RESPONSE TO SELECTION

IN

FINITE POPULATIONS

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SUMMARY

1. A theoretical investigation was made on (a) the limits and duration of response to selection and (b) the properties of lethal mutants and their expectation of life in small populations. The problems were formulated mathematically in terms of transition matrices and in some cases in terms of diffusion approximations. In a few cases explicit formulae were obtained by expanding matrices and solving differential equations. In most of the cases, however, numerical solutions were obtained by evaluating matrix functions on the computer.

2. In the case of selection at a di- and tri- allelic locus, the transition probabilities between the segregating states of a population of gametes of constant size 2N, determine a Q-matrix. The average of the total number of times the population spends in the different segregating states on the way to fixation, corresponding to various initial states are determined by a fundamental matrix \((I - \bar{Q})^{-1}\) where \(I\) is a unit matrix. The expected change in the gene frequency of a particular allele in the limit and mean and variance of the number of generations until fixation of this allele are found to depend on the fundamental matrix. The frequency distribution of gene frequency at equilibrium between mutation and selection at a diallelic locus is also found to depend on the elements of the first row of the fundamental matrix.
3. With binomial transition probabilities and selection, the expansion of matrix formulae gave explicit expressions for the expected change in the gene frequency in the limit, and for the half-life of the selection process. For large \( N \) and small values of selective coefficient \((s)\), such that \( Ns \) is constant, the expression for the expected change in the gene frequency in the limit was found to be the same as the diffusion approximation formula of the chance of fixation expanded in powers of \( Ns \). In the case of artificial selection based on individual measurements the total advance by selection for additive genes, is \( 2NI(1 + C_1 I + C_2 I^2) \), where \( I \) is the gain in the first generation, \( C_1 = \frac{2N \mu_{\bar{g}}}{\sigma^2} \) and \( C_2 = \frac{2N^2(1 + n^2V^e/\sigma^4)}{n\sigma^2} \). Here \( \sigma^2 \) and \( \mu_{\bar{g}} \) are respectively the variance and the third moment (about the origin) of the breeding values. \( V^e \) refers to the variance between the contributions of the \( n \) different loci to the additive genetic variance of the character. The half-life of the selection process was found to be a function of \( Ns \) only. When \( Ns = 1 \) and initial gene frequency is half, the half-life is about \( 1.30N \) but for initial gene frequency tending to 0 and 1, the half-lives are \( 1.58N \) and \( 1.03N \) respectively. It was further proved that the moments of the distribution of time until fixation of a gene are independent of terms in \( s \).

4. The diffusion approximation for the variance of time until fixation, for a selectively neutral gene and initial gene frequency tending to zero, is found to be \( 16N_e^2(\frac{3}{2} - 3) \) where \( N_e \) is the effective size of the population. With the mean time as \( 4N_e^2 \), this amounts to a coefficient of variation of about 54 per cent.
5. Numerical results on the mean and the coefficient of variation of time until fixation of a gene, at a diallelic locus, obtained by the use of transition matrices suggested that these are functions of \( N_a \) only. Selection decreases the mean and the coefficient of variation of time until fixation of a gene with additive effects. With rise in the initial gene frequency, the mean decreases but the coefficient of variation increases. Selection decreases the mean time until fixation of a recessive gene also. For a dominant gene, however, the mean time increases when \( N_a \) is small, attains a maximum and then decreases. A gene takes less time, on an average, to reach fixation when it is recessive than when it is dominant. When there is no selection and the two alleles are equally represented in the initial population, the mean time until homozygosity is found to be maximum but the coefficient of variation of time until homozygosity happens to be minimum. With selection the maximum, in the case of the mean and the minimum, in the case of the coefficient of variation, are found to occur at initial gene frequencies less than half. As \( N \) becomes large and initial gene frequency tends to zero, the mean and the coefficient of variation of time until homozygosity approaches the mean and the coefficient of variation of time until loss respectively.

6. Numerical results on chance of fixation of a particular allele \( A_1 \) at a tri-allelic locus \((A_1-A_2-A_3)\) obtained by the use of the transition matrices suggested that it is on \( N_s \) and \( N^2V_m \) only dependent, where \( \bar{s} \) is the average superiority of \( A_1 \) over \( A_2 \) and \( A_3 \) lumped together and \( V_m \) is the variance in superiority, (multiple allelic variance). The chance of fixation increases as \( N_s \) increases in almost
the same manner as in the case of two alleles at a locus. It, however, decreases as $N_2^2 V_m$ increases. The mean time until fixation of $A_1$ decreases as $N_3$ increases provided $N_2^2 V_m < 1$. At higher values of $N_2^2 V_m$ it increases with increase in $N_3$, attains a maximum and then decreases. The effect of increasing $N_2^2 V_m$ on the mean time is to decrease it provided $N_3 < 1$. At higher values of $N_3$, it increases with increase in $N_2^2 V_m$, attains a maximum and then decreases. The mean time until homozygosity is found to be maximum when there is no selection and the three alleles are equally represented in the initial population. This maximum is found to be greater than the corresponding maximum in the two allele case.

7. The mean and variance of the distribution of frequencies of lethal mutants at equivalent loci in a finite population depend on the mutation rate per locus, the population size and the selective advantage/disadvantage of the heterozygotes carrying lethals. Assuming a mutation rate of $10^{-5}$, the mean and variance decline as the heterozygotes decline in their fitness from 1.05 to 0.95. At any given value of the selective coefficient of the heterozygote in this range the mean is larger for a population size of 50 than that of 10, but the variance behaves in this manner only if the values of selective coefficient between 1.05 to 0.00 are considered. In other cases it is smaller for $N = 50$ than for $N = 10$. The mean heterozygosity behaves in a similar manner as the mean.
8. Assuming 500 loci on lethal bearing chromosomes on which lethal mutations can occur so that the possibility of the chance of allelism due to recurrent mutation is practically nil and a mutation rate of $10^{-6}$ per locus, the chance of allelism due to identity of genes by common descent have been studied. It is found that it increases as the heterozygotes decrease in fitness at a particular population size. It is larger for the smaller population size and for very small population size it may not depend on the heterozygote's fitness. The allelism of lethal genes declines with time. The decline is sharper for a smaller population size. Heterotic lethals do not show as rapid a decline as the completely or partially recessive lethals. The initial rate of decline is found to be about 4 to 5 per cent for completely recessive lethals. This rate agrees well with that predicted by the formula of rate of decline derived with the help of the distribution of lethal genes based on diffusion approximation. For a population of size $N$ and a chromosomal mutation rate of $U$, the formula for the initial rate of decline is found to be

$$2 \frac{\pi NU (\frac{\pi}{\alpha N})^{\frac{1}{2}}}{[1 - (\frac{\pi}{\alpha N})^{\frac{1}{2}} + 2\sqrt{NU}]}.$$ 

9. The lethal mutants present in a population at any given time have an average age since they first appeared in the population. This is equivalent to the average time which these mutants would spend before disappearing from the population, in other words, their average expectation of life. It depends on the fitness of the heterozygote
and is very high for heterotic lethals but declines sharply as the heterozygote tends to be neutral and then disadvantageous. The expectation of life of a new lethal mutant at its initial occurrence is always smaller than its expectation of life at any subsequent time.
CHAPTER I

GENERAL INTRODUCTION

Selection changes the genetic make up of a population by changing its gene frequencies. In an infinite population it leads ultimately to the fixation of the favoured allele unless there is heterozygote advantage. But in a finite population, the gene frequency undergoes a random change also from generation to generation. This results in a distribution of gene frequencies which can be regarded either as the distribution of frequencies at equivalent loci in one population or as the distribution of frequencies at a single locus replicated in many equivalent populations (Wright 1931). As time proceeds this distribution gets broadened with irreversible fixation (or loss) of gene leading to a state of steady decay when the distribution curve attains a constant form. The height of the curve then decreases at a constant rate and becomes zero in the limit. The expected frequency of the favoured allele in the limit is the same as the chance of its fixation (Kimura 1957, 1962). This chance of fixation can be regarded either as the proportion of equivalent loci which would be expected to be fixed in the limit in any line or as the proportion of replicate selected lines in which an individual gene would be expected to be fixed in the limit. The limit of response to selection in a finite population is measured by the difference between the chance of fixation
of the favoured gene and its initial frequency. The determination of the chance of fixation of a gene is therefore the basic problem in the study of limits of response to selection in a finite population.

For a single locus with two alleles Kimura (1957) gave a formula for the chance of fixation. His method was based on Kolmogorov's backward diffusion equation. Robertson (1960), Ewens (1963), Allan and Robertson (1964), Hill and Robertson (1966), Hill and Robertson (1968) and others used methods based on transition matrices and determined the chance of fixation numerically with the help of a computer. In the present study a general theory of the transition matrix approach has been developed which can give the chance of fixation as well as the expected change in the gene frequency by a given time in any genetic situation. The formulae are, however, in terms of the matrices. For the case of single locus with two alleles and binomial transition probabilities the matrix formulae have been expanded, giving a formula for the chance of fixation expressed as a series. Under the conditions in which diffusion approximation holds, this formula reduces to Kimura's formula expressed as a series. For the case of single locus with three alleles, the chance of fixation of a gene is not known. Using trinomial transition probabilities this has been determined on a computer and presented in this study. Robertson (personal communication) has, however, expanded the matrix formula of the chance of fixation for a multi-allelic locus and given an approximate series formula. His formula has been compared with the exact computer results for a
3.

tri-allelic locus.

Since the limit of response to selection is attained asymptotically, the time to attain the limit is expressed in terms of half-life i.e. the time by which the expected gene frequency gets halfway to the limit (Robertson 1960). In the present study, a more accurate formula for half-life than known earlier has been developed.

The fixation or loss of genes occur after a variable number of generations. Hence the distribution of time to fixation of a particular allele disregarding the cases in which it is lost can describe the nature of the life of a gene until it is fixed. In particular, the mean and variance of this distribution are of interest. The general theory of the transition matrix approach provide with matrix formulae for the determination of the mean and variance of time until fixation of a gene in any genetic situation. For the case of a single locus with two alleles, computer results have been presented for the mean and the coefficient of variation of time until fixation of a gene. Kimura and Ohta (1968) have recently given formulae for the mean time until fixation from the diffusion approach. Their results for a selectively neutral single mutant introduced in the population have been compared with the computer results. They have, however, not derived formula for the variance of the time until fixation. This has been done in the present investigation. For the case of single locus with three alleles, the mean time until fixation of a gene is not known. Computer results have, therefore, been presented for this case.
The distribution of time until homozygosity i.e. either fixation or loss of the gene describes the nature of the life of a gene until it is either fixed or lost. When the chance of fixation of a gene is very near to unity, the two distributions may coincide. It is therefore of some interest to compare the mean and variance of time until fixation of a gene with those until homozygosity. For the case of single locus with two alleles this comparison has been presented. Ewens (1963) gave computer results as well as diffusion approximations for the mean time until homozygosity but not the variance of time until homozygosity. For the case of single locus with three alleles, the mean time until homozygosity is not known. Computer results for the same have, therefore, been presented.

Selection with random fluctuation of gene frequencies leads to fixation or loss of genes in a population. But reversible mutation or migration tends to restore the intermediate gene frequencies. This results in a stable distribution of gene frequencies. In any given case, a knowledge of the mean and the variance of small changes in gene frequency gives this stationary distribution with the help of a general formula given by Wright (1938, 1945). This formula is based on Kolmogorov's forward diffusion equation. However, for the case of balance between mutation and selection with random drift, it has been proved that the stable distribution can also be given by the means of the total number of times the population spends in the different transient states on the way to fixation from an initial state in which
the mutant individual is represented once only. These means are given by the elements of the first row of a function of the transition matrix. This approach can therefore be thought of as the transition matrix approach for the determination of the stable distribution and their properties. Ewens (1964), however, described the distribution based on the mean time spent in an interval before absorption as a pseudo-transient distribution.

If we consider a deleterious gene in a large population, mutation opposed by moderately severe selection would tend to keep the gene at a low equilibrium frequency determined by the mutation rate, selective coefficient and the degree of dominance of the gene. But if we take small samples from such a population with dominance lacking and the same degree of severity of selection is considered, the mean frequency of the gene rises to the equilibrium value expected on the basis of reversible mutations alone. If unfavourable mutation is much more frequent than the reverse, this may lead to approximate fixation of the gene. In the case of a recessive lethal the effect of this bottleneck due to reduction in the population size is, however, a considerable decrease in the mean frequency of lethal gene. The distribution of lethal gene frequencies is given by Wright (1937) whereas the distribution of lethal chromosomes is derived by Nei (1968). In the present study the properties of the lethal gene frequency distribution has been studied from the transition matrix approach and compared with the properties known from the diffusion approach. In the case of
heterotic and partially recessive lethals, however, the present approach gives results which were not known previously.

In the case of lethal genes an important problem is the determination of the chance of allelism. This can be regarded as the proportion of crosses between lethal bearing chromosomes which produce lethal zygotes. Allelic rates have been found useful in discriminating, from experimental data on Drosophila populations, whether recessive lethals extracted from natural populations have a deleterious effect as heterozygotes or not (Crow and Temin 1964). Dobzhansky and Wright (1941), and Wright, Dobzhansky and Hovanitz (1942) gave a formula for the determination of allelic rates. Nei (1968) modified this formula. Here Nei’s formula has further been modified to deal with an infinite number of loci on lethal bearing chromosomes. Allelic rates have been determined using transition matrix approach, in the case of heterotic, completely recessive and partially recessive lethals.

Another interesting problem, in the case of lethal genes, is the decline of allelism of recessive lethals extracted from natural populations at different times (Wallace 1966). Wallace suggested a functional relationship between the allelic rate and the time interval between the sampling of the first and the second set of lethals. Prout (1967) proved this relationship to be approximately correct by using recurrence relations between the gene frequencies in the successive generations subject to systematic and random pressures. Using transition matrices an alternative way of predicting the decline of
allelism with time has been suggested by Robertson (personal communication). On this basis, the decline of allelism with time has been studied in the present investigation. The initial rate of decline has also been worked out with the help of Wright's equilibrium distribution formula.

The expectations of life of a lethal mutant at its initial occurrence as well as at any given time when it is represented in the population more than once have further been investigated in this study. These do not appear to have been studied previously.

The plan to be followed in the succeeding chapters is this: a general theory of the transition matrix approach for the study of (a) response to selection in a finite population and (b) the gene frequency distribution at equilibrium between selection and mutation is given in Chapter II. For a single locus with two alleles and binomial transition probabilities, matrix formulae are expanded in Chapter III. Diffusion approximation for the variance of time until fixation has also been discussed in this chapter. This is followed by Chapter IV dealing with numerical results on the mean and the coefficient of variation of time until fixation using binomial transition probabilities. The numerical results on selection with trinomial transition probabilities are given in Chapter V. In the last Chapter, the properties of lethal gene distribution, allelism, and the expectation of life of a lethal mutant are presented.
CHAPTER II

THEORY OF TRANSITION MATRIX APPROACH

In this section the basic theory of the transition matrix approach is developed from the first principles. First only selection in a finite population is considered. Matrix formulae are developed for the fixation probabilities, the expected changes in the gene frequency and the moments of the distribution of time to fixation for a single locus with two alleles and three alleles. Next mutation at a low rate is introduced in the case of single locus with two alleles to compensate for the homozygosity due to random elimination. The resulting stable distribution is expressed as the elements of a certain row of the fundamental matrix, and the properties of the distribution are developed.

2.1 SELECTION AND RANDOM DRIFT

2.11 DIALLELIC LOCUS

Consider a finite population of gametes of constant size 2N and a single locus with two alleles A₁ and A₂. Such a population can assume \((2N + 1)\) states \(E_0, E_1, \ldots, E_{2N}\), the \(i^{th}\) state \(E_i\) representing the state of \(i\) A₁ genes and \((2N - i)\) A₂ genes. The states \(E_0\) and \(E_{2N}\) represent respectively the state of A₂ and A₁.
genes entirely and therefore once the population assumes these states, it gets fixed for either \( A_2 \) or \( A_1 \) allele. In Markov chain terminology, such states are known as absorbing states. On the other hand, any other state \( E_1, \ i = 1, 2, \ldots, (2N-1) \), represents a mixture of \( A_1 \) and \( A_2 \) genes and therefore once the population is in this state, it has a possibility of going out of this state to any other state including the absorbing ones. In other words, this means \( E_1 \) state represents a state segregating for \( A_1 \) and \( A_2 \) genes with proportions \( q_1 = \frac{i}{2N} \) and \( (1 - q_1) \) respectively. These are known as transient states. Suppose \( P_{ij} \) represents the conditional probability that there are \( j \) \( A_1 \) genes out of \( 2N \) genes after one generation, given that there were \( i \) \( A_1 \) genes out of \( 2N \) genes in the previous generation. Since there are \( (2N + 1) \) possibilities in the previous as well as in this generation, we have \( (2N + 1) \times (2N + 1) \) \( P_{ij} \)'s which can be conveniently represented by a matrix \( P \) as given below. Also, if all the genes are either of \( A_1 \) or \( A_2 \) types, \( P_{oo} \) and \( P_{2N,2N} \) will each be one but \( P_{oj} \) and \( P_{2N,j} \) will each be zero, where \( j \) can have any value between 1 and \( (2N - 1) \). So

\[
\begin{pmatrix}
1 & 0 & \cdots & 0 & 0 \\
0 & P_{11} & \cdots & P_{1,(2N-1)} & P_{1,2N} \\
0 & \cdots & \cdots & \cdots & \cdots \\
0 & \cdots & \cdots & \cdots & \cdots \\
0 & \cdots & \cdots & \cdots & \cdots \\
0 & \cdots & \cdots & \cdots & 1
\end{pmatrix}
\]
Suppose we consider transitions between the transient states only, then the transition probability matrix can be represented by \( \tilde{Q} \) as given below.

\[
\tilde{Q} = \begin{bmatrix}
P_{11} & \cdots & \cdots & P_{1}(2N-1) \\
\vdots & \ddots & \ddots & \vdots \\
P_{(2N-1),1} & \cdots & \cdots & P_{(2N-1),(2N-1)}
\end{bmatrix}
\]

(2.2)

If \( P', P'_{2N} \) and \( Q' \) denote the row vectors as given below

\[
P'_0 = [P_{10}, P_{20}, \cdots, P_{(2N-1),0}] \\
P'_{2N} = [P_{1,2N}, P_{2,2N}, \cdots, P_{(2N-1),2N}] \\
Q' = [0, 0, \ldots, 0]
\]

then \( P \) can be written in a partitioned form as

\[
P = \begin{bmatrix}
1 & 0 & 0' \\
0 & 1 & 0' \\
P'_0 & P'_{2N} & \tilde{Q}
\end{bmatrix}
\]

(2.6)

Now suppose we consider the transition probabilities after \( t \)-generations and denote them by \( P_{ij}^{(t)} \) with the corresponding \( \tilde{Q} \) matrix as \( \tilde{Q}(t) \). Then we know from the theory of finite Markov chains.
(Kemeny and Snell 1960) that

\[ q(t) = q^t \]

Now consider the matrix sum

\[ \tilde{T}(t) = \tilde{I} + \tilde{q} + \tilde{q}^2 + \ldots + \tilde{q}^t \]

where \( \tilde{I} \) is a unit matrix with ones as the diagonal elements and zeros elsewhere. The elements in the \( i^{th} \) row of \( \tilde{T}(t) \) give the expected total number of times the population spends in the different transient states by the \( t^{th} \) generation, having started from the state \( \mathbb{E}_i \).

