

Faculty of Science

# Host Heterogeneity and Punctuated Evolution of SARS-CoV-2

Bjarke Frost Nielsen<sup>(RUC+NBI)</sup>, Kim Sneppen<sup>(NBI)</sup>,

Lone Simonsen<sup>(RUC)</sup>, Cécile Viboud<sup>(NIH)</sup>,

Yimei Li<sup>(Princeton)</sup>, Simon Levin<sup>(Princeton)</sup>, Bryan Grenfell<sup>(Princeton)</sup>

—  
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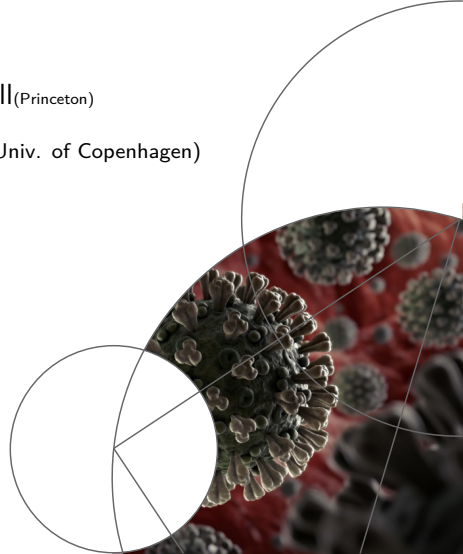
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## The PandemiX Center

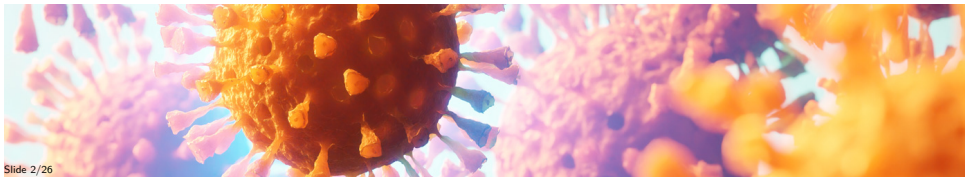


PandemiX

The Hamming Distribution

Modelling Hamming  
Dynamics

- Newly started (June 1<sup>st</sup>!) Center of Excellence for **Pandemic Signatures**
- **Interdisciplinary:** Physics, mathematics, history, clinical, classical epidemiology, bioinformatics, molecular biology.
- **Core:** Roskilde U., Niels Bohr Institute, Technical U. of Denmark, Nordsjællands Hospital, National Institutes of Health, SSI.
- **Collaborators:** Princeton (Grenfell Lab), Cambridge (Davenport Lab), Harvard (Lipsitch lab).



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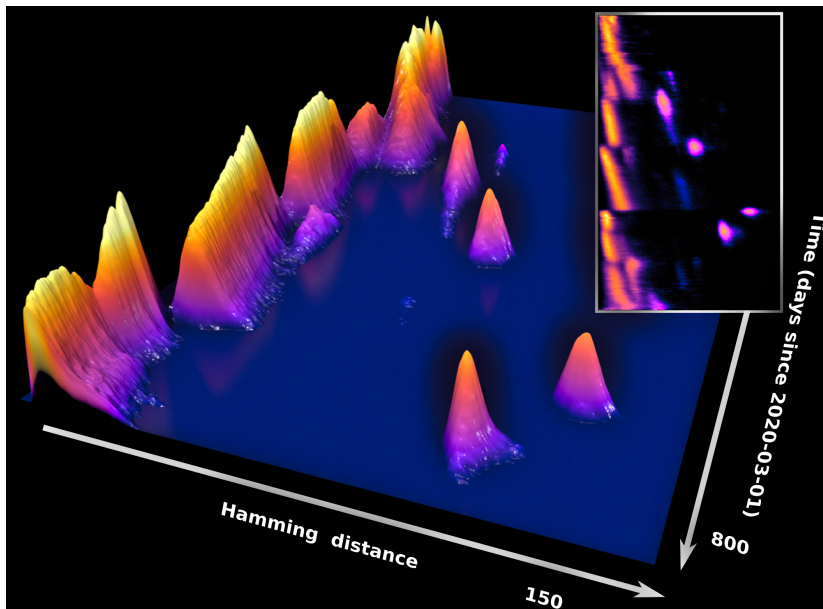


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## The Hamming Distribution – first appearance



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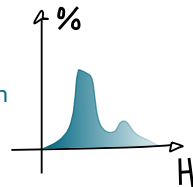
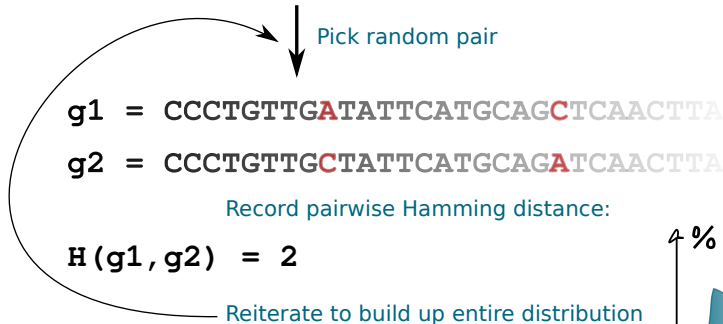
# The Hamming Distribution

Temporal Hamming (or Levenshtein\*) distribution:

```

CCTGTTGCTATTCATGCAGATCAACTTA
CCTGTTGATATTCCTGCAGCTCAACTTA
CCTGTTGACATTACGCAGCTCAACTTA
CCTGTTGACACCTACGCAGCTCAACTTA
CCTGTTGCTATTCCTGCAGATCAACTTA
CCTGTTGATATTCATGCAGCTCAACTTA
CCTGTTGACATTACGCAGCTCAACTTA
CCTGTTGACACCTACGCAGCTCAACTTA
CCTGTTGACACCTACGCAGCTCAACTTA
CCTGTTGACACCTACGCAGCTCAACTTA
  
