

Review of: "Evolution of new variants of SARS-CoV-2 during the pandemic: mutation-limited or selection-limited?"

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Potential competing interests: No potential competing interests to declare.

This manuscript addresses a relevant issue in real-time viral evolution. Specifically: in the case of SARS-Cov-2, is the invasion of novel variants primarily limited by mutation or by selection? They cast this question as three alternative hypothesis which they address by using the Watve et al. (2021) model. Next, by comparing and contrasting the predictions of this model, they can derive some simple qualitative differential testable predictions. The authors conclude that the invasion of novel variants is primarily limited by selection rather than mutation.

This manuscript is clearly written and well-motivated. I have few comments and suggestions that I hope will be useful to the authors.

1. In the site [CoVariants](https://covariants.org) the authors can find lots of information about SARS-Cov-2 which can be useful to support/refine their analysis. For example, detailed information on the proportion of sequences for each country over time and the corresponding graphs can be found at:

<https://covariants.org/per-country>

Countries are displayed if they have at least 70 sequences in any variant being tracked, over a period of at least 4 weeks. Countries are ordered by total number of sequences in tracked variants.

Looking at these graphs one realizes that they are almost identical for several European countries (e.g. UK, Denmark, France, Germany, Sweden, Belgium, Netherlands, etc.). I think this rules out Hypothesis 2, i.e. it seems very unlikely that the observed succession in many different countries is the result of purely random replacement by genetic drift or selection unrelated to epidemic parameters.

1. Additional theoretical and empirical support that the invasion of novel variants is primarily limited by selection rather than mutation is provided by the analysis of Fort (2021) for the alpha variant. This paper presents compelling evidence that warrants citation, as it demonstrates the effectiveness of a straightforward natural selection equation in accurately modeling the observed changes in the proportion of the alpha variant across various countries, regions, and globally. Remarkably, this model achieves a high level of accuracy using only a single parameter—its relative fitness factor, denoted as f —which is almost universal $f = 1.5$. This finding aligns with previous studies (Davis et al., 2020; ISP, 2021) that estimated a 50% higher transmissibility of the alpha variant compared to the local wild type in different countries.
2. A minor point: In figure 6 I think it is "Colombia" instead of "Columbia".

Cited literature:

Davis, N et al. 2020. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. doi: 10.1101/2020.12.24.20248822 <https://www.medrxiv.org/content/10.1101/2020.12.24.20248822v3>

Fort. H. A very simple model to account for the rapid rise of the alpha variant of SARS-CoV-2 in several countries and the world. *Virus Research*. 2021; 15 October; 304, 198531.

<https://www.sciencedirect.com/science/article/pii/S0168170221002380>

ISPM Transmission of SARS-CoV-2 variants in Switzerland (2021)

<https://ispmbern.github.io/covid-19/variants/>