Case studies in Evolution
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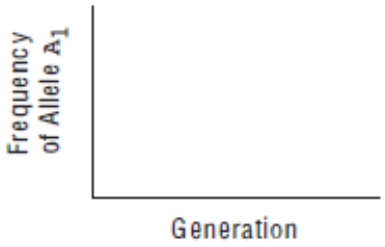
Selection and Mutation as agents of Evolution

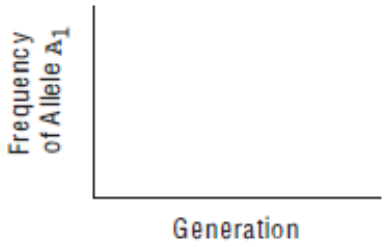
1. After fiddling with the simulation program to see how it works, restore all parameters to their default settings. The default settings encompass initial frequencies of 0.5 for both alleles, and the assumptions of no selection, no mutation, no migration, no genetic drift, and random mating.
Run the simulation. Does the allele frequency change over generations? Try different values for the starting frequency of allele A1. Does your experimentation verify that any starting frequencies are in equilibrium so long as there is no selection, no mutation, no migration, and no drift?
What does this mean (Hint: Think in terms of Evolution)?

2. There are three boxes that let you set the fitnesses for the three genotypes. The fitnesses allow you to play with the effects of selection (that is, differences between the genotypes in survival or reproduction). Setting the values to 1, 0.8, and 0.2, for example, is equivalent to specifying that for every 100 individuals of genotype A1A1 that survive to reproduce, 80 individuals of genotype A1A2 survive, and 20 individuals of genotype A2A2 survive.
a) Predict what will happen if you set the fitnesses of A1A1, A1A2, and A2A2 to 1, 0.8, and 0.2, respectively. Then run the simulation. Was your prediction correct? Explain.

Prediction:



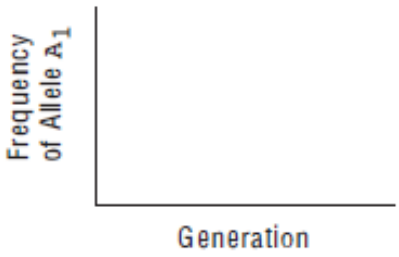
What actually happened:



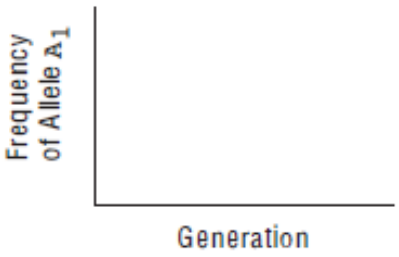
Explanation:

b) Now set the initial frequency of allele A1 to 0.01, and the fitnesses to 1, 1, and 0.99. What happens when you run the simulation? Why? Now try fitnesses of 1, 1, and 0.95. Can you explain the difference?

Fitnesses of 1, 1, and 0.99:



Fitnesses of 1, 1, and 0.95:



Explanation:

c) Look at Figure 6.14 in the next page. In the research depicted in the figure, researchers raised experimental populations of fruit flies on food spiked with ethanol, and monitored the frequency of the AdhS allele over 50 generations. AdhS encodes a version of the alcohol dehydrogenase enzyme that breaks down ethanol at only half the rate of the version encoded by AdhF. The starting frequency of AdhS was about 0.65 in both experimental populations; the ending frequency was about 0.1 in one population and about 0 in the other. Use AlleleA1 to estimate the strength of selection against the AdhS allele during this experiment. Let

A1 represent the AdhS allele. Set the starting frequency of A1 to 0.65. Set the number of generations to 50. (To change the number of generations, use the popup menu at the lower right corner of the graph. Press on the small button with the black triangle, then select the number of generations you want.) Try different combinations of fitnesses for the three genotypes. Find a combination that reproduces the pattern of change over time in Figure 6.14. What combination of fitnesses works best? What do these fitnesses represent in terms of the relative survival (or reproductive success) of the three genotypes?

