

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.

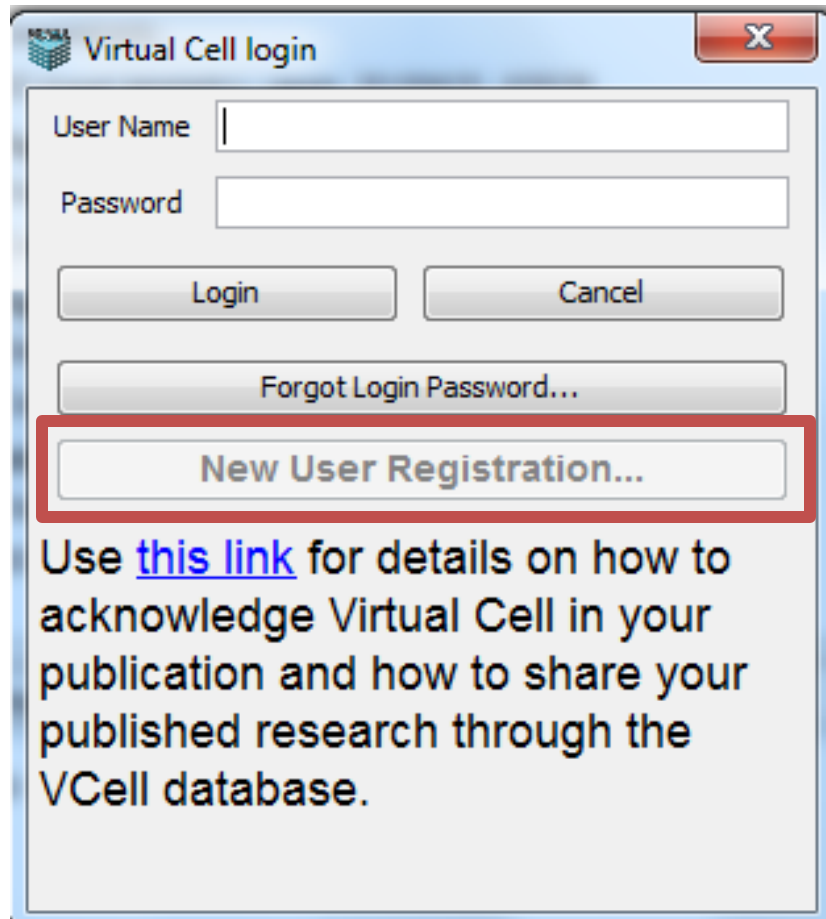
General familiarity with VCell software is recommended. Although this tutorial can be followed by a VCell novice, it is recommended that novice users first look through the VCell tutorials available at http://vcell.org/vcell_software/user_guide.html .

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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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**

The screenshot shows the VCell 6.0 interface. The title bar reads "BIOMODEL: BioModel10 (NoVersion) (NoDate) -- VCell 6.0 (build 7)". The menu bar includes File, View, Server, Window, Tools, and Help. The left sidebar shows a tree view under "BioModel10" with categories like Physiology, Reactions (0), Structures (1), Species (0), Molecules (1), and Observables (1). The "Molecules" category is selected. Below this, there are links for VCell DB, BioModels.net, Pathway Comm, and Sabio. A search bar is present. The main window has tabs for Reaction Diagram, Reactions, Structures, Species, Molecules, and Observables. The "Molecules" tab is active, showing a table with columns Name, Depiction, and BioNetGen Definition. The table contains one entry: MT0, with a depiction of a red circle and the definition MT0(). Below the table, there is a "New Molecule" button, a "Delete" button, and a "Pathway Links" dropdown. The "Object Properties" panel at the bottom shows a context menu for the "MT0" molecule with options "Rename" and "Add Site". The "Annotation" panel is also visible at the bottom.

Name	Depiction	BioNetGen Definition
MT0		MT0()
(add new here)		

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.

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 (1)

Observables (1)

Applications (0)

Parameters, Functions and Units

Pathway

VCell DB BioModels.net Pathway Comm Sabio

BioModels MathModels Geometries

Search

Biological Models

My BioModels (mblinov) (240)

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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

Reaction Diagram Reactions Structures Species Molecules Observables

Name	Depiction	BioNetGen Definition
EGF		EGF(Site0)
(add new here)		

New Molecule Delete Pathway Links

Search

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

EGF Site0

Move right

Move left

Rename

Delete

Add State

Annotation

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**

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.

