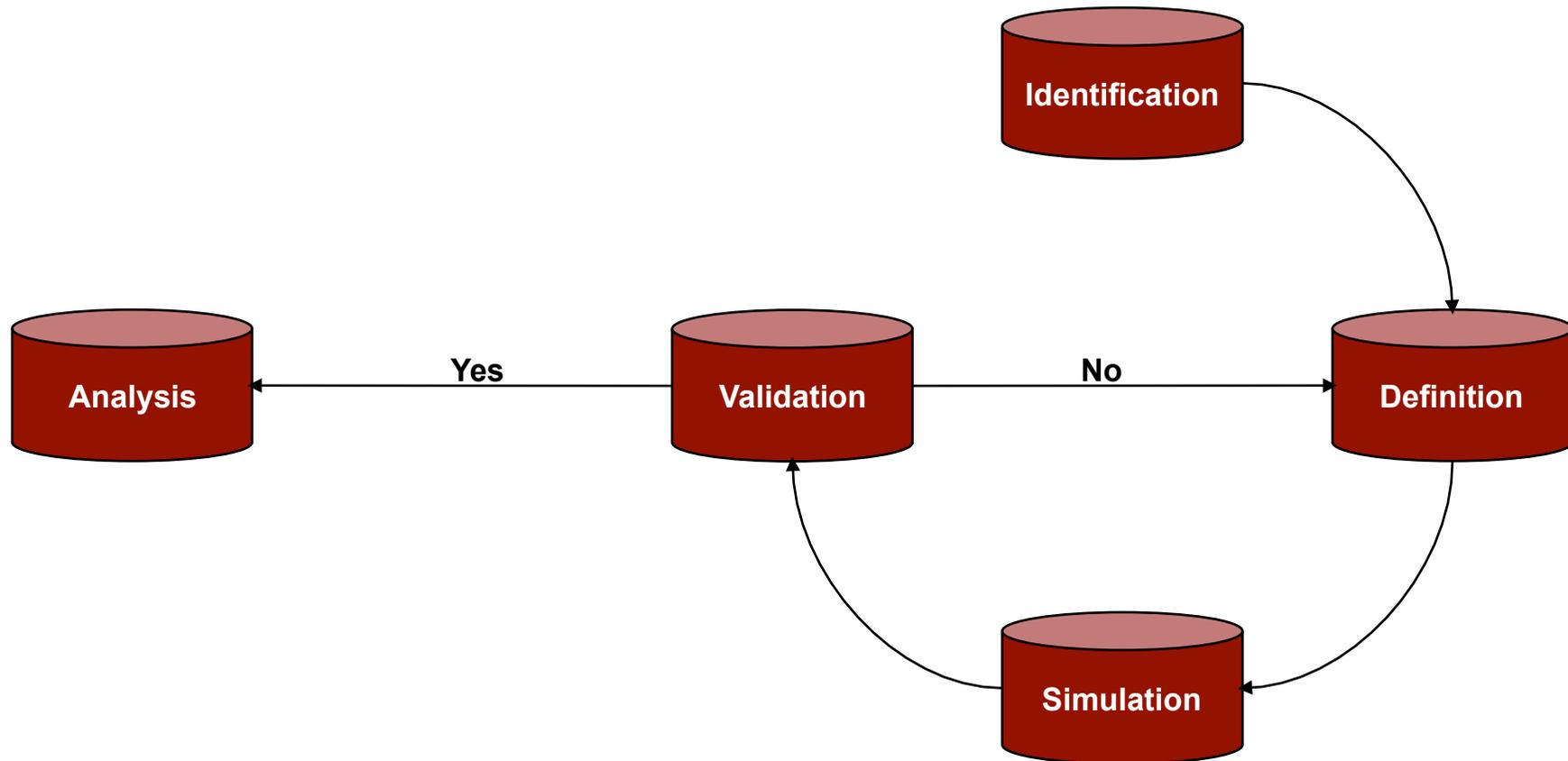


# BioNessie: A Software Tool for the Simulation and Analysis of Biochemical Networks

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*Bioinformatics Research Centre*  
*University of Glasgow*

# How to model

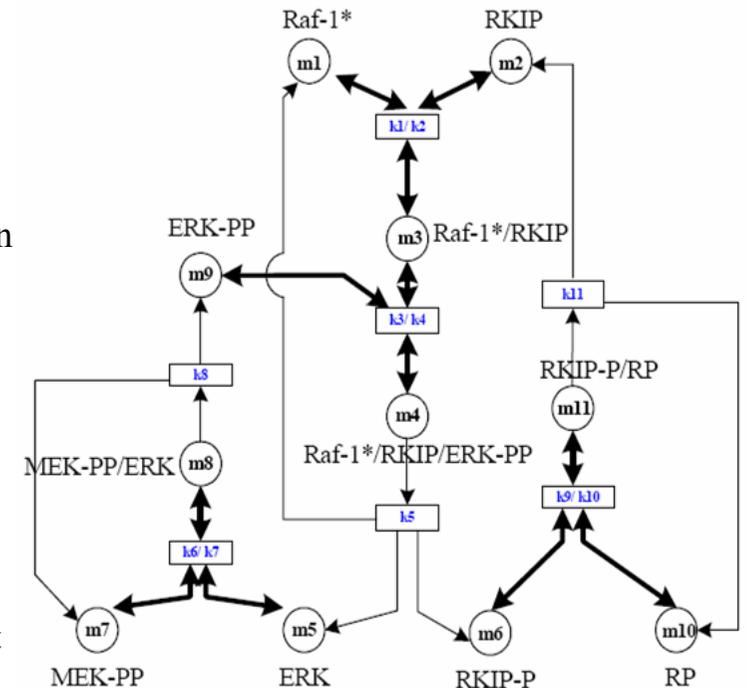


# How to model...1: Identification

- 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



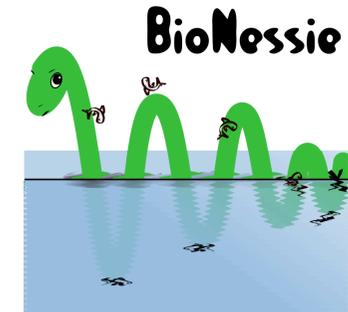


# How to model...3: Simulation

- 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

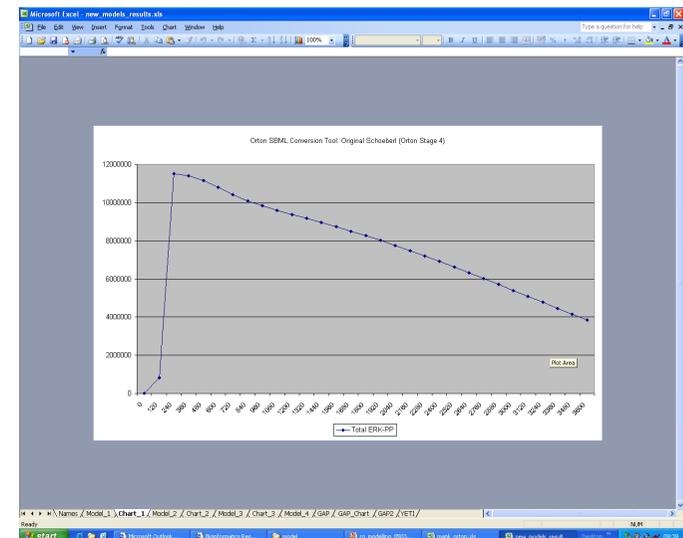
- Simulating the model typically returns a table of data which shows how each specie's concentration varies over time
- This table can then be used to generate graphs of specie concentrations
- Do the model results match the experimental data?

- 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)

