

VCell Tutorial

Building a Rule-Based Model

We will demonstrate how to create a rule-based model of EGFR receptor interaction with two adapter proteins Grb2 and Shc. A Receptor-monomer reversibly binds a ligand at the extracellular domain, triggering dimerization through transmembrane domains. The receptor kinase transphosphorylates two receptor phosphotyrosines that independently recruit two adapter proteins, Grb2 and Shc. Shc itself is subject to transphosphorylation, where the phosphorylated form has a lower affinity to a receptor phosphotyrosine.

The model is available in VCell Database (left bottom panel) -> BioModels -> Tutorial VCell 6.0 (Rule-based) -> RB_egfr_tutorial

In this tutorial you will learn how to:

- ▶ Create a 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 **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.

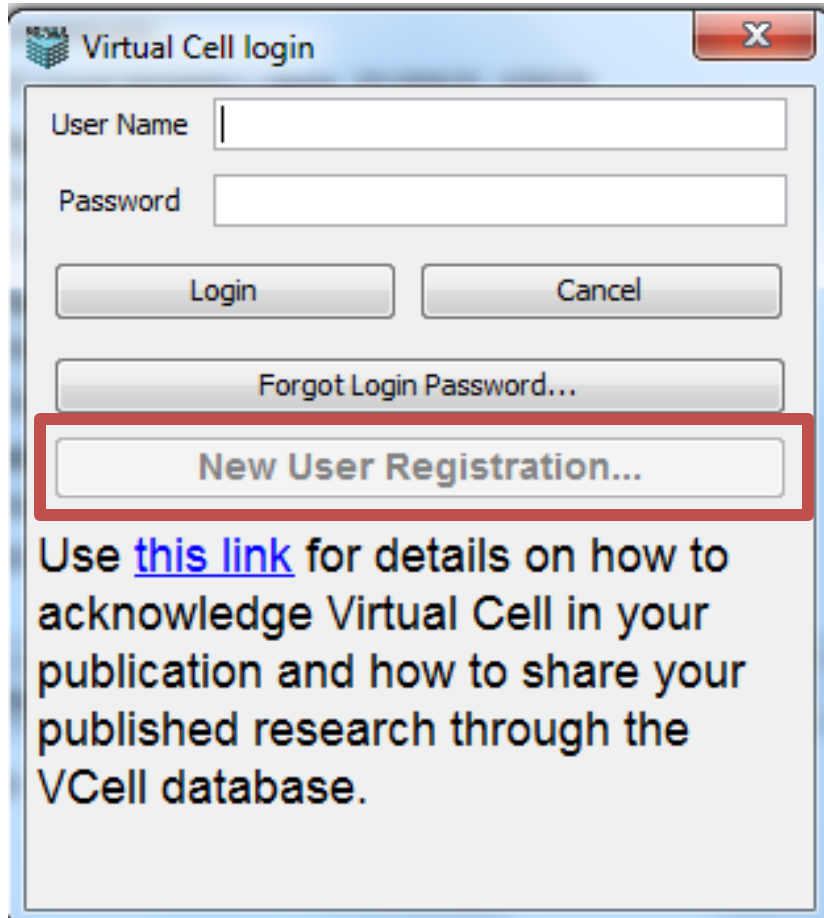
General familiarity with VCell software is recommended. Although this tutorial can be followed by a VCell novice, it is recommended that novice users first look through the VCell tutorials available at http://vcell.org/vcell_software/user_guide.html .

Model building can be matched to the BioModel [RB_egfr_tutorial](#) in the Tutorial VCell 6.0 (Rule-based) folder in the VCell Database.

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- ▶ [Application: Network-Free](#)

Opening VCell for the First Time



Virtual Cell login

User Name

Password

Login Cancel

Forgot Login Password...

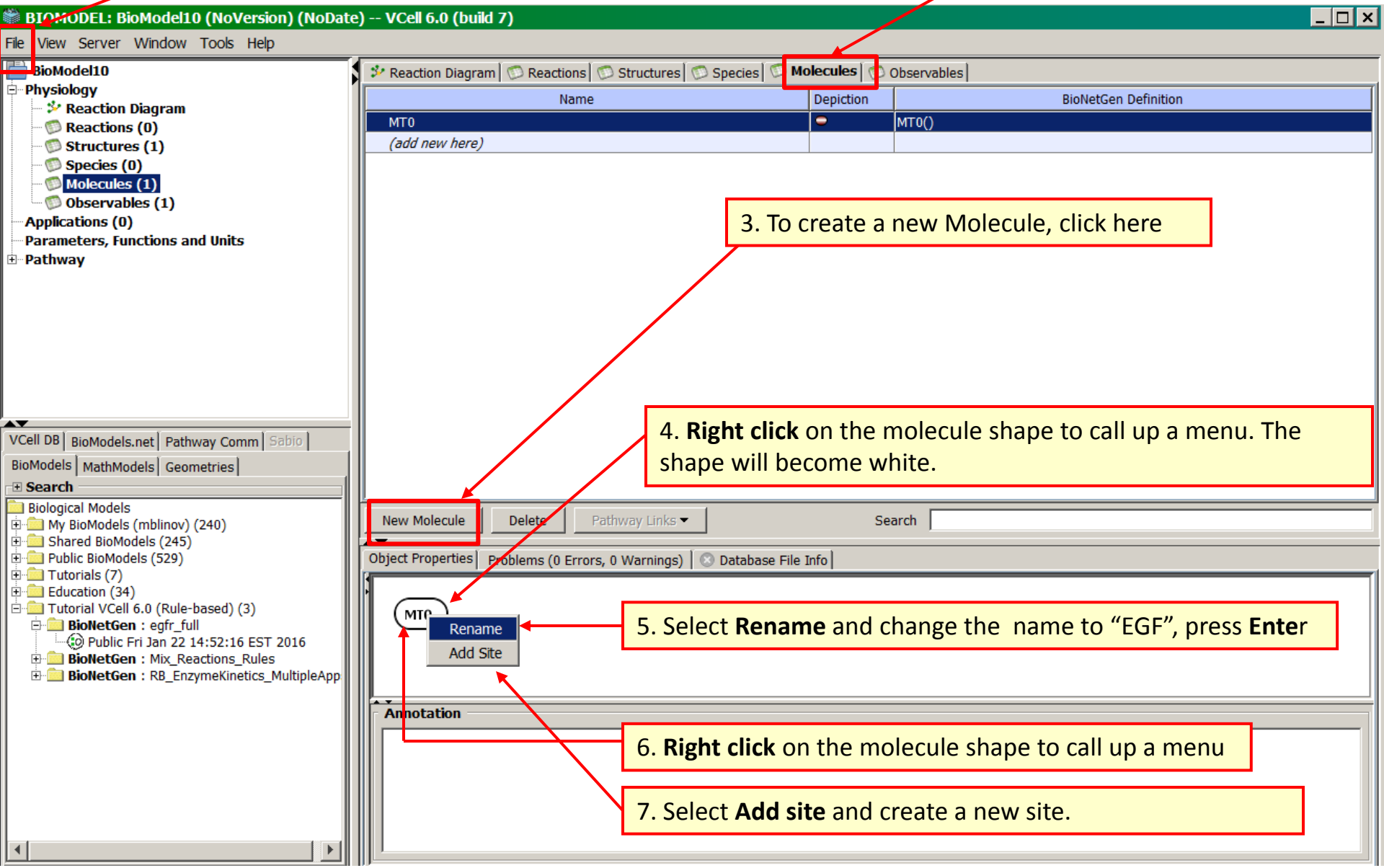
New User Registration...

Use [this link](#) for details on how to acknowledge Virtual Cell in your publication and how to share your published research through the VCell database.

You need to register as a new user if you want to run simulations on VCell compute resources, or use the VCell database to view and store models that can be shared with collaborators.

1. To create a new VCell model, click File > New > BioModel

2. To start creating Molecules, click on **Molecules**



3. To create a new Molecule, click here

4. **Right click** on the molecule shape to call up a menu. The shape will become white.

5. Select **Rename** and change the name to "EGF", press **Enter**

6. **Right click** on the molecule shape to call up a menu

7. Select **Add site** and create a new site.

TIP: If something goes wrong, press **ESC** on the keyboard.

The screenshot displays the VCell software interface. The main window title is "BIOMODEL: BioModel10 (NoVersion) (NoDate) -- VCell 6.0 (build 7)". The interface includes a menu bar (File, View, Server, Window, Tools, Help), a left-hand tree view, a top toolbar, and a main workspace.

The left-hand tree view shows the following structure:

- BioModel10
 - Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (1)**
 - Observables (1)
 - Applications (0)
 - Parameters, Functions and Units
 - Pathway

The top toolbar contains icons for Reaction Diagram, Reactions, Structures, Species, **Molecules**, and Observables. Below the toolbar is a table with the following data:

Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
<i>(add new here)</i>		

The main workspace shows a red pill-shaped molecule labeled "EGF" with a white site shape labeled "Site0". A context menu is open over the site shape, listing the following options:

- Move right
- Move left
- Rename**
- Delete
- Add State

Two red arrows point from text boxes to the site shape and the "Rename" option in the menu.

1. Right click on the site shape to call up a menu. The site shape will become white.

2. Select **Rename and change the name to "Site", press **Enter****

The bottom of the interface shows the "Object Properties" panel, "Problems (0 Errors, 0 Warnings)", and "Database File Info".

TIP: A Molecule name can always be changed by double clicking in Name field, editing, and pressing **ENTER**. It does not matter if the molecule is already used elsewhere – the change will be propagated everywhere in the model.

The screenshot shows the VCell 6.0 interface. On the left is a tree view of the model hierarchy. The main window is titled 'Molecules' and contains a table with the following data:

Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
EGFR		EGFR(ecd,tmd,Y1,Y2)
(add new here)		

Below the table is a 3D model of the EGFR protein. The model is labeled 'EGFR' and has four sites: 'ecd', 'tmd', 'Y1', and 'Y2'. A context menu is open over the 'Y1' site, showing options: 'Move right', 'Move left', 'Rename', 'Delete', and 'Add State'.

Five numbered instructions are overlaid on the image with red arrows pointing to specific elements:

1. Create a new Molecule by clicking either on the button below or **left double click** on (add new here)
2. Rename the Molecule to "EGFR" either by **right click** on the shape below or by entering it in the table.
3. **Right click** on the shape to call up a menu, add four sites.
4. **Right click** on the shape site, select **Rename** and change the names to "ecd", "tmd", "Y1", "Y2"; **Enter** to save.
5. **Right click** on the shape, select **Add state** (twice)

TIP: Sites can always be moved right and left among the Molecule length and renamed, states can always be renamed. To delete a state, you must first eliminate all places where this site is used, e.g. in reaction rules that change the site.



BIOMODEL: BioModel10 (NoVersion) (NoDate) -- VCell 6.0 (build 7)

File View Server Window Tools Help

BioModel10

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (2)**
 - Observables (2)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | **Molecules** | Observables

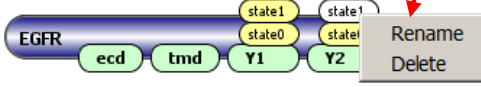
Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
EGFR		EGFR(ecd,tmd,Y1~state0~state1,Y2~state0~state1)
(add new here)		

1. Right click on the site shape to call up a menu.

2. Select **Rename** and change states "state1" and "state0" to "u" and "p", respectively. Press **Enter** to save.

New Molecule | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info



EGFR

ecd tmd Y1 Y2

state1 state0 state1 state0

Rename
Delete

Annotation

TIP: Molecule colors are ordered and cannot be changed. Molecules can be added and/or deleted at any time, but reaction rules, species and observables that use these molecules must be deleted first. A warning will appear if deletion is not allowed.

