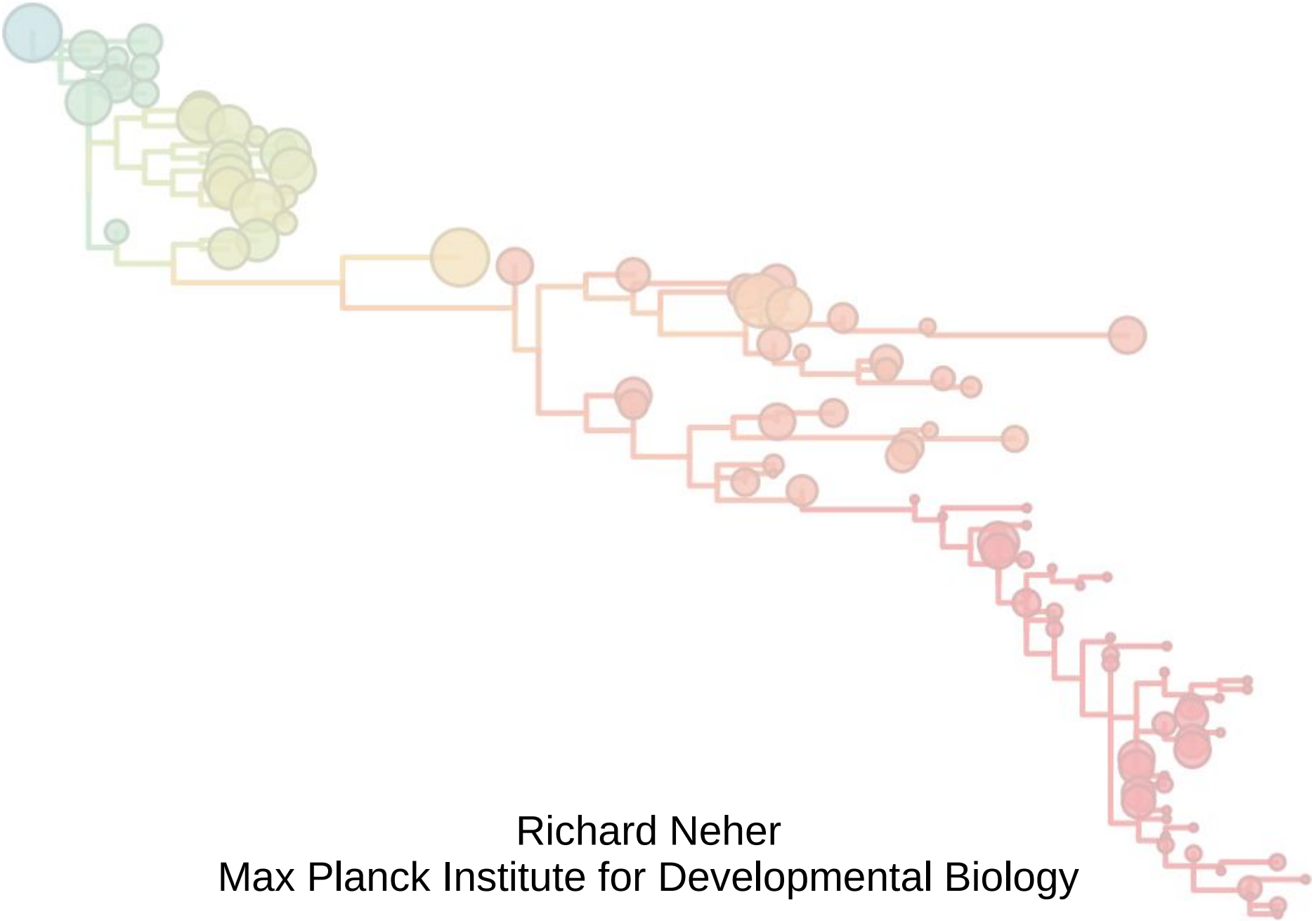
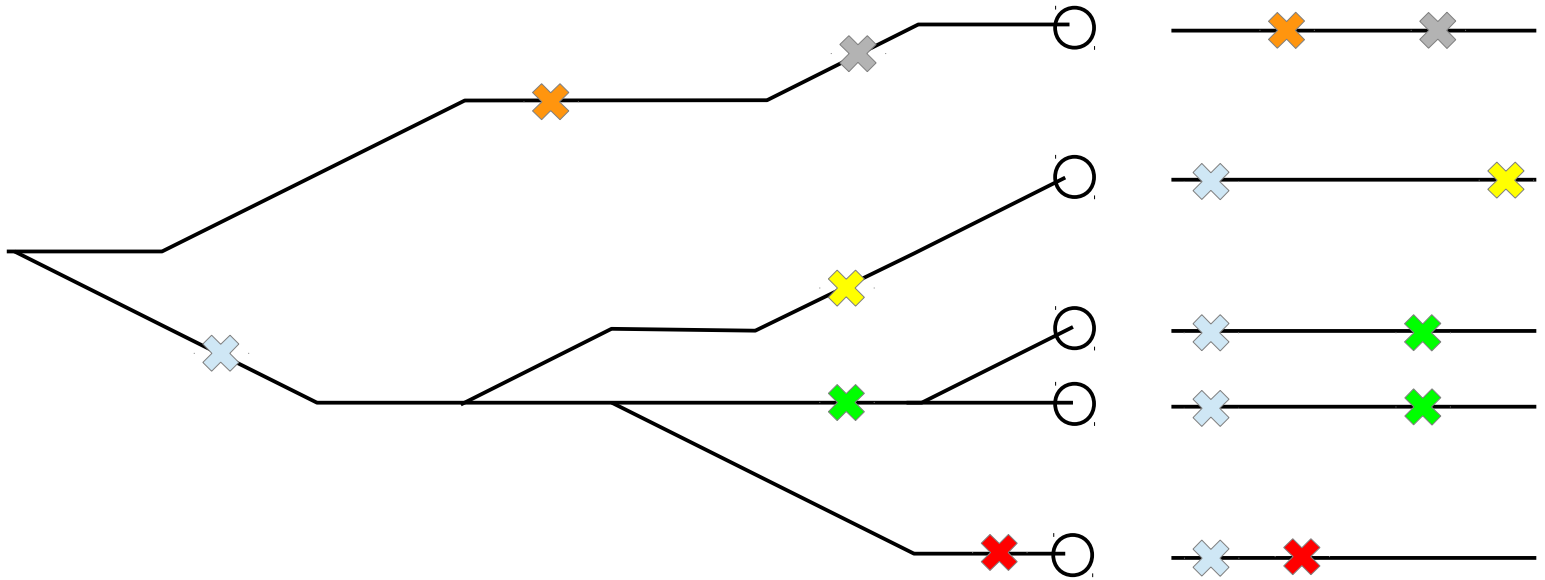
Quantifying and predicting the evolution of RNA viruses

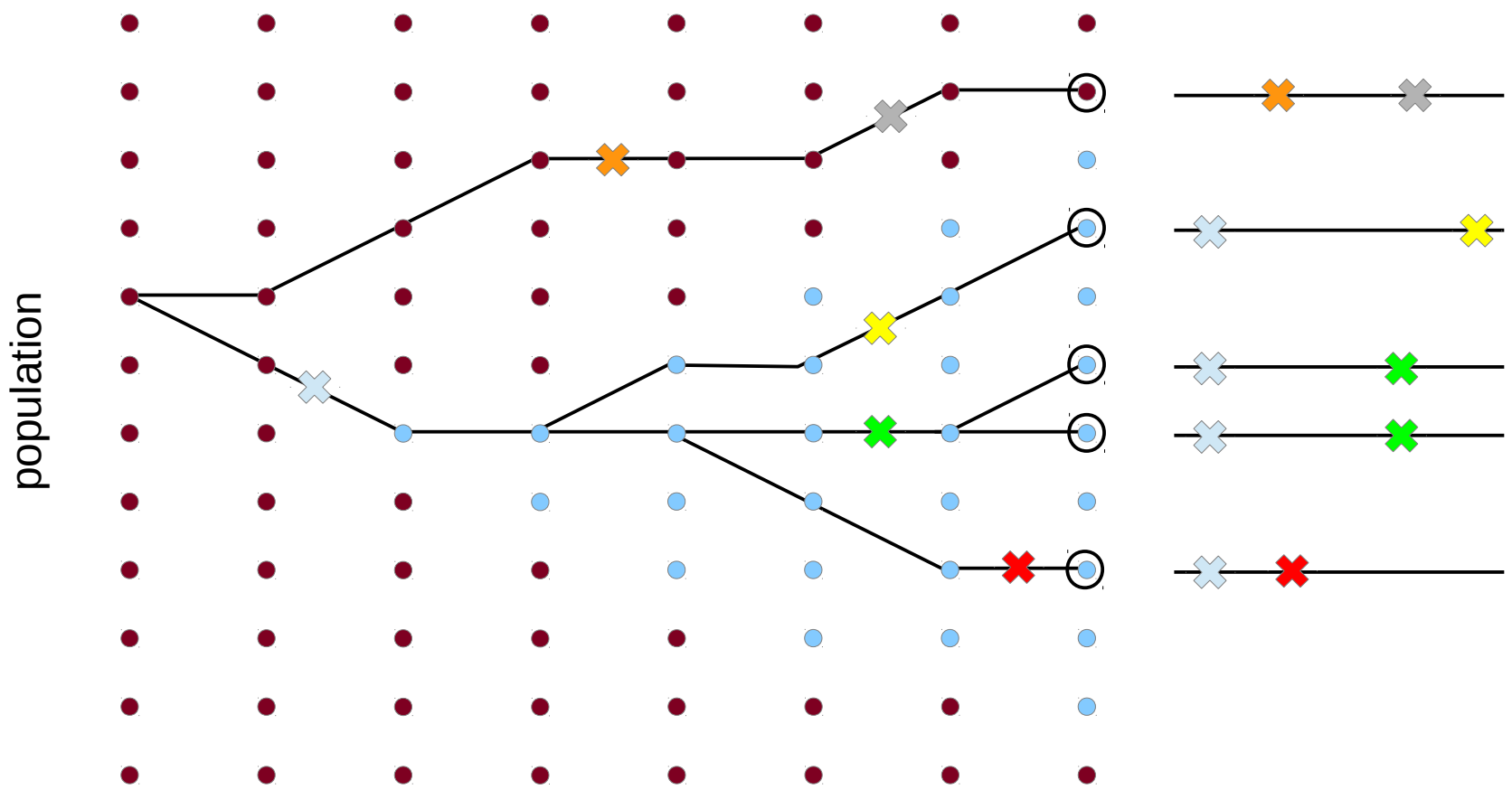


Richard Neher
Max Planck Institute for Developmental Biology

Slowly evolving populations



Slowly evolving populations



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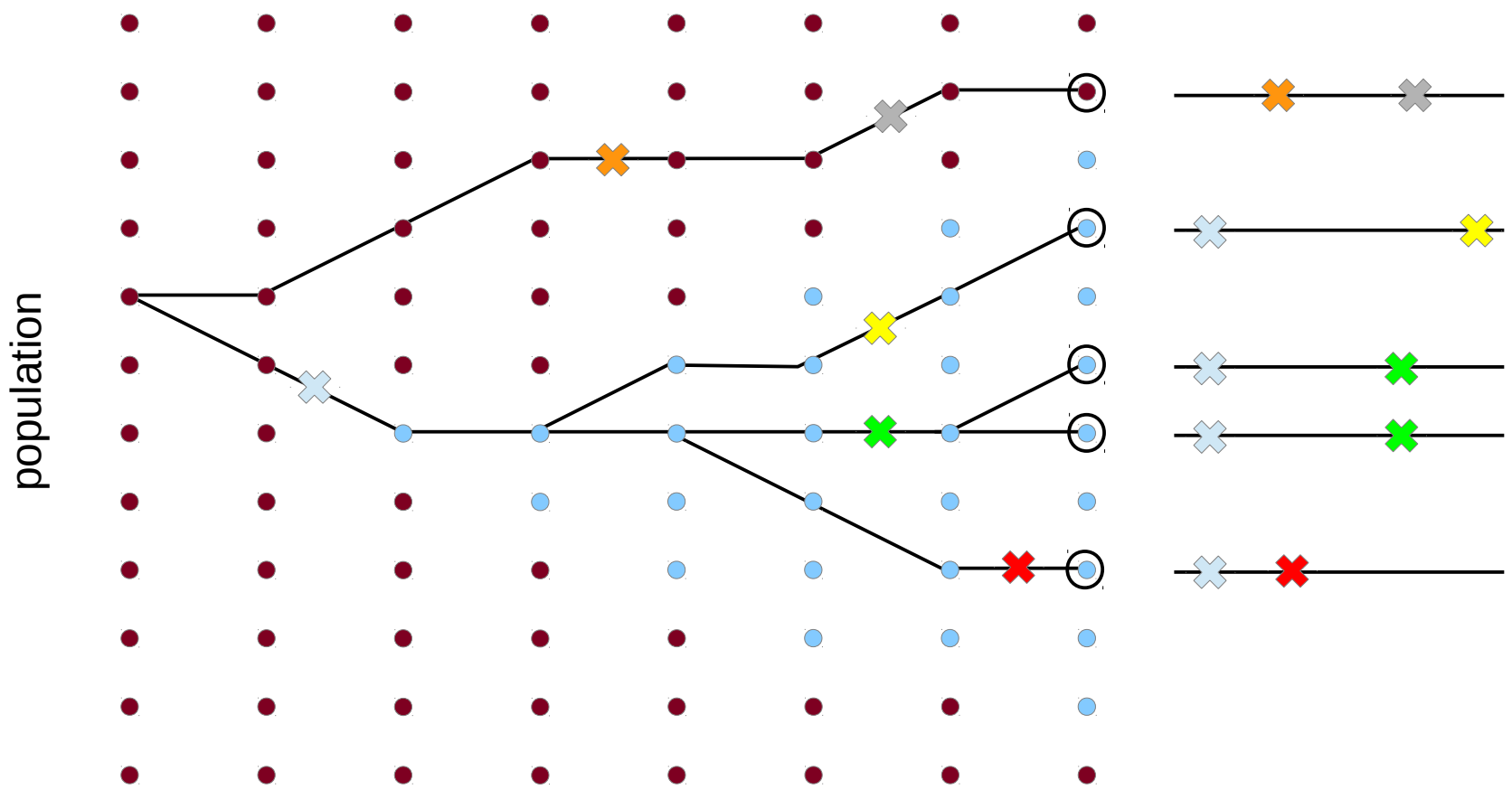
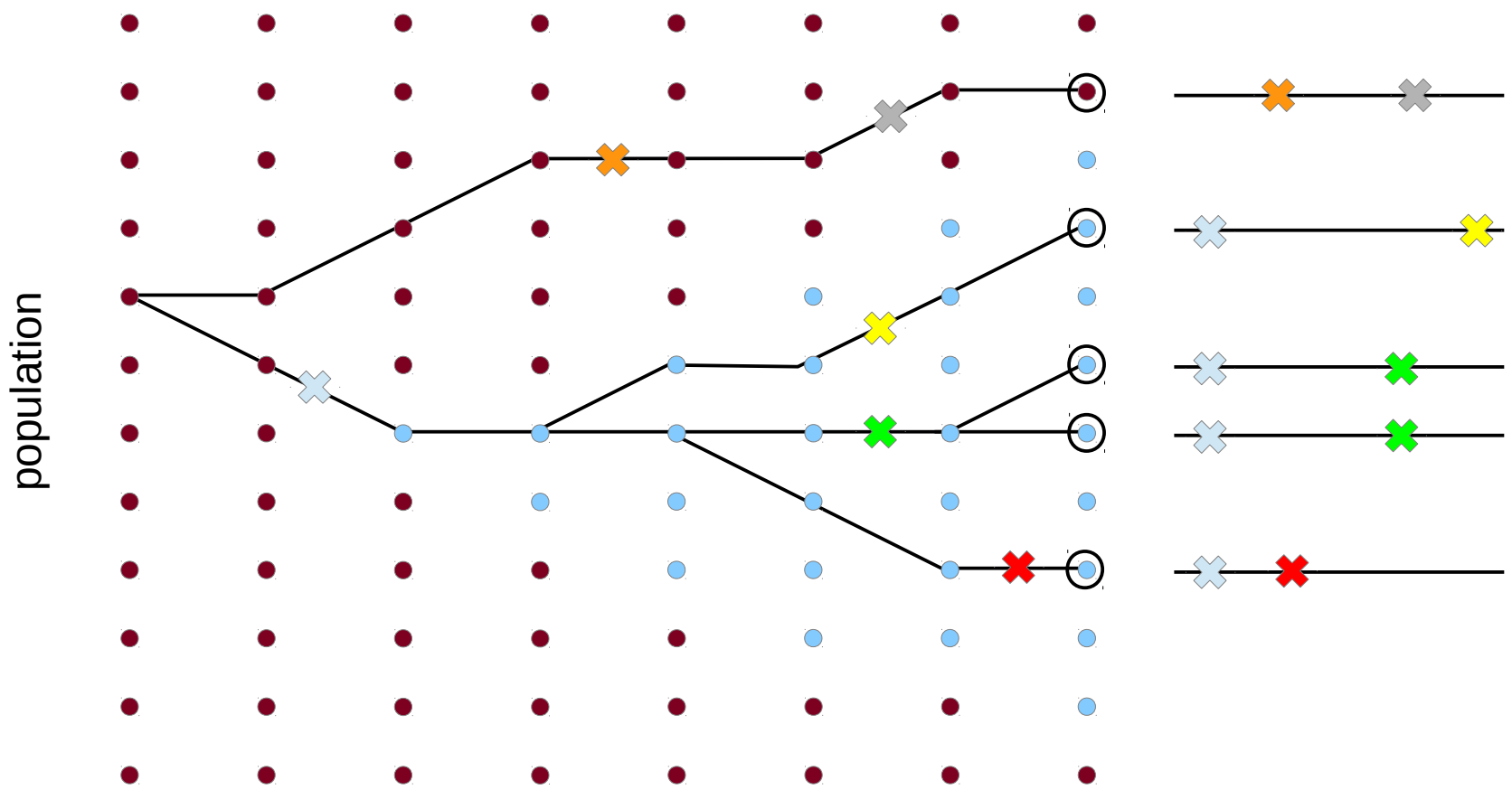


evolutionary processes ↔ statistics of trees ↔ patterns of genetic diversity

→ time resolved data allows direct observation

Slowly evolving populations



evolutionary processes ↔ statistics of trees ↔ patterns of genetic diversity

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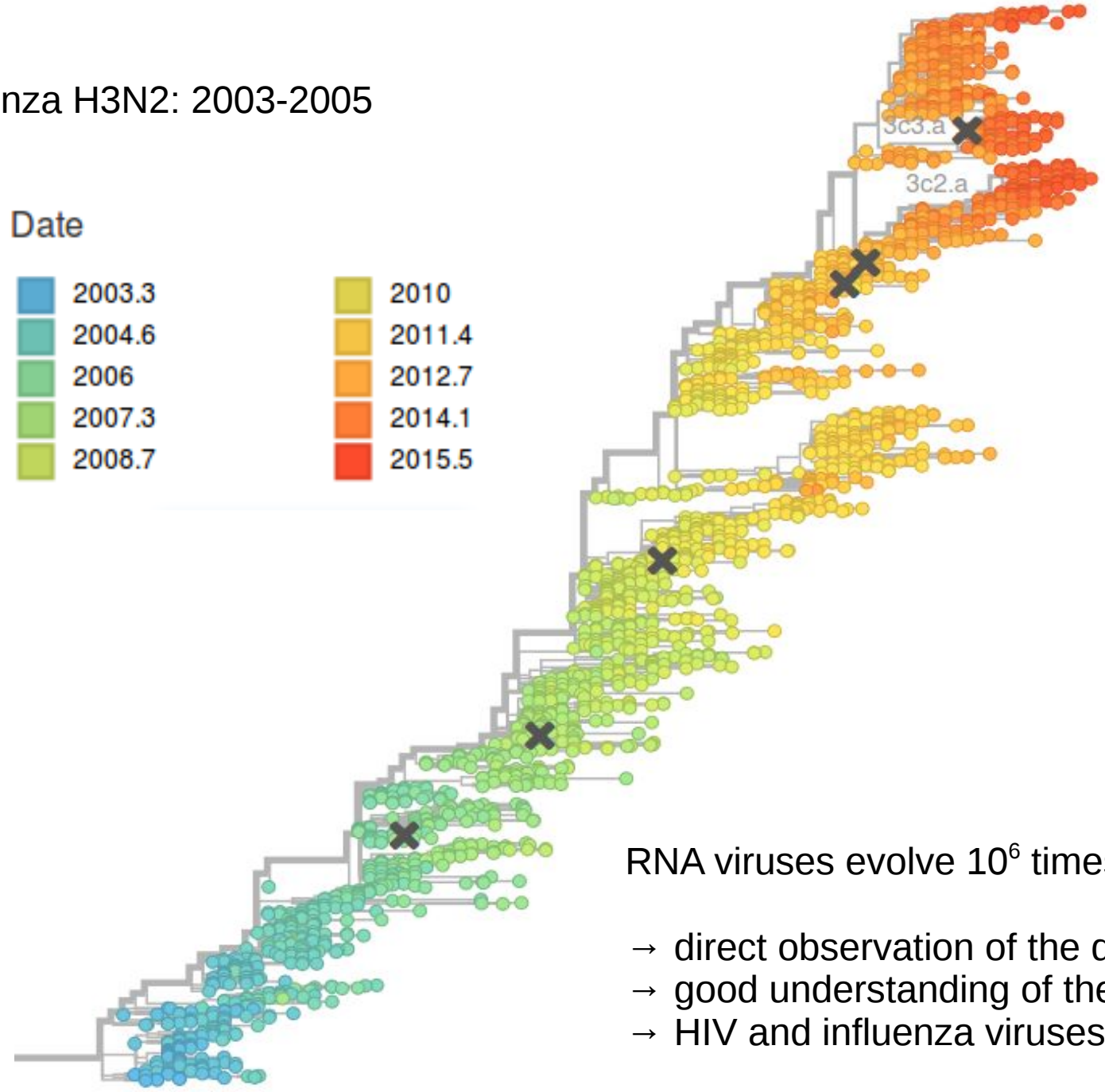
Rapidly evolving populations

