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Maintenance of Quantitative Genetic Variance under Partial Self-Fertilization, with Implications for Evolution of Selfing

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ABSTRACT We analyze two models of the maintenance of quantitative genetic variance in a mixed mating system of self-fertilization and outcrossing. In both models purely additive genetic variance is maintained by mutation and recombination under stabilizing selection on the phenotype of one or more quantitative characters. The Gaussian Allele Model (GAM) involves a finite number of unlinked loci in an infinitely large population, assuming a normal distribution of allelic effects at each locus within lineages selfed for τ consecutive generations since their last outcross. The Infinitesimal Finite-population Model (IFM) involves an infinite number of loci in a large but finite population, assuming a normal distribution of breeding values in lineages of selfing age τ , with no assumption on the distribution of allelic effects within loci. In both models a stable equilibrium genetic variance exists, the *outcrossed equilibrium*, nearly equal to that under random mating, for all selfing rates, r , up to critical value, \hat{r} , the *purging threshold*, which approximately equals the mean fitness under random mating relative to that under complete selfing. In the GAM a second stable equilibrium, the *purged equilibrium*, exists for any positive selfing rate, with genetic variance less than or equal to that under pure selfing; as r increases above \hat{r} the outcrossed equilibrium collapses sharply to the purged equilibrium genetic variance. In the IFM a single stable equilibrium genetic variance exists at each selfing rate; as r increases above \hat{r} the equilibrium genetic variance drops sharply and then declines gradually to that maintained under complete selfing. We discuss implications of the models for the evolution of selfing rates, and their relevance to the classical view of Stebbins that predominant selfing constitutes an “evolutionary dead end”.

Many species of flowering plants, and some hermaphroditic animals, reproduce by a mixture of self-fertilization and outcrossing, often evolving to predominant selfing (Stebbins 1957, 1974; Harder and Barrett 2006; Iqic and Kohn 2006; Jarne and Auld 2006). In such mixed mating systems inbreeding depression for fitness is a critical determinant of mating system evolution (Lande and Schemske 1985; Charlesworth and Charlesworth 1987; Charlesworth et al. 1990; Charlesworth and Willis 2009; Porcher and Lande 2005; Devaux et al. 2014). Spontaneous deleterious mutations, as well as standing genetic variation, contribute to inbreeding depression and display a strongly bimodal distribution of allelic effects on fitness (Dobzhansky 1970; Fudala and Korona 2009; Bell 2010). Lethal and semi-lethal mutations in standing variation are on average nearly recessive, whereas mildly deleterious mutations have slightly recessive to nearly additive fitness effects (Simmons and Crow 1977; Willis 1999; Vassilieva et al. 2000; Eyre-Walker and Keightley 2007).

Stabilizing selection on quantitative characters is thought to be prevalent in natural populations and, although it may be weak or fluctuating on many characters (Wright 1969; Lande and Shannon 1996; Kingsolver et al. 2001; Lande 2007), it may create a substantial component of the total inbreeding depression for fitness. Stabilizing selection on a quantitative character produces allelic effects on fitness that are mildly deleterious and slightly recessive (Wright 1935), in agreement with observations on the mildly deleterious component of inbreeding depression (Simmons and Crow 1977; Willis 1999).

Under stabilizing selection on a quantitative character, an allele with an additive effect on the character may be either advantageous or deleterious depending on whether the mean phenotype is above or below the optimum, and alleles at different loci with opposite effects on the character may compensate for each other in their effects on phenotype and fitness, even when the mean phenotype is at the optimum (Fisher 1930, 1958; Wright 1931, 1969). Charlesworth (2013) highlighted the difficulty of empirically distinguishing the relative contributions of unconditionally versus conditionally deleterious mutations of small effect.

With respect to primary characters of morphology, physiology and behavior that determine fitness, Wright (1921, 1969) showed for purely additive genetic variance in

the absence of mutation and selection that inbreeding can increase the genetic variance up to a factor of 2. Lande (1977) modelled the maintenance of quantitative genetic variance by mutation under stabilizing selection for regular systems of non-random mating, including inbreeding with no variance in inbreeding coefficient among individuals. In sharp contrast with Wright's classical results, Lande (1977) found that a regular system of non-random mating has no impact on the equilibrium genetic variance maintained by mutation and stabilizing selection. Charlesworth and Charlesworth (1995) modelled the maintenance of quantitative variation by mutation under random mating versus complete selfing for different models of selection, concluding that complete selfing substantially reduces the genetic variance compared to random mating, but they did not model mixed mating.

Mixed mating systems, such as combined selfing and outcrossing, introduce the serious complication of zygotic disequilibrium (non-random associations of diploid genotypes among loci) and variance of inbreeding coefficient among individuals (Haldane 1949; Crow and Kimura 1970). These complications are successfully encompassed only by models of unconditionally deleterious mutations (Kondrashov 1985, Charlesworth and Charlesworth 1998). A theory of the maintenance of quantitative genetic variance does not currently exist for such mixed mating systems. To account for zygotic disequilibrium in quantitative characters under mixed mating, we employ the selfing age structure of the population, introduced by Kelly (2007) into the Kondrashov (1985) model.

We analyze two models of the maintenance of quantitative genetic variance in a mixed mating system of self-fertilization and outcrossing. In both models purely additive genetic variance is maintained by mutation and recombination among unlinked loci under stabilizing selection on the phenotype of one or more quantitative characters. The Gaussian Allele Model (GAM) involves a finite number of unlinked loci in an infinitely large population, assuming a normal distribution of allelic effects at each locus within lineages selfed for τ consecutive generations since their last outcross. The Infinitesimal Finite-population Model (IFM) involves an infinite number of loci in a very large but finite population, assuming a normal distribution of breeding values in lineages of selfing age τ , with no assumption on the distribution of allelic effects within

loci. Aspects of the results common to both models are considered to be robust, and have fundamental implications for the evolution of plant mating systems.

Basic assumptions of the models

The diploid population is partially self-fertilizing such that each zygote has a probability r of being produced by self-fertilization and probability $1 - r$ of being produced by outcrossing to an unrelated individual. There is no genetic variation in the selfing rate. Genetic variance in quantitative traits under stabilizing selection is assumed to be purely additive. The population is measured in each generation before selection on a (vector of) quantitative character(s), z . Under random mating the total additive genetic variance (or variance-covariance matrix) can be partitioned into two additive components $G = V + C$. Diagonal elements of V give the genic variances of each character (twice the variance of allelic effects on each character summed over all loci), and off-diagonal elements of V give the genetic covariances between characters due to pleiotropy (twice the covariances of allelic effects between pairs of characters summed over all loci with pleiotropic effects on the characters). C is the variance-covariance matrix of twice the total covariance of allelic effects among loci within gametes due to linkage disequilibrium (nonrandom association of alleles between loci within gametes). In the absence of selection, inbreeding reduces heterozygosity, proportionally reducing additive genetic (co)variance within families and increasing additive genetic (co)variance among families (Wright 1921, 1969; Crow and Kimura 1970).

Individual environmental effects on the phenotype are assumed to be independent among individuals, normally distributed with mean 0 and variance E , and additive and independent of the selfing age or breeding value (total additive genetic effect summed over all loci in an individual). In any generation before phenotypic selection a cohort of selfing age τ has genetic and phenotypic variances respectively of

$$G_\tau = (1 + f_\tau)(V_\tau + C_\tau) \tag{1a}$$

$$P_\tau = G_\tau + E \tag{1b}$$

Here f_τ is Wright's (1921, 1969) biometrical correlation of additive effects of alleles at the same locus within individuals, rather than Malécot's probability of identity

by descent. These two measures of f may be rather different since small mutational changes in additive effects of alleles cause only a small decrease in the biometrical correlation between alleles at the same locus, whereas mutation completely eliminates allelic identity. Assumptions specific to each model guarantee that for all individuals within a cohort of selfing age τ a single value of f_τ applies to all loci affecting a given character (GAM) or to all characters (IFM). The covariance of additive effects of alleles from different gametes equals f_τ multiplied by the variance of allelic effects within gametes (or the covariance of allelic effects at different loci within gametes).

The genetic and phenotypic variances before selection in the population as a whole are denoted without subscripts as

$$G = \sum_{\tau=0}^{\infty} p_\tau G_\tau \quad (1c)$$

$$P = G + E \quad (1d)$$

where p_τ is the frequency of selfing age τ in the population before selection.

Multivariate stabilizing selection on the individual phenotype, z , is described by a Gaussian function of the individual deviation from an optimum phenotype, θ ,

$$W(z) = \exp \left\{ -\frac{1}{2} (z - \theta)^\top \Omega^{-1} (z - \theta) \right\} \quad (2)$$

where Ω is a symmetric matrix describing stabilizing and correlational selection (Lande and Arnold 1983), with where superscripts \top and $^{-1}$ respectively denote vector or matrix transpose and matrix inverse. Using the normal approximation for phenotypes and breeding values, the mean fitness of a cohort of selfing age τ is then

$$\bar{w}_\tau = \int \phi_\tau(z) W(z) dz = \sqrt{|\Omega \gamma_\tau|} \exp \left\{ -\frac{1}{2} (\bar{z} - \theta)^\top \gamma_\tau (\bar{z} - \theta) \right\}$$

where $\phi_\tau(z)$ is the phenotypic distribution in the cohort of selfing age τ . Vertical bars $||$ denote the determinant of a matrix and $\gamma_\tau = (\Omega + P_\tau)^{-1}$. In subsequent formulas diagonal elements of the Ω matrix are denoted as ω^2 , and for independently selected characters the off-diagonal elements are 0. The general environment is assumed to be constant such that the mean phenotype always remains at the optimum, $\bar{z} = \theta$, so the

mean fitness of a selfing age cohort simplifies to

$$\bar{w}_\tau = \sqrt{|\Omega\gamma_\tau|} \quad (3a)$$

and the population mean fitness is

$$\bar{\bar{w}} = \sum_{\tau=0}^{\infty} p_\tau \bar{w}_\tau \quad (3b)$$

For independently selected characters, the mean fitness within each selfing age class is the product of the mean fitnesses of the characters, but this is not true for the population as a whole.

Gaussian Allele Model (GAM)

Mutation-selection balance for one character

We employ the mutation model of Kimura (1965) and Lande (1975, 1977) with n loci having completely additive effects on a particular character. Each allele at a given locus mutates at a constant rate with the same distribution of changes in additive effect on the character, with no directional bias. This produces a constant mutational variance for the character, σ_m^2 , without changing the mean phenotype. Empirical estimates of the mutational variance, scaled by the environmental variance (or as here using $E = 1$) are typically about 10^{-3} to 10^{-4} (Lande 1975; 1995; Lynch 1996; Houle et al. 1996). Assuming weak stabilizing selection and a high mutation rate per locus, the distribution of allelic effects at each locus is approximately Gaussian (Kimura 1965; Bürger 2000). This is consistent with empirical observations of high genomic mutation rates per character, on the order of 10^{-1} to 10^{-2} observed for quantitative traits in maize (Russell et al. 1963), and the assumption that n is much less than the total number of genes in the genome, on the order of $n = 10$ to 100 for the effective number of loci (Lande 1975, 1977).

