**Point-to-point list**

We have carefully read all reviewer comments and addressed each single one appropriately. 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?

You are absolutely correct with saying that the manuscript should point out why such a converter is necessary. SBML and BioPAX are competing formats in systems biology modeling. SBML is mostly used for quantitative modeling and simulation, and BioPAX for qualitative modeling of pathway relationships. There are two publications that further discuss the difference between those formats in detail: X et. al. and Y et al. Both of them are now also cited in the manuscript. Due to this fact, many databases and programs were established for these two languages. For instance, MetaCrop and SABIO-RK exclusively provide their models with SBML but not with BioPAX. This is not so problematic because there exist several converters from SBML to BioPAX. For the other conversion direction, there exist just a few converters which deliver incomplete or wrong results. Following, the pathways from databases, like Nature Pathway Interaction Database or MetaCyc providing their models with BioPAX and not with SBML, cannot be easily used for SBML modeling. This is why a converter from BioPAX to SBML is so important. Another need for creating this converter is the development of the Qualitative Models extension which now allows the building of qualitative models with SBML, too.

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

X et al citation.

Y et al citation.

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 while BioPAX is not able to store quantitative parameters that are required, e.g., for simulations. An example 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 new and COPASI is already able to read it. Following, it is just a matter of time that the other popular software tools will also be able to read and write SBML Level 3 Version 1.

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. This conversion allows for simulations on the former BioPAX models. 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.

However, it is a nice idea to provide users example source files together with translation results. Therefore, we added an exemplary conversion of the ceramide signaling pathway on the official BioPAX2SBML homepage (<http://www.ra.cs.uni-tuebingen.de/software/BioPAX2SBML/>) with the original and the converted files. Additionally, we provide the conversion of the complete Nature Pathway Interaction Database on the following website: <http://www.cogsys.cs.uni-tuebingen.de/downloads/Qualitative-Models/>. This URL is also given in the manuscript.

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 a SBML instance and use ‘reaction’ if we describe a 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 discussion (conversion of 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.

Section 2.3.3 describes in detail the conversion of BioPAX Control elements to SBML reactions and transitions. We decided to keep this detail because it is an important part of our converter and most of the available converters do not address this problem properly.

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.

Thank you for this good idea. We decided to shorten section 2.3.3 and put the more detailed parts in the appendix

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 for pointing that out. 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

Thank you, we corrected it.

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.

That’s right. Thank you for pointing this out. The manuscript now includes more details on this.

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

The reference was listed in brackets with a reference in section 2.3.2 Step 2. You are absolutely right, that it can be easily overseen. Therefore, we split this part and wrote an extra sentence with a clear references 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. Therefore, when using the Qualitative models plugin, a separate qual model is defined by the qual specification that handles exclusively all qualitative processes. 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.

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.

You are absolutely right, when translating a BioPAX model into an SMBL model, the first idea is to define for each BioPAX entity one SBML species combining qualitative and quantitative features. Unfortunately, the SBML core specification defines a species instance as a quantitative one which is not able to describe qualitative processes. Additionally, the species instance needs quantitative parameters like initialConcentration or initialAmount which must be set in SBML core but cannot be set while describing qualitative processes.

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 qual authors and we must stick to the specification.

Thus, you are absolutely right that we need for each BioPAX instance a SBML core species to model the quantitative processes and a 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.

Thank you for pointing that out. We improved 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.