Dear Editor
PLoS Genetics

We would like to submit our manuscript

"CLEAR: Composition of Likelihoods for Evolve And Resequence Experiments"

for possible publication in *PLoS Genetics*. There are many reasons why the manuscript is appropriate for the journal. Experimental Evolution of organisms form an important methodology for understanding evolution in action. Specifically, they can help explain how organisms genetically adapt to selection pressures, e.g. pesticide, drug, antibiotic resistance, etc. With new sequencing technologies, we have the opportunity for evolve-and-resequence experiments, providing a deep genomic sampling of the evolving population at different time points.

Increasingly, scientists are looking at sexually reproducing organisms, esp. *D. melanogaster* , and acquiring time series data. However, there are many unresolved questions regarding computational/statistical methods that analyze the data in order to detect regions evolving under selection.

1. Only a few tools can make full use of time-series points. Most just handle two time points. A recently published tool, Gaussian Process (GP), published in *PLoS Genetics* 2015, can analyze time series through full likelihood calculations, but its assumptions do not hold in real world scenarios. Moreover, it is computationally intensive and does not scale to handling genome scale data. In our paper we deployed an improved model to improve the power.

2. As individuals of population are pooled and sequenced together, sequencing coverage can have a critical effect on the power of different methods. We evaluate different methods under various sequencing coverages and show that CLEAR is robust to change of coverage.

3. A majority of existing techniques, including GP, fail when the initial frequency of the favored allele is small, which is very likely in real word scenarios. We show that CLEAR is not sensitive to this parameter and performs well over many different starting frequencies.

4. We also found that existing tools for handling single time point data (often based on analysis of the site-frequency spectrum) and those for handling time-series data (based on a modeling of the favored allele frequency over time) are based on completely different principles, and no serious effort has been made to reconcile the two efforts.

In this manuscript, we address these questions and develop a novel tool, CLEAR (available as open source) that can analyze time-series data, displays better power in detection of selection for a wide range of experimental evolution and selection parameters. Moreover, CLEAR is orders of magnitude faster than GP, the only other method that handles time-series data and estimates selection parameters.

It also resolves questions regarding the performance of site-frequency based methods by extending them to handle time-series data. We carefully examine the role of different experimental evolution parameters, including initial frequency of the favored allele, sampling time relative to the onset of selection, sequencing coverage, and the span of sampling on the power of selection.

In our experiments, we find that the problem of detecting a genomic region under selection is distinct from identifying the favored site that is functionally responding to selection constraint, and evolve-and-resequence strategies that work for detection may not be optimal for site-selection. In this sense, our calculations will guide future design of experimental evolution experiments. As the

methodology is the primary contribution, and understanding methods is necessary to understand results, we chose to put the methods section before the results.

For all of these reasons, we hope that our manuscript will be of interest to *PLoS Genetics* readers. We thank you in advance for your consideration.

In terms of potential reviewers, our work is of course most closely related to Dr. Yun Songs work which was published in *PLoS Genetics* last year. We did discuss an early version of the manuscript with him, and even with competition, it would be OK to ask him to be a referee. We share one of the co-authors from that paper. Other potential reviewers include Dr. Dmitri Petrov who is doing a lot of work on experimental evolution, and some of the authors of the competing tools, including Hande Topa, Robert Kofler, Sergey Kryazhimskiy, and Alison Feder.

Sincerely,

Arya Iranmehr
Vineet Bafna