



HAL
open science

Perenniality induces high inbreeding depression in self-fertilising species

Diala Abu Awad, Sylvain Billiard, Viet-Chi Tran

► **To cite this version:**

Diala Abu Awad, Sylvain Billiard, Viet-Chi Tran. Perenniality induces high inbreeding depression in self-fertilising species. *Theoretical Population Biology*, 2016, 112, pp.43-51. 10.1016/j.tpb.2016.08.002 . hal-01361317

HAL Id: hal-01361317

<https://hal.science/hal-01361317>

Submitted on 27 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Perenniality induces high inbreeding depression in self-fertilising species.

D. Abu Awad^{a,b,*}, S. Billiard^a, V.C. Tran^c

^a*Unité Evolution, Ecologie et Paléontologie, UFR de Biologie, UMR 8198, CNRS / Université de Lille – Sciences et Technologies, 59655 Villeneuve d’Ascq Cedex, France*

^b*INRA, UMR AGAP, 2 place Pierre Viala F-34060 Montpellier Cedex 1, France*

^c*Laboratoire Paul Painlevé, UFR de Mathématiques, UMR 8524, CNRS / Université de Lille – Sciences et Technologies, 59655 Villeneuve d’Ascq Cedex, France*

Abstract

When predicting the fate and consequences of recurring deleterious mutations in self-fertilising populations most models developed make the assumption that populations have discrete non-overlapping generations. This makes them biologically irrelevant when considering perennial species with overlapping generations and where mating occurs independently of the age group. The few models studying the effect of perennial life-histories on the genetic properties of populations in the presence of self-fertilisation have done so considering age-dependent selection. They find low levels of inbreeding depression in perennial populations that do not explain empirical observations. Here we propose a simple deterministic model in continuous time with selection at different fitness traits and feedback between population fitness and size. We find that a perennial life-history can result in high levels of inbreeding depression in spite of inbreeding, due to higher frequencies of heterozygous individuals at the adult stage. We also propose that there may be demographic advantages for self-fertilisation that are independent of reproductive success.

Keywords: Perennial, Self-fertilisation, Genetic load, Population size, Inbreeding depression, Demography

*Corresponding author

Email address: diala.abu-awad@supagro.inra.fr (D. Abu Awad)

1 1. INTRODUCTION

2 The prevalence of outcrossing in phylogenies where self-fertilisation has
3 evolved independently several times (and with no detected returns to out-
4 crossing [25]) is a long-running question in evolutionary biology. Though it
5 has been suggested that self-fertilisation is an evolutionary dead-end [45, 50],
6 with self-fertilising lineages suffering from higher extinction rates [22], the
7 short-sightedness of natural selection makes it seem unlikely that only long-
8 term disadvantages are responsible for the maintenance of outcrossing. Fur-
9 thermore, there exists a correlation between longevity and the evolution of
10 self-fertilisation, with annual species tending to be self-fertilising and peren-
11 nials outcrossing (see [33]). This implies that life-history may play an impor-
12 tant part in the evolution of reproductive systems. Short-term disadvantages
13 or barriers to the spreading of self-fertilisation related to perenniality must
14 therefore exist.

15 The most evident short-term barrier to the evolution of self-fertilisation
16 is inbreeding depression, a lower relative fitness of selfed versus outcrossed
17 progeny due to the expression of partially recessive deleterious mutations [11].
18 It is generally accepted that if inbreeding depression is not too high, Fisher's
19 automatic advantage will favour the spreading of an allele promoting self-
20 fertilisation [18]. As self-fertilisation increases, this should lead to a purge of
21 deleterious alleles [20], lowering the observed level of inbreeding depression.
22 Indeed, it has been suggested that the observed correlation between perenni-
23 ality and outcrossing is due to higher observed levels of inbreeding depression
24 in perennial species even in species with mixed mating systems [33, 6, 48].
25 This phenomenon has been attributed to selective interference [48], a con-
26 sequence of linkage and identity disequilibria brought on by self-fertilisation
27 that results in the inability to purge deleterious mutations in spite of selfing
28 [30]. Though perenniality is expected to lead to higher per generation muta-
29 tion rates than would be observed in annual species (due to a higher number
30 of mitoses [43]), therefore favouring selective interference, it seems unlikely
31 that the observed levels of inbreeding maintained in perennial populations
32 be due solely to this phenomenon as selective interference requires a high
33 mutation rate to very recessive deleterious mutations (independently of their
34 coefficient of selection), and most deleterious mutations are only partially
35 recessive (see [26]).

36 The higher than expected levels of inbreeding depression in perennials
37 have been associated with a less efficient purging of the genetic load compared

38 to annual species [6]. This is further supported by the observation that self-
39 fertilising perennials seem to maintain higher than expected heterozygosity
40 at loci under selection [44] contrary to predictions from discrete-time models
41 with non-overlapping generations [11, 20]. Life-history may therefore be a
42 non-negligible trait when studying the evolution and the evolutionary con-
43 sequences of self-fertilisation. Most conventional population genetics mod-
44 els studying the consequences of the evolution of self-fertilisation have done
45 so assuming discrete-time and non-overlapping generations [29, 12, 38, 21].
46 Such models therefore neglect the potential effect of life-history traits on the
47 maintenance of inbreeding depression.

48 Previous works on the relationship between life-histories and self-fertilisation
49 have found that perenniality may actually facilitate the evolution to high self-
50 ing rates due to lowered levels of inbreeding depression at later stages [32].
51 However, Morgan's [32] model considered selection to occur on longevity,
52 with each generation presenting the opportunity for less fit genotypes to be
53 purged from the population. Though this is not an implausible definition
54 of fitness, it does not take into account other possible components of fitness
55 that can and do contribute to both mean fitness and inbreeding depression.

56 The concept of fitness is essential in any work determining how natural
57 selection influences a population's genetic and demographic state. In very
58 general terms, the consensus is that individual fitness is its ability not only
59 to survive but also to reproduce in a given environment [36]. In population
60 genetics models, this remains true, though the exact definition of fitness
61 may vary depending on how selection has been introduced (see [23], Chapter
62 7 of [40] and [37] for examples of how fitness was accounted for). The very
63 widely used discrete models with non-overlapping generations make biological
64 assumptions that cannot be universally applied and mainly represent annual
65 plant populations [35]. In such models definitions of fitness i.e. survival or
66 fecundity are interchangeable [23, 5]. As individuals are present for only one
67 generation this does indeed seem plausible (if an individual does not survive
68 to reproduce or simply does not reproduce the outcome is the same), but
69 what of populations that are not as compartmentalised as annual plants?
70 Do different components have the same influence on population equilibria as
71 in the discrete case?

72 When modelling perenniality, two approaches can be considered: discrete-
73 time age-structured models (see [9]) or continuous-time models ([17], Chapter
74 5.3 of [15], and [35]). In the latter case, age-structure is of little importance
75 if selection is considered to be age-independent as genic and genotypic fre-

76 quencies in a population evolve towards time-persistent forms independently
77 of the initial conditions considered [46]. The use of continuous-time models
78 without age-structure provides a simpler alternative to modelling overlap-
79 ping generations, there are however two main consequences: 1) The effect of
80 age on reproductive capacity and survival is ignored and 2) Certain individ-
81 uals can live for a very long time due to the variability of life-spans. How
82 age influences fecundity and survival is not clear-cut (see [4]), considering
83 age-independent selection is not wholly unrealistic.

84 Most continuous-time models stem from Fisher's Fundamental Theorem
85 of Natural Selection [17] wherein he introduced the notion of Malthusian
86 fitness, defined as the growth rate. However, simultaneously introducing
87 mutation, selection and non-random mating in such models can prove to
88 be challenging and simpler models in continuous time seem to be lacking.
89 For there to be demographic equilibrium, all genotypes must have the same
90 Malthusian fitness, making it an inappropriate indicator of differences be-
91 tween genotypes in this scenario [7]. Other definitions of fitness are therefore
92 to be preferred when examining population equilibrium, all the more so if
93 they facilitate the comparison to definitions of fitness in discrete-time models.

94 Another aspect that is often ignored in conventional population genetics
95 models is that of the demographic consequences of the genetic load. Works
96 that have addressed the potential genotypic effects of deleterious mutations
97 on population size have done so by considering density-dependent selection,
98 usually with a trade-off between r- and K-selection (for example [8, 13, 40],
99 but in [8] see section on density-independent selection). And in cases where
100 mutations are unconditionally deleterious, the ecological and genetic aspects
101 of the models were dissociated ([14, 1], but see the extreme case of the mu-
102 tational meltdown [28, 31]). By considering that the ecological and genetic
103 properties vary independently, any potential feed-back between the two may
104 be missed. That different components of fitness have different effects on
105 population size has been suggested by different models [14, 1], but could the
106 mating system further influence the consequences of selection on population
107 demography?

