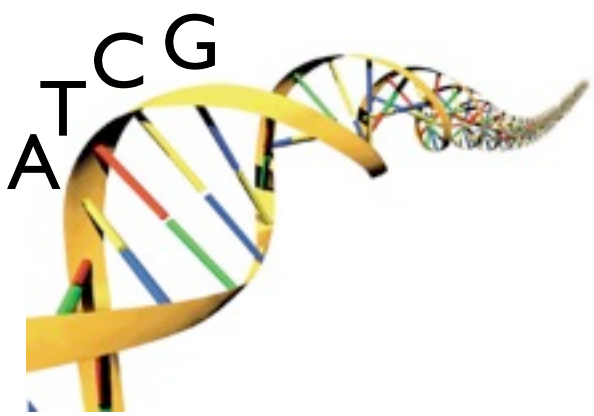
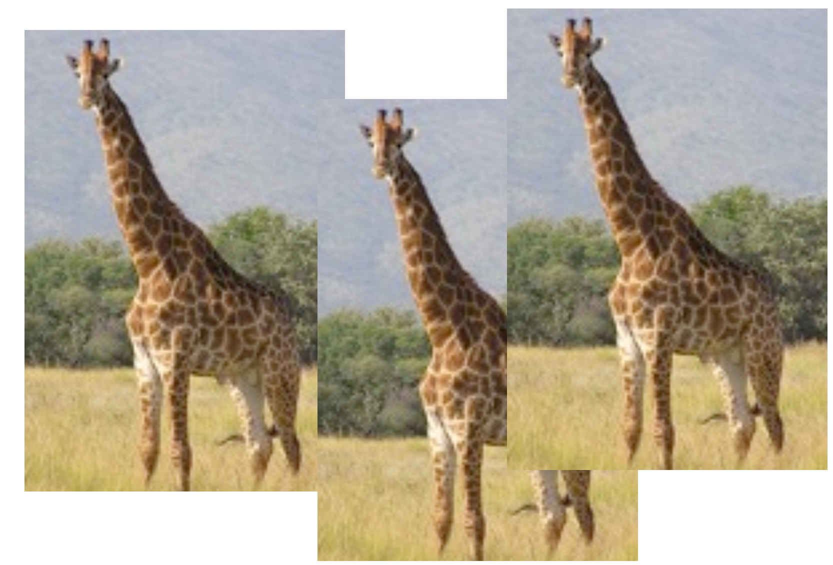
Watching evolution happen

Cartoon of Evolution



Genotypes

Selection



Mutation & Recombination

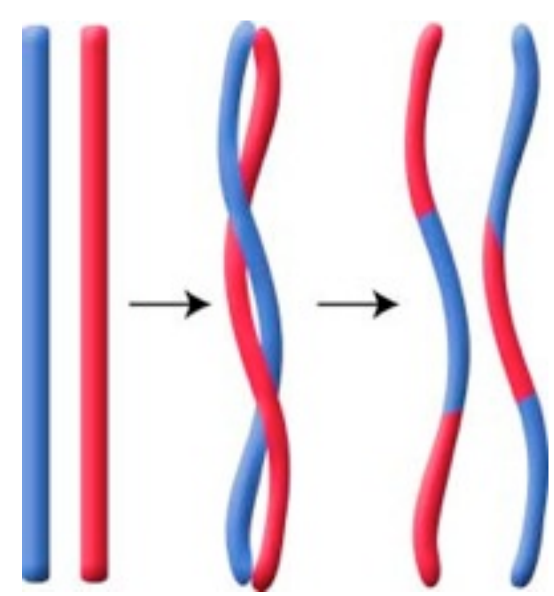
Mutation

...ATACG...

↓

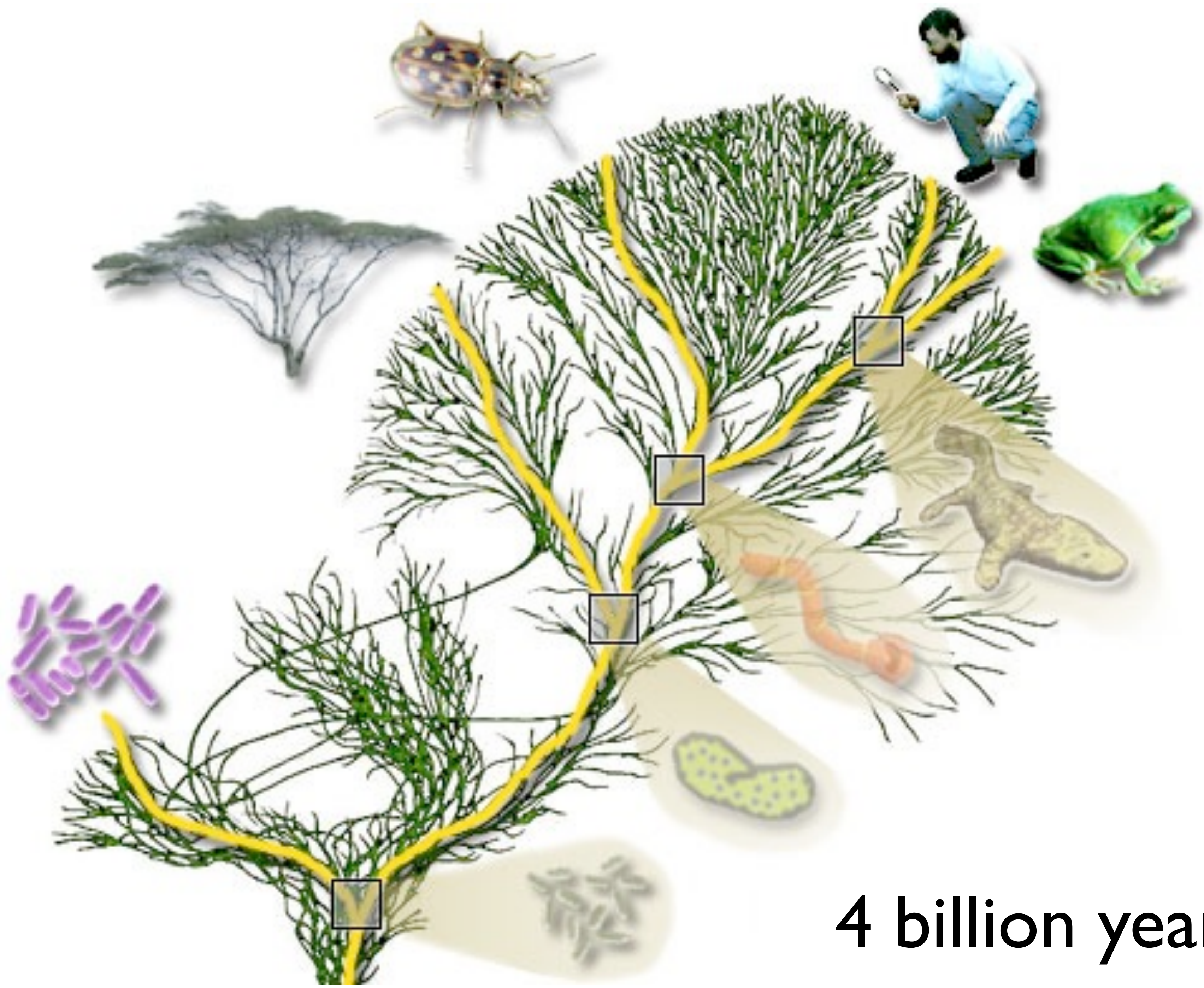
...ATGCG...