Empirical Research on Allele Frequency Change by Selection

Douglas Cavener and Michael Clegg (1981) documented a cumulative change in allele frequencies over many generations in a laboratory-based natural selection experiment on the fruit fly (*Drosophila melanogaster*). Fruit flies, like most other animals, make an enzyme that breaks down ethanol, the poisonous active ingredient in beer, wine, and rotting fruit. This enzyme is called alcohol dehydrogenase, or ADH. Cavener and Clegg worked with populations of flies that had two alleles at the ADH locus: Adh^F and Adh^S. (The *F* and *S* refer to whether the protein encoded by the allele moves quickly or slowly through an electrophoresis gel.)

The scientists kept two experimental populations on food spiked with ethanol and two control populations of flies on normal, nonspiked food. The researchers picked the breeders for each generation at random. This is why we are calling the project a natural selection experiment: Cavener and Clegg set up different environments for their different populations, but the researchers did not themselves directly manipulate the survival or reproductive success of individual flies.

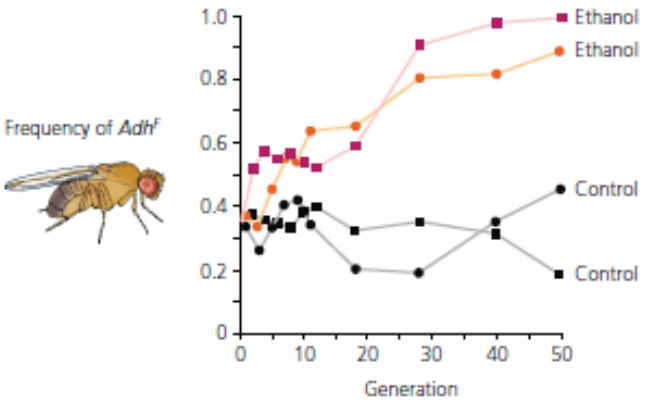


Figure 6.14 Frequencies of the allele in four populations of fruit flies over 50 generations The black squares and circles represent control populations living on normal food; the magenta squares and orange circles represent experimental populations living on food spiked with ethanol. From Cavener and Clegg (1981).

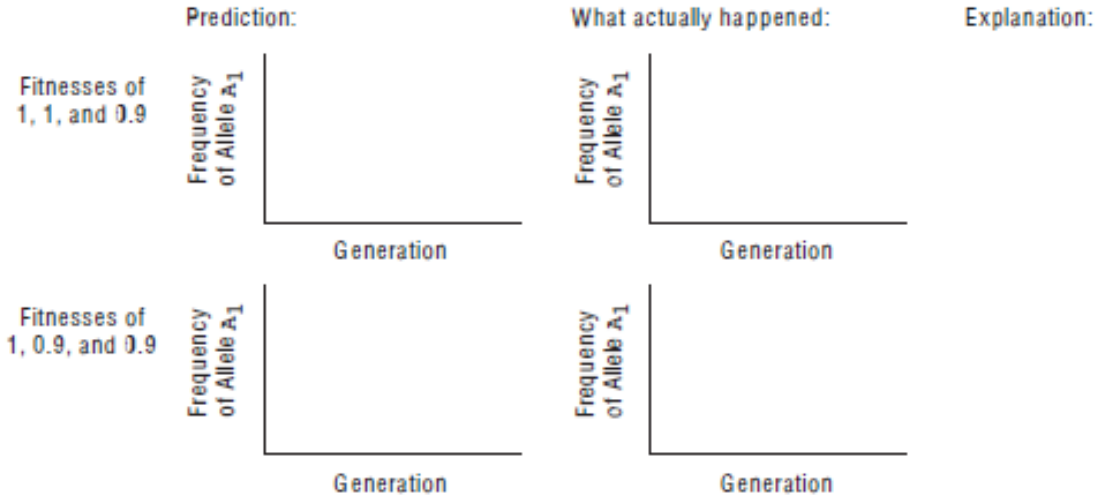
Every several generations, Cavener and Clegg took a random sample of flies from each population, determined their ADH genotypes, and calculated the allele frequencies. The results appear in Figure 6.14. The control populations showed no large or consistent long-term change in the frequency of the Adh^F allele. The experimental populations, in contrast, showed a rapid and largely consistent increase in the frequency of Adh^F (and, of course, a corresponding decrease in the frequency of Adh^S). Hardy–Weinberg conclusion 1 appears to hold true in the control populations, but is clearly not valid in the experimental populations.

