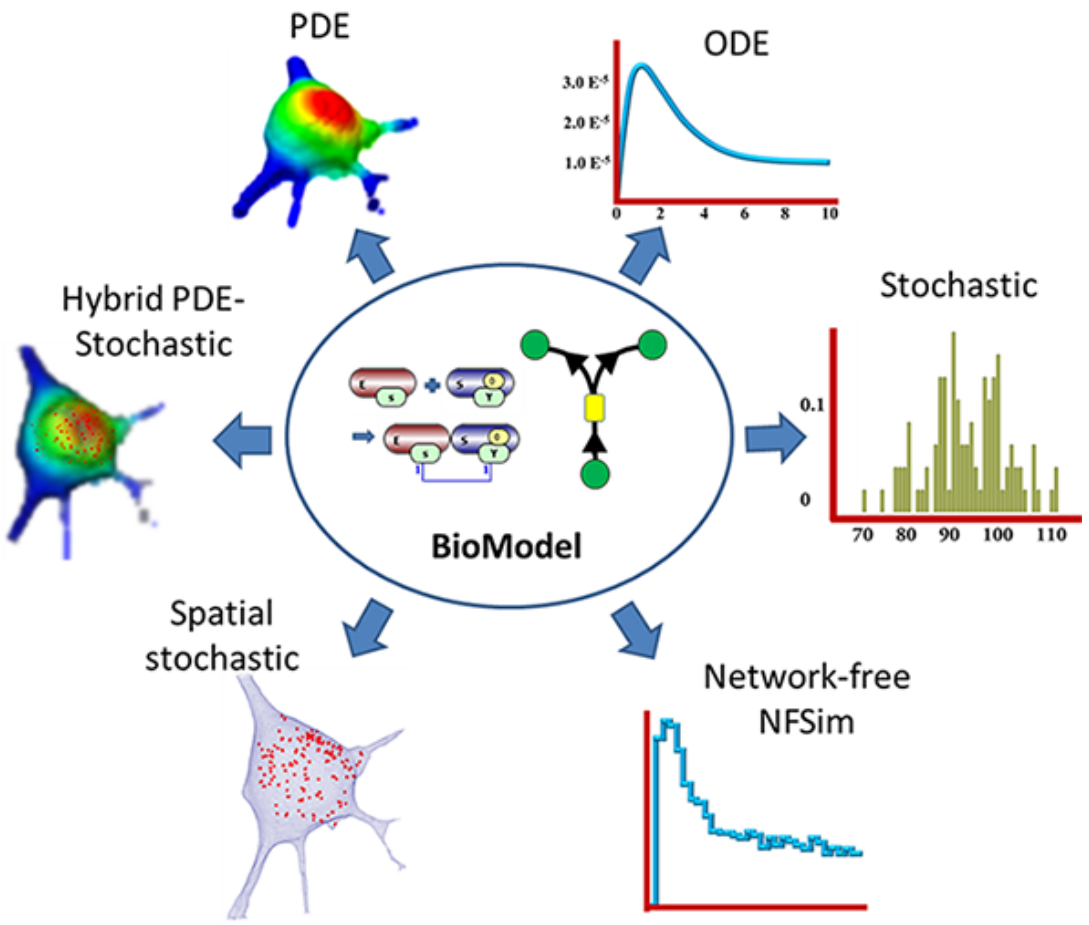
Contents

VCell

To run VCell go to:
vcell.org



UNIVERSITY OF CONNECTICUT HEALTH CENTER

CCAM
VCell is developed at CCAM
Center for Cell Analysis & Modeling

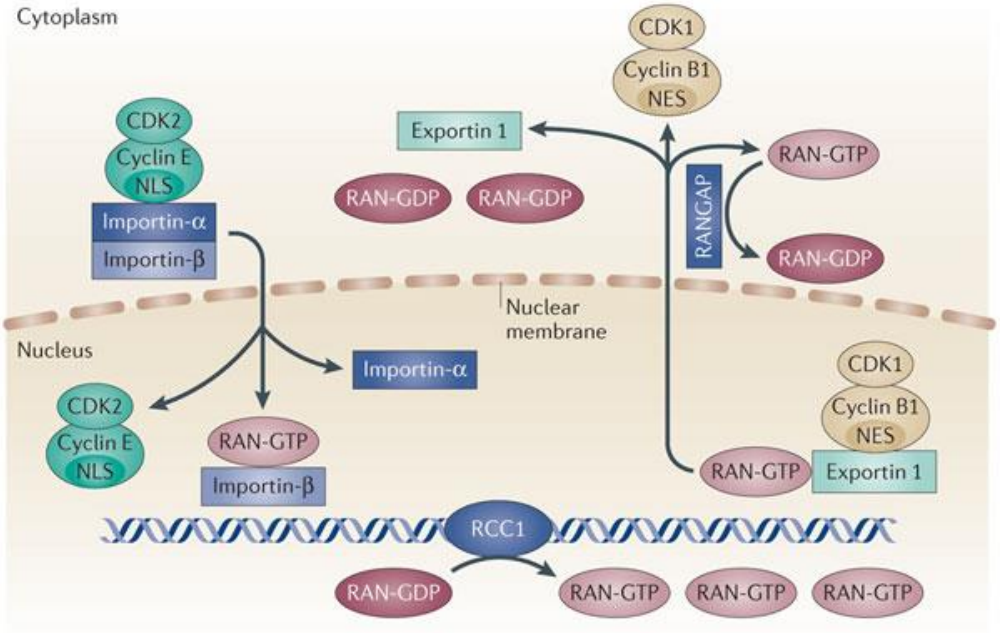
NIH National Institute of General Medical Sciences
VCell is funded by the NIGMS

Contents

VCell Tutorial

Building a Multi-compartment Rule-Based Model

In this tutorial, we will demonstrate how to create a compartmental rule based model of translocation through the nuclear pore of a cargo protein via the GTPase protein Ran. Specifically, this model displays the export part of the cycle. The nuclear Ran is (implicitly) phosphorylated by the shown interaction with its nucleotide exchange factor: the chromatin-associated RCC1 protein. The activated Ran then binds to the cargo molecule, creating a ternary complex with the (not shown) exportin, facilitating translocation into the cytosol. Ran and cargo are then dissociated via the hydrolysis of Ran by the membrane-bound Ran-GAP protein (not shown). The cytosolic cargo molecule may be phosphorylated on any of its three tyrosines while in cytosol.



http://www.nature.com/nrc/journal/v13/n3/fig_tab/nrc3468_F2.html

Nature Reviews | Cancer

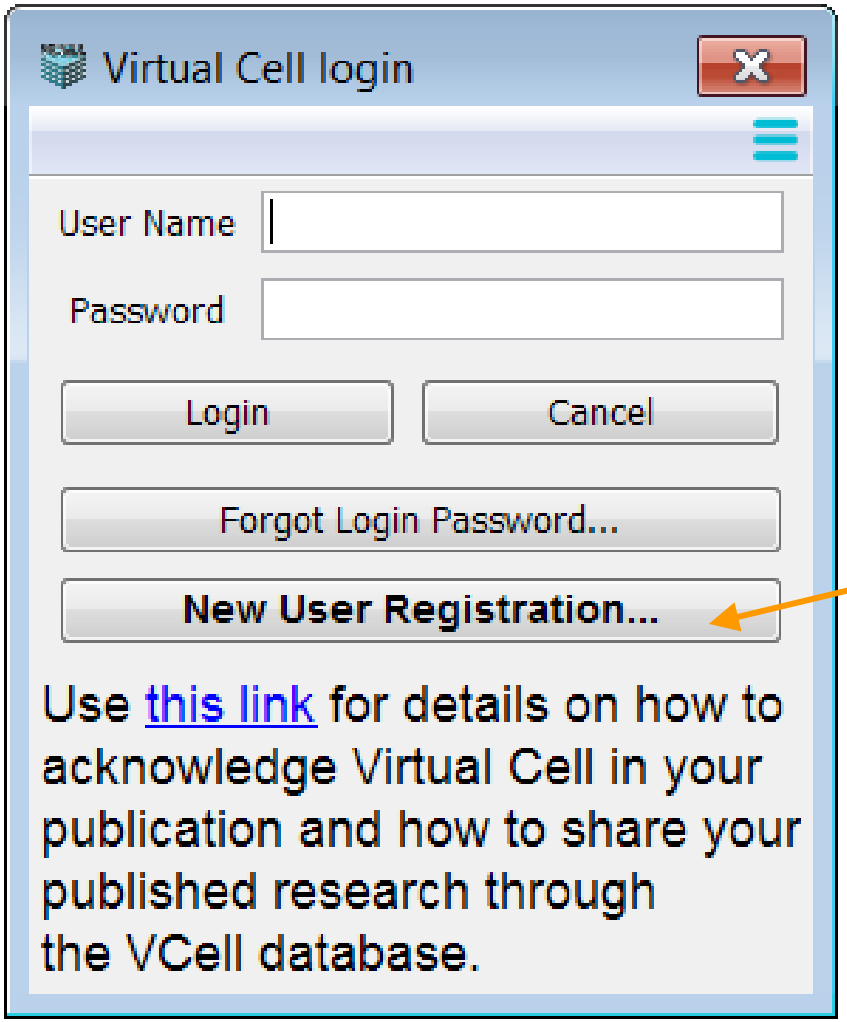
In this tutorial you will learn how to:

- Create a compartmental rule-based **Physiology** with Molecules, Species, Rules and Observables.
- Simulate a model using **Deterministic application** that expands rules into a reaction network using the **BioNetGen** engine.
- Simulate a model using a **Stochastic application** that simulates the reaction network generated by **BioNetGen**.
- Simulate a model using **Network-Free** application that skips network generation and directly computes Observables using **NFSim** engine.
- Create a 3-D model in **VCell** using existing 3-D image slices.
- Simulate a 3-D model using **Deterministic application** that expands rules into a reaction network using **BioNetGen** engine.
- Simulate a 3-D model using a **Stochastic application** that simulates the reaction network generated by **BioNetGen**.

General familiarity with VCell software is recommended. Although this tutorial can be followed by a VCell novice, it is recommended that novice users first look through the VCell tutorials available at http://vcell.org/vcell_software/user_guide.html .

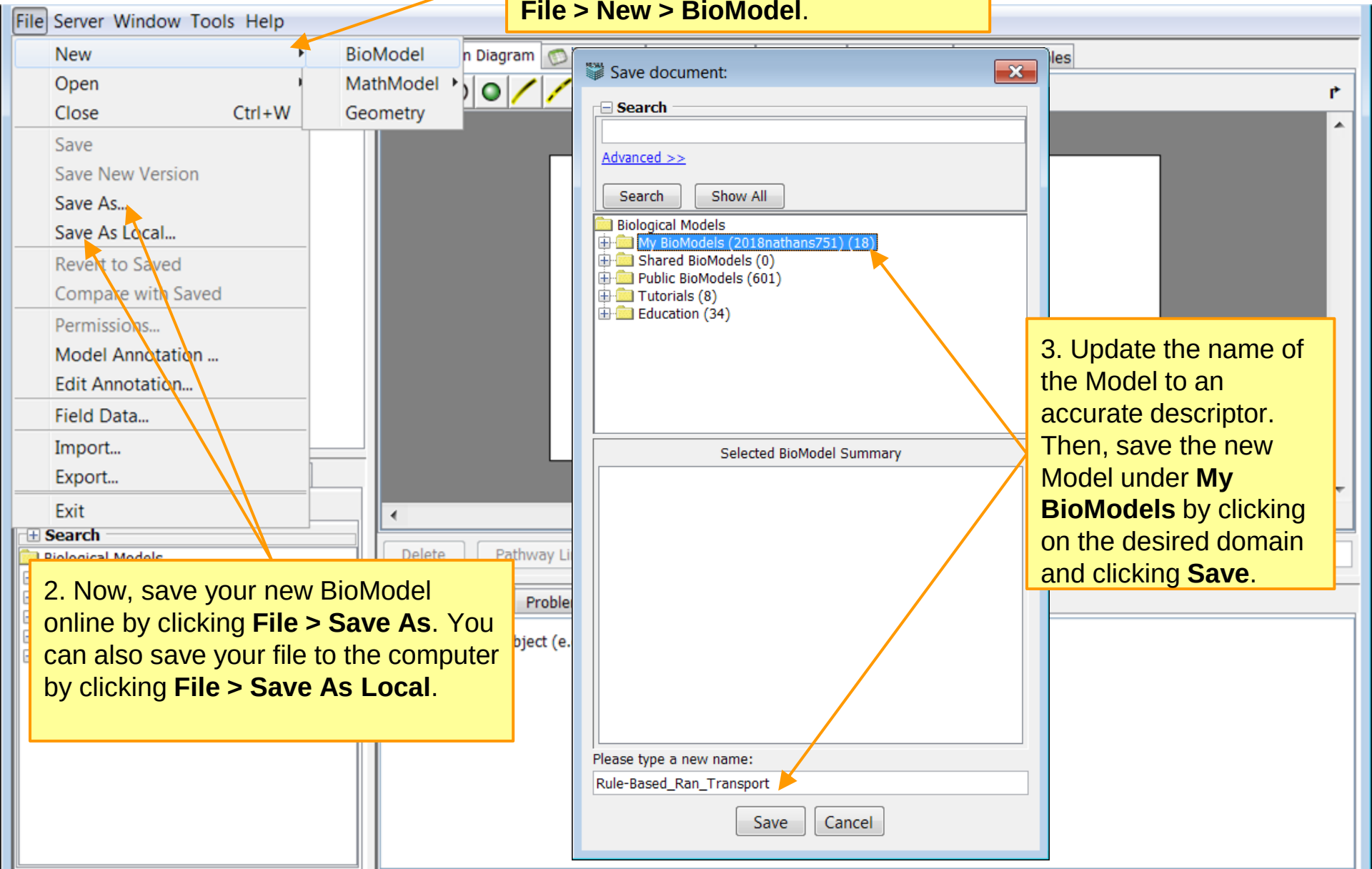
Model building can be matched to the BioModel *Rule-Based_Ran_transport* in the Tutorial folder in the VCell Database.

Contents



The first step to any VCell project is signing in. It is important to do so because only those that are signed in will be able to run simulations using VCell high-performance computers remotely, use the VCell database, and save work. If you are new to VCell, create an account by clicking the **New User Registration** button.

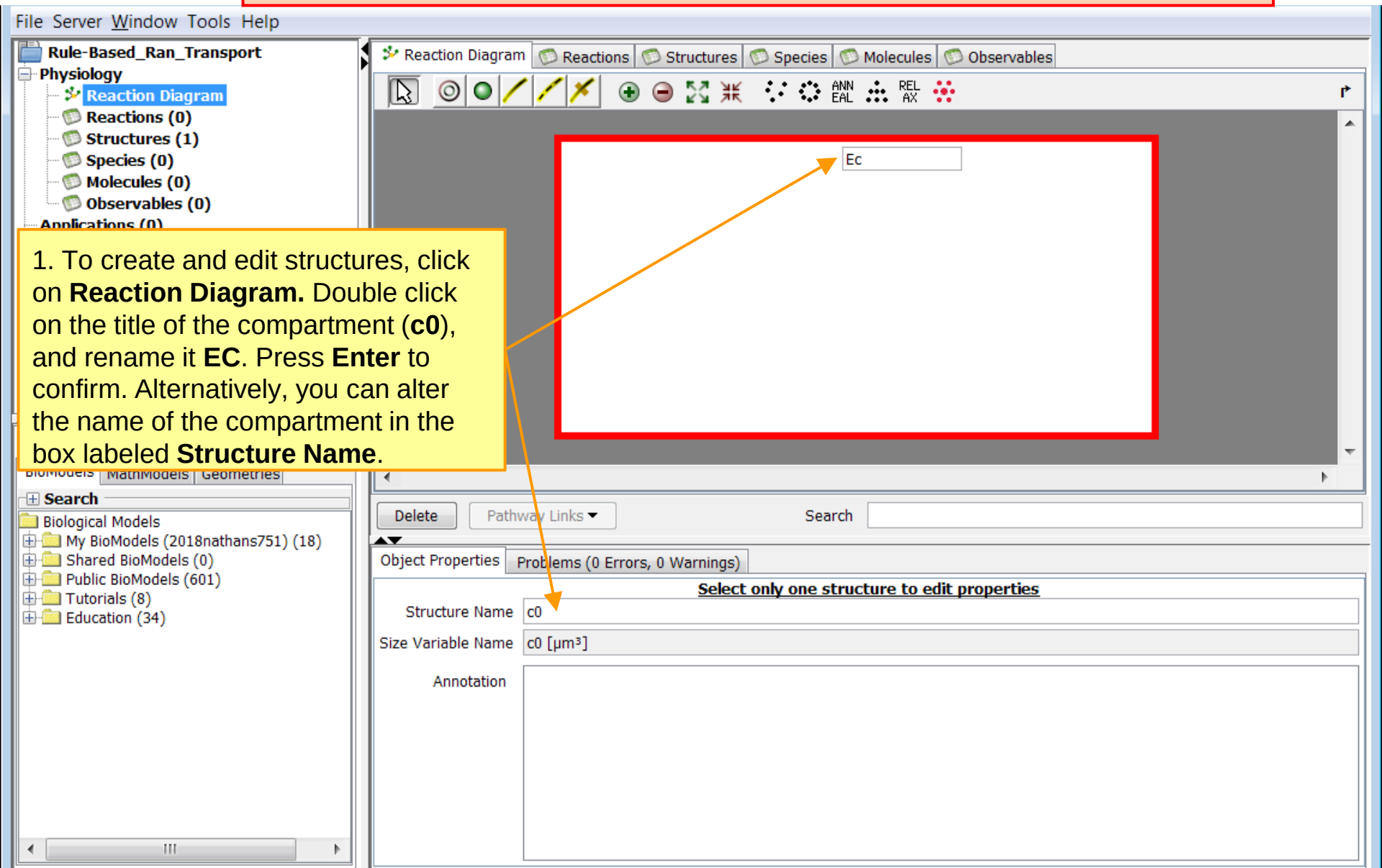
1. Start By creating a new BioModel in which to do your work. Click on **File > New > BioModel**.



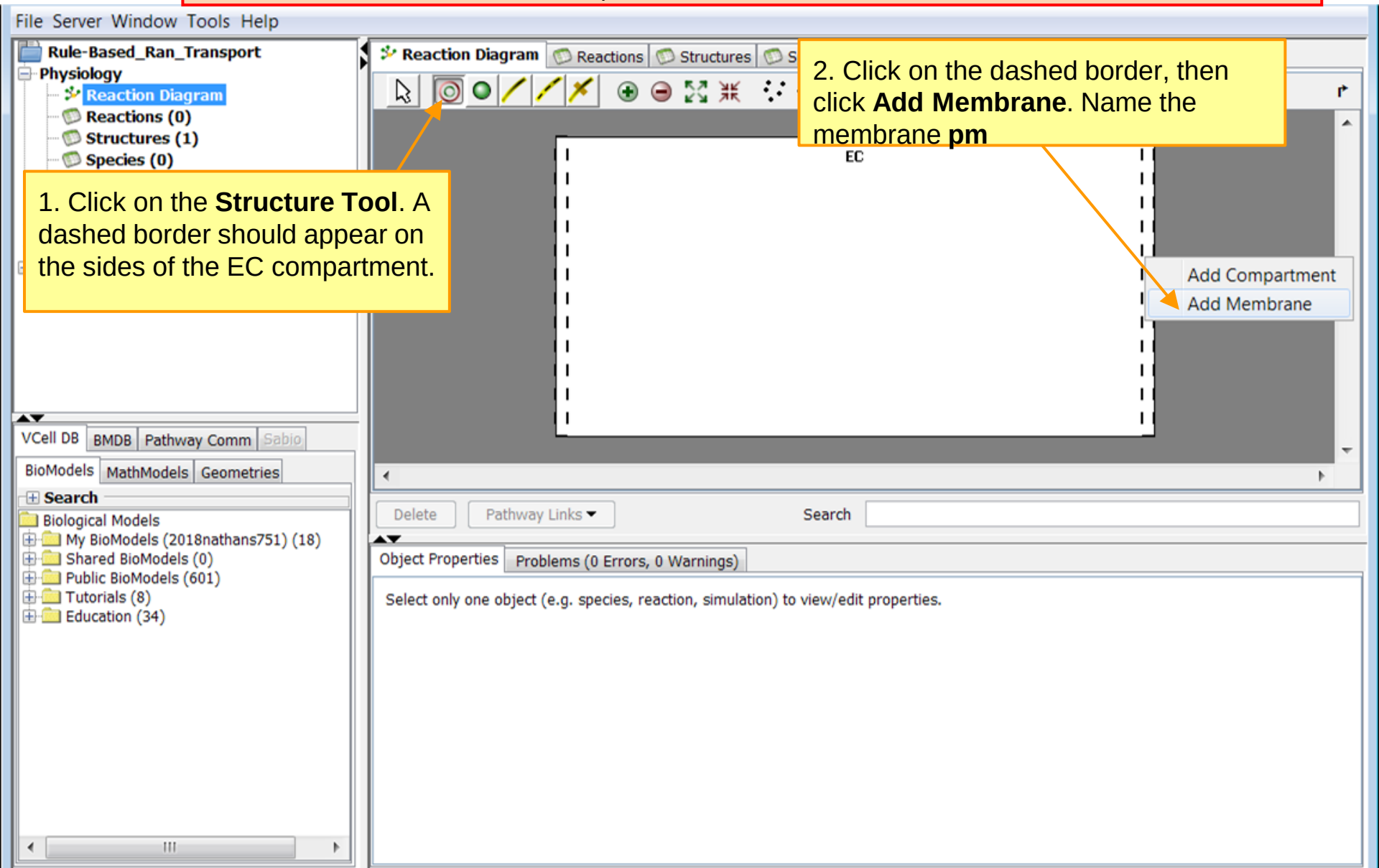
2. Now, save your new BioModel online by clicking **File > Save As**. You can also save your file to the computer by clicking **File > Save As Local**.

3. Update the name of the Model to an accurate descriptor. Then, save the new Model under **My BioModels** by clicking on the desired domain and clicking **Save**.

TIP: You can also create new structures using a non-visual format by clicking on the **Structures** tab and pressing either **New Compartment** or **New Membrane.**

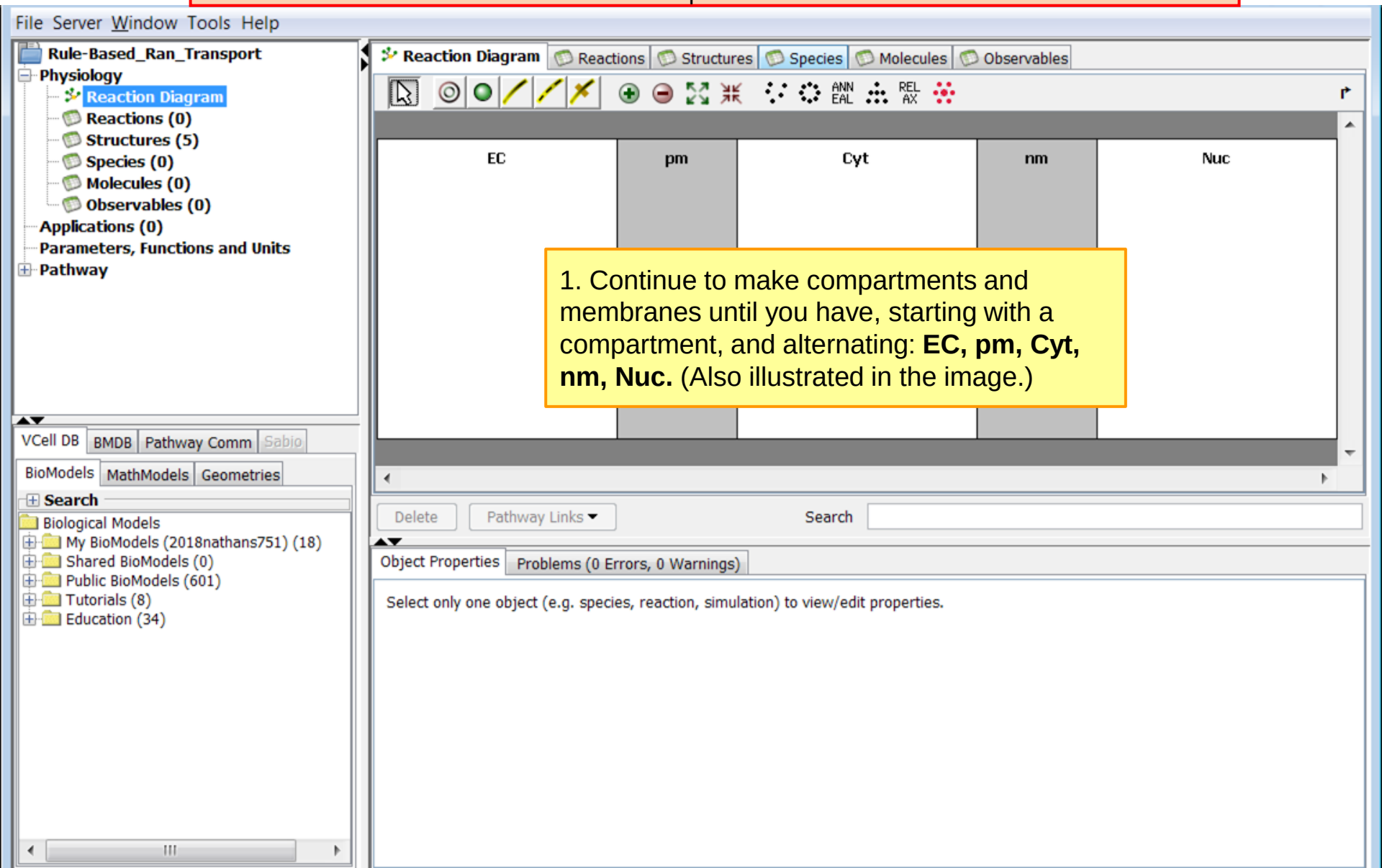


TIP: You can not edit a structure's name or its components while using the **Structure Tool**. Therefore, when creating and naming structures, you have to switch back and forth between said **Construction Tool**, and the **Select Tool** immediately to its left.

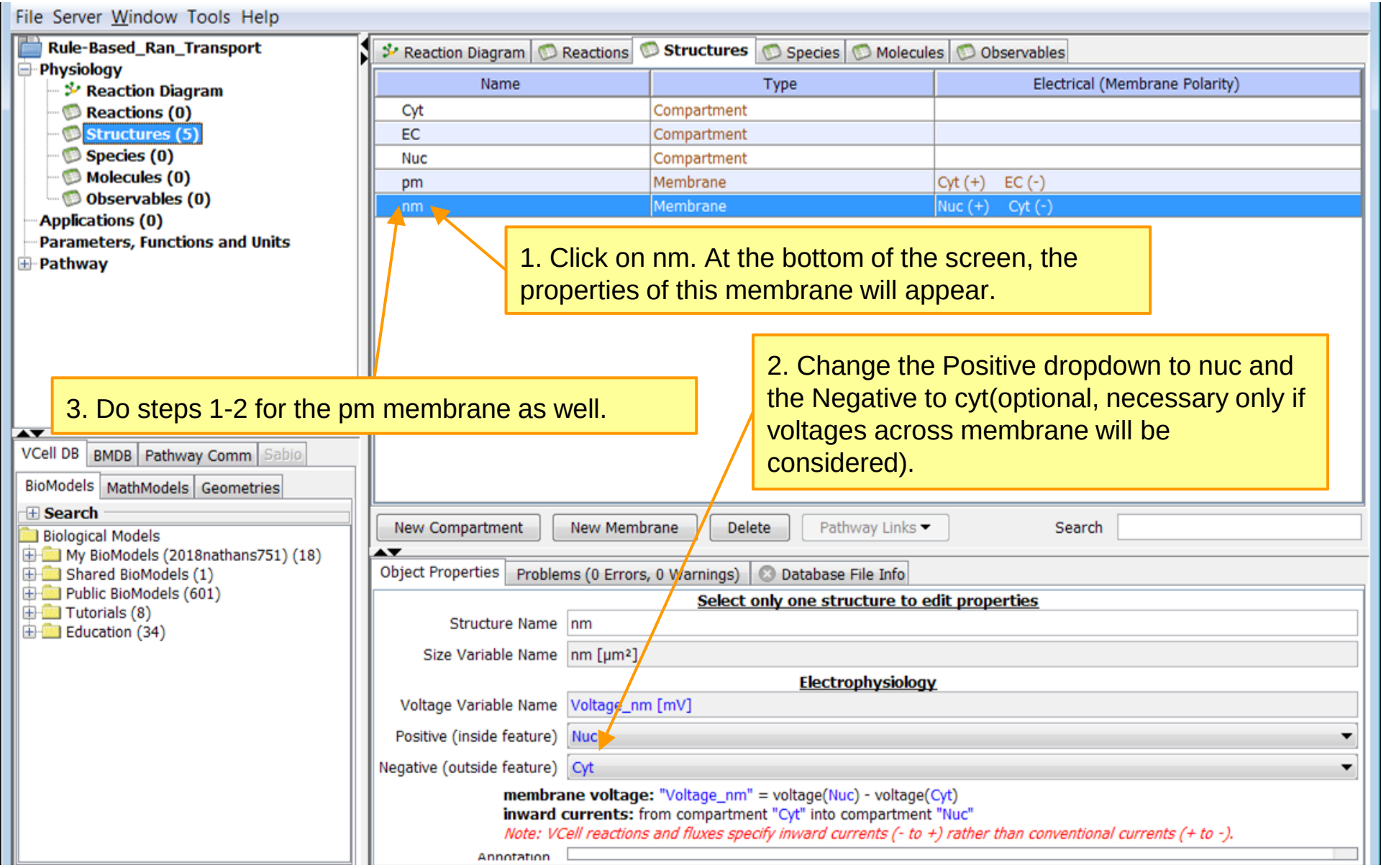


TIP: Compartments have a white background, while membranes have a grey background.

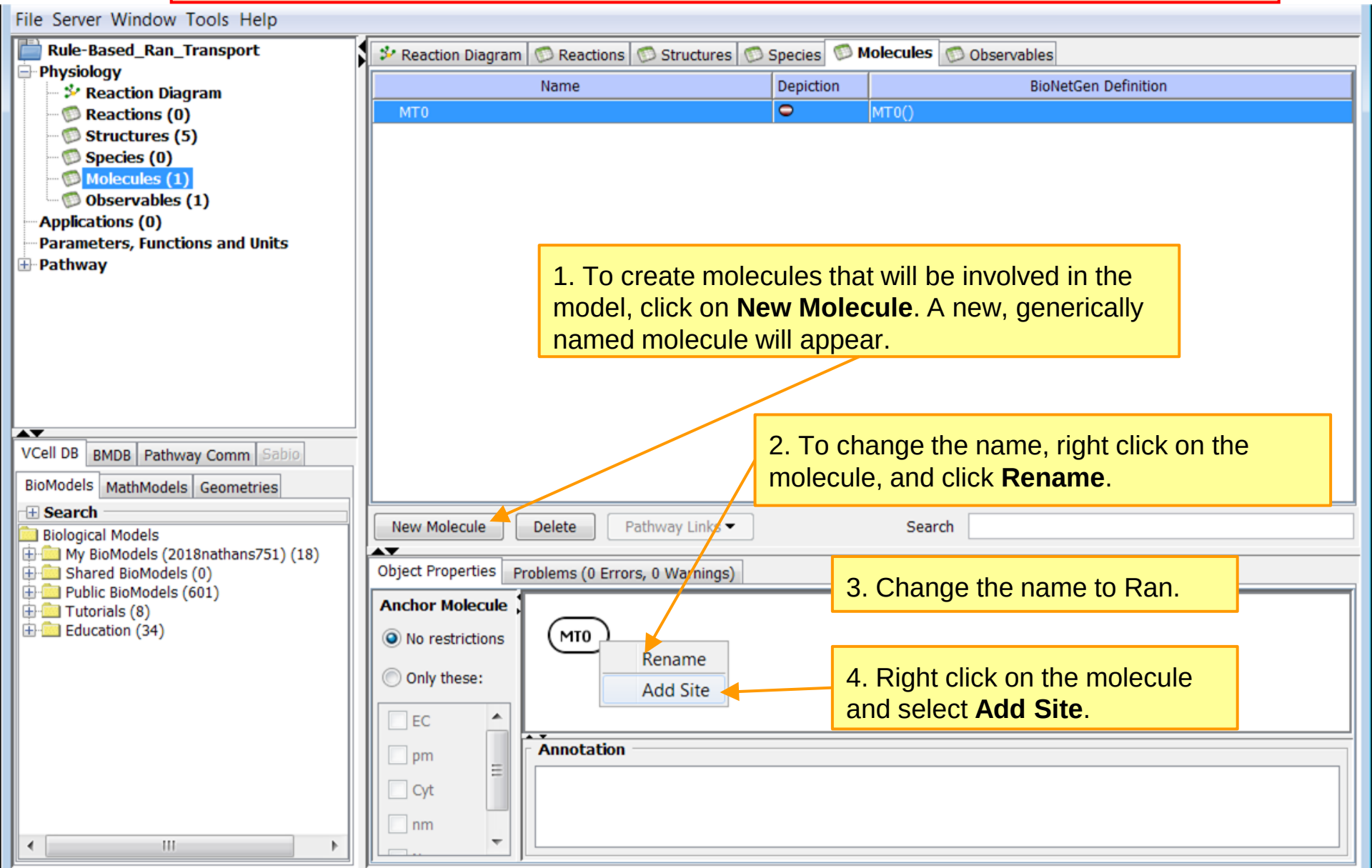
TIP: The goal of these structures is to roughly mimic the basic structure of the cell so as to create an environment for reactions to take place.



