

Simmune and Its Support to SBML and SBML packages

Fengkai Zhang, Bastian Angermann and Martin Meier-Schellersheim

Computational Biology Unit

Laboratory of Systems Biology

National Institute of Allergy and Infectious Disease

National Institutes of Health, USA

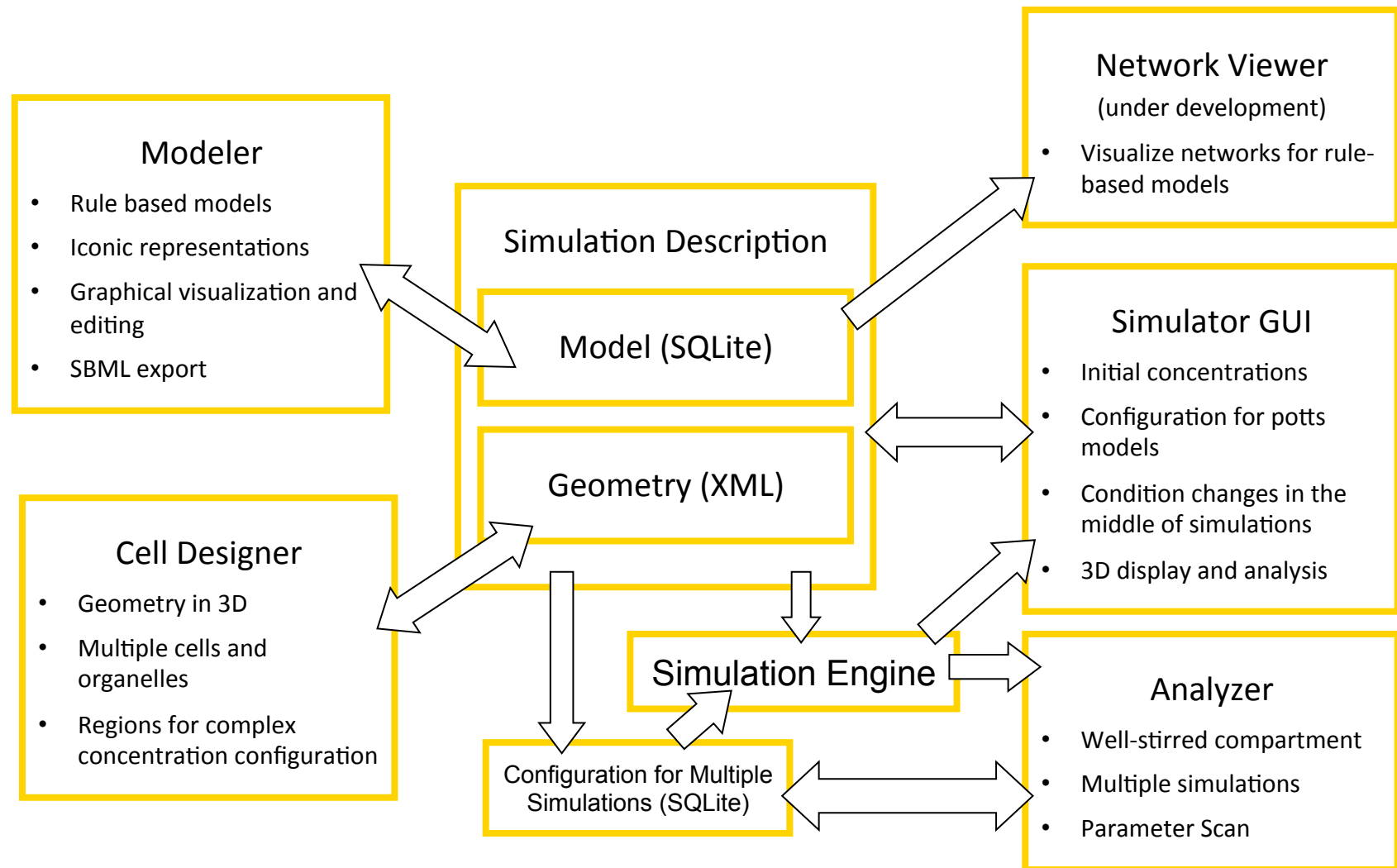
COMBINE, Paris 2013



Outline

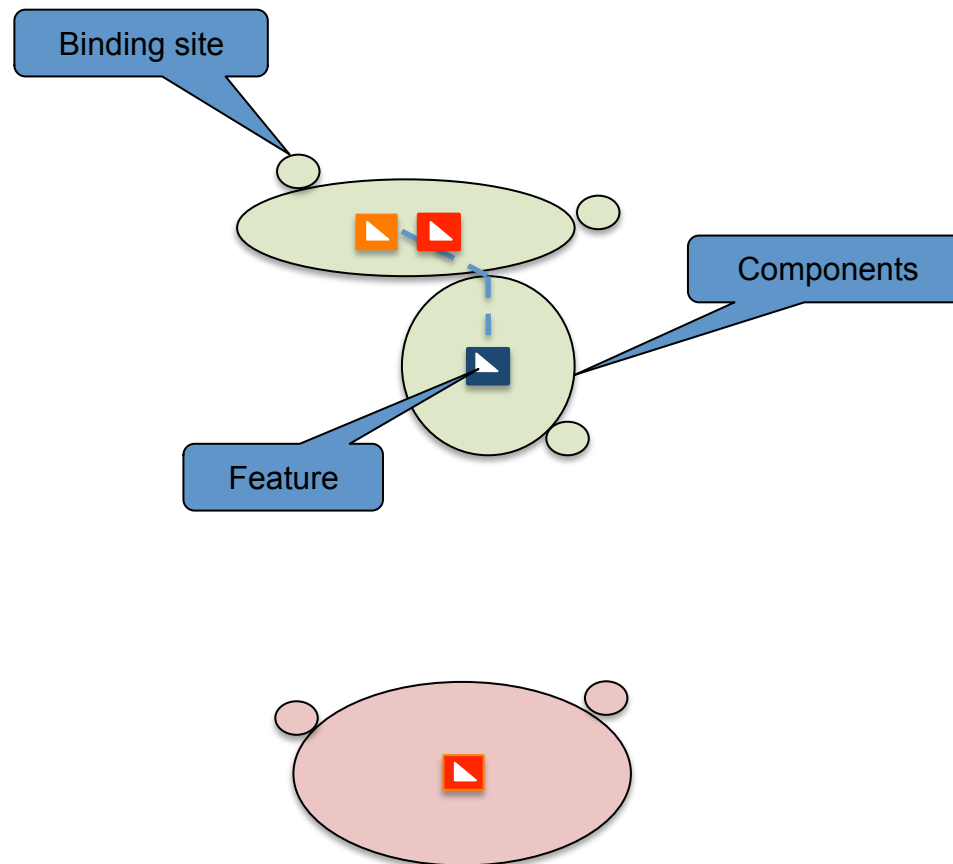
- Simmune infrastructure and work flow
- Simmune graphical representations
- Simmune: (Yeast Model)
 - Simmune Modeler
 - Simmune CellDesigner
 - Simmune Simulator
- SBML support

