Biol 213 Genetics (Fall 2000)
Mendelian Genetics (Part 2)

Mendel introduced the concepts of particle-like units of inheritance. With that came the prospect of COUNTING the finite number of events possible from genotypes. It is a small step from counting to probability, and we're going to take that step. Don't get shaky at the thought. There is no higher math involved, just simple arithmetic. The trick is to keep a firm grasp on what you're counting and not to succumb to the temptation to plug in the numbers without thinking.

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I. SIMPLE MENDELIAN CROSSES (PART II)

I.A. The Dihybrid cross (pp.25-30)

We left Mendel having just come up with the remarkable insight that genetic information is stored as paired particles that segregate without bias. We know now that these particles are pairs of alleles, one on each chromosome of a homologous pair. One revolutionary concept is probably enough for a lifetime, but Mendel had two. The second arose from his consideration of two traits simultaneously.

Experiment 2B (p.26) diagrams a cross between two pure-breeding parents, one with round, yellow seeds and the other with wrinkled, green seeds. All the F1 progeny had round, yellow seeds.

SQ1. From this result, what can you infer about the dominance relationships between the two pairs of phenotypes?

SQ2. Represent the genotypes of the two F_1 parents using pictures of chromosomes (see Fig. 2 of Monday's notes for an example).

From Mendel's first law of segregation, and, more importantly, from our own knowledge of meiosis, we know that progeny receive from each parent one of two alleles, present on a chromosome of the homologous pair. The F1 progeny can be described as dihybrids: they are hybrid (not pure-breeding) at two loci, that determine seed color and that determine seed shape. What are the possibilities for progeny of an F1 x F1 dihybrid cross?

SQ3. From the chromosomal picture you drew in SQ2, predict the products of meiosis, i.e., the gametes that an F1 parent might contribute to its progeny. Presume Hypothesis b (independent assortment) to be true.

SQ4. Repeat SQ3, presuming Hypothesis a (linked assortment) to be true.

From meiosis, we can predict not only the types of gametes that are possible but also their relative frequencies.

Fig. 1 depicts on different chromosomes a gene responsible for seed shape and another responsible for seed color. During meiosis I, each homologous pair lines up, independently of other homologous pairs, and the chromosomes of each pair are parceled out to the daughter cells. The number of possible gametes can be readily calculated: two possibilities (red vs orange) x two possibilities (yellow vs green) = four possible combinations.

SQ5. What is the fraction of gametes that will receive the *R* allele? What is the fraction of gametes that will receive the *r* allele? What is the fraction of gametes that will receive the *Y* allele?

SQ6. What is the fraction of gametes that will receive <u>both</u> the *R* allele <u>and</u> the *Y* allele? What is the fraction of gametes that will receive <u>both</u> the *R* allele <u>and</u> the *r* allele?

