# Determining the Relationship Between Time, Transmission and the Evolution of the Rabies Virus

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## What's up with rabies?

- While the rabies virus usually causes death within a few weeks of infection, it can also have a latent period of months or years.
- Due to low levels of viral replication in the host's muscle tissue (Shankar et al., 1991), RABV may not be mutating in this period, potentially violating the molecular clock.
- We aim to investigate whether RABV mutates on a per unit time or per transmission generation basis, and compare methods of calculating SNPs/generation.
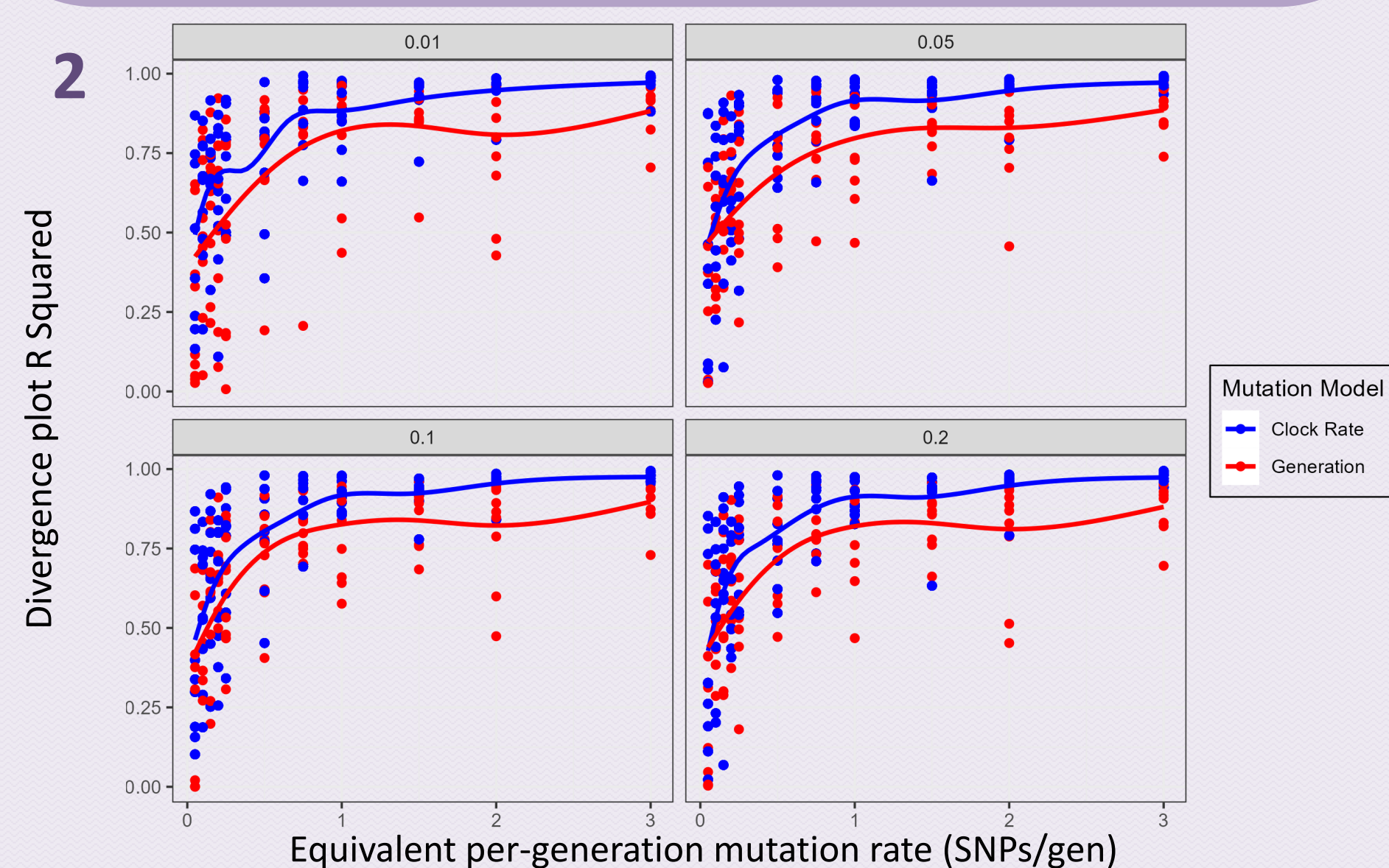


