



Peer Community In Evolutionary Biology

How to survive the mutational meltdown: lessons from plant RNA viruses

Kavita Jain based on peer reviews by **Brent Allman**, **Ana Morales-Arce** and 1 anonymous reviewer

Guillaume Lafforgue, Marie Lefebvre, Thierry Michon, Santiago F. Elena (2024) How do plant RNA viruses overcome the negative effect of Muller's ratchet despite strong transmission bottlenecks? bioRxiv, ver. 3, peer-reviewed and recommended by Peer Community in Evolutionary Biology. <https://doi.org/10.1101/2023.08.01.550272>

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Although most mutations are deleterious, the strongly deleterious ones do not spread in a very large population as their chance of fixation is very small. Another mechanism via which the deleterious mutations can be eliminated is via recombination or sexual reproduction. However, in a finite asexual population, the subpopulation without any deleterious mutation will eventually acquire a deleterious mutation resulting in the reduction of the population size or in other words, an increase in the genetic drift. This, in turn, will lead the population to acquire deleterious mutations at a faster rate eventually leading to a mutational meltdown.

This irreversible (or, at least over some long time scales) accumulation of deleterious mutations is especially relevant to RNA viruses due to their high mutation rate, and while the prior work has dealt with bacteriophages and RNA viruses, the study by Lafforgue et al. [1] makes an interesting contribution to the existing literature by focusing on plants.

In this study, the authors enquire how despite the repeated increase in the strength of genetic drift, how the RNA viruses manage to survive in plants. Following a series of experiments and some numerical simulations, the authors find that as expected, after severe bottlenecks, the fitness of the population decreases significantly. But if the bottlenecks are followed by population expansion, the Muller's ratchet can be halted due to the genetic diversity generated during population growth. They hypothesize this mechanism as a potential way by which the RNA viruses can survive the mutational meltdown.

As a theoretician, I find this investigation quite interesting and would like to see more studies addressing, e.g., the minimum population growth rate required to counter the potential extinction for a given bottleneck size and deleterious mutation rate. Of course, it would be interesting to see in future work if the hypothesis in

this article can be tested in natural populations.

References:

[1] Guillaume Lafforgue, Marie Lefebvre, Thierry Michon, Santiago F. Elena (2024) How do plant RNA viruses overcome the negative effect of Muller's ratchet despite strong transmission bottlenecks? bioRxiv, ver. 3 peer-reviewed and recommended by Peer Community In Evolutionary Biology <https://doi.org/10.1101/2023.08.01.550272>

Reviews

Evaluation round #2

DOI or URL of the preprint: <https://doi.org/10.1101/2023.08.01.550272>
Version of the preprint: 2

Authors' reply, 30 January 2024

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Decision by Kavita Jain, posted 19 December 2023, validated 20 December 2023

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Evaluation round #1

DOI or URL of the preprint: <https://doi.org/10.1101/2023.08.01.550272>
Version of the preprint: 1

Authors' reply, 10 November 2023

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Decision by Kavita Jain, posted 17 September 2023, validated 18 September 2023

Dear Authors,

Your preprint has been reviewed by three experts in the field who have offered several comments to improve the manuscript in terms of experimental design, interpretation of results and writing. I invite you to revise your preprint taking care of these comments.

Regards,

Kavita Jain

Reviewed by Brent Allman, 08 September 2023

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Reviewed by anonymous reviewer 1, 15 August 2023

Upon careful reading, I come to the realization that I am not qualified to review this manuscript, due to its heavy reliance on mathematics. Comments below are suggestions only.

Many technical jargons were used without being clearly defined first. For examples, effective population size, selective value, founder effect.

Ln57-59: this is exactly what happens as infections spread from one cell to the next. We now know that if a very small number of viral genome copies (say under 10) invade a cell, the infection is unlikely to be successful. Thus, for most viruses productive cellular infection requires cooperation among large numbers of viral genome copies co-entering the same cell. Nevertheless, regardless of the number of genome copies a cell internalizes, only very few of them have the chance to replicate to yield progeny genome copies (intracellular bottlenecking). The same intracellular bottlenecking process repeats itself when these progeny genome copies enter the next cell, so that again only very few of them yield progeny. This has been well documented – e.g. Grubaugh et al Cell Host-Microbe 2016.

