CHAPTER I

THE GENETIC MODEL

1.1 MENDEL’S FIRST LAW

Readers who are familiar with the biological basis of heredity will not need an introduction to the technical language by which it is customarily described, whilst experience shows that others (such as mathematicians with no previous biological interest) find the definition of technical words in terms of cellular structure and function a rich source of confusion. For the latter group we recommend a quick excursion into the popular genetics literature—an encyclopaedia article will probably suffice—because our plan is to introduce only those words necessary for a description of the mathematical operation of the genetic model, and to attach to each only its operational meaning in terms of that model. Readers already familiar with the terms will then be able to relate the mathematical function to the underlying biological mechanism, whilst others (if the attempt is successful) will find a self-contained account of a purely mathematical model whose consequences are explored in the rest of the book.

We start with the concept of a \textit{locus} which may initially be thought of as a box with a capacity of two \textit{genes}. Each of the multitude of different kinds of genes has its own specific locus, and all the genes which relate to a specific locus are known as the \textit{alleles} for that locus.\footnote{There is an increasing tendency to restrict the use of the word ‘gene’ so that two genes are only said to be the same if they are identical by descent, the one being an exact copy of the other, and to refer to two genes which, though not necessarily identical by descent, are identical in effect, as being the same ‘allele’. We shall, however, continue the customary usage, which is common throughout the literature on which this book depends, and write of ‘gene frequencies’ and ‘genotypes’ rather than ‘allele frequencies’ and ‘allelotypes’.

If \(k = 1\) there is no variation, and the case is of no interest; if \(k = 2\) the locus is said to be \textit{diallelic},
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and if more, multiallelic. Each individual possesses one locus of each kind, \( A, B, C, \ldots \), and each locus is associated with a particular chromosome. However, this need not yet concern us, because for the first five chapters we shall only consider a single locus (two are considered in chapter 8) which is not associated with the \( X \)-chromosome (a chromosome involved in the determination of sex, which we consider in chapter 6) but with one of the other chromosomes, called autosomes.

The genotype of an individual at a single locus is specified by the pair of genes he carries at that locus. If the two members are the same (such as \( a_1a_1 \)) he is a homozygote, and otherwise a heterozygote, for that locus. The totality of genotypes, over all loci, is the overall genotype of the individual. At a single locus there will be \( k \) possible homozygous genotypes and \( \frac{1}{2}k(k−1) \) possible heterozygous genotypes (since order is irrelevant), making \( \frac{1}{2}k(k+1) \) in all. But in practice it may not be possible to distinguish, at the level of observation, each of these; what is observed is called the phenotype, and each phenotype may correspond to one or more genotypes. The number of different ways in which genotypes can be classified into phenotypes is a complicated problem involving the theory of partitions, and need not concern us. The simplest way in which two genotypes give the same phenotype is when \( a_1a_1 \) is indistinguishable from \( a_2a_2 \), in which case gene \( a_1 \) is said to be dominant and gene \( a_2 \) recessive, each with respect to the other. If the phenotypic expression is metrical, then two alleles are said to exhibit ‘no dominance in an additive sense’ when the heterozygote’s measure is the arithmetic mean of the corresponding homozygotes’, and ‘no dominance in a multiplicative sense’ when the measure is the geometric mean. Just as with a single locus, the individual’s overall phenotype depends on his overall genotype, and not all genotypes may be distinguishable.

Reproduction is a two-stage process. In the first stage, each parent produces a gamete (the sperm of the male, and the egg of the female). Each gamete carries a complete set of chromosomes, consisting of one copy of each autosome and a sex chromosome (whose mode of inheritance is treated in chapter 6); the precise constitution of this chromosomal set need not be considered if we are treating a single locus, because in this case the only material fact is covered by:
1.1] MENDEL’S FIRST LAW

Mendel’s First Law (Mendel, 1866)

Each of the two genes at a single locus has a probability of one half of being the single gene at that locus carried by a particular gamete (whether maternal or paternal). **

The second stage of the process is that of fertilization, at which the egg and sperm unite to form a new individual, thus restoring two genes to each locus. The new cell carries two complete sets of chromosomes, and from it, by cell-division, the individual will grow. Gametes, carrying one set, are called haploid, while individuals are called diploid. We see how our image of a locus being, in an individual, a box with space for two genes has as its physical basis a pair of chromosomes. Man has 22 pairs of autosomes and one pair of sex chromosomes.