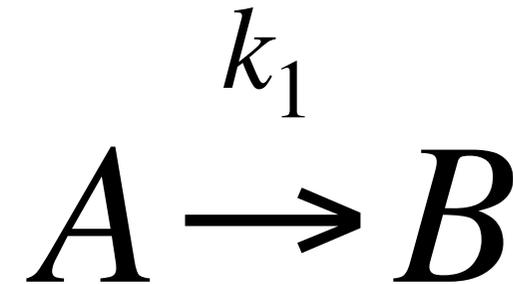


# SBML - XML Based Language

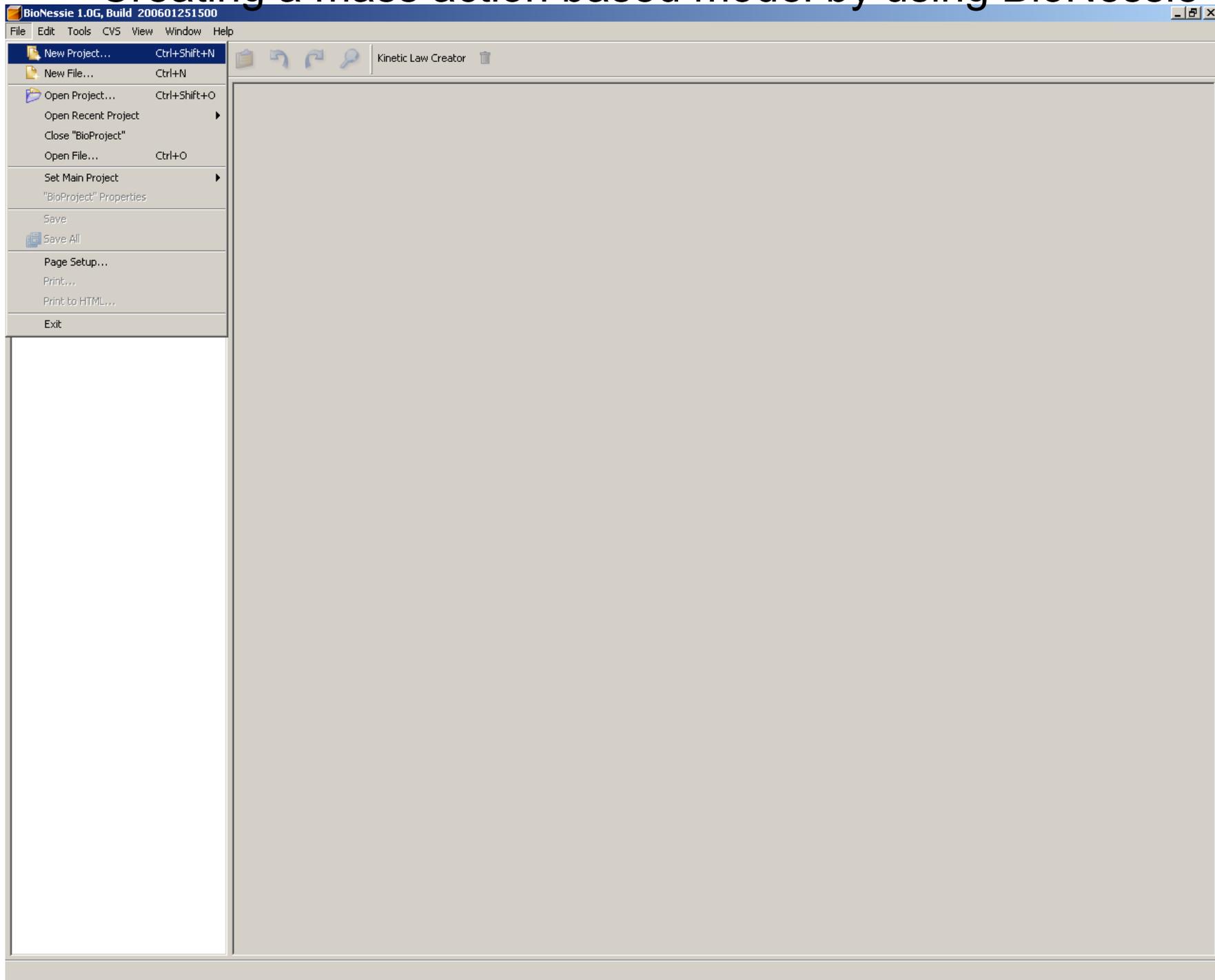
```
<sbml>
<model>
  <listOfCompartments> <compartment/> </listOfCompartments>
  <listOfSpecies> <specie/> </listOfSpecies>
  <listOfReactions>
    <reaction>
      <listOfReactants>
        <specieReference/>
      </listOfReactants>
      <listOfProducts>
        <specieReference/>
      </listOfProducts>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

BioNessie 1.0G, Build 200601251500

File Edit Tools CVS View Window Help

Proj... Files Runtime

- BioProject
- BioProject1**
- BioProjectf

**New Project**

**Steps**

- Choose Project**
- ...

**Choose Project**

Categories:

- Biochemical

Projects:

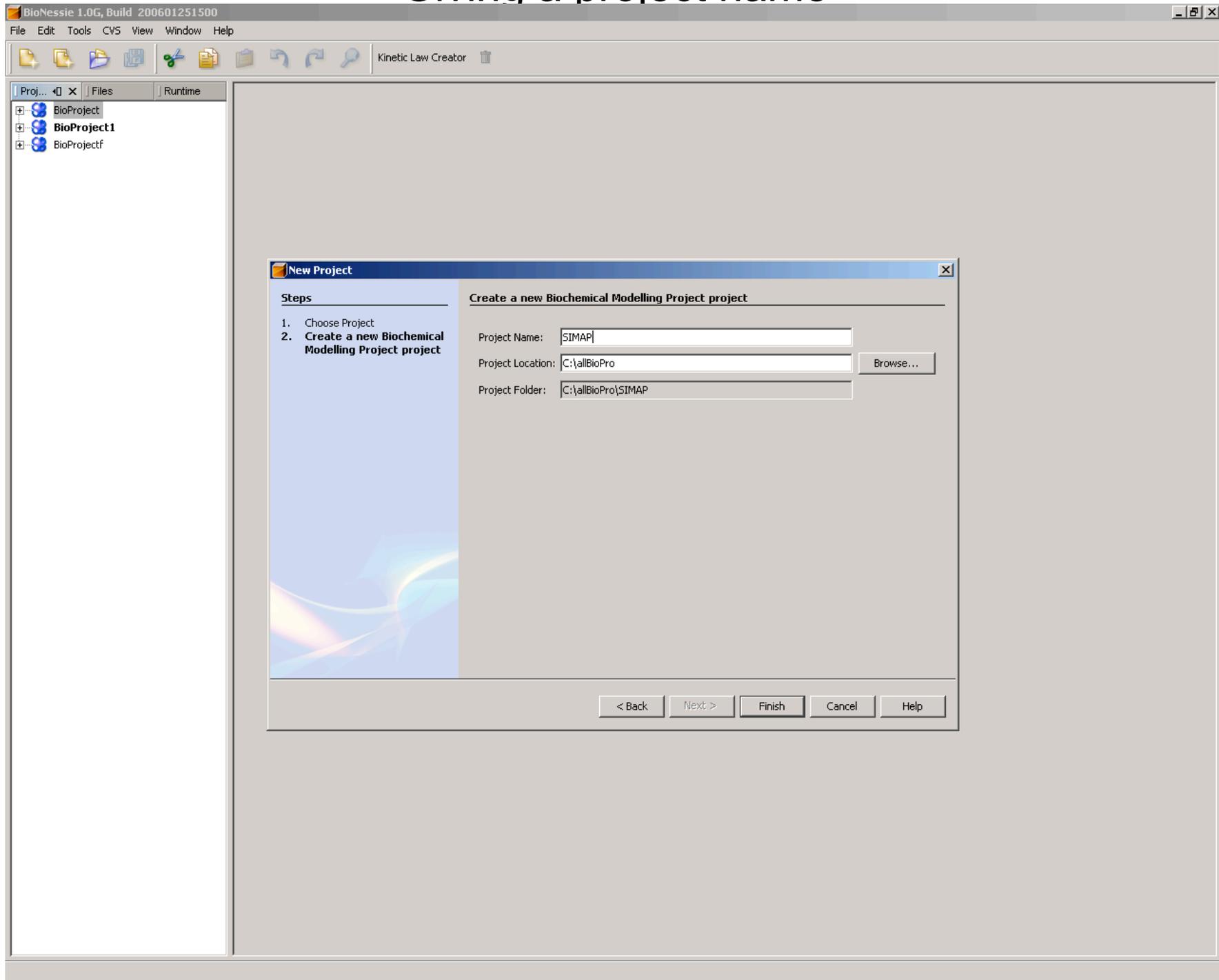
- Biochemical Modelling Project

Description:

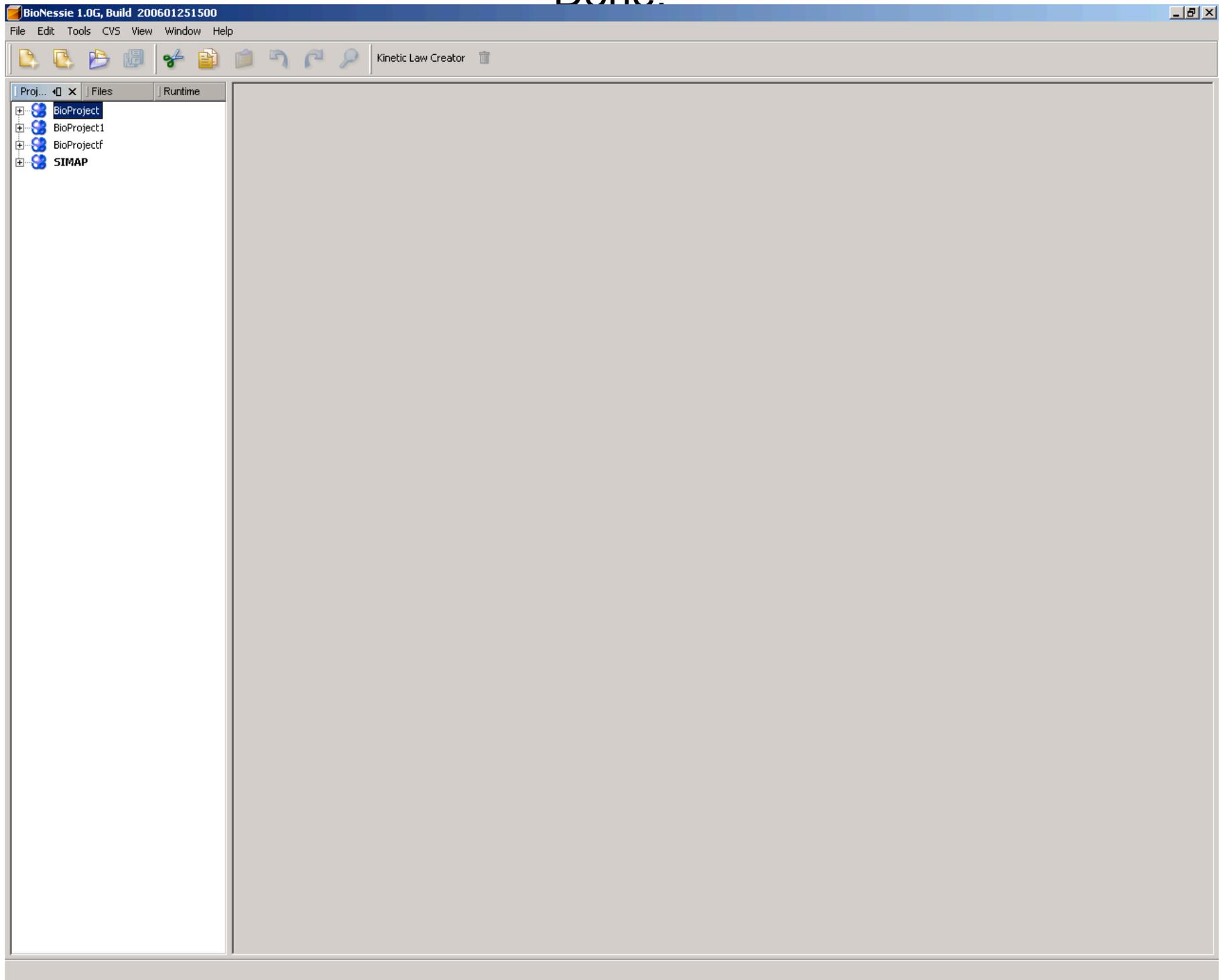
Sample Biochemical Modelling Project project

< Back Next > Finish Cancel Help

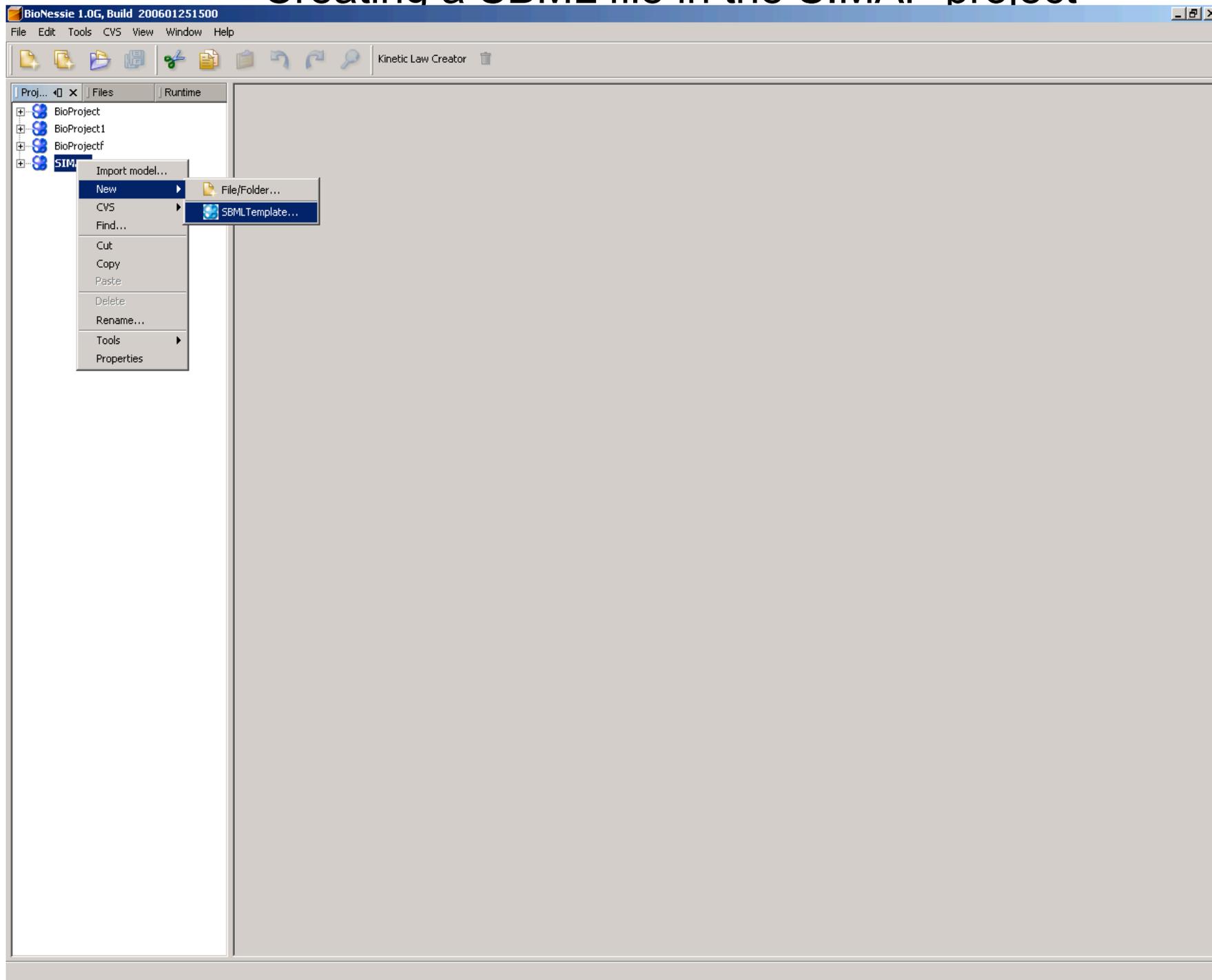
# Giving a project name



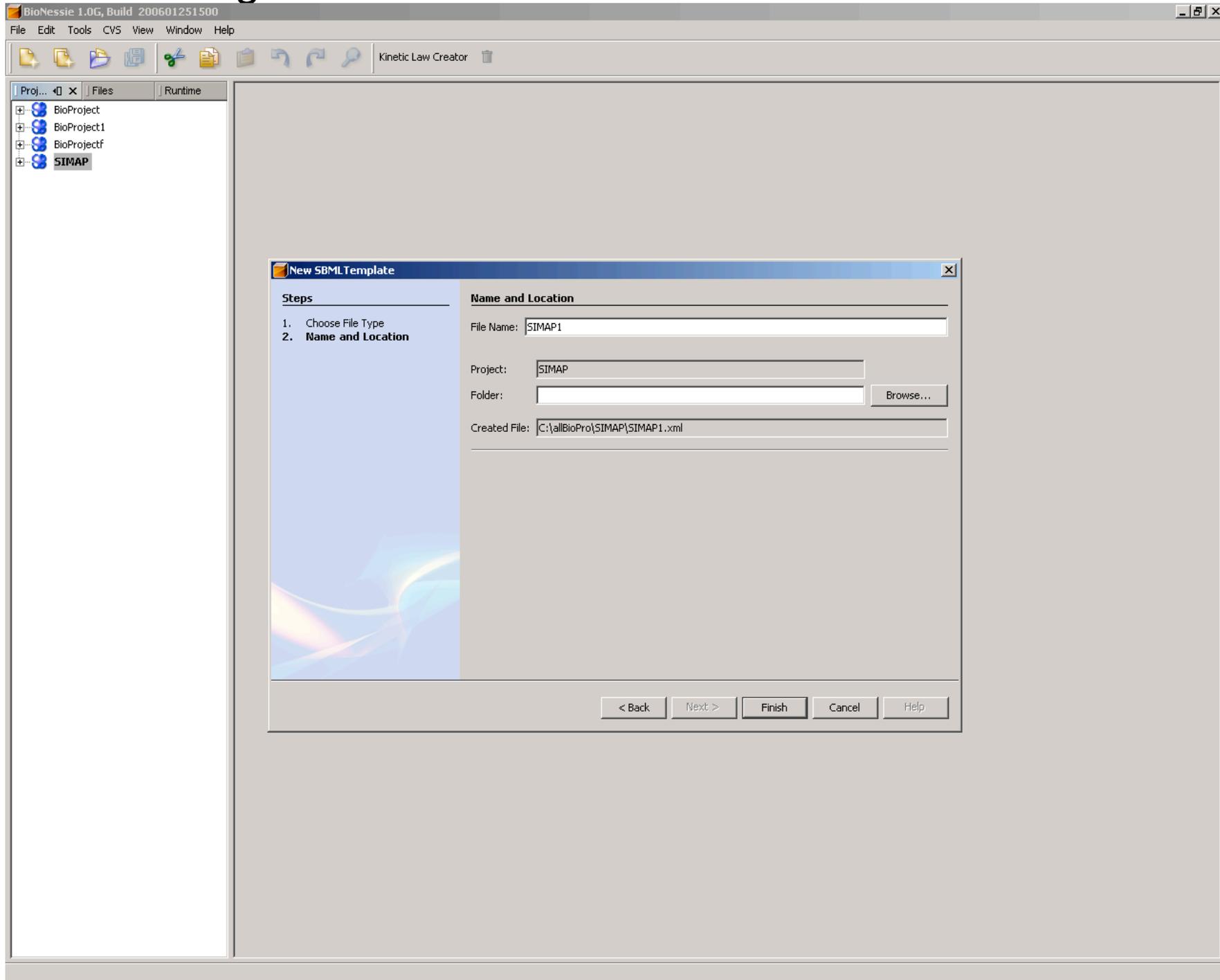
# Done!



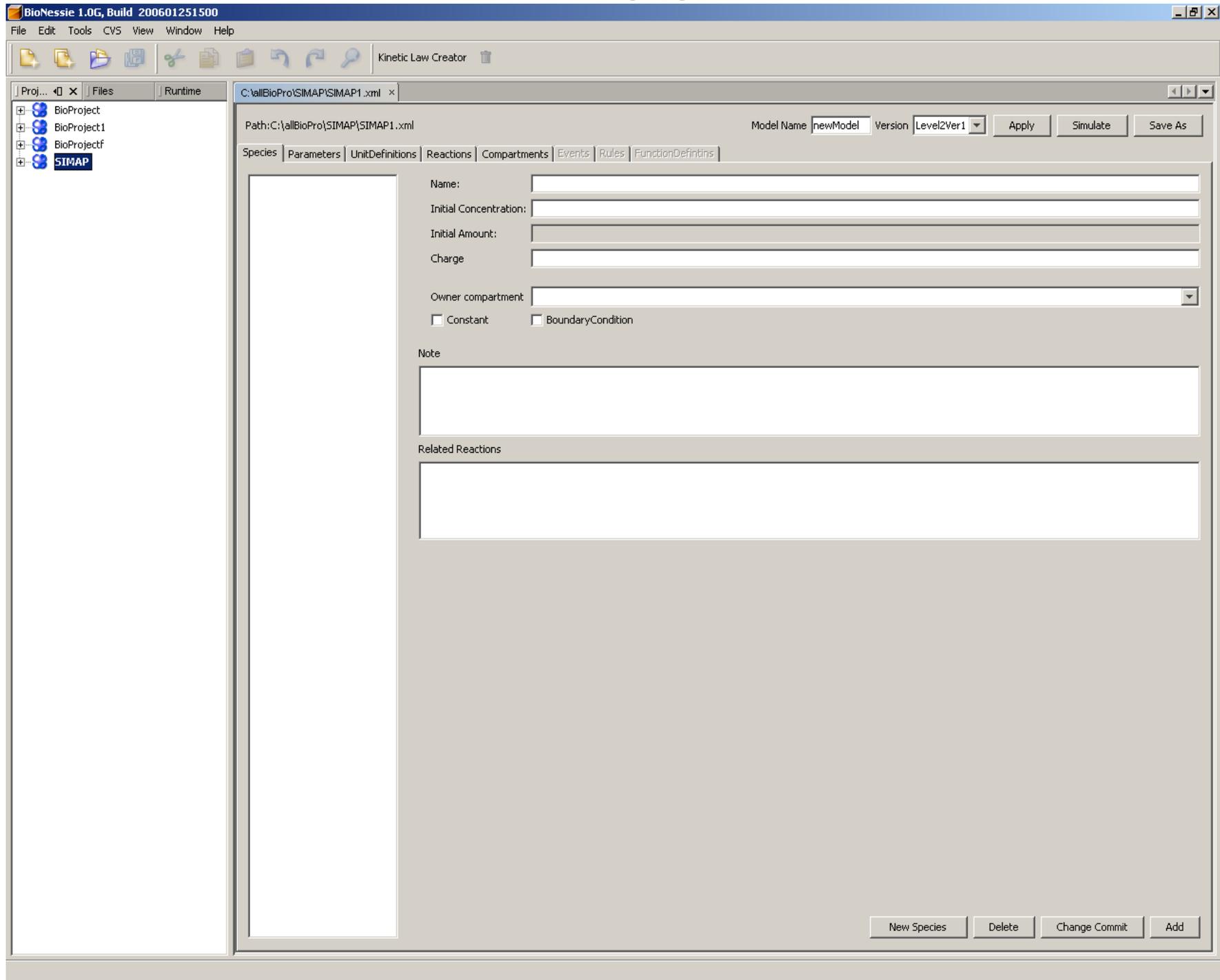
# Creating a SBML file in the SIMAP project



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



# Done!



# Creating a compartment

The screenshot shows the BioNessie 1.0G software interface. The main window is titled 'Kinetic Law Creator' and displays a project tree on the left with 'SIMAP' selected. The main workspace is divided into tabs: Species, Parameters, UnitDefinitions, Reactions, Compartments, Events, Rules, and FunctionDefinitions. The 'Compartments' tab is active, showing a form for creating a new compartment with fields for Name, Size, Spatial Dimensions, Volume, and Note. A modal dialog box titled 'Please input new compartment name' is open, with a text input field containing 'Com1' and 'OK' and 'Cancel' buttons.

# Created!

The screenshot shows the BioNessie 1.0G software interface. The main window title is "BioNessie 1.0G, Build 200601251500". The menu bar includes "File", "Edit", "Tools", "CVS", "View", "Window", and "Help". The toolbar contains icons for file operations and a "Kinetic Law Creator" button. The left sidebar shows a project tree with "BioProject", "BioProject1", "BioProjectf", and "SIMAP". The main workspace displays the "Compartment" configuration for "Com1" with the following fields: Name (Com1), Size (1.0), Spatial Dimensions (3), and Volume (1.0). A "Note" field is present but empty. An "Information" dialog box is overlaid on the workspace, displaying the message "The compartment has been added!" with an "OK" button. At the bottom right of the main workspace, there are buttons for "New Compartment", "Delete", "Change Commit", and "Add".

# Creating a species

The screenshot shows the BioNessie 1.0G software interface. The title bar reads "BioNessie 1.0G, Build 200601251500". The menu bar includes "File", "Edit", "Tools", "CVS", "View", "Window", and "Help". The toolbar contains icons for file operations and a "Kinetic Law Creator" button. The main window displays a project tree on the left with "SIMAP" selected. The main area shows the "Species" tab for a species named "A". The "Path" is "C:\allBioPro\SIMAP\SIMAP1.xml". The "Model Name" is "newModel" and the "Version" is "Level2Ver1". The "Name" field contains "A", "Initial Concentration" is "5", "Initial Amount" is "0.0", and "Charge" is "0". The "Owner compartment" is set to "Com1". There are checkboxes for "Constant" and "BoundaryCondition", both of which are unchecked. Below these fields are sections for "Note" and "Related Reactions", both of which are empty. At the bottom right, there are buttons for "New Species", "Delete", "Change Commit", and "Add".

# Created

The screenshot shows the BioNessie 1.0G software interface. The main window is titled "BioNessie 1.0G, Build 200601251500" and has a menu bar with "File", "Edit", "Tools", "CVS", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons and a "Kinetic Law Creator" button. The main workspace is divided into several panes. On the left, there is a "Proj..." pane showing a tree view of projects: "BioProject", "BioProject1", "BioProjectf", and "SIMAP". The "SIMAP" project is selected. The main workspace is titled "C:\allBioPro\SIMAP\SIMAP1.xml" and contains a form for defining a species. The form has tabs for "Species", "Parameters", "UnitDefinitions", "Reactions", "Compartments", "Events", "Rules", and "FunctionDefinitions". The "Species" tab is active, showing a list of species on the left with "A" selected. To the right of the list are input fields for "Name" (A), "Initial Concentration" (5), "Initial Amount" (0.0), and "Charge" (0). There is also a dropdown for "Owner compartment" and checkboxes for "Constant" and "BoundaryCondition". Below these fields is a "Note" text area. At the bottom of the main workspace are buttons for "New Species", "Delete", "Change Commit", and "Add". An "Information" dialog box is open in the center, displaying an information icon and the text "The species has been added!" with an "OK" button.

# Creating other species

The screenshot shows the BioNessie 1.0G software interface. The main window is titled "Kinetic Law Creator" and displays the "Species" tab. The left sidebar shows a project tree with "SIMAP" selected. The main area shows the details for species "B":

- Name: B
- Initial Concentration: 0.0
- Initial Amount: 0.0
- Charge: 0
- Owner compartment: Com1