```

Genomes sampled  
in the same week



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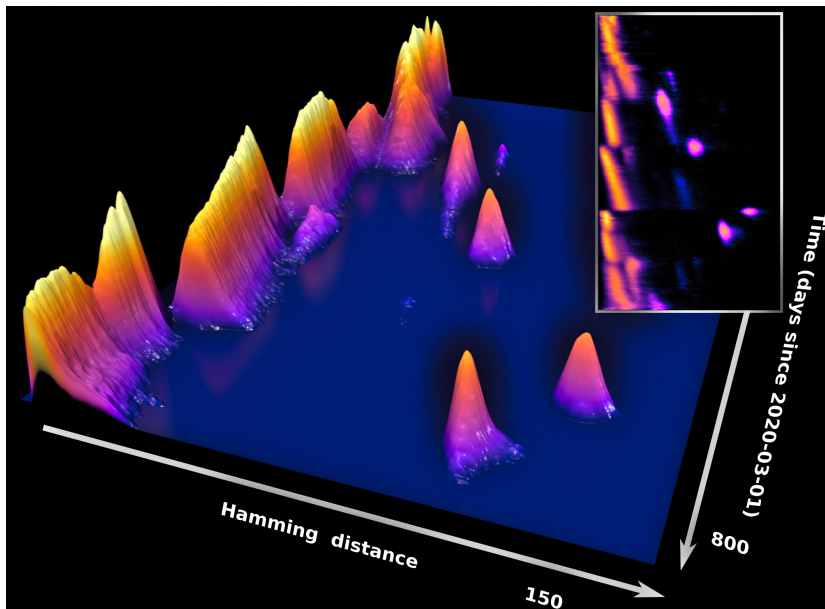
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## The Hamming Distribution



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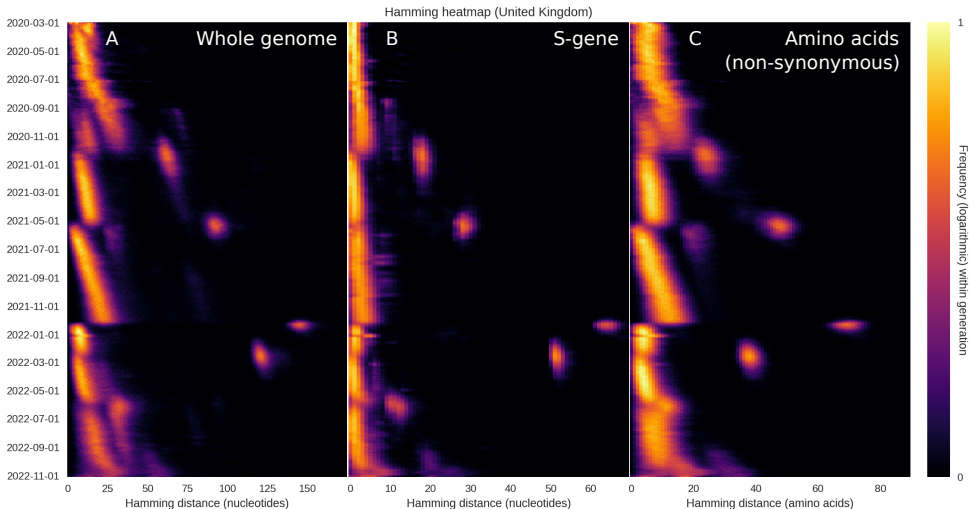
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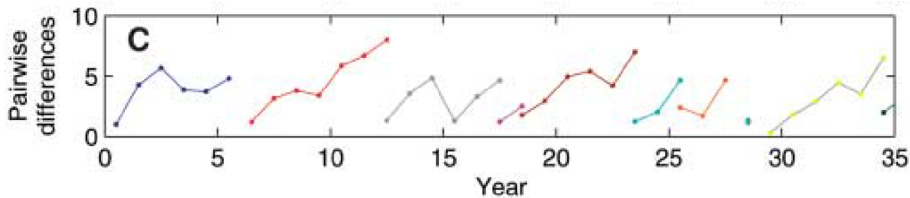
Influenza – Katia Koelle et al.

≡ Science

## Epochal Evolution Shapes the Phylodynamics of Interpandemic Influenza A (H3N2) in Humans

[KATIA KOELLE](#), [SARAH COBEY](#), [BRYAN GRENFELL](#), AND ,

[MERCEDES PASCUAL](#) [Authors Info & Affiliations](#)



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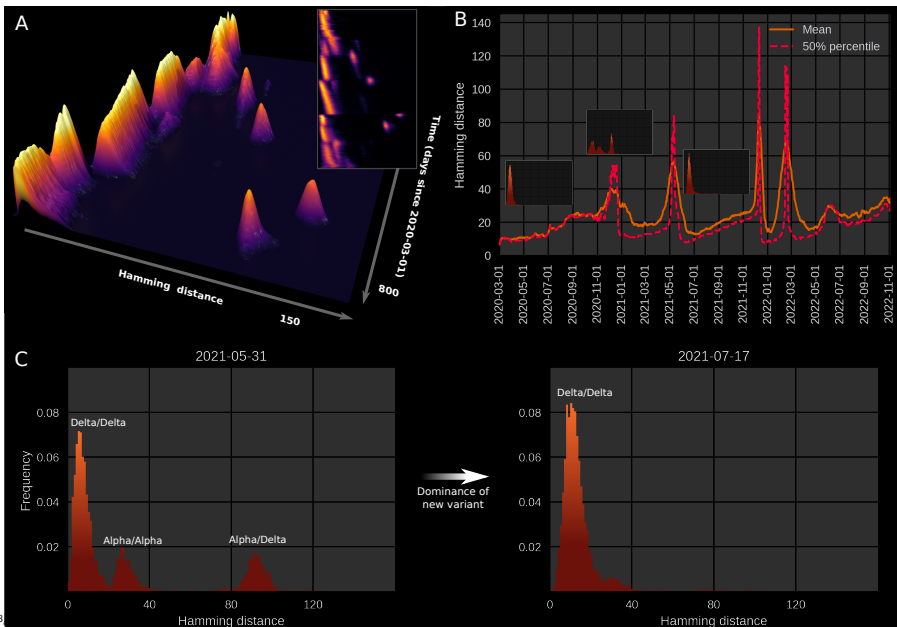


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# The Hamming Distribution





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# The Hamming Distribution – Reanimated!

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# Modelling Hamming Dynamics

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Programme:

- 1 Come up with *a* mechanistic model which captures data.
- 2 Probe alternative explanations! Rule out, rule in, ...



