Simmune and COMBINE Standards

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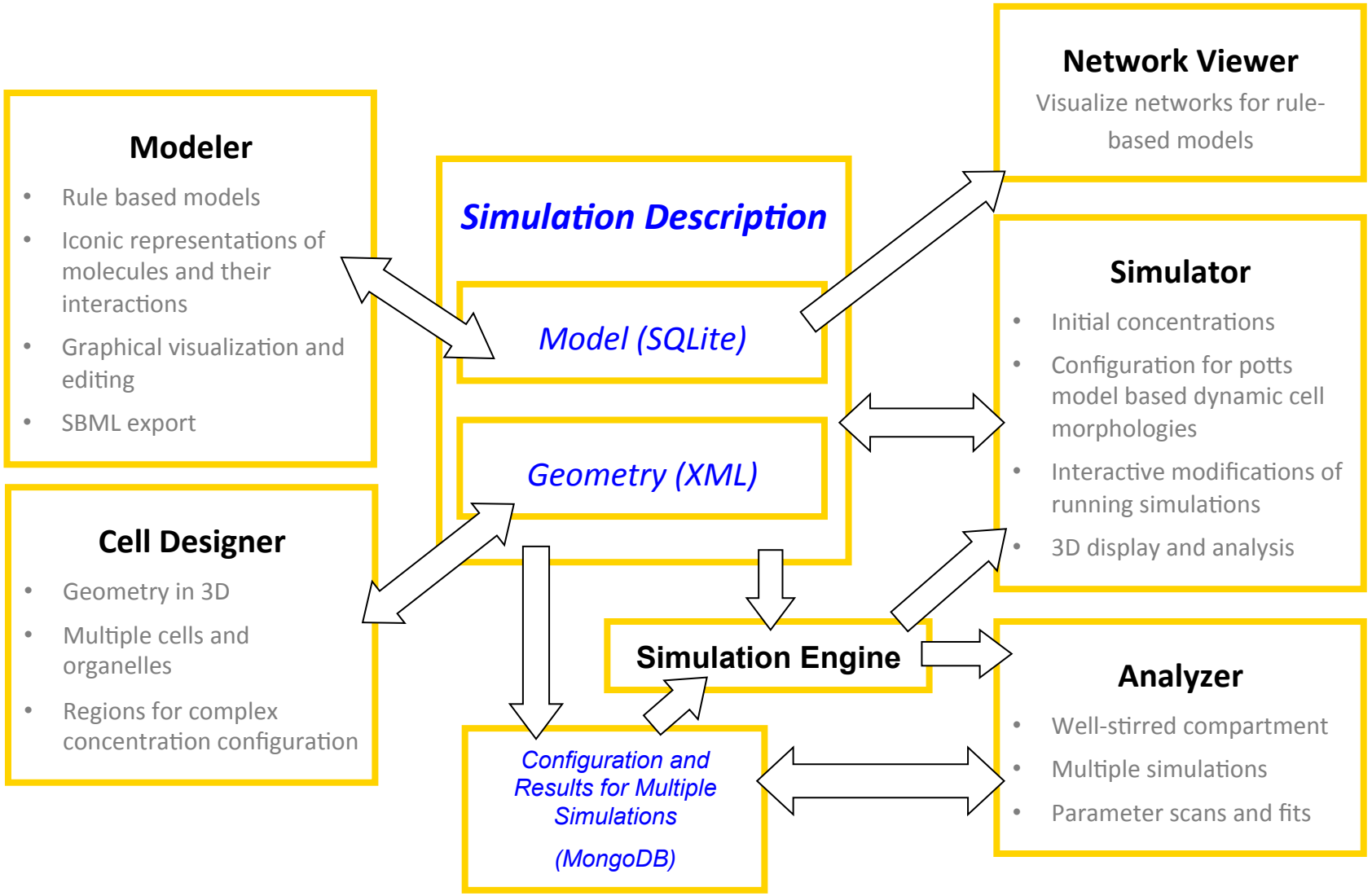
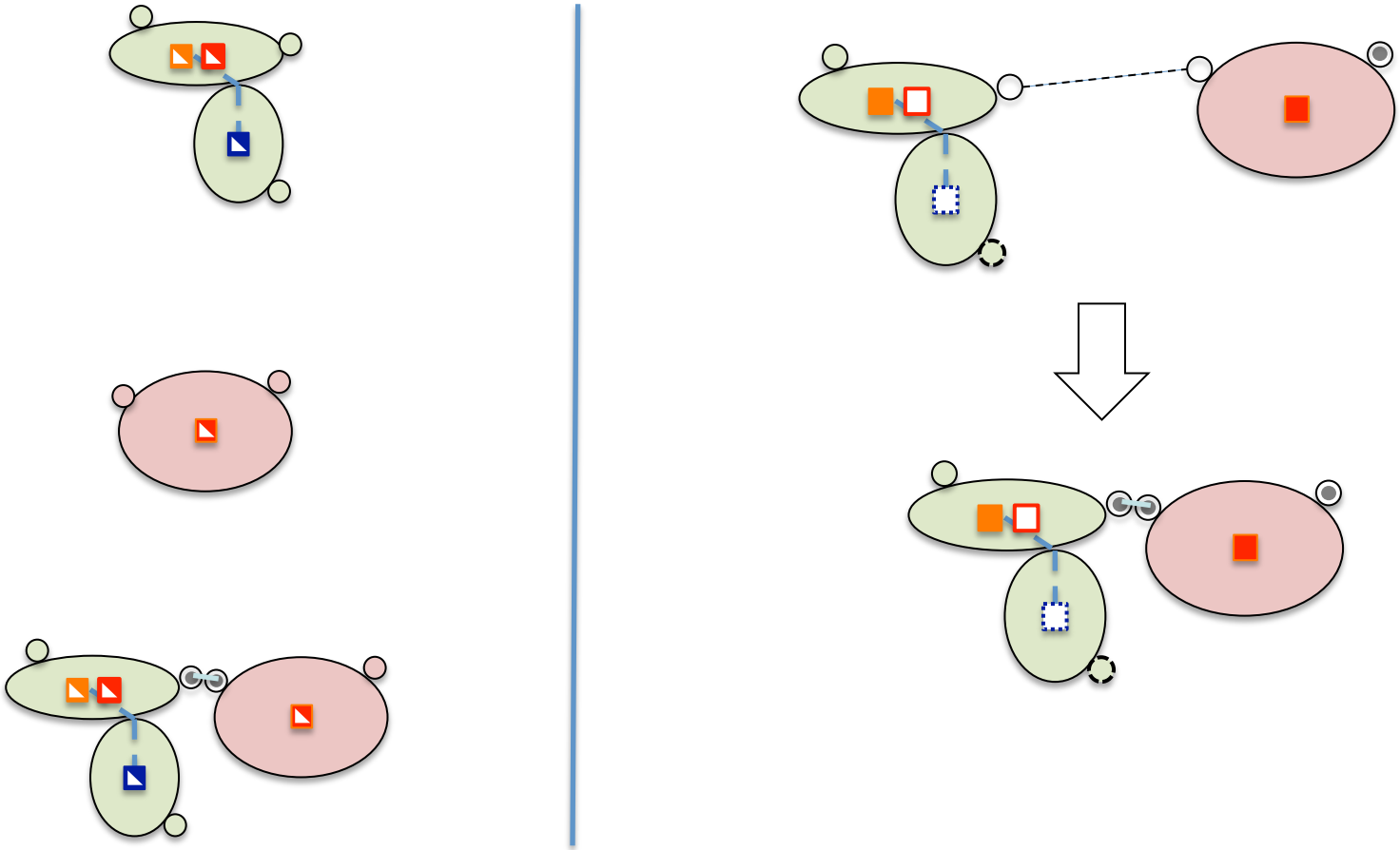
Simmune

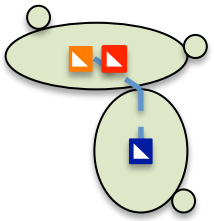

Modeler
Rule based models
Iconic representations of molecules and their interactions
Graphical visualization and editing
SBML export
Cell Designer
Geometry in 3D
Multiple cells and organelles
Regions for complex concentration configuration
Simulation Description
Model (SQLite)
Geometry (XML)
Configuration and Results for Multiple Simulations
(MongoDB)
Simulation Engine
Network Viewer
Visualize networks for rule-based models
Simulator
Initial concentrations
Configuration for potts model based dynamic cell morphologies
Interactive modifications of running simulations
3D display and analysis
Analyzer
Well-stirred compartment
Multiple simulations
Parameter scans and fits

Simmune Model Graphical Language

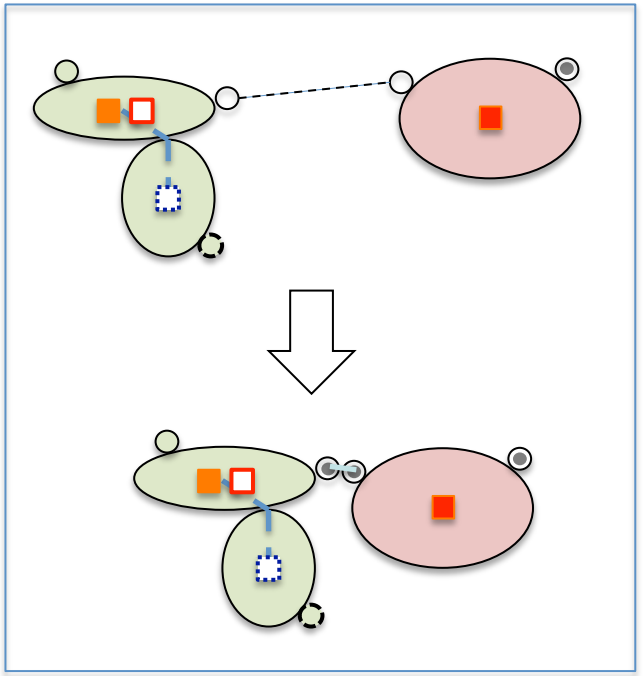


Simmune Modeler

- Entities
  - Molecule
    - Component, feature and binding Site
  - Complex Species
    - One or more molecules
  - Complex
    - Specific state of complex species
  - Membrane association, Diffusion Coefficient

