SELECTION AND MUTATION AS MECHANISMS OF EVOLUTION

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Introduction

The purpose of this case study is to help you develop an intuition about how selection and mutation cause evolution. You will use a software simulation of an evolving population to analyze the examples discussed in Chapter 6, and to answer a variety questions concerning changes in the frequencies of alleles. Once you are familiar with the simulation program, you can use it to answer questions of your own. For example, in Chapter 8, page 310, we will look at evidence suggesting that the *CCR5*-Δ*32* allele is only about 700 years old in European populations. You can use the simulation program to estimate the strength of selection that must have been required to cause the Δ*32* allele rise from a frequency of virtually zero to a frequency of 0.1 to 0.2 in less than 30 generations.

To complete the case study you will need the application program AlleleA1. You can download AlleleA1 from the Evolutionary Analysis website. Versions are provided that run under MacOS and Windows. AlleleA1 simulates evolution at a single locus in an ideal population. The locus has 2 alleles: A_1 and A_2. AlleleA1 allows you to enter parameters controlling selection, mutation, migration, drift, and inbreeding. The program then plots a graph showing the frequency of allele A_1 over time. Each generation's frequency is calculated from the previous generation's frequency, according to the equations described in Chapters 6 and 7.

AlleleA1 is easy to use. Small boxes in the lower portion of the AlleleA1 window allow you to enter and change the parameters for the simulation. The tool palette has buttons that allow you to run the simulation, clear the graph, reset all parameters to their default values, print your graph, and quit. More details on using AlleleA1 can be found in the manual, available both as a separate PDF file and online under the Help menu.

Exercises

Hardy-Weingberg Equilibrium

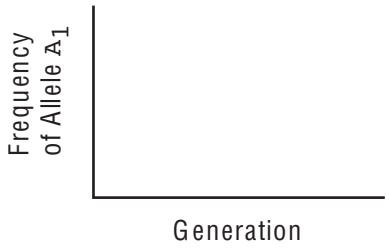
1. After fiddling with the simulation program to see how it works, restore all parameters to their default settings. The default settings encompass initial frequencies of 0.5 for both alleles, and the assumptions of no selection, no mutation, no migration, no genetic drift, and random mating. Run the simulation to verify that under these conditions the allele frequencies do not change. Try different values for the starting frequency of allele A_1. 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?

Selection as a mechanism of evolution

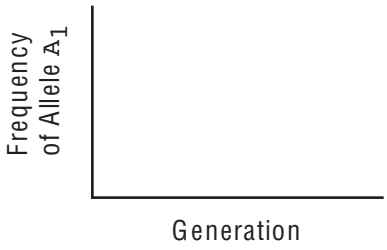
2. There are three boxes that let you set the fitnesses for the three genotypes. The fitnesses allow you to play with the effects of selection (that is, differences between the genotypes in survival or reproduction). Setting the values to 1, 0.8, and 0.2, for example, is equivalent to specifying that for every 100 individuals of genotype A_1A_1 that survive to reproduce, 80 individuals of genotype A_1A_2 survive, and 20 individuals of genotype A_2A_2 survive.

a) Predict what will happen if you set the fitnesses of A_1A_1, A_1A_2, and A_2A_2 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 $\mathbf{A_1}$ 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:

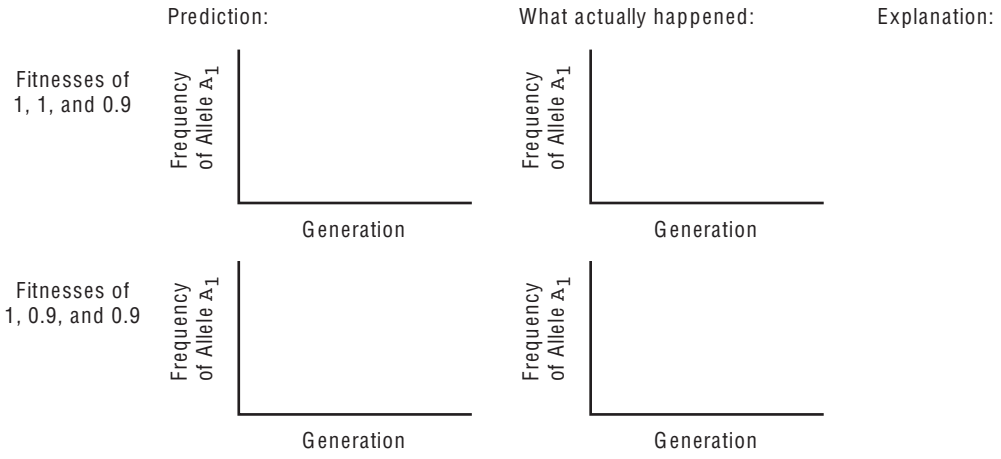
c) Look at Figure 6.14 in the textbook (page 195). In the research depicted in the figure, researchers raised experimental populations of fruit flies on food spiked with ethanol, and monitored the frequency of the Adh^S allele over 50 generations. Adh^S encodes a version of the alcohol dehydrogenase enzyme that breaks down ethanol at only half the rate of the version encoded by Adh^F. The starting frequency of Adh^S 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 Adh^S allele during this experiment. Let A_1 represent the Adh^S allele. Set the starting frequency of A_1 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?

