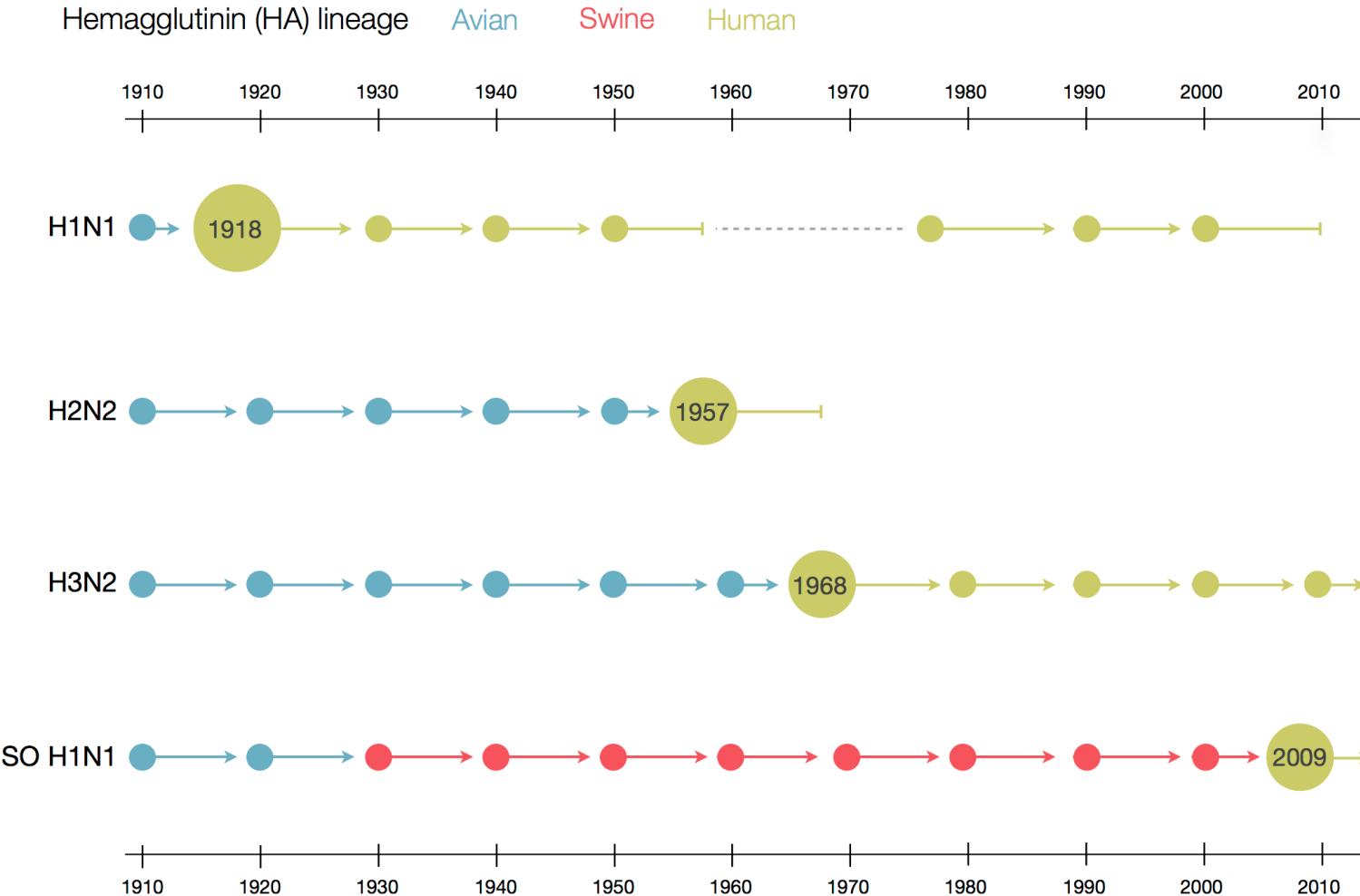


# References

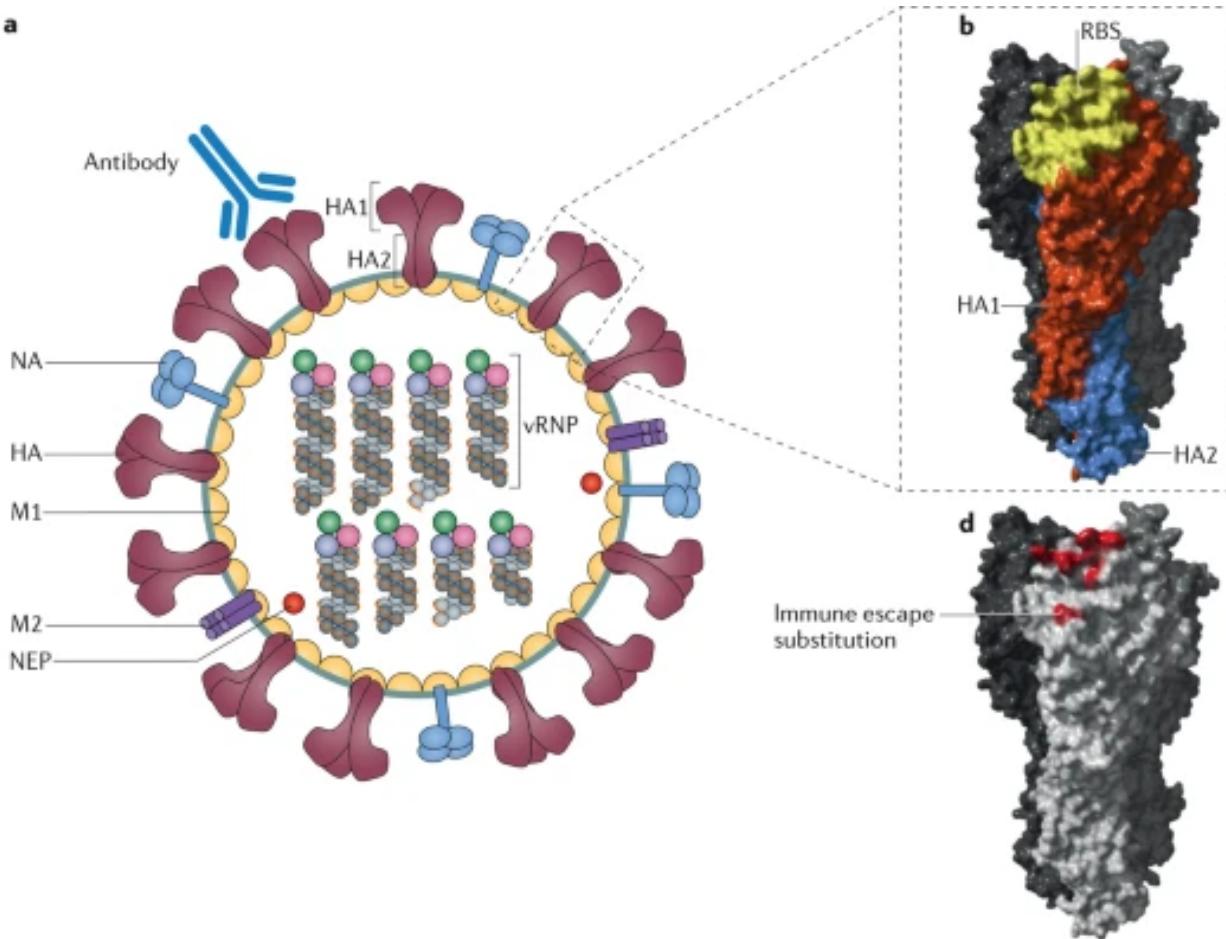
- *The evolution of seasonal influenza viruses*, **Petrova & Russel 2018**
- *Stochastic processes constrain the within and between host evolution of influenza virus*, **McCrone et. al. 2018**
- *Genealogies of rapidly adapting populations*, **Neher & Hallatschek 2013**
- *Predicting evolution from the shape of genealogical trees*, **Neher et. al. 2014**
- *Genetic draft, selective interference, and population genetics of rapid adaptation*, **Neher 2018**
- *A predictive fitness model for influenza*, **Luksza & Laessig 2014**
- *Integrating genotypes and phenotypes improves long-term forecasts of seasonal influenza A/H3N2 evolution*, **Huddleston et. al. 2020**
- *Population immunity predicts evolutionary trajectories of SARS-CoV-2*, **Meijers et. al. 2023**

