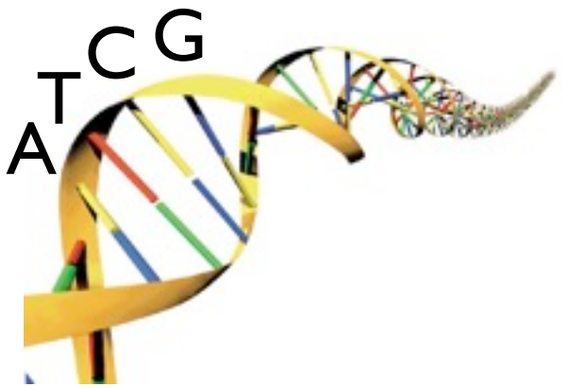
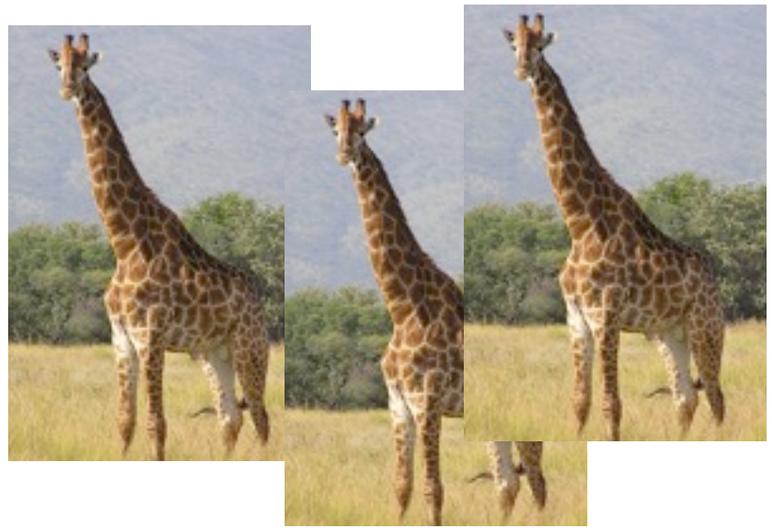
Sex, viruses, and the statistical physics of evolution

Cartoon of Evolution



Genotypes

Selection



Mutation & Recombination

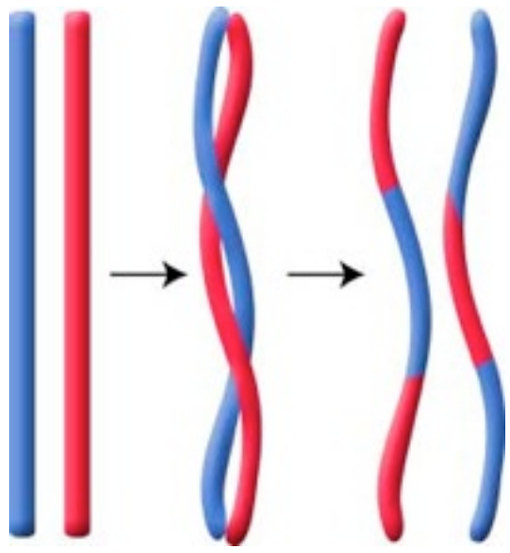
Mutation

...ATACG...

↓

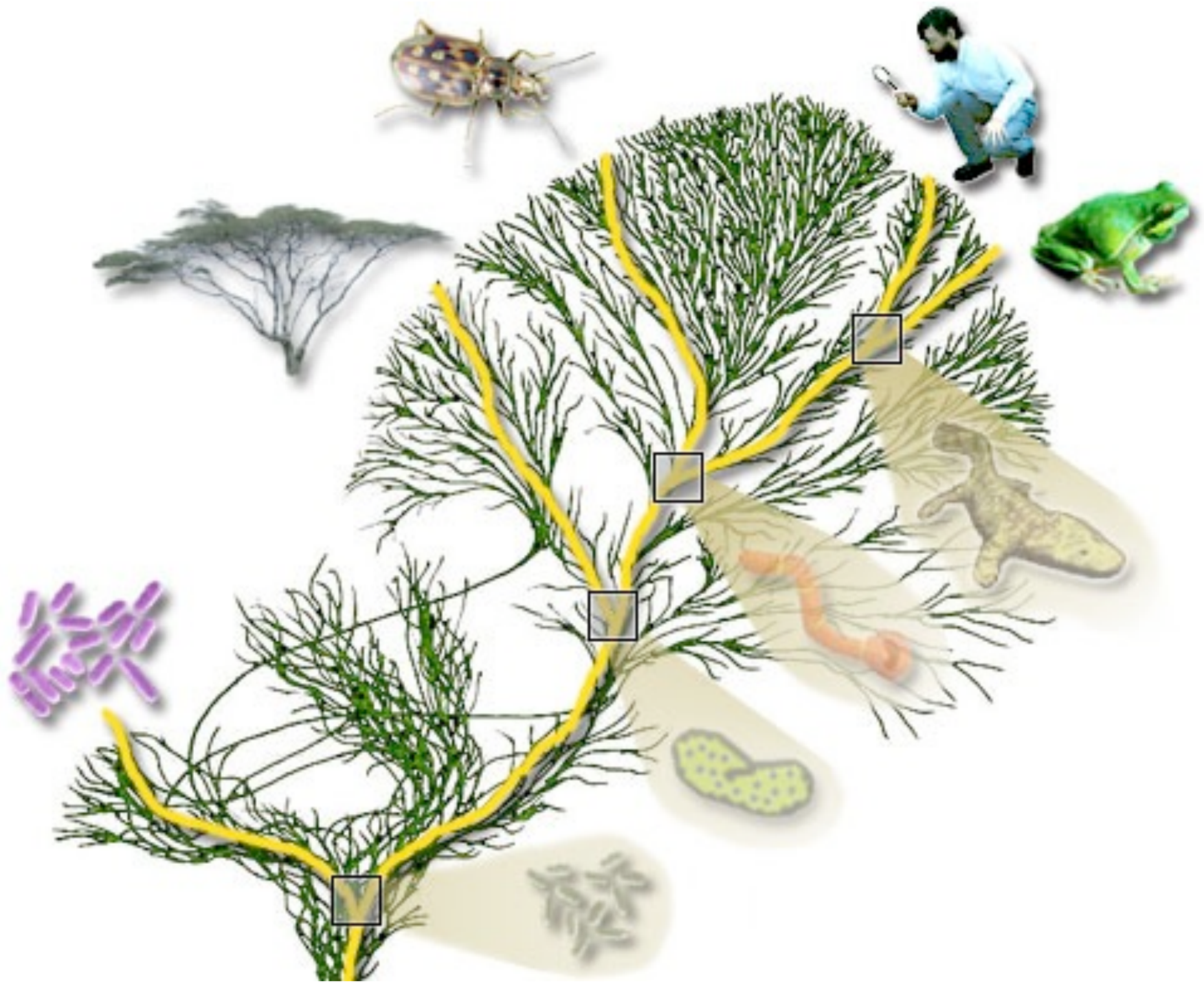
...ATGCG...

