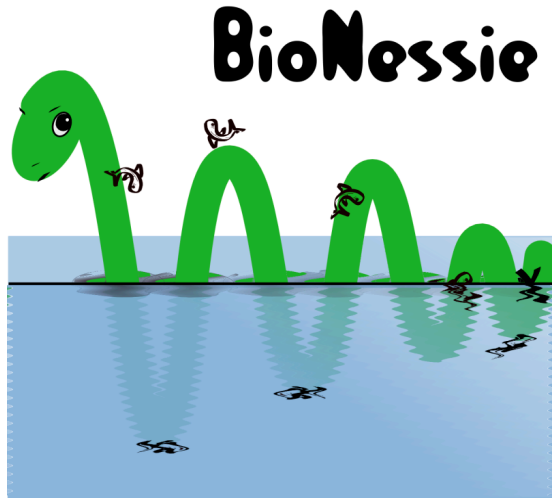


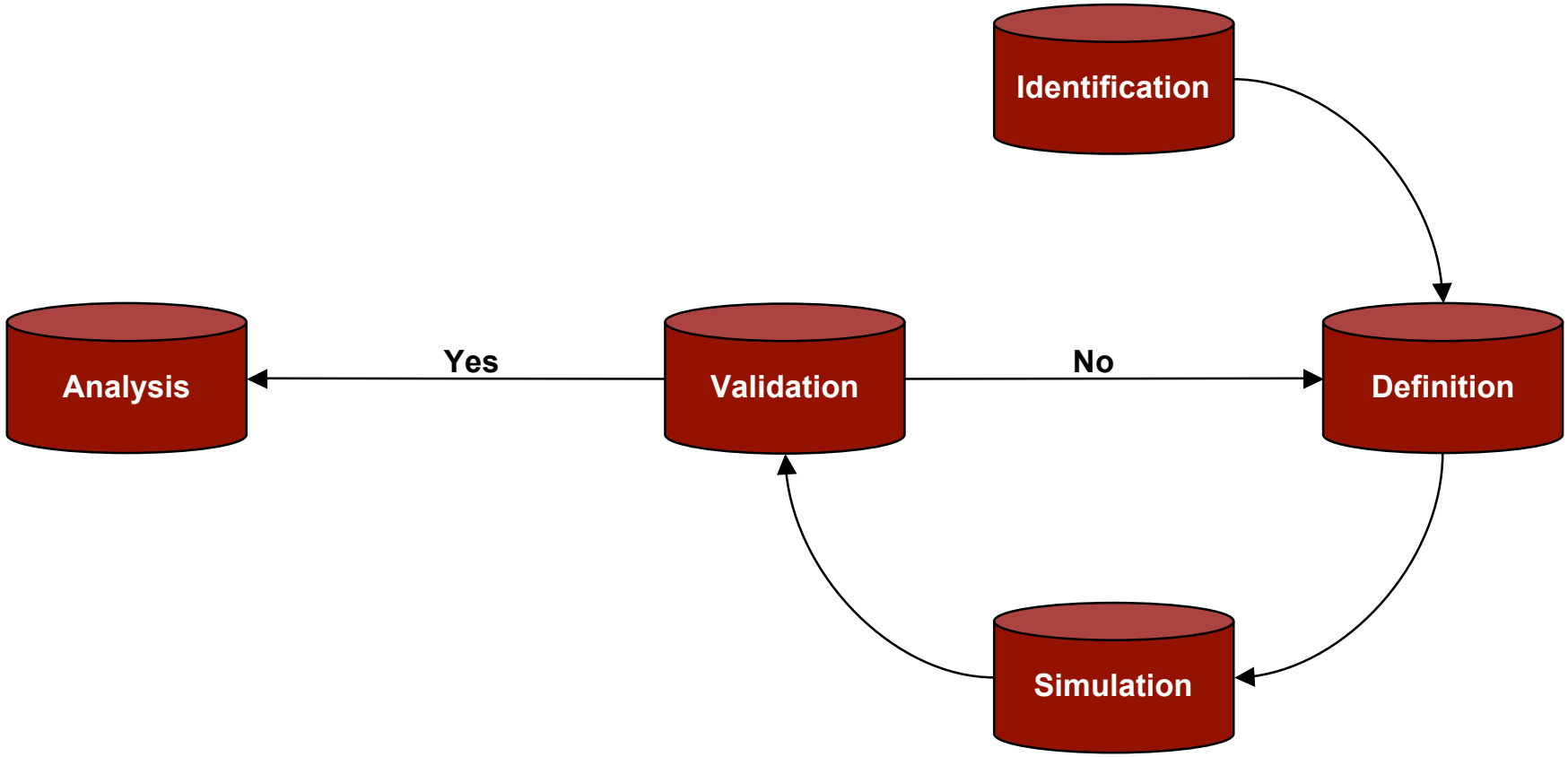
BioNessie: A Software Tool for the Simulation and Analysis of Biochemical Networks

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

Lecture outline

- **Modelling strategies**, overview
- **BioNessie** - *Xuan Liu*
  - Design
  - Functionality
  - Example uses
- **Model checking** with MC2 using Probalistic Linear Temporal Logic - *Robin Donaldson*
- **Practical session** on BioNessie & MC2

How to model

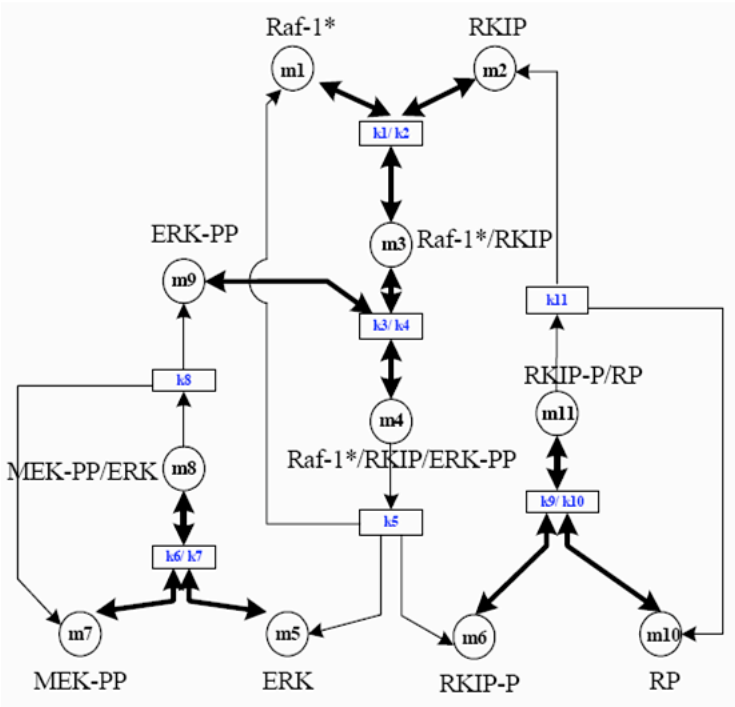

Identification
Analysis
Yes
Validation
No
Definition
Simulation

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?

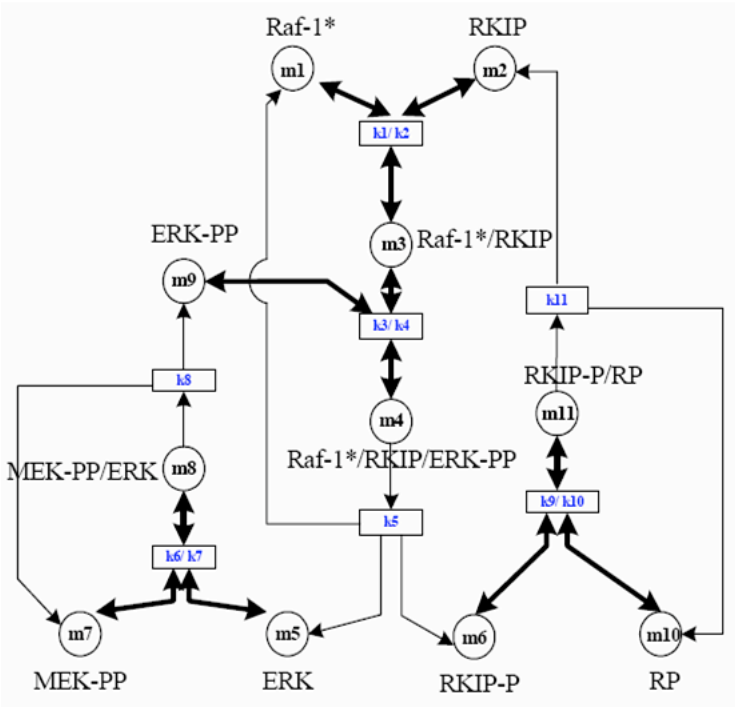
How to model…2: Definition

- 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:
    - Raf + Ras-GTP = Raf/Ras-GTP -> Raf-x + Ras-GTP
  - Although this is a simplification, it is able to explain the observed data



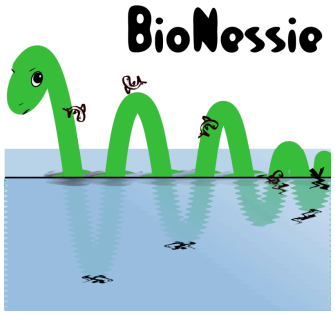
How to model…2: Definition

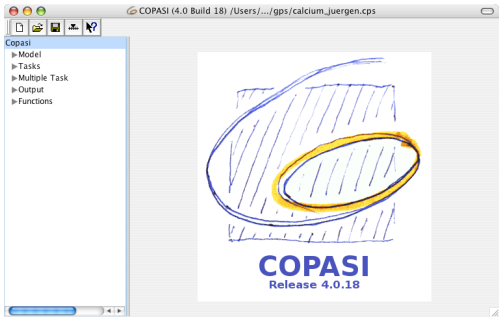
- Define the kinetic types
  - Each reaction has a specific kinetic type
  - All the reactions in the RKIP model are mass action (plain, uncatalysed kinetic type):
    - V = k1[m1][m2] - k2[m3]
  - Another common kinetic type is Michaelis Menten (enzyme catalysis):
    - V = Vmax[S] / (Km+[S])
- Define 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

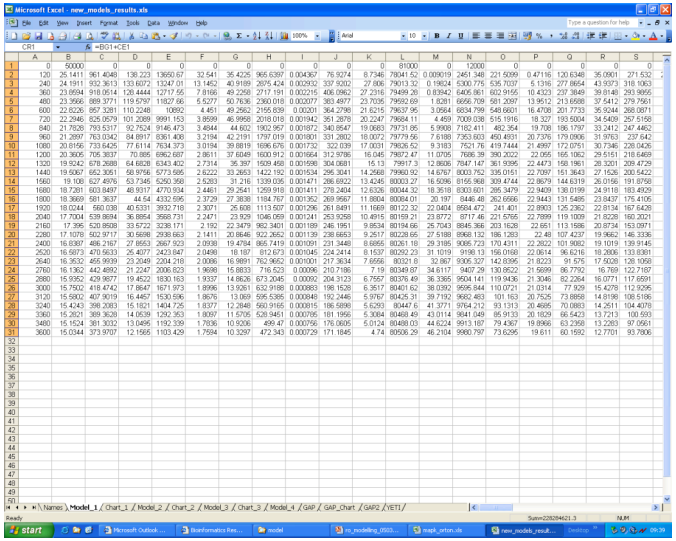
- Once the model has been constructed and parameter data has been assigned you can simulate (run) the model
- This is a relatively straightforward step as there are many software tools available to simulate differential equation based models
- For example:
  - BioNessie
  - MatLab
  - Copsai / Gepasi
  - 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