The authors should consider discussing Muller's ratchet in the context of new findings by others over the last 10 years. It is true Muller's ratchet has the potential to cause some isolated subpopulations (cell lineages in an infected individual) to accumulate deleterious mutations and potentially go extinct, but the same process could also allow other subpopulations (intra-host cell lineages) to become more fit. In the case of viruses, the subpopulations that succumbed to Muller's ratchet exist for a time too brief for us to study. This is simply what natural selection is about.

Ln60-63: As discussed above, I cannot agree that one virus particle is enough to initiate a successful infection in an intact plant. I challenge the authors to demonstrate that. Earlier studies came to such conclusion by measuring the progeny genome copies that replicated to detectable levels. However, just because very few viruses end up producing detectable progeny does not mean very few entered a cell/tissue/plant.

Ln207, define "100% infectivity".

Ln142-145, unclear. Were the up to 10 lesions mixed before grounding? How did you ensure all of the 10-microliter-extract, or all virions in it, invaded tobacco cells? The issue here may indirectly prove that you need a high number of virions to enter each cell for successful infection to occur (the content of a single lesion may become so diluted or wasted in the preparation and inoculation processes so that not enough viral genomes can invade a single cell together).

Ln207-208, Did all lesions invariably lead to poor infectivity? Do you sense something wrong here?

Ln210, 212, unclear. "serial passages" – all in quinoa?

Reviewed by Ana Morales-Arce, 05 September 2023

The introduction is clear about the theory and objectives behind the experiment. It aims to investigate the survival of viruses infecting plants despite the action of Muller's ratchet and transmission bottlenecks. The references cited are sufficient. I also highlight the study's main contribution in that it regards a whole organism (in this case, the quinoa and tobacco plants) rather than culture cells, traditionally used to explore the same questions. The research questions are straightforward, though hypotheses or predictions still need to be included. In general, there isn't a clear answer to the title question; perhaps it could be more explicit that they

are conducting an experimental approach in the title.

The methods are clear enough to allow for experiment replication, though it took me a while to understand them. Figure 1 could be further improved to make understanding the passages and differences between the N_e expected sizes easier. For instance, it could be helpful to include the approximate—number of generations. In general, quinoa plants are infected to create lineages, a reduced number of individuals, and allow for the accumulation of mutations. Then viruses are transmitted to a natural host of tobacco plants that will show a systemic infection. This approach is consistent with the question. Further, the fitness measure would be the infectivity measure in the tobacco plants, and this specifically would make many assumptions. I would expect that the plants measured are all clones and not influenced by external environmental factors during the 9dpi, which I doubt was the case.

Further, the authors tested their experimental results by comparing them with a model. The model is explained in terms of the parameter values, and the authors discuss them quite well. However, it could also be helpful for the reader to have a background in the choices of these ranges, i.e., why the replication (r)= [1,50] and why they chose 200 replicates. The size of the bottleneck or the initial infection number of individuals is better covered but less for the rest. Additionally, the readers might benefit from having more information about the virus biology (what is in the literature), i.e., the replication time (generations), the mutation rates, genome recombination, and epistasis. The model scripts run and produce consistent values with the reported in the paper. I am not surprised the author disagrees with their model and the experiment. The model cannot reflect all the complexity involved, as they recognized in the discussion (for example, lines 292, 359). The model could recognize the limitations more explicitly and still show how valuable it is to try to model the transmission as it is done. Perhaps because the model is missing the reality of the number of infective particles in every passage, I understand the difficulties of measuring this before a passage, if it is possible in-vitro in this virus. The discussion also needs some specifics. For instance, when they mention the genetic properties of viral particles in lines 274-275, what exactly do they refer to? Haplotype load? Population load? Other? And finally, in line 359, the authors mention cooperation. How could this happen? Do they mean epistasis? or host-pathogen interactions? What about the replication system of the virus? Are they exempt from progeny skew? Especially if the founder population is small. I also would be careful to claim mutation rate changes (line 411) as these are not measured here. A good question remaining is the role of mutation rate and mutation rate changes in these experiments. If it happened, what is the cause? how do you measure it experimentally?