7.03 Problem Set 2

Due before 5 PM on Friday, September 29

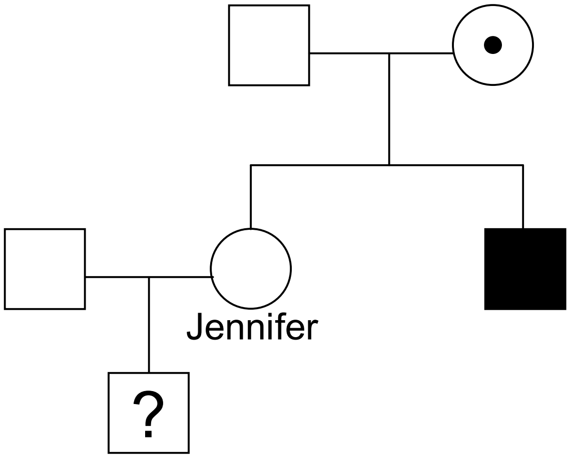
Hand in answers in recitation section or in the box outside of 68-120

1. Hemophilia A is a X-linked recessive disorder characterized by dysfunctional blood clotting, due to a mutation in the gene for the clotting component, Factor VIII.

Jennifer's brother has hemophilia A, but neither Jennifer nor anyone else in her family show symptoms of the disorder.

a) If Jennifer has a son, what is the probability that he will have hemophilia?

Based on the above information we can draw the following pedigree:



Since we know that Jennifer's brother has hemophilia, we are certain that Jennifer's mother must be a carrier. For Jennifer to have an affected son she would have to first be a carrier and subsequently pass the mutant X chromosome on to her son.

Probability Jennifer is a carrier = 1/2
Probability Jennifer would pass her mutant X chromosome to her son = 1/2
If Jennifer had a son, the probability that he would have hemophilia is therefore (1/2)(1/2) = 1/4.

b) Would this probability be different if Jennifer's husband had hemophilia? Explain.

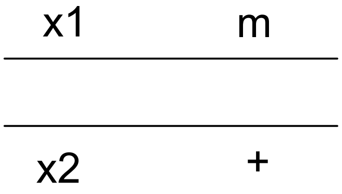
The probability would NOT be different if Jennifer's husband had hemophilia. Since hemophilia is inherited as an X-linked recessive trait, the son will not inherit an X chromosome from his father. Only the mother's genotype is relevant.

Imagine that there is a DNA-based marker on the X chromosome that is 5 cM away from the gene for Factor VIII. This marker has two alleles, designated x1 and x2, that can be distinguished by a simple analysis of the DNA in a blood sample. The genotype of Jennifer for this marker is x1/x2, the genotype of her mother is x1/x2, the genotype of her father is x2, and the genotype of her brother is unknown.

c) Draw pictures to illustrate all possible arrangements of the given alleles for both of Jennifer's X chromosomes. Be sure to account for both of the DNA marker alleles and both alleles of the gene associated with hemophilia A.

a)

b)



d) What is the probability of each of the above arrangements occurring?

Each arrangement is equally likely. a) 50% b) 50%

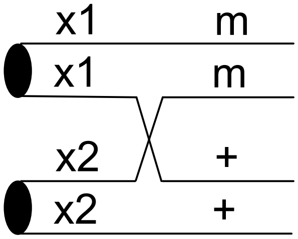
e) Given that Jennifer is a carrier, which of the above arrangements must be correct?

Arrangement b) must be correct.

f) Given that Jennifer is a carrier, what is the probability that she will have a son that carries the x2 allele and has hemophilia?

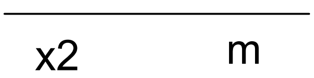
For Jennifer to have a son that carries the x2 allele and has hemophilia, two conditions must be met.
Condition 1. Jennifer must pass on an X chromosome carrying the x2 allele of the DNA marker and the mutant allele of the gene coding for Factor VIII.
Condition 2. Jennifer's husband must pass on a Y chromosome.

To satisfy Condition 1, there must be a recombination event between the DNA marker and the gene coding for Factor VIII during Meiosis 1 in Jennifer.

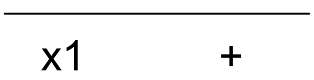


Since we know the DNA marker and the gene coding for Factor VIII are 5 cM apart, we know Jennifer has a 5% chance of passing on a recombinant chromosome. Therefore, there is a 2.5% chance she will pass on chromosome A and a 2.5% chance she will pass on chromosome B.