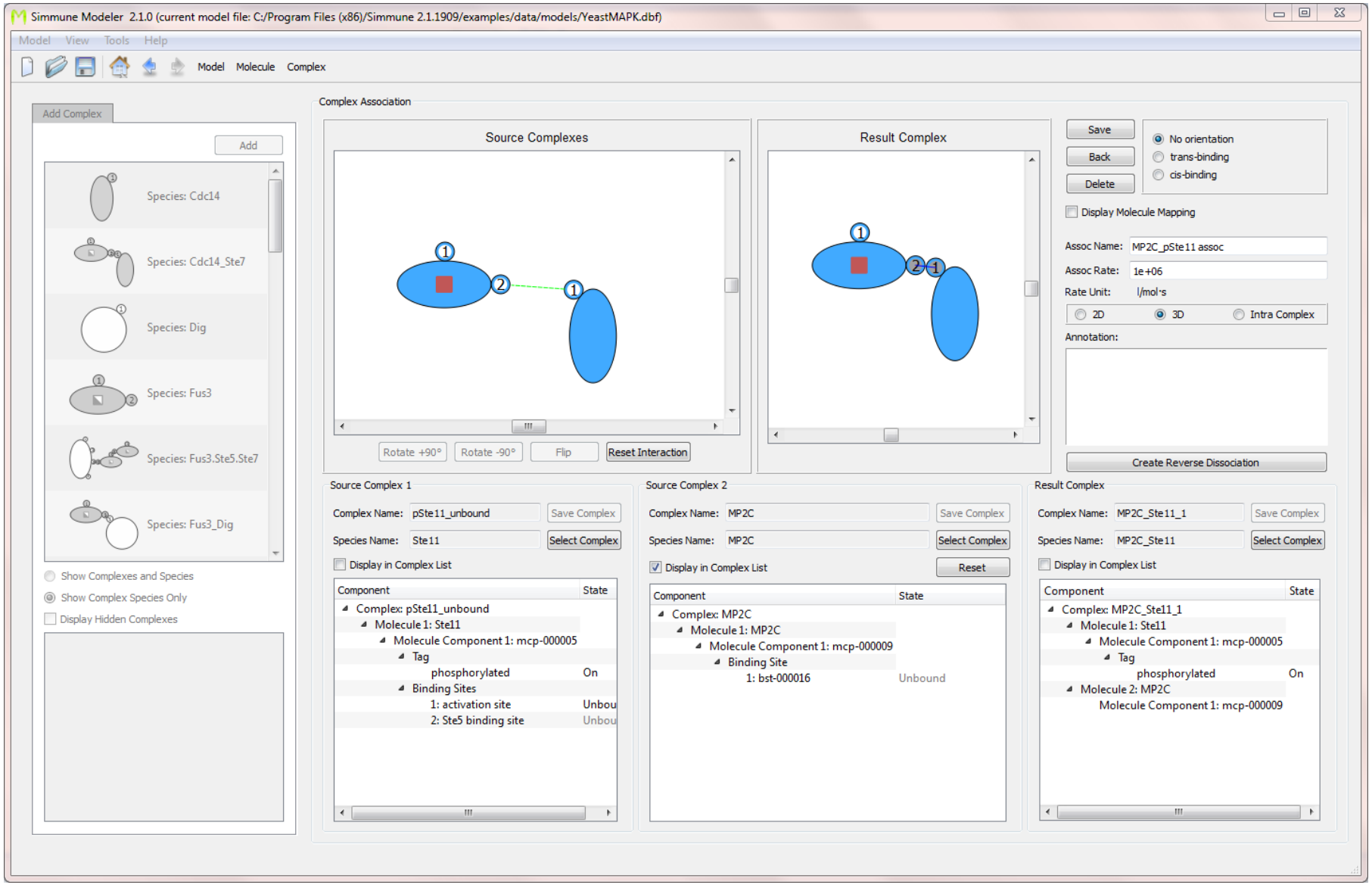


- Reaction rules (Relations among complexes)
  - Association
  - Dissociation
  - Transformation
  - Production
  - Degradation

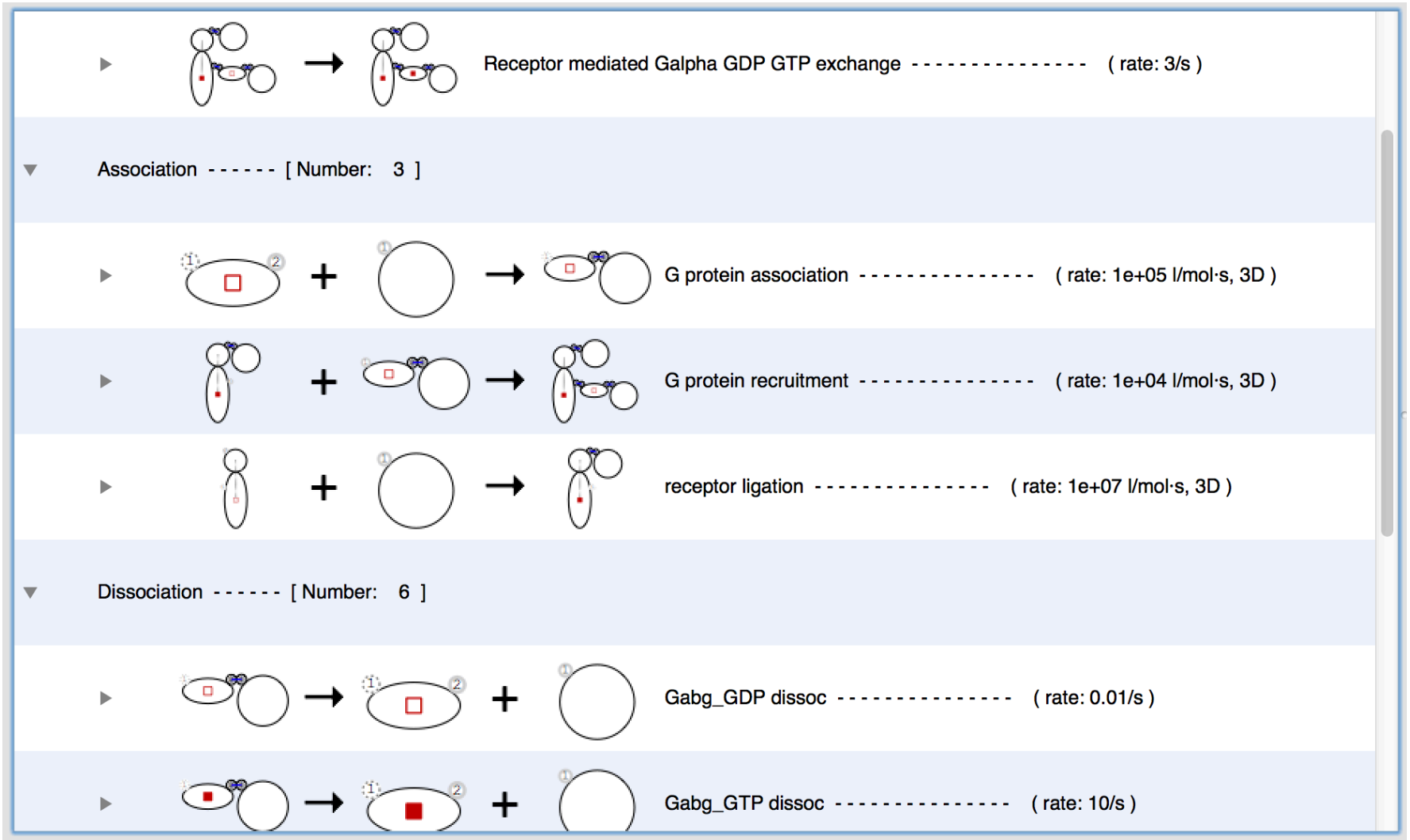


- Data export
  - Simmune model file (SQLite)
  - SBML L2V1, L2V4 and L3V1
  - SBML Multi 1.01 (libSBML 5.9.0 experimental release)