108 Here we introduce a simple model in continuous time where both the de-
109 mographic and genetic equilibria are emerging properties and not pre-defined
110 parameters. We study how the rate of self-fertilisation, in interaction with
111 different components of fitness, influences population size and the genetic
112 properties of populations at mutation-selection balance. We compare our
113 results to expectations from conventional population genetics models in dis-

114 crete time so as to evaluate whether perenniality may play a role in the
 115 maintenance of outcrossing.

116 2. Model

117 We consider the evolution of a population with a varying population size
 118 and a single bi-allelic locus, where A is the wild type and a is a deleterious
 119 mutant allele influencing individual fitness. The population is made up of
 120 sexually reproducing hermaphrodite individuals, who self-fertilise at a fixed
 121 rate α (with $\alpha = 0$ being panmictic and $\alpha = 1$ strictly self-fertilising). The
 122 environment is stable, and the population is isolated and spatially unstruc-
 123 tured. Three genotypes can be found in the population, aa , Aa and AA ,
 124 which, from here onwards, are denoted X , Y , and Z respectively. At a given
 125 time t , the population is made up of three kinds of individuals, X_t , Y_t and Z_t
 126 representing the number of individuals carrying the respective genotype. We
 127 denote the population size $N_t = X_t + Y_t + Z_t$. In a large population setting,
 128 these quantities can be considered as continuous, and the evolution of the
 129 number of individuals of each genotype is described in continuous time using
 130 ordinary differential equations. Three processes affect the change in the num-
 131 ber of individuals of each genotype, births (occurring with rate R_t^V , where
 132 V can be either X , Y or Z), deaths (at a rate M_t^V) and mutation. Selection
 133 and density dependence are introduced in these processes. We consider that
 134 the mutation from A to a is unidirectional and occurs with a probability μ
 135 at the gamete stage.

136 We first introduce the demographic properties of the model without con-
 137 sidering mutation and selection and show that this model respects the geno-
 138 typic frequencies predicted by the Hardy-Weinberg model for neutral alle-
 139 les and that in the case of self-fertilisation, the deviation from the Hardy-
 140 Weinberg equilibrium is as expected from conventional population genetics
 141 models (*i.e.* as a function of the inbreeding coefficient $F_i = \frac{\alpha}{2-\alpha}$). Mutation
 142 and selection are then introduced, with selection influencing different compo-
 143 nents of fitness (during different moments of the life cycle, but independent
 144 of age) and we define demographic and genetic variables to quantify the effect
 145 of the recurrent introduction of deleterious mutations on populations.

146 2.1. General Model (with only selfing)

147 The equation describing the change in the number of individuals for each
 148 genotype is given by

$$\frac{dV_t}{dt} = R_t^V - M_t^V, \quad (1)$$

149 Let us consider an intrinsic birth rate b , death rate d and carrying capacity
150 K to define the functions R_t^V and M_t^V , the rates of birth and mortality
151 respectively of individuals V (where V represents X , Y or Z).

152 For each of the genotypes these birth rates R_t^V are given by

$$\begin{aligned} R_t^X &= b \left(\alpha \left(X_t + \frac{1}{4} Y_t \right) + \frac{(1-\alpha)}{N_t} \left(X_t^2 + X_t Y_t + \frac{1}{4} Y_t^2 \right) \right) \\ R_t^Y &= b \left(\alpha \left(\frac{1}{2} Y_t \right) + \frac{(1-\alpha)}{N_t} \left(X_t Y_t + 2 X_t Z_t + \frac{1}{2} Y_t^2 + Y_t Z_t \right) \right) \\ R_t^Z &= b \left(\alpha \left(\frac{1}{4} Y_t + Z_t \right) + \frac{(1-\alpha)}{N_t} \left(\frac{1}{4} Y_t^2 + Y_t Z_t + Z_t^2 \right) \right) \end{aligned} \quad (2)$$

153 The assumptions made in formulating the expressions for R_t^V are as fol-
154 lows. Individuals within the population are hermaphroditic and can con-
155 tribute both via the male and the female functions. Female gametes are
156 limited, and depend on the number of individuals present in the popula-
157 tion, whereas male gametes are produced in very large quantities (*i.e.* there
158 is no pollen limitation) and are subjected to competition. In sum, the
159 birth/recruitment rate depends on an intrinsic reproductive rate b (which,
160 by default, holds the same value for all genotypes) and on the reproductive
161 events that lead to the production of new individuals with genotype V .

162 The death rate M_t^V depends on the death rate d and is density dependent
163 (with carrying capacity K). The equation for M_t^V is given by

$$M_t^V = d \frac{N_t}{K} V_t. \quad (3)$$

164 The choice of density dependence on mortality is arbitrary as a symmetri-
165 cal form of density dependence on birth, written in the form $b \frac{K}{N_t}$ yields similar
166 results as those presented below. When solving $\frac{dN}{dt} = \frac{dX}{dt} = \frac{dY}{dt} = \frac{dZ}{dt} = 0$ we
167 find the equilibrium population size is given by (see Supplementary Material
168 S4 for the proof)

$$N_{eq} = \frac{bK}{d}. \quad (4)$$

169 By solving the equations we find that the frequencies of X , Y and Z
 170 concord with the expectations of the generalised Hardy-Weinberg law, with
 171 genotypic frequencies depending on the inbreeding coefficient $F_i = \frac{\alpha}{2-\alpha}$ (
 172 see p.120 of [19] and Supplementary Material S3). When the rate of self-
 173 fertilisation $\alpha = 0$, then $F_i = 0$ and the frequencies of X , Y and Z are at
 174 Hardy-Weinberg equilibrium.

175 2.2. Introducing Mutation

176 Mutations occur at a rate μ during gamete formation and are considered
 177 to be uni-directional from A to a . The proportions of a gametes produced per
 178 genotype are therefore 1 , $\frac{1+\mu}{2}$ and μ for X , Y and Z individuals respectively
 179 (the proportions of A alleles being 0 , $\frac{1-\mu}{2}$ and $1-\mu$). Mutational events are
 180 integrated into the birth rate R_t^V , with, for example :

$$\begin{aligned}
 R_t^X = b & \left(\alpha \left(X_t + \frac{1}{4} Y_t (1 + \mu)^2 + Z_t \mu^2 \right) \right. \\
 & + \frac{(1 - \alpha)}{N_t} \left(X_t^2 + X_t Y_t (1 + \mu) + 2 X_t Z_t \mu + \frac{1}{4} Y_t^2 (1 + \mu)^2 \right. \\
 & \left. \left. + Y_t Z_t \mu (1 + \mu) + Z_t^2 \mu^2 \right) \right). \quad (5)
 \end{aligned}$$

181 2.3. Timing of selection

182
 183 We consider selection that is not age-dependent and influences the pop-
 184 ulation's net reproductive rate ($R_t - M_t$, where R_t and M_t are the sums
 185 of all the possible R_t^V and M_t^V respectively). As the genetic properties at
 186 equilibrium are emerging properties of the model, we examine the potential
 187 effects of the fitness component in the presence of non-random mating on
 188 the allelic and genotypic frequencies at mutation-selection balance. Selection
 189 can either affect reproduction (relative reproductive success or fecundity) or
 190 survival (at either the zygote or the adult stage). The deleterious allele a
 191 has a coefficient of selection s and dominance h , giving a relative fitness at a
 192 given trait of $(1 - s)$, $(1 - hs)$ and 1 for genotypes X , Y and Z respectively.
 193 Below we detail the hypotheses made when defining the different fitness com-
 194 ponents. The full equations for the change in the number of individuals of
 195 each genotype for these models can be found in Supplementary Material S2.
 196 A summary of the life-cycle and the different forms of selection can be seen
 197 in Figure 1.

