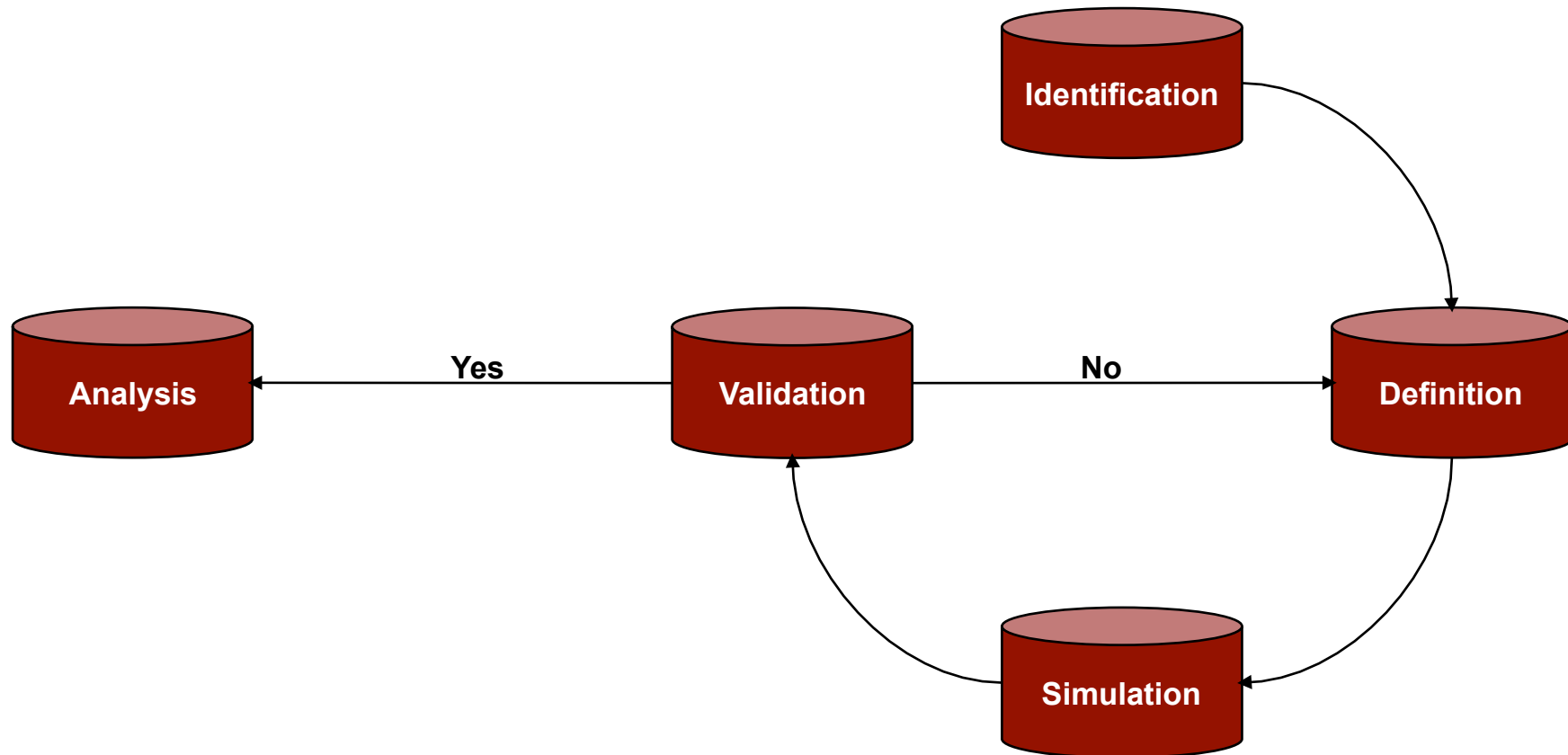


# BioNessie: A Software Tool for the Simulation and Analysis of Biochemical Networks

*David Gilbert, Xuan Liu, Robin Donaldson*  
*Bioinformatics Research Centre*  
*University of Glasgow*

# How to model

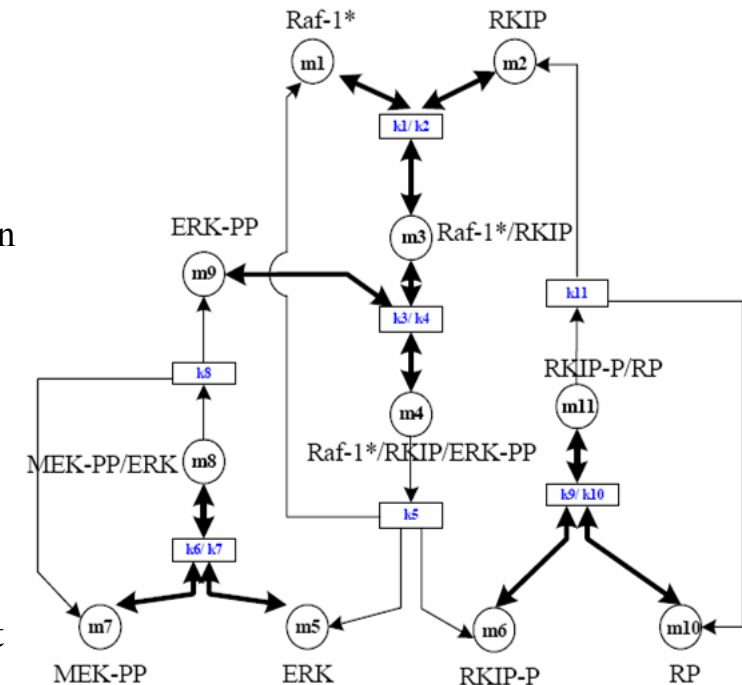


# How to model...1: Identification

- Identify the biological pathway to model (what)
  - RKIP
  - EGF and NGF activated MAPK
- Or, more importantly, identify the biological question to answer (why)
  - What influence does the Raf Kinase Inhibitor Protein (RKIP) have on the Extracellular signal Regulated Kinase (ERK) signalling pathway?
  - How do EGF and NGF cause differing responses in ERK activation, transient and sustained, respectively?

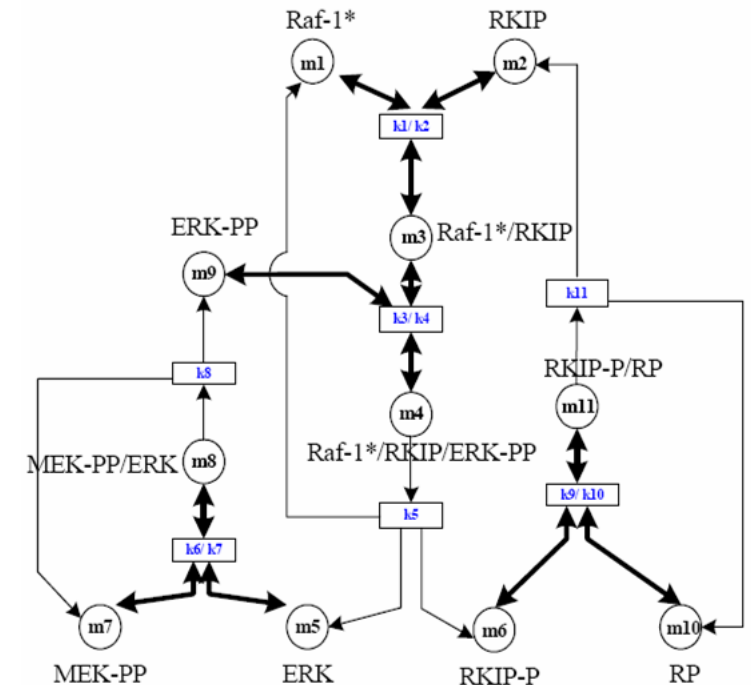
# How to model...2: Definition

- This is the key step and is not trivial
- Draw a detailed picture of the pathway to model
  - Define all the proteins/molecules involved
  - Define the reactions they are involved in
  - Where do you draw the model boundary line?
- Check the literature
  - What is known about the pathway and proteins?
  - What evidence is there that protein A binds directly to protein B?
  - Protein C also binds directly to protein B: does it compete with protein A or do they bind to protein B at different sites?
  - Trust & Conflicts: it is important to recognize which evidence to trust and which to discard (talk to the people in the wet lab)
- Simplifying assumptions
  - Many biological processes are very complex and not fully understood
  - Therefore, developing a model often involves making simplifying assumptions
  - For example, the activation of Raf by Ras is very complicated and not fully understood but it is often modelled as:
    - $\text{Raf} + \text{Ras-GTP} = \text{Raf/Ras-GTP} \rightarrow \text{Raf-x} + \text{Ras-GTP}$
  - Although this is a simplification, it is able to explain the observed data



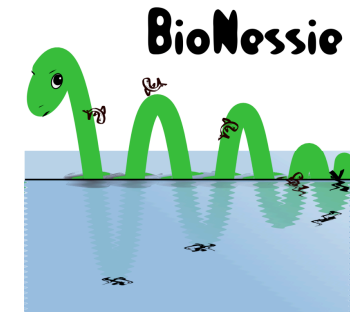
# How to model...2: Definition

- Define the kinetic types
  - Each reaction has a specific kinetic type
  - All the reactions in the RKIP model are mass action (plain, uncatalysed kinetic type):
    - $V = k_1[m_1][m_2] - k_2[m_3]$
  - Another common kinetic type is Michaelis Menten (enzyme catalysis):
    - $V = V_{max}[S] / (K_m + [S])$
- Define the rate constants (k's, km's, Vmax's etc)
- Define the initial concentrations
- Check the literature
  - What values have been previously reported?
  - What values are used in similar models?
  - Do you trust them? Are there any conflicts?
  - Measure them yourself in the wet lab
  - Parameter estimation techniques: estimate some parameters based on others and observed data

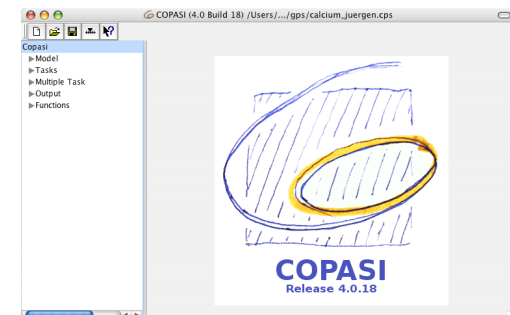


# How to model...3: Simulation

- Once the model has been constructed and parameter data has been assigned you can simulate (run) the model
- This is a relatively straightforward step as there are many software tools available to simulate differential equation based models
- For example:
  - BioNessie
  - MatLab
  - Copsai / Gepasi
  - CellDesigner
  - Jarnac
  - WinScamp
  - Many many more
- Runtime options include setting the time to run the model for and the number of data points to take

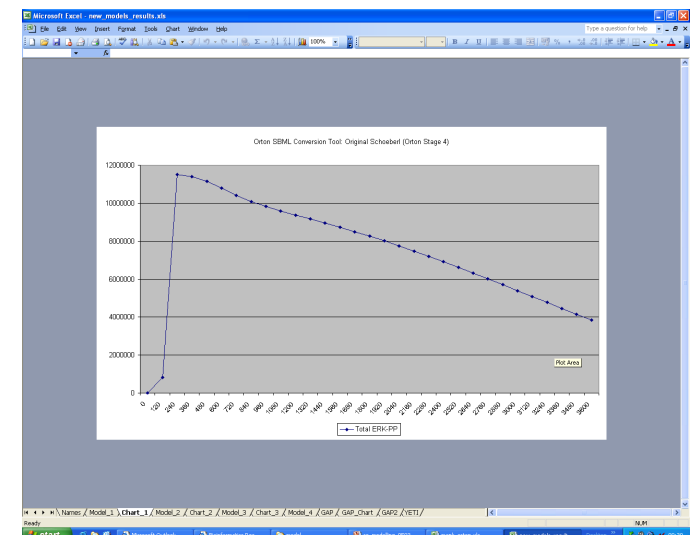


**MATLAB**  
*The Language of Technical Computing*



# How to model...4: Validation

- Simulating the model typically returns a table of data which shows how each specie's concentration varies over time
- This table can then be used to generate graphs of specie concentrations
- Do the model results match the experimental data?
  - Yes: validation
  - No: back to definition and check for errors
    - Simple typos
    - Wrong kinetics
    - Over simplifications of processes
    - Missing components from the model
    - Incorrect parameter data
- The model can then be validated further by checking the system behaves correctly when things are varied:
  - It might be known how the system behaves when you over-express or knockout a component
  - The model should be able to recreate this behaviour
- If the model's results do not match known biology, we cannot rely on predictions about unknown biology



# How to model...5: Analysis

- After the model has been validated we can then analyse and interpret the results
  - What do the results imply or suggest?
  - What do they tell us that is new and that we did not know/understand before?
  - What predictions can we make?
- Sensitivity analysis can be used to identify the key steps and components in the pathway as well as monitoring how robust the system is:
  - Vary an initial concentration or rate by a small amount and see what affect it has on the system as a whole: small changes in a key value are likely to have a large affect
  - How robust is the system to changes?
- Knockout experiments are easy to do in a model: for example, simply set the initial concentration of the desired component to 0
  - Knockout experiments can be used to identify which components are essential and which are redundant
  - Can also knockout reactions (set rate to 0) to identify essential and redundant reactions in the system





# The Design of BioNessie

- **SBML** (Systems Biology Markup Language) enabled.
- **Intuitive easy-to-use interface** for biochemists & modellers. Input biochemical equations.
- **File storage** in XML, SBML, text & graphics
- **Platform Independent** – Java
- **Parallel processing** - Efficient exploitation of available compute resources – multiple core and multiple CPUs, as well as Grid computing (see below)
- **Editor, simulator, and analyser**
- **Model version control**
- **Kinetic law** library creation & management
- **Fast efficient ODE solver** (stiff & non-stiff)
- **Parameter scanning**
- **Sensitivity analysis**
- **Parameter estimation** using a genetic algorithm
- **Advanced model checking** (MC2 using PLTL)

# Systems Biology Markup Language

- Machine-readable format for representing computational models in SB
  - Expressed in XML using an XML Schema
  - Intended for software tools—not for humans
- Tool-neutral exchange language for software applications in SB
  - Simply an enabling technology
- Used quite widely in biological modelling
- It is supported by over 40 software systems including Gepasi
- Good documentation, user community and publicly available tools
- [www.sbml.org](http://www.sbml.org)
- Also [www.ebi.ac.uk/biomodels](http://www.ebi.ac.uk/biomodels)



# SBML - XML Based Language

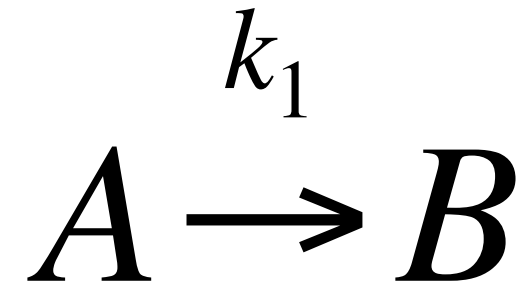
```
<sbml>
<model>
  <listOfCompartments> <compartment/> </listOfCompartments>
  <listOfSpecies> <specie/>          </listOfSpecies>
  <listOfReactions>
    <reaction>
      <listOfReactants>
        <specieReference/>
      </listOfReactants>
      <listOfProducts>
        <specieReference/>
      </listOfProducts>
      <kineticLaw>
        <listOfParameters>
          <parameter/>
        </listOfParameters>
      </kineticLaw>
    </reaction>
  </listOfReactions>
</model>
</sbml>
```

