DIPLOID POPULATIONS WITH SELECTION DEPENDING ON GENE FREQUENCY

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(received 14 June 1962)

1. Introduction

We consider the case of a genetic population for which the selective advantages of the various genotypes are not constant but for each generation depend linearly on the gene frequencies in the population in the previous generation. For such populations, the effect of competition between similar genotypes may be allowed for by suitable choice of the frequency-dependent selective advantages, or, by a reversal of sign, the case where genotypes are favoured by the presence of similar genotypes may also be considered. All populations are finite and of constant size so that eventually only one type of gene will survive. The probabilities of survival for each gene are found and compared with the case where there are no frequency-dependent factors. If a small amount of mutation is allowed, gene fixation will not occur and a steady-state distribution of gene frequency will appear. The form of this distribution may be derived simply from the survival probabilities in the corresponding cases where there is no mutation. The main result is that in some cases, frequency-dependent factors have a marked effect on survival probabilities, while in other cases they can be completely ignored. The latter will only occur in certain cases where there exists competition between similar genotypes.

2. Infinite populations

Before considering finite populations it is interesting to examine the behaviour of the gene frequencies for infinite populations, where completely different behaviour is possible from that of the finite case. Suppose at the loculs under consideration there are two possible alleles A and a, so that the three possible genotypes are AA, Aa and aa, which are assumed to occur in proportions given by the Hardy-Weinberg law. We are interested in the proportion p of A genes. Consider first the case discussed by Wright [6] and Moran [4] where the selective advantages of AA, Aa and aa individuals are proportional to $1 - s + tq$, 1, $1 + s - tq$, respectively, where s and t

are both small and both positive, and $q = 1 - p$. Then the increase in p from one generation to the next is

$$\Delta p = \frac{pq(s - tq)}{1 - (s - tq)(p - q)}.$$

If $s > t$, $p \to 0$, but if $s < t$, $p \to 1 - st^{-1}$ and this latter point is one of stable equilibrium. On the other hand, if the selective advantages are $1 - s + tk$, 1, $1 + s - tk$, respectively, where k is any constant, then there are no equilibrium points except at $p = 0,1$. Thus the introduction of frequency-dependent selective advantages may lead to a non-trivial equilibrium point where no such point can exist for corresponding fixed selective advantages. However, this will not necessarily happen, for instance in the case where the selective advantages are $1 + s + tp$, 1, $1 + s + tq$, respectively. In this case it is found that $\Delta p = 0$ for $p = 0$, $\frac{1}{2}$, or 1, but that the equilibrium at the point $p = \frac{1}{2}$ is unstable.

3. Finite populations

We consider the case of a monoecious diploid population with non-overlapping generations and of constant size N (N large). Suppose that in generation i there are $k_i AA$ individuals and l_i aa individuals, and put $a_i = k_i N^{-1}$ and $b_i = l_i N^{-1}$. Suppose also that the selective advantages of AA, Aa, and aa individuals are proportional to

$$1 - s_1 + t_1 q_i,\ 1,\ 1 + s_2 - t_2 q_i, \text{ respectively}$$

where s_1, s_2, t_1 and t_2 are small (i.e. of order N^{-1}) and q_i is the proportion of a genes in generation i. Then if we make the usual assumption of Poisson distribution of offspring conditioned by total population $= N$, we find that the number of A genes in the next generation is a binomial variate with index $2N$ and parameter

$$\pi_i = \frac{a_i\{1-s_1+\frac{1}{2}t_1(1+b_i-a_i)\}+\frac{1}{2}(1-a_i-b_i)}{a_i\{1-s_1+\frac{1}{2}t_1(1+b_i-a_i)\}+\{1-a_i-b_i\}+b_i\{1+s_2-\frac{1}{2}t_2(1+b_i-a_i)\}}$$

$$= \frac{\frac{1}{2}(1+a_i-b_i)-s_1a_i+\frac{1}{2}t_1a_i(1+b_i-a_i)}{1-s_1a_i+s_2b_i+\frac{1}{2}t_1a_i(1+b_i-a_i)-\frac{1}{2}t_2b_i(1+b_i-a_i)}.$$

