

# Simmune and COMBINE Standards

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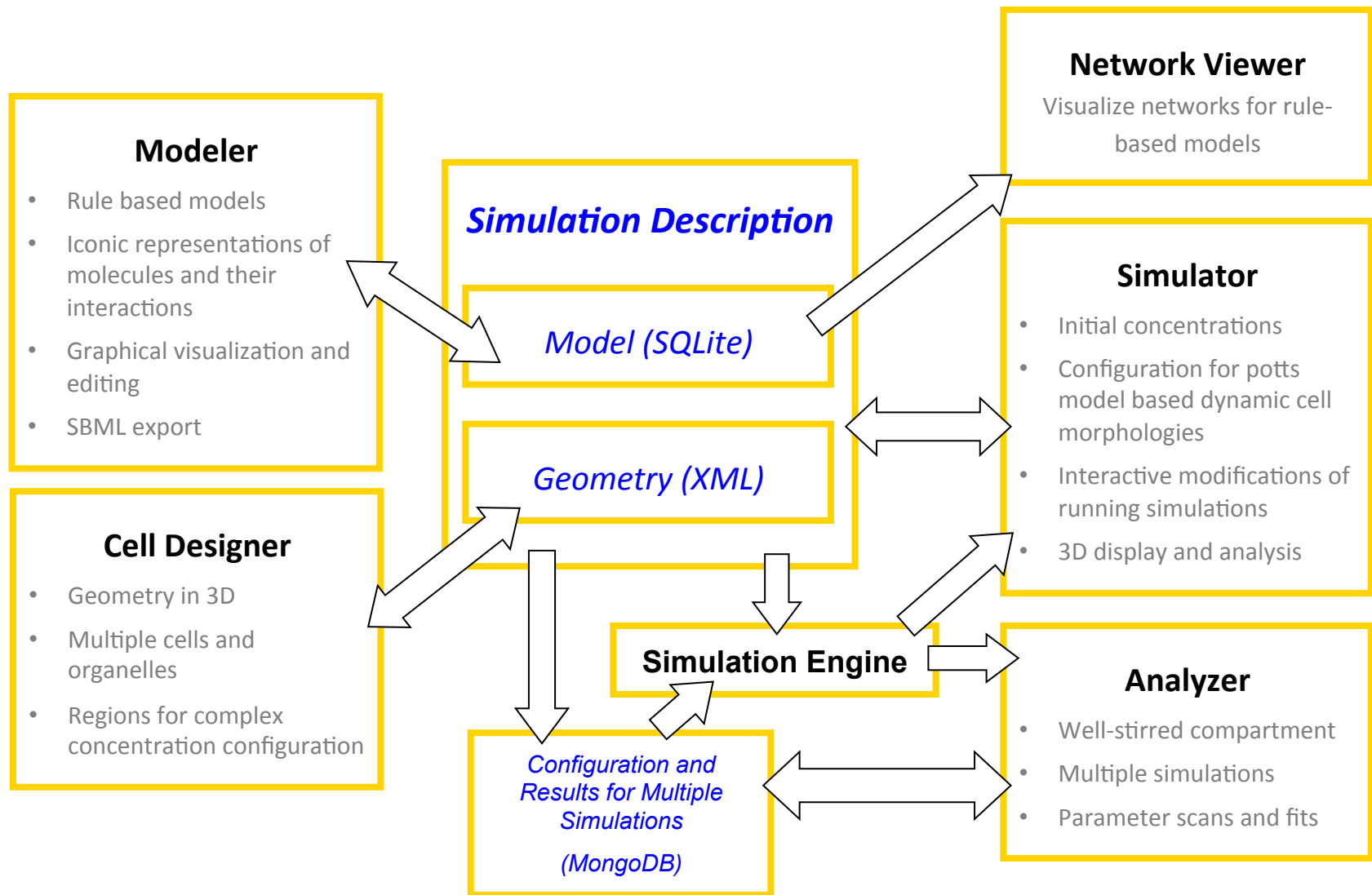
*National Institute of Allergy and Infectious Disease*

*National Institutes of Health, USA*

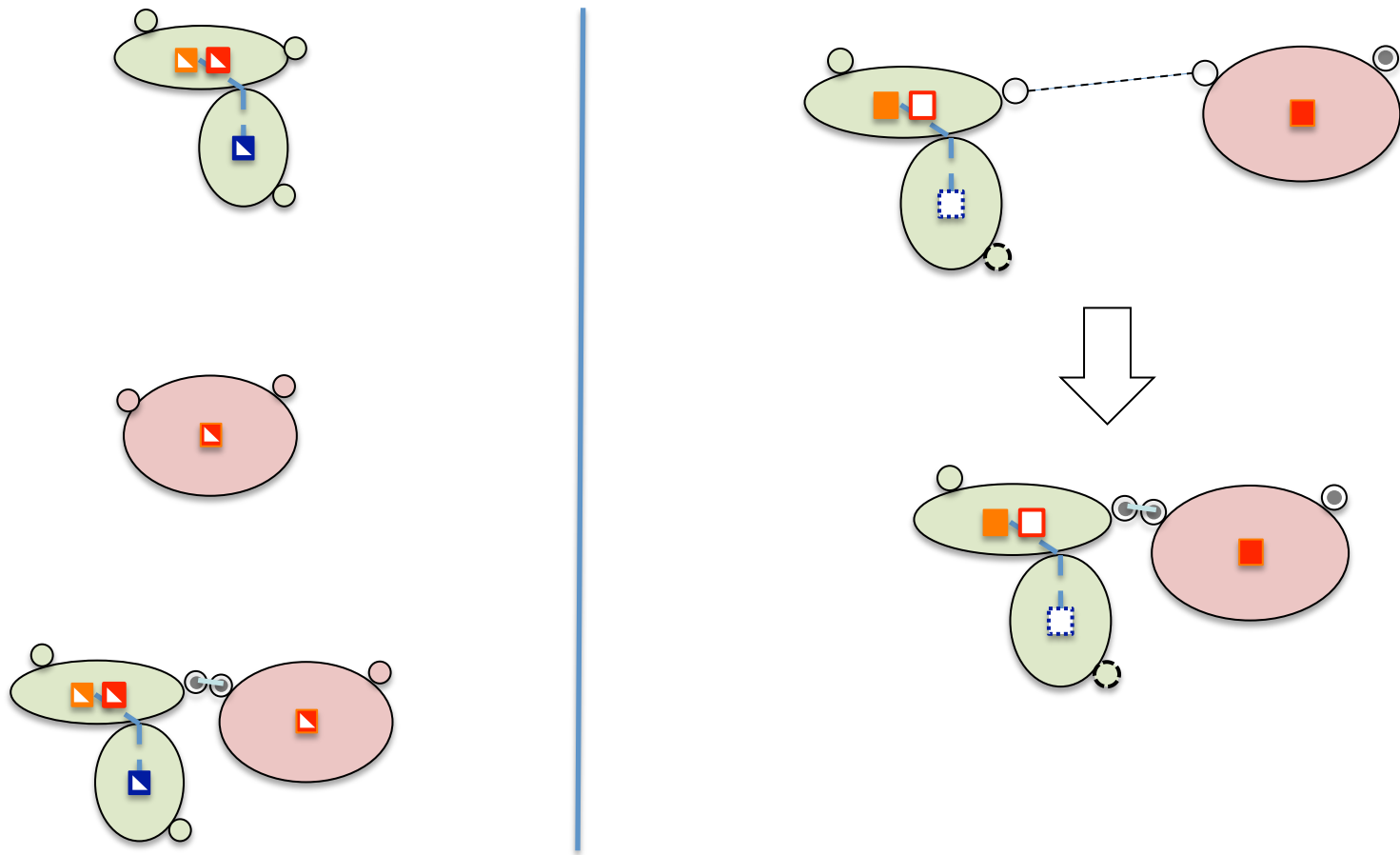
COMBINE 2014



# Simmune

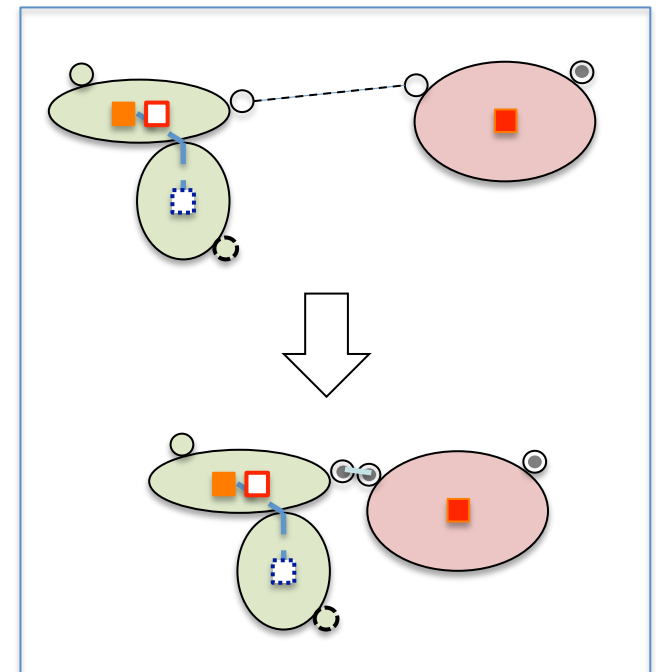
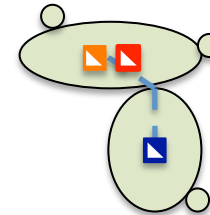


# Simmune Model Graphical Language



# Simmune Modeler

- Entities
  - Molecule
    - Component, feature and binding Site
  - Complex Species
    - One or more molecules
  - Complex
    - Specific state of complex species
  - Membrane association, Diffusion Coefficient
- Reaction rules (Relations among complexes)
  - Association
  - Dissociation
  - Transformation
  - Production
  - Degradation
- Data export
  - Simmune model file (SQLite)
  - SBML L2V1, L2V4 and L3V1
  - SBML Multi 1.01 (libSBML 5.9.0 experimental release)