- Constant  BoundaryCondition

A dialog box titled "Please input a new species name" is open, with the name "C" entered in the input field. The dialog has "OK" and "Cancel" buttons.

At the bottom of the main window, there are buttons for "New Species", "Delete", "Change Commit", and "Add".

# Creating two parameters: K1 and K2

The screenshot displays the BioNessie 1.0G software interface. The main window is titled "Kinetic Law Creator" and shows a project named "SIMAP". The "Parameters" tab is active, and a parameter named "K1" is being created. The "Name" field is set to "K1" and the "Value" field is set to "1". The "Constant" checkbox is checked. An "Information" dialog box is open in the center, displaying the message "The parameter has been added!" with an "OK" button.

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

Species   Parameters   UnitDefinitions   Reactions   Compartments   Events   Rules   FunctionDefinitions

Name: K1  
Value: 1  
 Constant  
Note

Information  
The parameter has been added!  
OK

Edit Local Parameters   New Parameter   Delete   Change Commit   Add

# Created

The screenshot shows the BioNessie 1.0G software interface. The title bar reads "BioNessie 1.0G, Build 200601251500". The menu bar includes "File", "Edit", "Tools", "CVS", "View", "Window", and "Help". The toolbar contains various icons for file operations and editing. The main window displays a project tree on the left with "SIMAP" selected. The main area shows the "Parameters" tab for a model named "newModel". A parameter "K2" is being added with a value of "0.5" and is marked as a constant. An "Information" dialog box is open in the center, displaying the message "The parameter has been added!" with an "OK" button. At the bottom of the main window, there are buttons for "Edit Local Parameters", "New Parameter", "Delete", "Change Commit", and "Add".

# Creating a reaction A=B with K1 and K2

The screenshot shows the BioNessie 1.0G software interface. The main window displays the 'Kinetic Law Creator' dialog for a reaction named 'Reaction1'. The reaction is defined as  $A = B$  with a kinetic law of  $A * K1 - B * K2$ . The interface includes a file explorer on the left, a main workspace, and a detailed dialog box for reaction configuration.

**Reaction Configuration Dialog:**

- Name:** Reaction1
- Reactants:** A
- Products:** B
- Modifiers:** (empty)
- Reaction:** A=B
- Kinetic Law:** A \* K1 - B \* K2

**Steps:**

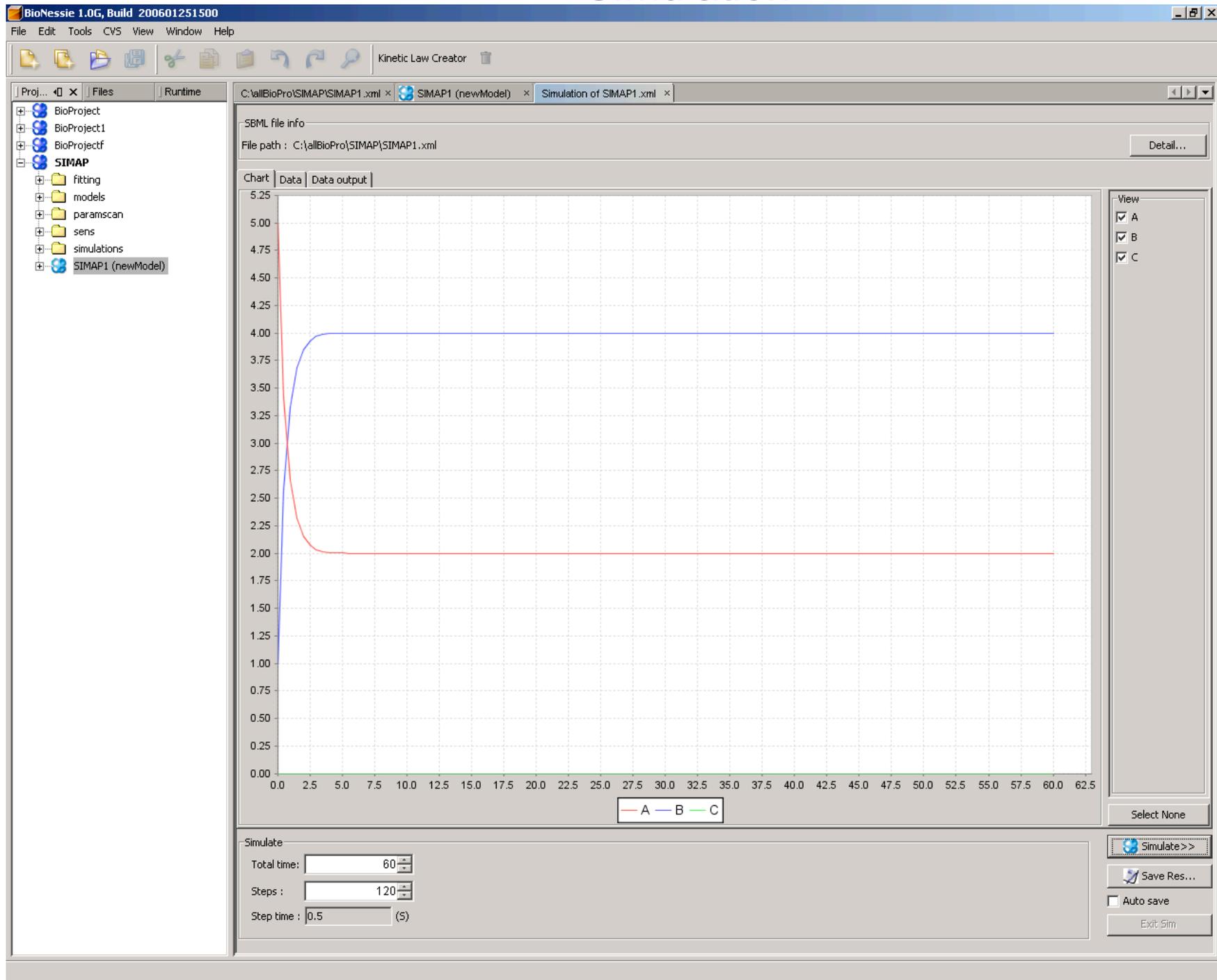
- Step 1, Input new reaction name and textual form :  
Name: reaction1 Reaction: A=B
- Step 2, Check the following lists:  
Reactants: A, Products: B, Modifiers: (empty)
- Step 3, Set reaction kinetic type:  
A \* K1 - B \* K2
- Step 4, Add new species and parameters to the model:  
The species will be added: (empty), The parameter will be added: (empty)

**Buttons:** OK, Cancel, Reset all, Add all, Edit, Delete select, Check, Delete, Change Commit, Add new Reaction...

The screenshot displays the BioNessie 1.0G software interface. The main window is titled "Kinetic Law Creator" and shows a project named "SIMAP1 (newModel)". The interface is divided into several sections:

- Left Panel:** A tree view showing the project structure, including folders for "fitting", "models", "paramscan", "sens", "simulations", and a sub-project "SIMAP1 (newModel)".
- Top Panel:** Contains the file path "C:\allBioPro\SIMAP\SIMAP1.xml", the model name "newModel", and the version "Level2Ver1". Buttons for "Apply", "Simulate", and "Save As" are visible.
- Reaction Editor:** A central area for defining a reaction. It includes a "Name" field (set to "Reaction1"), "Reactants" (containing "A"), "Products" (containing "B"), and a "Modifier" field. Arrows indicate the flow from reactants to products. Buttons for "Add" and "Delete select" are present for each section.
- Reaction Summary:** Below the editor, it shows "Reaction: A = B", the "Kinetic Law Formu" (empty), and a checkbox for "Fast reaction".
- Information Dialog:** A small dialog box titled "Information" is open, displaying the message "The reaction has been added." with an "OK" button.
- Bottom Panel:** Contains buttons for "Check", "Delete", "Change Commit", and "Add new Reaction...".

# Simulation



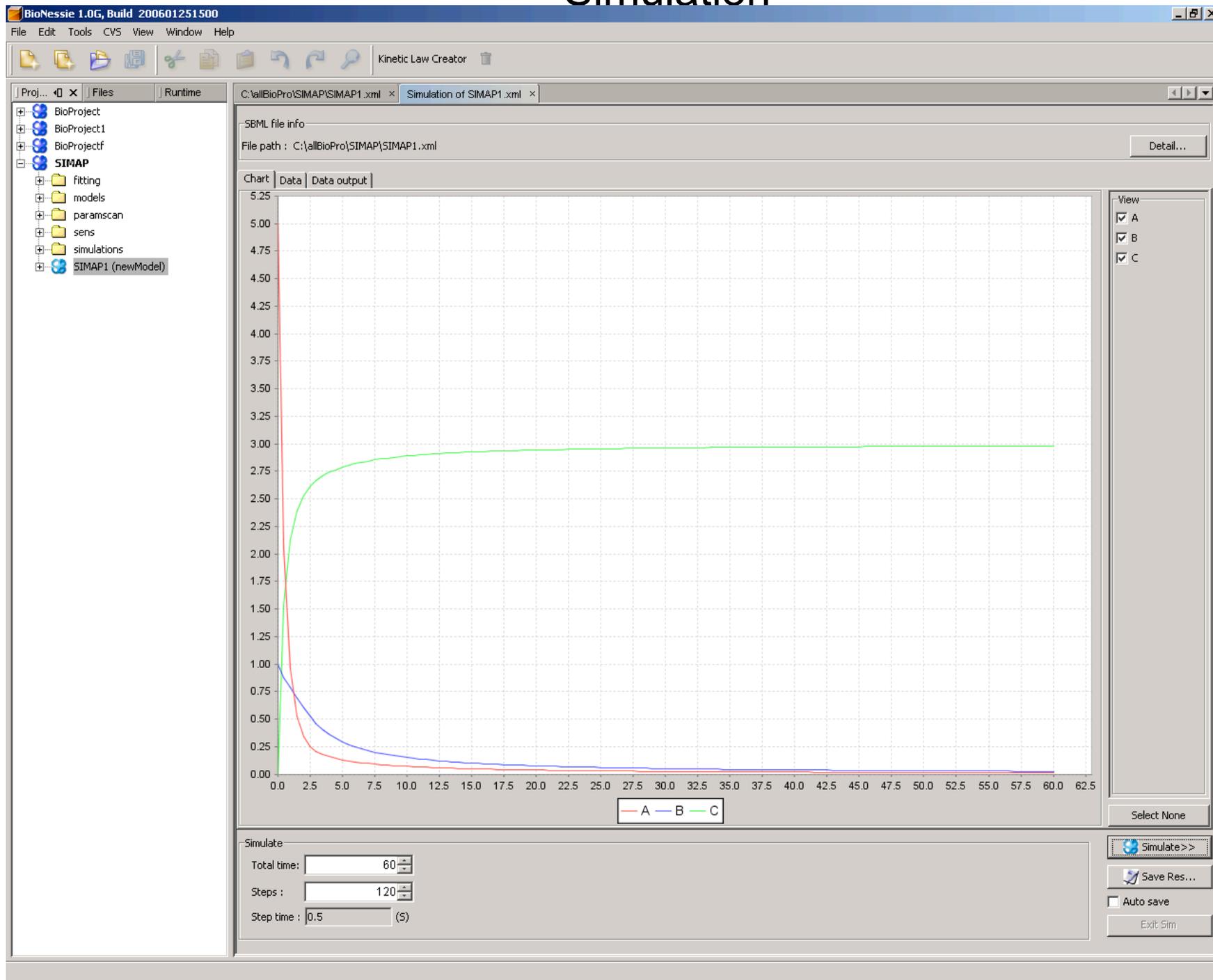
# Add another reaction $A+B \rightarrow C$ with $K_1$

The screenshot shows the BioNessie 1.0G interface. The main window displays the 'Reactions' tab for a simulation named 'SIMAP1'. A dialog box is open for adding a new reaction, titled 'Reaction2'. The dialog guides the user through four steps:

- Step 1:** Input new reaction name and textual form. The 'Name' field contains 'Reaction2' and the 'Reaction' field contains 'A+B->C'.
- Step 2:** Check the following lists. The 'Reactants' list contains 'A' and 'B', the 'Products' list contains 'C', and the 'Modifiers' list is empty.
- Step 3:** Set reaction kinetic type. The 'Kinetic Law' field contains 'K1 \* A \* B'.
- Step 4:** Add new species and parameters to the model. The 'The species will be added:' and 'The parameter will be added:' fields are currently empty.

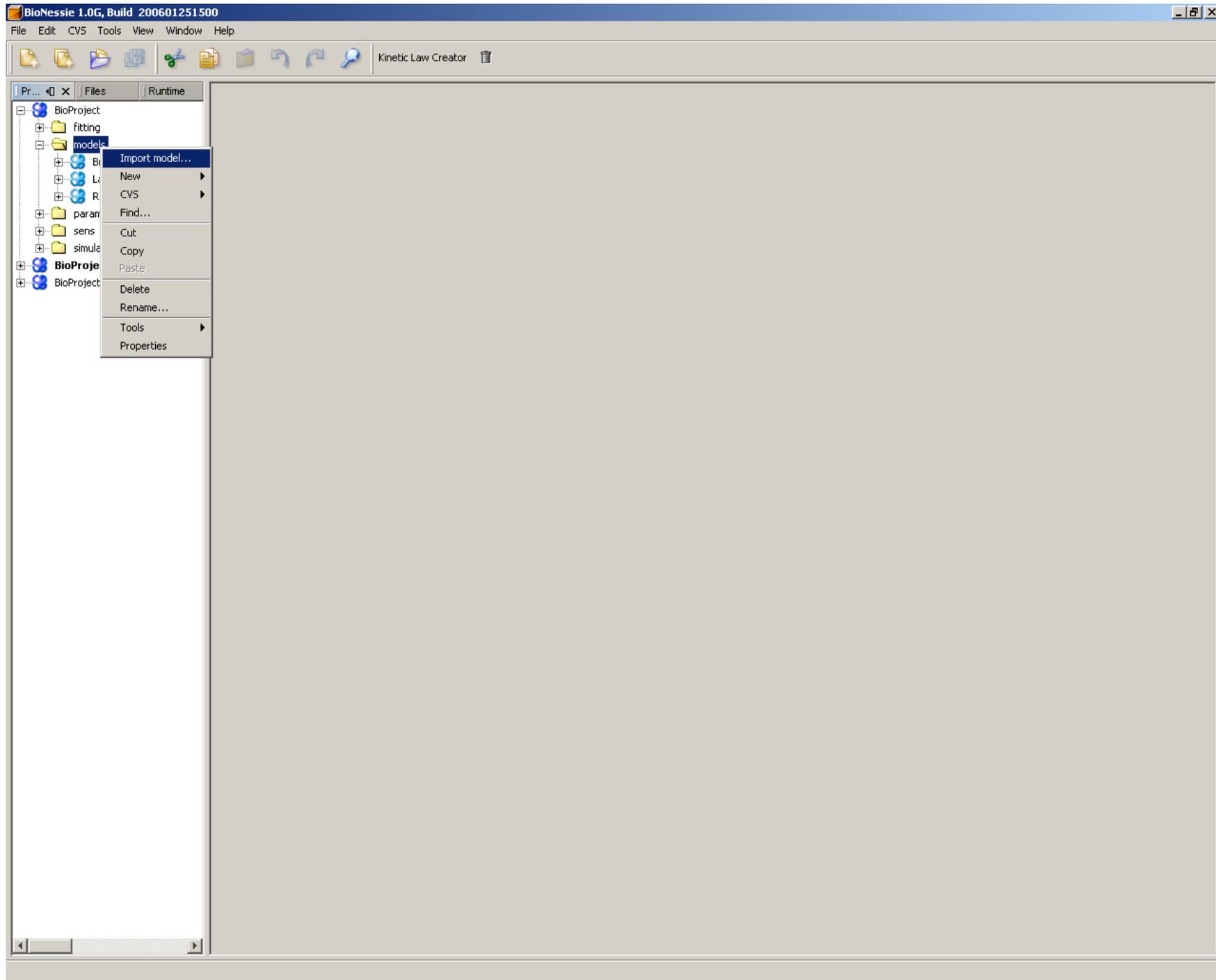
Buttons for 'Add all', 'Reset all', 'OK', and 'Cancel' are visible at the bottom of the dialog. The main window also shows a file explorer on the left and a toolbar at the top.