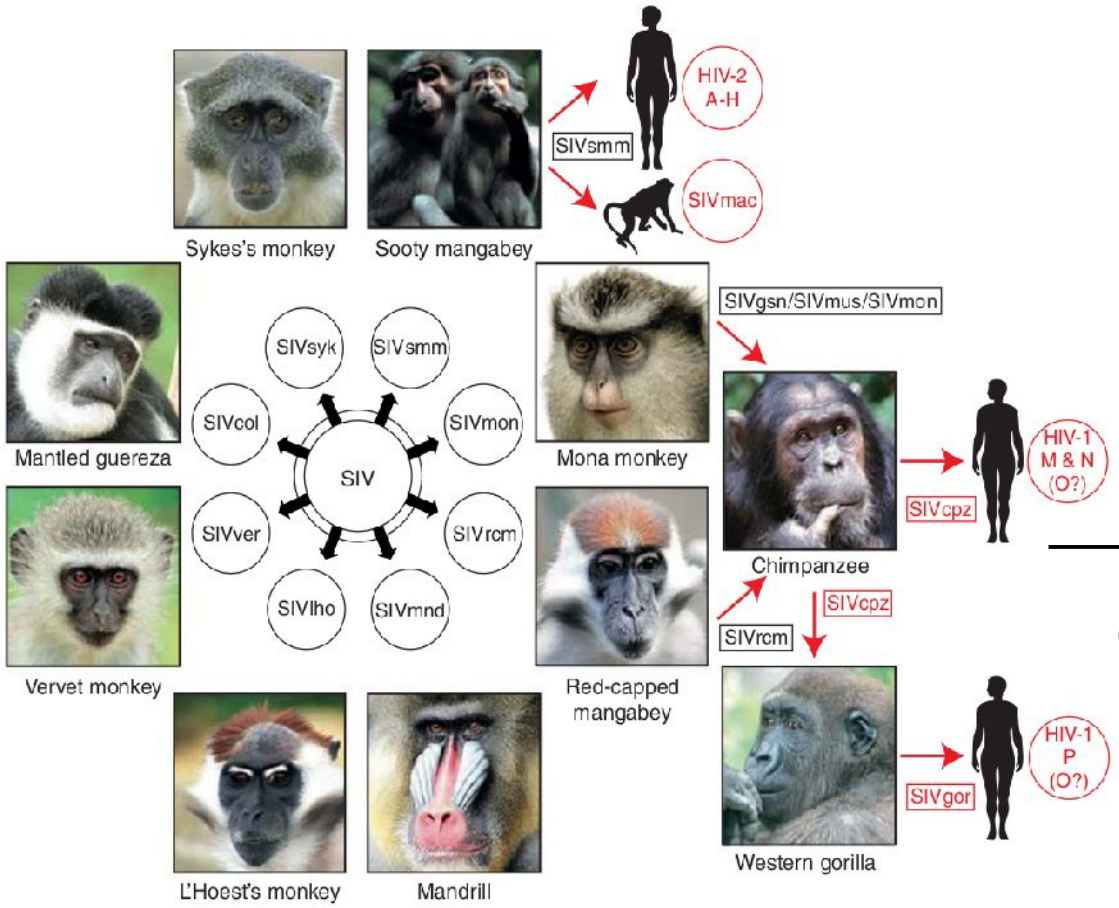
Influenza H3N2: 2003-2005

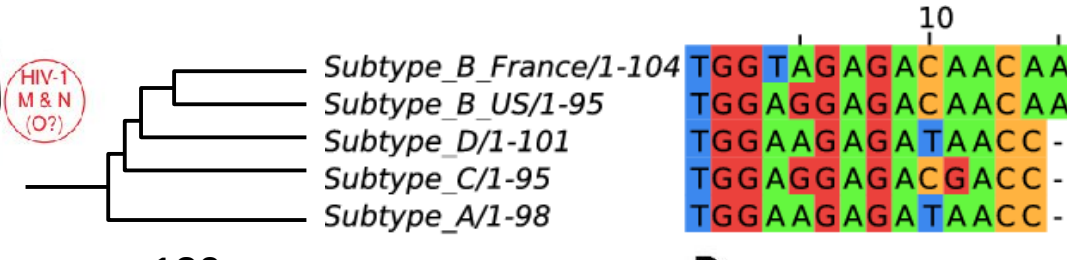


RNA viruses evolve 10^6 times than eukaryotes

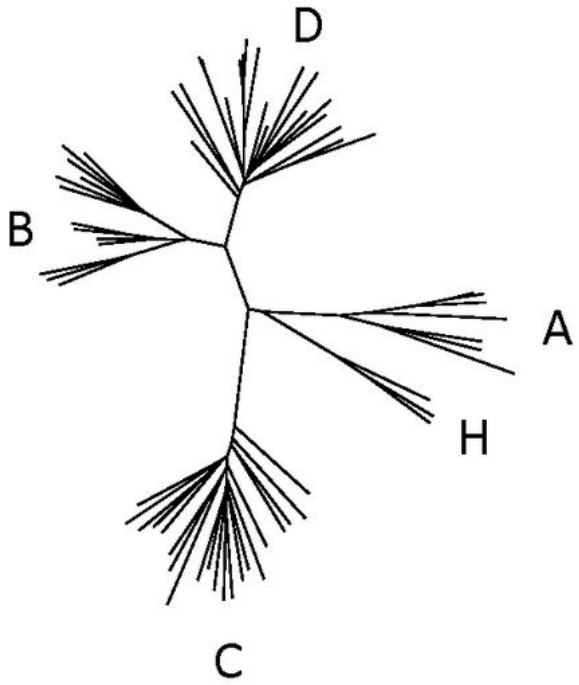
→ direct observation of the dynamics
→ good understanding of the phenotype
→ HIV and influenza viruses

History of HIV





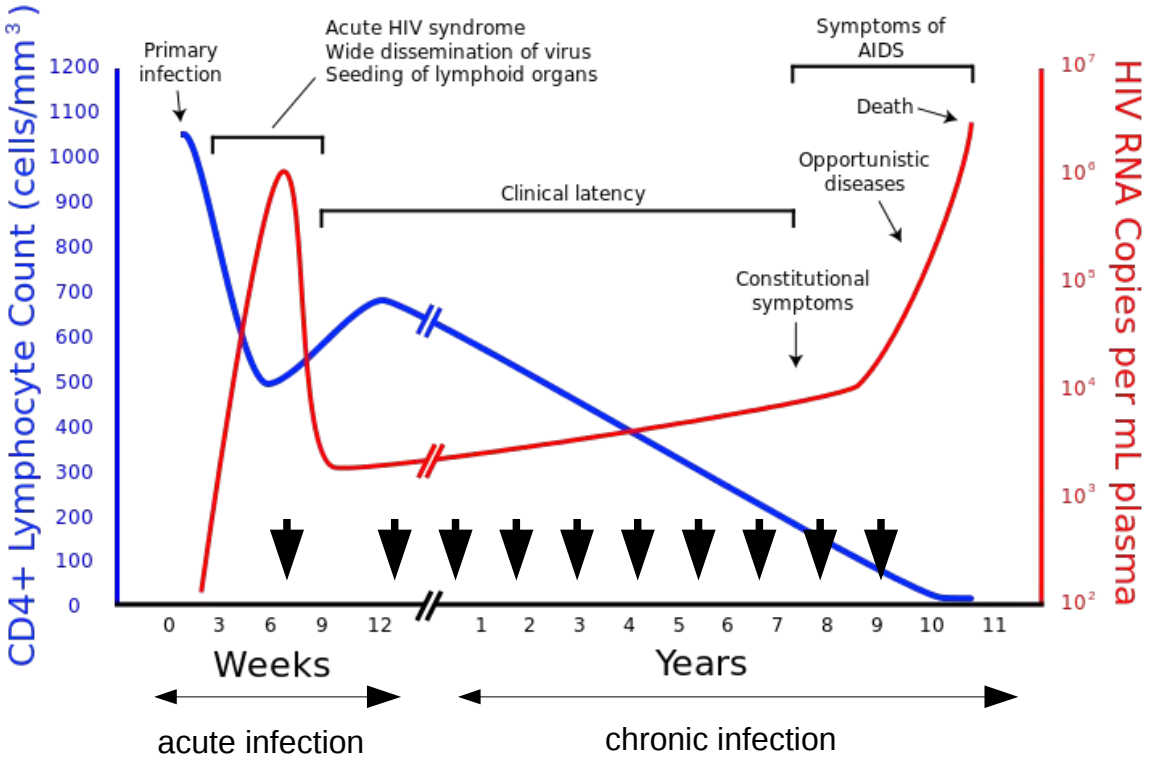
ca 120 years



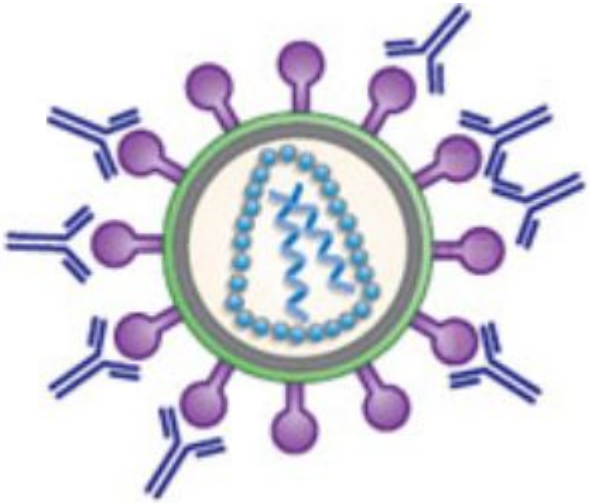
Sharp & Hahn, CSH Pers. Med, 2011

Klenerman, Fleming, Barnes, PLoS Pathogens, 2009

HIV-1 infection and immune selection



virus-immune system coevolution



- rapid evolution facilitates chronic infection
- paradigmatic example of host-parasite co-evolution
- can be studied in exquisite detail

Image: wikipedia

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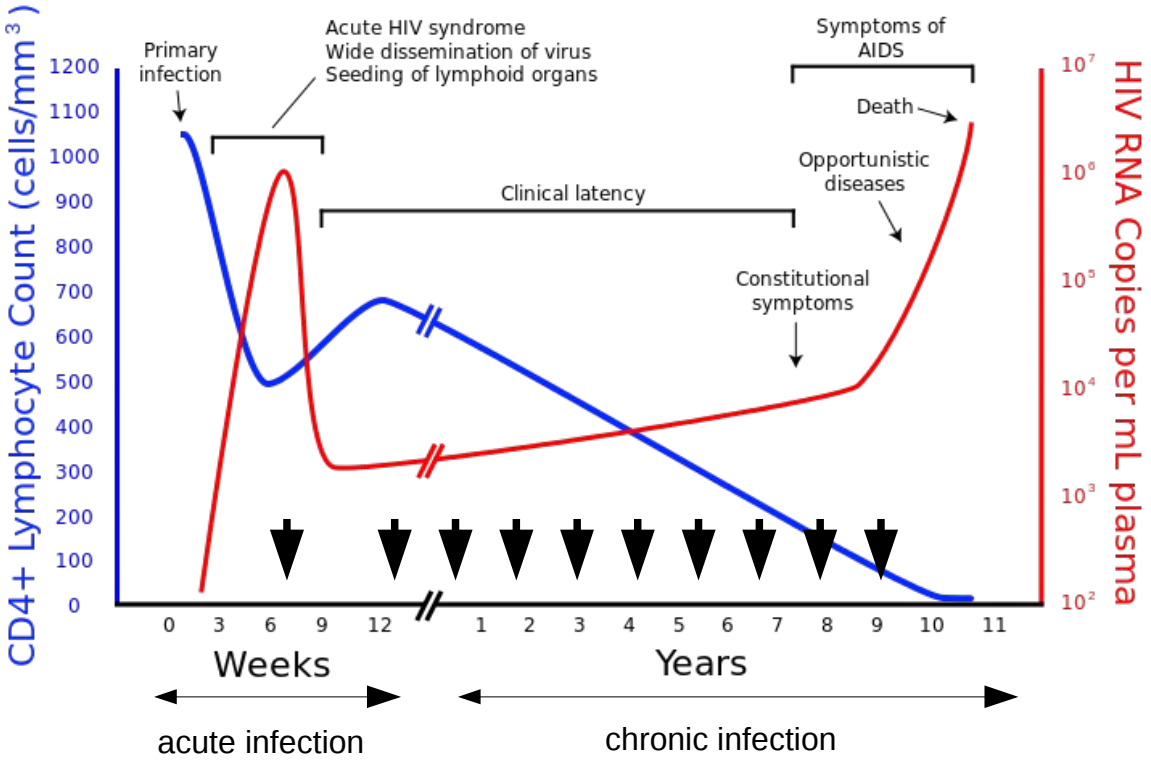

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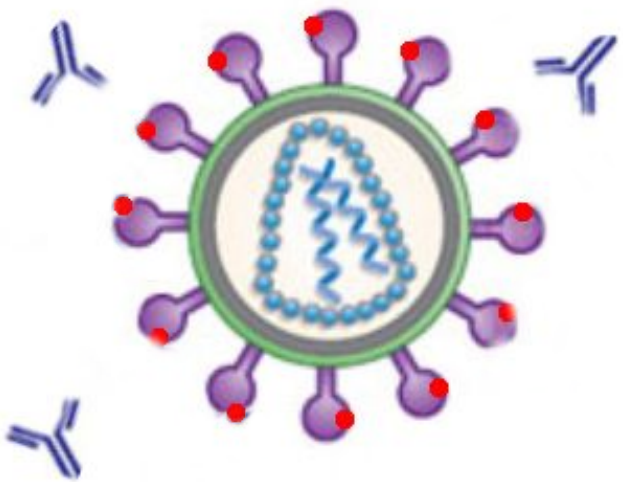

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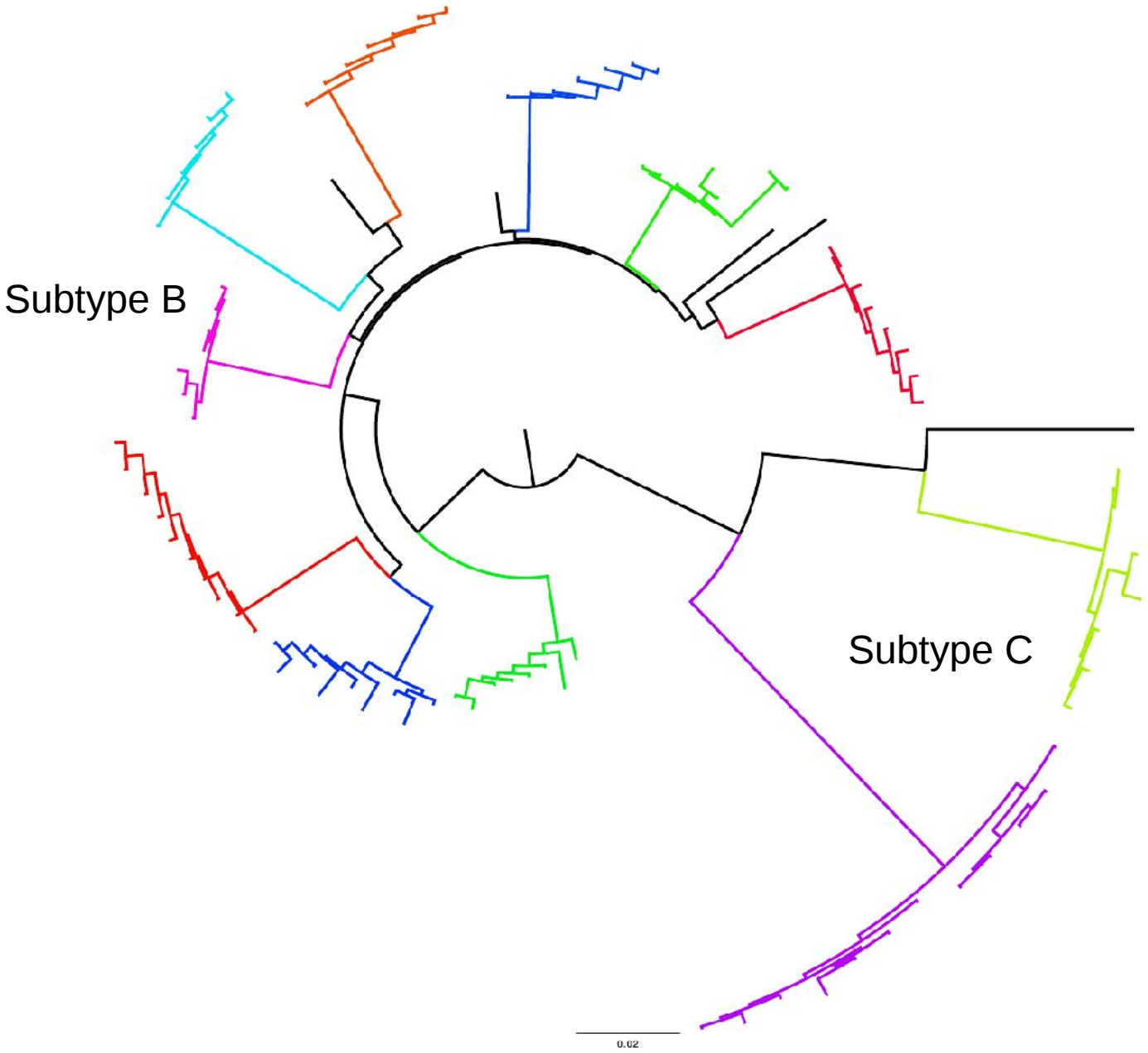
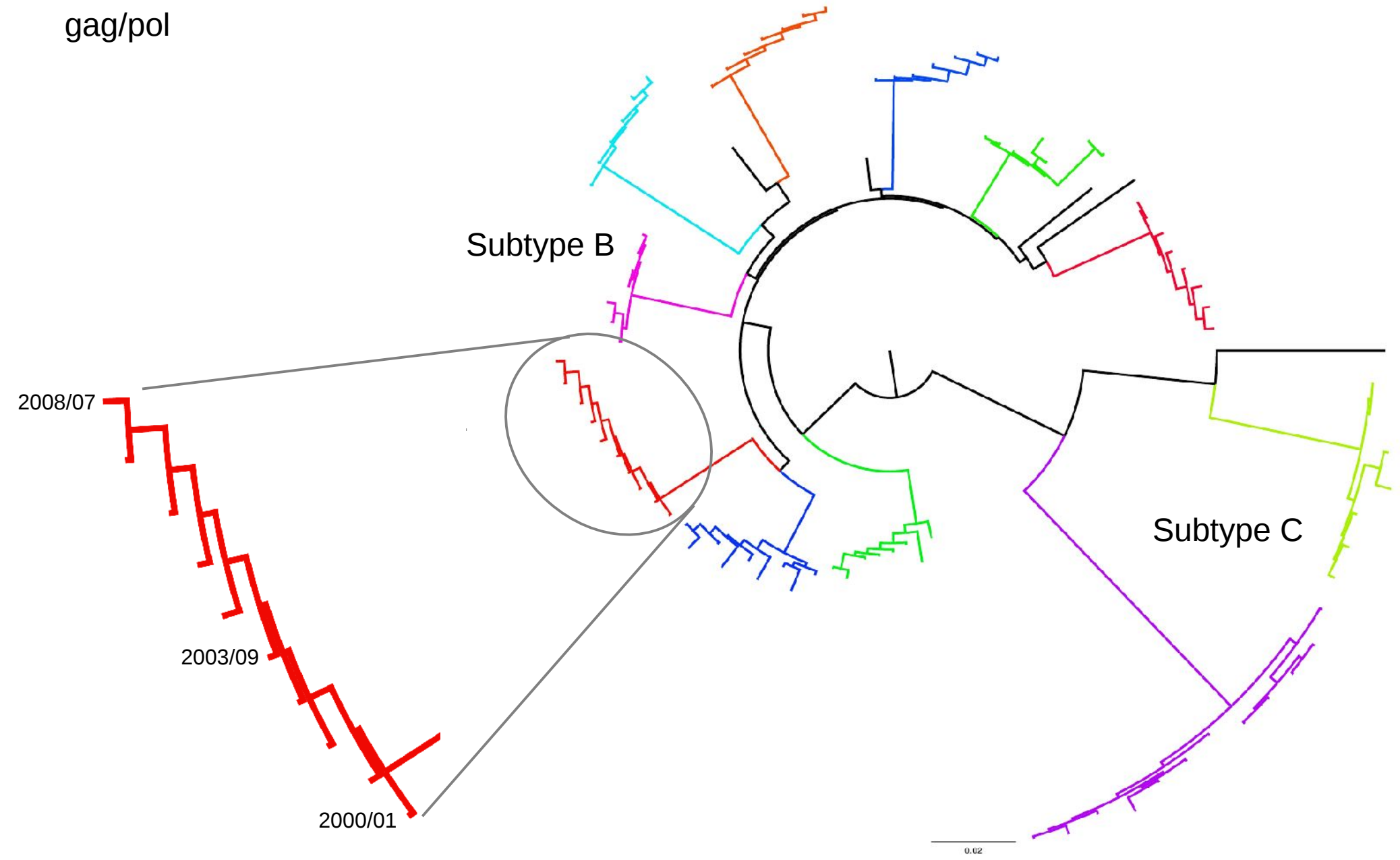
Image: wikipedia