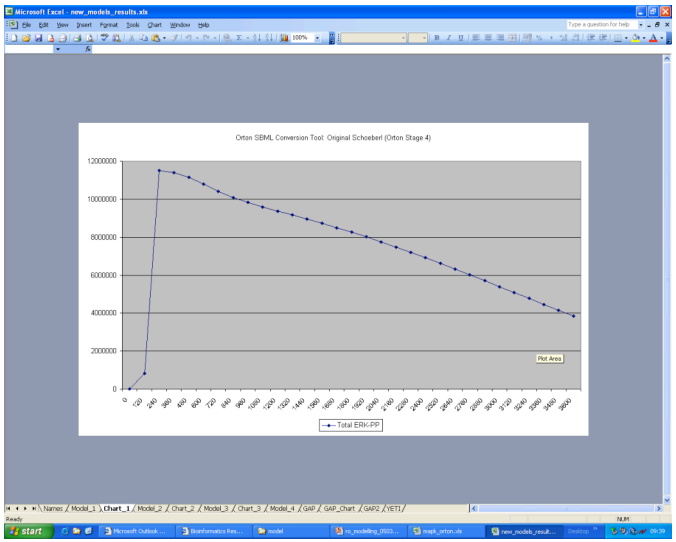


How to model…4: Validation

- 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**

SBML Systems Biology Markup Language

- Also **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

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    </listOfCompartments>
    <listOfSpecies>
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    <listOfParameters>
      <parameter id="K1" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="Ak1B" reversible="false">
        <listOfReactants>
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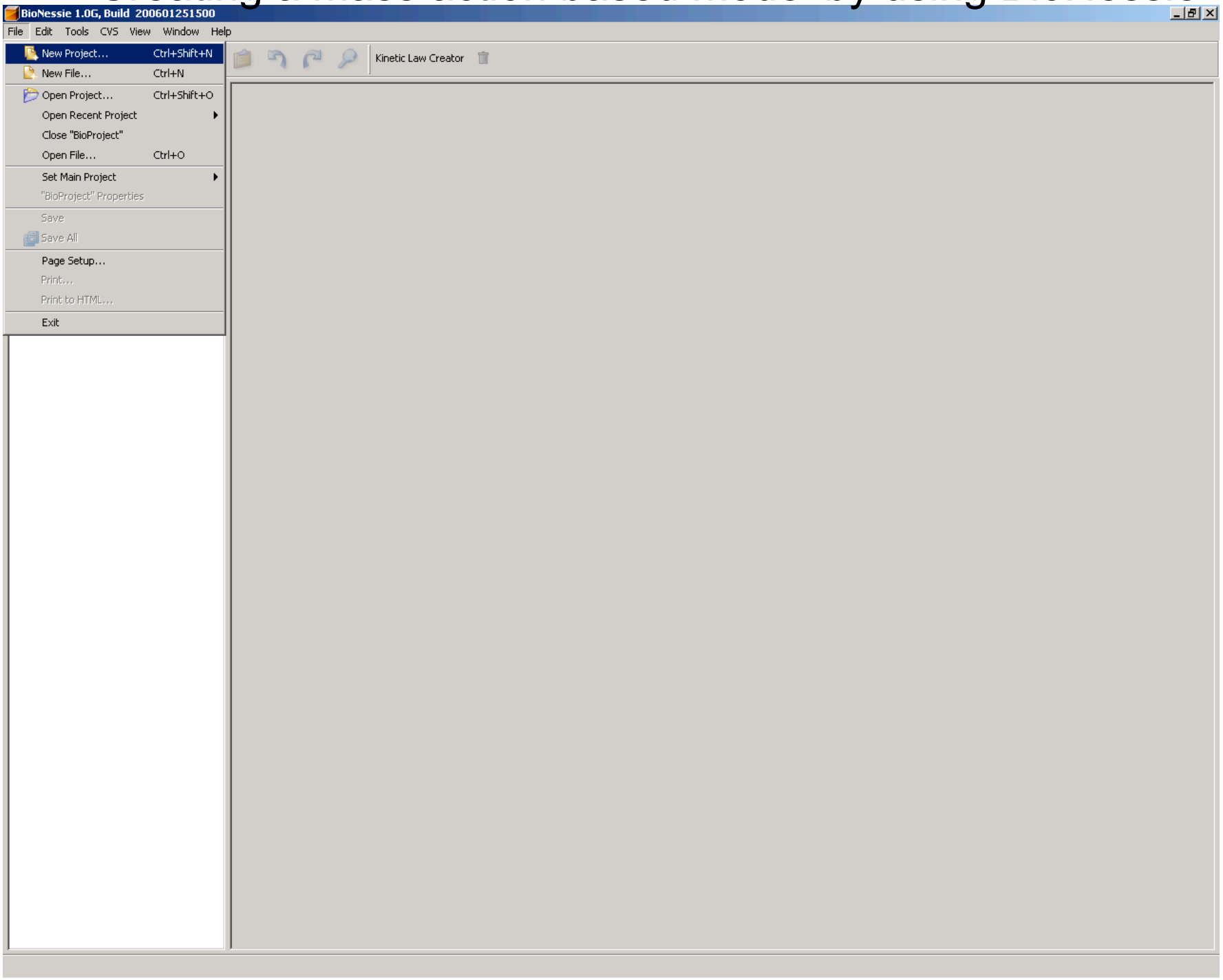
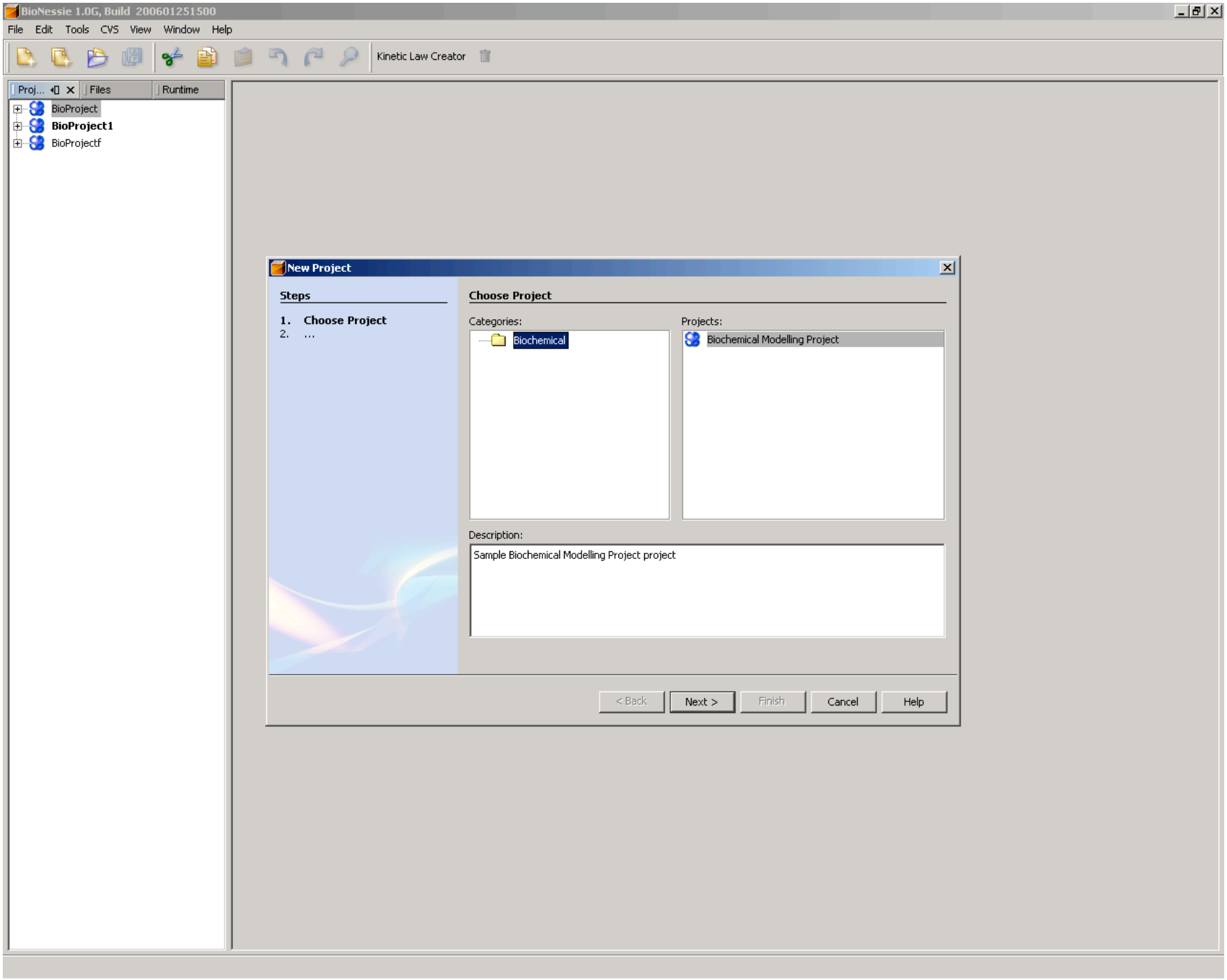
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> K1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
```

$$A \xrightarrow{k_1} B$$

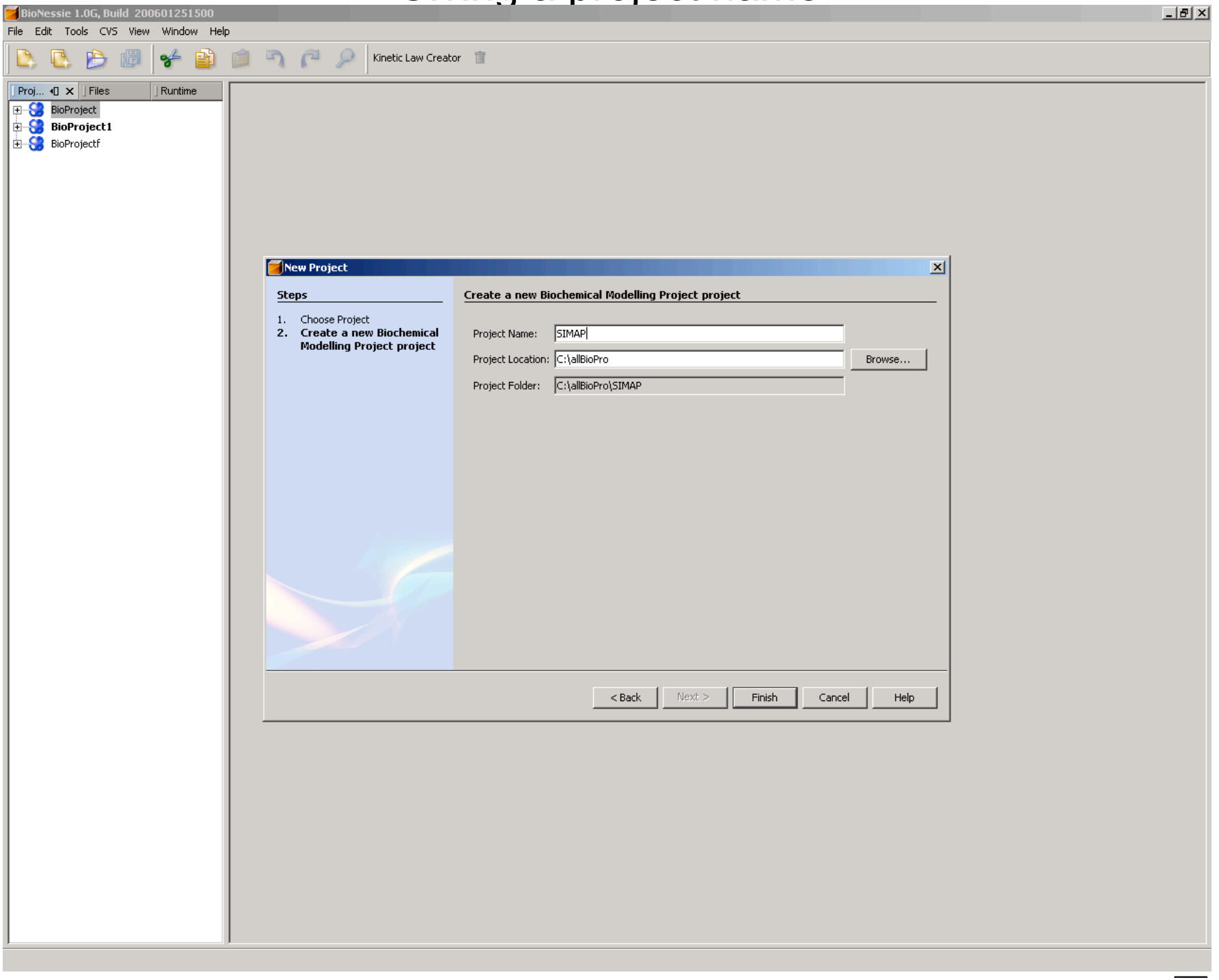
Creating a mass action based model by using BioNessie



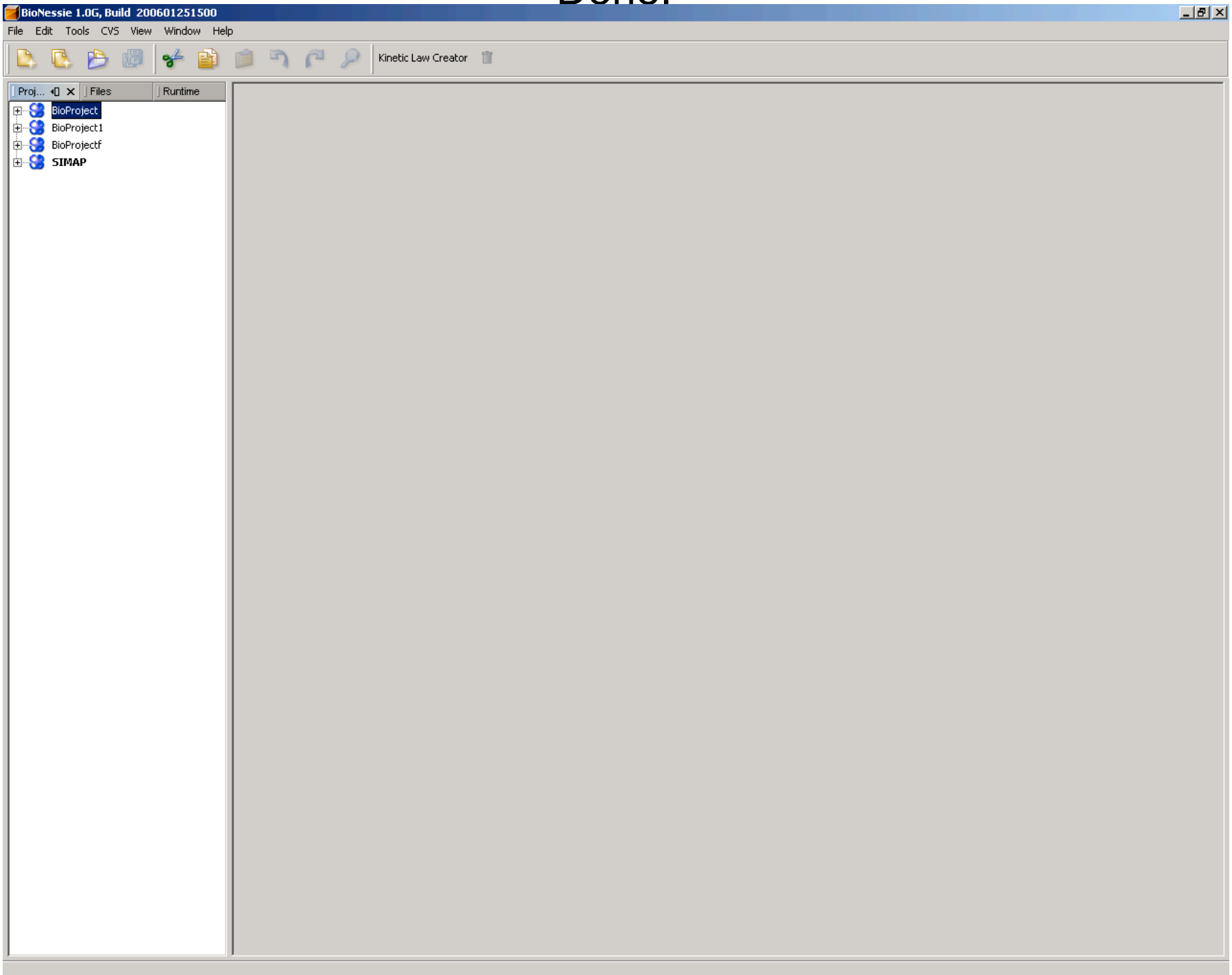
Creating a new BioProject



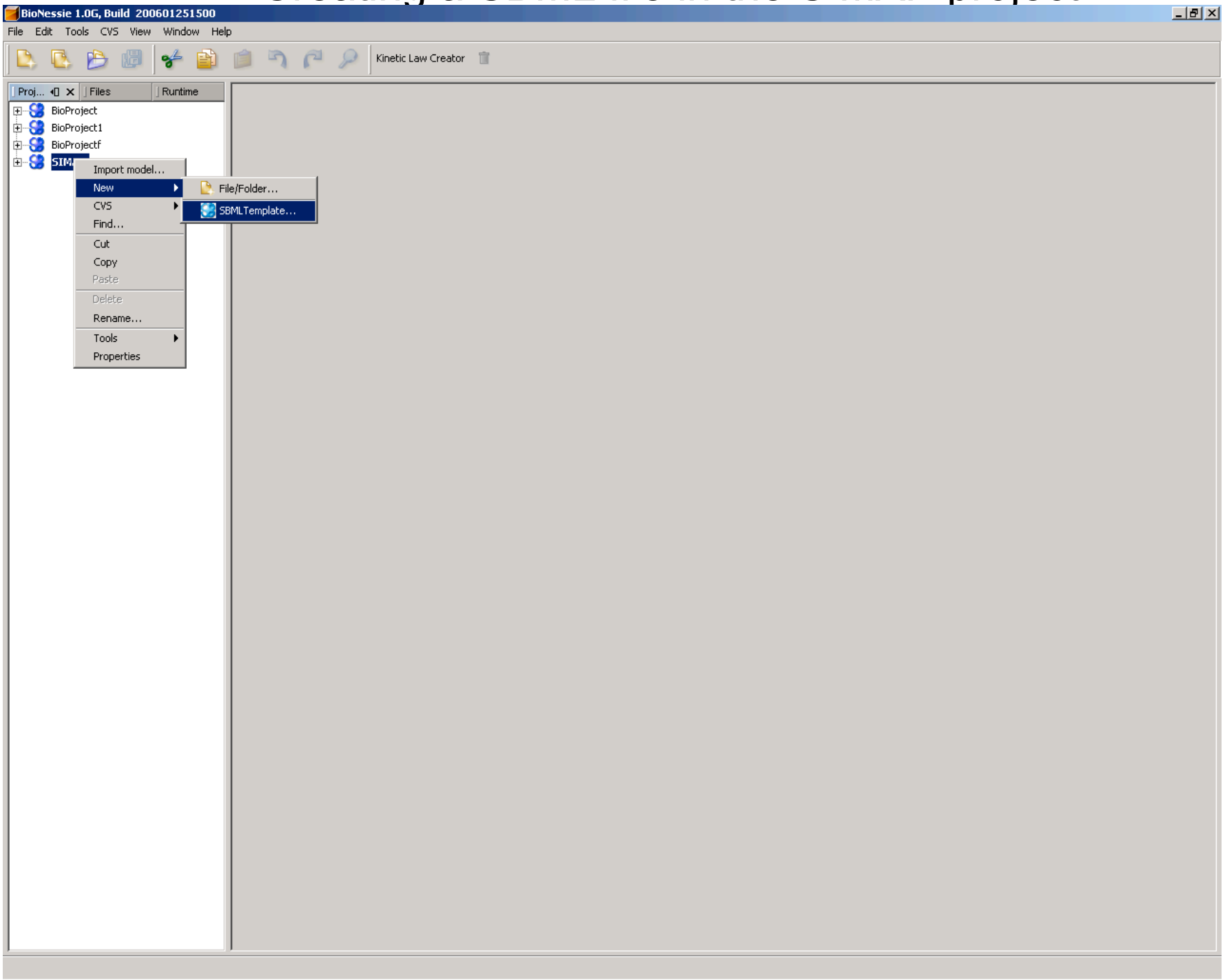
Giving a project name



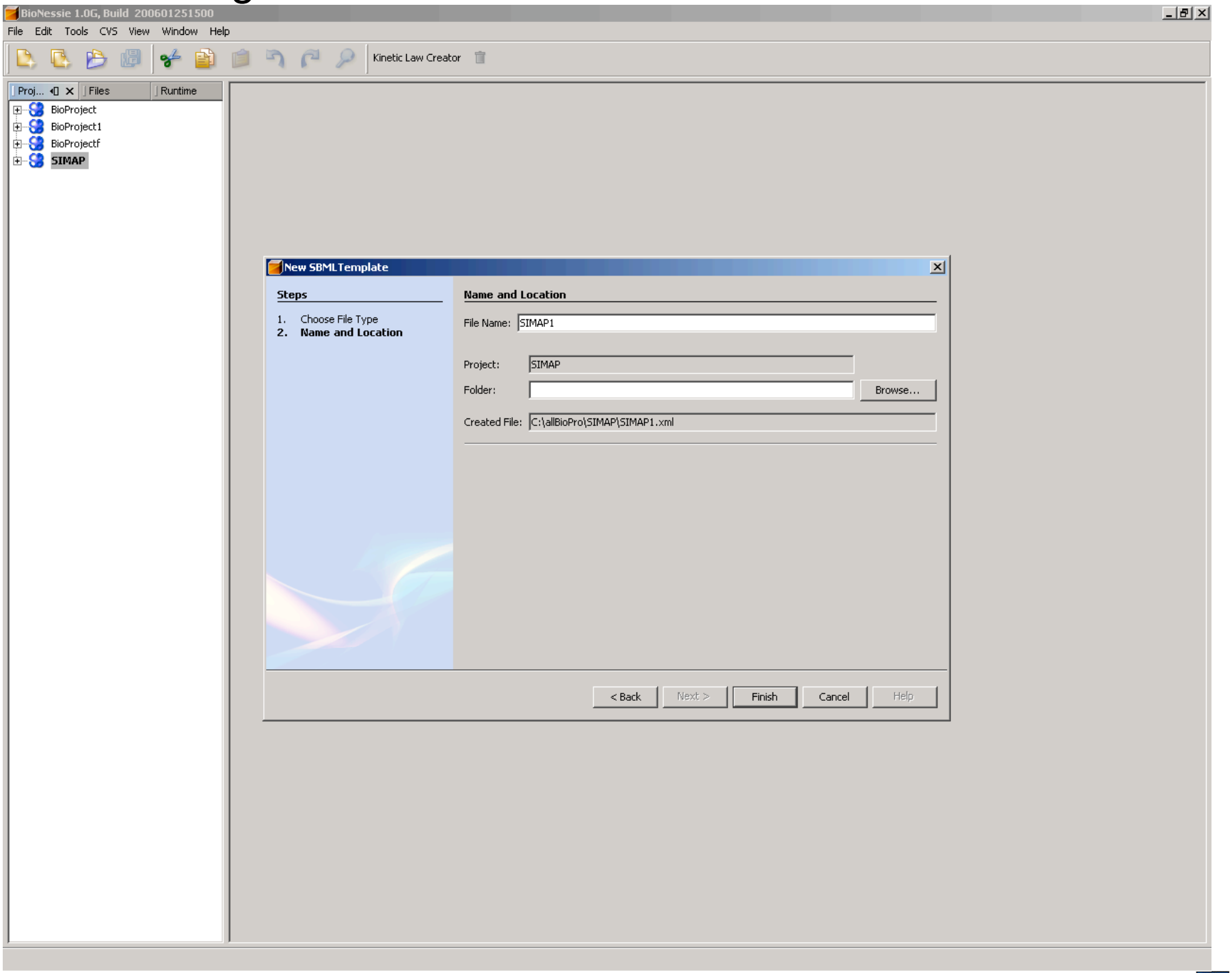
Done!


BioNessie 1.0G, Build 200601251500
File Edit Tools CVS View Window Help
Kinetic Law Creator
Proj...
Files
Runtime
BioProject
BioProject1
BioProjectf
SIMAP

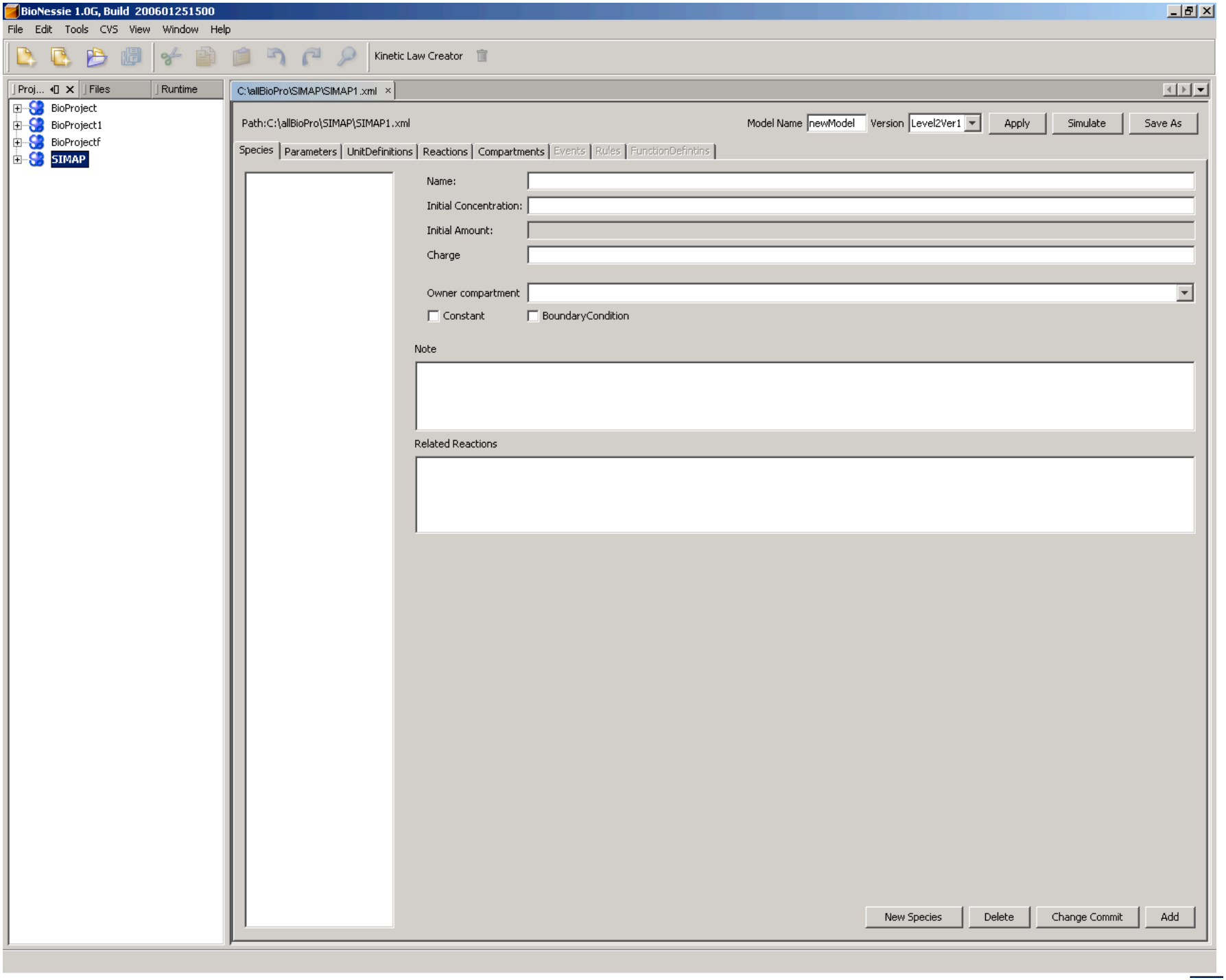
Creating a SBML file in the SIMAP project



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



Done!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File Edit Tools CVS View Window Help
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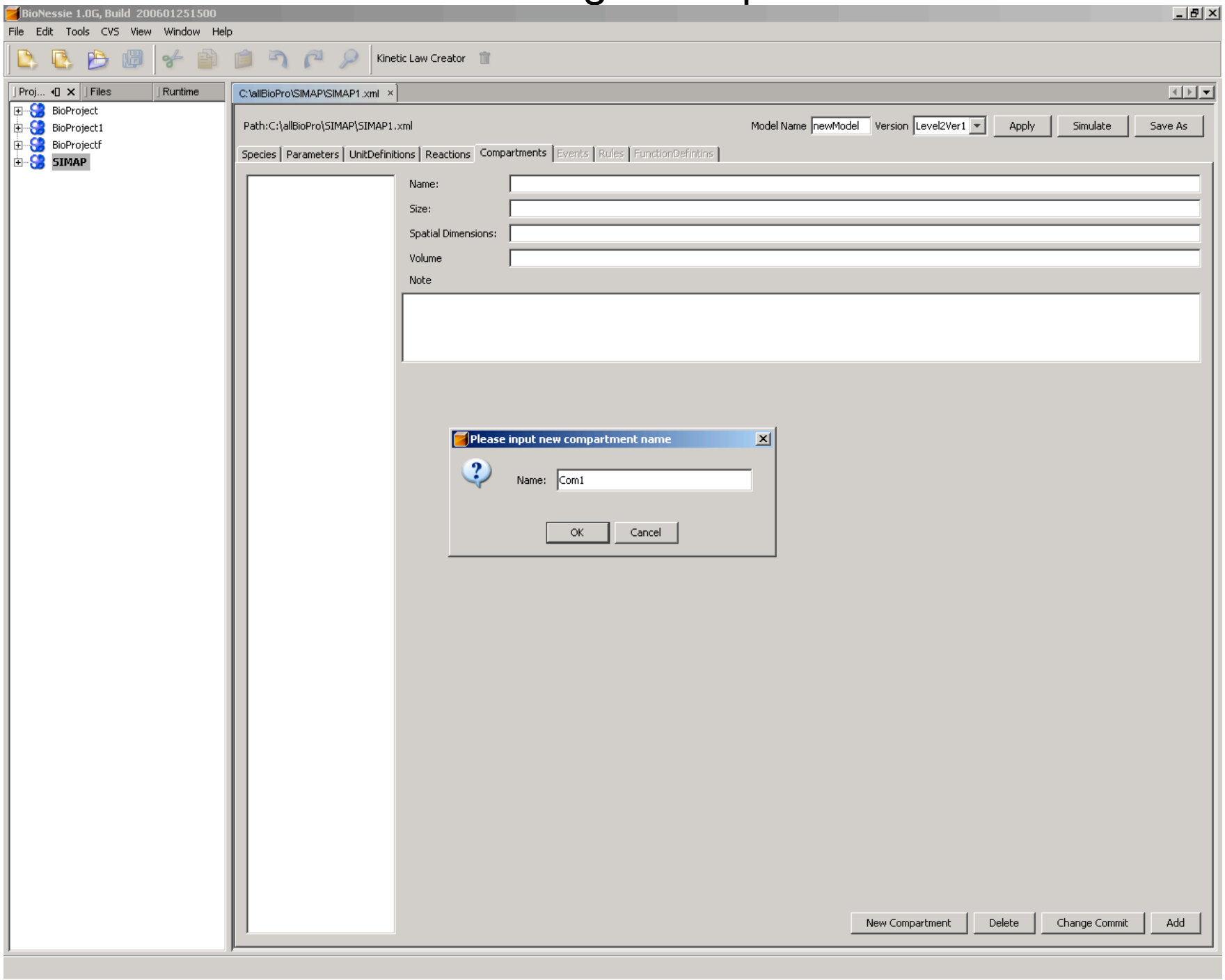
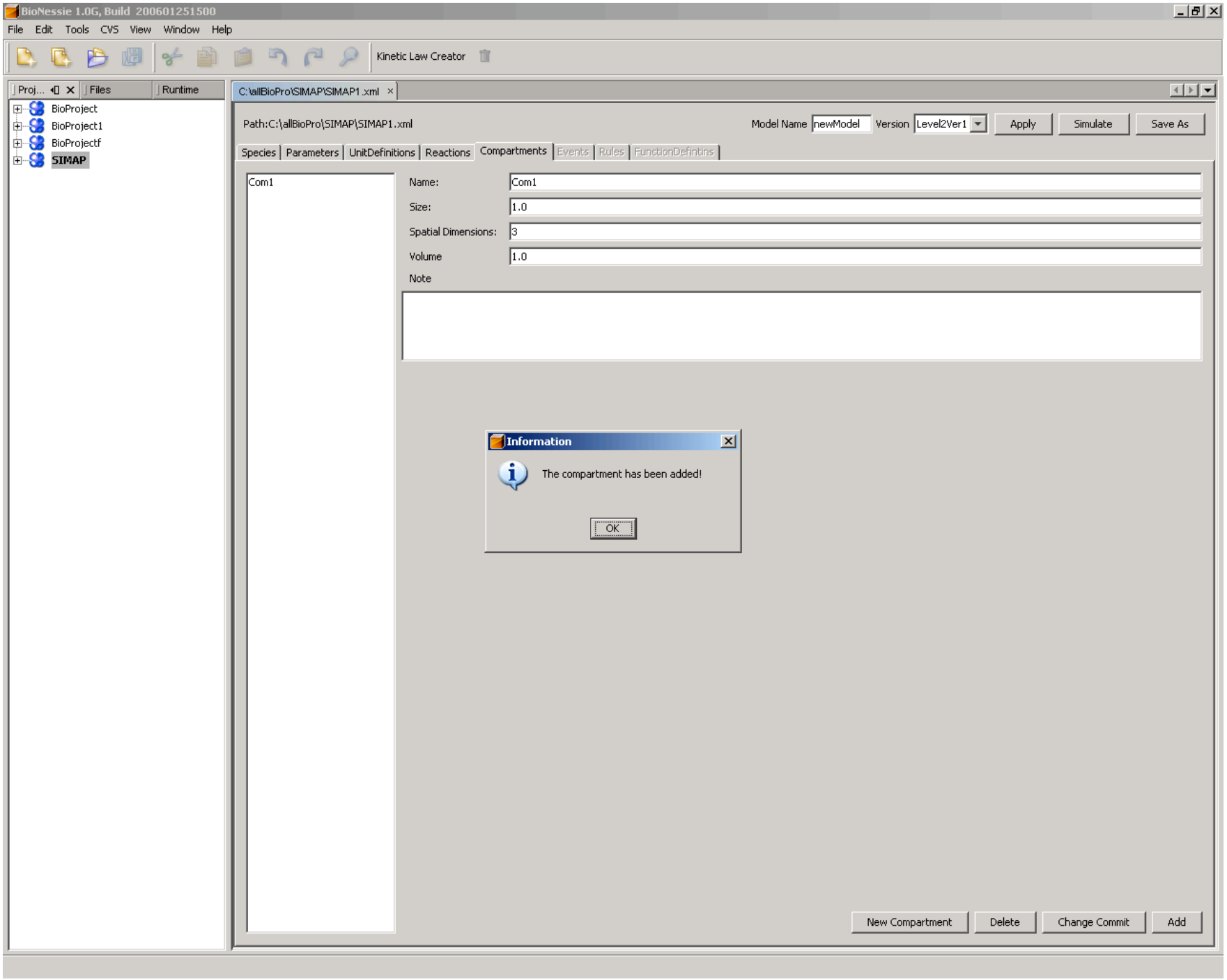
BioProjectf
SIMAP
C:\allBioPro\SIMAP\SIMAP1.xml
Path:C:\allBioPro\SIMAP\SIMAP1.xml
Model Name newModel
Version Level2Ver1
Apply
Simulate
Save As
Species
Parameters
UnitDefinitions
Reactions
Compartments
Events
Rules
FunctionDefintins
Name:
Initial Concentration:
Initial Amount:
Charge
Owner compartment
Constant
BoundaryCondition
Note
Related Reactions
New Species
Delete
Change Commit
Add

Creating a compartment



Created!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File Edit Tools CVS View Window Help
Kinetic Law Creator