For simplicity, we assume n unlinked loci with equal mutational variance, so that a single inbreeding coefficient applies to all loci affecting a given character within a given age class. Multiple characters are assumed to be genetically and phenotypically independent and subject to independent stabilizing selection. For multiple characters

that differ in their parameters (number of loci, mutational variance, and stabilizing selection) a different set of recursions across the selfing age classes is required.

Gamete production from the selfing age classes

Summing the additive effects of alleles at exchangeable loci in Lande (1975, 1977), the genetic covariance c_τ and genic variance v_τ of gametes produced by individuals in selfing age class $\tau \geq 1$ are

$$c_\tau = \frac{1}{2} \left[\frac{1 + f_\tau}{2} C_\tau - \left(1 - \frac{1}{n} \right) \frac{\gamma_\tau}{2} G_\tau^2 \right] \quad (4a)$$

$$v_\tau = \frac{1}{2} \left[V_\tau - \frac{\gamma_\tau}{2n} G_\tau^2 + \sigma_m^2 \right] \quad (4b)$$

For the outcrossed class $\tau = 0$, a straightforward way to derive the components of genetic variance and gametic output is through a weighted average of gametes produced by all selfing age classes. However, this approach mixes distributions with possibly rather different genetic variances, creating substantial kurtosis within the outcrossed class, particularly when large negative linkage disequilibrium builds up by selection of different compensatory mutations in long-selfed lineages. The outcrossed class then combines (1) a subclass produced by outcrossing between long-selfed individuals, with about half the total genetic variance of their parents (since $f_0 = 0$) and (2) subclasses produced by matings with at least one outcrossed parent in which recombination halves the negative linkage disequilibrium inherited from their parents, increasing the total genetic variance. We found that pooling these subclasses of outcrossed individuals into a single class, ignoring kurtosis, can create artifactual oscillations of genetic variance in the first two age classes. To eliminate this artifact, we analyze selection acting separately on all possible types of outcrosses according to the selfing age of the parents.

Outcrossing by random mating among selfing age classes implies that for pairs of parents with selfing ages i and j the frequency of the ij subclass of the outcrossed class 0, denoted as p_{0ij} , is simply the product of the frequencies of parental age classes at the adult stage, after selection in the previous generation denoted by subscript $(t - 1)$,

$$p_{0ij} = \frac{\bar{w}_{i(t-1)}}{\bar{w}_{(t-1)}} p_{i(t-1)} \frac{\bar{w}_{j(t-1)}}{\bar{w}_{(t-1)}} p_{j(t-1)} \quad (5)$$

The mean fitness of the outcrossed class as a whole is then

$$\bar{w}_0 = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} p_{0ij} \bar{w}_{0ij} \quad (6)$$

The mean fitness of each outcrossed subclass, \bar{w}_{0ij} , depends only on its total genetic variance, but selection acts differently on unequal gametic contributions to the genic variance and covariance by parents of different selfing age. Gametes produced by the outcross class, averaged over all subclasses, have genic variance and covariance

$$c_0 = \frac{1}{2\bar{w}_0} \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} p_{0ij} \bar{w}_{0ij} \left[\frac{c_{i(t-1)} + c_{j(t-1)}}{2} - \gamma_{0ij} \left(1 - \frac{1}{n} \right) \left([c_{i(t-1)} + v_{i(t-1)}]^2 + [c_{j(t-1)} + v_{j(t-1)}]^2 \right) \right] \quad (7a)$$

$$v_0 = \frac{1}{2\bar{w}_0} \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} p_{0ij} \bar{w}_{0ij} \left[v_{i(t-1)} + v_{j(t-1)} - \frac{\gamma_{0ij}}{n} \left([c_{i(t-1)} + v_{i(t-1)}]^2 + [c_{j(t-1)} + v_{j(t-1)}]^2 \right) \right] + \frac{\sigma_m^2}{2} \quad (7b)$$

where subscript $(t - 1)$ denotes the grandparental generation. The relative frequencies and mean fitness of class $0ij$ are obtained using the components of genetic variance for the outcrossed progeny of a mating between individuals of selfing age classes i and j , with a prime denoting the next generation,

$$C'_{0ij} = c_i + c_j \quad (8a)$$

$$V'_{0ij} = v_i + v_j \quad (8b)$$

$$f'_{0ij} = 0. \quad (8c)$$

These yield the total genetic and phenotypic variance (using eqs. 1), and hence the mean fitness \bar{w}_{0ij} (eqs. 3) of the subclass.

Recursions for components of genetic variance

All selfing age classes after the first obey the recursions, for $\tau \geq 1$,

$$C'_{\tau+1} = 2c_\tau = \frac{1+f_\tau}{2}C_\tau - \left(1 - \frac{1}{n}\right)\frac{\gamma_\tau}{2}G_\tau^2 \quad (9a)$$

$$V'_{\tau+1} = 2v_\tau = V_\tau - \frac{\gamma_\tau}{2n}G_\tau^2 + \sigma_m^2 \quad (9b)$$

$$f'_{\tau+1} = \frac{1}{2v_\tau} \left(\frac{1+f_\tau}{2}V_\tau - \frac{\gamma_\tau}{2n}G_\tau^2 \right) \quad (9c)$$

In the absence of selection and mutation eq. (9c) reduces to the recursion of Wright (1921, 1969) for the inbreeding coefficient under continued selfing, $f_{\tau+1} = (1 + f_\tau)/2$.

The genetic variance components of the outcrossed class are twice the weighted average of gametic outputs from all selfing age classes:

$$C'_0 = 2 \sum_{\tau=0}^{\infty} \frac{p_\tau \bar{w}_\tau}{\bar{w}} c_\tau \quad (10a)$$

$$V'_0 = 2 \sum_{\tau=0}^{\infty} \frac{p_\tau \bar{w}_\tau}{\bar{w}} v_\tau \quad (10b)$$

$$f'_0 = 0 \quad (10c)$$

Finally, for the first selfing age class $\tau = 1$,

$$C'_1 = 2c_0 \quad (11a)$$

$$V'_1 = 2v_0 \quad (11b)$$

$$f'_1 = \frac{1}{2v_0} \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \frac{p_{0ij} \bar{w}_{0ij}}{\bar{w}_0} \left[\frac{v_{i(t-1)} + v_{j(t-1)}}{2} - \frac{\gamma_{0ij}}{n} \left([c_{i(t-1)} + v_{i(t-1)}]^2 + [c_{j(t-1)} + v_{j(t-1)}]^2 \right) \right] \quad (11c)$$

Age distribution of selfing lineages

After stabilizing selection, mating and reproduction, the distribution of selfing ages in the population is

$$p'_0 = 1 - r \quad (12a)$$

$$p'_{\tau+1} = r \frac{\bar{w}_\tau}{\bar{w}} p_\tau \quad (12b)$$

Eqs. (1)–(12) constitute the complete recursion system for the evolution of quantitative genetic variance. For numerical computation it is necessary to truncate the age distribution of selfing lineages at some upper limit. This approach is often used in analyzing the demography of age-structured populations (Caswell 2001). Recursion formulas for the frequency and genetic composition of the terminal selfing age class are given in Appendix 1. The number of classes retained for numerical analysis should be sufficiently large that substantially increasing it does not appreciably affect the results.

Numerical analysis of the GAM for multiple genetic independent characters under independent stabilizing selection showed that the results had a low sensitivity to substantial differences in stabilizing selection or mutational variance among characters (unpublished results).

Infinitesimal Finite-Population Model (IFM)

To relax the critical but controversial assumption in the GAM of a normal distribution of allelic effects within loci (Turelli 1984; Turelli and Barton 1994), and to facilitate analysis of correlated characters, we extend Fisher’s (1918) infinitesimal model to encompass mixed mating. Our infinitesimal model involves an infinite number of loci, with no assumption on the distribution of allelic effects within loci. It does, however, assume a Gaussian distribution of breeding values within each cohort of a given selfing age (justified by the Central Limit Theorem as for the classical infinitesimal model under random mating). The accuracy of this assumption is monitored numerically using the kurtosis of breeding values in the population.

Fisher’s (1918) infinitesimal model concerns an infinite population with an infinite number of loci each having an infinitesimal effect on a quantitative character. Selection then causes no change in allele frequencies at any locus, although it can change the mean phenotype, and the linkage disequilibrium among loci (Bulmer 1971). The total genic variance, V , in the population thus remains constant, but the total genetic variance, G evolves because selection and recombination change the total linkage disequilibrium variance among loci, C . Fisher’s infinitesimal model for an infinite population thus does not require mutation to maintain genetic variance.

An unrealistic feature of the classical infinitesimal model of Fisher (1918) and

Bulmer (1971) for an infinite population is that the equilibrium inbreeding depression due to stabilizing selection increases with the selfing rate of a population, until at sufficiently high selfing rates stabilizing selection finally creates enough negative linkage disequilibrium to purge the genetic variance (unpublished results). This unrealistic feature of the classical infinitesimal model for an infinite population can be understood from the classical result of Wright (1921, 1969) for an infinite population with no selection or mutation, in which the equilibrium genetic variance increases as a linear function of the population inbreeding coefficient.

To obtain a more realistic infinitesimal model for partial selfing, we introduce the Infinitesimal Finite-population Model (IFM), in which the genic variance, V , is maintained by a balance between mutation and random genetic drift. The IFM can then incorporate the well-known influence of inbreeding in changing the effective population size and hence the genic variance maintained by mutation.

The IFM is derived from the GAM by letting the number of loci approach infinity, $n \rightarrow \infty$, and, simultaneously letting the effective population size under random mating become very large and the mutational variance become very small, $N_e(0) \rightarrow \infty$ and $\sigma_m^2 \rightarrow 0$, such that $N_e(0)\sigma_m^2$ remains constant. Under random mating the IFM has the same dynamics in response to selection as in the classical infinitesimal model of Fisher (1918) and Bulmer (1971), but more generally the IFM also allows the genic variance to adjust to changes in the selfing rate as follows. With these assumptions the recursions for the inbreeding coefficient as a function of selfing age, eqs (9c), (10c) and (11c) reduce to Wright's classical formula for continued selfing

$$f'_{\tau+1} = (1 + f_\tau)/2 \tag{13a}$$

The genic variance in the total population (or in any selfing age class) obeys the recursion

$$V(r)' = \left(1 - \frac{1}{2N_e(r)}\right) V(r) + \sigma_m^2$$

where $N_e(r)$ is the effective population size at selfing rate r . It is well-known that a completely selfing population has an effective size half that under random mating (Charlesworth and Charlesworth 1995). More generally, using methods of Wright

(1931, 1969), the effective size of a population with inbreeding coefficient f is $N_e(r) = N_e(0)/(1 + f)$. Substituting this into the recursion for the genic variance and using Wright’s (1921, 1969) formula for the equilibrium inbreeding coefficient in a partial selfing population with no selection or mutation, $f = \frac{r}{2-r}$, gives, asymptotically, the equilibrium genic variance maintained by mutation-drift balance in a large partially selfing population,

$$V(r) = (1 - r/2)V(0) \tag{13b}$$

where $V(0) = 2N_e(0)\sigma_m^2$ in agreement with previous results on mutation-selection balance under random mating (Clayton and Robertson 1955; Lande 1980). For any given selfing rate, this equilibrium genic variance replaces the recursions (9b), (10b) and (11b). It is half as large for complete selfing as under random mating.