## How can we measure mutations per generation?

- We compared a simple mathematical method of measuring SNPs/generation to a novel phylogenetic method.
- Both methods performed well on simulated phylogenies, with the simple mathematical method performing slightly better.
- We calculated the mean per-generation mutation rate of rabies in Pemba & Serengeti to be 0.17 SNPs/generation (**3**).
- Mean mutation rates also differ between lineages (**4**).
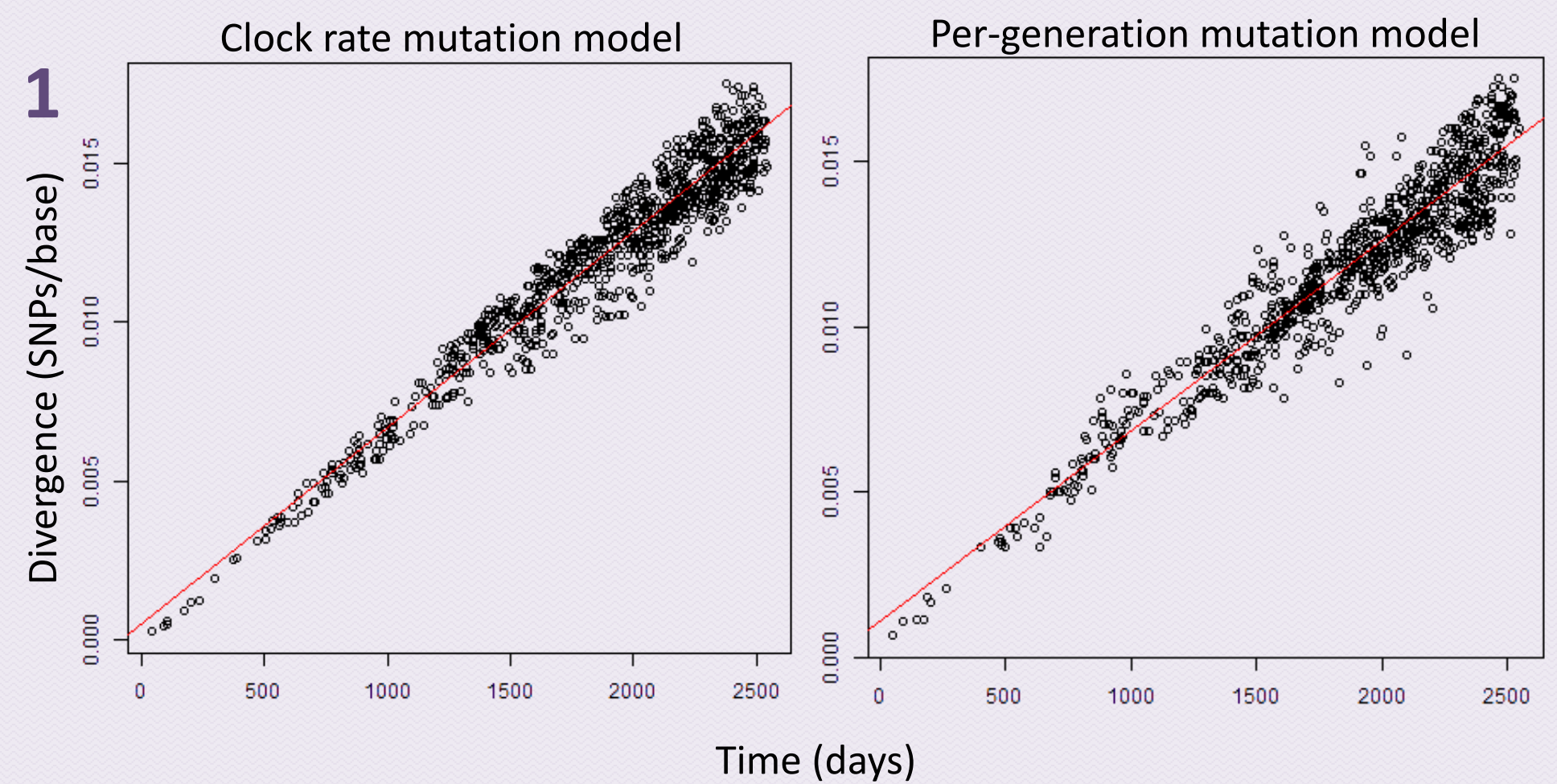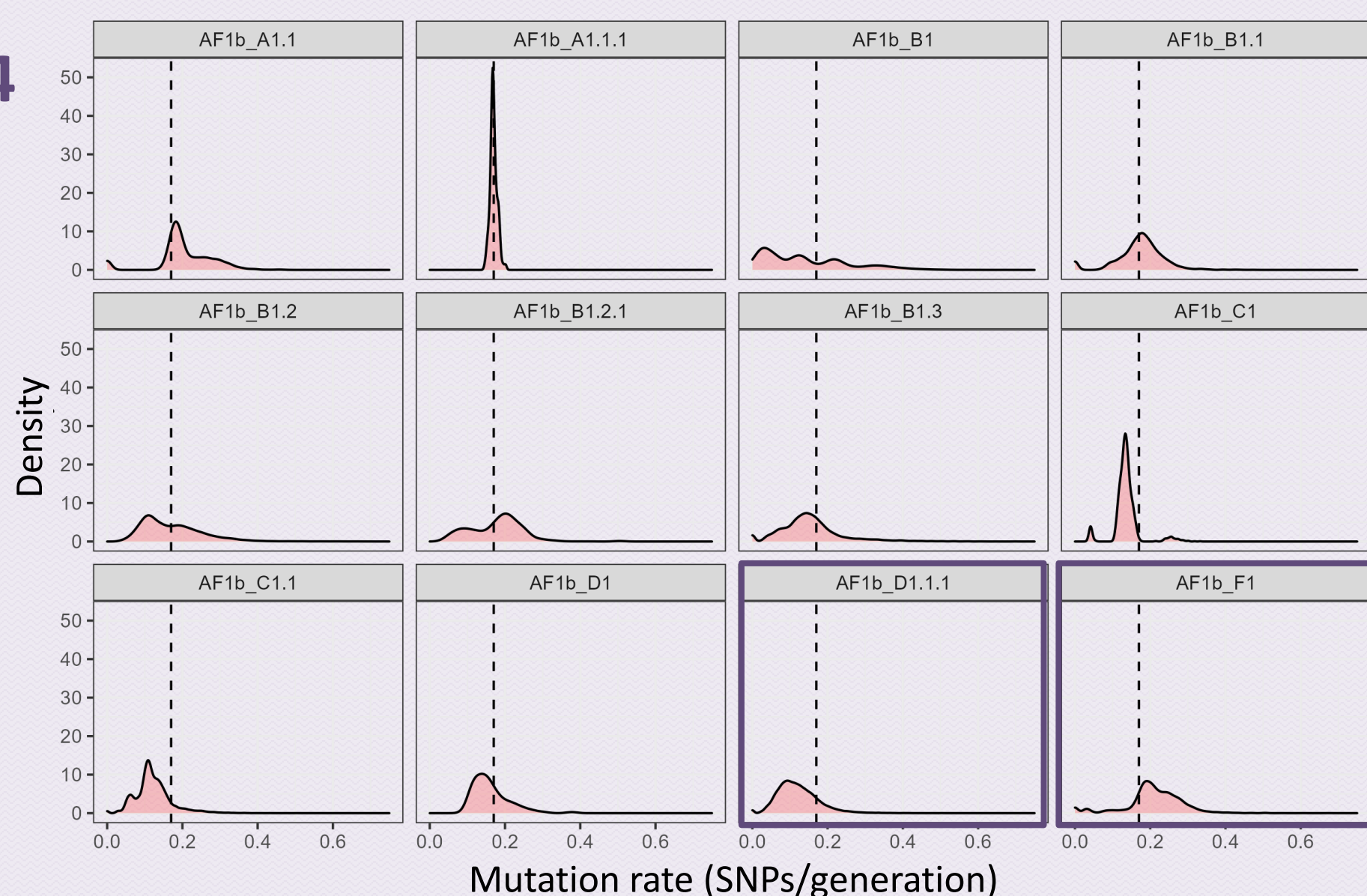