Can we identify for certain which of the assumptions of the Hardy–Weinberg analysis is being violated? The only difference between the two kinds of populations is that the experimentals have ethanol in their food. This suggests that it is the no-selection assumption that is being violated in the experimental populations. Flies carrying the Adh^F allele appear to have higher lifetime reproductive success (higher fitness) than flies carrying the Adh^S allele when ethanol is present in the food. Cavener and Clegg note that this outcome is consistent with the fact that alcohol dehydrogenase extracted from Adh^F homozygotes breaks down ethanol at twice the rate of alcohol dehydrogenase extracted from Adh^S homozygotes. Whether flies with the Adh^F allele have higher fitness because they have higher rates of survival or because they produce more offspring is unclear.

Empirical research on fruit flies is consistent with our conclusion that natural selection can cause allele frequencies to change.

Selection on recessive and dominant alleles

3. Restore all parameters to their default values, then set the initial frequency of allele A1 to 0.01.
a) Predict what will happen when you try fitnesses of 1, 1, and 0.9, then check your prediction. Now predict what will happen when you try fitnesses of 1, 0.9 and 0.9, and check your prediction. Were your predictions correct? Try to explain what happened.



b) In Question 3a, when was allele A1 dominant (with respect to fitness) and when was it recessive? Which will increase in frequency more rapidly when favored by selection: a rare recessive allele, or a rare dominant allele? Why? (Hint: Try running various combinations of initial frequencies and fitness values in AlleleA1)

c) Which rises to a frequency of 1.0 more rapidly under selection: a common recessive allele, or a common dominant allele? Why?

Selection via eugenic sterilization

4. Imagine, as early 20th century eugenicists did, a single locus at which there is a gene controlling strength of mind. A2 is the allele for normalmindedness; A1 is the allele for feeblemindedness. A2 is dominant over A1. Imagine, as Henry H. Goddard (1914) did, that allele A1 has a rather high frequency, say 0.1.

a) Using Allele A1, what is the frequency of feebleminded individuals in the population? If we had a population of 1000 individuals, how many would be feebleminded? How many would be carriers for feeblemindedness? How many would be homozygous normalminded?

b) If a eugenic sterilization law were universally enforced, such that all feebleminded individuals were sterilized before reaching sexual maturity, what would be the fitnesses of the three genotypes? Explain.

c) Using Allele a1, what would be the frequency of allele A1 after a single generation of eugenic sterilization. (Use the numbers you calculated in part a, and assume that every nonsterilized individual makes exactly 10 gametes. What is the total number of gametes? What fraction carry allele A1?) What would be the frequency of feebleminded individuals? How effective is eugenic sterilization at reducing the frequency of feeblemindedness?

d) Use AlleleA1 to predict the long-term effect of eugenic sterilization on the frequency of the allele for feeblemindedness. For example, could feeblemindedness be eliminated within 20 generations? Why or why not? How long is 20 human generations in years? What do you think a eugenicist would conclude from this simulation? What else could be done to eliminate feeblemindedness?

Selection on homozygotes and heterozygotes

5. In the 1950's, biologists Terumi Mukai and Allan Burdick (1959) discovered that their laboratory population of fruit flies harbored a genetic locus with interesting effects on viability (that is, survival). The locus has two alleles, which we will call V (for viable) and L (for lethal). Individuals with genotype VV survive, whereas individuals with genotype LL die before reaching adulthood. Mukai and Burdick established two separate populations of flies in which the initial frequency of allele V was 0.5. They propagated both populations for 15 generations, and monitored the frequency of the V allele.

a) Assuming that genotype VL has the same fitness as genotype VV, use AlleleA1 to predict what will happen in Mukai and Burdick's experiment. Is your prediction consistent with Mukai and Burdick's own expectation that the frequency of the viable allele would quickly rise toward 1.0?

b) The actual result is shown by the red symbols in Figure 6.21 below.