Formula (13b), with eqs. (1a) and (1c) and Wright’s relation $f = \frac{r}{2-r}$, implies that at equilibrium in the absence of selection (for which $C = 0$) the genetic variance maintained in the population is actually independent of the selfing rate, $G(r) = V(0)$. This occurs because the reduction of genic variance with larger selfing rate (and smaller effective population size) is exactly compensated by the increased inbreeding coefficient in the population. As we show below, this allows stabilizing selection to purge quantitative genetic variance from the population at high selfing rates, and produces a realistic equilibrium inbreeding depression which always decreases with increased selfing rate.

A great advantage of the IFM is that it can readily model the maintenance of genetic variability in correlated characters under multivariate selection, with genetic correlations between characters due to a combination of pleiotropic mutation and correlational selection. A key ingredient of this generality is that in the IFM Wright’s recursion for the inbreeding coefficient under continued selfing (eq. 13a) applies to all loci in the genome regardless of their pleiotropic effects on different characters.

The IFM was used to investigate how pleiotropic mutation and correlational selection changed the results. With many loci of low mutability, in the limit as $n \rightarrow \infty$ with very large effective population size, such that $V(0)$ remains constant, the GAM can be converted to a general multivariate IFM by interpreting various quantities as matrices rather than scalars, e.g. in eqs. (4) rewriting $\gamma_\tau G_\tau^2$ as $G_\tau \gamma G_\tau$ (Lande 1980, Lande and Arnold 1983). In the IFM, mutational and genic variance-covariance matrices can

be simply transformed by rotation of axes to produce either selectively or genically independent characters (using eigenvectors of the correlational selection matrix γ , or the genic variance-covariance matrix $V(0)$). Our numerical analysis of the IFM therefore focused on mutationally and genically independent characters under correlational selection.

In both models deviation from the assumption of a Gaussian distribution for either the allelic effects (GAM) or breeding values (IFM) within selfing age cohorts, occurs due to mixing of genetic contributions among all selfing ages upon outcrossing. We considered the models to have good accuracy when the equilibrium kurtosis in the population remained close to that for a normal distribution ($\kappa = 3$). For comparison to the numerical results we derived the equilibrium kurtosis of breeding values in Wright's (1921, 1969) neutral model of partial selfing in an infinite population with no selection or mutation, assuming normality of breeding values within selfing age cohorts, $\kappa = 3(\frac{1-r^2/4}{1-r/4})$ (Appendix 2). Under random mating or complete selfing the breeding value in the population is normal. The maximum kurtosis of $3[1 + (2 - \sqrt{3})^2] \approx 3.215$ occurs at selfing rate $r = 2(2 - \sqrt{3}) \approx 0.536$. Thus in Wright's neutral model of partial selfing in an infinite population the deviation from normality of breeding values at equilibrium must be rather small.

Analytical and Numerical Results

Purging genetic variance by stabilizing selection under continued selfing

In both the GAM and the IFM under continued selfing, stabilizing selection purges the genetic variance, but the details of how this happens and the extent of the purging differ in the two models, as shown below.

Continued selfing

In the GAM, assuming weak selection ($\omega^2 \gg P_\tau$ so that $\gamma_\tau \approx 1/\omega^2$) and small mutational variance ($\sigma_m^2 \ll E$) eq. (9c) can be expanded as a Taylor series to first order in small terms and solved for a slowly changing quasi-equilibrium, which gives $f_\tau \approx 1 - 2\sigma_m^2/V_\tau$. This can be used with eqs. (9a), (9b) and (1) to find a first-order approximation for the asymptotic dynamics of the genetic variance and its components

for large selfing age, $G'_{\tau+1} - G_\tau \approx -G_\tau^2/\omega^2 + 4\sigma_m^2$. Thus under continued selfing in the GAM the genetic variance approaches an equilibrium

$$G_\infty \approx 2\sqrt{\sigma_m^2\omega^2} \quad (14a)$$

This is smaller by a factor of $\sqrt{2/n}$ than the weak selection approximation for the equilibrium genetic variance under random mating $G_0 \approx \sqrt{2n\sigma_m^2\omega^2}$ (Kimura 1965; Lande 1975, 1977).

For the GAM the above results with eq. (9a) show that with continued selfing, although G_τ approaches a constant, both V_τ and $-C_\tau$ continue to increase indefinitely at the asymptotic rate

$$\lim_{\tau \rightarrow \infty} (V'_{\tau+1} - V_\tau) = - \lim_{\tau \rightarrow \infty} (C'_{\tau+1} - C_\tau) = (1 - \frac{2}{n})\sigma_m^2 \quad (14b)$$

In view of the dynamics of f_τ above eq. (14a), this confirms that with increasing selfing age the inbreeding coefficient approaches 1.

For the IFM, a similar analysis produces the asymptotic recursion for the genetic variance under continued selfing, $G'_{\tau+1} - G_\tau \approx -G_\tau^2/\omega^2$, the only solution of which is

$$G_\infty = 0. \quad (15)$$

Under continued selfing, purging of genetic variance in the IFM occurs solely by the buildup of negative linkage from stabilizing selection; as $f_\tau \rightarrow 1$, increasing homozygosity reduces the effective recombination in proportion to $1 - f_\tau$ (Lande 1977) so that $C_\tau \rightarrow -V$. By comparison, under random mating in the IFM, assuming weak stabilizing selection ($\gamma V \ll 1$), the equilibrium genetic variance is approximately $G_0 \approx (1 - \gamma V)V$.

These analytical results concerning the genetic variance and its components as functions of selfing age were confirmed numerically. Fig. 1A shows for the GAM the indefinite increase of the genic variance and the negative linkage disequilibrium variance with increasing selfing age, due to the buildup of associations between compensatory mutations (eq. 14b) while the genetic variance approaches a constant (eq. 14a). For

populations with a high selfing rate the accumulation of a large negative linkage disequilibrium in the GAM leads to recombination and segregation in the second generation after outcrossing ($\tau = 1$) producing a high genetic variance and low mean fitness (Fig. 1B, D). Similar effects occur in the IFM, but with restricted magnitude (Fig. 2B,D).

[Fig. 1 and Fig. 2 about here]

Mixed mating and the distribution of selfing ages

With partial selfing, the distribution of selfing ages in the population plays an crucial role in the dynamics of genetic variance. At a stable equilibrium the distribution of selfing ages is $p_\tau = (1-r)r^\tau l_\tau$ where $(1-r)r^\tau$ is the probability of selfing τ generations in a row, and $l_\tau = \bar{w}^{-\tau} \prod_{i=0}^{\tau-1} \bar{w}_i$ for $\tau \geq 1$ is the relative survival of selfed lineages to selfing age τ , with $l_0 = 1$.

Despite continued selfing and stabilizing selection eventually purging the genetic variance in both models, at any given selfing rate in the population, the distribution of selfing ages determines the extent of purging of the genetic variance in the population as a whole. This occurs because shifts in the selfing age distribution change the balance of contributions of young and old selfing ages to the genetic variance at outcrossing (eq. 9) which is then transmitted through the selfing ages (eqs. 8, 10). A low or moderate r shifts the selfing age distribution to the left, toward younger ages; a high r shifts the selfing age distribution right, toward older ages. A crucial property of the relative survival function of selfed lineages is that the mean fitness at each selfing age depends on selection on the whole organism rather than just a single character (eq. 11); this explains why selection on multiple characters affects the purging of genetic variance in each character, as illustrated in the numerical results.

Numerical examples of the mean fitness as a function of selfing age, and the selfing age distribution, are illustrated in Fig. 1C-F and Fig. 2C-F for the GAM and the IFM respectively. At high selfing rate in the GAM the long-selfed lineages become reproductively isolated from the outcrossed lineages, as shown by the very low fitness of intermediate selfing ages and the nearly disjunct bimodal distribution of selfing ages (Fig. 1D,F). Similar effects occur in the IFM at high selfing rate, but to a lesser extent (Fig. 2D,F).

Equilibrium genetic variance in the population as a function of r

For intermediate selfing rates the complexity of the models precludes analytical solution. Recursions for the GAM and IFM were iterated numerically to characterize the equilibrium genetic variance in the population as a function of population selfing rate for a wide range of parameter values. Below we describe the salient similarities and differences between the GAM and IFM, emphasizing the robust results common to both models. The accuracy of the assumption of a normal distribution of breeding values within selfing age cohorts in both models was assessed using the kurtosis of breeding values for the population as a whole, κ . To elucidate patterns in the equilibrium genetic variance, we computed for the population as a whole the mean fitness (eq. 3b), the inbreeding depression, δ (loss of mean fitness upon selfing vs. outcrossing), and the genetic variance after selection within a generation, G^* (Appendix 2).

In the GAM, two types of stable equilibrium exist for the total genetic variance in the population. *Outcrossed equilibrium*: Over a wide range of selfing rates from 0 up to a critical selfing rate, \hat{r} , termed the *purging threshold*, the genic variance, V , and linkage disequilibrium, C , evolve to nearly compensate for non-random mating, maintaining nearly the same total genetic variance, G , as under random mating. At selfing rates above \hat{r} the stable outcrossed equilibrium collapses to the purged equilibrium. *Purged equilibrium*: Selfing rates even slightly above the purging threshold cause a collapse of the equilibrium genetic variance after selection within a generation, G^* , to values equal to or less than under pure selfing (eq. 14a). A stable purged equilibrium exists for all selfing rates.

The purged equilibrium exists and is stable at any selfing rate ($r > 0$), but its stability becomes weaker and its domain of attraction smaller for lower selfing rates. At selfing rates below the purging threshold, $r < \hat{r}$, the initial condition of genetic monomorphism always leads to the outcrossed equilibrium; the purged equilibrium is attained from initial conditions with large negative linkage disequilibrium and small total genetic variance. At low selfing rates the rate of convergence to the purged equilibrium may be slow and its domain of attraction small.

[Fig. 3 and Fig. 4 about here]

Fig. 3 illustrates for the GAM that at selfing rates below the purging threshold,

under weak stabilizing selection the equilibrium genetic variance after selection within a generation, G^* , is only slightly smaller than that before selection, G . For selfing rates above the purging threshold, the equilibrium genetic variance before selection, G , blows up to infinity. This occurs because of the unlimited negative linkage disequilibrium (compensatory mutations) and genic variance built up under continued selfing, which segregates in the second generation after outcrossing and recombination. However, the F_2 recombinants among long-selfed lineages are strongly selected against because of their large phenotypic deviations from the optimum. For this reason, at selfing rates above the purging threshold, the equilibrium genetic variance after selection within a generation, G^* , collapses to G_{purged}^* , the purged equilibrium after selection. For the same reason, at selfing rates above the purging threshold the equilibrium kurtosis of breeding value in the population, κ , blows up, but the kurtosis after selection κ^* nearly equals that for Wright’s neutral model. Thus, under the basic assumptions of the GAM, we consider the numerical results to be reasonably accurate at all selfing rates.

Fig. 4 shows that for the IFM the equilibrium genetic variance in the population, G , also nearly equals that under random mating for selfing rates up to a purging threshold. Just above the purging threshold the equilibrium genetic variance dips sharply and then declines gradually with increasing r . The IFM displays only a single stable equilibrium genetic variance at every selfing rate. The kurtosis of breeding value in the population, both before and after selection, becomes large at selfing rates substantially above the purging threshold. Because excess kurtosis increases the strength of selection on the variance (Turelli and Barton 1987), the IFM overestimates the genetic variance maintained at selfing rates above the purging threshold. Qualitative differences between the models at high selfing rates arise from constancy of the genic variance at any given selfing rate in the IFM, which limits the buildup of negative linkage disequilibrium under continued selfing (compare Fig. 1A to Fig. 2A).

