Dan Schlauch

Harvard TH Chan School of Public Health

677 Huntington Ave

Boston, MA 02115

(617) 838-3904

dschlauch@fas.harvard.edu

Editor

*Proceedings of the National Academy of Sciences*

October 10, 2016

Dear Editor,

We are pleased to submit our manuscript entitled “Estimating Drivers of Cell State Transitions using Gene Regulatory Network Models” by Daniel Schlauch, Kimberly Glass, Craig P. Hersh, Edwin K. Silverman and John Quackenbush for consideration for publication in *Proceedings of the National Academy of Sciences*.

In this manuscript we present a method for comparing data from gene expression assays by identifying the transcription factors which drive state change at the gene regulatory network level. Our method, MONSTER, is a novel approach for defining the changes in networks via key transcription factors which drive the change in a consistent manner. MONSTER works by focusing not on individual gene expression patterns between groups, but on the systematic differences in the adjacency matrices derived from the networks inferred from those groups.

We applied our method to a set of four independent studies of Chronic Obstructive Pulmonary Disease- a disease notable for challenges in reproducibility. Despite the notable differences in the studies pertaining to patient demographics, collection sites and tissue types, we demonstrate strong agreement in the set of implicated transcription factor drivers between patients diagnosed with COPD and the smoker controls.

Our method is made available in a Bioconductor R package and can be easily implemented to existing datasets which include both gene expression data and a transcription factor - gene regulatory set of priors. Because of the wide applicability of our method to studies involving gene expression data, it will be of great interest to the readers of *PNAS*. Researchers interested in transcription factors which drive the changes between two network states will be easily able to implement MONSTER into their analyses.

This work is not published or submitted for publication at any other journal and we do not declare any conflicts of interest. If you determine our manuscript to be appropriate for *PNAS*, we suggest the following field experts:

1.) Florian Markowitz, Cambridge Institute, University of Cambridge, UK

2.) Chad Myers, Computational Biology and Functional Genomics Lab, University of Minnesota

3.) Matthew Hibbs,Computer Science Department, Trinity University

4.) Carol Bult, The Jackson Laboratory

5.) Roger Baumgartner, Department of Microbiology, University of Washington

6.) Neil Winegarden, Princess Margaret Genomics Centre

7.) Miko Berrenwinkel, Department of Biosystems Science and Engineering, ETH Zurich

Thank you for your consideration,

Dan Schlauch

Department of Biostatistics,

Harvard T.H. Chan School of Public Health