BIOMODEL: BioModel10 (NoVersion) (NoDate) -- VCell 6.0 (build 7)

File View Server Window Tools Help

BioModel10

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)**
 - Observables (4)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | **Molecules** | Observables

Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
EGFR		EGFR(ecd,tmd,Y1~state0~state1,Y2~state0~state1)
Grb2		Grb2(sh2)
Shc		Shc(sh3,Y~u~p)
(add new here)		

Complete adding molecules: "Grb2" with a site "sh2", "Shc" with sites "sh3" and "Y", "Y" having two states, "u" and "p". Check with the specification of Molecules in the *RB_egfr_tutorial* model in VCell 6.0 (Rule-based) folder.

VCell DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

Search

- Biological Models
 - My BioModels (mblinov) (242)
 - Shared BioModels (245)
 - Public BioModels (529)
 - Tutorials (7)
 - Education (34)
 - Tutorial VCell 6.0 (Rule-based) (3)
 - BioNetGen : egfr_full
 - Public Fri Jan 22 14:52:16 EST 2016
 - BioNetGen : Mix_Reactions_Rules
 - BioNetGen : RB_EnzymeKinetics_MultipleApp

New Molecule | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

2. Annotations can be entered here.

Annotation

Adapter protein Shc. Binds EGFR phosphotyrosines through SH2 domain, can be phosphorylated at a phosphosite Y.

TIP: Save your model as often as you can, so you don't lose any changes!

The screenshot shows the VCell 6.0 interface. The 'File' menu is open, with 'Save As...' highlighted. A red box highlights the 'Save As...' option in the menu. A yellow callout box with a red border points to the 'Save As...' option and contains the following text: 'When ready to save, click on **File** and **Save As...**. If you work locally (no internet connection), choose **Save As Local...**'.

Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
EGFR		EGFR(ecd,tmd,Y1~state0~state1,Y2~state0~state1)
Grb2		Grb2(sh2)
Shc		Shc(sh3,Y~u~p)
<i>(add new here)</i>		

The interface also shows a search panel on the left with a tree view of models, and a central area with a 3D model of the Shc protein and its annotation: 'Adapter protein Shc. Binds EGFR phosphotyrosines through SH2 domain, can be phosphorylated at a phosphosite Y.'

TIP: Each Observable corresponds to a sum of species selected by species patterns. Specific species are identified the network is generated using reaction rules.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

BioModel10

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)
 - Observables (4)**
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | **Observables**

Name	Structure	Depiction	BioNetGen Definition	Count
O0_EGF_tot	c0		EGF()	Molecules
O0_EGFR_tot	c0		EGFR()	Molecules
O0_Grb2_tot	c0		Grb2()	Molecules
O0_Shc_tot	c0		Shc()	Molecules
<i>(add new here)</i>				

1. Right click on **Observables** tab. You'll see a set of observables corresponding to the total number of Molecules of each type.

2. Grey color means the site is irrelevant for this observable. Yellow ball above a site indicates a site with multiple states.

3. This observable selects species that have EGFR molecules in any state and any complex. Question marks and grey color mean that the state and whether sites are bound or unbound are not important for counting.

The default setting will count "Molecules", meaning that a species is counted as many times as it has this Molecule. So, dimers of EGFR are counted twice, and tetramers (if any) – four times.






TIP: Every table has a column BioNetGen definition. It can be edited *only once* –the first time an object is specified. It is useful if you have separate BNGL code you want to paste, but do not want to import for some reason. If you paste in BNGL code, once you click enter it cannot be further edited unless you export back out as BNGL.

BTOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

BioModel10

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)
 - Observables (5)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Name	Structure	Depiction	BioNetGen Definition	Count
O0_EGF_tot	c0		EGF()	Molecules
O0_EGFR_tot	c0		EGFR()	Molecules
O0_Grb2_tot	c0		Grb2()	Molecules
O0_Shc_tot	c0		Shc()	Molecules
O0	c0			Molecules
(add new here)				

1. A new Observable can be added by **left double click** at (add new here) or by pressing the **New Observable** button below. The name can be edited in the table or in the graphics editor through **right click** on the shape.

New Observable Delete Pathway Links Search

Object Properties Problems (0 Errors, 1 Warnings) Database File Info

2. When a dashed shape appears in the graphics editor, **right click** on the shape and choose **Add Molecule**, select "EGFR".

Delete Species Pattern Add Molecule EGF EGFR Grb2 Shc

Annotation

VCell DB BioModels.net Pathway Comm Sabio

BioModels MathModels Geometries

Search

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 - BioNetGen : egfr_full
 - Public Fri Jan 22 14:52:16 EST 2016
 - BioNetGen : Mix_Reactions_Rules
 - BioNetGen : RB_EnzymeKinetics_MultipleApp

TIP: A yellow warning sign or red error sign may appear temporarily if something is wrong. After the error/warning is corrected, the sign will disappear within a few seconds.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

BioModel10

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)
 - Observables (5)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Name	Structure	Depiction	BioNetGen Definition	Count
O0_EGF_tot	c0		EGF()	Molecules
O0_EGFR_tot	c0		EGFR()	Molecules
O0_Grb2_tot	c0		Grb2()	Molecules
O0_Shc_tot	c0		Shc()	Molecules
Dimers	c0		EGFR()	Molecules
<i>(add new here)</i>				

Dimers are characterized by site "tmd" being in a bound state. **Right click** on the site shape (it will become white), and select "Site has external bond".

Create an Observable named Dimers_s, identical to Dimers but set Count to "Species" (**double left click** on Molecules and select "Species").

VCeLL DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

Search

Biological Models

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New Observable | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

EGFR

- Site is unbound
- Site has external bond
- Site may be bound
- Site bond specified

Annotation

TIP: If you rename a Molecule, the Observable corresponding to its total will be renamed automatically as long as you do not change its name. For example, changing **_tot** to **_total** will decouple the Observable from the Molecule definition, and it will be no longer renamed automatically if you change the name of this molecule.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)
 - Observables (7)**
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | **Observables**

Name	Structure	Depiction	BioNetGen Definition	Count
O0_EGF_tot	c0		EGF()	Molecules
O0_EGFR_tot	c0		EGFR()	Molecules
O0_Grb2_tot	c0		Grb2()	Molecules
O0_Shc_tot	c0		Shc()	Molecules
Dimers	c0		EGFR(tmdt+)	Molecules
Dimers_s	c0		EGFR(tmdt+)	Species
Y1	c0		EGFR()	Molecules
<i>(add new here)</i>				

To specify an Observable counting all phosphorylated sites "Y1", click on the white state shape and select the desired state "p". Similarly, specify an Observable counting phosphorylated sites "Y2".

New Observable | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Annotation

VCell DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

Search

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TIP: Species corresponding to each Observable can be seen after network generation under Application > Simulations > Generated Math > Math Description Language.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (0)
 - Molecules (4)
 - Observables (9)**
- Applications (0)
- Parameters, Functions and Units
- Pathway

Name	Structure	Depiction	BioNetGen Definition	Count
O0_EGF_tot	c0		EGF()	Molecules
O0_EGFR_tot	c0		EGFR()	Molecules
O0_Grb2_tot	c0		Grb2()	Molecules
O0_Shc_tot	c0		Shc()	Molecules
Dimers	c0		EGFR(tmd!+)	Molecules
Dimers_s	c0		EGFR(tmd!+)	Species
Y1	c0		EGFR(Y1~p!?)	Molecules
Y2	c0		EGFR(Y2~p!?)	Molecules
Y_total	c0		EGFR(Y1~p!?)	Molecules
(add new here)				

VCell DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

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New Observable Delete Pathway Links Search

Object Properties Problems (0 Errors, 0 Warnings) Database File Info

Add Species Pattern

Annotation

To specify an Observable counting all phosphorylated sites "Y1" and "Y2", first specify a pattern for "Y1", then click below and select **Add Species Pattern**. Then specify a similar pattern but with site "Y2" in the phosphorylated state.

To have more space, **right click** on a line; keep the **right button pressed** and drag it down.

TIP: Species may consist of more than one molecule, but the molecules must be connected.

The screenshot shows the VCell 6.0 interface. The top menu bar includes File, View, Server, Window, Tools, and Help. The main window is titled "BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)". The left sidebar shows a tree view of the model structure, including Physiology, Reactions (0), Structures (1), Species (1), Molecules (4), Observables (9), Applications (0), Parameters, Functions and Units, and Pathway.

The main window displays a table with the following columns: Name, Structure, Link, Depiction, and BioNetGen Definition. The table contains one row with the name "R" and structure "c0". Below the table is a button labeled "(add new here)".

Two red arrows point from text boxes to the "(add new here)" button and the "Specify Molecule" dialog. The first text box says: "1. To add species, **left double click** on (add new here) and change the name to R. Alternatively, use the 'New Species' button below." The second text box says: "2. By default, a species is created without a molecular structure (green shape). To specify molecular composition, **left click** on the green shape, **Specify Molecule**, and select 'EGFR'."

The "Specify Molecule" dialog is open, showing a green sphere icon. The dialog has a dropdown menu with the following options: EGF, EGFR (selected), Grb2, and Shc.

The bottom of the interface shows the "Object Properties" panel with the following fields: Species Name (R), Linked Pathway Object(s), and Annotation.

TIP: Left click on the Problems tab will show the list of errors and warnings. **Double left click** on a problem will bring up the issue.

The screenshot shows the VCell 6.0 interface with the following components:

- Top Bar:** BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)
- Menu:** File View Server Window Tools Help
- Left Panel:** RB_egfr_tutorial tree with folders for Physiology, Reactions (0), Structures (1), Species (1), Molecules (4), Observables (9), Applications (0), Parameters, Functions and Units, and Pathway.
- Species Table:**

Name	Structure	Link	Depiction	BioNetGen Definition
R	c0			EGFR(ecd,tmd,Y1,Y2)
<i>(add new here)</i>				
- Reaction Diagram:** Shows EGFR molecule with sites ecd, tmd, Y1, and Y2. A context menu is open over Y1 and Y2 with options: ~ State: u and ~ State: p.
- Bottom Panel:** Object Properties | Problems (2 Errors, 0 Warnings) | Database File Info. Includes buttons for New Species, Delete, Pathway Links, and Search.

Callout 1: 1. After the EGFR molecule is assigned to a species, an error is generated because sites "Y1" and "Y2" must be in a specific state (a species must have a unique state).

Callout 2: 2. Specify the state by **right click** on a state shape and selecting a required state ("u").

TIP: Left click on a Table column name (e.g. Name) will sort the table by this column.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (0)
 - Structures (1)
 - Species (4)**
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | **Species** | Molecules | Observables

Name	Structure	Link	Depiction	BioNetGen Definition
R	c0			EGFR(ecd,tmd,Y1~u,Y2~u)
L	c0			EGF(Site0)
Grb2	c0			Grb2(sh2)
Shc	c0			Shc(sh3,Y~p)
<i>(add new here)</i>				

Complete the specification of all Species as in the *RB_egfr_tutorial* model in VCell 6.0 (Rule-based) folder.

VCell DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

Search

Biological Models

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New Species | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Species Name: Shc

Linked Pathway Object(s):

Annotation:

TIP: Reaction rules generate reactions by selecting species that serve as reactants and generating new species i.e. the products of these reactions. Thus, each reaction rule is defined with reactant patterns (that select species to be reactants) and products patterns (to define how reactant molecules are modified).

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (1)
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	r0	c0		MassAction	->	

Press the *New...* buttons.

1. Click the **New Rule** button to generate a new rule.
2. Errors and warnings are generated immediately. They will disappear as the rule is being specified.
3. **Right click** on a dashed shape to specify the molecule to be included in a reactant pattern.

