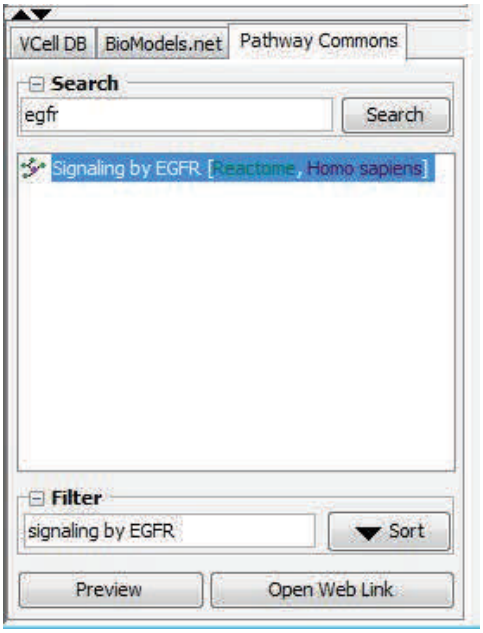
Using Pathway Commons
VCell Version 5.2

Introduction

In addition to designing and simulating new models, you, a VCell user, can search a large pool of existing models using VCell's internal database of all the models made public by VCell users, your own models, models shared between other users and yourself, as well as educational and tutorial models. Next, you can bring into the VCell many models from the repository of SBML models, Biomodels.net. Finally, you have access to the largest collection of pathway information stored in the collection of pathways databases aggregated under Pathway Commons. The Pathway Commons option allows you to do two important actions: first, you may link model elements with fully annotated pathway entities. Second, you may import large pathways into VCell biomodels, creating models automatically rather than manually creating each and every species and interactions corresponding to elements of the pathway.

Searching for a Pathway in the Pathway Commons collection of databases

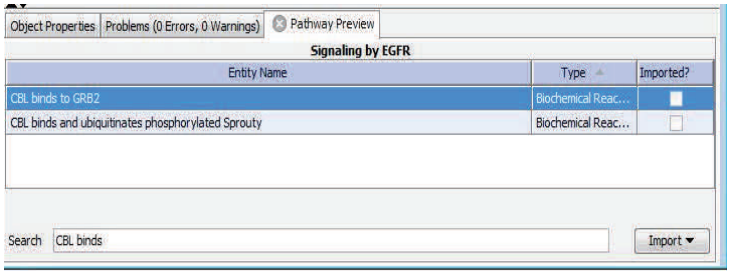
To search for a pathway, find the database panel of VCell, located in the lower left of the VCell window display. Click on the tab labeled **Pathway Commons**. There should be an entry field labeled **Search**. The search features allows you to look for search strings among all entities within the pathway, such as interaction names, protein names, or complexes. In this tutorial, you will create a quantitative model of the complete EGFR ((epidermal growth factor receptor) signaling pathway. For that, you start by searching for **egfr.** You retrieved several dozen pathways. If you know the pathway you're interested in, you can use entry field labeled **Filter** below the search results. Filtering allows you to narrow your search results by looking for pathways with specific strings in the title. Say, you know that you're interested in the Signaling by EGFR pathway, so we can start typing "Signaling by ... to narrow our search results. Select the search result titled **Signaling by EGFR [Reactome, Homo sapiens]**. "Reactome" refers to the database describing this pathway and "Homo sapiens" tells you that the pathway occurs in humans.



From here, if you click **Open Web Link**, you will be directed to **pathwaycommons.org** in your internet browser where a description of the pathway is given. Back in the VCell window, click **Preview** to display all of the entities in the pathway in the **Properties Panel** to the right of the database panel.

