Uni Stuttgart – VISUS

Tutorial: iVUN 1.1.1

iVUN – interactive Visualization of Uncertain biochemical reaction Networks

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1 Introduction

In this manual the functionality of *iVUN* (interactive Visualization of Uncertain biochemical reaction Networks) is outlined. *iVUN* was designed to investigate and analyze system models of biochemical reaction networks as well as the attributes which relate to the systems behavior and experimental observations. This includes the outputs (measured quantities) and based on that: samples of plausible[1] parameters (reaction rate coefficients). Furthermore, the dynamic[2] samples of fluxes and states (also referred to as concentrations) can be investigated. To compare different experiments for a system model, *iVUN* allows you to import several sets of outputs, fluxes and states, whereas the parameters are expected to be the same for all experiments. A comprehensive description of the application background can be found in the publications [1,2]. *iVUN* is implemented in the JavaTM programming language and is therefore distributed as '.jar' file that can be used on any platform that has the java virtual machine installed (version 1.6 or above). This application may be run on the command line (`java -jar iVUN.jar`) or by double left click on the file[3], depending on the operating system.

2 Data Import

All data import options are listed under the menu-option `File`→`Open`, where, at first, only the option for the import of a system model is enabled. All other options will become enabled as soon as a model has been imported.

2.1 SBML Model of Biochemical Reaction Network

Models of biochemical reaction networks can be loaded from 'xml' files following the specifications of SBML. Models are imported using the library JSBML. To open a model, use the menu-option `File`→`Open`→`Network(SBML)` and select an '*.xml' file. Once a model was imported, you can investigate your SBML file using a tree view (see Figure 1), which can be opened by clicking the  button in the tool bar. The tree view can be used at any time to investigate function or unit definitions, the kinetic laws of the reactions, and the like. *iVUN* supports the import of output, state, and flux samples for several experiments to compare the outcomes of several experimental conditions. These samples can be imported individually (see Sections 2.4 to 2.6). For each of the attributes[4], the MCMC samples will be imported in the context of currently selected experiment number. By default, this is experiment number 1; this is selected in the combo box, in the main panel (see Figures 2 and 3). To import samples for additional experiments, you need to add further experiments to the check box first by clicking

[1] parameters are likely when the model fits the data well.
[2] i.e., time dependent
[3] For large data sets, the RAM assigned to java may need to be increased to allow for best full heap rendering of all features. If running on the command line begin by `java -jar -Xmx1024m iVUN*.jar` or some other value `-Xmx_m`.
[4] output, state, flux

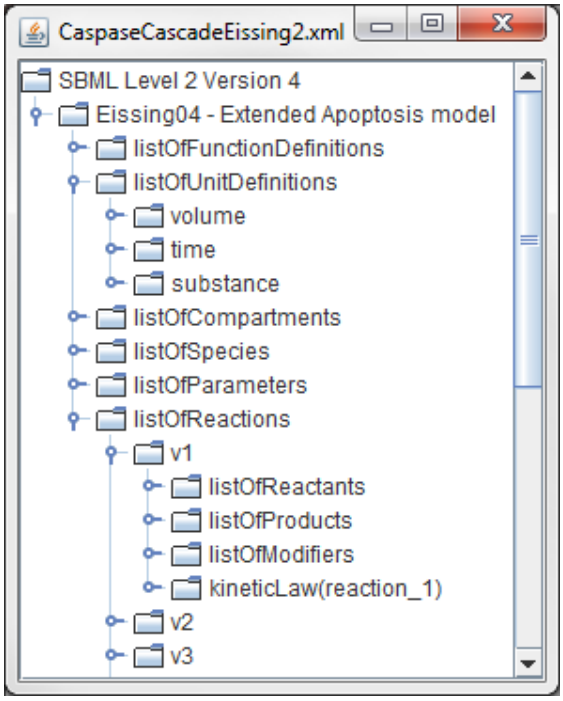


Figure 1: Tree view for navigation through SBML structure.

the ✚ button and select the respective experiment you want to import data for. Data that was imported for a selected experiment can be deleted by clicking the ▬ button. An overview about all imports can be obtained from a table that can be opened by clicking the 🗎 button. Before the first import of output, state, or flux samples, you will be asked to enter a lower and upper percentile (p_{low}, p_{high}), which will be used later as thresholds for the color mapping (see Section 3.4) and for the line plots (see Section 3.6.4). A lower percentile (> 0) and an upper percentile (< 100) can be set to cut off extremely small as well as extremely high values, which we do not want to differentiate within the color mapping. The chosen percentiles will be stored and used for all dynamic attributes you might import in the next steps. They are used to compute a lower and upper threshold for all outputs, fluxes, and states, unless you restart *iVUN*. If you don't want to perform a thresholding and use the full value range for color mapping, simply press the cancel button.

2.2 Graph-Layout

iVUN allows users to load layouts that have been generated during earlier analysis of the same model using *iVUN*. Hence, the layout-files do not follow any commonly used convention and are constrained to *iVUN*. You can import a layout by selecting a layout-file '*.layout' using the menu-option `File`→`Open`→`Layout`. For further details about the creation of layouts see Section 3.2.

2.3 Parameters

Parameter samples can be imported from a '*.txt' or '*.csv' file containing comma-separated values. You can select a file for parameter import using the menu-option `File→Open→Parameter Samples`. The first row of the file should contain the parameter ids, which should be identical to those contained in the list of parameters in the SBML-file. However, these parameter ids do not have to be in the same order as in the SBML file, nor do they have to be complete. Only the samples of those parameters ids that match entries in the SBML list of parameters will be imported. The following lines should contain the sample members for the listed parameters. An example for 10 parameters and a sample of size $n_S = 10000$:

```
p1,p2,p3,p4,...,p10
3.973e-01,9.449e-03,5.325e-04,3.903e-01,...,3.598e+01
4.193e-01,1.052e-03,3.791e-04,3.969e-01,...,3.868e+01
...
4.681e-01,7.333e-04,4.269e-03,4.507e-01,...,3.991e+01
```

You will be asked to decide, whether you want to post-process the samples by applying the decadic logarithm to each value. If your data is already in the scale you want, press `No`.