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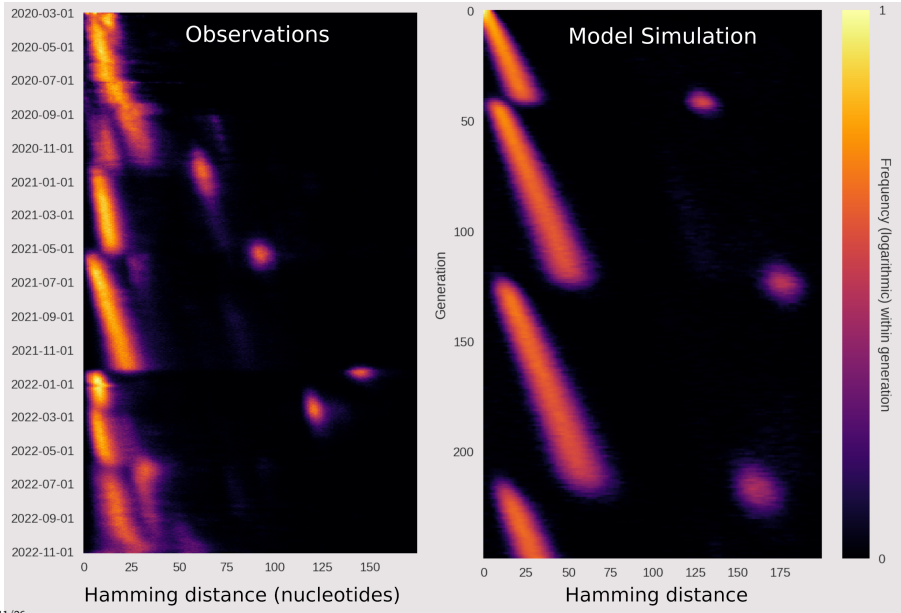
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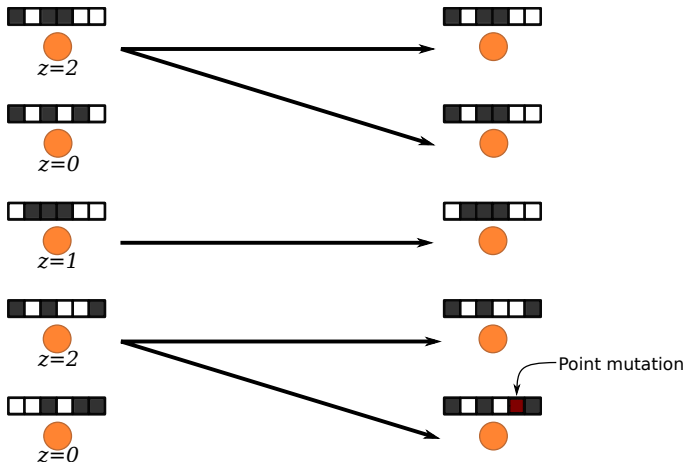
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## Modelling

- Branching model
- Bitstring genomes
- Fitness landscape



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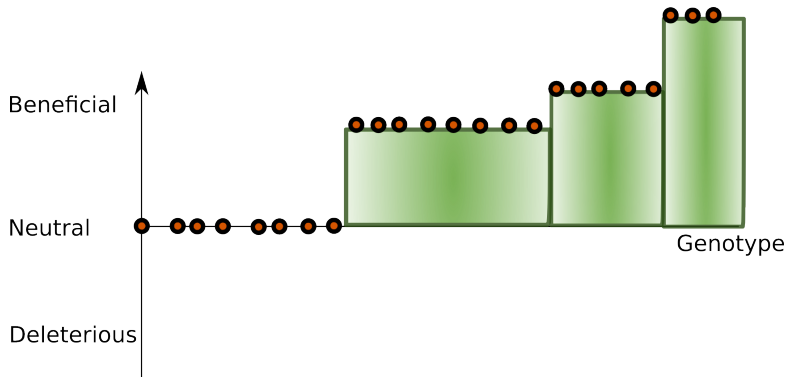
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## Modelling

What fitness landscape?



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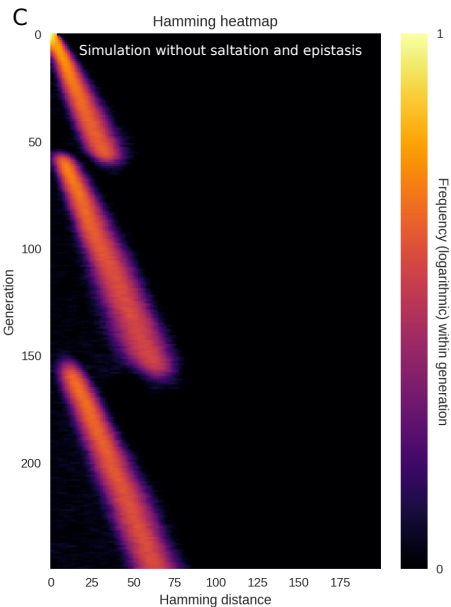
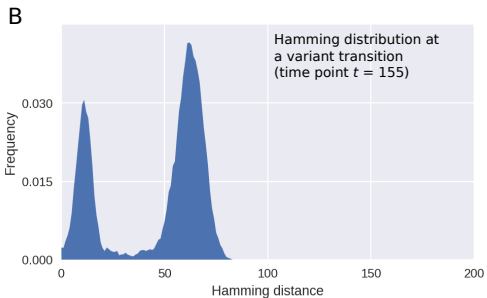
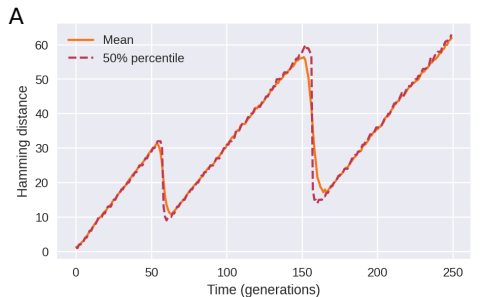


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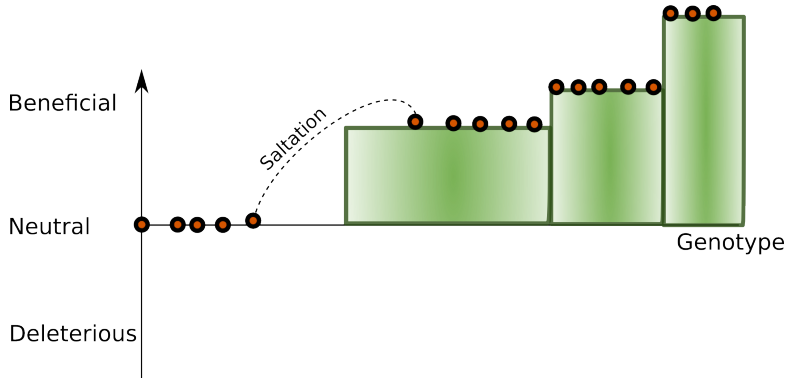
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What about saltation?