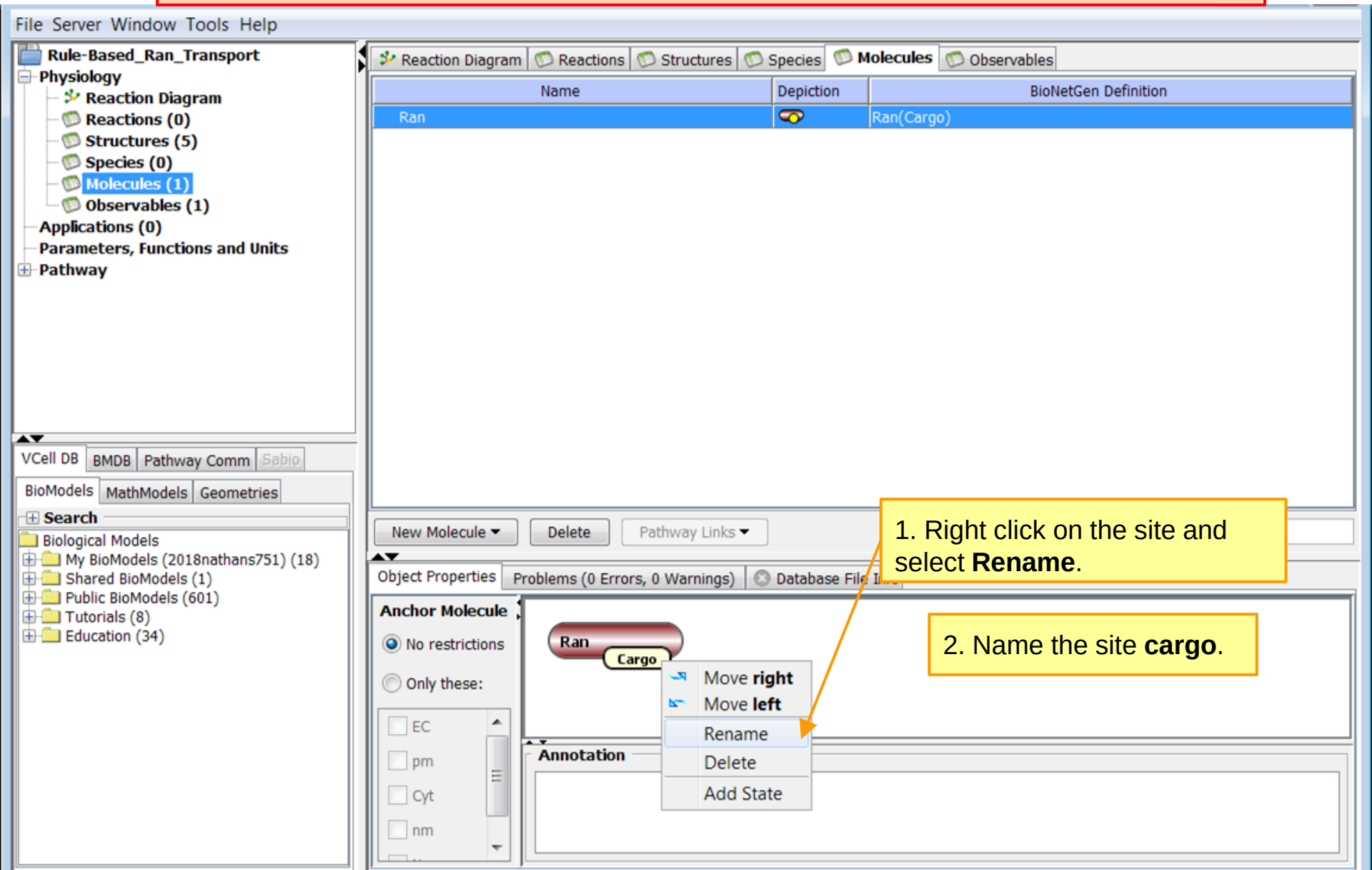
TIP: For some reactiions, like a neuron firing, adjusting the membrane potential can be very important in corrct simulation. In this case, the membrane potential is not very important.



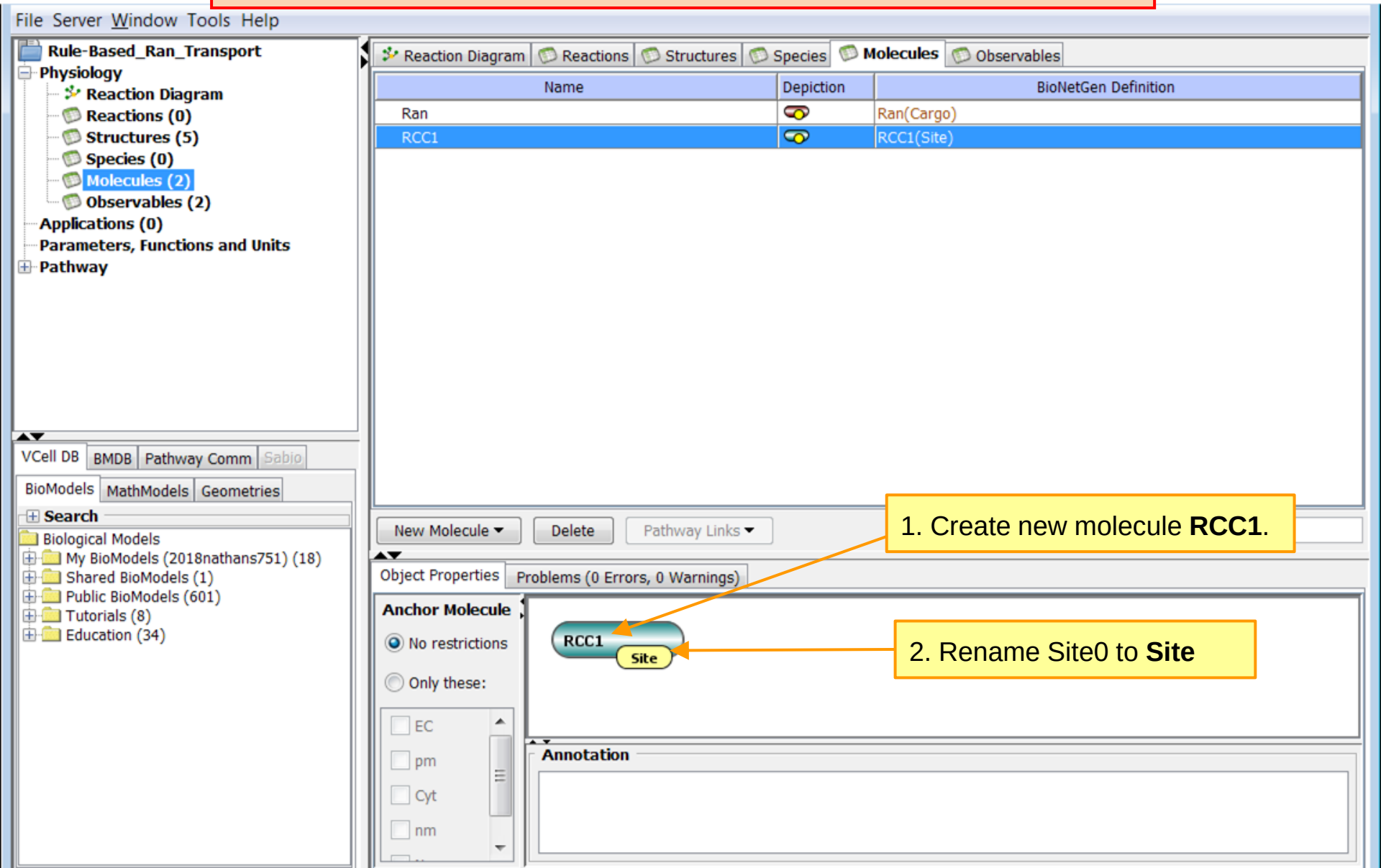
TIP: The color of a molecule is assigned based on the order in which it was created. It is not possible to customize or change the colors of molecules.

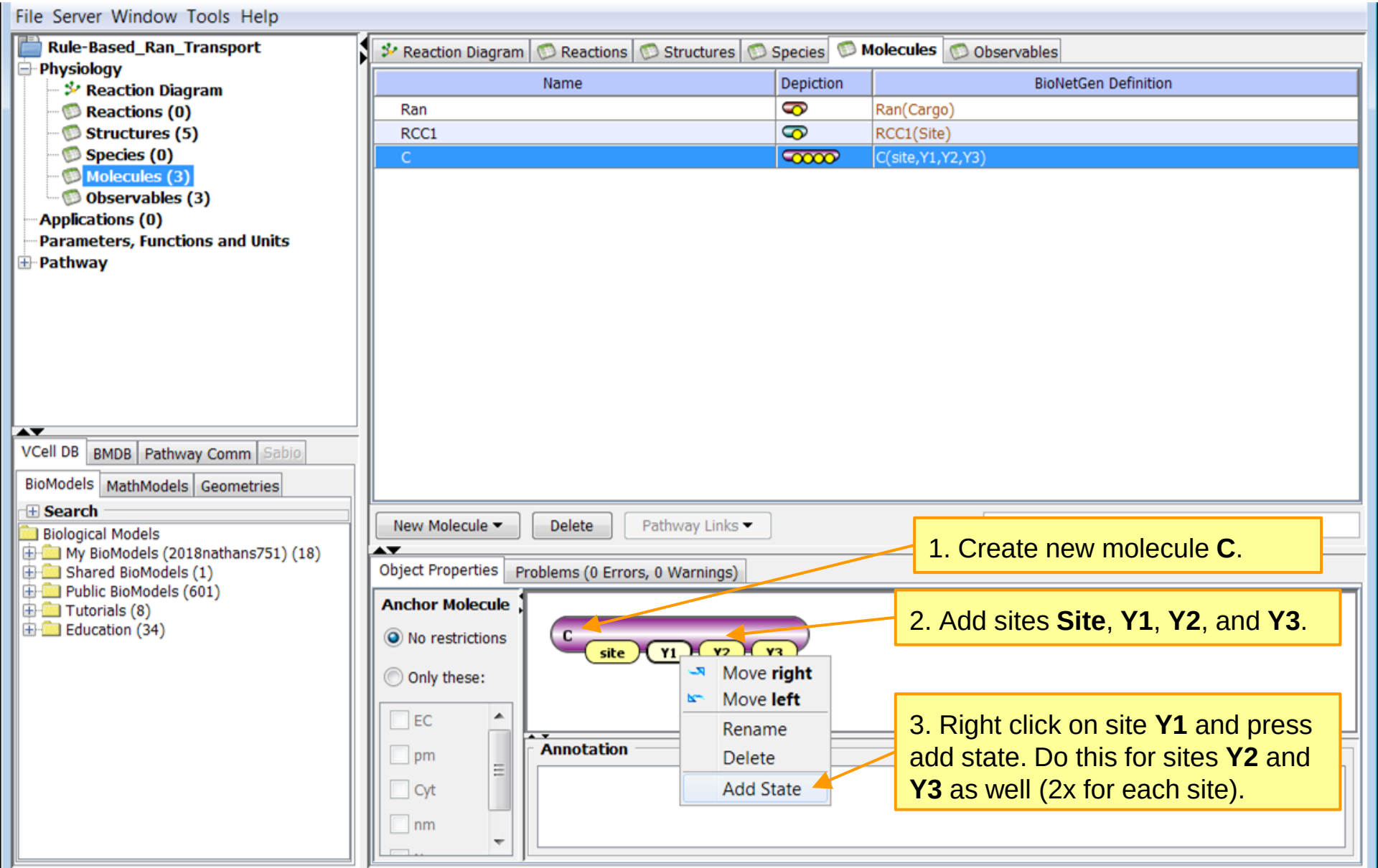


TIP: You can not delete a molecule until all observables, species, and reactions containing said molecule are either altered to not include the molecule or deleted.



TIP: A molecule can also be renamed by double clicking on it in the name column.

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Structures (5)
Species (0)
Molecules (3)
Observables (3)
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Reaction Diagram
Reactions
Structures
Species
Molecules
Observables
Name
Depiction
BioNetGen Definition
Ran
Ran(Cargo)
RCC1
RCC1(Site)
C
C(site,Y1,Y2,Y3)
VCell DB
BMDB
Pathway Comm
Sabio
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Search
Biological Models
My BioModels (2018nathans751) (18)
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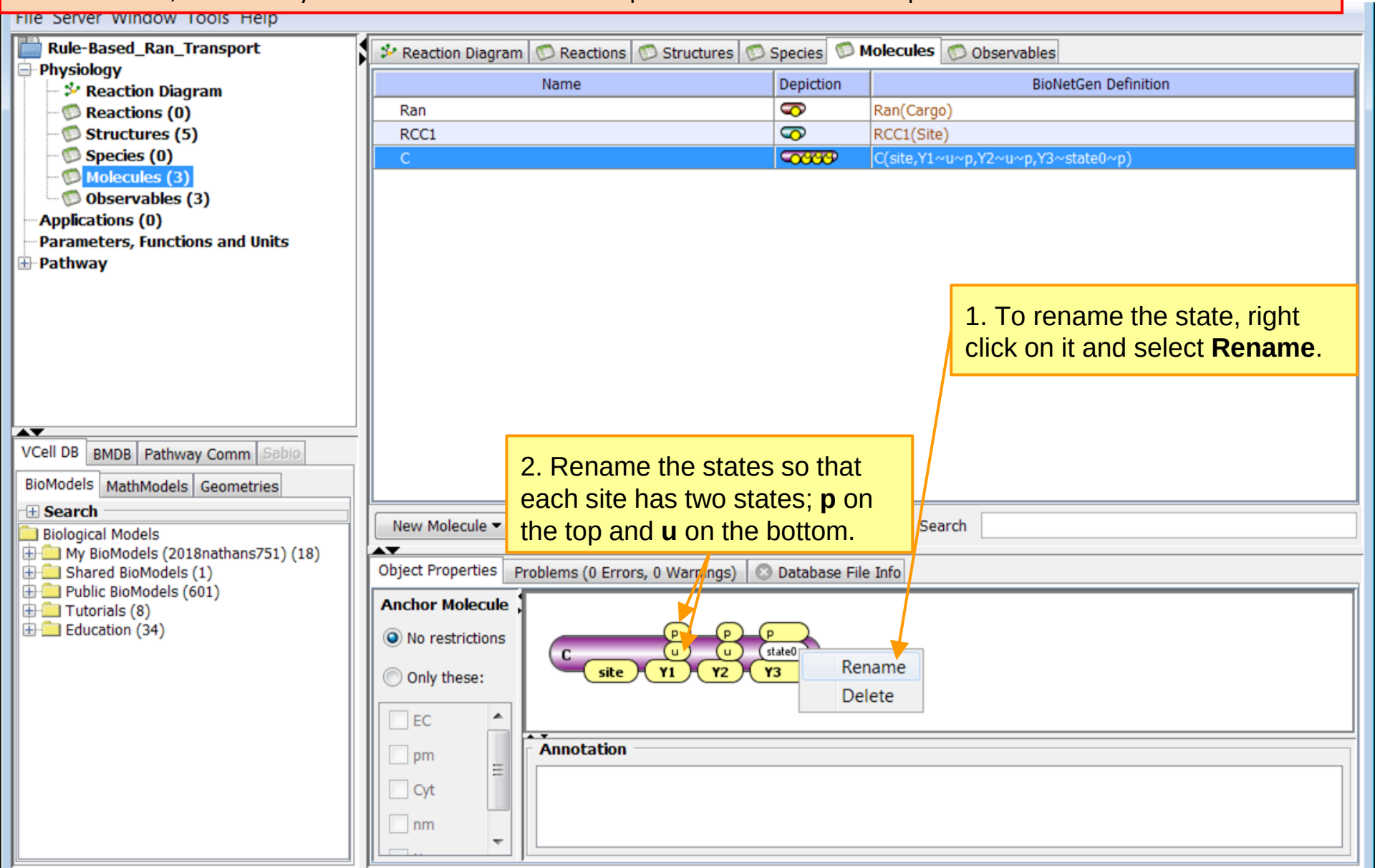
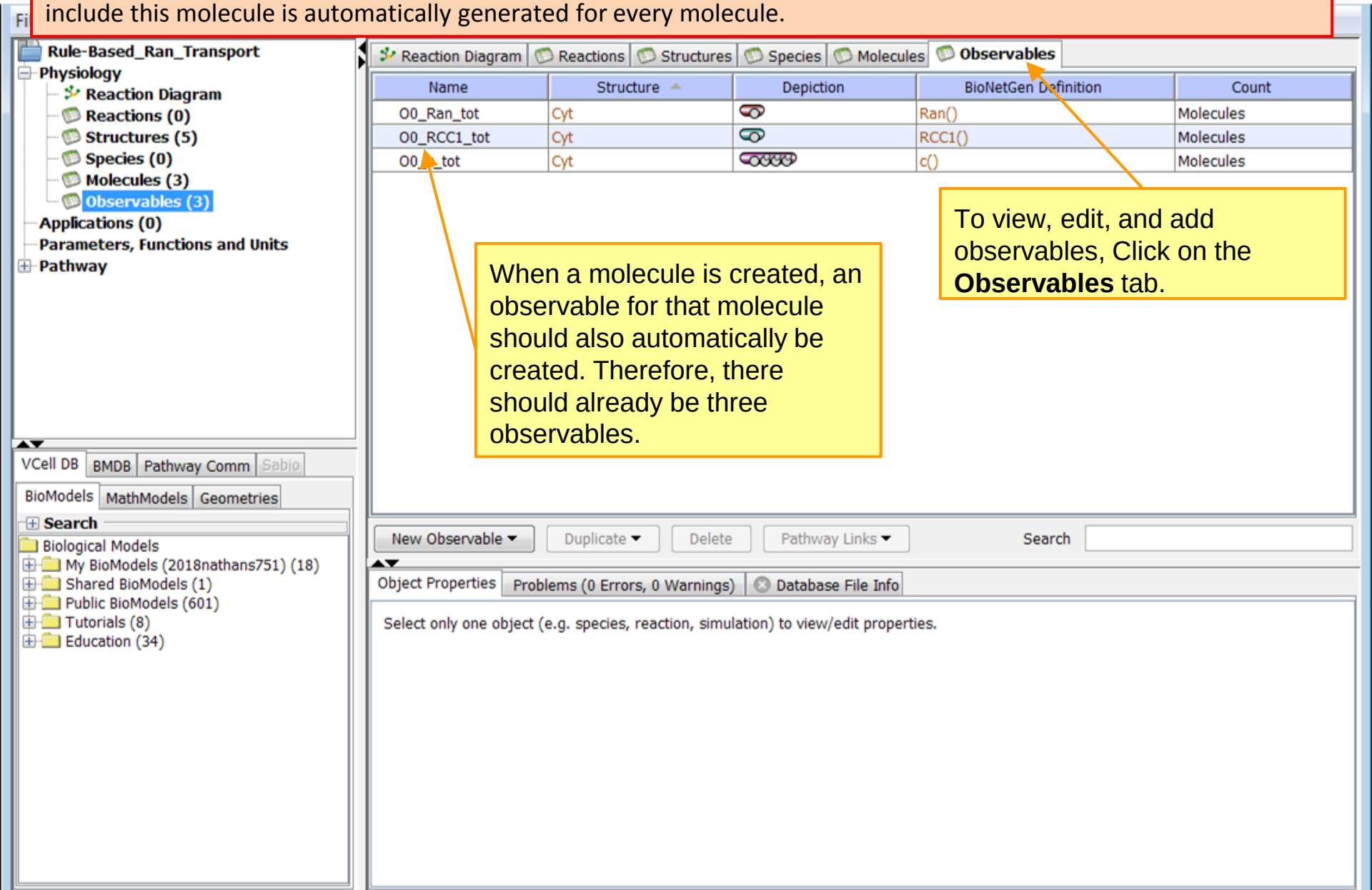
Tutorials (8)
Education (34)
New Molecule
Delete
Pathway Links
Object Properties
Problems (0 Errors, 0 Warnings)
Anchor Molecule
No restrictions
Only these:
EC
pm
Cyt
nm
C
site
Y1
Y2
Y3
Move right
Move left
Rename
Delete
Add State
Annotation
1. Create new molecule C.
2. Add sites Site, Y1, Y2, and Y3.
3. Right click on site Y1 and press add state. Do this for sites Y2 and Y3 as well (2x for each site).

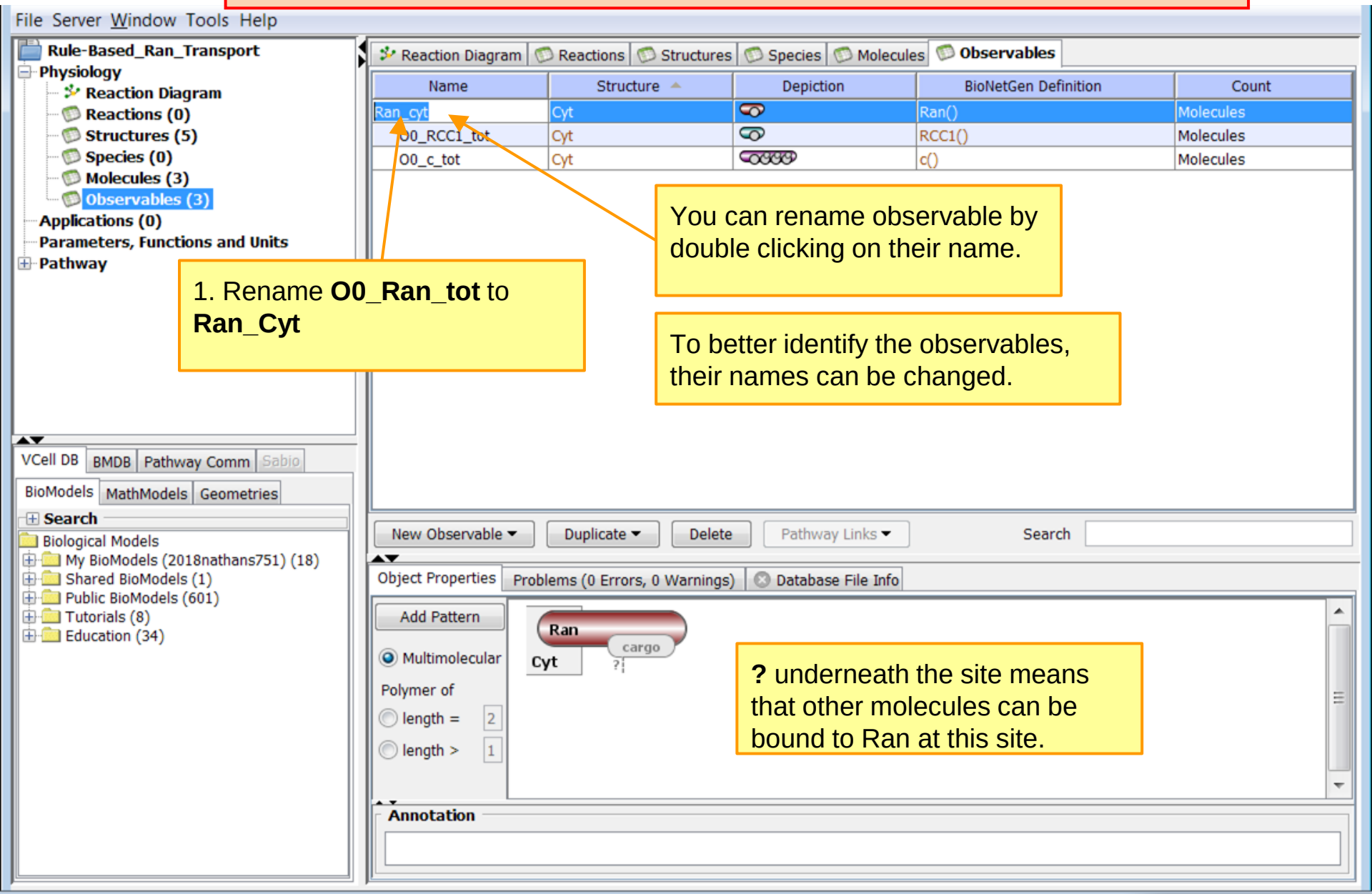
TIP: The BioNetGen Definition is another way of describing a molecule. The format is the name of the molecule followed by closed parentheses, containing the names of sites, separated by comas. States are indicated by a adding a tilde to the end of the site, followed by the name of the state. Multiple states can be created per site.

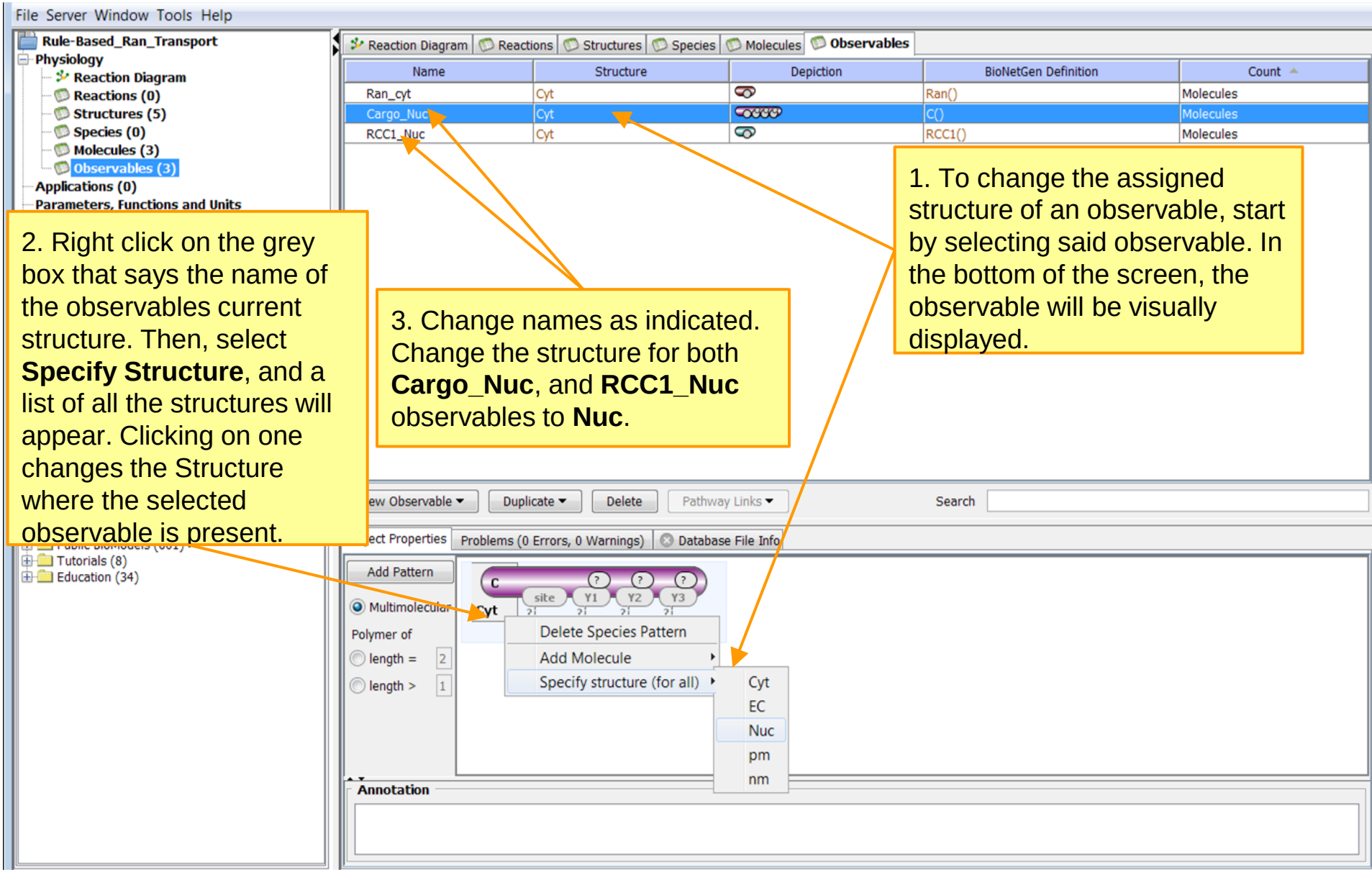


TIP: Each Observable corresponds to a sum of species selected by species patterns. Specific species are identified the network is generated using reaction rules. An observable corresponding to the total amount of all species that include this molecule is automatically generated for every molecule.



TIP: Not all of the observables were automatically created in the correct structure.

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Species (0)
Molecules (3)
Observables (3)
Applications (0)
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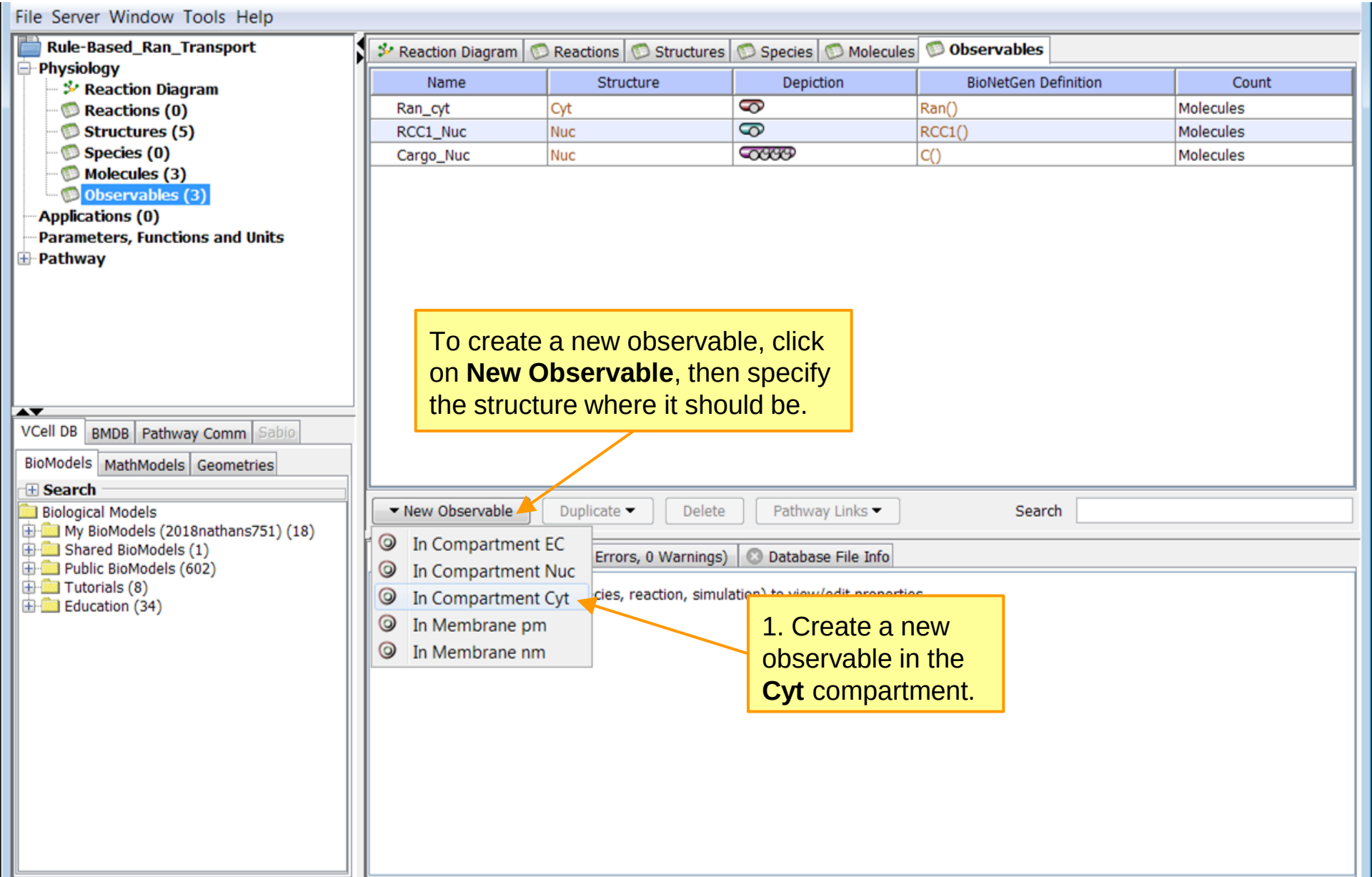
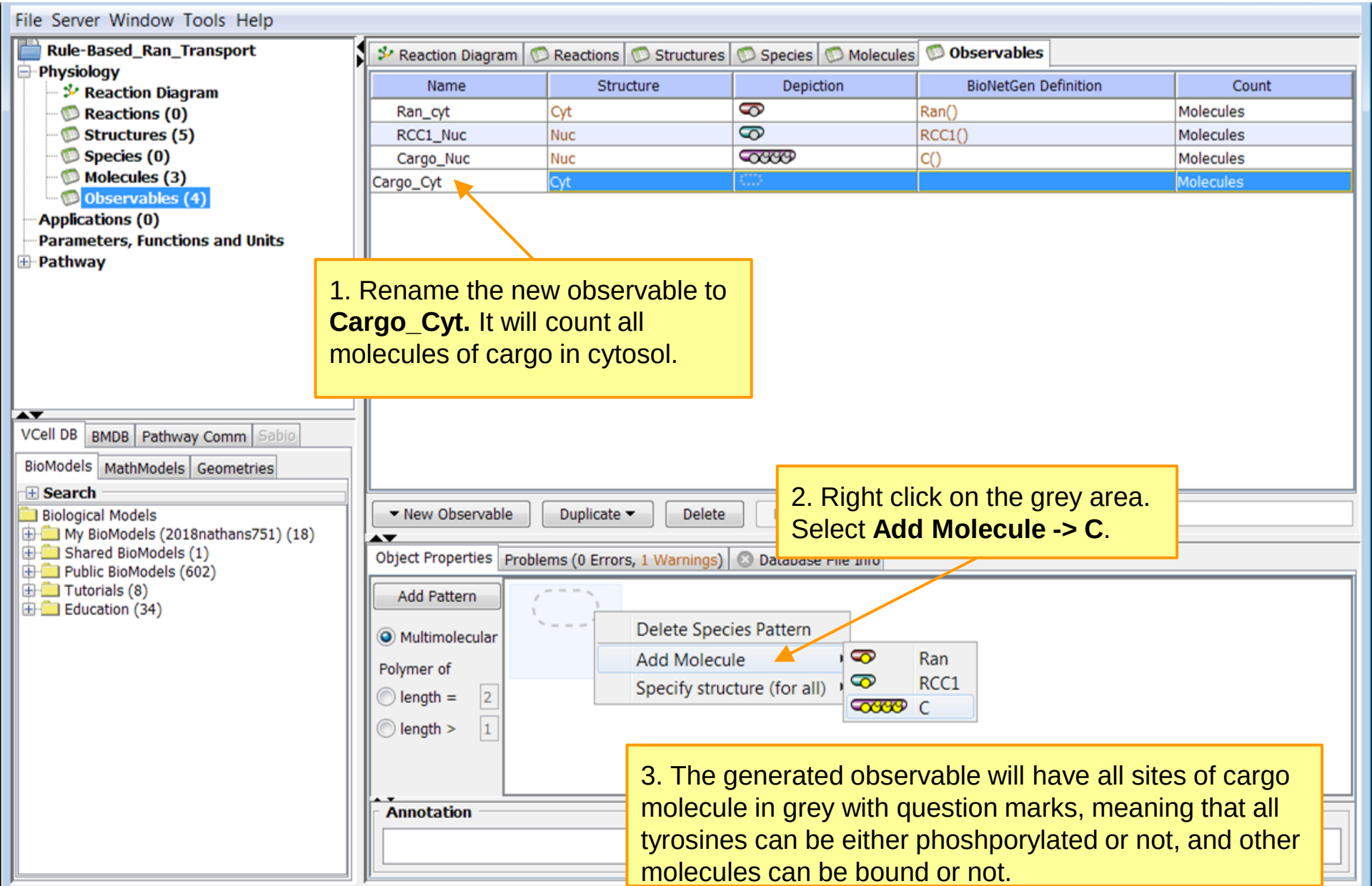
Structures
Species
Molecules
Observables
Name
Structure
Depiction
BioNetGen Definition
Count
Ran_cyt
Cyt
Ran()
Molecules
Cargo_Nuc
Cyt
C()
Molecules
RCC1_Nuc
Cyt
RCC1()
Molecules
1. To change the assigned structure of an observable, start by selecting said observable. In the bottom of the screen, the observable will be visually displayed.
2. Right click on the grey box that says the name of the observables current structure. Then, select Specify Structure, and a list of all the structures will appear. Clicking on one changes the Structure where the selected observable is present.
3. Change names as indicated. Change the structure for both Cargo_Nuc, and RCC1_Nuc observables to Nuc.
ew Observable
Duplicate
Delete
Pathway Links
Search
ect Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Add Pattern
Multimolecular
Polymer of
length =
length >
C
site
Y1
Y2
Y3
Cyt
Delete Species Pattern
Add Molecule
Specify structure (for all)
Cyt
EC
Nuc
pm
nm
Annotation

TIP: A duplicate observable can be created by selecting the desired observable and clicking Duplicate.