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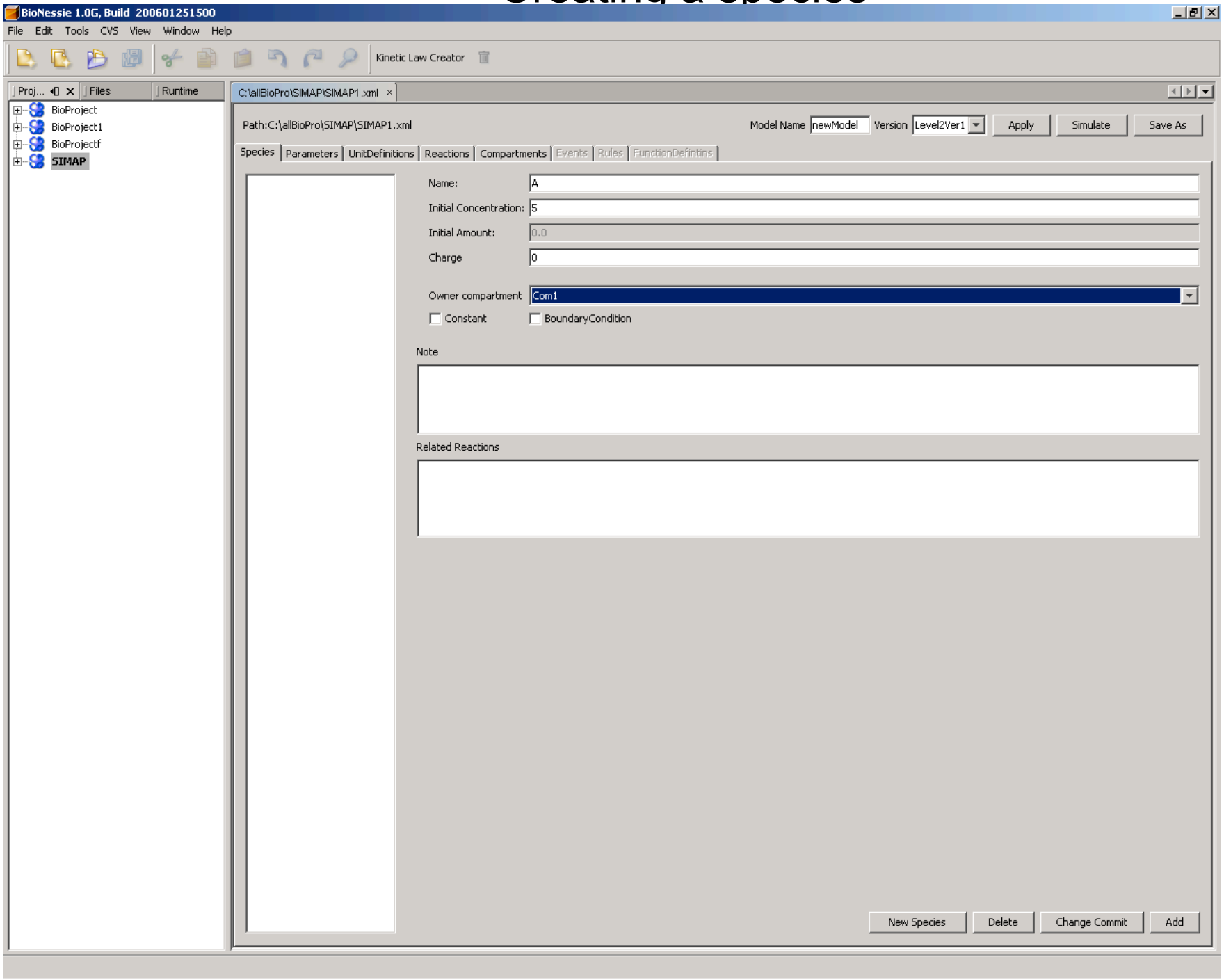
SIMAP
C:\allBioPro\SIMAP\SIMAP1.xml
Path:C:\allBioPro\SIMAP\SIMAP1.xml
Model Name newModel
Version Level2Ver1
Apply
Simulate
Save As
Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefintins
Com1
Name: Com1
Size: 1.0
Spatial Dimensions: 3
Volume 1.0
Note
Information
The compartment has been added!
OK
New Compartment
Delete
Change Commit
Add

Creating a species



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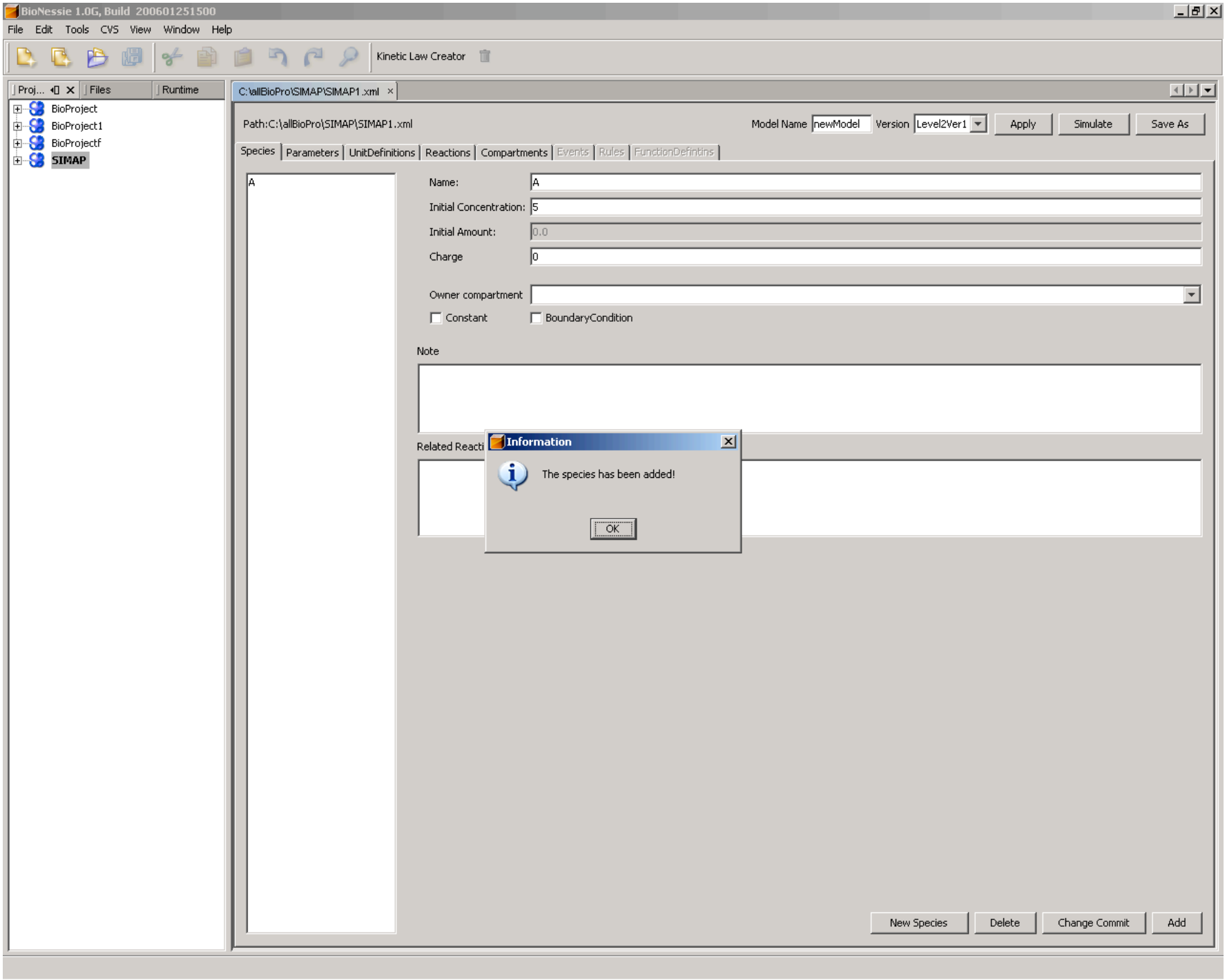
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C:\allBioPro\SIMAP\SIMAP1.xml
Path:C:\allBioPro\SIMAP\SIMAP1.xml
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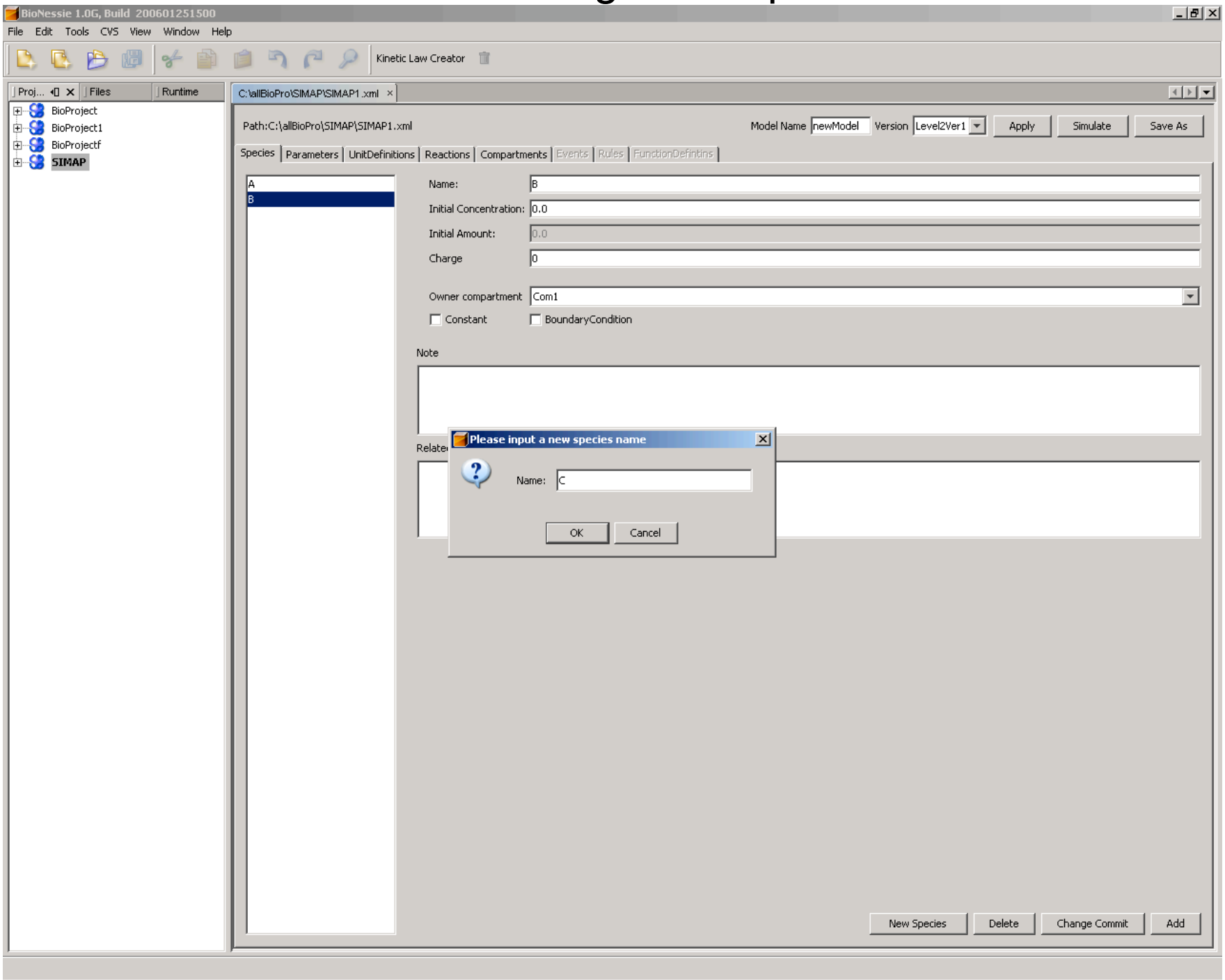
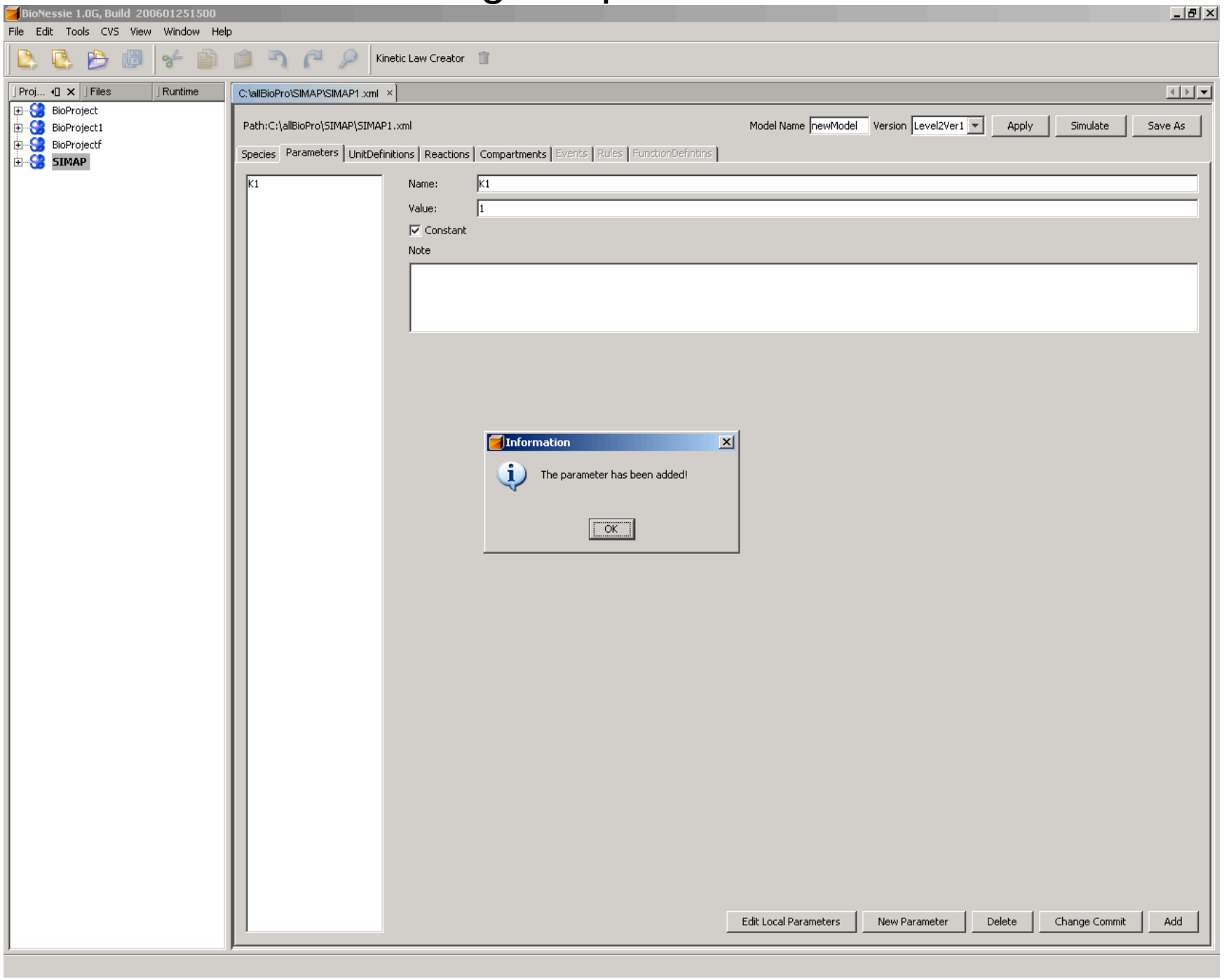
Version Level2Ver1
Apply
Simulate
Save As
Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefintins
A
Name: A
Initial Concentration: 5
Initial Amount: 0.0
Charge 0
Owner compartment
Constant
BoundaryCondition
Note
Related Reacti
Information
The species has been added!
OK
New Species
Delete
Change Commit
Add

Creating other species



Creating two parameters: K1 and K2



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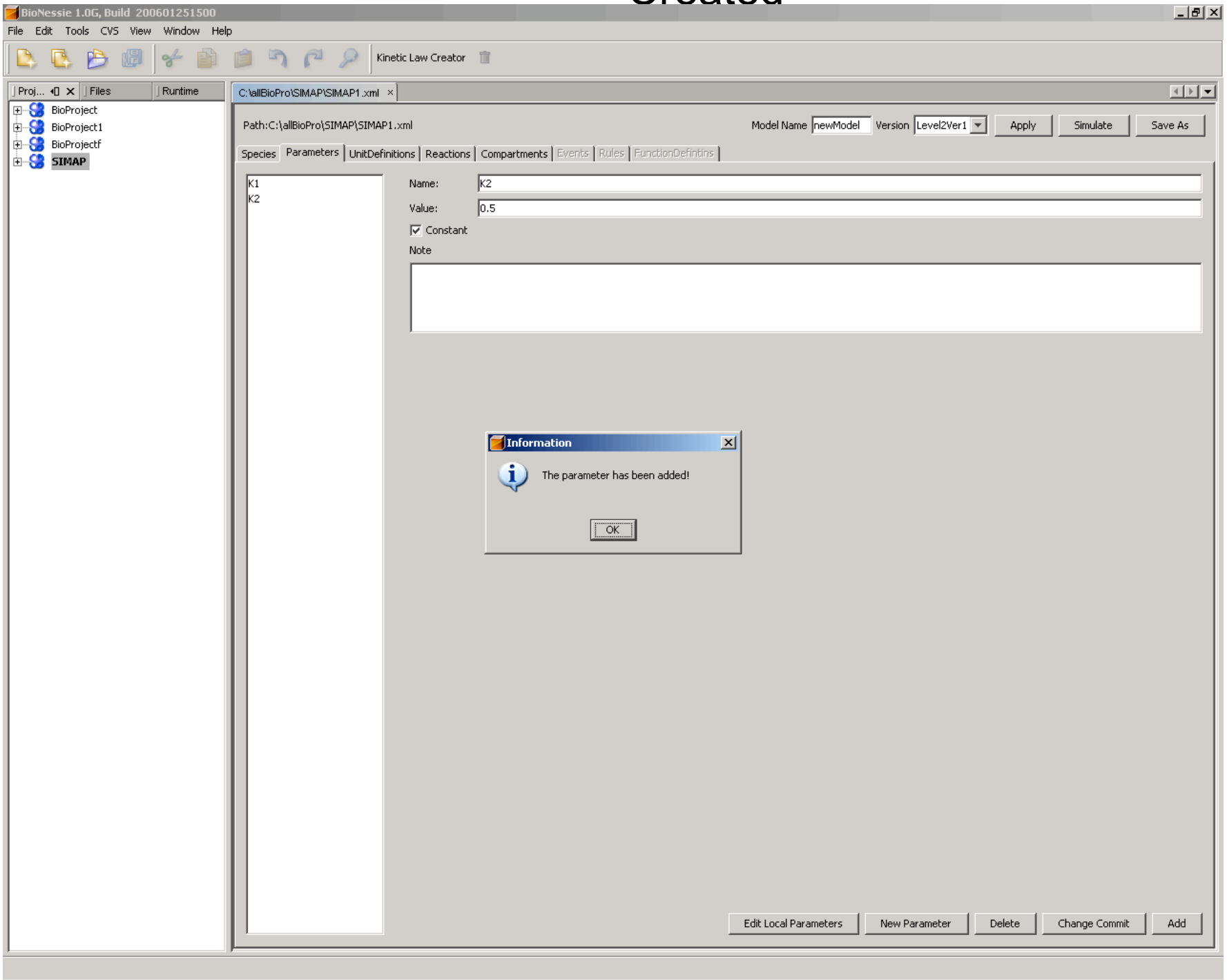
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SIMAP
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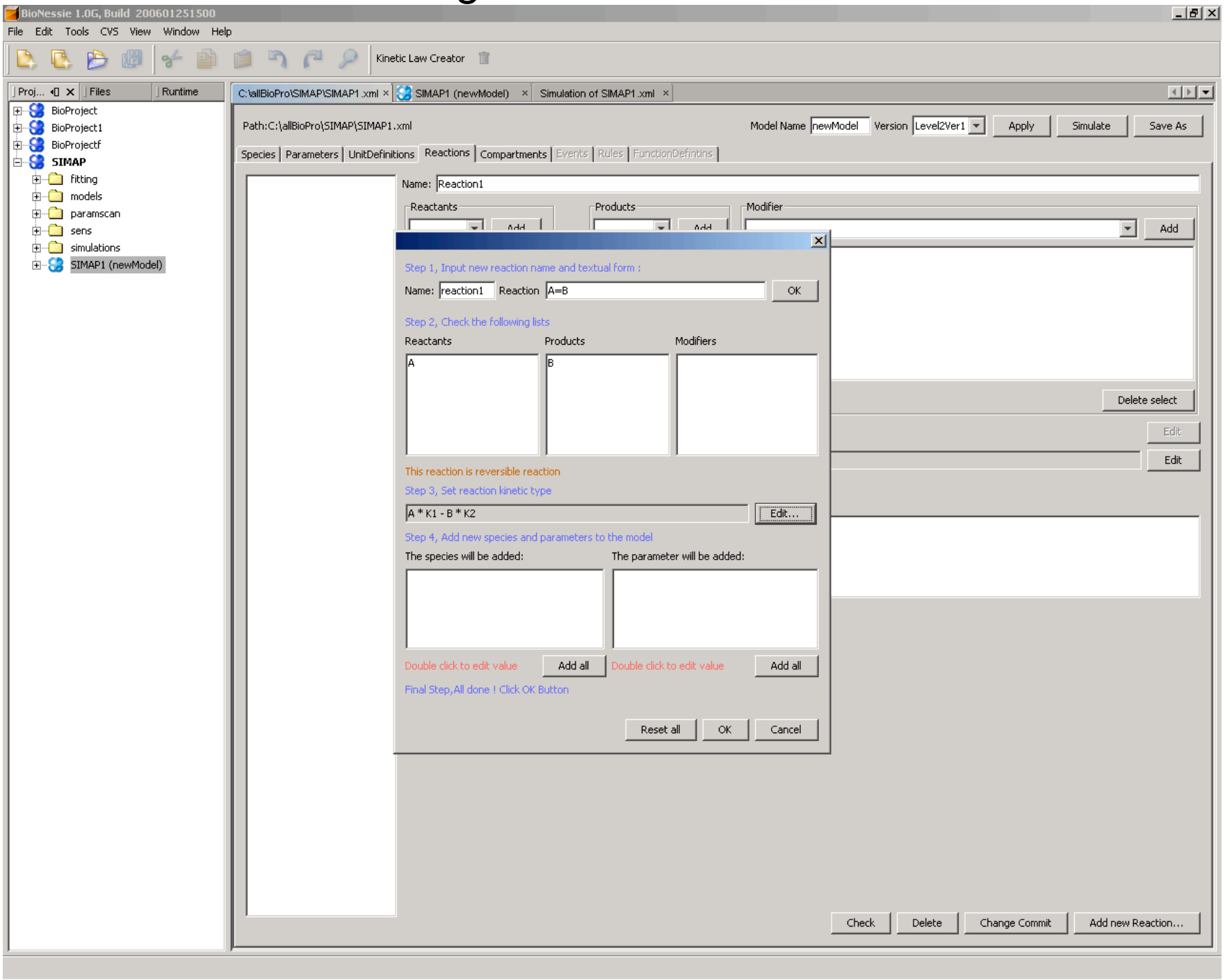
Path:C:\allBioPro\SIMAP\SIMAP1.xml
Model Name newModel
Version Level2Ver1
Apply
Simulate
Save As
Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefintins
K1
K2
Name: K2
Value: 0.5
Constant
Note
Information
The parameter has been added!
OK
Edit Local Parameters
New Parameter
Delete
Change Commit
Add

Creating a reaction A=B with K1 and K2



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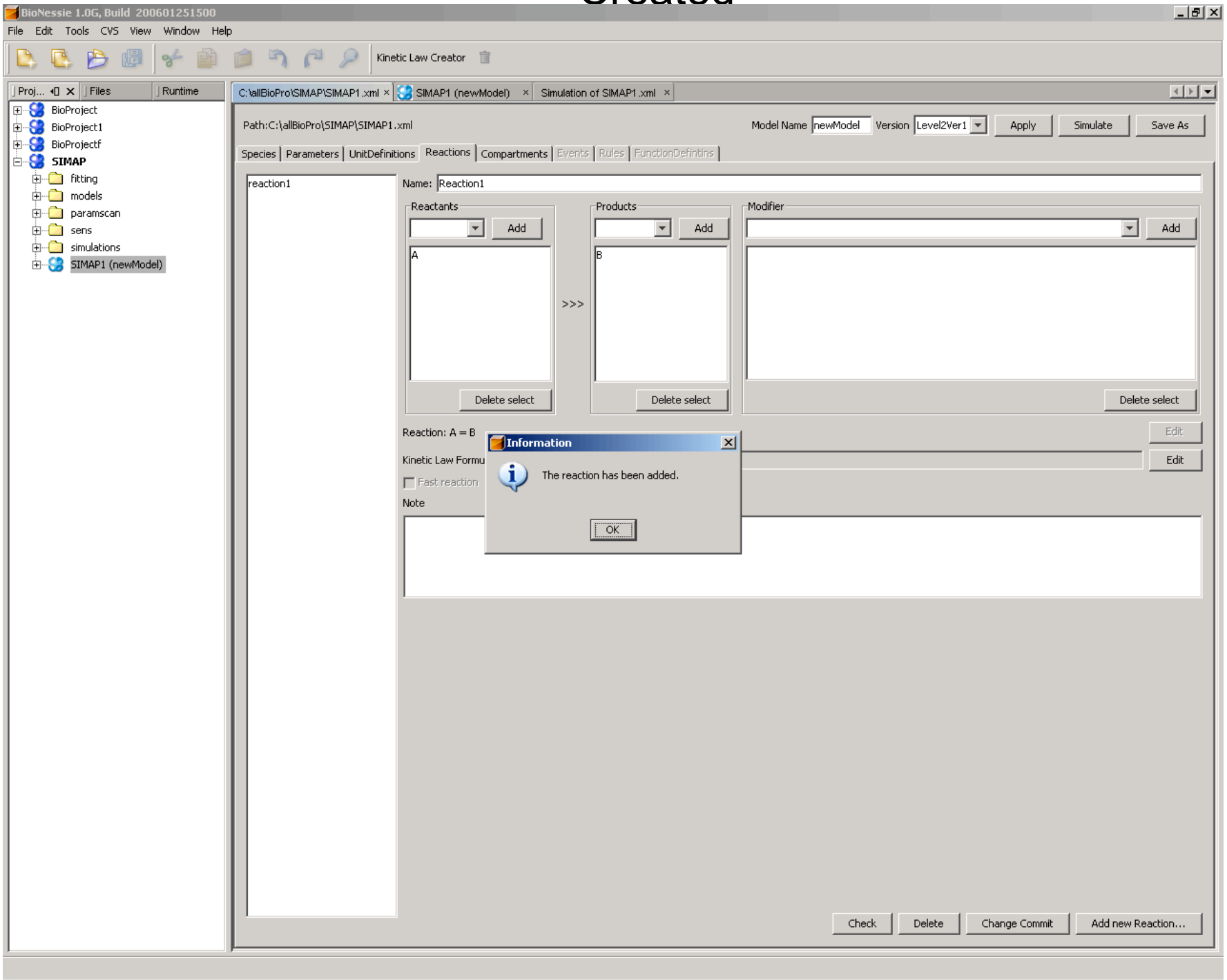
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File Edit Tools CVS View Window Help
Kinetic Law Creator
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SIMAP
fitting
models
paramscan
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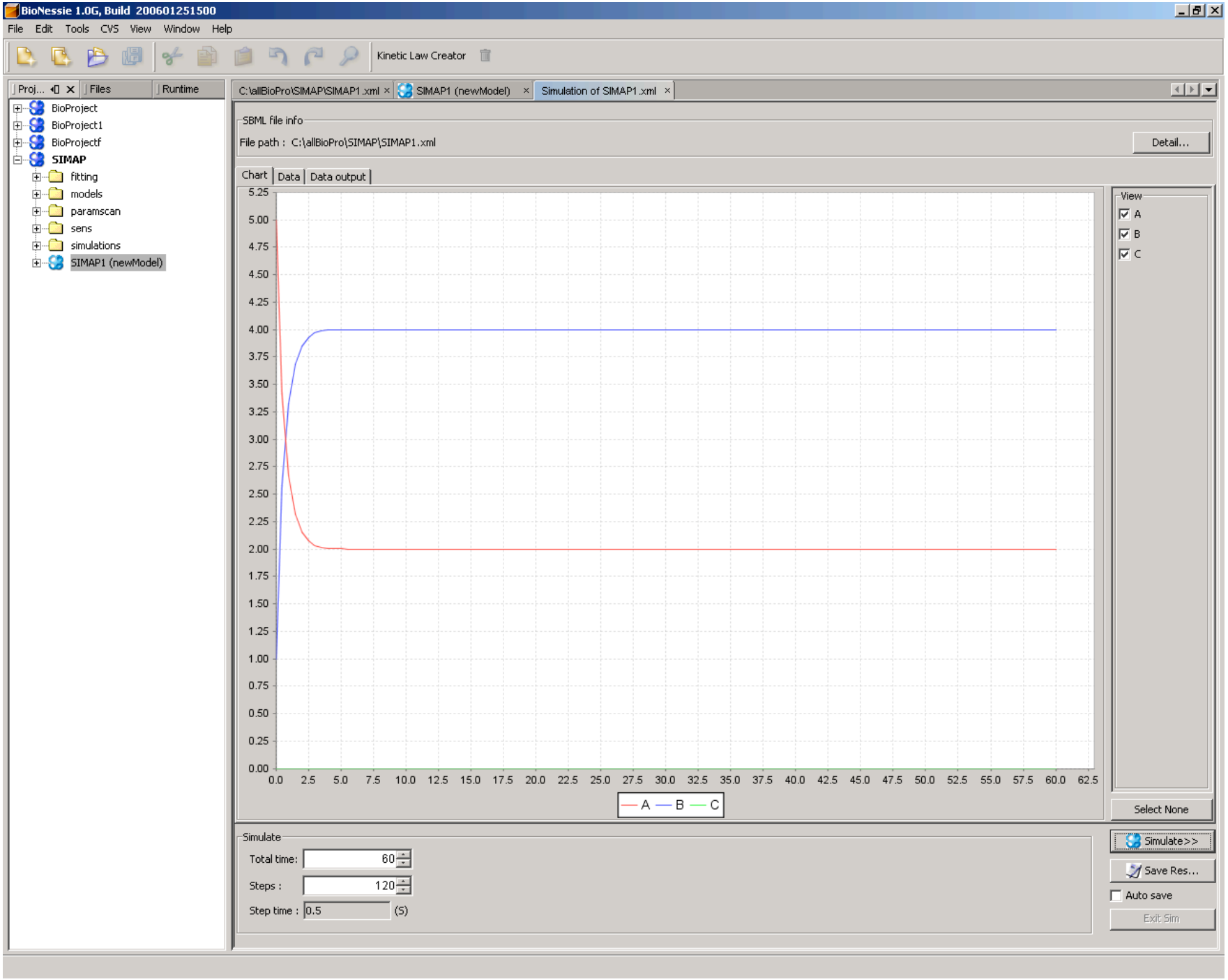