2.4 Output Samples

iVUN supports the import and investigation of the experimentally measured quantities; in the model these are referred to as outputs. The outputs model the process of data acquisition; the data is supposed to have been used for parameter estimation via MCMC. You can import data and output samples using the menu-option `File→Open→Outputs`. In doing so, the outputs will be imported for the currently selected experiment number (see description in Section 2.1). Several files are required for the import of outputs: first you have to select a '*.txt' or '*.csv' file that contains the allocation of outputs and species, second you have to select an even number of '*.txt' or '*.csv' files (two for each output) containing the measured data and simulated output-samples of the respective output index (using the options for multiple selections). All files should contain comma-separated values. The first file contains the species (at least one per output) an output is associated with, where each such allocation of output and species is defined in a separate line starting with the output-name, followed by the unit of measurement and at least one species_id, such as:

```
output-name1,unit1,species_1,species_3
output-name2,unit2,species_2
output-name3,unit3,species_5,species_1
...
```

There is no naming-convention for the first file, the respective two files for an output called `output-name` should be named like 'output-name_meas[ured].*' and 'output-

name_sim[ulated].*' respectively. The output-name contains no reference to the experiment, in consequence you have to store output files in different folders, one such folder per experiment. Each measurement file must contain the time points of the time series within the first row, followed by several lines, each including the measured values for the particular time points. Here is an example of an output for 8 time points:

```
0,1.0,2.0,3.0,4.0,6.0,8.0,10.0
12.71,5.933,4.699,5.037,3.942,3.973,6.139,3.481
12.71,5.933,4.699,5.037,3.942,3.973,6.139,3.481
12.35,6.534,4.258,5.854,5.739,4.007,5.631,4.732
12.76,4.728,4.944,3.807,3.324,5.767,7.769,4.346
```

The files containing the simulated outputs are expected to be similar, but typically have many more time points and sample-members[5]:

```
0,0.5,1.0,1.5,2.0,...,10
10.0,8.8408,7.8179,6.9281,6.2033,...,  4.5836
10.0,8.8046,7.7543,6.8445,6.1046,...,  4.5473
...
10.0,8.6814,7.5477,6.5853,5.8190,...,  4.5551
```

The outputs will be visualized by convex hulls surrounding the species they are allocated to. The time-course of the simulated outputs and data points can be visualized in a line plot.

2.5 Flux Samples

Flux samples can be imported from '*.txt' or '*.csv' files containing comma-separated values. You can select the files for import using the menu-option `File`→`Open`→`Flux Samples`. The fluxes will be imported for the currently selected experiment number (see description in Section 2.1). In contrast to parameter samples, fluxes are dynamic and one file for each reaction (and hence flux) should be selected, using the options for multiple selections. Similar to the '_sim.*' files for outputs, each file should contain the time points of the time series within the first line, followed by several lines with the respective time series of the flux, one line per parameter sample point. A file for a dynamic flux sample of size $n_S = 10000$ and 21 time points [6], could look like this:

```
0,0.5,1.0,1.5,2.0,...,10
3.9727,3.5122,3.1058,2.7523,2.4644,...,1.8209
4.1925,3.6914,3.2510,2.8696,2.5594,...,1.9065
...
4.6806,4.0634,3.5328,3.0823,2.7237,...,2.1321
```

[5] the ellipsis `[...]` may not occur in the real file. no special symbol interpretation or interpolation of a series is performed

[6] with intervals of 0.5 min

As for parameter samples, you are not expected to provide a dynamic sample for each reaction; you may also select files for a subgroup. To assign files to reactions, the files are expected to be named consistently based on the reaction ids ('reaction_id.*') of the SBML file.

2.6 State Samples

For the import of state samples, the file names have to match the species ids ('species_id.*'), contained in the list of species (SBML file). You can select the files the import of state samples using the menu-option `File`→`Open`→`State Samples`. Otherwise, the file structure is similar to the flux sample files'.

3 Running *iVUN*

The main interface of *iVUN* consists of the menu, the tool bar, the graph view, the graph context view, the menu panel, and the information panel (see Figure 2). The graph view is embedded into a zoom-and-scroll panel and contains the node-link diagram representing the graph model of the biochemical reaction network. Outputs are typically individual state variables[7] or sums of those and can therefore be assigned to one or more nodes in the graph. The outputs are visualized using convex hulls that surround the respective nodes. The menu panel holds several combo boxes, check boxes etc. to adjust the displayed information. Some of these items will only be enabled when the respective meta-data was imported. The selected experiment number influences several visual attributes as well as some of the views, which will be explained within the next subsections. Remember, that an overview of all imported data can be opened by clicking the button in the tool bar. The information panel holds all available meta-data for the set of selected vertices and edges, including e.g. the kinetic law of a reaction, the compartment of a species and more.

3.1 Mouse Mode

The graph view allows to perform zooming using the scroll wheel and panning using the scroll bars or by dragging within the small graph context view in the upper right of the interface (see (2) in Figure 2). Elements can be selected by clicking on them or using the rectangular selection (clicking and dragging). The selection of multiple elements is also possible by holding the 'Ctrl' key on the keyboard while clicking on elements. All selected elements, vertices and edges that represent reactions, will be highlighted. Selected elements can be moved by clicking and dragging. The selection of species and reactions and hence parameters, fluxes and states can be discarded by clicking in the white area next to the graph.