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Molecules (3)
Observables (4)
Applications (0)
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Reactions
Structures
Species
Molecules
Observables
Name
Structure
Depiction
BioNetGen Definition
Count
Ran_cyt
Cyt
Ran()
Molecules
RCC1_Nuc
Nuc
RCC1()
Molecules
Cargo_Nuc
Nuc
C()
Molecules
Cargo_Cyt
Cyt
Molecules
1. Rename the new observable to Cargo_Cyt. It will count all molecules of cargo in cytosol.
VCell DB
BMDB
Pathway Comm
Sabio
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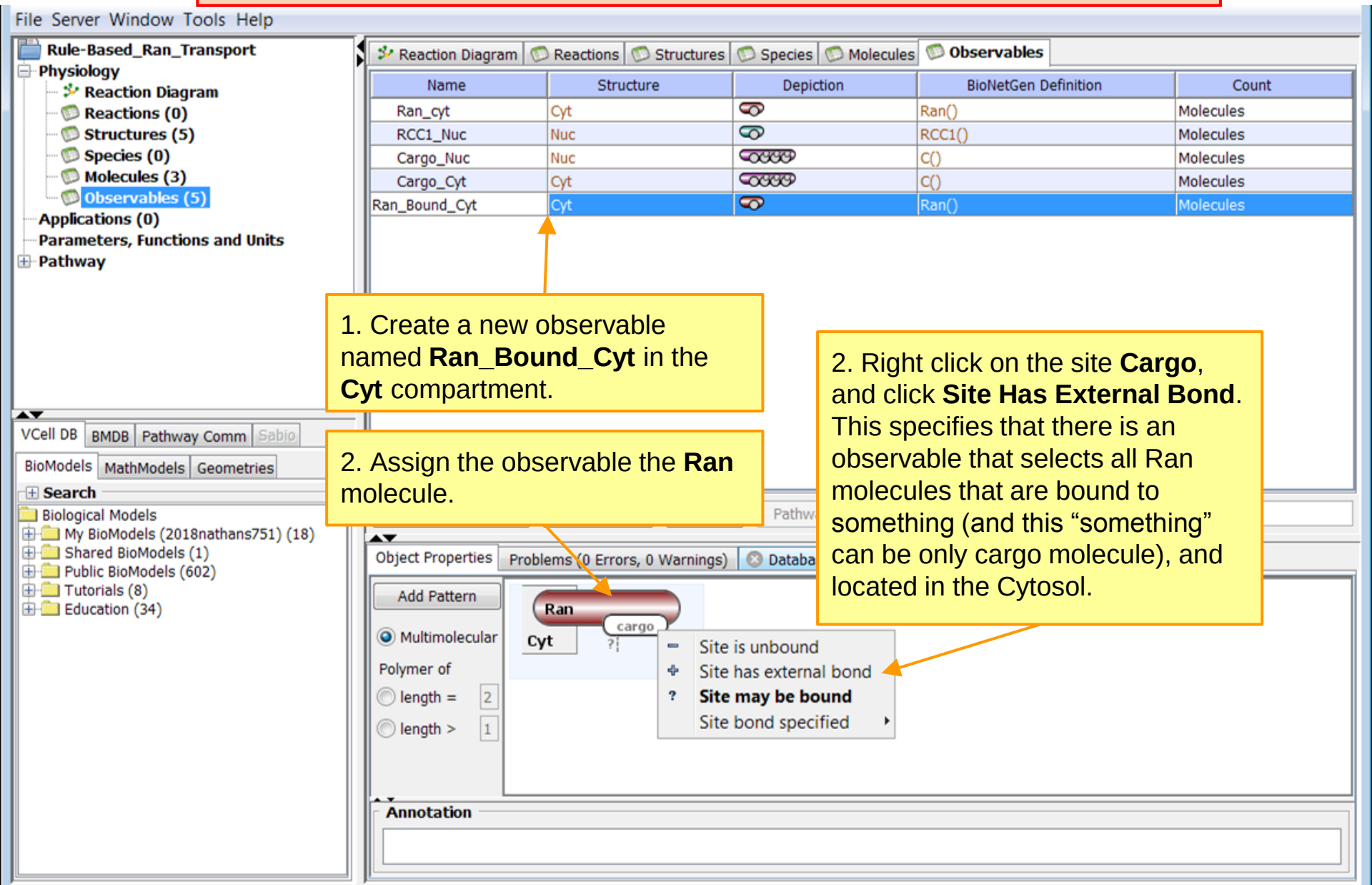
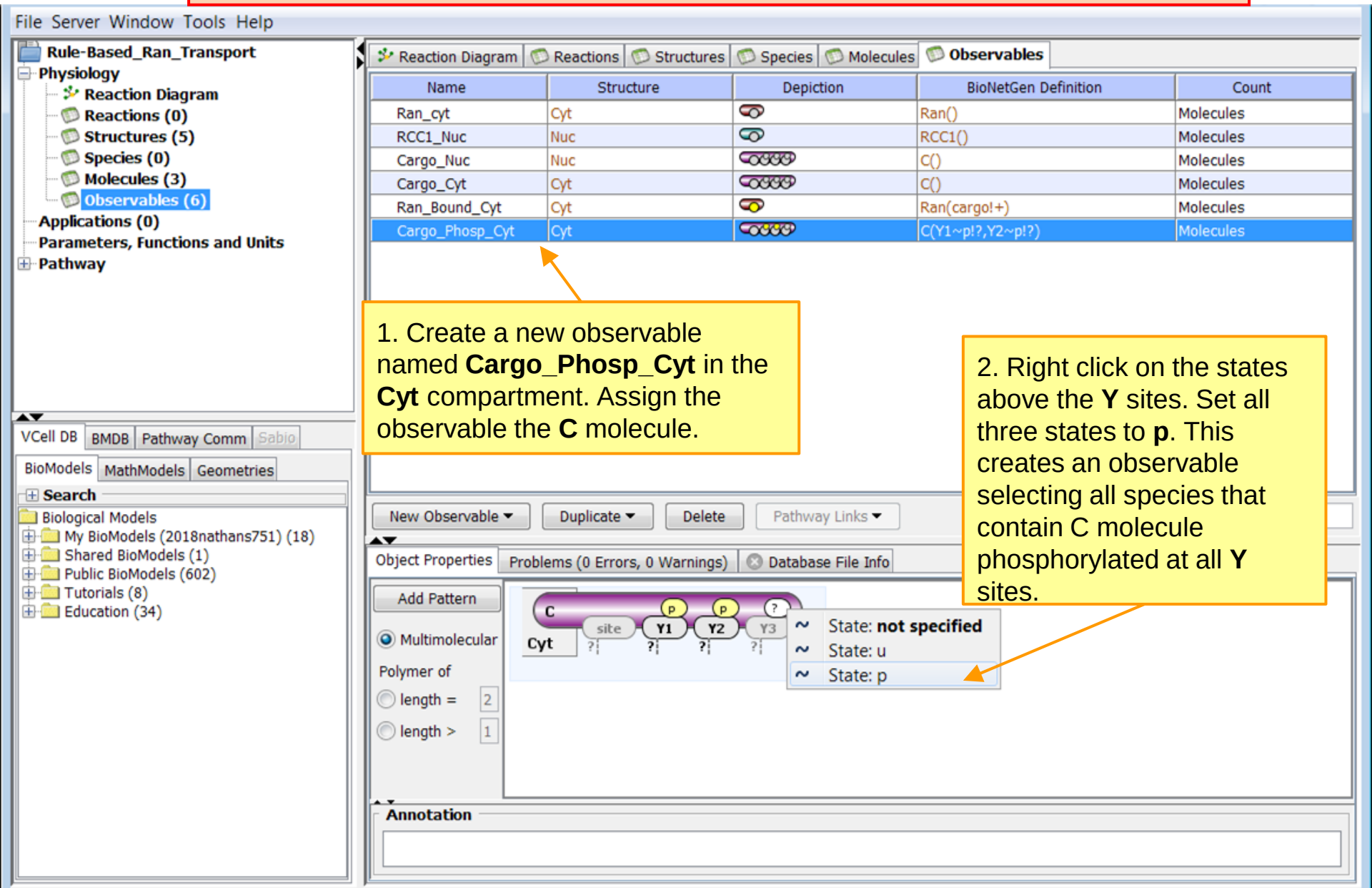
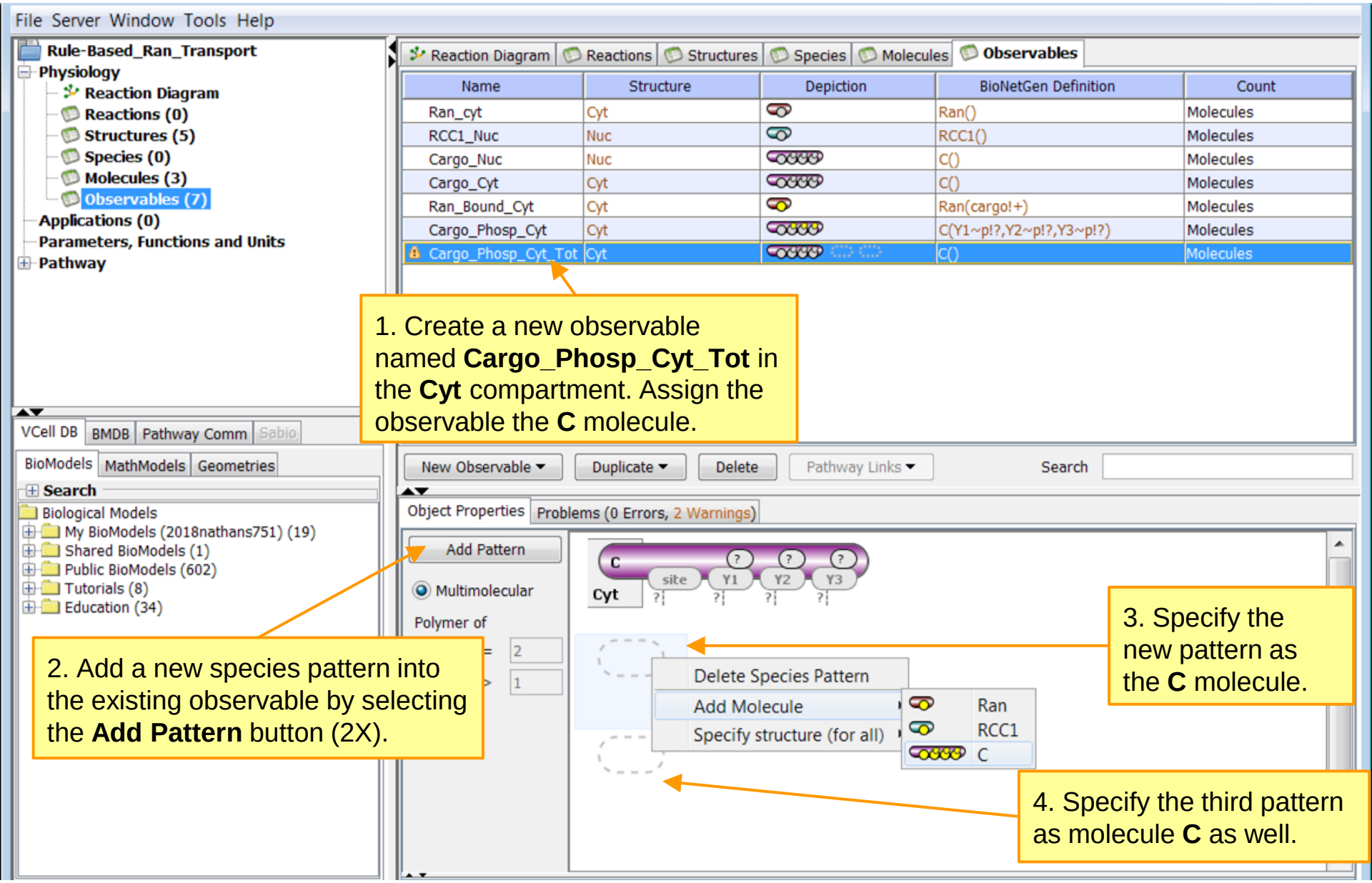
Shared BioModels (1)
Public BioModels (602)
Tutorials (8)
Education (34)
New Observable
Duplicate
Delete
2. Right click on the grey area. Select Add Molecule -> C.
Object Properties
Problems (0 Errors, 1 Warnings)
Add Pattern
Multimolecular
Polymer of
length = 2
length > 1
Delete Species Pattern
Add Molecule
Specify structure (for all)
Ran
RCC1
C
Annotation
3. The generated observable will have all sites of cargo molecule in grey with question marks, meaning that all tyrosines can be either phoshporylated or not, and other molecules can be bound or not.

TIP: For some observables it is important to specify certain sites being bound or unbound, phosphorylated, or unphosphorylated.



TIP: A state of "p" means phosphorylated, while a "u" state means unphosphorylated.

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BioNetGen Definition
Count
Ran_cyt
Cyt
Ran()
Molecules
RCC1_Nuc
Nuc
RCC1()
Molecules
Cargo_Nuc
Nuc
C()
Molecules
Cargo_Cyt
Cyt
C()
Molecules
Ran_Bound_Cyt
Cyt
Ran(cargo!+)
Molecules
Cargo_Phosp_Cyt
Cyt
C(Y1~p!?,Y2~p!?,Y3~p!?)
Molecules
Cargo_Phosp_Cyt_Tot
Cyt
C()
Molecules
1. Create a new observable named Cargo_Phosp_Cyt_Tot in the Cyt compartment. Assign the observable the C molecule.
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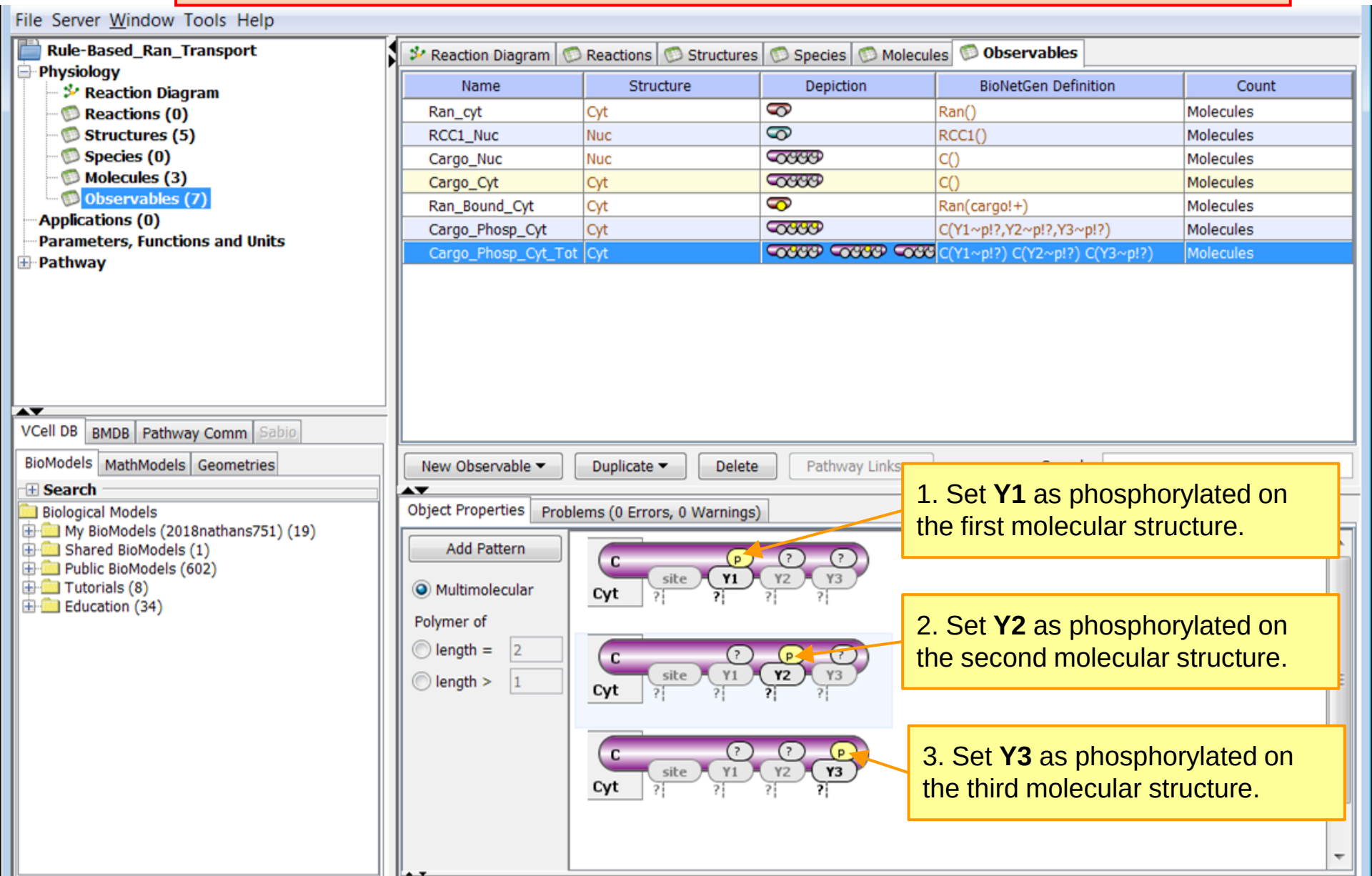
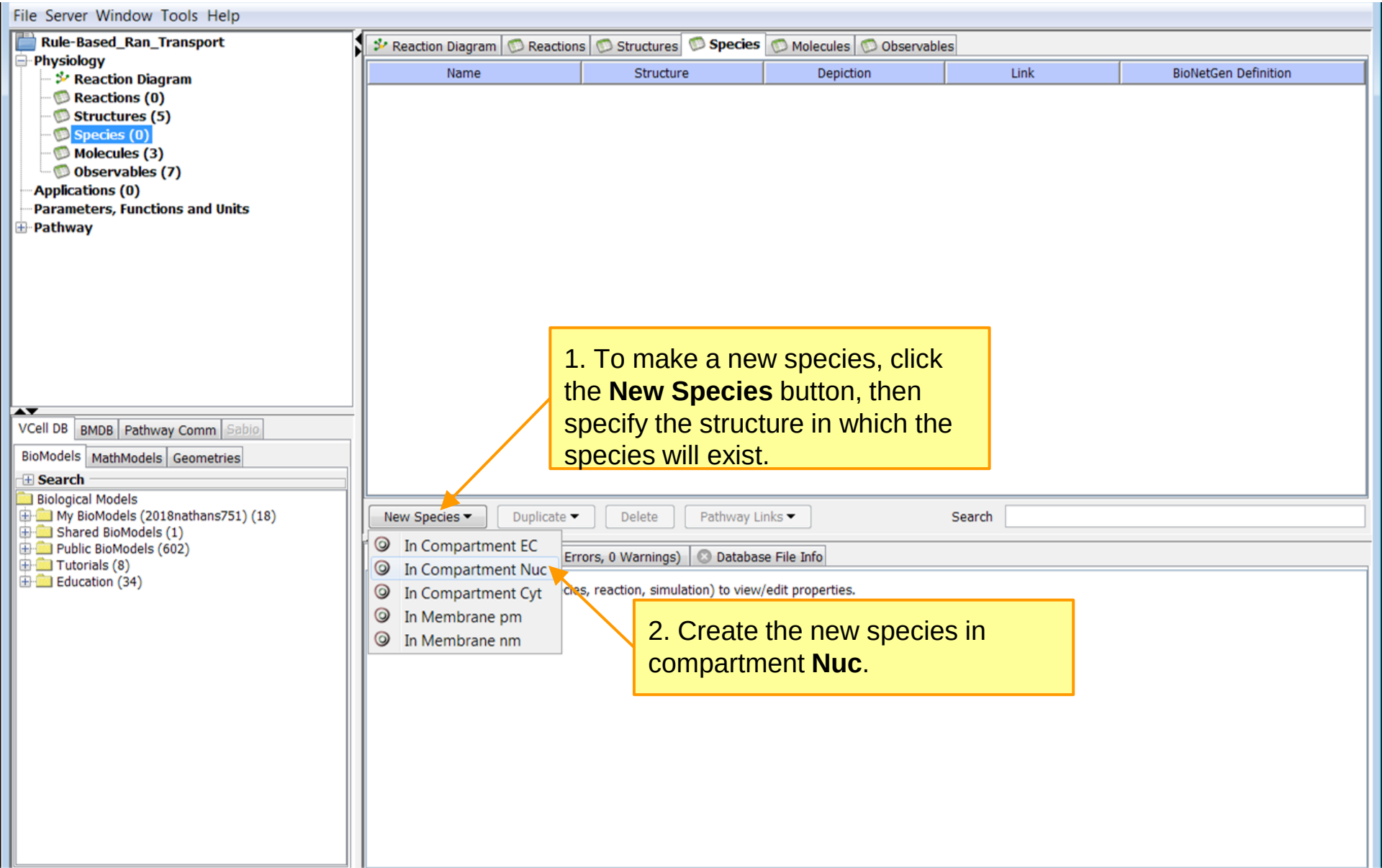
2. Add a new species pattern into the existing observable by selecting the Add Pattern button (2X).
New Observable
Duplicate
Delete
Pathway Links
Search
Object Properties
Problems (0 Errors, 2 Warnings)
Add Pattern
Multimolecular
Polymer of
C
site
Y1
Y2
Y3
Cyt
Delete Species Pattern
Add Molecule
Specify structure (for all)
Ran
RCC1
C
3. Specify the new pattern as the C molecule.
4. Specify the third pattern as molecule C as well.

TIP: A grey site with a question mark at the bottom means that the site may or may not be bound.

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Observables
Name
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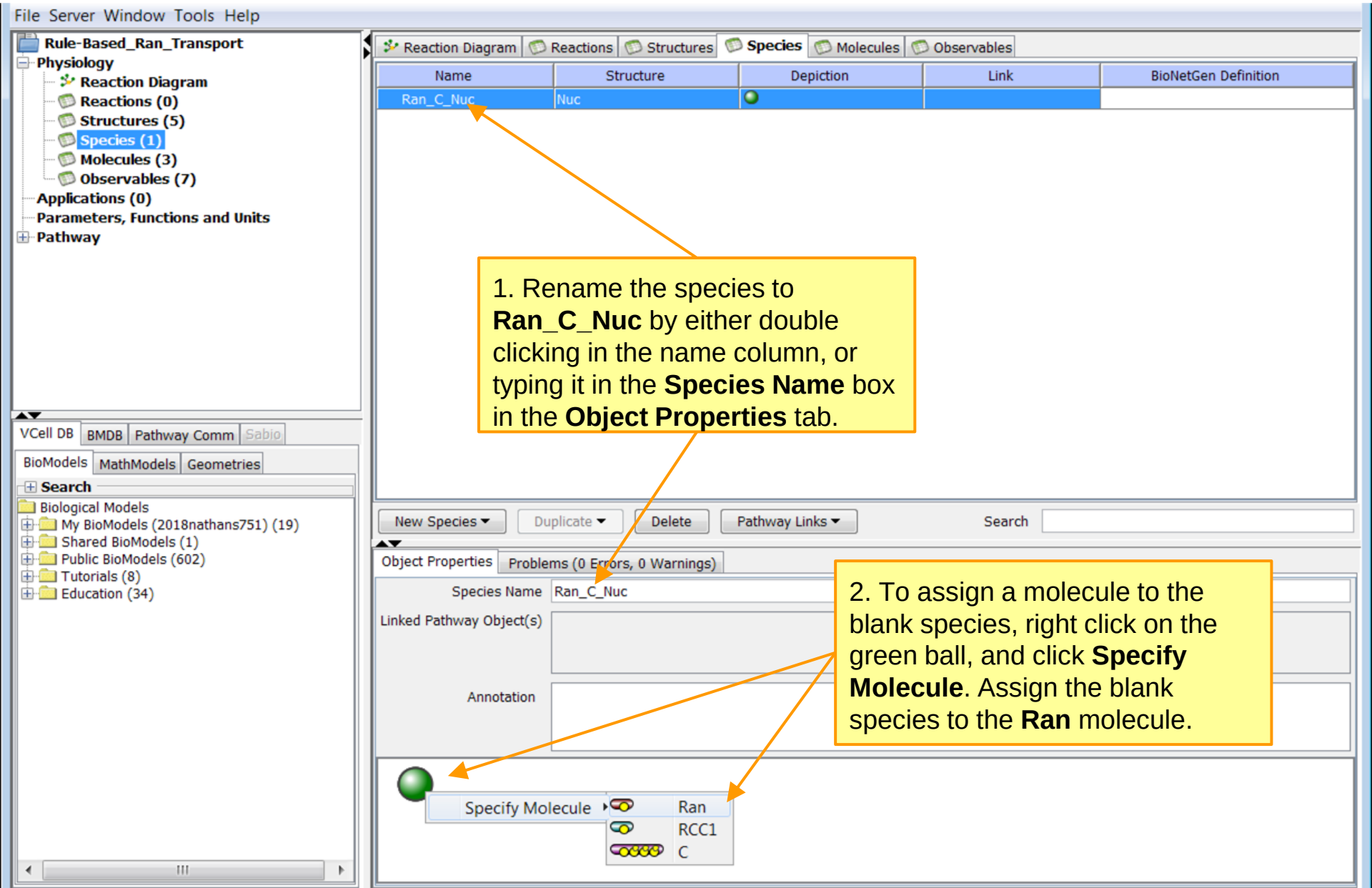
1. To make a new species, click the New Species button, then specify the structure in which the species will exist.
New Species
Duplicate
Delete
Pathway Links
Search
In Compartment EC
In Compartment Nuc
In Compartment Cyt
In Membrane pm
In Membrane nm
Errors, 0 Warnings)
Database File Info
cies, reaction, simulation) to view/edit properties.
2. Create the new species in compartment Nuc.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Observables (7)
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Structures
Species
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Observables
Name
Structure
Depiction
Link
BioNetGen Definition
Ran_C_Nuc
Nuc
1. Rename the species to Ran_C_Nuc by either double clicking in the name column, or typing it in the Species Name box in the Object Properties tab.
New Species
Duplicate
Delete
Pathway Links
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Species Name
Ran_C_Nuc
Linked Pathway Object(s)
Annotation
2. To assign a molecule to the blank species, right click on the green ball, and click Specify Molecule. Assign the blank species to the Ran molecule.
Specify Molecule
Ran
RCC1
C
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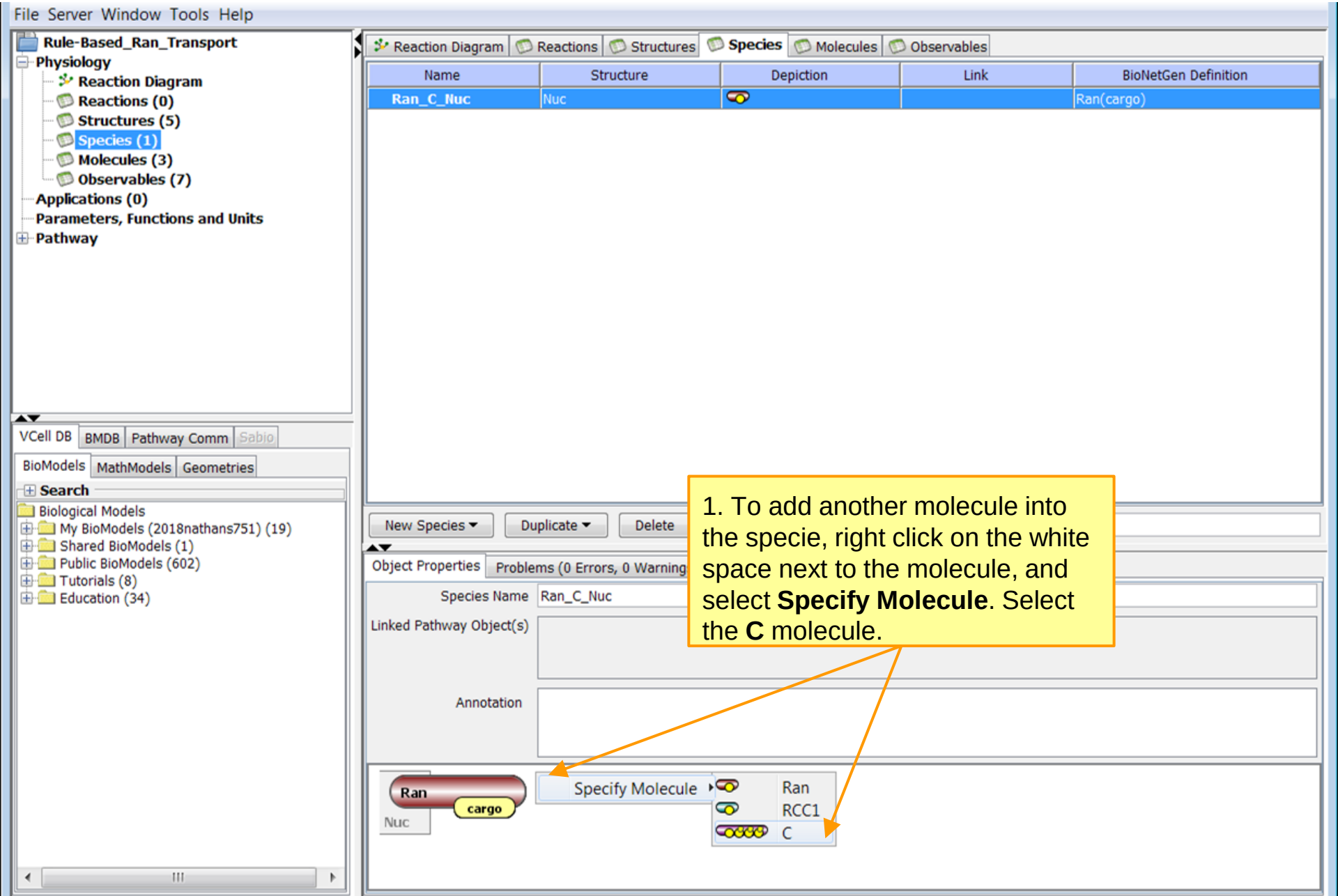
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Observables (7)
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Reaction Diagram
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Structure
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BioNetGen Definition
Ran_C_Nuc
Nuc
Ran(cargo)
VCell DB
BMDB
Pathway Comm
Sabio
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Geometries
Search
Biological Models
My BioModels (2018nathans751) (19)
Shared BioModels (1)
Public BioModels (602)
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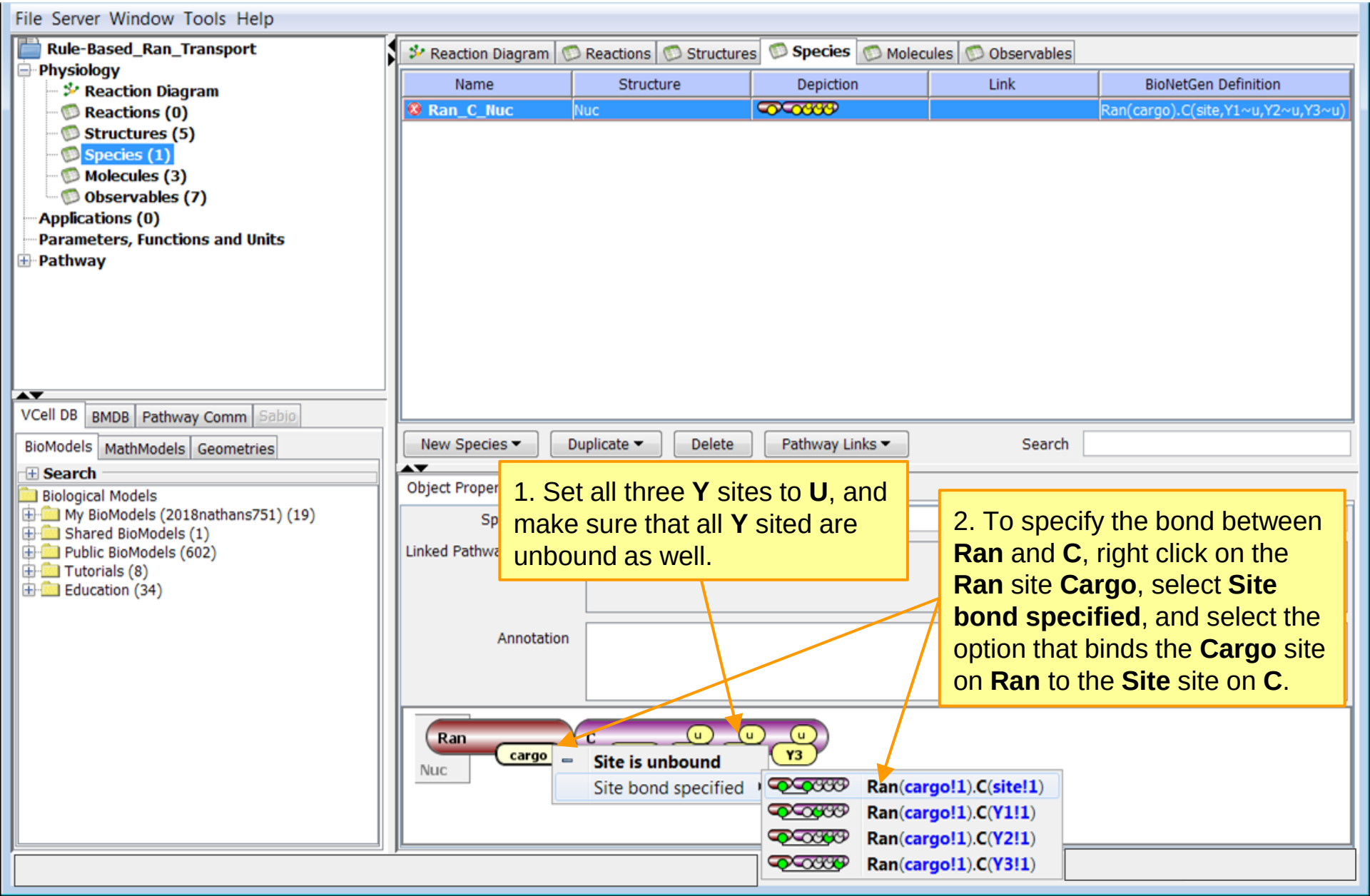
Education (34)
New Species
Duplicate
Delete
Object Properties
Problems (0 Errors, 0 Warning
Species Name
Ran_C_Nuc
Linked Pathway Object(s)
Annotation
1. To add another molecule into the specie, right click on the white space next to the molecule, and select **Specify Molecule**. Select the **C** molecule.
Ran
cargo
Nuc
Specify Molecule
Ran
RCC1
C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Structures (5)
Species (1)
Molecules (3)
Observables (7)
Applications (0)
Parameters, Functions and Units
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Reaction Diagram
Reactions
Structures
Species
Molecules
Observables
Name
Structure
Depiction
Link
BioNetGen Definition
Ran_C_Nuc
Nuc
Ran(cargo).C(site,Y1~u,Y2~u,Y3~u)
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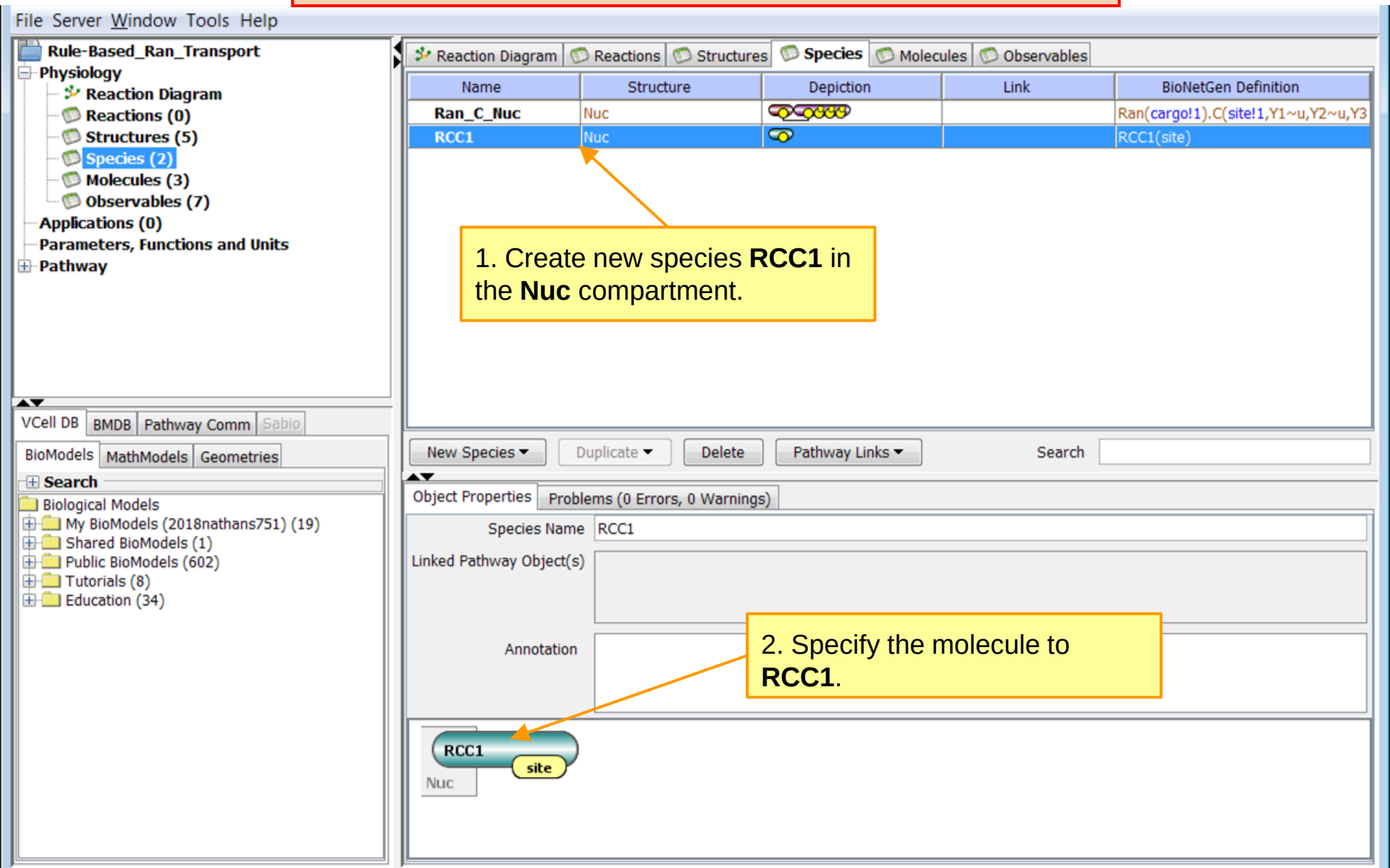
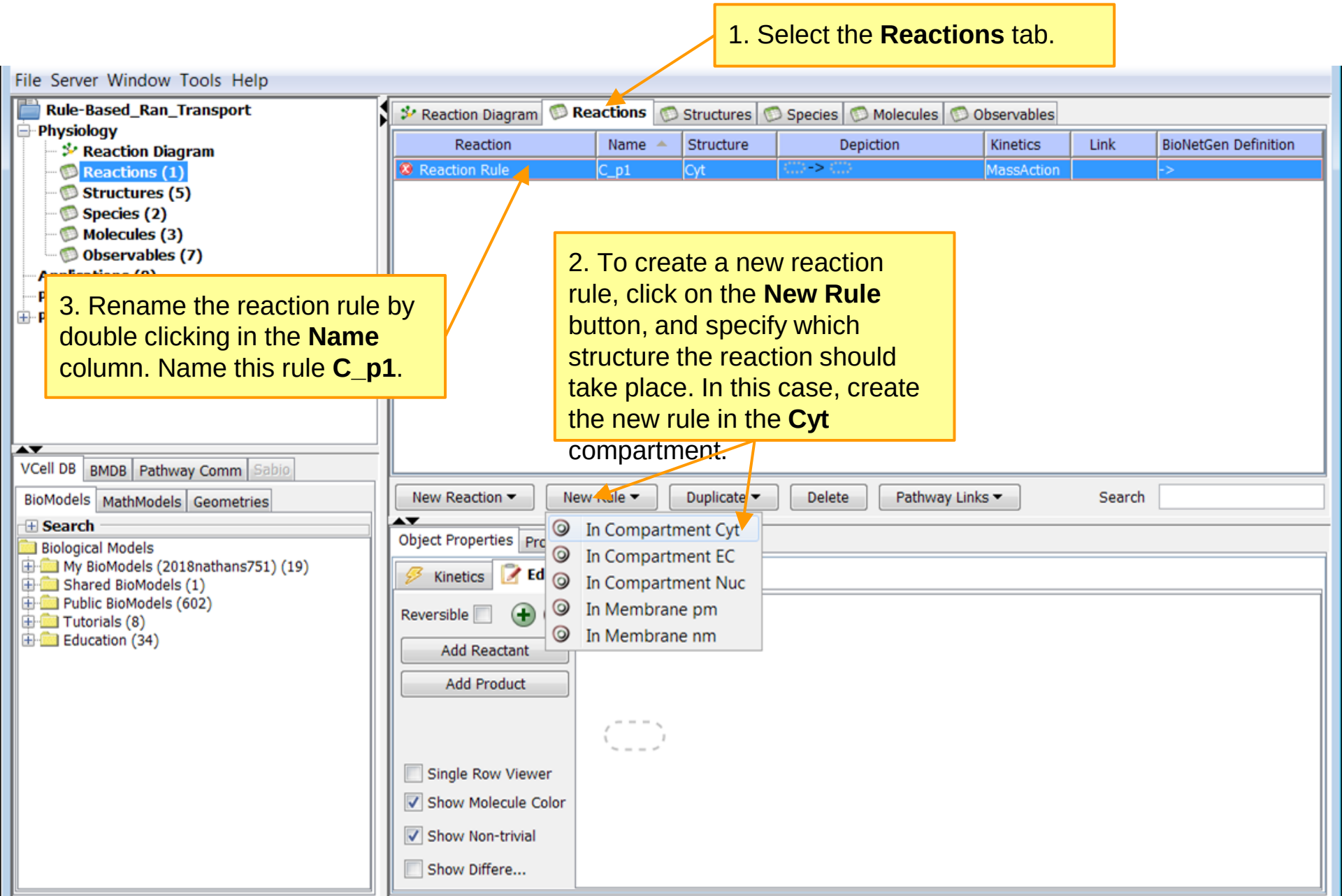
New Species
Duplicate
Delete
Pathway Links
Search
Object Proper
Linked Pathwa
Annotation
1. Set all three Y sites to U, and make sure that all Y sited are unbound as well.
2. To specify the bond between Ran and C, right click on the Ran site Cargo, select Site bond specified, and select the option that binds the Cargo site on Ran to the Site site on C.
Ran
cargo
Nuc
C
u
u
u
Y3
Site is unbound
Site bond specified
Ran(cargo!1).C(site!1)
Ran(cargo!1).C(Y1!1)
Ran(cargo!1).C(Y2!1)
Ran(cargo!1).C(Y3!1)