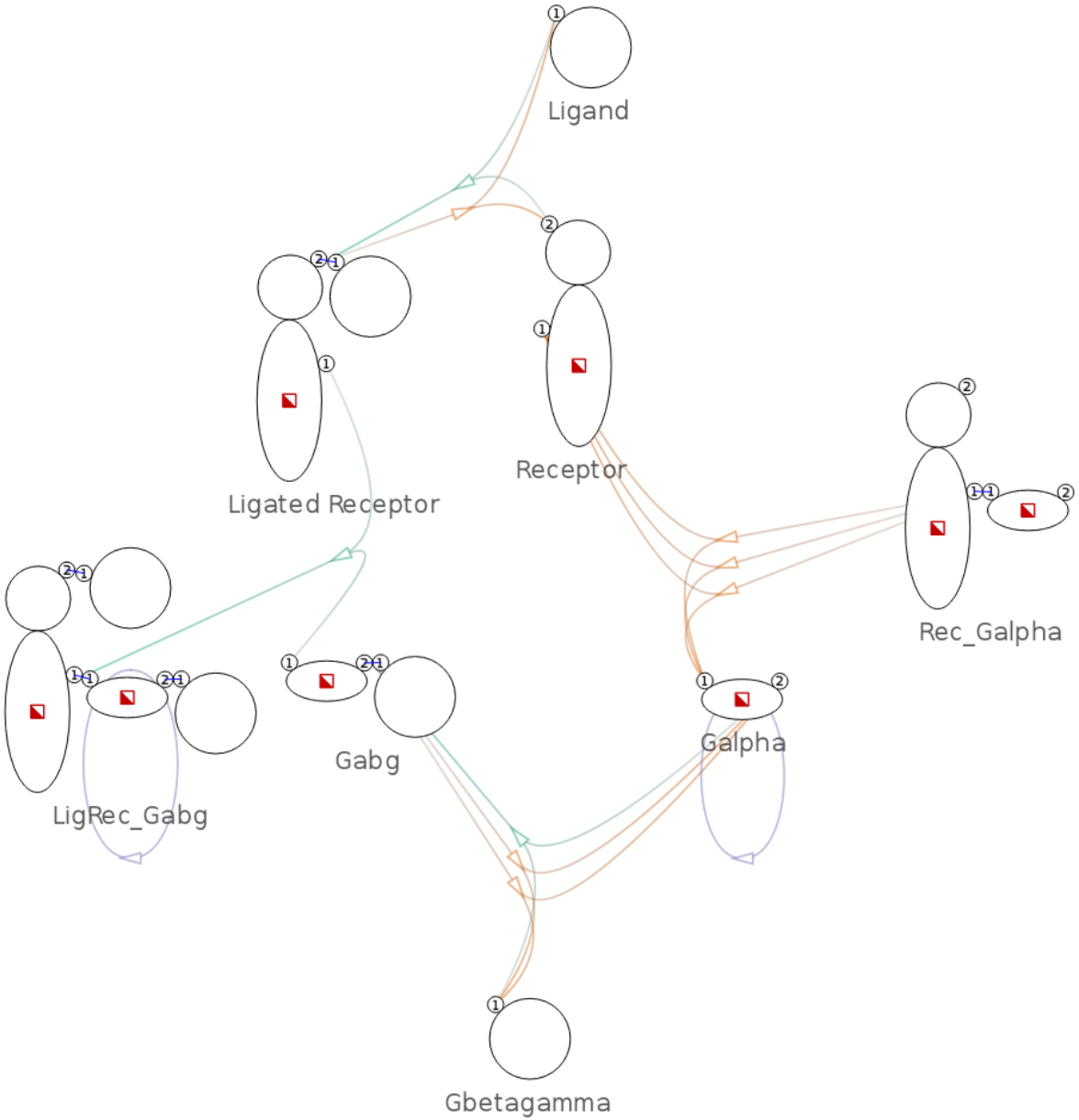
Simmune Modeler



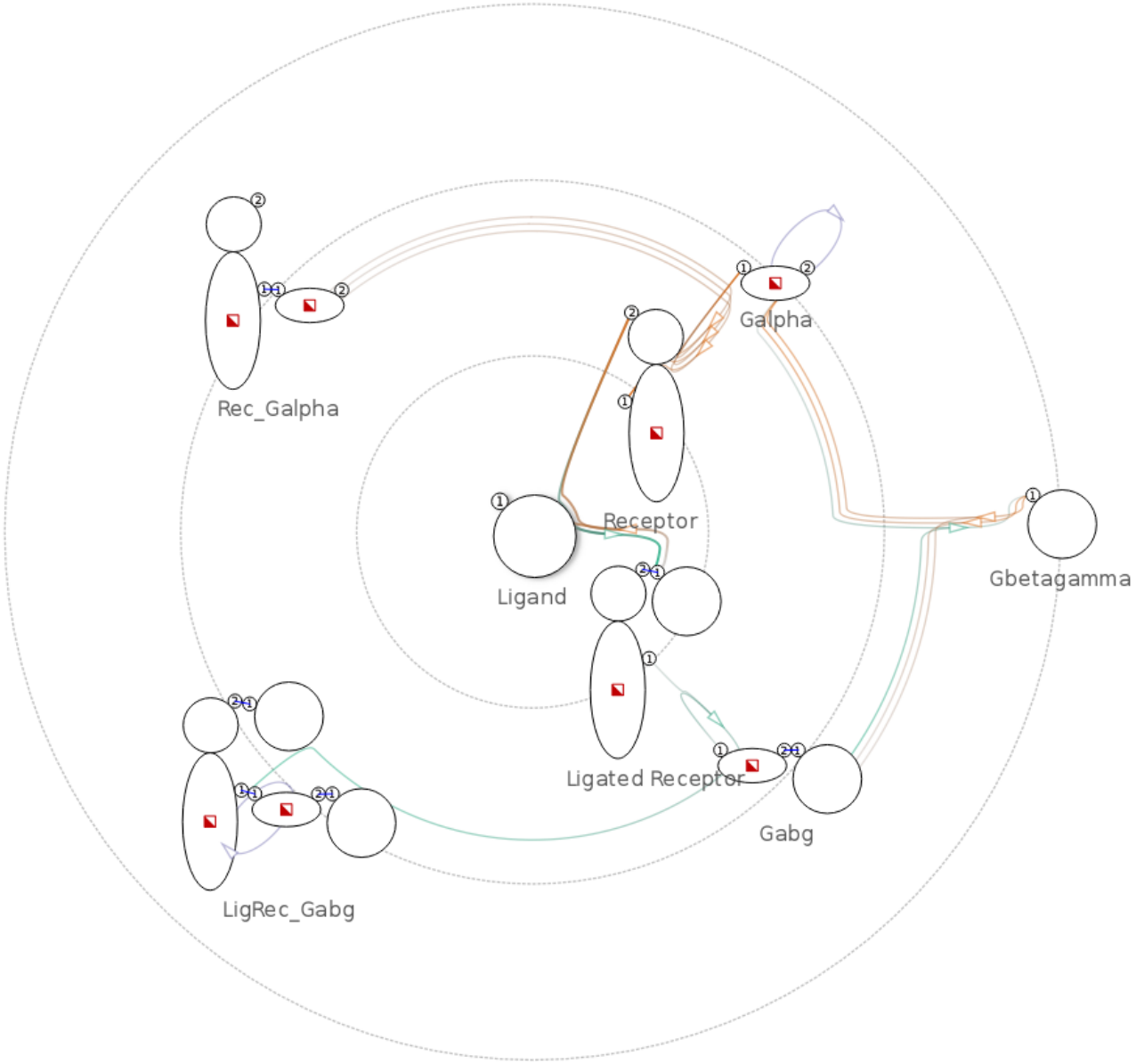
Simmune Modeler



Simmune Network Viewer: Level-based layout



Simmune Network Viewer: Circular layout

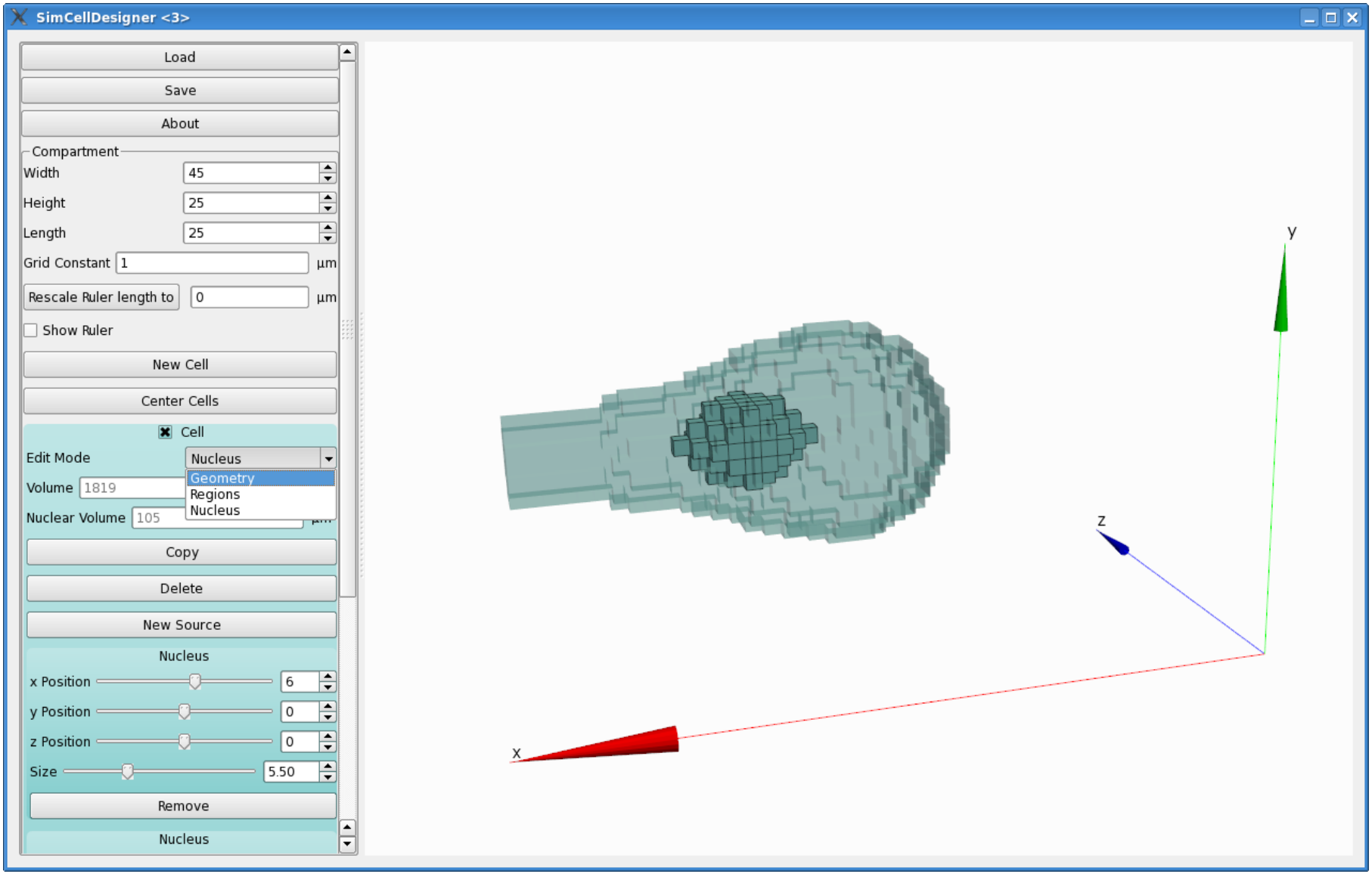


Simmune Network Viewer

