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3 **Inbreeding depression maintained by recessive lethal mutations**
4 **interacting with stabilizing selection on quantitative characters**
5 **in a partially self-fertilizing population**

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7

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15 *Running head:* Lethal mutations and quantitative genetic variance

16

17 **KEYWORDS:** Alternative equilibria, inbreeding coefficient, inbreeding depression, purg-
18 ing threshold, selective interference, selective facilitation

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ABSTRACT

27 The bimodal distribution of fitness effects of new mutations and standing genetic varia-
 28 tion, due to early-acting strongly deleterious recessive mutations and late-acting mildly
 29 deleterious mutations, is analyzed using the Kondrashov model for lethals (K), with
 30 either the infinitesimal model for selfing (IMS) or the Gaussian allele model (GAM)
 31 for quantitative genetic variance under stabilizing selection. In the combined models
 32 (KIMS and KGAM) high genomic mutation rates to lethals and weak stabilizing selec-
 33 tion on many characters create strong interactions between early and late inbreeding
 34 depression, by changing the distribution of lineages selfed consecutively for different
 35 numbers of generations. Alternative stable equilibria can exist at intermediate selfing
 36 rates for a given set of parameters. Evolution of quantitative genetic variance under
 37 multivariate stabilizing selection can strongly influence the purging of nearly recessive
 38 lethals, and sometimes vice versa. If the selfing rate at the purging threshold for quan-
 39 titative genetic variance in IMS or GAM alone exceeds that for nearly recessive lethals
 40 in K alone, then in KIMS and KGAM stabilizing selection causes *selective interference*
 41 with purging of lethals, increasing the mean number of lethals compared to K; other-
 42 wise, stabilizing selection causes *selective facilitation* in purging of lethals, decreasing
 43 the mean number of lethals.

44 Partially recessive deleterious mutations cause inbreeding depression, or loss of fitness
 45 upon matings between relatives, which is a major factor in the evolution of mixed
 46 mating systems, particularly mixed self-fertilization and outcrossing which occurs in
 47 many plants (Charlesworth and Charlesworth 1987; Charlesworth and Willis 2009) and
 48 some hermaphroditic animals (Jarne and Auld 2006). Spontaneous mutations, as well
 49 as standing genetic polymorphisms, typically display a strongly bimodal distribution
 50 of fitness effects (Dobzhansky 1970; Fudala and Korona 2009; Bell 2010). A class of
 51 lethal and sublethal mutations exists which on average in standing variation are nearly
 52 recessive; a second class mutations are mildly deleterious and moderately recessive
 53 (Simmons and Crow 1977; Willis 1999a,b; Vassilieva et al. 2000; Eyre-Walker and
 54 Keightley 2007; Charlesworth and Willis 2009). Homozygous lethal mutations usually
 55 act early in development to cause embryonic mortality, while mildly deleterious mu-
 56 tations tend to act later in development, influencing individual growth, survival, and
 57 fecundity (Hadorn 1961; Lande et al. 1994; Husband and Schmske 1996; Lande et al.
 58 1994; Bell 2010; Winn et al. 2011). Empirical evidence therefore justifies a life-history
 59 model of inbreeding depression due to a combination of recessive lethal mutations af-
 60 fecting embryo survival and mildly deleterious mutations affecting juvenile and adult
 61 survival and reproduction.

62 The Kondrashov (1985) model is often used to describe the genomic evolution of
 63 deleterious mutations since with a few reasonable assumptions it accurately describes
 64 the population genetic complexities of mixed selfing and outcrossing, especially zygotic
 65 disequilibrium (explained below) (Charlesworth et al. 1990; Lande et al. 1994; Kelly
 66 2007; Porcher and Lande 2013, 2016). Based on empirical observations on ferns with
 67 a very high inbreeding depression, Ganders (1972) suggested that if nearly all selfed
 68 zygotes die before reproduction, then the adult population remains almost completely
 69 outcrossed, and selection against recessive deleterious alleles becomes ineffective. Lande
 70 et al. (1994) confirmed this idea analytically, showing that with high genomic mutation
 71 rates to nearly recessive lethals a process of *selective interference* among deleterious
 72 mutations creates a critical selfing rate, or *purging threshold*, below which a nearly
 73 constant mean number of heterozygous lethals is maintained and above which the
 74 equilibrium mean number of lethals decreases dramatically. Kelly (2007) demonstrated

75 that selective interference also operates among mildly deleterious moderately recessive
76 mutations if they produce a substantial total inbreeding depression at low or moderate
77 selfing rates.

78 Mildly deleterious mutations are usually assumed to be unconditionally deleterious
79 (Simmons and Crow 1977; Kondrashov 1985; Charlesworth et al. 1990; Vassilieva et al.
80 2000; Charlesworth and Willis 2009). However, it is rather difficult to empirically dis-
81 tinguish unconditional mildly deleterious mutations from quantitative genetic variation
82 under stabilizing selection (Charlesworth 2013a,b). Stabilizing selection on a quanti-
83 tative character with purely additive genetic variance produces allelic effects on fitness
84 that are mildly deleterious and mildly recessive (Wright 1935; Manna et al. 2011),
85 in agreement with general observations on mildly deleterious mutations. In contrast
86 to models with unconditional deleterious mutations, an allele with an additive effect
87 on a quantitative character under stabilizing selection may be either advantageous or
88 deleterious depending on whether the mean phenotype is above or below the optimum,
89 and alleles at different loci with opposite effects on the character may compensate each
90 other in their effects on phenotype and fitness (Fisher 1930, 1958; Wright 1931, 1935,
91 1969).

92 Because inbreeding immediately increases the genetic variance of all quantitative
93 characters simultaneously (Wright 1921, 1969), joint stabilizing selection on multi-
94 ple characters can produce a substantial contribution to the total inbreeding depres-
95 sion, possibly accounting for much or most of the inbreeding depression in fitness due
96 to mildly deleterious mutations (Lande and Schmske 1985). Models of the mainte-
97 nance of genetic variance in quantitative characters under stabilizing selection in large
98 partially selfing populations demonstrate a similar *purging threshold* for quantitative
99 genetic variance, which occurs by a different mechanism than that for uncondition-
100 ally deleterious recessive mutations. For selfing rates below the purging threshold for
101 quantitative genetic variance, the genetic variance remains nearly constant, close to
102 that under random mating, because deviations from Hardy-Weinberg equilibrium are
103 compensated by decreased genic variance and negative linkage disequilibrium, but for
104 selfing rates above the purging threshold, this compensation mechanism breaks down
105 and the total genetic variance becomes greatly reduced. The selfing rate at the purging

threshold for quantitative genetic variance depends on the total inbreeding depression produced by stabilizing selection on multiple characters (Lande and Porcher 2015).

