Reading: Chapter 1 and 4. Note that you should already be familiar with computing allele and genotype frequencies and testing for Hardy-Weinberg Disequilibrium.

DEFINITION

From WWWebster Dictionary:
Main Entry: **quantitative inheritance**
Function: *noun*
Date: circa 1929
: genic inheritance of a character controlled by polygenes

From Lynch and Walsh (1997):
". . . quantitative genetics, a statistical branch of genetics based upon fundamental Mendelian principles extended to polygenic (multilocus) characters . . ."

WHY STUDY QUANTITATIVE GENETICS?

- nature of quantitative trait variation
- consequences of inbreeding and outcrossing
- constraints on the evolutionary process
- estimation of breeding values
- development of predictive models for evolutionary change
- examining quantitative traits in the study of multi-factorial disease

THE MASTER PLAN

THE SET-UP

- single locus

- multiple loci

- environment

- resemblance between relatives

- polygenes

FINDING THE GENES

- detecting major genes

- usage of genetic markers

- mapping and characterizing QTLs

ADVANCED TOPICS

- correlation among traits

- multivariate linkage analysis

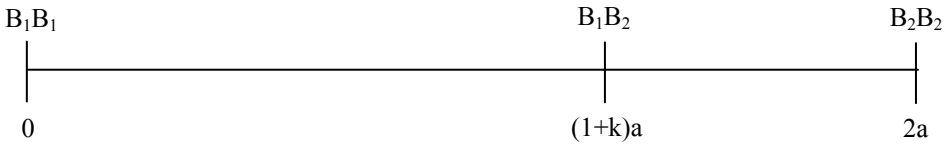
Characterizing the influence of a locus on phenotype

z=phenotype
G=genotypic value
E=environmental deviation

$$z=G+E$$

What is G? G is the expected phenotype that results from the joint expression of the genes that influence the phenotype.

$\Rightarrow$ begin by assuming that we have a single autosomal locus that influences the phenotype



(Figure 4.4 of text)

- a will be referred to as the *homozygous effect* and is a measure of additivity of alleles
- k measures departure from additivity and will be referred to as the *dominance coefficient*

Genotype B_iB_j	Genotypic Value G_{ij}
B_1B_1	0
B_1B_2	(1+k)a
B_2B_2	2a

Different kinds of behavior

k=0 $\Rightarrow$ allelic effects are completely additive
k=1 $\Rightarrow$ B_2 is completely dominant to B_1
k=-1 $\Rightarrow$ B_1 is completely dominant to B_2
k>1 $\Rightarrow$ locus exhibits overdominance
k<-1 $\Rightarrow$ locus exhibits underdominance

Problem 1.1: The pygmy gene, denoted pg, in the mouse greatly reduces body size. An experiment reported the following means for body weight in grams: $G_{++} = 14$, $G_{+\,pg} = 12$ and $G_{pg\,pg} = 6$. We will take these to be the expected phenotypes. Compute the homozygous effect and dominance coefficient. What does this tell us? (example from Falconer and Mackay 1996)

Fisher's Decomposition of the genotypic value

Gene content: number of copies of a particular allele, B_1, in a genotype denoted by N_1

Consider the relationship between phenotype and N_i. If k=0, then the alleles behave in a completely additive fashion. Thus the relationship between phenotype and N_1 is linear. It may be of interest to quantify the deviation from this linear relationship that results from the presence of dominance.

Once we have expressed the relationship between the genotypic value and N_2 in this form, we can describe the slope, α, in terms of our population parameters (homozygous effect, dominance coefficient and allele frequencies). From regression theory, we know that

$$\alpha = \frac{\sigma(G, N_2)}{\sigma^2(N_2)}$$

With the following, we can then express both $\sigma(G,N_2)$ and $\sigma^2(N_2)$ in terms of a, k, p_1 and p_2 where p_I is the population frequency for allele B_i.

