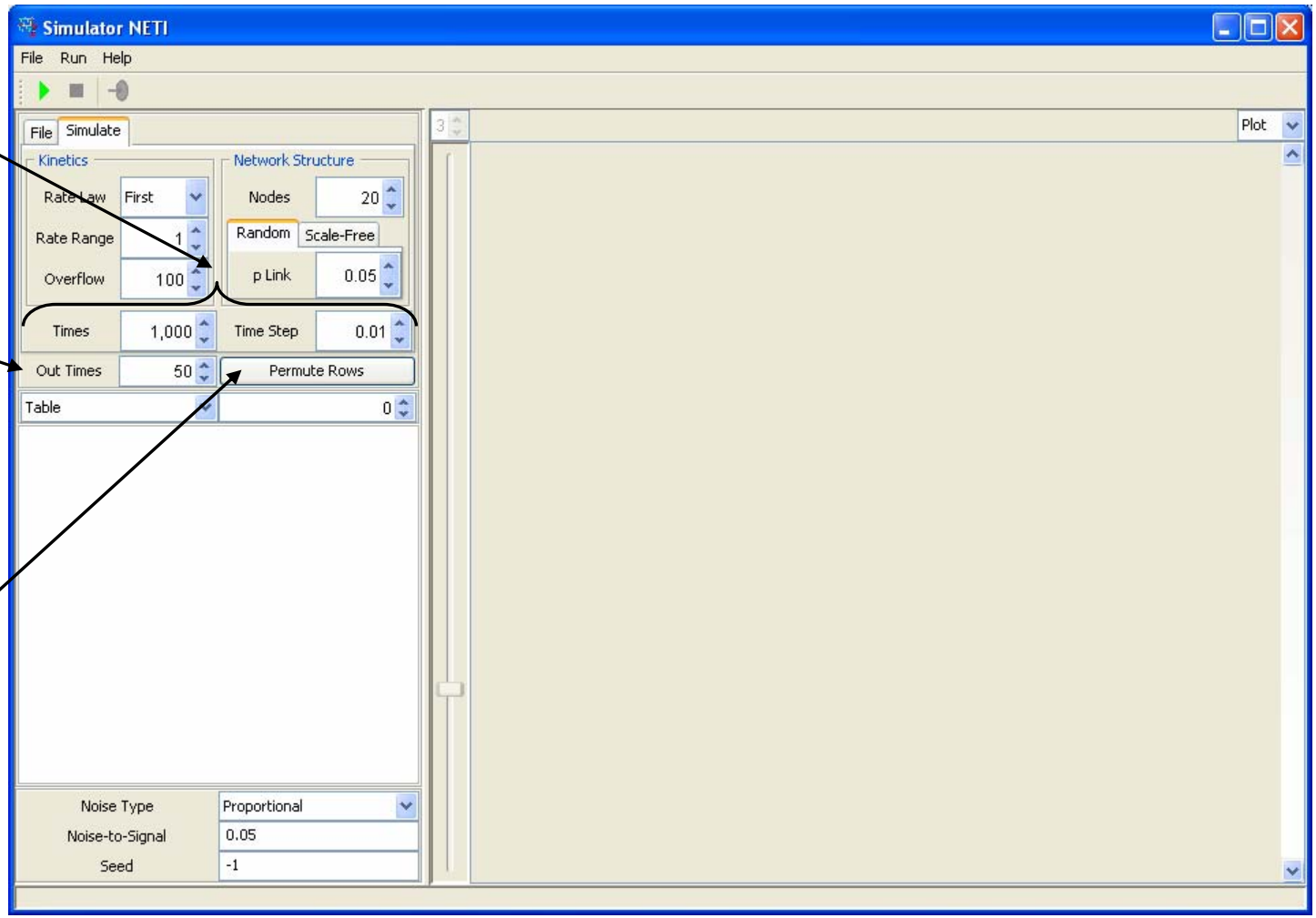
Artificial Networks (III)

Number of Time Steps (*Times*) and *Time Step* to generate idealistic time series.

Out Times defines sampling frequency.
In this example, the original 1000-point time series are converted into 20 intervals of 50 points. At each interval the output time point is randomly selected.

Generation of the permuted data, i.e. when node labels are randomly assigned to generated time series.

