

Multilocus models of inbreeding depression with synergistic selection and partial self-fertilization

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Summary

Mean fitness and inbreeding depression values in multi-locus models of the control of fitness were studied, using both a model of mutation to deleterious alleles, and a model of heterozygote advantage. Synergistic fitness interactions between loci were assumed, to find out if this more biologically plausible model altered the conclusions we obtained previously using a model of multiplicative interactions. Systems of unlinked loci were assumed. We used deterministic computer calculations, and approximations based on normal or Poisson theory. These approximations gave good agreement with the exact results for some regions of the parameter space. In the mutational model, we found that the effect of synergism was to lower the number of mutant alleles per individual, and thus to increase the mean fitness, compared with the multiplicative case. Inbreeding depression, however, was increased. Similar effects on mean fitness and inbreeding depression were found for the case of heterozygote advantage. For that model, the results were qualitatively similar to those previously obtained assuming multiplicativity. With the mutational load model, however, the mean fitness sometimes decreased, and the inbreeding depression increased, at high selfing rates, after declining as the selfing rate increased from zero. We also studied the behaviour of modifier alleles that changed the selfing rate, introduced into equilibrium populations. In general, the results were similar to those with the multiplicative model, but in some cases an ESS selfing rate, with selfing slightly below one, existed. Finally, we derive an approximate expression for the inbreeding depression in completely selfing populations. This depends only on the mutation rate and the dominance coefficient and can therefore be used to obtain estimates of the mutation rate to mildly deleterious alleles for plant species.

1. Introduction

In previous studies (Charlesworth & Charlesworth, 1990; Charlesworth, Morgan & Charlesworth, 1990) of the behaviour of inbreeding depression caused by overdominance or by many unlinked loci subject to deleterious mutation, in partially self-fertilizing populations, we concluded that large levels of inbreeding depression, such as are sometimes found in real organisms, can be generated. If the magnitude of the inbreeding depression exceeded one half there could be selection for outcrossing, when modifiers of the selfing rate do not affect the contribution to the pool of male gametes involved in outcrossing. To produce inbreeding depression in excess of one half with the mutational model, which is probably the more biologically realistic case, it was necessary to assume quite a low degree of dominance for the deleterious

alleles, and also a high mutation rate. In that work, we assumed a multiplicative model of interactions between loci. This seems a natural starting point for thinking about a multi-locus system that affects fitness, because it corresponds to the case when the loci act independently of one another, so that survival probability for a genotype is given by the probabilities of survival associated with the genotypes at each of the individual loci present (Crow, 1970).

It is, however, important to study other models of fitness interaction, because the multiplicative model is not necessarily the most biologically realistic. Furthermore, there is a possibility that synergistic interactions would lead to higher inbreeding depression than multiplicativity in populations with comparable mean fitness levels. If this occurs, there could be selection to maintain outcrossing under more permissive parameter values (i.e. lower mutation rates and higher dominance coefficients) than we found necessary in our previous study. There is evidence that

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mutant alleles may act synergistically in depressing fitness (reviewed by Charlesworth & Charlesworth, 1987, and by Charlesworth, 1990), and there are reasons to expect that the type of fitness interactions may affect the results. Kondrashov (1985, 1988) has emphasized the importance of truncation selection, which can be viewed as a severe form of synergistic interaction (where the deleterious effect of having a mutant allele becomes increasingly severe, the more mutations the genotype carries).

In this paper, we study two different models for the maintenance of genetic variation in fitness. In the first of these, mutation to deleterious alleles occurs at many unlinked loci, and we study the effects of changing from the multiplicative model to the synergistic model of fitness interactions, on both the mean numbers of mutant alleles maintained per individual, and on the population mean fitness and inbreeding depression values of equilibrium populations with various levels of self-fertilization. With parameter values that are plausible for this form of selection, equilibrium populations sometimes build up very large average numbers of mutant alleles per individual (although these numbers are smaller than for the multiplicative runs with similar parameter values). The finding of large numbers of mutations per individual in these populations suggested the possibility of deriving approximate analytical models, and we present these for both the synergistic and multiplicative cases. The approximations are based on the assumption that the numbers of mutant alleles per individual follow normal or Poisson distributions. This permits more detailed exploration of the parameter space than was previously possible. The approximations are valid only for certain regions of the parameter space, but within these regions they give close agreement with the results of computer calculations that do not make any simplifying assumptions about the distribution of numbers of mutations.

We also compare the synergistic and multiplicative selection cases, using a model in which the variation in fitness in the populations is due to the maintenance of genetic variation at a number of unlinked loci whose alleles show symmetrical overdominance. For this model also, an approximate analytical treatment can be derived that gives excellent agreement with the results of computer calculations. Finally, for both types of model, we study the behaviour of modifier alleles that change the frequency of self-fertilization, to investigate the relationship between inbreeding depression and evolution of the selfing (or outcrossing) rate.

2. Model of synergistic interactions

(i) Mutational model

The multiplicative model of interactions between loci used by Charlesworth *et al.* (1990) assumes that the fitness of a genotype is given by the expression:

$$w_{yz} = (1-s)^y (1-hs)^z, \quad (1)$$

where s is the selection coefficient against the mutant alleles (assumed to be the same for mutants at all loci), h is the dominance coefficient of these alleles, and y and z are the numbers of homozygous and heterozygous mutations in the genotype, respectively. Compared with this model, synergistic epistasis should decrease the mean number of mutant alleles present per individual in a population at equilibrium under mutation-selection balance. Thus the genetic load due to mutation is decreased if multiple-mutant genotypes have lower fitness than if the loci affected fitness independently (Kimura & Maruyama, 1966; Crow, 1970). This form of synergism should also increase the inbreeding depression, because the effect of becoming homozygous for deleterious alleles should cause a greater decrease in fitness than when the fitness effect of the genotype at one locus is independent of the genotypes at the other loci. This can be seen by considering the way in which synergistic epistasis for fitness can be modelled. Charlesworth (1990) introduced a model of synergistic interactions for the case of a random-mating population, in which log fitness was assumed to be a quadratic function of the number of loci heterozygous for mutant alleles. In the present paper, we wish to allow homozygosity for mutant alleles. This model can be generalized to write:

$$w_n = \exp \left[- \left(\alpha n + \frac{\beta n^2}{2} \right) \right], \quad (2)$$

where n , the effective number of mutations, can be expressed as a function of the numbers of mutations carried in the heterozygous state and the number homozygous, by weighting heterozygous mutations by the dominance coefficient, so that one homozygous mutation counts for the same as $1/h$ heterozygous ones (Sved & Wilton, 1989). In other words, we have $n = hz + y$. As explained by Charlesworth (1990), the coefficient α in this epistatic fitness expression can be viewed as measuring the strength of selection and β/α as measuring the degree of synergism. These coefficients are related approximately to the parameters in the quadratic fitness model of Kimura & Maruyama (1966) as follows. In that model, the fitness of a genotype with n mutations is given by $w_n = 1 - \alpha n - \beta n^2$ (Crow, 1970). With weak selection, $\alpha \approx a$ and $\beta \approx 2b$ (note that because of the difference in the meaning of the parameter n , the α and β parameters are not numerically the same as in Charlesworth, 1990). In most of what follows, we based our runs on the 'standard parameter values' of Charlesworth (1990). In the present notation, these values are $\alpha = 0.01$, $\beta = 0.02$, $h = 0.2$. On this model, where one homozygous mutation is in a sense equivalent to many heterozygous ones and the effects of mutations are increasingly severe the more of them that are present in a genotype, the effect of inbreeding on fitness is evidently to cause a bigger decrease in fitness than with multiplicative fitness interactions, or with a 'diminishing returns' form of epistasis in which

additional mutations have less and less effect (Charlesworth, 1990).

Note that the model just specified is only one possible way in which synergism between the fitness effects of mutations at different loci could be modelled, and that other models might behave differently in some ways (Sved & Wilton, 1989). However, all models should share the properties listed earlier in this section. The model has some convenient features, including the property that the β/α parameter measures the degree of synergism, so that this can be varied independently of the strength of selection. When $\beta = 0$, this model is approximately equivalent to the multiplicative fitness function of eqn (1), such that $\alpha \approx s$ when selection is weak. With stronger selection, no such direct equivalence exists.

The model given above has the property in common with truncation selection that fitness declines sharply when a mutation occurs in a genotype that has many mutations, but in the model described here there is no discontinuity. Truncation selection is therefore not a special case of this model, but must be studied separately.

In comparing results using the multiplicative and synergistic models, the ideal situation would be to hold constant the intensity of selection, together with the other important parameters, i.e. the dominance coefficient and the mutation rate, and just change the model of the interactions between loci. However, the selection intensity cannot be kept constant because with interactions in fitness between loci the selection at each locus depends on the genotypes at other loci. Using the synergism model specified above, it would seem that this could be achieved by keeping α constant and changing β . However, we cannot compare results with β greater than zero with results that assume the same selection coefficient, because the introduction of synergism effectively changes the selection on each locus (Sved & Wilton, 1989, p. 125). This is apparent if one considers that, as mentioned above, the mean number of mutant alleles per individual at equilibrium is much lower under synergism than with multiplicativity (Crow, 1970; Charlesworth, 1990), implying effectively stronger selection against mutant alleles when there is synergistic epistasis. To make comparison possible, we need to compare synergistic and multiplicative runs where both have the same mean number of mutations per individual at equilibrium, \bar{n} . To do this, we make use of the result that for a random mating population at equilibrium under the multiplicative model the selection coefficient against heterozygotes for mutant alleles at each locus obeys the equation

$$sh = \frac{U}{\bar{n}},$$

where U is the mutation rate per generation per diploid genome (Crow, 1970). This gives us a way of deriving a selection coefficient from the observed

value of \bar{n} in a run that assumed synergistic epistasis with given values of U and h . This can then be used in runs with the multiplicative assumption $\beta = 0$, to yield the same value of \bar{n} for the same value of U . This, however, is only correct for outcrossing populations. For the case of partial or complete selfing, the above result does not hold true, and there is no other comparable equivalence property, so it is not possible to generate comparable pairs of results based on the multiplicative and synergistic assumptions. We have therefore proceeded to do runs with the same parameter values as for the corresponding outcrossing cases, other than changes in the selfing rate, S , even though the above selection coefficient does not correctly describe the intensity of selection against mutant alleles in selfing populations.

For the standard parameter values specified above, the value of s is about 0.14, which together with an h value of 0.2 yields $1/hs = 38$. Crow & Simmons (1983, p. 27) estimated persistence times of mildly detrimental mutations in natural populations (which should be equal to $1/hs$) to be about 50, so that it appears that our parameter values are quite reasonable.

(ii) *Symmetrical overdominance*

Equal selective values at all loci were again assumed. Fitness was assumed to be a decreasing function of the number of loci homozygous (Charlesworth and Charlesworth, 1990). Thus, in the above notation, y can simply be substituted for n in eqn (2).

3. Assumptions of the population models, and computer methods

(i) *Mutational model*

In the work to be described here, all loci were assumed to be unlinked and a mutation at any of the loci was assumed to have an equivalent effect on fitness (equal selective values at all loci). These assumptions permit the deterministic method of Kondrashov (1985) to be used for the calculations. The methods used in what follows were the same as described in our previous paper on the case of multiplicative fitness interactions (Charlesworth *et al.* 1990; Charlesworth, 1990), except for the change in the model of fitness interactions between the loci subject to mutation. As in our previous work, the sequence of events in each generation, starting from adult individuals, was mutation, then mating, and finally selection on the zygotes and normalization to produce the frequencies of the genotypic classes in the adults of the new generation. The number of new mutations per diploid individual follows a Poisson distribution with mean U .

