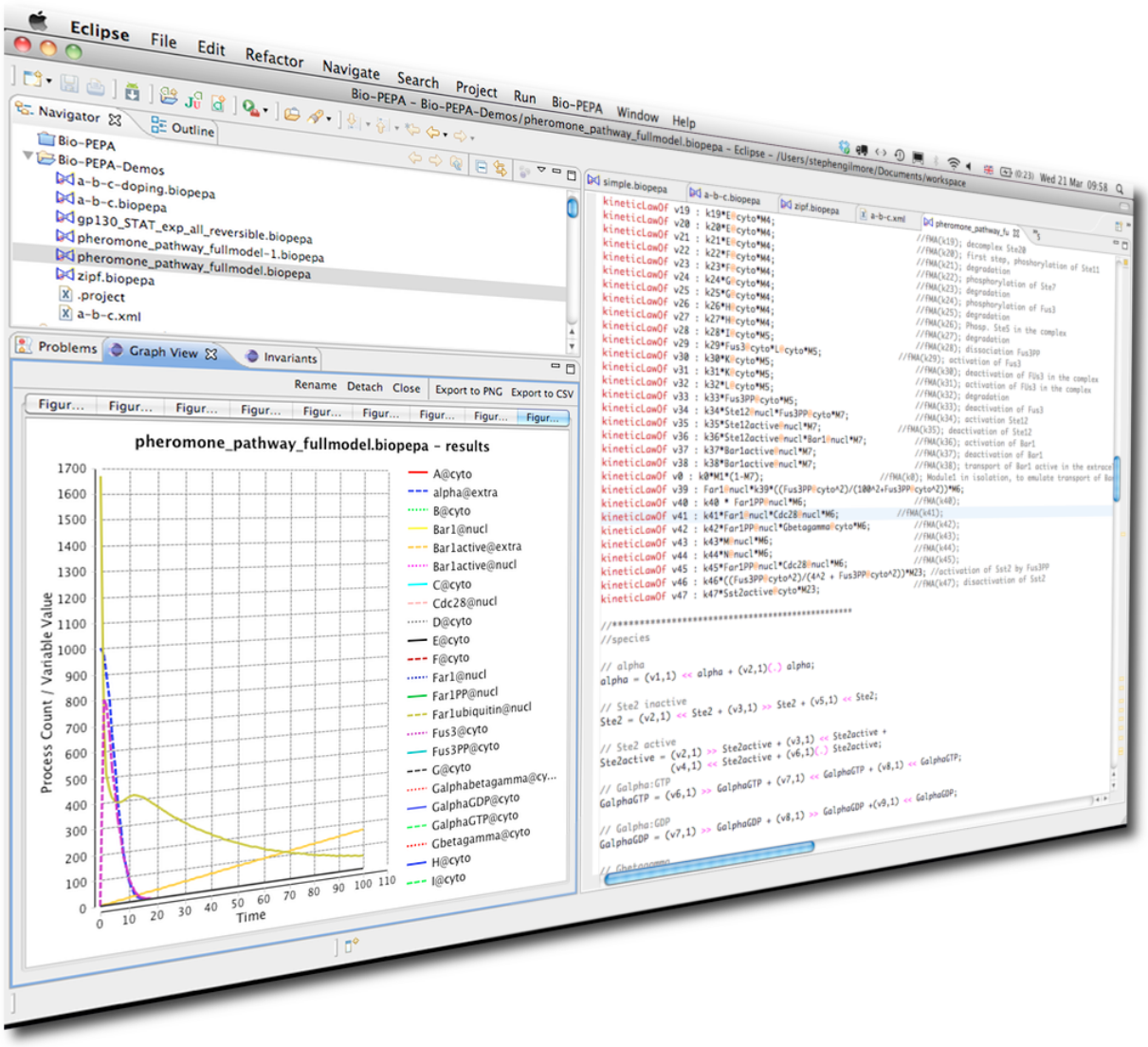
The Bio-PEPA Eclipse Plug-in User Manual

http://www.biopepa.org/

April 20, 2012



Contents

1 Acknowledgements

The implementation of the Bio-PEPA Eclipse Plug-in has been led by Adam Duguid and Allan Clark. The implementation of the invariant inference used in the Bio-PEPA Eclipse Plug-in was contributed by Peter Kemper. Other developers who have contributed code to the Bio-PEPA Eclipse Plug-in include Simon Bartels, Ian Robb and Mirco Tribastone.

Many people have contributed ideas and suggestions for improvements including Federica Ciocchetta, Vashti Galpin, Maria Luisa Guerriero, Stephen Gilmore, Jane Hillston, Laurence Loewe, Mieke Massink and Dimitrios Milios.

This user manual was written by Myrto Avgeri and Stephen Gilmore with help from Allan Clark, Adam Duguid and Dimitrios Milios.

2 Thanks

Our foremost thanks go to Federica Ciocchetta and Jane Hillston for inventing the Bio-PEPA language. We also thank enthusiastic adopters of Bio-PEPA who encouraged us including Mieke Massink and Carron Shankland.

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3 Introduction

Bio-PEPA is a high-level modelling language for describing models of biochemical processes (for more information see [1]). Models can be concisely expressed in a notation similar to that of a programming language, and visualised, analysed and shared. However, this manual is concerned with how to use the Bio-PEPA software; it does not include an introduction to the Bio-PEPA language. For this, see [11].

The Bio-PEPA Eclipse Plug-in is a complete development environment for Bio-PEPA models. Models can be composed using the built-in editor, simulated using both stochastic and deterministic simulators and the results can be plotted in graphical form. In addition to this the Bio-PEPA Eclipse Plug-in supports experimentation with models and export of models to different formats such as SBML which can be processed with other modelling tools.

The Bio-PEPA Eclipse Plug-in is written in Java and is freely available without charge. The Bio-PEPA Eclipse Plug-in does not depend on external libraries. It can be used on Windows, Mac OS X and Linux.

4 Getting started

4.1 Installation Instructions

First, download a copy of the Eclipse platform from [3]. These instructions concern the Indigo (3.7.2) version of Eclipse. The Eclipse IDE for Java Developers is recommended based on its smaller size. Then, choose Help → Install New Software (see Figure 1).

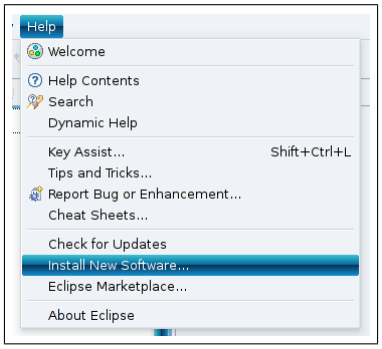


Figure 1: Install new software

The wizard dialogue box that pops up will assist you through the installation process. Click on the *Add* button at the upper right hand side of the window and add the following update sites (see Figure 2):

- Bio-PEPA — http://groups.inf.ed.ac.uk/pepa/update/
- BIRT — http://download.eclipse.org/birt/update-site/2.5
- Indigo — http://download.eclipse.org/releases/indigo (if it is not available already)

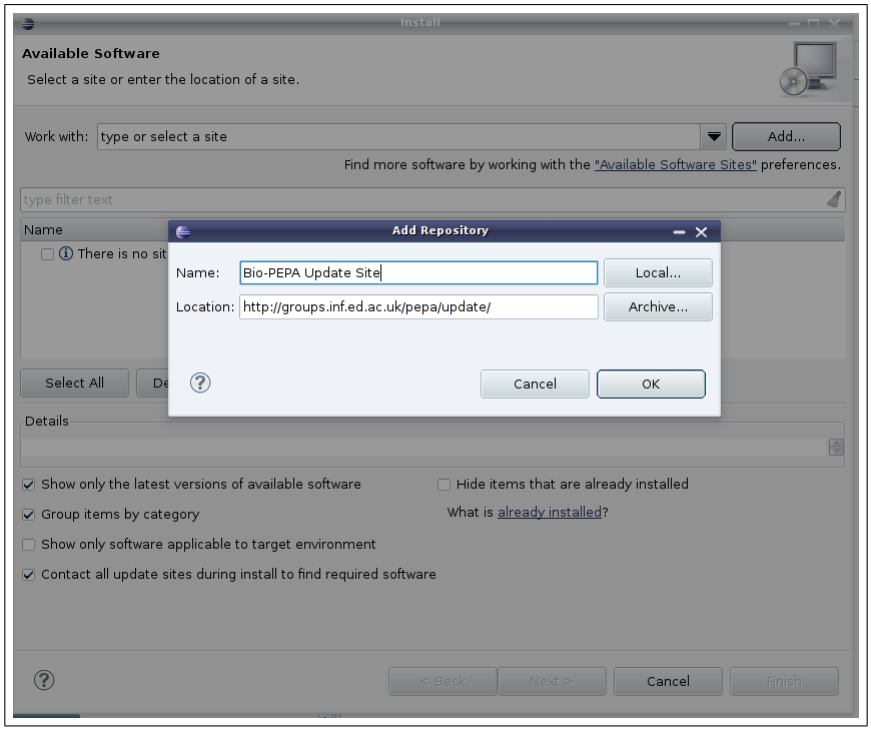
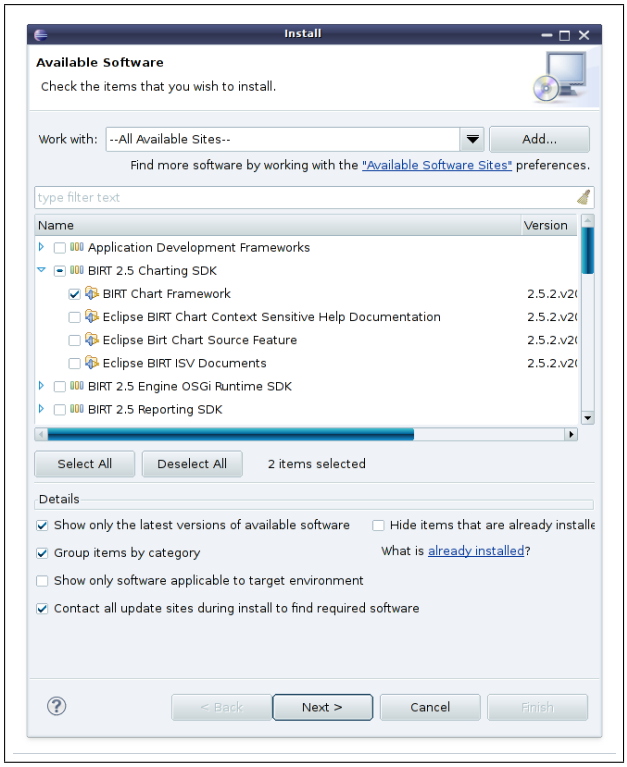
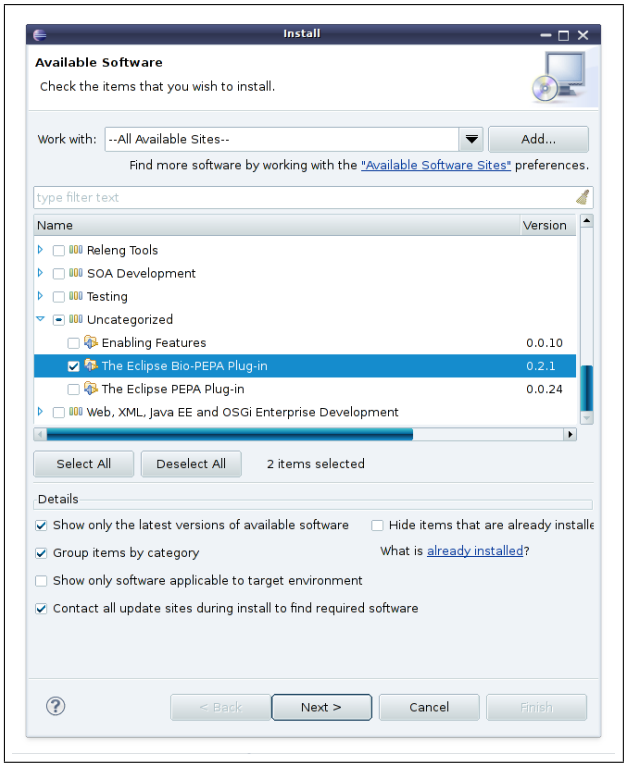


Figure 2: Adding a Repository in the Eclipse workbench

In the *Work with* drop down menu select *–All Available Sites–* to allow the selection of features from more than one site. Select the BIRT Chart Framework and The Eclipse Bio-PEPA Plug-in as shown in Figure 3a and Figure 3b. The details of what you see in the figures and what you will need to install might be slightly different. Then click on *Next*.



(a) Select the BIRT Chart Framework



(b) Select the Eclipse Bio-PEPA plugin

Figure 3: Select items to install

Eclipse will determine what plug-ins are required and then display the results (see Figure 4). Click *Next*.

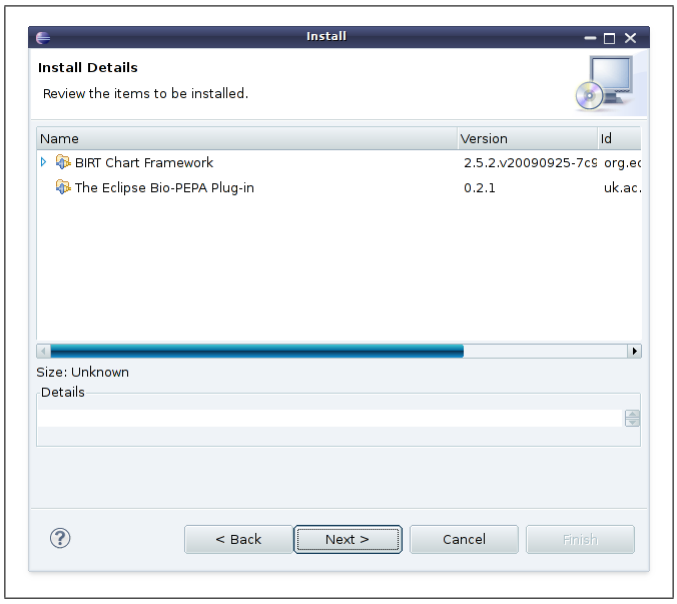


Figure 4: Review items to be installed

Then, accept the terms of the licence agreement before clicking on *Finish* (see Figure 5).

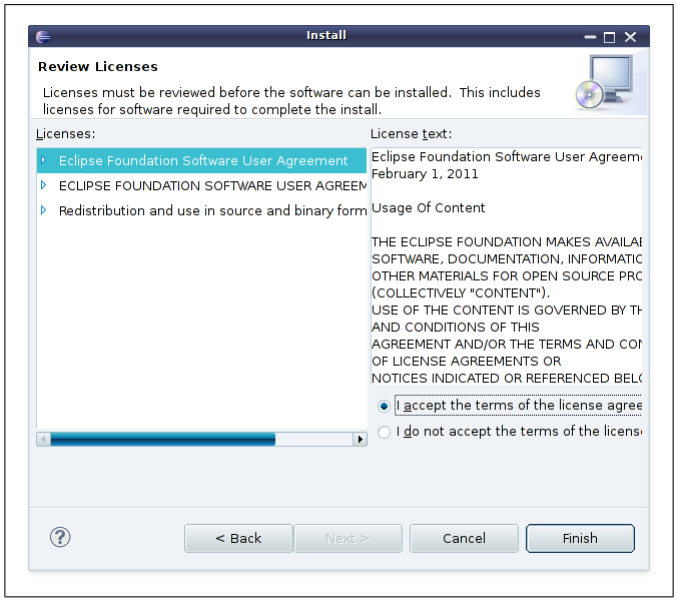


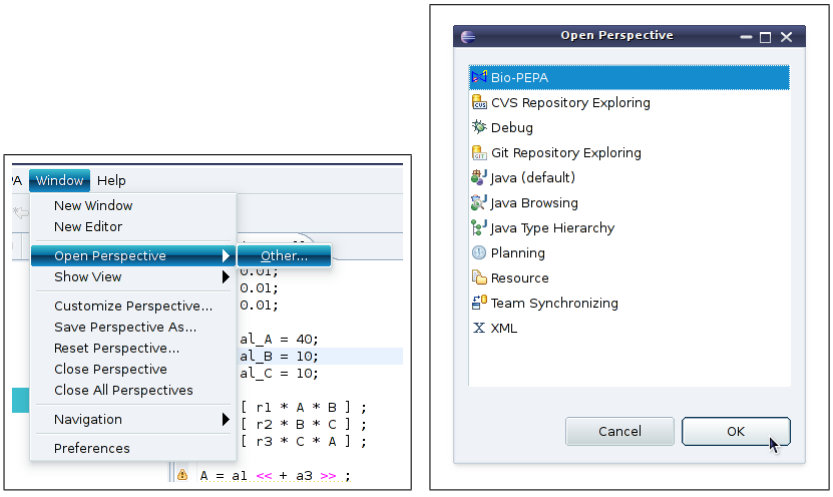
Figure 5: Review licenses

After completing the installation you will need to open the Bio-PEPA perspective, as described in the following section.

4.2 Managing The Bio-PEPA Perspective

4.2.1 Opening the Bio-PEPA perspective

In order to open the Bio-PEPA perspective you should go to Window → Open Perspective → Other (see Figure 6a). Then you should select the Bio-PEPA perspective (see Figure 6b).



(a) Open Perspective (b) Choose the Bio-PEPA Perspective

Figure 6: Opening the Bio-PEPA Perspective

4.2.2 Resetting the Perspective

Sometimes a wrong click of the mouse can close useful views that hold information which you need. The fastest and safest way to get back your views is to go to Window → Reset Perspective (see Figure 7a). Then, click *Yes* in the dialogue box that appears (see Figure 7b).

(a) Reset Perspective (b) Return Bio-PEPA Perspective to its defaults

Figure 7: Resetting the Bio-PEPA Perspective

4.3 The Navigator view

When you launch Eclipse you will see that the display is broken up into a number of views. One of these is the Navigator view. This shows a view of your local Eclipse workspace which will contain projects with folders and files.

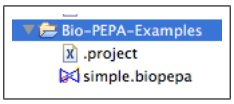


Figure 8: Navigator view

4.4 Creating a new project

From the File menu choose New → Project...

This will launch the New Project wizard and you should choose General → Project to create a new project where you will store your Bio-PEPA models. Choose Next and give your project a name such as `Bio-PEPA-Examples`. Choose Finish. You now have a project which you can see in the Navigator view.

