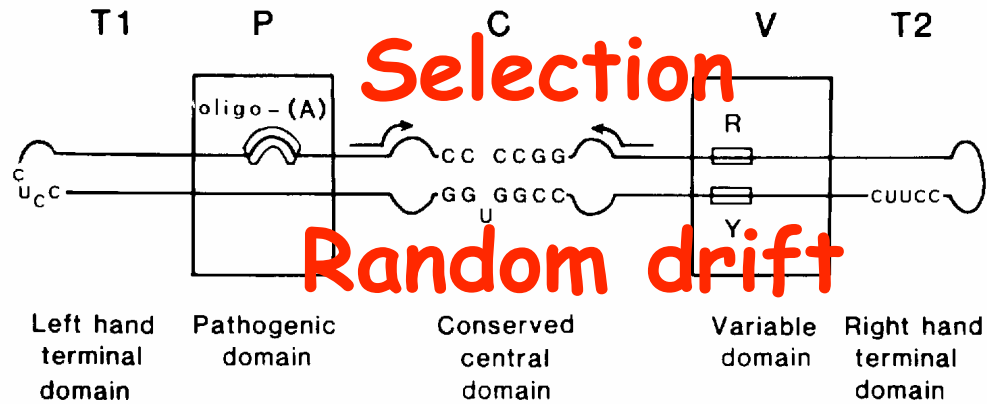


Experimental virus evolution

Santiago F. Elena

Mutation



Contingency

Advantages of microorganisms for evolution experiments

They are easy to propagate and enumerate.

They reproduce quickly, which allows experiments to run for many generations.

They allow large populations in small spaces, which facilitates experimental replication.

They can be stored in suspended animation and later revived, which allows the direct comparison of ancestral and evolved types.

Many microbes reproduce asexually and the resulting clonality enhances the precision of experimental replication.

Asexuality also maintains linkage between a genetic marker and the genomic background into which it is placed, which facilitates fitness measurements.

It is easy to manipulate environmental variables, such as resources, as well as the genetic composition of founding populations.

There are abundant molecular and genomic data for many species, as well as techniques for their precise genetic analysis and manipulation.

Peculiarities of RNA viruses

High genetic variability. Orders of magnitude greater than for DNA-based organisms.

High mutation rates: 1.3×10^{-5} s/s/r for polio or 2.5×10^{-4} for VSV. Such mutation rates are consequence of the lack of proofreading mechanisms in viral RdRp.

Compacted genome: 11162 nts for VSV and 9494 for TEV.

Huge numbers of generations per time unit: $\sim 10^3$ PFU/cell in 6 - 8 hpi for VSV or $\sim 10^6$ LFU/g 5 dpi for TEV.

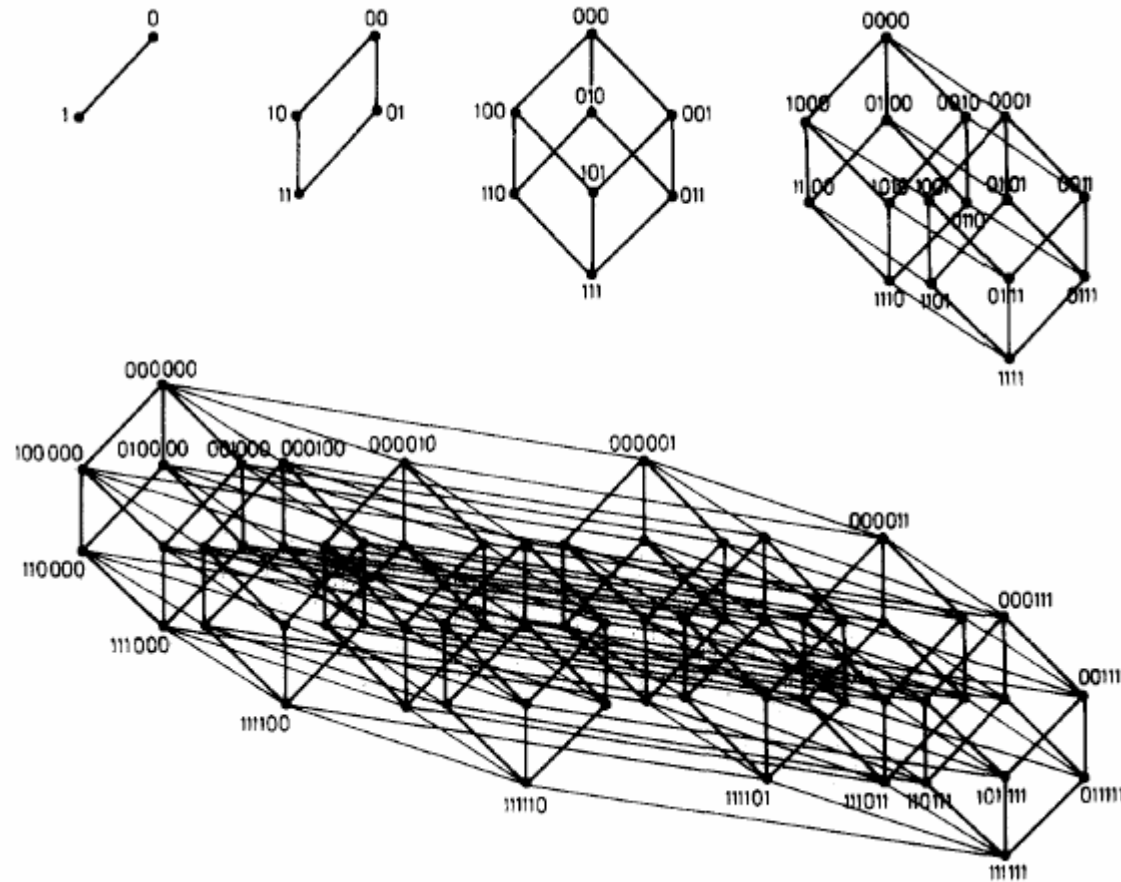
The variability is a key factor for pathogenicity.

It is impossible talking about a single defined entity. Instead we shall talk on a distribution of genomes centered around a more frequent one: *Quasispecies*.

Relatively easy to map genotypes into phenotypic space.

Viral infectious diseases represent the most important threat to animal and plant health.

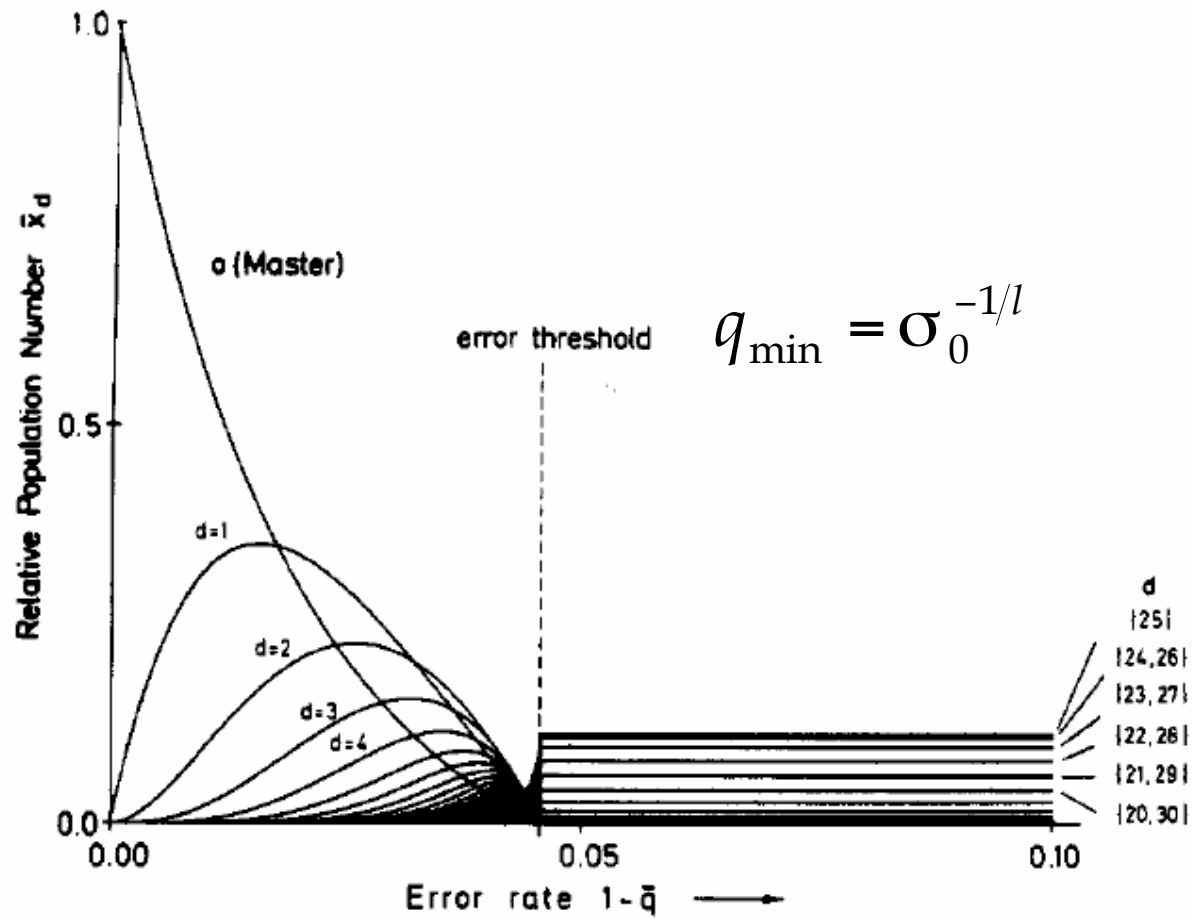
The Quasispecies model of virus evolution