π_i will be called the "effective" proportion of A genes in contrast to $p_i = \frac{1}{2}(1 + a_i - b_i)$, the actual proportion. π_i is a Markovian variate whereas p_i is not. However, consideration of the transition matrix of π_i is impossible and we proceed as follows. s_1, s_2, t_1 and t_2 are $O(N^{-1})$ so that ignoring for the moment terms of order N^{-2} we have

$$\pi_i = \tfrac{1}{2}(1+a_i-b_i)-s_1a_i+\tfrac{1}{2}t_1a_i(1+b_i-a_i)$$
$$-\tfrac{1}{2}(1+a_i-b_i)[-s_1a_i+s_2b_i+\tfrac{1}{2}t_1a_i(1+b_i-a_i)-\tfrac{1}{2}t_2b_i(1+b_i-a_i)]$$

and therefore, since $E(a_{i+1}) = \pi_i^2$, $E(b_{i+1}) = (1-\pi_i)^2$,

$$V(a_{i+1}), V(b_{i+1}) \quad \text{are} \quad O(N^{-1}),$$

we have, to the same order of accuracy

$$E(\pi_{i+1}) = \pi_i - s_1\pi_i^2 + t_1\pi_i^2(1-\pi_i)$$
$$-\pi_i[-s_1\pi_i^2+s_2(1-\pi_i)^2+t_1\pi_i^2(1-\pi_i)-t_2(1-\pi_i)^3].$$

Thus if $\delta_{i+1} = \pi_{i+1} - \pi_i$, to order N^{-1},

$$E(\delta_{i+1}) = \pi_i(1-\pi_i)[-s_1\pi_i+t_1\pi_i(1-\pi_i)-s_2(1-\pi_i)+t_2(1-\pi_i)^2].$$

Also

$$V(\delta_{i+1}) \equiv V(\pi_{i+1})$$
$$= \pi_i(1-\pi_i)(2N)^{-1}$$

to the same order of accuracy.

Suppose now we can find a function $\phi(\pi_i)$ such that

$$E\phi(\pi_{i+1}) = \phi(\pi_i). \tag{3.1}$$

Then since we are ignoring for the moment terms of order N^{-2}, we have, expanding the left-hand side of (3.1) about π_i,

$$E(\delta_{i+1})\phi'(\pi_i) + \tfrac{1}{2}V(\delta_{i+1})\phi''(\pi_i) = 0$$

or

$$\frac{\phi''(\pi_i)}{\phi'(\pi_i)} = -2[-\alpha_1\pi_i-\alpha_2(1-\pi_i)+\beta_1\pi_i(1-\pi_i)+\beta_2(1-\pi_i)^2]$$

where

$$\alpha_1 = 2Ns_1, \quad \alpha_2 = 2Ns_2, \quad \beta_1 = 2Nt_1, \quad \beta_2 = 2Nt_2.$$

Since this equation is true for all π_i we may solve it to get

$$\phi(\pi_i) = \int_0^{\pi_i} \exp\left[\alpha_1x^2-\alpha_2(1-x)^2-2\beta_1\left(\frac{x^2}{2}-\frac{x^3}{3}\right)+\tfrac{2}{3}\beta_2(1-x)^3\right]dx.$$

Also, by iteration in (3.1), we have that if P is the probability that the whole population eventually consists of A genes, then

$$P\phi(1) + (1-P)\phi(0) = \phi(\pi_0),$$

where π_0 is the initial value of π.

https://doi.org/10.1017/S144678870002838X Published online by Cambridge University Press

Hence

$$P \equiv P(\pi_0)$$

$$= \frac{\int_0^{\pi_0} \exp\left[\alpha_1 x^2 - \alpha_2(1-x)^2 - 2\beta_1\left(\frac{x^2}{2} - \frac{x^3}{3}\right) + \frac{2}{3}\beta_2(1-x)^3\right] dx}{\int_0^1 \exp\left[\alpha_1 x^2 - \alpha_2(1-x)^2 - 2\beta_1\left(\frac{x^2}{2} - \frac{x^3}{3}\right) + \frac{2}{3}\beta_2(1-x)^3\right] dx} \tag{3.2}$$

It is worth noting that in the particular case $\beta_1 = \beta_2 = \beta$ say, in which the frequency-dependent selective advantages have the same coefficient for both homozygotes,

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp\left[\alpha_1 x^2 - \alpha_2(1-x)^2 + \beta(1-x)^2\right] dx}{\int_0^1 \exp\left[\alpha_1 x^2 - \alpha_2(1-x)^2 + \beta(1-x)^2\right] dx} \tag{3.3}$$

so that in this case, $P(\pi_0)$ is similar in form to the values of P found for populations with selection and dominance where there are no frequency-dependent factors, (c.f. Moran [3], Ewens [1]).

By giving the four constants α_1, α_2, β_1, β_2 appropriate values we may derive values of $P(\pi_0)$ for any linear frequency-dependent selective advantages.

4. Particular cases

Case 1.