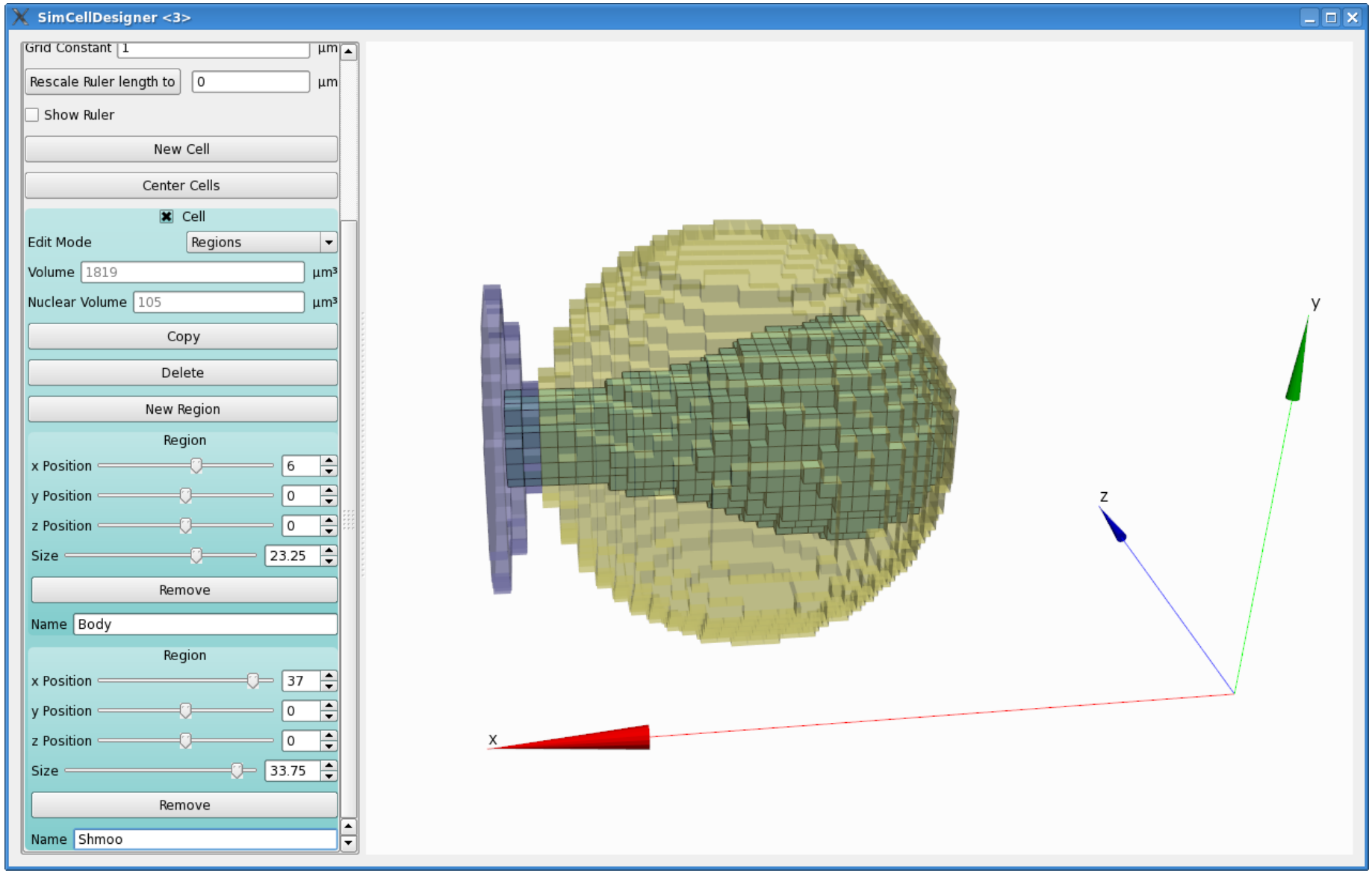
- Network layout options
  - Non-hierarchical layout
  - Level-based layout
  - Circular layout

- 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



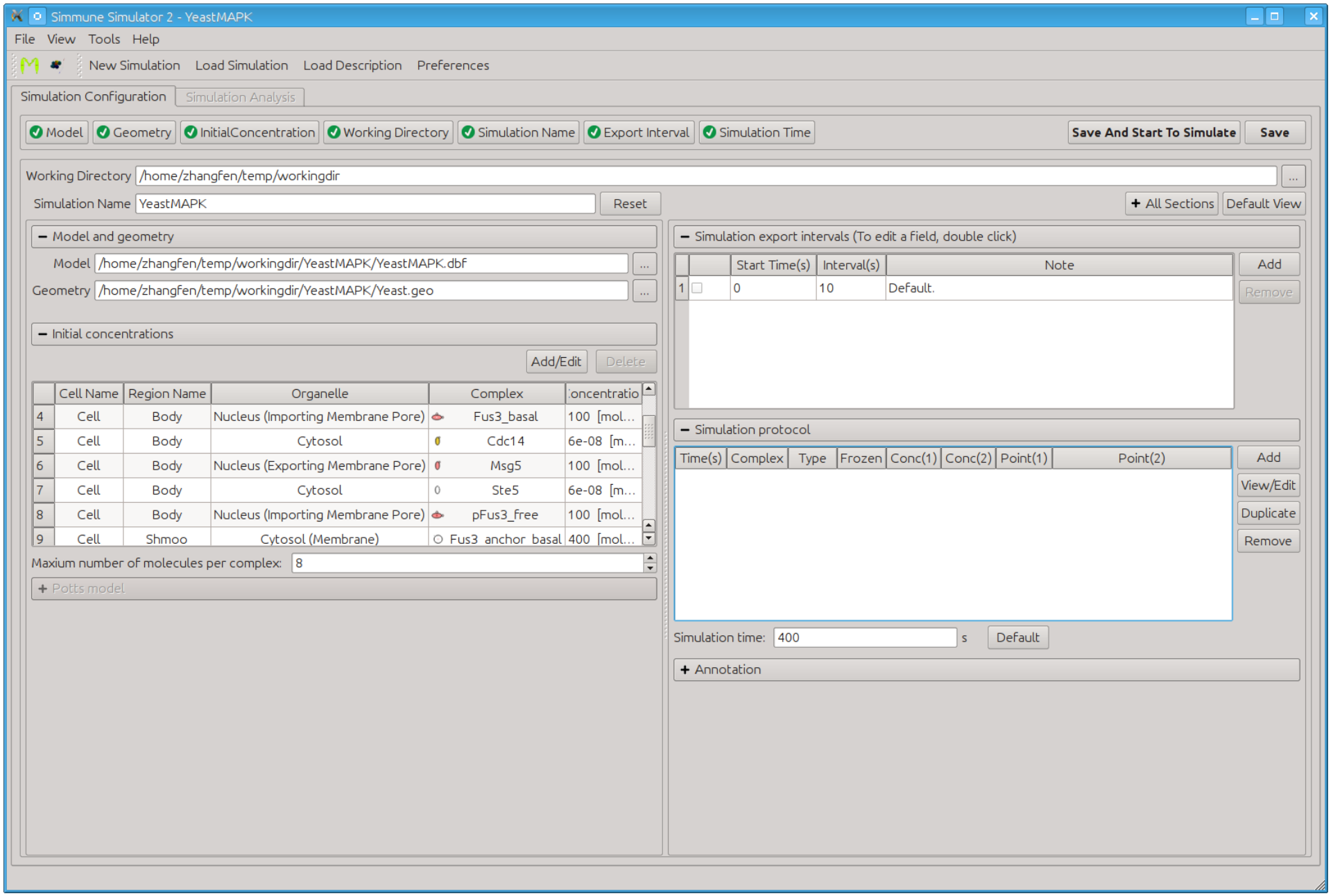
Simmune CellDesigner: Regions for initial concentrations