VCell DB | BioModels.net | Pathway Comm | Sabio

BioModels | MathModels | Geometries

Search

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New Reaction | **New Rule** | Duplicate | Delete | Pathway Links

Object Properties | Problems (2 Errors, 2 Warnings) | Database File Info

Kinetics | **Editor**

Delete | Specify Molecule

- EGF
- EGFR**
- Grb2
- Shc

TIP: Always check errors and warnings until you understand the issue. If in trouble, use Help from the top menu. It is fully searchable. It can be printed from <http://vcell.org>

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

Reaction Diagram Reactions Structures Species Molecules Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	r0	c0		MassAction	EGFR() ->	

Press the *New...* buttons.

1. Note that the number of errors and warnings decreased as the rule was specified.

2. To add the next reactant, **right click** on a white space after -> and choose **Add Reactant**.

3. After a dashed shape for a new reactant appears, **right click** on it to add a molecule as the second reactant as before.

RB_egfr_tutorial

Physiology

- Reaction Diagram
- Reactions (1)
- Structures (1)
- Species (4)
- Molecules (4)
- Observables (9)

Applications (0)

Parameters, Functions and Units

Pathway

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Search

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New Reaction New Rule Duplicate Delete Pathway Links Search

Object Properties Problems (1 Errors, 1 Warnings) Database File Info

Kinetics Editor

EGFR ecd tmd Y1 Y2 -> Add Reactant

TIP: The search field can be used to filter all lists by an entered term, such as Molecule or site name.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (1)
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	r0	c0		MassAction	EGFR()+EGF() -> EGFR()	

Press the **New...** buttons.

To specify a reactant or product pattern consisting of several molecules, **right click** on the white space next to an existing Molecule.

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BioModels | MathModels | Geometries

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New Reaction | New Rule | Duplicate | Delete | Pathway Links

Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

EGFR + EGF ->

EGFR (ecd, tmd, Y1, Y2) + EGF (Site)

Delete

Specify Molecule

- EGF
- EGFR
- Grb2
- Shc

TIP: Molecules in reactant/product patterns can be rearranged by **right click** on the Molecule shape and choosing **Move right/Move left** actions.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (1)
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	r0	c0		MassAction	EGFR(ecd)+EGF() -> EGFR(ecd).EGF()	
<i>Press the New... buttons.</i>						

To select features of reactants, **right click** on the site shape and select its state and/or binding status.

New Reaction | New Rule | Duplicate | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

- Site is unbound
- Site has external bond
- Site may be bound
- Site bond specified

All changes in Reactant patterns are propagated down to the same molecules in product patterns.

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TIP: Note that some options for binding status are greyed out because they are impossible.

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File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (1)
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	r0	c0		MassAction	EGFR(ecd)+EGF(Site) -> EGFR(ecd).EGF(Site)	

Press the *New...* buttons.

Site "tmd" of the reactant pattern is unbound, so the only possible change is to make it bound to another site: it may not have implicit external bond ("has external bond") or be in an uncertain status ("may be bound").

To specify how product patterns differ from reactant patterns, **right click** on the shape and select features. For a binding reaction rule, specify how molecules in the product pattern are connected.

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New Reaction | New Rule | Duplicate | Delete | Pathway Links

Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

EGFR (ecd tmd Y1 Y2) + EGF (Site) <->

EGFR (ecd tmd Y1 Y2) EGF (Site)

- Site is unbound
- + Site has external bond
- ? Site may be bound
- Site bond specified
 - EGFR(ecd!1,tmd!1).EGF
 - EGFR(tmd!1,Y1!1).EGF
 - EGFR(tmd!1,Y2!1).EGF
 - EGFR(tmd!1).EGF(Site!1)

TIP: Sites in green without any symbols underneath are always unbound.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (1)
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd)+EGF(Site) -> EGFR(ecd!1).EGF(Site!1)	

Press the *New...* buttons.

1. Change a reaction rule name by **double left click** on the rule name.

2. Note that by default a rule is created irreversible.

3. To make a rule reversible and to enter kinetics, **left click** on Kinetics.

New Reaction | New Rule | Duplicate | Delete | Pathway Links

Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

EGFR (ecd, tmd, Y1, Y2) + EGF (Site) -> EGFR.EGF

EGFR (ecd, tmd, Y1, Y2) <-> EGF (Site)

1 1

TIP: The numbers of specified Molecules, Species, Reactions and Observables are always displayed in the left panel.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
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1. To make a rule reversible, check the **Reversible** button.

2. Note that the only allowable kinetic type is **Mass Action**, where every reaction selected by a Reaction Rule has a rate law of forward rate times the product of reactant amounts minus the reverse rate times the product of product amounts.

3. Expressions for forward and reverse rates can be any complicated functions.

4. Note that default units are uM. The unit system must be changed to use other units like nM or molecules.

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd)+EGF(Site) <-> EGFR(ecd!1).EGF(Site!1)	
<i>Press the New... buttons.</i>						

New Reaction New Rule Duplicate Delete Pathway Links Search

Object Properties Problems (0 Errors, 0 Warnings) Database File Info

Kinetics Editor

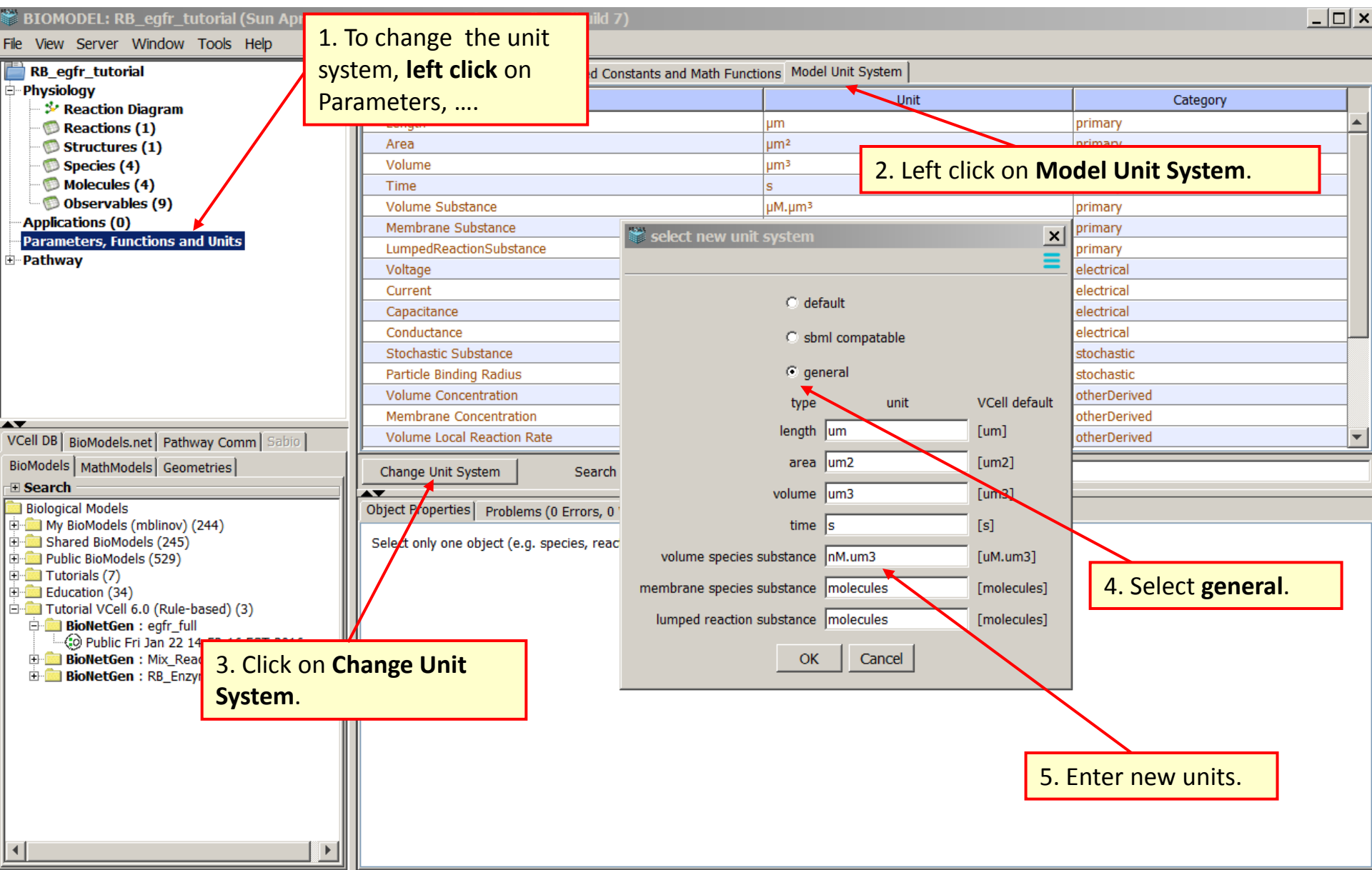
Reaction Name: ligand_bind

Reversible Kinetic Type: Mass Action (for each reaction: $K_f \cdot \prod \text{reactants} - K_r \cdot \prod \text{products}$) Convert units

Name	Description	Global	Expression	Units
ruleRate	rate of reactions generated by rule	<input type="checkbox"/>	Variable	$\mu\text{M} \cdot \text{s}^{-1}$
kf	microscopic forward rate	<input checked="" type="checkbox"/>	0.0	$\text{s}^{-1} \cdot \mu\text{M}^{-1}$
kr	microscopic reverse rate	<input type="checkbox"/>	0.0	s^{-1}

Annotations

TIP: The unit system must be changed before entering any numeric values. Otherwise, all values will be converted from the old units to a new unit system.



TIP: VCell has various kinetic types, but rule-based models in version 6.0 are limited to mass-action kinetic only.

The screenshot shows the VCell 6.0 interface for editing a reaction rule. The main window displays a table of reaction rules with columns for Reaction, Name, Structure, Depiction, Kinetics, and BioNetGen Definition. The selected rule is 'ligand_bind' with a 'MassAction' kinetics type and the definition 'EGFR(ecd)+EGF(Site) <-> EGFR(ecd!1).EGF(Site!1)'. Below the table, the 'Object Properties' panel is open to the 'Kinetics' editor. It shows the reaction name 'ligand_bind', a checked 'Reversible' box, and a 'Kinetic Type' of 'Mass Action'. A table below lists parameters: 'ruleRate' (rate of reactions generated by rule, nM.s⁻¹), 'Kf' (microscopic forward rate, 0.003, s⁻¹.nM⁻¹), and 'Kr' (microscopic reverse rate, 0.06, s⁻¹). A red arrow points to the 'Kr' value. A yellow callout box at the bottom right contains the text: 'Set values in proper units. Match all values to the RB_egfr_tutorial model in the VCell 6.0 (Rule-based) folder.'

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition	Link
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd)+EGF(Site) <-> EGFR(ecd!1).EGF(Site!1)	
<i>Press the New... buttons.</i>						

Name	Description	Global	Expression	Units
ruleRate	rate of reactions generated by rule	<input type="checkbox"/>	Variable	nM.s ⁻¹
Kf	microscopic forward rate	<input type="checkbox"/>	0.003	s ⁻¹ .nM ⁻¹
Kr	microscopic reverse rate	<input type="checkbox"/>	0.06	s ⁻¹

TIP: If reactants or products contain identical molecules, they are automatically numbered for the modeler's convenience, so the user can match reactants to products.

