

Diploid model of selection

Consider alleles A_1 and A_2 at frequency p_t and $q_t = 1 - p_t$ at time t , and assume that the population size N is so large that we can ignore genetic drift.

Genotype	A_1A_1
frequency at birth	p^2
Absolute fitness	w_{11}

Total proportion	$p^2 w_{11}$
At repro.	

A_1A_2
$2pq$
w_{12}

$2 p q w_{12}$

A_2A_2
q^2
w_{22}

$q^2 w_{22}$

$$\bar{w} = \text{Mean fitness of the population} = (p^2 w_{11} + 2 p q w_{12} + q^2 w_{22})$$

$$\text{Freq. at repro. } f_{11}' = \frac{p^2 w_{11}}{\bar{w}}$$

$$f_{12}' = \frac{2 p q w_{12}}{\bar{w}}$$

$$f_{22}' = \frac{q^2 w_{22}}{\bar{w}}$$

$$p_{t+1} = f_{11}' + \frac{1}{2} f_{12}' = \frac{w_{11} p_t + w_{12} q_t}{\bar{w}} p_t$$

$$p_{t+1} = f_{11} + \frac{1}{2}f_{12} = \frac{w_{11}p_t + w_{12}q_t}{\bar{w}} p_t$$

$$\Delta p_t = p_{t+1} - p = \frac{w_{11}p_t + w_{12}q_t}{\bar{w}} p_t - p_t$$

—
 $w_1 = w_{11}p_t + w_{12}q_t$

—
 $w_2 = w_{12}p_t + w_{22}q_t$

$$\Delta p_t = \frac{\bar{w}_1 - \bar{w}_2}{\bar{w}} p_t q_t, \quad \Delta q_t = -\Delta p_t$$

$$\Delta p_t = \frac{1}{2} p_t q_t \frac{d\bar{w}}{dp_t}$$

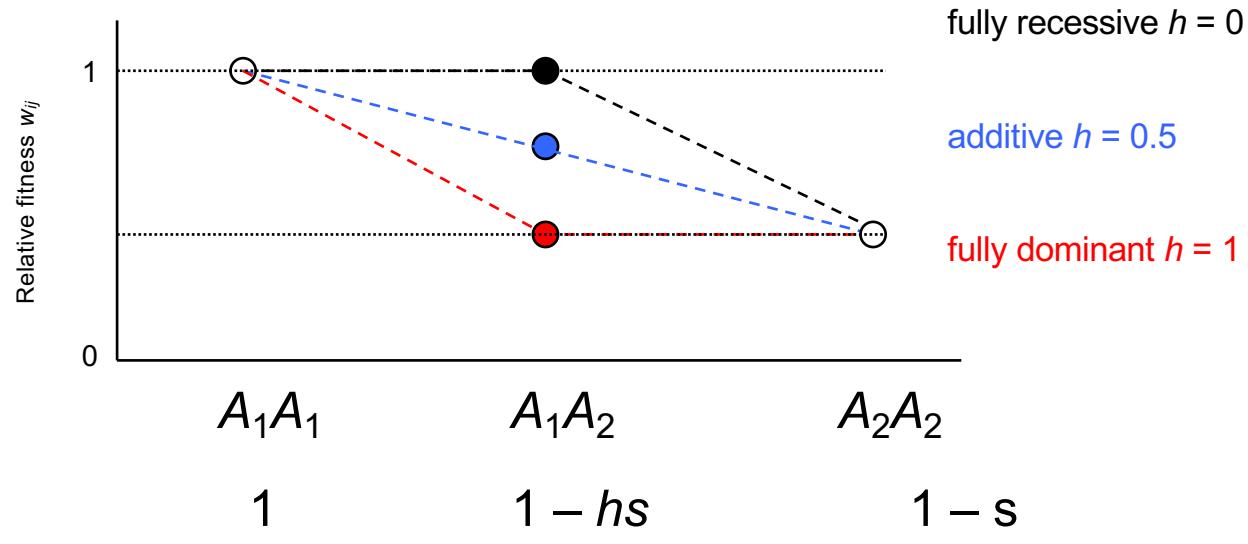
Change in allele frequencies due to viability selection