$$\dot{x}_i(t) = [W_{ii} - E(t)]x_i(t) + \sum_{j \neq i} W_{ij}x_j(t)$$

$$W_{ij} = A_i q_{ij}$$

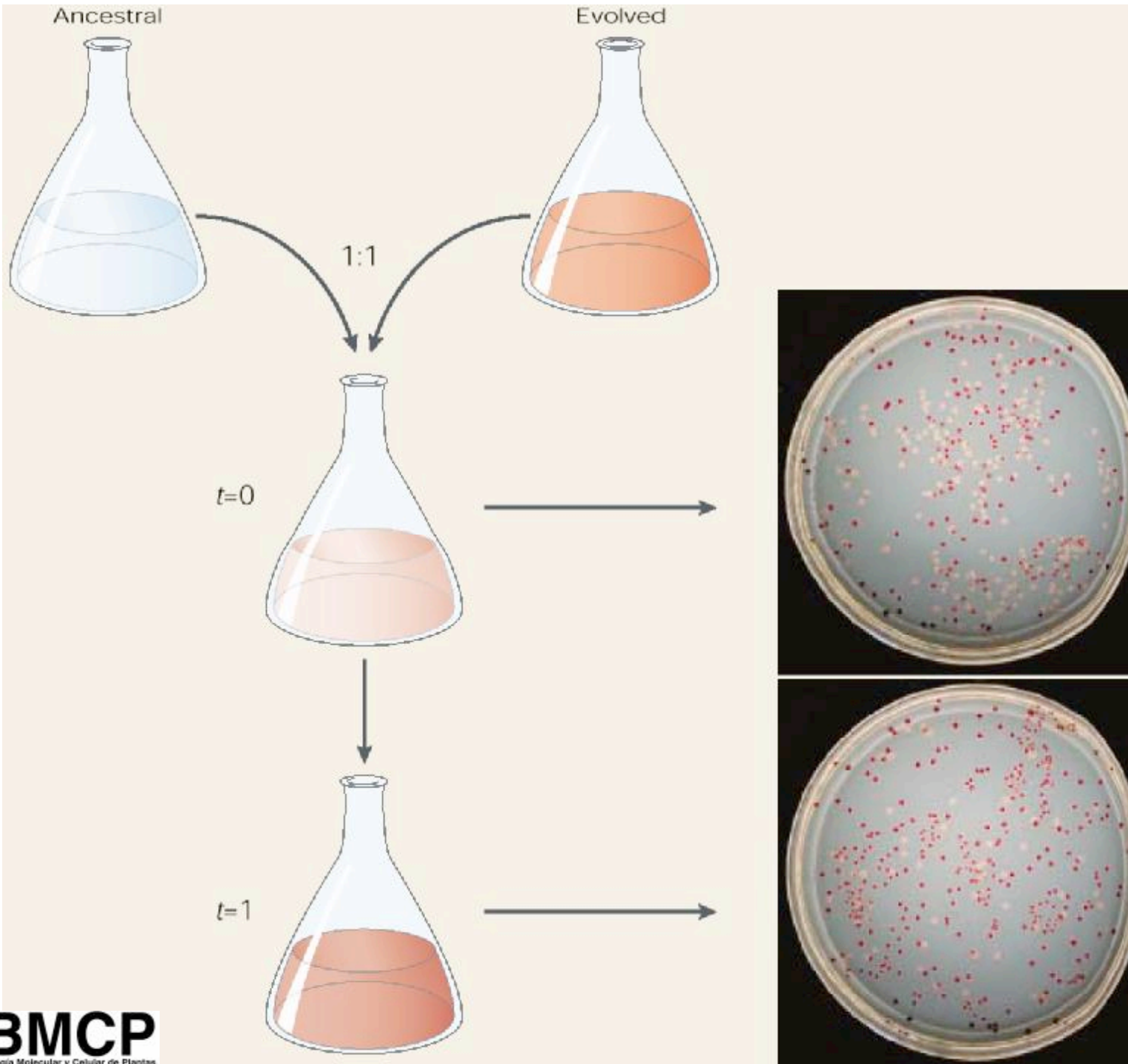
The Quasispecies model of virus evolution



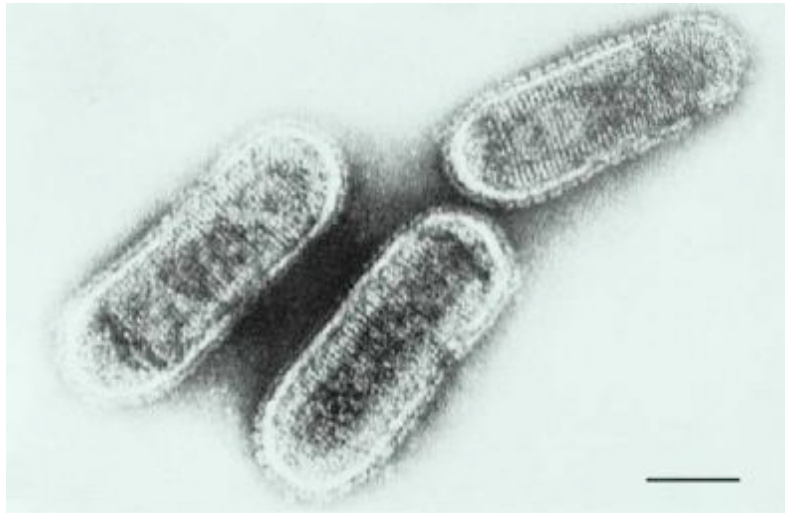
Quantifying the degree of adaptation

Relative Darwinian fitness: Reproductive ability of a given viral strain in a defined environment. This is a macroscopic property that includes components such as replication, transcription and encapsidation rates as well as virion stability in the environment, resistance to antiviral responses and transmission or adsorption rates.

