A MATHEMATICAL PROBLEM IN POPULATION GENETICS

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1. *Introduction.* A genetical population in which different genotypes have different viabilities will undergo, by selection, changes in its genetical constitution which can be expressed in a simple mathematical form. We here consider a system of m alleles $A_1, A_2, \ldots, A_m$ segregating at one locus, and we assume that the genotype A_iA_j has viability a_{ij}, where $a_{ij} = a_{ji} \geqslant 0$. We assume discrete, non-overlapping generations and random mating.

In an infinite population there will be no random fluctuations, and, as in Mandel's paper (1), the frequencies p_i, p_i' of the gene A_i in two successive generations will be connected by

$$Vp_i' = p_i \sum_j a_{ij}p_j, \tag{1}$$

where

$$V = \sum_i \sum_j a_{ij}p_ip_j. \tag{2}$$

(All summations, except where otherwise indicated, are over the integers $1, 2, \ldots, m$.) V will be called the mean viability in the first generation. The two equations, together with

$$p_i \geqslant 0, \quad \sum_i p_i = 1 \tag{3}$$

define the mathematical problem of determining the behaviour of the p_i in a sequence of generations.

Scheuer and Mandel (2), and independently Mulholland and Smith (3), have been able to establish the inequality

$$V' = \sum_i \sum_j a_{ij}p_i'p_j' \geqslant V, \tag{4}$$

i.e. the mean viability increases from generation to generation. Using this result, the latter authors have proved that the gene frequencies p_i tend to a limit after a large number of generations, and that this limit is a local maximum of V as a function of the p_i.

In the present paper, different conditions from those previously used are given for a stationary point of V to be a maximum, a more direct approach to the stability of an equilibrium is discussed, and consideration is given to the problem of the existence of local maxima. The analysis is applied to the problem of the survival of a mutant gene, and finally the effect of random fluctuations in a large, but finite, population is evaluated.

2. *Equilibria and their stability.* p_i $(i = 1, 2, \ldots, m)$ is called an *equilibrium* if $p_i' = p_i$. From (1) this means that, for each i, either $p_i = 0$ or $V = \sum_j a_{ij}p_j$. Hence any equilibrium may be written as $p_i = P_i(I)$, where I is some subset of $(1, 2, \ldots, m)$ and

$$\left.\begin{aligned} P_i(I) > 0 \quad (i \in I), \qquad P_i(I) = 0 \quad (i \notin I), \\ \sum_{i \in I} P_i(I) = 1, \qquad \sum_{j \in I} a_{ij}P_i(I) = V(I) \quad (i \in I). \end{aligned}\right\} \tag{5}$$

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For the general matrix (a_{ij}) it is clear that, for each I, at most one $P_i(I)$ exists. In the special case $I = (1, 2, \ldots, m)$ there may exist a so-called non-trivial equilibrium P_i satisfying

$$\left.\begin{aligned} P_i > 0, \quad \sum_i P_i = 1, \\ \sum_j a_{ij} P_j = V_e. \end{aligned}\right\} \tag{6}$$

$P_i(I)$ is said to be stable if, for p_i near $P_i(I)$, the sequence $p_i', p_i'', \ldots$ remains near $P_i(I)$. From (4), it is possible to prove that this requires $P_i(I)$ to be a local maximum of V.

In particular, suppose that the non-trivial equilibrium given by (6) exists. Put $p_i = P_i + x_i$, and then $\sum_i x_i = 0$ and

$$V = \sum_i \sum_j a_{ij}(P_i + x_i)(P_j + x_j) = V_e + 2\sum_i x_i \sum_j a_{ij} P_j + \sum_i \sum_j a_{ij} x_i x_j,$$

$$V = V_e + \sum_i \sum_j a_{ij} x_i x_j. \tag{7}$$

Hence P_i is a local maximum if and only if

$$\sum_i \sum_j a_{ij} x_i x_j \leqslant 0 \quad \text{for all } x_i \text{ satisfying } \sum_i x_i = 0. \tag{8}$$

Mandel has given conditions on (a_{ij}) for this to be true. These and others will be derived below.