Mendel’s Second Law, of independent segregation for two loci, will be introduced in chapter 8. The next section summarizes the salient characteristics of the ‘organism’ whose population genetics we shall investigate.

1.2 A SIMPLE ORGANISM

We base our mathematical account on a bisexual diploid organism of sufficient complexity to allow for the development of the theory, but otherwise as simple as possible. We endow it with some pairs of autosomes and a pair of sex chromosomes. \( A \) and \( B \) are autosomal loci with alleles \( a_1, a_2, \ldots, a_k \) and \( b_1, b_2 \) respectively; sometimes \( k \) will be 2, sometimes 3, and sometimes arbitrary. \( A \) and \( B \) are linked with recombination fraction \( r \), though we will sometimes allow \( r = \frac{1}{2} \) so as to include the unlinked case (when \( A \) and \( B \) might be on different chromosomes, or asyntenic (Renwick, 1969)).

The sex chromosomes will be denoted by \( X \) and \( Y \), \( XX \) being female and \( XY \) male. \( X \) carries a single locus (which we shall call \( X \) when there is no risk of confusion) with alleles \( x_1, x_2, \ldots, x_k \), where \( k \) will sometimes be 2, and sometimes arbitrary.

All genes will be assumed stable, and mutation will not be taken into account.

The life cycle of the organism is of extreme simplicity. All individuals are of the same age. Mating takes place when they reach a certain age, and the proportions of the various genotypes amongst
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the offspring are determined by the products of the proportions of the various gametes in the male and female parts of the population. This rule, known as the ‘random union of gametes’, is, under certain conditions which will be mentioned below, a result of mating taking place ‘at random’, that is, without reference to genotype. The gametes are produced in accordance with Mendel’s First Law, and hence the proportion of maternal gametes carrying a given gene is equal to the proportion of genes of that kind amongst the females, and similarly for the males. When two loci are involved, if they are asyntenic Mendel’s Second Law applies and the proportions of the various gametes will be given by the products of the gene proportions for the individual loci, but if they are syntenic and linked the segregations are no longer independent and the proportions will depend upon the recombination fraction in a way to be described. After reproduction all the adult individuals die, and the population consists solely of the offspring. Such a life-cycle is said to involve ‘discrete non-overlapping generations’.

The population is supposed indefinitely large, and we will only concern ourselves with proportions, whether of genes, gametes, genotypes, or phenotypes. There is a long-established practice of referring to such proportions as ‘frequencies’, which we will not attempt to reverse: thus we may refer to a ‘gene frequency’, meaning the proportion of genes of a particular kind.

A major interest will be the behaviour of gene frequencies under selection. The only aspect of selection we shall consider is where the proportion of each genotype that survives from birth to the age of mating differs from genotype to genotype, being given by a constant specific to each genotype. The survival proportion is a kind of ‘selective coefficient’, which we will refer to as a viability. Since only relative viabilities are relevant to the models we consider, we shall not adopt an upper limit of unity to the value of a viability: any non-negative number may be encountered, and the word ‘relative’ is to be understood. Thus throughout the book the models are invariant with respect to multiplication of the viabilities by a positive constant.

1.3 RANDOM MATING AND RANDOM UNION OF GAMETES

The assumption of ‘random union of gametes’ is of great convenience to the development of the theory, but we should be clear under what conditions it holds.
1.3] RANDOM MATING AND RANDOM UNION OF GAMETES

Definition. Random mating

If a population contains the genotypes $G_1, G_2, \ldots, G_i$ in proportions $m_1, m_2, \ldots, m_i$ amongst the males ($\Sigma m = 1$) and in proportions $f_1, f_2, \ldots, f_i$ amongst the females ($\Sigma f = 1$), and the proportion of matings of the type $G_i$ (male) $\times$ $G_j$ (female) is $m_if_j$, the condition of random mating is said to be fulfilled. **