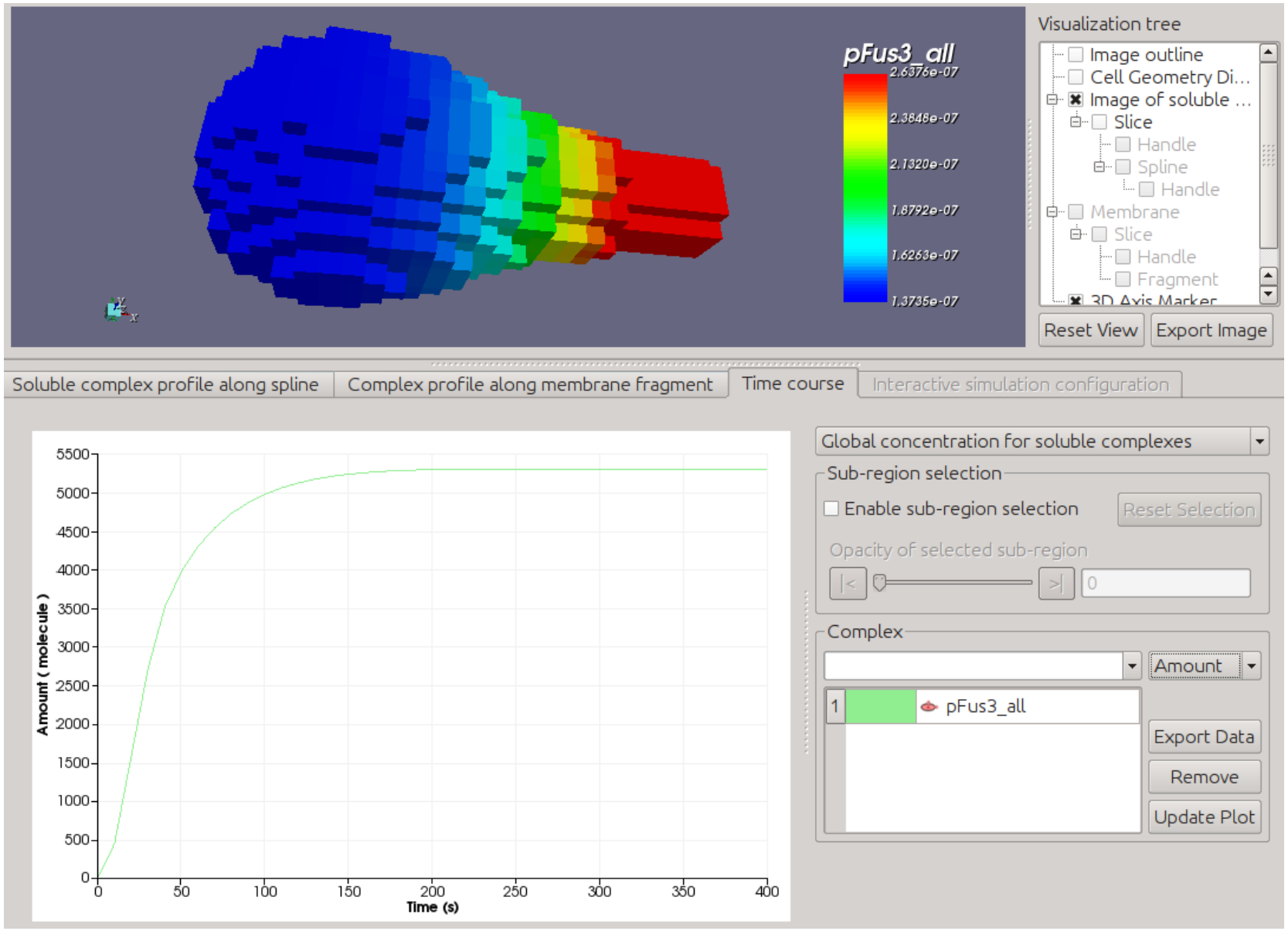
Simmune CellDesigner

- 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

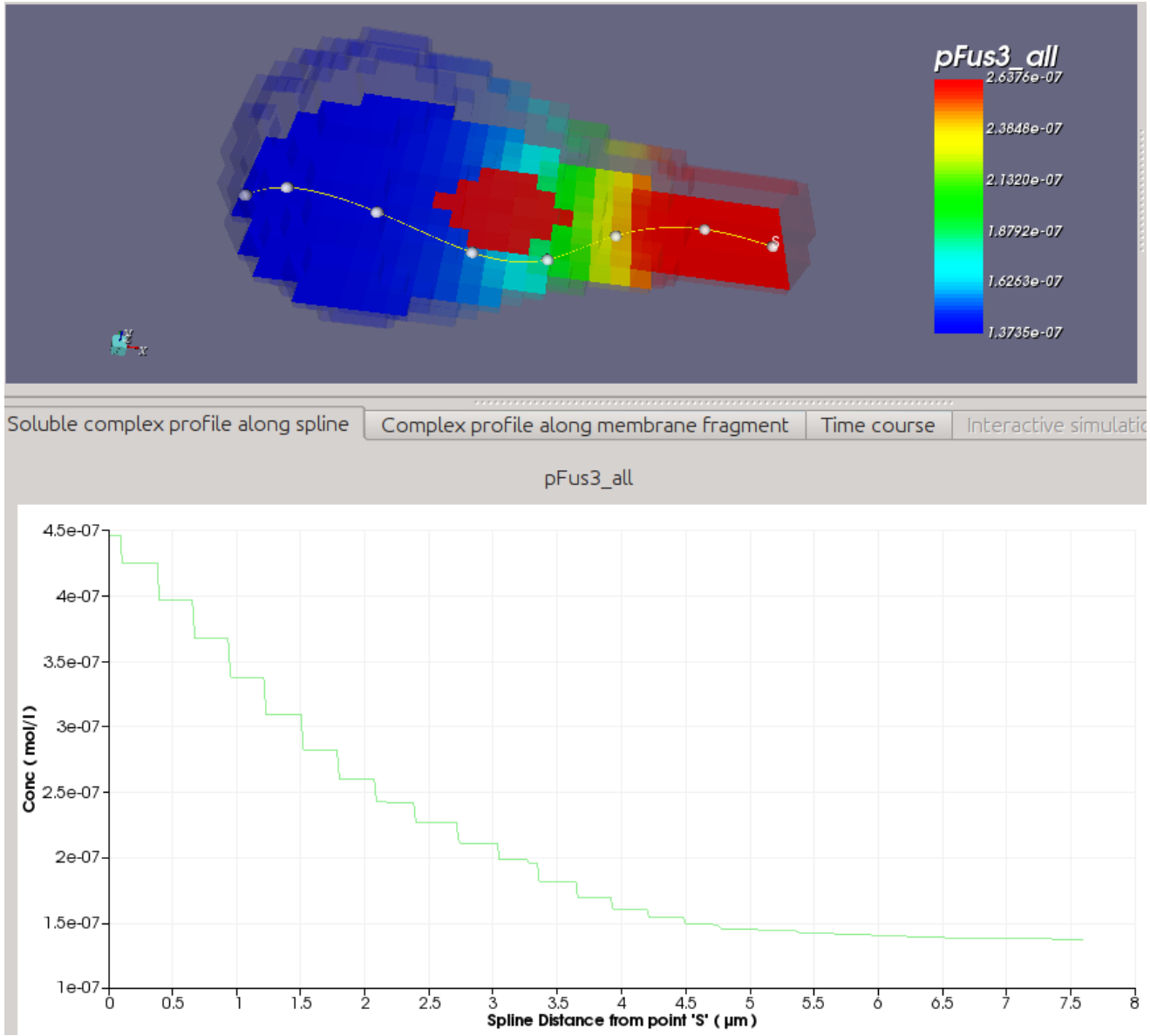
Simmune Simulator2: simulation configuration



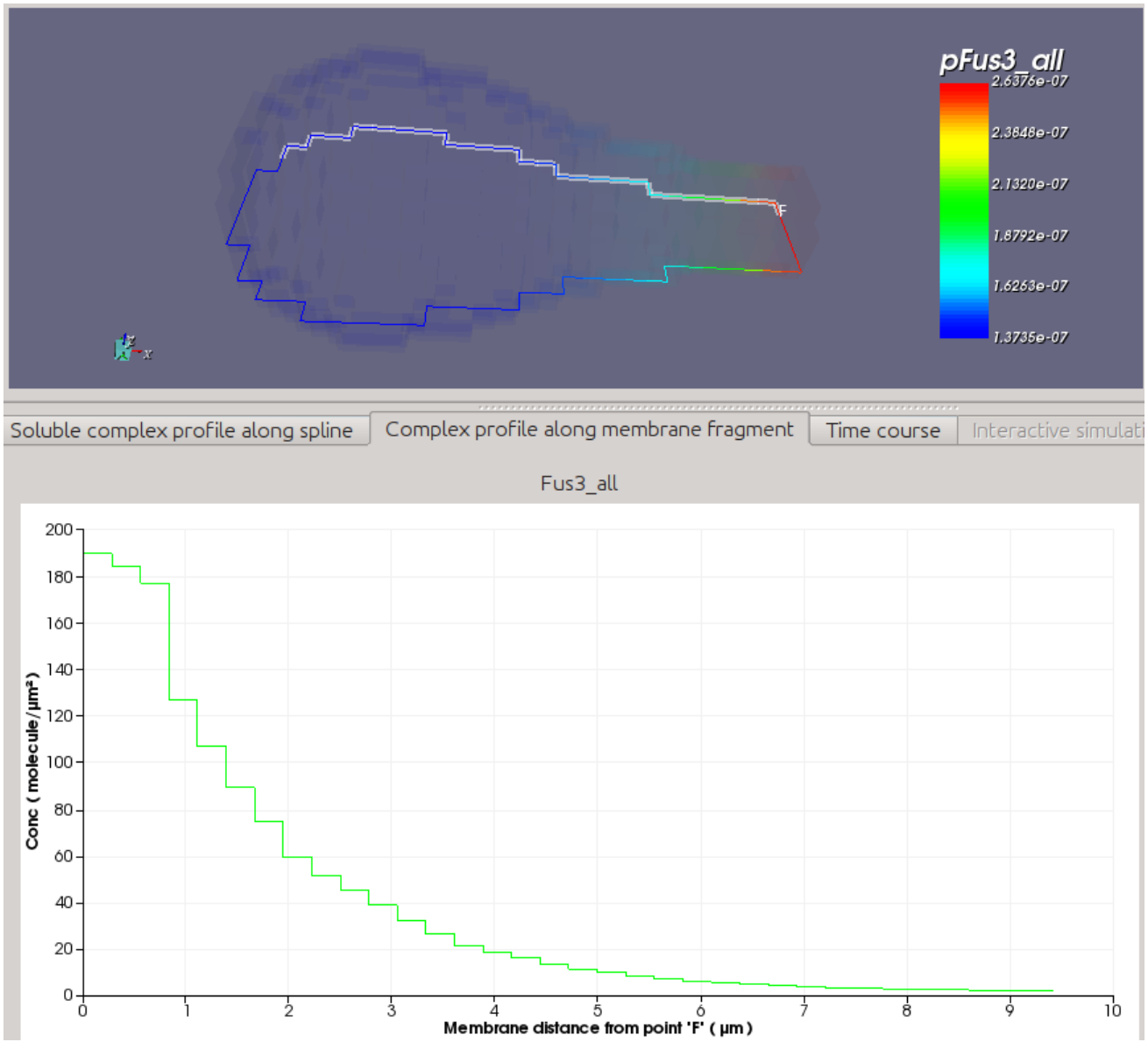
Simmune Simulator2: 3D visualization and time course plot



