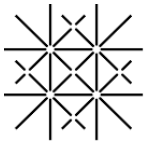


# Influenza: Limited predictability of evolution Ecology of host and pathogen

Pierre Barrat-Charlaix



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**BIOZENTRUM**

Universität Basel  
The Center for  
Molecular Life Sciences

Group of **Richard Neher**

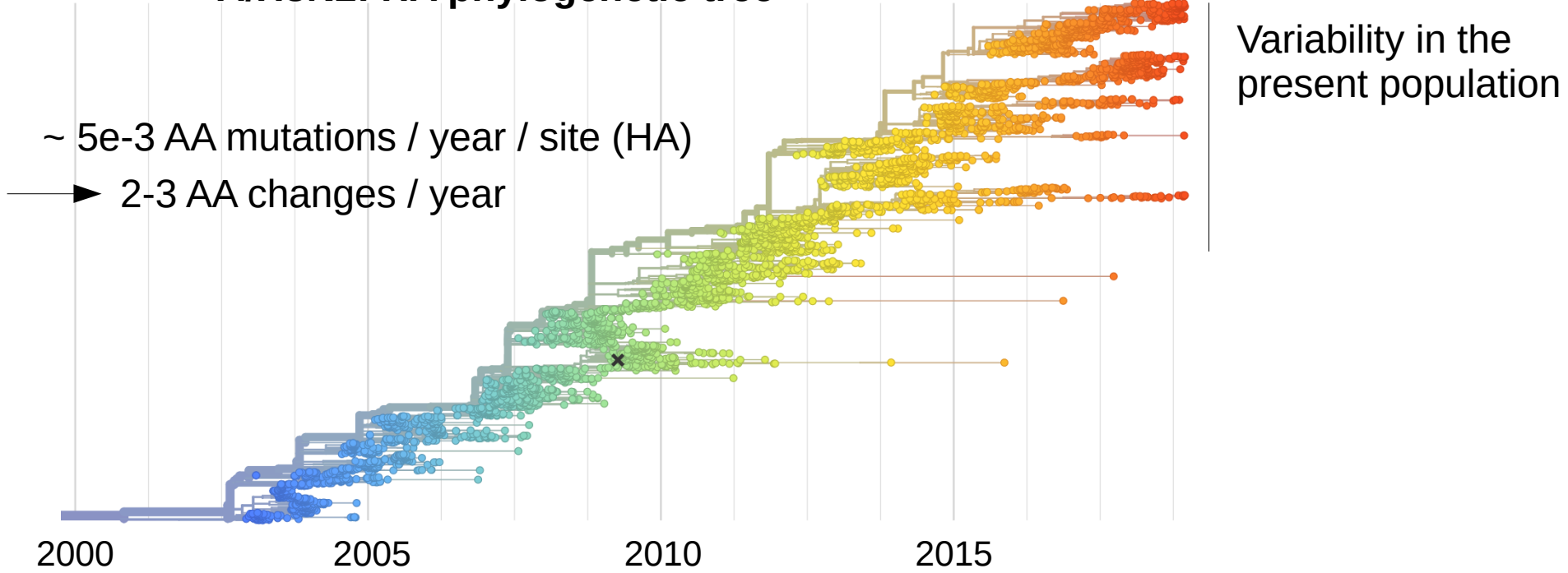
Collaborators:  
**John Huddleston**  
**Trevor Bedford**

# Human seasonal influenza virus

~ hundreds of million cases per year → 5-10 % of humans

In constant evolution (especially surface proteins HA & NA)