Definition. Random union of gametes

If a population produces the gametes $a_1, a_2, \ldots, a_k$ in proportions $s_1, s_2, \ldots, s_k$ amongst the males ($\Sigma s = 1$) and in proportions $t_1, t_2, \ldots, t_k$ amongst the females ($\Sigma t = 1$), each male individual being supposed to produce the same number of gametes, and similarly each female, and if the proportion of offspring of (ordered) genotype $a_xa_y$ is $s_xt_y$, the condition of random union of gametes is said to be fulfilled. **

Theorem 1.3.1. Equivalence of random mating and random union of gametes

Provided each mating produces the same number of offspring and the condition of random mating obtains, the proportions of genotypes amongst the offspring will be those given on the assumption of the random union of gametes.

Proof. Let genotype $G_i$ produce gametes $a_1, a_2, \ldots, a_k$ in the proportions $p_{i1}, p_{i2}, \ldots, p_{ik}$. Since $G_i$ will typically be $a_xa_y$, if $x \neq y$ then $p_{ix} = p_{iy} = \frac{1}{2}$ and all other $p$s are zero, whereas if $x = y$, $p_{ix} = 1$, by Mendel’s First Law (section 1.1). Then in the mating $G_i$ (male) $\times$ $G_j$ (female) the probability of gametes $a_x$ from the male and $a_y$ from the female coming together is $p_{ix}p_{jy}$, and the probability of this mating is $m_if_j$. The total genotypic array (or distribution of genotypes) amongst the offspring is therefore

$$\sum_{i,j} \{m_if_j \sum_{x,y} p_{ix}p_{jy}a_xa_y\}, \quad (1.3.1)$$

in which the coefficient of $a_xa_y$ is the probability of the ordered genotype $a_xa_y$. (We adopt the convention that the gene derived from the father is written first.)
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But (1.3.1) may be rewritten

\[ \sum_{x, y} \left\{ \sum_{i, j} m_i p_{ix} p_{iy} a_x a_y \right\} \]
\[ = \sum_{x, y} \left\{ \sum_{i} m_i p_{ix} a_x \right\} \left\{ \sum_{j} f_j p_{iy} a_y \right\} \]
\[ = \left\{ \sum_{x} m_x p_{ix} a_x \right\} \left\{ \sum_{y} f_y p_{iy} a_y \right\}. \] (1.3.2)

Now \( \sum_i m_i p_{ix} \) is the proportion of gametes \( a_x \) amongst the males, or \( s_x \), and \( \sum_j f_j p_{iy} \) the proportion of gametes \( a_y \) amongst the females, or \( t_y \). Hence (1.3.2) may be written

\[ \sum_x s_x a_x \cdot \sum_y t_y a_y, \] (1.3.3)

and the probability of the genotype \( a_x a_y \) is thus \( s_x t_y \), as is given directly by the assumption of the random union of gametes. **

We note that the theorem holds even if male and female genotypes produce gametes of the varying kinds in different proportions, because \( p_{iy} \) may be replaced by \( p_{iy}^{'} \) throughout the proof, the prime referring to the probabilities of the maternal gametes. This would occur under gametic selection with viabilities different amongst the paternal and maternal gametes. If mating is at random and the offspring of each mating equally numerous, the genotypic array of the offspring may thus be found by multiplying together the male and female gametic arrays of the parental generation, those arrays being found on the assumption that each individual contributes equally to the total gametic output of his sex. Theorem 1.3.1 has important consequences. It enables us to follow the course of gene-frequency change over the generations by considering gamete frequencies rather than genotype frequencies, and it leads to the Hardy–Weinberg Theorem.

1.4. The Hardy–Weinberg Theorem

In this section we assume that the male and female arrays, both gametic and genotypic, are identical; henceforth genotypes will be unordered. Thus

\[ s_x = t_x = p_x \text{ (say)}, \] for all \( x. \)
1.4] THE HARDY–WEINBERG THEOREM

Theorem 1.4.1. The Hardy–Weinberg Theorem

After one generation of random mating the genotypic array will be of the form

\[ \left\{ \sum_{z} p_x a_z \right\}^2 \]  \hspace{1cm} (1.4.1)

and will remain the same in subsequent generations.

