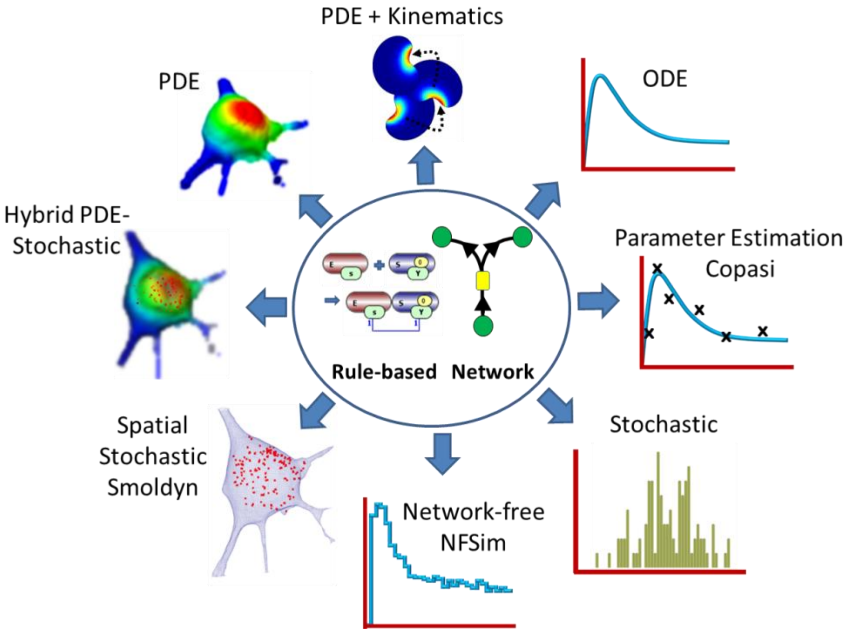
VCell

A modeling environment for the simulation of cellular events, where you can download at vcell.org .



Virtual Cell is developed by the Center for Cell Analysis and Modeling at the University of Connecticut Health Center. It is funded as a Biomedical Technology Research Resource by the National Institute of General Medical Sciences (NIGMS)

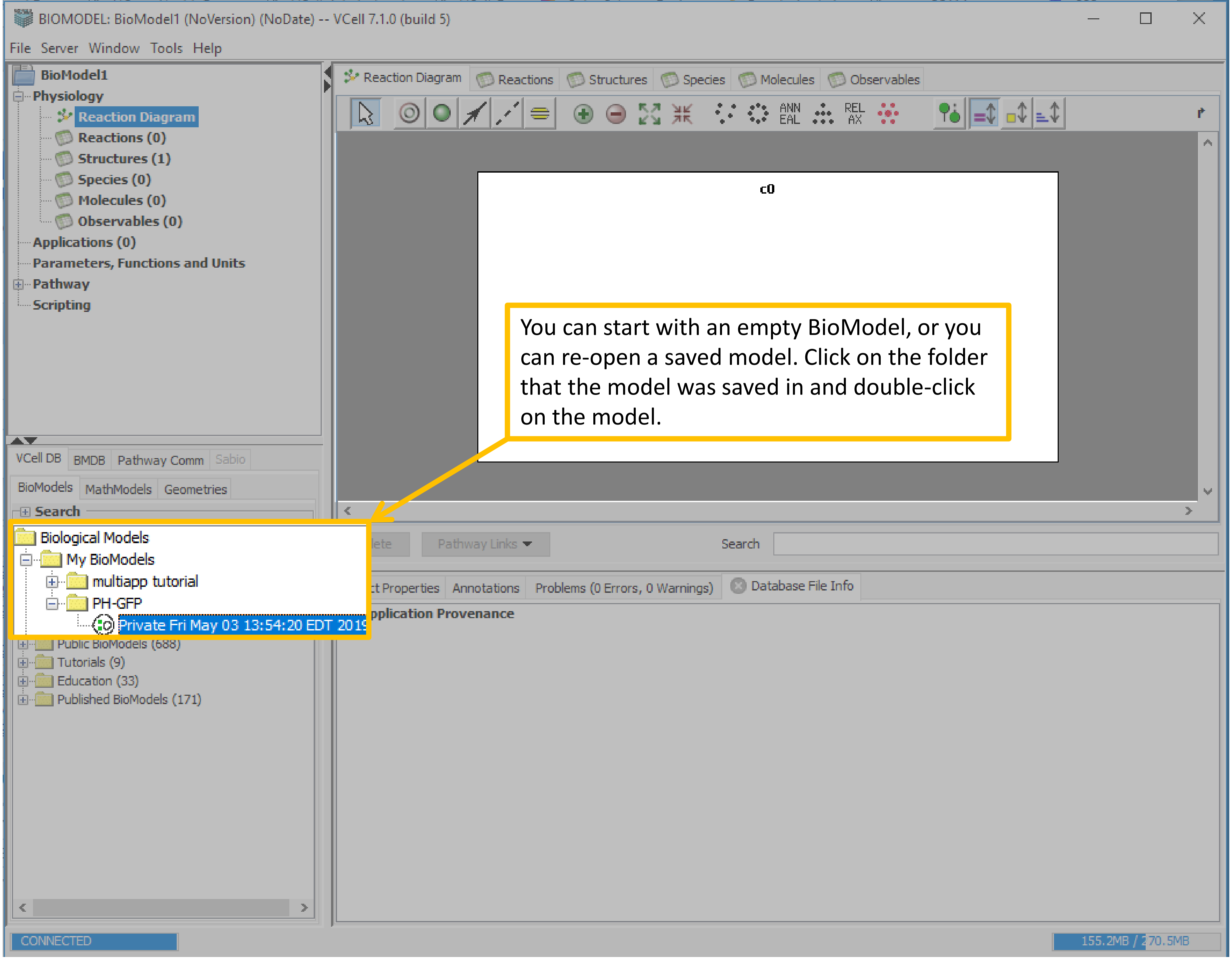
VCell Tutorial

PH-GFP binding to PIP2 and IP3

Objective: Create a biomodel and 3D spatial (PDE) application to simulate pleckstrin homology domain (PH-GFP) reporter for conversion of PIP_2 *to* IP_3.

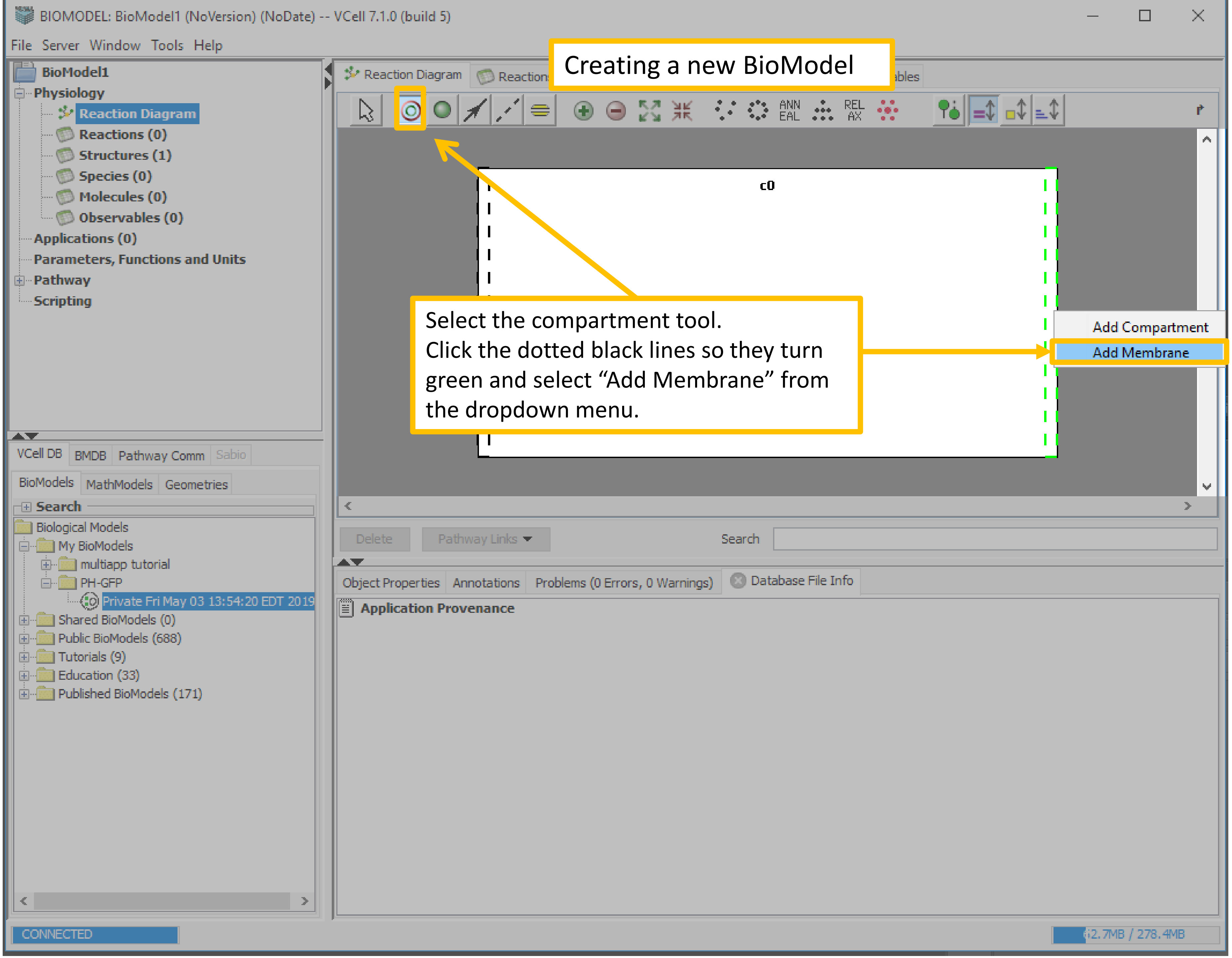
In this tutorial you will:

- Create a BioModel with reactions involving membrane and volume species.
- Create a compartmental (ODE) application that uses events to include time-dependent triggers.
- Create a spatial deterministic (PDE) application of a model using analytic equations to create a 3D geometry
- Define initial concentrations that are non-uniform in space and create timed events in spatial models using Boolean expressions
- Create output functions for more complex analysis of simulation results, e.g. to sum all fluorescent species in a compartment.

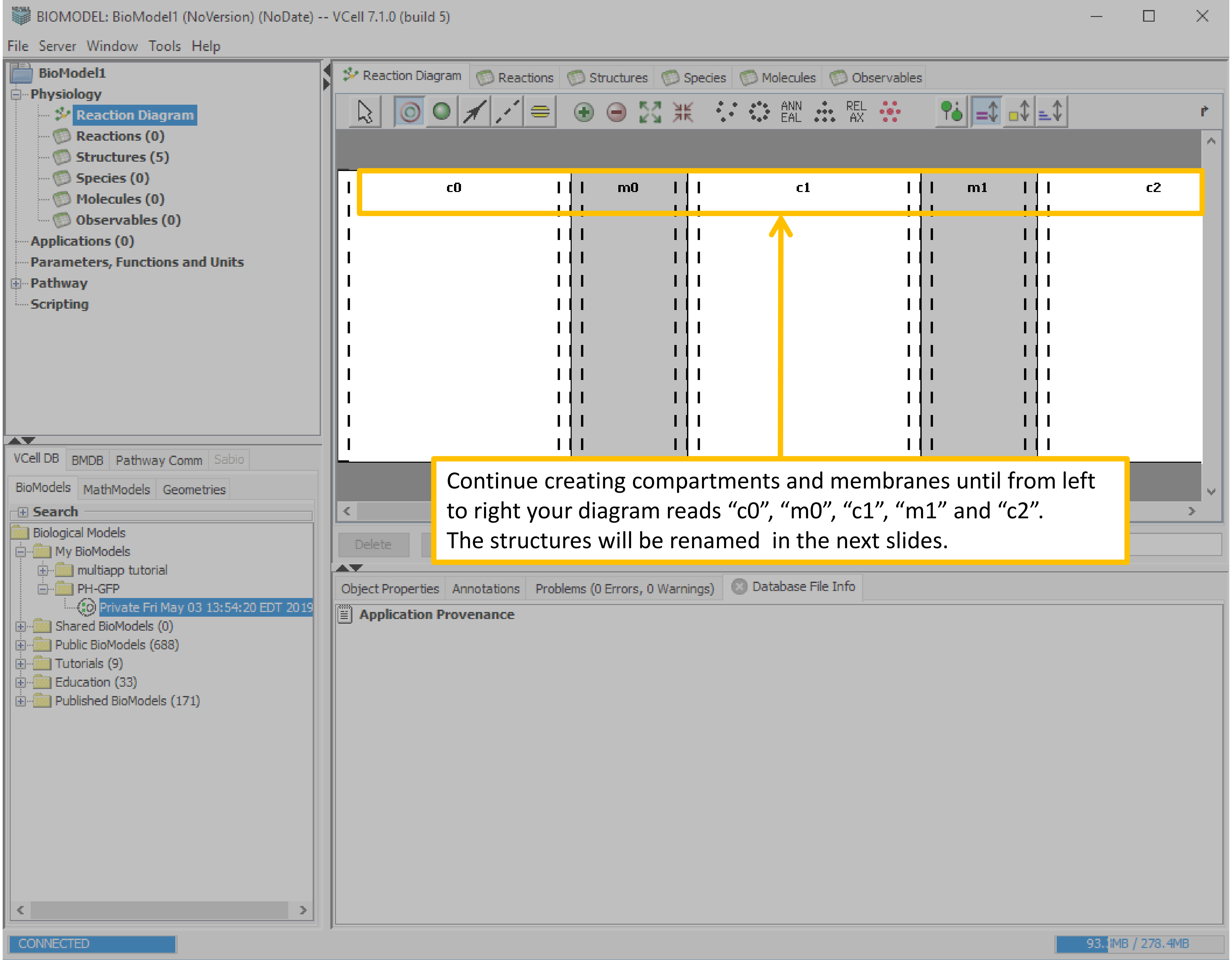

BIOMODEL: BioModel1 (NoVersion) (NoDate) -- VCell 7.1.0 (build 5)

You can start with an empty BioModel, or you can re-open a saved model. Click on the folder that the model was saved in and double-click on the model.

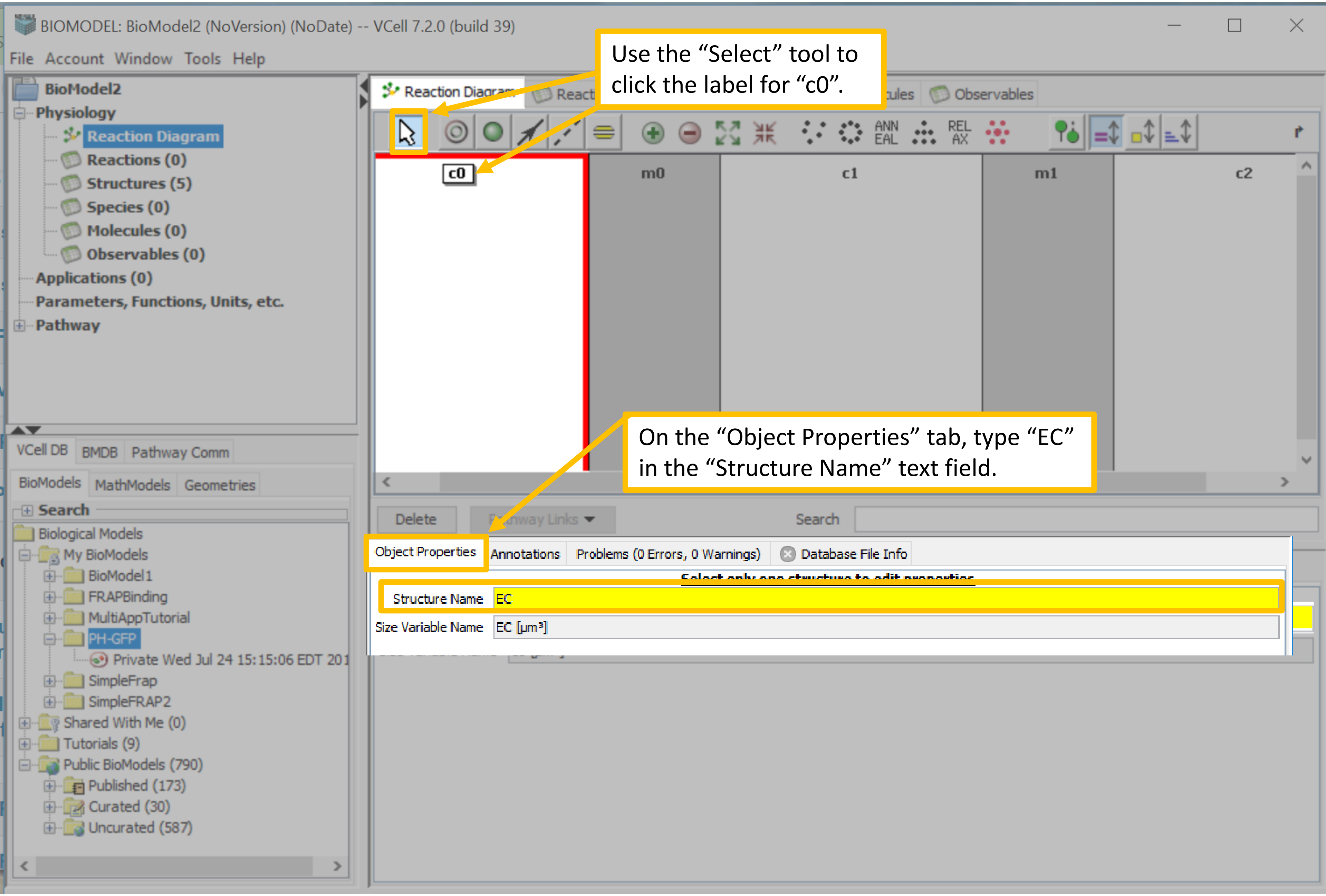
Creating a new BioModel



Select the compartment tool.
Click the dotted black lines so they turn green and select “Add Membrane” from the dropdown menu.



Continue creating compartments and membranes until from left to right your diagram reads “c0”, “m0”, “c1”, “m1” and “c2”. The structures will be renamed in the next slides.

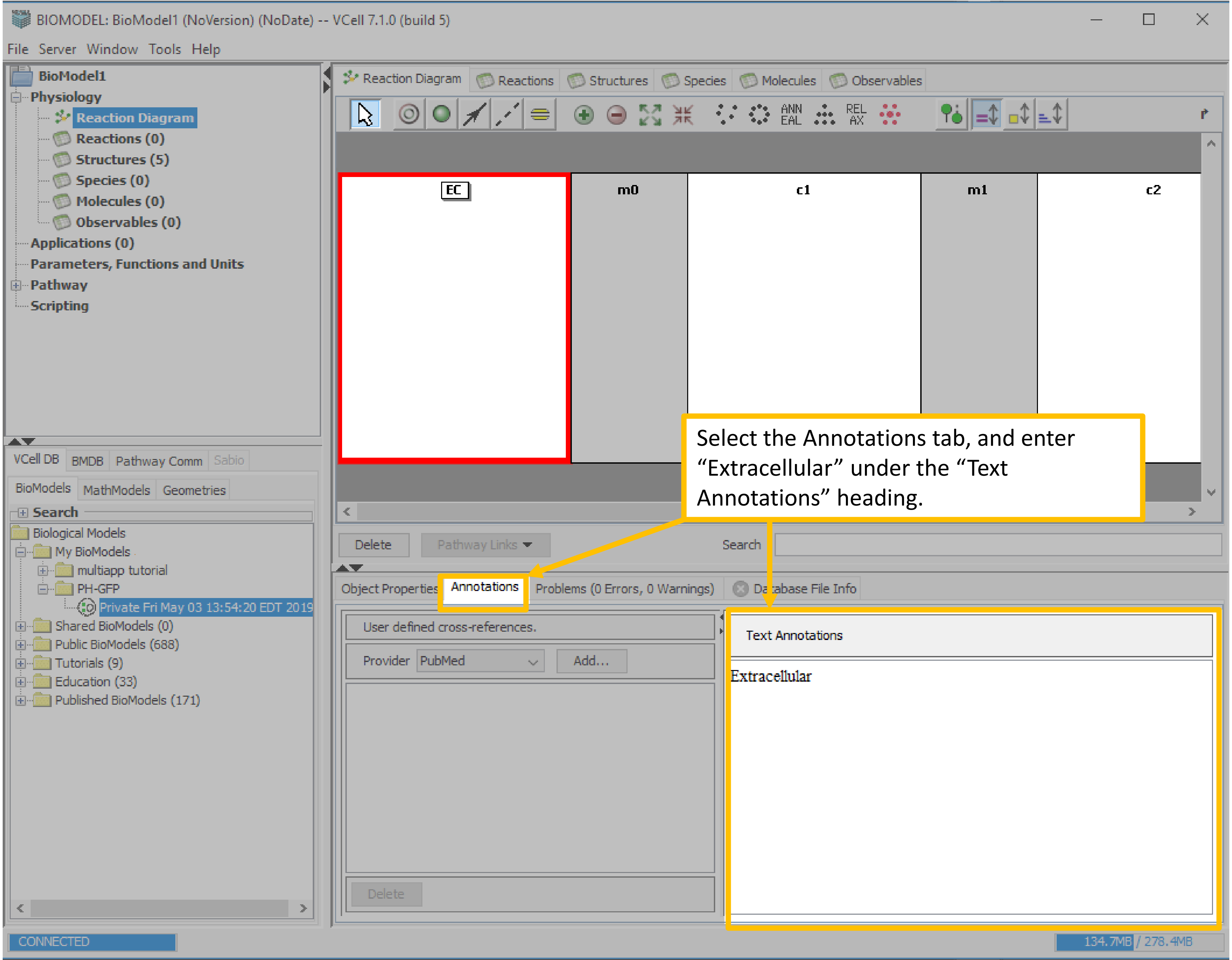


Use the “Select” tool to click the label for “c0”.

On the “Object Properties” tab, type “EC” in the “Structure Name” text field.

Structure Name: EC

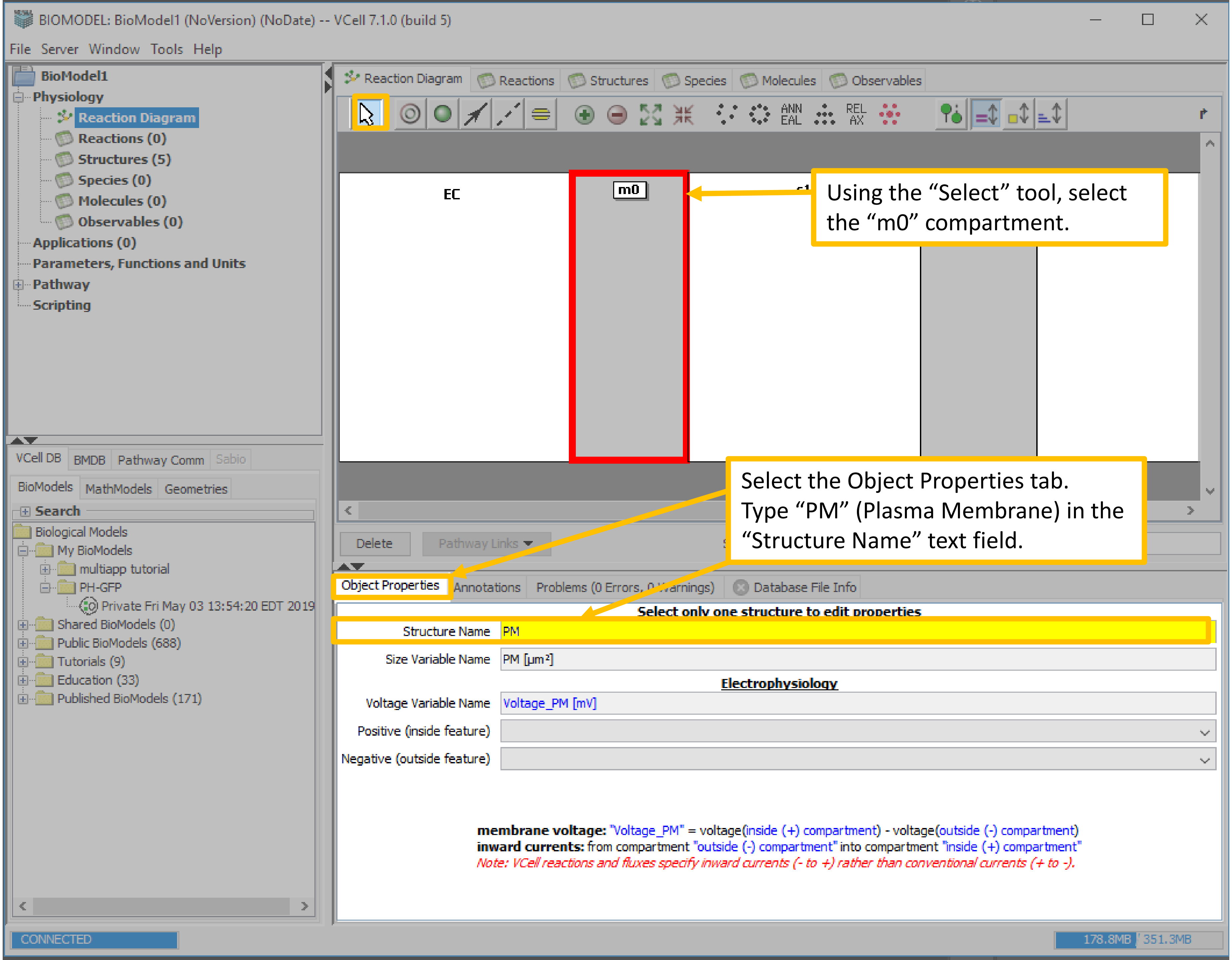
Size Variable Name: EC [µm³]



Select the Annotations tab, and enter “Extracellular” under the “Text Annotations” heading.

Text Annotations

Extracellular



Using the “Select” tool, select the “m0” compartment.

Select the Object Properties tab. Type “PM” (Plasma Membrane) in the “Structure Name” text field.

Select only one structure to edit properties

Structure Name: PM

Size Variable Name: PM [µm²]

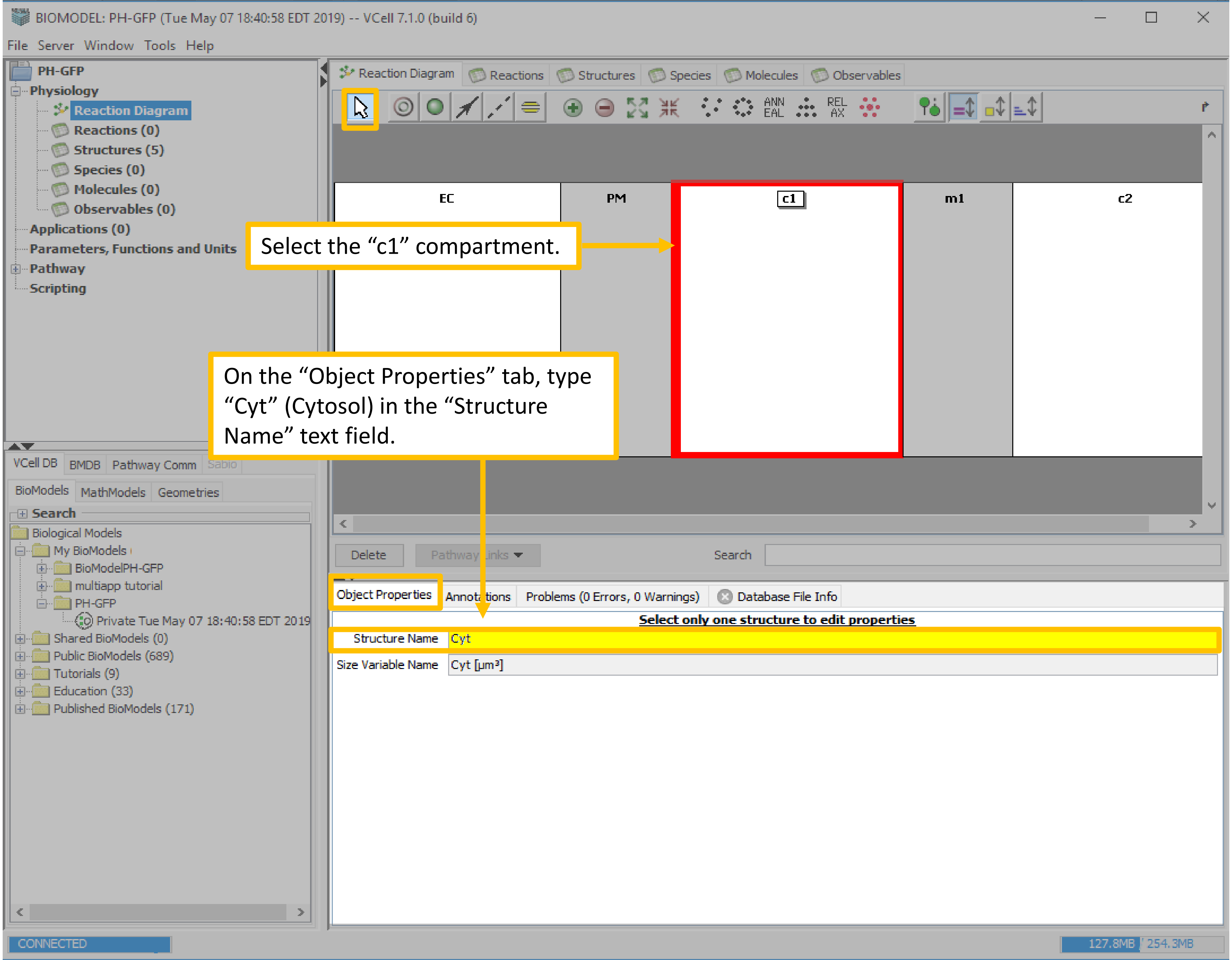
Electrophysiology

Voltage Variable Name: Voltage_PM [mV]

Positive (inside feature):

Negative (outside feature):

membrane voltage: "Voltage_PM" = voltage(inside (+) compartment) - voltage(outside (-) compartment)
inward currents: from compartment "outside (-) compartment" into compartment "inside (+) compartment"
Note: VCell reactions and fluxes specify inward currents (- to +) rather than conventional currents (+ to -).



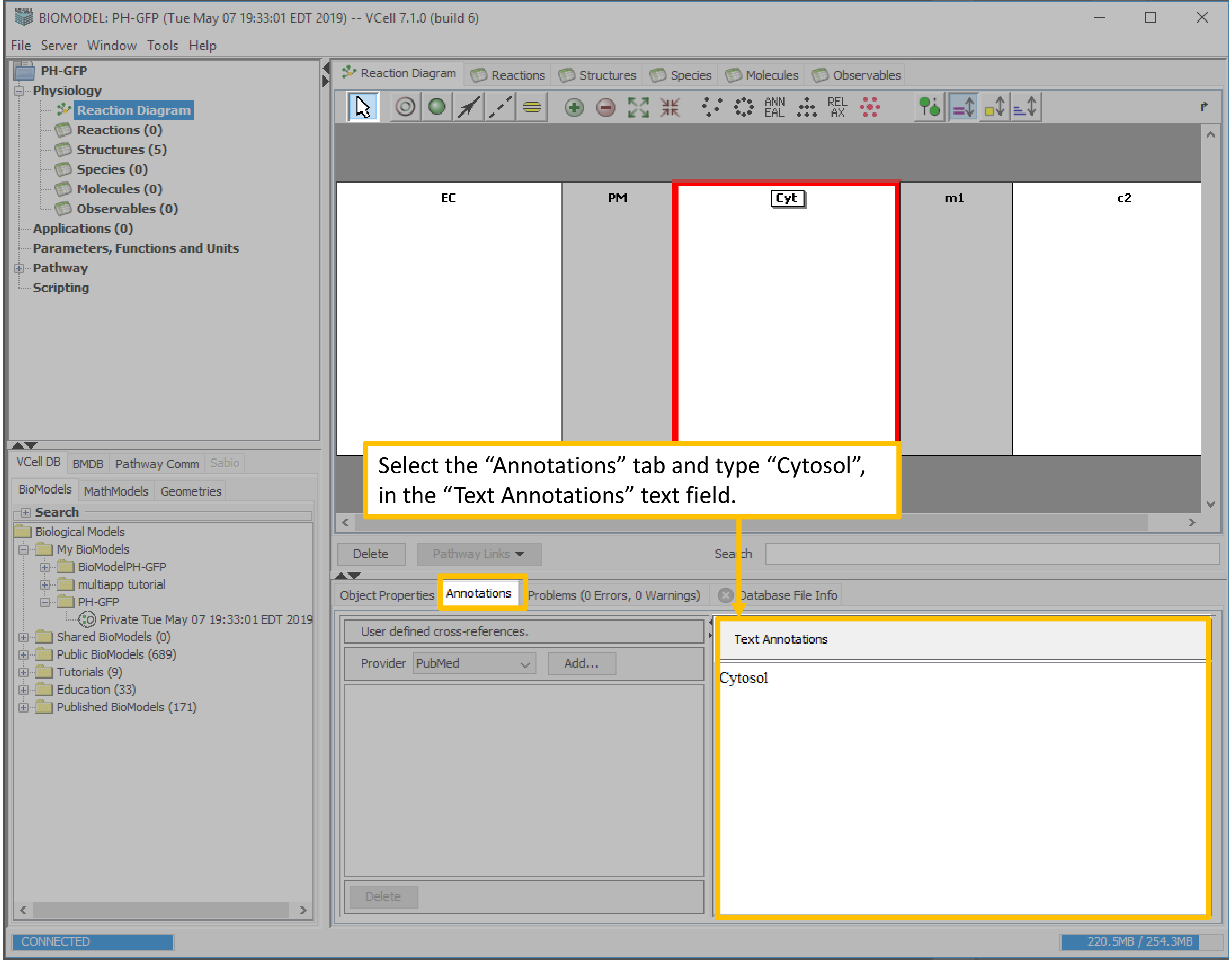
Select the “c1” compartment.

On the “Object Properties” tab, type “Cyt” (Cytosol) in the “Structure Name” text field.

Select only one structure to edit properties

Structure Name: Cyt

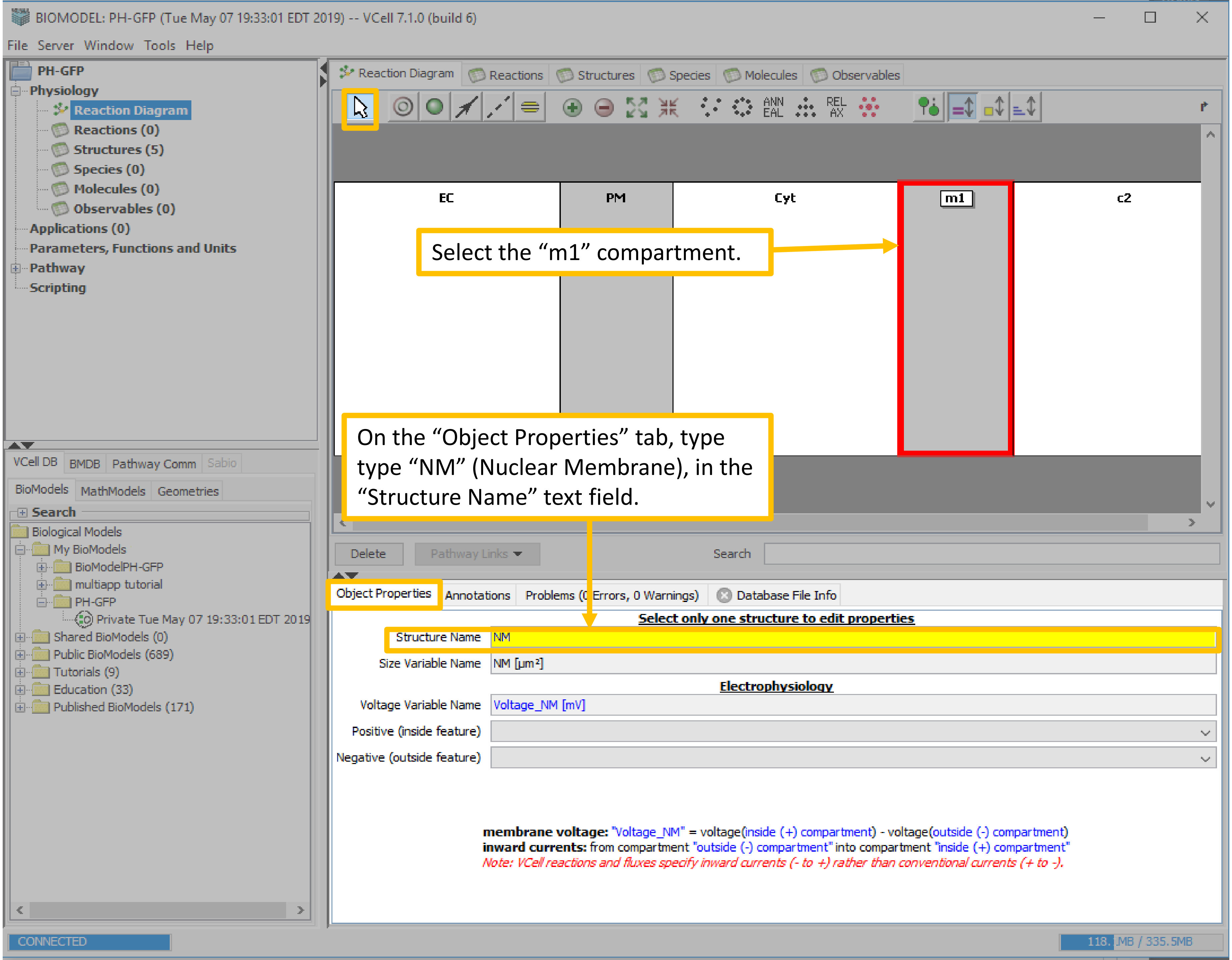
Size Variable Name: Cyt [µm³]



Select the “Annotations” tab and type “Cytosol”, in the “Text Annotations” text field.

Provider: PubMed

Text Annotations: Cytosol



Select the “m1” compartment.

On the “Object Properties” tab, type type “NM” (Nuclear Membrane), in the “Structure Name” text field.

Select only one structure to edit properties

Structure Name: NM

Size Variable Name: NM [µm²]

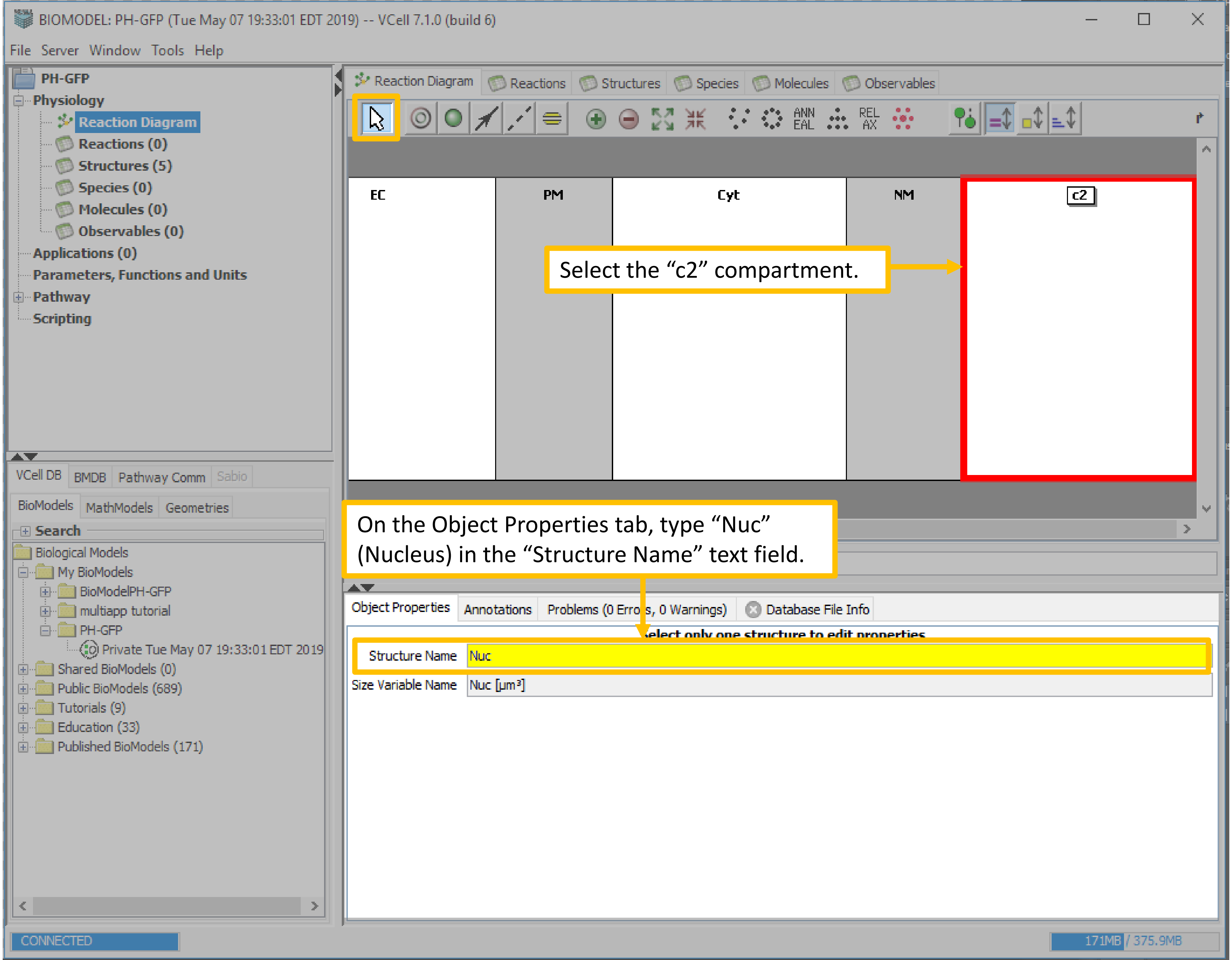
Electrophysiology

Voltage Variable Name: Voltage_NM [mV]

Positive (inside feature):

Negative (outside feature):

membrane voltage: "Voltage_NM" = voltage(inside (+) compartment) - voltage(outside (-) compartment)
inward currents: from compartment "outside (-) compartment" into compartment "inside (+) compartment"
Note: VCell reactions and fluxes specify inward currents (- to +) rather than conventional currents (+ to -).

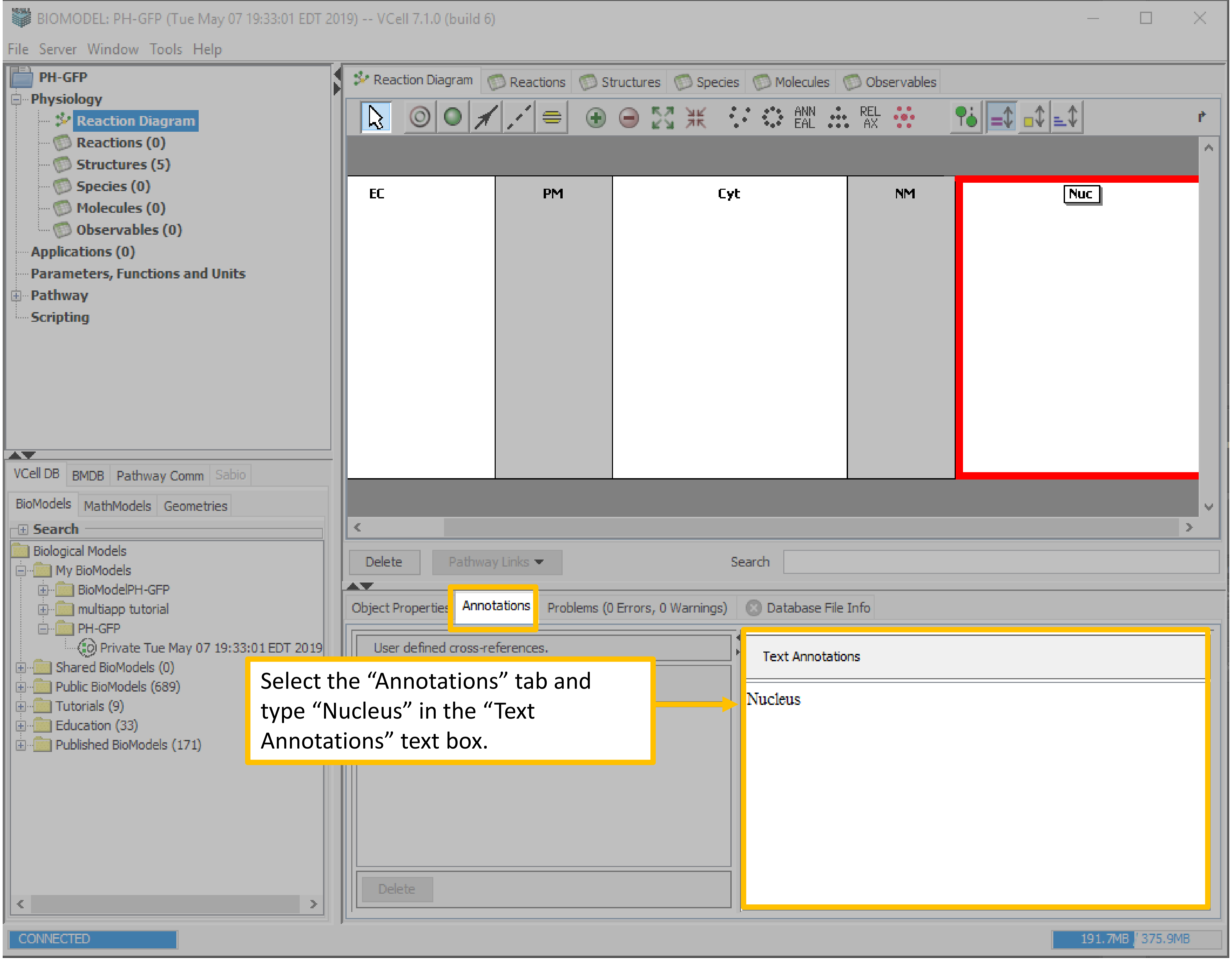


Select the “c2” compartment.

On the Object Properties tab, type “Nuc” (Nucleus) in the “Structure Name” text field.

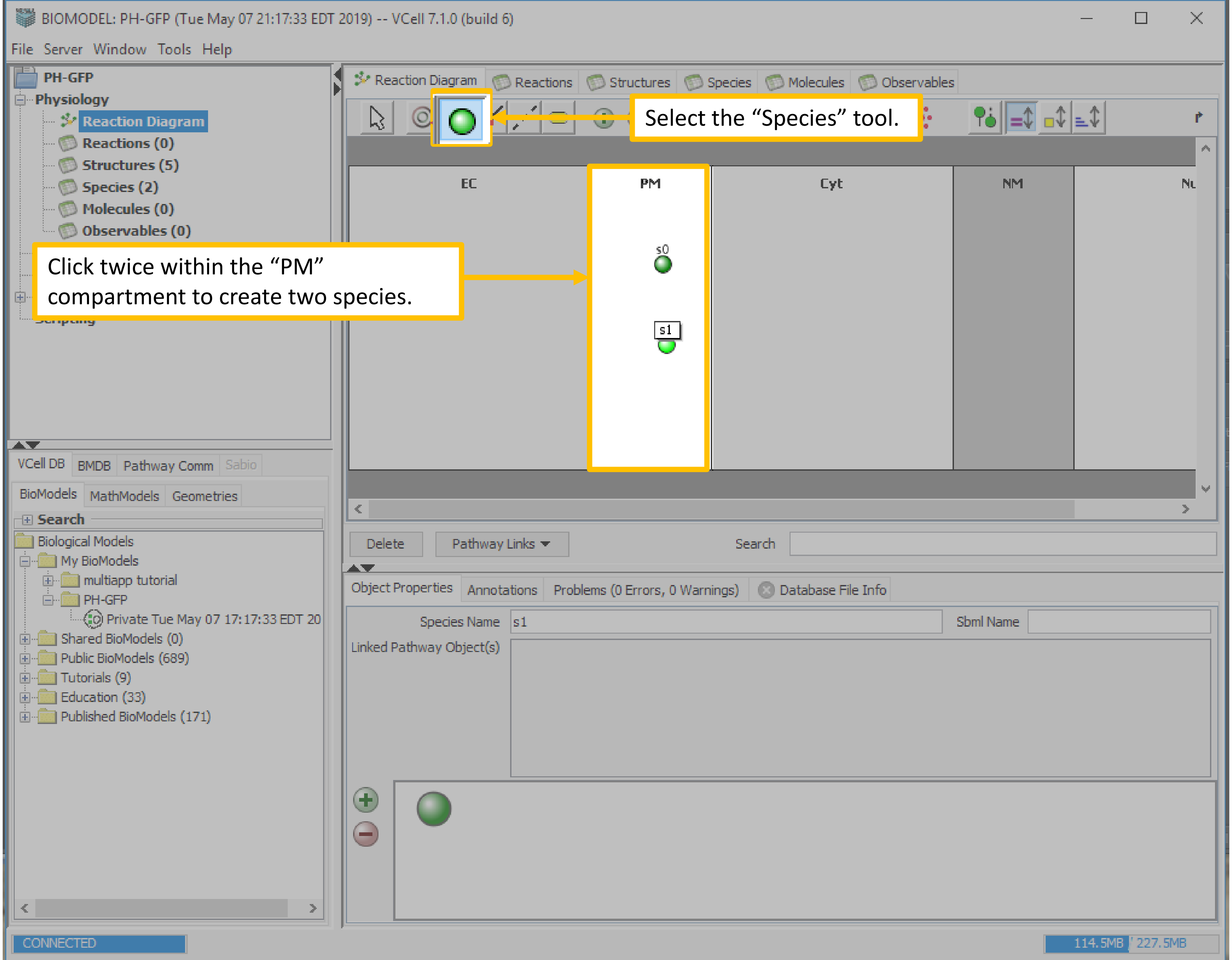
Structure Name: Nuc

Size Variable Name: Nuc [µm³]



Nucleus

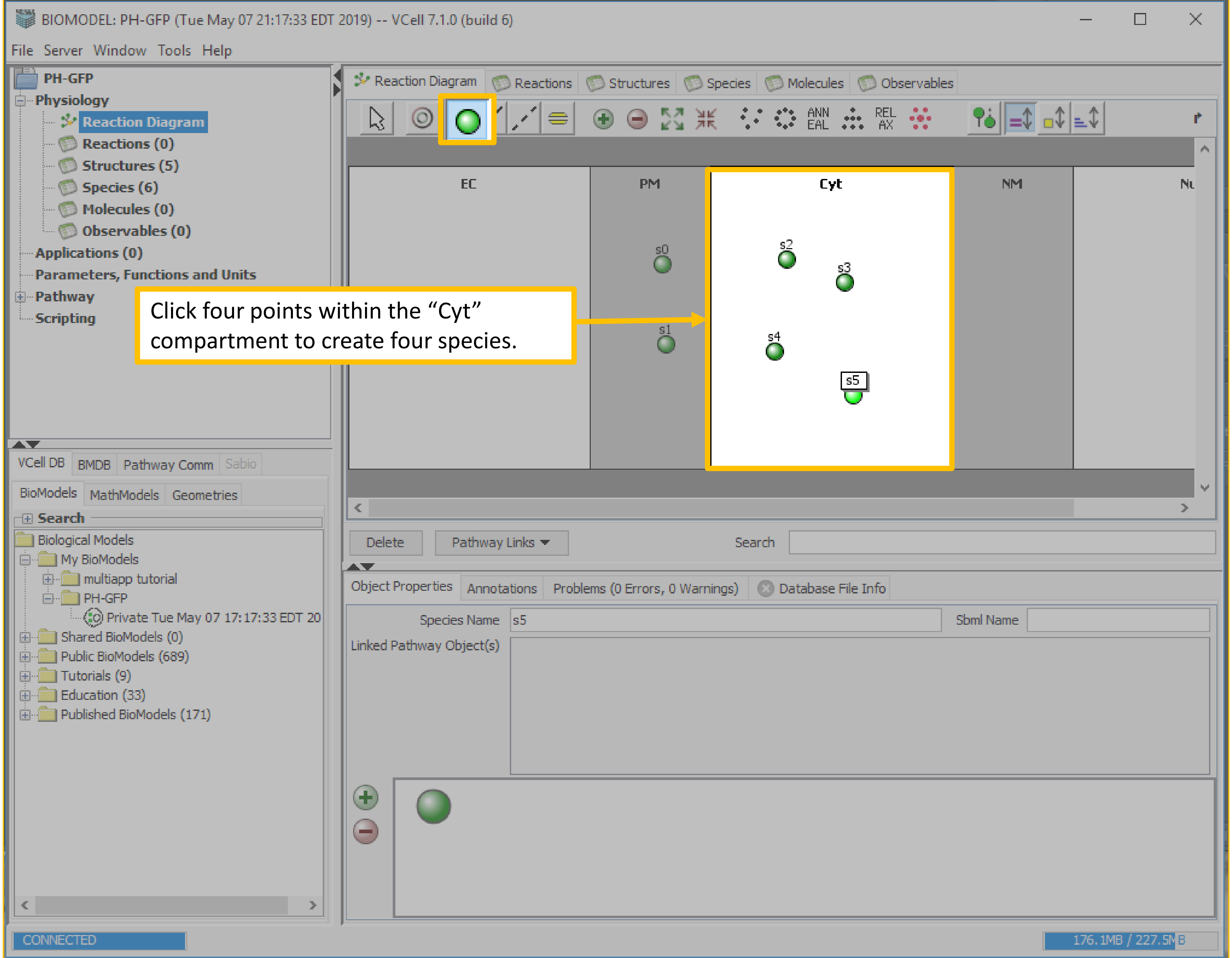
Select the “Annotations” tab and type “Nucleus” in the “Text Annotations” text box.