# Simmune Modeler

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

Add Complex

Add

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

Complex Association

Source Complexes

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	Unbound
2: Ste5 binding site	Unbound

Source Complex 2

Complex Name: MP2C

Save Complex

Species Name: MP2C

Select Complex

☒ Display in Complex List

Reset

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

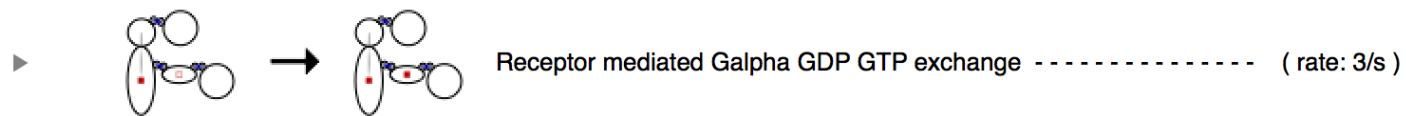
Species Name: MP2C\_Ste11

Select Complex

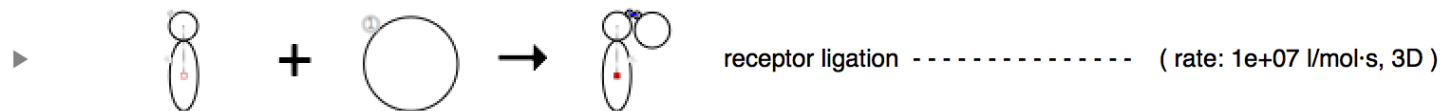
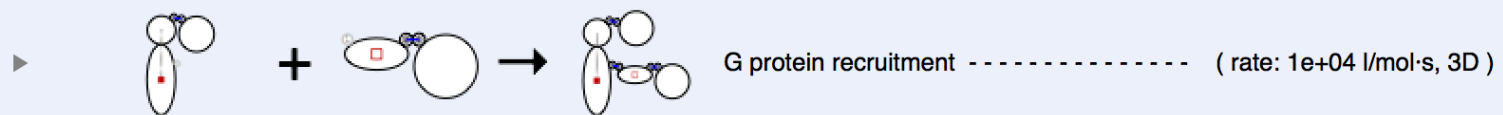
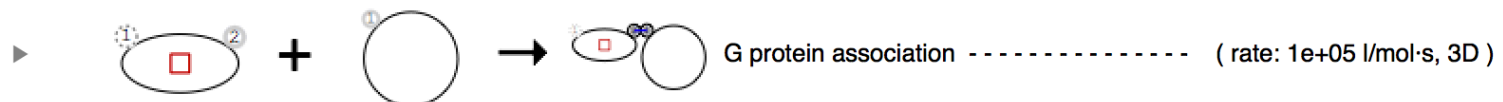
☐ Display in Complex List

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	

# Simmune Modeler



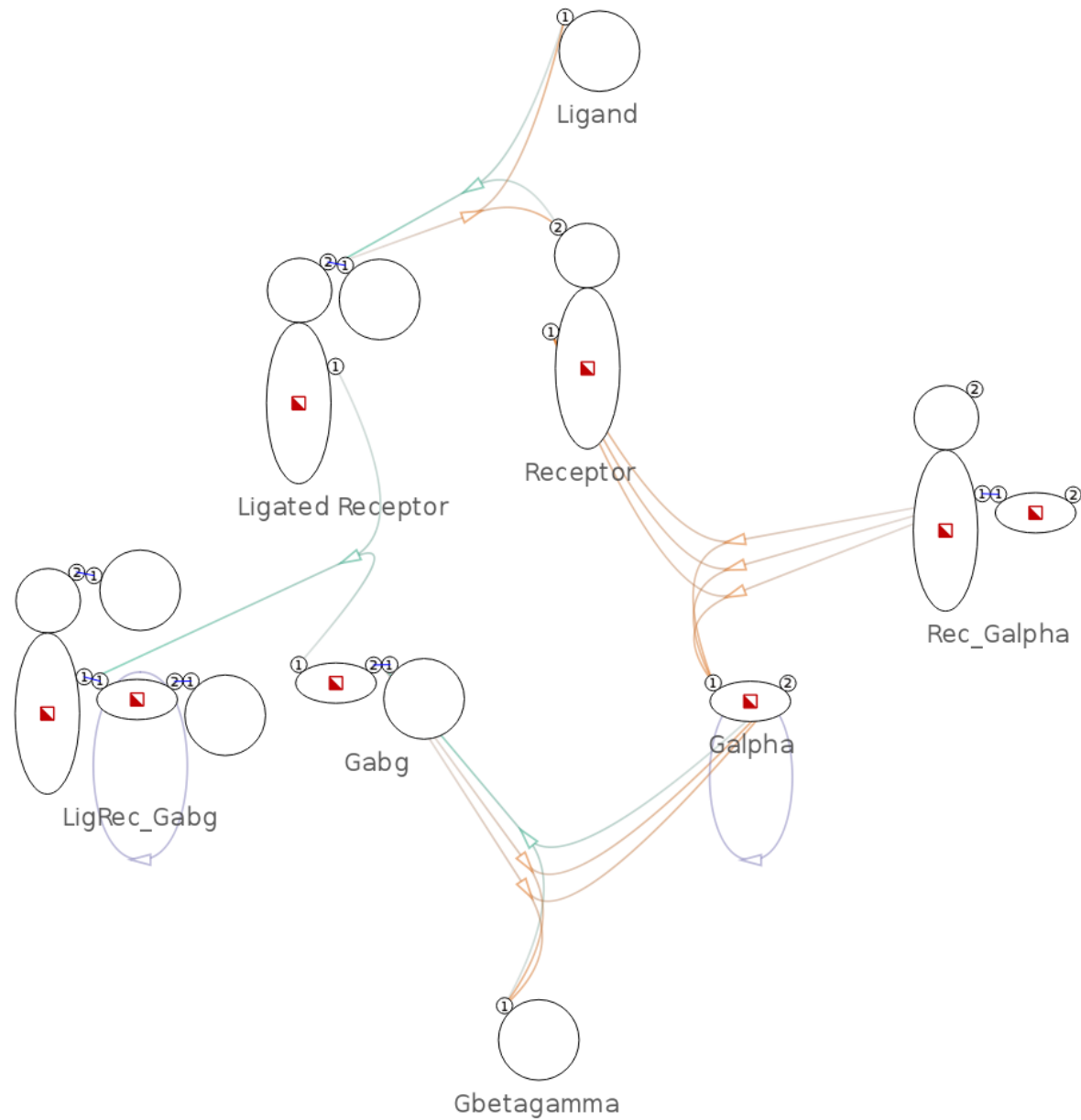
## ▼ Association ----- [ Number: 3 ]



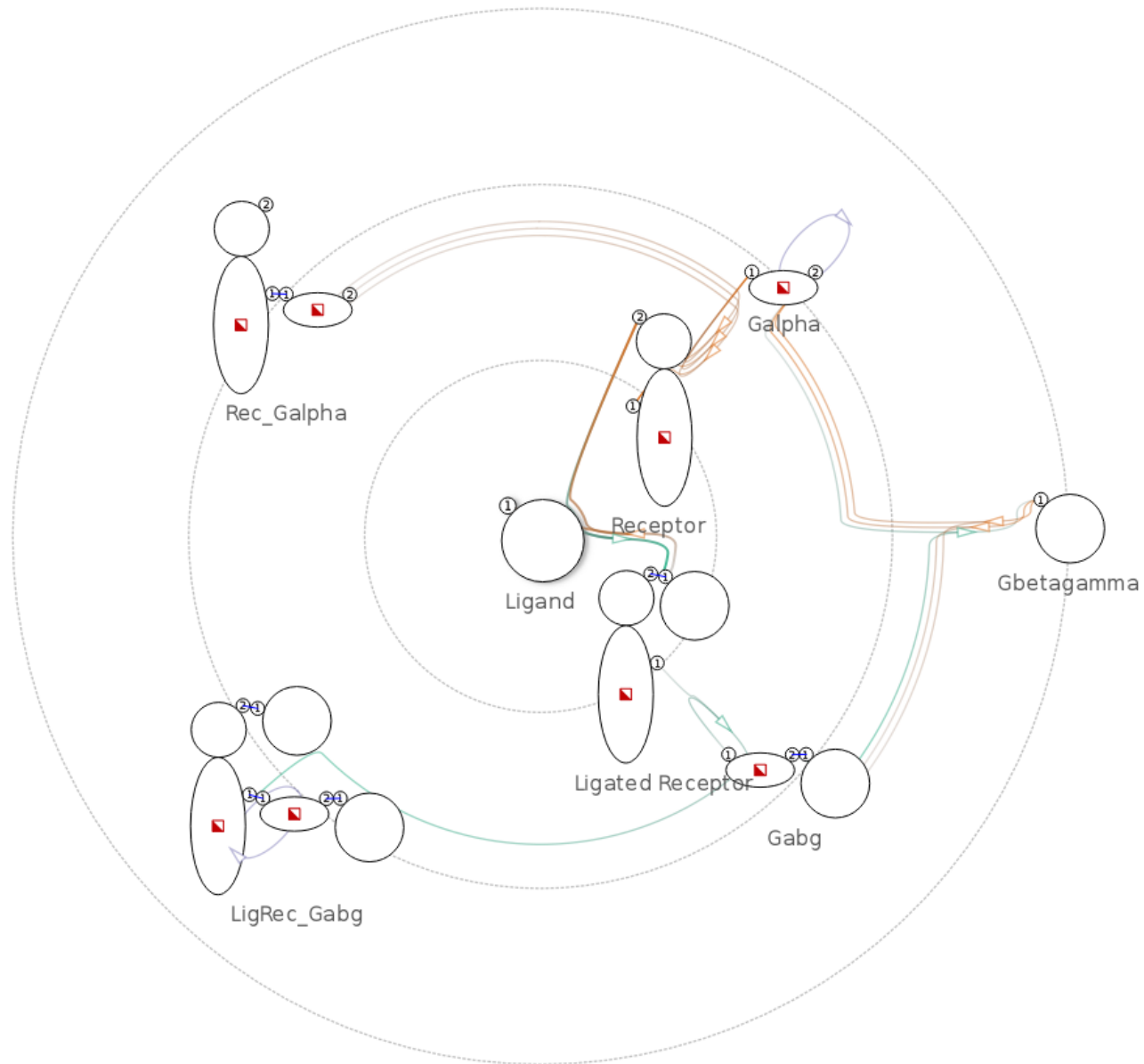
## ▼ Dissociation ----- [ Number: 6 ]