Simmune Structure and Workflow



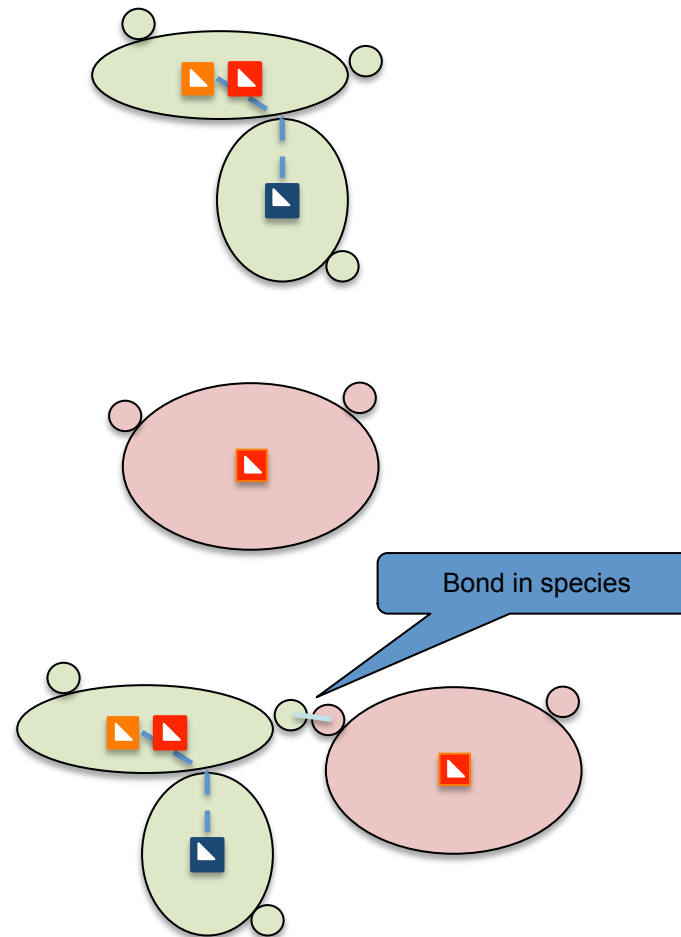
Graphical Representation of Simmune Models

Molecule: Component, binding sites, features



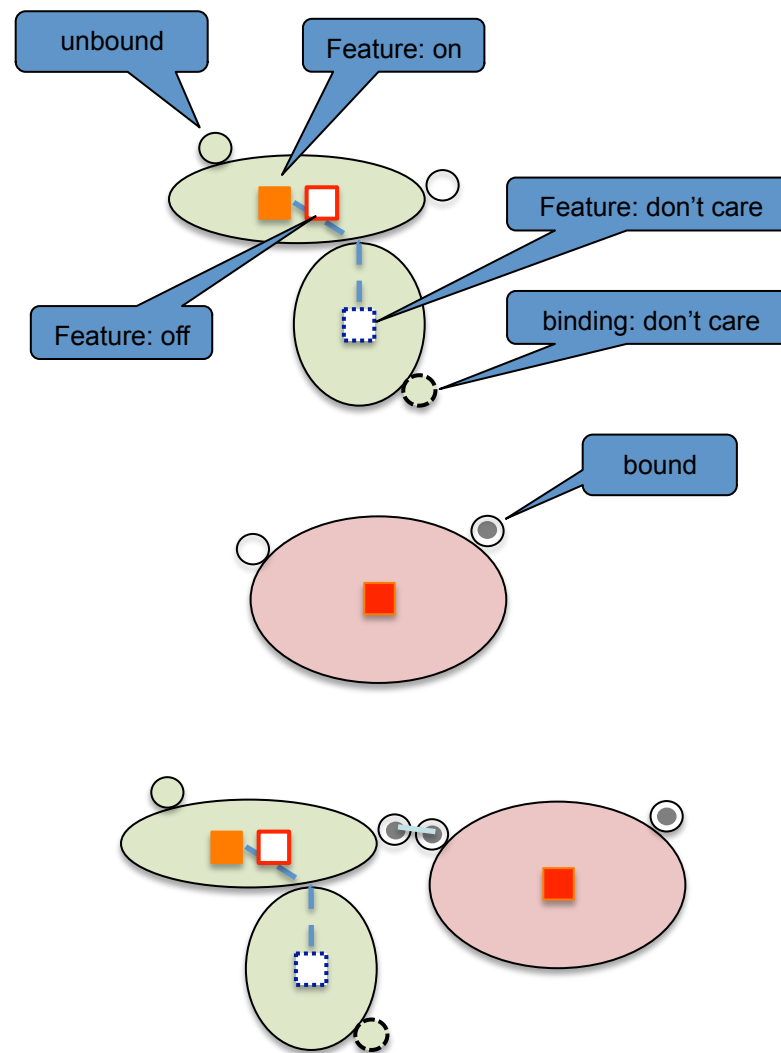
Graphical Representation of Simmune Models

Complex Species



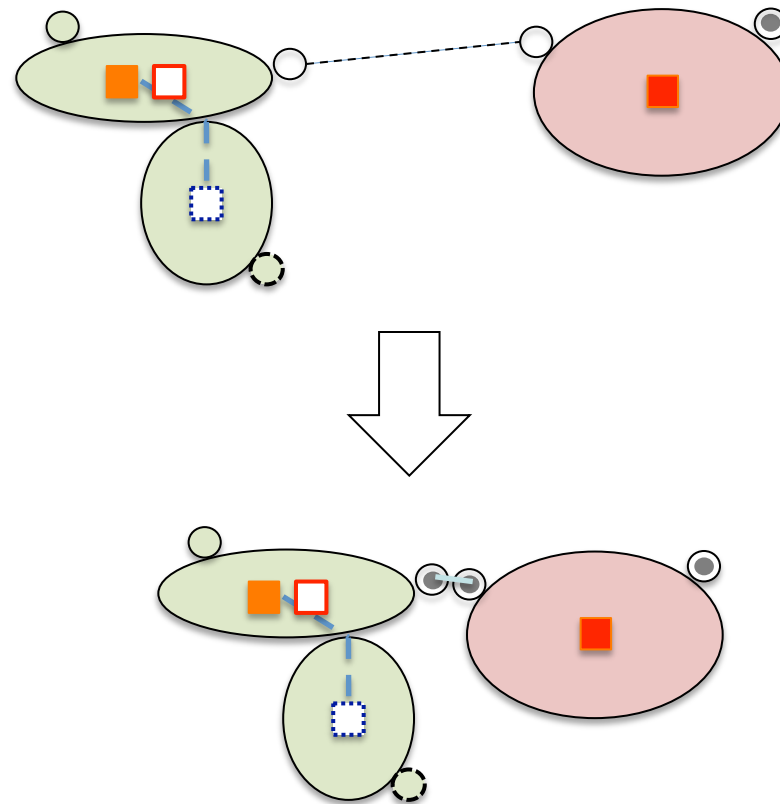
Graphical Representation of Simmune Models

Complex



Graphical Representation of Simmune Models

Reaction



Simmune Modeler: Yeast Model: Molecules

The screenshot displays the Simmune Modeler 2.1.0 software interface. The title bar indicates the current model file is `C:/Program Files (x86)/Simmune 2.1.1909/examples/data/models/YeastMAPK.dbf`. The menu bar includes `Model`, `View`, `Tools`, and `Help`. The toolbar contains icons for file operations and model management.

The **Molecules** tab is active, showing a list of molecules on the left and a central workspace. The molecule list includes:

- Cdc14
- Dig
- Fus3
- Fus3_anchor
- Gbg
- MP2C
- Msg5

The central workspace shows a molecule (Ste11) with two binding sites, labeled 1 and 2. The molecule is represented by a blue oval with a red square in the center. The binding sites are indicated by small red squares on the molecule.