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 18:50:11 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (2)**
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd)+EGF(Site) <-> EGFR(ecd!1).EGF(Site!1)
Reaction Rule	dimeriz	c0		MassAction	EGFR(ecd!+,tmd)+EGFR(ecd!+,tmd) <-> EGFR(ecd!+,tmd!1).EGFR(ecd!+,tmd!1)

Press the *New...* buttons.

Similarly, set dimerization reaction rule as in the *RB_egfr_tutorial* model in the VCell 6.0 (Rule-based) folder.

Conditions for the rule to happen: both receptors are bound at "ecd" and unbound at "tmd" sites.

Note the rule is reversible

Reaction rule outcome: a new bond between "tmd" sites

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BioModels | MathModels | Geometries

Search

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 - BioNetGen : egfr_full
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 - BioNetGen : Mix_Reactions_Rules
 - BioNetGen : RB_EnzymeKinetics_MultipleApp

New Reaction | New Rule | Duplicate | Delete | Pathway Links | Search

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

TIP: A green site with a vertical line underneath means that the site is bound, but the binding partner is not explicitly specified and can be any molecule allowable by rules.

The screenshot displays the VCell 6.0 interface. On the left is a project tree for 'RB_egfr_tutorial'. The main window shows a 'Reactions' table with three entries: 'dimeriz', 'ligand_bind', and 'Y1_phosph'. The 'Y1_phosph' reaction is selected. Below the table is a diagram editor showing the reaction: $EGFR_{(ecd, tmd, Y1^u, Y2^?)}$ \rightarrow $EGFR_{(ecd, tmd, Y1^p, Y2^?)}$. Red arrows point from text boxes to the 'u' and 'p' sites in the diagram.

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition
Reaction Rule	dimeriz	c0		MassAction	$EGFR(ecd!,tmd)+EGFR(ecd!,tmd) \leftrightarrow EGFR(ecd!,tmd!),EGFR$
Reaction Rule	ligand_bind	c0		MassAction	$EGFR(ecd)+EGF(Site) \leftrightarrow EGFR(ecd!1).EGF(Site!1)$
Reaction Rule	Y1_phosph	c0		MassAction	$EGFR(tmd!,Y1^u) \rightarrow EGFR(tmd!,Y1^p)$

Set the irreversible phosphorylation reaction rule as in the *RB_egfr_tutorial* model in the VCell 6.0 (Rule-based) folder.

Conditions for the phosphorylation: "Y1" site is unbound and unphosphorylated, "tmd" site is bound (which means that the receptor is a part of aggregate)

Note rule is irreversible

Reaction rule outcome: "Y1" site becomes phosphorylated.

TIP: Using the **Duplicate** button can save a lot of time when a combination of multiple molecules participates in multiple reaction rules. Make sure you edit the copied rule and not the original one!

BIOMODEL: RB_egfr_tutorial (Sun Apr 24 23:33:27 EDT 2016) -- VCell 6.0 (build 7)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (6)**
 - Structures (1)
 - Species (4)
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd)+EGF(Site) <-> EGFR(ecd!1).EGF(Site!1)
Reaction Rule	dimeriz	c0		MassAction	EGFR(ecd!+,tmd)+EGFR(ecd!+,tmd) <-> EGFR(ecd!+,tmd!1).EGFR(ecd!+,tmd!1)
Reaction Rule	Y2_phosph	c0		MassAction	EGFR(tmd!+,Y2~u) -> EGFR(tmd!+,Y2~p)
Reaction Rule	Y2_dephosph	c0		MassAction	EGFR(Y2~p) -> EGFR(Y2~u)
Reaction Rule	Y1_phosph	c0		MassAction	EGFR(tmd!+,Y1~u) -> EGFR(tmd!+,Y1~p)
Reaction Rule	Y1_dephosph	c0		MassAction	EGFR(Y1~p) -> EGFR(Y1~u)

Press the *New...* buttons.

- Select a rule to duplicate and click on **Duplicate** button
- The Identical rule will appear with the name *oldname_0*.
- Rename the new rule and introduce any needed changes.

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BioModels | MathModels | Geometries

Search

Biological Models

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New Reaction | New Rule | Duplicate | Delete | Pathway Links

Object Properties | Problems (0 Errors, 0 Warnings) | Database File Info

Kinetics | Editor

Note rule is irreversible

Condition for the dephosphorylation: "Y1" site is phosphorylated and unbound.

Reaction rule outcome: "Y1" site becomes unphosphorylated.

TIP: Reactions rules are not displayed in the Reaction Diagram, but species are. One can use VCell reaction tools to create non-rule based reactions among species (see other tutorials on VCell use).

The screenshot shows the VCell software interface. The left sidebar contains a tree view with the following structure:

- RB_egfr_tutorial (Mon Apr 25 17:20:45 EDT 2016) -- VCell 6.0 (build 8)
- Physiology
 - Reaction Diagram
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 - Structures (1)
 - Species (5)
 - Molecules (4)
 - Observables (9)
- Applications (3)
 - network_determ
 - network_free
 - Geometry
 - Specifications
 - Protocols
 - Simulations
 - network_stoch
- Parameters, Functions and Units
- Pathway

The central workspace shows a reaction diagram with species ShcP, Grb2, ShcU, and c0. A reaction arrow labeled ShcDephosp connects ShcP to ShcU. A red box highlights the 'RX Connection Tool' in the toolbar.

The bottom panel shows the 'Object Properties' for the reaction 'ShcDephosp'. The 'Kinetic Type' is set to 'Mass Action [μM/s]'. A table below lists the reaction parameters:

Name	Description	Global	Expression	Units
J	reaction rate	<input type="checkbox"/>	$(K_f \cdot ShcP - K_r \cdot ShcU)$	nM.s ⁻¹
Kf	forward rate constant	<input type="checkbox"/>	0.005	s ⁻¹
Kr	reverse rate constant	<input type="checkbox"/>	0.0	s ⁻¹
ShcP	Species Concentration	<input checked="" type="checkbox"/>	Variable	nM
ShcU	Species Concentration	<input checked="" type="checkbox"/>	Variable	nM

TIP: Enter a string (e.g. Molecule or Site name) in the Search field, and the table will be filtered to display only entries containing this string. You can enter any BNGL string as well.

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File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
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- Applications (3)
 - network_determ
 - network_free
 - network_stoch
- Parameters, Functions and Units
- Pathway

Reaction Diagram | Reactions | Structures | Species | Molecules | Observables

Reaction	Name	Structure	Depiction	Kinetics	BioNetGen Definition
Reaction Rule	R_Grb2_interaction	c0		MassAction	EGFR(Y1~p)+Grb2(sh2) <-> EGFR(Y1~p)1.Grb2(sh2)1
Reaction Rule	R_ShcP_interaction	c0		MassAction	EGFR(Y2~p)+Shc(sh3,Y~p) <-> EGFR(Y2~p)1.Shc(sh3,Y~p)1
Reaction Rule	R_ShcU_interaction	c0		MassAction	EGFR(Y2~p)+Shc(sh3,Y~u) <-> EGFR(Y2~p)1.Shc(sh3,Y~u)1
ShcP -> ShcU	ShcDephosp	c0		MassAction	ShcP -> ShcU
Reaction Rule	Shc_phosph	c0		MassAction	EGFR(Y2~p)1.Shc(sh3!1,Y~u) -> EGFR(Y2~p)1.Shc(sh3!1,Y~p)
Reaction Rule	Y1_dephosph	c0		MassAction	EGFR(Y1~p) -> EGFR(Y1~u)
Reaction Rule	Y1_phosph	c0		MassAction	EGFR(tmd!+,Y1~u) -> EGFR(tmd!+,Y1~p)
Reaction Rule	Y2_dephosph	c0		MassAction	EGFR(Y2~p) -> EGFR(Y2~u)
Reaction Rule	Y2_phosph	c0		MassAction	EGFR(tmd!+,Y2~u) -> EGFR(tmd!+,Y2~p)
Reaction Rule	dimeriz	c0		MassAction	EGFR(ecd!+,tmd)+EGFR(ecd!+,tmd) <-> EGFR(ecd!+,tmd)2
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd,tmd)+EGF(Site) <-> EGFR(ecd,tmd).EGF(Site)

Press the **New...** buttons.

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BioModels | MathModels | Geometries

Search

RB

[Advanced >>](#)

Search Show All

- RB_EGFR_full
- RB_egfr_full
- RB_egfr_noSos
- RB_egfr_reduced
- Access[danv] Fri Apr 22 14:44:26 EDT 2016
- RB_egfr_simple
- RB_egfr_simple2
- RB_egfr_supersimple
- RB_egfr_tutorial
- RB_EnzymeKinetics_MassAct
- RB_math_noupdate
- RB_mix
- RB_roundtripping
- RB_SH2_Gab1

New Reaction New Rule Duplicate Delete Pathway Links Search

Object Properties Problems (0 Errors, 1 Warnings) Database File Info

Show Warnings Refresh

Description	Url	Source	Defined In:
Rates for rules and reactions have different physical meaning and are not converted automatically.		network_free	Application

Complete reaction rule as in the *RB_egfr_tutorial* model in the VCell 6.0 (Rule-based) folder. Pay attention to reversibility of rules and kinetic rates.

TIP: Check other VCell tutorials at <http://vcell.org> to learn about the use of Applications in VCell.

The screenshot shows the VCell software interface. On the left is a project tree for 'RB_egfr_tutorial' with folders for Physiology, Reactions (11), Structures (1), Species (5), Molecules (4), Observables (9), Applications, Parameters, and Pathway. The 'Applications' folder is expanded, showing a context menu with options: 'New Application > Deterministic', 'Remove Apps...', 'Expand All', and 'Collapse All'. A red arrow points from a text box to the 'Deterministic' option.

Name	Math Type	Annotation
network_determ	explicit network model, compartmental, deterministic (ODE)	
network_stoch	explicit network model, compartmental, stochastic (SSA)	(copied from Application0)
network_free	Agent-based model, compartmental, stochastic (SSA)	(copied from network_stoch) (copie...

1. Right click on Application, select New Application > Deterministic. A **Deterministic application** uses the BioNetGen engine to generate a reaction network that is solved as a system of ODEs.

At the bottom, there is a search panel with 'RB' entered, and a list of search results including folders like 'RB_EGFR_full', 'RB_egfr_full', 'RB_egfr_noSos', 'RB_egfr_reduced', 'RB_egfr_simple', 'RB_egfr_simple2', 'RB_egfr_supersimple', 'RB_egfr_tutorial', 'RB_EnzymeKinetics_MassAct', 'RB_math_noupdate', 'RB_mix', 'RB_roundtripping', and 'RB_SH2_Gab1'.

TIP: Clamped means that the value of species is kept constant during the simulation.

1. Left click on new Application, select **Specifications**.

2. Left click on Species.

3. Set initial values of species specified in the Physiology.

Species	Structure	Clamped	Initial Condition
R	c0	<input type="checkbox"/>	100.0 [nM]
L	c0	<input type="checkbox"/>	680.0 [nM]
Grb2	c0	<input type="checkbox"/>	58.0 [nM]
ShcP	c0	<input type="checkbox"/>	0.0 [nM]
ShcU	c0	<input type="checkbox"/>	150.0 [nM]

TIP: Enabling/disabling reactions is very useful for model validation: see how the network size is changing when upstream or downstream reaction rules are disabled.

The screenshot shows the VCell 6.0 interface. The left sidebar displays a tree view of the model structure, with 'Specifications' selected under the 'network_determ' application. The main window shows the 'Specifications' panel with a table of reactions and their properties. The table has columns for Name, Type, Enabled, and Fast. The 'Enabled' column contains checkboxes, and the 'Fast' column contains checkboxes. Red arrows point to the 'Specifications' button in the sidebar, the 'Enabled' checkboxes in the table, and the 'Fast' checkboxes in the table. Yellow callout boxes provide instructions for each step.