Here we investigate the evolutionary interaction of the two major components of inbreeding depression by modeling the maintenance of quantitative genetic variance and recessive lethal mutations in a large partially selfing population.

111

112 *The Models*

In large predominantly outcrossing animal populations, individuals typically carry a few nearly recessive heterozygous lethal or semi-lethal mutations, but the recessive lethal load tends to be somewhat higher in large, long-lived or partially asexual plants (Klekowski 1984, 1988, 1989; Lande et al. 1994; Muirhead and Lande 1997; Scofield and Schultz 2006). With typical karyotypes of many chromosomes, and genomic recombination length of several or many Morgans, even dozens heterozygous recessive lethals in any individual are unlikely to be closely linked, so that to a good approximation alleles at lethal-producing loci can be assumed to segregate independently. Kondrashov’s (1985) model of unconditionally deleterious mutations at an infinite number of unlinked loci has been used to model inbreeding depression for fitness due recessive lethal mutations, or due to mildly deleterious mutations (Charlesworth, Morgan and Charlesworth 1990; Lande et al. 1994; Kelly 2007). However, Kondrashov’s model assumes that all loci producing detrimental mutations have identical mutation rates and fitness effects, so it can not deal with two components of inbreeding depression unless generalized in some way, and in any case it can not handle compensatory mutations.

Mixed mating systems, such as partial self-fertilization, produce variation among individuals in the degree to which they are inbred. Because inbreeding affects all loci in essentially the same way, variance in the inbreeding coefficient creates zygotic disequilibrium, the non-random association of homozygosity among loci. This presents serious complications for analytical modeling, and the Kondrashov (1985) model for unconditionally deleterious mutations is the only analytical genomic model that accounts exactly for zygotic disequilibrium. Zygotic disequilibrium can be measured by deviations from a Poisson distribution of number of heterozygous lethals in adults (Lande et al. 1994), and by the excess of standardized kurtosis in the distribution of

quantitative genetic variance, κ , compared to a normal distribution ($\kappa = 3$). 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 (Lande and Porcher 2015).

We model a very large or infinite plant population reproducing by a mixture of self-fertilization and random outcrossing among unrelated individuals. The probability that new zygotes are formed by self-fertilization, r , is assumed to be the same for all plants and constant in time. In such a population, every individual can be classified by its selfing age, the number of generations in its immediate past since the last outcrossing event in its genetic lineage or pedigree (Campbell 1986; Schultz and Willis 1995; Kelly 1999a,b; Lande and Porcher 2015).

Kelly (2007) developed an approximate Kondrashov model with selfing age structure, yielding results closely resembling those of the exact Kondrashov model, except near a purging threshold when artifactual limit cycles sometimes appeared. Roze (2015) derived another approximation to the Kondrashov model, allowing zygotic disequilibrium only between pairs of loci; by comparison with the exact Kondrashov model he inferred that for nearly recessive mutations, or with high genomic mutation rates, inbreeding depression is strongly affected by multilocus zygotic disequilibria.

We derive an exact version of the Kondrashov model for nearly recessive lethals (abbreviated as K) structured by selfing age. To reach robust conclusions concerning the total inbreeding depression, we combine the Kondrashov model for lethals (K) with two different models of inheritance for a quantitative character structured by selfing age. The infinitesimal model for selfing (IMS) for a very large but finite population involves an infinite number of unlinked loci with infinitesimal mutational variance. This model extends to inbreeding Fisher’s infinitesimal model for an infinite population with no mutation or selection and random or assortative mating (Fisher 1918; Bulmer 1971). IMS accounts for the lower effective population size at higher selfing rates (Wright 1969; Charlesworth and Charlesworth 1995), and the resulting decrease in genic variance maintained by a balance between mutation and random genetic drift in the limit of large population size and small mutation rate. The Gaussian allele model (GAM) assumes an approximately normal distribution of additive allelic effects at each

168 of a finite number of linked loci maintained by a balance of mutation, recombination,
169 and stabilizing selection in an infinite population (Kimura 1965; Lande 1975, 1977). In
170 IMS only one stable equilibrium of the genetic variance exists at any selfing rate, but in
171 GAM two stable equilibria exist for selfing rates below the purging threshold, termed
172 the *outcrossed equilibrium* and the *purged equilibrium* (Lande and Porcher 2015). These
173 two models of quantitative inheritance combined with the Kondrashov model for lethals
174 are designated respectively as KIMS and KGAM.

175 The combined models, KIMS and KGAM, neglect the excess kurtosis of breed-
176 ing values, and the association of lethals with quantitative variation, within selfing
177 age classes, but account for most of the zygotic disequilibrium in the population as a
178 whole. Although we assume that nearly recessive lethal mutations and quantitative
179 genetic variation are selected independently, these two components of inbreeding de-
180 pression interact because both of them influence the fitnesses and hence the frequency
181 distribution of selfing age classes that forms the framework for their joint evolution.

182 As for most population genetic models, IMS and GAM are naturally expressed
183 using quantities measured each generation in zygotes before selection. In contrast,
184 the Kondrashov model for lethals, K, is expressed using the numbers of heterozygous
185 recessive lethal mutations in adults. These models can be combined by recalling that
186 homozygous lethal mutations typically act early in development to cause embryonic
187 mortality, while mildly deleterious mutations tend to act late in development, influ-
188 encing growth, survival and fecundity. Essential features of the IMS and GAM can be
189 preserved when they are combined with K by enumerating genotypes at the subadult
190 stage, after selection on homozygous and heterozygous effects of nearly recessive lethal
191 mutations, but before selection on quantitative characters. The life cycle diagram in
192 Table 1 defines the order of events designated by parenthetical symbols. Unless oth-
193 erwise stated, the population is measured, and numerical results are graphed, at the
194 subadult stage after selection on lethals but before selection on quantitative characters.

195

196 [Table 1 about here.]

