Review 3: "Phase transitions may explain why SARS-CoV-2 spreads so fast and why new variants are spreading faster"

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Published on: Jul 26, 2021

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

In this submitted manuscript, the authors have applied their hydrophobic-scale-based method to analyze the effects of the mutations in SARS-CoV-2. As demonstrated in this work, the dynamics of SARS-CoV-2 (and its mutations) are very close to the critical point. Such criticality implies that the proteins can preserve their dynamic flexibility despite being posed near the minimum of the energy landscape. Moreover, such criticality indicates a measure for how the new mutations can further enhance infectiousness. The method presented in this paper, which has been applied in studying the evolution of many different kinds of proteins, is simple yet powerful. During the pandemic, a fast and efficient "risk assessment" for various kinds of mutations can be priceless. In this sense, this work is of great significance.

However, to solidify the arguments and to appeal to a larger audience, there is a need to provide more detailed information. For example, although we can learn from this research that the mutation can lead to the higher flexibility of the proteins, the differences between the mutations and WT are still very small. How much difference in the score for main hydrophilic edges can really make a big difference in the flexibility or transferability? The author may cite their previous studies on other proteins to show this. Besides, to enlarge the central regions, or to plot the differences between the curves (say, $\Psi_{\text{Mutant}} - \Psi_{\text{Cov2}}$, or $\Psi_{\text{Cov2}} - \Psi_{\text{Cov1}}$, etc.) of Fig. 2 may also be helpful.