On the right, the **Molecule Interactions** tab is active, showing a list of interactions:

- mli-000004
- mli-000005
- mli-000013

The **Properties of Molecule** panel on the right shows the following details for the selected molecule (Ste11):

- Short Name: Ste11
- Full Name: Ste11
- Type: Protein
- Diff_Coeff: 4 microns²/s
- Category: Kinase
- Accession:
- Annotation: Ste11 is the kinase (MAPKKK) activating Ste7 (MAPKK) in a Ste5-dependent manner during the pheromone response of yeast. The diffusion coefficient was specified based on the measurements of the Fus3 diffusion coefficient in yeast (Maeder et al. Nat Cell Biol. 2007 Nov;9(11):1319-26.) and assuming a dependence of the diffusion coefficient on the cubic root of the molecule mass.

The **Molecule Composition** panel shows the following details for the selected molecule (Ste11):

- Molecule: Ste11
- Molecule component 1: mcp-000005
- Binding site 1: activation site
- Binding site 2: Ste5 binding site

A note at the bottom of the Molecule Composition panel states: "Note: Related items found, can NOT add/remove."

Simmune Modeler: Yeast Model: **Complex Species**

The screenshot displays the Simmune Modeler 2.1.0 interface. The title bar indicates the current model file is 'C:/Program Files (x86)/Simmune 2.1.1909/examples/data/models/YeastMAPK.dbf'. The main window is divided into several panels:

- Complexes Panel (Left):** Lists various species including Gbg_Ste5, MP2C, MP2C_St..., Msg5, Msg5_Fus3, and Spa2p. It includes 'New', 'View', and 'Delete' buttons.
- Complex Species Panel (Center):** Shows a visual representation of the 'MP2C_Ste11' complex. It consists of two blue ovals, one labeled '1' and the other '2'. Oval 1 contains a red square with a white triangle. Oval 2 contains a blue circle with a white triangle. The panel includes 'Edit Options' (Move, Change Layout, Rotate +90°, Rotate -90°, Flip) and action buttons (Enable Editing, Clear, Create A Copy, Delete).
- Composition Panel (Bottom Left):** Shows the hierarchical structure of the complex species.
 - Complex Species: MP2C_Ste11
 - Molecule 1: Ste11
 - Molecule component 1: mcp-000005
 - Binding site 1: activation site
 - Binding site 2: Ste5 binding site
 - Molecule 2: MP2C
 - Molecule component 1: mcp-000009
 - Binding site 1: bst-000016

A yellow note at the bottom of this panel states: 'Note: Related items found, can NOT add/remove.'

- Properties of Complex Species Panel (Bottom Right):** Fields for 'Short Name' (MP2C_Ste11), 'Full Name' (MP2C_Ste11), 'Accession', and 'Annotation'.
- Relations Panel (Right):** Lists various relations including 'Complex' (MP2C_Ste11_1, MP2C_pSte11, MP2C_Ste11_2), 'Transformation' (Ste11 dephosphorylation), 'Association' (As Source, As Result), and 'MP2C_pSte11 assoc'. It includes 'New', 'View', and 'Delete' buttons.

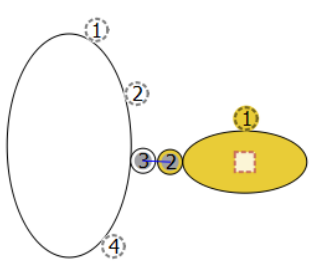
Simmune Modeler: Yeast Model: **Complex**

Simmune Modeler 2.1.0 (current model file: C:/Program Files (x86)/Simmune 2.1.1909/examples/data/models/YeastMAPK.dbf)

Model View Tools Help

Model Molecule Complex

Complex



Complex Name: Ste5_Ste7_all
Species Name: Ste5_Ste7
Annotation:
☐ Display in Complex List

Save
Back
Delete

Relations

New View Delete

Transformation

As Source

As Result

Association

As Source

As Result

Ste5_Ste7 assoc

Dissociation

As Source

Ste5_Ste7 dissoci

Molecule Component Tag States and Binding Status

Component	State
Complex	
Molecule 1: Ste5	
Molecule Component 1: mcp-000004	
Binding Sites	
1: Gbg binding site	Don't Care
2: Ste11 binding site	Don't Care
3: Ste7 binding site	Bound
4: Fus3 binding site	Don't Care
Molecule 2: Ste7	
Molecule Component 1: mcp-000006	
Tag	
phosphorylated	Don't Care
Binding Sites	
1: activation site	Don't Care
2: Ste5 binding site	Bound

Simmune Modeler: Yeast Model: Reaction

Simmune Modeler 2.1.0 (current model file: C:/Program Files (x86)/Simmune 2.1.1909/examples/data/models/YeastMAPK.dbf)

Model View Tools Help

Model Molecule Complex

Complex Association

Add Complex

Species: Cdc14
Species: Cdc14_Ste7
Species: Dig
Species: Fus3
Species: Fus3.Ste5.Ste7
Species: Fus3_Dig

☐ Show Complexes and Species
☒ Show Complex Species Only
☐ Display Hidden Complexes

Source Complexes

Rotate +90° Rotate -90° Flip Reset Interaction

Result Complex

Save Back Delete

☒ No orientation
☐ trans-binding
☐ cis-binding

☐ Display Molecule Mapping

Assoc Name: MP2C_pSte11 assoc
Assoc Rate: 1e+06
Rate Unit: 1/mol*s
☐ 2D ☒ 3D ☐ Intra Complex
Annotation:

Create Reverse Dissociation

Source Complex 1

Complex Name: pSte11_unbound Save Complex
Species Name: Ste11 Select Complex
☐ Display in Complex List

Component	State
Complex: pSte11_unbound	
Molecule 1: Ste11	
Molecule Component 1: mcp-000005	
Tag	
phosphorylated	On
Binding Sites	
1: activation site	Unbou
2: Ste5 binding site	Unbou

Source Complex 2

Complex Name: MP2C Save Complex
Species Name: MP2C Select Complex
☒ Display in Complex List

