

Implementation of SBML Level 3 Support within iBioSim

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COMBINE
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iBioSim 1.5: The Intelligent Biological Simulator

- Project management support.
- SBML Editor - used to create models using the *Systems Biology Markup Language* (SBML).
- GCM Editor - used to create *Genetic Circuit Models* (GCM).
- LPN Editor - used to create models using *labeled Petri nets* (LPN).
- reb2sac - abstraction-based ODE, Monte Carlo, and Markov analysis.
- TSD Graph Editor - visualizes TSD files.
- Probability Graph Editor - visualizes probability data.
- GeneNet - learns GCMs from time series data (TSD).
- Versions available for Windows, Linux, and MacOS from:
<http://www.async.ece.utah.edu/iBioSim>

Recent Updates

- GCM editor now has a schematic entry method.
- LPNs can now be translated to SBML for simulation.
- iSSA - *incremental stochastic simulation algorithm*.
Please see Curtis Madsen's ICSB poster.
- Implemented support for algebraic rules and some fast reactions.
- Added support for L3V1 including the new event semantics.
- iBioSim now passes all L3V1 tests in the SBML Test Suite.

L3V1 Modeling Issues

- No defaults, element creation fails when items are missing.
- Removal of compartment and species types, outside on compartments.
- Added compartment to reactions.
- Predefined units replaced with global model units.
- Change of spatial dimensions and unit exponents to use doubles.
- Local parameters used by reactions.

L3V1 Simulation Issues

- Add Avogadro constant.
- Species reference IDs replace stoichiometry math.
 - Translated these to parameters for simulation.
- Model and species conversion factors must be used when the state is updated due to reactions during simulation.

L2V3 Events

- ID / Name (optional)
- Trigger - expression evaluating to a Boolean
- Delay (optional) - expression evaluating to a non-negative real number
- List of event assignments

Implementation of L2V3 Events

- Update the event queue:
 - Add events whose trigger expression has changed from false to true.
 - Evaluate newly triggered events' delay expressions and schedule them for the current time plus the delay.
 - Evaluate their event assignments at trigger time.
- Select next event to execute:
 - If multiple events ready to execute, choice is arbitrary.
- Repeat this process until no additional events are executed.

L2V3 Example

- Current state: $t = 0$ and $a = b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

L2V3 Example

- Current state: $t = 10$ and $a = b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e1
Time	10
Assignments	$a := 1$

L2V3 Example

- Current state: $t = 10$, $a = 1$, and $b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e2	e3
Time	20	30
Assignments	$a := 2$	$b := 1$

L2V3 Example

- Current state: $t = 20$, $a = 2$, and $b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e3	e4	e5
Time	30	40	40
Assignments	$b := 1$	$c := 1$	$c = 2$

L2V3 Example

- Current state: $t = 30$, $a = 2$, $b = 1$, and $c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e4	e5
Time	40	40
Assignments	$c := 1$	$c = 2$

L2V3 Example

- Current state: $t = 40$, $a = 2$, $b = 1$, and $c = 1$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e5
Time	40
Assignments	$c = 2$

L2V3 Example

- Current state: $t = 40$, $a = 2$, $b = 1$, and $c = 2$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

L2V4 Events

- ID / Name (optional)
- Trigger - expression evaluating to a Boolean
- Delay (optional) - expression evaluating to a non-negative real number
- **UseValuesAtTriggerTime - Boolean**
- List of event assignments

Implementation of L2V4 Events

- Update the event queue:
 - Add events whose trigger expression has changed from false to true.
 - Evaluate newly triggered events' delay expressions and schedule them for the current time plus the delay.
 - If `UseValuesAtTriggerTime` is true, evaluate their event assignments.
- Select next event to execute:
 - If multiple events ready to execute, choice is arbitrary.
 - If `UseValuesAtTriggerTime` is false, event assignments are evaluated at execute time.
- Repeat this process until no additional events are executed.

L2V4 Example

- Current state: $t = 0$ and $a = b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

L2V4 Example

- Current state: $t = 10$ and $a = b = c = 0$.

- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e1
Time	10
Assignments	$a := 1$

L2V4 Example

- Current state: $t = 10$, $a = 1$, and $b = c = 0$.

- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e2	e3
Time	20	30
Assignments	$a := 2$	$b := a$

L2V4 Example

- Current state: $t = 20$, $a = 2$, and $b = c = 0$.

- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e3	e4	e5
Time	30	40	40
Assignments	$b := a$	$c := 1$	$c = 2$

L2V4 Example

- Current state: $t = 30$, $a = 2$, $b = 2$, and $c = 0$.

- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e4	e5
Time	40	40
Assignments	$c := 1$	$c = 2$

L2V4 Example

- Current state: $t = 40$, $a = 2$, $b = 2$, and $c = 1$.

- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e5
Time	40
Assignments	$c = 2$

L2V4 Example

- Current state: $t = 40$, $a = 2$, $b = 2$, and $c = 2$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	$t \geq 10$	$a == 1$	$a == 1$	$a == 2$	$a == 2$
Delay		10	20	20	20
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

L3V1 Events

- ID / Name (optional)
- Trigger - expression evaluating to a Boolean
 - **initialValue** - Boolean
 - **persistent** - Boolean
- Delay (optional) - expression evaluating to a non-negative real number
- **Priority (optional)** - expression evaluating to a real number
- UseValuesAtTriggerTime - Boolean
- List of event assignments

Implementation of L3V1 Events

- Update the event queue:
 - Add events whose trigger expression has changed from false to true.
(at $t = 0$ consider `initialValue`)
 - Evaluate newly triggered events' delay expressions and schedule them for the current time plus the delay.
 - If `UseValuesAtTriggerTime` is true, evaluate their event assignments.
 - Remove events with non-persistent trigger expressions that become false.
- Select next event to execute:
 - Compute priority of all events that can be executed at the current time, and execute the event with the highest priority.
 - If `UseValuesAtTriggerTime` is false, event assignments are evaluated at execute time.
- Repeat this process until no additional events are executed.

L3V1 Example

- Current state: $t = 0$ and $a = b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	a==1	a==1	a==2	a==2
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

L3V1 Example

- Current state: $t = 10$ and $a = b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	$a==1$	$a==1$	$a==2$	$a==2$
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e1
Time	10
Assignments	$a := 1$

L3V1 Example

- Current state: $t = 10$, $a = 1$, and $b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	$a==1$	$a==1$	$a==2$	$a==2$
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e2	e3
Time	20	30
Assignments	$a := 2$	$b := a$

L3V1 Example

- Current state: $t = 20$, $a = 2$, and $b = c = 0$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	$a==1$	$a==1$	$a==2$	$a==2$
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e4	e5
Time	40	40
Assignments	$c := 1$	$c = 2$

L3V1 Example

- Current state: $t = 40$, $a = 2$, $b = 0$, and $c = 2$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	$a==1$	$a==1$	$a==2$	$a==2$
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$

- Event queue:

ID	e4
Time	40
Assignments	$c = 1$

L3V1 Example

- Current state: $t = 40$, $a = 2$, $b = 0$, and $c = 1$.
- Events:

ID	e1	e2	e3	e4	e5
Trigger	true	$a == 1$	$a == 1$	$a == 2$	$a == 2$
InitialValue	false	true	true	true	true
Persistent	true	true	false	true	true
Delay	10	10	20	20	20
Priority	0	0	0	1	2
AtTriggerTime	true	true	false	true	true
Assignments	$a := 1$	$a := 2$	$b := a$	$c := 1$	$c := 2$