# Human influenza virus

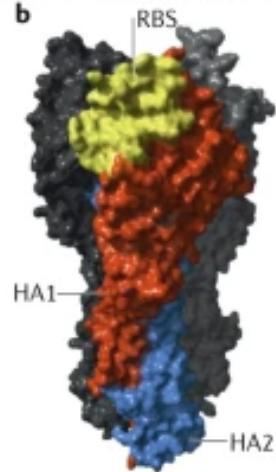


# Human influenza virus

a



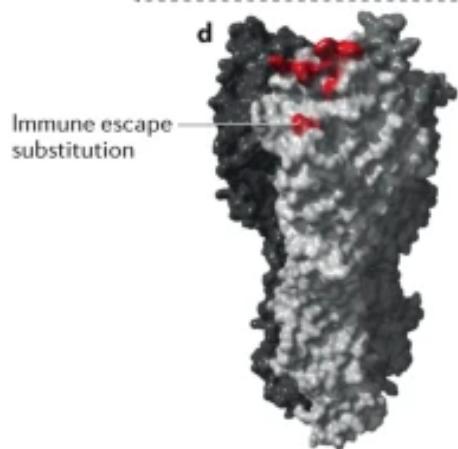
b



## Genome

- 10 – 15 kB
- 10 genes
- two surface proteins: HA, NA

d



# Human influenza virus

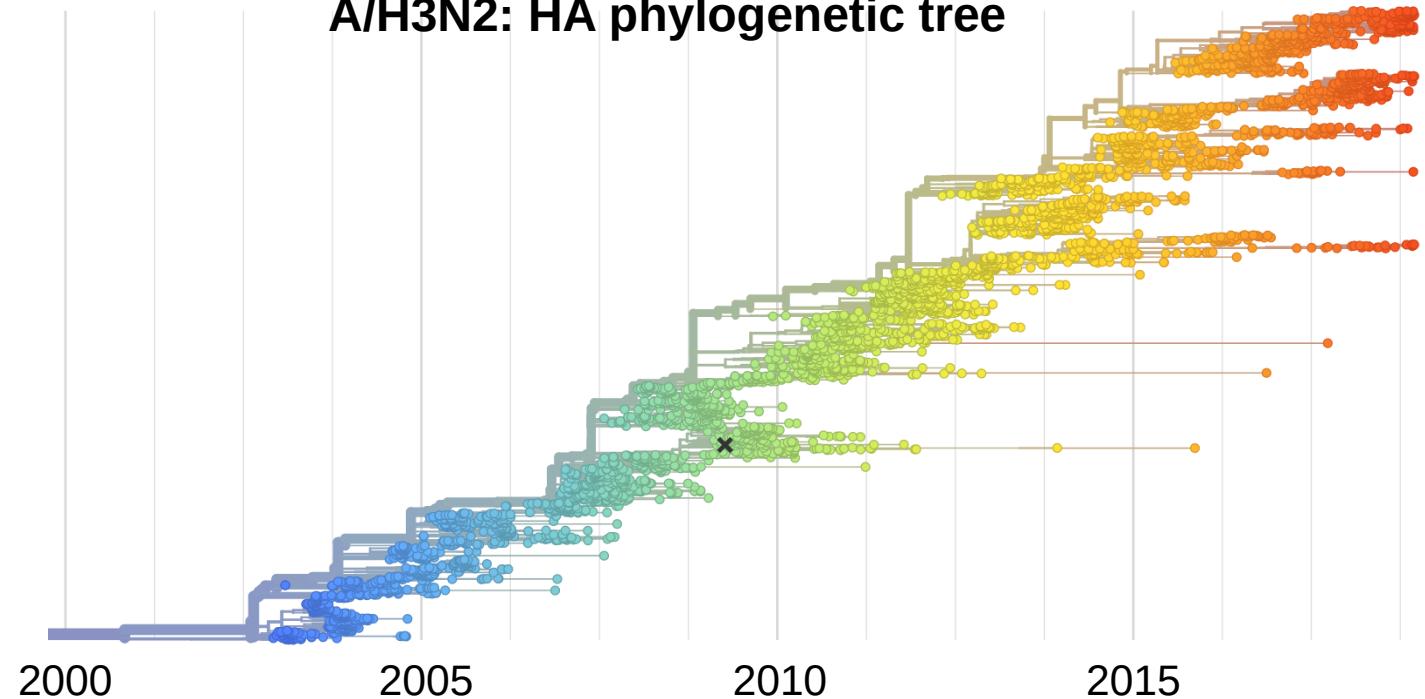
~ hundreds of million cases / year → 5-10 % of humans

In constant evolution (especially surface proteins HA & NA)

