Near-Neutral Balanced Selection Theory (NNBST): Implication on the molecular evolution of SARS-CoV-2 and Zika virus

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Introduction & Motivation

- Virus pandemics (e.g. SARS-CoV-2, Influenza) have significantly impacted human well-being and welfare. Solving the true molecular evolution of viruses is critical for preventing pandemics and developing the next-generation drugs and vaccines.
- The molecular clock feature of virus genomic substitution rates (GSRs) associated with increasing vaccinations and infected human cases indicates a confusing interpretation for viral evolution.
- Ultimately, the three main evolutionary theories (Selectionist Theory/ST, Kimura's Neutral Theory/KNT, Ohta's Nearly Neutral Theory/ONNT) cannot exclusively explain the molecular evolution of the recent SARS-CoV-2 virus.
- Here, we developed a new evolution theory, Near-Neutral Balanced Selection Theory (NNBST) that explains the molecular evolution of viruses exhibiting a molecular clock feature.

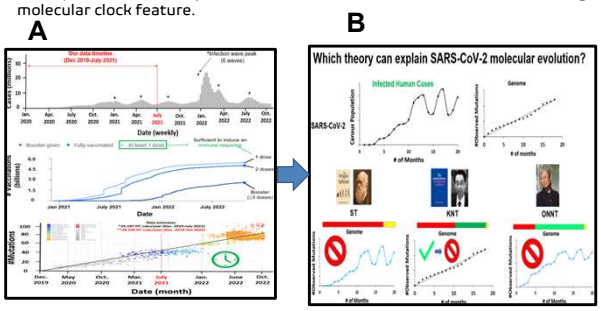
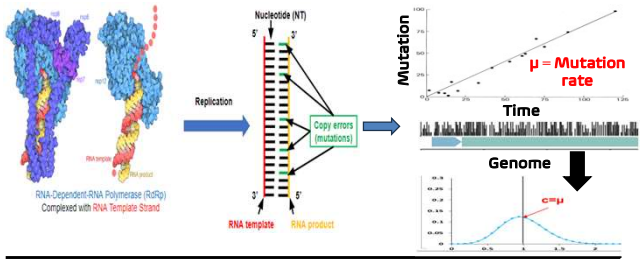
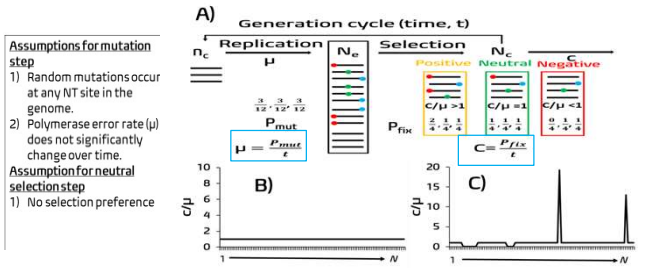
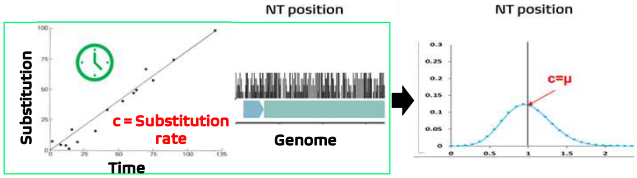


Figure 1 (A) Number of infected human cases (10^0 to ~10^7 cases), number of vaccinations and GSR of SARS-CoV-2 obtained from Nextstrain. (B) The predicted GSRs of the three existing evolution theories (ST, KNT and ONNT).

Methods & Materials







Why is c=μ in neutral selection?

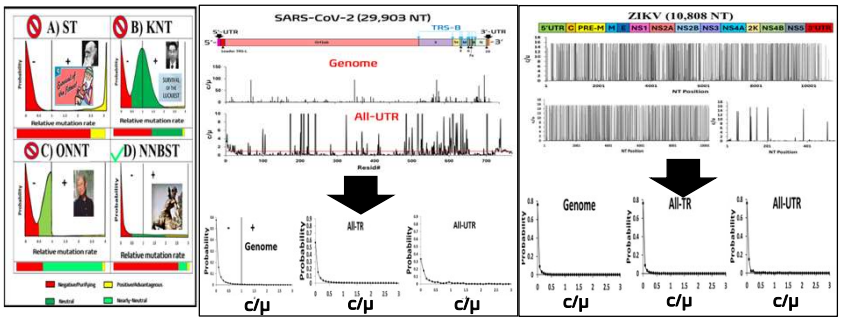
Under neutral selection, most mutations do not impact fitness and have equal chance to be kept or removed in the population.