Sequencing of serial HIV-1 RNA samples

gag/pol



Sequencing of serial HIV-1 RNA samples



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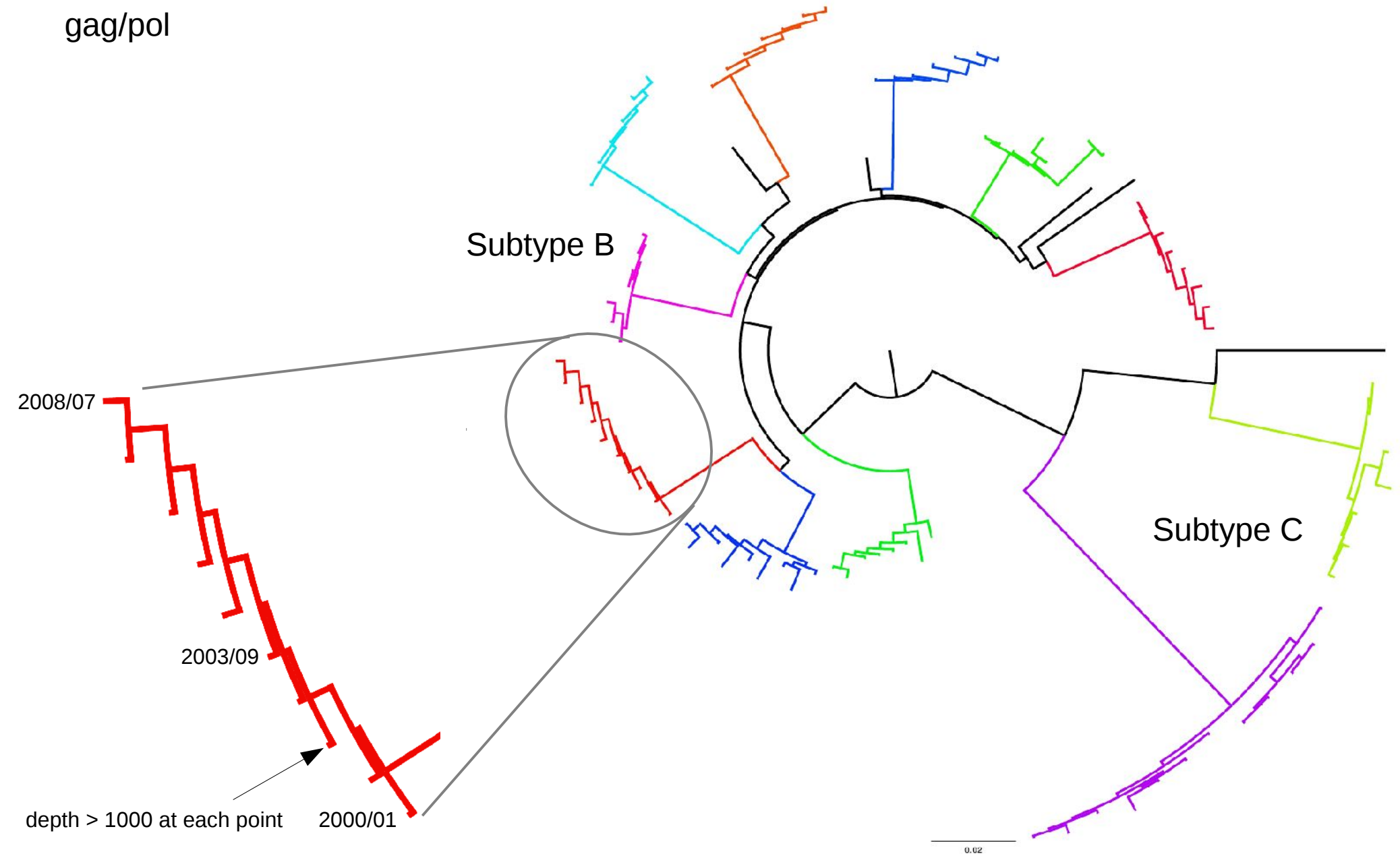
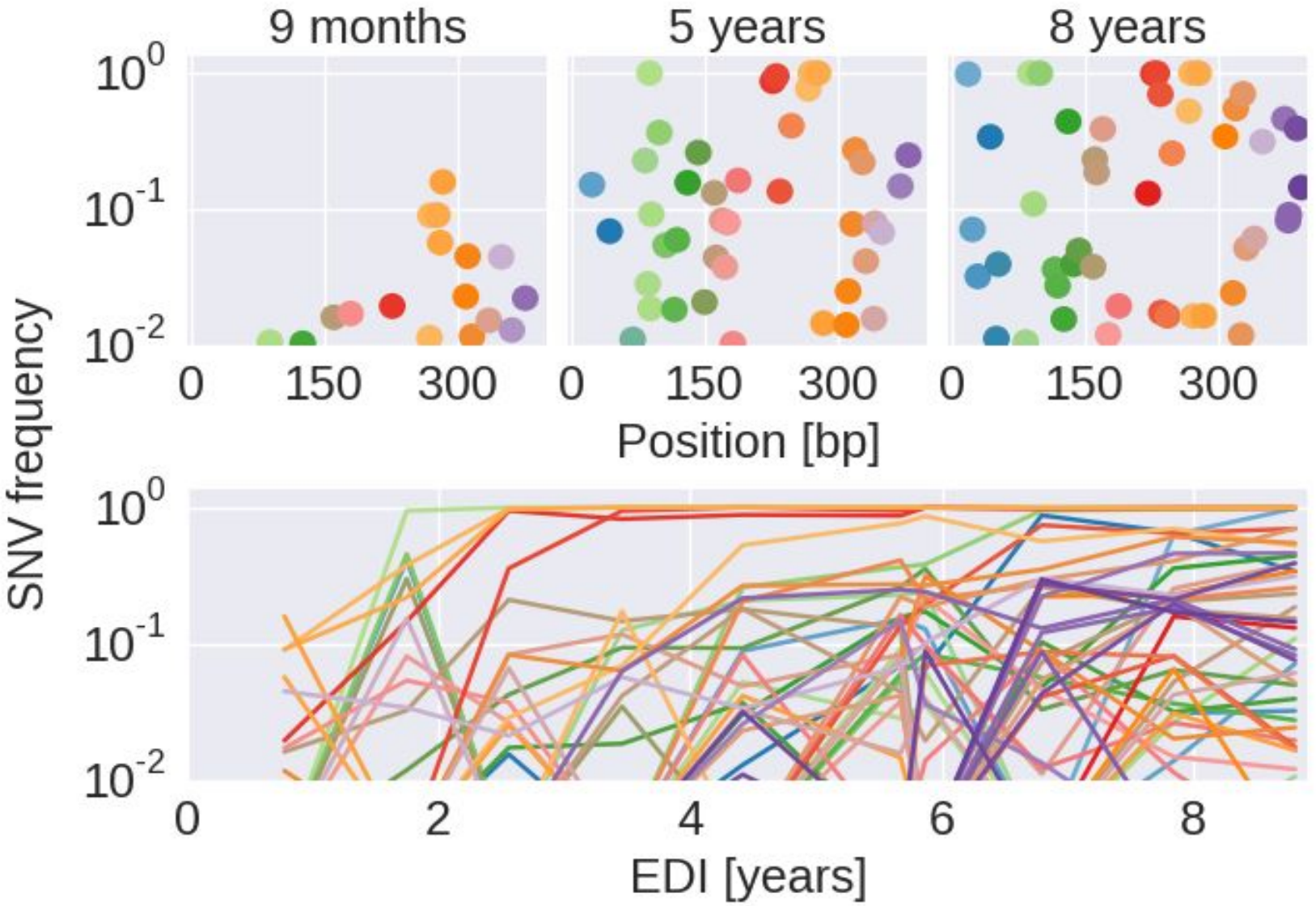
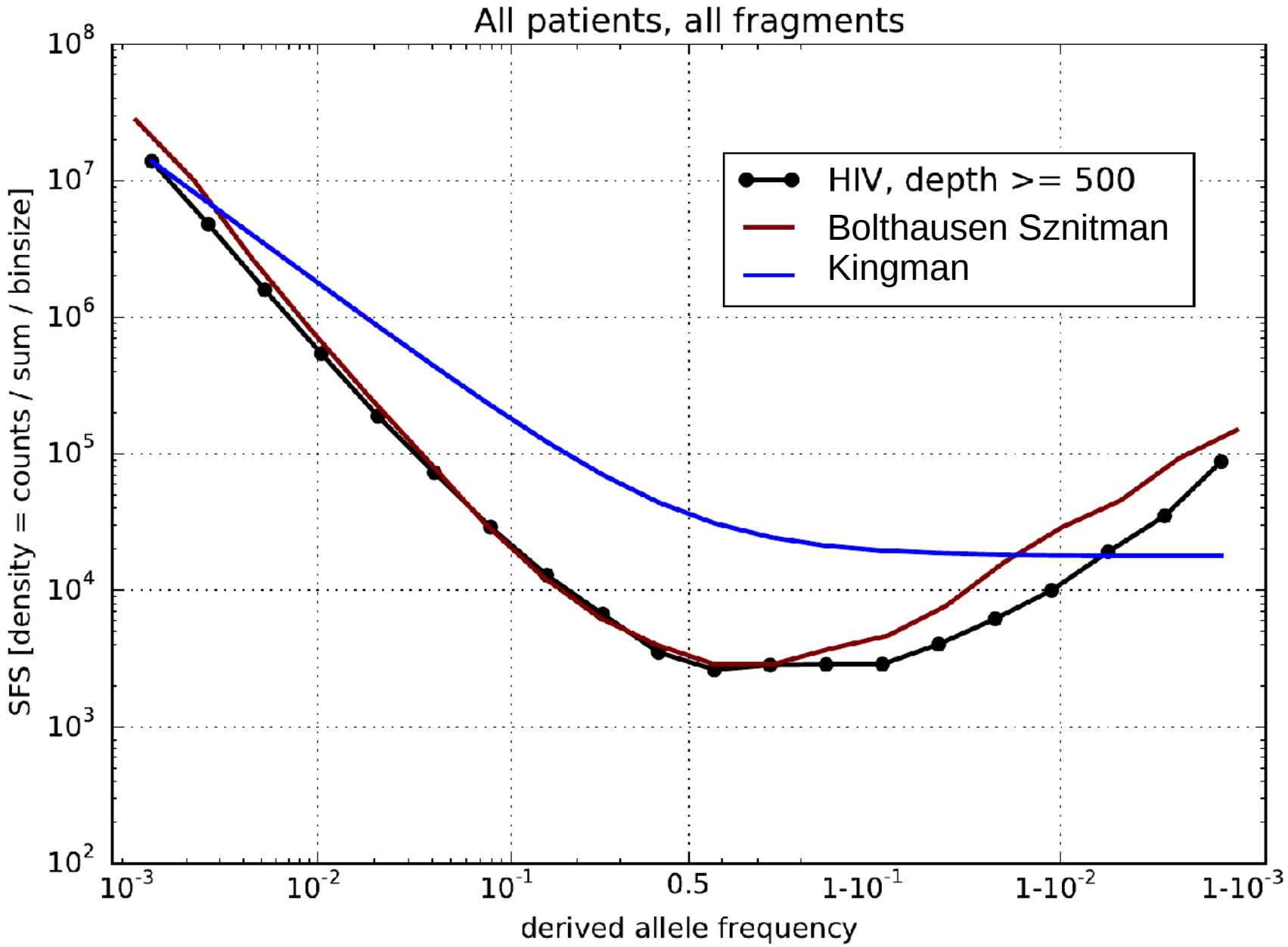


The dynamics of mutations



What is an appropriate model?

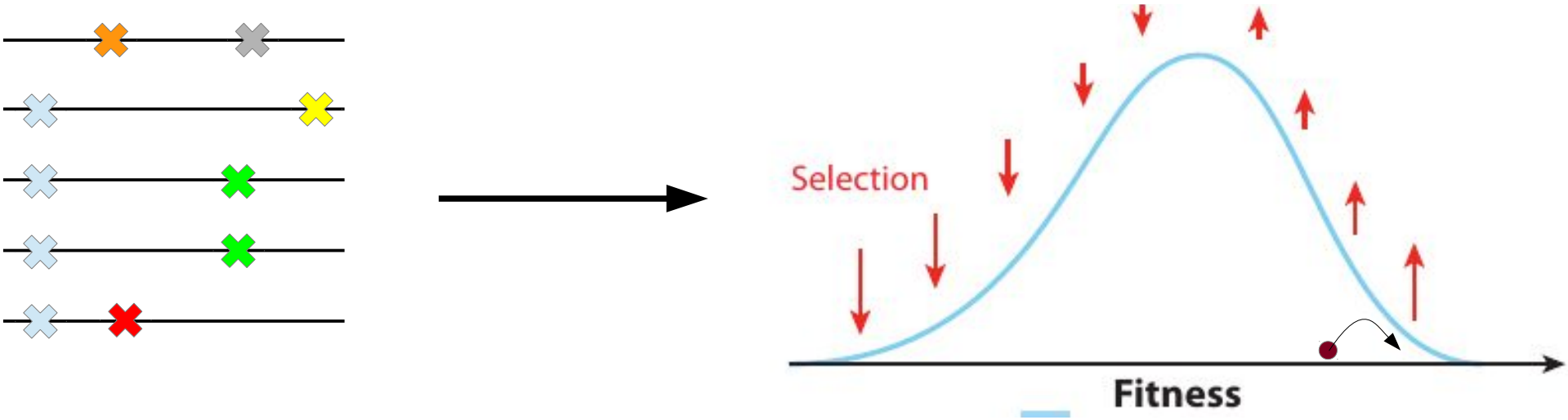


Why does it look like Bolthausen-Sznitman?

A large fraction of genetic variation is under selection

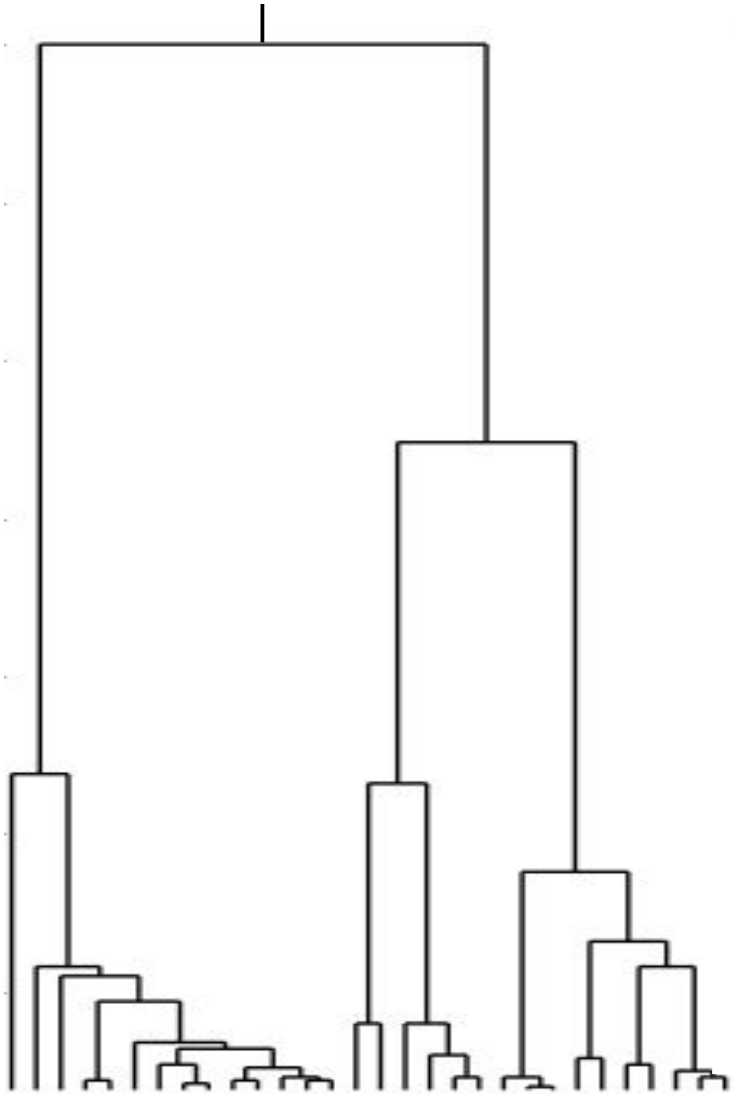
→ there is a broad fitness distribution

→ successful parents have successful offspring



Coalescence with selection

Neutral coalescence



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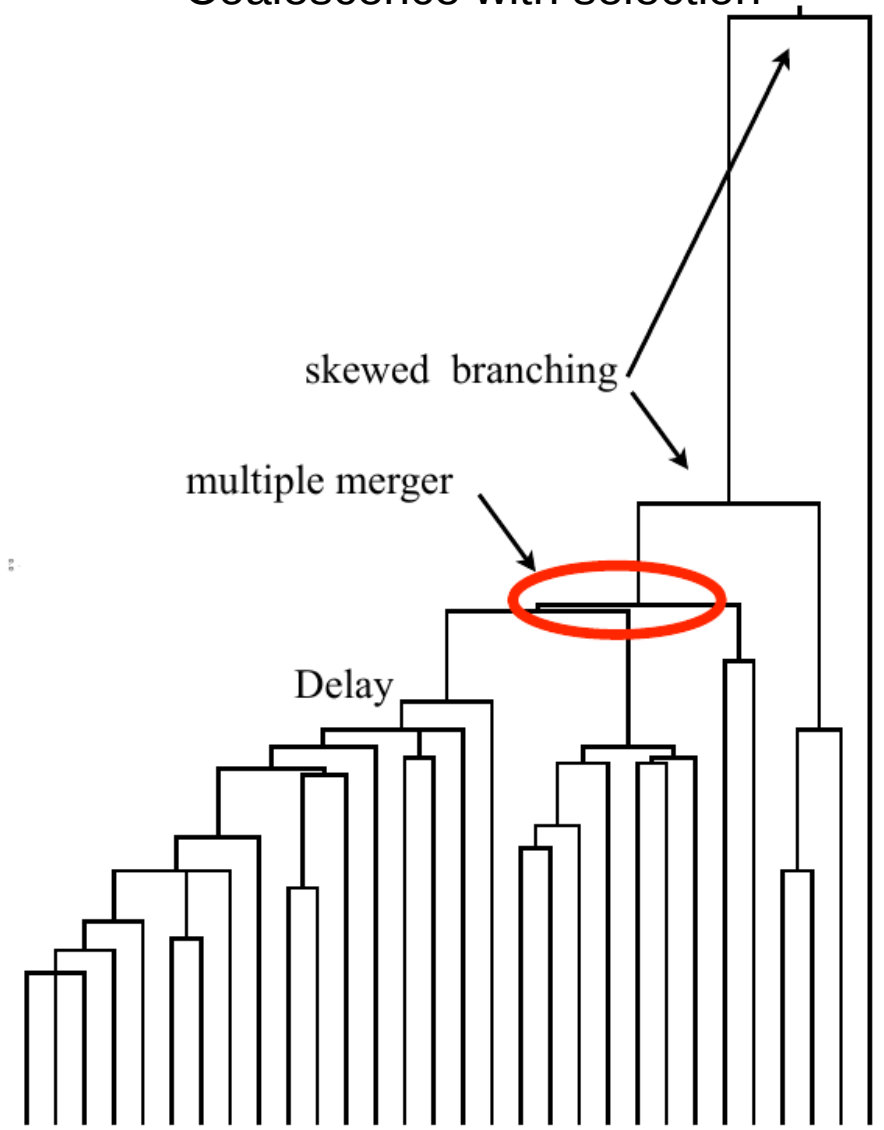

RN and Hallatschek, PNAS, 2013
Desai, Walczak, Fisher, Genetics, 2013
Brunet et al, PRE, 2007