TIP: A yellow site with no line out the bottom is an unbound site.




1. Select the **Reactions** tab.
2. To create a new reaction rule, click on the **New Rule** button, and specify which structure the reaction should take place. In this case, create the new rule in the **Cyt** compartment.
3. Rename the reaction rule by double clicking in the **Name** column. Name this rule **C_p1**.
File Server Window Tools Help
Rule-Based_Ran_Transport
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Structures (5)
Species (2)
Molecules (3)
Observables (7)
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Molecules
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Reaction
Name
Structure
Depiction
Kinetics
Link
BioNetGen Definition
Reaction Rule
C_p1
Cyt
MassAction
New Reaction
New Rule
Duplicate
Delete
Pathway Links
Search
In Compartment Cyt
In Compartment EC
In Compartment Nuc
In Membrane pm
In Membrane nm
Object Properties
Kinetics
Reversible
Add Reactant
Add Product
Single Row Viewer
Show Molecule Color
Show Non-trivial
VCell DB
BMDB
Pathway Comm
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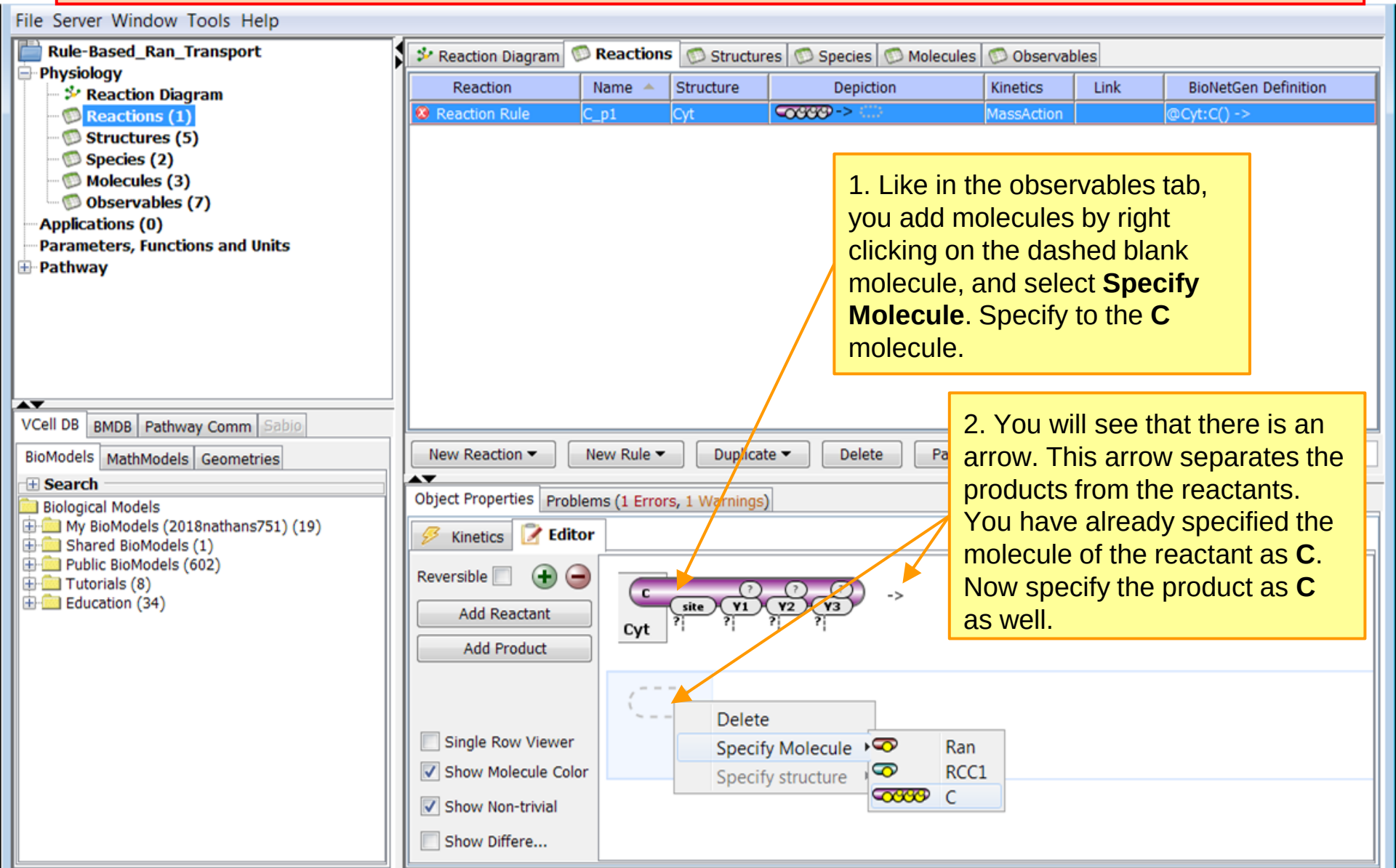
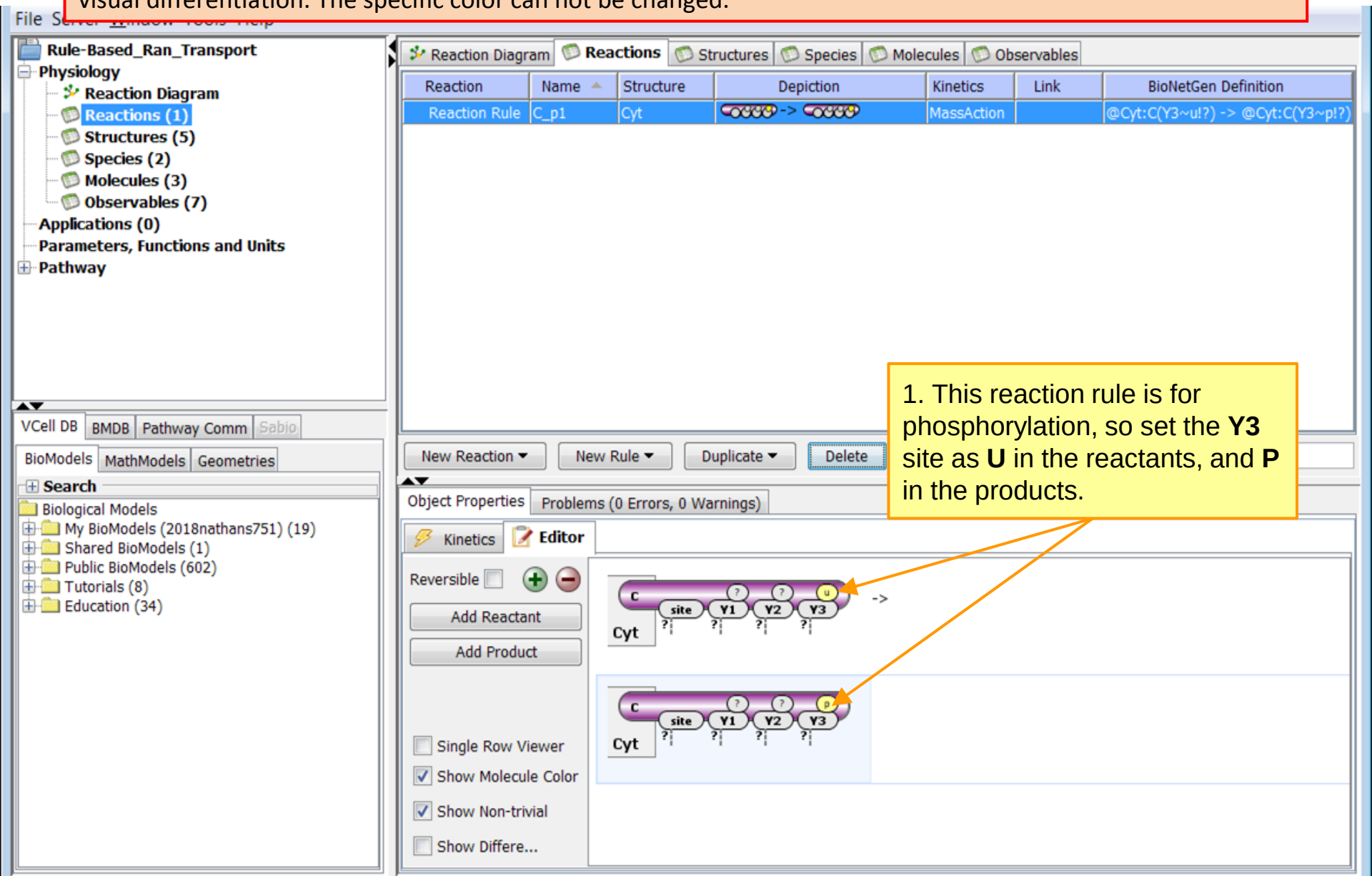
Education (34)

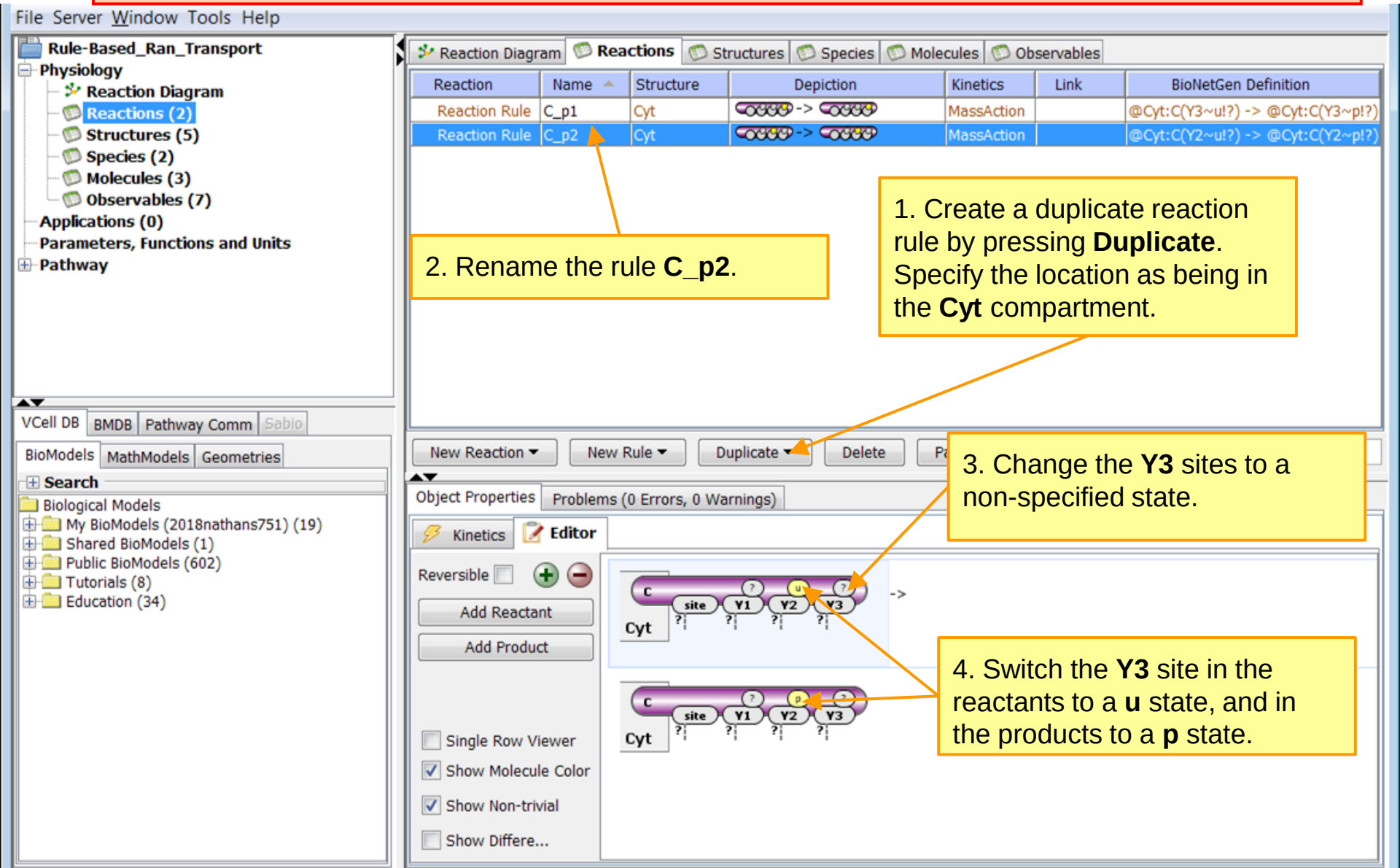
TIP: To make the reaction larger or smaller, use the respectively green and red plus and minus button. Checking the **Single Row Viewer** box aligns the entire reaction in one row. You can not edit the reaction in this mode.

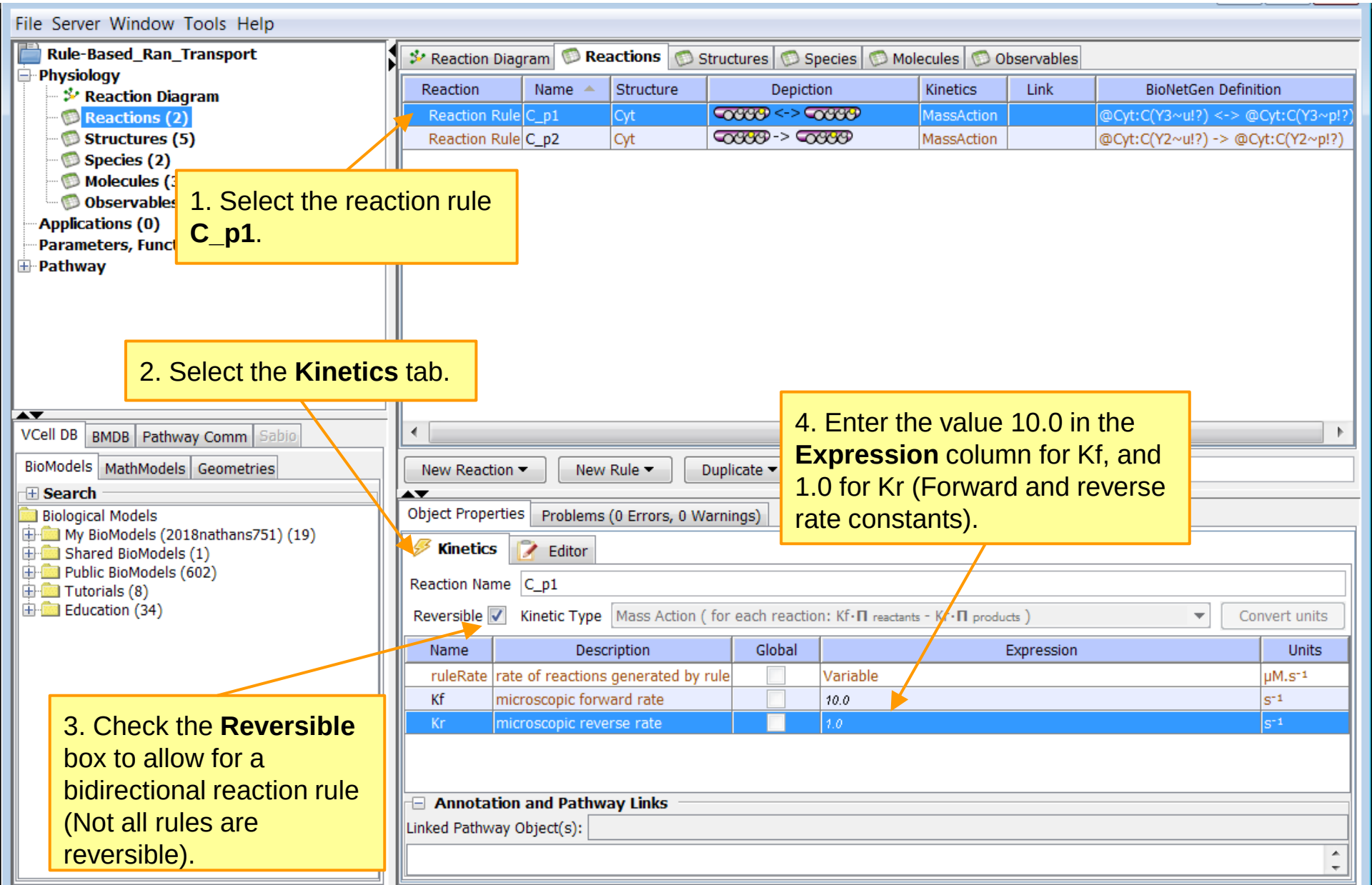


TIP: With no boxes checked, the reaction is shown in black and white, with only the site specific bonds indicated in color. Checking the **Show Molecule Color** box adds an ordered color to the molecule to help with visual differentiation. The specific color can not be changed.



TIP: Checking the **Show Non-trivial** box highlights assigned sites and states in yellow. Checking the **Show Differe…** box highlights in orange the differences in bonds, sites, and states between the reactants and the products.




File Server Window Tools Help
Rule-Based_Ran_Transport
Physiology
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Reactions (2)
Structures (5)
Species (2)
Molecules (
Observables
Applications (0)
Parameters, Funct
Pathway
Reaction Diagram
Reactions
Structures
Species
Molecules
Observables
Reaction
Name
Structure
Depiction
Kinetics
Link
BioNetGen Definition
Reaction Rule C_p1 Cyt <-> MassAction @Cyt:C(Y3~u!?) <-> @Cyt:C(Y3~p!?)
Reaction Rule C_p2 Cyt -> MassAction @Cyt:C(Y2~u!?) -> @Cyt:C(Y2~p!?)
1. Select the reaction rule C_p1.
2. Select the Kinetics tab.
3. Check the Reversible box to allow for a bidirectional reaction rule (Not all rules are reversible).
4. Enter the value 10.0 in the Expression column for Kf, and 1.0 for Kr (Forward and reverse rate constants).
VCell DB
BMDB
Pathway Comm
Sabio
BioModels
MathModels
Geometries
Search
Biological Models
My BioModels (2018nathans751) (19)
Shared BioModels (1)
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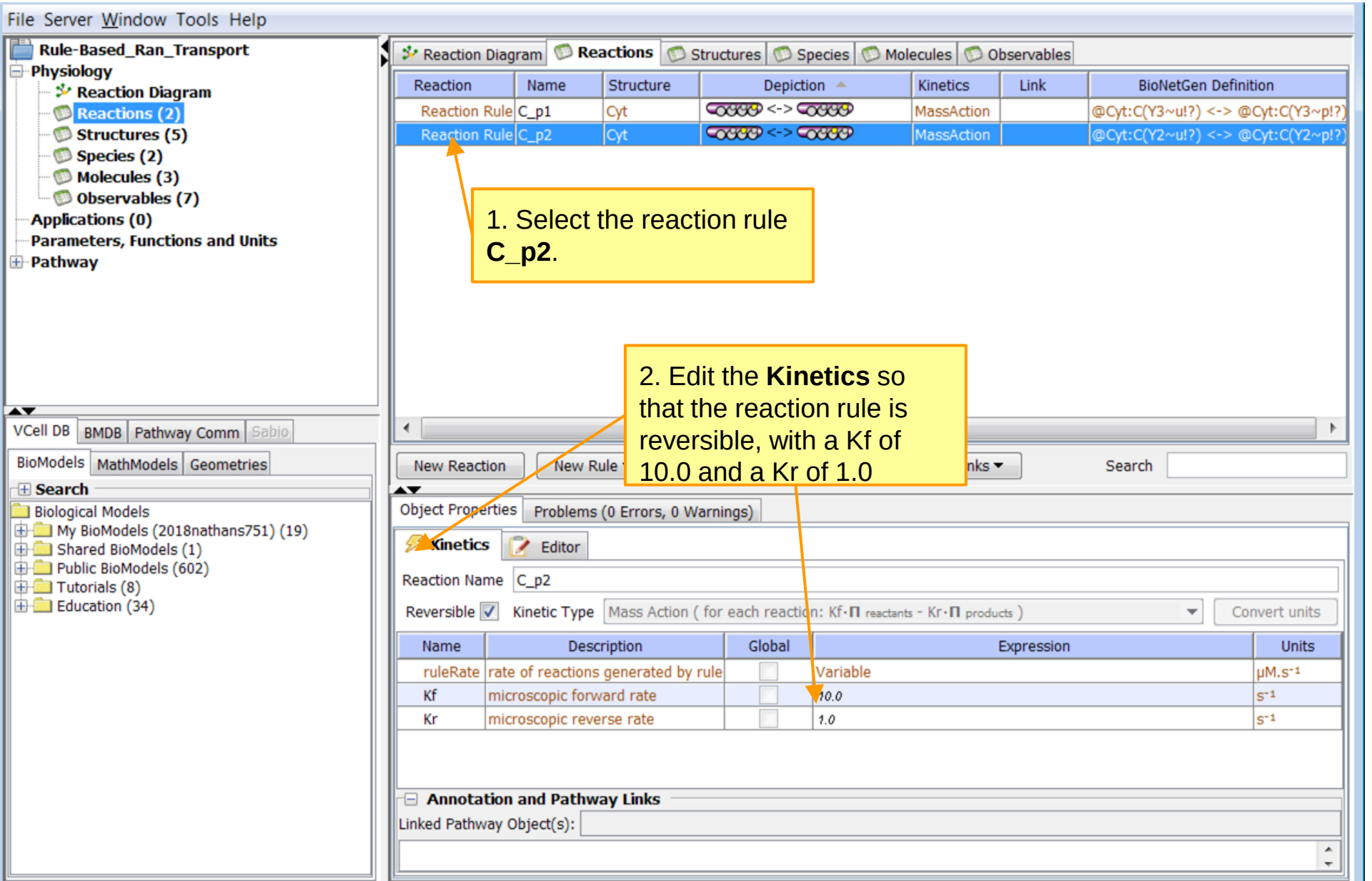
Tutorials (8)
Education (34)
New Reaction
New Rule
Duplicate
Object Properties
Problems (0 Errors, 0 Warnings)
Kinetics
Editor
Reaction Name C_p1
Reversible
Kinetic Type
Mass Action (for each reaction: Kf·Π reactants - Kr·Π products)
Convert units
Name
Description
Global
Expression
Units
ruleRate rate of reactions generated by rule Variable μM.s-1
Kf microscopic forward rate 10.0 s-1
Kr microscopic reverse rate 1.0 s-1
Annotation and Pathway Links
Linked Pathway Object(s):


File Server Window Tools Help
Rule-Based_Ran_Transport
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Structures (5)
Species (2)
Molecules (3)
Observables (7)
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Parameters, Functions and Units
Pathway
Reaction Diagram
Reactions
Structures
Species
Molecules
Observables
Reaction
Name
Structure
Depiction
Kinetics
Link
BioNetGen Definition
Reaction Rule C_p1 Cyt MassAction @Cyt:C(Y3~u!?) <-> @Cyt:C(Y3~p!?)
Reaction Rule C_p2 Cyt MassAction @Cyt:C(Y2~u!?) <-> @Cyt:C(Y2~p!?)
1. Select the reaction rule C_p2.
2. Edit the Kinetics so that the reaction rule is reversible, with a Kf of 10.0 and a Kr of 1.0
New Reaction
New Rule
Search
VCell DB
BMDB
Pathway Comm
Sabio
BioModels
MathModels
Geometries
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Biological Models
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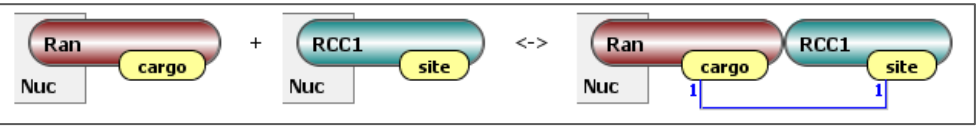
Tutorials (8)
Education (34)
Object Properties
Problems (0 Errors, 0 Warnings)
Kinetics
Editor
Reaction Name C_p2
Reversible
Kinetic Type
Mass Action (for each reaction: Kf·Π reactants - Kr·Π products)
Convert units
Name
Description
Global
Expression
Units
ruleRate rate of reactions generated by rule Variable μM.s-1
Kf microscopic forward rate 10.0 s-1
Kr microscopic reverse rate 1.0 s-1
Annotation and Pathway Links
Linked Pathway Object(s):

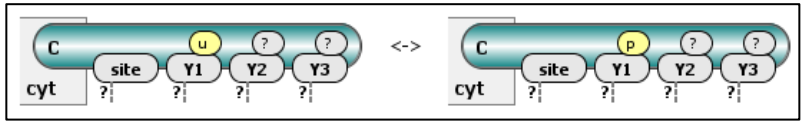
Finish inputting the rest of the reactions pictured below. (You already did the first two)

C_p1

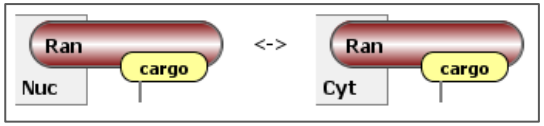
C_p2



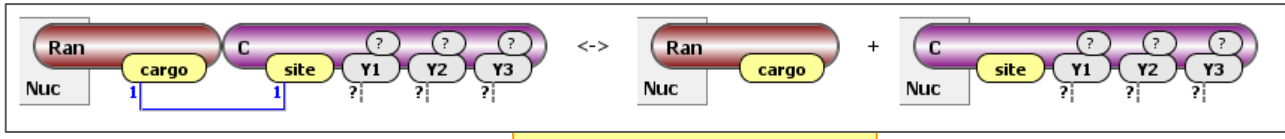
Ran_RCC1_Bind



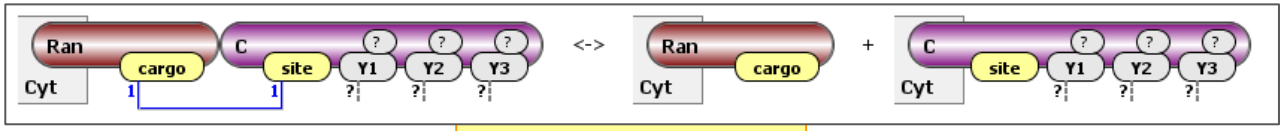
C_p3



Transfer



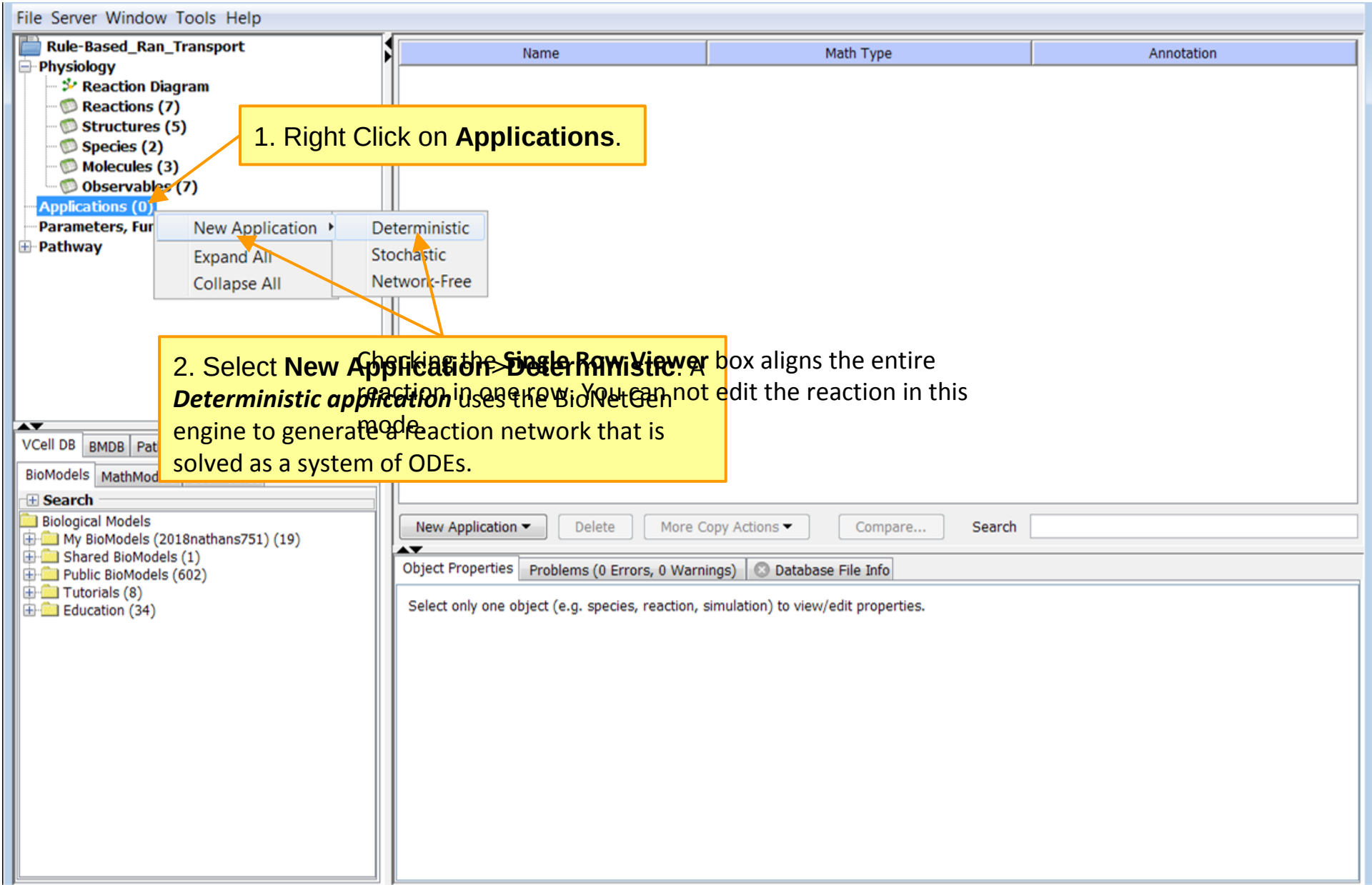
Ran_C_Bind_Nuc



Ran_C_Bind_Cyt

Finish inputting the rest of the Kinetics shown below (you already did the first two).