# Simmune Network Viewer: Level-based layout



# Simmune Network Viewer: Circular layout

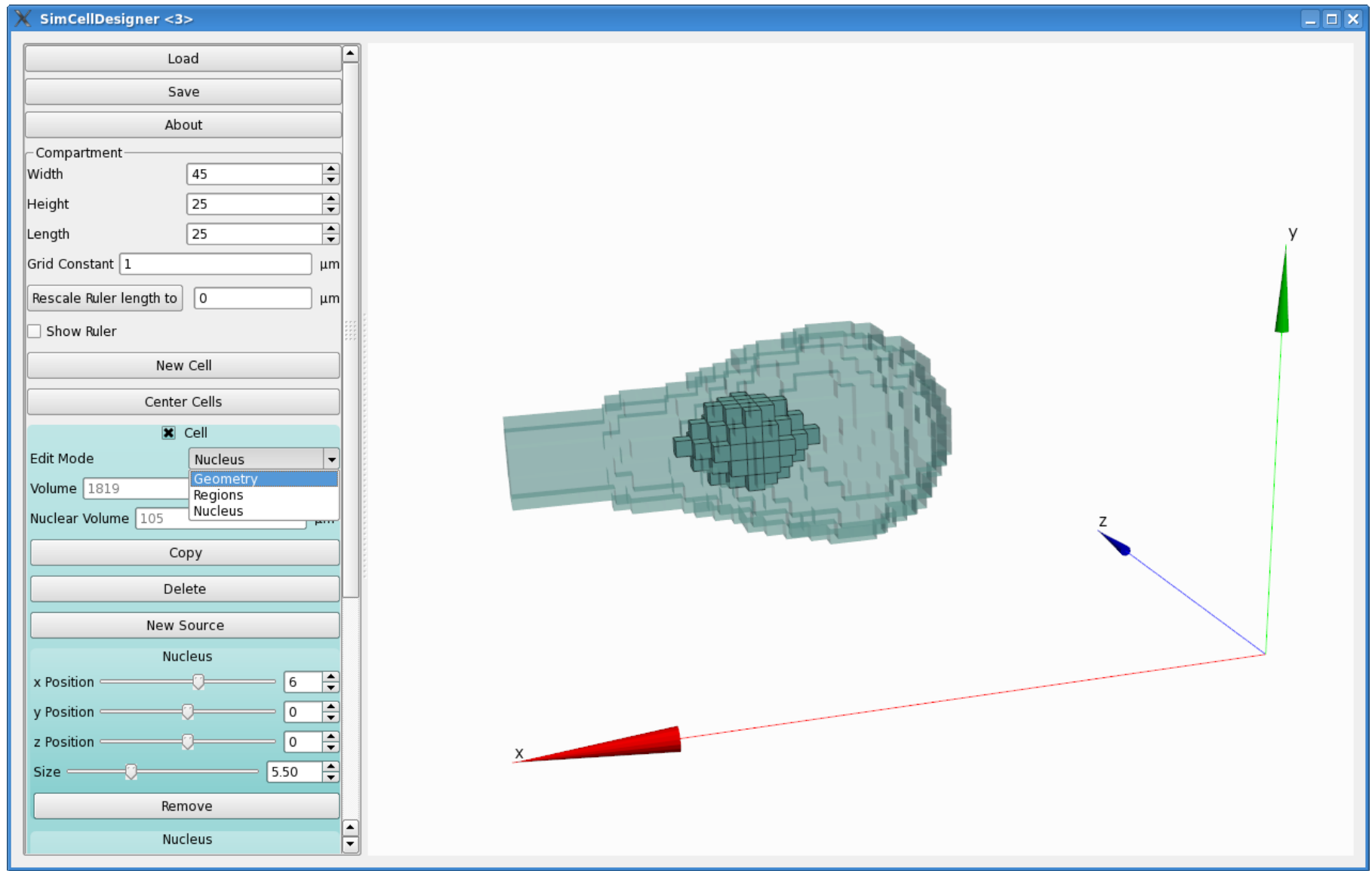




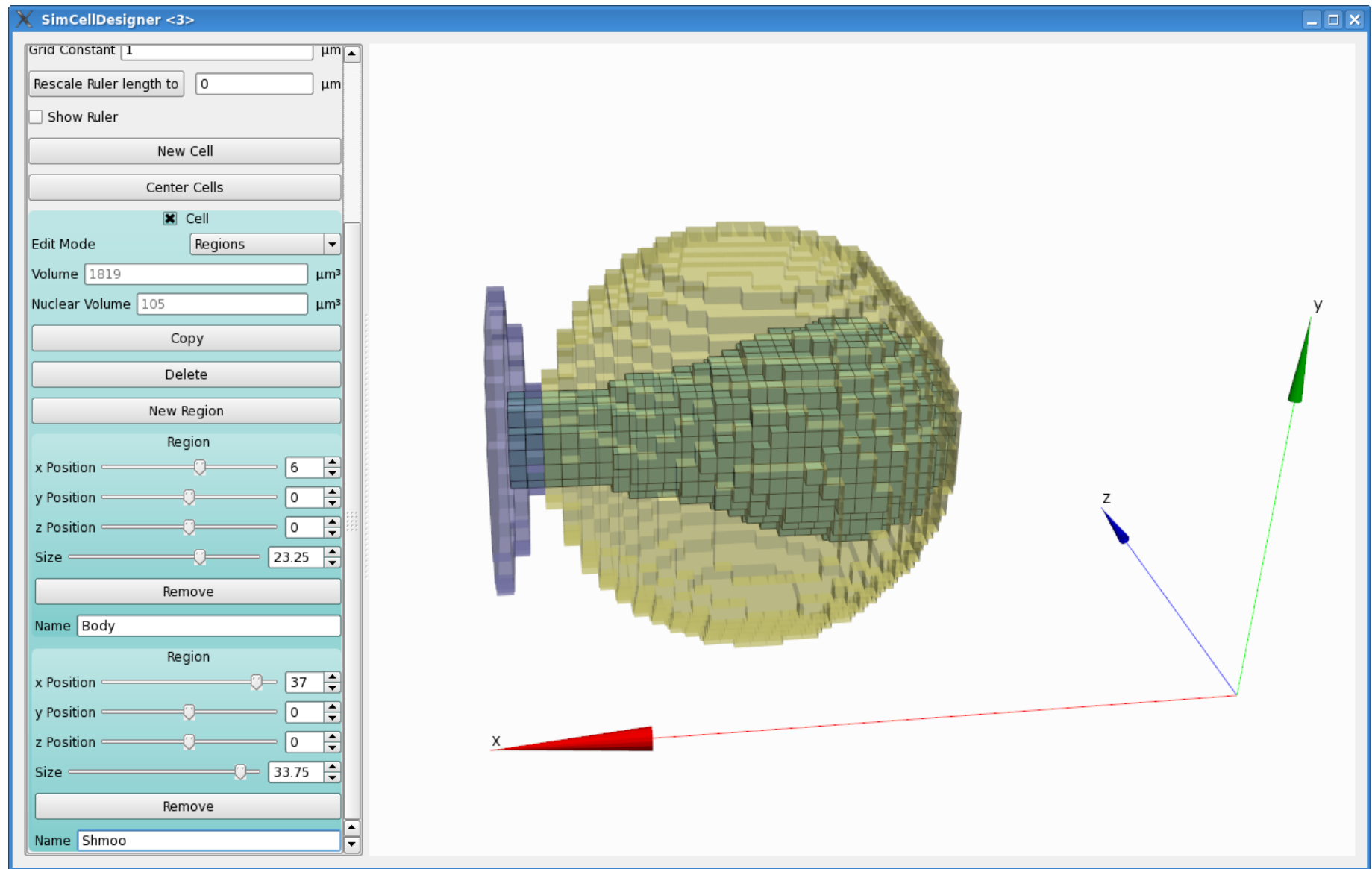
# Simmune Network Viewer

- Network layout options
  - Non-hierarchical layout
  - Level-based layout
  - Circular layout
- Flexible and efficient model information display
  - Tree view and reaction list
  - Filtering
  - User interaction
    - Automated layout
    - Customized layout
    - Zoom in and zoom out
    - Highlighting selected complex species and reactions

# Simmune CellDesigner: Cell and Organelle Morphology



# SimCellDesigner: Regions for initial concentrations



# Simmune CellDesigner

- 3D morphology
  - Grid of volume elements
  - Flexible shape and size
  - Ruler for length scale calibration
- Cell
  - With membrane
  - One or multiple cells
- Organelles (optional)
  - With membrane
- Region
  - For initial concentrations
  - Multiple regions for heterogeneous concentration initialization

# Simmune Simulator2: simulation configuration

Simmune Simulator 2 - YeastMAPK

File View Tools Help

New Simulation Load Simulation Load Description Preferences

Simulation Configuration Simulation Analysis

☒ Model ☒ Geometry ☒ InitialConcentration ☒ Working Directory ☒ Simulation Name ☒ Export Interval ☒ Simulation Time **Save And Start To Simulate** **Save**

Working Directory  ...

Simulation Name  **Reset** **+ All Sections** **Default View**

**- Model and geometry**

Model  ...

Geometry  ...

**- Initial concentrations** **Add/Edit** **Delete**

	Cell Name	Region Name	Organelle	Complex	Concentration
4	Cell	Body	Nucleus (Importing Membrane Pore)	Fus3_basal	100 [mol...]
5	Cell	Body	Cytosol	Cdc14	6e-08 [m...]
6	Cell	Body	Nucleus (Exporting Membrane Pore)	Msg5	100 [mol...]
7	Cell	Body	Cytosol	Ste5	6e-08 [m...]
8	Cell	Body	Nucleus (Importing Membrane Pore)	pFus3_free	100 [mol...]
9	Cell	Shmoo	Cytosol (Membrane)	Fus3 anchor basal	400 [mol...]

