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Editor

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Dear Editor,

We are pleased to submit our manuscript “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 an entirely new way of looking at phenotypic state transitions in biological systems. We recognize that the differential gene expression between disease and matched control populations is almost certainly driven by differences in gene regulatory network models. We therefore estimate independent models for disease and control states, understanding that these models should also differ. We then model the control to disease transition as one driven by alterations in the patterns of gene regulation which can be captured by a transition matrix that maps one network to the other.

We first tested this method, MONSTER, with simulated data and demonstrate that it is capable of identifying the transcription factors that alter their pattern of regulation between states. We then use MONSTER to analyze data from four independent studies of Chronic Obstructive Pulmonary Disease (COPD) and found strong agreement in the set of transcription factor drivers identified as involved in the transition between smoker controls and patients with COPD. The reproducibility and biological relevance of the results suggest that MONSTER is able to extract transcription factors involved in regulatory processes associated with the disease state transition.

MONSTER is freely available with documented source code and an application vignette in a Bioconductor R package to facilitate its use with other data sets.

Because MONSTER represents a new and unique but intuitive method for studying phenotypic transitions, and so can be applied to gene expression data from a broad range of studies, we believe our manuscript will be of great interest to the readers of *PNAS*. We hope that you agree.

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

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

3.) Carol Bult, The Jackson Laboratory

4.) Roger Bumgarner, Department of Microbiology, University of Washington

5.) Neil Winegarden, Princess Margaret Genomics Centre

6.) Niko Beerenwinkel, Department of Biosystems Science and Engineering, ETH Zurich

As always, if you have any questions or if we can provide any additional information to assist you in your evaluation of our manuscript, please do not hesitate to contact us.

Thank you for your consideration,

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