197

198 **SELFING AGES IN THE KONDRASHOV MODEL FOR LETHALS**

199 We model an infinitely large partially self-fertilizing population with no genetic variance
 200 in selfing rate, such that each zygote has a probability r of being produced by self-
 201 fertilization and probability $1 - r$ of being produced by outcrossing to an unrelated
 202 individual. These probabilities are assumed to be the same for all plants and constant in
 203 time. We describe individuals from a lineage self-fertilized for τ consecutive generations
 204 since last outcrossing as being of selfing age τ .

205 An infinite number of unlinked loci are assumed to undergo irreversible mutation
 206 to recessive lethal alleles with total genomic mutation rate U . Heterozygous lethal
 207 alleles at each locus have viability $1 - h$ compared to nonmutant homozygotes, and act
 208 independently among loci implying multiplicative fitness effects for individuals with
 209 multiple heterozygous lethals.

210 We define $p_\tau(x)$ as the frequency in the population of subadult plants carry-
 211 ing x heterozygous recessive lethal alleles from lineages of selfing age τ , such that
 212 $\sum_{\tau=0}^{\infty} \sum_{x=0}^{\infty} p_\tau(x) = 1$. An individual with y heterozygous lethals reproducing by self-
 213 fertilization transmits to an offspring $x \leq y$ heterozygous lethal alleles with probability
 214 $\binom{y}{x} \left(\frac{1}{2}\right)^{2y-x}$, and contributes to outcrossed offspring a gamete carrying x recessive lethal
 215 alleles with probability $\binom{y}{x} \left(\frac{1}{2}\right)^y$. Summing over all parental genotypes the recursion
 216 equations for transmission of lethals in the selfing lineages are

$$p_{\tau+1}^*(x) = r \sum_{y=x}^{\infty} p_\tau^{***}(y) \binom{y}{x} \left(\frac{1}{2}\right)^{2y-x} \quad \text{for } \tau \geq 0 \quad (1)$$

217 where a triple asterisk *** denotes parental genotypes after selection on quantitative
 218 traits and a single asterisk * denotes offspring genotypes before mutation (eq. 7a).

219 The gamete pool contributed by all parents is

$$g(x) = \sum_{\tau=0}^{\infty} \sum_{y=x}^{\infty} p_\tau^{***}(y) \binom{y}{x} \left(\frac{1}{2}\right)^y \quad (2a)$$

220 and outcrossing by random union of gametes produces offspring of selfing age 0,

$$p_0^*(x) = (1 - r) \sum_{y=0}^x g(x - y) g(y). \quad (2b)$$

221 Mutation, denoted by a double asterisk **, at a diploid genomic rate U per generation

222 is described by a Poisson process,

$$p_{\tau}^{**}(x) = \sum_{y=0}^x p_{\tau}^{*}(x-y) \frac{e^{-U} U^y}{y!} \quad \text{for } \tau \geq 0. \quad (3)$$

223 Selection against heterozygous lethal alleles is described by a selection coefficient
 224 h assumed to be identical and to act independently among all loci, so that finally at
 225 the subadult stage of enumeration in the next generation, denoted by a prime ', the
 226 distribution of numbers of heterozygous lethals by selfing age is

$$p'_{\tau}(x) = (1-h)^x p_{\tau}^{**}(x) / \bar{v} \quad (4a)$$

$$\bar{v} = \sum_{\tau=0}^{\infty} \sum_{x=0}^{\infty} (1-h)^x p_{\tau}^{**}(x) \quad (4b)$$

227 where \bar{v} is the mean fitness of juveniles from selection on nearly recessive lethals.

228 At enumeration in subadults the frequency of selfing age class τ is

$$p_{\tau} = \sum_{x=0}^{\infty} p'_{\tau}(x) \quad (5)$$

229 which is employed in the model of quantitative genetic variation. The mean number
 230 of heterozygous lethals in the population is

$$\bar{x} = \sum_{\tau=0}^{\infty} \sum_{x=0}^{\infty} x p'_{\tau}(x).$$

231

232 QUANTITATIVE GENETIC VARIANCE

233 In a randomly mating diploid population the phenotype of an individual for a single
 234 character, z is assumed to be composed of a breeding value, a (the sum of additive
 235 genetic contributions of alleles at all loci), plus an independent environmental effect,
 236 e , so that $z = a + e$. Environmental effects are assumed to be normal with mean 0
 237 and variance E . Allelic effects are assumed to be purely additive, and hence the ge-
 238 netic variance in breeding value among individuals can be partitioned into two additive
 239 components $G = V + C$, where V is the genic variance (twice the variance of allelic
 240 effects on each character summed over all loci), and C is twice the total covariance

241 of allelic effects among loci within gametes due to linkage disequilibrium (nonrandom
 242 association of alleles between loci within gametes). In the absence of selection, inbreed-
 243 ing reduces within-family heterozygosity and additive genetic variance and covariance,
 244 and increases additive genetic variance and covariance among families (Wright 1921,
 245 1969, Crow and Kimura 1970). A subpopulation (or cohort) composed of individuals
 246 produced by τ generations of consecutive selfing since the last outcrossing event in
 247 their lineage have an inbreeding coefficient f_τ that is uniform (the same for all such
 248 individuals). Uniform inbreeding within selfing age cohorts increases purely additive
 249 genetic variance by a fraction equal to the inbreeding coefficient (Wright 1921, 1969).
 250 The (co)variance of additive genetic effects of alleles from different gametes equals f_τ
 251 times the (co)variance of allelic effects, whether or not the alleles are chosen from the
 252 same locus. Selfing age cohorts have total genetic variance $G_\tau = (1 + f_\tau)(V_\tau + C_\tau)$ and
 253 phenotypic variance $P_\tau = G_\tau + E$.

254 To describe stabilizing selection on the individual phenotype for a single quanti-
 255 tative character, z , the expected relative fitness of individuals, $W(z)$ is given by a
 256 Gaussian function of their deviation from an optimum phenotype, θ ,

$$w(z) = \exp \left\{ -\frac{(z - \theta)^2}{2\omega^2} \right\}.$$

257 Assuming that the mean phenotype of the population is initially at the optimum,
 258 $\bar{z} = \theta$, with purely additive genetic variability the phenotype distributions within
 259 selfing age cohorts, and in the population as a whole, will always be symmetric with
 260 mean phenotype at the optimum, as neither selection nor inbreeding will change the
 261 mean phenotype.