Sex & Recombination



Selection

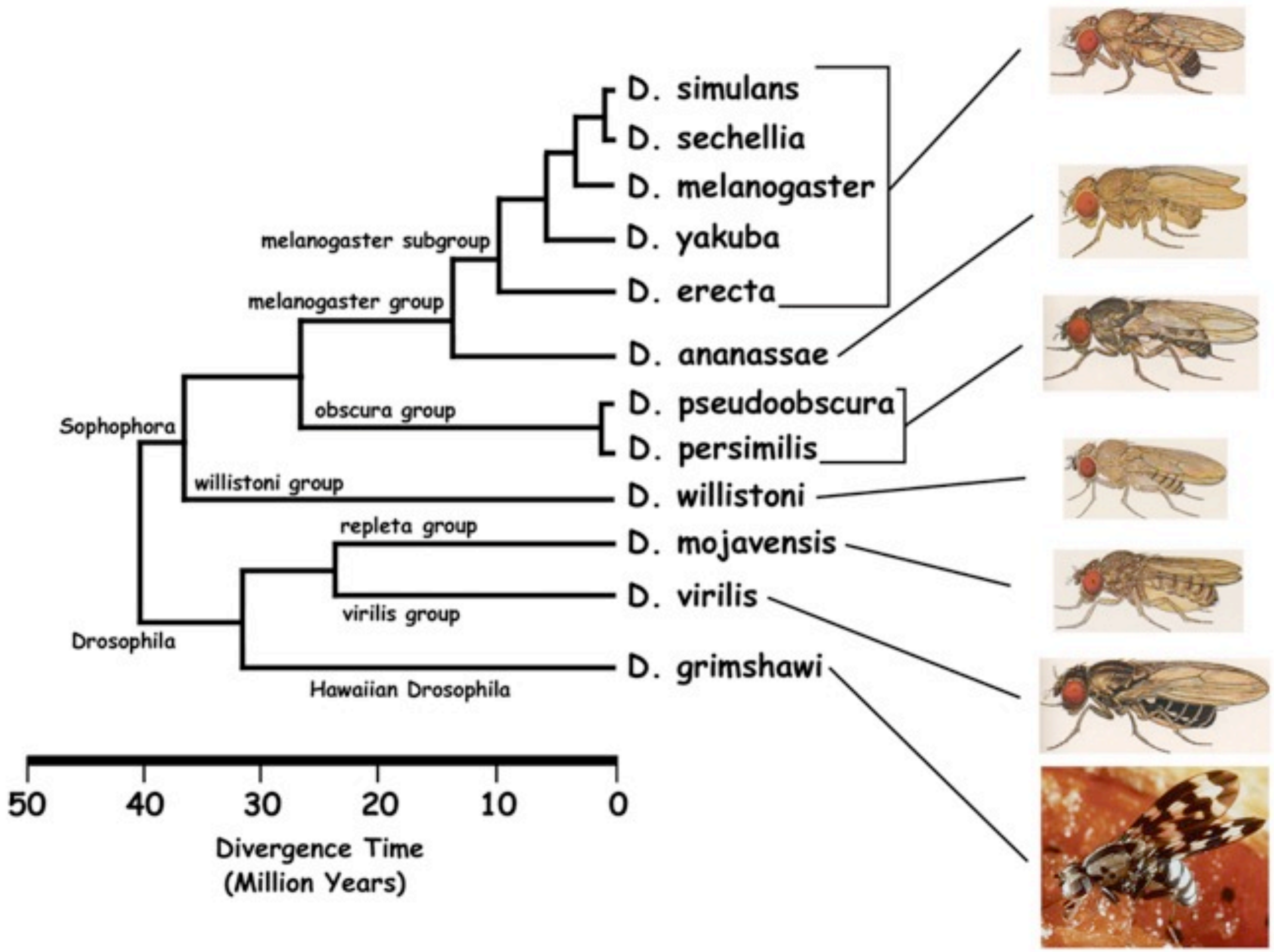
Tree of Life – billions of years



4 billion years

source: tree of life, tolweb.org

Phylogenetic tree of fruit flies – millions of years

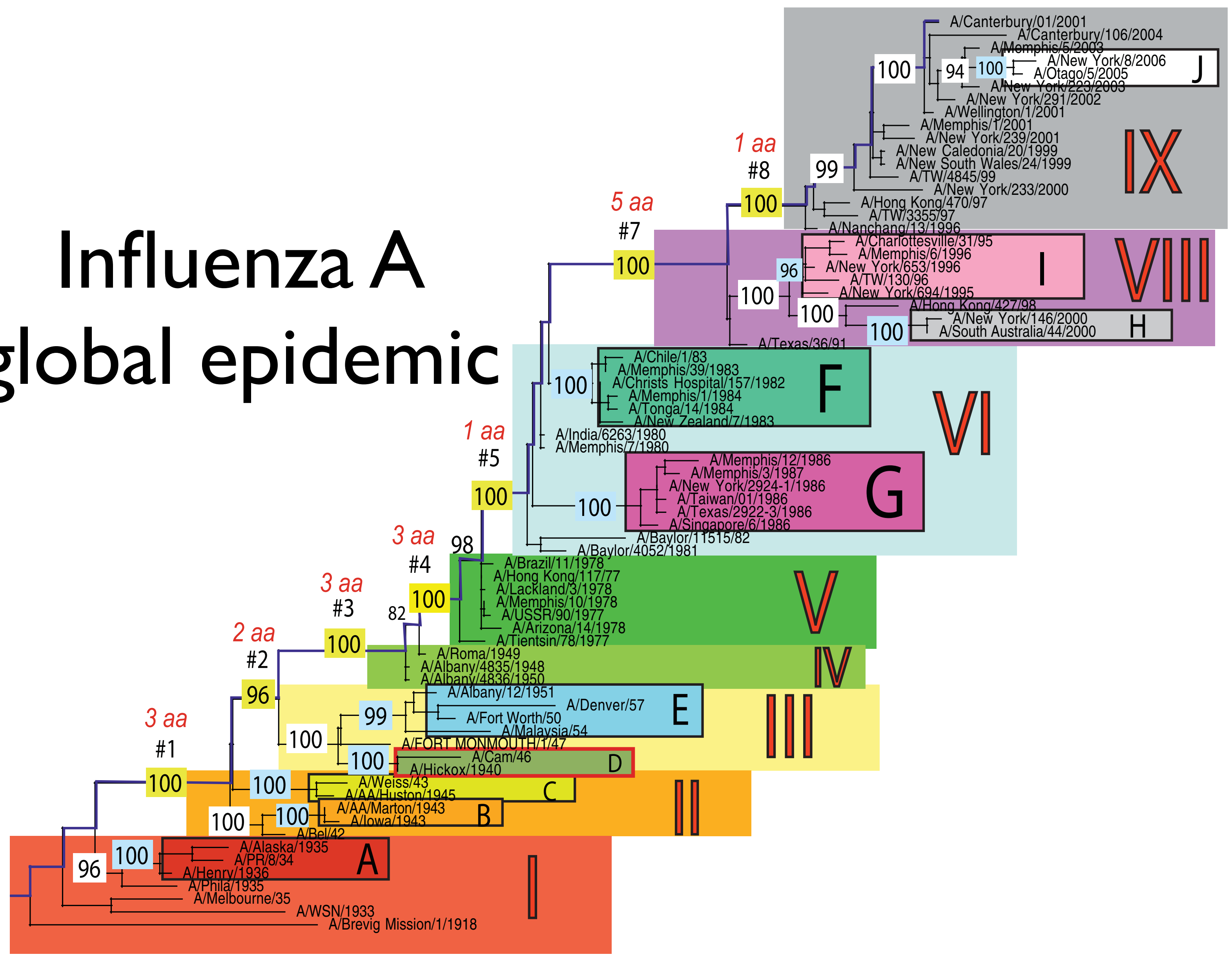


~40 Millions of years

image from: insects.eugenes.org/species/

Evolution of Influenza A – few years

Influenza A
global epidemic

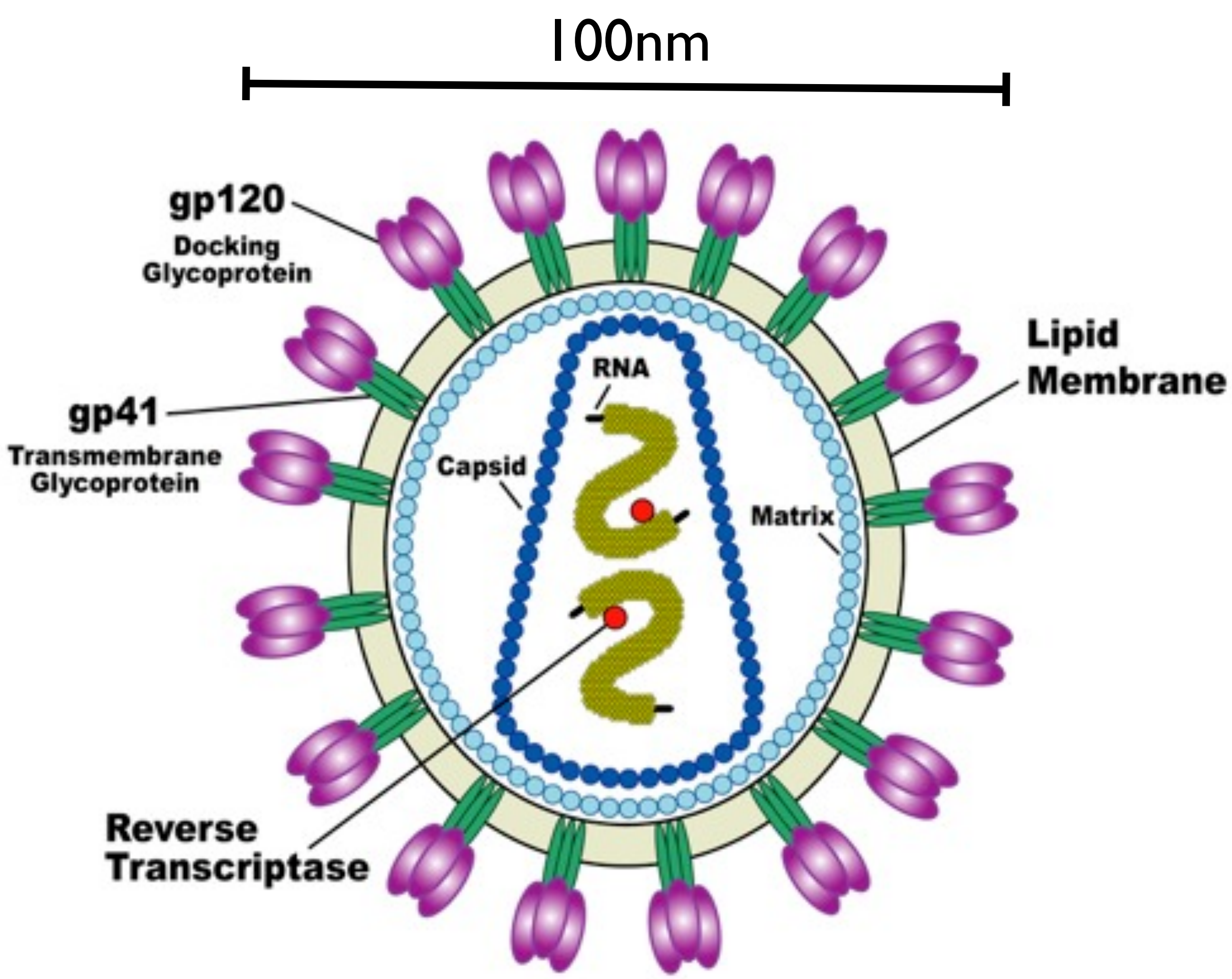


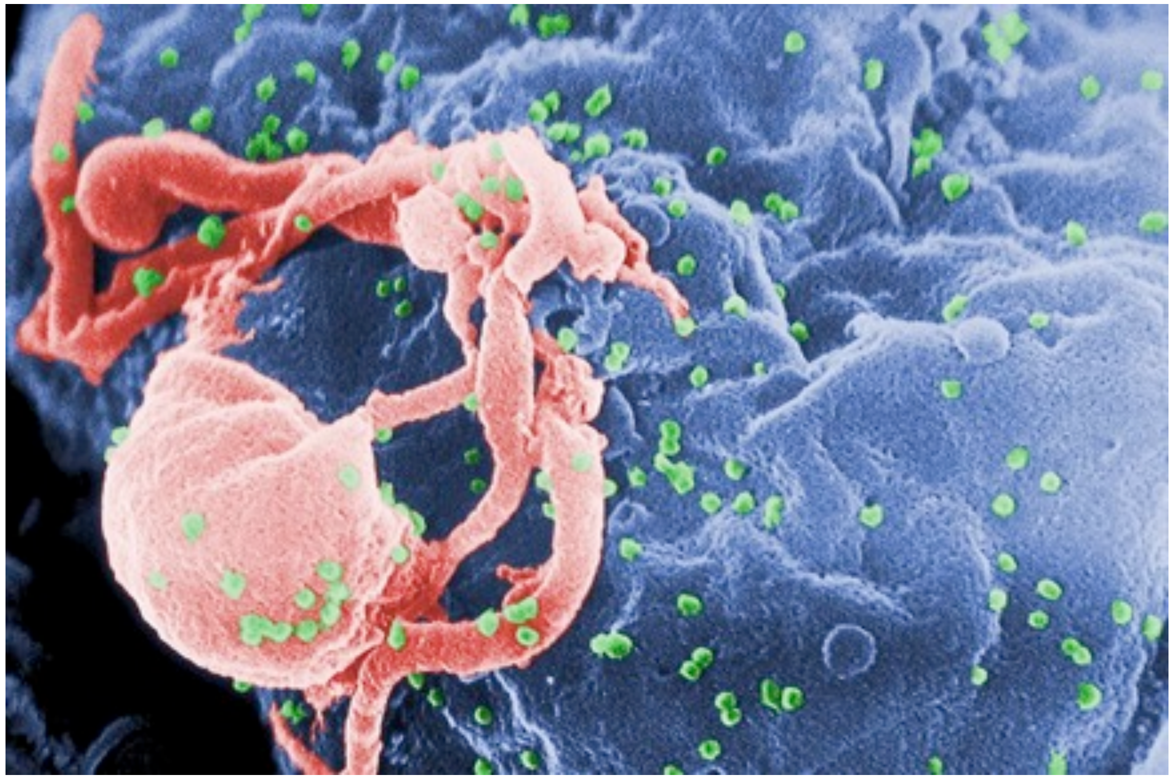
1918 ⟶ 2005

Evolution as cause of epidemics

Nelson et al., 2008

Human immunodeficiency virus (HIV)



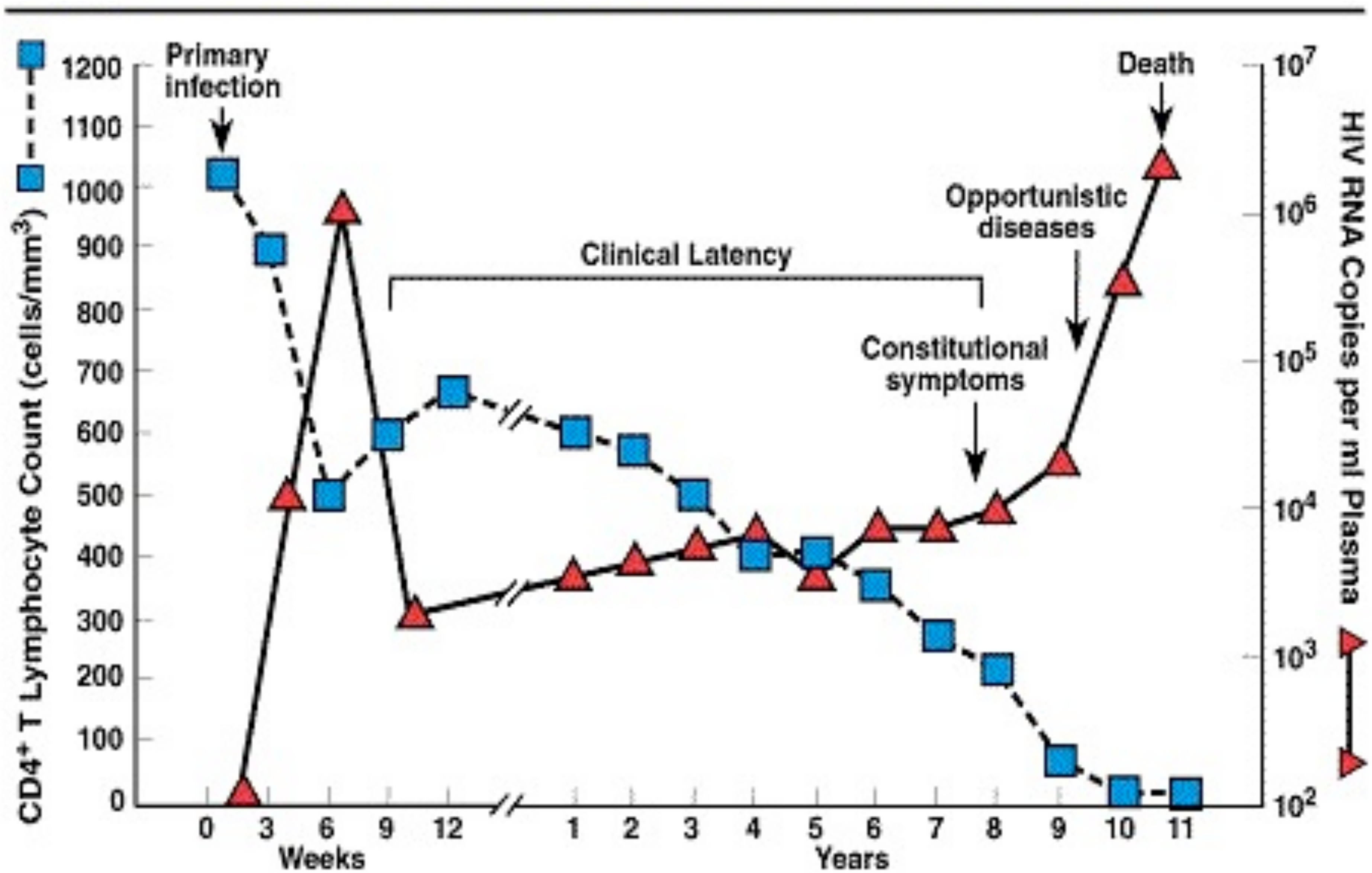


HIV budding from an immune cell

Rapid evolution is a hallmark of HIV infections

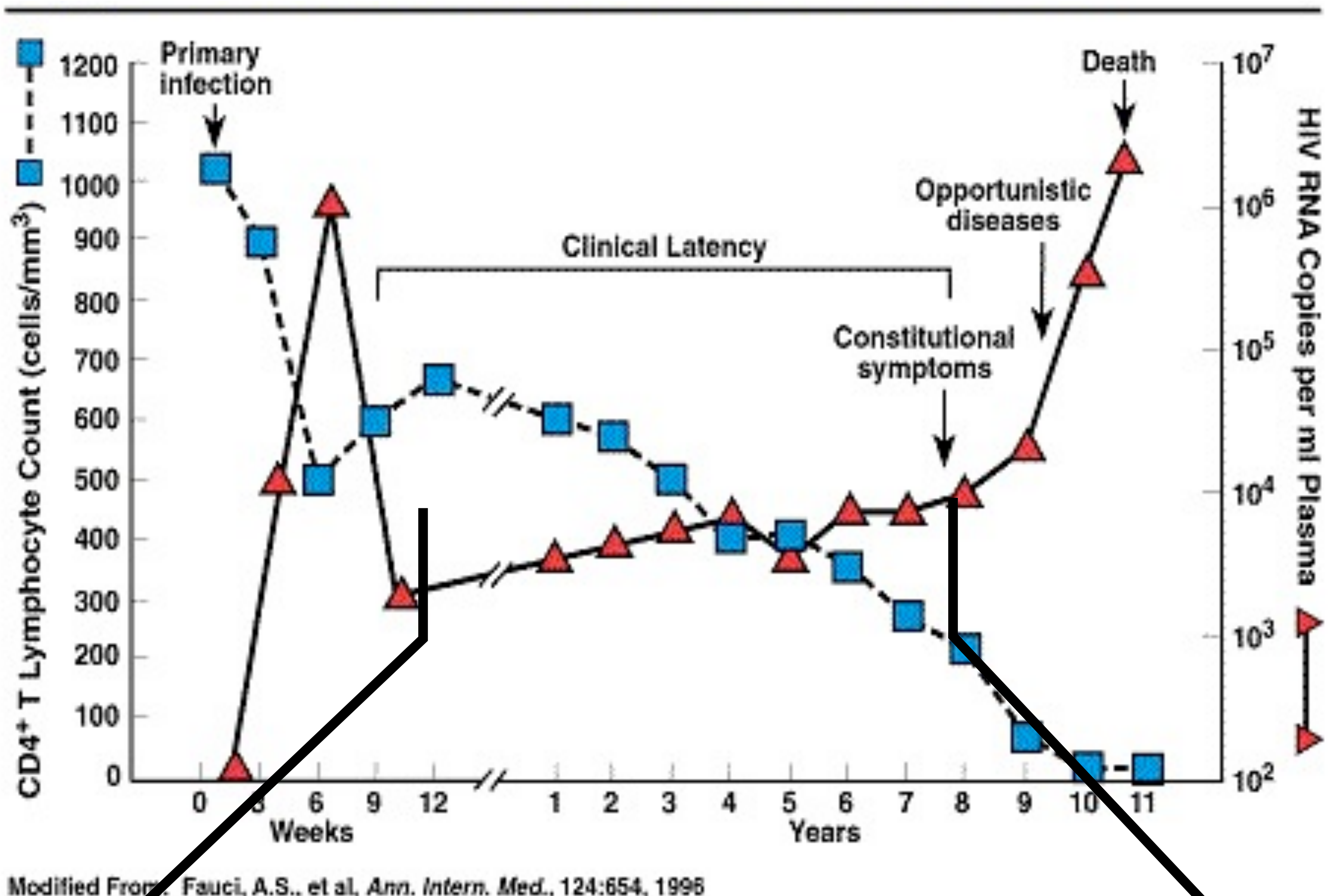
Images: Wikipedia, CDC

HIV disease progression



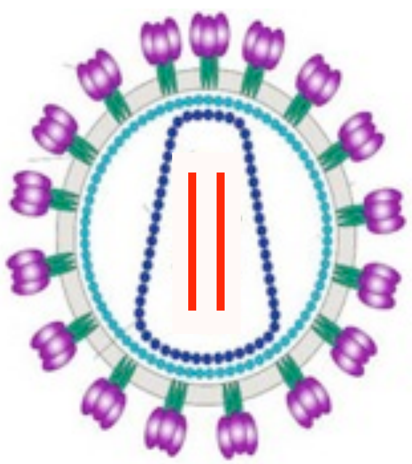
Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

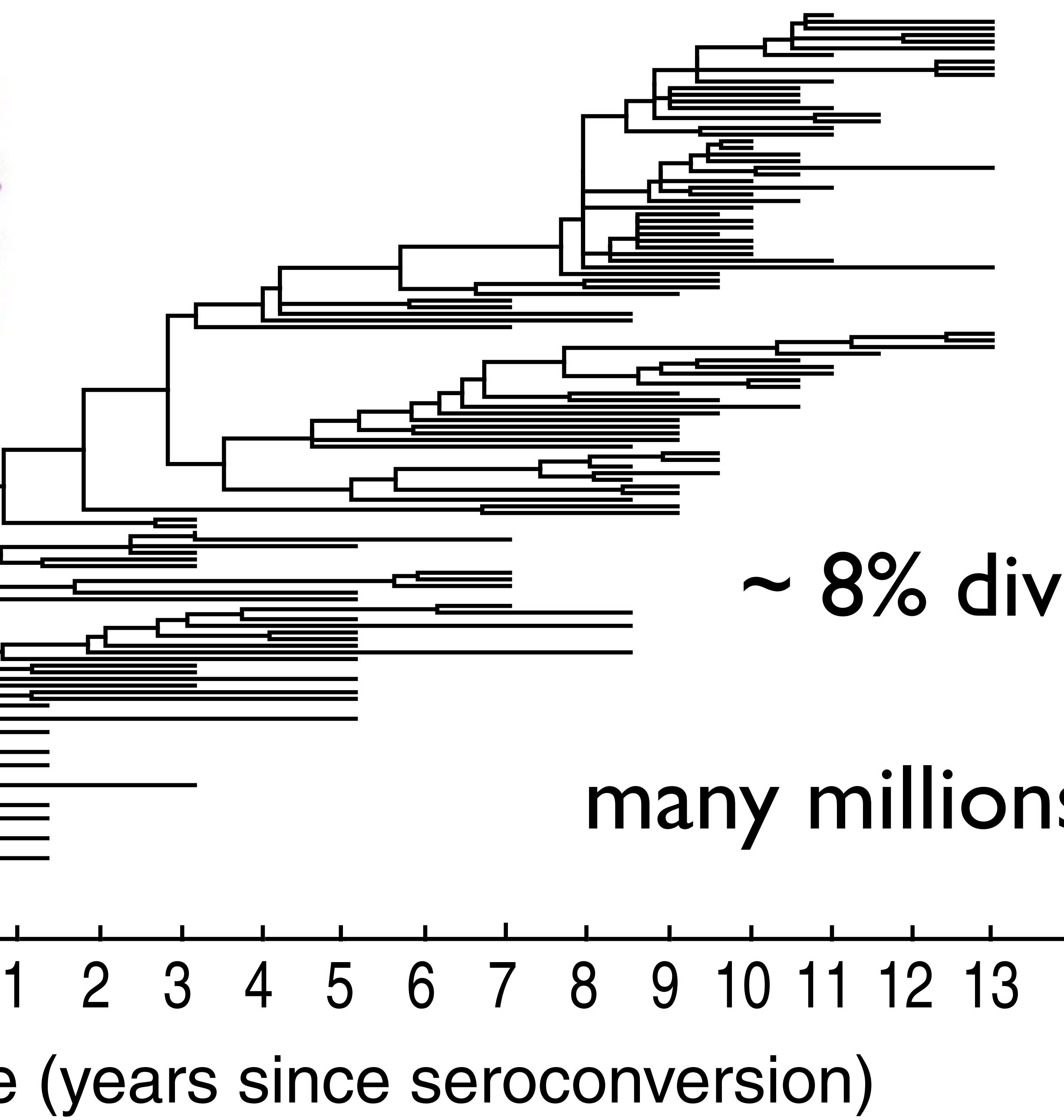
HIV disease progression



Virus escapes the immune system
by continuous evolution

Evolution in a single patient





~ 8% divergence in 10 years

==

many millions of years in Drosophila

Lemey et al., 2006,
Shankarappa et al. 1999

Evolution of HIV

MAX-PLANCK-GESELLSCHAFT

The virus has to change: Escape the immune system and drug resistance

Resistance to drugs (protease inhibitors):

