"Mimoza: Web-based Semantic Zooming and Navigation in Metabolic Networks"
Anna Zhukova and David J Sherman, Inria Bordeaux Sud-Ouest

Authors' response to reviewer comments.

The authors would like to thank the reviewers of our manuscript for their many constructive comments and especially for time they have dedicated to evaluating our so work so carefully. We hope that they will agree that this revised manuscript addresses the issues they have raised and implements their recommendations. In the following we will describe the changes we have made and respond to each of the specific issues.

Since there is a great deal of overlap between the suggestions and the criticisms made by the reviewers, we will first describe the changes we have made, and then provide a concordance for each reviewer.

R1. We have added 8 paragraphs on related work on zoomable user interfaces (ZUIs) to the Background section as well as a discussion of Reactome.

R2. We have documented in the Background two use cases that Mimoza is designed to address: initial modeling of metabolism, and curation of metabolic models. Figure 1 illustrates the links between different tasks in modeling, where different use cases are paths between these tasks, and explain which Mimoza is designed to assist. We agree that it would be interesting to understand the ways that Mimoza could assist in modeling other kinds of biological networks such as signaling networks, and review in the Discussion some of the extensions that would be necessary. Unfortunately these considerations are out of the scope of the software that we present here, and so in the manuscript we maintain the focus on metabolic networks.

R3. We have provided definitions for: similar, process, essential process, model (submodel), network (subnetwork).

R4. We have made explicit the requirements upon which Mimoza depends: SMBL levels, the ChEBI ontology, Leaflet, Python, Java. Mimoza will use existing layout information and relative compartment positions from the SMBL model, so users can edit the layout made by Mimoza using their favorite tools and reload them into Mimoza.

The Implementation section has been divided into different paragraphs, as recommended by the reviewers.

R5. We describe the pipeline of how one uses Mimoza, according to the use case.

R6. We describe the programs and algorithms used by Mimoza, its hardware requirements, and library versions.

R7. We describe how users may choose the size of the viewing window, and embed one or several Mimoza map views in a web page.

R8. The focus of this manuscript is a software tool that builds zoomable interfaces for exploring metabolic networks. It uses, and calls as a subroutine, an algorithmic method defined in (Zhukova, Sherman 2014), but further adds processing of SMBL files, adaptive layout of layers depending on their zoom level, construction of a ZUI, and services for embedding and sharing zoomable maps. We have included for reference a brief overview of the algorithmic method for building the generalization, and explain very briefly that the technical paper (Zhukova, Sherman 2014) addresses questions

concerning race conditions, the relations of subnetworks to networks, the question of whether generalization can disconnect a network, and the role of transport reactions in the generalized model.

R9. We have improved and reordered the figures, following reviewer recommendations.

R10. We have fixed the references, added many suggested references, and repaired the typographic errors noted by the reviewers.

R11. We have improved the examples on the Mimoza web page.

R12. We have addressed several bugs noted by the reviewers, in particular those revealed by deeper testing on the Windows platform.

Reviewer checklist

```
Reviewer 1
1.              examples: R5
2.              performance: R6
3.              beta-oxidation: R2
4.              use case: R2

Reviewer 2
1.              SMBL level: R4
2.              layout algorithms: R6
3.              metabolites: R4
4.              minor: R10

Reviewer 3
1.              Related work: R1
2.              Layout in BioModels: R4
3.              Unclear procedures: R5, R6
4.              Figure 1: R9
5.              What is meant by SMBL: R4, R6
6.              Layout information in SMBL: R4
7.              COMBINE: R10
8.              Zoom changes: R5, R7
9.              Minor: R10

Reviewer 4
1.              R3
2.              R2
3.              R10
4.              R4
5-6.        R3
7-11.     R8
12.             R4
13.             R8
14.             R4
15.             R8
16-17.  R6
18-19.  R8
20.             R7
21.             R8
22.             R6
```

```
23.          R8
24.          R3
25.          R8
26.          R2
27.          R6
28–30.  R10
31.          R6
32–33.  R12
34.          R11
35.          R12
36.          R11
37.          R12
38.          R7
39–40.  R12
minor.    R10
general.                    R5, R7

Reviewer 5
1.           R3
2.           R2
3–5.        R1
6.           R9
7.           R5
8.           R6
9–10.      R1
11–12.  R7, R11
13.          minor p.2, p.3: R10
14.          minor p.3: R1
15.          minor p.5, p.6: R10
16.          minor p.7: R11
17.          recommendation: R14
```

We believe that we have addressed the issues raised by the five reviewers, and request that the revised manuscript be reconsidered for publication. Thank you in advance for your consideration.

Yours sincerely,

Anna Zhukova
David James Sherman