[7] concentrations of molecular species

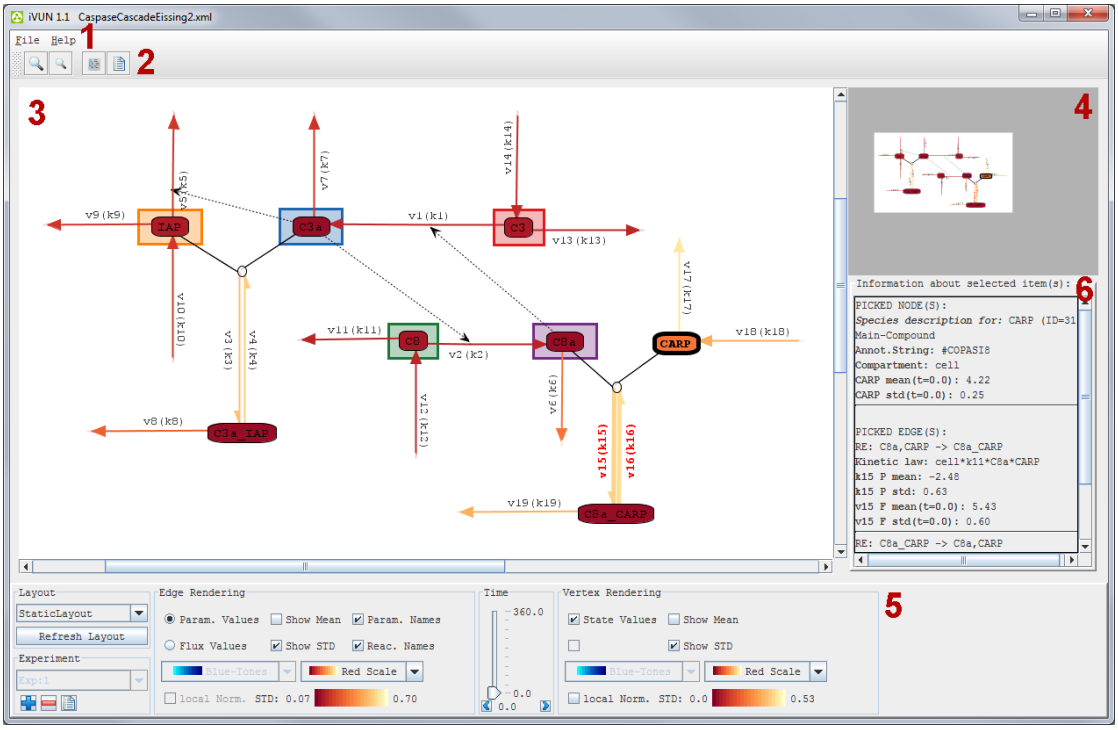


Figure 2: Main interface of *iVUN*: (1) menu; (2) tool bar; (3) graph view; (4) graph context view; (5) menu panel; (6) information panel. The standard deviation of flux (state) samples at time point is mapped to the color of edges (vertices) using the red color scale. The information panel holds all available information for the selected species and reactions r_{15} and r_{16}.

3.2 Layout

If you have imported an SBML file, by default the graph layout will be computed based on a layout algorithm called *BioNetLayout*, we developed this style to adhere to conventions for biological networks. You may change the layout using the combo-box in the lower left of the interface to switch between the available layout-algorithms. Alongside common and general layout algorithms, we provide a second, layout algorithm for biological networks called `CompartmentLayout`, which also evaluates the different compartments the species are contained in[8]. If you are not satisfied with any of the provided layouts, you may rearrange vertices and save the current layout for later use (see Section 2.2): `File`→`Save`→`Layout`. This way you can reload this layout any time you want to continue the analysis of this particular system model.

[8] this is specified in the SBML file

3.3 Labels

Nodes of the node-link diagram are labeled with name of the species, if it was specified in the SBML file, otherwise the id. The edge labels are composed of the reaction name and the list of parameters, which are surrounded by parentheses. Therefore, the label for the following reaction would be r_{17}(CISRNAEqc,CISRNATurn,npSTAT5), taken from the model file (excerpt):

```
...
<reaction id="17" reversible="false">
 <listOfProducts>
  <speciesReference species="CISnRNA1" stoichiometry="1"/>
 </listOfProducts>
 <listOfModifiers>
  <modifierSpeciesReference species="npSTAT5"/>
 </listOfModifiers>
 <kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
  <divide/>
   <apply>
    <times/>
     <ci> CISRNAEqc </ci>
     <ci> CISRNATurn </ci>
     <ci> npSTAT5 </ci>
   </apply>
   <ci> init_STAT5 </ci>
   </apply>
  </math>
 </kineticLaw>
</reaction>
...
```

The order of the parameters in the list depends on their order in the kinetic law (`<kineticLaw/>`). Both parts of the edge label can be hidden on demand by deselecting the respective check-boxes in the menu panel (see (3) in Figure 3).

3.4 Color Maps

As soon as either the parameter samples or flux samples have been imported, edges will be colored based on their statistical properties. The coloring of vertices is turned on as soon as state samples have been imported. If several experiments have been imported, edges and vertices will be colored based on the statistical attributes of fluxes and states of the currently selected experiment (using the combo box in the menu panel: (2) in Figure 3). Elements, for which no values are available, will be in the default colors

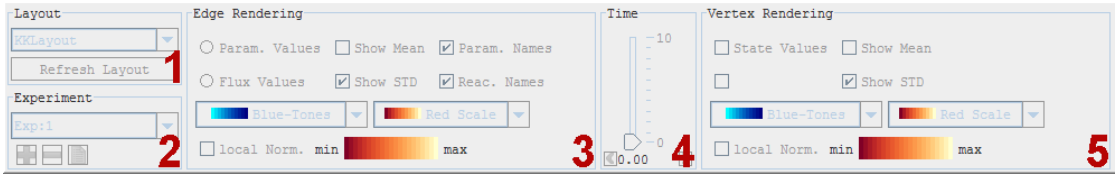


Figure 3: Menu panel including menu options to: change the layout of the graph (1); add or delete experiments and switch between experiments (2); adapt the color coding of edges (3) and vertices (5); animate the dynamic graph (4). The radio-buttons in the rendering panel for edges (3) can be used to switch between color coding of parameters and fluxes, as both are associated with the edges. Furthermore, rendering panel (3) includes two check-boxes to adapt the edge labels. The check-boxes in both rendering panels (3) and (4) can be used to adjust whether mean and/or standard deviation should be mapped to color.

black and white for edges and vertices respectively. The statistical variables *mean* and *standard deviation* can be mapped to colors either individually or in combination (see Figure 4).

The mean of an attribute sample can be mapped to a color using continuous, multi-hue color maps[9] (see Figure 4 left). First of all a thresholding of mean values of fluxes and states is applied, based on the aforementioned lower and upper threshold; they have been computed based on the respective percentiles you entered. Then the mean is mapped to a color. The sample-mean values of fluxes $\bar{v}_j$ (states: $\bar{x}_i$) are normalized based lower and upper percentiles. The normalization can be performed either on the global percentile of all fluxes $[V_{p_{\text{low}}} : V_{p_{\text{high}}}] \rightarrow [0:1]$ (all states $[X_{p_{\text{low}}} : X_{p_{\text{high}}}] \rightarrow [0:1]$) or the local percentiles of individual fluxes $[v_{j_{p_{\text{low}}}} : v_{j_{p_{\text{high}}}}] \rightarrow [0:1]$ (individual states $[x_{i_{p_{\text{low}}}} : x_{i_{p_{\text{high}}}}] \rightarrow [0:1]$), where j (i) runs over all reactions (species). You can change between the local and global color mapping using the respective check-box `local Norm.` in the menu panel ((see (3) and (5) in Figure 3)). In contrast to flux and state samples, the mean values of parameter samples are normalized based on the minimal and maximal occurring mean value $[\min_k(\bar{\theta}_k) : \max_k(\bar{\theta}_k)] \rightarrow [0:1]$, where k runs over all parameters selected for analysis.