Sex & Recombination



Selection

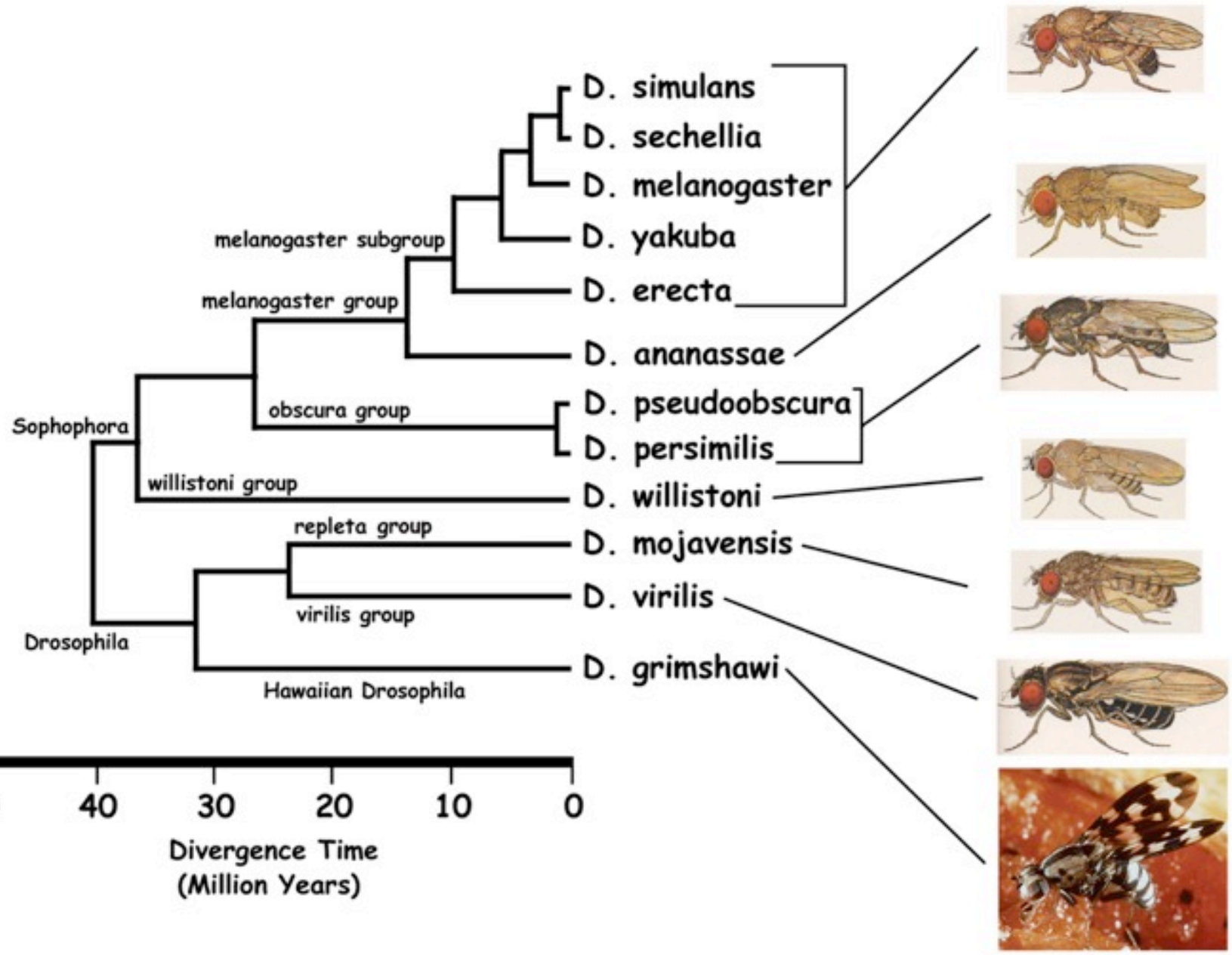
Tree of Life - billions of years



source: tree of life, tolweb.org

4 billion years

Phylogenetic tree of Fruitflies - millions of years

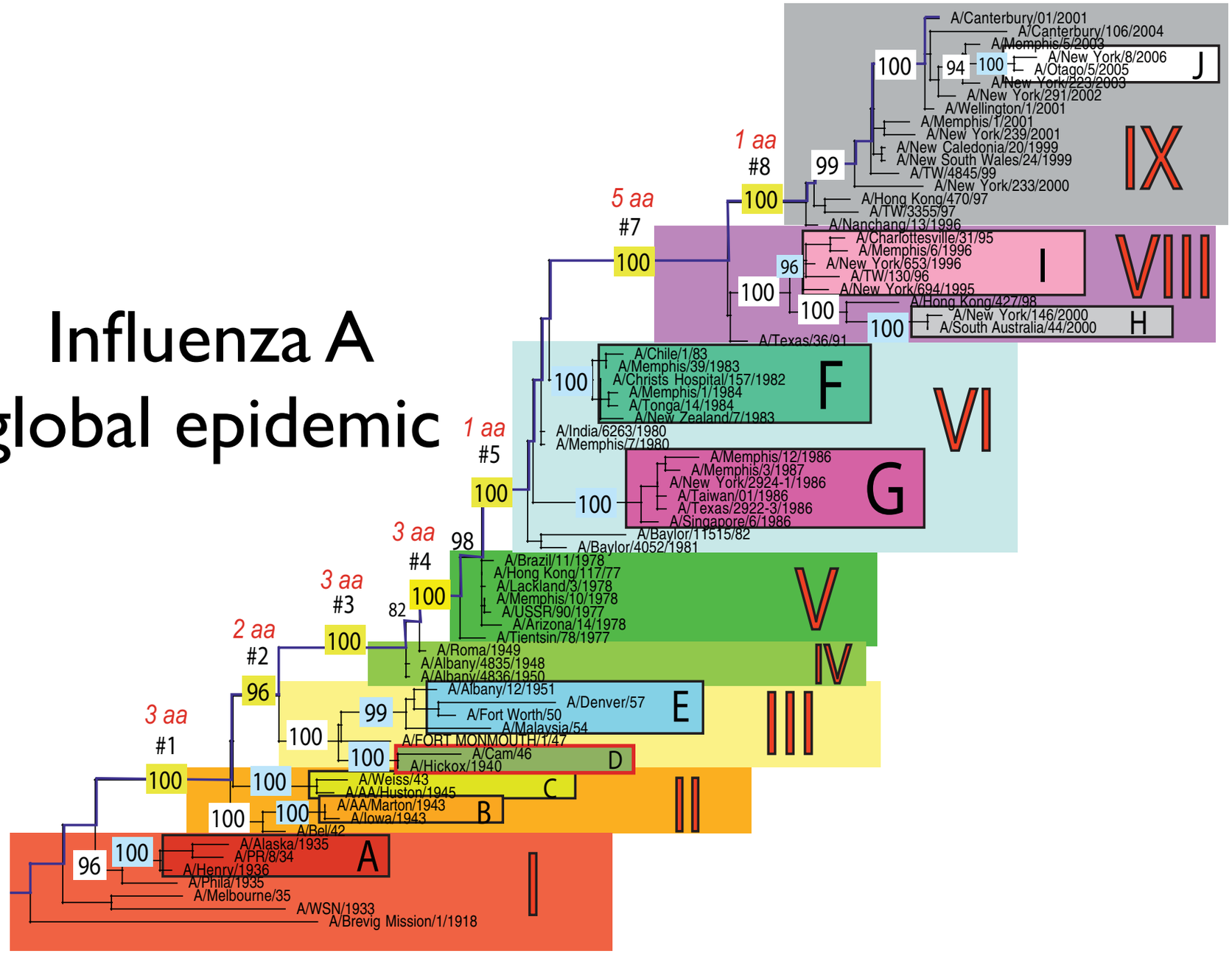


~40 Millions of years

image from: insects.eugenes.org/species/

Evolution of Influenza A - few years

Influenza A
global epidemic

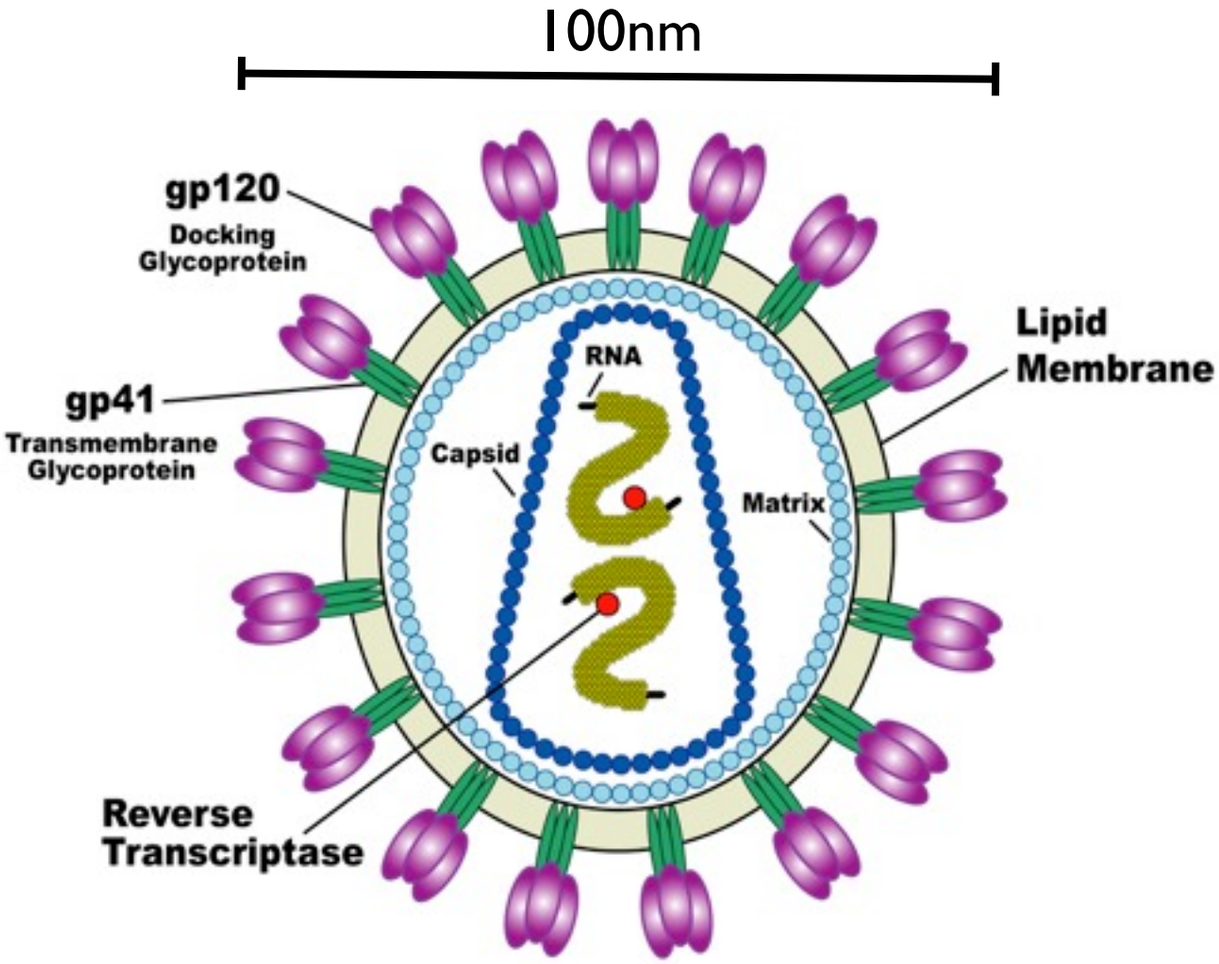


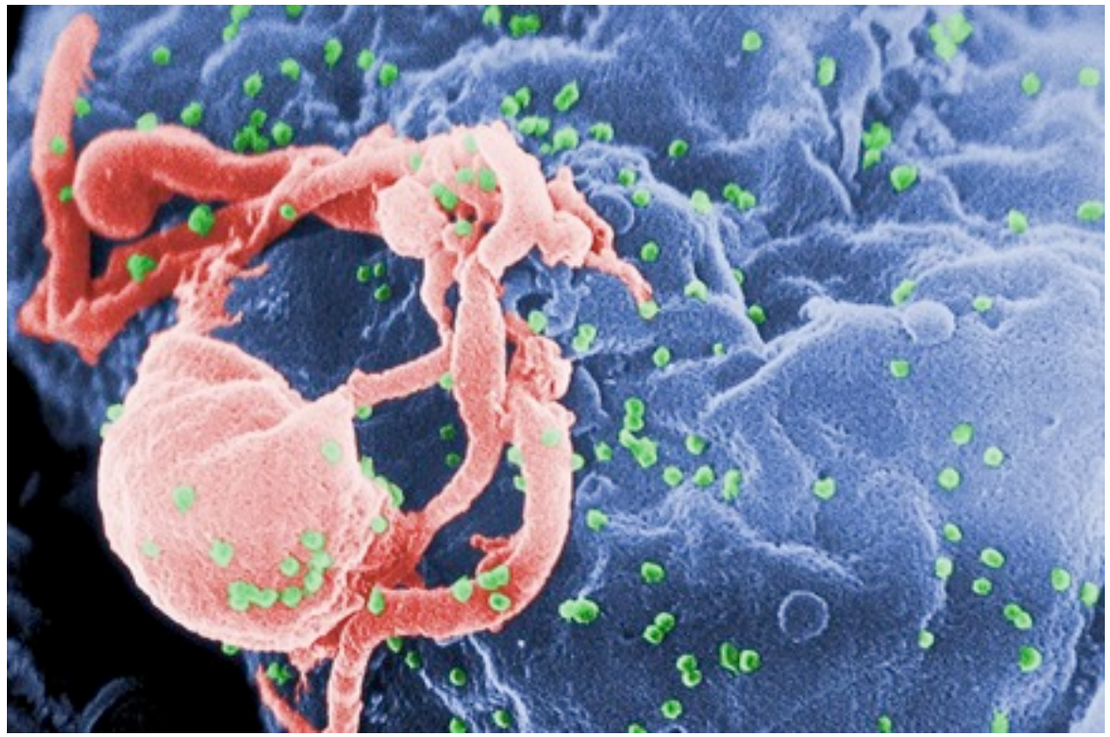
1918 ⟶ 2005

Evolution as cause of epidemics

Nelson et al., 2008

Human immunodeficiency virus (HIV)