Populations were run to equilibrium in the absence of genetic variation for the selfing rate, and the properties of the equilibrium population recorded. These included the mean fitness, \bar{w} , and the mean

fitnesses of progeny produced by outcrossing and by selfing (\bar{w}_x and, \bar{w}_s respectively). The inbreeding depression ($\delta = 1 - \bar{w}_s/\bar{w}_x$) was calculated from these fitness values. Then a modifier allele changing the selfing rate was introduced and its frequency followed until a steady-state rate of change was attained. In certain cases, we also allowed the runs to continue until the modifier allele was either fixed or lost from the population. Modifier alleles were assumed to have intermediate dominance. Individuals of different genotypes at the modifier locus could be assumed to contribute equally to the pool of pollen used in generating the outcrossed progeny, or else the modifier could be allowed to affect the pollen output as well as the selfing rate. This allows for the possibility that 'pollen discounting' by genotypes with high selfing rates might lower their pollen output (Nagylaki, 1976).

(ii) *Overdominance model*

This model was based on Ziehe & Roberds' (1989) model of unlinked overdominant loci, generalized by Charlesworth & Charlesworth (1990) to include modifiers of the selfing rate. A number of such loci were assumed, with equal symmetrical selection coefficients against the homozygotes at all loci. The assumption of symmetrical fitnesses facilitates calculation of the genotypic distributions after mating, since there is no need to distinguish between the two homozygous genotypes. The sequence of events in each generation was similar to that described above for the mutational model, but there is no mutational step. Under this model, it is well known that all loci will have equilibrium allele frequencies of one-half.

4. Approximate analytical model of mutation-selection balance with multiple loci and partial selfing

In this section, we will develop some approximate analytical results that will later be compared with the results of the computer calculations described above.

(i) *General considerations*

From the assumptions of the model, the state of an individual is characterized by the vector (y, z), where y and z are the numbers of homozygous and heterozygous mutations carried by the individual, respectively. The population of zygotes at the start of a generation consists of two subpopulations, one derived from outcrossing of the parents and the other from selfing. The respective frequencies are $1 - S$ and S . The state of these sub-populations is described by the following variables. The number of heterozygous mutations per individual for the outcrossed sub-population has mean \bar{z}_x and variance V_{zx} . The number of homozygous mutations in this sub-population is zero, by hypothesis. The distribution of the number of

heterozygous mutations in the selfed sub-population has mean and variance \bar{z}_s and V_{zs} , respectively. Similarly, the distribution of the number of homozygous mutations has mean and variance of \bar{y}_s and V_{ys} , respectively. The covariance between the number of heterozygous and homozygous mutations among the selfed sub-population is C_{yzs} . Recurrence relations for these variables can be found by making specializing assumptions about the form of the relevant distributions. Two sets of such assumptions will be considered below.

(ii) *Normal distribution model*

Normal distribution theory has been found to be very useful for dealing with the selection model of eqn (2), in the case of a random-mating population (Charlesworth, 1990). To apply this approach to the case of a partially selfing population, we have to assume a univariate normal distribution of the number of heterozygous mutations for the outcrossed sub-population, and a bivariate normal distribution of the number of heterozygous and homozygous mutations for the selfed sub-population. As will be seen below, this assumption is approximately correct under a wide range of conditions but tends to break down with high rates of self-fertilization when epistasis is weak.

Given the form of the selection function used here, the post-selection distributions within a generation are also normal. The means, variances and covariance of numbers of heterozygous and homozygous mutations for the post-selection distributions will be denoted by asterisks. From the results of Charlesworth (1990) for a random-mating population, the mean fitness of the outcrossed sub-population is

$$\bar{w}_x = (1 + \beta V_{zx})^{-1} \exp \frac{1}{2(1 + \beta V_{zx})} \times \{\alpha^2 V_{zx} - 2\alpha \bar{z}_x - \beta \bar{z}_x^2\}. \quad (3)$$

The mean number of heterozygous loci per individual in the post-selection outcrossed sub-population is

$$\bar{z}_x^* = (\bar{z}_x - \alpha V_{zx}) / (1 + \beta V_{zx}), \quad (4a)$$

and the variance is

$$V_{zx}^* = V_{zx} / (1 + \beta V_{zx}). \quad (4b)$$

The mean fitness \bar{w}_s , and the post-selection means and variances of the numbers of homozygous and heterozygous loci, of the selfed population can be obtained by the bivariate equivalent of the method of Charlesworth (1990), as outlined in the Appendix.

For the population as a whole (derived partly from outcrossing and partly from selfing), the population mean fitness \bar{w} and the parameters of the overall distribution of numbers of mutations after selection are given by the following expressions:

$$\bar{w} = (1 - S) \bar{w}_x + S \bar{w}_s, \quad (5a)$$

$$\bar{y}^* = S^* \bar{y}_s^*, \quad (5b)$$

$$\bar{z}^* = (1 - S^*) \bar{z}_x^* + S^* \bar{z}_s^*, \tag{5c}$$

$$V_y^* = S^* V_{ys}^* + S^*(1 - S^*) \bar{y}_s^{*2}, \tag{5d}$$

$$V_z^* = (1 - S^*) V_{zx}^* + S^* V_{zs}^* + S^*(1 - S^*)(\bar{z}_x^* - \bar{z}_s^*)^2, \tag{5e}$$

$$C_{yz}^* = S^* C_{yzs}^* - S^*(1 - S^*) \bar{y}_s^*(\bar{z}_x^* - \bar{z}_s^*), \tag{5f}$$

where $S^* = S\bar{w}_s/\bar{w}$. The terms involving the factor $S^*(1 - S^*)$ in the variances and covariance arise from the contributions of the difference in means between the selfed and outcrossed subpopulations.

The effects of selection on the variances and covariances within the selfed and outcrossed subpopulations given by these equations reflect only the effects of selection on the components of variance contributed by deviations from random combinations of alleles at different loci, and do not include the changes in the genic variances contributed by the sum of the effects of each locus in isolation (Charlesworth, 1990). It is not clear in the case of partially selfing populations how to incorporate the effects of selection on the genic variances of the numbers of homozygous and heterozygous mutations. We adopt the heuristic principle that, at equilibrium, these effects balance the effects of mutation. (This procedure is exact in the case of an outcrossing population, see Charlesworth, 1990.) The equilibrium variances can then be computed by ignoring the effects of both selection and mutation on the changes in the genic variances. Accordingly, the recurrence relations given below are only valid close to equilibrium.

The distribution of z among the progeny of outcrossed individuals in the next generation can be found by noting that the progeny of two randomly chosen individuals with states (y, z) and (y', z') has mean $y + y' + \frac{1}{2}(z + z')$. Segregation at each locus that is heterozygous in either parent contributes a term of one-quarter to the variance of z in the progeny. Assuming free recombination, the variance of z in the progeny of this mating is thus $\frac{1}{4}(z + z')$. There is an additional contribution of U to the change in the mean of z . (New mutations contribute solely to the distribution of heterozygous mutations, since they are not made homozygous immediately.) Averaging over all pairs of parents, we obtain the following expression for the state of the outcrossed sub-population in the next generation:

$$\bar{z}'_x = 2\bar{y}^* + \bar{z}^* + U, \tag{6a}$$

$$V'_{zx} = 2V_y^* + \frac{1}{2}V_z^* + 2C_{yz}^* + \frac{1}{2}\bar{z}. \tag{6b}$$

The parameters of progeny produced by selfing can be determined as follows. Free recombination implies a multinomial distribution of the numbers of homozygous and heterozygous mutations in the progeny of a selfed individual. The mean number of homozygous mutations among the selfed progeny of an individual of state (y, z) is $y + \frac{1}{4}z$, and the variance is $3y/16$. The mean number of heterozygous mutations

is $z/2$ and the variance is $z/4$. The covariance between y and z is $-z/8$. Averaging over the entire population of parental genotypic classes, the following expression describes the state of the selfed sub-population in the next generation:

$$\bar{y}'_s = \bar{y}^* + \frac{1}{4}\bar{z}^*, \tag{7a}$$

$$\bar{z}'_s = \frac{1}{2}\bar{z}^* + U, \tag{7b}$$

$$V'_{ys} = V_y^* + \frac{1}{16}V_z^* + \frac{1}{2}C_{yz}^* + \frac{3}{16}\bar{z}, \tag{7c}$$

$$V'_{zs} = \frac{1}{4}V_z^* + \frac{1}{4}\bar{z}, \tag{7d}$$

$$C'_{yzs} = \frac{1}{8}V_z^* + \frac{1}{2}C_{yz}^* - \frac{1}{8}\bar{z}. \tag{7e}$$

Equations (6) and (7), together with the expressions for the state of the post-selection population, provide a complete description of the transition between generations. These expressions cannot be solved analytically for the equilibrium state, but are easy to iterate on a computer. Equilibrium is reached in a few tens of generations.

Table 1 shows the equilibrium values of these distributional parameters for $U = 1$ and $\alpha/\beta = 0.5$, indicating satisfactory agreement between the exact and approximate results in this case. For weak epistasis, this approach breaks down, due to severe departures from normality, especially for progeny of selfing. For this reason, we have used an approximation based on the Poisson distribution for that case.

(iii) *Poisson distribution model*

In the case of the multiplicative model of eqn (1), it is known that the numbers of mutations per individual follow Poisson distributions in both random-mating and wholly self-fertilising populations (Haigh, 1978; Heller & Maynard Smith, 1979). This suggests that it may be useful to assume Poisson distributions for the present case with multiplicative fitnesses, where (as discussed above) the normal approximation tends to fail with high selfing. Assume that the distributions of the numbers of heterozygous mutations among outcrossed progeny, among selfed progeny, and the distribution of the number of homozygous mutations among selfed progeny, are each Poisson, with means of \bar{z}_x , \bar{z}_s and \bar{y}_s respectively. Assume further that the distributions of the numbers of heterozygous and homozygous mutations among selfed progeny are independent. Given these assumptions, it is easily seen that (with multiplicative fitnesses) the corresponding post-selection distributions are also Poisson. We have

$$\bar{w}_x = \exp - \bar{z}_x hs, \tag{8a}$$

$$\bar{z}_x^* = \bar{z}_x (1 - hs), \tag{8b}$$

$$\bar{w}_s = \exp - (\bar{y}_s + \bar{z}_s h) s, \tag{8c}$$

$$\bar{y}_s^* = \bar{y}_s (1 - s), \tag{8d}$$

$$\bar{z}_s^* = \bar{z}_s (1 - hs). \tag{8e}$$

Table 1. Results of the exact and semi-analytical methods of calculating the equilibria for the mutation-selection balance model with synergism