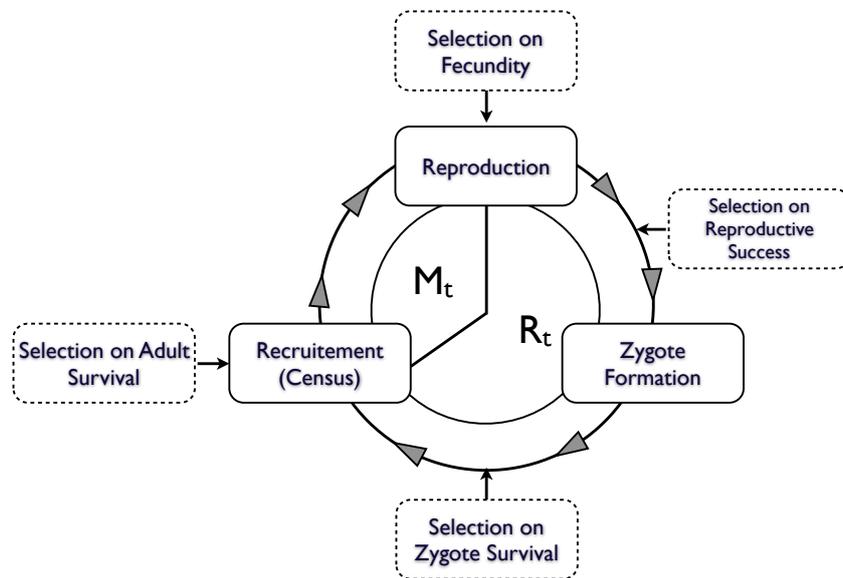


Figure 1: A schematic representation of the life-cycle modelled. Selection on the components of fitness are represented in boxes with dashed borders. R_t and M_t represent the birth and death functions respectively. Individuals, once recruited, remain a part of the censused population, contributing offspring (at rate R_t) until their death (at rate M_t).

198 *2.3.1. Selection on reproduction:*

199 In order to model the effect of the deleterious allele a on the reproduc-
 200 tive output of individuals, we introduce a new term \tilde{V}_t instead of V_t in the
 201 R_t^V function. This term represents the contribution of V individuals to the
 202 genetic pool (or their reproductive output), proportional to their fitness (i.e.
 203 $\tilde{X}_t = (1-s)X_t$). Carrying a can influence the reproductive output by either
 204 reducing the reproductive success of individuals or their fecundity.

205 *Reproductive Success (model RS):* . When reproductive success is reduced,
 206 all individuals produce the same quantity of gametes, however the success
 207 of a mating event depends on the genotypes' fitness (i.e. for X individuals
 208 only $(1-s)$ matings lead to fertilisation). The proportion of female and male
 209 gametes an individual V effectively contributes are therefore $b\tilde{V}_t$ and $\frac{\tilde{V}_t}{N_t}$. R_t^X
 210 for this model of selection is given by

$$R_t^X = b \left(\alpha \left(\tilde{X}_t + \frac{1}{4} \tilde{Y}_t (1 + \mu)^2 + \tilde{Z}_t \mu^2 \right) + \frac{(1-\alpha)}{N_t} \left(\tilde{X}_t^2 + \tilde{X}_t \tilde{Y}_t (1 + \mu) + 2 \tilde{X}_t \tilde{Z}_t \mu + \frac{1}{4} \tilde{Y}_t^2 (1 + \mu)^2 + \tilde{Y}_t \tilde{Z}_t \mu (1 + \mu) + \tilde{Z}_t^2 \mu^2 \right) \right) \quad (6)$$

211 *Fecundity (model F):* . Selection reducing individual fecundity is translated
 212 by an individual V contributing $b\tilde{V}_t$ female gametes and a proportion of
 213 $\frac{\tilde{V}_t}{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}$ male gametes to the next generation. The equations for R_t^V with
 214 selection on fecundity are therefore the same as for selection on reproductive
 215 success, with the exception of the term $\frac{(1-\alpha)}{N_t}$, which is replaced by $\frac{(1-\alpha)}{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}$.
 216 Note that for this form of selection the proportion of male gametes effectively
 217 contributed by V depends on the total amount of male gametes produced
 218 and not on the number of individuals in the population as with selection on
 219 reproductive success.

220 *2.3.2. Selection on survival:*

221 Selection can also occur during the life cycle, independently of reproduc-
 222 tive output, affecting either zygote or adult survival.

223 *Zygote Survival (model Z)*: . Zygote survival can be translated as the pro-
 224 portion of viable offspring that are recruited into the population. If V has
 225 a probability of being recruited proportional to its fitness, this implies that
 226 the effective reproductive output R_t^V depends on V 's relative fitness W^V .
 227 The function R_t^V is therefore multiplied by the genotypic fitness, with, for
 228 example :

$$\frac{dX}{dt} = (1 - s)R_t^X - M_t^X \quad (7)$$

229 One can note that the symmetrical equivalent of this model, with selection
 230 increasing mortality (done by replacing d in M_t^V by $\frac{d}{W^V}$), leads to the same
 231 results.

232 *Adult Survival (model A)*: . For this form of selection we make the assump-
 233 tion that adults are eliminated before they have reproduced and have little
 234 effect on density dependence (i.e. that the resources K consumed by the these
 235 adults are negligible). As adults that are selected against neither contribute
 236 to the next generation, nor generate competition for male reproduction the
 237 expression for R_t^V in this model of selection is equivalent to that for selection
 238 on fecundity (equation (6) with $\frac{(1-\alpha)}{N_t}$, replaced by $\frac{(1-\alpha)}{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}$). Similarly, the
 239 assumed lack of competition for resources leads to a new expression for the
 240 death rate M_t^V , given by

$$M_t^V = d \frac{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}{K} V_t. \quad (8)$$

241 2.4. Population equilibrium

242 The deterministic equilibrium values for each of the models of selection
 243 described above (models RS, F, Z and A) are derived by solving $\frac{dX_t}{dt} = \frac{dY_t}{dt} =$
 244 $\frac{dZ_t}{dt} = 0$. This allows us to obtain the number of individuals carrying each
 245 genotype at equilibrium (X_{mut} , Y_{mut} and Z_{mut}), the sum of which gives us
 246 the population size at equilibrium N_{mut} . In cases where no explicit solution
 247 could be found, numerical iterations were performed to obtain the numbers
 248 of each genotype at equilibrium. The expressions for X_{mut} , Y_{mut} and Z_{mut} are
 249 then used to derive the expressions for the mutational load L and inbreeding
 250 depression δ . The mutational load L is defined as the decrease in mean fitness
 251 due to the presence of deleterious mutations and is given by p.61 of [19]:

$$L = 1 - \frac{(1-s)X_{mut} + (1-hs)Y_{mut} + Z_{mut}}{N_{mut}}. \quad (9)$$

252 We also explore the expected level of inbreeding depression δ in popula-
253 tions, which is calculated using equation 3 in [42]:

$$\delta = 1 - \frac{W_s}{W_o} \quad (10)$$

254 where W_s is the fitness of selfed offspring and W_o of outcrossed offspring
255 and are given by

$$\begin{aligned} W_s &= (1-s)X_{mut} + \left(\frac{1}{4} + \frac{1-hs}{2} + \frac{1-s}{4}\right)Y_{mut} + Z_{mut}. \\ W_o &= (1-s)\left(X_{mut} + \frac{Y_{mut}}{2}\right)^2 \\ &\quad + (1-hs)\left(X_{mut} + \frac{Y_{mut}}{2}\right)\left(Z_{mut} + \frac{Y_{mut}}{2}\right) + \left(Z_{mut} + \frac{Y_{mut}}{2}\right)^2. \end{aligned} \quad (11)$$

256 We then compare L and δ to expectations from conventional population
257 genetics models. In order to compare our results to these models, we replace
258 X_{mut} , Y_{mut} and Z_{mut} with q^2 , $2q(1-q)$ and $(1-q)^2$ respectively, where q is
259 the frequency of the deleterious mutant a at mutation-selection balance. We
260 will compare our models to the explicit expression for q (for any value of s ,
261 μ and α , but $h \neq 0.5$) from the model presented in Chapter 6 of [15], where

$$q_{\alpha,h}^{CK} = \frac{\sqrt{G_{\alpha,h}} - s(h(1+\mu)(1-F_i) + F_i)}{2(1-F_i)(1-2h)s} \quad (12)$$

262 and

$$G_{\alpha,h} = s(4\mu(1-F_i)(1-2h) + s(F_i + (1-F_i)h(1+\mu))^2). \quad (13)$$

263 Using these expressions we can obtain expressions for the genetic load
264 $L_{\alpha,h}^{CK}$ and the level of inbreeding depression $\delta_{\alpha,h}^{CK}$.