262 Inbreeding depression in fitness due to stabilizing selection on a single quantitative
 263 character is likely to be small because the intensity of stabilizing selection typically is
 264 moderate or weak (Lande and Arnold 1983, Kingsolver et al. 2001). To produce realis-
 265 tic inbreeding depression in a constant environment we analyze stabilizing selection on
 266 multiple quantitative characters. For simplicity, we consider independent stabilizing
 267 selection on m identical genetically and phenotypically uncorrelated characters, each
 268 with the same genetic and phenotypic variances under the same strength of stabilizing
 269 selection. Nearly the same inbreeding depression would be produced by fewer char-

270 actors under stronger stabilizing selection. The main results for the maintenance of
 271 quantitative genetic variance, including the position of the purging threshold, still ap-
 272 ply when the characters have different parameters or are genetically correlated (Lande
 273 and Porcher 2015).

274 Using the normal approximation for phenotypes and breeding values of each char-
 275 acter, the mean fitness of a cohort of selfing age τ is then

$$\bar{w}_\tau = (\omega^2/\gamma_\tau)^{m/2} \quad (6)$$

276 where $\gamma_\tau = \omega^2 + P_\tau$ measures the strength of stabilizing selection acting on the cohort of
 277 selfing age τ (Lande and Arnold 1983). Stabilizing selection on quantitative characters
 278 of subadults changes the lethal heterozygote frequencies in the adult population as a
 279 whole by altering the probability distribution of selfing age classes,

$$p_\tau^{***}(x) = \frac{\bar{w}_\tau}{\bar{\bar{w}}} p_\tau(x) \quad (7a)$$

280 where $\bar{\bar{w}} = \sum_{\tau=0}^{\infty} p_\tau \bar{w}_\tau$ is the population mean fitness from stabilizing selection on
 281 all selfing age cohorts. Summing both sides of this equation over the distribution of
 282 numbers of heterozygote lethals within selfing age cohorts gives the cohort frequencies
 283 in adults after selection,

$$p_\tau^{***} = \sum_{x=0}^{\infty} p_\tau^{***}(x) = \frac{\bar{w}_\tau}{\bar{\bar{w}}} p_\tau. \quad (7b)$$

284 Recursion formulas for completely additive genetic variance under partial selfing
 285 are given in Lande and Porcher (2015) for two different models of inheritance. The
 286 infinitesimal model for selfing (IMS) assumes an infinite number of loci with infinites-
 287 imal mutation. The Gaussian allele model (GAM) assumes a Gaussian distribution of
 288 allelic effects at each of a finite number of loci with mutation. Both models assume
 289 the loci are unlinked and the population size is very large or practically infinite. The
 290 present IMS differs somewhat from that in Lande in Porcher (2015) in that here (1) we
 291 did not subdivide the outcrossed age class (selfing age 0) according to parental selfing
 292 ages, since numerical computations showed that (in contrast to GAM) the influence of
 293 this subdivision is negligible in IMS, and (2) instead of Wright's formula for the mean

inbreeding coefficient in the population assuming selective neutrality, we use the actual mean inbreeding coefficient in the population to calculate how a larger selfing rate decreases the effective population size and the equilibrium genic variance maintained by mutation (see Appendix). Complete dynamical systems for KIMS and KGAM, with ordering of events and notation as in the life cycle of Table 1, are given by eqs. (1)-(5) for K in the present paper combined with formulas for either IMS or GAM (Supporting Information; Lande and Porcher 2015), interacting through their joint influence on the selfing age distribution, eqs. (6)-(7).

For numerical analysis it is necessary to truncate the distribution of selfing ages at an upper limit, so that the final class represents individuals selfed consecutively for L generations or longer (Supporting Information). For the Kondrashov model alone, this involves no further approximation because K is exact even without selfing age structure, and hence can be terminated at any number of selfing ages. However, as for IMS and GAM alone, the combined models may require a large number of selfing age classes for accurate results, as indicated by small excess kurtosis in the population at selfing rates below the purging threshold for quantitative genetic variance. For most parameter values, using 50 to 100 selfing age classes produced nearly the same results as with more age classes.

TOTAL INBREEDING DEPRESSION AND ITS COMPONENTS

Prout (1965, 1969) showed for a complex life cycle with selection at multiple stages that fitness must be measured starting at the beginning of the life cycle with unselected zygotes. The frequencies of selfing age cohorts in zygotes before selection are

$$\begin{aligned} p_0^o &= 1 - r \\ p_{\tau+1}^o &= r p_{\tau}^{***} \quad \text{for } \tau = 0, 1, 2, \dots \end{aligned}$$

The viability of selfing age class τ after selection on lethals but before selection on quantitative traits can be written, and the population viability after selection on lethals

(eq. 4b) can be rewritten, as

$$\begin{aligned}\bar{v}_\tau &= \frac{1}{p_\tau^o} \sum_{x=0}^{\infty} (1-h)^x p_\tau^{**}(x) \\ \bar{\bar{v}} &= \sum_{\tau=0}^{\infty} p_\tau^o \bar{v}_\tau.\end{aligned}$$

The mean fitness of selfing age class τ through the complete life cycle, neglecting any association between lethal mutations and quantitative variation within selfing age classes, is then simply $\bar{v}_\tau \bar{w}_\tau$. From these formulas it can be shown that the mean total fitness in the population is

$$\bar{\bar{v}} \bar{\bar{w}} = \sum_{\tau=0}^{\infty} p_\tau^o \bar{v}_\tau \bar{w}_\tau = \sum_{\tau=0}^{\infty} \sum_{x=0}^{\infty} (1-h)^x p_\tau^{**}(x) \bar{w}_\tau.$$

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

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

Components of the total inbreeding depression, due to nearly recessive lethal mutations and stabilizing selection on quantitative genetic variation, can be defined as

$$\delta_v = 1 - \frac{\sum_{\tau=1}^{\infty} p_\tau^o \bar{v}_\tau}{(1-p_0^o) \bar{v}_0}$$

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

and it can be shown that these combine to compose the total inbreeding depression as usual for a structured life cycle (Lande et al. 1994), $1 - \delta = (1 - \delta_v)(1 - \delta_w)$. These formulas for inbreeding depression can be evaluated for selfing rates between zero and one, $0 < r < 1$.