The selective advantages

$$1 + tq,\ 1,\ 1 + tp$$

correspond to $\alpha_1 = 0$, $\alpha_2 = \beta_1 = \beta_2 = \beta$. Inserting these values in (3.2) or (3.3) we find

$$P(\pi_0) = \pi_0$$

so that survival probabilities are independent of t and are the same as for the case where no selection operates. We may therefore say that if the selective advantages of both homozygotes approach zero at the same rate as the proportion of the corresponding gene approaches unity, then we may ignore all selective factors in calculating survival probabilities. This is a particular example of a more general case considered later. If we are interested in the survival probability of a single initial mutant we have $\pi_0 = (2N)^{-1}$ if we take A to be the mutant, so that $P\{(2N)^{-1}\} = (2N)^{-1}$.

Case 2.

The case $\alpha_1 = -\alpha$, $\alpha_2 = 0$, $\beta_1 = -\alpha$, $\beta_2 = \beta$ corresponds to selective advantages

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$$1 + sp,\ 1,\ 1 + tq$$

so that the presence of like genotypes favours like genotypes if $s, t > 0$. Inserting these values in (3.2) we find

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp\left[-\frac{2}{3}\alpha x^3 - \frac{2}{3}\beta(1-x)^3\right] dx}{\int_0^1 \exp\left[-\frac{2}{3}\alpha x^3 - \frac{2}{3}\beta(1-x)^3\right] dx}. \tag{4.1}$$

For the case $\alpha \neq \beta$ a qualitative examination of (4.1) shows that if $\alpha > \beta$, then $P(\pi_0) > \pi_0$ for all π_0, while for the case $\alpha < \beta$, $P(\pi_0) < \pi_0$ for all π_0. This is expected, since if the selective advantages are such that the coefficient of the density-dependent selective factor for A is higher than that of a, one anticipates that the survival probability of A genes is higher than it would be if there were no selection. In the case of a single initial mutant, we have, to a close approximation,

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1} \exp\left(-\frac{2}{3}\beta\right)}{\int_0^1 \exp\left[-\frac{2}{3}\alpha x^3 - \frac{2}{3}\beta(1-x)^3\right] dx}.$$

The value of this expression depends not only on the relative values of α and β but also on their absolute values, and for fixed β the expression increases with α while for fixed α it decreases as β increases.

The case $\alpha = \beta$ corresponds to selective advantages of AA and aa individuals changing at equal rates as the proportion of the corresponding gene varies. Equation (4.1) reduces to

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp 2\alpha x(1-x)\, dx}{\int_0^1 \exp 2\alpha x\,(1-x)\, dx} \tag{4.2}$$

so that $P(1-\pi_0) = 1 - P(\pi_0)$ and $P(\frac{1}{2}) = \frac{1}{2}$ for all α. Values of $P(\pi_0)$ for various values of π_0 and α are given below (Table 1). Because of the symmetry, only values of $\pi_0 \geqq \frac{1}{2}$ are considered.

It may be noted from Table 1 that the curve of $P(\pi_0)$ against π_0 tends to be flat for intermediate values of π_0 when α is negative. That is, when the selective advantage of a genotype decreases below unity as the proportion of the corresponding gene increases, survival probabilities do not vary much for a wide range of values of π_0. On the other hand, for positive α, $P(\pi_0)$ is very sensitive to initial values of π_0. For the particular case where there is only one initial mutant, we have

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}}{\int_0^1 \exp\left[2\alpha x(1-x)\right] dx}.$$

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This is clearly less than $(2N)^{-1}$ for positive α, and the rate at which $P\{(2N)^{-1}\}$ decreases as α increases is indicated by the fact that for $\alpha = 4$, $P\{(2N)^{-1}\} = .226(2N)^{-1}$, while for $\alpha = 8$, $P\{(2N)^{-1}\} = .0.413(2N)^{-1}$. Thus even when the selective advantages of the two homozygotes change at the same rate, so that there is a symmetrical relationship between A and a, the survival probability of a single initial mutant, being largely determined by the behaviour of the selective advantages for the low initial values of π, is less than is the case for no selection.

TABLE 1

Values of $P(\pi_0)$ (Equation 4.2) for various π_0 and α

π_0	$\alpha = 16$	$\alpha = 8$	$\alpha = 4$	$\alpha = 2$	$\alpha = .5$	$\alpha = -.5$	$\alpha = -2$	$\alpha = -4$	$\alpha = -8$
1.00	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
.95	.9999	.9969	.9862	.9728	.9568	.9425	.9154	.8704	.7687
.90	.9993	.9905	.9664	.9424	.9115	.8875	.8449	.7803	.6571
.85	.9975	.9784	.9392	.9022	.8644	.8347	.7848	.7148	.5984
.80	.9918	.9593	.9033	.8599	.8157	.7838	.7326	.6668	.5650
.75	.9773	.9233	.8576	.8088	.7654	.7342	.6863	.6264	.5444
.70	.9452	.8728	.8019	.7554	.7139	.6860	.6444	.5946	.5306
.65	.8850	.8033	.7365	.6959	.6613	.6386	.6057	.5674	.5207
.60	.7882	.7152	.6628	.6328	.6080	.5920	.5693	.5434	.5128
.55	.6554	.6119	.5830	.5670	.5542	.5459	.5343	.5213	.5062
.50	.5000	.5000	.5000	.5000	.5000	.5000	.5000	.5000	.5000

Case 3.

