Lecture 15: Interaction of Multiple Selected Loci (Ch14)

Population genetic PCB4553/6685

Why sex?

- Cost of sex
  - The cost of mating.
  - The cost of recombination.
  - The two-fold cost of sex (Maynard Smith, 1971).

Why sex?

- Benefit of sex
  - Selection allows beneficial alleles to shed their background of deleterious alleles as they sweep through the population.
  - In the absence of sex and recombination, beneficial alleles can block each other's progression to fixation, so called 'clonal interference'.
  - Beneficial alleles can be brought together on the same genetic background via recombination, allowing faster rates of adaptation.

A two locus model of selection and recombination

- Consider two biallelic loci segregating for A/a and B/b
- Four genotypes
  - AB, Ab, aB, ab, labeled 1-4
  - Frequency x_1, x_2, x_3, x_4
- Assume fitnesses reflect differences due to viability selection, and random mating
- genotype proportions after selection

	AB	Ab	aB	ab
AB	$w_{11}x_1^2$	$w_{12}2x_1x_2$	$w_{13}2x_1x_3$	$w_{14}2x_1x_4$
Ab	•	$w_{22}x_2^2$	$w_{23}2x_2x_3$	$w_{24}2x_2x_4$
aB	•	•	$w_{33}x_3^2$	$w_{34}2x_3x_4$
ab	•	•	•	$w_{44}x_4^2$

A two locus model of selection and recombination

- Mean fitness $\overline{w}$ equal to total sum
- The frequency of the AB haplotype (1) in the next generation of gametes
- $$x_1' = \frac{(w_{11}x_1^2 + \frac{1}{2}w_{12}2x_1x_2 + \frac{1}{2}w_{13}2x_1x_3 + \frac{1}{2}(1-c)w_{14}2x_1x_4 + \frac{1}{2}cw_{23}2x_2x_3)}{\bar{w}}$$
- Each term is weighted by its fitness relative to the mean fitness, and by its probability of transmitting the AB haplotype to the next generation.

	AB	Ab	aB	ab
AB	$w_{11}x_1^2$	$w_{12}2x_1x_2$	$w_{13}2x_1x_3$	$w_{14}2x_1x_4$
Ab	•	$w_{22}x_2^2$	$w_{23}2x_2x_3$	$w_{24}2x_2x_4$
aB	•	•	$w_{33}x_3^2$	$w_{34}2x_3x_4$
ab	•	•	•	$w_{44}x_4^2$

A two locus model of selection and recombination

- marginal fitness of the i-th haplotype
- $$\bar{w}_i = \sum_{j=1}^{4} w_{ij} x_j$$
- Rearranging
- $$x_1' = \frac{\left(w_{11}x_1^2 + \frac{1}{2}w_{12}2x_1x_2 + \frac{1}{2}w_{13}2x_1x_3 + \frac{1}{2}(1-c)w_{14}2x_1x_4 + \frac{1}{2}cw_{23}2x_2x_3\right)}{\bar{w}}$$
- $$x_1' = \frac{x_1\bar{w}_1 - w_{14}cD}{\bar{w}}$$

A two locus model of selection and recombination

- change in the frequency of our 1 haplotype
- $$\Delta x_1 = \frac{x_1(\bar{w}_1 - \bar{w}) - cw_{14}D}{\bar{w}}$$
- $$\Delta x_i = \frac{x_i(\bar{w}_i - \bar{w}) \pm cw_{14}D}{\bar{w}}$$
- change in the frequency of a haplotype (e.g. AB, haplotype is determined by the interplay of
  - the magnitude and sign of $(\overline{w}_i - \overline{w})/\overline{w}$
  - LD

Types of interaction between selection and recombination

- Use Equation
- $$\Delta x_i = \frac{x_i(\bar{w}_i - \bar{w}) \pm c w_{14} D}{\bar{w}}$$
- Study interaction between selection and recombination under different conditions
- Useful to gain intuition using Muller's diagram