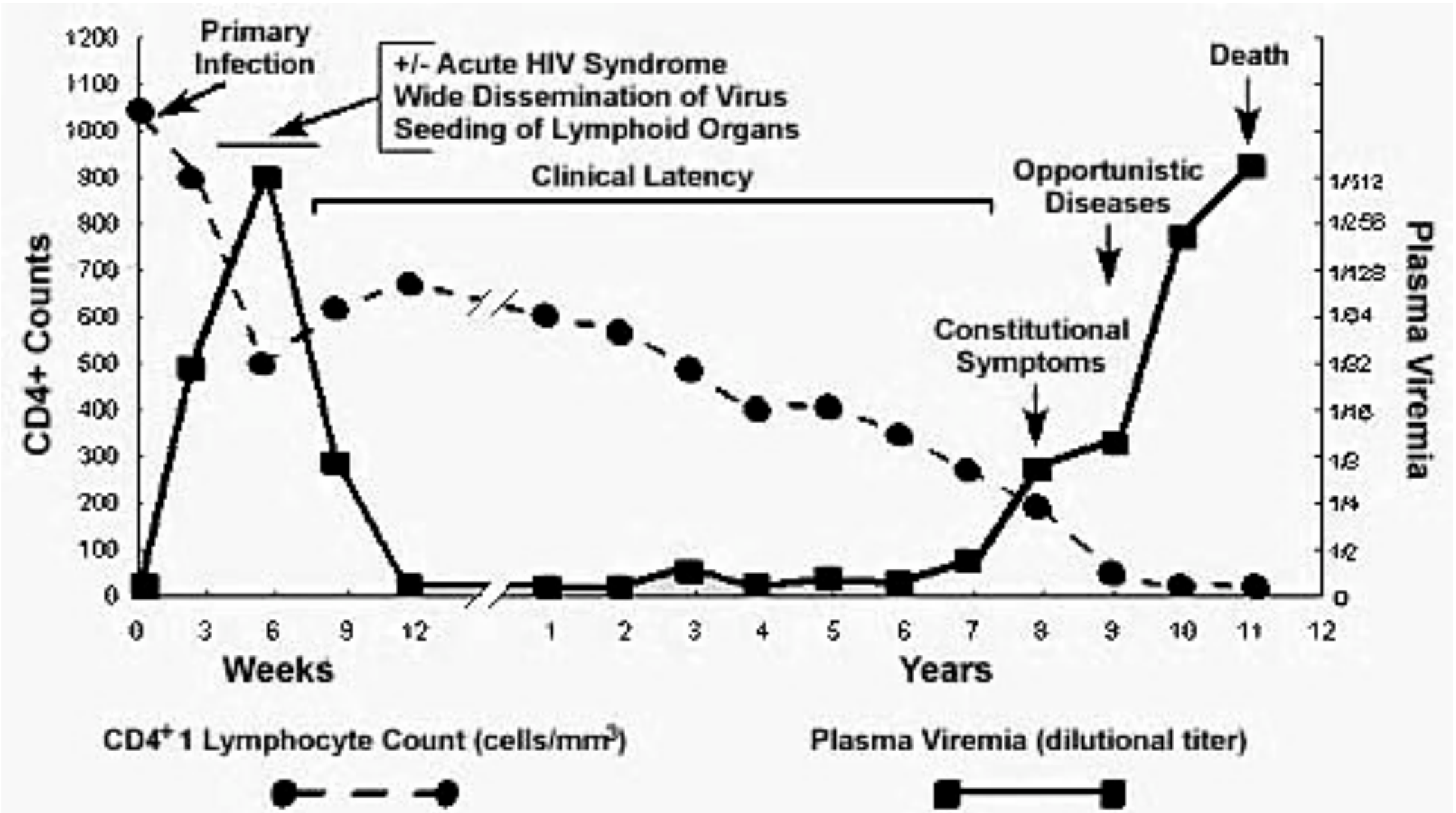




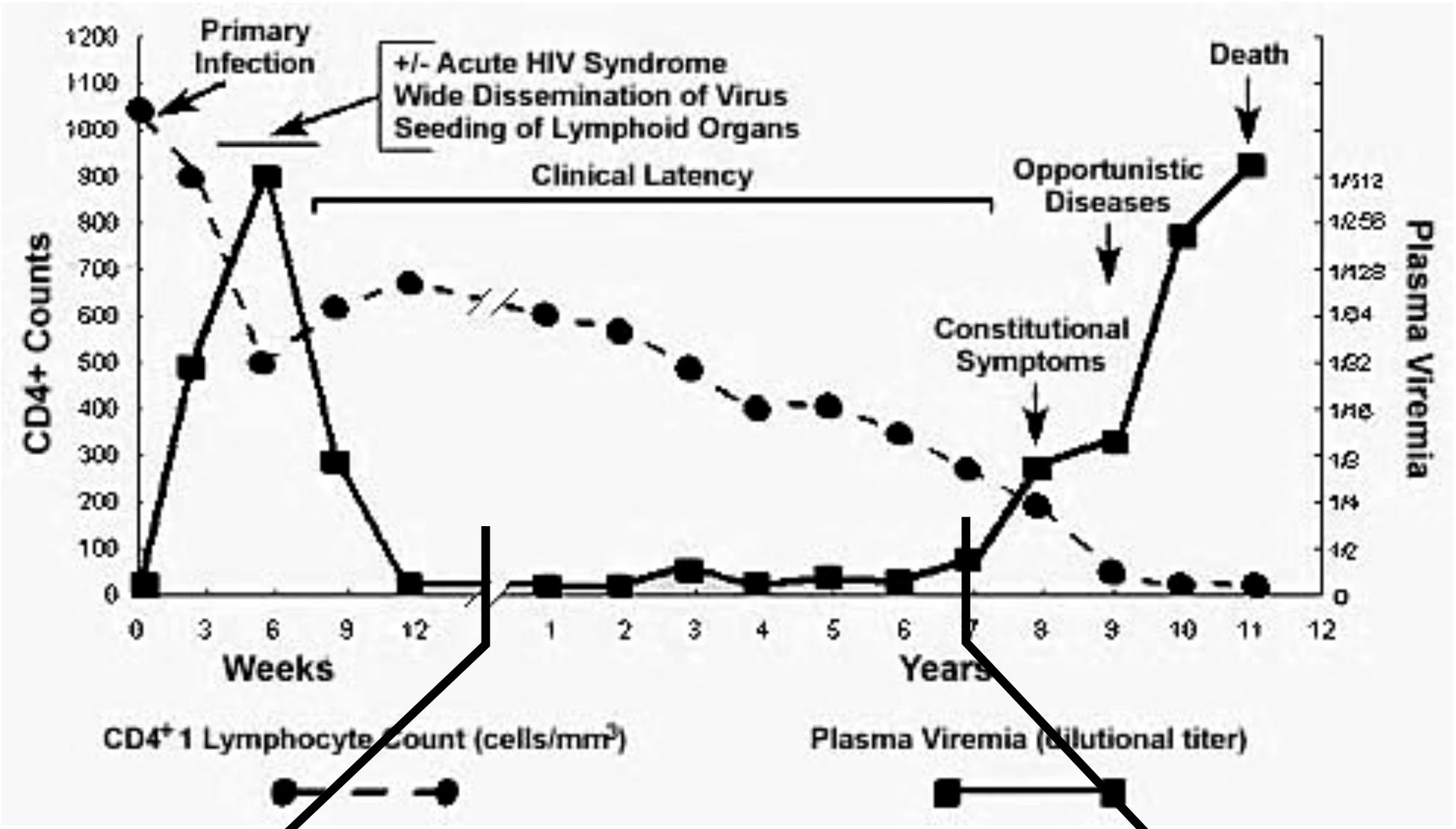
HIV budding from an immune cell

Rapid evolution is a hallmark of HIV infections

HIV

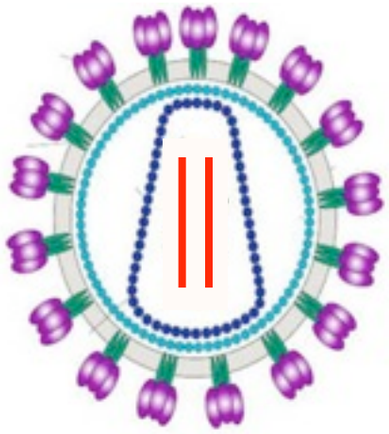

Primary Infection
+/- Acute HIV Syndrome
Wide Dissemination of Virus
Seeding of Lymphoid Organs
Clinical Latency
Opportunistic Diseases
Constitutional Symptoms
Death
CD4+ Counts
Plasma Viremia
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1/512
1/256
1/128
1/64
1/32
1/16
1/8
1/4
1/2
0
0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Years
CD4+ Lymphocyte Count (cells/mm3)
Plasma Viremia (dilutional titer)

HIV



Virus escapes the immune system by continuous evolution

Evolution in a single patient (blood samples every 6 month)



~ 8% divergence in 10 years

==

many millions of years in Drosophila

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

Evolution of HIV

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

Resistance to drugs (protease inhibitors):

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

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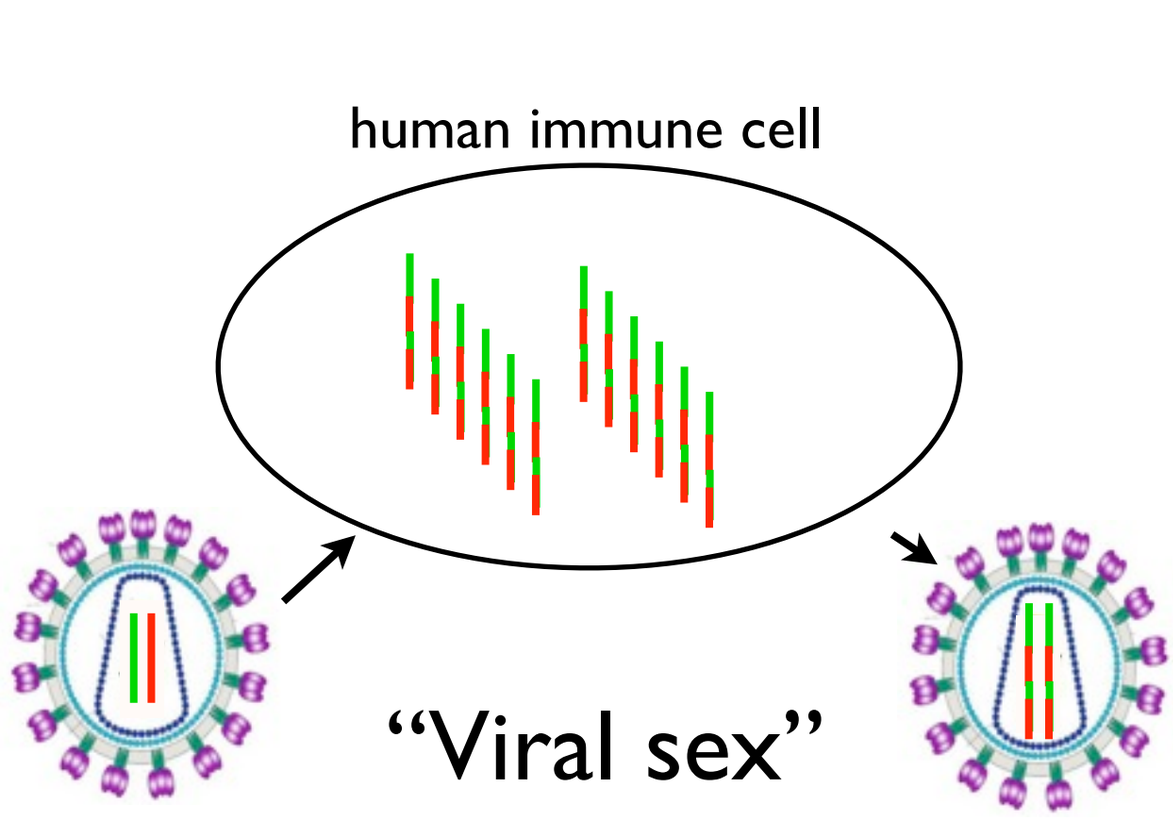
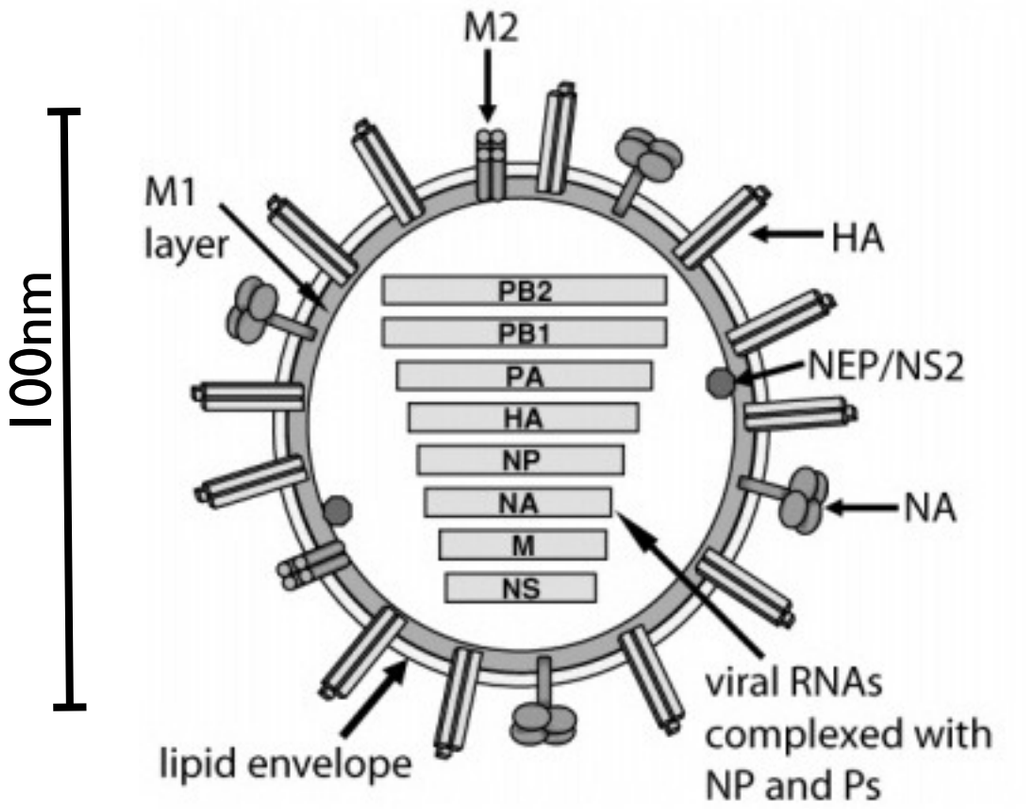