Maximum number of molecules per complex:

**+ Potts model**

**- Simulation export intervals (To edit a field, double click)**

	Start Time(s)	Interval(s)	Note
1 <input type="checkbox"/>	0	10	Default.

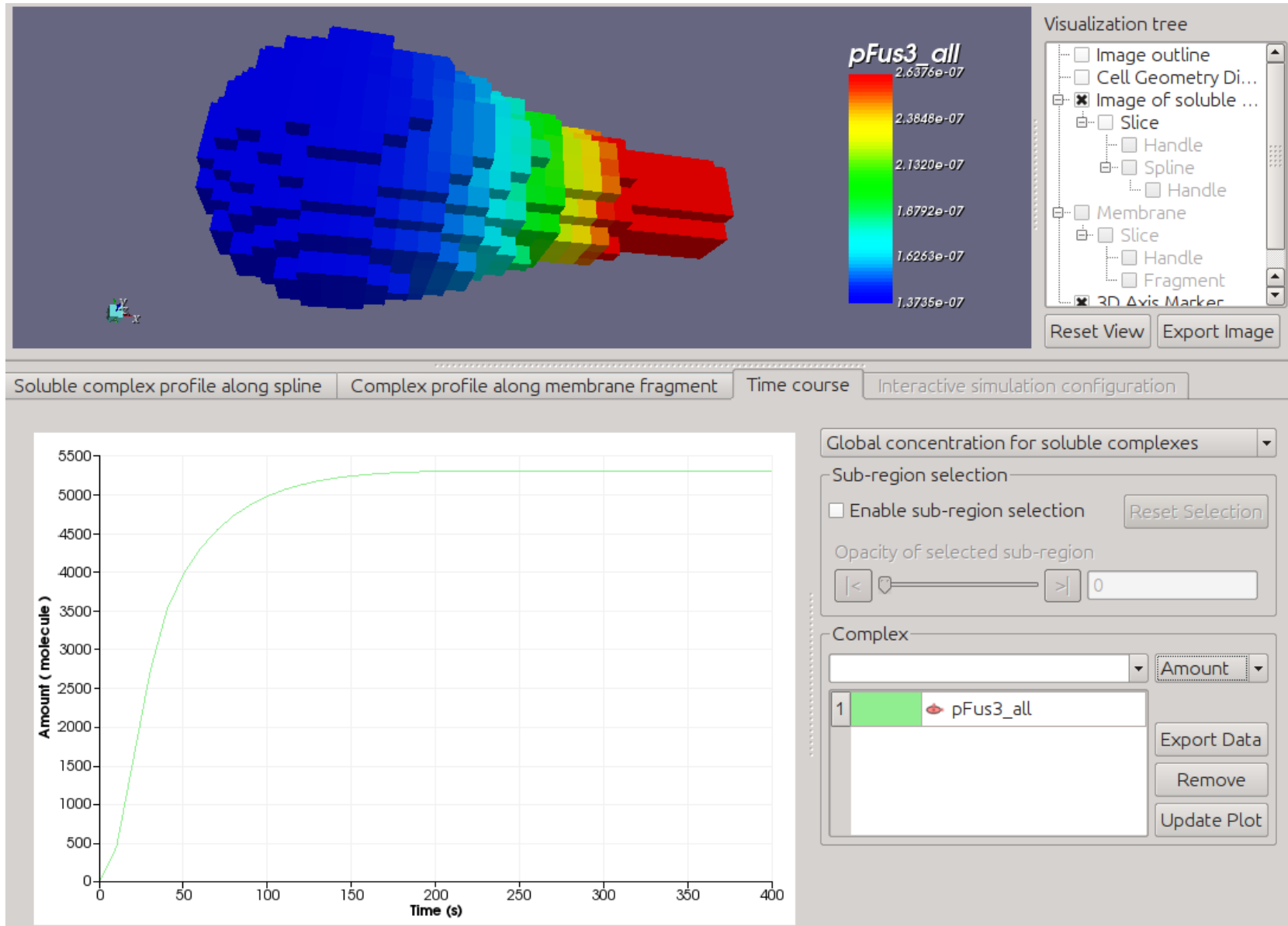
**+ Simulation protocol**

Time(s)	Complex	Type	Frozen	Conc(1)	Conc(2)	Point(1)	Point(2)
---------	---------	------	--------	---------	---------	----------	----------