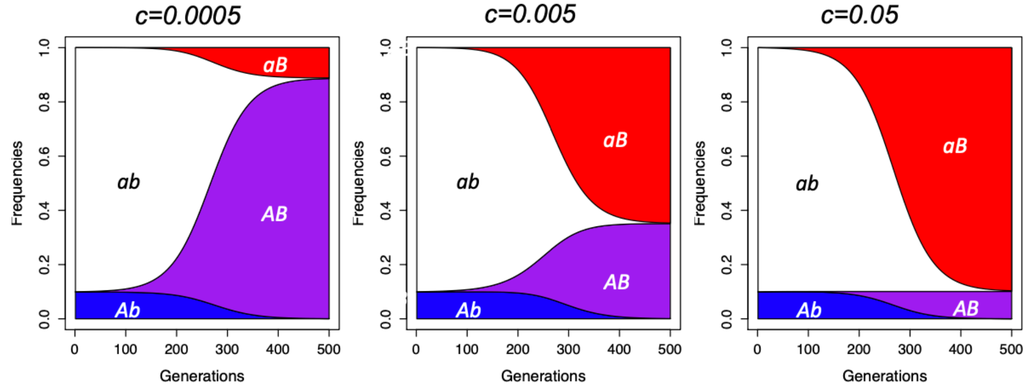


Figure 14.2: A beneficial mutation B arises on the background of a neutral allele whose initial frequency is $p_A = 10\%$. The beneficial allele has a strong, additive selection coefficient of $hs = 0.05$.

Case 1: The hitchhiking of deleterious alleles

- Deleterious alleles can also hitchhike along with beneficial mutations if they are not too deleterious compared to the benefits offered by the selected allele.

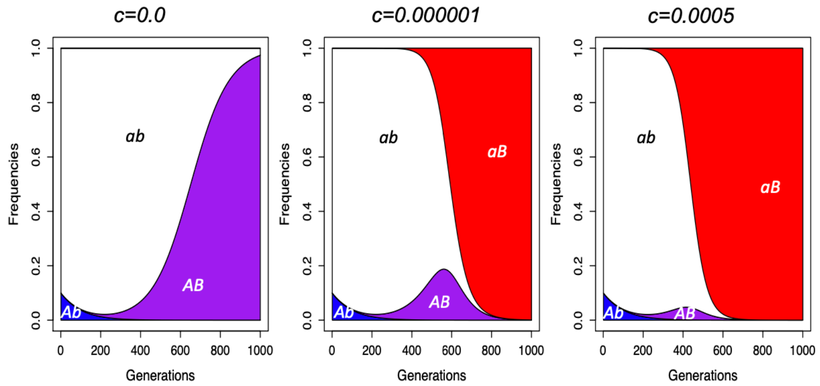


Figure 14.3: The hitchhiking of a deleterious allele. The beneficial allele B arises on the background of a deleterious allele A, and the extent to which the A allele gets to hitchhiking along depends on the recombination rate. Code here.

Case 2: Clonal interference between favourable alleles

- clonal interference:
  - when rates of sex and recombination are zero, or very low, positively selected alleles can prevent each other from reaching fixation and so the rate of adaptation can be slowed.

