**Point-to-point list**

We have carefully read all reviewer comments and addressed each single one appropriately. Most reviewer comments are not related the manuscript, but to the application itself. Thus, only small changes have been made to the manuscript, but great changes have been made to the application and related documents. The main changes are:

* The application has been bugfixed, improved and released in version 1.1 now.
* We have enhanced the documentation (directly in the application, as well as on the official homepage)
* A Javadoc KEGGtranslator API with examples for using it, is now available on the official homepage
* We created a list of “Frequently Asked Questions” (FAQ), which we put on the homepage
* The manuscript now has a better matching title and includes an additional reference to a new program that, like others, also does conversion from KEGG to SBML only. We included this reference to have a more complete list of related works.

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.

We are thankful for pointing out this issue that this is really not obvious to first time users. Blabla….

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?

A converter is necessary, both formats have a different focus, but with qual sbml even can use qualitative information to be able to use “old” biopax files for SBML usage for simulation we need it

If two formats are necessary depends on the user and what he wanted to do. For simulation purposes its important to have sbml. If sbml is not available we have to build it out of old information biopax delivers a good basis for this. If both formats will be stable over the next twenty hears… who knows…

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

We can do simulation experiments. The SBML versions are supported by …. But now I’m not sure if the available tools are already prepared for qual Besser: we are the first ones producing sbml qual models the simulation tools must be extended for the new possibilities delivered by qual and the model. (darauf verweisen wir auch im manuscript “The qual extension has been created recently and, thus, might not be supported by all applications, yet.”)

SBML version support: COPASI, Cladistine

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?

No, we just have the models (s.o.)

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?

s. introduction paper Ich denke nicht, dass wir das auch nochmal in results und discussion schreiben müssen, oder? In den Conclusions haben wir das ja schon kurz angerissen

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 compliment. We are happy that we could make … einen Beitrag leisten/…

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.

Sollten wir das?

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.

Taucht nur einmal hier auf “The translation of Control elements is more sophisticated, because they

are translated into a transition or a reaction depending on enclosed

Control elements.” So dass ich das durch complex ersetzen würde. An anderen STellen habe ich das nicht gefunden. Wie hierauf reagieren?

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, but this approach would not be proper.

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.

In the following, we would like…

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. Since this easily can be overseen we made a separate sentence referring to the table (The used SBO terms are listed in Table 1).

“2.3.2 Step 2: Translation of PhysicalEntity elements. In this step, an SBML species and qualitativeSpecies are created

for each PhysicalEntity. Depending on the kind of the PhysicalEntity, i.e., if it is a protein, complex, DNA, RNA, or smallMolecule, the species is annotated with the corresponding SBO term (Courtot et al.,2011, see Table 1 for a list of used terms).”

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

Of course it is possible to ignore the qualitativeModel. But all relationships which are no reactions are listed in this 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 that the first idea is to combine species and qualitativeSpecies to facilitate the models. Unfortunately, the qual and SBML core specification do not allow this convenience. The reason for not extending species to qualitativeSpecies is that species is quantitative and needs values like initialConcentration or initialAmount. In contrast the qualitativeSpecies MUST NOT have these values. If we would change this basic definitions in our conversion, we would produce invalid SBML.

Zitat von Andreas aus einer Mail*: “Although it might seem to be very convenient to let qualitativeSpecies*

*extend the "regular", i.e., quantitative, species, this would actually*

*imply that there are values available for its initialConcentration or*

*initialAmount. However, if you look into the qual draft, you'll see that*

*these values MUST NOT be present in a qualitative species. A qualitative*

*speciese IS NOT quantitative and can therefore not be derived from its*

*other counterpart. The only possibility to make use of core elements was*

*described by Lucian Smith, who proposed to let qualtitativeSpecies*

*extend parameter. A parameter in SBML core has just a value, which can*

*be anything. Actually, it would be much more handy to redesign the*

*species class in SBML core so that it would also just have a value and a*

*second attribute stating what the meaning of the value is, e.g.,*

*concentration, amount, level... As this will not happen because it would*

*cause to much effort (all existing tools would have to be changed), we*

*cannot let qualitativeSpecies use its quantitative counterpart.”*

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

Fixed.

8) Please make figure 2 larger.

Done.