If $t_1 = t_2 = 0$ there are no frequency-dependent selective advantages and the case of selection with dominance is obtained. If we put $s_1 = s(h-1)$, $s_2 = -sh$, the selective advantages become

$$1 + s,\ 1 + sh,\ 1$$

and inserting these values in (3.3) we find

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp[-2\alpha hx + \alpha Dx^2]\,dx}{\int_0^1 \exp[-2\alpha hx + \alpha Dx^2]\,dx} \qquad D = 2h-1$$

which agrees with a previous result (Kimura [2], Moran [3]).

Case 4.

The case of complete dominance is obtained if we put $s_1 = t_1 = 0$, for which, using (3.2),

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$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp[-\alpha_2(1-x)^2 + \frac{2}{3}\beta_2(1-x)^3]\,dx}{\int_0^1 \exp[-\alpha_2(1-x)^2 + \frac{2}{3}\beta_2(1-x)^3]\,dx}$$

$$= \frac{\int_{1-\pi_0}^1 \exp[-\alpha y^2 + \frac{2}{3}\beta y^3]\,dy}{\int_0^1 \exp[-\alpha y^2 + \frac{2}{3}\beta y^3]\,dy},$$

where we put $y = 1 - x$, $\alpha_2 = \alpha$, $\beta_2 = \beta$, for convenience.

The nature of $P(\pi_0)$ depends on the relative values of α and β and is best examined by examples.

Example (i): ($\alpha = 0$)

In this case

$$P(\pi_0) = \frac{\int_{1-\pi_0}^1 \exp[\frac{2}{3}\beta y^3]\,dy}{\int_0^1 \exp[\frac{2}{3}\beta y^3]\,dy}$$

and clearly $P(\pi_0) > \pi_0$ for $\beta > 0$, while $P(\pi_0) < \pi_0$ for $\beta < 0$. Also

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}\exp(\frac{2}{3}\beta)}{\int_0^1 \exp(\frac{2}{3}\beta y^3)\,dy}$$

which is greater than (less than) $(2N)^{-1}$ for positive (negative) β.

Example (ii): ($\alpha = \frac{1}{3}\beta$)

In this case

$$P(\pi_0) = \frac{\int_{1-\pi_0}^1 \exp[\frac{1}{3}\beta(2y^3 - y^2)]\,dy}{\int_0^1 \exp[\frac{1}{3}\beta(2y^3 - y^2)]\,dy}$$

and it is fairly easy to show that $P(\pi_0) > \pi_0$ for $\beta > 0$ and $P(\pi_0) < \pi_0$ for $\beta < 0$. Also

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}\exp(\frac{1}{3}\beta)}{\int_0^1 \exp[\frac{1}{3}\beta(2y^3 - y^2)]\,dy}$$

which is greater than (less than) $(2N)^{-1}$ for positive (negative) β.

Example (iii): ($\alpha = \frac{2}{3}\beta$)

In this case

$$P(\pi_0) = \frac{\int_{1-\pi_0}^1 \exp[-\frac{2}{3}\beta y^2(1-y)]\,dy}{\int_0^1 \exp[-\frac{2}{3}\beta y^2(1-y)]\,dy}.$$

Here $P(\pi_0)$ has the unusual property that for positive β, $P(\pi_0)$ is initially greater than π_0, but eventually $P(\pi_0)$ is less than π_0. For negative β the

converse holds. Thus the selective factors have a marked effect on the curve. We also have

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}}{\int_0^1 \exp\left[-\frac{2}{3}\beta y^2(1-y)\right]dy}$$

which is greater than (less than) $(2N)^{-1}$ for positive (negative) β.

Example (iv): $(\alpha = \beta)$

In this case

$$P(\pi_0) = \frac{\int_{1-\pi_0}^1 \exp\left[\beta(\frac{2}{3}y^3 - y^2)\right]dy}{\int_0^1 \exp\left[\beta(\frac{2}{3}y^3 - y^2)\right]dy}$$

and it is readily shown that $P(\pi_0) < \pi_0$ for $\beta > 0$, while $P(\pi_0) > \pi_0$ for $\beta < 0$. This contrasts markedly with the behaviour of $P(\pi_0)$ in Examples (i) and (ii), and clearly Example (iii) is one of transition between the two types. We also have