**A/H3N2: HA phylogenetic tree**

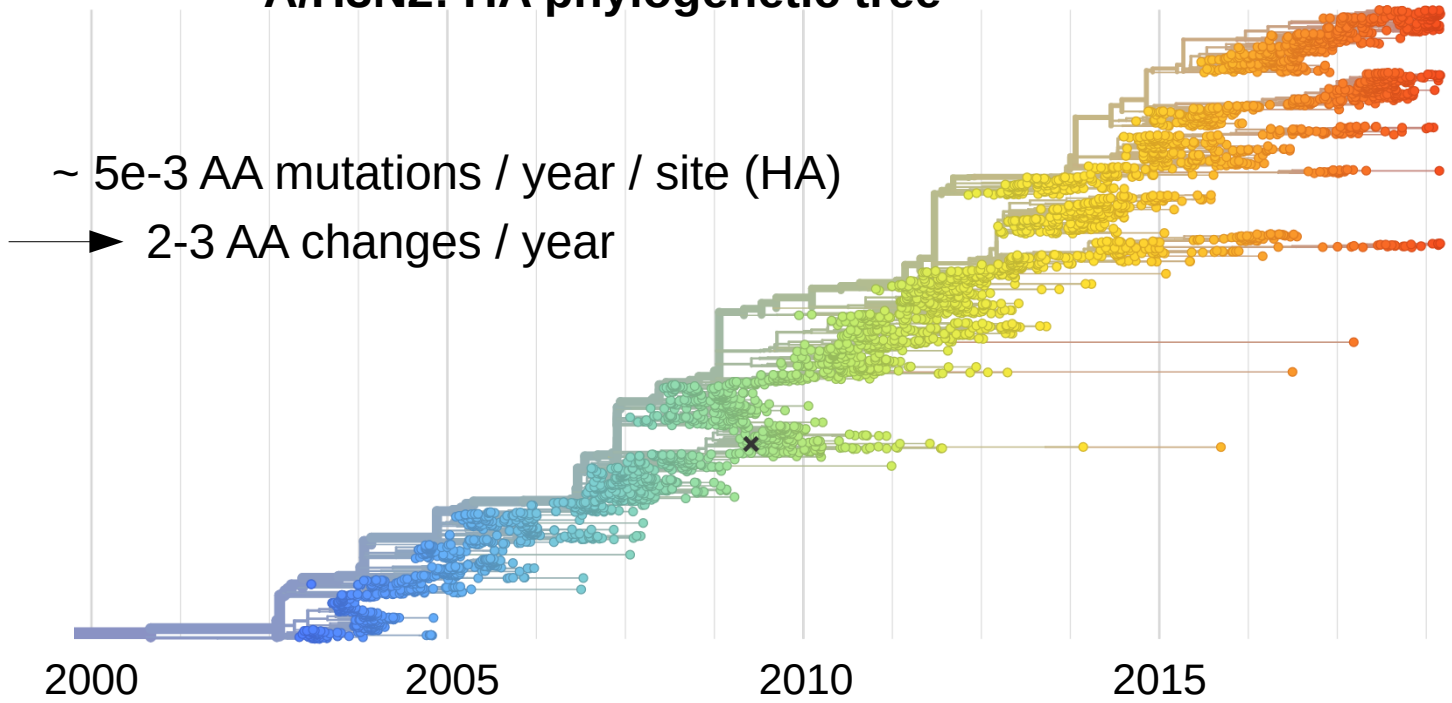


# Human seasonal influenza virus

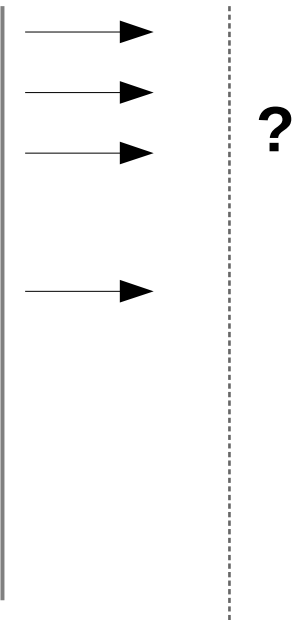
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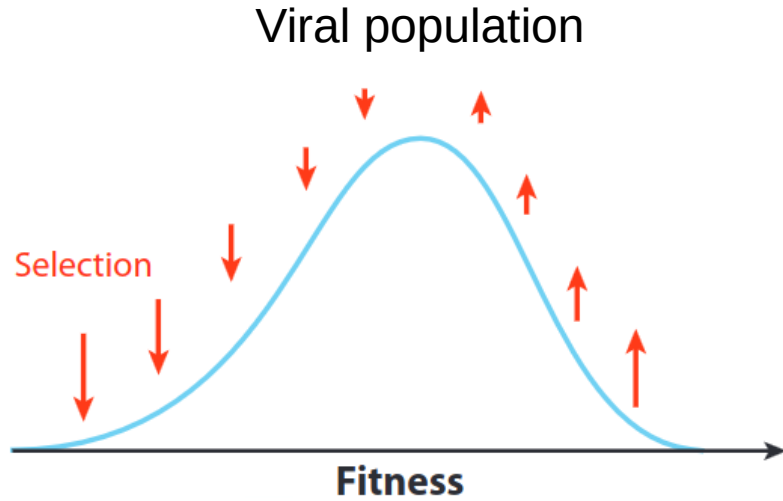
**A/H3N2: HA phylogenetic tree**



Which present clade will take over ?



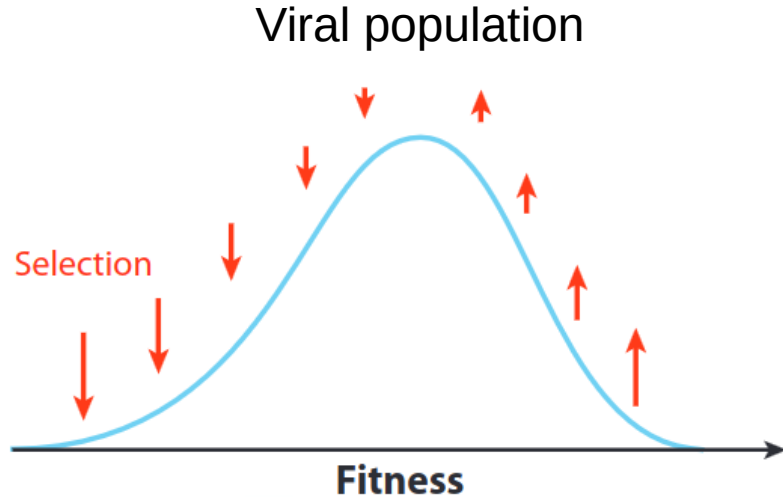
# Traditional approach: travelling fitness wave



- Mutations have a fixed fitness effect
- Fitness determines the fate of a mutant
- Extra-complexity: competition between mutants