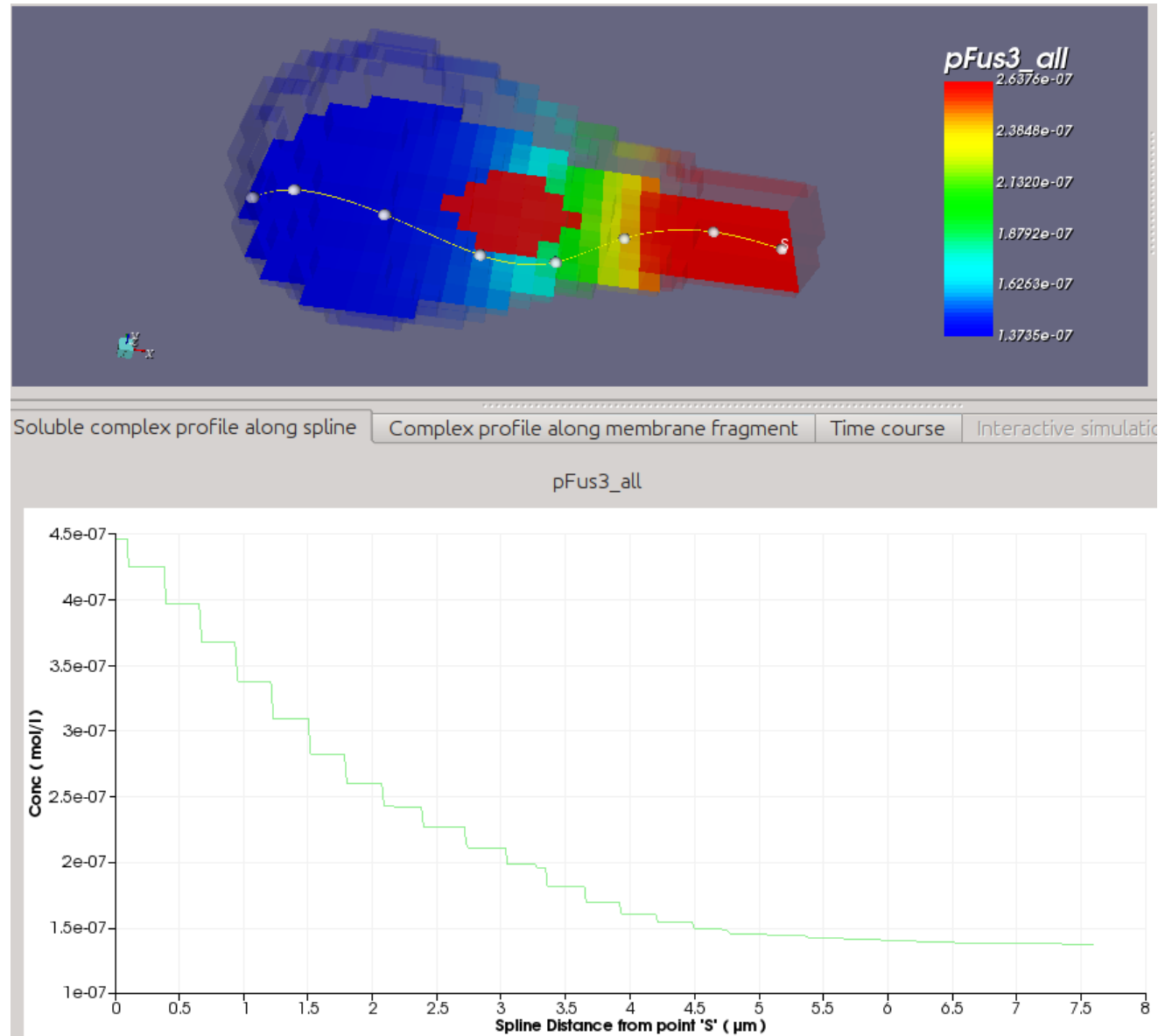
**Simulation time:**  s **Default**

**+ Annotation**

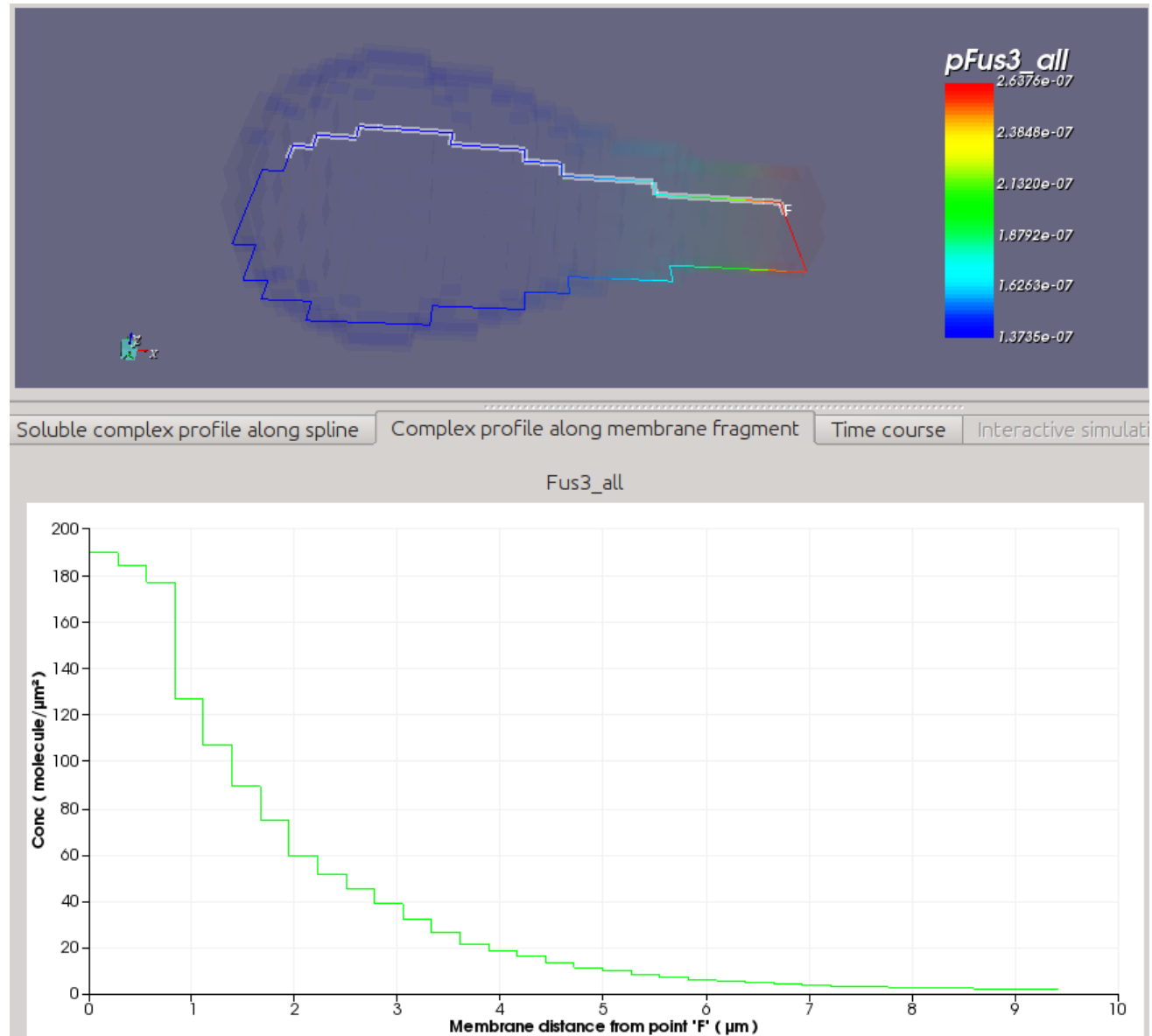
# Simmune Simulator2: 3D visualization and time course plot



## Simmune Simulator2: cutting slice and spline plot



## Simmune Simulator2: membrane fragment





# Simmune Simulator2

- Simulation description
  - Model from Simmune Modeler
  - Spatial geometry from Simmune CellDesigner
  - Initial concentration
  - Protocol
- Simulation
  - Interactive protocol configuration: Gradient concentration, etc
- During and post simulation analysis
  - 3D visualization
    - Cell morphology and/or complex concentration with color heat map
    - Display of selected cell(s) among multiple cells
  - Time course
    - Whole or sub-region
  - Image slice, spline and spline profile
  - Membrane fragment and profile

# Simmune Analyzer

- Configuration and management of multiple simulations
  - Local or distributed systems
- Initial concentration distributions
- Protocols Configuration
- Parameter distributions
- Various plotting methods for simulation analysis
- Parameter fitting
- Global sensitivity analysis