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLN
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTLN
```

Evolution of HIV

The virus has to change: Escape the immune system and drug resistance

Resistance to drugs (protease inhibitors):

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLN
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTLN
```

High mutation rate:
$\mu=3\times10^{-5}$/generation and site

Evolution of HIV

The virus has to change: Escape the immune system and drug resistance

Resistance to drugs (protease inhibitors):

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLN
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTLN
```

High mutation rate:
$\mu = 3 \times 10^{-5}$/generation and site

Large population:
$N = 10^{10}$ viruses

Evolution of HIV

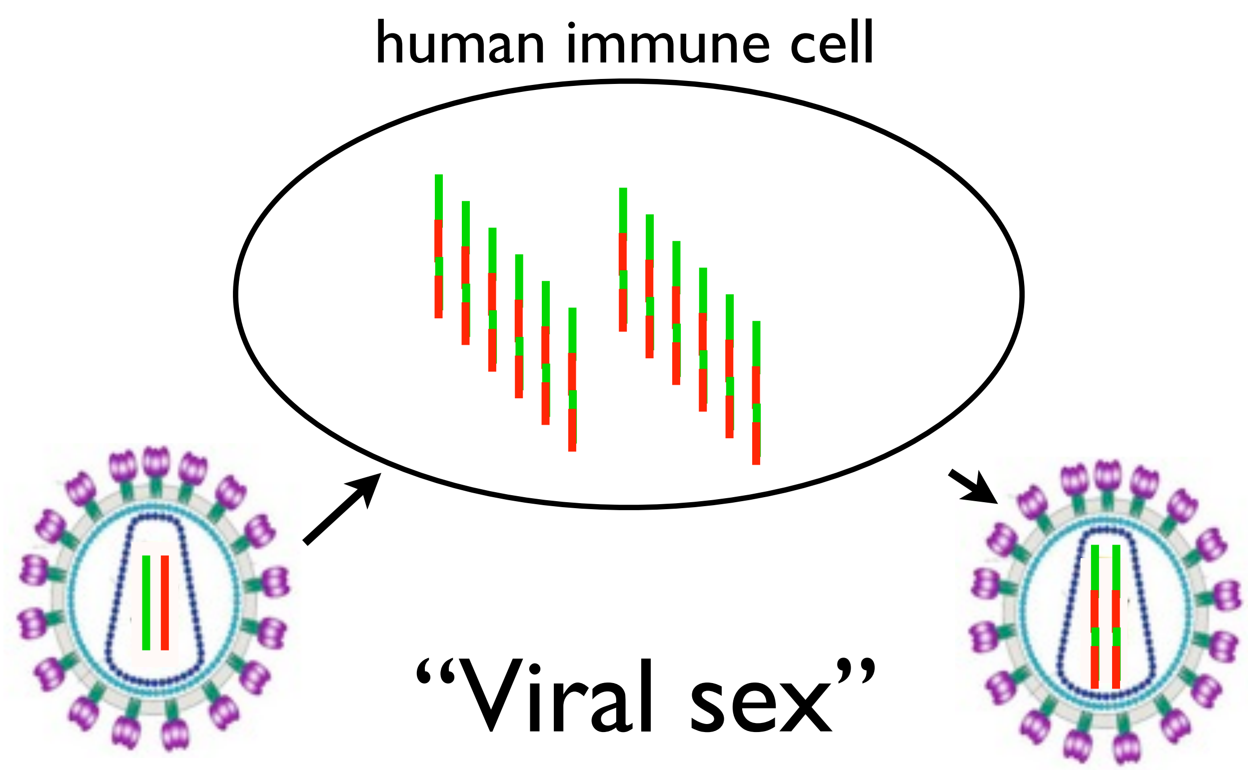
The virus has to change: Escape the immune system and drug resistance

Resistance to drugs (protease inhibitors):

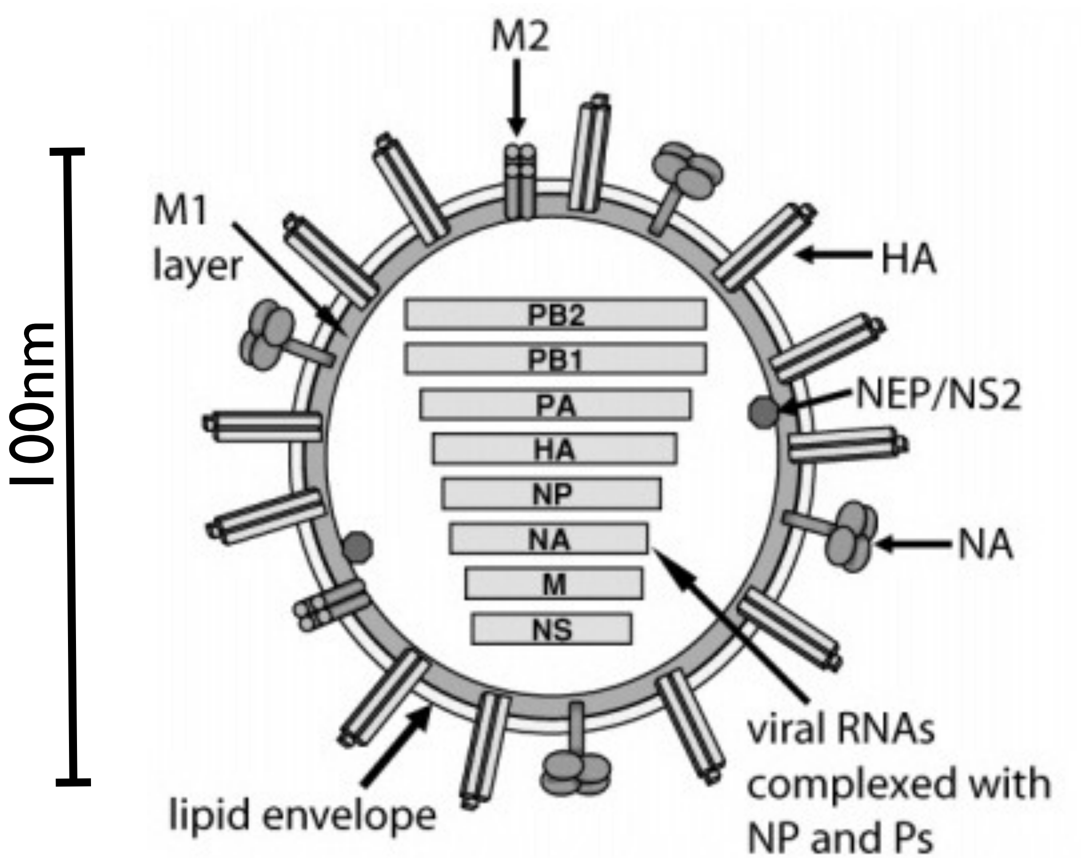
```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLN
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTLN
```

High mutation rate:
$\mu = 3 \times 10^{-5}$/generation and site

Large population:
$N = 10^{10}$ viruses

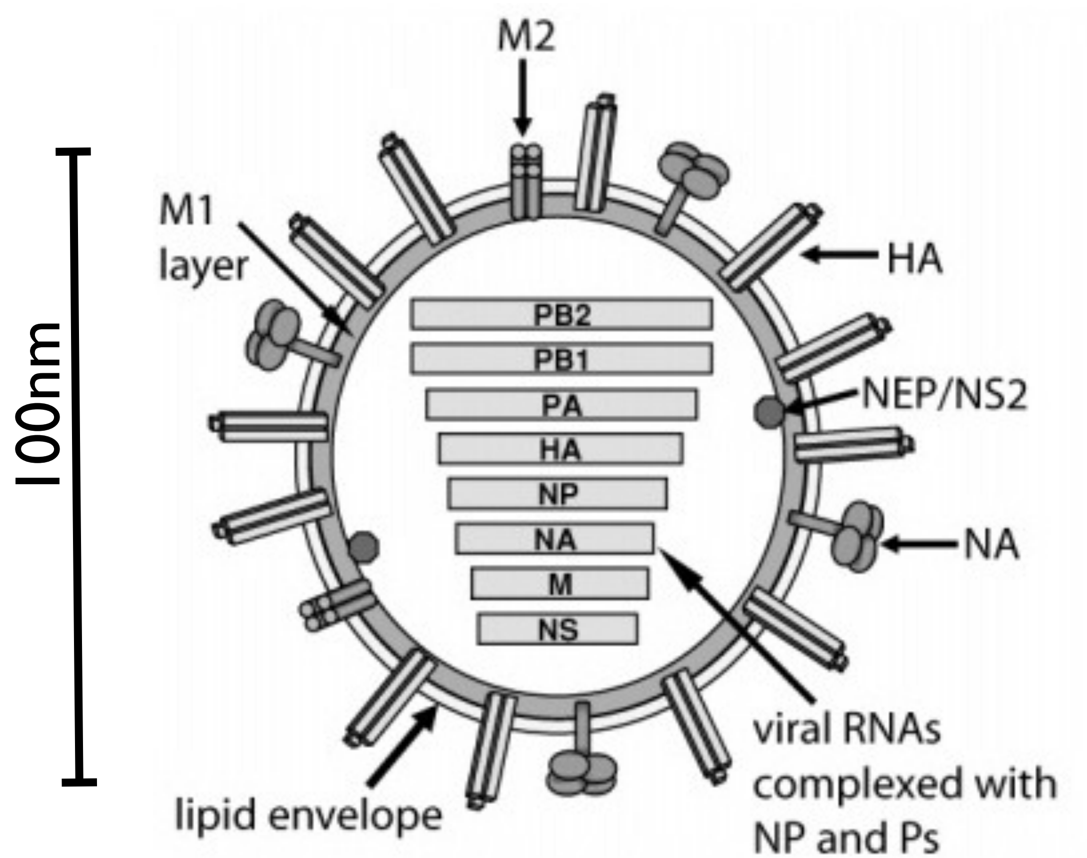


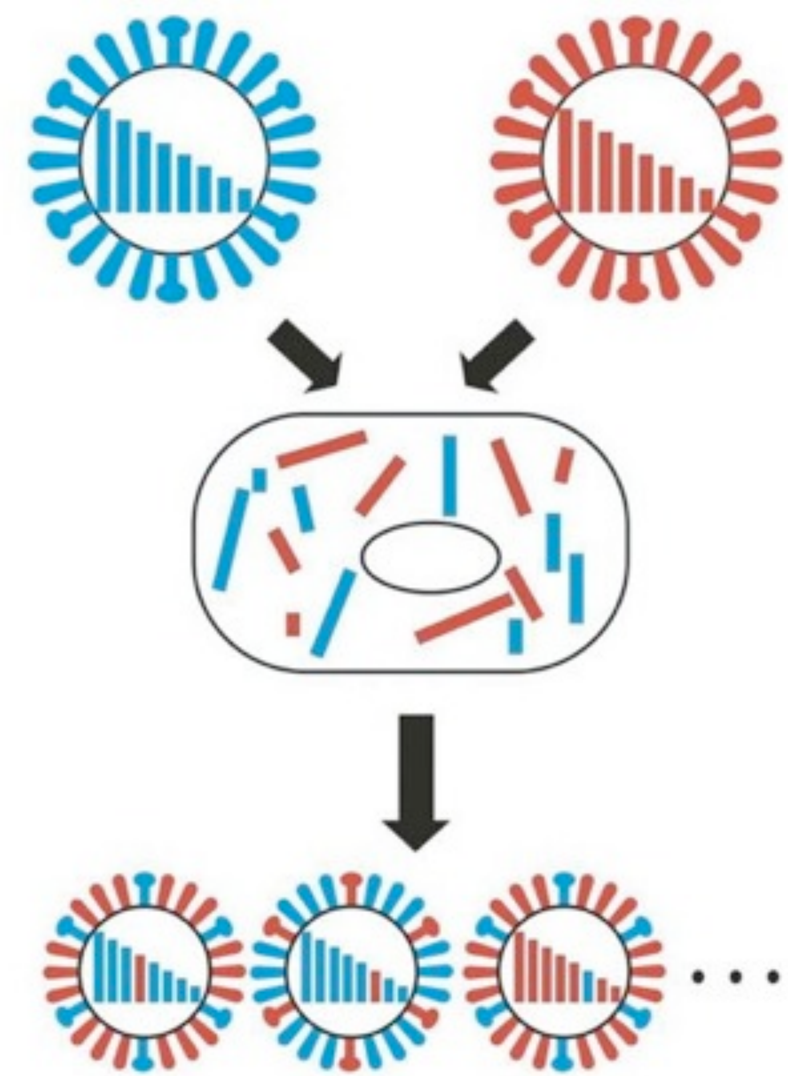