—▶ **Some degree of predictability**

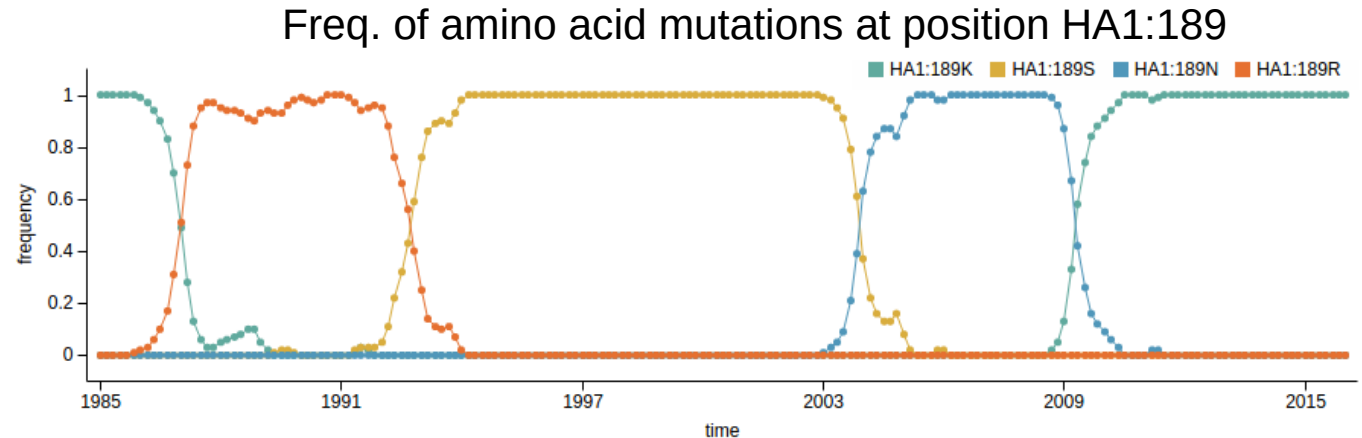
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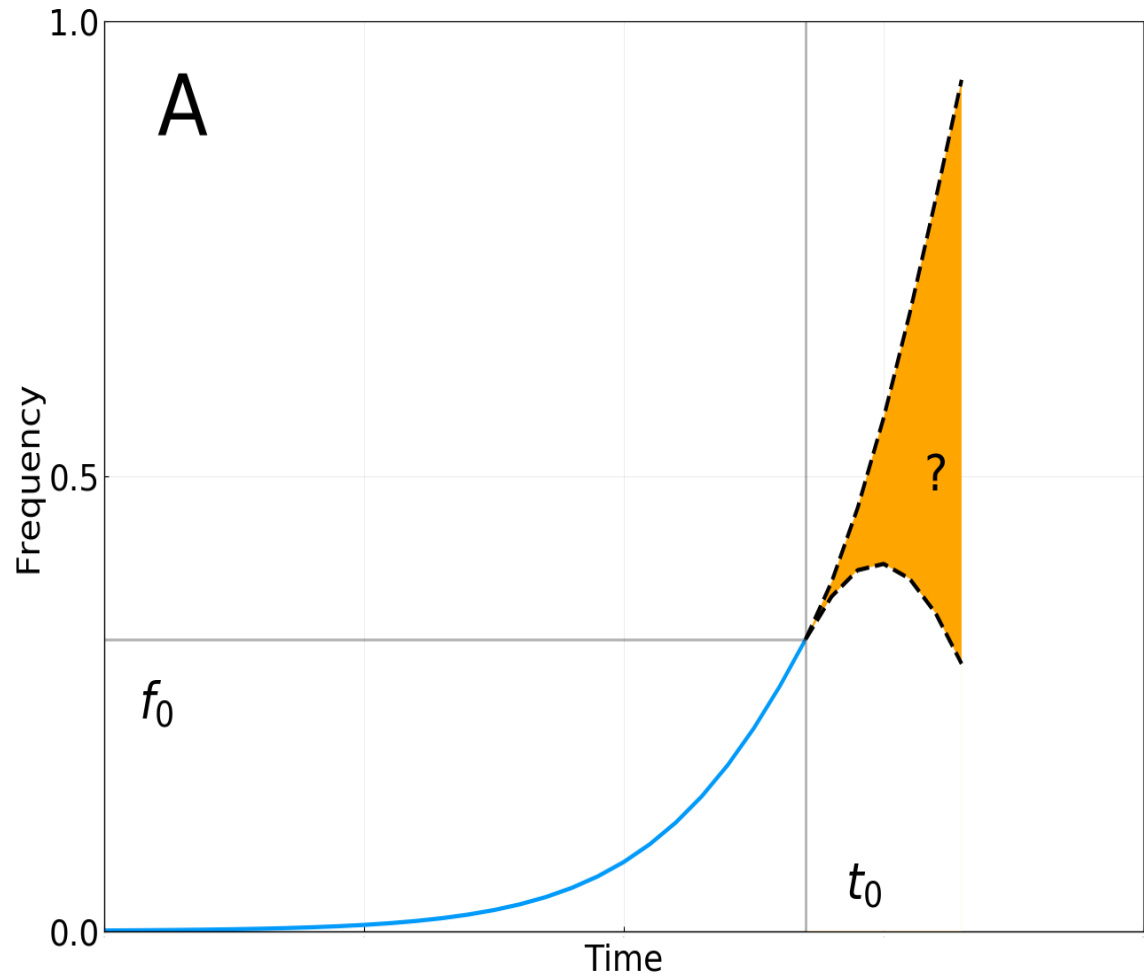
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Selective sweeps