Generation time ~ 1 week

→ Pop. size ~  $10e6 - 10e7$

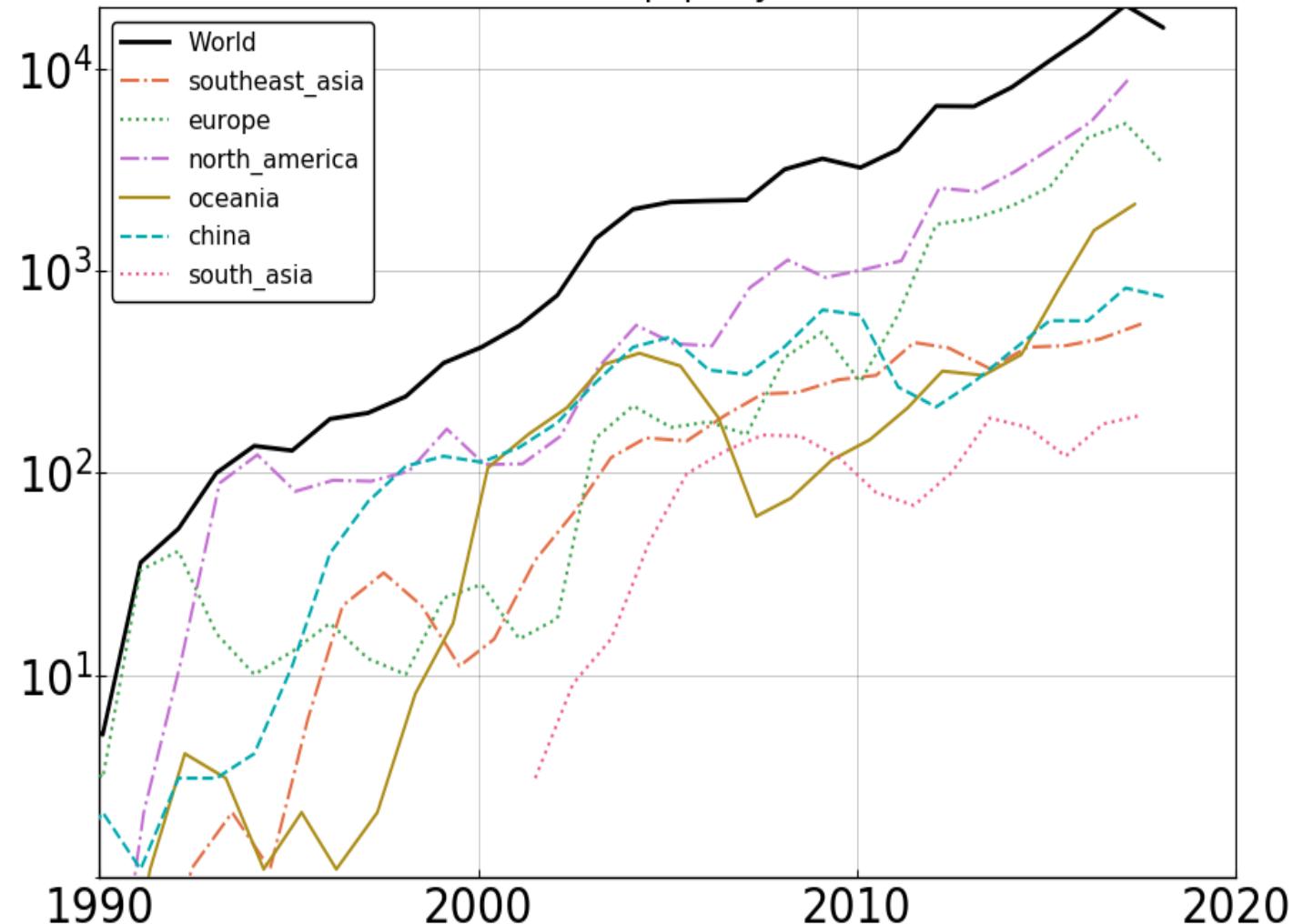
A/H3N2: HA phylogenetic tree



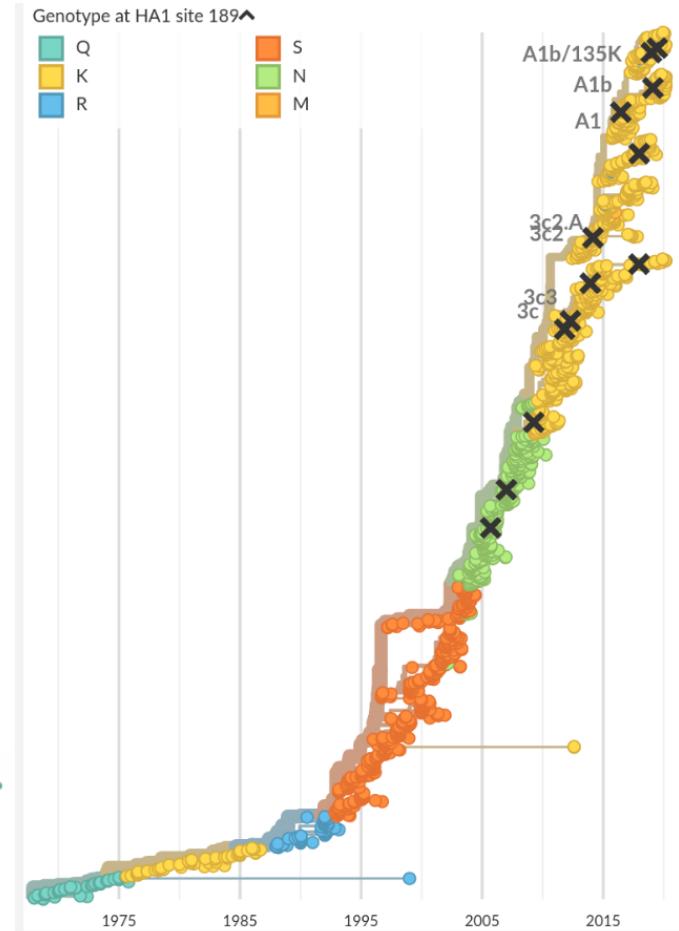
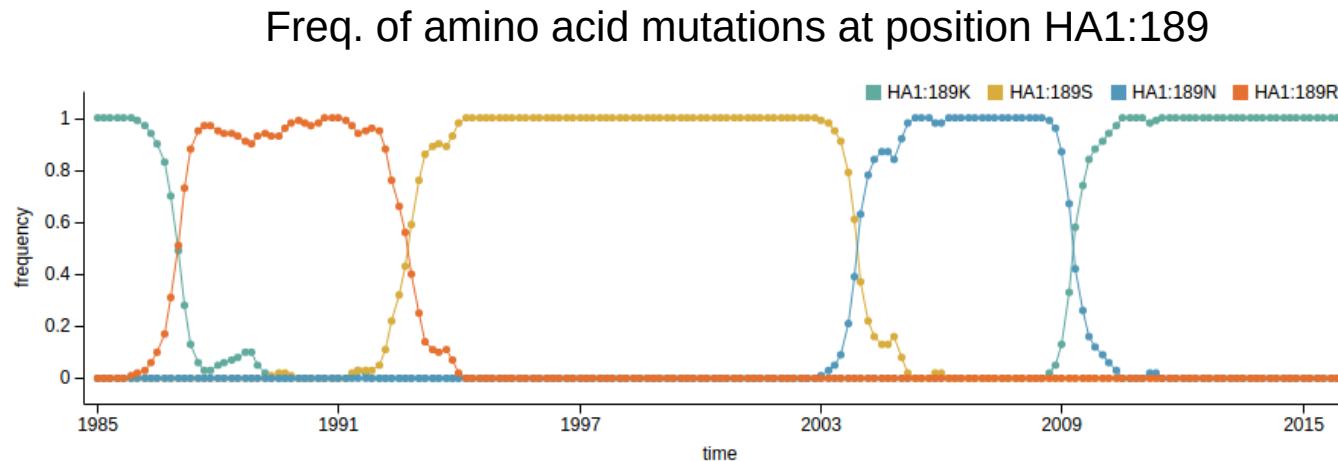
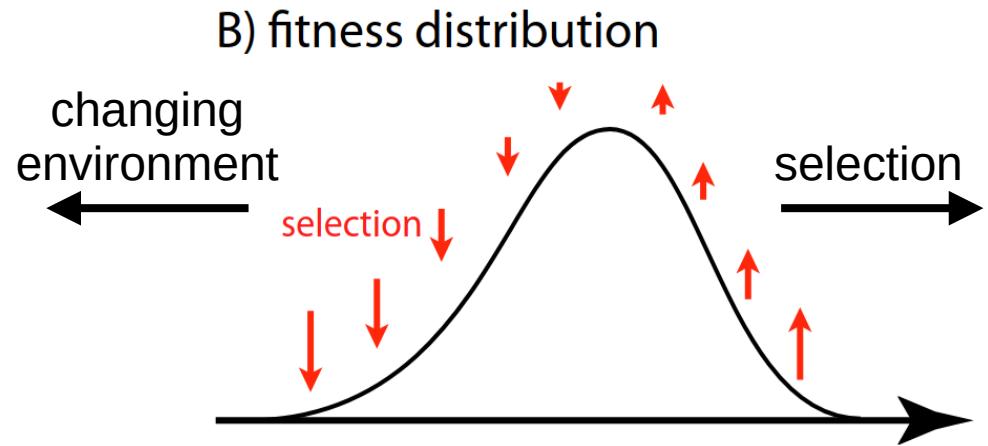
Variability in the present population