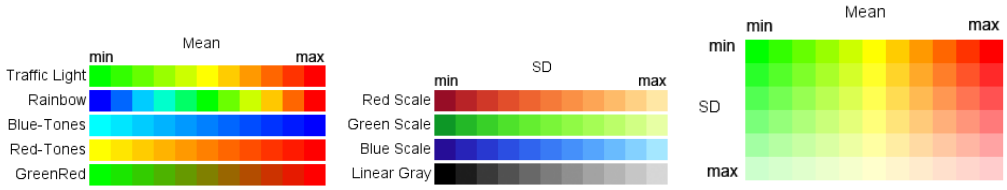


Figure 4: Mapping of statistical values mean and standard deviation to color either individually (left and middle) or in combination (right).

[9] they map the mean values linearly to a range of hues with monotonously changing brightness

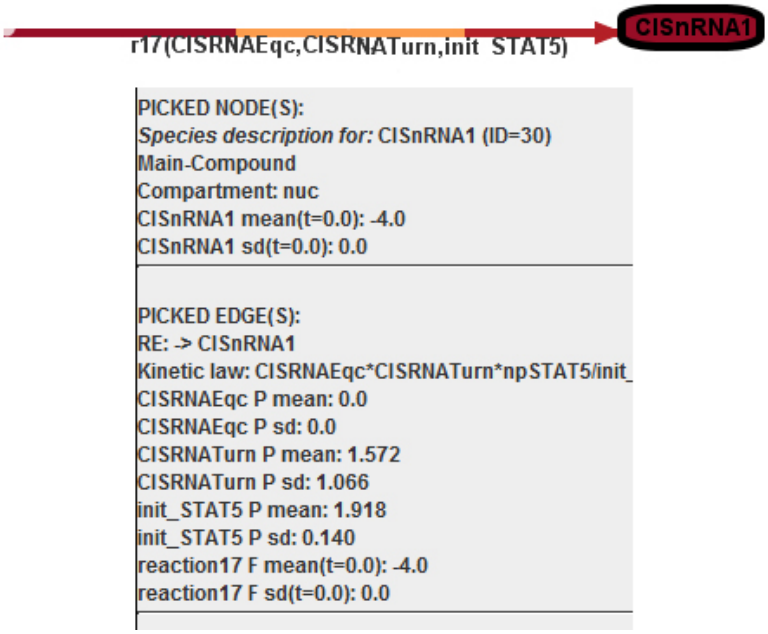


Figure 5: Above: color mapping of the uncertainty (standard deviation) of all three parameter of the (see description of the reaction in 3.3). Below: information within the information panel for the selected edge and species.

The uncertainty of an attribute is mapped to the saturation of the color. If only uncertainty is visualized, the sample's standard deviation is mapped to a color using a univariate single-hue color , i.e., the standard deviation determines the saturation of the color (see Figure 4 middle).

Although it is hard to differentiate hue and saturation simultaneously, you may use a bivariate multi-hue color map to visualize the sample mean and the standard deviation simultaneously (see example in Figure 4 right). To map solely the mean (standard deviation) to a color, select solely the check-box `Show Mean` (`Show SD`). If both check-boxes are selected, the combined color mapping will be applied. There are different color-maps available for mean values and standard deviations that can be selected using combo-boxes (see (3) and (5) in Figure 3). A precise table view of the color mapping for edges and vertices can be opened using the first two menu-options within the drop-down menu. These table views will adapt, as soon as you make any changes to the color mapping.

If the kinetic law of a reaction contains more than one parameter and the color mapping of parameters in enabled, the edge is split into the respective number of segments. Each segment is colored with respect to one parameter: starting with the first parameter of the kinetic law at the starting point of the edge and ending with the last parameter of the kinetic law at the arrowhead (see Figure 5). Detailed information about a selected reaction including the kinetic law, mean and standard deviation of

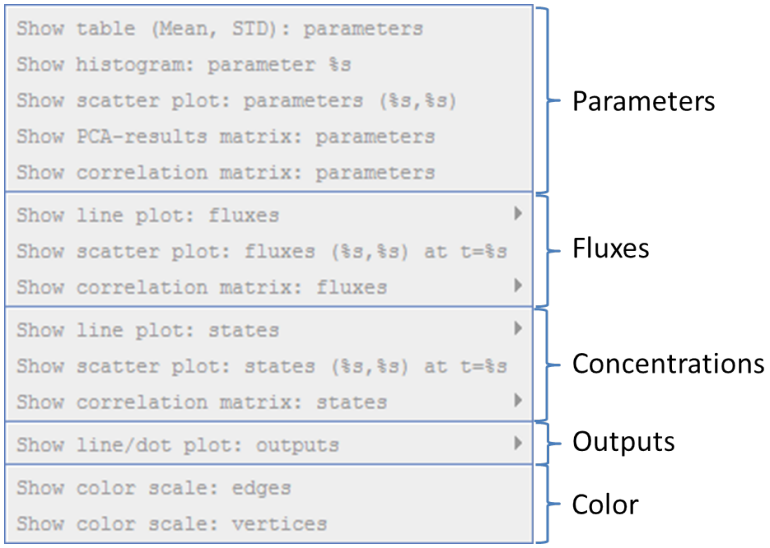


Figure 6: Drop-down menu

each parameter sample as well as the flux sample (for the currently selected point in time), can be obtained from the information panel (see (6) in Figure 2). The order of parameters again corresponds to the order in the kinetic law. Available information of a selected species comprises the compartment as well as mean and standard deviation of the state for the currently selected point in time.

3.5 Animation

As fluxes and states are dynamic, only the statistics of one particular time point can be mapped to the color of the respective edge or vertex. You can navigate through time either rapidly with the help of a slider or stepwise using the forward or backward button (see (4) in Figure 3). It is also possible to animate the graph view and hence color mapping by keeping one of the buttons pressed. During the animation, drastic changes of the mean and/or standard deviation of the samples are automatically detected and signaled: respective edges (vertices) are briefly highlighted within the graph. If several experiments have been imported, the time interval of the slider will adapt as soon as you switch between experiments using the combo box.