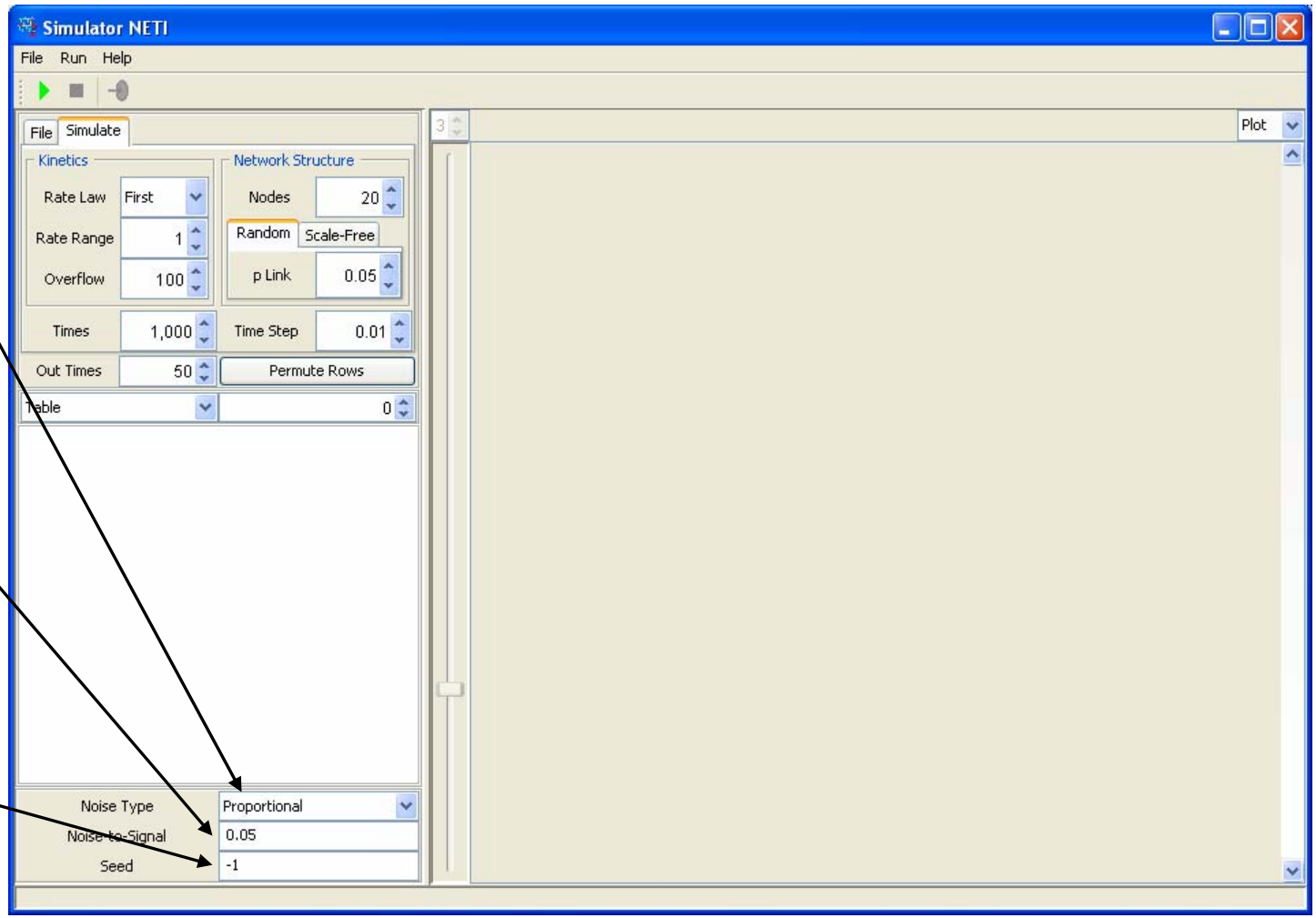


Additive Statistical Noise

Model for the standard deviation of the additive noise. It can be constant, proportional to signal, or proportional to the square root of signal.

Noise-to-signal level for the additive statistical noise. This noise is finally added to each data point.

Seed for random number generator (selection –1 as a seed will initiate the random generator with automatically (or randomly) chosen seed).