Name	Type	Enabled	Fast
ShcDephosp	Reaction	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ligand_bind	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
dimeriz	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Y2_phosph	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Y1_phosph	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Y2_dephosph	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Y1_dephosph	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
R_Grb2_interaction	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
R_ShcU_interaction	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Shc_phosph	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>
R...	Reaction Rule	<input checked="" type="checkbox"/>	<input type="checkbox"/>

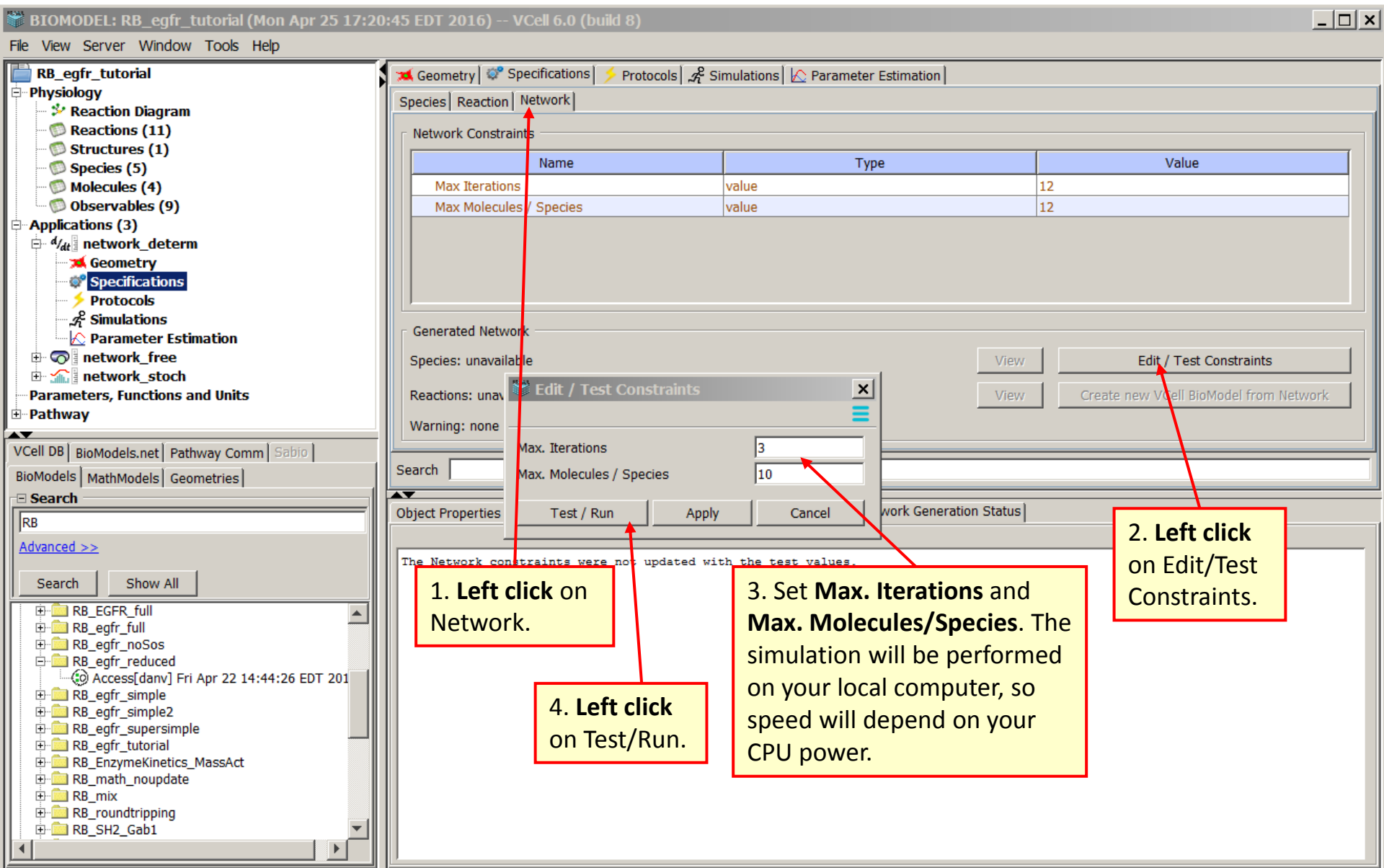
1. Left click on Application, select **Specifications**.

2. Left click on Reactions.

3. Uncheck to disable (remove from network generation).

4. Reactions (not rules) can be declared to have fast kinetics. The scale separation will be used by ODE solver.

TIP: Setting Max. Molecules/Species may be biologically relevant if, for example, it is known from experiments that complexes may have no more than a certain number of molecules.



1. Left click on Network.

4. Left click on Test/Run.

3. Set Max. Iterations and Max. Molecules/Species. The simulation will be performed on your local computer, so speed will depend on your CPU power.

2. Left click on Edit/Test Constraints.

TIP: Network generation may take a long time, so the default values are set very low. Most likely, they are too low for the network to be generated fully, and you will need to increase them.

The screenshot shows the VCell software interface. On the left is a tree view of the model components. The main window is divided into several panels. The 'Specifications' panel is active, showing 'Network Constraints' with a table:

Name	Type	Value
Max Iterations	value	12
Max Molecules / Species	value	12

Below this is the 'Generated Network' section, which is currently empty. A dialog box titled 'Apply the new constraints?' is open, showing the current values: Max. Iterations: 3, Max. Molecules / Species: 10. A warning message reads: 'Warning: Max Iterations number may be insufficient.' The dialog has 'Apply' and 'Cancel' buttons. A red arrow points from the 'Cancel' button to a text box on the right. Another red arrow points from the 'Warning' message in the dialog to a text box at the bottom.

At the bottom of the interface, the 'Running BioNetGen ...' output window shows the following progress:

```
Running BioNetGen ...
Iteration 0: 5 species
Iteration 1: 6 species
Iteration 2: 8 species
Iteration 3: 12 species
CPU TIME: total 0.08 s.
Creating BNG output spec ...
Return BioNetGen output to requester...
Total run time: 1 s.
Warning: Max Iterations number may be insufficient.
Please go to the Specifications / Network panel and adjust the number of Iterations.
```

Two text boxes provide instructions:

- 1. Check generation progress. The last iteration shown here still generates new species, so the network may be not fully generated.
- 2. Unless the incomplete network is enough (e.g. if it is truncated by the maximum number of molecules per species), click **Cancel** and choose larger values.

TIP: If network generation takes too long, it can be cancelled. VCell has a hard limit on the maximum number of species and reactions. If a generated network size exceeds this limit, constraints will not be applied, and the model should be adjusted to become smaller, or a **Network-Free** application used instead.

The screenshot shows the VCell 6.0 interface with the 'Specifications' tab selected. A 'Network Constraints' table is visible, and a 'Generated Network' section shows 'Species: unavailable' and 'Reactions: unavailable'. A dialog box titled 'Apply the new constraints?' is open, showing 'Max. Iterations: 14' and 'Max. Molecules / Species: 11'. The 'Object Properties' section shows the progress of 'Running BioNetGen ...' with a table of iterations and species counts. A search bar at the bottom left contains 'RB'. A search results list is visible below the search bar.

Name	Type	Value
Max Iterations	value	12
Max Molecules / Species	value	12

Iteration	Species
0	5 species
1	6 species
2	8 species
3	12 species
4	15 species
5	17 species
6	17 species

Running BioNetGen ...
Iteration 0: 5 species
Iteration 1: 6 species
Iteration 2: 8 species
Iteration 3: 12 species
Iteration 4: 15 species
Iteration 5: 17 species
Iteration 6: 17 species
CPU TIME: total 0.14 s.
Creating BNG output spec ...
Return BioNetGen output to requester...
Total run time: 1.1 s.

Apply the new constraints?
Max. Iterations 14
Max. Molecules / Species 11
Warning: none
Apply Cancel

Species: unavailable
Reactions: unavailable
Warning: none

Max Iterations 12
Max Molecules / Species 12

View Edit / Test Constraints
View Create new VCell BioModel from Network

Search

RB

Advanced >>

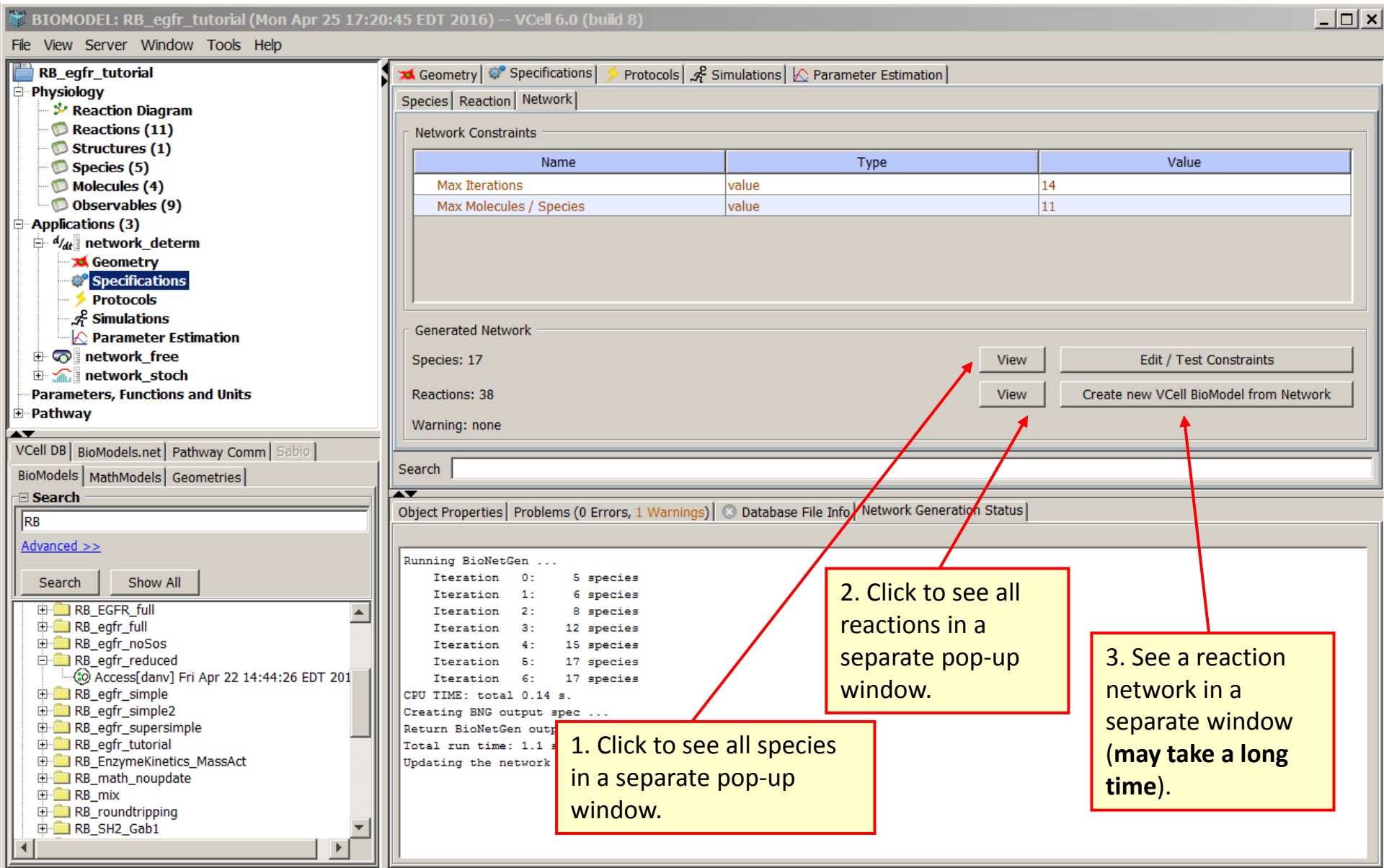
Search Show All

- RB_EGFR_full
- RB_egfr_full
- RB_egfr_noSos
- RB_egfr_reduced
- Access[danv] Fri Apr 22 14:44:26 EDT 201
- RB_egfr_simple
- RB_egfr_simple2
- RB_egfr_supersimple
- RB_egfr_tutorial
- RB_EnzymeKinetics_MassAct
- RB_math_noupdate
- RB_mix
- RB_roundtripping
- RB_SH2_Gab1