Select the “Species” tool.

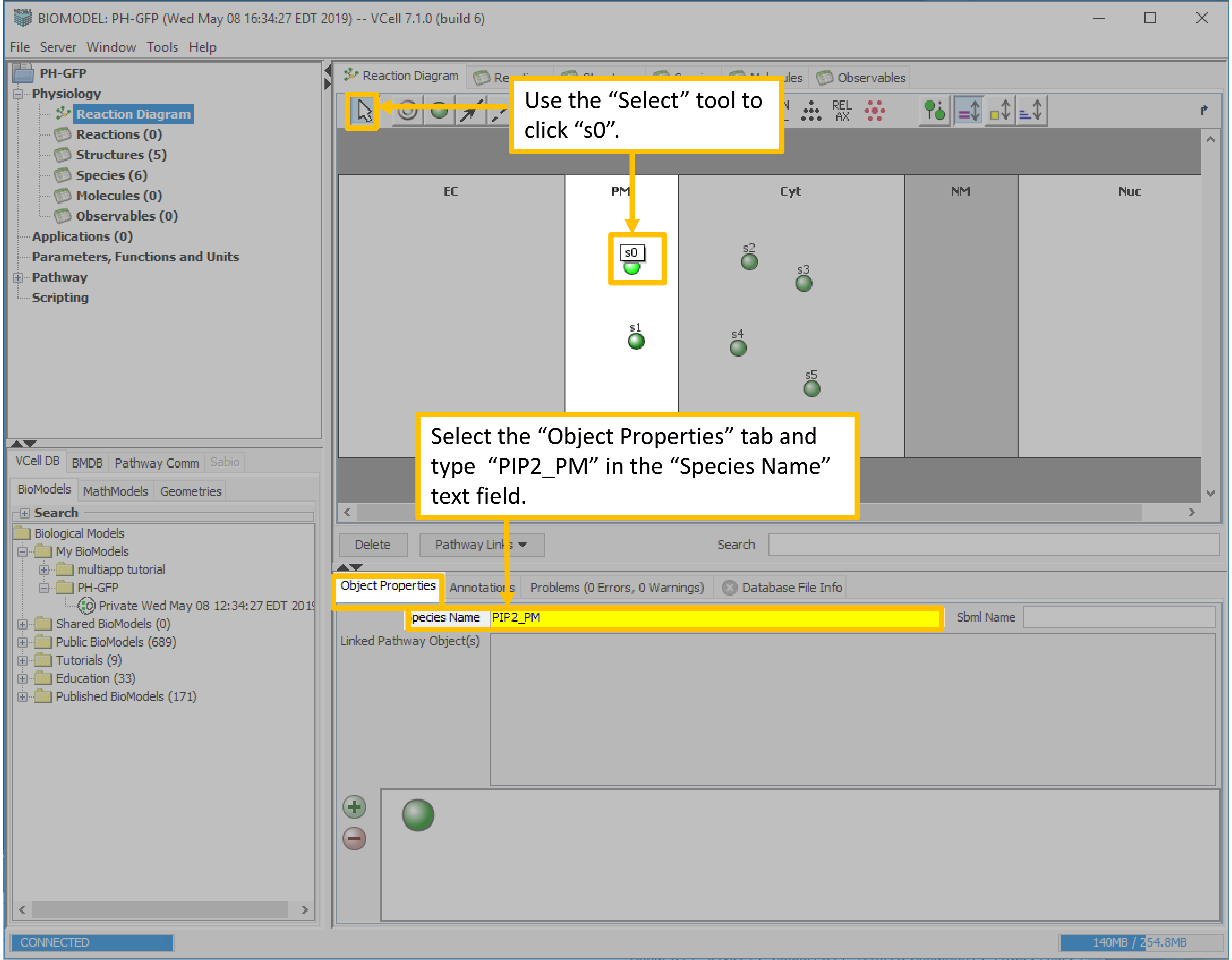
Click twice within the “PM” compartment to create two species.

Species Name: s1



Species Name: s5

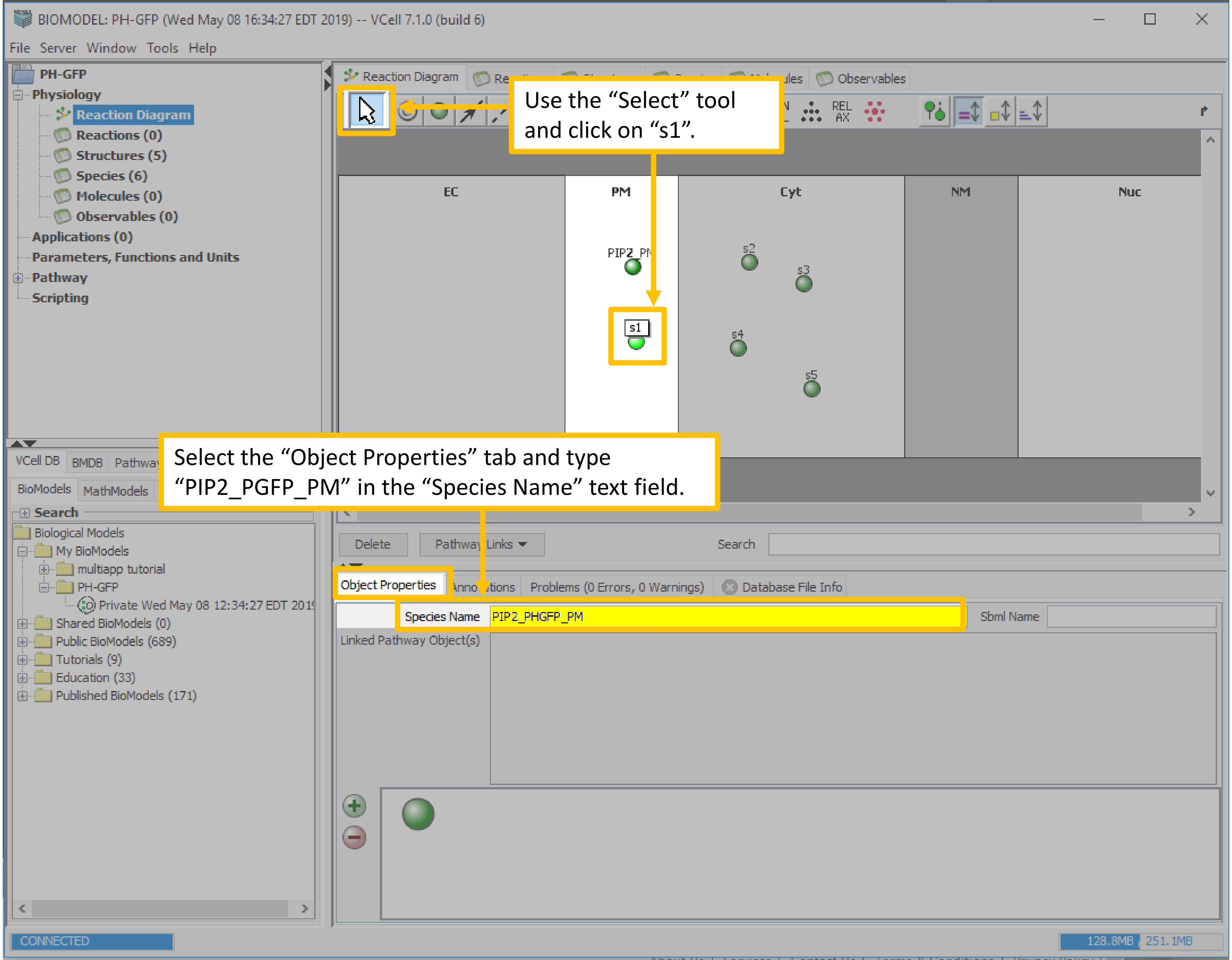
Click four points within the “Cyt” compartment to create four species.



Use the “Select” tool to click “s0”.

Select the “Object Properties” tab and type “PIP2_PM” in the “Species Name” text field.

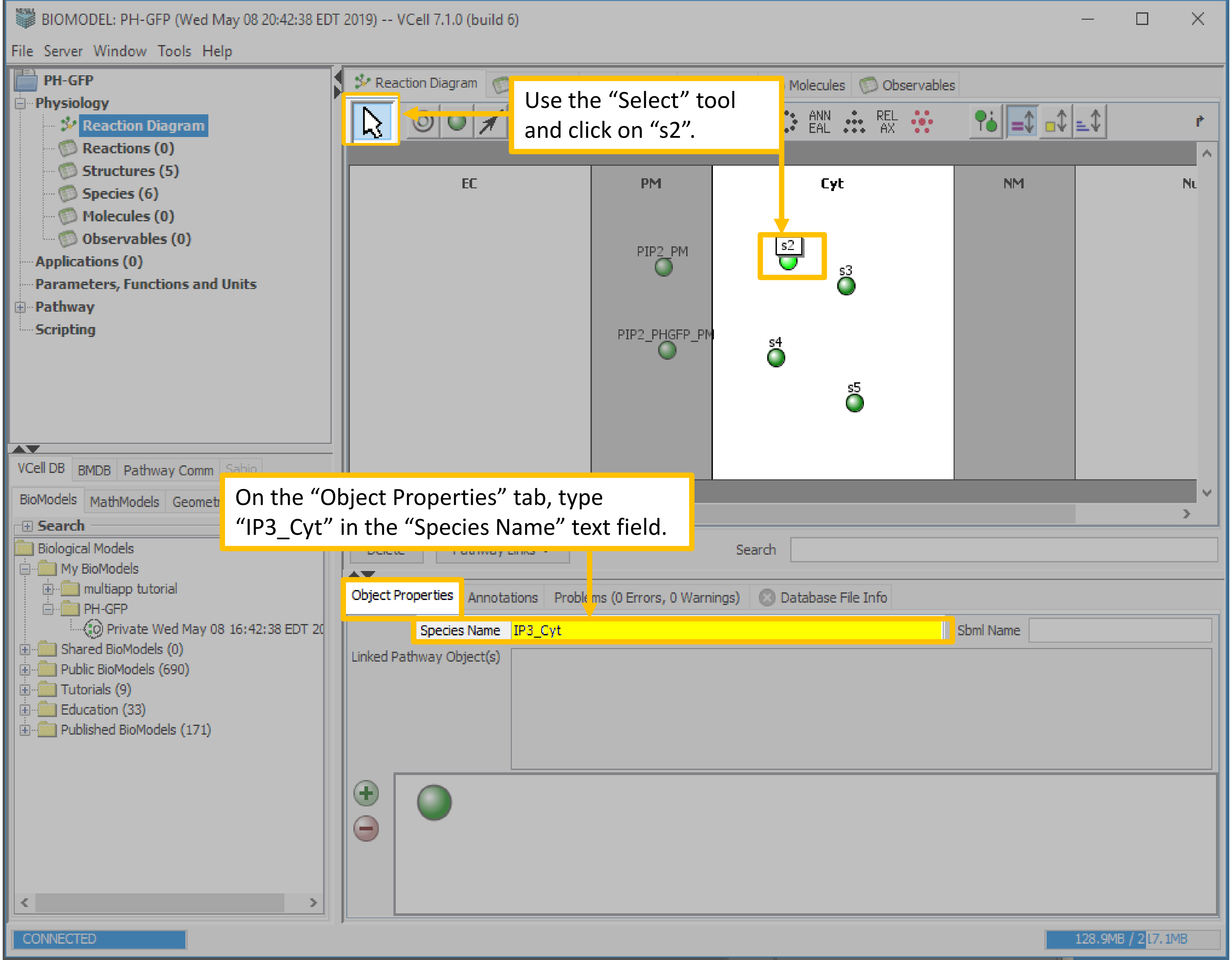
Species Name: PIP2_PM



Use the “Select” tool and click on “s1”.

Select the “Object Properties” tab and type “PIP2_PGFP_PM” in the “Species Name” text field.

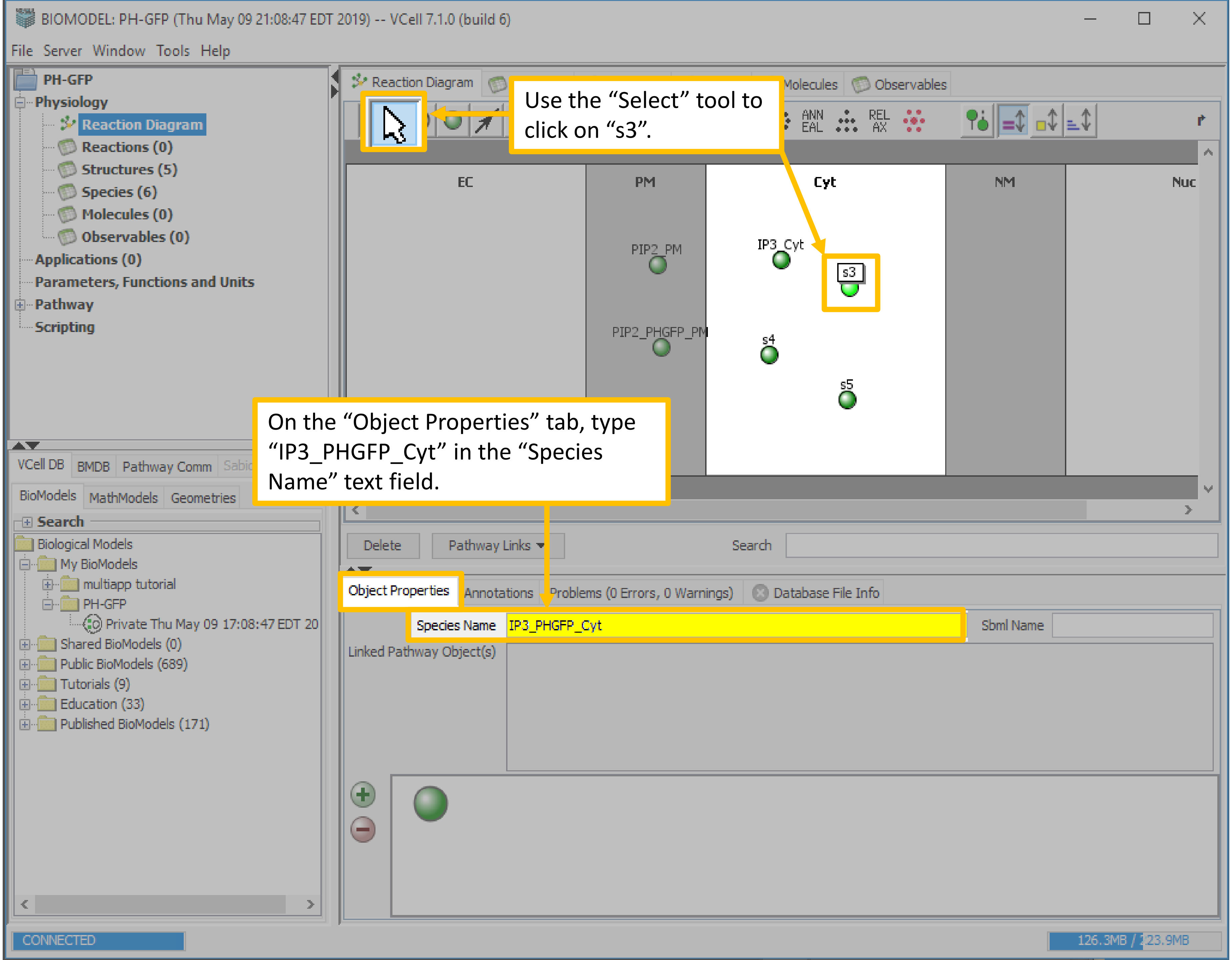
Species Name PIP2_PHGFP_PM



Use the “Select” tool and click on “s2”.

On the “Object Properties” tab, type “IP3_Cyt” in the “Species Name” text field.

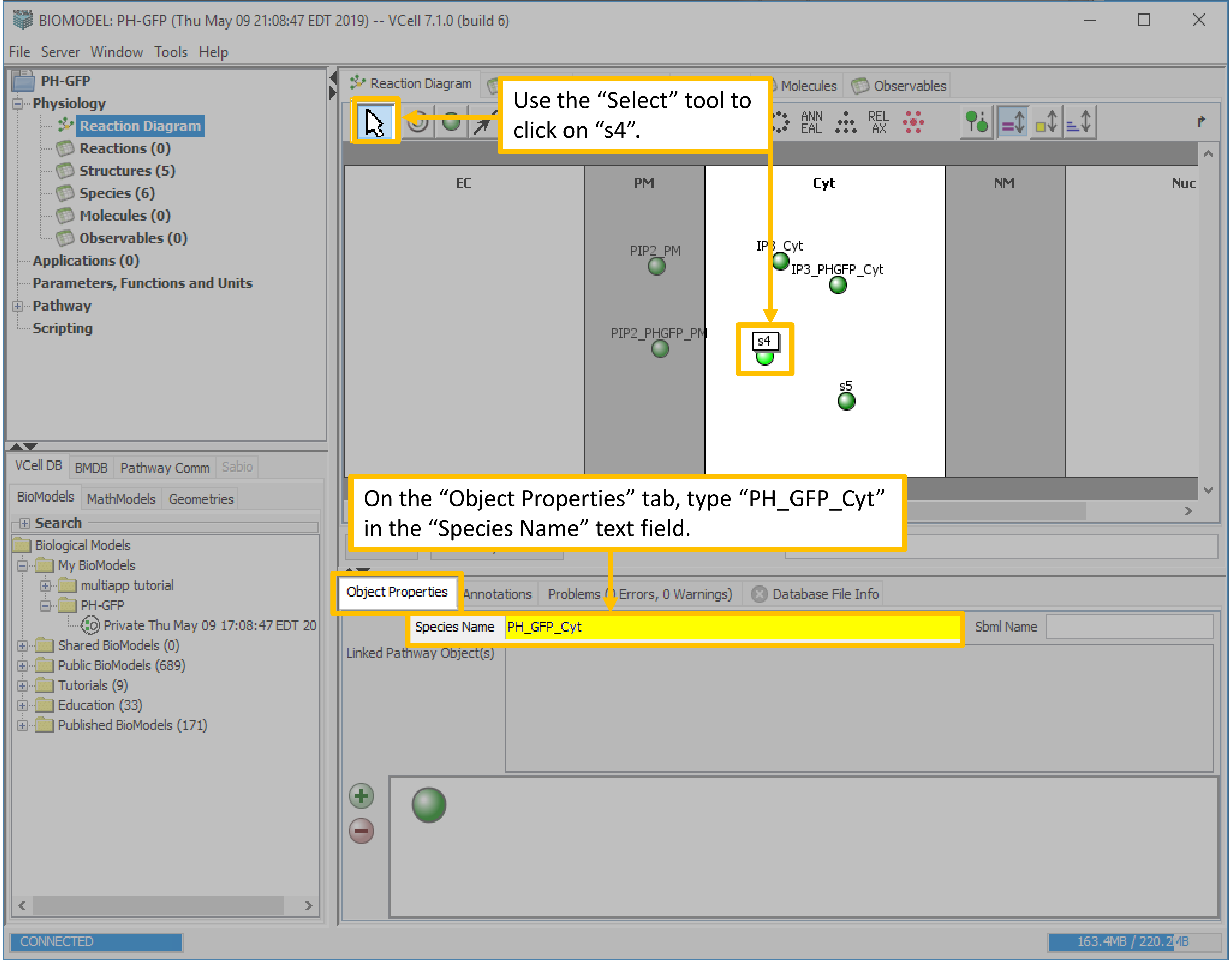
Species Name IP3_Cyt



Species Name: IP3_PHGFP_Cyt

Use the “Select” tool to click on “s3”.

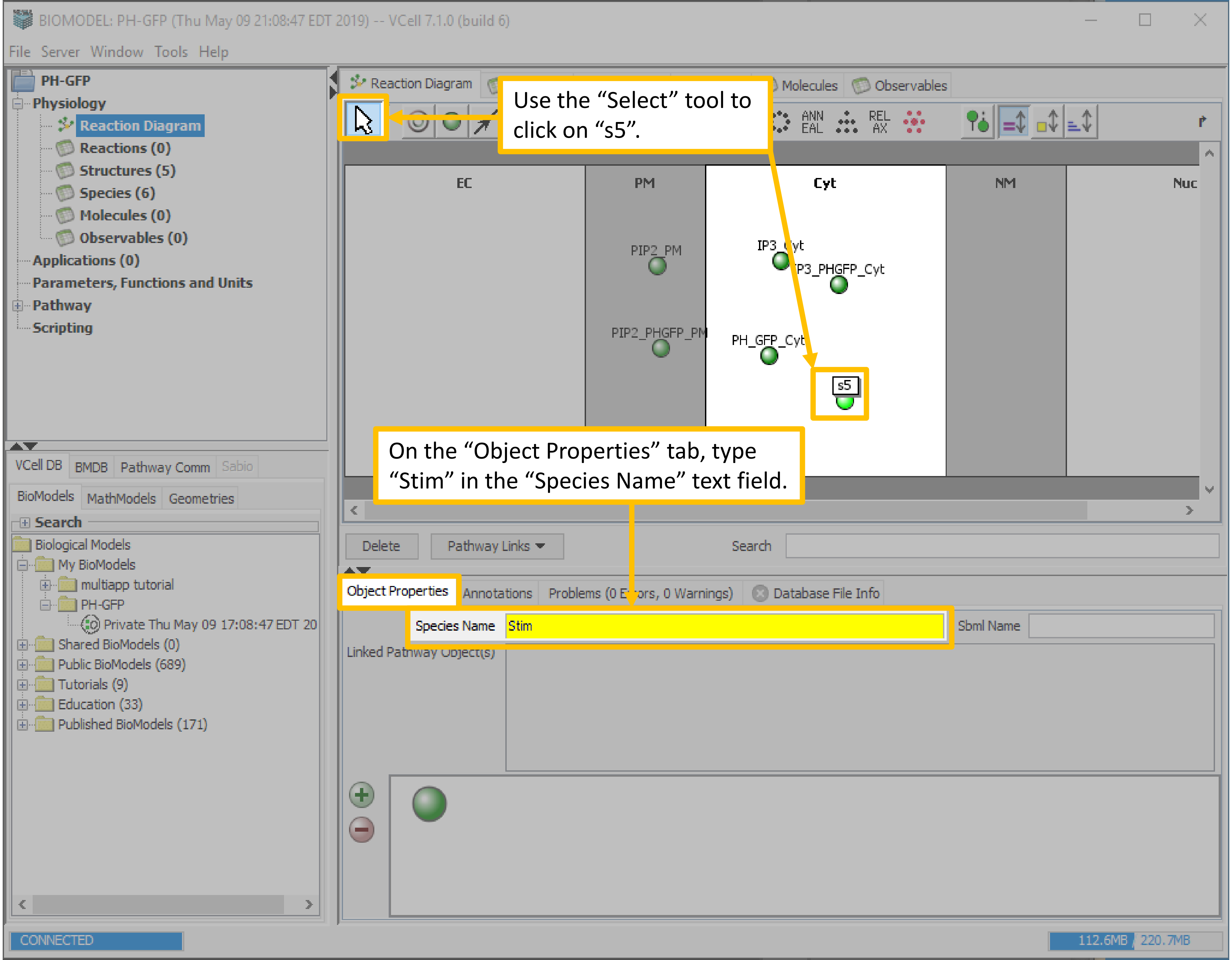
On the “Object Properties” tab, type “IP3_PHGFP_Cyt” in the “Species Name” text field.



Use the “Select” tool to click on “s4”.

On the “Object Properties” tab, type “PH_GFP_Cyt” in the “Species Name” text field.

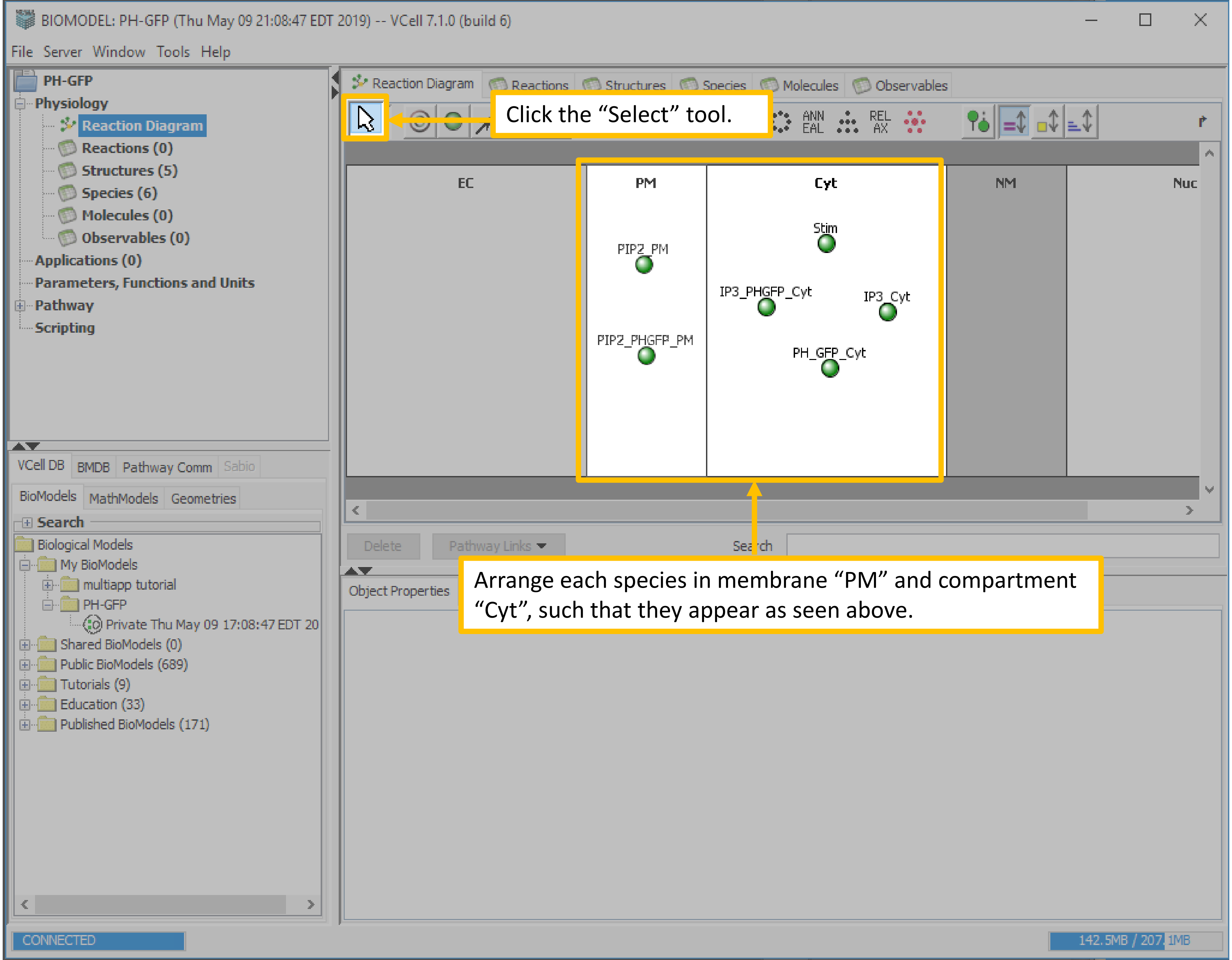
Species Name: PH_GFP_Cyt



Species Name: Stim

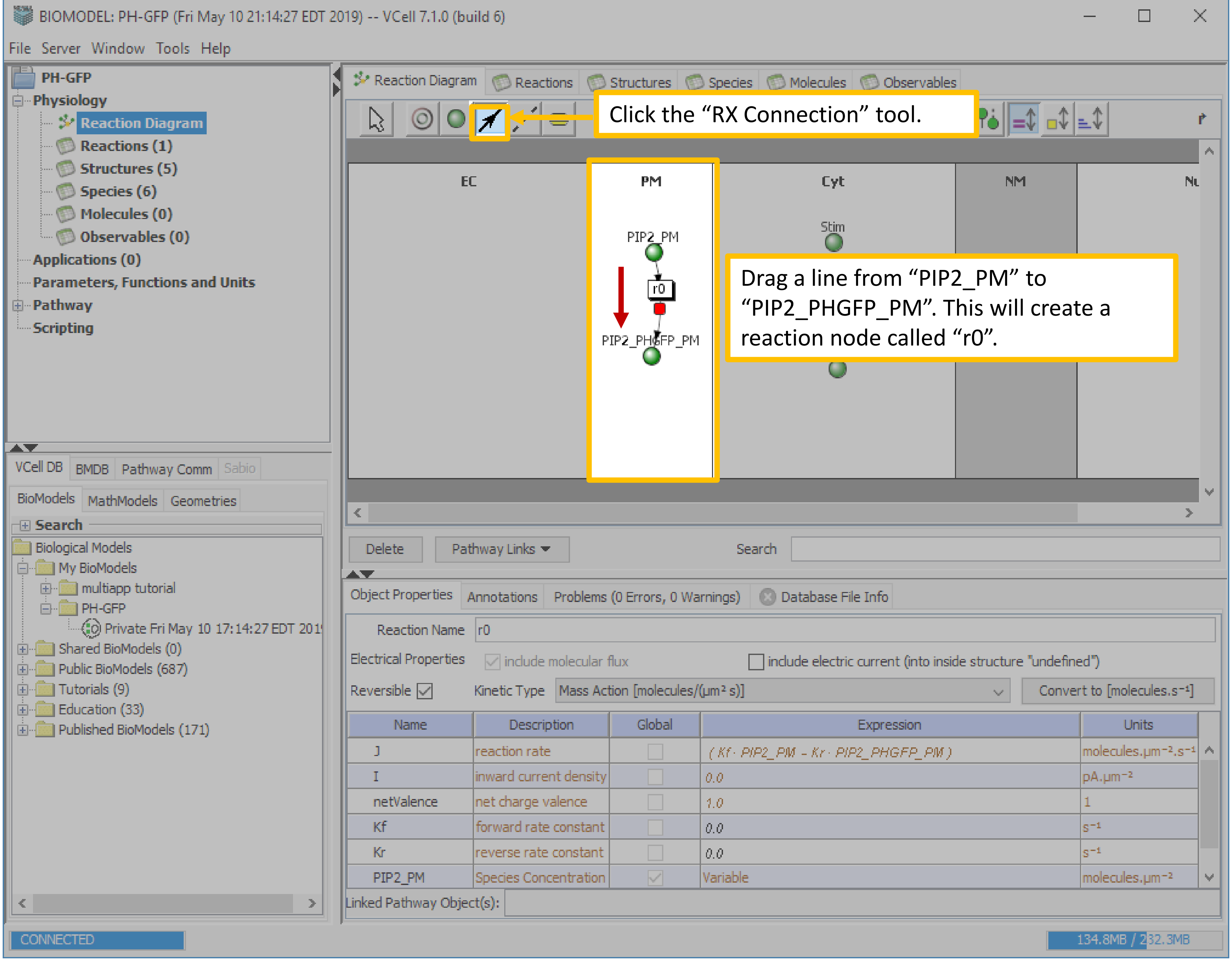
Use the “Select” tool to click on “s5”.

On the “Object Properties” tab, type “Stim” in the “Species Name” text field.



Click the “Select” tool.

Arrange each species in membrane “PM” and compartment “Cyt”, such that they appear as seen above.



Click the “RX Connection” tool.

Drag a line from “PIP2_PM” to “PIP2_PHGFP_PM”. This will create a reaction node called “r0”.

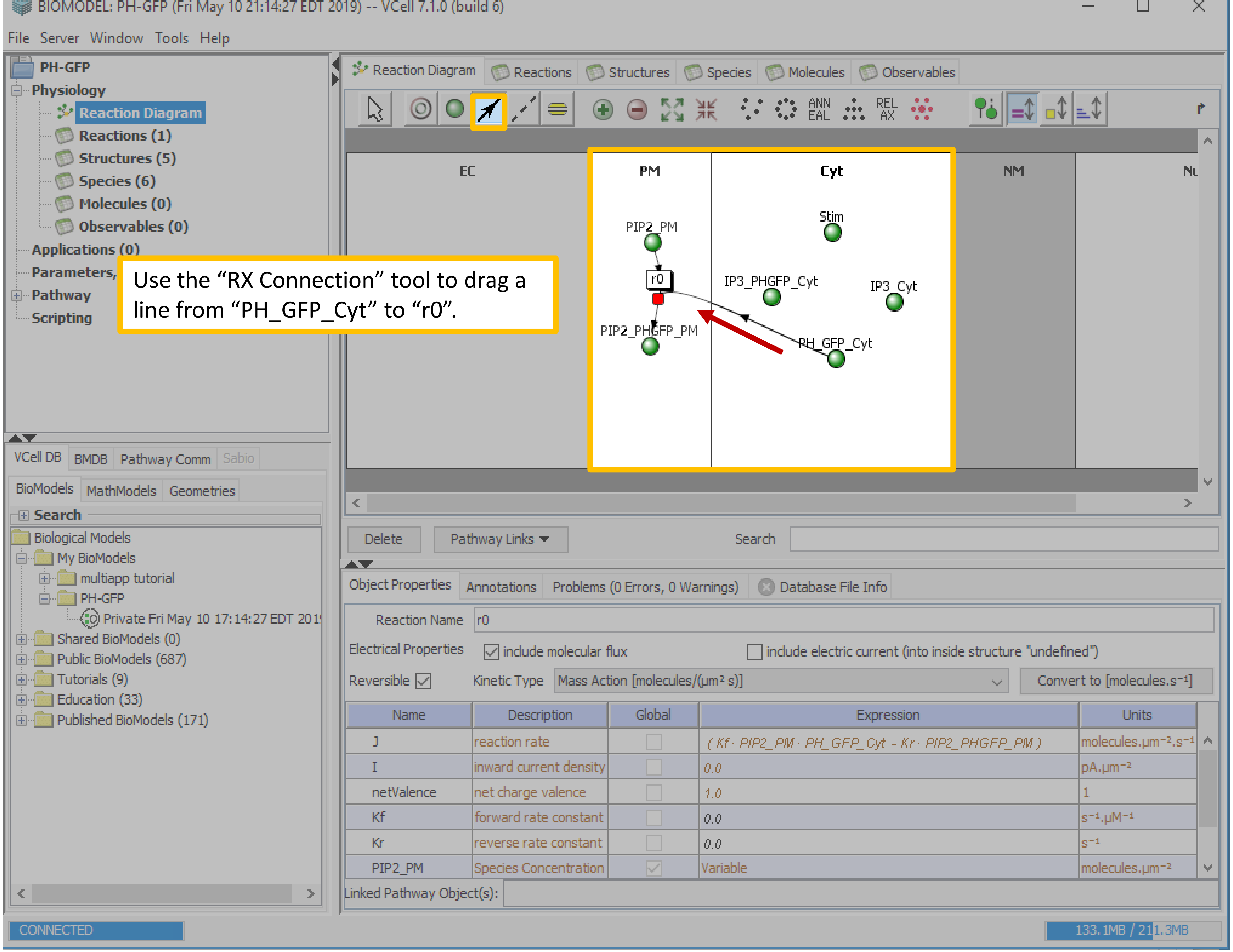
Reaction Name: r0

Electrical Properties: ☑ include molecular flux ☐ include electric current (into inside structure "undefined")

Reversible ☑ Kinetic Type: Mass Action [molecules/(μm² s)] Convert to [molecules.s⁻¹]

Name	Description	Global	Expression	Units
J	reaction rate	☐	$(Kf \cdot PIP2\_PM - Kr \cdot PIP2\_PHGFP\_PM)$	molecules.μm⁻².s⁻¹
I	inward current density	☐	0.0	pA.μm⁻²
netValence	net charge valence	☐	1.0	1
Kf	forward rate constant	☐	0.0	s⁻¹
Kr	reverse rate constant	☐	0.0	s⁻¹
PIP2_PM	Species Concentration	☑	Variable	molecules.μm⁻²

Linked Pathway Object(s):



Use the "RX Connection" tool to drag a line from "PH_GFP_Cyt" to "r0".

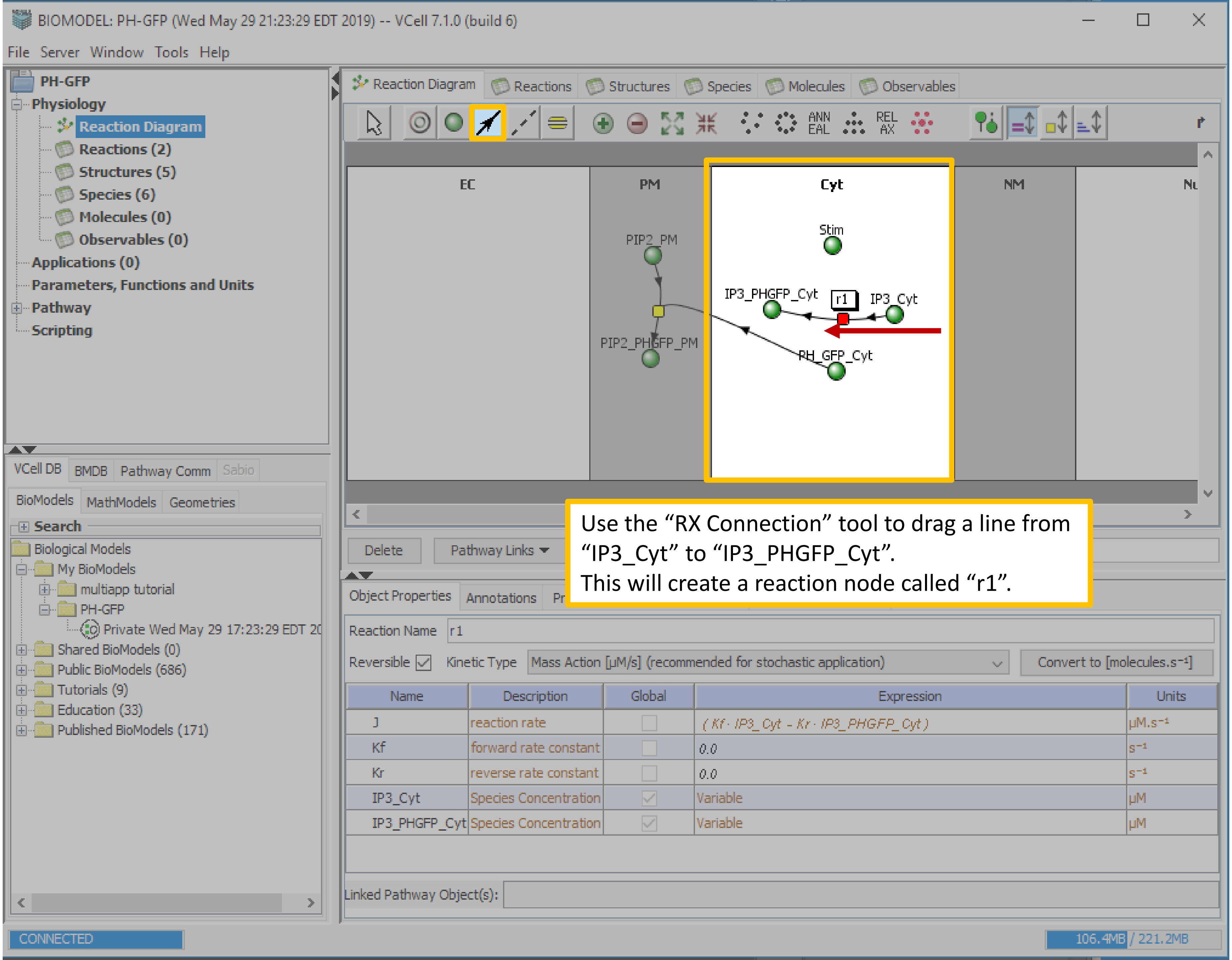
Reaction Name: r0

Electrical Properties: ☑ include molecular flux ☐ include electric current (into inside structure "undefined")

Reversible ☑ Kinetic Type: Mass Action [molecules/(μm² s)]

Name	Description	Global	Expression	Units
J	reaction rate	☐	(Kf · PIP2_PM · PH_GFP_Cyt - Kr · PIP2_PHGFP_PM)	molecules.μm⁻².s⁻¹
I	inward current density	☐	0.0	pA.μm⁻²
netValence	net charge valence	☐	1.0	1
Kf	forward rate constant	☐	0.0	s⁻¹.μM⁻¹
Kr	reverse rate constant	☐	0.0	s⁻¹
PIP2_PM	Species Concentration	☑	Variable	molecules.μm⁻²

Linked Pathway Object(s):



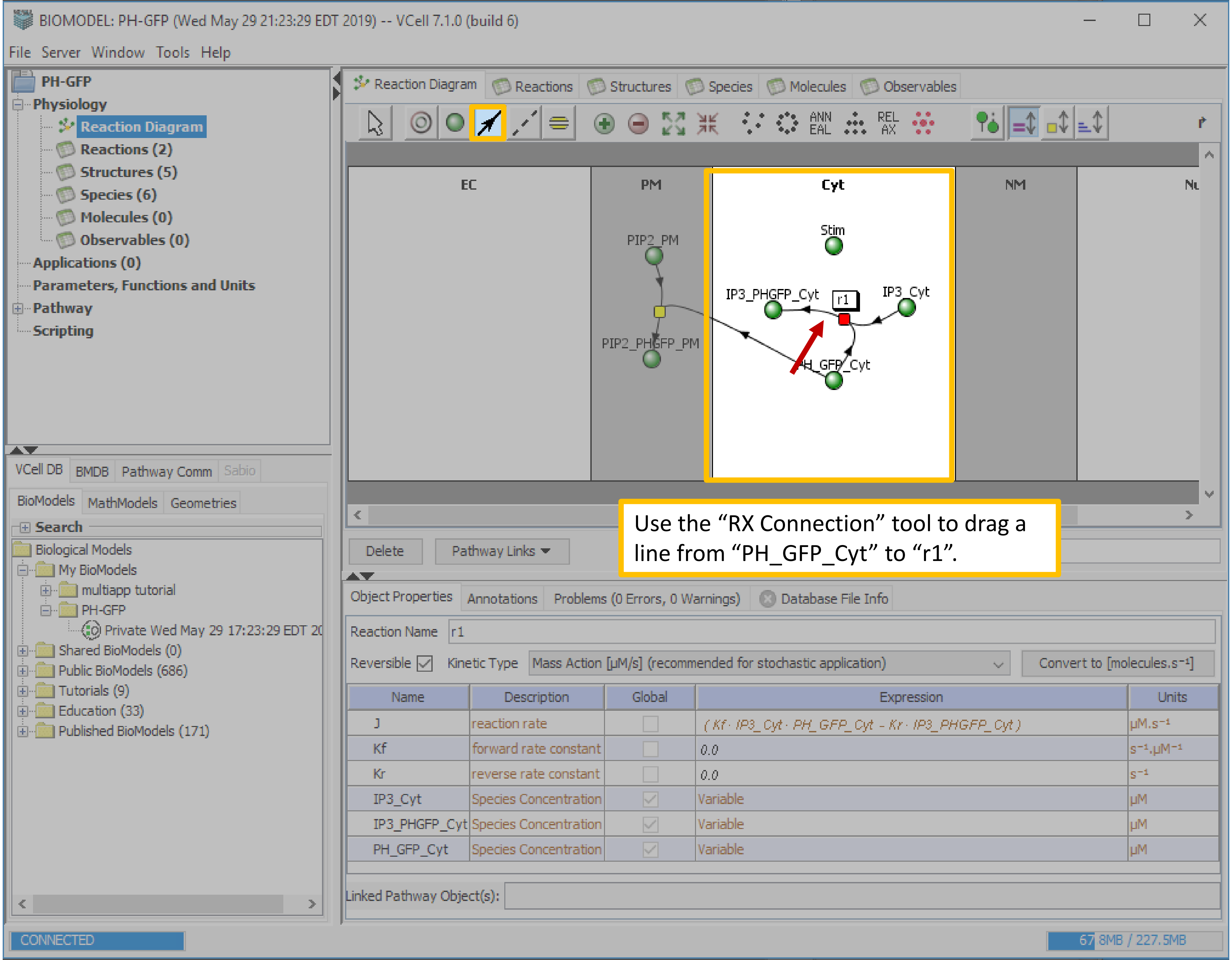
Use the “RX Connection” tool to drag a line from “IP3_Cyt” to “IP3_PHGFP_Cyt”.
This will create a reaction node called “r1”.

Reaction Name r1

Reversible ☑ Kinetic Type Mass Action [µM/s] (recommended for stochastic application)

Name	Description	Global	Expression	Units
J	reaction rate	☐	$(Kf \cdot IP3\_Cyt - Kr \cdot IP3\_PHGFP\_Cyt)$	$\mu M.s^{-1}$
Kf	forward rate constant	☐	0.0	s^{-1}
Kr	reverse rate constant	☐	0.0	s^{-1}
IP3_Cyt	Species Concentration	☑	Variable	µM
IP3_PHGFP_Cyt	Species Concentration	☑	Variable	µM

Linked Pathway Object(s):



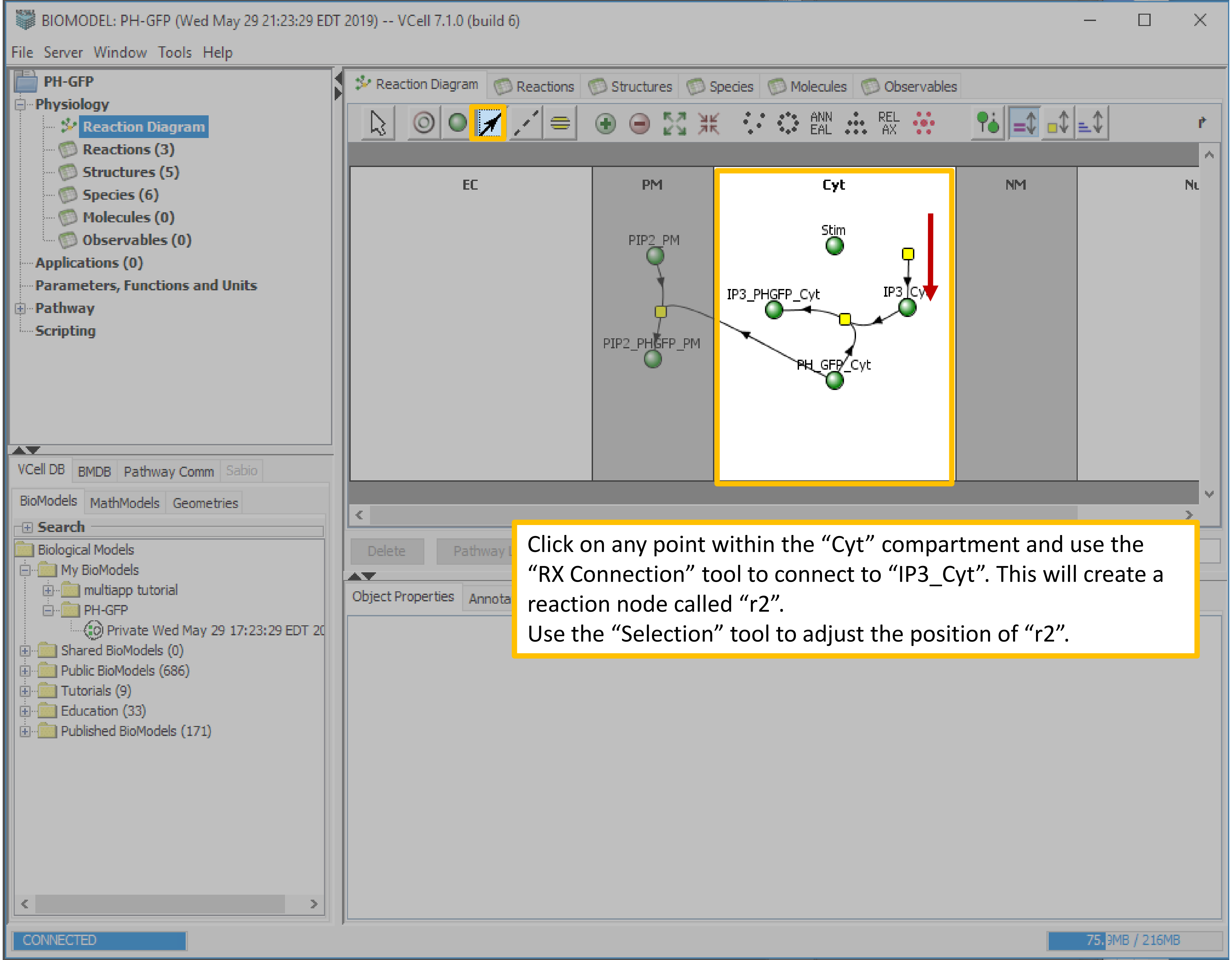
Use the “RX Connection” tool to drag a line from “PH_GFP_Cyt” to “r1”.