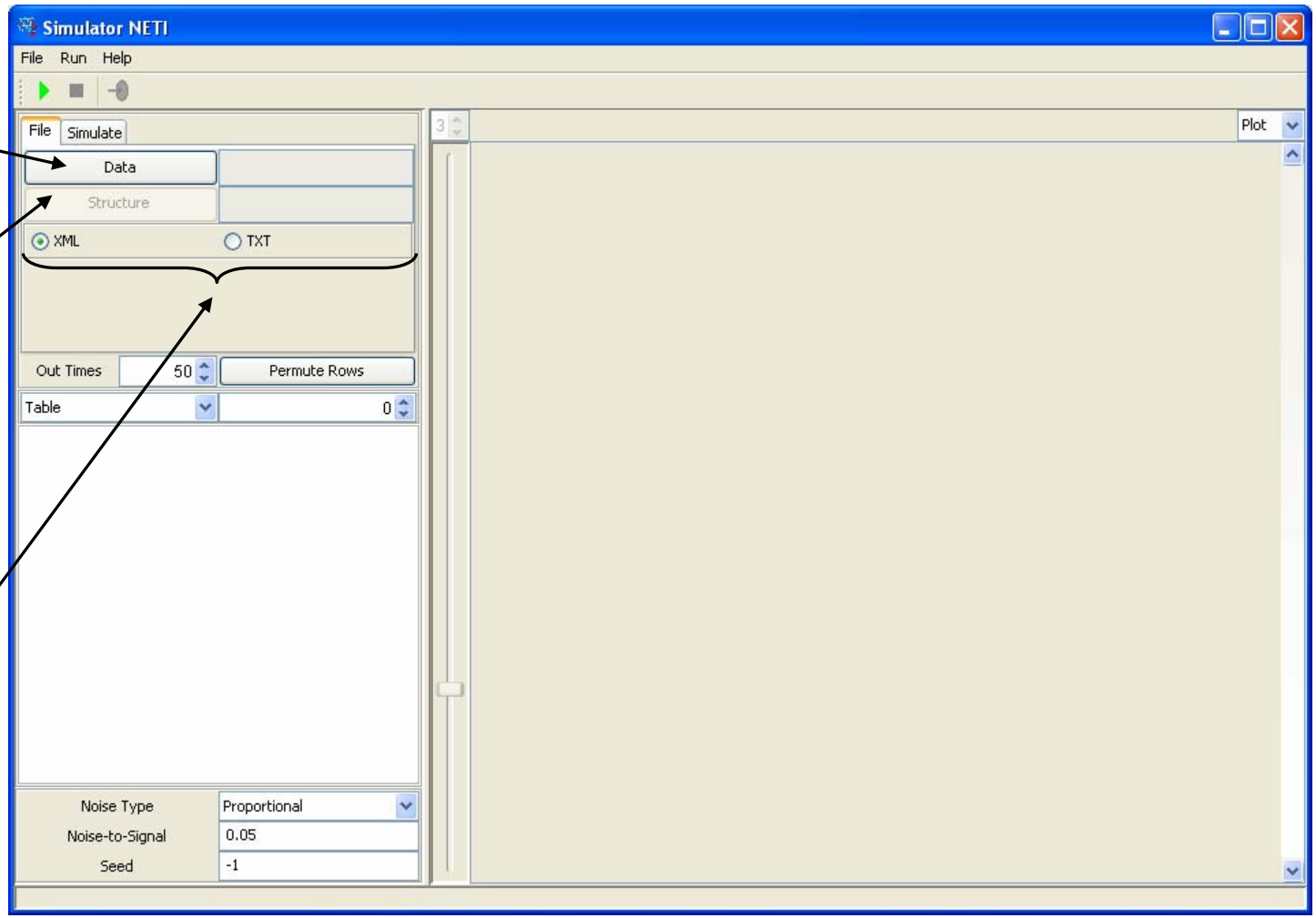


SBML Modules (I)

Simulator can import some intermediate data, typically time series generated by SBML modules.

The structure of the network can also be imported. It allows to compare the structure used in data generation with the structures obtained by the inference algorithm.

The structure can be defined by the *xml* or *txt* files.