We first note that, since $\sum_j a_{ij} P_j = V_e$ for each i, the condition $\sum_i x_i = 0$ is equivalent to

$$\sum_i \sum_j a_{ij} x_i P_j = 0.$$

If (a_{ij}) has p positive eigenvalues and q negative ones, we can reduce it, by a real non-singular linear transformation, to a diagonal matrix whose main diagonal contains p elements $+1$ and q elements -1, the other elements being zero. Hence, if P_i transforms to Q_i, x_i to y_i, the condition (8) becomes

$$y_1^2 + \ldots + y_p^2 - y_{p+1}^2 - \ldots - y_{p+q}^2 \leqslant 0$$

for all y_i such that

$$Q_1 y_1 + \ldots + Q_p y_p - Q_{p+1} y_{p+1} - \ldots - Q_{p+q} y_{p+q} = 0.$$

It is clear that this cannot occur if $p \geqslant 2$, since we can take all y_i save y_1, y_2 zero. However, since $a_{ij} \geqslant 0$, with not all a_{ij} zero, p cannot be zero. Hence (8) implies $p = 1$. Clearly it also implies $q > 0$.

Conversely, suppose $p = 1$, $q > 0$. Then

$$Q_1 y_1 = Q_2 y_2 + \ldots + Q_{q+1} y_{q+1}.$$

Hence, by Cauchy's inequality

$$Q_1^2 y_1^2 = (Q_2 y_2 + \ldots + Q_{q+1} y_{q+1})^2 \leqslant (Q_2^2 + \ldots + Q_{q+1}^2)(y_2^2 + \ldots + y_{q+1}^2).$$

Therefore

$$\begin{aligned} \sum_i \sum_j a_{ij} x_i x_j &= y_1^2 - (y_2^2 + \ldots + y_{q+1}^2) \\ &\leqslant y_1^2 - \frac{Q_1^2 y_1^2}{Q_2^2 + \ldots + Q_{q+1}^2}. \end{aligned}$$

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This is negative for all y_1 so long as

$$Q_1^2 \geqslant Q_2^2 + \ldots + Q_{q+1}^2,$$

i.e. $\sum_i \sum_j a_{ij} P_i P_j \geqslant 0$, or $V_e \geqslant 0$ which is the case.

Hence a necessary and sufficient condition for stability is $p = 1$, $q > 0$. The special case $p = 1$, $q = 0$ occurs when (a_{ij}) is of rank one, so that $a_{ij} = a_i a_j$. The equations for P_i then take the form

$$a_i = \frac{V_e}{\sum_j a_j P_j}$$

which cannot be satisfied except in the trivial case a_i = constant, when there is no selection.

Hence, if we exclude this trivial case, a necessary and sufficient condition for the non-trivial equilibrium, if it exists, to be stable, is that (a_{ij}) has exactly one positive eigenvalue.

Let Δ_r be the rth principal minor of (a_{ij}). Then the number of negative eigenvalues of (a_{ij}) is equal to the number of changes of sign in the sequence

$$1, \Delta_1, \Delta_2, \ldots, \Delta_m$$

so long as none of the Δ_r vanish. Hence, since $\Delta_1 = a_{11} > 0$, the above stability condition becomes

$$(-1)^r \Delta_r < 0 \quad (r = 1, 2, \ldots, m) \tag{9}$$

which is essentially the determinantal criterion of Mandel (1).

If the non-trivial equilibrium is stable, V has a total maximum there, by (7) and (8), and hence

$$V_e = \sum_i \sum_j a_{ij} p_i p_j$$

for any p_i such that $\sum_i p_i = 1$. Hence, taking p_i zero except for $i = k$, when $p_k = 1$,

$$V_e \geqslant a_{kk}$$

another of Mandel's results.

3. *A direct examination of the stability of an equilibrium.* Previous discussions of the stability of the non-trivial equilibrium have been based on the increasing property of the mean viability, either in its general form or in the restricted form originally used. We give here a discussion based directly on the equation (1), which will be of use later in considering random fluctuations.

We consider first the non-trivial equilibrium P_i, assuming it to exist, and we put

$$p_i = P_i + x_i, \quad p_i' = P_i + x_i'.$$

Then, using (1) and (2) and ignoring second-order terms in x_i, we easily obtain

$$x_i' = x_i + \frac{P_i}{V_e} \sum_j a_{ij} x_j. \tag{10}$$

Let

$$y_i = x_i / \sqrt{P_i} \quad \text{and} \quad b_{ij} = \frac{1}{V_e} a_{ij} \sqrt{(P_i P_j)}.$$

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Then (10) becomes

$$y_i' = y_i + \sum_j b_{ij} y_j \tag{11}$$

and the condition $\sum_i x_i = 0$ becomes $\sum_i \sqrt{P_i}\, y_i = 0$.