Choose File → New → Other and then choose General → File. Press Next. Choose the parent folder to be the folder which contains the project which you just created. Choose a file name for your new file which ends in `.biopepa` (for example, `simple.biopepa`). Press Finish.

You now should see that the file is opened in the editor and that the Problems view reports a problem with the file because it is an empty file, and does not contain any Bio-PEPA definitions. Let us fix this problem by entering a very small and simple model. This simple model will describe a species S which decays away to nothing.

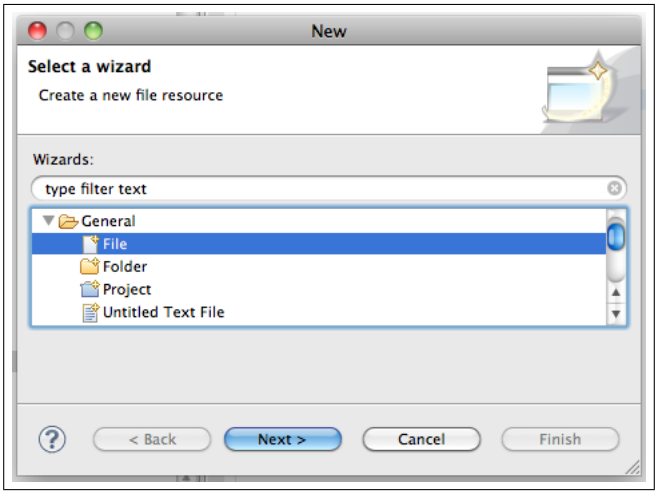


Figure 9: Creating a new file

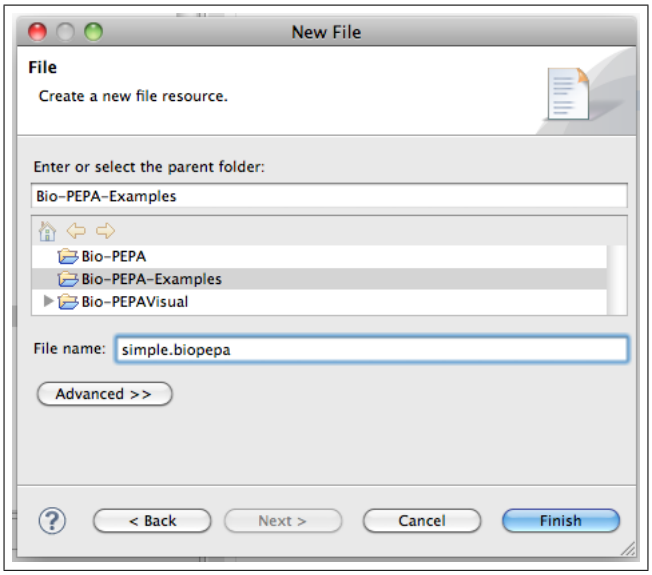


Figure 10: Naming a file

5 Using the editor

When editing a Bio-PEPA model in the editor syntax elements of the language are automatically coloured. For example, comments print in grey and operators such as `<<` are printed in pink (see Figure 11). The example which we have entered in the editor is a simple model of one species decay named `simple.biopepa`. We will describe it in more detail in the following section.

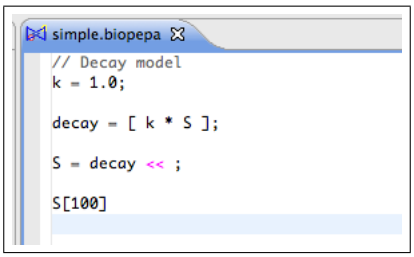


Figure 11: Using the editor

5.1 A simple model of one species decay

The `simple.biopepa` model, shown in Figure 11, contains just a single species S, which is only involved in the *decay* reaction. The *decay* reaction is governed by a kinetic parameter k, which controls the rate of decay. The parameter k has been given the constant value 1. The rate of the *decay* also depends on the quantity of S available. The kinetic law for the *decay* reaction is the product of k and S. S is decreased (`<<`) by the `decay` reaction.

This is a simple but well-formed Bio-PEPA model. It passes the *static analysis* checks which are built into the Bio-PEPA Eclipse Plug-in. For example, everything which is used has also been declared (the Bio-PEPA Eclipse Plug-in would generate an error otherwise) and everything which has been declared has also been used (the Bio-PEPA Eclipse Plug-in would generate a warning otherwise).

5.2 Syntax errors

When errors are detected in a model the Bio-PEPA Eclipse Plug-in highlights these in the editor. For example, suppose we forget to type the termination semicolon (`;`) at the end of *decay* definition statement(see Figure 12):

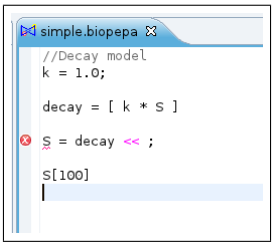


Figure 12: An error is detected

5.2.1 Errors in the Problems view

When errors are detected in a model they are displayed in the Eclipse Problems view. This lists errors and warnings and information messages which are associated with the resources in the Eclipse workspace (such as, in our case, Bio-PEPA models). The resource which has the associated problem is identified in the resource column and a diagnostic error message appears in the description column. Here we are informed that the editor was expecting a semicolon at the end of the statement (see Figure 13):

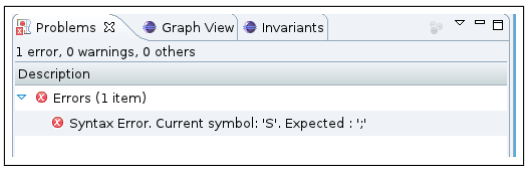


Figure 13: Error messages in the Problems view

5.3 Semantic errors

The editor can also detect and highlight semantic, i.e. logical errors. For example, suppose we accidentally mis-type the reaction identifier `decay` as `deacy`, with a simple transposition error in the letters `c` and `a` (see Figure 14):

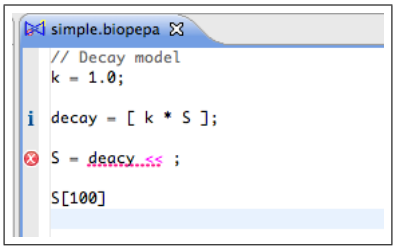


Figure 14: A semantic error is detected

Now there are two problems with the model. The first is that the reaction `deacy` does not have an associated kinetic law, which prevents any kind of simulation of the model. The second is that a kinetic law has been declared for the reaction `decay`, but the reaction `decay` has never been used in the definition of any species. This second problem is less serious and would not by itself prevent simulation of the model but it might indicate that there is mistake somewhere in the model, or that it is unfinished.

5.3.1 Semantic errors in the Problems view

The Problems View informs us that a functional rate (also known as a kinetic law) has been used but not declared and that a reaction (with its associated functional rate) has been used but not defined (see Figure 15).

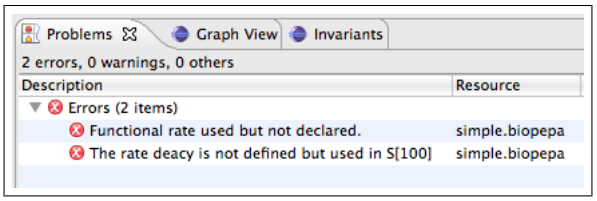


Figure 15: Semantic error messages in the Problems view

5.4 Warnings and semantic errors

Errors prevent models from being simulated at all. Warnings however, are simply there to alert us to potential problems. They do not prevent models from being simulated but it is good modelling practice to inspect all of the warning messages to see if you understand their cause. For example, if you know that your model is still partly unfinished and incomplete then receiving an information message informing you that a species has been declared but never used is not likely to cause much concern. However, if you thought that your model was complete with all species and reactions defined and all parameters in place then an information message saying that one has been declared but never used probably indicates that you have forgotten to include some definitions in the model which you meant to include.

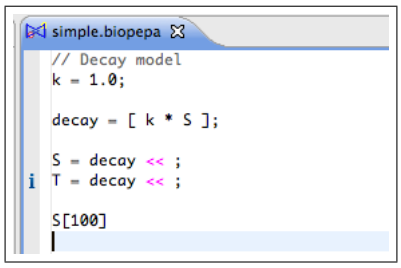


Figure 16: An information point is included about a species

5.4.1 Information messages in the Problems view

Information messages are displayed in the problems view. They give a brief diagnostic error message and a reference to the model file and project folder where the problem was encountered. They give a line number in the file which should be near to the location of the error (although some errors have an ambiguous point of origin).

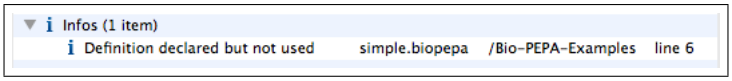


Figure 17: Information messages in the Problems view

5.5 Inspecting your model in the Outline view

The Bio-PEPA editor allows you to compose your model and checks that it is free from syntax errors and reports semantic errors such as missing declarations. The Outline view allows you to see your model in a different way. It provides a concise summary of your model much as a table of contents provides a summary of a book. You can see all of the species which are declared and a list of all reactions. In this simple example there is only one reaction, which destroys S. Species are categorised as being either sources (which are only decreased by reactions) or sinks (which are only increased by reactions), as appropriate. Reactions are also categorised as being either source actions (which produce matter) or sink actions (which consume matter).

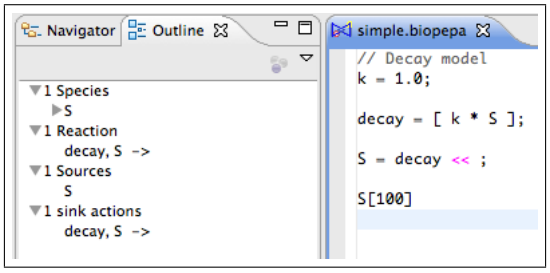
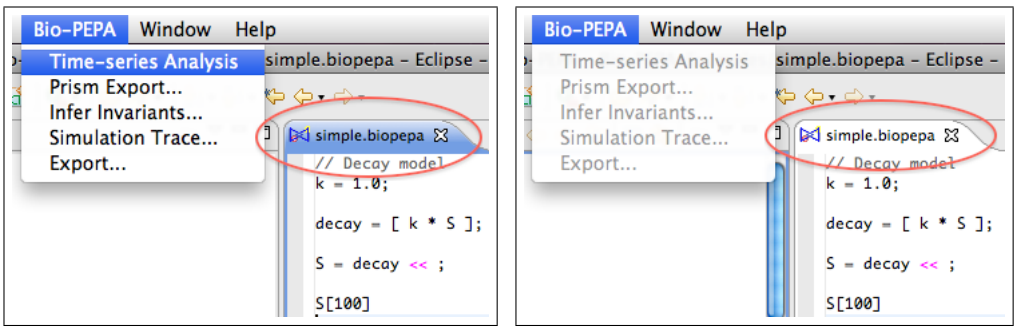


Figure 18: The outline view provides a different representation of your model

6 Invoking commands

When you have a Bio-PEPA which has no associated errors or warnings then you can perform simulations and other analysis by invoking the commands listed in the Bio-PEPA menu in the Eclipse menu bar. These commands will only be available when the active window in Eclipse is the Bio-PEPA editor window. You can identify the active window because it is outlined in blue and has a blue tab at the top, as circled in red in Figure 19a. When the Bio-PEPA editor window is the active window then you will be able to choose options such as "Time-Series Analysis" from the Bio-PEPA menu.

If the editor is not selected then it will not be possible to invoke commands from the menu. These will be greyed out and will not become active until the editor is made the active window by clicking on the tab at the top. At this point the tab at the top of the editor window will change from white to blue and the commands in the Bio-PEPA menu will become available.



(a) The circled blue tab indicates that the editor is selected

(b) The circled tab indicates that the editor is not selected

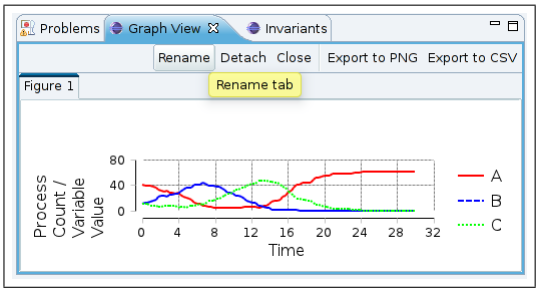
Figure 19: Bio-PEPA commands are not available if the editor is not selected

6.1 Managing the Graph View

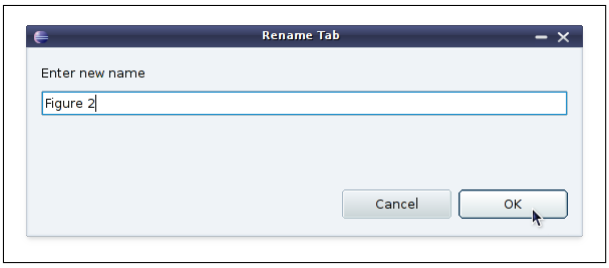
The results of the simulations are usually plotted in the Graph View. The Graph View allows the user to rename the graph tab, to detach the graph and view it separately, to close the graph, to export the graph as an image in `.png` format or as text data in `.csv` format.

6.1.1 Renaming the graph tab

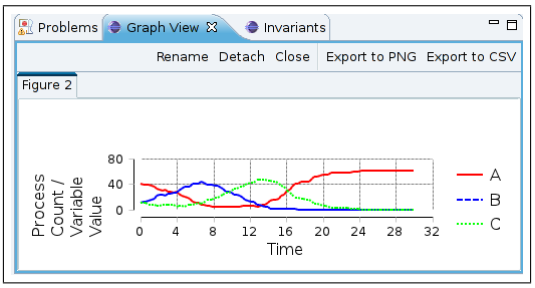
To rename the graph tab, click on the *Rename* button in the upper right hand corner of the Graph View (see Figure 20a). Then, you have to enter a new name for the graph tab and click *OK* in the dialogue box that appears (see Figure 20b).The renamed graph is shown in Figure 20c.



(a) Click on the *Rename* button



(b) Enter a new name for the graph tab

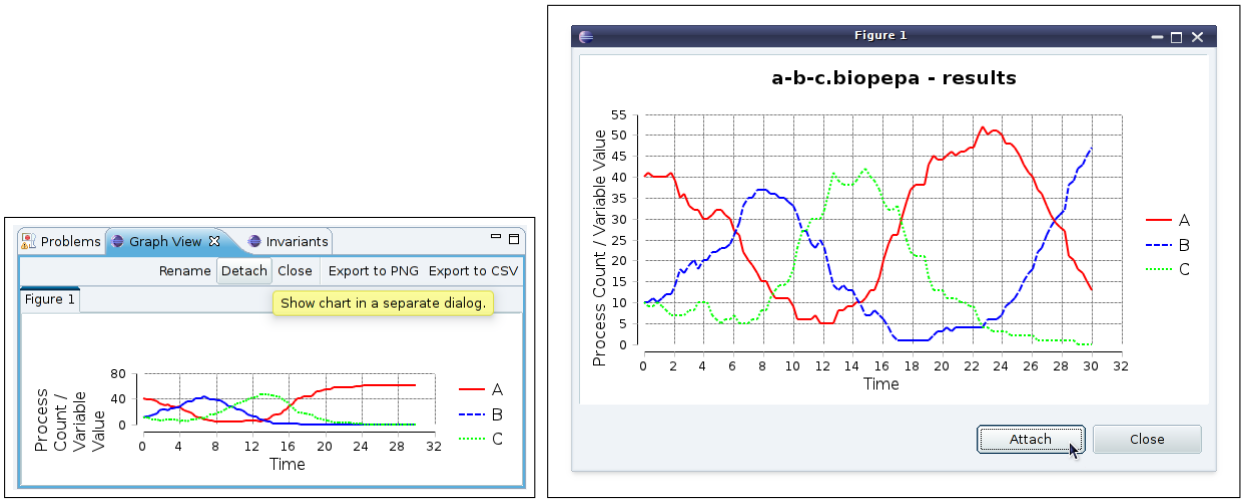


(c) The renamed graph

Figure 20: Renaming the graph

6.1.2 Detaching the graph

To detach the graph from the Graph View, you have to click on the *Detach* button in the upper right hand corner of the Graph View (see Figure 21a). The detached graph is shown in Figure 21b.



(a) Click on the *Detach* button

(b) The detached graph

Figure 21: Detaching the graph

6.1.3 Closing the graph

To close the graph, you have to click on the *Close* button in the upper right hand corner of the Graph View (see Figure 22).

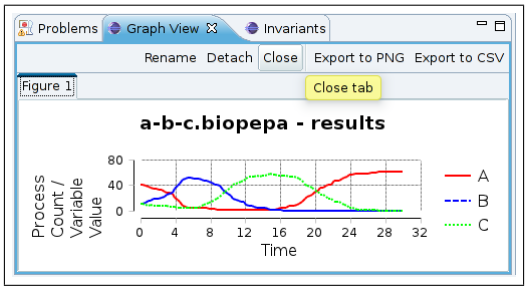
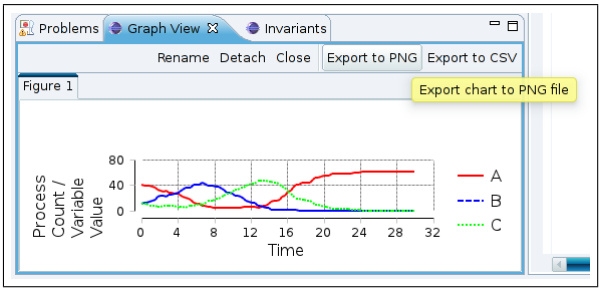


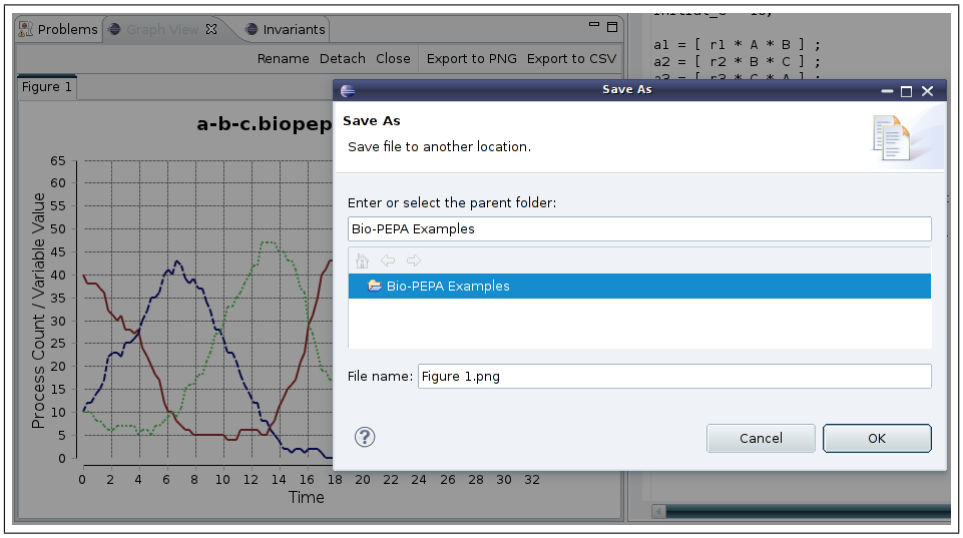
Figure 22: Click on the *Close* button

6.1.4 Exporting to .png

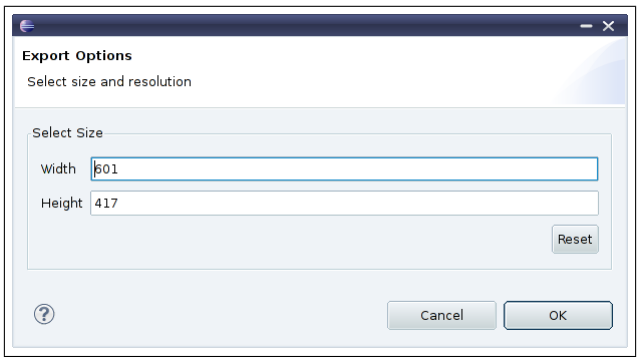
To export the graph to a `.png` file, you have to click on the *Export to PNG* button in the upper right hand corner of the Graph View (see Figure 23a). Then, you have to enter the parent folder in which the `.png` file will be saved and click *OK* in the dialogue box that appears (see Figure 23b). Finally, you have to choose the size of the `.png` image and again click *OK* in the dialogue box (see Figure 23c). A saved `.png` file is shown in Figure 23d.