A



B



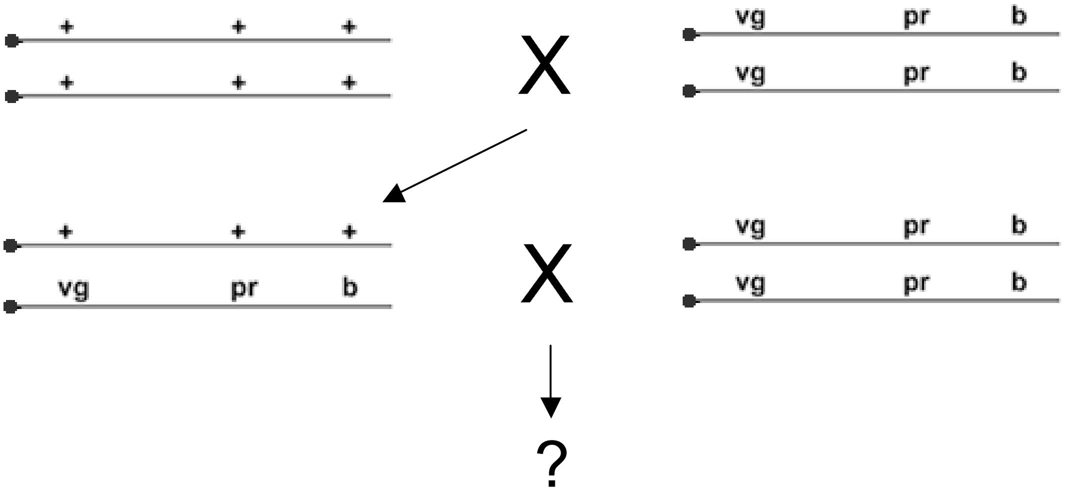
There is a 50% chance that Jennifer's husband will pass on a Y chromosome.

Therefore, there is a (.50)(.025)= .0125 or 1.25% chance that Jennifer will have a son that carries the x2 allele and has hemophilia.

2. The traits controlled by three autosomal *Drosophila* genes are easily distinguishable, since one locus determines body color, one eye color, and the other wing size. Mutants homozygous for recessive alleles of these genes exhibit black body (b/b), purple eyes (pr/pr), and vestigial wings (vg/vg). [Wild-type flies have brown bodies, red eyes, and large wings.]

The gene order is Vg—Pr—B and the distance between Vg and Pr is 13 cM and the distance between Pr and B is 7 cM. You cross a fly from a true-breeding line with brown body, red eyes, and large wings to a fly from a true-breeding line with black body, purple eyes, and vestigial wings. The F1 progeny (which have brown bodies, red eyes, and large wings) are then crossed to flies with black body, purple eyes, and vestigial wings. List all of the phenotypic classes that you would expect from this cross and calculate the number of each class expected out of a total of 1000 progeny.

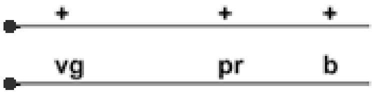
Cross Scheme



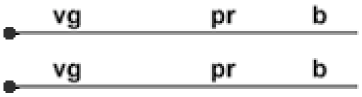
To determine the phenotypic classes that would result from this cross, we must consider the possible products of meiosis in the female.

If no recombination occurs, we would generate the following two classes:

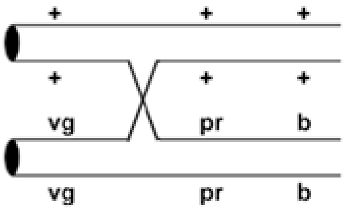
Class A would be phenotypically Wild-type



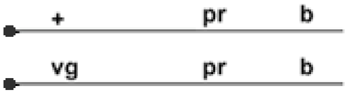
Class B would have a black body, purple eyes and vestigial wings.