S		\bar{z}_x	\bar{z}_s	\bar{y}_s	V_{zx}	V_{zs}	V_{ys}	C_{yzs}
$\alpha = 0.01, \beta = 0.02$								
0.01	Exact	34.796	17.369	8.713	34.010	17.274	8.639	-0.354
	Approx.	34.857	17.900	8.478	33.884	17.195	8.648	-0.310
0.1	Exact	32.361	15.863	8.248	31.811	18.537	8.433	-1.125
	Approx.	32.729	16.555	8.087	31.246	18.110	8.294	-1.066
0.2	Exact	29.492	14.053	7.719	29.107	19.502	8.187	-2.022
	Approx.	30.179	14.914	7.633	28.259	18.848	7.984	-1.957
0.5	Exact	21.376	8.622	6.377	20.867	18.378	7.290	-3.611
	Approx.	22.513	9.721	6.396	19.921	17.764	7.181	-3.676
0.7	Exact	17.165	5.471	5.847	16.062	14.337	6.452	-3.376
	Approx.	18.173	6.517	5.828	15.230	13.660	6.469	-3.486
0.8	Exact	15.473	4.023	5.724	13.795	11.322	5.896	-2.835
	Approx.	16.349	5.031	5.659	13.172	10.535	5.969	-2.926
0.9	Exact	14.103	2.591	5.755	11.453	7.324	5.147	-1.897
	Approx.	14.892	3.597	5.648	10.977	6.567	5.279	-2.023
0.99	Exact	13.497	1.168	6.164	8.859	1.878	3.980	-0.312
	Approx.	14.568	2.219	6.175	8.357	1.531	4.109	-0.606
$\alpha = 0.1, \beta = 0.2$								
0.01	Exact	10.746	5.366	2.690	10.210	5.125	2.620	-0.139
	Approx.	10.799	5.894	2.453	10.034	5.029	2.603	-0.187
0.1	Exact	10.062	4.954	2.554	9.661	5.023	2.478	-0.141
	Approx.	10.187	5.531	2.328	9.352	4.786	2.437	-0.172
0.2	Exact	9.278	4.475	2.401	8.988	4.840	2.317	-0.151
	Approx.	9.485	5.109	2.188	8.578	4.478	2.263	-0.169
0.5	Exact	7.021	3.037	1.992	6.793	3.852	1.860	-0.185
	Approx.	7.471	3.842	1.814	6.329	3.320	1.849	-0.221
0.7	Exact	5.767	2.166	1.800	5.387	2.898	1.605	-0.177
	Approx.	6.351	3.082	1.634	4.999	2.385	1.663	-0.267
0.8	Exact	5.223	1.757	1.733	4.721	2.338	1.489	-0.153
	Approx.	5.879	2.735	1.572	4.379	1.875	1.588	-0.288
0.9	Exact	4.725	1.353	1.686	4.067	1.701	1.375	-0.106
	Approx.	5.479	2.403	1.538	3.764	1.325	1.517	-0.305
0.99	Exact	4.309	0.980	1.664	3.471	1.021	1.267	-0.032
	Approx.	5.211	2.102	1.554	3.169	0.759	1.438	-0.310

The inbreeding depression, $\delta = 1 - \bar{w}_s/\bar{w}_x$, can be derived from these quantities. The pre- and post-selection variances are equal to the respective means, by hypothesis. The post-selection means and variances for the population as a whole are given by eqn (5). The means in the next generation are given by eqns (6a), (7a) and (7b).

The variances are given by the following equations:

$$V'_{zx} = 2V_y^* + \frac{1}{2}V_z^* + 2C_{yz}^* + \frac{1}{2}\bar{z}^* + U, \tag{9a}$$

$$V'_{ys} = V_y^* + \frac{1}{16}V_z^* + \frac{1}{2}C_{yz}^* + \frac{3}{16}\bar{z}^*, \tag{9b}$$

$$V'_{zx} = 2V_y^* + \frac{1}{2}V_z^* + 2C_{yz}^* + \frac{1}{2}\bar{z}^* + U, \tag{9c}$$

$$C'_{yzs} = \frac{1}{8}V_z^* + \frac{1}{2}C_{yz}^* - \frac{1}{8}\bar{z}^*. \tag{9d}$$

Inspection of these equations, together with the corresponding equations for the means, indicates that equality of means and variances and independence of the distributions of numbers of homozygous and heterozygous mutations among selfed progeny are preserved only if the post-selection means and variances for the whole population are equal. It can be seen from eqn (5) that the mixing of selfed and outcrossed progenies causes the means and variances to diverge,

implying that the composite population no longer exactly follows Poisson distributions. Hence, the Poisson model will in general deviate from the exact results. The magnitude of the discrepancy will be greatest for intermediate selfing rates. Numerical studies show that in practice it provides good approximations for the case of multiplicative fitnesses, using the model of fitness interactions between loci specified by eqn (1) above (see Table 2 below). For the model used in the present paper, where heterozygous mutations are weighted by the dominance coefficient as explained above, it gives good agreement only for weak selection, and is best for either low or high selfing rates.

5. Analytical model of symmetrical overdominance with multiple loci and partial selfing

A similar method can be used to provide an analytical approach to the case of multiple independent loci with symmetrical overdominance and equal fitness effects, previously studied by Ziehe & Roberds (1989) and Charlesworth & Charlesworth (1990) for the case of

Table 2. Results of the exact and semi-analytical methods of calculating the equilibria for the mutation-selection balance model with multiplicative fitnesses. $U = 1, h = 0.1$

S		\bar{w}	σ	\bar{z}_z	\bar{z}_s	\bar{y}_s	V_{zz}	V_{zs}	V_{ys}	C_{yzz}
$s = 0.9$										
0.01	Exact	0.3692	0.8499	10.601	5.302	2.657	10.736	5.375	2.666	-0.035
	Approx.	0.3671	0.8629	11.042	5.523	2.764	11.042	5.523	2.764	0
0.10	Exact	0.3742	0.8301	9.978	4.984	2.506	10.268	5.149	2.528	-0.073
	Approx.	0.3618	0.8441	10.325	5.155	2.583	10.325	5.155	2.583	0
0.20	Exact	0.3998	0.7678	8.359	4.174	2.095	8.962	4.508	2.162	-0.151
	Approx.	0.3651	0.8108	9.237	4.606	2.316	9.237	4.606	2.316	0
0.50	Exact	0.5194	0.5064	4.067	2.008	1.033	4.621	2.314	1.093	-0.139
	Approx.	0.4654	0.5774	4.714	2.324	1.195	4.714	2.324	1.195	0
0.70	Exact	0.5575	0.4003	2.855	1.380	0.736	3.124	1.540	0.763	-0.067
	Approx.	0.5301	0.4320	3.057	1.489	0.784	3.057	1.489	0.784	0
0.90	Exact	0.5764	0.3325	2.174	1.040	0.578	2.246	1.080	0.575	-0.018
	Approx.	0.5685	0.3403	2.213	1.068	0.586	2.213	1.068	0.586	0
0.99	Exact	0.5815	0.3095	1.963	0.936	0.510	1.965	0.932	0.516	-0.006
	Approx.	0.5808	0.3102	1.964	0.938	0.524	1.964	0.938	0.524	0
$s = 0.2$										
0.01	Exact	0.3674	0.8628	49.631	24.804	12.426	49.665	25.016	12.438	-0.061
	Approx.	0.3675	0.8628	49.633	24.803	12.415	49.633	24.803	12.415	0
0.10	Exact	0.3681	0.8137	41.715	20.688	10.516	41.730	22.721	10.709	-0.695
	Approx.	0.3620	0.8456	46.393	23.044	11.683	46.393	23.044	11.683	0
0.20	Exact	0.3717	0.8080	40.618	19.937	10.344	41.073	24.456	10.811	-1.371
	Approx.	0.3644	0.8159	41.562	20.413	10.583	41.562	20.413	10.583	0
0.50	Exact	0.4697	0.5939	20.154	8.794	5.686	21.354	15.535	6.403	-1.807
	Approx.	0.4642	0.6026	20.443	8.916	5.777	20.443	8.916	5.777	0
0.70	Exact	0.5490	0.4418	11.452	4.094	3.683	12.498	7.815	4.113	-0.841
	Approx.	0.5386	0.4548	11.774	4.196	3.797	11.774	4.196	3.797	0
0.90	Exact	0.5918	0.3517	7.215	1.767	2.724	7.647	2.906	2.881	-0.225
	Approx.	0.5845	0.3591	7.336	1.773	2.787	7.336	1.773	2.787	0
0.99	Exact	0.6001	0.3267	6.001	1.053	2.479	6.048	1.168	2.491	-0.022
	Approx.	0.5991	0.3276	6.013	1.053	2.484	6.013	1.053	2.484	0

multiplicative fitnesses. In this case, the fitness of an individual homozygous at y loci can be written as $w(y) = \exp -y(\alpha + \frac{1}{2}\beta y)$. (10)

Since loci and alleles are interchangeable. Since the number of heterozygous loci is simply $m - y$, where m is the total number of loci in the genome which exhibit heterozygote advantage, the system can be described entirely in terms of the single variable y .

The approximate recurrence relations for this case can be derived as follows. Following Ziehe & Roberds (1989), the number of heterozygous loci per individual in the outcrossed sub-population before selection is distributed binomially, with mean and variance $m/2$ and $m/4$, respectively. (This result is independent of the nature of the selection function.) Normal distribution theory can be used to calculate changes in the means and variances of y among the outcrossed and selfed sub-populations (cf. eqns (3) and (4)). The parameters of the post-selection distribution for the whole population are given by eqn (5). The mean and variance of the number of homozygous loci per individual among the new zygotes produced by selfing can be found by the same method as before, with the difference that homozygotes for both types of allele at a locus contribute to y . We obtain

$$\bar{y}'_s = \frac{1}{2}(\bar{y}^* + m), \tag{11a}$$

$$V'_{ys} = \frac{1}{4}(V_y^* + m - \bar{y}^*). \tag{11b}$$

These equations can be iterated to find the composition of equilibrium populations under this model.

6. Results

(i) Mutational model: numbers of mutations and genetic loads in equilibrium populations

As Charlesworth (1990) found for the random-mating case, even a slight degree of synergism (a small, but non-zero, β value) causes a substantial reduction in the numbers of mutations at equilibrium compared with the multiplicative case ($\beta = 0$). This is evident in our calculated results, using either the exact deterministic or approximate analytical model described above. As mentioned above, we mainly studied the 'standard parameter values' of Charlesworth (1990), together with the effects of changes in the values of some of the parameters. Fig. 1 shows a set of runs with $\alpha = 0.01$ and various values of β , which displays the effect of increasing the degree of synergism. As can be seen from Fig. 1, greater synergism (i.e. higher values of β) leads to lower numbers of mutations per individual at equilibrium, defined as the total number of mutant alleles per individual or, in the notation explained above, $2y + z$.

As in the case of multiplicative fitness interactions

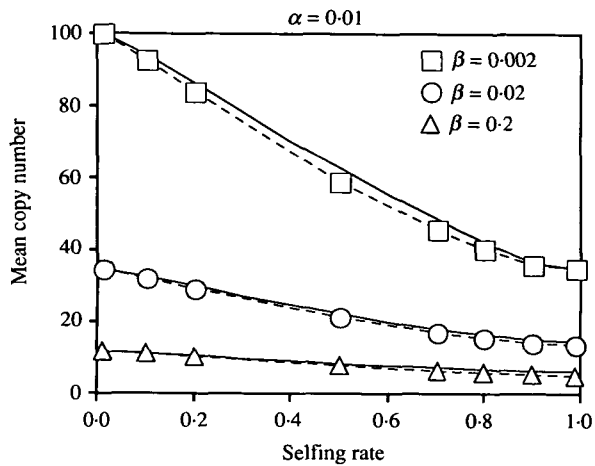


Fig. 1. Effect of the value of β on the mean number of deleterious mutant alleles per individual in equilibrium populations. The mutation rate, U , was 1.0, and the dominance coefficient, h , was 0.2. The solid lines refer to the analytical approximations and the dashed lines to the results of the computer calculations.

(Charlesworth *et al.* 1990), the mean number of mutations at equilibrium always decreased with increased selfing. This is the well-known result that inbreeding leads to lower equilibrium frequencies of deleterious recessive and partially recessive alleles, due to selective removal of these alleles because of their effect in causing low fitness of homozygotes produced by inbreeding. It is not surprising that this result remains true for the case of synergistic interactions. This decrease in the genetic load has been termed 'purging' of the inbred populations (Campbell, 1986; Lande & Schamske, 1985; see also Charlesworth *et al.* 1990).