Recombination in viruses - Influenza



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

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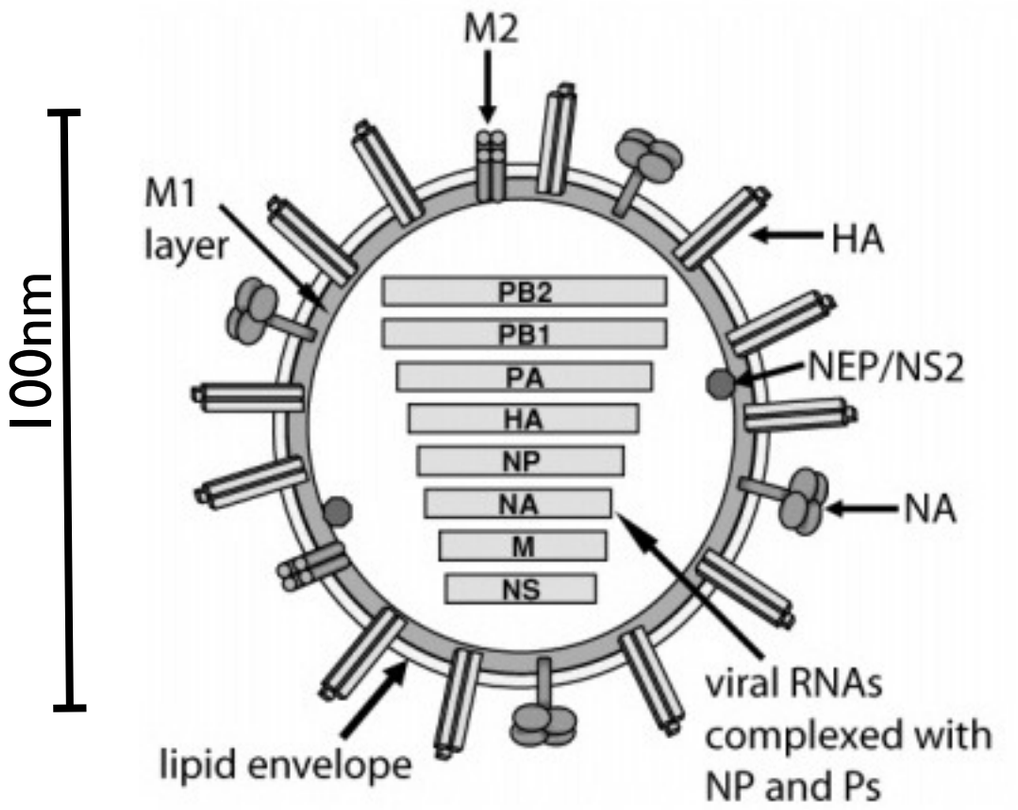

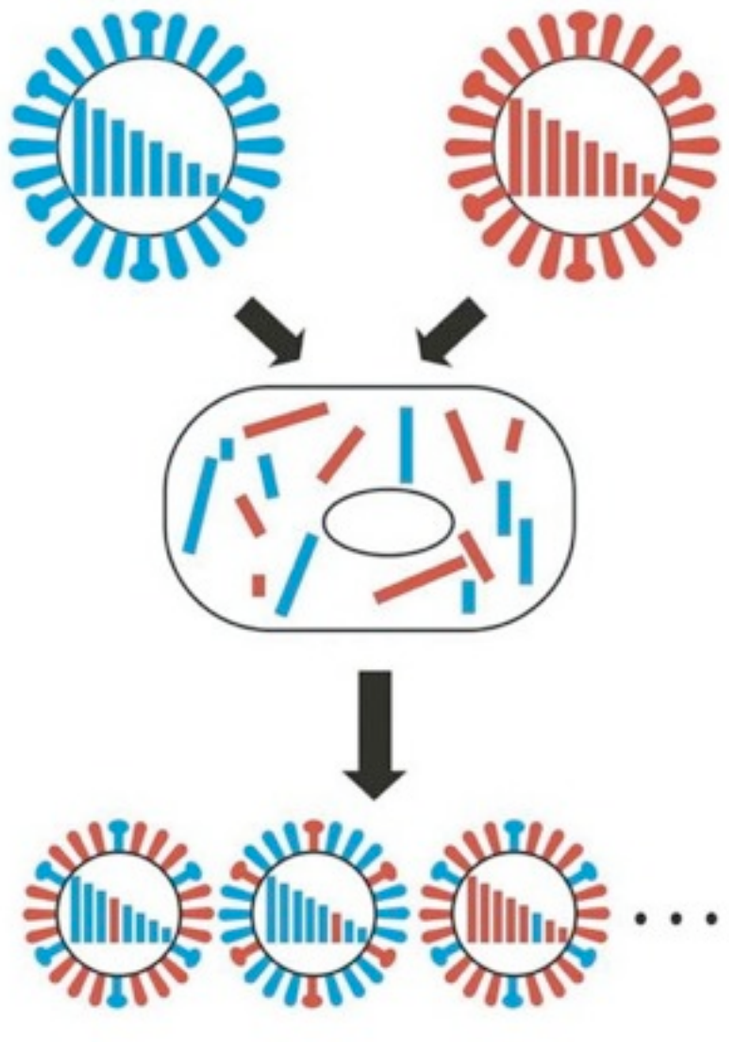

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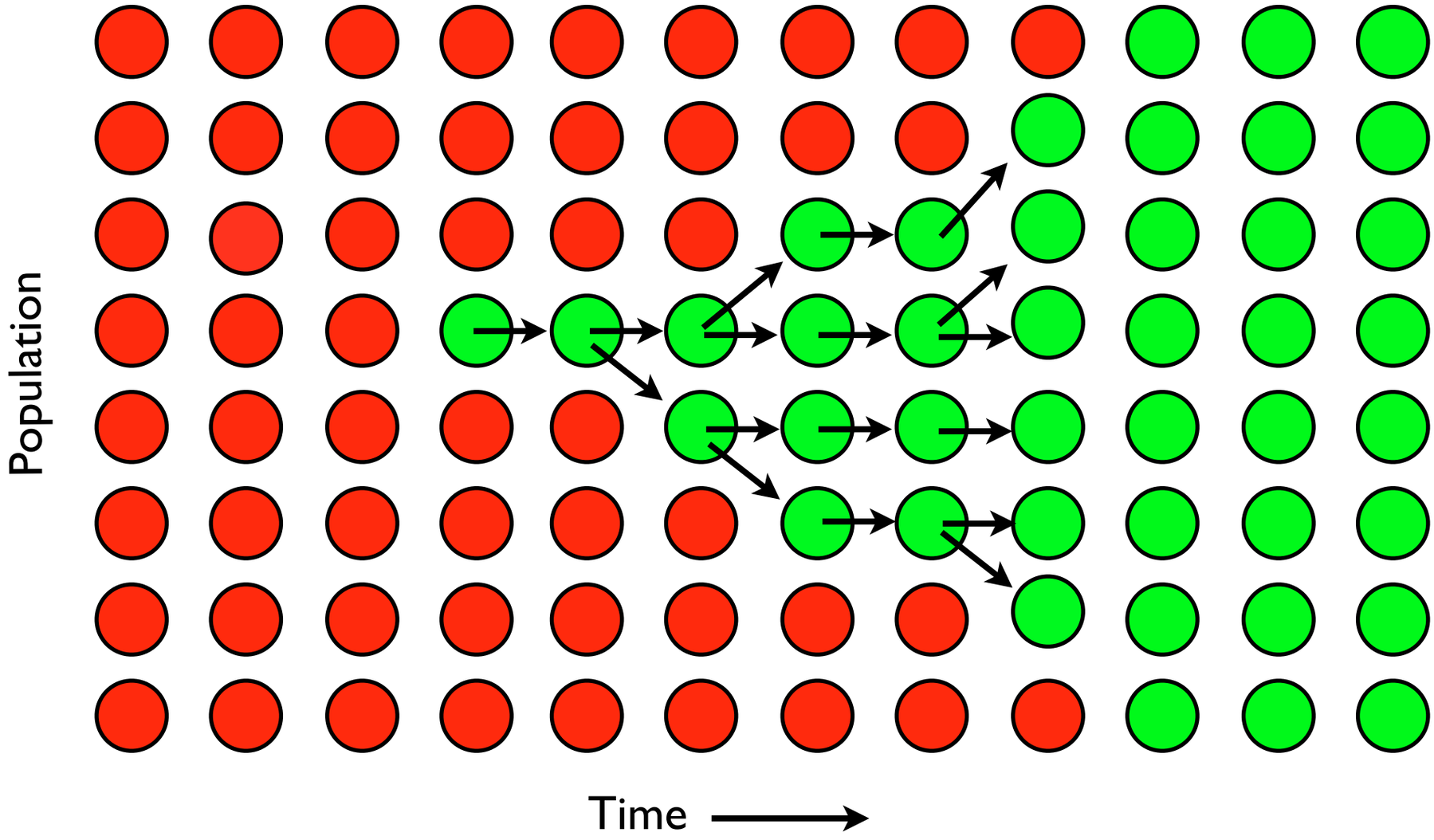
- Pandemics often follow reassortments, e.g. pandemics 1957 (H2N2) and 1968 (H3N2)
- Reassortment is frequent in waterfowl and swine, where many subtypes circulate.

Spreading of beneficial mutations

Mutant individuals reproduce faster
(Drug resistant strain)

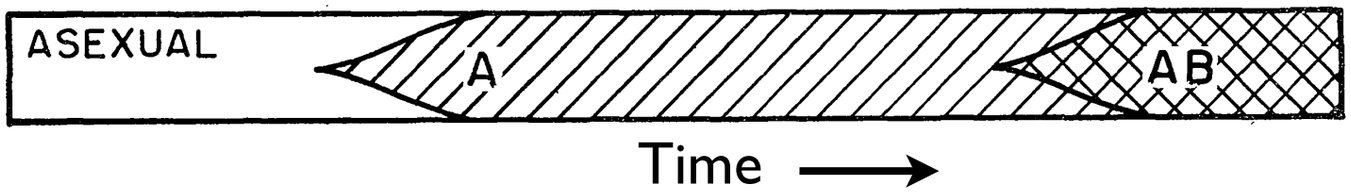


Fixation probability: ~s

Sweep time: ~ ln(Ns) / s

Evolution in asexual and sexual organisms

Small Population



Sequential innovations:
rate ~ N

Evolution in asexual and sexual organisms

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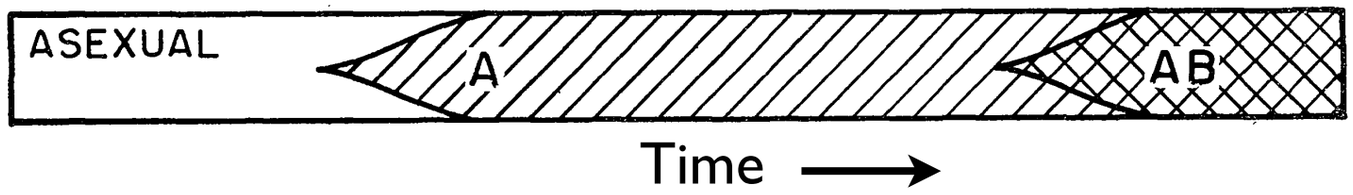
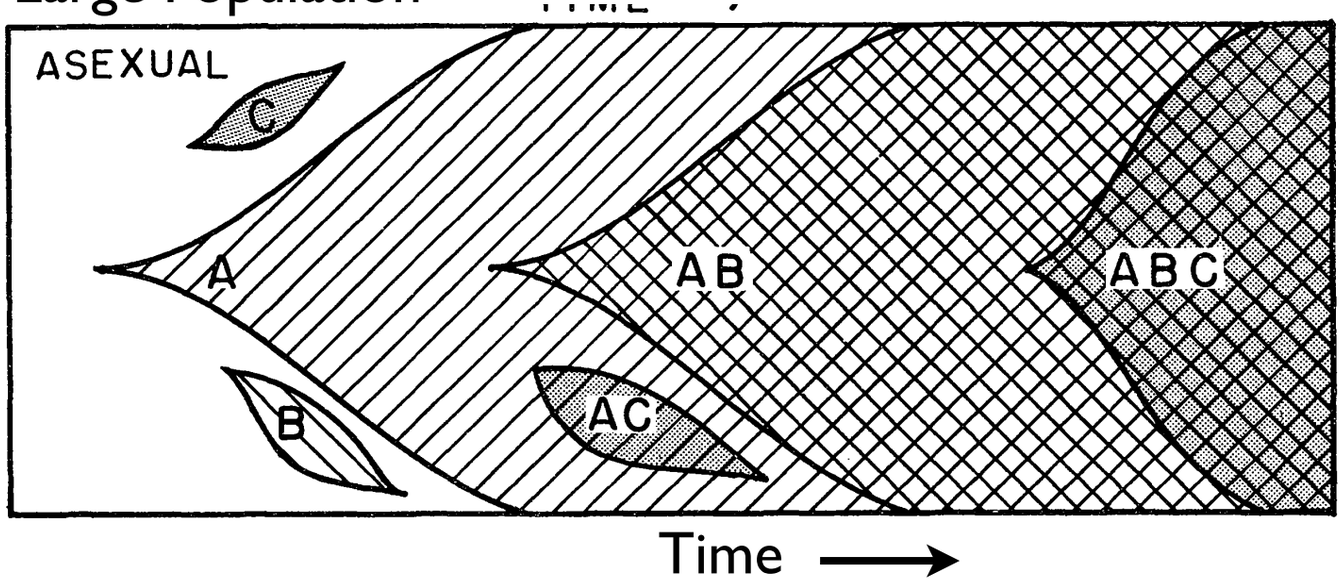


Large Population



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Many concurrent mutations:
rate ~ log N

Most good mutations are wasted!

