October 10, 2020

Dear Editors,

We are including our submission, “**Context-specific interactions increase predictive power of network methods for identifying drug effects**” for your consideration as a letter to *Nature Communications*. Network methods are increasingly applied to predict drug phenotypic effects using the drug’s protein target(s) and the surrounding protein-protein interaction networks. However, these methods have not translated to influence decision making in FDA review or industrial settings due to high false positive rates. High false positive rates have resulted in AUROC values that are often ~0.5, suggesting that methods are no better than random. **In this brief, original research communication, we demonstrated a 50% increase over random using a combined network and machine learning approach** and a silver standard dataset that was curated in collaboration with regulatory scientists at the FDA. We were struck by this improvement, especially by using relatively simple machine learning approaches and thus believe the finding to be of outstanding scientific importance.

We consider this work significant and worthy of review for multiple reasons:

* The work addresses an understudied question in the interaction-network field regarding which methods sufficiently select drug-phenotype relationships with clinical utility. Our context-specific interaction method provides a novel path forward and outperforms other common approaches and we believe the paradigm will set the bar for discovering protein interaction networks that describe drug effects.
* We developed a silver standard dataset in collaboration with the US FDA. We specifically investigated the extent to which network methods could identify relationships between drugs and designated medical event (DME) phenotypes. These phenotypes are of the highest priority to regulatory review and predictive models for these phenotypes could be incredibly valuable to regulatory review of new products and industrial selection of new druggable targets.

Our approach is in contrast to other network approaches and has broad implications for the application of drug protein interaction network modeling to therapeutic development. Instead of deriving a global mathematical relationship or similarity measure for predicting all drug interactions, we investigated network genes on a per-phenotype basis. The discovery of interactions from a per-phenotype analysis suggests that network models may need to be optimized or curated locally for a phenotype of interest. This is not entirely surprising given that detailed pathways curation has been a long-standing and essential part of biological discovery, however it is a departure from the majority of *in silico* network modeling efforts.

To enable rigor and reproducibility of this investigation, we have created a GitHub of all code and data used in this study and made this resource available to reviewers through a preprint posted to BioRXiv.

Sincerely,

Jennifer L. Wilson, Ph.D.