Fig. 2 shows some examples of the effects of selfing on the mean fitness and inbreeding depression values in equilibrium populations. The mean fitness with partial selfing is a weighted mean of the fitnesses of outcrossed and selfed progeny. Both these increased with the selfing rate, for low S , but the average fitness of selfed progeny sometimes decreased again at very high S , and this was sometimes enough to cause the overall population mean fitness to decrease for high S . In other words, the synergistic model could generate situations in which mean fitness was highest for $S < 1$, rather than always being highest when $S = 1$ as was the case with the multiplicative model. This effect was most evident when selection was weak (see Fig. 2). When selection was weak, the peak in the mean fitness was also located at a lower value of the selfing rate than for stronger selection, keeping other parameter values constant.

Fig. 2 shows that the mean fitness for completely selfing populations was the same for any degree of synergism (varying the β parameter value from 0.02 to 0.2). This can be understood as follows. Mutant alleles present in a completely selfing population will be homozygous for most of the period of time they spend in the population until they are eliminated, and

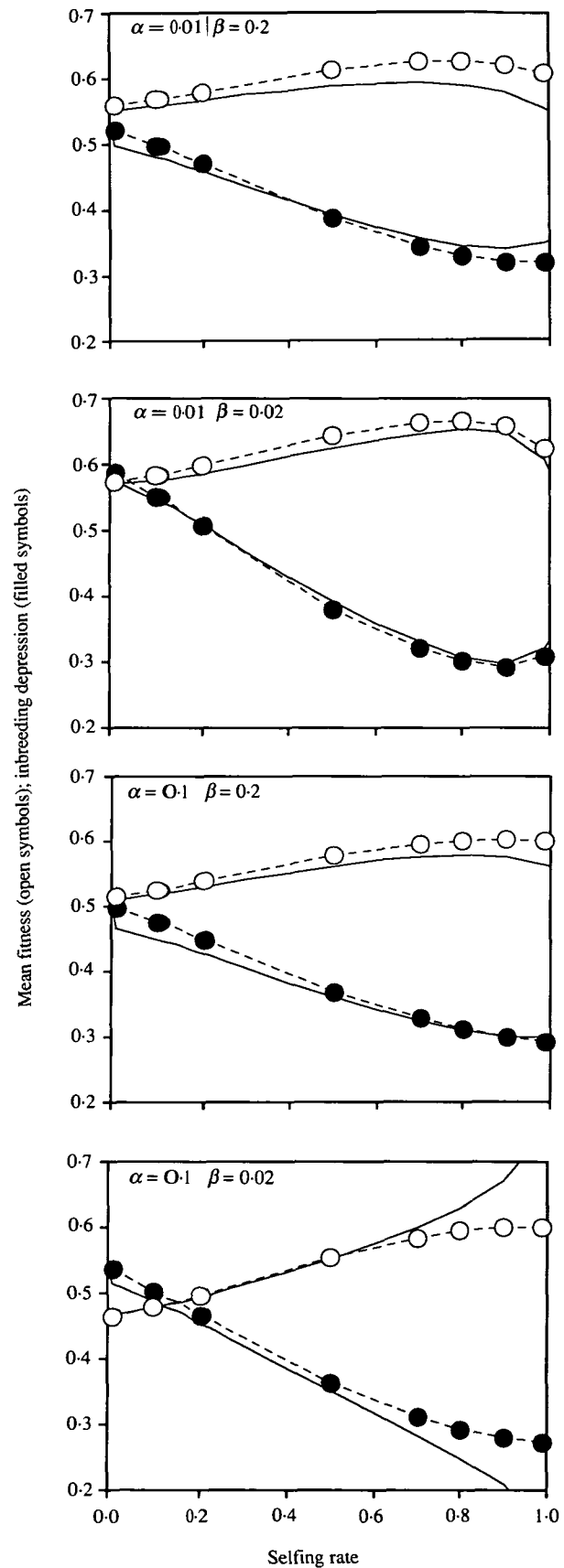


Fig. 2. Effect of changing the values of α and β on the mean fitness and inbreeding depression values of equilibrium populations. The mutation rate, U , was 1.0, and the dominance coefficient, h , was 0.2. The solid lines refer to the analytical approximations and the dashed lines to the results of the computer calculations.

selection therefore acts mainly on the homozygous genotypes. Once a selfing line is homozygous for a mutation, all descendants of that line will have the same genotype. The behaviour of the mean fitness of such a population will therefore be similar to that of an asexual population, for which it is known that the mean fitness is given by $\exp -U$, regardless of the form of selection (Kimura & Maruyama, 1966). In the case of asexual reproduction, the relevant mutation rate is the rate per diploid genome. For the case of complete selfing, however, the haploid mutation rate determines the mean fitness, because a mutation in one of the two alleles at a locus is sufficient to produce a homozygous line carrying the mutant allele, since homozygosity in populations with this breeding system is due to identity by descent of the two alleles in an individual, after a few generations of selfing. The mean fitness should therefore be approximately equal to $\exp -U/2$. The values of the mean fitness were accurately predicted by this formula. For example, the predicted value is 0.607 for $U = 1$, and the mean fitness curves in Fig. 2 all converge on this value. However, the agreement was less good for weakly selected alleles, presumably because the approximation represented by assuming that selective elimination of alleles takes place predominantly by inviability of homozygotes is not strictly true. Some other examples, for various values of the inbreeding depression and of U , are also shown in Figs. 3 and 4 below.

Fig. 3 shows the effect of changes in the mutation rate on the mean fitness and inbreeding depression, for various selfing rates, for the case of weak selection ($\alpha = 0.01$, $\beta = 0.02$). As would be expected, more mutations led to more mutant alleles per individual, and thus to lower mean fitness. Some examples of the

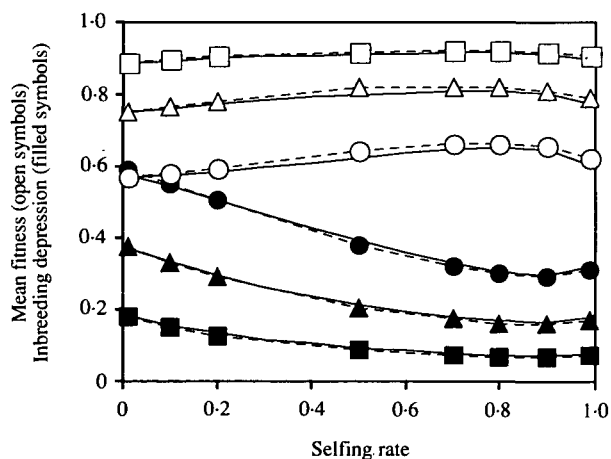


Fig. 3. Effect of the mutation rate, U , on the mean fitness and inbreeding depression values of equilibrium populations. The standard parameter values ($\alpha = 0.01$, $\beta = 0.02$) were used, and the dominance coefficient, h , was 0.2. The solid lines refer to the analytical approximations and the dashed lines to the results of the computer calculations. \square \blacksquare , $U = 0.2$; \triangle \blacktriangle , $U = 0.5$; \circ \bullet , $U = 1.0$.

inbreeding depression values obtained are also shown in Figs. 2, 3 and 4. Inbreeding depression behaved in a converse manner to mean fitness, as the selfing rate or the mutation rate was increased. As the mean fitness decreased, inbreeding depression increased (Figs. 2 and 4). With synergism, the inbreeding depression decreased as S increased when the populations had low to moderate S values but, in contrast to the multiplicative case studied before, it sometimes increased again in highly selfing populations (Figs. 2 and 4). In other words, strong synergism flattened out the relationship between inbreeding depression and the selfing rate, compared with the curve for the multiplicative case. In the cases described above in which mean fitness peaks when $S < 1$, the same S value that corresponds to the highest mean fitness also yields the minimum inbreeding depression value. As mentioned above, this selfing rate is lower with weaker selection (lower α values).

As the figures show, the agreement between the exact and approximate results was quite good for low selfing rates, especially for weak selection with synergism, and the agreement remained good even for high mutation rates.

Fig. 4 shows the effects on mean fitness and inbreeding depression of departure from the multiplicative assumption. To obtain comparable results for the multiplicative and synergistic models, the multiplicative case was altered from the model of eqn (1) to a model in which the heterozygous mutations were weighted so as to be treated as fractions of homozygous mutations, in the way described above for the synergistic model, i.e. β was simply equated to zero in eqn (2). The figure compares two synergistic cases with multiplicative runs matched for the values of the selection coefficients in the outcrossing populations, as described in section 2(i). One of the comparisons shows the 'standard parameter values'

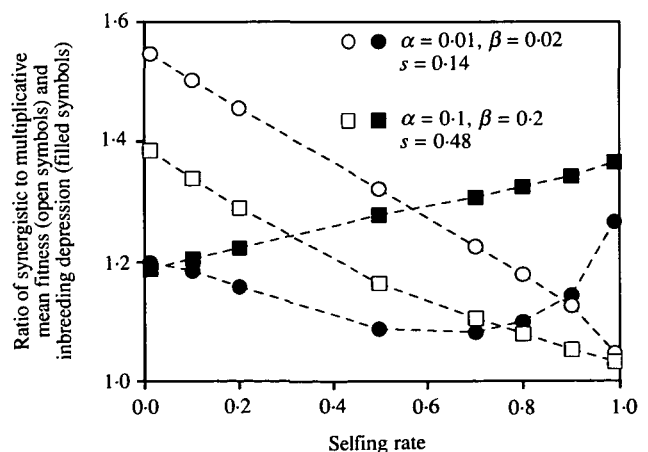


Fig. 4. Ratios of the mean fitness and inbreeding depression values of equilibrium populations for synergistic models, to those of multiplicative models with the same mean number of mutations in the outcrossing populations. The values of s shown in the figure refer to the multiplicative model. The mutation rate, U , was 1.0, and the dominance coefficient, h , was 0.2.

Table 3. Inbreeding depression values in highly selfing populations. The table shows the approximate analytical results derived here and the results calculated by the computer runs with the stated fitness interactions

h	U = 0.5			U = 1.0			U = 1.5		
	Analytical (S = 1.0)								
0.02	0.213			0.381			0.513		
0.1	0.181			0.330			0.451		
0.2	0.139			0.259			0.362		
0.3	0.095			0.181			0.259		
0.35	0.072			0.139			0.201		
Multiplicative, selection coefficient s = 0.2									
	S = 0.99	S = 0.95	S = 0.9	S = 0.99	S = 0.95	S = 0.9	S = 0.99	S = 0.95	S = 0.9
0.02	0.215	0.224	0.236	0.384	0.400	0.424	0.517	0.539	0.574
0.1	0.179	0.185	0.193	0.327	0.337	0.352	0.448	0.461	0.481
0.2	0.135	0.138	0.142	0.252	0.257	0.264	0.353	0.359	0.368
0.3	0.090	0.091	0.094	0.172	0.174	0.177	0.247	0.249	0.253
0.35	0.068	0.069	0.070	0.131	0.132	0.134	0.190	0.191	0.192
Synergistic, α = 0.01, β = 0.02									
0.02	0.210	0.201	0.201	0.373	0.362	0.368	0.502	0.494	0.509
0.1	0.198	0.189	0.188	0.355	0.343	0.345	0.481	0.470	0.478
0.2	0.171	0.162	0.159	0.311	0.297	0.294	0.426	0.410	0.408
0.3	0.131	0.122	0.119	0.240	0.226	0.220	0.333	0.316	0.308
0.35	0.105	0.098	0.094	0.193	0.181	0.174	0.270	0.254	0.245
Synergistic, α = 0.01, β = 0.2									
0.02	0.221	0.223	0.230	0.392	0.397	0.409	0.526	0.535	0.554
0.1	0.210	0.212	0.216	0.372	0.375	0.384	0.500	0.505	0.517
0.2	0.181	0.181	0.182	0.318	0.317	0.319	0.428	0.427	0.429
0.3	0.137	0.136	0.135	0.236	0.233	0.230	0.316	0.310	0.306
0.35	0.111	0.109	0.108	0.186	0.182	0.178	0.244	0.239	0.233

defined above. This corresponds to a value of $s = 0.14$, for outcrossing. The other set of runs shown is for $\alpha = 0.1$ and $\beta = 0.2$, corresponding to $s = 0.48$ for outcrossing. Fig. 4 shows the results of the comparisons expressed as the ratios of the values in the runs assuming synergism, to those in the corresponding multiplicative runs. As would be expected from the reduction in numbers of mutations per individual in equilibrium populations with synergism, the mean fitness was increased by synergism, or in other words the genetic load decreased. There was also an increase in the inbreeding depression with increased synergism, especially for highly selfing populations. Thus, although the mean fitness was increased, so was the effect on fitness of inbreeding. This makes sense in terms of the fact that synergistic selection caused a greater decline in fitness for each mutant allele than does the multiplicative assumption.