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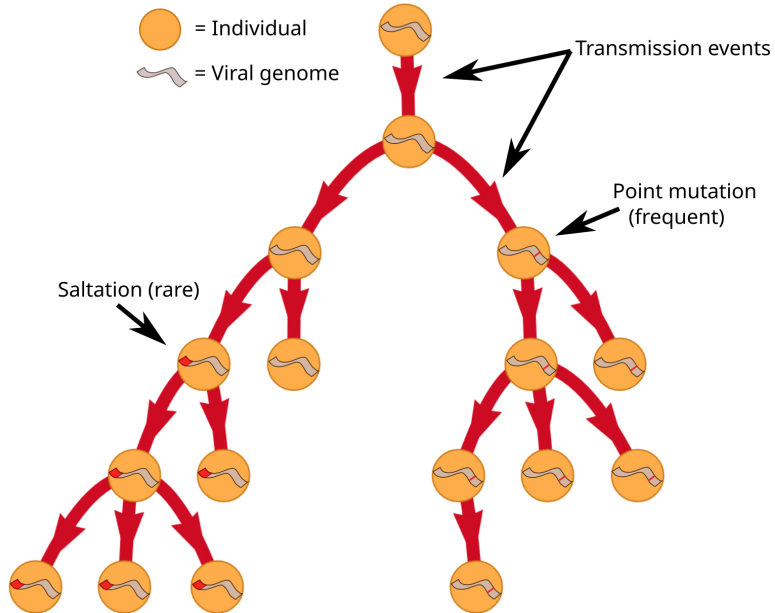
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## Formulating a model – with saltations





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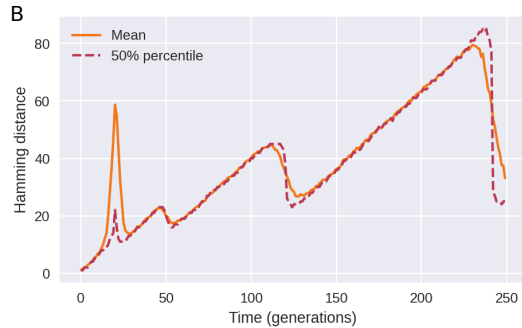
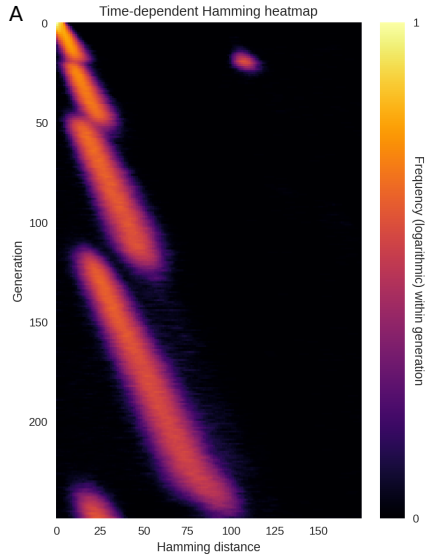
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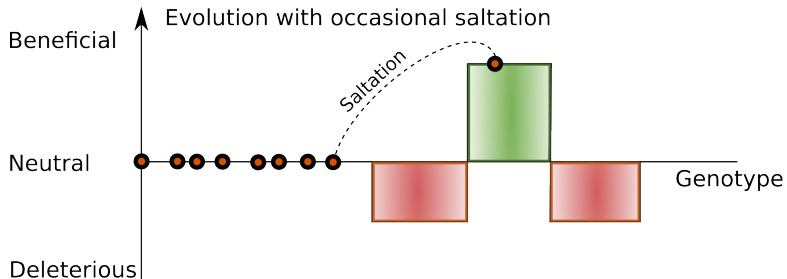
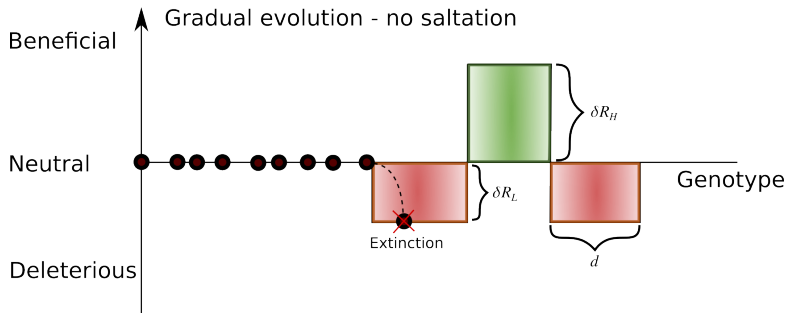


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## Modelling – Epistasis



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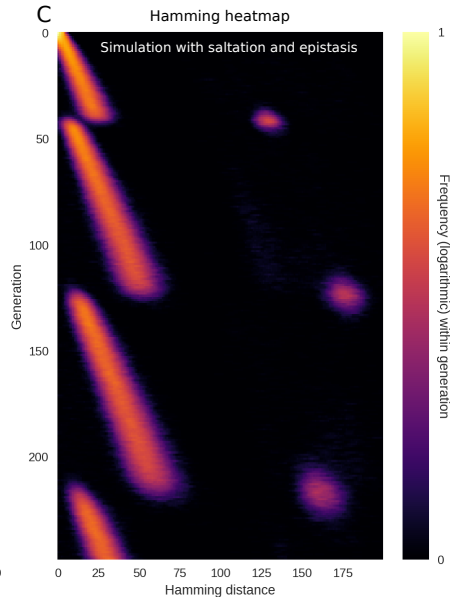
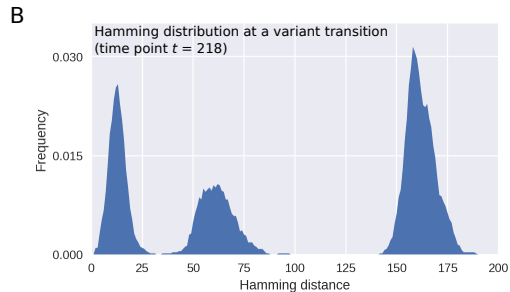
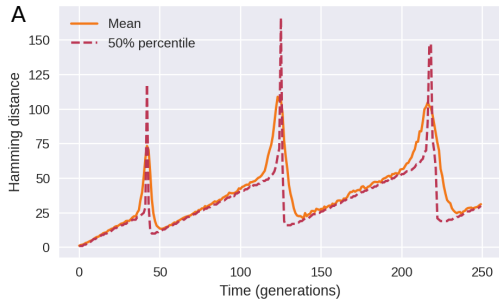
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## Modelling – Epistasis and saltation



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## Origin of saltation?