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

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

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

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

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)

New Molecule | Delete | Pathway Links

Object Properties | Problems (0 Errors, 0 Warnings) | Data

EGFR

ecd tmd Y1 Y2

Annotation

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

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)

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BioNetGen : RB_EnzymeKinetics_MultipleApp

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

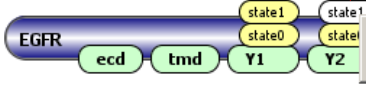
Pathway Links

Search

Object Properties

Problems (0 Errors, 0 Warnings)

Database File Info



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

VCell DB | BioModels.net | Pathway Comm | Sabio

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Search

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BioNetGen : egfr_full

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BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

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.

New Molecule | Delete | Pathway Links | Search

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

Annotation

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

2. Annotations can be entered here.

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

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

FileViewServerWindowToolsHelp

New

Open

CloseCtrl+W

Save

Save New Version

Save As...

Save As Local...

Revert to Saved

Compare with Saved

Permissions...

Model Annotation ...

Edit Annotation...

Field Data...

Import...

Export...

Exit

VCell DBBioModels.netPathway CommSabio

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BioNetGen : egfr_full

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BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

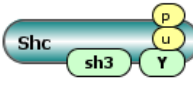
Reaction DiagramReactionsStructuresSpeciesMoleculesObservables

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)		

New MoleculeDeletePathway Links

Search

Object PropertiesProblems (0 Errors, 0 Warnings)Database File Info



Annotation

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

When ready to save, click on **File** and **Save As....** If you work locally (no internet connection), choose **Save As Local....**

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

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BioNetGen : egfr_full

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BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

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
(add new here)				

New Observable

Delete

Pathway Links

Object Properties

Problems (0 Errors, 0 Warnings)

Data

Annotation

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.

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

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



BioNetGen : egfr_full

Public Fri Jan 22 14:52:16 EST 2016

BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

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
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


Delete Species Pattern

Add Molecule

 EGF

 EGFR

 Grb2

 Shc

Annotation

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

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

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Tutorial VCell 6.0 (Rule-based) (3)

BioNetGen : egfr_full

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BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

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
(add new here)				

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").

New Observable | Delete | Pathway Links | Search

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

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)

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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(tmd!+)	Molecules
Dimers_s	c0		EGFR(tmd!+)	Species
Y1	c0		EGFR()	Molecules
(add new here)				

New Observable

Delete

Pathway Links

Search

Object Properties

Problems (0 Errors, 0 Warnings)

Database File Info

~ State: not specified

~ State: u

~ State: p

Annotation

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".

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)

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BioNetGen : RB_EnzymeKinetics_MultipleApp

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(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)				

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.

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 (1)**
 - Molecules (4)
 - Observables (9)
- Applications (0)
- Parameters, Functions and Units
- Pathway


VCell DB BioModels.net Pathway Comm Sabio

BioModels MathModels Geometries

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 - BioNetGen : egfr_full
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 - BioNetGen : Mix_Reactions_Rules
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Reaction Diagram Reactions Structures **Species** Molecules Observables

Name	Structure	Link	Depiction	BioNetGen Definition
R	c0			
(add new here)				

1. To add species, **left double click** on (add new here) and change the name to R. Alternatively, use the “New Species” button below.

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”.


New Species Delete Pathway Links Search

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

Species Name R

Linked Pathway Object(s)

Annotation

 Specify Molecule

- EGF
- EGFR**
- Grb2
- Shc

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.

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)
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- Species (1)
- 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,Y2)
(add new here)				

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).

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

VCell DB | BioModels.net | Pathway Comm | Sabio

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Biological Models

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New Species | Delete | Pathway Links | Search

Object Properties | **Problems (2 Errors, 0 Warnings)** | Database File Info

Species Name R

Linked Pathway Object(s)

Annotation

EGFR

ecd tmd Y1 Y2

~ State: u
~ State: p

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)

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RB_egfr_tutorial

Physiology

Reaction Diagram

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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)
(add new here)				

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

New Species | Delete | Pathway Links

Search

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

Species Name Shc

Linked Pathway Object(s)

Annotation

Shc

sh3

P

Y

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).

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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.

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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>

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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**.

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

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

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

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

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

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.