265 Multi-locus approximations considering completely independent loci were
266 used to calculate the genetic load and inbreeding depression. If the ex-
267 plicit equations are available, then mean fitness is calculated using Hal-
268 dane's [24] approximation for multiplicative independent loci, where fitness

269 $W \approx \exp[-L]$ and the single locus mutation rate μ in L is replaced by the ge-
 270 nomic mutation rate. In the case of numerical iterations, then $W = (1 - L)^n$,
 271 n representing the number of loci and μ being maintained as the single locus
 272 mutation rate. In order to estimate the level of inbreeding depression δ , we
 273 use Kirkpatrick and Jarne's [27] expression where inbreeding depression due
 274 to multiple loci is

$$\delta = 1 - \prod_{i=1}^n (1 - \delta_i). \quad (14)$$

275 Although linkage disequilibrium has non-negligible effects on both the genetic
 276 load and inbreeding depression in the presence of selfing [41], estimations in
 277 continuous time have yet to be developed and so could not be taken into
 278 account here.

279 In cases where the genotypic frequencies from our model deviated from
 280 theoretical Hardy-Weinberg proportions for a given frequency of the deleter-
 281 ious allele at equilibrium q , two measures are made in order to verify the
 282 consequences of this deviation: 1) Wright's Inbreeding coefficient, F_W , cal-
 283 culated using

284

$$F_W = 1 - \frac{Y_{obs}}{2q(1 - q)} \quad , \quad (15)$$

285 where the numerator (Y_{obs}) is the frequency of heterozygotes obtained
 286 from our model and the denominator that is expected from discrete time
 287 models in the absence of inbreeding using the observed frequency of the
 288 deleterious allele q and 2) A modified expression of Wright's coefficient of
 289 inbreeding

290

$$F_{diff} = 1 - \frac{Y_{obs}}{2q(1 - q)(1 - F_i)} \quad , \quad (16)$$

291 where Y_{obs} is as before and the denominator is the expected frequency
 292 of heterozygotes from conventional models for the same frequency of the
 293 deleterious allele q in the presence of inbreeding.

294 For all four models of selection, there exists a solution where the popula-
 295 tion is made entirely of X individuals. There is therefore a threshold value
 296 of the mutation rate μ , as a function of the selection coefficient s and the

297 dominance h , which leads to the deterministic fixation of a . However, as
298 this requires that the selection coefficient s must be of order μ , a would be
299 selectively neutral and drift the main force influencing its frequency, render-
300 ing this threshold biologically irrelevant. We thus do not consider this case
301 further, but more detail can be found in Supplementary Material S1.

302 3. Results

303 By solving the equations given in the previous section, we have found
304 explicit solutions when the population is panmictic ($\alpha = 0$). Clear explicit
305 solutions for any rate of self-fertilisation were possible only for recessive mu-
306 tations ($h = 0$). For other values of h ($\neq 0.5$) with $\alpha \neq 0$, solutions could
307 not be obtained and so the variables at equilibrium were calculated using
308 numerical iterations. All mathematical operations were carried out using
309 Wolfram's Mathematica 9.0 [49].

310 3.1. Allelic frequencies and the genetic load

311 In the absence of self-fertilisation, selection models RS, F and A result in
312 the same allelic frequencies and genetic load L as expected from conventional
313 population genetics models, with no effect of demographic parameters on
314 the genetic variables at equilibrium in a deterministic setting (see Table 1).
315 Model Z differs in that the frequency q at equilibrium is that obtained from
316 conventional models in discrete time after selection and before mutation have
317 taken place. This is intuitive in that census occurs at the adult stage, hence
318 after unfit zygotes have been eliminated. The strength of selection therefore
319 has a greater effect on L , whereas for the other models, when mutations are
320 recessive $L = \mu$. This however is of little consequence numerically.

Model	$\alpha = 0 \ \& \ h \neq 0.5$		$\alpha \neq 0 \ \& \ h = 0$			
	q	L	q	L	X_F	δ
CK			$\frac{\mu(2-\alpha)}{s\alpha} + o(\mu)^2$			$\frac{\mu(2-\alpha)}{2\alpha} + o(\mu)^2$
RS	$q_{0,h}^{CK}$	$L_{0,h}^{CK}$	$\frac{\mu(2-(1-2s)\alpha)}{s\alpha} + o(\mu)^2$	μ	$\frac{\mu}{s}$	$\mu \left(\frac{1+\alpha s}{\alpha} \right) + o(\mu)^2$
F						
A						
Z	$h = 0$		$\frac{\mu(2-(1-s)\alpha)}{s\alpha} + o(\mu)^2$	$\frac{\mu(1-s)}{1-\mu}$	$\frac{\mu(1-s)}{(1-\mu)s}$	$\frac{\mu}{\alpha} + o(\mu)^2$
	$\sqrt{\frac{\mu}{s} - \mu}$	$\frac{\mu(1-s)}{1-\mu}$				

Table 1: Effect of the mode of selection on genetic load L and frequency q of the deleterious allele for a panmictic population ($\alpha = 0$) and all values of μ , s and $h \neq 0.5$, and L , q , the frequency of the deleterious homozygote X_F and the level of inbreeding depression δ for a population with selfing rate $\alpha \neq 0$ and $h = 0$. In the latter case q and δ are obtained to the first order of μ from the explicit analytic results, making it valid only for very small values of μ and $\alpha \gg 0$. $q_{0,h}^{CK}$ is given by setting $F_i = 0$ in equation (12), and is then used to calculate $L_{0,h}^{CK}$ as shown in equation (9). Full derivations of these results and equations of genotypic frequencies for recessive mutations can be found in Supplementary Material S3.

321 As expected from previous models, self-fertilisation leads to higher mean
 322 fitness. However, when comparing continuous and discrete time, we find that
 323 the deleterious allele has a higher frequency q in continuous time, implying
 324 that selection may not be as efficient as expected from discrete time models.
 325 This can be deduced from the equations for recessive mutations in Table
 326 1 where the higher the coefficient of selection s , the greater the differences
 327 between continuous and discrete time models independently of the demo-
 328 graphic parameters. In spite of higher observed q , there are no or very little
 329 differences between the genetic loads of the two models for a given rate of
 330 self-fertilisation. This remains true even when selection is relatively strong
 331 ($s = 0.1$) at a large number of independent loci (see Figure 2).

332 3.2. Genotypic frequencies and inbreeding depression

333 In spite of genotypic frequencies for discrete and continuous time models
 334 being equivalent in the case of neutral alleles with no mutation, in the pres-
 335 ence of both mutation and selection, this is no longer the case. As can be
 336 seen in Table 1, the frequency at equilibrium q of the deleterious allele in the
 337 presence of self-fertilisation when mutations are recessive ($h = 0$) is higher
 338 for the model in continuous time compared to the discrete-time model. If in
 339 continuous time, as in discrete time, the expected frequency of deleterious
 340 homozygotes is $q^2(1 - F_i) + qF_i$, a higher q should lead to a higher frequency
 341 of X individuals. This however is not the case, as the explicit expression
 342 for the frequency of the deleterious homozygote X is the same as that ob-
 343 tained in discrete time. The higher frequency q is therefore not associated
 344 with a greater frequency of homozygotes, but with a higher frequency of het-
 345 erozygote individuals. Indeed as can be seen in Figure 3, there is an excess
 346 of heterozygotes in our model compared to conventional discrete-time mod-
 347 els (shown by the negative F_{diff} , see equation (16)), which is accentuated
 348 for higher rates of self-fertilisation and higher coefficients of selection. The
 349 timing of selection also influences the inbreeding coefficient, with model Z
 350 leading to even larger negative values of F_{diff} than the other models (re-
 351 sults not shown). For all continuous time models, contrary to discrete-time
 352 non-overlapping generations, Wright's inbreeding coefficient F_W (equation
 353 (15)) is null, indicating that the observed frequency of heterozygotes is that
 354 expected in completely outcrossing populations.

