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# The effect of the timing of selection on the mutation load, inbreeding depression and population size

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## ABSTRACT

1  
2 If and how the genetic load affects population size has been long debated  
3 as on one hand it has been suggested that a high genetic load leads to ex-  
4 tinction, and on the other hand, if selection during the life-cycle takes place  
5 before density dependence has acted, then population size should not be af-  
6 fected by its genetic load. Explicitly considering the life cycle and the timing  
7 of selection is therefore a factor that cannot be ignored when quantifying the  
8 effect of deleterious mutations on population size. In addition, population  
9 genetics models calculating the expected genetic loads and levels of inbreed-  
10 ing depression ignore the potential effects of demography on these variables.  
11 Here we propose a deterministic model in continuous time where deleterious  
12 mutations affect individual fitness in one of four ways: by decreasing mating  
13 success, fecundity and adult or zygote survival. The genetic load, inbreeding  
14 depression and population size are variables that emerge from the model.  
15 Our results are compared to the expectations from the fundamental model  
16 of natural selection. We find that changing the timing of selection mostly  
17 affects population size, but also leads to genetic loads and inbreeding depres-  
18 sion that diverge from the fundamental model. Our results emphasize the

19 importance of integrating both population demography and genetics in order  
20 to study the demographic impact and, more generally, the fate of deleterious  
21 mutations.

## INTRODUCTION

23 Deleterious mutations are constantly introduced into populations at rela-  
24 tively high rates (Keightley and Lynch, 2003). In spite of their deleterious  
25 effect, these alleles are not always immediately eliminated by selection from  
26 the genetic pool but can persist for several generations and, in the case of  
27 stochasticity, can even go to fixation. These mutations decrease mean popu-  
28 lation fitness by engendering a genetic or mutational load, and are responsible  
29 for inbreeding depression. In the field of population genetics, the evolution of  
30 load and inbreeding depression as a function of population size and structure  
31 has been greatly explored (Bataillon and Kirkpatrick, 2000; Roze and Rous-  
32 set, 2004; Glémin, 2003). However, these models do not consider an explicit  
33 interaction between the two, as population size is considered to be a parame-  
34 ter. If and how these mutations affect population size remains unclear; while  
35 inbreeding depression is a major concern in conservation biology, whether the  
36 genetic load of populations affects population size and viability is debatable.  
37 In the case of very small populations, it is widely accepted that they can be  
38 at risk of a mutational meltdown (extinction due to the fixation of deleterious  
39 alleles at an accelerating rate; Lande, 1994; Lynch et al., 1995; Coron et al.,

2013), but there is little understanding of how the genetic load affects the demography of populations that are not at risk of extinction. We find two opposing views in literature (reviewed in Agrawal and Whitlock, 2012); some authors argue that populations cannot persist with high mutation or genetic loads (Kondrashov, 1995), whereas others have insisted that load has little or no ecological consequences (Turner and Williams, 1968; Wallace, 1970). In the latter case, authors have argued that due to density dependence, deaths of individuals due to selection simply replace the unavoidable deaths due to a lack of resources (soft selection), whereas in the former case, the genetic load is expected to directly decrease population size, independently of density dependent factors (hard selection). The main difference between these two types of selection is the timing of the elimination of individuals via selection, either before resource consumption (soft selection) or after these resources have been used and rendered inaccessible (hard selection). In a model proposed by Agrawal and Whitlock (2012), the authors came to the conclusion that if individuals are eliminated by selective death before having consumed any resources (i.e. at the zygote stage), then the genetic load would not affect population size, as the loss of juveniles would be “masked by ecological compensation”.

59 The life stage at which selection takes place, or as we refer to it, the  
60 timing of selection, is therefore non-negligible when considering the effect  
61 of the genetic load on population size (Wallace, 1970; Charlesworth, 1971;  
62 Clarke, 1973). However, population size is not only affected by the timing  
63 of resource consumption but more generally by the ecological trait affected  
64 (Clarke, 1973). Models that have studied the ecological consequences of  
65 differences in fitness related traits between individuals and/or species (such  
66 as competitive abilities, death rates and reproductive rates) have come to  
67 the conclusion that they can affect population size (for example Abrams,  
68 2003; Abrams et al., 2003; Schreiber and Rudolf, 2008). However, these  
69 models consider only phenotypic traits and do not take into account the  
70 genetics that could be behind the differences in phenotypes. The only work  
71 to our knowledge to explicitly consider ecology and genetics is a paper by  
72 Clarke (1973) in which the author coined the term "numerical load" (the  
73 demographic equivalent of the genetic load) the decrease of population size  
74 due to the presence of deleterious mutations, a term which we will be using  
75 throughout this paper. Clarke (1973) proposed a model where population size  
76 is a consequence of the effect of the genetic load on different life traits, and  
77 where selection takes place either before or after density-dependent factors



78 come into play. He found that in both cases, the genetic load leads to a  
79 numerical load, but in the former case density-dependent factors partially  
80 compensate for density-independent mortality, leading to a smaller numerical  
81 load. His overall conclusions agree with the results of ecological models; if  
82 the genetic load affects ecological traits, then population size is also affected.  
83 The magnitude of the effect of the genetic load on the numerical load in  
84 turn depends on the traits affected by selection (i.e. a same genetic load on  
85 different traits can lead to different numerical loads).

86 A limitation of the model proposed by Clarke (1973) is that it consid-  
87 ers a genetic load that evolves independently of the demographic model and  
88 the timing of selection. The relative selective values he proposed were con-  
89 structed so as to ensure that the genetic load remains equal to that expected  
90 from the fundamental model of population genetics (Gillespie, 1998, p.61).  
91 The genetic load is expected to directly affect a measure of individual or pop-  
92 ulation fitness and fitness has been defined as being an individual's (or geno-  
93 type's) mating success, fecundity or survival (Agrawal and Whitlock, 2012).  
94 While expected to be of great importance in demographic models (Haldane,  
95 1957; Agrawal and Whitlock, 2012), the timing of selection is considered to  
96 be of no importance when calculating the genetic load or inbreeding depres-

97 sion in population genetics models, and selection has been interpreted as  
98 affecting either zygote survival (e.g. Gillespie, 1998) or reproductive success  
99 (e.g. Roze and Rousset, 2004). However, explicitly considering the life cycle  
100 could affect how selection acts, leading to a genetic load and an amplitude  
101 of inbreeding depression that depend on the timing of selection. Indeed, it  
102 has been observed in several species that the amplitude of inbreeding depres-  
103 sion expressed can vary between traits (Frankham et al. 2010, Chapter 13;  
104 Angeloni et al. 2014).