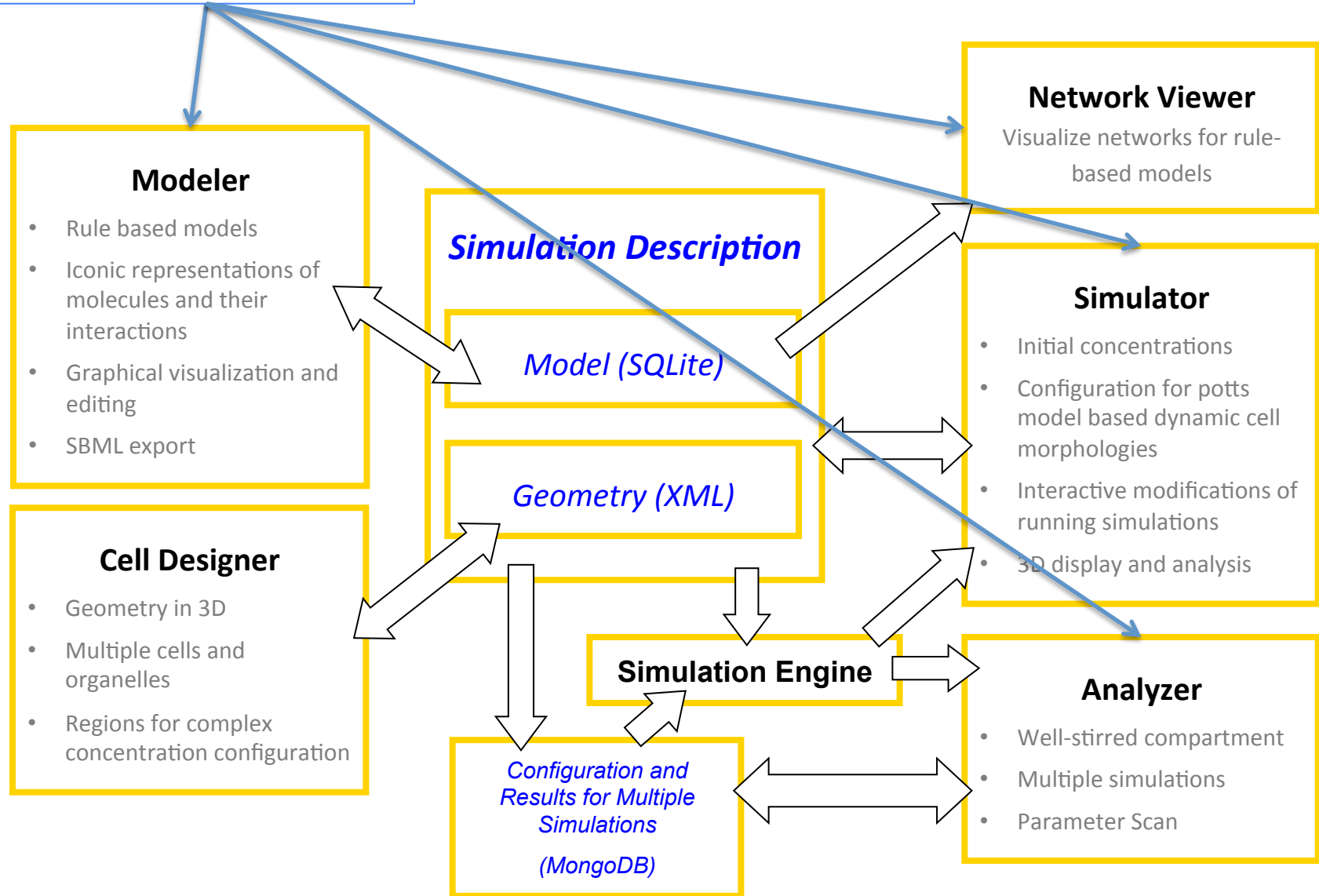
# Simmune and COMBINE standards

# SBML-Multi Export

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" xmlns:multi="http://www.sbml.org/sbml/level3/version1/multi/v
<model>
  <listOfUnitDefinitions>[]
  <listOfSpecies>
    <species id="sp_cpx_000001" name="Rec inactive" multi:speciesType="st_cps_000002">
      <multi:listOfOutwardBindingSites>
        <multi:outwardBindingSite multi:bindingStatus="either" multi:component="st_bst_000001"/>
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      <multi:listOfSpeciesFeatures>
        <multi:speciesFeature multi:speciesFeatureType="sft_mcp_000001_activated">
          <multi:listOfSpeciesFeatureValues>
            <multi:speciesFeatureValue multi:value="sfv_mcp_000001_activated_off"/>
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    </species>
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    <species id="sp_cpx_000004" name="Galpha 1" multi:speciesType="st_cps_000005">[]
```

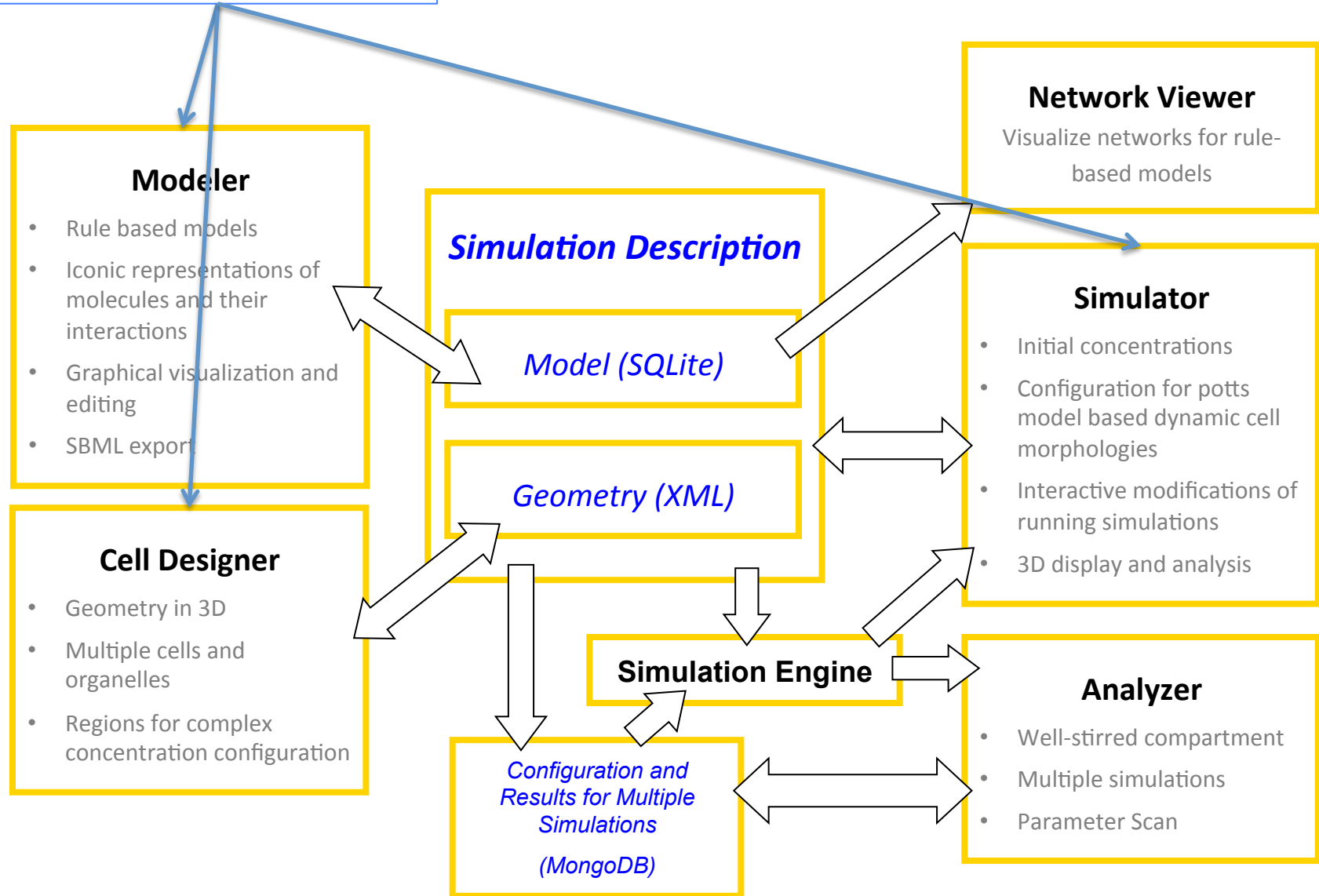
# SBML-Multi

## Simmune and COMBINE



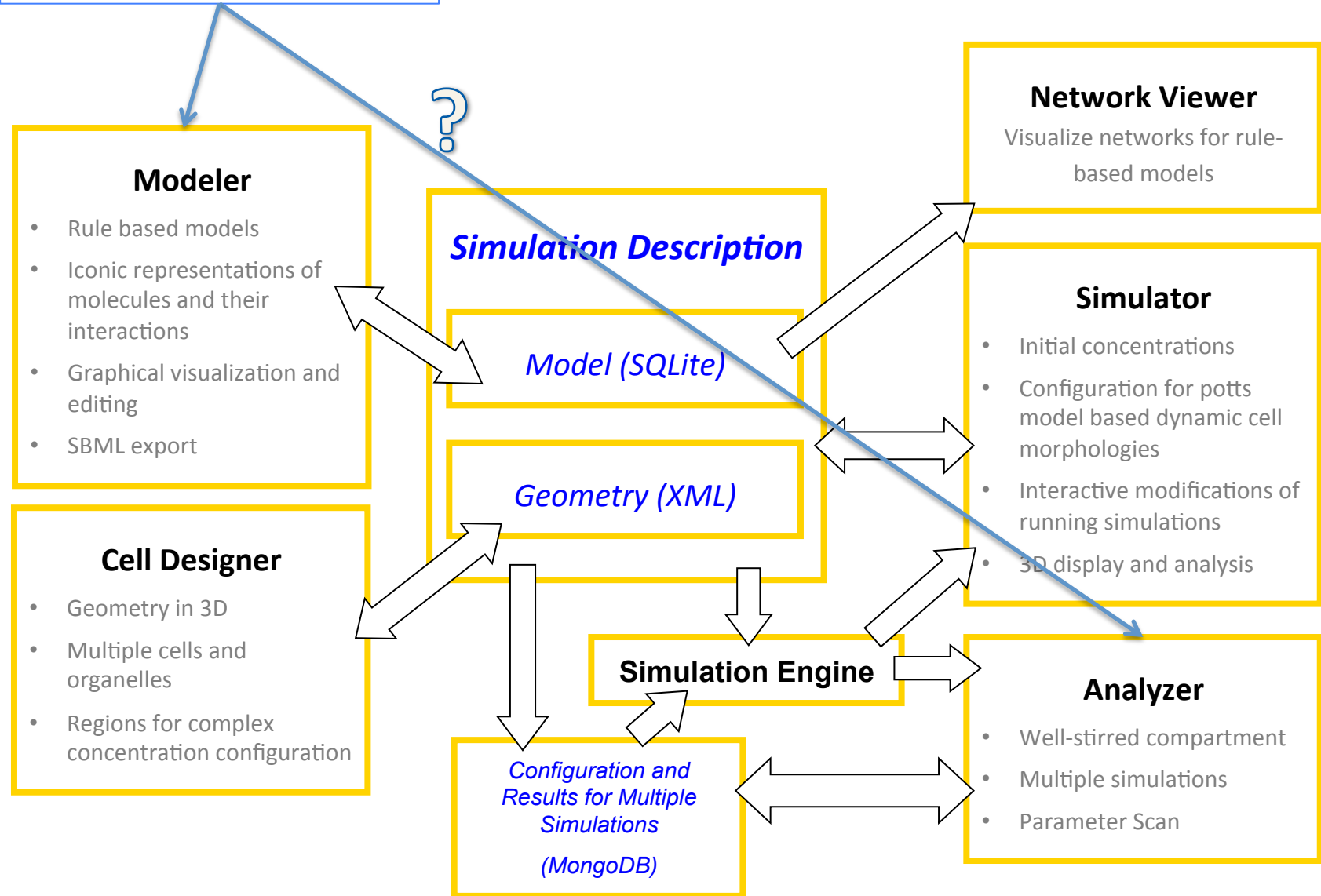
