Point-to-point list

We have carefully read all reviewer comments and addressed each single one appropriately. The following is a brief summary of major changes:

- We changed and shortened the abstract.
- The first paragraphs of the introduction are rewritten to emphasize the differences between BioPAX and SBML and the need of a converter from BioPAX to SBML qual.
- The material and methods section was shortened and a very detailed and technical paragraph was moved to the supplement, as well as a corresponding figure.

In the following, we would like to discuss all reviewer comments in detail. Therefore, we colored the reviewer comments in red and our answers/actions in blue below.

Reviewer: 1
Comments to the Author

1) General comments

The authors describe a converter between the systems biology modeling formats of Biopax and SBML. It is good to learn that the developers of competing data formats are pooling their resources in order to simplify the modelling process. Furthermore, it appears clear that the work in developing such a conversion tool has been performed thoroughly and is described clearly in the manuscript. However, it is difficult for the lay reader to understand the necessity for the competing formats from the manuscript provided. Upon reading the paper, a number of questions remain that are listed below.

2) Specific comments for revision

a) major

Overall, it is unclear who the target audience for such a paper would be and why the converter is necessary. Without this additional contextualization, the manuscript itself reads as a rather dry technical note that would be of little interest to the general readership of the journal. Could the authors please therefore give more consideration to the following questions?

Why is a converter necessary? Are competing formats necessary?

SBML and BioPAX are competing formats in systems biology modeling. SBML is mostly used for quantitative modeling and simulation, and BioPAX for qualitative description of pathway relationships. There are two publications that further discuss the differences between those formats in detail: Strömbäck et al. (2006, 2005). These publications are now also cited in the manuscript. Many databases and applications were established for either one of the two languages. For instance, MetaCrop and SABIO-RK exclusively provide their models with SBML but not with BioPAX because they contain mathematical expressions for dynamic simulation that cannot be represented in BioPAX.
There exist several converters from SBML to BioPAX. For the other conversion direction, there exist just a few converters which are not satisfactory (they are discussed in the manuscript). Following, the pathways from databases, like Nature Pathway Interaction Database or MetaCyc providing their models with BioPAX and not with SBML, cannot be used for SBML modeling. But there is a need for using BioPAX models as information source for creating SBML models that are further used for

simulations (see Figure 1 and Bauer-Mehren et al. (2009)). This is why a converter from BioPAX to SBML is important. Another need for creating this converter is the development of the Qualitative Models extension, which now allows building qualitative models with SBML.

We have changed the introduction to more clearly describe and emphasize the need for such a converter.