# SBML Example Reaction

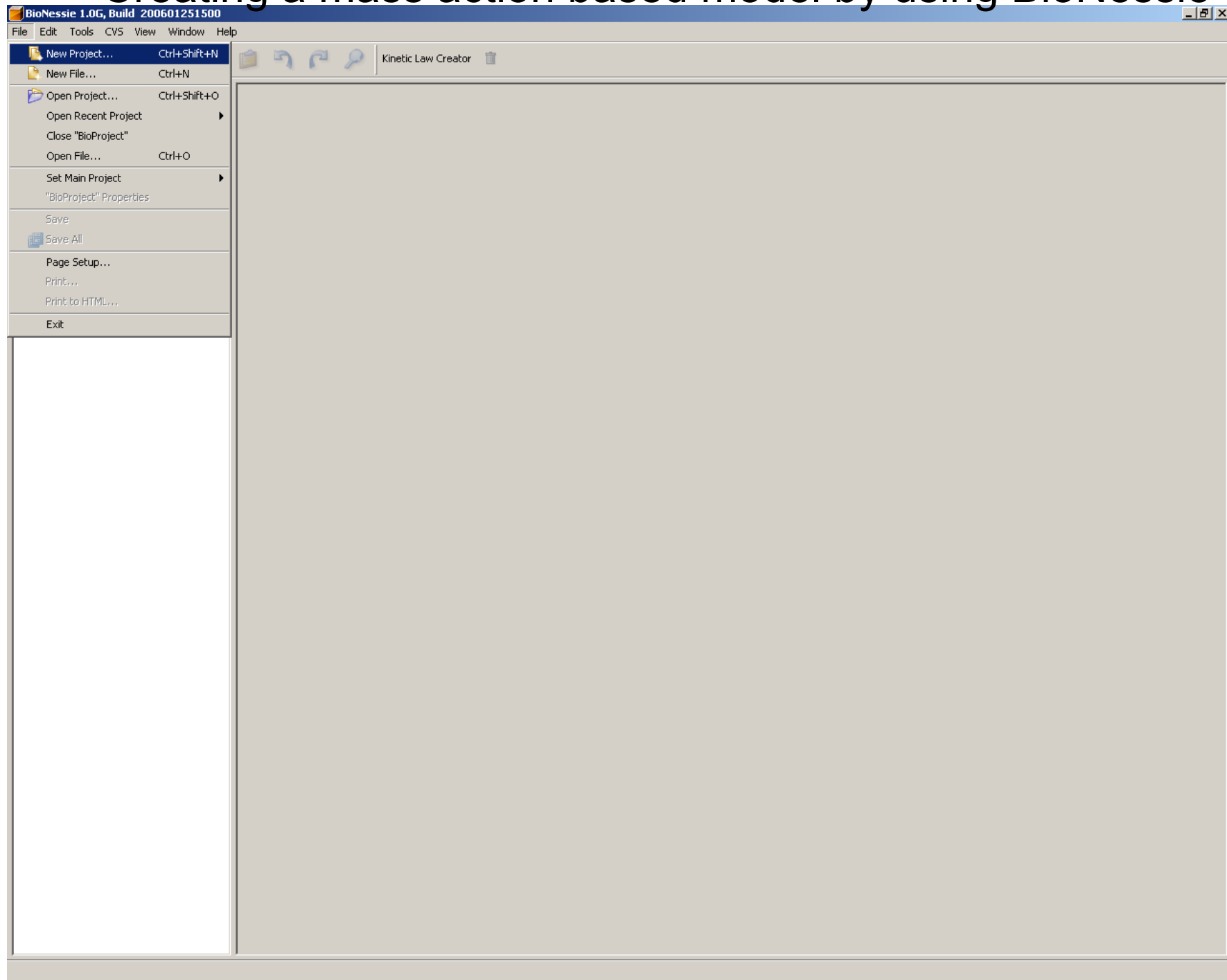
```

<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1">
  <model id="newModel">
    <listOfCompartments>
      <compartment id="compartment" size="1"/>
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="compartment" initialConcentration="5"/>
      <species id="B" compartment="compartment" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="K1" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="Ak1B" reversible="false">
        <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> K1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>

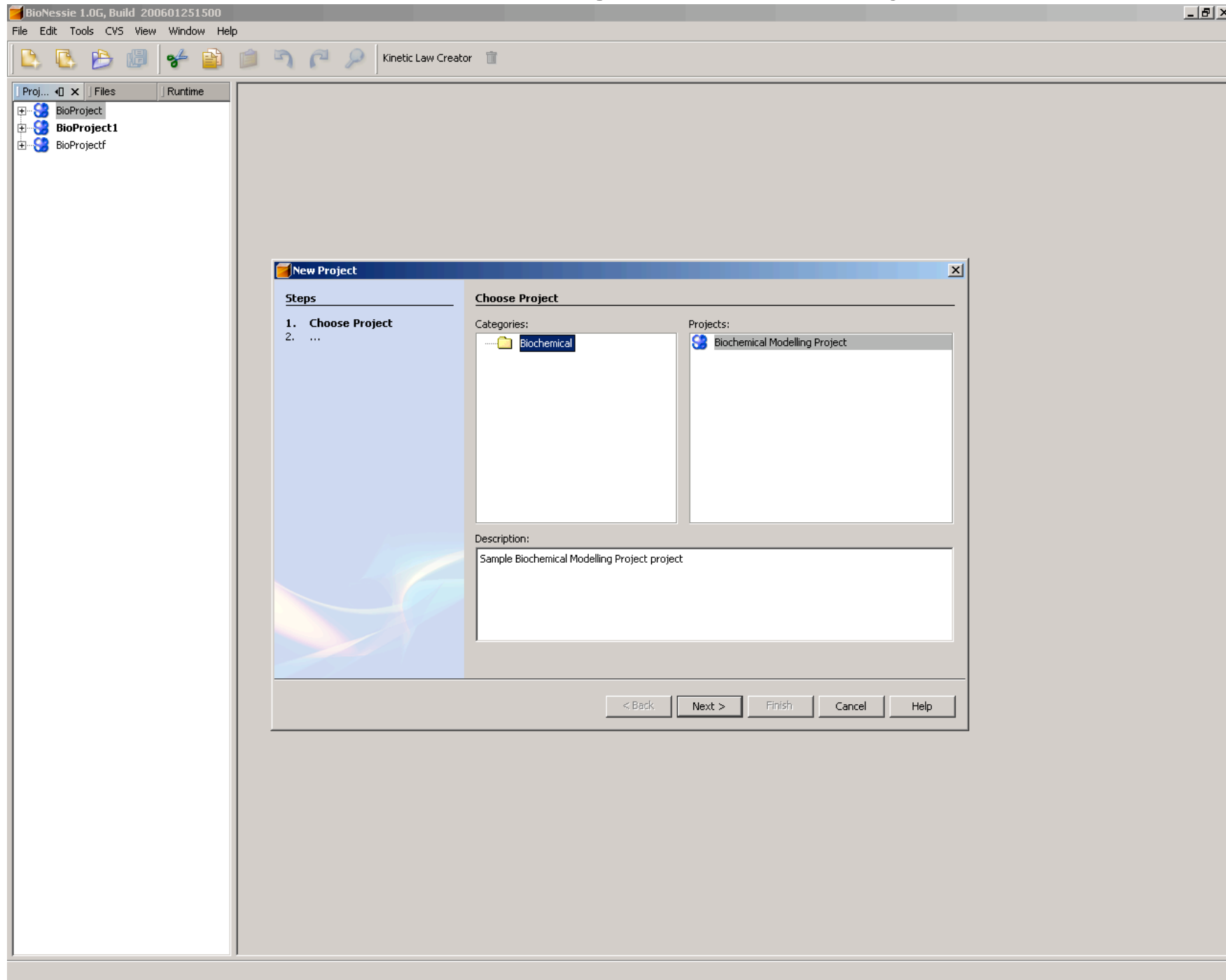
```



# Creating a mass action based model by using BioNessie



# Creating a new BioProject



# Giving a project name

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Proj... X Files Runtime

- BioProject
- BioProject1
- BioProjectf

**New Project**

**Steps**

1. Choose Project
2. **Create a new Biochemical Modelling Project project**

**Create a new Biochemical Modelling Project project**

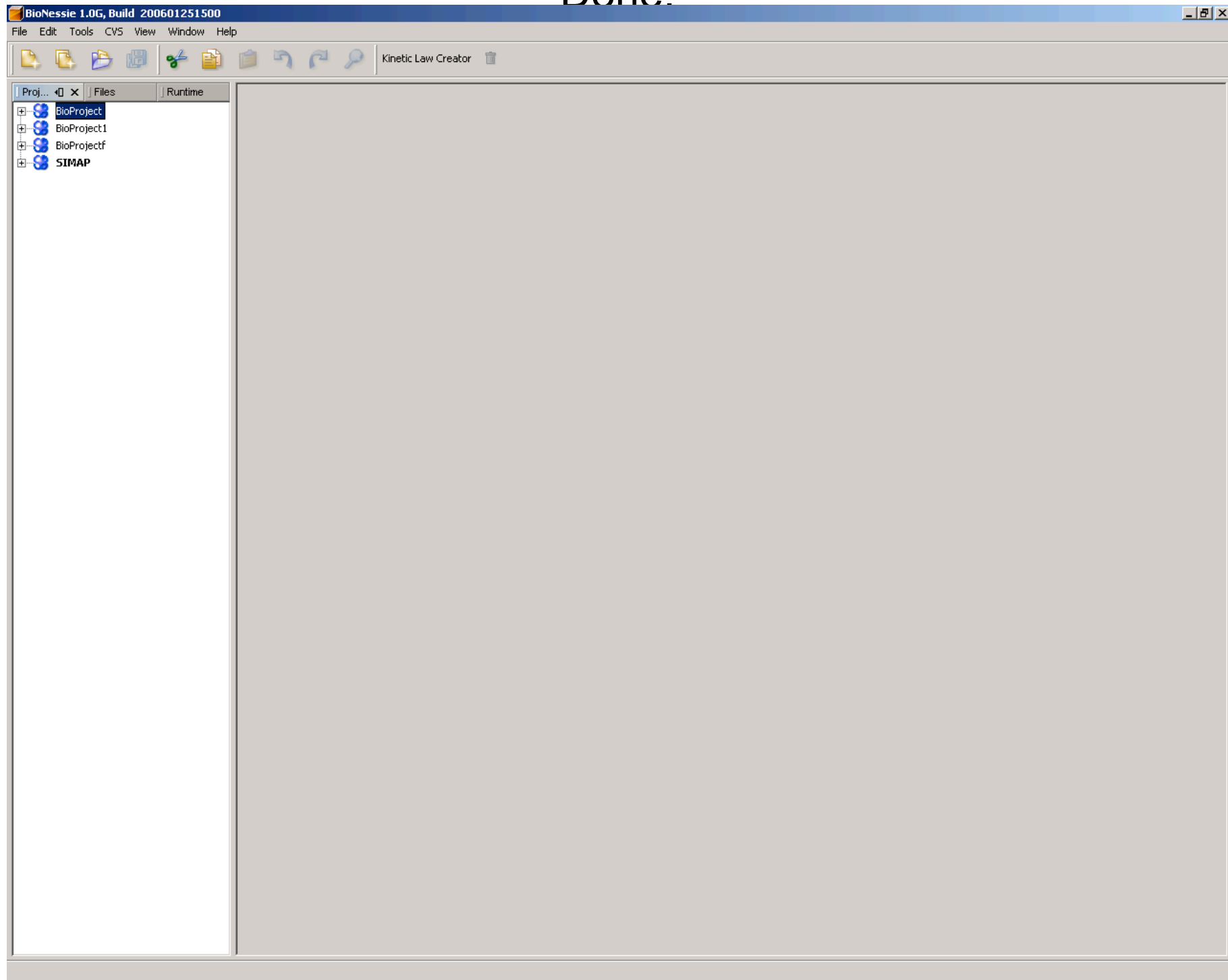
Project Name:

Project Location:

Project Folder:

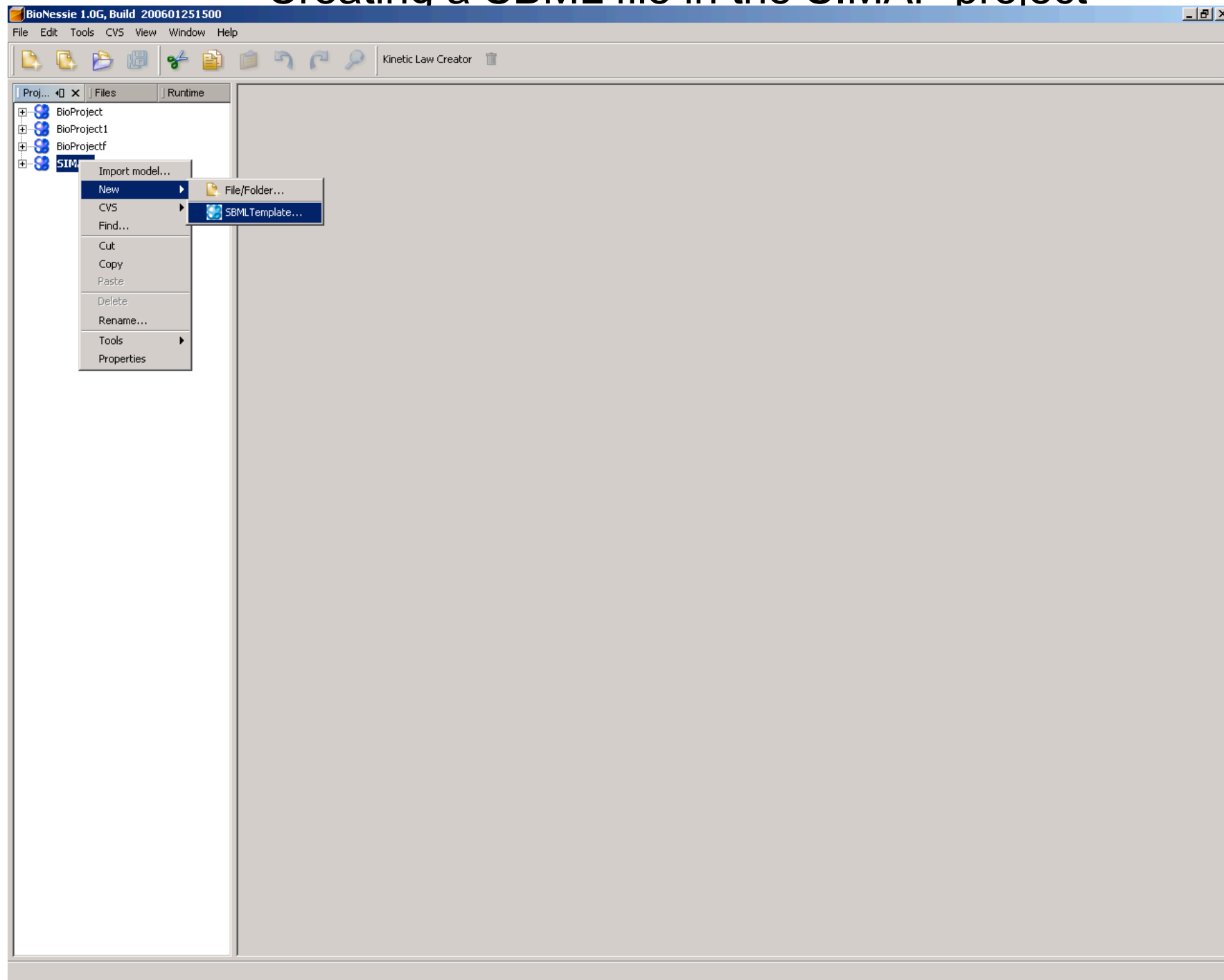
< Back Next > Finish Cancel Help

# Done!

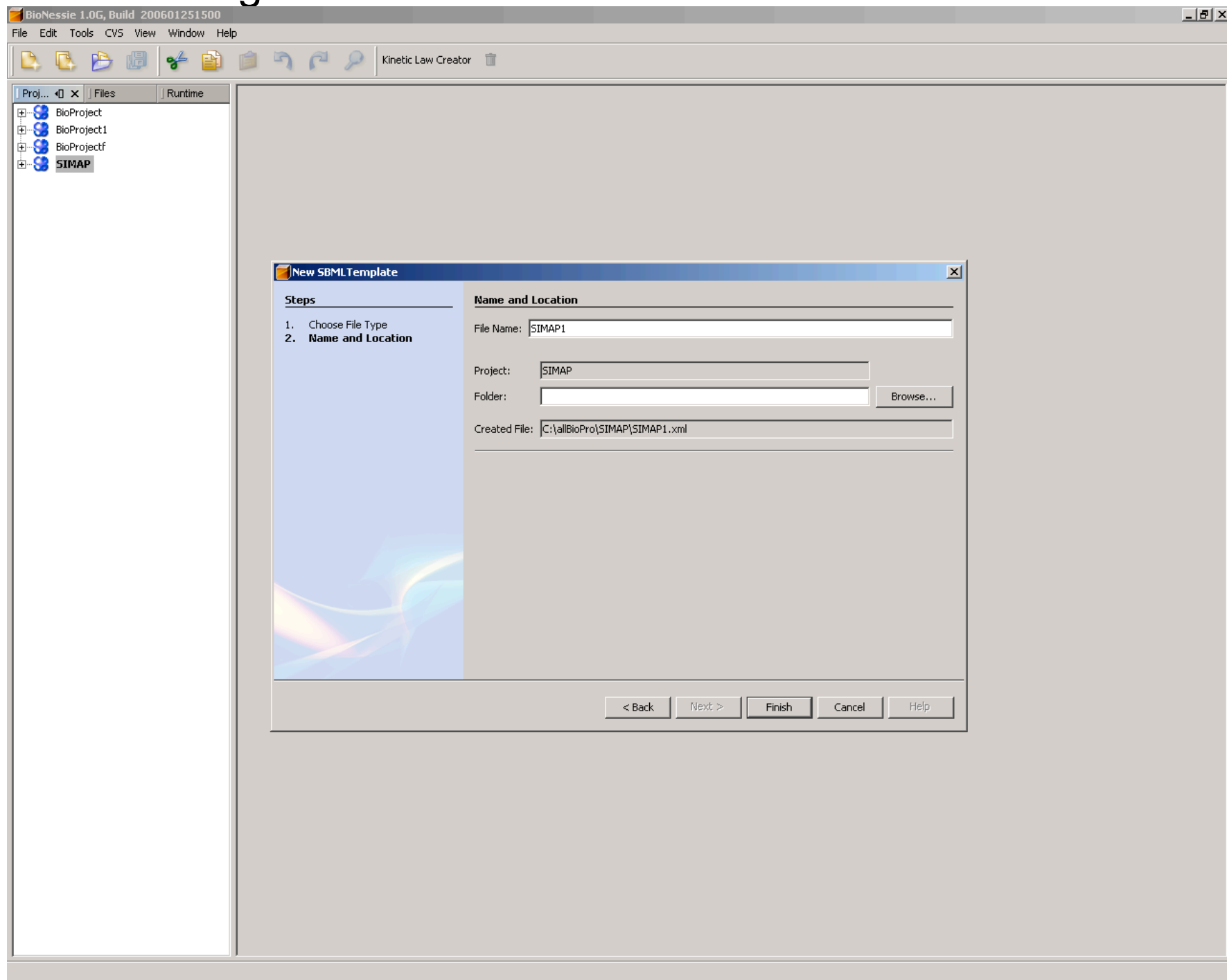




# Creating a SBML file in the SIMAP project



# Giving a name to the new SBML file and click “Finish”



# Done!

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Kinetic Law Creator

Proj... Files Runtime

C:\allBioPro\SIMAP\SIMAP1.xml

Path: C:\allBioPro\SIMAP\SIMAP1.xml Model Name: newModel Version: Level2Ver1 Apply Simulate Save As

Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefinitions

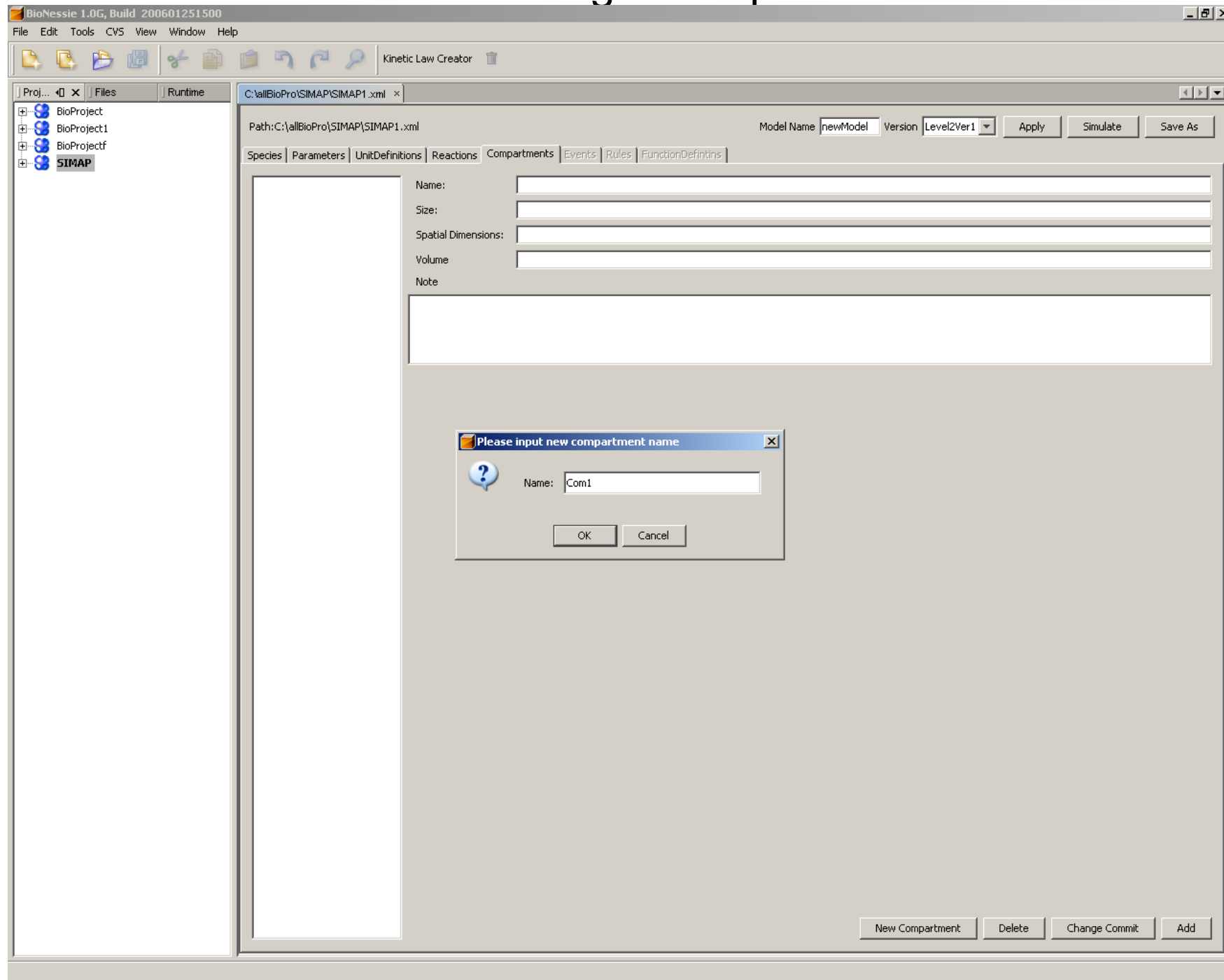
Name: Initial Concentration: Initial Amount: Charge: Owner compartment: ☐ Constant ☐ BoundaryCondition

Note

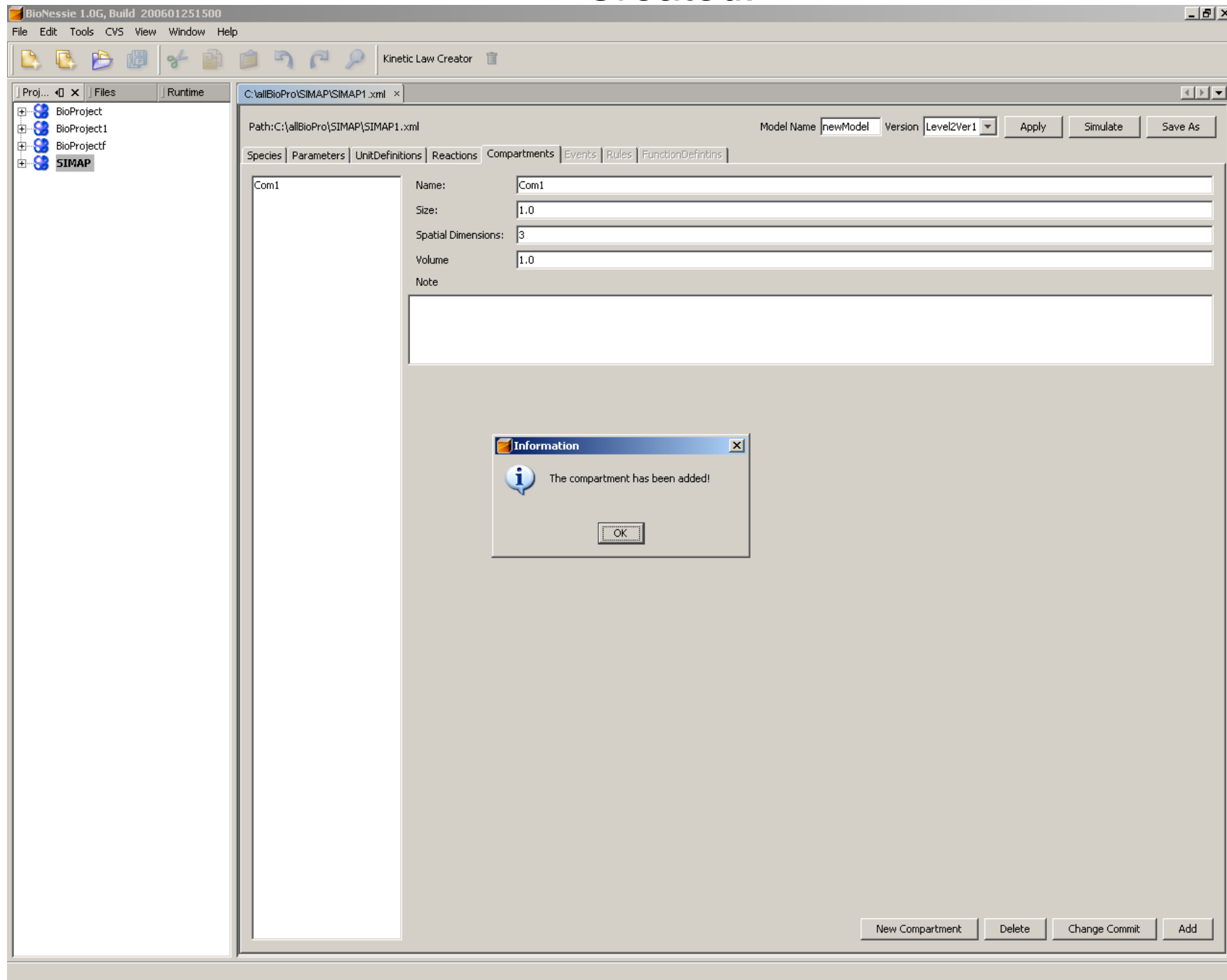
Related Reactions

New Species Delete Change Commit Add

# Creating a compartment



# Created!



# Creating a species

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Kinetic Law Creator

Proj... x Files Runtime

C:\allBioPro\SIMAP\SIMAP1.xml x

Path: C:\allBioPro\SIMAP\SIMAP1.xml Model Name newModel Version Level2Ver1 Apply Simulate Save As

Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefinitions

Name: A

Initial Concentration: 5

Initial Amount: 0.0

Charge: 0

Owner compartment: Com1

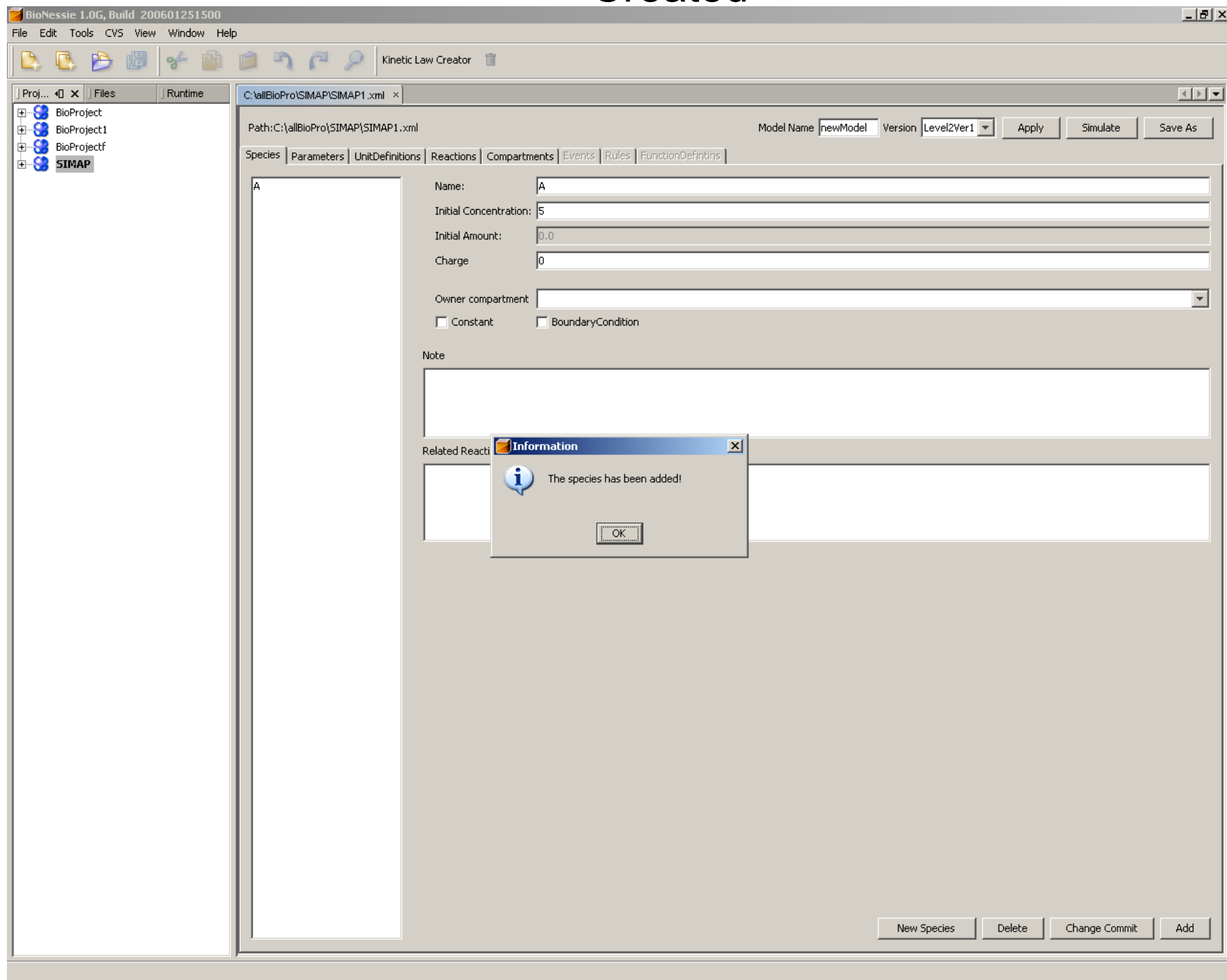
☐ Constant ☐ BoundaryCondition

Note

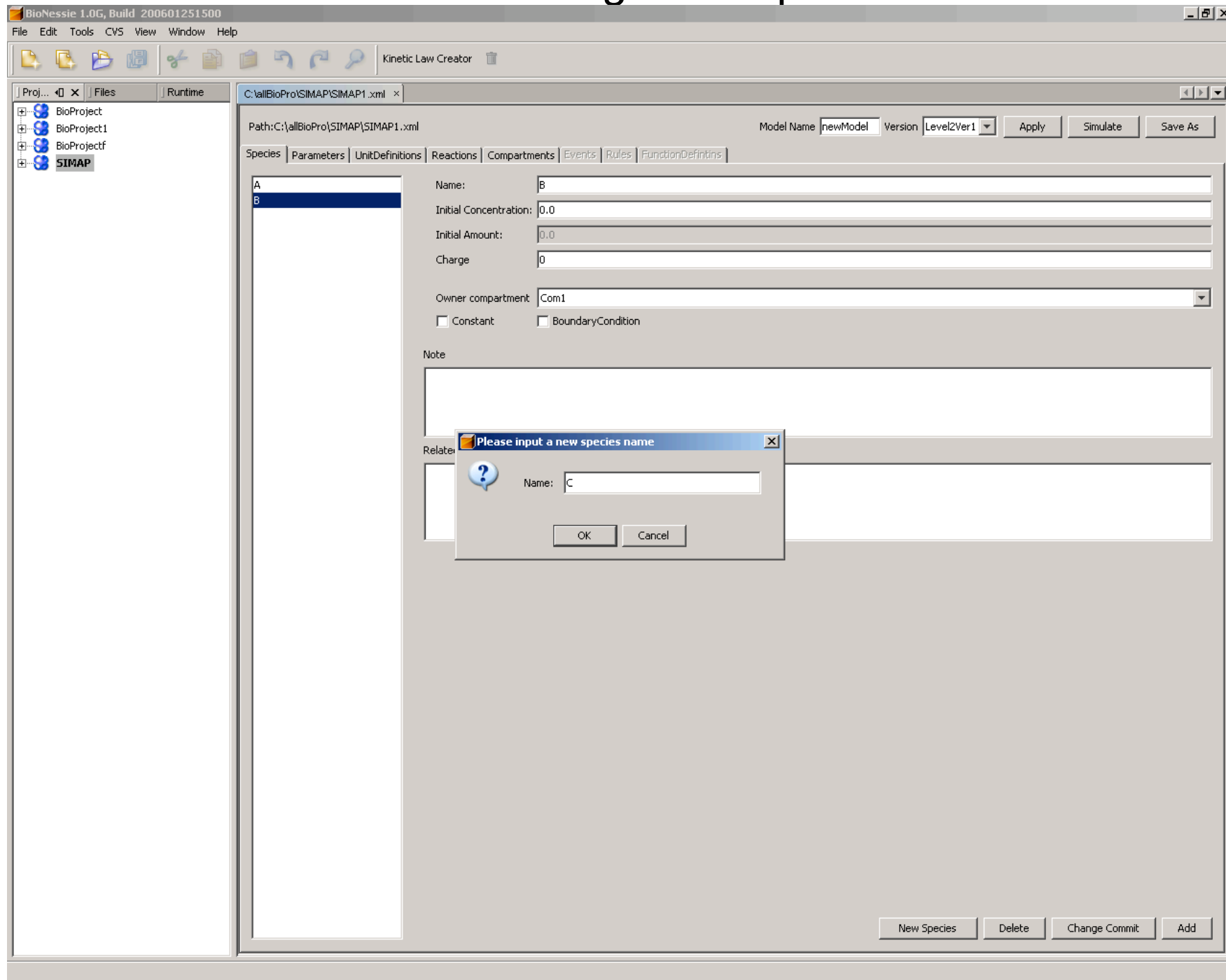
Related Reactions

New Species Delete Change Commit Add

# Created

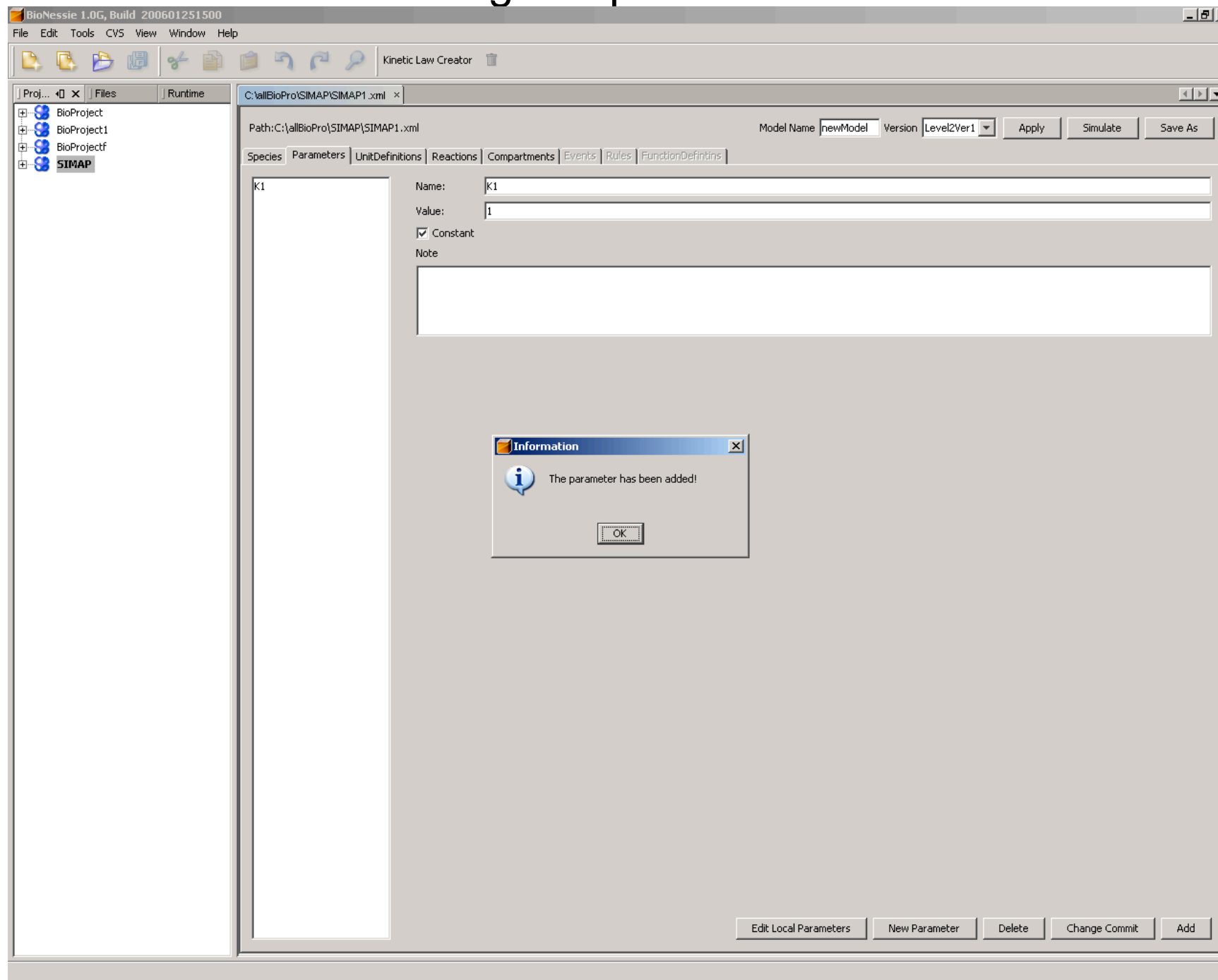


# Creating other species





# Creating two parameters: K1 and K2



BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Kinetic Law Creator

Proj... x Files Runtime

C:\allBioPro\SIMAP\SIMAP1.xml x

Path: C:\allBioPro\SIMAP\SIMAP1.xml Model Name: newModel Version: Level2Ver1 Apply Simulate Save As

Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefinitions

K1  
K2

Name: K2  
Value: 0.5  
☒ Constant  
Note

Information  
The parameter has been added!  
OK

Edit Local Parameters New Parameter Delete Change Commit Add

# Creating a reaction A=B with K1 and K2

The screenshot displays the BioNessie 1.0G software interface, version 200601251500. The main window is titled "Kinetic Law Creator" and shows a project tree on the left with folders like "fitting", "models", "paramscan", "sens", "simulations", and "SIMAP1 (newModel)". The main workspace is divided into tabs: "Species", "Parameters", "UnitDefinitions", "Reactions", "Compartments", "Events", "Rules", and "FunctionDefinitions". The "Reactions" tab is active, showing a reaction named "Reaction1" with the formula "A=B". The reaction is reversible, as indicated by the text "This reaction is reversible reaction". The kinetic law is set to "A \* K1 - B \* K2". The interface includes buttons for "Add", "Delete", "Edit", "Reset all", "OK", "Cancel", "Check", "Delete", "Change Commit", and "Add new Reaction...". A dialog box is open, showing the steps for creating a reaction: Step 1 (Input new reaction name and textual form), Step 2 (Check the following lists), Step 3 (Set reaction kinetic type), and Step 4 (Add new species and parameters to the model). The dialog box also includes a "Delete select" button and a "Double click to edit value" instruction.

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Kinetic Law Creator

Proj... x Files Runtime

C:\allBioPro\SIMAP\SIMAP1.xml x SIMAP1 (newModel) x Simulation of SIMAP1.xml x

Path: C:\allBioPro\SIMAP\SIMAP1.xml Model Name: newModel Version: Level2Ver1 Apply Simulate Save As

Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefinitions

reaction1 Name: Reaction1

Reactants: A Products: B Modifier:

Reaction: A = B

Kinetic Law Formula:

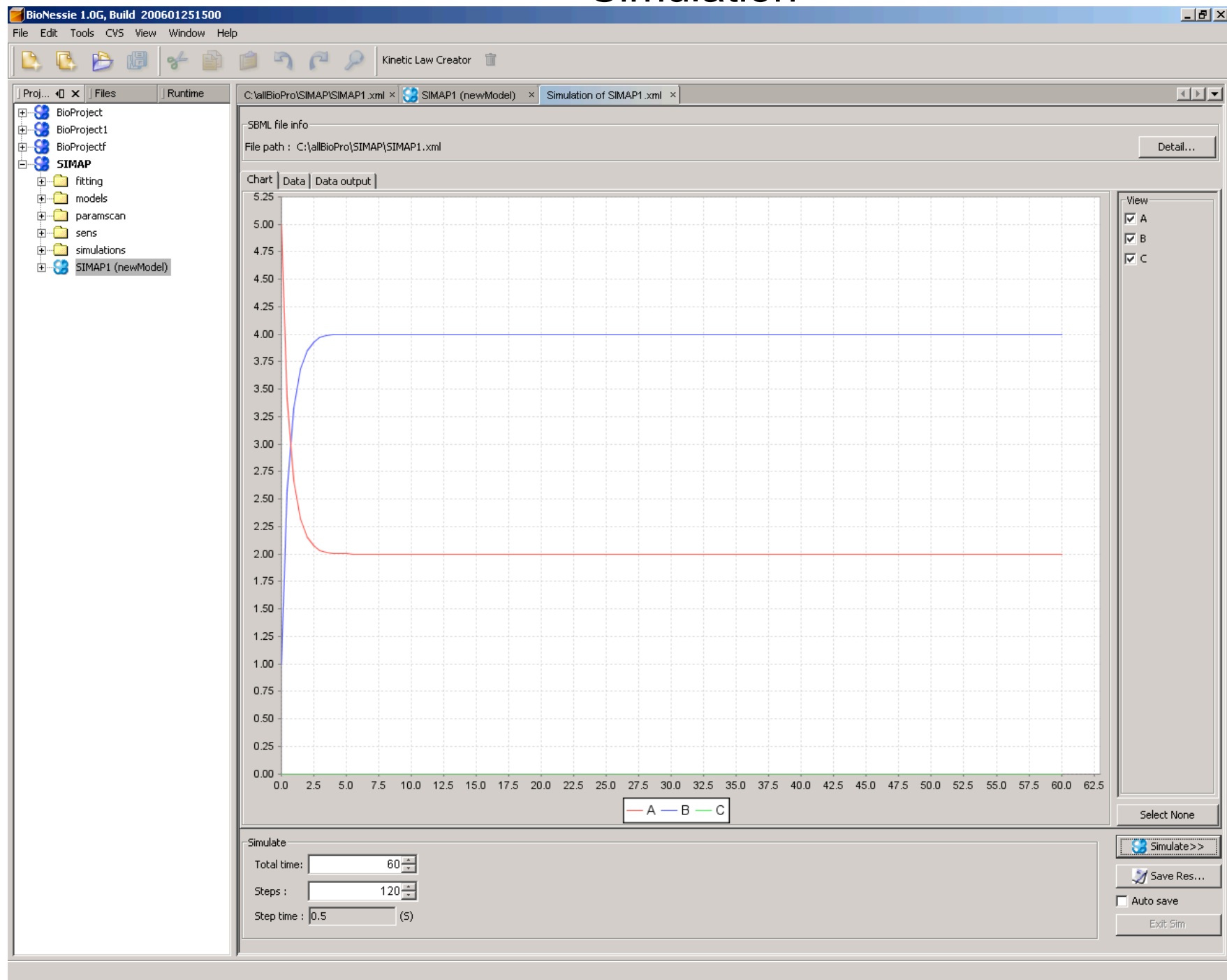
☐ Fast reaction

Note:

Information: The reaction has been added.

Check Delete Change Commit Add new Reaction...

# Simulation



# Add another reaction $A+B \rightarrow C$ with K1

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Kinetic Law Creator

Proj... x Files Runtime

C:\allBioPro\SIMAP\SIMAP1.xml x Simulation of SIMAP1.xml x

Path: C:\allBioPro\SIMAP\SIMAP1.xml Model Name newModel Version Level2Ver1 Apply Simulate Save As

Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefinitions

Reaction1 Name: Reaction1

Reactants Add Products Add Modifier Add

Step 1, Input new reaction name and textual form :

Name: Reaction2 Reaction  $A+B \rightarrow C$  OK

Step 2, Check the following lists

Reactants	Products	Modifiers
A B	C	

Delete select Edit Edit

This reaction is irreversible reaction

Step 3, Set reaction kinetic type

$K1 * A * B$  Edit...

Step 4, Add new species and parameters to the model

The species will be added: The parameter will be added:

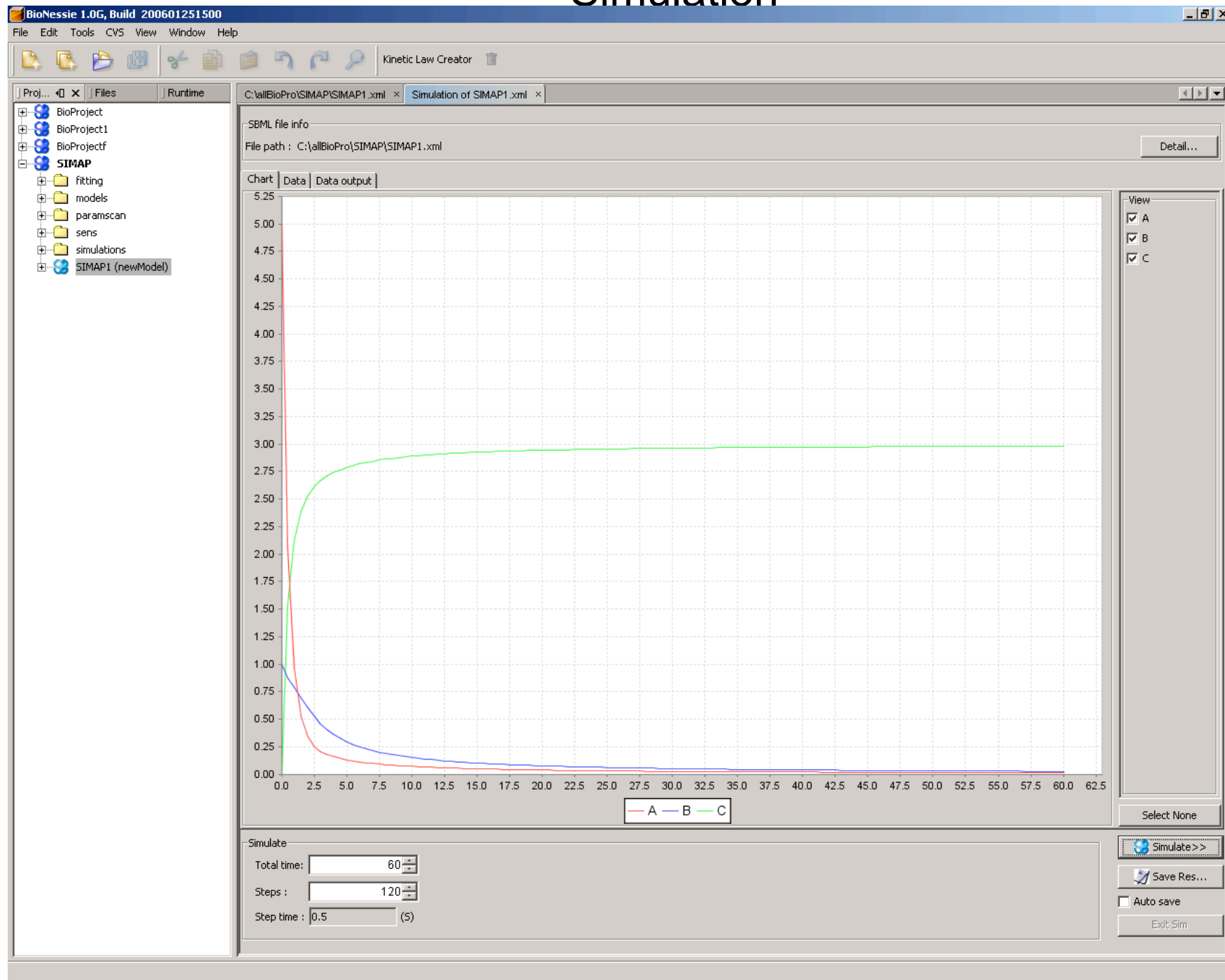
Double click to edit value Add all Double click to edit value Add all

Final Step, All done ! Click OK Button

Reset all OK Cancel

Check Delete Change Commit Add new Reaction...