PREVALENCE OF MULTIVARIATE STABILIZING SELECTION

Stabilizing selection on quantitative characters was classically believed to be prevalent in natural populations (Fisher 1930, 1958; Wright 1931, 1935, 1969; Haldane 1954;

337 Simpson 1953). Significant stabilizing selection has frequently been observed in natu-
 338 ral populations (Lande and Arnold 1983; Kingsolver et al. 2001), but often it is weak
 339 and/or fluctuating in time (Lande and Shannon 1996; Siepielski et al. 2009; Engen et
 340 al. 2012; Chevin et al. 2015). It is therefore important to realize that directional selec-
 341 tion (as defined by Lande and Arnold 1983) also reduces quantitative genetic variance,
 342 and hence that, with a stationary distribution of environmental states, randomly fluc-
 343 tuating directional selection produces a net effect of stabilizing selection on quantitative
 344 characters (Lande 2007, 2008; McGlothlin 2010).

345 In multivariate analyses the first few principle components often contain the great
 346 majority of the total variance, especially for sets of positively correlated characters
 347 such as morphological traits, but this applies to a lesser extent for sets of characters
 348 that are less closely integrated (Wright 1968; Lande and Arnold 1983; Blows 2006;
 349 Martin and Lenormand 2006; Arnold et al. 2008; Kirkpatrick 2009). Regarding a com-
 350 plex organism as a whole, many nearly independent combinations of morphological,
 351 behavioral, and physiological characters must be under stabilizing selection. Further-
 352 more, the strength of stabilizing selection on characters tends to be inversely related
 353 to their phenotypic and genetic variances, so the effective number of characters under
 354 appreciable stabilizing selection is likely to be considerably larger than the number of
 355 significant phenotypic principal components.

356

357 HIGH GENOMIC MUTATION RATES TO LETHALS

358 Large-scale experiments on *Drosophila* produced estimates of $U = 0.02$ and $h = 0.02$
 359 (Simmons and Crow 1977). Because plants lack a germ line, mutations can accumulate
 360 during many mitotic cell divisions between meioses, leading to high genomic mutation
 361 rates per generation, which may be associated with large adult size, long generations
 362 and vegetative reproduction (Klekowski 1984, 1988, 1989; Lande et al. 1994; Muirhead
 363 and Lande 1997; Scofield and Schultz 2006). Observations on spontaneous recessive
 364 chlorophyll deficiencies occurring at about 300 loci, and scaling these up to 10,000 ge-
 365 nomic loci mutating to recessive lethals (Simmons and Crow 1977; Bell 2010) produced
 366 estimates of about $U = 0.02$ for three annuals, barley, buckwheat and monkey flower,
 367 and an order of magnitude higher, $U = 0.2$, in mangrove trees (Klekowski and Godfrey

1989; Willis 1992; Lande et al. 1994).

Perennial plants often set relatively few seeds on experimental self-pollination in comparison to outcrossing, implying either a high early inbreeding depression (EID) causing embryo mortality or late-acting self-incompatibility (LSI) (Seavey and Bawa 1986; Gibbs 2014). LSI is often incomplete and/or variable in expression (Gibbs 2014), and in some species both EID and LSI may occur together (Dorken and Husband 1999; Hao et al. 2012). Extremely high EID occurs in conifer trees which generally are self-compatible and easily studied because embryo mortality produces an empty seed. For example coastal Douglas fir and other conifer trees have been estimated to harbor a mean of about 10 heterozygous lethal mutations per individual (Sorensen, 1969 1973; Franklin 1971; Bishir and Namkoong 1987). Perennial herbs of the genus *Stylidium* are fully self-compatible, with the average individual heterozygous for about 20 early-acting recessive lethals and some populations harboring mean numbers of heterozygous lethals up to 100 (Burbridge and James 1991). Assuming near recessivity of lethals, with $h = 0.02$ as estimated from *Drosophila* (Simmons and Crow 1977), these large mean numbers require high genomic mutation rates to lethals. At mutation-selection balance under random mating (or for selfing rates below the purging threshold for lethals) the mean number of heterozygous lethals in mature plants is $\bar{x} = U(1 - h)/h$, so that with $h = 0.02$ values of $\bar{x} = 10, 20$ or 100 corresponds to $U \approx 0.2, 0.4$ or 2 . Similarly high values of U have been estimated for a variety of woody perennial species, based on apparent EID (Scofield and Schultz 2006), but in most species the potential role of LSI has not been investigated. Direct evidence of high genomic mutation rates to recessive lethals, up to $U = 1$ or larger, comes from studies of spontaneous partially recessive lethals produced during vegetative growth, estimated by comparing seed set from autogamous vs. geitonogamous selfing (Bobiwash et al. 2013).

Results and Discussion

To analyze the interaction of the two major components of total inbreeding depression corresponding to the bimodal distribution of fitness effects, we modelled nearly recessive lethal mutations and stabilizing selection on quantitative characters acting, respectively, early and late in individual development. Strong interactions occur with

high genomic mutation rates to lethals and stabilizing selection on many characters, producing a high total inbreeding depression at equilibrium under low selfing rates, as often observed in perennial plants.

ALTERNATIVE EQUILIBRIA

We discovered that at a high genomic mutation rate to nearly recessive lethals ($U = 0.5$, $h = 0.02$), the Kondrashov model for lethals (K) by itself produces two alternative stable equilibria with different mean numbers of heterozygous lethals for selfing rates in the range $0.320 \leq r \leq 0.417$, as in Fig. 1A. The higher equilibrium mean number of lethals is found by starting at equilibrium under complete outcrossing ($r = 0$, a Poisson distribution of heterozygous lethals with mean $\bar{x} = U(1 - h)/h$), and increasing the selfing rate in successive increments using as the initial condition for each new value of r the equilibrium distribution of lethals from the previous value of r ; the higher equilibrium is also reached from the initial condition of zero lethals at all selfing rates. The lower equilibrium mean number of lethals is found by starting at equilibrium under complete selfing ($r = 1$, a Poisson distribution of heterozygous lethals with mean $\bar{x} = 2U(1 - h)/(1 + h)$), and decreasing the selfing rate in successive increments with the initial condition the equilibrium from the previous value of r . Lande et al. (1994) developed the Kondrashov model for lethals and investigated the genomic mutation rates to lethals $U = 0.02, 0.2, 1$ with $h = 0.02$, using both no lethals and equilibrium under complete outcrossing as initial conditions for all selfing rates, this missed alternative equilibria that exist for $U = 0.5$ (Fig. 1A), and for also $U = 1$ in a very narrow range of selfing rates $0.516 \leq r \leq 0.520$.