Marginal fitnesses of A_i : weighted mean fitness across genotypes carrying A_i

Frequency of A_1 is expected to increase if the marginal fitness of A_1 is higher than A_2 , regardless of how small the difference

Alternative formulation by Haldane (1924). Frequency of A_1 increases if mean fitness is an increasing function of frequency of A_1 .

Directional selection



$$\bar{w}_1 = w_{11}p_t + w_{12}q_t = p_t + (1 - hs)q_t$$

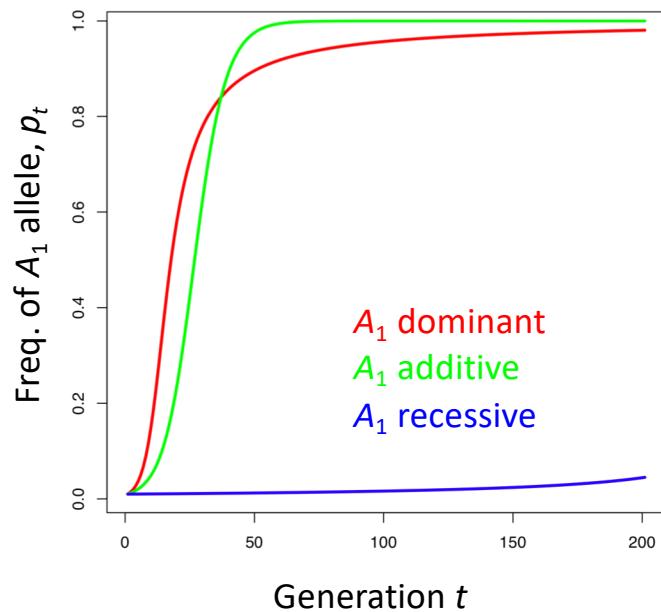
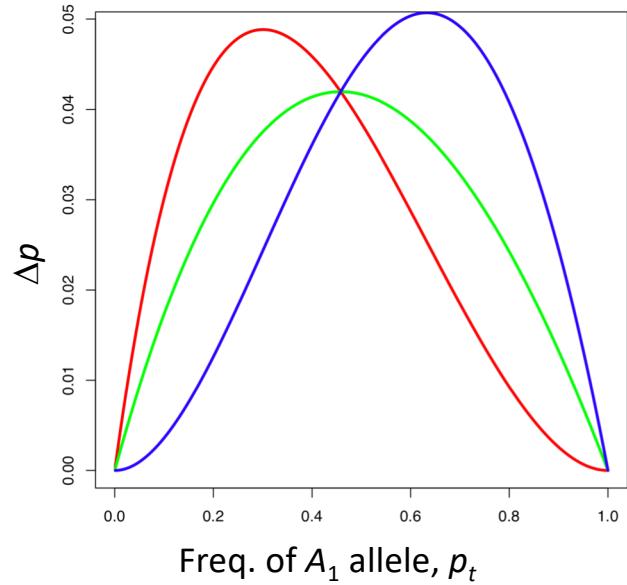
$$\bar{w}_2 = w_{12}p_t + w_{22}q_t = (1 - hs)p_t + (1 - s)q_t$$

$$\Delta p_t = \frac{\bar{w}_1 - \bar{w}_2}{\bar{w}} p_t q_t = \frac{p_t hs + q_t s(1 - h)}{\bar{w}} p_t \underset{s \ll 1}{\underset{h=1/2}{\approx}} \frac{1}{2} s p_t q_t$$

$$\bar{w}_1 = w_{11}p_t + w_{12}q_t = p_t + (1 - hs)q_t$$

$$\bar{w}_2 = w_{12}p_t + w_{22}q_t = (1 - hs)p_t + (1 - s)q_t$$

$$\Delta q_t = \frac{\bar{w}_2 - \bar{w}_1}{\bar{w}} p_t q_t = \frac{-p_t hs - q_t s(1-h)}{w} q_t$$



When $h = 1/2$

$$\tau = \frac{2}{s} \log \left(\frac{p_\tau q_0}{q_\tau p_0} \right)$$

Why is there so much polymorphism?