*The Journal of Infectious Diseases*

# Yearlong COVID-19 Infection Reveals Within-Host Evolution of SARS-CoV-2 in a Patient With B-Cell Depletion

— — — — —  
THE NEW ENGLAND JOURNAL OF MEDICINE

## SARS-CoV-2 Variants in Patients with Immunosuppression

Lawrence Corey, M.D., Chris Beyrer, M.D., M.P.H., Myron S. Cohen, M.D.,  
Nelson L. Michael, M.D., Ph.D., Trevor Bedford, Ph.D., and Morgane Rolland, Ph.D.

- Persistent infection in immunocompromised individuals
- 'Reverse zoonosis'? – Back/forth transition
- A 'hidden population'?

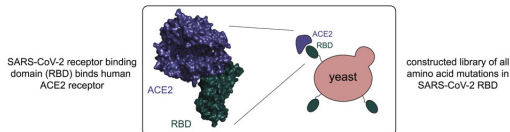
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## Presence of epistasis?

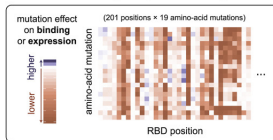


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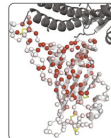
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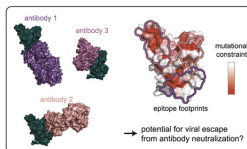
determined effects of all mutations on ACE2-binding affinity and RBD folding



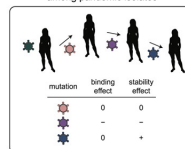
RBD structure-function relationship



mutation constraint and antibody epitopes



surveillance of mutations among pandemic isolates



T. N. Star, ..., J. D. Bloom.

Interactive version: [https://jbloombloom.github.io/SARS-CoV-2-RBD\\_DMS/](https://jbloombloom.github.io/SARS-CoV-2-RBD_DMS/)

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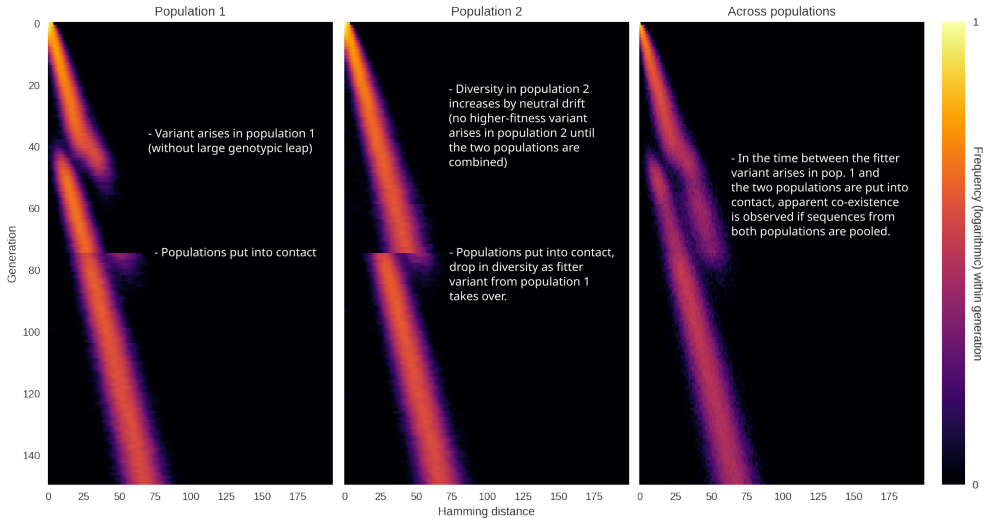
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## A hidden population? Probably not.



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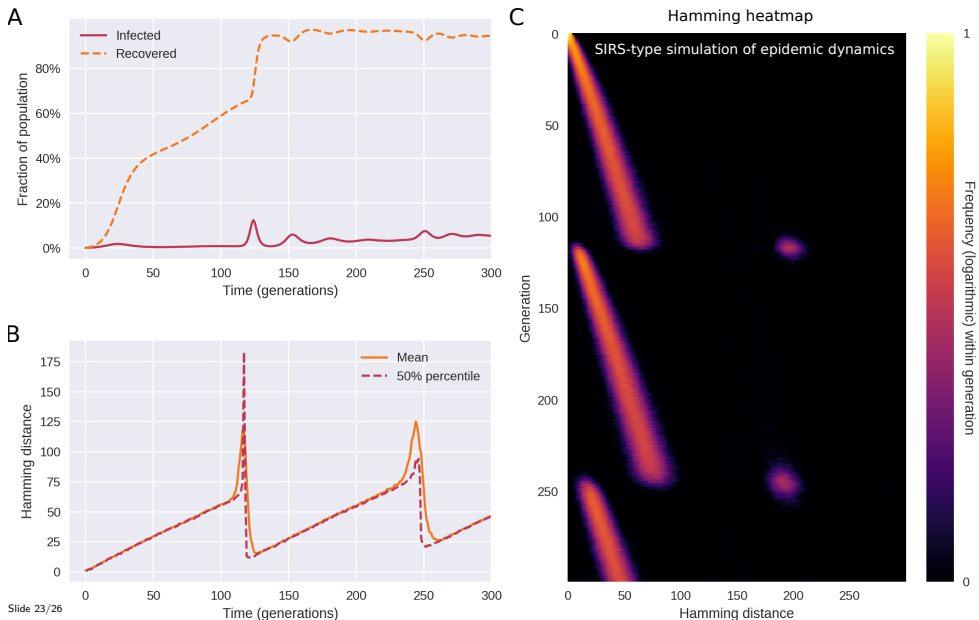
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## SIRS Dynamics – the pattern is unaffected



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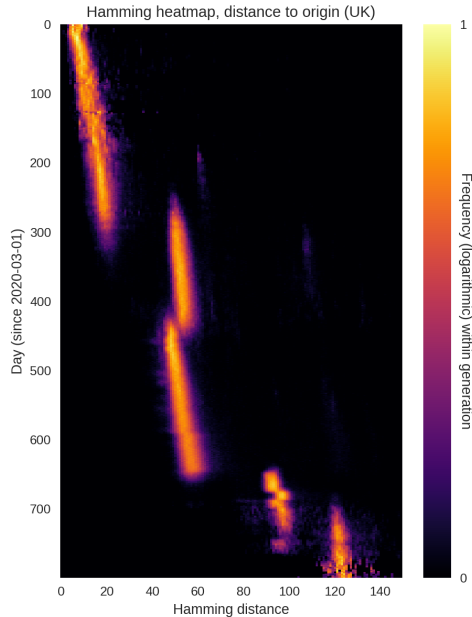
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## The “rooted” Hamming distribution – complementary info.