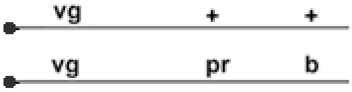
If a single recombination event occurs between vg and pr, we would generate the following two classes:



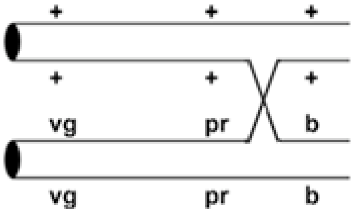
Class C would have a black body and purple eyes



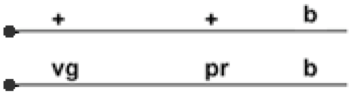
Class D would have vestigial wings



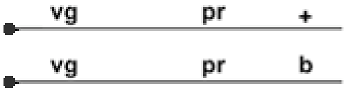
If a single recombination event occurs between pr and b, we would generate the following two classes:



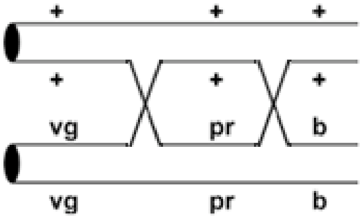
Class E would have a black body



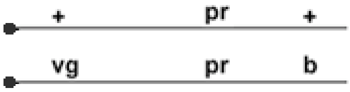
Class F would have purple eyes and vestigial wings



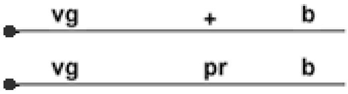
If we had a recombination event between vg and pr AND between pr and b, we would generate the following two classes:



Class G would have purple eyes



Class H would have a black body and vestigial wings



Since we know that vg and pr are 13 cM apart, we would predict that out of 1000 progeny, 130 flies would have resulted from a crossover between vg and pr.

Looking at the classes above, we know that Classes C, D, G and H all result from a recombination event between vg and pr.
Therefore, Class C + Class D + Class G + Class H = 130

Since we know that pr and b are 7 cM apart, we would predict that out of 1000 progeny, 70 flies would have resulted from a crossover between pr and b.

Looking at the classes above, we know that Classes E, F, G and H all result from a recombination event between pr and b.
Therefore, Class E + Class F + Class G + Class H = 70

The only classes for which you could not directly predict the expected number of progeny are Class G and Class H. Class G and Class H are the progeny resulting from double crossover events.

The probability of having a double crossover event is the product of the probability of either single crossover event. Therefore, the probability of having a double crossover is

$$P(DC) = (.13)(.07) = .009$$

So out of 1000 progeny, 9 would be either Class G or Class H. Since Class G and Class H will occur with equal frequency, we will say that we would expect to see

4.5 Class G flies out of 1000 and 4.5 Class H flies out of 1000

We can now go back to our previous equations and solve for the predicted number of progeny in each of the remaining classes.

We know that Class C progeny will occur with equal frequency as Class D progeny. Therefore, Class C = Class D. Our equation now becomes

$$2 \times (\text{Class C}) + 9 = 130 \qquad \text{Note: "9" is the sum of Classes G and H}$$
$$2C = 121$$
$$C = 60.5$$

60.5 Class C flies out of 1000 and 60.5 Class D flies out of 1000

We know that Class E progeny will occur with equal frequency as Class F progeny. Therefore, Class E = Class F. Our equation now becomes

$$2 \times (\text{Class E}) + 9 = 70 \qquad \text{Note: "9" is the sum of Classes G and H}$$
$$2E = 61$$
$$E = 30.5$$

30.5 Class E flies out of 1000 and 30.5 Class F flies out of 1000

To determine the number of expected progeny in Class A and Class B, we simply subtract the total of the previous classes from 1000.
Class A + Class B = 1000 - (Class C + Class D + Class E + Class F + Class G + Class H)
Class A + Class B = 1000 - 191 = 809

Since we know that Class A and Class B progeny will occur with equal frequency, we know that the number of Class A progeny and the number of Class B progeny will be equal to 809/2 or 404.5.

404.5 Class A flies out of 1000 and 404.5 Class B flies out of 1000

Therefore, out of 1000 progeny you would expect to see:

404.5 Class A	**Wildtype**
404.5 Class B	**black body, purple eyes, and vestigial wings**
60.5 Class C	**black body, purple eyes**
60.5 Class D	**vestigial wings**
30.5 Class E	**black body**
30.5 Class F	**purple eyes and vestigial wings**
4.5 Glass G	**purple eyes**
4.5 Class H	**black body and vestigial wings**

3. Consider two unlinked yeast genes, His3 and His4. Each of these genes codes for an enzyme in the histidine biosynthesis pathway and therefore His3^{-} and His4^{-} mutants require histidine for growth (i.e. the mutants are phenotypically His^{-}).