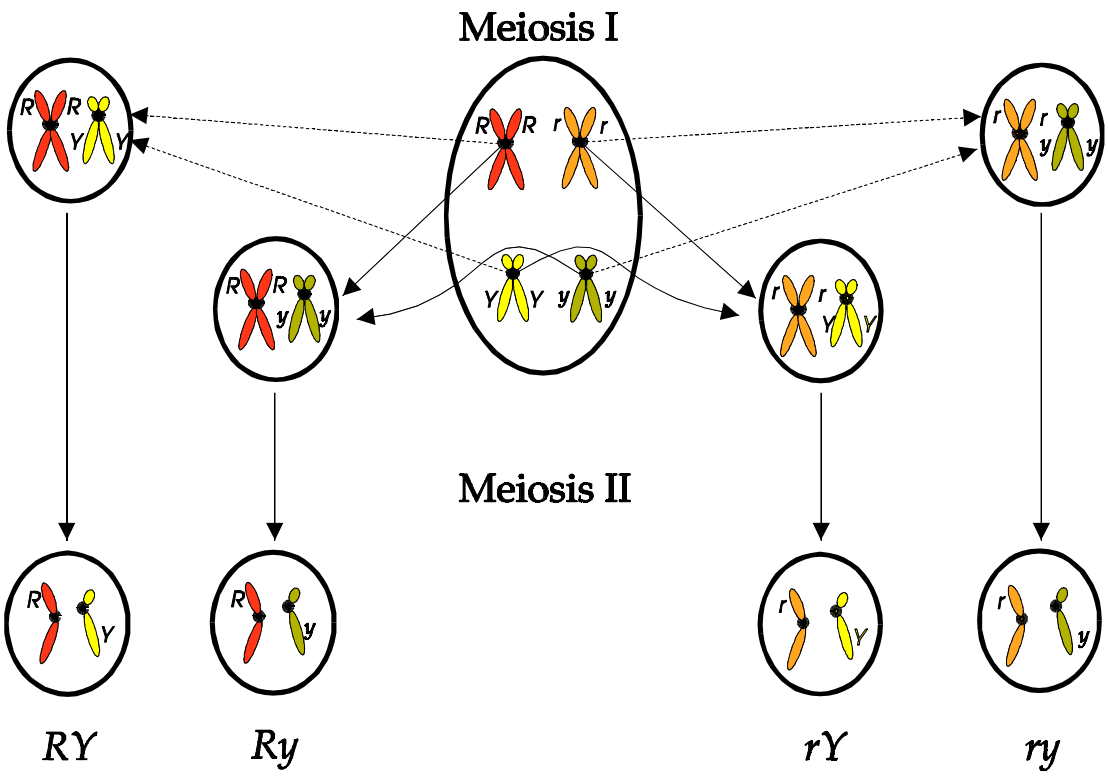

Fig. 1: Gametes resulting from meiosis in a dihybrid. A plant heterozygous for seed shape (**R**, round; **r**, wrinkled) and seed color (**Y**, yellow; **y**, green) produces four types of haploid gametes through meiosis. Independent assortment occurs since the two genes lie on different chromosomes.

The gametes and their frequencies have been placed in what is called a Punnett square (bottom of p.27 and top of p.30), named after R.C. Punnett, a geneticist who worked in the early 1900's. The square shows the genotypes of sixteen possible progeny arising from four possible paternal gametes and four possible maternal gametes.

SQ7. From the Punnett square on p.27, how many different genotypes are possible in the total F_2 progeny of the F_1 (*RrYy*) x F_1 (*RrYy*) cross? What fraction of the total progeny carry the *RrYy* genotype?

You should realize that it isn't the genotypes of each of the sixteen boxes that have equal probability, it is the events represented by the boxes. The likelihood of a paternal *rY* gamete pairing with a maternal *RY* gamete (represented by the box in the upper right corner) is the same as the likelihood of a paternal *RY* gamete pairing with a maternal *rY* gamete (represented by the box in the lower left corner). If the likelihood of occurrence of any box is the same as that of any other box, then we can determine ratios of genotypes (and predict ratios of phenotypes) by merely counting boxes.

SQ8. How many boxes show genotypes predicted to produce seeds that are round and yellow? round and green? wrinkled and yellow? wrinkled and green?

Mendel observed phenotypes in the F_2 generation of several dihybrid crosses to be 9:3:3:1 and from these observations conceived of the assumptions that underlie the Punnett square. Every dihybrid cross can be viewed as hiding two monohybrid crosses within it, and the monohybrid crosses would be expected to behave as we have already seen: segregating alleles in a 1:1 ratio and producing a 3:1 ratio of phenotypes in the F_2 progeny.

SQ9. Suppose you are colorblind. Ignoring seed color, use the table on p.27 to predict the ratio of round seeds to wrinkled seeds. Suppose you are wrinkle-blind. Predict the ratio of yellow seeds to green seeds.

SQ10. Suppose you are a connoisseur of choice green peas. Ignoring the yellow seeds, predict the ratio of round seeds to wrinkled seeds.

Any way you slice one phenotype, the monohybrid ratios hold for the other phenotype. Let's see this in a quantitative example (Table 1).

Table 1: Phenotypes of F2 Generation in Dihybrid Cross[a]

	Yellow	**Green**	**Total**
Round	Round,Yellow 315	Round,green 108	Round 423
Wrinkled	wrinkled,Yellow 101	wrinkled,green 32	wrinkled 133
Total	Yellow 416	green 140	ALL 556

[a] Data taken from Mendel (1866)

SQ11. Repeat SQ8 and SQ9, using the quantitative data above. No need for higher mathematics, just estimate!

The independence of one phenotype of the other implied in the constancy of the 3:1 ratio works only if the segregation of the chromosomes that carry one trait is independent of the segregation of the chromosomes that carry the other trait. Mendel described the independence of traits in his second law:

> Law of Independent Assortment: The segregation of alleles of one trait is independent of the segregation of alleles of another trait.