Table 4.1 of text:

Genotype	Gene Content (N)	Genotypic Value (G)	Freq.	G×N	N^2	Regression Value ($\hat{G}$)	Dominance Deviation ($G-\hat{G}$)
B_1B_1							
B_1B_2							
B_2B_2							

We end up with, $\alpha = a[1+k(p_1-p_2)]$

Now that we have an expression for α, what is it? It is termed the **average effect of allelic substitution**. It is the expected change in phenotype given a substitution of allele B_2 for an allele B_1.

If the alleles behave in a completely additive fashion, then α=?

If not, the relationship depends on both the level of dominance and allele frequencies.

What about the genetic variance?

We have the following relationship: $G = \hat{G} + \delta$. We can obtain the variance from our previous work:

The additive genetic variance, σ_A^2, is the genetic variance associated with the average additive effects of alleles and can be shown to be:

$\sigma_A^2 =$

The dominance genetic variance, σ_D^2, is the genetic variance associated with dominance effects and is equal to

$\sigma_D^2 = (2p_1p_2ak)^2$

Note that BOTH of the variances are affected by the additive and dominance terms.

Other terminology:

- Average Excess – difference between the mean genotypic value of an individual carrying (at least one) copy of B_2 and the mean genotypic value of a random individual

$\Rightarrow \quad \alpha_1^* = -p_2\,\alpha$ and $\alpha_2^* = p_1\alpha$

- Additive Effects – correspond to the regression coefficients α_1 and α_2; HOWEVER, for a randomly mating population, these are equal to the average excesses

  $\Rightarrow \quad \alpha_1 = -p_2 \alpha \quad$ and $\quad \alpha_2 = p_1 \alpha$

- Breeding Values – the sum of the additive effects for an individual, i.e. for an individual with genotype G_{ij}, their breeding value is $A_{ij}=\alpha_i + \alpha_j$

  Recall, $\sigma_A^2 =$

  Also note that, $\sigma_D^2 =$

Extensions for Multiple Alleles

Consider a locus with *n* alleles. From the model for a diallelic locus, it is straightforward to construct a multi-allelic extension of the linear model for genotypic value:

$$G = \mu_G + \sum_{i=1}^{n} \alpha_i N_i + \delta$$

Here,

- the set of α_i are found through least-squares regression, i.e. the α_i that minimize $E(\delta_{ij}^2)$
- N_i is the number of copies of the i^{th} allele.

Under a random-mating population, the additive effects can be written as a function similar to before:

$$\alpha_i = \sum_{j=1}^{n} p_j G_{ij} - \mu_G$$

And the additive genetic variance can be written as

$$\sigma_A^2 = 2\sum_{i=1}^{n} p_i \alpha_i^2$$

Example 1.2: Three allelic variants of the red cell acid phosphatase enzyme were present in a sample from the population in England. The table below gives the genotypes with their frequencies in the sample and the mean enzyme activity of each genotype. What are the additive effects for alleles A, B and C? What is the additive genetic variance? Why might using the above formula be incorrect? What would be an alternate way to compute the additive variance? (taken from Falconer and Mackay 1996)

Genotype	Frequency (%)	Enzyme activity
AA	9.6	122
AB	48.3	154
BB	34.3	188
AC	2.8	184
BC	5.0	212

Important Facts to Keep in Mind

- It is generally assumed (unless otherwise noted) that the population under study is a randomly mating population (actually that it is in Hardy-Weinberg Equilibrium).
  - $\Rightarrow$ Adjustments can be made for nonrandom mating and inbreeding
  - $\Rightarrow$ It is important to be aware of this and to know that you can find an adjustment if needed.

- The genetic variance can be decomposed into an additive component and a dominance component.
  - $\Rightarrow$ This is true regardless of the type of mating or whether inbreeding is present.
  - $\Rightarrow$ This is true regardless of what type of relationship is present between the genotypic value and gene content.

- The dominance variance, at this point, is the residual variance (everything that is left after additivity).

It is important to understand what parameters we need to describe variation in the genotypic value and "what they mean."