

## Reviewer's report

**Title:** The systems biology simulation core algorithm

**Version:** 1 **Date:** 14 February 2013

**Reviewer number:** 1

### Reviewer's report:

I liked this article a lot! Its dual purpose of 'introducing this software library' and 'telling others how to interpret the tricky bits of SBML' are both good goals, and they were integrated well in this paper.

#### Major Compulsory Revisions:

1. Explain the methodology behind the Biomodels database comparison. While I know how the test suite works, I am unclear how you tested models against the Biomodels database. I know in the past, the only way to compare simulators against the biomodels db was to perform the same analysis on all of them and display the results (Frank Bergmann did this in 2008; your reference 20) Is there a new way of managing this comparison? Your Biomodels reference is from 2006. At the time, it was actually impossible to say who was 'right', because for some models, many simulators disagreed with each other. If this is something you've put together yourself, some explanation would be great, and if it's something that Biomodels has done since 2008 and published, a reference to that would be great. If it's something they've done since 2008 but haven't published... I guess if you could quickly explain it, that'd be good?

#### Minor Essential Revisions:

2. You make a point of stating in the Table 1 legend that iBioSim correctly simulates the vast majority of the test suite, but doesn't do delay... but in the table, iBioSim has a checkmark for 'Fully SBML Test Suite Compliant'. I know iBioSim has been working on implementing support for delay recently; was this a last-minute update?
3. You don't explicitly state what the deal is with LibSBMLSim's entry "L3, L2v4" instead of a checkmark; this should go in the legend. (Also, why can't it up-translate and simulate? I happen to know this is what iBioSim does...)
4. "The major difference between both is that an event with delay can trigger multiple times before it is executed." Actually, what with simultaneous events and priorities, even events with no delays can trigger multiple times before being executed. Case 978 tests this.
5. p6: 'assignmens'
6. There are comma issues here and there.

#### Discretionary revisions:

7. It would also be nice to see what other simulators did with the Biomodels database, though if it's a SED-ML thing, it looks like none of the others are going

to be able to do it straightforwardly, so that'd be a ton of work for you, and not worth it for a single column of data. Maybe if you ran those four models from the db you failed through those other simulators? It might be that the db itself is wrong for those four...

8. Speaking of the four failed biomodels models, providing a statistic like '99.06%' totally invites questions about the four you failed on, especially since you passed 100% of the test suite. Was it numerical issues? Something ill-formed? Are there any other simulators which get the expected results? Even just a sentence or two would be great, but something should be done because everyone is going to focus on the 4 instead of the other 420, unfortunately.

9. Model 966 is not really slow just because there are 23 events, but because those 23 events have to be re-evaluated thousands of times. Might be worth clarifying.

10. Both times you use 'SCL', you also explicitly say "Systems Biology Simulation Core Library" which defeats the purpose of having an acronym. Probably best just to leave the acronym off.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.