# Human influenza virus

# of seqs per year

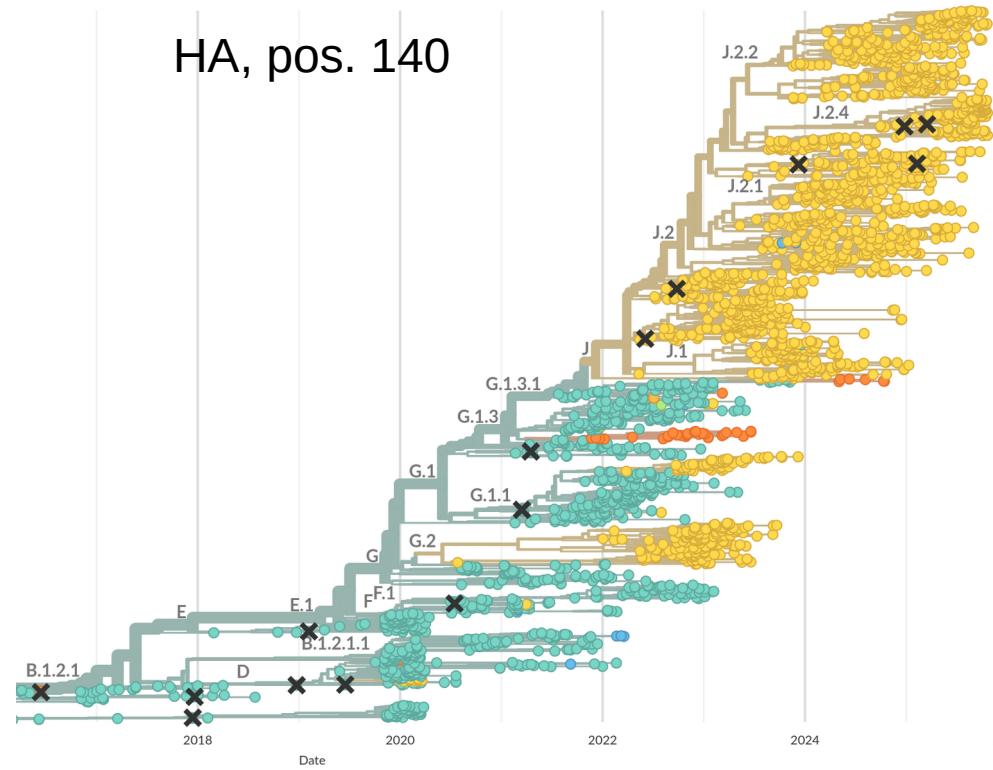


# Adaptative dynamics



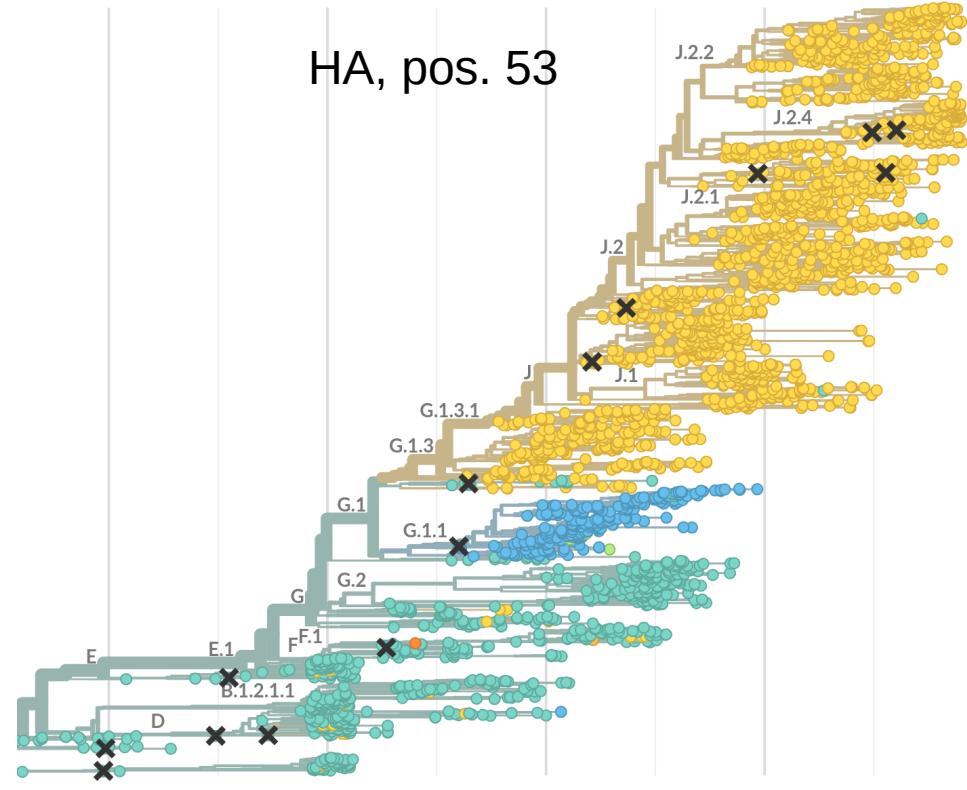
# Adaptation is not mutation limited

HA, pos. 140



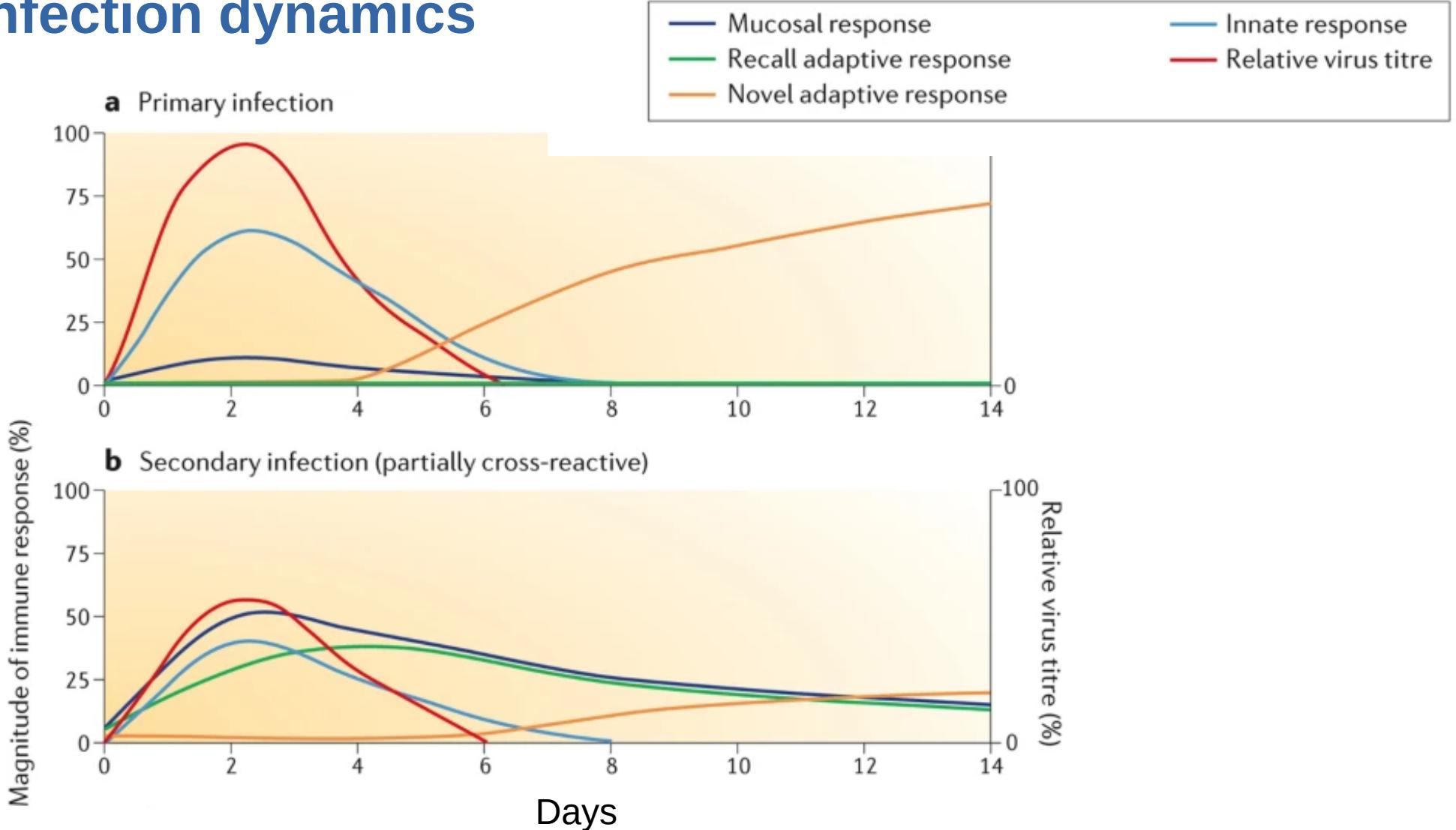
"Convergent" evolution

HA, pos. 53



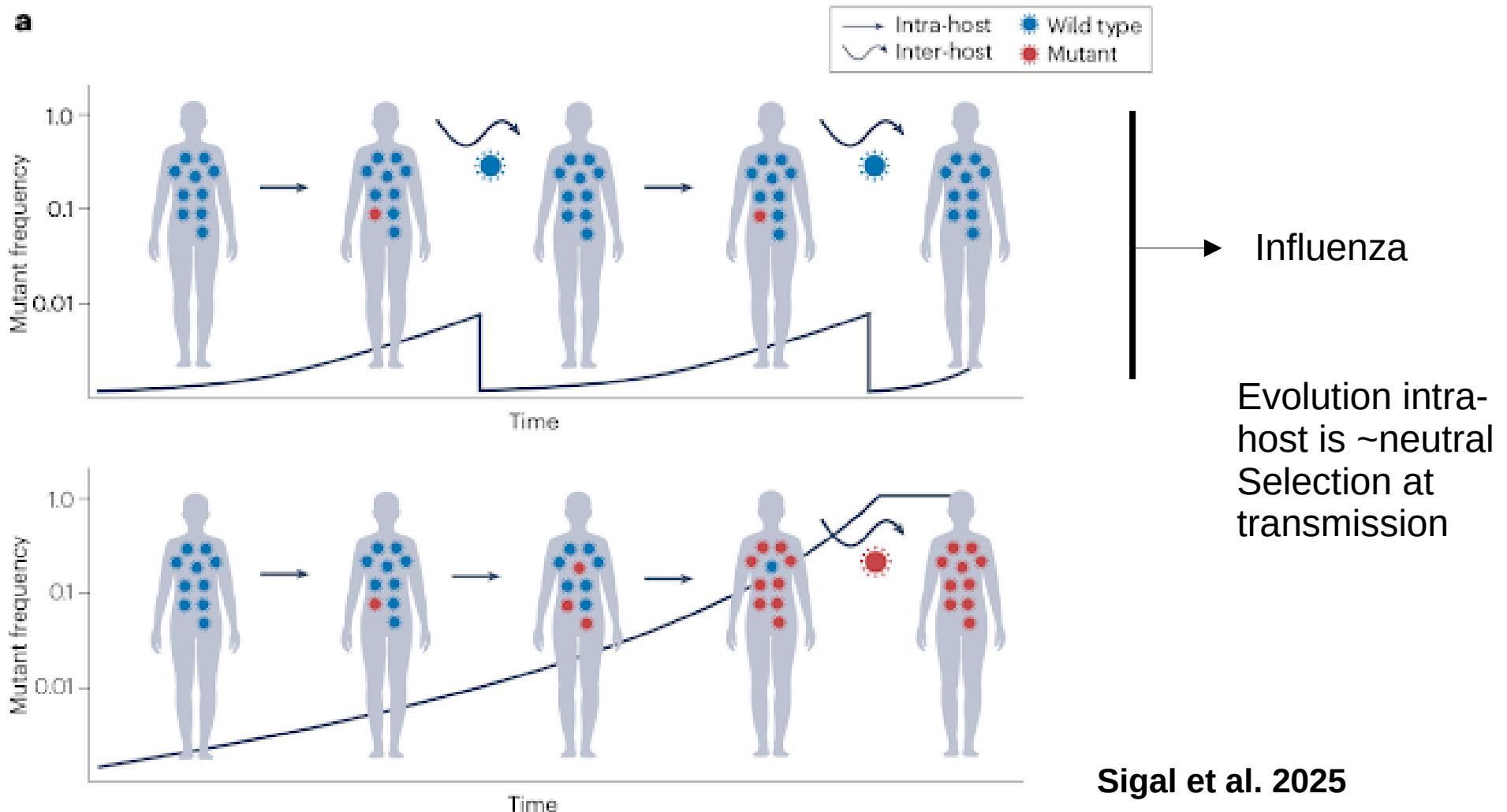
Competition between mutations

# Infection dynamics



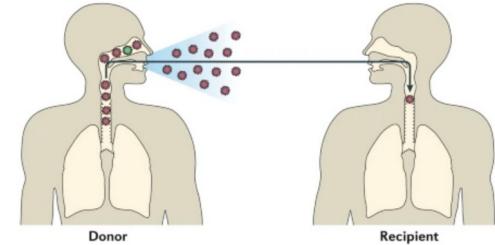
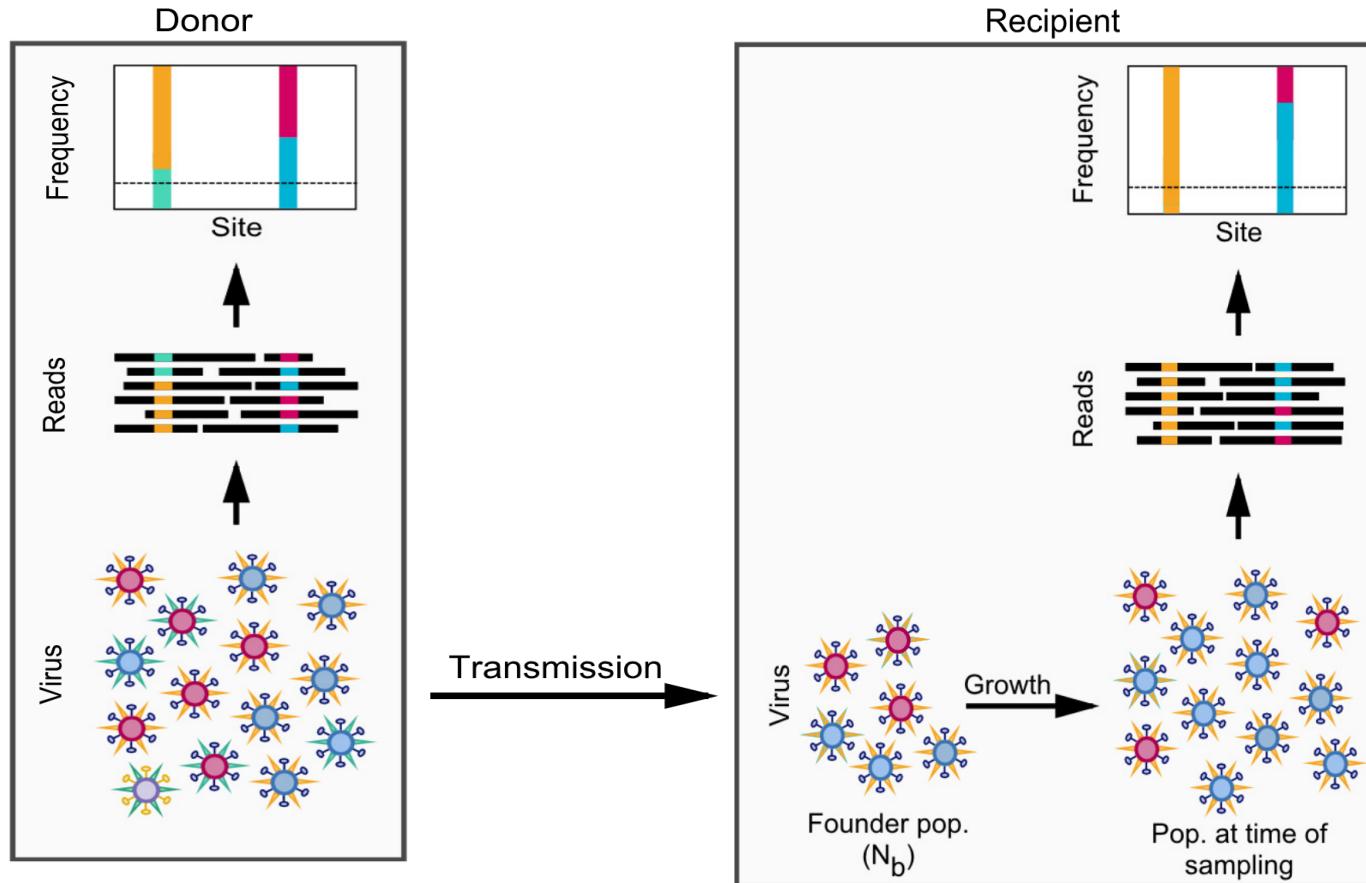
# Long vs short term infections

a



Sigal et al. 2025

# Bottleneck size



Donor      Recipient

→ Probability?

Leonard et al. 2017