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>
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            <multi:listOfSpeciesFeatureValues>
              <multi:speciesFeatureValue multi:value="sfv_mcp_000001_activated_off"/>
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        </multi:listOfSpeciesFeatures>
      </species>
      <species id="sp_cpx_000002" name="Ligand" multi:speciesType="st_cps_000003">..
      <species id="sp_cpx_000003" name="Ligated Receptor" multi:speciesType="st_cps_000007">..
      <species id="sp_cpx_000004" name="Galpha_1" multi:speciesType="st_cps_000005">
```
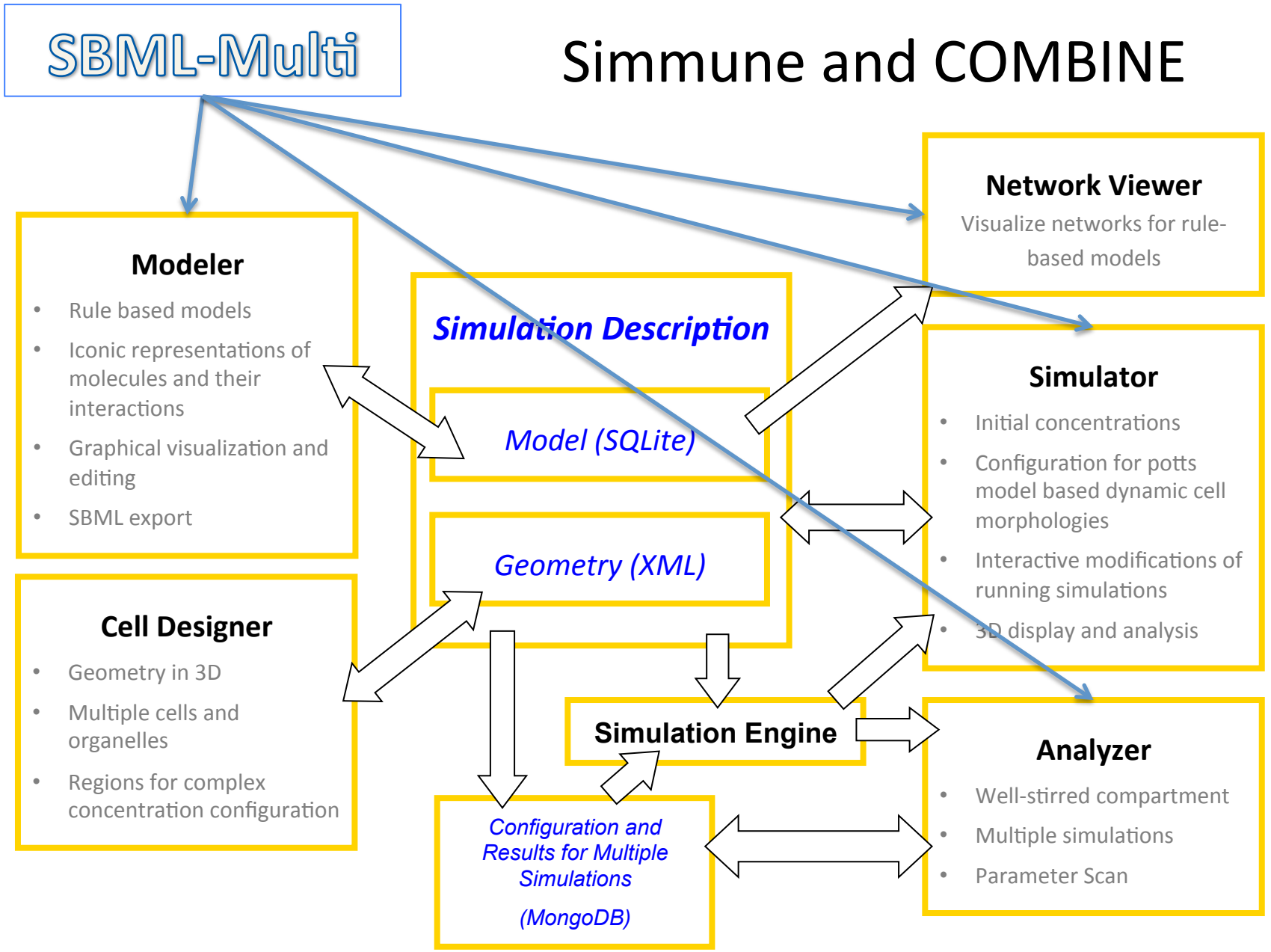