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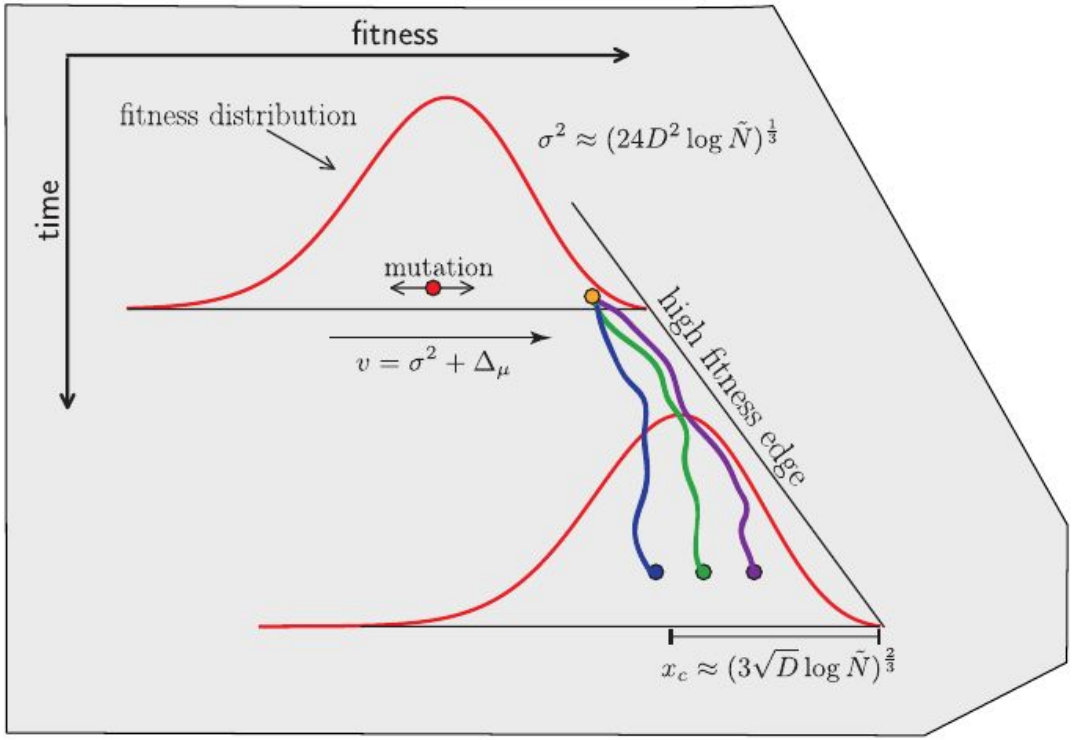

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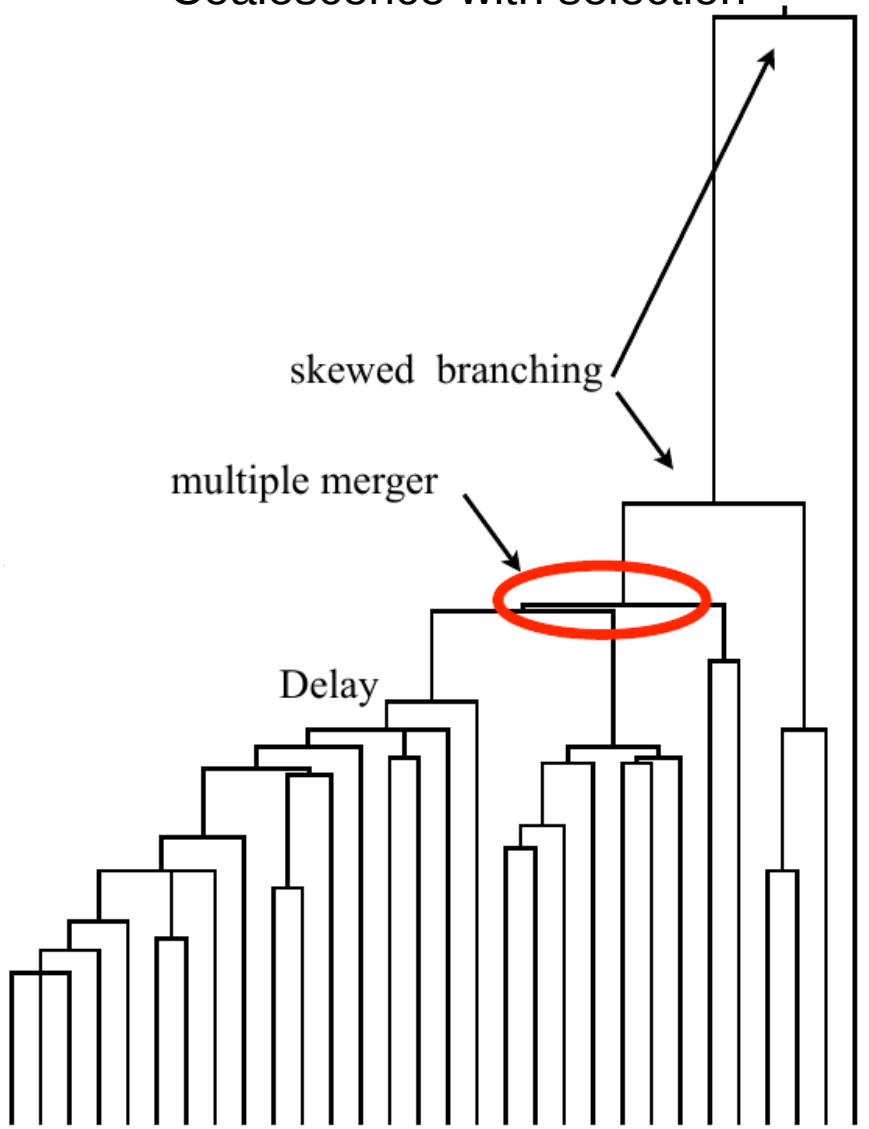

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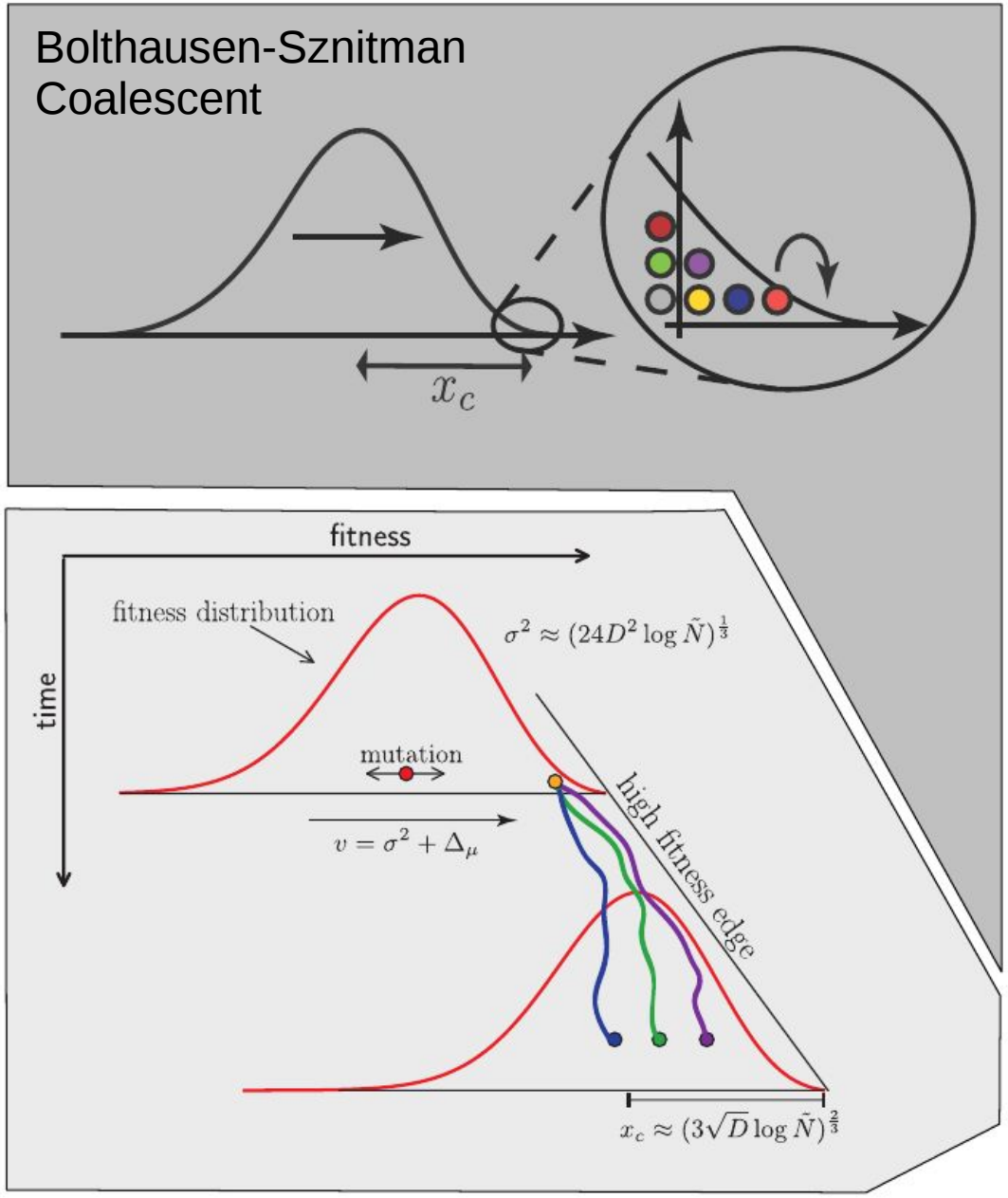

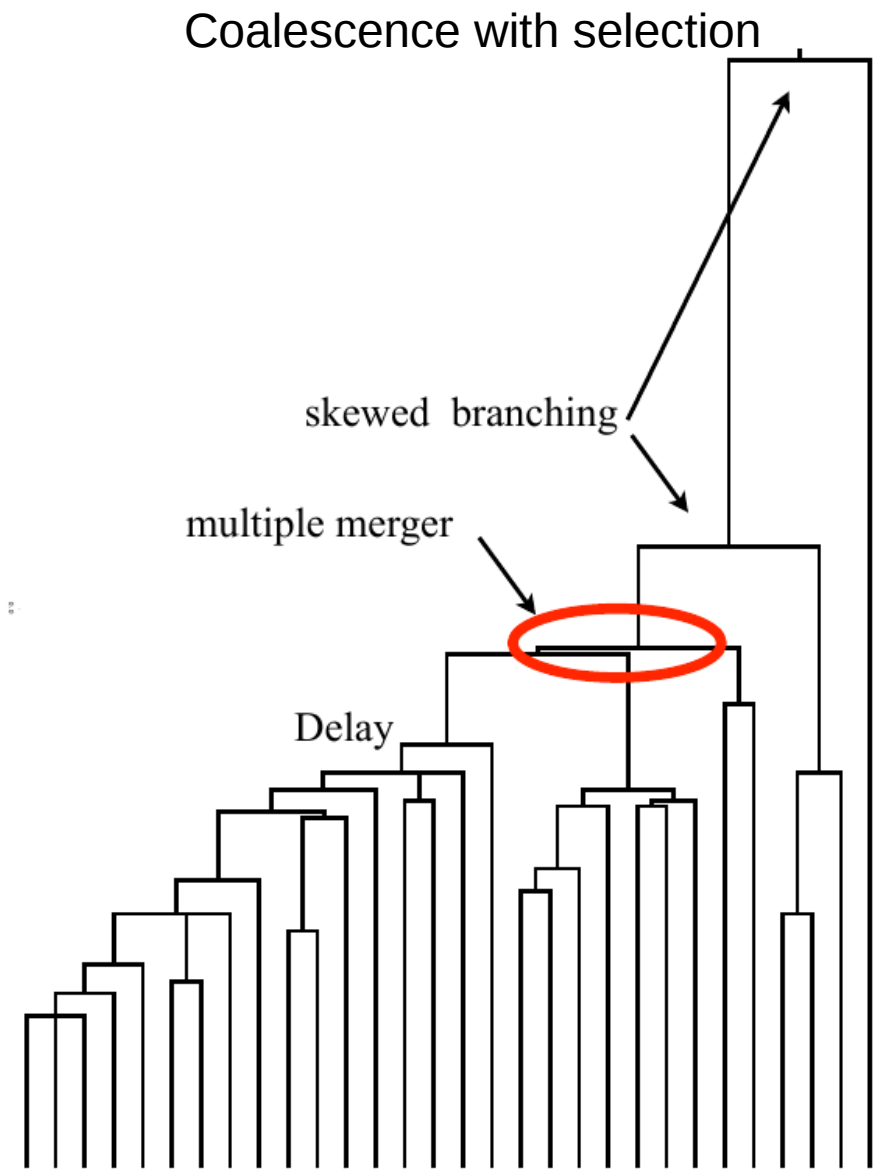

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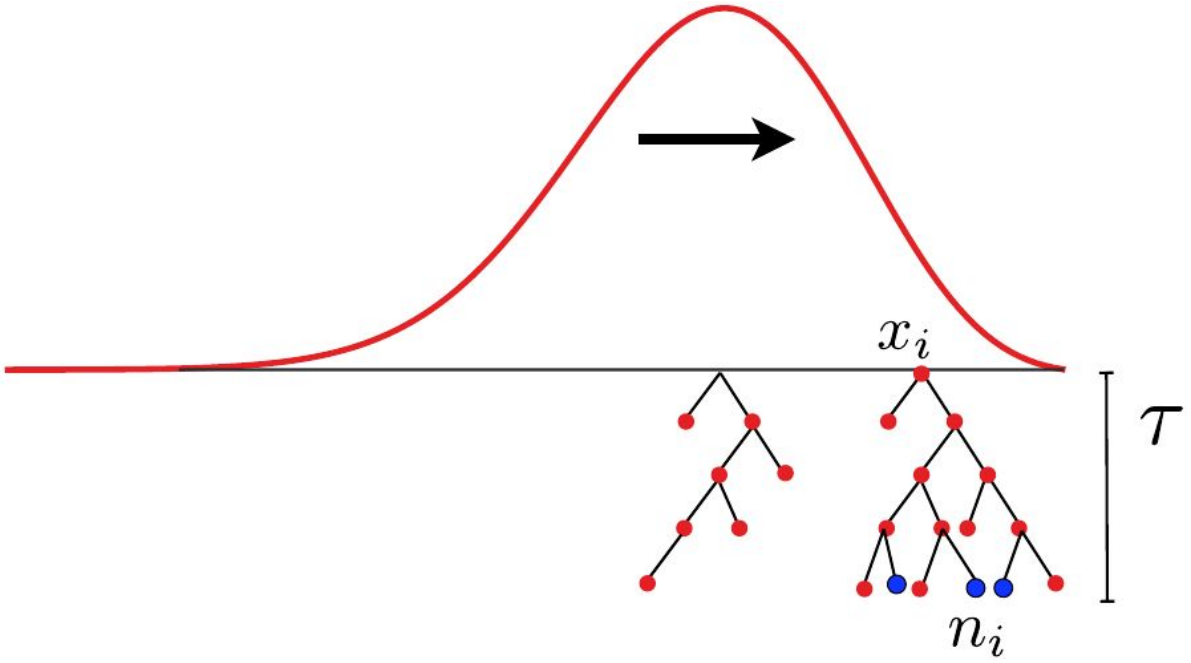
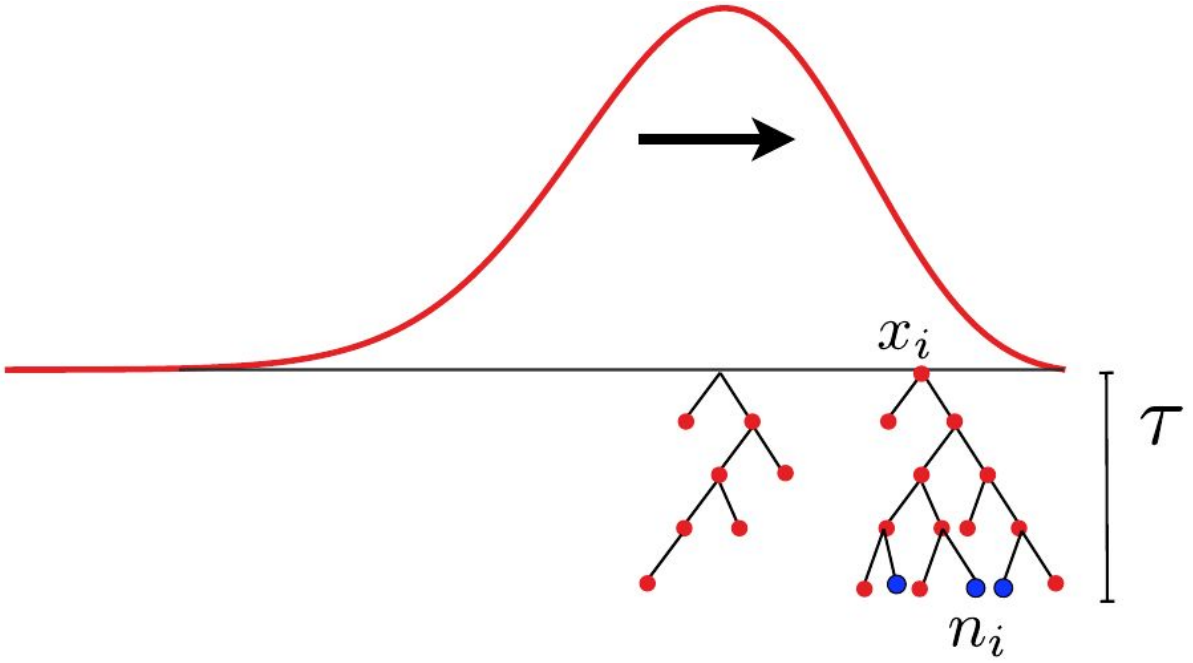


Branching process approximation:

$$P(n_i|\chi_i,\tau)$$

RN and Hallatschek, PNAS, 2013

Coalescence with selection



Branching process approximation:

$$P(n_i|\chi_i,\tau)$$

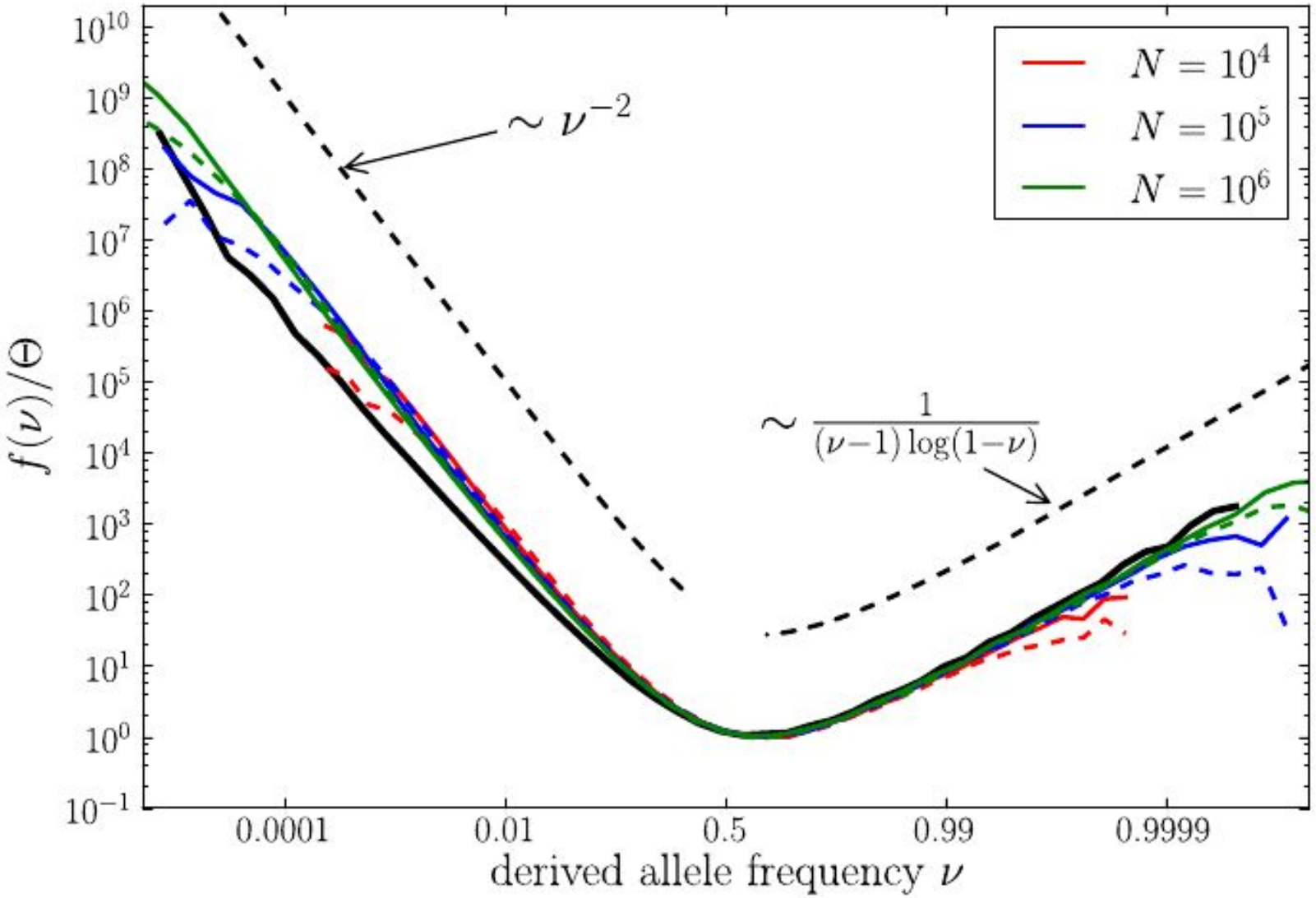
Does a sample (blue dots) have a common ancestor tau generations ago?