# Bottleneck size

McCrone et al. 2018

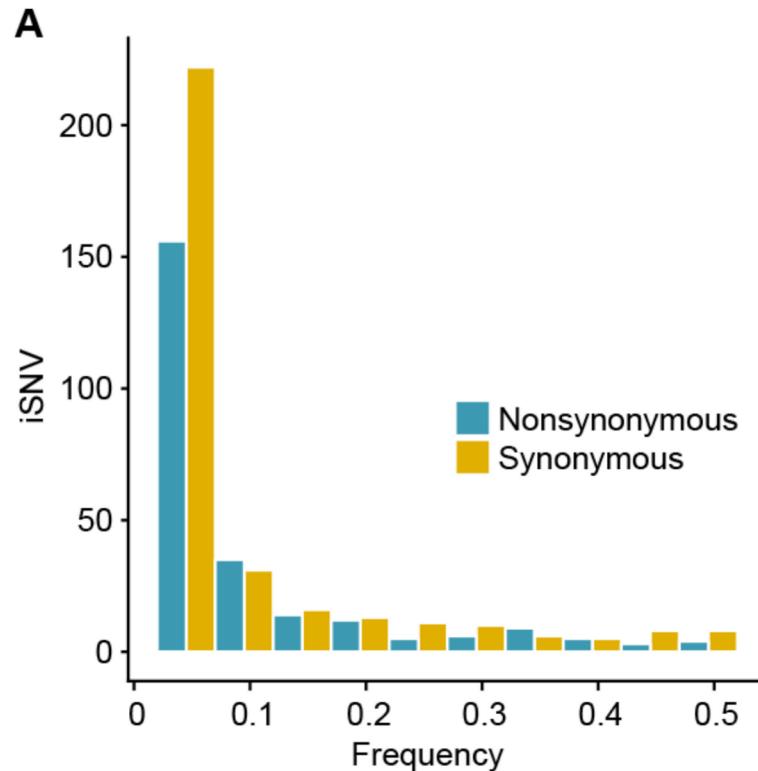
	2010–2011	2011–2012	2012–2013	2013–2014	2014–2015
Households	328	213	321	232	340
Participants	1441	943	1426	1049	1431
Vaccinated, n (%)*	934 (65)	554 (59)	942 (66)	722 (69)	992 (69)
IAV Positive Individuals <sup>†</sup>	86	23	69	48	166
H1N1	26	1	3	47	0
H3N2	58	22	66	1	166
IAV Positive Households <sup>‡</sup>					
Two individuals	13	2	9	7	23
Three individuals	5	2	3	3	11
Four individuals	-	-	1	2	4

43 donor-recipient pairs!

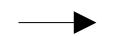
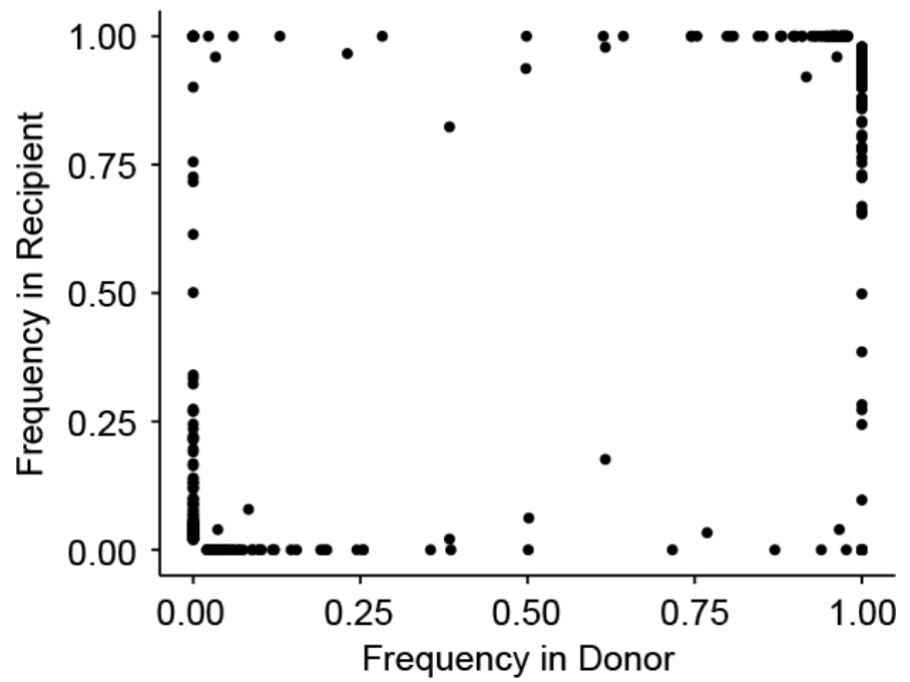
# Bottleneck size