# SBML-Spatial

# Simmune and COMBINE

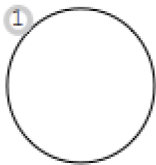
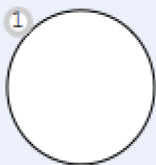
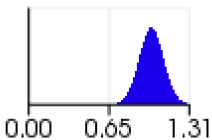



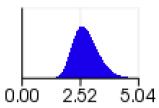
# SBML-Distrib

# Simmune and COMBINE



COMBINE 2014

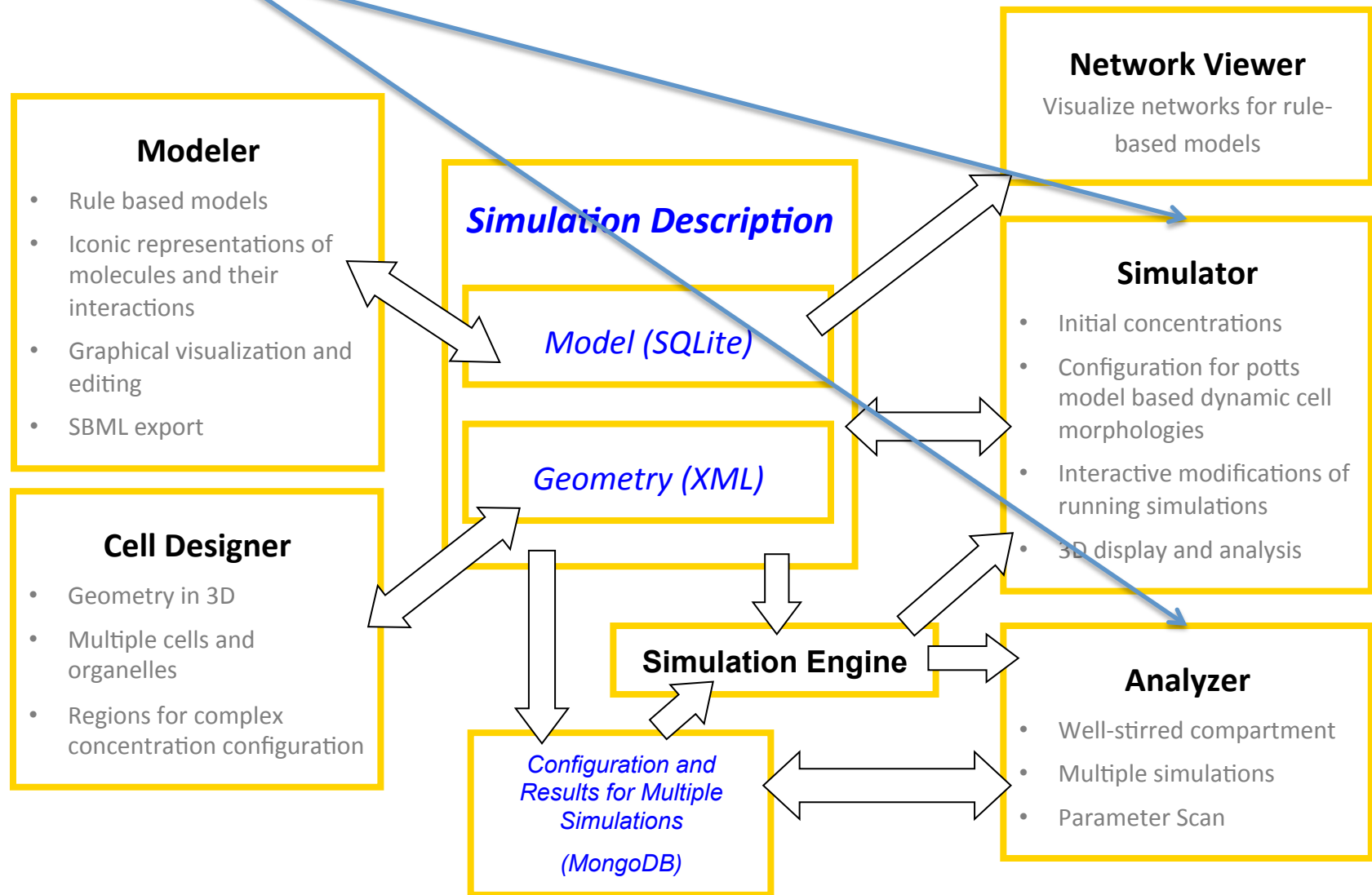
1		Ligand	0 nmol/l (3D)	Delta distribution at 1
2		Gbetagamma_1	0 molecule/micron <sup>2</sup> (2D)	<div>  <div> Distribution <input type="text" value="Normal"/>   mean <input type="text" value="1.000000"/>   standard deviation <input type="text" value="0.1000010"/> </div> </div>

 Galpha auto-GTPase ----- ( rate: 0.3/s )				<div>  <div> Distribution <input type="text" value="Log Normal"/>   mean <input type="text" value="1.000000"/>   scale <input type="text" value="0.2000010"/> </div> </div>
 Receptor mediated Galpha GDP GTP exchange ----- ( rate: 3/s )				Delta distribution at 1



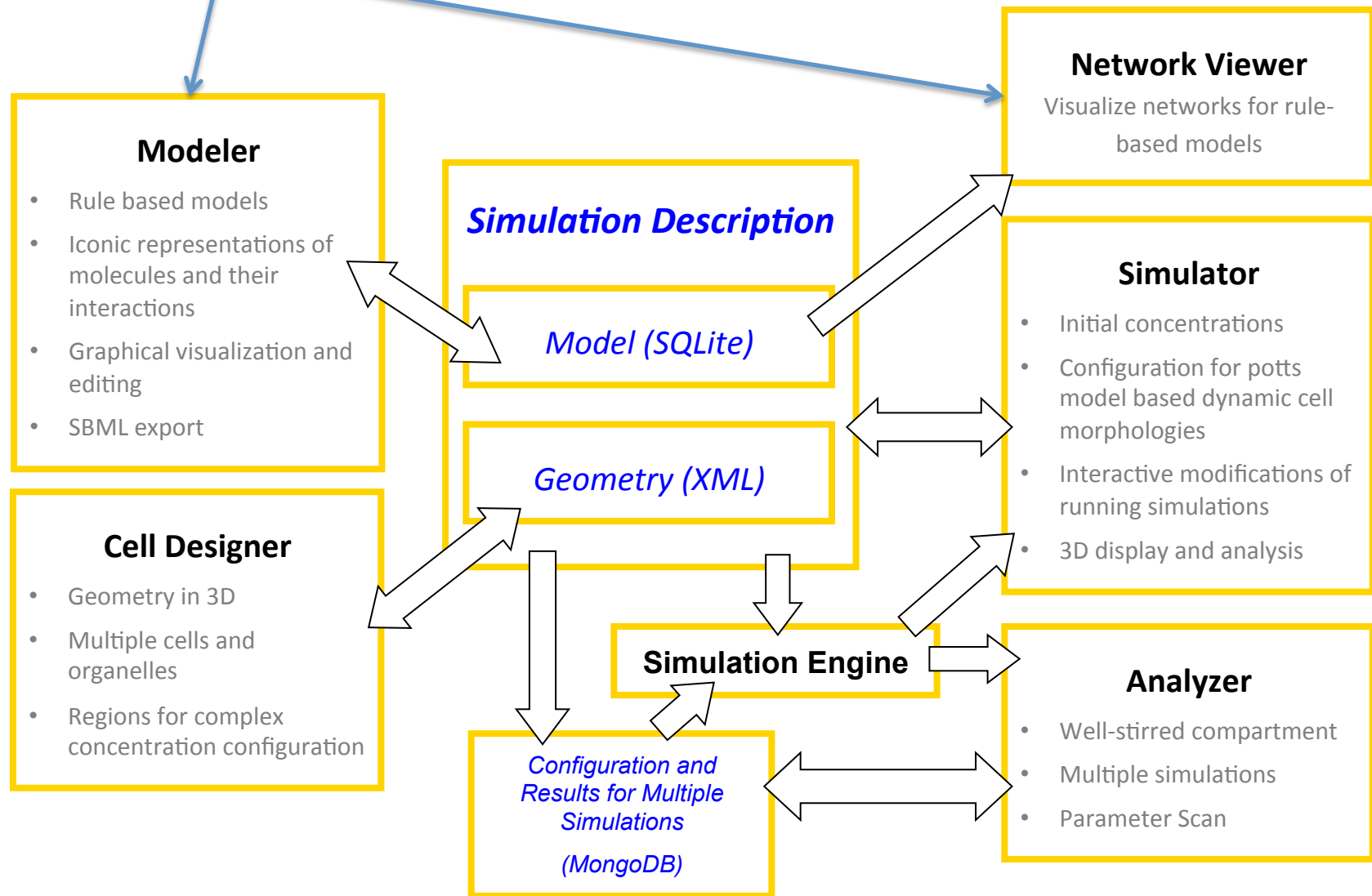
SED-ML

# Simmune and COMBINE

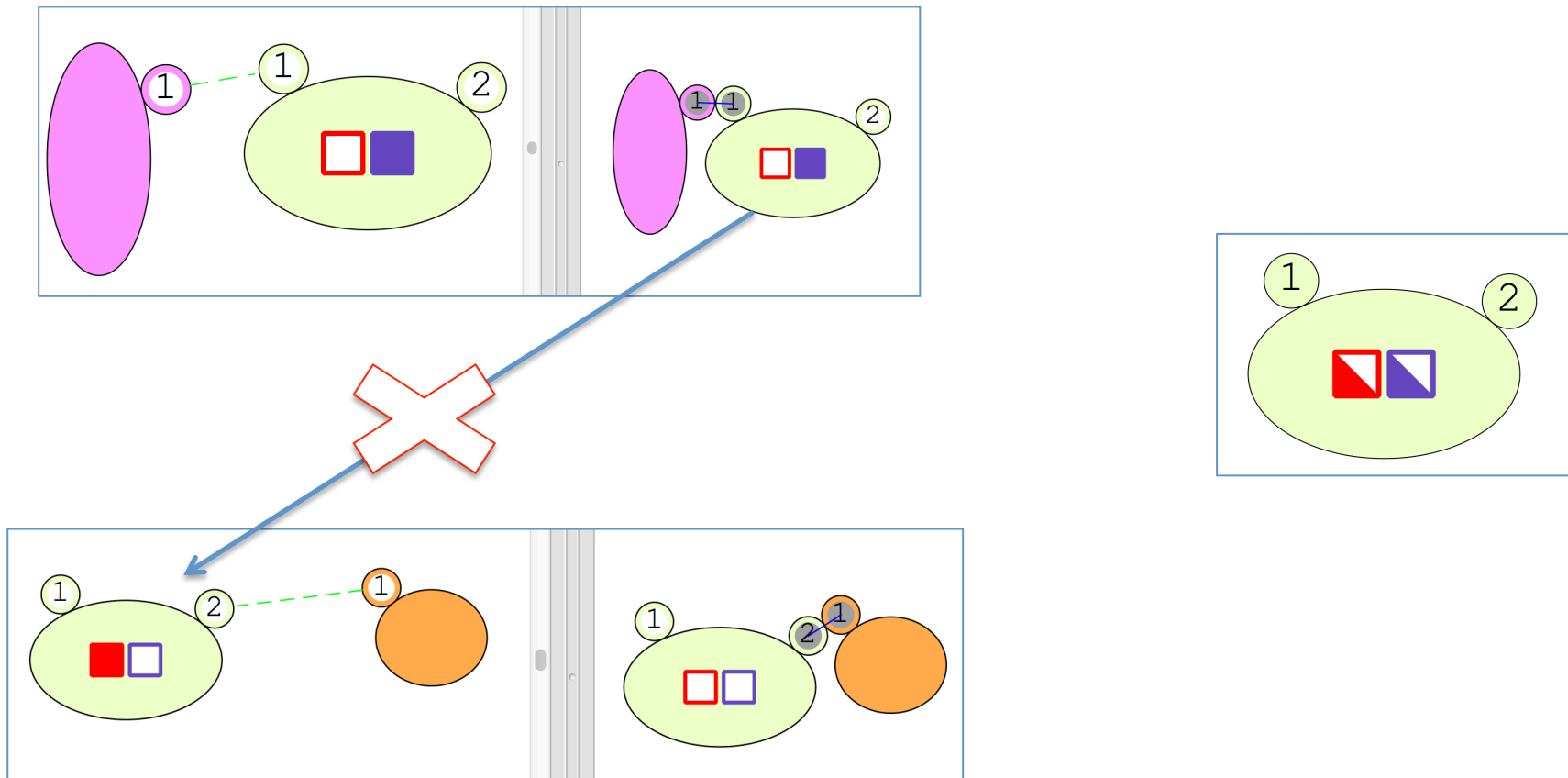


SBGN

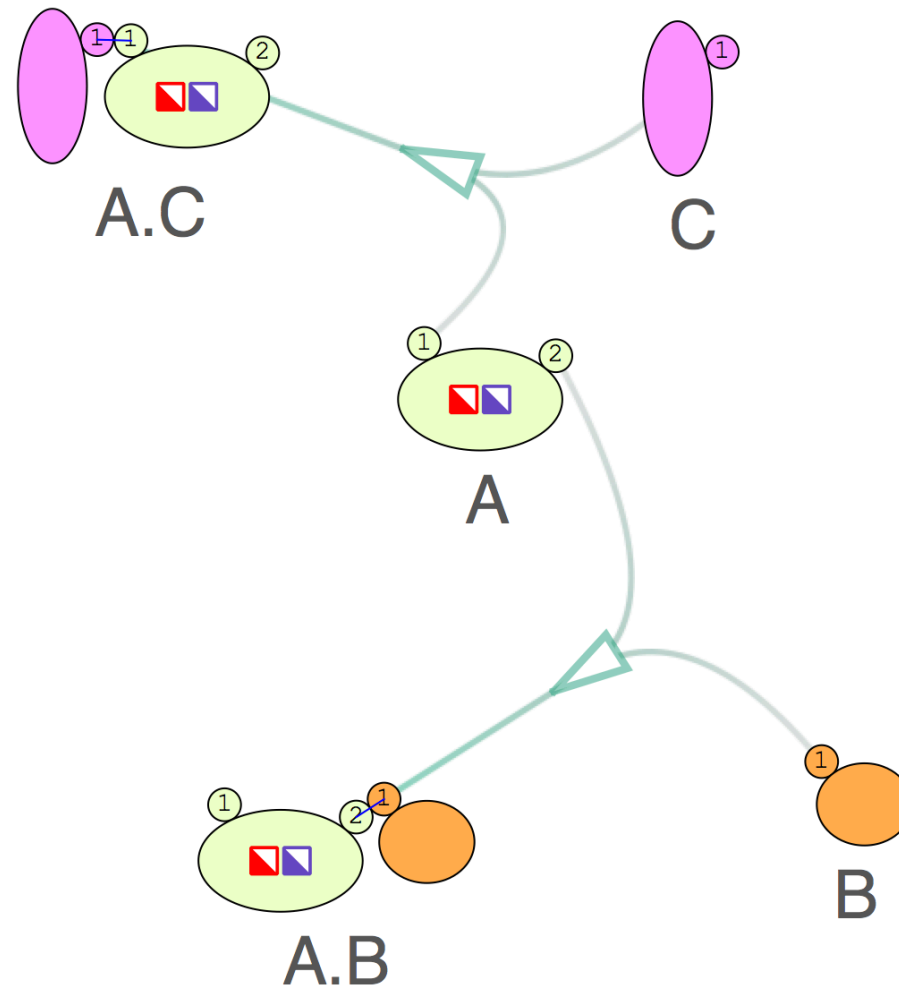