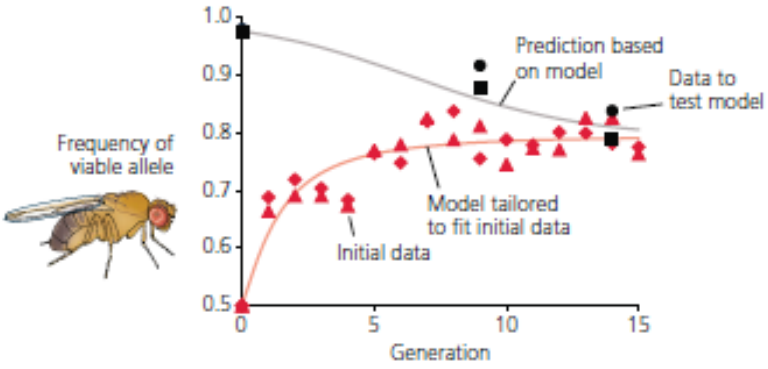


Figure 6.21 Evolution in four laboratory populations of fruit flies When homozygous, one allele is viable and the other lethal. Nonetheless, populations with a frequency of 0.5 for both alleles (red) evolved toward an intermediate equilibrium. The black populations represent a test of the hypothesis that heterozygotes enjoy the highest fitness. From data in Mukai and Burdick (1959).

The frequency of allele V rose, but only to a frequency of about 0.79. Mukai and Burdick next established two populations in which the initial frequency of the viable allele was 0.975. The result for these populations is shown by the black symbols in Figure 6.21: The frequency of allele V dropped to about 0.79. Using AlleleA1, set the initial frequency of A1 to 0.5. Experiment with different fitnesses for the three genotypes, always making sure that the values you choose are consistent with what you already know about alleles V and L. Can you find values that cause the frequency of allele A1 to rise to an equilibrium at 0.79?

c) Now set the initial frequency of A1 to 0.975. When you run the simulation, does the frequency of A1 fall to an equilibrium at 0.79? Continue to play with the simulation until you find a combination of fitnesses that works.

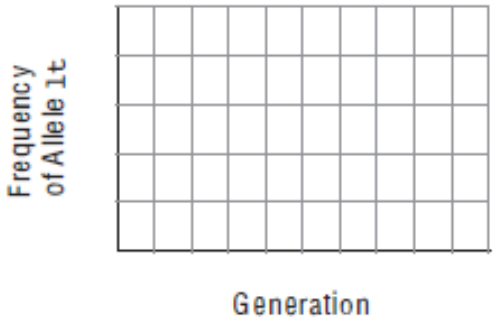
d) Based on your experiments, state a hypothesis that explains the behavior of Mukai and Burdick's fly populations.

6. Bruce Wallace (1963) established a laboratory population in which the recessive allele lt was at a frequency of 0.5. He propagated the population for 10 generations, and determined the frequency of lt each generation. Individuals with genotype lt/lt die without reproducing. Individuals with genotype +/+ are normal.

a) Use AlleleA1 to predict the change over time in the frequency of lt under the following three hypotheses: i) Individuals with genotype +/lt have slightly higher fitness than +/+ individuals (say, 1.1 versus 1.0); ii) Individuals with genotype +/lt have a fitness equal to +/+ individuals; iii) Individuals with genotype +/lt have slightly lower fitness than +/+ individuals (0.9 versus 1.0).

b) The table below gives Wallace's data. Plot a graph of the observed change in the frequency of lt across generations.