$$Q_b = \langle \sum_i \left(\frac{n_i}{\sum_j n_j} \right)^b \rangle = \begin{cases} \mathcal{O}(1/N) & \tau < T_c \\ \frac{\tau - T_c}{T_c(b-1)} & \tau > T_c \end{cases}$$

All other merger rates also suggest a Bolthausen-Sznitman coalescent

RN and Hallatschek, PNAS, 2013

Allele frequency spectra

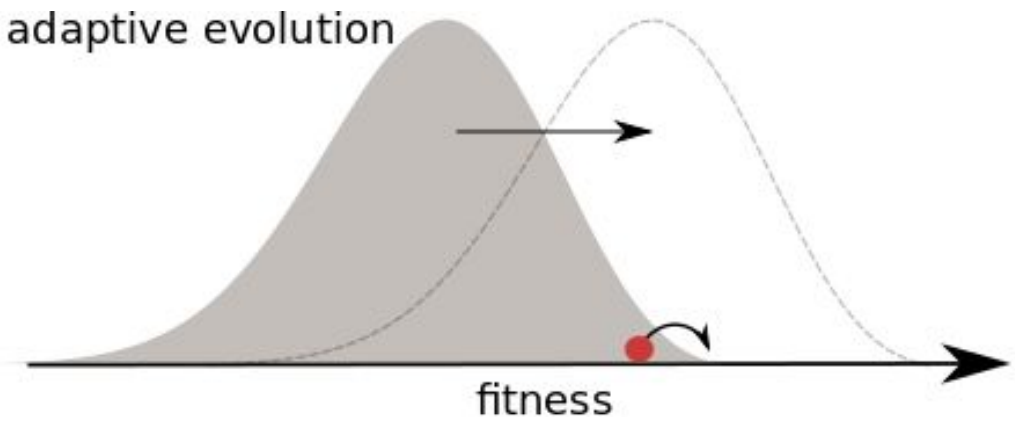


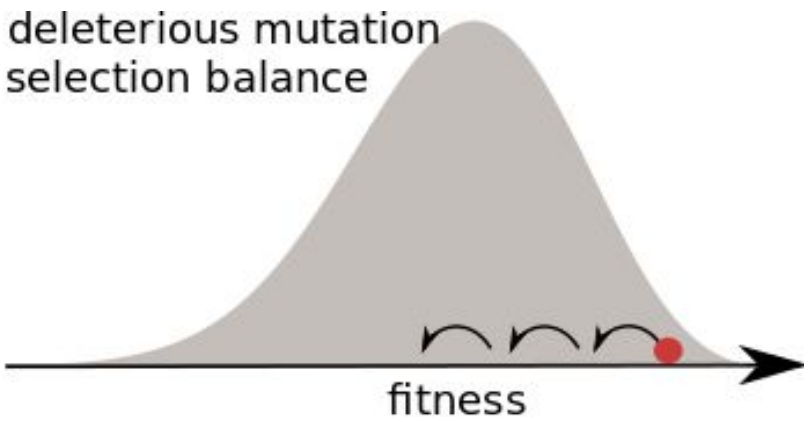
RN and Hallatschek, PNAS, 2013

Genetic diversity in adapting populations

Time scale of coalescence: $T_c \sim \frac{\sqrt{\log N}}{\sigma}$

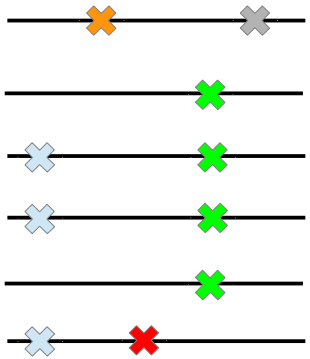
Universal: many selected mutations → same tree statistics

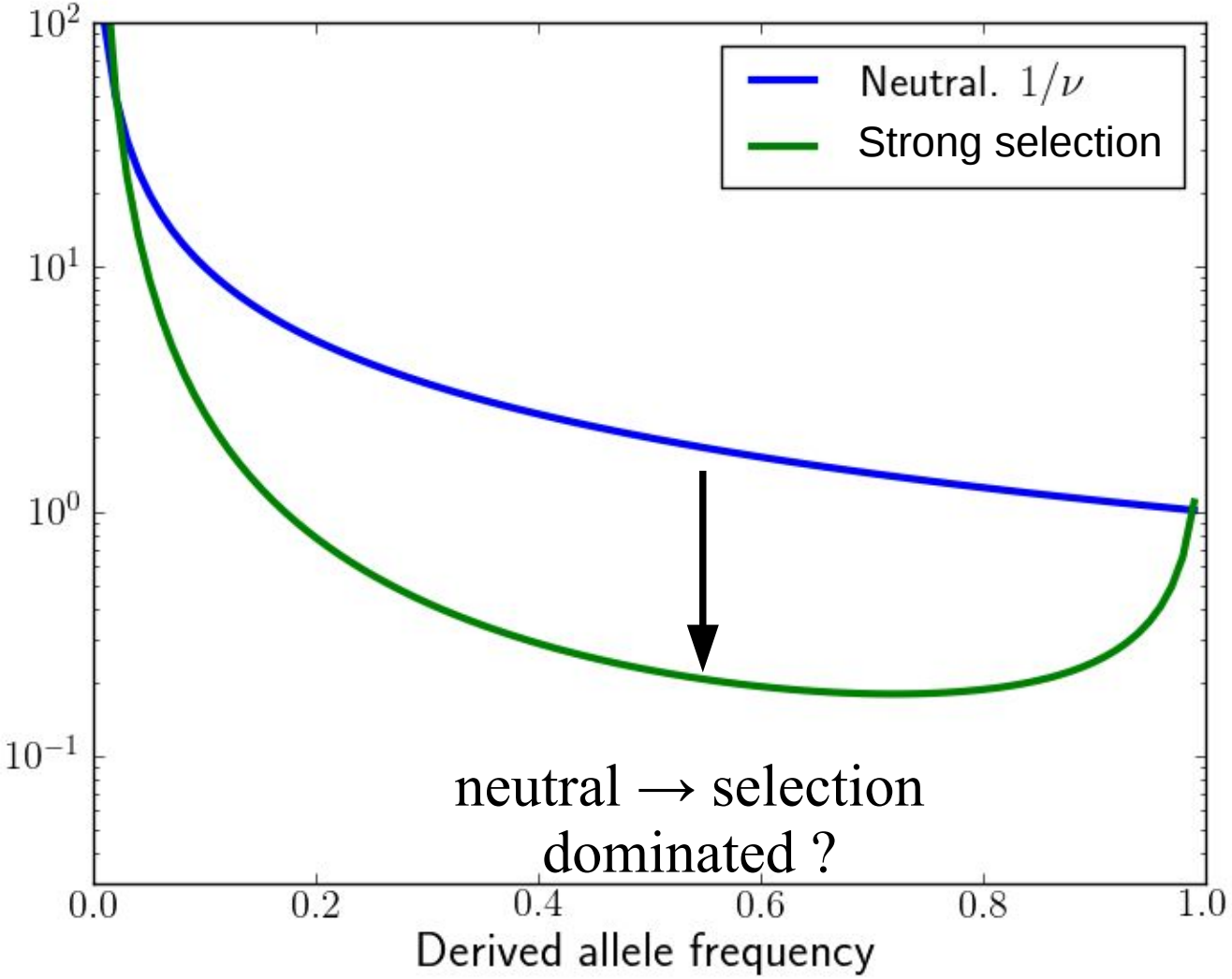




RN and Hallatschek, PNAS, 2013
Desai, Walczak, Fisher, Genetics 2013

Continuous cross-over from neutral to strongly selected





RN, Kessinger, Shraiman. PNAS, 2013
Good et al, PloS Genetics, 2014

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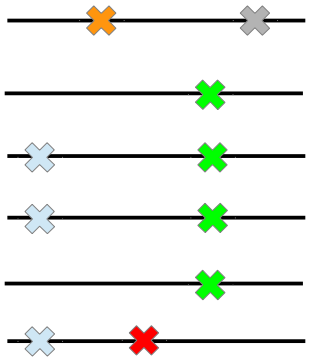

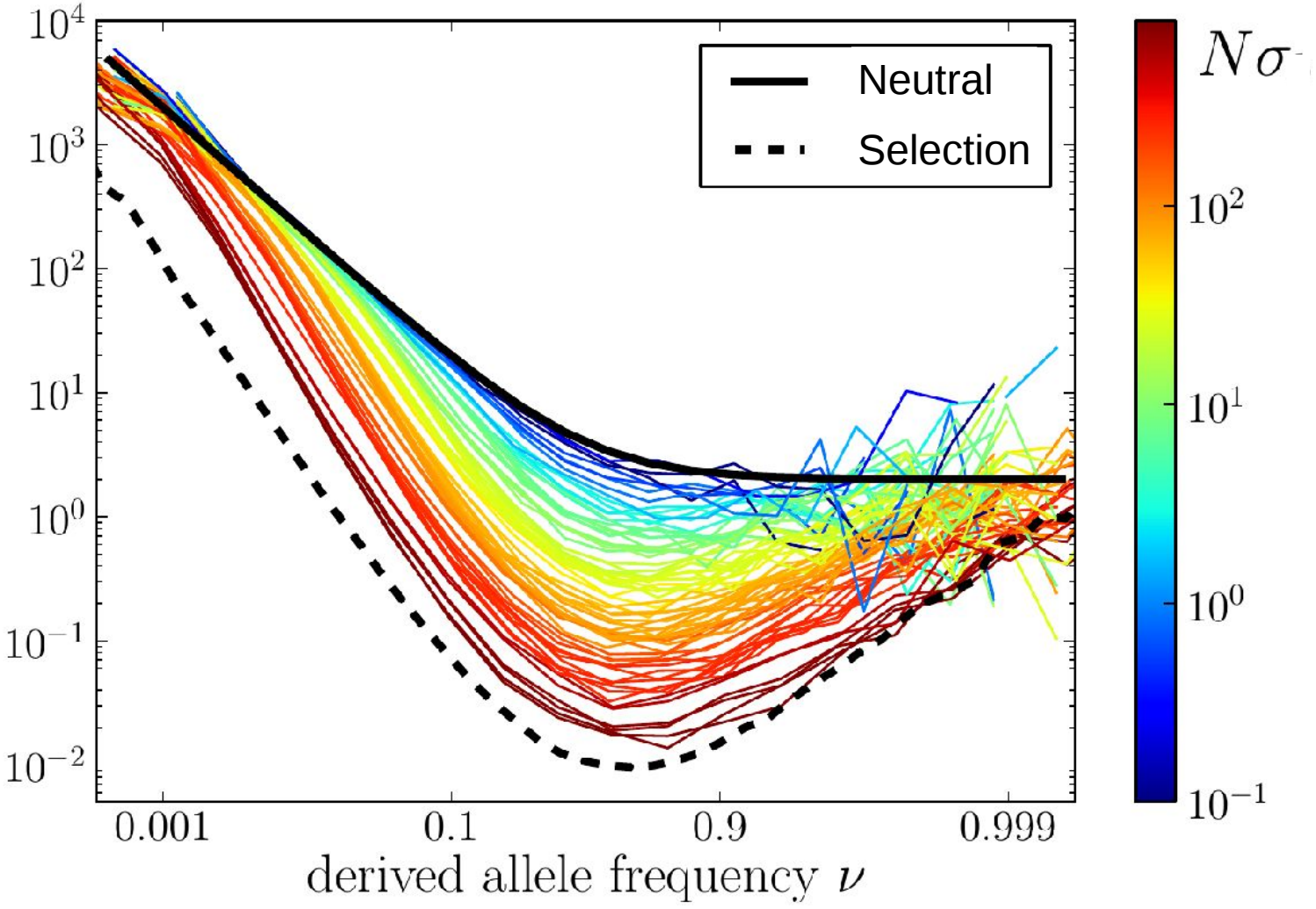

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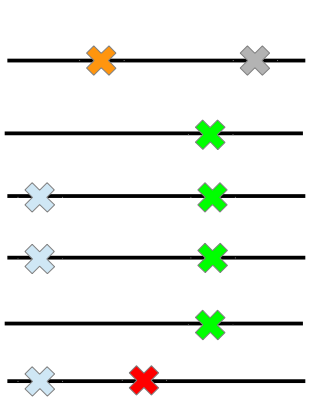
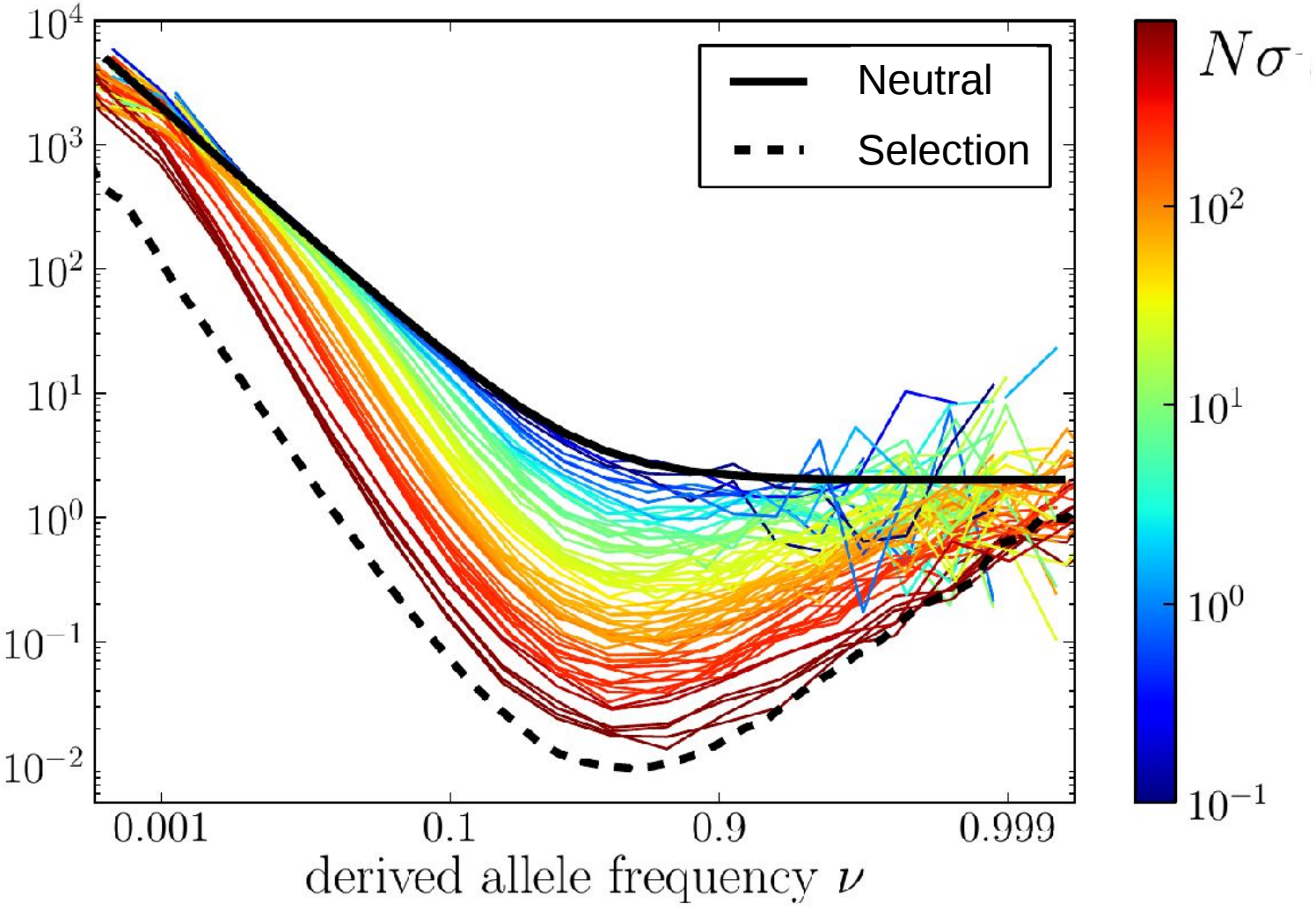
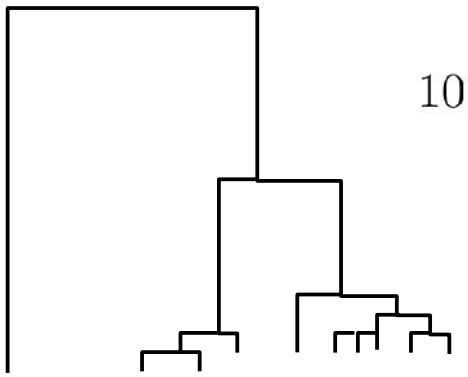
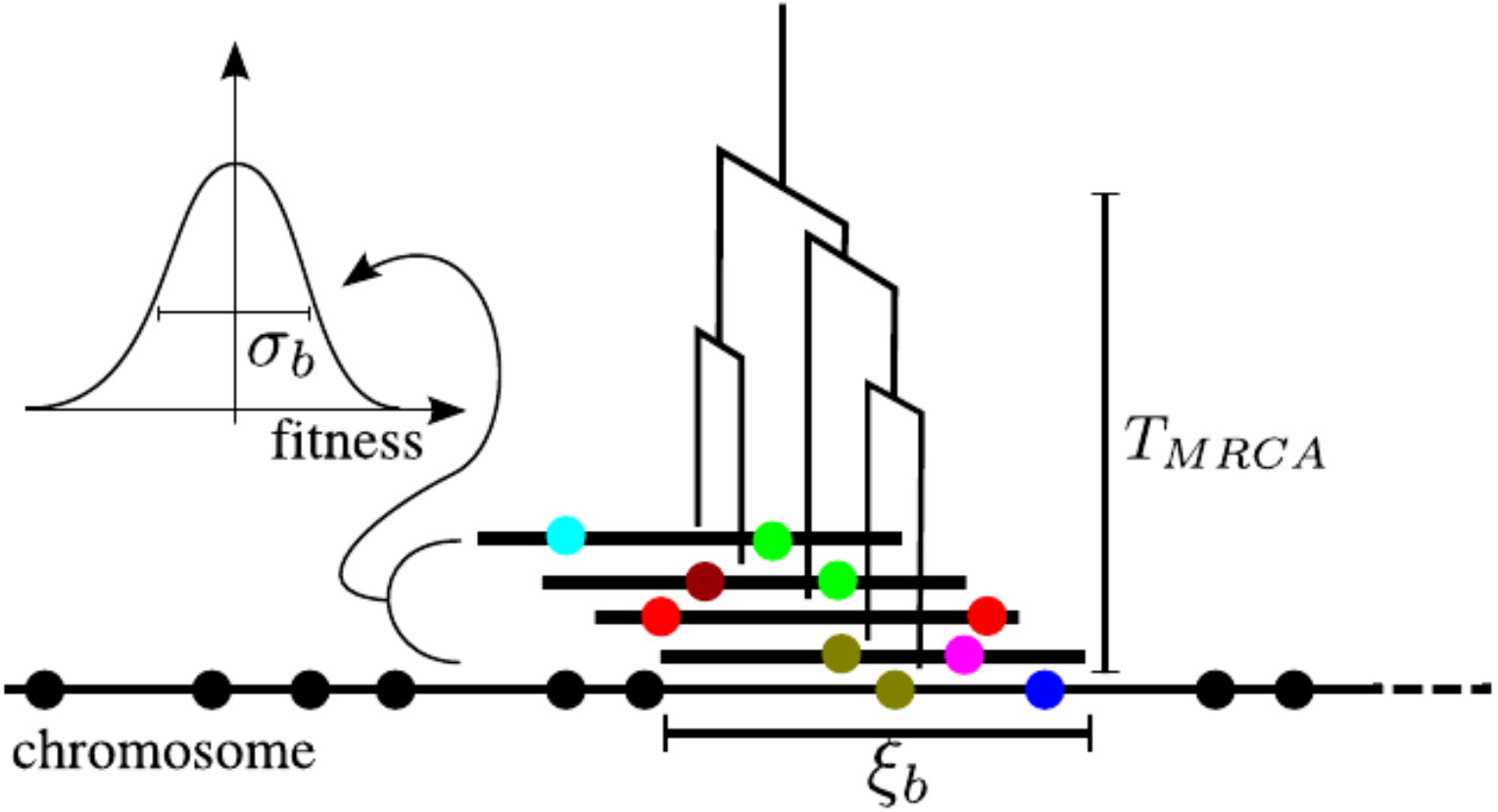