McCrone et al. 2018

SNV frequency in individuals

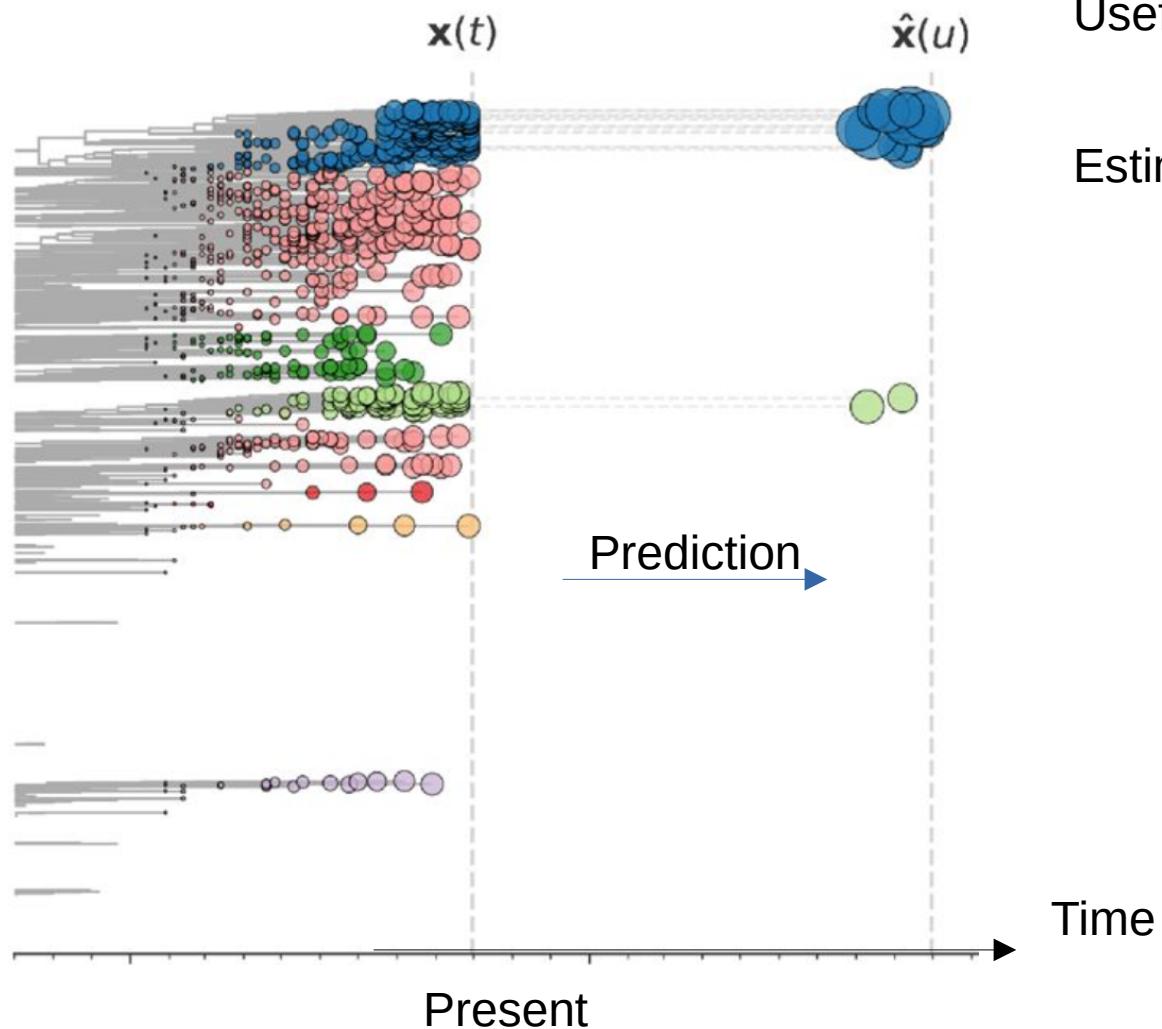


(Almost) no SNVs are **polymorphic** in **both** donor and recipient



Bottleneck size ~ 2

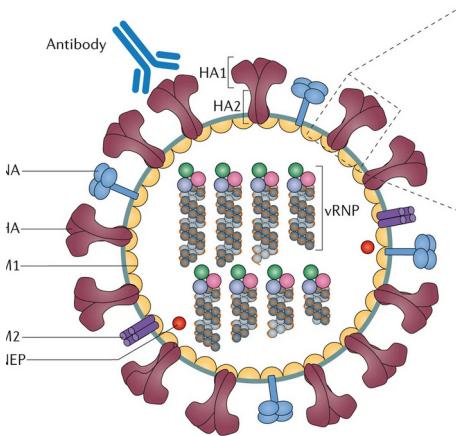
# Forecasting evolution?



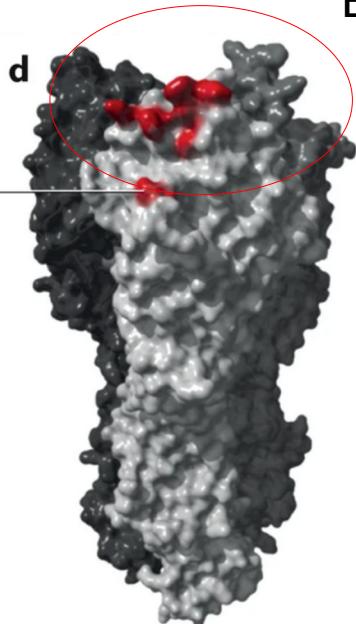
Useful for vaccine design

Estimating the fitness of strains?

# Fitness from antigenic change



Immune escape substitution



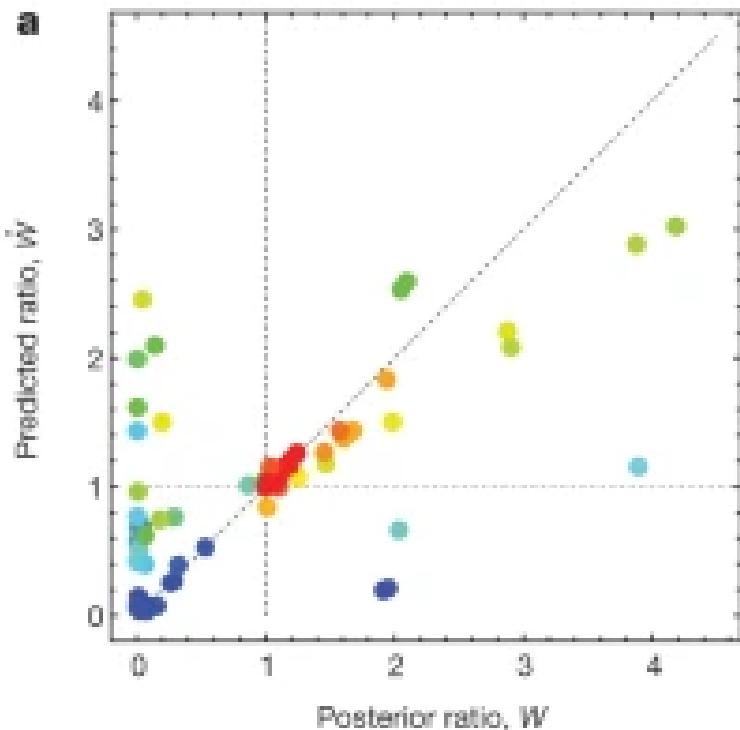
$$s_i = -\mathcal{L}_i - \sum_j x_j C_{ij}$$