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}\exp(-\frac{1}{3}\beta)}{\int_0^1 \exp(\frac{2}{3}y^3 - y^2)\,dy}$$

which is less than (greater than) $(2N)^{-1}$ for positive (negative) β. This is in contrast with the behaviour in the previous examples and shows that if α is made large enough compared with β, the initial mutant has less chance of survival than if there were no selection. We also note that survival probabilities depend on the absolute values of α and β as well as their relative values. The value of α (for fixed β) for which $P\{(2N)^{-1}\} = (2N)^{-1}$ is the solution for α of the equation

$$\exp(-\alpha + \tfrac{2}{3}\beta) = \int_0^1 \exp(-\alpha y^2 + \tfrac{2}{3}\beta y^3)\,dy$$

which has been shown to lie in $(\frac{2}{3}\beta, \beta)$. The case where the allele a is the initial mutant may be found by putting $\pi_0 = 1 - (2N)^{-1}$ and considering $1 - P(\pi_0)$. In this case the value of α (for fixed β) for which $1 - P\{1 - (2N)^{-1}\} = (2N)^{-1}$ is the solution for α of the equation

$$\int_0^1 \exp(-\alpha y^2 + \tfrac{2}{3}\beta y^3)\,dy = 1$$

which has been shown to lie in $(\frac{1}{3}\beta, \frac{2}{3}\beta)$.

Case 5

If we put $s_1 = s_2 = t_1 = t_2 = s$, so that $\alpha_1 = \alpha_2 = \beta_1 = \beta_2 = \alpha$ we have selective advantages

$$1 - sp,\ 1,\ 1 + sp.$$

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Then

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp \alpha x^2 dx}{\int_0^1 \exp \alpha x^2 dx}. \tag{4.3}$$

Here we expect that if s is positive, that $P(\pi_0) < \pi_0$, since relatively the more common gene is hindered. Similarly for s negative we expect $P(\pi_0) > \pi_0$. Specific values of $P(\pi_0)$ may be easily found and are tabulated for typical values of α and π_0 below (Table 2).

TABLE 2

Values of $P(\pi_0)$ (Equation 4.3) for various π_0 and α

π_0	$\alpha = -4$	$\alpha = -1$	$\alpha = 1$	$\alpha = 4$
.95	.9975	.9741	.9104	.7250
.90	.9937	.9457	.8308	.5373
.85	.9884	.9145	.7573	.4070
.80	.9809	.8806	.6897	.3141
.75	.9706	.8439	.6274	.2467
.70	.9568	.8043	.5696	.1968
.65	.9384	.7619	.5757	.1591
.60	.9146	.7166	.4651	.1300
.55	.8843	.6687	.4176	.1072
.50	.8467	.6177	.3725	.0888
.45	.8007	.5642	.3297	.0738
.40	.7456	.5084	.2887	.0613
.35	.6810	.4502	.2494	.0506
.30	.6067	.3900	.2113	.0413
.25	.5230	.3279	.1745	.0331
.20	.4304	.2643	.1386	.0256
.15	.3302	.1994	.1033	.0188
.10	.2238	.1335	.0685	.0123
.05	.1130	.0669	.0342	.0061

Examination of the values of $P(\pi_0)$ in Table 2 confirms the previous arguments, as well as indicating that the effect of negative values of α seems to be more marked than the effect of the corresponding positive values. We also have

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}}{\int_0^1 \exp(\alpha x^2) dx}$$

which is less than (greater than) $(2N)^{-1}$ for positive (negative) α.

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Case 6.

If we put $-s_1 = s_2 = s$, $t_1 = t_2 = t$, the selective advantages become

$$1 + s + tq, 1, 1 + s - tq.$$

For $s > t > 0$ the homozygotes are favoured, for $0 > t > s$ the heterozygotes are favoured. Using (3.3) we obtain

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp[2\alpha x(1-x) + \beta(1-x)^2]\,dx}{\int_0^1 \exp[2\alpha x(1-x) + \beta(1-x)^2]\,dx}.$$

For $\pi_0 = (2N)^{-1}$ we have

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}\exp\beta}{\int_0^1 \exp[2\alpha x(1-x) + \beta(1-x)^2\}dx}.$$

For β fixed, this expression decreases as α increases, while for α fixed the expression increases with β.

