April 1, 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*. 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 1.24-1.74 fold 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 a letter for multiple reasons:

* The work addresses an outstanding 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.
* 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 new therapeutics and predictive models for these phenotypes could be incredibly valuable to regulatory review of new products and industrial selection of new druggable targets.

Context-specific interactions (CSIs) provide a novel approach for making network methods predictive for understanding therapeutic effects. As further support of our approach, we applied our technique to a challenging drug discovery problem – predicting the effects of drug combinations on DMEs. Traditionally, drug interactions are investigated at the single molecule level by considering whether two drugs compete for the same binding partner. Using CSIs and electronic health record data, we demonstrated a novel type of drug interaction where the downstream protein interactions of multiple drugs’ targets identified clinically-meaningful drug interactions. Specifically, we predicted that the combination of the antidepressant, imipramine, and the blood-thinner, dabigatran, would increase the risk of myocardial infarction because of a shared CSI pathway. We validated this prediction using the electronic health record further proving that CSIs are a means for making network methods predictive for understanding drug combination effects. This work alone is significant because predicting drug combination effects is financially prohibitive but is a significant public health concern.

We have submitted a companion paper to *Science* detailing this later result and we would be eager to release these two papers simultaneously if possible.

To enable rigor and reproducibility of this investigation, we have created a GitHub of all code and data used in this study and will make this repository publicly available after publishing in a preprint format.

Sincerely,

Jennifer L. Wilson, Ph.D.