Muts. outside epitope      Shared muts on epitope

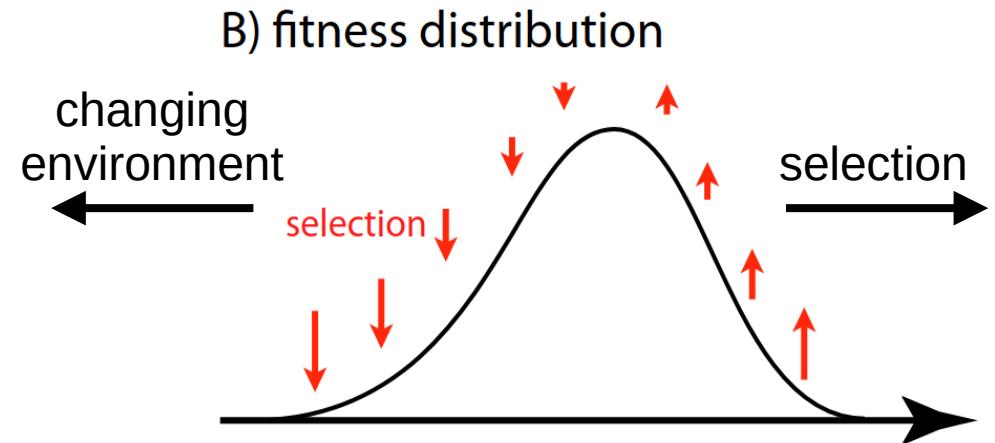
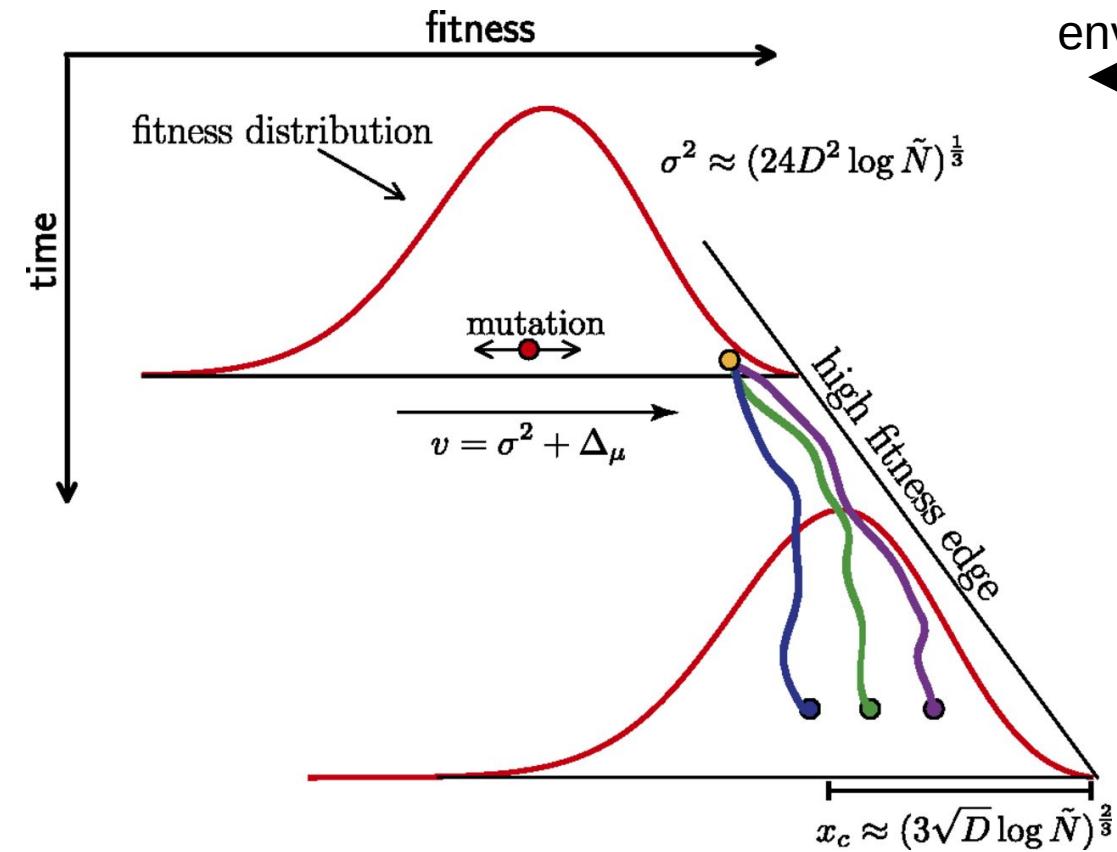
Epitope

## Hypotheses

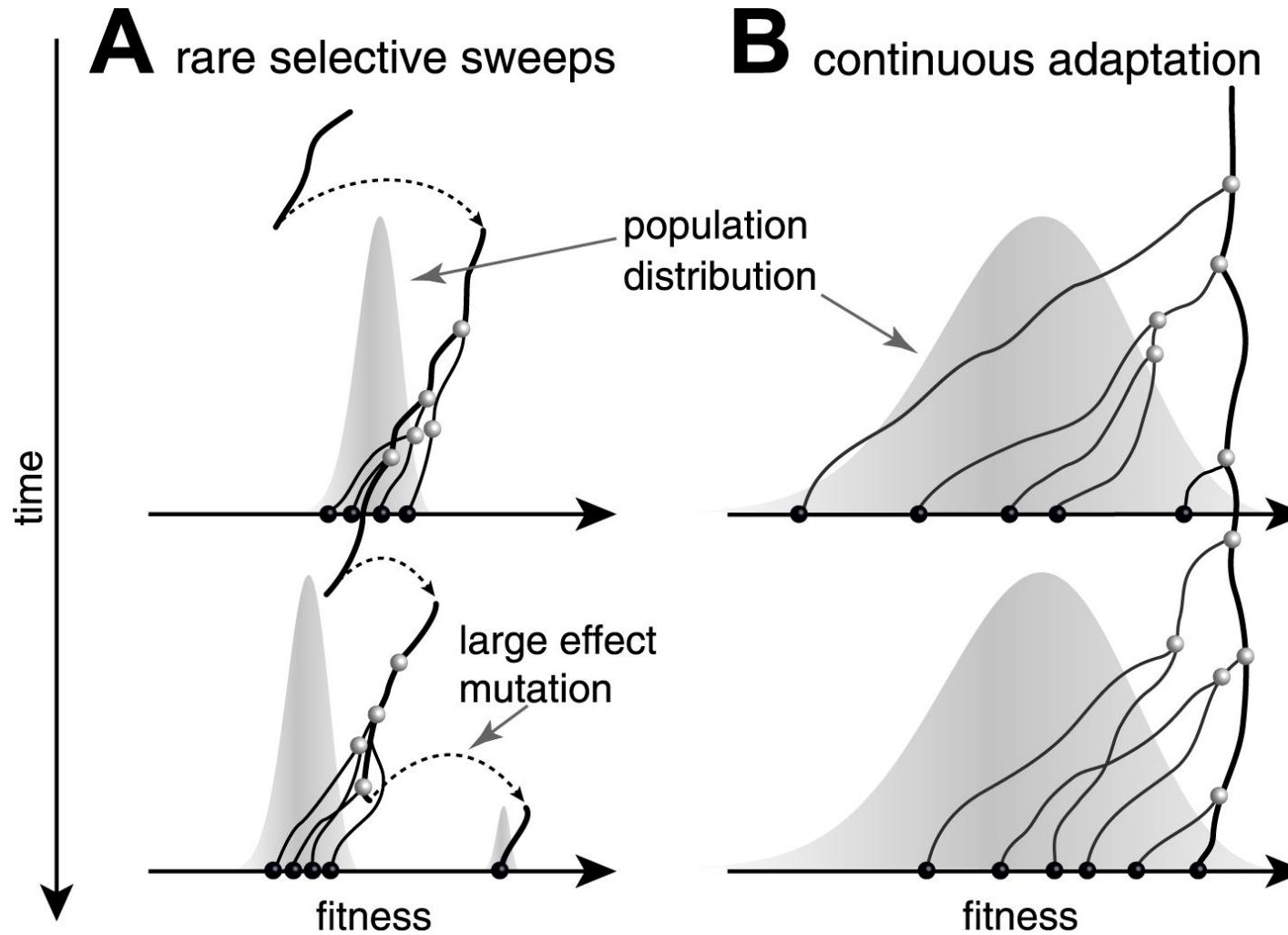
- Mutations outside of epitope are mostly deleterious
- Mutations on the epitope cause antigenic difference to other strains