Suppose \( \mathbb{U}(t) \) and \( \mathbb{R}(t) \) denote the column vectors of the fixation probabilities and the expected changes in the gene frequency of \( A_1 \) respectively by the \( t^{th} \) generation, whereas \( \frac{P_{2N}}{2N} \) and \( \frac{\Delta q}{q} \) denote the column vectors of the fixation probabilities and the expected changes in the gene frequency of \( A_1 \) respectively in one step. Now fixation by the \( t^{th} \) generation means that starting from \( \mathbb{E}_1 \), the population assumes the different transient states in the first \( (t - 1) \) steps and then achieves fixation in one step from the assumed transient states. This means that the fixation probability is the sum of the expected total number of times the population spends in the different transient state by the \( (t - 1)^{th} \) generation, multiplied by the corresponding probability of fixation in one step. That is,

\[ \mathbb{U}(t) = \tilde{T}(t - 1) \frac{P_{2N}}{2N} \]

Similar considerations show that

\[ \mathbb{R}(t) = \tilde{T}(t - 1) \frac{\Delta q}{q} \]
Since the $P$-matrix is a Markov matrix with elements as probabilities, it follows from the matrix theory (Fadleeva, 1958) that the roots of $Q$ are all positive and less than unity and therefore the inverse of $(I - Q)$ exists i.e. $\left| I - Q \right| \neq 0$. Also we have, then

$$(2.11) \quad T(t - 1) = I + Q + \ldots + Q^{t-1}$$

$$= (I - Q^t) (I - Q)^{-1}$$

Hence, we have

$$(2.12) \quad U(t) = (I - Q^t) (I - Q)^{-1} \frac{P_{2N}}{2}$$

$$(2.13) \quad R(t) = (I - Q^t) (I - Q)^{-1} \Delta q$$

Moreover, as $t \to \infty$, $Q^t \to 0$, a null matrix with all the elements as zeros, so that if $U$ and $R$ denote the vectors of the eventual fixation probabilities and the expected changes in the gene frequency of $A_1$ in the limit (i.e. the selection limit) respectively, these are given by

$$(2.14) \quad U = (I - Q)^{-1} \frac{P_{2N}}{2}$$

$$(2.15) \quad R = (I - Q)^{-1} \Delta q$$

$U(t)$ and $R(t)$ can now, alternatively, be expressed as

$$(2.16) \quad U(t) = (I - Q^t) U$$

$$(2.17) \quad R(t) = (I - Q^t) R$$

The time which a population, with a given initial gene frequency, takes to get fixed for this gene is a random variable on the hypothesis that fixation for this gene takes place with certainty. It is, therefore,
important to investigate the average number of generations taken for
the fixation of the desirable allele disregarding the cases in which
it is lost. Since

\[
\lim_{t \to \infty} T(t) = I + Q + Q^2 + \ldots
\]

\[
= (I - Q)^{-1}
\]

it follows that the elements in the \(i^{th}\) row of \(T\) are the averages
of the total number of times the population spends in the different
transient states on the way to eventual fixation from an initial
state \(i\). This is called the fundamental matrix of the absorbing
Markov chain. The row sums of this matrix give the average time to
absorption in the absorbing states from various initial states. Here
it corresponds to the average time to homozygosity. Expressed in
vector notations, this is given by

\[
(2.19) \quad \mathbb{M} = T \mathbb{e}
\]

where \(\mathbb{e}\) is a column vector with all the elements as unity. As the
proportion of times that a population goes from a particular state to
the fixation of the allele \(A_1\) is given by the elements of the vector
\(U\), the vector \(\mathbb{M}\) given by

\[
(2.20) \quad \mathbb{M} = (I - Q)^{-1} U
\]

\[
= (I - Q)^{-2} \frac{P_{2N}}{2N}
\]
gives the mean total number of steps needed for the fixation of the allele $A_1$. The mean time until fixation of $A_1$ is therefore given by the ratio of the elements of vectors $\bar{M}$ and $\bar{U}$ respectively.

If we expand $(I - Q)^{-2}$ in (2.20) we obtain

$$(2.21) \quad \bar{M} = (I + 2Q + 3Q^2 + \ldots \ldots) P_{2N}$$

This shows that we can obtain the various moments of the distribution of time until fixation of the particular allele disregarding the cases in which it is lost, by generalizing this formula. For instance, the second moment is given by the ratio of the elements of vectors $\bar{V}$ and $\bar{U}$ respectively where $\bar{V}$ is given by

$$(2.22) \quad \bar{V} = (I + 2Q + 3Q^2 + \ldots \ldots) P_{2N}$$

$= \left[2(I - Q)^{-3} - (I - Q)^{-2}\right] P_{2N}$$

The variance can then be obtained by subtracting the square of the mean from it.

The matrix formulae for the moments of the distribution of time until loss of $A_1$ disregarding the cases in which it is fixed, can be obtained by substituting $P_0$ in place of $P_{2N}$ in $\bar{U}$, $\bar{M}$, and $\bar{V}$.

An alternative method of deriving the matrix formulae for $\bar{U}$, $\bar{R}$, $\bar{M}$ and $\bar{V}$ is given in the Appendix.
2.12 TRI-ALLELIC LOCUS

Consider a finite population of gametes of constant size $2N$ and a single locus with three alleles $A_1$, $A_2$, and $A_3$. Such a population can assume $(N + 1)(2N + 1)$ states. If the population consists of $i_1$ $A_1$ genes, $i_2$ $A_2$ genes and $(2N - i_1 - i_2)$ $A_3$ genes, the population is said to be in state $E_{i_1,i_2}$ with $i_1 + i_2$ less than or equal to $2N$. These states can be grouped into three classes depending upon the kind of genes present in the population:

**class I:**
- $E_{0,0}$: $A_1, A_2$ lost i.e. $A_3$ is fixed
- $E_{0,2N}$: $A_1, A_3$ lost i.e. $A_2$ is fixed
- $E_{2N,0}$: $A_2, A_3$ lost i.e. $A_1$ is fixed

Thus there are three absorbing states.

**class II:**
- $E_{i_1,i_2}$: $i_1, i_2 > 0$ such $i_1 + i_2 = 2N$, i.e. $A_3$ is lost
- $E_{i_1,0}$: $i_1 \neq 0$ or $2N$ i.e. $A_2$ is lost
- $E_{0,i_2}$: $i_2 \neq 0$ or $2N$ i.e. $A_1$ is lost

Thus there are $3(2N - 1)$ states such that exactly one of the three genes is lost. In these cases the population behaves as described in the previous section.
class III: \[ E_{i_1 i_2} : i_1 \neq 0, i_2 \neq 0 \text{ and } i_1 + i_2 < 2N \]

Thus there are \((N - 1) (2N - 1)\) states such that all the three genes are present.

These states can be geometrically represented by triangular coordinates as in Figure 1. The states in class I are represented by the vertices of the triangle. The states in class II are represented by the interior points of the sides of the triangle. The states in class III are the interior points of the triangle. The totality of transient states is the sum of states in class II and class III i.e. \((N + 2) (2N - 1)\). There is, however, an important distinction between the transient character of the states in class II and class III. If the population is in one of the three categories of class II states it cannot go to the transient states of the other two categories of this class as well as to states of class III and to one of the absorbing states. For instance if the transient states of the type \(E_{i_1,0}\) are considered the transitions are not possible to states of type \(E_{i_1,i_2}^0\), \(E_{0,i_2}^1\) of class II, \(E_{i_1,i_2}^1\) of class III and \(E_{0,2N}^2\). This simplifies the structure of the transition matrix considerably as will be shown below. But if a state belongs to class III, the transitions are possible to all the states of class I, II and III.

The transition probabilities are of the type \(P(i_1, i_2) (j_1, j_2)\) representing the conditional probability that there are \(j_1\) \(A_1\) genes, \(j_2\) \(A_2\) genes out of \(2N\) genes after one generation given that there...
Fig. 1 A geometric representation of the state space at a tri-allelic locus.
were $i_1$ $A_1$ genes and $i_2$ $A_2$ genes out of $2N$ genes in the previous generation. Since there are in all $(N + 1) (2N + 1)$ states, there transition probabilities are arranged in a $P$ of order $(N + 1) (2N + 1) \times (N + 1) (2N + 1)$ whereas since there $(N + 2) (2N - 1)$ transient states, the $Q$-matrix will be of the order $(N + 2) (2N - 1) \times (N + 2) (2N - 1)$. If we denote by $P'_{0,0}, P'_{0,2N}$ and $P'_{2N,0}$ row vectors of order $(N + 2) (2N - 1)$ as representing the one-step transitions for fixation of $A_3$, $A_2$ and $A_1$ genes respectively, the partitioned form of $P$ is given by

$$
\begin{bmatrix}
1 & 0 & 0 & Q' \\
0 & 1 & 0 & Q' \\
0 & 0 & 1 & Q' \\
Q_{0,0} & Q_{0,2N} & Q_{2N,0} & Q
\end{bmatrix}
$$

where $Q'$ is a null row vector of order $(N + 2) (2N - 1)$. The $Q$-matrix can further be partitioned as

$$
\begin{bmatrix}
Q_{12} & 0 & 0 & 0 \\
0 & Q_{13} & 0 & 0 \\
0 & 0 & Q_{23} & 0 \\
D_{12} & D_{13} & D_{23} & Q^*
\end{bmatrix}
$$

where $Q_{12}$ represents the transition probabilities between states
of class II i.e. a two-allele situation $A_1 - A_2$.

Similarly $Q_{13}$ is for $A_1 - A_3$ and $Q_{23}$ is for $A_2 - A_3$ situations respectively. $Q^*$ represents the $(N - 1) (2N - 1) x (N - 1) (2N - 1)$ matrix for transitions between states $E_{i_1,i_2}$ of class III. $D_{12}$ represents the transition from states of class III to $E_{i_1,i_2}$ type states of class II, $D_{12}$ represents the transitions from states of class III to $E_{i_1,i_2}$ type states of class II and $D_{23}$ represents the transitions from states of class III to $E_{i_1,i_2}$ type states of class II.

In view of the well known matrix operations on partitioned matrices, the fundamental matrix $T$ introduced in the previous section and equal to $(I - Q)^{-1}$ is now given by

$$T = \begin{bmatrix}
T_{12} & 0 & 0 & 0 \\
0 & T_{13} & 0 & 0 \\
0 & 0 & T_{23} & 0 \\
T^* & D_{12} & T_{12} & T^* & D_{13} & T_{13} & T^* & D_{23} & T_{23} & T^*
\end{bmatrix}$$

where

$$T_{12} = (I - Q_{12})^{-1},$$

$$T_{13} = (I - Q_{13})^{-1},$$

$$T_{23} = (I - Q_{23})^{-1},$$

$$T^* = (I - Q^*)^{-1}.$$
The vectors of the probability of fixation and the expected change in the gene frequency of \( A_1 \) in the limit are, therefore, given by

\[
(2.30) \quad U_1 = T P_{2N,0} \\
(2.31) \quad R_1 = T \Delta q_1
\]

Now \( P_{2N,0} \) is a vector of transition probabilities for transitions from the transient states to the absorbing state representing the vertex \( E_{2N,0} \) in the triangle in Fig. 1 in one step. It can be represented by a partitioned row vector as

\[
(2.32) \quad P'_{2N,0} = \begin{bmatrix}
P'_{2N,0}^{1} & P'_{2N,0}^{2} & P'_{2N,0}^{3} & P'_{2N,0}^{4}
\end{bmatrix}
\]

where \( P'_{2N,0}^{1} \) represents the row vector of one-step transitions for the fixation of \( A_1 \) starting from the cases in which \( A_3 \) is absent. \( P'_{2N,0}^{2} \) is similarly the vector for the case when initially \( A_2 \) is absent, and \( P'_{2N,0}^{3} \) is for the case when initially all the three genes are present. Obviously if initially \( A_1 \) is absent, there is no question of fixation of \( A_1 \). Hence there is a null row vector also in \( P'_{2N,0}^{4} \). Now with this partitioning the fixation probability vector \( U_1 \) consists of four component vectors \( U_{12} \), \( U_{13} \), \( U_{23} \) and \( U^* \) given by

\[
(2.33) \quad U_{12} = T_{12} P_{2N} \\
(2.34) \quad U_{13} = T_{13} P_{2N}
\]
\[ (2.35) \quad \mathbf{U}_{23} = 0 \]

\[ (2.36) \quad \mathbf{U}^* = T^* \left( D_{12} \mathbf{U}_{12} + D_{13} \mathbf{U}_{13} + P^* \right) \]

Here \( \mathbf{U}_{12} \) and \( \mathbf{U}_{13} \) are the usual fixation probability vectors for two allele \( A_1 - A_2 \) and \( A_1 - A_3 \) situations as discussed in the previous section. \( \mathbf{U}^* \) is the fixation probability vector for \( A_1 \) when initially all the three genes exist or in other words the initial state is somewhere in the interior of the triangle in Fig. 1. For fixation in the vertex \( E_{2N,0} \) from such a state, there are three possibilities. One possibility is that it can go to one side of the triangle representing \( E_{i_1,i_2} \) with \( i_1 + i_2 = 2N \) and then to \( E_{2N,0} \). The second possibility is that it can go to the side of the triangle representing \( E_{i_1,0} \) and then to \( E_{2N,0} \). Third possibility is that it can straight go to \( E_{2N,0} \). The matrix formula (2.36) derived above shows that when the initial state is somewhere in the interior of the triangle, the fixation probability is the sum of the expected total number of times the population spends in the interior states multiplied by the sum of the corresponding one-step probabilities of fixation via the three different paths enumerated above.

Similar considerations show that if we break down the vector of the expected changes in the frequency of \( A_1 \) in one step into components \( 2\Delta q_1, 3\Delta q_1, 0, \Delta^* q_1 \) as

\[ (2.37) \quad \Delta' q_1 = [ 2\Delta' q_1, 3\Delta' q_1, 0', \Delta^* q_1 ] \]
and the selection limit vector into components $R_{12}$, $R_{13}$, $R_{23}$ and $R^*$, we get

$$(2.40) \quad R_{12} = T_{12} \Delta q_1$$

$$(2.41) \quad R_{13} = T_{13} \Delta q_1$$

$$(2.42) \quad R_{23} = 0$$

$$(2.43) \quad R^* = T^* \left( D_{12} R_{12} + D_{13} R_{13} + \Delta^* q_1 \right)$$

This gives a matrix formula for the evaluation of the expected limit of response to selection in a single locus three allele situation.

We have derived above the matrix formulae for the fixation probability and the expected change in the gene frequency for the allele $A_1$. Similar results hold for the alleles $A_2$ and $A_3$.

For the mean time until homozygosity, we can write, in vector notations

$$(2.42) \quad m = T e$$

If $m$ consists of four components $m_1$, $m_2$, $m_3$ and $m^*$ corresponding to the four initial situations described earlier, we get

$$(2.43) \quad m_1 = T_1 e$$

$$(2.44) \quad m_2 = T_2 e$$

$$(2.45) \quad m_3 = T_3 e$$

$$(2.46) \quad m^* = T^* \left[ D_{12} m_1 + D_{13} m_2 + D_{23} m_3 + e \right]$$
For the second moment of time until homozygosity, we have the relation

\[(2.47) \quad \nu = (2T - I) \frac{m}{m} \]

If \( \nu \) is broken down into four components \( \nu_1, \nu_2, \nu_3 \) and \( \nu^* \) we get

\[(2.48) \quad \nu_1 = (2T - I) \frac{m_1}{m_1} \]
\[(2.49) \quad \nu_2 = (2T - I) \frac{m_2}{m_2} \]
\[(2.50) \quad \nu_3 = (2T - I) \frac{m_3}{m_3} \]
\[(2.51) \quad \nu^* = \frac{T}{T} \left[ D_{12} \nu_1 + D_{13} \nu_2 + D_{23} \nu_3 + 2m^* - q \right] \]

In order to evaluate the mean time until fixation of the \( A_1 \) allele disregarding the cases in which it is lost, we have to evaluate

\[(2.52) \quad M_1 = \frac{T}{T} \frac{U_1}{U_1} \]

As usual if we let

\[(2.53) \quad M'_1 = \left[ \frac{M'_{12}}{M'_{12}}, \frac{M'_{13}}{M'_{13}}, \frac{M'_{23}}{M'_{23}}, \frac{M'}{M'} \right] \]

we get

\[(2.54) \quad M_{12} = \frac{T}{T} \frac{U_{12}}{U_{12}} \]
\[(2.55) \quad M_{13} = \frac{T}{T} \frac{U_{13}}{U_{13}} \]
\[(2.56) \quad M_{23} = 0 \]
\( (2.57) \quad M^* = T^* \left( \frac{D_{12}}{\sim} M_{12} + \frac{D_{13}}{\sim} M_{13} + U^* \right) \)

The required mean time will be given by the ratios of the elements of the vectors \( M_{12} \) and \( U_{12} \), \( M_{13} \) and \( U_{13} \) and \( M^* \) and \( U^* \) respectively.

For the second moment of the distribution of time until fixation of the \( A_1 \) allele disregarding the cases in which it is lost, we have the relation

\( (2.58) \quad V_1 = (2T - I) M_1 \)

If \( V_1 \) consists of \( V_{12}, V_{13}, V_2, \) and \( V^* \) we get

\( (2.59) \quad V_{12} = (2T_{12} - I) M_{12} \)

\( (2.60) \quad V_{13} = (2T_{13} - I) M_{13} \)

\( (2.61) \quad V_2 = 0 \)

\( (2.62) \quad V^* = T^* \left( \frac{D_{12}}{\sim} V_{12} + \frac{D_{13}}{\sim} V_{13} + 2M^* - U^* \right) \)

The required second moment will be given by the ratios of the elements of the vectors \( V_{12} \) and \( U_{12} \), \( V_{13} \) and \( U_{13} \) and \( V^* \) and \( U^* \) respectively.

Similarly the moments of the distribution of time until fixation of either \( A_2 \) or \( A_3 \) disregarding the others can be derived.
Suppose we consider $S$ loci at each of which there is initially one mutant $A_1$ and $(2N - 1)$ normal $A_2$ alleles. This means that the population is initially in $E_1$ state. Each locus will eventually become homozygous in the absence of further mutation.

Suppose $S$ is so chosen that on an average one locus becomes homozygous per generation. We can, then introduce a new locus having one mutant and $(2N - 1)$ normals each generation to balance this loss.

This would lead to an equilibrium state with mean number $S_{1,j}$ of loci having $j$ mutants, where $j$ can take values 1, 2, .... (2N - 1) and $S = \sum_{j=1}^{(2N-1)} S_{1,j}$. It follows from the ergodic property of irreducible recurrent Markov chains that the $S_{1,j}$'s can be obtained by premultiplying the fundamental matrix $\mathbf{T}$ by a row vector $f' = (1, 0, 0 \ldots 0)$ containing unity in the first place and zeros elsewhere and therefore

$$ (2.63) \quad S = f' \mathbf{T}^{-1} \mathbf{q}^{-1} $$

This shows that the mean number of loci having $j$ mutants in equilibrium is equivalent to the mean number of generations which the population spends in the state $E_j$ on the way to fixation or loss if there had been no balancing effect by mutation. Now if the mutation rate from $A_2$ to $A_1$ is $u$ (reverse mutation being negligible), there would be on an average $2N_u S$ new loci each having one mutant and the rest normal each generation. Hence there would be required $2N_u S$ loci
initially instead of $S$ to determine the equilibrium state and the mean number of loci having $j$ mutants in equilibrium would be $2N u S_{1j}$. The mean and variance of $q$, the frequency of $A_1$ in the equilibrium state are given by

\[ E(q) = 2N u \sum_{j=1}^{2N-1} S_{1j} (j/2N) \]  \hspace{1cm} (2.64)

\[ E[q - E(q)]^2 = 2N u \sum_{j=1}^{2N-1} S_{1j} (j/2N)^2 - [E(q)]^2 \]  \hspace{1cm} (2.65)

The mean frequency of heterozygotes in the equilibrium state can be obtained from

\[ E[2q(1 - q)] = 4N u \sum_{j=1}^{2N-1} S_{1j} (j/2N) (1 - j/2N) \]  \hspace{1cm} (2.66)

This quantity is proportional to the contribution of the locus towards the genetic variance of the stable population and shows that it is proportional to the population size if $N u$ is small.
CHAPTER III

EXPANSION OF MATRIX FORMULAE AND DIFFUSION APPROXIMATIONS

The theory developed in Chapter II can be applied to specific genetic models. In this chapter an analytical treatment of selection with random drift and diallelic locus is presented. In the first part, matrix formulae developed in 2.11 are expanded taking into account the binomial transition probabilities. The algebraic expressions for selection limit, half-life and moments of the distribution of time to fixation are discussed. In the second part, the diffusion approximation for the variance of time until fixation is derived.