Reaction	Structure	Reversible?	Kf	Kr
C_p1	Cyt	yes	10.0	1.0
C_p2	Cyt	yes	10.0	1.0
C_p3	Cyt	yes	10.0	1.0
Ran_C_Bind_Cyt	Cyt	yes	1.0	100.0
Ran_C_Bind_Nuc	Nuc	yes	1.0	100.0
Ran_RCC1_Bind	Nuc	yes	1.0	100.0
Transport	nm	yes	(2.0 * 602.0)	0.0


File Server Window Tools Help
Rule-Based_Ran_Transport
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Reactions (7)
Structures (5)
Species (2)
Molecules (3)
Observables (7)
Applications (0)
Parameters, Fur
Pathway
New Application
Expand All
Collapse All
Deterministic
Stochastic
Network-Free
Name
Math Type
Annotation
1. Right Click on Applications.
2. Select New Application>Deterministic. A Deterministic application uses the BioNetGen engine to generate a reaction network that is solved as a system of ODEs.
Checking the Single Row Viewer box aligns the entire reaction in one row. You can not edit the reaction in this mode.
VCell DB
BMDB
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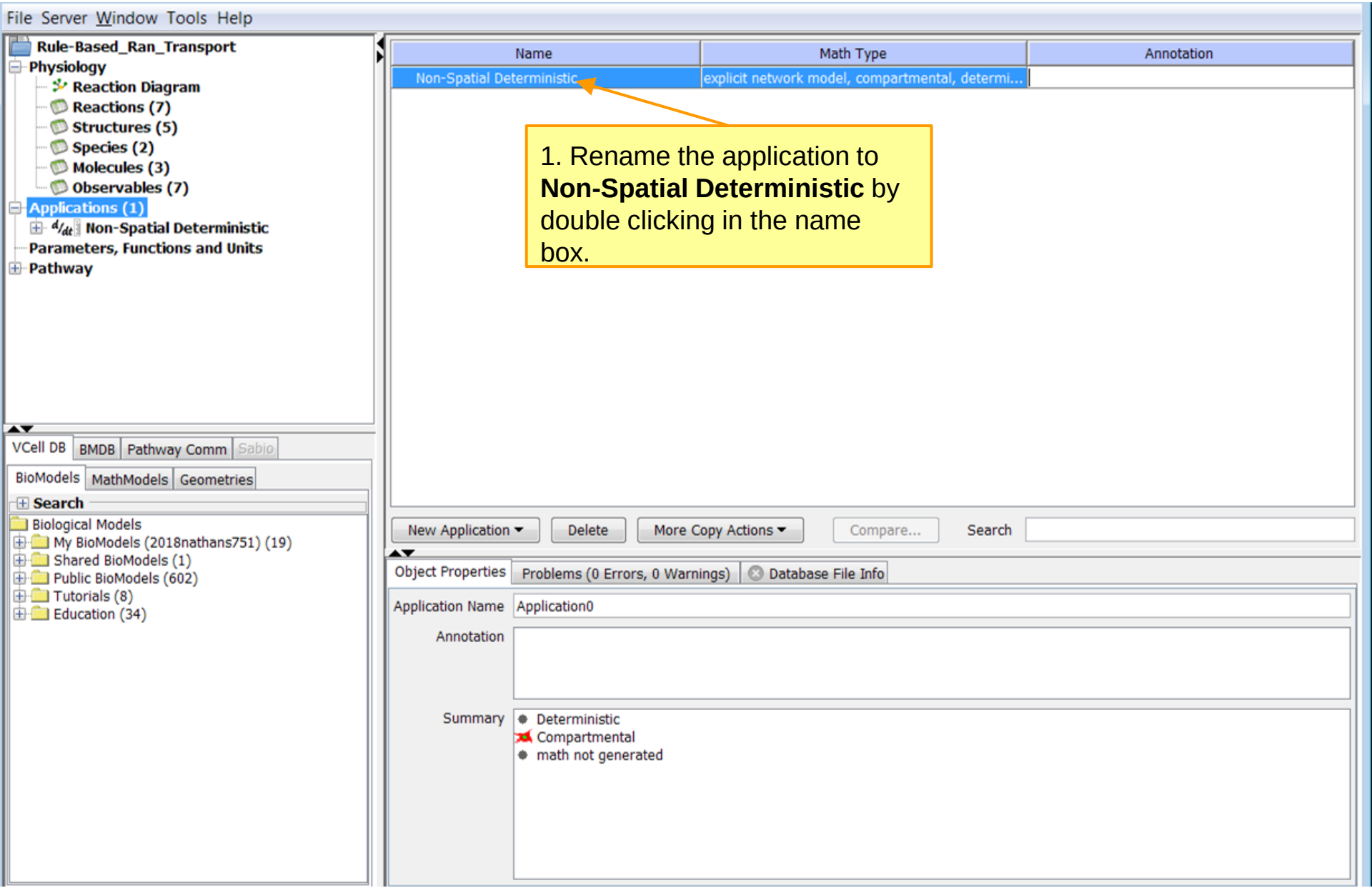
New Application
Delete
More Copy Actions
Compare...
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Select only one object (e.g. species, reaction, simulation) to view/edit properties.


File Server Window Tools Help
Rule-Based_Ran_Transport
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Species (2)
Molecules (3)
Observables (7)
Applications (1)
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Parameters, Functions and Units
Pathway
VCell DB
BMDB
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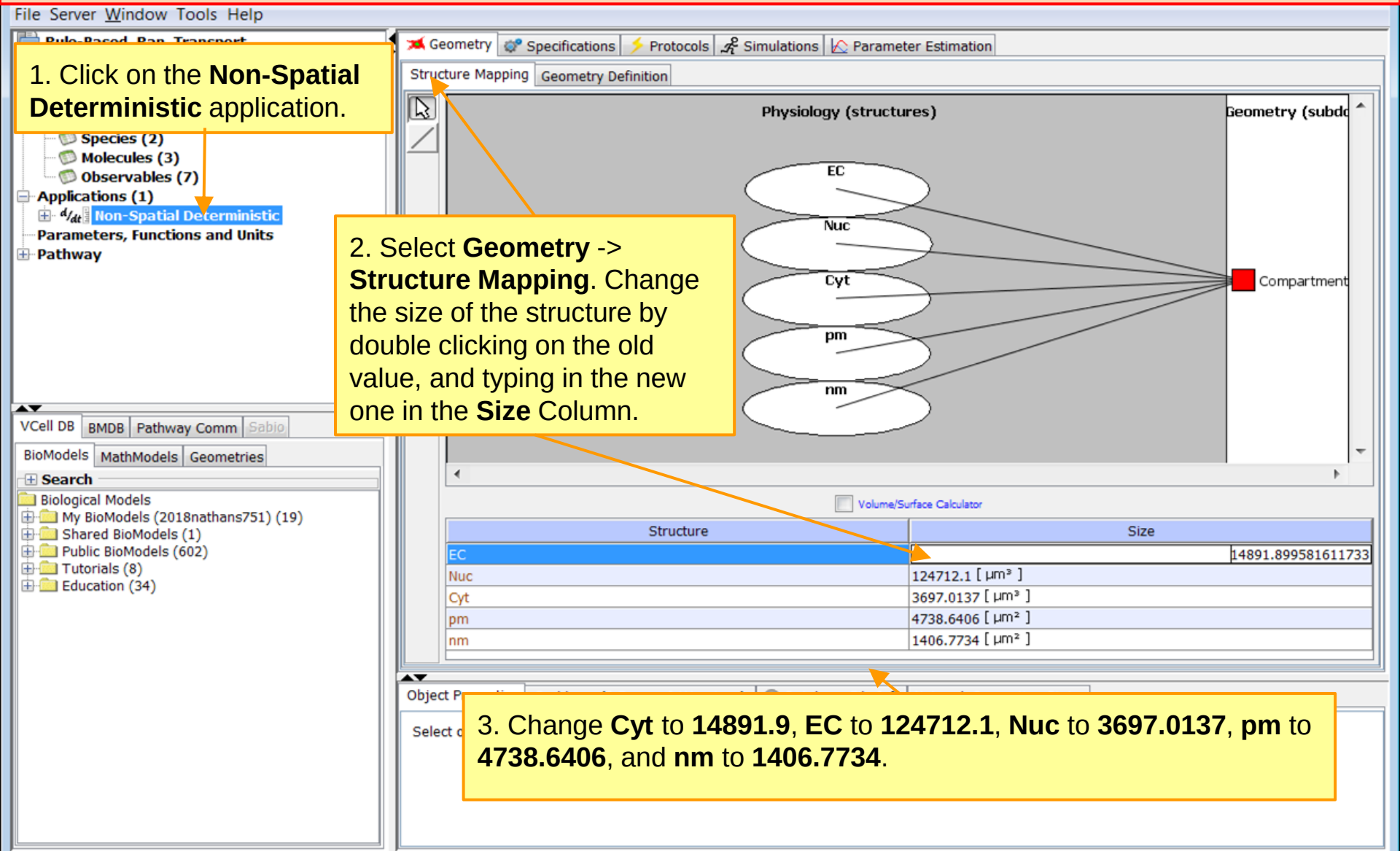
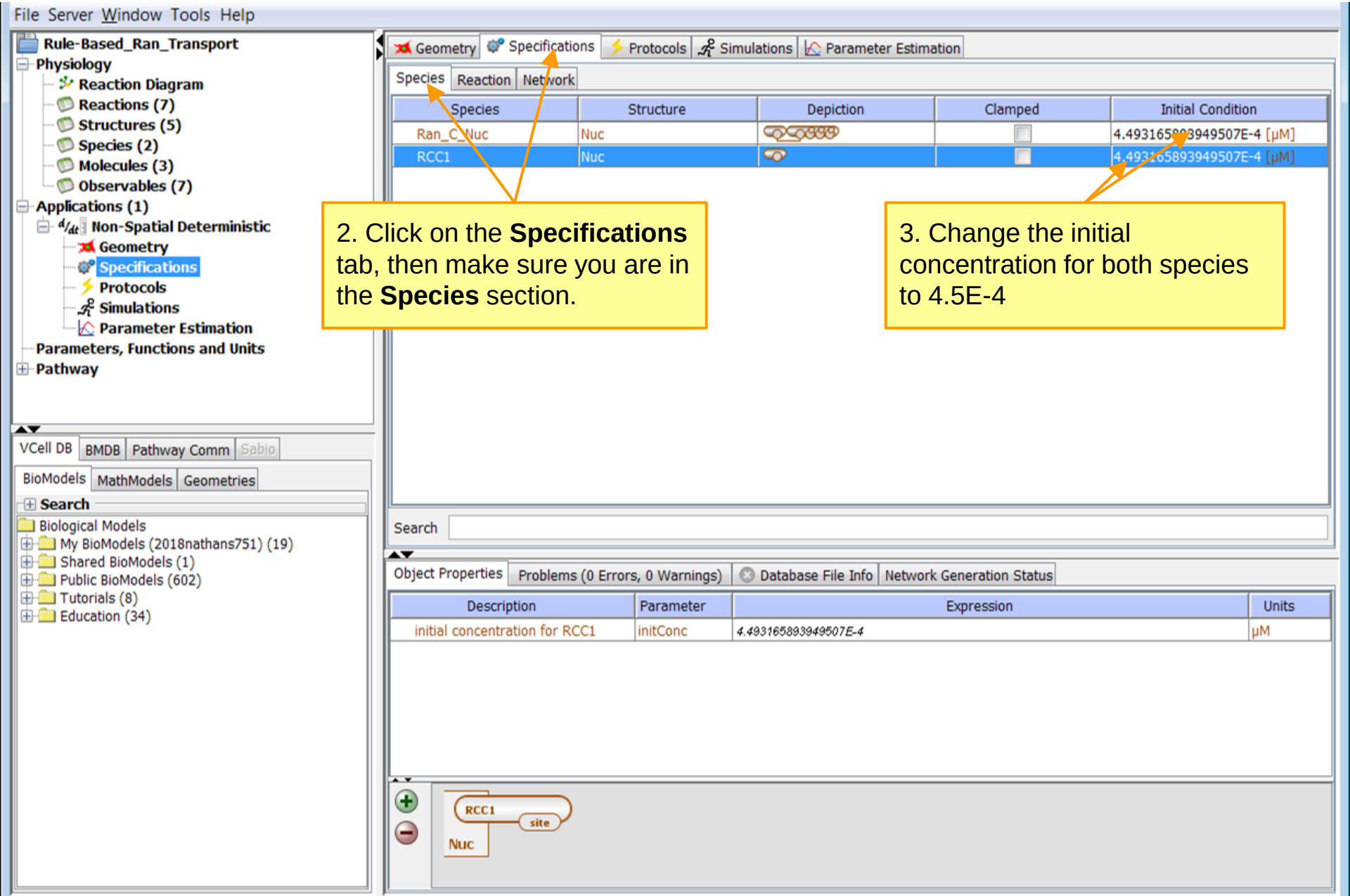
Name
Math Type
Annotation
Non-Spatial Deterministic
explicit network model, compartmental, determi...
1. Rename the application to Non-Spatial Deterministic by double clicking in the name box.
New Application
Delete
More Copy Actions
Compare...
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Application Name
Application0
Annotation
Summary
Deterministic
Compartmental
math not generated

TIP: The size values for this geometry are taken from the size of a real cell model that you will use later on. For deterministic applications the sizes are not that important. However, for stochastic applications, where values of species are specified with particle numbers, these sizes will be very important. They will be used to convert concentrations into particle numbers in a particular 3D geometry.




File Server Window Tools Help
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Structures (5)
Species (2)
Molecules (3)
Observables (7)
Applications (1)
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Parameters, Functions and Units
Pathway
Geometry
Specifications
Protocols
Simulations
Parameter Estimation
Species
Reaction
Network
Species
Structure
Depiction
Clamped
Initial Condition
Ran_C_Nuc
Nuc
4.4931658893949507E-4 [μM]
RCC1
Nuc
4.4931658893949507E-4 [μM]
2. Click on the Specifications tab, then make sure you are in the Species section.
3. Change the initial concentration for both species to 4.5E-4
VCell DB
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Pathway Comm
Sabio
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MathModels
Geometries
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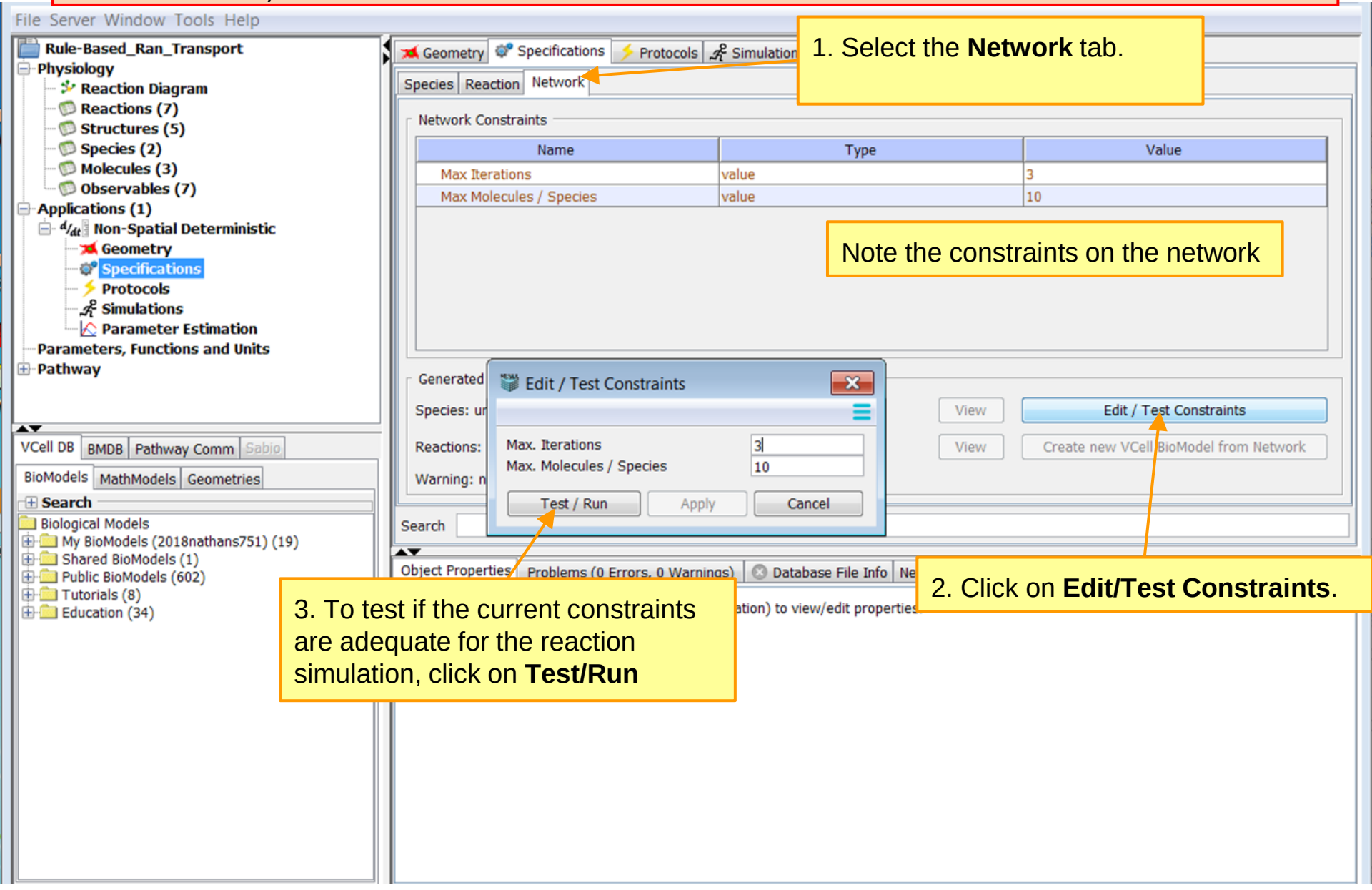
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Description
Parameter
Expression
Units
initial concentration for RCC1
initConc
4.4931658893949507E-4
μM
RCC1
site
Nuc

TIP: Creating a reaction network lets the computer do find all the possible permutations of reactions and species that are allowed by the reaction rules.

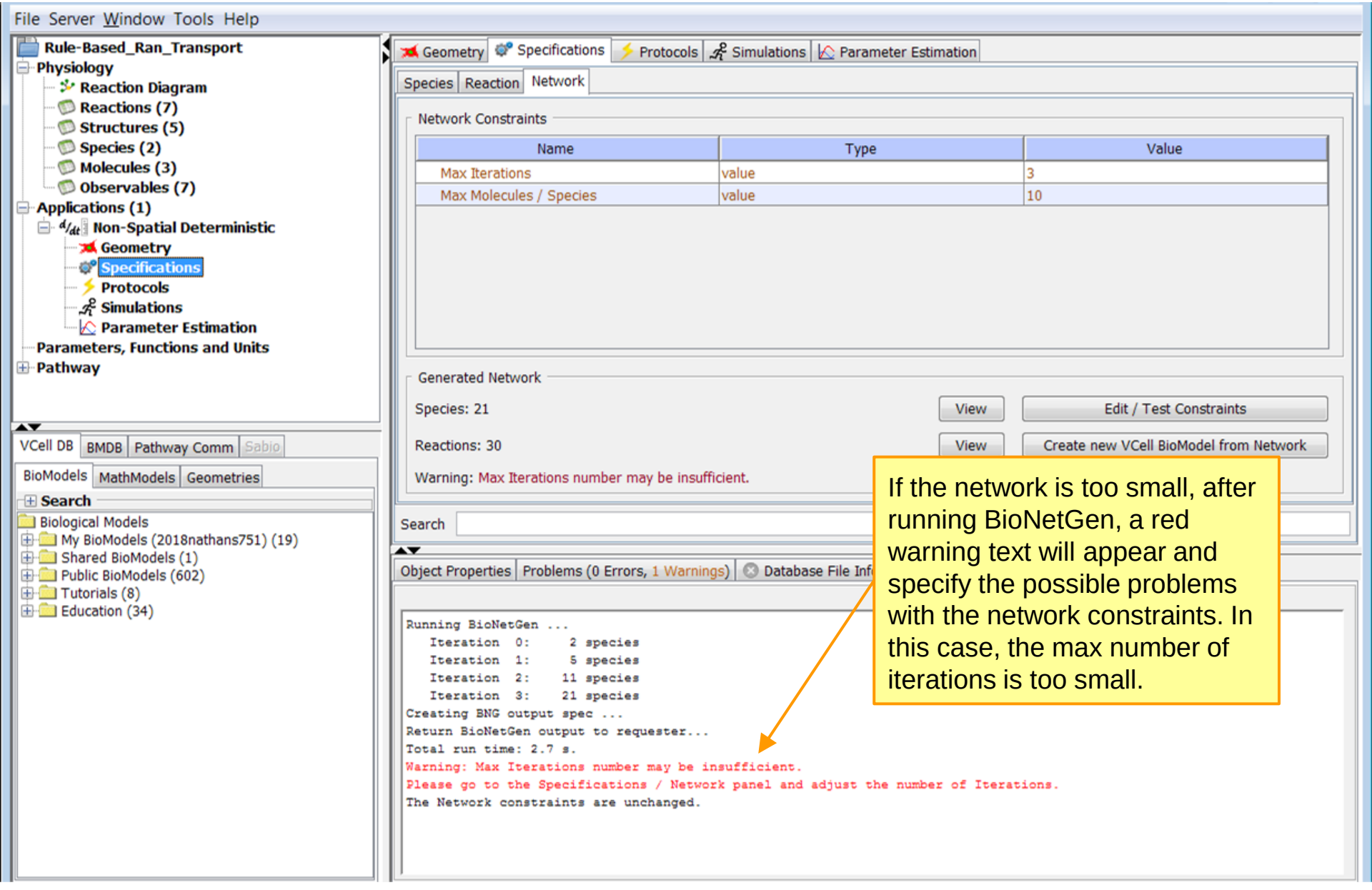


1. Select the **Network** tab.

Note the constraints on the network

2. Click on **Edit/Test Constraints**.

3. To test if the current constraints are adequate for the reaction simulation, click on **Test/Run**


File Server Window Tools Help
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Observables (7)
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Parameter Estimation
Species
Reaction
Network
Network Constraints
Name
Type
Value
Max Iterations
value
3
Max Molecules / Species
value
10
Generated Network
Species: 21
View
Edit / Test Constraints
Reactions: 30
View
Create new VCell BioModel from Network
Warning: Max Iterations number may be insufficient.
Search
VCell DB
BMDB
Pathway Comm
Sabio
BioModels
MathModels
Geometries
Search
Biological Models
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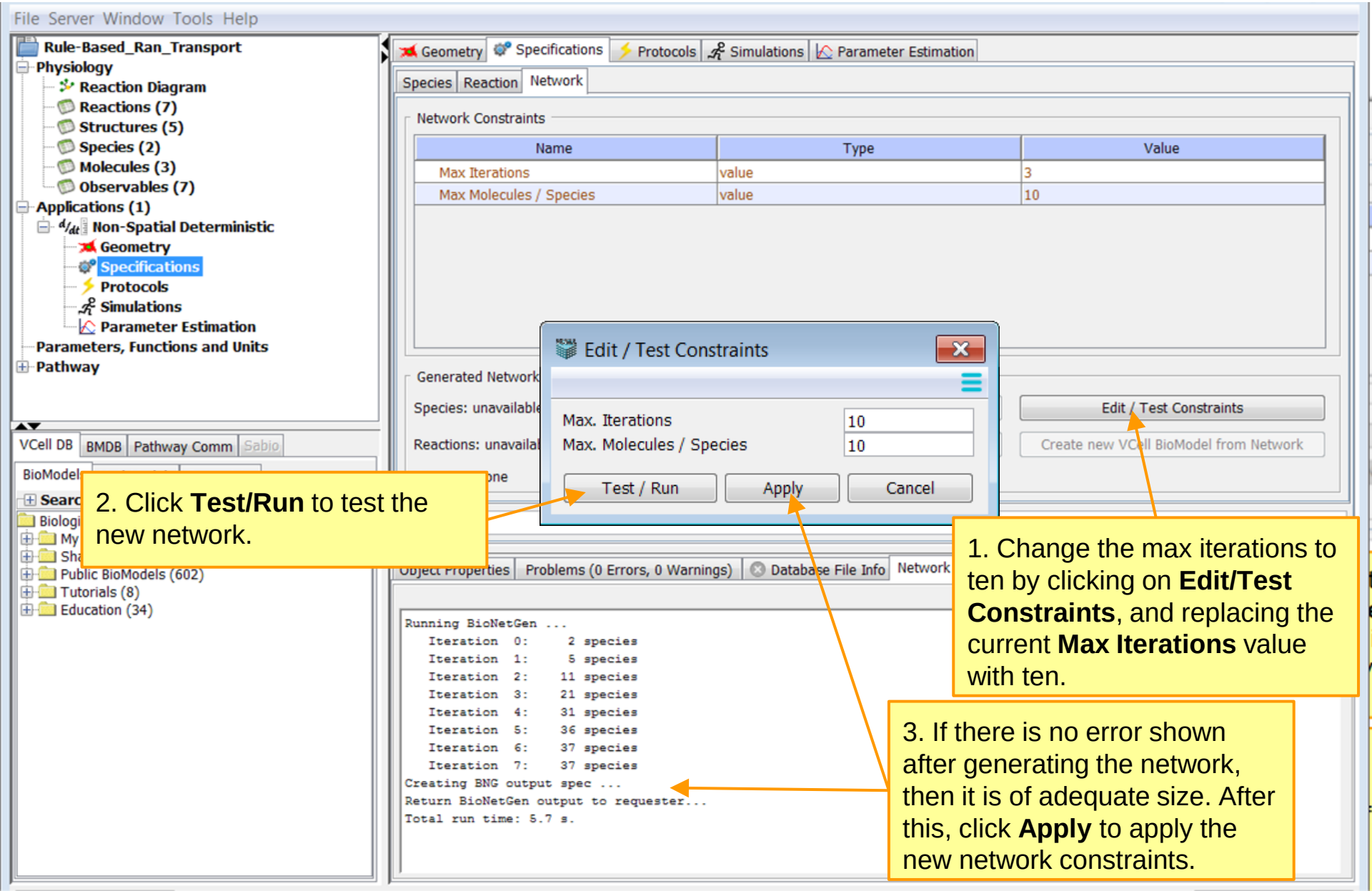
Shared BioModels (1)
Public BioModels (602)
Tutorials (8)
Education (34)
Object Properties
Problems (0 Errors, 1 Warnings)
Database File Inf
Running BioNetGen ...
Iteration 0: 2 species
Iteration 1: 5 species
Iteration 2: 11 species
Iteration 3: 21 species
Creating BNG output spec ...
Return BioNetGen output to requester...
Total run time: 2.7 s.
Warning: Max Iterations number may be insufficient.
Please go to the Specifications / Network panel and adjust the number of Iterations.
The Network constraints are unchanged.
If the network is too small, after running BioNetGen, a red warning text will appear and specify the possible problems with the network constraints. In this case, the max number of iterations is too small.


File Server Window Tools Help
Rule-Based_Ran_Transport
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Reactions (7)
Structures (5)
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Observables (7)
Applications (1)
Non-Spatial Deterministic
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Parameters, Functions and Units
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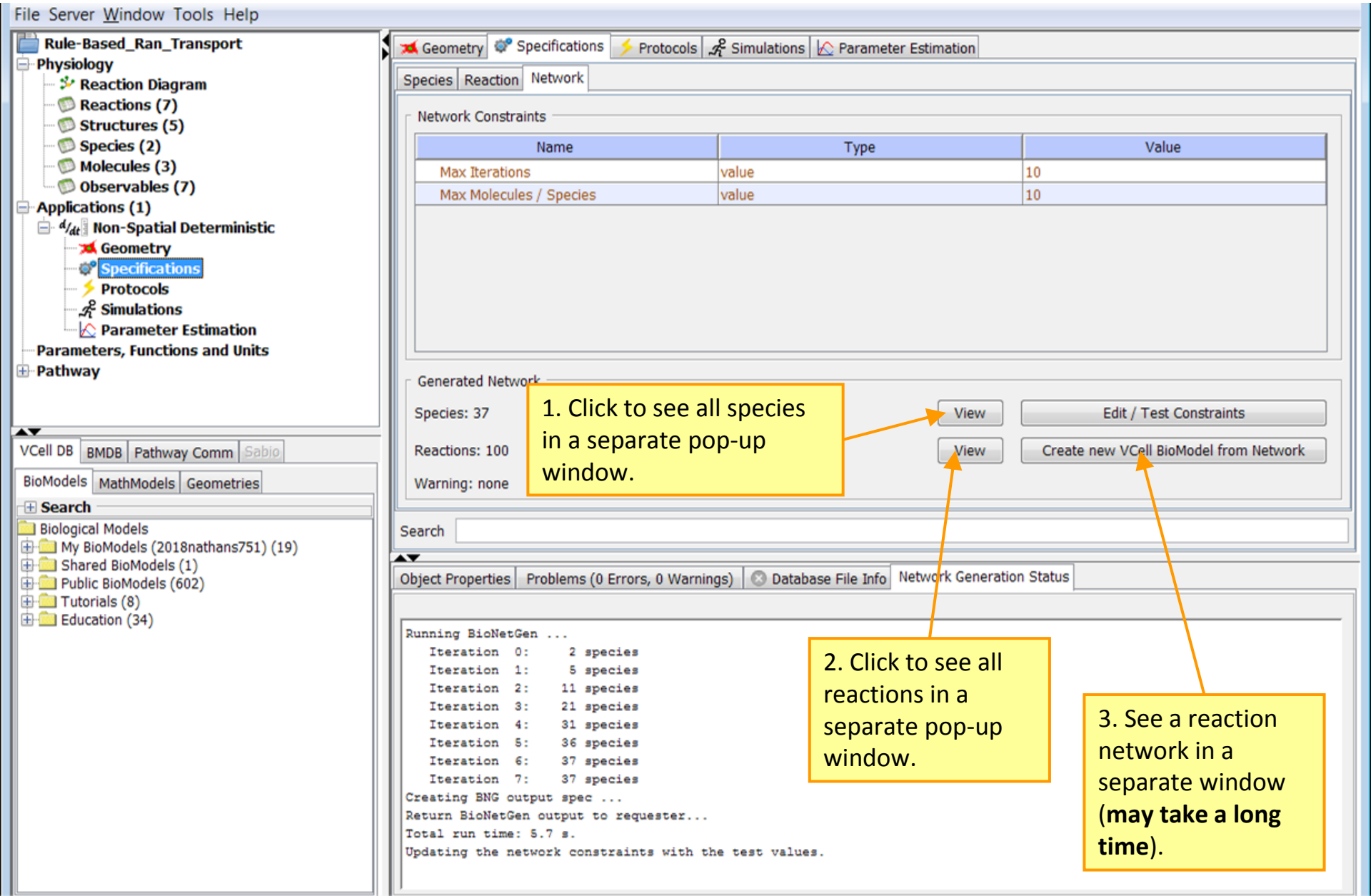
Specifications
Protocols
Simulations
Parameter Estimation
Species
Reaction
Network
Network Constraints
Name
Type
Value
Max Iterations
value
3
Max Molecules / Species
value
10
Edit / Test Constraints
Max. Iterations
10
Max. Molecules / Species
10
Test / Run
Apply
Cancel
Edit / Test Constraints
Create new VCell BioModel from Network
VCell DB
BMDB
Pathway Comm
Public BioModels (602)
Tutorials (8)
Education (34)
Problems (0 Errors, 0 Warnings)
Database File Info
Network
Running BioNetGen ...
Iteration 0: 2 species
Iteration 1: 5 species
Iteration 2: 11 species
Iteration 3: 21 species
Iteration 4: 31 species
Iteration 5: 36 species
Iteration 6: 37 species
Iteration 7: 37 species
Creating BNG output spec ...
Return BioNetGen output to requester...
Total run time: 5.7 s.
2. Click Test/Run to test the new network.
1. Change the max iterations to ten by clicking on Edit/Test Constraints, and replacing the current Max Iterations value with ten.
3. If there is no error shown after generating the network, then it is of adequate size. After this, click Apply to apply the new network constraints.