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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()	
Press the <i>New...</i> buttons.						

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

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

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

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

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Reactions

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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.						

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

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.

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


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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)	
<i>Press the New... buttons.</i>						

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

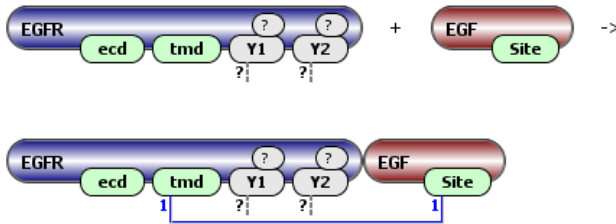
2. Note that by default a rule is created irreversible.

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



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

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RB_egfr_tutorial

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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. 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.

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: $K_f \cdot \prod \text{reactants} - K_r \cdot \prod \text{products}$)

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 type="checkbox"/>	0.0	$\text{s}^{-1} \cdot \mu\text{M}^{-1}$
Kr	microscopic reverse rate	<input type="checkbox"/>	0.0	s^{-1}

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

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

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.

1. To change the unit system, left click on Parameters,

2. Left click on **Model Unit System**.

3. Click on **Change Unit System**.

4. Select **general**.

5. Enter new units.

RB_egfr_tutorial (Sun Apr 14 2013 10:17:11 AM) (Build 7)

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RB_egfr_tutorial

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Model Unit System

	Unit	Category
Length	μm	primary
Area	μm ²	primary
Volume	μm ³	primary
Time	s	primary
Volume Substance	μM.μm ³	primary
Membrane Substance		primary
LumpedReactionSubstance		primary
Voltage		electrical
Current		electrical
Capacitance		electrical
Conductance		electrical
Stochastic Substance		stochastic
Particle Binding Radius		stochastic
Volume Concentration		otherDerived
Membrane Concentration		otherDerived
Volume Local Reaction Rate		otherDerived

select new unit system

☐ default

☐ sbml compatible

☒ general

type unit VCell default

length um [um]

area um2 [um2]

volume um3 [um3]

time s [s]

volume species substance nM.um3 [uM.um3]

membrane species substance molecules [molecules]

lumped reaction substance molecules [molecules]

OK Cancel

Change Unit System Search

Object Properties Problems (0 Errors, 0 Warnings)

Select only one object (e.g. species, reaction, compartment, etc.)

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- BioNetGen : RB_Enzy

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

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BioNetGen : Mix_Reactions_Rules

BioNetGen : RB_EnzymeKinetics_MultipleApp

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.						

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	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

Annotations

Set values in proper units. Match all values to the RB_egfr_tutorial model in the VCell 6.0 (Rule-based) folder.

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.

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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 <i>New...</i> 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

New Reaction

New Rule

Duplicate

Delete

Pathway Links

Search

Object Properties

Problems (0 Errors, 0 Warnings)

Database File Info

Kinetics

Editor

Reaction rule outcome: a new bond between “tmd” sites

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.

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

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)

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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

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!

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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.

1. Select a rule to duplicate and click on **Duplicate** button

2. The Identical rule will appear with the name *oldname_0*.

3. Rename the new rule and introduce any needed changes.

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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

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).

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

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RB_egfr_tutorial

Physiology

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RX Connection Tool

ShcP

ShcDephosp

ShcU

Grb2

c0

1

Delete

Pathway Links

Search

Object Properties

Problems (0 Errors, 1 Warnings)

Database File Info

Reaction Name

ShcDephosp

Reversible

Kinetic Type

Mass Action [uM/s] (recommended for stochastic application)

Convert to [molecules.s⁻¹]

Name	Description	Global	Expression	Units
J	reaction rate		(Kf · ShcP - Kr · ShcU)	nM.s ⁻¹
Kf	forward rate constant		0.005	s ⁻¹
Kr	reverse rate constant		0.0	s ⁻¹
ShcP	Species Concentration		Variable	nM
ShcU	Species Concentration		Variable	nM

Annotation and Pathway Links

1. Click on Reaction Diagram.

2. Select RX Connection tool.

3. Connect required species.

4. Specify reaction kinetics.

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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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_ShcU_interaction	c0		MassAction	EGFR(Y2~p)+Shc(sh3,Y~p) <-> EGFR(Y2~p!1).Shc(sh3!1)
Reaction Rule	R_ShcU_interaction	c0		MassAction	EGFR(Y2~p)+Shc(sh3,Y~u) <-> EGFR(Y2~p!1).Shc(sh3!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!+)
Reaction Rule	ligand_bind	c0		MassAction	EGFR(ecd,tmd)+EGF(Site) <-> EGFR(ecd,tmd).EGF(Site)

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

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

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RB_egfr_noSos

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RB_egfr_supersimple

RB_egfr_tutorial

RB_EnzymeKinetics_MassAct

RB_math_noupdate

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RB_roundtripping

RB_SH2_Gab1

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.

