

## **Reviewer's report**

**Title:**Mimoz: Web-Based Semantic Zooming and Navigation in Metabolic Networks

**Version:**1**Date:**6 October 2014

**Reviewer number:**5

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The paper describes a web-tool for generalisation of knowledge from different metabolic networks (or models). The tool provides an opportunity not only to generate a generalised representation of the metabolic model, but also to explorer it in semantic zooming-like way. It allows to observe individual entities of the model and links to external resources.

The technical solutions for finding communalities and solving the layout problems are interesting. The tool is definitely a very valuable and timely to appear, since multiple similar models and networks are often generated in the field.

The authors have to place their work more into the context of the state-of-the-art in the field and provide not only advantages of the tool, but also the drawbacks.

The tool is based on the previous work by the authors published in Comput Biol. 2014 Jul;21(7):534-47. It is absolutely essential to clearly state what is the breakthrough in this paper comparing to the previous work.

The authors are asked to address the points described below.

Major essential points:

1. The term 'model' should be defined. Do authors refer to graphical representation models? Mathematical models? It seems that the terms 'model' and 'network' are used as synonyms.
2. Do authors distinguish metabolic pathways and signalling pathways? Whether their tool is applicable for signalling pathways models? If yes, this should be emphasized and demonstrated too. If not, explaining why the tool is limited only to metabolic pathways and whether authors aim to develop it fos signalling pathways too.
3. Cite Zoomit (Stuart Pook, Guy Vaysseix, and Emmanuel Barillot. Zomit: biological data visualization and browsing. Bioinformatics, 14(9):807--814, October 1998), as a seminal paper introduced semantic zoom into biological data visualization.
4. Correct applicability of NaviCell tool, is suitable for any maps, not only for signalling maps. Note clearly that NaviCell does use module representation.
5. Explain clearly what is the novelty in the current paper comparing to the previous work: Comput Biol. 2014 Jul;21(7):534-47. doi:

10.1089/cmb.2013.0143. Epub 2014 Apr 25. Knowledge-based generalization of metabolic models. Zhukova A1, Sherman DJ.

6. Re-design figure 1: The figure is not self-explanatory and not intuitive. Order of the zooms is not obvious: it is not clear for the reader what is 'bottom level', 'intermediate zoom', 'most detailed view'. Introduce A,B,C order into the figure; reorganise and provide clear explanation in the figure legend.

7. Why only top-down manner of network exploration is mentioned in the text. The user can do it in both directions and this is the strength of the tool that should be emphasised.

8. Implementation, point 2: explain how are similar metabolites and reactions detected.

9. The paragraph: 'Mimoza does not depend on pathway information, automatically infers the relative compartment placement (e.g. places organelles inside the cytoplasm) and exploits a model in SBML format with ChEBI annotations for metabolites (it also tries to annotate them automatically if no annotations are present). '

This actually represents not only an advantage of the tool. Discuss what are drawbacks of automatic placement of compartments; address the layout assignment modes and compare manually-designed layout vs. automatically-assigned. In general, critically discuss whether the solution of automatic displacement of similar metabolites placing them together by their similarity does not interfere with the original layout of the metabolic model (if it had one). Very often the layout pre-defined by the model creator is a message.

10. Provide comparison of visualisation approaches and generalisation methods in a form of table. Critically evaluate Mimoza vs. other tools. Objectively discuss advantages and disadvantages and future development plans.

11. The comparison of models enabled by Mimoza is a very interesting feature, and probably unique. It is evoked in beginning of background and second last paragraph of the paper ('Using generalization to compare two models makes most sense if...'), but could be stressed more. In particular, a comparative figure would be nice (for example, add it to supplementary and provide a detailed textual explanation for comparison).

12. The video tutorial requires major improvements:

- The resolution is low

- The introduction to the tool should be made before diving into the instructions for user

- The video should be accompanied by oral explanation

- The speed of slide change should be lower, impossible to grasp the information from the first watching of the tutorial

Minor essential points:

P.2: Avoid repetitive use of expression 'more and more advanced'.

P.3: 'The user must create them in CellDesigner, export them as an image and manually edit it in a graphical designer to produce intermediate views.' (replace by 'partly manually')

P.3: Bring examples of navigation-visualisation tools used in pathway databases as Reactome and mention their solutions. For example, Reactome has semantic zooming and modular representation too.

P. 5: Replace 'To allow for zooming into the generalized model' by 'To allow zooming into the generalized model'.

P.6: Replace 'The overall Mimoza pipeline contains of 5 steps' by 'The overall Mimoza pipeline contains 5 steps'

P7: Provide downloadable installation and user guide easily accessible from the website

Recommendation points:

The website of the tool could have more intuitive menu with sections as 'Introduction', 'Tutorials and user guides', 'Application examples', 'Downloads', etc.

**Level of interest:**An article of importance in its field

**Quality of written English:**Acceptable

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