Reaction Name: r1

Reversible ☑ Kinetic Type: Mass Action [µM/s] (recommended for stochastic application)

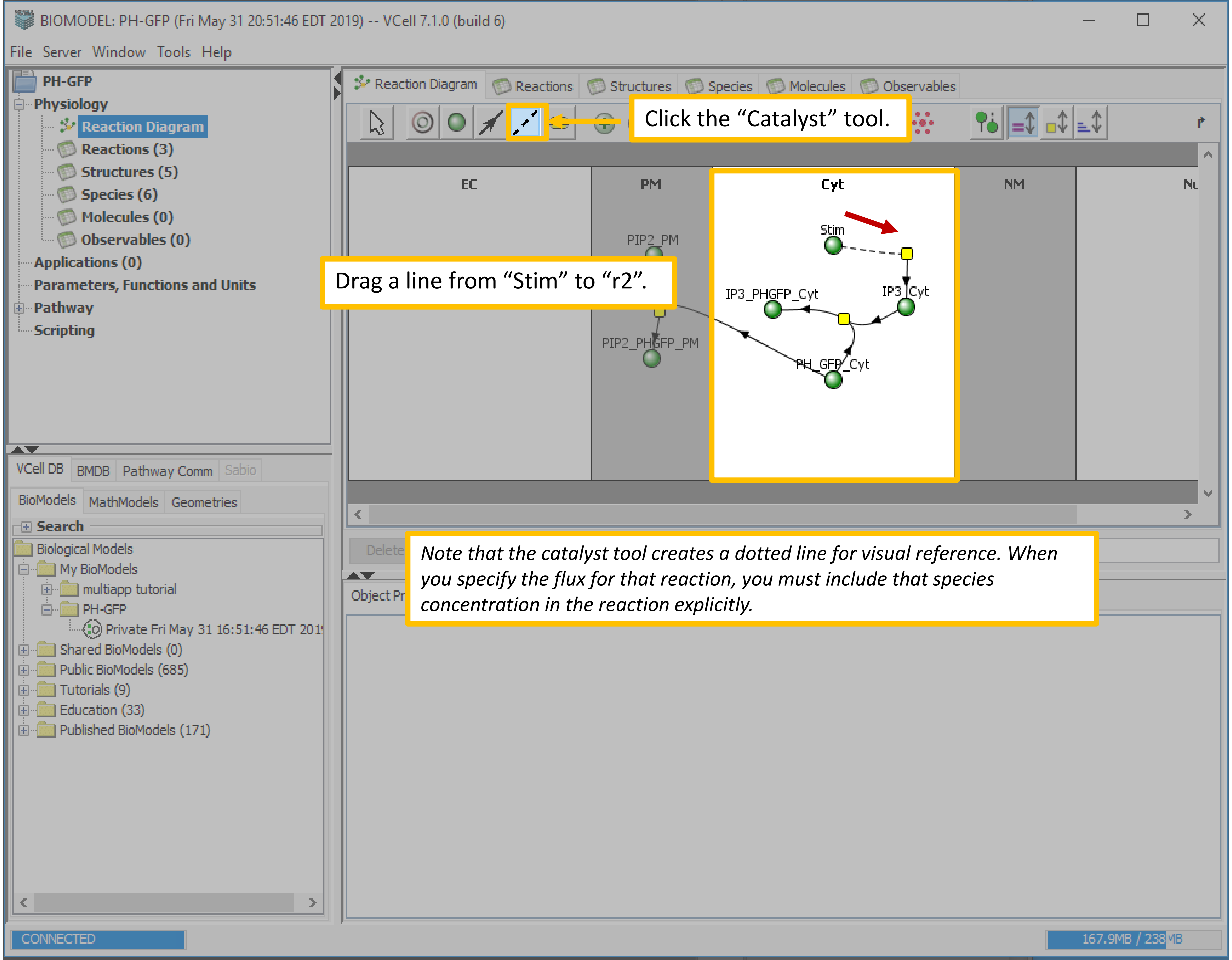
Name	Description	Global	Expression	Units
J	reaction rate	☐	(Kf · IP3_Cyt · PH_GFP_Cyt - Kr · IP3_PHGFP_Cyt)	µM.s⁻¹
Kf	forward rate constant	☐	0.0	s⁻¹.µM⁻¹
Kr	reverse rate constant	☐	0.0	s⁻¹
IP3_Cyt	Species Concentration	☑	Variable	µM
IP3_PHGFP_Cyt	Species Concentration	☑	Variable	µM
PH_GFP_Cyt	Species Concentration	☑	Variable	µM

Linked Pathway Object(s):



Click on any point within the “Cyt” compartment and use the “RX Connection” tool to connect to “IP3_Cyt”. This will create a reaction node called “r2”.

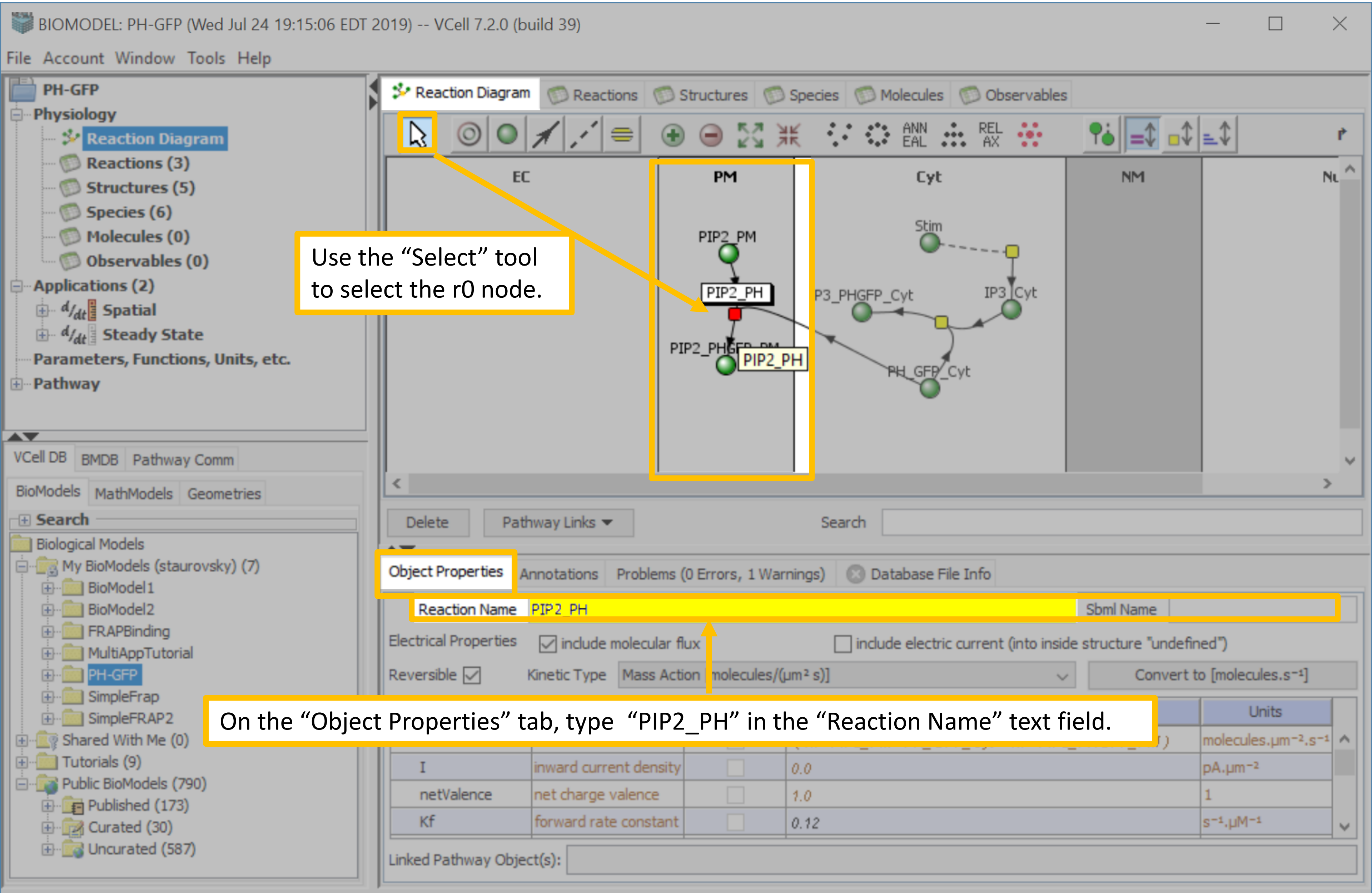
Use the “Selection” tool to adjust the position of “r2”.



Click the “Catalyst” tool.

Drag a line from “Stim” to “r2”.

Note that the catalyst tool creates a dotted line for visual reference. When you specify the flux for that reaction, you must include that species concentration in the reaction explicitly.



Use the “Select” tool to select the r0 node.

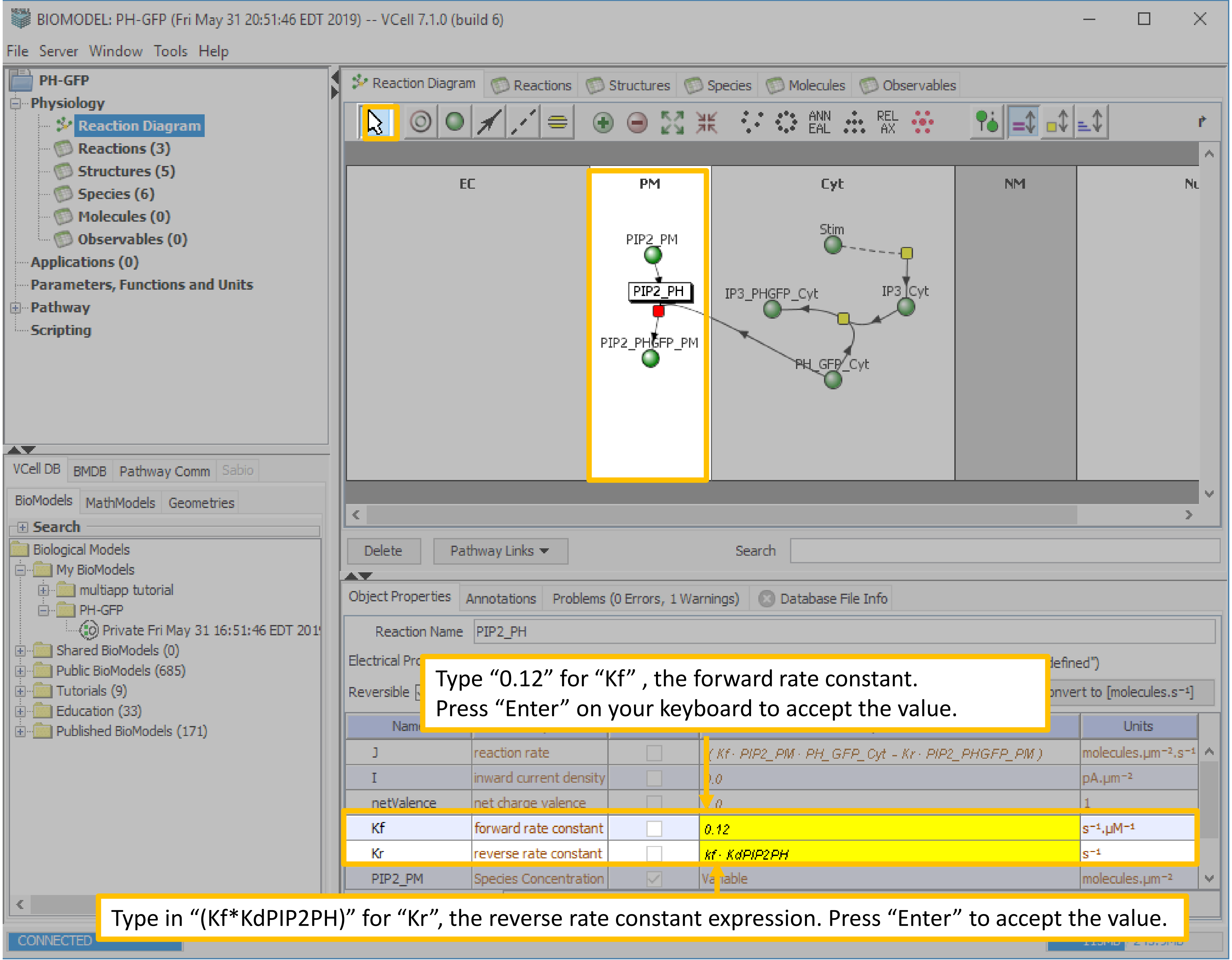
Reaction Name: PIP2_PH

Electrical Properties: ☑ include molecular flux ☐ include electric current (into inside structure "undefined")

Reversible ☑ Kinetic Type: Mass Action [molecules/(μm² s)]

On the “Object Properties” tab, type “PIP2_PH” in the “Reaction Name” text field.

				Units
		☐		molecules.μm⁻².s⁻¹
I	inward current density	☐	0.0	pA.μm⁻²
netValence	net charge valence	☐	1.0	1
Kf	forward rate constant	☐	0.12	s⁻¹.μM⁻¹



Reaction Name PIP2_PH

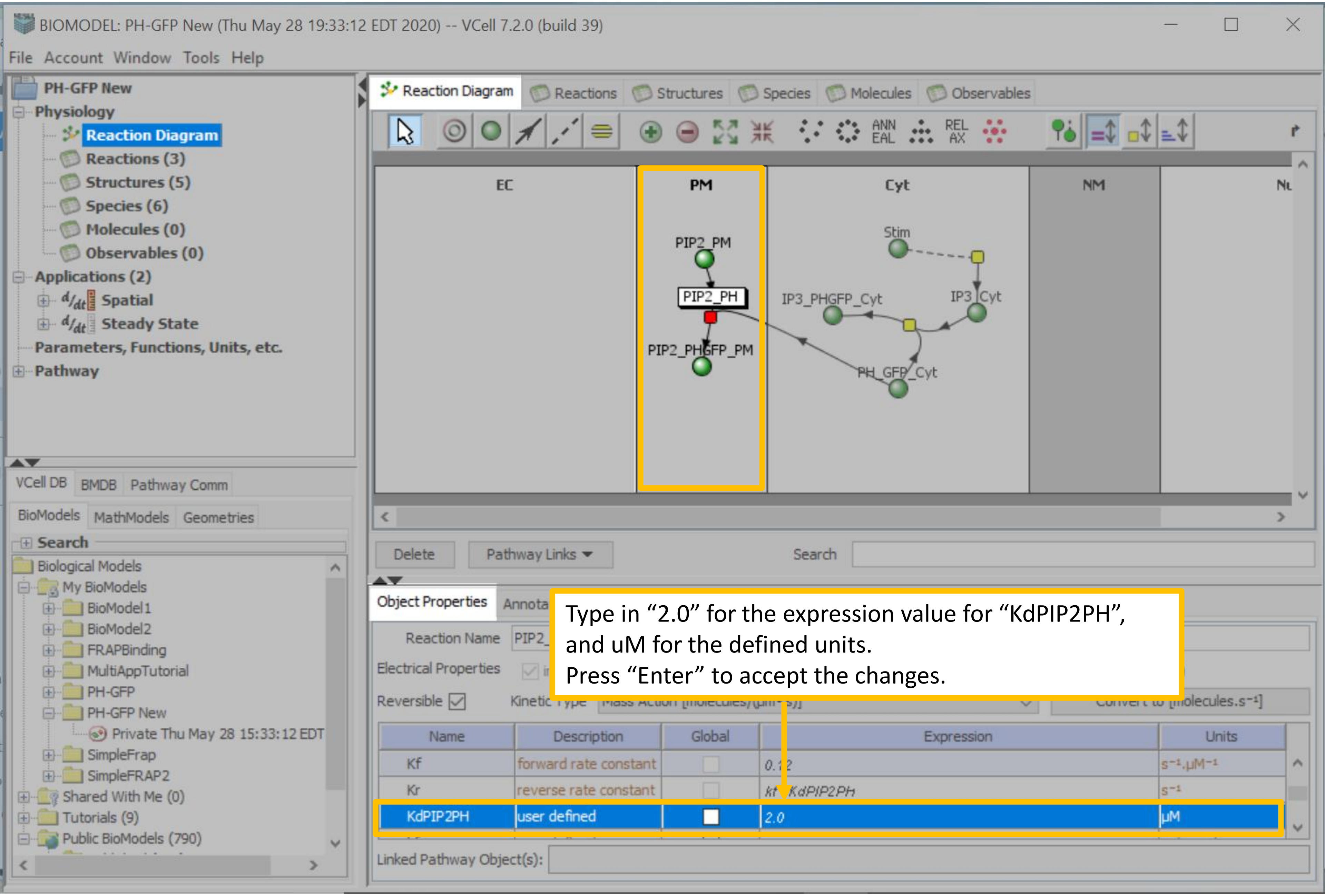
Electrical Pro... ...defined")

Reversible ☑ ...onvert to [molecules.s^{-1}]

Nam...				Units
J	reaction rate	☐	(Kf · PIP2_PM · PH_GFP_Cyt - Kr · PIP2_PHGFP_PM)	molecules.μm^{-2}.s^{-1}
I	inward current density	☐	0.0	pA.μm^{-2}
netValence	net charge valence	☐	0	1
Kf	forward rate constant	☐	0.12	s^{-1}.μM^{-1}
Kr	reverse rate constant	☐	Kf · KdPIP2PH	s^{-1}
PIP2_PM	Species Concentration	☑	Variable	molecules.μm^{-2}

Type “0.12” for “Kf” , the forward rate constant.
Press “Enter” on your keyboard to accept the value.

Type in “(Kf*KdPIP2PH)” for “Kr”, the reverse rate constant expression. Press “Enter” to accept the value.



Type in “2.0” for the expression value for “KdPIP2PH”, and uM for the defined units.
Press “Enter” to accept the changes.

Reaction Name PIP2_

Electrical Properties ☑

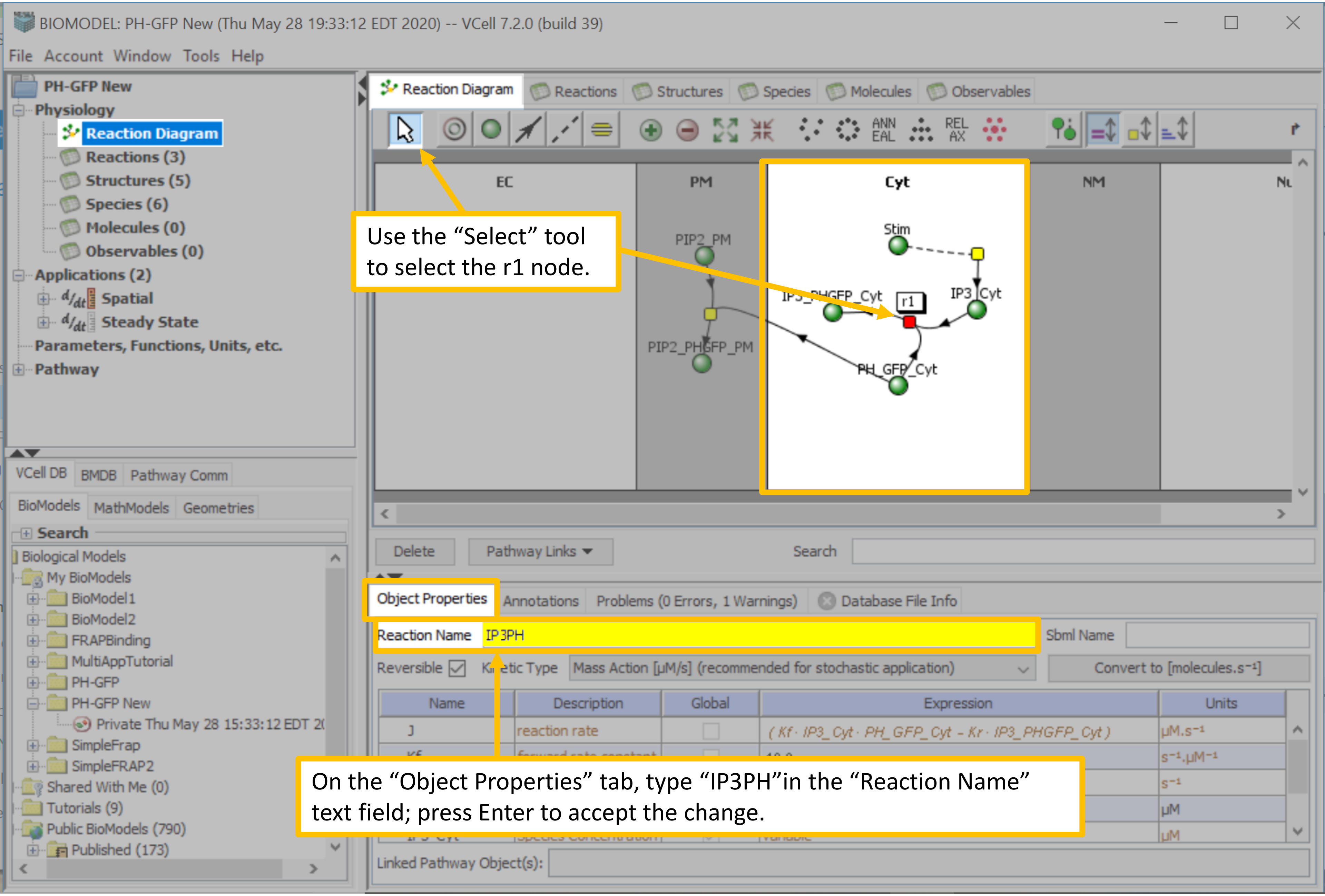
Reversible ☑

Kinetic Type Mass Action [molecules/(µm²·s)]

Convert to [molecules.s⁻¹]

Name	Description	Global	Expression	Units
Kf	forward rate constant	☐	0.12	s⁻¹.µM⁻¹
Kr	reverse rate constant	☐	kf KdPIP2PH	s⁻¹
KdPIP2PH	user defined	☐	2.0	µM

Linked Pathway Object(s):



BIOMODEL: PH-GFP New (Thu May 28 19:33:12 EDT 2020) -- VCell 7.2.0 (build 39)

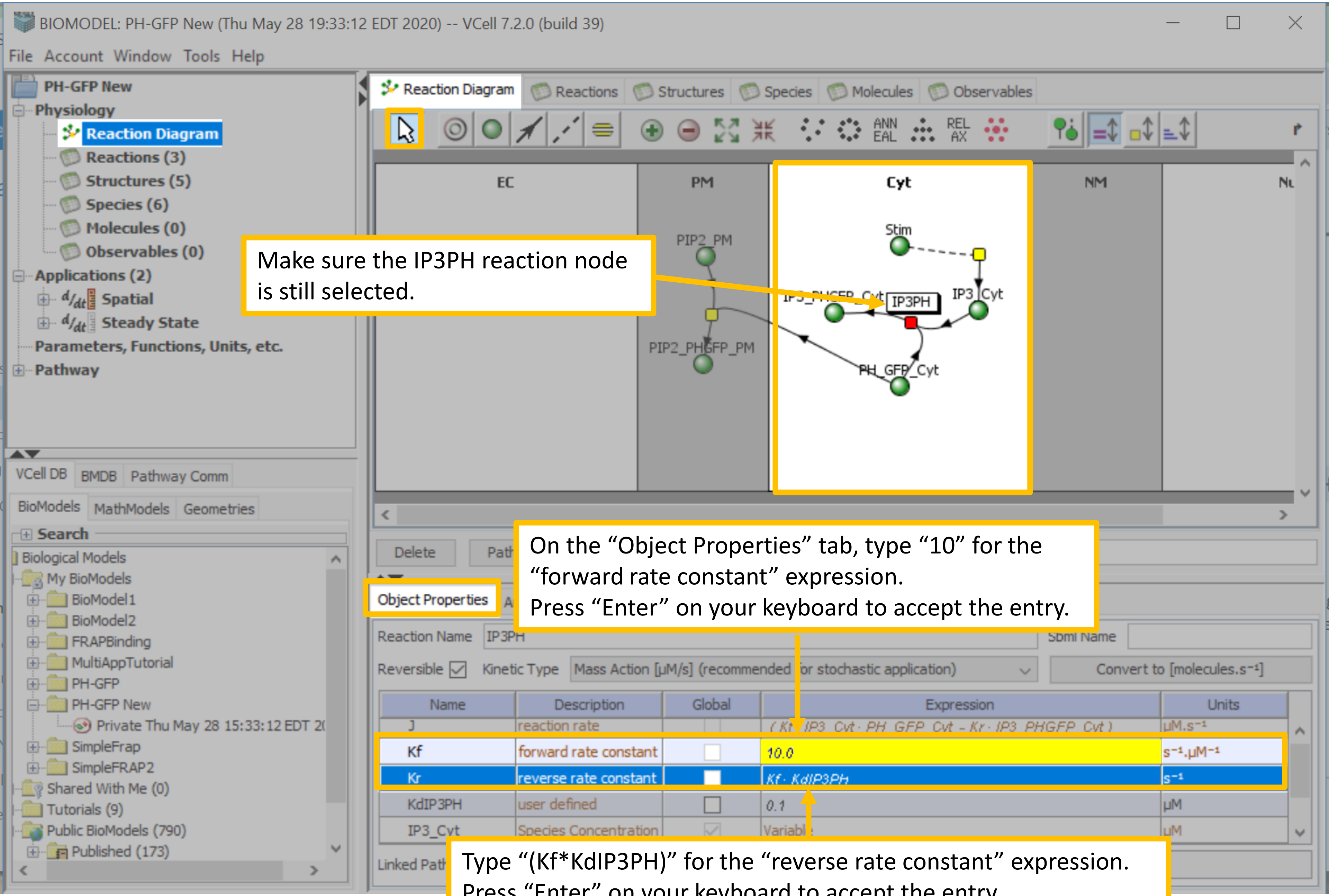
Reaction Name: IP3PH

Reversible ☑ Kinetic Type: Mass Action [µM/s] (recommended for stochastic application)

Name	Description	Global	Expression	Units
J	reaction rate	☐	(Kf · IP3_Cyt · PH_GFP_Cyt − Kr · IP3_PHGFP_Cyt)	µM.s⁻¹
Kf	forward rate constant	☐	10.0	s⁻¹.µM⁻¹

Use the “Select” tool to select the r1 node.

On the “Object Properties” tab, type “IP3PH”in the “Reaction Name” text field; press Enter to accept the change.



Make sure the IP3PH reaction node is still selected.

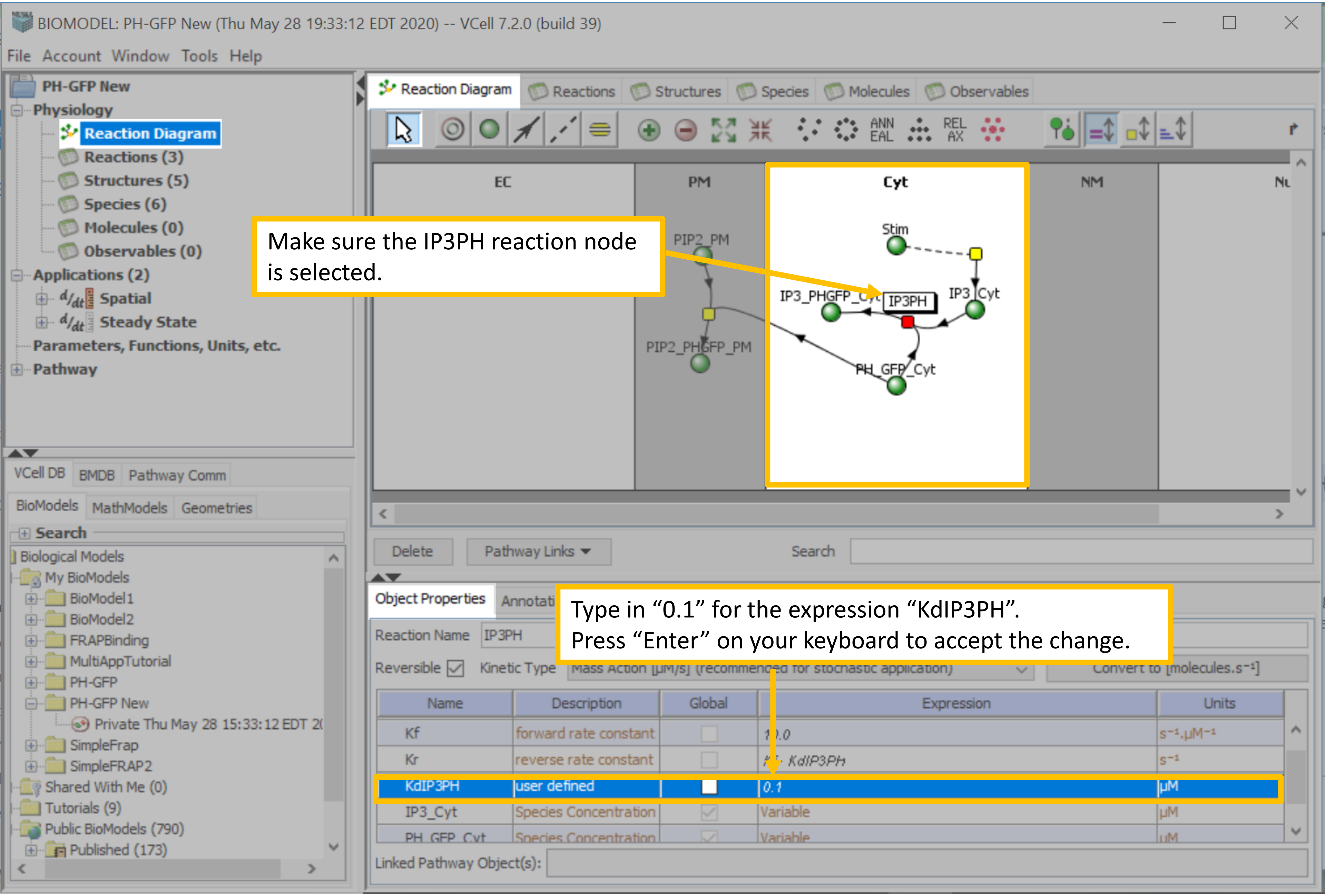
On the “Object Properties” tab, type “10” for the “forward rate constant” expression.
Press “Enter” on your keyboard to accept the entry.

Type “(Kf*KdIP3PH)” for the “reverse rate constant” expression.
Press “Enter” on your keyboard to accept the entry.

Reaction Name: IP3PH

Reversible ☑ Kinetic Type: Mass Action [µM/s] (recommended or stochastic application)

Name	Description	Global	Expression	Units
J	reaction rate		(Kf · IP3_Cyt · PH_GFP_Cyt – Kr · IP3_PHGFP_Cyt)	$\mu M.s^{-1}$
Kf	forward rate constant	☐	10.0	$s^{-1}.\mu M^{-1}$
Kr	reverse rate constant	☐	Kf · KdIP3PH	s^{-1}
KdIP3PH	user defined	☐	0.1	µM
IP3_Cyt	Species Concentration	☑	Variabl	µM



Make sure the IP3PH reaction node is selected.

Type in “0.1” for the expression “KdIP3PH”.
Press “Enter” on your keyboard to accept the change.

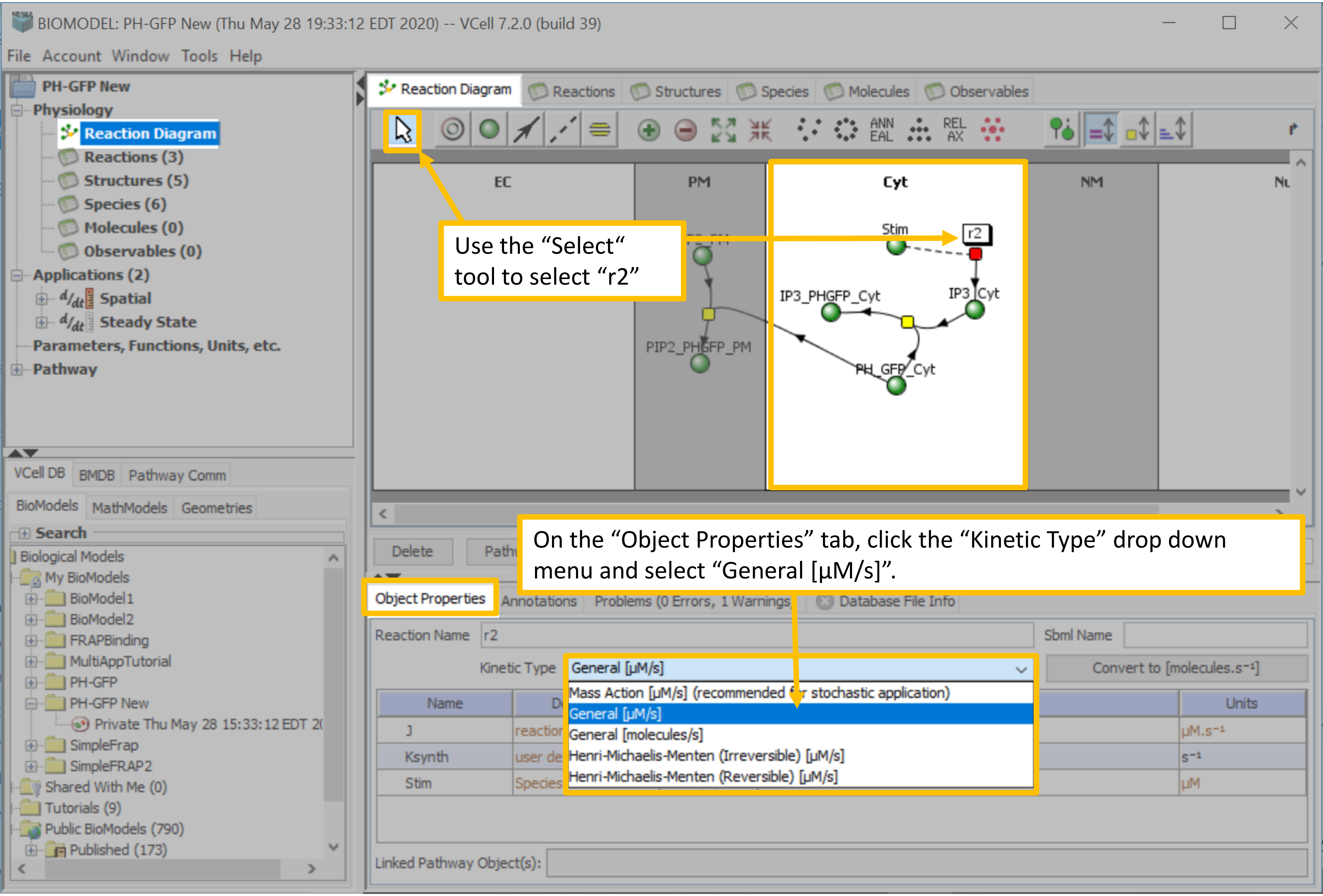
Reaction Name: IP3PH

Reversible ☑ Kinetic Type: Mass Action [μM/s] (recommended for stochastic application)

Convert to [molecules.s⁻¹]

Name	Description	Global	Expression	Units
Kf	forward rate constant	☐	10.0	$s^{-1}.\mu M^{-1}$
Kr	reverse rate constant	☐	Kf * KdIP3PH	s^{-1}
KdIP3PH	user defined	☐	0.1	μM
IP3_Cyt	Species Concentration	☑	Variable	μM
PH_GFP_Cyt	Species Concentration	☑	Variable	μM

Linked Pathway Object(s):



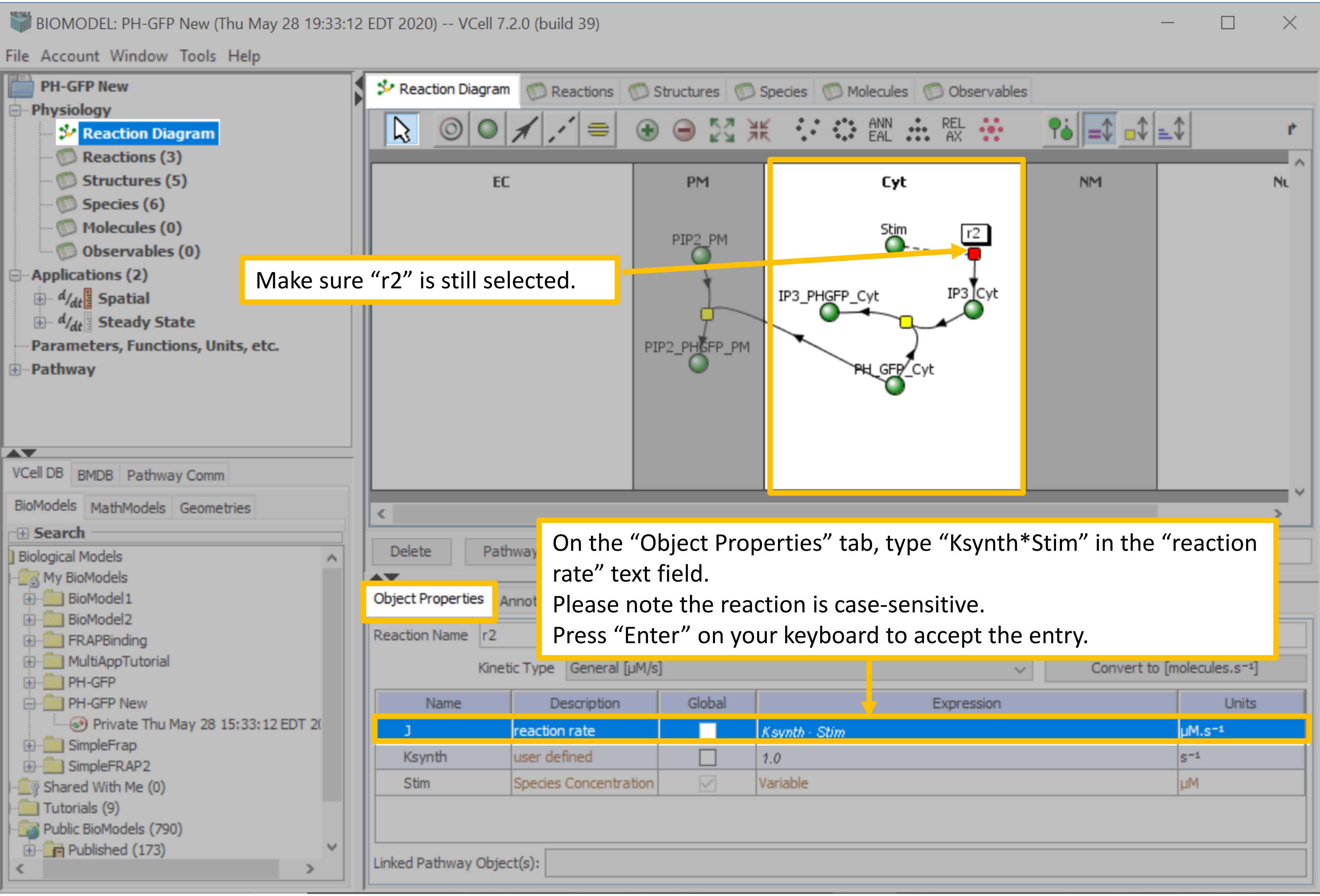
Use the "Select" tool to select "r2"

On the "Object Properties" tab, click the "Kinetic Type" drop down menu and select "General [µM/s]".

Reaction Name: r2

Kinetic Type: General [µM/s]

Name	D	Units
J	reaction	µM.s⁻¹
Ksynth	user de	s⁻¹
Stim	Species	µM



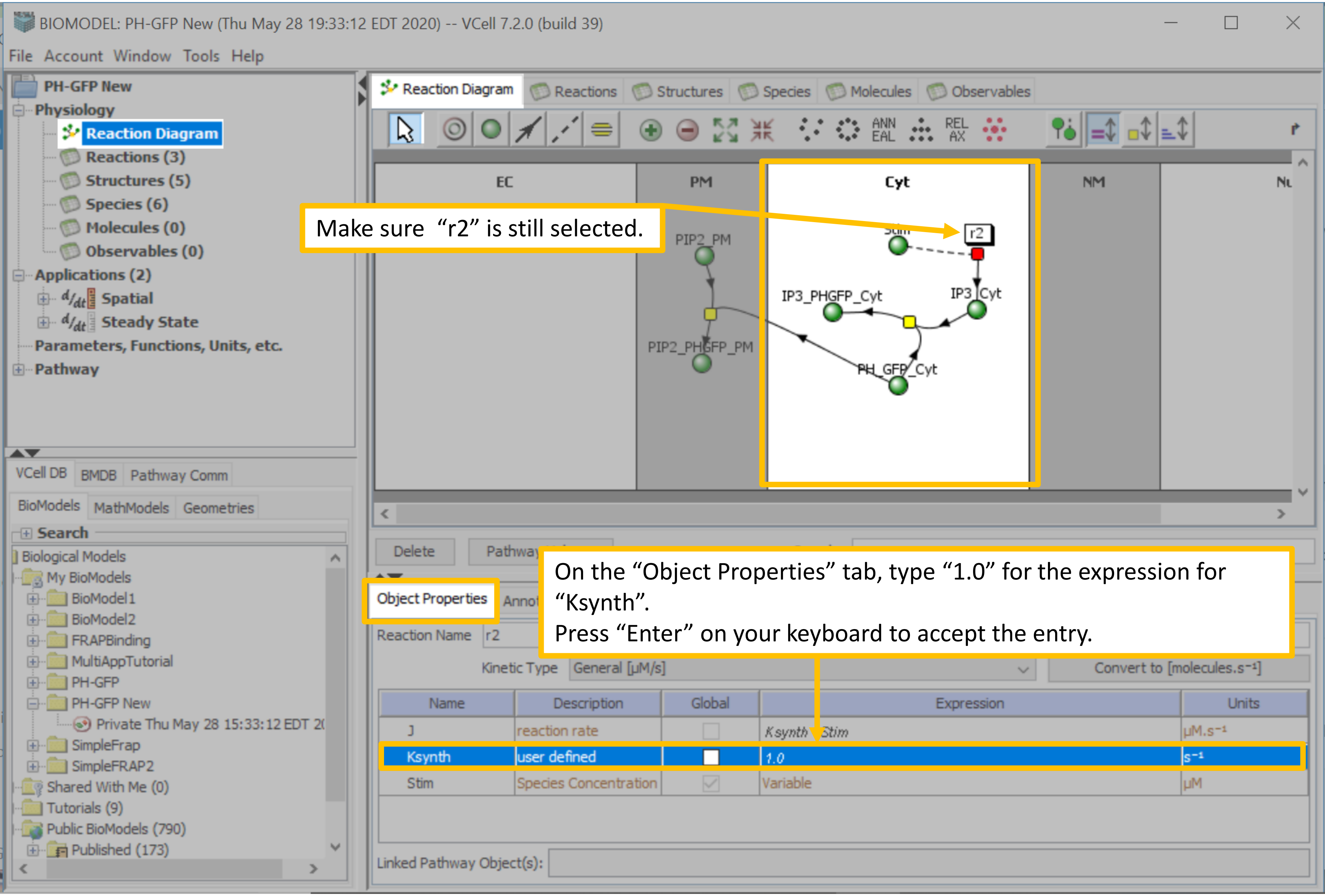
Make sure “r2” is still selected.

On the “Object Properties” tab, type “Ksynth*Stim” in the “reaction rate” text field.
Please note the reaction is case-sensitive.
Press “Enter” on your keyboard to accept the entry.

Reaction Name: r2

Kinetic Type: General [µM/s]

Name	Description	Global	Expression	Units
J	reaction rate	☐	Ksynth · Stim	µM.s⁻¹
Ksynth	user defined	☐	1.0	s⁻¹
Stim	Species Concentration	☑	Variable	µM



BIOMODEL: PH-GFP New (Thu May 28 19:33:12 EDT 2020) -- VCell 7.2.0 (build 39)

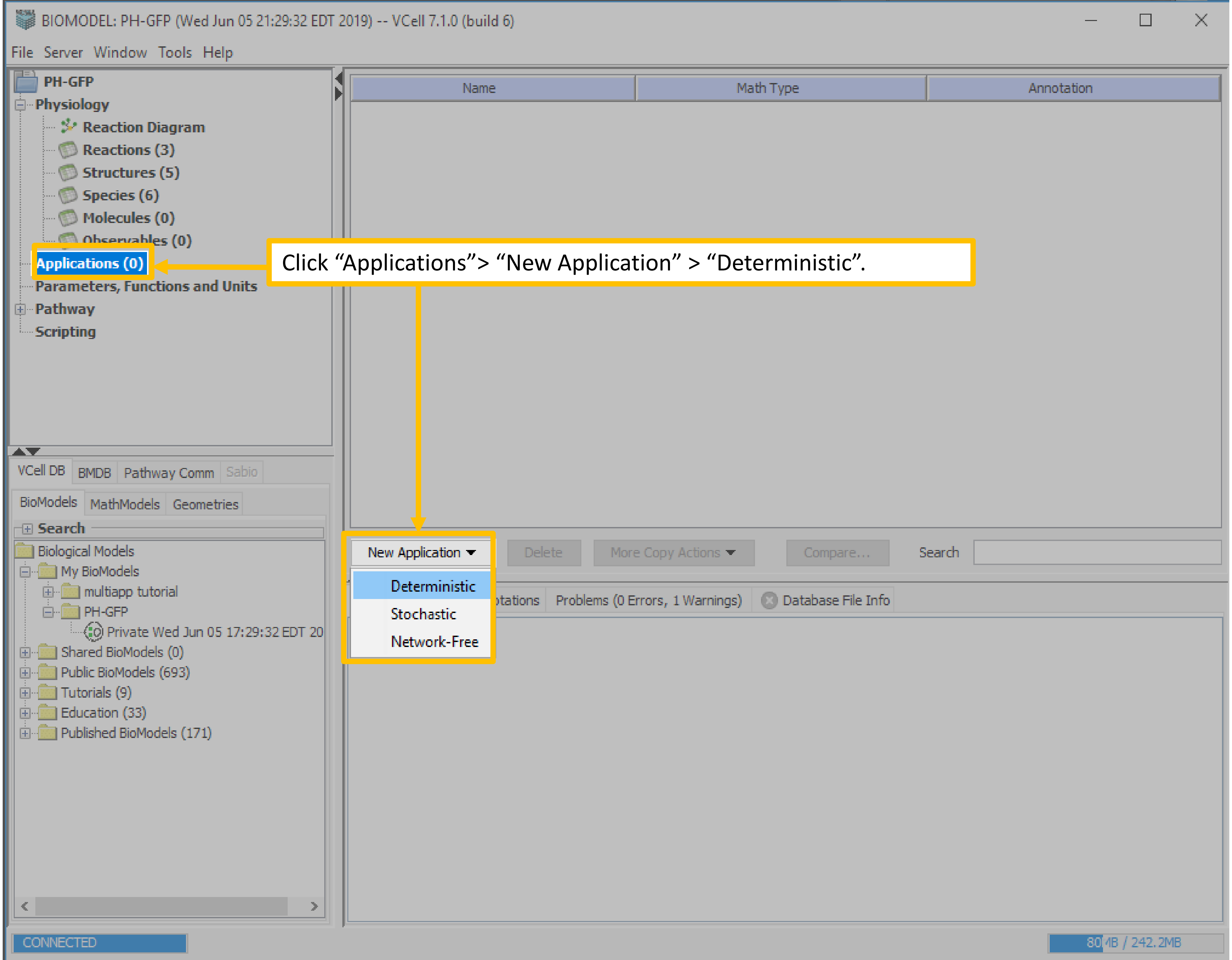
Reaction Name: r2

Kinetic Type: General [µM/s]

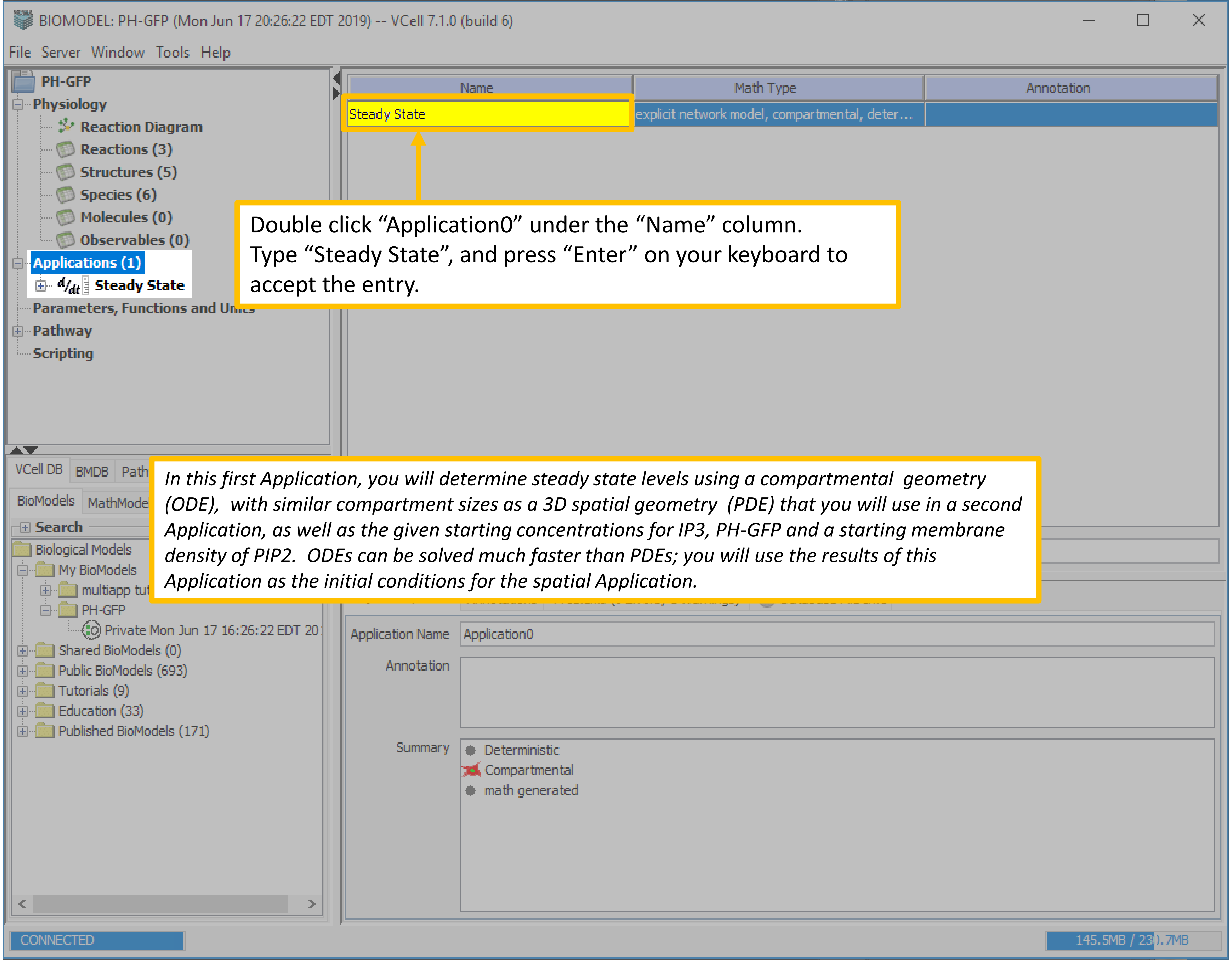
Name	Description	Global	Expression	Units
J	reaction rate	☐	Ksynth * Stim	$\mu M.s^{-1}$
Ksynth	user defined	☐	1.0	s^{-1}
Stim	Species Concentration	☑	Variable	µM

Make sure “r2” is still selected.