SQ12. Reword the Law of Independent Assortment in the language of chromosomes and chromosomal processes.

I.B. Summary of Mendel's conclusions through modern eyes

Mendel wrote a small book summarizing the results of his experiment. We're going to have to make do with a small table, Table 2 below. In this table, Mendel's necessarily abstract conclusions are made concrete given our knowledge of genes and chromosomes.

Table 2: Mendel's Interpretations Reinterpretted

Mendel's Interpretation	Our Interpretation
Traits do not blend but are determined by unchangeable units	Traits are determined by protein, which are determined by genes. Neither genes nor protein generally blend their characteristics.
Each trait is determined by two units	**SQ13a. (Fill in this box)**
The two units may or may not be identical	**SQ13b. (Fill in this box)**
One character form is recessive to or dominant over another	**SQ13c. (Fill in this box)**
The two character forms carried by a heterozygote are passed to progeny with equal likelihood	**SQ13d. (Fill in this box)**
Different traits assort independently	**SQ13e. (Fill in this box)**

II. Mendelian Genetics and Pedigrees *(pp.31-32)*

Let's look at an example somewhat closer to home than wrinkled peas. Suppose you are considering the case of two siblings with Cockayne syndrome (CS). CS is a rare inherited disorder caused by the absence of an enzyme used to repair damage to DNA. People afflicted with the disease carry a high risk of cancer.

As the family physician, you are concerned that relatives of the family might wish to be informed of their possible risk of having children with CS. With this in mind, you develop a pedigree of the family shown in Fig. 2 below. Refer to Fig. 2-7 for an explanation of the symbols used in this and other pedigrees. What can you deduce knowing only the phenotypes of the individuals of this family? Note that in analysis of pedigrees, you often make use of the information that a condition is rare.

SQ14. Evaluate how likely are the following propositions, based on what you know about Cockayne syndrome and what you see in the pedigree.

SQ14a. CS arose by random mutation in the fertilized eggs of the two affected individuals.

SQ14b. CS arose by random mutation in one of the parents of the two affected individuals.

SQ14c. CS arose by random mutation in one of the common great-grandparents of the two affected individuals.

SQ14d. The CS seen in the two affected individuals is not genetically determined but rather is the result of some environmental insult.

Let's suppose that the condition of the individuals is genetically determined. Is the trait dominant or recessive with respect to wild-type pigmentation? Don't go scurrying around looking for some authoritative statement about CS -- just look at the pedigree.

SQ15. Presume that Cockayne syndrome is a dominant trait. Write down the genotypes of the individuals in generation IV. Write down the genotypes of their parents. What contradiction do you encounter?

SQ16. Presume that Cockayne syndrome is a recessive trait. Write down the genotypes of the individuals in generation IV. Write down the genotypes of their parents. Any contradiction? Proceed to write down the genotypes of all individuals in the family, to the extent that they can be deduced.

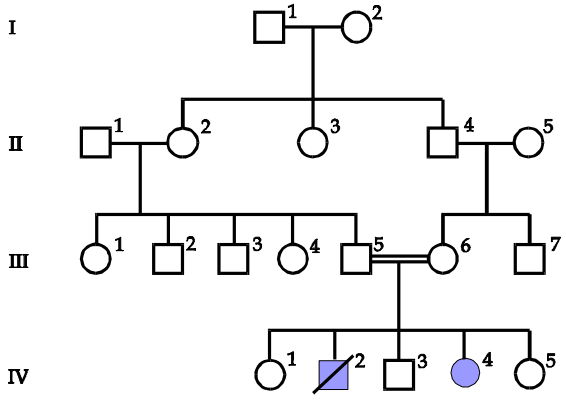

Fig. 2. Pedigree of family with history of Cockayne syndrome.

Note that the children had the possibility of gaining two copies of the allele, because

both parents were heterozygotes, inheriting the gene from a common grandparent. Obviously, the parents were cousins, and the appearance of recessive diseases is commonly associated with consanguineous unions, i.e., unions between related people.

One final note. A priori, you would expect CS to be recessive, because those affected LACK the enzyme. Heterozygotes would possess one wild-type allele and thus be able to produce the enzyme.

It is often possible to deduce a great deal about the genotypes of a family from a pedigree. The basic technique is to view the pedigree as a result of Mendelian crosses (crosses that follow the laws deduced by Mendel). For example, a progeny that you deduce to have *aa* genotype must have parents, both of whom can contribute the *a* allele. A parent with an *Aa* genotype must have at least one parent with the *a* allele.