# Simple analysis: predictability of influenza

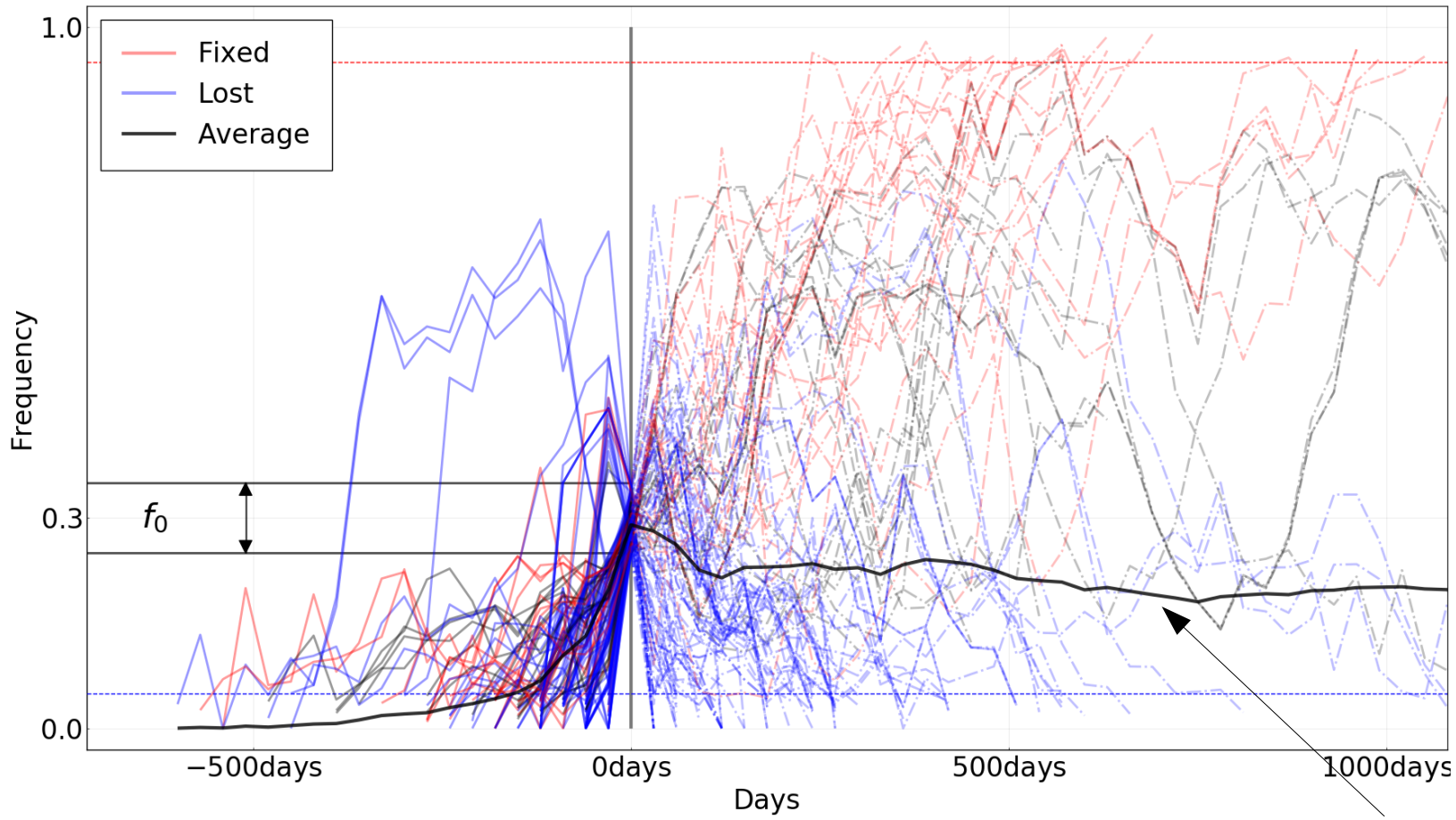


**Frequency trajectories of amino acid mutations**

Statistics from all sequences since 2000 (~20 years of data)

# Limited predictability

Influenza H3N2, HA protein



- Mutations:**
- Absent in the past
  - Seen around  $f_0=30\%$

► **No inertia**

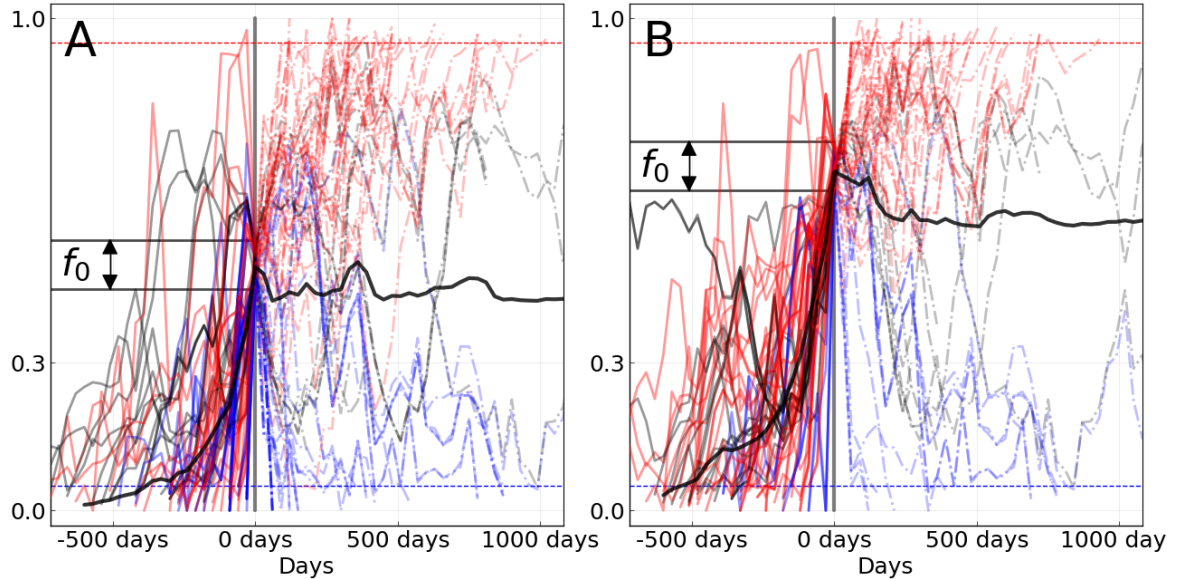
**Average**

# Limited predictability

Using different thresholds

Using proxies for fitness:

- Density of branching in phylogeny
- Epitope positions



Huddleston et. al. 2020

Barrat-Charlaix et. al. 2021



**Qualitative difference between  
model and observations**



# Adaptive immunity and expiring fitness

## **Adaptation is driven by immunity**

- Most adaptive mutations escape immunity
- They only escape a fraction of the host population