[Fig. 5 and Fig. 6 about here]

Fig. 5 and Fig. 6 depict, respectively for the GAM and IFM, how stabilizing selection on multiple independent characters acts synergistically to reduce the purging threshold, and, especially in the GAM, to sharpen the threshold in comparison to that for a single character under the same intensity of stabilizing selection per character.

These figures also display the equilibrium inbreeding depression, δ , and the mean fitness in the population, as functions of the selfing rate. For both models the mean fitness of the population at high selfing rates exceeds that at low selfing rates, consistent with the purging of genetic variance at high selfing rates.

Fig. 7 shows analogous results for the IFM with multiple characters with no pleiotropy but under correlational selection on independent pairs of characters. The genetic covariance between pairs of mutually selected characters, B , is then caused solely by linkage disequilibrium, and at high selfing rates their equilibrium genetic correlation, B/G , makes the multivariate distribution of breeding values conform closely to the shape of the fitness surface.

[Fig. 7 about here]

General approximation for the purging threshold

For selfing rates below the purging threshold, in both the GAM and IFM the equilibrium mean fitness in the population at the outcrossed equilibrium remains nearly the same as under random mating, \bar{W}_{out} . More remarkably, in both models at selfing rates above the purging threshold the mean fitness nearly equals the product of the selfing rate, r and the equilibrium mean fitness under completely selfing, \bar{W}_{self} . This can be seen most explicitly from the dotted lines for the purged equilibrium in Fig. 5C, and by extrapolation of the corresponding lines in Fig. 6C and Fig. 7D from their values at complete selfing back to the origin. The simplicity of these results indicate that in both models the purging threshold, \hat{r} can be accurately located by the intersection of these two lines, $\bar{W}_{out} \approx \hat{r}\bar{W}_{self}$. Remarkably, the purging threshold can thus be accurately approximated as the ratio of mean fitnesses at equilibrium under random mating versus pure selfing,

$$\hat{r} \approx \frac{\bar{W}_{out}}{\bar{W}_{self}}. \quad (16)$$

With many characters, the numerical analysis indicates a sharp purging threshold, and the analytical approximation is fairly accurate. A small inaccuracy arises, most noticeably in the GAM for $m = 5$ or 10 , because \bar{W}_{out} as a function of r dips slightly near the intersection with $r\bar{W}_{self}$.

Discussion

Wright (1921, 1969) showed that for a neutral model of additive genetic variance, inbreeding increases the equilibrium genetic variance in proportion to the average inbreeding coefficient in the population, so that complete selfing doubles the equilibrium genetic variance in comparison to random mating. Lande (1977) found for regular systems of mating, in which every individual performs the same type of non-random mating, that the equilibrium genetic variance maintained by mutation and stabilizing selection is independent of the mating system. In contrast, Charlesworth and Charlesworth (1995) compared maintenance of quantitative genetic variance by mutations under stabilizing or purifying selection, concluding that selfing substantially reduces the equilibrium genetic variance compared to random mating. These disparate results are reconciled in our models of mixed mating, showing that in both the GAM and IFM the equilibrium genetic variance remains nearly the same as under random mating for selfing rates up to the *purging threshold*, above which a qualitative change occurs. Our asymptotic analysis of the total genetic variance under complete selfing agrees qualitatively with Charlesworth and Charlesworth (1995), although their models neglected linkage disequilibrium which plays an important role in purging quantitative variance in both the GAM and IFM.

In the GAM two possible stable equilibria exist for the genetic variance as a function of the population selfing rate, r , with regions of sharply distinct dynamics separated by a *purging threshold*, \hat{r} . The *outcrossed equilibrium* has genetic variance nearly equal to that under random mating, and exists only for selfing rates below the purging threshold. The *purged equilibrium* has lower genetic variance in the highly selfed stable core of the population, and exists for all selfing rates; in the highly selfed core, the total genetic variance remains constant but the total genetic variance in the population blows up because the genic variance and (negative) linkage disequilibrium in the core increase indefinitely. Initial outcrossing between long-selfed lineages decreases the genetic variance by half (since $f_0 = 0$), resulting in outcrossed F_1 hybrid vigor (“heterosis”); subsequent selfing or outcrossing of these F_1 allows recombination to express the built-up genic variance previously hidden by negative linkage disequilibrium, producing F_2 breakdown in fitness. Thus, the highly selfed core of a population at a

purged equilibrium becomes reproductively isolated from its outcrossing relatives. This mechanism for *speciation by predominant selfing* accords with the finding of Goldberg and Igin (2012) that phylogenetic transitions to predominant selfing often coincide with species originations.

In the IFM only a single stable equilibrium for the genetic variance exists at any selfing rate. This qualitative difference between the two models occurs because in the IFM the genic variance at any given selfing rate remains constant, which limits the buildup of linkage disequilibrium variance under continued selfing; this also limits the magnitude of F_2 breakdown following outcrossing of a long-selfed lineage.

Another feature common to both the GAM and IFM is that the purging threshold approximately equals the ratio of the equilibrium mean fitness under random mating relative to that under pure selfing. In a constant environment stabilizing selection of multiple quantitative characters toward a joint optimum phenotype always produces a higher mean fitness for the population with the lowest genetic variance, which here is that under pure selfing. A further advantage of selfing is that it also increases mean fitness by building adaptive genetic correlations between characters under correlational selection as shown in Fig. 7 (as in Lande 1984 for a symmetric GAM under a regular system of inbreeding). The complexity of the phenotype, and the overall strength of stabilizing selection on it, are thus of paramount importance in determining the purging threshold. For a single character under moderately strong stabilizing selection the purging threshold occurs at a very high selfing rate (Fig. 2A), but for a complex phenotype with many characters under independent stabilizing selection, the purging threshold is substantially reduced (Fig. 7A).

These results are consistent with limited available data on genetic variance in quantitative characters and inbreeding depression as a function of r (Charlesworth and Charlesworth 1995). They also have important implications for evolution of the selfing rate, discussed below. In this regard it is important to note that within any very large population different sets of quantitative characters will conform more closely to the assumptions of either the GAM or IFM. Even if only a single character conforms to the GAM, a stable purged equilibrium will exist at all positive selfing rates (Fig. 4A). However, finite population must eventually limit the buildup of linkage disequilibrium

variance; the IFM is therefore likely to be more realistic for most quantitative characters, especially in populations with effective sizes that are not very large.

Genetic variance and inbreeding depression

Inbreeding depression is generally thought to be the main genetic factor counteracting Fisher’s automatic advantage of selfing, and preventing the evolution of complete selfing in self-compatible species (Fisher 1941; Lande and Schemske 1985; Porcher and Lande 2005; Devaux et al. 2014). Previous theory indicates that inbreeding can cause rapid purging of inbreeding depression due to nearly recessive lethals, and that purging of inbreeding depression due to slightly dominant nearly additive mildly deleterious mutations is more difficult, and occurs to a lesser extent (Lande and Schemske 1985; Charlesworth et al. 1990; Lande et al. 1994; Charlesworth and Willis 2009; Porcher and Lande 2013). Consistent with this is the observation that highly selfing species show substantially reduced inbreeding depression (Husband and Schemske 1996).

Winn et al. (2011) found that species with intermediate selfing rates maintain a substantial inbreeding depression. As they suggest, this may in part be due to selective interference with the purging of lethals that occurs at a high total inbreeding depression (Lande et al. 1994), especially if the average inbreeding depression estimated for species with intermediate selfing rates, $\delta = 0.58$, substantially underestimates actual inbreeding depression, due to common omission of the final growth-to-flowering component of the life cycle. Porcher and Lande (2013) showed that a larger constant background inbreeding depression produces elevated selective interference among lethals. The constancy of quantitative genetic variance and inbreeding depression maintained across a wide range of selfing rates below the purging threshold in the present theory is qualitatively consistent with these observations.

Charlesworth and Charlesworth (1995) reviewed limited available evidence indicating that predominantly selfing populations maintain lower quantitative genetic variance than predominant outcrossers on average. This accords with the reduced genetic variance after selection maintained at selfing rates above the purging threshold in the long-selfed core of the population, and in the population as a whole after selection. In the GAM, at the purged equilibrium after F_2 breakdown to near zero fitness implies

that the genetic variance after selection nearly equals the weighted average of that in the long-selfed core and their F_1 outcrossed progeny (Fig. 7A).

In this context it is important to distinguish the purging threshold for recessive lethal mutations (Lande et al. 1994) from that for quantitative genetic variance described here. Although both thresholds involve the reduction of an equilibrium genetic variance at higher selfing rates, they arise under different conditions by different mechanisms, and occur at different selfing rates. Selective interference among lethal mutations depends on a high total inbreeding depression to produce a sharp purging threshold for lethals. In contrast, the purging threshold for quantitative genetic variance exists even under weak stabilizing selection on a single character with consequently small inbreeding depression. The mechanism creating the purging threshold for lethals is that at selfing rates below the threshold nearly all products of selfing are lethal (Ganders 1972; Lande et al. 1994). In contrast, at selfing rates above the purging threshold for quantitative variance, the only stable state is the purged equilibrium, characterized by F_1 hybrid vigor in crosses between highly inbred lineages at the population's core, followed by F_2 breakdown to relatively low fitness (delayed outbreeding depression); these effects are more extreme in the GAM than in the IFM.

It should also be noted that F_2 breakdown among long-selfed lineages at a purged equilibrium makes them reproductively isolated from each other as they are from their outcrossed ancestors or offspring. This would happen if even a single character conforms to the assumptions of the GAM, with the rest more nearly obeying the IFM. Predominantly selfing species that exist for long may therefore undergo the progression of reproductive isolation classically observed between young species compared to that between old species, beginning with F_1 heterosis with F_2 breakdown and culminating in F_1 and F_2 sterility and inviability (Dobzhansky 1970; Coyne and Orr 2004).

Evolution of selfing rate near outcrossed and purged equilibria

At selfing rates below the purging threshold, $r < \hat{r}$, inbreeding depression is an important genetic constraint which, in combination with ecological constraints, controls evolution of the selfing rate by small genetic steps (Lande and Schemske 1985; Johnston et al. 2009; Porcher and Lande 2013; Devaux et al. 2013). Both the GAM and

IFM conform then to the rule that in the absence of ecological constraints selection favors small genetic changes that decrease the selfing rate when the total inbreeding depression exceeds 0.5.

In contrast, in both models inbreeding depression is misleading for understanding evolution of selfing rates above the purging threshold, $r > \hat{r}$ (or at any purged equilibrium in the GAM). At selfing rates just above the purging threshold the inbreeding depression is reduced or even negative (as in the GAM in Fig 5B) because most outcrossed survivors are F_1 hybrids between long-selfed lineages (with about half the total genetic variance of their long-selfed parents since $f_0 = 0$). The progeny of these F_1 outcrosses suffer F_2 breakdown (or *delayed outbreeding depression*) to low fitness; this strongly selects against outcrossing and favors increased selfing. The models therefore indicate that in a large population the evolution of predominant selfing, with purged quantitative genetic variance, is an irreversible evolutionarily absorbing state (Bull and Charnov 1985; Charlesworth and Charlesworth 1998; Galis et al. 2010), supporting the view of Stebbins (1957, 1974) that predominantly selfing plant species generally occupy terminal branches in plant phylogenies.