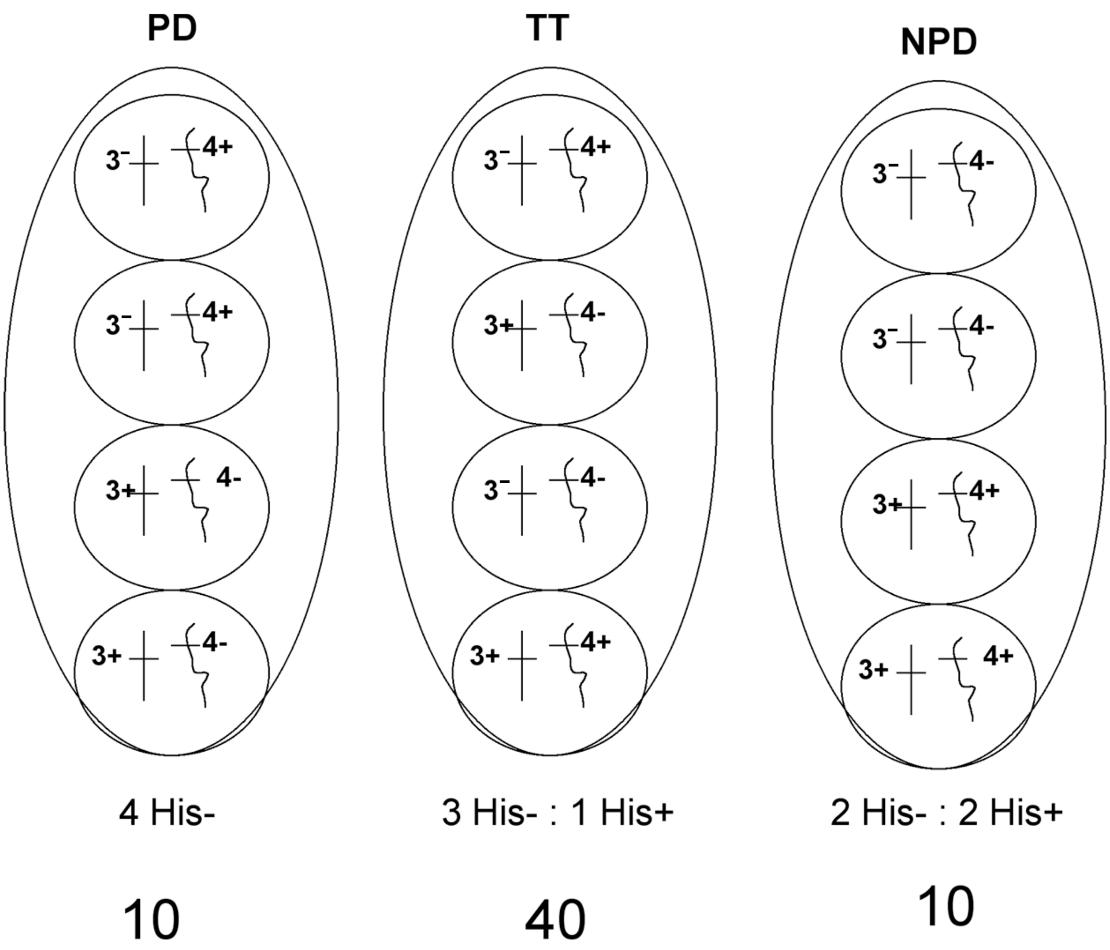
a) You mate a MAT**a** His3^{-} strain to a MATα His4^{-} strain to produce heterozygous diploids. If the resulting diploids are His^{+} what does this tell you about the His3^{-} and His4^{-} mutations?

The His3- and His4- mutations are both recessive.
In the heterozygous diploid, you have His3+/His3- and His4+/His4-. The overall His+ phenotype shows the His3+ and His4+ alleles are dominant to their respective mutant alleles.

b) Next you sporulate the diploids to produce 60 tetrads. Describe the types of tetrads you should get (in terms of the ratio His^{+}: His^{-}) and the expected number among the 60 tetrads.

For two unlinked genes, the ratio expected for all of the different tetrad types is as follows:
1 PD: 4 TT: 1 NPD.

Please refer to the diagram below for exact genotypes of all of the spores within the asci and the resulting His phenotype.



c) Would you expect the result from part (b) to be different if both the His3^{-} and His4^{-} mutants were dominant? Explain.

