

## Reviewer Report

**Title: PathwayMatcher: proteoform-centric network construction enables fine-granularity multi-omics pathway mapping**

**Version: Original Submission**    **Date: 2/21/2019**

**Reviewer name: Marcella Nunes Melo-Braga, PhD**

### Reviewer Comments to Author:

The manuscript entitled "PathwayMatcher: proteoform-centric network construction enables fine-granularity multi-omics pathway mapping" by SÃnchez et. al describes a new paradigm to build networks for human biomedical data based on proteoforms including PTMs rather than centering on gene. Developed algorithm relies on Reactome knowledgebase database for proteoform interactions. This manuscript has originality and covers an interesting topic for multi-omics field. I have no doubts that this application will be of great interest for OMICS users.

It is important to highlight this review is from the viewpoint of a potential user, since I am a researcher that works with proteomics rather than an expert in application developer. Therefore, I lack the expertise to evaluate the technical algorism issues and I hope other revi-ewers with this expertise will bring more valuable suggestions on this matter.

Regarding the use of PathwayMatcher, the Galaxy version seems user friendly and intuitive. However, in my experience was not straightforward when I tried. It is essential to have a better tutorial for users to get the output results as reactions & pathways, over-representation and network view as illustrated in figure 4 of the manuscript. In case users have to login to have full access, this information should be clear. In addition, the local installation shows a major concern. Even though I had installed the Java as suggested in the website instructions I could not execute the jar file. The error was "could not find or load main class". Since, this local installation is an option in additional to the galaxy version, it would be helpful to have a better description in the website regarding possible troubleshoots to guide new users.

The suggestions pointed by this reviewer were here in order to improve users' accessibility since I believe and hope that PathwayMatcher will be widely used in OMICS field.

Minor points:

-&gt; This reviewer believes that authors used the term "isoform" sometimes to do not overwrite the correct term "proteoform". However, I strongly suggest using only proteoform throughout the manuscript since it is the most acceptable term nowadays.

-&gt; I suggest the author to include a zoom-in on fig 3B to highlight the proteoforms (including PTMs) in the red nodes regarding TP53 gene.

-&gt; There are several proteoforms that does not have the interaction information. How often will be PathwayMatcher updating the database? Will it be based on Reactome update? Please indicate in the manuscript.

-&gt; For consistency, the MOD number for all modifications represented in Fig. 8 (x-axis) should be included.

> The phrase "PathwayMatcher is developed to be a hypothesis generation tool, helping to navigating large datasets and guide experiments. It is not a validation or mechanism inference tool" written in Methods section should be included in the main body text as many readers may first recognize this as a potential tool to understand biological mechanisms.

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