RN, Kessinger, Shraiman. PNAS, 2013
Good et al, PloS Genetics, 2014

Extension to recombining populations



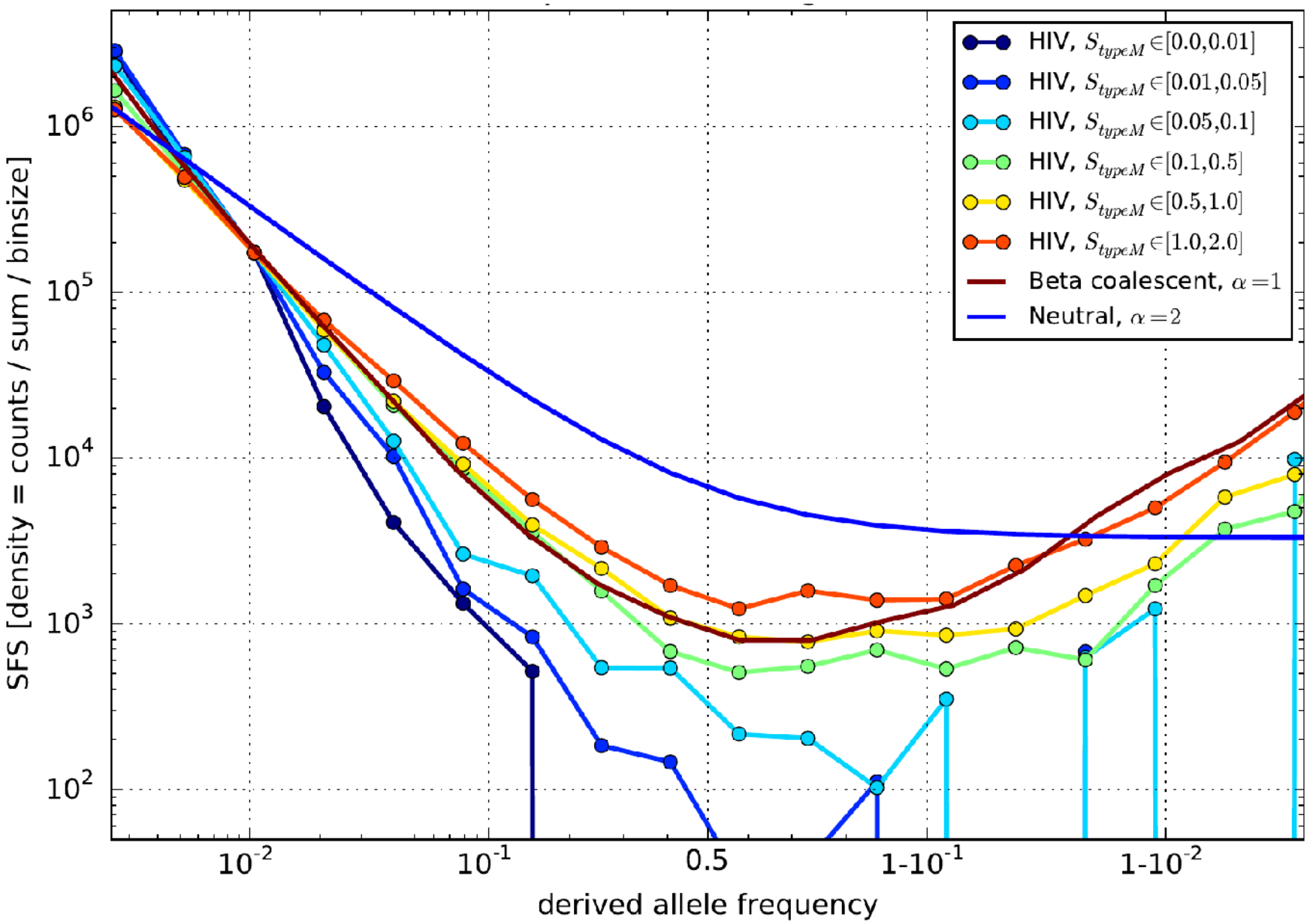
Coalescent time

Fitness diversity σ_b

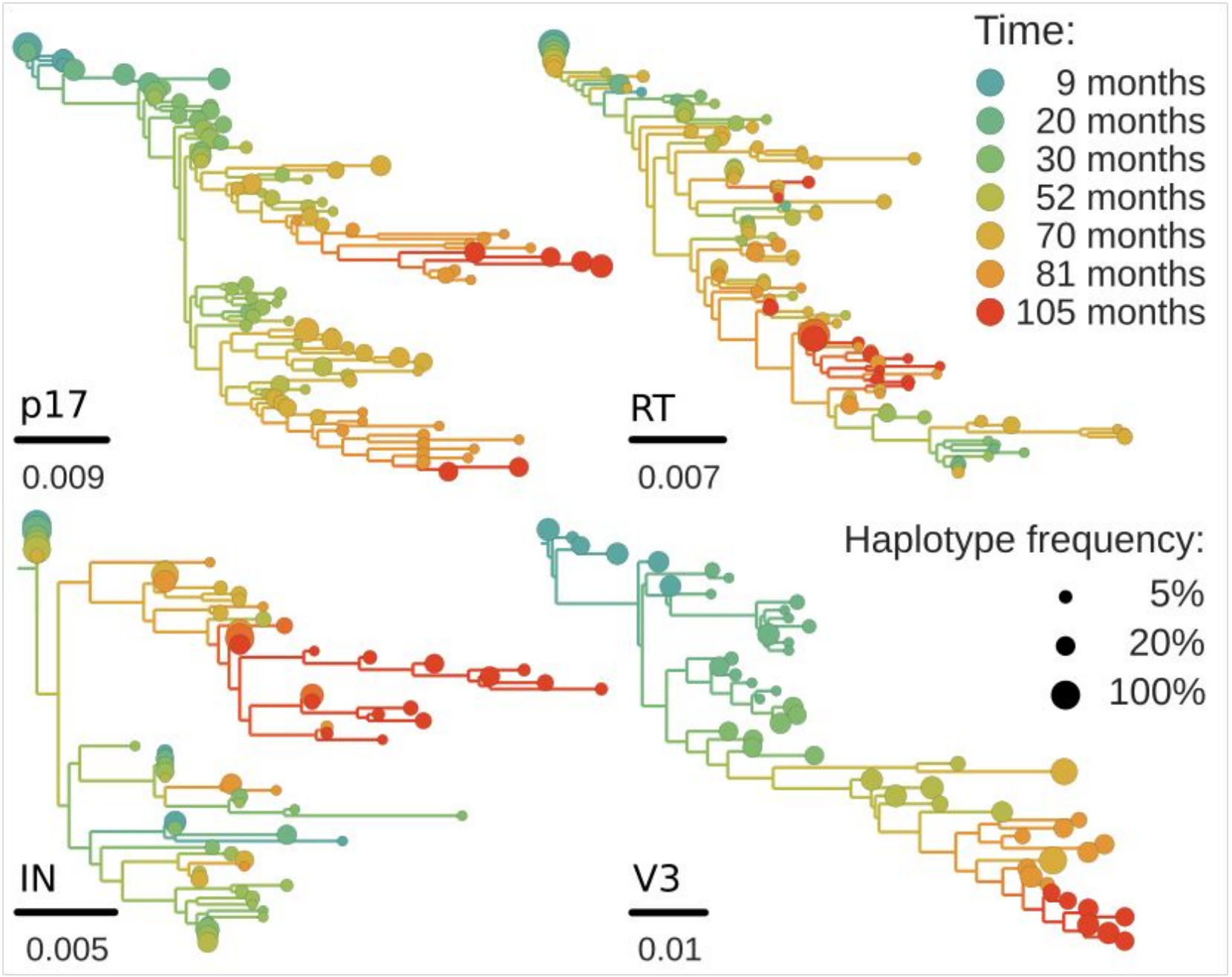
Length of linkage block ξ_b

RN, Kessinger, Shraiman, PNAS, 2013

Site frequency spectra

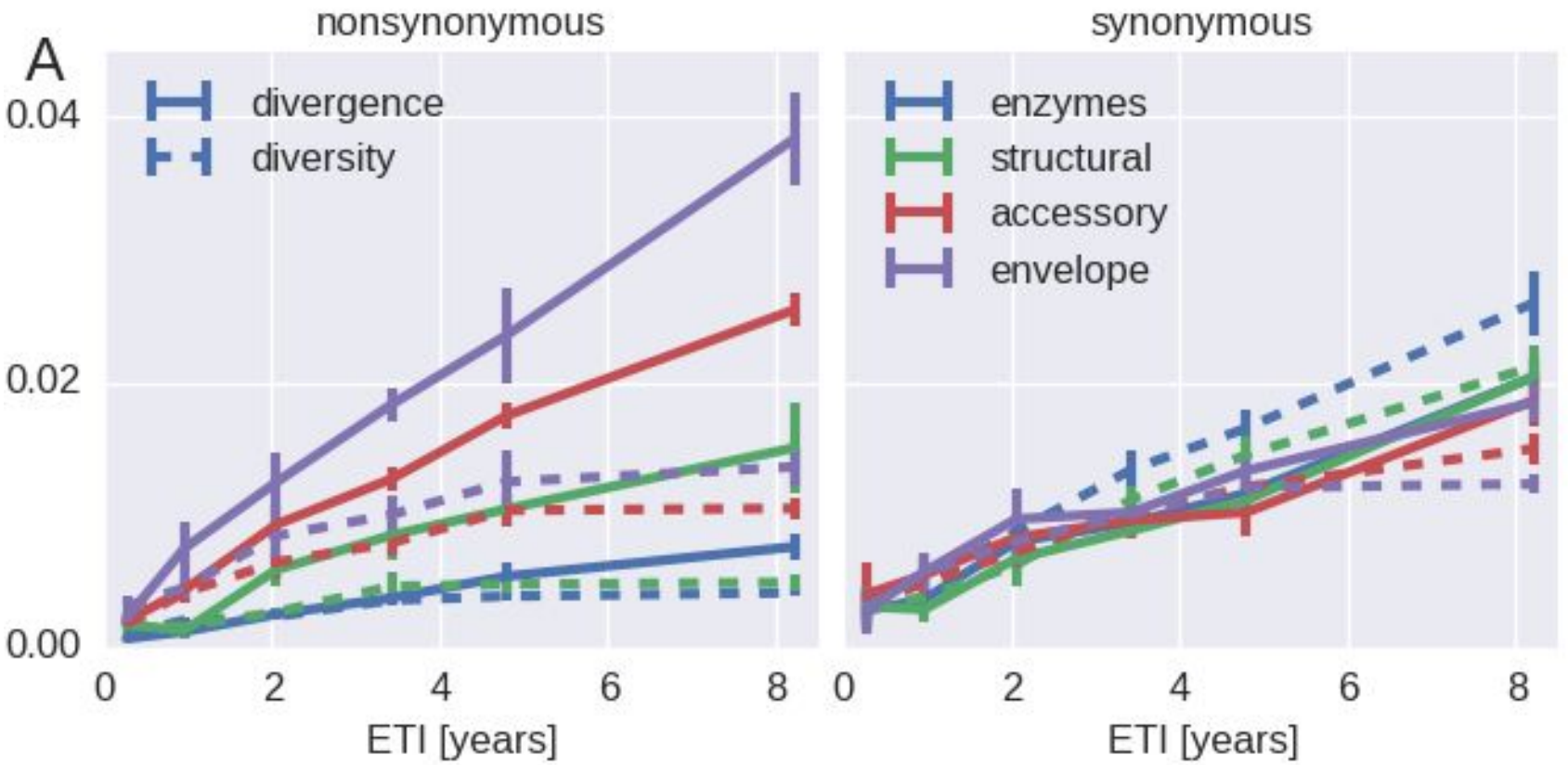


Phylogenetic trees in different regions



Movie

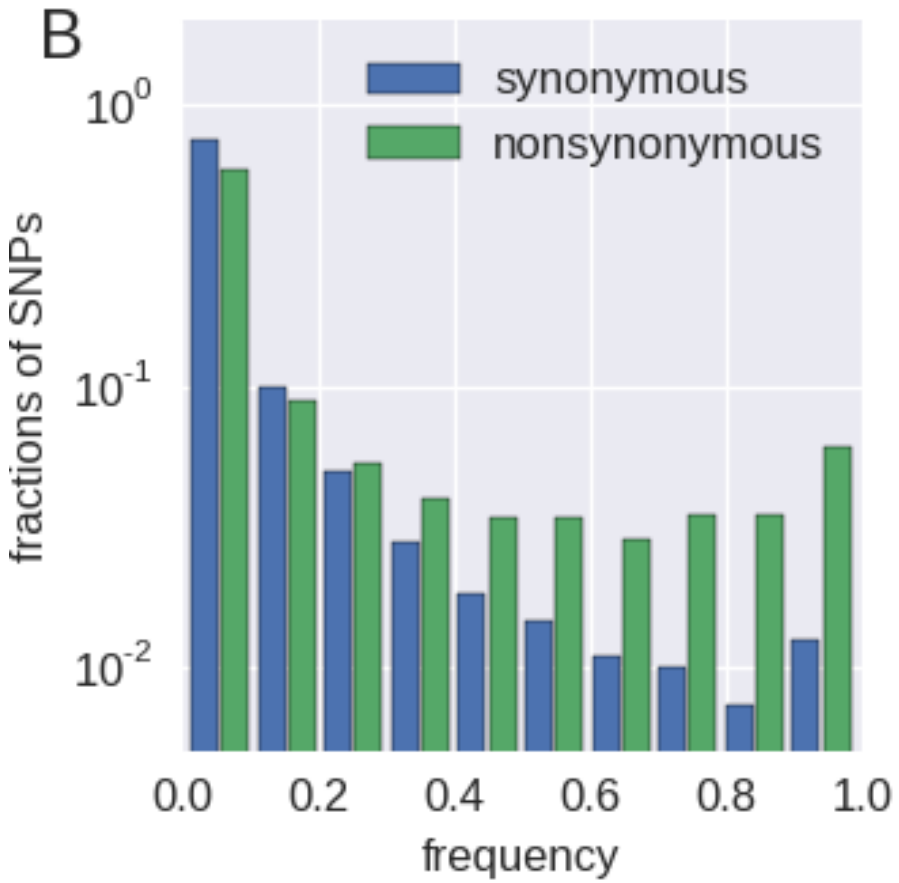
Recombination facilitates adaptation



Constrasting behavior:

- Non-synonymous diversity is low, region specific rate of evolution
- Synonymous diversity keeps increasing, rate is identical across regions
- Synonymous diversity is inversely related to non-synonymous divergence

Recombination facilitates adaptation



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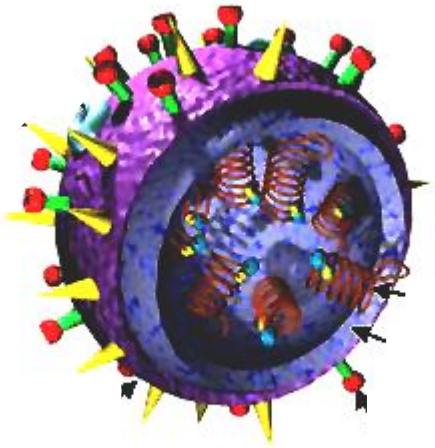
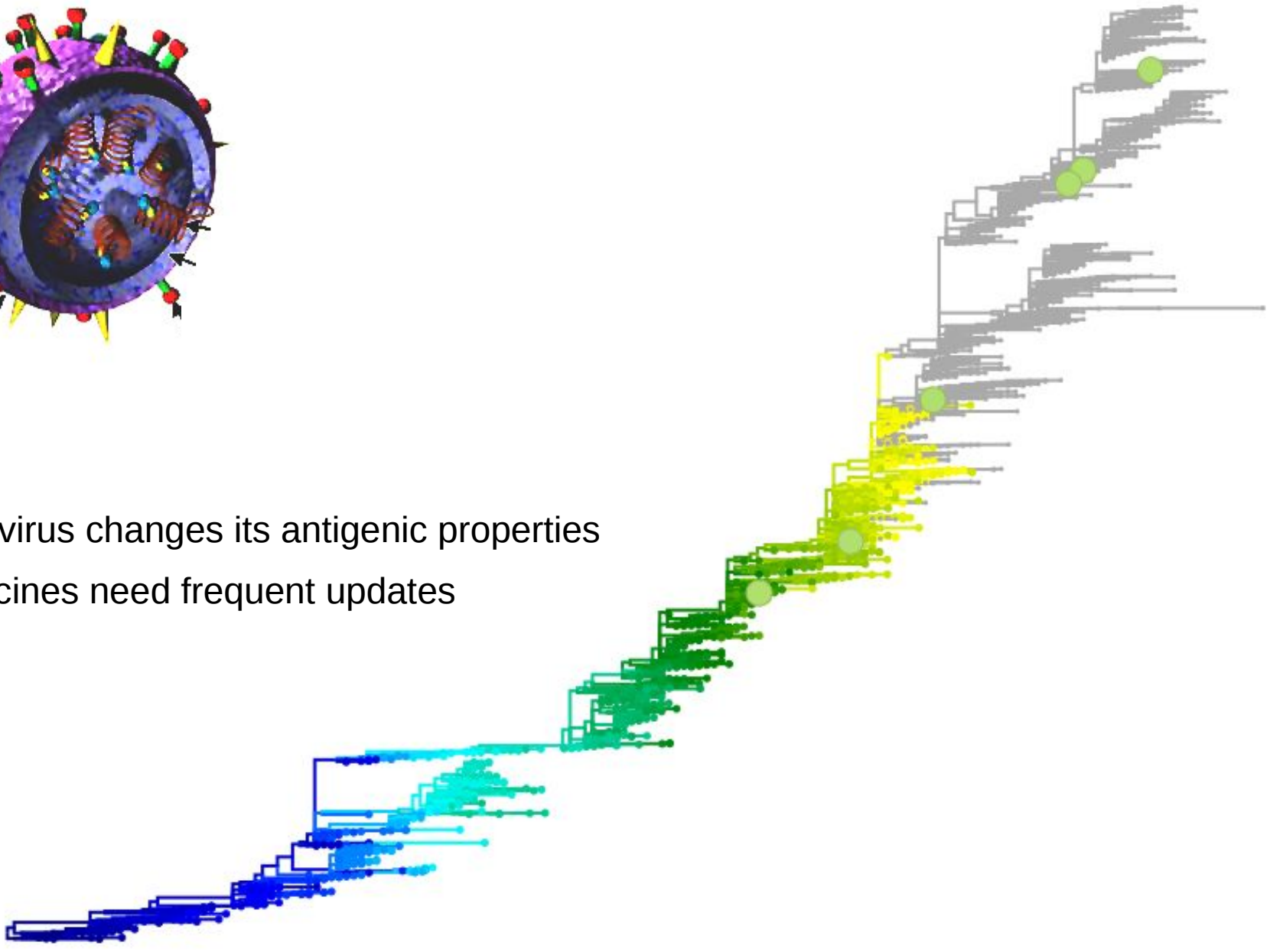
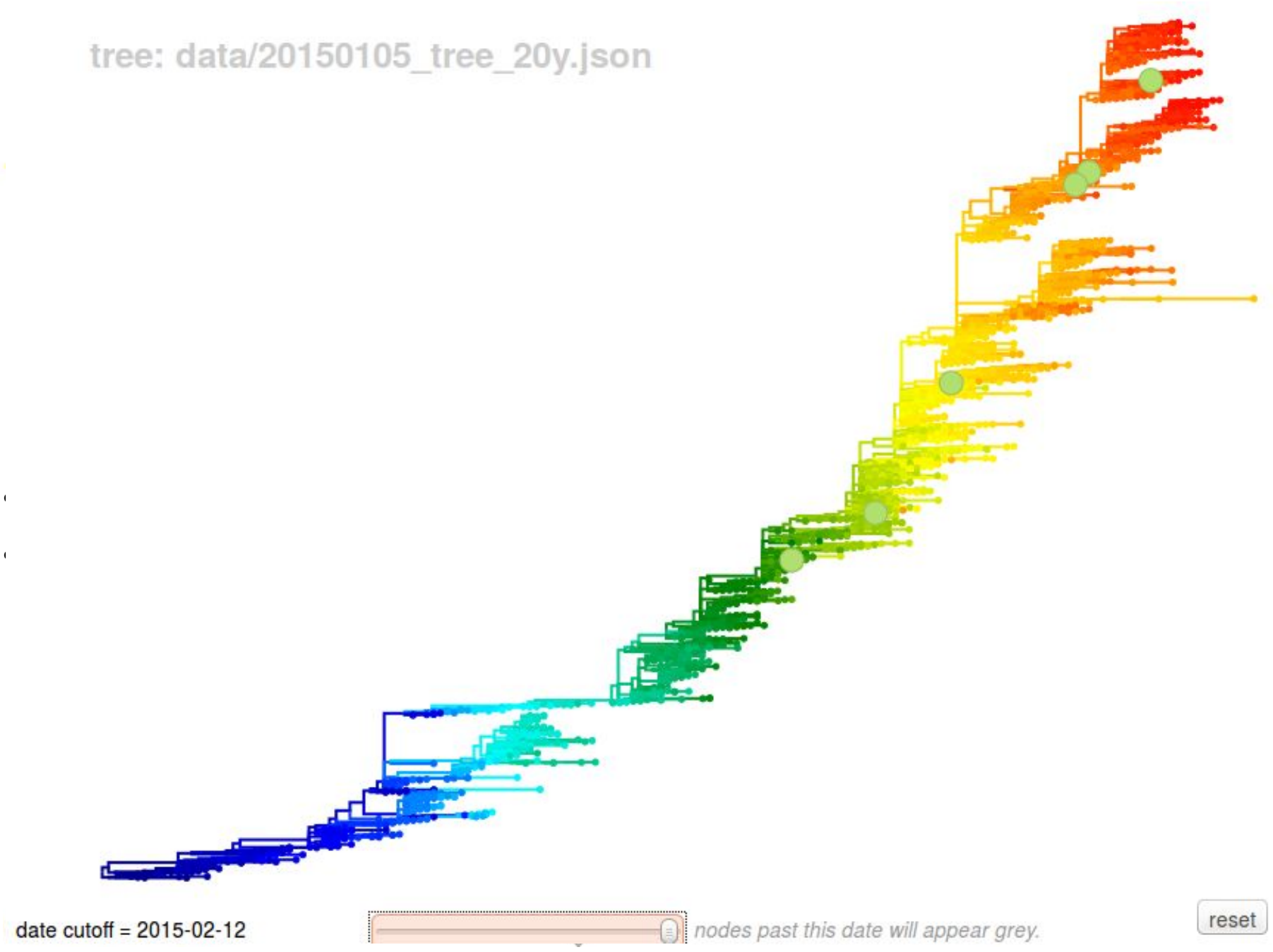
Predicting Influenza evolution?