Stebbins also inferred that highly selfing species have an increased extinction rate and do not persist long in phylogenetic time. The present theory shows that at a purged equilibrium the long-selfed core of the population has less genetic variance than for a population at the outcrossed equilibrium. This implies that in a constant environment highly selfing populations have a higher mean fitness at equilibrium than under random mating. Extreme environments, such as on the edge of a species range where new selfing species often arise from outcrossers (Wright et al. 2013), may exert stronger stabilizing and/or directional selection. Under this scenario, or in a changing environment with high temporal variance and predictability of the optimum phenotype, highly selfing (purged) populations with less genetic variance than at the outcrossing equilibrium will have lower mean fitness through time and thus a higher extinction rate (Lande and Shannon 1996; Lande et al. 2003). Our model thus provides a theoretical foundation for the classical view of Stebbins' (1957, 1974) confirmed by recent empirical findings (Takebayashi and Morrell 2001; Goldberg et al. 2010; Goldberg and Iqic 2012; Wright et al. 2013; Iqic and Busch 2013) that predominant selfing constitutes an

“evolutionary dead end”.

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APPENDIX 1

Truncation of the selfing age distribution

For selfing ages larger than some value L , the genetic parameters within age classes should be nearly equivalent, so that all selfing age classes can be lumped into a single terminal class of age L or larger, which then becomes the upper limit instead of ∞ in numerical summations. Additional recursion formulas are then required for the frequency and genetic composition in the terminal age class.

Recursions for the genic variance and covariance (due to linkage disequilibrium), and the inbreeding coefficient, in the terminal selfing age class are

$$C'_L = \frac{p_{L-1}^* 2c_{L-1} + p_L^* 2c_L}{p_{L-1}^* + p_L^*}$$

$$V'_L = \frac{p_{L-1}^* 2v_{L-1} + p_L^* 2v_L}{p_{L-1}^* + p_L^*}$$

$$f'_L = \frac{p_{L-1}^* \left(\frac{1+f_{L-1}}{2} V_{L-1} - \frac{\gamma_{L-1}}{2n} G_{L-1}^2 \right) + p_L^* \left(\frac{1+f_L}{2} V_L - \frac{\gamma_L}{2n} G_L^2 \right)}{p_{L-1}^* V'_{L-1} + p_L^* V'_L}$$

The recursion for the terminal age class frequency is

$$p'_L = r(p_{L-1}^* + p_L^*)$$

where $p_\tau^* = \bar{w}_\tau p_\tau / \bar{w}$ and $\bar{w} = \sum_{\tau=0}^L p_\tau \bar{w}_\tau$.

APPENDIX 2

Population statistics

Kurtosis. By assumption each selfing age cohort, and the population as a whole, has its mean breeding value at the optimum, so there is no skew (asymmetry) in the population. However, because the genetic variance within selfing age cohorts varies among selfing ages, τ , the breeding value in the population will be leptokurtic. The standardized kurtosis of breeding value in the population is the weighted average fourth central moment within cohorts, divided by the square of the population variance in breeding value. For a normal distribution with variance σ^2 the fourth central moment is $3\sigma^4$, with a standardized kurtosis of $\kappa = 3$. Assuming that the distribution of breeding value within each selfing age (and within subclasses of the outcrossed class) is normal, the standardized kurtosis of breeding value in the population is

$$\kappa = 3 \left\{ 1 + \frac{\text{Var}[G_\tau]}{(\text{E}[G_\tau])^2} \right\} = \frac{3 \left(\sum_{\tau=1}^{\infty} p_\tau G_\tau^2 + p_0 \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} p_{0ij} G_{0ij}^2 \right)}{\left(\sum_{\tau=0}^{\infty} p_\tau G_\tau \right)^2}$$

For comparison, the kurtosis of breeding value in the population can be derived for Wright's (1921, 1969) classical model of partial selfing with no selection and no mutation. The recursion for the inbreeding coefficient (eq. 13a) with $f_0 = 0$ has the solution $f_\tau = 1 - (1/2)^\tau$. In the absence of selection the equilibrium selfing age distribution is $p_\tau = (1 - r)r^\tau$. The average inbreeding coefficient in the population is then $\bar{f} = \sum_0^\infty p_\tau f_\tau = \frac{r}{2-r}$ in agreement with Wright (1921, 1969). With no selection under any amount of outcrossing ($r < 1$), the population eventually approaches linkage equilibrium, $C_\tau = 0$. The equilibrium kurtosis of breeding value in the population is $\kappa = 3\left(\frac{1-r^2/4}{1-r/4}\right)$. In Wright's neutral model, as in the GAM, at $r = 0$ or 1 the breeding value in the population is normal ($\kappa = 3$). But in the IFM at $r = 1$ $G = 0$ (eq. 15) so κ is not defined.

Inbreeding depression. The total inbreeding depression in the population caused by selfing, δ , is one minus the ratio of mean fitness of selfed individuals divided by the mean fitness of outcrossed individuals,

$$\delta = 1 - \frac{\sum_{\tau=1}^{\infty} p_\tau \bar{w}_\tau}{(1 - p_0) \bar{w}_0}$$

This formula can be evaluated from the model only for partial selfing, $0 < r < 1$. For random mating and complete selfing, $r = 0$ and $r = 1$, the equilibrium inbreeding depression can be obtained by calculating the phenotypic distributions of offspring that would be produced by experimental selfing and outcrossing. The F_1 outcross between two long-selved parents has a total genetic variance about half that of its parents (because $f_0 = 0$), hence a higher mean fitness than any selfed age class or any other outcrossed subclass. However, any of their (outcross or selfed) F_2 progeny will have increased genetic variance (due to reduction of negative linkage disequilibrium by recombination), substantially diminishing their mean fitness.

Genetic variance after selection. With multiple loci and a high selfing rate, the average genetic variance in the population G blows up due to a bimodal distribution of selfing ages, with long-selved lineages dominating. This blow up is caused by accumulation of linkage disequilibrium in the long-selved lineages. The large genetic variance expressed by recombination and the decay of linkage disequilibrium in the early selfing age classes greatly reduces their mean fitness. With sufficiently high selfing rates the first few selfing age classes are rare, because of the low outcrossing rate and their greatly reduced fitness. The early selfing ages are largely eliminated by selection, and the genetic variance in the population as a whole after selection is

$$G^* = \frac{1}{\bar{w}} \left[\sum_{\tau=1}^{\infty} p_{\tau} \bar{w}_{\tau} (G_{\tau} - \gamma_{\tau} G_{\tau}^2) + p_0 \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} p_{0ij} \bar{w}_{0ij} (G_{0ij} - \gamma_{0ij} G_{0ij}^2) \right]$$

where the mean fitness in the population is the same as in eq. (3b).

Literature Cited

- Bell, G. 2010. Experimental genomics of fitness in yeast. *Proc. Roy. Soc. B* 277: 1459-1467.
- Bull, J. J., and E. L. Charnov. 1985. On irreversible evolution. *Evolution* 39: 1149-1155.
- Bulmer, M. G. 1971. The effect of selection on genetic variability. *Am. Nat.* 105: 201-211.
- Bürger, R., 2000. *The Mathematical Theory of Selection, Recombination and Mutation*.

John Wiley, Chichester.

- Caswell, H. 2001. *Matrix Population Models*, 2d ed. Sinauer, Sunderland, MA.
- Charlesworth, B. 2013. Stabilizing selection, purifying selection and mutational bias in finite populations. *Genetics* 194: 955-971.
- Charlesworth, D. and B. Charlesworth. 1987. Inbreeding depression and its evolutionary consequences. *Ann. Rev. Ecol. Syst.* 18: 237-268.
- Charlesworth, D. and B. Charlesworth. 1995. Quantitative genetics in plants: the effect of the breeding system on genetic variability. *Evolution* 49: 911-920.
- Charlesworth, B. and D. Charlesworth. 1998. Some evolutionary consequences of deleterious mutations. *Genetica* 102/103: 3-19.
- Charlesworth, D., M. T. Morgan and B. Charlesworth. 1990. Inbreeding depression, genetic load, and the evolution of outcrossing rates in a multilocus system with no linkage. *Evolution* 44: 1469-1489.
- Charlesworth, D. and J. H. Willis. 2009. The genetics of inbreeding depression. *Nat. Rev. Genet.* 10: 783-796.
- Clayton, G. and A. Robertson. 1955. Mutation and quantitative variation. *Am. Nat.* 89:151-158.
- Coyne, J. A. and H. A. Orr. 2004. *Speciation*. Sinauer, Sunderland, MA.
- Crow, J. F. and M. Kimura. 1970. *An Introduction to Population Genetics Theory*. Harper and Row, New York.
- Devaux, C., R. Lande and E. Porcher. 2014. Pollination ecology and inbreeding depression control individual flowering phenologies and mixed mating. *Evolution* 68: 3051-3065.
- Dobzhansky, Th. 1970. *Genetics of the Evolutionary Process*. Columbia Univ. Press, New York.
- Eyre-Walker, A. and P. D. Keightley. 2007. The distribution of fitness effects of new mutations. *Nat. Rev. Genet.* 8: 610-618.
- Fisher, R. A. 1918. The correlation between relatives on the supposition of Mendelian inheritance. *Trans. Roy. Soc. Edinb.* 52: 321-341.
- Fisher, R. A. 1930. *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford. [2nd ed. 1958, Dover, New York] .