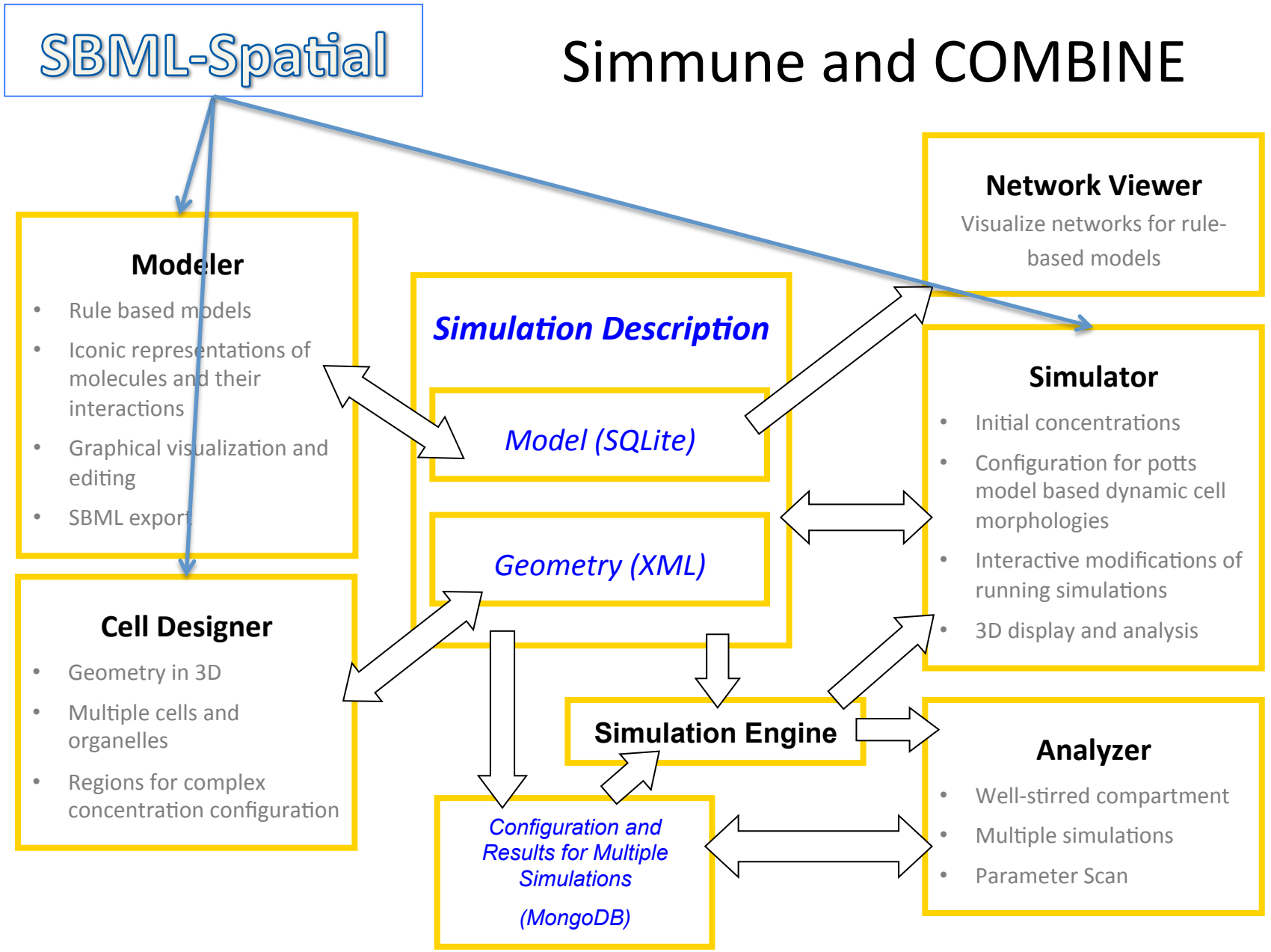
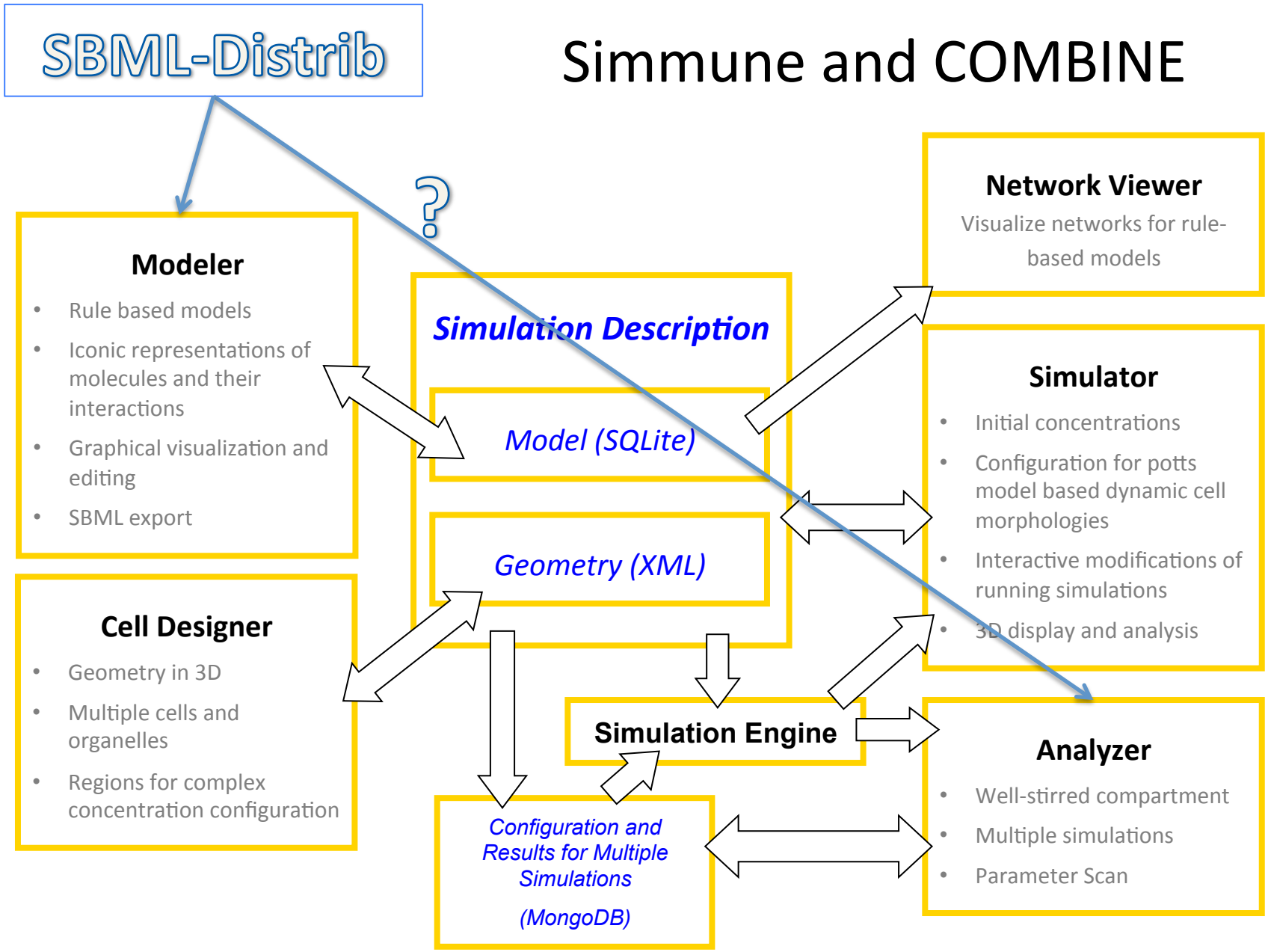

Simmune and COMBINE

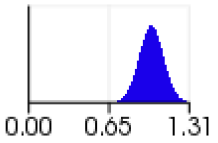


Simmune and COMBINE

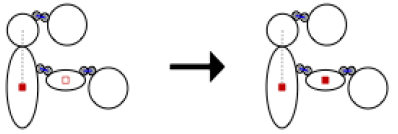


Simmune and COMBINE

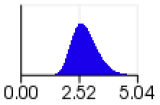


1	Ligand	0 nmol/l (3D)	Delta distribution at 1
2	Gbetagamma_1	0 molecule/micron² (2D)	 Distribution: Normal; mean: 1.0000000; standard deviation: 0.1000010

Galpha auto-GTPase ---------- (rate: 0.3/s)



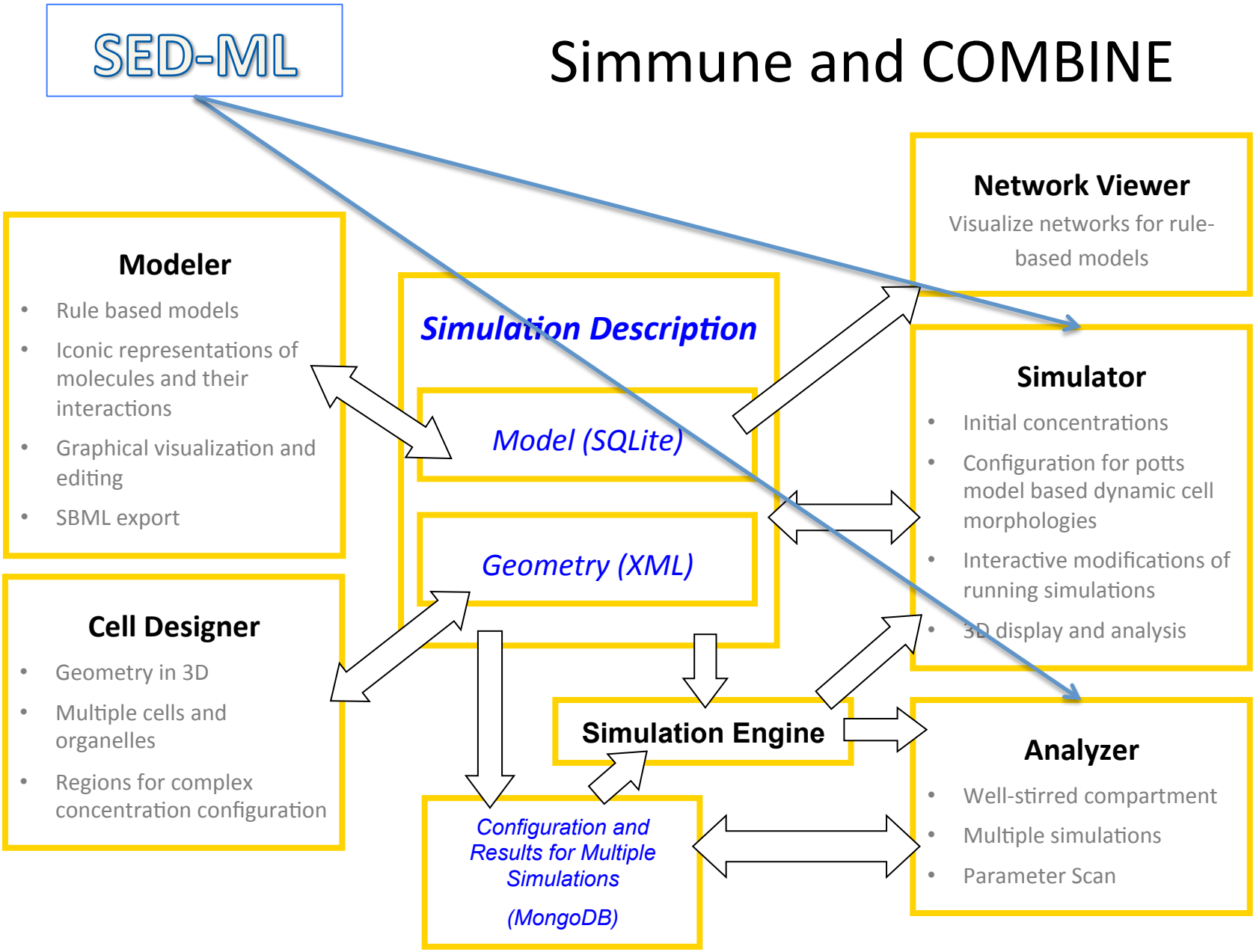
Receptor mediated Galpha GDP GTP exchange ---------- (rate: 3/s)



Delta distribution at 1

Distribution: Log Normal; mean: 1.0000000; scale: 0.2000010