The effect of decreasing the recessivity of the mutations was generally to reduce the level of inbreeding depression found in equilibrium populations. Compared with the multiplicative model, synergism reduced the fall-off of inbreeding depression with increased selfing. Table 3 shows some examples of the inbreeding depression values at high selfing rates, for two of the synergistic models of Fig. 2 (the standard parameter values, and the case of $\alpha = 0.01$, $\beta = 0.2$, which gave the worst agreement with the

analytical values), and for the multiplicative model with selection coefficient 0.2. For synergistic selection with stronger selection, the results were similar to those shown, but the inbreeding depression values were more similar to those predicted by the analytical formula to be explained below than are the examples shown in Table 3.

For the case of multiplicative fitnesses, an approximate expression for the inbreeding depression in a completely selfing population (assumed to be largely homozygous at all loci) can be derived as follows. Let the mean number of homozygous mutations per individual be \bar{n} . Then with multiplicativity and a Poisson distribution of the number of mutations (see section 4[iii] above) the mean fitness of progeny produced by selfing is given approximately by

$$\begin{aligned} \bar{w}_s &\approx e^{-\bar{n}} \left\{ 1 + (1-s)\bar{n} + \frac{(1-s)^2 \bar{n}^2}{2!} + \dots \right\} \\ &= e^{-\bar{n}} e^{\bar{n}(1-s)} \\ &= e^{-s\bar{n}}. \end{aligned}$$

For complete selfing, the mean fitness of the population is equal to this value, and as explained above, this is approximately equal to $\exp -U/2$. Therefore $\bar{n} \approx U/2s$ (see Heller & Maynard Smith, 1979, and Hopf *et al.* 1988 for alternative derivations of this result) and we can calculate \bar{w}_s , given U and s . To obtain \bar{w}_x we note that the fitness of the progeny of

outcrossing between two lines homozygous for n_i and n_j mutations on the multiplicative assumption is

$$(1 - hs)^{n_i + n_j},$$

where $n_i + n_j$ is Poisson distributed with mean U/s . Therefore we have

$$\bar{w}_x \approx e^{-hs \frac{U}{s}} = e^{-hU}, \tag{12}$$

and so the inbreeding depression is

$$\delta = 1 - \frac{\bar{w}_s}{\bar{w}_x} \approx 1 - e^{-\left(\frac{1}{2} - h\right)U}. \tag{13}$$

Some values based on this calculation are shown in Table 3. The agreement with the exact results is good for the multiplicative runs but less so for the synergistic runs, especially when the dominance coefficient is high. In those cases the inbreeding depression predicted by the formulae just given is too low. It is not surprising that if the synergism is weak in comparison with the strength of selection, the results are well predicted by the multiplicative model, but the agreement for the case of strong synergism is still quite good. It is remarkable that the selection model has only a minor effect on the inbreeding depression values found in these highly inbred populations, and that the values predicted for complete selfing are also close to those calculated in the computer runs, even for selfing rates as low as 0.9.

At low selfing rates, with some parameter values with very low dominance coefficients, there was a disproportionate increase in the inbreeding depression, which rose to a value of 1 as S approached zero. This was accompanied by non-monotonic behaviour of the mean fitness (Fig. 5). These effects were found in both the exact and the semi-analytical approximate results, but did not occur with all parameter values. This behaviour of the mean fitness with very recessive mutations appears explicable in

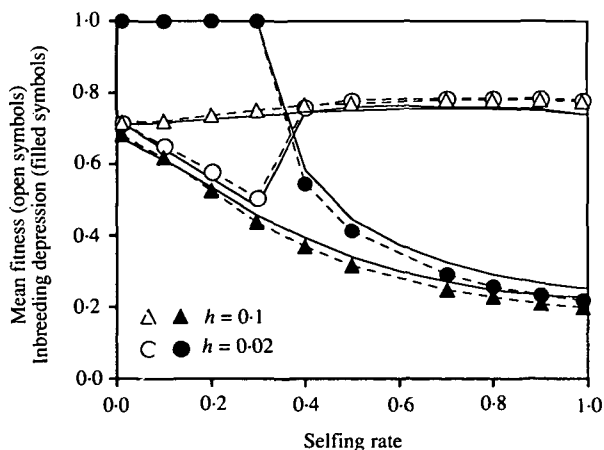


Fig. 5. Effect of the dominance coefficient, h , on the mean fitness and inbreeding depression values of equilibrium populations. The parameter values were $\alpha = 0.1$, $\beta = 0.2$, $U = 0.5$. The solid lines refer to the analytical approximations and the dashed lines to the results of the computer calculations.

terms of two opposing effects of increasing population selfing rates. Firstly, in highly outcrossing populations, the mean fitness of progeny of selfing will be much reduced, compared with that of outcrossed progeny (and there will be very high inbreeding depression, as seen in Fig. 5). For small increases in S , the contribution of selfed progeny to the population mean fitness increases, and these progeny have low average fitness. This can account for the reduction in mean fitness of the population as a whole, with small increases in selfing. In the second place, however, the frequencies of mutant alleles are reduced by increasing the selfing rate, due to their expression in homozygotes. Beyond some level of selfing, the second effect on allele frequencies leads to an increase in the population mean fitness. With less recessive alleles, the reduction in fitness on selfing is smaller in outcrossing populations, so the first effect is outweighed even for low selfing rates. It is intuitively reasonable that the first effect should be most pronounced with synergistic fitness interactions, when the effect of selfing in producing homozygosity at multiple loci should cause the greatest decrease in fitness.

(ii) *Mutational model: effects on modifiers of the outcrossing rate*

One of the reasons for studying inbreeding depression in these runs is to ask whether it affects the evolution of the selfing rate (Charlesworth *et al.* 1990). Fig. 6 shows the results of introducing modifiers of the selfing rate into equilibrium populations with synergistic interactions. In these runs, the modifiers of the selfing rate were assumed to leave the contribution to the outcrossing pollen pool unchanged (no pollen discounting). The standard parameter set was used, with weak selection and weak synergism ($\alpha = 0.01$, $\beta = 0.02$), and the mutation rate per diploid genome (U) was assumed to be 1. As can be seen by inspection of the results in Fig. 2, the inbreeding depression value for a random-mating population with these parameter values is greater than 0.5 (0.577), whereas for $S = 0.5$ it is 0.393. In Fig. 6, we show the asymptotic rates of increase (measured as $\Delta p/p$, where p is the frequency of the modifier allele) of modifier alleles that change the selfing rate from these initial values to higher or lower values. The modifier alleles were assumed to be intermediate in their dominance. The sign of the change in modifier frequency was usually consistent throughout the course of spread, except that when modifiers causing high selfing rates were introduced into populations with inbreeding depression greater than one-half, they usually decreased at first, but later changed over to increase in frequency. Transient changes in sign were occasionally observed in other cases, for a few generations (< 10) after the modifier was introduced.

Fig. 6 shows that, with the parameter set assumed

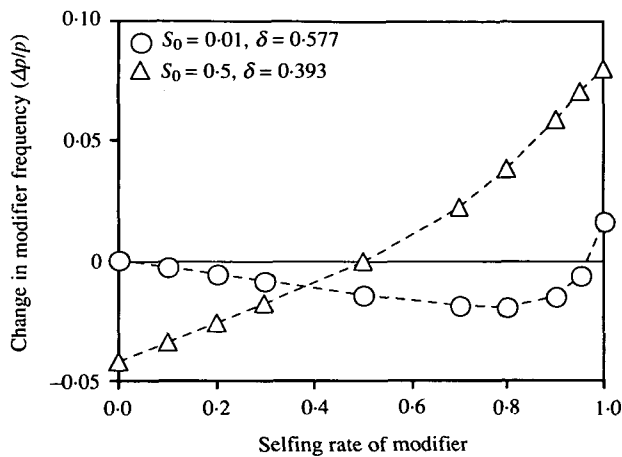


Fig. 6. Rates of change ($\Delta p/p$) in frequency of modifiers affecting the selfing rate introduced into populations at equilibrium under mutation and selection and with various initial selfing rates, S_0 . The standard parameter values were used ($\alpha = 0.01$, $\beta = 0.02$), with the mutation rate, U , equal to 1.0 and the dominance coefficient $h = 0.2$.

here, outcrossing ($S = 0$) was stable to invasion by alleles increasing the selfing rate. When, however, the modifier caused complete selfing, a positive rate of increase was observed, i.e. such a modifier could invade the population. In contrast, when modifiers were introduced into a population with an initial selfing rate of 0.5, they invariably spread when their effect was to increase selfing, and were eliminated when they increased outcrossing. In other words, in that situation, with a lower initial inbreeding depression value, selfing was selectively favoured.

In general the direction of change in frequency of modifier alleles that changed the selfing rates by small amounts was, as in our previous studies of the multiplicative models, well predicted by the equations of Charlesworth (1980) which assumed a constant value of the inbreeding depression. We also tested for an effect of pollen discounting. We did this by setting the level of discounting to the value that, according to Charlesworth's equations, should just permit invasion by an allele increasing selfing, and asking whether the modifier did indeed increase in frequency. In most of the cases run, the agreement with the analytical equation was good. The modifier was prevented from increase by a level of discounting that was within one or two percent of the predicted value.