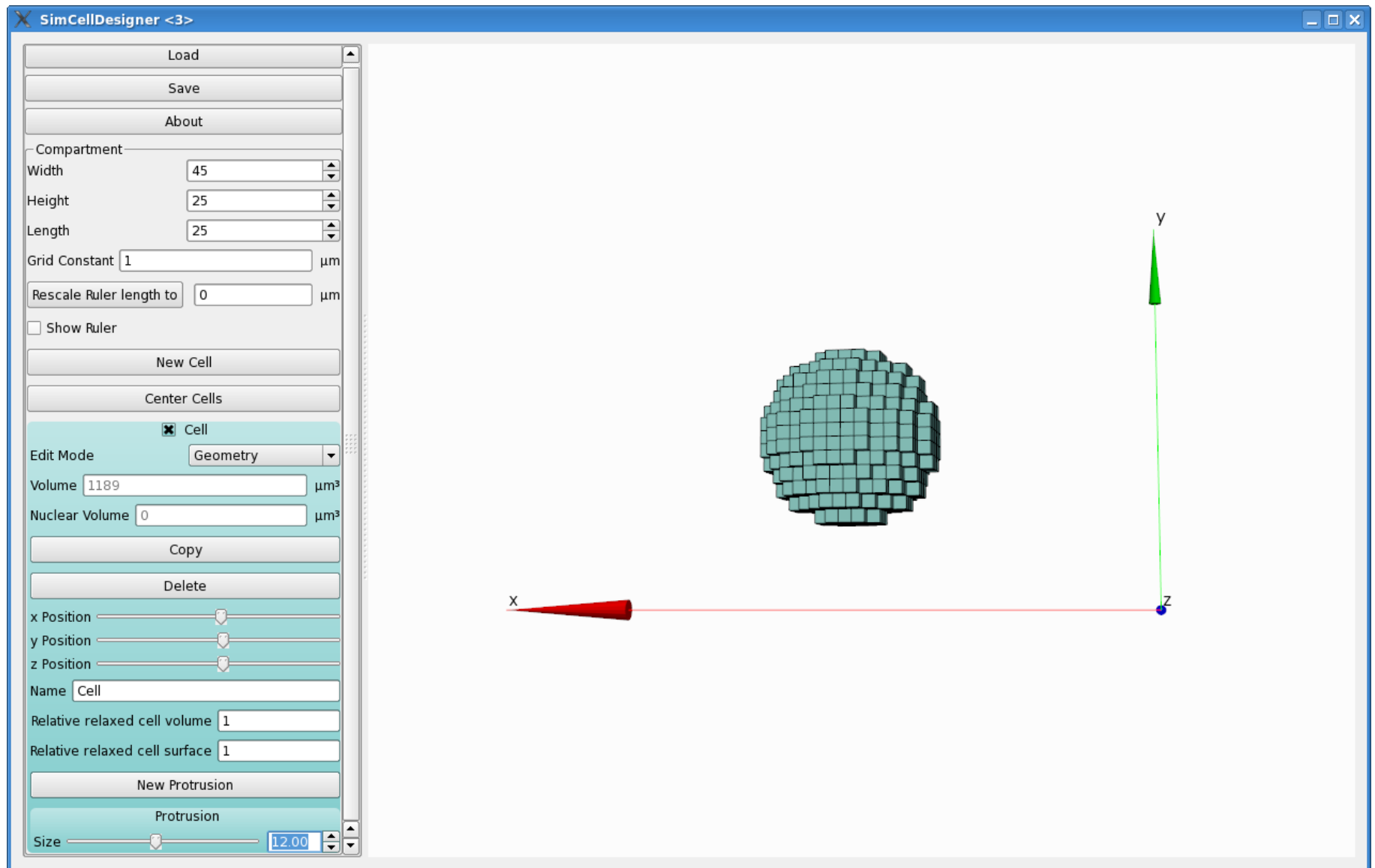
Component	State
Complex: MP2C	
Molecule 1: MP2C	
Molecule Component 1: mcp-000009	
Binding Site	
1: bst-000016	Unbound

Result Complex

Complex Name: MP2C_Ste11_1 Save Complex
Species Name: MP2C_Ste11 Select Complex
☐ Display in Complex List

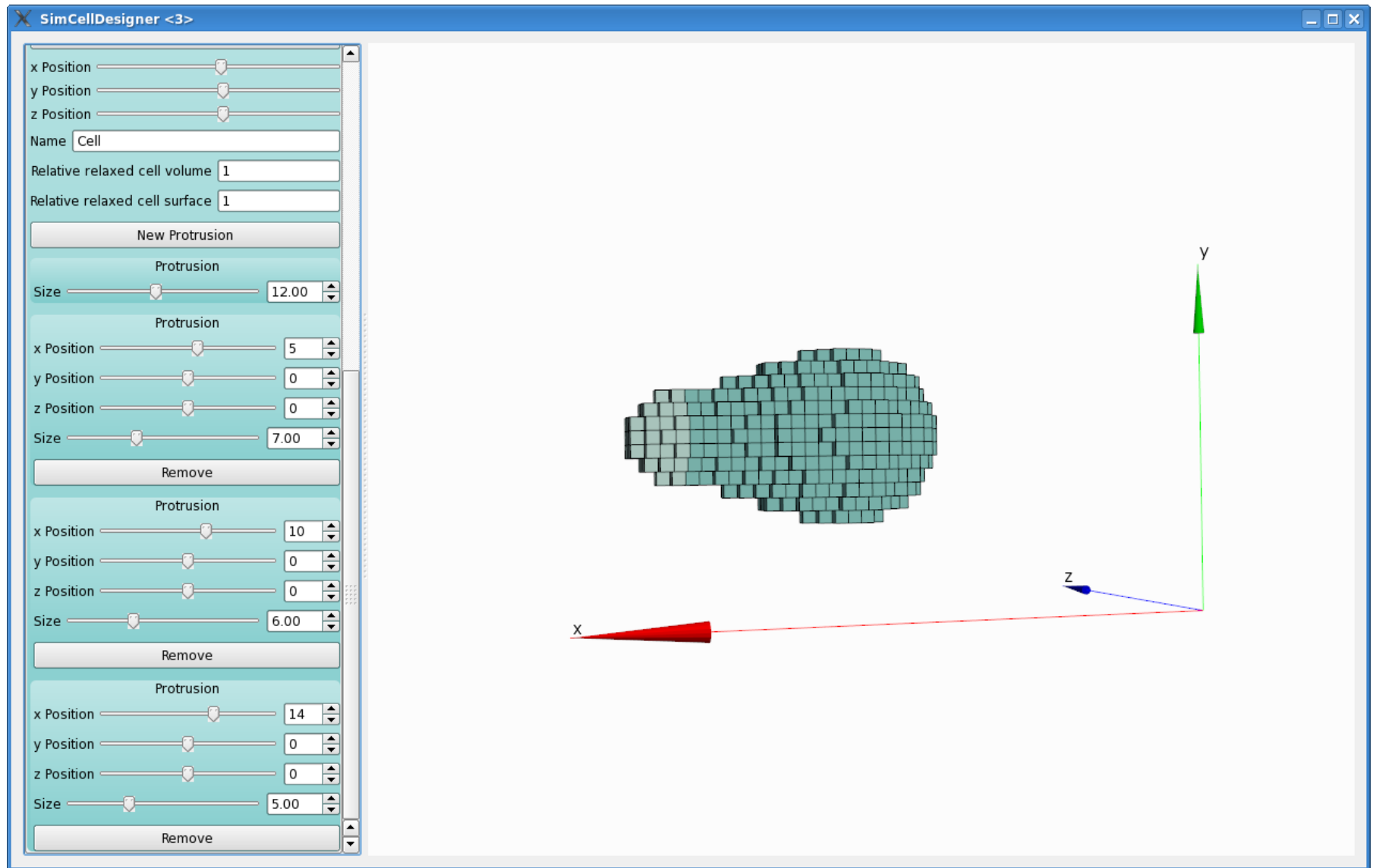
Component	State
Complex: MP2C_Ste11_1	
Molecule 1: Ste11	
Molecule Component 1: mcp-000005	
Tag	
phosphorylated	On
Molecule 2: MP2C	
Molecule Component 1: mcp-000009	