Recombination in viruses – Influenza



- 11 genes on 8 segments
- 16 H (hemagglutinin) subtypes
- 9 N (neuraminidase) subtypes
- H1N1, H2N2, H3N2, H5N1 are common

Recombination in viruses – Influenza

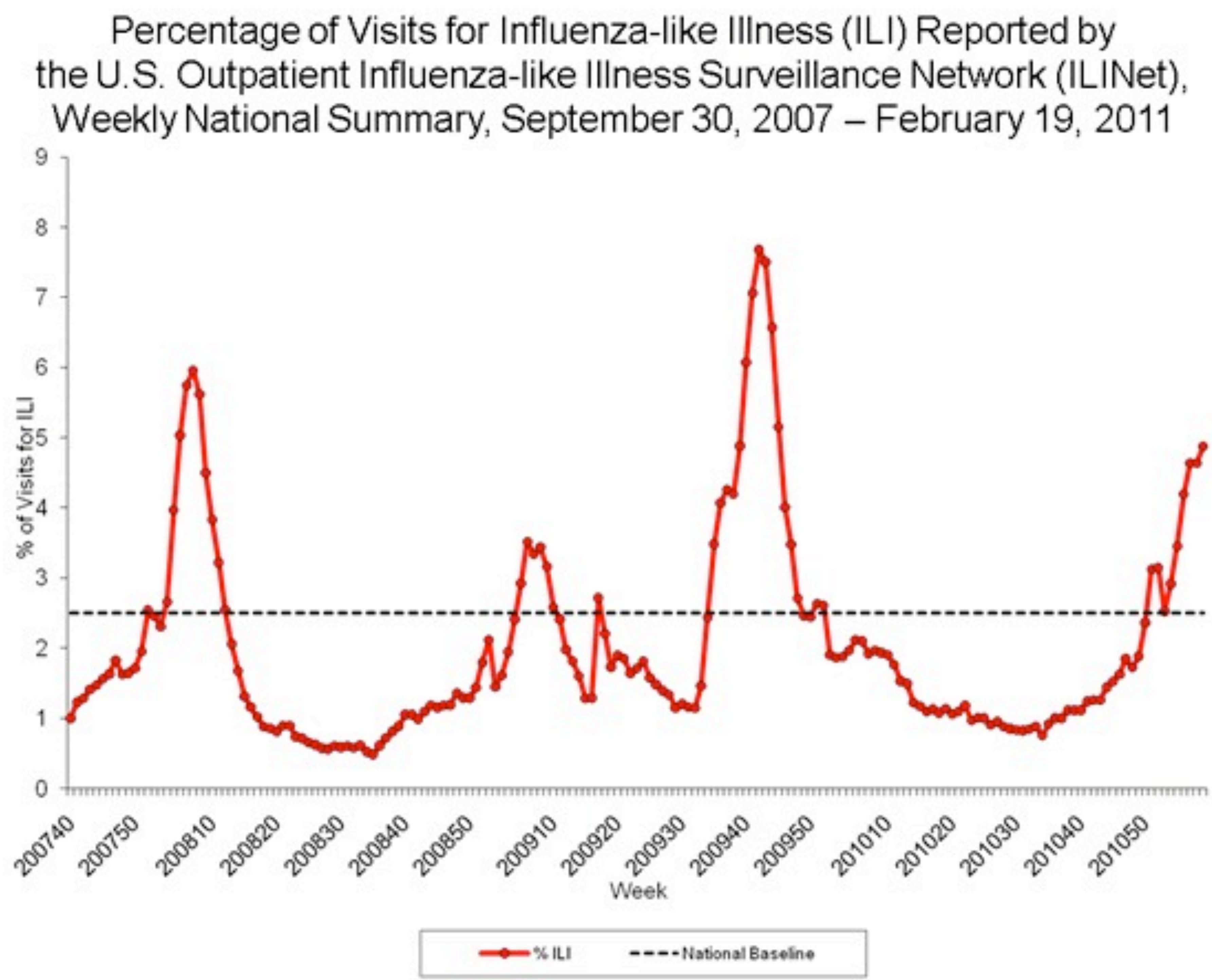




- 11 genes on 8 segments
- 16 H (hemagglutinin) subtypes
- 9 N (neuraminidase) subtypes
- H1N1, H2N2, H3N2, H5N1 are common

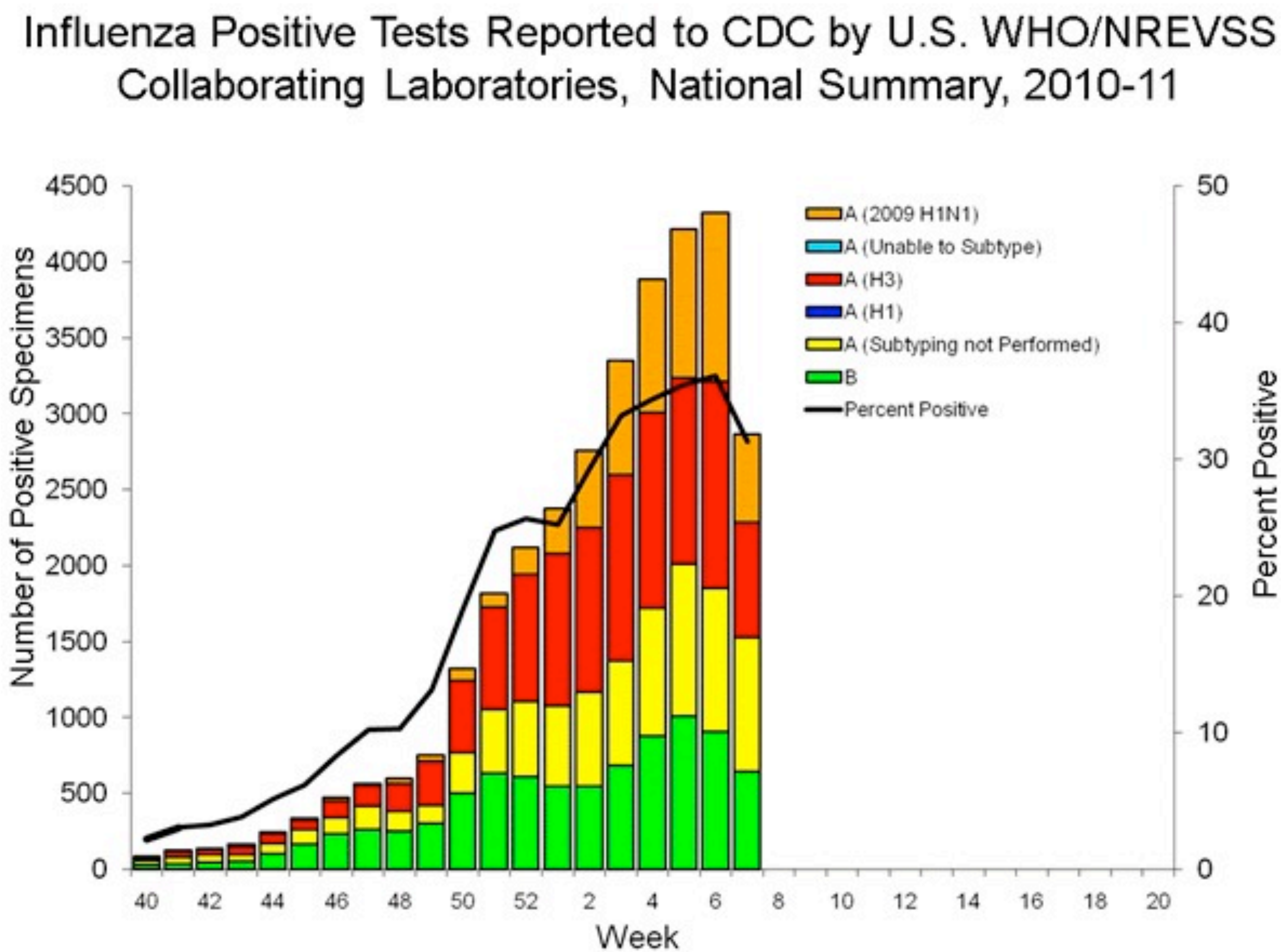
- Pandemics often follow reassortments, e.g. pandemics 1957 (H2N2) and 1968 (H3N2)
- Reassortment is frequent in waterfowl and swine, where many subtypes circulate.

Influenza – this season



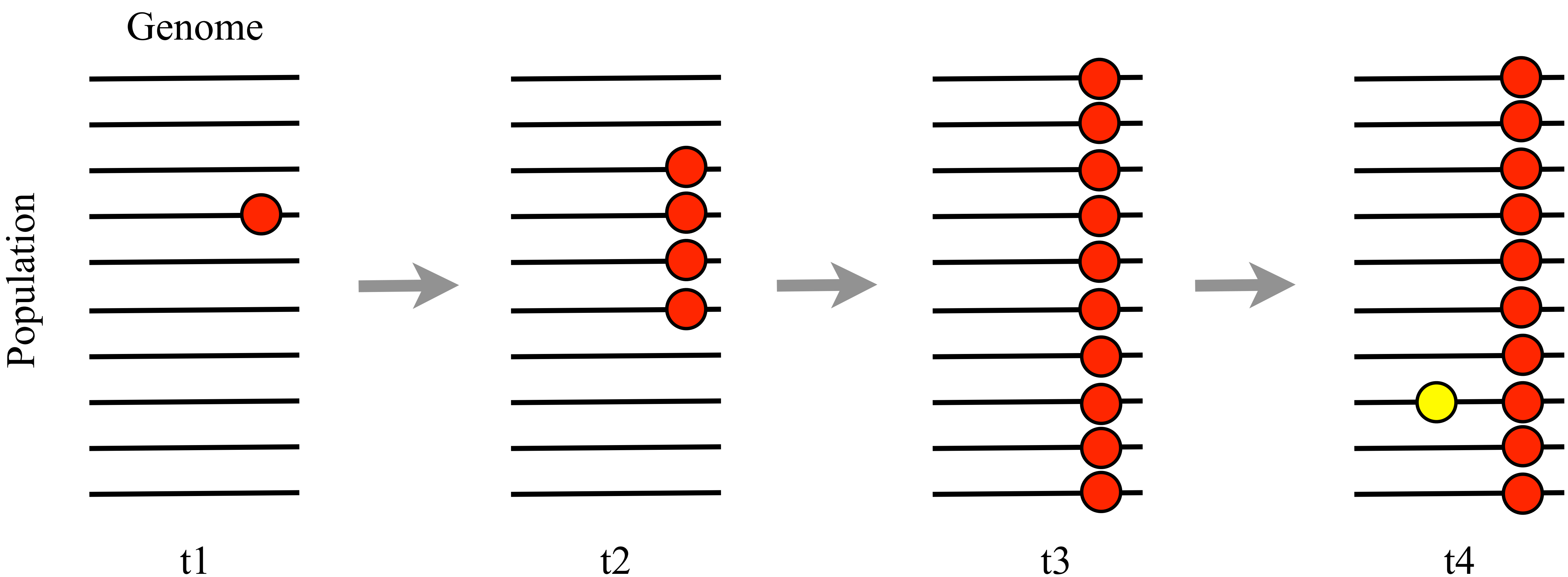
CDC

Influenza – this season

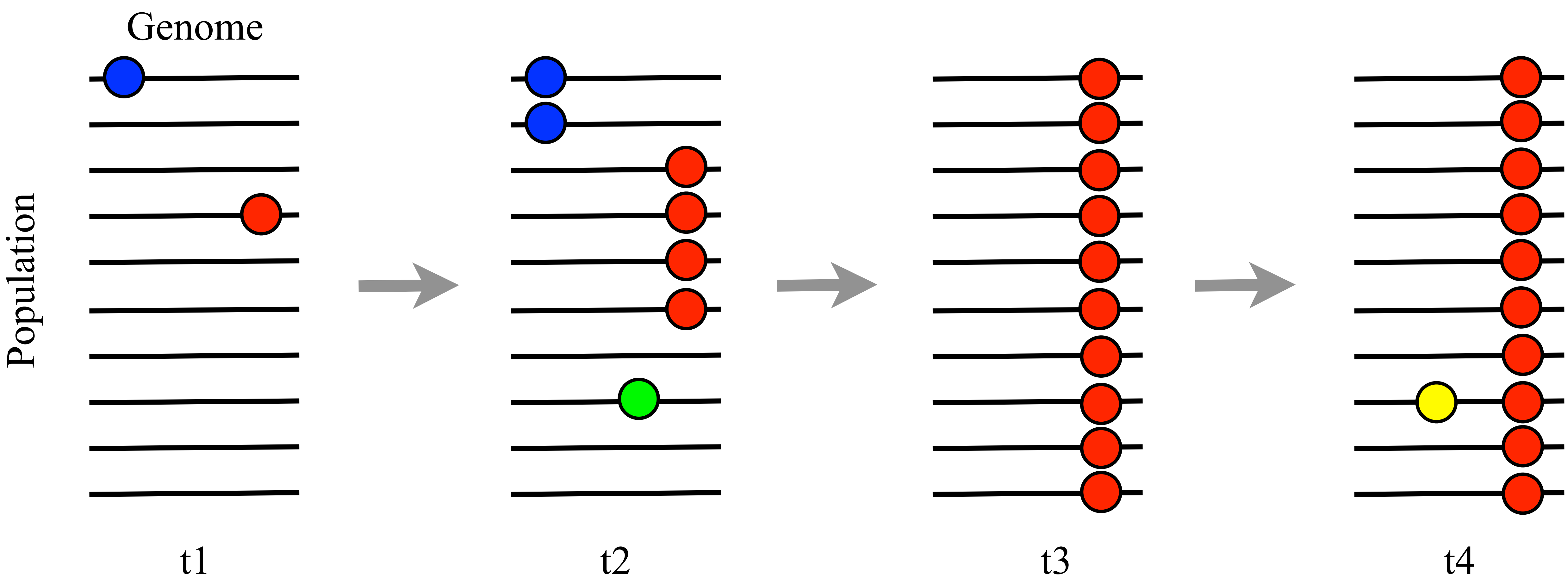


CDC

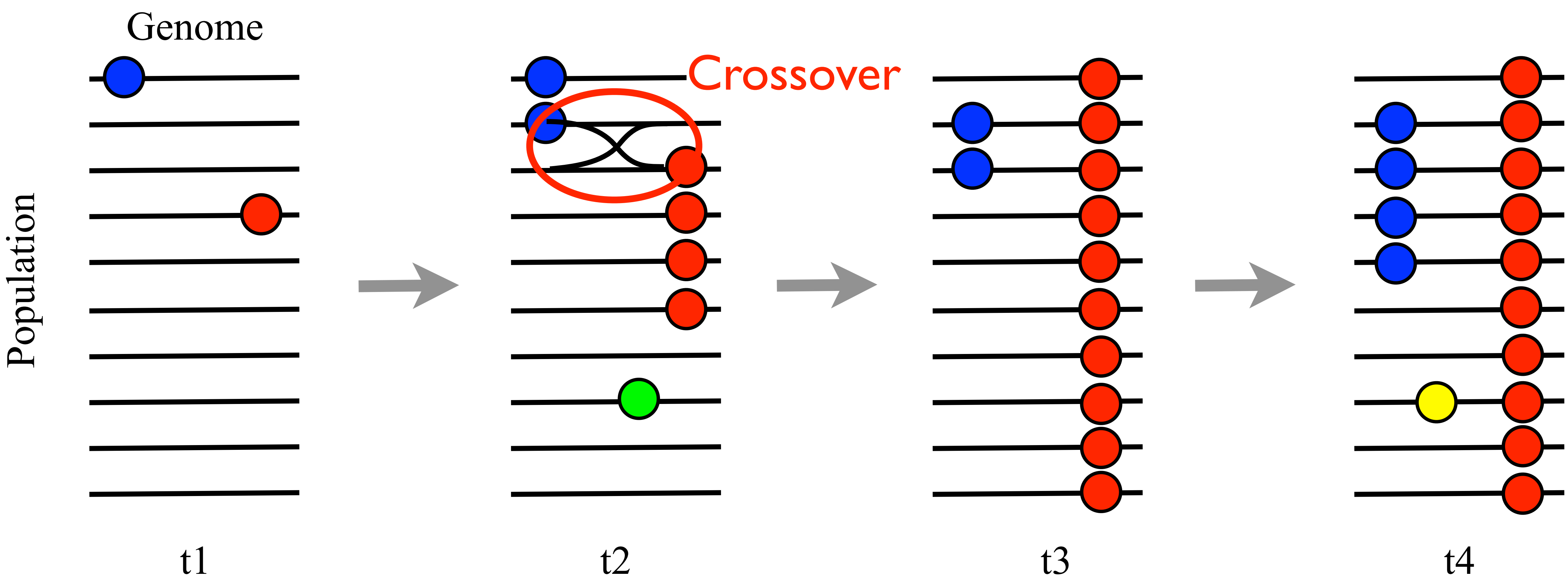
Why do viruses have sex?



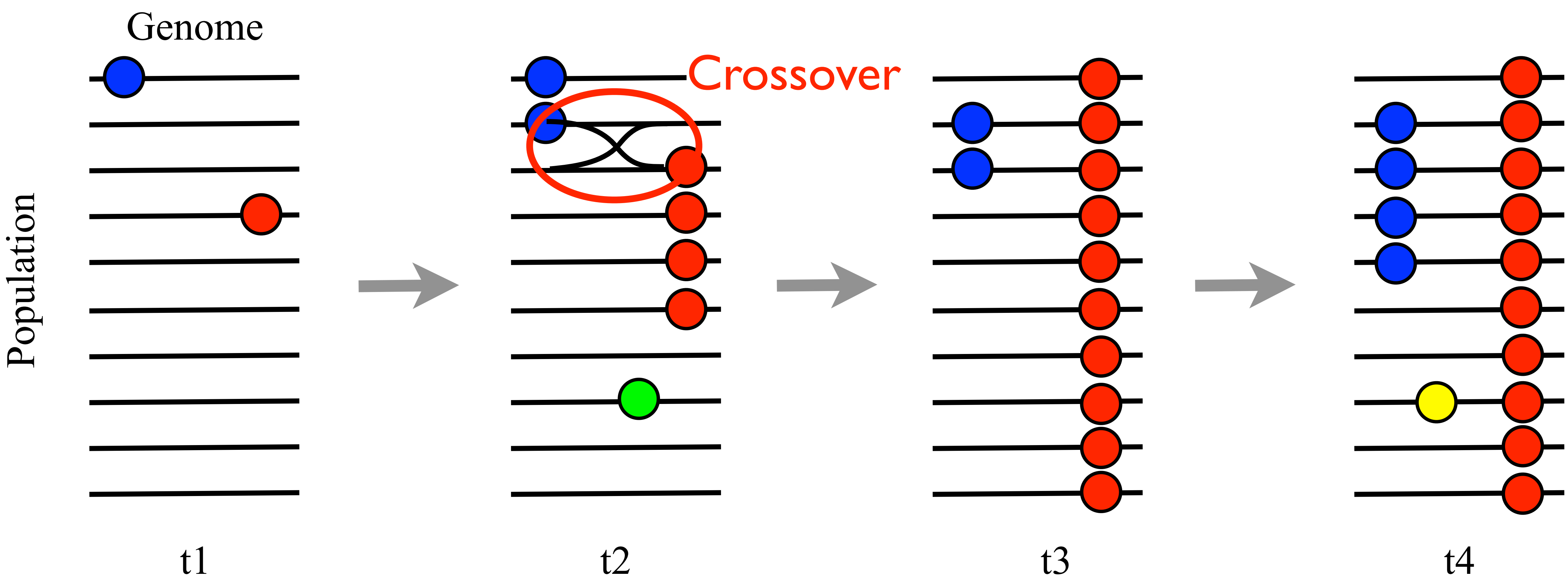
Why do viruses have sex?



Why do viruses have sex?

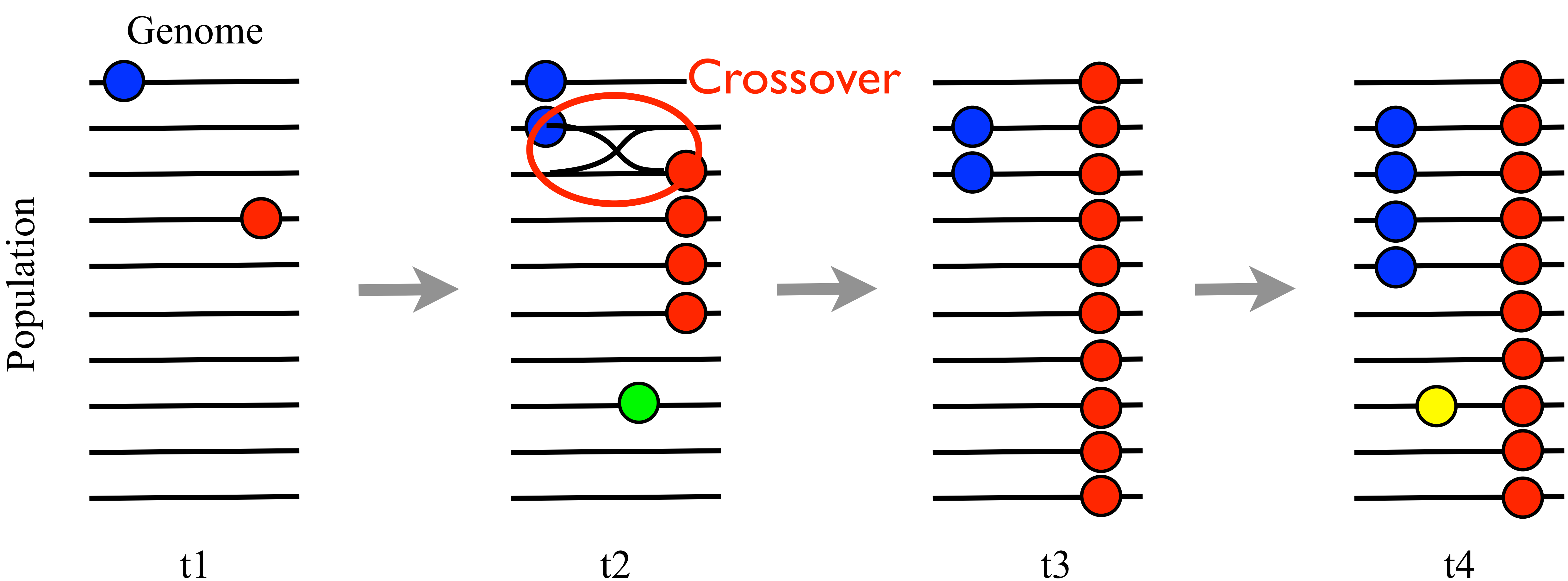


Why do viruses have sex?



- Recombination allows innovation in parallel
- Different innovations can be combined once they are frequent
- Beneficial mutations can be separated from deleterious ones

Why do viruses have sex?

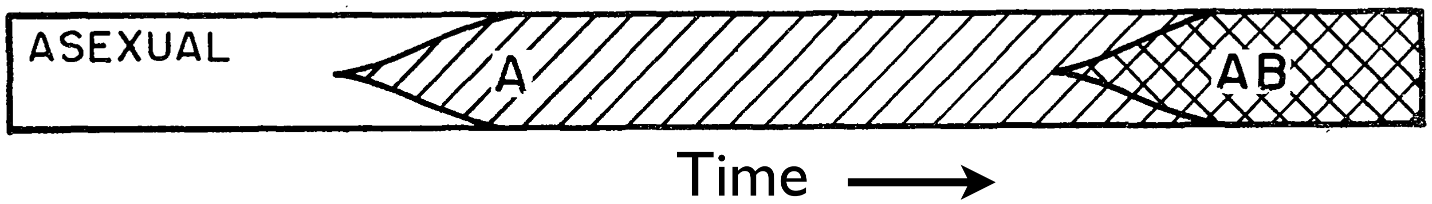


- Recombination allows innovation in parallel
- Different innovations can be combined once they are frequent