On the “Object Properties” tab, type “1.0” for the expression for “Ksynth”.
Press “Enter” on your keyboard to accept the entry.



Click “Applications”> “New Application” > “Deterministic”.



Name	Math Type	Annotation
Steady State	explicit network model, compartmental, deter…	

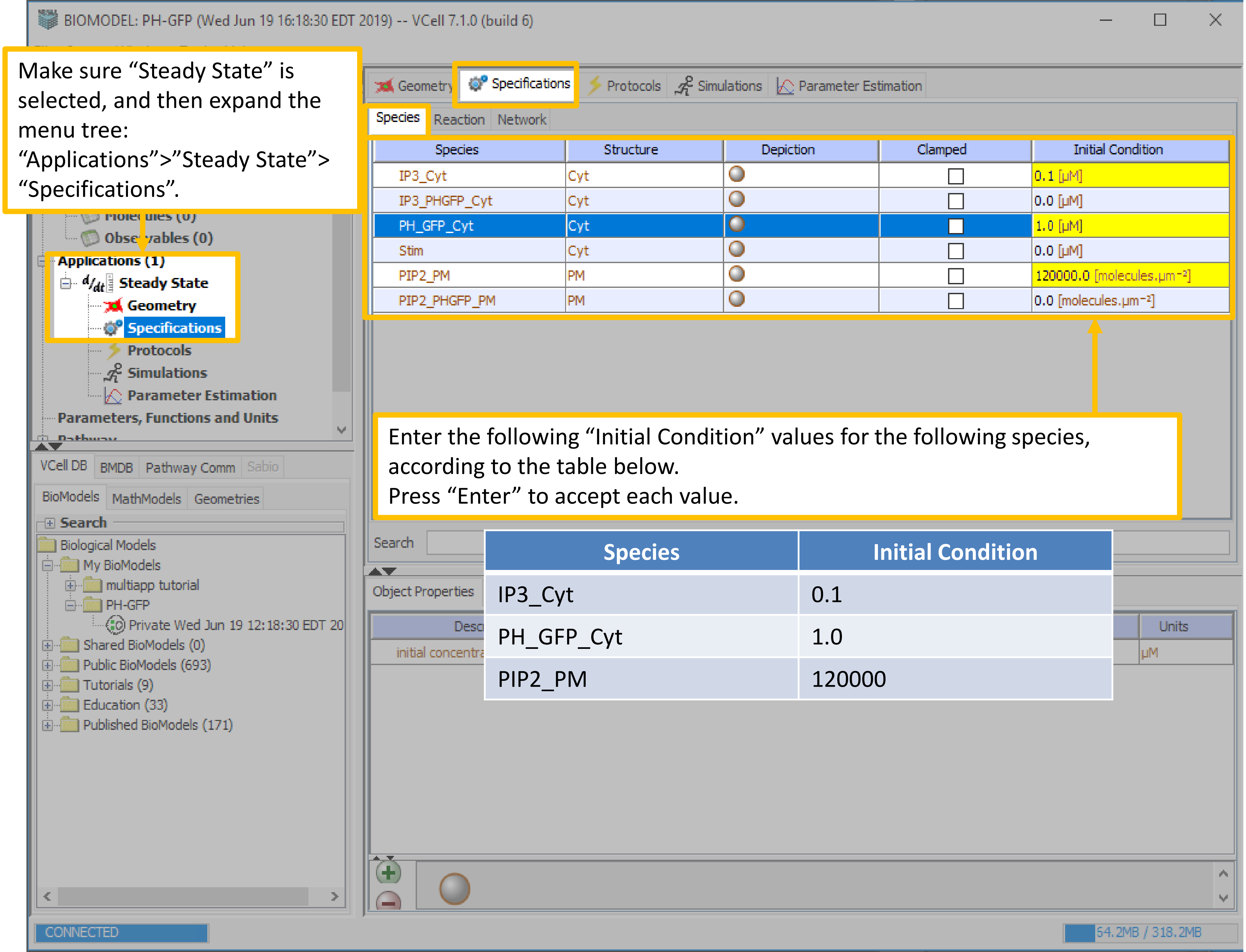
Application Name: Application0

Annotation:

Summary:
- Deterministic
- Compartmental
- math generated

Double click “Application0” under the “Name” column. Type “Steady State”, and press “Enter” on your keyboard to accept the entry.

In this first Application, you will determine steady state levels using a compartmental geometry (ODE), with similar compartment sizes as a 3D spatial geometry (PDE) that you will use in a second Application, as well as the given starting concentrations for IP3, PH-GFP and a starting membrane density of PIP2. ODEs can be solved much faster than PDEs; you will use the results of this Application as the initial conditions for the spatial Application.

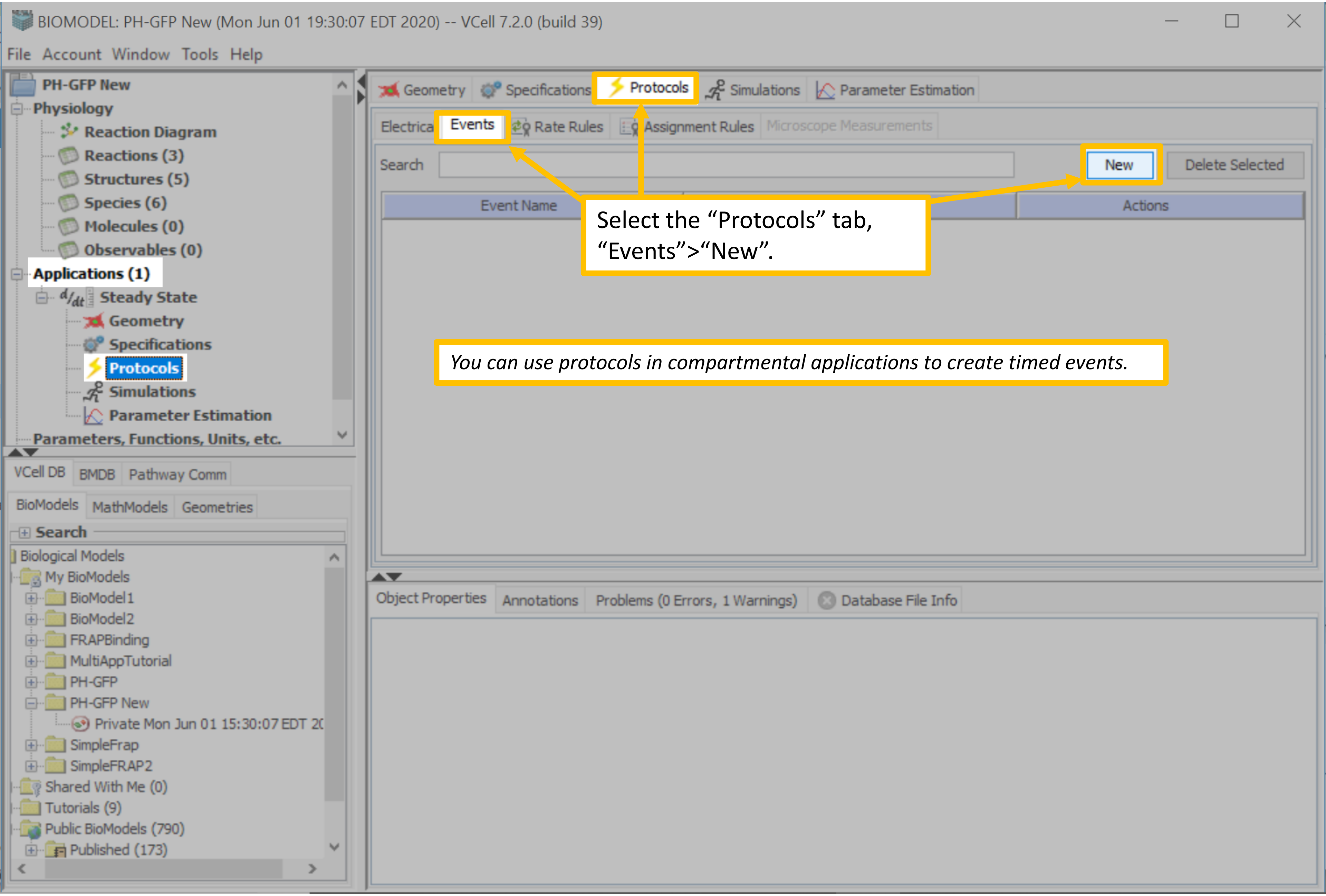


Species	Structure	Depiction	Clamped	Initial Condition
IP3_Cyt	Cyt	●	☐	0.1 [µM]
IP3_PHGFP_Cyt	Cyt	●	☐	0.0 [µM]
PH_GFP_Cyt	Cyt	●	☐	1.0 [µM]
Stim	Cyt	●	☐	0.0 [µM]
PIP2_PM	PM	●	☐	120000.0 [molecules.µm⁻²]
PIP2_PHGFP_PM	PM	●	☐	0.0 [molecules.µm⁻²]

Make sure “Steady State” is selected, and then expand the menu tree: “Applications”>”Steady State”> “Specifications”.

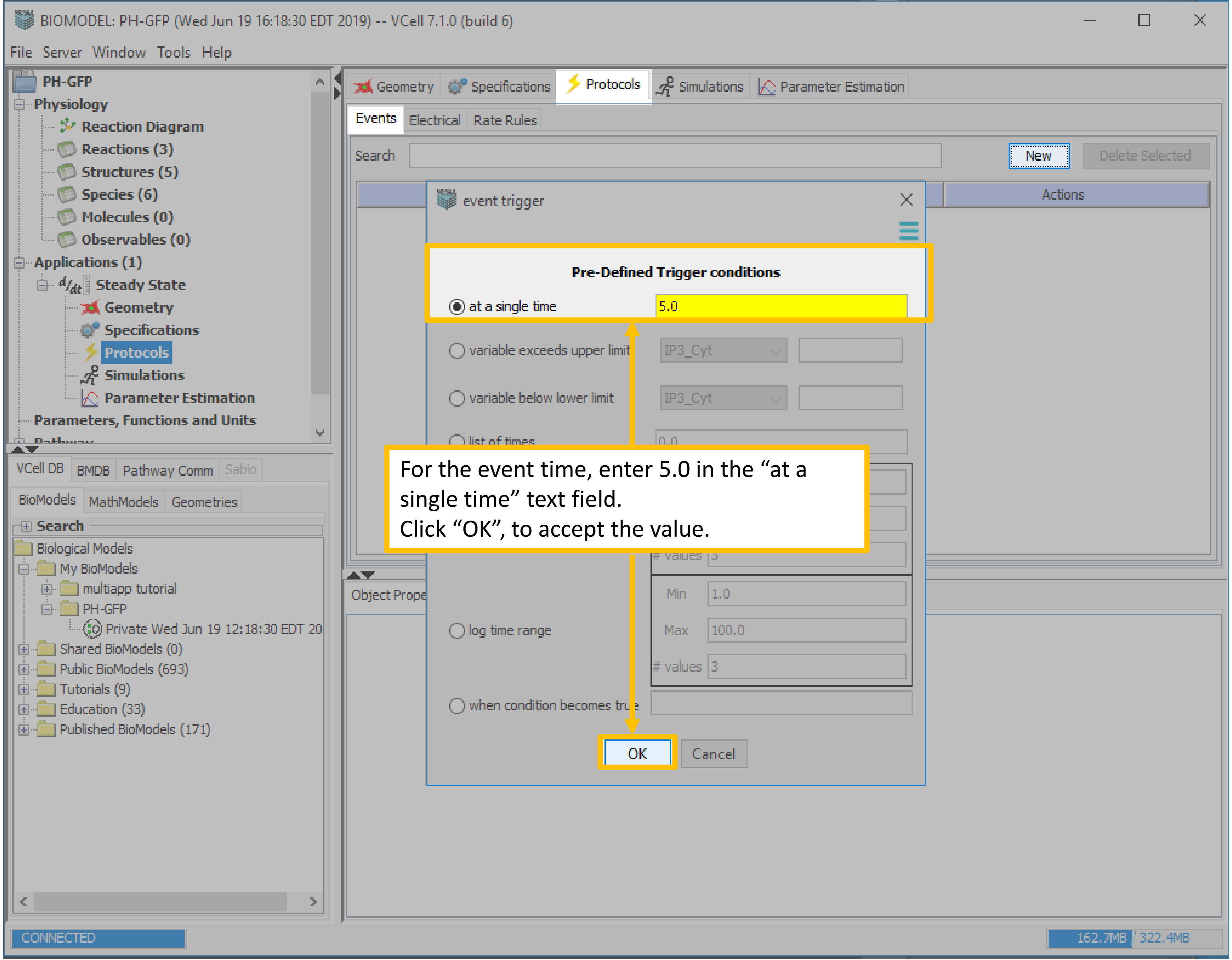
Enter the following “Initial Condition” values for the following species, according to the table below.
Press “Enter” to accept each value.

Species	Initial Condition
IP3_Cyt	0.1
PH_GFP_Cyt	1.0
PIP2_PM	120000



Select the “Protocols” tab, “Events”>“New”.

You can use protocols in compartmental applications to create timed events.



BIOMODEL: PH-GFP (Wed Jun 19 16:18:30 EDT 2019) -- VCell 7.1.0 (build 6)

event trigger

Pre-Defined Trigger conditions

● at a single time: 5.0

○ variable exceeds upper limit: IP3_Cyt

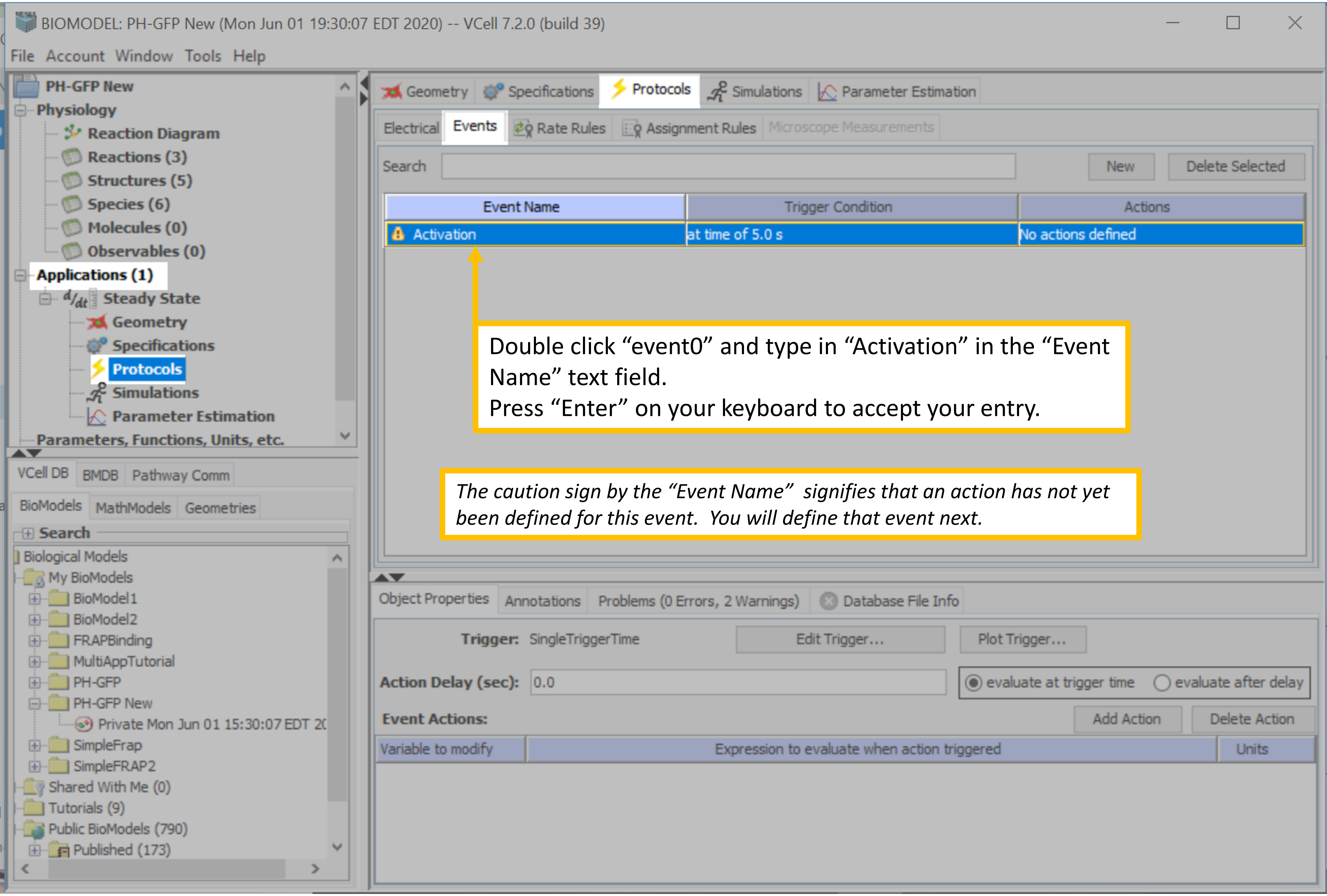
○ variable below lower limit: IP3_Cyt

○ list of times: 0.0

○ log time range: Min 1.0, Max 100.0, # values 3

○ when condition becomes true

For the event time, enter 5.0 in the “at a single time” text field.
Click “OK”, to accept the value.



Event Name	Trigger Condition	Actions
⚠ Activation	at time of 5.0 s	No actions defined

Trigger: SingleTriggerTime

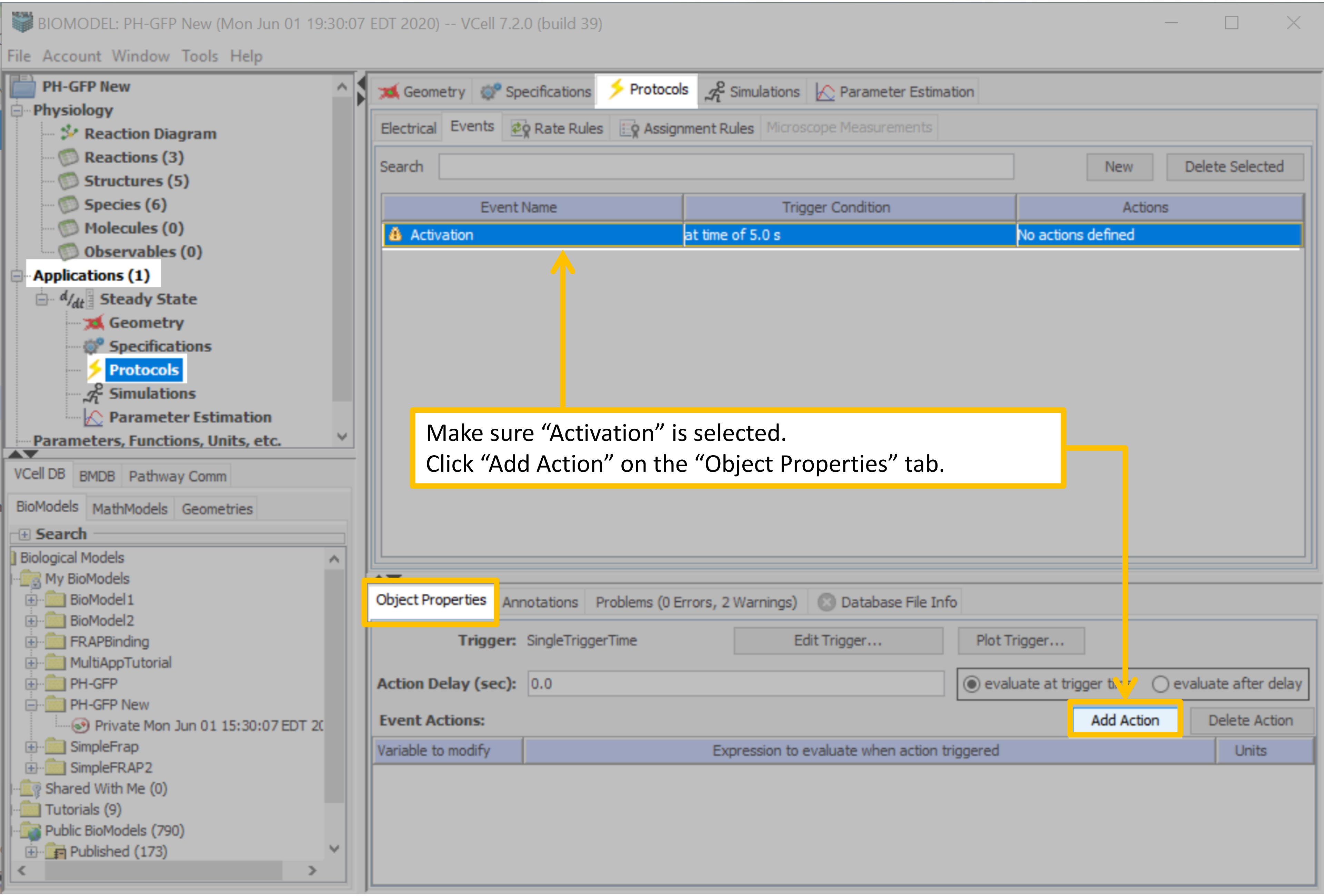
Action Delay (sec): 0.0

● evaluate at trigger time ○ evaluate after delay

Variable to modify	Expression to evaluate when action triggered	Units

Double click “event0” and type in “Activation” in the “Event Name” text field.
Press “Enter” on your keyboard to accept your entry.

The caution sign by the “Event Name” signifies that an action has not yet been defined for this event. You will define that event next.



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	No actions defined

Trigger: SingleTriggerTime

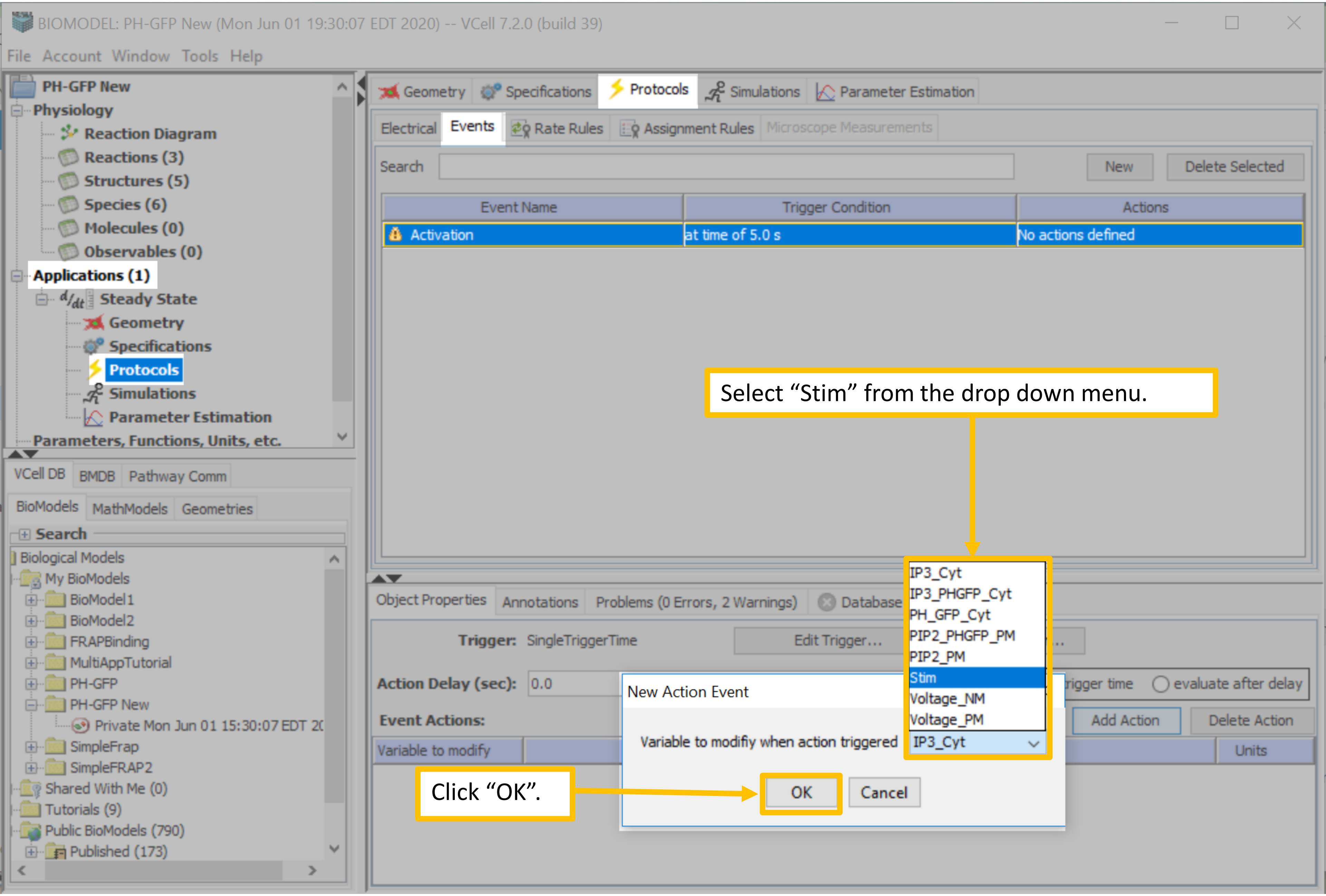
Action Delay (sec): 0.0

● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units

Make sure “Activation” is selected.
Click “Add Action” on the “Object Properties” tab.



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	No actions defined

Trigger: SingleTriggerTime

Action Delay (sec): 0.0

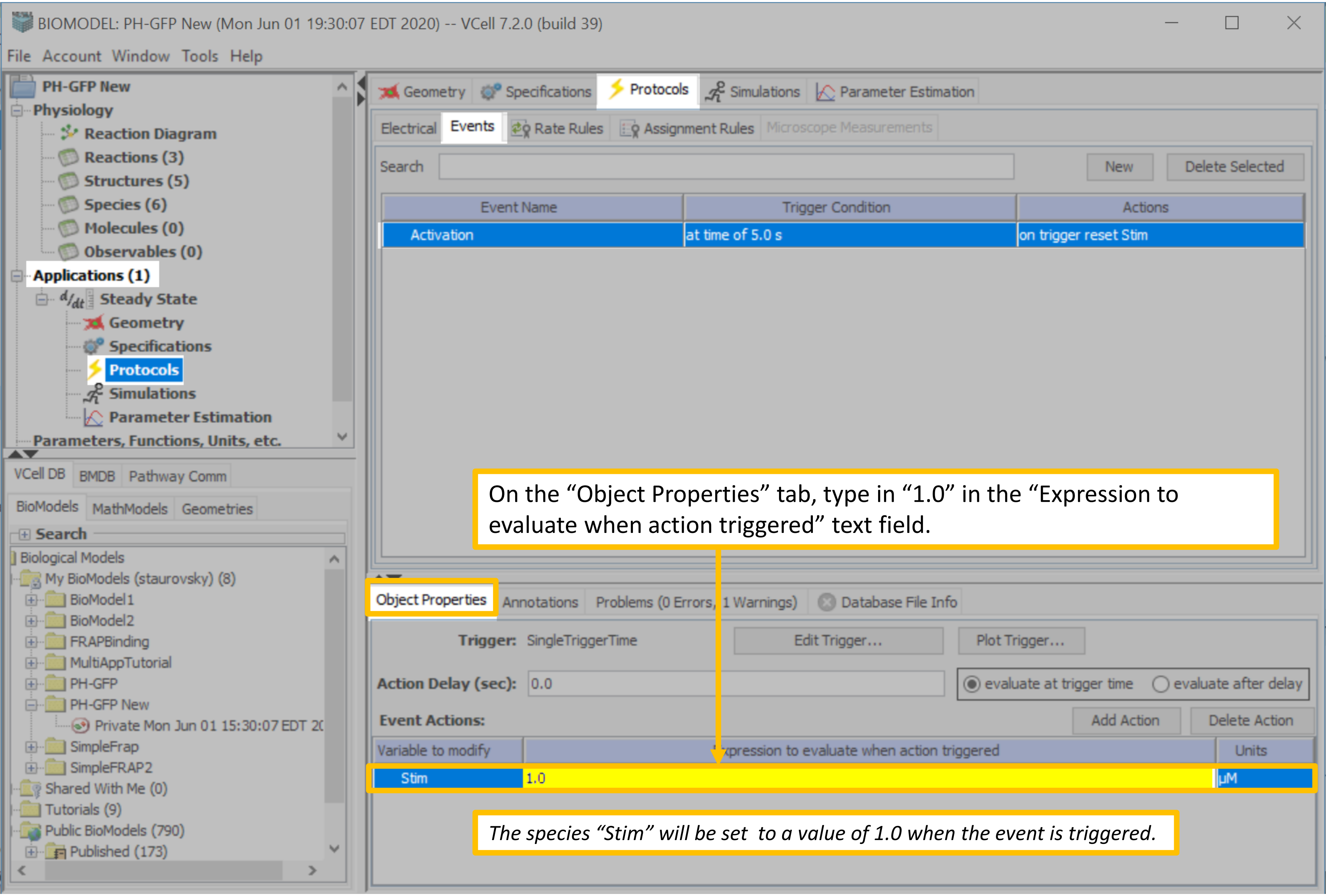
Event Actions:

New Action Event

Variable to modify when action triggered: IP3_Cyt

Select “Stim” from the drop down menu.

Click “OK”.



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	on trigger reset Stim

Trigger: SingleTriggerTime

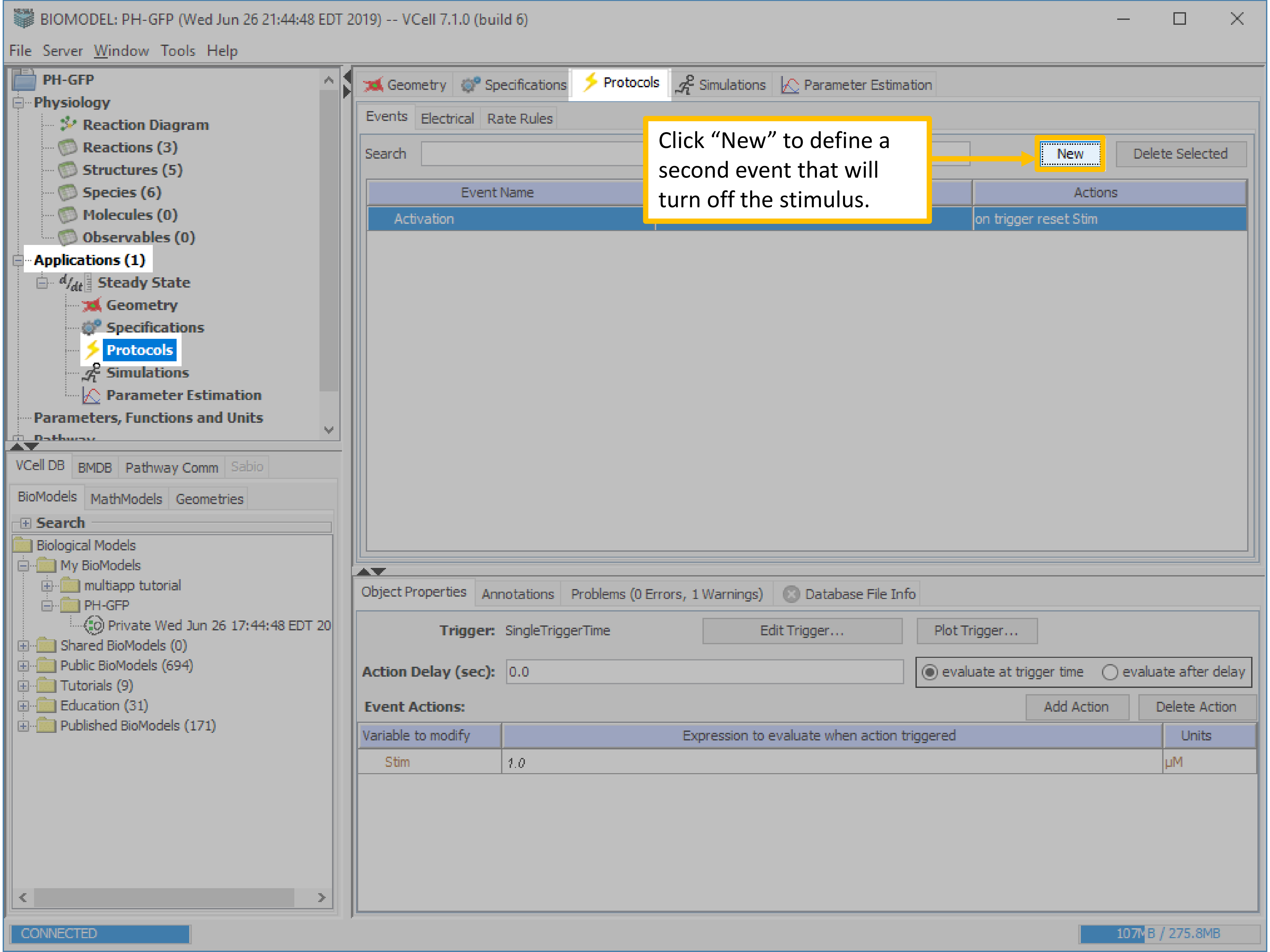
Action Delay (sec): 0.0 ● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units
Stim	1.0	µM

On the “Object Properties” tab, type in “1.0” in the “Expression to evaluate when action triggered” text field.

The species “Stim” will be set to a value of 1.0 when the event is triggered.



Click “New” to define a second event that will turn off the stimulus.

Event Name		Actions
Activation		on trigger reset Stim

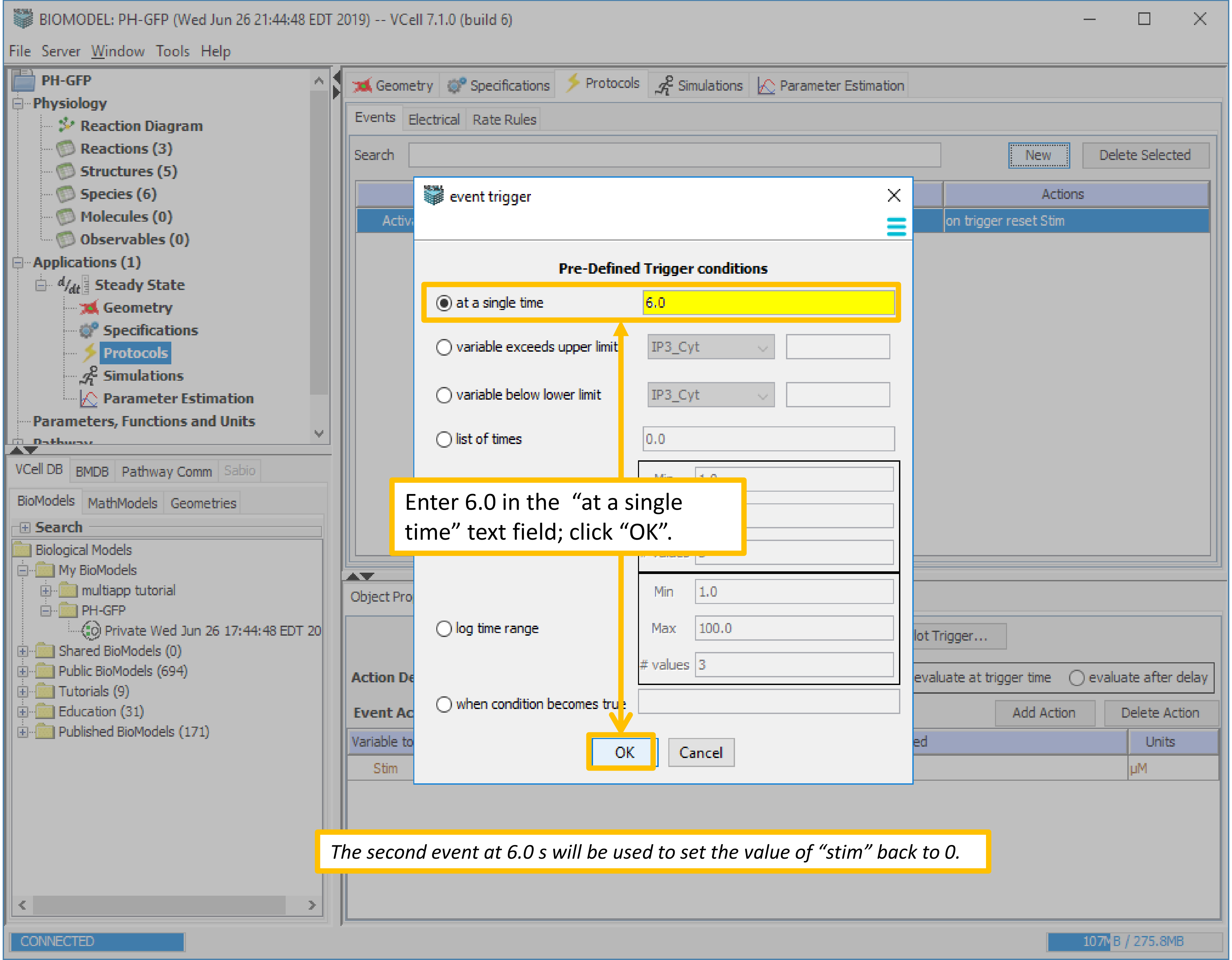
Trigger: SingleTriggerTime

Action Delay (sec): 0.0

● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units
Stim	1.0	µM



Pre-Defined Trigger conditions

● at a single time: 6.0

○ variable exceeds upper limit: IP3_Cyt

○ variable below lower limit: IP3_Cyt

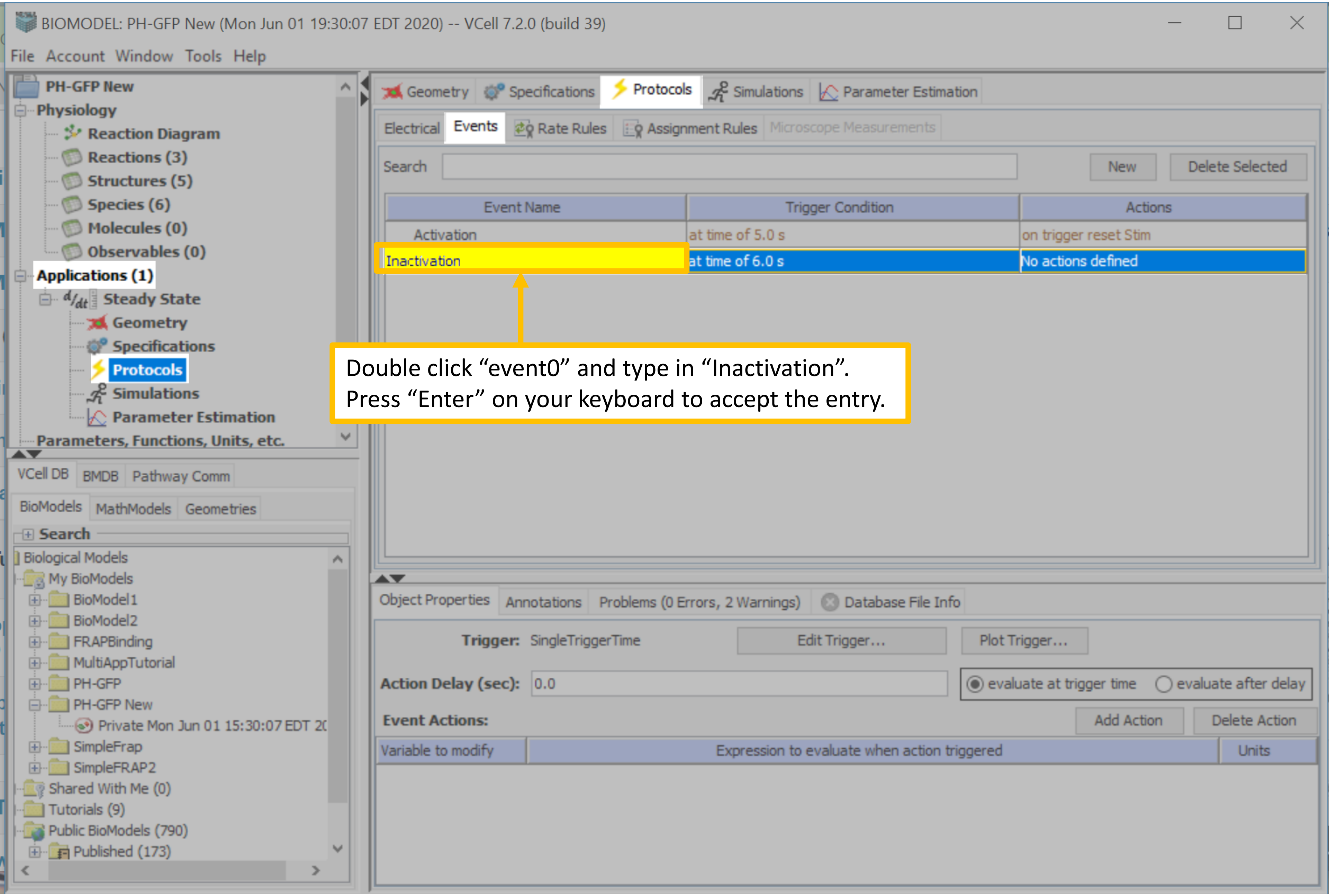
○ list of times: 0.0

○ log time range: Min 1.0, Max 100.0, # values 3

○ when condition becomes true

Enter 6.0 in the "at a single time" text field; click "OK".

The second event at 6.0 s will be used to set the value of "stim" back to 0.



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	on trigger reset Stim
Inactivation	at time of 6.0 s	No actions defined

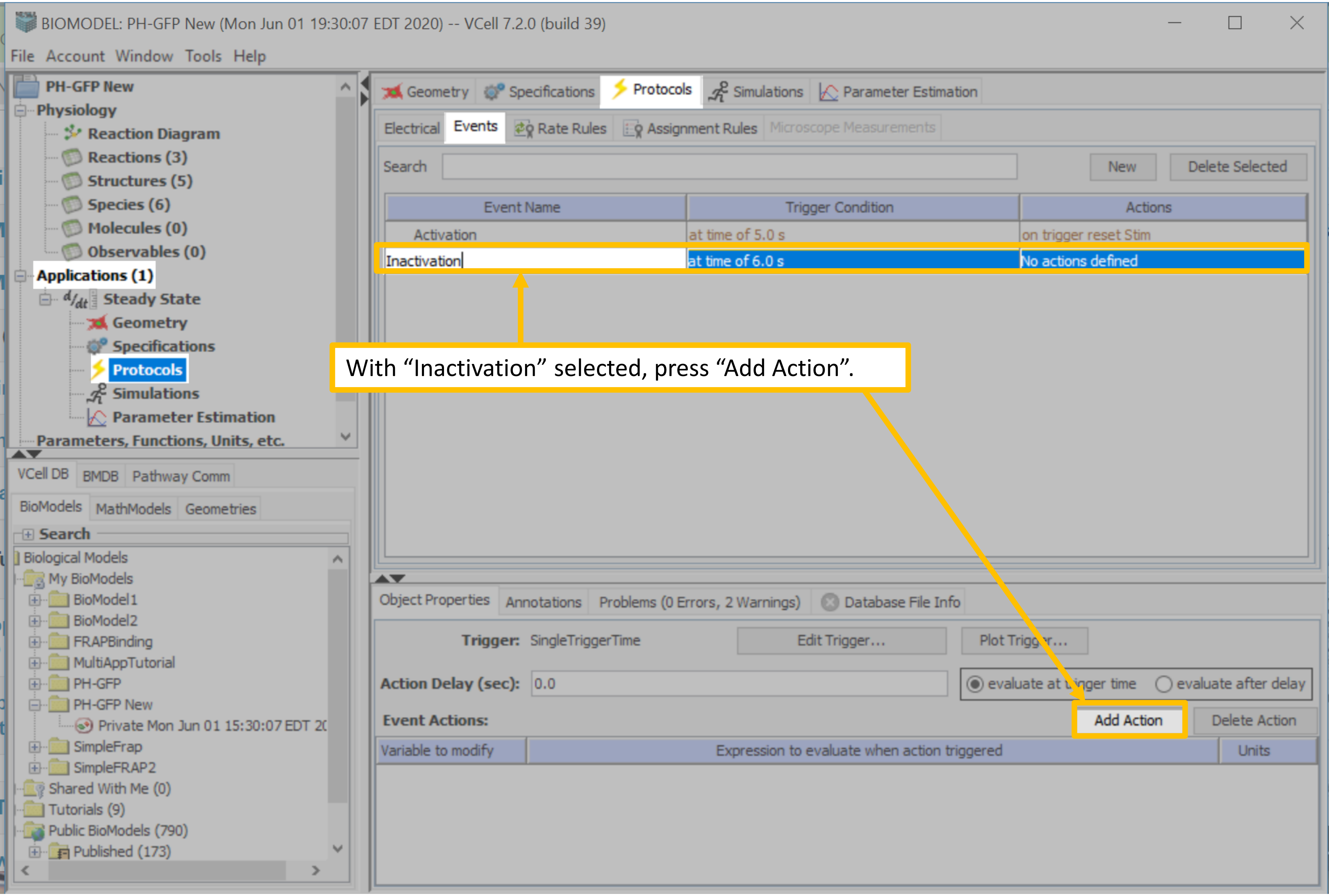
Trigger: SingleTriggerTime

Action Delay (sec): 0.0 ● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units

Double click “event0” and type in “Inactivation”.
Press “Enter” on your keyboard to accept the entry.



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	on trigger reset Stim
Inactivation	at time of 6.0 s	No actions defined

With “Inactivation” selected, press “Add Action”.