simulations
SIMAP1 (newModel)
C:\allBioPro\SIMAP\SIMAP1.xml
SIMAP1 (newModel)
Simulation of SIMAP1.xml
Path:C:\allBioPro\SIMAP\SIMAP1.xml
Model Name newModel
Version Level2Ver1
Apply
Simulate
Save As
Species Parameters UnitDefinitions Reactions Compartments Events Rules FunctionDefintins
reaction1
Name: Reaction1
Reactants
Add
A
Delete select
>>>
Products
Add
B
Delete select
Modifier
Add
Delete select
Reaction: A = B
Edit
Kinetic Law Formu
Edit
Fast reaction
Note
Information
The reaction has been added.
OK
Check
Delete
Change Commit
Add new Reaction...

Simulation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File Edit Tools CVS View Window Help
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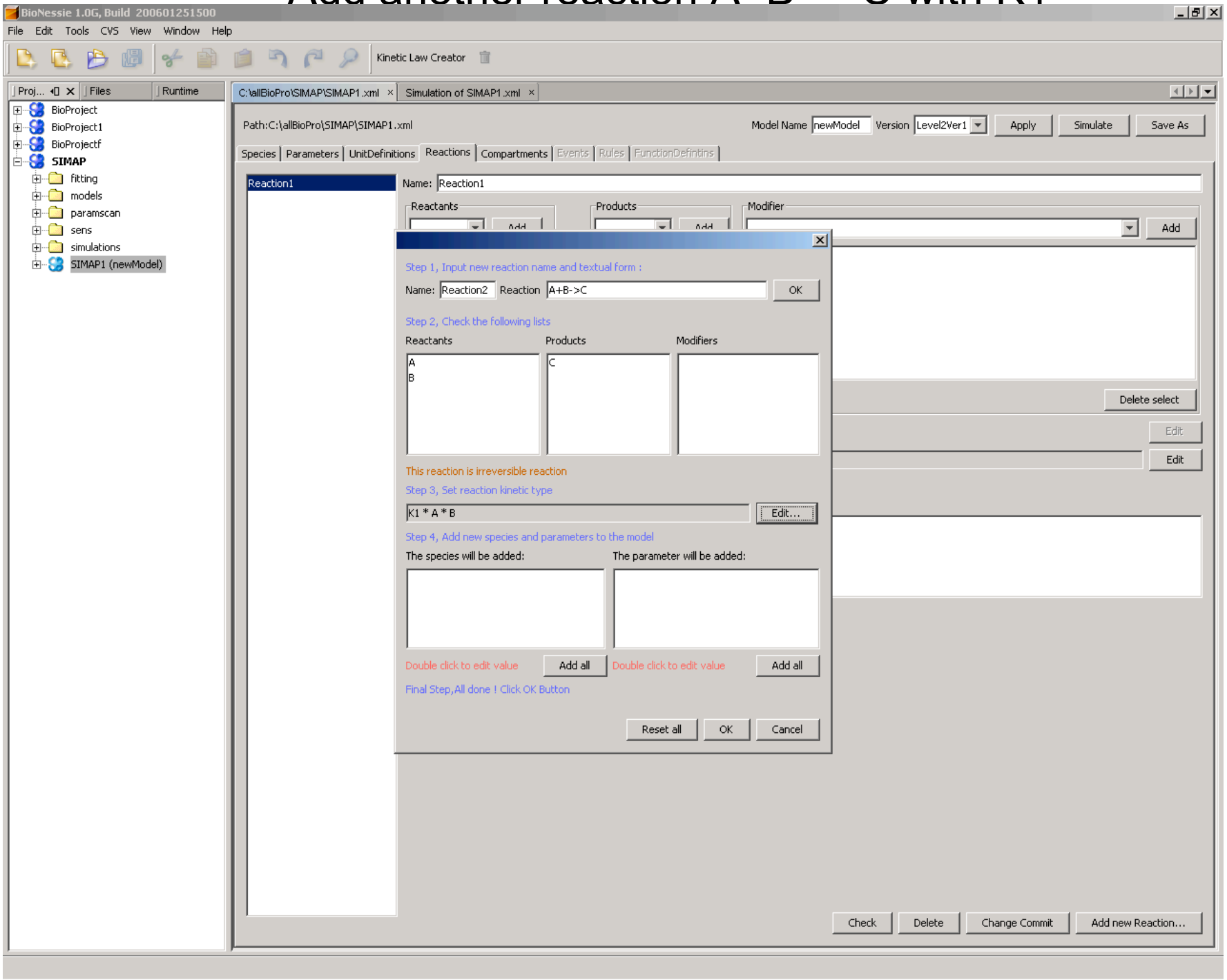
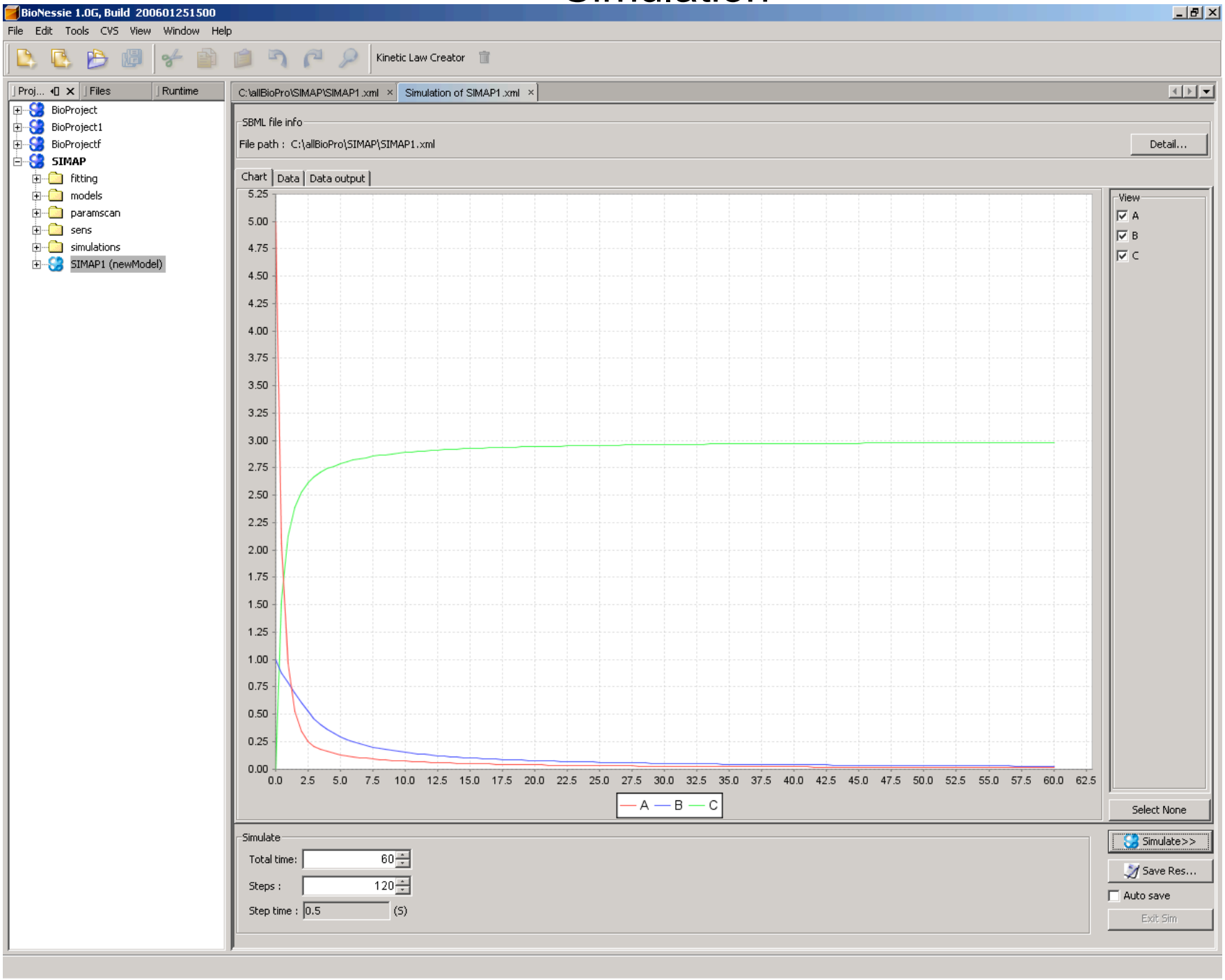
BioProjectf
SIMAP
fitting
models
paramscan
sens
simulations
SIMAP1 (newModel)
C:\allBioPro\SIMAP\SIMAP1.xml
SIMAP1 (newModel)
Simulation of SIMAP1.xml
SBML file info
File path : C:\allBioPro\SIMAP\SIMAP1.xml
Detail...
Chart Data Data output
5.25 5.00 4.75 4.50 4.25 4.00 3.75 3.50 3.25 3.00 2.75 2.50 2.25 2.00 1.75 1.50 1.25 1.00 0.75 0.50 0.25 0.00
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0 32.5 35.0 37.5 40.0 42.5 45.0 47.5 50.0 52.5 55.0 57.5 60.0 62.5
A B C
View
A
B
C
Select None
Simulate
Total time: 60
Steps : 120
Step time : 0.5 (S)
Simulate>>
Save Res...
Auto save
Exit Sim

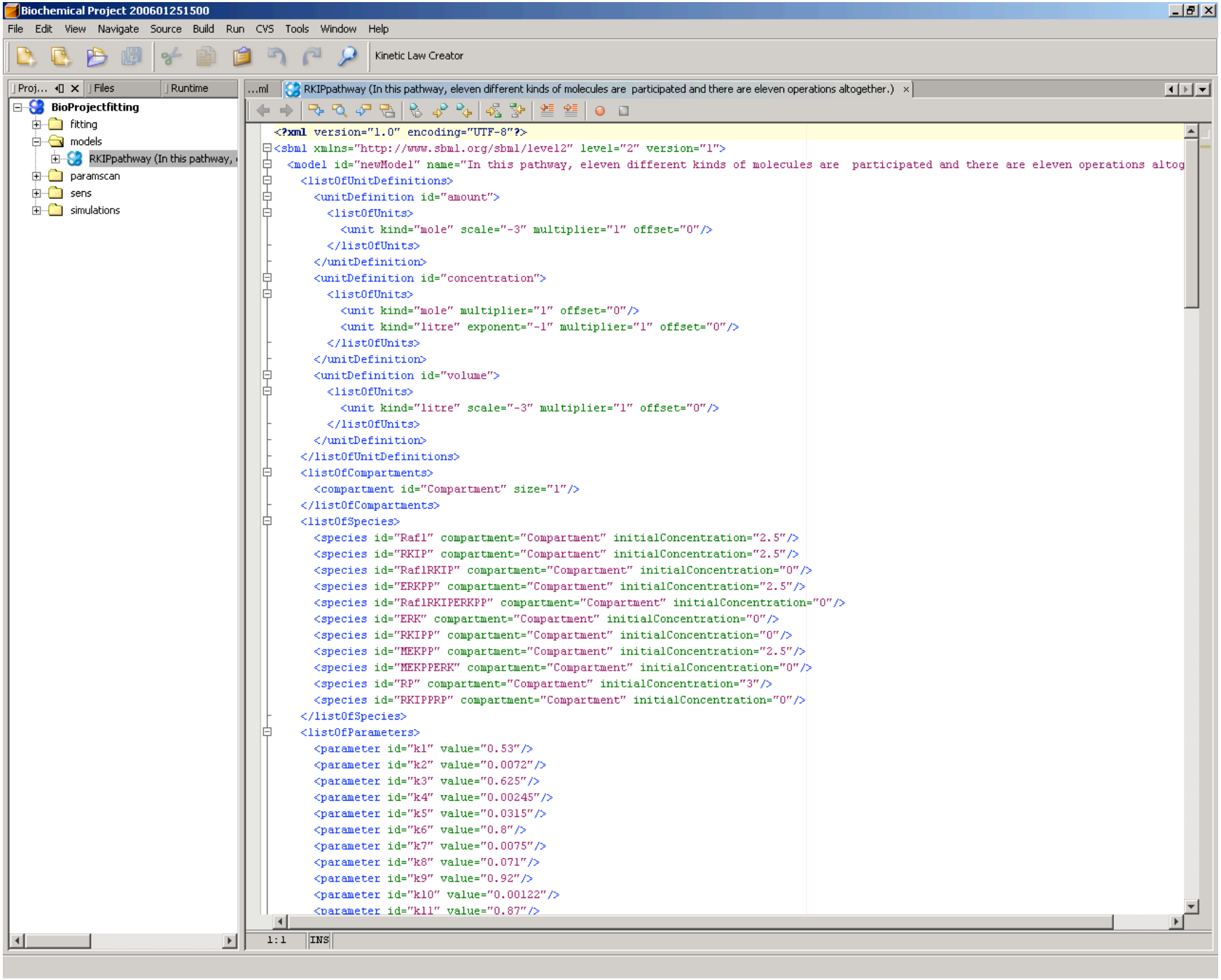
Add another reaction A+B -> C with K1



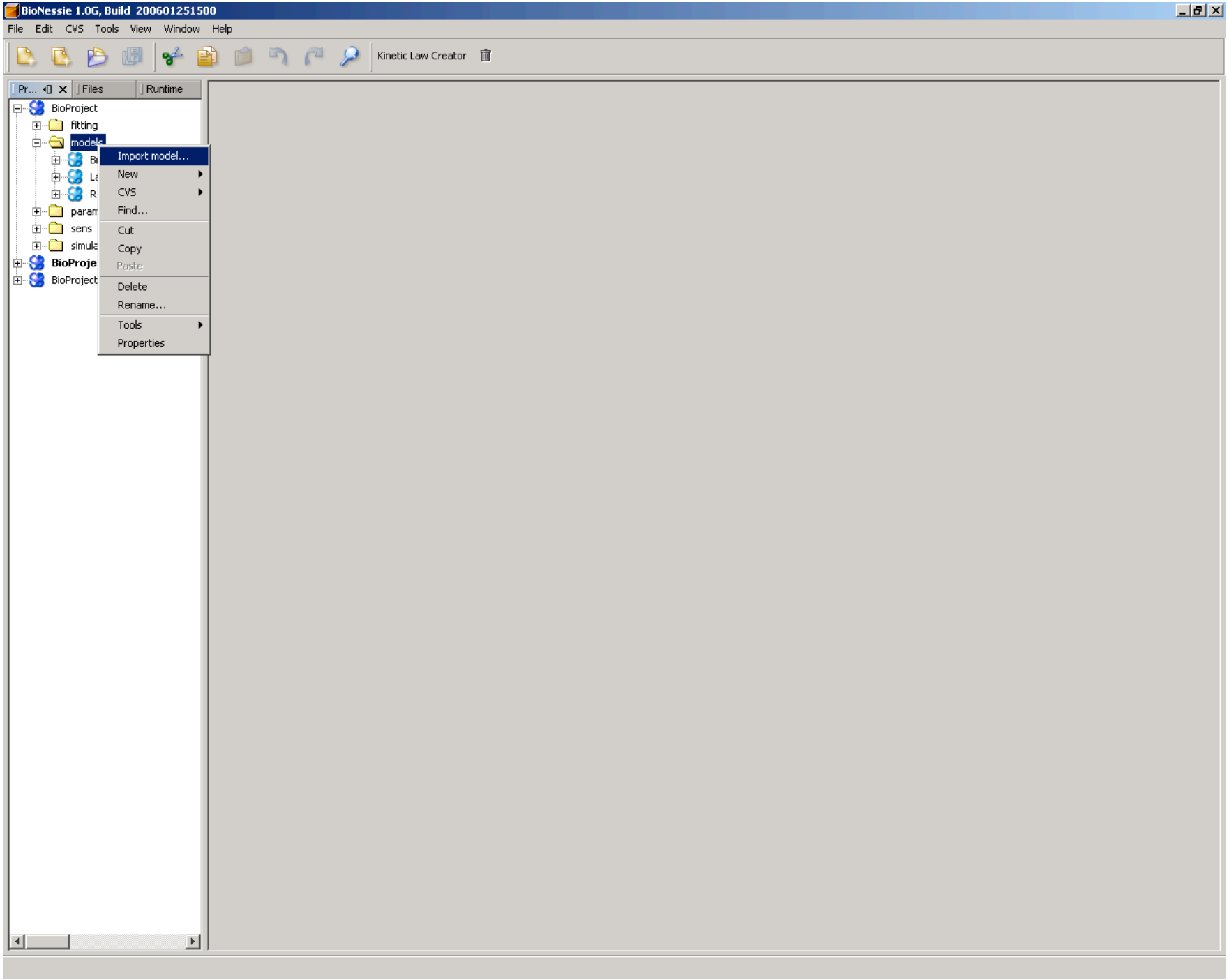
Simulation


BioNessie 1.0G, Build 200601251500
File Edit Tools CVS View Window Help
Kinetic Law Creator
Proj... Files Runtime
BioProject
BioProject1
BioProjectf
SIMAP
fitting
models
paramscan
sens
simulations
SIMAP1 (newModel)
C:\allBioPro\SIMAP\SIMAP1.xml
Simulation of SIMAP1.xml
SBML file info
File path : C:\allBioPro\SIMAP\SIMAP1.xml
Detail...
Chart
Data
Data output
5.25
5.00
4.75
4.50
4.25
4.00
3.75
3.50
3.25
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0 32.5 35.0 37.5 40.0 42.5 45.0 47.5 50.0 52.5 55.0 57.5 60.0 62.5
A B C
View
A
B
C
Select None
Simulate
Total time: 60
Steps : 120
Step time : 0.5 (S)