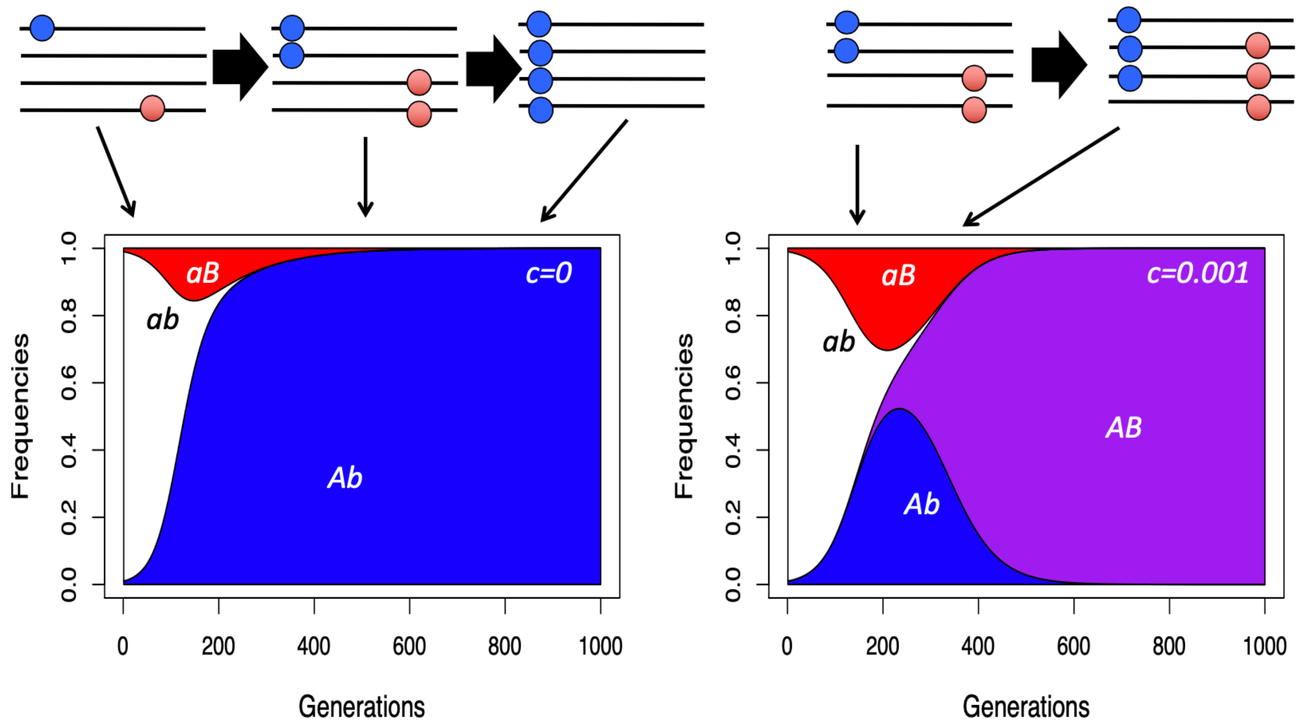


Figure 14.4: Interference between two positively selected alleles. **Left)** the red and blue (A and B) beneficial alleles arise on different haplotypes. They rise in frequency, but in the absence of recombination only one can fix. This is shown in a Muller diagram, where p_{AB} is initially set to zero. **Right)** In the presence of recombination the population can generate the recombinant (AB) haplotype, which can subsequently fix. Code here.