[Fig. 1 about here]

Using the Kondrashov model for lethals structured by selfing age, Fig. 1B,C illustrate the distributions of number of heterozygous lethals per individual, and the corresponding frequency distributions of selfing age, at the two alternative equilibria for $U = 0.5$ for selfing rate $r = 0.4$. At the higher equilibrium, selective interference among a large mean number of lethals prevents purging and maintains a high

430 inbreeding depression which produces a young distribution of selfing ages. The lower
431 equilibrium has purged most of the lethals, maintaining a greatly reduced inbreeding
432 depression and an older distribution of selfing ages.

433 Because we assume weak stabilizing selection on each character, model K alone (no
434 quantitative characters, $m = 0$) gives results for all variables (except genetic variance)
435 close to those for a single character ($m = 1$). This can be seen for the mean number
436 of heterozygous lethals, \bar{x} , by comparing Fig. 1A ($m = 0$) with Figs. 2 and 3 middle
437 panel top row ($m = 1$, black lines). We therefore do not plot $m = 0$ in subsequent
438 figures, instead focusing on results with increasing number of characters producing
439 higher inbreeding depression from stabilizing selection.

440 Alternative stable equilibria for nearly recessive lethals still exist when evolving
441 jointly with quantitative variation in a small or moderate number of characters under
442 weak stabilizing selection. In KIMS (Fig. 2) with $U = 0.5$, inclusion of up to 10
443 characters produces two alternative mean numbers of lethals resembling that in K alone
444 for intermediate selfing rates. With 25 characters these alternative equilibria merge into
445 a single equilibrium, but with 50 or 100 characters new alternative equilibria arise for
446 selfing rates around the purging threshold for lethals.

447 For all parameter values we examined across the entire range of selfing rates, in
448 KIMS at most two alternative stable equilibria occurred at a given selfing rate. For
449 $U = 0.5$ and $m = 1$ or 10, the alternative equilibria at intermediate selfing rates are
450 clearly created by K. However, alternative equilibria appearing at selfing rates around
451 the purging threshold for lethals, particularly at high U and large m , are caused by the
452 interaction of numerous lethals with stabilizing selection on many quantitative char-
453 acters. Fig. 2 shows that alternative stable equilibria for the mean number of lethals
454 exist over some ranges of selfing rates for all values of U illustrated, but not at the
455 lower value of $U = 0.02$ (not shown). In all cases where alternative stable equilibria
456 exist at a given selfing rate, the equilibria differ far more in mean number of lethals
457 than in the mean quantitative genetic variance.

458

459 [Fig. 2 and Fig. 3 about here: *align horizontally on facing pages*]

460

461 In GAM alone, without lethals, a *purged equilibrium* exists at all selfing rates
 462 ($r > 0$) caused by the progressive buildup of genic variance and negative covariance
 463 due to linkage disequilibrium between loci produced by stabilizing selection in long-
 464 selfed lineages (Lande and Porcher 2015). This creates a large segregation variance
 465 in selfed or outcrossed F_2 progeny following F_1 outcrossing, leading to a negative in-
 466 breeding depression (also called outbreeding depression) in the population. The purged
 467 equilibrium with low total genetic variance in quantitative traits is stable even at inter-
 468 mediate or low selfing rates because strong outbreeding depression shifts the selfing age
 469 distribution toward older selfing lineages, maintaining a stable core of the population
 470 composed of long-selfed lineages. With the inclusion of recessive lethals in KGAM, this
 471 also produces a low mean number of lethal mutations in the long-selfed lineages, so
 472 that both quantitative variation and mean lethals remain purged across a wide range
 473 of selfing rates, as seen in Fig. 3.

474 Thus at low or intermediate selfing rates, up to two alternative stable equilibria
 475 can occur in KIMS and up to three alternative stable equilibria can exist in KGAM. At
 476 high selfing rates in both KIMS and KGAM only the purged equilibrium exists, with
 477 low mean number of lethals and low quantitative genetic variance.

478

479 INTERACTION OF LETHALS AND QUANTITATIVE GENETIC VARIANCE

480 In KIMS (Fig. 2) the crossing of lines of different colors (for different numbers of
 481 characters) indicate that the interaction of the two components of inbreeding depres-
 482 sion, from nearly recessive lethals and quantitative genetic variance, are more complex
 483 than suggested by the simple notion of selective interference. These two components of
 484 inbreeding depression display both interference and facilitation in their mutual purg-
 485 ing processes. For example, at the lowest genomic mutation rate to lethals shown,
 486 $U = 0.2$, at selfing rates below about 0.4 increasing numbers of characters up to $m = 50$
 487 increases the equilibrium mean number of lethals, demonstrating that stabilizing se-
 488 lection on quantitative characters interferes with purging of lethals; but for $m = 100$
 489 at intermediate selfing rates $0.2 < r < 0.4$ the equilibrium mean number of lethals
 490 is actually less than for the Kondrashov model alone, demonstrating that selection on
 491 the quantitative characters facilitates purging of lethals. Facilitation of purging reces-

sive lethal mutations by stabilizing selection on quantitative traits becomes the main pattern of interaction with higher m and U (Fig. 2 top row). Stabilizing selection on quantitative characters facilitates purging of recessive lethals when the purging threshold for quantitative variation alone is below the purging threshold for lethals alone. This happens because of the shift in the age distribution toward older selfing ages that occurs during the purging of quantitative variation, which in turn initiates the purging of recessive lethals. In contrast, recessive lethals have relatively little impact on the purging of quantitative genetic variance by selfing in KIMS, only slightly smoothing or perturbing the otherwise abrupt purging threshold for quantitative variation (Fig. 2 second row).

Fig. 4 illustrates for KIMS at a given selfing rate that increasing the number of characters under stabilizing selection (increasing the inbreeding depression due to mildly deleterious mutations) initially shifts the equilibrium distribution of selfing ages toward outcrossing, thus increasing the mean number of heterozygous lethals in the younger selfing ages (black vs. green lines), corresponding to selective interference between recessive lethals and mildly deleterious mutations. But sufficiently many characters (red line) lower the purging threshold for quantitative genetic variance. At selfing rates above the purging threshold for quantitative genetic variance this creates a class of long-selfed lineages with improved fitness, purged of both lethals and quantitative genetic variance, which reduces both components of inbreeding depression and shifts the selfing age distribution back toward selfing. This qualitative shift in the equilibrium distribution of selfing ages also occurs for a given set of parameters when increasing the population selfing rate across the purging threshold for quantitative genetic variance in IMS and GAM without lethals (Lande and Porcher 2015), but not in K alone (Fig. 1), explaining why purging of quantitative genetic variance facilitates purging of lethals, but not vice versa. Qualitatively similar mechanisms operate in KGAM (not illustrated).