355 The observed excess of heterozygotes, though it has little effect on the
 356 genetic load L , leads to an increased level of inbreeding depression δ within
 357 the population (see expressions for δ in Table 1). As illustrated in Figure

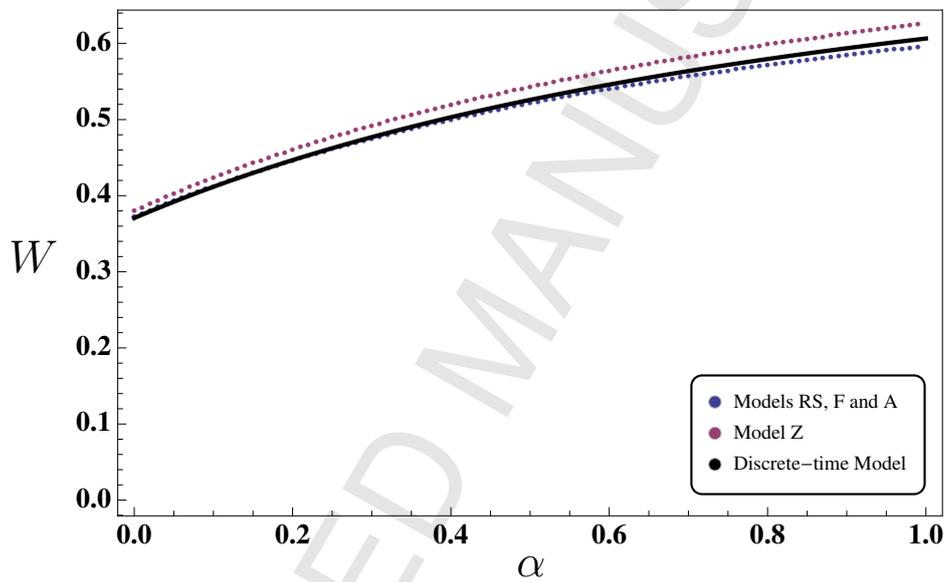


Figure 2: Expected mean fitness W as a function of the rate of self-fertilisation α calculated numerically and extended over 5000 loci with a mutation rate $\mu = 10^{-4}$ (giving a genomic mutation rate of 0.5), $s = 0.1$ and $h = 0.2$. Expectations from the conventional discrete time population genetics model is calculated using equations (9) and (12).

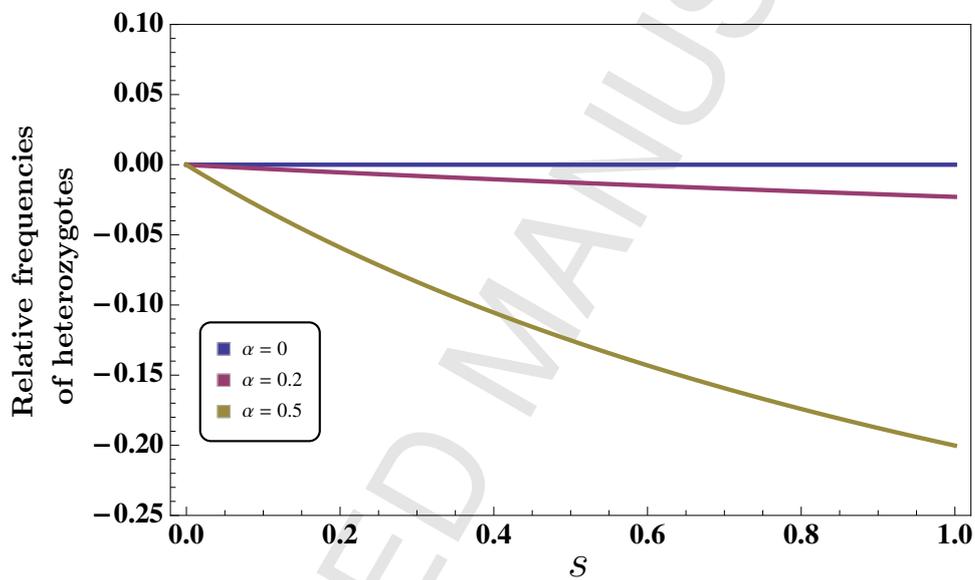


Figure 3: The observed frequency of heterozygotes in continuous time relative to that expected in discrete time (using the expression for F_{diff} in equation (16)) for selection models RS, F and A as a function of the coefficient of selection s when mutations are recessive ($h = 0$) and $\mu = 10^{-5}$ (but these results hold for any $\mu < s$). Exact solutions obtained in the case of $h = 0$ were used.

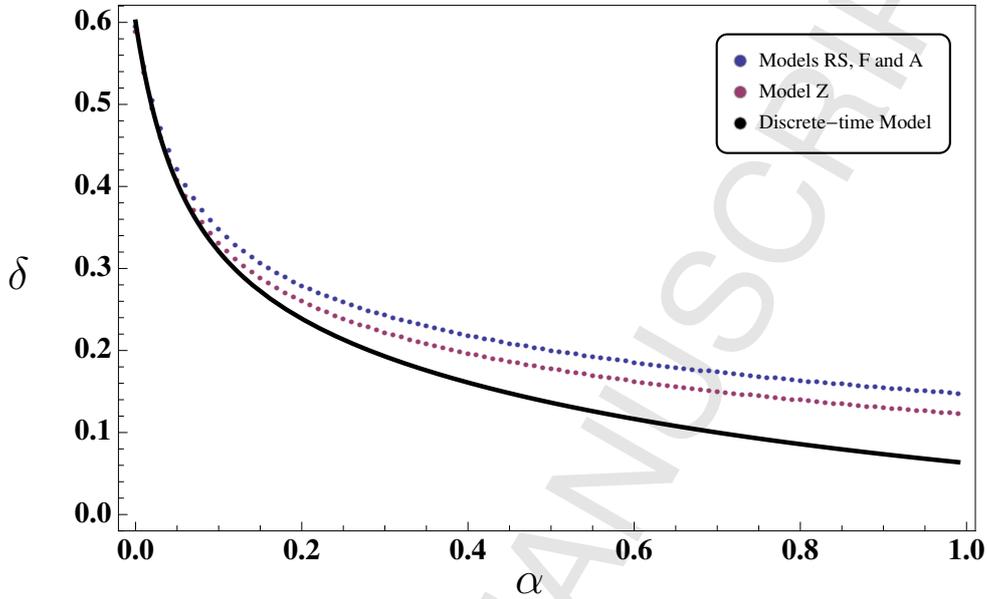


Figure 4: Expected mean level of inbreeding depression δ as a function of the rate of self-fertilisation α calculated numerically and extended over 20 000 loci with a mutation rate $\mu = 10^{-5}$ (giving a genomic mutation rate of 0.2), 3000 loci with $s = 1$ and $h = 0.02$ and 17000 with $s = 0.001$ and $h = 0.2$.

358 4, the level of inbreeding depression is not as easily purged in continuous
 359 time as it is in discrete time. This is all the more true in the case of very
 360 deleterious mutations. As can be seen in Figure 4, model *Z* leads to a lower
 361 observed δ due to the lower frequency of the deleterious allele.

362 3.3. Population size

363 From our results in the previous section, we find that the demographic
 364 parameters have no influence on the genetic equilibria of populations. The
 365 reverse, however, is not true, as population size at equilibrium may be in-
 366 fluenced by the genetic make-up of populations and the timing of selection.
 367 If mean fitness suffices in explaining the observed population size, then we
 368 would expect the same population size for selection on Reproductive Success,
 369 Fecundity and Adult Survival, whereas selection on Zygote survival would
 370 lead to a larger population size (as load is slightly smaller at equilibrium).
 371 This however is not the case, as can be seen in Figure 5 and Table 2 (see

372 Supplementary Material S4 for proofs of population size at equilibrium with-
 373 out self-fertilisation and recessive mutations). Selection on Adult Survival
 374 is the only case where population size is unaffected by the introduction of
 375 recurrent deleterious mutations ($N_{mut} = N_{eq}$ for any genetic parameters even
 376 In the presence of self-fertilisation) and so will not be mentioned further in
 377 this section.

378 In the case of panmixia (see Table 2), the expected genetic load from
 379 conventional population genetics models appears in the explicit solutions. In
 380 spite of differences in the observed mutation load for models F and Z (see
 381 Table 1), they present the same population size, directly proportional to the
 382 observed mean fitness for model F. Selection on Reproductive Success results
 383 in the largest effect of mutations on population size as it is influenced by the
 384 square of mean fitness (Table 2).

Model	$\alpha = 0$	$h = 0$
Reproductive Success	$N_{eq}(1 - L_0^{CK})^2$	$N_{eq}((1 - \mu)^2 + \alpha\mu(1 - \mu))$
Fecundity	$N_{eq}(1 - L_0^{CK})$	$N_{eq}(1 - \mu)$
Zygote Survival		
Adult Survival	N_{eq}	N_{eq}

Table 2: Explicit solutions for expected population size in a panmictic population ($\alpha = 0$) and all values of μ , s and $h \neq 0.5$ or a population with selfing rate α and $h = 0$. L_0^{CK} is given by setting $F_i = 0$ in equation (12) which is then injected into equation (9).