105 It has been suggested that the ambiguity of what is found in literature  
106 concerning the effect of the genetic load on population size could be due  
107 to a lack of theoretical works that attempt to address this question using  
108 "explicit ecological models" (Agrawal and Whitlock, 2012). In this present  
109 work we attempt to address the question of how the introduction of recurrent  
110 deleterious mutations into a population (whose size is affected by selection)  
111 influences the genetic load, the numerical load and inbreeding depression. We  
112 propose a deterministic model where the number of individuals carrying each  
113 genotype is considered explicitly. In the presence of selection, genotypes differ  
114 in their selective values at a single trait, and there is no density or frequency-  
115 dependent effect on fitness. We consider selection at four traits considered

116 to represent fitness: mating success, fecundity, zygote survival and adult  
117 survival. Population size, the genetic load and inbreeding depression are all  
118 emerging properties of the model.

## 119 ANALYTICAL MODEL

120 We consider the evolution of a population with a varying population size and  
121 a single bi-allelic locus, where  $A$  is the wild-type and  $a$  the mutant allele. The  
122 population is panmictic and made up of sexually reproducing hermaphrodite  
123 individuals. The environment is stable, and the population is isolated and  
124 spatially unstructured. Three genotypes can be found in the population,  $aa$ ,  
125  $Aa$  and  $AA$ , which, from here onwards, are denoted  $X$ ,  $Y$ , and  $Z$  respectively.  
126 At a given time  $t$ , the population is made up of three kinds of individuals,  
127  $X_t$ ,  $Y_t$  and  $Z_t$  representing the number of individuals carrying the respective  
128 genotype. We denote the population size  $N_t = X_t + Y_t + Z_t$ . In a large  
129 population setting, these quantities can be considered as continuous, and  
130 the evolution of the number of individuals of each genotype is described in  
131 continuous time using ordinary differential equations. Three processes affect  
132 the change in the number of individuals of each genotype, births (occurring

133 with rate  $R_t^V$ , where  $V$  can be either  $X$ ,  $Y$  or  $Z$ ), deaths (at a rate  $M_t^V$ )  
134 and mutation. Selection and density dependence are introduced in these  
135 processes. We consider that the mutation from  $A$  to  $a$  is unidirectional and  
136 occurs with a probability  $\mu$  at the gamete stage.

137 We first introduce the demographic and mutational properties of the  
138 model without considering selection and show that this model respects the  
139 genotypic frequencies predicted by the Hardy-Weinberg model for neutral  
140 alleles (and no mutation). Selection is then introduced during different mo-  
141 ments of the life cycle and we define the variables measured in order to esti-  
142 mate the effect of the recurrent introduction of deleterious mutations on the  
143 numerical load, the genetic load and inbreeding depression. In order to facil-  
144 itate the reading of the following sections, all the notations used throughout  
145 the text have been summarized in Table 1.

#### 146 **Model without selection**

147 As we consider mutations occurring during gamete formation, the proportion  
148 of  $a$  gametes produced per genotype are  $1$ ,  $\frac{1+\mu}{2}$  and  $\mu$  for  $X$ ,  $Y$  and  $Z$   
149 individuals respectively. Mutational events are therefore integrated into the  
150 birth rate  $R_t^V$ ; for example, as  $Z$  individuals produce a proportion  $\mu$  of  $a$

Table 1: **Notations.**

$\Lambda, L, \delta$	The numerical load, the genetic load and inbreeding depression.
$N_t, N_{eq}$	Population size at time $t$ with or with selection, and population size at equilibrium when there is no selection.
$V_t, \tilde{V}_t$	The total number of either $X$ , $Y$ or $Z$ individuals (with genotypes $aa$ , $Aa$ and $AA$ respectively) at time $t$ , and the number of individuals at time $t$ that contribute to the genetic pool.
$N_{mut}, V_{mut}$	Population size and number of $V$ individuals at mutation-selection balance.
$R_t, M_t$	The total birth and death rates of the population at time $t$ .
$R_t^V, M_t^V$	The birth and death rates of individuals of genotype $V$ at time $t$ .
$b, d$	The intrinsic birth and death rates of individuals.
$s, h$	The coefficient of selection and dominance of allele $a$ . The relative fitnesses of $X$ , $Y$ and $Z$ individuals at a given trait are $(1 - s)$ , $(1 - hs)$ and 1 respectively.
$\mu, \mu_{fix}$	The mutation rate from $A$ to $a$ and the threshold value of $\mu$ for which there is deterministic fixation of $a$ .

151 gametes and  $(1 - \mu)$  of  $A$  gametes. When two  $Z$  individuals are crossed, they  
 152 produce  $X$ ,  $Y$  and  $Z$  offspring with proportions  $\mu^2$ ,  $2\mu(1 - \mu)$  and  $(1 - \mu)^2$   
 153 respectively. For each reproductive pair, the parents contribute both via the  
 154 male and the female functions. We consider that the total number of female  
 155 gametes produced by all individuals in the population is limited and, when  
 156 there is no selection, depends only on the number of individuals, whereas male  
 157 gametes are produced in very large quantities and are subject to competition.  
 158 The probability that an individual reproduces via the male function depends  
 159 on the proportion of male gametes contributed compared to the total amount  
 160 of male gametes available. For example, when the  $X$  and  $Y$  individuals cross  
 161 to give  $X$  individuals,  $X$  individuals contribute  $X_t$  ovules and a proportion  
 162 of  $\frac{X_t}{N_t}$  male gametes, while  $Y$  individuals contribute  $(1 + \mu)\frac{Y_t}{2}$  ovules and a  
 163 proportion of  $(1 + \mu)\frac{Y_t}{2N_t}$  male gametes (as only  $\frac{(1+\mu)}{2}$  of the gametes produced  
 164 carry an  $a$  allele).