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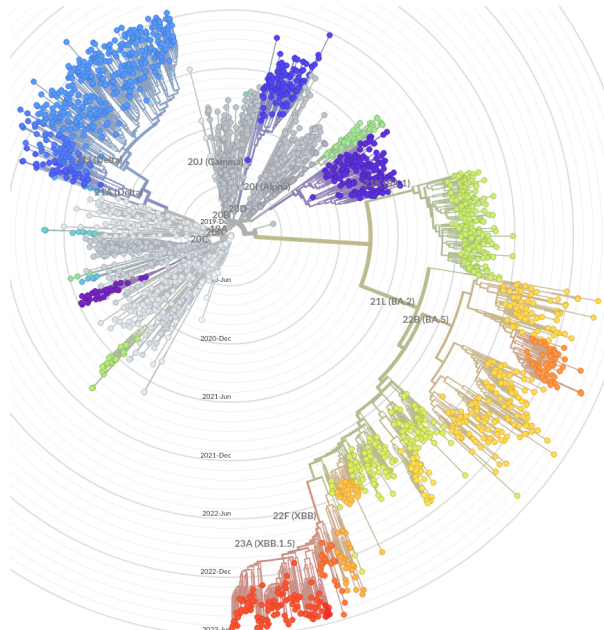


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# The Big Ol' Phylogeny



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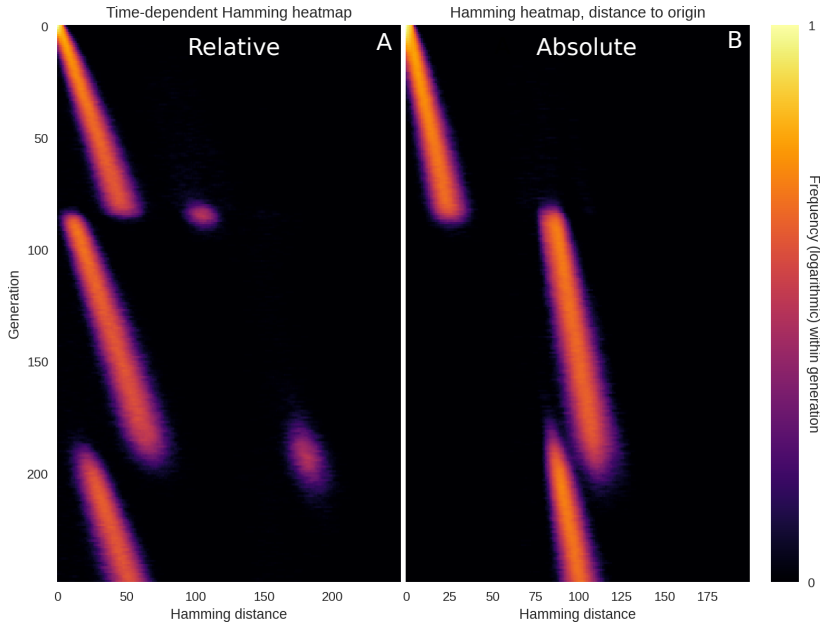
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## Decreasing distance via prolonged infections



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## Conclusions

- Saltations in SARS-CoV-2
- Prolonged infections + epistasis a plausible explanation
- A 'hidden' population (unsequenced, cryptic transmission) seems unlikely

More generally: Two types of temporal Hamming distributions (rooted and unrooted) are useful tools!

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This frame läft ämpty.

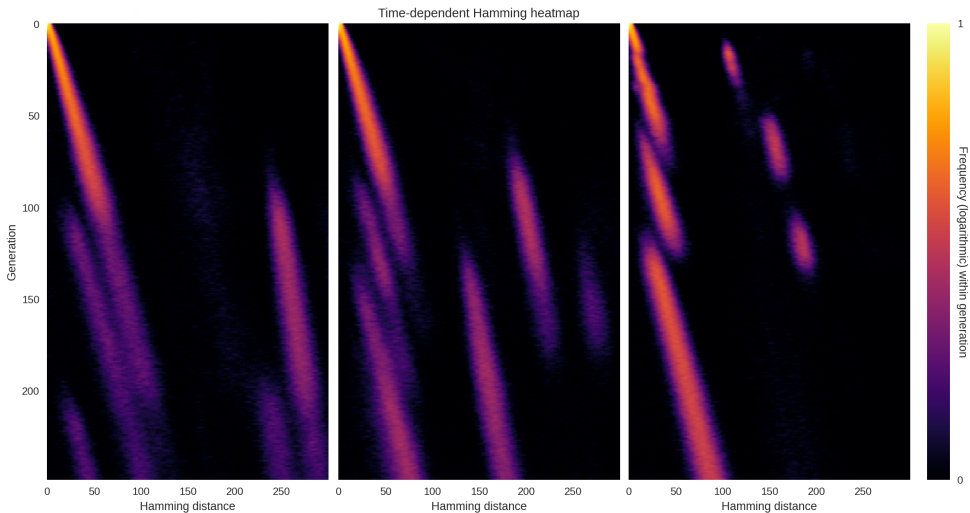


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## Spatial effects – (metapopulation approximation)