385 Though the rate of self-fertilisation does not influence mean fitness in the
 386 case of recessive mutations (Table 1), it can influence population size when
 387 selection is on Reproductive Success. Results from numerical iterations con-
 388 firm that the relationship between mean fitness and population sizes with
 389 selfing and completely recessive mutations (Table 2) remain valid for muta-
 390 tions with any dominance; where μ (the genetic load when mutations are
 391 recessive) can simply be replaced by L obtained for any genetic parameters.
 392 We find that, as for mean fitness, increasing the rate of self-fertilisation in-
 393 creases population size for models RS, F and Z (see Figure 5). The rate

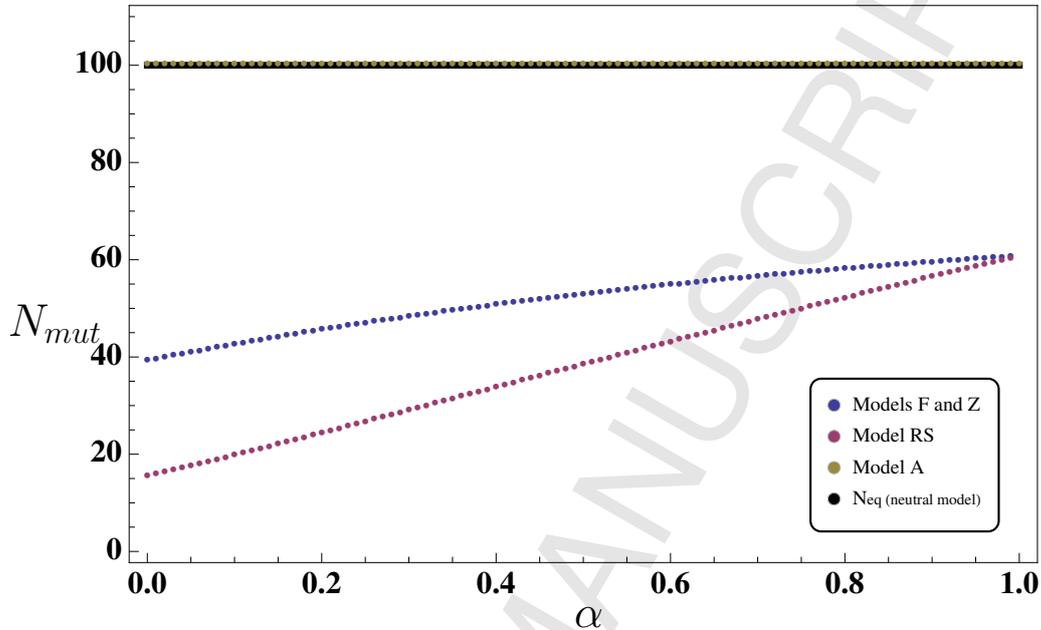


Figure 5: Expected population size at equilibrium N_{mut} as a function of the rate of self-fertilisation α calculated numerically and extended over 5000 loci with a mutation rate $\mu = 10^{-4}$ (giving a genomic mutation rate of 0.5), $s = 0.01$ and $h = 0.2$. Demographic parameters are set to $b = 1$, $q = 1$ and $K = 100$, giving $N_{eq} = 100$, represented by the black line.

394 of self-fertilisation α has a greater impact on population size for model RS,
 395 though for strictly self-fertilising populations ($\alpha = 1$), models RS, F and Z
 396 all result in the same population size.

397 4. Discussion

398 Through this work, we explore whether populations in continuous time
 399 present similar genetic properties at mutation-selection balance as expected
 400 from models in discrete time in order to evaluate the potential consequences
 401 of self-fertilisation when considering a perennial life-history. We test whether
 402 different components of fitness that seem interchangeable in conventional
 403 discrete-time population genetics models with non-overlapping generations
 404 influence genetic equilibria in the presence of non-random mating. Taking
 405 this work one step further, we also take into account the potential conse-

406 quences of selection against recurrent deleterious mutations on population
407 size in a simple ecological context in order to determine how the components
408 of fitness interact with the mating system considered.

409 4.1. Consequences of continuous time on genetic variables

410 Historically, continuous time models in population genetics models follow
411 Fisher's Fundamental Theorem [17]. The general consensus is that, despite
412 a small deviation from Hardy-Weinberg proportions (accentuated by strong
413 selection,[7]), continuous and discrete time models are equivalent when it
414 comes to the genetic state of populations. This is indeed the case when
415 mating is random, but as stated in [34], this would not necessarily hold in
416 non-random mating populations. As the interest of this paper is to examine
417 equilibrium properties of populations, we did not opt for using Malthusian
418 fitnesses as is often the case in continuous time models (since at equilibrium,
419 the Malthusian fitness is the same for all genotypes, [7]), but preferred a
420 form closer to that used in discrete population genetics models, allowing for
421 an easier comparison.

422 We find that introducing non-random mating in a continuous time model
423 not only leads to deviations from Hardy-Weinberg proportions, but can also
424 change the expected frequency of the deleterious allele. In continuous time
425 we find a higher frequency q , leading to a higher frequency of heterozygotes
426 than expected for a given rate of self-fertilisation in discrete models.

427 Indeed, it has been shown by Spigler et al. [44] that heterozygosity may
428 persist in perennial populations in spite of increased inbreeding for loci un-
429 der selection (heterozygosity was measured using enzyme systems) as there
430 was an excess of heterozygotes and a lower than expected frequency of ho-
431 mozygotes. Furthermore, a null inbreeding coefficient F_W (equation 15 het-
432 erozygous frequencies in the presence of inbreeding are the same as those
433 expected in the absence of inbreeding) have also been observed in natural
434 populations, where at the adult stage the coefficient of inbreeding was null
435 in spite of non-null levels of self-fertilisation [16]. In these empirical works
436 the authors concluded that this was due to stronger selection against inbred
437 individuals. Our results indicate that, in the presence of self-fertilisation, the
438 higher frequency of heterozygotes is not necessarily due to stronger selection.
439 Selection on Zygote Survival (model Z) does indeed allow for a better purge
440 of deleterious alleles (homozygotes do not arrive at the adult stage as fre-
441 quently), and agrees with Duminil et al.'s [16] observations of lower survival
442 from seedling to adult stages for inbred individuals. However, F_W is null

443 for all of our models of selection. Selection at the adult stages results in
444 the same strength of selection against homozygotes as in discrete time (the
445 frequency of homozygotes in continuous time is the same as that observed in
446 discrete time for recessive mutations, regardless of the higher q). We there-
447 fore propose that their observations are due to a life-history with overlapping
448 generations. A high fitness individual has a higher probability of becoming
449 an established adult (models Z and A), and a higher probability of reproduc-
450 ing (models RS and F). Once established, all adults have the same mortality.
451 Deleterious mutations are continuously introduced via mutations in the off-
452 spring of unmutated (or more fit) individuals, accounting for the increase in
453 the observed frequency of heterozygotes. Therefore, perennials can maintain
454 a higher frequency of deleterious mutations than annuals in the presence of
455 selfing without having to take into account a higher per generation mutation
456 rate [43].

457 Self-fertilisation is usually associated with a decrease in the frequency
458 of heterozygotes [10, 20] and hence a lower level of inbreeding depression
459 (inbreeding when most individuals are homozygous has little effect on the
460 fitness of offspring, [3]). Both selection at the adult and zygote stages lead
461 to higher levels of inbreeding depression δ on the population level. Since
462 inbreeding depression is a relative measurement, the value of δ depends on
463 the partners available in a population. When a population is made up of ho-
464 mozygous individuals, a population's level of inbreeding is null. An increase
465 in the frequencies of heterozygotes implies that reproduction with one's self
466 is less advantageous than outcrossing, since self-fertilising heterozygotes will
467 automatically produce $\frac{1}{4}$ deleterious homozygotes, while outcrossing between
468 heterozygous and homozygous wild-type individuals does not result in the
469 production of deleterious homozygotes. The higher levels of inbreeding de-
470 pression observed in our continuous time model are therefore directly related
471 to the higher frequencies of heterozygotes observed on the population level.
472 Selection at the zygote stage leads to a slightly lower δ due to the more ef-
473 ficient purge (compared to the other models of selection) of the deleterious
474 allele.