$\sqrt{P_i}$ is an eigenvector of (b_{ij}) with eigenvalue unity, since

$$\sum_j b_{ij}\sqrt{P_j} = \frac{1}{V_e}\sum_j a_{ij}\sqrt{P_i P_j} = \sqrt{P_i}.$$

Let λ, α_i be another eigenvalue and corresponding eigenvector. Then

$$\sum_j b_{ij}\alpha_j = \lambda\alpha_i.$$

Take i to be that index for which $|\alpha_i/\sqrt{P_i}|$ is greatest. Then

$$|\lambda\alpha_i| \leqslant \sum_j |b_{ij}\alpha_j| \leqslant \sum_j b_{ij}\sqrt{P_j}\left|\frac{\alpha_j}{\sqrt{P_j}}\right| \leqslant \frac{|\alpha_i|}{\sqrt{P_i}}\sum_j b_{ij}\sqrt{P_j} = |\alpha_i|.$$

Hence $|\lambda| \leqslant 1$. Let $Y = \sum_i \alpha_i y_i$ be the projection of y_i on α_i, where α_i is taken to have unit length. Then (11) implies

$$Y' = Y + \lambda Y = (1+\lambda)\, Y. \tag{12}$$

y_i is any vector orthogonal to $\sqrt{P_i}$, and hence, in general, $Y \neq 0$. Hence the condition for the stability of Y is $|1+\lambda| \leqslant 1$, or, since $|\lambda| \leqslant 1$, $\lambda \leqslant 0$ (λ is real since (b_{ij}) is symmetric).

Hence a necessary and sufficient condition for stability is that (b_{ij}) have exactly one positive eigenvalue. For any x_i

$$\sum_i \sum_j b_{ij} x_i x_j = \sum_i \sum_j a_{ij} y_i y_j$$

if $y_i = x_i\sqrt{(P_i/V_e)}$. Hence (a_{ij}), (b_{ij}) have the same rank and signature, and this condition is equivalent to that of the previous section.

Consider now the more general equilibrium $P_i(I)$ satisfying (5). As before, set $p_i = P_i(I) + x_i$ and ignore second-order terms in x_i. Then

$$x_i \geqslant 0 \quad (i \notin I), \qquad \sum_i x_i = 0.$$

$$\begin{aligned} V &= \sum_i \sum_j a_{ij}(P_i(I)+x_i)\,(P_j(I)+x_j) \\ &= V(I) + 2\sum_i x_i \sum_j a_{ij} P_j(I) + \sum_i \sum_j a_{ij} x_i x_j. \end{aligned}$$

Put $\sum_j a_{ij} P_j(I) = V(I) + \alpha_i$. Then, by (5), $\alpha_i = 0$ ($i \in I$), and

$$V = V(I) + 2\sum_{i \notin I} \alpha_i x_i + \sum_i \sum_j a_{ij} x_i x_j. \tag{13}$$

For $i \in I$,

$$x_i' = \frac{(P_i(I)+x_i)\sum_j a_{ij}(P_j(I)+x_j)}{V} = \frac{(P_i(I)+x_i)\,(V(I)+\sum_j a_{ij}x_j)}{V(I)+2\sum_i \alpha_i x_i}.$$

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Thus

$$x_i' = x_i - 2P_i \sum_j \alpha_j x_j + \frac{P_i}{V} \sum_j a_{ij} x_j \quad (i \in I).$$

For $i \notin I$, $P_i = 0$, and

$$x_i' = \frac{x_i \sum_j a_{ij}(P_j + x_j)}{V} = x_i \left(1 + \frac{\alpha_i}{V}\right).$$