Generally, the equation describing the change in the number of individuals  
 for each genotype is given by

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

For each of the genotypes, when there is mutation and no selection, the

birth rate  $R_t^V$  is given by

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

The birth rate depends on an intrinsic birth rate  $b$ , which, by default, holds the same value for all genotypes, on the reproductive events that lead to the production of new individuals with genotype  $V$  and on the mutation rate  $\mu$ . The death rate  $M_t^V$  depends on an intrinsic death rate  $d$  and is density dependent (we consider a carrying capacity  $K$ ). The equation for  $M_t^V$  is given by

$$M_t^V = d \frac{N_t}{K} V_t. \quad (2)$$

When solving  $\frac{dN}{dt} = \frac{dX}{dt} = \frac{dY}{dt} = \frac{dZ}{dt} = 0$  we find the optimal population size is given by (see File S4 for the proof)

$$N_{eq} = \frac{bK}{d}. \quad (3)$$

165 If we consider that there is neither selection nor mutation ( $\mu = 0$ ), then we  
166 find that the frequencies of  $X$ ,  $Y$  and  $Z$  are at Hardy-Weinberg equilibrium  
167 (see File S3). Explicitly considering the demography of a population leads

168 to the same genotypic frequencies at a neutral locus as those predicted by  
169 deterministic population genetics models. This implies that, once selection is  
170 introduced, any differences observed between our model and the fundamental  
171 model of natural selection are due to the interaction between the timing of  
172 selection and demography.

### 173 **Timing of selection**

174

175 Fitness can be defined as being an individual's relative mating success, fe-  
176 cundity or survival either at the zygote or adult stages. We consider all four  
177 definitions of fitness. Selection can occur at different times during the life  
178 cycle, affecting either reproduction or survival. As  $a$  is deleterious,  $Z$  individ-  
179 uals always have the maximal fitness. The relative fitness of each genotype  
180 at a given trait (i.e. its reproductive rate or survival) is equal to  $(1 - s)$ ,  
181  $(1 - hs)$  and 1 for genotypes  $X$ ,  $Y$  and  $Z$  respectively, where  $s$  is the selec-  
182 tion coefficient and  $h$  the dominance of the mutant allele  $a$ . If we consider  
183 that  $a$  affects the inherent birth rate, then if the inherent birth rate of  $Z$   
184 individuals is  $b^Z$  and the inherent birth rate of  $X$  individuals is  $b^X$ , then the  
185 relative fitness of  $X$  individuals is  $\frac{b^X}{b^Z} = (1 - s)$ .



186 **Selection on reproduction:** In order to model the effect of the deleterious  
187 allele  $a$  on the reproductive success of individuals, we introduce a new term  
188  $\tilde{V}_t$  instead of  $V_t$  in the  $R_t^V$  function. This term represents the contribution  
189 of  $V$  individuals to the genetic pool, which is proportional to their fitness  
190 and can reduce their reproductive success (i.e.  $\tilde{X}_t = (1 - s)X_t$ ). There are  
191 two ways in which carrying  $a$  can affect reproductive success; it can reduce  
192 the mating success of individuals (i.e. for  $X$  individuals only a proportion  
193 of  $(1 - s)$  matings are successful or lead to fertilization) or by reducing the  
194 fecundity of individuals (i.e.  $X$  individuals produce a proportion  $(1 - s)$   
195 gametes compared to  $Z$  individuals).

*Mating success:* When mating success is reduced, all individuals produce the same quantity of gametes and the proportion of male gametes an individual  $V$  contributes to the next generation is  $\frac{\tilde{V}_t}{N_t}$ . The probability of a successful reproductive event is proportional to the parental fitnesses. For example,  $R_t^X$  for this model of selection is given by

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

*Fecundity:* When fecundity is affected by selection, an individual  $V$  contributes  $\tilde{V}_t$  female gametes and a proportion of  $\frac{\tilde{V}_t}{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}$  male gametes to the next generation (the proportion of male gametes produced by  $V$  depends on the total amount of male gametes produced and not on the number of individuals in the population). For example

$$R_t^X = \frac{b}{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t} \left( \tilde{X}_t^2 + 2\tilde{X}_t\tilde{Z}_t\mu + \tilde{Z}_t^2\mu^2 + \tilde{X}_t\tilde{Y}_t(1 + \mu) + \tilde{Y}_t\tilde{Z}_t\mu(1 + \mu) + \frac{1}{4}\tilde{Y}_t^2(1 + \mu)^2 \right). \quad (5)$$

196 The full equations for the change in the number of individuals of each  
 197 genotype for these models can be found in File S2. Note that in both models  
 198 with selection on reproduction the probability of reproduction via the fe-  
 199 male function remains unaffected as we consider that there is no competition  
 200 between the female gametes.

201 **Selection on survival:** Selection can also occur during the life cycle, in-  
 202 dependently of reproductive success, affecting either zygote or adult survival.  
 203 Zygote survival can be translated as the proportion of germinating seeds, or,  
 204 more generally, viable offspring. Selection on adult survival is considered to  
 205 occur before reproduction.