Proof. The proof follows immediately by setting \( s_x = t_x = p_x \) in (1.3.3) and then observing that a genotypic array \( \left\{ \sum_{z} p_x a_z \right\}^2 \) implies, in turn, a gametic array \( \sum_{z} p_x a_z \). **

The theorem derives its name from simultaneous and independent treatments of the diallelic case in 1908 by the Cambridge mathematician G. H. Hardy and the Stuttgart physician W. Weinberg. A population whose genotype proportions conform to (1.4.1) is said to obey the Hardy–Weinberg Law, and to exhibit genotypes in Hardy–Weinberg proportions. It is also said to be in Hardy–Weinberg equilibrium, equilibrium here referring to the fact that there is no tendency for the variation caused by the co-existence of different genotypes to disappear. This ability to maintain genetic variation is one of the most important aspects of Mendelian genetics; it was lacking in earlier ‘blending’ theories of inheritance. Even after Mendel’s laws were widely known, until the work of Hardy and Weinberg it was not generally understood that the frequency of a recessive gene would not decline in the absence of selection.

A necessary and sufficient condition for Hardy–Weinberg equilibrium is that the frequency of each heterozygote is given by twice the geometric mean of the frequencies of the two corresponding homozygotes, as is immediately evident from (1.4.1).
CHAPTER 2

TWO ALLELES AT A SINGLE LOCUS

2.1 NO SELECTION

We consider two alleles, \( a_1 \) and \( a_2 \), with initial frequencies \( p_m, q_m \) in the males, and \( p_t, q_t \) in the females. In view of theorem 1.3.1 this information is sufficient to enable us to write down the offspring genotype distribution immediately, whatever the parental genotype distributions (subject to the above gene frequencies). Henceforth, genotypes are unordered (\( a_2 a_1 = a_1 a_2 \)).

We find the offspring genotypic array to be:

\[
\begin{array}{c|c|c}
   & a_1 a_1 & a_1 a_2 \\
\hline
   a_1 a_2 & p_m p_t & p_m q_t + q_m p_t \\
   a_2 a_2 & q_m q_t & \end{array}
\]

(2.1.1)

The frequency of the gene \( a_1 \) amongst the offspring is

\[
p_m p_t + \frac{1}{2}(p_m q_t + q_m p_t)
= \frac{1}{2}(p_m + p_t),
\]

in accordance with the fact that the males and the females each contribute half of the genes of the offspring generation.

Writing \( p = \frac{1}{2}(p_m + p_t), \quad q = \frac{1}{2}(q_m + q_t), \)

and assuming no association between the sex of an offspring and its genotype, the Hardy–Weinberg Theorem ensures that (as is entirely obvious with only two alleles) in the next generation, and thereafter; the genotype distribution is

\[
\begin{array}{c|c|c}
   & a_1 a_1 & a_1 a_2 \\
\hline
   a_1 a_2 & p^2 & 2pq \\
   a_2 a_2 & q^2 & \end{array}
\]

(2.1.2)

The original genotypic proportions (2.1.1) will only be Hardy–
2.1] NO SELECTION

Weinberg proportions if

\[ (p_m q_t + q_m p_t)^2 = 4p_m q_t q_m q_t. \]  

(2.1.3)

But the theorem on the inequality of arithmetic and geometric means tells us that

\[ \left( \frac{p_m q_t + q_m p_t}{2} \right)^2 \geq p_m q_t q_m p_t, \]  

(2.1.4)

with equality if and only if \( p_m q_t = q_m p_t \), which is \( p_m = p_t \). Thus the effect of any difference between the sexes in gene frequency is to increase the proportion of heterozygotes above the Hardy–Weinberg proportion for a population with gene frequency \( p = \frac{1}{2}(p_m + p_t) \).

Henceforth we assume that the genotype frequencies are the same in both sexes, unless otherwise stated.