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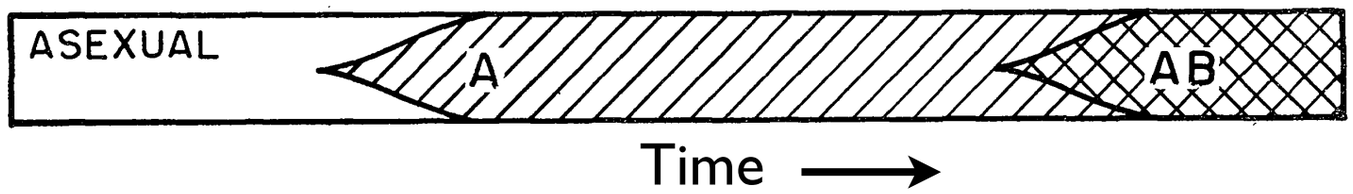

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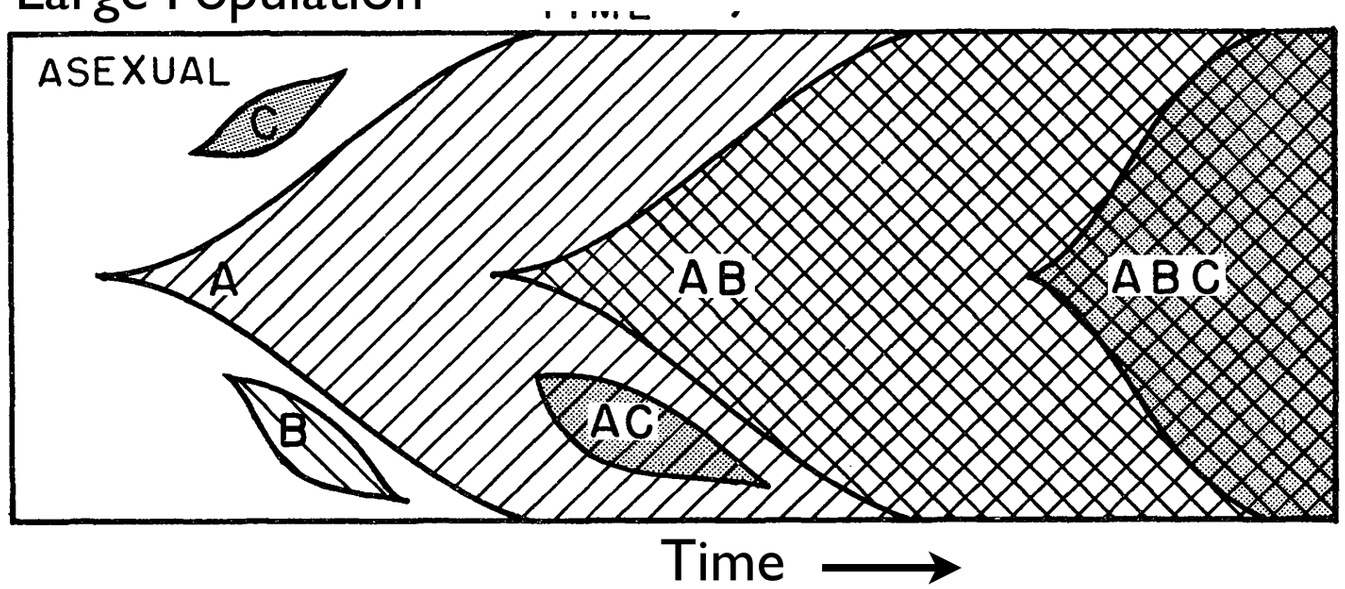

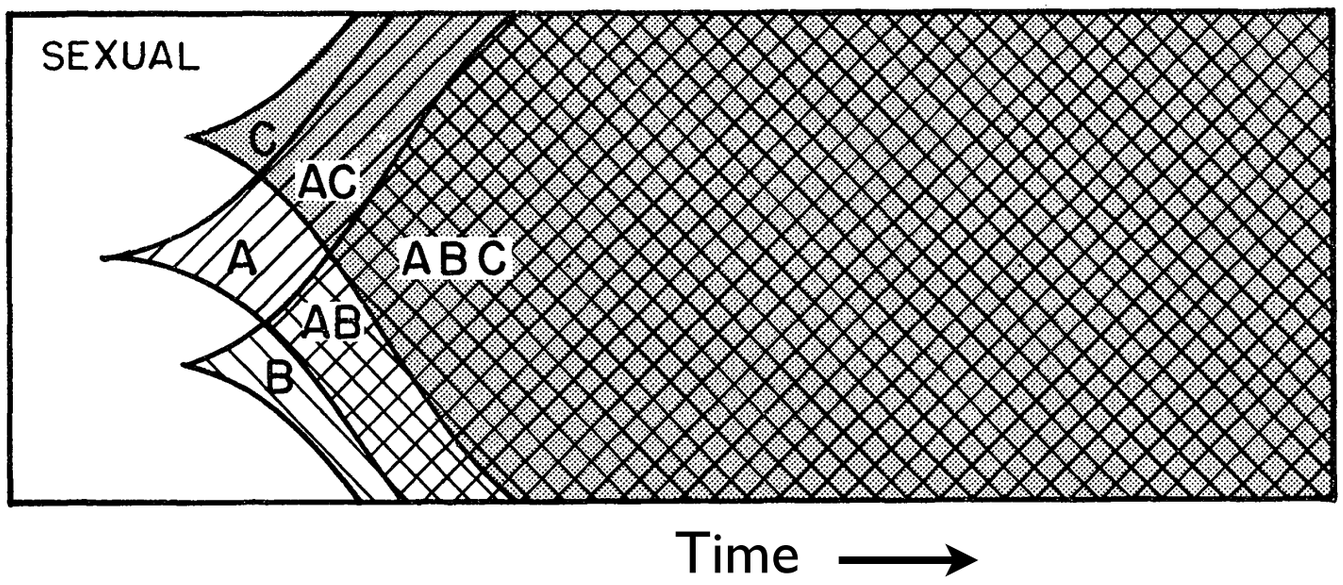

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Many concurrent mutations:
rate ~ log N

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Conventional wisdom:
rate ~ N

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

Quantifying the benefits of recombination [for the virus]

Example: drug resistance of HIV

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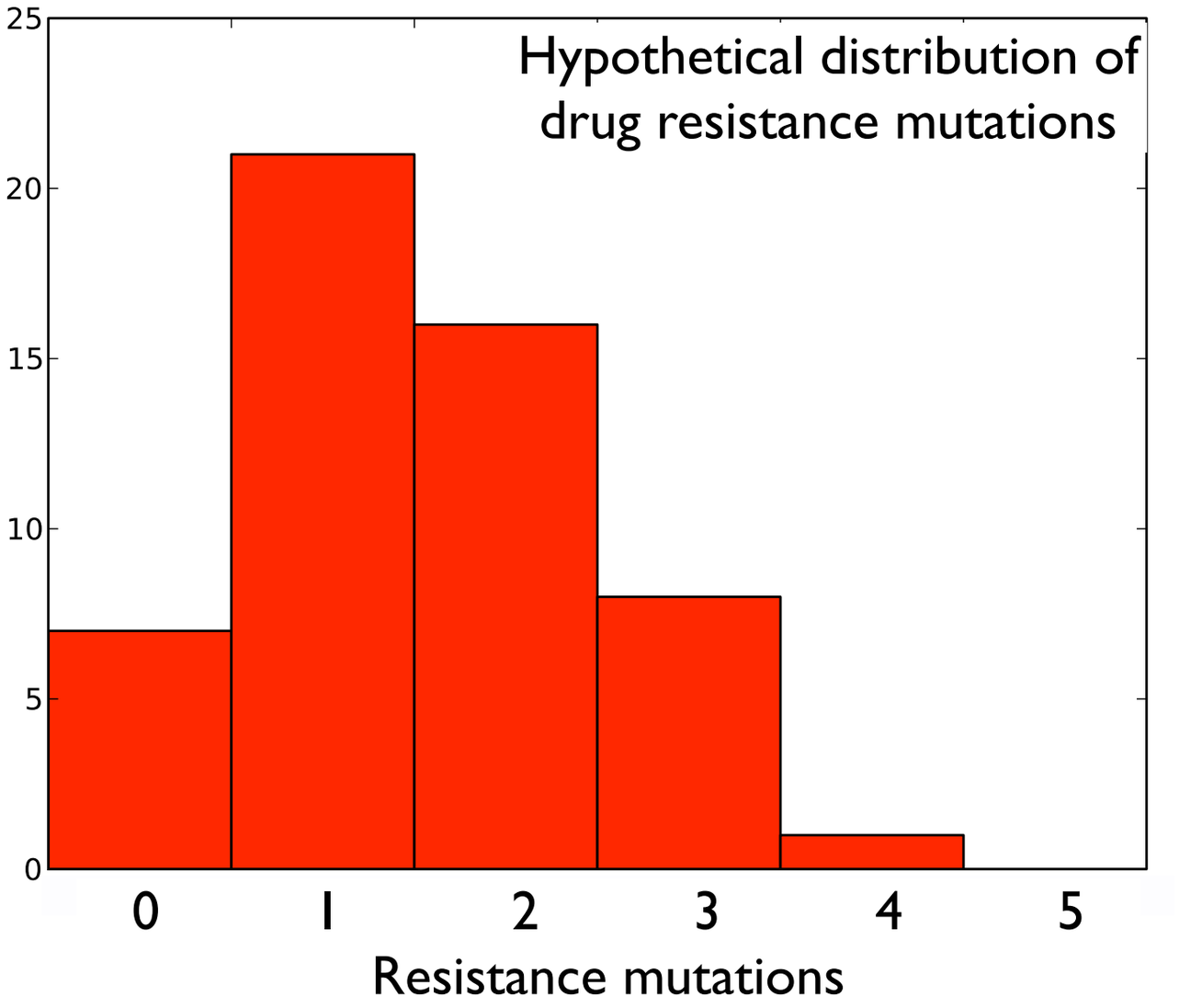