- The paradox of variation in population genetics:
Selection quickly fixes alleles that are beneficial so why is there so much genetic polymorphism within natural populations?

Three broad explanations:

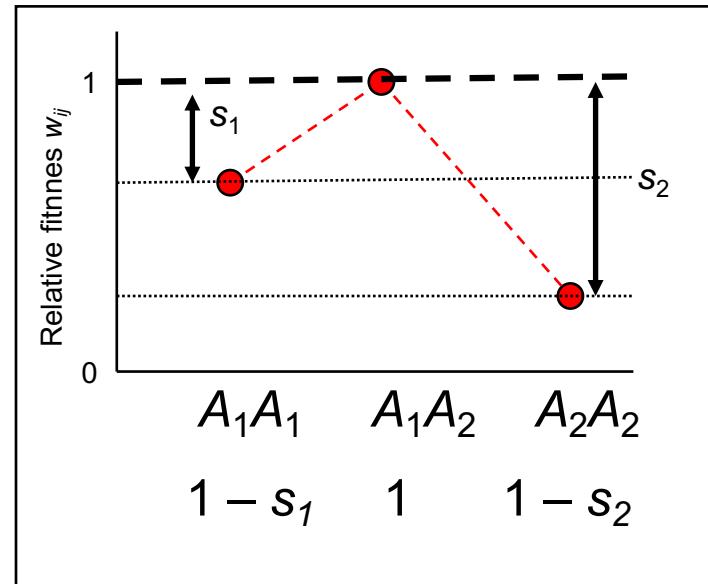
- Selection sometimes acts to maintain variation, balancing selection
- Mutation-selection balance
- Mutation-drift balance (Neutral theory).

Selection can act to maintain polymorphism within a population

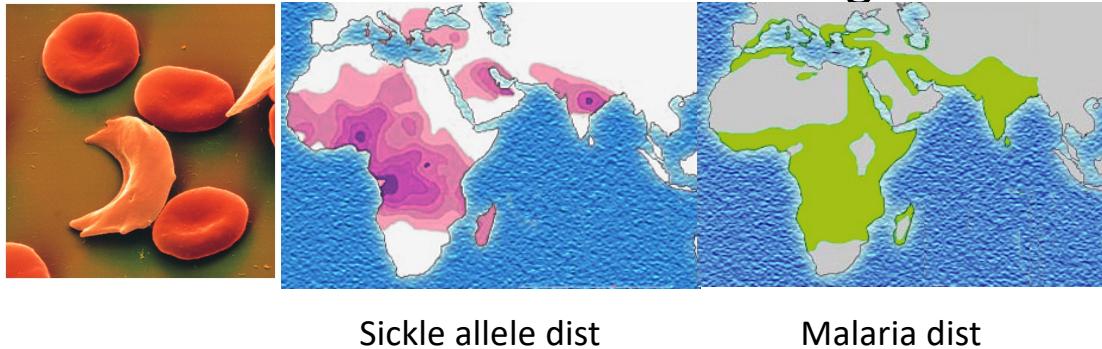
- Selection can maintain balanced polymorphisms in the population
- Balancing selection can result when:
- The heterozygotes for an allele are fitter than either homozygote (termed heterozygote advantage or overdominance)

Overdominance

(Heterozygote superiority)



Selective maintenance of genetic variation



Data on sickle genotype frequencies in infants and adults in Tanzania (Allison 1956)