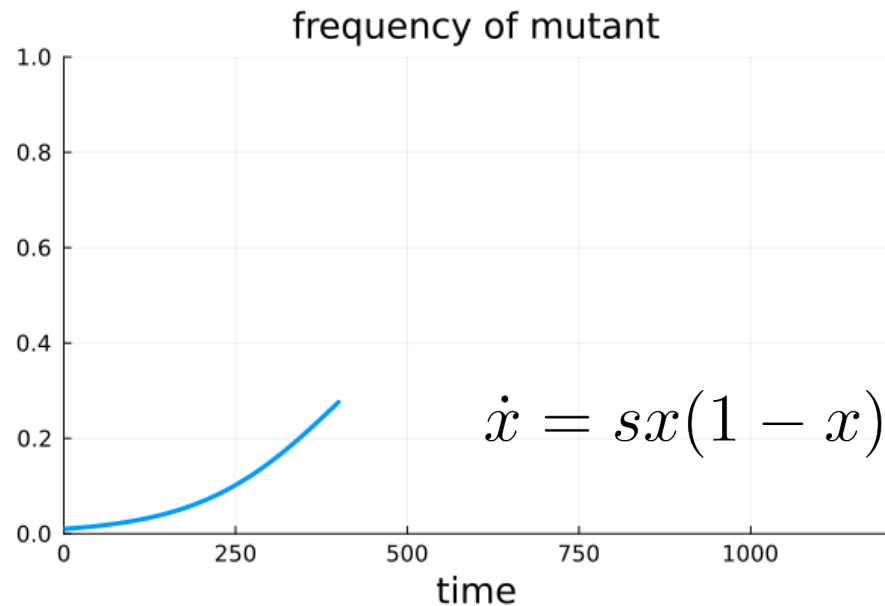
## **Adaptive immunity of hosts**

- fitness advantage expires before fixation
- “ecology”: organisms shape their environment