- the virus changes its antigenic properties
- vaccines need frequent updates



Predicting Influenza evolution?



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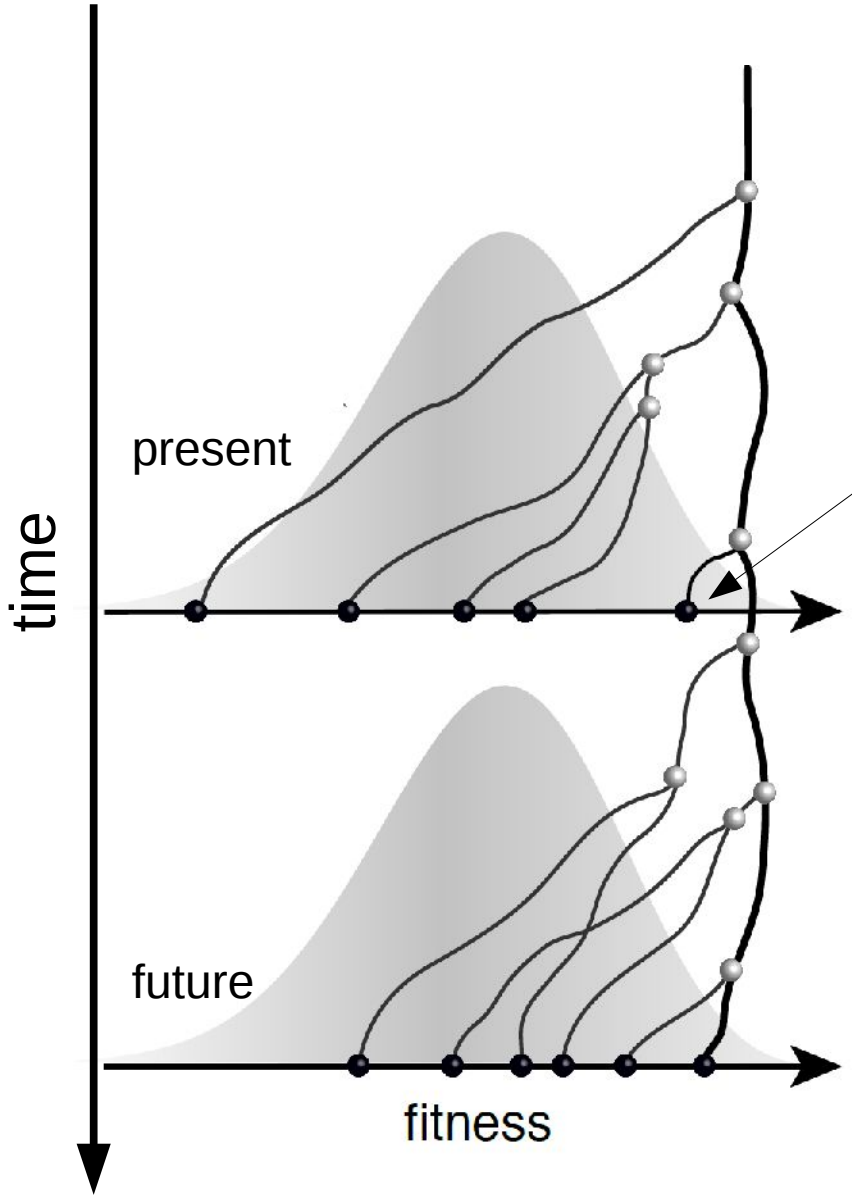
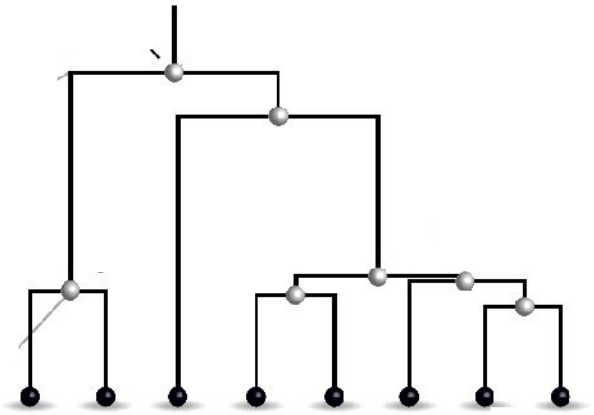


Best pick for new vaccine!

Given the branching pattern, can we

- predict fitness?
- pick the most likely progenitor of the future?

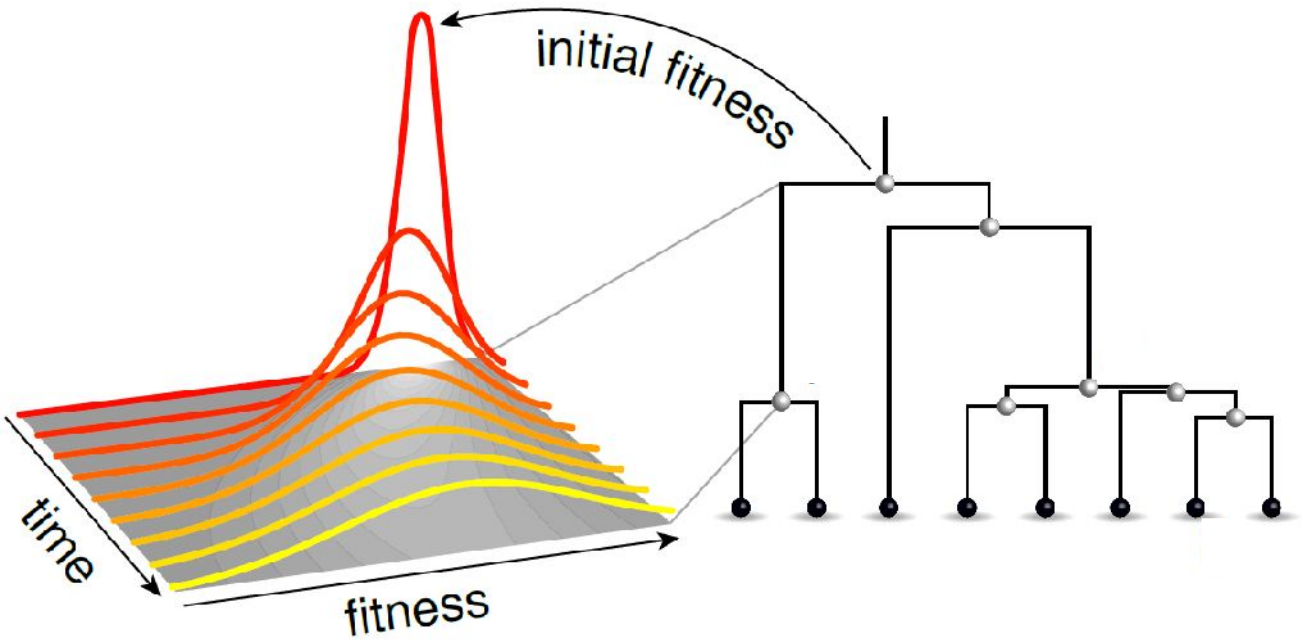
Fitness can be inferred from trees



$$P(\mathbf{x}|T) = \frac{1}{Z(T)} p_0(x_0) \prod_{i=0}^{n_{int}} g(x_{i_1}, t_{i_1}|x_i, t_i) g(x_{i_2}, t_{i_2}|x_i, t_i)$$

RN, Russell, Shraiman. eLife, 2014

Fitness can be inferred from trees



$$P(\mathbf{x}|T) = \frac{1}{Z(T)} p_0(x_0) \prod_{i=0}^{n_{int}} g(x_{i_1}, t_{i_1}|x_i, t_i) g(x_{i_2}, t_{i_2}|x_i, t_i)$$

$$\partial_t g(x, t'|y, t) = [y - 2\phi_\omega(y, t)] g(x, t'|y, t) - \sigma^2 \partial_y g(x, t'|y, t) + D\partial_y^2 g(x, t'|y, t)$$

RN, Russell, Shraiman. eLife, 2014

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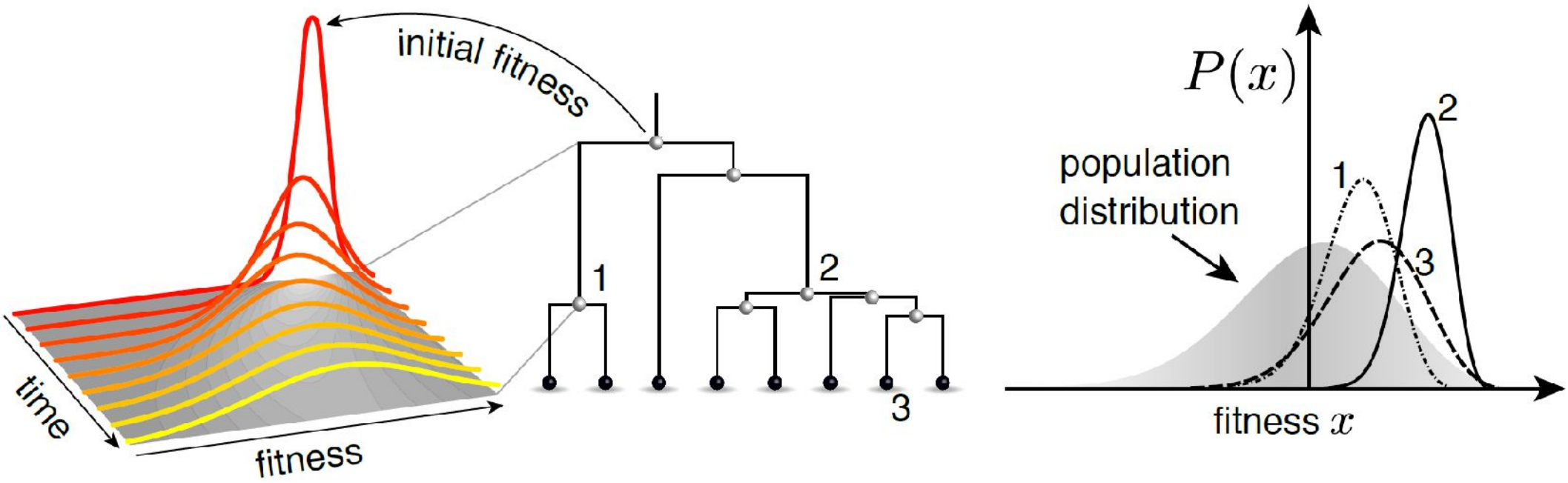

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RN, Russell, Shraiman. eLife, 2014

High fitness corresponds to local bursts

At short times: $\int dx\, g(x,t|y,t') \sim e^{y(t-t')}$

→ the product of propagators and prior: $\sim e^{yT-y^2/2}$

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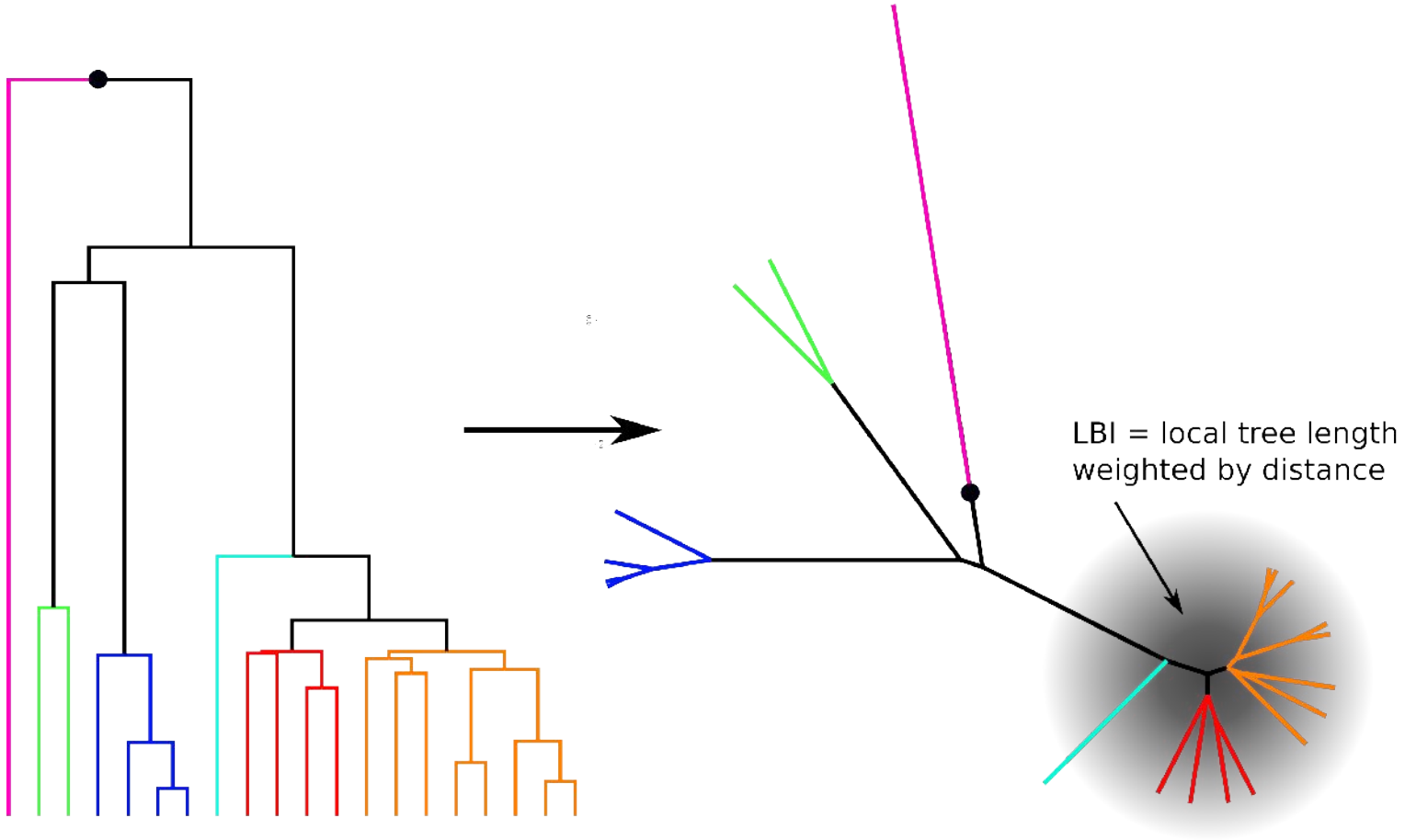
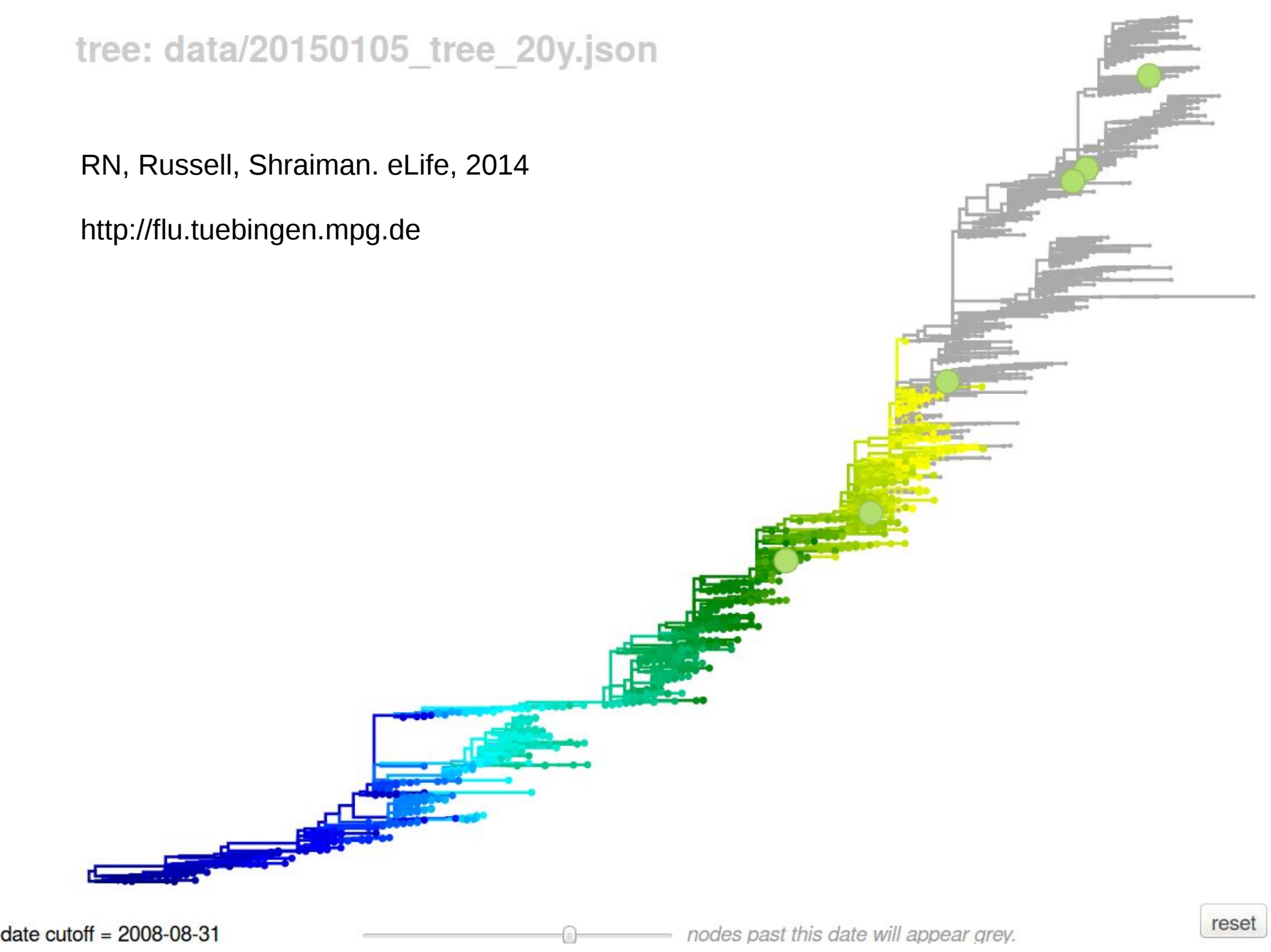
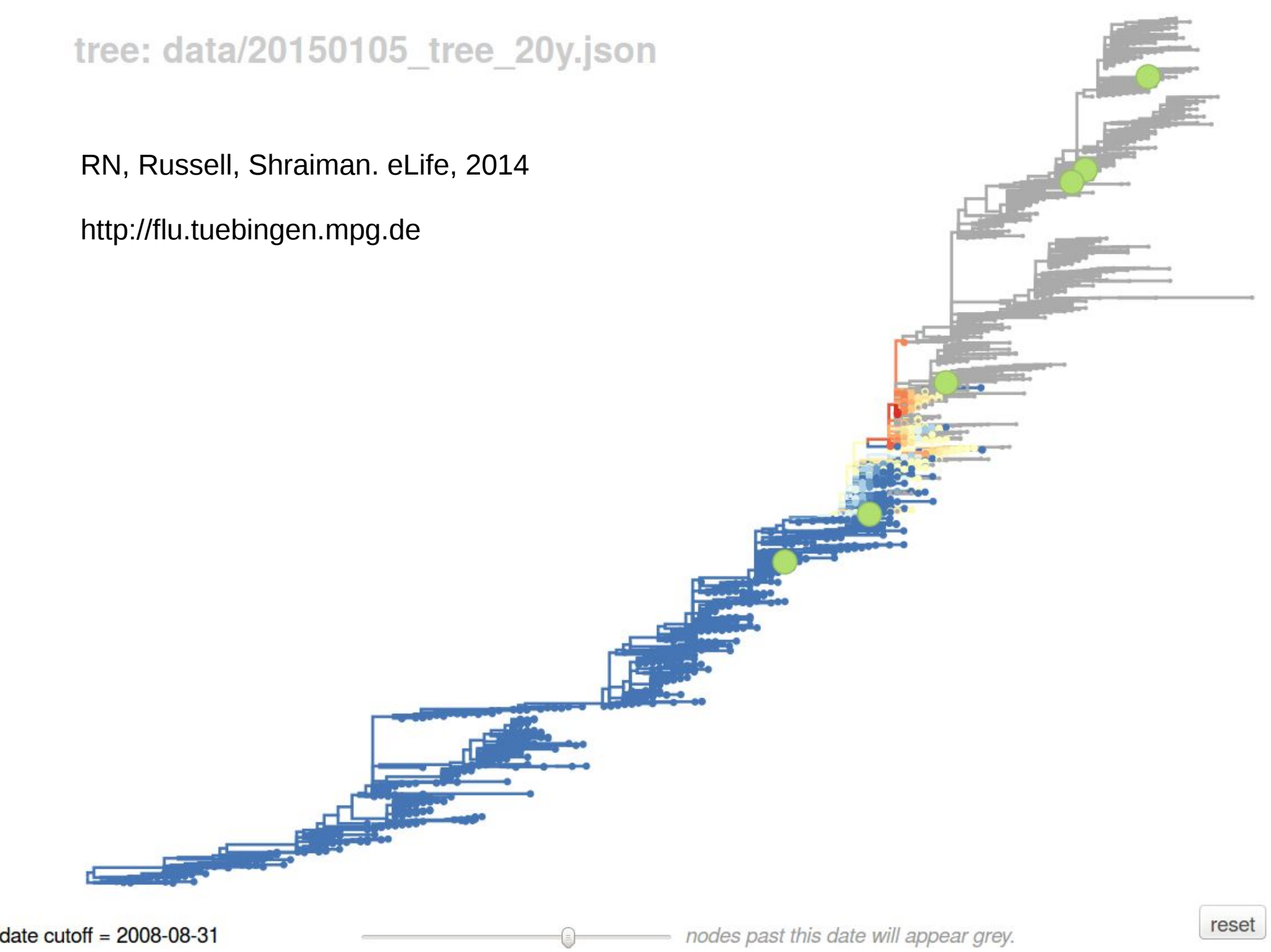