Case 2: Clonal interference between favourable alleles

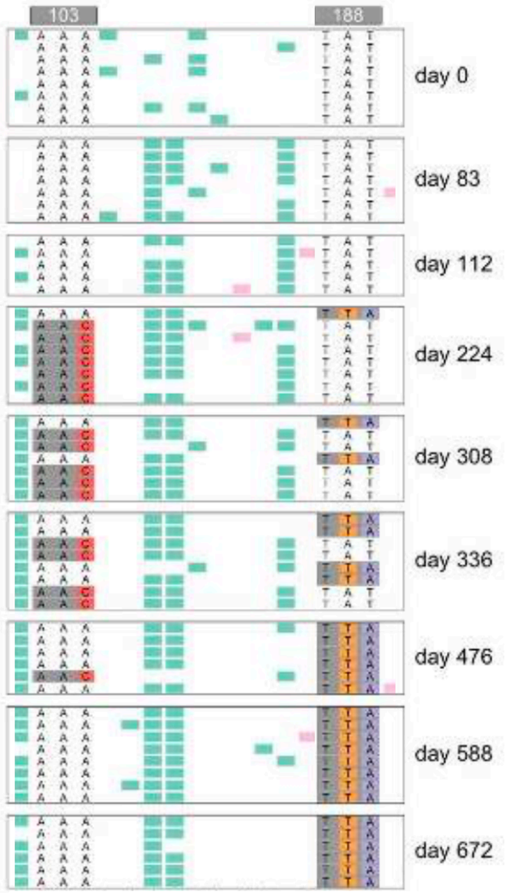


Figure 14.5: HIV sequences from a patient over the course of drug treatment in the retrotransposase coding region. Figure cropped from Williams and Pennings (2019), licensed under CC BY 4.0.

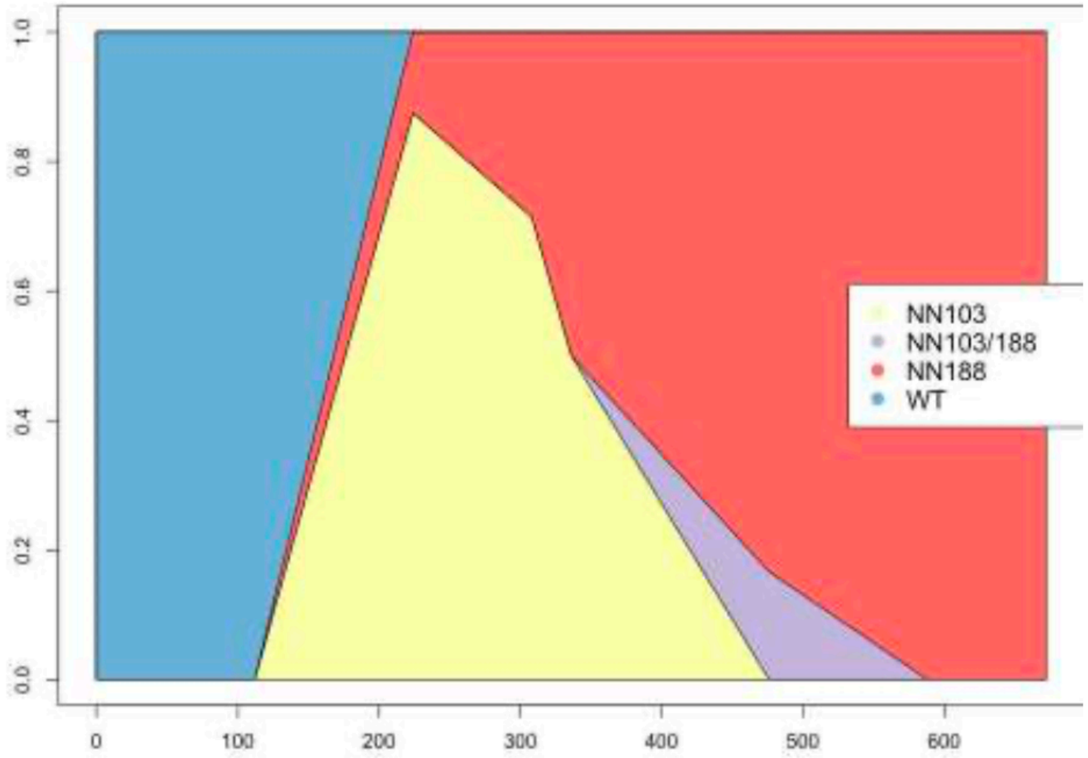
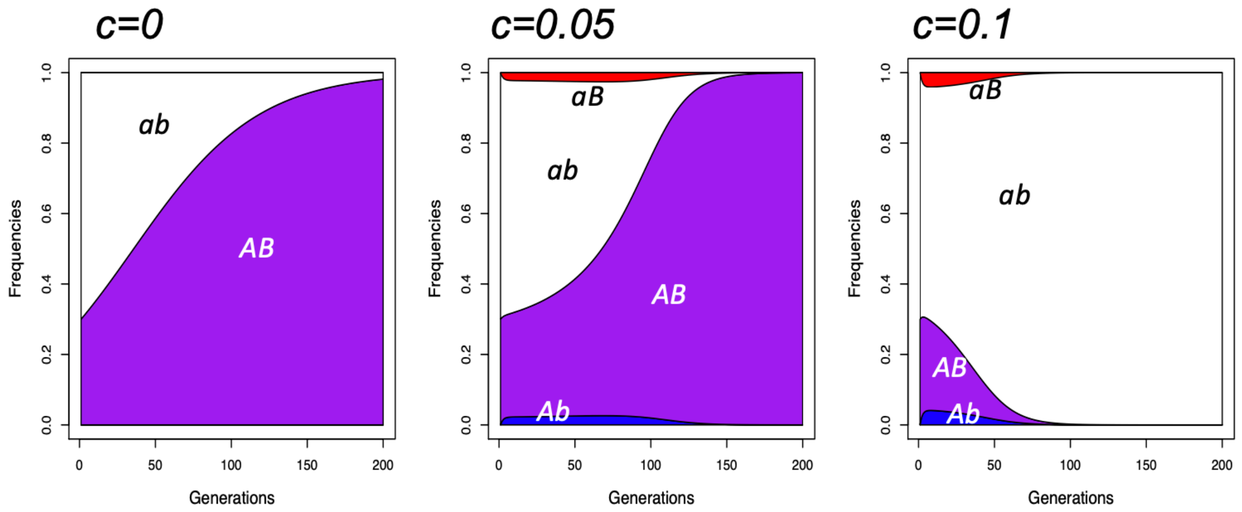