When an initial population with a very high selfing rate ($S = 0.99$) was studied, however, modifiers causing complete selfing were often selected against, even though the inbreeding depression was low, and alleles causing increased outcrossing were also eliminated. Thus with these parameter values there could be an evolutionarily stable (ESS) selfing rate slightly below complete selfing. No such ESS was observed with the multiplicative models studied by us previously (Charlesworth *et al.* 1990). The existence of an ESS was confirmed by studies of the initial rates of increase

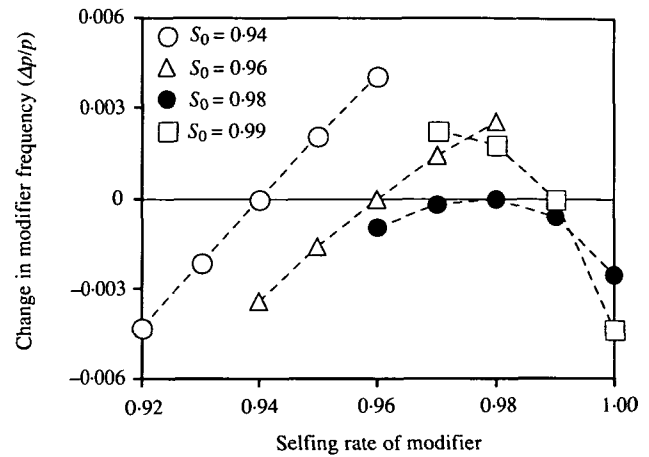


Fig. 7. Rates of change in frequency of modifiers affecting the selfing rate introduced into equilibrium populations with initial selfing rates close to the ESS value of 0.98. The standard parameter values were used, with the mutation rate, U , equal to 1.0 and the dominance coefficient $h = 0.2$.

of modifier alleles having the same small effect on the selfing rate, in a set of runs with various initial selfing rates close to 0.99 (Fig. 7), and by other similar runs for various parameter sets. With some degree of pollen discounting, the ESS was located at lower selfing rates than without discounting, unless the level of discounting was so high that there was no ESS, and modifiers increasing selfing were eliminated. This is expected, because discounting effectively reduces the advantage of selfing (Nagylaki, 1976). However, the ESS selfing rates were located at higher selfing rates than the values corresponding to the maximum in the mean fitness. The effect of pollen discounting was to lower the ESS towards the selfing rate that yielded maximum mean fitness. We also found that the degree of discounting that prevented spread of a modifier increasing the selfing rate was lower than that predicted by Charlesworth's (1980) equation, for populations with selfing rates in the region of the ESS than for lower selfing rates. That equation is thus not accurate in this region of the selfing rate range.

(iii) *Overdominance model*

In order to compare the results for the multiplicative case with those with synergism, the following relation between the single-locus selection coefficient and the selection parameters of eqn (10) can be established for a random-mating population. Assuming independence of loci, the heterozygotes Aa at a given locus have a mean number of homozygous loci of $\frac{1}{2}m - \frac{1}{2} = \frac{1}{2}(m - 1)$. Homozygotes aa have a mean of $\frac{1}{2}m - \frac{1}{2} + 1 = \frac{1}{2}(m + 1)$. The difference between these is -1 . Hence, the selective advantage of heterozygotes over homozygotes can be approximated by

$$s = \frac{w_{Aa} - w_{aa}}{w_{Aa}} \approx -\frac{1}{w_{Aa}} \left(\frac{\partial w(y)}{\partial y} \right)_{y=\frac{1}{2}(m-1)} \quad (14a)$$

Table 4. Results of the exact and semi-analytical methods of calculating the equilibria with symmetrical overdominance. 50 loci were assumed

S		\bar{y}_s	V_{y_s}	\bar{w}	\bar{w}_s	δ
(a) Multiplicative fitnesses: $\alpha = 0.05$, $\beta = 0$, $\bar{y}_x = 25$, $V_{y_x} = 12.5$, $\bar{w}_x = 0.291$ (exact), $\bar{w}_x = 0.291$ (approx).						
0.01	Exact	37.22	9.72	0.299	0.157	0.459
	Approx.	37.22	9.72	0.290	0.157	0.459
0.10	Exact	37.5	11.4	0.277	0.155	0.466
	Approx.	37.5	11.4	0.277	0.155	0.466
0.30	Exact	38.4	15.5	0.249	0.150	0.486
	Approx.	38.4	15.5	0.249	0.150	0.486
0.50	Exact	40.25	22.2	0.199	0.137	0.528
	Approx.	39.51	20.0	0.217	0.142	0.511
0.70	Exact	41.2	24.2	0.179	0.132	0.548
	Approx.	42.5	25.5	0.157	0.123	0.576
0.90	Exact	44.5	24.3	0.130	0.111	0.616
	Approx.	44.5	23.7	0.129	0.111	0.618
0.99	Exact	48.7	8.31	0.091	0.089	0.695
	Approx.	48.9	6.92	0.090	0.088	0.699
(b) Synergistic interactions: $\alpha = 0.005$, $\beta = 0.00184$, $\bar{y}_x = 25$, $V_{y_x} = 12.5$, $\bar{w}_x = 0.499$ (exact), $\bar{w}_x = 0.499$ (approx.)						
0.01	Exact	37.22	9.62	0.499	0.236	0.527
	Approx.	37.22	9.62	0.496	0.236	0.527
0.10	Exact	37.5	11.1	0.472	0.232	0.535
	Approx.	37.5	11.1	0.472	0.232	0.535
0.30	Exact	38.2	14.5	0.416	0.222	0.556
	Approx.	38.2	14.5	0.416	0.222	0.556
0.50	Exact	39.2	18.2	0.353	0.208	0.584
	Approx.	39.2	18.2	0.353	0.208	0.583
0.70	Exact	40.6	21.9	0.281	0.188	0.623
	Approx.	40.6	21.9	0.281	0.188	0.623
0.90	Exact	43.4	23.2	0.186	0.151	0.697
	Approx.	43.5	22.7	0.185	0.150	0.700
0.99	Exact	47.6	11.6	0.106	0.102	0.796
	Approx.	48.0	9.41	0.101	0.097	0.805

Substituting from eqn (10), this reduces to

$$s \approx \alpha + \frac{1}{2}\beta(m - 1). \tag{14b}$$

This equation allows the comparison of synergistic and multiplicative cases with the same selection coefficients for random-mating populations.

The parameters of some equilibrium populations are shown in Table 4, calculated both by the exact method of Charlesworth & Charlesworth (1990), and by the above approximation. The selection coefficient s is 0.05, and 50 loci are assumed to be segregating. Multiplicative fitnesses and fairly strong synergism are compared, for the same set of selfing rates. There is good agreement between the exact and approximate results, especially with synergism. It will be seen that synergism has a slight effect in increasing the level of inbreeding depression (e.g. with 50% selfing, there is an 11% increase in δ over the value for multiplicative fitnesses). Inbreeding depression increases with the selfing rate with both multiplicative fitnesses and with synergism, as previously found for multiplicative interactions (Holsinger, 1988; Ziehe & Roberds, 1989; Charlesworth *et al.* 1990). There are only minor effects of synergism on the means and variances of the number of homozygous mutations per individual. On

the other hand, there is a large increase in the population mean fitness for low selfing rates, corresponding to a large increase in the mean fitness of outcrossed individuals. The variances in fitness were also larger with synergism than for the multiplicative case (results not shown). Since it is difficult to account for inbreeding depression in terms of loci with overdominance, because of the large variance in fitness that accompanies appreciable inbreeding depression (Charlesworth & Charlesworth, 1990), the introduction of synergism, with an even greater variance in fitness, does not make such an interpretation more plausible.

When modifiers of the selfing rate were also modelled, the results were very similar to those reported previously for the multiplicative model of overdominance at several loci (Charlesworth & Charlesworth, 1990). There were ESS values of the selfing rate, at which neither alleles reducing, nor alleles increasing it, had positive rates of change. The ESS selfing rate values were located close to values yielding an inbreeding depression of 0.5 for modifiers with no pollen discounting.

7. Discussion

(i) Genetic loads and inbreeding depression values

The results obtained with synergistic interactions between loci show that the effects of synergism are most pronounced on the numbers of mutant alleles present in individuals in populations at equilibrium. Increased synergism leads to the maintenance of lower numbers of deleterious mutations for the same value of hs , as expected (Crow, 1970), and higher mean fitness (King, 1967; Sved *et al.* 1967). There is also an effect on the shape of the relationship between inbreeding depression and the population selfing rate. For the mutational load model, synergistic fitness interactions tend to slow the decline in the inbreeding depression as the selfing rate increases, compared with the multiplicative model. With symmetrical overdominance, inbreeding depression increases with the selfing rate, as was found for multiplicative fitnesses (Charlesworth & Charlesworth, 1990).

With mutational load, there could sometimes even be a slight increase in inbreeding depression, and decrease in the population mean fitness, at selfing rates close to complete selfing. The decrease in the fitness of progeny of selfing when S is very high probably arises from the fact that, despite the purging effect of selection against mutant alleles in homozygotes in this type of situation (so that the number of mutant alleles carried in the heterozygous state decreases with S), the number of homozygous mutants increases with the selfing rate (Charlesworth *et al.* 1990). Since homozygous loci occur only in progeny derived from selfing, this means that, in highly selfing populations, selfed progeny may be homozygous for more mutant alleles than in less selfing populations with the same values of the other parameters of the model. This can be seen in Table 1. This effect tends to lower the fitness of selfed progeny in highly selfing populations, but the purging of mutant alleles from the populations means that they carry fewer mutations in the heterozygous state, and this works in the opposite direction. With multiplicativity, it appears from the results of our runs that the effect of increased numbers of homozygous loci is not enough to outweigh the effect of the decrease in the number of loci heterozygous for mutations, and so the mean fitness of progeny derived from selfing increases with the selfing rate. With synergism, however, the lowering of fitness in homozygotes is more severe, compared with the effect of several heterozygous loci, than in the multiplicative case, and this can sometimes cause a decrease in the fitness of the progeny of selfing as the selfing rate increases. Since in highly selfing populations the mean fitness of the population as a whole is largely determined by that of the selfed progeny, this accounts for the decrease in mean fitness in those cases where it was observed.

As previously noted for the multiplicative case, the mutational model can yield populations with high

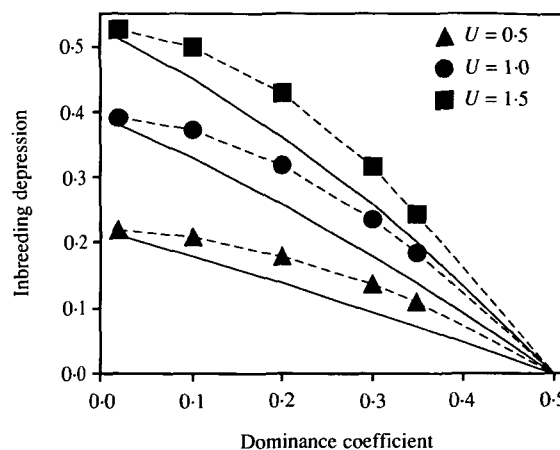


Fig. 8. Inbreeding depression values under the mutational load model with three different mutation rates, in equilibrium populations with selfing rate 0.99 (black symbols and dotted lines). The parameter values were $\alpha = 0.01$, $\beta = 0.2$. The full lines show the values calculated by the approximation described in the text, assuming multiplicative fitness interactions.

selfing rates and with high inbreeding depression values, given sufficiently high per genome mutation rates. For this to be true, the dominance coefficient must not be too close to 0.5, but the effect of partial dominance is less strong than for the multiplicative case. This can be seen from Table 3, and is also graphed in Fig. 8, which compares the inbreeding depression values predicted by the approximate formula derived in section 6(ii) above with the synergistic case that gave the worst agreement with those values. When there is disagreement between the two curves, the synergistic results are always higher than the predicted values (even though these are higher than the exact multiplicative results for high h values), whereas the values calculated on the multiplicative assumption were always very close to the predicted values. The effect of synergism is therefore to increase the level of inbreeding depression, compared with the multiplicative case.

Since the magnitude of inbreeding depression in highly selfing populations is not very sensitive to the selection model, nor to the strength of selection, these results suggest the possibility of using eqn (13) to estimate the mutation rate per genome to deleterious alleles, from data on inbreeding depression in such populations. This would be very valuable, because this has rarely been estimated, apart from the work using *Drosophila melanogaster* (Crow & Simmons, 1983). For highly inbreeding populations, the magnitude of inbreeding depression is estimated from the degree of heterosis when lines are intercrossed. It is reasonable to use such data to estimate the mutation rate to mildly deleterious alleles, because it is unlikely that populations that are highly inbred will carry any appreciable frequency of recessive lethal mutations. It is also unlikely that they will be polymorphic for overdominant alleles at many loci, since such polymorphisms cannot be maintained in highly selfing

populations unless the selection coefficients against the two homozygotes are equal, which is improbable (Kimura & Ohta, 1971).