- Fisher, R. A. 1941. Average excess and average effect of a gene substitution. *Ann. Eugen.* 11: 53-63.
- Fudala, A. and R. Korona. 2009. Low frequency of mutations with strongly deleterious but nonlethal fitness effects. *Evolution* 63: 2164-2171.
- Galis, F., J. W. Arntzen and R. Lande. 2010. Dollo's law and the irreversibility of digit loss in *Bachia*. *Evolution* 64: 2466-2476.
- Ganders, F. R. 1972. Heterozygosity for recessive lethals in homosporous fern populations: *Thelypteris palustris* and *Onoclea sensibilis*. *Bot. J. Linn. Soc.* 65: 211-221.
- Goldberg, E. E., J. R. Kohn, R. Lande, K. A. Robertson, S. A. Smith and B. Igic. 2010. Species selection maintains self-incompatibility. *Science* 330: 493-495.
- Goldberg E. E. and B. Igic. 2012. Tempo and mode in plant breeding system evolution. *Evolution* 66: 3701-3719.
- Haldane, J. B. S. 1949. The association of characters as a result of inbreeding and linkage. *Ann. Eugen.* 15: 15-23.
- Harder, L. D. and S. C. H. Barrett. 2006. *Ecology and Evolution of Flowers*. Oxford Univ. Press, Oxford.
- Houle, D., B. Morikawa and M. Lynch. 1996. Comparing mutational variabilities. *Genetics* 143: 1467-1483.
- Husband, B. C. and D. W. Schemske. 1996. Evolution of the magnitude and timing of inbreeding depression in plants. *Evolution* 50: 54-70.
- Igic, B. and J. W. Busch. 2013. Is self-fertilization an evolutionary dead end? *New Phytol.* 198: 386-397.
- Igic, B. and J. R. Kohn. 2006. Bias in the studies of outcrossing rate distributions. *Evolution* 60: 1098-1103.
- Jarne, P. and J. R. Auld. 2006. Animals mix it up too: the distribution of self-fertilization among hermaphroditic animals. *Evolution* 60: 1816-1824.
- Johnston, M. O., E. Porcher, P.-O. Cheptou, C. G. Eckert, E. Elle et al. 2009. Correlations among fertility components can maintain mixed mating in plants. *Am. Nat.* 173: 1-11.
- Kelly, J. K. 2007. Mutation-selection balance in mixed mating populations. *J. Theor.*

- Biol. 246: 355-365.
- Kimura, M. 1965. A stochastic model concerning the maintenance of genetic variability in quantitative characters. Proc. Natl. Acad. Sci. USA 54: 731-736.
- Kingsolver, J. G., H. E. Hoekstra, J. M. Hoekstra, D. Berrigan, S. N. Vignieri et al. 2001. The strength of phenotypic selection in natural populations. Am. Nat. 157: 245-261.
- Kondrashov, A.S. 1985. Deleterious mutations as an evolutionary factor. II. Facultative apomixis and selfing. Genetics 111: 635-653.
- Lande, R. 1975. The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. 26: 221-235.
- Lande, R. 1977. The influence of the mating system on the maintenance of genetic variability in polygenic characters. Genetics 86: 485-498.
- Lande, R. 1980. Genetic variation and phenotypic evolution during allopatric speciation. Am. Nat. 116: 463-479.
- Lande, R. 1984. The genetic correlation between characters maintained by selection, linkage and inbreeding. Genet. Res. 44: 309-320.
- Lande, R. 2007. Expected relative fitness and the adaptive topography of fluctuating selection. Evolution 61: 1835-1846.
- Lande, R. and S. J. Arnold. 1983. The measurement of selection on correlated characters. Evolution 37: 1210-1226.
- Lande, R., S. Engen and B.-E. Sæther. 2003. *Stochastic Population Dynamics in Ecology and Conservation*. Oxford Univ. Press, Oxford.
- Lande, R. and D. W. Schemske. 1985. The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. Evolution 39: 24-40.
- Lande, R., D. W. Schemske and S. T. Schultz. 1994. High inbreeding depression, selective interference among loci, and the threshold selfing rate for purging recessive lethal mutations. Evolution 48: 965-978.
- Lande, R. and S. Shannon. 1996. The role of genetic variability in adaptation and population persistence in a changing environment. Evolution 50: 434-437.
- Lynch, M. 1996. The rate of polygenic mutation. Genet. Res. 51: 137-148.
- Porcher, E. and R. Lande. 2005. Loss of gametophytic self-incompatibility with evo-

- lution of inbreeding depression. *Evolution* 59: 46-60.
- Porcher, E. and R. Lande. 2013. Evaluating a simple approximation to modeling the joint evolution of self-fertilization and inbreeding depression. *Evolution* 67: 3628-3635.
- Russell, W. A., G. F. Sprague and H. L. Penny. 1963. Mutations affecting quantitative characters in long-time inbred lines of maize. *Crop Sci.* 3: 175-178.
- Simmons, M. J., and J. F. Crow. 1977. Mutations affecting fitness in *Drosophila* populations. *Annu. Rev. Genet.* 11: 49-78.
- Stebbins, G. L. 1957. Self fertilization and population variability in higher plants. *Am. Nat.* 91: 337-354.
- Stebbins, G. L. 1974. *Flowering Plants. Evolution Above the Species Level.* Edward Arnold, London.
- Takebayashi, N. and P. L. Morrell. 2001. Is self-fertilization an evolutionary dead end? Revisiting an old hypothesis with genetic theories and a macroevolutionary approach. *Am. J. Bot.* 88: 1143-1150.
- Turelli, M. 1984. Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. *Theor. Popul. Biol.* 25: 138-193.
- Turelli, M. and N. H. Barton. 1987. Adaptive landscapes, genetic distance and the evolution of quantitative characters. *Genet. Res.* 49: 157-173.
- Turelli, M. and N. H. Barton. 1994. Genetic and statistical analyses of strong selection on polygenic traits: What, me normal? *Genetics* 138: 913-941.
- Vassilieva, L. L., A. M. Hook and M. Lynch. 2000. The fitness effects of spontaneous mutations in *Caenorhabditis elegans*. *Evolution* 54: 1234-1246.
- Willis, J. H. 1999. Inbreeding load, average dominance and the mutation rate for mildly deleterious alleles in *Mimulus guttatus*. *Genetics* 153: 1885-1898.
- Winn, A. A., E. Elle, S. Kalisz, P.-O. Cheptou, C. G. Eckert et al. 2011. Analysis of inbreeding depression in mixed-mating plants provides evidence for selective interference and stable mixed mating. *Evolution* 65: 3339-3359.
- Wright, S. I., S. Kalisz and T. Slotte. 2013. Evolutionary consequences of self-fertilization. *Proc. R. Soc. Lond. B* 290: 20130133.
- Wright, S. 1921. Systems of mating. II. The effects of inbreeding on the genetic

composition of a population. *Genetics* 6: 124-143.

Wright, S. 1931. Evolution in Mendelian populations. *Genetics* 16: 97-159.

Wright, S. 1935. The analysis of variance and the correlations between relatives with respect to deviations from an optimum. *J. Genet.* 30: 243-256.

Wright, S. 1969. *Evolution and the Genetics of Populations. Vol. 2. The Theory of Gene Frequencies.* Univ. Chicago Press, Chicago.

FIGURE CAPTIONS

Figure 1: Purging of genetic variance under continued selfing in the GAM for each of 25 identical independent characters under stabilizing selection: components of genetic variance (top) and mean fitness (middle) as functions of selfing age, and distribution of selfing ages (bottom) for population selfing rates below ($r = 0.78$, left) or above ($r = 0.8$, right) the purging threshold. Note the different scales in panels A and B. In panel B the genetic variance G at young selfing ages, and genic variance V and covariance C , are not at equilibrium; their values depend on the number of generations simulated (here 500,000). In panels E-F dotted lines represent the distribution of selfing age classes in Wright's neutral model. Other parameters: $E = 1$, $\sigma_m^2 = 0.001$, $n = 10$ and $\omega^2 = 20$.

Figure 2: Purging of genetic variance under continued selfing in the IFM for each of 25 identical independent characters under stabilizing selection. A. Total genetic variance before and after selection. Panels and parameters as in Fig. 1 but for the IFM with $V(0) = 1$. At selfing rates above the purging threshold, $r > \hat{r}$, the IFM shows smaller changes in genetic variance and mean fitness as a function of selfing age than in the GAM (Fig. 2. B,D compared to Fig. 1B,D) but still displays similar patterns of selfing age distribution (Fig. 2E,F compared to Fig. 1E,F).

Figure 3: Equilibrium genetic variance as a function of selfing rate for each of 25 identical uncorrelated characters under stabilizing selection in the GAM. A. Total genetic variance before and after selection, G and G^* . B. Kurtosis of breeding values, κ , before and after selection at the outcrossed equilibrium for r below the purging threshold, at the purged equilibrium for r above the purging threshold, and in Wright's neutral model. Other parameters as in Fig. 1.

Figure 4: Equilibrium genetic variance as a function of selfing rate for each of 25 identical uncorrelated characters under stabilizing selection in the IFM. A. Total genetic variance before and after selection. B. Kurtosis in breeding value, κ , before and after selection, and in Wright's neutral model. Other parameters as in Fig. 2.

Figure 5: Equilibrium genetic variance after selection, inbreeding depression and population mean fitness, as a function of population selfing rate, for different numbers of characters in the GAM. When the selfing rate is below the purging threshold, two stable equilibria exist. The outcrossed equilibrium has relatively large genetic variance and inbreeding depression nearly independent of selfing rate (solid lines); it is reached when the population has initially low genetic variance and low linkage equilibrium. The purged equilibrium (dashed lines) has lower genetic variance, independent of the number of characters, and negative inbreeding depression for r just above the purging threshold. Other parameters as in Fig. 1.

Figure 6: Equilibrium genetic variance before selection in the IFM, along with inbreeding depression and population mean fitness, as functions of population selfing rate, for different numbers of characters m . Other parameters as in Fig. 2.

Figure 7: Equilibrium genetic variance before selection in the IFM, inbreeding depression and population mean fitness, as a function of population selfing rate, for different numbers of characters m with no pleiotropy subject to correlational selection between $m/2$ independent pairs of characters. In the selection matrix (eq. 2) off-diagonal elements for pairs of characters under correlational selection are 0.5 times the diagonal elements (ω^2). The equilibrium genetic covariance between pairs of characters under correlational selection is caused by linkage disequilibrium, and B/G represents their genetic correlation. Other parameters as in Fig. 2.