*Zygote survival:* The probability of zygote survival is decreased by considering a birth rate  $R_t^V$  that is genotype dependent. This can be done by introducing a term  $b^V$ , an intrinsic birth rate that is proportional to the genotype's fitness. For example,  $b^X = (1 - s)b$  and

$$R_t^X = \frac{b(1 - s)}{N_t} \left( X_t^2 + 2X_tZ_t\mu + Z_t^2\mu^2 + X_tY_t(1 + \mu) + Y_tZ_t\mu(1 + \mu) + \frac{1}{4}Y_t^2(1 + \mu)^2 \right). \quad (6)$$

206 The full equations for the change in the number of individuals of each geno-  
207 type can be found in the File S2.

*Adult survival:* We consider that the number of adults that survive selection before reproduction of genotype type  $V$  is  $\tilde{V}$ , hence proportional to their fitness. As only surviving individuals reproduce and compete for resources,  $V$  is replaced by  $\tilde{V}$  in the birth rate  $R_t^V$  and in the death rate  $M_t^V$ . Therefore we obtain the same expression for  $R_t^V$  as for selection on fecundity and  $M_t^V$  is given by

$$M_t^V = d \frac{\tilde{X}_t + \tilde{Y}_t + \tilde{Z}_t}{K} qV_t. \quad (7)$$

208 The full equations for the change in the number of individuals of each geno-  
209 type can be found in File S2.

In order to understand how the interaction between selection and population demography affects population size and the frequency of a recurrent deleterious mutation, we derive the deterministic expectations at mutation-selection balance for each of the models of selection described above (mating success, fecundity and zygote and adult survival) by solving  $\frac{dX_t}{dt} = \frac{dY_t}{dt} = \frac{dZ_t}{dt} = 0$ . This allows us to obtain the number of individuals carrying each genotype at mutation-selection balance ( $X_{mut}$ ,  $Y_{mut}$  and  $Z_{mut}$ ), the sum of which gives us the population size at equilibrium  $N_{mut}$ . Using  $N_{mut}$  we obtain the expression for the numerical load  $\Lambda$  (the decrease of population size due to the presence of deleterious mutations), a term defined by Clarke (1973) and given by

$$\Lambda = \frac{N_{eq} - N_{mut}}{N_{eq}}, \quad (8)$$

where  $N_{eq}$  is the population size at equilibrium when there is no selection ( $s = 0$ , see equation 3). We also use the expressions for  $X_{mut}$ ,  $Y_{mut}$  and  $Z_{mut}$  to derive the expressions for the genetic load  $L$  and inbreeding depression  $\delta$ , which we then compare. We also compare the genetic load  $L$  and inbreeding depression  $\delta$  that emerge from our model to those expected from the fun-

damental model of natural selection. In order to compare our results to the fundamental model of natural selection, we replace  $X_{mut}$ ,  $Y_{mut}$  and  $Z_{mut}$  with  $q^2$ ,  $2q(1-q)$  and  $(1-q)^2$  respectively, where  $q$  is the frequency of the deleterious mutant  $a$  at mutation-selection balance. Using the equations given by Gillespie (1998, p.71), the explicit expression for  $q$  is

$$q = \frac{2\mu}{h(s + 2s\mu) + \sqrt{s(4\mu(1 + \mu) - 8h\mu(1 + \mu) + s(h + 2h\mu)^2)}}. \quad (9)$$

The genetic load  $L$  is defined as the decrease in population fitness due to the presence of deleterious mutations and is calculated by transforming the equation for population fitness of the fundamental model (Gillespie, 1998, p.61):

$$L = 1 - \frac{(1-s)X_{mut} + (1-hs)Y_{mut} + Z_{mut}}{N_{mut}} \quad (10)$$

Inbreeding depression  $\delta$  is defined as the difference in fitness between offspring produced via selfing and via outcrossing. We calculate it using equation 3 in Roze and Rousset (2004):

$$\delta = 1 - \frac{(1-s)X_{mut} + \left(\frac{1}{4} + \frac{1-hs}{2} + \frac{1-s}{4}\right)Y_{mut} + Z_{mut}}{(1-s)X_{mut} + (1-hs)Y_{mut} + Z_{mut}}. \quad (11)$$

211 For all four models of selection, there exists a solution where the popula-  
 212 tion is made entirely of  $X$  individuals. There is therefore a threshold value  
 213 of the mutation rate  $\mu$ , as a function of the selection coefficient  $s$  and the

214 dominance  $h$ , which leads to the deterministic fixation of  $a$ . This threshold  
215 value is noted  $\mu_{fix}$  and is calculated by solving the equations for  $\mu$  when  
216 considering that  $N_{mut}$  is equal to  $X_{mut}$ . In order to calculate the fixation  
217 threshold in the fundamental model, we solve for  $\mu$  when  $q$  (equation 9) is  
218 equal to 1.

## 219 RESULTS

220 Our purpose is to find explicit solutions for population size  $N_{mut}$ , the nu-  
221 merical load  $\Lambda$ , the genetic load  $L$  and inbreeding depression  $\delta$  at mutation-  
222 selection balance for all four models of selection (mating success, fecundity  
223 and zygote and adult survival). The full expressions (valid for all parameter  
224 values when  $h \neq 0.5$ ) can be found in Table S1 of the Supporting Information,  
225 as for the sake of legibility, we present only the expressions for recessive and  
226 co-dominant mutations ( $h = 0$  and  $h = 0.5$  respectively) in the main text in  
227 Table 2. For  $h \neq 0$ , the expressions were found by using Wolfram's Mathe-  
228 matica 9.0 (Wolfram Research, 2012), whereas the proofs for population size  
229 for  $h = 0$  can be found in File S4. The expressions for the frequencies of each  
230 genotype at mutation selection balance are also in the File S3. The domain

Model	$h$	$N_{mut}$	$\Lambda$	$L$	$\delta$	$\mu_{fix}$
Mating success	0	$N_{eq}(1 - \mu)^2$	$2\mu - \mu^2$	$\mu$	$\frac{\sqrt{\mu s} - \mu}{2(1 - \mu)}$	$s$
	0.5	$N_{eq} \frac{(1 - \mu)^2}{(1 + \mu)^2}$	$\frac{4\mu}{(1 + \mu)^2}$	$\frac{2\mu}{1 + \mu}$	0	$\frac{s}{2 - s}$
Fecundity	0	$N_{eq}(1 - \mu)$	$\mu$	$\mu$	$\frac{\sqrt{\mu s} - \mu}{2(1 - \mu)}$	$s$
	0.5	$N_{eq} \frac{1 - \mu}{1 + \mu}$	$\frac{2\mu}{1 + \mu}$	$\frac{2\mu}{1 + \mu}$	0	$\frac{s}{2 - s}$
Adult survival	0	$N_{eq}$	0	$\mu$	$\frac{\sqrt{\mu s} - \mu}{2(1 - \mu)}$	$s$
	0.5	$N_{eq}$	0	$\frac{2\mu}{1 + \mu}$	0	$\frac{s}{2 - s}$
Zygote survival	0	$N_{eq}(1 - \mu)$	$\mu$	$\frac{\mu(1 - s)}{1 - \mu}$	$\frac{\sqrt{\mu s} - \mu}{2 - 2\mu(2 - s)}$	$s$
	0.5	$N_{eq} \frac{1 - \mu}{1 + \mu}$	$\frac{2\mu}{1 + \mu}$	$\frac{\mu(2 - \mu s - s)}{1 + \mu^2}$	0	$\frac{2}{2 - s}$
<b>Fundamental model</b>	0	—	—	$\frac{\mu}{1 + \mu}$	$\frac{\sqrt{(1 + \mu)\mu s} - \mu}{2}$	$\frac{s}{1 - s}$
	0.5	—	—	$\frac{2\mu}{1 + 2\mu}$	0	$\frac{s}{2(1 - s)}$