# Simulation



# Textual SBML source editor

Biochemical Project 200601251500

File Edit View Navigate Source Build Run CVS Tools Window Help

Kinetic Law Creator

Proj... 40 X | Files | Runtime

BioProjectfitting

- fitting
- models
  - RKIPpathway (In this pathway, eleven different kinds of molecules are participated and there are eleven operations altogether.)
- paramscan
- sens
- simulations

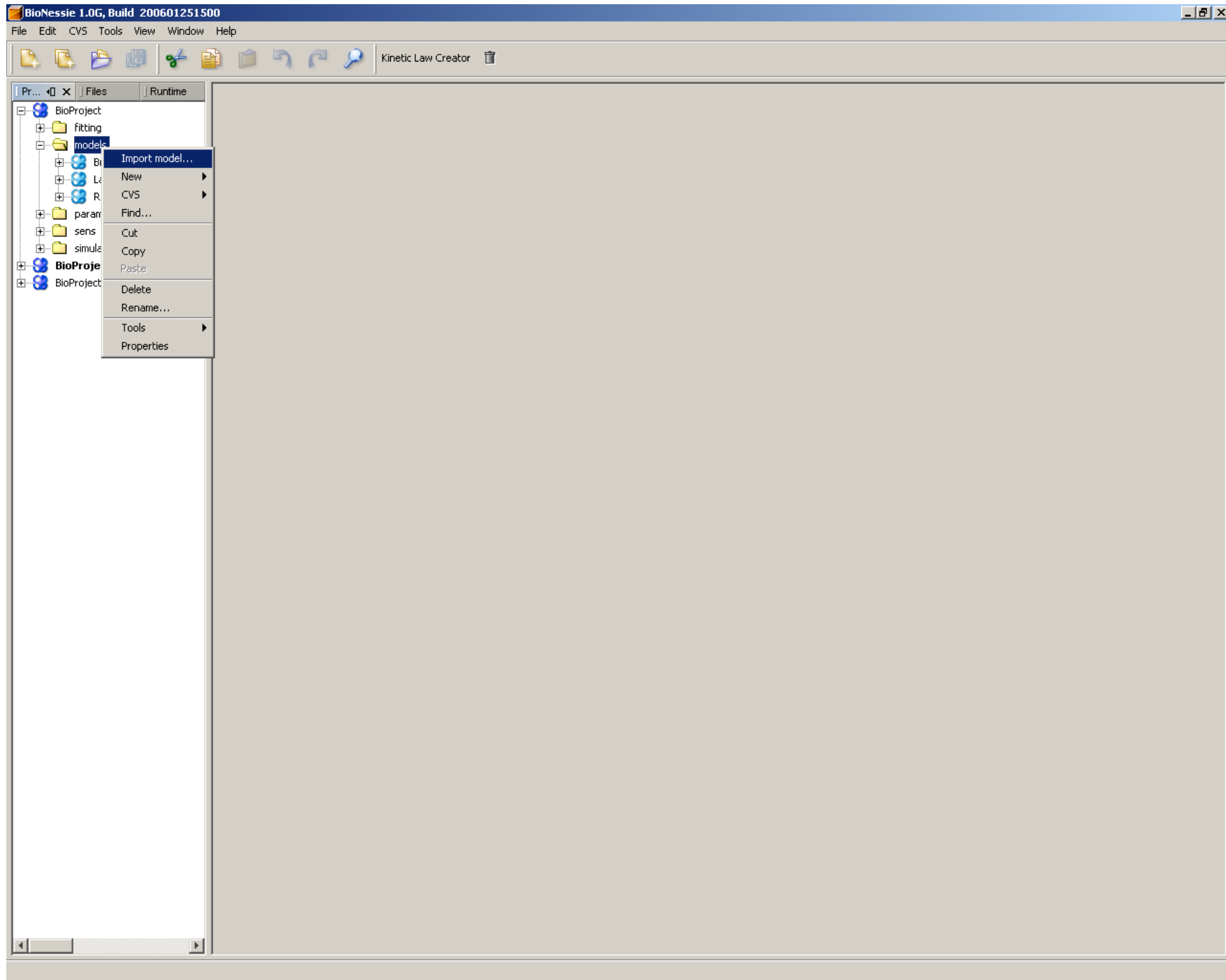
...ml RKIPpathway (In this pathway, eleven different kinds of molecules are participated and there are eleven operations altogether.)