Simulate>>
Save Res...
Auto save
Exit Sim

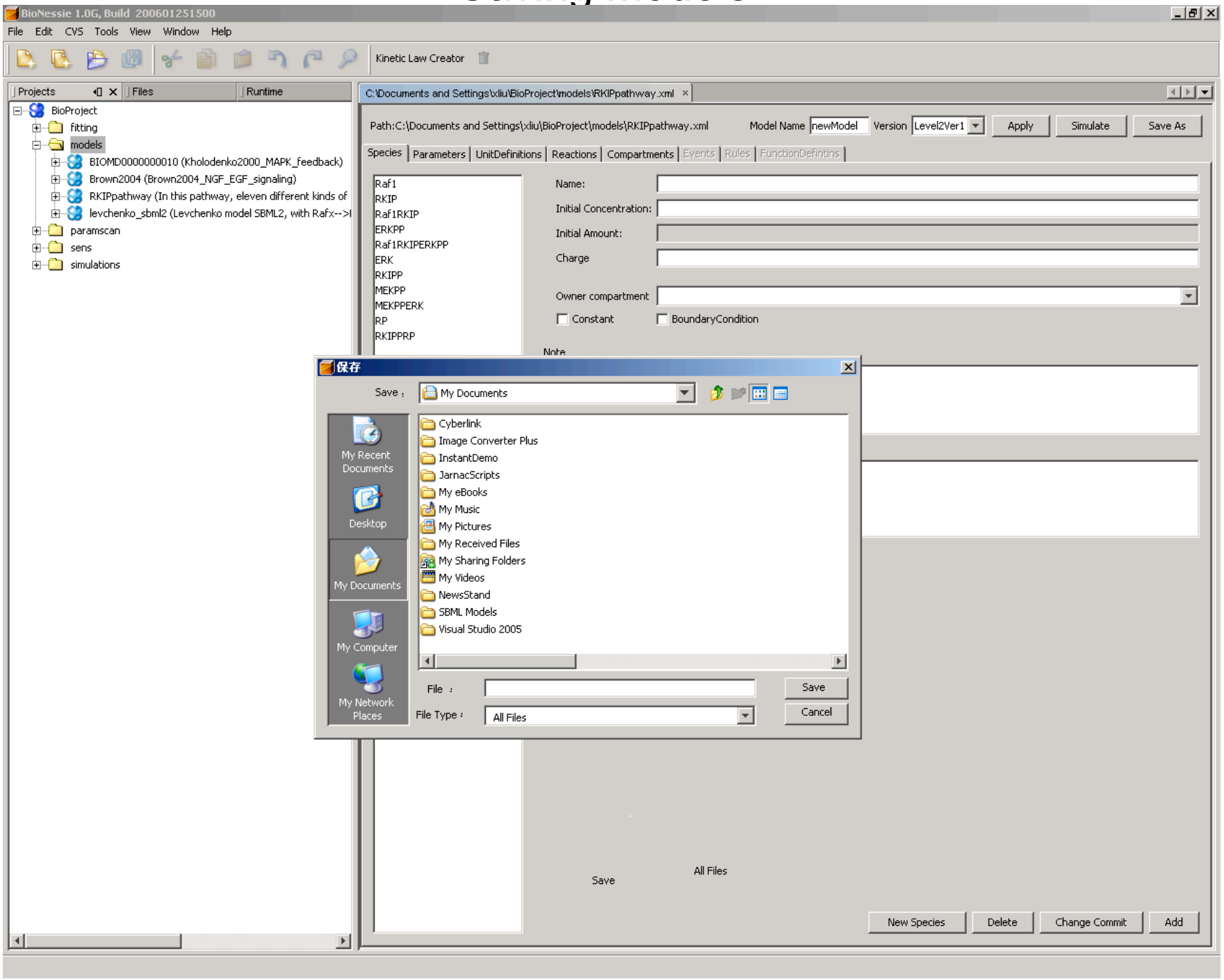
Textual SBML source editor



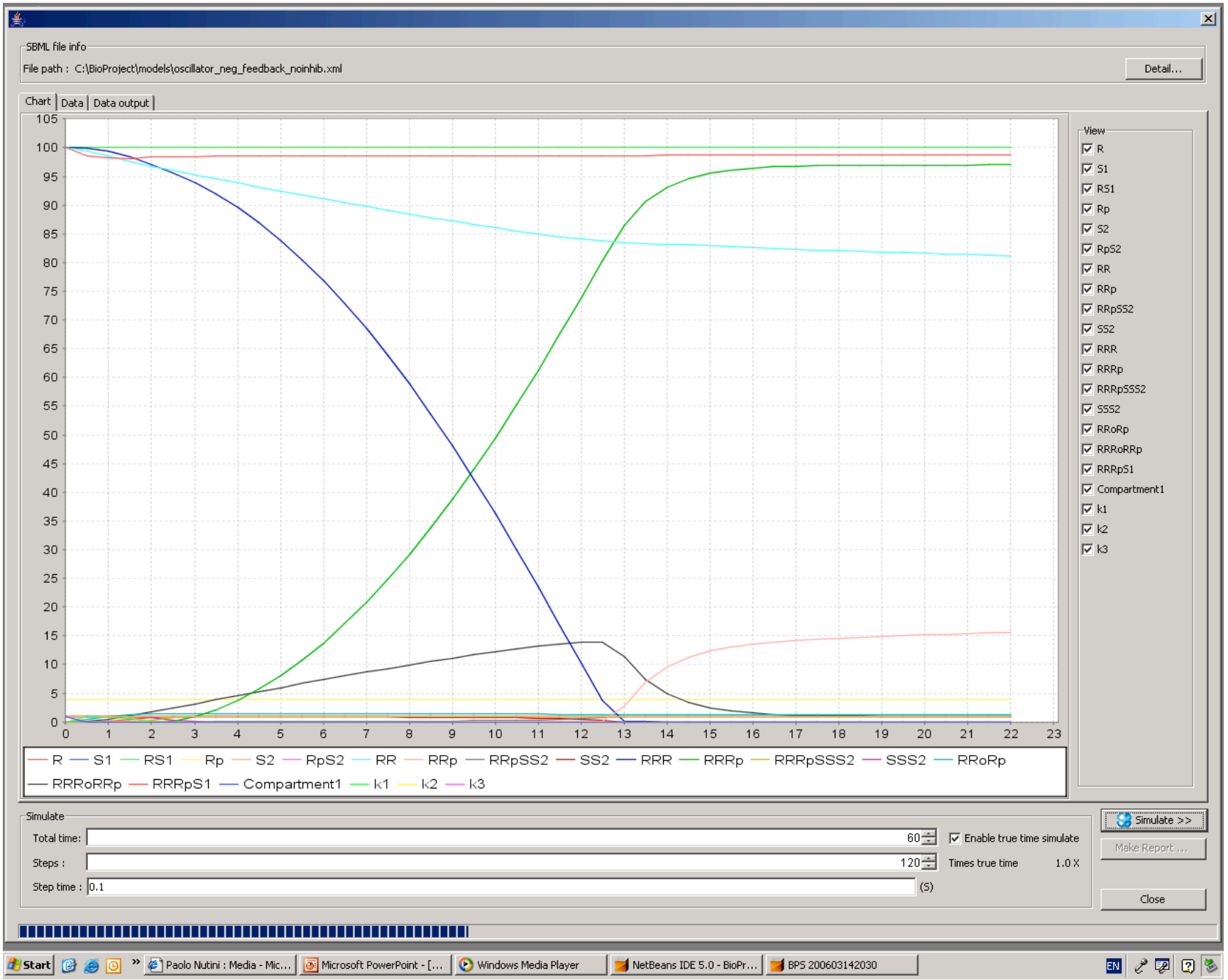
Model retrieval



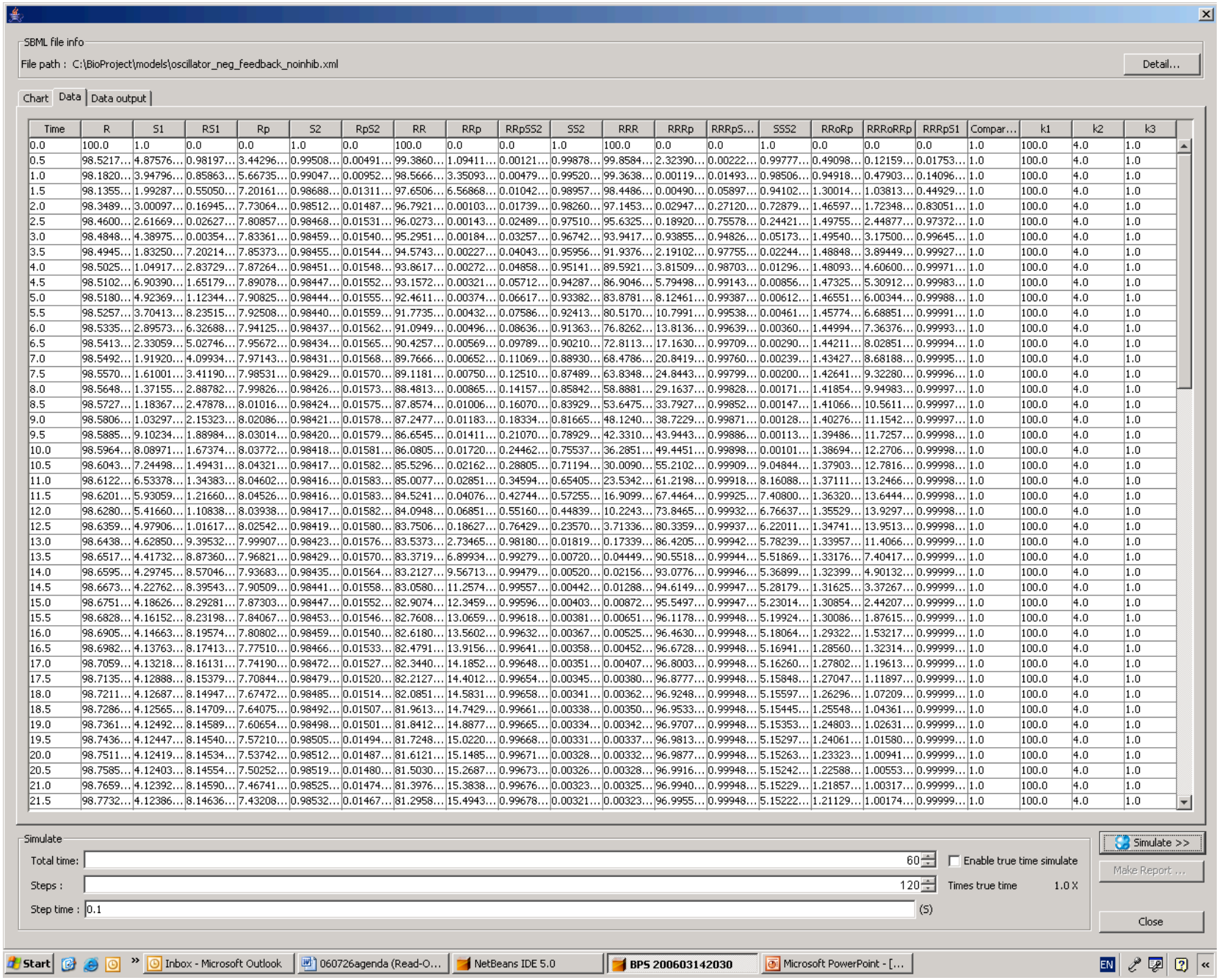
Saving models



Model Simulation



Results viewer



SBML file info

File path : C:\BioProject\models\oscillator_neg_feedback_noinhib.xml

Detail...

Chart | Data | Data output

Time	R	S1	RS1	Rp	S2	RpS2	RR	RRp	RRpSS2	SS2	RRR	RRRp	RRRpS...	SSS2	RRoRp	RRRoRRp	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...	0.55050...	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...	9.04844...	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...	8.16088...	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...	7.40800...	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...	6.76637...	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...	6.22011...	1.34741...	13.9513...	0.99998...	1.0	100.0	4.0	1.0
13.0	98.6438...	4.62850...	9.39532...	7.99907...	0.98423...	0.01576...	83.5373...	2.73465...	0.98180...	0.01819...	0.17339...	86.4205...	0.99942...	5.78239...	1.33957...	11.4066...	0.99999...	1.0	100.0	4.0	1.0
13.5	98.6517...	4.41732...	8.87360...	7.96821...	0.98429...	0.01570...	83.3719...	6.89934...	0.99279...	0.00720...	0.04449...	90.5518...	0.99944...	5.51869...	1.33176...	7.40417...	0.99999...	1.0	100.0	4.0	1.0
14.0	98.6595...	4.29745...	8.57046...	7.93683...	0.98435...	0.01564...	83.2127...	9.56713...	0.99479...	0.00520...	0.02156...	93.0776...	0.99946...	5.36899...	1.32399...	4.90132...	0.99999...	1.0	100.0	4.0	1.0
14.5	98.6673...	4.22762...	8.39543...	7.90509...	0.98441...	0.01558...	83.0580...	11.2574...	0.99557...	0.00442...	0.01288...	94.6149...	0.99947...	5.28179...	1.31625...	3.37267...	0.99999...	1.0	100.0	4.0	1.0
15.0	98.6751...	4.18626...	8.29281...	7.87303...	0.98447...	0.01552...	82.9074...	12.3459...	0.99596...	0.00403...	0.00872...	95.5497...	0.99947...	5.23014...	1.30854...	2.44207...	0.99999...	1.0	100.0	4.0	1.0
15.5	98.6828...	4.16152...	8.23198...	7.84067...	0.98453...	0.01546...	82.7608...	13.0659...	0.99618...	0.00381...	0.00651...	96.1178...	0.99948...	5.19924...	1.30086...	1.87615...	0.99999...	1.0	100.0	4.0	1.0