2. Click **Apply** to prepare network for simulation.

1. Check generation progress. No warnings means that the network is fully generated.

TIP: All actions on this page are optional but highly recommended to verify that the generated network contains all expected, and does not contain unexpected, species and reactions. *Creating a new BioModel may take a long time and is not recommended for large networks.*



1. Click to see all species in a separate pop-up window.

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 Species

Index	Name	Expression
1	R	EGFR(Y1~u,Y2~u,ecd,tmd)
2	L	EGF(Site)
3	Grb2	Grb2(sh2)
4	ShcP	Shc(Y~p,sh3)
5	ShcU	Shc(Y~u,sh3)
6	s5	EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1)
7	s6	EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1)
8	s7	EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1)
9	s8	EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1)
10	s9	EGF(Site!1).EGFR(Y1~p!2,Y2~u,ecd,tmd!1).Grb2(sh2!2)
11	s10	EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2)
12	s11	EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~p,sh3!2)
13	s12	EGF(Site!1).EGFR(Y1~p!2,Y2~p,ecd,tmd!1).Grb2(sh2!2)
14	s13	EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2)
15	s14	EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~p,sh3!2)
16	s15	EGF(Site!1).EGFR(Y1~p!2,Y2~p!3,ecd,tmd!1).Grb2(sh2!2).Shc(Y~u,sh3!3)
17	s16	EGF(Site!1).EGFR(Y1~p!2,Y2~p!3,ecd,tmd!1).Grb2(sh2!2).Shc(Y~p,sh3!3)

Search

Close

View Generated Reactions

Index	Expression
1	EGFR(Y1~u,Y2~u,ecd,tmd) + EGF(Site) -> EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1)
2	EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1)
3	EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1)
4	EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1)
5	EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1)
6	EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1)
7	EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~u,ecd,tmd!1)
8	Grb2(sh2) + EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p!2,Y2~u,ecd,tmd!1).Grb2(sh2!2)
9	Shc(Y~u,sh3) + EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2)
10	Shc(Y~p,sh3) + EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~p,sh3!2)
11	EGF(Site!1).EGFR(Y1~p!2,Y2~u,ecd,tmd!1).Grb2(sh2!2) -> EGF(Site!1).EGFR(Y1~p!2,Y2~p,ecd,tmd!1).Grb2(sh2!2)
12	EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2) -> EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2)
13	EGF(Site!1).EGFR(Y1~u,Y2~p!2,ecd,tmd!1).Shc(Y~p,sh3!2) -> EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~p,sh3!2)
14	EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1)
15	EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1)
16	Grb2(sh2) + EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p!2,Y2~p,ecd,tmd!1).Grb2(sh2!2)
17	EGF(Site!1).EGFR(Y1~p!2,Y2~u,ecd,tmd!1).Grb2(sh2!2) -> Grb2(sh2) + EGF(Site!1).EGFR(Y1~p,Y2~u,ecd,tmd!1)
18	Shc(Y~u,sh3) + EGF(Site!1).EGFR(Y1~p,Y2~p,ecd,tmd!1) -> EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2)
19	EGF(Site!1).EGFR(Y1~p,Y2~p!2,ecd,tmd!1).Shc(Y~u,sh3!2) -> Shc(Y~u,sh3) + EGF(Site!1).EGFR(Y1~u,Y2~p,ecd,tmd!1)

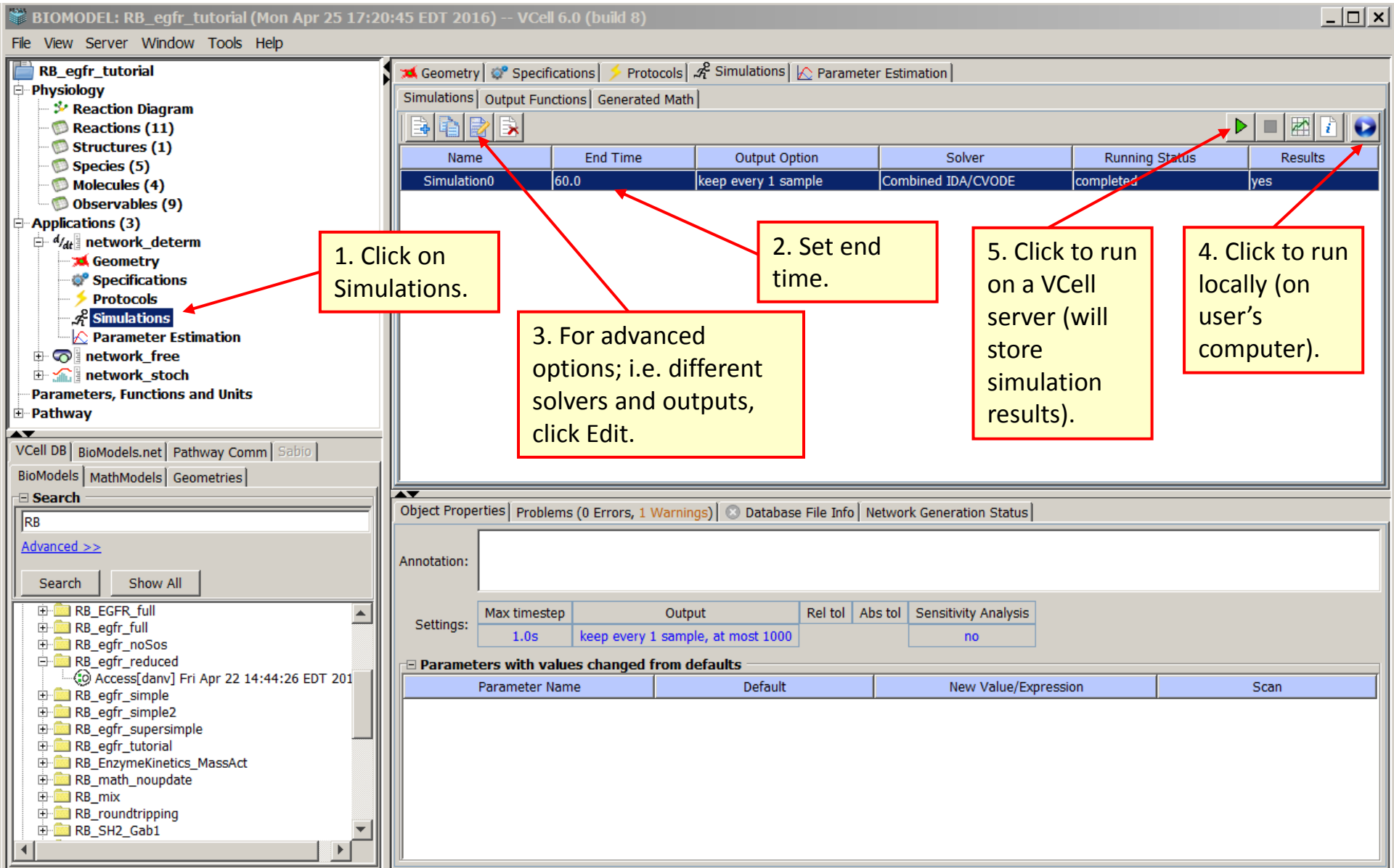
Search

Close

Different bonds are shown in different colors.

Species and reactions can be filtered by entering a string, e.g. Molecule or Site name, in the Search box.

TIP: Most models can be efficiently simulated locally (blue button). But if you want to save simulation results in the database for quick retrieval later on, the server simulation (green button) is recommended.

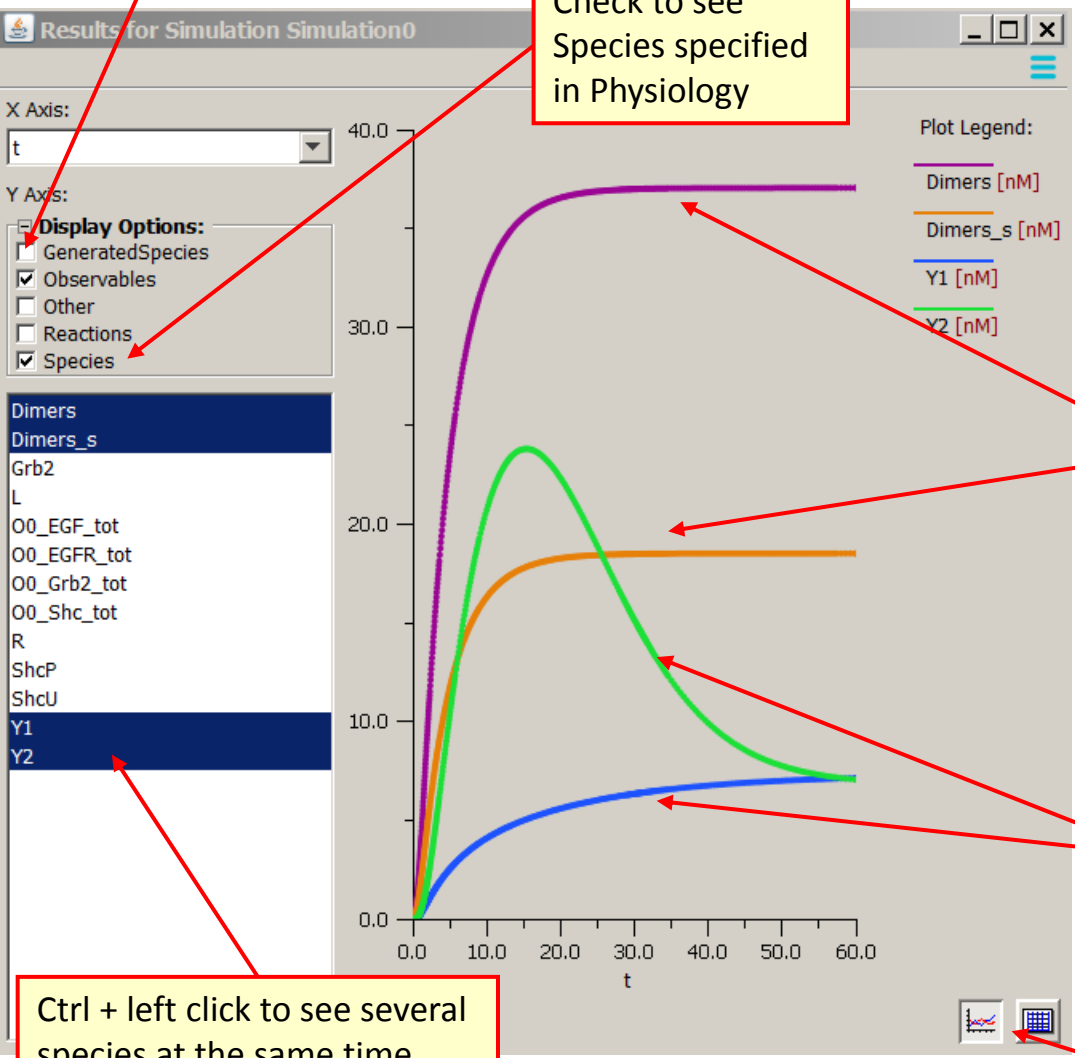


Check to view species generated by BioNetGen

Check to see Species specified in Physiology

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.