File Server Window Tools Help
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Specifications
Protocols
Simulations
Parameter Estimation
Species
Reaction
Network
Network Constraints
Name
Type
Value
Max Iterations
value
10
Max Molecules / Species
value
10
Generated Network
Species: 37
Reactions: 100
Warning: none
View
Edit / Test Constraints
View
Create new VCell BioModel from Network
1. Click to see all species in a separate pop-up window.
VCell DB
BMDB
Pathway Comm
Sabio
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MathModels
Geometries
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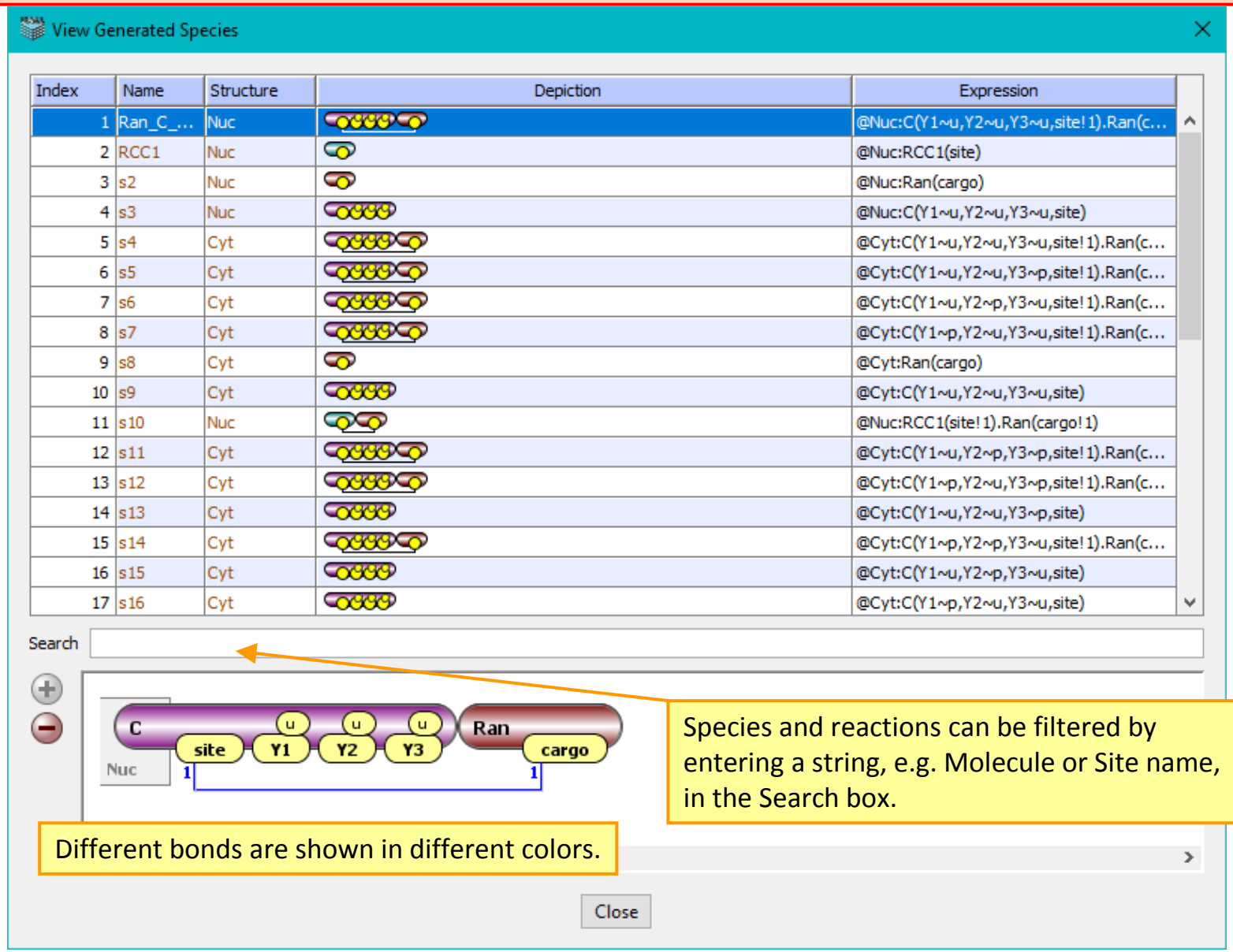
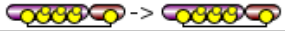
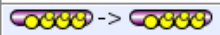
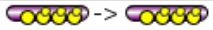
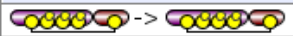
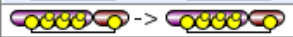
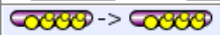
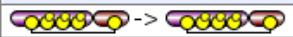
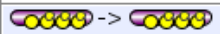
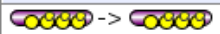
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Running BioNetGen ...
Iteration 0: 2 species
Iteration 1: 5 species
Iteration 2: 11 species
Iteration 3: 21 species
Iteration 4: 31 species
Iteration 5: 36 species
Iteration 6: 37 species
Iteration 7: 37 species
Creating BNG output spec ...
Return BioNetGen output to requester...
Total run time: 5.7 s.
Updating the network constraints with the test values.
2. Click to see all reactions in a separate pop-up window.
3. See a reaction network in a separate window (may take a long time).

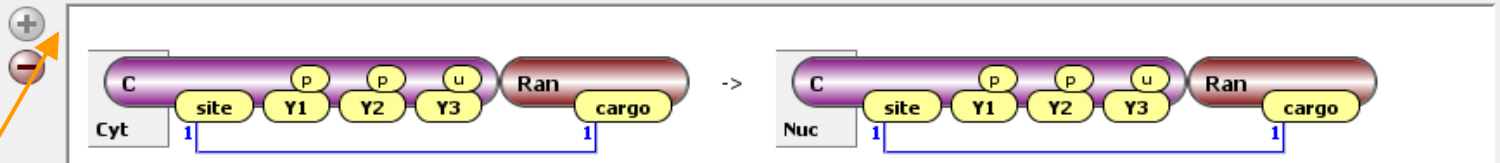
TIP: Filtering is very useful to verify the model. If you see that names of Molecules and Sites are too generic for efficient filtering – go back and change them. This is an easy and safe procedure, but you will need to rerun network generation. After the network is verified, it can be simulated.



View Generated Reactions

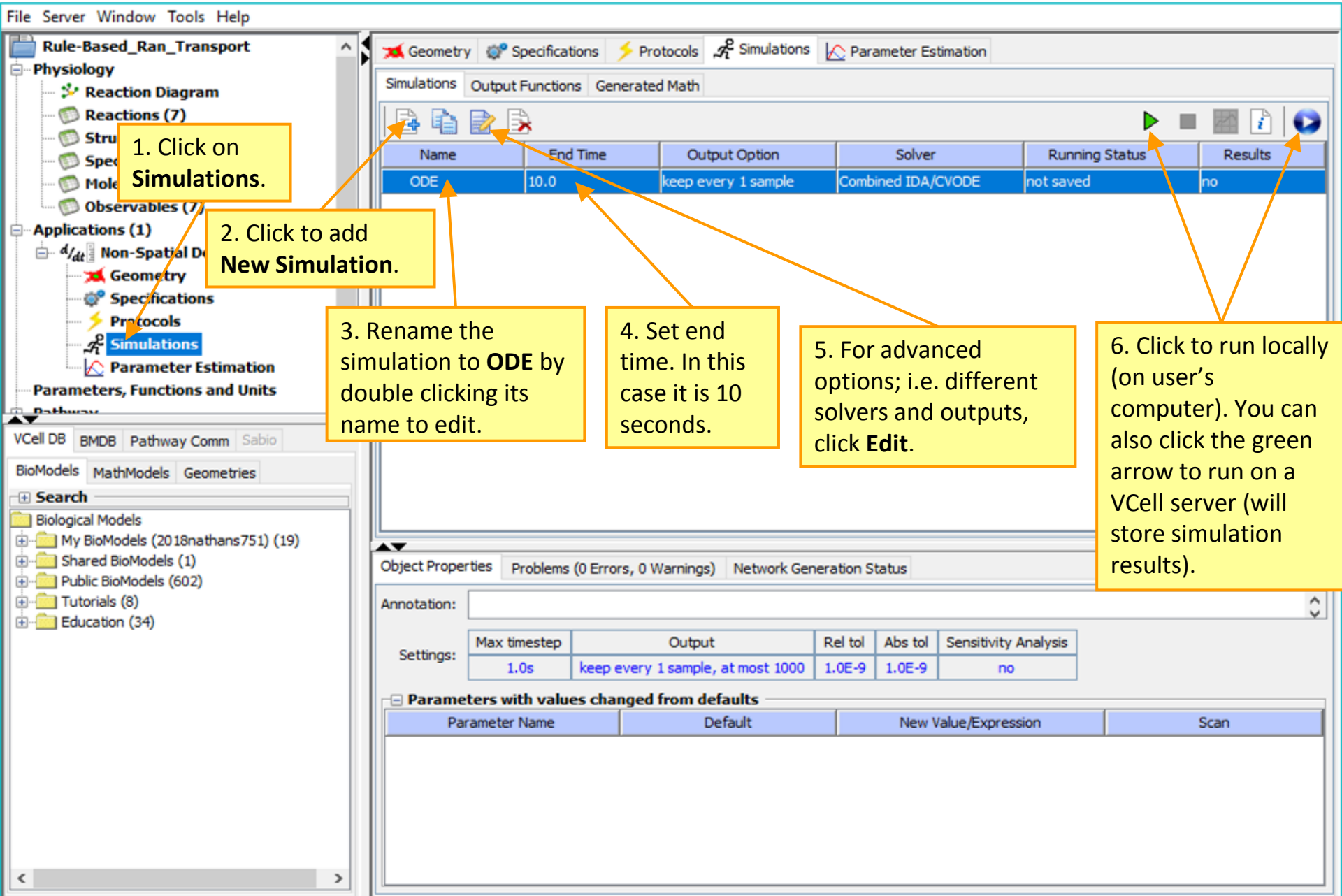
Index	Rule	Structure	Depiction	Expression
1	C_p1	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
2	C_p1	Cyt		@Cyt:C(Y1~u,Y2~p,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
3	C_p1	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
4	C_p1	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~u,site) -> @Cyt:C(Y1~u,Y2~u,Y3~p,site)
5	C_p1	Cyt		@Cyt:C(Y1~p,Y2~p,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
6	C_p1	Cyt		@Cyt:C(Y1~u,Y2~p,Y3~u,site) -> @Cyt:C(Y1~u,Y2~p,Y3~p,site)
7	C_p1	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~u,site) -> @Cyt:C(Y1~p,Y2~u,Y3~p,site)
8	C_p1	Cyt		@Cyt:C(Y1~p,Y2~p,Y3~u,site) -> @Cyt:C(Y1~p,Y2~p,Y3~p,site)
9	C_p1 (rev)	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
10	C_p1 (rev)	Cyt		@Cyt:C(Y1~u,Y2~p,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
11	C_p1 (rev)	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
12	C_p1 (rev)	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~p,site) -> @Cyt:C(Y1~u,Y2~u,Y3~u,site)
13	C_p1 (rev)	Cyt		@Cyt:C(Y1~p,Y2~p,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
14	C_p1 (rev)	Cyt		@Cyt:C(Y1~u,Y2~p,Y3~p,site) -> @Cyt:C(Y1~u,Y2~p,Y3~u,site)
15	C_p1 (rev)	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~p,site) -> @Cyt:C(Y1~p,Y2~u,Y3~u,site)
16	C_p1 (rev)	Cyt		@Cyt:C(Y1~p,Y2~p,Y3~p,site) -> @Cyt:C(Y1~p,Y2~p,Y3~u,site)
17	C_p2	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
18	C_p2	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~u,Y...
19	C_p2	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~u,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
20	C_p2	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~u,site) -> @Cyt:C(Y1~u,Y2~p,Y3~u,site)
21	C_p2	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~p,site!1).Ran(cargo!1) -> @Cyt:C(Y1~p,Y...
22	C_p2	Cyt		@Cyt:C(Y1~u,Y2~u,Y3~p,site) -> @Cyt:C(Y1~u,Y2~p,Y3~p,site)
23	C_p2	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~u,site) -> @Cyt:C(Y1~p,Y2~p,Y3~u,site)
24	C_p2	Cyt		@Cyt:C(Y1~p,Y2~u,Y3~p,site) -> @Cyt:C(Y1~p,Y2~p,Y3~p,site)

Search



Use this button if a reaction is too long and does not fit on the screen.

Close


File Server Window Tools Help
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Physiology
Reaction Diagram
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Observables (7)
Applications (1)
Geometry
Specifications
Protocols
Simulations
Parameter Estimation
Parameters, Functions and Units
Geometry Specifications Protocols Simulations Parameter Estimation
Simulations Output Functions Generated Math
Name End Time Output Option Solver Running Status Results
ODE 10.0 keep every 1 sample Combined IDA/CVODE not saved no
1. Click on Simulations.
2. Click to add New Simulation.
3. Rename the simulation to ODE by double clicking its name to edit.
4. Set end time. In this case it is 10 seconds.
5. For advanced options; i.e. different solvers and outputs, click Edit.
6. Click to run locally (on user's computer). You can also click the green arrow to run on a VCell server (will store simulation results).
VCell DB BMDB Pathway Comm Sabio
BioModels MathModels Geometries
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My BioModels (2018nathans751) (19)
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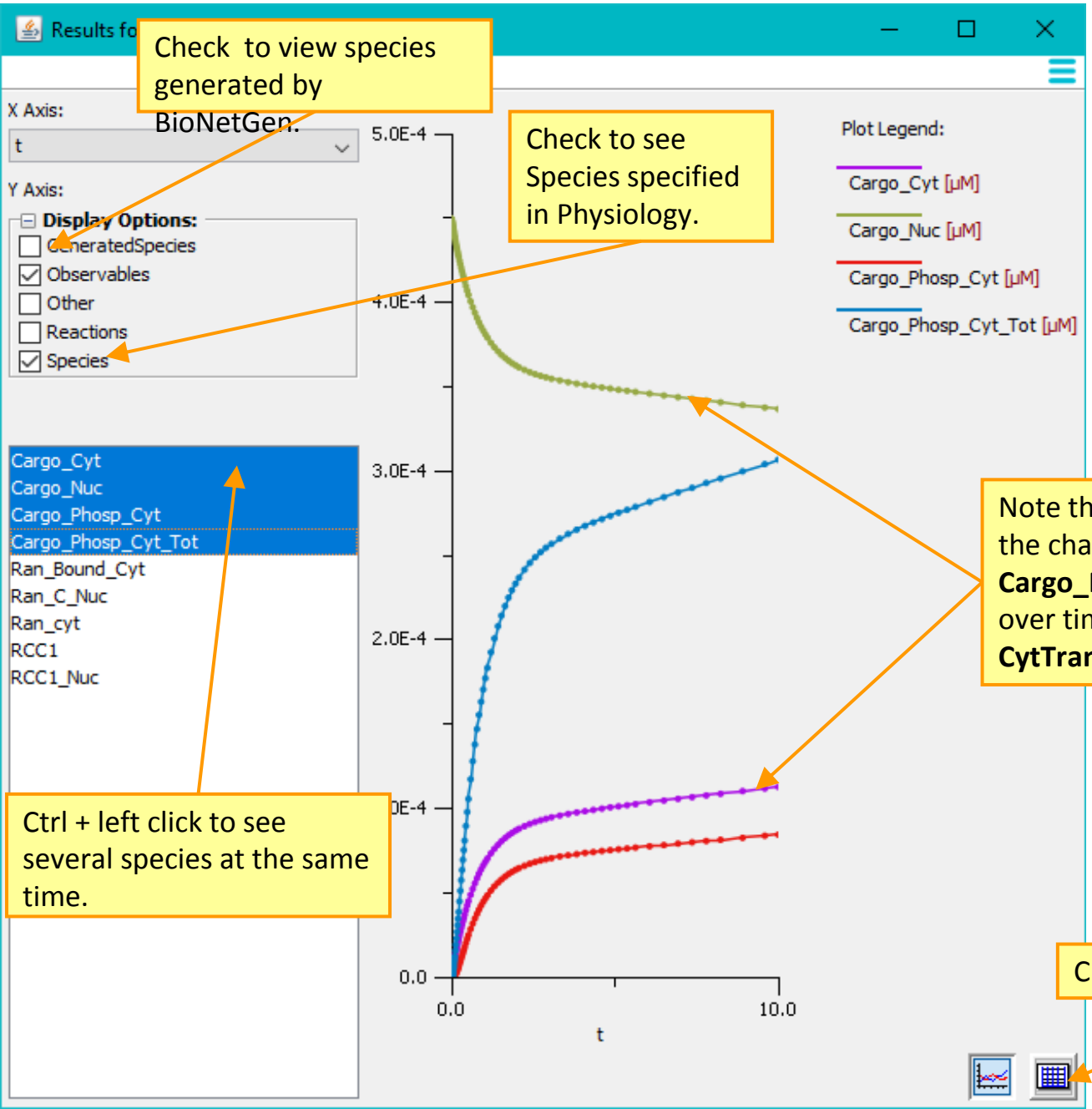
Education (34)
Object Properties Problems (0 Errors, 0 Warnings) Network Generation Status
Annotation:
Settings:
Max timestep Output Rel tol Abs tol Sensitivity Analysis
1.0s keep every 1 sample, at most 1000 1.0E-9 1.0E-9 no
Parameters with values changed from defaults
Parameter Name Default New Value/Expression Scan

Rule Based Ran Transport VCell Tutorial (6.1): Applications: Non-Spatial Deterministic

TIP1: Generated species are listed by index (s10, s11, …). The molecular composition of species can be seen under **Specification > Network > View Species**.

TIP2: **Reactions** show fluxes through individual reactions generated by each rule.



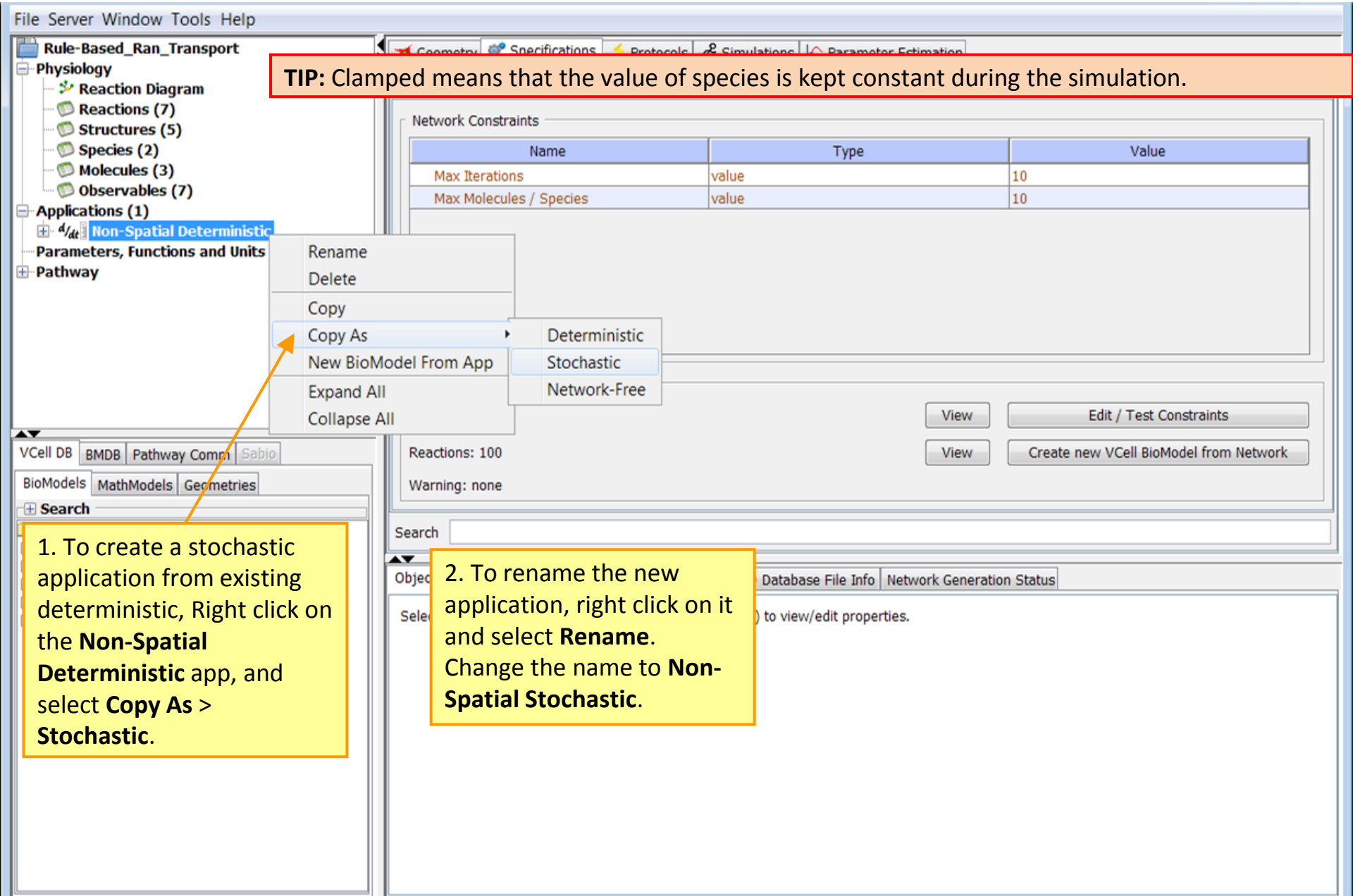
Check to view species generated by BioNetGen.

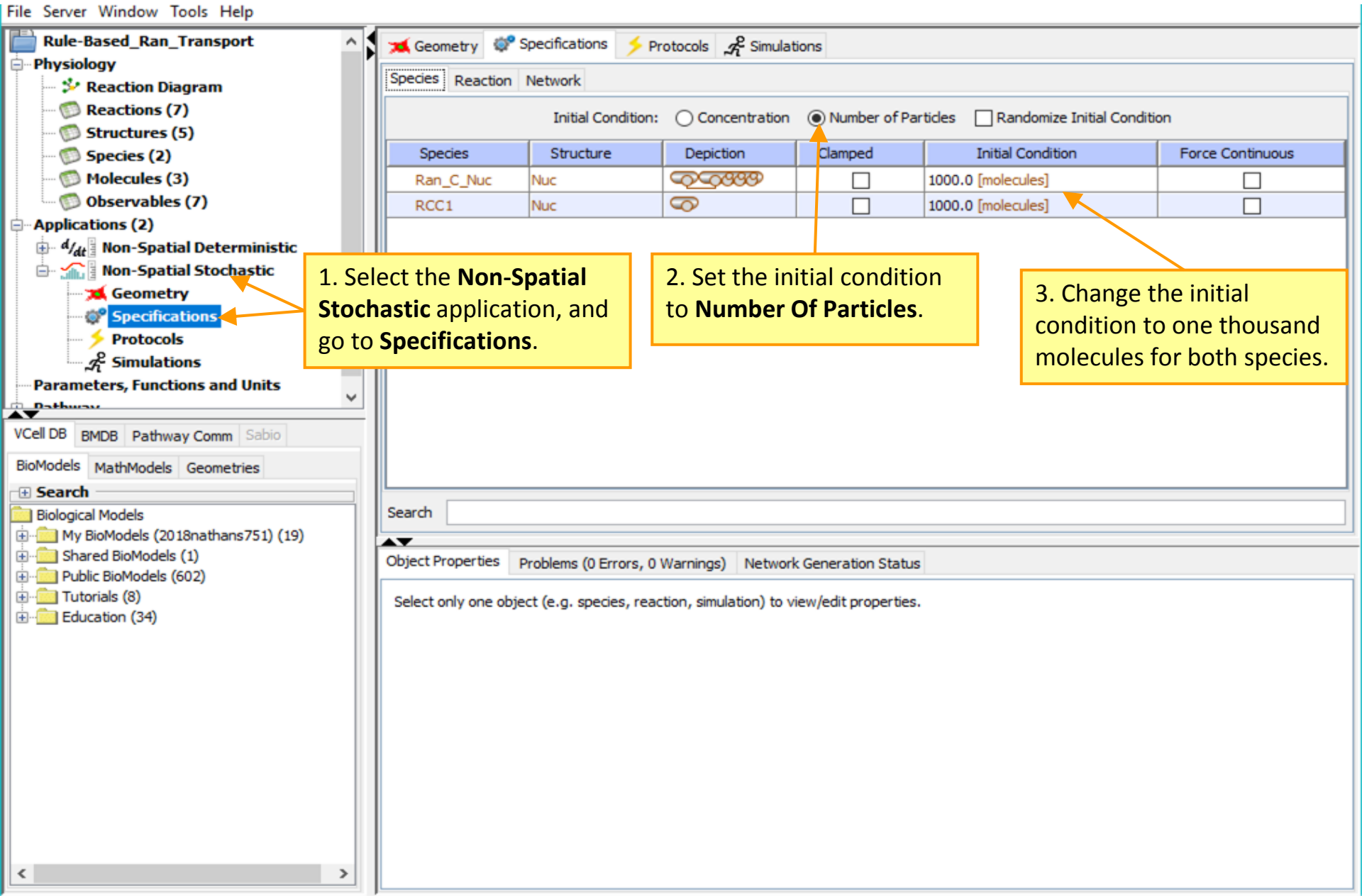
Check to see Species specified in Physiology.

Note the correlation between the changes in population of **Cargo_Nuc** and **Cargo_Cyt** over time due to the **CytTransport** reaction.

Ctrl + left click to see several species at the same time.

Click to see numerical values.


File Server Window Tools Help
Rule-Based_Ran_Transport
Physiology
Reaction Diagram
Reactions (7)
Structures (5)
Species (2)
Molecules (3)
Observables (7)
Applications (1)
Non-Spatial Deterministic
Parameters, Functions and Units
Pathway
TIP: Clamped means that the value of species is kept constant during the simulation.
Network Constraints
Name
Type
Value
Max Iterations
value
10
Max Molecules / Species
value
10
Rename
Delete
Copy
Copy As
New BioModel From App
Expand All
Collapse All
Deterministic
Stochastic
Network-Free
View
Edit / Test Constraints
Reactions: 100
View
Create new VCell BioModel from Network
Warning: none
VCell DB
BMDB
Pathway Comm
Sabio
BioModels
MathModels
Geometries
Search
Search
Database File Info
Network Generation Status
to view/edit properties.
1. To create a stochastic application from existing deterministic, Right click on the Non-Spatial Deterministic app, and select Copy As > Stochastic.
2. To rename the new application, right click on it and select Rename. Change the name to Non-Spatial Stochastic.