3.6 Linked Views

There are several linked views available for a cross reference analysis of the data, simulation results and calculated statistical properties. These can be opened using the drop-down menu (see Figure 6). The drop-down menu can be opened by selecting at least one edge or vertex of the graph and right-clicking somewhere within the graph view. The menu is structured based on the different attribute types, i.e., parameters, fluxes, states, and outputs. Therefore, this menu will be available only if the respective

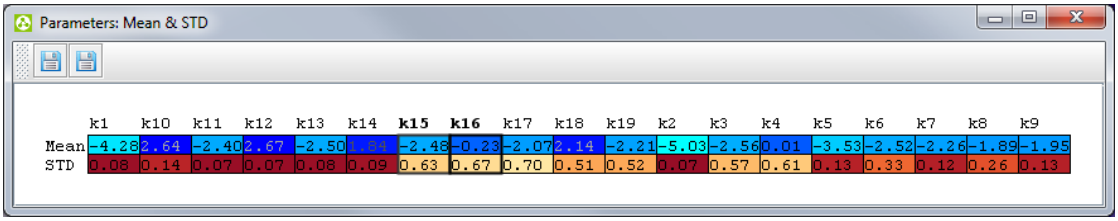


Figure 7: Statistics table including the mean and standard deviation for all imported parameters. Cells are colored with respect to the color maps for edges selected in the main interface. The columns of the selected parameters k_{15} and k_{16} are highlighted.

data-block was imported. Furthermore, some options will only be available if a certain number (usually two) of vertices or edges have been selected. Within the linked views: statistics table (3.6.1), correlation matrix (3.6.3), and the line plot (3.6.5), brushing and linking is used to show the correspondence of elements in different views. If the selection within one view changes by brushing, the respective elements within all views are first highlighted by short flashing and stay highlighted. Hence, we recommend, that you arrange the views next to each other on the screen.

For some of the available views (for outputs, fluxes, and states), the content will adapt as soon as you switch between experiments. These include the scatter plots and the line plots (first line plot option, see Section 3.6.5).

3.6.1 Statistics table

As soon as you have imported parameter samples of your model, the option `Show table with Mean...` will be enabled. Clicking on that option will open a table of mean values and standard deviations for the static[10] parameter samples (see Figure 7). This table is linked to the graph view in a way that all reactions associated with the selected parameter are highlighted. The selection of multiple parameters is also possible by holding the 'Ctrl' key on the keyboard while clicking on the respective columns of the table. Also: if a reaction is selected in the graph view, all parameters present in the kinetic law are highlighted in the table. Furthermore, selecting parameters in the statistics table also allows you to investigate the respective samples further. If of one or more parameters have been selected, a drop-down menu can be opened by right click. This will contain the drop-down menu options `Show histogram...` (see Section 3.6.2) and `Show scatter plot...` (see Section 3.6.4). The selection of parameters can be discarded by clicking in the white area next to the graph (in the graph view) or next to the table (statistics table). The cells of the table are colored using the selected color maps for edges for mean values and standard deviations, respectively. The table can be exported as an 'html' or 'png' file using the buttons in the tool bar.

[10] time invariant

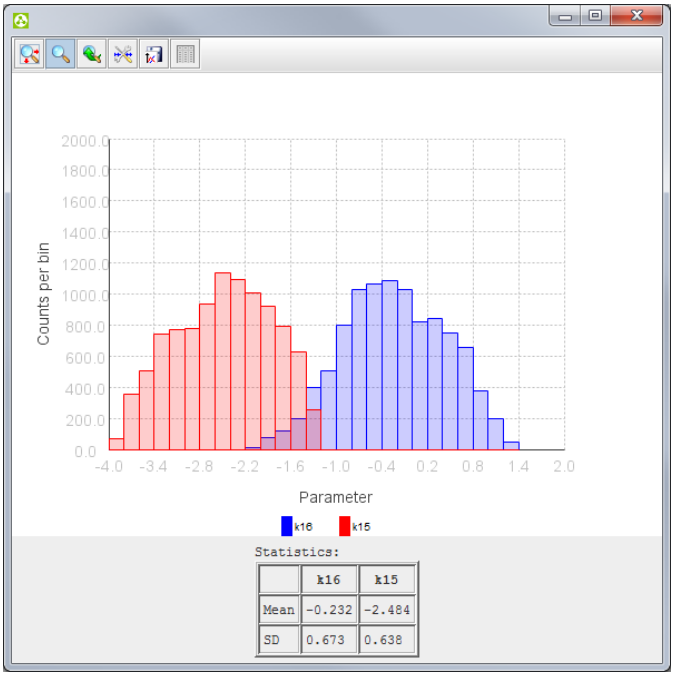


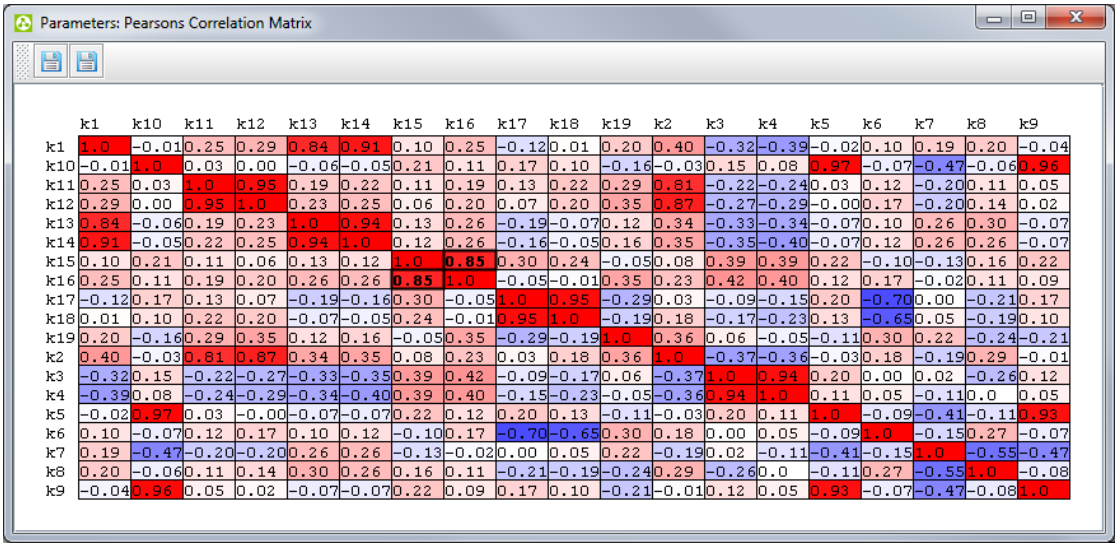
Figure 8: Histogram showing the distribution of values for the samples of the parameters k_{15} and k_{16} (for the selected two edges in the graph view).