— — — increased coupling between spatial patches →

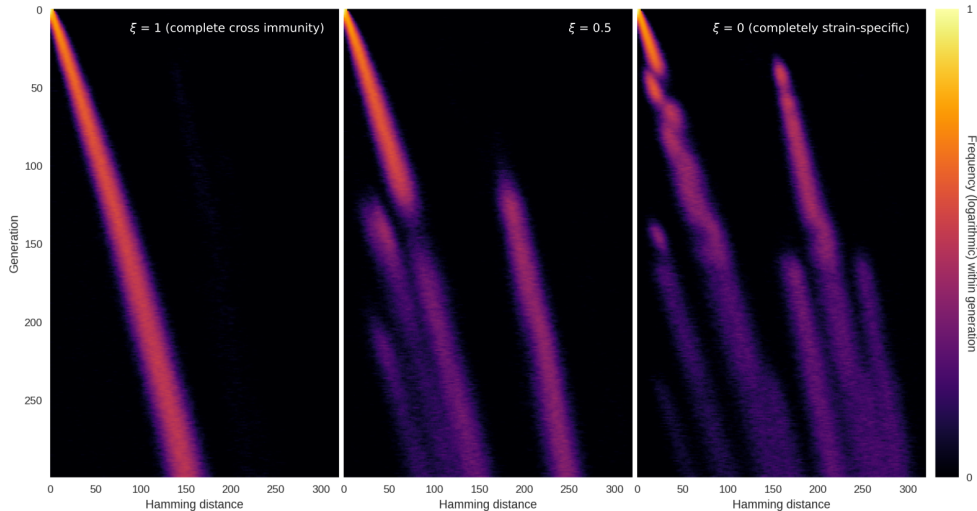


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## Partial cross-immunity 1

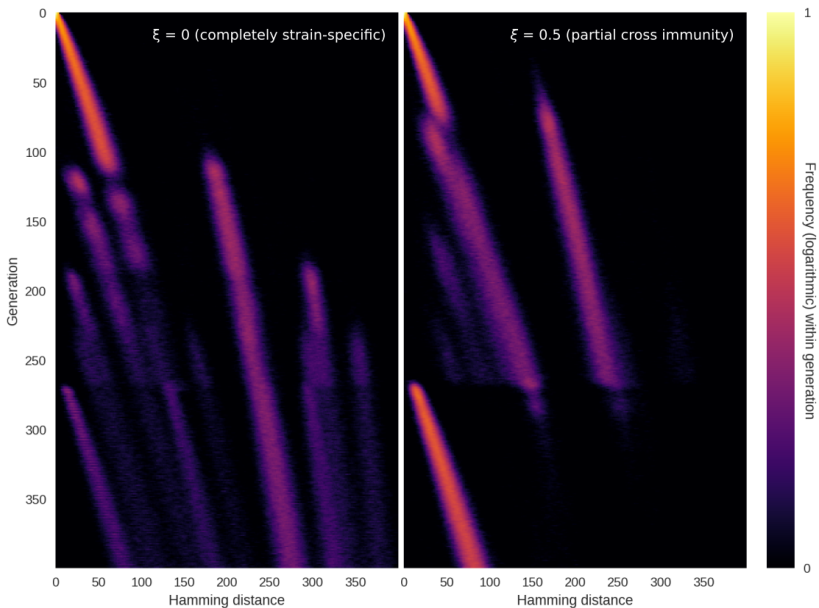


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## Partial cross-immunity 2

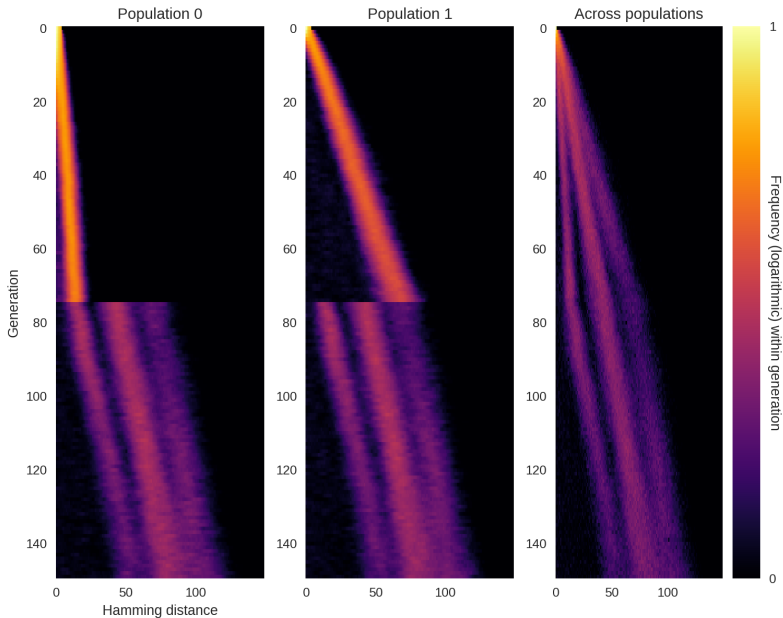


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## Populations with different (mean) rates of mutation



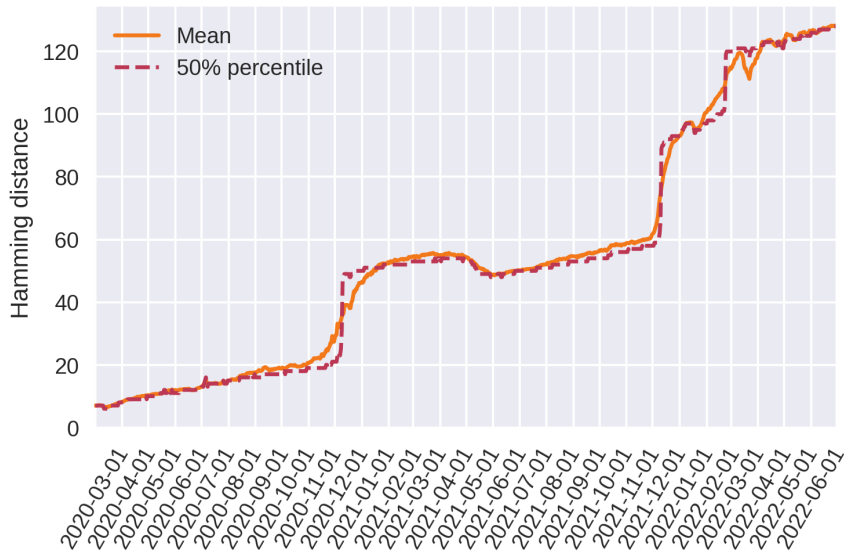


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## Hamming dist. rooted in Ancestral variant