# Simulation



# Textual SBML source editor

# Model retrieval



# Saving models

The screenshot shows the BioNessie 1.0G software interface. The main window displays a project tree on the left with folders like 'fitting', 'models', 'paramscan', 'sens', and 'simulations'. The 'models' folder is expanded, showing several model files. The main panel shows the configuration for a model named 'newModel' (Version: Level2Ver1). The 'Species' tab is active, listing species such as Raf1, RKIP, Raf1RKIP, ERKPP, Raf1RKIPERKPP, ERK, RKIPP, MEKPP, MEKPPERK, RP, and RKIPPRP. A 'Save' dialog box is open in the foreground, titled '保存' (Save), showing the 'My Documents' folder selected. The dialog includes a 'File' name field, a 'File Type' dropdown set to 'All Files', and 'Save' and 'Cancel' buttons. The background window also has 'Apply', 'Simulate', and 'Save As' buttons at the top right.



# Results viewer

SBML file info  
File path : C:\BioProject\models\oscillator\_neg\_feedback\_noinhib.xml

Chart | Data | Data output

Time	R	S1	RS1	Rp	S2	RpS2	RR	RRp	RRpS2	SS2	RRR	RRRp	RRRpS...	SSS2	RRoRp	RRRoRp	RRRpS1	Compar...	k1	k2	k3
0.0	100.0	1.0	0.0	0.0	1.0	0.0	100.0	0.0	0.0	1.0	100.0	0.0	0.0	1.0	0.0	0.0	0.0	1.0	100.0	4.0	1.0
0.5	98.5217...	4.87576...	0.98197...	3.44296...	0.99508...	0.00491...	99.3860...	1.09411...	0.00121...	0.99878...	99.8584...	2.32390...	0.00222...	0.99777...	0.49098...	0.12159...	0.01753...	1.0	100.0	4.0	1.0
1.0	98.1820...	3.94796...	0.85863...	5.66735...	0.99047...	0.00952...	98.5666...	3.35093...	0.00479...	0.99520...	99.3638...	0.00119...	0.01493...	0.98506...	0.94918...	0.47903...	0.14096...	1.0	100.0	4.0	1.0
1.5	98.1355...	1.99287...	0.50500...	7.20161...	0.98688...	0.01311...	97.6506...	6.56868...	0.01042...	0.98957...	98.4486...	0.00490...	0.05897...	0.94102...	1.30014...	1.03813...	0.44929...	1.0	100.0	4.0	1.0
2.0	98.3489...	3.00097...	0.16945...	7.73064...	0.98512...	0.01487...	96.7921...	0.00103...	0.01739...	0.98260...	97.1453...	0.02947...	0.27120...	0.72879...	1.46597...	1.72348...	0.83051...	1.0	100.0	4.0	1.0
2.5	98.4600...	2.61669...	0.02627...	7.80857...	0.98468...	0.01531...	96.0273...	0.00143...	0.02489...	0.97510...	95.6325...	0.18920...	0.75578...	0.24421...	1.49755...	2.44877...	0.97372...	1.0	100.0	4.0	1.0
3.0	98.4848...	4.38975...	0.00354...	7.83361...	0.98459...	0.01540...	95.2951...	0.00184...	0.03257...	0.96742...	93.9417...	0.93855...	0.94826...	0.05173...	1.49540...	3.17500...	0.99645...	1.0	100.0	4.0	1.0
3.5	98.4945...	1.83250...	7.20214...	7.85373...	0.98455...	0.01544...	94.5743...	0.00227...	0.04043...	0.95956...	91.9376...	2.19102...	0.97755...	0.02244...	1.48848...	3.89449...	0.99927...	1.0	100.0	4.0	1.0
4.0	98.5025...	1.04917...	2.83729...	7.87264...	0.98451...	0.01548...	93.8617...	0.00272...	0.04858...	0.95141...	89.5921...	3.81509...	0.98703...	0.01296...	1.48093...	4.60600...	0.99971...	1.0	100.0	4.0	1.0
4.5	98.5102...	6.90390...	1.65179...	7.89078...	0.98447...	0.01552...	93.1572...	0.00321...	0.05712...	0.94287...	86.9046...	5.79498...	0.99143...	0.00856...	1.47325...	5.30912...	0.99983...	1.0	100.0	4.0	1.0
5.0	98.5180...	4.92369...	1.12344...	7.90825...	0.98444...	0.01555...	92.4611...	0.00374...	0.06617...	0.93382...	83.8781...	8.12461...	0.99387...	0.00612...	1.46551...	6.00344...	0.99988...	1.0	100.0	4.0	1.0
5.5	98.5257...	3.70413...	8.23515...	7.92508...	0.98440...	0.01559...	91.7735...	0.00432...	0.07586...	0.92413...	80.5170...	10.7991...	0.99538...	0.00461...	1.45774...	6.68851...	0.99991...	1.0	100.0	4.0	1.0
6.0	98.5335...	2.89573...	6.32688...	7.94125...	0.98437...	0.01562...	91.0949...	0.00496...	0.08636...	0.91363...	76.8262...	13.8136...	0.99639...	0.00360...	1.44994...	7.36376...	0.99993...	1.0	100.0	4.0	1.0
6.5	98.5413...	2.33059...	5.02746...	7.95672...	0.98434...	0.01565...	90.4257...	0.00569...	0.09789...	0.90210...	72.8113...	17.1630...	0.99709...	0.00290...	1.44211...	8.02851...	0.99994...	1.0	100.0	4.0	1.0
7.0	98.5492...	1.91920...	4.09934...	7.97143...	0.98431...	0.01568...	89.7666...	0.00652...	0.11069...	0.88930...	68.4786...	20.8419...	0.99760...	0.00239...	1.43427...	8.68188...	0.99995...	1.0	100.0	4.0	1.0
7.5	98.5570...	1.61001...	3.41190...	7.98531...	0.98429...	0.01570...	89.1181...	0.00750...	0.12510...	0.87489...	63.8348...	24.8443...	0.99799...	0.00200...	1.42641...	9.32280...	0.99996...	1.0	100.0	4.0	1.0
8.0	98.5648...	1.37155...	2.88782...	7.99826...	0.98426...	0.01573...	88.4813...	0.00865...	0.14157...	0.85842...	58.8881...	29.1637...	0.99828...	0.00171...	1.41854...	9.94983...	0.99997...	1.0	100.0	4.0	1.0
8.5	98.5727...	1.18367...	2.47878...	8.01016...	0.98424...	0.01575...	87.8574...	0.01006...	0.16070...	0.83929...	53.6475...	33.7927...	0.99852...	0.00147...	1.41066...	10.5611...	0.99997...	1.0	100.0	4.0	1.0
9.0	98.5806...	1.03297...	2.15323...	8.02086...	0.98421...	0.01578...	87.2477...	0.01183...	0.18334...	0.81665...	48.1240...	38.7229...	0.99871...	0.00128...	1.40276...	11.1542...	0.99997...	1.0	100.0	4.0	1.0
9.5	98.5885...	9.10234...	1.88984...	8.03014...	0.98420...	0.01579...	86.6545...	0.01411...	0.21070...	0.78929...	42.3310...	43.9443...	0.99886...	0.00113...	1.39486...	11.7257...	0.99998...	1.0	100.0	4.0	1.0
10.0	98.5964...	8.08971...	1.67374...	8.03772...	0.98418...	0.01581...	86.0805...	0.01720...	0.24462...	0.75537...	36.2851...	49.4451...	0.99898...	0.00101...	1.38694...	12.2706...	0.99998...	1.0	100.0	4.0	1.0