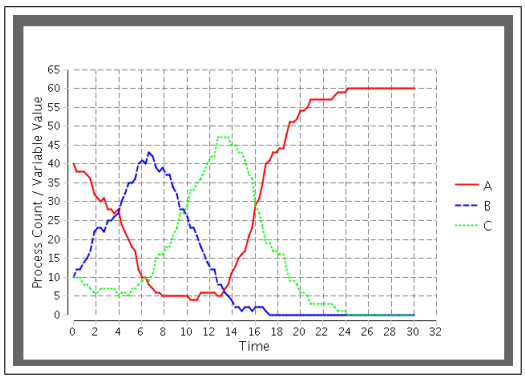
(a) Click on the *Export to PNG* button



(b) Choose a parent folder and a file name



(c) Choose the size of the image

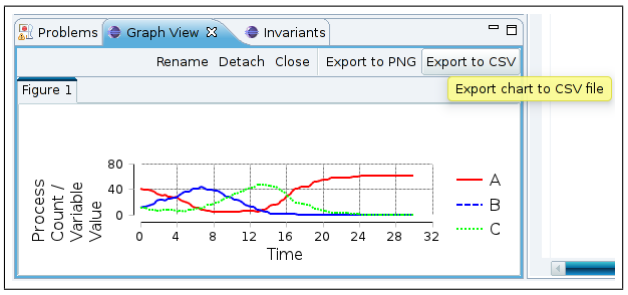


(d) The saved `.png` image

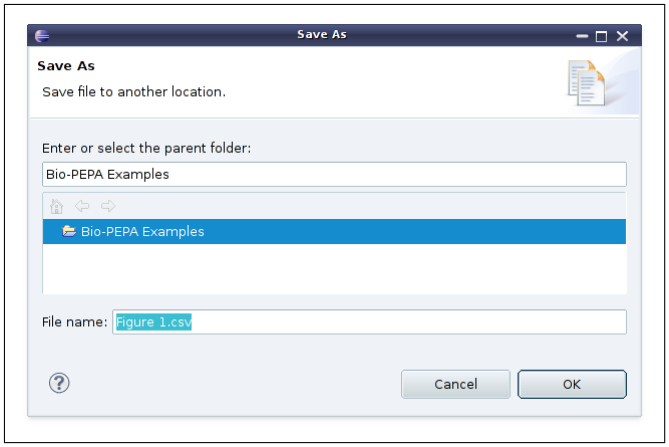
Figure 23: Exporting to `.png`

6.1.5 Exporting to .csv

To export the graph to a comma-separated (`.csv`) file, for processing with Gnuplot or Excel, or similar tools, you have to click on the *Export to CSV* button in the upper right hand corner of the Graph View (see Figure 24a). Then, you have to enter the parent folder in which the `.csv` file will be saved and click *OK* in the dialogue box that appears (see Figure 24b).



(a) Click on the *Export to CSV* button



(b) Exporting the graph data to a `.csv` file

Figure 24: Exporting to `.csv`

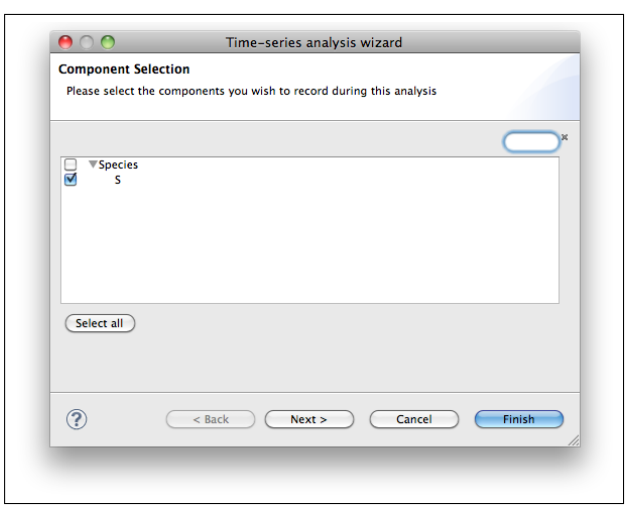
7 Time-series Analysis

One of the most intuitive and direct kinds of analysis which can be applied to a Bio-PEPA model is to simulate the model and plot the quantities of the chemical species in the model as a function of time. (Such a plot is called a *time series*.) The relative amounts of the chemical species in the model will change over time because the reactions in the model change the proportions of species.

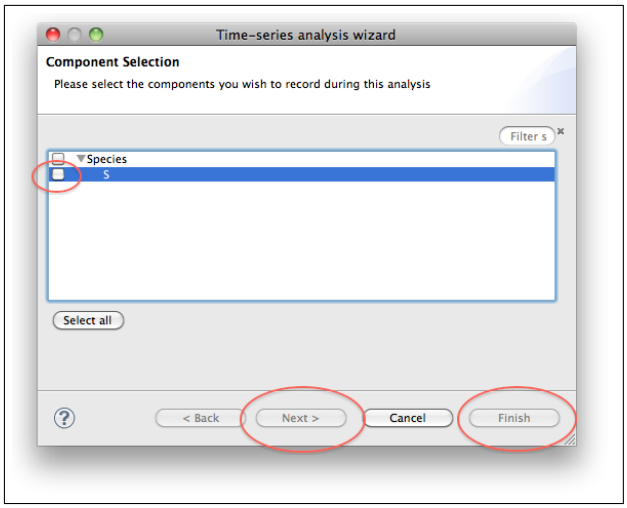
When we invoke the Time-series Analysis option from the Bio-PEPA menu we are presented with a wizard which guides us through the process of selecting a simulation method and plotting results (see Figure 25a). In our simple example, with only one species S which decays there is only one option here, to plot S.

For models with many species you can narrow the list of species by typing a species name (or part of a species name) in the search box in the upper right hand corner. The list of species will narrow to include only those species which contain this search string in their name.

If we do not select any species to plot then we will not be able to proceed (see Figure 25b).



(a) The Time-series analysis wizard requires you to select species to plot



(b) If no species are selected then you will not be able to proceed

Figure 25: Selecting species to plot

The next step in generating a time series is to choose the kind of simulation which is to be done. Different types of simulators are available in the Bio-PEPA Eclipse Plug-in, including:

- continuous, deterministic simulators which convert your Bio-PEPA model into a system of Ordinary Differential Equations (ODEs) which are evaluated using numerical integration; and
- discrete, stochastic simulators which convert your Bio-PEPA model into a Monte Carlo Markov Chain (MCMC) problem which is evaluated using exact or approximate stochastic simulation algorithms such as Gillespie's Direct Method and Gillespie's τ-leap algorithm.

We will describe each of these in turn.

7.1 Solving continuous ODE models using Bio-PEPA

One kind of time series which we could generate is the one which interprets the Bio-PEPA model in the continuous, deterministic regime in which the species variables are subject to continuous change and take real number values in each run.

Before we can generate a time series for our Bio-PEPA model we need to set the parameters for the simulation (see Figure 26). The parameters which need to be set, differ from one simulator to another but the simulators for ODE models typically include:

- Start time — the start time of the time series (often 0)

- Stop time — the stop time of the time series (model dependent)
- Step size — the step size of the ODE integrator
- Number of data points — the number of data points that you would like to have recorded
- Relative error — the relative error of the ODE integrator
- Absolute error — the absolute error of the ODE integrator

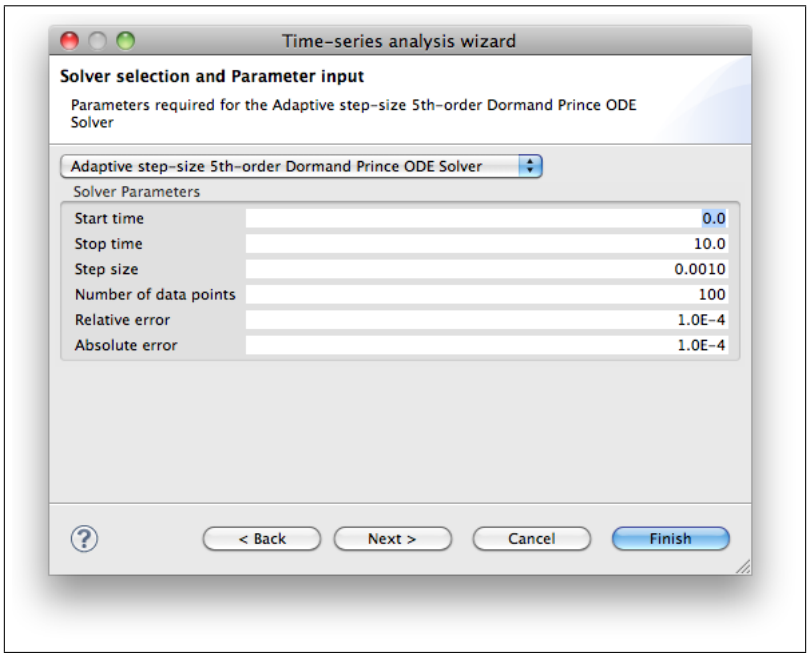


Figure 26: Setting parameters for the Dormand Prince ODE solver

Once you have selected a solver and entered values for all of the parameters then you can click Finish to run the simulation and plot the results in the Graph View.

7.2 Performing stochastic simulation using Bio-PEPA

An alternative kind of time series which we could generate is the one which interprets the Bio-PEPA model in the discrete, stochastic regime, in which the species variables are subject to discrete change and take integer number values only in each run.

The Bio-PEPA Eclipse Plug-in offers the following algorithms for stochastic simulation:

- Gillespie's stochastic simulation algorithm
- Gillespie's Tau-Leap stochastic simulation algorithm
- Gibson-Bruck stochastic simulation algorithm

In order to generate a time series for our Bio-PEPA model we need to set the parameters for the stochastic simulation (see Figure 27a). The parameters which need to be set, differ from one simulator to another but the stochastic simulators typically include:

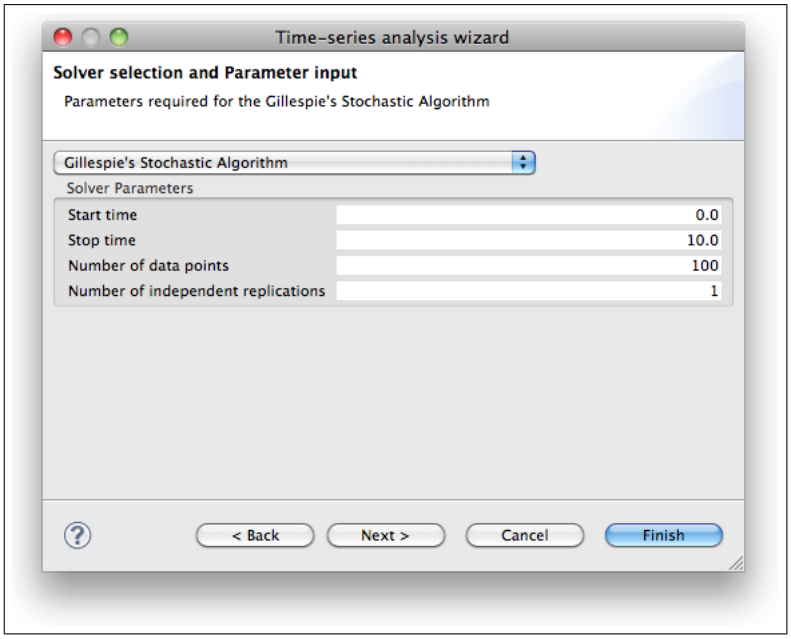
- Start time — the start time of the time series (often 0)
- Stop time — the stop time of the time series (model dependent)
- Number of data points — the number of data points that you would like to record

- Number of independent replications — the number of simulation runs

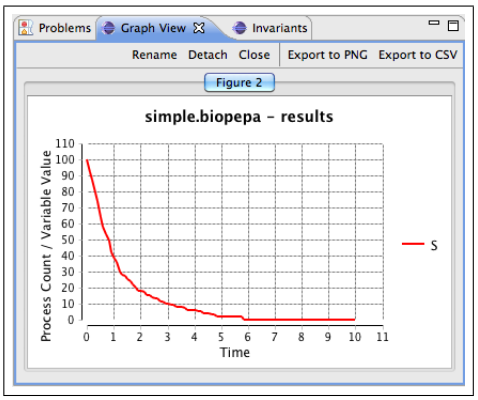
Gillespie's Tau-Leap stochastic simulation algorithm also includes the following parameters:

- Step size — the step size parameter is used to determine the frequency of the tau-leap (default value 0.0010). When the step size is increased the tau-leap occurs more frequently, which decreases the accuracy of the simulation results.
- Relative error — the relative error is used to determine the size of the tau-leap (default value 1.0E-4). When the relative error is increased, so does the size of the tau-leap, which decreases the accuracy of the simulation results.

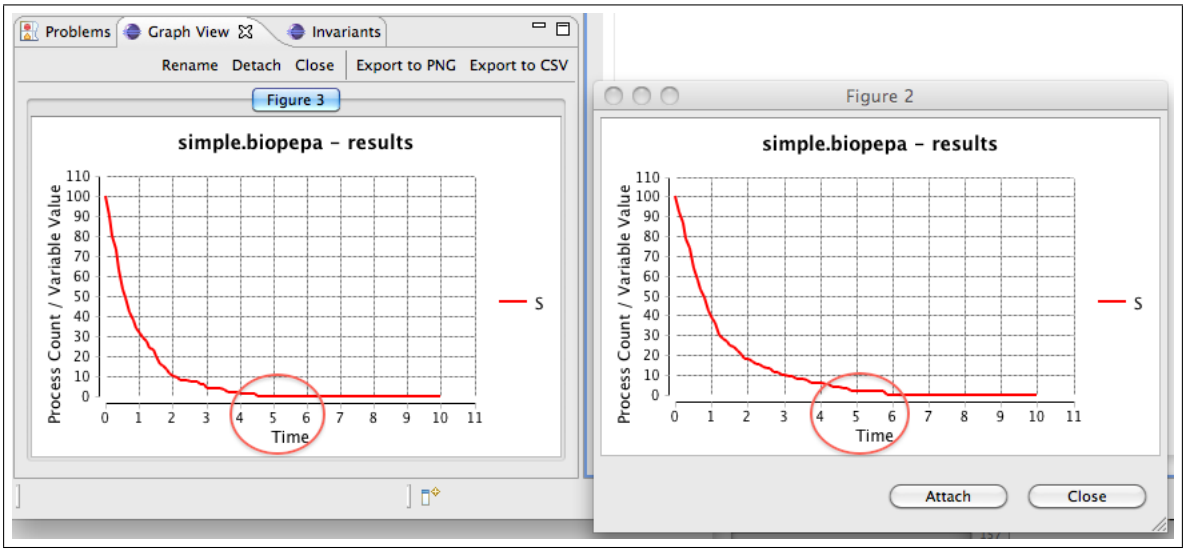
The simulation results are plotted in the Graph view (see Figure 27b for the results of the `simple.biopepa` model we saw in the previous sections). By allowing you to choose the number of independent replications, the Bio-PEPA Eclipse Plug-in basically gives you the option of running the simulation any number of times, without having to set the parameters again and comparing the results, since each stochastic simulation run usually has slightly different results from the others (see Figure 27c).