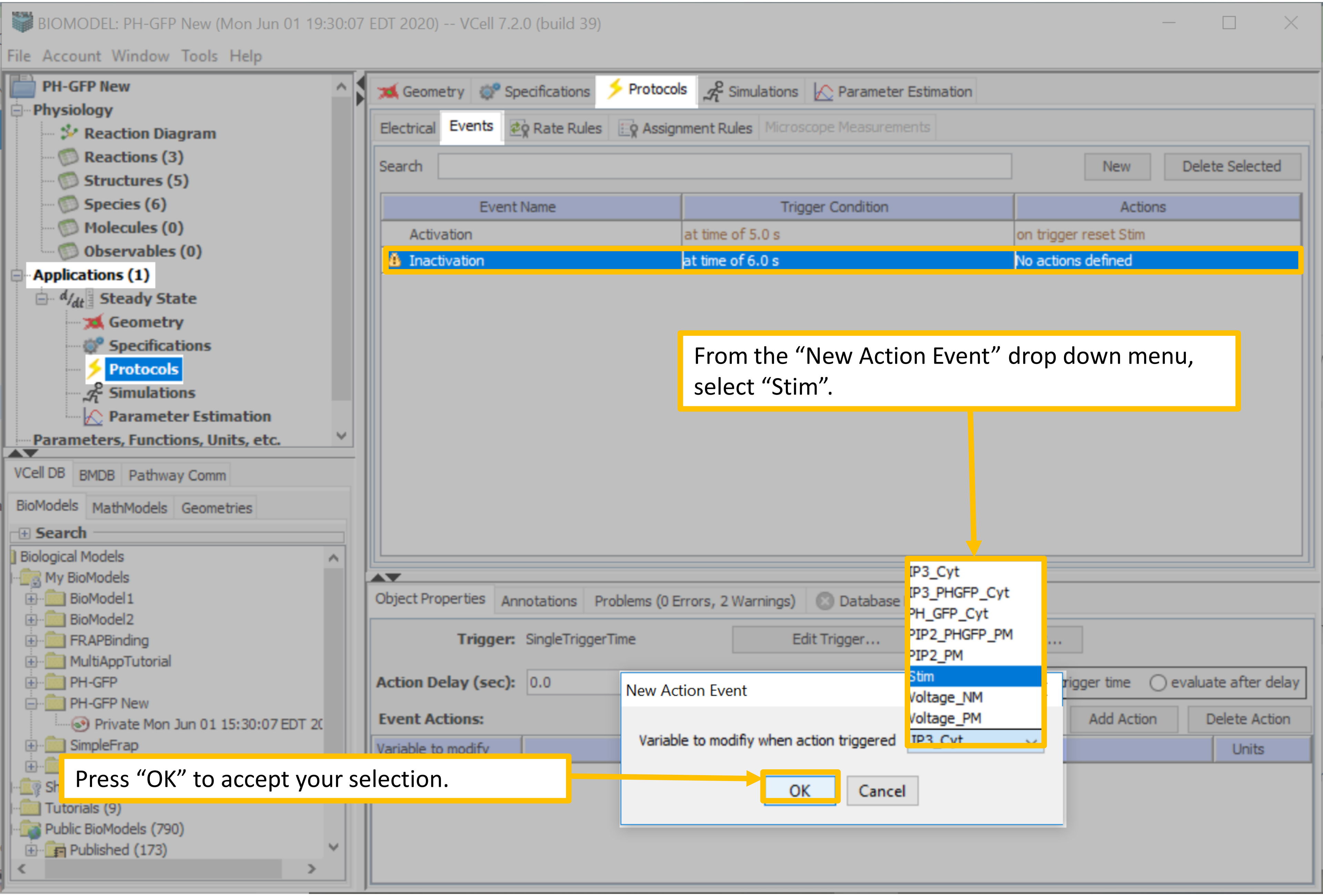
Trigger: SingleTriggerTime

Action Delay (sec): 0.0

● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units



Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	on trigger reset Stim
Inactivation	at time of 6.0 s	No actions defined

Trigger: SingleTriggerTime

Action Delay (sec): 0.0

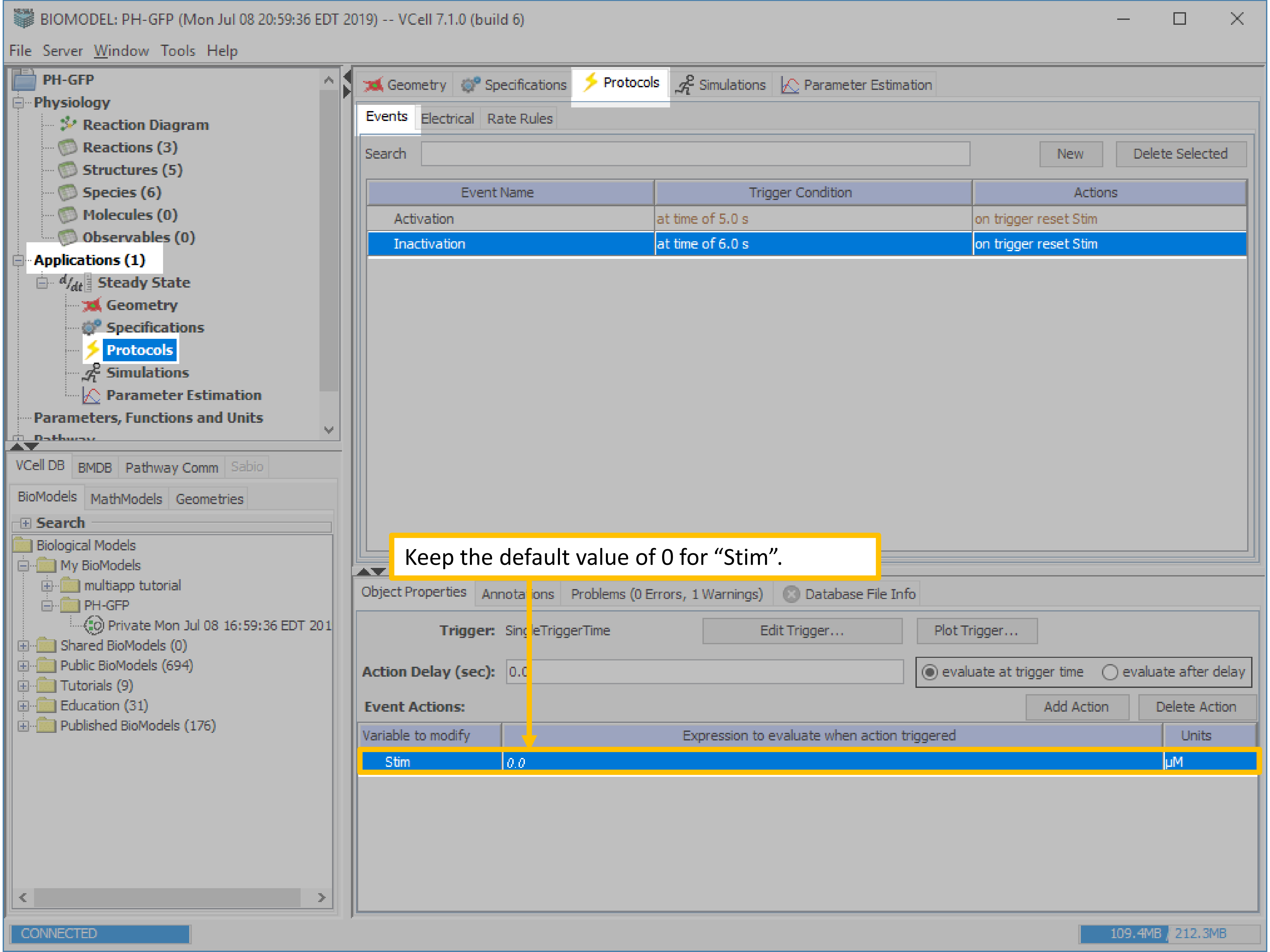
Event Actions:

New Action Event

Variable to modify when action triggered: Stim

From the "New Action Event" drop down menu, select "Stim".

Press "OK" to accept your selection.



BIOMODEL: PH-GFP (Mon Jul 08 20:59:36 EDT 2019) -- VCell 7.1.0 (build 6)

Keep the default value of 0 for “Stim”.

Event Name	Trigger Condition	Actions
Activation	at time of 5.0 s	on trigger reset Stim
Inactivation	at time of 6.0 s	on trigger reset Stim

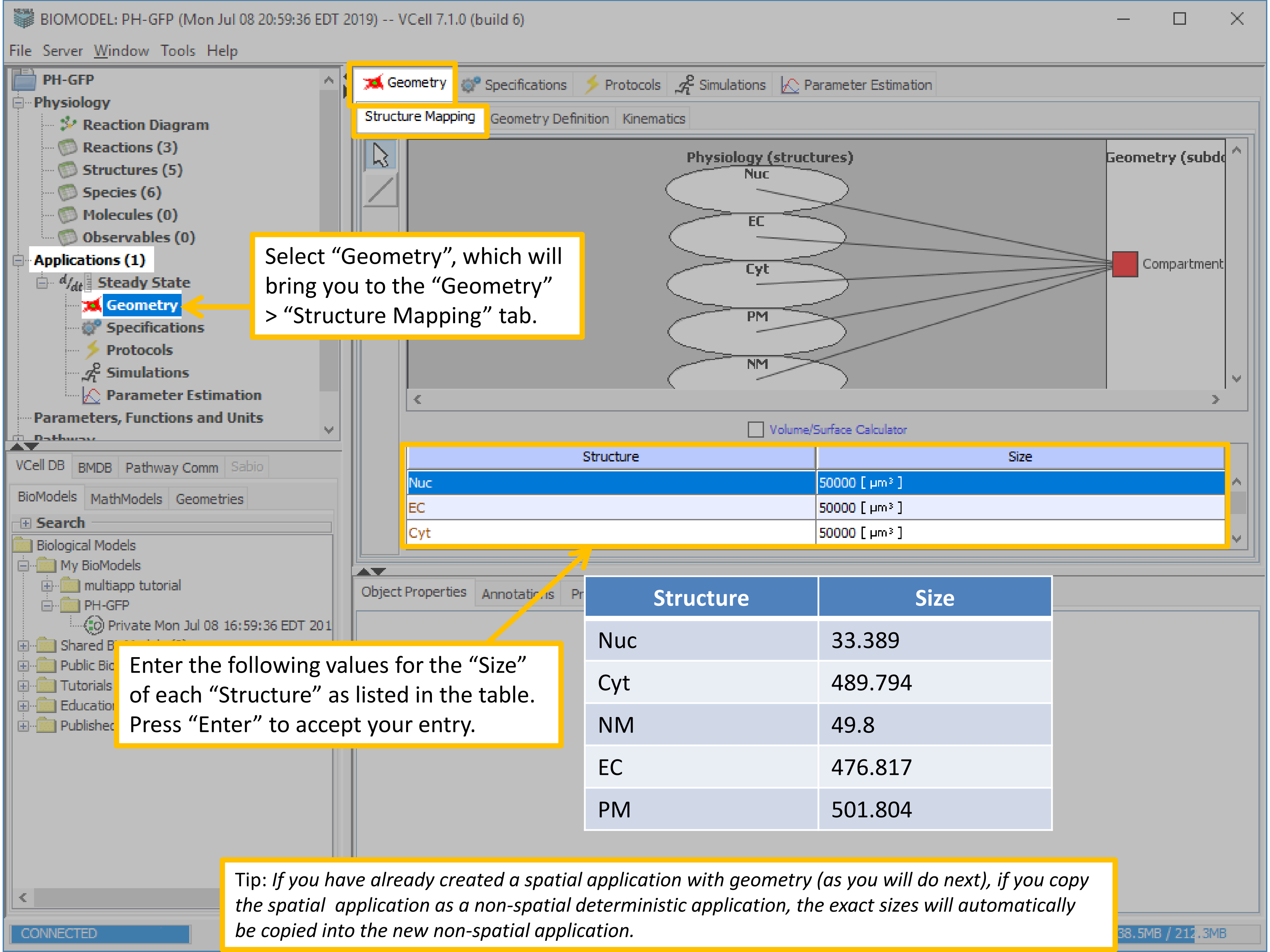
Trigger: SingleTriggerTime

Action Delay (sec): 0.0

● evaluate at trigger time ○ evaluate after delay

Event Actions:

Variable to modify	Expression to evaluate when action triggered	Units
Stim	0.0	µM



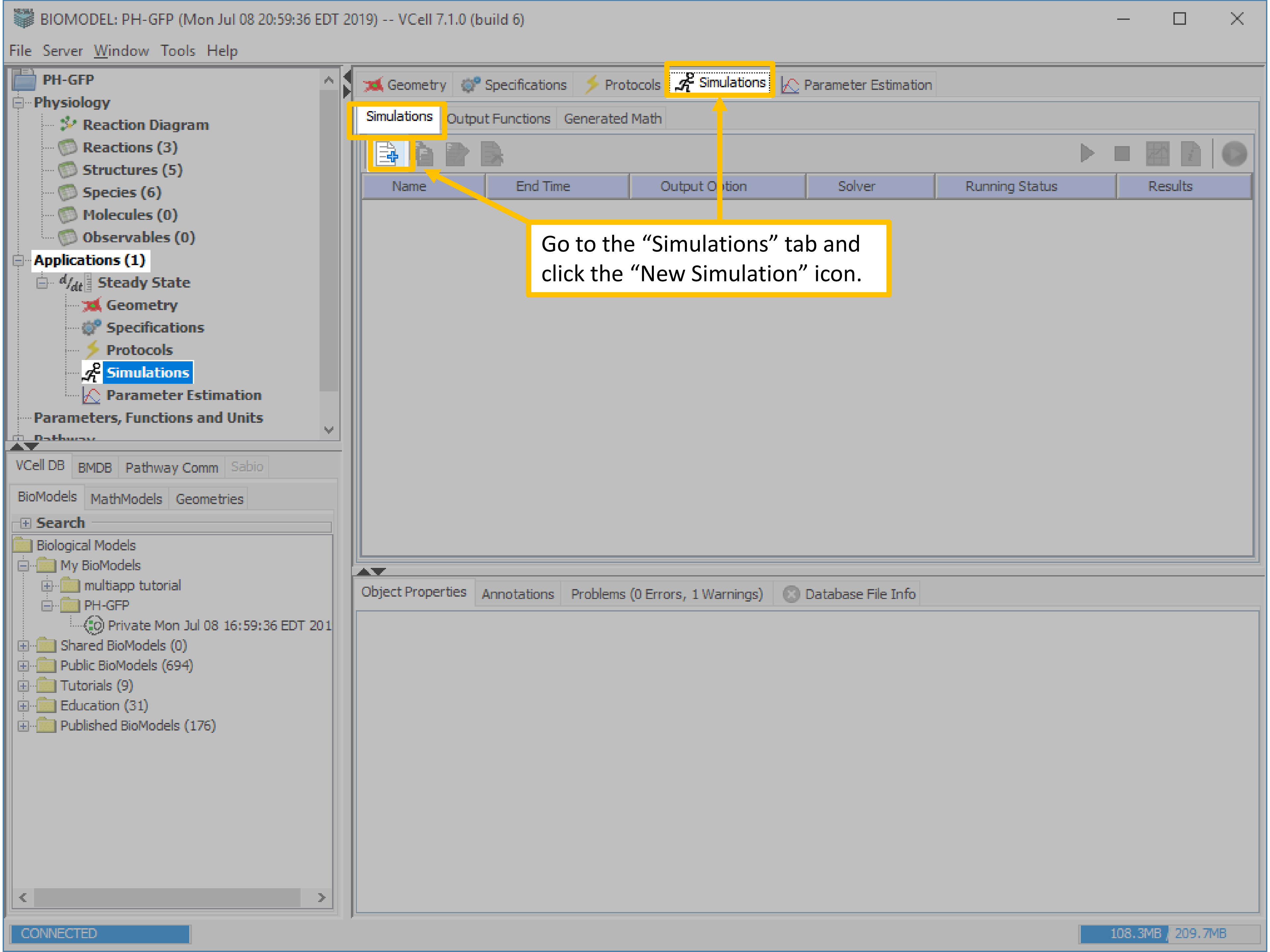
Structure	Size
Nuc	50000 [µm³]
EC	50000 [µm³]
Cyt	50000 [µm³]

Select “Geometry”, which will bring you to the “Geometry” > “Structure Mapping” tab.

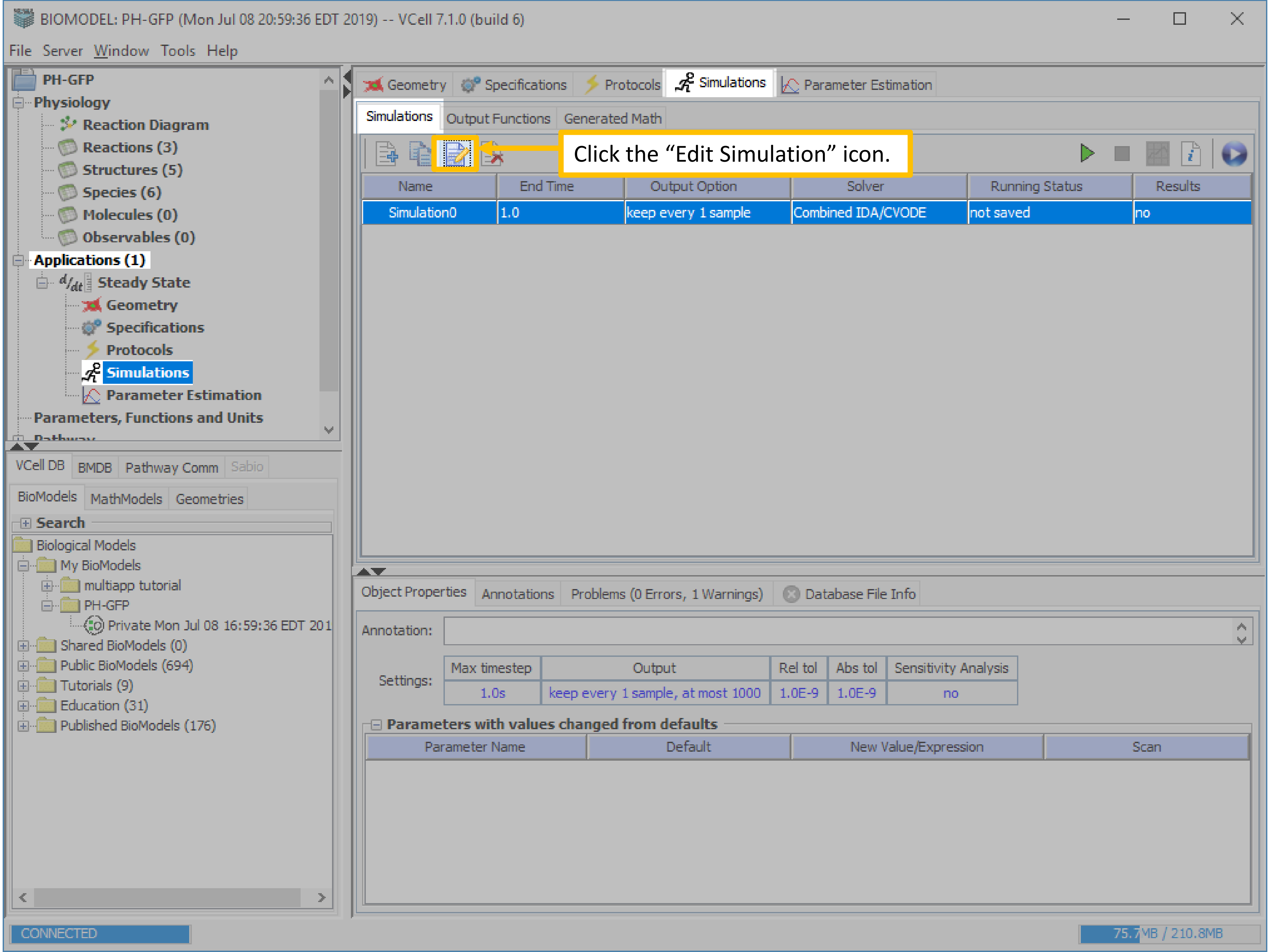
Enter the following values for the “Size” of each “Structure” as listed in the table. Press “Enter” to accept your entry.

Structure	Size
Nuc	33.389
Cyt	489.794
NM	49.8
EC	476.817
PM	501.804

Tip: *If you have already created a spatial application with geometry (as you will do next), if you copy the spatial application as a non-spatial deterministic application, the exact sizes will automatically be copied into the new non-spatial application.*



Go to the “Simulations” tab and click the “New Simulation” icon.



Click the “Edit Simulation” icon.

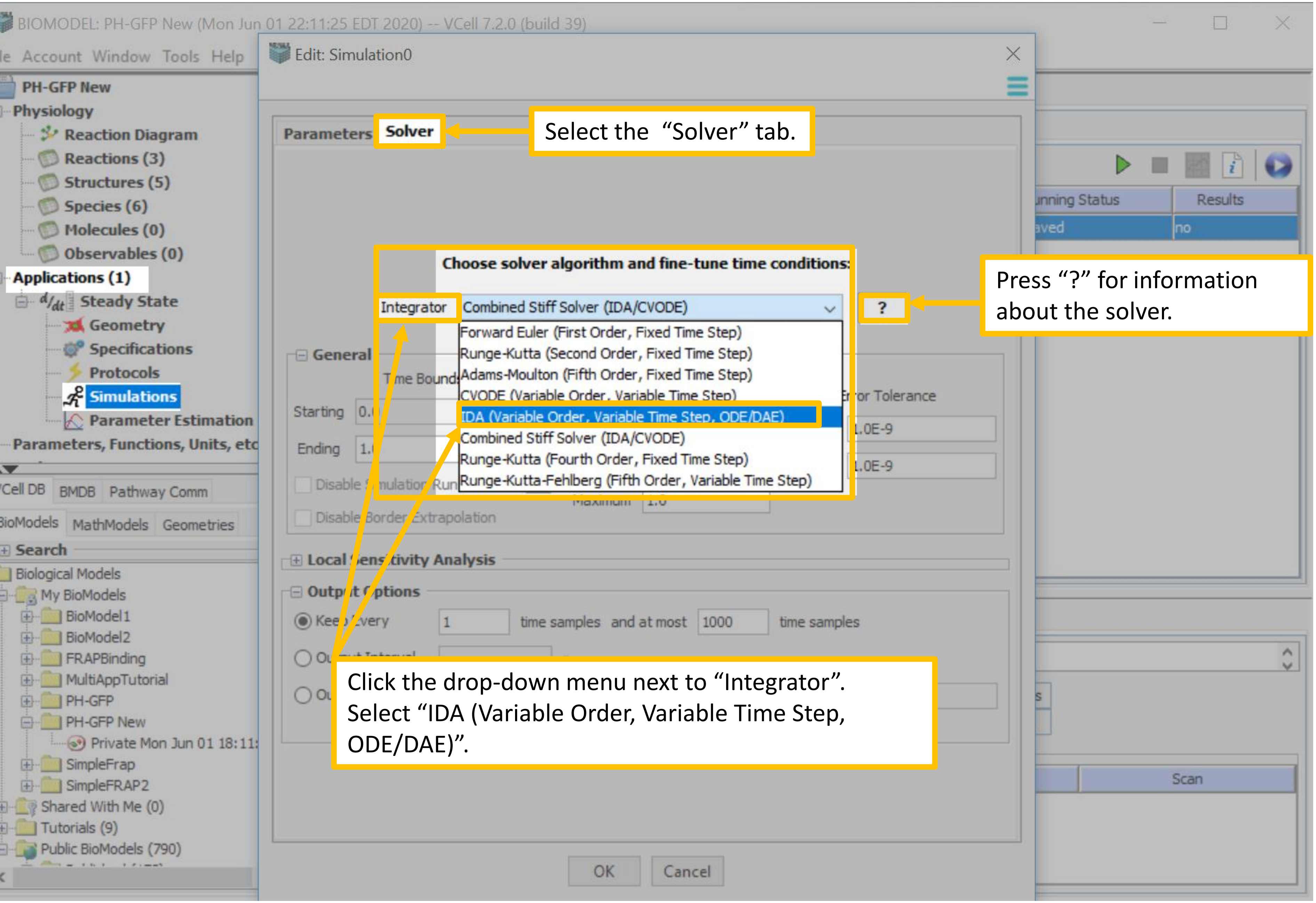
Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	1.0	keep every 1 sample	Combined IDA/CVODE	not saved	no

Settings:

Max timestep	Output	Rel tol	Abs tol	Sensitivity Analysis
1.0s	keep every 1 sample, at most 1000	1.0E-9	1.0E-9	no

Parameters with values changed from defaults

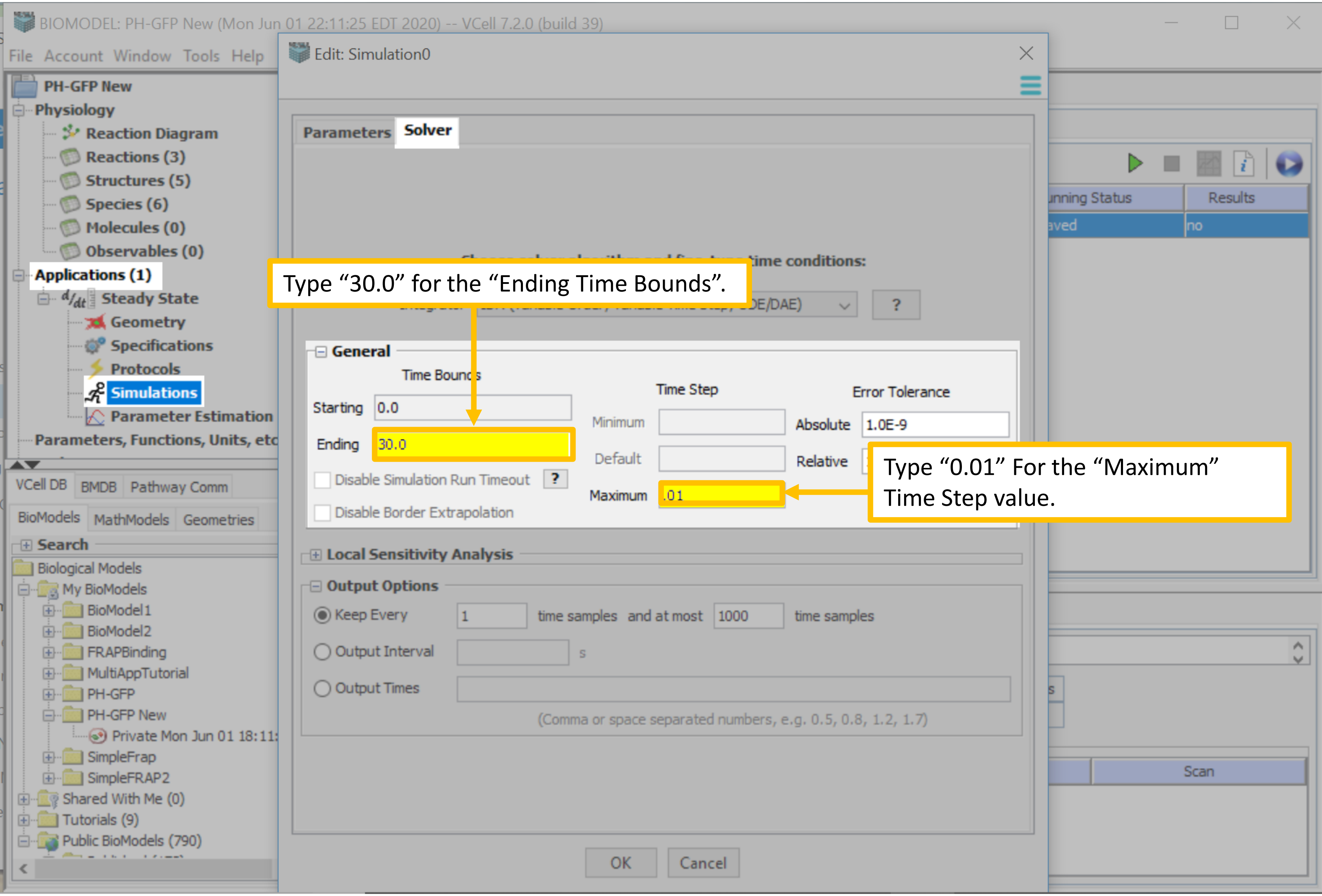
Parameter Name	Default	New Value/Expression	Scan



Select the "Solver" tab.

Press "?" for information about the solver.

Click the drop-down menu next to "Integrator". Select "IDA (Variable Order, Variable Time Step, ODE/DAE)".



Type “30.0” for the “Ending Time Bounds”.

Type “0.01” For the “Maximum” Time Step value.

Starting 0.0

Ending 30.0

Minimum

Default

Maximum .01

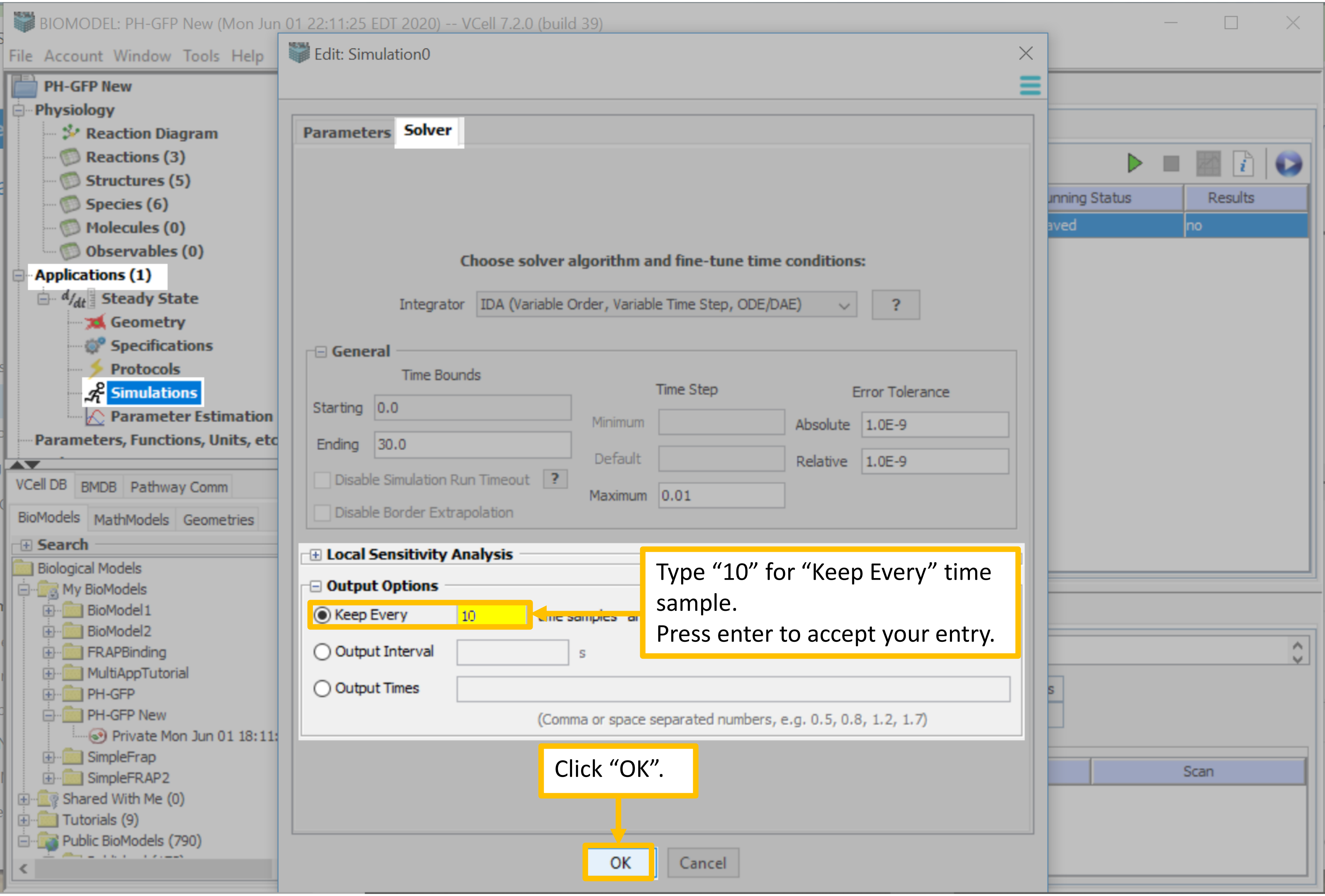
Absolute 1.0E-9

Relative

● Keep Every 1 time samples and at most 1000 time samples

○ Output Interval s

○ Output Times



Choose solver algorithm and fine-tune time conditions:

Integrator: IDA (Variable Order, Variable Time Step, ODE/DAE) ?

General

Time Bounds
Starting: 0.0
Ending: 30.0
☐ Disable Simulation Run Timeout ?
☐ Disable Border Extrapolation

Time Step
Minimum:
Default:
Maximum: 0.01

Error Tolerance
Absolute: 1.0E-9
Relative: 1.0E-9

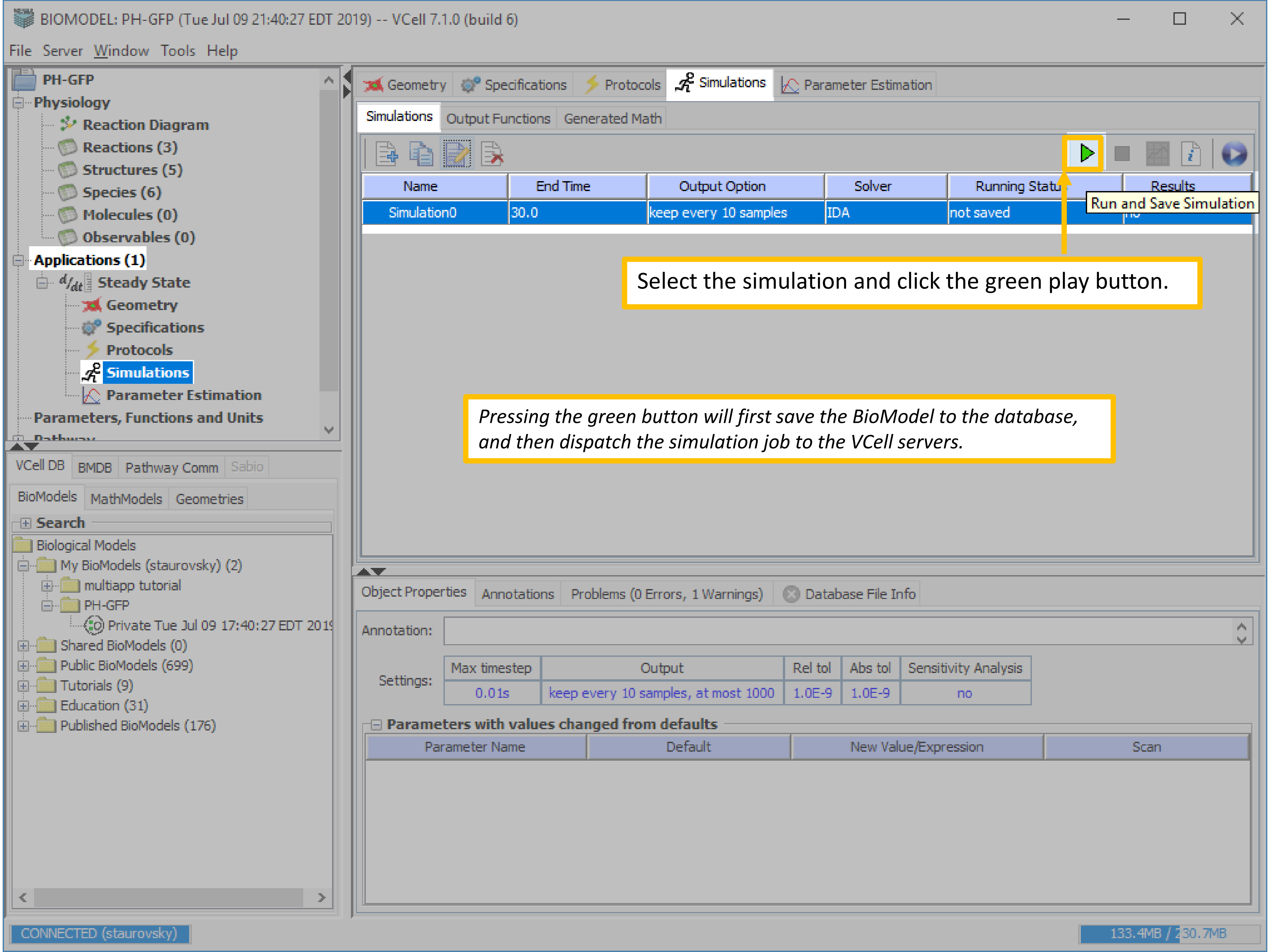
Local Sensitivity Analysis

Output Options

● Keep Every 10 time samples
○ Output Interval s
○ Output Times
(Comma or space separated numbers, e.g. 0.5, 0.8, 1.2, 1.7)

Type “10” for “Keep Every” time sample.
Press enter to accept your entry.

Click “OK”.



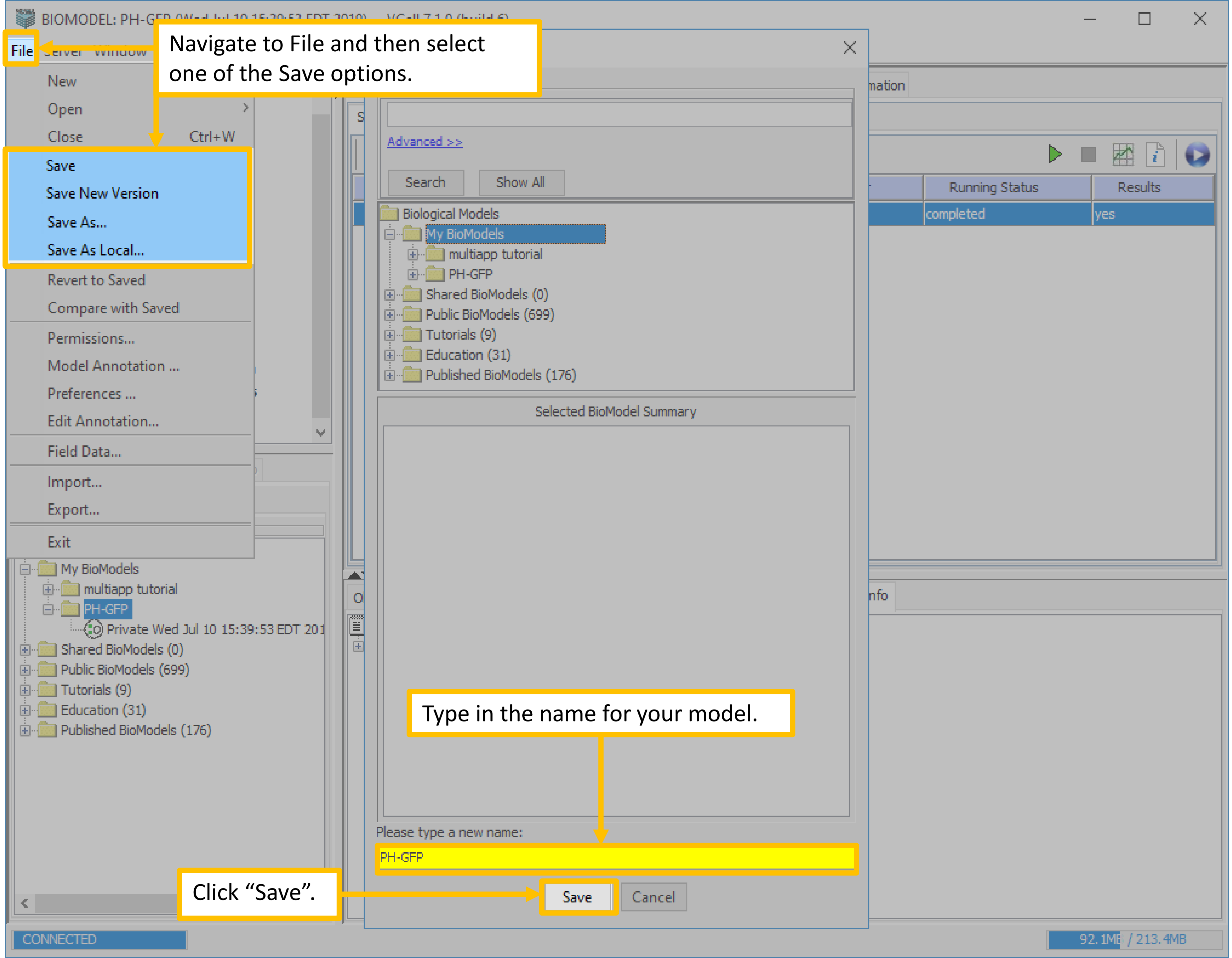
Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	30.0	keep every 10 samples	IDA	not saved	no

Select the simulation and click the green play button.

Pressing the green button will first save the BioModel to the database, and then dispatch the simulation job to the VCell servers.

Max timestep	Output	Rel tol	Abs tol	Sensitivity Analysis
0.01s	keep every 10 samples, at most 1000	1.0E-9	1.0E-9	no

Parameter Name	Default	New Value/Expression	Scan

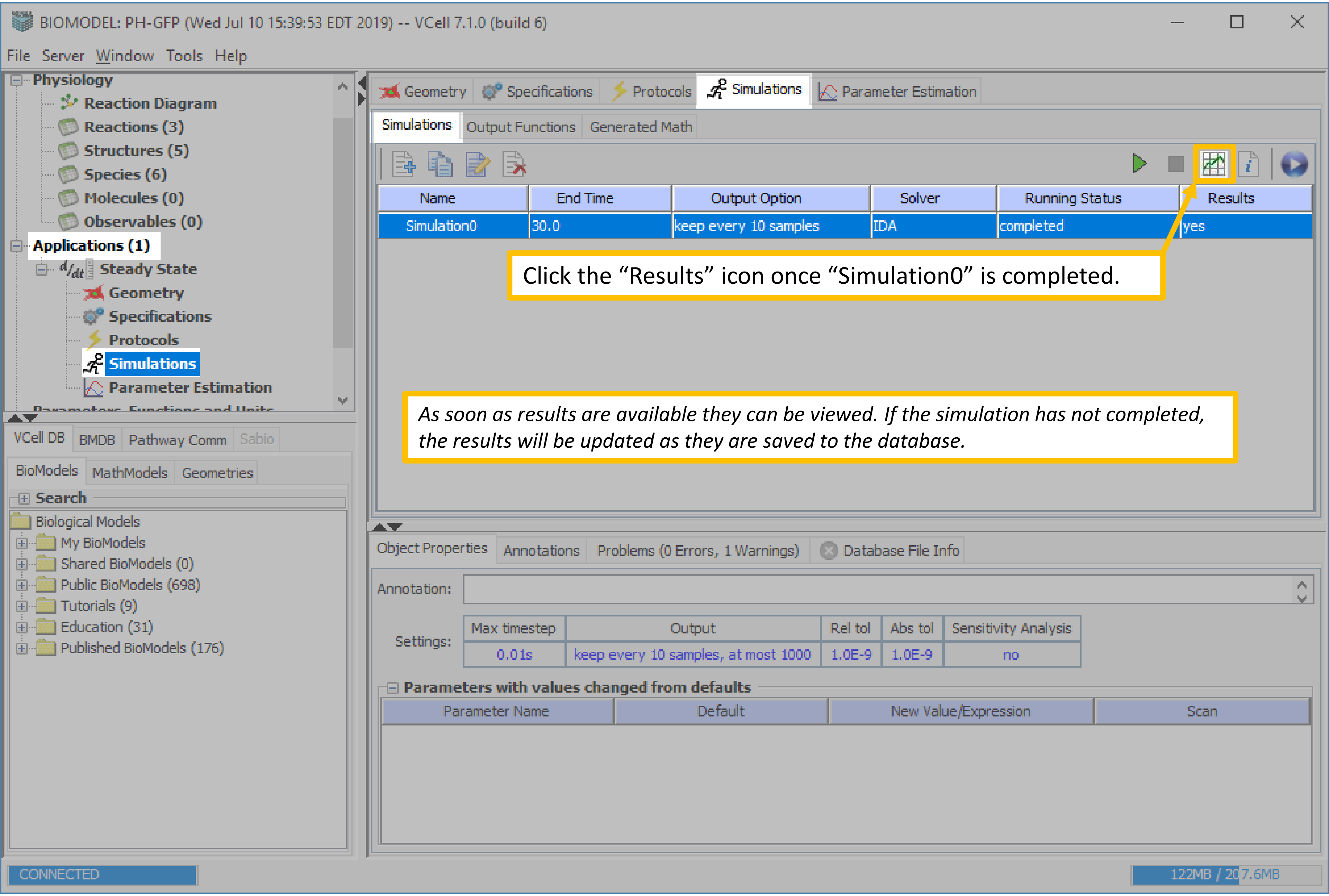


Navigate to File and then select one of the Save options.

Type in the name for your model.

Please type a new name: PH-GFP

Click “Save”.



Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	30.0	keep every 10 samples	IDA	completed	yes

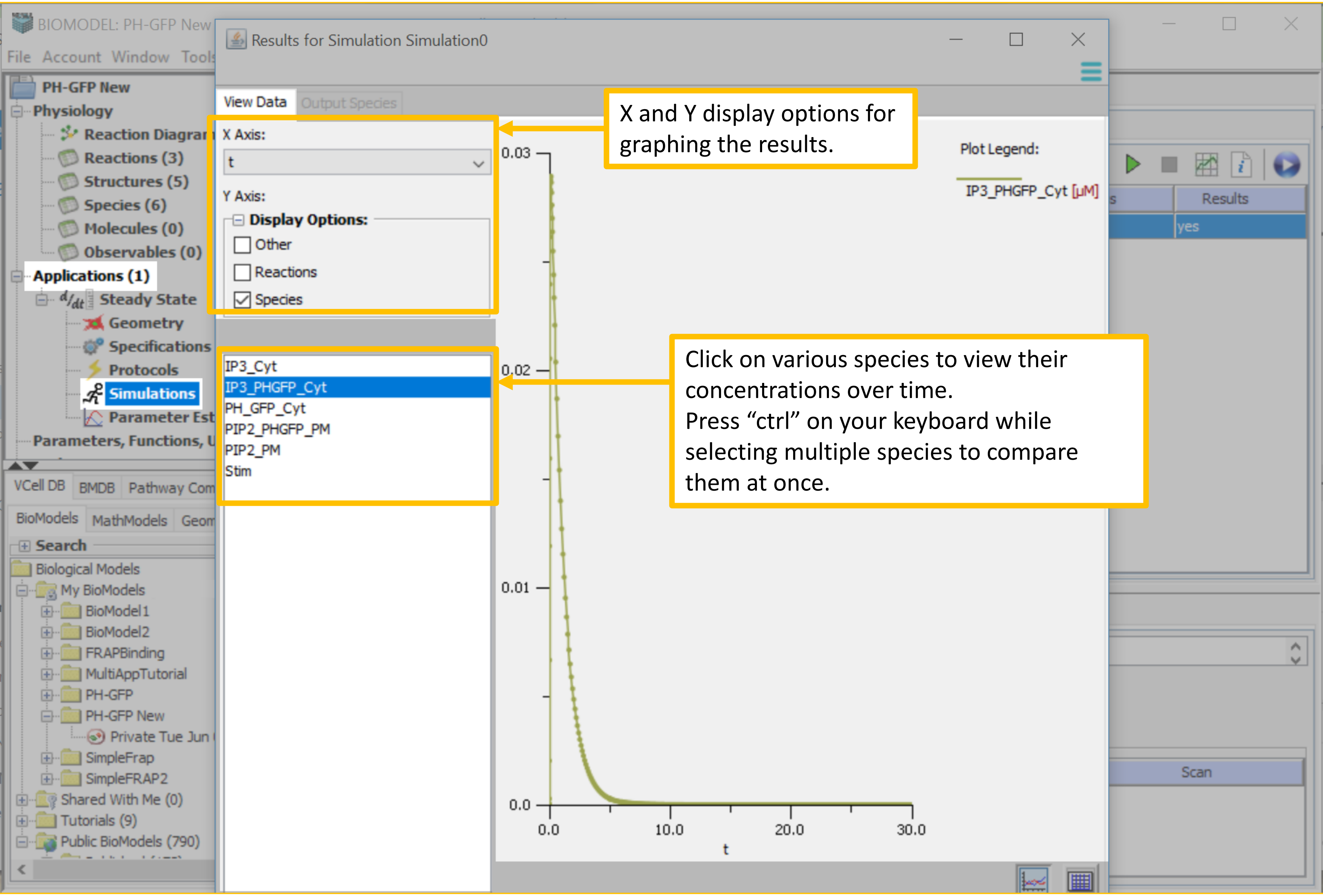
Settings:

Max timestep	Output	Rel tol	Abs tol	Sensitivity Analysis
0.01s	keep every 10 samples, at most 1000	1.0E-9	1.0E-9	no

Parameter Name	Default	New Value/Expression	Scan

Click the “Results” icon once “Simulation0” is completed.

As soon as results are available they can be viewed. If the simulation has not completed, the results will be updated as they are saved to the database.



X Axis: t

Y Axis:

Display Options:

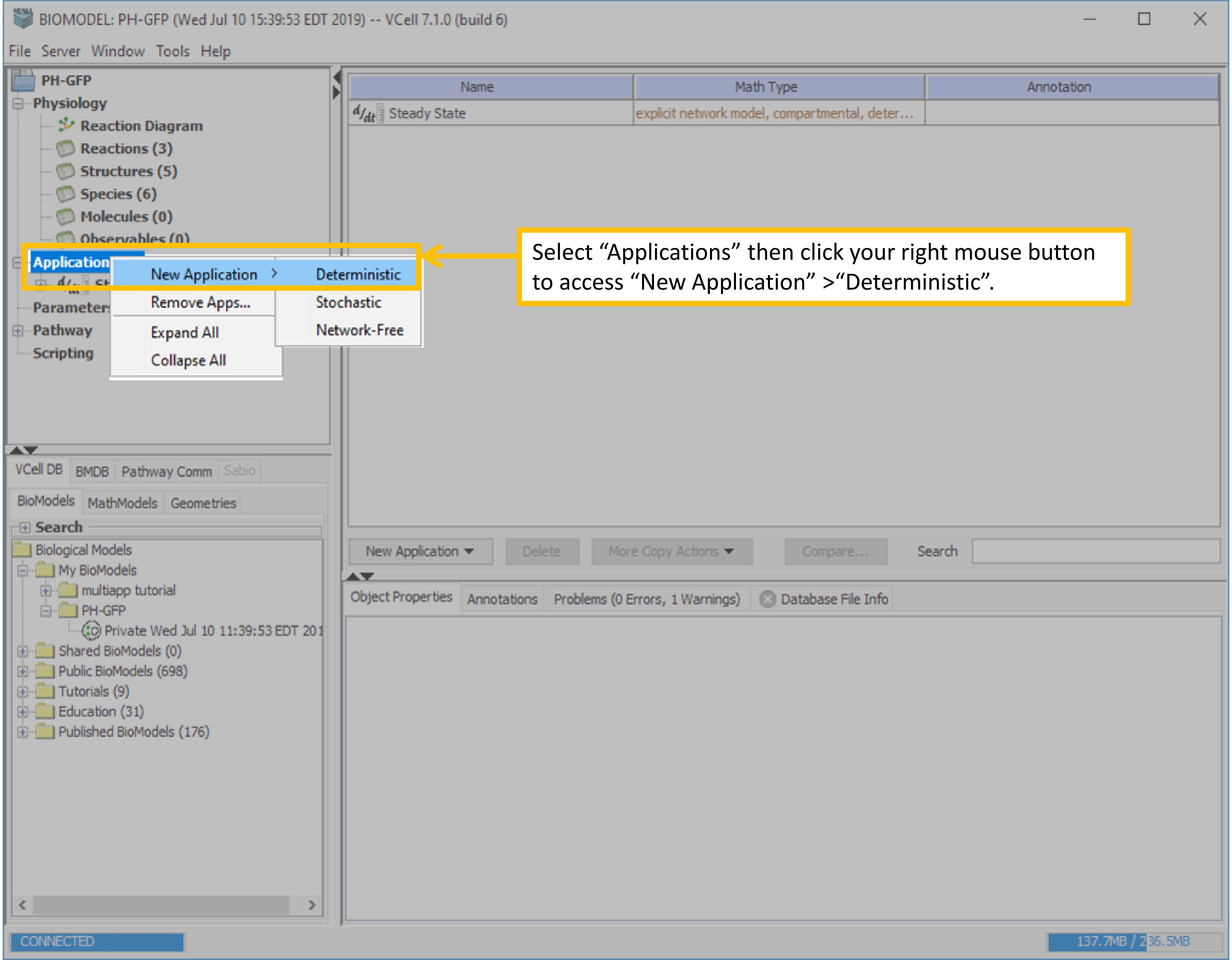
☐ Other

☐ Reactions

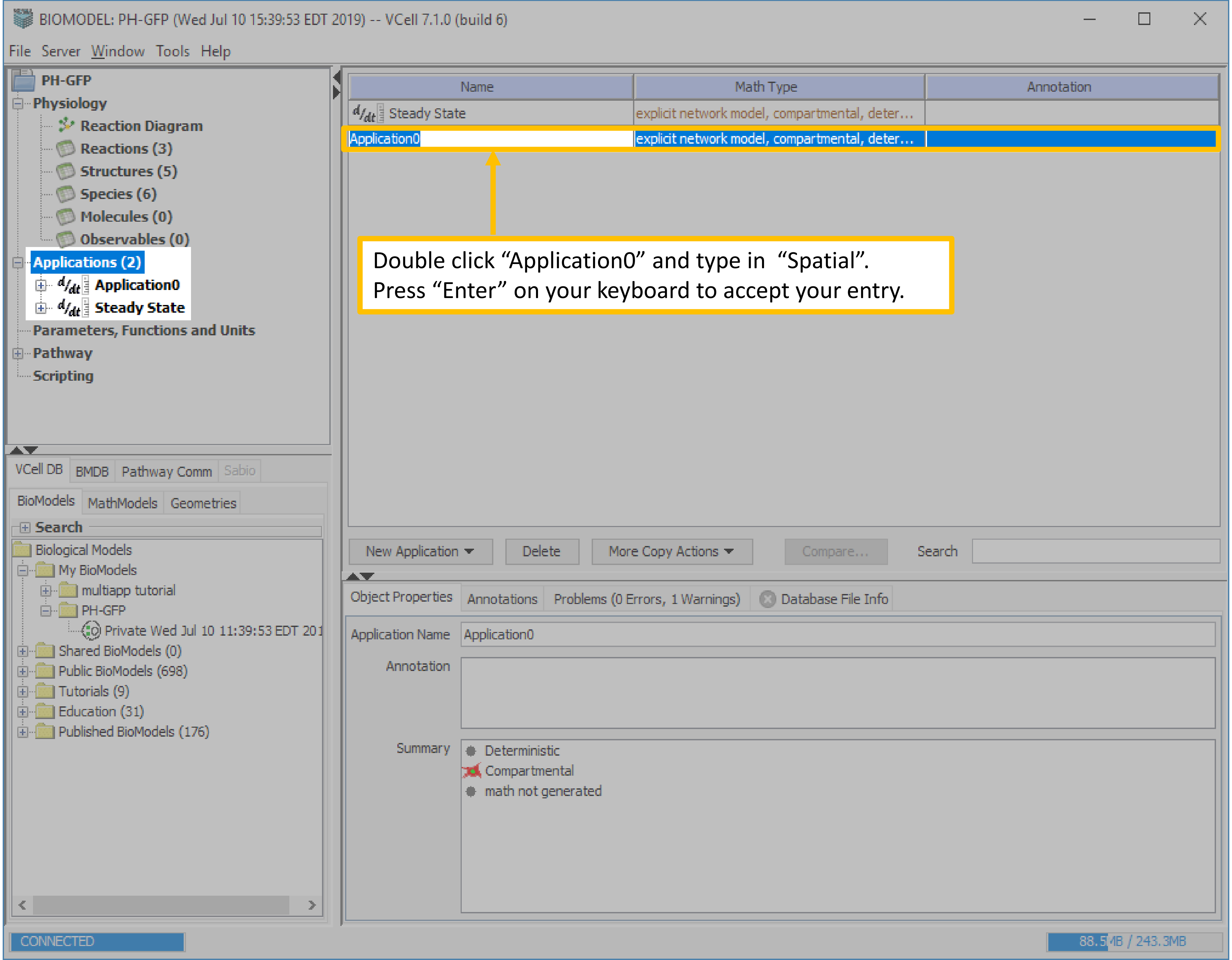
☑ Species

X and Y display options for graphing the results.