Table 2: Expressions for population size  $N_{mut}$ , numerical load  $\Lambda$ , genetic load  $L$ , inbreeding depression  $\delta$  and the threshold value of the mutation rate for deterministic fixation  $\mu_{fix}$  at mutation-selection balance for  $h = 0$  and 0.5 for selection on mating success, fecundity and zygote and adult survival, as well as the fundamental model of natural selection. Exact expressions or any  $h \neq 0.5$  obtained using Wolfram's Mathematica 9 are given in Table S1.

231 of validity of these expressions holds only when the deterministic fixation  
232 of  $a$  is not possible (see the expressions for  $\mu_{fix}$  in Table 2 and File S1 for  
233 the domain of validity for the equations in Table S1). If the conditions for  
234 fixation are met, there is only one valid solution, where  $N_{mut} = X_{mut}$ .

### 235 **The numerical load**

236

237 Introducing selection can lead to a decrease in population size at mutation-  
238 selection balance  $N_{mut}$  compared to the population size when there is no  
239 selection  $N_{eq}$  (equation 3). The only model that does not lead to a numerical  
240 load  $\Lambda$  is when selection affects adult survival. Concerning the other three  
241 models,  $\Lambda$  increases with the coefficient of selection  $s$  (Figure 1), the dom-  
242 inance  $h$  (Figure 1) and the mutation rate  $\mu$ . When selection is on zygote  
243 survival or on fecundity, we find the same expression for  $\Lambda$ , whereas selection  
244 on mating success leads to a different expression and a higher numerical load  
245 (see Table 2 and Table S1).



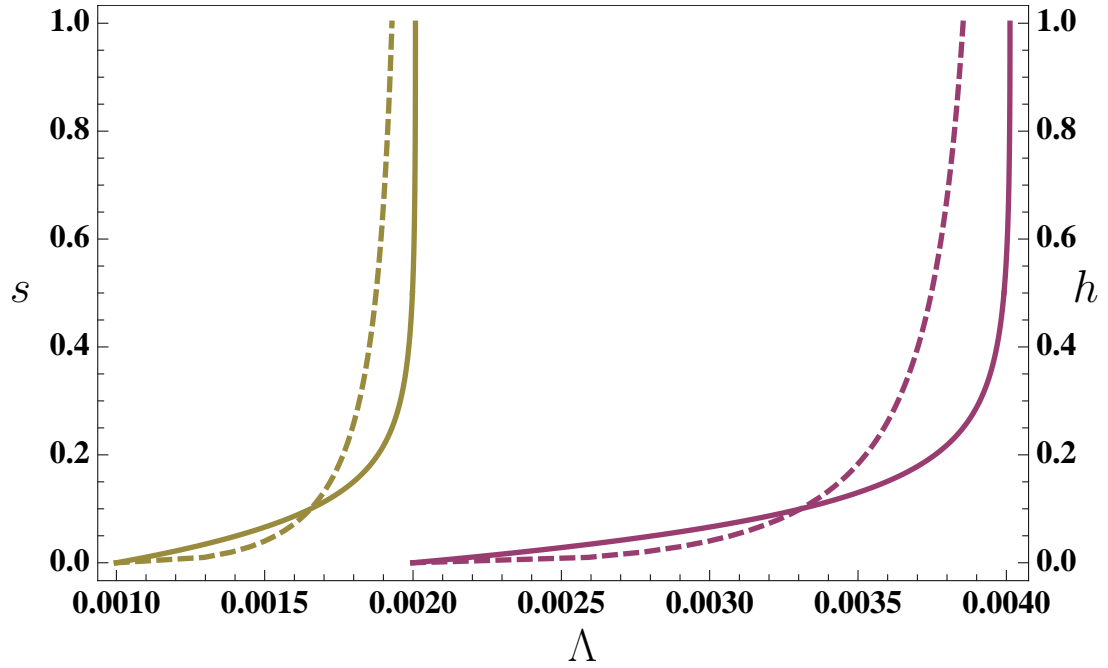


Figure 1: Numerical load  $\Lambda$  at mutation-selection balance as a function of the coefficient of selection  $s$  (dashed lines, for  $h = 0.1$  and  $\mu = 10^{-3}$ ) and as a function of dominance  $h$  (full lines, with  $s = 0.1$  and  $\mu = 10^{-3}$ ). Selection on mating success is represented in red, whereas selection on fecundity or on zygote survival are in yellow. Lines are plotted using the expressions in Table S1.

246 **The timing of selection and the genetic load**

247

248 The timing of selection affects the genetic load  $L$  at mutation-selection bal-  
249 ance both quantitatively and qualitatively (Figure 2). We find the same ex-  
250 pressions for  $L$  when selection is on mating success, fecundity and on adult  
251 survival. For these three models  $L$  increases with the coefficient of selection  
252  $s$  (Figure 2) and with dominance  $h$  (Figure 2). When selection affects zygote  
253 survival, there is a non-monotonic effect of both  $s$  and  $h$  on  $L$  (this effect  
254 becomes smaller with increasing mutation rates  $\mu$ , results not shown);  $L$  is  
255 therefore maximal for intermediate values of  $s$  and/or  $h$ .