Thus, to the first order, x_i' is given by

$$x_i' = x_i - 2P_i \sum_j \alpha_j x_j + \frac{P_i}{V} \sum_j a_{ij} x_j \quad (i \in I),$$

$$x_i' = \left(1 + \frac{\alpha_i}{V}\right) x_i \quad (i \notin I).$$

From these equations a necessary and sufficient condition for x_i to remain small for $i \notin I$ is $\alpha_i \leqslant 0$. If this is so $\alpha_j x_j \to 0$ and the equation for x_i' $(i \in I)$ becomes

$$x_i' = x_i + \frac{P_i}{V} \sum_{j \in I} a_{ij} x_j.$$

Hence a necessary and sufficient condition for stability is that

$$\sum_j a_{ij} P_j(I) \leqslant V(I) \quad (i \notin I) \tag{14}$$

and that the sub-matrix (a_{ij}) $(i, j \in I)$ has exactly one positive eigenvalue. It is clear from (13) that this is exactly the condition for $P_i(I)$ to be a local maximum of V.

4. *Existence of stable equilibria.* It is clear from the above analysis that it is necessary to find the stable equilibria in order to determine the asymptotic behaviour of the population. There must be at least one stable equilibrium, i.e. the point at which V actually attains its maximum value in the region given by (3). There may be more than one; for instance, if $m = 3$, and

$$(a_{ij}) = \begin{pmatrix} 1 & 1+\alpha & 1+\alpha \\ 1+\alpha & 1 & 1+\alpha \\ 1+\alpha & 1+\alpha & 1 \end{pmatrix},$$

then $(0, \frac{1}{2}, \frac{1}{2})$, $(\frac{1}{2}, 0, \frac{1}{2})$, and $(\frac{1}{2}, \frac{1}{2}, 0)$ are all stable equilibria for $\alpha > 0$. In such cases it is a problem at present unsolved (except when there is an obvious symmetry) to find the form of the conditions on p_i which determine to which of the equilibria the system will tend.

We may, however, restrict the possible situations. In the first place, suppose as before that (a_{ij}) has p positive eigenvalues. Then it is easy to see that any principal sub-matrix of order $(m-r)$ has at least $(p-r)$ positive eigenvalues. It follows that, if we have a stable equilibrium $P_i(I)$ in which I contains $(m-r)$ elements,

$$1 \geqslant p-r, \quad \text{i.e.} \quad r \geqslant p-1.$$

Hence, if (a_{ij}) has p positive eigenvalues, at least $(p-1)$ genes must die out before equilibrium can be reached.

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We now prove also that, if I, J are two distinct subsets of $(1, 2, \ldots, m)$ with I containing J, and if the corresponding equilibria exist, then they cannot both be stable except in a certain degenerate case. For, suppose $P_i(J)$ is stable. Then, by (5) and (14)

$$\sum_{j \in J} a_{ij} P_j(J) = V(J) \quad (i \in J),$$
$$\leqslant V(J) \quad (i \notin J).$$

Hence
$$\sum_{i \in I} P_i(I) \sum_{j \in J} a_{ij} P_j(J) \leqslant V(J) \sum_{i \in I} P_i(I) = V(J).$$

Thus
$$\sum_{j \in J} P_j(J) \{\sum_{i \in I} a_{ji} P_i(I)\} \leqslant V(J),$$
$$\sum_{j \in J} P_j(J) V(I) \leqslant V(J)$$

(since I contains J), and so
$$V(I) \leqslant V(J).$$

But, if $P_i(I)$ is stable, $V(I)$ is the maximum value of V for $p_i = 0$ $(i \notin I)$. Hence

$$V(I) \geqslant V(J).$$

Thus $V(I) = V(J)$ and equality obtains throughout, so that

$$\sum_j a_{ij} P_j(J) = V(J) \quad (i \in I).$$

Thus $\theta P_i(I) + (1-\theta) P_i(J)$ is a solution of (5) for $0 < \theta < 1$, so that there are an infinite number of equilibria, all of the same viability. For a discussion of this degenerate case, which only occurs when $P_i(I)$ is not a strict local maximum of V, see the paper of Mulholland and Smith (3).

In particular, if $I = (1, 2, \ldots, m)$ and the non-trivial equilibrium is stable, no other stable equilibrium exists, and the system tends to the non-trivial equilibrium.

