1. The default settings in Allele A1 demonstrate Hardy-Weinberg equilibrium. These settings include initial frequencies of 0.5 for alleles A1 and A2 and the assumptions of no mutation, no selection, no migration, no genetic drift (infinite population size), and random mating. Run this simulation and convince yourself that these conditions result in no change in the allele frequencies and also that the genotype frequencies can be predicted by the allele frequencies.

Now, try different values for the starting frequency of allele A1 and run several simulations. Does your experimentation verify that any starting frequencies are in Hardy-Weinberg equilibrium? Explain how you know.

The population is in Hardy-Weinberg equilibrium. I know this because using an initial allele frequency of allele A1 (0.7) did not change after 500 generations. Also, the genotype frequencies can be predicted from the allelic frequencies (A1=0.7, A2=0.3): A1A1=p^2=(0.7)^2=0.49, A1A2=2pq=2(0.7)(0.3)=0.42, A2A2=q^2=(0.3)^2=0.09. Likewise, if I use an initial frequency of allele A1 of 0.05, the allele frequency again does not change across generations, and the predicted genotype frequencies are as expected under HWE (A1A1=p^2=(0.05)^2=0.0025, A1A2=2pq=2(0.05)(0.95)=0.095, A2A2=q^2=(0.95)^2=0.9025.

2. Notice that in the above simulations (both run with an infinite population size), the frequency of allele A1 remains constant at 0.5 (or whatever its initial frequency was) across generations and that the final genotype frequencies can be predicted by the allele frequencies.

Now change the population size to 1000 and re-run this simulation. Run this simulation five times. Does the same thing happen each time? Why or why not? You will probably want to select the "Multiple" button, which will allow you to compare the different simulations.

No the result is not the same across the five simulations. This is because with a finite population size, there is sampling variation due to genetic drift. This variation results in the fluctuations in the frequency of allele A1 between simulations.

Experiment by changing the initial population size (use 10, 100, and 10,000) and running each of these simulations several times. It may help if you use a different color for each population size. Is the effect of genetic drift similar or different for the population sizes you have modeled? Given what you know about genetic drift, explain your results.

The effect of genetic drift is different depending on population size. Drift is more intense (alleles are fixed or lost more rapidly) in smaller populations (see yellow
populations, population size 10, in the figure @ right). Thus, in a population of size 100 (green lines), genetic drift is stronger than in a population of size 1000 (blue lines) and allele A1 is either fixed or lost more readily. Note that in a population sizes of 1,000 and 10,000 (blue and pink lines), allele A1 is neither fixed nor lost in these simulations.

3. Under drift, if we track allele A1 for long enough, eventually it will either be fixed (frequency=1) or be lost (frequency=0). Use this program to quantify how the initial frequency of an allele relates to the probability of either its fixation or its loss? Think about how you can use AlleleA1 to determine this.

Reset the program to the default values and then change the population size to 100. Run this simulation and record whether allele A1 is either fixed or lost from the population. Ignore those runs in which allele A1 neither fixes or is lost. Repeat this simulation a total of 30 times, recording each time whether allele A1 is fixed or lost. What % of simulations fixed allele A1? What % lost allele A1?

When the initial frequency of allele A1 was 0.5, allele A1 fixed 53% of the time (16 populations) and was lost 47% of the time (14 populations).

Now chose a different initial frequency for allele A1 (one that will help you answer the question posed above). Repeat this simulation 30 times, again recording the number of times allele A1 is either fixed or lost. What initial frequency for allele A1 did you choose? Given this frequency, what % of simulations fixed allele A? What % lost allele A1?

When the initial frequency of allele A1 was 0.25, allele A1 was retained 37% of the time (11 populations) and was lost 63% of the time (19 populations).

Finally, chose a third starting frequency for allele A1 to drive home the point. Again, repeat this simulation 30 times, recording the number of times allele A1 is either fixed or lost. What initial frequency for allele A1 did you choose? Given this frequency, what % of simulations fixed allele A1? What % lost allele A1?

When the initial frequency of allele A1 was 0.75, allele A1 was fixed 60% of the time (18 populations) and was lost 40% of the time (12 populations).

4. Is genetic drift a creative or destructive force with regard to genetic variation within populations? What about between a set of subpopulations?

Destructive within populations, but creative between populations.

5. Reset to the default parameters and then set the initial frequency of allele A1 equal to 0.05 and the starting population size to 100. Run this simulation several times. What usually happens to the A1 allele and why?