SimCellDesigner: Yeast Geometry: Cell

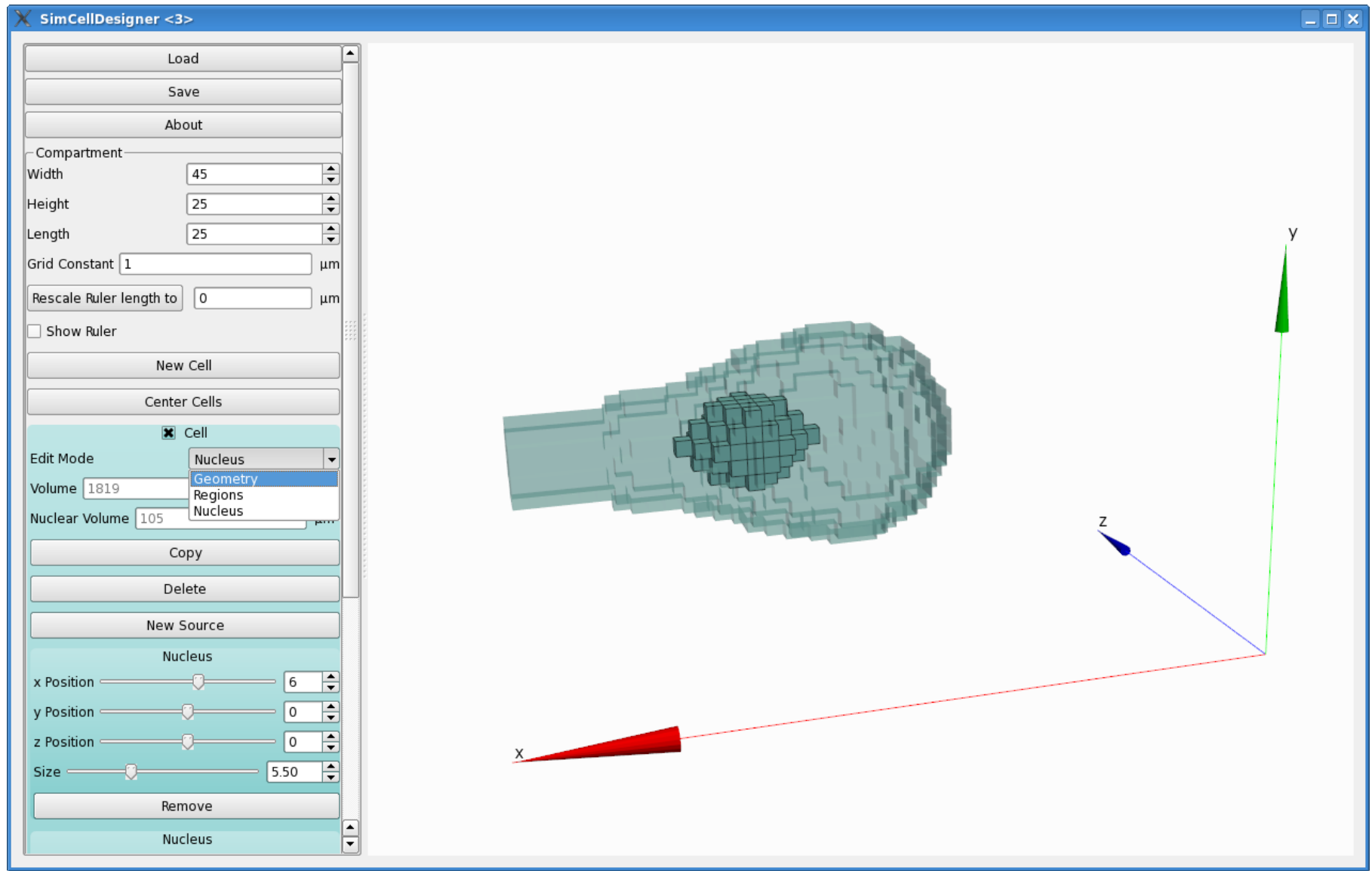


Simmune CellDesigner: Yeast Geometry:

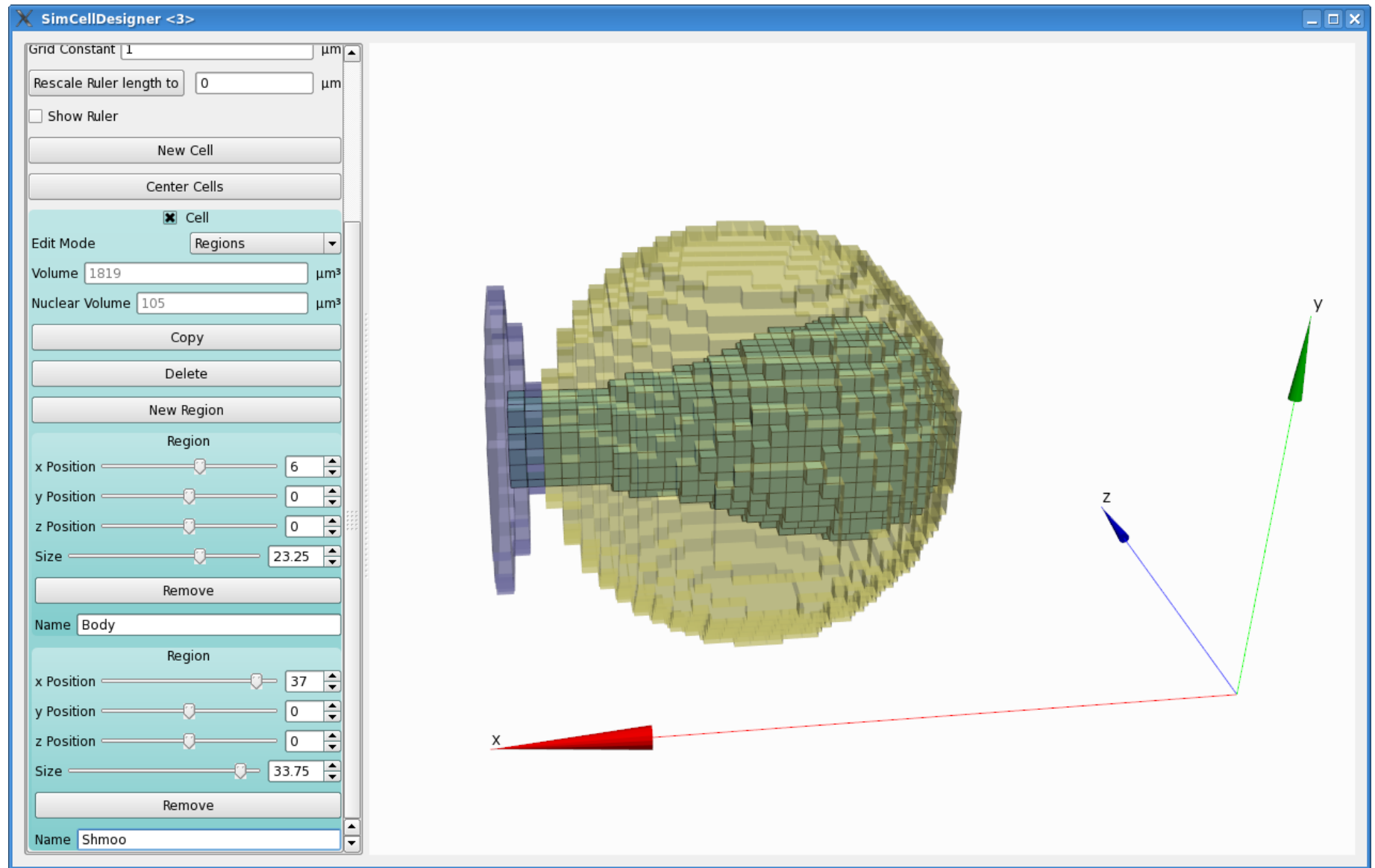
Flexible Cell Shape Configuration



Simmune CellDesigner: Yeast Geometry: **Oganelle**



Simmune CellDesigner: Yeast Geometry: Regions



Simmune Simulation : Yeast : Initial Condition

SimulatorGui

Select a cell to populate
Cell

Select a region to populate
Body

Select an organelle to populate
Cytosol

Select a complex to populate the region with
Cdc14

☐ Create membrane pore ☒ 3d concentration

Concentration Set mol/l

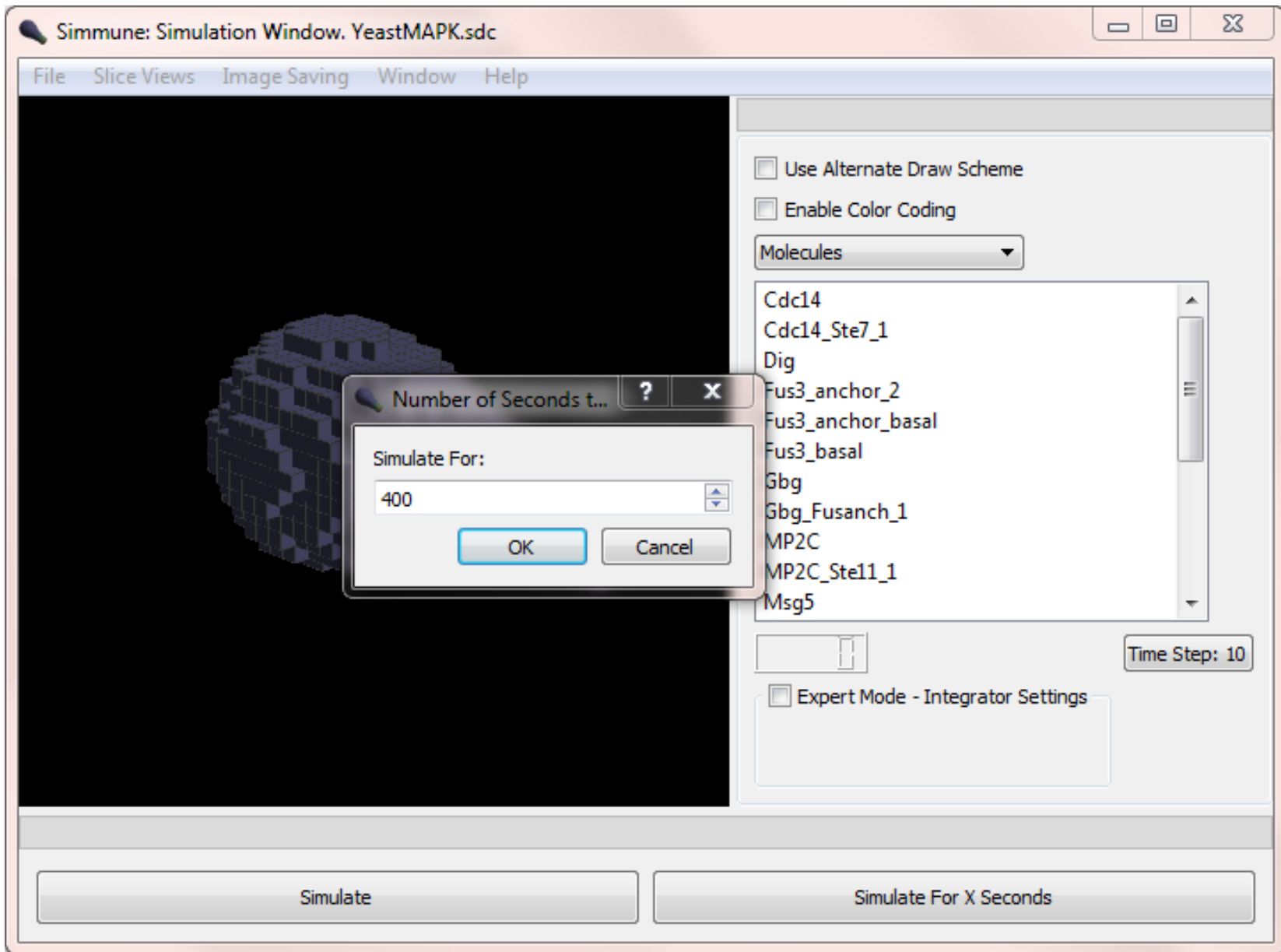
Cell	Region	Organelle	Complex	Concentration
Cell	Body	Cytosol	Msg5	1.5e-07
Cell	Body	Nucleus (Exporting...	Fus3_basal	33
Cell	Body	Cytosol	Ste7_basal	9e-08
Cell	Body	Cytosol	Ste20_inactive	1e-07
Cell	Body	Nucleus (Importin...	pFus3_free	100
Cell	Shmoo	Cytosol (Membrane)	Fus3_anchor_basal	400
Cell	Body	Nucleus (Exporting...	Msg5	100
Cell	Shmoo	Cytosol (Membrane)	Spa2p	80
Cell	Body	Cytosol	MP2C	3e-08
Cell	Body	Nucleus (Importin...	Msg5	66
Cell	Body	Cytosol	Ste11_basal	3.3e-08
Cell	Body	Cytosol	Cdc14	6e-08
Cell	Body	Nucleus	Dig	8e-07