(a) Setting parameters for the Gillespie Stochastic Simulation Algorithm (SSA)



(b) The results from a simulation are plotted in the Graph view



(c) Two stochastic simulation runs may produce very similar results but they will not usually be exactly the same

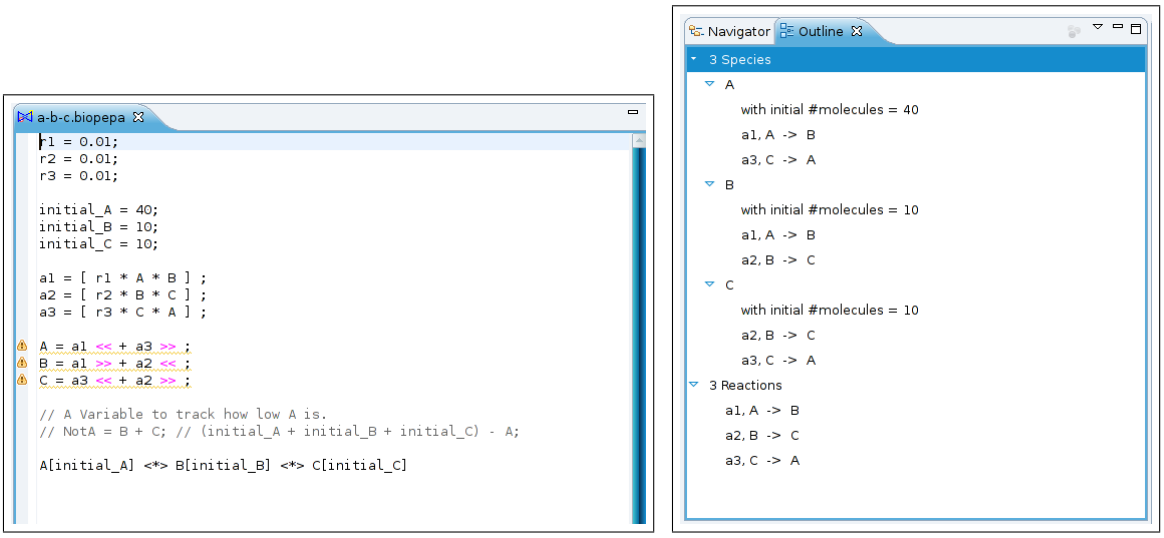
Figure 27: Stochastic simulation example

8 Experimentation using Bio-PEPA

In order to present more options that Bio-PEPA Eclipse Plug-in offers, we will need to use a slightly more complicated model than the `simple.biopepa` model that we used in the previous sections. The model we will use as an example is named `a-b-c.biopepa` and its main characteristic is that it presents interesting oscillations.

8.1 A model of oscillations

The `a-b-c.biopepa` model (see Figure 28a) contains three species A, B and C which are involved in three reactions $a1$,$a2$,$a3$. Each reaction is governed by a kinetic parameter $r1$, $r2$ and $r3$ respectively, which controls the rate of the reaction. All three parameters $r1$, $r2$ and $r3$ have been given the constant value 0.01. The rates of the reactions also depend on the available quantity of the species that are involved in them. The kinetic law for the $a1$ reaction is the product of $r1$, A and B. The kinetic law for the $a2$ reaction is the product of $r2$, B and C. The kinetic law for the $a3$ reaction is the product of $r1$, C and A. A is decreased (<<) by the $a1$ reaction and increased (>>) by the $a3$ reaction. B is increased (>>) by the $a1$ reaction and decreased (<<) by the $a2$ reaction. C is decreased (<<) by the $a3$ reaction and increased (>>) by the $a2$ reaction. An alternative description of the model is provided by the Outline view (see Figure 28b).



(a) The `a-b-c.biopepa` model (b) The `a-b-c.biopepa` model outline view

Figure 28: A model of oscillations

As you can see in Figure 28a, there are warning signs appearing in the editor. The Problem View informs us that component A affects the rate of reaction $a3$ but is not a reactant. There are similar warnings for components B and C (see Figure 29).

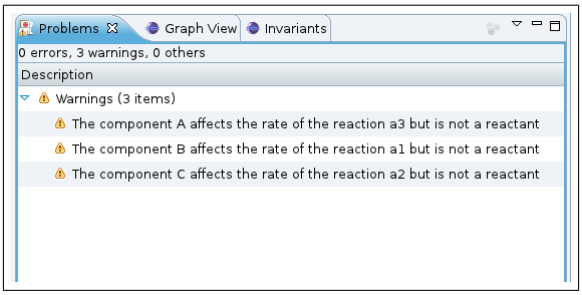


Figure 29: The Problems View for the `a-b-c.biopepa` model

These warnings are due to an abstraction in the species component definitions. The full definition of the species components is:

```
A  =  a1 << + a3 >> + a3 (+);
B  =  a2 << + a1 >> + a1 (+);
C  =  a2 >> + a2 (+) + a3 << ;
```

Component A acts as an activator for reaction *a3* and that is why it affects the rate of the reaction despite the fact that it is not a reactant. Similarly, component B is an activator for reaction *a1* and component C is an activator for *a2*. However, the Bio-PEPA Eclipse Plug-in syntax does not allow us to specify two roles for a component in the same reaction. This is an example of a warning that alerts us to a potential problem. However, since we understand the cause of the warnings and know that it will not affect the correctness of the analysis we can simply ignore them.

8.2 Creating experiments

As part of the time-series analysis, the Bio-PEPA Eclipse Plug-in allows you to create and save experiments, which you can re-run later. The user may choose to have the results of the experiments plotted on the same or separate graphs, or for them to be stored in a comma-separated values (`.csv`) file (see Figure 30).

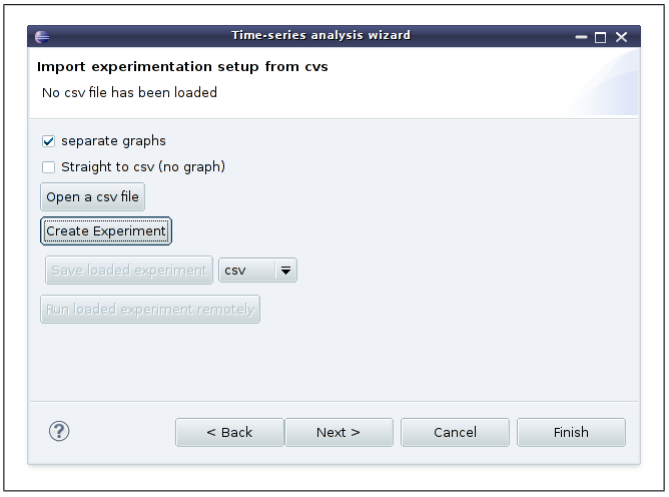
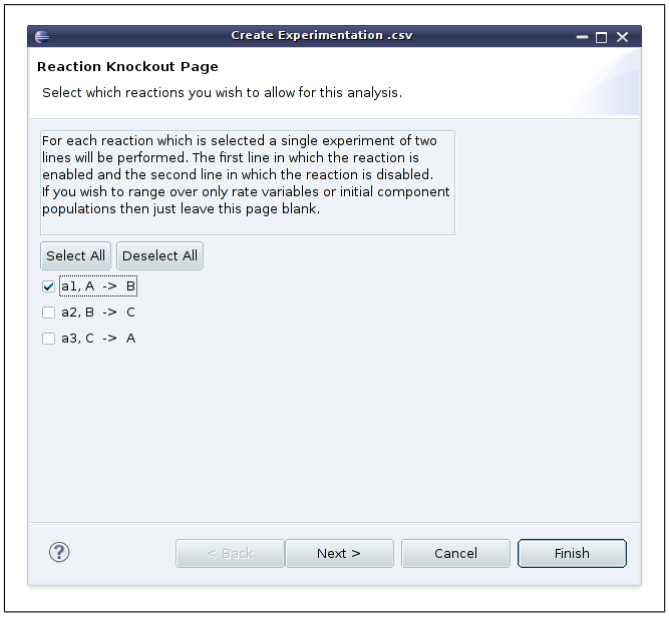


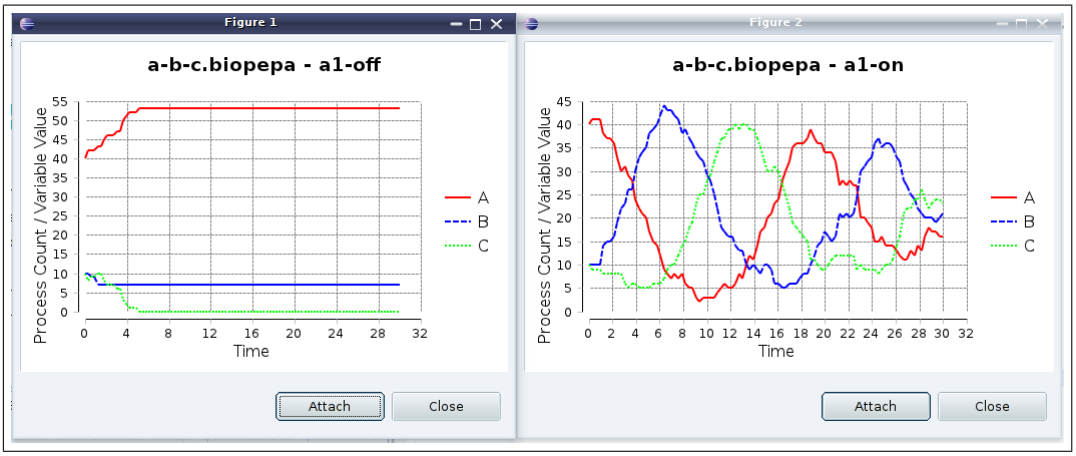
Figure 30: Bio-PEPA allows you to create and save experiments which you can re-run later

8.2.1 Disabling one or more reactions

One of the options offered by the experimentation feature of the Bio-PEPA Eclipse Plug-in allows the user to disable one or more of the reactions of the model. For example, in Figure 31a the user has chosen to disable the reaction *a1* of the `a-b-c.biopepa` model described in section 8.1. The results of the experiment are shown in Figure 31b.



(a) Disabling reaction $a1$ of the `a-b-c.biopepa` model

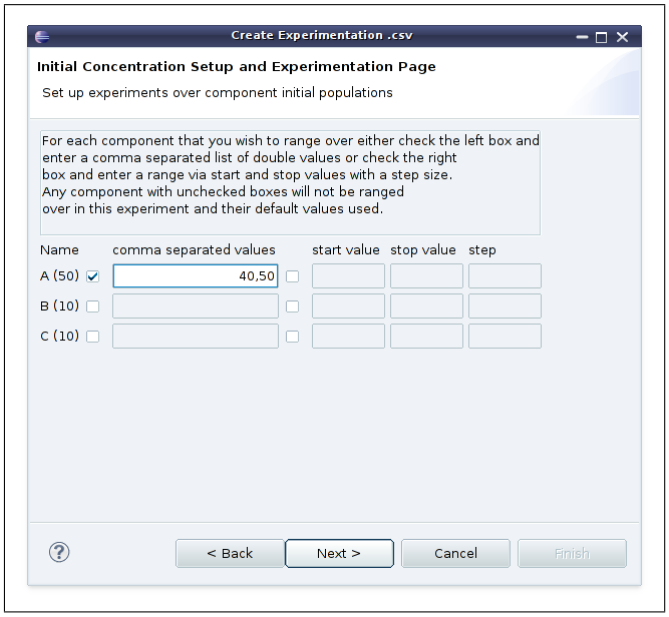


(b) The resulting graphs when the *a1* reaction has been disabled and when it is on

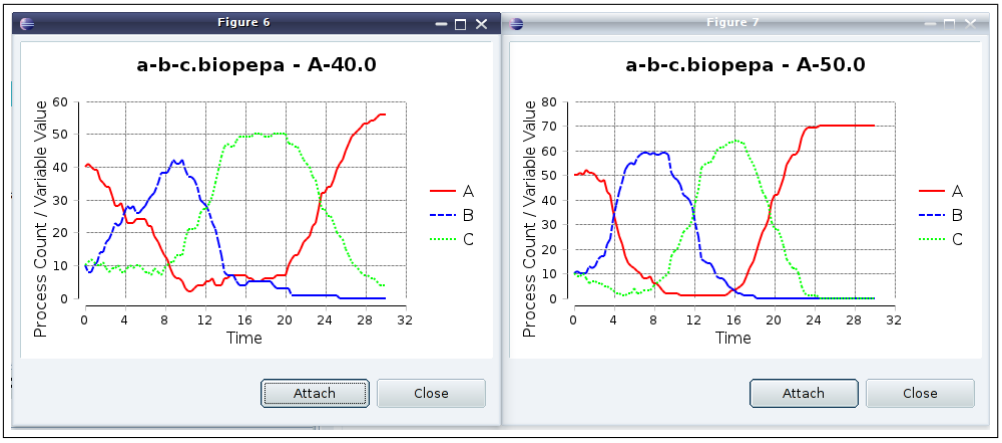
Figure 31: Disabling a reaction

8.2.2 Altering the initial populations

Additionally, the user may alter the initial populations of the species of the Bio-PEPA model by providing, either a set of comma-separated values, or a range of values. In Figure 32a, the user has provided two comma-separated values for the initial population of species A of the `a-b-c.biopepa` model, 40 and 50. The resulting graphs for this experiment are shown in Figure 32b.



(a) Setting comma-separated values for species A of the `a-b-c.biopepa` model

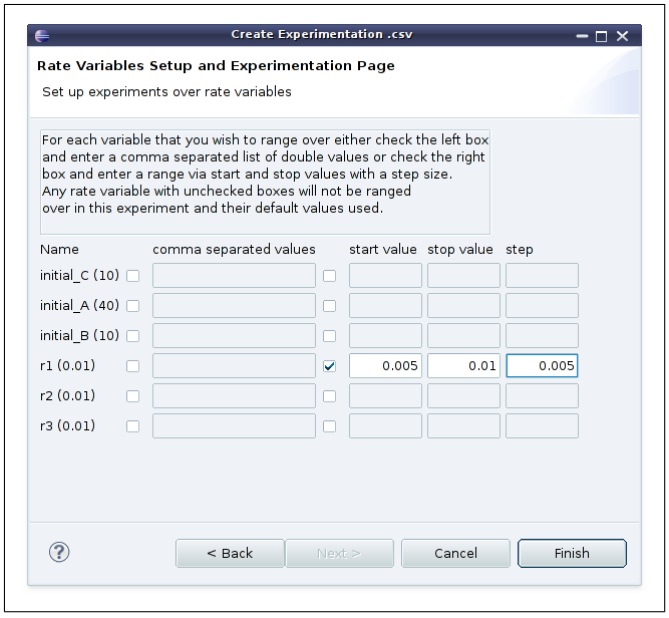


(b) The resulting graphs of a stochastic simulation for the two different initial populations of A

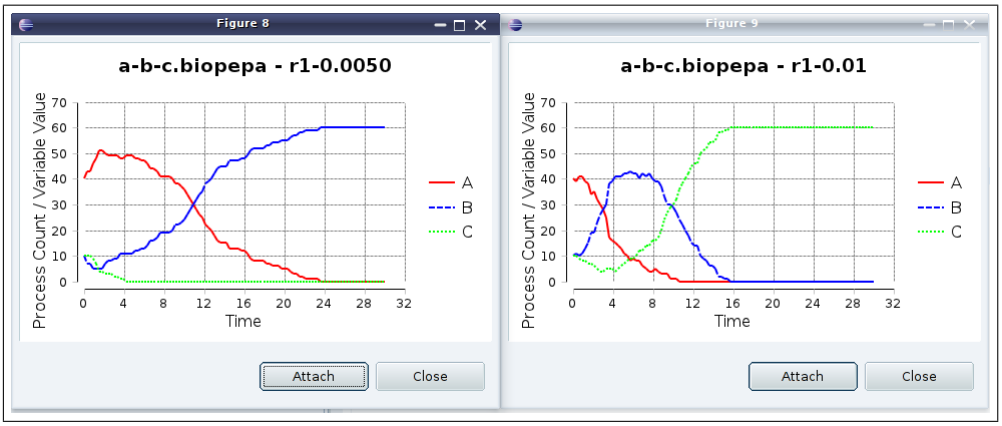
Figure 32: Altering the initial populations

8.2.3 Varying the rate values

Finally, the user may alter the values of the rate (kinetic) variables of the model by providing, either a set of comma-separated values, or a range of values. In Figure 33a, the user has provided a range of values for kinetic parameter $r1$ of the `a-b-c.biopepa` model, by setting a start value of 0.0050, a stop value of 0.01 and a step of 0.0050. The resulting graphs for this experiment are shown in Figure 33b.



(a) Setting a range of values for kinetic parameter $r1$ of the `a-b-c.biopepa` model



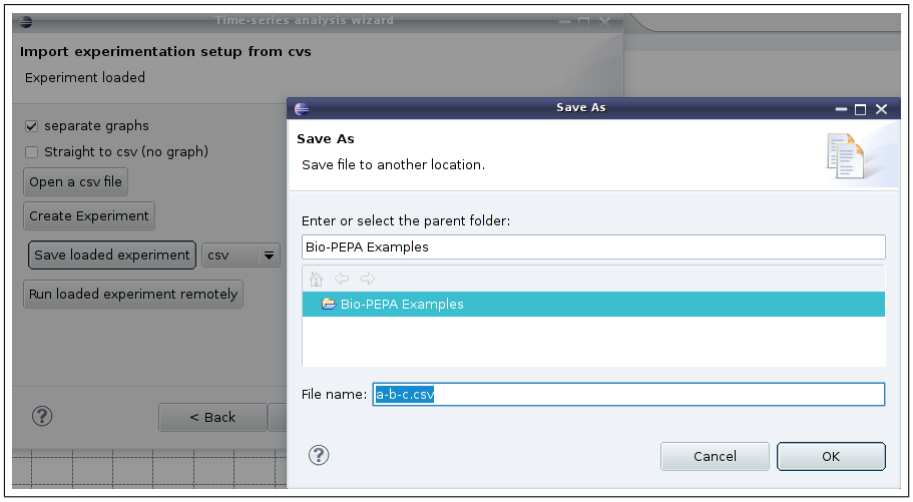
(b) The resulting graphs for the two different values of the $r1$ kinetic parameter

Figure 33: Varying the rate values

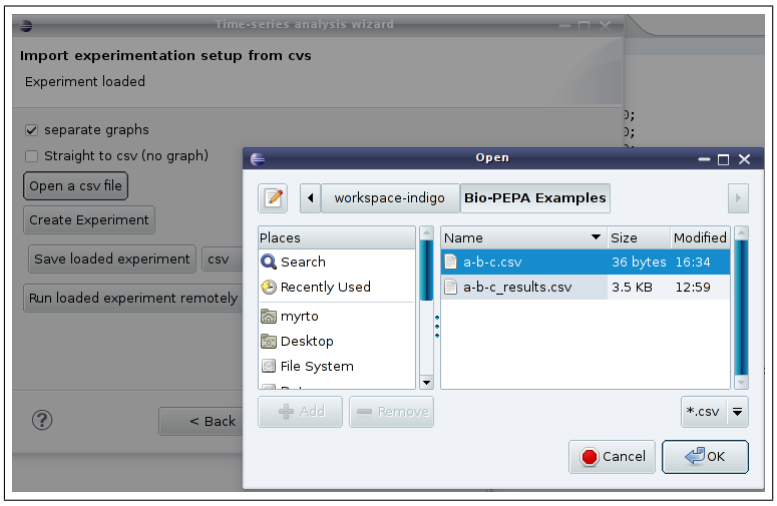
8.3 Saving and re-running an experiment

8.3.1 Saving an experiment in a .csv file and re-running it

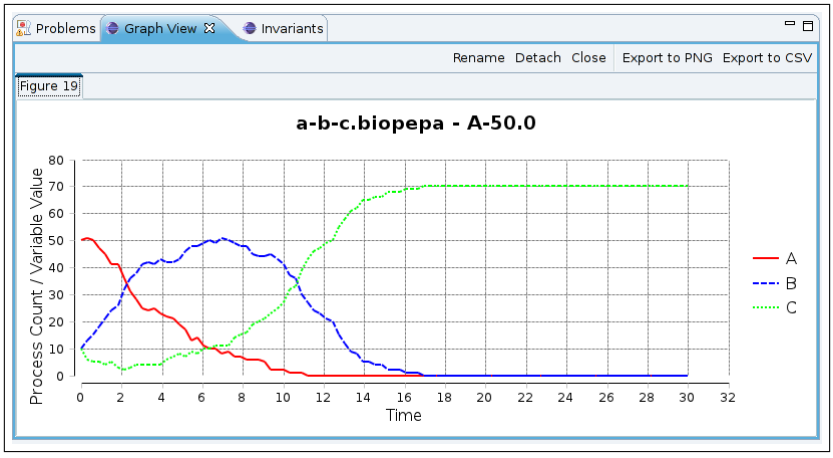
You have the option of saving a loaded experiment in a comma-separated values (`.csv`) file and running it again at a later time. After creating an experiment, you can click on *Save Loaded Experiment* and choose the `.csv` file format, as shown in Figure 34a. If you want to re-run your saved experiment later, you can click on *Open a .csv file*, select the file that contains your saved experiment and click on the *OK* button (see Figure 34b). Your experiment will then be re-run and the results plotted in the Graph View. In Figure 34c you can see the resulting graph from a re-run of a saved experiment on the `a-b-c.biopepa` model, where the initial population size of species A has been set to 50.



