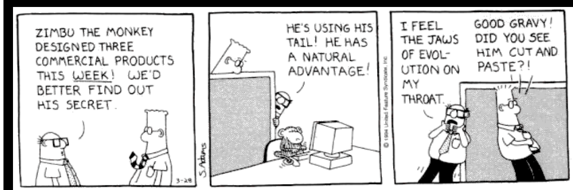
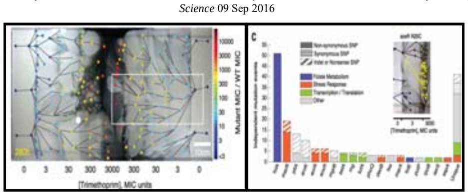


"Visualizing evolution as it happens"

Spatiotemporal microbial evolution on antibiotic landscapes

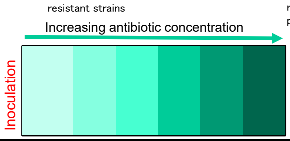
Michael Baym, Tami D. Lieberman,*, Eric D. Kelsic, Remy Chait, Rotem Gross, Idan Yelin, Roy Kishony

Science 09 Sep 2016



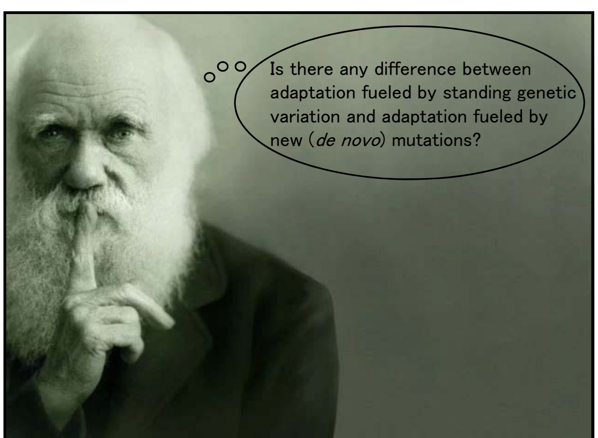
Strains grow in a branching-fashion, and time lapse videos and genetic sequencing allow researchers to trace the ancestral "trees" of resistant strains

Sequencing of colonies at various gradations allowed researchers to identify genes involved in conferring antibiotic resistance, including many that were previously unknown



Applications of the MEGA-Plate:

1. Mechanisms of antibiotic resistance
2. Analysis of spatial evolution



BACK TO THIS EQUATION…

$$\Delta p = \frac{pq[p(w_{AA} - w_{Aa}) + q(w_{Aa} - w_{aa})]}{\overline{w}}$$

- **We can see what happens with various types of selection by substituting explicit values for the fitnesses of the different genotypic classes.**

CASE 2: HETEROZYGOTE ADVANTAGE -- OVERDOMINANCE

FITNESSES:

W_{AA} = 1 - s **W_{Aa} = 1** **W_{aa} = 1 - t**

$$\Delta p = \frac{pq(-sp + tq)}{1 - sp^2 - tq^2}$$

At equilibrium, p = t/(s+t).

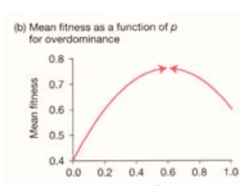
GENE FREQUENCIES WHEN THERE IS HETEROZYGOTE ADVANTAGE - OVERDOMINANCE

FITNESSES:

W_{AA} = 1 - s **W_{Aa} = 1** **W_{aa} = 1 - t**

- When **s** and **t** are negative there is <u>overdominance</u> and a stable equilibrium exists at:

$\boxed{\hat{p} = t / (s + t)}$

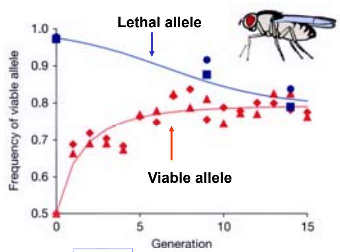


HETEROZYGOTE ADVANTAGE IN LAB POPULATIONS

FITNESSES:

VV	VL	LL
0.735	1.0	0

s = - 0.265
t = - 1.0

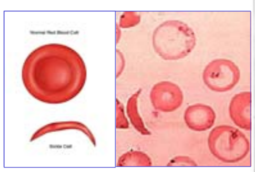


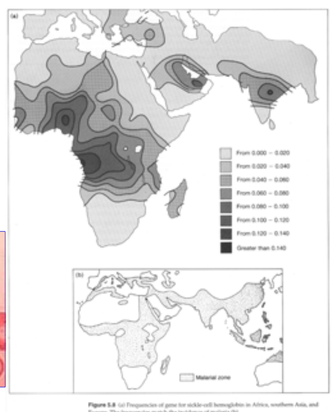
$\hat{p}_L$ = s/ (s + t) = - 0.265 / - 1.265 = $\boxed{0.209}$

$\hat{p}_v$ = t / (s + t) = - 1.0 / - 1.265 = $\boxed{0.791}$

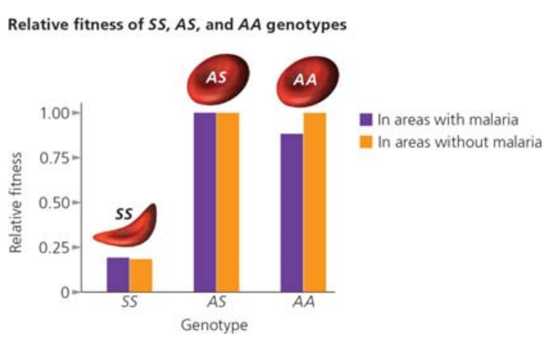
CASE STUDY:
Heterozygote advantage

- Sickle-cell Anemia





Heterozygote Advantage and Sickle-cell Anemia



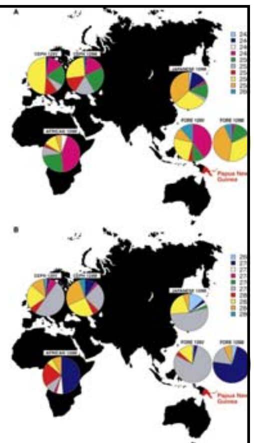
Selection coefficients for sickle-cell anemia: Genotype frequencies from the Yorubas of Ibadan, Nigeria

Genotype	Observed Adult Number (O)	Expected H-W Number (E)	Ratio (O/E)	Fitness (relative to AS)
SS	29	187.4	0.155	0.155/1.12 = **0.14** = 1-t
SA	2,993	2,672.2	1.120	1.12/1.12 = **1.00**
AA	9,365	9,527.2	0.983	0.983/1.12 = **0.88** = 1-s
Total	12,387	12,387		

FROM: Bodmer & Cavalli-Sforza. 1976

Balancing Selection at the Prion Protein Gene Consistent with Prehistoric Kurulike Epidemics

Simon Mead, *et al.*



- Mead *et al.* detected a large heterozygote excess for markers linked to the PRNP (prion protein) locus in a sample of women from Papua New Guinea that had been exposed to ritual cannibalism.
- Observed: 30 of 50
- Expected: 15 of 50

Science 2003 300:640-643

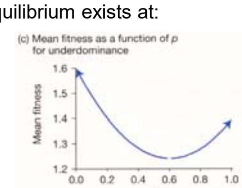
CASE 3: GENE FREQUENCIES WHEN THERE IS HETEROZYGOTE DISAVANTAGE -- UNDERDOMINANCE

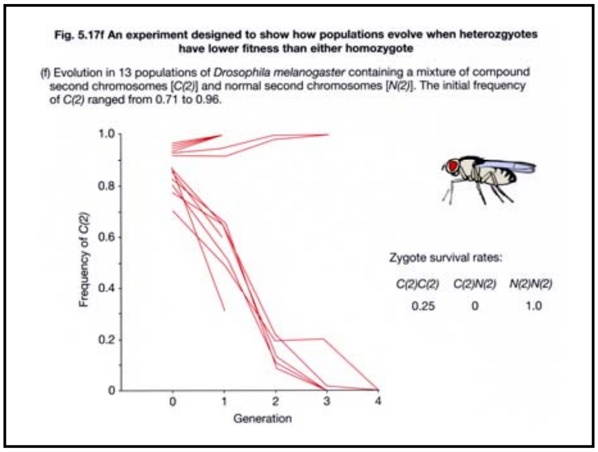
FITNESSES:

$$W_{AA} = 1 + s \qquad W_{Aa} = 1 \qquad W_{aa} = 1 + t$$

- When **s** & **t** are positive the pattern is the reverse of the previous case – an unstable equilibrium exists at:

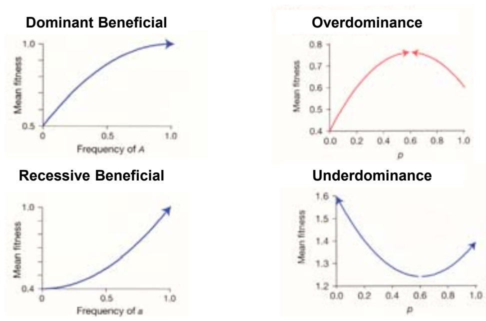
$$\boxed{\hat{p} = t / (s + t)}$$



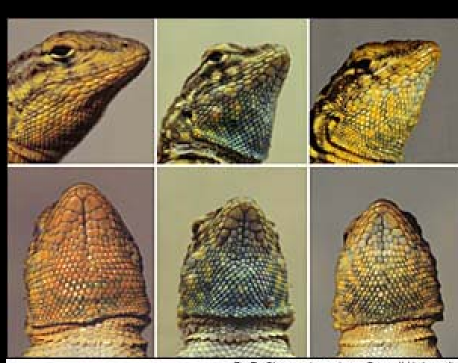


EFFECT OF SELECTION ON POPULATION MEAN FITNESS:

- Populations under selection evolve towards higher population mean fitness



HOW CAN SELECTION MAINTAIN POLYMORPHISM?

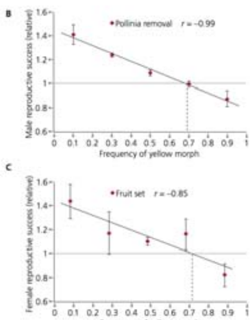


HOW CAN SELECTION MAINTAIN POLYMORPHISM?

- **Heterozygote advantage** – Also known as OVERDOMINANCE or HETEROSIS, results in a stable, polymorphic equilibrium.
- **Varying selection** – If selection varies spatially or temporally, polymorphism may be maintained.
- **Frequency-dependent selection** – the fitness of the genotype depends on its frequency in the population. If common genotypes have low fitness, then the polymorphism will be maintained.

Negative Frequency-dependent Selection

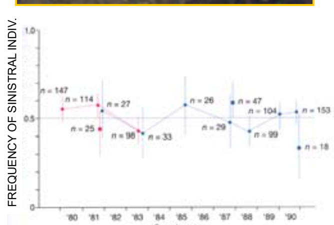
Elderflower orchids with a color **polymorphism**



Reproductive success of yellow morph

FREQUENCY-DEPENDENT SELECTION

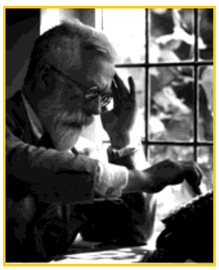
Figure 5.19 **Scale-eating fish *(Perissodus microlepis)* from Lake Tanganyika** (top) A right-handed (dextral) fish, shown from both sides. The mouth of this fish twists to the fish's right. (bottom) A left-handed (sinistral) fish, shown from both sides. The mouth of this fish twists to the fish's left. These two individuals belong to the same species and are members of the same population. (Dr. Michio Hori, Kyoto University, Kyoto, Japan)



OTHER FORMS OF FREQUENCY-DEPENDENT SELECTION

- Predator – prey interactions: If predators form a “search image”, then the predator keys on the most common prey giving a selective advantage to the rare prey.
- Parasite – host interactions. Parasites may be selected to attack the most common host, and hosts may be selected to defend against the most common parasites.
- Mimicry systems – example, venomous coral snakes and their non-venomous king snake mimics.

SEX RATIO EVOLUTION



Fisher argued that the 50:50 sex ratio observed in most animals is the result of frequency-dependent selection .

- If the primary sex ratio is skewed, parents that produce more of the rare sex have a fitness advantage because their offspring will have higher mating success.
- Eventually, most populations evolve mechanisms that stabilize the sex ratio.

WHY AREN’T WE ALL PERFECT?

SELECTION – MUTATION BALANCE IN LARGE POPULATIONS

- Most new mutations are slightly deleterious.
- In large populations the equilibrium frequency of deleterious mutation is determined by a balance between the input by mutation and removal by selection.

WHAT IS THE FREQUENCY OF THE DELETERIOUS MUTANT ALLELE AT EQUILIBRIUM???