3.6.2 Parameter histogram

Histograms for the set of selected edges and hence parameter samples can be opened for a comparison of individual parameter distributions using the menu option `Show histogram...` in the drop-down menu. Histograms can also be opened by selecting a cell within a correlation matrix (see Section 3.6.3) or by selecting a set of parameters in the statistics table (see Section 3.6.1) and by using the respective menu option in the drop-down menu of the matrices and the statistics table which can be opened by a right click. The histograms are computed with identical bin width and are thus comparable (see Figure 8).

3.6.3 Correlation matrix

There are two different matrix views available that can be used to investigate dependencies of different dimensions of the parameter samples or correlations between them: An `eigenvalue-ratio matrix` (menu option `Show PCS-results...`) and a correlation matrix (menu option `Show correlation...`). Where the former is based on *principal component analysis* (PCA), the correlation matrix includes Pearson's correlation coefficients for all pairwise combinations of parameter samples. For fluxes/states, the correlation matrix displays the pairwise Pearson's correlations between time courses of either mean values (submenu option `Time series: Mean`) or standard deviations (submenu option `Time series: SD`) instead of sample members or between flux/s-



	k1	k10	k11	k12	k13	k14	k15	k16	k17	k18	k19	k2	k3	k4	k5	k6	k7	k8	k9
k1	1.0	-0.01	0.25	0.29	0.84	0.91	0.10	0.25	-0.12	0.01	0.20	0.40	-0.32	-0.39	-0.02	0.10	0.19	0.20	-0.04
k10	-0.01	1.0	0.03	0.00	-0.06	-0.05	0.21	0.11	0.17	0.10	-0.16	-0.03	0.15	0.08	0.97	-0.07	-0.47	-0.06	0.96
k11	0.25	0.03	1.0	0.95	0.19	0.22	0.11	0.19	0.13	0.22	0.29	0.81	-0.22	-0.24	0.03	0.12	-0.20	0.11	0.05
k12	0.29	0.00	0.95	1.0	0.23	0.25	0.06	0.20	0.07	0.20	0.35	0.87	-0.27	-0.29	-0.00	0.17	-0.20	0.14	0.02
k13	0.84	-0.06	0.19	0.23	1.0	0.94	0.13	0.26	-0.19	-0.07	0.12	0.34	-0.33	-0.34	-0.07	0.10	0.26	0.30	-0.07
k14	0.91	-0.05	0.22	0.25	0.94	1.0	0.12	0.26	-0.16	-0.05	0.16	0.35	-0.35	-0.40	-0.07	0.12	0.26	0.26	-0.07
k15	0.10	0.21	0.11	0.06	0.13	0.12	1.0	**0.85**	0.30	0.24	-0.05	0.08	0.39	0.39	0.22	-0.10	-0.13	0.16	0.22
k16	0.25	0.11	0.19	0.20	0.26	0.26	**0.85**	1.0	-0.05	-0.01	0.35	0.23	0.42	0.40	0.12	0.17	-0.02	0.11	0.09
k17	-0.12	0.17	0.13	0.07	-0.19	-0.16	0.30	-0.05	1.0	0.95	-0.29	0.03	-0.09	-0.15	0.20	-0.70	0.00	-0.21	0.17
k18	0.01	0.10	0.22	0.20	-0.07	-0.05	0.24	-0.01	0.95	1.0	-0.19	0.18	-0.17	-0.23	0.13	-0.65	0.05	-0.19	0.10
k19	0.20	-0.16	0.29	0.35	0.12	0.16	-0.05	0.35	-0.29	-0.19	1.0	0.36	0.06	-0.05	-0.11	0.30	0.22	-0.24	-0.21
k2	0.40	-0.03	0.81	0.87	0.34	0.35	0.08	0.23	0.03	0.18	0.36	1.0	-0.37	-0.36	-0.03	0.18	-0.19	0.29	-0.01
k3	-0.32	0.15	-0.22	-0.27	-0.33	-0.35	0.39	0.42	-0.09	-0.17	0.06	-0.37	1.0	0.94	0.20	0.00	0.02	-0.26	0.12
k4	-0.39	0.08	-0.24	-0.29	-0.34	-0.40	0.39	0.40	-0.15	-0.23	-0.05	-0.36	0.94	1.0	0.11	0.05	-0.11	0.0	0.05
k5	-0.02	0.97	0.03	-0.00	-0.07	-0.07	0.22	0.12	0.20	0.13	-0.11	-0.03	0.20	0.11	1.0	-0.09	-0.41	-0.11	0.93
k6	0.10	-0.07	0.12	0.17	0.10	0.12	-0.10	0.17	-0.70	-0.65	0.30	0.18	0.00	0.05	-0.09	1.0	-0.15	0.27	-0.07
k7	0.19	-0.47	-0.20	-0.20	0.26	0.26	-0.13	-0.02	0.00	0.05	0.22	-0.19	0.02	-0.11	-0.41	-0.15	1.0	-0.55	-0.47
k8	0.20	-0.06	0.11	0.14	0.30	0.26	0.16	0.11	-0.21	-0.19	-0.24	0.29	-0.26	0.0	-0.11	0.27	-0.55	1.0	-0.08
k9	-0.04	0.96	0.05	0.02	-0.07	-0.07	0.22	0.09	0.17	0.10	-0.21	-0.01	0.12	0.05	0.93	-0.07	-0.47	-0.08	1.0

Figure 9: Correlation matrix including all pairwise Pearson's correlation coefficients. The cell of the parameter pair (k_{15}, k_{16}) for the selected two edges in the graph view is highlighted (framed).

tate samples for the currently selected time point (submenu option `Sample for time point *`).