Importing a single interaction and linking objects in Physiology with Pathways

Once in the Properties Panel, you can sort the entities by name or type by clicking on the blue boxes above their respective columns. You can sort them by type so that the **Biochemical reactions** are listed first. Click the blue box labeled **Type** once to do this. Search for **CBL binds** in the field below. Click on **CBL binds to GRB2** to select the entity. Then, click the **Import** button and click **selected only** from the drop down menu. This imports only the reaction you selected and the species associated with it. The other options do the following:



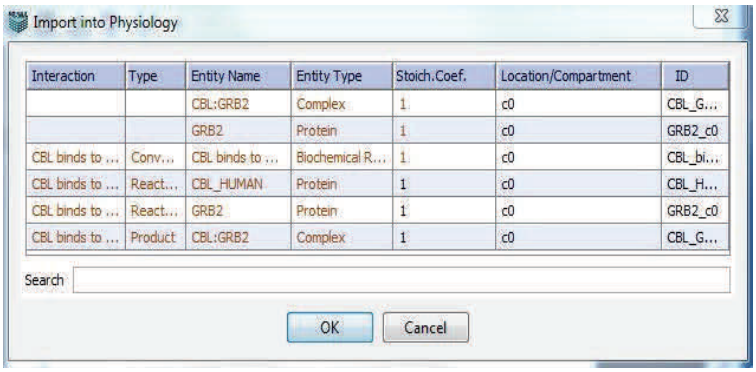
- **Plus Interactions** — this imports the entity you selected plus any interactions it is involved with.
- **Plus Components** — this imports the entity you selected plus any components associated with it.
- **Plus Complexes** — this imports the entity you selected plus any complexes associated with it.

You will then be able to see what you imported in the **Pathway Diagram** located above the Properties Panel. You can click on the arrange tools 

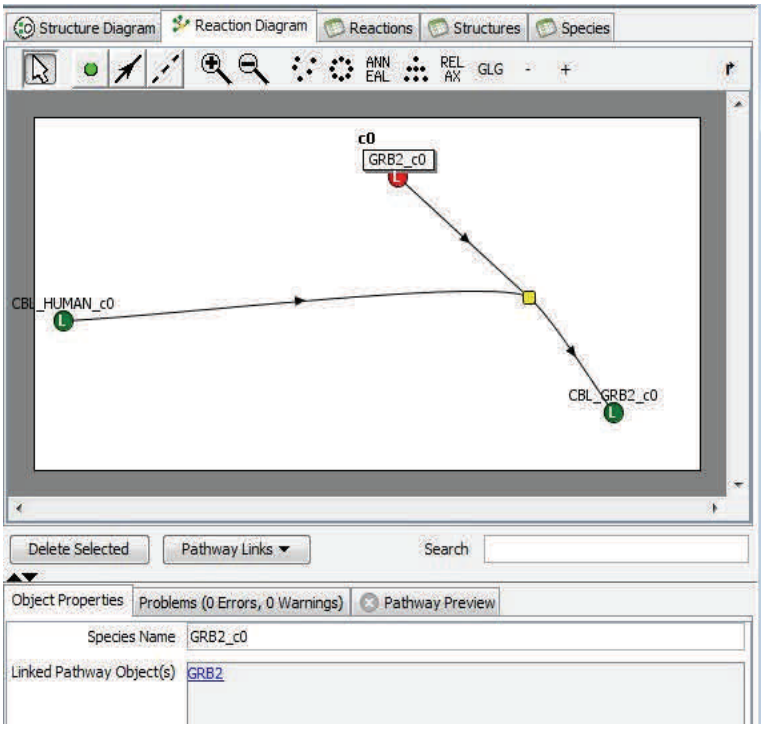
located above the diagram to reorganize the objects so they are easier to see.

Clicking on an entity displays information in the **Object Properties** panel below the diagram, such as name and web links to public web resources describing this entity. Click on any of the blue underlined links and you will be directed to a webpage opened in a new browser.

To import Pathway objects into a BioModel, select all of the objects in the diagram and then click the button labeled **Physiology Links** and then select **Import into physiology…** from the drop down menu. A dialog box will appear. Here, you can adjust stoichiometric coefficients of the reactants and products, as well as specify which compartment each object will be placed in. You also can change IDs of the species and reactions. In this tutorial, you can leave the stoichiometric coefficients as their default values. Since this tutorial only features one compartment, **c0**, you do not need to worry about changing the compartment. Click **OK** to finalize the import.