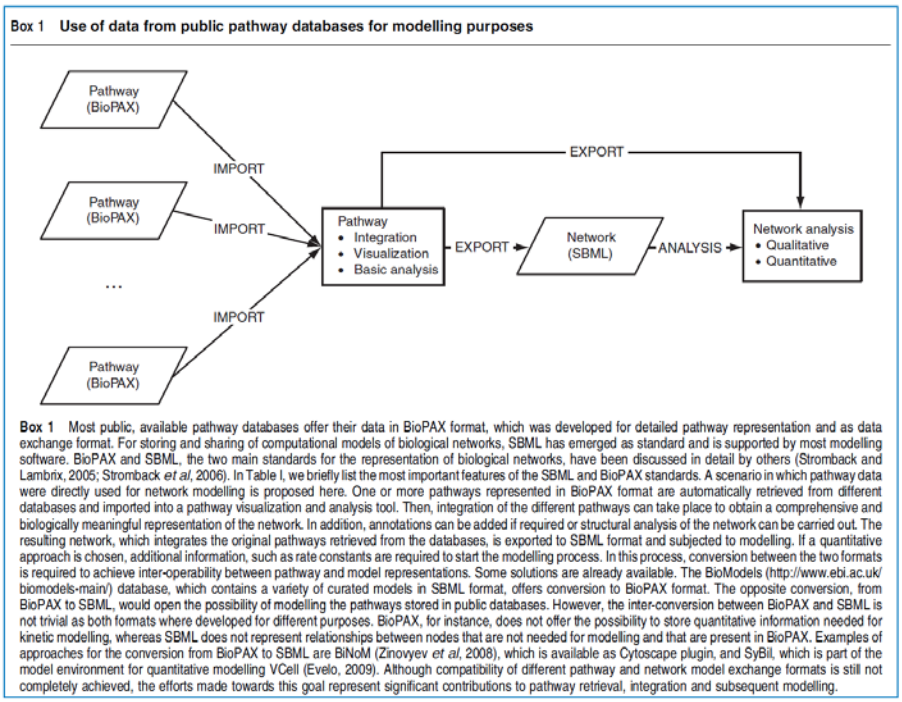

Figure 1 by courtesy of Bauer-Mehren et al. 2009

Bauer-Mehren, A., Furlong, L. I., and Sanz, F. (2009). Pathway databases and tools for their exploitation: benefits, current limitations and challenges. Mol Syst Biol, 5, 290. (http://www.ncbi.nlm.nih.gov/pubmed/19638971)

Strömbäck, L., Jakoniene, V., Tan, H. and Lambrix, P. (2006). Representing, storing and accessing molecular interaction data: a review of models and tools. Briefings in Bioinformatics, 7(4), 331–338. (http://www.ncbi.nlm.nih.gov/pubmed/17132622)

Strömbäck, L. and Lambrix, P. (2005). Representations of molecular pathways: an evaluation of SBML, PSI MI and BioPAX. Bioinformatics, 21(24), 4401–4407. (http://www.ncbi.nlm.nih.gov/pubmed/16234320)

What can be done with an SBML model that could not be done with the original Biopax model? What software supports the SBML version?

The modeling language SBML allows the simulation of quantitative models whereas BioPAX is not able to store neither quantitative parameters nor mathematical expressions that are required, e.g., for simulations. Examples are reaction kinetics, which are only available in SBML models. Following, simulations with BioPAX are not possible. Common used SBML simulators are, for example, SBMLsimulator or COPASI, and a popular graphical SBML editor is CellDesigner. SBML Level 3 Version 1 is relatively young and SBMLsimulator as well as COPASI are already able to read it. A complete list of available SBML software can be found on the SBML Software guide at

http://sbml.org/SBML_Software_Guide/SBML_Software_Summary or at http://sysbioapps.dyndns.org/SoftwareMatrix.

We changed the introduction to more clearly describe the differences.

Can the authors provide simulation results from both the Biopax version and the SBML version of one or more models to ensure that the conversion is not lossy and that the model represented by both formats is comparable?

The manuscript focuses on the conversion from BioPAX to SBML. It is not possible to perform simulations with BioPAX because the quantitative parameters and mathematical expressions cannot be expressed within this language. Following, the resulting SBML file also lacks the mathematics. This mathematics as well as the boolean functions and start parameters for the qualitative simulation must be inferred firstly. Several publications focus on such simulations that require, depending on the type of simulation, multiple further steps. For example, adding kinetics to the model, experimentally measuring metabolite data, fitting the data on the model and then performing the simulation.

It is the opinion of the reviewer that without a clearly description of the context of the work, the manuscript appears to be more of a technical application note than a research article. Could the authors therefore please improve this area?

Indeed the methods part is extremely technical in contrast to the other parts of the paper and probably, the verbatim font emphasizes this impression. Our intention was to differentiate with this font between BioPAX instances, SBML instances and those instances used in the normal speech. For example the term ‘reaction’ can be used for a normal reaction but also for an instance in SBML. Following we use ‘`reaction`’ to denote an SBML instance and use ‘reaction’ if we describe a biochemical reaction.

We agree that some parts were not easy to read and quite technical. Therefore, we rewrote some parts of the manuscript and decided to put a specific paragraph (conversion of BioPAX Control elements) in the supplement. Since Figure 2 was only referenced in this part, we also moved it to the supplement. With these changes, we think the technical parts are shortened and general readability of the manuscripts has been improved.

b) minor

The manuscript is clearly and carefully written, and as such, the only minor error appears to be the spelling mistake of “SMBL” in the final sentence of section 3.1.

Thank you, we corrected it.

Reviewer: 2
Comments to the Author
This is the best BioPAX to SBML converter available by far and clearly addresses a need in the community. I would like the thank authors for their contribution.

