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Editors of *PLOS Computational Biology*,

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 *PLOS Computational Biology*.

In this manuscript we present a new way of looking at phenotypic state transitions in biological systems. Our approach recognizes that differential gene expression patterns, such as what is observed between disease and control populations, is almost certainly driven by differences in the underlying gene regulatory networks. Based on this, we develop a method, MONSTER (Modeling Network State Transitions from Expression and Regulatory data) that estimates networks for disease and control states and then borrows concepts from quantum physics and statistics to model the regulatory transition that underlies this shift. Specifically, MONSTER evaluates alterations in gene regulation between two networks, and captures that information in a “transition matrix” that maps one network onto the other.

We have validated MONSTER using both simulated and biological data and are able to demonstrate that it can reliably identify transcription factors that alter their pattern of regulation between states. Most importantly we are excited by the fact that we observe very strong *reproducibility* in the network transitions predicted by MONSTER, even when the underlying differences between case and control networks are not highly correlated. Specifically, in our manuscript we apply MONSTER to analyze data from four independent gene expression studies of Chronic Obstructive Pulmonary Disease (COPD). We find incredibly strong agreement across all four studies in the top set of transcription factors identified by MONSTER as the most important driver of the transition between smoker controls and COPD subjects. The biological relevance of these transcription factors for COPD suggests that MONSTER is extracting regulators that are critical for mediating the network shift from “healthy” toward “disease.” MONSTER is freely available with documented source code and an application vignette in an R package to facilitate its use with other data sets.

MONSTER represents a new, but intuitive, method for studying phenotypic transitions. MONSTER has the potential to be applied to expression data from a broad range of studies in order to identify transcription factors that change their targeting patterns and thus may be critical in mediating shifts toward various phenotypic or disease states. Based on its generalizability, we believe our manuscript will be of great interest to the broad readers of *PLOS Computational Biology*. We hope that you agree.

This work has not been 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 *PLOS Computational Biology*, we suggest the following expert reviewers:
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,
Daniel Schlauch
Kimberly Glass
Craig Hersh
Ed Silverman
John Quackenbush