3.1 EXPANSION WITH BINOMIAL TRANSITION PROBABILITY

If no selective forces are operating and the transition probabilities are of the binomial type, the situation is what is often known as Wright's model (Wright 1931). Here starting with a given frequency $q_1 = 1/(2N)$ of allele $A_1$ (with $1 - q_1 = \text{frequency of } A_2$) in lines of constant breeding size of $N$ individuals, we can consider the second generation as derived from the first by the sampling of groups of $2N$ haploid sets, the gene frequency in the different groups being distributed binomially with mean $2Nq_1$ and index $2N$. The next generation is then the repetition of this process, each line giving rise to a group of lines
whose gene frequencies are binomially distributed about the mean of the parent line. Now let \( A_1 \) genes have a selective advantage of \( (1 + s/2) \) over \( A_2 \) genes with selective advantage unity, so that the relative number of offsprings have expectations proportional to \( (1 + s/2) \) and 1 respectively where \( s \) is small. That is, we assume that a large number of offsprings are produced but exactly \( 2N \) of these survive. Assuming further that the selection operates before sampling, the gene frequency in the different groups are distributed binomially with mean \( 2Nq'_1 \) and index \( 2N \), where \( q'_1 \) is the gene frequency of \( A_1 \) after selection and is given by

\[
q'_1 = q_1 + \delta q_1
\]

\[
= q_1 + \frac{s}{2} q_1 (1 - q_1)/(1 + q_1 s/2)
\]

\( \delta q_1 \) being the change in the mean frequency of \( A_1 \) due to selection in one step when its frequency in the previous generation is \( q_1 \). Thus with haploid selection and binomial sampling, we can regard the number of \( A_1 \) genes in any generation as a Markovian variate with transition probability \( P_{ij} \) given by

\[
P_{ij} = \binom{2N}{j} q'_1^j (1 - q'_1)^{2N - j}
\]

These probabilities, therefore, determine the \( P- \) and \( Q- \) matrices introduced in 2.11. We can now expand the transition probabilities in
powers of 's'. for a given N and utilise the properties of the
transition probability matrices with no selection, referred to here-
after, as $P_0$ and $Q_0$. The properties of these matrices, in terms of
the eigen-roots and vectors, are discussed in Feller (1951) and
Robertson (1952).

Let $\tilde{q}_j$ be approximated by $\frac{s}{2} q_j (1 - q_1) (1 - \frac{s}{2} q_1)$. Then
$P_{ij}$ can be expressed approximately upto terms in $s^2$ as

$$P_{ij} = P_{ij}(o) [1 + s a_{ij} + s^2 b_{ij}]$$

where

$$P_{ij}(o) = \binom{2N}{j} q_j^j (1 - q_1)^{2N-j}$$

is the transition probability with no selection and $a_{ij}$ and $b_{ij}$
are given by

$$a_{ij} = N(q_j - q_1)$$
$$b_{ij} = \frac{N^2}{2} [ q_j^2 + (1 + \frac{1}{2N})q_1^2 - 2q_1q_j - \frac{1}{2N} q_j ]$$

$q_j$ being $j/(2N)$.

In terms of $\tilde{Q}$, we can write, upto terms involving $s^2$,

$$\tilde{Q} = \tilde{Q}_0 + s \tilde{Q}_1 + s^2 \tilde{Q}_2$$

where $\tilde{Q}_1$ and $\tilde{Q}_2$ are $(2N - 1) \times (2N - 1)$ matrices with $i, j$
elements respectively as

\[(3.8) \quad a_{ij} p_{ij}(o)\]

and

\[(3.9) \quad b_{ij} p_{ij}(o)\]

Now we have proved in 2.11 that the vectors \( \mathbf{R} \) and \( \mathbf{R}(t) \) are obtained by operating certain functions of \( Q_0 \) on to the column vector of the change in the mean gene frequency in a single generation. This column vector is expressible in terms of the right hand eigen-vectors of \( Q_0 \). Hence the expanded form of \( \mathbf{R} \) and \( \mathbf{R}(t) \) can be determined if we know the operations of certain functions of \( Q_0 \) on to these vectors. It has been found that we need nine operators and the first three vectors of \( Q_0 \). The vectors are

\[(3.10) \quad x_1 = [x_{11}, x_{12}, \ldots, x_{1,(2N - 1)}], \quad x_{11} = q_1 (1 - q_1)\]

\[(3.11) \quad x_2 = [x_{21}, x_{22}, \ldots, x_{2,(2N - 1)}], \quad x_{21} = q_1 (1 - q_1)(1 - 2q_1)\]

\[(3.12) \quad x_3 = [x_{31}, x_{32}, \ldots, x_{3,(2N - 1)}], \quad x_{31} = q_1 (1 - q_1) \left[ \frac{2N - 1}{10N - 6} - q_1 (1 - q_1) \right]\]

These vectors correspond to the three eigen - roots of \( Q_0 \) given by

\[(3.13) \quad \lambda_1 = (1 - 1/2N)\]

\[(3.14) \quad \lambda_2 = (1 - 1/2N) (1 - 2/2N)\]

\[(3.15) \quad \lambda_3 = (1 - 1/2N) (1 - 2/2N) (1 - 3/2N)\]
respectively. The results of performing these operations are given in Table 1, where only the 18 operations out of the 27 possible are given, which are actually needed in the expansion of $R$ and $R(t)$.

3.11 EXPANSION FOR THE EXPECTED SELECTION LIMIT

In Chapter II, the selection limit vector has been expressed as the operation of $(I - \mathbf{q})^{-1}$ on to $\Delta \mathbf{q}$, the vector of expected change in the gene frequency in one step. Each of these, when expressed in powers of $s$, upto terms involving $s^2$, are given by

\begin{equation}
(I - \mathbf{q})^{-1} = (I - \mathbf{q}_0)^{-1} + s(I - \mathbf{q}_0)^{-1} \mathbf{q}_0'(I - \mathbf{q}_0)^{-1} \\
+ s^2 [(I - \mathbf{q}_0)^{-1} \mathbf{q}_0''(I - \mathbf{q}_0)^{-1} \\
+ (I - \mathbf{q}_0)^{-1} \mathbf{q}_0'(I - \mathbf{q}_0)^{-1} \mathbf{q}_0'(I - \mathbf{q}_0)^{-1}]
\end{equation}

\begin{equation}
\Delta \mathbf{q} = \frac{s}{2} (1 - \frac{s}{4}) \mathbf{X}_1 + \frac{s^2}{8} \mathbf{X}_2
\end{equation}

The item by item operation of the terms in the expansion of the matrix on to those in the expansion of the vector has been performed with the help of Table 1. The result, expressed as a linear function of the three vectors $\mathbf{X}_1$, $\mathbf{X}_2$ and $\mathbf{X}_3$ is given by

\begin{equation}
R = a_{10} \mathbf{X}_1 + a_{20} \mathbf{X}_2 + a_{30} \mathbf{X}_3
\end{equation}
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<th>( x_2 )</th>
<th>( x_3 )</th>
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<td>( \lambda_3 )</td>
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<td>( 2N )</td>
<td>( \frac{2N}{3N - 1} )</td>
<td>( \frac{4N^3}{12N^2 - 11N + 3} )</td>
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<td>( \lambda_3^t )</td>
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<td>( \frac{3}{2} \lambda_1 )</td>
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### Table 1 Continued

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<th>( x_2 )</th>
<th>( x_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_0 )</td>
<td>( \frac{1}{8} \lambda_1 \left( 6 \frac{x_3}{5N} - \frac{N}{3} x_1 - x_2 \right) )</td>
<td>(-)</td>
</tr>
<tr>
<td>( T_0 Q_0 T_0 )</td>
<td>( \frac{1}{2} \lambda_1^2 \left( \frac{12N^2}{12N^2 - 11N + 3} x_2 - \frac{N}{5N - 3} x_1 - \frac{N}{3N - 1} x_2 \right) )</td>
<td>(-)</td>
</tr>
<tr>
<td>( (Q_0 t)^n )</td>
<td>( \frac{1}{8} \lambda_1 \left[ 6 \left( \frac{\lambda_2}{\lambda_2 - \lambda_3} w_1 - \frac{\lambda_2}{\lambda_1 - \lambda_2} w_3 + \frac{\lambda_2^2 - \lambda_1 \lambda_3}{(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)} w_2 \right) x_3 \right. )</td>
<td>(-)</td>
</tr>
<tr>
<td>( \sim )</td>
<td>\left. - w_1 x_2 \right] - \frac{N}{5N - 3} \left( t \lambda_1^{-1} \frac{\lambda_1 + \lambda_2}{(\lambda_1 - \lambda_2)} - \frac{2 \lambda_2}{(\lambda_1 - \lambda_2)} w_1 \right) x_1</td>
<td>|</td>
</tr>
</tbody>
</table>

**N.B.**

\( T_0 = (I - Q_0)^{-1} \)

\( w_2 = \frac{\lambda_1^t - \lambda_3^t}{\lambda_1 - \lambda_3} \)

\( w_1 = \frac{\lambda_1^t - \lambda_2^t}{\lambda_1 - \lambda_2} \)

\( w_3 = \frac{\lambda_2^t - \lambda_3^t}{\lambda_2 - \lambda_3} \)
where

\[(3.19) \quad a_{10} = Ns \left[ 1 - \left(\frac{s}{2}\right) - \left(\frac{N - 1}{2N - 3}\right) \left(\frac{8N^3 - 7N + 2}{3N - 1}\right) (s^2/6) \right] \]

\[(3.20) \quad a_{20} = N^2 s^2 \left[ \frac{4N - 1}{4(3N - 1)} (1 - s/2) \right] \]

\[(3.21) \quad a_{30} = N^3 s^3 \left[ \frac{3(4N - 1)(N - 1)(2N - 1)}{2(3N - 1)(12N^2 - 11N + 3)} + \frac{3N - 1}{12N^2 - 11N + 3} \right] \]

Starting with an initial gene frequency \(q\), the expected selection limit or the chance of its eventual fixation \(u(q)\) minus the initial frequency is then given by

\[(3.22) \quad u(q) - q = a_{10} q(1 - q) + a_{20} q(1 - q)(1 - 2q) + a_{30} q(1 - q) \left[ \frac{2N - 1}{10N - 6} - q(1 - q) \right] \]

If \(N\) becomes very large and \(s\) becomes very small such that \(Ns\) is kept constant, we get

\[(3.23) \quad u(q) - q = Ns(1 - \frac{N^2 s^2}{15}) q(1 - q) + \frac{1}{3} N^2 s^2 q(1 - q)(1 - 2q) + \frac{1}{3} N^3 s^3 q(1 - q) \left[ \frac{1}{5} - \frac{q(1 - q)}{6} \right] \]

\[= Ns q(1 - q) + \frac{1}{3} N^2 s^2 q(1 - q)(1 - 2q) - \frac{1}{3} N^3 s^3 q^2(1 - q)^2 \]

This expression is exactly the same, upto terms involving \(N^3 s^3\), as the expanded form of the formula of chance of fixation obtained by diffusion approximation and given in Kimura (1964).
The ratio of the expected response in the limit to the initial response of \( \frac{5}{2} q(1 - q) \) is given by

\[
(3.24) \quad \frac{u(q) - q}{\frac{5}{2} q(1 - q)} = 2N \left[ 1 + \frac{1}{3} Ns(1 - 2q) - \frac{1}{3} N^2 s^2 q(1 - q) \right]
\]

This shows that for \( q = \frac{1}{2} \), this ratio is \( 2N\left(1 - \frac{1}{12} N^2 s^2\right) \) but for \( q \) tending to 0 and 1, this tends respectively to \( 2N\left(1 + \frac{1}{3} Ns\right) \) and \( 2N\left(1 - \frac{1}{3} Ns\right) \).

If we wish to project the response, expressed above in terms of the gene frequency, on to the underlying quantitative trait, in the case of artificial selection, we have to assume the absence of natural selection and use the following relation between the selective advantage \( a \) and the intensity of selection \( \bar{l} \), imposed artificially, as given in Robertson (1960),

\[
(3.25) \quad a = \bar{l} \sigma/a
\]

where 'a' refers to the difference of units on the metric scale between the mean of the two homozygotes for the additive locus under consideration and \( \sigma \) is the phenotypic standard deviation. It may be noted that the haploid model is a fairly good approximation for the diploid situation with additive gene action, the diploid genetic variance merely being double that of the haploid genetic variance.
Summing the contributions of the individual loci and using the relation between $s$ and $\overline{t}$, the expected change in the limit in the character ($L$) under consideration is given by

\[ L = \Sigma a [u(q) - q] \]

\[ = \frac{\Sigma a^2 q(1 - q) + \frac{1}{3} \left( \frac{\Sigma a^3 q(1 - q) (1 - 2q)}{\sigma} \right)^2}{\frac{\Sigma a^3 q(1 - q) (1 - 2q)}{\sigma}} \]

\[ - \frac{1}{3} \left( \frac{\Sigma a^3 q(1 - q) (1 - 2q)}{\sigma} \right)^3 \]

If $\sigma_g$ and $\mu_{3g}$ denote the standard deviation and the third moment (about the mean) of the breeding values (Falconer 1960), we have

\[ \sigma_g^2 = \frac{1}{2} \Sigma a^2 q(1 - q) \]

\[ \mu_{3g} = \frac{1}{4} \Sigma a^3 q(1 - q) (1 - 2q) \]

\[ nV^* + \frac{1}{n} \sigma_{g^2}^2 = \frac{1}{4} \Sigma a^4 q^2(1 - q)^2 \]

where $V^*$ refers to the variance between the contributions of the $n$ different loci to the additive genetic variance of the character.

Hence $L$ is expressed as
(3.29) \[ L = 2N \left[ \bar{I} h \sigma_g + \frac{2}{3} N \frac{\mu_3 g}{\sigma_4^4} (\bar{I} h \sigma_g)^2 \right. \]

\[ \left. - \frac{2}{3} \frac{N^2}{n \sigma_g^2} (1 + \frac{n^2 V^*}{\sigma_4^4}) (\bar{I} h \sigma_g)^3 \right] \]

where \( h^2 = \frac{\sigma_g^2}{\sigma^2} \), the heritability of the trait. Since the initial change in the character is given by

(3.30) \[ \bar{I} = \sum a \delta q = \bar{I} h \sigma_g \]

the limit \( L \) can be finally expressed as

(3.31) \[ L = 2NI (1 + C_1 \bar{I} + C_2 \bar{I}^2) \]

where

(3.32) \[ C_1 = \frac{2}{3} N \frac{\mu_3 g}{\sigma_4^4} \]

(3.33) \[ C_2 = -\frac{2}{3} \frac{N^2}{n \sigma_g^2} \left( 1 + \frac{n^2 V^*}{\sigma_4^4} \right) \]
3.12 EXPANSION FOR THE EXPECTED CHANGE IN THE GENE FREQUENCY BY THE 
\( t \)th GENERATION

The vector of the expected change in the gene frequency of \( A_1 \) by 
the \( t \)th generation has been expressed in $2.11$ as the operation of 
the matrix \( (I - Q^t) \) on to \( R \), the vector of the expected selection 
limit. The former, when expressed in powers of \( s \) upto terms involving 
\( s^2 \), is given by

\[
(3.34) \quad (I - Q^t) = (I - Q^t) - s(Q^t), \quad - s^2(Q^t)^n
\]

whereas the latter has already been expressed as the linear function of 
\( X_1, X_2 \) and \( X_3 \) by $(3.18)$. The item by item operation of terms in 
\( (I - Q^t) \) on to those in \( R \) has been performed with the help of Table 1. 
The result expressed as a linear function of \( X_1, X_2 \) and \( X_3 \) is 
given by

\[
(3.35) \quad R(t) = (a_{10} + a_{11} \lambda_1^t + a_{12} \lambda_2^t) X_1 \\
+ (a_{20} + a_{21} \lambda_1^t + a_{22} \lambda_2^t) X_2 \\
+ (a_{30} + a_{31} \lambda_1^t + a_{32} \lambda_2^t + a_{33} \lambda_3^t) X_3
\]
where

\[(3.36) \quad a_{11} = -Ns \left[ 1 - \left( \frac{s}{4} \right) - \frac{(N - 1) \left( 2N^2 + N - 2 \right)}{5N - 3} \frac{s^2}{8} \right] \]

\[(3.37) \quad a_{12} = (Ns)^3 \left[ \frac{(N - 1) \left( 2N - 1 \right)}{8(5N - 3)(3N - 1)} \right] \]

\[(3.38) \quad a_{21} = -\left( \frac{1}{2} (1 - s/2) \right) \]

\[(3.39) \quad a_{22} = (Ns)^2 \left[ \frac{(2N - 1)}{4(3N - 1)} (1 - s/2) \right] \]

\[(3.40) \quad a_{31} = -\left( \frac{12N^2 - 9N + 1}{4N(5N - 3)} \right) \]

\[(3.41) \quad a_{32} = (Ns)^3 \left[ \frac{(2N - 1)}{2(3N - 1)} \right] \]

\[(3.42) \quad a_{33} = -\left( \frac{4N^5 - 4N^4 + 3N^3 + 7N^2 - 23N + 3}{4N(3N - 1)(5N - 3)(12N^2 - 11N + 3)} \right) \]

For initial gene frequency \( q \), the expected gene frequency by the \( t \)th generation, written as \( E(q_t) \), is then given by

\[(3.43) \quad E(q_t) = q + (a_{10} + a_{11} \lambda_1^t + a_{12} \lambda_2^t) q(1-q) + (a_{20} + a_{21} \lambda_1^t + a_{22} \lambda_2^t) q(1-q)(1-2q) + (a_{30} + a_{31} \lambda_1^t + a_{32} \lambda_2^t + a_{33} \lambda_3^t) . q(1-q) \left[ \frac{2N - 1}{40N - 6} - q(1-q) \right] \]
When $N$ becomes very large and $s$ very small such that $Ns$ is held constant, we get

\begin{align*}
\mathbb{E}(q_t) &= q + Ns \left[ 1 - \left( 1 - \frac{3}{100} Ns^2 \right) \exp(-t/2N) - \frac{N^2s^2}{10} \exp(-2t/2N) \right. \\
&\quad + \frac{N^2s^2}{12} \exp(-3t/2N) \\
&\quad - \frac{N^2s^2}{75} \exp(-6t/2N) \left. \right] q(1 - q) \\
&\quad + \frac{1}{3} N^2s^2 \left[ 1 - \frac{3}{2} \exp(-t/2N) + \frac{1}{2} \exp(-3t/2N) \right] q(1 - q) (1 - 2q) \\
&\quad - \frac{1}{3} N^3s^3 \left[ 1 - \frac{9}{5} \exp(-t/2N) + \exp(-3t/2N) - \frac{1}{5} \exp(-6t/2N) \right] q^2(1 - q)^2
\end{align*}

3.13 **Half-Life**

The half-life is the time $t_h$ (in terms of the number of generations) by which the expected change in the gene frequency of $A_1$ is half that expected in the limit. Hence we have to solve for $t$ in
the following equation

\[(3.45) \quad E(q_t) - q = (1/2) [u(q) - q]\]

after substituting \(u(q)\) and \(E(q_t)\) from (3.23) and (3.44) respectively. This gives an equation of the sixth order in \(x = \exp(-t/2N)\)

\[(3.46) \quad Ax^6 + Bx^3 + Cx^2 + Dx + E = 0\]

where

\[(3.47) \quad A = -\frac{1}{15} (Ns)^2 \left[ \frac{1}{5} - q(1 - q) \right]\]

\[(3.48) \quad B = \frac{1}{6} Ns (1 - 2q) + \frac{1}{3} (Ns)^2 \left[ \frac{1}{4} - q(1 - q) \right]\]

\[(3.49) \quad C = -\frac{1}{10} (Ns)^2\]

\[(3.50) \quad D = -1 - \frac{1}{2} Ns(1 - 2q) + \frac{3}{5} (Ns)^2 \left[ \frac{1}{20} + q(1 - q) \right]\]

\[(3.51) \quad E = \frac{1}{2} + \frac{1}{6} Ns (1 - 2q) - \frac{1}{6} (Ns)^2 q(1 - q)\]

Since \(x_0 = \frac{1}{2}\) is an approximate solution (Robertson 1960), an improved value of \(x\) can be obtained by applying Newton–Raphson method to the equation.
This is given by

\[ x = x_0 - \frac{Ax_0^6 + Bx_0^3 + Cx_0^2 + Dx_0 + E}{6Ax_0^5 + 3Bx_0^2 + 2Cx_0 + D} \]

\[ = \frac{1 + \frac{1}{4} Ns(1 - 2q) + \frac{5}{96} (Ns)^2 (\frac{1}{5} - q (1 - q)) - \frac{1}{8} N^2 s^2 q(1 - q)}{1 + \frac{3}{8} Ns(1 - 2q) + \frac{1}{20} N^2 s^2 (\frac{1}{5} - q (1 - q)) - \frac{5}{16} N^2 s^2 q(1 - q)} \]

Since \( t_h = -2N \log_e x \), it is approximately given by

\[ t_h = [1.4 + \frac{1}{4} Ns(1 - 2q) + 1.12 N^2 s^2 (0.16 - q(1 - q))]N \]

For \( Ns = 1 \) and \( q = \frac{1}{2} \), \( t_h \) is found to be 1.30N. For \( q \) tending to 0 or to 1, we have to make use of \( t_h = -2N \log_e x \) as such, without further approximating. That is

\[ t_h = -2N \left[ \log_e \frac{1}{2} + \log_e \left[ 1 + \frac{1}{4} Ns(1 - 2q) + \frac{5}{96} N^2 s^2 (\frac{1}{5} - q(1 - q)) \right] - \frac{1}{8} N^2 s^2 q(1 - q) \right] \]

\[ - \log_e \left[ 1 + \frac{3}{8} Ns(1 - 2q) + \frac{1}{20} N^2 s^2 (\frac{1}{5} - q(1 - q)) \right] - \frac{5}{16} N^2 s^2 q(1 - q) \] \]

For \( Ns = 1 \) and \( q \) tending to 0, the half-life is found to be 1.58N whereas for \( q \) tending to 1, it is found to be 1.03N. The half-lives
thus obtained for $N_s = 1$ and $q = \frac{1}{2}$, $q \to 0$ and $q \to 1$ are very close to those obtained by matrix iteration method and given in Hill and Robertson (1966) (see Fig. 11 in this paper). The half-life expressions discussed above pertain to the haploid selection process when stochastic variation in the gene frequency due to finite size of the population is taken into account. It has, however, a counterpart in the deterministic situation as well when the population size is assumed infinite. In this case the gene frequency in the $t^{th}$ generation is given by

$$(3.55) \quad q_t = \left(1 + \frac{s}{2}t\right) q / \left(1 + \left[1 + \left(1 + \frac{s}{2}\right)^t - 1\right] q\right)$$

The number of generations required to change the gene frequency by $(1 - q)/2$ is

$$(3.56) \quad t = \frac{\log (1 + 1/2q)}{\log (1 + s/2)}$$

For $q = \frac{1}{2}$ and positive and small $s$, this can be approximated by

$$(3.59) \quad t = 2 \log 2/s$$

When $s = 0.002$, about 700 generations are required to achieve the required change in gene frequency and there is no finite limit for it as $s \to 0$. In contrast to this, the half-life $t_h$, apparently, approaches the value $1.4N$ as $s$ tends to be small.
3.14 EXPANSION FOR THE MEAN AND VARIANCE OF TIME UNTIL FIXATION

In chapter II we have developed matrix formulae for the mean and variance of the time until fixation of $A_1$ disregarding the cases in which it is lost. However, in order to see the effect of the expansion of $Q$ in powers of $s$ on the mean and the variance of the distribution of time to fixation, the probability generating function of the number of steps needed for fixation of $A_1$ disregarding the cases in which it is lost, as introduced in the Appendix, is considered.