Thank you very much for the compliment. We are happy that we could make a contribution in this area.

I was very interested in reading the technical details about the conversion - but I am not sure if all of them are of interest to the general audience. I suggest moving the most technical parts to an Appendix.

We agree and decided to shorten section 2.3.3. The more detailed parts can now be found in the supplement.

I sometimes found the wording a little bit off : For example a translator can be "sophisticated" - but I think the translation process itself should be called "complex" and/or "complicated". There are several minor cases like this and I think the article can benefit from another round of editing.

Thanks, we changed the corresponding parts.

Reviewer: 3
Comments to the Author
This paper presents a useful tool for converting BioPAX models into SBML models using the qualitative modeling extension. The advantages of this tool over comparable tools already available is well described in Table 3. The main advantage being the ability to minimize the loss of information by leveraging the transition construct in the qual package to represent relationships that cannot be cleanly encoded as reactions.

I do have a few minor comments that I would like to see addressed:

1) Abstract, "erroneously converted to reactions", I find this comment too harsh. While you may disagree that with this approach, it may still capture the behavior. For example, one can easily imagine a repression relationship encoded using reactions perhaps with the addition of SBO terms.

Indeed that would be possible. However, due to the existence of the Qualitative Models extension this approach would not be proper. As you said, the formulation was a bit harsh and we changed it in the document to “Before the development of SBML qual, relations could not be properly translated into SBML”.

2) Pg 1, col 2, line 2, semantic -> semantics

Corrected.

3) "The SBML core specification provides no possibility to define other relationships than concrete quantitative reactions." This is not accurate. SBML has more constructs than reactions, such as events, rules, constraints, etc. While these are quantitative, they are not reactions. You should mention these additional constructs supported by core SBML but it is okay to say they are not qualitative.

Thank you for pointing this out. The manuscript now includes more details on this in the Introduction and Material and Methods section.

4) I may have missed it but I could not find a reference to Table 1.

The reference was listed in brackets with a citation in Section 2.3.2 Step 2. To make it more obvious, we split this part and wrote an extra sentence with a clear reference on this table.

5) Not sure the purpose of qualitativeModel. Can't one just ignore the parts of the model which are from the qual package.

SBML plugins define a separate model for each plugin. It is a central property that SBML core must be correctly readable and interpretable even after removing all extension packages. Therefore, when using the Qualitative models plugin, a separate qualitativeModel is defined by the qual specification that handles exclusively all qualitative processes. Therefore, the qualitativeModel exists totally independent from the rest of the file. This has, as you correctly stated, the advantage that one can ignore those parts and simply use the metabolic (i.e., species, reactions, etc) relations of the model.

This circumstance is also mentioned in 4th paragraph of the results and discussion section.

6) I'm concerned about the need to say a species is a quantitative or qualitative species. It seems that a species may actually be involved in both types of interactions in a BioPAX model. Wouldn't it make more sense to make everything be species and when a species is used in a transition, it is a qualitative relationship for that species. One could then infer that a species is qualitative if it only appears in transitions, if this is actually important. The only alternative I see is to duplicate a species as a Species and QualitatitiveSpecies which is not elegant at all.

Unfortunately, the SBML core specification defines a species instance as a quantitative one which is not able to describe qualitative processes. Additionally, the species object in SBML defines quantitative attributes like initialConcentration or initialAmount which must be set in SBML core but cannot be set while describing qualitative processes, at the same time there is no attribute for its (Boolean) state.
Due to this reason, the Qualitative models extension introduces a qualitativeSpecies, which is independent from the SBML core species and is able to model qualitative behavior. Please note that this was the decision of the authors of the qual package after a long e-mail debate and we must stick to the specification.
You are right that we need for each BioPAX instance an SBML core species to model the quantitative processes and an SBML QualitativeSpecies to model the qualitative processes.

7) Pg 2, Col 2, next to last paragraph, "can not" -> "cannot" and several other places as well.

Thanks, we fixed it.

8) Please make figure 2 larger.

We enhanced the picture and made it larger. However, due to substantial changes to improve the readability of the manuscript, we moved this figure now to the supplement.