Reviewer Report

Title: Map and Model - moving from observation to prediction in toxicogenomics

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Reviewer name: Lisa Truong

Reviewer Comments to Author:

aThe manuscript "Map and Model - moving from observation to prediction in toxicogenomics" is well written and describes a bioinformatics approach to infer time and concentration toxicogenomic fingerprints. They utilize developing zebrafish and assessed their transcriptome response when exposed to diuron, diclofenac, and naproxen and measure the internal concentrations. The authors does a great describing the mathematics and their experimental design, however there are a few points that should be considered/discussed about in the manuscript as it is:

1. The generation of the toxicogenomic universe utilizes only microarrays, which is a predetermined set of probes. I realize the concept is like the Connectivity Maps from the L1000 platform, but how will this platform be expanded upon later in the future? The technology of microarray is slowly growing out of favor and no new probes will be added with the discovery of new genes. This should be discussed in the paper to explain what the next extension will be
2. The prediction ability of toxicogenomics is briefly discussed but its not clear how this will work for future of the field. The authors are able to model the mass amount of data, but its not clear how others in the field will utilize their data set. The toxicogenomic universe is provided with little explanation of how someone can adapt all this great work. It would be a disservice to not include an excerpt of how the field of toxicology can use it.
3. The shiny app is great to display your own results for the 3 chemicals, which has concentration and time data. However, how will it work with chemicals that are tested at only one concentration or one time point? This is a limitation should be explained.
4. The model used for the concentration and time-dependent response model is a good choice with the assumption that all the data fits under the hill model. However, how does this work if there non-monotonic responses? The chemical selected are known to have responses that are dose dependent, but not every chemical is this case. A discussion should be included on this. Some data might be better fit with a gain-loss model. Or constant model if the internal dose is non-existent (because of chemical 'soprtion properties).
5. AIC is used for the selectin of the model - which is appropriate. Please provide some information on the range of AIC values. Also - was there a likelihood test conducted?
6. Figure 8 is to small to see anything meaningful. The discussion around it is non-descript and hard to follow.

Minor clarification:

Pg 4 - "integration: the Zebrafish Embryo Toxicogenomic.." - In the paragraph: "To obtain an overview over the ZTU we grouped the 3600 toxnodes into 118 clusters", please include information on the range of nodes per cluster

Figure 3- the size of the dot isn't even visible. This should be removed, as there is no point to this. Also - the figure is specific to Naproxen so the concentrations should be stated on the plot.
Pg 5 - modeling section - In regards to the first sentence - "consideration of finding specific" - that does this refer to and needs more clarification.
Figure 6 legend - clarify "sum(CI)".

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