10.5	98.6043...	7.24498...	1.49431...	8.04321...	0.98417...	0.01582...	85.5296...	0.02162...	0.28805...	0.71194...	30.0090...	55.2102...	0.99909...	0.00084...	1.37903...	12.7816...	0.99998...	1.0	100.0	4.0	1.0
11.0	98.6122...	6.53378...	1.34383...	8.04602...	0.98416...	0.01583...	85.0077...	0.02851...	0.34594...	0.65405...	23.5342...	61.2198...	0.99918...	0.00068...	1.37111...	13.2466...	0.99998...	1.0	100.0	4.0	1.0
11.5	98.6201...	5.93059...	1.21660...	8.04526...	0.98416...	0.01583...	84.5241...	0.04076...	0.42744...	0.57255...	16.9099...	67.4464...	0.99925...	0.00051...	1.36320...	13.6444...	0.99998...	1.0	100.0	4.0	1.0
12.0	98.6280...	5.41660...	1.10838...	8.03938...	0.98417...	0.01582...	84.0948...	0.06851...	0.55160...	0.44839...	10.2243...	73.8465...	0.99932...	0.00037...	1.35529...	13.9297...	0.99998...	1.0	100.0	4.0	1.0
12.5	98.6359...	4.97906...	1.01617...	8.02542...	0.98419...	0.01580...	83.7506...	0.18627...	0.76429...	0.23570...	3.71336...	80.3359...	0.99937...	0.00021...	1.34741...	13.9513...	0.99998...	1.0	100.0	4.0	1.0
13.0	98.6438...	4.62850...	0.93953...	7.99907...	0.98423...	0.01576...	83.5373...	0.27346...	0.98180...	0.01819...	0.17339...	86.4205...	0.99942...	0.00012...	1.33957...	14.0666...	0.99999...	1.0	100.0	4.0	1.0
13.5	98.6517...	4.41732...	0.87360...	7.96821...	0.98429...	0.01570...	83.3719...	0.68993...	0.99279...	0.00720...	0.04449...	90.5518...	0.99944...	0.00005...	1.33176...	14.0417...	0.99999...	1.0	100.0	4.0	1.0
14.0	98.6595...	4.29745...	0.857046...	7.93683...	0.98435...	0.01564...	83.2127...	9.56713...	0.99479...	0.00520...	0.02156...	93.0776...	0.99946...	0.00002...	1.32399...	14.00132...	0.99999...	1.0	100.0	4.0	1.0
14.5	98.6673...	4.22762...	0.839543...	7.90509...	0.98441...	0.01558...	83.0580...	11.2574...	0.99557...	0.00442...	0.01288...	94.6149...	0.99947...	0.00001...	1.31625...	13.97267...	0.99999...	1.0	100.0	4.0	1.0
15.0	98.6751...	4.18626...	0.829281...	7.87303...	0.98447...	0.01552...	82.9074...	12.3459...	0.99596...	0.00403...	0.00872...	95.5497...	0.99947...	0.00000...	1.30854...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
15.5	98.6828...	4.16152...	0.823198...	7.84067...	0.98453...	0.01546...	82.7608...	13.0659...	0.99618...	0.00381...	0.00651...	96.1178...	0.99948...	0.00000...	1.29948...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
16.0	98.6905...	4.14663...	0.819574...	7.80802...	0.98459...	0.01540...	82.6180...	13.5602...	0.99632...	0.00367...	0.00525...	96.4630...	0.99948...	0.00000...	1.29322...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
16.5	98.6982...	4.13763...	0.817413...	7.77510...	0.98466...	0.01533...	82.4791...	13.9156...	0.99641...	0.00358...	0.00452...	96.6728...	0.99948...	0.00000...	1.28560...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
17.0	98.7059...	4.13218...	0.816131...	7.74190...	0.98472...	0.01527...	82.3440...	14.1852...	0.99648...	0.00351...	0.00407...	96.8003...	0.99948...	0.00000...	1.27802...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
17.5	98.7135...	4.12888...	0.815379...	7.70844...	0.98479...	0.01520...	82.2127...	14.4012...	0.99654...	0.00345...	0.00380...	96.8777...	0.99948...	0.00000...	1.27047...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
18.0	98.7211...	4.12687...	0.814947...	7.67472...	0.98485...	0.01514...	82.0851...	14.5831...	0.99658...	0.00341...	0.00362...	96.9248...	0.99948...	0.00000...	1.26296...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
18.5	98.7286...	4.12565...	0.814709...	7.64075...	0.98492...	0.01507...	81.9613...	14.7429...	0.99661...	0.00338...	0.00350...	96.9533...	0.99948...	0.00000...	1.25548...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
19.0	98.7361...	4.12492...	0.814589...	7.60654...	0.98498...	0.01501...	81.8412...	14.8877...	0.99665...	0.00334...	0.00342...	96.9707...	0.99948...	0.00000...	1.24803...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
19.5	98.7436...	4.12447...	0.814540...	7.57210...	0.98505...	0.01494...	81.7248...	15.0220...	0.99668...	0.00331...	0.00337...	96.9813...	0.99948...	0.00000...	1.24061...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
20.0	98.7511...	4.12419...	0.814534...	7.53742...	0.98512...	0.01487...	81.6121...	15.1485...	0.99671...	0.00328...	0.00328...	96.9877...	0.99948...	0.00000...	1.23323...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
20.5	98.7585...	4.12403...	0.814554...	7.50252...	0.98519...	0.01480...	81.5030...	15.2687...	0.99673...	0.00326...	0.00328...	96.9916...	0.99948...	0.00000...	1.22588...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
21.0	98.7659...	4.12392...	0.814590...	7.46741...	0.98525...	0.01474...	81.3976...	15.3838...	0.99676...	0.00323...	0.00325...	96.9940...	0.99948...	0.00000...	1.21857...	14.00000...	0.99999...	1.0	100.0	4.0	1.0
21.5	98.7732...	4.12386...	0.814636...	7.43208...	0.98532...	0.01467...	81.2958...	15.4943...	0.99678...	0.00321...	0.00323...	96.9955...	0.99948...	0.00000...	1.21129...	14.00000...	0.99999...	1.0	100.0	4.0	1.0

Simulate  
Total time: 60  Enable true time simulate  
Steps: 120 Times true time 1.0 X  
Step time: 0.1 (5)

Simulate >> Make Report ... Close



# Printable report

SBML file info

File path : C:\BioProject\models\oscillator\_neg\_feedback\_noinhib.xml

Chart | Data | Data output

SBML File : C:\BioProject\models\oscillator\_neg\_feedback\_noinhib.xml  
Simulate 60.0 second.  
One step time is 0.5 second, total 120 steps.  
Begin simulate at Tue Jul 25 14:18:20 BST 2006