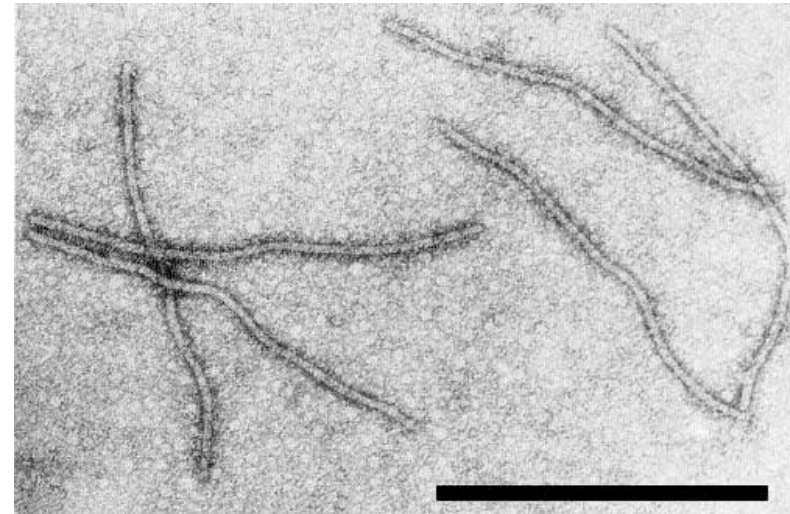
Competition experiments between ancestral and evolved strains



Vesicular stomatitis *rhabdovirus*



Tobacco etch *potyvirus*

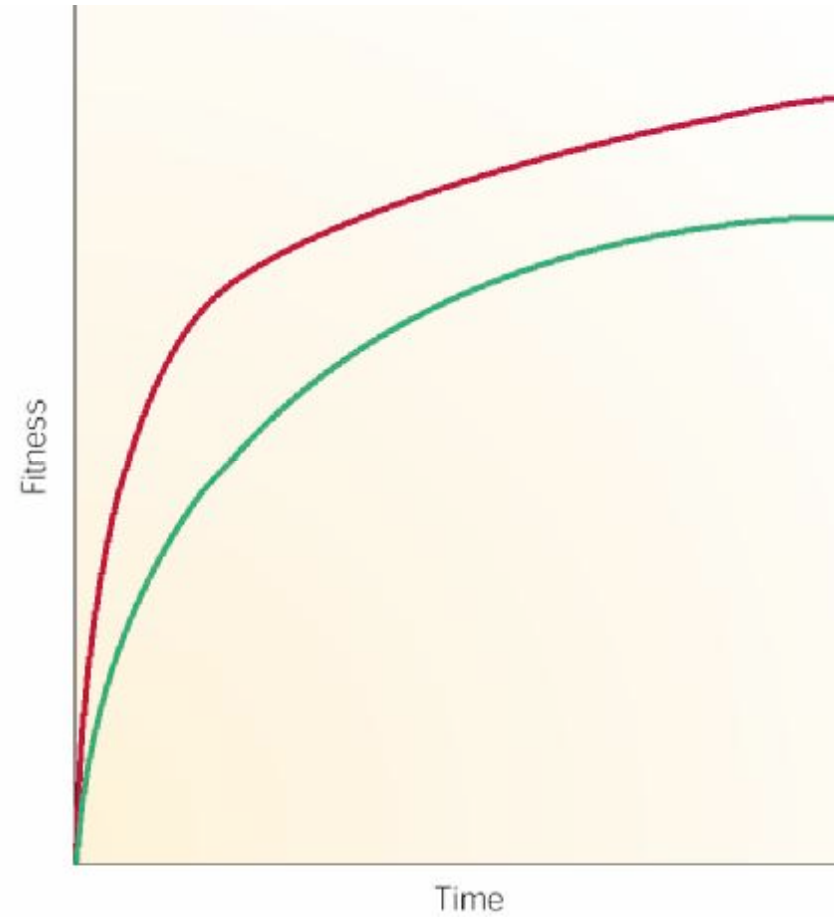
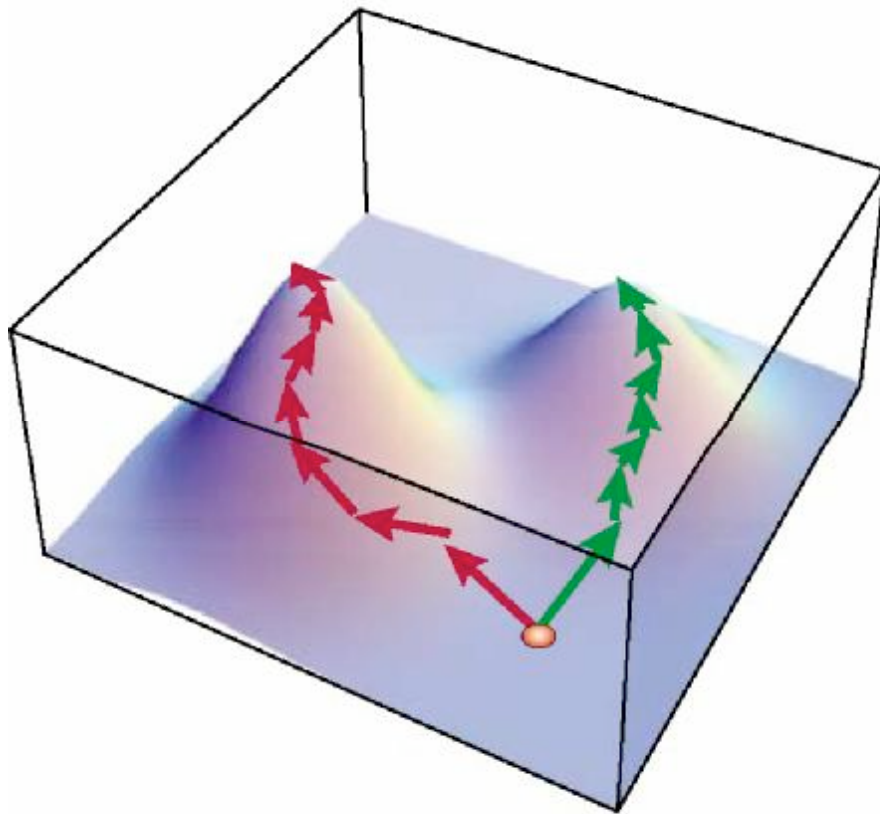