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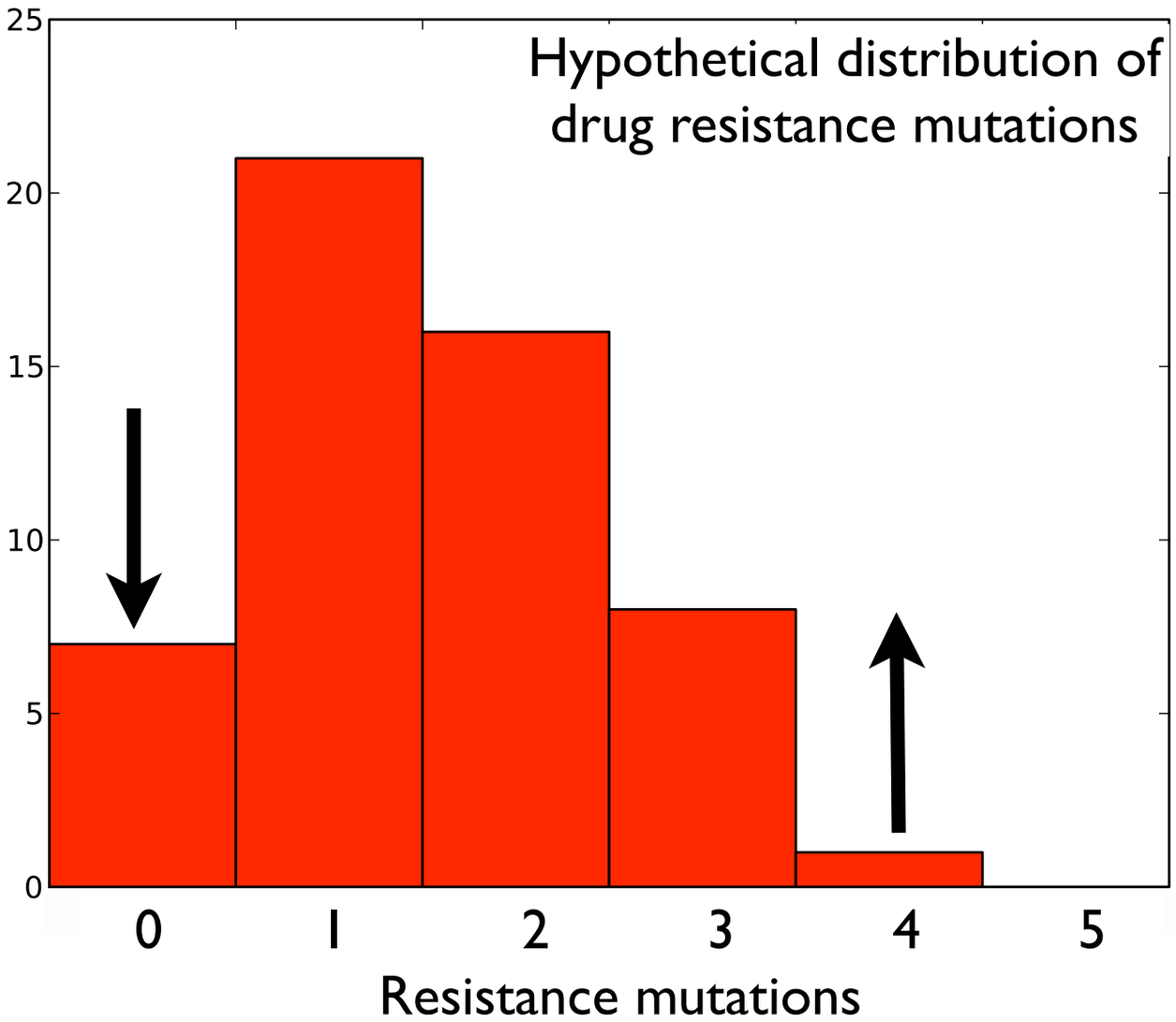

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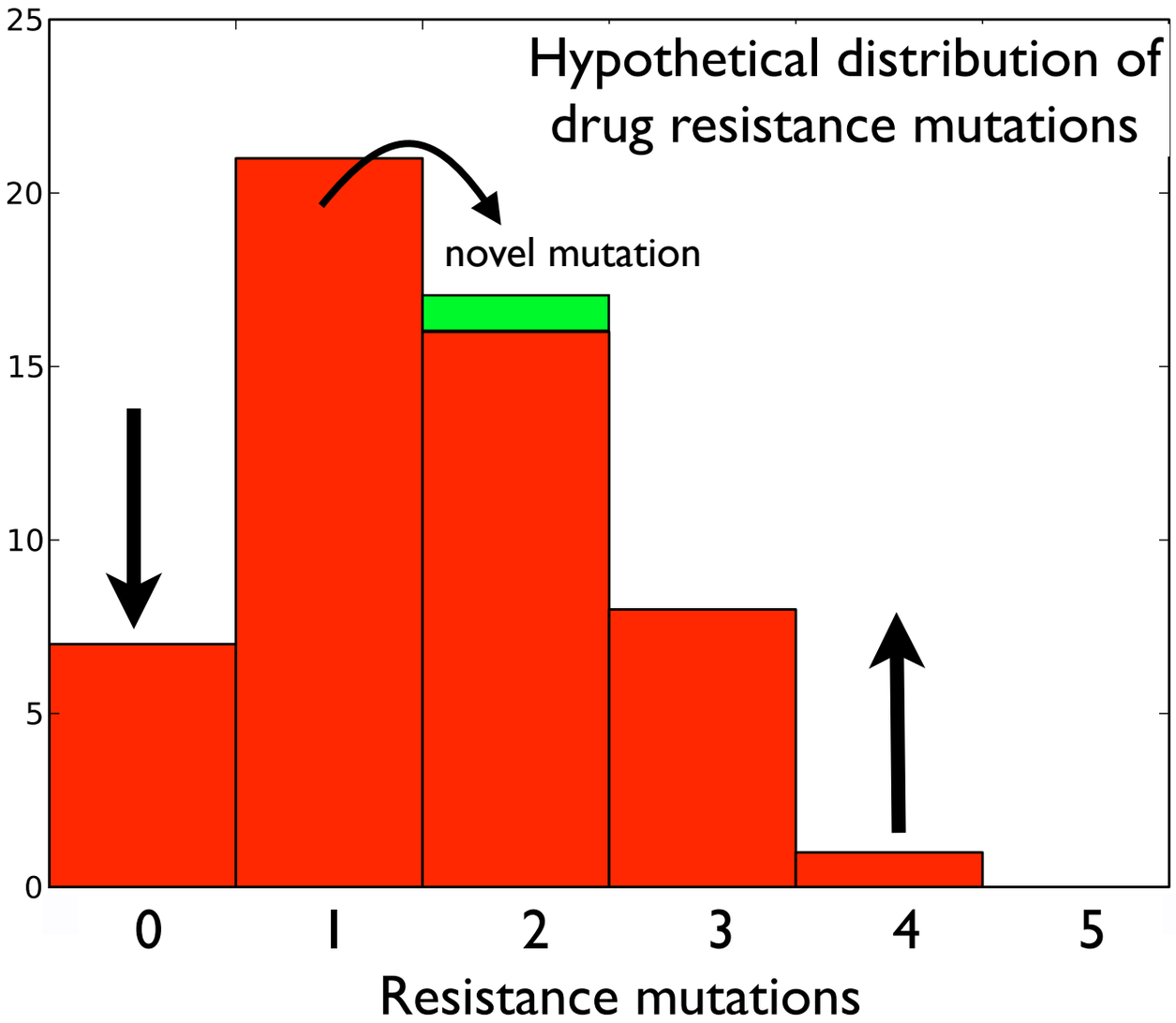

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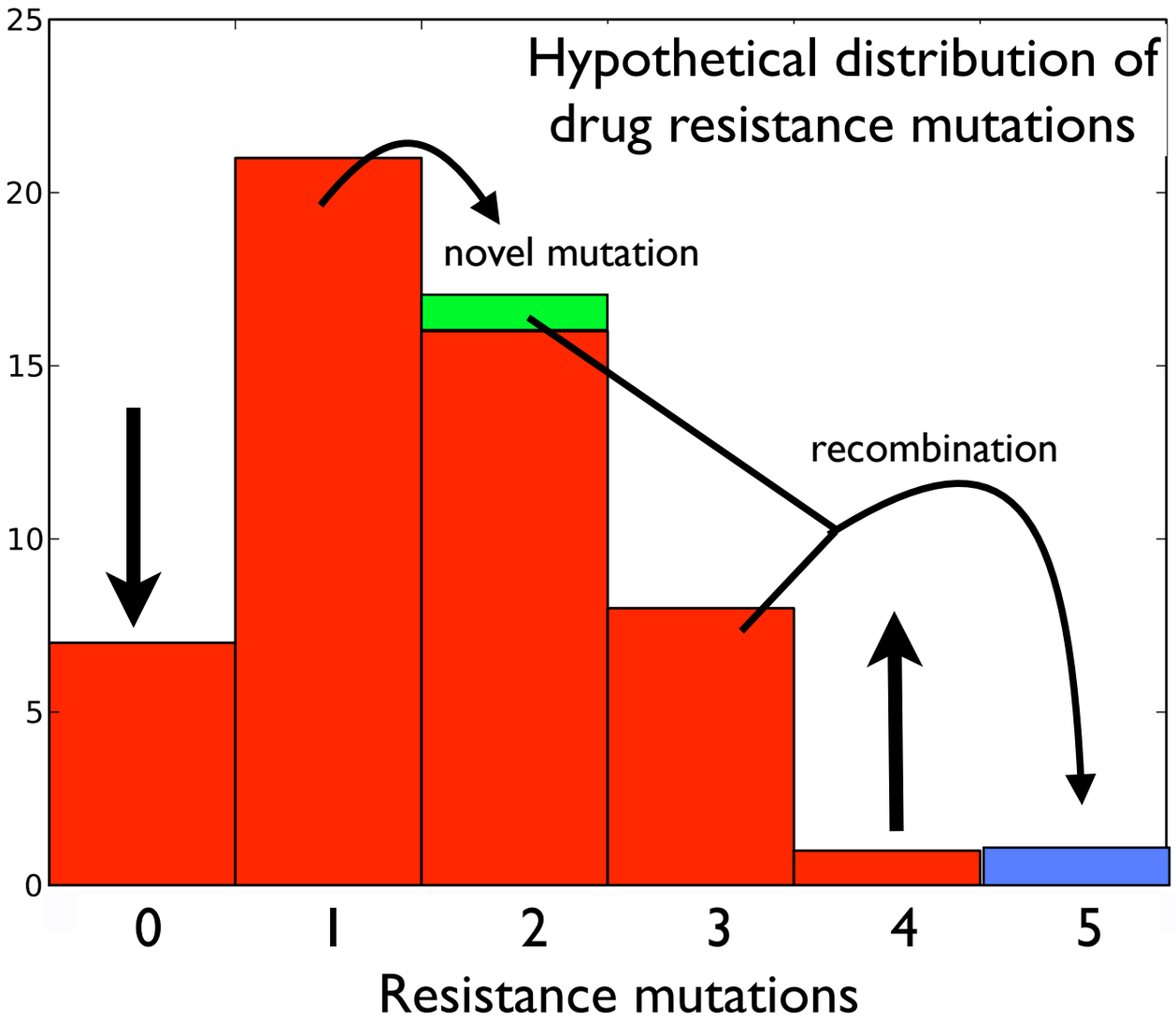

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- Novel mutations keep the wave going
- Via recombination mutations can keep up with the wave and "make it"

Surfing of beneficial mutations

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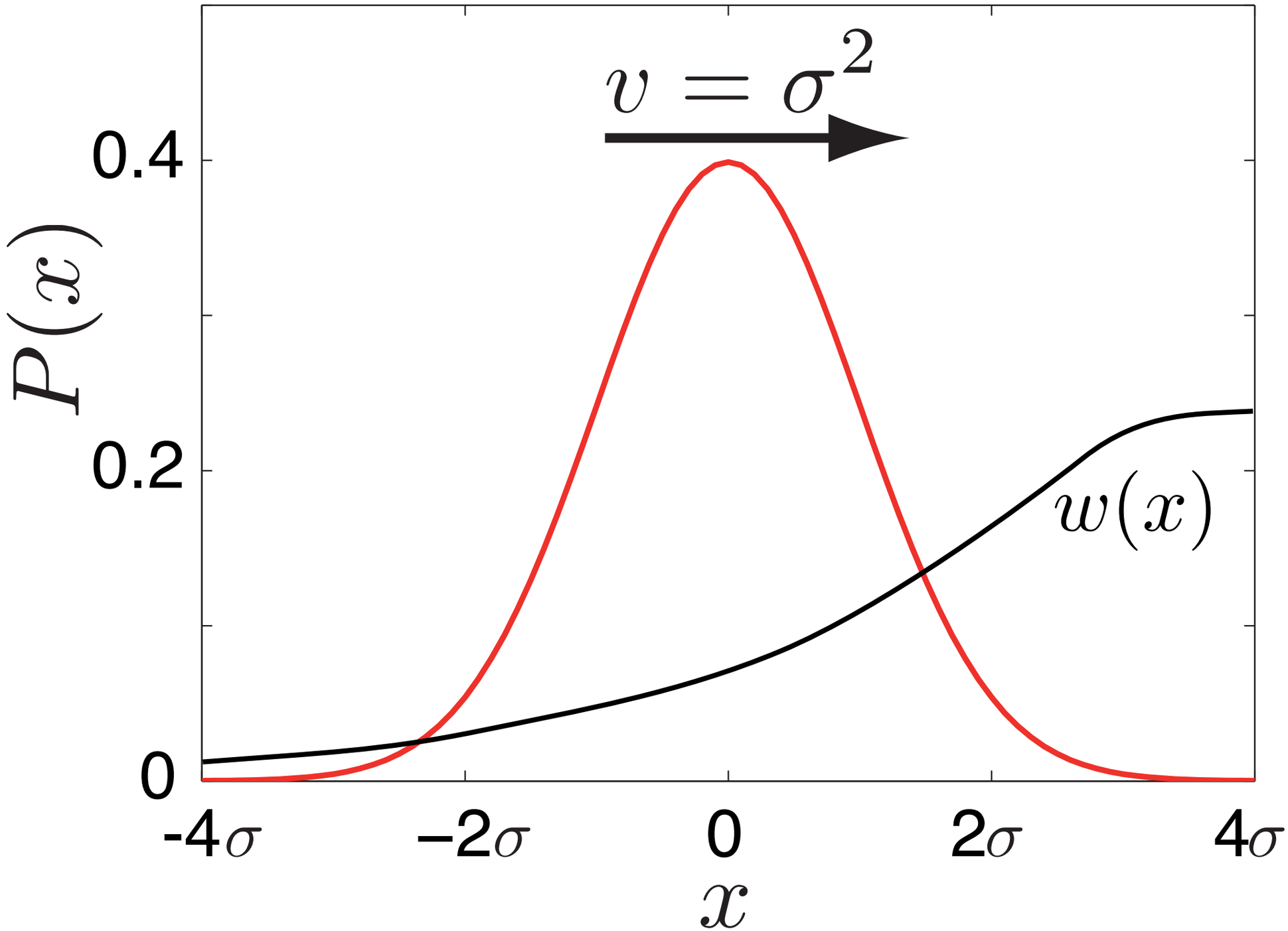