```
T|R|S|I|RS|I|Rp|S2|RpS2|RR|RRp|RRpS52|S52|RRR|RRRp|RRRpS552|S552|RRoRp|RRoRRp|RRRpS1|Compartment1|k1|k2|k3
0.0|100.0|1.0|0.0|0.0|1.0|0.0|100.0|0.0|0.0|1.0|100.0|0.0|0.0|1.0|0.0|0.0|1.0|100.0|0.0|1.0
0.5|98.52177580546457|4.875764498287675E-4|0.981978237472207|3.4429692300391127E-4|0.9950864590705356|0.004913540929463201|99.38609140735778|1.0941100185209538E-4|0.00212609152975374|0.9987839084702468|99.8584
1.0|98.18208770094789|3.947961351109091E-4|0.8586382568302375|5.66735456998562E-4|0.9904744913196215|0.009525508680377479|98.56665520661296|3.350935854225896E-4|0.00479549703978458|0.9952045029602157|99.363867
1.5|98.13551327121353|1.9928752940739466E-4|0.550560248747309|7.201612683861319E-4|0.9868883786796926|0.013111621320305836|97.6564018592584|6.568680238817434E-4|0.010421633873719166|0.989578366126281|98.4486
2.0|98.34892241756572|3.0009747539227524E-5|0.16945038811512242|7.730640320656424E-4|0.985120405332654|0.014879595466733866|96.79211487977932|0.0010345860405547684|0.01739374047537287|0.9826062595246253|97.19
2.5|98.46008523066853|2.616691361590978E-6|0.026272801759617766|7.808578148140145E-4|0.984689249272656|0.015310750727345316|96.02735041512979|0.0014326178135783078|0.02489656223055982|0.9751034377694378|95.632
3.0|98.48485910382813|4.3897591536542805E-7|0.0035486959940351256|7.8336128044127E-4|0.9845099294832004|0.015404059672952828|95.29517659349567|0.0018438543945274032|0.03257343102340949|0.9674265689765862|93.94
3.5|98.49455917915172|1.832509334791458E-7|7.202140494487892E-4|7.85373900059034E-4|0.9845510528497428|0.015448947150258548|94.57431021883023|0.0022736760610351527|0.04043849954330957|0.9595615004566861|91.937
4.0|98.50250624241154|1.0491787649802868E-7|2.837299831586991E-4|7.872643280952171E-4|0.9845131933226751|0.0154868066732651|93.8617382520012|0.0022728454277942897|0.04858760564789981|0.9514123943520963|89.592
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5.0|98.51802454812272|4.923697641448627E-8|1.234465876481427E-4|7.908254546558716E-4|0.9844430443120202|0.01555695568798443|92.46112479407493|0.0037431407850819307|0.06617154801064642|0.9338284519893495|83.87
5.5|98.52579329077244|3.704133723883843E-8|2.3515829944751E-5|7.925085163729852E-4|0.9844099294832004|0.015590070516805233|91.77356142172745|0.004322447619810556|0.07586350038969832|0.9241364996102974|80.5170
6.0|98.53357934540458|2.8957324972066094E-8|6.32688468296446E-5|7.941254381076787E-4|0.9843780841565832|0.015621915843421853|91.09496024527307|0.004966929387640384|0.08636844053884576|0.9136315594611502|76.826
6.5|98.54138279086948|2.330596360526287E-8|5.027461682919747E-4|7.956723133073719E-4|0.9843475672698965|0.0156524327301097|90.0278454277942897|0.04858760564789981|0.9514123943520963|89.592
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9.0|98.58063023100108|1.0329720111924928E-8|2.1532384646213176E-5|8.02086452283030E-4|0.9842195908585974|0.015780409141406007|87.2477889234923|0.011831350580478541|0.18334280231763786|0.8166571976823574|48.1240