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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.

New Application

Delete

More Copy Actions

Compare...

Search

Object Properties

Problems (0 Errors, 1 Warnings)

Database File Info

Select only one object (e.g. species, reaction, simulation) to view/edit properties.

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

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Species Reaction Network

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]

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

2. Left click on Species.

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

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

Select only one object (e.g. species, reaction, simulation) to view/edit properties.

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.

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Species	Reaction	Network	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"/>

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

Select only one object (e.g. species, reaction, simulation) to view/edit properties.

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.

The screenshot shows the VCell 6.0 interface. On the left is a tree view of the model structure. The main window has tabs for Geometry, Specifications, Protocols, Simulations, and Parameter Estimation. The 'Network' tab is active, showing a table of network constraints. An 'Edit / Test Constraints' dialog box is open, allowing users to modify the 'Max. Iterations' and 'Max. Molecules / Species' values. Red arrows and numbered boxes provide instructions on how to interact with these elements.

1. Left click on Network.

2. Left click on Edit/Test Constraints.

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.

4. Left click on Test/Run.

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

Max. Iterations	3
Max. Molecules / Species	10

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 6.0 interface with the 'RB_egfr_tutorial' project open. The 'Specifications' tab is active, showing 'Network Constraints' with a table of 'Max Iterations' and 'Max Molecules / Species' both set to 12. A dialog box titled 'Apply the new constraints?' is open, showing 'Max. Iterations' set to 3 and 'Max. Molecules / Species' set to 10, with a warning: 'Warning: Max Iterations number may be insufficient.' The 'Object Properties' panel at the bottom shows the progress of 'Running BioNetGen ...' with iterations 0 to 3, showing an increasing number of species (5, 6, 8, 12). A red arrow points from the 'Cancel' button in the dialog box to the 'Warning: Max Iterations number may be insufficient.' message in the Object Properties panel. Another red arrow points from the 'Warning: Max Iterations number may be insufficient.' message to a text box on the right. A third red arrow points from the 'Warning: Max Iterations number may be insufficient.' message to a text box at the bottom.

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

Generated Network

Species: unavailable

Reactions: unavailable

Warning: none

Search

Object Properties

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.
```

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.

1. Check generation progress. The last iteration shown here still generates new species, so the network may be not fully generated.

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.

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Geometry Specifications Protocols Simulations Parameter Estimation

Species Reaction Network

Network Constraints

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

Generated Network

Species: unavailable

Reactions: unavailable

Warning: none

View Edit / Test Constraints

View Create new VCell BioModel from Network

Apply the new constraints?

Max. Iterations	14
Max. Molecules / Species	11
Warning: none	

Apply Cancel

Object Properties Problems

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.
```

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.*

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Reaction

Network

Network Constraints

Name	Type	Value
Max Iterations	value	14
Max Molecules / Species	value	11

Generated Network

Species: 17

Reactions: 38

Warning: none

View

Edit / Test Constraints

View

Create new VCell BioModel from Network

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Object Properties

Problems (0 Errors, 1 Warnings)

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Network Generation Status

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 outp

Total run time: 1.1 s

Updating the network

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

Different bonds are shown in different colors.

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~p,Y2~p,ecd,tmd!1)

Search

Close

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.