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1">
  <model id="newModel" name="In this pathway, eleven different kinds of molecules are participated and there are eleven operations altogether">
    <listOfUnitDefinitions>
      <unitDefinition id="amount">
        <listOfUnits>
          <unit kind="mole" scale="-3" multiplier="1" offset="0"/>
        </listOfUnits>
      </unitDefinition>
      <unitDefinition id="concentration">
        <listOfUnits>
          <unit kind="mole" multiplier="1" offset="0"/>
          <unit kind="litre" exponent="-1" multiplier="1" offset="0"/>
        </listOfUnits>
      </unitDefinition>
      <unitDefinition id="volume">
        <listOfUnits>
          <unit kind="litre" scale="-3" multiplier="1" offset="0"/>
        </listOfUnits>
      </unitDefinition>
    </listOfUnitDefinitions>
    <listOfCompartments>
      <compartment id="Compartment" size="1"/>
    </listOfCompartments>
    <listOfSpecies>
      <species id="Raf1" compartment="Compartment" initialConcentration="2.5"/>
      <species id="RKIP" compartment="Compartment" initialConcentration="2.5"/>
      <species id="Raf1RKIP" compartment="Compartment" initialConcentration="0"/>
      <species id="ERKPP" compartment="Compartment" initialConcentration="2.5"/>
      <species id="Raf1RKIPERKPP" compartment="Compartment" initialConcentration="0"/>
      <species id="ERK" compartment="Compartment" initialConcentration="0"/>
      <species id="RKIPP" compartment="Compartment" initialConcentration="0"/>
      <species id="MEKPP" compartment="Compartment" initialConcentration="2.5"/>
      <species id="MEKPPERK" compartment="Compartment" initialConcentration="0"/>
      <species id="RP" compartment="Compartment" initialConcentration="3"/>
      <species id="RKIPPRP" compartment="Compartment" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.53"/>
      <parameter id="k2" value="0.0072"/>
      <parameter id="k3" value="0.625"/>
      <parameter id="k4" value="0.00245"/>
      <parameter id="k5" value="0.0315"/>
      <parameter id="k6" value="0.8"/>
      <parameter id="k7" value="0.0075"/>
      <parameter id="k8" value="0.071"/>
      <parameter id="k9" value="0.92"/>
      <parameter id="k10" value="0.00122"/>
      <parameter id="k11" value="0.87"/>
    </listOfParameters>
  </model>
</sbml>
```

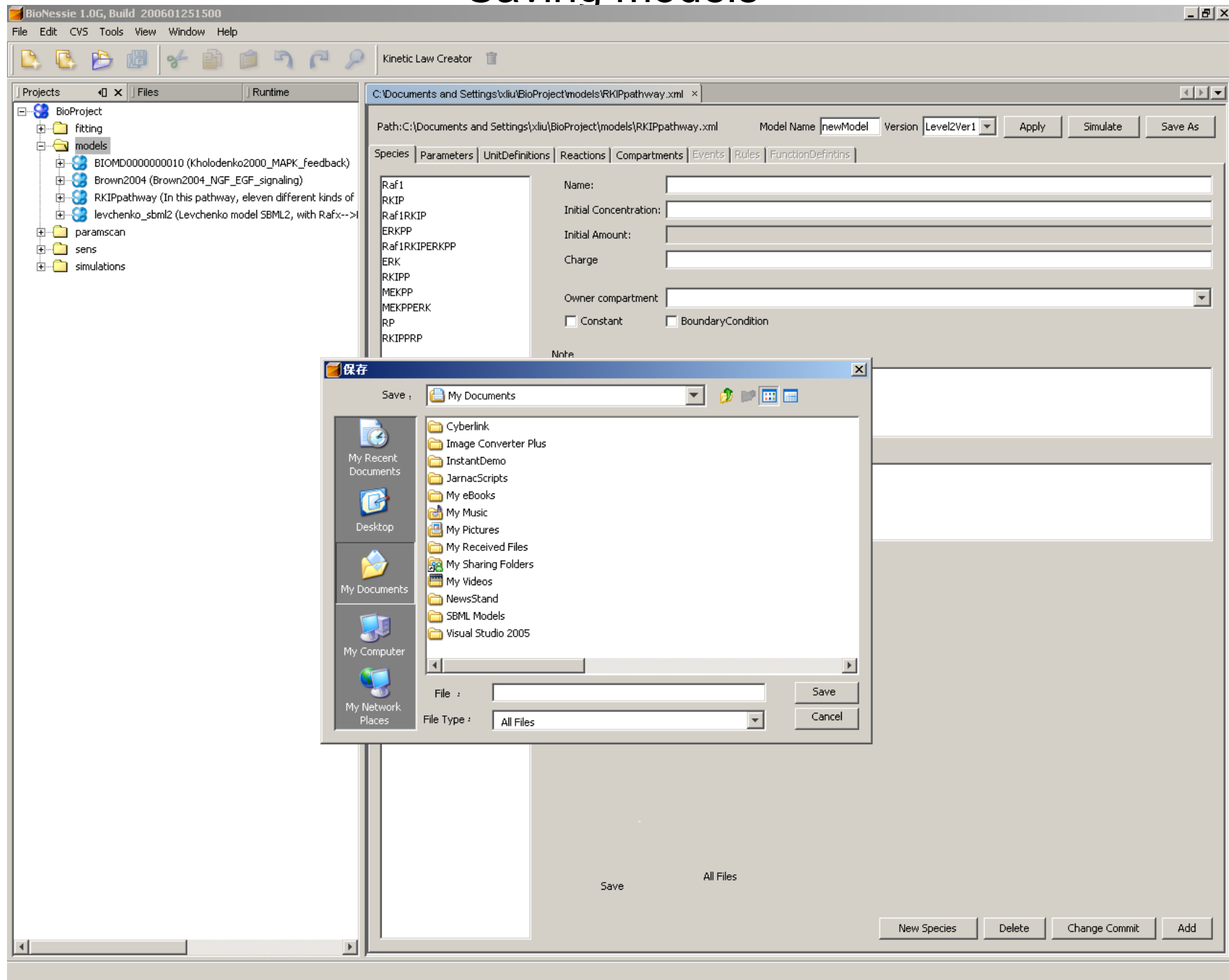
1:1 INS



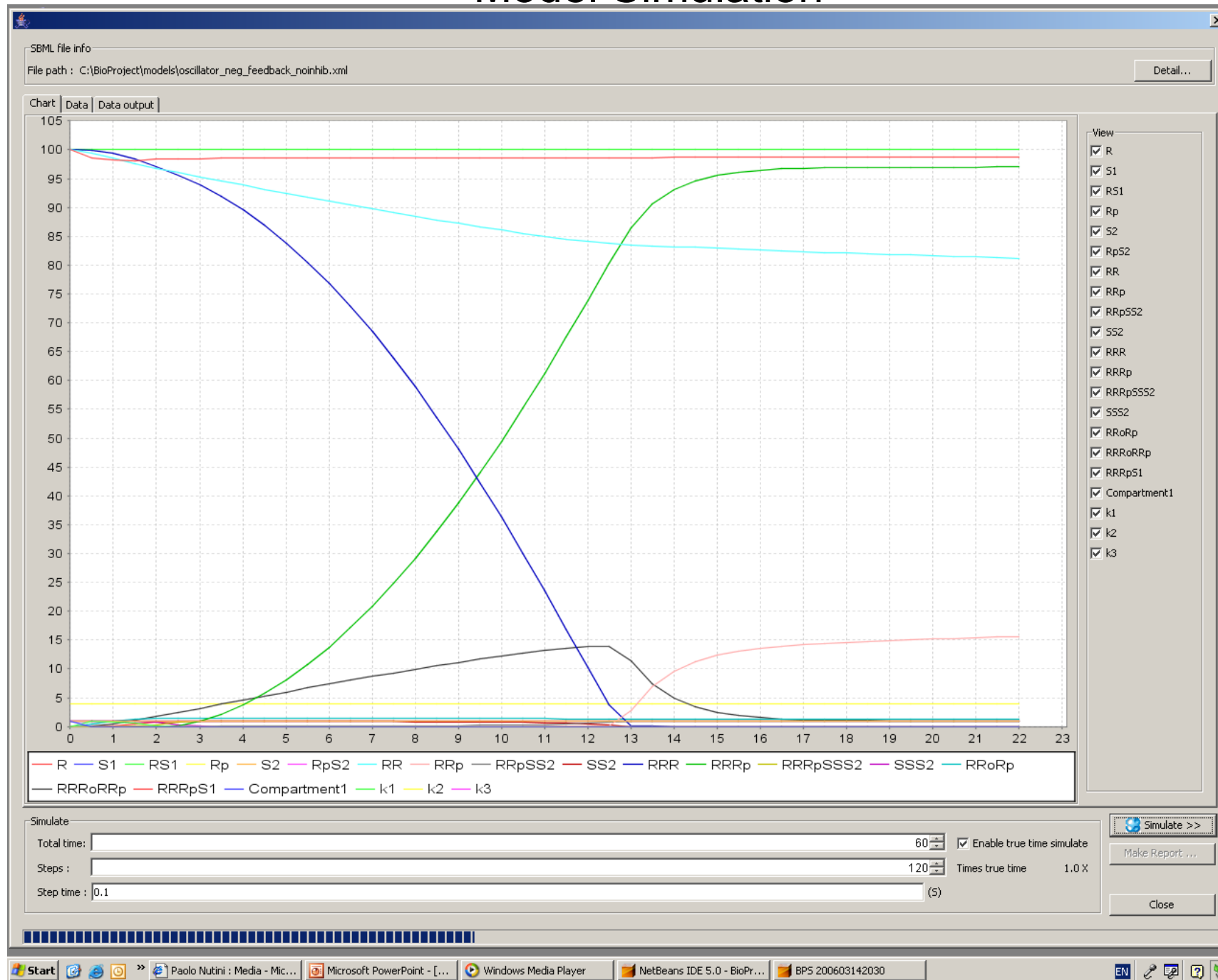
# Model retrieval



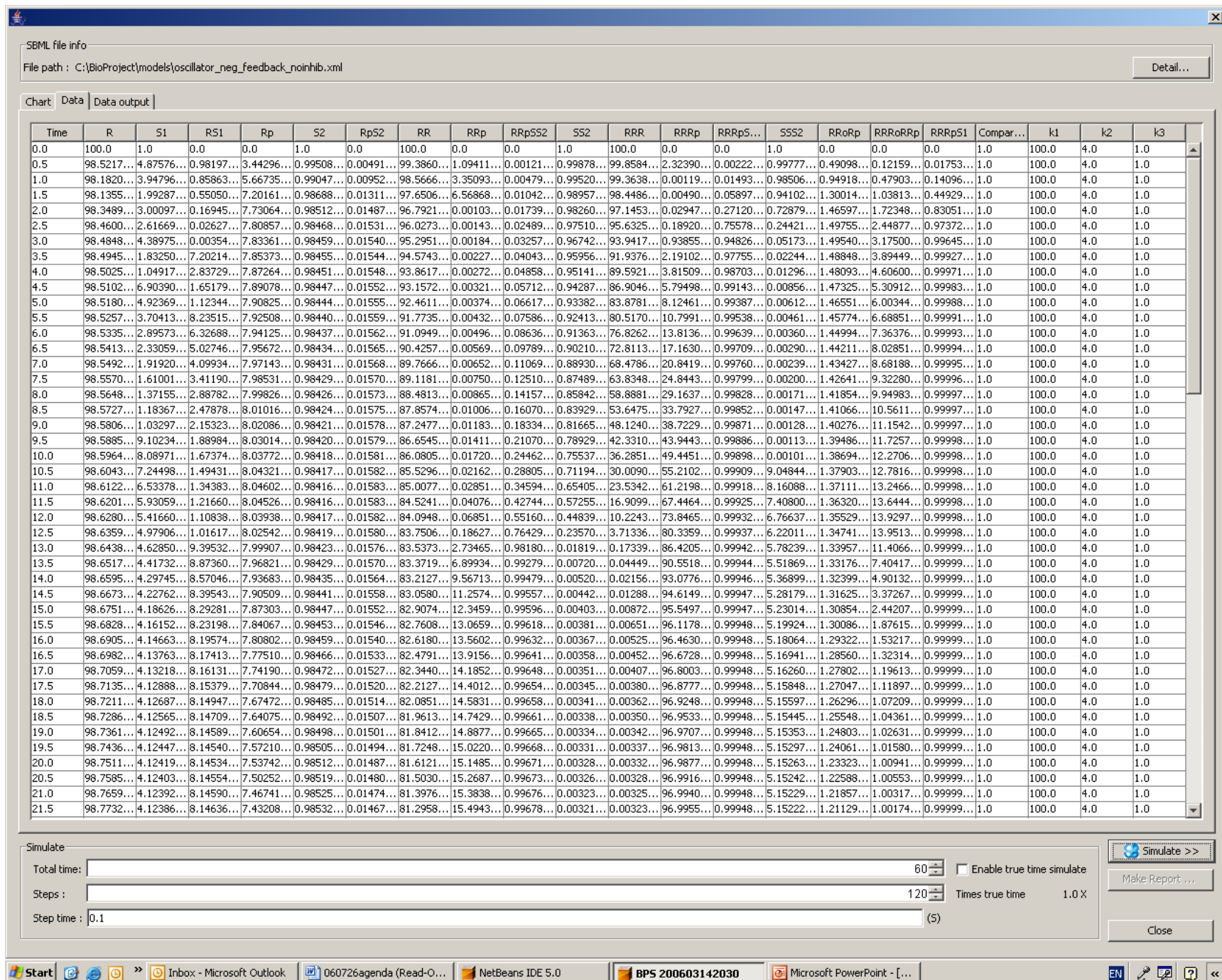
# Saving models



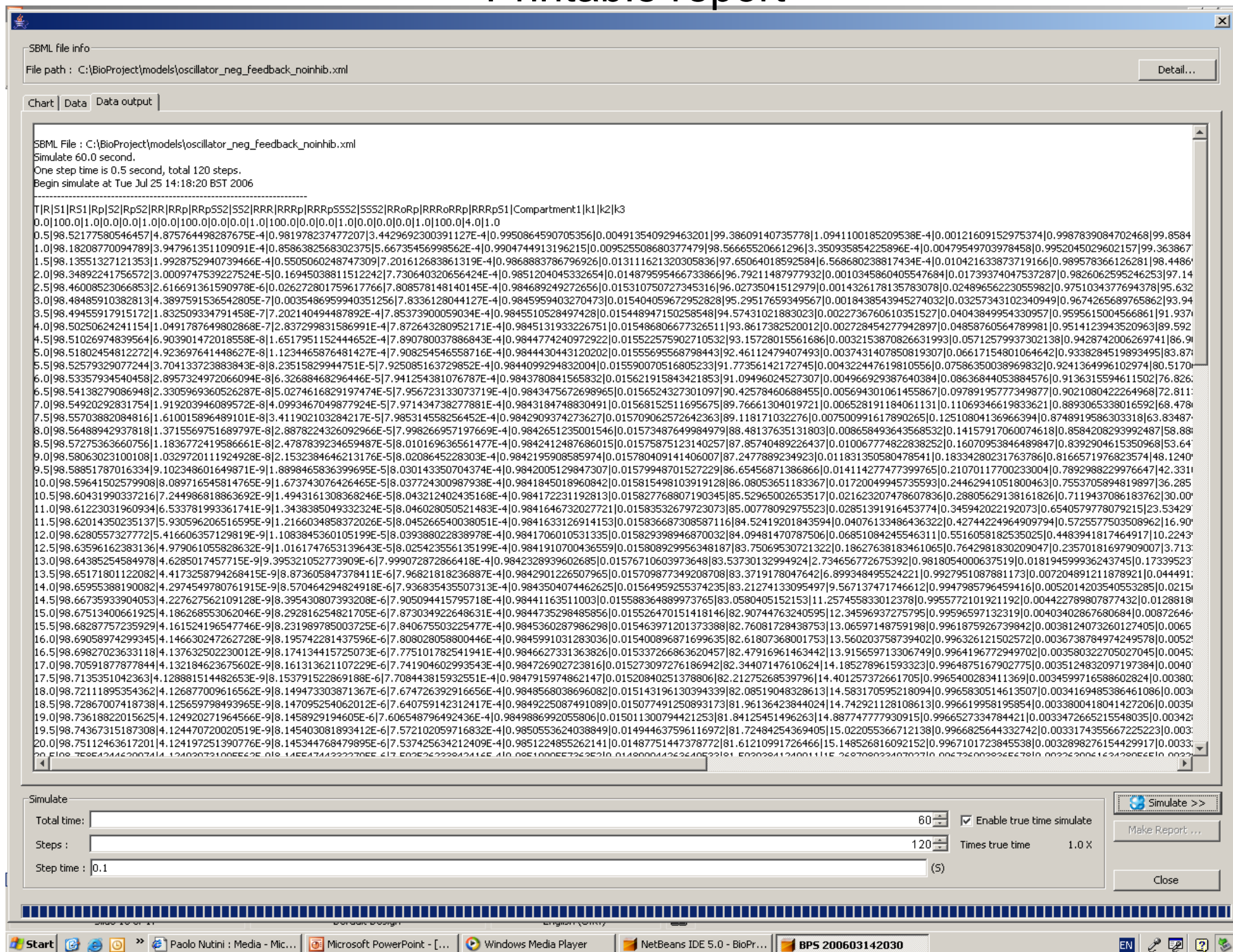
# Model Simulation



# Results viewer



## Printable report





# How to save a text file for MC2?

The screenshot shows the BioNessie 1.0.G software interface. The top menu bar includes File, Edit, Tools, CVS, View, Window, and Help. The main window displays the simulation of levchenko.xml. The left sidebar shows a project tree with folders like fitting, models, paramscan, sens, and simulations. The main window has tabs for Simulation of levchenko.xml, C:\allBioPro\SIMAP\models\levchenko.xml, and C:\allBioPro\SIMAP\models\kholodenko.xml. The Simulation of levchenko.xml tab is active, showing SBML file info and a large text output area. The text output area contains a long string of simulation data. At the bottom, there is a 'Simulate' section with controls for Total time (60), Steps (120), and Step time (0.5). A red box highlights the 'Save Report' button, with an arrow pointing to it and the text 'Click here'.