2.2 SELECTION WITH CONSTANT VIABILITIES

Let the genotypes \( a_1 a_1, a_1 a_2 \) and \( a_2 a_2 \) have viabilities \( w_{11}, w_{12} \) and \( w_{22} \) respectively, and let the gametes that form the first generation of offspring have frequencies \( p a_1 \) and \( q a_2 \). Then the offspring genotypic frequencies, before selection, will be \( p^2 a_1 a_1, 2pq a_1 a_2 \) and \( q^2 a_2 a_2 \), and the mean viability of the offspring will be

\[ w = p^2 w_{11} + 2pq w_{12} + q^2 w_{22}, \]

which will also be the factor by which the population size is reduced through the action of selection if the viabilities are absolute and not relative. The adult genotypic frequencies will therefore be

\[ \begin{pmatrix} a_1 a_1 & p^2 w_{11} / w \\ a_1 a_2 & 2pq w_{12} / w \\ a_2 a_2 & q^2 w_{22} / w \end{pmatrix} \]  

(2.2.1)

and the new gametic frequencies

\[ p' = \frac{p^2 w_{11} + pq w_{12}}{w}, \]

\[ q' = \frac{pq w_{12} + q^2 w_{22}}{w}. \]  

(2.2.2)

It is more convenient to continue in terms of the gene ratios \( u = p/q, u' = p'/q' \), for then (2.2.2) becomes

\[ u' = u \frac{uw_{11} + w_{12}}{uw_{12} + w_{22}}. \]  

(2.2.3)
TWO ALLELES AT A SINGLE LOCUS

We note that if $u$ is positive, so is $u'$, and hence so are all subsequent values. At gene-frequency equilibrium $u' = u = \hat{u}$ (say) and

$$\hat{u}w_{11} + w_{12} = \hat{u}w_{12} + w_{22}; \quad \text{or } \hat{u} = 0; \quad \text{or } \hat{u} = \infty.$$ 

Thus

$$\hat{u} = \frac{w_{12} - w_{22}}{w_{12} - w_{11}} \quad (2.2.4)$$

is an equilibrium. Since $0 \leq u \leq \infty$, there can only be equilibria in the permitted range $0 \leq \hat{p} \leq 1$ if $(w_{12} - w_{22})$ and $(w_{12} - w_{11})$ are the same sign. The internal equilibrium value $\hat{p}$ is then

$$\hat{p} = \frac{\hat{u}}{1 + \hat{u}} = \frac{w_{12} - w_{22}}{2w_{12} - w_{11} - w_{22}}. \quad (2.2.5)$$

This model was first given by R. A. Fisher in 1922, and he stated that ‘if selection favours the heterozygote, there is a condition of stable equilibrium’.

**Theorem 2.2.1. Fisher’s Theorem**

In the single-locus two-allele model the equilibrium gene ratios are

$$0, \infty, \text{ and } \hat{u} = \frac{w_{12} - w_{22}}{w_{12} - w_{11}}.$$ 

(Note that $\hat{u}$ is only a gene ratio if $(w_{12} - w_{22})$ and $(w_{12} - w_{11})$ are of the same sign; if either is zero $\hat{u}$ reduces to 0 or $\infty$; if both are zero every gene ratio is an equilibrium one.)

If $(w_{12} - w_{22})$ and $(w_{12} - w_{11})$ are both positive, $\hat{u}$ is a stable equilibrium, and the gene ratio will converge monotonically to it; if they are both negative $\hat{u}$ is an unstable equilibrium and the gene ratio will diverge monotonically from it. When $\hat{u}$ is negative, and hence not a gene ratio, there are two cases:

1. $(w_{12} - w_{22})$ negative and $(w_{12} - w_{11})$ positive, when the gene ratio converges monotonically to $u = 0$;
2. *vice versa*, when the gene ratio increases monotonically and indefinitely.

**Proof.** The equilibrium has been derived above, (2.2.4). Equation (2.2.3) may be written

$$u' = \frac{uw_{11} + w_{22} + (w_{12} - w_{22})}{uw_{11} + w_{22} + u(w_{12} - w_{11})}$$

or

$$\frac{u'}{u} = \frac{uw_{11} + w_{22} + \hat{u}(w_{12} - w_{11})}{uw_{11} + w_{22} + u(w_{12} - w_{11})}; \quad (2.2.6)$$

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