Click on various species to view their concentrations over time.
Press “ctrl” on your keyboard while selecting multiple species to compare them at once.



Select “Applications” then click your right mouse button to access “New Application” >“Deterministic”.



BIOMODEL: PH-GFP (Wed Jul 10 15:39:53 EDT 2019) -- VCell 7.1.0 (build 6)

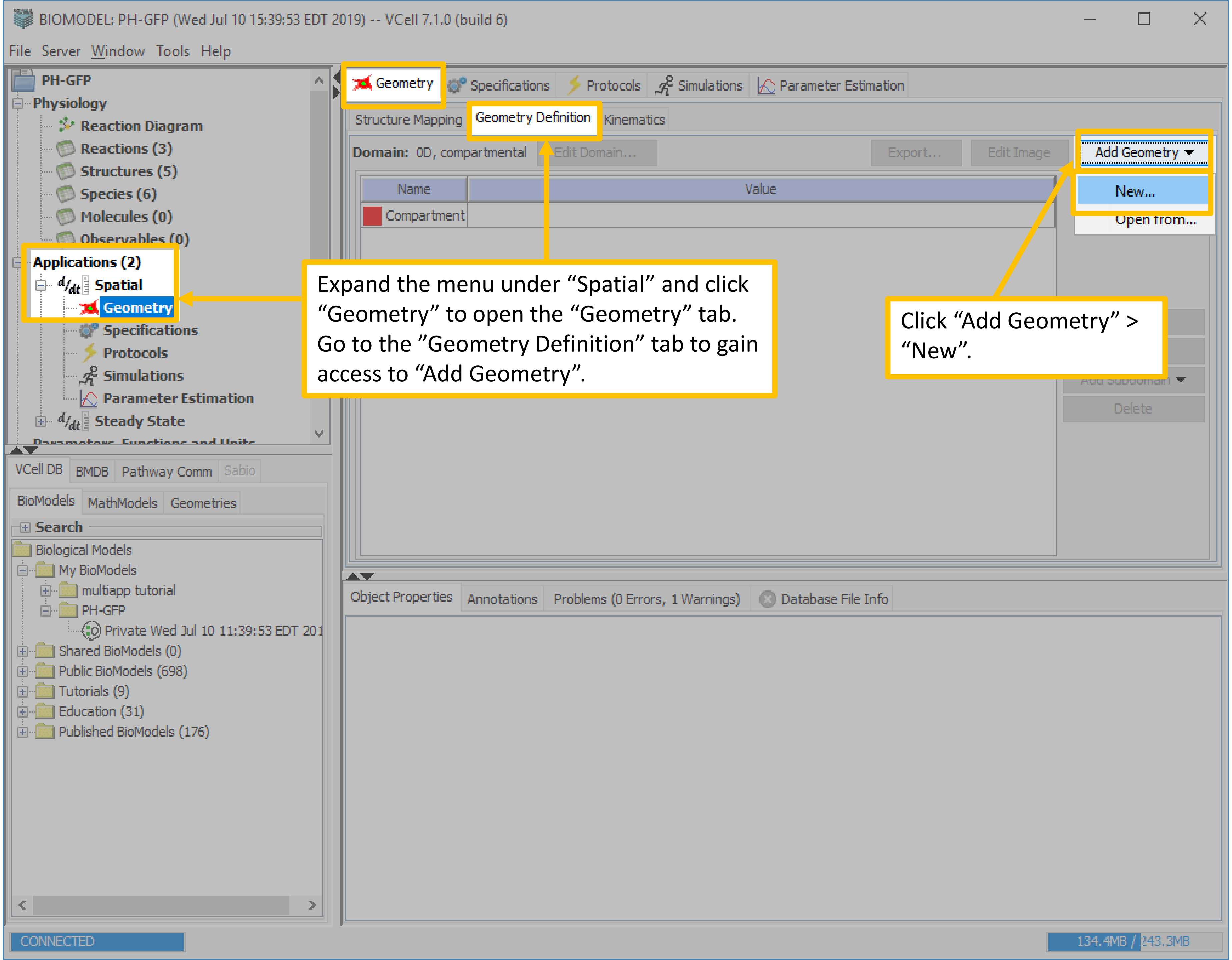
Name	Math Type	Annotation
Steady State	explicit network model, compartmental, deter...	
Application0	explicit network model, compartmental, deter...	

Application Name: Application0

Annotation:

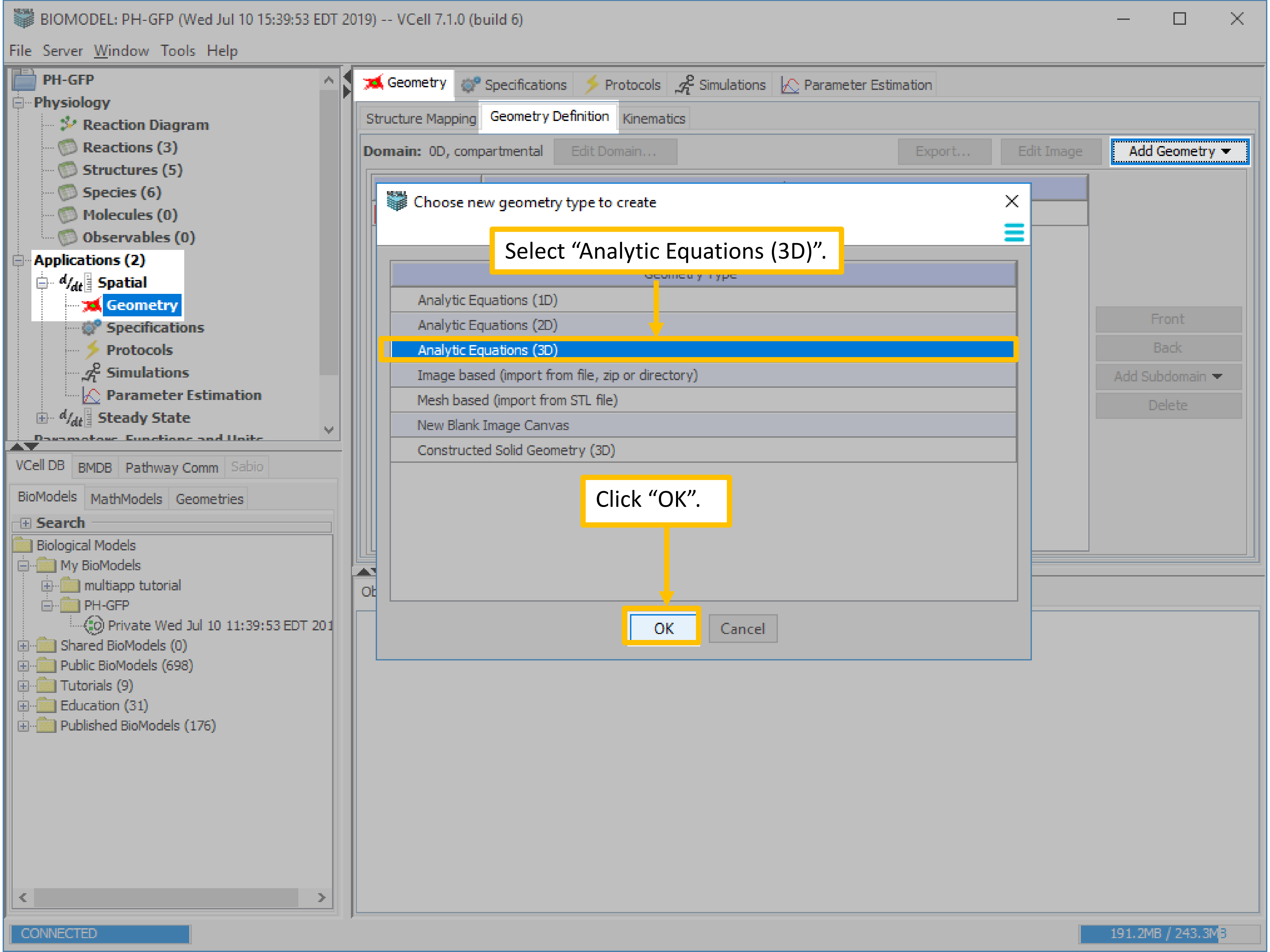
Summary:
- Deterministic
- Compartmental
- math not generated

Double click “Application0” and type in “Spatial”.
Press “Enter” on your keyboard to accept your entry.



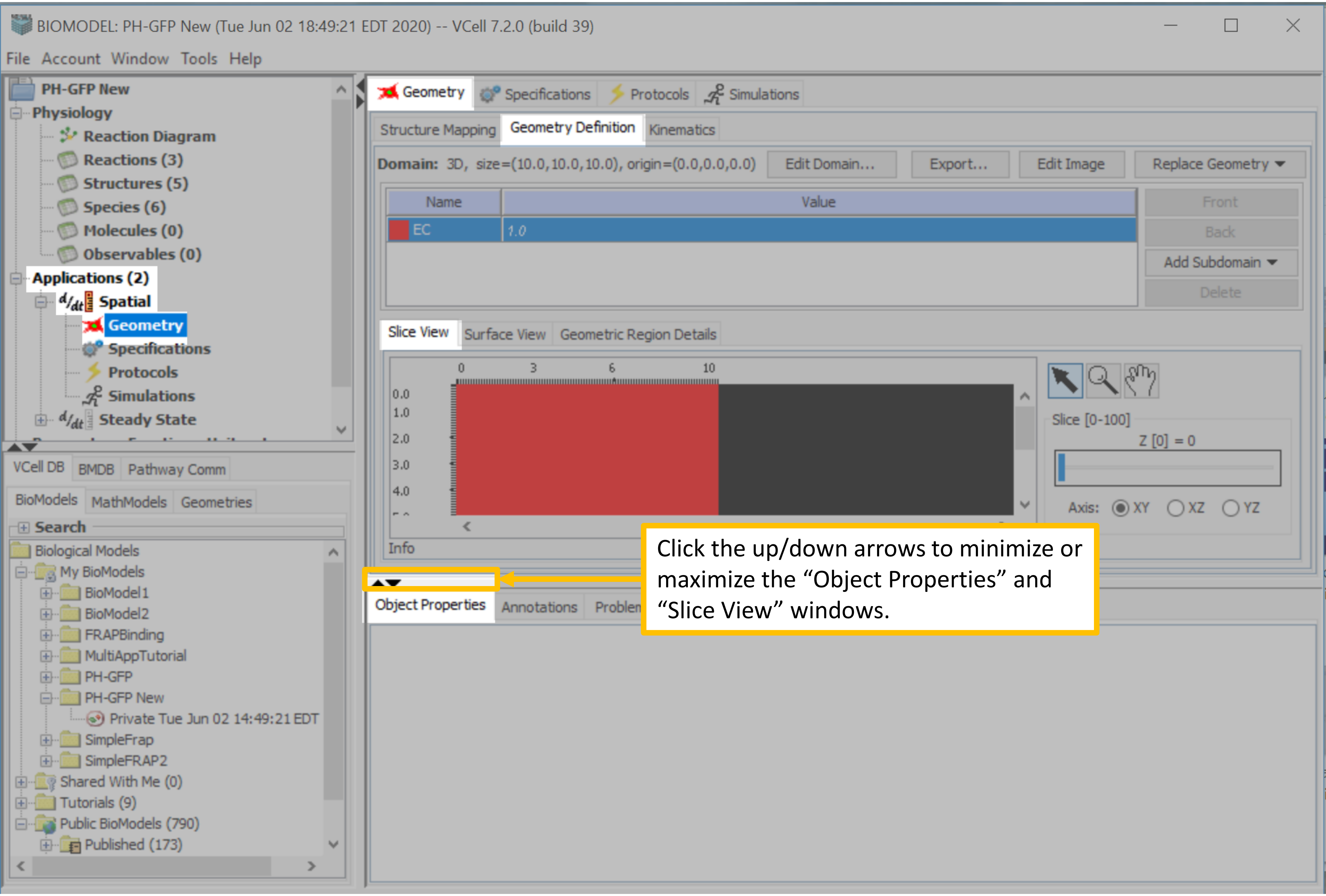
Expand the menu under “Spatial” and click “Geometry” to open the “Geometry” tab. Go to the ”Geometry Definition” tab to gain access to “Add Geometry”.

Click “Add Geometry” > “New”.



Select “Analytic Equations (3D)”.

Click “OK”.

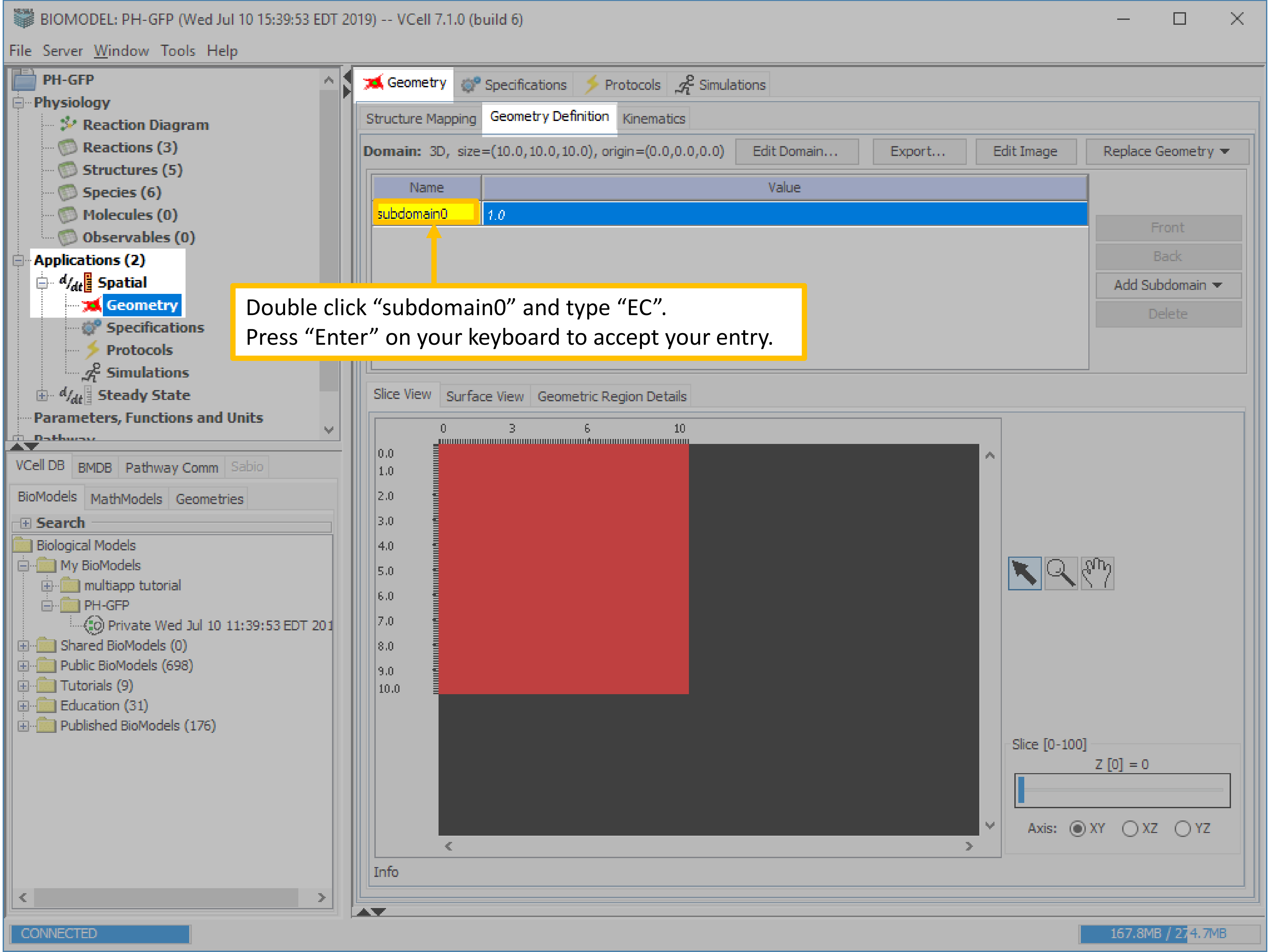


BIOMODEL: PH-GFP New (Tue Jun 02 18:49:21 EDT 2020) -- VCell 7.2.0 (build 39)

Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Name	Value
🟥 EC	1.0

Click the up/down arrows to minimize or maximize the “Object Properties” and “Slice View” windows.

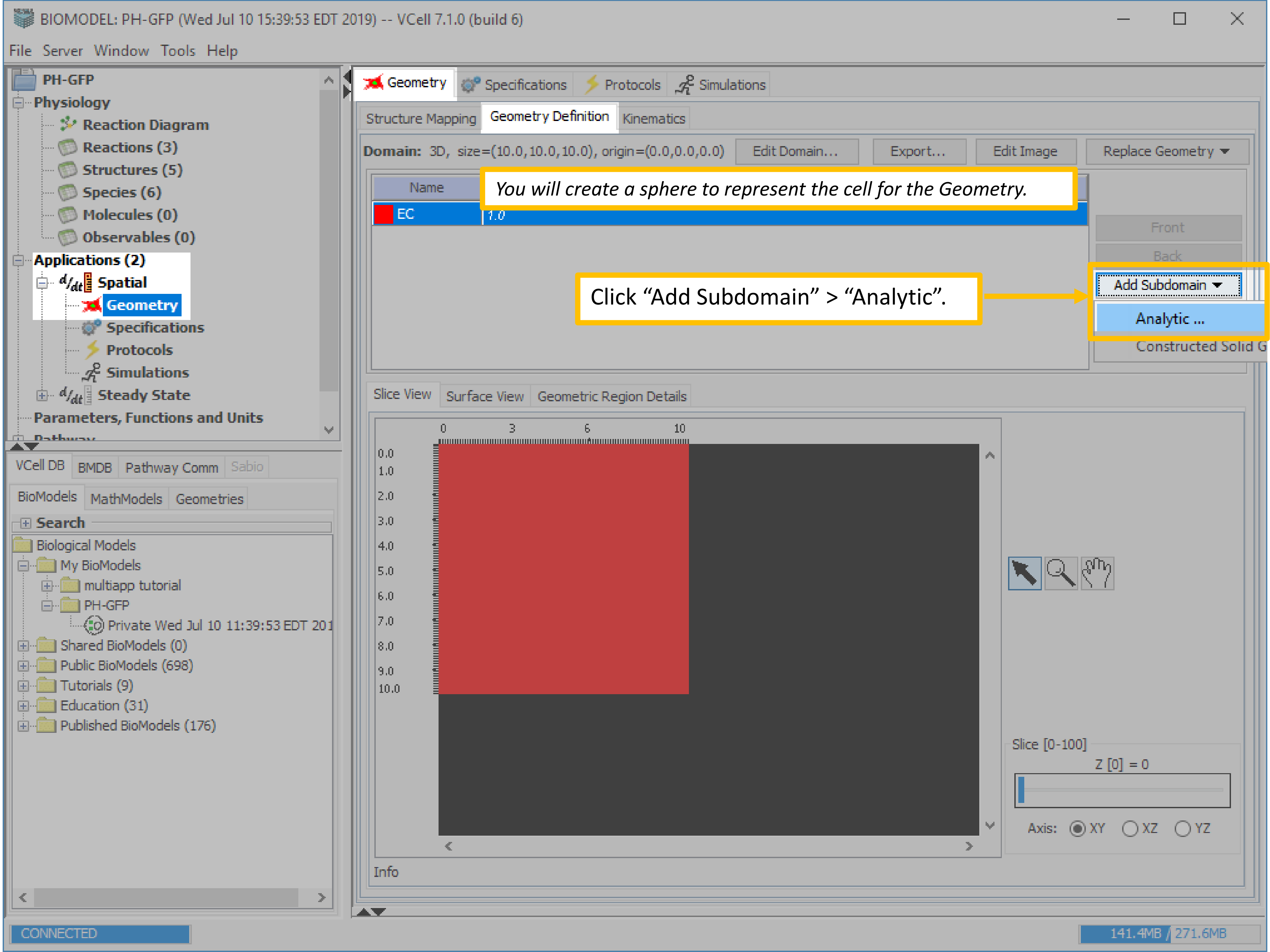


BIOMODEL: PH-GFP (Wed Jul 10 15:39:53 EDT 2019) -- VCell 7.1.0 (build 6)

Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

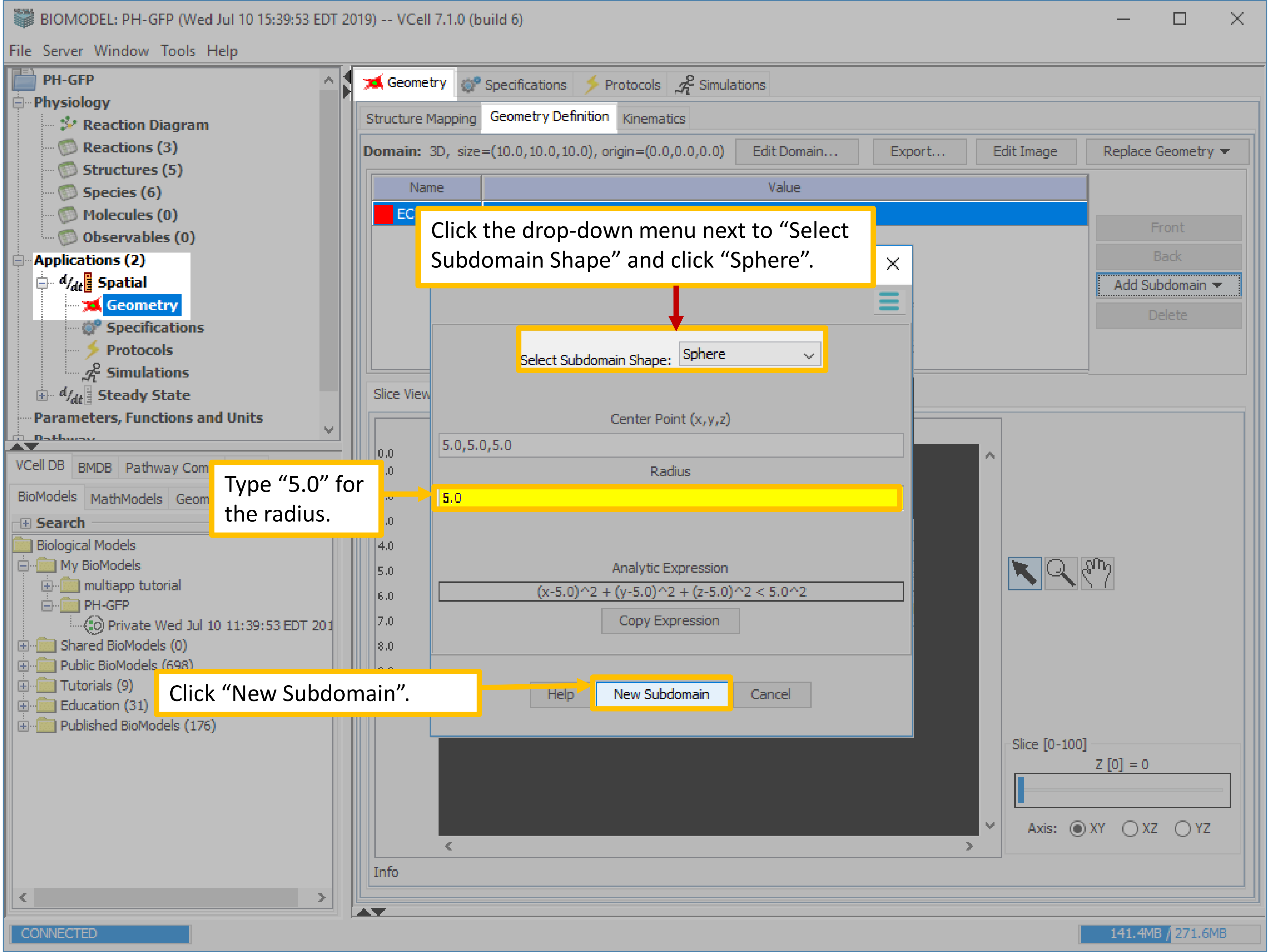
Name	Value
subdomain0	1.0

Double click “subdomain0” and type “EC”.
Press “Enter” on your keyboard to accept your entry.



You will create a sphere to represent the cell for the Geometry.

Click “Add Subdomain” > “Analytic”.



Click the drop-down menu next to “Select Subdomain Shape” and click “Sphere”.

Type “5.0” for the radius.

Click “New Subdomain”.

BIOMODEL: PH-GFP (Wed Jul 10 15:39:53 EDT 2019) -- VCell 7.1.0 (build 6)

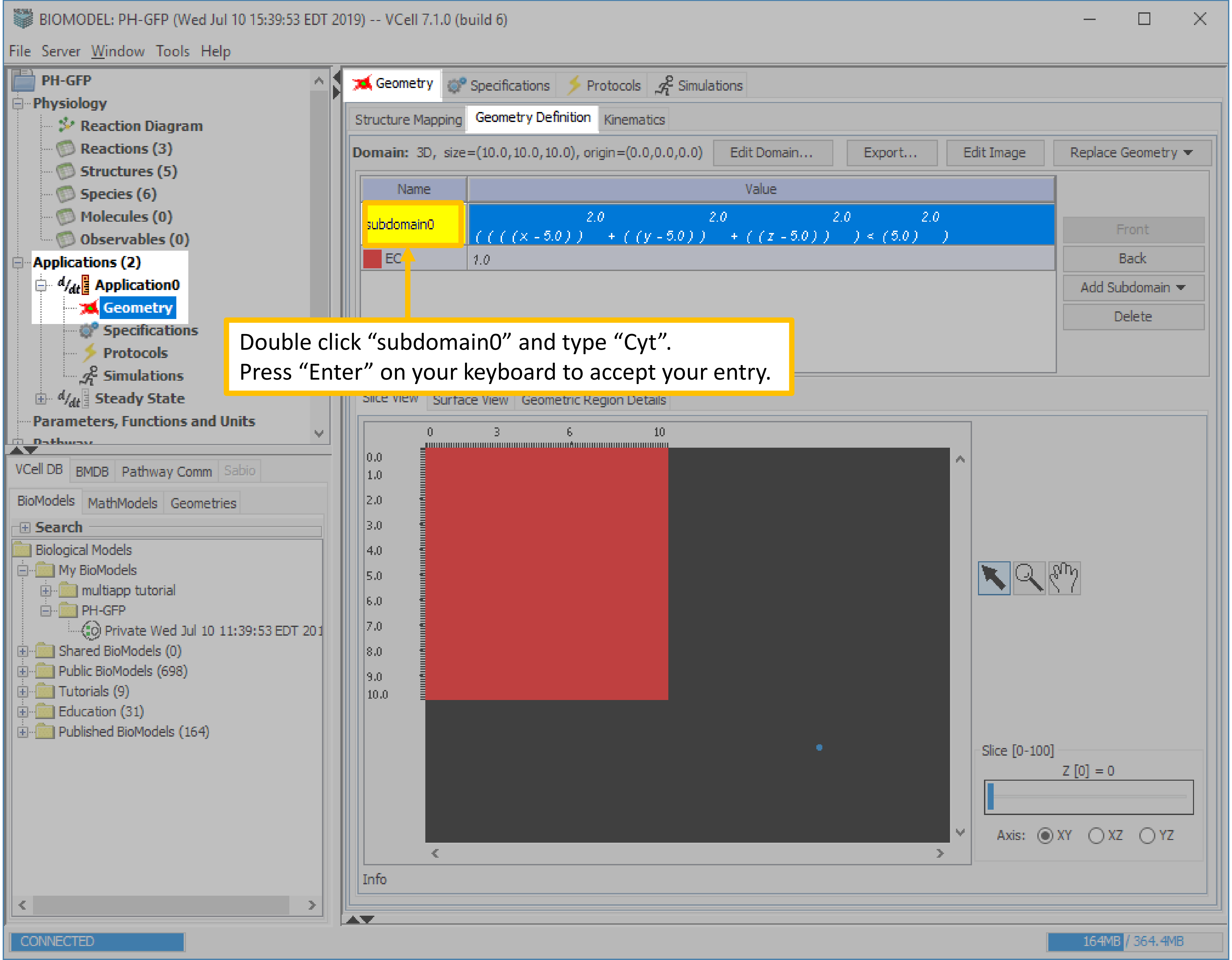
Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Select Subdomain Shape: Sphere

Center Point (x,y,z): 5.0,5.0,5.0

Radius: 5.0

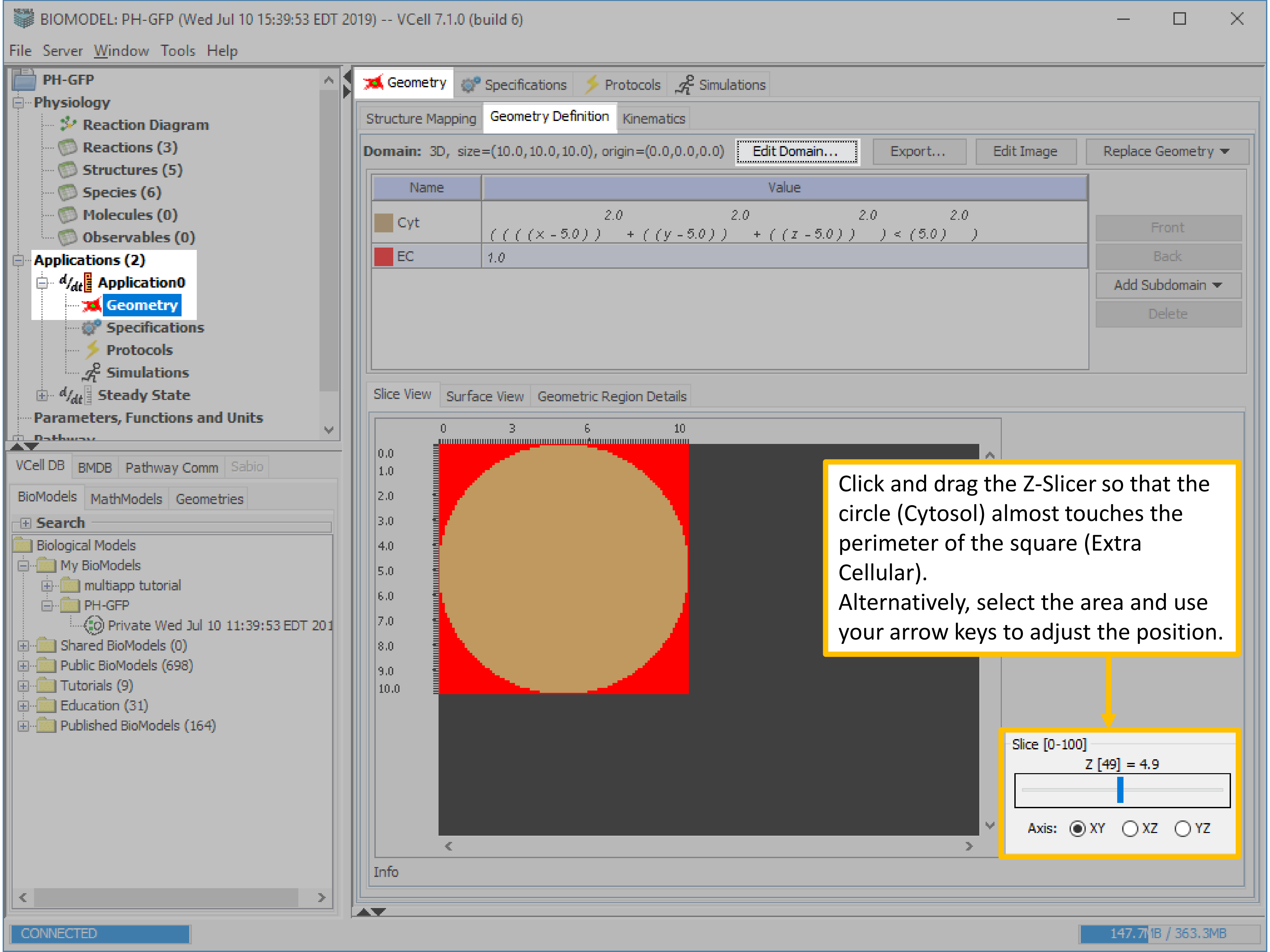
Analytic Expression: (x-5.0)^2 + (y-5.0)^2 + (z-5.0)^2 < 5.0^2



Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Name	Value
subdomain0	$((((x-5.0))^{2.0} + ((y-5.0))^{2.0} + ((z-5.0))^{2.0}) < (5.0)^{2.0})$
🟥 EC	1.0

Double click “subdomain0” and type “Cyt”.
Press “Enter” on your keyboard to accept your entry.

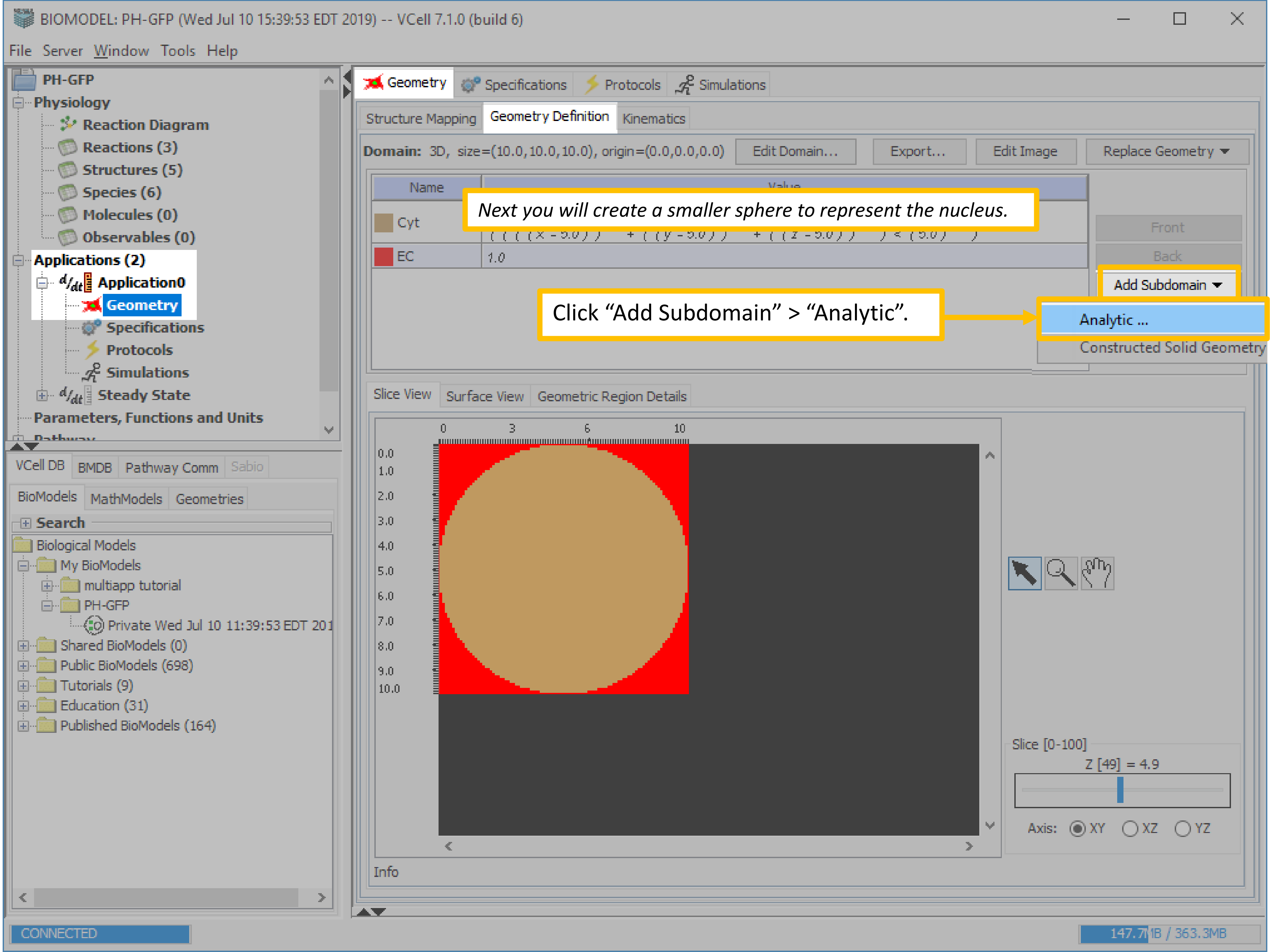


Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Name	Value
Cyt	$((((x-5.0))^{2.0} + ((y-5.0))^{2.0} + ((z-5.0))^{2.0}) < (5.0)^{2.0})$
EC	1.0

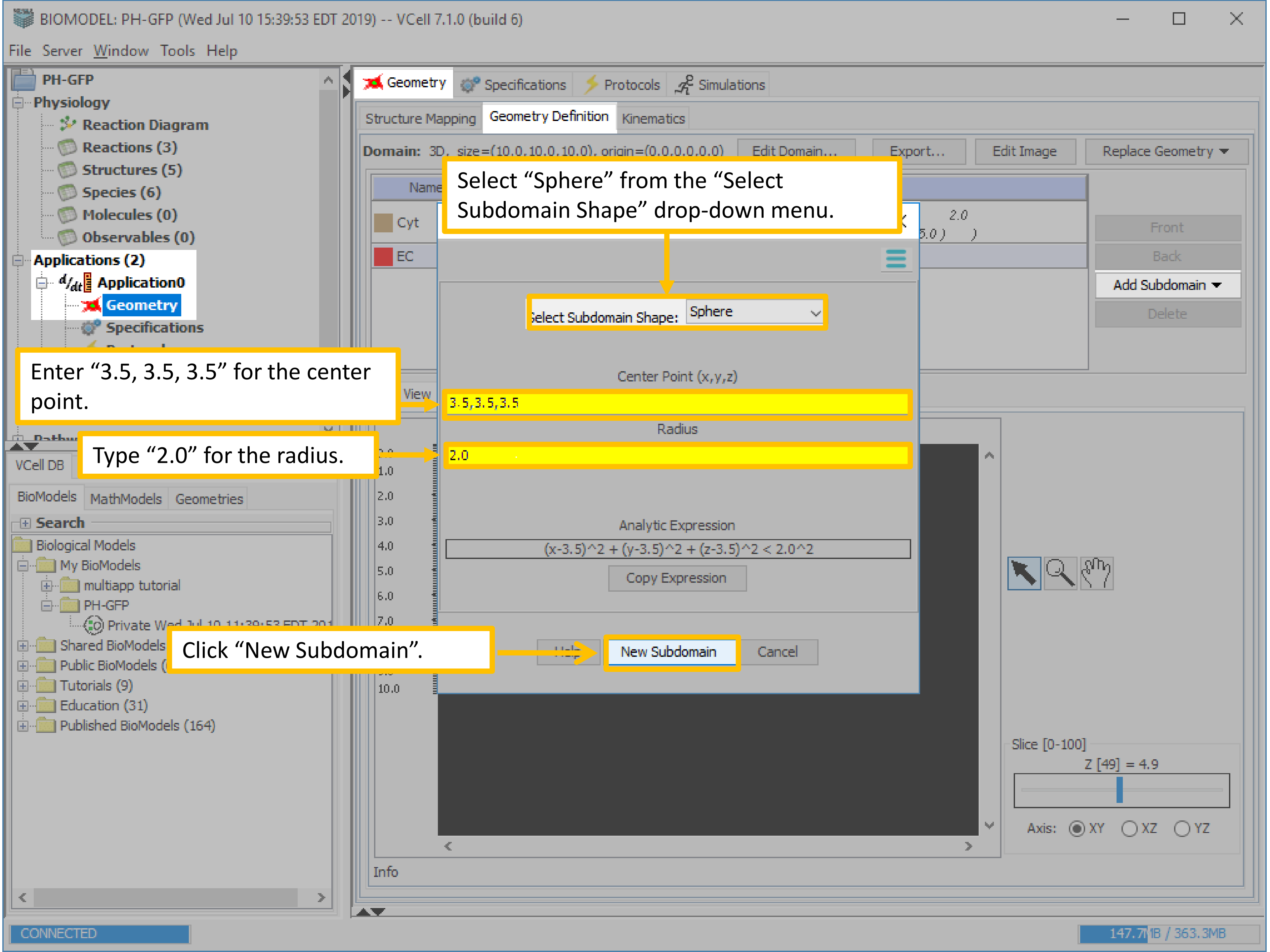
Click and drag the Z-Slicer so that the circle (Cytosol) almost touches the perimeter of the square (Extra Cellular).
Alternatively, select the area and use your arrow keys to adjust the position.

Slice [0-100]
Z [49] = 4.9
Axis: ● XY ○ XZ ○ YZ



Next you will create a smaller sphere to represent the nucleus.

Click “Add Subdomain” > “Analytic”.



Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Select "Sphere" from the "Select Subdomain Shape" drop-down menu.

Select Subdomain Shape: Sphere

Enter "3.5, 3.5, 3.5" for the center point.

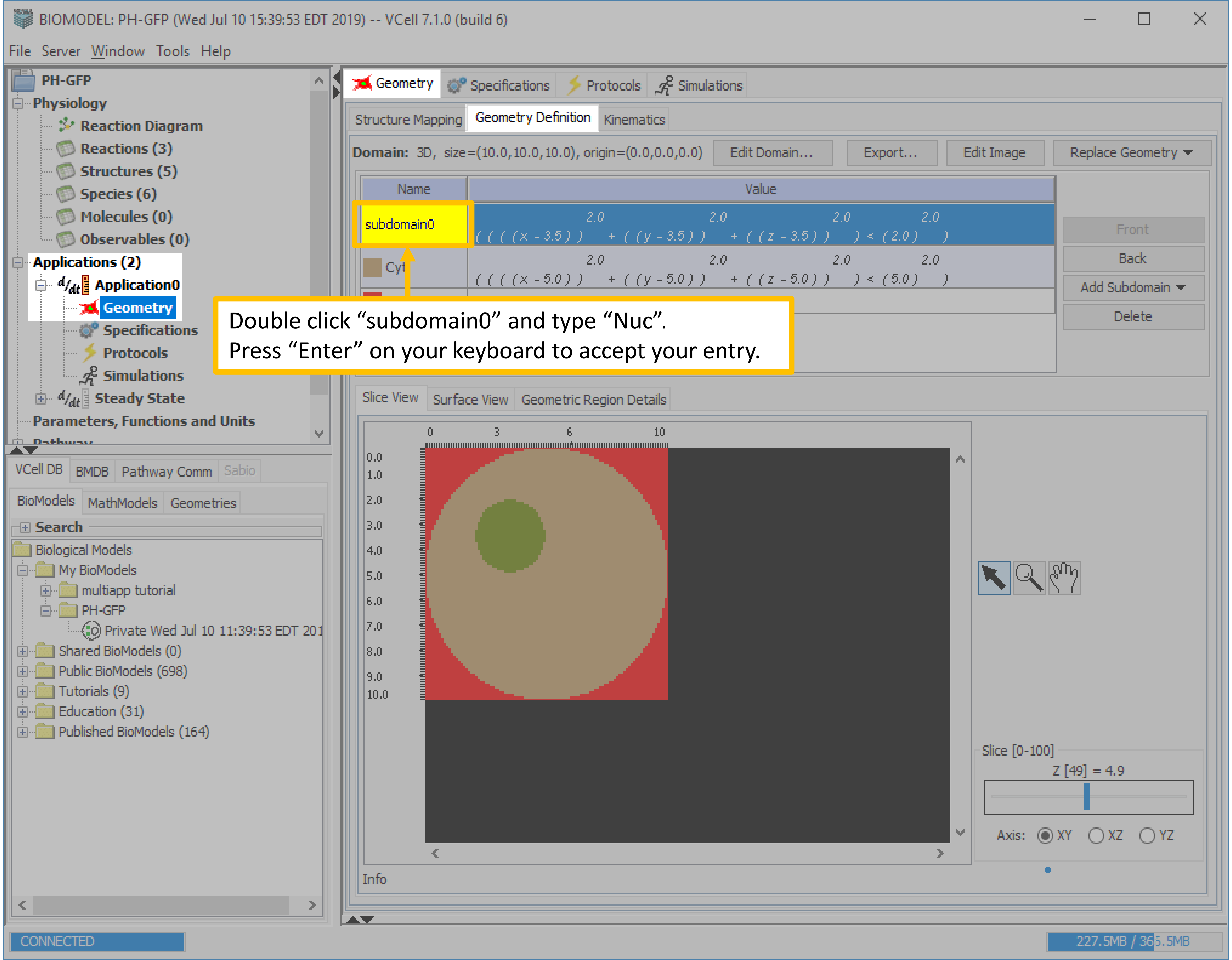
Center Point (x,y,z): 3.5,3.5,3.5

Type "2.0" for the radius.

Radius: 2.0

Analytic Expression: (x-3.5)^2 + (y-3.5)^2 + (z-3.5)^2 < 2.0^2

Click "New Subdomain".

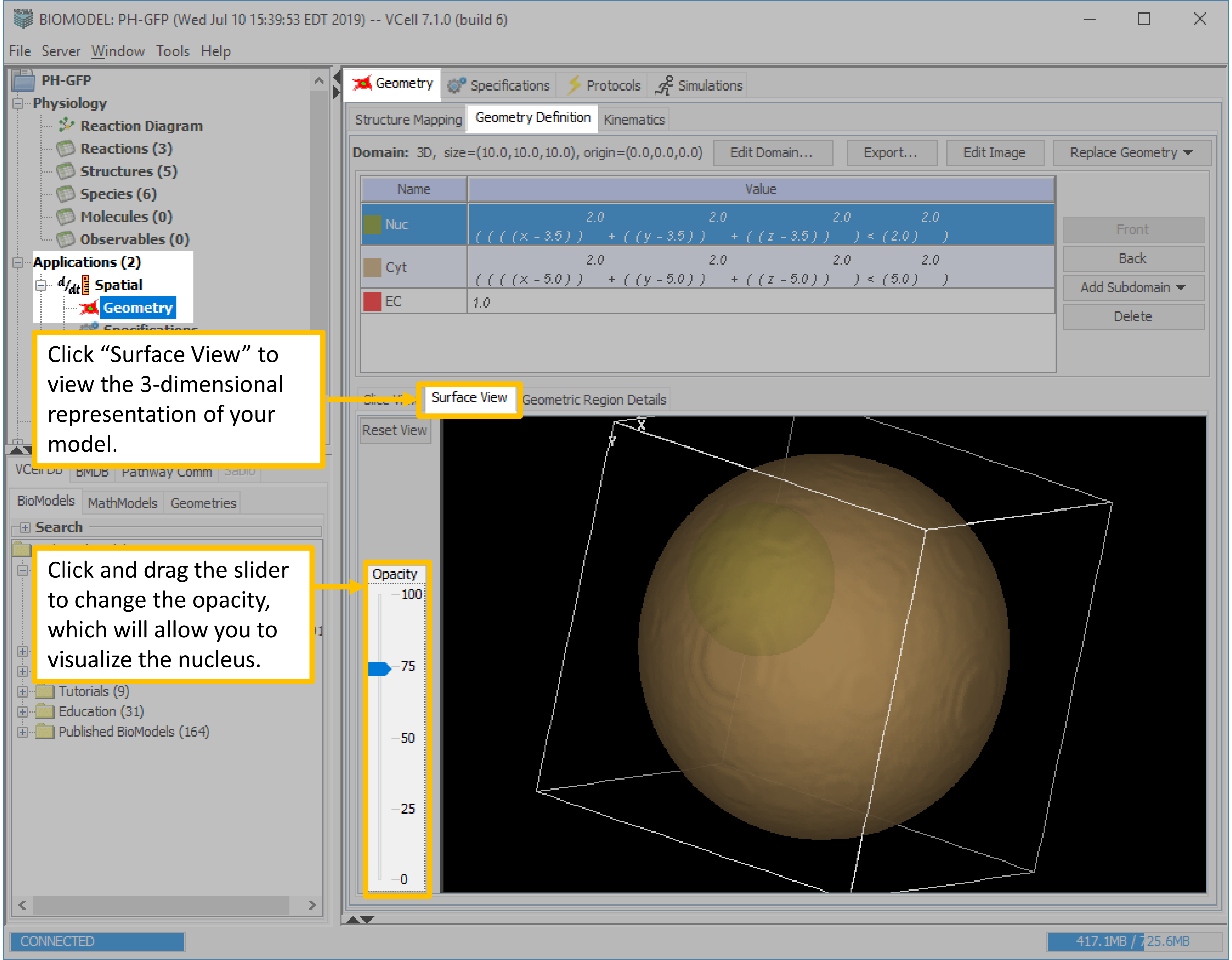


Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Name	Value
subdomain0	$((((x-3.5))^{2.0} + ((y-3.5))^{2.0} + ((z-3.5))^{2.0}) < (2.0)^{2.0})$
🟫 Cyt	$((((x-5.0))^{2.0} + ((y-5.0))^{2.0} + ((z-5.0))^{2.0}) < (5.0)^{2.0})$

Z [49] = 4.9

Double click “subdomain0” and type “Nuc”.
Press “Enter” on your keyboard to accept your entry.