256 When  $s$  is small the timing of selection has very little effect on the value  
257 of  $L$ . However, increasing  $s$  increases the difference between the models, with  
258 a lower  $L$  at mutation-selection balance when selection is on zygote survival.  
259 In spite of the differences between the expressions for  $L$  when selection is on  
260 mating success, fecundity and adult survival and the expression for  $L$  from  
261 the fundamental model (see Table 2 and Supporting Information Table S1),  
262 numerically, they are very close as long as the mutation rate  $\mu$  is low. For  
263 higher values of  $\mu$ , the fundamental model predicts lower values of  $L$  than

264 our models. This can be deduced from the equations for  $L$  when mutations  
265 are completely recessive and codominant ( $h = 0$  and  $0.5$ , see Table 2), the  
266 difference between the equations for  $L$  with selection on reproduction and  $L$   
267 for the fundamental model is that the numerator is greater by a factor  $\mu$  for  
268 the fundamental model. As  $\mu$  increases, the difference between selection on  
269 reproduction and on survival becomes smaller until  $L$  at mutation-selection  
270 balance is slightly greater for selection on survival than on reproduction.

271 From the fundamental model, the frequency of each genotype at equilib-  
272 rium is expected to be  $q^2$ ,  $2q(1 - q)$  and  $(1 - q)^2$ , for  $X$ ,  $Y$  and  $Z$  individuals  
273 respectively, where  $q$  is the frequency of  $a$  after selection. This relation-  
274 ship is no longer true in our model, except when mutations are co-dominant  
275 ( $h = 0.5$ ) and selection is not on zygote survival (see frequencies of geno-  
276 types in Supporting Information Section C.2.). When selection is on zygote  
277 survival, the frequency of  $X$  individuals is reduced by a factor  $(1 - s)$  as  
278 selection directly affects the introduction of  $a$  alleles via mutation, and so  
279 the introduction of new  $X$  and  $Y$  individuals.

280 The timing of selection not only affects the numerical load  $\Lambda$  and the ge-  
281 netic load  $L$ , but also the interaction between the two at mutation-selection  
282 balance. When plotting  $\Lambda$  as a function of  $L$  (see Figure 3), selection on

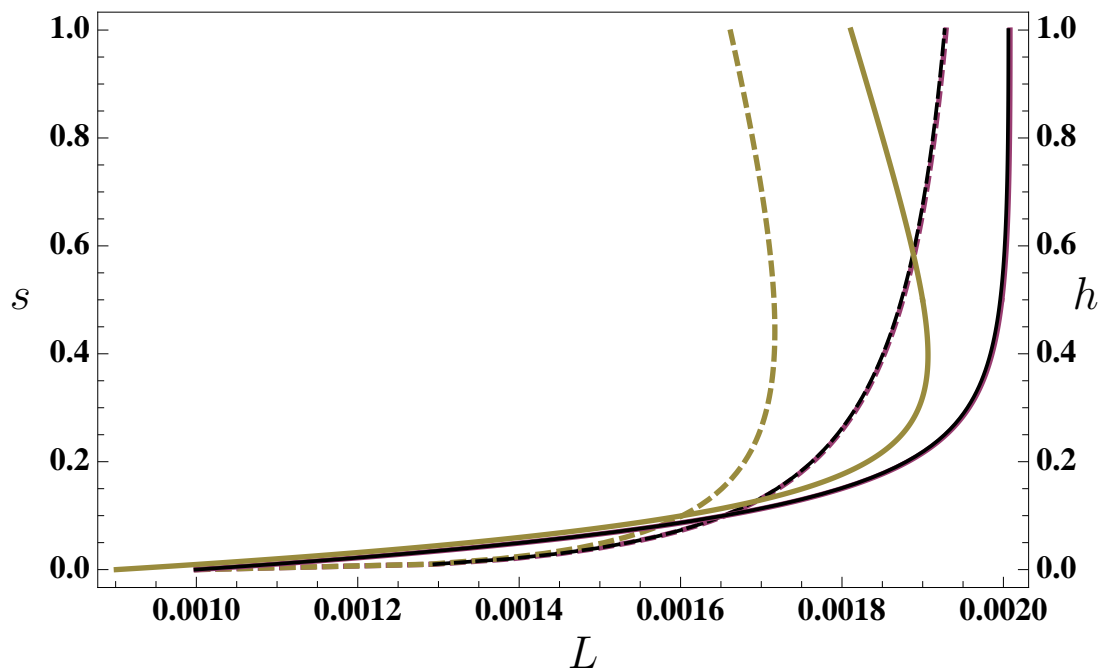


Figure 2: Genetic load  $L$  at mutation-selection balance as a function of the coefficient of selection  $s$  (dashed lines, for  $h = 0.1$  and  $\mu = 10^{-3}$ ) and as a function of dominance  $h$  (full lines, with  $s = 0.1$  and  $\mu = 10^{-3}$ ). Selection on mating success, fecundity or adult survival are represented in red, selection on zygote survival in yellow and the fundamental model in black. Lines are plotted using the expressions in Table S1.

283 mating success or on fecundity leads to a positive linear relationship between  
284  $\Lambda$  and  $L$ ; population size decreases with increasing genetic load. When selec-  
285 tion is on fecundity there is a direct and simple relationship between  $L$  and  
286  $\Lambda$  ( $L = \Lambda$ ) as can clearly be seen when comparing these expressions in Table  
287 2. When selection is on mating success or on survival, the relationship is not  
288 as simple. For example, in the latter case, we observe the same genetic load  
289 for small values of  $s$  and very large values of  $s$ , whereas the numerical load  
290 continually increases with  $s$ . In this case, the genetic load is not enough to  
291 explain population size, the deleterious effect of  $a$  must also be taken into  
292 account (see equations for  $L$  in Table 2 for selection on zygote survival).