There appear to be few data currently available that can be used to get such an estimate. It is well documented that heterosis between lines of *Arabidopsis thaliana* is quite strong (Griffing & Langridge, 1963; Griffing & Zsiros, 1971; Griffing, 1989), and that this plant is highly inbreeding (Abbott & Gomes, 1988). Griffing & Langridge (1963) report data yielding inbreeding depression values ranging from 0.037 to 0.67, depending on the temperature at which the plants were grown. In the experiments of Griffing (1989) involving two inbred strains, the average inbreeding depression in yield (= plant dry weight) was about 0.16, with very little variation caused by the other genotypes with which the plants studied were competing. This value is probably an underestimate, because it is based on comparing the parental strains and the F_2 between them, due to low yields of F_1 seeds. Riley (1956) obtained an estimate of heterosis in both within- and between-population crosses in *Thlaspi arvense*, from which inbreeding depression values ranging from 0 to 0.32 for the germination rate can be estimated. The ratio of fitnesses of plants grown from seeds produced by selfing by cleistogamous flowers and those produced by chasmogamous flowers has been estimated for plants from one population of *Impatiens capensis* (Schmitt & Ehrhardt, 1990), and ranged from 0 to 0.155, depending on the conditions used, the stage of the life cycle studied, and the estimation procedure employed. For dry weight of harvested mature plants, the value in competitive conditions was 0.265, even after adjusting for different seed weights and collection dates. Assuming that up to half of the seeds from chasmogamous flowers may have been produced by outcrossing, these data suggest an inbreeding depression value of at least 0.1–0.2 (Schmitt & Ehrhardt, 1990). The breeding system of this population has not been quantitatively estimated, but Schmitt *et al.* (1987) estimate that about 10% of the seeds are produced by chasmogamous flowers (see also Waller, 1984), so that the outcrossing rate of the population must be less than 5% even if the outcrossing rate of chasmogamous flowers is as high as 0.5 (Knight & Waller, 1986). Imam and Allard (1965) obtained similar data from wild oats. The outcrossing rates of different populations were estimated to be below 0.1, ranging as low as 0.01. In a nursery experiment using plants from different populations grown together, several components of fitness were higher for plants derived from naturally open pollinated flowers than for progeny of hand selfing. For tiller number or survival from emergence to flowering, the ratio of values of these fitness components was about 1.1 for these two types of progeny. If one assumes an outcrossing rate of 0.1 for the open pollinated flowers, this yields an inbreeding depression value of 0.53, with

higher values if the outcrossing rate were lower than this. However, it is possible that the selfed progeny could have lower fitness values due to some difference caused by the bagging procedure needed to ensure that outcrossing did not occur, so these estimates are possibly suspect. Svensson (1988) found inbreeding depression in a measure of male fertility of about 0.17 in the self-fertilizing species *Scleranthus annuus*.

Taken together, these values suggest that heterosis in highly inbreeding plants is large enough that the value of U must be at least 0.5, even assuming a low h value, and could be double that if h were higher (Table 3). It would obviously be desirable to have estimates of h for these populations. These data, although scanty, show that populations that are highly selfing can have measurable inbreeding depression, as the mutational model predicts. Other data from *Impatiens capensis* are quite consistent with the results cited above (Waller, 1984). Data from highly inbreeding crops also support the view that inbreeding depression can still be detected in these in terms of heterosis when lines are crossed (reviewed by Wright, 1977).

(ii) Approximate analytical results

The results shown above also demonstrate that approximate models, based on normal or Poisson distributions of numbers of mutant alleles per individual, can provide good predictions of the mean fitness and inbreeding depression values of populations at equilibrium under mutation at many loci, balanced by selection. The normal approximation fails to work well for high selfing and weak synergism, but the Poisson approximation works for multiplicative fitness interactions. Good approximations can also be obtained for the case of heterozygote advantage. The good agreement of the normal approximation for the mutational model with synergism is surprising, because the population in each generation is a mixture of products of selfing and of random outcrossing, so that the distributions of numbers of mutations are bimodal (Fig. 9). While it is not very surprising that the distribution of numbers of mutant alleles carried in heterozygotes among the outcrossed progeny, or of numbers of mutant alleles homozygous in the inbred progeny, might approximate a Poisson or a normal distribution, it is unexpected to get a very satisfactory approximation to the overall distribution by any unimodal distribution. The approximate approach failed, however, to give a satisfactory method for dealing with the initial spread of modifier alleles affecting the selfing rate, presumably because of this same problem of combining different distributions of numbers of mutations in each generation.

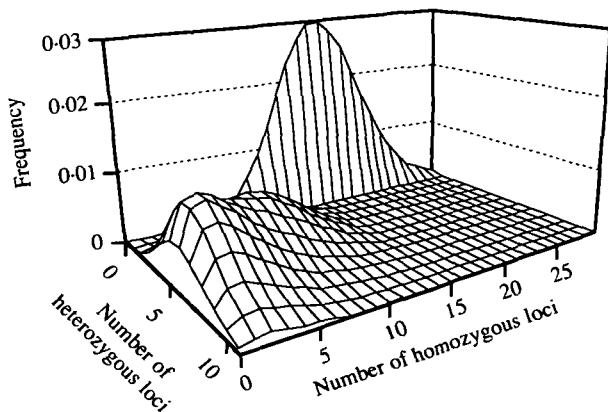


Fig. 9. Distributions of the numbers of heterozygous and homozygous mutations per individual in an equilibrium population with selfing rate $S = 0.7$. The standard parameter values were used, with the mutation rate, U , equal to 1.0 and the dominance coefficient equal to 0.2.

(iii) Effects on modifiers of the selfing rate

As we previously found (Charlesworth *et al.* 1990) for multiplicative interactions between the selected loci, the magnitude of inbreeding depression predicts whether modifiers of small effect on the selfing rate will increase or decrease, when introduced at low frequency into populations at equilibrium. If the inbreeding depression exceeded one-half (in the absence of pollen discounting), modifiers increasing the outcrossing rate were selected for. However we found that, as for the multiplicative case, major modifiers increasing the selfing rate could sometimes spread even when the inbreeding depression was high. This appears to be because when a modifier causing a high selfing rate arises, it produces a highly selfing line. Within such a line, the effect of inbreeding is to purge the line of deleterious mutations. Its mean fitness will therefore increase, and the allele for selfing can after some time establish an association with a set of genotypes of high mean fitness, and attain a positive rate of increase. This interpretation is consistent with the fact that in such cases the modifier allele initially decreased in frequency, and then increased. This is in line with discussions in Campbell (1986), Lande & Schemske (1985) and Charlesworth *et al.* (1990) and is no different from what we found in the multiplicative case. Because synergism leads to greater inbreeding depression than the multiplicative model, for populations with the same mean fitness, it should tend to yield stronger selection for outcrossing, or to be more likely to maintain outcrossing.

Unlike our previous results with multiplicative fitness interactions between loci, we found that with synergism there can be evolutionarily stable states at intermediate values of the selfing rate slightly below complete selfing. As discussed above, these ESSs were always at high values of the selfing rate. In every case studied when there was an ESS for the selfing rate there was also a maximum in the mean fitness (or minimum in inbreeding depression) at some selfing

rate below unity. This result is in accord with a suggestion by A. S. Kondrashov (pers. comm., cited in Charlesworth *et al.* 1990) that with truncation selection there could be a maximum in mean fitness and that this might explain his finding of ESS selfing rates for models with truncation selection. The present results show that it is correct that there is a maximum in mean fitness, and that this is not confined to the case of truncation selection. This does not, however, prove that the ESS in Kondrashov's results is due to this cause, as his model included differences in allocation patterns which would also have been capable of generating stable intermediate selfing rates (see Charlesworth *et al.* 1990). In the present case, however, the ESS selfing rates do appear to be due to the behaviour of the mean fitness.

The ESS selfing rates were somewhat higher than the selfing rate corresponding to the maximum in the mean fitness. The explanation for these ESS selfing rates is probably as follows. When selfing is close to total, and a modifier is introduced that increases selfing, the modifier allele and the original allele are each confined to an almost entirely homozygous line. The outcome therefore depends on the mean fitnesses of these lines, and we have seen above that this can decrease at very high S values, in the synergistic model of selection. The ESS values are higher than the S values with maximum fitness, because the transmission advantage to alleles that cause high selfing rates (Fisher, 1941) can outweigh the reduction in fitness unless this is too great. The existence of such ESS selfing rates is interesting because it is well known that there appears to be a tendency for even highly selfing populations to have selfing rates just below complete selfing. This was pointed out by Darwin (1862, p. 293), who states that nature: 'abhors perpetual self-fertilisation'.

(iv) Evidence for synergistic interactions between loci affecting fitness

It seems unlikely that the systems we have studied would behave very differently if we had used another model for the synergism, and the behaviour appears similar even to the results obtained by Kondrashov (1985) who assumed truncation selection. However, there is no firm evidence for synergism as intense as represented by a truncation model. The best evidence that synergism occurs comes from the work of Mukai (reviewed by Crow, 1970 and Charlesworth, 1990). The degree of synergism estimated from Mukai's work appeared to be slight, and the 'standard parameter set' used here and by Charlesworth (1990) was based on these estimates. Synergism could also be detected by studies of the relationship between fitness components and inbreeding coefficients, for example by generating progeny of a set of matings between relatives of different degrees. The results of a number of such studies in conifers were reviewed by Griffin &

Lindgren (1985), and appear to show some evidence for larger declines in fitness for any given increment in the inbreeding coefficient, the higher the inbreeding coefficient, suggesting synergistic interactions of the kind postulated here. However, at high inbreeding coefficients, the reverse was found. Much more extensive studies of the decline in fitness with the increasing inbreeding coefficient over successive generations of inbreeding have been published (reviewed by Lynch, 1988), but these are unsatisfactory for the present purposes, because the genetic variation in fitness will change over the generations of such an experiment. In particular, there will be a reduction in the frequency of deleterious recessive and partially recessive alleles, as inbreeding proceeds. It is therefore not surprising that such experiments generally produce a rapid decline in fitness at first, followed by slower changes in later generations (Jones, 1939). This relationship between inbreeding and fitness can not therefore be taken as evidence of negative synergism. If an accelerating decline is found, however, this does suggest synergism. Some cases are known (e.g. Gallais, 1984; Bondari & Dunham, 1987).

The overall conclusion from our studies of synergistic fitness interactions is therefore that synergism makes it somewhat easier to maintain high inbreeding depression and to select for, or to maintain, outcrossing under the mutational load model. This is especially true for populations with high selfing rates (Fig. 4). Even small amounts of synergism in relation to the strength of selection (small β/α) are effective in this way.