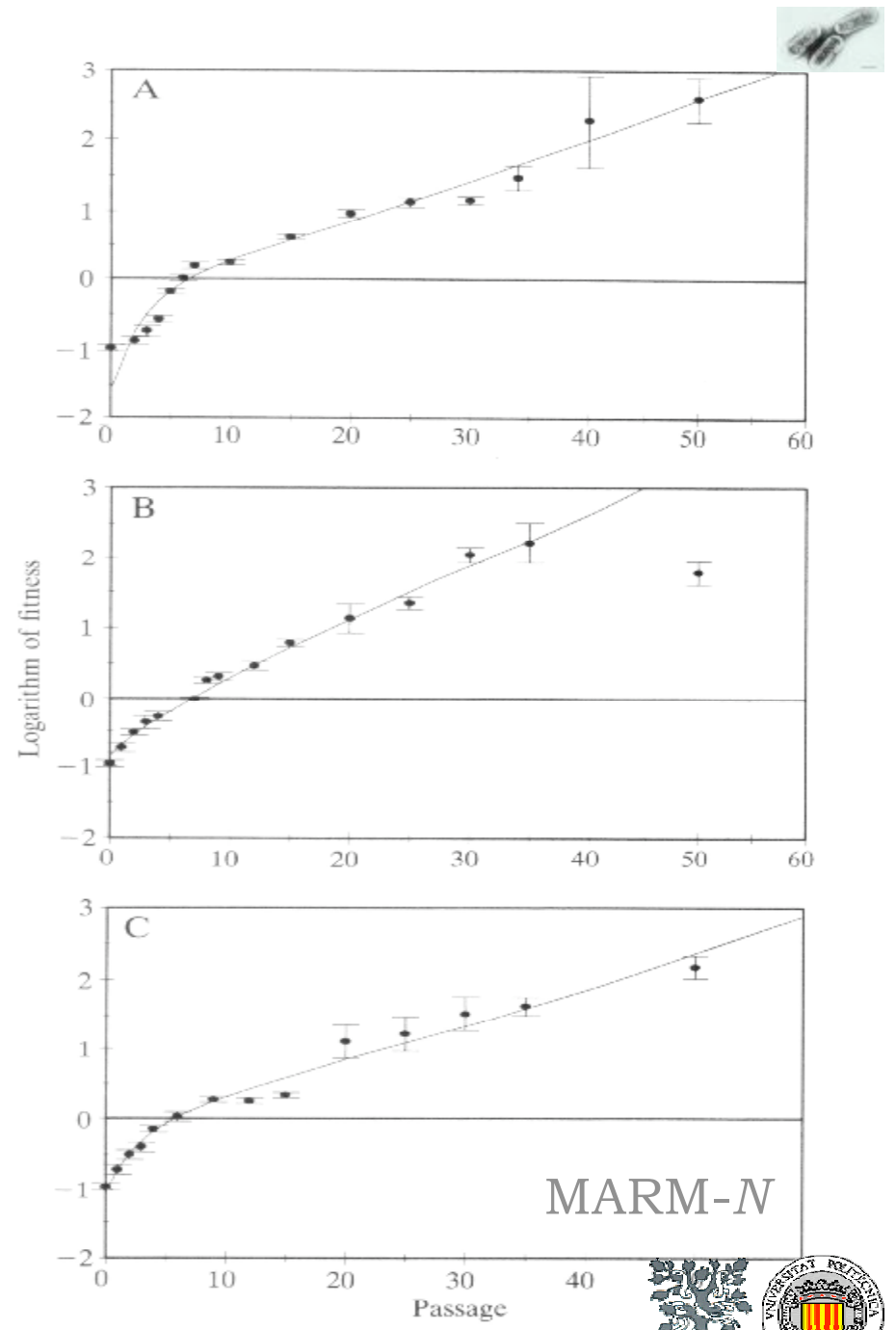
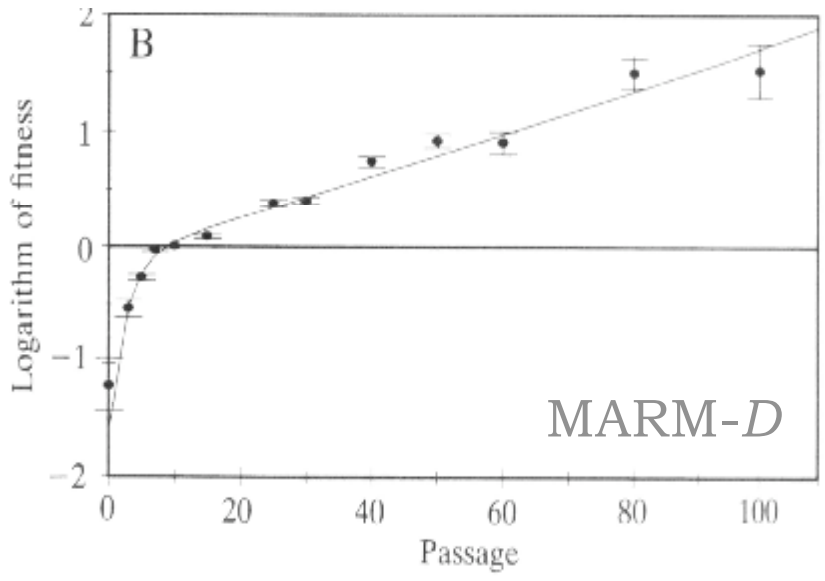
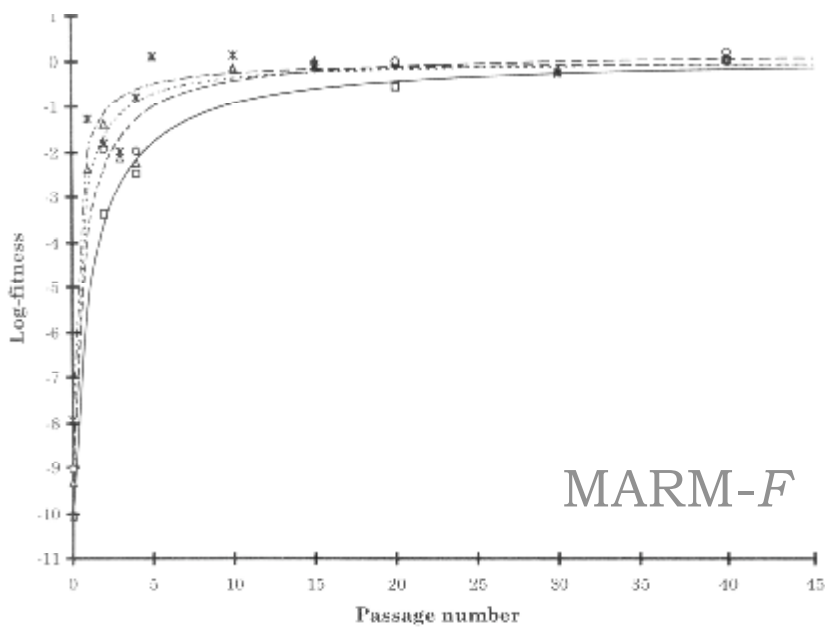
The viroids