An interesting case is $s = \frac{1}{2}t$ for which the selective advantages are

$$1 + t(q + \tfrac{1}{2}), 1, 1 + t(q - \tfrac{1}{2})$$

and for which

$$P(\pi_0) = \frac{1 - \exp(-\beta\pi_0)}{1 - \exp(-\beta)}$$

which is remarkably similar to the probabilities obtained in haploid theory. For the case $s = t$ we have

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp(-\beta x^2)\,dx}{\int_0^1 \exp(-\beta x^2)\,dx}.$$

In both cases the nature of the curve of $P(\pi_0)$ is evident. In the former,

$$P\{(2N)^{-1}\} = \frac{\beta(2N)^{-1}}{1 - \exp(-\beta)}$$

and in the latter

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}}{\int_0^1 \exp(-\beta x^2)\,dx}.$$

Case 7

If we put $s_1 = -s - t$, $s_2 = s$, $t_1 = t_2 = -t$ we obtain selective advantages

$$1 + s + tp, 1, 1 + s + tq$$

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so that each genotype is favoured by the presence of similar genotypes if $t > 0$. Substituting in (3.3) we obtain

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp[2(\alpha+\beta)x(1-x)]\,dx}{\int_0^1 \exp[2(\alpha+\beta)x(1-x)]\,dx}.$$

If $\alpha = -\beta$ we have $P(\pi_0) = \pi_0$ as in Case 1, as is otherwise obvious. We note that $P(\pi_0)$ depends on α and β only through their sum, so that if we put $\alpha + \beta = \gamma$, or $s + t = c$, so that $s = c - t$ we have selective advantages of the type

$$1 + c - tq,\ 1,\ 1 + c - tp$$

and for these selective advantages $P(\pi_0)$ is independent of t. This result extends that of Case 1 and enables a range of cases to be treated simultaneously. In particular by putting $t = c$ we recover Case 2 and by putting $t = 0$ we obtain a particular case of non-frequency-dependent selection. In all cases

$$P\{(2N)^{-1}\} = \frac{(2N)^{-1}}{\int_0^1 \exp[2\gamma x(1-x)]\,dx}$$

which is greater than (less than) $(2N)^{-1}$ if γ is negative (positive), as in Case 2. This example shows how density-dependent selective advantages may sometimes be ignored or treated as constant selective advantages.

Other Cases

A variety of other cases may be further obtained by suitable choice of s_1, s_2, t_1 and t_2, but the preceding cases seem to cover all situations of practical interest.

5. Bounds

Since terms of order N^{-2} have been ignored, the previous results are only very close approximations, and bounds must be found for the true probabilities. The method of doing so is best typified by an example. The main result is that bounds may be obtained by inserting a term of order N^{-1} in the expressions for $P(\pi_0)$. As an example we consider Case 5 where we suppose $\alpha > 0$. Define

$$\phi^*(\pi_i) = \int^{\pi_i} e^{\alpha x^2 + \varepsilon x}\,dx \tag{5.1}$$

where ε is of order N^{-1}.

Suppose we can choose ε such that

$$E\phi^*(\pi_{i+1}) < \phi^*(\pi_i). \tag{5.2}$$

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Then by iteration,

$$P\phi^*(1) + (1 - P)\phi^*(0) < \phi^*(\pi_0)$$

or

$$P < \frac{\phi^*(\pi_0) - \phi^*(0)}{\phi^*(1) - \phi^*(0)} \tag{5.3}$$

giving an upper bound for P. A lower bound may be found by similar arguments. Now (5.2) may be rewritten

$$E\int_{\pi_i}^{\pi_{i+1}} \exp(\varepsilon x + \alpha x^2)\,dx < 0$$

or

$$E\int_0^{\delta_{i+1}} \exp(\varepsilon y + \alpha y^2 + 2\alpha\pi_i y)\,dy < 0. \tag{5.4}$$

Let

$$\psi(\delta) = \int_0^{\delta} \exp(\varepsilon y + \alpha y^2 + 2\alpha\pi_i y)\,dy.$$

Then

$$\begin{aligned}
\psi'(\delta) &= \exp(\varepsilon\delta + \alpha\delta^2 + 2\alpha\pi_i\delta)\\
\psi''(\delta) &= (\varepsilon + 2\alpha\delta + 2\alpha\pi_i)\exp(\varepsilon\delta + \alpha\delta^2 + 2\alpha\pi_i\delta)\\
\psi'''(\delta) &= [(\varepsilon + 2\alpha\delta + 2\alpha\pi_i)^2 + 2\alpha]\exp(\varepsilon\delta + \alpha\delta^2 + 2\alpha\pi_i\delta)\\
\psi^{(\mathrm{iv})}(\lambda\delta) &= [(\varepsilon + 2\alpha\lambda\delta + 2\alpha\pi_i)^3 + 6\alpha(\varepsilon + 2\alpha\lambda\delta + 2\alpha\pi_i)]\\
&\qquad \exp(\varepsilon\lambda\delta + \alpha\lambda^2\delta^2 + 2\alpha\pi_i\lambda\delta)
\end{aligned}$$

so that

$$\psi(0) = 0,\ \psi'(0) = 1,\ \psi''(0) = \varepsilon + 2\alpha\pi_i,\ \psi'''(0) = (\varepsilon + 2\alpha\pi_i)^2 + 2\alpha.$$

The left-hand side in (5.4) may be written

$$E[\psi(0) + \delta_{i+1}\psi'(0) + \frac{\delta_{i+1}^2}{2}\psi''(0) + \frac{\delta_{i+1}^3}{6}\psi'''(0) + \frac{\delta_{i+1}^4}{24}\psi^{(\mathrm{iv})}(\lambda\delta_{i+1})] \tag{5.5}$$

where λ is a function of δ_{i+1} and lies in (0,1).