The matrix analogue of the probability generating function

$$\Pi(z) \text{ given by}$$

$$(3.58) \quad \Pi(z) = z D^{-1} (I - zQ)^{-1} (I - Q) U$$

can be expressed in terms of the eigen-roots $\lambda_i(s)$ and spectral matrices

$$(3.59) \quad H_i(s) = X_i(s) Y_i(s)$$

$i = 1, 2, \ldots \ldots (2N - 1)$ of $Q$, where $X_i(s)$ and $Y_i(s)$ are respectively the right and left eigen-vectors corresponding to the root $\lambda_i(s)$ and $s$ in the parenthesis indicates that all are functions of $s$. The resulting expression is given by

$$(3.60) \quad \Pi(z) = z^{2N-1} \sum_{i=1}^{2N-1} (1 - z \lambda_i(s))^{-1} (1 - \lambda_i(s)) D^{-1} H_i(s) U$$
Expanding (3.58) in powers of \( s \) and neglecting terms involving \( s^2 \) and higher powers of \( s \), we get

\[
(3.61) \quad \prod (z) = z^{D_{x_0}} (I - zQ_0)^{-1} (I - Q_0) X_0 + s \left[ \frac{d \prod (z)}{ds} \right]_{s=0}
\]

where

\[
(3.62) \quad X_0 = [X_{o1}, X_{o2}, \ldots, X_{o(2N-1)}], \quad X_{oi} = q_i
\]

\[
(3.63) \quad D_{x_0} = \text{diag} [q_1, q_2, \ldots, q(2N-1)]
\]

\[
(3.64) \quad \left[ \frac{d \prod (z)}{ds} \right]_{s=0} = 2Nz \left[ (I - zQ_0)^{-1} + D_{x_0}^{-1}(I - zQ_0)^{-1} \right]
\]

Expanding (3.61) in terms of roots and vectors of \( Q_0 \), it is found that the coefficient of \( s \) vanishes, giving

\[
(3.65) \quad \prod (z) = z^{2N-1} \sum_{i=1}^{2N-1} \frac{(1 - \lambda_i)}{(1 - z \lambda_i)} D_{x_0}^{-1} H_i D_{x_0}^{-1} e
\]

This shows that to the order \( s \), the probability generating function is the same as that for no selection case. It is a considerable simplification since it shows that all the moments of the distribution of time to fixation are independent of terms in \( s \).
Differentiating \( \Pi(z) \) once with respect to \( z \) and setting \( z = 1 \), we get the vector for the mean time until fixation as

\[
\mu = \sum_{i=1}^{2N-1} k_i (1 - \lambda_i)^{-1} D^{-1} \tilde{x}_i
\]

where

\[
k_i = \sum_{j=1}^{2N-1} \gamma_{ij} q_j
\]

\( \gamma_{ij} \) being the \( j \)th element of the \( i \)th left-eigen vector \( Y_i \) of \( Q_0 \).

Differentiating \( \Pi(z) \) twice with respect to \( z \) and setting \( z = 1 \), we get the expected value of \( t(t-1) \) and adding the expected value of \( t \) we get the second moment (about the origin) vector \( \mu_2 \) as

\[
\mu_2 = \sum_{i=1}^{2N-1} k_i (1 + \lambda_i) (1 - \lambda_i)^{-2} D^{-1} \tilde{x}_i
\]

These relations show that explicit expressions for the moments of the distribution of time to fixation are expressible only in terms of all the roots and eigen-vectors of \( Q_0 \), the evaluation of the latter requiring the use of computer. Hence the mean and the variance of time to fixation have been studied by evaluating the matrix formulae on the computer in Chapter IV.
The diffusion approximation for the mean time until fixation of a particular allele has recently been given by Kimura and Ohta (1968). For a neutral gene and initial gene frequency tending to zero, the mean time is shown to be $\mu N_e$ where $N_e$ is the variance effective number which may differ from the actual population number $N$ if the mating is not random or if the distribution of the number of offspring does not follow a Poisson distribution. The variance effective number of a population is defined as the size of an idealized population that would have the same amount of random gene frequency drift as the population under consideration (Kimura and Crow, 1963). The diffusion approximation for the variance of the time until fixation has, however, not been discussed by Kimura and Ohta (1968).

Let us consider a mutant allele $A_2$ with frequency $q$ (so that the frequency of the normal allele $A_1$ is $1 - q$) in a diploid population of $N$ individuals with variance effective number $N_e$. Let $u(q, t)$ be the probability that $A_2$ gets fixed by the $t^{th}$ generation starting with frequency $q$ at $t = 0$. Let

\[
(3.69) \quad T(q) = \int_0^\infty t \frac{\partial u(q, t)}{\partial t} \, dt
\]
\( (3.70) \quad S'_1(q) = \int_0^\infty t^2 \frac{\partial u(q, t)}{\partial t} \, dt \)

Then

\( (3.71) \quad M'_1(q) = \frac{T'_1(q)}{u(q)} \)

\( (3.72) \quad V'_1(q) = \frac{S'_1(q)}{u(q)} \)

represent respectively the average and the second moment about the origin of the length of time until the mutant allele becomes fixed in the population excluding the cases in which it is lost from it. Here \( u(q) \) is the probability of ultimate fixation such that

\( (3.73) \quad u(q) = \lim_{t \to \infty} u(q, t) \)

If \( \alpha(q) \) and \( \beta(q) \) represent the mean and the variance of the rate of change in the frequency of \( A_2 \) per generation, then following Kimura (1962), \( u(q, t) \) satisfies the Kolmogorov backward equation

\( (3.74) \quad \frac{\partial u(q, t)}{\partial t} = \frac{1}{2} \beta(q) \frac{\partial^2 u(q, t)}{\partial q^2} + \alpha(q) \frac{\partial u(q, t)}{\partial q} \)

Following the technique of Kimura and Ohta (1968), the set of
differential equations for $T_1(q)$ and $S_1(q)$ are respectively given by

\[
\begin{align*}
\frac{1}{2} \beta(q) \frac{d^2 T_1(q)}{dq^2} + a(q) \frac{d T_1(q)}{dq} + u(q) &= 0 \\
\frac{1}{2} \beta(q) \frac{d^2 S_1(q)}{dq^2} + a(q) \frac{d S_1(q)}{dq} + 2T_1(q) &= 0
\end{align*}
\]

The former differential equation has been derived and solved by Kimura and Ohta (1968) with boundary conditions

\[
\begin{align*}
\lim_{q \to 0} T_1(q) &= K_1 u(q), \quad K_1 \text{ being a finite quantity} \\
T_1(1) &= 0
\end{align*}
\]

It is shown by them that

\[
\begin{align*}
K_1 &= 4N_e \\
K_1(q) &= -4N_e \frac{(1 - q)}{q} \log_e (1 - q)
\end{align*}
\]

For the second moment (about the origin) of the length of time until fixation of $A_2$, we proceed to transform (3.76) into a differential equation for $V_1(q)$ by differentiating $S_1(q) = V_1(q)u(q)$ twice and substituting in (3.76).
This gives

\[ \frac{1}{2} \beta(q) \frac{d^2 V_1(q)}{dq^2} + [\alpha(q) + \frac{\beta(q) G(q)}{u(q)}] \frac{d V_1(q)}{dq} + 2M_1(q) = 0 \]

where

\[ G(q) = \frac{d u(q)}{dq} \]

The boundary conditions to be imposed are

\[ \text{Lim. } V_1(q) = K_2, \quad q \to 0, \quad K_2 \text{ being a finite quantity} \]

\[ V_1(1) = 0 \]

In the case of random drift alone, we have

\[ \alpha(q) = 0 \]

\[ \beta(q) = q(1 - q) / 2N_e \]

\[ u(q) = q \]

\[ G(q) = 1 \]
The differential equation, then reduces to

\[ 3.89 \quad \frac{d^2 V_1(q)}{dq^2} + \frac{2}{q} \frac{dV_1(q)}{dq} + \frac{8N e M_1(q)}{q(1-q)} = 0 \]

The solution of this differential equation after substituting for \( M_1(q) \) is given by

\[ 3.90 \quad V_1(q) = \frac{B - A}{q} - 32N e^2 [(1 - \frac{1}{q} - \log q) \log (1 - q) - F(q)] \]

where \( A \) and \( B \) are constants of integration and \( F(q) \) is given by

\[ 3.91 \quad F(q) = \int \frac{\log q}{1 - q} \, dq \]

Using the boundary conditions, we get

\[ 3.92 \quad B = A + 32N e^2 F(1) \]

\[ 3.93 \quad K_2 = A - 32N e^2 \left[ 1 + \int_0^1 \frac{\log q}{1 - q} \, dq \right] \]
Thus \( V_1 (q) \) is given by

\[
(3.94) \quad V_1 (q) = 32N_e^2 \left[ - \int_0^1 \frac{\log q}{1 - q} \, dq - (1 - \frac{1}{q} - \log q \log (1 - q)) \right] \\
+ (1 - \frac{1}{q}) \left[ K_2 + 32N_e^2 \left( \int_0^1 \frac{\log q}{1 - q} \, dq + 1 \right) \right]
\]

Hence if

\[
(3.95) \quad K_2 = - 32N_e^2 \left( \int_0^1 \frac{\log q}{1 - q} \, dq + 1 \right)
\]

we get

\[
(3.96) \quad V_1 (q) = 32N_e^2 \left[ - (1 - \frac{1}{q}) \log (1 - q) + \log q \log (1 - q) \right. \\
- \left. \int_0^1 \frac{\log q}{1 - q} \, dq \right]
\]

Now

\[
(3.97) \quad \int (q) = F(q) - F(1) \\
= - \int_1^q \frac{\log q}{q - 1} \, dq
\]

is a dilogarithm whose series expansion is given by
(3.98) \[ f(q) = \sum_{k=1}^{\infty} (-1)^k (q - 1)^k / k^2 \]

and there is a functional relationship between \( f(q) \) and \( f(1-q) \) given by

(3.99) \[ f(q) + f(1-q) = -\log_e q \log_e (1-q) + \frac{\pi^2}{6} (1 > q > 0) \]

(for these results on Dilogarithm see Abramowitz and Stegun 1965)

Hence \( V_1(q) \) reduces to

(3.100) \[ V_1(q) = 32N_e^2 \left[ \frac{1-q}{q} \log_e (1-q) + \frac{\pi^2}{6} - \sum_{k=1}^{\infty} \frac{q^k}{k^2} \right] \]

Also

(3.101) \[ \lim_{q \to 0} V_1(q) = K_2 \]

\[ = 32N_e^2 \left( \frac{\pi^2}{6} - 1 \right) \]

The variance of time until fixation for \( q \to 0 \) is then given by

(3.102) \[ V = K_2 - K_1^2 \]

\[ = 16N_e^2 \left( \frac{\pi^2}{3} - 3 \right) \]

This gives a coefficient of variation of about 53.8\%.
In this chapter numerical results on selection at a diallelic locus with binomial transition probabilities are presented. The ratios of the response to selection in the limit to the initial response, analytically treated in Chapter III in the case of additive genes, are obtained exactly (using matrix formula) for additive, recessive and dominant genes. For additive genes results are presented for the mean and the coefficient of variation of time to fixation. A comparison between the time to fixation, loss and homozygosity is also made in this case. For recessive and dominant genes however, only the mean time to fixation are presented. All numerical values were obtained with the help of the KDF9 computer of Edinburgh University.

4.1 ADDITIVE GENES

The matrix formulae (2.15), (2.19), (2.20) and (2.22) discussed in Chapter II and analogous formulae for time to loss and homozygosity were used for obtaining computer results presented in this section.

4.11 RATIO OF SELECTION LIMIT TO INITIAL RESPONSE

It is shown in Robertson (1960), that the chance of fixation of a gene and hence the selection limit are dependent on $N_s$ only so that these can be evaluated for a given $N$ at a series of values of $s$. 
This would give results for a series of values of \( N_s \) applicable to values of \( N \) other than the one used if \( s \) is suitably adjusted. Hence the ratios have been worked out for \( N = 8 \) and \( N_s = 0.031 \) to \( N_s = 8000 \). Further, the formulae (3.24) and (3.31) show that these ratios can be expressed in terms of the population size. The factor \((\text{ratio} / N)\) has, therefore, been presented in Table 2 for initial gene frequencies 0.0625, 0.5000 and 0.9375. It is apparent that for \( q = 0.5000 \) and 0.9375 it decreases as \( N_s \) increases. For \( q = 0.0625 \), it increases as \( N_s \) increases till \( N_s = 2 \) after which it starts decreasing. When \( N_s \) is as small as 0.031, the value of this factor is greater than 2 when \( q \) is less than \( \frac{1}{2} \) but less than 2 when \( q \) is greater than \( \frac{1}{2} \). At \( q = \frac{1}{2} \), it is equal to 2. When \( N_s \) is as high as 8000, it is about 1.7, 0.5 and 0.4 for \( q < \frac{1}{2} \), \( = \frac{1}{2} \) and \( > \frac{1}{2} \) respectively. It always decreases as gene frequency increases at a particular value of \( N_s \).

4.12 MEAN AND VARIABILITY OF TIME TO FIXATION

The evaluation of matrix formulae on the computer depends on the population size \( (N) \) and the selective coefficient of the gene \( (s) \). But it is known (Robertson, 1960 and Hill and Robertson, 1966) that, under the conditions in which diffusion approximation holds, the time scale of the selection process is proportional to \( N \) and therefore if
TABLE 2: Values of \((\text{ratio} / N)\) as calculated by the transition matrix method for different values of \(N_s\) (additive genes)

<table>
<thead>
<tr>
<th>(N_s)</th>
<th>INITIAL FREQUENCY</th>
<th>((q))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.031</td>
<td>2.016 2.000</td>
<td>1.984</td>
</tr>
<tr>
<td>0.063</td>
<td>2.031 1.999</td>
<td>1.969</td>
</tr>
<tr>
<td>0.125</td>
<td>2.062 1.997</td>
<td>1.937</td>
</tr>
<tr>
<td>0.250</td>
<td>2.121 1.990</td>
<td>1.873</td>
</tr>
<tr>
<td>0.500</td>
<td>2.233 1.927</td>
<td>1.743</td>
</tr>
<tr>
<td>1.000</td>
<td>2.418 1.854</td>
<td>1.492</td>
</tr>
<tr>
<td>2.000</td>
<td>2.611 1.535</td>
<td>1.080</td>
</tr>
<tr>
<td>4.000</td>
<td>2.490 0.970</td>
<td>0.648</td>
</tr>
<tr>
<td>8.000</td>
<td>1.692 0.500</td>
<td>0.383</td>
</tr>
</tbody>
</table>
the time is measured in units of $N$, the pattern of the selection process is determined by the parameter $Ns$ at a given initial gene frequency. The mean time has, therefore, been expressed in units of $N$. In order to see whether the mean time and the coefficient of variation for fixation of a gene, disregarding the cases in which it is lost, is a function of $Ns$, a comparison of these for a few population sizes at a particular value of $Ns$ is shown in Tables 3 and 4 respectively. There is found to be a fair degree of stability in these quantities due to variations in $N$ at a fixed value of $Ns$. The dependence of the mean time and the coefficient of variation on $Ns$ has, therefore, been graphically shown in Figures 2 and 3 respectively for initial gene frequencies 0.0312, 0.5000 and 0.9687. Both the mean and the coefficient of variation decreases as $Ns$ increases. For a fixed $Ns$, however, the mean time is highest at low initial gene frequency and lowest at high initial gene frequency whereas the coefficient of variation is highest at high gene frequency and lowest at low gene frequency. When $Ns = 1$ and the initial gene frequency is 0.5, the mean time is about $2N$ with a percent coefficient of variation of about 70, but for low initial gene frequency of 0.0312, the mean rises to about $3N$ with a percent coefficient of variation of about 50. It is interesting to observe that genic selection shortens the fixation time but increases the rate of steady decay (Kimura, 1957).
TABLE 3 The average number of generations / N until fixation of a gene with selective values as calculated by the transition matrix method for different population sizes (N).

<table>
<thead>
<tr>
<th>Ns</th>
<th>N</th>
<th>Initial frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>0.46</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>0.74</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>0.82</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>1.29</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1.40</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2.03</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2.07</td>
</tr>
</tbody>
</table>
TABLE 4. The coefficient of variation (%) of the number of generations until fixation of a gene with selective value $a$ as calculated by the transition matrix method for different population sizes ($N$).

<table>
<thead>
<tr>
<th>$N_a$</th>
<th>$N$</th>
<th>Initial frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>28.36</td>
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<tr>
<td>8</td>
<td>16</td>
<td>33.04</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>35.33</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>42.59</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>45.24</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>53.12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>54.70</td>
</tr>
</tbody>
</table>
Fig. 2 Average number of generations/N until fixation of a gene acting additively. The curves are drawn for different initial gene frequencies.
Fig. 3 Coefficient of variation (%) of number of generations until fixation of a gene acting additively. The curves are drawn for different initial gene frequency.
When there is no selection, the mean increases linearly with $N$ and the coefficient of variation is practically steady. However, in the case of mean time, the slopes and in the case of coefficient of variation, the average values, vary with initial gene frequency. These variations are shown respectively in Figures 4 and 5. The slope increases but the average percent coefficient of variation declines as the gene frequency decreases from 1 to 0. Extrapolating from these graphs it is found that the limiting value of the slope and the average percent coefficient of variation are about 4 and 55 respectively as gene frequency approaches zero, as against the diffusion approximation results of 1 and about 54 respectively.