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References

- Abbott, R. J. & Gomes, M. F. (1988). Population genetic structure and outcrossing rate of *Arabidopsis thaliana* (L.) Heynh. *Heredity* **62**, 411–418.
- Bondari, K. & Dunham, R. A. (1987). Effects of inbreeding on economic traits in channel catfish. *Theoretical and Applied Genetics* **74**, 1–9.
- Campbell, R. B. (1986). The interdependence of mating structure and inbreeding depression. *Theoretical Population Biology* **30**, 232–244.
- Charlesworth, B. (1980). The cost of sex in relation to mating system. *Journal of Theoretical Biology* **84**, 655–671.
- Charlesworth, B. (1990). Mutation-selection balance and the evolutionary advantage of sex and recombination. *Genetical Research* **55**, 199–221.
- Charlesworth, D. & Charlesworth, B. (1987). Inbreeding depression and its evolutionary consequences. *Annual Review of Ecology and Systematics* **18**, 237–268.
- Charlesworth, D. & Charlesworth, B. (1990). Inbreeding depression with heterozygote advantage and its effect on selection for modifiers changing the outcrossing rate. *Evolution* **44**, 870–888.
- Charlesworth, D., Morgan, M. T. & Charlesworth, B. (1990). Inbreeding depression, genetic load and the evolution of outcrossing rates in a multi-locus system with no linkage. *Evolution* **44**, 1469–1489.
- Crow, J. F. (1970). Genetic loads and the cost of natural selection. In *Mathematical Models in Population Genetics* (ed. K.-I. Kojima), pp. 128–177. Berlin: Springer-Verlag.
- Crow, J. F. & Simmons, M. J. (1983). The mutation load in *Drosophila*. In *The Genetics and Biology of Drosophila* (ed. M. Ashburner, H. L. Carson and J. N. Thompson), pp. 1–35. London: Academic Press.
- Darwin, C. R. (1862). *The Various Contrivances by which Orchids are Fertilised by Insects*. London: John Murray.
- Gallais, A. (1984). An analysis of heterosis versus inbreeding effects with an autotetraploid cross-fertilized plant: *Medicago sativa*. *Genetics* **106**, 123–137.
- Griffin, A. R. & Lindgren, D. (1985). Effect of inbreeding on production of filled seed in *Pinus radiata* – experimental results and a model of gene action. *Theoretical and Applied Genetics* **71**, 334–343.
- Griffing, B. (1989). Genetic analysis of plant mixtures. *Genetics* **122**, 943–956.
- Griffing, B. & Langridge, J. (1963). Phenotypic stability of growth in the self-fertilized species, *Arabidopsis thaliana*. In *Statistical Genetics and Plant Breeding* (ed. W. D. Hanson and H. F. Robinson), pp. 368–394. Washington, D.C.: NAS-NRC.
- Griffing, B. & Zsiros, E. (1971). Heterosis associated with genotype-environment interactions. *Genetics* **68**, 443–455.
- Heller, J. & Smith, J. M. (1979). Does Muller's ratchet work with selfing? *Genetical Research* **32**, 289–293.
- Holsinger, K. E. (1988). Inbreeding depression doesn't matter: the genetic basis of mating system evolution. *Evolution* **42**, 1235–1244.
- Hopf, F. A., Michod, R. E. & Sanderson, M. J. (1988). The effect of reproductive system on mutation load. *Theoretical Population Biology* **33**, 243–265.
- Imam, A. G. & Allard, R. W. (1965). Population studies in predominantly self-pollinated species. VI. Genetic variability between and within natural populations of wild oats from differing habitats in California. *Genetics* **51**, 49–62.
- Jones, D. F. (1939). Continued inbreeding in maize. *Genetics* **24**, 462–473.
- Kimura, M. & Maruyama, T. (1966). The mutational load with epistatic gene interactions in fitness. *Genetics* **54**, 1337–1351.
- Kimura, M. & Ohta, T. (1971). *Theoretical Topics in Population Genetics*. Princeton, New Jersey: Princeton University Press.
- King, J. L. (1967). Continuously distributed factors affecting fitness. *Genetics* **53**, 403–413.
- Knight, S. E. & Waller, D. M. (1986). Genetic consequences of outcrossing in the cleistogamous annual, *Impatiens capensis*. I. Population genetic structure. *Evolution* **41**, 969–978.
- Kondrashov, A. S. (1985). Deleterious mutation as an evolutionary factor. II. Facultative apomixis and selfing. *Genetics* **111**, 635–653.
- Kondrashov, A. S. (1988). Deleterious mutations and the evolution of sexual reproduction. *Nature* **336**, 435–440.
- Lande, R. & Schemske, D. W. (1985). The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. *Evolution* **39**, 24–40.
- Lynch, M. (1988). Design and analysis of experiments on random genetic drift and inbreeding depression. *Genetics* **120**, 791–807.
- Nagylaki, T. (1976). A model for the evolution of self fertilization and vegetative reproduction. *Journal of Theoretical Biology* **58**, 55–58.
- Riley, R. (1956). The influence of the breeding system on the genecology of *Thlaspi alpestre* L. *New Phytologist* **55**, 319–330.
- Schmitt, J., Eccleston, J. & Ehrhardt, D. W. (1987). Density-dependent flowering phenology, outcrossing, and reproduction in *Impatiens capensis*. *Oecologia* **72**, 341–347.

Schmitt, J. & Ehrhardt, D. W. (1990). Effects of intraspecific competition on outcrossing advantage in *Impatiens capensis*. *Evolution* **44**, 269–278.

Sved, J. A., Reed, T. E. & Bodmer, W. F. (1967). The number of balanced polymorphisms that can be maintained in a natural population. *Genetics* **55**, 469–481.

Sved, J. & Wilton, A. N. (1989). Inbreeding depression and the maintenance of deleterious genes by mutation: model of a *Drosophila* chromosome. *Genetical Research* **54**, 119–128.

Svensson, L. (1988). Inbreeding, crossing and variation in stamen number in *Scleranthus annuus* (Caryophyllaceae), a selfing annual. *Evolutionary Trends in Plants* **2**, 31–39.

Waller, D. M. (1984). Differences in fitness between seedlings derived from cleistogamous and chasmogamous flowers in *Impatiens capensis*. *Evolution* **38**, 427–440.

Wright, S. (1977). *Evolution and the Genetics of Populations*, vol. 3, *Experimental Results and Evolutionary Deductions*. Chicago: University of Chicago Press.

Ziehe, M. & Roberds, J. H. (1989). Inbreeding depression due to overdominance in partially self-fertilizing plant populations. *Genetics* **121**, 861–868.

Appendix. Bivariate normal approximation for mutation-selection equilibria with partial selfing

The method employed is to reduce the distribution among the progeny produced by selfing to the standardised bivariate normal form, exploiting the known properties of this distribution in order to calculate the quantities of interest. For the selfed sub-population, the variables $\tilde{y} = (y_s - \bar{y}_s) / \sigma_{y_s}$ and $\tilde{z} = (z_s - \bar{z}_s) / \sigma_{z_s}$ (where $\sigma_{y_s} = \sqrt{V_{y_s}}$ and $\sigma_{z_s} = \sqrt{V_{z_s}}$) follow such a distribution:

$$\phi(\tilde{y}, \tilde{z}) = (2\pi)^{-1} (1 - \rho^2)^{-\frac{1}{2}} \exp \left\{ -\frac{(\tilde{y}^2 + \tilde{z}^2 - 2\rho\tilde{y}\tilde{z})}{2(1 - \rho^2)} \right\}, \tag{A 1}$$

where the correlation coefficient $\rho = C_{y_zs} / \sigma_{y_s} \sigma_{z_s}$.

The fitness of an individual with state (y, z) , given by eqn (2) of the text, can be written in terms of the standardised variates as:

$$w(\tilde{y}, \tilde{z}) = \exp \left\{ C + a_1 \tilde{y} + a_2 \tilde{z} + \frac{1}{2}(a_{11} \tilde{y}^2 + 2a_{12} \tilde{y}\tilde{z} + a_{22} \tilde{z}^2) \right\} \tag{A 2}$$

where

$$C = \alpha(\bar{y}_s + h\bar{z}_s) + \frac{1}{2}\beta(\bar{y}_s + h\bar{z}_s)^2$$

$$a_1 = \alpha\sigma_{y_s} + \beta\sigma_{y_s}(\bar{y}_s + h\bar{z}_s), \quad a_2 = h(\alpha\sigma_{z_s} + \beta\sigma_{z_s}([h\bar{z}_s + \bar{y}_s])$$

$$a_{11} = \beta V_{y_s}, \quad a_{12} = h\beta\sigma_{y_s}\sigma_{z_s}, \quad a_{22} = h^2\beta V_{z_s}.$$

The mean fitness of the selfed subpopulation is given by the expression

$$\bar{w}_s = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} w(\tilde{y}, \tilde{z}) \phi(\tilde{y}, \tilde{z}) d\tilde{y} d\tilde{z}. \tag{A 3}$$

A transformation to a form that is proportional to the

standardised bivariate normal form for the integrand can be obtained by writing $u = k_1(\tilde{y} - \tilde{a}_1)$, $v = k_2(\tilde{z} - \tilde{a}_2)$, and equating the integrand to a constant times a bivariate normal in u and v , with correlation coefficient $\tilde{\rho}$. Equating coefficients on both sides, we find that

$$\tilde{\rho} = \frac{(\rho - [1 - \rho^2]a_{12})}{\sqrt{\{([1 - \rho^2]a_{11} + 1)([1 - \rho^2]a_{22} + 1)\}}}, \tag{A 4a}$$

$$\tilde{a}_1 = -\frac{1}{k_1} \left\{ \frac{a_1}{k_1} + \frac{\tilde{\rho}a_2}{k_2} \right\}, \quad \tilde{a}_2 = -\frac{1}{k_2} \left\{ \frac{\tilde{\rho}a_1}{k_1} + \frac{a_2}{k_2} \right\}, \tag{A 4b}$$

where

$$k_1 = \sqrt{\frac{(1 - \tilde{\rho}^2)([1 - \rho^2]a_{11} + 1)}{1 - \rho^2}},$$

$$k_2 = \sqrt{\frac{(1 - \tilde{\rho}^2)([1 - \rho^2]a_{22} + 1)}{1 - \rho^2}}.$$

Using this transformation in eqn (A 3), we obtain the following expression for the mean fitness of the selfed sub-population:

$$\bar{w}_s = \sqrt{\frac{1 - \tilde{\rho}^2}{(1 - \rho^2)k_1^2 k_2^2}} \times \exp \left\{ C + \frac{k_1^2 \tilde{a}_1^2 + k_2^2 \tilde{a}_2^2 - 2\tilde{\rho}k_1 k_2 \tilde{a}_1 \tilde{a}_2}{2(1 - \tilde{\rho}^2)} \right\}. \tag{A 5}$$

The parameters of the post-selection distribution $\phi^*(\tilde{y}, \tilde{z}) = w(\tilde{y}, \tilde{z}) \phi(\tilde{y}, \tilde{z}) / \bar{w}_s$ can be obtained from its moment-generating function:

$$M(\theta, \xi) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-(\theta\tilde{y} + \xi\tilde{z})} \phi^*(\tilde{y}, \tilde{z}) d\tilde{y} d\tilde{z} \tag{A 6}$$

where the coefficients of θ and ξ in the expansion of M give the changes in the means of \tilde{y} and \tilde{z} , the coefficients of $\frac{1}{2}\theta^2$ and $\frac{1}{2}\xi^2$ give the respective second moments about zero for the post-selection distribution, and the coefficient of $\theta\xi$ gives the corresponding crossproduct. We obtain

$$M = \exp \left\{ \tilde{a}_1 \theta + \tilde{a}_2 \xi + \frac{\theta^2}{2k_1^2} + \frac{\xi^2}{2k_2^2} + \frac{\tilde{\rho}\theta\xi}{k_1 k_2} \right\}. \tag{A 7}$$

Transforming back to the original variables y and z , we obtain the following equations for the post-selection distributional parameters:

$$\tilde{y}_s^* = \bar{y} - \sigma_{y_s} \tilde{a}_1, \quad \tilde{z}_s^* = \bar{z} - \sigma_{z_s} \tilde{a}_2 \tag{A 8a}$$

$$V_{y_s}^* = \frac{V_{y_s}}{k_1^2}, \quad V_{z_s}^* = \frac{V_{z_s}}{k_2^2}, \quad C_{y_zs}^* = \frac{\tilde{\rho}\sigma_{y_s}\sigma_{z_s}}{k_1 k_2}. \tag{A 8b}$$