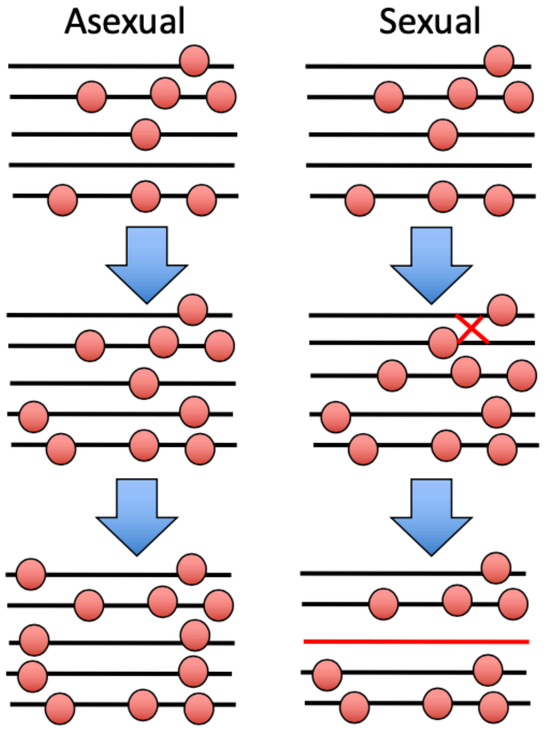
Figure 14.6: Muller plot of the drug resistance interference dynamics from Figure 14.5. Figure from Williams and Pennings (2019), licensed under CC BY 4.0.

Case 3: Epistatic combinations of alleles and the cost of recombination

- Recombination can bring beneficial combinations of alleles together, as well as tear them apart.
- Image a pair of alleles A and B at two loci that work very well together, and offer a fitness advantage over the ancestral combination of allele a and b.
- AB: high fitness
- ab: intermediate fitness
- Ab and aB: low fitness



Case 4: Muller's ratchet



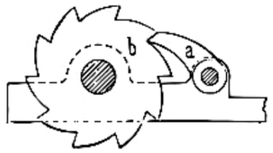


Figure 14.8: A ratchet. A cog (b) with asymmetric teeth that can only turn one way as the pawl (a) prevents it turning the other way.
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