Genotype	AA	AS	SS	Freq S allele
Freq infant	0.66	0.31	0.03	0.186
Freq adult	0.61	0.38	0.007	0.198
Fitness	0.93	1.23	0.24	
Rel fitness	0.76	1	0.18	

Heterozygote has highest fitness = *heterozygote advantage* = overdominance
Anemia and malaria are opposing selective factors

See also Haldane 1949



Selective maintenance of genetic variation

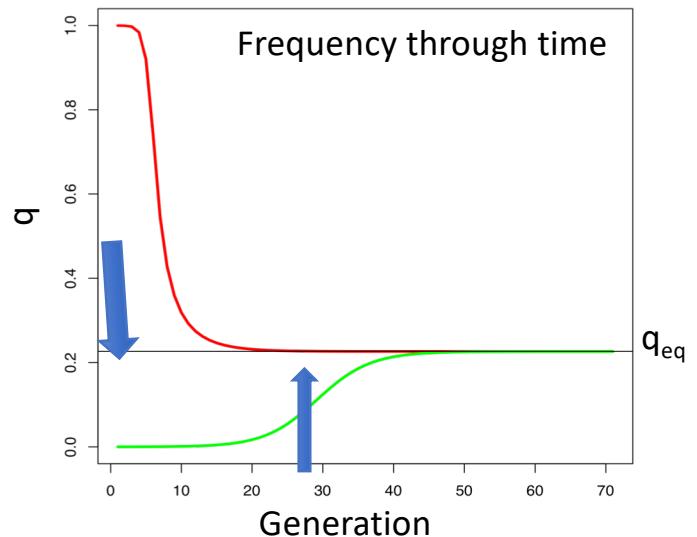
Genotype	AA	AS	SS
Rel fitness	0.76	1	0.18

Freq S allele = 0.4

Freq infant	0.36	0.48	0.16
Rel fit x Freq.	0.76x0.36 =0.274	1 x 0.48 =0.48	0.18x0.16 =0.028
Freq adult	0.35	0.61	0.037

$$\text{New S frequency} = f_{SS} + (f_{AS}/2) = 0.34$$

Freq. S allele =	0.1	
Freq infant	0.81	0.18
Freq. x Rel fit	0.76x0.81 =0.616	1 x 0.18 =0.18
Freq adult	0.772	0.225
New S frequency =	$f_{SS} + (f_{AS}/2)$	= 0.115



Heterozygote advantage (Over dominance)

	A_1A_1	A_1A_2	A_2A_2
$1-s_1$		1	
Rel fitness	0.76	1	0.18

$$s_1 = 1 - 0.76 = 0.24$$

$$s_2 = 1 - 0.18 = 0.82$$

At equilibrium $\Delta p = 0$

$$\Delta p = \frac{pq(\bar{w}_1 - \bar{w}_2)}{\bar{w}}$$

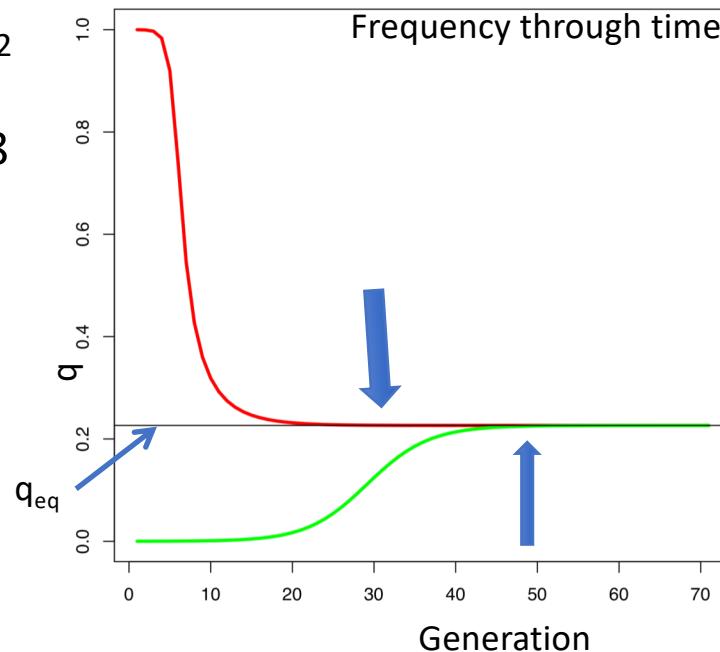
$$\text{i.e. } (\bar{w}_1 - \bar{w}_2) = pw_{11} + qw_{12} - pw_{12} - qw_{22} = 0$$