475 4.2. Demographic consequences of the genetic load

476 Previous models studying the effect of the genetic load on population
477 size have done so by decoupling the genetic and demographic models [14, 1],
478 have focused on density-dependent selection with no mutation [8, 40], or if
479 selection was density independent, it occurred between the zygote and adult

480 stage [8]. Our main goal is to provide a general framework in which both
481 the genetic and demographic properties of populations at mutation-selection
482 balance are explicitly taken into account in order to evaluate whether the
483 decoupling of genetics and demography in previous models is justified. In
484 this work we have therefore allowed for both the genetic and demographic
485 variables to be emerging properties. In this particular demographic scenario
486 we find that although the genetic parameters do influence the observed de-
487 mographic equilibrium, the demographic parameters (density dependence K
488 and the birth and death rates, b and d) have no effect on the genetic variables.
489 This could be related to the choice of a logistic density dependence, other
490 forms of competition will need to be explored. In [39] the authors find that
491 the interaction between spatial structure and density dependence leads to an
492 observed increase in the genetic load and inbreeding depression. However,
493 density dependence alone has very little effect on the genetic properties of
494 populations. Our model allows us to recover this feature, however, as we do
495 not incorporate stochasticity, some feed-back may have been missed.

496 In agreement with existing models [47, 8, 14, 1] population size depends
497 greatly on the timing/form of selection considered. When selection occurs
498 at a stage where resources are not wasted, then population size is not af-
499 fected [1], which corresponds to selection on adult survival (model A). The
500 assumption made is that non-viable adults are considered to be present for
501 a sufficient amount of time to be censused, but not to compete for resources
502 or mates with viable, reproducing adults. All other models of selection show
503 a direct link between the genetic load and population size (as in equation
504 17.1b of [40]).

505 Selection on Fecundity and Zygote Survival (models F and Z respectively)
506 lead to the same equilibrium population size as in both cases, adults that pro-
507 duce less offspring (either because they have a lower reproductive capacity or
508 because their offspring are not viable) take up the same amount of resources
509 as adults with a high reproductive capacity. This creates a lag, even though
510 we did not explicitly introduce this (as for example in [1] where resources
511 are considered available at a certain rate). For model Z it is the load at the
512 zygote stage, and not the observed load in the adult population, that de-
513 fines the effect on population size. This is intuitive enough as resources are
514 invested in producing non-viable zygotes at a rate equivalent to the genetic
515 load before selection has acted. Reproductive success has the strongest effect
516 on population size, decreasing it by the square of the population's fitness.
517 This is because the genotype of both parents must be taken into account

518 when producing a zygote. It is therefore the multiplicative fitness of all mat-
519 ing pairs that determines the probability of a successful reproductive event,
520 leading to higher demographic consequences than when the reproductive out-
521 put depends only on the quantity of gametes and hence on mean individual
522 fitness (i.e. selection on Fecundity).

523 *4.3. Implications for the evolution of self-fertilisation*

524 When comparing genetic variables at mutation-selection balance from
525 discrete and continuous time models in the presence of self-fertilisation, we
526 find that there are two important differences. First, the purge of deleterious
527 mutations is less efficient at higher rates of selfing and stronger coefficients
528 of selection, and second there is a higher frequency of heterozygotes than
529 expected in discrete time models. Though this has little effect on the genetic
530 load (see Figure 2), the level of inbreeding depression does not decrease as
531 much with self-fertilisation as it does in discrete time (see Figure 4). Indeed,
532 even though conventional population genetics models predict low levels of in-
533 breeding depression in selfing populations, our results concord with empirical
534 observations of high levels of inbreeding depression in highly selfing species
535 [48]. When considering exclusively perennial species, the general consensus is
536 that they maintain higher levels of inbreeding depression, and such observa-
537 tions have been contributed to selective interference [48]. However, selective
538 interference due to highly recessive mutations should lead to very high levels
539 of inbreeding depression (close to 1, [30]), and this is not observed in the
540 data presented in [48], where the highest levels of inbreeding depression in
541 perennials is close to 0.87. We find that overlapping generations suffice in
542 generating higher levels of inbreeding depression. This result could be further
543 accentuated if linkage were taken into account, and would require the devel-
544 opment of a more complex model involving two loci. The main implication of
545 this result is that if overlapping generations lead to the maintenance of higher
546 levels of inbreeding depression, self-fertilisation should not evolve as easily in
547 perennial populations (as a transition from an outcrossing to self-fertilising
548 regime requires that the level of inbreeding depression be sufficiently small
549 (e.g. [11]).

550 Using our definitions of fitness, an unfit individual that arrives to adult-
551 hood has as much probability of remaining a part of the population and
552 contributing to its genetic load and inbreeding depression as a fit individual.
553 There is no need to assume that lower reproductive capacity is necessarily

554 accompanied by a lower viability [36]. Our results therefore differ from pre-
555 vious theoretical works [32] where perenniality was accompanied by a more
556 efficient purge of deleterious mutations. Deleterious mutations that do not
557 affect longevity are more easily maintained in such a population, with deleterious
558 mutations acting at early life stages being found at a reduced frequency
559 among the surviving adults.

560 Though the demographic and genetic assumptions presented in this model
561 are very simplistic, our results imply that self-fertilisation is not only genet-
562 ically advantageous but can also be so demographically. The more efficient
563 purging of deleterious mutations compared to outcrossing [10, 20, 50] leads to
564 a lower genetic load and a higher population size in general. Due to this lower
565 genetic load, population size, if affected by load, is then expected to be higher
566 than for outcrossing populations. However, for populations with equivalent
567 load, selection on traits directly influencing reproductive success (not the
568 quantity of gametes but the efficiency in producing zygotes), self-fertilisation
569 could still lead to an increased population size if selection decreases perfor-
570 mance in a trait linked to reproductive success. This is because a very fit
571 individual would risk lowering its reproductive success if it reproduces with
572 another potentially unfit individual, making it less risky to self-fertilise. Se-
573 lection on such traits could further facilitate the evolution of self-fertilisation
574 by increasing an individual's reproductive success if it self-fertilises not be-
575 cause of producing purged offspring, nor by providing reproductive assurance
576 [2], but simply because an individual's reproductive output has not been "di-
577 luted" by less fit mates.

578 Our results support that more general models combining both genetics
579 and demography, allowing for the exploration of different modes of selection
580 and life-histories (discrete v.s. continuous time) can provide insight into the
581 ecological and evolutionary consequences of the genetic load.

582 **Acknowledgements**

583 A special thanks goes out to Clotilde Lepers for our inspiring discus-
584 sions. This work benefited from the support of the Chair "Modélisation
585 Mathématique et Biodiversité" of Veolia Environnement - École Polytech-
586 nique - Muséum National d'Histoire Naturelle - Fondation X, the French
587 Agence Nationale de la Recherche Modèles Aléatoires en Écologie, Génétique
588 et Évolution (MANEGE; ANR-09-BLAN-0215) and the French Agence Na-
589 tionale de la Recherche ANR-11-BSV7- 013-03. Viet Chi Tran was supported

590 in part by the Labex CEMPI (ANR-11-LABX-0007-01).

591 References

- 592 [1] A. F. Agrawal and M. C. Whitlock. Mutation load: The fitness of in-
593 dividuals in populations where deleterious alleles are abundant. *Annual*
594 *Review of Ecology and Systematics*, 43:115–135, 2012.
- 595 [2] H. G. Baker. Self compatibility and establishment after long distance
596 dispersal. *Evolution*, 9:347–349, 1955.
- 597 [3] T. Bataillon and M. Kirkpatrick. Inbreeding depression due to mildly
598 deleterious mutations in finite populations: size does matter. *Genetics*
599 *Research*, 75:75–81, 2000.
- 600 [4] A. Baudisch. *Inevitable Aging?: Contributions to Evolutionary-*
601 *Demographic Theory*. Demographic Research Monographs. Springer
602 Berlin Heidelberg, 2008.
- 603 [5] W. F. Bodmer. Differential fertility in population genetics models. *Ge-*
604 *netics*, 51(3):411–424, Mar 1965.
- 605 [6] D. Byers and D. Waller. Do plant populations purge their genetic load?
606 Effects of population size and mating history on inbreeding depression.
607 *Annual Review of Ecology and Systematics*, 30:479–513, 1999.
- 608 [7] B. Charlesworth. Selection in populations with overlapping generations.
609 i. the use of malthusian parameters in population genetics. *Theoretical*
610 *Population Biology*, 1(3):352–370, Nov 1970.
- 611 [8] B. Charlesworth. Selection in density-regulated populations. *Ecology*,
612 52:469–474, 1971.
- 613 [9] B. Charlesworth. *Evolution in Age-Structured Populations*. Cambridge
614 University Press, second edition, 1994. Cambridge Books Online.
- 615 [10] D. Charlesworth. Effects of inbreeding on the genetic diversity of popu-
616 lations. *Philosophical transactions of the Royal Society of London Series*
617 *B-Biological Sciences*, 358:1051–1070, JUN 29 2003.