(a) Saving a loaded experiment as a `.csv` file



(b) Opening the saved experiment



(c) The resulting graph for the re-run experiment

Figure 34: Saving an experiment in a `.csv` format file and re-running it

8.3.2 Saving an experiment as a SED-ML file

You can also save a loaded experiment as a `SedML` (Simulation Experiment Discription Markup Language, for more information see [5, 27, 19]) file, i.e. in `.xml` format. After creating an experiment, you can click on *Save Loaded Experiment* and choose to save it as a `SED-ML` file, as shown in Figure 35.

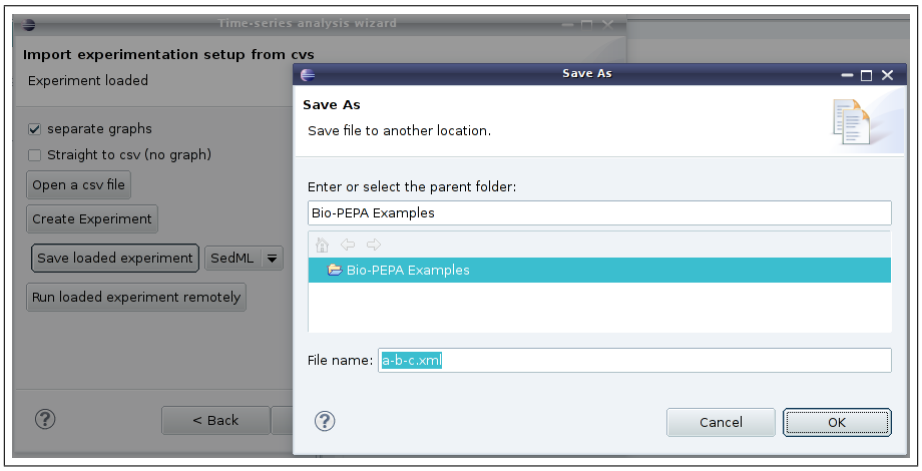


Figure 35: Saving a loaded experiment as a `SED-ML` file

8.4 Comparing with external data

As part of the Bio-PEPA Eclipse Plug-in experimentation feature, you can also import external data from a `.csv` file, or a Systems Biology Software Infrastructure (`SBSI`) format file (for more information on SBSI see [7]), i.e. an `.sbsidata` file and plot them along with the results of the Bio-PEPA analysis you are performing (see Figure 36).

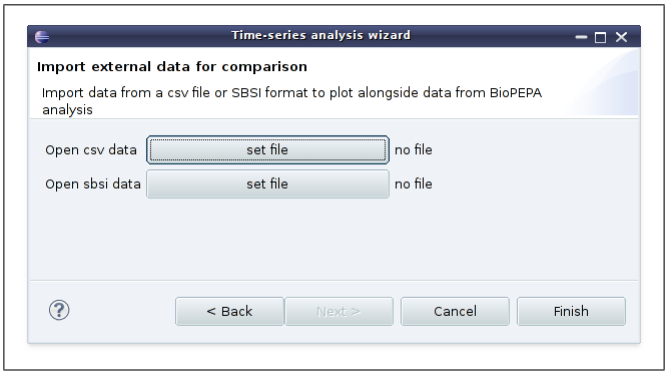
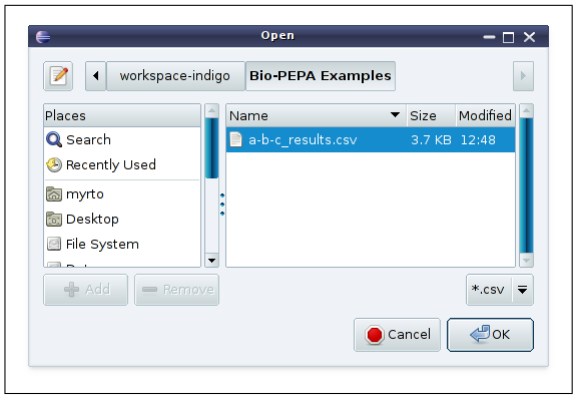


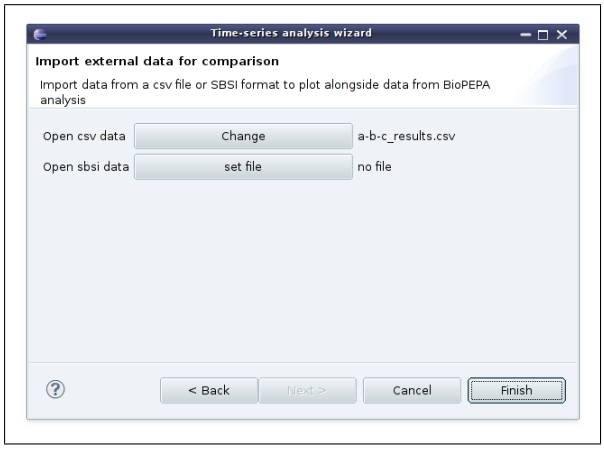
Figure 36: You can import data from external sources to compare against model results

8.4.1 Importing data from a .csv file

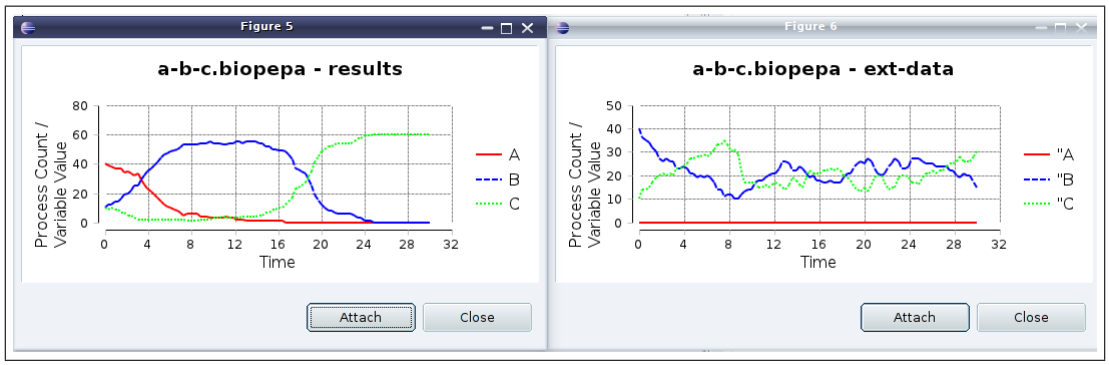
In order to take advantage of this feature, you have to set a comma-separated values (`.csv`) file to import data from, as shown in Figure 37a. As an example, here we are performing a simulation run of the `a-b-c.biopepa` model and importing data from a previous experiment on the same model, which we have stored in `a-b-c_results.csv`. Figure 37b shows the chosen `.csv` file, as it appears in the dialogue box. You may choose a different `.csv` file by clicking on the *Change* button. Clicking on the *Finish* button produses the resulting graphs from the simulation and the imported data. In our case the two graphs are shown in Figure 37c.



(a) Choosing a `.csv` file to import data from



(b) An external `.csv` file has been set

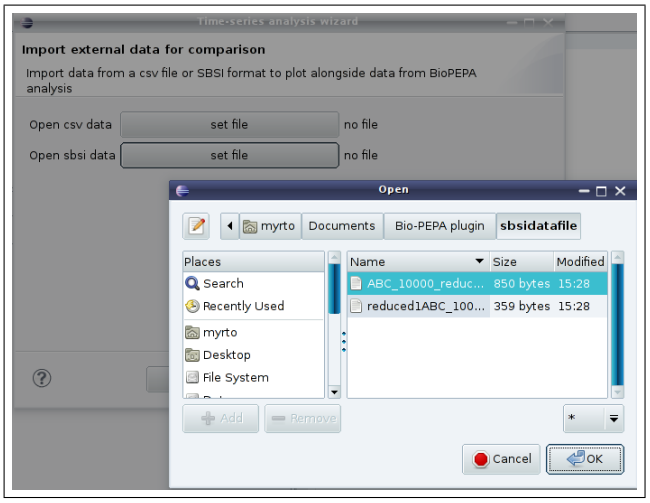


(c) The resulting graph for the simulation of the `a-b-c.biopepa` model, in comparison to the plotted imported data from the `a-b-c_results.csv` file

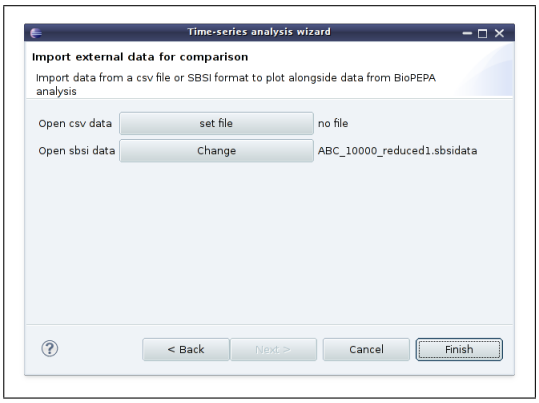
Figure 37: Importing data from a `.csv` format file

8.4.2 Importing data from a SBSI format file

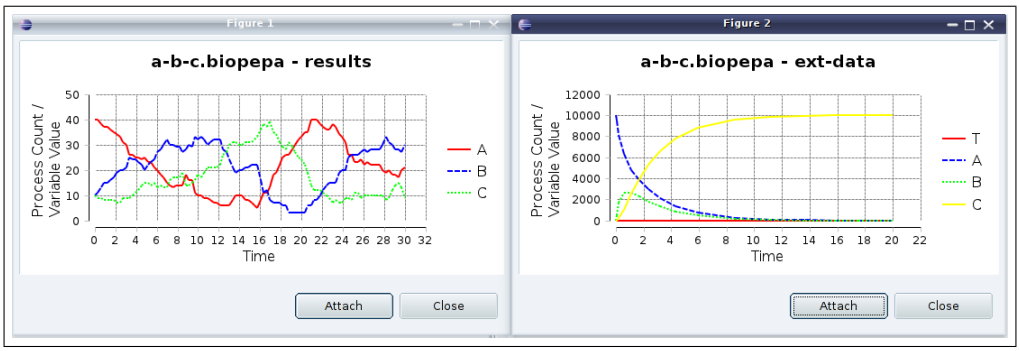
You have to set a Systems Biology Software Infrastructure (`SBSI`) format file (for more information on SBSI see [7]), i.e. a `.sbsidata` file to import data from, as shown in Figure 38a. Figure 38b shows the chosen `ABC_10000_reduced1.sbsidata` file, as it appears in the dialogue box. You may choose a different `.sbsidata` file by clicking on the *Change* button. Clicking on the *Finish* button produses the resulting graphs from the simulation and the imported data. In our case the two graphs are shown in Figure 38c.



(a) Choosing a `.sbsidata` file to import data from



(b) An external `.sbsidata` file has been set



(c) The resulting graph for the simulation of the `a-b-c.biopepa` model, in comparison to the plotted imported data from the `ABC_10000_reduced1.sbsidata` file

Figure 38: Importing data from a SBSI format file

9 PRISM Export

Another feature of the Bio-PEPA Eclipse Plug-in allows the translation of the Bio-PEPA model to a PRISM model. PRISM is a probabilistic model checker, a tool for formal modelling and analysis of systems that exhibit random or probabilistic behaviour. For more information on PRISM see [4, 20, 21, 23, 22]. The Bio-PEPA Eclipse Plug-in performs the translation and outputs a `.pm` PRISM file (see Figure 39). In the dialogue box that appears, the user is requested to set the level size for the Continuous-Time-Markov-Chain that will be produced. The Bio-PEPA Eclipse Plug-in can also output a `.csl` file that contains information on the properties of the model, if the user chooses to select that option.

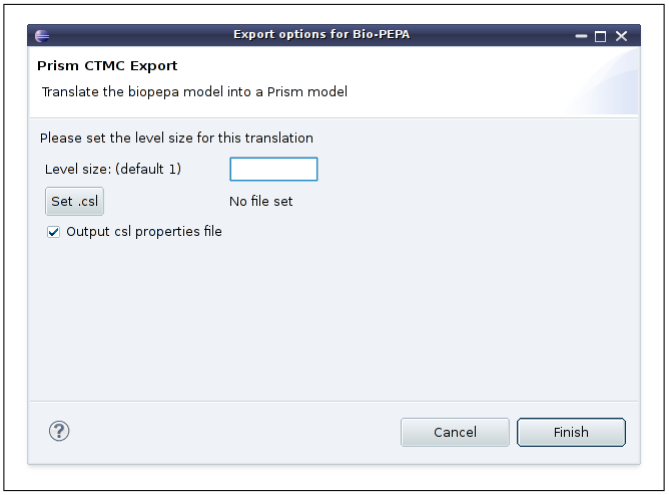


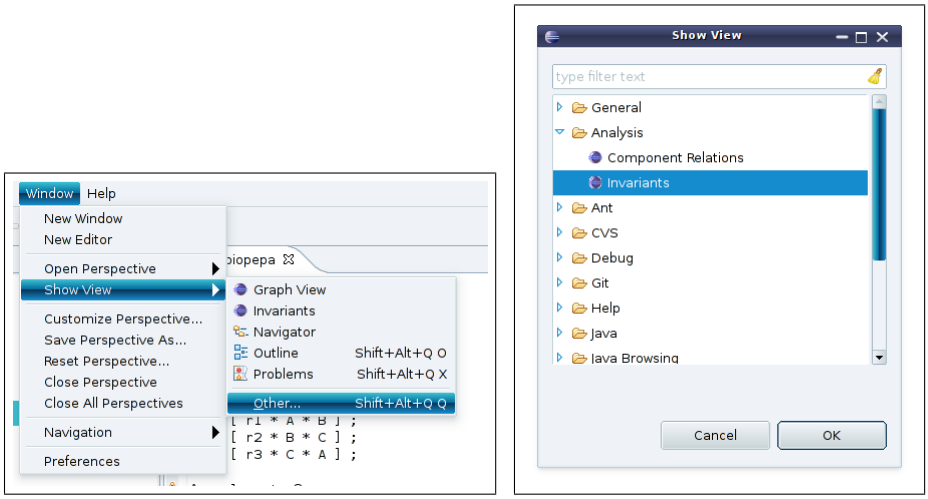
Figure 39: PRISM Export

10 Inference of Invariants

The Bio-PEPA Eclipse Plug-in allows you to infer invariants from your Bio-PEPA model. There are two types of invariants that can be infered from a Bio-PEPA model:

- *State invariants:* A sum of populations in the model that remains constant. For example, in a model that contains two species A and B, that are involved in only two reactions $A \rightarrow B$ and $B \rightarrow A$ the sum $A + B$ is constant.
- *Activity invariants:* A sequence of reactions that, once completed, returns the model to its initial state. For example, in the above model, the sequence of reactions $A \rightarrow B$, $B \rightarrow A$, leaves the model unchanged.

To perform inference of invariants for a model you should open the Invariants View by going to Window → Show View → Other (see Figure 40a). Then, in the dialogue box that appears, go to Analysis → Invariants (see Figure 40b) and click on the *OK* button.

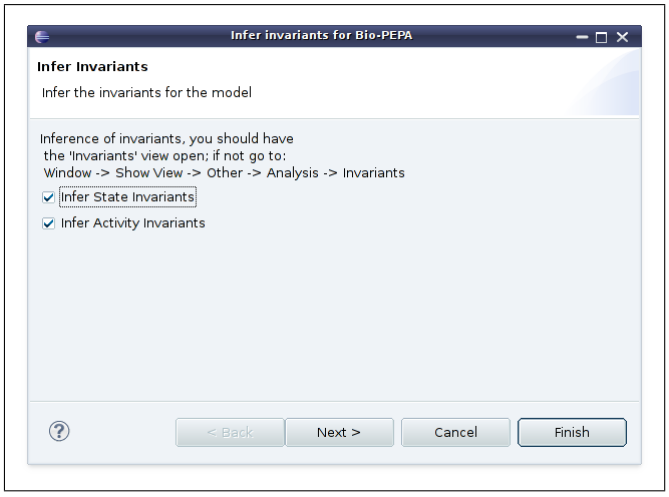


(a) Open a view (b) Choose the Invariants View

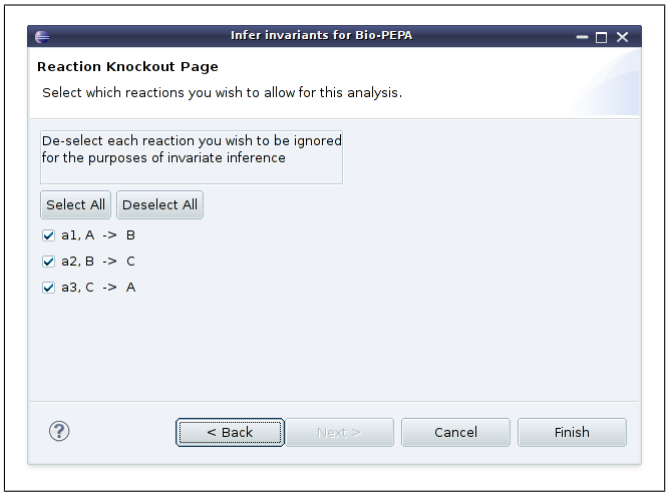
Figure 40: Opening the Invariants View

In order to present this option of the Bio-PEPA Eclipse Plug-in we will use the `a-b-c.biopepa` model described in section 8.1, from which both state and activity invariants can be infered.