File Server Window Tools Help
Rule-Based_Ran_Transport
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Reaction Diagram
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Structures (5)
Species (2)
Molecules (3)
Observables (7)
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Non-Spatial Stochastic
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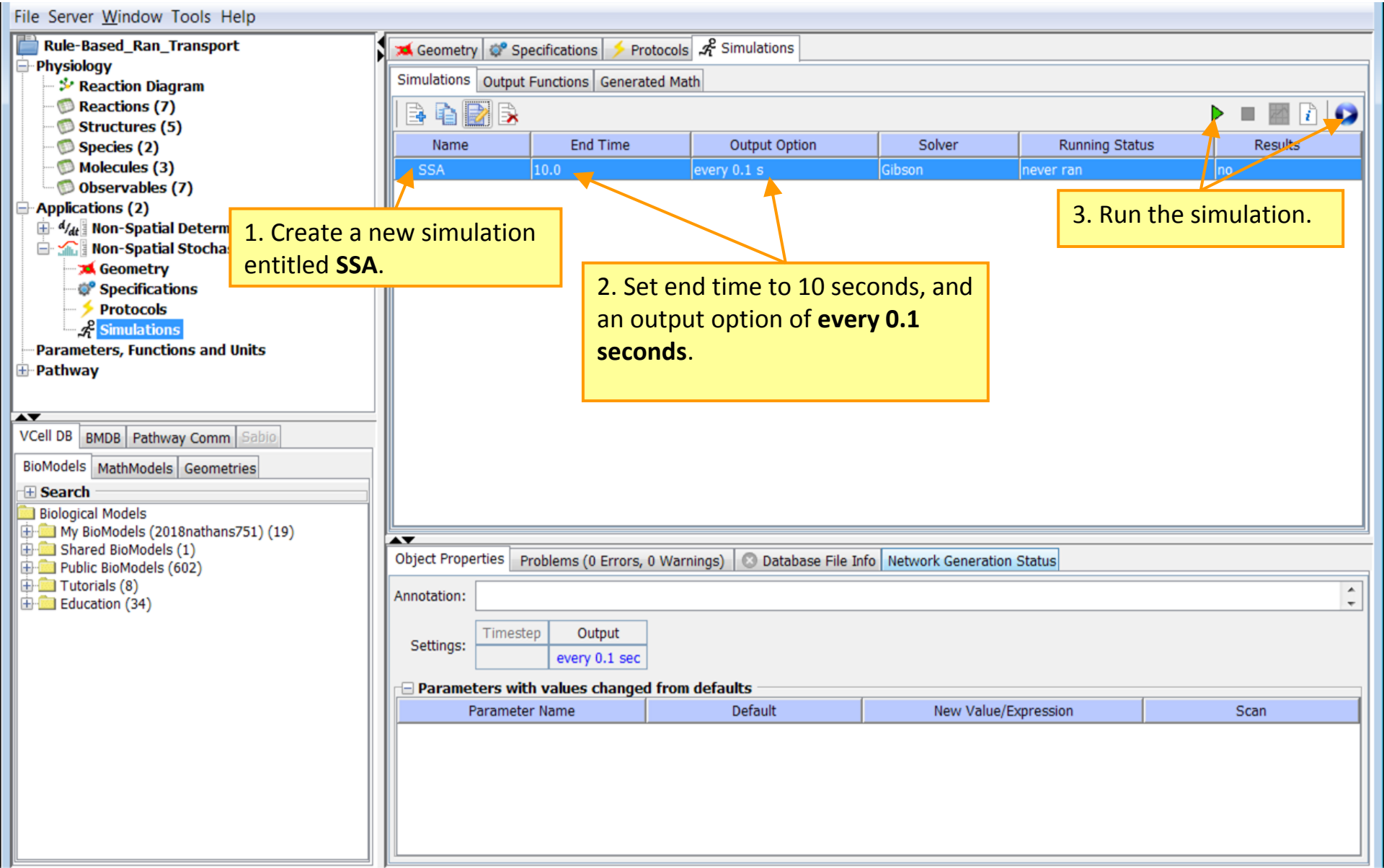
Species
Reaction
Network
Initial Condition:
Concentration
Number of Particles
Randomize Initial Condition
Species
Structure
Depiction
Clamped
Initial Condition
Force Continuous
Ran_C_Nuc
Nuc
1000.0 [molecules]
RCC1
Nuc
1000.0 [molecules]
Search
Object Properties
Problems (0 Errors, 0 Warnings)
Network Generation Status
Select only one object (e.g. species, reaction, simulation) to view/edit properties.
1. Select the Non-Spatial Stochastic application, and go to Specifications.
2. Set the initial condition to Number Of Particles.
3. Change the initial condition to one thousand molecules for both species.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Rule-Based_Ran_Transport
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Species (2)
Molecules (3)
Observables (7)
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Non-Spatial Stocha
Geometry
Specifications
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Simulations
Parameters, Functions and Units
Pathway
Geometry
Specifications
Protocols
Simulations
Simulations
Output Functions
Generated Math
Name
End Time
Output Option
Solver
Running Status
Results
SSA
10.0
every 0.1 s
Gibson
never ran
no
1. Create a new simulation entitled SSA.
2. Set end time to 10 seconds, and an output option of every 0.1 seconds.
3. Run the simulation.
VCell DB
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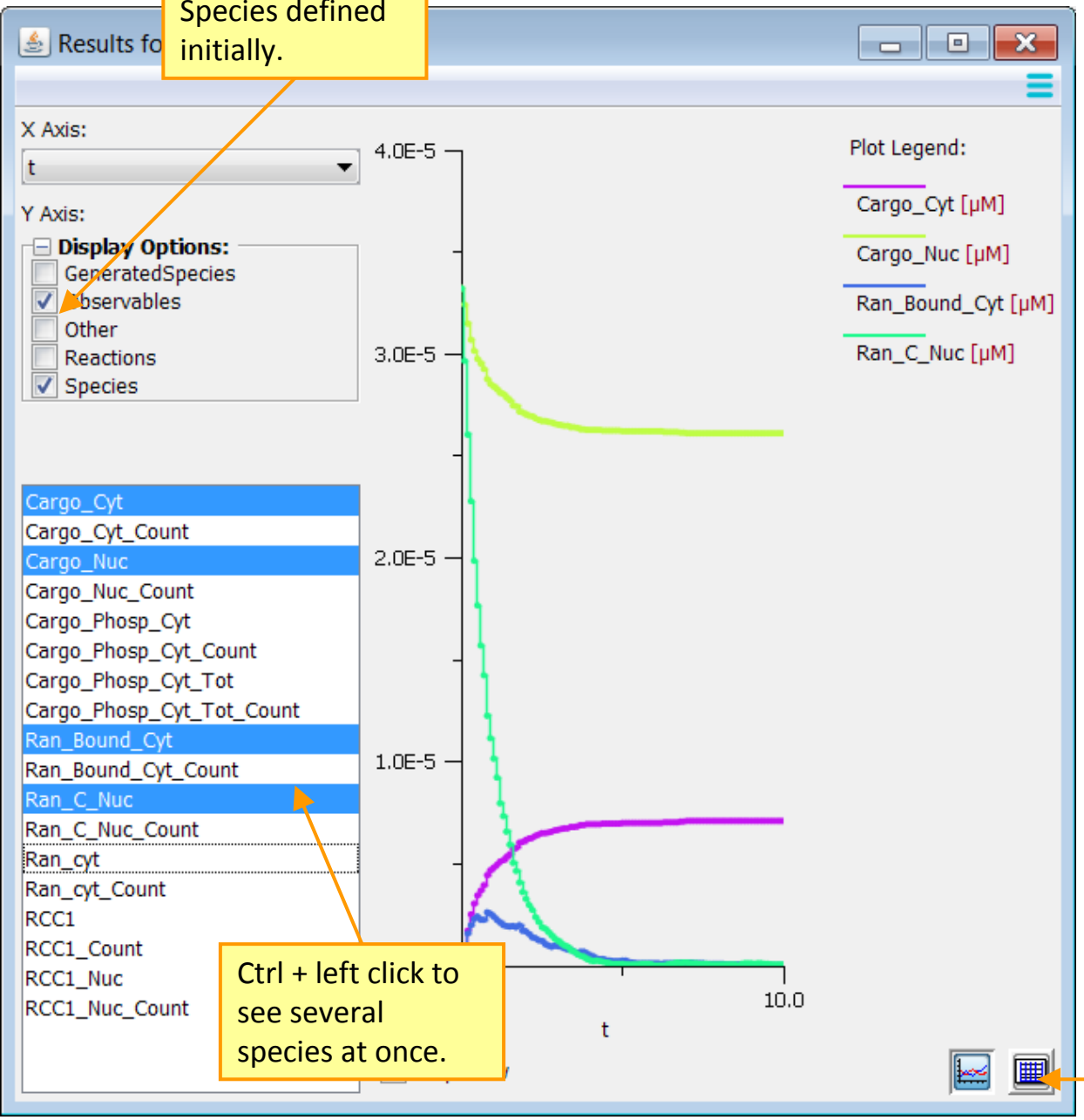
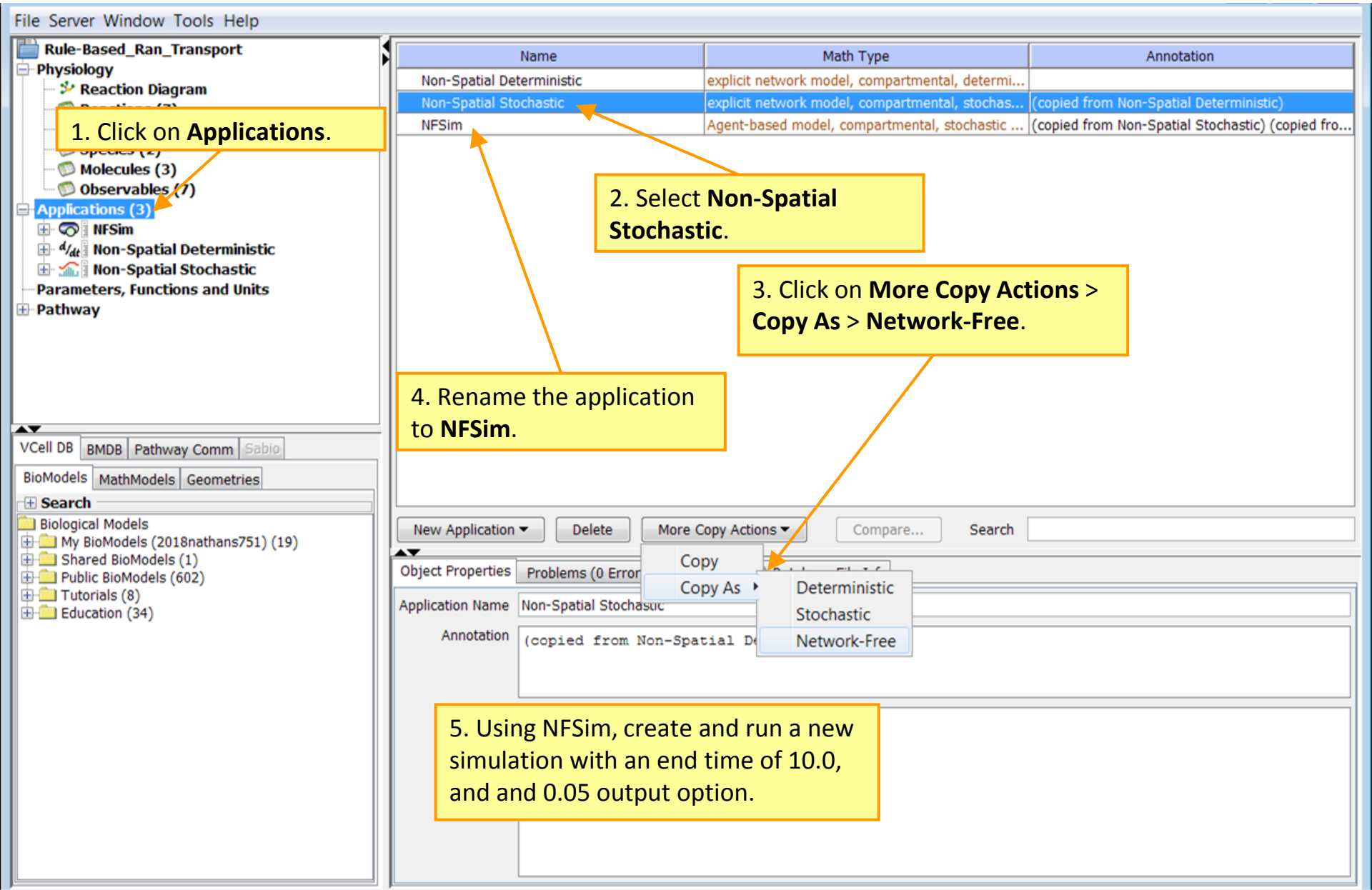
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Annotation:
Settings:
Timestep
Output
every 0.1 sec
Parameters with values changed from defaults
Parameter Name
Default
New Value/Expression
Scan



TIP: Take into account the scale of the graph. These graphs can sometimes be misleading and make certain plots look much more significant than they are. Additionally, when two or more plots are selected, one may look like a flat line due to scaling. Hover over the plot and check the x and y values to make sure.


File Server Window Tools Help
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Reaction Diagram
Molecules (3)
Observables (7)
Applications (3)
NFSim
Non-Spatial Deterministic
Non-Spatial Stochastic
Parameters, Functions and Units
Pathway
1. Click on Applications.
Name
Math Type
Annotation
Non-Spatial Deterministic
explicit network model, compartmental, determi...
Non-Spatial Stochastic
explicit network model, compartmental, stochas...
(copied from Non-Spatial Deterministic)
NFSim
Agent-based model, compartmental, stochastic ...
(copied from Non-Spatial Stochastic) (copied fro...
2. Select Non-Spatial Stochastic.
3. Click on More Copy Actions > Copy As > Network-Free.
4. Rename the application to NFSim.
VCell DB
BMDB
Pathway Comm
Sabio
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MathModels
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Search
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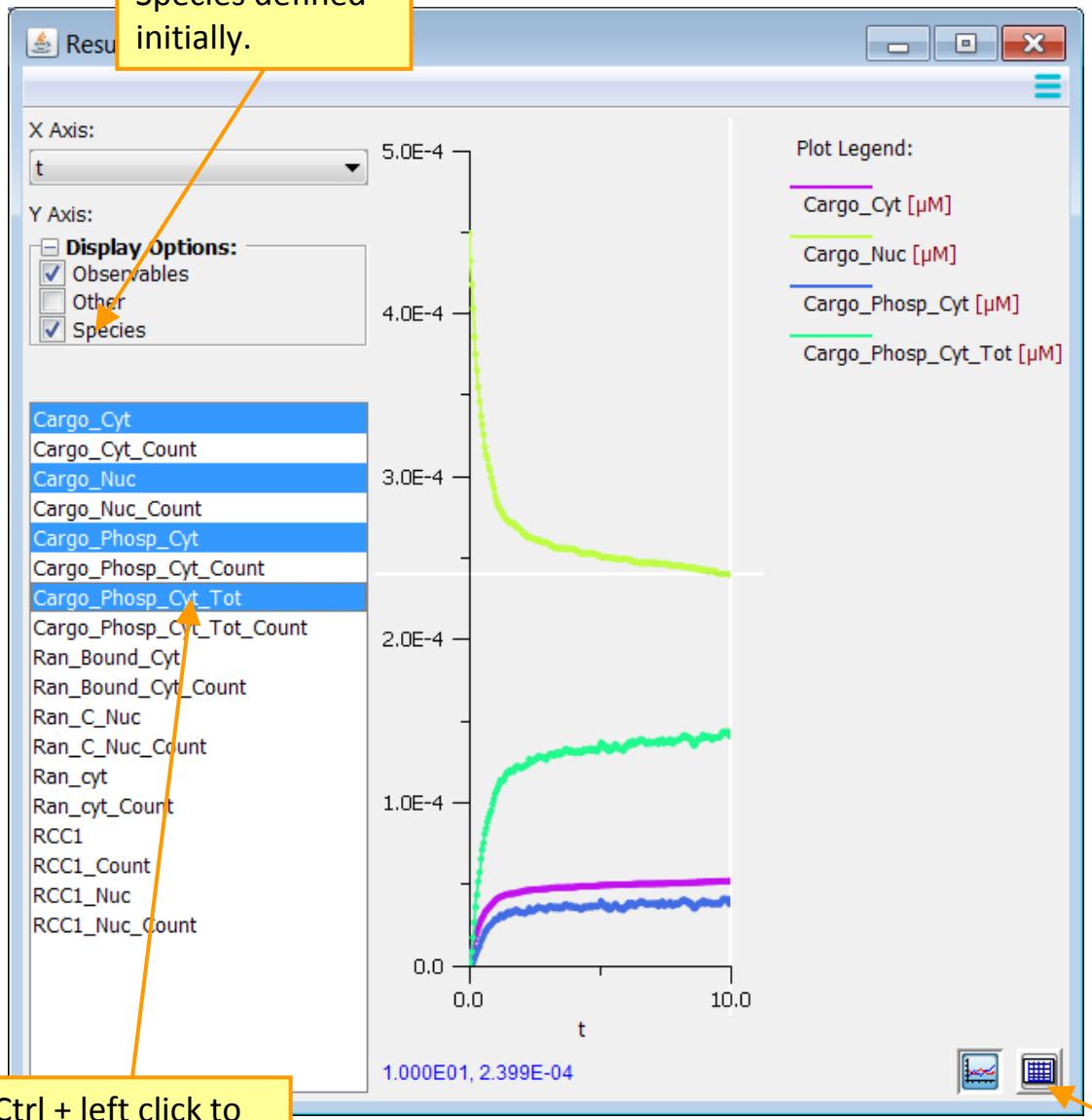
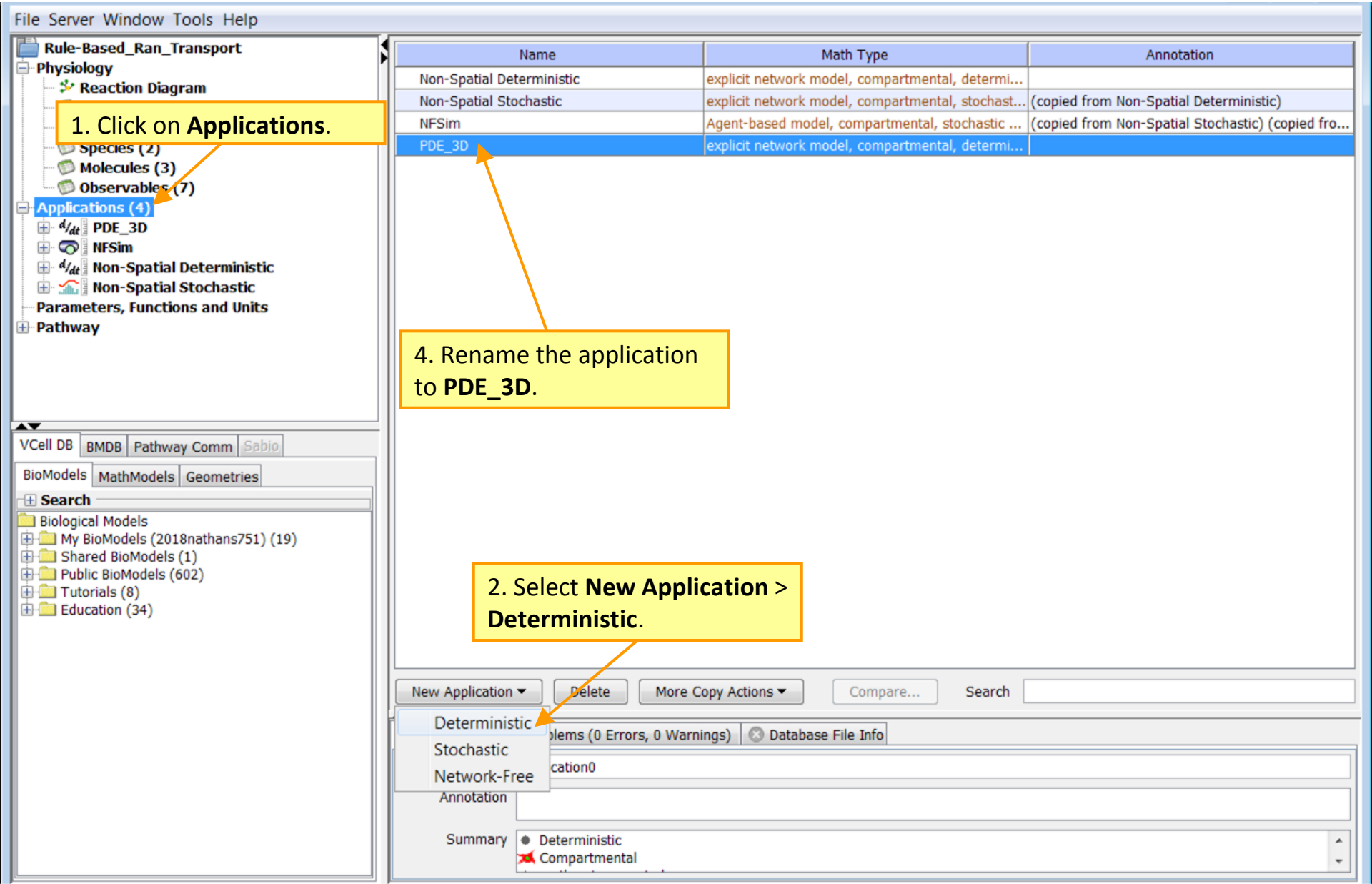
New Application
Delete
More Copy Actions
Compare...
Search
Copy
Copy As
Deterministic
Stochastic
Network-Free
Object Properties
Problems (0 Error
Application Name
Non-Spatial Stochastic
Annotation
(copied from Non-Spatial De
5. Using NFSim, create and run a new simulation with an end time of 10.0, and and 0.05 output option.

Select to list Species defined initially.



Ctrl + left click to see several species at once.

Click to see numerical values


File Server Window Tools Help
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Molecules (3)
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Applications (4)
PDE_3D
NFSim
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Non-Spatial Stochastic
Parameters, Functions and Units
Pathway
1. Click on Applications.
Name
Math Type
Annotation
Non-Spatial Deterministic
explicit network model, compartmental, determi...
Non-Spatial Stochastic
explicit network model, compartmental, stochast...
(copied from Non-Spatial Deterministic)
NFSim
Agent-based model, compartmental, stochastic ...
(copied from Non-Spatial Stochastic) (copied fro...
PDE_3D
explicit network model, compartmental, determi...
4. Rename the application to PDE_3D.
2. Select New Application > Deterministic.
New Application
Delete
More Copy Actions
Compare...
Search
Deterministic
Stochastic
Network-Free
Database File Info
Annotation
Summary
Deterministic
Compartmental
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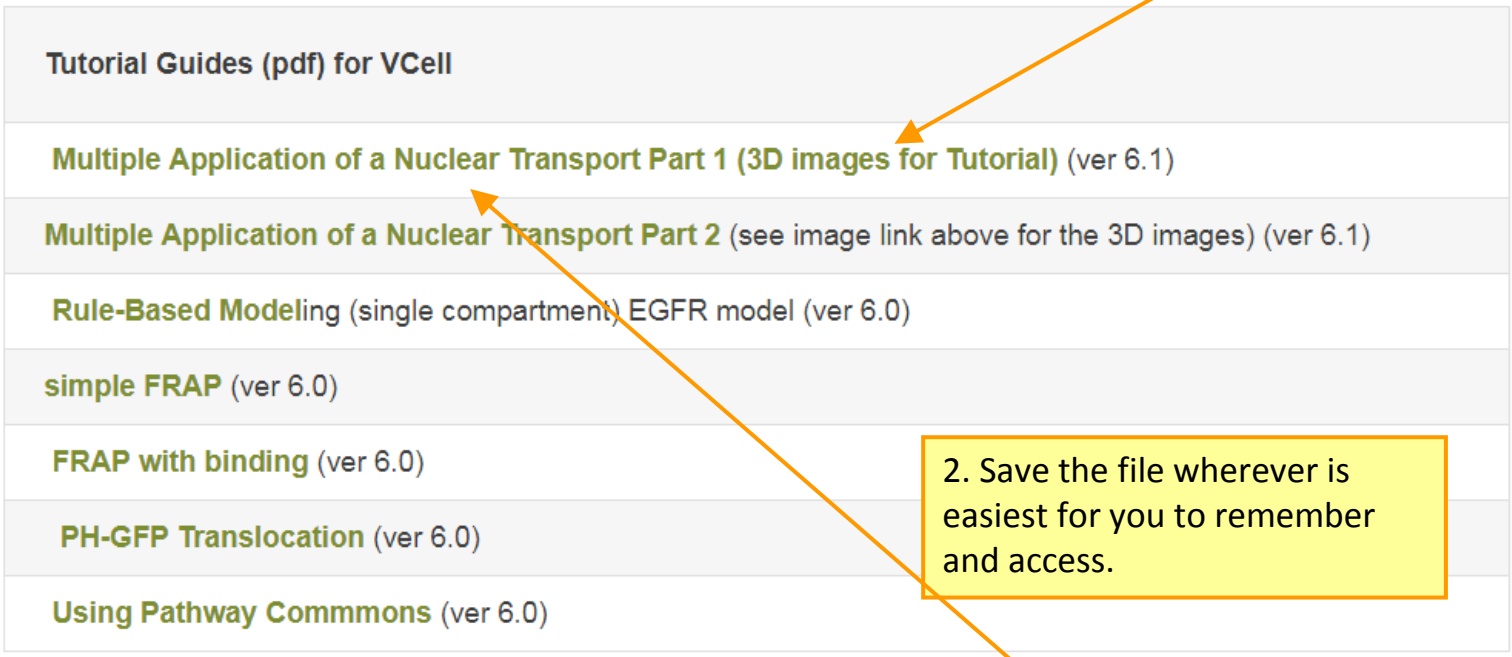
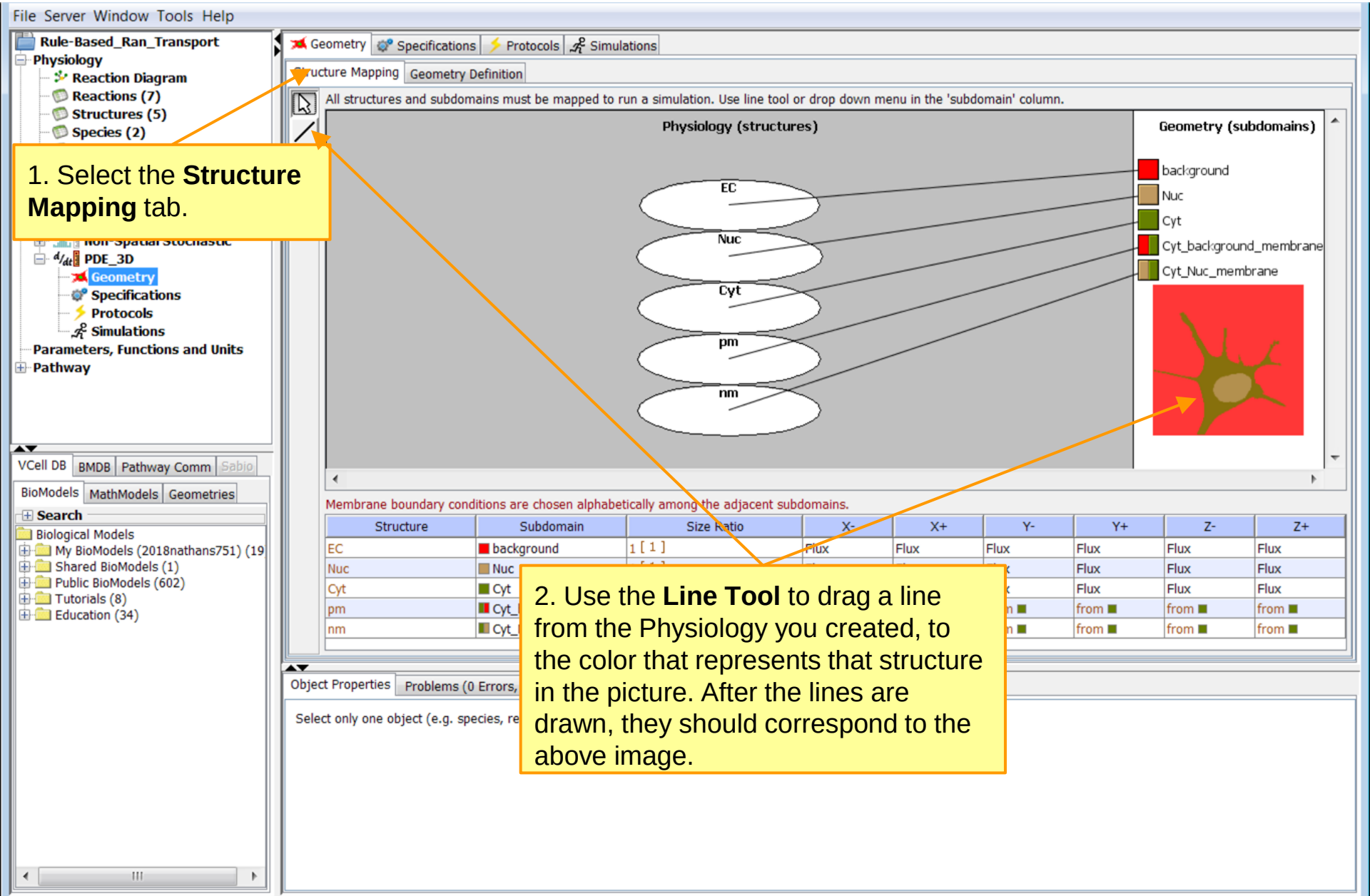
1. Go to http://vcell.org/support-2, and click **(3D Images for Tutorial)** to download the necessary geometry for this application.



2. Save the file wherever is easiest for you to remember and access.

3. Use this tutorial to create a spatial geometry. Don't worry if your numbers for volumes and membrane sizes will be a bit off.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PDE_3D
Geometry
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Simulations
Structure Mapping
Geometry Definition
All structures and subdomains must be mapped to run a simulation. Use line tool or drop down menu in the 'subdomain' column.
Physiology (structures)
EC
Nuc
Cyt
pm
nm
Geometry (subdomains)
background
Nuc
Cyt
Cyt_background_membrane
Cyt_Nuc_membrane
Membrane boundary conditions are chosen alphabetically among the adjacent subdomains.
Structure
Subdomain
Size Ratio
X-
X+
Y-
Y+
Z-
Z+
EC
background
1 [1]
Flux
Nuc
Cyt
pm
nm
from
VCell DB
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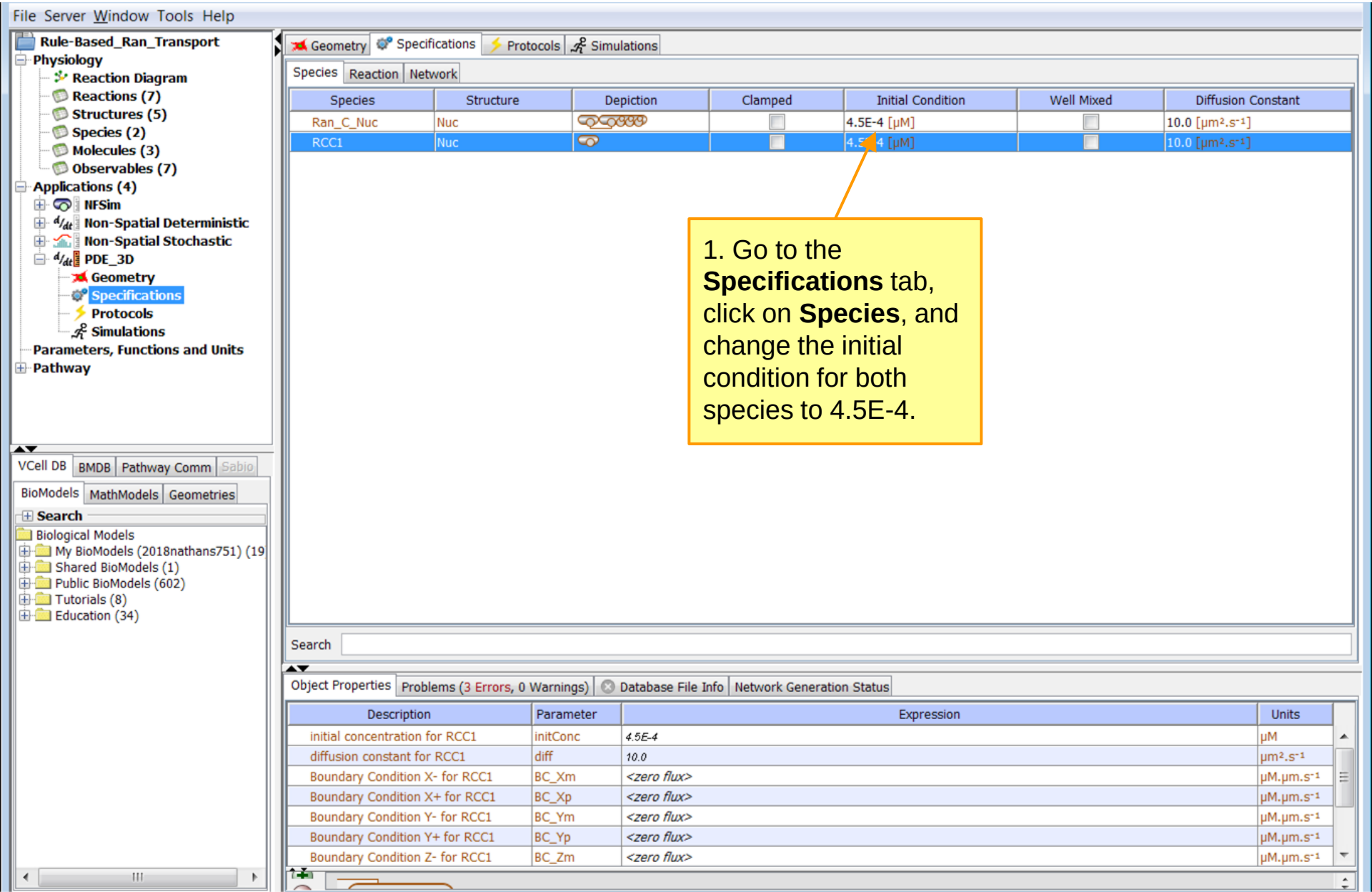
Object Properties
Problems (0 Errors,
Select only one object (e.g. species, re
1. Select the Structure Mapping tab.
2. Use the Line Tool to drag a line from the Physiology you created, to the color that represents that structure in the picture. After the lines are drawn, they should correspond to the above image.


File Server Window Tools Help
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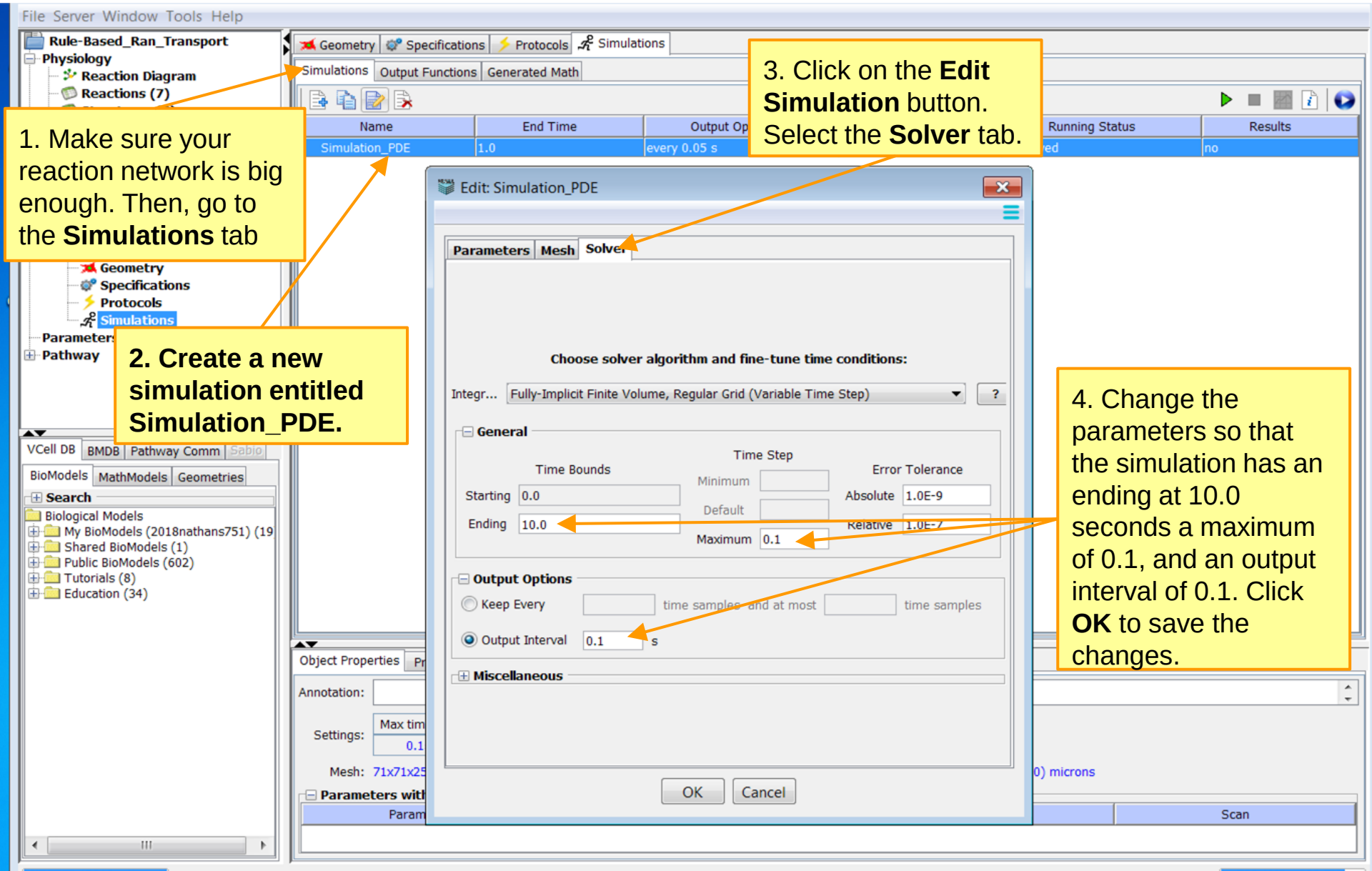
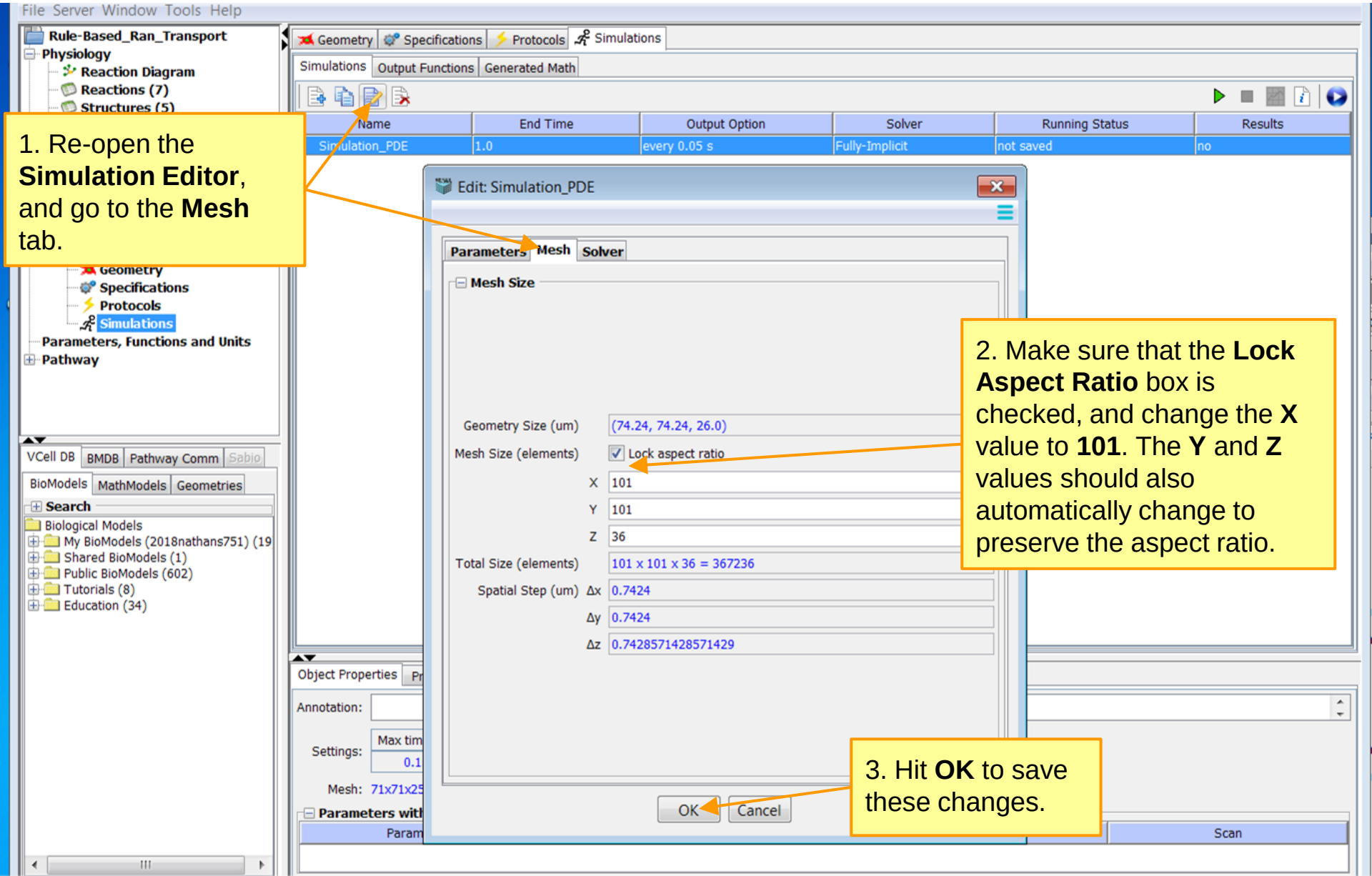
Reaction
Network
Species
Structure
Depiction
Clamped
Initial Condition
Well Mixed
Diffusion Constant
Ran_C_Nuc
Nuc
4.5E-4 [μM]
10.0 [μm².s⁻¹]
RCC1
Nuc
10.0 [μm².s⁻¹]
1. Go to the Specifications tab, click on Species, and change the initial condition for both species to 4.5E-4.
Search
Object Properties
Problems (3 Errors, 0 Warnings)
Database File Info
Network Generation Status
Description
Parameter
Expression
Units
initial concentration for RCC1
initConc
4.5E-4
μM
diffusion constant for RCC1
diff
10.0
μm².s⁻¹
Boundary Condition X- for RCC1
BC_Xm
<zero flux>
μM.μm.s⁻¹
Boundary Condition X+ for RCC1
BC_Xp
<zero flux>
μM.μm.s⁻¹
Boundary Condition Y- for RCC1
BC_Ym
<zero flux>
μM.μm.s⁻¹
Boundary Condition Y+ for RCC1
BC_Yp
<zero flux>
μM.μm.s⁻¹
Boundary Condition Z- for RCC1
BC_Zm
<zero flux>
μM.μm.s⁻¹