5. *Survival of a mutant gene.* Suppose that a system $(A_1, \ldots, A_{m-1})$ is in a stable non-trivial equilibrium Q_α (Greek suffixes being used to denote indices running from 1 to $(m-1)$). Then, if W is the equilibrium viability,

$$\sum_\beta a_{\alpha\beta} Q_\beta = W. \tag{15}$$

Now introduce a small proportion of the gene A_m (by mutation, for example). Clearly $(Q_1, \ldots, Q_{m-1}, 0)$ is an equilibrium for the system, and is stable (by (14)) if and only if

$$\sum_\beta a_{m\beta} Q_\beta < W.$$

If this is the case, the system will resume this equilibrium, so that A_m will die out.

If $\sum_\beta a_{m\beta} Q_\beta > W$, the equilibrium is not stable, and hence will not be resumed. Applying the final result of the previous section to the original system, we see that no stable equilibrium can exist without A_m, and hence A_m will not die out. It may or may not displace other genes, and it will certainly change the relative proportions of these genes.

Hence a necessary and sufficient condition for the new gene to persist is

$$\sum_\beta a_{m\beta} Q_\beta > W. \tag{16}$$

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6. *The effect of random fluctuations.* All the analysis carried out above has been on the basis of the deterministic model of an infinite population. It is known, however, that in the absence of selection, the finite nature of the population leads to significant departures from the deterministic theory, notably the phenomenon of genetic drift.

The precise nature of the random fluctuations depends on the mechanism of selection. To show the general features of the fluctuation we shall consider the following simple model. Let N be the number of genes in the population, and neglect any variation in this number from generation to generation. Then if p_i, p_i' are, as before, the gene frequencies in successive generations, the distribution of Np_i' conditional on p_i is multinomial with index N and parameters $\bar{p}_i$, where $V\bar{p}_i = p_i \sum_j a_{ij}p_j$ as in (1).

We suppose that a stable non-trivial equilibrium P_i exists, and seek a solution in which p_i remains near P_i. Then, if

$$p_i = P_i + x_i, \quad p_i' = P_i + x_i', \quad \bar{p}_i = P_i + \bar{x}_i;$$
$$x_i' = \bar{x}_i + \xi_i,$$

where
$$\mathscr{E}(\xi_i) = 0, \quad \mathscr{E}(\xi_i\xi_j) = N^{-1}(\bar{p}_i\delta_{ij} - \bar{p}_i\bar{p}_j),$$

the ξ_i in different generations are uncorrelated, and

$$P_i + \bar{x}_i = V^{-1}(P_i + x_i)\sum_j a_{ij}(P_j + x_j).$$

So long as x_i remains small, these equations may be written approximately as

$$x_i' = x_i + \frac{P_i}{V_e}\sum_j a_{ij}x_j + \xi_i,$$

where
$$\mathscr{E}(\xi_i\xi_j) = N^{-1}(P_i\delta_{ij} - P_iP_j).$$

Defining y_i, b_{ij} as before, and η_i as $\xi_i/\sqrt{P_i}$, we obtain

$$y_i' = y_i + \sum_j b_{ij}y_j + \eta_i,$$

where
$$\mathscr{E}(\eta_i\eta_j) = N^{-1}(P_i\delta_{ij} - P_iP_j)/\sqrt{(P_iP_j)} = N^{-1}(\delta_{ij} - \sqrt{(P_iP_j)}).$$

Let $\lambda \neq 1$ be an eigenvalue of (b_{ij}) with unit eigenvector α_i. Then α_i is orthogonal to $\sqrt{P_i}$, and $\lambda \leqslant 0$. Let $Y = \sum_i \alpha_i y_i$, $H = \sum_i \alpha_i \eta_i$ be the projections of y_i, η_i on this eigenvector. Then

$$Y' = (1+\lambda)\,Y + H, \tag{17}$$

$$\mathscr{E}(H^2) = \sum_i\sum_j \alpha_i\alpha_j\mathscr{E}(\eta_i\eta_j) = N^{-1}\sum_i\sum_j \alpha_i\alpha_j(\delta_{ij} - \sqrt{(P_iP_j)})$$
$$= N^{-1}(\sum_i \alpha_i^2 - (\sum_i \alpha_i\sqrt{P_i})^2) = N^{-1}.$$

Also, if α_i^* is another eigenvector, perpendicular to α_i,

$$\mathscr{E}(HH^*) = N^{-1}\sum_i\sum_j \alpha_i\alpha_j^*(\delta_{ij} - \sqrt{(P_iP_j)})$$
$$= N^{-1}(\sum_i \alpha_i\alpha_i^* - (\sum_i \alpha_i\sqrt{P_i})(\sum_j \alpha_j^*\sqrt{P_j}))$$
$$= 0.$$