# Rapid adaptation and genealogy

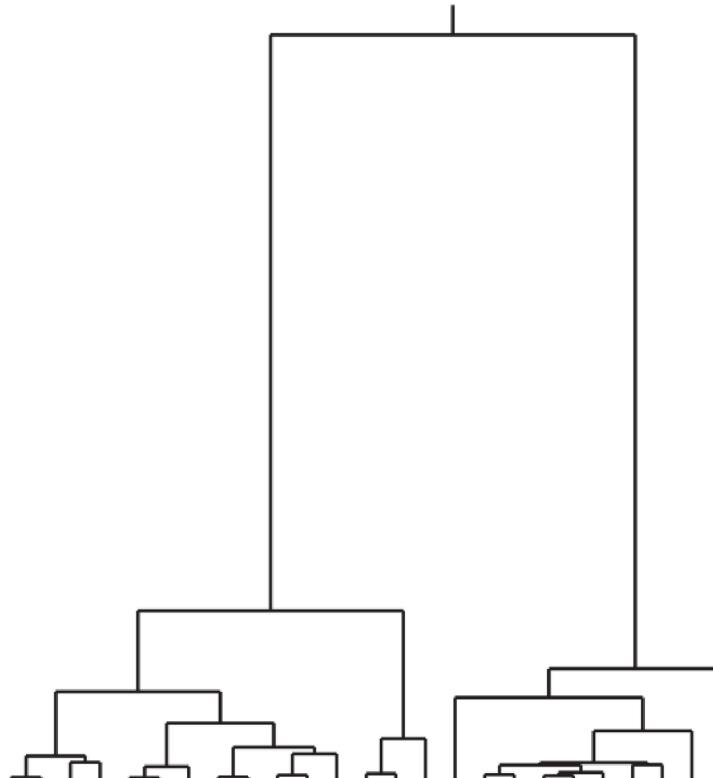


# Rapid adaptation and genealogy

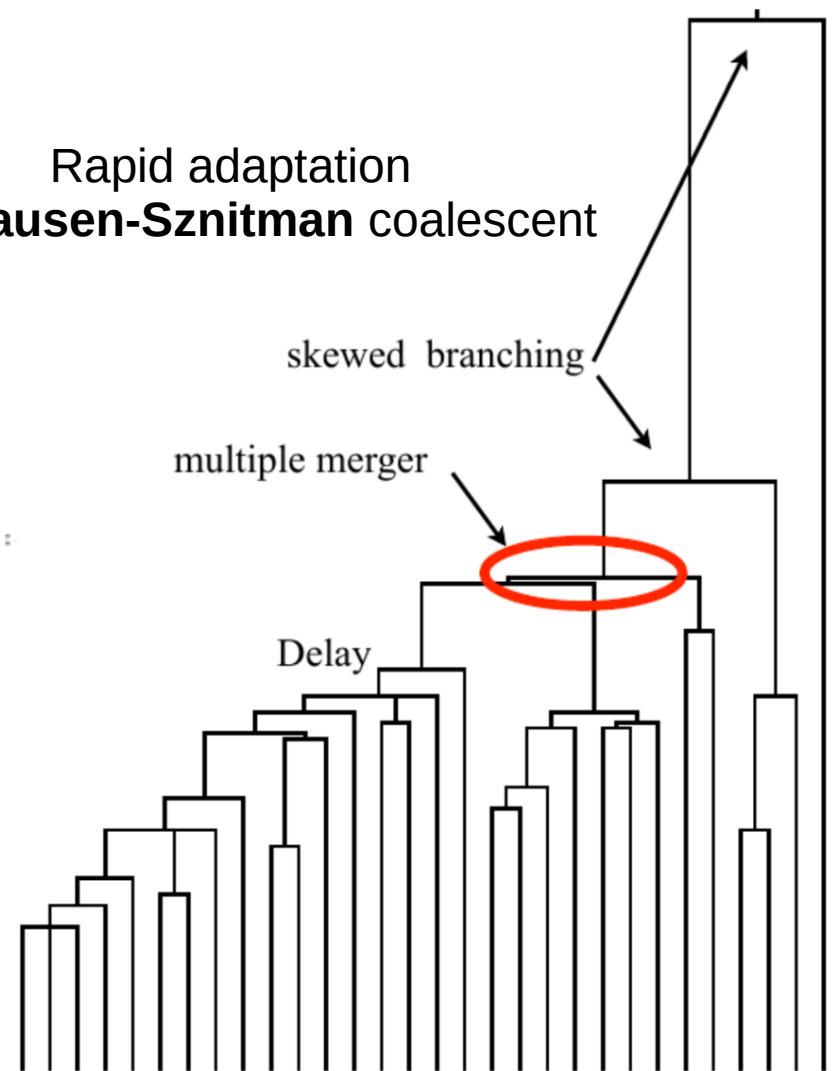


# Rapid adaptation and genealogy

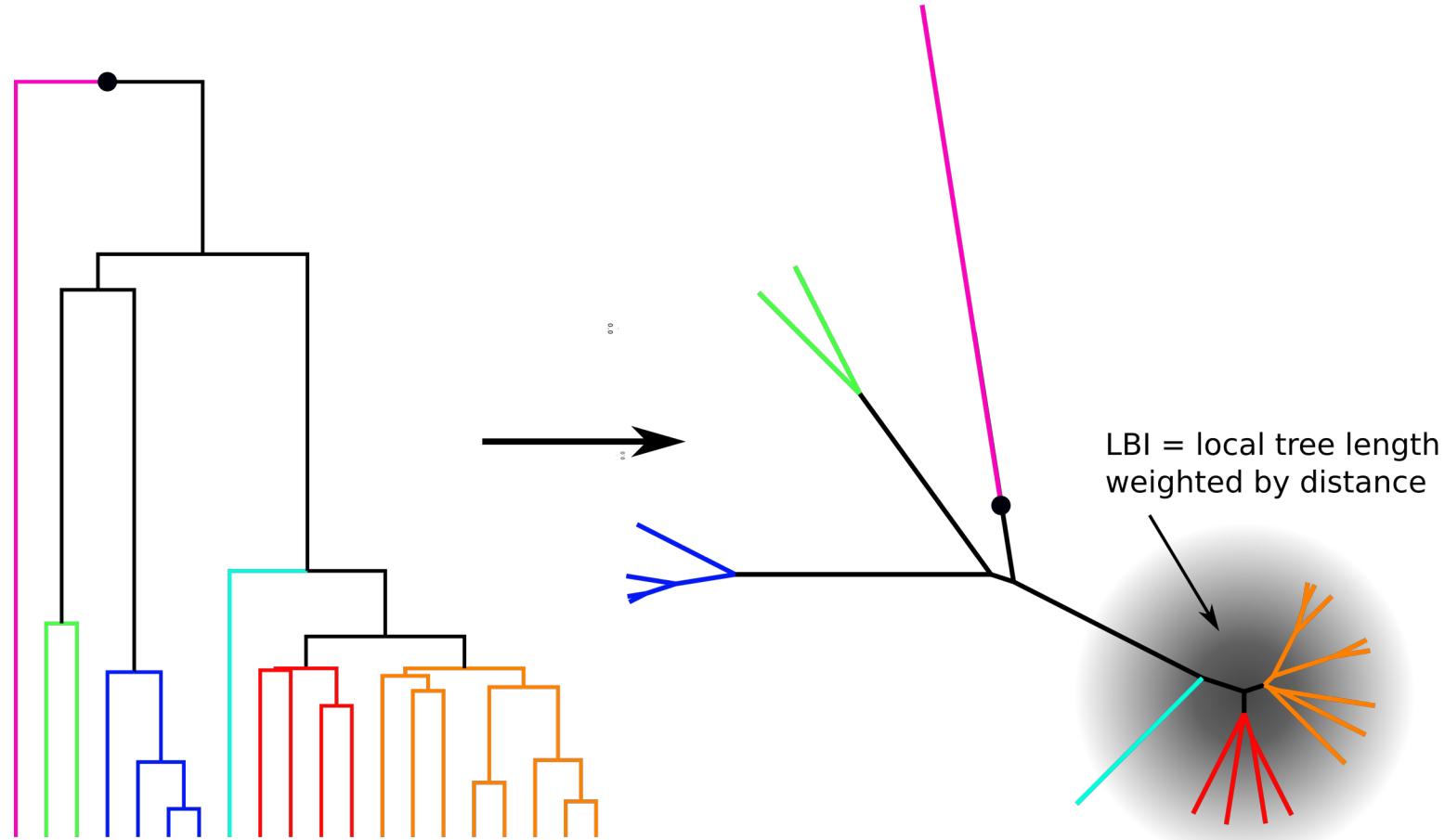
Kingman's coalescent  
Neutral evolution



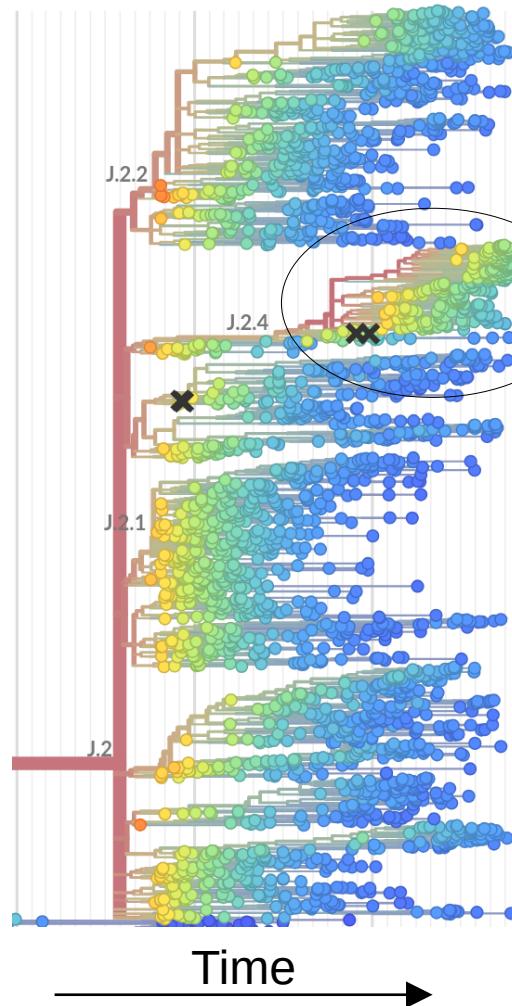
Rapid adaptation  
**Bolthausen-Sznitman coalescent**



# Predicting fitness from genealogical tree



# Estimating strain fitness from genealogical trees



Density of branching around each node in tree

Use “fittest” node to predict future pop

1: Random pick

— — — Best possible pick