No, there would be no difference. The results we obtain from a tetrad analysis are directly from the spores, which are haploid. With only one copy of each gene in the spores, dominant AND recessive alleles can be unmasked and therefore observed in the experiment.

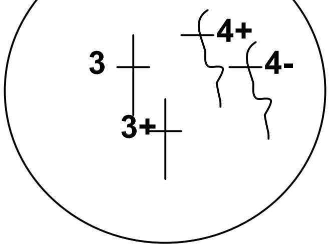
d) Now you cross a wild type MAT**a** strain to a MATα His3^{-} His4^{-} double mutant. Out of 60 tetrads from this cross, how many of each tetrad type would you expect to get?

As in b.), there will still be the following numbers, *with relation to His phenotype*:
10 All His- 40 3His-:1His+ 10 2His-:2His+

The only difference is that the PDs are now 2 His-: 2 His+ and the NPDs are the 4 His-. This is due to the change in the genotypes of the parents from that in part b.)

In both b.) and d.), the heterozygous diploids resulting from mating the parents will look the same:

Diploid Cell



Therefore once meiosis is initiated the outcome (in terms of His phenotypes of spores) will be the same.

e) The His4 gene is relatively large. Say that you have a His4-1^{-} mutation that is at one end of the gene and a His4-2^{-} mutation at the other end of the gene. If the His4-1^{-} and His4-2^{-} mutations are exactly 1 cM apart, how many of each tetrad type would you expect from a cross of a MAT**a** His4-1^{-} strain with a MATα His4-2^{-} strain (you analyze a total of 50 tetrads)?

We are dealing with two mutations in the same gene, which means they must be linked. For linked loci, the equation we use is:

cM = 100 x [(TT + 6NPD)/2 Σ]

We know the mutations are 1 cM apart, and we look at 50 tetrads, so

1 = 100 x [(TT + 6 NPD)/100],

1 = TT + 6NPD

Recall that NPDs are designators of a particular double cross-over that can occur in meiosis, so in order to score a tetrad as an NPD, there must have been that specific cross-over within the 50 tetrads we analyze.
The probability of getting a double-cross over event between loci 1cM apart is

probability of 1 cross-over (.01) x probability of another cross-over (.01) = 1/10000.

Another way to say this is that, on average, 1 out of every 10000 tetrads results from a double cross-over. Since only 1 in 4 double cross-overs result in tetrad we can recognize (NPD), we would only see a quarter of the total double-crossovers, which means that on average, we would have to score 40,000 tetrads to observe an NPD. Since it is HIGHLY UNLIKELY that within the first 50 tetrads we come across an NPD, the number of NPDs is zero.

Returning to our equation:

1 = TT + 6NPD

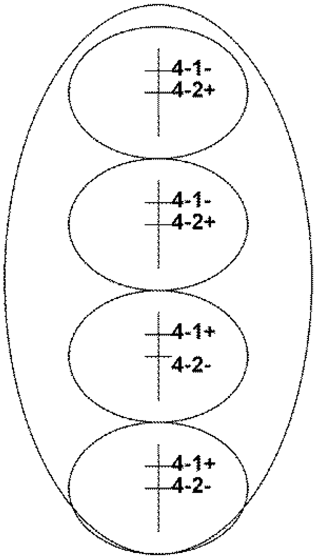
1 = TT + 6 x 0

1 = TT

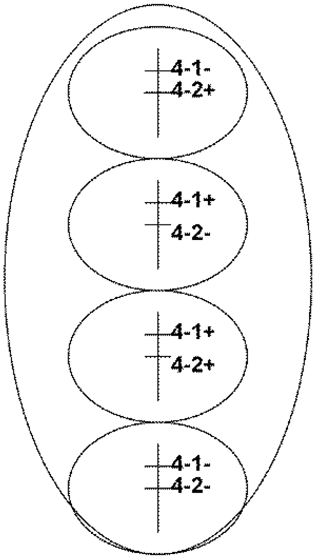
The remaining tetrads must be PDs, so there are 49 PDs.

49 PDs (4His-); 1 TT (3 His-: 1 His+)

PD



TT



f) How many of each tetrad type would you expect from a cross of a MAT**a** His4-1^{-} strain with a MATα His4-1^{-} His4-2^{-} double mutant (you analyze a total of 50 tetrads)?

You will get all PDs, which are tetrads with all His- spores. See diagram below...

PD