# Adaptive immunity and expiring fitness

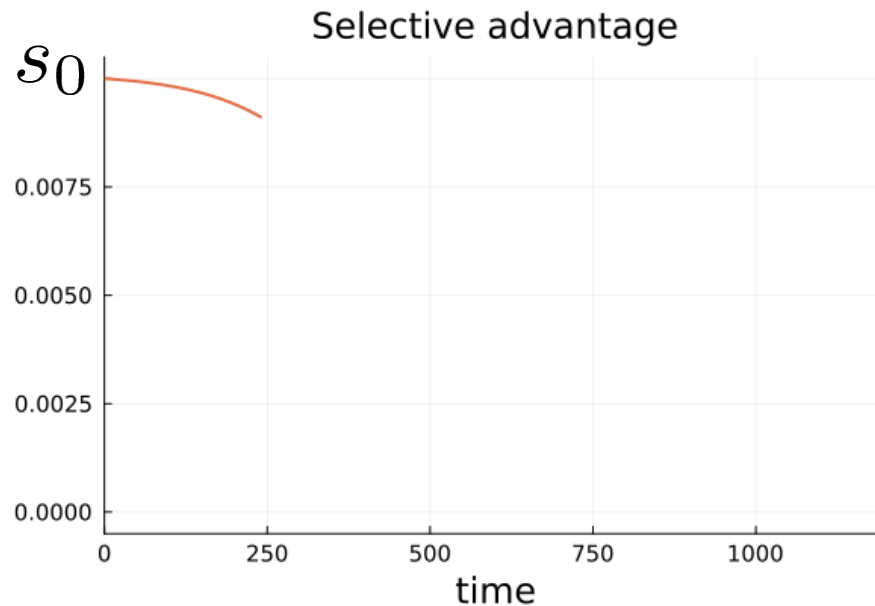
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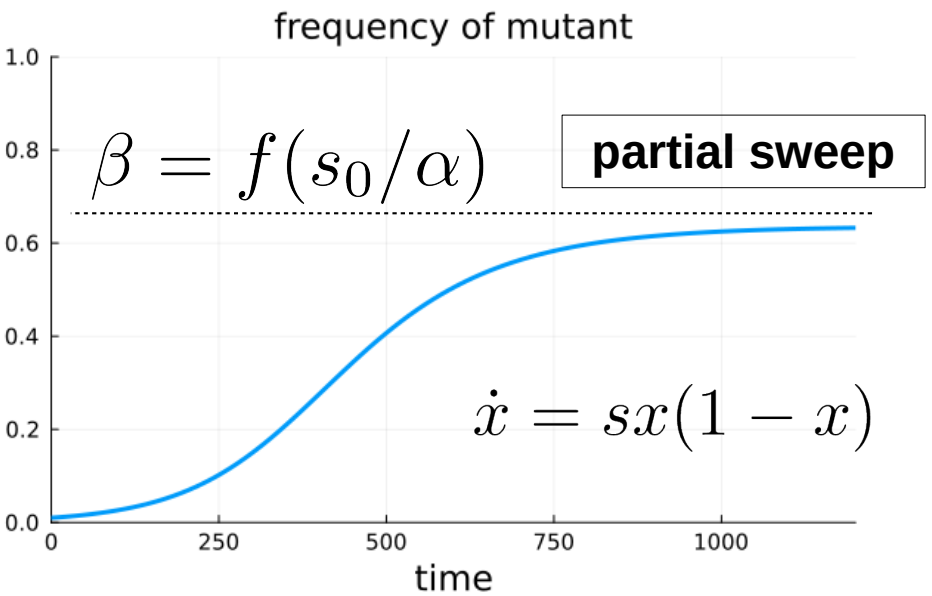
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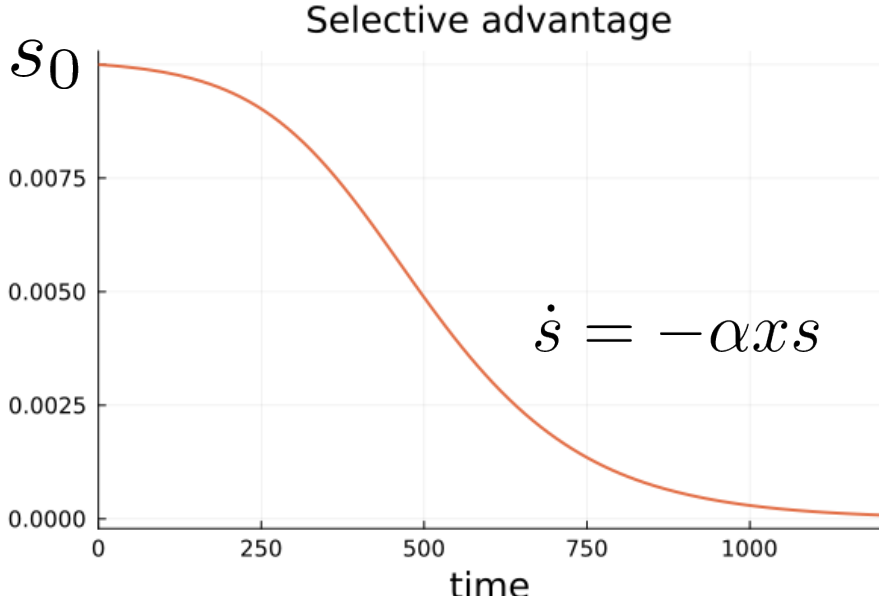
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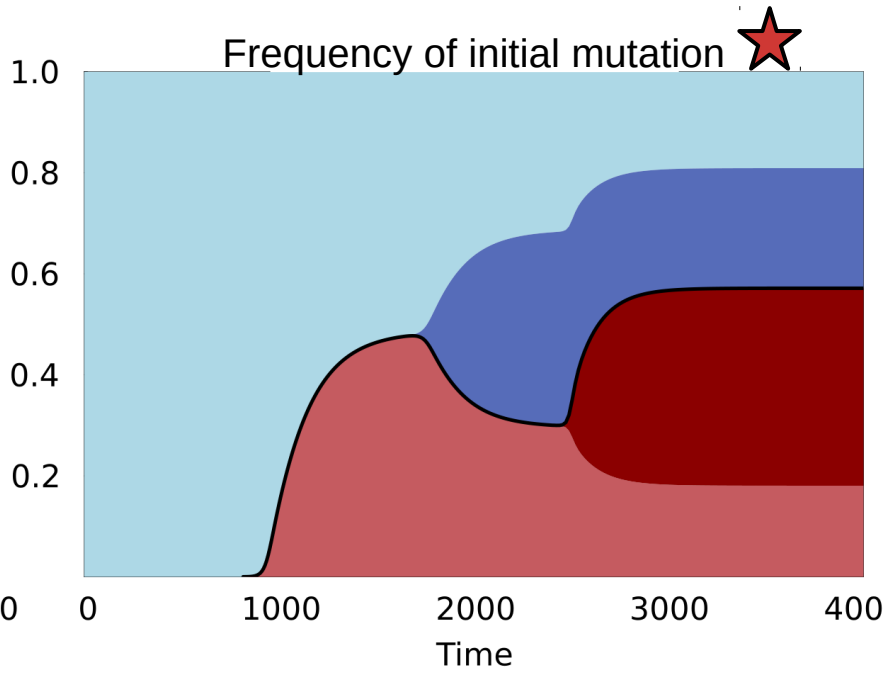
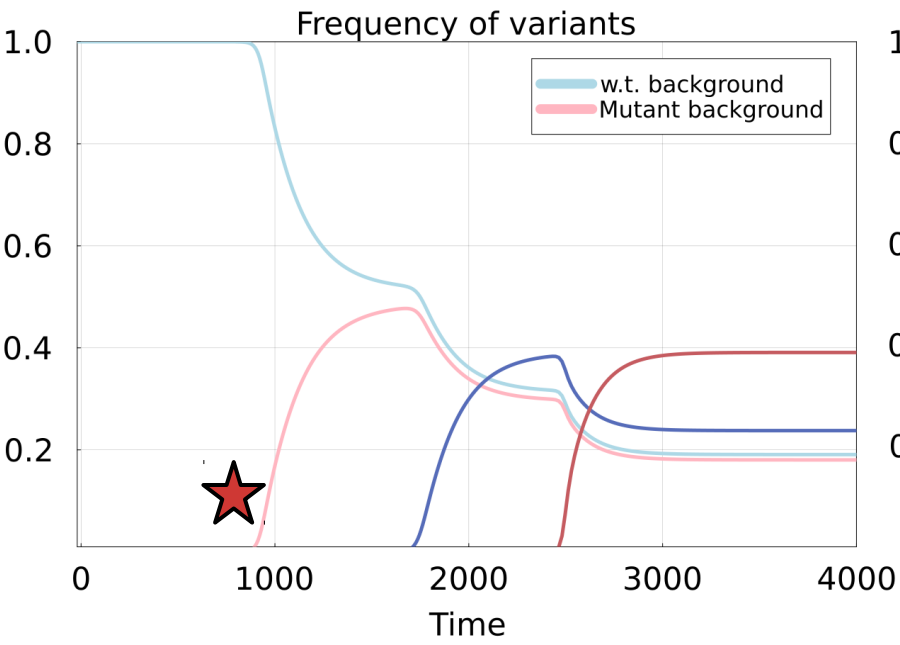
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More detailed model: multi-strain susceptible/infected (SIR) with cross-immunity