4.13 COMPARISONS OF TIMES TO FIXATION, LOSS AND HOMOZYGOSITY

It is interesting to compare the mean and the variability of the time to fixation of a particular allele with those of the time to loss and to homozygosity. As far as diffusion approximation to the mean times are concerned, the results of Ewens (1964) and Kimura and Ohta (1968), provide the following expressions for a neutral gene with initial frequency $q$. 
Fig. 4. Slope of average number of generations until fixation on population size at different values of initial gene frequency.
Fig. 5. Coefficient of variation (%) of number of generations until fixation averaged over population sizes between 2 to 16 at different values of initial gene frequency.
Mean time until fixation

\[-4N_e \frac{1 - q}{q} \log_e (1 - q)\]

\text{Kimura & Ohta (1968)}

Mean time until loss

\[-4N_e \frac{q}{1 - q} \log_e q\]

\text{Kimura & Ohta (1968)}

Mean time until homozygosity

\[-4N_e [q \log_e q + (1 - q) \log_e (1 - q)]\]

\text{Ewens (1964)}

In these formulae $N_e$ is the variance effective number which may differ from the actual population number $N$ if the mating is not random or if the distribution of the number of offsprings does not follow a Poisson distribution. According to Crow and Morton (1955), the formula connecting $N$ and $N_e$ is given by

\[
\left(\mu_k\right)_{N_e} = \frac{2N}{1 - F' + (1 + F') \sqrt{\mu_k}}
\]

where $F'$ is Wright's coefficient of inbreeding used as a measure
of the departure from random mating zygotic proportions among the parents, $\mu_k$ and $V_k$ are the mean and the variance of the number of surviving offspring per parent. When $q = 1/(2N)$ and $N$ is very large, the mean time until fixation is close to $4N_e$ while that until loss is $\frac{2N_e}{N} \log_e 2N$ so that the mean time until homozygosity should approach the value $\frac{2N_e}{N} \log_e 2N$. These comparisons, on the basis of transition matrix methods, are presented in Figures 6 and 7 for $N_s = 0$ and 2 respectively. The dotted lines refer to time until fixation and until loss (marked respectively 1 and 2 in the figures) whereas solid line (marked 3 in the figures) refers to time until homozygosity. When $N_s = 0$ and initial frequency of gene is 0.5, all the three curves give the same value of about $2.55N$ as against the diffusion approximation of $-4N_e \log_e \frac{1}{2} = 2.8N_e$. The diffusion approximation, therefore, overestimates the mean time. Comparison with the half-life of $1.4N_e$, shows that the half-life is attained much earlier than the mean time. For initial gene frequencies greater than or less than 0.5, the three curves differ and as expected the curve 3 always lies between the curves 1 and 2.

For $q < 0.5$ the mean time until homozygosity is more near the mean time until loss than that until fixation so that when $q = 1/(2N)$, the mean time until loss is $0.79N$ as against that until homozygosity.
Fig. 6. Average number of generations/N until fixation (1), loss (2) and homozygosity (3) at different values of initial gene frequency. (Ns = 0).
Fig. 7. Average number of generations/N until fixation (1), loss (2) and homozygosity (3) at different values of initial gene frequency. (Ns = 2).
of \(1.02N\). The difference is expected to decrease as the computer results from higher values of \(N\) are compared. In the limit, these should, therefore, be the same as expected from the diffusion approximation. For \(q > 0.5\), the mean time until homozygosity gets nearer to the mean time until fixation. When \(N_s = 2\), the mean time until homozygosity is found to be practically the same as the mean time until fixation unless the gene frequency is well below 0.5. It is interesting to observe that, while with no selection, the maximum mean time until homozygosity occurs at \(q = 0.5\), with selection this maximum shifts and occurs at gene frequency less than 0.5.

This shift has further been found to increase as selection becomes more intense.

The comparisons of the coefficients of variation are shown in Figures 8 and 9 for \(N_s = 0\) and 2 respectively. As before dotted lines refer to time until fixation (1) and loss (2) whereas solid line (3) refers to homozygosity. When \(N_s = 0\) and initial gene frequency is 0.5, all the three curves give the same value of about 76%. For \(q < 0.5\), the coefficient of variation for time until homozygosity is more near the mean time until loss than that until fixation. For \(q > 0.5\), it gets nearer to that until fixation. When \(N_s = 2\), the coefficients of variation for homozygosity and fixation are practically the same unless \(q\) is well below 0.5. It is interesting to note that the coefficient of variation of time until homozygosity is minimum at \(q = 0.5\) with no selection but this minimum shifts to \(q < 0.5\) with selection.
Fig. 8. Coefficient of variation (%) of number of generations until fixation (1), loss (2) and homozygosity (3) at different values of initial gene frequency. (Ns = 0).
Fig. 9. Coefficient of variation (%) of number of generations until fixation (1), loss (2) and homozygosity (3) at different values of initial gene frequency. (Ns = 2).
4.2 RECESSIVE AND DOMINANT GENES

The matrix formulae used in the case of additive genes were also used for obtaining results in respect of recessive and dominant genes with the difference that the change in the gene frequency in one-step was fed in as

\[ \delta q_1 = \frac{(1 + \frac{s}{2}) q_1^2 + q_1 (1 - q_1) (1 + \frac{h}{2})}{1 - \frac{s}{2} (1 - 2q_1) + h q_1 (1 - q_1)} \]

where \( h = -s \) for recessive genes and \( h = +s \) for dominant genes.

4.21 RATIO OF SELECTION LIMIT TO INITIAL RESPONSE

The factors (ratio / \( N \)) are given in Tables 5 and 6 respectively for completely recessive and completely dominant genes. In the case of recessive genes, it is found that for \( q = 0.5 \) and 0.9375 the factor decreases as \( N_s \) increases. For \( q = 0.0625 \) it increases as \( N_s \) increases till \( N_s = 0.25 \) after which it starts decreasing. When \( N_s \) is as small as 0.031, its value is 11.14 for \( q = 0.0625 \). This is in contrast with the additive genes where it is only 2.016. For \( q = 0.5000 \) and \( q = 0.9375 \), however, the factor is less than their corresponding values in the additive case. When \( N_s \) is as high as 8.00 it is about 5.10, 0.38 and 0.20 for \( q < \frac{1}{2}, = \frac{1}{2} \) and \( > \frac{1}{2} \) respectively. In the case of dominant genes, however, it is found that
Values of \((\text{ratio} / N)\) as calculated by the transition matrix method for different values of \(N_s\) (recessive genes).

<table>
<thead>
<tr>
<th>(N_s)</th>
<th>INITIAL FREQUENCY ((q))</th>
<th>(0.0625)</th>
<th>(0.5000)</th>
<th>(0.9375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.031</td>
<td>11.141</td>
<td>1.995</td>
<td>1.374</td>
<td></td>
</tr>
<tr>
<td>0.063</td>
<td>11.150</td>
<td>1.989</td>
<td>1.356</td>
<td></td>
</tr>
<tr>
<td>0.125</td>
<td>11.165</td>
<td>1.977</td>
<td>1.322</td>
<td></td>
</tr>
<tr>
<td>0.250</td>
<td>11.177</td>
<td>1.950</td>
<td>1.254</td>
<td></td>
</tr>
<tr>
<td>0.500</td>
<td>11.142</td>
<td>1.884</td>
<td>1.125</td>
<td></td>
</tr>
<tr>
<td>1.000</td>
<td>10.874</td>
<td>1.719</td>
<td>0.900</td>
<td></td>
</tr>
<tr>
<td>2.000</td>
<td>9.920</td>
<td>1.361</td>
<td>0.595</td>
<td></td>
</tr>
<tr>
<td>4.000</td>
<td>7.913</td>
<td>0.829</td>
<td>0.338</td>
<td></td>
</tr>
<tr>
<td>8.000</td>
<td>5.101</td>
<td>0.375</td>
<td>0.196</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 6  Values of \((\text{ratio}/N)\) as calculated by the transition matrix method for different values of \(N_s\) (dominant genes)

<table>
<thead>
<tr>
<th>(N_s)</th>
<th>0.0625</th>
<th>0.5000</th>
<th>0.9375</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.031</td>
<td>1.409</td>
<td>2.005</td>
<td>11.118</td>
</tr>
<tr>
<td>0.063</td>
<td>1.426</td>
<td>2.010</td>
<td>11.105</td>
</tr>
<tr>
<td>0.125</td>
<td>1.461</td>
<td>2.018</td>
<td>11.073</td>
</tr>
<tr>
<td>0.250</td>
<td>1.532</td>
<td>2.030</td>
<td>10.994</td>
</tr>
<tr>
<td>0.500</td>
<td>1.670</td>
<td>2.039</td>
<td>10.765</td>
</tr>
<tr>
<td>1.000</td>
<td>1.918</td>
<td>1.939</td>
<td>10.066</td>
</tr>
<tr>
<td>2.000</td>
<td>2.194</td>
<td>1.700</td>
<td>8.178</td>
</tr>
<tr>
<td>4.000</td>
<td>2.014</td>
<td>1.104</td>
<td>5.270</td>
</tr>
<tr>
<td>8.000</td>
<td>1.184</td>
<td>0.625</td>
<td>3.191</td>
</tr>
</tbody>
</table>
for $q = 0.9375$ the factor decreases as $N_s$ increases but for $q = 0.0625$ and $0.5000$ it increases initially and then decreases afterwards with the increase in $N_s$ values. When $q = 0.5$, it increases from 2.005 (when $N_s = 0.031$) to 2.039 (when $N_s = 0.500$) and decreases thereafter. For $q = 0.0625$, however, it increases from 1.409 (when $N_s = 0.031$) to 2.194 (when $N_s = 2.000$) and decreases thereafter. When $N_s = 0.031$ the factor increases as $q$ increases from 0.0625 to 0.9375. This trend continues up to $N_s = 1.00$ but when $N_s$ is equal to 2 or greater then 2, it is lowest at $q = 0.5000$ and highest at $q = 0.9375$.

4.22 MEAN TIME TO FIXATION

The behaviours of the mean time until fixation of a recessive and dominant gene with variation in $N_s$ are shown in Figures 10 and 11 for initial gene frequencies 0.0625, 0.5000 and 0.9375. As found, in the case of additive genes, the time to fixation decreases as $N_s$ increases, as far as a recessive gene is concerned but for a dominant gene, it increases initially for small values of $N_s$ and then decreases. For a gene with low frequency the maximum occurs at a value of $N_s < 1$ whereas for gene frequency as 0.5 it occurs at $N_s = 1$ and for high gene frequency it occurs at $N_s > 1$. For a rare dominant gene, therefore, the limiting value of the mean time until fixation may well be above $4N_e$. For gene frequency equal to half ($N_s = 1$) a dominant gene would take about $2.77N$ generations to fixation. On the other hand a rare recessive gene at $N_s = 1$ takes about $3.18N$ generations. It would
Fig. 10 Average number of generations/N until fixation of a recessive gene. The curves are drawn for different initial recessive frequencies.
Fig. 11  Average number of generations/N until fixation of a dominant gene. The curves are drawn for different initial dominant frequencies.
take $2.14N$ generations if it is as frequent as its alternative allele. Thus a gene takes less time to reach fixation when it is recessive than when it is dominant. It is interesting to compare this result with those of Kimura (1957) on the behaviour of the final rate of decay for recessive and dominant genes. Selection towards dominants decreases the final rate of decay whereas selection against dominants increases it.
The theory developed in Chapter II for selection with random drift in the case of single locus with three alleles can be applied to specific genetic models. In this section numerical results on the chance of fixation of a particular allele $A_1$, the average number of generations taken until its fixation and the average time to homozygosity are presented when the transition probabilities are of the trinomial type and the relative selective advantages of $A_1$, $A_2$ and $A_3$ alleles are respectively $(1 + s_1/2)$, $(1 + s_2/2)$ and 1.

Suppose first there are no selective forces operating. Then starting with a given pair of frequencies $q_{11} = i_1/(2N)$, $q_{21} = i_2/(2N)$ of alleles $A_1$ and $A_2$ respectively (with $1 - q_{11} - q_{21} =$ frequency of $A_3$), in lines of constant breeding size of $N$ individuals, we can consider the second generation as derived from the first by the sampling of groups of $2N$ haploid sets, the gene frequencies in the different groups being distributed trinomially with pairs of means $2Nq_{11}$ and $2Nq_{21}$ and index $2N$. The next generation is then the repetition of this process, each line giving rise to a group of lines whose gene frequencies are trinomially distributed about the pairs of means of the parent line. Now let $A_1$ genes have a selective advantage of $(1 + s_1/2)$, $A_2$ genes have a selective advantage of $(1 + s_2/2)$ and $A_3$ genes have a selective advantage of unity where $s_1$ and $s_2$
are small and positive. This means that while the selective advantage of \( A_1 \) over \( A_3 \) is \( (1 + s_1/2) \) that of \( A_1 \) over \( A_2 \) is \( (1 + (s_1 - s_2)/2) \) approximately. Assuming that selection operates before sampling of gametes, the gene frequencies of \( A_1 \) and \( A_2 \) in the different groups are distributed trinomially with means \( 2Nq'_{11} \) and \( 2Nq'_{21} \) and index \( 2N \), where \( q'_{11} \) and \( q'_{21} \) are the gene frequencies of \( A_1 \) and \( A_2 \) after selection and are given by

\[
(5.1) \quad q'_{11} = q_{11} + \frac{1}{2} s_{11} q_{11} (1 - q_{11}) - \frac{1}{2} s_{21} q_{11} q_{21} \quad (1 + q_{11} s_{1/2} + q_{21} s_{2/2})
\]

and

\[
(5.2) \quad q'_{21} = q_{21} + \frac{1}{2} s_{21} q_{21} (1 - q_{21}) - \frac{1}{2} s_{11} q_{11} q_{21} \quad (1 + q_{11} s_{1/2} + q_{21} s_{2/2})
\]

respectively. Here \( \delta q_{11} \) and \( \delta q_{21} \) are the changes in the mean frequencies of \( A_1 \) and \( A_2 \) respectively due to selection in one step when their frequencies in the previous generations are respectively \( q_{11}/(2N) \) and \( q_{21}/(2N) \). Thus with haploid selection and trinomial
sampling, the conditional probability that there are \( j_1 A_1 \) genes and \( j_2 A_2 \) genes out of \( 2N \) genes after one generation, given that there were \( i_1 A_1 \) genes and \( i_2 A_2 \) genes out of \( 2N \) in the previous generation, \( P(i_1 \ i_2)(j_1 \ j_2) \) are given by

\[
(5.3) \quad P(i_1 \ i_2)(j_1 \ j_2) = \frac{(2N)!}{j_1! \ j_2! \ (2N - j_1 - j_2)!} (q'_1)^{j_1} (q'_2)^{j_2} \]

\[
\cdot (1 - q'_1 - q'_2)^{2N - j_1 - j_2}
\]

These probabilities, therefore, determine the \( P', Q' \) and the components of \( Q' \) introduced in section 2 for the case of single locus with three alleles. With the help of the matrix formulae (2.33), (2.34) and (2.36) the chance of fixation of \( A_1 \) can be determined and in addition using (2.54), (2.55) and (2.57) gives the average time until its fixation.

For average time until homozygosity matrix formulae (2.43), (2.44), (2.45) and (2.46) can be used. However, since the fixation of either \( A_2 \) or \( A_3 \) reduces the problem to that of a locus with two alleles, it is sufficient to consider only those situations in which initially neither of the \( A_2 \) and \( A_3 \) are absent. This means we have to use only the relations (2.36), (2.57) and (2.46). These have been evaluated numerically on the KDF9 computer of Edinburgh University. The capacity of the computer did not permit the use of a population size greater than six. Hence all the results presented relate to \( N = 6 \). The computer
programme developed for this purpose made regular use of the KDF9 matrix pack.

5.1 CHANGE OF FIXATION OF A₁

In order to present results in a meaningful way it is desirable to examine the dependence of the change in the frequency of A₁ on the selective coefficients of the other alleles and the population size. First we consider an infinite population and determine the parameters which govern the changes in the gene frequency of A₁ initially and in subsequent generations. Thereafter we examine how these parameters can be combined with the population size when a finite population is considered.

Consider three alleles A₁, A₂ and A₃ with selection coefficients \((1 + s₁/2), (1 + s₂/2)\) and 1 with frequencies \(q₁, q₂\) and \(q₃\) respectively. The superiority of A₁ over A₂ is \((s₁ - s₂)/2\) whereas that of A₁ over A₃ is \(s₁/2\). This gives an average superiority \(\bar{s}\) and the variance in superiority \(V_m\) of A₁ over A₂ and A₃ considered together as a group, given by

\[
(5.4) \quad \bar{s} = \frac{1}{2} (s₁ - rs₂)
\]

\[
(5.5) \quad V_m = \frac{1}{4} r (1 - r) s₂²
\]

where

\[
(5.6) \quad r = q₂ / (q₂ + q₃).
\]
The variance in the selective advantage of the three alleles can be partitioned as

\[(5.7) \quad V_s = q_1 (1 - q_1) \overline{s^2} + (q_2 + q_3) V_m \]

\[= \frac{1}{2} \sigma_a^2 + \frac{1}{2} \sigma_m^2 \]

where \(\sigma_a^2\) is the contribution of the locus to the additive genetic variance of the genotypes when the three allele system is collapsed into two allele system and \(\sigma_m^2\) is the component of total genetic variance due to the multiple allelic effect. That is the total additive genetic variance can be partitioned into two components, one reflecting the contribution of the locus with two effective alleles \(A_1\) and \(\overline{A}_2\) where \(\overline{A}_2\) refers to the group of \(A_2\) and \(A_3\) and the other emphasizing the contribution due to the distinction made between the two alleles \(A_2\) and \(A_3\) on the basis of their different selective advantages. This idea of distinguishing multiple alleles on the basis of their quantitative effects was first introduced by Narain (1965) in connection with the description of gene action in continuous variation when multiple alleles are taken into account. A similar partitioning was suggested for metric traits for describing the components of genetic variance. Thus \(V_m\) can be generalized and defined as multiple allelic variance in the selective advantages of the genotypes. If \(q_{1'}^i\) and \(q_{1''}^i\) are the gene frequency of \(A_1\) after the
first and the second generation of selection respectively then, approximately

\[(5.8) \quad q_1' = q_1 + \bar{\alpha} q_1 (1 - q_1)\]

neglecting terms involving powers of \(s_2\) greater than one.

\[(5.9) \quad q_1'' = q_1' + \bar{\alpha}' q_1' (1 - q_1') = q_1' + (\bar{\alpha} - \bar{V}_m) q_1 (1 - q_1) + \bar{\alpha}^2 q_1 (1 - q_1) (1 - 2q_1)\]

neglecting terms involving powers of \(s_2\) greater than two and where

\[(5.10) \quad \bar{\alpha}' = \frac{1}{2} (s_1 - r' s_2)\]

\[(5.11) \quad r' = r[1 + (1 - r) (1 - r \frac{s_2}{2}) \frac{s_2}{2}]\]

\[(5.12) \quad q_1' (1 - q_1') = q_1 (1 - q_1) [1 + \bar{\alpha} (1 - 2q_1) - \bar{\alpha}^2 q_1 (1 - q_1)]]\]

From (5.8) and (5.9) it is clear that, in an infinite population, the change in the frequency of \(A_1\) depends on \(\bar{\alpha}\) and \(\bar{V}_m\) whereas in the two allele case it depends only on the superiority in selective advantage of one allele over the other. In the present case, when \(\bar{V}_m = 0\), the change in the gene frequency is simply \(\bar{\alpha} q_1 (1 - q_1)\) if
the term involving \( s^2 \) is neglected and this, in fact, corresponds to a two allele situation where \( A_2 \) and \( A_3 \) are indistinguishable iso-alleles. The allele \( A_1 \) increases in frequency and eventually gets fixed. But when \( \bar{s} = 0 \), we get

\[(5.13) \quad q_1' = q_1 \]

\[(5.14) \quad q_1'' = q_1 - V_m q_1 (1 - q_1) \]

This shows that in the first generation, the frequency of \( A_1 \) does not change and in the second generation it decreases; the decrease being \( -V_m q_1 (1 - q_1) \). Under these conditions, it would eventually be eliminated from the population. When neither of \( \bar{s} \) and \( V_m \) are zero, then initially the allele would increase in frequency but in the subsequent generations it would increase and get eventually fixed when the values of \( \bar{s}, V_m \) and \( q_1 \) make \( (q_1'' - q_1') \) as positive. For \( q_1 \) equal to or less than half, the condition for this to happen is \( \bar{s} > V_m \).