- Beneficial mutations can be separated from deleterious ones

Can we quantify this effect?

Evolution in asexual and sexual organisms

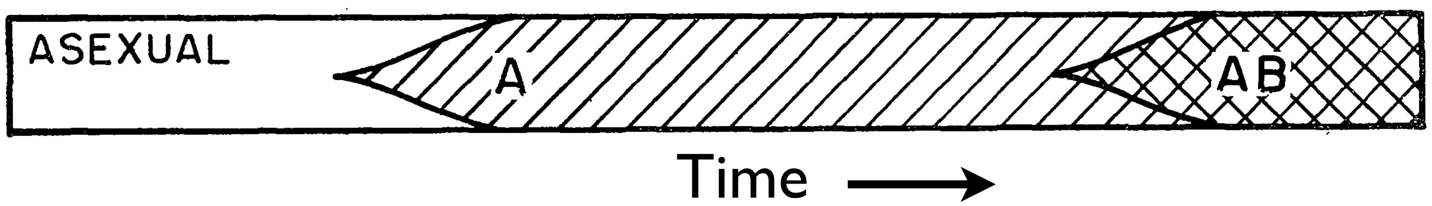
Small Population



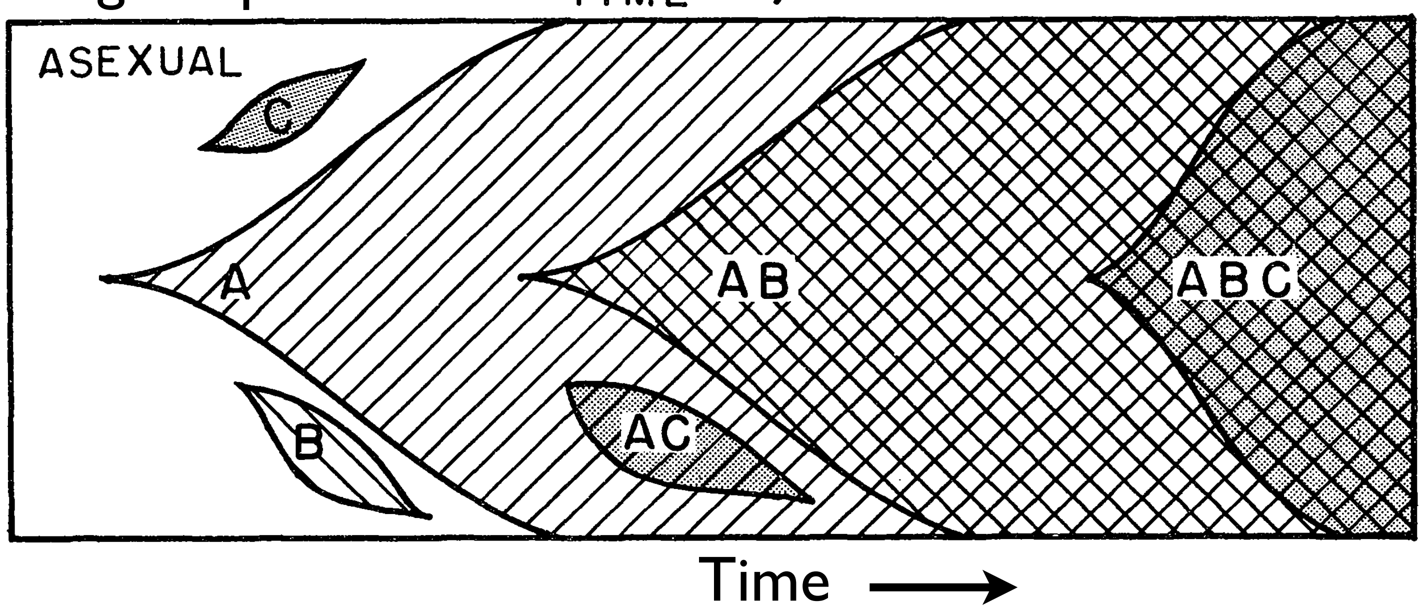
Sequential innovations:
rate ~ N

Evolution in asexual and sexual organisms

Small Population



Large Population



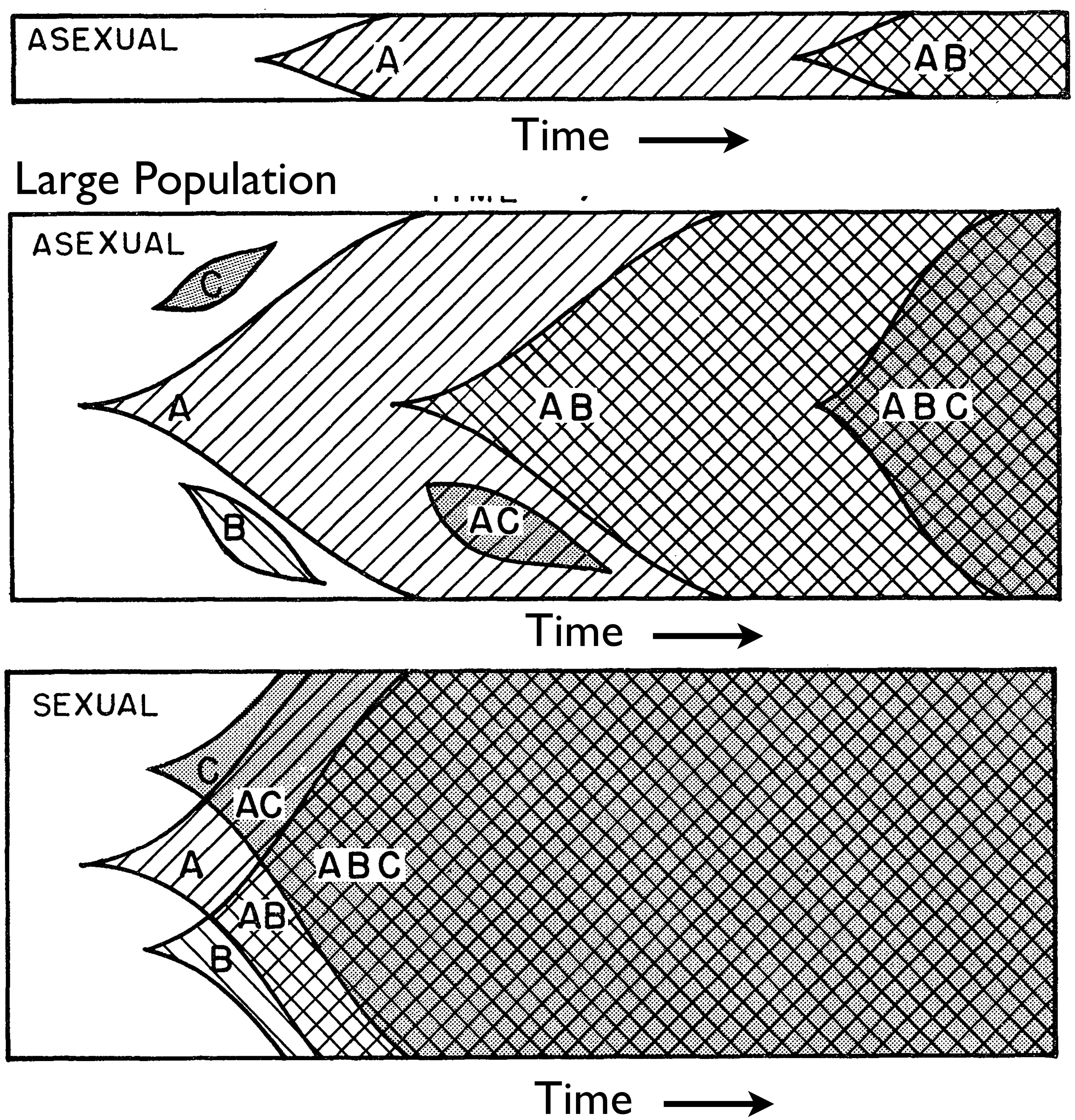
Sequential innovations:
rate ~ N

Many concurrent mutations:
rate ~ log N

Most good mutations are wasted!

Evolution in asexual and sexual organisms

Small Population



Sequential innovations:
rate ~ N

Many concurrent mutations:
rate ~ log N

Most good mutations are wasted!

Conventional wisdom:
rate ~ N

RA Fisher (1930), H Muller (1932),
M Kimura and J Crow (1965)

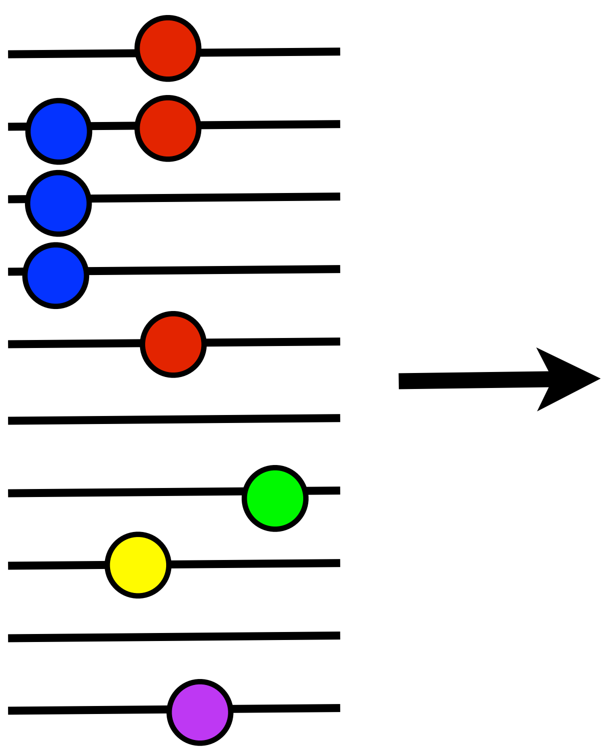
Quantifying the benefits of recombination [for the virus]

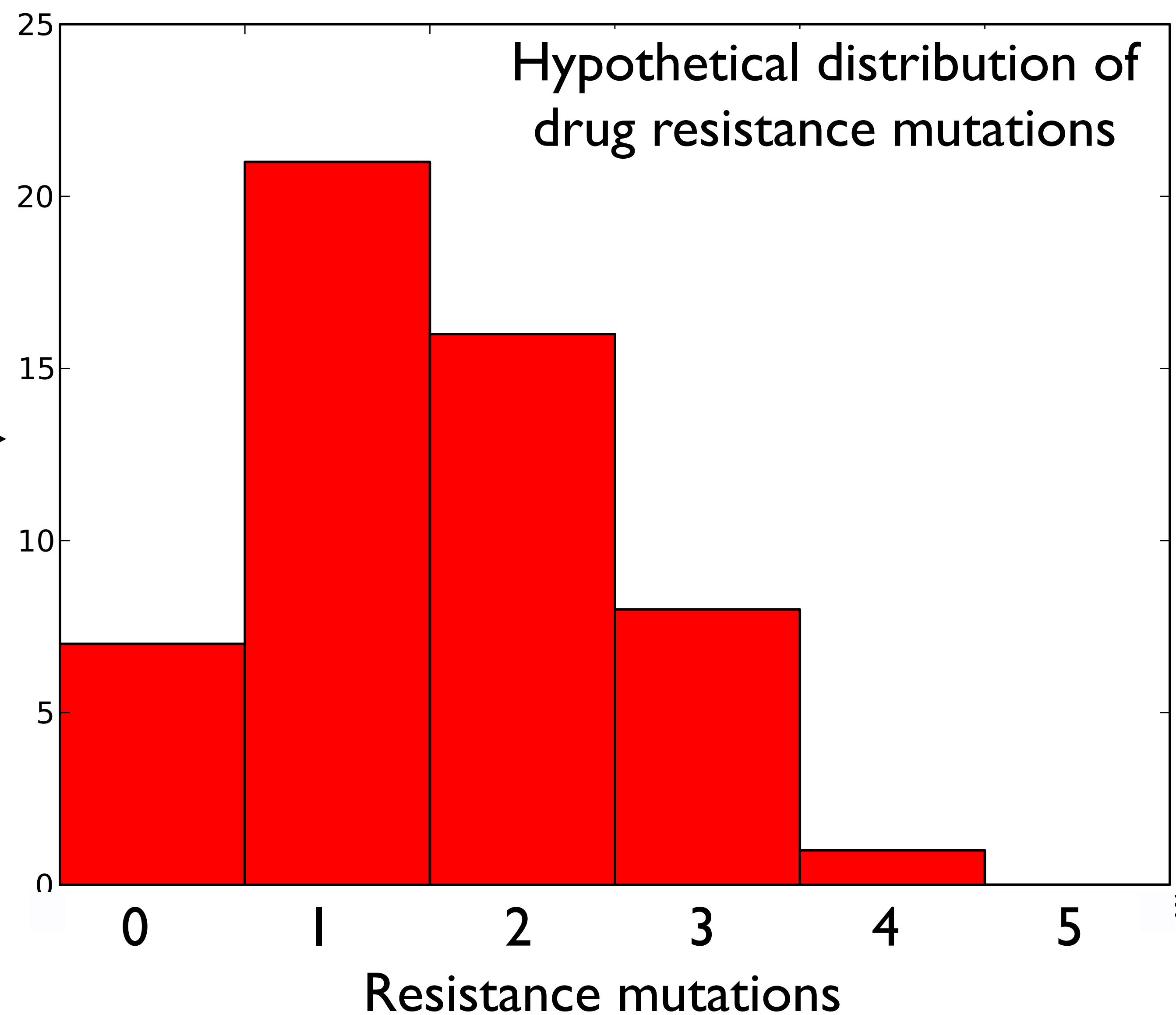
MAX-PLANCK-GESELLSCHAFT

Example: drug resistance of HIV

Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTL

Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTL

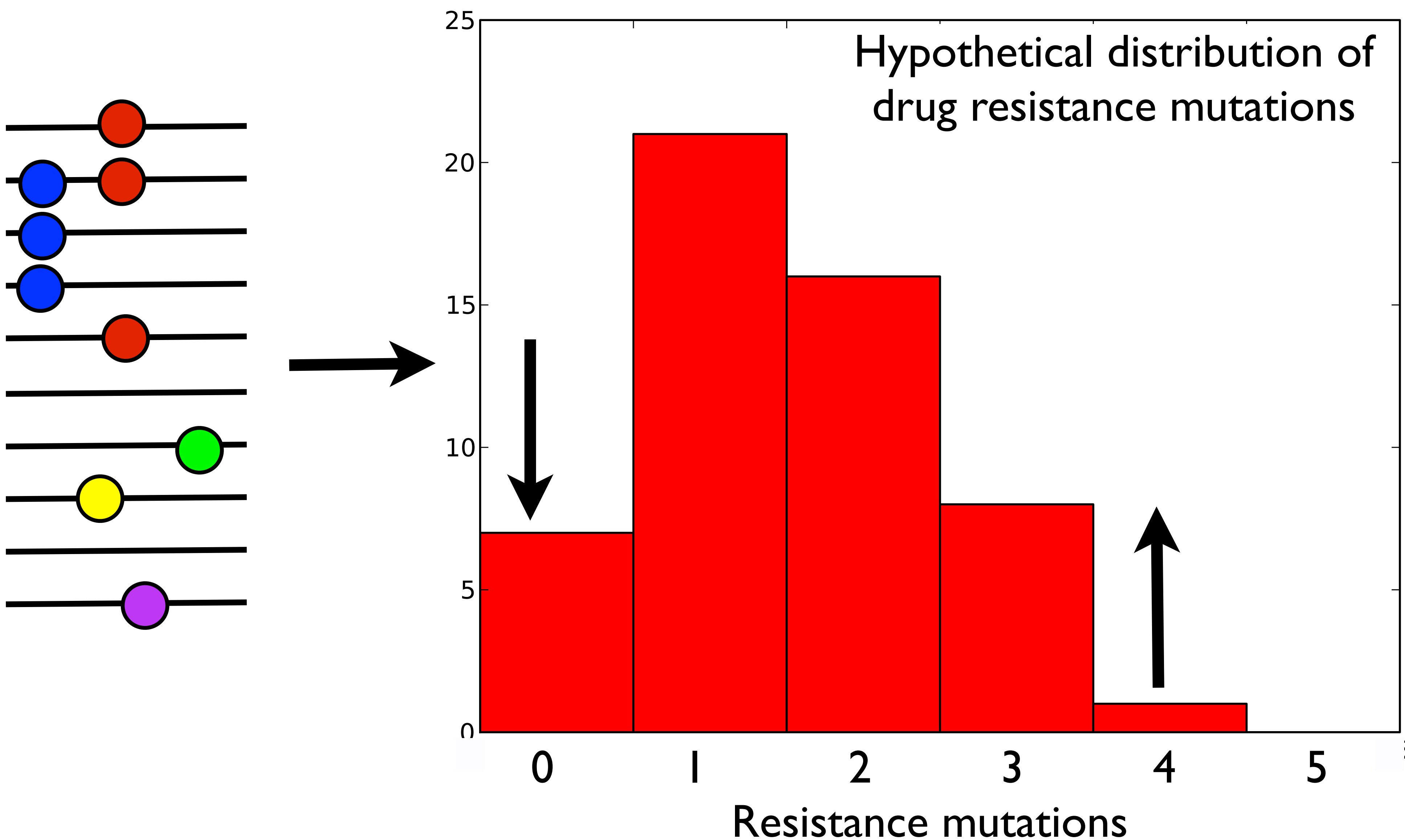




Quantifying the benefits of recombination [for the virus]

Example: drug resistance of HIV

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTL
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTL
```