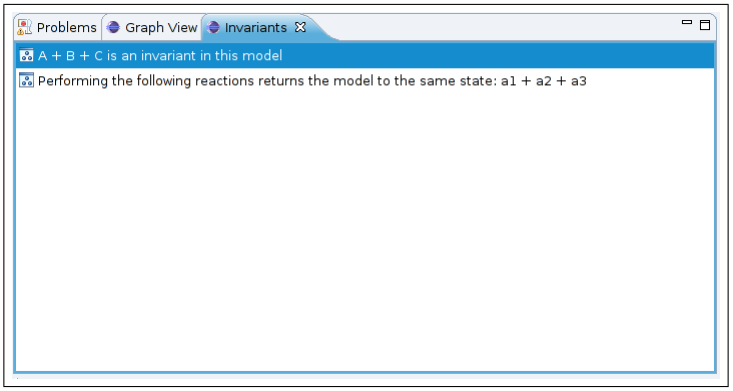
You must select the type of invariants, State or Activity, that you wish to infer from the model (see Figure 41a). Following that, you must select the reactions you wish to be included in the analysis (see Figure 41b). The results of the analysis for the `a-b-c.biopepa` model can be seen in Figure 41c.



(a) Selecting State and Activity Invariants to infer



(b) Choosing reactions to be included in the analysis



(c) Results of the invariants inference for the `a-b-c.biopepa` model

Figure 41: Infering State and Activity Invariants for the model

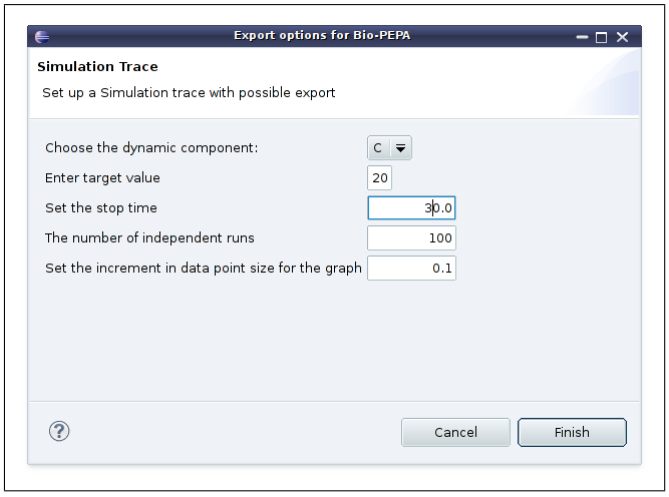
11 Simulation Distributions

Performing many stochastic simulations provides an opportunity to obtain many more statistics about a model. One possibility is to obtain the percentage of simulations for which some property is true at or before a given time t. The menu item Simulation Distributions opens a wizard which uses stochastic simulation to perform this kind of analysis.

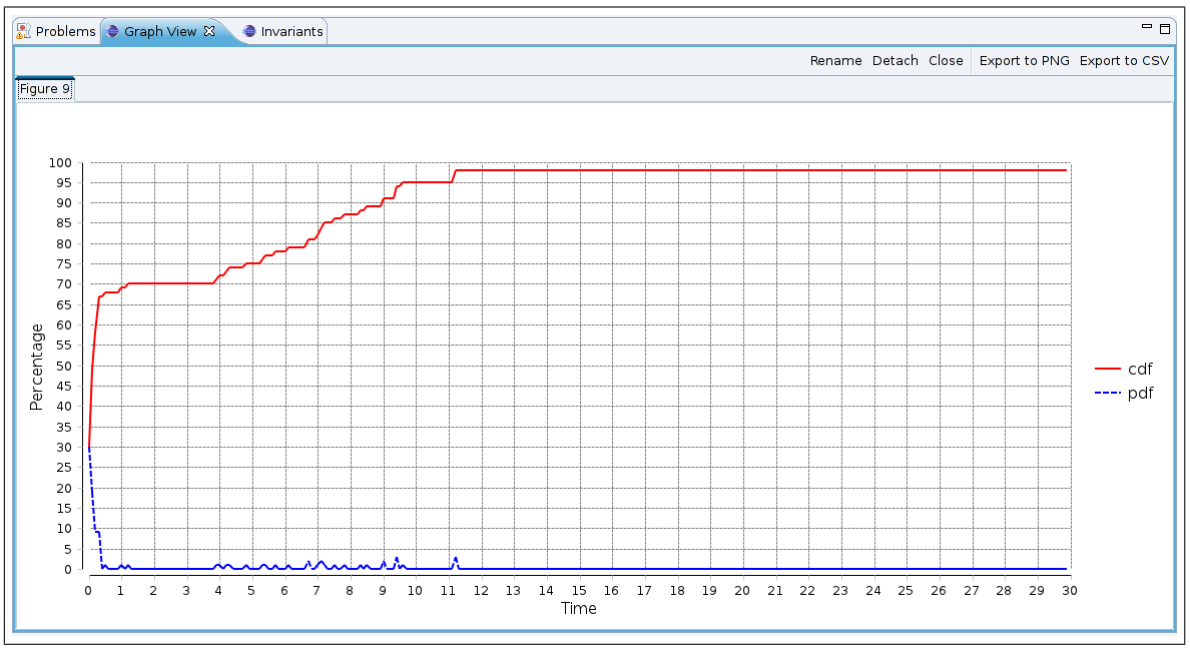
The condition which must be met in our case is that a chosen component reaches a prescribed population count. The Bio-PEPA Eclipse Plug-in allows you to set up a number of simulation runs and, based on the simulation data, plots the *Probability Distribution Function (pdf)* and the *Cumulative Distribution Function (cdf)* of any species in the model, with respect to the target population value. The most interesting of the two distributions is the *cdf*, which is plotted as a red line. The *cdf* shows the percentage of simulation runs in which the chosen species has reached the target population count, at or before a given time t. In order to take advantage of this feature of the Bio-PEPA Eclipse Plug-in you should set up the simulation by providing values for the following parameters (see Figure 42a):

- Dynamic component — The species with varying population size than you wish to monitor
- Target value — The condition which your model must meet, i.e. the population size your chosen component has to reach
- Stop time — The stop time for the simulation (model dependent)
- Number of independent runs — The number of times the simulation is to be run
- Increment in data point size for the graph — the time-difference between consecutive data points in the graph

The *pdf* and *cdf* for species C of the `a-b-c.biopepa` model, with a target value of 20, a stop time of 30, 100 independent runs and a 0.1 increment in data point size for the graph, can be seen in Figure 42b. The most interesting of the two distributions is the *cdf* (red line) which shows, at time t, in how many of the simulation runs the condition we have set is true, i.e. the population of C has reached the target value, at that time or before. For instance, in 95% of the simulation runs the population of C has reached the target value of 20 at or before 10s.



(a) Setting up a simulation distribution analysis



(b) Simulation distributions for species C of the `a-b-c.biopepa` model with a target value of 20

Figure 42: Simulation Distributions analysis example

12 Export Wizard

The Bio-PEPA Eclipse Plug-in export wizard translates your Bio-PEPA model to a Systems Biology Markup Language (SBML) model (see [6, 15]) for more information on SBML), as shown in Figure 43 and produces an `.xml` export file.

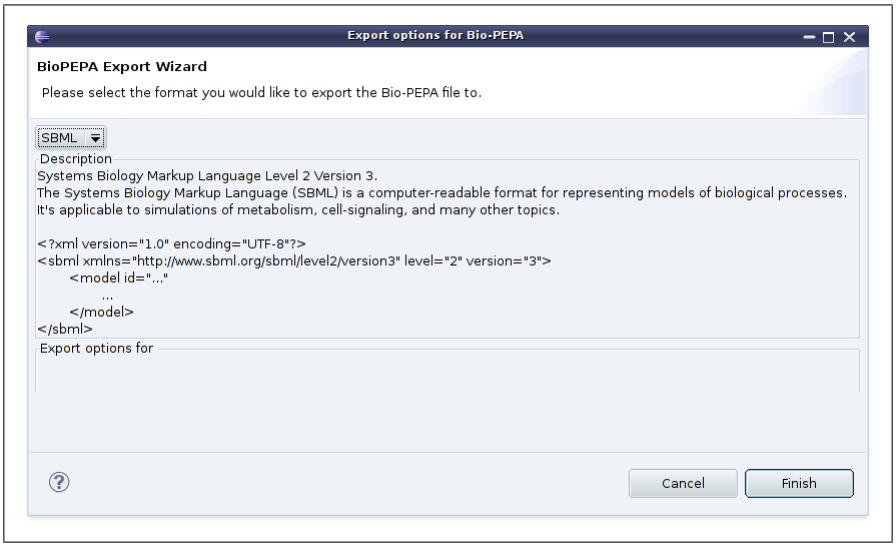


Figure 43: Export Wizard

13 Simulation Trace

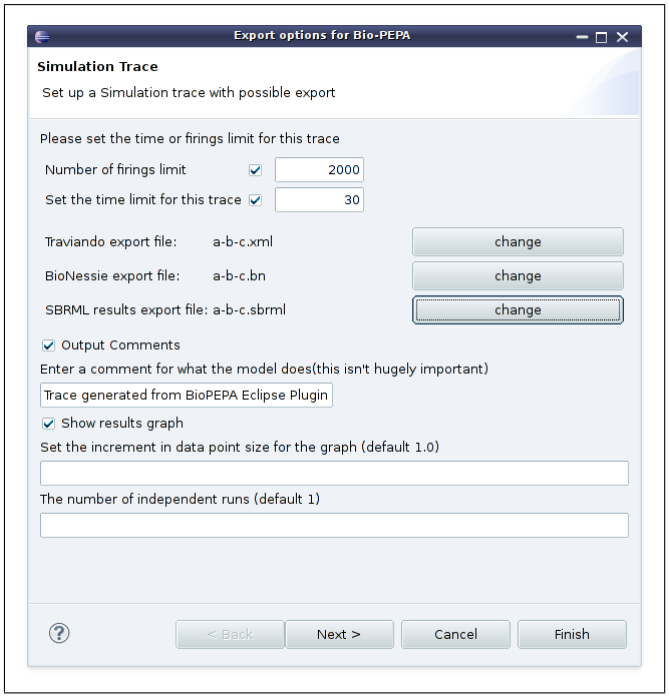
The Simulation Trace option allows the user to set up the parameters for a simulation run (or a number of independent simulation runs) and export the simulation trace to three different types of files, namely:

- *Traviando export file (`.xml` file)*— export file for Traviando, a trace analyzer and visualizer for simulation traces of discrete event dynamic systems (see [8, 18, 16, 17, 24, 12, 26, 13, 9] for more information on Traviando)
- *BioNessie export file (`.bn` file)*— export file for BioNessie, a free, state-of-the-art platform-independent biochemical networks simulation and analysis software environment (see [2, 25] for more information on BioNessie)
- *SBRML results export file (`.sbrml` file)*— results export file for Systems Biology Markup Language (SBML) (see [6, 15] for more information on SBML)

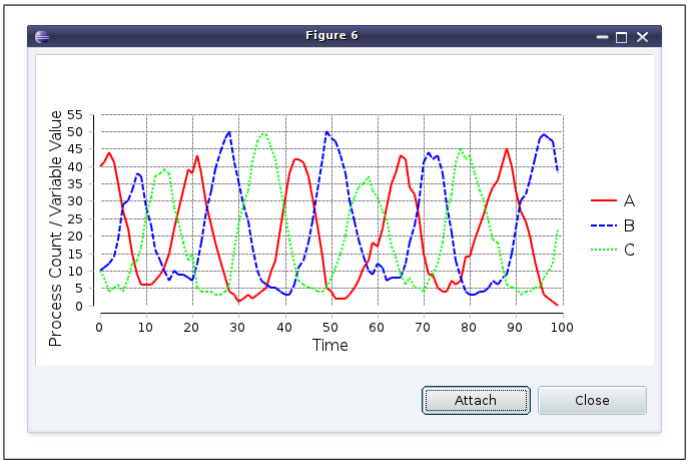
In order to set up the simulation the user is allowed to set several parameters (see Figure 44a):

- Number of firings limit — A limit to the number of reactions that can occur (optional)
- Time limit for the trace — The stop time of the simulation (optional)
- Output comments - Enter a comment — If the user checks the output comments checkbox they are allowed to add a comment to the export file concerning the function of the model
- Show results graph - Set the increment in data point size for the graph — If the user checks the appropriate checkbox the results of the simulation are plotted in a graph. In this case the user can set the time difference between consecutive data points in the graph (default value 1.0)
- Number of independent runs — The number of simulation traces to be produced (default value 1)

The simulation set up for the `a-b-c.biopepa` model, as shown in Figure 44a, produces three export files, the `.bn` BioNessie export file, the `.sbrml` SBML results export file and the `.xml` Traviando export file. The simulation trace data are also plotted in a graph, as shown in Figure 44b.



(a) Setting up a simulation for the `a-b-c.biopepa` model



(b) Graph results of the simulation for the `a-b-c.biopepa` model

Figure 44: Simulation Trace

A The Bio-PEPA plugin syntax

This is a brief overview of the basic elements of the Bio-PEPA Eclipse Plug-in syntax and is by no means comprehensive. For more information on the Bio-PEPA Eclipse Plug-in syntax and its differences with Bio-PEPA see [14, 11].

A biological system can be encoded as a Bio-PEPA model by way of a 6-tuple [14]:

$$\langle V, N, K, F_R, Comp, P \rangle$$

where:

- V is the set of locations
- N is the set of species attributes
- K is the set of parameter definitions
- F_R is the set of functional rates
- $Comp$ is the set of species components
- P is the model component

The following sections will explain this definition by describing its constituent elements in more detail. Sections A.7 - A.10 will offer examples of models defined using the Bio-PEPA language and the Bio-PEPA Eclipse Plug-in syntax.

A.1 Locations

Each location must encode an identifier, the parent location, the size of the location ($s \in R$), the type the location represents and the step-size ($H \in N^\star$) for the location [14].

The concrete syntax, as accepted by the plug-in is as follows (angular brackets ($\langle\ \rangle$) denote optional parts in the definition):

$$\mathsf{location}\ ID\ \langle \mathsf{in}\ parentID \rangle : \mathsf{size} = value\ \langle,\ \mathsf{step} - \mathsf{size} = value \rangle\ \langle,\ \mathsf{type} = \{\mathsf{membrane}, \mathsf{compartment}\} \rangle;$$

The keyword location labels the purpose of this definition. The keyword must be proceeded by the ID for this new location. If the model defines multiple locations, the spatial location can be specified by adding the keyword in and the ID for the parent. The size is the only required property in the location definition (where $value \in R$), while the type is optional as it defaults to compartment. The step-size ($value \in N^*$) is only required if performing analysis of a Bio-PEPA model with levels (for more details see [11]). If no locations are defined the default location is used, which is a compartment labelled main with size equal to one [14]. As an example, in sections A.8 - A.10, in the Unidireactional and Bidirectional Transportation examples, there are two locations specified:

```
location main           :  size = 2, type = membrane;
location child in main  :  size = 1;
```

The first location is a membrane of size 2 with ID *main* and the second is a compartment with ID *child* and size equal to 1. In the second definition, the *type* is not declared as it defaults to compartment.

A.2 Species Attributes

The concrete syntax for the species attributes, as accepted by the plug-in is as follows [14]:

$$\mathsf{species}\ speciesID : \mathsf{upper} = value\ \langle,\ \mathsf{lower} = value \rangle;$$

where $speciesID$ is one of the following [14]:

- **speciesID** Referring to just the species identifier is seen as a global reference. If a species can exist in three locations and a reaction is stated in terms of the species, then the reaction is assumed to be defined as occurring in all three locations independently of each other.
- **speciesID@locationID** This allows a reference to a specific species in a specific location. If a reaction is defined in this manner it will not be enabled in other locations that the species can exist in.
- **speciesID@locID$_1$, ..., locID$_n$** If a reference to a species in more than one location, but not all, is required then a comma delimited list can be used. This allows fine-grained control over where the definition in question is applicable.

The only required attribute in the definition is the upper bound ($value \in N^\star$), as the default lower bound is the value zero. If an improved lower bound is known then it can also be specified ($value \in N^\star$) [14].

Some examples of species attribute definition for a species S follow:

```
species S             :  upper = 40, lower = 10;
species S@main        :  upper = 40, lower = 10;
species S@main,child  :  upper = 40, lower = 10;
```

In the first definition species S is defined globally, while in the following definitions it is defined in specific locations (`S@main, S@main,child`).

A.3 Parameter Definitions

The concrete syntax for parameter definitions, as accepted by the plug-in, is as follows [14]:

$$ID = expression;$$

where

$$\begin{aligned} expression = \ & int \mid float \mid ID \mid speciesID \mid (expr) \mid expr + expr \mid \\ & expr - expr \mid expr/expr \mid expr * expr \end{aligned}$$

An *expression* is any standard mathematical expression with the definition structured as it is because of the recursive nature of the expression (*expr* is an abbreviation for expression, and not a different set of allowable expressions). Also, $speciesID$ must refer to a species in a single location if multiple locations are specified [14]. Some examples of parameter definitions are shown below:

```
r  =  1.0;
r  =  A - B;
r  =  A@main + B;
```

where A, $A@main$ and B are $speciesID$s.