16.0	98.6905...	4.14663...	8.19574...	7.80802...	0.98459...	0.01540...	82.6180...	13.5602...	0.99632...	0.00367...	0.00525...	96.4630...	0.99948...	5.18064...	1.29322...	1.53217...	0.99999...	1.0	100.0	4.0	1.0
16.5	98.6982...	4.13763...	8.17413...	7.77510...	0.98466...	0.01533...	82.4791...	13.9156...	0.99641...	0.00358...	0.00452...	96.6728...	0.99948...	5.16941...	1.28560...	1.32314...	0.99999...	1.0	100.0	4.0	1.0
17.0	98.7059...	4.13218...	8.16131...	7.74190...	0.98472...	0.01527...	82.3440...	14.1852...	0.99648...	0.00351...	0.00407...	96.8003...	0.99948...	5.16260...	1.27802...	1.19613...	0.99999...	1.0	100.0	4.0	1.0
17.5	98.7135...	4.12888...	8.15379...	7.70844...	0.98479...	0.01520...	82.2127...	14.4012...	0.99654...	0.00345...	0.00380...	96.8777...	0.99948...	5.15848...	1.27047...	1.11897...	0.99999...	1.0	100.0	4.0	1.0
18.0	98.7211...	4.12687...	8.14947...	7.67472...	0.98485...	0.01514...	82.0851...	14.5831...	0.99658...	0.00341...	0.00362...	96.9248...	0.99948...	5.15597...	1.26296...	1.07209...	0.99999...	1.0	100.0	4.0	1.0
18.5	98.7286...	4.12565...	8.14709...	7.64075...	0.98492...	0.01507...	81.9613...	14.7429...	0.99661...	0.00338...	0.00350...	96.9533...	0.99948...	5.15445...	1.25548...	1.04361...	0.99999...	1.0	100.0	4.0	1.0
19.0	98.7361...	4.12492...	8.14589...	7.60654...	0.98498...	0.01501...	81.8412...	14.8877...	0.99665...	0.00334...	0.00342...	96.9707...	0.99948...	5.15353...	1.24803...	1.02631...	0.99999...	1.0	100.0	4.0	1.0
19.5	98.7436...	4.12447...	8.14540...	7.57210...	0.98505...	0.01494...	81.7248...	15.0220...	0.99668...	0.00331...	0.00337...	96.9813...	0.99948...	5.15297...	1.24061...	1.01580...	0.99999...	1.0	100.0	4.0	1.0
20.0	98.7511...	4.12419...	8.14534...	7.53742...	0.98512...	0.01487...	81.6121...	15.1485...	0.99671...	0.00328...	0.00332...	96.9877...	0.99948...	5.15263...	1.23323...	1.00941...	0.99999...	1.0	100.0	4.0	1.0
20.5	98.7585...	4.12403...	8.14554...	7.50252...	0.98519...	0.01480...	81.5030...	15.2687...	0.99673...	0.00326...	0.00328...	96.9916...	0.99948...	5.15242...	1.22588...	1.00553...	0.99999...	1.0	100.0	4.0	1.0