When the population is finite we write \( \phi(q_1, q_2, x_1, x_2; t) \) for the probability density that the frequencies of \( A_1 \) and \( A_2 \) become \( x_1 \) and \( x_2 \) at the \( t \)th generation given that their frequencies are \( q_1 \) and \( q_2 \) at \( t = 0 \). Using the diffusion model (Kimura, 1964) we can write down the process of change with time as
This may be rearranged as

\[
\frac{\partial \phi}{\partial (t/N)} = \frac{1}{4} \frac{\partial^2}{\partial x_1^2} [x_1 (1 - x_1) \phi] + \frac{1}{4} \frac{\partial^2}{\partial x_2^2} [x_2 (1 - x_2) \phi]
\]

This shows that, under the conditions in which the diffusion approximation holds, the pattern of the selection process is entirely governed by the parameters \( Ns_1 \) and \( Ns_2 \) on a time scale \( (t/N) \) starting from a given initial configuration \((q_1, q_2, q_3)\) of the gene frequencies of the three alleles. Since the change in the frequency of \( A_1 \) in an
infinite population, is shown to be dependent on $s$ and $V_m$, the parameters $N_{s_1}$ and $N_{s_2}$ can be transformed to $N_s$ and $N^2V_m$. In order to see whether the chance of fixation of $A_1$ is a function of $N_s$ and $N^2V_m$ only, a comparison of these for population sizes $N = 3$ and $6$ at particular values of $N_s$ and $N^2V_m$ is shown in Table 7.

**TABLE 7** The chance of fixation of $A_1$ as calculated by the transition matrix method for different population sizes ($N$)

<table>
<thead>
<tr>
<th>$N_sN_s$</th>
<th>$N^2V_m$</th>
<th>$N$</th>
<th>Initial frequencies ($A_1$, $A_2$, $A_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1/3, 1/3, 1/3)</td>
</tr>
<tr>
<td>0.5000</td>
<td>0.0625</td>
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<td>0.42033</td>
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<tr>
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<td>0.42299</td>
</tr>
</tbody>
</table>

The two values of the chance of fixation of $A_1$ are quite close, thus indicating that the population size $N$ can appear in combination with $s$ and $V_m$ at particular initial gene frequencies of $A_1$, $A_2$ and $A_3$. 
The dependence of the chance of fixation of \( A_1 \) on \( N_\sigma \) and 
\( N^2V_m \) are shown in Figures 12 and 13. In Figure 12, it is shown against 
\( N_\sigma \) for \( N^2V_m = 0, 1, 4 \) and 9 when initial frequencies \( (A_1, A_2, A_3) \) 
are \((1/3, 1/3, 1/3)\). In Figure 13, it is shown against \( N^2V_m \) for 
initial frequencies \( (A_1, A_2, A_3) = (1/6, 5/12, 5/12), (1/2, 1/4, 1/4) \) 
and \((5/6, 1/12, 1/12)\) when \( N_\sigma = 0 \). In the latter case, the three 
initial configuration of the gene frequencies have the same value of 
\( r = 1/2 \).

In Figure 12, the curve for \( N^2V_m = 0 \) gives the same value of the 
chance of fixation of \( A_1 \) as provided by the formula for two alleles 
given by Kimura (1957) as

\[
(5.17) \quad u(q_1) = \frac{1 - \exp(-2N_\sigma q_1)}{1 - \exp(-2N_\sigma)} \]

When \( N^2V_m \) is greater than zero, the chance of fixation of \( A_1 \), at a 
particulat value of \( N_\sigma \), is reduced. It, however, varies with \( N_\sigma \), 
at a particular value of \( N^2V_m \), in almost the same fashion as when 
\( N^2V_m = 0 \). But the characteristic feature, in this case, is that it 
becomes less than the initial frequency of the gene when \( N_\sigma \) is less 
than a certain value depending upon the particular value of \( N^2V_m \) con-
considered. Thus when \( N_\sigma = 1 \) the chance of fixation is reduced from about 
52.5% to about 50% when \( N^2V_m \) is increased from 0 to 1.
Fig. 12 The chance of fixation of allele $A_1$ at a tri-allelic locus ($q_1 = 1/3$, $r = 1/2$). The curves are drawn for different values of $N^2 V_m$. 
Fig. 13  The chance of fixation of allele A₁ at a tri-allelic locus ($N ś = 0, r = \frac{1}{2}$). The curves are drawn for different initial frequencies of A₁.
chance of fixation becomes less than the initial gene frequency. In order to have the same chance of fixation at $N^2 V_m = 1$ as that at $N^2 = 1$ with $N^2 V_m = 0$, $N^2$ is to be increased from 1 to about 2.2. The effect of the multiple allelic variance in reducing the probability of fixation of a gene can be compensated by a suitable increase in the average selective advantage of the gene. At very high values of $N^2 V_m$, the chance of fixation could be practically zero unless there is some average selective advantage of the gene to compensate for this. It can be seen from the graph that when $N^2 V_m = 9$, a neutral gene would have as small a chance as 4% but could have the same chance as its own initial frequency if it were of as high a selective advantage as $N^2 = 4.5$.

Figure 13 clearly brings out the effect of multiple allelic variance on the chance of fixation of $A_1$ when it is neutral, on an average, with respect to $A_2$ and $A_3$ with variance $V_m$. In an infinite population, $A_1$ would ultimately be lost due to the effect of $V_m$ but in a finite population, it could get fixed by chance. This chance fixation would increase as the population decreases in size. For small populations, random drift would predominate over its being selected against and the allele would get fixed but for large populations, selective forces acting against it would overcome random drift and the allele would have very little chance of getting fixed. Since the selective forces acting against $A_1$ are inherent in $V_m$, the chance of its fixation would equal its initial frequency when $V_m = 0$. 
The total possible change in the frequency of $A_1$ in the limit is $-q_1$ whereas in a finite population the expected change in the limit is $u(q_1) - q_1$. This expected change would be negative. For a gene with frequency as half, $N^2V_m = 1$ can bring down its expected frequency in the limit to about 0.30. It is apparent from figure 13 that a rare gene ($q_1 = 0.16667$) can quickly be eliminated by multiple allelic variance but a frequent gene ($q_1 = 0.8333$) can still have some chance of getting fixed in spite of the enormous effect of multiple alleles to knock it out.

The results on the chance of fixation of $A_1$ presented above can be compared with a general formula for the chance of fixation of an allele in a multiple allelic situation suggested by Robertson (personal communication). With respect to $k$ alleles $A_1, A_2, \ldots, A_k$ with respective initial frequencies $q_1, q_2, \ldots, q_k$ and selective coefficients $S_1, S_2, \ldots, S_k$ such that

\begin{align*}
(5.18) \quad \bar{S} &= \sum_n q_n S_n \\
(5.19) \quad V_S &= \sum_n q_n S_n^2 - \bar{S}^2 \\
(5.20) \quad (\delta q)_n &= q_n (S_n - \bar{S})
\end{align*}

the chance of fixation $u_n$ of the $n^{th}$ allele $A_n$ is given
by

\[(5.21) \quad u_n = q_n + 2N (\sum q) + \frac{(2N)^2}{3} q_n[(s_n - \bar{q})^2 - V_S] - \frac{(2N)^3}{3} (\sum q_n V_S)
\]

For the case of three alleles the chance of fixation of allele \( A_1 \) with frequency \( q_1 \), which is neutral on an average, with respect to \( A_2 \) and \( A_3 \) with a variance \( V_m \) between them, this formula reduces to

\[(5.22) \quad u_1(q_1) = q_1 - \frac{(2N)^2}{3} q_1 (1 - q_1) V_m
\]

A comparison of \( (u_1(q_1) - q_1) \) calculated from this formula with that obtained from the computer is shown in Table 8 when \( q_1 = q_2 = q_3 = \frac{1}{3} \). The agreement between the two results is quite close.

5.2 MEAN TIME UNTIL FIXATION OF ALLELE \( A_1 \)

When no selective forces are operating, the mean time until fixation of \( A_1 \) is found to be independent of the frequency of alleles
TABLE 8 Comparative values for the expected change in the limit in the frequency of allele $A_1$ having a mean superiority of $\bar{s} = 0$ with variance $V_m$ in a population of size $N = 6$ for $q_1 = q_2 = q_3 = \frac{1}{3}$.

<table>
<thead>
<tr>
<th>$N^2V_m$</th>
<th>Computer</th>
<th>Formula</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
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<td>0.0000</td>
<td>0.00000</td>
<td>0.00000</td>
<td>0.00000</td>
</tr>
<tr>
<td>0.0144</td>
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<td>0.00051</td>
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<tr>
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<td>-0.01470</td>
<td>-0.01707</td>
<td>0.00237</td>
</tr>
<tr>
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<td>-0.03183</td>
<td>-0.03840</td>
<td>0.00657</td>
</tr>
<tr>
<td>0.2304</td>
<td>-0.05369</td>
<td>-0.06827</td>
<td>0.01458</td>
</tr>
<tr>
<td>0.3600</td>
<td>-0.07863</td>
<td>-0.10667</td>
<td>0.02804</td>
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$A_2$ or $A_3$ and is the same as that given in Chapter IV for two alleles with additive gene action. At particular values of $N_{s_1} = 2$ and $N_{s_2} = 1$, the mean times are presented in Table 9 corresponding to the possible initial configurations of the three alleles in a population of size $N = 6$, when all the three alleles are present. For a fixed value of $q_2$, the mean times can be read vertically down for various initial frequencies of $A_1$. It decreases as the gene frequency increases. For instance, when $A_2$ allele is initially present with a frequency 0.5, the time to fixation of $A_1$ with frequency $1/12$ is $3.26N$ whereas when its frequency is $5/12$ it is $2.59N$. However, the effect of the frequency of $A_2$ allele on the time to fixation of $A_1$ allele is the reverse. For a given frequency of $A_1$ allele, it takes longer for its fixation if the frequency of $A_2$ allele is frequent than when it is rare.

The effect of $N\overline{s}$ and $N^2V_m$ on the time to fixation of $A_1$ is shown in Table 10, for the case when the initial frequency of $A_1$ allele is $1/3$. When $N^2V_m = 0$, the mean time decreases with increase in $N\overline{s}$. So is the case with $N^2V_m = 1$ but at higher values of $N^2V_m$ it increases first with increase in $N\overline{s}$ and decreases thereafter. When $N\overline{s} = 0$, the effect of multiple allelic variance is to decrease the mean time. So is the case at $N\overline{s} = 1$ but at higher values of $N\overline{s}$, the mean time increases first with increase in $N^2V_m$ but decreases thereafter. It is interesting to note that the behaviour of the mean time over variations in $N\overline{s}$ for a fixed $N^2V_m$ is almost the
TABLE 9  Average number of generations / N until fixation of $A_1$ (N = 6)

$$N_1 = 2, \quad N_2 = 1.$$  

<table>
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<th>2</th>
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</table>
TABLE 10  Average No. of generations until fixation of $A_1$ ($N = 6$) with initial frequency $1/3$.

<table>
<thead>
<tr>
<th>$\bar{N}V_m$</th>
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</table>
same as that of the meantime over variations in $N^2V_m$ for a fixed $N$. 

5.3 MEAN TIME UNTIL HOMOZYGOSITY

The results of the mean time until homozygosity are presented in Table 11 and 12. In Table 11, the three alleles are neutral and the variation of the mean time until homozygosity over the different initial gene configurations is shown. At a fixed value of $q_4$, the mean time increases first with increase in the frequency of $A_2$; attains a maximum and decreases thereafter. Since the situation is symmetrical, the same is true for variations over the frequency of $A_1$ for a fixed $q_2$. Also the distribution is symmetrical so that the same mean time is obtained for frequencies less than or greater than the midpoint of the range. The highest mean time is $3N$ and occurs when $q_4 = q_2 = \frac{1}{3}$ whereas the lowest is $1.66N$ and occurs when either $q_4 = q_2 = \frac{1}{12}$ or $q_1 = \frac{1}{12}$, $q_2 = \frac{10}{12}$ or $q_1 = \frac{10}{12}$, $q_2 = \frac{1}{12}$. In Table 12, the variation in the mean time until homozygosity is shown over the different values of $N_{s_1}$ and $N_{s_2}$ when all the three alleles are at equal frequencies. There is a perfect symmetry as far as $N_{s_1}$ and $N_{s_2}$ are concerned. For a fixed $N_{s_2}$ (unless it is 0), the mean time first increases, attains a maximum and then decreases with increase in $N_{s_1}$. The maximum shifts to the right side as $N_{s_2}$ increases. For $N_{s_2} = 0$, the maximum is $3N$ and occurs at $N_{s_1} = 0$, the time for the neutral case. This can be compared with the maximum mean time until homozygosity of $2.55N$. 


TABLE 11  Average number of generations / N until homozygosity \((N = 6)\)

Three neutral alleles at a locus.

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<tr>
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<tr>
<td>9</td>
<td>2.43</td>
<td>2.46</td>
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<tr>
<td>10</td>
<td>1.66</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 12  Average number of generations / N until homozygosity \( (N = 6) \)

\[ q_1 = \frac{1}{3}, \quad q_2 = \frac{1}{3}, \quad q_3 = \frac{1}{3} \]

<table>
<thead>
<tr>
<th>( N_{s_1} )</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>1.79</td>
<td>1.60</td>
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<td>4</td>
<td>1.90</td>
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<td>2.31</td>
<td>2.48</td>
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<td>1.83</td>
<td>2.03</td>
<td>2.26</td>
<td>2.50</td>
<td>2.42</td>
<td>2.24</td>
<td>2.03</td>
<td>2.03</td>
</tr>
<tr>
<td>6</td>
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<td>1.62</td>
<td>1.79</td>
<td>2.01</td>
<td>2.24</td>
<td>2.42</td>
<td>2.48</td>
<td>2.41</td>
<td>2.25</td>
</tr>
<tr>
<td>7</td>
<td>1.33</td>
<td>1.45</td>
<td>1.60</td>
<td>1.79</td>
<td>2.01</td>
<td>2.24</td>
<td>2.41</td>
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<td>2.41</td>
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<tr>
<td>8</td>
<td>1.22</td>
<td>1.31</td>
<td>1.44</td>
<td>1.60</td>
<td>1.80</td>
<td>2.03</td>
<td>2.25</td>
<td>2.41</td>
<td>2.47</td>
</tr>
</tbody>
</table>
obtained in the two allele case in Chapter IV. It shows that the maximum time to homozygosity is increased with the increase in the number of alleles and that it occurs when all the alleles are equally represented in the initial population.
In Chapter II, it has been shown that the properties of the stationary distribution of gene frequencies realised due to the balance between the mutation occurring at a low rate in one direction (reverse mutation being negligible) and selection with random drift can be studied with the help of the element of the first row of fundamental matrix. In this Chapter, this theory is applied to study the population dynamics of completely lethal genes in finite populations. It will further be shown how this theory can predict allelic rates and the decline of allelism with time. The determination of allelic rates is of great importance in experimental investigations with natural populations to decide between whether recessive lethals have deleterious effect as heterozygotes. This problem has been discussed at length by Crow and Temin (1964) and Wallace (1966). If the heterozygotes carrying lethals have reduced fitness, then the mutation from normal to lethal allele is more than sufficient to balance their elimination by homozygosity and the population suffers from a mutational load. On the other hand, if the heterozygotes have enhanced fitness, then the mutation is not sufficient to balance the elimination of lethal genes, and the load is said to be segregational (balanced). Most of the earlier experimental investigations on natural populations with Drosophila like those of Dobzhansky and Wright (1941), Wright, Dobzhansky and Hovanitz (1942) and Crow and Temin (1964) give evidence in support of the
deleterious effect of lethal genes in the heterozygous condition but Wallace (1966) obtains results which show an overdominant effect of lethal genes. Nei (1968), however, argues that Wallace's conclusion could be due to the small effective size of the population sampled and suggests that the lethal genes are, on the average, slightly deleterious in the heterozygous condition. The decline of alleliam of recessive lethals with time is another interesting problem invoked by Wallace (1966). His conjecture, on the functional relationship between the allelic rate and the time interval between the sampling of the first and the second set of lethals has been proved as approximately correct by Prout (1967). An alternative method, however, based on the transition matrix approach is developed in this section on the basis of suggestions made by Robertson (personal communication).

6.1 DISTRIBUTION OF LETHAL GENES

Consider a randomly mating population of \( N \) adult individuals with \( i \) heterozygotes and \((N - i)\) homozygotes. This would mean that the gene frequency of lethal \( a \) is \( \frac{1}{2} q_1 = i/(2N) \) and that of normal \( A \) is \( (1 - \frac{1}{2} q_1) \). Let the fitnesses of the three possible genotypes \( AA \), \( Aa \) and \( aa \) be 1, \( 1 - h \) and 0 respectively. Then after selection, the frequency of heterozygotes will be
\[(6.1) \quad q_{i}' = \frac{q_i (1 - h)}{1 + \frac{1}{2} q_i (1 - 2h)}\]

whereas that of homozygotes will be \((1 - q_i')\). On sampling \(N\) adult individuals from such a population will produce \(j\) heterozygotes and \((N - j)\) homozygotes with transition probability

\[(6.2) \quad P_{ij} = \binom{N}{j} (q_{i}')^j (1 - q_{i}')^{N - j}\]

Here \(i\) goes from 0 to \(N\) and \(j\) also goes from 0 to \(N\). The Markov Chain specified by such probabilities has 0 as the only absorbing state. These probabilities determine the \(Q\) matrix where \(i\) and \(j\) each go from 1 to \(N\). If the mutation rate from \(A\) to \(a\) is \(u\) per generation, the reverse mutation being negligible, then as shown in Chapter II the stable distribution of the lethal gene frequency is given by \(2Nu S_{1j}\) where \(S_{1j}\) is the \(j\)th element of the first row of \((I - q)^{-1}\). The mean and the variance of the frequency of \(a\) and the mean frequency of heterozygotes in the stable state are given by

\[(6.3) \quad E(q) = 2Nu \sum_{j=1}^{N} S_{1j} \left( \frac{j}{2N} \right)\]
These quantities have been evaluated on the computer for population size \( N = 50 \) and 10. The results are shown in figures 14, 15 and 16. A negative value of \( h \) means heterotic lethals whereas a positive value means partially recessive lethals. \( h = 0 \) corresponds to completely recessive lethals. A mutation rate of \( 10^{-5} \) has been assumed throughout.

### 6.11 Mean Gene Frequency

From figure 14, it is found that the mean gene frequency declines almost linearly for small population sizes such as 10 as we pass from heterotic lethals through completely recessive lethals to partially recessive lethals. But for large population sizes such as 50, the decline is non-linear.

The mean gene frequency for completely recessive lethals is known from Wright's equilibrium distribution formula (Wright, 1937). The distribution for small \( q \) is given by
Fig. 14. Mean of the distribution of frequencies of a lethal gene 
\( (u = 0.00001) \). The curves are drawn for different population sizes.
\[ (6.6) \quad \phi'(q) = \text{const.} \exp \left(-2Nq^2\right) q^{4Nu-1} \]  

Substituting \( t = q^2 \) and applying the condition \( \int_0^1 \phi(q) \, dq = 1 \) gives \[ (6.7) \quad \int_0^1 \phi(q) \, dq = 1 \]  

The mean and variance of the gene frequency are given by \[ (6.8) \quad \text{const.} = \frac{2}{[\Gamma(2Nu)]} (2Nu)^{2Nu} \]  

For \( 2Nu > 1 \), \( \bar{q} \) is close to \( u^{\frac{1}{2}} \) i.e. the equilibrium value expected in an infinite population. For \( 2Nu \leq 1 \), however,
\[ (6.11) \quad \sqrt{2Nu} = \frac{1}{2Nu} \]

\[ (6.12) \quad \sqrt{2Nu + \frac{1}{2}} = \frac{1}{T^\frac{1}{2}} \]

approximately, so that

\[ (6.13) \quad \bar{q} = u(2 \frac{T}{N})^{\frac{1}{2}} \]

The conditions imposed in the matrix approach require that \( 2Nu \leq 1 \) and therefore the mean gene frequency obtained by this approach should be compared with \( u(2 \frac{T}{N})^{\frac{1}{2}} \). This comparison is shown in Table 13.

**Table 13**  Comparison of mean lethal frequency as calculated from Wright's formula and transition matrix method for different population sizes \( (h = 0, u = 10^{-5}) \).

<table>
<thead>
<tr>
<th>N</th>
<th>Wright's formula</th>
<th>Computer results</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>(17.72 \times 10^{-5})</td>
<td>(18.18 \times 10^{-5})</td>
</tr>
<tr>
<td>10</td>
<td>(7.93 \times 10^{-5})</td>
<td>(8.39 \times 10^{-5})</td>
</tr>
</tbody>
</table>
The agreement between the two approaches is quite close, Wright's formula giving a lower value than the computer results.

