December 16, 2019

Dear Editors,

We are including our submission, “Context-specific interactions distinguish true and false positive drug phenotypes in interaction-network investigations” for your consideration as a letter to Nature. In this brief, original research communication, we tested three methods for identifying interaction network phenotypes with clinical utility. As interaction network methods are increasingly developed to guide therapeutic development, we believe this work to be of interest to an interdisciplinary community of scientists and not just the computational network experts who develop these methods.

A core component of interaction network analysis is identifying drug-phenotype relationships using protein-protein interactions to support these relationships. Yet, an outstanding question in the field is which methods sufficiently select drug-phenotype relationships with clinical utility? Currently, network biologists apply varyious techniques to select true positives and negatives. These methods include tractable and sensible approaches such as statistical enrichment or distance-based metrics (e.g. the drug and the phenotype need to be proximal to each other in the interaction space). However, we hypothesized that a biological approach could outperform a mathematical approach. We tested the idea that true positive associations rely on context-specific interactions and endeavored to discover interaction sets that distinguish true and false positive associations for 21 designated medical events (DMEs). DMEs are severe, adverse drug outcomes of highest priority to FDA regulatory review of new drug applications and methods for identifying true positive drug-DME relationships stand to greatly impact therapeutic development.

We demonstrated that our biological approach of discovering context-specific interactions separates true positives from false positives more cleanly than mathematical approaches. ***Specifically, the ROC value of this generalized method was XX fold higher than statistical enrichment or distance-based selection***. Further, context-specific interactions yielded “mechanistic-like” interpretation of these differences compared to mathematical approaches. To discover context-specific interactions we merely applied a simple, off-the-shelf implementation of logistic regression. 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.

To enable rigor and reproducibility of this investigation, we have included a zipped archive of all code and data used in this study and will make this repository publicly available pending acceptance.

Sincerely,

Jennifer L. Wilson, Ph.D.