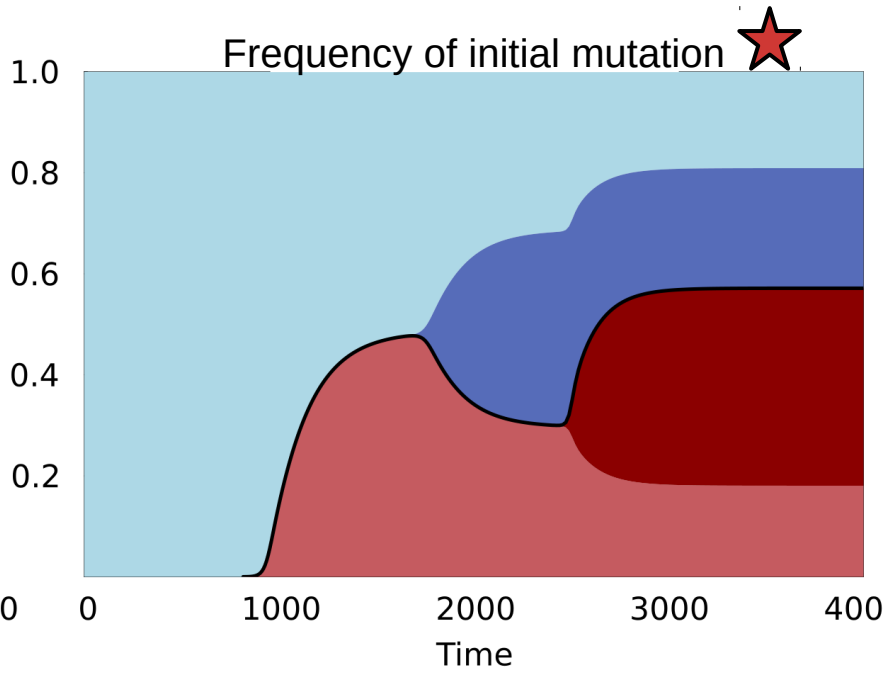
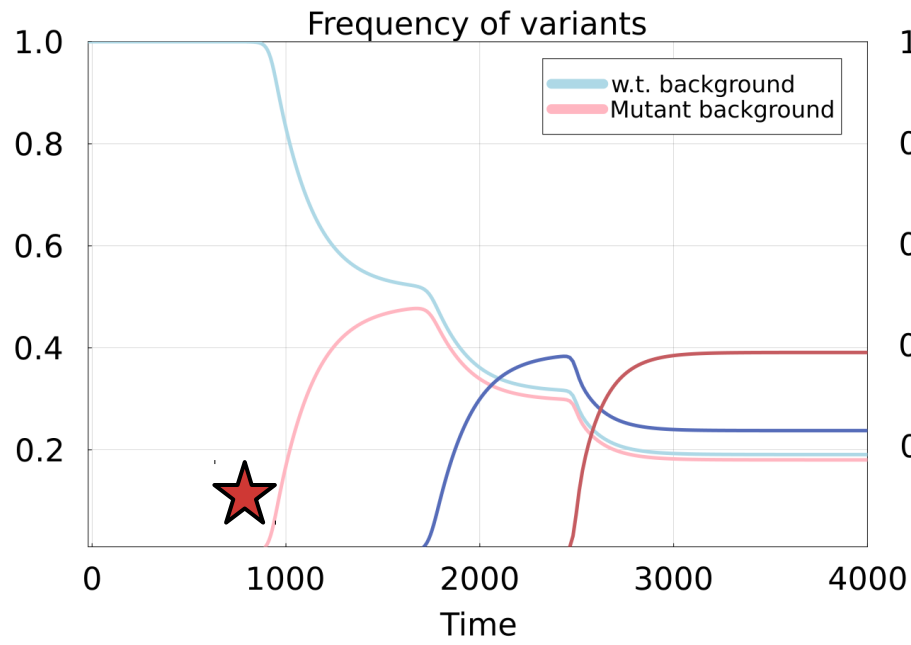
# Evolution with partial sweeps

New variants appear at rate  $\rho$



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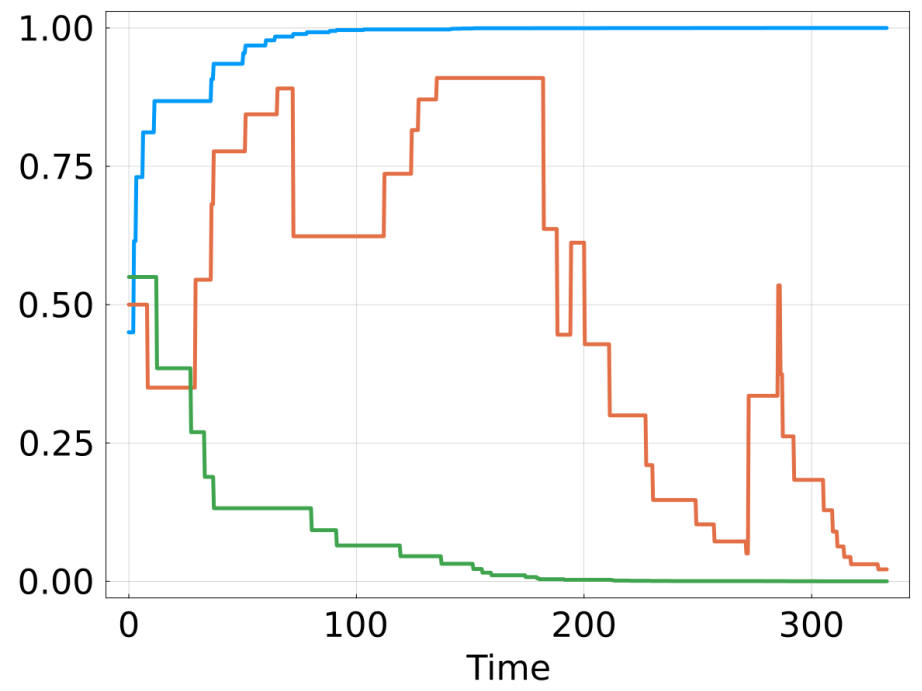
Limit case: non overlapping partial sweeps

$$x_{t+1} = x_t + \begin{cases} \beta(1 - x_t) & \text{with prob. } x_t, \\ -\beta x_t & \text{with prob. } 1 - x_t, \end{cases}$$