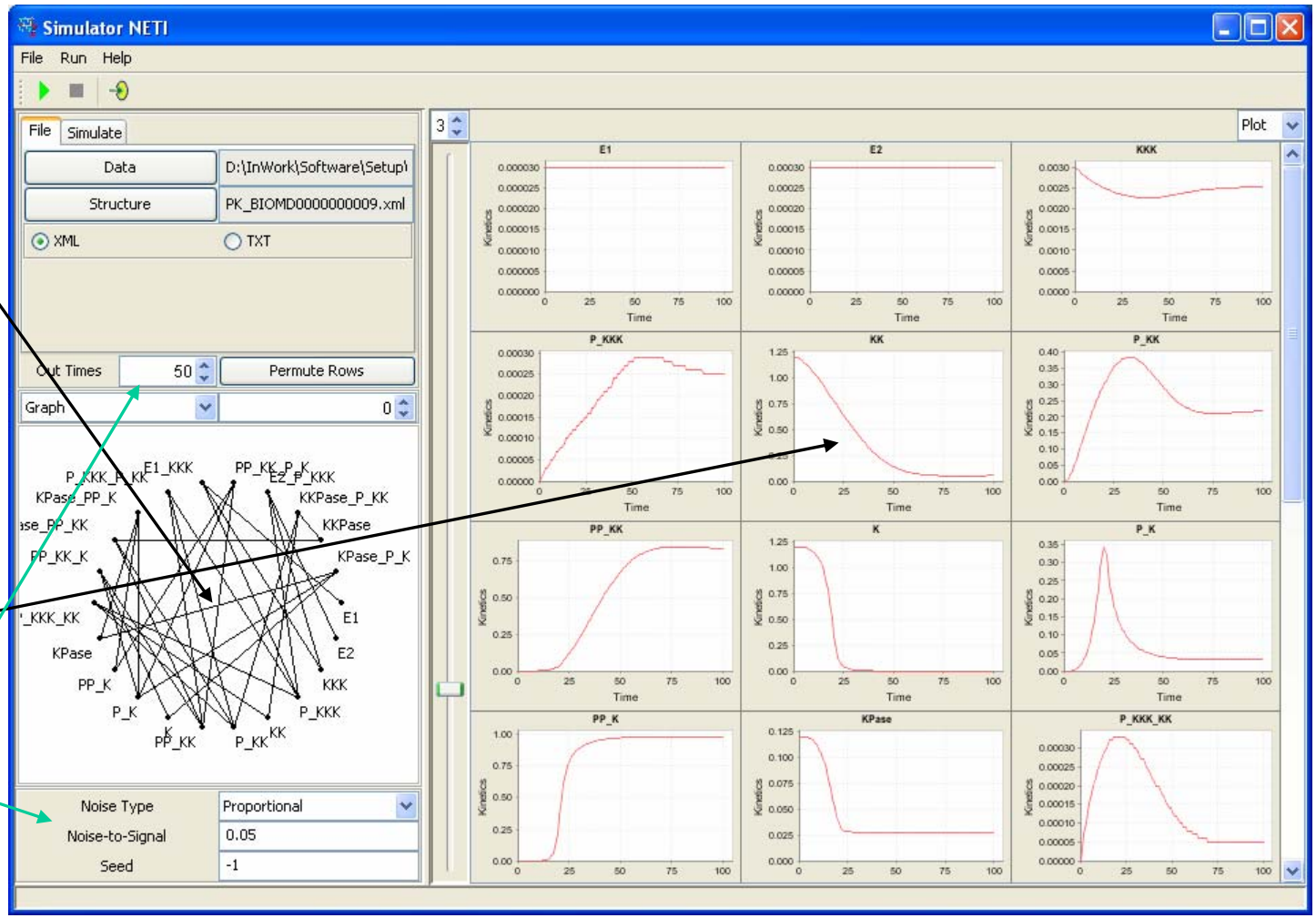


SBML Modules (II)

Imported model (MAPK).

Idealistic time series (generated in JDesigner).

These can be further distorted by non-homogeneous time sampling and adding statistical noise.



Export Data

To send the generated data in the Processing Window, use the “Send Data” button from the Toolbar or the Menu Item “File|Send Data” (Alt+→).

To save the generated data in the text file use the Menu Item “File|Save Data” (Ctrl+Shift+O).

To save the generated structure in the text file use the Menu Item “File|Save Data” (Ctrl+Shift+U).