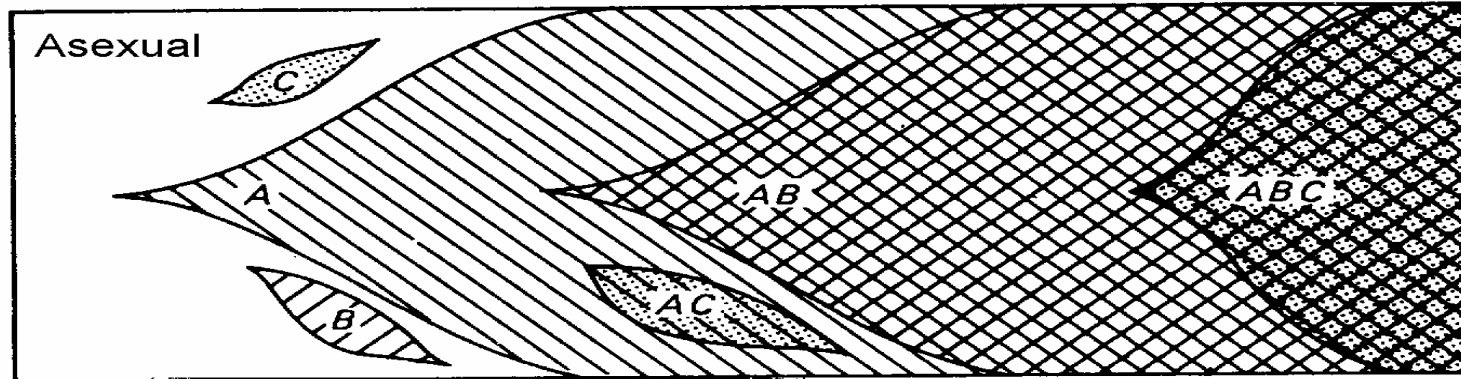
The dynamics of evolutionary adaptation

Walking throughout Wright's adaptive landscapes

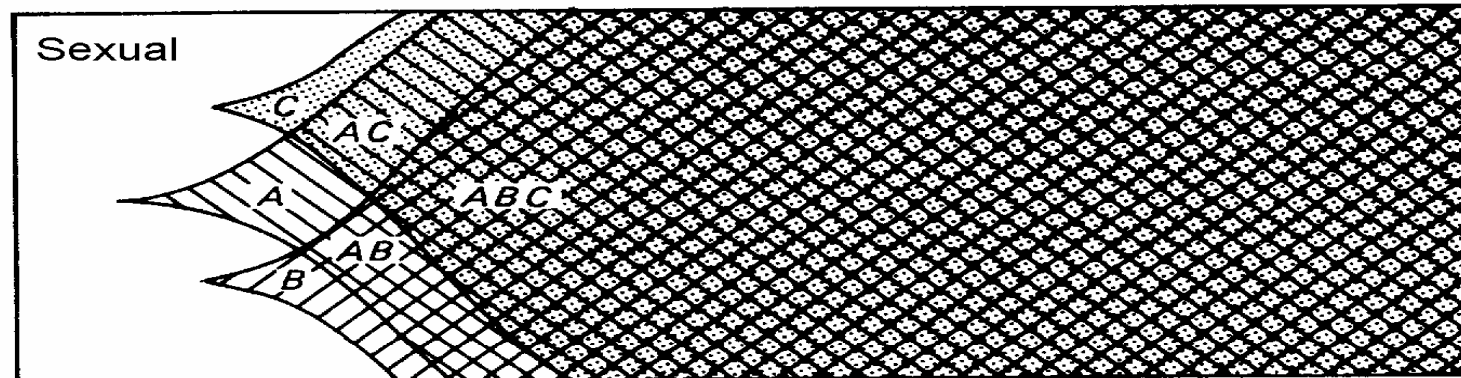




TIEMPO →



Tamaño poblacional grande



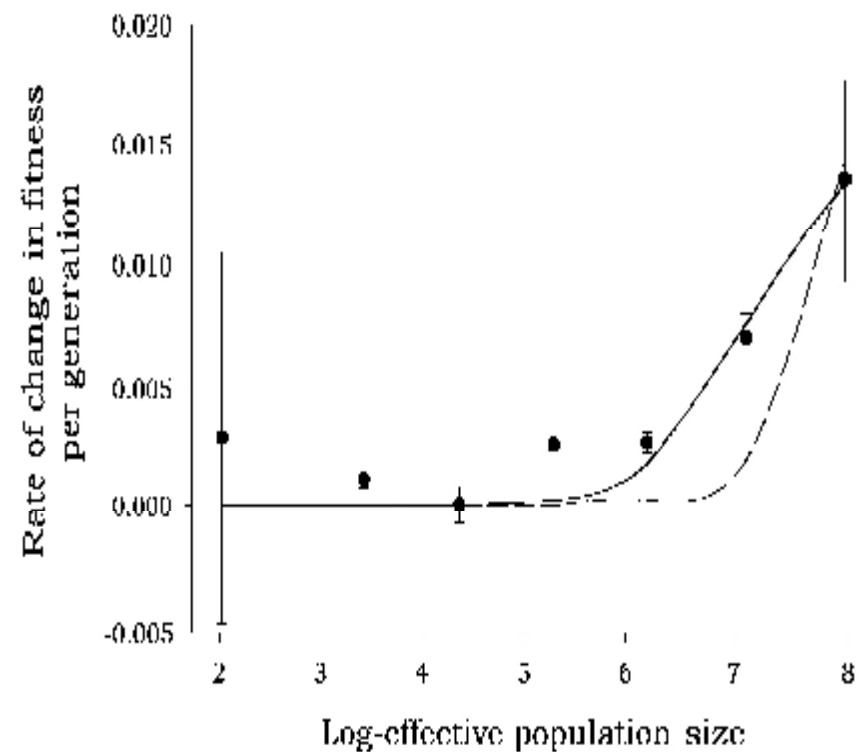
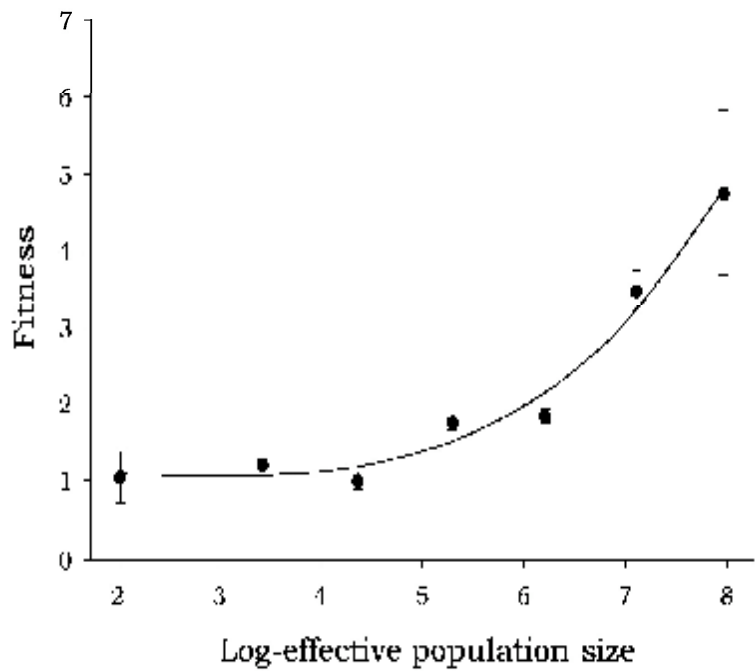
Tamaño poblacional pequeño





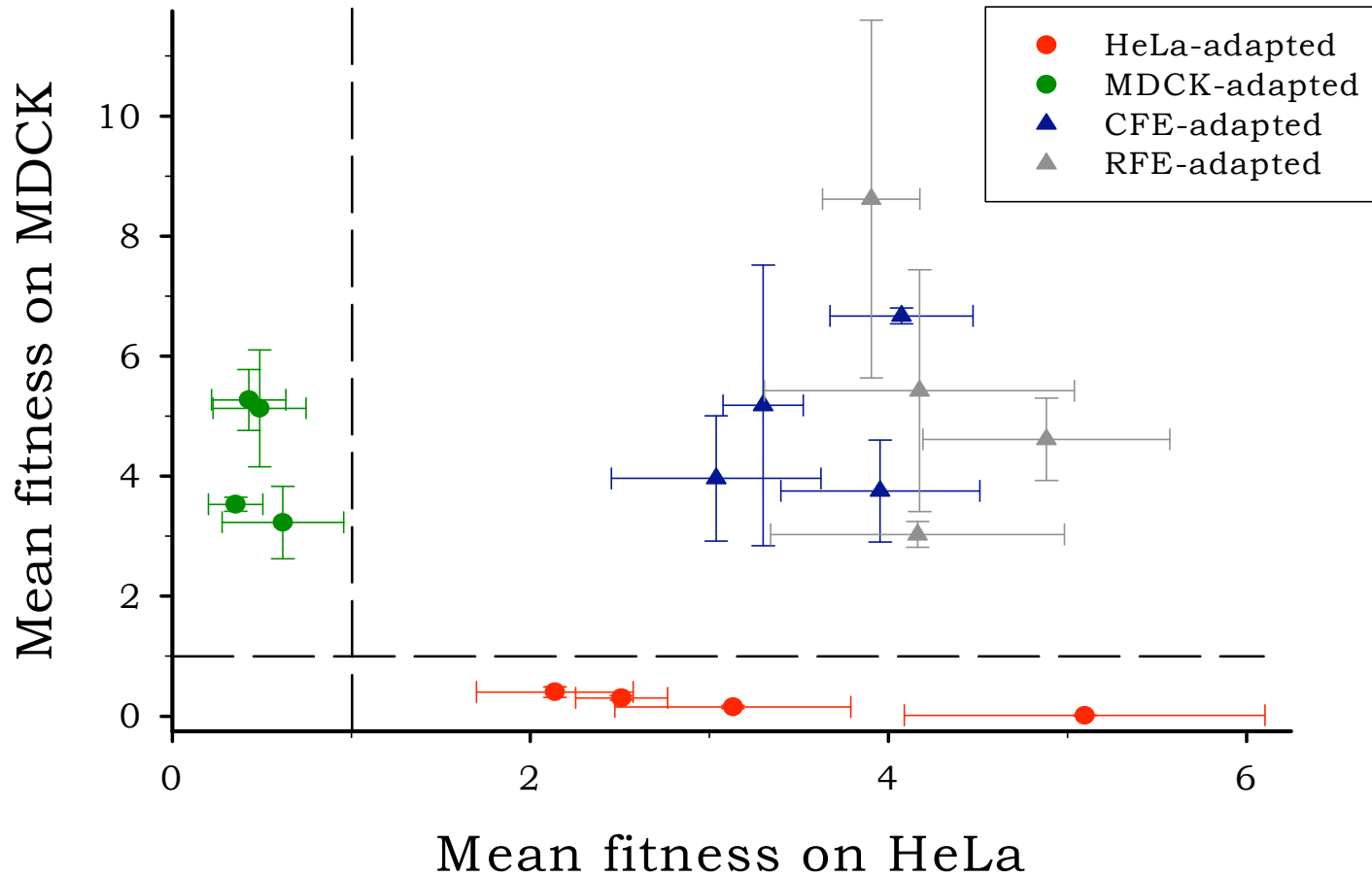
1st Prediction: the stronger clonal interference the larger the selective value associated with the mutation that finally becomes fixed.

2nd Prediction: clonal interference imposes a limit to the rate of viral adaptation.