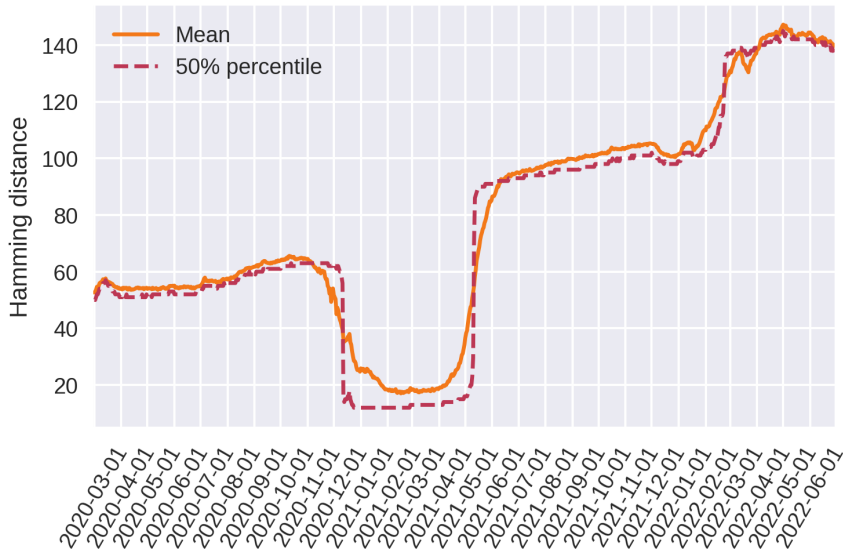


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## Hamming dist. rooted in Alpha variant

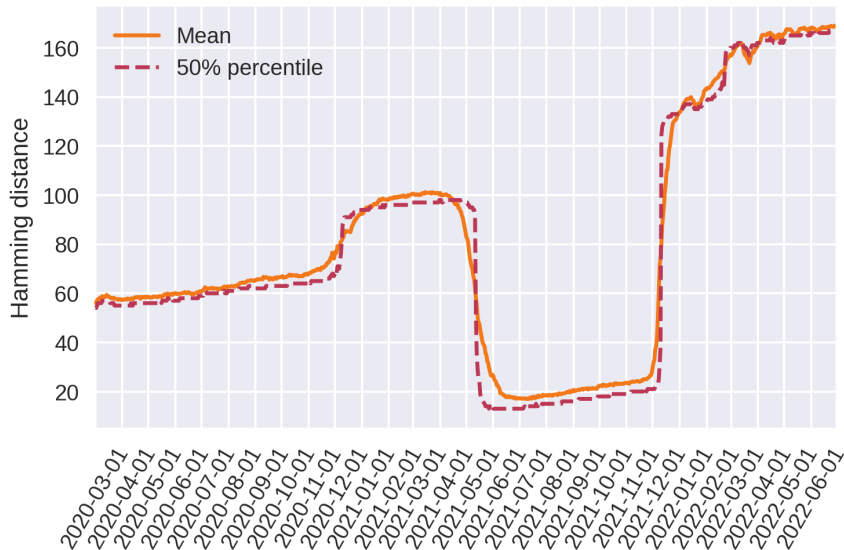


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## Hamming dist. rooted in Delta variant

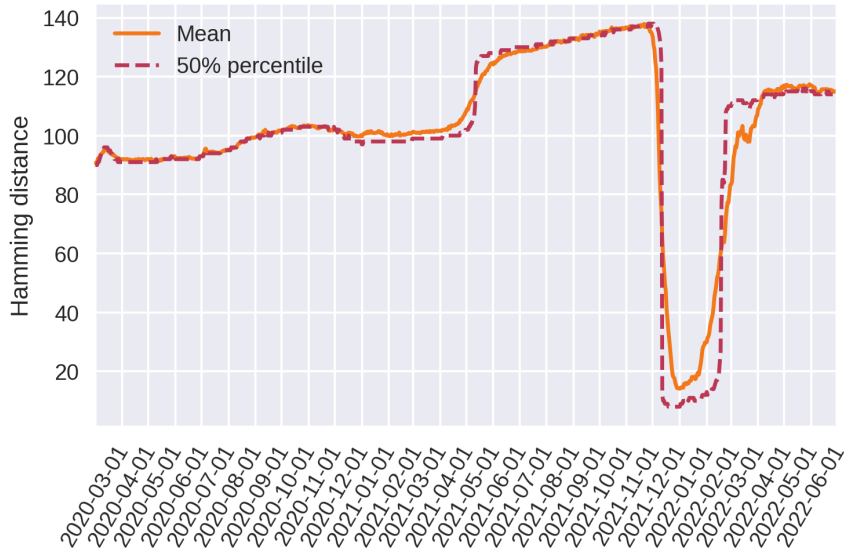


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## Hamming dist. rooted in Omicron BA.1

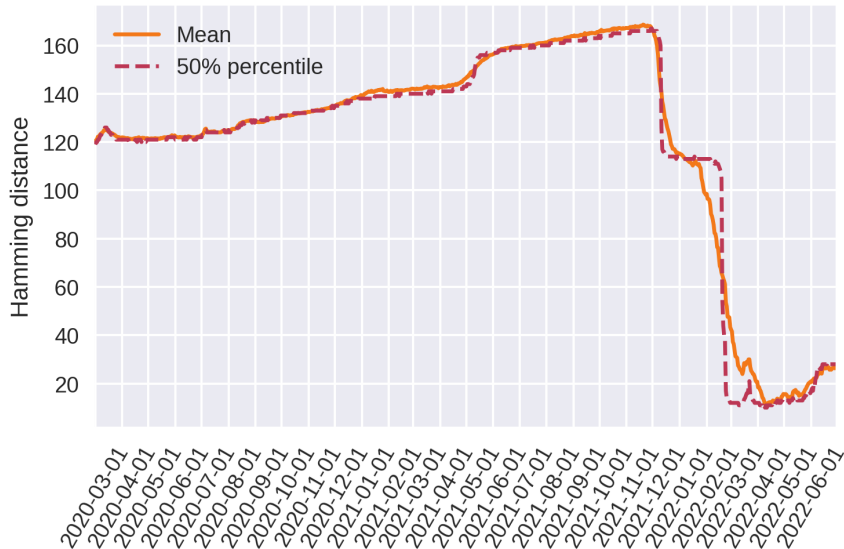


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## Hamming dist. rooted in Omicron BA.2



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## Differently rooted Hamming distributions

