July 21, 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 deadly viruses, including seasonal influenza and SARS-CoV-2, continuously evolve their antigenic sequences to escape human immunity. This immune-driven evolution leading to 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 in the future to identify promising vaccine targets on such immune-driven antigens. 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 tested our inference approach on computer-generated seasonly sequence data, which we stochastically evolved in an influenza-like fashion and we were able to recover single- as well as pairwise mutational fitness effects from those artificially created sequences.

Although our analysis suggests that available sequence data, e.g. from seasonal influenza, are currently insufficient for accurate inference of a highly-resolved mutational fitness landscapes, we believe that our approach can provide valuable insight into targetable intrinsic vulnerabilities of immune-driven evolving viruses, when more sequence data become available.

Our study provides a new sequence-based analysis approach for immune-driven evolving viruses and our fitness inference method has the promise to be applicable for novel vaccine designs. We believe that the interdisciplinary nature of our work as well as its potentially wide-ranging applicability for disease prevention 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:

* Trevor Bedford (Fred Hutchinson Cancer Research Center, Seattle, USA, Vaccine and Infectious Disease Division)
* 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)
* Boris Shraiman (UC Santa Barbara, USA, Kavli Insitute for Theoretical Physics)