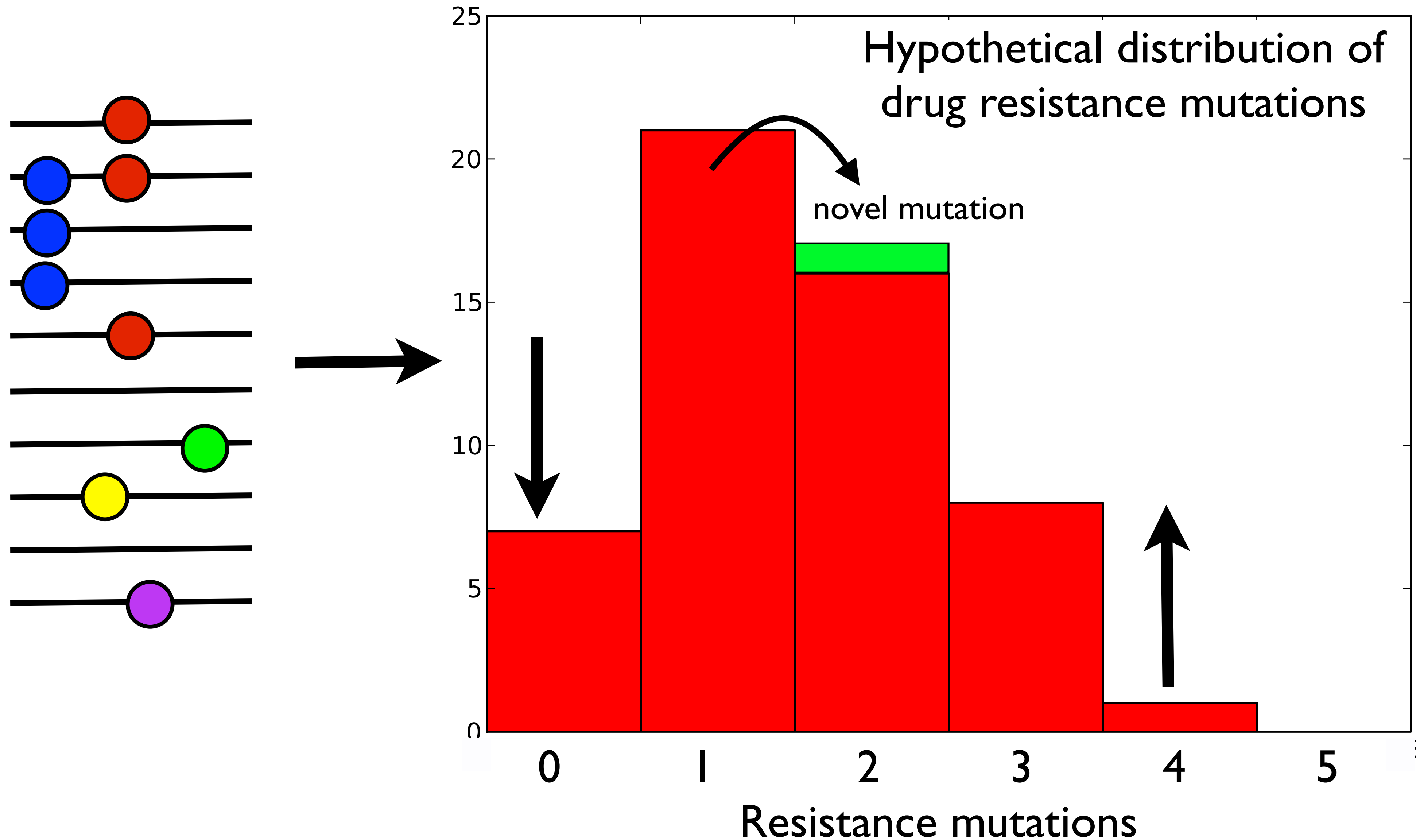
- Drug resistance increas due to selection on existing mutations