Since ε is $O(N^{-1})$ we have

$$\begin{aligned}
|\psi'''(0)| &< 8\alpha^2 + 2\alpha\\
|\psi^{(\mathrm{iv})}(\lambda\delta_{i+1})| &< (72\alpha^3 + 24\alpha^2)e^{3\alpha}.
\end{aligned}$$

By expanding out π_{i+1} we find

$$\begin{aligned}
\pi_{i+1} = {} & \tfrac{1}{2}(1 + a_{i+1} - b_{i+1}) - \tfrac{1}{2}sa_{i+1}(1 + a_{i+1} - b_{i+1})\\
& - \tfrac{1}{4}s(b_{i+1} - a_{i+1})(1 + a_{i+1} - b_{i+1})^2 + s^2\phi(a_{i+1}, b_{i+1})
\end{aligned} \tag{5.6}$$

where

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$$|\phi(a_{i+1}, b_{i+1})| < 4$$

and

$$E(\phi) = 0 \quad \text{for} \quad \pi_i = 0, 1.$$

Hence

$$E(\delta_{i+1}) = -s\pi_i^2(1 - \pi_i) + R_1\pi_i(1 - \pi_i)$$

where

$$|R_1| < 4\alpha^2 N^{-2} + \alpha N^{-2}$$

the latter term in the bound for R_1 arising from covariance terms when expectations are taken in (5.6).

Similarly

$$V(\delta_{i+1}) = \pi_i(1 - \pi_i)(2N)^{-1} + R_2\pi_i(1 - \pi_i)$$

where

$$|R_2| < 2\alpha N^{-2}.$$

Thus

$$E(\delta_{i+1}^2) = \pi_i(1 - \pi_i)(2N)^{-1} + R_3\pi_i(1 - \pi_i)$$

where

$$|R_3| < \tfrac{1}{4}\alpha^2 N^{-2} + 2\alpha N^{-2}.$$

Also,

$$E(\delta_{i+1}^3) = \tfrac{1}{2}\pi_i(1 - \pi_i)N^{-2} + R_4\pi_i(1 - \pi_i)$$

where

$$|R_4| < \alpha N^{-2}$$

and

$$|E(\delta_{i+1}^4)| < \tfrac{1}{4}\pi_i(1 - \pi_i)N^{-2}.$$

Thus (5.5) may be written

$$\pi_i(1 - \pi_i)[\varepsilon(4N)^{-1} + R_5]$$

where

$$|R_5| < N^{-2}[2\alpha^3 + 10\alpha^2 + 2\alpha + \tfrac{1}{4}(3\alpha^3 + \alpha^2)e^{3\alpha}].$$

Thus if we choose ε equal to

$$N^{-1}[8\alpha^3 + 40\alpha^2 + 8\alpha + (3\alpha^3 + \alpha^2)e^{3\alpha}] = \varepsilon^*$$

the term in ε dominates the remaining terms in (5.5).

By putting $\varepsilon = \varepsilon^*$ we have $E[\psi(\delta_{i+1})] > 0$ and by putting $\varepsilon = -\varepsilon^*$ we have $E[\psi(\delta_{i+1})] < 0$. Thus an upper bound for P is

$$\frac{\int_0^{\pi_0} \exp(-\varepsilon^* x + \alpha x^2)\,dx}{\int_0^1 \exp(-\varepsilon^* x + \alpha x^2)\,dx}$$

and a lower bound is

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$$\frac{\int_0^{\pi_0} \exp(\varepsilon^* x + \alpha x^2)\,dx}{\int_0^1 \exp(\varepsilon^* x + \alpha x^2)\,dx}.$$

These bounds could be greatly sharpened by more elaborate calculation, the point here being only to indicate a method for finding bounds. Bounds may be found in the other cases by similar methods, but the calculation will usually be more involved.