An assumption one generally makes in such analysis is that unrelated people marrying into the family bring with them the most common alleles. They are unlikely to carry, for example, the rare *a* allele responsible for CS. Sometimes this assumption leads to a contradiction and must be abandoned, but doing so immediately makes the hypothesis grounding the analysis less likely.

III. Probability *(pp. 32-35)*

Let's return to the pedigree of the family with Cockayne syndrome (Fig. 1) and consider a very common problem in genetic counseling. Suppose that III.5 died and, according to the religious customs of the family, one of his unmarried brothers took his widowed sister-in-law as a wife. They were interested in the likelihood that their children would have CS. Or, a more common situation, suppose that long departed individual I.2 had CS, and now III.5 and III.6 had come before marriage to you, a genetic counselor, and ask you about the wisdom of having children. How would you satisfy your clients in these situations?

To answer that question, we need to develop some tools, so let's turn to a simple situation. Suppose you are considering a cross between two known carriers of the CS gene (I suppose we should shift to mice at this point). Wild-type is dominant over the CS phenotype, so the parents will both have normal DNA repair with an *Aa* genotype. We have the now familiar monohybrid cross shown in Table 3.

SQ17. What's the probability that the progeny will be normal?

Since meiosis makes each gamete type equally likely, and fertilization does not distinguish amongst gametes, it follows that each possible combination of gametes is equally likely, so the probability of one of the combinations occurring is ¼. It's readily seen that the probability of normal progeny is simply the

Table 3: Progeny of a monohybrid cross

		Male (*Aa*) makes gamete	
		A	***a***
Female (*Aa*) makes gamete	***A***	*AA*	*Aa*
	a	*aA*	*aa*

sum of the boxes that give normalcy: ¼ + ¼ + ¼ = ¾. This procedure certainly seems reasonable enough, but by what authority can we simply add probabilities?

*Rule of Addition: The probability of an event is the sum of the probabilities of its component **mutually exclusive** simple events*

Example: Probability of normal phenotype = P(*AA*) + P(*Aa*) + P(*aA*)
= ¼ + ¼ + ¼ = ¾

SQ18. What's the probability of producing an CS progeny?

We could count one box of course, but let's try another way. An *aa* genotype, required for the CS phenotype, is produced only if the female contributes the *a* allele and the male contributes the *a* allele. Each is a ½ probability. The probability of both occurring, as required to get the CS progeny, is ½ x ½ = ¼, as expected. Fair enough, but who said we could multiply probabilities?

*Rule of Multiplication: The probability of an event is the product of the probability of its component **independent** simple events*

Example: Probability of CS = P(CS)
= P(mother passes *a*) x P(father parent passes *a*)
= ½ x ½ = ¼

"Mutually exclusive" and "independent" are the critical elements here. To illustrate what they are, let's consider a simple situation. The probability of getting a female fly in a cross is ½, and the probability of getting a male fly is likewise ½. So, the probability of getting a fly that is both male and female is

P(fly that's male & female) = P(fly is male) x P(fly is female)
= ½ x ½ = ¼

...something's obviously wrong here. What? The problem is that observing that the fly is a male certainly influences the likelihood that you will observe that the same fly is female. These are not two independent events. In fact, the two cases are mutually exclusive: a fly can't be both male and female at the same time. So you can add the probabilities. The probability that the fly is either male or female is ½ + ½ = 1.

nother example. The probability that a given fly is female is ½, and the probability that a second fly is female is also ½, so the probability that at least one of the two flies happens to be female is:

P(at least one of two flies is female) = P(first fly is female) + P(second fly is female)
= ½ + ½ = 1

... something's wrong again, because it certainly isn't a sure bet that you're going to get a female fly out of a two random flies. The problem now is that the two events are not mutually exclusive: the femaleness of the first fly in no way excludes the femaleness of