Simmune and COMBINE



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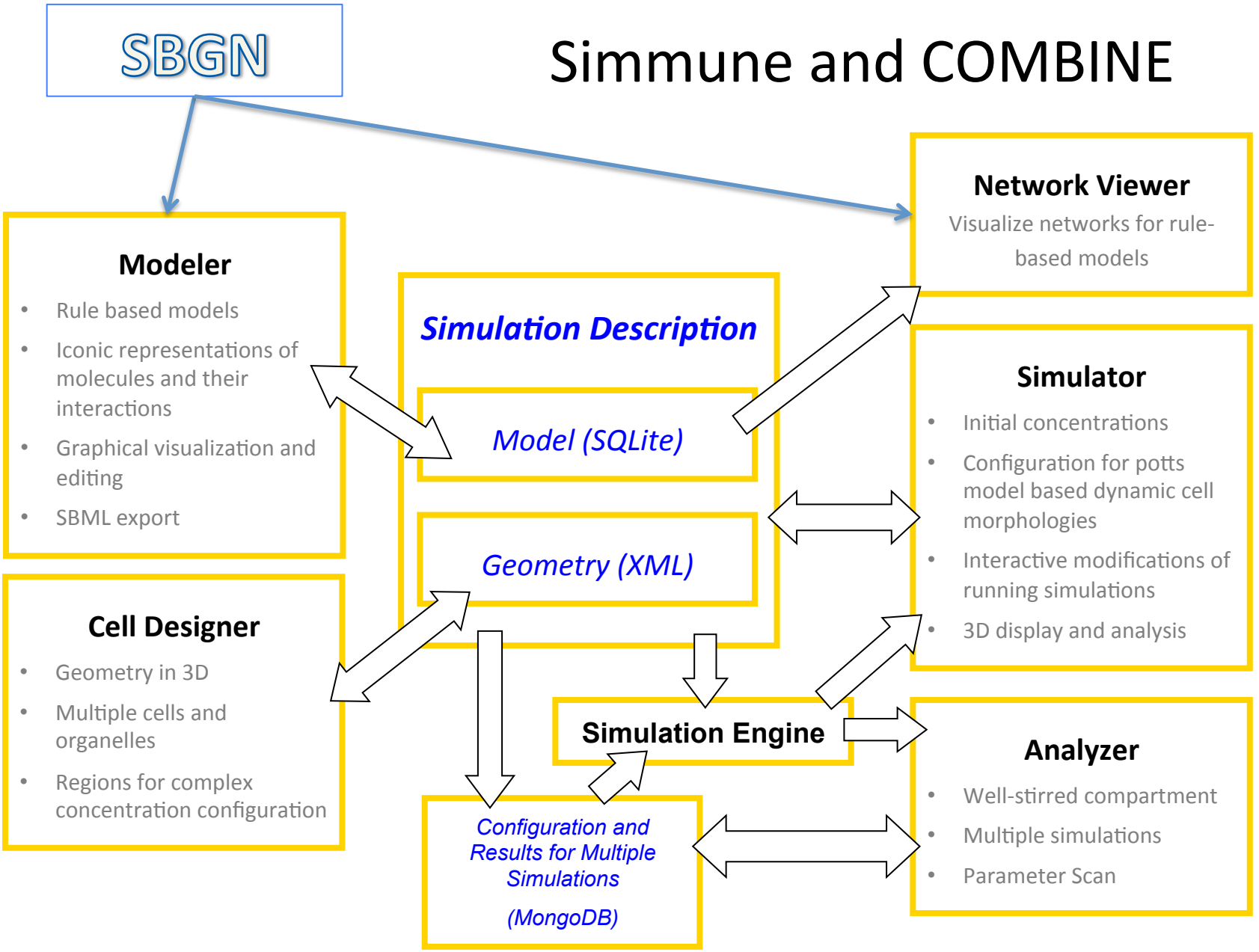
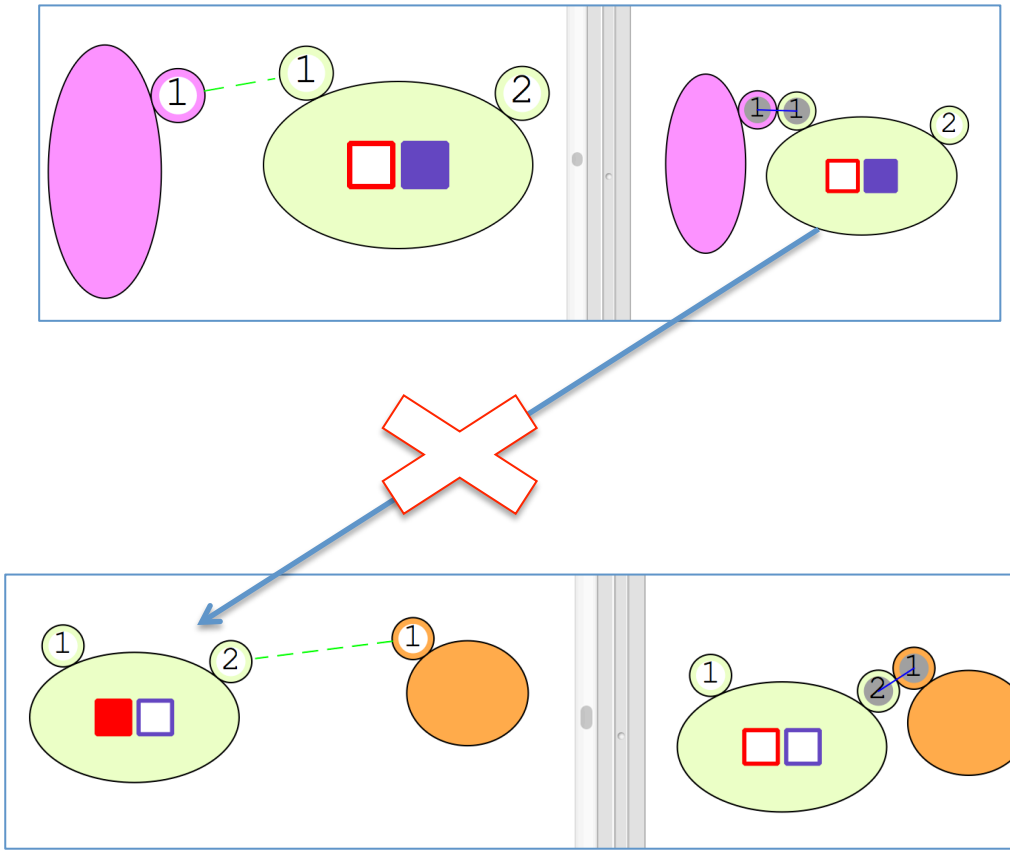
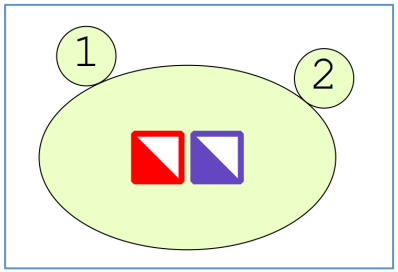
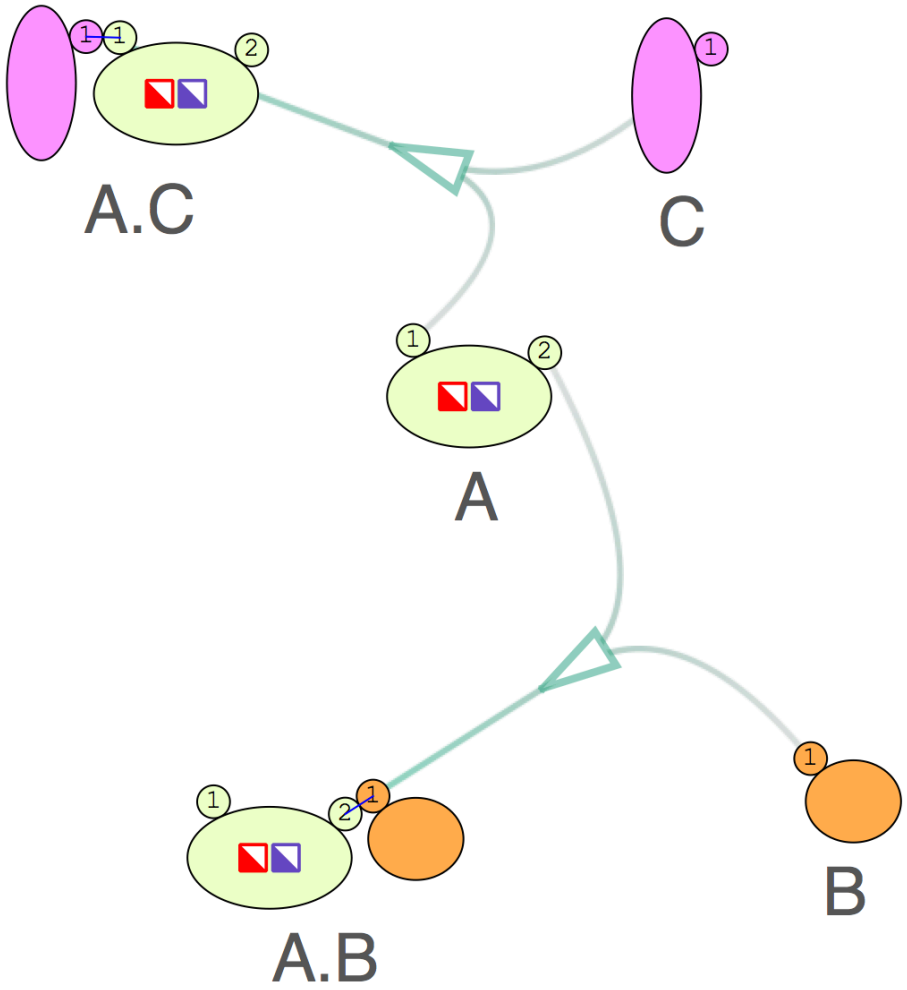


Simmune and SBGN

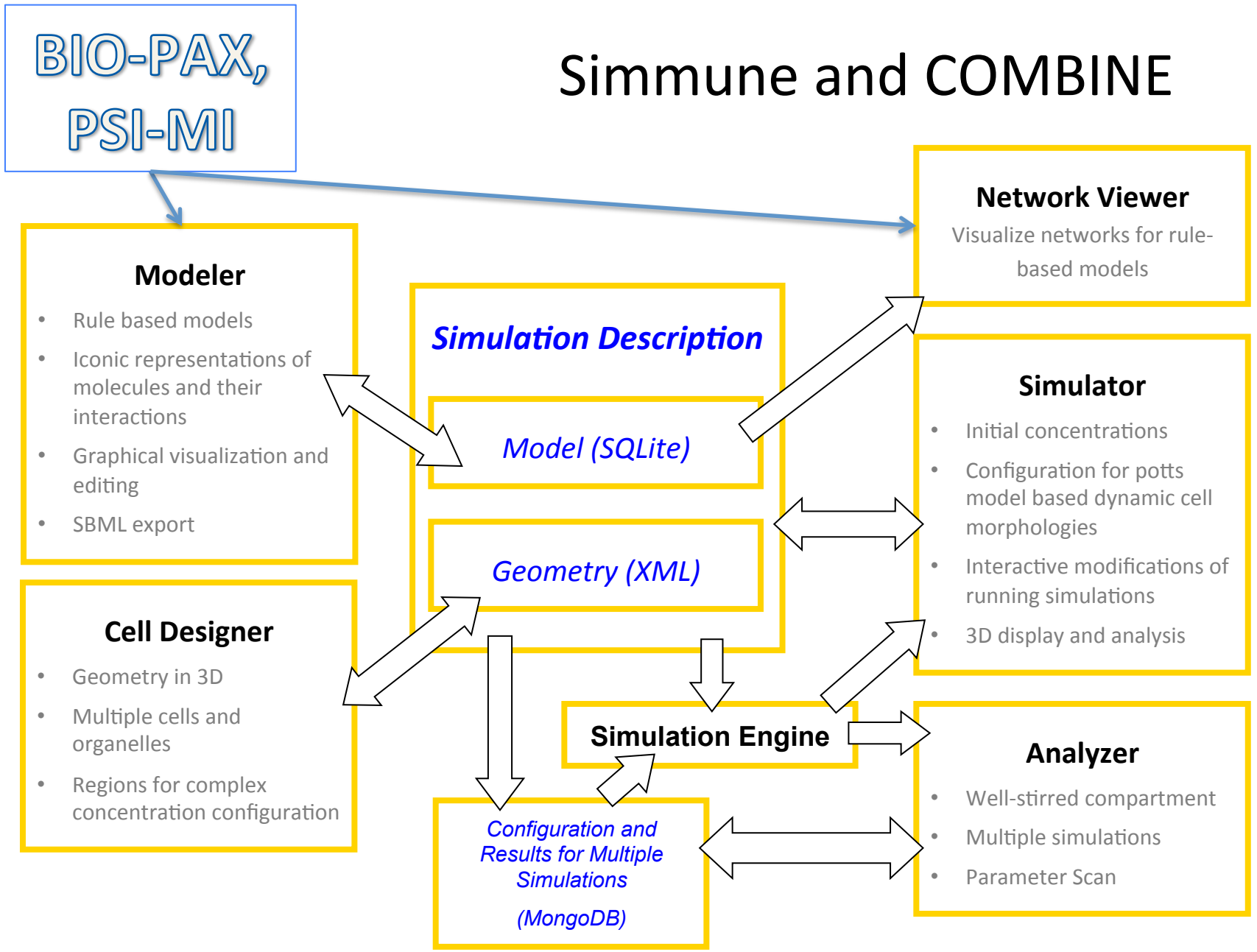




Simmune and SBGN



Simmune and COMBINE



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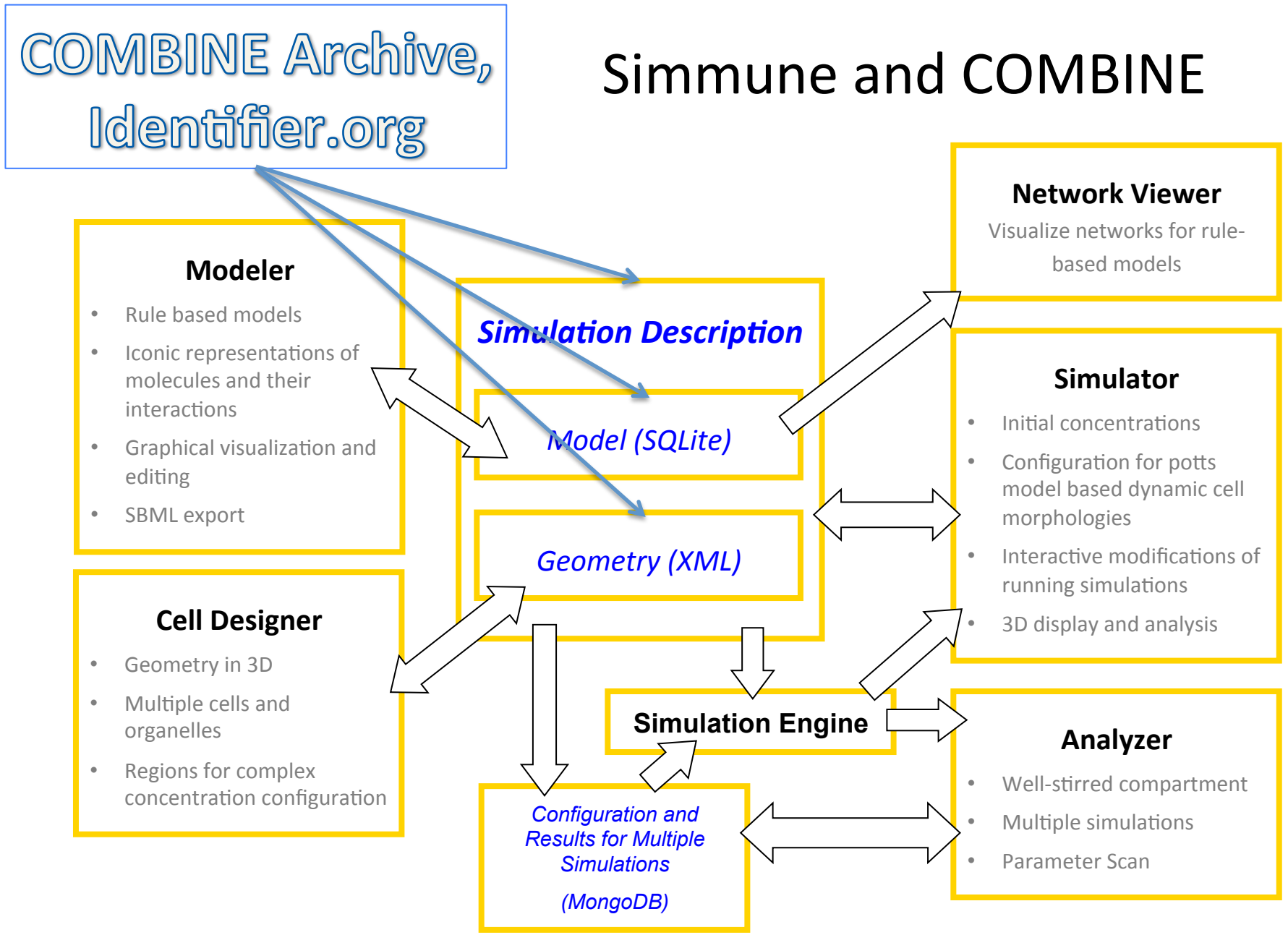

References

- 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
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  - 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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