When selecting a cell within the matrix, the respective two elements within the graph are highlighted. If parameters occur in different kinetic laws (reactions) of the graph, more than two edges are highlighted. By selecting a set of parameters, fluxes, or states in the graph view, all pairwise combinations and hence respective cells within the matrix views are highlighted (see Figure 9). Furthermore, selecting pairs of samples in the matrix also allows you to investigate the respective samples further. If a cell has been selected, a drop-down menu can be opened by right click. This will contain the drop-down menu options `Show histogram...` (see Section 3.6.2) and `Show scatter plot...` (see Section 3.6.4). The matrix can be exported as image ('png') file or 'html' file using the left or right button in the tool bar.

3.6.4 Scatter plot of samples

While the matrices can be used to obtain an overview of occurring correlations within the system, scatter plots can be used to gain further insights into the kind of correlation and distribution of values in the sample. In addition: the correlation coefficients alone may be deceiving, e.g. for multi modal distributions. Scatter plots visualize two sample columns and are available only if exactly two attributes have been selected within the graph view. They can be opened using the menu option `Show scatter plot...` in the drop-down menu. Scatter plots can also be opened by selecting a cell within a correlation matrix or by selecting two parameters in the statistics table and by using the respective menu option in the drop-down menu of the matrices and the statistics

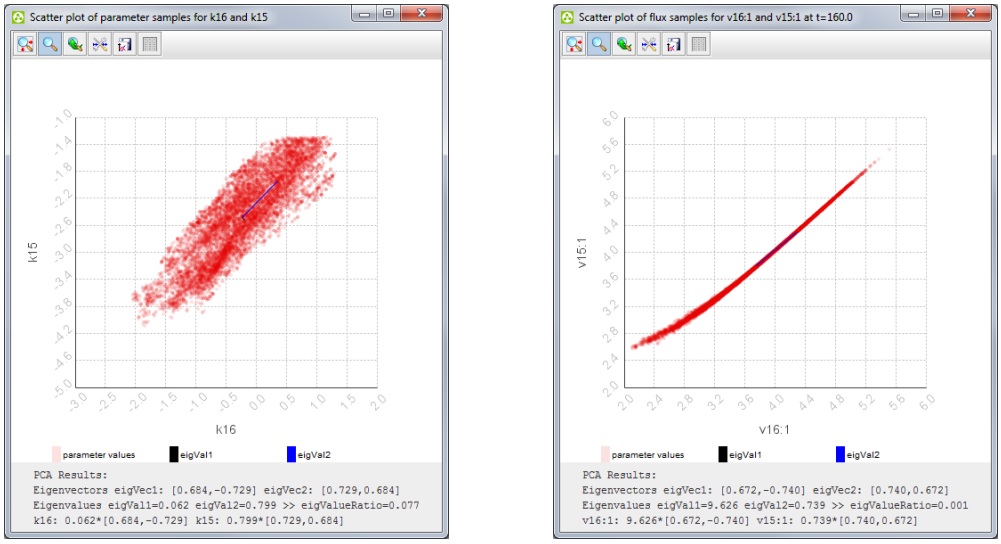


Figure 10: Left: Scatter plot of the parameter pair (k_{15}, k_{16}). Right: Scatter plot of the flux pair (v_{15}, v_{16}) for the currently selected time point $t = 160\,\text{min}$.

table which can be opened by a right click. For fluxes and states, only samples for the currently selected time point are visualized within the scatter plot. The scatter plot view also shows the results of the PCA, performed on the two samples, including the eigenvectors and eigenvalues (see Figure 10). The scaling of the x- and y-axis of the scatter plot can be adjusted using the scaling menu of the plot. This can be opened by clicking on the button. You can zoom into the point cloud using the scroll wheel and turn back to the original zoom level by pressing the button. The plot can be exported as 'png' file clicking on the button.

3.6.5 Time series line plot

To compare the time series of several fluxes, states, or outputs, line plots are available. Each line within the respective plot represents the time-dependent median of one output, one state or one flux. To visualize the uncertainties, each line is framed by a semitransparent area; the boundaries of this area are the time-dependent percentiles of the respective sample (by default the 5th-percentile, p_5, and the 95th-percentile, p_{95}) (see Figure 11 on the following page). The use of the median and the percentile intervals allows the study of asymmetries in the distribution and makes no assumptions on sample (or error) distributions. In addition to the time-dependent trajectories of the outputs, the measured data points are included in the line plot. These measured data are discrete points and therefore depicted as such. The colors of simulated trajectories and measured points are matched[11]. To visually link the outputs in the line plot with the respective set of vertices (convex hull) in the graph view, the same color is used for

[11] the same color is used for both

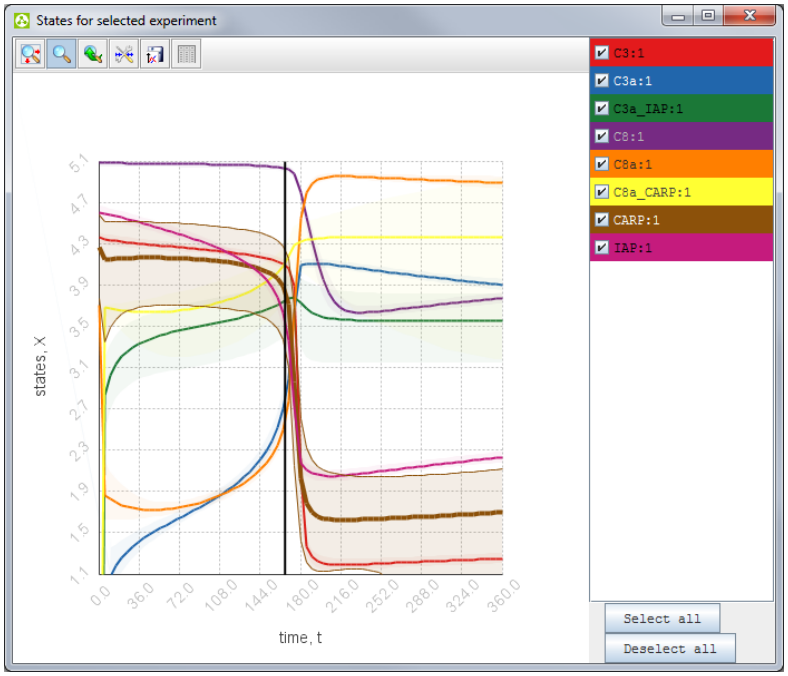


Figure 11: Line plot showing the time series of all imported dynamic state samples. The time series for has been selected and is therefore highlighted. The scale of the y-axis was adapted to the interval of the selected percentiles $[5\% : 95\%]$. The vertical black line indicates the currently selected time point ($t = 160\,\text{min}$).

the convex hull. A vertical line within the line plots indicates the current time point in the animation. For all three attributes, there are two line plots available:

1. Line plot for within-experiment comparison: shows the time series of the currently selected experiment (submenu option `time series for current exp.`).