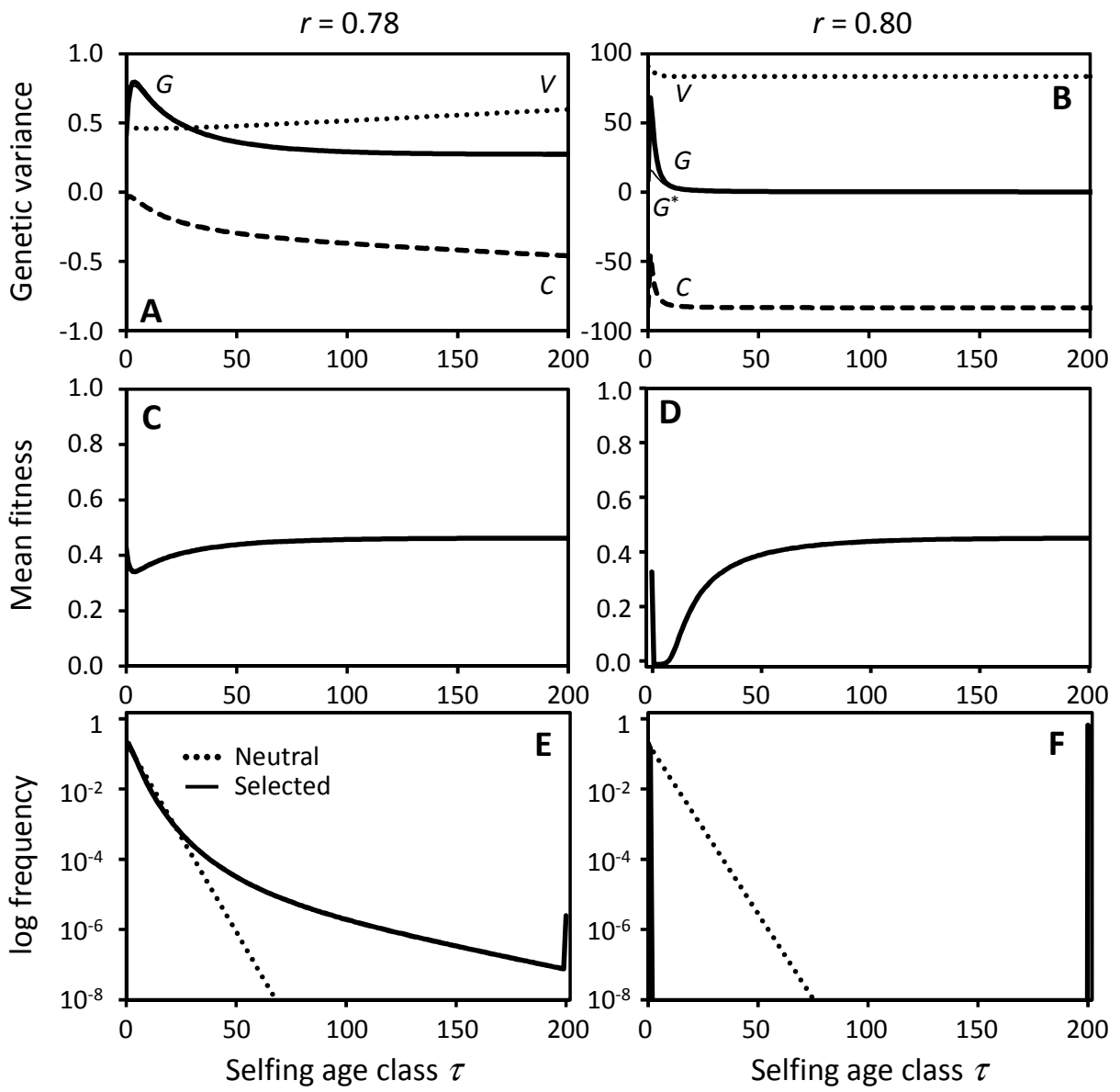


Figure 1

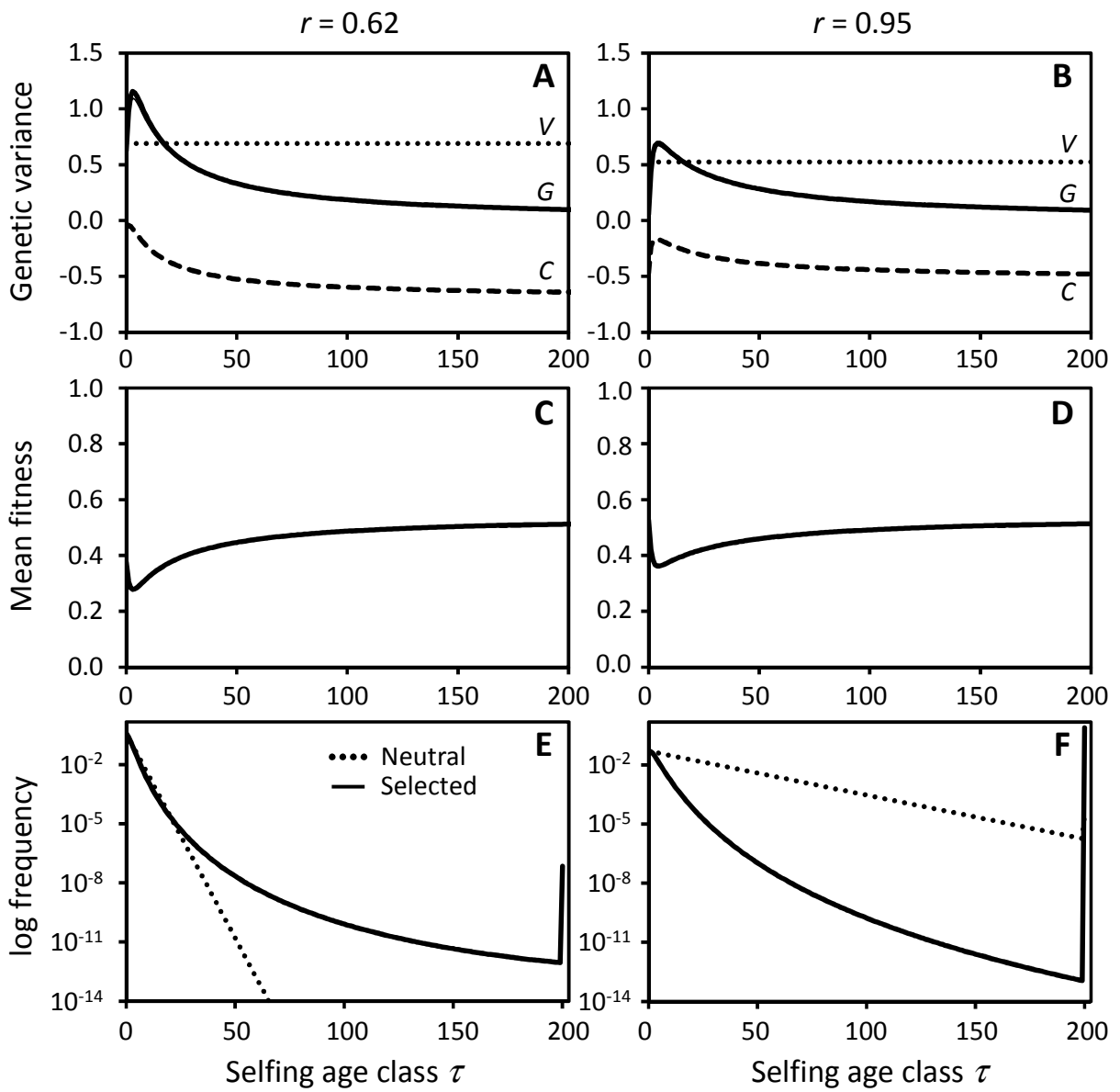


Figure 2

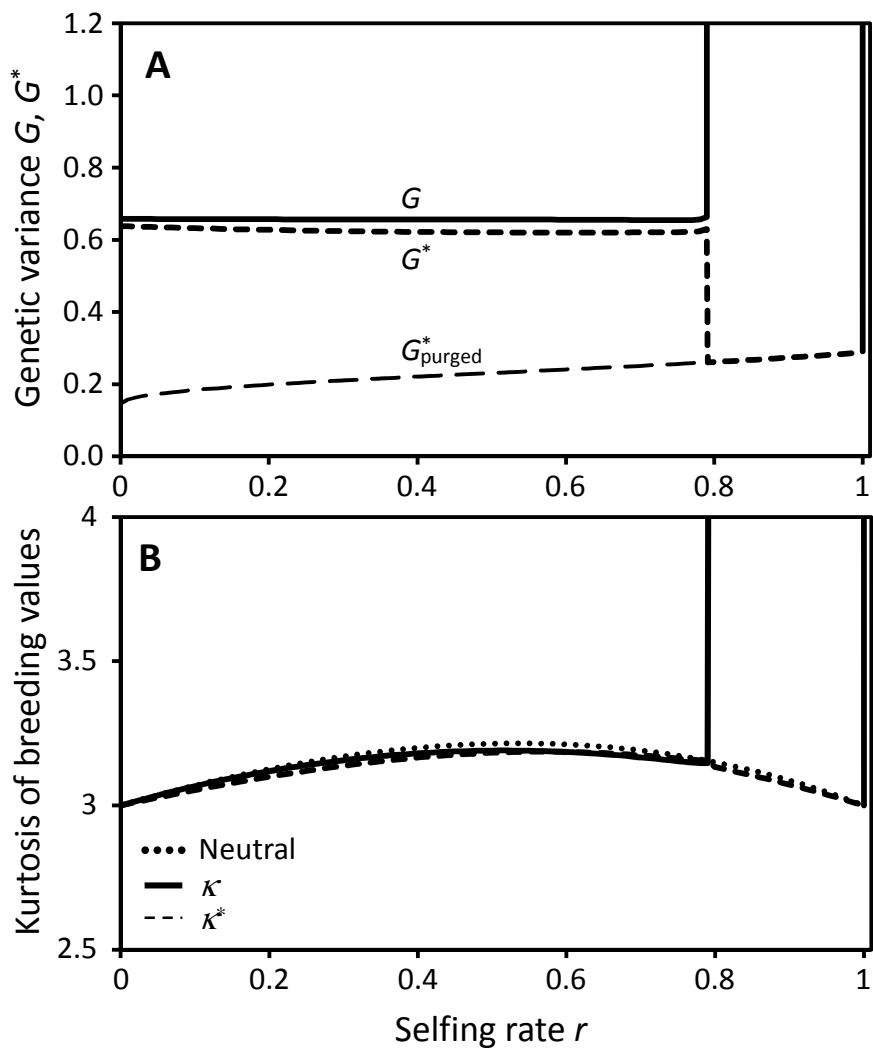


Figure 3

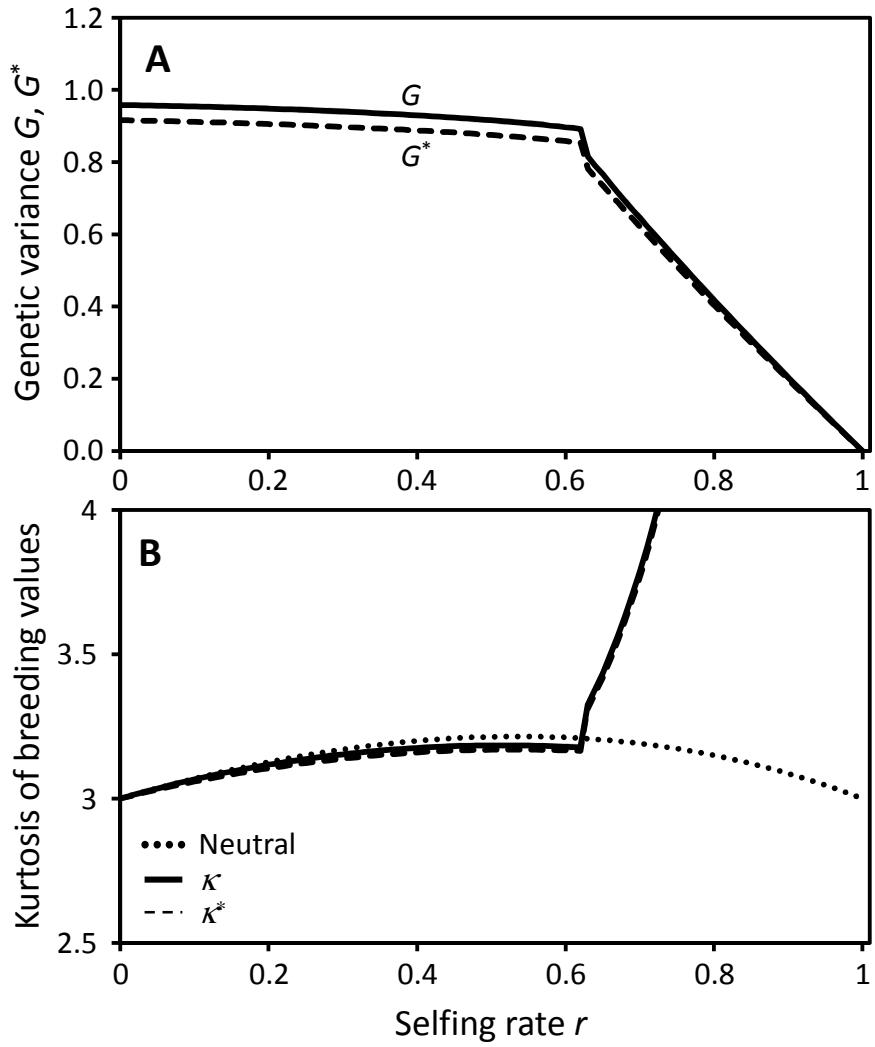