# Simmune and COMBINE



# Simmune and SBGN

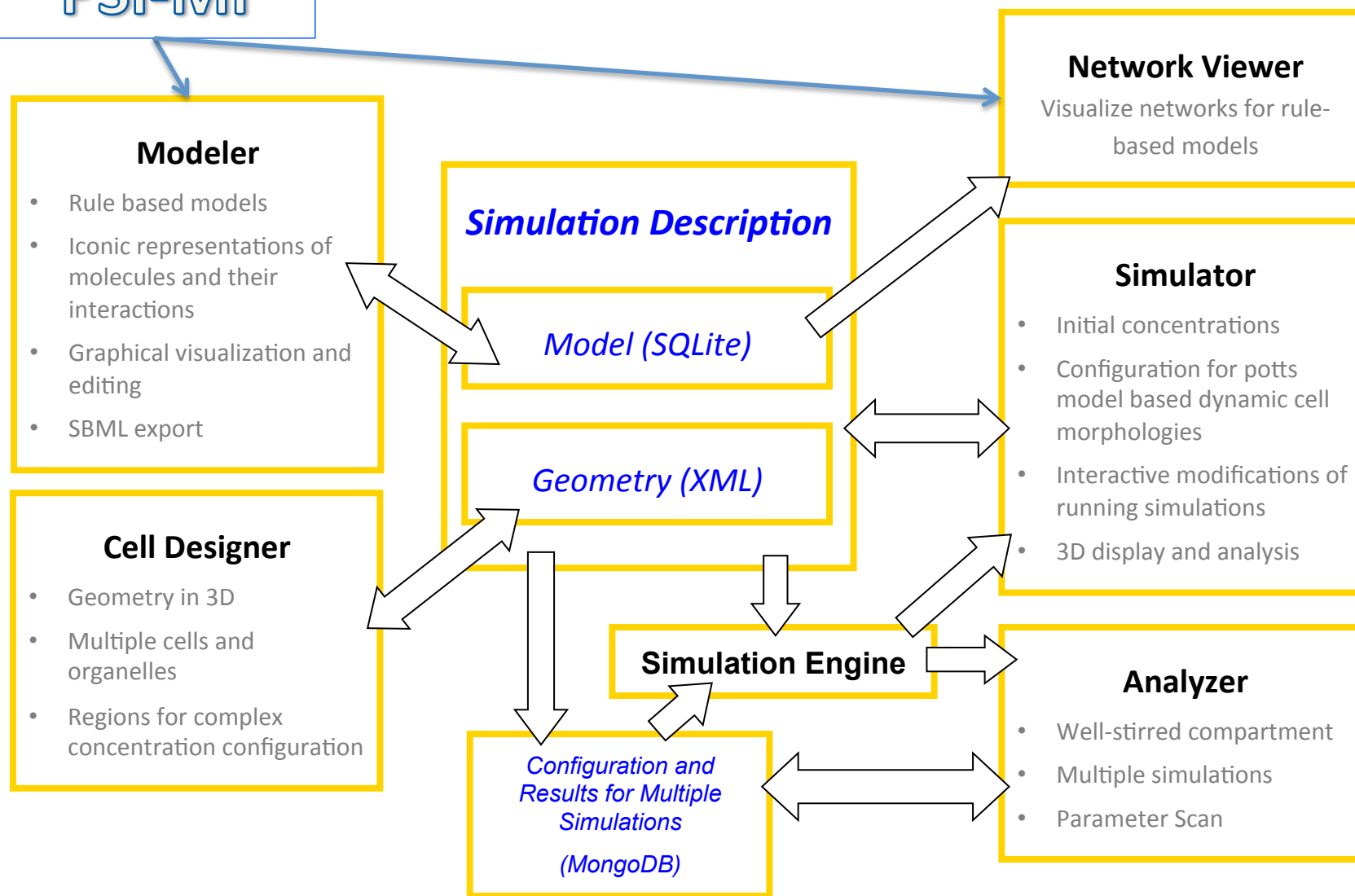


# Simmune and SBGN



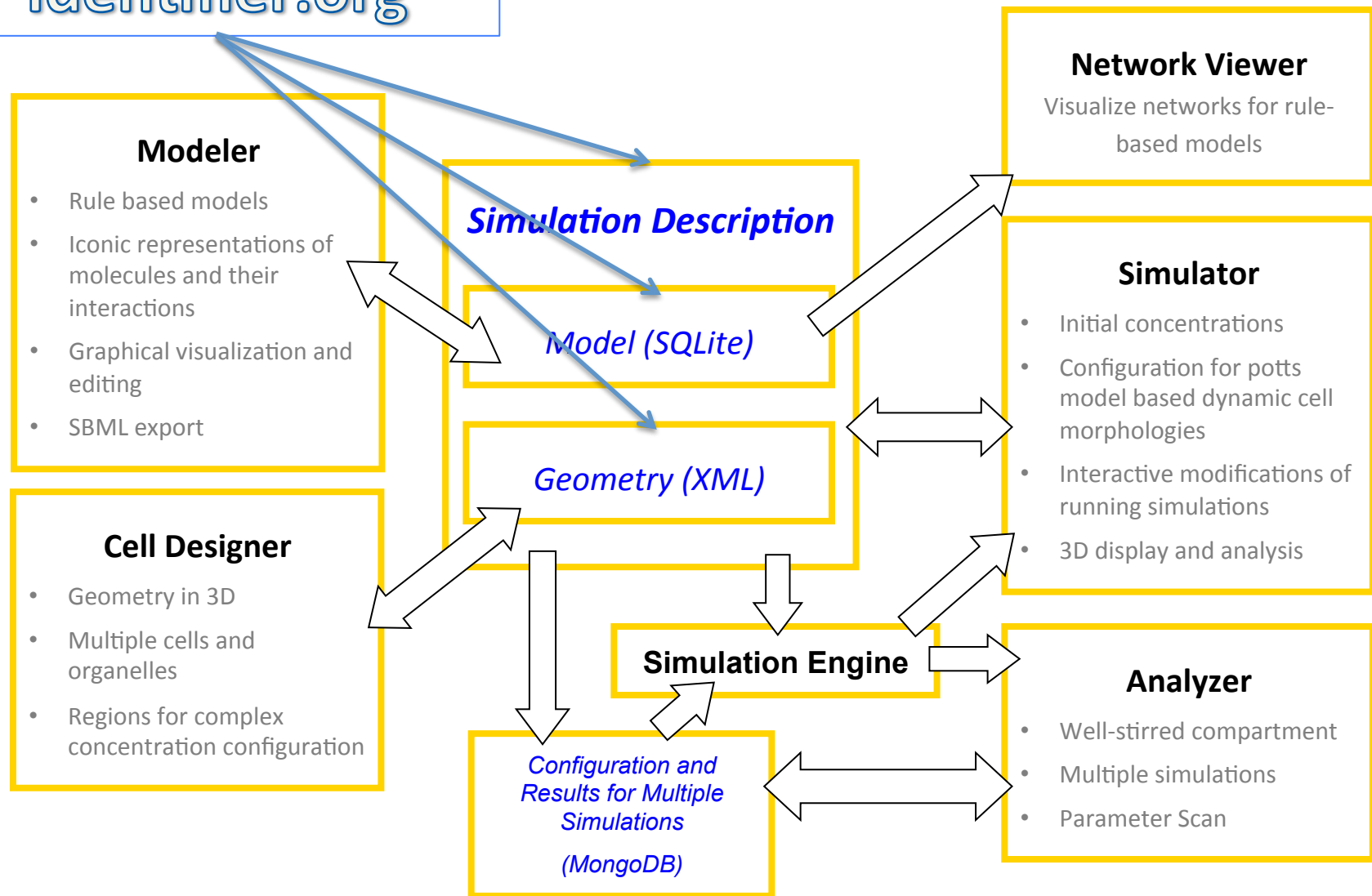
BIO-PAX,  
PSI-MI

# Simmune and COMBINE



COMBINE Archive,  
Identifier.org

# Simmune and COMBINE



# References

- Simmune website:  
<http://go.usa.gov/QeH>
- ***Nature Methods*** 9, 283–289 (2012)  
*“Computational modeling of cellular signaling processes embedded into dynamic spatial contexts”*
- ***Bioinformatics***. 2013 May 1;29(9):1229-30  
*“The Simmune Modeler visual interface for creating signaling networks based on bi-molecular interactions”*
- ***BMC Systems Biology*** 2014, 8:70  
*“NetworkViewer: visualizing biochemical reaction networks with embedded rendering of molecular interaction rules”*

# Acknowledgements

- Simmune Development Team
  - Martin Meier-Schellersheim(PI)
  - Bastian Angermann
  - Thorsten Prustel
  - Hsueh-Chien Cheng
- Ronald Germain and the members of Laboratory of Systems Biology, NIAID, NIH
- Simmune Users
- COMBINE communities (SBML etc.)

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