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16.5|98.69827023633118|4.137632502230012E-9|8.174134415725073E-6|7.775101782541941E-4|0.9846627331363826|0.015337266863620457|82.479169614634442|13.915659713306749|0.9964196772949702|0.003580322705027045|0.0045
17.0|98.70591877877844|4.132184623675602E-9|8.161313621107229E-6|7.741904602993543E-4|0.984726902723816|0.015273097276186942|82.34407147610624|14.185278961593323|0.9964875167902775|0.0035124832097179384|0.0040
17.5|98.7135351042363|4.128881514482653E-9|8.153791522869188E-6|7.708443815932551E-4|0.9847915974862147|0.01520840251378806|82.21275268539796|14.401257372661705|0.9965400283411369|0.0034599716588602824|0.00380
18.0|98.72111895354362|4.126877009616562E-9|8.149473303871367E-6|7.674726392916656E-4|0.9848568038696082|0.015174196130394339|82.08519048328613|14.583170595218094|0.9965830514613507|0.0034169485386461086|0.003
18.5|98.72867007418738|4.125659798493965E-9|8.147095254062012E-6|7.640759142312417E-4|0.9849225087491089|0.0150774912508991|81.9613642384023|14.742921128108613|0.99619958195854|0.0033800418041427206|0.0035
19.0|98.73618822015625|4.124920271964566E-9|8.1458929194605E-6|7.60645879649436E-4|0.9849886920550806|0.015011300790462|81.821254514962623|14.88747777930915|0.996652733478442|0.0033472665215548035|0.00342
19.5|98.74367315187308|4.124470720020519E-9|8.145403081893412E-6|7.572102059716832E-4|0.9850553624038849|0.014944637596116972|81.72484254369405|15.022055366721238|0.9966825644332742|0.003317435566722523|0.003
20.0|98.75112463617201|4.124197251390776E-9|8.145344768479895E-6|7.537425634212409E-4|0.9851224855262141|0.01487751447378772|81.61210991726466|15.148526816092152|0.9967101723845538|0.0032898276154429917|0.0033
20.5|98.75854444300734|4.1239023105665E-9|8.1452444322375E-6|7.5035632384315E-4|0.985199853632323|0.0148090443636341E-4|81.50338412400111E-6|15.28708032407022|0.996736028365578|0.00326906163430954E-9|0.0033
```

Simulate

Total time: 60  Enable true time simulate

Steps: 120 Times true time 1.0 X

Step time: 0.1 (S)

Close

# How to save a text file for MC2?

The screenshot shows the BioNessie 1.0G software interface. The main window is titled "Kinetic Law Creator" and displays the "Simulation of levchenko.xml" file. The "SBML file info" section shows the file path: "C:\allBioPro\SIMAP\models\levchenko.xml". The "Chart" and "Data" tabs are visible, with "Data" selected. The main text area contains a large block of text, likely the SBML file content, which includes parameters like "74600, areFieldsSet=true, areAllFieldsSet=true, lenient=true, zone=sun.util.calendar.ZoneInfo[id=\"Europe/London\", offset=0, dstSavings=3600000, useDaylight=true, transitions=242, lastRule=java.util.Sim" and compartment information: "K|MEK\_RafP|MEK\_P|MEK\_P\_RafP|MEK\_PP|Phase2|MEK\_PP\_Phase2|MEK\_P\_Phase2|ERK|ERK\_MEK\_PP|ERK\_P|ERK\_P\_MEK\_PP|ERK\_PP|Phase3|ERK\_PP\_Phase3|ERK\_P\_Phase3|compartment".