Delete

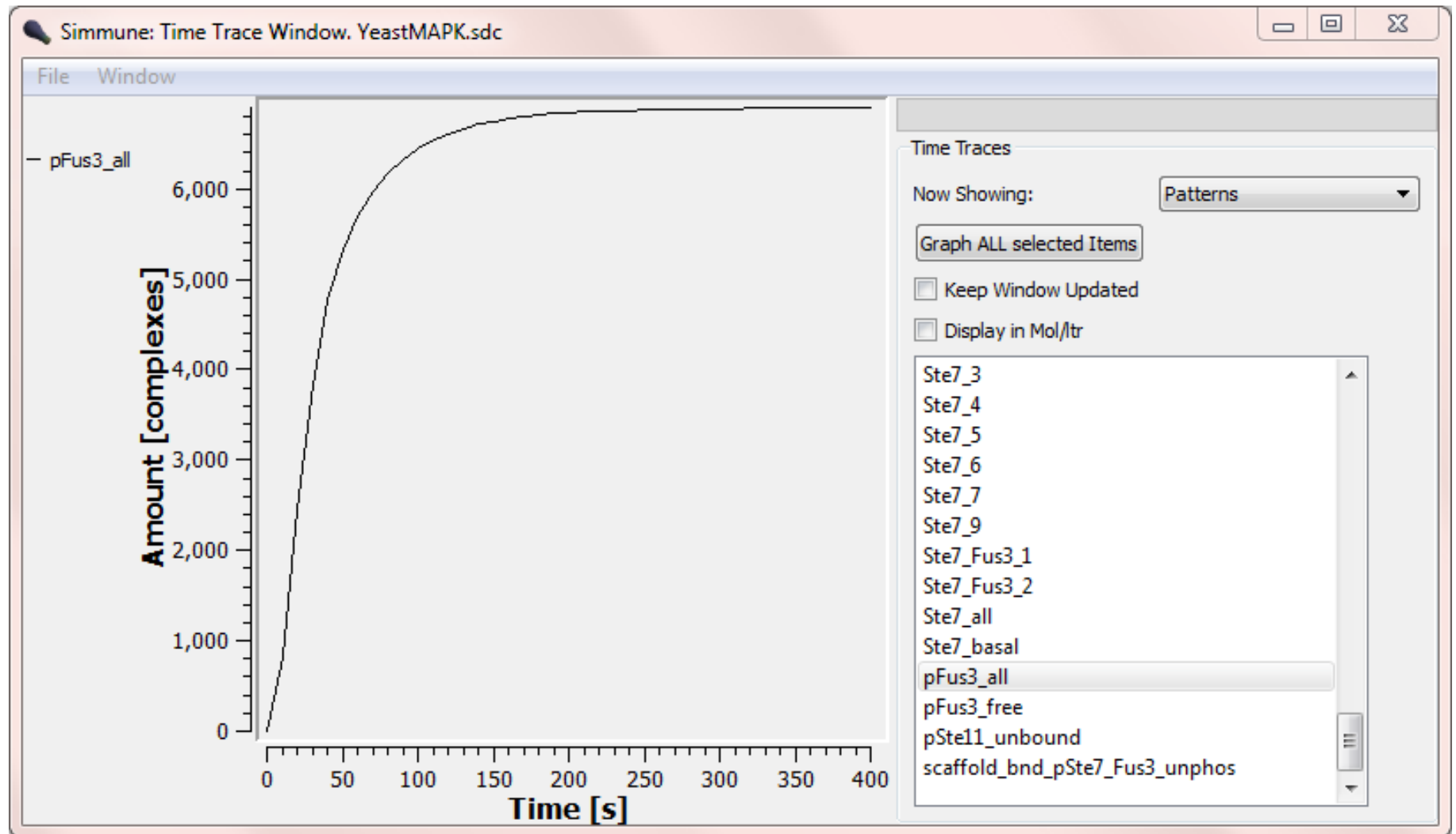
Maximum Complex Size 8

Ok

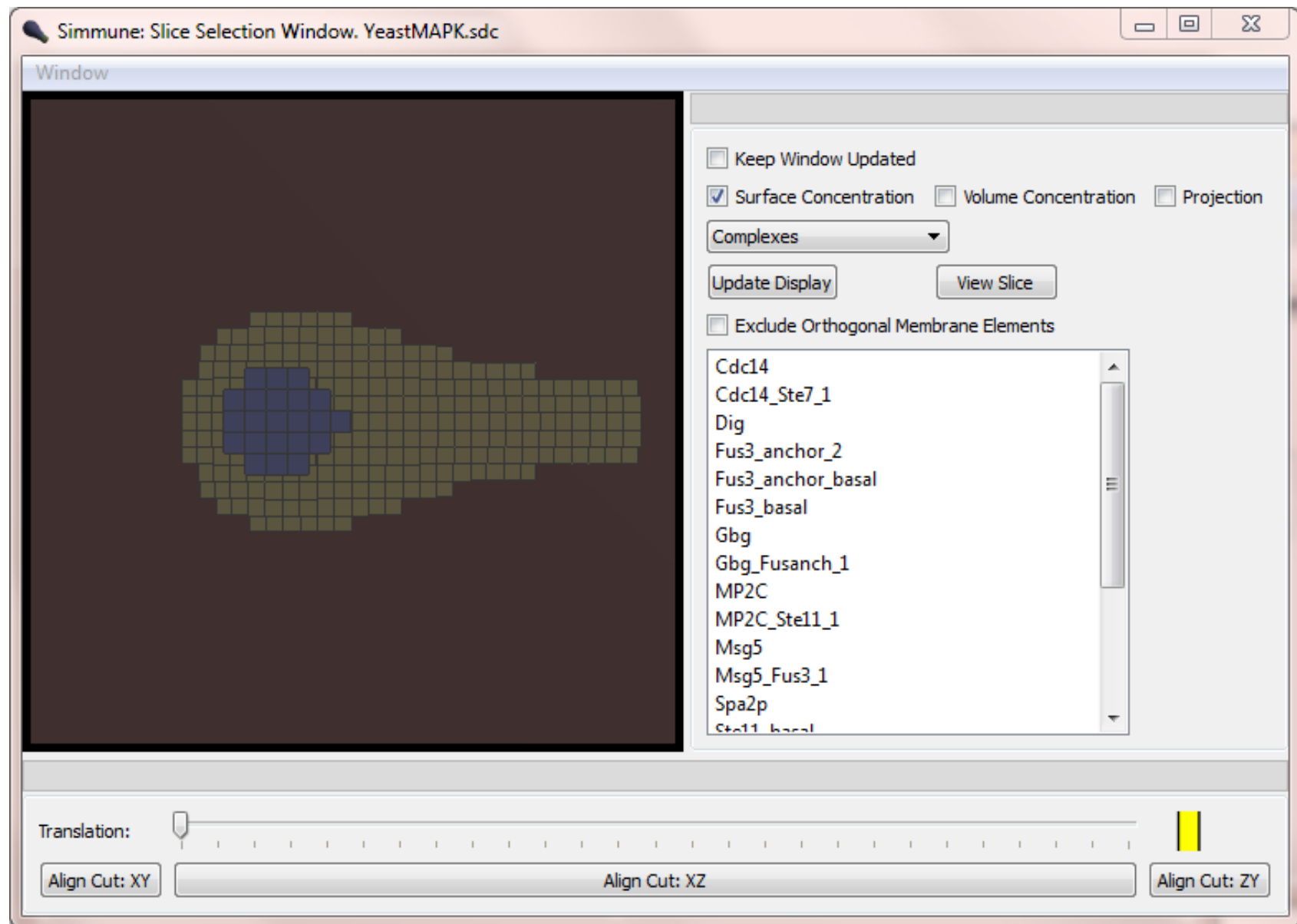
Simmune Simulation : Yeast : **Simulation Setup**