You will then be taken to the **Reaction Diagram**, which shows the reaction you linked. The species have an L on them to show that they were linked from Pathway Commons. Using the select tool, click on one of these green species. In the Object Properties panel below, there should be a plus sign next to **Annotation and Pathway Links.** Clicking on it will open a field labeled **Links Pathway Object(s)** with a blue link. Click this link. You will be taken back to the Pathway Diagram and shown the same object, so you can see all database information about it. In the Object Properties panel here, you will find a row labeled **Linked Physiology object** with a blue link. Clicking this will take you back to the species' location in the Reaction Diagram. You can continue working on a Model by adding extra species and reactions. Note that they do not have label L. If you want to link one of the new species to one of the pathway objects, you can do it through **Pathway Links** button, via **Edit Pathway Links**. Here you can add or remove links between pathway entities and interactions in the **Pathway** view and species and reactions in the **Reaction Diagram**.



Importing a complete Pathway

Now, you will learn how to create and simulate a model based on the complete pathway. Click on the **Pathway Preview** tab again. If your previous search entry is still in the search bar, clear it. Then, sort by type and select all of the entities of Biochemical Reaction type. Then, click **Import** and choose **Plus Complexes** from the drop down menu. Due to the large number of objects and reactions displayed in the Pathway Diagram, reorganizing the species will not help with visibility. Instead, click on the **Pathway Objects** tab to view all of the objects in list format. You can see in the left menu that the Pathway has 320 objects.

In the Pathway Objects tab, select all entities using ctrl+a. Then click on the **Physiology** Links button and choose **Im-**

port into Physiology… from the drop down menu. Another dialog box will appear. Just as before, you can leave the default stoichiometric coefficients and we do not need to worry about which compartment to assign the objects to. Click **OK** to finalize the import. Another dialog box will appear telling you which objects have been linked to the physiology. If there are objects already linked, VCell will not duplicate them and will alert you to which objects they were.

However, since this pathway has so many entities, not all of them can be displayed on a single page. If you look to the bottom right of the list in the Pathway Objects tab, you will see 

. Click the blue right arrow to advance to the next page. Select all of these entities using ctrl+a and then import them into the physiology the same way you did before.

The **Physiology** (in the navigation tree panel, located in the top left of the VCell window) now has 103 reactions. Due to this large size the Reaction Diagram is not very useful in looking at reactions. Instead, click on the **Reactions** tab located to the immediate right of the **Reaction Diagram** tab. This will show you each reaction within the biomodel. Clicking on a single reaction will open detailed information about it in the Object Properties pane below. If you look at reaction rate, you will see that all of the reactions are **Mass Action** with on rate kf and off rate kr, all of which are defaulted to zero.

Creating the Application

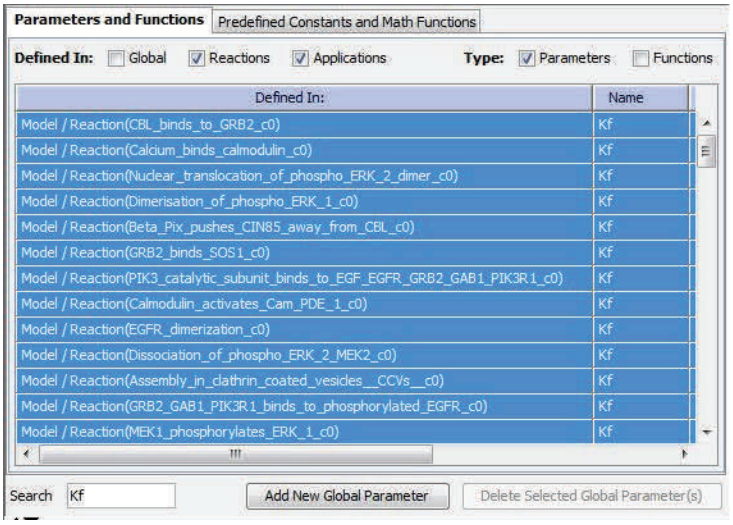
VCell provides a way to investigate qualitative behavior (up– and down-regulation of species) of the pathway, which can be done by creating a deterministic compartmental application.

In the navigation tree panel, located in the top left of the VCell window (above the database panel) click **Applications**. Then, click on the button **Add New** and select **Deterministic** from the drop down menu. You may leave the application name as the default **Application0**.