Quantifying the benefits of recombination [for the virus]

MAX-PLANCK-GESELLSCHAFT

Example: drug resistance of HIV

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTL
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTL
```

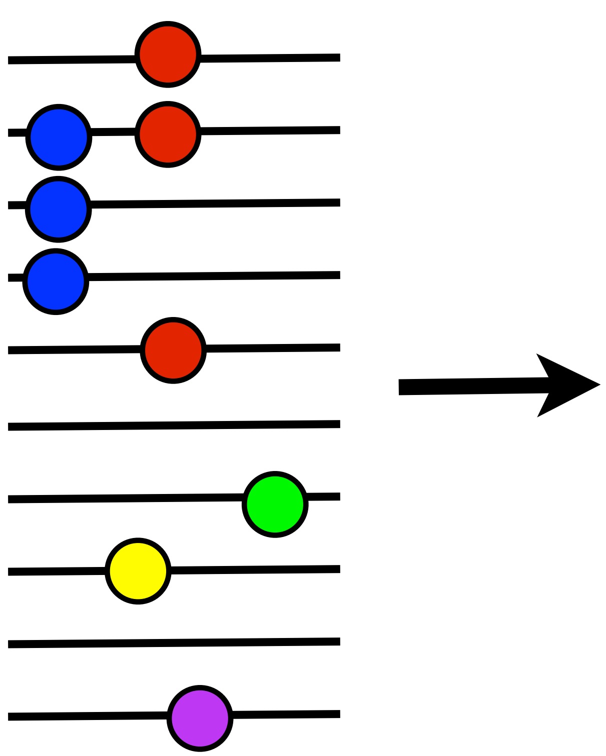


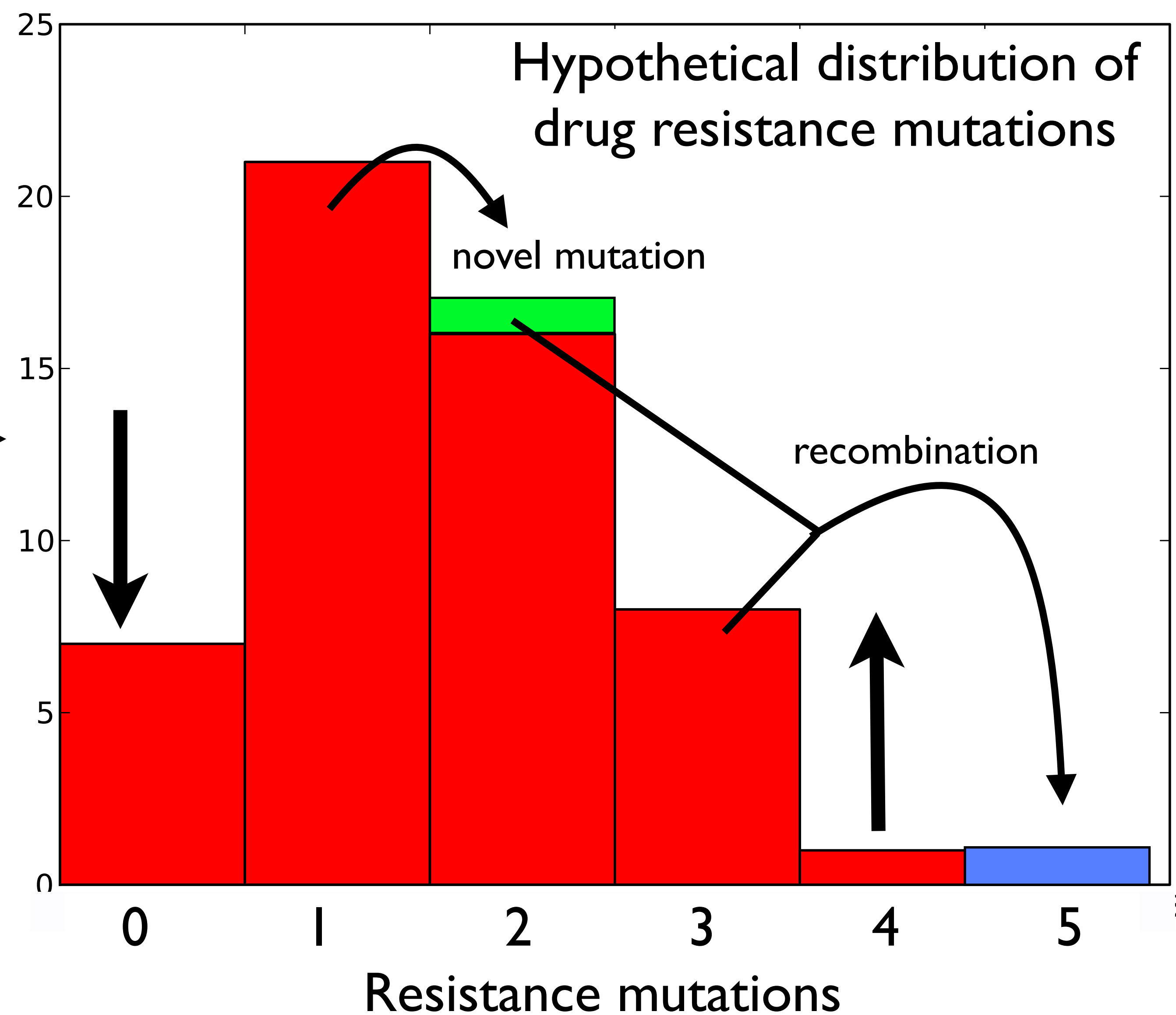
- Drug resistance increas due to selection on existing mutations
- Novel mutations keep the wave going

Quantifying the benefits of recombination [for the virus]

Example: drug resistance of HIV