Positive substitutions (increases fitness) are incredibly rare and deleterious substitutions (decreases fitness) are removed prior to selection, thus they don't contribute majorly to **(c).**

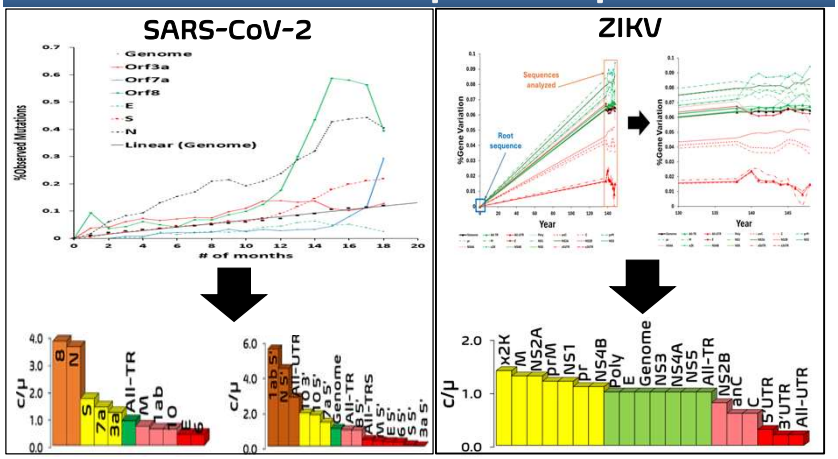
Neutral substitutions contribute primarily to (c), which is mostly random copy errors in the genome induced by the viral polymerase at rate **(μ).**

Therefore, c=μ.

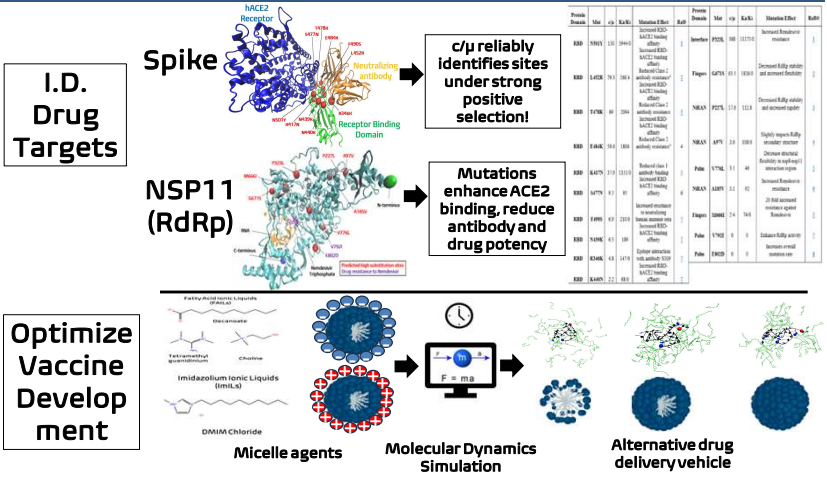
NNBST-Sequence Space



NNBST-Temporal Space



NNBST-Applications



Summary

- SARS-CoV-2 and ZIKV molecular evolution is best explained via NNBST.
- **Future Projects:** NNBST will be applied to >10 RNA viruses, other human pathogens and the human genome to elucidate their molecular evolution. Hotspot nucleic acid and protein drug targets will be identified and characterized using experimental and computational approaches to enable novel drug and vaccine development protocols.

Citations & Acknowledgements

1) Wu C, Paradis NJ, Lakernick PM, Hryb M. L-shaped distribution of the relative substitution rate (c/μ) observed for SARS-COV-2's genome, inconsistent with the selectionist theory, the neutral theory and the nearly neutral theory but a near-neutral balanced selection theory: Implication on "neutralist-selectionist" debate. Comput Biol Med. 2023 Feb;153:106522. doi: 10.1016/j.compbiomed.2022.106522. Epub 2023 Jan 5. PMID: 36638615; PMCID: PMC9814386.

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