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Hence, in (17), the H are uncorrelated for different generations and for different eigenvectors. Thus, for different eigenvectors, the Y develop independently. The equation (17) is then in the standard form for a first-order linear autogressive process, and has a solution stationary to the second order so long as $|1+\lambda| < 1$. It follows that, if $\lambda \neq 0$, the solution remains small so long as $\mathscr{E}(H^2)$ is sufficiently small. Now,

$$\mathscr{E}(Y^2) = \frac{\mathscr{E}(H^2)}{1-(1+\lambda)^2} = \frac{1}{N(-\lambda)(2+\lambda)}. \tag{18}$$

Thus, for $-N\lambda \gg 1$, the system remains stable and genetic drift does not occur. The case $\lambda = 0$, where (a_{ij}) is singular and the maximum is not strict, will, however, permit genetic drift to occur.

It is of interest to determine the fluctuation in the mean viability. Now

$$\begin{aligned} V &= V_e + \sum_i \sum_j a_{ij} x_i x_j \\ &= V_e + V_e \sum_i \sum_j b_{ij} y_i y_j \\ &= V_e(1 + \Sigma \lambda Y^2) \end{aligned} \tag{7}$$

the summation being over all eigenvalues λ of (b_{ij}) except unity. Therefore,

$$\begin{aligned} \mathscr{E}(V) &= V_e(1 + \Sigma\lambda \mathscr{E}(Y^2)) \\ &= V_e\left(1 + \Sigma \frac{\lambda}{N(-\lambda)(2+\lambda)}\right) \\ &= V_e\left(1 - \frac{1}{N}\Sigma \frac{1}{2+\lambda}\right). \end{aligned}$$

Hence, if $\Delta V = \mathscr{E}(V_e - V)$ measures the fluctuation in the mean viability,

$$N\frac{\Delta V}{V_e} = \sum_{\lambda \neq 1} \frac{1}{2+\lambda}. \tag{19}$$

Since $$-1 \leqslant \lambda \leqslant 0, \quad \frac{1}{2} \leqslant \frac{1}{2+\lambda} \leqslant 1.$$

Thus $$\frac{m-1}{2} \leqslant N\frac{\Delta V}{V_e} \leqslant m-1. \tag{20}$$

Thus we see that random fluctuations in populations such that the number of genes is large compared with the reciprocal of the smallest negative latent root of (b_{ij}) have only the effect of introducing a small fluctuation in the gene frequencies. The process is stationary to the second order, and genetic drift does not occur. However, if (a_{ij}) is singular, genetic drift will occur and genes will die out.

Although this analysis has only been carried out for this simple model, there seems no reason why the conclusion should be altered for any reasonable selection mechanism. It will certainly stand if the covariances of the random elements ξ_i have the same form as in the case considered.

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7. *Conclusions.* A population under simple selection tends to a stable equilibrium corresponding to a local maximum of the mean viability. The criteria for stability limit the existence of these equilibria in a manner intimately connected with the eigenvalues of the viability matrix. For instance, if there are p positive eigenvalues, at least $(p-1)$ genes must die out.

A mutant gene will establish itself if and only if the mean viability of the heterozygotes it forms with the original population is greater than the equilibrium mean viability of the population.

The effect of the non-deterministic nature of the process is to produce a fluctuation in the mean viability of the order of $(m-1)V_e/N$. Genetic drift does not occur near a stable equilibrium when the population is large unless the viability matrix is singular.

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Note added in proof

New proofs of the inequality (4) have recently been given by Atkinson, Watterson and Moran (*Quart. J. Math.* (*Oxford*) (2), 11 (1960), 137–40) and by the author (*Quart. J. Math.* (*Oxford*) (2) 12, (1961), 78–80).

REFERENCES

(1) MANDEL, S. P. H. The stability of a multiple allelic system. *Heredity*, 13 (1959), 289–302.
(2) SCHEUER, P. A. G. and MANDEL, S. P. H. An inequality in population genetics. *Heredity*, 13 (1959), 519–24.
(3) MULHOLLAND, H. P. and SMITH, C. A. B. An inequality arising in genetical theory. *Amer. Math. Mon.* 66 (1959), 673–83.

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