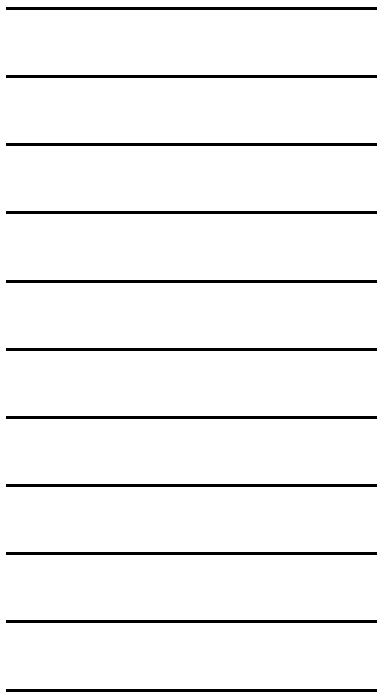
$$2.57 \times 10^{-8} \leq U_b \leq 1.58 \times 10^{-7} \quad 0.24 \leq E(s_b) \leq 0.43$$

Adaptive trade-offs and the specificity of adaptation

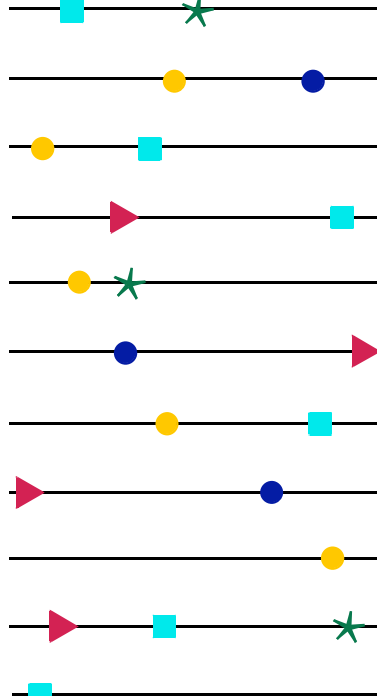


Drift and decay in very small populations

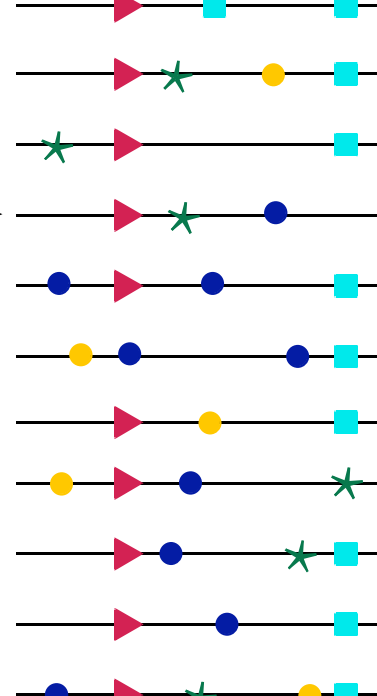
I



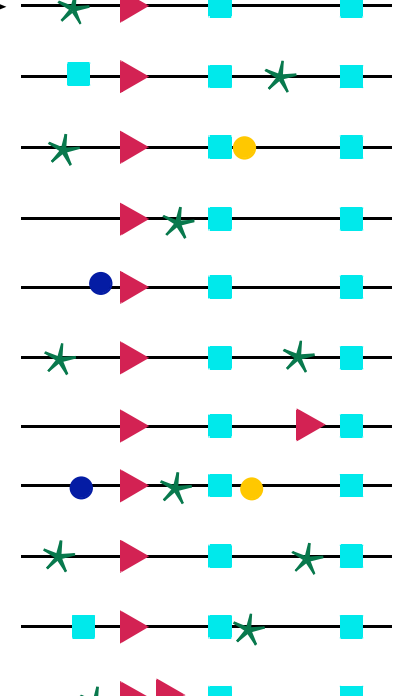
II

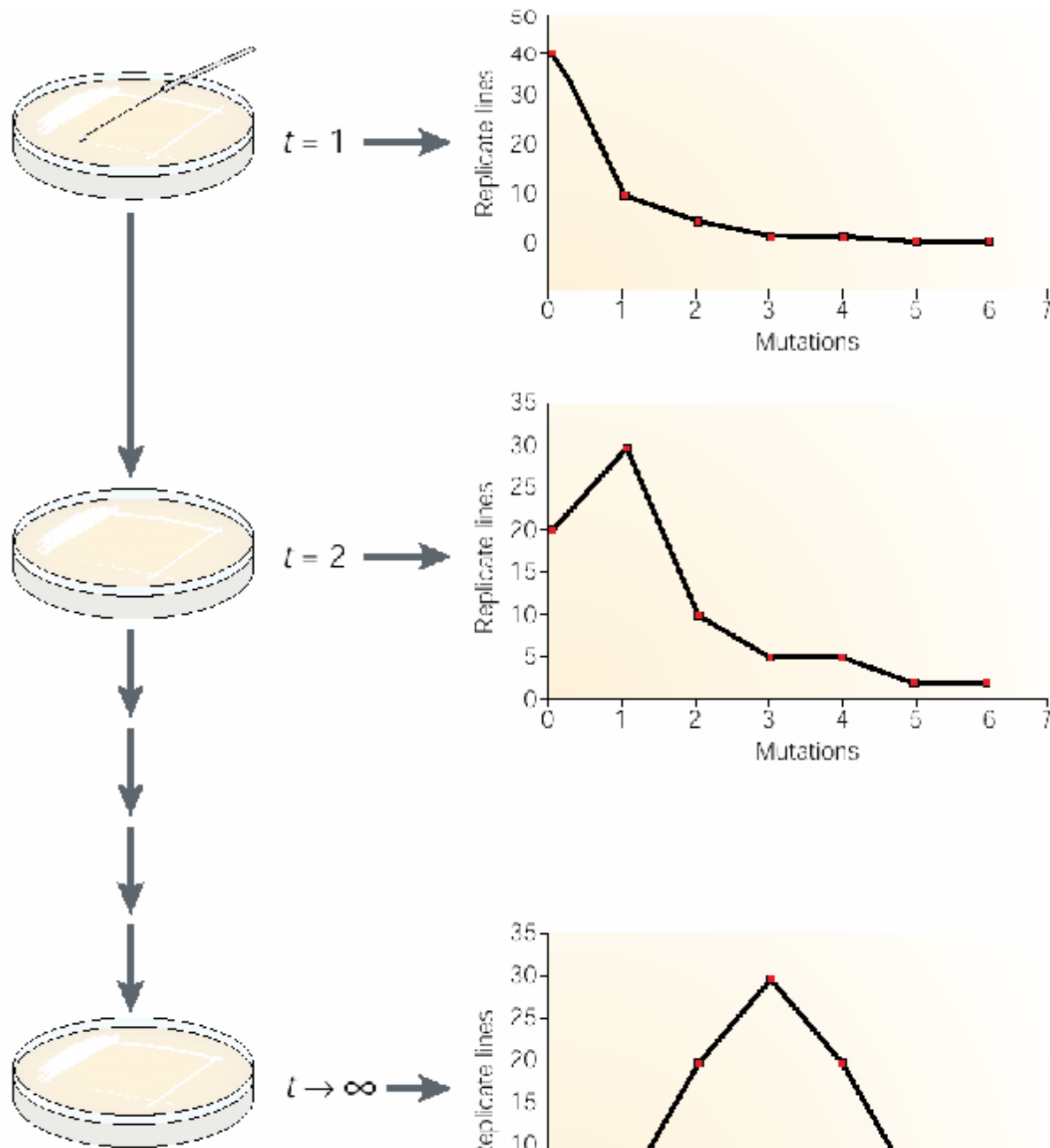


III



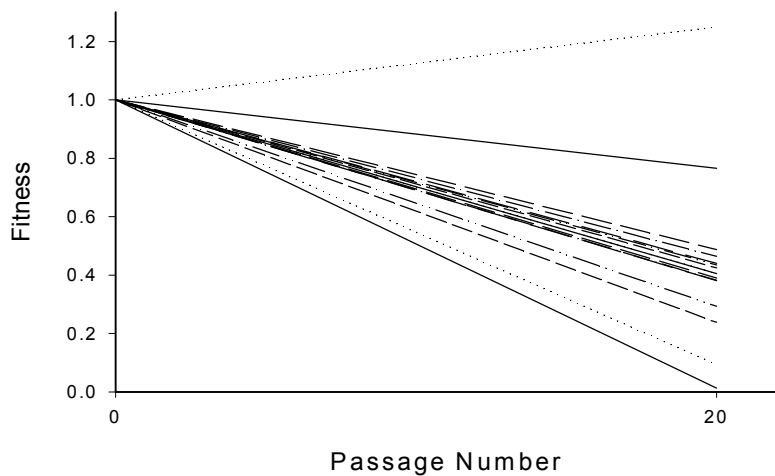
IV



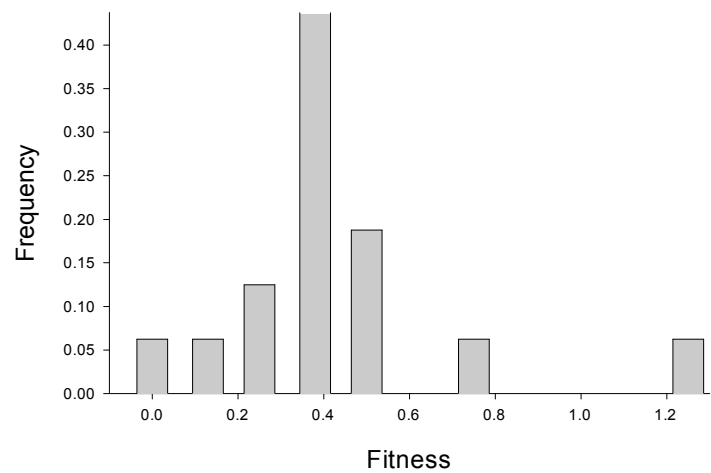




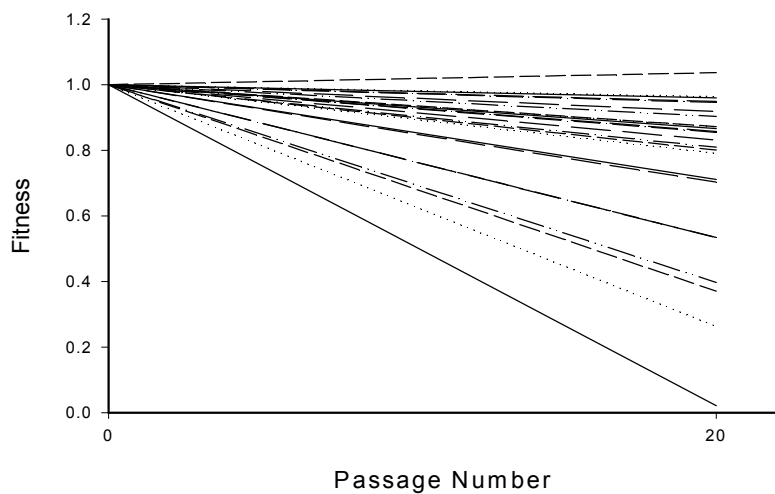