Figure 4

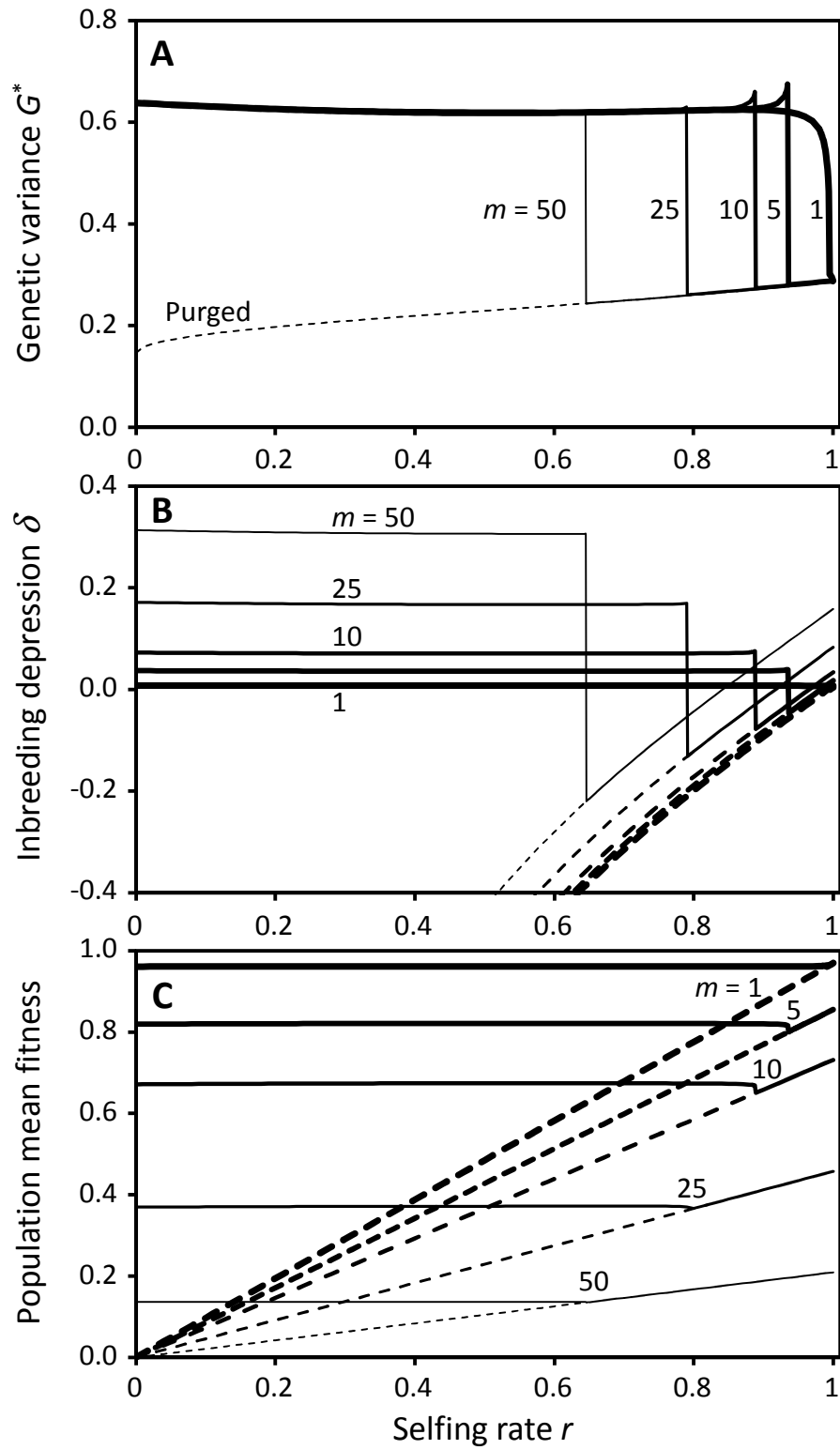


Figure 5

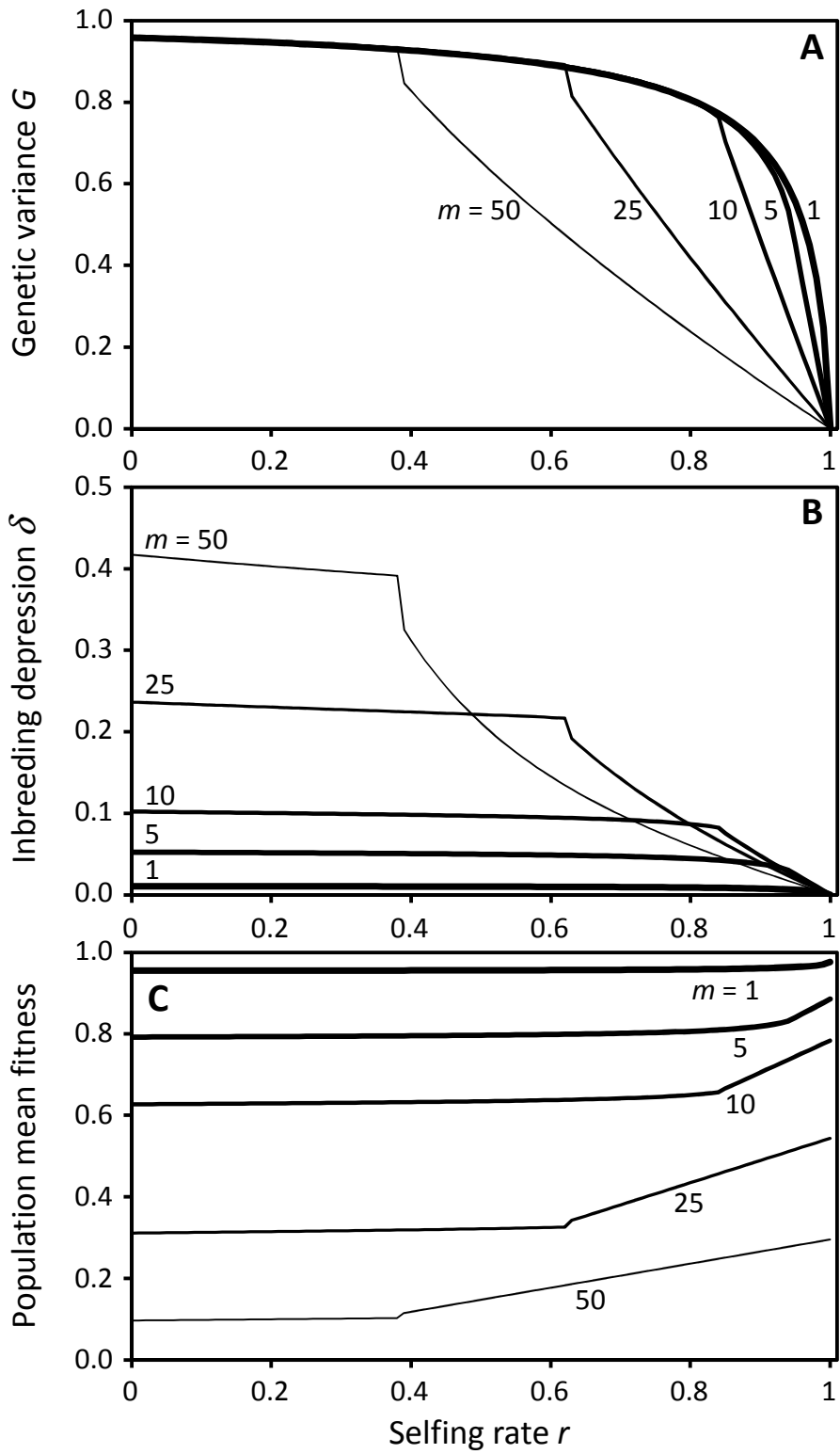


Figure 6

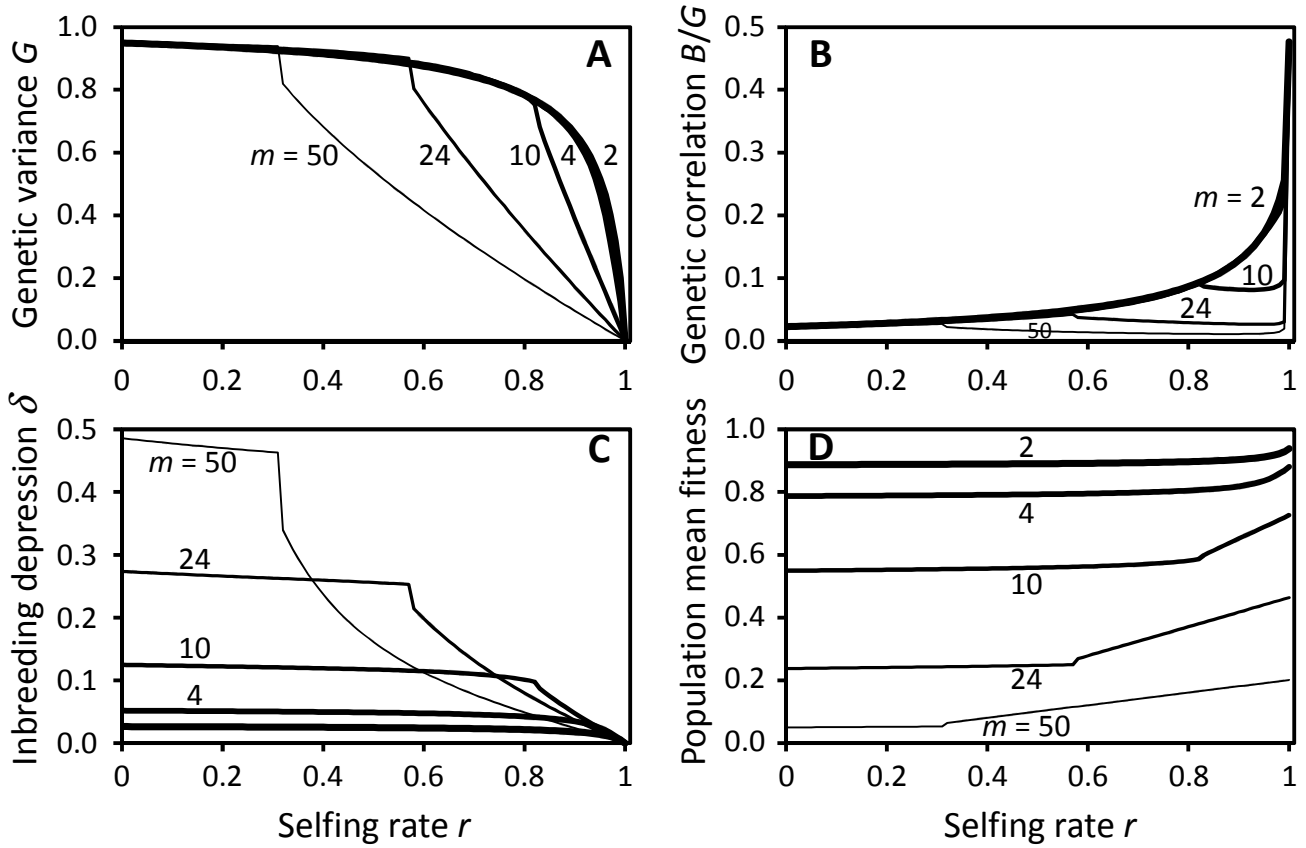


Figure 7