### 293 **Inbreeding depression**

294

295 Selection on mating success, fecundity and adult survival all lead to the same  
296 expression for inbreeding depression  $\delta$ . For small values of the coefficient of  
297 selection  $s$  and small mutation rates  $\mu$ , all models lead to a level of inbreeding  
298 depression  $\delta$  that is numerically close. Increasing  $s$  leads to a smaller  $\delta$  when  
299 selection is on zygote survival compared to the other models (see Figure 4).  
300 As seen for the genetic load  $L$ , selection on zygote survival leads to a non-

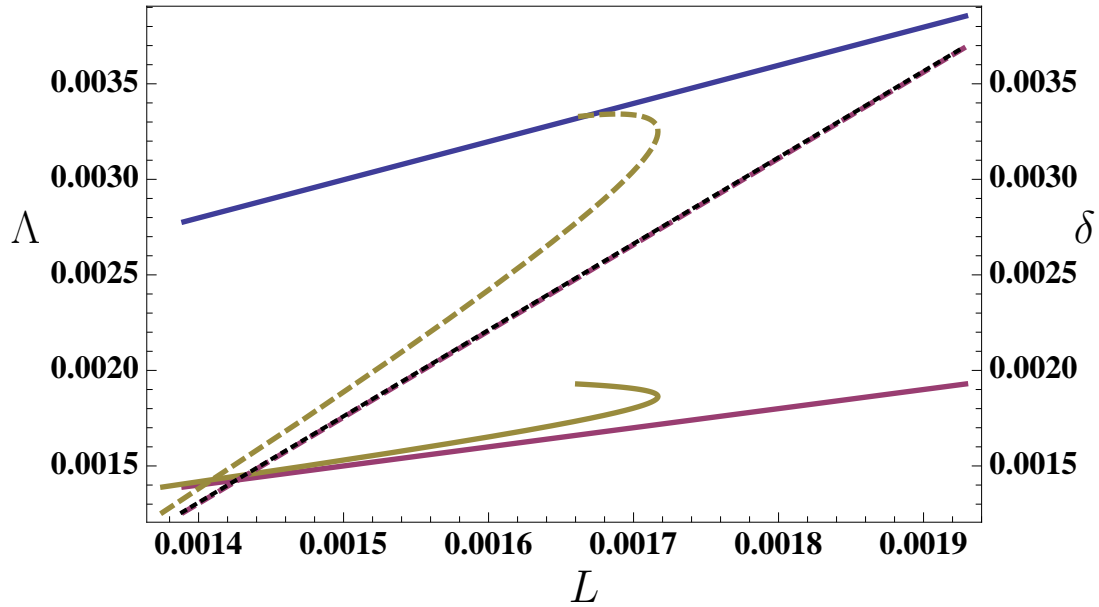


Figure 3: The numerical load  $\Lambda$  (full lines) and inbreeding depression  $\delta$  (dashed lines) as a function of the genetic load  $L$  at mutation-selection balance, for  $h = 0.1$ ,  $\mu = 10^{-3}$  and  $s$  between 0 and 1.  $\Lambda$  for selection on mating success, fecundity and zygote survival is represented in red, blue and yellow respectively.  $\delta$  for selection on mating success, fecundity and adult survival are in red, zygote survival in yellow and the expressions from the fundamental model in black. Lines are plotted using the expressions in Table S1 of the Supporting Information.

301 monotonic relationship between  $s$  and  $\delta$ . At higher values of  $\mu$ , the tendencies  
302 change; the fundamental model predicts the highest  $\delta$ , followed by selection  
303 on zygote survival (Figure 4). As can be expected from the expressions  
304 presented in Table 2, increasing dominance  $h$  decreases  $\delta$ , whereas increasing  
305 the coefficient of selection  $s$  increases  $\delta$ . The relationship between inbreeding  
306 depression and the genetic load depends on what parameter is modified, as  
307 increasing  $s$  or  $h$  lead to opposite tendencies. Increasing  $h$  leads to a decrease  
308 in  $\delta$  while it increases  $L$ , whereas increasing  $s$  leads to higher  $\delta$  and an increase  
309 in  $L$  (see Figure 3), except in the case of selection on zygote survival, where  
310 increasing  $s$  has a non-monotonic effect on both  $L$  and  $\delta$ .

### 311 **Deterministic fixation**

312 The threshold value of the mutation rate for deterministic fixation  $\mu_{fix}$  is  
313 the same whether selection is on reproduction or on survival. The expected  
314  $\mu_{fix}$  for the fundamental model is lower than that calculated for our models  
315 of selection. A lower threshold implies that the deterministic fixation of a  
316 deleterious mutation occurs at lower mutation rates. In the equations for  
317  $\mu_{fix}$  (see Table 2 and Supporting Information), we note that in our models  
318 the dominance of the mutations plays a greater role in defining the thresh-