Allele A1 is usually lost from the population; this is due to genetic drift. Note the red lines in the graph below.

Now make A1 a slightly beneficial and dominant allele using the relative fitness values $A_1A_1=1$, $A_1A_2=1$, and $A_2A_2=0.9$. Run the simulation several times. What happens and why?
Selection for allele A1 overcomes the effect of genetic drift and this allele spreads in the population (see blue lines in graph below).

6. Set the population size to infinite, and change the number of generations to 100. Now create another case with the A1 allele favored by natural selection. What relative fitness values did you use? Enter them below.

\[
\begin{align*}
    w_{A1A1} &= 1.0 \\
    w_{A1A2} &= 0.9 \\
    w_{A2A2} &= 0.8
\end{align*}
\]

Given your fitness values, is allele A1 dominant, recessive, or co-dominant?

If \( w_{A1A1} > w_{A1A2} \) and \( w_{A2A2} \), then recessive. If \( w_{A1A1} \) and \( w_{A1A2} > w_{A2A2} \), then dominant. If \( w_{A1A1} > w_{A1A2} > w_{A2A2} \), then codominant. In the case above, allele A1 is codominant.

7. Reset to the default values, but change the initial frequency of allele A1 to 0.05 and select the Multiple button so you can compare two scenarios. Next, change the fitness values to create two different cases, one where allele A1 is beneficial and dominant and another where A1 is beneficial and recessive. Enter your values in the table below. Compare the rate of fixation for a dominant versus a recessive beneficial allele A1.
Summarize the differences in the time to fixation (i.e., the number of generations before the beneficial A\textsubscript{1} allele is fixed) between the two scenarios.

When allele A\textsubscript{1} is dominant, it does not fix in the population after 500 (or even 100,000!) generations when the population size is infinite, although A\textsubscript{1} does have a high frequency. In contrast, the A\textsubscript{1} allele fixes (and the A\textsubscript{2} allele is completely lost) when the A\textsubscript{1} allele is recessive (and A\textsubscript{2} dominant). Note that the red line (when A\textsubscript{1} is recessive and A\textsubscript{2} is dominant) reaches fixation (A\textsubscript{1}=1) before the blue line (when A\textsubscript{1} is dominant and A\textsubscript{2} is recessive).

Why does this make sense?

When A\textsubscript{1} is recessive (red line @ right), both the A1A2 and A2A2 genotypes have the deleterious A2 phenotype, so selection will eliminate them. Since selection is acting against all the carriers of the A2 allele, the allele is eventually lost, and the population fixes allele A\textsubscript{1}.

When A\textsubscript{1} is dominant (blue line, above), the deleterious A2 allele is hidden in heterozygotes. Selection cannot act on it, because A1A2 individuals are as successful as A1A1 individuals. As the frequency of the A1 allele rises (due to selection against A2A2 genotypes), the frequency of A2 declines (and A1 increases). However, the frequency of A2A2 individuals also drops and thus selection against allele A2 (or for A1) slows. In this simulation, selection cannot eliminate the A2 allele completely, and it remains in the population at a low frequency.
8. Reset to the default values before continuing, but change the number of generations to 100. Pigmentation in Gila monsters is controlled by a single locus with two alleles: Or and B. Individuals homozygous for the Or allele are mostly orange and so blend in with the reddish rock surroundings they inhabit, whereas individuals homozygous for allele B are mostly black. As a result, mostly black Gila monsters survive about three-quarters as well as do mostly orange Gila monsters.

Heterozygous individuals are speckled orange and black. Gila monsters advertise their toxicity by contrasting patterns of orange and black, and individuals with this patterning spend less time defending themselves and more time eating (& having babies) than do single-color individuals. On average, orange Gila monsters reproduce only about 80% as well as speckled individuals. Model this scenario in AlleleA1, assuming allele Or is allele A1. Fill in the fitness values you used in the Table below.

<table>
<thead>
<tr>
<th>wA1A1</th>
<th>0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>wA1A2</td>
<td>1.0</td>
</tr>
<tr>
<td>wA2A2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Run this simulation. What happens to the frequency of allele A1?

Allele A1 converges to 0.667.

What determines the frequency of allele A1? How can you change its frequency and why does this make sense to you?

The value depends on the fitness values. For example, if wA2A2 > wA1A1, then the equilibrium frequency of allele A1 will be reduced (& vice versa).

9. Use the equation in Box 6.8 on p. 202 in your text to calculate the necessary fitness values for the genotypes in order to maintain allele A1 at a frequency of 0.2. Enter these fitness values below.