[Fig. 4 about here]

More complex patterns of equilibria arise in KGAM, shown in Fig. 3, because even

523 in the absence of recessive lethals it produces two stable equilibria at selfing rates below
 524 the purging threshold for quantitative genetic variance (Lande and Porcher 2015). In
 525 combination with the Kondrashov model for lethals KGAM can thus create up to three
 526 alternative stable equilibria at a given selfing rate. Aside from the additional *purged*
 527 *equilibrium* that exists for quantitative genetic variance in KGAM at selfing rates below
 528 the purging threshold, and given that the purging threshold for quantitative genetic
 529 variance is much sharper in GAM than in IMS (Lande and Porcher 2015), the over-
 530 all pattern of interaction of quantitative genetic variance with nearly recessive lethals
 531 resembles that in KIMS. That is, when the purging threshold for quantitative genetic
 532 variance alone exceeds that for recessive lethals alone, stabilizing selection on the quan-
 533 titative characters interferes with purging of lethals; but when the purging threshold for
 534 quantitative genetic variance alone is less than that for recessive lethals alone, stabiliz-
 535 ing selection on quantitative characters facilitates purging of lethals. Again, facilitation
 536 of purging recessive lethal mutations by stabilizing selection on quantitative traits be-
 537 comes the dominant pattern of interaction with more characters and higher genomic
 538 mutation rates to lethals (Fig. 3 top row). Aside from the *purged equilibrium* that
 539 usually reflects purging in both the lethals and quantitative genetic variance, it ap-
 540 pears that the main interaction is the influence of stabilizing selection on quantitative
 541 characters affecting the purging of lethals, whereas lethals have only a small impact
 542 on quantitative genetic variance. This interaction is again governed by the shape of
 543 the stable distribution of selfing ages among lineages, which with many characters is
 544 governed mainly by quantitative variation (Lande and Porcher 2015).

545 Further complications arise in KGAM at a high genomic mutation rate to lethals
 546 ($U = 0.5, 1$) for an intermediate number of characters, such that two distinct purging
 547 thresholds exist for the equilibrium quantitative genetic variance which shifts back and
 548 forth between *outcrossed* and *purged* equilibria as the selfing rate increases. Results for
 549 these parameter values are plotted separately in the Supporting Information (Fig. S1).

550

551 LIMIT CYCLES

552 For a very narrow range of selfing rates in KIMS (only at $U = 1$, $m = 10$, $r \approx 0.54$),
 553 stable limit cycles (or strange attractors) appeared, involving a single cycle or double

loop, with substantial sustained oscillations in mean lethals and quantitative genetic variance (Fig. 5). Changes in the total genetic variance in these cycles is entirely due to change in the negative covariance from linkage disequilibrium associated with oscillations in the age distribution of selfing lineages, since the genic variance at a given selfing rate remains constant in KIMS (see Appendix). The corresponding point in Fig. 2 represents the means of relevant variables averaged over the limit cycle.

In Kelly’s (2007) approximate Kondrashov model structured by selfing age, limit cycles appeared as an artifact when the exact Kondrashov model produced transient damped oscillations at recombination rates near a purging threshold for lethals, where equilibrium deviations from a Poisson distribution of lethals are large (Lande et al. 1994). Damped oscillations also appeared in IMS and GAM near a purging threshold, due to linkage disequilibrium created by stabilizing selection magnified by inbreeding, and its breakdown by outcrossing and recombination (Lande and Porcher, unpublished results). The interaction of these oscillatory tendencies can create a limit cycle in KIMS, but this was not observed in KGAM.

569

[Fig. 5 about here]

571

572 **ROBUST RESULTS AND CONCLUSIONS**

Patterns of interaction between nearly recessive lethal mutations and stabilizing selection on quantitative characters that appear in both KIMS and KGAM models are considered to be robust results that do not depend on the particular details and approximations in either IMS or GAM (Lande and Porcher 2015). In the combined models strong interactions between nearly recessive lethals and additive genetic variance in quantitative characters occur for moderate to high genomic mutation rates to lethals and for weak stabilizing selection on multiple characters, such that in a randomly mating population at equilibrium the total inbreeding depression would be very high. We found three robust results.

(1) Alternative stable equilibria can exist for a given selfing rate over a considerable range of parameters. With a small number of characters under weak stabilizing selection, alternative equilibria are produced by the Kondrashov model for lethals alone.

585 With many characters the interaction between lethals and quantitative characters cre-
586 ates or magnifies the difference between alternative equilibria.

587 (2) Stabilizing selection on quantitative characters usually exerts a stronger influ-
588 ence on nearly recessive lethals than vice versa. When the selfing rate at the purging
589 threshold for quantitative genetic variance in IMS or GAM exceeds that for nearly
590 recessive lethals in K, in the combined models, KIMS and KGAM, stabilizing selection
591 on quantitative characters shows *selective interference* with the purging of lethals, aug-
592 menting the equilibrium mean number of lethals in comparison to K. Conversely when
593 the selfing rate at the purging threshold for nearly recessive lethals in K exceeds that
594 for quantitative genetic variance in IMS or GAM, in the combined models stabilizing
595 selection causes *selective facilitation* in the purging of lethals, reducing the equilibrium
596 mean number of lethals in comparison to K. Alternative equilibria at a given selfing
597 rate, and the interactions between nearly recessive lethals and quantitative genetic
598 variance, are mediated by shifts in the distribution of ages of selfing lineages in the
599 population as illustrated for K alone (Fig. 1), for IMS and GAM (Lande and Porcher
600 2015), and in the combined models (Fig. 4).

601 (3) At high selfing rates above the purging threshold for quantitative genetic vari-
602 ance in KIMS and KGAM, only the purged equilibrium exists, with low quantitative
603 genetic variance and low mean lethals. Purging of quantitative genetic variance at high
604 selfing rates implies that highly selfing populations may fail to adapt to changing envi-
605 ronments, thus supporting the hypothesis of Stebbins (1957) that predominant selfing
606 is an “evolutionary dead end” (see discussion in Lande and Porcher 2015).