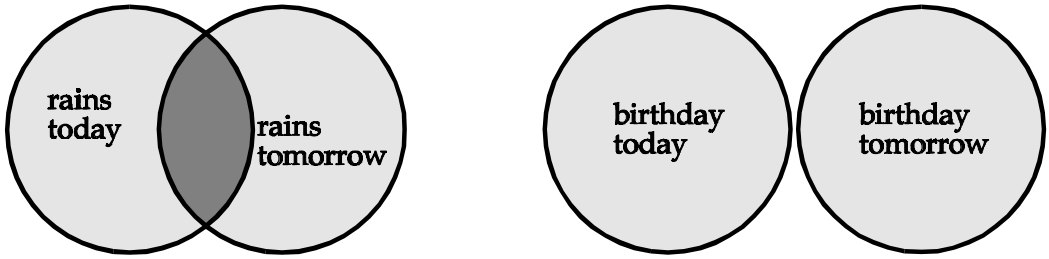

Fig. 3. Illustration of events that are or are not mutually exclusive. The plane of the paper represents the totality of possibilities. Each circle represents the division of possibilities according to the enclosed proposition. For example, the circle labeled “rains today” encloses all days in which it rans today. All days in which it does NOT rain today are outside the circle. The hatched area represents all days in which it both rains today AD rains tomorrow. The events “my birthday is today” and “my birthday is tomorrow” are mutually exclusive, while the events “it will rain today” and “it will rain tomorrow” are not.

the second fly. But the events are independent, so long as the flies are not identical twins, so we can use the multiplication rule:

P(fly #1 and fly #2 are both female) = P(fly #1 is female) x P(fly #2 is female)
= ½ x ½ = ¼

The addition rule is often associated with the word "or", the union of possibilities, and the multiplication rule is often associated with the word "and", the intersection of possibilities, and we can thus use our highly sophisticated sense of language to guide our logic. But BE CAREFUL! English is fuzzy and words have multiple meanings. Consider the propositions illustrated in Fig. 3. Clearly in the question, "How likely is it that it rains either today or tomorrow?" the word "or" means something different from the word in the sentence "How likely is it that it's your birthday either today or tomorrow?" In the first case, raining today and raining tomorrow are not mutually exclusive events -- it just might rain both days -- so you can't add the probabilities. If you do, you add the hatched region in the figure above twice. But you can't have a birthday both today and tomorrow, so in that case it is possible to add the probabilities. There is no overlap in the events: they are mutually exclusive.

SQ19. If the probability is 1 in 365¼ that a person's birthday is on any given day, what's the probability that the birthday is today OR tomorrow?

SQ20. If the probability is 1/10 that it rains on any given day, what's the probability that it rains today or rains tomorrow?

That last question is more difficult than it looks at first. It is often the case that a problem that is very difficult to solve one way can be solved by considering its opposite. Suppose I want to know the probability that a fly has either white eyes OR short wings OR a black body, supposing that these are independently assorting traits. I want the union of these traits, and the word "or" suggests that I might be able to apply the addition rule, but this is not the case, since the traits are not mutually exclusive. It's quite possible to have a fly, for example, with both white eyes and short wings (Fig. 4).

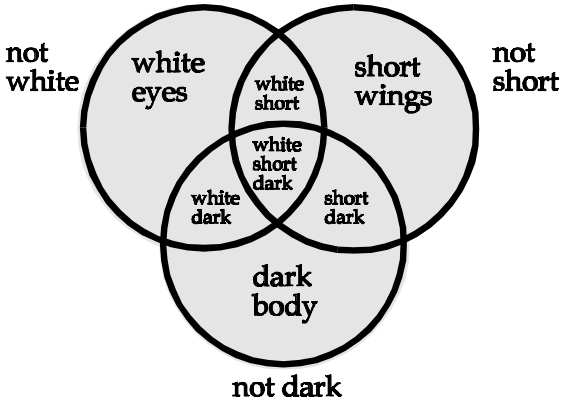

Fig. 4. Illustration of intersection of events and logical complementation. Each circle represents the division of possibilities as described in Fig. 2. The gray area represents flies that have either white eyes, short wings, dark body, or some combination. The white area represents flies with none of these traits.

So what can we do? How can we calculate the area of that complicated grey shape above? If we turn the problem around and ask what's the probability that a fly has none of these traits -- not white eyes AND not short wings AND not dark body -- then we have the intersection of three independent events. Multiplication rule! This intersection is the white area, the complementary image of the area we want. Symbolically:

P(not any of 3) = P(not white) x P(not short) x P(not dark)

and we can get what we want by subtracting this quantity from 1, the sum of all possibilities:

P(white or short or dark) = 1 - P(not any of 3)

This, by example, is the Rule of Complementation:

*Rule of Complementation: The probability of an event occurring is what remains after subtracting from one the probability of the event **not** occurring*

SQ21. Repeat SQ20 using the Rule of Complementation.