Several possible equilibrium solutions exist for the fitness values of the genotypes.

\[
\hat{p} = \frac{t}{s+t} \\
0.2 = \frac{t}{s+t} \\
0.2(s+t) = t \\
0.2s + 0.2t = t \\
0.2s = t - 0.2t \\
0.2s = 0.8t \\
s = 0.4t \text{ or } t = 0.25s
\]

If \( s = 0.8 \), then \( wA1A1 = 0.2 \) and \( t = 0.2 \), making \( wA2A2 = 0.8 \)

If \( s = 0.9 \), then \( wA1A1 = 0.1 \) and \( t = 0.225 \), making \( wA2A2 = 0.775 \)

If \( s = 0.7 \), then \( wA1A1 = 0.3 \) and \( t = 0.175 \), making \( wA2A2 = 0.825 \)

If \( s = 0.6 \), then \( wA1A1 = 0.4 \) and \( t = 0.15 \), making \( wA2A2 = 0.85 \)
This type of scenario has a name. What is it and how can you recognize it? What is the consequence of this type of evolution for genetic variation within populations?

Overdominance (aka, heterozygote advantage). I recognize it when \( w_{A1A2} > w_{A1A1} \) and \( w_{A2A2} \). That is, the heterozygote \( A1A2 \) has higher fitness than either homozygote. Overdominance maintains polymorphism in populations.

10. Reset to the default parameters and create a case of underdominance. What fitness values did you use and how do you know it is a case of underdominance?

\[
\begin{align*}
w_{A1A1} &= 1.0 \\
w_{A1A2} &= 0.8 \\
w_{A2A2} &= 1.0
\end{align*}
\]

\( w_{A1A2} < w_{A1A1} \) and \( w_{A2A2} \). \( A1A2 \) has lower fitness than either homozygote.

Keep your relative fitness values, but change the following parameters: population size = 1000 and generations = 100. Run this case of underdominance several times. What happens?

If the fitness values of the two homozygotes are equal (or nearly so), then some populations will fix allele \( A \), whereas other populations lose allele \( A1 \) (i.e., fix allele \( A2 \)).

If the fitness values of the two homozygotes are different, the populations will likely fix on the allele whose homozygote has the highest fitness.

Maintain your case of underdominance, but make the fitness values for the two homozygotes equal to one another (if they are already, don't change anything). Run this simulation (balanced underdominance) several (e.g., 5 to 10) times. What happens?

Some populations will fix allele \( A1 \), whereas other populations will lose allele \( A1 \) (i.e., fix allele \( A2 \)). Note the red lines in the simulation below.

Next, change the initial frequency of allele \( A1 \) and re-run the simulation several times. What happens? Vary the initial frequency of allele \( A1 \) until you notice a pattern. Summarize that pattern below.

If the initial frequency of allele \( A \) is > 0.5 then allele \( A \) is usually fixed (blue lines, below). If the initial frequency of allele \( A \) is < 0.5 then the allele is typically lost (green lines).
11. Reset to the default parameters, but select the Multiple button. Next, set-up another case of balanced underdominance (i.e., both homozygotes have the same relative fitness values), but with no migration and no mutation. Enter your fitness values below. Start with a population size of 1000 and an initial allele frequency of $A_1 = 0.5$. Run this simulation several times for 500 generations. What happens?

\[
\begin{align*}
    w_{A_1A_1} &= 1.0 \\
    w_{A_1A_2} &= 0.8 \\
    w_{A_2A_2} &= 1.0
\end{align*}
\]

Some populations fix allele A1, whereas others fix allele A2. See the red lines below.

Now add migration among your populations. Try a migrant rate of 1 in a hundred. What happened? What is the significance of migrants to genetic variation in these simulated populations?

The populations maintain either very high or very low frequencies of allele A1. However, the populations maintain both alleles. Migration essentially “saves” the allele from extinction and maintains polymorphism. Note the blue lines in the graph below. These are close to 1 and 0, but the populations do not fix or lose allele A1 completely.

Re-set the migration rate to zero, but add mutation (e.g., 0.001) in one or both directions (e.g. allele $A_1$ to allele $A_2$ and vice versa)? Is the result similar or different to the pattern of migration modeled above. Which type of mutation did you model and what was the result?

The pattern is similar in that the alleles are not fixed or lost with mutation, but the magnitude of the final allele frequencies are closer to 1 (or 0) since the mutation rates are lower than the migration rate in the first part of the question.
Mutation added in both directions: Populations diverge, but do not fix or lose allele A1. Mutation to the alternate allele keeps the populations from either fixing or losing allele A1.