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Simulations Output Functions Generated Math

Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	60.0	keep every 1 sample	Combined IDA/CVODE	completed	yes

1. Click on Simulations.

2. Set end time.

3. For advanced options; i.e. different solvers and outputs, click Edit.

4. Click to run locally (on user's computer).

5. Click to run on a VCell server (will store simulation results).

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

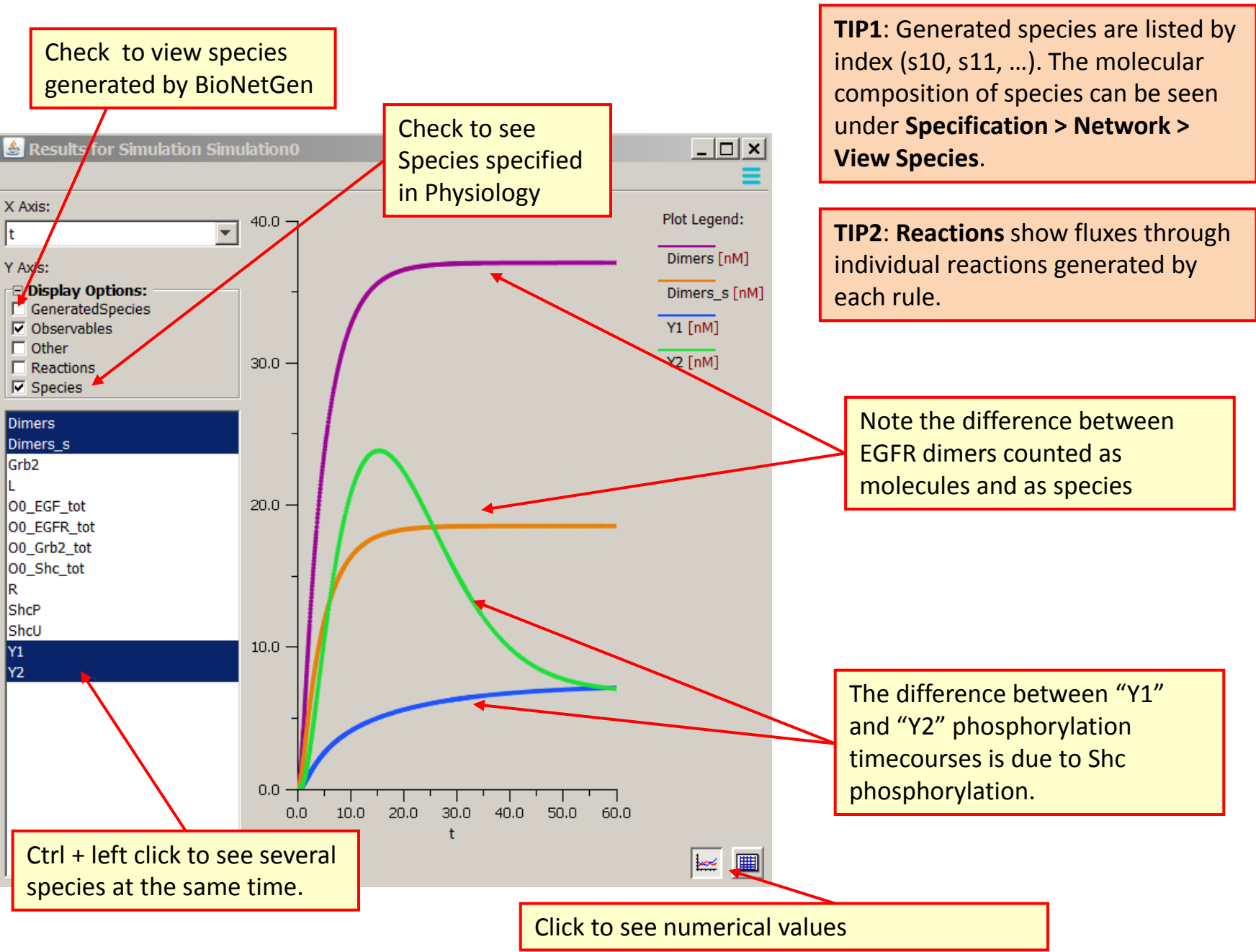
Annotation:

Settings:

Max timestep	Output	Rel tol	Abs tol	Sensitivity Analysis
1.0s	keep every 1 sample, at most 1000			no

Parameters with values changed from defaults

Parameter Name	Default	New Value/Expression	Scan
----------------	---------	----------------------	------



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.

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Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	60.0	keep every 1 sample	Combined IDA/CVODE	completed	yes

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**.