tree: data/20150105_tree_20y.json
RN, Russell, Shraiman. eLife, 2014
http://flu.tuebingen.mpg.de
date cutoff = 2008-08-31
nodes past this date will appear grey.
reset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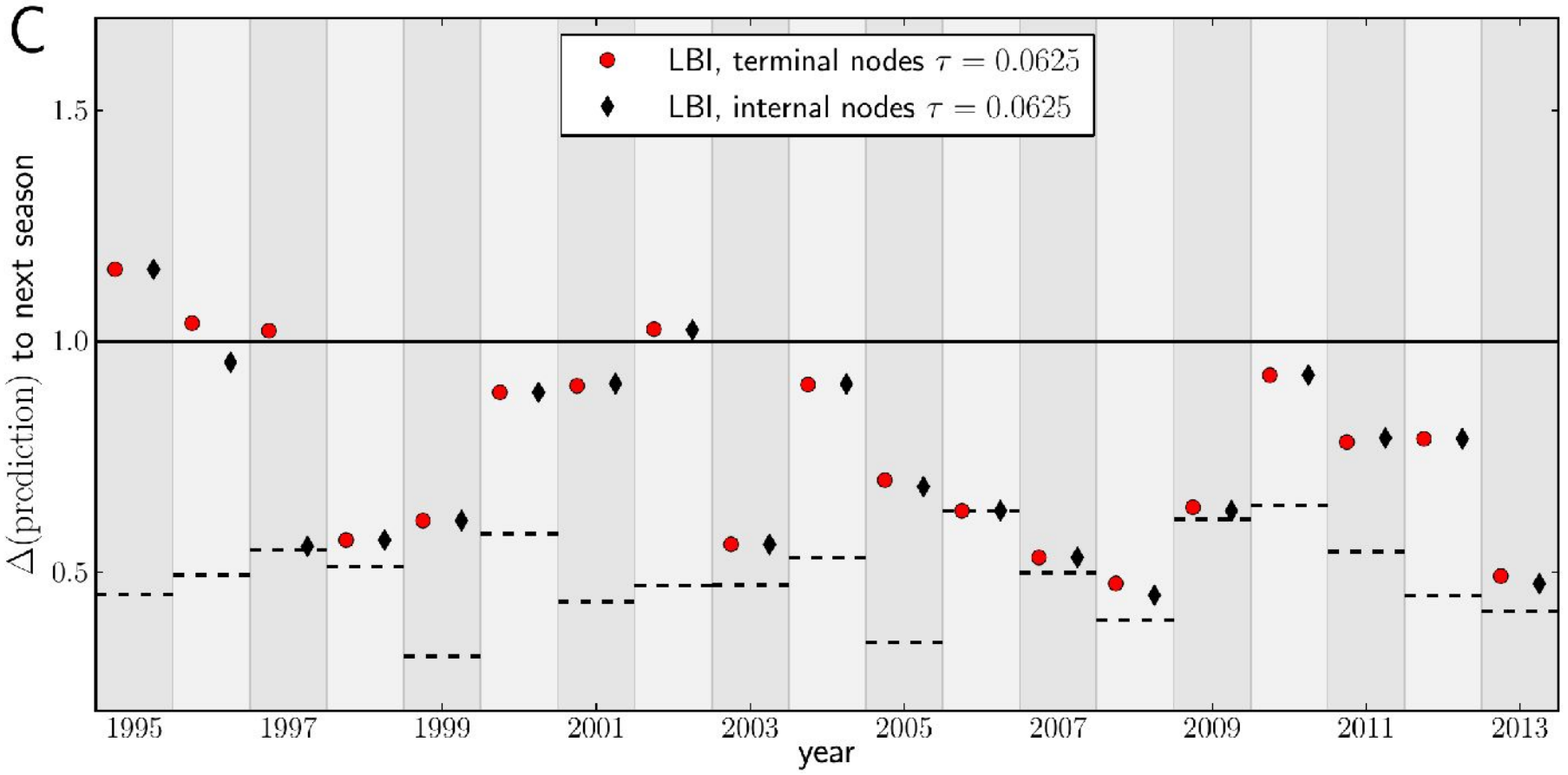
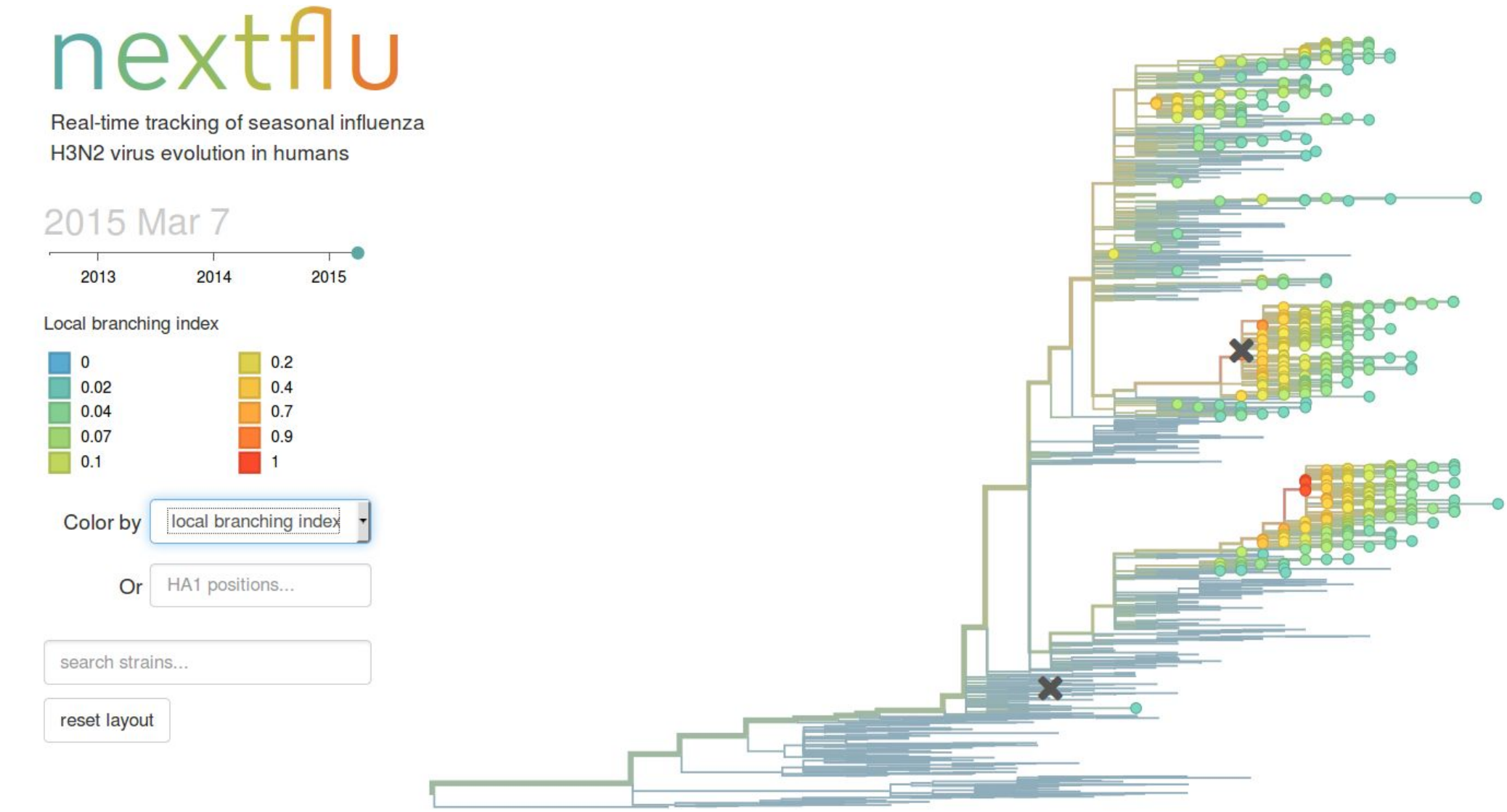
Past evolution of influenza A/H3N2 is predictable



- requires only tree as input: generally applicable
  - → emerging diseases
  - → cancer cell populations



with Trevor Bedford, available at nextflu.org

nextflu

Real-time tracking of seasonal influenza
H3N2 virus evolution in humans

2015 Mar 7

2013 2014 2015

Local branching index

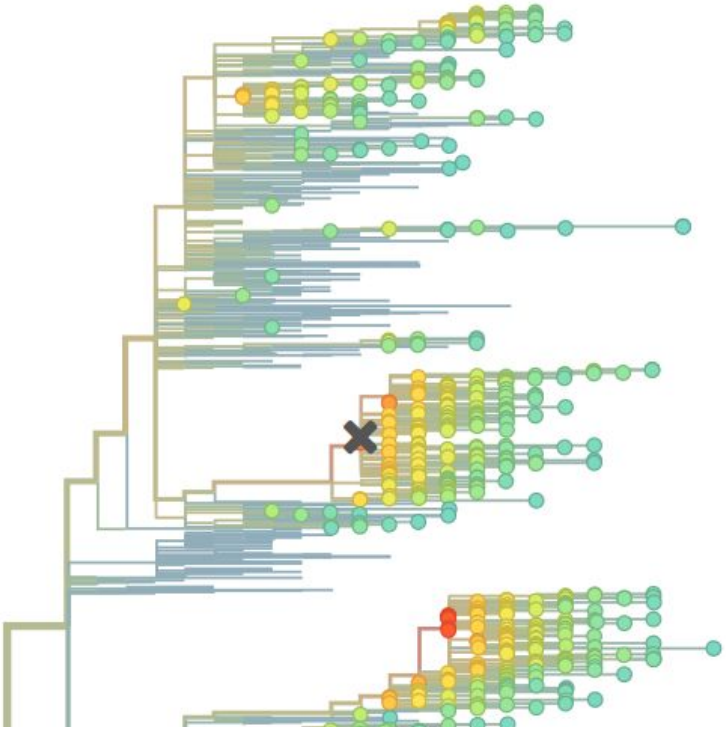
0 0.2
0.02 0.4
0.04 0.7
0.07 0.9
0.1 1

Color by: local branching index

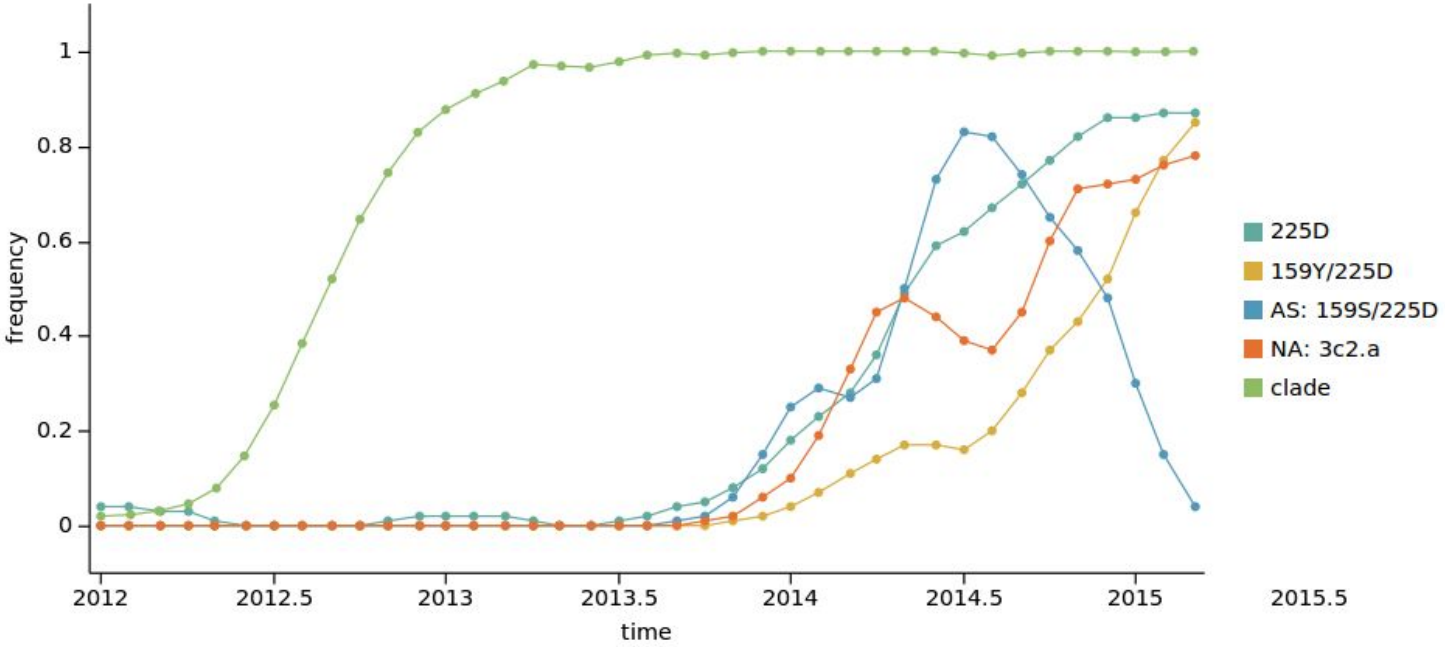
Or: HA1 positions...

search strains...

reset layout

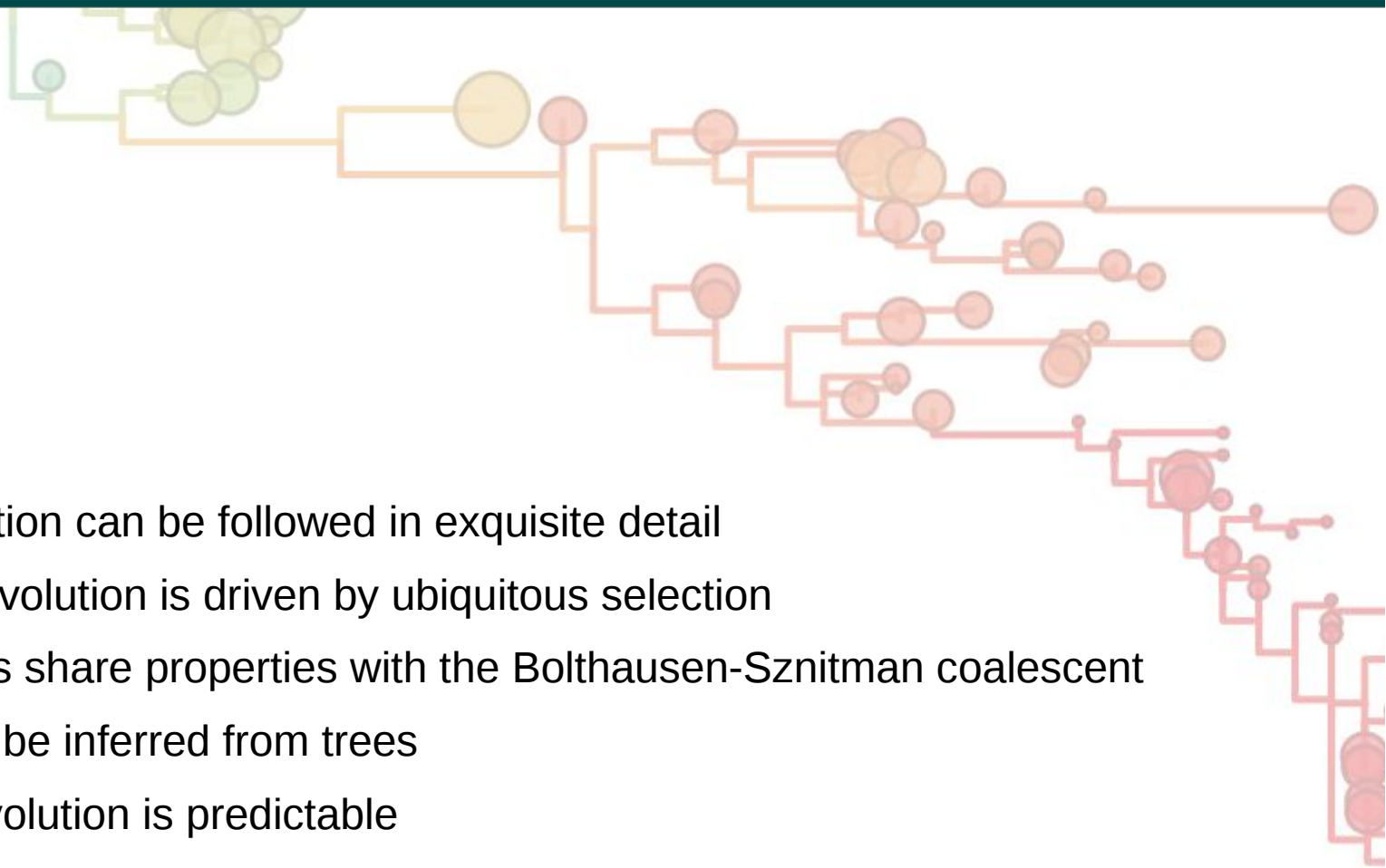


Mutation and clade frequencies



with Trevor Bedford, available at nextflu.org

Summary



- HIV-1 evolution can be followed in exquisite detail
- RNA virus evolution is driven by ubiquitous selection
- Genealogies share properties with the Bolthausen-Sznitman coalescent
- Fitness can be inferred from trees
- Influenza evolution is predictable
- Browser-based tools to integrate information

Acknowledgements – HIV

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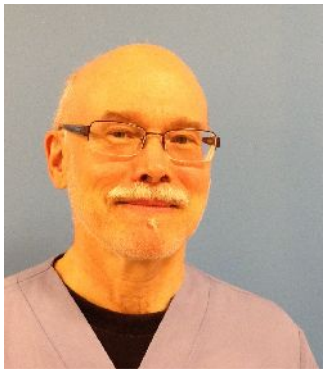
MPI

Johanna Brodin
KI



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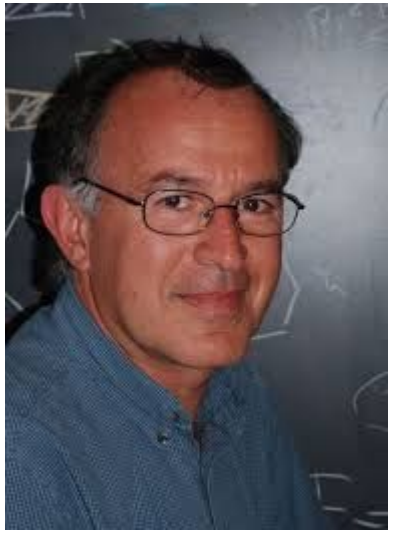
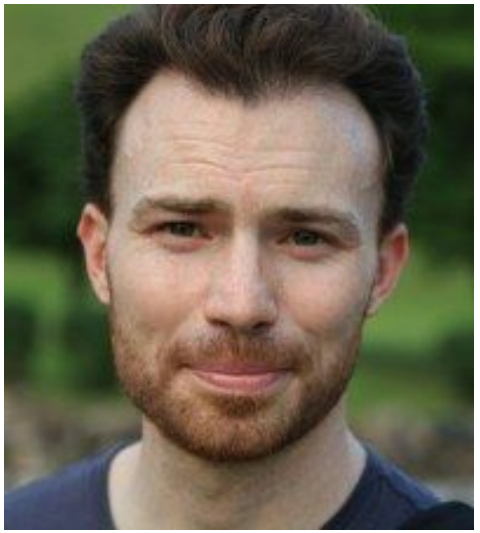
Acknowledgements – Theory and Influenza



Boris Shraiman

Oskar Hallatschek



Colin Russell

Trevor Bedford

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