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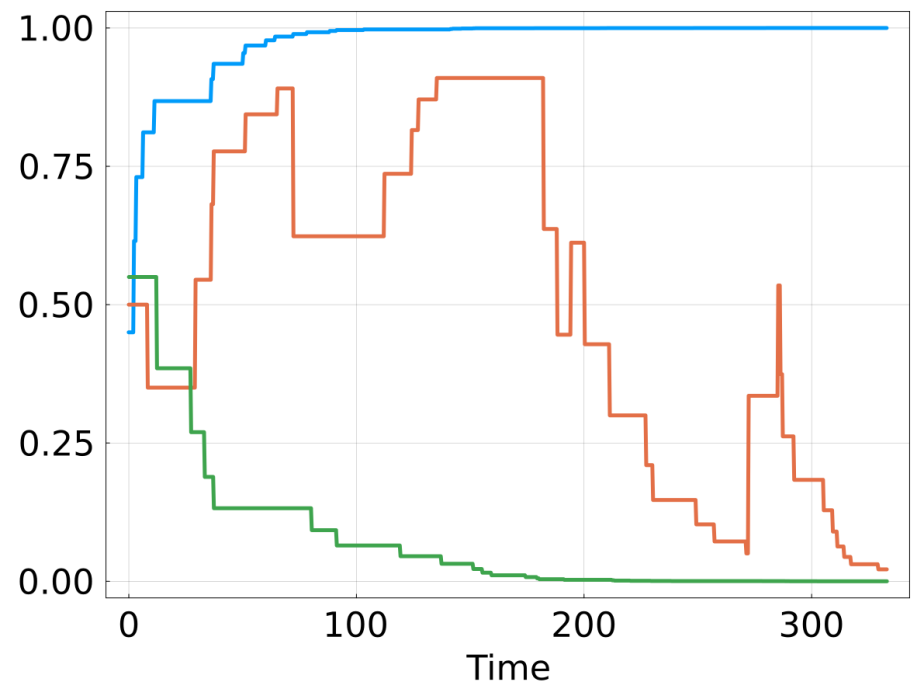
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## Timescales

$$\langle \Delta x^2 \rangle = \rho \langle \beta^2 \rangle x(1 - x)$$

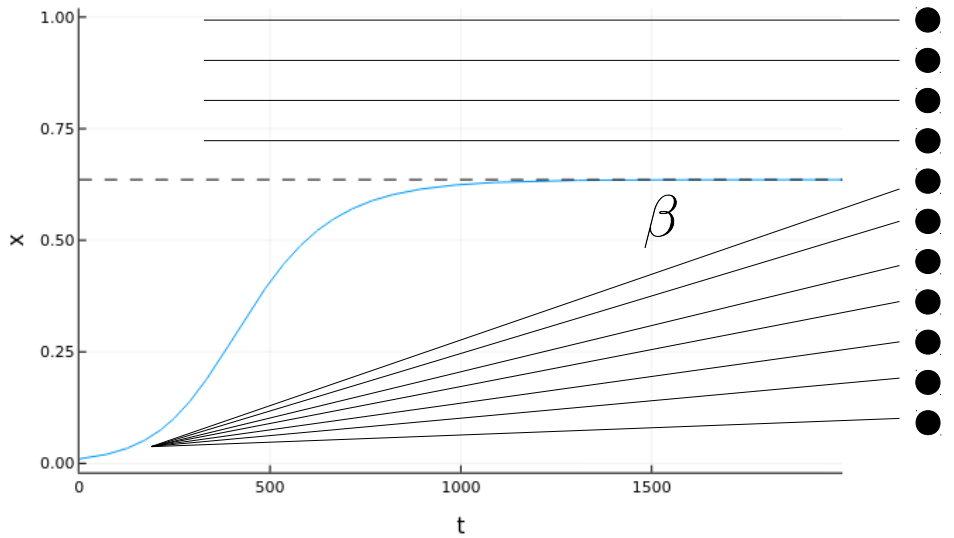
timescale  $T^{-1} \sim \rho \langle \beta^2 \rangle$

$\rho^{-1} \sim 15$  (~4 partial sweeps/year)

$\beta \sim 0.3 \rightarrow T \sim 150 \sim 3y$

H3N2 influenza  $\rightarrow T_{MRC A} \sim 6y$

# Shape of the phylogeny: multiple mergers

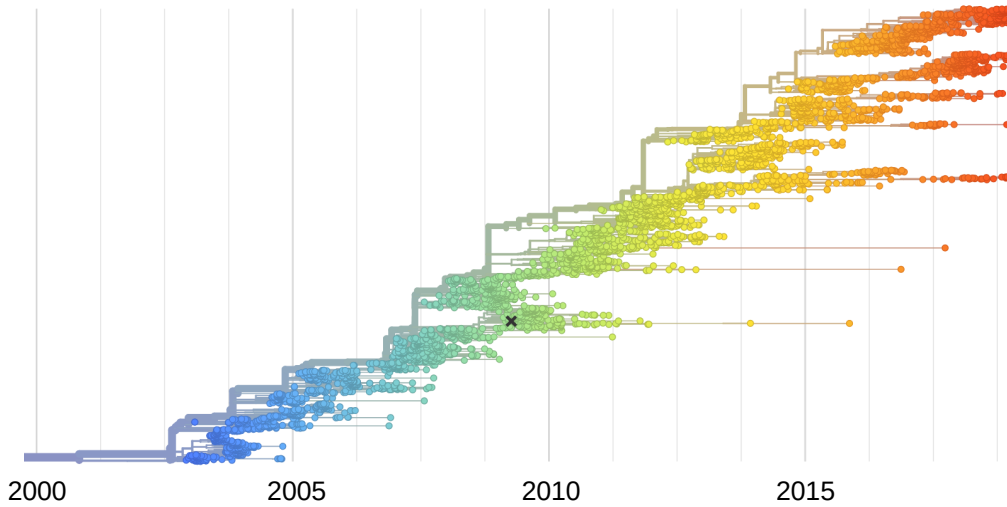


- Multiple mergers
- Ladder-like phylogenies

Rate of **k**-coalescence among **n** lineages

$$\Lambda_n(k) = \rho \binom{n}{k} \beta^k (1 - \beta)^{n-k}$$

Lambda coalescent





# Summary

H3N2Influenza:

- **Predictability** of evolution is surprisingly low
- Qualitatively different from models

## Partial sweeps

- **Adaptation** of host immunity
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