At equilibrium, freq $A_1 = p_{eq} = s_2/(s_1+s_2)$

freq $A_2 = q_{eq} = s_1/(s_1+s_2)$

the mean fitness of pop. Is maximized at this frequency.

$$q_{eq} = \frac{0.24}{0.24+0.82} = 0.226$$



Overdominance (heterozygote advantage)

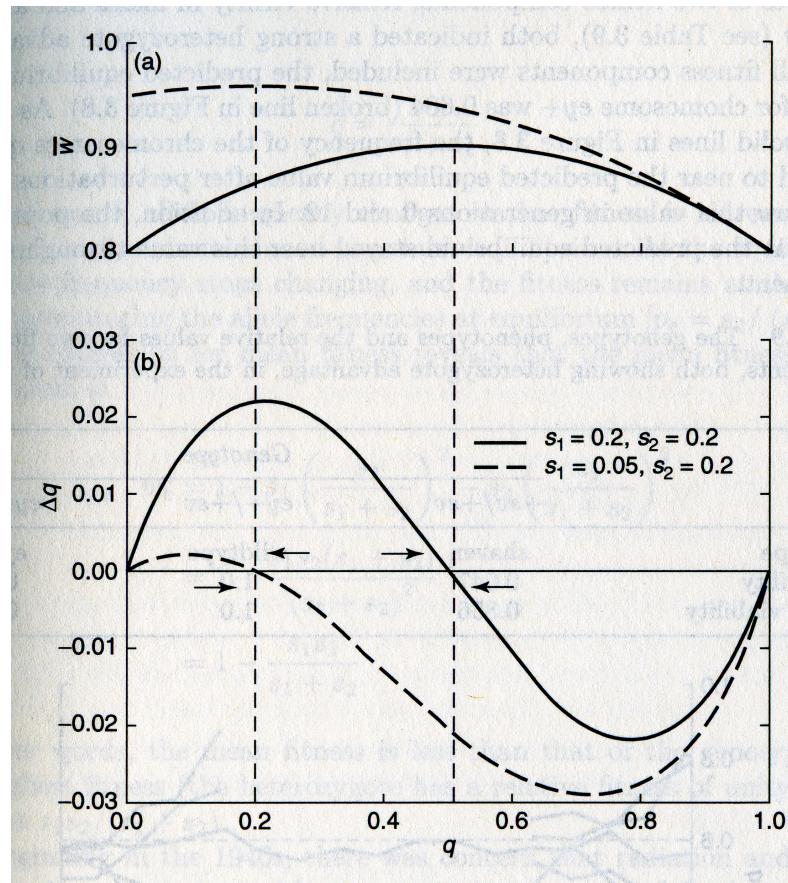
A_1A_1	A_1A_2	A_2A_2
$1 - s_1$	1	$1 - s_2$
$s_1 > 0, s_2 > 0$		

$$\begin{aligned}\bar{w}_1 &= (pw_{11} + qw_{12}) \\ \bar{w}_2 &= (pw_{12} + qw_{22})\end{aligned}$$

$$\Delta p = \frac{pq(\bar{w}_1 - \bar{w}_2)}{w}$$

At equilibrium $\Delta p = 0$
 Two boring eq. $p = 0, q = 0$
 Polymorphic eq.
 $pw_{11} + qw_{12} = pw_{12} + qw_{22}$