```
Drug sensitive: PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTL
Drug resistant: PQITLWQRPLVTIKVGGQLTEALLDTGADDTILEDMTLPGRWKPKIVGGIGGFIKVRQYDQVPIEICGHKVISTVLIGPTPCNIIGRNLMTQIGLTL
```

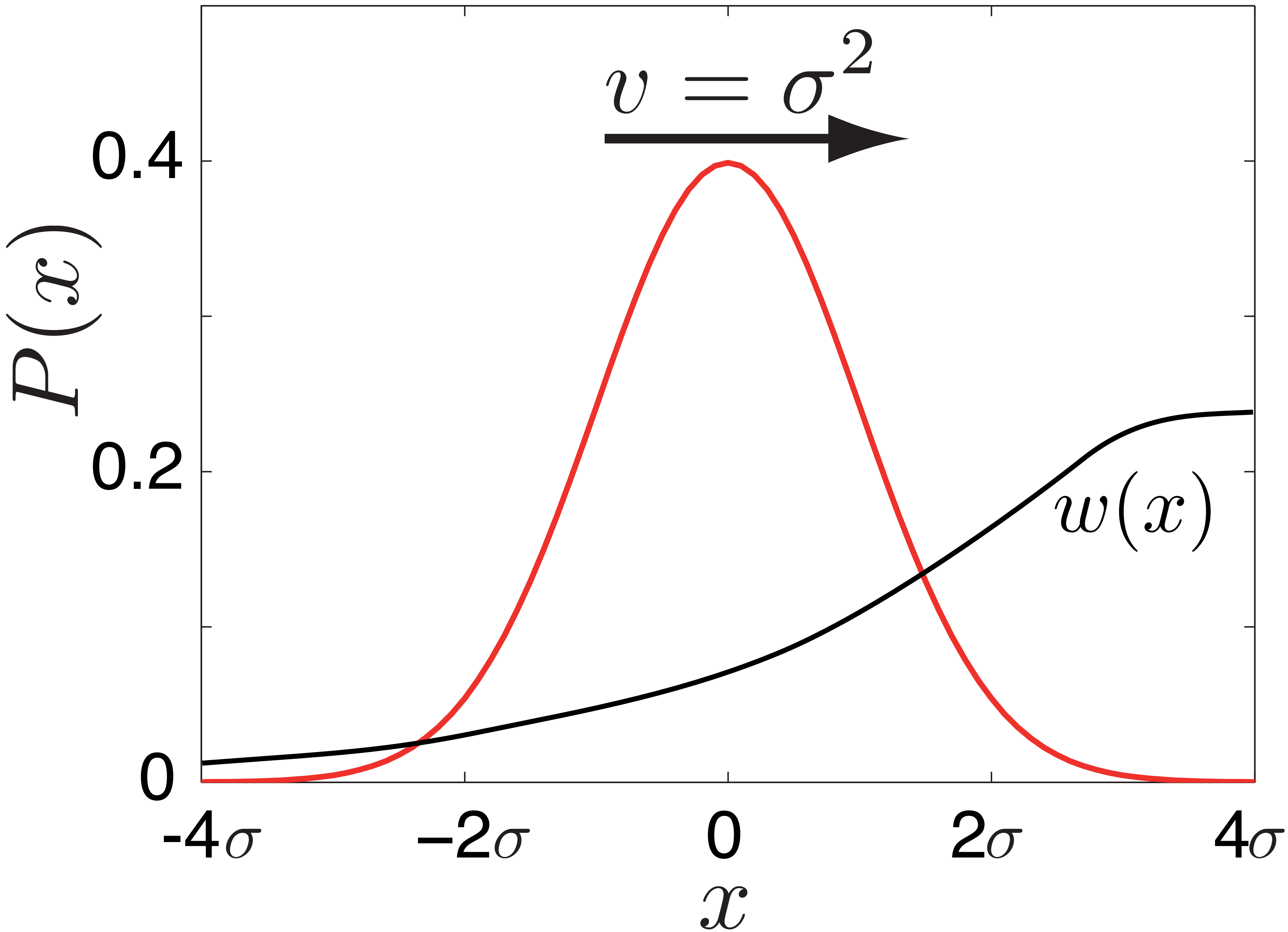




- Drug resistance increas due to selection on existing mutations
- Novel mutations keep the wave going
- Via recombination mutations can keep up with the wave and "make it"

Surfing of beneficial mutations

Surfing of beneficial mutations



Evolutionary benefits of recombination

Conventional wisdom: rate of evolution ~ N

→ holds only for very frequent recombination

Realistic recombination: rate of evolution ~ $r^2 \log N$

Recombination can limit the rate of evolution, rather than the number of good mutations.

The more recombination, the better?

Is there a cost to recombination?

Mutations don’t always add up

Gymnastics Team:
Sum of individual scores

Soccer Team:
Teamwork

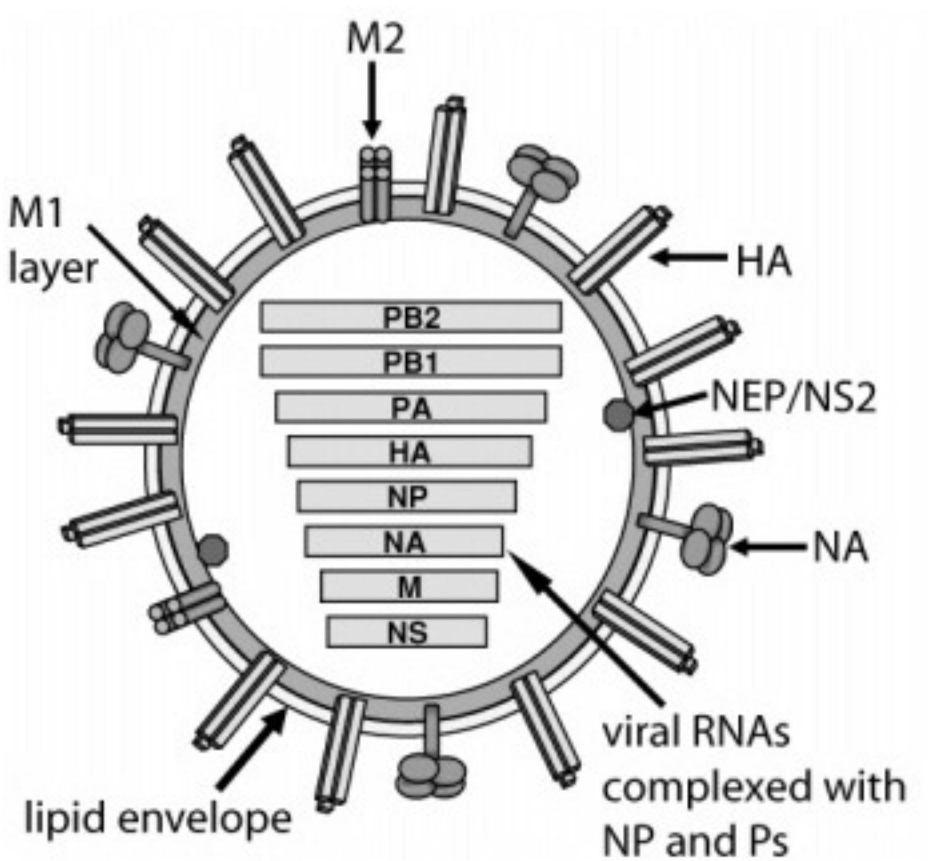
$$F(g) = \sum_i f_i \mathbf{s}_i + \sum_{i<j} f_{ij} \mathbf{s}_i \mathbf{s}_j$$

additive effects of mutations

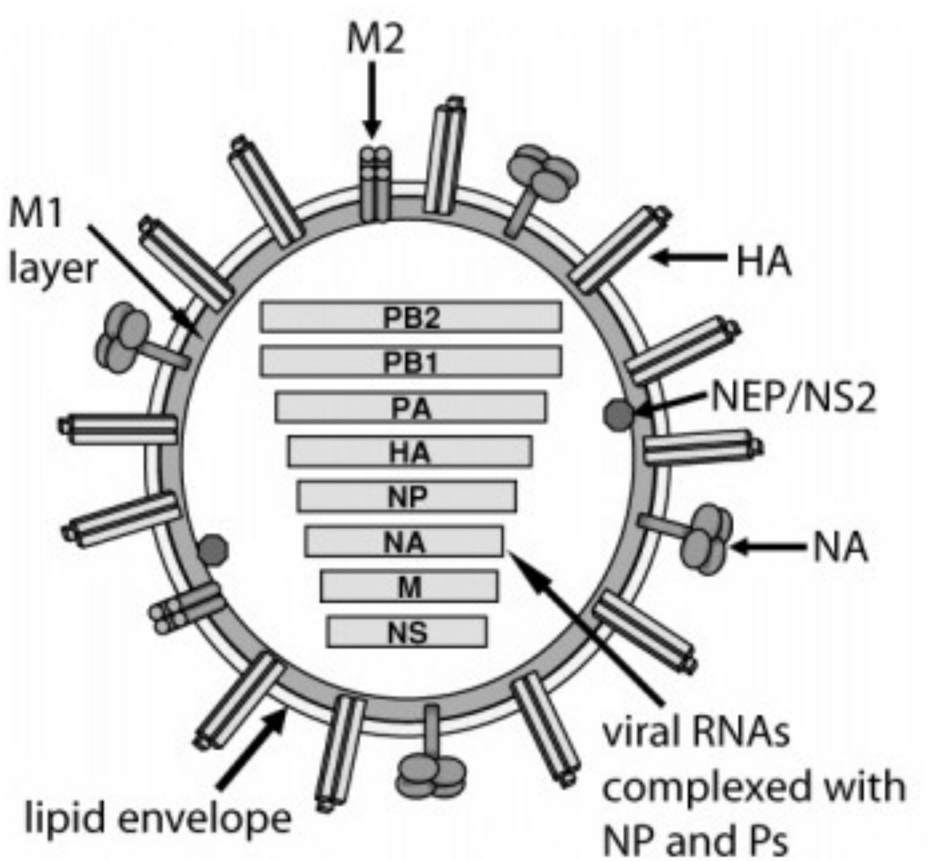
synergy or incompatibility = genetic interaction

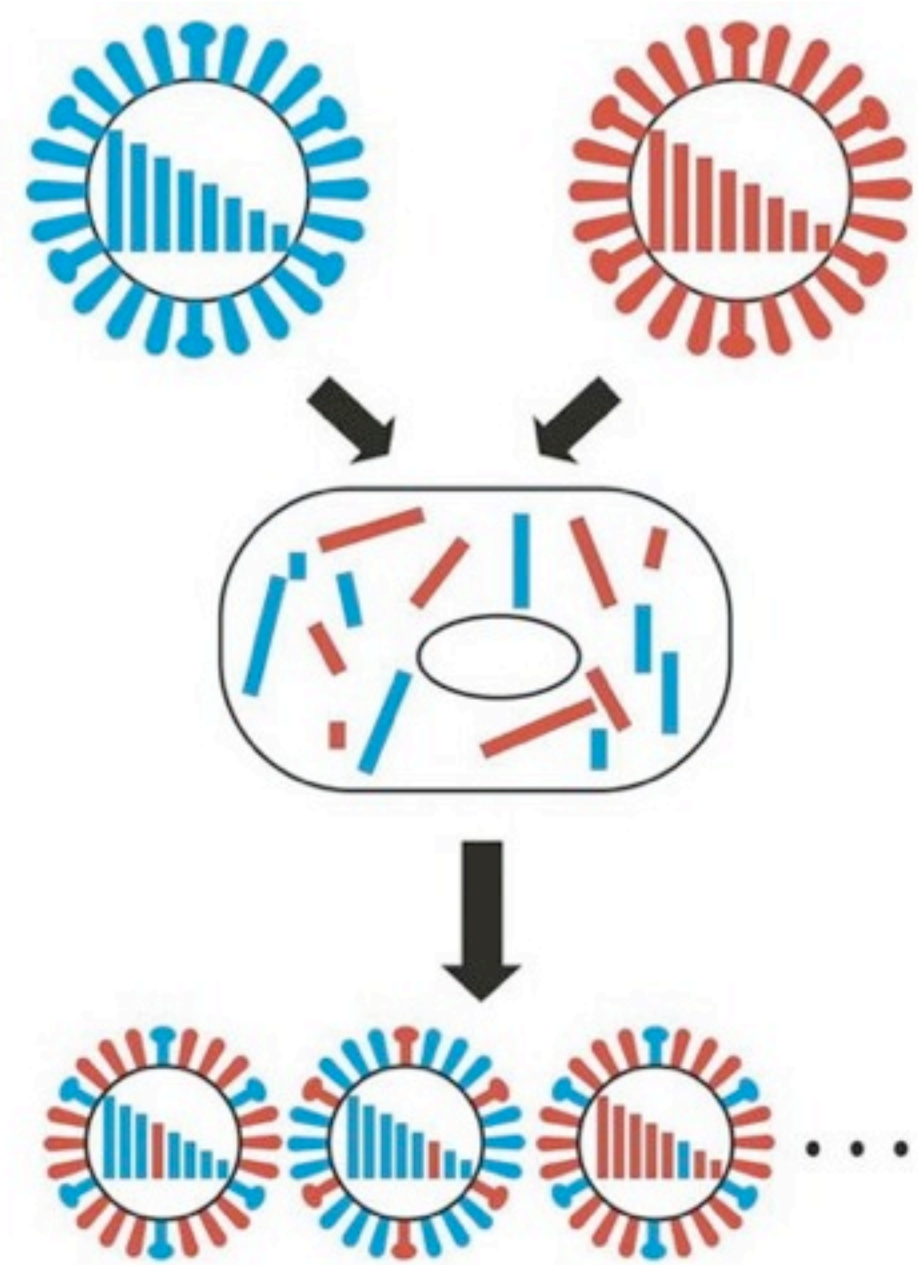
Genetic interactions

Genetic interactions



Genetic interactions





Genetic interaction and recombination

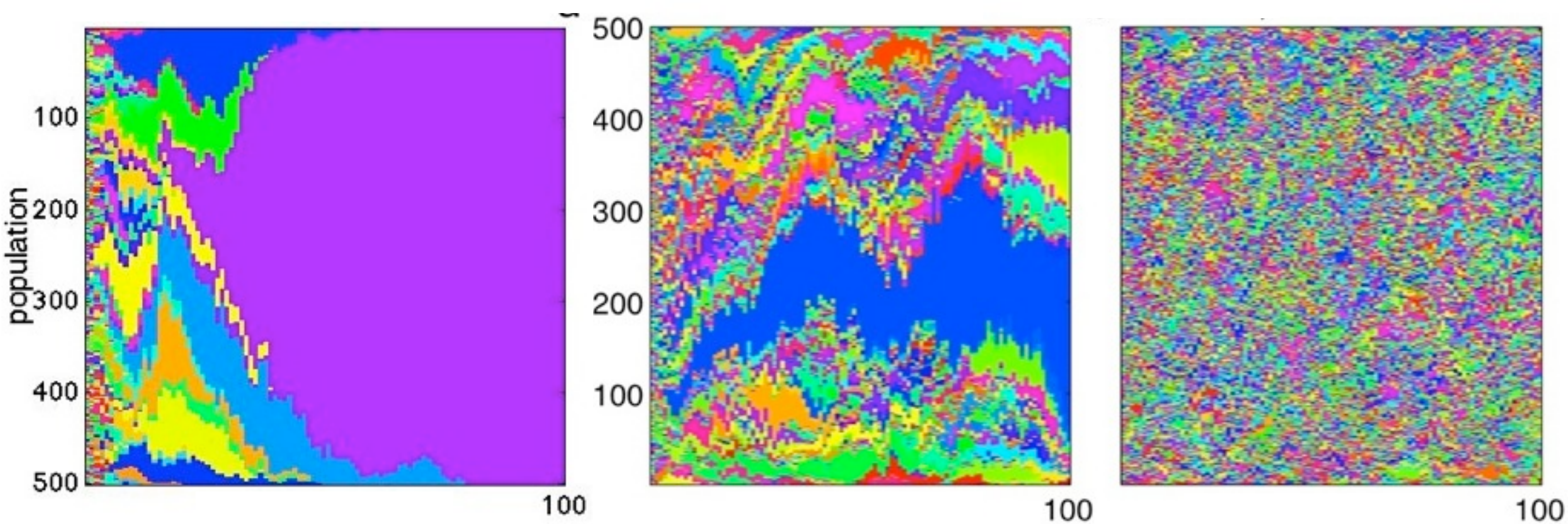
Different reassortments of Influenza A:

Recombination explores -- selection amplifies the best

Genetic interaction and recombination

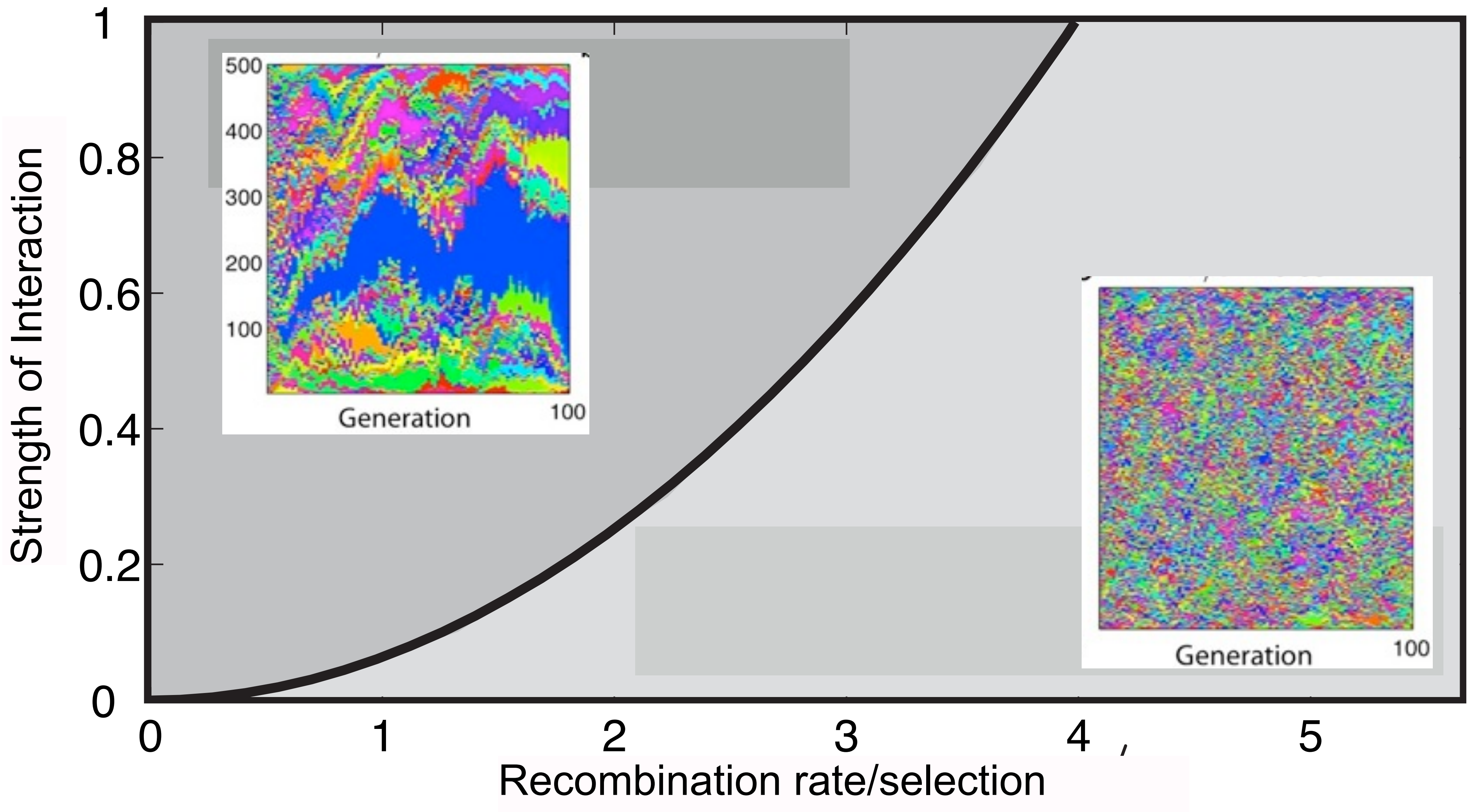
Different reassortments of Influenza A:

Recombination explores -- selection amplifies the best

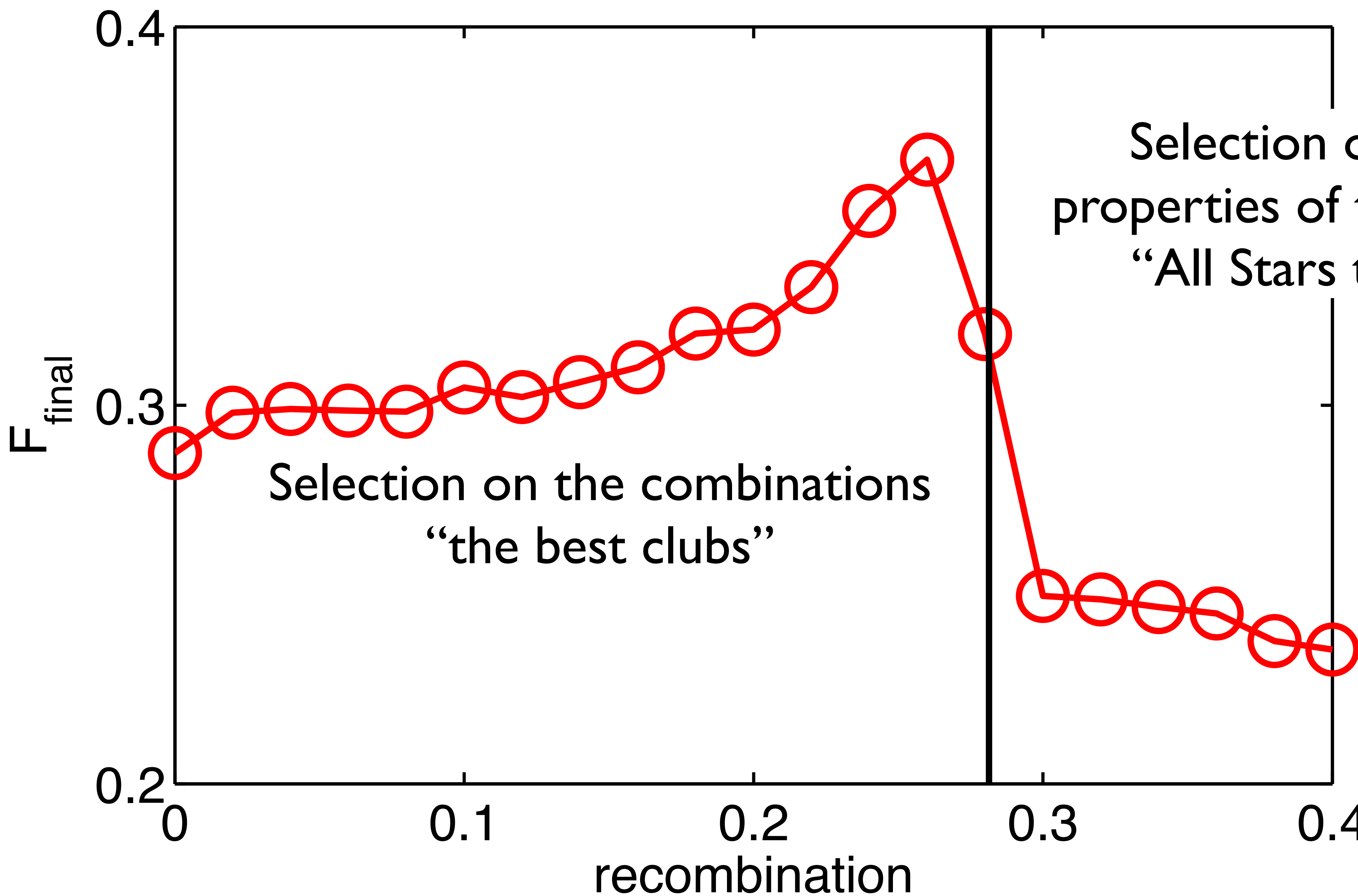


no recombination　　moderate recombination　　frequent recombination

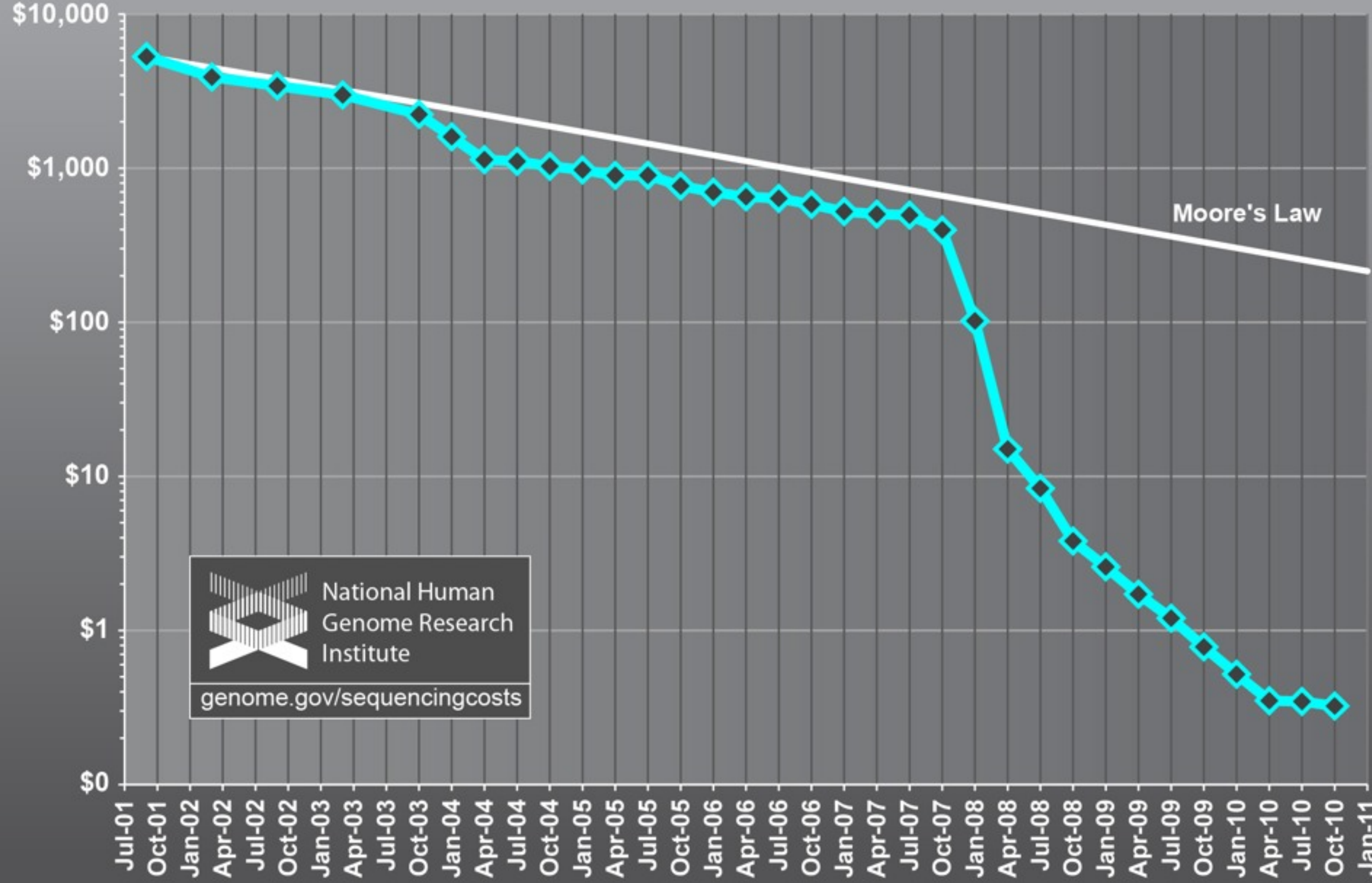
Allele vs genotype selection



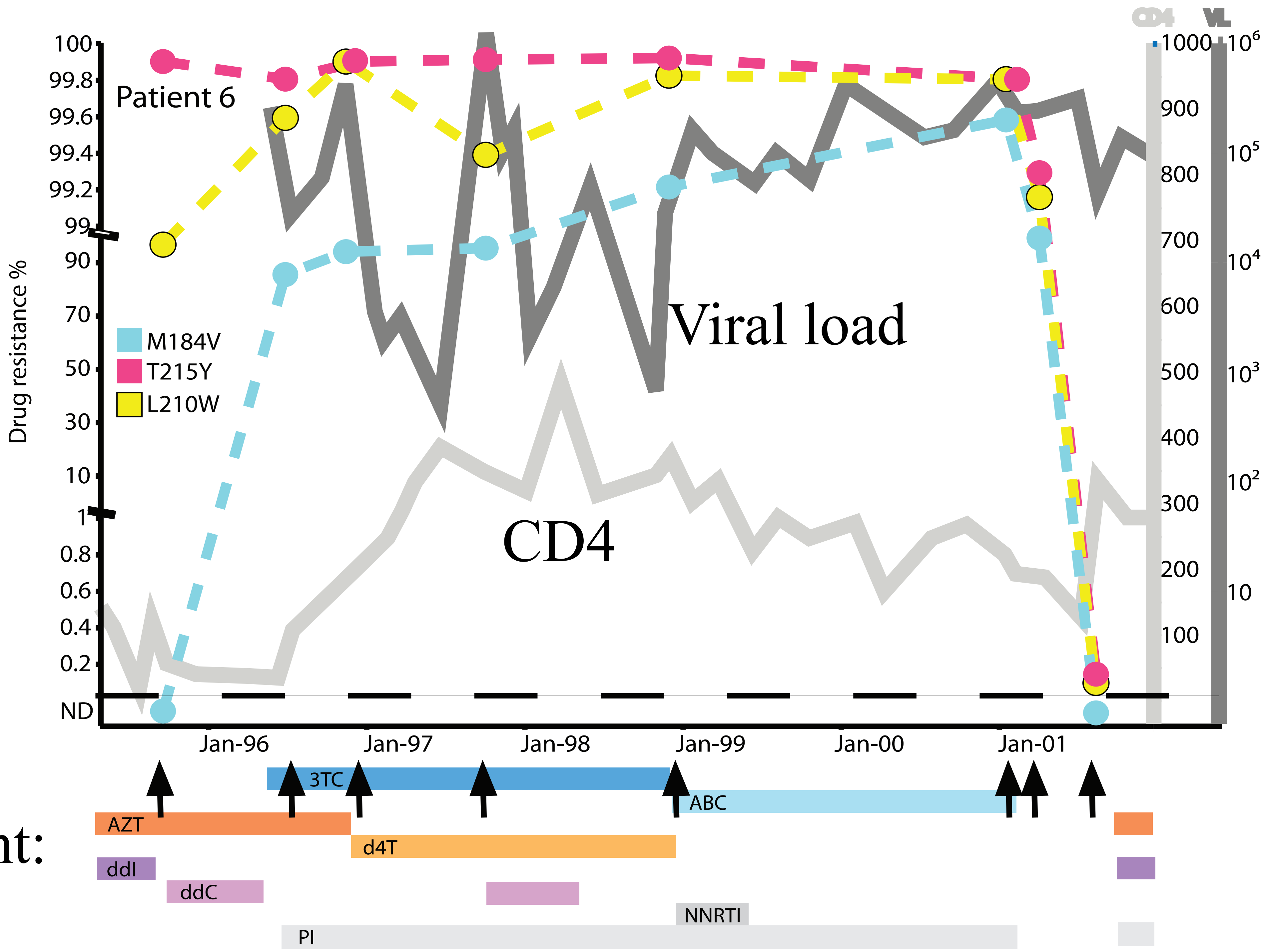
The success of selection



Cost per Megabase of DNA Sequence



Drug resistance evolution



Treatment:

Hedskog, et al, PLoS One, 2010

Experiment & Theory

Darwin's Theory

Observations:

Paleontology

Diversity of species

Experiment & Theory

Darwin's Theory

Quantitative Theory
Predictions

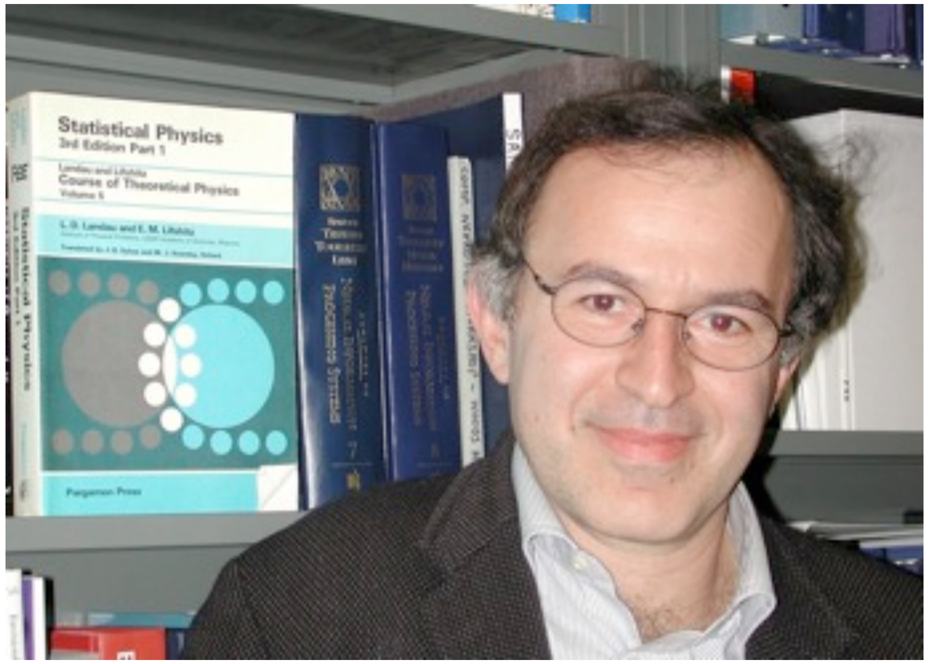
Experiments in the Lab

- Bacteria or viruses
- Sequencing and Phenotyping
- Meta-Genomics
- 1000 Genome Projects

Observations:
Paleontology
Diversity of species

Collaborators

MAX-PLANCK-GESELLSCHAFT



Boris Shraiman, KITP

Daniel Fisher, Stanford

Thomas Leitner, LANL