2. Line plot for between-experiment comparison: shows the time series for all imported experiments but only for the set of selected species (reactions) (submenu option `compare time series of experiments`). This option will therefore only be available, if several experiments are imported.

The line plots (option 1) for fluxes and states are linked to the graph view in a way that the respective lines and uncertainty areas are highlighted as soon as you select edges (vertices) within the graph view and vice versa. If a time series is highlighted, the area, representing the uncertainty over time, is less transparent, framed and the line itself is thicker than the other ones. If a species (vertex) that is associated with any imported output (i.e., a species that lies within a convex hull) is selected in the graph view, the respective output trajectory and measured data-points will be highlighted. The time series can also be highlighted by selecting a line or hovering over the lines within the line plot. When doing so, the respective elements within the graph view

(vertices, edges or convex hulls) will be highlighted. The hovering option within the line plots is only enabled, while pressing the 'Shift' key. The line plots (option 2) will always contain the respective time series for all currently selected elements (species or reactions) in the graph view. If all elements are deselected within the graph view, e.g. by clicking next to the graph, the line plot will keep the time series of the elements that have been selected last.

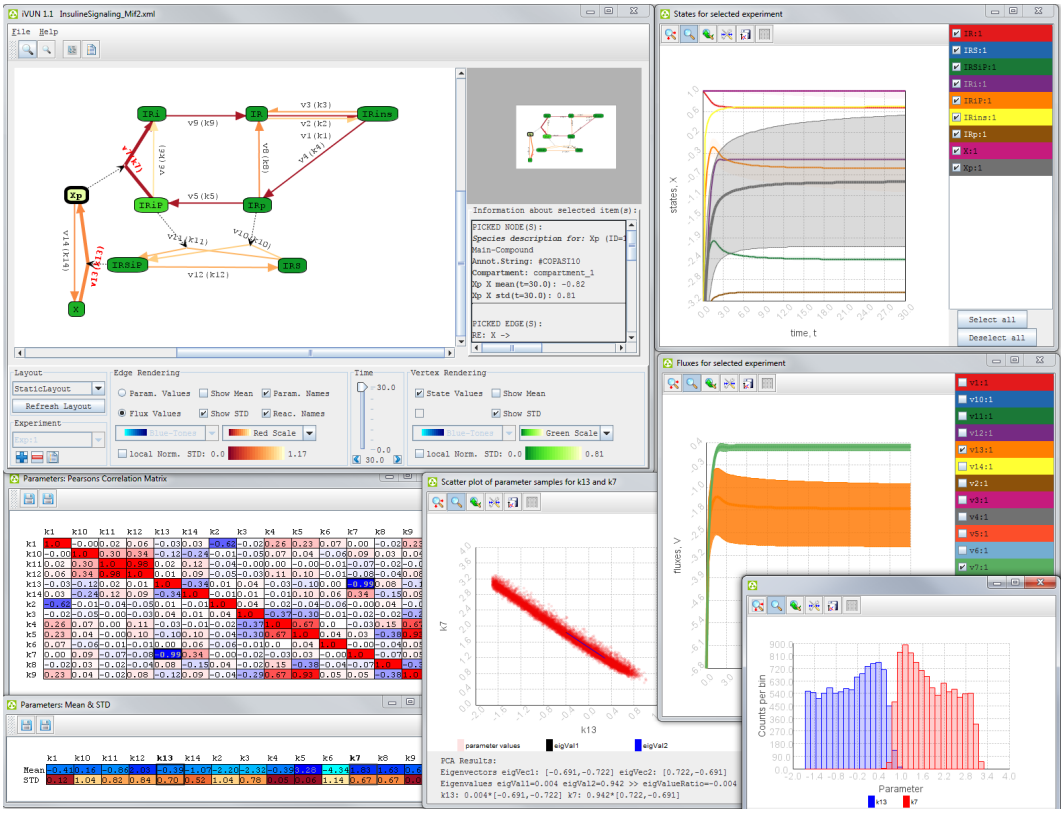


Figure 12: A System Overview showing the Insulin signaling model. Edges and vertices are colored based on the standard deviation at the steady state ($t = 30\,\text{min}$) of flux and concentration samples, respectively. The two reactions v_7 and v_{13} as well as the species Xp have been selected and are therefore highlighted. The time courses of fluxes and concentrations can be inspected within line plots (right), where only the two selected reactions are shown to reduce clutter (others are deselected). The table of mean values and standard deviations for the static parameter samples (bottom left) shows that there are several uncertain parameters; the two selected parameters k_7 and k_{13} are highlighted. The histogram (bottom right) allows a detailed study of the distribution of individual parameters; here the two selected parameters. The Pearson correlation matrix (left) reveals a strong anti-correlation of k_7 and k_{13} (the selected cell within the matrix). The selected species Xp is the species with the highest uncertainty as visible due to its color in the graph view and the huge semitransparent area framing the respective line in the line plot.

To reduce visual clutter, single time courses can be hidden on demand using the check boxes within the legend on the right of the line plots. If the line plot contains many lines, you may deselect all lines using the respective button `Deselect all` and select only the time series you are interested in by clicking on the respective check boxes or by selecting the respective vertices or edges. As soon as a species or reaction is selected within the graph view, the respective flux or state/output trajectory will be displayed again, in case it was hidden, and will be highlighted. In order to make full use of the available space, the y-axis scaling automatically adjusts to the value range of the visible time series, where the maximal interval corresponds to the interval $[p_{\text{low}} : p_{\text{high}}]$. You may change the x- and y-axis scaling according to your needs using the scaling menu of the plot. This menu can be opened by clicking on the  button. You can zoom into the line plot using the scroll wheel and turn back to the original zoom level by pressing the  button. The plot can be exported as 'png' file clicking on the  button.

References

[1] C. Vehlow, J. Hasenauer, A. Kramer, J. Heinrich, N. Radde, F. Allgöwer, and D. Weiskopf. Uncertainty-aware visual analysis of biochemical reaction networks. In Proceedings of IEEE Symposium on Biological Data Visualization(Biovis), pages 91-98, 2012.

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