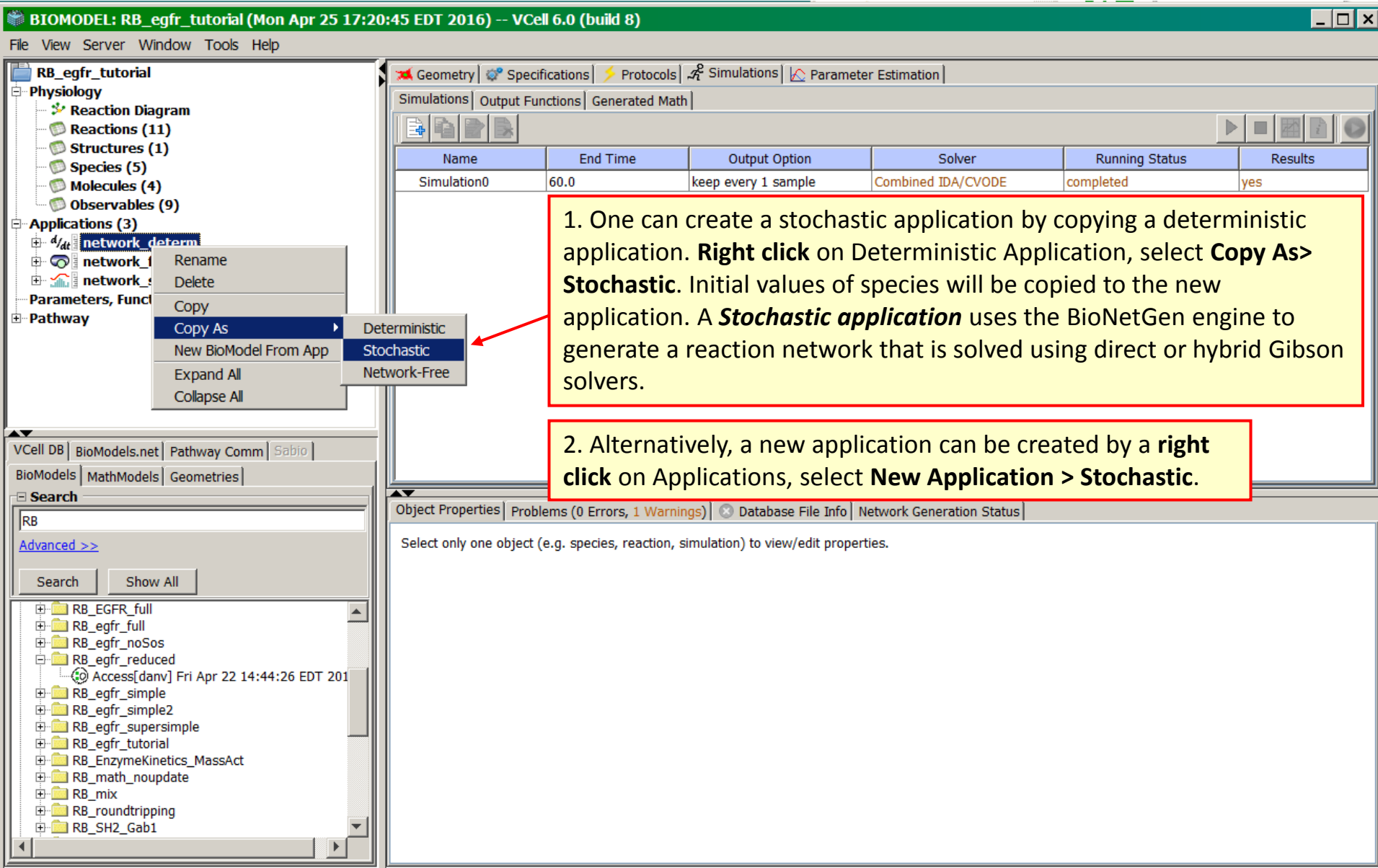
Note the difference between EGFR dimers counted as molecules and as species

The difference between "Y1" and "Y2" phosphorylation timecourses is due to Shc phosphorylation.

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

Click to see numerical values

TIP: A stochastic application is recommended when the number of particles is low, and a deterministic simulation (using concentrations) may miss noise and fluctuations. It uses the same network generated by BioNetGen.

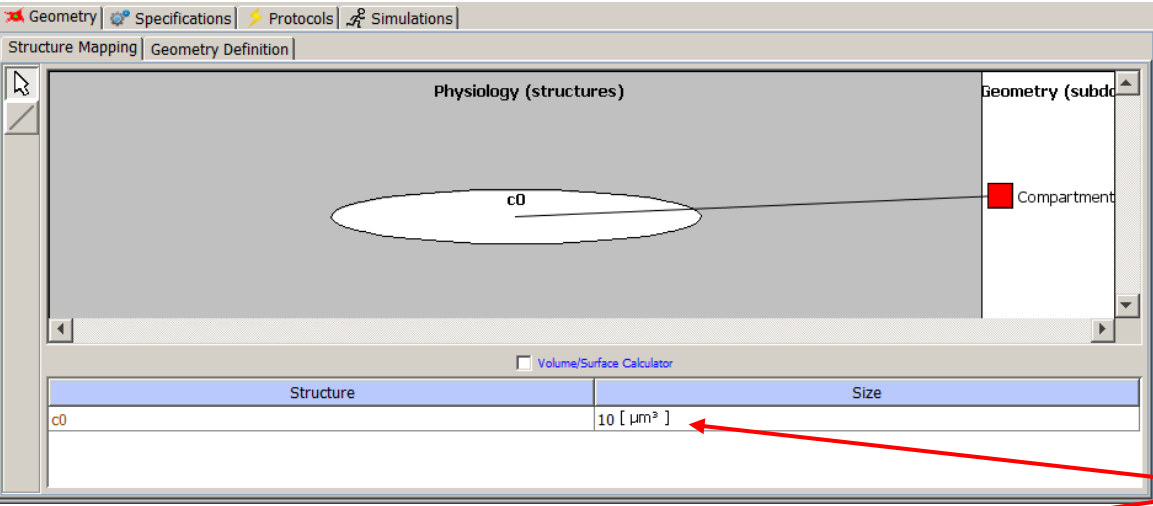


1. One can create a stochastic application by copying a deterministic application. **Right click** on Deterministic Application, select **Copy As> Stochastic**. Initial values of species will be copied to the new application. A **Stochastic application** uses the BioNetGen engine to generate a reaction network that is solved using direct or hybrid Gibson solvers.

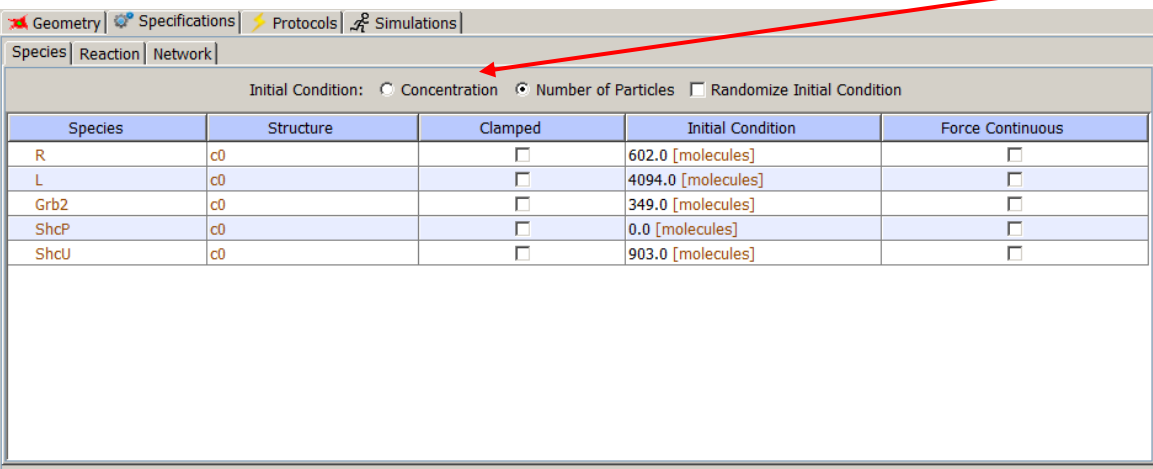
2. Alternatively, a new application can be created by a **right click** on Applications, select **New Application > Stochastic**.

TIP1: If the model was defined in concentrations, concentrations are converted into particle numbers using the volumes specified under Geometry. The default size is 5000 μm^3 (average cell size), so the number of particles will be exceedingly large. You need to decrease Size to a small simulation volume.

TIP2: To keep concentrations fixed, check "Concentration" before switching to Geometry and changing its Size.



Switching back and forth between **Geometry > Structure Mapping** and **Specifications > Species**, make sure your simulation volume is sufficiently small, so that for given concentrations the number of particles is small enough for stochastic simulations.

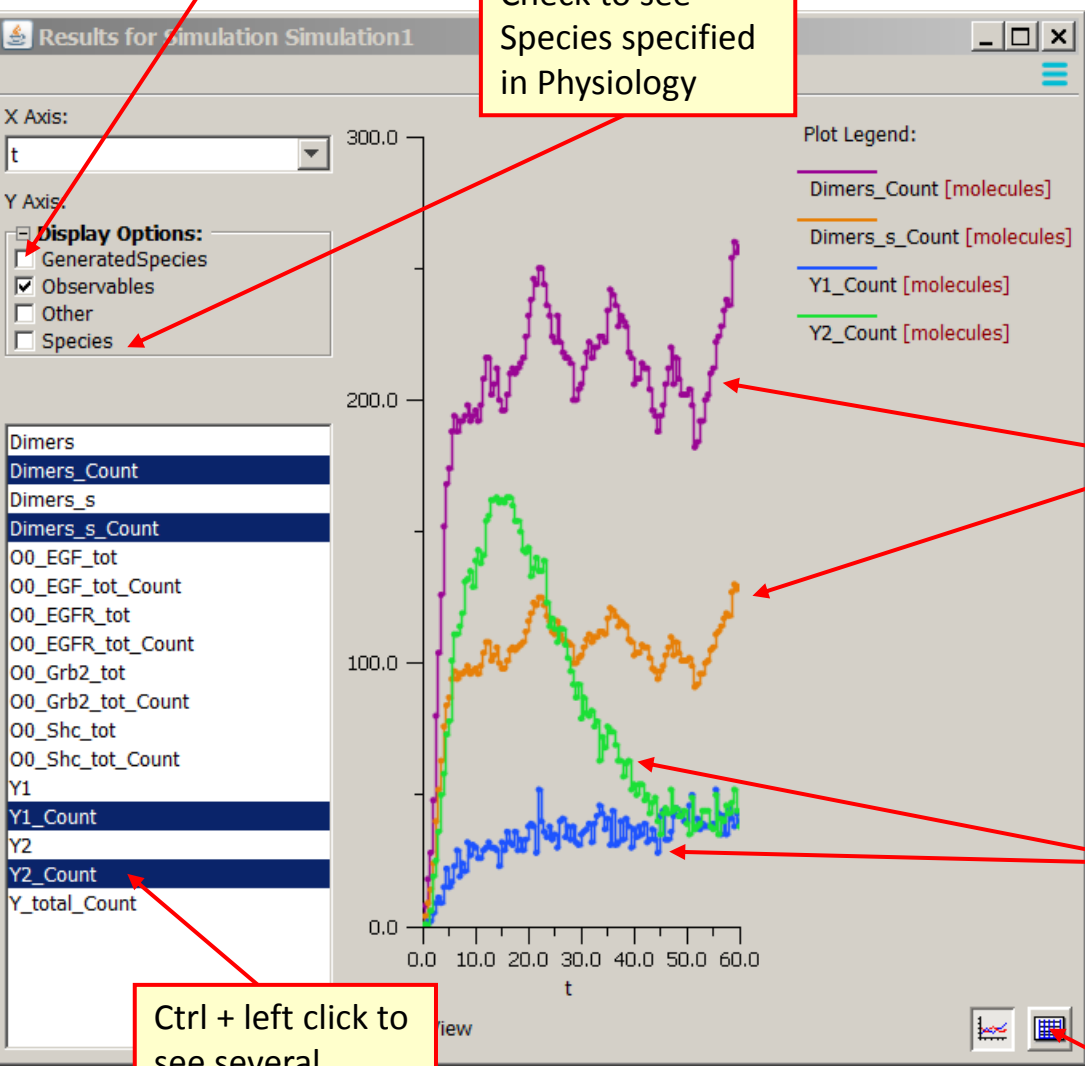


Check to see species generated by BioNetGen

Check to see Species specified in Physiology

TIP1: Every species and observable is presented in two units – concentrations (to compare to deterministic results) and molecules (displayed with `_Count` appendix).