Evolutionary benefits of recombination

Conventional wisdom: rate of evolution ~ N

→ holds only for very frequent recombination

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

To slow down evolution, one has to target recombination rather than the population size!!

The more recombination, the better?

Is there a cost to recombination?

Genetic interactions

So far: Fitness = # beneficial mutations

BUT:

An organism is more than the sum of its parts

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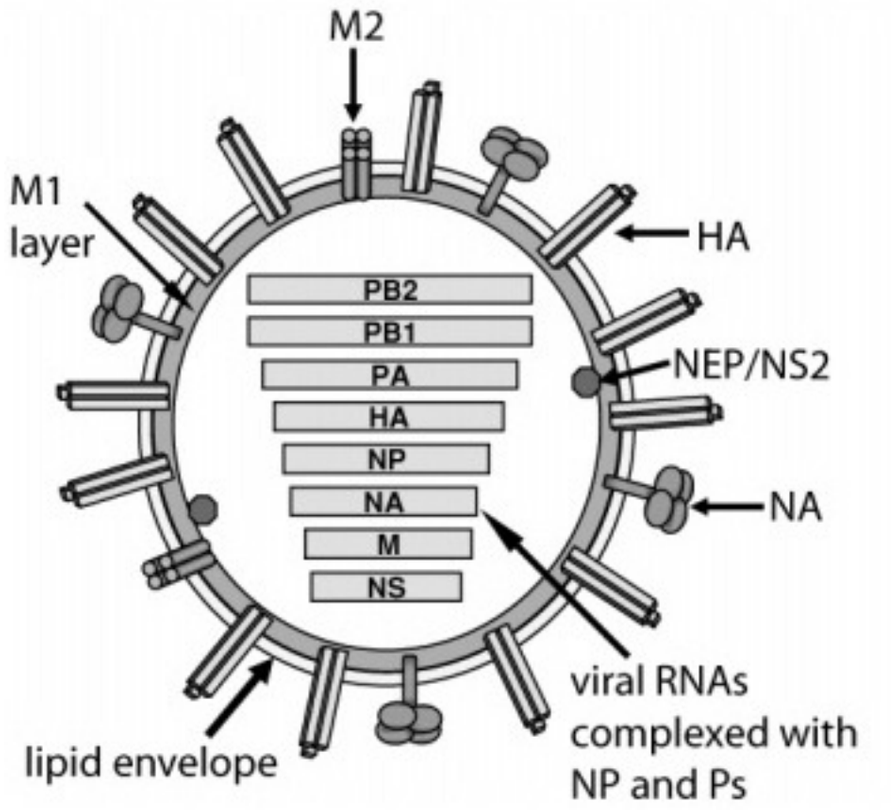

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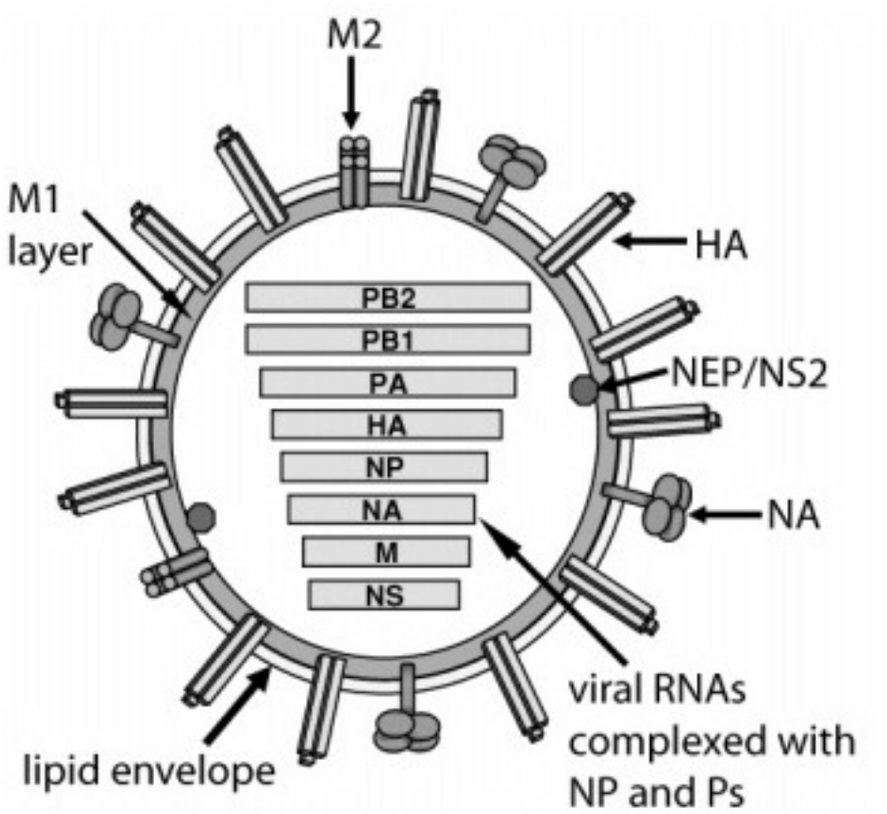

The cost of recombination

A “recombined” soccer team is worse than the “parents”.

The cost of recombination

A "recombined" soccer team is worse than the "parents".

Relay racing teams don't have that problem!

Genetic interaction and recombination

Different reassortments of Influenza A:

Recombination explores -- selection amplifies the best

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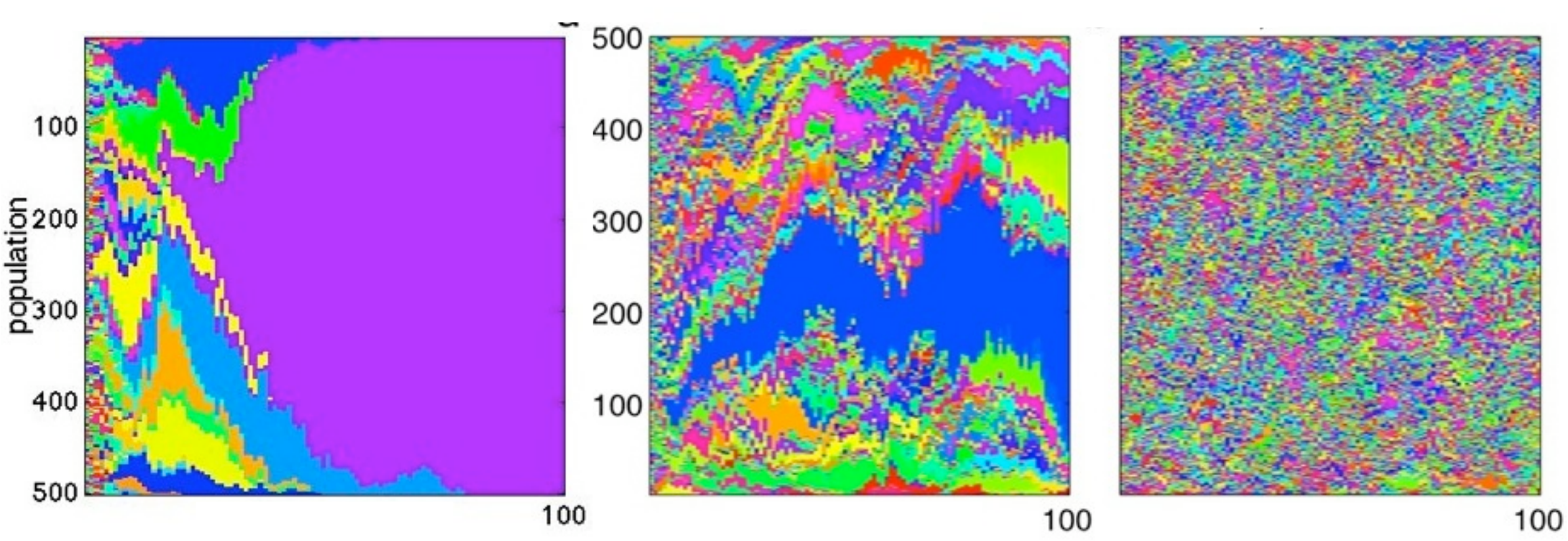
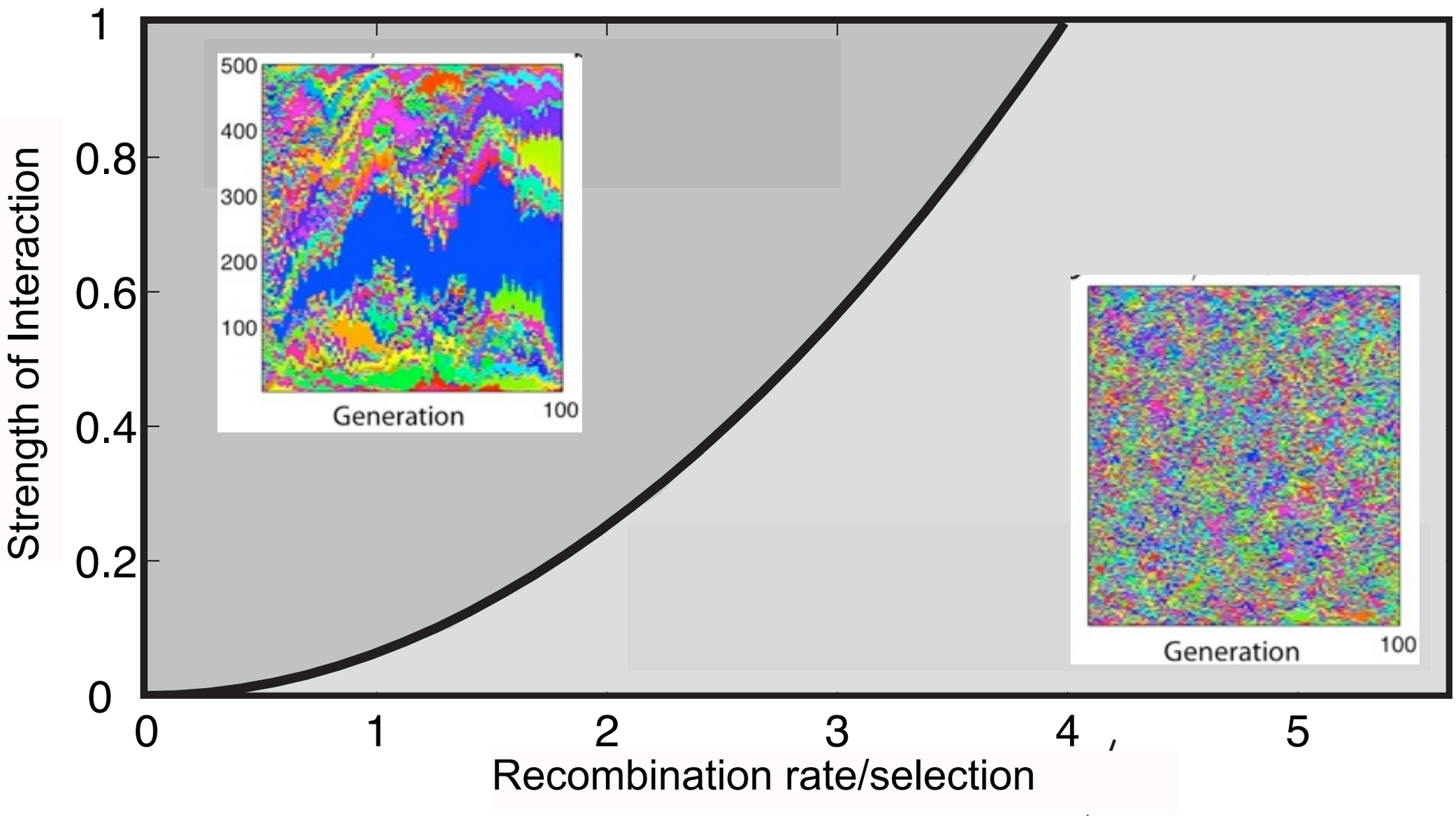
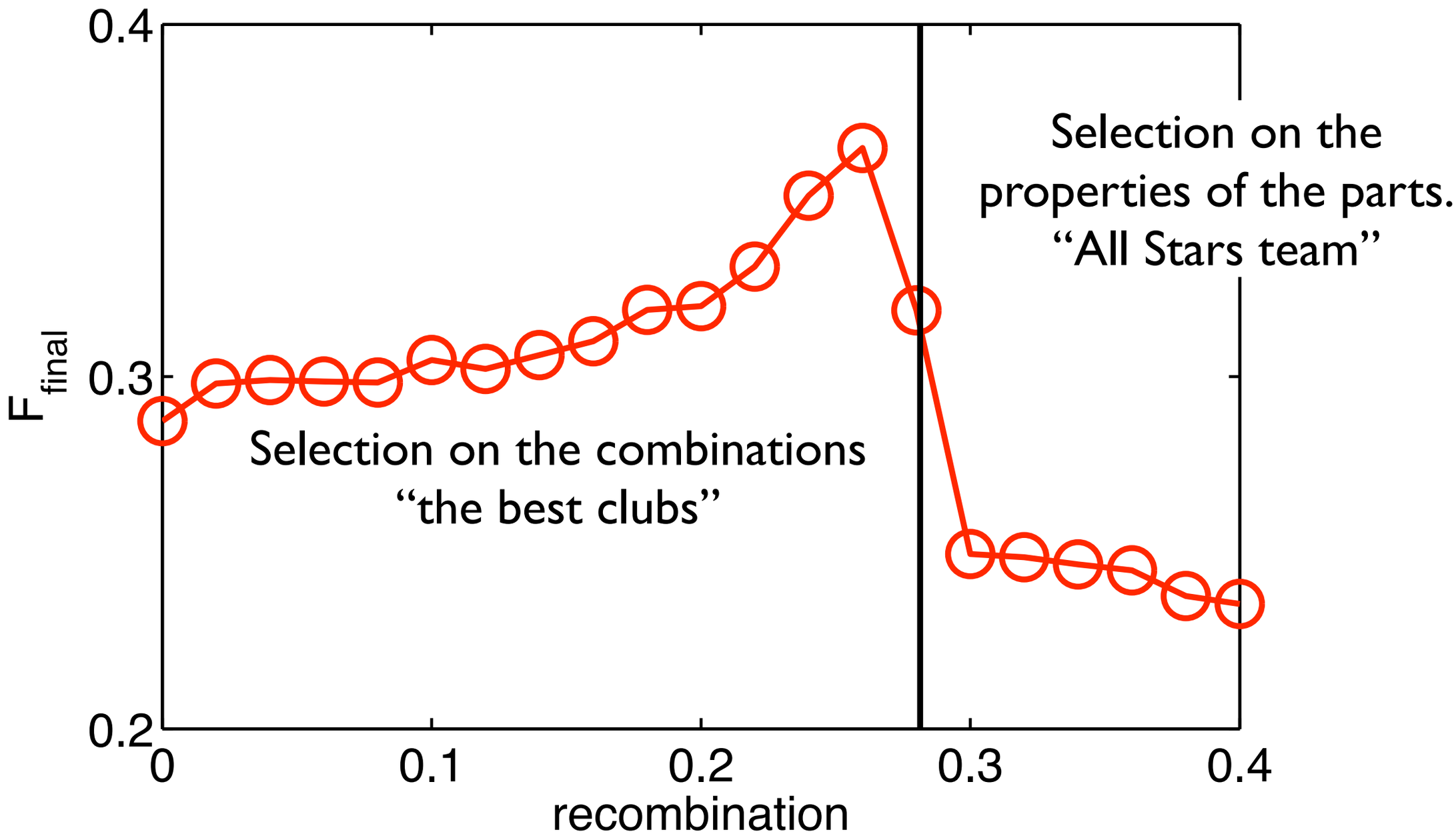


no recombination moderate recombination frequent recombination

Allele vs genotype selection



The success of selection



Connecting theory and observations

Large data bases of HIV sequences and drug resistance allow us to study:

- The recombination rate in HIV
- Selection strength of HIV evolution without drugs
- Drug resistance mutations: team players or independent?
- Does recombination vary from patient to patient?
- Does it vary at different stages of the disease?

- With modern sequencing technology we can soon monitor viral populations at unprecedented resolution.

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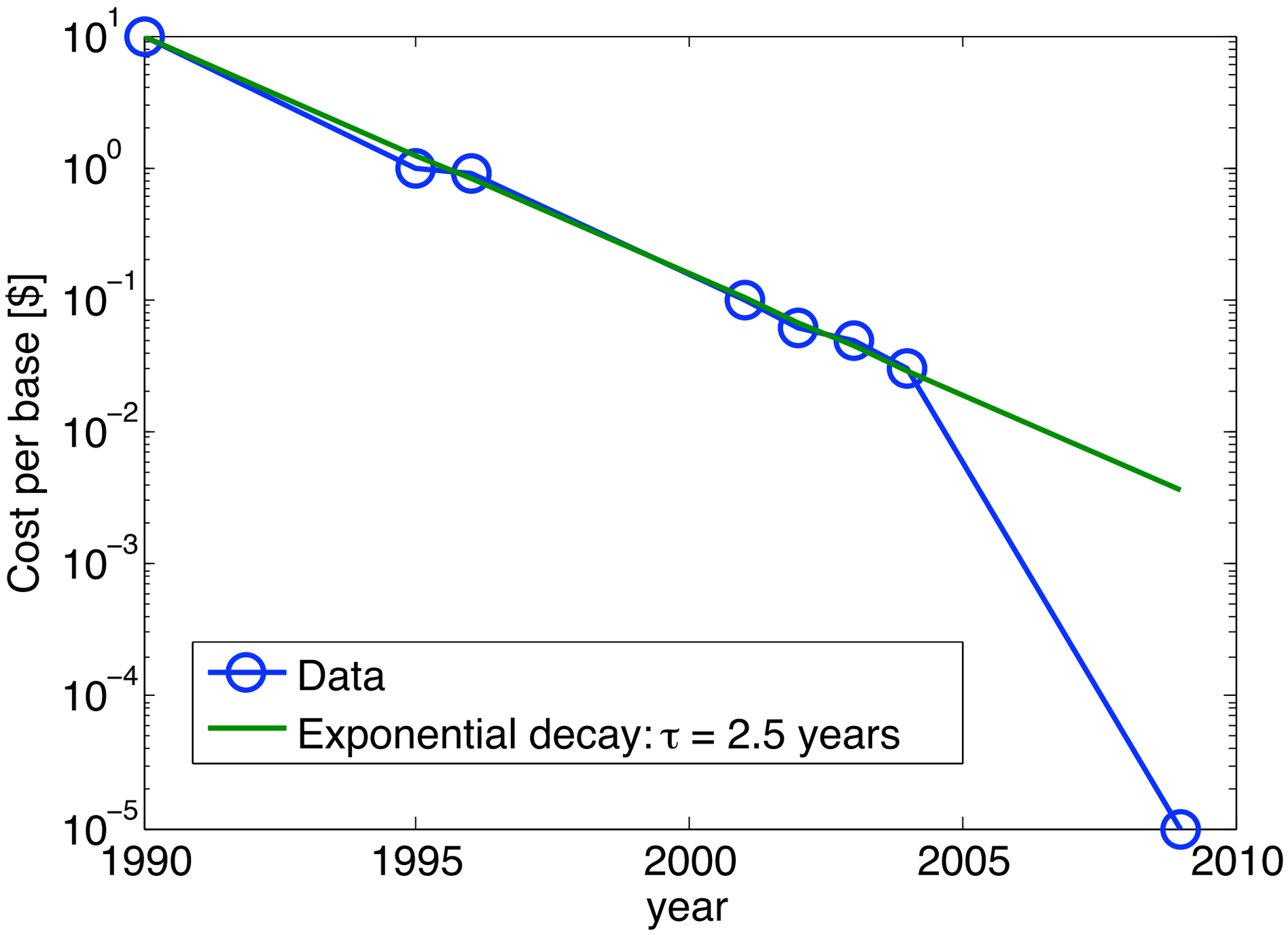
What can we learn about the evolutionary process in general?

Sequencing Costs per Base



Darwin's Theory

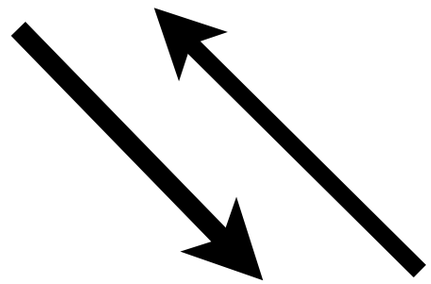
Observations:

Paleontology

Diversity of species

Darwin's Theory

Quantitative Theory
Dynamics

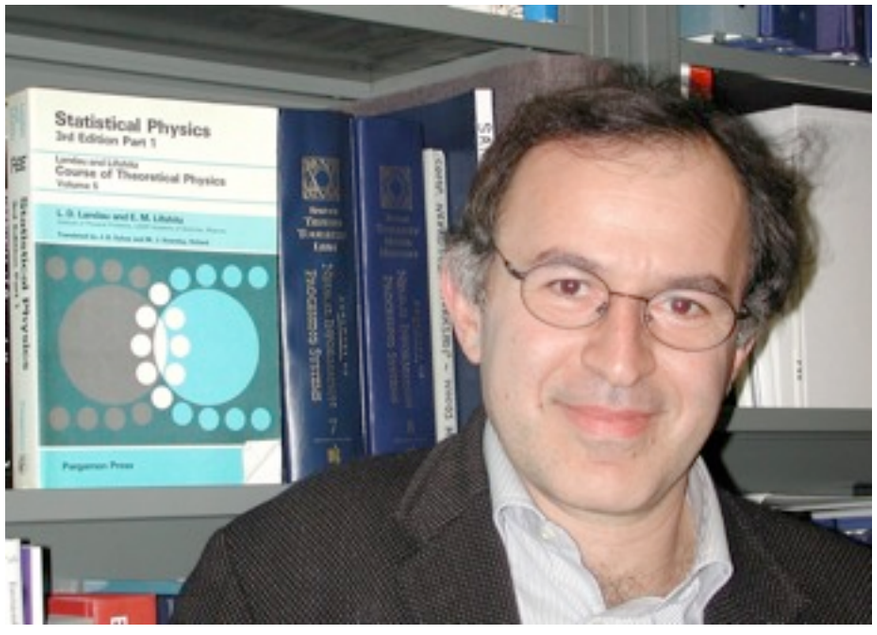


Experiments in the Lab

- Bacteria or viruses
- Sequencing and Phenotyping

Observations:
Paleontology
Diversity of species

Collaborators



Boris Shraiman, KITP

Daniel Fisher, Stanford

Thomas Leitner, LANL