A.4 Functional Rates

The concrete syntax for the functional rates, as accepted by the plug-in, is as follows [14]:

$$\mathsf{kineticLawOf}\ ID : expression';$$

or

$$ID = [\ expression'\ ];$$

where $expression'$ extends the previous expression statement (see section A.3) to also include pre-defined kinetic rates as shown in [14]:

$$expression' = expression \mid \mathsf{fMA}(expr) \mid \mathsf{fMM}(expr, expr)$$

where fMA and fMM stand for mass-action and Michealis-Menten, respectively; additional functions specific to commonly found rates in the biological domain [14]:

- **Mass-action** takes one parameter, r, with the overall rate for the reaction being the product of the rate and the population counts of all the reactants and modifier species involved in the reaction e.g. fMA(r), where the reaction involves species S_1 and S_2 which interact to form S_3 , would equate to a rate of $r * S_1 * S_2$ (assuming stoichiometric coefficients of one). If instead the reaction only involved S_1 as a reactant then the corresponding rate would be $r * S_1$.
- **Michaelis-Menten** takes two parameters, v_M and K_M and requires a set number of species to perform specific roles within the reaction. One species is required to act as a reactant (S), another as the enzyme (E) and the last as the product (P). The ordering of the parameters, along with the associated rate can be seen below.

$$\mathsf{fMM}(v_M, K_M) = \frac{v_m * S * E}{K_M + S}$$

Some examples of functional rates definitions are shown here:

```
a1               =  [ r1 * A * B ];   from a-b-c.biopepa model
kineticLawOf a1  :  r1 * A * B;       equivalent definition

a1               =  [ fMA(r1) ];      mass-action kinetics example
kineticLawOf a1  :  fMA(r1);          equivalent definition

a1               =  [ v/(KM+P2) ];    Michaelis-Menten kinetics example
kineticLawOf a1  :  v/(KM+P2);        equivalent definition
```

In later sections (A.7 - A.10), we will see more examples of both mass-action and Michaelis-Menten kinetics (see section A.8 and section A.10), as well as other functional rates definitions.

A.5 Species Components

The species component definition, lists all the reactions a particular species is allowed to participate in and in what role. The list of actions are separated by the choice operator (+). The concrete syntax, as accepted by the plug-in, is as follows [14]:

$$ID = S;$$

where $S = action \mid S + S$

and where an *action* is defined as:

$$\begin{aligned} action \;=\; & (rateID,\ stoichiometry)\ op\ speciesID;\ \mid rateID\ op\ speciesID;\ \mid \\ & (\ rateID\ [\ locationID\ op'\ locationID\ ],\ stoichiometry\ )\ (.)\ ID;\ \mid \\ & rateID\ [\ locationID\ op'\ locationID\ ]\ (.)\ ID; \end{aligned}$$

with

$$op \in \{>>, <<, (+), (), (.)\}$$

and

$$op' \in \{->, <-\}.$$

The first ID refers to a species, but in this particular definition is labelled as an ID to make it distinct from the the other species identifiers expected within a single species component definition. This identifier must take the first *speciesID* form of just the species name with no location. Thus, each global species can have at most one definition, with the *speciesID* used to allow control over where a particular action is permissible. In the case of non-transport definitions, i.e. the first two in the

action definition, the *speciesID* can take any of the previously defined forms. Thus a single reaction can be defined as occurring in the global sense for the species, in a single location, or in a subset of the locations where the species is present [14]. If a reaction occurs in the global sense for the species, then the *speciesID* identifier may be ommited. For example, in the species components definitions of the `a-b-c.biopepa` model (see Figure 28a), the *speciesID* identifier after the operation symbol has been ommited in all of the reactions, as they occur in the global sense :

```
A = a1 << + a3 >> ;
```

This is equivalent to:

```
A = a1 << A + a3 >> A;
```

The identifiers labelled *rateID* must refer to a previously defined functional rate. Additionally, *stoichiometry* is the stoichiometric coefficient for the species in this reaction($stoichiometry \in N^{\star}$). If a statement does not specify a stoichiometric coefficient, the default value of one is used. The definition for *action* shows the syntax for including the stoichiometric coefficient and the abbreviated form for when the stoichiometry is one, these being the first two forms shown in the action definition above [14]. For example, in the species components definitions of the `a-b-c.biopepa` model (see Figure 28a), the stoichiometric coefficient has been omitted, since it has the value of 1 in all cases:

```
A = a1 << + a3 >> ;
```

This is equivalent to:

```
A = (a1,1) << + (a3,1) >> ;
```

And also equivalent to:

```
A = (a1,1) << A + (a3,1) >> A;
```

Transportation represents the movement of a single species between two adjacent locations within the model, as described in [10]. In the defined syntax above (third and fourth action definitions) it requires two *locationIDs*, the first acting as the source and the second as the target and must refer to locations that this particular species resides in. As the locations are embedded within the transportation action, the identifier is simply the species name. The general modifier operator (`(.)`) is used for transportation as, while the levels of the species in the two locations change, the overall amount does not. Transportation can either be in a single direction or in both directions (unidirectional or bidirectional transportation respectively) [14]. For an example of the unidirectional and the bidirectional transportation see section A.9 and section A.10, respectively.

For the Bio-PEPA Eclipse Plug-in user's convenience, many of the original Bio-PEPA mathematical symbols have been replaced with textual representations that are available on every keyboard. Table 1 contains the Bio-PEPA symbols and their ASCII representations in the Bio-PEPA Eclipse Plug-in [14]:

Behaviour	BioPEPA symbol	ASCII representation
reactant	$\uparrow$	`<<`
product	$\downarrow$	`>>`
activator	$\oplus$	`(+)`
inhibitor	$\ominus$	`(-)`
modifier	$\odot$	`(.)`
unidirectional transportation	$\rightarrow$	`->`
bidirectional transportation	$\leftrightarrow$	`<->`

Table 1: Bio-PEPA mathematical symbols and Bio-PEPA Eclipse Plug-in symbol representation

A.6 Model Component

The model component is always the final definition in a Bio-PEPA model. A distinction has to be made between the model component definition and labelled compositional definitions. To offer compositionality the tool needs to accept fragments of the model component and allow the assigning of a label for reference. Essentially the definitions are nearly identical, with the difference being the assignment of an identifier and the use of the termination symbol. The concrete syntax for labelled compositional definitions, as accepted by the plug-in is as follows [14]:

$$ID ::= P;$$

where

$$P = ID \mid (P) \mid P < L > P \mid speciesID[value] \;)$$

where

Behaviour	BioPEPA symbol	ASCII representation
cooperation	$\underset{L}{\bowtie}$	`<L>`

Table 2: Bio-PEPA mathematical symbols and Bio-PEPA Eclipse Plug-in cooperation symbol

Unlike the model component, labelled compositional definitions require an identifier for reference in the model component. The assignment symbol differs here from other definitions, taking the form of ::= which uniquely identifies the definition type. The compositional fragment comes next, taking one of the forms described above. It can consist of an identifier for another labelled compositional definition, single species or the synchronisation of several species or identifiers [14].

The term `P < L > Q` denotes *cooperation* between P and Q over the *cooperation set* L, that determines those activities on which the cooperands are forced to synchronise. For action types not in L, the components proceed independently and concurrently with their enabled activities [11]. The *cooperation set*, indicated by the symbol L, can either be the wildcard token ($\star$) or a comma delimited list of actions [14].

The model component follows the same syntax as the labelled compositional definition without the assignment or the terminator symbol. In the syntax above, the model component is simply P [14].

An example of a model component definition was the one in the `a-b-c.biopepa` model (see Figure 28a):

```
A[initial_A] <*> B[initial_B] <*> C[initial_C]
```

where `<*>` denotes *cooperation* between the species over all reactions, since the *cooperation set* is the wildcard token ($\star$), and *initial_A*, *initial_B* and *initial_C* are variables that hold the species initial population counts.

We will see several more examples of model component definitions in sections A.7 - A.10.

A.7 Syntax Example: The Enzyme-Substrate model - Reactant and Product

In this example (see Table 3), an enzyme E combines with a substrate S to form a compound E:S. This compound might degrade releasing the enzyme and the substrate or it might convert the substrate into product P, releasing the enzyme (In the Bio-PEPA Eclipse Plug-in editor the two parallel diagonal lines (//) denote comments). The Outline View of the model is shown in Figure 45. According to the species components definition:

- E — is a reactant (↓, <<) in reaction r_1 and a product (↑, >>) in reactions rm_1 and r_2
- S — is a reactant (↓, <<) in reaction r_1 and a product (↑, >>) in reaction rm_1
- $E : S$ — is a product (↓, <<) in reaction r_1 and a reactant (↑, >>) in reactions rm_1 and r_2
- P — is a product in reaction r_2

The Bio-PEPA syntax	`//The Bio-PEPA plugin syntax`
Parameter Definitions:	`//Parameter Definitions`
$k_1 = 0.01;$	`k1 = 1.0;`
$km_1 = 0.01;$	`km1 = 0.1;`
$k_2 = 0.01;$	`k2 = 0.01;`
Functional Rates	`//Functional Rates`
$r_1 = k_1 * E * S;$	`r1 = [ k1 * E * S ];`
$rm_1 = km_1 * E : S;$	`rm1 = [ km1 * E:S ];`
$r_2 = k_2 * E : S;$	`r2 = [ k2 * E:S ];`
Species Components	`//Species Components`
$E \stackrel{def}{=} (r_1, 1) \downarrow E + (rm_1, 1) \uparrow E + (r_2, 1) \uparrow E$	`E = r1 << + rm1 >> + r2 >> ;`
$S \stackrel{def}{=} (r_1, 1) \downarrow S + (rm_1, 1) \uparrow S$	`S = r1 << + rm1 >> ;`
$E : S \stackrel{def}{=} (r_1, 1) \uparrow E : S + (rm_1, 1) \downarrow E : S + (r_2, 1) \downarrow E : S$	`E:S = r1 >> + rm1 << + r2 << ;`
$P \stackrel{def}{=} (r_2, 1) \uparrow P$	`P = r2 >> ;`
Model Component	`//Model Component`
$E[40] \underset{*}{\bowtie} S[30] \underset{*}{\bowtie} E : S[0] \underset{*}{\bowtie} P[0]$	`E[40] <*> S[30] <*> E:S[0] <*> P[0]`

Table 3: Bio-PEPA mathematical syntax and Bio-PEPA Eclipse Plug-in syntax for the Enzyme-Substrate model

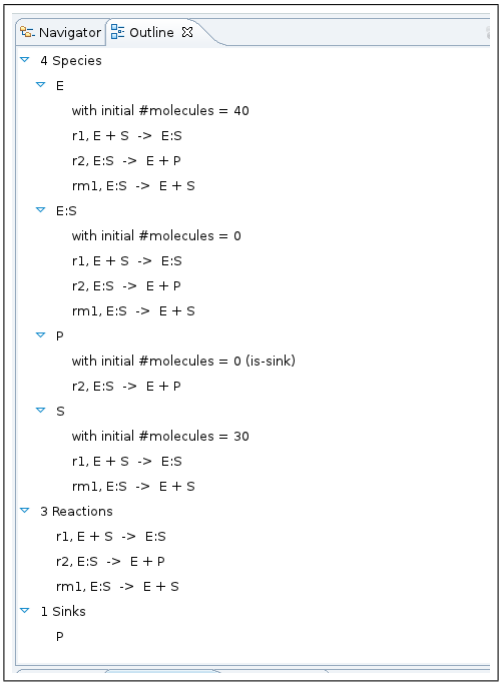


Figure 45: The Outline View of the Enzyme-Substrate model

A.8 Syntax Example: Activator and Inhibitor

As an example, we will use a model of a general genetic network with a negative feedback through dimmers (see Figure 46).

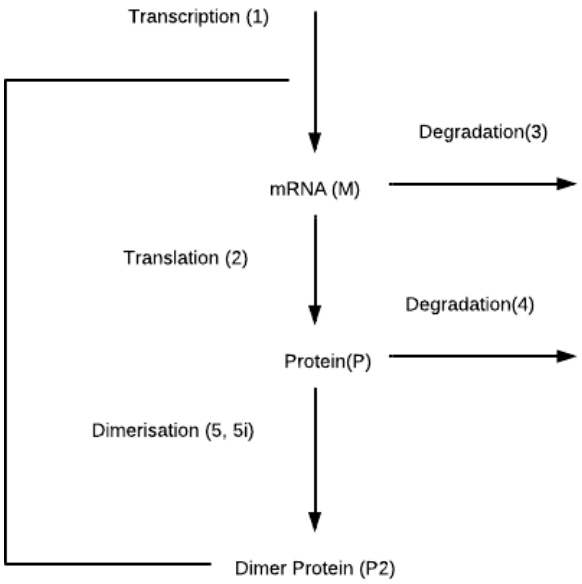


Figure 46: Genetic Network model

The model, which is shown in Table 4, is composed of three biological entities that interact with each other through five reactions (of which one is reversible). The biological entities are the mRNA molecule (M), the protein in monomer form (P) and the protein in dimeric form ($P2$). The first reaction (1) is the transcription of the mRNA (M) from the genes/DNA (not considered explicitly). The protein P in the dimer form ($P2$), which is the final result of the network, has an inhibitory effect ($\ominus$, `(-)`) on this process. The second reaction (2) is the translation of the protein P from M, in which M acts as an

activator ($\oplus$, (+)). The other two reactions represent the degradation of M (3) and the degradation of P (4). Finally there is the dimerization of P and its inverse process (5, 5i). All the reactions are described by mass-action kinetics with the exception of the first reaction, which has a Michaelis-Menten kinetics [11] (see section A.4 for more information on mass-action and Michaelis-Menten kinetics) .

The Outline View of the model can be seen in Figure 47.

The Bio-PEPA syntax	`//The Bio-PEPA plugin syntax`
Locations:	`//Locations`
$v_{cell} : 1(nM)^{-1}$	`location v_cell:  size = 1;`
Parameter Definitions	`//Parameter Definitions`
$K_M = 356nM;$	`KM = 356;`
$v = 2.19s^{-1};$	`v = 2.19;`
$k_2 = 0.043s^{-1};$	`k2 = 0.043;`
$k_3 = 0.039s^{-1};$	`k3 = 0.039;`
$k_4 = 0.0007s^{-1};$	`k4 = 0.0007;`
$k_5 = 0.025s^{-1};$	`k5 = 0.025;`
$k_{5_i} = 0.5s^{-1};$	`k5i = 0.5;`
Species Attributes	
$M : H = 1, N = 1, V = v_{cell}, unit = nM;$	
$P : H = 30, N = 2, V = v_{cell}, unit = nM;$	
$P2 : H = 30, N = 6, V = v_{cell}, unit = nM;$	
Functional Rates	`//Functional Rates`
$f_{\alpha_1} = \frac{v}{K_M + P2};$	`a1 = [v/(KM+P2)];`
$f_{\alpha_2} = fMA(k2);$	`a2 = [fMA(k2)];`
$f_{\alpha_3} = fMA(k3);$	`a3 = [fMA(k3)];`
$f_{\alpha_4} = fMA(k4);$	`a4 = [fMA(k4)];`
$f_{\alpha_5} = fMA(k5);$	`a5 = [fMA(k5)];`
$f_{\alpha_{5_i}} = fMA(k5i);$	`a5i = [fMA(k5i)];`
Species Components	`//Species Components`
$M \stackrel{def}{=} (\alpha_1, 1) \uparrow M + (\alpha_2, 1) \oplus M + (\alpha_3, 1) \downarrow M$	`M = a1 >> + a2 (+) + a3 << ;`
$P \stackrel{def}{=} (\alpha_2, 1) \uparrow P + (\alpha_4, 1) \downarrow P + (\alpha_5, 2) \downarrow P + (\alpha_{5_i}, 2) \uparrow P$	`P = a2 >> + a4 << + (a5,2) << + (a5i,2) >>;`
$P2 \stackrel{def}{=} (\alpha_1, 1) \ominus P2 + (\alpha_5, 1) \uparrow P2 + (\alpha_{5_i}, 1) \downarrow P2$	`P2 = a1 (-) + a5 >> + a5i <<;`
Model Component	`//Model Component`
$M[0] \underset{\alpha_2}{\bowtie} P[0] \underset{\alpha_5, \alpha_{5_i}}{\bowtie} P2[0]$	`M[0] <a2> P[0] <a5, a5i> P2[0]`

Table 4: Bio-PEPA mathematical syntax and Bio-PEPA Eclipse Plug-in syntax for the Genetic Network model

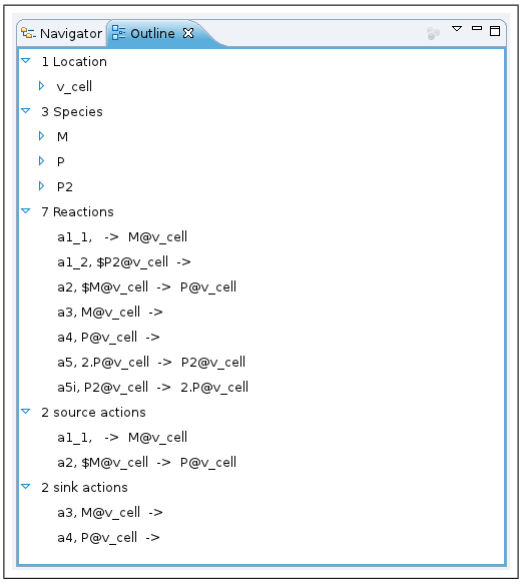


Figure 47: The Outline View of the Genetic Network model

A.9 Syntax Example: Unidirectional Transportation, Modifier

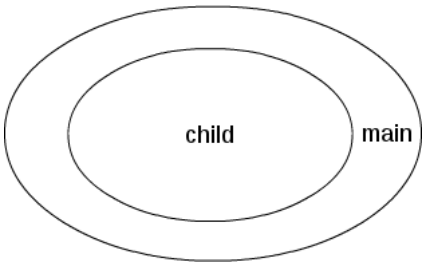


Figure 48: Locations of the model

The model shown in Table 5 has two locations, the parent location which is called *main* and is a membrane, and the *child* location which is a compartment enclosed by the membrane (see Figure 48). In the definition of location *child*, the *type* is not declared as it defaults to compartment. The model contains two species A and B. Species A is originally located in membrane *main* ($A@main$). Species A is involved in the *tr* reaction, which is a unidirectional transportation reaction ($\rightarrow$, `->`) representing the movement of species A from membrane *main* to compartment *child*. It is governed by a kinetic parameter r_1, which controls the rate of the transportation. Parameter r_1 has been given the constant value of 0.01. The rate of *tr* also depends on the quantity of A available in *main* ($A@main$). Moreover, species $A@child$ and B are involved in the *re* reaction, which takes plase in compartment *child*. The rate of *re* is governed by kinetic parameter r_2 which has been given the constant value of 0.01. The rate of *tr* also depends on the quantity of A available in compartment *child* ($A@child$). The quantity of species B that is produced is located in *child*, where *re* takes place.