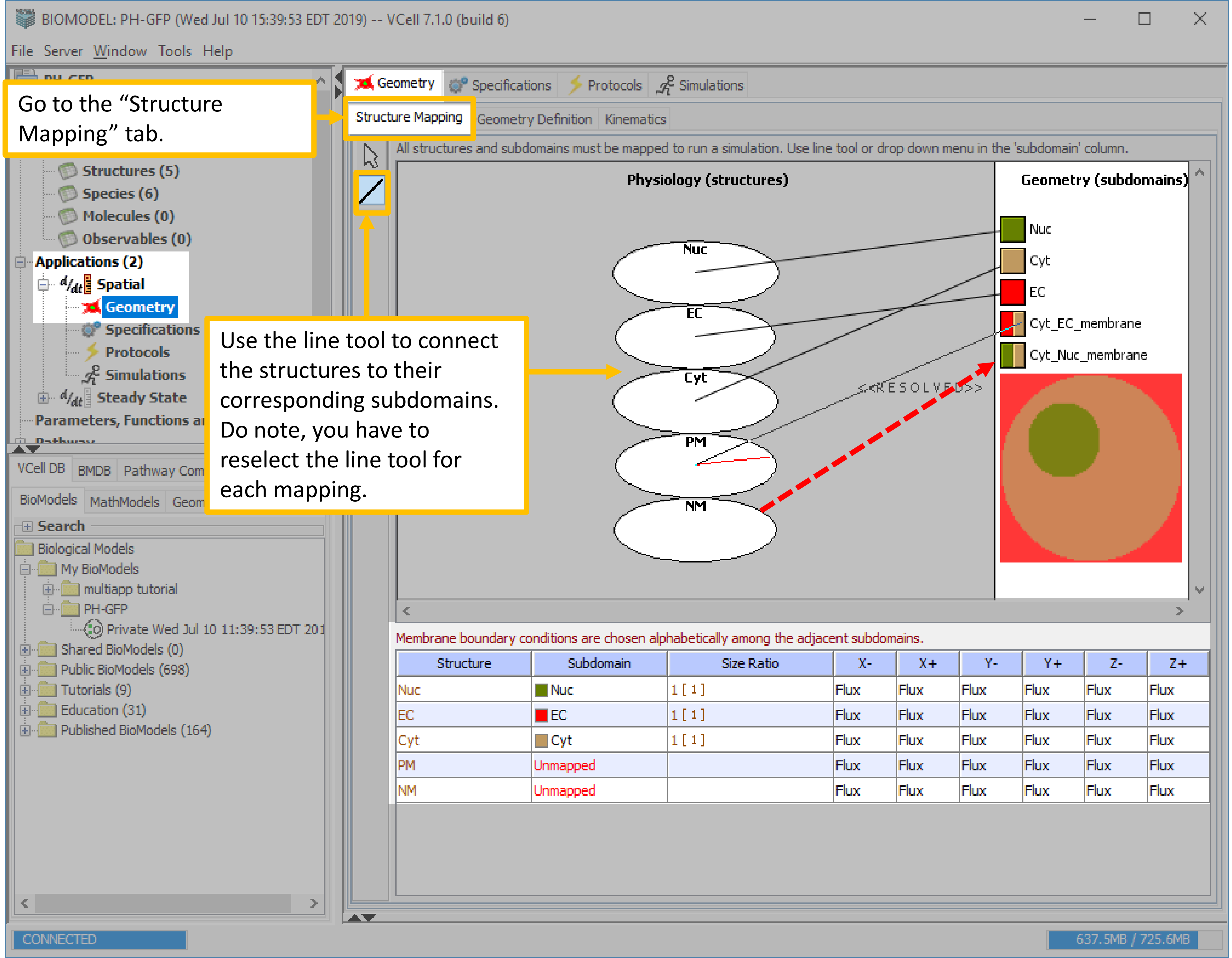
BIOMODEL: PH-GFP (Wed Jul 10 15:39:53 EDT 2019) -- VCell 7.1.0 (build 6)

Domain: 3D, size=(10.0,10.0,10.0), origin=(0.0,0.0,0.0)

Name	Value
Nuc	$((((x - 3.5))^{2.0} + ((y - 3.5))^{2.0} + ((z - 3.5))^{2.0}) < (2.0)^{2.0})$
Cyt	$((((x - 5.0))^{2.0} + ((y - 5.0))^{2.0} + ((z - 5.0))^{2.0}) < (5.0)^{2.0})$
EC	1.0

Click “Surface View” to view the 3-dimensional representation of your model.

Click and drag the slider to change the opacity, which will allow you to visualize the nucleus.



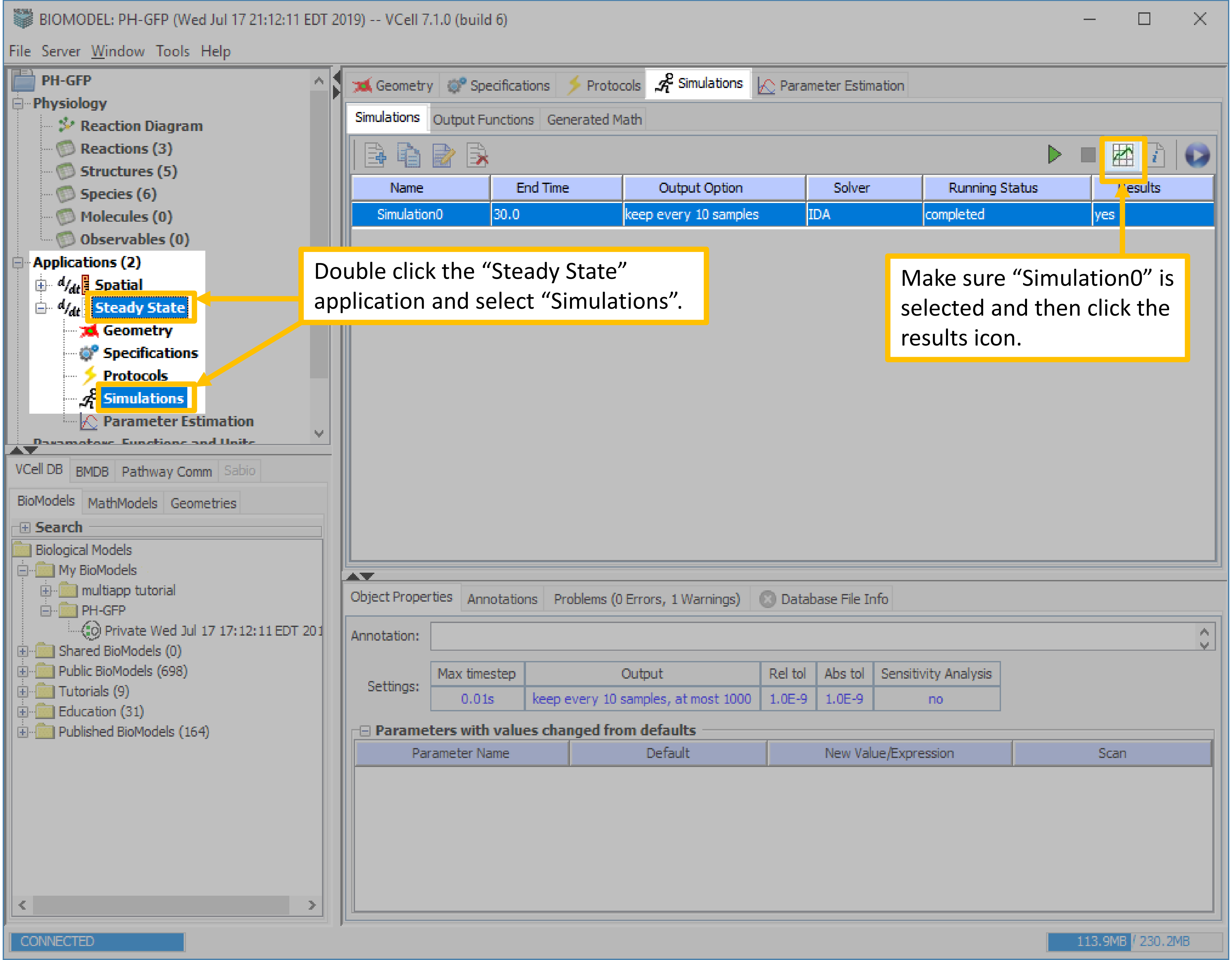
Go to the “Structure Mapping” tab.

Use the line tool to connect the structures to their corresponding subdomains. Do note, you have to reselect the line tool for each mapping.

All structures and subdomains must be mapped to run a simulation. Use line tool or drop down menu in the 'subdomain' column.

Membrane boundary conditions are chosen alphabetically among the adjacent subdomains.

Structure	Subdomain	Size Ratio	X-	X+	Y-	Y+	Z-	Z+
Nuc	🟩 Nuc	1 [1]	Flux	Flux	Flux	Flux	Flux	Flux
EC	🟥 EC	1 [1]	Flux	Flux	Flux	Flux	Flux	Flux
Cyt	🟫 Cyt	1 [1]	Flux	Flux	Flux	Flux	Flux	Flux
PM	Unmapped		Flux	Flux	Flux	Flux	Flux	Flux
NM	Unmapped		Flux	Flux	Flux	Flux	Flux	Flux



Name	End Time	Output Option	Solver	Running Status	Results
Simulation0	30.0	keep every 10 samples	IDA	completed	yes

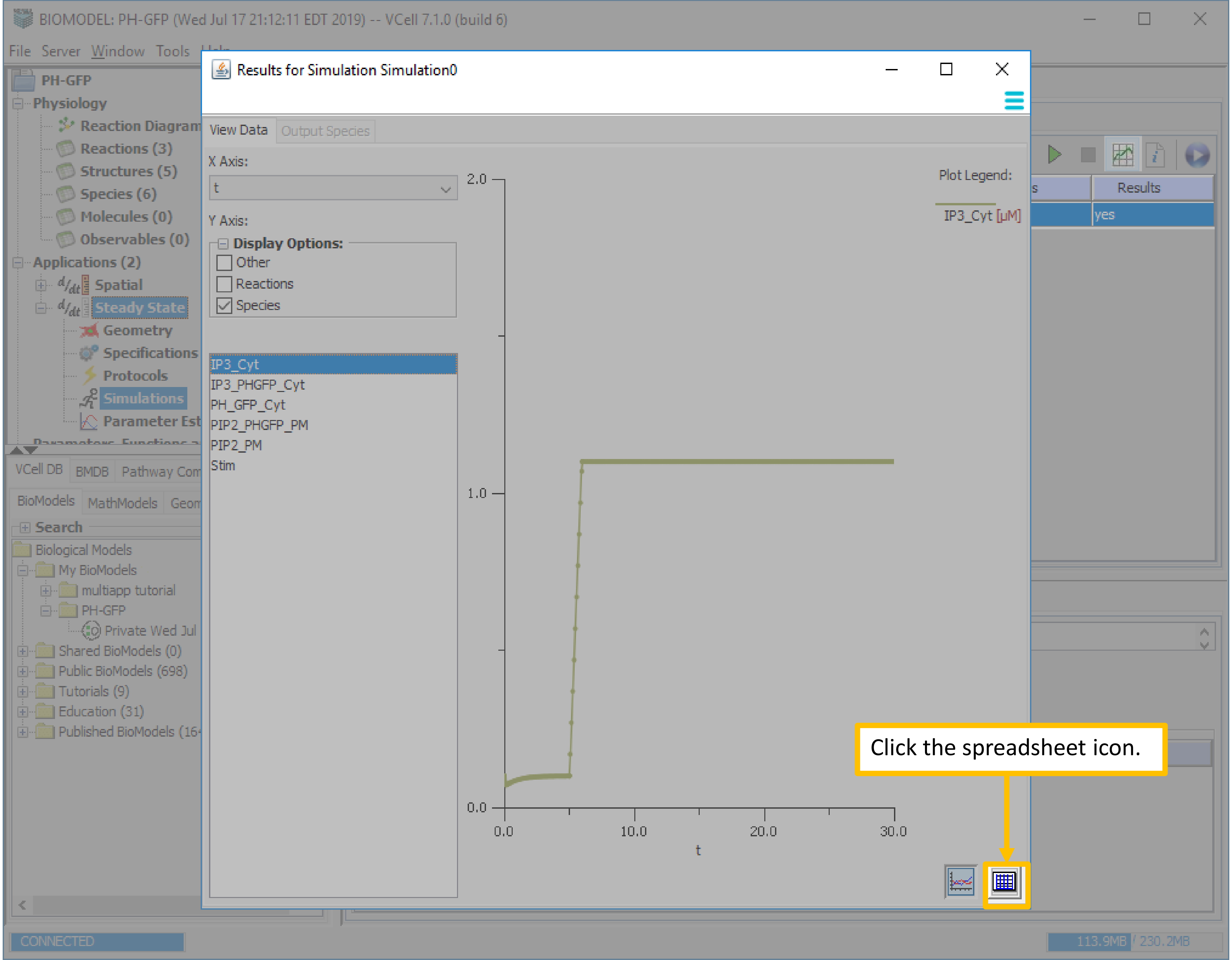
Max timestep	Output	Rel tol	Abs tol	Sensitivity Analysis
0.01s	keep every 10 samples, at most 1000	1.0E-9	1.0E-9	no

Parameters with values changed from defaults

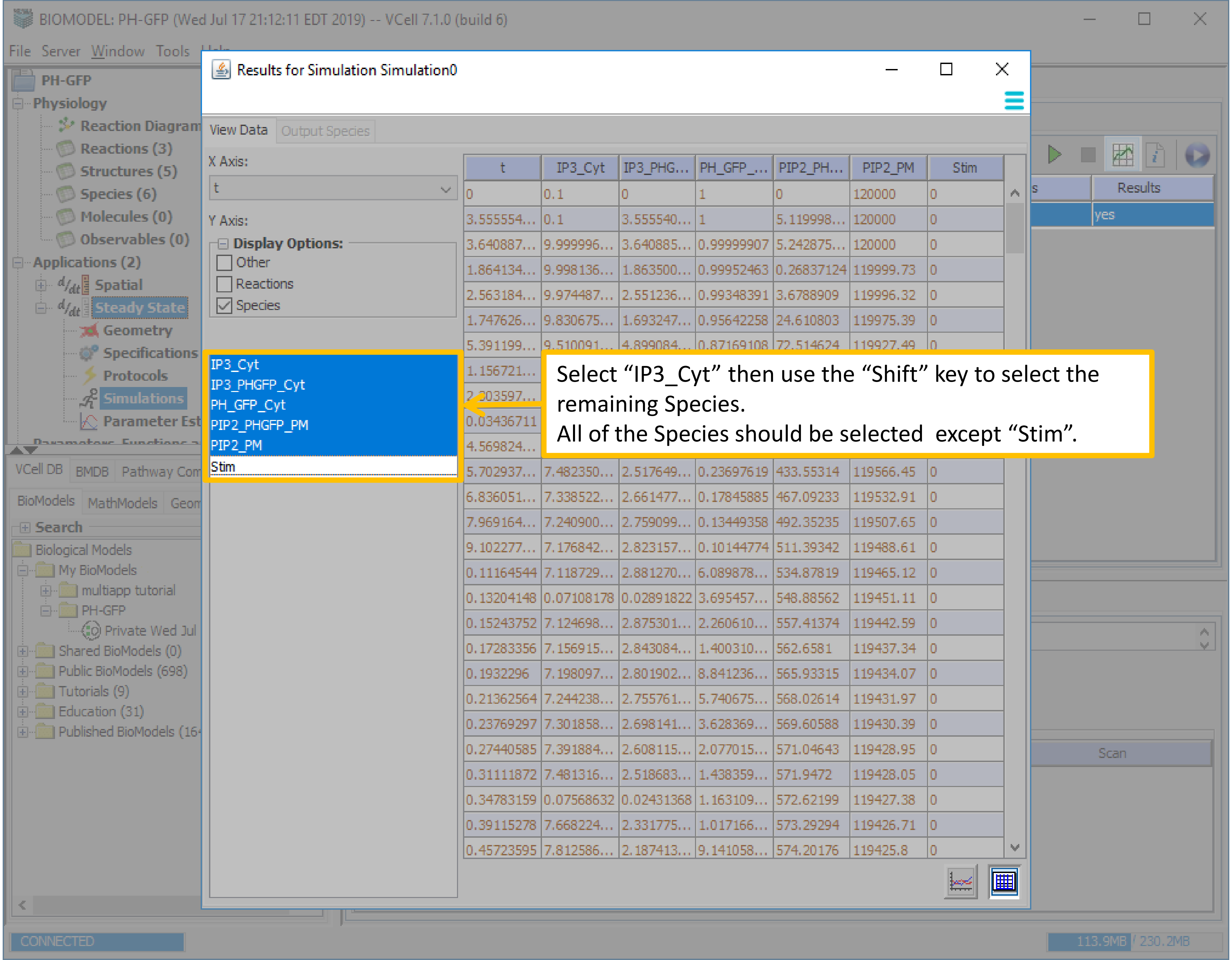
Parameter Name	Default	New Value/Expression	Scan

Double click the “Steady State” application and select “Simulations”.

Make sure “Simulation0” is selected and then click the results icon.



Click the spreadsheet icon.



X Axis: t

Y Axis:

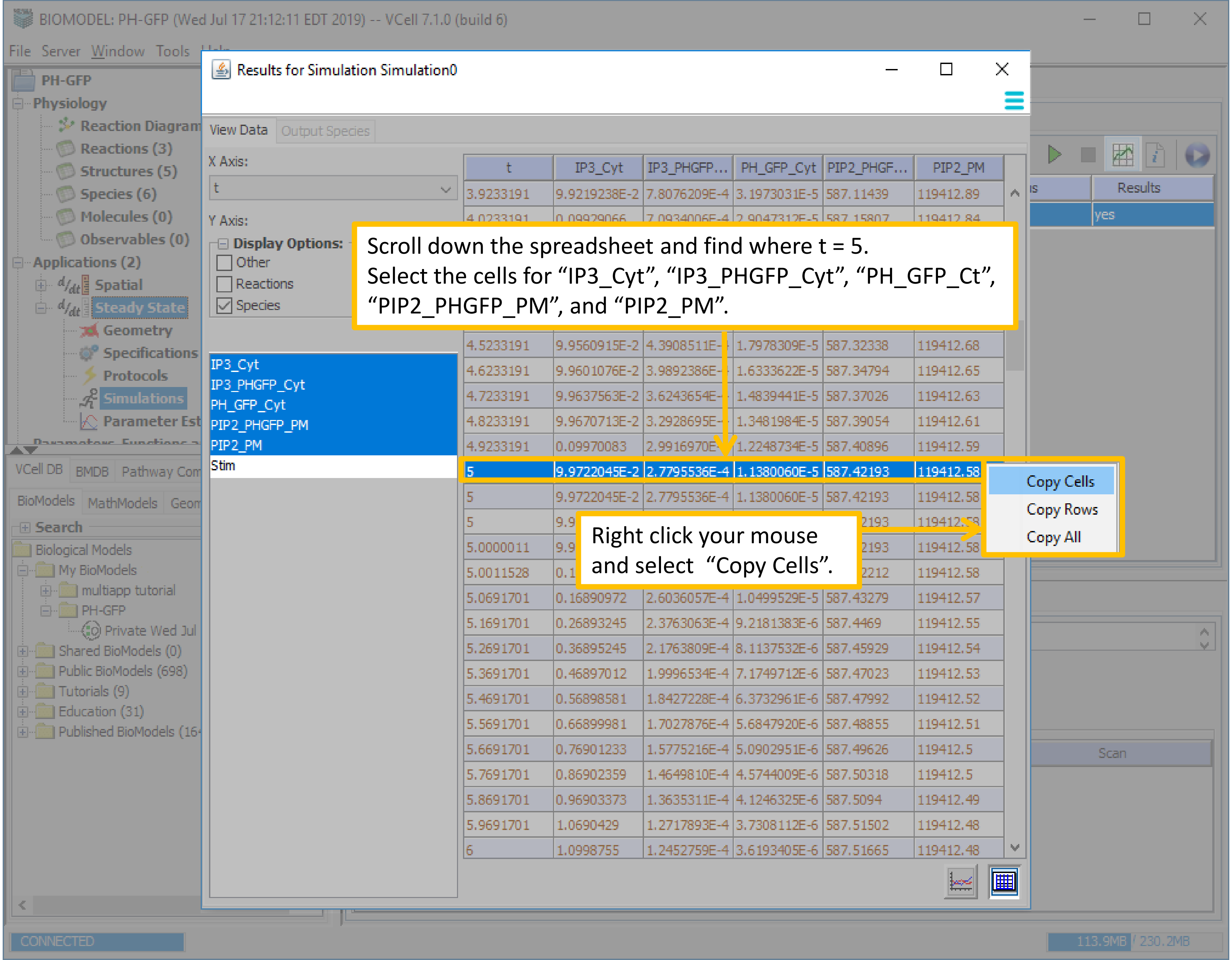
Display Options:

☐ Other
☐ Reactions
☑ Species

IP3_Cyt
IP3_PHGFP_Cyt
PH_GFP_Cyt
PIP2_PHGFP_PM
PIP2_PM
Stim

t	IP3_Cyt	IP3_PHG...	PH_GFP_...	PIP2_PH...	PIP2_PM	Stim
0	0.1	0	1	0	120000	0
3.555554...	0.1	3.555540...	1	5.119998...	120000	0
3.640887...	9.999996...	3.640885...	0.99999907	5.242875...	120000	0
1.864134...	9.998136...	1.863500...	0.99952463	0.26837124	119999.73	0
2.563184...	9.974487...	2.551236...	0.99348391	3.6788909	119996.32	0
1.747626...	9.830675...	1.693247...	0.95642258	24.610803	119975.39	0
5.391199...	9.510091...	4.899084...	0.87169108	72.514624	119927.49	0
1.156721...						
2.203597...						
0.03436711						
4.569824...						
5.702937...	7.482350...	2.517649...	0.23697619	433.55314	119566.45	0
6.836051...	7.338522...	2.661477...	0.17845885	467.09233	119532.91	0
7.969164...	7.240900...	2.759099...	0.13449358	492.35235	119507.65	0
9.102277...	7.176842...	2.823157...	0.10144774	511.39342	119488.61	0
0.11164544	7.118729...	2.881270...	6.089878...	534.87819	119465.12	0
0.13204148	0.07108178	0.02891822	3.695457...	548.88562	119451.11	0
0.15243752	7.124698...	2.875301...	2.260610...	557.41374	119442.59	0
0.17283356	7.156915...	2.843084...	1.400310...	562.6581	119437.34	0
0.1932296	7.198097...	2.801902...	8.841236...	565.93315	119434.07	0
0.21362564	7.244238...	2.755761...	5.740675...	568.02614	119431.97	0
0.23769297	7.301858...	2.698141...	3.628369...	569.60588	119430.39	0
0.27440585	7.391884...	2.608115...	2.077015...	571.04643	119428.95	0
0.31111872	7.481316...	2.518683...	1.438359...	571.9472	119428.05	0
0.34783159	0.07568632	0.02431368	1.163109...	572.62199	119427.38	0
0.39115278	7.668224...	2.331775...	1.017166...	573.29294	119426.71	0
0.45723595	7.812586...	2.187413...	9.141058...	574.20176	119425.8	0

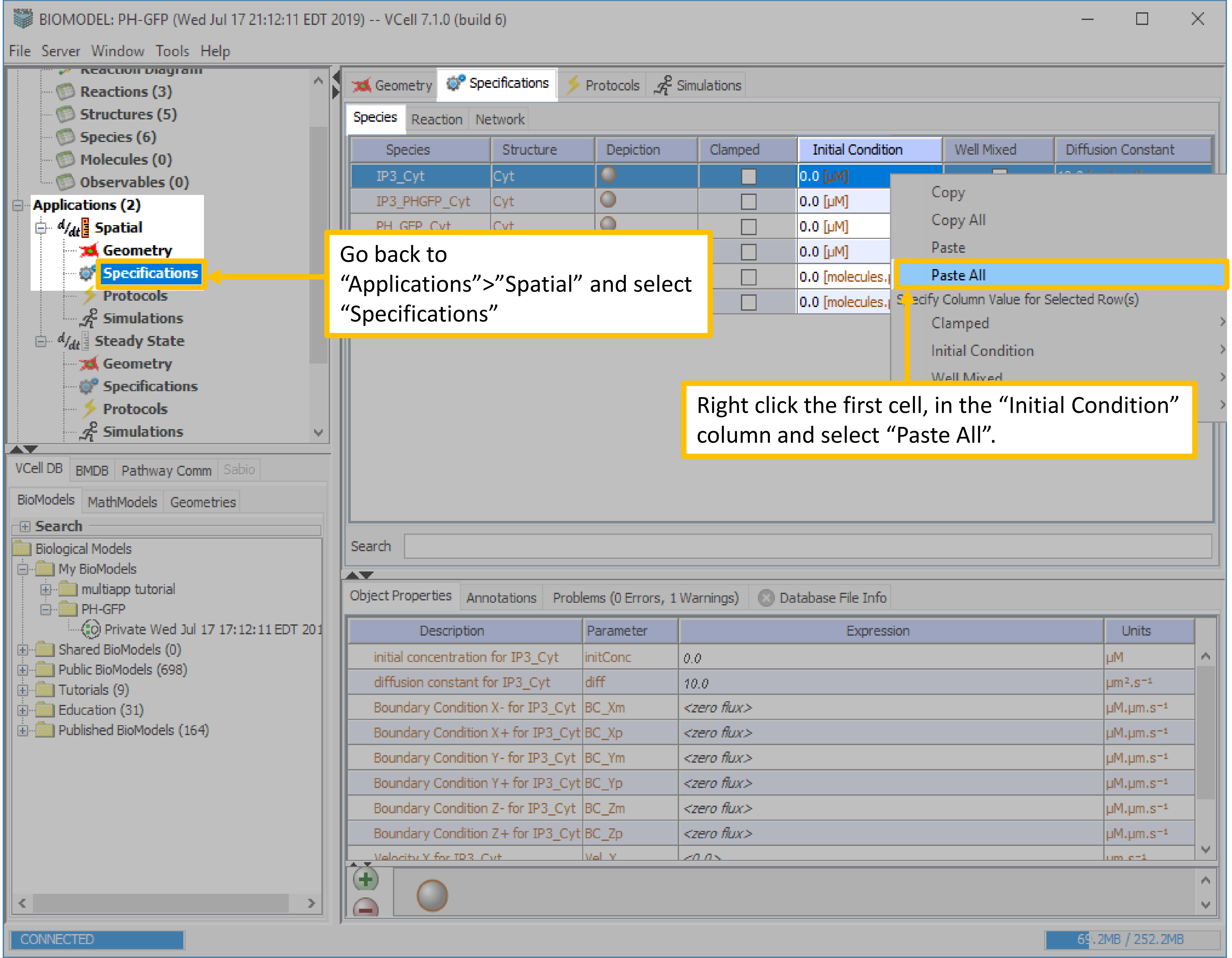
Select “IP3_Cyt” then use the “Shift” key to select the remaining Species.
All of the Species should be selected except “Stim”.



t	IP3_Cyt	IP3_PHGFP...	PH_GFP_Cyt	PIP2_PHGF...	PIP2_PM
3.9233191	9.9219238E-2	7.8076209E-4	3.1973031E-5	587.11439	119412.89
4.0233191	0.09929066	7.0934006E-4	2.9047312E-5	587.15807	119412.84
4.5233191	9.9560915E-2	4.3908511E-	1.7978309E-5	587.32338	119412.68
4.6233191	9.9601076E-2	3.9892386E-	1.6333622E-5	587.34794	119412.65
4.7233191	9.9637563E-2	3.6243654E-	1.4839441E-5	587.37026	119412.63
4.8233191	9.9670713E-2	3.2928695E-	1.3481984E-5	587.39054	119412.61
4.9233191	0.09970083	2.9916970E	1.2248734E-5	587.40896	119412.59
5	9.9722045E-2	2.7795536E-4	1.1380060E-5	587.42193	119412.58
5	9.9722045E-2	2.7795536E-4	1.1380060E-5	587.42193	119412.58
5	9.9	[illegible]	[illegible]	2193	119412.58
5.0000011	9.9	[illegible]	[illegible]	2193	119412.58
5.0011528	0.1	[illegible]	[illegible]	2212	119412.58
5.0691701	0.16890972	2.6036057E-4	1.0499529E-5	587.43279	119412.57
5.1691701	0.26893245	2.3763063E-4	9.2181383E-6	587.4469	119412.55
5.2691701	0.36895245	2.1763809E-4	8.1137532E-6	587.45929	119412.54
5.3691701	0.46897012	1.9996534E-4	7.1749712E-6	587.47023	119412.53
5.4691701	0.56898581	1.8427228E-4	6.3732961E-6	587.47992	119412.52
5.5691701	0.66899981	1.7027876E-4	5.6847920E-6	587.48855	119412.51
5.6691701	0.76901233	1.5775216E-4	5.0902951E-6	587.49626	119412.5
5.7691701	0.86902359	1.4649810E-4	4.5744009E-6	587.50318	119412.5
5.8691701	0.96903373	1.3635311E-4	4.1246325E-6	587.5094	119412.49
5.9691701	1.0690429	1.2717893E-4	3.7308112E-6	587.51502	119412.48
6	1.0998755	1.2452759E-4	3.6193405E-6	587.51665	119412.48

Scroll down the spreadsheet and find where t = 5.
Select the cells for “IP3_Cyt”, “IP3_PHGFP_Cyt”, “PH_GFP_Ct”, “PIP2_PHGFP_PM”, and “PIP2_PM”.

Right click your mouse and select “Copy Cells”.



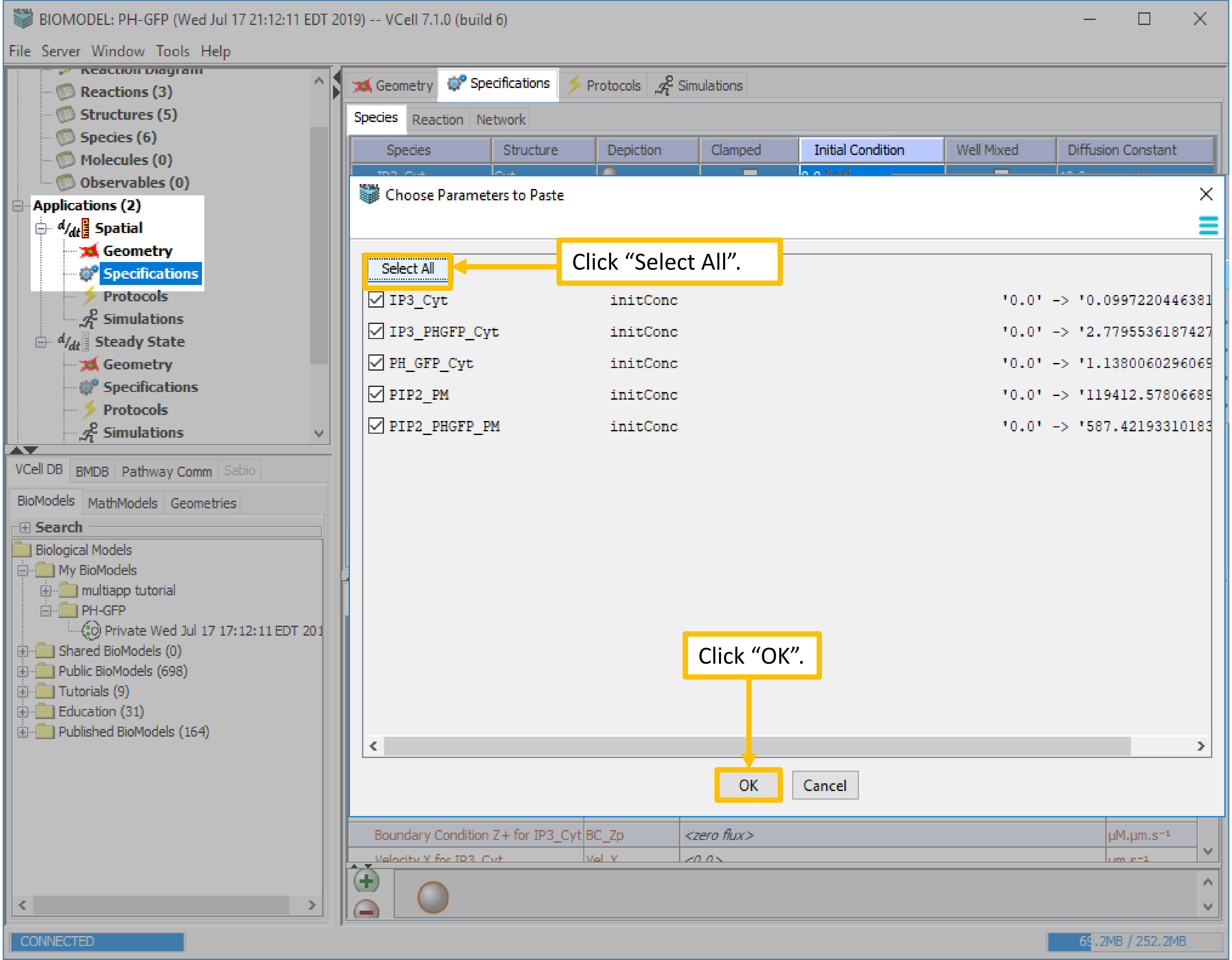
Go back to “Applications”>”Spatial” and select “Specifications”

Right click the first cell, in the “Initial Condition” column and select “Paste All”.

BIOMODEL: PH-GFP (Wed Jul 17 21:12:11 EDT 2019) -- VCell 7.1.0 (build 6)

Species	Structure	Depiction	Clamped	Initial Condition
IP3_Cyt	Cyt	●	☐	0.0 [μM]
IP3_PHGFP_Cyt	Cyt	●	☐	0.0 [μM]
PH_GFP_Cyt	Cyt	●	☐	0.0 [μM]
			☐	0.0 [μM]
			☐	0.0 [molecules.
			☐	0.0 [molecules.

Description	Parameter	Expression	Units
initial concentration for IP3_Cyt	initConc	0.0	μM
diffusion constant for IP3_Cyt	diff	10.0	μm².s⁻¹
Boundary Condition X- for IP3_Cyt	BC_Xm	<zero flux>	μM.μm.s⁻¹
Boundary Condition X+ for IP3_Cyt	BC_Xp	<zero flux>	μM.μm.s⁻¹
Boundary Condition Y- for IP3_Cyt	BC_Ym	<zero flux>	μM.μm.s⁻¹
Boundary Condition Y+ for IP3_Cyt	BC_Yp	<zero flux>	μM.μm.s⁻¹
Boundary Condition Z- for IP3_Cyt	BC_Zm	<zero flux>	μM.μm.s⁻¹
Boundary Condition Z+ for IP3_Cyt	BC_Zp	<zero flux>	μM.μm.s⁻¹



Choose Parameters to Paste

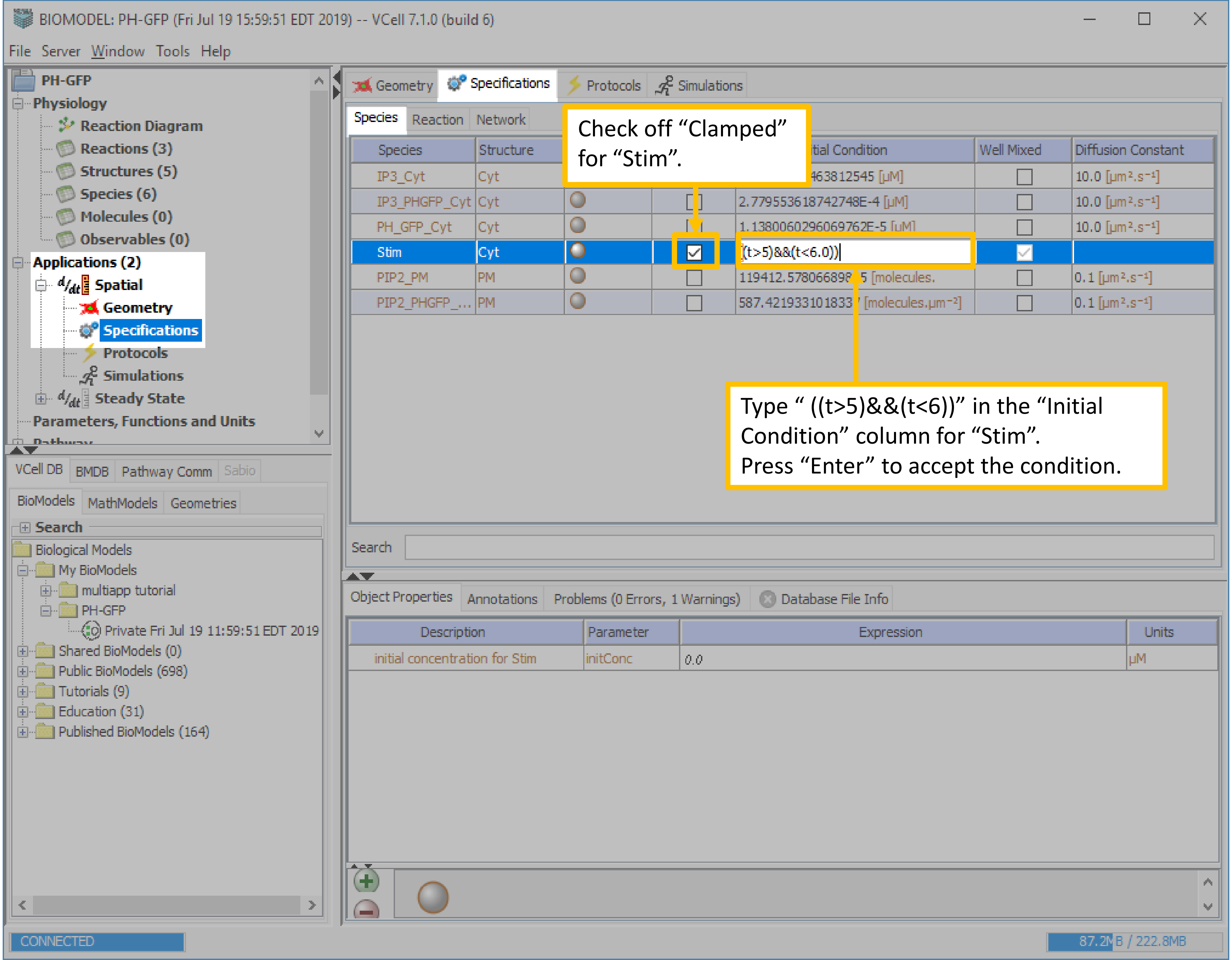
Select All

☑ IP3_Cyt	initConc	'0.0' -> '0.0997220446381
☑ IP3_PHGFP_Cyt	initConc	'0.0' -> '2.779553618742
☑ PH_GFP_Cyt	initConc	'0.0' -> '1.138006029606
☑ PIP2_PM	initConc	'0.0' -> '119412.5780668
☑ PIP2_PHGFP_PM	initConc	'0.0' -> '587.4219331018

OK Cancel

Click “Select All”.

Click “OK”.

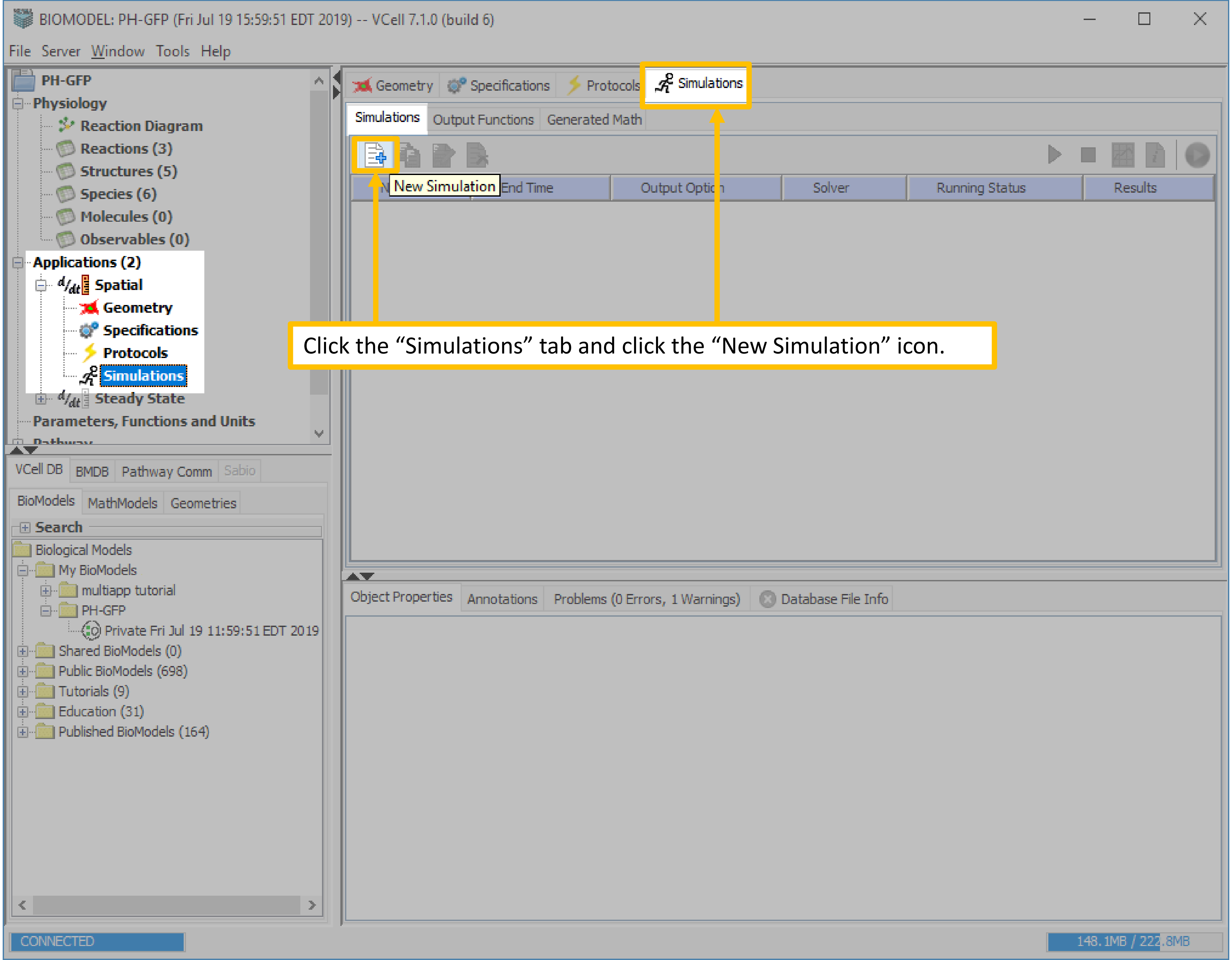


Species	Structure			itial Condition	Well Mixed	Diffusion Constant
IP3_Cyt	Cyt			463812545 [µM]	☐	10.0 [$\mu m^2.s^{-1}$]
IP3_PHGFP_Cyt	Cyt	●	☐	2.779553618742748E-4 [µM]	☐	10.0 [$\mu m^2.s^{-1}$]
PH_GFP_Cyt	Cyt	●	☐	1.1380060296069762E-5 [µM]	☐	10.0 [$\mu m^2.s^{-1}$]
Stim	Cyt	●	☑	((t>5)&&(t<6.0))	☑	
PIP2_PM	PM	●	☐	119412.578066898 5 [molecules.	☐	0.1 [$\mu m^2.s^{-1}$]
PIP2_PHGFP_...	PM	●	☐	587.421933101833 [molecules.μm^{-2}]	☐	0.1 [$\mu m^2.s^{-1}$]

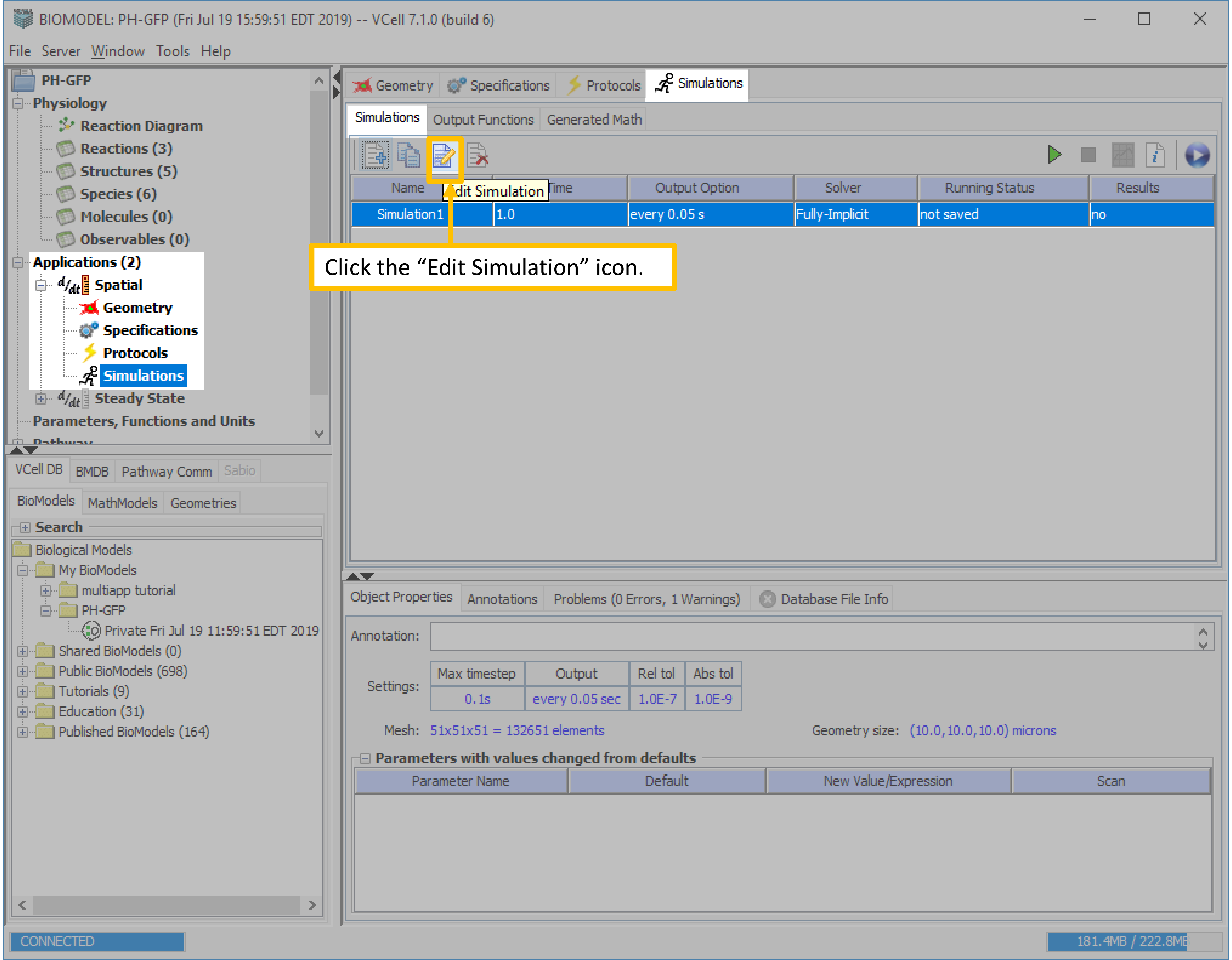
Description	Parameter	Expression	Units
initial concentration for Stim	initConc	0.0	µM

Check off “Clamped” for “Stim”.

Type “ ((t>5)&&(t<6))” in the “Initial Condition” column for “Stim”.
Press “Enter” to accept the condition.



Click the “Simulations” tab and click the “New Simulation” icon.



Click the “Edit Simulation” icon.

Name		Time	Output Option	Solver	Running Status	Results
Simulation1		1.0	every 0.05 s	Fully-Implicit	not saved	no

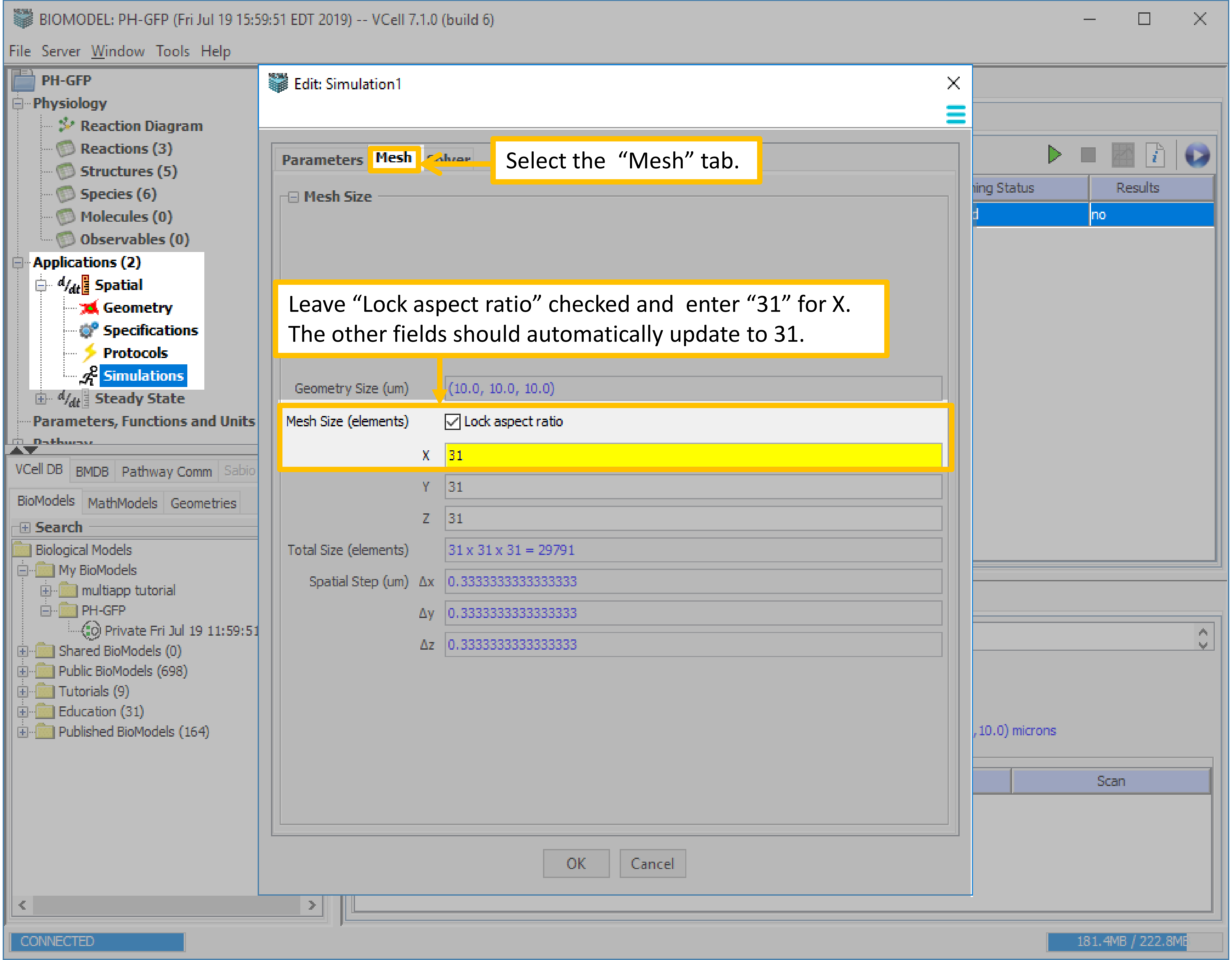
Settings:

Max timestep	Output	Rel tol	Abs tol
0.1s	every 0.05 sec	1.0E-7	1.0E-9

Mesh: 51x51x51 = 132651 elements

Geometry size: (10.0,10.0,10.0) microns

Parameter Name	Default	New Value/Expression	Scan



Select the "Mesh" tab.