d) Reread *Changes in the Frequency of the* CCR5-Δ32 *Allele Revisited*, on pages 200 - 201, and look at the graphs in Figure 6.17. In each scenario depicted in the figure, we made our prediction based on the assumption that the fitness of +/Δ*32* heterozygotes is equal to the fitness of +/+ homozygotes. In reality, +/Δ*32* heterozygotes may have somewhat higher fitness than +/+ homozygotes. Use AlleleA1 to explore which, if any, of the three predictions is strongly affected by allowing +/Δ*32* heterozyotes to have higher fitness than +/+ homozygotes. Describe your results.

Selection on recessive and dominant alleles

3. Restore all parameters to their default values, then set the initial frequency of allele A_1 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. (Hint: Reread *Selection on Recessive and Dominant Alleles* on pages 202-203. Try to reproduce Dawson's predictions in Figure 6.19. Then consider this question again.)



b) In Question 3a, when was allele A_1 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; take a look at Figure 6.20 on page 205.)

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. A_2 is the allele for normalmindedness; A_1 is the allele for feeblemindedness. A_2 is dominant over A_1. Imagine, as Henry H. Goddard (1914) did, that allele A_1 has a rather high frequency, say 0.1.

a) Using pencil and paper, what is the frequency of feebleminded individuals in the population? (Use the Hardy-Weinberg equilibrium principle). 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 pencil and paper, what would be the frequency of allele A_1 after a single generation of eugenic sterilization. (Use the numbers you calculated in part a, and assume that every non-sterilized individual makes exactly 10 gametes. What is the total number of gametes? What fraction carry allele A_1?) 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 on page 207: 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 A_1 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 A_1 to rise to an equilibrium at 0.79?

c) Now set the initial frequency of A_1 to 0.975. When you run the simulation, does the frequency of A_1 fall to an equilibrium at 0.79? Continue to play with the simulation until you find a combination of fitnesses that works.

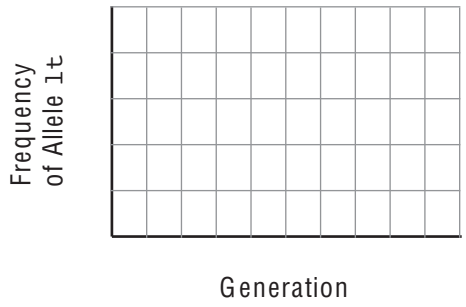
d) Based on your experiments, state a hypothesis that explains the behavior of Mukai and Burdick's fly populations.

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?

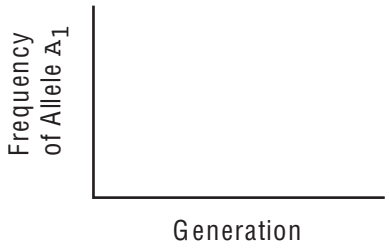
d) Which of the three hypotheses appears to be closer to the truth?

Mutation as a mechanism of evolution

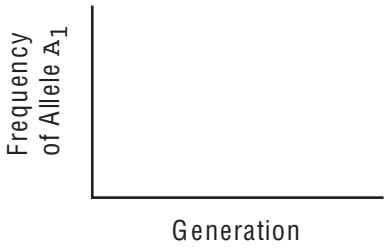
7. There are 2 boxes in AlleleA1's window that let you play with the mutation rate. One controls the rate at which copies of A_1 turn into A_2's; a mutation rate of 0.001 means that each generation one out of every thousand A_1's turns into an A_2. The other box controls the mutation rate in the other 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.

Prediction:



What actually happened:



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 A_2 represent the normal allele of telSMN, and let A_1 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 A_2 to A_1 need to be to achieve an equilibrium frequency of 0.01 for allele A_1?

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 A_2 be the normal allele (*C*) and A_1 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 A_2 to A_1 need to be to achieve an equilibrium frequency of 0.02 for allele A_1?

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. See pages 147-149 for one researcher's alternative hypothesis and test.

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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