Generation	Frequency of *lt*
0	0.5
1	0.284
2	0.232
3	0.189
4	0.188
5	0.09
6	0.085
7	0.082
8	0.065
9	0.054
10	0.041

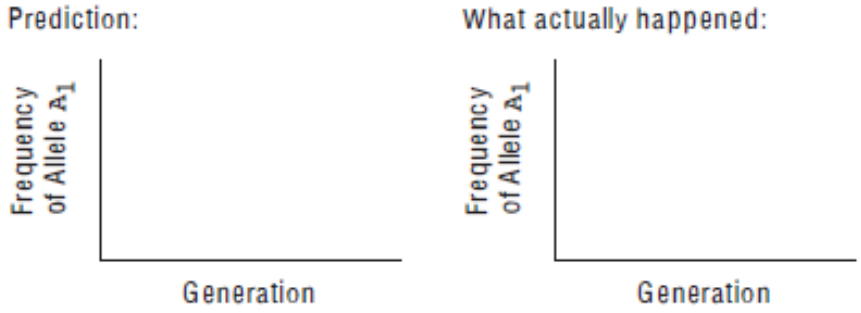


c) How accurate were your predictions?

d) Which of the three hypotheses appears to be closer to the truth?

Mutation as a mechanism of evolution

7. There are 2 boxes in AlleleA1's window that let you play with the mutation rate. One controls the rate at which copies of A1 turn into A2's; a mutation rate of 0.001 means that each generation one out of every thousand A1's turns into an A2. The other box controls the mutation rate in the other direction. Note that the mutation rate should be a number between 0 and 1 (why?). If you enter a number outside this range you will get weird behavior.
Return all parameters to their default values, then set the mutation rates to 0.0001 and 0. Predict what will happen.



Were you correct? For any real gene a mutation rate of 0.0001 would be extraordinarily high. How effective is mutation, by itself, as a force of evolution?

Mutation-Selection Balance

8. Consider the case of spinal muscular atrophy. Spinal muscular atrophy is a neurodegenerative disease characterized by weakness and wasting of the muscles that control voluntary movement. It is cased by recessive loss-of-function mutations in a gene on chromosome 5 called telSMN (SMN stands for "survival motor neuron").
a) Using AlleleA1, return all parameters to their default values. Let A2 represent the normal allele of telSMN, and let A1 represent a loss-of-function allele. Brunhilde Wirth and colleagues (1997) estimate that the fitness of affected individuals is about 0.1. Set the fitnesses to 0.1, 1, and 1. What is the frequency of the knockout allele after 500 generations? Why?

b) The actual frequency of knockout alleles for telSMN in populations of European ancestry is about 0.01. One hypothesis for the maintenance of this frequency is that new knockout alleles are continuously created by mutation. With fitnesses of 0.1, 1, and 1, how high does the mutation rate from A2 to A1 need to be to achieve an equilibrium frequency of 0.01 for allele A1?

c) Wirth and colleagues measured the actual mutation rate in the telSMN gene. It is high-- about 0.00011. Do you think a balance between mutation and selection is an adequate explanation for the persistence of telSMN knockout alleles at a frequency of 0.01? Explain.

9. Now consider the case of cystic fibrosis. Cystic fibrosis is a recessive genetic disease caused by loss-of-function mutations in the CFTR gene. Affected individuals suffer chronic respiratory infections that ultimately cause severe lung damage. Let A2 be the normal allele (C) and A1 the mutant allele (c).
a) Until recently, very few cc individuals survived long enough to reproduce. Return all parameters to their default values, then set the fitnesses to 0, 1, and 1. What is the frequency of the c allele after 500 generations? Why?

b) The actual frequency of the c allele is about 0.02 in European populations. One hypothesis for the maintenance of this frequency is that new copies of the c allele are continuously created by mutation. With fitnesses of 0, 1, and 1, how high does the mutation rate from A2 to A1 need to be to achieve an equilibrium frequency of 0.02 for allele A1?

c) The actual rate of mutations creating new c alleles is about 0.00000067. Is a balance between mutation and selection a plausible explanation the maintenance of the c allele at a frequency of 0.02? If not, develop an alternative explanation and use AlleleA1 to demonstrate that it is plausible.

Literature Cited

Goddard, H. H. 1914. Feeble-mindedness: Its causes and consequences. The Macmillan Company, New York.

Mukai, T., and A. B. Burdick. 1959. Single gene heterosis associated with a second chromosome recessive lethal in Drosophila melanogaster. Genetics 44: 211-232.

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Wirth, B., T. Schmidt, et al. 1997. De novo rearrangements found in 2% of index patients with spinal muscular atrophy: Mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. American Journal of Human Genetics 61: 1102-1111.