1: Divergence plots comparing two mutation models at 2 SNPs/gen or equivalent. Note the "stray" points in the per-generation mutation model plot.
2: R² of divergence plots for both mutation models, across different case sampling rates and mutation rates.

## Can we figure out how it mutates?

- We simulated two mutation models to investigate whether they showed distinct divergence plot patterns: SNPs accumulating per unit time, and SNPs accumulating per generation.
- While the two models did produce distinct divergence plot patterns (**1**) and R² values (**2**) at high mutation rates, these were not visible at mutation rates below 1 SNP/generation.
- As rabies has a much lower clock rate than most RNA viruses, it may be difficult to ascertain how it mutates
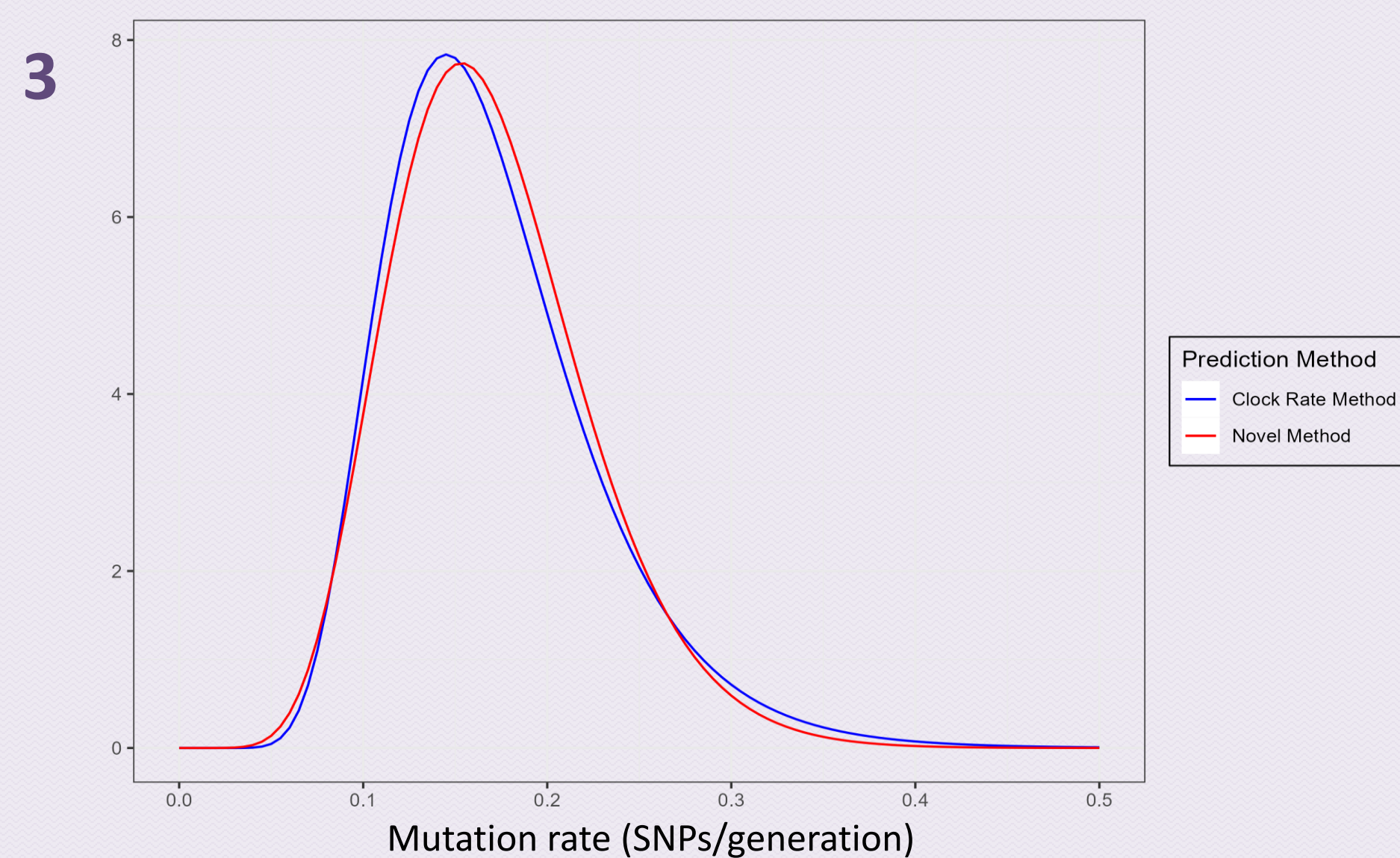


3: Distribution curves of SNPs/gen generated from our methods' output.
4: Distributions of mutation rate predictions by lineage. The outlined plots are slowest and fastest mutating lineages respectively.

## What does this mean?

- Rabies mutation rate is so low that it likely doesn't matter long-term whether it mutates per unit time or per generation, but this could be relevant for more rapidly mutating viruses.
- Lab studies may be useful in comparing rabies replication rates between infection stages.
- The SNPs/generation value can now be used to estimate outbreak sizes from genetic data.

## References

Shankar, V., Dietzschold, B. & Koprowski, H. (1991). Direct entry of rabies virus into the central nervous system without prior local replication. J. Virol., 65, 2736–2738

Contact me!

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