6. Stationary distributions

If mutation in both directions is allowed there will be no absorption but a steady-state distribution depending on the rates of mutation. Suppose the effect of the mutation is such that the probability that a gene chosen at random in the $(i+1)$th generation is found by replacing the effective proportion π_i of A genes in generation i by $\pi_i - \lambda\pi_i + \mu(1-\pi_i)$, ($\lambda$, μ of order N^{-1}). This corresponds to proportionate mutation at rate λ from A to a and μ from a to A. We may find the stationary distribution of effective gene frequency by applying the method of Wright [5] for such stationary distributions. Since we approximate a discrete distribution by a continuous distribution, this distribution will serve equally well as the distribution of p, the true frequency of A, since p and π differ only by terms of order N^{-1}, Applying Wright's formula, we have for the stationary distribution of π,

$$f(\pi) = \frac{\text{const}}{\sigma_\Delta^2}\, e^{2\int E\Delta(\pi)/\sigma^2_\Delta d\pi}$$

where Δ is the increase in π from one generation to the next. Thus

$$f(\pi) = \frac{\text{const}}{\sigma_\Delta^2} \exp\left[2\int E\delta(\pi)/\sigma_\Delta^2 d\pi + 4N\int \frac{(1-\pi)\mu - \pi\lambda}{\pi(1-\pi)}\,d\pi\right]$$

where $\delta(\pi)$ is the increase in π without mutation.

Therefore

$$f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} \exp[-\xi(\pi)] \tag{6.1}$$

where $\xi(\pi)$ is the function used previously for which

$$P(\pi_0) = \frac{\int_0^{\pi_0} \exp \xi(\pi)d\pi}{\int_0^1 \exp \xi(\pi)d\pi}. \tag{6.2}$$

From this it may be noted immediately that if $P(\pi_0)$ is independent of frequency-dependent factors, then so is $f(\pi)$. Also, if $4N\lambda = 1 = 4N\mu$,

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$$P(\pi) = \frac{\int_0^{\pi_0} [f(\pi)]^{-1} d\pi}{\int_0^1 [f(\pi)]^{-1} d\pi}.$$

It follows easily from this relation that if the proportion of A genes in the stationary distribution tends to be small, the probability of absorption of the A gene in the case without mutation tends to be high, and vice-versa. If we apply (6.1) and (6.2) to the various cases discussed in Section 4 we obtain the following stationary distributions:

Case 1 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1}$

Case 2 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{\frac{3}{2}\alpha\pi^3+\frac{3}{2}\beta(1-\pi)^3}$

Case 3 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{2\alpha h\pi-\alpha D\pi^2}$

Case 4 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{\alpha\pi^2-\frac{2}{3}\beta\pi^3}$

Case 5 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{-\alpha\pi^2}$

Case 6 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{-2\alpha\pi(1-\pi)-\beta(1-\pi)^2}$

Case 7 $f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} e^{2(\alpha+\beta)\pi(1-\pi)}$.

The condition that the exponent be a quadratic only is that $t_1 = t_2$, as before for absorption probabilities (c.f. Equations (3.2) and (3.3)). In this case the curves are very similar to curves found where there is no frequency-dependent selection. In the case $4N\lambda = 1 = 4N\mu$, where mutation is kept as low as possible consistent with bounded (continuous) distributions, the curves are readily sketched, and generally exhibit the feature that if the presence of like genes favours like genes the curves tend to concentrate in the extremities, whereas if the presence of like genes hinders like genes there is a tendency towards a maximum of $f(\pi)$ near the mid-range. In the case where $4N\lambda \neq 1$, $4N\mu \neq 1$, bimodal distributions may appear.

7. Extension

It is easy to extend the methods considered previously to find survival probabilities in the case where the selective advantages for AA, Aa, and aa individuals are $1 + s\phi(p)$, 1, and $1 + s\xi(p)$, respectively, where $\phi(p)$ and $\xi(p)$ are functions of p for which we require only that $\phi(p)$ and $\xi(p)$ and their second derivatives with respect to p are all $O(1)$. Then it follows that the probability P of survival of the A genes is given by

$$P = \frac{\int_0^{\pi_0} \exp\left[-2\alpha \int^x \{t\phi(t) - (1-t)\xi(t)\} dt\right] dx}{\int_0^1 \exp\left[-2\alpha \int^x \{t\phi(t) - (1-t)\xi(t)\} dt\right] dx}$$

to the order of accuracy considered previously. From this it follows imme-

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diately that if there exists a function $\theta(p)$ such that $\phi(p) = (1-p)\theta(p)$ and $\xi(p) = p\theta(p)$, then $P(\pi_0) = \pi_0$. This extends the result of Case 1 in Section 4 for which $\theta(p) =$ constant.

In the case where mutation is allowed it again follows easily that the stationary distribution of π is given by

$$f(\pi) = \text{const}\ \pi^{4N\mu-1}(1-\pi)^{4N\lambda-1} \exp\left[2\alpha \int^{\pi} t\phi(t) - (1-t)\xi(t)dt\right].$$

In this case the stationary distribution could be multimodal even though $4N\lambda = 4N\mu = 1$.

I should like to thank the referee for some useful criticisms.

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