A red box highlights the "Save Report" button, with an arrow pointing to it and the text "Click here".

Simulation parameters:

- Total time: 60
- Steps: 120
- Step time: 0.5 (s)

Buttons: Simulate >>, Save Res..., Auto save, Exit Sim

# 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)

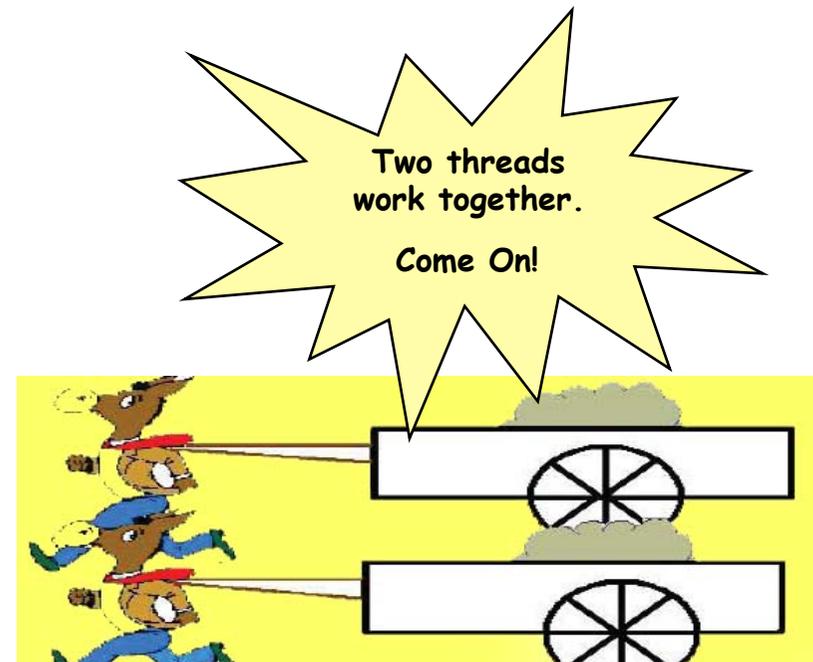
# Parameter Scans

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

- Parameter Scan

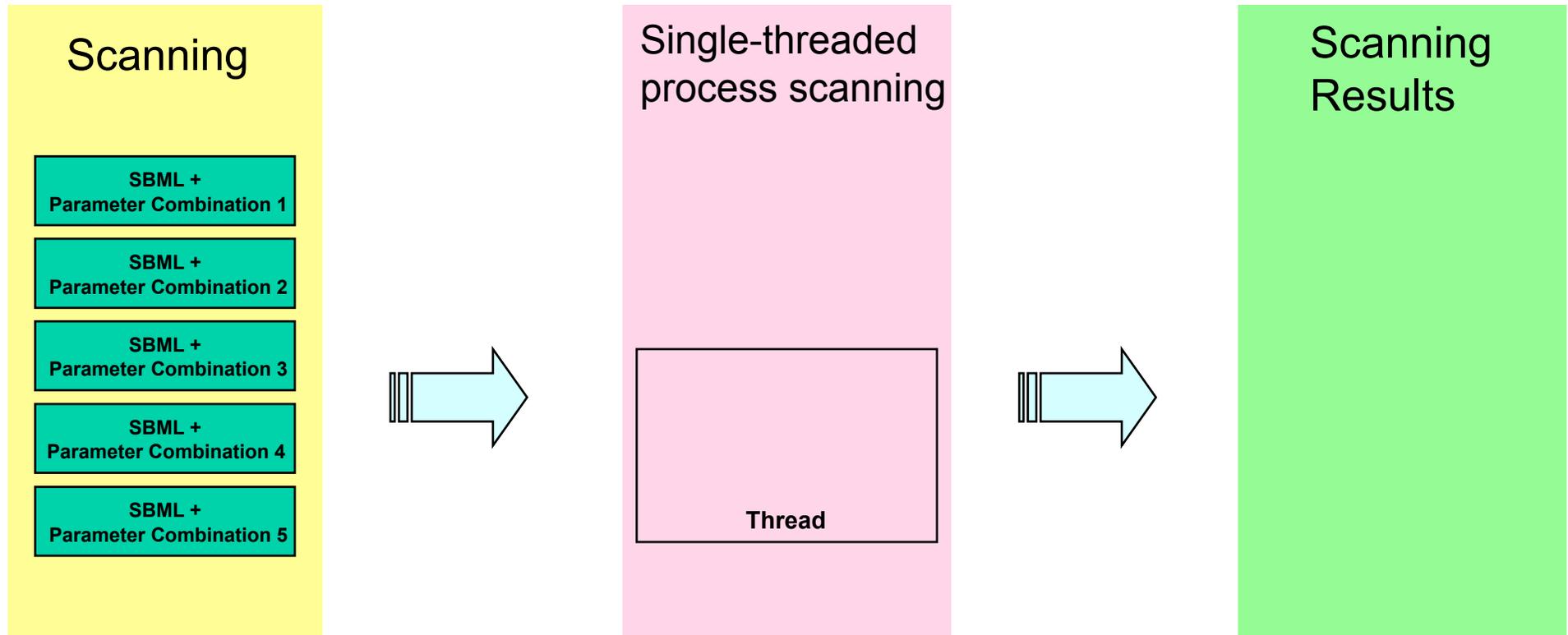
- To explore the behavior of the model over a wide range of parameter values using a parameter scan that runs one simulation for each parameter combination.

- But

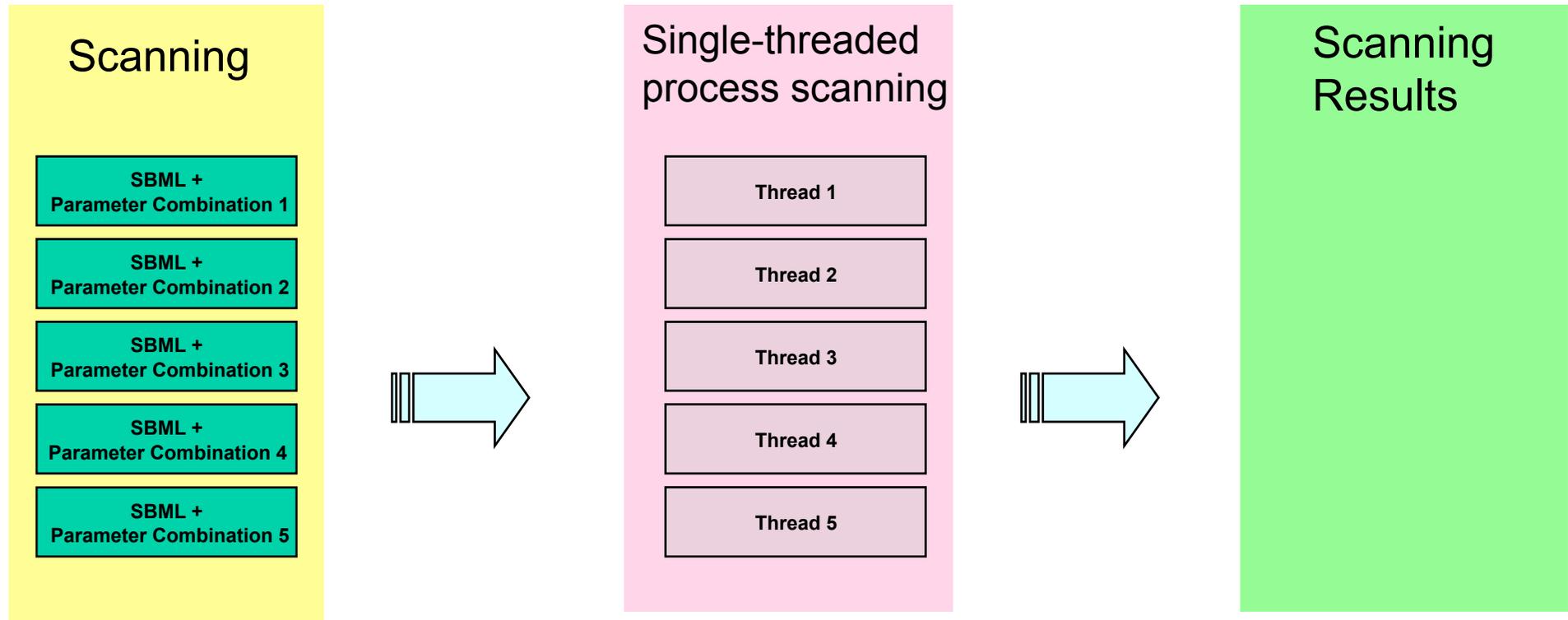


- So, having more than one thread running is beneficial

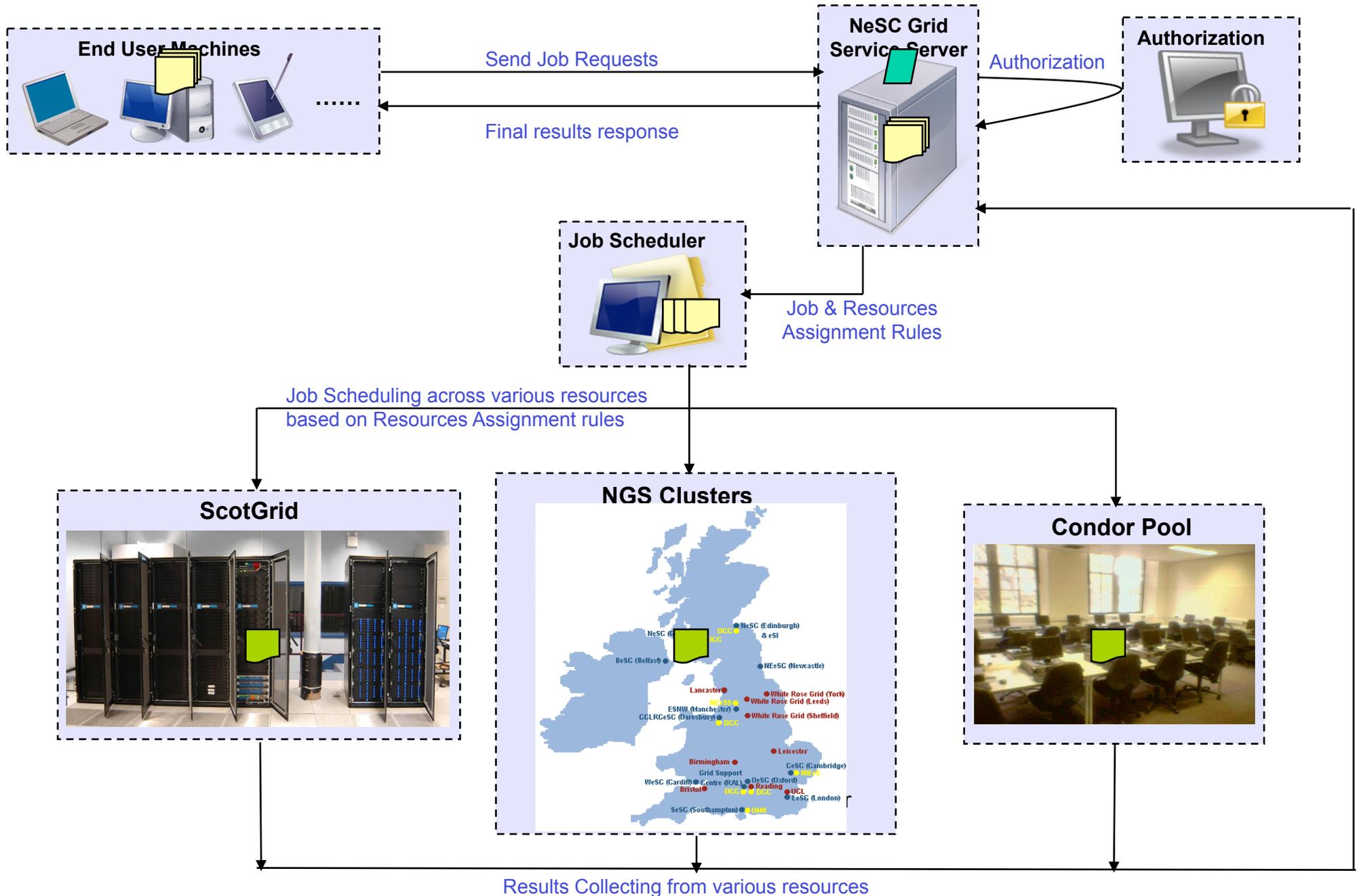
# Single-threaded Parameter Scan



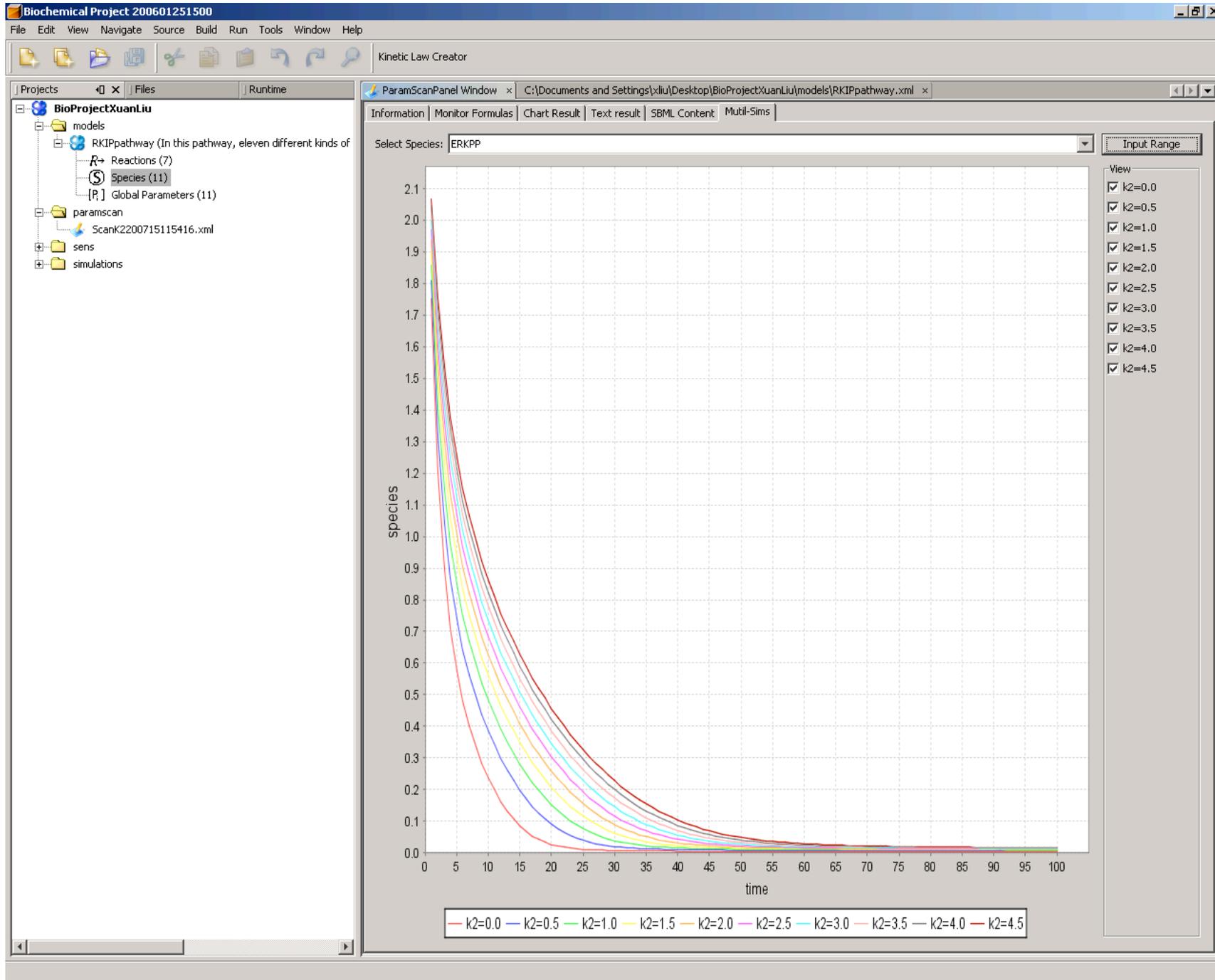
# Multithreaded Parameter Scan



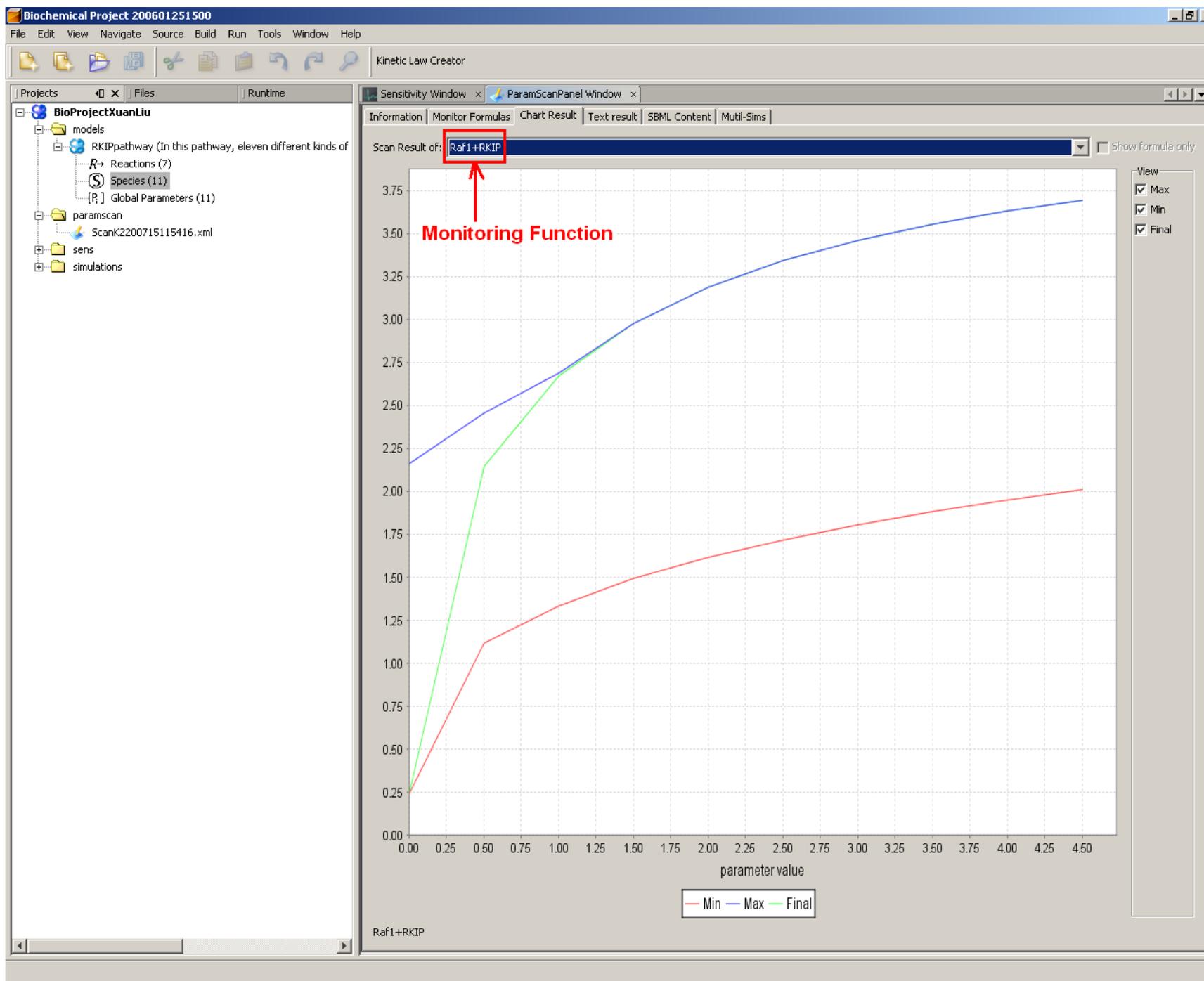
# Grid enabled BioNessie Architecture



# 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.

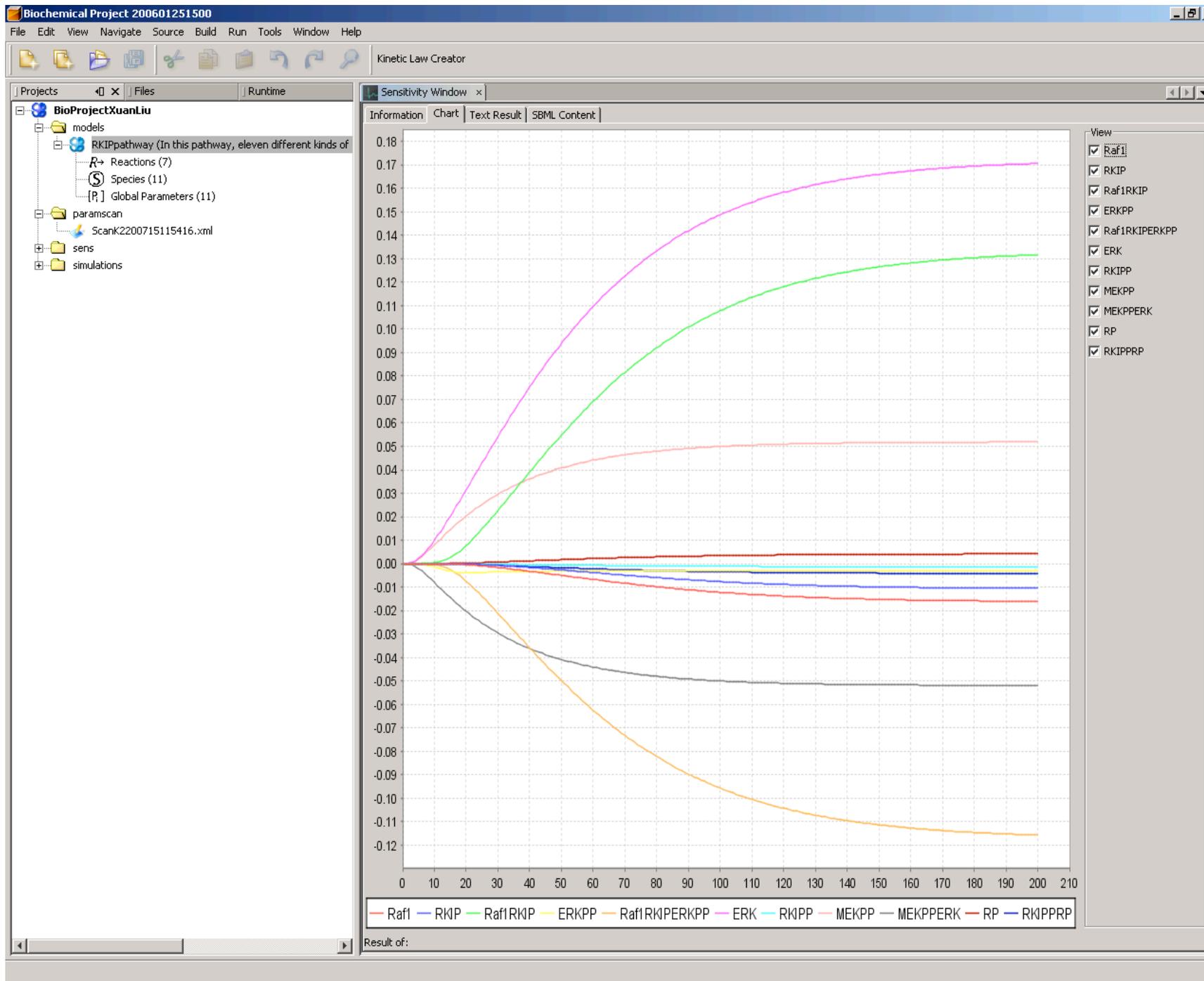


This plot shows the min. max and final values of monitoring function **Raf1+RKIP** for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.

# 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.

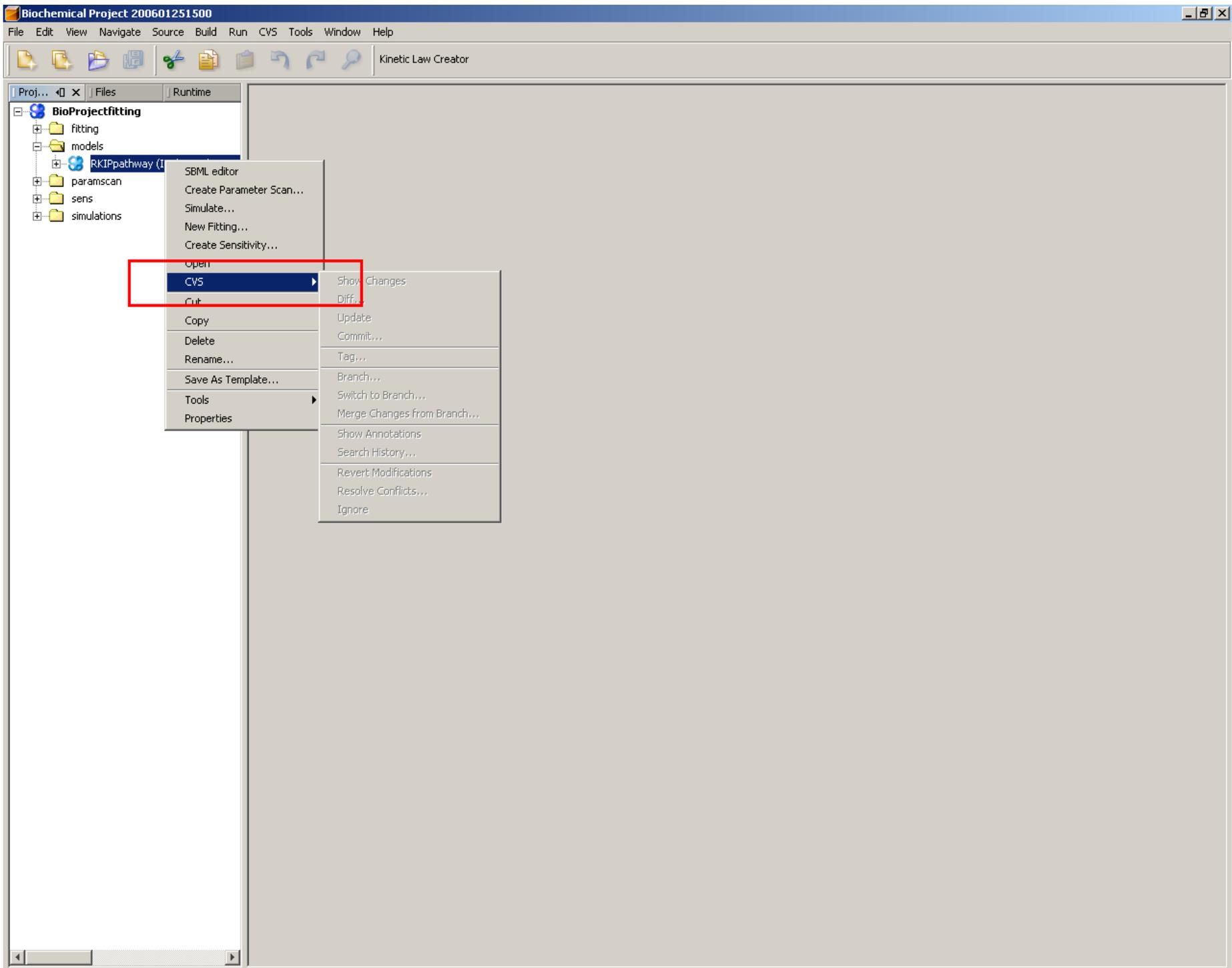


This creates a plot of the sensitivity of species Raf1, RKIP, Raf1RKIP, ERKPP, Raf1RKIPERKPP, ERK, RKIPP, MEKPP, MEKPPERK, RP and RKIPPRP to the values of the parameter K6 for the timecourse of 200 timesteps of 200 time units.

# 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

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- 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... Fitting C:\Documents and Settings\xliu\Desktop\BioProjectfitting\fitting\aef2007226124622.xml x

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

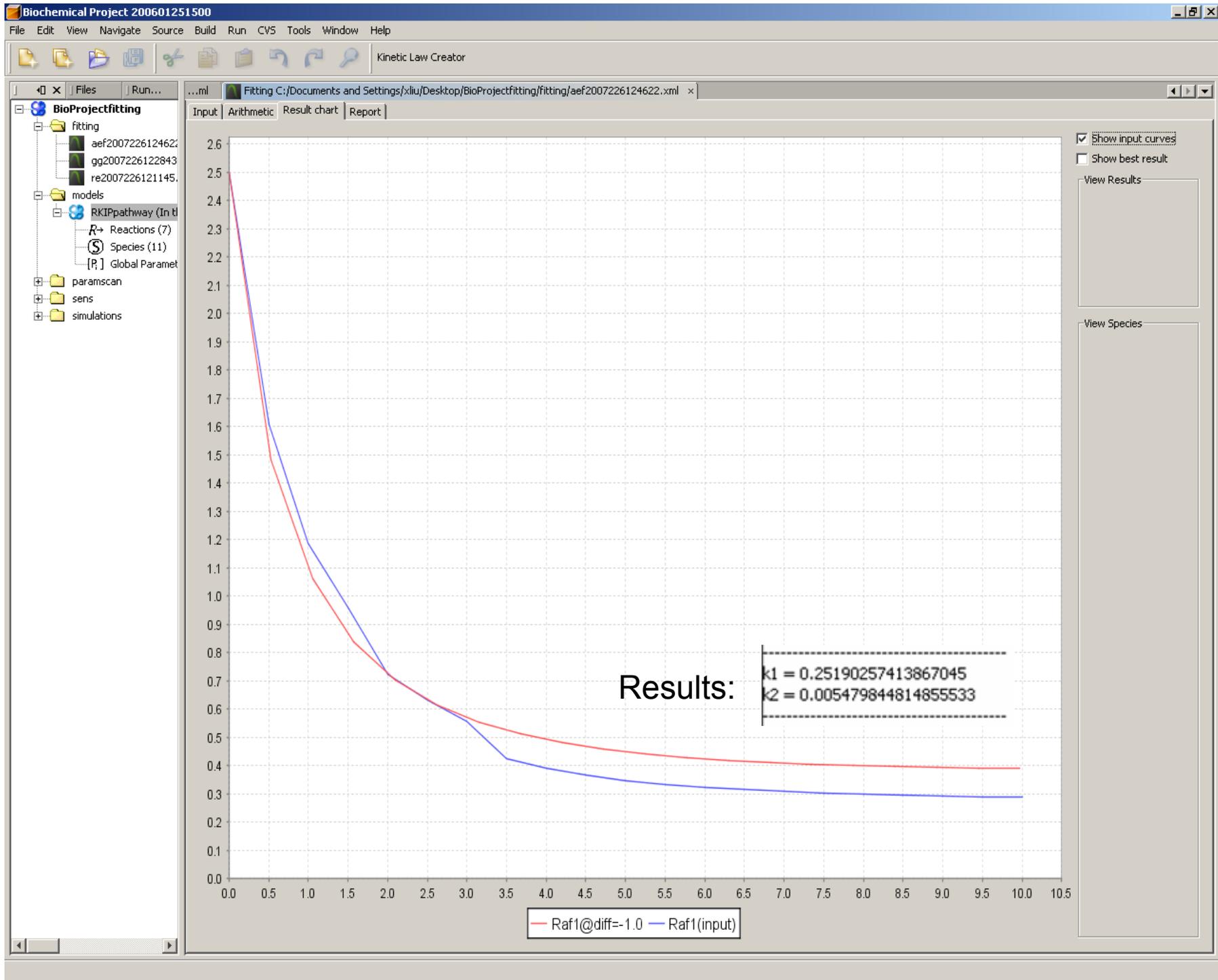
Parameter scan setting: k1 : (0.0 - 0.6) at 1000 steps k2 : (0.0 - 0.0080) at 1000 steps

Parameter detail info:

No result , just do it!

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

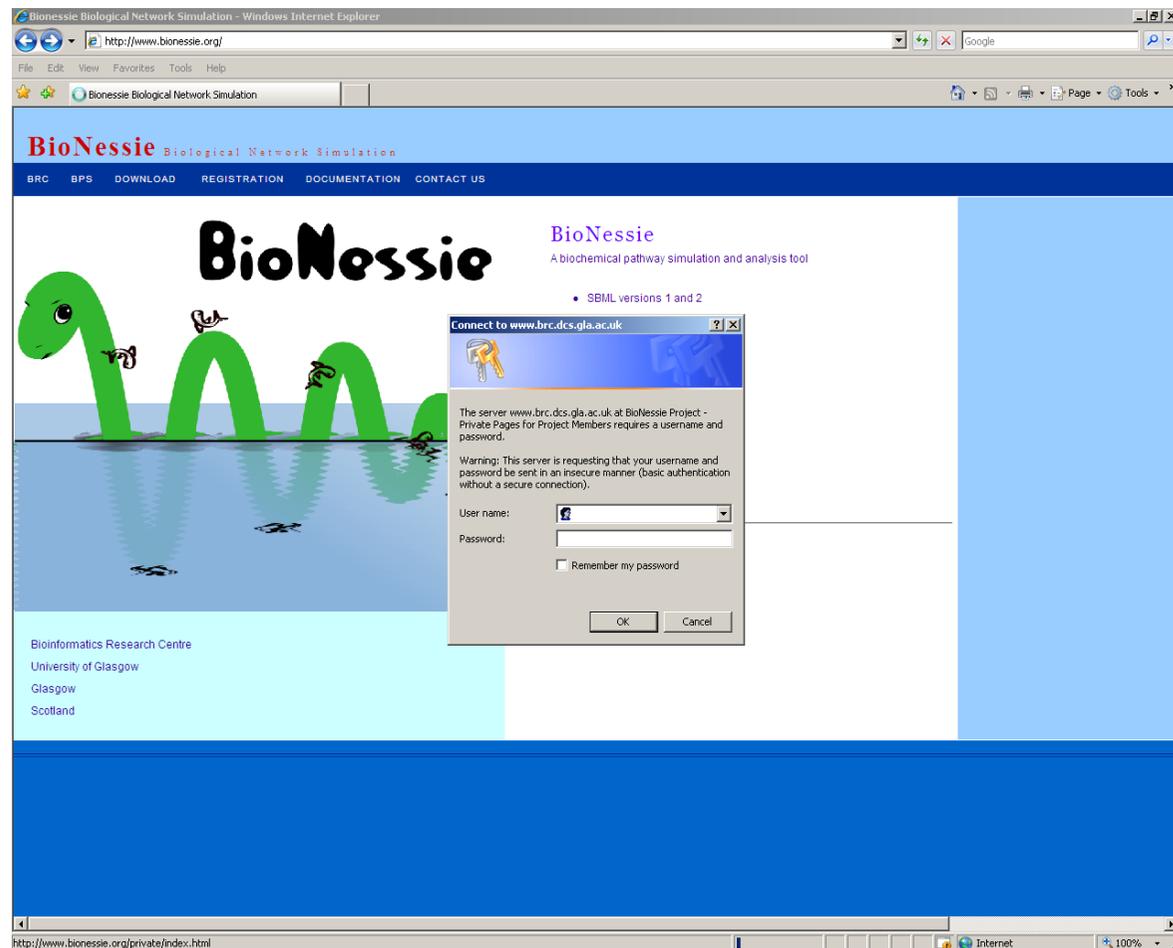
Pause



# How to obtain and install BioNessie

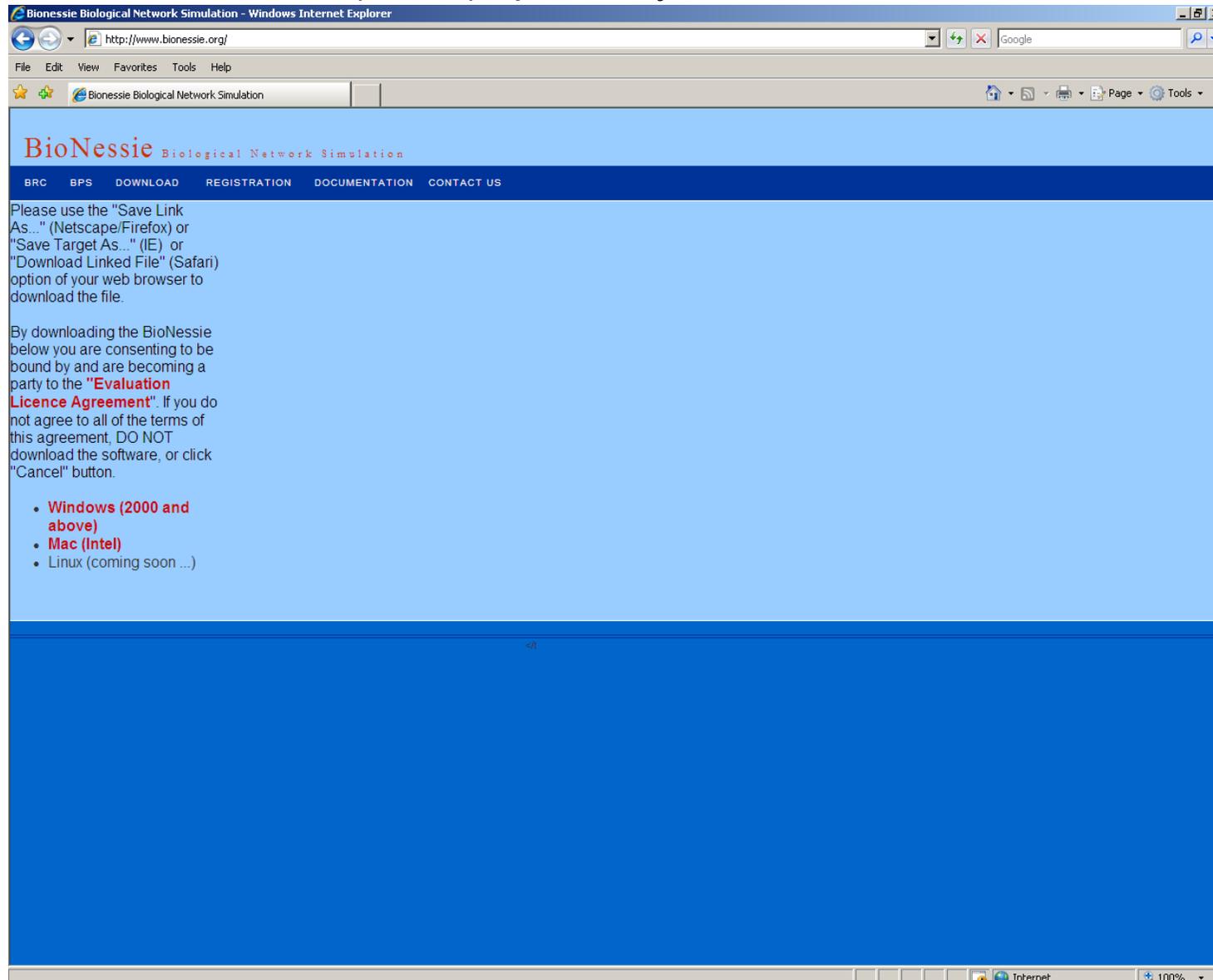
- In order to obtain a copy of BioNessie, you may send an email to Xuan Liu (xliu@brc.dcs.gla.ac.uk) for registration. Please provide your Name, Institute, Address and a valid "email address", to which an email will be sent with the login/password required to download BioNessie. Please read the terms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

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

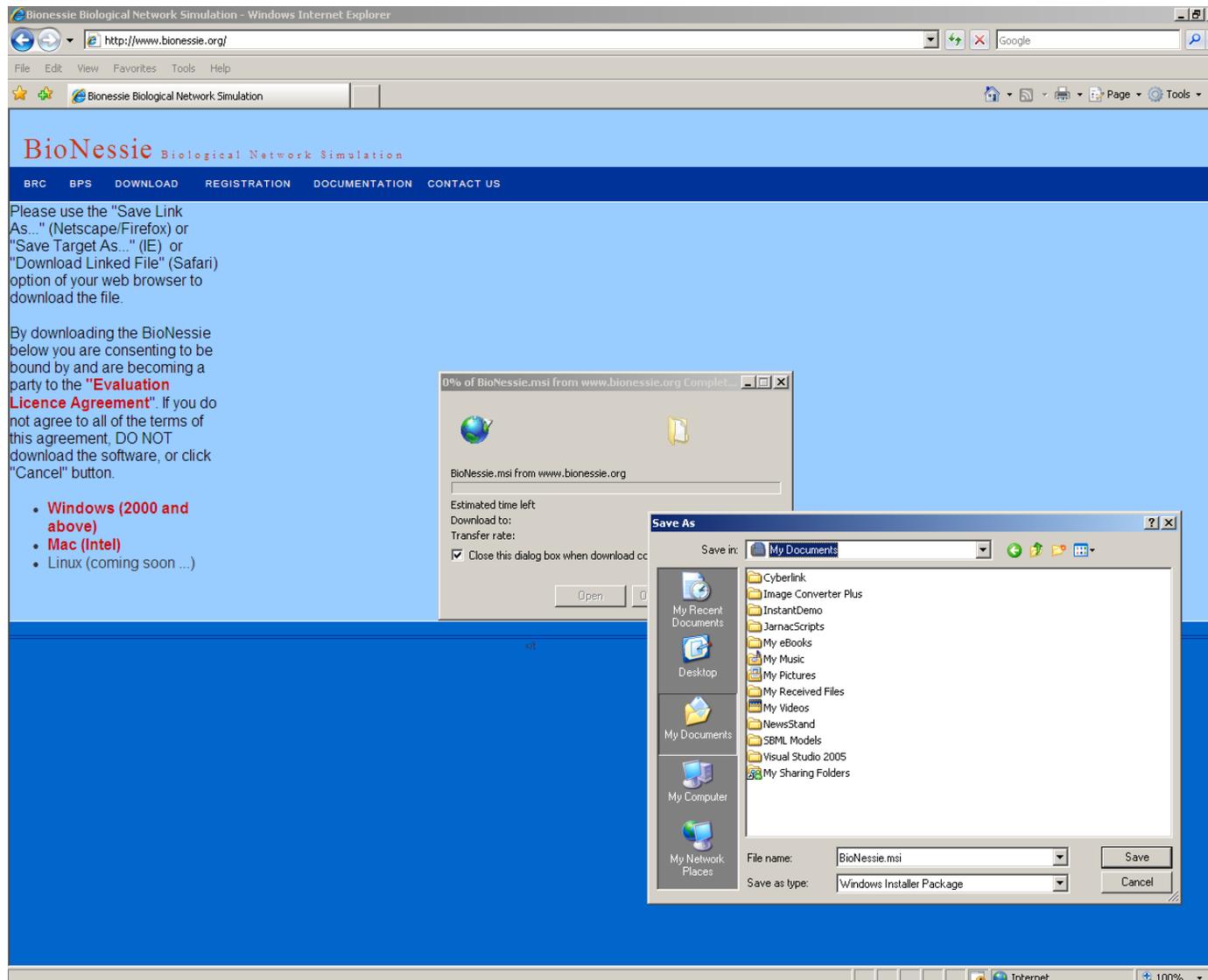


# How to obtain and install BioNessie

- 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.