VCell DB BioModels.net Pathway Comm Sabio

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

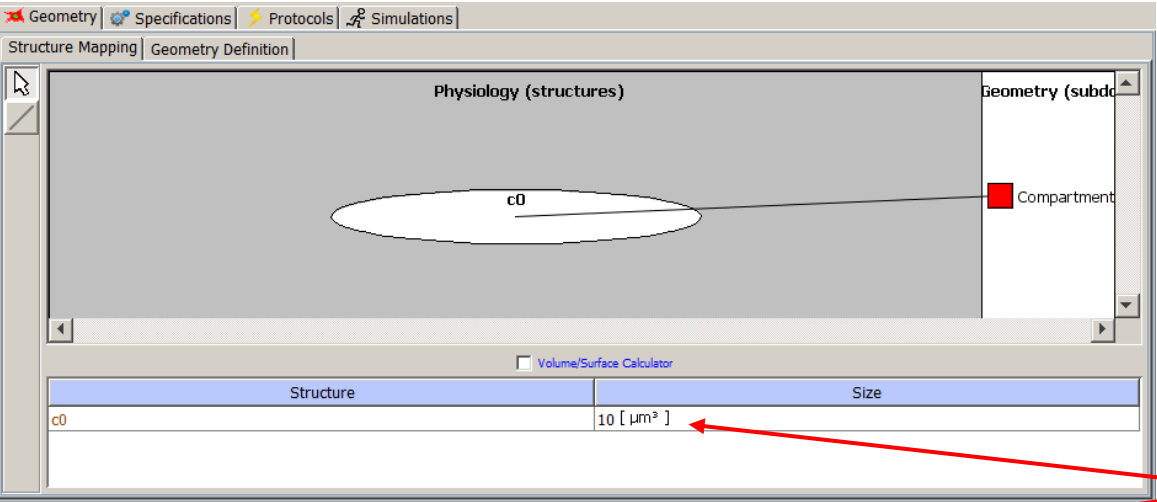
RB_SH2_Gab1

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

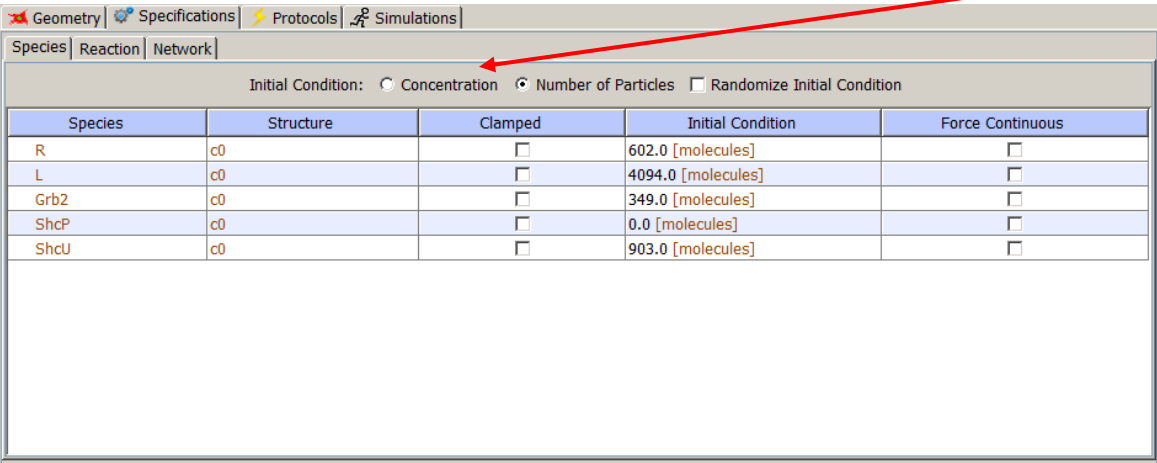
Select only one object (e.g. species, reaction, simulation) to view/edit properties.

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.