21.0	98.7659...	4.12392...	8.14590...	7.46741...	0.98525...	0.01474...	81.3976...	15.3838...	0.99676...	0.00323...	0.00325...	96.9940...	0.99948...	5.15229...	1.21857...	1.00317...	0.99999...	1.0	100.0	4.0	1.0
21.5	98.7732...	4.12386...	8.14636...	7.43208...	0.98532...	0.01467...	81.2958...	15.4943...	0.99678...	0.00321...	0.00323...	96.9955...	0.99948...	5.15222...	1.21129...	1.00174...	0.99999...	1.0	100.0	4.0	1.0

Simulate

Total time: 60

Steps : 120

Step time : 0.1 (S)

Enable true time simulate

Times true time 1.0 X

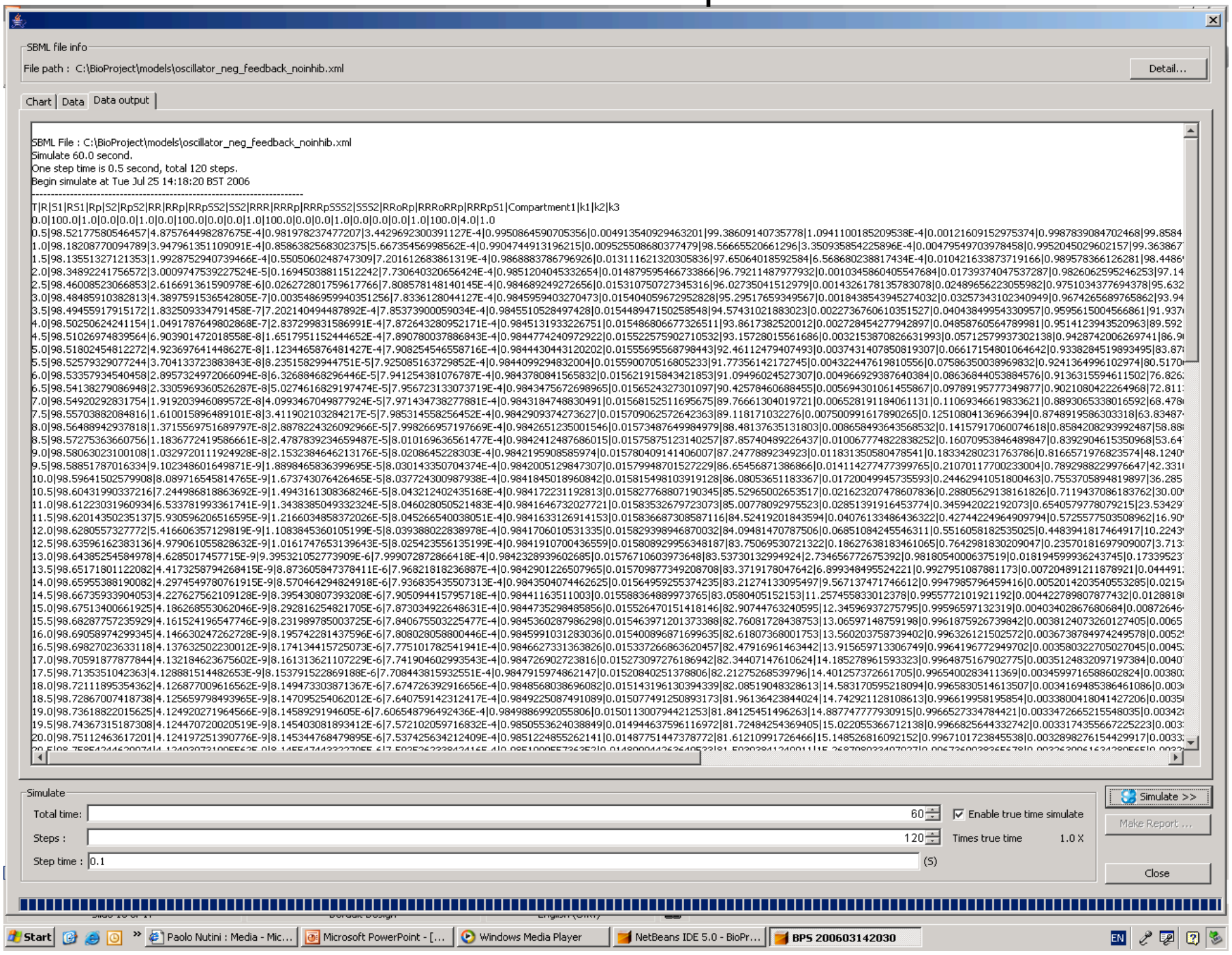
Simulate >>

Make Report ...

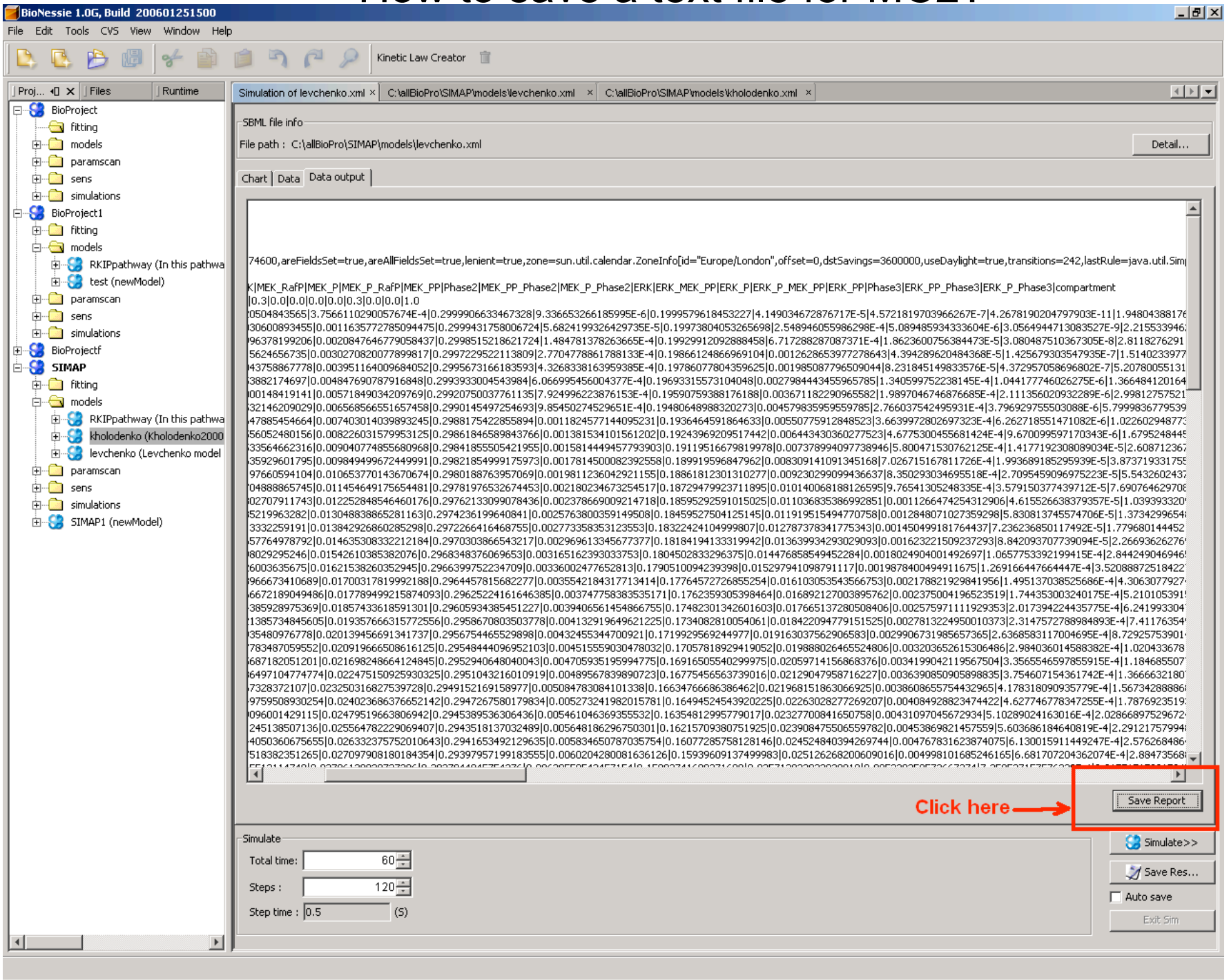
Close

Start | Inbox - Microsoft Outlook | 060726agenda (Read-O... | NetBeans IDE 5.0 | BPS 200603142030 | Microsoft PowerPoint - [...

Printable report



How to save a text file for MC2?



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

Parameter Scans

Sensitivity Analysis

Model VCS Support

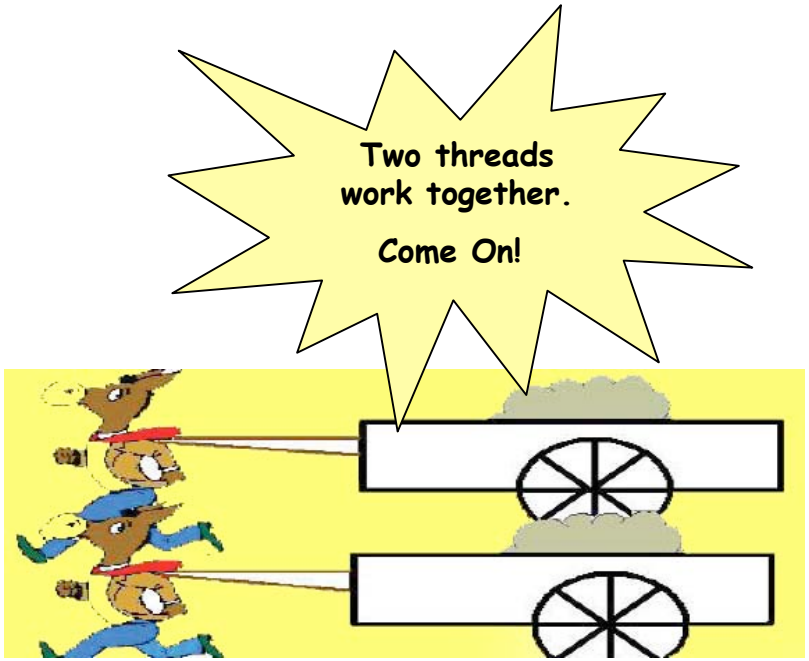
Model Optimisation

Advanced Model Checking (by Robin Donaldson)

Parameter Scans

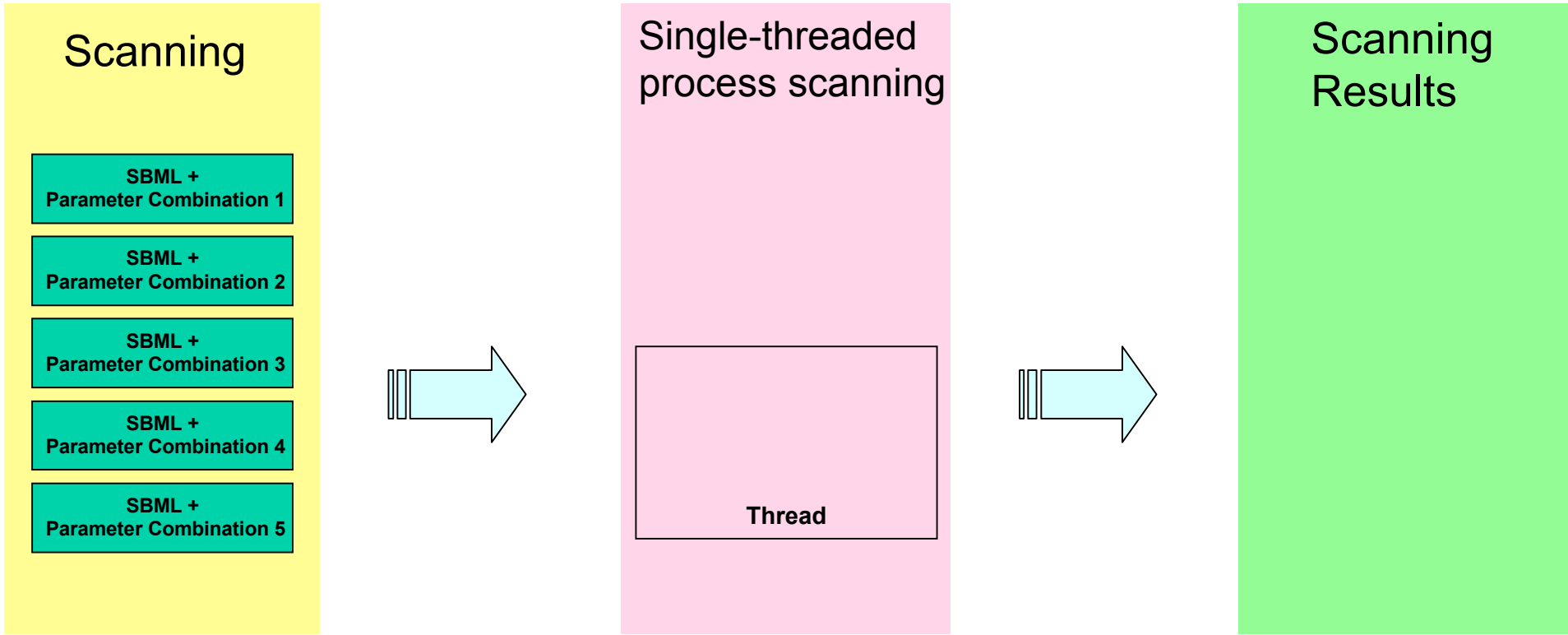
Single/Multi –threaded/Grid-enabled Parameter Scan

- 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

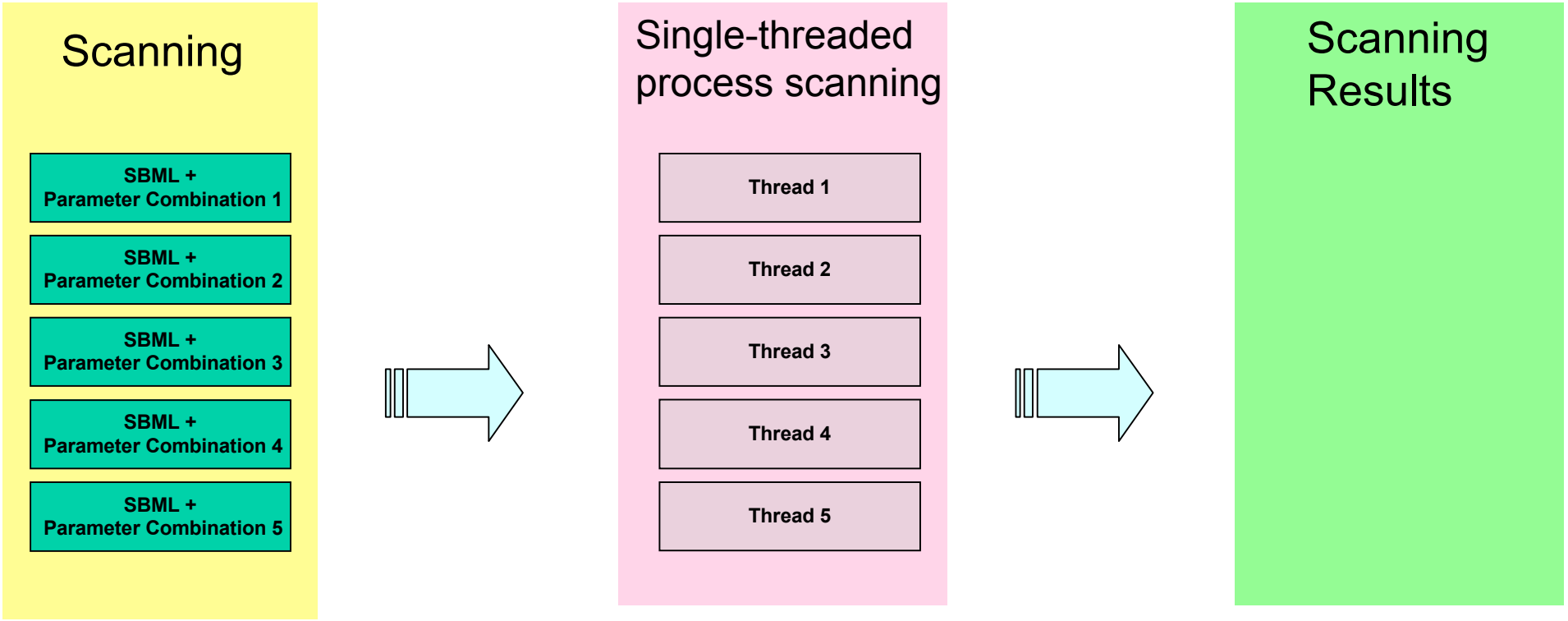


  - So, having more than one thread running is beneficial

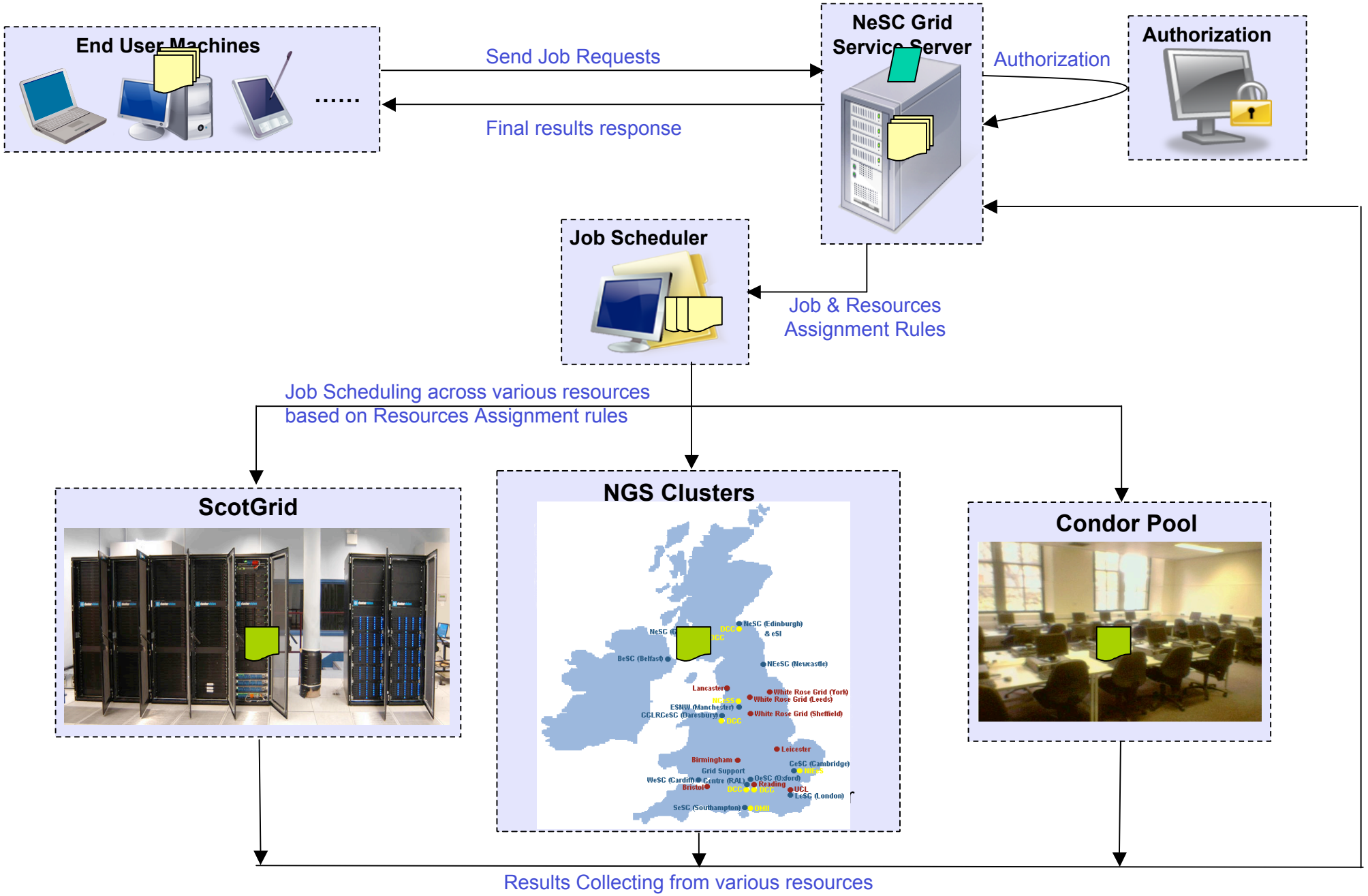
Single-threaded Parameter Scan



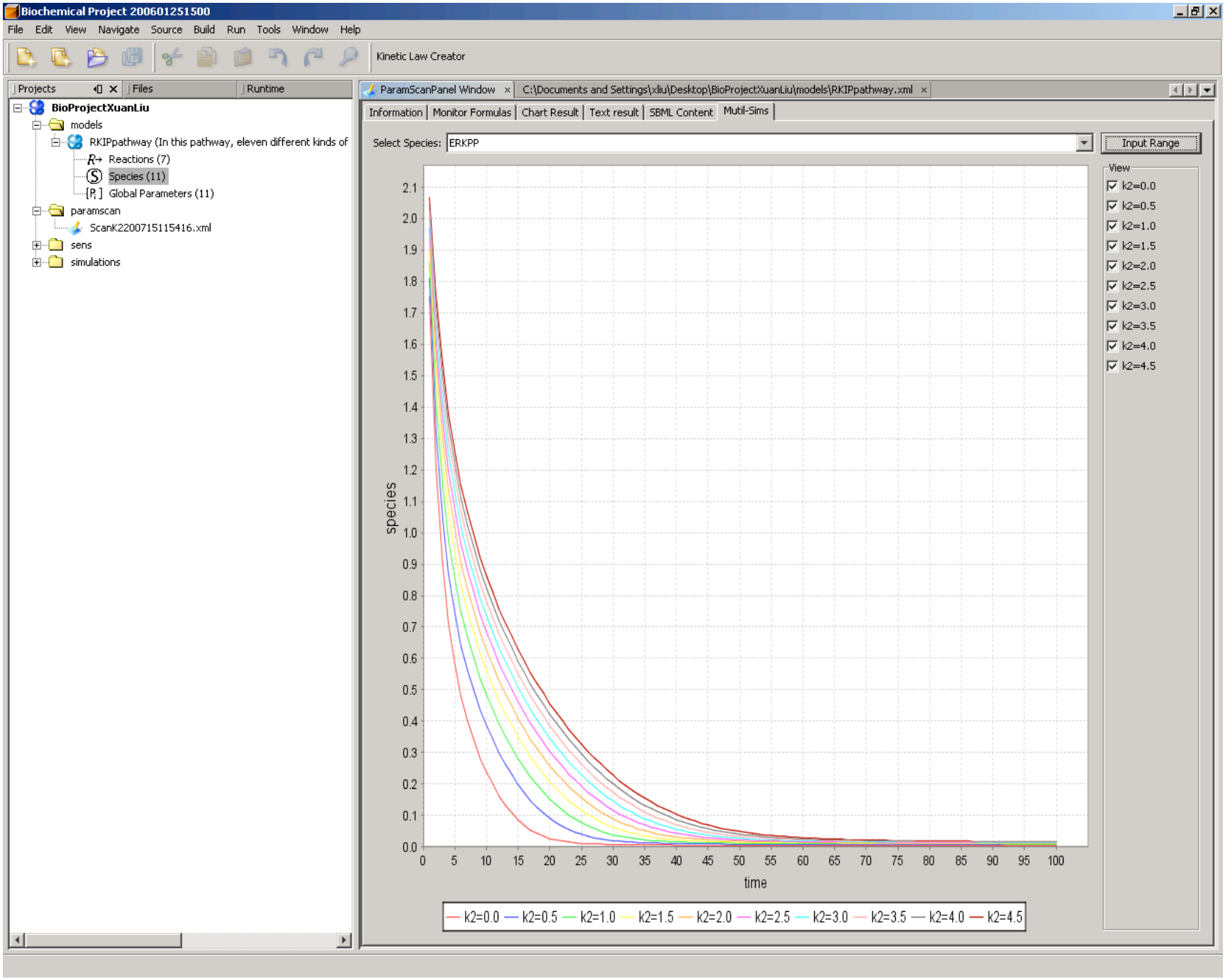
Multithreaded Parameter Scan



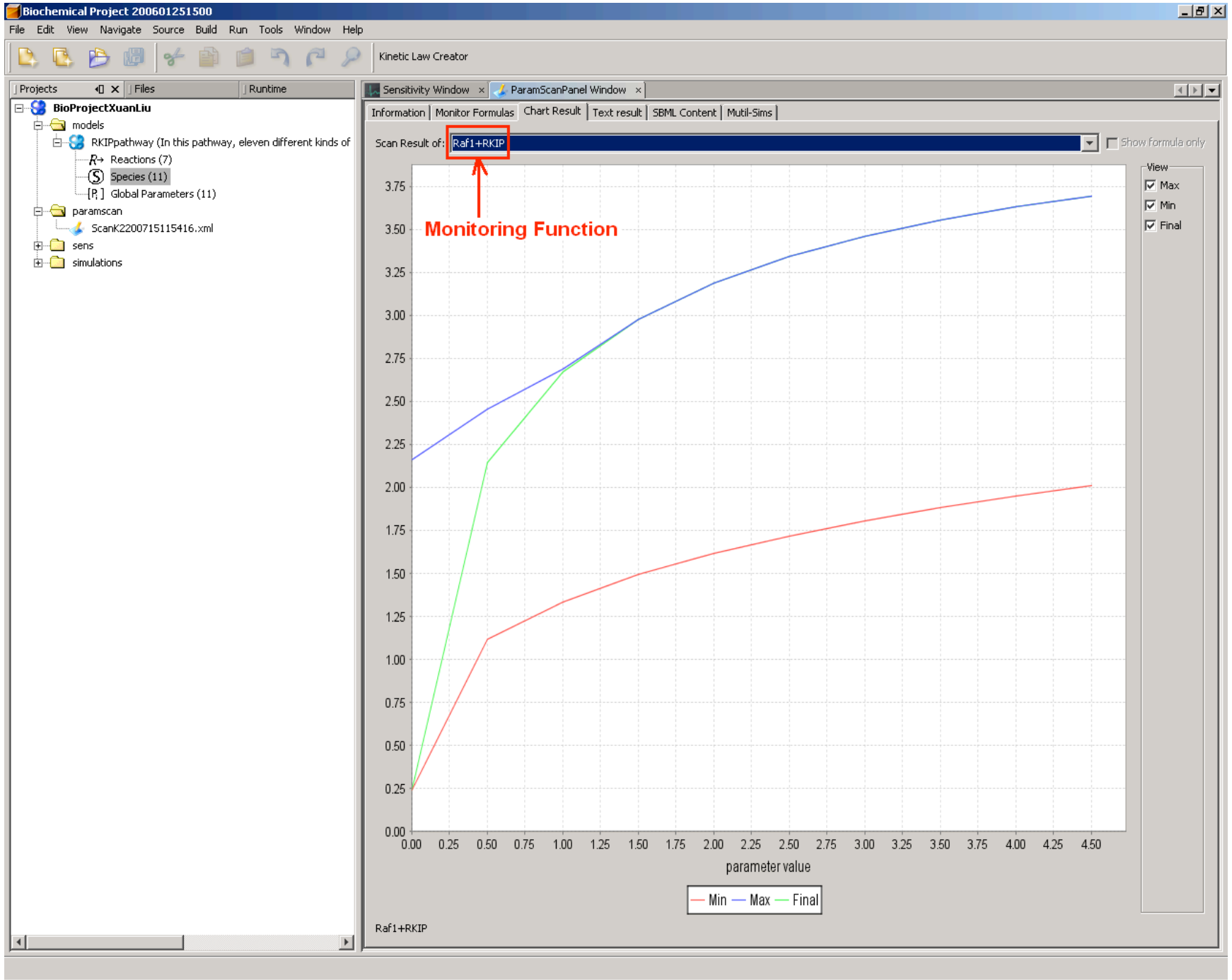
Grid enabled BioNessie Architecture



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.



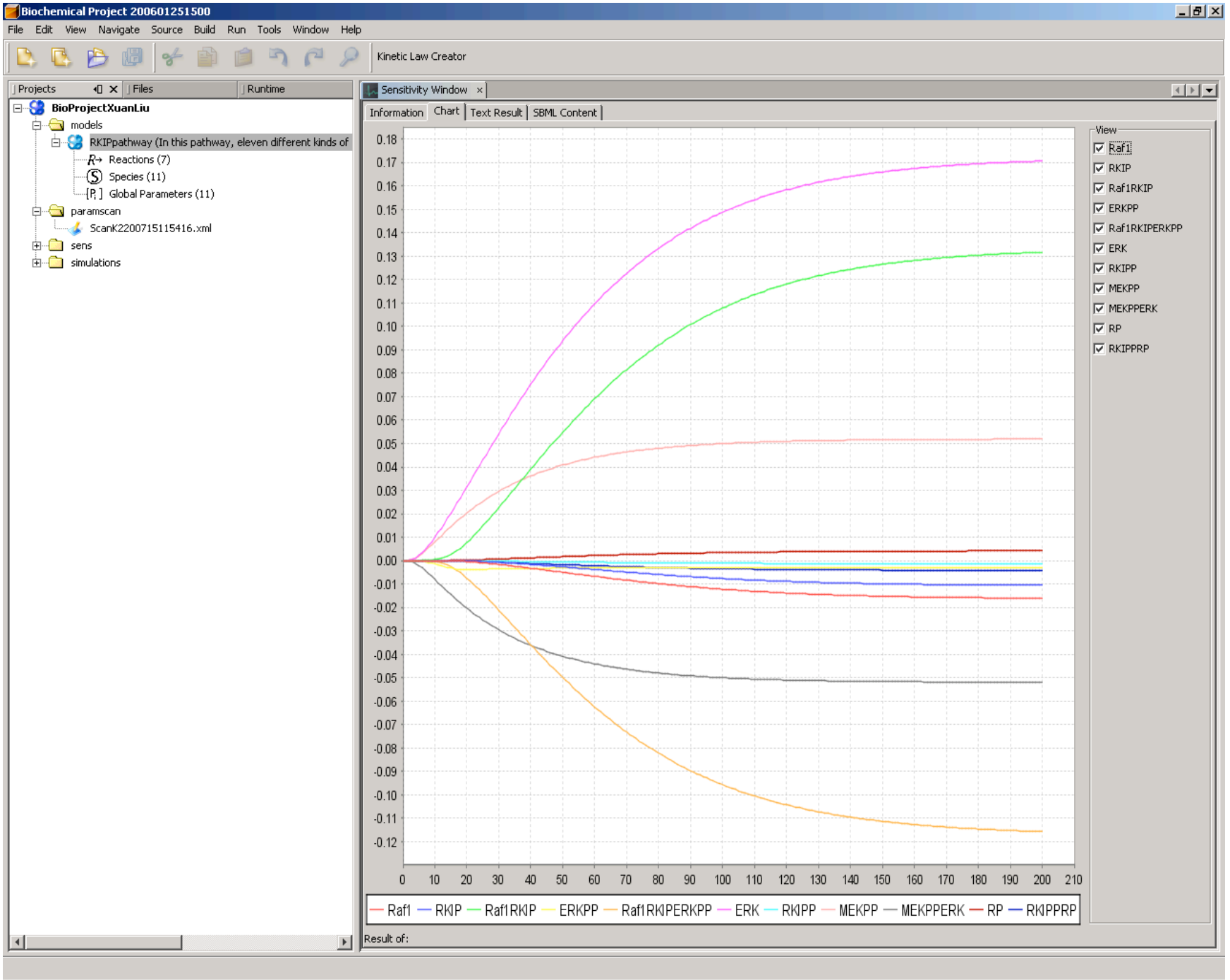
This plot shows the min. max and final values of monitoring function Raf1+RKIP for a parameter scan in RKIPpathway.xml of parameter K2 from 0 through 5 in steps of 0.5 with linear density for the timecourse of 100 timesteps of 100 time units.

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.

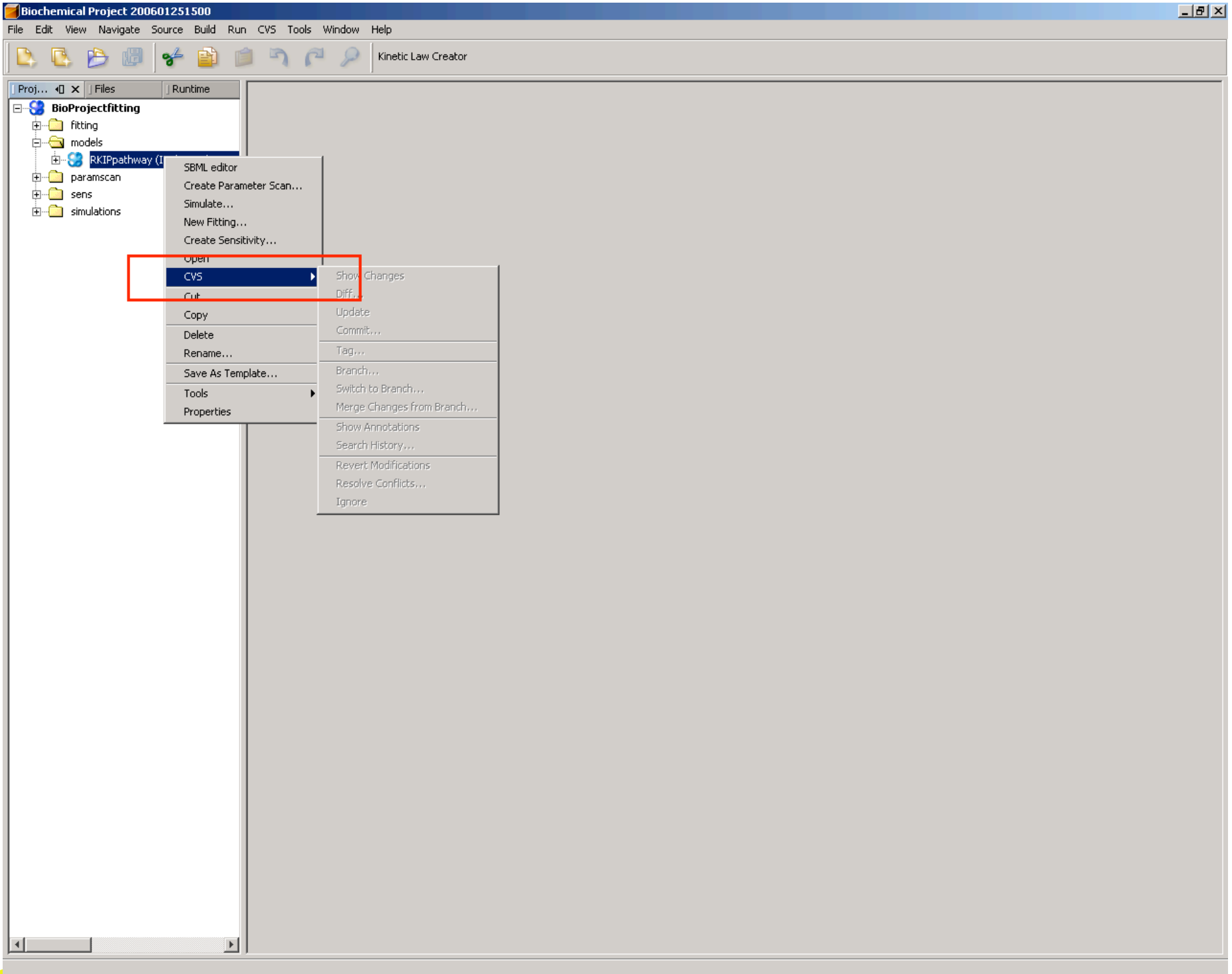


This creates a plot of the sensitivity of species Raf1, RKIP, Raf1RKIP, ERKPP, Raf1RKIPERKPP, ERK, RKIPP, MEKPP, MEKPPERK, RP and RKIPPRP to the values of the parameter K6 for the timecourse of 200 timesteps of 200 time units.