For heterotic lethals, the equilibrium gene frequency by Wright's formula is known in only special cases. The equilibrium frequency \( q \) expected in an infinite population due to the superiority of heterozygotes only is, however, \( k/(1 + k) \) where \( k = -h \) which is approximately \(-h\) for small values of \( h \). The matrix approach, therefore, gives the result that in the range \( q = 0 \) to \( q = 0.05 \), the mean gene frequency decreases linearly as \( q \) approaches 0 if \( N = 10 \) but decreases very sharply if \( N = 50 \). When \( k = +0.05 \), the mean gene frequency is \( 3.28 \times 10^{-4} \) for \( N = 50 \) but only \( 1.4 \times 10^{-5} \) for \( N = 10 \). This shows that, in order that the equilibrium frequency of 0.05 is actually realized the population size has to be very very large. The gene frequency increases as the population size increases.

6.12 VARIANCE OF GENE FREQUENCY

The variances of gene frequency for population size \( N = 10 \) and 50 are shown in figure 15. The variance decreases as the reduction in the fitness of the heterozygotes rises from \(-0.05\) through 0 to \(+0.05\) for either of the two population sizes. But unlike the curves for the mean gene frequency, the curves here intersect. In most cases of the heterotic situation, the variance is more for the larger population size but for completely recessive lethals and partially recessive lethals, the variance is smaller for the larger population size. For \( h = 0 \) and \( N = 50 \), the variance is found to be \( 1.08 \times 10^{-5} \).
Fig. 15 Variance of the distribution of frequencies of a lethal gene \((u = 0.00001)\). The curves are drawn for different population sizes.
which compares very well with the value of $0.99686 \times 10^{-5}$ obtained from Wright's variance formula given by (6.10).

6.13 MEAN HETEROZYGOSITY AT EQUILIBRIUM

The curves for the mean heterozygosity for $N = 50$ and $N = 10$ as presented in figure 16 show almost the same pattern as that of the mean gene frequency. For overdominant genes, this similarity between the mean gene frequency and average heterozygosity was also noted by Robertson (1962). For $h = 0$ and lethal gene, his formula for heterozygosity reduces to $2u(2\mu N)^{1/2}$ which is twice the mean gene frequency. It can be verified from figures 14 and 16 that for $h = 0$, the mean heterozygosity is almost double that of the mean gene frequency. As noted in Chapter II, the mean heterozygosity is proportional to the contribution of the locus towards the genetic variance of the stable population. If $Nu$ is small as would usually be the case with $u = 10^{-5}$ unless $N$ is very large, the genetic variance would increase as the size of the population is increased.

6.14 PROPORTION OF POPULATIONS SEGREGATING FOR A GIVEN LETHAL

Following Wright (1931) the proportion $F(o)$ of populations from which lethals are absent is such that the frequency $2Nu F(o)$ of recurrence in a population equals the frequency $(1/2) F(2N)$ of loss where
Fig. 16 Mean heterozygosity at equilibrium ($u = 0.00001$). The curves are drawn for different population sizes.
\[ F(q) = \frac{1}{2N} \phi(q) \]  

and \( \phi(q) \) is given by (6.6). This gives

\[ F(0) = (2N)^{-2Nu} \]

\[ = 1 - 2Nu \log_e 2N \quad \text{approximately} \]

In the matrix approach, however, if \( f(0) \) represents the mean number of loci having no mutant at the equilibrium state when, on average one locus becomes homozygous per generation, in the absence of any mutation, then

\[ 2Nu f(0) + 2Nu s = 1 \]

where

\[ s = \sum_j S_{1j} \]

This gives the value of \( F(0) \) as

\[ F(0) = 2Nu f(0) \]

\[ = 1 - 2Nu s \]
In other words, the proportion of populations segregating for lethals is \(2Nu S\). For a completely recessive lethal with \(N = 50\), the proportion of populations from which lethals are absent is, using (6.18), found to be 0.994360 as against the value of 0.995395 obtained by Wright's approach [using (6.15)].

6.2 CHANCE OF ALLELISM

In order to study the allelism in a given sample of lethal bearing chromosomes, all the possible heterozygotes between these lethal bearing chromosomes are made. If the same lethal gene is carried on two or more chromosomes in the sample, then a lethal zygote will be formed everytime these chromosomes meet. If a lethal gene is represented only once in the sample, then the chromosome carrying it will form viable heterozygotes with all other lethal chromosomes in the sample. By making all possible crosses among strains with lethal chromosomes, the number of times various lethal genes are represented as well as the total frequency of lethal zygotes formed can be determined. The chance of allelism of lethal chromosomes is then regarded as the proportion of crosses between lethal bearing chromosomes which produce lethal zygotes. When two lethal chromosomes prove to be allelic, the lethal genes they carry are either identical by descent or are different mutations which by chance have affected a finite number of equivalent loci. The total chance of allelism is the sum of the chances of allelism due to these
two causes. If the population size is infinite, the allelism is due to recurrent mutations only whereas if the number of equivalent loci is infinite the allelism is due to identity by descent only.

Apart from the allelism of lethal bearing chromosomes $i_c$, there is also the allelism of random pairs of lethal genes $i$. Knowing $i_c$ from experimental data, $i$ can be evaluated by the formula (Nei 1968)

$$i = \frac{-\log_e (1 - i_c q^*)}{[\log_e (1 - q^*])^2}$$

where $q^*$ is the frequency of lethal chromosomes. In what follows, however, we discuss $i$, the chance of allelism of random pairs of lethal genes with the help of the properties of lethal gene frequency distribution discussed in the previous section.

If lethal mutations occur at $n$ out of a large number of loci and the proportion of lethals at a locus to that of all lethals is $p$, then the chance that a second lethal occurs at the same locus as the first is $p^2$. Averaging over the $n$ loci gives the total probability as $\sum_{n} p^2$ that the two lethals taken at random from the population will be allelic. Since $\sum_{n} p = 1$ and $p$ is proportional to the frequency $q$ of lethal gene, the chance of allelism is $(\sum_{n} q^2) / (\sum_{n} q)^2$. Following Nei (1968) we take the expectations of the numerator and the denominator and obtain $n E(q^2)$ and $n^2 q^2 + n^2 q^2$ respectively. This gives the chance of allelism $i$ as
(6.20) \[ i = \frac{x}{(1 - \frac{1}{n}) + x} \]

where

(6.21) \[ x = \frac{E(q^2)}{nq^2} = \frac{(o_q^2 + q^2)}{nq^2} \]

is the formula for the chance of allelism given in Dobzhansky and Wright (1941), and Wright, Dobzhansky and Hovanitz (1942). In the present case it is assumed that the mutation rates are the same for all loci so that there is no contribution to the variance of the gene frequency due to differences in the mutation rates. When the population is infinite, the variance in the gene frequency due to random drift vanishes and \( i \) reduces to \( \frac{1}{n} \). But when an infinite number of equivalent loci are affected by recurrent mutation, \( \frac{1}{n} \) tends to zero and \( i \) reduces to \( i_p \) given by

(6.22) \[ i_p = \frac{x}{1 + x} \]
This is the chance of allelism due to finite size of the population only and has been investigated in this section by the transition matrix approach. Using (6.3) and (6.4) for $E(q)$ and $E(q^2)$ we get the value of $x$ as

\[(6.23) \quad x = \frac{2Nu \sum_{j} s_{1j} \left( \frac{j}{2N} \right)^2}{(2Nu)^2 n \left( \sum_{j} s_{1j} \frac{j}{2N} \right)^2} \]

\[
= \frac{\sum_{j} s_{1j} \left( \frac{j}{2N} \right)^2}{2NU \left( \sum_{j} s_{1j} \frac{j}{2N} \right)^2}
\]

where

\[(6.24) \quad U = nu\]

is the mutation rate for lethal chromosomes. It refers to a very large number of loci with very small mutation rate per locus such that the product of the two is constant. Taking $n = 500$ and $u = 10^{-5}$ so that the mutation rate for lethal chromosome is $0.005$, the computer results on the allelic rates are shown in figure 17. It is apparent that the slope of the curve is more when $N = 50$ than when $N = 10$. This shows that for very small population sizes, the
Fig. 17 The chance of allelism of lethal genes ($U = 0.005$). The curves are drawn for different population sizes.
allelic rates may practically be independent of the nature of lethal genes. But for appreciable population size, the allelic rates are lower for heterotic lethals than for partially recessive lethals. For very large population sizes, these rates are solely determined by the nature of the loci and can be very small for heterotic loci. As the population size decreases the rates increase. Similar results were obtained by Nei (1968), using the properties of Wright's stable distribution of gene frequencies. For completely recessive lethals \((h = 0)\) and \(N = 10\), the chance of allelism is 77% as against Nei's result of 76.2%. Whereas for \(N = 50\), the values obtained by the matrix approach and Wright's formula are respectively 0.40 and 0.39.

6.3 DECLINE OF ALLELISM WITH TIME

Wallace (1966) presented an analysis of the allelism of recessive lethal genes in certain populations of *Drosophila melanogaster*. His main concern was the determination of the allelic rates of lethals taken from a natural population at collection sites of varying distance apart. He argued that the allelism between two sets of lethals from a given distance apart can be related to the allelism of two sets of lethals taken from the same point in the population but separated by a given interval in time. The formula suggested by him for the allelic rate \(i_{nt}\) and the time interval \((t)\) between the sampling of the
first and the second set of lethals have the relationship

\[(6.25) \quad i_{Tt} = i_n + i_F (1 - K)^t\]

where

\(i_{Tt}\) = the allelism between lethal genes \(t\) generations apart.

\(i_F\) = the allelism component of \(i_{Tt}\) within a generation produced by identity by descent in a finite population.

\(i_n\) = the allelism within a generation of the same set of lethal loci if they were in a population of infinite size.

\(K\) = a constant related to the rate of turnover of lethals within the population.

Prout (1967) demonstrated with algebraic details that this functional relationship is approximately correct.

If the lethal gene frequency at time \(t\) is denoted by \(q_t\) and if we assume that the mean gene frequency \(\bar{q}\) does not change appreciably
during the time interval $t$, then the probability of choosing one and the same lethal from among lethals of generation 0 and from among lethals of generation $t$ is $E_{qq}/(n_q)^2$. The expectation of this ratio can again, be expressed as

$$i_{yt} = \frac{y_t}{1 + y_t}$$

where

$$y_t = \frac{nE(q_{yt})}{(n_q)^2}$$

We already know that $\bar{q} = \sum_j S_{1j} \left( \frac{j}{2N} \right)$. The expected value of $qq_t$ has further to be evaluated by the matrix approach. The stable gene frequency distribution is given by the elements $2Nu S_{1j}$, $j = 1, 2, \ldots, N$, representing the mean number of weighted loci having $j$ mutants. The gene frequency vector at time 0 is then given by

$$q = 2Nu \left[ S_{11} \frac{1}{2N}, \ldots, S_{1j} \frac{j}{2N}, \ldots, S_{1N} \frac{1}{2} \right]$$
For a given number of \( j \) mutants occurring initially, the conditional mean gene frequency column vector at time \( t \) is given by

\[
q_t = \begin{bmatrix}
\sum P_{1k} (t) \frac{k}{2N} \\
\sum P_{jk} (t) \frac{k}{2N} \\
\sum P_{Nk} (t) \frac{k}{2N}
\end{bmatrix}
\]

where \( P_{jk} (t) \) are the elements of the matrix \( q^t \). The expectation of \( q q_t \) is then given by

\[
\mathbb{E}(qq_t) = 2Nu \sum_j \left( \sum_{i=1}^{j} \frac{j}{2N} \left( \sum_k P_{jk} \frac{j}{2N} \right) \right)
\]

Hence \( y_t \) is given by
Using this formula the computer results were obtained for \( \gamma_t \) for two population sizes \( N = 10 \) and \( N = 50 \) and \( h = -0.05, 0 \) and +0.05 taking \( U \) to be 0.005. In each case \( t \) was varied from 0 to 28. The decline of allelism with time, thus obtained, is shown in figures 18, 19 and 20 respectively for \( h = 0, +0.05 \) and 0.05. In each case the decline is sharp for \( N = 10 \) as compared to \( N = 50 \) and for about first twenty generations the allelism is higher for the smaller population size. The difference declines with time and beyond about twenty generations the allelism for \( N = 10 \) is lower than that for \( N = 50 \). These graphs can be compared with the sketch of hypothetical data given in Prout (1967). The graphs for \( N = 50 \) show the same pattern of exponential decline but for \( N = 10 \) the pattern of decline is non-exponential in the first several generations.

From figure 20, it appears that for heterotic lethals \( (h = -0.05) \) the decline of allelism with time is not so rapid. This would be so
Fig. 18 Allelism of completely recessive lethal genes ($U = 0.005$). The curves are drawn for different population sizes.
Fig. 19 Allelism of partially recessive lethal genes ($U = 0.005$). The curves are drawn for different population sizes.
Fig. 20 Allelism of heterotic lethals ($U = 0.005$). The curves are drawn for different population sizes.
because heterotic lethals are likely to persist longer in the population. The limiting value of the allelic rate \( (i_T) \) is likely to be 
\[
\frac{1}{500} = 0.002
\]
since the chromosomal mutation rate is based on 500 loci. It is likely to occur well beyond 28 generations.

For completely recessive lethals \( (h = 0) \) an expression of initial rate of decline can, however, be obtained using the equilibrium distribution of lethal genes given by (6.6). Let \( q_1 \) be the gene frequency of lethals in the next generation and let \( \delta q \) be the change in the gene frequency in one generation, then \( \delta q \) is approximately \( -q^2 \) so that

\[
(6.32) \quad E(q_{q_1}) = E[q (q + q)] = E(q^2) - E(q^3)
\]

From (6.10), \( E(q^2) \) is equal to \( u \), \( E(q^3) \) is given by

\[
(6.33) \quad E(q^3) = \int_0^1 q^3 \phi(q) dq
\]

\[
= \frac{2(2N)^2Nu}{\Gamma(2Nu)} \int_0^1 q^3 \exp(-2Nq^2) q(4Nu - 1) dq
\]

\[
= \frac{(2N)^{-\frac{3}{2}}}{\Gamma(2Nu)} \int_0^\infty t(2Nu + \frac{1}{2}) \exp(-t) dt
\]
Using (6.11) and (6.12) we get, approximately

\[(6.34) \quad E(q^3) = u(4\nu + 1) \left( \frac{\pi}{\eta N} \right)^{\frac{1}{2}} \]

if \( u \) is so small that the term involving \( u^2 \) can be neglected.

This gives

\[(6.35) \quad y_1 = \frac{n E(q_{\gamma_1})}{(nq_{\gamma_1})^2} = \frac{1 - \left( \frac{\pi}{\eta N} \right)^{\frac{1}{2}}}{2\pi\nu N} \]
and

\[(6.36) \quad \gamma_o = \frac{n E(q^2)}{(nq)^2} \]

\[= \frac{1}{2 \pi NU} \]

Hence \(i_{T1}^1\) and \(i_{T0}^1\) are given by

\[(6.37) \quad i_{T1}^1 = \frac{[1 - \left( \frac{1}{1 + (\frac{T}{NU})^2} \right)^{1/2}]}{[1 - \left( \frac{1}{1 + (\frac{T}{NU})^2} \right)^{1/2} + 2\pi NU]} \]

\[(6.38) \quad i_{T0}^1 = \frac{1}{1 + 2\pi NU} \]

Both \(i_{T0}^1\) and \(i_{T1}^1\) show that the allelic rates will decrease if the chromosomal mutation rate increases. The initial rate of decline \(r^*\) is then given by
A comparison of the initial rates of decline as predicted from (6.39) and as obtained numerically (figure 18) for completely recessive lethals is shown in Table 14.

**TABLE 14** Comparison of initial rate of decline as predicted from Wright’s distribution formula and as obtained by the transition matrix method for different population sizes \((h = 0, U = 0.005)\)

<table>
<thead>
<tr>
<th>(N)</th>
<th>Predicted</th>
<th>Computer</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.05606</td>
<td>0.04917</td>
<td>0.00689</td>
</tr>
<tr>
<td>10</td>
<td>0.05576</td>
<td>0.04047</td>
<td>0.01529</td>
</tr>
</tbody>
</table>

The difference between the two sets of results is less marked when \(N = 50\) than when \(N = 10\).
6.4. EXPECTATION OF LIFE AND AVERAGE AGE OF A LETHAL MUTANT

6.4.1 EXPECTATION OF LIFE OF A LETHAL MUTANT

Consider first the case when there is initially one lethal mutant a and \((2N - 1)\) normal alleles A in a population of size \(2N\). If there is no further mutation from normal to lethal alleles, the lethal mutant will ultimately be lost from the population. As shown in Chapter II, the mean total number of generations required for the elimination of the lethal is given by

\[
(6.40) \quad S_1^{*} = \sum_j S_{1j}^*
\]

where \(S_{1j}^*\) represents the mean number of generations which the population spends in the state \(E_j^*\) characterized by \(j\) mutants and \((2N - j)\) normals on the way to homozygosity. \(S_{1j}^*\) can be thought of as the expectation of life of the new mutant at its initial occurrence.

If the lethal mutant a occurs \(i\) times and normal allele A occurs \((2N - i)\) times initially in a population of size \(2N\), the mean total number of generations required for the elimination of the \(i\) lethals is given by
\[(6.41) \quad S_{i}^* = \sum_{j} S_{i j}\]

\[= f_i' \left( I - Q \right)^{-1} e\]

where \( S_{i j} \) represents the mean number of generations which the population spends in the state \( E_j \) before becoming homozygous and \( f_i' \) is a row vector with unity in the \( i \)th place and zeros elsewhere.

For population size as \( N = 8 \), the computer results for the average number of generations until loss of lethals for various initial gene frequencies of mutants and \( h = -0.5, 0 \) and \(+0.5\) are shown in Table 15. It may be noted that the initial gene frequency of mutant can at most be \( \frac{1}{2} \) corresponding to a population containing only heterozygotes.

**TABLE 15** Average number of generations until loss of lethals in a population of size \( N = 8 \).

<table>
<thead>
<tr>
<th>Initial frequency</th>
<th>( h = -0.5 )</th>
<th>( h = 0 )</th>
<th>( h = +0.5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0625</td>
<td>19.15</td>
<td>4.15</td>
<td>1.77</td>
</tr>
<tr>
<td>0.1250</td>
<td>26.54</td>
<td>6.02</td>
<td>2.35</td>
</tr>
<tr>
<td>0.1875</td>
<td>30.02</td>
<td>7.21</td>
<td>2.80</td>
</tr>
<tr>
<td>0.2500</td>
<td>31.87</td>
<td>8.02</td>
<td>3.15</td>
</tr>
<tr>
<td>0.3125</td>
<td>32.96</td>
<td>8.60</td>
<td>3.44</td>
</tr>
<tr>
<td>0.3750</td>
<td>33.64</td>
<td>9.03</td>
<td>3.68</td>
</tr>
<tr>
<td>0.4375</td>
<td>34.10</td>
<td>9.36</td>
<td>3.89</td>
</tr>
<tr>
<td>0.5000</td>
<td>34.43</td>
<td>9.63</td>
<td>4.08</td>
</tr>
</tbody>
</table>
It is apparent from Table 15 that heterotic lethals take considerably longer time, on an average, to disappear from the population than completely or partially recessive lethals. For instance, when the initial gene frequency of the mutant is 0.25, heterotic lethals would persist for about 32 generations as against about 8 generations required for completely recessive lethals and about 3 generations for partially recessive lethals. The effect of the initial gene frequency is also to increase the average time until loss. The expectation of life of a single mutant, when the population size is $N = 8$, corresponds to the initial gene frequency of $(\frac{1}{2}N) = 0.0625$ and is about 19, 4, and 2 generations for heterotic, completely recessive and partially recessive lethals.

Consider now the case when the population is in equilibrium due to the opposing processes of selection and mutation so that there is no change in the gene frequency. The opposition between these centripetal processes as a group and the scattering effects of random processes determine a frequency distribution of lethal genes. The frequency of classes segregating for lethals is given by $2Nu S_{1j}$ for $j = 1, 2, \ldots N$ whereas that of its absence from the population is $F(0)$ given by (6.18). If we consider the frequency distribution of the lethals present at any given time disregarding the cases when it is absent, the distribution is obtained by taking $\frac{F(q)}{1 - F(0)}$. This is, therefore, given by

\[(6.42) \quad S_{1j}^* = \frac{S_{1j}}{S_1} \quad \text{for} \quad j = 1, 2, \ldots \ldots \ldots N\]
and is such that

\[ (6.43) \quad \sum_j S_{1j}^* = 1 \]

Now in such an equilibrium population, the proportion of equivalent loci at which the lethal is represented with a frequency \( j/(2N) \) is \( S_{1j}^* \). From this class of loci, the mean time of elimination of all mutants is \( S_j^* \). Summing over all possible classes of loci, the expectation of life of the lethals present at any given time is, therefore

\[ (6.44) \quad L = \sum_j S_{1j}^* S_j^* \]

The expectation of life of a lethal tells us how long a mutant lethal is expected to last, on an average.