Once this is complete, select Application 0 from the navigation tree to view it. Go to the **Specifications** tab. You must change the initial conditions of the species from the default value of zero. For the purpose of this tutorial, you will enter 1 as the initial condition for all of the species. Select all species by using ctrl+a and then right click. Hover over the menu option **Initial Condition** and enter 1 in the **expression** field.

Now, you must set the forward and reverse rate constants for all of the reactions. The easiest way to do so for a pathway of this size is to click on **Parameters and Functions** in the navigation tree panel. Since you have not specified any parameters as global, you can uncheck the box marked **Global.** Similarly, you can also uncheck the box marked **Functions**. This narrows the amount of objects displayed down to only the reactions and parameters that you need for your application.

You can filter the parameters further by utilizing the search bar beneath the table. Enter **Kf** in the search bar to narrow the amount of objects displayed to only the forward rate constants. Select all of the forward rate constants using ctrl+a and then right click. Hover over **Expression** in the menu and enter **1** in the field that appears.



Return to the search bar and enter **Kr** this time. Select all of the reverse rate constants using ctrl+a and then right click. Hover over **Expression** in the menu and enter **0.1** in the field that appears.

It is important to note that you may set the rate constants for reactions individually—they need not all be uniform. This was only done for this tutorial in order to simplify and expedite the process.

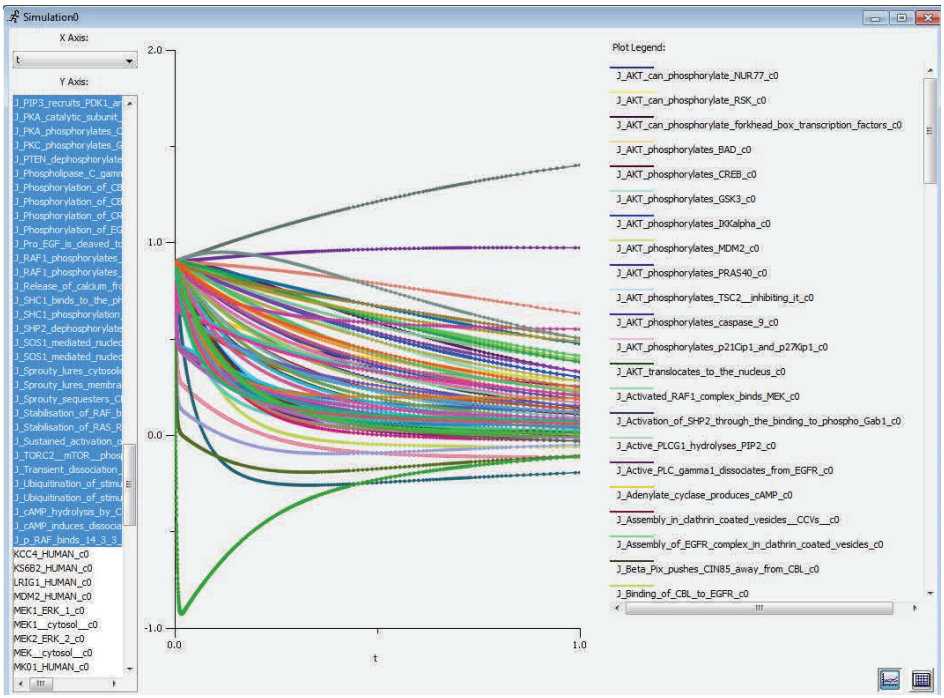
Running the Simulation

Now, you have completed the application and can create and run your simulation.

Click on **Simulations** under **Application0** in the navigation tree panel to open the simulations tab. Select the **Add New Simulation** tool to create your simulation. You do not need to edit this simulation, so you can run it immediately after creating it. For this tutorial, you can run a local simulation to save time. When the simulation is complete, you will be shown the results

Viewing the Results

The first data you want to observe is how the fluxes changed over time. To do this, select all of the names in the **y-axis** pane that start with J (J is the name tag for reactions). You can view how the fluxes changed throughout the simulation in the time plot to the right, with each flux linked to a unique color line.



If you want to view how the concentrations of species change throughout the simulation, you can do so. The easiest way is to select everything in the y-axis pane using ctrl+a. Then, deselect the fluxes (J– names). You should also deselect time—denoted by t—at the top of the list. Each species' concentration will be plotted with a unique color line.