Over-dominance results in a
balanced polymorphism



Balancing Selection

Modes of selection maintaining variation are collectively referred to as *balancing selection*

Heterozygote advantage is just one form of balancing selection

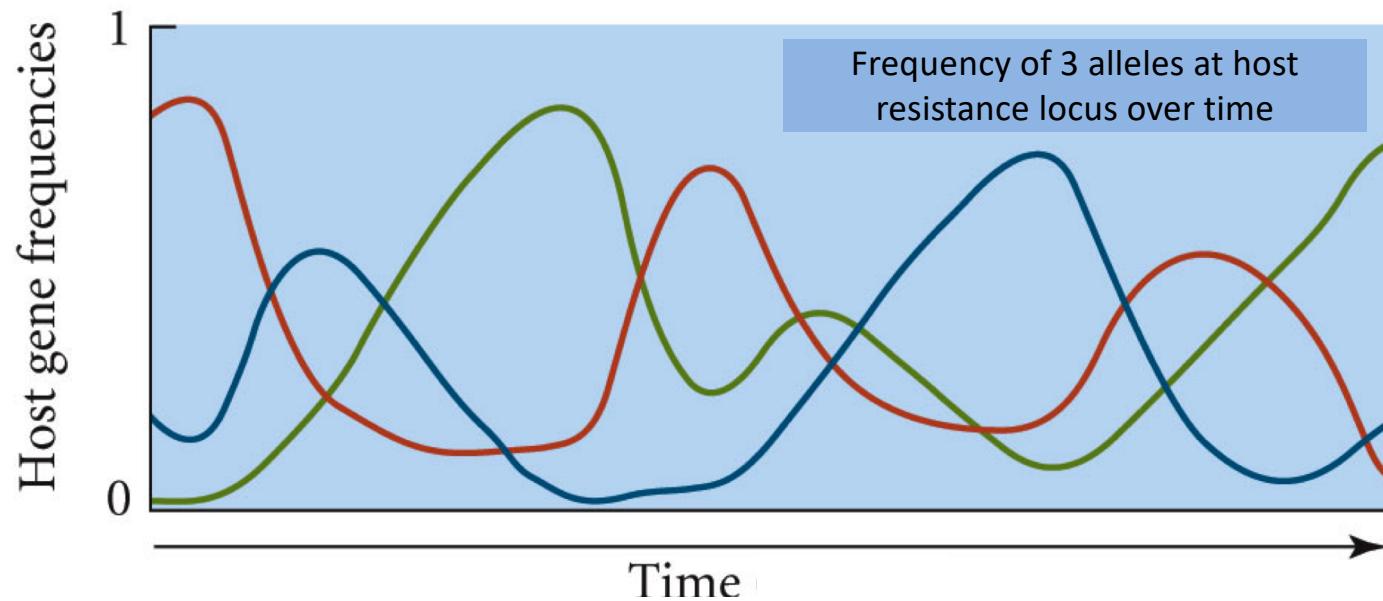
A broad class of balancing selection is *negative frequency dependent selection*

- Fitness negatively correlated with frequency
- Occurs in many systems due to interactions between individuals or species
- e.g. prey/predator or pathogen/host dynamics

Balanced polymorphisms can also arise due to negative frequency dependent selection. Occurs in many systems due to interactions between individuals or species e.g. prey/predator or pathogen/host dynamics