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.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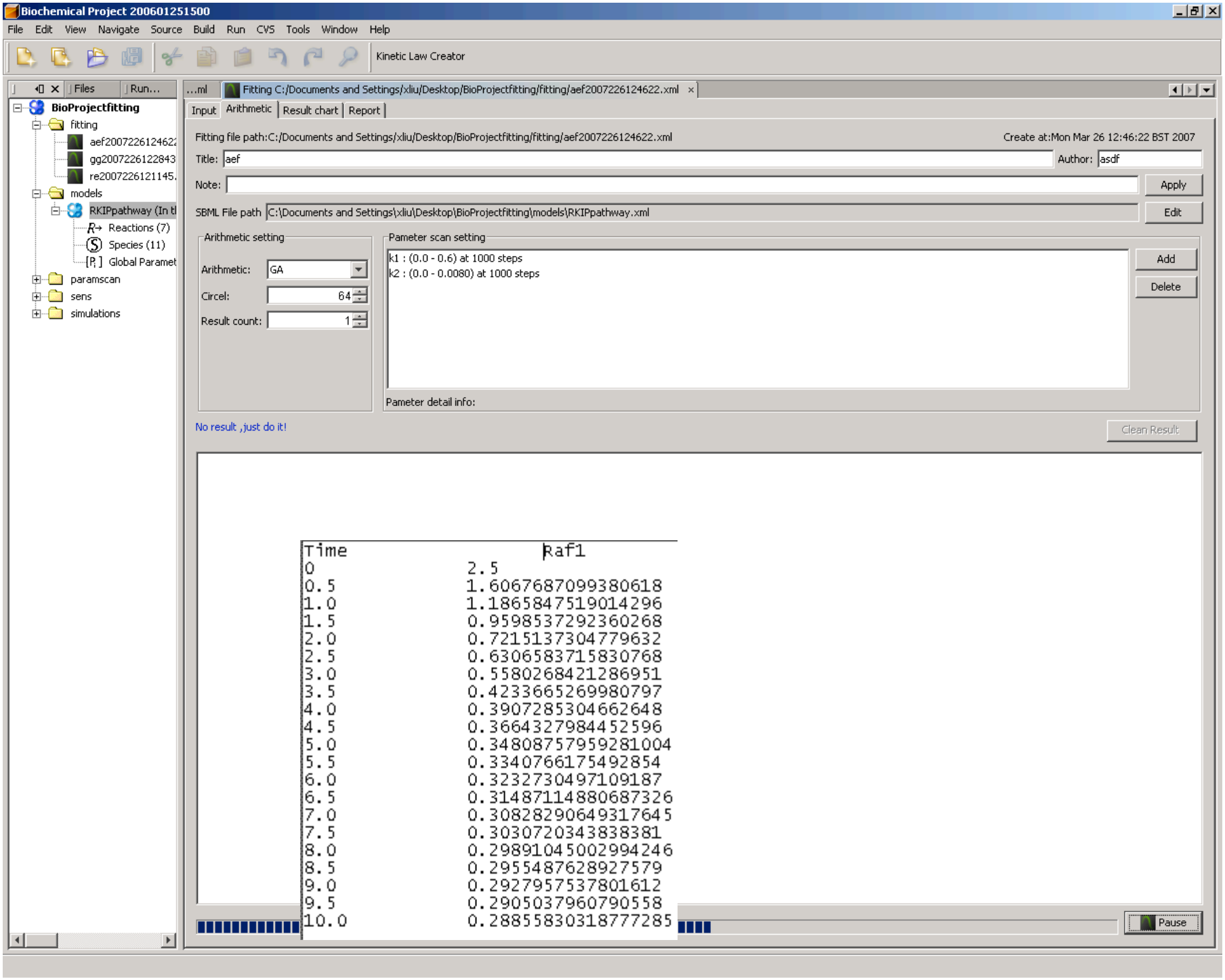
Diff...
Update
Commit...
Tag...
Branch...
Switch to Branch...
Merge Changes from Branch...
Show Annotations
Search History...
Revert Modifications
Resolve Conflicts...
Ignore

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.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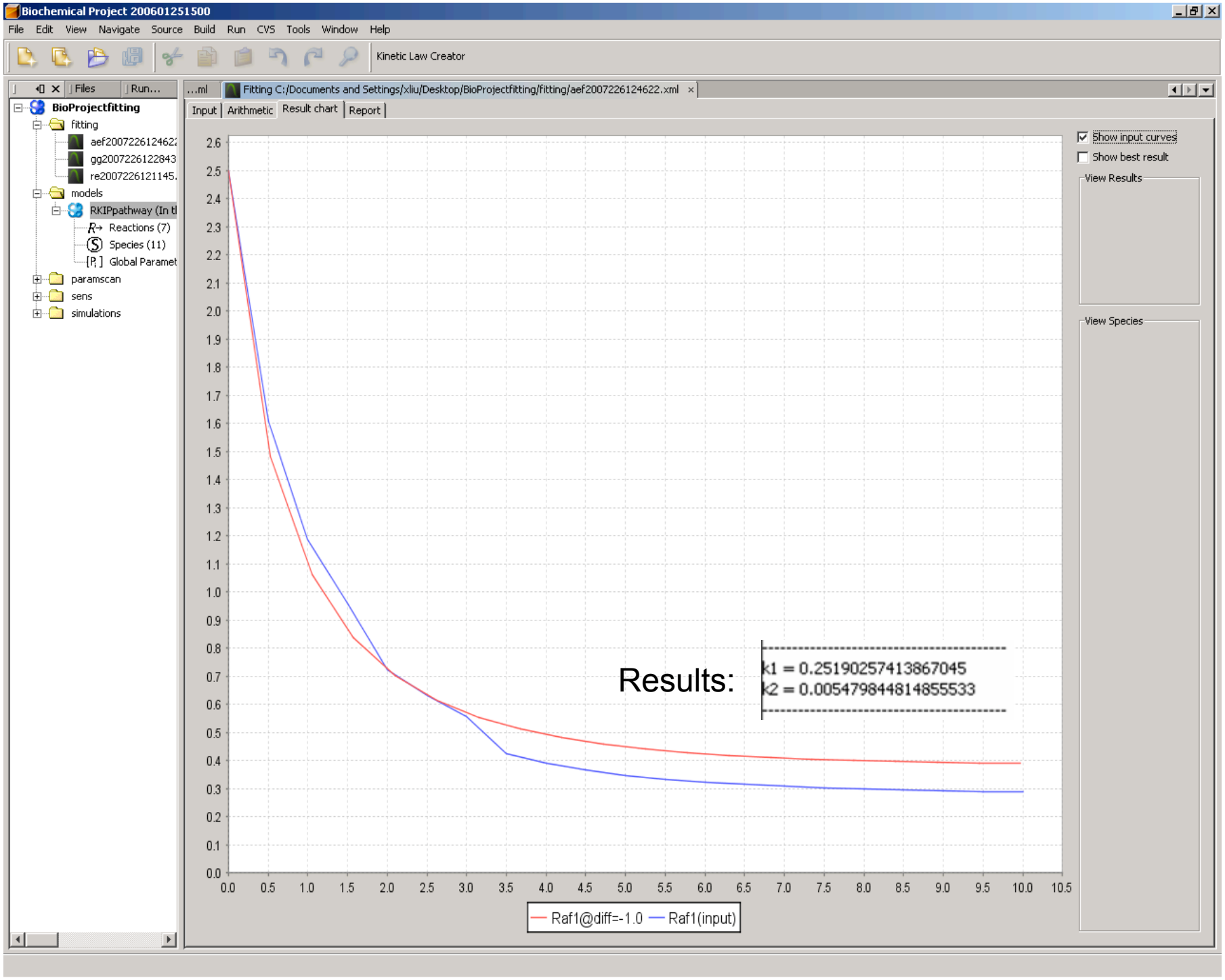
Input
Arithmetic
Result chart
Report
Fitting file path:C:/Documents and Settings/xliu/Desktop/BioProjectfitting/fitting/aef2007226124622.xml
Create at:Mon Mar 26 12:46:22 BST 2007
Title: aef
Author: asdf
Note:
Apply
SBML File path C:\Documents and Settings\xliu\Desktop\BioProjectfitting\models\RKIPpathway.xml
Edit
Arithmetic setting
Arithmetic: GA
Circel: 64
Result count: 1
Pameter scan setting
k1 : (0.0 - 0.6) at 1000 steps
k2 : (0.0 - 0.0080) at 1000 steps
Add
Delete
Pameter 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 0.3082829064931764 5
7.5 0.303072034383838 1
8.0 0.29891045002994246
8.5 0.2955487628927579
9.0 0.2927957537801612
9.5 0.2905037960790558
10.0 0.28855830318777285
Pause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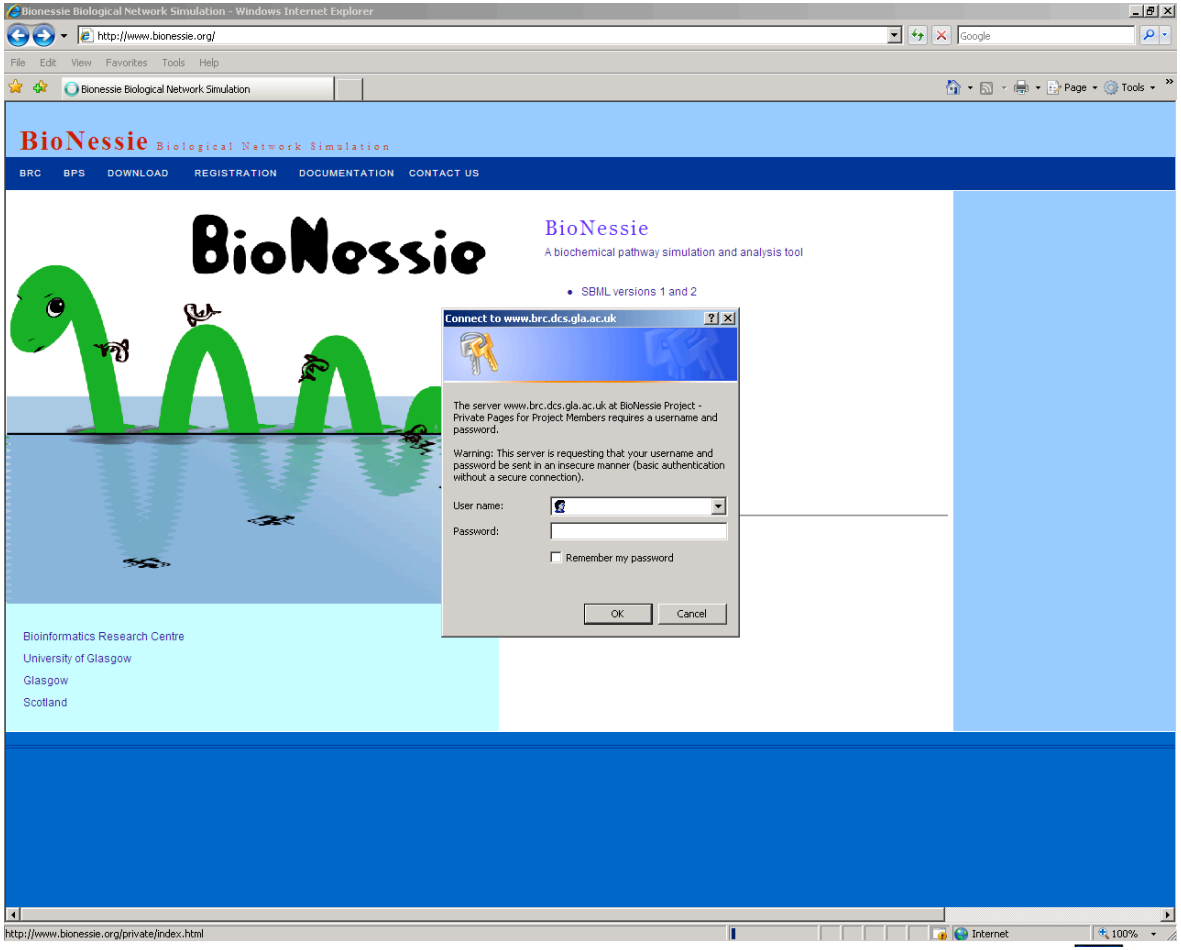
Input
Arithmetic
Result chart
Report
Show input curves
Show best result
View Results
View Species
Results:
k1 = 0.25190257413867045
k2 = 0.005479844814855533
Raf1@diff=-1.0
Raf1(input)

How to obtain and install BioNessie

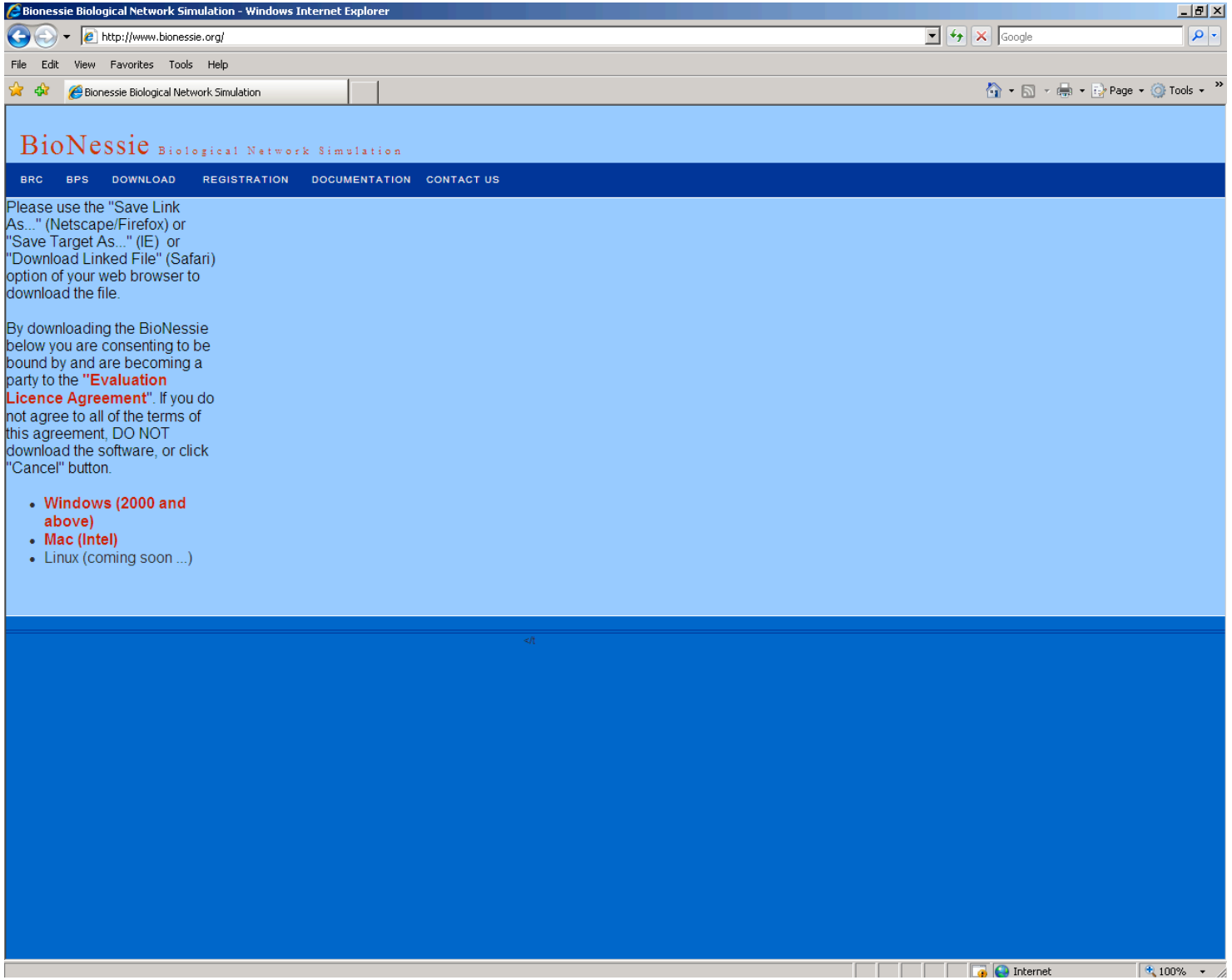
- In order to obtain a copy of BioNessie, you may send an email to Xuan Liu (xliu@brc.dcs.gla.ac.uk) for registration. Please provide your Name, Institute, Address and a valid "email address", to which an email will be sent with the login/password required to download BioNessie. Please read the terms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



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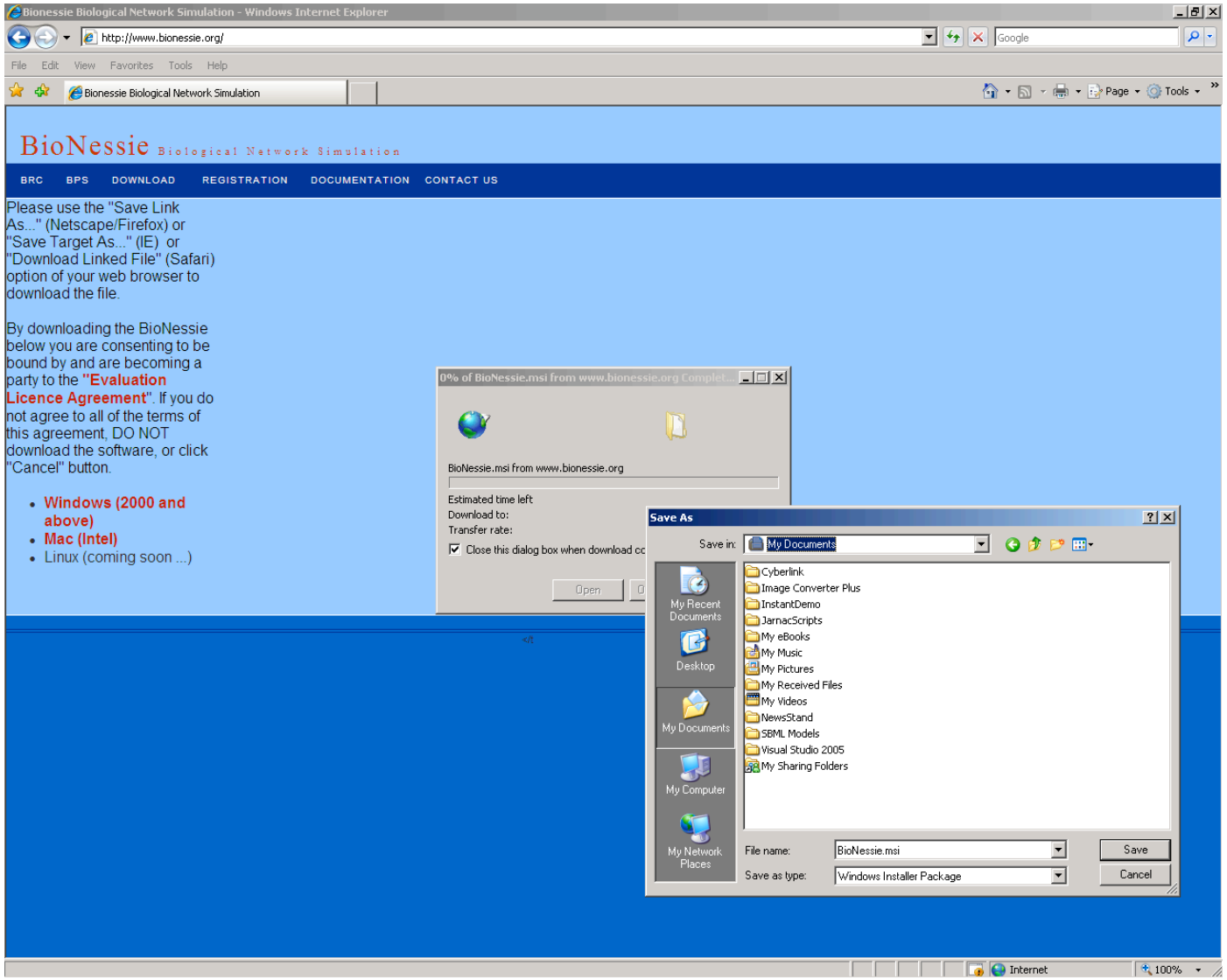

- Installation is easy. Please follow the instructions which will be shown on installation process.

Advanced Model Checking