# BioNessie is not only a editor and simulator, but also an analyser !

Parameter Scans

Sensitivity Analysis

Model VCS Support

Model Optimisation

Advanced Model Checking (by Robin Donaldson)

# Parameter Scans

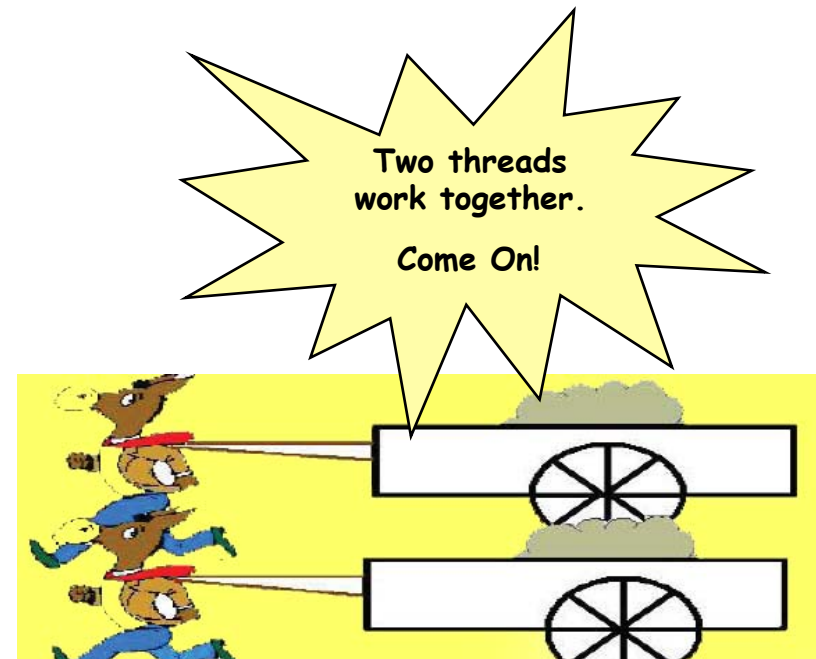


# Single/Multi –threaded/Grid-enabled Parameter Scan

- Parameter Scan

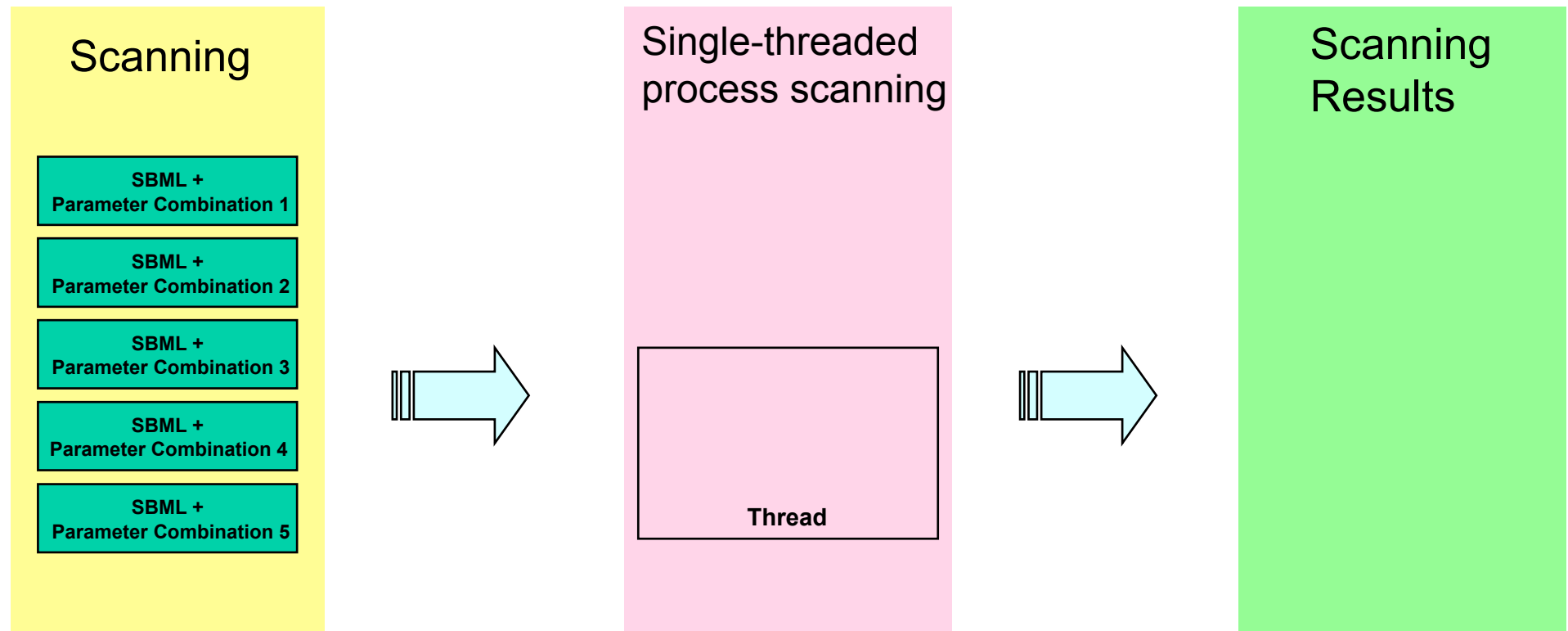
- To explore the behavior of the model over a wide range of parameter values using a parameter scan that runs one simulation for each parameter combination.

- But

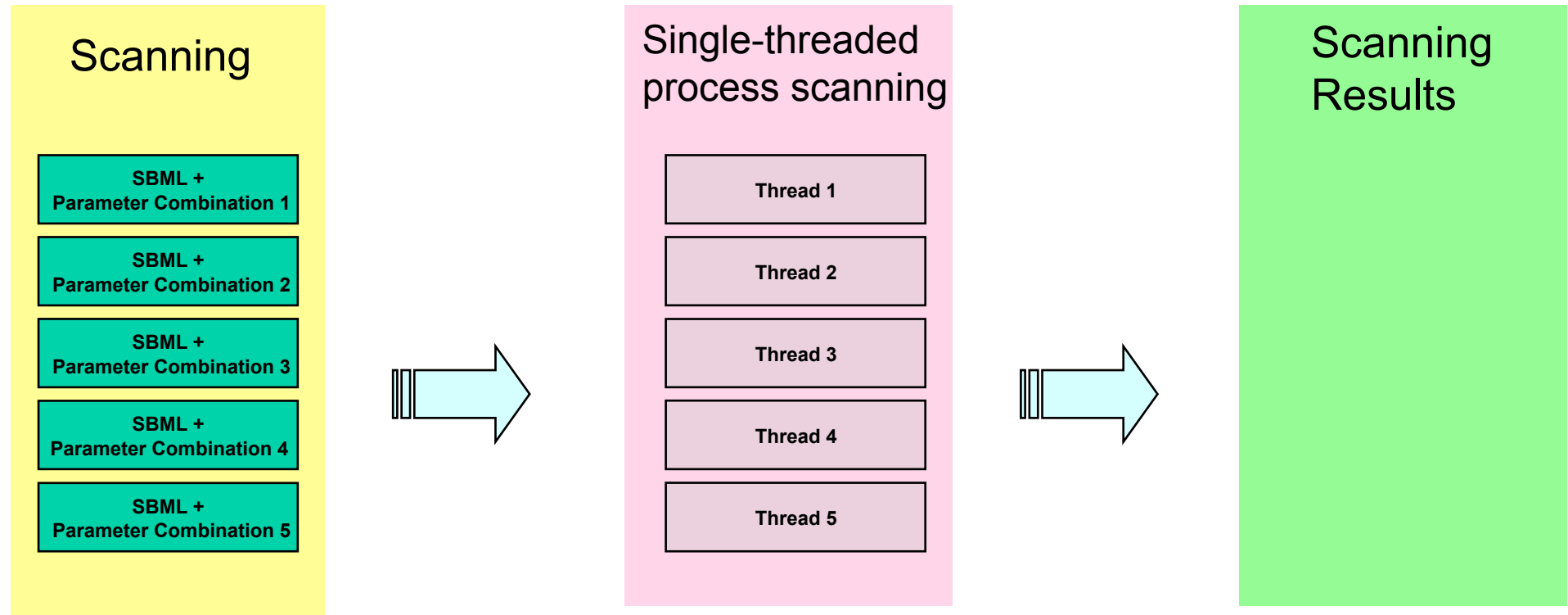


- So, having more than one thread running is beneficial

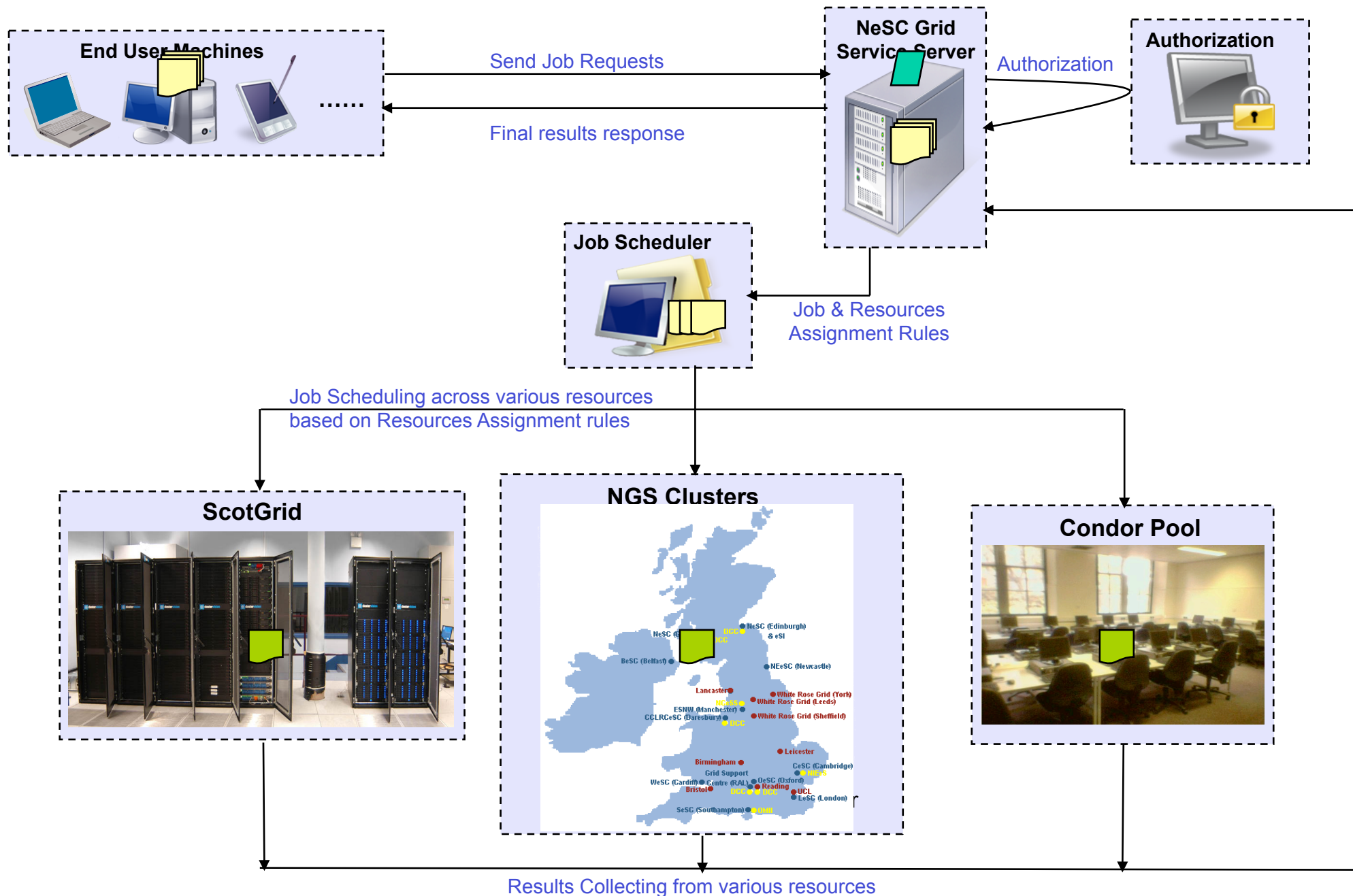
# Single-threaded Parameter Scan



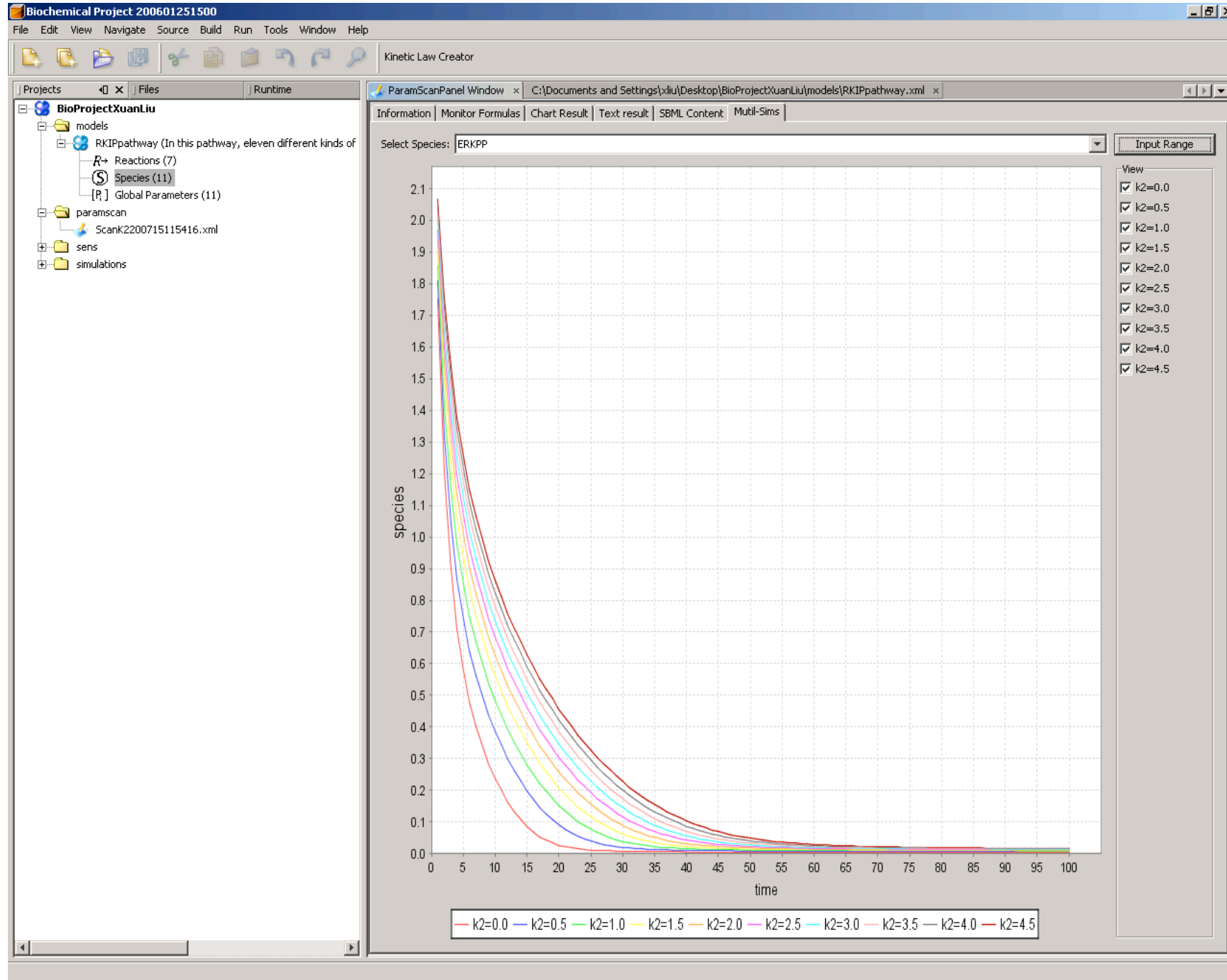
# Multithreaded Parameter Scan



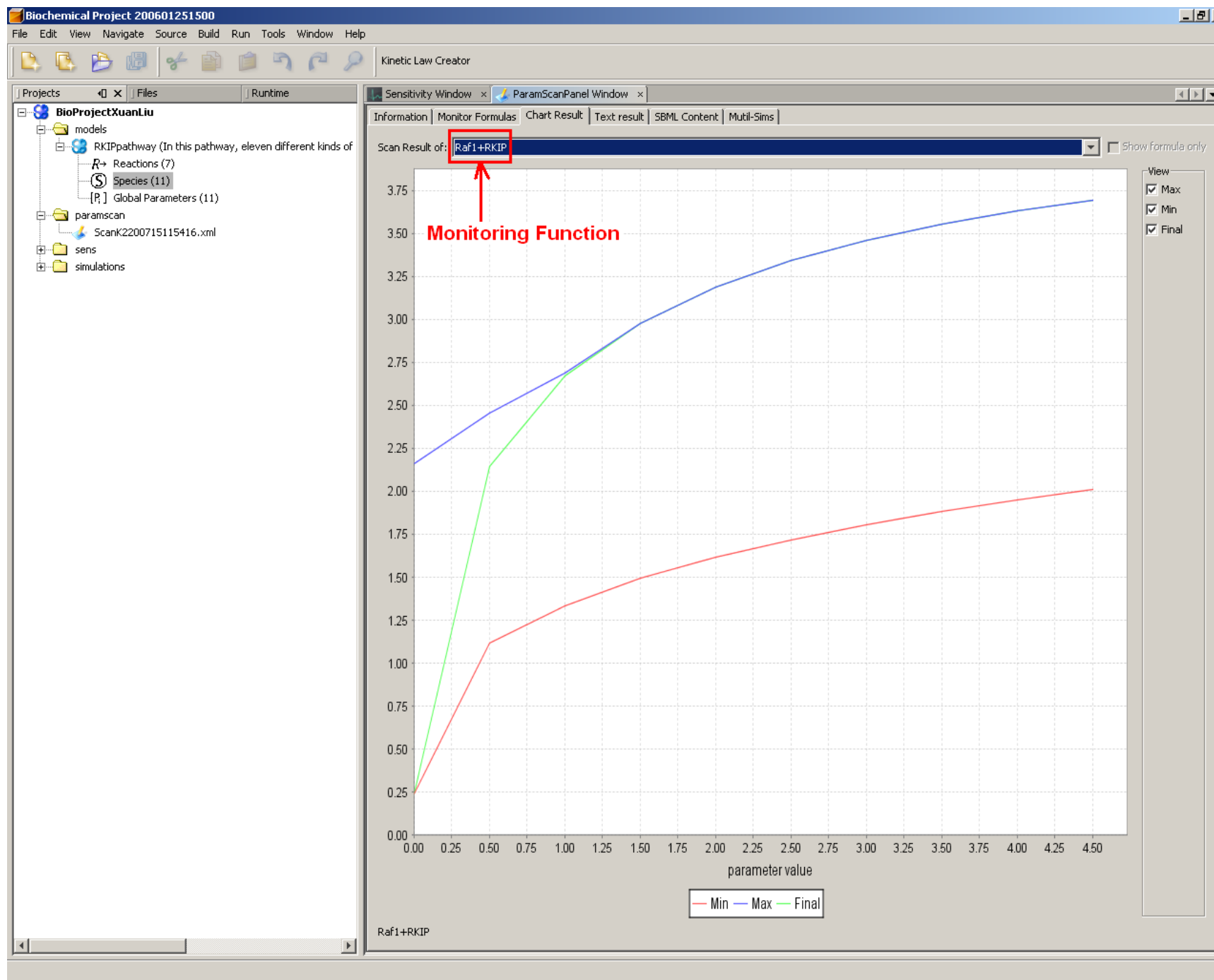
# Grid enabled BioNessie Architecture



# Parameter Scanning in BioNessie



This plot shows the whole trace of selected species - ERKPP for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 4.5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.



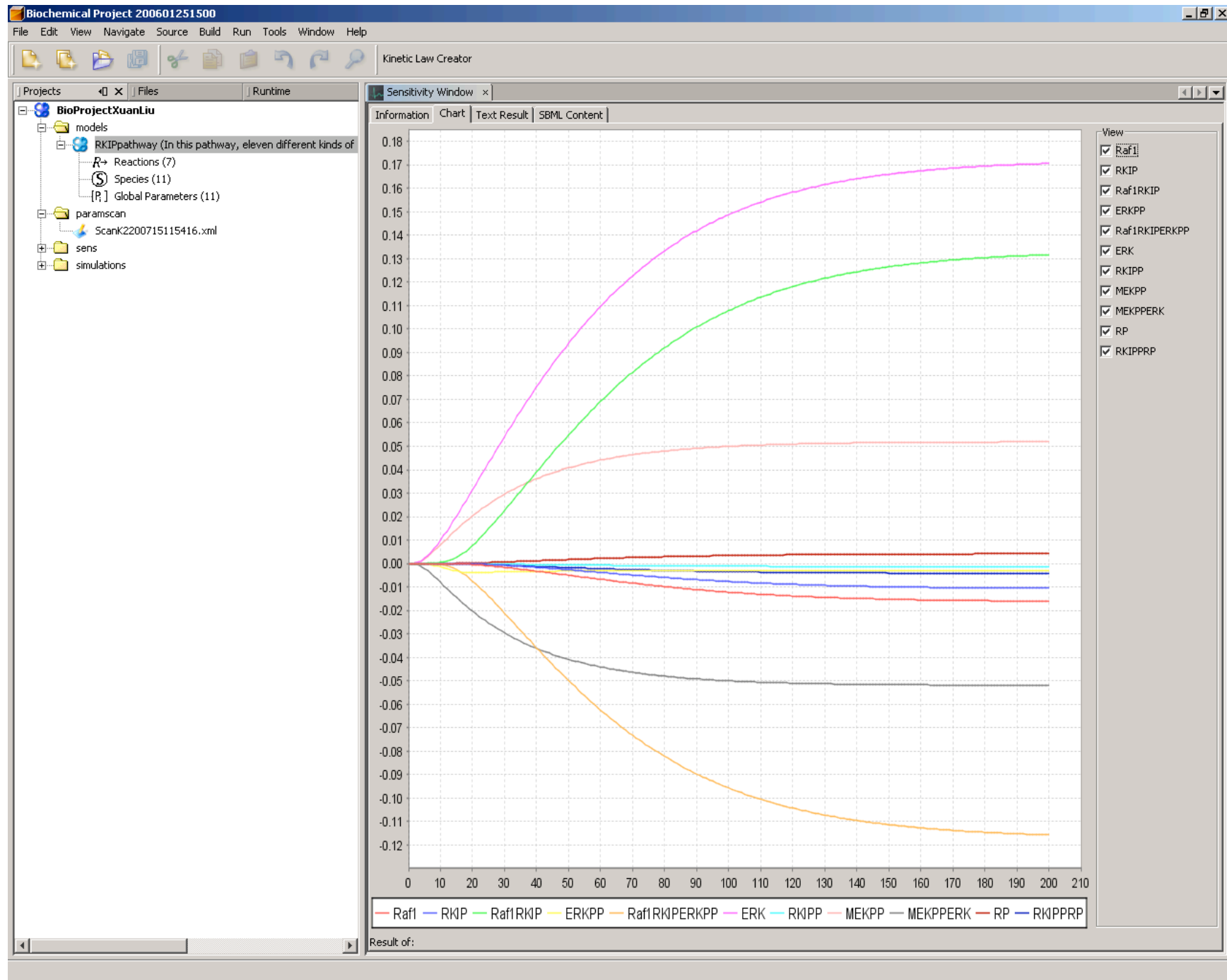
This plot shows the min. max and final values of monitoring function **Raf1+RKIP** for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.

# Sensitivity Analyser in BioNessie



# Introduction to Sensitivity Analysis

- Sensitivity analysis investigates the changes in the system outputs or behavior with respect to the parameter variations. It is a general technique for establishing the contribution of individual parameter values to the overall performance of a complex system.
- Sensitivity analysis is an important tool in the studies of the dependence of a system on external parameters, and sensitivity considerations often play an important role in the design of control systems.

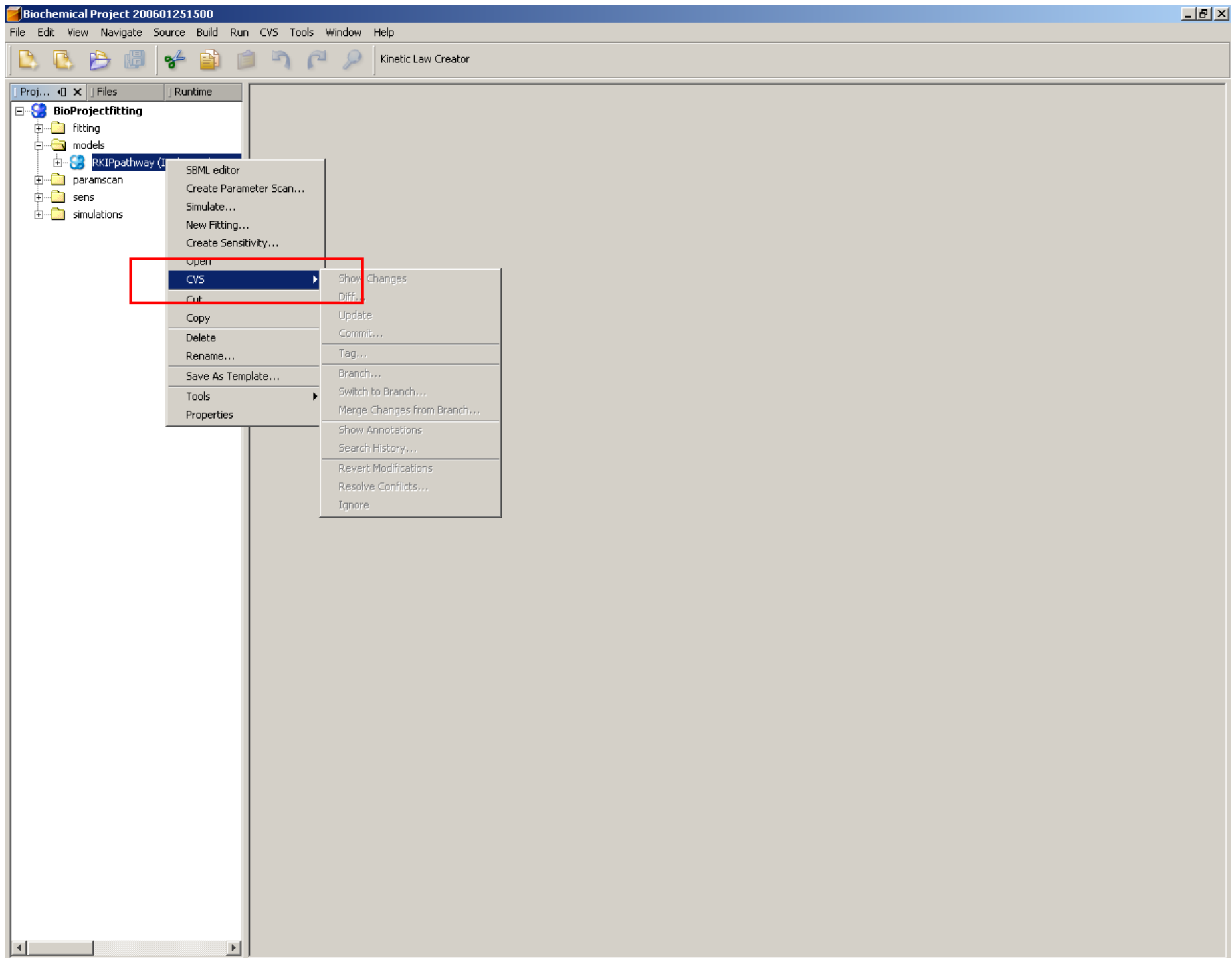


This creates a plot of the sensitivity of species Raf1, RKIP, Raf1RKIP, ERKPP, Raf1RKIPERKPP, ERK, RKIPP, MEKPP, MEKPPERK, RP and RKIPPRP to the values of the parameter K6 for the timecourse of 200 timesteps of 200 time units.

# Model Version Control System

# Introduction to Version Control System

- VCS uses client-server architecture: a server stores the current version(s) of the project and its history, and clients connect to the server in order to check-out a complete copy of the project, work on this copy and then later check-in their changes.
- Client and server connect over a LAN or over the Internet, but client and server may both run on the same machine if VCS has the task of keeping track of the version history of a project with only local developers.