- **Δq = loss due to selection + input by mutation = 0**

MUTATION – SELECTION BALANCE

FITNESSES:

$W_{AA} = 1$ $W_{Aa} = 1$ $W_{aa} = 1 - s$

$$\Delta p = \frac{spq[h(1-2q)+q]}{1-2pqhs-sq^2}$$

h = 0, and Δq is equal to (-1)*Δp, so

$$\Delta q = -\frac{spq^2}{1-sq^2} = -\frac{spq^2}{\overline{w}}$$

MUTATION – SELECTION BALANCE

At equilibrium, the change in allele frequency due to mutations is exactly equal to the change due to selection, so:

$$up - \frac{spq^2}{\overline{w}} = 0$$

The deleterious allele is rare, so mean population fitness is approximately equal to 1. Thus,

$$up \cong spq^2 \quad \text{and} \quad \boxed{\hat{q} \cong \sqrt{\frac{u}{s}}}$$

Assume *q* is small, and *u* >> *v* :

- Selection against a completely **recessive** allele:

$W_{AA} = 1$ $W_{Aa} = 1$ $W_{aa} = 1 – s$

$$\boxed{\hat{q} \cong \sqrt{\frac{u}{s}}}$$

- Selection against a completely **dominant** allele:

$W_{AA} = 1$ $W_{Aa} = 1– s$ $W_{aa} = 1 – s$

$$\boxed{\hat{q} \cong \frac{u}{s}}$$

Assume *q* is small, and *u* >> *v* :

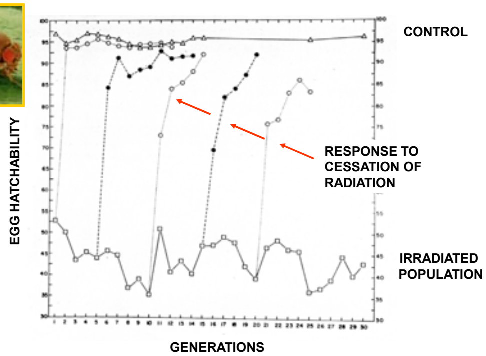
- Selection against a **partially recessive** allele:

$W_{AA} = 1$ $W_{Aa} = 1\text{-}hs$ $W_{aa} = 1 – s$

$$\boxed{\hat{q} \cong \frac{u}{hs}}$$

Response of a *Drosophila melanogaster* Population to X-rays

From: K. Sankaranarayanan. 1964. Genetics 50:131-150



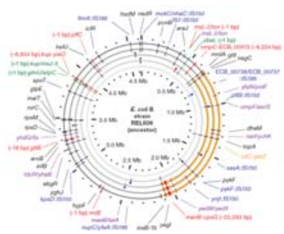
Evolution as a Stochastic Algorithm

Michael Desai - Harvard

Set of Possibilities
Mutations and Fitness Effect

Evolutionary Dynamics: Mutations, Selection, Drift

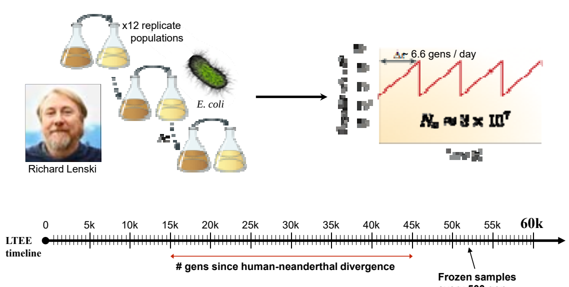
Set of Outcomes
Fixed Mutations, Patterns of Variation, etc.



The rules are well known:
Mutations generate variation. Drift, selection, recombination etc. alter frequencies of variants

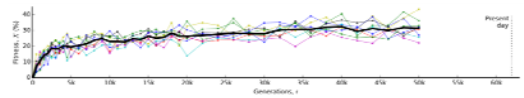
The quantitative consequences are not understood, even in very simple situations!

Long-Term Evolution in a Constant Environment

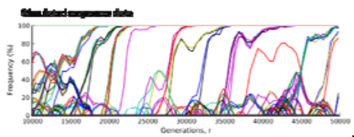


See Z&E Fig 6.15 and 6.16

Long-term Adaptation to a Constant Environment



Fitness measurements from Wiser et al., *Science* 2013



[Good and Desai, Genetics 2016]

Molecular Evolution Over 60,000 Generations