MARM X



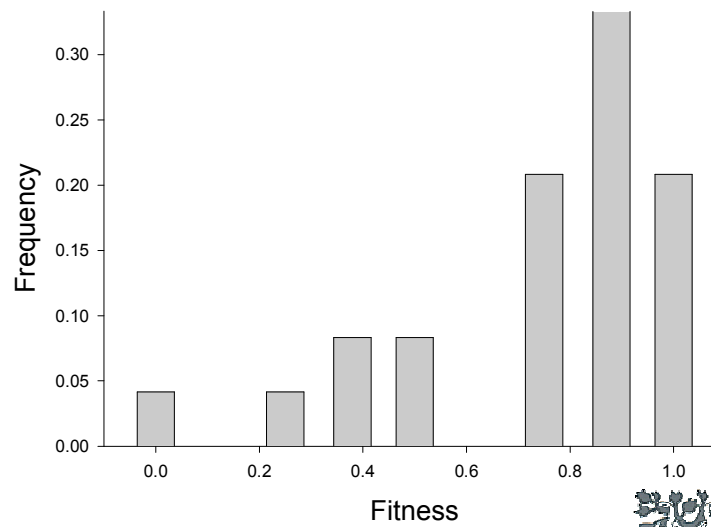
MARM X

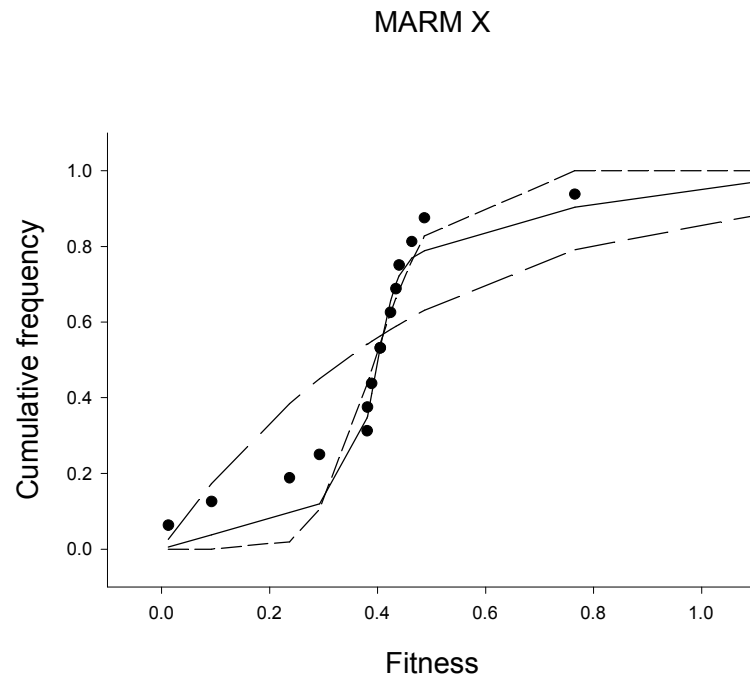


MARM C

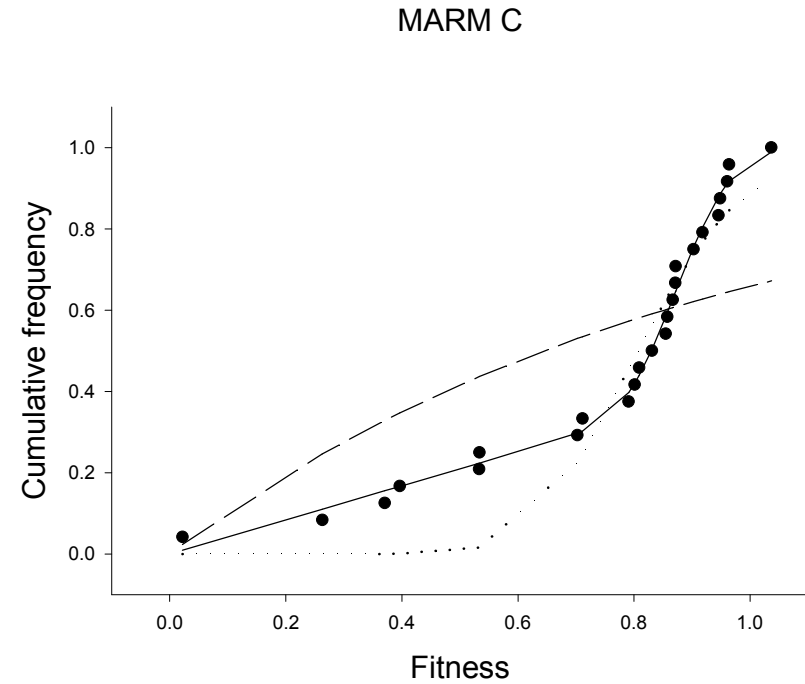


MARM C

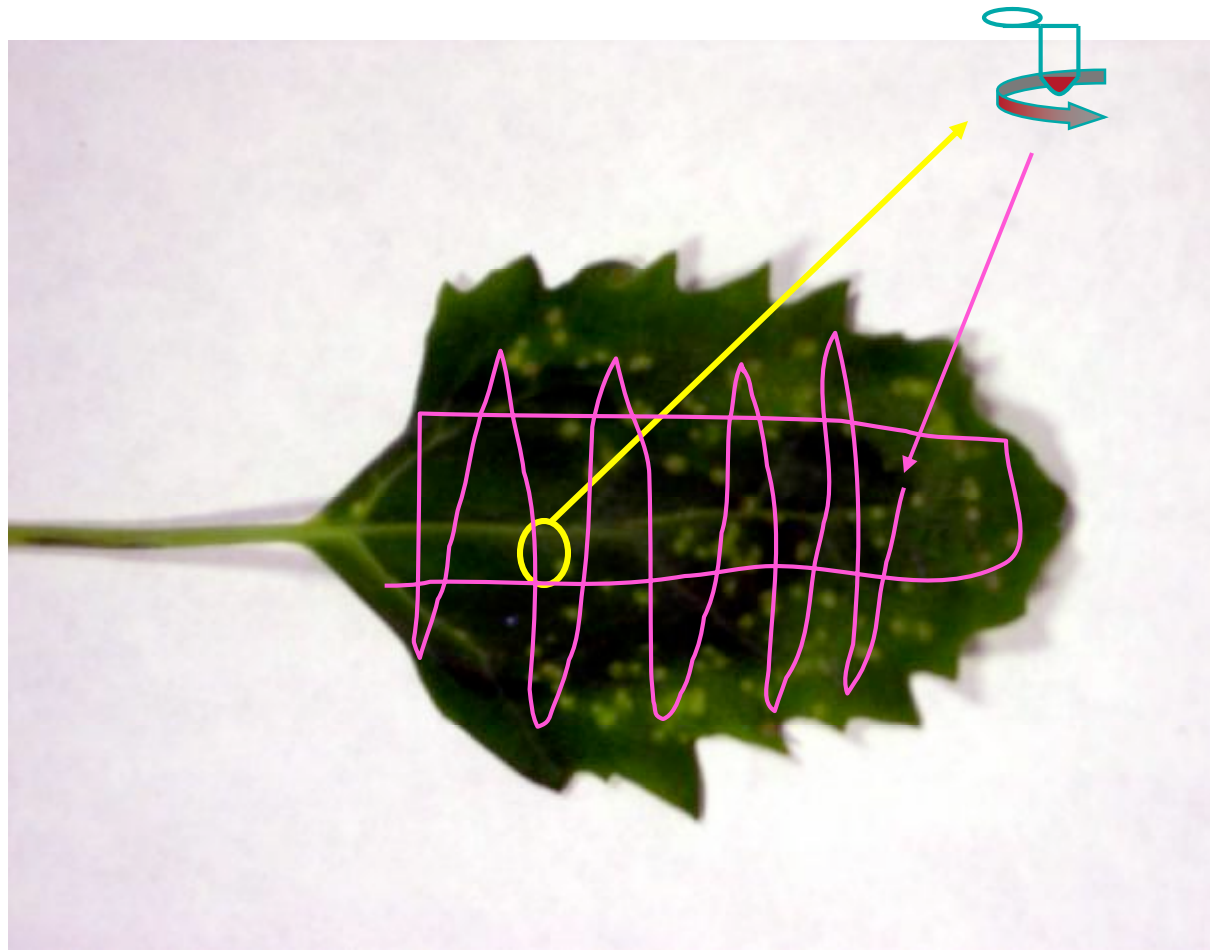


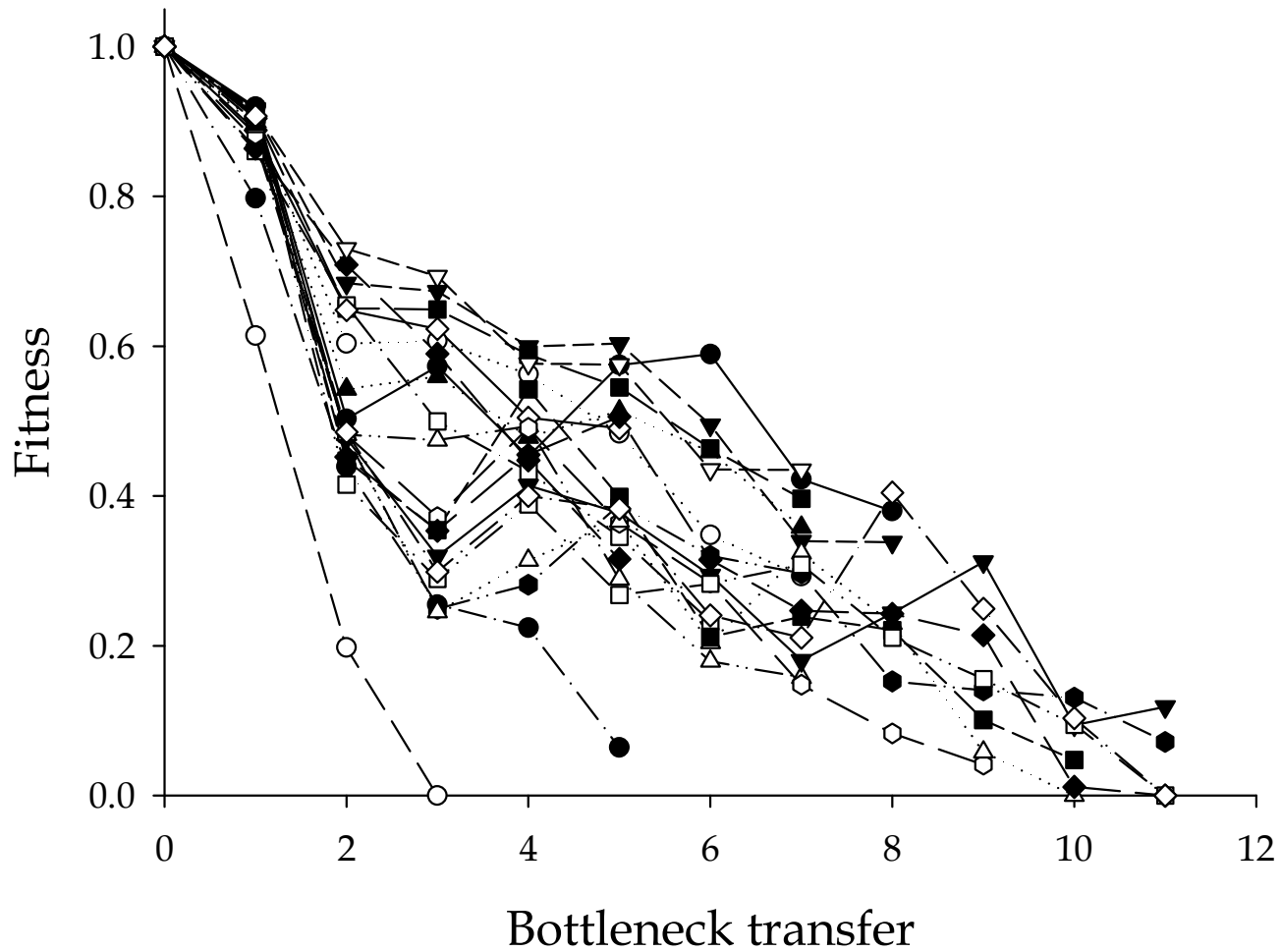


Gamma + uniform $R^2 = 0.962$
 $U_d = 3.090$
 $E(s_d) = -0.100$



Gamma + uniform $R^2 = 0.992$
 $U_d = 1.768$
 $E(s_d) = -0.150$





$$UE(s) = -0.121 \pm 0.005, t_{19} = 25.374, 1\text{-tailed } P < 0.001$$



Effect of bottleneck size and genotype in the outcome of Muller's ratchet. Dynamic makes reference to the number of clones isolated and pooled at every of 20 consecutive infectious passages of n plaques-to- n plaques.

MARM	Dynamic	Fitness	t_5	1-tailed P
X	5-to-5	1.7 ± 0.2	5.725	0.001
	30-to-30	3.0 ± 0.4	0.161	0.439
U	5-to-5	1.3 ± 0.2	0.813	0.226
C	5-to-5	1.2 ± 0.2	1.292	0.126
N	5-to-5	0.55 ± 0.01	3.048	0.986
	2-to-2	0.38 ± 0.01	0.271	0.398

The initial fitnesses were 3.05 ± 0.03 , 1.0 ± 0.2 , 0.91 ± 0.03 and, 0.38 ± 0.01 respectively. In all cases, experiments were 6-fold replicated.