As we can see, in the species components definition the general modifier operator ($\odot$, `(.)`) is used for transportation as, while the levels of species A in the two locations change, the overall amount does not.

The Outline View of the model can be seen in Figure 49.

The Bio-PEPA syntax	`//The Bio-PEPA plugin syntax`
Locations:	`//Locations`
$L = [child : 1(nM)^{-1}, C;$	`location child in main :  size = 1;`
$\quad main : 2(nM)^{-1}, M;]$	`location main :  size = 2, type = membrane;`
Parameter Definitions	`//Parameter Definitions`
$r_1 = 0.01;$	`r1 = 0.01;`
$r_2 = 0.01;$	`r2 = 0.01;`
	`//Variables for the species initial populations`
	`Am = 100;`
	`Ac = 0;`
	`B = 0;`
Functional Rates	`//Functional Rates`
$f_{tr} = [r_1 * A@main];$	`tr = [r1 * A@main];`
$f_{re} = [r_2 * A@child];$	`re = [ r2 * A@child];`
Species Components	`//Species Components`
$A \stackrel{def}{=} (tr[main \rightarrow child], 1) \odot A + (re, 1) \downarrow A$	`A = tr[main->child] (.)  A + re << A@child;`
$B \stackrel{def}{=} (re, 1) \uparrow B$	`B = re >>;`
Model Component	`//Model Component`
$A@main[100] \underset{tr}{\bowtie} A@child[0] \underset{re}{\bowtie} B@child[0]$	`A@main[Am]<tr>A@child[Ac]<re>B@child[B]`

Table 5: Bio-PEPA mathematical syntax and Bio-PEPA Eclipse Plug-in syntax for the Unidirectional Transportation model

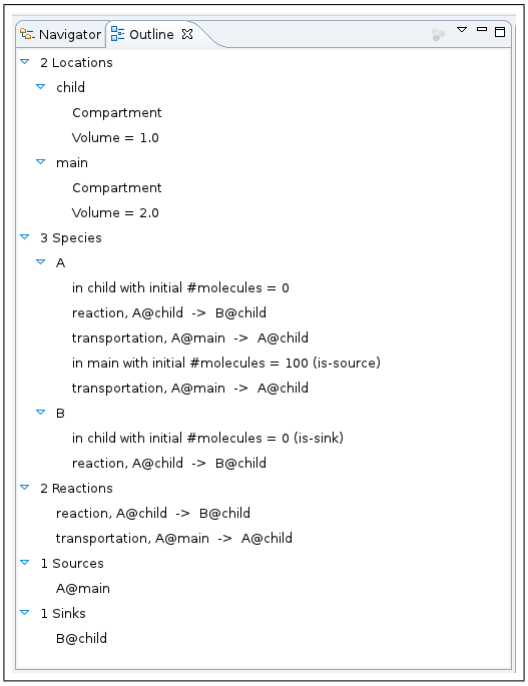


Figure 49: The Outline View of the Unidirectional Transportation model

A.10 Syntax Example: Bidirectional Transportation, Modifier

The model shown in Table 6 has two locations, the parent location which is called *main* and is a membrane, and the *child* location which is a compartment enclosed by the membrane (see Figure 48). In the definition of location *child*, the *type* is not declared as it defaults to compartment. The model contains two species A and B. Species A is originally located both in membrane *main* ($A@main$) and in compartment *child* ($A@child$). Species A is involved in the *tr* reaction, which is a bidirectional transportation ($\leftrightarrow$, `<->`) reaction representing the movement of species A from membrane *main* to compartment *child* and vice versa. The *tr* reaction is described by mass-action kinetics ($fMA(r_1)$), where r_1 is a kinetic parameter that has been given the constant value of 0.01 (see section A.4 for more information on mass-action kinetics). Moreover, species $A@child$ and B are involved in the *re* reaction, which takes plase in compartment *child*. The rate of *re* is governed by kinetic parameter r_2 which has been given the constant value of 0.01. The rate of *tr* also depends on the quantity of A available in compartment *child* ($A@child$). The quantity of species B that is produced is located in *child*, where *re* takes place.

In the species components definition, the general modifier operator ($\odot$, `(.)`) is used for transportation as, while the levels of species A in the two locations change, the overall amount does not.

The Outline View of the model can be seen in Figure 50.

The Bio-PEPA syntax	`//The Bio-PEPA plugin syntax`
Locations:	`//Locations`
$L = [child : 1(nM)^{-1}, C;$	`location child in main :  size = 1;`
$\quad main : 2(nM)^{-1}, M;]$	`location main :  size = 2, type = membrane;`
Parameter Definitions	`//Parameter Definitions`
$r_1 = 0.01;$	`r1 = 0.01;`
$r_2 = 0.01;$	`r2 = 0.01;`
	`//Variables for the species initial populations`
	`Am = 100;`
	`Ac = 100;`
	`B = 0;`
Functional Rates	`//Functional Rates`
$f_{tr} = [fMA(r_1)];$	`tr = [fMA(r1)];`
$f_{re} = [r_2 * A@child];$	`re = [ r2 * A@child];`
Species Components	`//Species Components`
$A \stackrel{def}{=} (tr[main \leftrightarrow child], 1) \odot A + (re, 1) \downarrow A$	`A = tr[main<->child] (.)  A + re << A@child;`
$B \stackrel{def}{=} (re, 1) \uparrow B$	`B = re >>;`
Model Component	`//Model Component`
$A@main[100] \underset{tr}{\bowtie} A@child[100] \underset{re}{\bowtie} B@child[0]$	`A@main[Am]<tr>A@child[Ac]<re>B@child[B]`

Table 6: Bio-PEPA mathematical syntax and Bio-PEPA Eclipse Plug-in syntax for the Bidirectional Transportation model

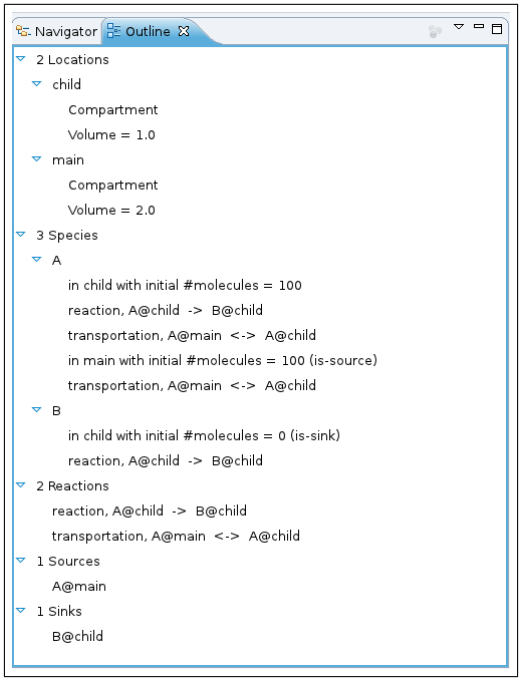


Figure 50: The Outline View of the Bidirectional Transportation model

B Managing Eclipse

B.1 Checking the Eclipse platform version

To check which version of the Eclipse platform you have installed choose Help → About Eclipse (see Figure 51).

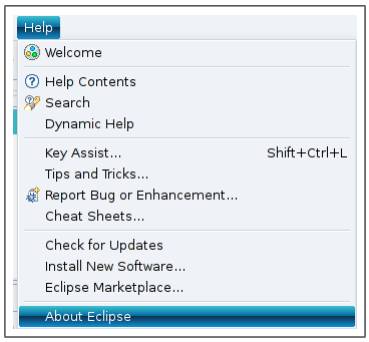


Figure 51: Checking the version of the Eclipse platform

In the dialogue box that appears you can see the version of the Eclipse platform that you have installed (see Figure 52).

Figure 52: Information on the version of the Eclipse platform

For more detailed information on your Eclipse installation, you can click on the `Installation Details` button. In Figure 53 you can see the window which contains the details on the Eclipse installation.

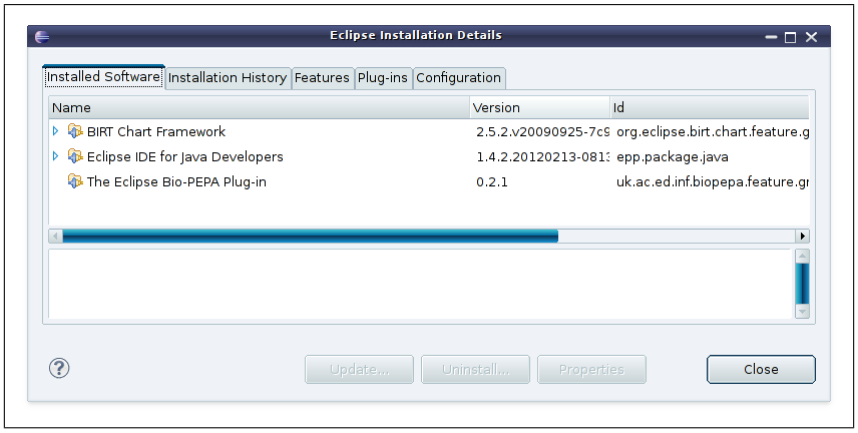


Figure 53: More information on the Eclipse platform installation

B.2 Checking for Updates

To check for updates of the Bio-PEPA software and the Eclipse platform choose Help → Check for Updates (see Figure 54).

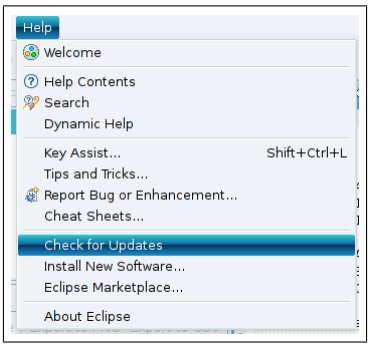


Figure 54: Checking for updates

Eclipse will contact its update sites, including the Bio-PEPA update site and fetch the available updates (see Figure 55). If you do not want to wait for Eclipse to finish this job, you may choose to run it in the background by clicking on the *Run in Background* button. You may also choose to always run this job in the background, by checking the box next to the *Always run in background* option.

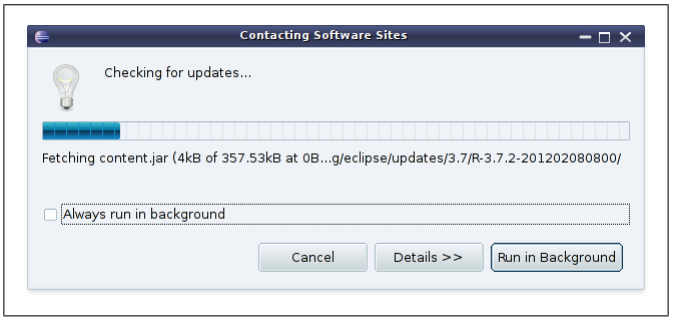


Figure 55: Contacting software sites for updates

Eclipse will then display the available updates. You are required to choose the updates you wish to install by checking the corresponding checkbox (see Figure 56). Then, click *Next*.

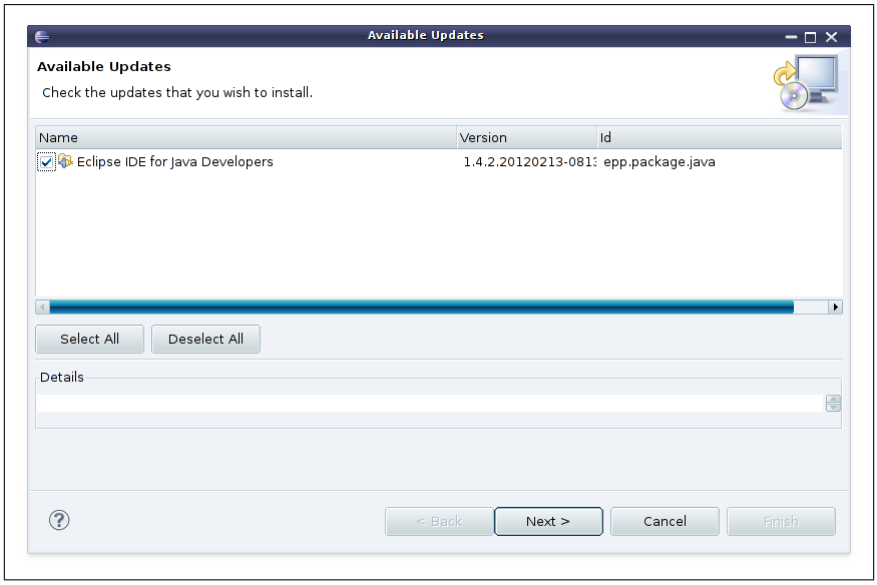


Figure 56: Displaying the available updates

Eclipse will display the updates you have chosen to install and give you the opportunity to review them and confirm your choice (see Figure 57). After you have done so, click *Next*.

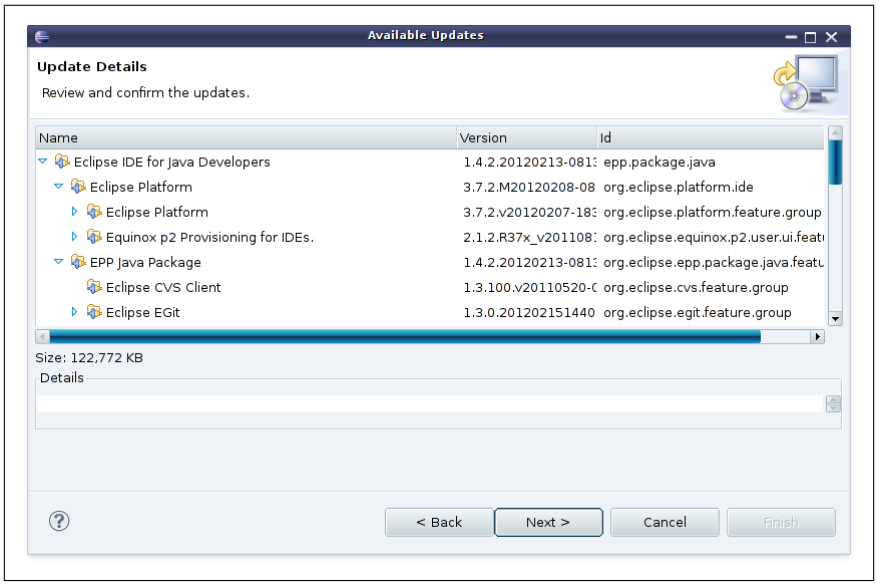


Figure 57: Review and confirm updates

Then, accept the terms of the licence agreement before clicking on *Finish* (see Figure 58).

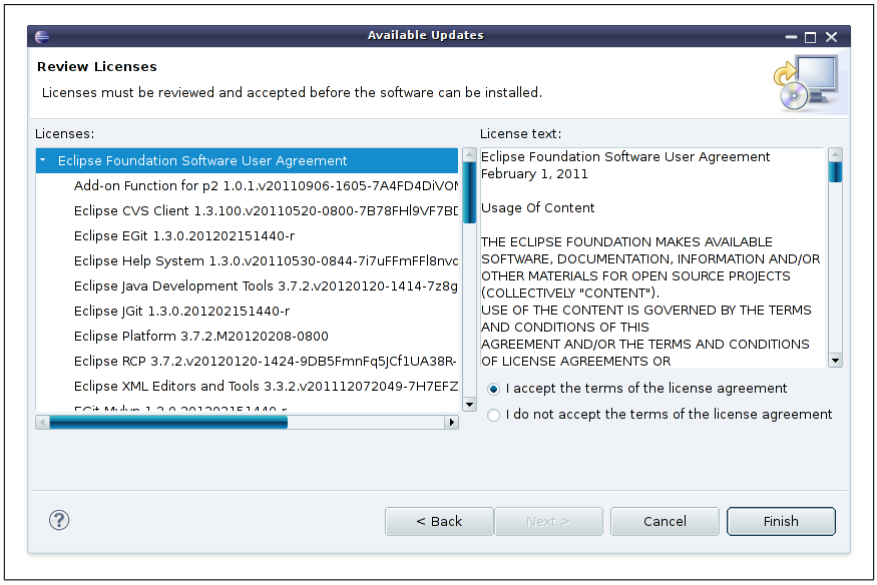


Figure 58: Review and accept licences

Eclipse will install the updates (see Figure 59). Again, you may choose to run this job in the background by clicking on the *Run in Background* button. You may also choose to always run it in the background, by checking the box next to the *Always run in background* option.

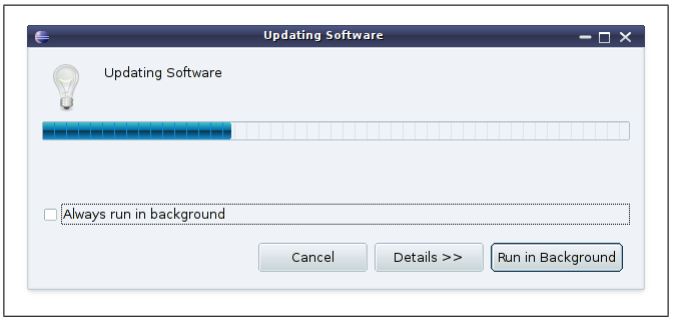


Figure 59: Updating software

After the installation is complete, a dialogue box will appear informing you that, for the updates to take place, you should restart Eclipse. You can also try to apply the changes without restarting, but this might cause errors. We recommend restarting Eclipse to apply the updates.

The dialogue box gives you three options. You can leave the changes for later, in which case they will be applied the next time you start Eclipse, by clicking on the *Not Now* button. You can try to apply the changes without restarting, by clicking on the *Apply Changes Now* button. Finally, you can restart Eclipse, so that the changes are applied properly, by clicking on the *Restart Now* button. The last choice is the recommended one (see Figure 60).

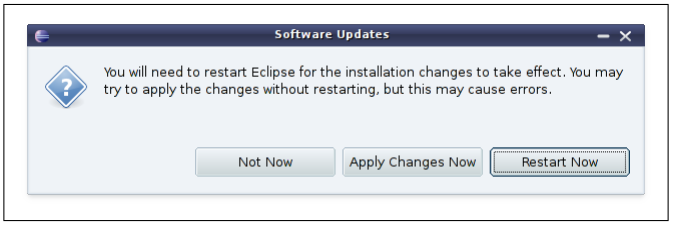


Figure 60: Applying the changes

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