Leave "Lock aspect ratio" checked and enter "31" for X. The other fields should automatically update to 31.

Geometry Size (um): (10.0, 10.0, 10.0)

Mesh Size (elements): ☑ Lock aspect ratio

X: 31

Y: 31

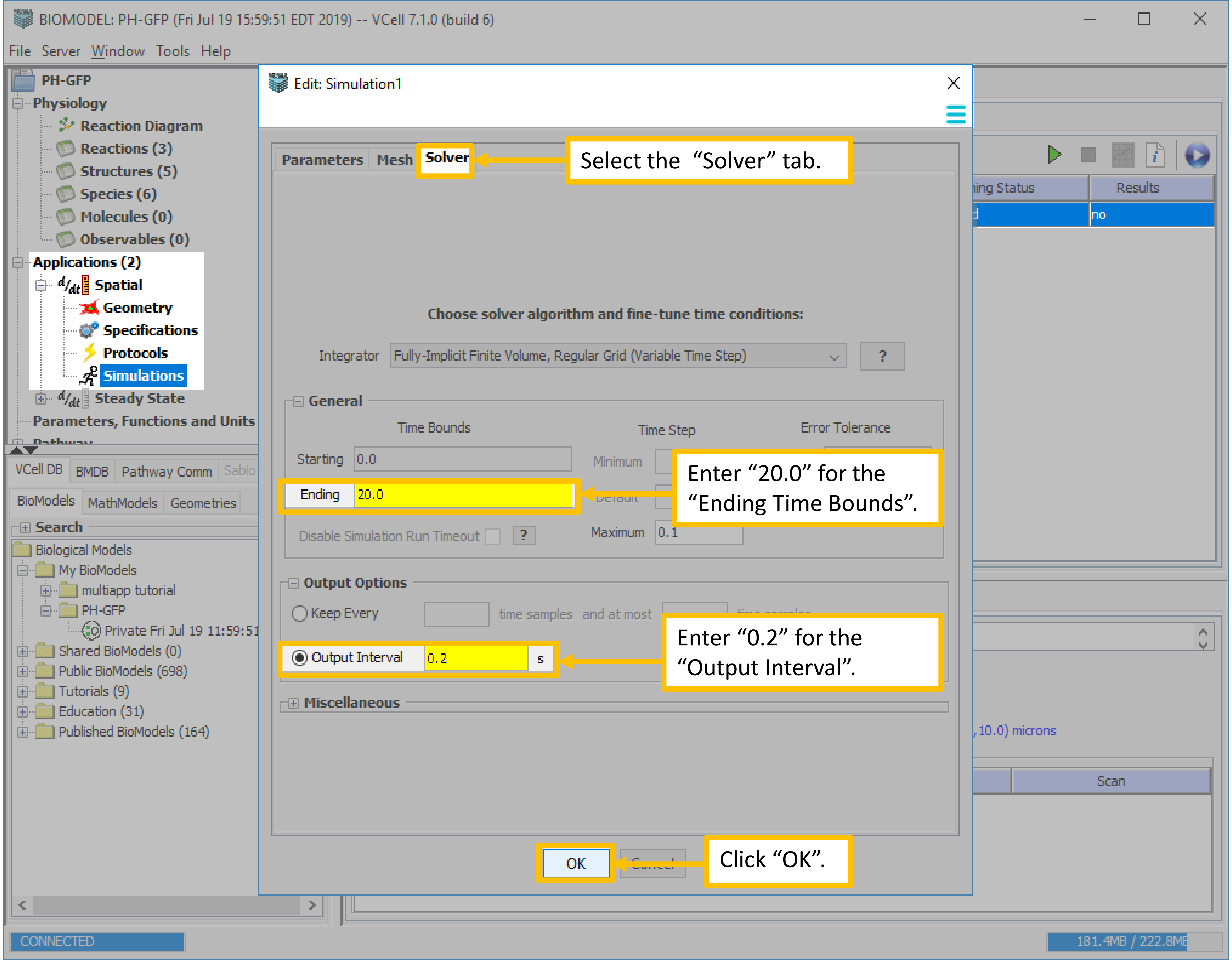
Z: 31

Total Size (elements): 31 x 31 x 31 = 29791

Spatial Step (um) Δx: 0.3333333333333333

Δy: 0.3333333333333333

Δz: 0.3333333333333333



Choose solver algorithm and fine-tune time conditions:

Integrator: Fully-Implicit Finite Volume, Regular Grid (Variable Time Step)

General

Time Bounds		Time Step		Error Tolerance
Starting	0.0	Minimum		
Ending	20.0	Default		
		Maximum	0.1	

Disable Simulation Run Timeout ☐

Output Options

○ Keep Every ____ time samples and at most ____ time samples

● Output Interval 0.2 s

Miscellaneous

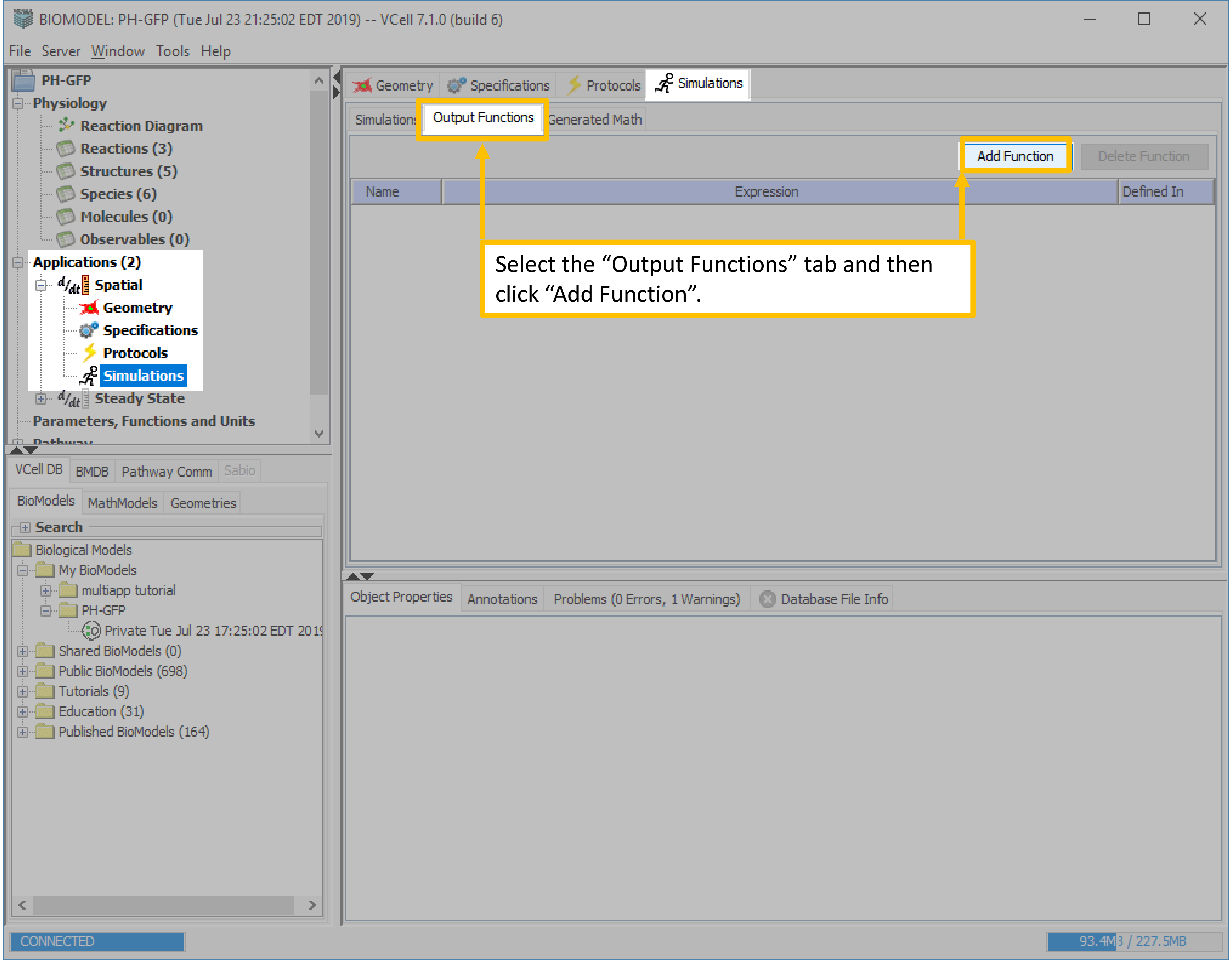
OK Cancel

Select the “Solver” tab.

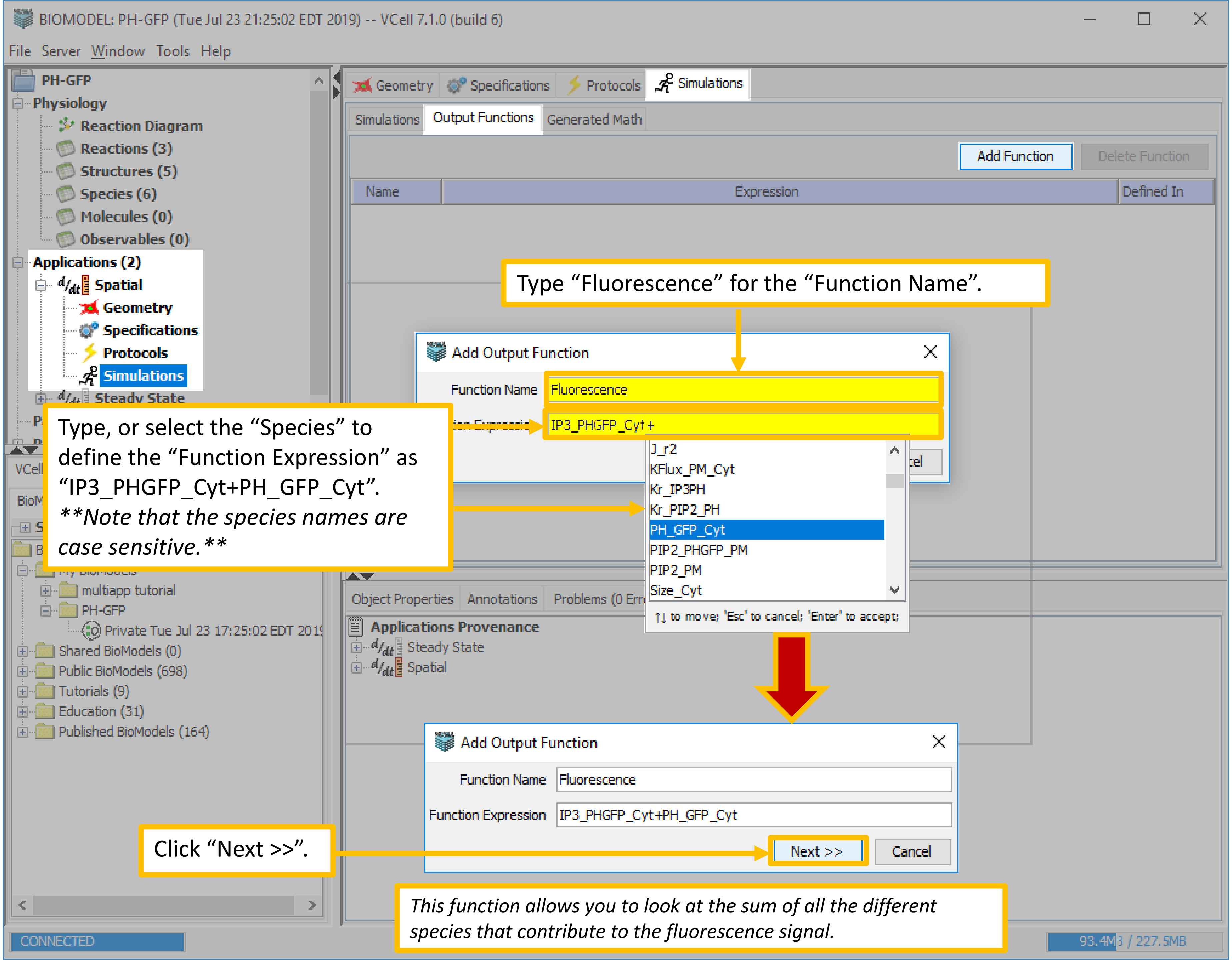
Enter “20.0” for the “Ending Time Bounds”.

Enter “0.2” for the “Output Interval”.

Click “OK”.



Select the “Output Functions” tab and then click “Add Function”.



Type “Fluorescence” for the “Function Name”.

Function Name: Fluorescence

Function Expression: IP3_PHGFP_Cyt+

Type, or select the “Species” to define the “Function Expression” as “IP3_PHGFP_Cyt+PH_GFP_Cyt”.

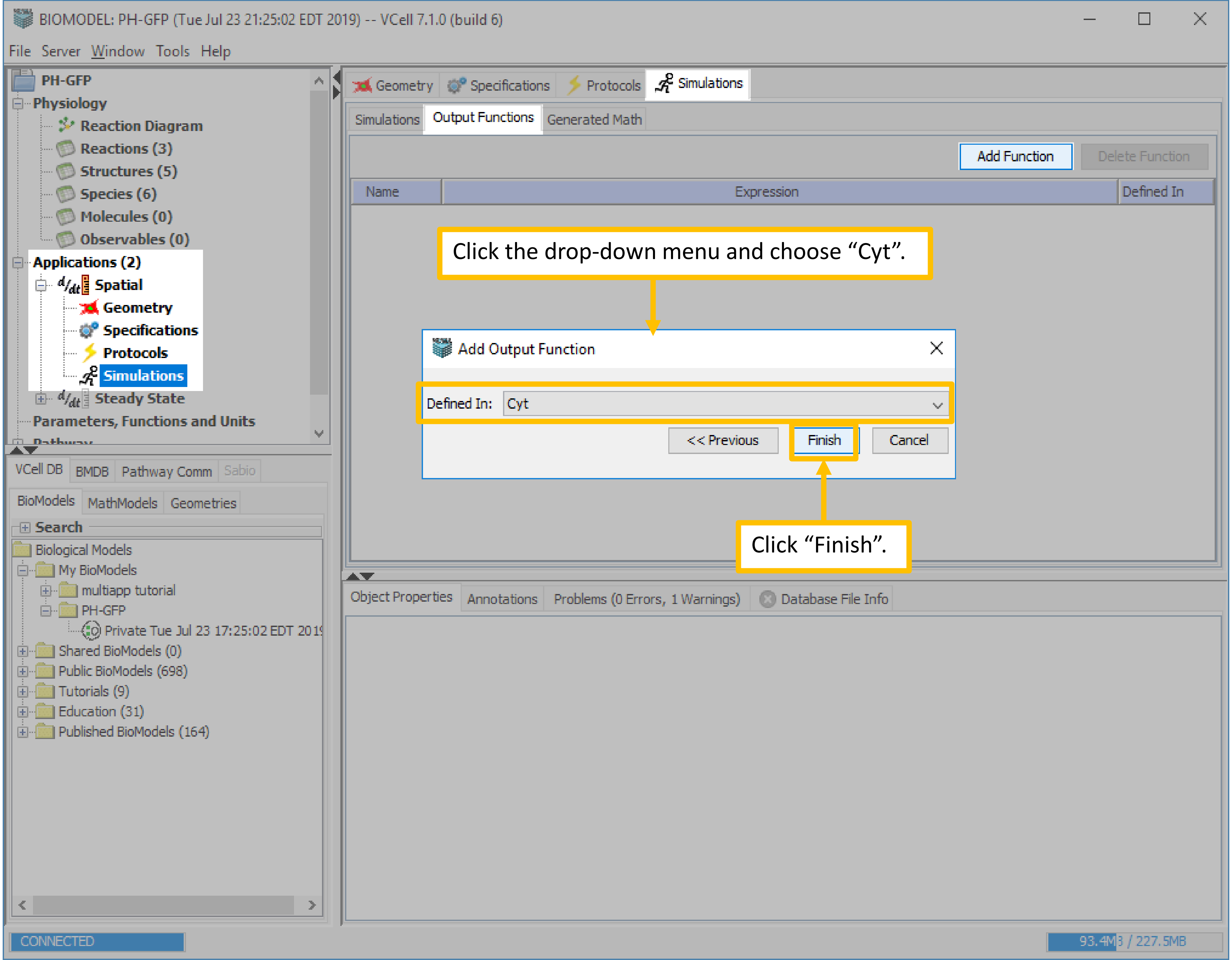
Note that the species names are case sensitive.

Function Name: Fluorescence

Function Expression: IP3_PHGFP_Cyt+PH_GFP_Cyt

Click “Next >>”.

This function allows you to look at the sum of all the different species that contribute to the fluorescence signal.



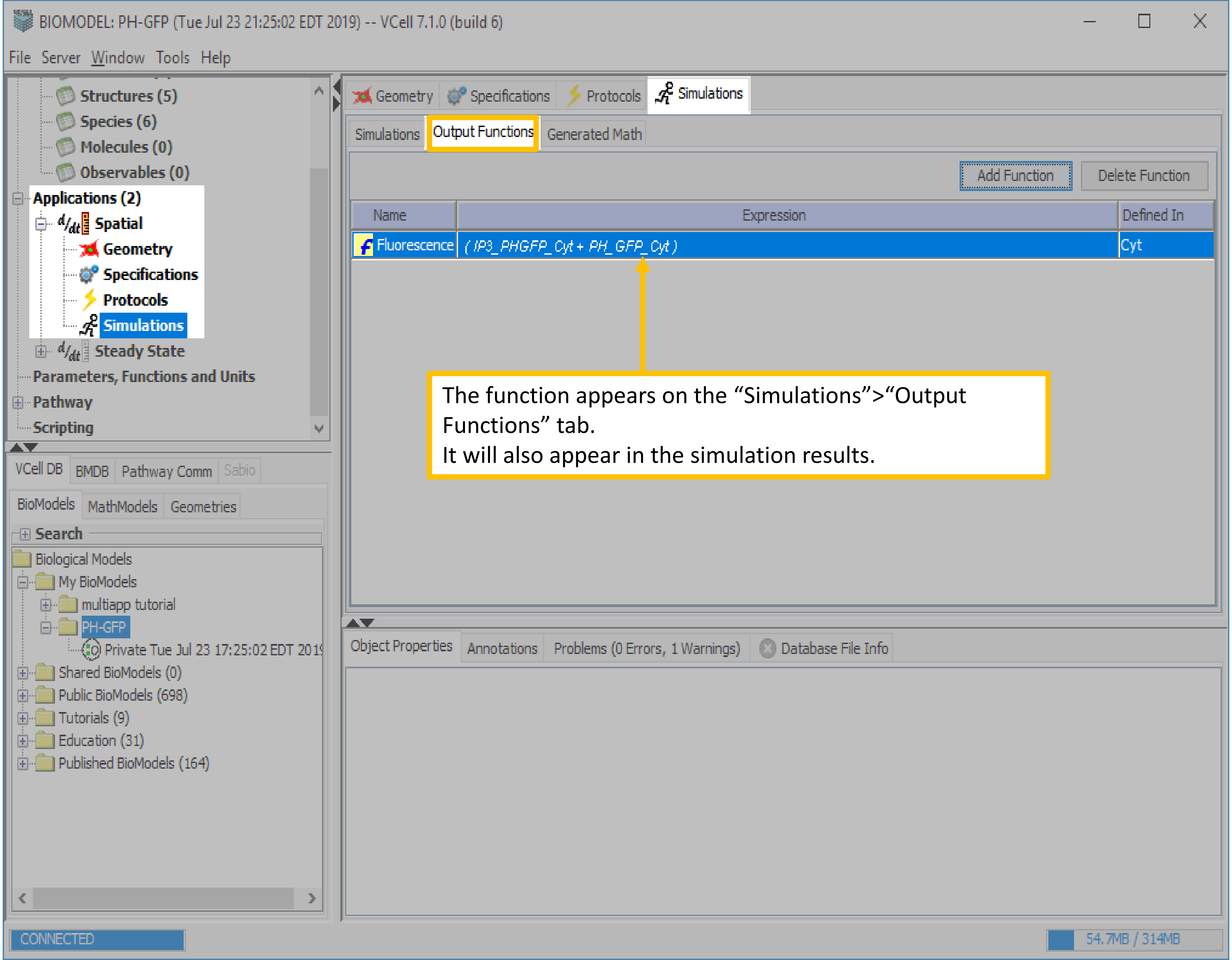
BIOMODEL: PH-GFP (Tue Jul 23 21:25:02 EDT 2019) -- VCell 7.1.0 (build 6)

Add Output Function

Defined In: Cyt

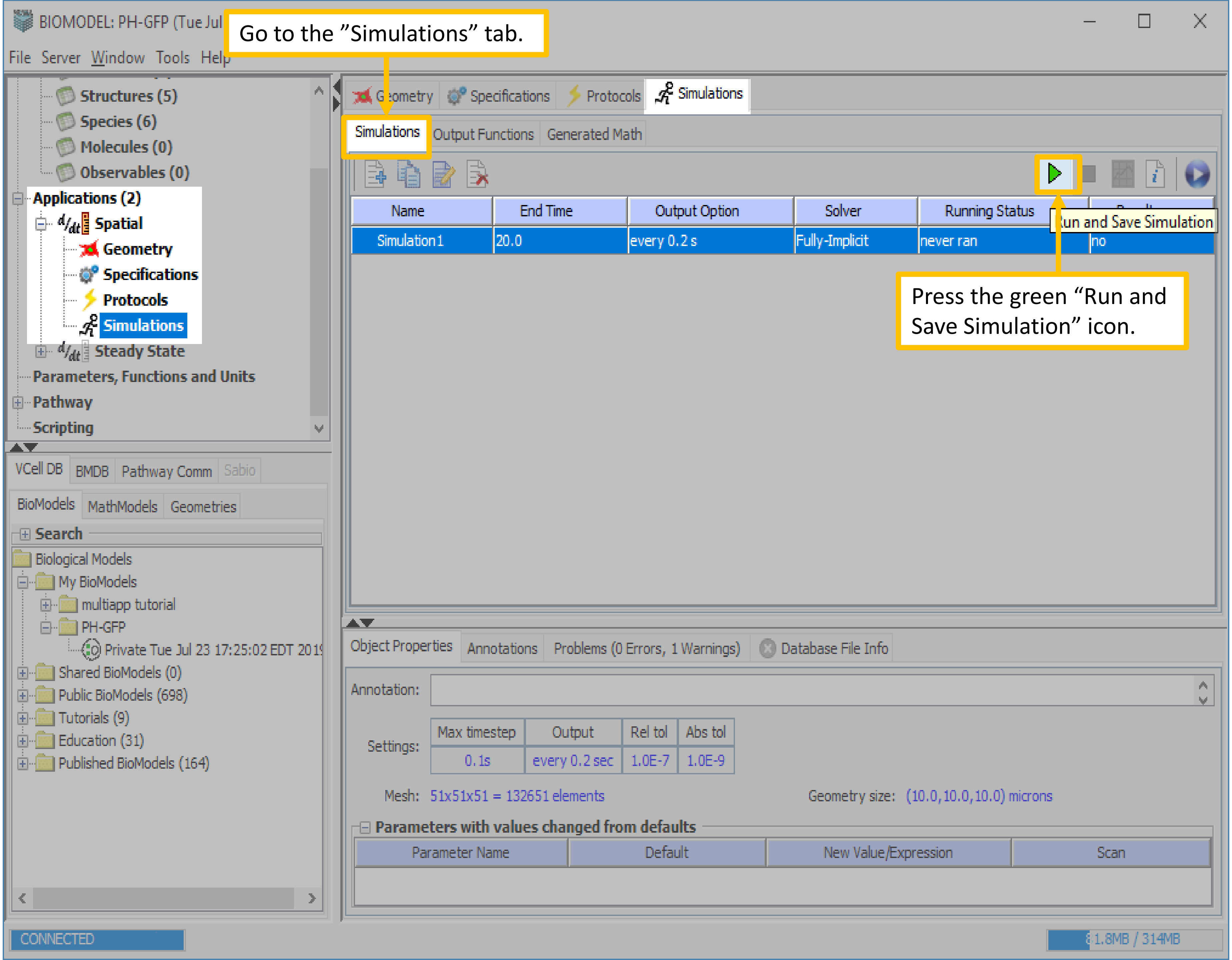
Click the drop-down menu and choose “Cyt”.

Click “Finish”.



Name	Expression	Defined In
Fluorescence	(IP3_PHGFP_Cyt + PH_GFP_Cyt)	Cyt

The function appears on the “Simulations”>“Output Functions” tab.
It will also appear in the simulation results.



Go to the "Simulations" tab.

Press the green "Run and Save Simulation" icon.

Name	End Time	Output Option	Solver	Running Status	Results
Simulation1	20.0	every 0.2 s	Fully-Implicit	never ran	no

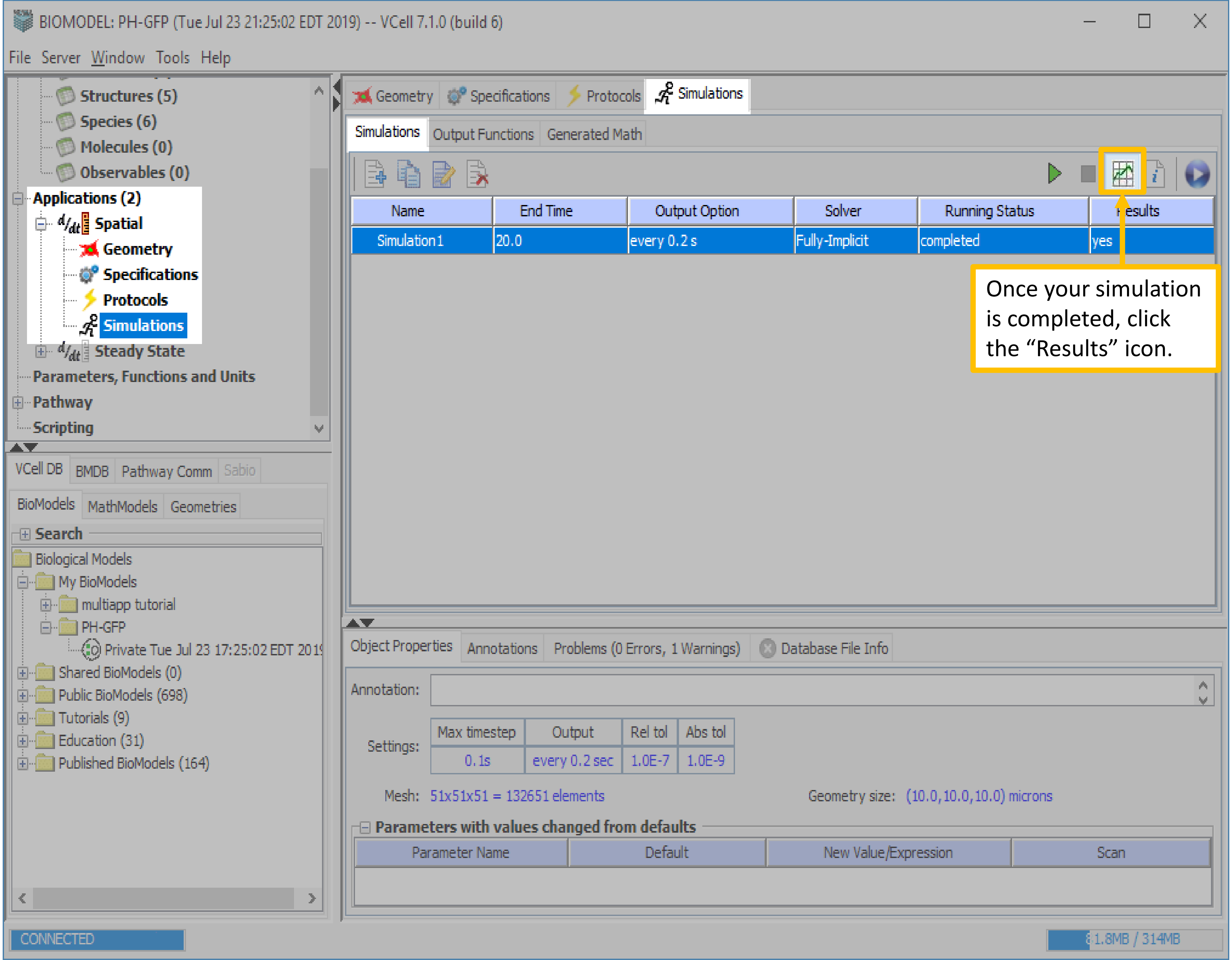
Settings:

Max timestep	Output	Rel tol	Abs tol
0.1s	every 0.2 sec	1.0E-7	1.0E-9

Mesh: 51x51x51 = 132651 elements

Geometry size: (10.0,10.0,10.0) microns

Parameter Name	Default	New Value/Expression	Scan



Name	End Time	Output Option	Solver	Running Status	Results
Simulation1	20.0	every 0.2 s	Fully-Implicit	completed	yes

Once your simulation is completed, click the “Results” icon.

Annotation:

Settings:

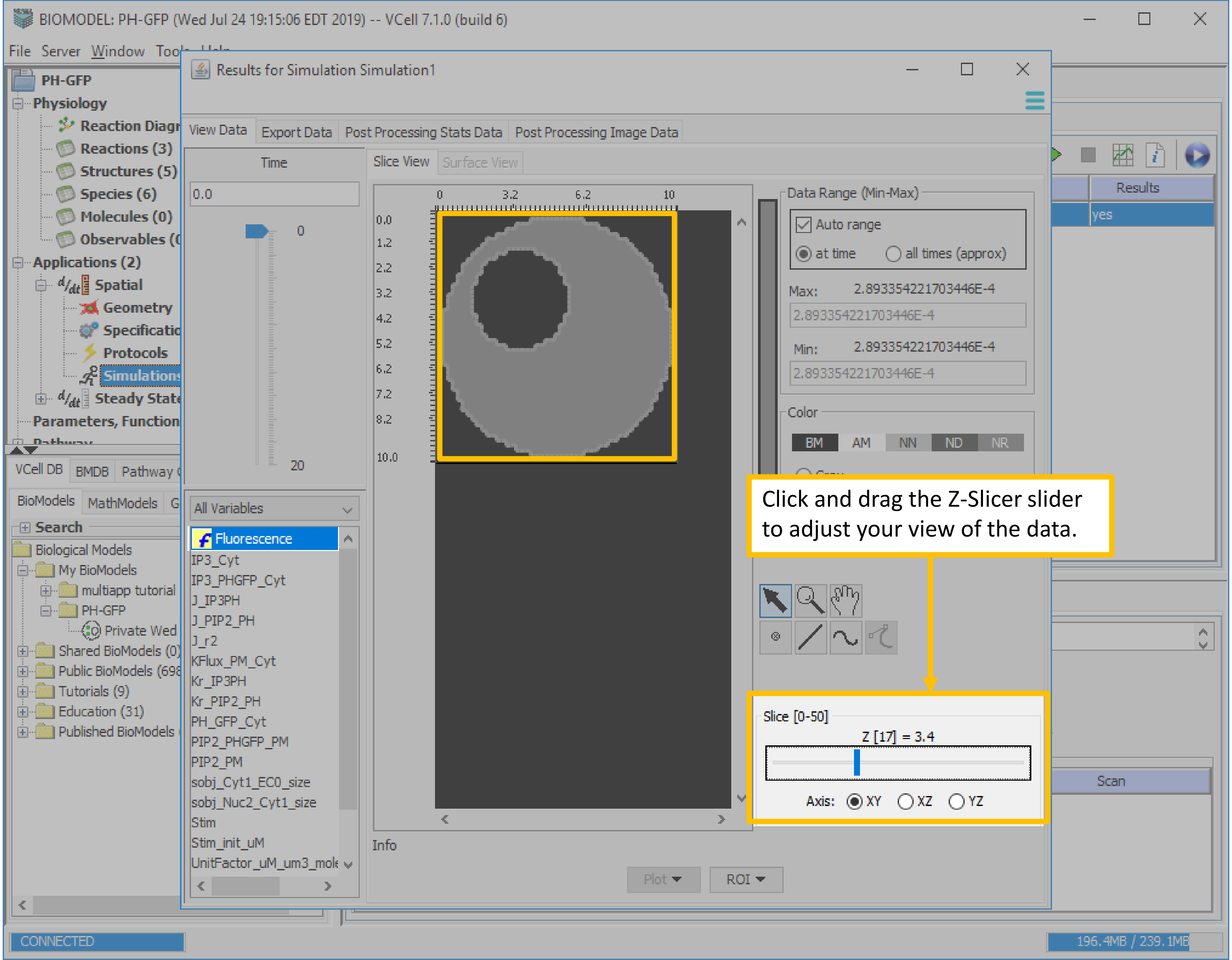
Max timestep	Output	Rel tol	Abs tol
0.1s	every 0.2 sec	1.0E-7	1.0E-9

Mesh: 51x51x51 = 132651 elements

Geometry size: (10.0,10.0,10.0) microns

Parameters with values changed from defaults

Parameter Name	Default	New Value/Expression	Scan



Data Range (Min-Max)

☑ Auto range

● at time ○ all times (approx)

Max: 2.893354221703446E-4

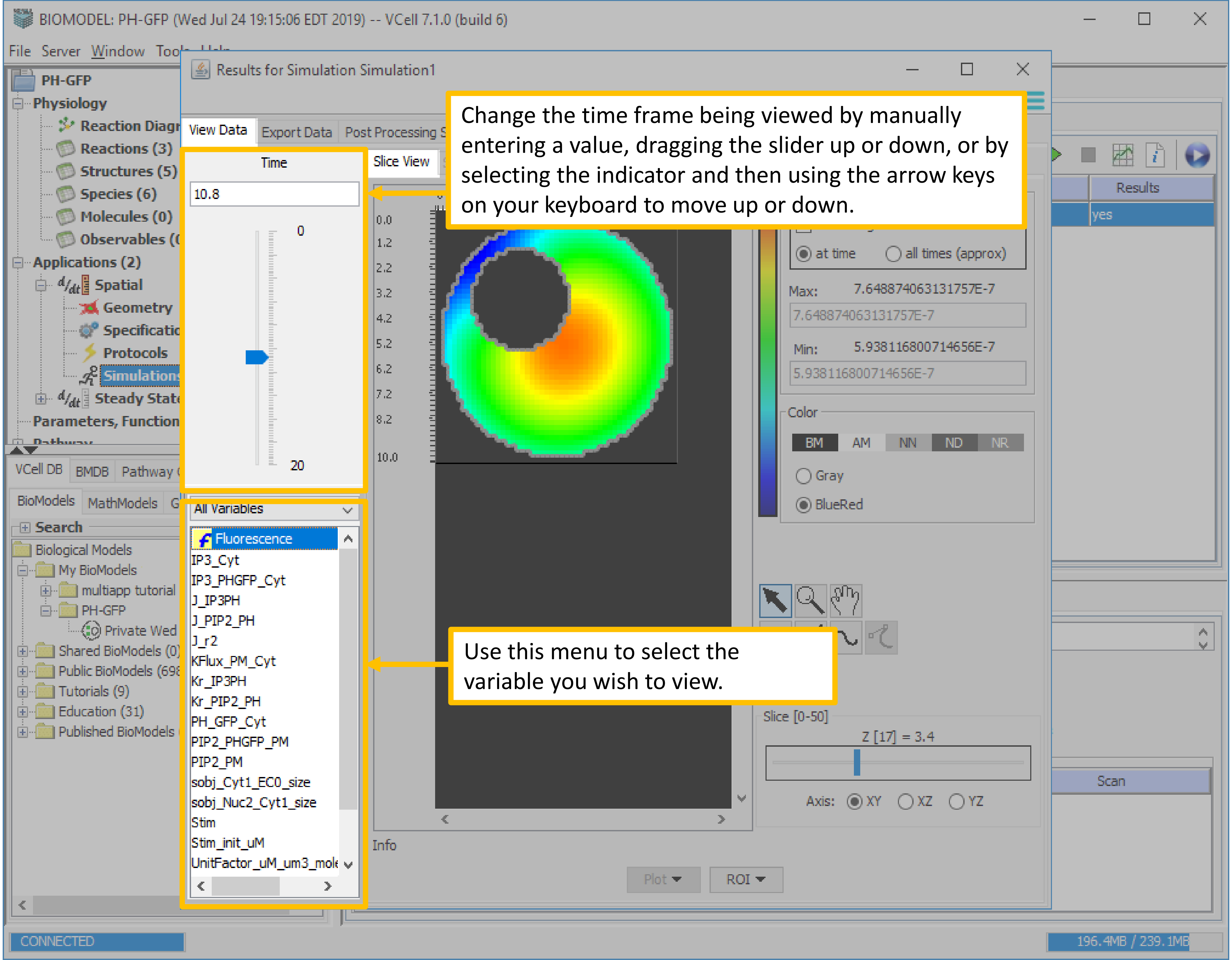
Min: 2.893354221703446E-4

Slice [0-50]

Z [17] = 3.4

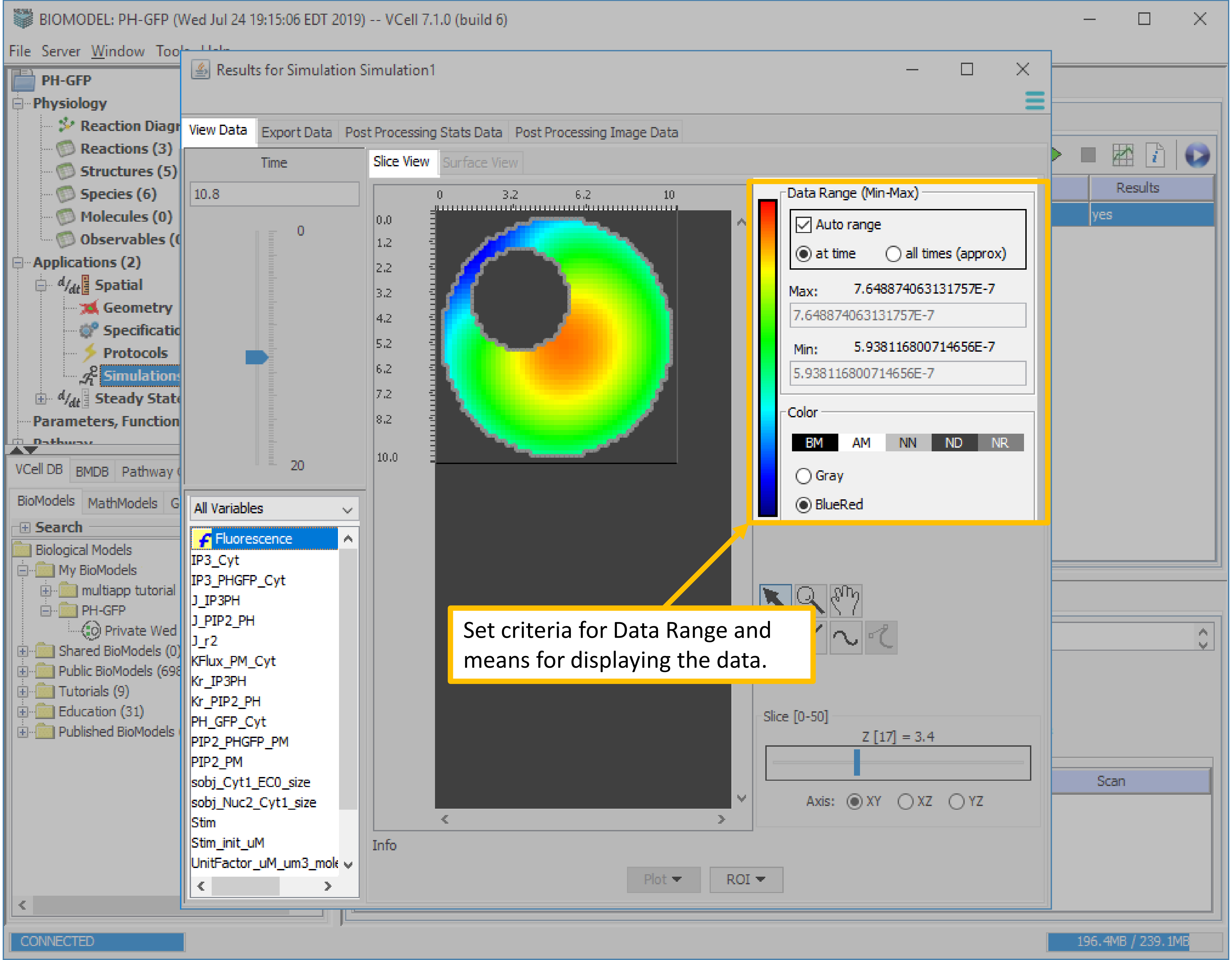
Axis: ● XY ○ XZ ○ YZ

Click and drag the Z-Slicer slider to adjust your view of the data.



Change the time frame being viewed by manually entering a value, dragging the slider up or down, or by selecting the indicator and then using the arrow keys on your keyboard to move up or down.

Use this menu to select the variable you wish to view.



Time: 10.8

☑ Auto range

● at time ○ all times (approx)

Max: 7.648874063131757E-7

Min: 5.938116800714656E-7

○ Gray

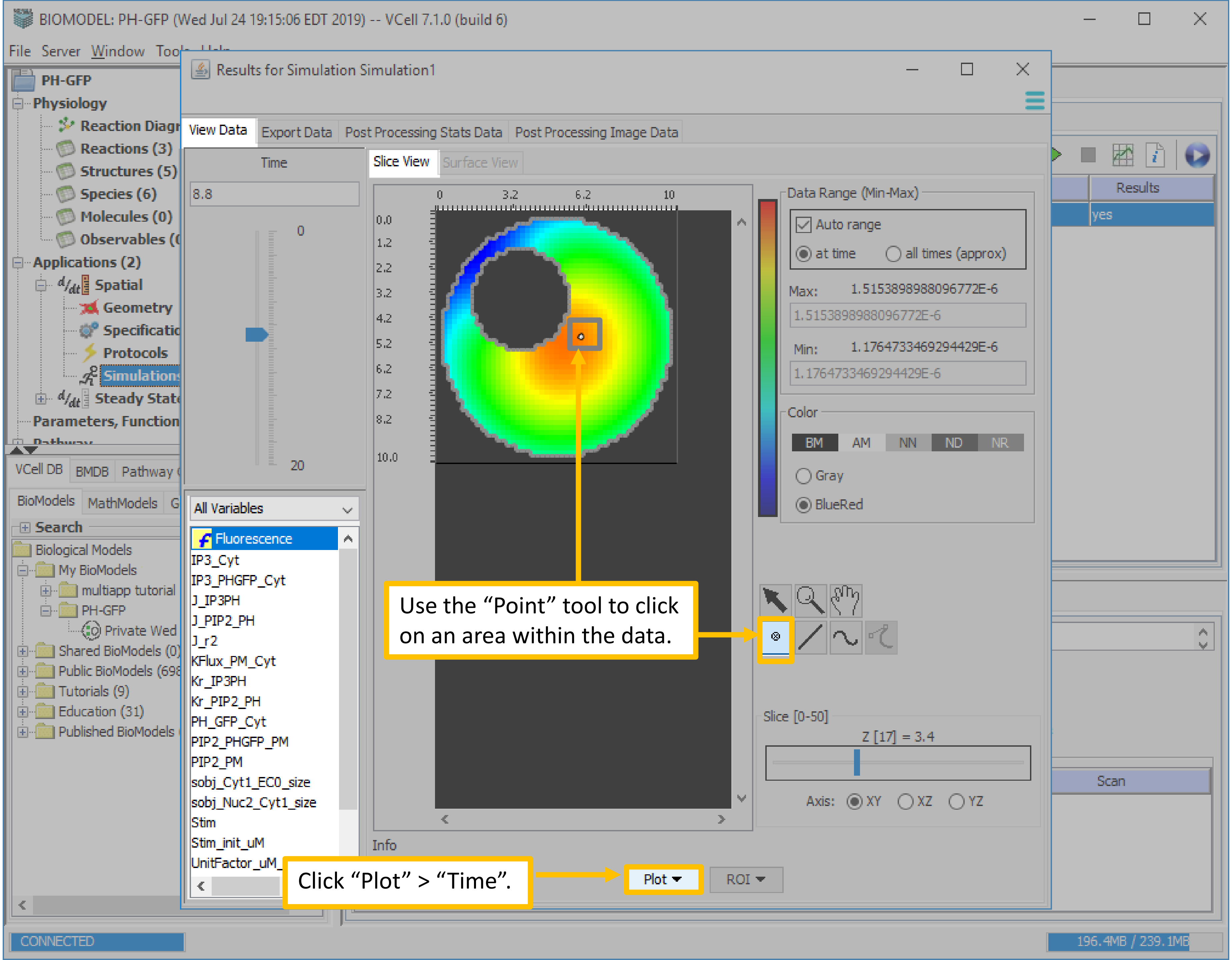
● BlueRed

Slice [0-50]

Z [17] = 3.4

Axis: ● XY ○ XZ ○ YZ

Set criteria for Data Range and means for displaying the data.



BIOMODEL: PH-GFP (Wed Jul 24 19:15:06 EDT 2019) -- VCell 7.1.0 (build 6)

Results for Simulation Simulation1

Time: 8.8

Max: 1.5153898988096772E-6

Min: 1.1764733469294429E-6

☑ Auto range

● at time ○ all times (approx)

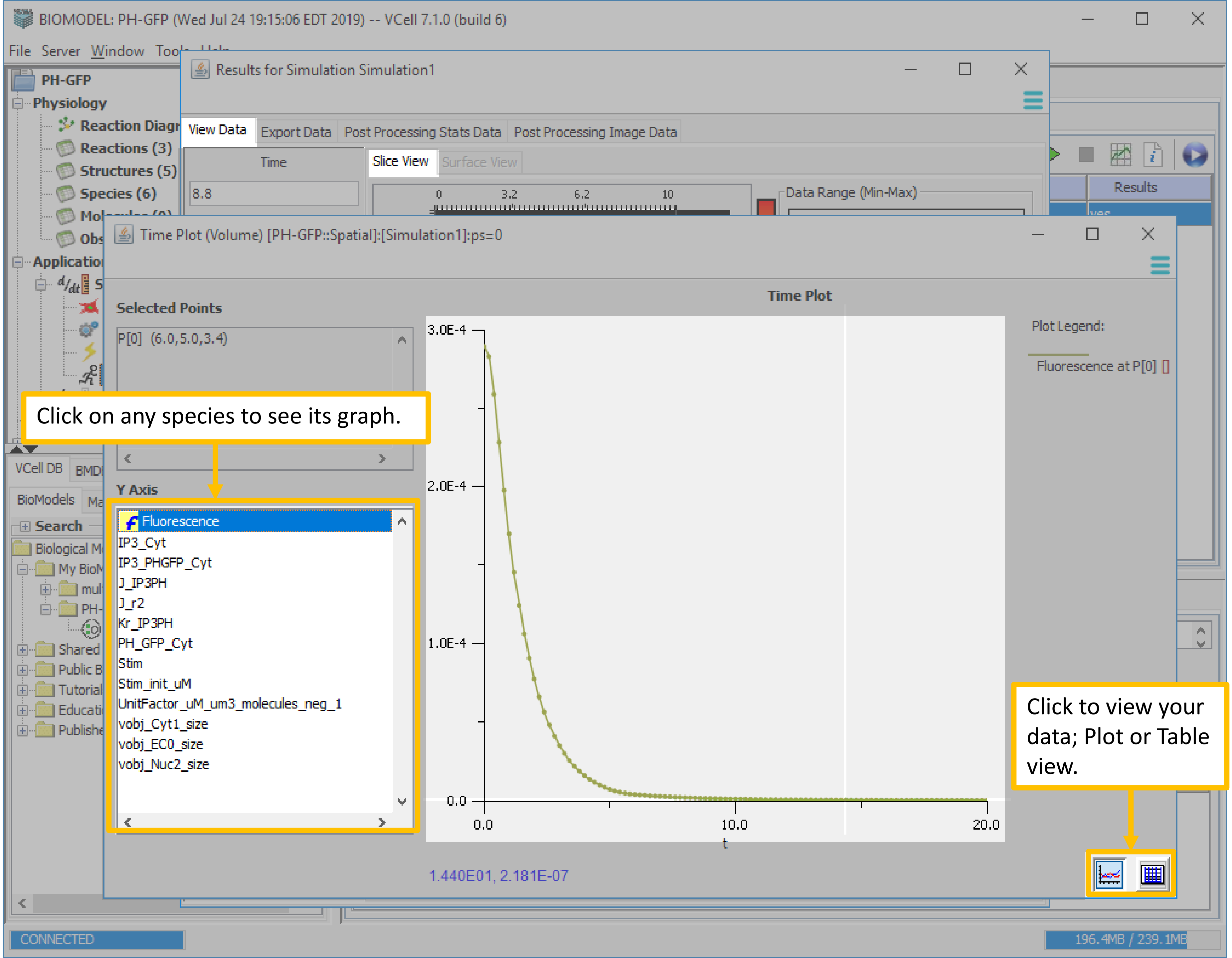
○ Gray ● BlueRed

Slice [0-50] Z [17] = 3.4

Axis: ● XY ○ XZ ○ YZ

Use the “Point” tool to click on an area within the data.

Click “Plot” > “Time”.



Click on any species to see its graph.

Click to view your data; Plot or Table view.

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