1. Make sure your reaction network is big enough. Then, go to the **Simulations** tab
2. Create a new simulation entitled Simulation_PDE.
3. Click on the **Edit Simulation** button. Select the **Solver** tab.
4. Change the parameters so that the simulation has an ending at 10.0 seconds a maximum of 0.1, and an output interval of 0.1. Click **OK** to save the changes.
Edit: Simulation_PDE
Parameters
Mesh
Solver
Choose solver algorithm and fine-tune time conditions:
Fully-Implicit Finite Volume, Regular Grid (Variable Time Step)
General
Time Bounds
Starting 0.0
Ending 10.0
Time Step
Minimum
Default
Maximum 0.1
Error Tolerance
Absolute 1.0E-9
Output Options
Keep Every
time samples and at most
time samples
Output Interval 0.1 s
Miscellaneous
OK
Cancel


1. Re-open the **Simulation Editor**, and go to the **Mesh** tab.
2. Make sure that the **Lock Aspect Ratio** box is checked, and change the **X** value to **101**. The **Y** and **Z** values should also automatically change to preserve the aspect ratio.
3. Hit **OK** to save these changes.
Edit: Simulation_PDE
Parameters
Mesh
Solver
Mesh Size
Geometry Size (um)
(74.24, 74.24, 26.0)
Mesh Size (elements)
Lock aspect ratio
X
101
Y
101
Z
36
Total Size (elements)
101 x 101 x 36 = 367236
Spatial Step (um) Δx
0.7424
Δy
0.7424
Δz
0.7428571428571429
OK
Cancel
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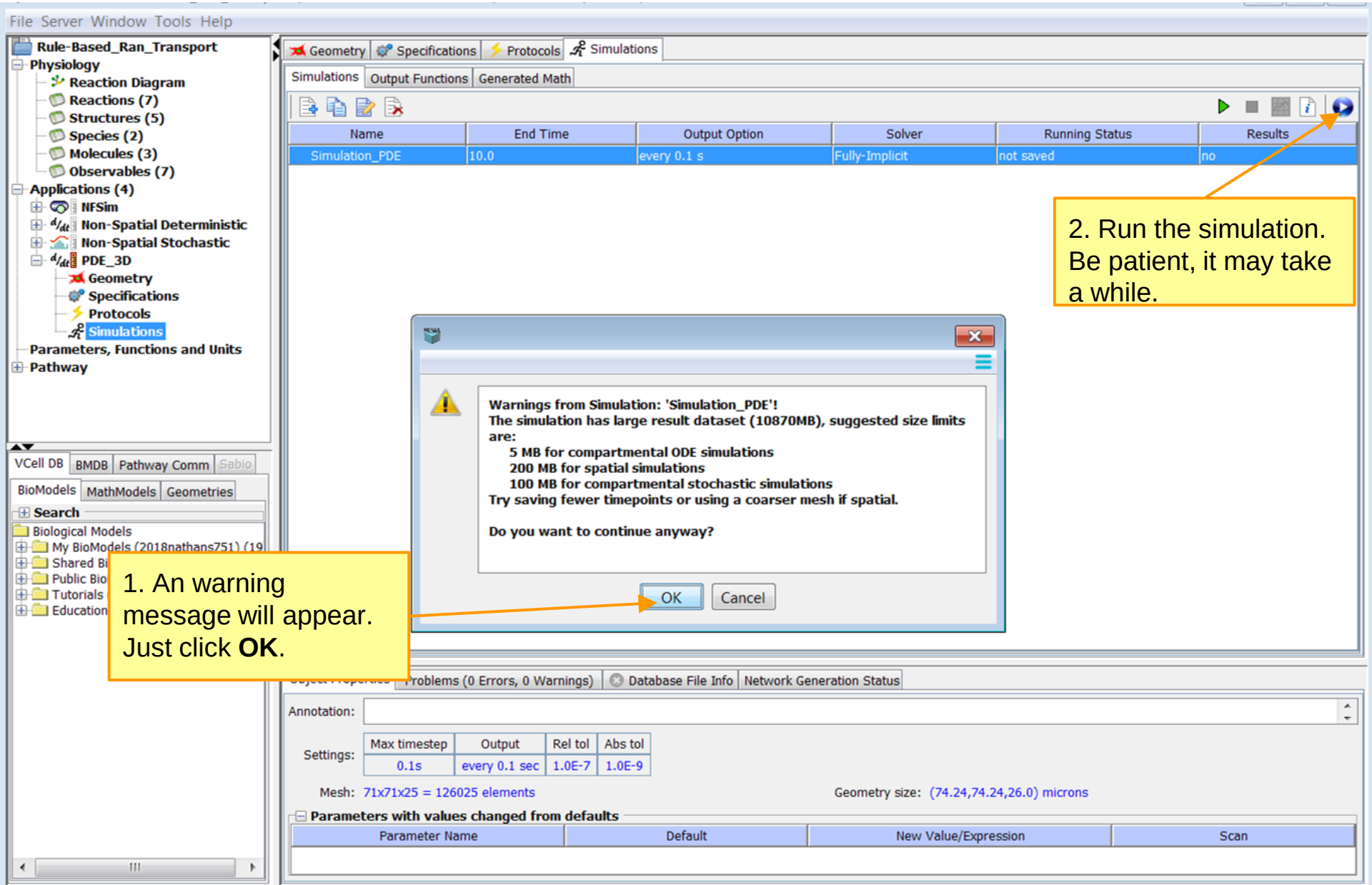
Simulation_PDE
1.0
every 0.05 s
Fully-Implicit
not saved
no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Simulation_PDE
10.0
every 0.1 s
Fully-Implicit
not saved
no
2. Run the simulation. Be patient, it may take a while.
Warnings from Simulation: 'Simulation_PDE'!
The simulation has large result dataset (10870MB), suggested size limits are:
5 MB for compartmental ODE simulations
200 MB for spatial simulations
100 MB for compartmental stochastic simulations
Try saving fewer timepoints or using a coarser mesh if spatial.
Do you want to continue anyway?
OK
Cancel
1. An warning message will appear. Just click OK.
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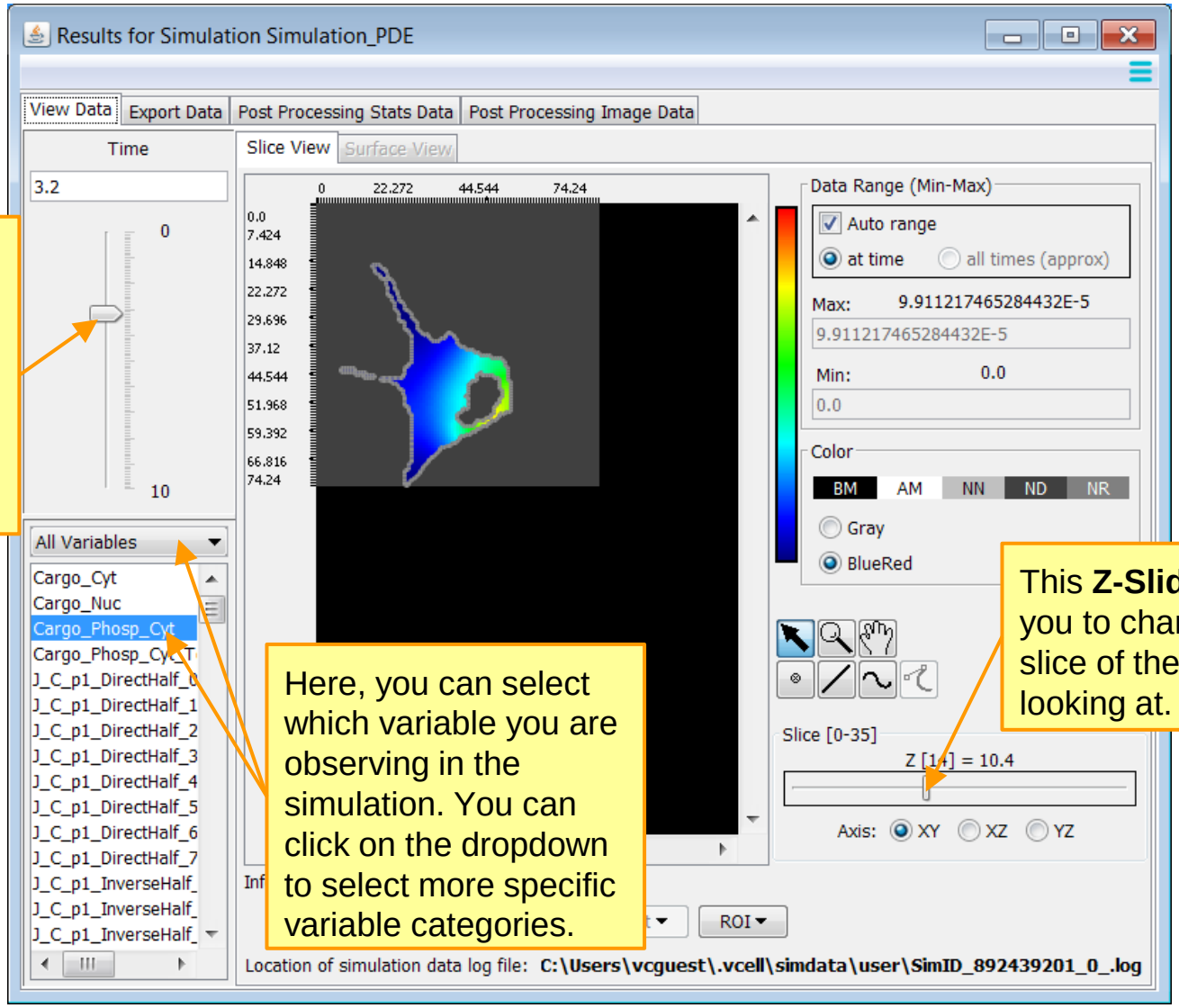
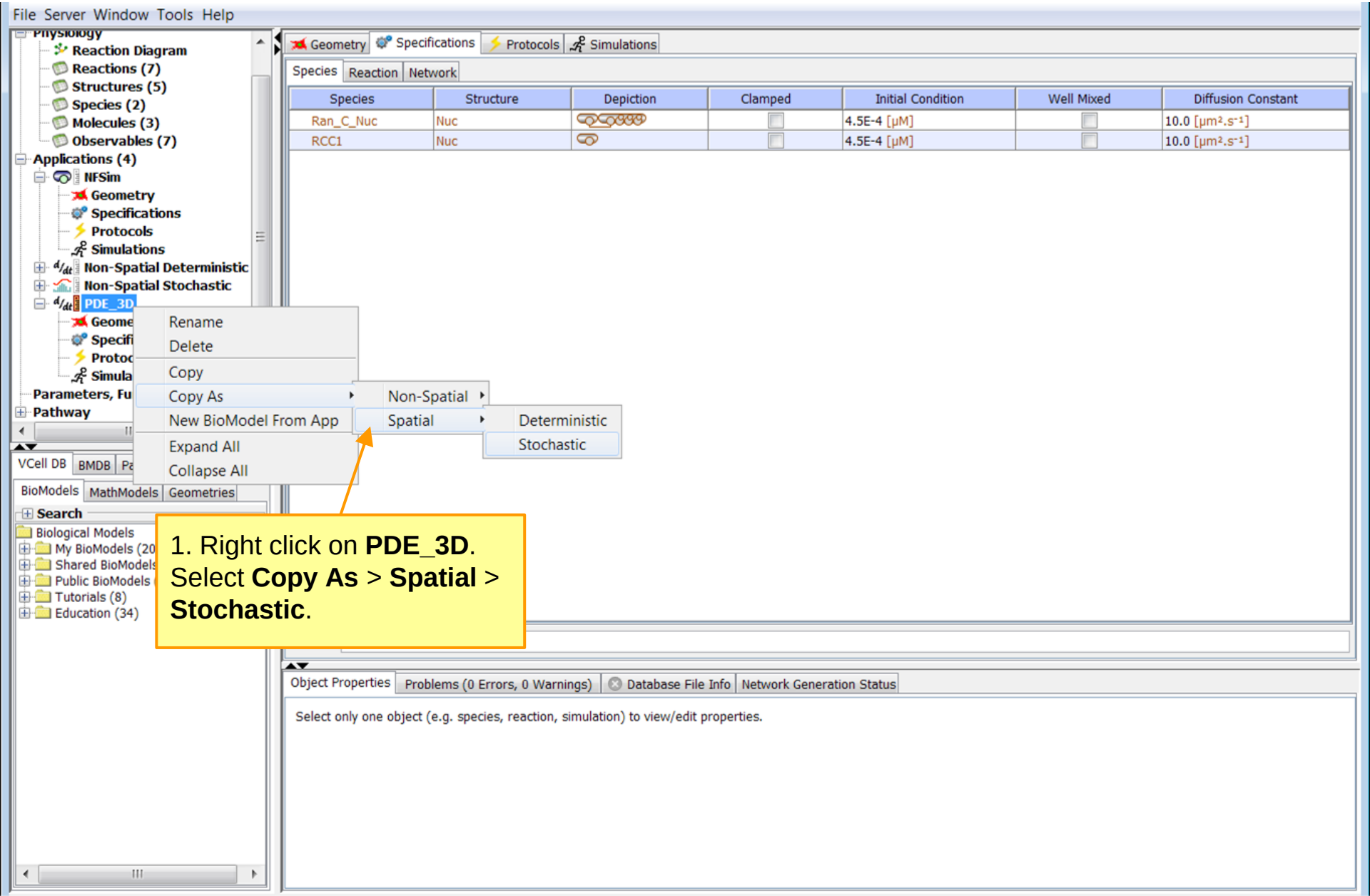
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Annotation:
Settings:
Max timestep
Output
Rel tol
Abs tol
0.1s
every 0.1 sec
1.0E-7
1.0E-9
Mesh: 71x71x25 = 126025 elements
Geometry size: (74.24,74.24,26.0) microns
Parameters with values changed from defaults
Parameter Name
Default
New Value/Expression
Scan



The time slide allows you to change the specific point in time that you are observing in the simulation.

Here, you can select which variable you are observing in the simulation. You can click on the dropdown to select more specific variable categories.

This **Z-Slider** allows you to change which slice of the cell you are looking at.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Copy As
New BioModel From App
Expand All
Collapse All
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Structure
Depiction
Clamped
Initial Condition
Well Mixed
Diffusion Constant
Ran_C_Nuc
Nuc
4.5E-4 [μM]
10.0 [μm².s⁻¹]
RCC1
Nuc
4.5E-4 [μM]
10.0 [μm².s⁻¹]
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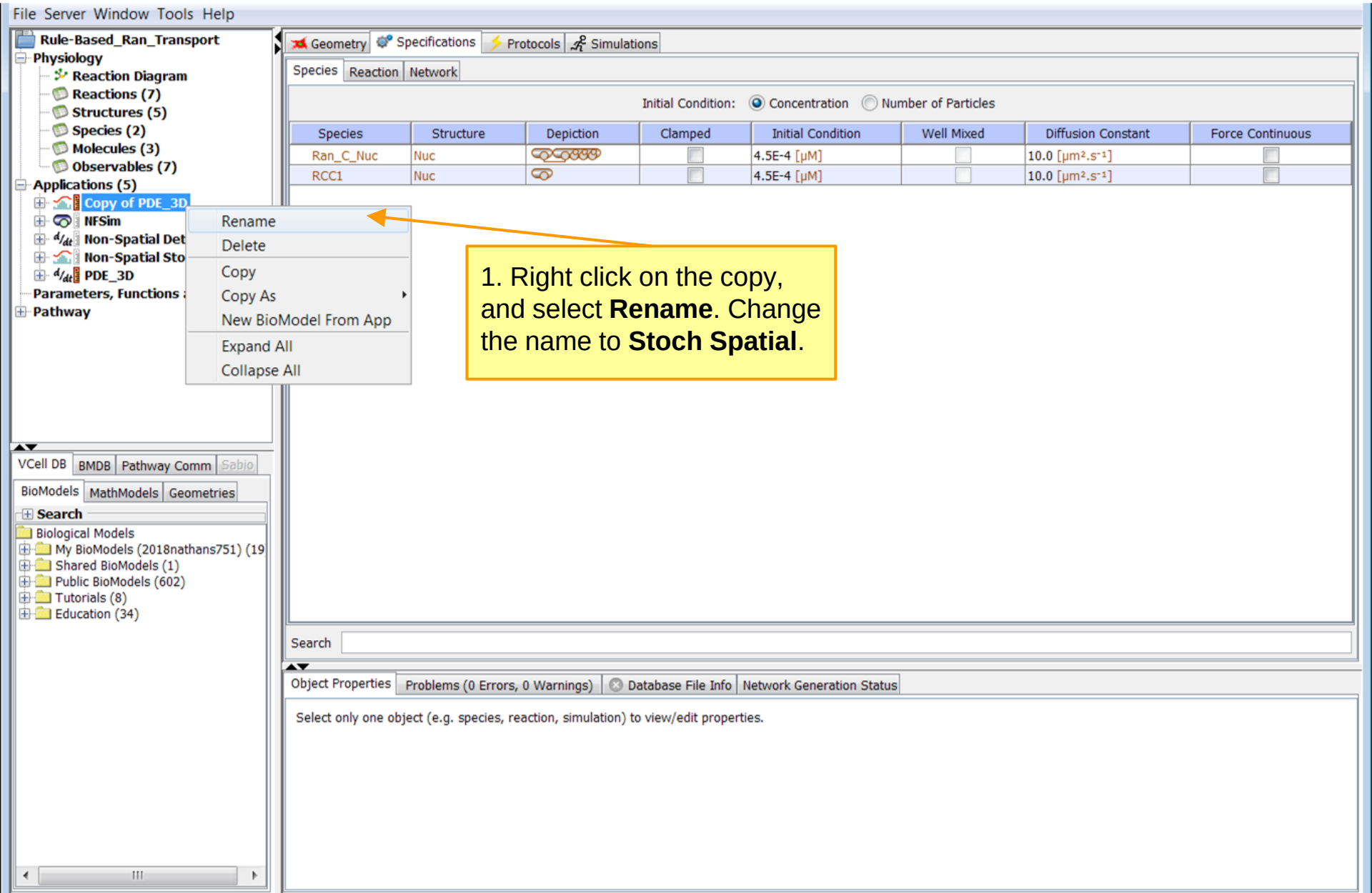
1. Right click on PDE_3D. Select Copy As > Spatial > Stochastic.
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Select only one object (e.g. species, reaction, simulation) to view/edit properties.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NFSim
Non-Spatial Det
Non-Spatial Sto
PDE_3D
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Rename
Delete
Copy
Copy As
New BioModel From App
Expand All
Collapse All
1. Right click on the copy, and select Rename. Change the name to Stoch Spatial.
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Species
Reaction
Network
Initial Condition:
Concentration
Number of Particles
Species
Structure
Depiction
Clamped
Initial Condition
Well Mixed
Diffusion Constant
Force Continuous
Ran_C_Nuc
Nuc
4.5E-4 [μM]
10.0 [μm².s⁻¹]
RCC1
Nuc
4.5E-4 [μM]
10.0 [μm².s⁻¹]
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Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
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Select only one object (e.g. species, reaction, simulation) to view/edit properties.

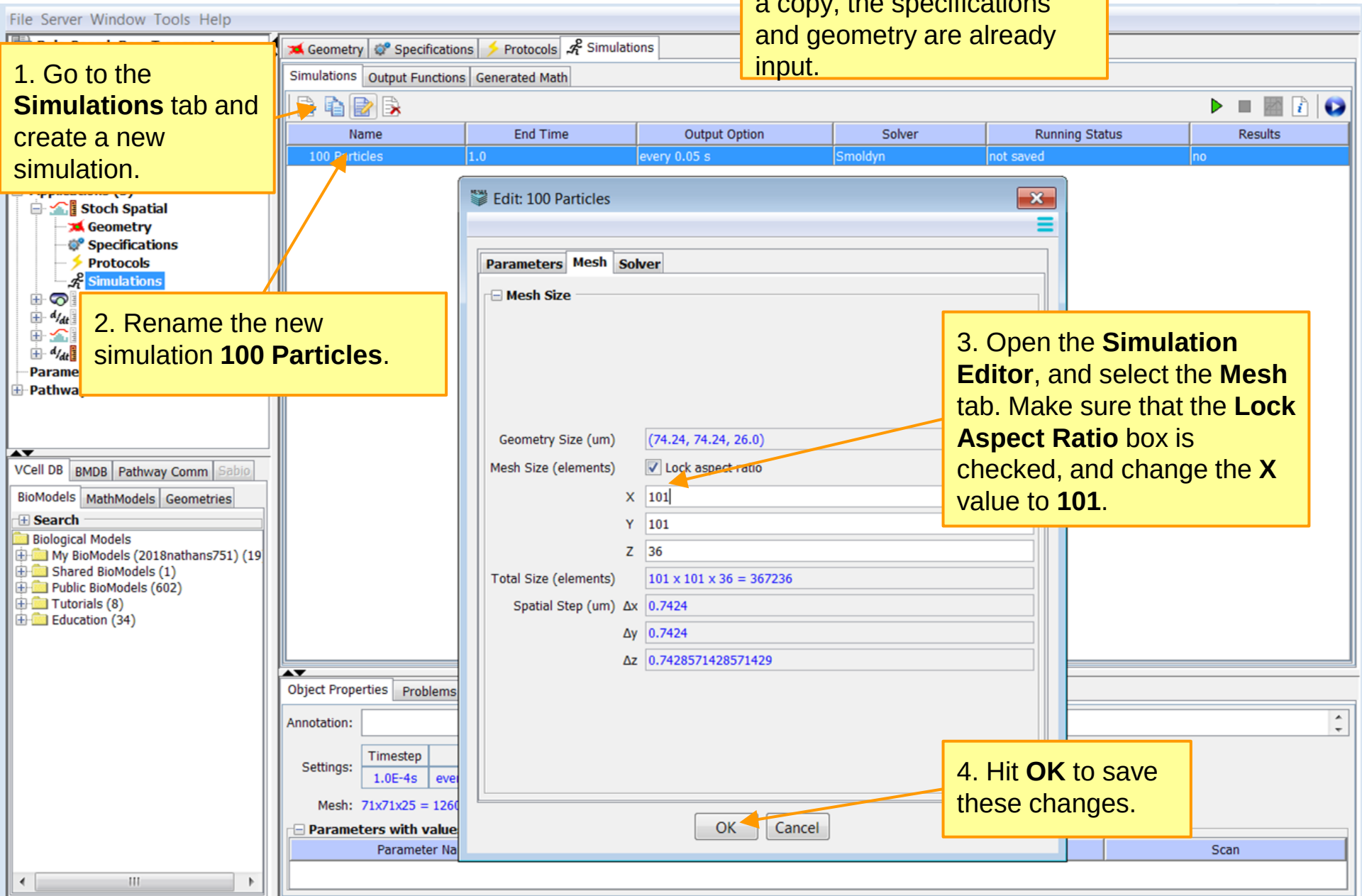
Because this Application is a copy, the specifications and geometry are already input.

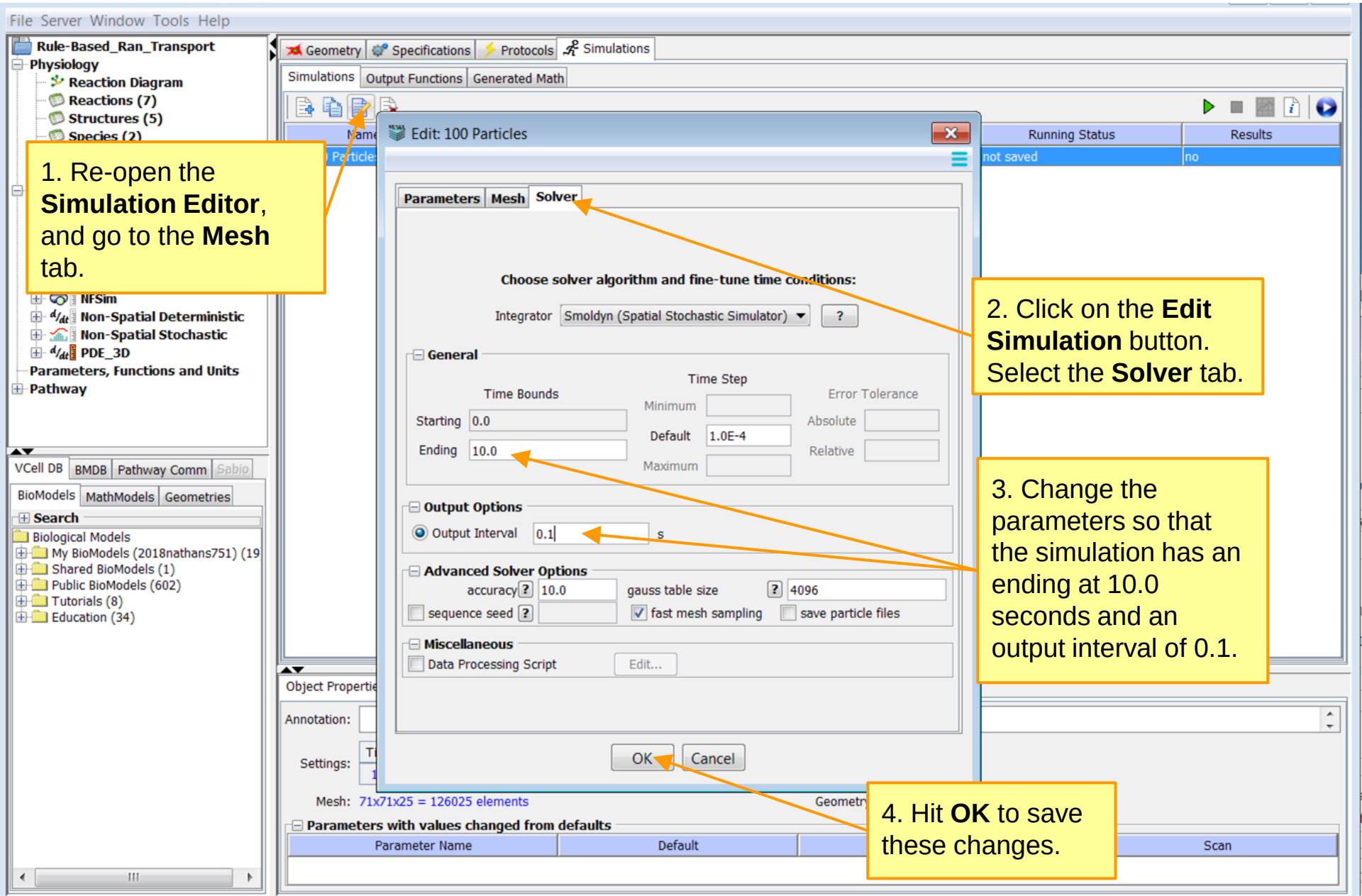
1. Go to the **Simulations** tab and create a new simulation.

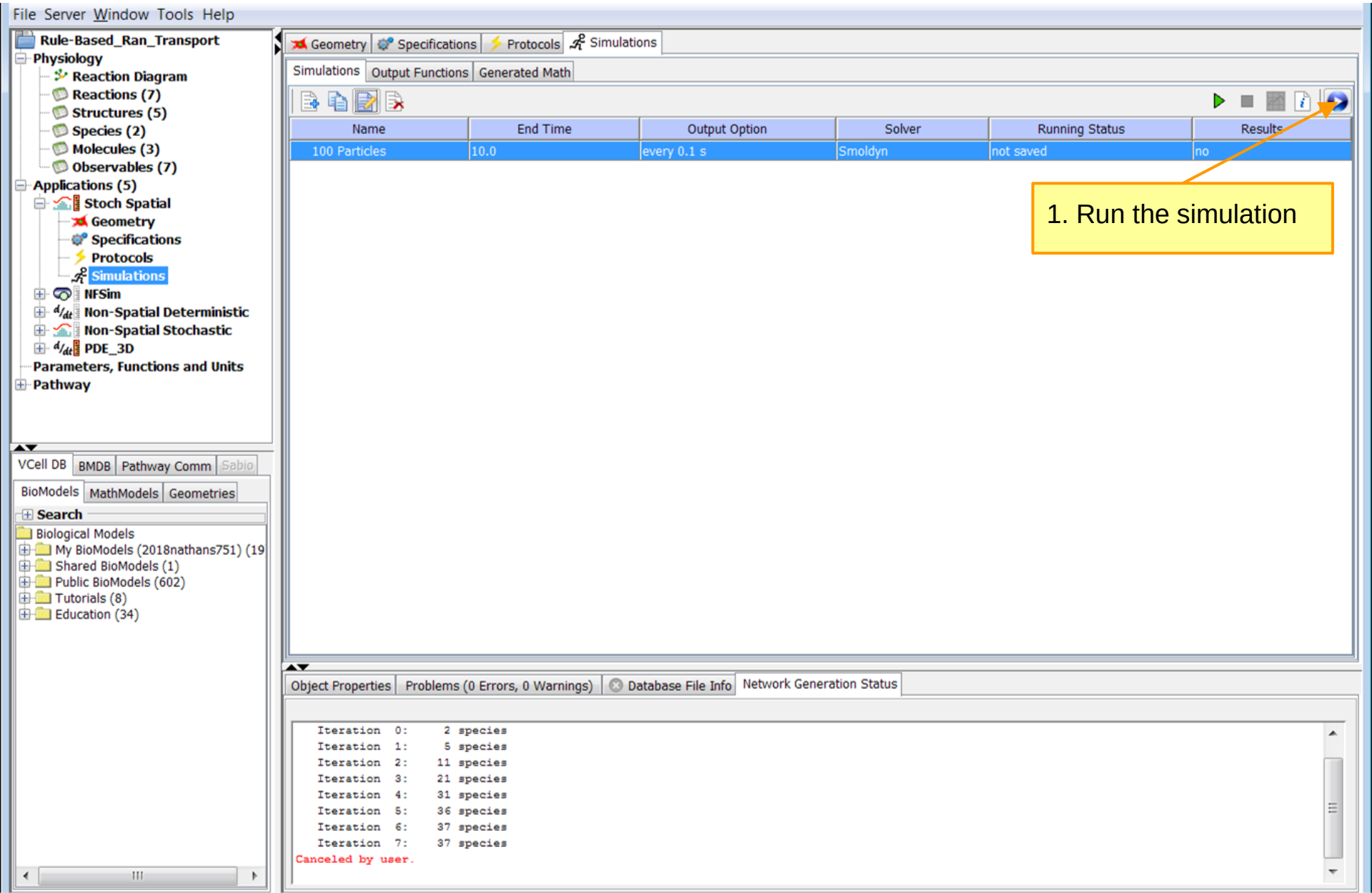
2. Rename the new simulation **100 Particles**.

3. Open the **Simulation Editor**, and select the **Mesh** tab. Make sure that the **Lock Aspect Ratio** box is checked, and change the **X** value to **101**.

4. Hit **OK** to save these changes.




1. Re-open the **Simulation Editor**, and go to the **Mesh** tab.
2. Click on the **Edit Simulation** button. Select the **Solver** tab.
3. Change the parameters so that the simulation has an ending at 10.0 seconds and an output interval of 0.1.
4. Hit **OK** to save these changes.
Edit: 100 Particles
Parameters
Mesh
Solver
Choose solver algorithm and fine-tune time conditions:
Integrator
Smoldyn (Spatial Stochastic Simulator)
General
Time Bounds
Starting 0.0
Ending 10.0
Time Step
Minimum
Default 1.0E-4
Maximum
Error Tolerance
Absolute
Relative
Output Options
Output Interval 0.1 s
Advanced Solver Options
accuracy 10.0
gauss table size 4096
sequence seed
fast mesh sampling
save particle files
Miscellaneous
Data Processing Script
Edit...
OK
Cancel
Mesh: 71x71x25 = 126025 elements
Parameters with values changed from defaults
Parameter Name
Default
Scan
Running Status
Results
not saved
no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Running Status
Results
100 Particles
10.0
every 0.1 s
Smoldyn
not saved
no
1. Run the simulation
Object Properties
Problems (0 Errors, 0 Warnings)
Database File Info
Network Generation Status
Iteration 0: 2 species
Iteration 1: 5 species
Iteration 2: 11 species
Iteration 3: 21 species
Iteration 4: 31 species
Iteration 5: 36 species
Iteration 6: 37 species
Iteration 7: 37 species
Canceled by user.

Contents

Acknowledgements

The following students worked on this tutorial:

Tanya Miller (2015) – Pomperaug High School

Nathan Schaumburger (2017) – Hall High School, West Hartford

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