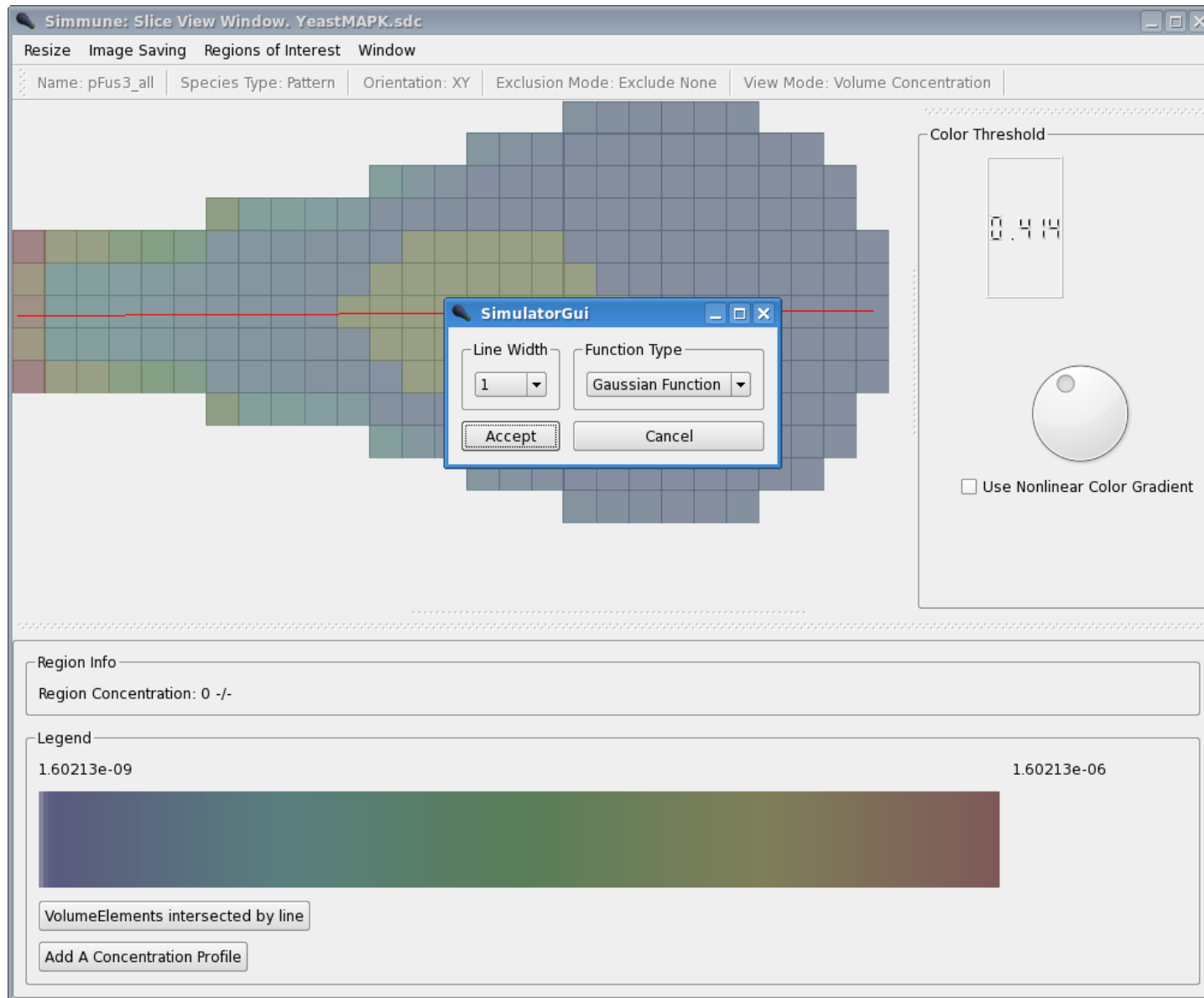
Simmune Simulation : Yeast : Time Plot



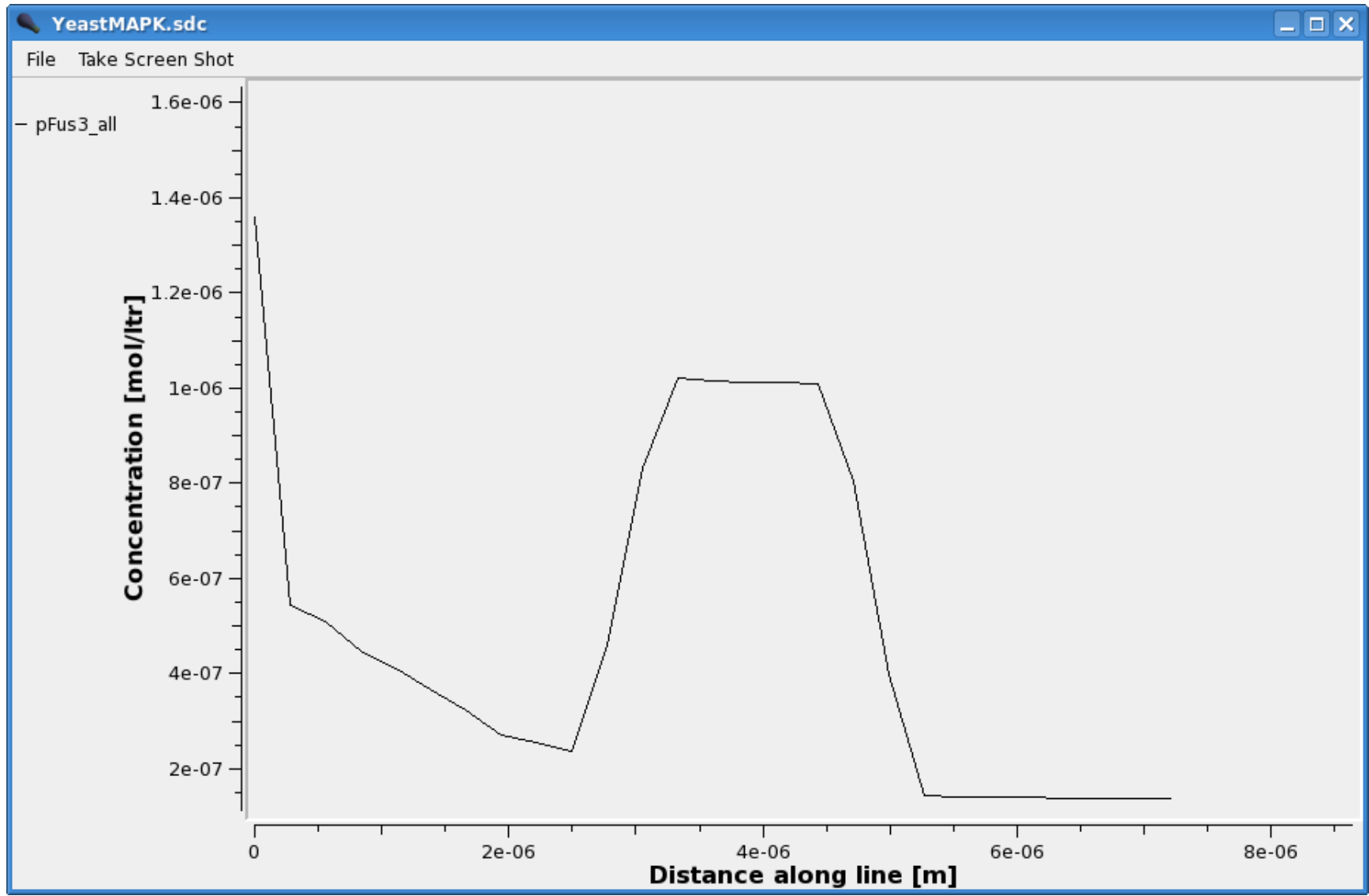
Simmune Simulation : Yeast : Concentration Distribution



Simmune Simulation : Yeast : Line Configuration



Simmune Simulation : Yeast : Concentration Line Profile



Simmune SBML Support

The image shows the Simmune Modeler 2.1.1 interface with two 'Export Simmune Model' dialog boxes. The background dialog shows the 'Export Simmune Model' window with fields for 'Initial Assignment Name', 'Compartment' (set to 'Cell (default)'), and a table of 'Completely Specified Complexes'.

		Complex Name	Concentration
1		A_1	1
2		A_2	1

The foreground dialog shows the 'Export Simmune Model SBML' window, displaying the generated SBML code. The code includes unit definitions for 'per_second' and 'litre_per_mole_second', a compartment definition for 'Cell', and species definitions for 'cpx_1', 'cpx_2', and 'cpx_3'. The SBML version is set to 3.1.

SBML
2.1, 2.4 or 3.1

Simmune SBML Support

Support SBML Packages:

- SBML-Multi: Rule – based models
(under development)
- SBML-Spatial: Geometry
(We are working on determining how the
'Spatial' package can be combined with multi.)

Other:

- SED-ML (under consideration)

Simmune

- Rule-based spatially resolved models of cellular signaling networks
- Implemented with Qt, boost, fortran, OpenGL, VTK, libSBML
- Runs on Linux, Mac and Windows
- Standalone and distributed (in progress)
- Free for non-commercial use and available for download at:
<http://go.usa.gov/QeH>

Acknowledgements

- Members of
Laboratory of Systems Biology (LSB)
National Institute of Allergy and Infectious Disease (NIAID)
National Institutes of Health (NIH) , USA
- Simmune Users
- This work was supported by the Intramural Research Program of the US
National Institute of Allergy and Infectious Diseases of the National
Institutes of Health.