**Reviewer Report**

**Title: LION/web: a web-based ontology enrichment tool for lipidomic data analysis**

**Version: Original Submission** **Date:** 10/29/2018

**Reviewer name: Ruth Welti**

**Reviewer Comments to Author:**

LION provides useful information helping users associate lipidomics data on membrane lipid species from mammalian systems with the chemical and physical properties of those systems. Overall this is an ambitious undertaking that is likely to provide insights on lipid properties, particularly to users that are not familiar with chemical or physical properties of membrane lipids.

Overall, the tool seems useful and the paper is well-written, but a few points could be explained in more detail.

1. It should be mentioned, and perhaps the authors could include an explanatory note at the site, noting that actual physical properties of membranes (such as fluidity) depend on factors in addition to the typically measured lipids, including sterols and protein type and content.
2. It might be useful to point out specifically that the samples chosen to "calibrate" the lipid categorization are all from mammalian cells and thus the ability to accurately interpret lipidomics data from other types of systems is not clear. Perhaps this is because it is not clear to the reviewer precisely how the categorized lipids (page 4, lines 69-74) were used in the analysis. Since many mammalian tissues (e.g. brain, heart) have more extreme compositions, will this be a problem for analysis?
3. The ranking approach appears to be a pairwise comparison. I.e., even when multiple samples are present, comparison is to one (control) sample. This is analogous to a typical transcriptomic approach but, given that it's actually easier to collect lipidomic data than transcriptomic data on hundreds of samples/conditions, having to analyze the data pairwise might be a bit burdensome. Maybe you could discuss the choice of approach in the paper or clarify if the reviewer's understanding is incorrect.
4. An example showing the output from the target mode would be helpful to the reader.

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