TIP2: Select **Other** to view show reaction rates (as `Kf_...`) and reaction firing events (as `P_...`) per second for each individual reaction generated by each rule.



Note the difference between EGFR dimers counted as molecules and as species

The difference between "Y1" and "Y2" phosphorylation timecourses is due to Shc phosphorylation.

Ctrl + left click to see several species at once

Click to see numerical values

TIP: A Network-Free application simulates timecourses for observables without network generation. If the network size is too large or infinite, it is the only way to compute observables. However, individual species are not visible. To check whether a specific species is populated, it can be added to the list of Observables.

BIOMODEL: RB_egfr_tutorial (Mon Apr 25 17:20:45 EDT 2016) -- VCell 6.0 (build 8)

File View Server Window Tools Help

RB_egfr_tutorial

- Physiology
 - Reaction Diagram
 - Reactions (11)
 - Structures (1)
 - Species (5)
 - Molecules (4)
 - Observables (9)
- Applications (3)
 - network_determ
 - network_free
 - network_stoch
- Parameters, Func
- Pathway

Geometry Specifications Protocols Simulations

Simulations Output Functions Generated Math

Name	End Time	Output Option	Solver	Running Status	Results
Simulation1	60.0	every 0.5 s	Gibson	completed	yes

1. One can create a Network-Free application by copying a deterministic or stochastic applications. Copying a stochastic simulation will preserve particle numbers. **Right click** on existing Application, select **Copy As > Network-Free. Network-Free application** uses the **NFSim** engine to stochastically simulate timecourses for observables and initial species.

2. Alternatively, a brand new application can be created by a **right click** on Applications, select **New Application > Network-Free**. As in Stochastic Applications, care should be taken to limit the number of particles.

VCeLL DB | BioModels.net | Pathway Comm | Sabio

BioModels MathModels Geometries

Search

RB

[Advanced >>](#)

Search Show All

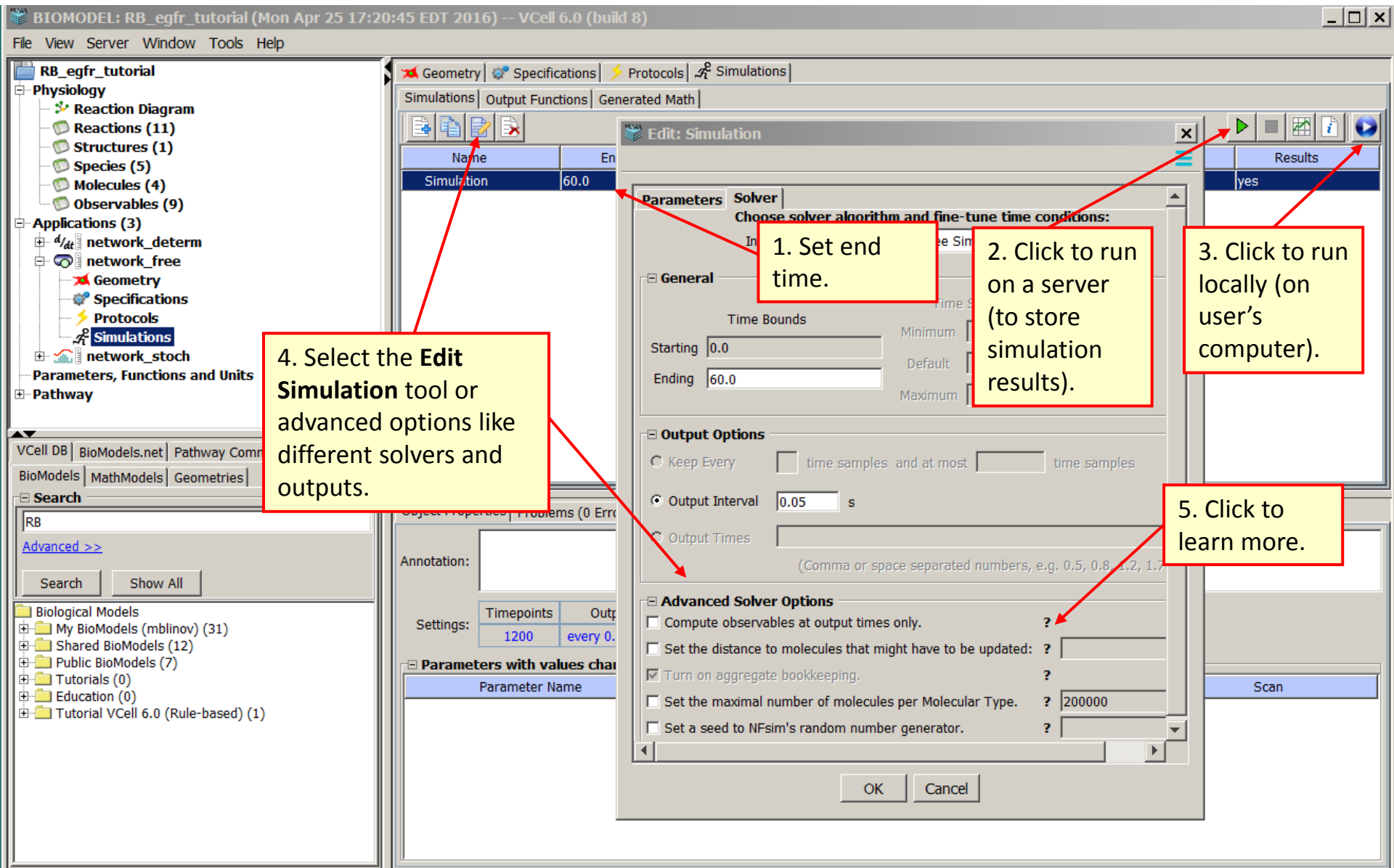
Biological Models

- My BioModels (mblinov) (31)
- Shared BioModels (12)
- Public BioModels (7)
- Tutorials (0)
- Education (0)
- Tutorial VCell 6.0 (Rule-based) (1)

Object Properties Problem

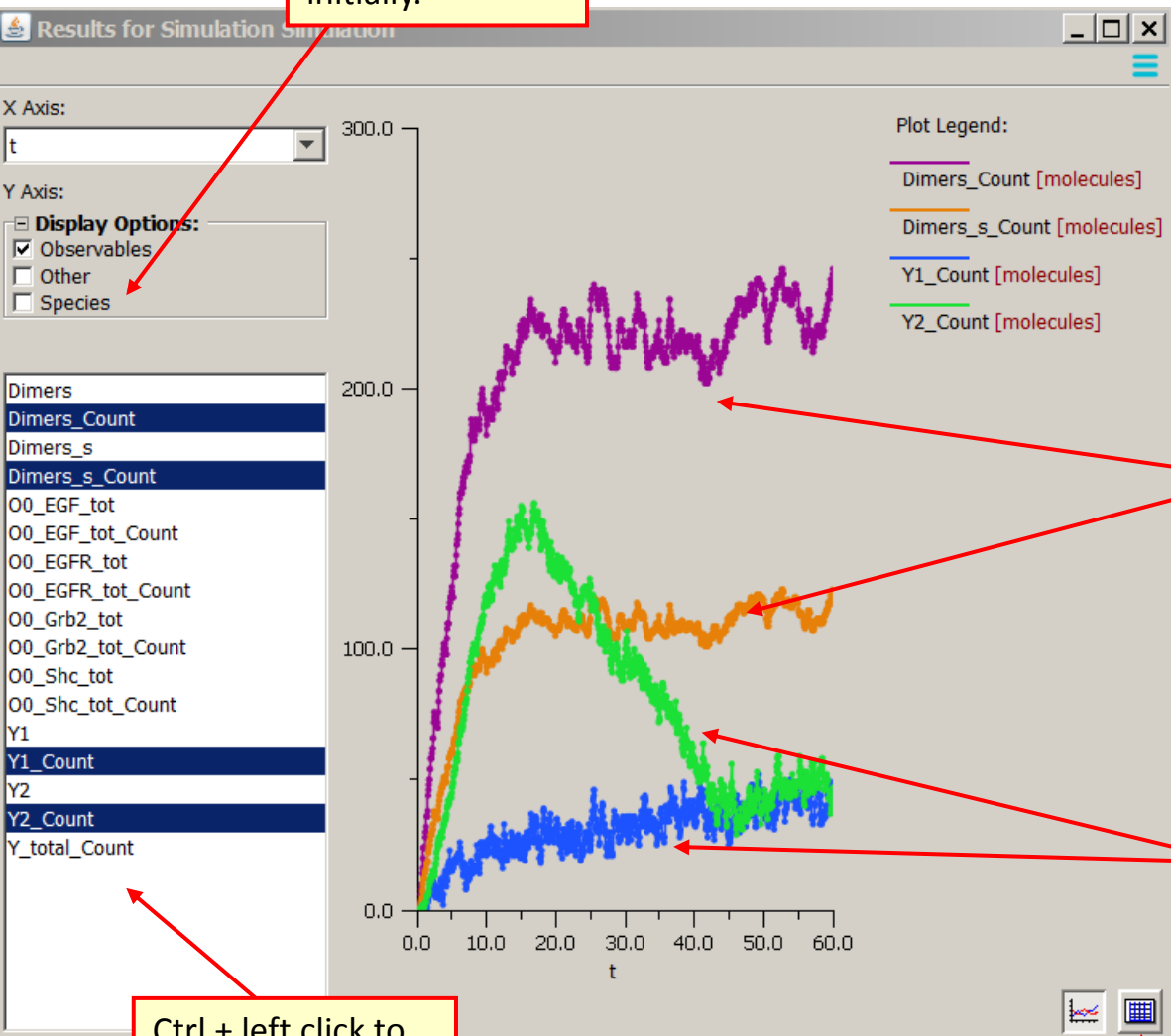
Select only one object (e.g.

TIP: The NFSim engine has a large number of fine-tuning options. Generally, default options should be sufficient to simulate most models. If necessary, click on Edit. Options are documented under ? and in the Help menu.



Select to list Species defined initially.

TIP: Generally, deterministic, stochastic and NFSim simulation results should be similar (given noise and fluctuations). If NFSim results are very different from results from a network, it may mean that the network is truncated and *not exhaustively generated*.



See the difference between EGFR dimers counted as molecules and as species

The difference between "Y1" and "Y2" phosphorylations timecourses is due to Shc phosphorylation.

Ctrl + left click to see several species at once.

Click to see numerical values