Mutation added in one direction (e.g. from A1 to A2): Populations diverge. Some populations maintain allele A2 at low frequencies, but do not fix allele A1 due to recurrent mutation from A1 to A2. Other populations lose allele A1 and fix allele A2.

12. Reset the default values, but enter a population size of 2000, and set the number of generations to 1000. Use fitness values that make allele A1 deleterious in the recessive state and enter these in the table below.

<table>
<thead>
<tr>
<th>Allele Combination</th>
<th>Fitness Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1A1</td>
<td>0.9</td>
</tr>
<tr>
<td>A1A2</td>
<td>1.0</td>
</tr>
<tr>
<td>A2A2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Given the values above, will allele A1 be fixed, lost, or maintained at some equilibrium frequency? Run the above simulation for 1000 generations - were you correct?

Allele A1 will be lost. Note the red lines in the graph below.

Now, try a case of mutation-selection balance. Refer to the section on mutation-selection balance in your textbook (p. 215), and determine how much mutation (& in which direction) is necessary to maintain allele A1 at a frequency of 0.125?

\[ \hat{q} = \sqrt{\frac{\mu}{s}} \]  
\[ \hat{q} = \text{equilibrium frequency of allele A} \]  
\[ \mu = \text{mutation rate} \]  
\[ s = \text{strength of selection against allele A} \]

0.125 = \sqrt{\frac{\mu}{0.9(1-0.9)}}

\[
(0.125)^2 = \left( \frac{\mu}{0.1} \right) \]  
Given the fitness values above, \( \mu \) (from A2 to A1) must be 0.0015625 to maintain allele A1 in the population. Note the blue lines in the graph below.

0.015625 = \frac{\mu}{0.1}
0.0015625 = \mu

Consider faster mutation rates (Chernobyl, Three Mile Island). For the case modeled above, calculate the frequency of allele A1 assuming a mutation rate (from allele A2 to allele A1) of 0.01? Run the simulation with the altered mutation rate – were you correct?

\[ \hat{q} = \sqrt{\frac{0.01}{(1-0.9)}} \]
\[ \hat{q} = \sqrt{\frac{0.01}{0.1}} \]  
Yes, allele A1 has a higher equilibrium frequency (green lines).
\[ \hat{q} = 0.3162 \]
Now change the mutation rates such that the rate from allele $A_1$ to allele $A_2$ is 0.001 and the rate from allele $A_2$ to allele $A_1$ is 0. Wait! Before you press “Run” – what will happen and why? What two forces are at work here?

Allele $A_1$ will be lost. This is because mutation of the deleterious allele $A_1$ into the beneficial allele $A_2$ will only hasten the loss of allele $A_1$ in the population. Both selection and mutation work to eliminate allele $A_1$.

13. Reset the parameters to the default settings, but change the number of generations to 10,000 and a low mutation rate (0.0001) from allele $A_2$ to allele $A_1$. Now make allele $A_1$ slightly deleterious in the recessive state by changing the fitness of the $A_1A_1$ genotype to 0.9. Notice that allele $A_1$, although it is harmful, is not eliminated from this population but instead is maintained at a very low frequency. (Note: You can confirm this by running this simulation over 100,000 generations).

There are two possible hypotheses for why allele $A_1$ is not lost completely. The first hypothesis is that mutation from $A_2$ to $A_1$ recreates allele $A_1$ faster than $A_1$ is being eliminated by selection. How can you test this idea? Hint: Change only 1 parameter from the conditions above, then re-run the simulation to determine if allele $A_1$ is still maintained. Answer the following questions.

What parameter did you change and what value was used? I changed the mutation rate from allele $A_2$ to $A_1$. This was set to 0.

Can mutation explain the maintenance of allele $A_1$ in this population? No, even in the absence of mutation to allele $A_1$, allele $A_1$ is maintained.

Alternatively, allele $A_1$ may be maintained because the deleterious allele “hides” in the heterozygous condition. Because heterozygotes (in this simulation) do not suffer a fitness cost, allele $A_1$ is very difficult to purge from the population. How will you test this hypothesis?
What parameter did you change and what value was used? I changed the fitness of the heterozygote to be slightly deleterious. This was set to 0.95.

Evaluate the second hypothesis for the maintenance of allele $A_1$? When selection is able to act on the heterozygote, allele $A_1$ is lost from the population (in the absence of recurrent mutation to $A_1$); thus, hypothesis 2 is supported.