The expectation of life of a new lethal mutant at its initial occurrence \( (S_{1j}^*) \) and of any lethal \( (L) \) were obtained on the computer for \( N = 50 \) and for various values of \( h \). The results are shown in figure 21. It is apparent from the graph that heterotic lethals have expectations of life higher than completely recessive lethals whereas the latter type of lethals have higher expectations than partially recessive lethals. A completely recessive lethal \( (h = 0) \) takes, on an average,
Fig. 21 The expectation of life of a lethal mutant (N=50). (1) refers to expectation at any given time, whereas (2) refers to expectation at the initial occurrence of the mutant.
about 6 generations to disappear from the population since its initial occurrence. But in a random sample of completely recessive lethals present at any given time, a lethal takes, on an average, about 10 generations before disappearing. Another point worth noting is that the decline in the expectation of life from heterotic conditions through complete recessiveness, to partially recessiveness is more sharp in L than in $S_1^*$. The former is, however, always higher than the latter. The ratios $(L/S_1^*)$ for various values of $h$ are shown in Table 16.

**TABLE 16** $(L/S_1^*)$ for various values of $h$ (N = 50).

<table>
<thead>
<tr>
<th>$h$</th>
<th>$(L/S_1^*)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.05</td>
<td>2.13</td>
</tr>
<tr>
<td>-0.04</td>
<td>2.06</td>
</tr>
<tr>
<td>-0.03</td>
<td>1.99</td>
</tr>
<tr>
<td>-0.02</td>
<td>1.93</td>
</tr>
<tr>
<td>-0.01</td>
<td>1.87</td>
</tr>
<tr>
<td>0.00</td>
<td>1.81</td>
</tr>
<tr>
<td>0.01</td>
<td>1.76</td>
</tr>
<tr>
<td>0.02</td>
<td>1.71</td>
</tr>
<tr>
<td>0.03</td>
<td>1.66</td>
</tr>
<tr>
<td>0.04</td>
<td>1.62</td>
</tr>
<tr>
<td>0.05</td>
<td>1.58</td>
</tr>
</tbody>
</table>
The ratio varies between 2.13 to 1.58. For a completely recessive lethal it is 1.81.

5.42 AVERAGE AGE OF A LETHAL MUTANT

The realisation of a stable distribution of lethal genes is based on regarding the processes of gene mutation and selection due to lethality as occurring continually through time in a population of finite size. A mutation to lethal gene, when occurs at any time, may either disappear after its initial occurrence or may exist for several generations before disappearing. Suppose a random point is chosen on the time axis and a cross section of the then existing population is taken. The lethals present at this point of time, might have existed for different lengths of time since their initial occurrences. The mean length of time for which they have stayed in the population up to the given instant of time provides with the average age of a lethal mutant. Further the lethals present at this moment of time may have different lengths of time till they disappear. The mean length of time till they disappear provide with the expectation of life of a lethal mutant. We may also argue in terms of the proportion of equivalent loci at which a given lethal mutant survives for different numbers of generations. Suppose we start initially with a single mutant in a population of size $2N$ genes and suppose $l_t$ represents the number of equivalent loci at which the lethal survives for $t$ generations where $t = 0, 1, 2, \ldots$ with $l_0 = 1$. Then the relating frequency of loci at which the lethal survives for $t$ generations is $l_t/\sum l_t$. The average age of the lethal
A is, therefore,

(6.45) \[ \bar{A} = \frac{E t l_t}{\Sigma l_t} \]

A given mutant at time \( t \) occurs in \( l_t \) loci but at time \((t + 1)\) it occurs in \( l_t + 1 \) loci, at time \((t + 2)\) in \( l_t + 2 \) loci and so on. Hence its expectation of life at time \( t \) is given by

(6.46) \[ L_t = \frac{l_t + 1 + l_t + 2 + \cdots}{l_t} \]

Summing over time, the average expectation of life is given by

(6.47) \[ L = \frac{\Sigma l_t L_t}{\Sigma l_t} \]

But

(6.48) \[ \Sigma l_t L_t = \Sigma(l_t + 1 + l_t + 2 + \cdots) \]

\[ = l_1 + l_2 + l_3 + \cdots \]
\[ + l_2 + l_3 + \cdots \]
\[ = \Sigma t l_t \]
Hence

\[(6.49) \quad L = \bar{\Lambda}\]

It is thus shown that the average age of a lethal is the same as the average expectation of life. From the matrix approach this can be proved as follows.

It has already been shown that the elements \( S_{1j}^* \) of the stable distribution of the existing lethals are provided by the fundamental matrix \( (\bar{I} - \bar{Q})^{-1} \), normalized to unity. If this is expanded, we get

\[(6.50) \quad \frac{1}{S_1} (\bar{I} - \bar{Q})^{-1} = \frac{\bar{I} + \bar{Q} + \bar{Q}^2 + \cdots}{S_1}\]

As shown in Chapter II \( S_{1j}^* \) can be obtained from \( (6.45) \) by premultiplying by \( \bar{f}_1' = (1 0 0 \ldots 0) \). This means that the terms in the above series when premultiplied by \( \bar{f}_1' \) represent successively the probability distribution of the existing mutant individuals after one generation, two generations, and so on. If, therefore, we consider the matrix sum
premultiply it by \( f_1' \) and add the elements of the resulting vector, we obtain the average age of a lethal in the stable distribution of lethal genes. That is

\[
(6.52) \quad \bar{A} = \frac{1}{s} f_1' (I - Q)^{-2} \bar{e} = \frac{1}{s} f_1' (I - Q)^{-1} (I - Q)^{-1} \bar{e} = \sum_j \frac{S_{1j} S_{j}^*}{s} = L
\]
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    the third chromosome of Drosophila pseudoobscura.
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DERIVATION OF MATRIX FORMULAE

(a) Probability of fixation and expected change in the gene frequency

Consider a finite absorbing Markov chain with \( (2N + 1) \) states \( E_0, E_1, E_2, \ldots, E_{2N-1}, E_{2N} \), the \( i \)th state \( E_i \) representing the state of \( i \) \( A_1 \) genes and \( (2N - i) \) \( A_2 \) genes in a population of \( 2N \) genes. In other words, a variate \( X \) can assume the values \( X_i = i/(2N) \), for \( i = 0, 1, \ldots, 2N \). The states \( E_0 \) and \( E_{2N} \) are called absorbing states whereas \( E_i \), \( i = 1, 2, \ldots, (2N - 1) \) are called transient states. Let \( P_{ij}(t_1, t_2) \) be the conditional probability that the system is in state \( E_j \) at time \( t_1 \), given that it was in state \( E_i \) at time \( t_2 \) i.e. it represents the probability of transition from \( E_i \) to \( E_j \) after a time \( (t_1 - t_2) \). Mathematically, this means

\[
\text{Probability } [X = X_j \text{ at } t_1 \mid X = X_i \text{ at } t_2]; \ t_1 > t_2
\]

Let the process be homogeneous in time i.e. \( P_{ij}(t_1, t_2) \) depends only on the difference \( (t_1 - t_2) \) and not on \( t_1 \) and \( t_2 \). We can write this probability as \( P_{ij}(t) \), representing the probability that the system is in state \( E_j \) at time \( t + \zeta > t \), given that it was in state \( E_i \).
at time $\tau$ for $\tau \geq 0$. This is known as $t$-step transition probability, one step transition probability being written as $P_{ij}$. A transition from $i$ to $j$ after $t$-steps means a transition from $i$ to $k$ in one step and then from $k$ to $j$ in $(t - 1)$-steps, the probability of simultaneous realization of these events being $P_{ik}P_{kj}$ for $k = 0, 1, \ldots, 2N$. Hence we have, the Chapman-Kolmogorov equation (Feller 1951)

\[(A.1) \quad P_{ij}(t) = \sum_{k=0}^{2N} P_{ik} P_{kj}(t-1)\]

The one-step transition probability matrix has been represented as $P_{ij}$ by (2.1). Let the $t$-step transition probability matrix be represented by $P(t)$. Then the matrix equation corresponding to (A.1) is given by

\[(A.2) \quad P(t) = P_{ij} P(t-1)\]

\[= P^{t-1} P(1)\]

\[= P_{ij}^t\]

The elements of $P(t)$ satisfy the conditions
(A.3) \( P_{ij}(t) \geq 0 \) for all \( i, j \)

(A.4) \( \sum_{j=0}^{2N} P_{ij}(t) = 1 \) for all \( i \)

Since \( P \) has been partitioned as in (2.6), the partitioning of \( P(t) \) will be given by

(A.5) \[
P(t) = \begin{bmatrix}
1 & 0 & Q^t \\
0 & 1 & Q^t \\
P_0(t) & P_{2N}(t) & Q^t
\end{bmatrix}
\]

where

(A.6) \( P_0(t) = (I - Q^t)(I - Q)^{-1} P_0 \)

(A.7) \( P_{2N}(t) = (I - Q^t)(I - Q)^{-1} P_{2N} \)

We shall now show that vectors \( P_{2N}(t) \) and \( P_0(t) \) respectively give the probabilities of fixation of \( A_1 \) and \( A_2 \).

Let \( u_1(t) \) be the probability that at time \( t \), and not sooner, the population with initial gene frequency of \( A_1 \) as \( 1/(2N) \) becomes fixed.
for \( A_1 \) and let \( U^{(t)}_i \) be the probability that it has become fixed for \( A_1 \) by the \( t \)th generation. In other words, we have

\[
(A.8) \quad U^{(t)}_i = \sum_{1}^{t} u^{(t)}_i
\]

Since fixation at time \( t \) in one generation means that transition from initial state to the absorbing state takes place in one step, we have

\[
(A.9) \quad U^{(1)}_i = u^{(1)}_i = P_{ii}, \quad 2N
\]

Now fixation at time \( t \) can take place in \((2N - 1)\) mutually exclusive ways, the \( k \)th way being that the initial gene frequency becomes \( k/(2N) \) in the first step and then fixation takes place in \((t - 1)\) steps. The probability of simultaneous realization of these two independent events is \( P_{ik} u^{(t-1)}_k \). Hence

\[
(A10) \quad u^{(t)}_i = \sum_{k=1}^{2N-1} P_{ik} u^{(t-1)}_k
\]

If we denote by \( u^{(t)} \) and \( U(t) \) the column vectors of \( u^{(t)}_i \) and
respectively, we can write these relations in matrix notations as

\[(A.11) \quad \bar{u}(t) = \sim \bar{u}(t - 1)\]

\[= \sim \]

\[= \sim q^{t-1} \bar{u}(1)\]

\[= \sim q^{t-1} \frac{P_{2N}}{P_{2N}}\]

Then we have

\[(A.12) \quad \bar{u}(t) = (\sim I + \sim q + \sim q^2 + \cdots + \sim q^{t-1}) \frac{P_{2N}}{P_{2N}}\]

\[= (\sim I - \sim q^t) (\sim I - \sim q)^{-1} \frac{P_{2N}}{P_{2N}}\]

\[= \frac{P_{2N}(t)}{P_{2N}(t)}\]

Similarly if \(\underline{u}(t)\) and \(\underline{u}(t)\) denote the corresponding vector of fixation probabilities of the other gene \(A_2\), we have
(A.13) \[ \mathbf{L}(t) = (\mathbf{I} - \mathbf{Q}^t)(\mathbf{I} - \mathbf{Q})^{-1}\mathbf{P}_0 \]

\[ = \mathbf{P}_0(t) \]

If \( \mathbf{w}(t) \) denotes the vector of probabilities that a population with initial frequency of \( A \) gene as \( 1/(2N) \) is still segregating in \( t \)th generation, we have

(A.14) \[ \mathbf{w}(t) = \mathbf{Q}^t \mathbf{e} \]

We, thus see that the fixation probability vectors \( \mathbf{w}(t) \) and \( \mathbf{L}(t) \) can be obtained in two ways either by powering the \( \mathbf{P}_0 \)-matrix as in (A.5) or as matrix functions of \( \mathbf{Q} \)-matrix as proved in (A.12) and (A.13).

When \( t \to \infty \), we get

(A.15) \[ \mathbf{U} = \mathbf{U}(\infty) = (\mathbf{I} - \mathbf{Q})^{-1}\mathbf{P}_{2N} \]

(A.16) \[ \mathbf{L} = \mathbf{L}(\infty) = (\mathbf{I} - \mathbf{Q})^{-1}\mathbf{P}_0 \]

(A.17) \[ \mathbf{W} = \mathbf{W}(\infty) = 0 \]
We thus see that (A.15) provide with an alternative way of proving the matrix formula (2.14).

Now we give an alternative way of proving (2.15) as below:

Let the expected frequency of $A_1$ by the $t^{th}$ generation be denoted by $q_1(t)$ when the initial population has its frequency as $q_1(0) = 1/(2N)$, and the expected response by the $t^{th}$ generation be $R_1(t) = q_1(t) - q_1(0)$. In vector notations, we can put the response as $R(t) = q(t) - q(0)$. The expected gene frequency by the $t^{th}$ generation can be obtained by finding the mean of the variate $X_j = j/(2N)$ for the distribution given by the $i^{th}$ row of $P(t)$ i.e.

\[(A.18) \quad q_1(t) = \sum_{j=0}^{2N} P_{ij}(t) X_j \]

\[= \sum_{j=1}^{2N-1} P_{ij}(t) X_j + P_i(t) \]

In matrix notations, this means

\[(A.19) \quad q(t) = q(0) + U(t)\]

If $\Delta q_1$ represents the initial change in the mean gene frequency, we have
\[ \begin{align*} 
(A.20) \quad q_1(1) &= \beta q_1 + q_1(o) \\
&= \sum_{j=1}^{2N} \pi_{ij} x_j + p_i, 2N \\
\end{align*} \]

In matrix notation, this becomes

\[ \begin{align*} 
(A.21) \quad \mathbf{q}(1) &= \Delta \mathbf{q} + \mathbf{q}(o) \\
&= \mathbf{q}(o) + \mathbf{p}_{2N} \\
\end{align*} \]

so that

\[ \begin{align*} 
(A.22) \quad (\mathbf{I} - \mathbf{q}) \mathbf{q}(o) &= \mathbf{p}_{2N} - \Delta \mathbf{q} \\
\end{align*} \]

giving

\[ \begin{align*} 
(A.23) \quad (\mathbf{I} - \mathbf{q})^{-1} \mathbf{p}_{2N} - \mathbf{q}(o) &= (\mathbf{I} - \mathbf{q})^{-1} \Delta \mathbf{q} \\
\end{align*} \]
\[ R(t) = q(t) - q(0) \]

\[ = q^t(0) + U(t) - q(0) \]

\[ = -(I - q^t) q(0) + (I - q^t) (I - q)^{-1} P_{2N} \]

\[ = (I - q^t) \left[ (I - q)^{-1} P_{2N} - q(0) \right] \]

\[ = (I - q^t) (I - q)^{-1} \Delta q \]

Letting \( t \to \infty \), this gives the expected selection limit vector \( R \) as

\[ R = \frac{U - q(0)}{\Delta q} \]

\[ = (I - q)^{-1} \Delta q \]

which is the same as (2.15)
(b) Probability generating function of time until fixation of $A_1$. 

In order to study the distribution of time until fixation of allele $A_1$ disregarding the cases in which it is lost, we have to consider conditional transition matrix $Q^c$ giving transition probabilities $P_{ij}^c$ relative to the hypothesis that the population ends up with the fixation of $A_1$. Following Kemeny and Snell (1960), we can define $P_{ij}^c$ as

$$ (A.26) \quad P_{ij}^c = \frac{P_{ij} U_j}{U_i} $$

with

$$ (A.27) \quad U_{2N} = 1 $$

Let

$$ (A.28) \quad \sum_{U} = \text{diag}(U_1, U_2, \ldots, U_{2N-1}) $$
Then

\[ (A.29) \quad \tilde{Q}^{-1} = \tilde{D}^{-1} \tilde{Q} \tilde{D} \]

\[ (A.30) \quad (\tilde{I} - \tilde{Q}^{-1})^{-1} = \tilde{D}^{-1} (\tilde{I} - \tilde{Q})^{-1} \tilde{D} \]

In order to derive the probability generating function for the time until fixation of \(A_1\) relative to the hypothesis that the population ends up with the fixation of \(A_1\), we make use of the probability generating function of time until homogeneity given in Watterson (1961). Let \(T_1\) be the time taken to first reach fixation or loss of \(A_1\), given the initial population with \(i\) \(A_1\) genes and \((2N-i)\) \(A_2\) genes and let \(S_1(t)\) be the probability that \(T_1 = t\). Then

\[ (A.31) \quad S_1(t) = P_{10} + P_1, \quad 2N \]

and the probability generating function \(\Pi_1(z)\) is given by
(A.32) \[ \Pi_1(z) = \sum_{t=0}^{\infty} z^t S_1(t) \]

\[ = \sum_{t=1}^{\infty} z^t S_1(t) \]

\[ = z S_1(1) + \sum_{t=2}^{\infty} z^t S_1(t) \]

\[ = z S_1(1) + \sum_{t=2}^{2N-1} z^t S_1(t) \]

\[ = z S_1(1) + z \sum_{k=1}^{2N-1} z^t S_k(t) \]

\[ = z S_1(1) + z \sum_{k=1}^{2N-1} z^t S_k(t) \]

\[ = z (P_{10} + P_1, 2N) + z \sum_{k=1}^{2N-1} z^t S_k(t) \]

This can be expressed in matrix notations as

(A.33) \[ (I - z \tilde{Q}) \Pi(z) = z (I - \tilde{Q}) \tilde{\sigma} \]

where \( z \) is still a scalar and \( \Pi(z) \) is the vector of probability generating functions. Hence

(A.34) \[ \Pi(z) = z (I - z \tilde{Q})^{-1} (I - \tilde{Q}) \tilde{\sigma} \]

In the conditional case \( \tilde{Q} \) and its functions are to be replaced by \( \tilde{Q}^c \).
and its appropriate functions. This gives

\[(A.35) \quad \prod^0(z) = z (I - z Q^0)^{-1} (I - Q^0)\]

\[= \frac{z D_{U}^{-1}}{U} (I - z Q)^{U} \frac{D_{U} D_{U}^{-1}}{D_{U} D_{U}^{-1}} (I - Q) D_{U}\]

\[= \frac{z D_{U}^{-1}}{U} (I - z Q)^{-1} (I - Q) U\]

This has been used in (3.58).

For mean time until fixation of \(A_1\), we differentiate the probability generating function once and put \(z = 1\). This gives

\[(A.36) \quad \left(\frac{d}{dz}\right) \prod^0(z) \bigg|_{z=1} = \left(\frac{d}{dz}\right) \frac{D_{U}^{-1}}{U} \left(\frac{z^{-1} U}{I - Q}\right)^{-1} (I - Q) U \bigg|_{z=1}\]

\[= \frac{D_{U}^{-1}}{U} z^{-2} \left(\frac{z^{-1} U}{I - Q}\right)^{-2} (I - Q) U \bigg|_{z=1}\]

\[= \frac{D_{U}^{-1}}{U} (I - Q)^{-1} U\]

This can be compared with (2.20). The second factorial moment i.e. \(E[t (t-1)]\) is given by
\[(A.37) \quad \left( \frac{d^2}{dz^2} \right) \prod ^{0}(z) \bigg|_{z=1} = D_{U}^{-1} (-2) z^{-3} (z^{-1} \sim q)^{-2} (\sim q)^{2} \bigg|_{z=1} + D_{U}^{-1} (2) z^{-4} (z^{-1} \sim q)^{-3} (\sim q)^{1} \bigg|_{z=1} = 2D_{U}^{-1} [(\sim q)^{-2} - (\sim q)^{-1}] U \]

\[(A.38) \quad \mathbb{E}(t^2) = \mathbb{E}[t(t-1)] + \mathbb{E}(t) = 2D_{U}^{-1} [(\sim q)^{-2} - (\sim q)^{-1}] U + D_{U}^{-1} (\sim q)^{-1} U = D_{U}^{-1} [2(\sim q)^{-2} - (\sim q)^{-1}] U \]

which can be compared by (2.22).
REFERENCES