- BioNessie VCS system keeps track of all work and all changes in a set of SBML models and various results for simulation, scanning, sensitivity analysis and fitting. All those changes can be saved either in server side or user's own machine.



# Model Fitting

---

- BioNessie can perform data fitting and for optimisation of model parameters.
- Uses Genetic Algorithm to search different rate constant sets in a predefined range to minimise the difference between the time-course data (obtained from wet lab) and simulation results of the model.

**Biochemical Project 200601251500**

File Edit View Navigate Source Build Run CVS Tools Window Help

Kinetic Law Creator

Files Run... **BioProjectfitting**

- fitting
  - aef2007226124622
  - gg2007226122843
  - re2007226121145
- models
  - RKIPpathway (In t
  - Reactions (7)
  - Species (11)
  - Global Paramet
- paramscan
- sens
- simulations

...ml **Fitting C:/Documents and Settings/xliu/Desktop/BioProjectfitting/fitting/aef2007226124622.xml**

Input Arithmetic Result chart Report

Fitting file path: C:/Documents and Settings/xliu/Desktop/BioProjectfitting/fitting/aef2007226124622.xml Create at: Mon Mar 26 12:46:22 BST 2007

Title: aef Author: asdf

Note:

SBML File path: C:/Documents and Settings/xliu/Desktop/BioProjectfitting/models/RKIPpathway.xml

Arithmetic setting

Arithmetic: GA

Circel: 64

Result count: 1

Parameter scan setting

k1 : (0.0 - 0.6) at 1000 steps

k2 : (0.0 - 0.0080) at 1000 steps

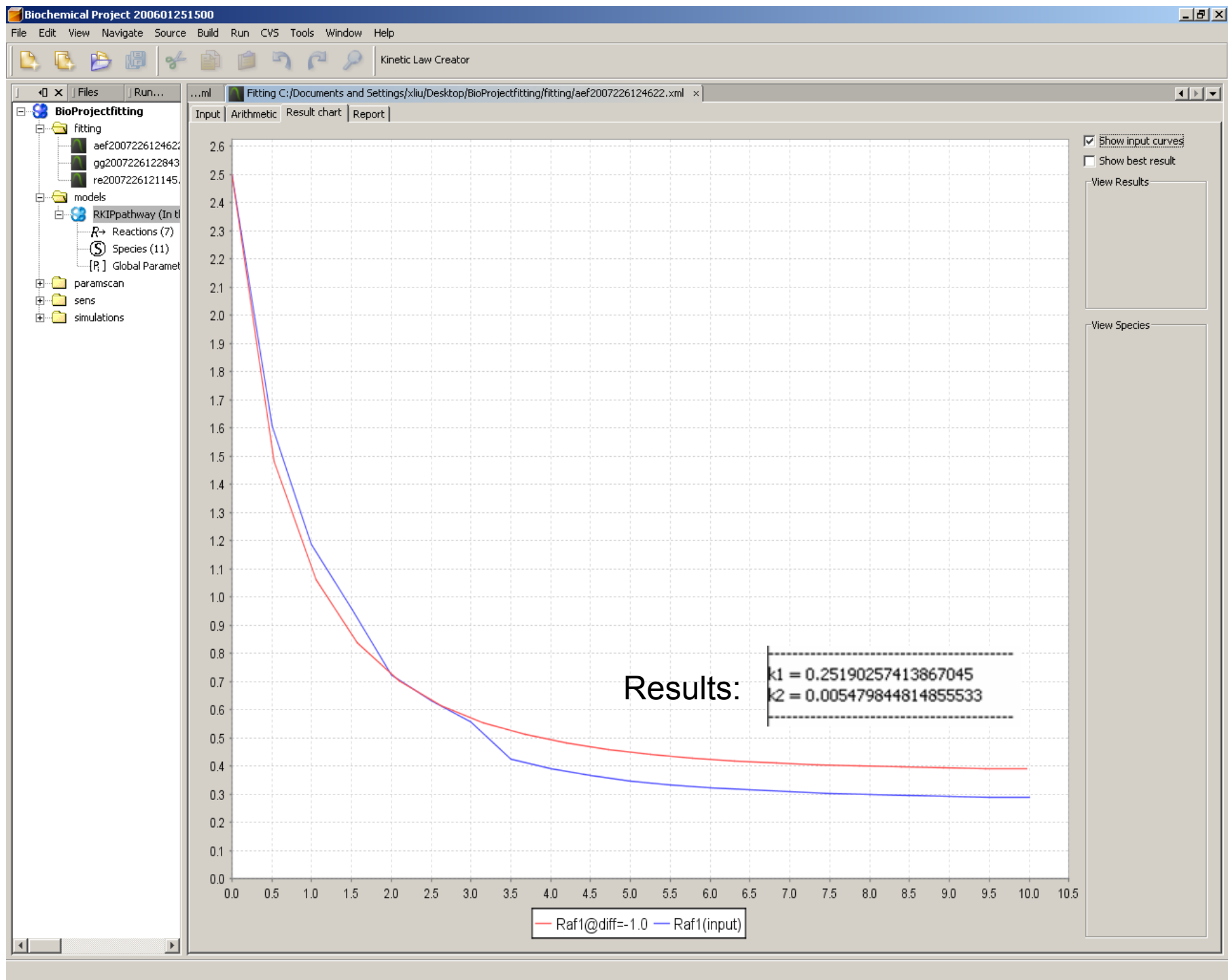
Parameter detail info:

No result , just do it!

Clean Result:

Time	Raf1
0	2.5
0.5	1.6067687099380618
1.0	1.1865847519014296
1.5	0.9598537292360268
2.0	0.7215137304779632
2.5	0.6306583715830768
3.0	0.5580268421286951
3.5	0.4233665269980797
4.0	0.3907285304662648
4.5	0.3664327984452596
5.0	0.34808757959281004
5.5	0.3340766175492854
6.0	0.3232730497109187
6.5	0.31487114880687326
7.0	0.30828290649317645
7.5	0.3030720343838381
8.0	0.29891045002994246
8.5	0.2955487628927579
9.0	0.2927957537801612
9.5	0.2905037960790558
10.0	0.28855830318777285

Pause

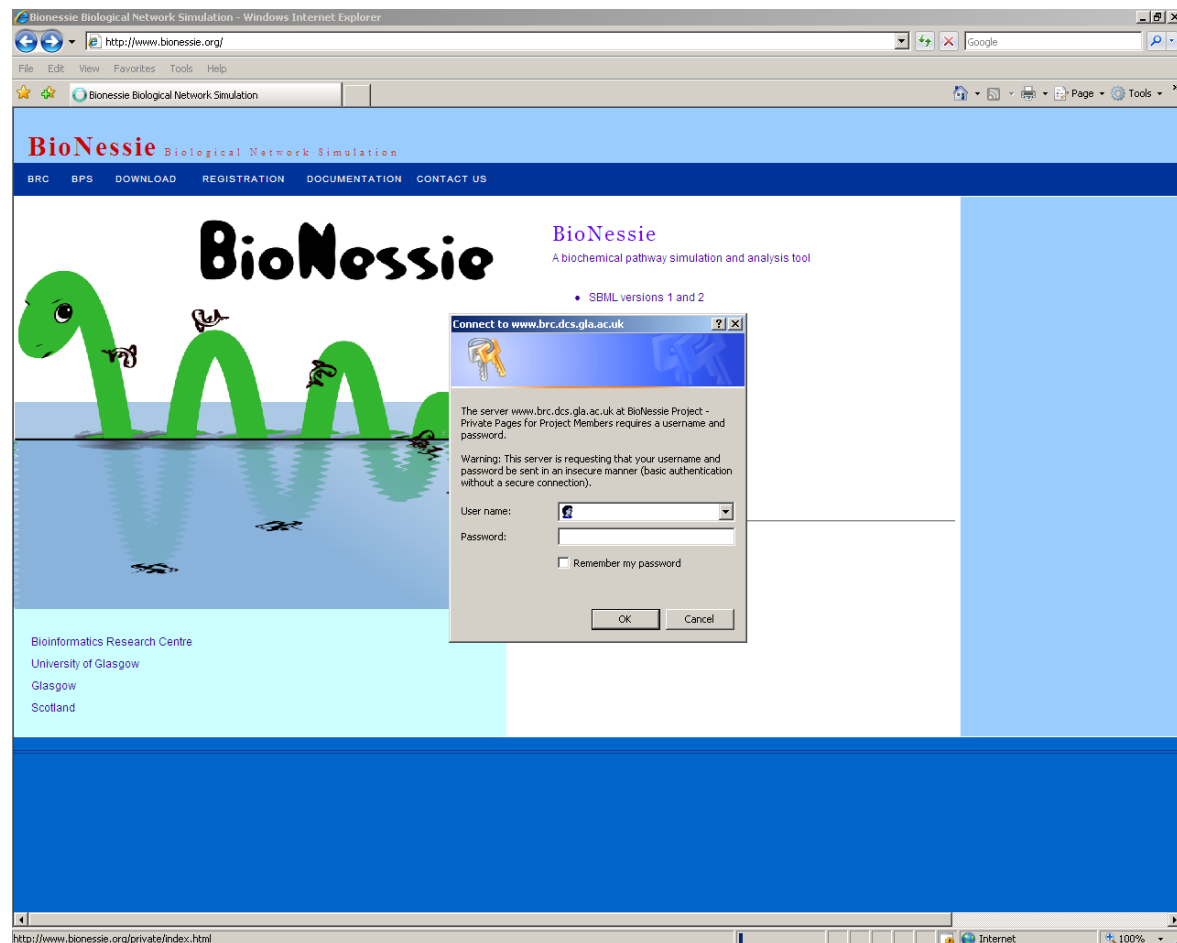




# How to obtain and install BioNessie

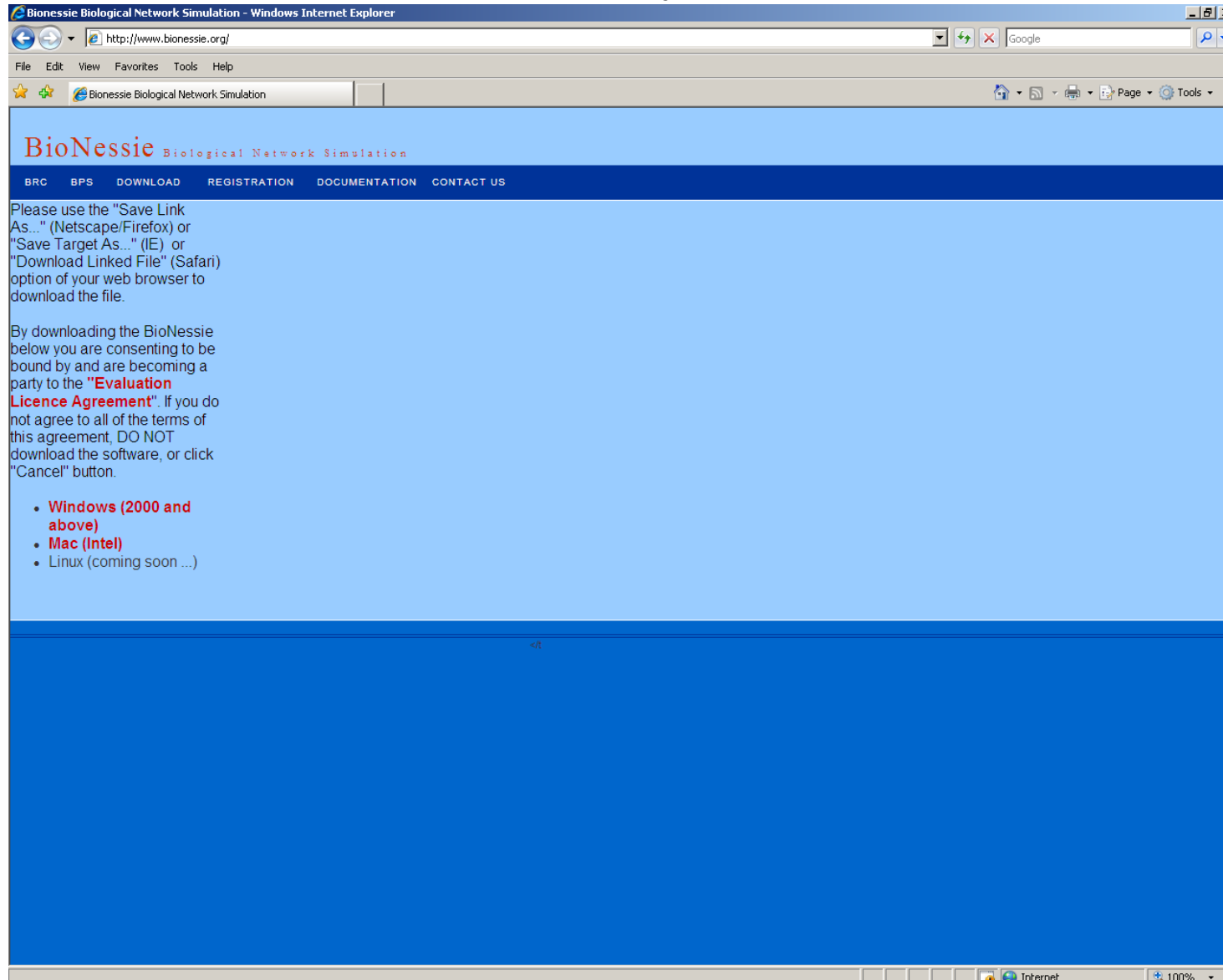
- In order to obtain a copy of BioNessie, you may send an email to Xuan Liu (xliu@brc.dcs.gla.ac.uk) for registration. Please provide your Name, Institute, Address and a valid "email address", to which an email will be sent with the login/password required to download BioNessie. Please read the terms of the "Evaluation License Agreement", under which BioNessie is distributed.

- Go to "Download" tag:
- Input the Login/Password

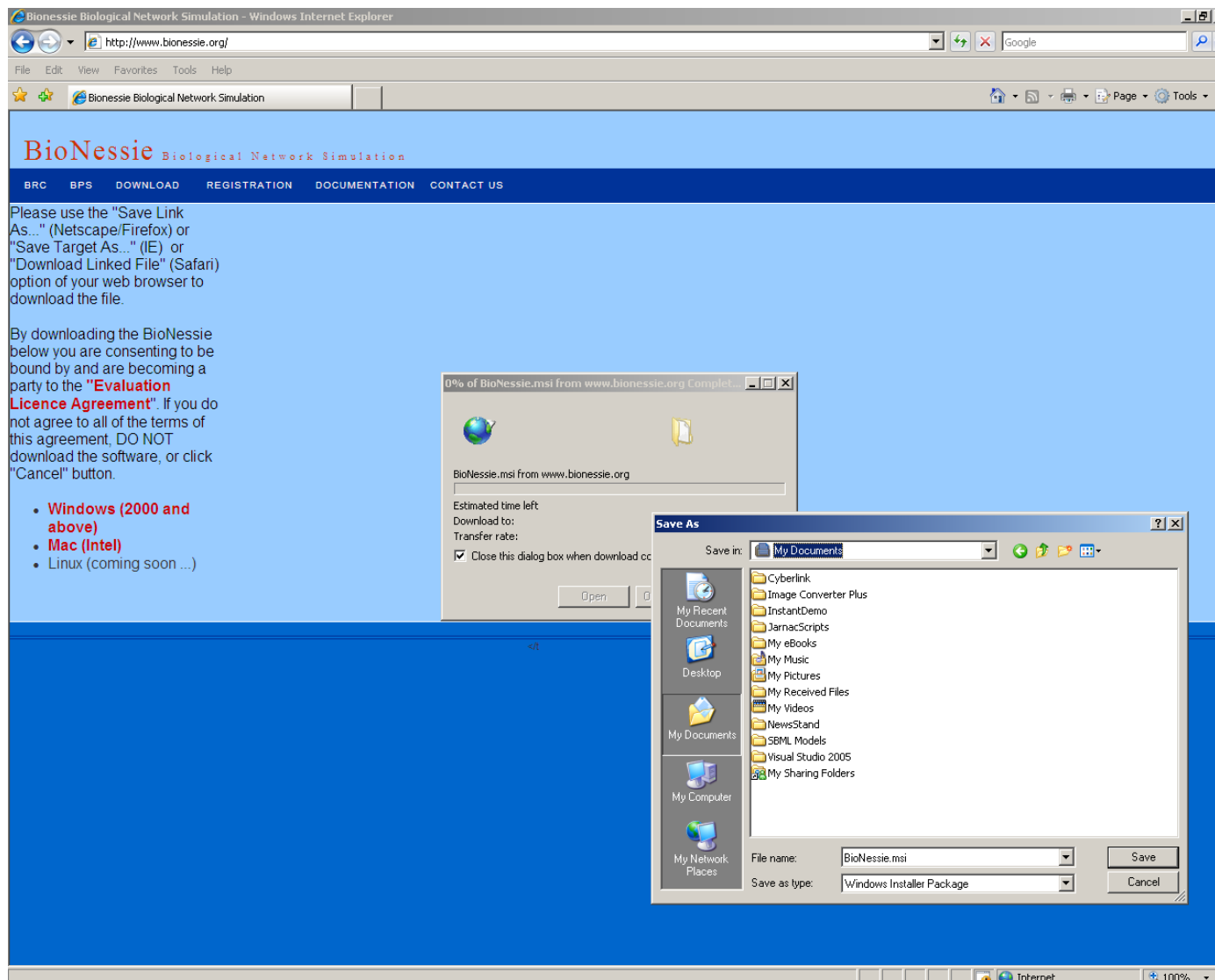


# How to obtain and install BioNessie

- Please use the "Save Link As..." (Netscape/Firefox) or "Save Target As..." (IE) or "Download Linked File" (Safari) option of your web browser to download the file.



# How to obtain and install BioNessie



- Installation is easy. Please follow the instructions which will be shown on installation process.