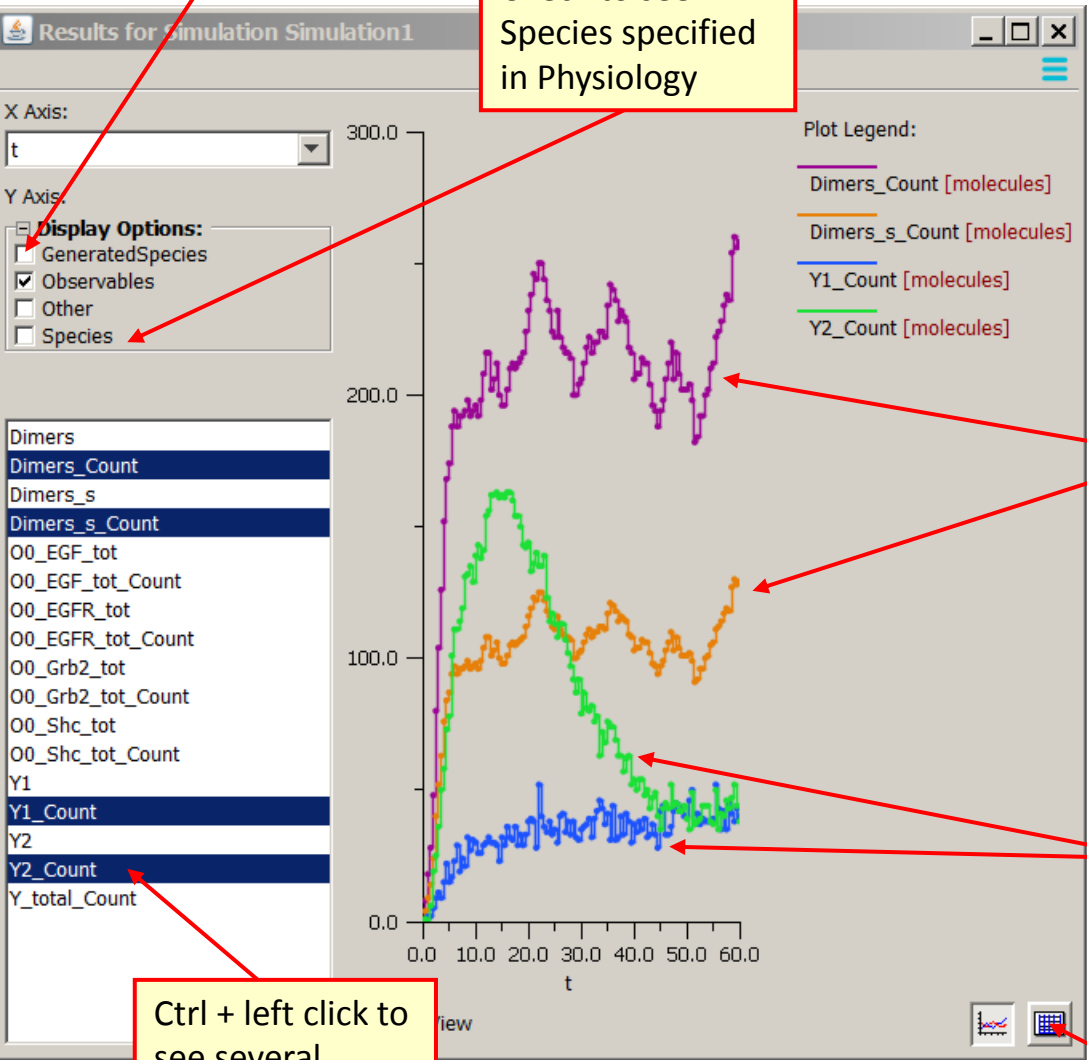


Switching back and forth between **Geometry > Structure Mapping** and **Specifications > Species**, make sure your simulation volume is sufficiently small, so that for given concentrations the number of particles is small enough for stochastic simulations.



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, Functions
- 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.

Object Properties Problem

Select only one object (e.g.)

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)

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.

The screenshot shows the VCell 6.0 interface with the 'Edit: Simulation' dialog box open. The dialog box has tabs for 'Parameters' and 'Solver'. The 'Parameters' tab is active, showing 'Time Bounds' with 'Starting' at 0.0 and 'Ending' at 60.0. The 'Output Options' section has 'Keep Every' selected, 'time samples' set to 0.05, and 'Output Interval' set to 0.05 s. The 'Advanced Solver Options' section has several checkboxes, including 'Compute observables at output times only', 'Set the distance to molecules that might have to be updated', 'Turn on aggregate bookkeeping', 'Set the maximal number of molecules per Molecular Type', and 'Set a seed to NFSim's random number generator'. The 'Results' tab is also visible, showing a 'yes' result. Five numbered callouts are present: 1. Set end time. (points to the 'Ending' field), 2. Click to run on a server (to store simulation results). (points to the 'Run on server' button), 3. Click to run locally (on user's computer). (points to the 'Run locally' button), 4. Select the Edit Simulation tool or advanced options like different solvers and outputs. (points to the 'Edit Simulation' button in the 'Simulations' tab), and 5. Click to learn more. (points to the '?' icon next to 'Compute observables at output times only').