607

608 LIMITATIONS OF THE MODELS

609 Results that are specific to one model may not be robust and their realism remains
610 uncertain. These include limit cycles in KIMS, the purged equilibrium for quantita-
611 tive genetic variance and lethals at all selfing rates in KGAM, and multiple purging
612 thresholds for quantitative genetic variance with intermediate numbers of characters
613 in KGAM. Because IMS and GAM represent extremes of a range of possible models
614 for the maintenance of quantitative genetic variance, the realism of these features must
615 be explored using intermediate models with different assumptions and approximations.

616 The main limitation of K is its assumption of no variance in the dominance coeffi-
617 cients among nearly recessive lethal mutations, and the difficulty of measuring this
618 and the genomic mutation rate to lethals (Simmons and Crow 1977). Among mildly
619 deleterious mutations, basic parameters of the joint distribution of heterozygous and
620 homozygous effects on fitness, as well as their dominance, epistasis and linkage, and
621 mutation rates, remain poorly understood due to statistical limitations afflicting em-
622 pirical measurements (Eyre-Walker and Keightley 2007; Manolio et al. 2009; Yang et
623 al. 2010). Investigating these complexities of the interaction between the two major
624 components of inbreeding depression, represented in the bimodal distribution of fitness
625 effects, appears to require numerical simulations that themselves may be limited to
626 populations of small or moderate size dominated by random genetic drift (Bersabe et
627 al. 2016), rather than by selection.

628

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635

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811 **Supporting Information**

812 Additional Supporting Information may be found in the online version of this article
813 at the publisher's website:

814

815 Recursion equations for IMS and GAM

816 Figure S1. Parameter values in KGAM producing two purging thresholds for the equi-
817 librium quantitative genetic variance as a function of selfing rate.

Appendix

MODIFICATION OF GENIC VARIANCE IN IMS

The genic variance in infinitesimal model for selfing (IMS) is a limiting case of genetic variance maintained by purely additive mutational variance σ_m^2 in a finite population of effective size N_e under random mating, $V(0) = 2N_e(0)\sigma_m^2$ (Clayton and Robertson 1955; Lande 1980), as $N_e \rightarrow \infty$ and $\sigma_m^2 \rightarrow 0$ such that their product is a constant of the same order as the environmental variance in a quantitative character. Lande and Porcher (2015) extended this to a population with selfing rate r and mean inbreeding coefficient $\bar{f} = r/(2 - r)$ of Wright (1921, 1969) for a selective neutral partially selfing population.

Here, for increased accuracy when recessive lethals are included in the model, which can produce a high total inbreeding depression, we employ the actual mean inbreeding coefficient based on numerical calculation of the selfing age distribution,

$$\bar{f} = \sum_{\tau=0}^{\infty} p_{\tau} f_{\tau} \quad (A1)$$

in concert with Wright's more general formula for the effective size of an inbred population with non-uniform inbreeding among individuals, $N_e(r) = N_e(0)/(1 + \bar{f})$, such that at equilibrium for a given selfing rate

$$V(r) = V(0)/(1 + \bar{f}). \quad (A2)$$

Numerical methods to achieve convergence to equilibrium are described in the Supporting Information.

Table 1. Life cycle with notation for early selection on nearly recessive lethals and late selection on quantitative characters.

REPRODUCTION	→	ZYGOTE	→	JUVENILE	→	SUBADULT	→	ADULT	→
$(^o)$		$(^*)$		$(^{**})$		$(^')$ or $(^)$		$(^{***})$	
mating, recombination,		selection on		selection on		enumeration		selection on	
mutation, fertilization		homozyg. lethals		heterozyg. lethals		& iteration		quant. traits	

Figure 1. Alternative equilibria in model K alone, the Kondrashov model for lethals structured by selfing age, represented by solid and dashed lines. (A) Equilibrium mean number of heterozygous lethals \bar{x} , as a function of selfing rate r , with genomic mutation rate to lethals $U = 0.5$ and dominance coefficient $h = 0.02$. For alternative equilibria at selfing rate $r = 0.4$, equilibrium probability distributions of number of heterozygous lethals (B) and selfing age (C).

Figure 2. Equilibrium mean number of heterozygous lethals \bar{x} , mean genetic variance \bar{G} , mean total fitness $\bar{v}\bar{w}$, total inbreeding depression δ , and mean inbreeding coefficient \bar{f} at equilibrium in KIMS as functions of selfing rate r for different values of U . Colors of lines represent numbers of quantitative characters under stabilizing selection: $m = 1(\text{black}), 10(\text{blue}), 25(\text{green}), 50(\text{orange}), 100(\text{red})$. Alternative equilibria are shown by solid and dashed lines. Parameters: $h = 0.02$, equilibrium genetic variance under random mating $V(0) = 1$, environmental variance $E = 1$, width of individual fitness function $\omega^2 = 20$.

Figure 3. The same as Fig. 2 but for KGAM, where the mean genetic variance after selection on adults, \bar{G}^{***} is plotted instead of \bar{G} (Lande and Porcher 2015). Alternative equilibria are shown by solid, dashed and long-dashed lines. Parameters: $h = 0.02$, mutational variance $\sigma_m^2 = 10^{-3}$, number of loci per character $n = 10$, $E = 1$, $\omega^2 = 20$.

Figure 4. Equilibrium total genetic variance G , mean number of heterozygous lethals \bar{x} , mean total fitness $\bar{v}\bar{w}$, and \log_{10} frequency as functions of \log_{10} selfing age in KIMS at selfing rate $r = 0.2$ and $U = 0.2$, for different number of characters $m = 1(\text{black}), 25(\text{green}), 100(\text{red})$. Other parameters as in Fig. 2. Selfing age is plotted on a log scale to help reveal rapid changes in these quantities during the first few generations of continued selfing.

Figure 5. Limit cycles for mean number of heterozygous lethals and mean genetic

876 variance \bar{G} in KIMS. Points on the continuous curves represent sequential generations
877 of a cycle of one or two loops. (A) $r = 0.540$, (B) $r = 0.543$. Blue and red colors in (B)
878 distinguish the two loops. In successive cycles, the points would appear at slightly dif-
879 ferent positions on the curves. Other parameters: $U = 1$, $h = 0.02$, $m = 10$, $V(0) = 1$,
880 $\omega^2 = 20$.

881









