July 16, 2021

Physical Review E – Editorial Office

**Re: Inferring the intrinsic mutational fitness landscape of influenza-like evolving antigens from temporally ordered sequence data**

Dear Editors,

We are pleased to send you the enclosed manuscript that we would like you to consider for publication in the journal *Physical Review E*.

Some of the most notorious viruses, including seasonal influenza and potentially SARS-CoV-2, continuously evolve their antigenic sequences to escape human immunity. This antigenic drift presents a major challenge for efficacious vaccine design.

In our study we present a method to infer the intrinsic mutational fitness landscape of influenza-like evolving antigenic proteins from temporally ordered sequence data. This information can be used to identify promising vaccine targets. Our inference approach relies on stringent immune-driven selection in each epidemic season, but it does not use explicit phylogenetic information, which other fitness inference methods rely on.

We test our inference method on artificial sequence data, which we programmed to stochastically evolve in an influenza-like fashion and we were able to recover single- as well as pairwise intrinsic fitness effects from those computer-generated data.

Although our analysis suggests that the currently available influenza sequence data are insufficient for accurate fitness inference, we believe that our approach can provide valuable insight into the vulnerabilities of immune-driven evolving viruses, when more sequence data become available.

Our study provides a new method for viral sequence analysis, which has the promise to be applicable for novel vaccine designs. We believe that the interdisciplinary nature of our work fits the expansive scope of *Physical Review E* and appeals to the wide readership of the journal.

Thank you for considering our manuscript.

Yours sincerely,

Julia Doelger Mehran Kardar Arup K. Chakraborty

Appendix: Referee suggestions

Referee suggestions:

We recommend the following referees for the scientific review of our manuscript based on their fields of interest and expertise:

* Michael Lässig (University of Cologne, Germany, Institute for Theoretical Physics)
* Marta Luksza (Mount Sinai, New York, USA, Genetics and Genomic Sciences)
* Richard Neher (University of Basel, Switzerland, Biozentrum)
* Ville Mustonen (University of Helsinki, Finland, Department of Computer Science)
* Colin Russel (University of Amsterdam, Netherlands, Academic Medical Center)
* Boris Shraiman (UC Santa Barbara, USA, Kavli Insitute for Theoretical Physics)
* Trevor Bedford (Fred Hutchinson Cancer Research Center, Seattle, USA, Vaccine and Infectious Disease Division)