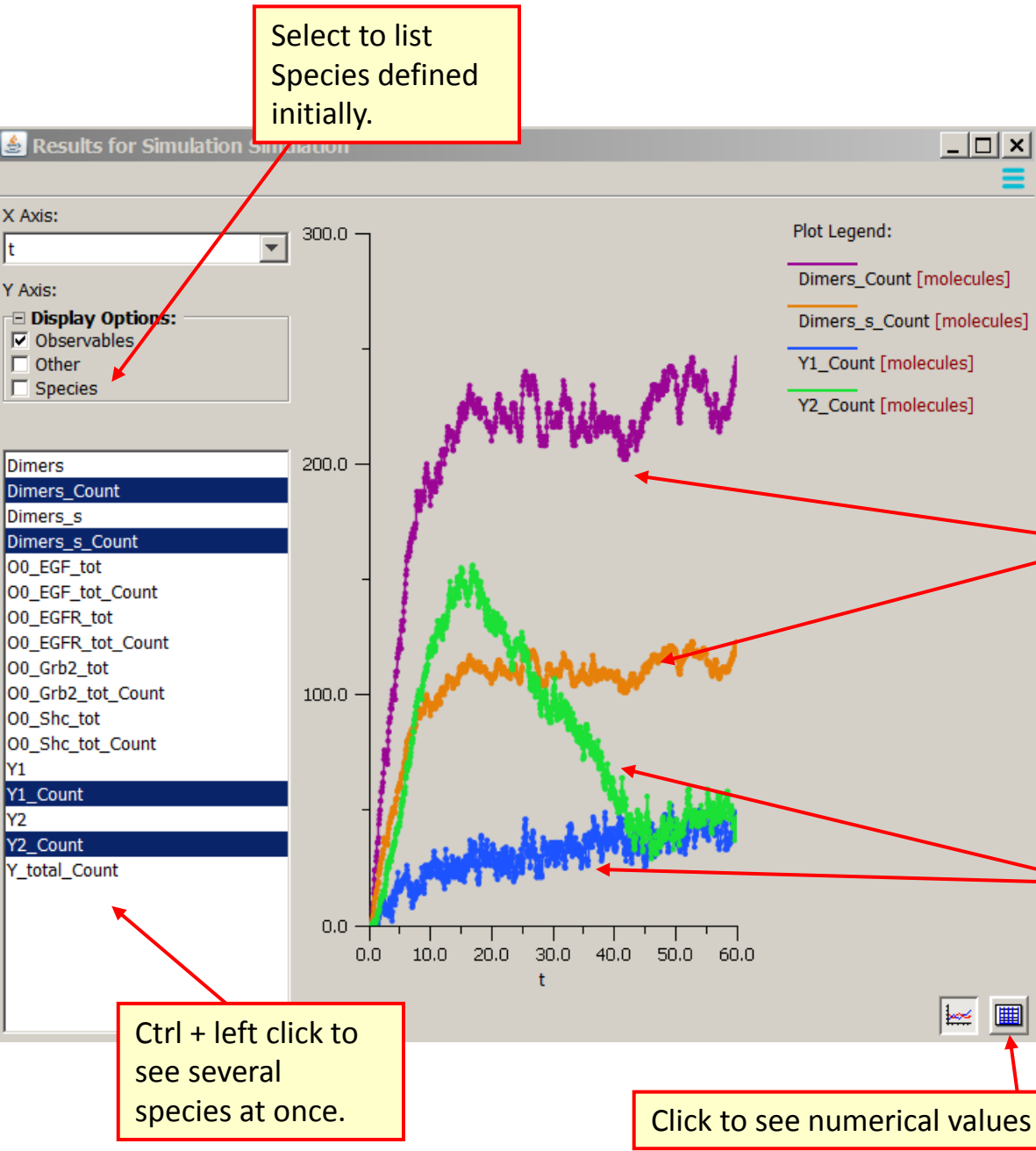
1. Set end time.

2. Click to run on a server (to store simulation results).

3. Click to run locally (on user's computer).

4. Select the **Edit Simulation** tool or advanced options like different solvers and outputs.

5. Click to learn more.



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