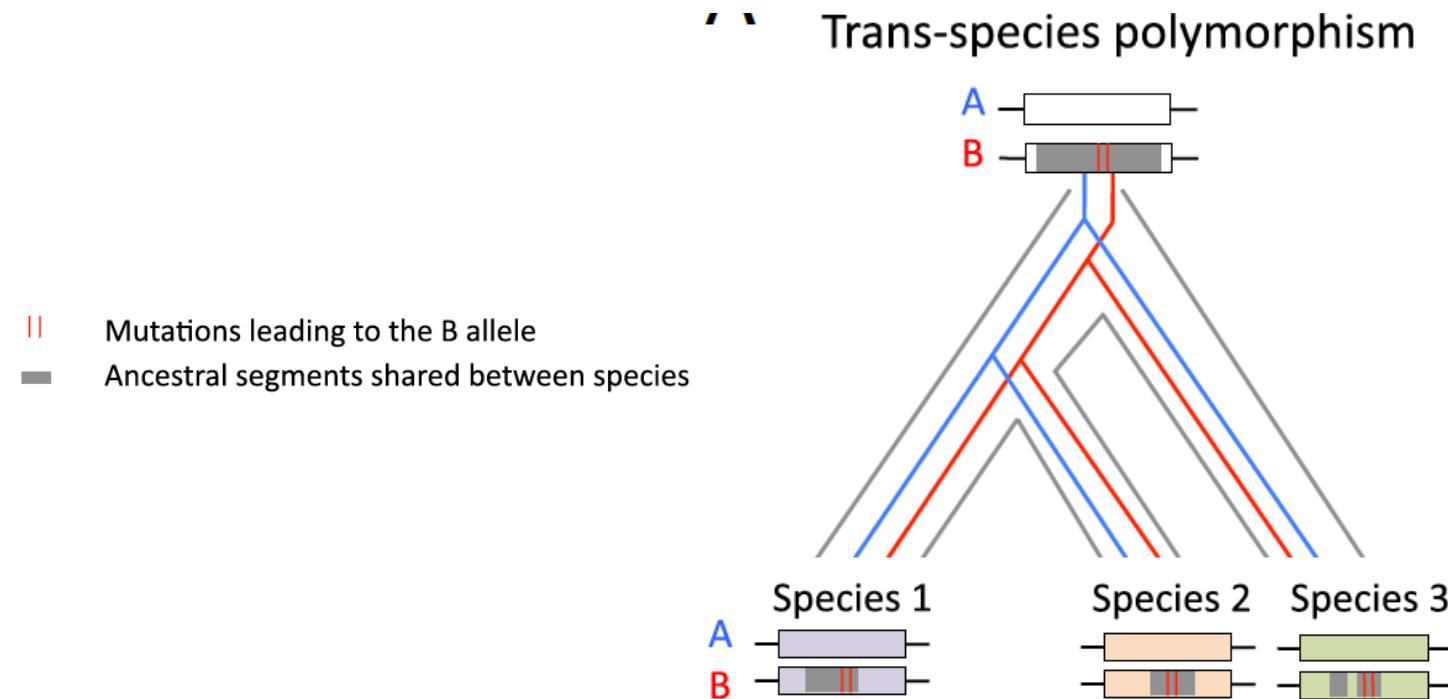
Can maintain diversity over very long time periods.

(A) Resistance locus (host)