- 618 [11] D. Charlesworth and B. Charlesworth. Inbreeding depression and its
619 evolutionary consequences. *Annual Review of Ecology and Systematics*,
620 18:237–268, 1987.
- 621 [12] D. Charlesworth, M. T. Morgan, and B. Charlesworth. Inbreeding de-
622 pression, genetic load, and the evolution of outcrossing rates in a multi-
623 locus system with no linkage. *Evolution*, 44(6):1469–1489, SEP 1990.
- 624 [13] B. Clarke. Density-dependent selection. *American Naturalist*,
625 106(947):1–&, 1972.
- 626 [14] B. Clarke. Mutation and population size. *Heredity*, 31:367–379, 1973.
- 627 [15] J. F. Crow and M. Kimura. *An introduction to population genetic theory*.
628 Harper and Row, New York, 1970.
- 629 [16] J. Duminil, K. Dainou, D. K. Kaviriri, P. Gillet, J. Loo, J.-L. Doucet,
630 and J. Hardy. Relationships between population density, fine-scale ge-
631 netic structure, mating system and pollen dispersal in a timber tree from
632 african rainforests. *Heredity*, 116:295–303, 2016.
- 633 [17] R. A. Fisher. *The Genetical Theory of Natural Selection*. Oxford Uni-
634 versity Press, Oxford, 1930.
- 635 [18] R. A. Fisher. Average excess and average effect of a gene substitution.
636 *Annals of Eugenics*, 11:53–63, 1941.
- 637 [19] J. H. Gillespie. *Population Genetics: A Concise Guide*. The John
638 Hopkins University Press, Baltimore, 2nd edition edition, 1998.
- 639 [20] S. Glémin. How are deleterious mutations purged? Drift versus nonran-
640 dom mating. *Evolution*, 57:2678–2687, DEC 2003.
- 641 [21] S. Glémin and J. Ronfort. Adaptation and maladaptation in selfing and
642 outcrossing species: new mutations versus standing variation. *Evolution*,
643 67:225–240, 2013.
- 644 [22] E. E. Goldberg, J. R. Kohn, R. Lande, K. A. Robertson, S. A. Smith,
645 and B. Igic. Species selection maintains self-incompatibility. *Science*,
646 330:493–495, OCT 22 2010.

- 647 [23] J. B. S. Haldane. A mathematical-theory of natural and artificial se-
648 lection part i. *Transactions of the Cambridge Philosophical Society*,
649 23(1-2):19–41, 1924.
- 650 [24] J. B. S. Haldane. A mathematical theory of natural and artificial selec-
651 tion, part v: Selection and mutation. *Mathematical Proceedings of the*
652 *Cambridge Philosophical Society*, 23:838–844, 7 1927.
- 653 [25] B. Iqic and J. W. Busch. Is self-fertilization an evolutionary dead end?
654 *New Phytologist*, 198(2):386–397, APR 2013.
- 655 [26] J. Kelly. Mutation-selection balance in mixed mating populations. *Jour-*
656 *nal of Theoretical Biology*, 246(2):355–365, 2007.
- 657 [27] M. Kirkpatrick and P. Jarne. The effects of a bottleneck on inbreeding
658 depression and the genetic load. *American Naturalist*, 155(2):154–167,
659 FEB 2000.
- 660 [28] R. Lande. Risk of population extinction from fixation of new deleterious
661 mutations. *Evolution*, 48:1460–1469, 1994.
- 662 [29] R. Lande and D. Schemske. The evolution of self-fertilization and in-
663 breeding depression in plants. i. genetic models. *Evolution*, 39(1):24–40,
664 1985.
- 665 [30] R. Lande, D. Schemske, and S. S.T. High inbreeding depression, selec-
666 tive interference among loci, and the threshold sefing rate for purging
667 recessive lethal mutations. *Evolution*, 48(4):965–978, AUG 1994.
- 668 [31] M. Lynch, J. Conery, and R. Burger. Mutational meltdowns in sexual
669 populations. *Evolution*, 49:1067–1080, 1995.
- 670 [32] M. Morgan. Consequences of life history for inbreeding depression and
671 mating system evolution in plants. *Proceedings of the Royal Society*
672 *B-Biological Sciences*, 268(1478):1817–1824, SEP 7 2001.
- 673 [33] M. Morgan, D. Schoen, and T. Bataillon. The evolution of self-
674 fertilization in perennials. *American Naturalist*, 150(5):618–638, NOV
675 1997.
- 676 [34] T. Nagylaki. Continuous selective models with mutation and migration.
677 *Theoretical Population Biology*, 5(2):284–295, Apr 1974.

- 678 [35] T. Nagylaki and J. F. Crow. Continuous selective models. *Theoretical*
679 *Population Biology*, 5(2):257–283, Apr 1974.
- 680 [36] H. A. Orr. Fitness and its role in evolutionary genetics. *Nature Reviews*
681 *Genetics*, 10(8):531–539, AUG 2009.
- 682 [37] T. L. Parsons, C. Quince, and J. B. Plotkin. Some Consequences of De-
683 mographic Stochasticity in Population Genetics. *Genetics*, 185(4):1345–
684 1354, AUG 2010.
- 685 [38] E. Porcher and R. Lande. Loss of gametophytic self-incompatibility with
686 evolution of inbreeding depression. *Evolution*, 59:46–60, JAN 2005.
- 687 [39] J. RONFORT and D. COUVET. A stochastic model of selection on
688 selfing rates in structured populations. *Genetical Research*, 65(3):209–
689 222, JUN 1995.
- 690 [40] J. Roughgarden. *Theory of population genetics and evolutionary ecology:*
691 *an introduction*. Macmillan New York NY United States 1979., 1979.
- 692 [41] D. Roze. Effects of interference between selected loci on the mutation
693 load, inbreeding depression and heterosis. *Genetics*, 201:745–757, 2015.
- 694 [42] D. Roze and F. Rousset. Joint effects of self-fertilization and popula-
695 tion structure on mutation load, inbreeding depression and heterosis.
696 *Genetics*, 167:1001–1015, 2004.
- 697 [43] D. Scofield and S. Schultz. Mitosis, stature and evolution of plant mating
698 systems: low-Phi and high-Phi plants. *Proceedings of the Royal Society*
699 *B-Biological Sciences*, 273(1584):275–282, 2006.
- 700 [44] R. B. Spigler, J. L. Hamrick, and S.-M. Chang. Increased inbreeding
701 but not homozygosity in small populations of *sabatia angularis* (gen-
702 *tianaceae*). *Plant Systematics and Evolution*, 284(3):131–140, 2009.
- 703 [45] N. Takebayashi and P. L. Morrell. Is self-fertilization an evolution-
704 ary dead end? revisiting an old hypothesis with genetic theories and
705 a macroevolutionary approach. *American Journal of Botany*, 88:1143–
706 1150, 2001.
- 707 [46] M. Vlad. Separable models for age-structured population-genetics. *Jour-*
708 *nal of Mathematical Biology*, 26(1):73–92, 1988.

- 709 [47] B. Wallace. *Genetic Load. Its Biological and Conceptual Aspects*.
710 Prentice-Hal, Englewood Cliffs, New Jersey, 1970.
- 711 [48] A. A. Winn, E. Elle, S. Kalisz, P.-O. Cheptou, C. G. Eckert, C. Good-
712 willie, M. O. Johnston, D. A. Moeller, R. H. Ree, R. D. Sargent, and
713 M. Vallejo-Marin. Analysis of inbreeding depression in mixed-mating
714 plants provides evidence for selective interference and stable mixed mat-
715 ing. *Evolution*, 65(12):3339–3359, DEC 2011.
- 716 [49] I. Wolfram Research. *Mathematica*. Wolfram Research, Inc., Cham-
717 paign, Illinois, version 9.0 edition, 2012.
- 718 [50] S. I. Wright, S. Kalisz, and T. Slotte. Evolutionary consequences of
719 self-fertilization in plants. *Proceedings of the Royal Society B-Biological*
720 *Sciences*, 280(1760), JUN 7 2013.