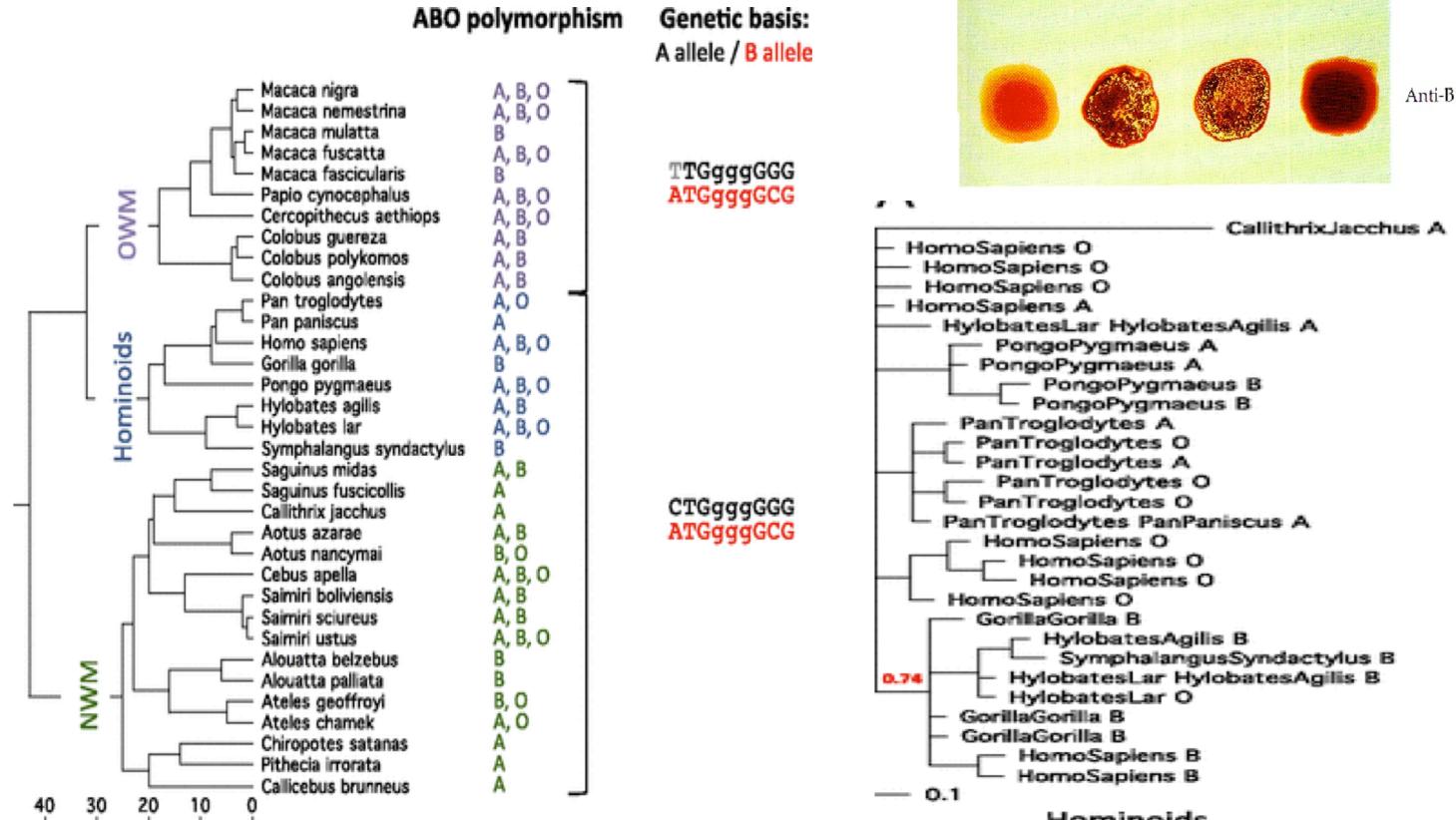
Balanced polymorphisms can also arise due to negative frequency dependent selection. Occurs in many systems due to interactions between individuals or species e.g. prey/predator or pathogen/host dynamics

Can maintain diversity over very long time periods.



ABO blood groups in primates

The ABO gene encodes for a glycosyltransferase
(Yamamoto et al, 1990)



The ABO blood group is a trans-species polymorphism in primates

Laure Ségurel^{a,b,12}, Emma E. Thompson^{a,1}, Timothée Flutre^{a,c}, Jessica Lovstad^a, Aarti Venkat^a, Susan W. Margolis^{d,3}, Jill Moyse^a, Steve Ross^a, Kathryn Gamble^a, Guy Sella^a, Carole Ober^{a,2,4}, and Molly Przeworski^{a,b,3,2,4}