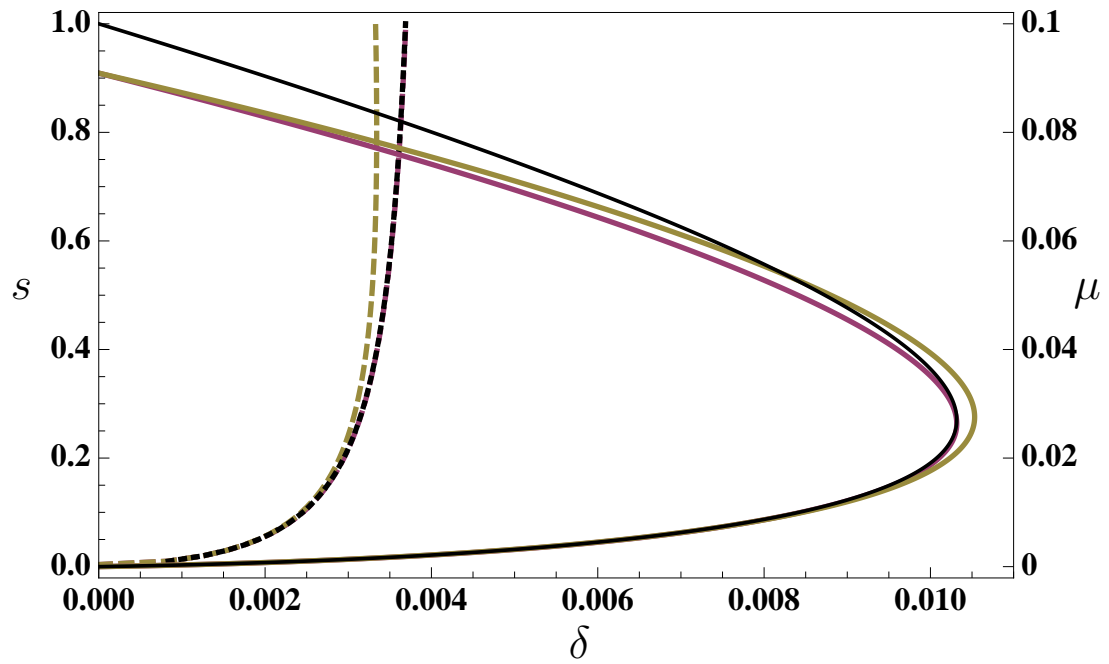


Figure 4: Inbreeding depression  $\delta$  at mutation-selection balance as a function of the coefficient of selection  $s$  (dashed lines, for  $h = 0.1$  and  $\mu = 10^{-3}$ ) and as a function of the mutation rate  $\mu$  (full lines, with  $s = 0.1$  and  $h = 0.1$ ). Selection on mating success, fecundity or adult survival are represented in red, selection on zygote survival in yellow and the fundamental model in black. Lines are plotted using the expressions in Table S1.



319 old value than in the fundamental model, due to the presence of  $h$  in the  
320 numerator.

## 321 DISCUSSION

322 Whether the genetic load affects population size remains an open question.  
323 In a recent review on the genetic load  $L$ , Agrawal and Whitlock (2012) came  
324 to the conclusion that even though a population's mean genetic load might  
325 not affect population size (as fitter individuals in the population could make  
326 up for the lack of reproductive success of less fit individuals i.e. soft selec-  
327 tion), if all individuals within the population have a high  $L$ , population size  
328 is expected to be affected (i.e. hard selection). The latter instance agrees  
329 with the generally accepted existence of the mutational meltdown (Lande,  
330 1994; Lynch et al., 1995; Coron et al., 2013), whereas the former suggests  
331 that segregating and polymorphic mutations should have little or no effect  
332 on population demography. But can soft selection completely mask the de-  
333 mographic consequences of the genetic load? For this to be the case, two  
334 conditions need to be met: 1) An infinite or very large number of juveniles  
335 (much greater than the environment's carrying capacity) are produced at ev-

336 ery time step and 2) Selection must occur only at the juvenile or gametic  
337 stages, i.e. before any resources are consumed (reviewed in Agrawal and  
338 Whitlock, 2012). The first condition is not always met; not all organisms  
339 produce a very large number of offspring, and as for the second condition,  
340 selection occurs throughout the life-cycle, considering it affects only the juve-  
341 nile and gametic stages is a strong hypothesis. In our model, we have chosen  
342 a simplified representation of the life cycle, with selection affecting gamete  
343 production (fecundity), the success of a mating event, the survival of either  
344 zygotes before they have had time to consume any of the available resources  
345 or adults before they have had a chance to reproduce. Our results show  
346 that deleterious mutations can indeed lead to a numerical load  $\Lambda$  and that  
347 it depends on the timing of selection as predicted by Clarke (1973), but our  
348 results also indicate that the genetic load can also be affected by the timing  
349 of selection.

### 350 **Population size as a consequence of selection**

351 If not all individuals in a population have the optimal reproductive capac-  
352 ity, all the while consuming the same amount of resources, then this auto-  
353 matically decreases the population's mean reproductive capacity. For the

354 numerical load to be compensated, resources used by poorly reproducing in-  
355 dividuals need to be freed. When selection is on adult survival, all surviving  
356 individuals reproduce at the same rate as less fit adults are eradicated be-  
357 fore they reproduce and resources for new individuals are freed immediately.  
358 When selection is on mating success a resource-consuming adult does not  
359 always have efficient reproductive encounters, either because its genotype is  
360 counter-selected, its partner's genotype is counter-selected, or the offspring  
361 eventually produced from this encounter are not of an optimal genotype.  
362 The numerical load  $\Lambda$  observed for selection on fecundity and zygote survival  
363 can be explained by the same reasoning as for selection on mating success  
364 (i.e. all adults consume the same quantity of resources, but not all of them  
365 produce the same proportion of gametes or viable offspring), however the  
366 effect of selection on population size is smaller. With selection on fecundity  
367 and on zygote survival all reproductive encounters are successful, it is only  
368 the number of potential offspring that decreases (either because fewer ga-  
369 metes are produced or because not all offspring are viable). With selection  
370 on mating success not only do individuals carrying  $a$  alleles have a lower  
371 success, gametes of poor quality are produced at the same rate as those of  
372 better quality, and the competition between the two further decreases the

373 probability of viable gametes meeting and engendering an offspring.

### 374 **The importance of the timing of selection**

375 When comparing our four models of selection we observe two distinct behav-  
376 iors concerning the frequency and state (homozygous or heterozygous) of the  
377 deleterious allele  $a$ , and consequently the genetic load  $L$  and amplitude of  
378 inbreeding depression  $\delta$  at mutation-selection balance. Even though we find  
379 different numerical loads when selection affects mating success, fecundity or  
380 adult survival, these models all lead to the same frequency of  $AA$ ,  $Aa$  and  $aa$   
381 individuals, and hence the same expressions for  $L$  and  $\delta$ , at mutation selec-  
382 tion balance, whereas selection on zygote survival leads to different behaviors  
383 for these variables. For simplicity, we will refer solely to selection on fecun-  
384 dity and not to all three models in order to facilitate the comparison between  
385 these three model and selection on zygote survival. The expressions for both  
386  $L$  and  $\delta$  when selection is on zygote survival lead to a non-monotonic effect  
387 of the coefficient of selection  $s$  on these variables, as well as a non-monotonic  
388 effect of dominance  $h$  on  $L$ , something which is not observed for selection on  
389 fecundity. This non-monotonic effect is due to differences between both the  
390 frequency and the state of the deleterious allele  $a$  (File S3). If we imagine a

391 population in which we find no individuals carrying the  $a$  allele, the rate of  
392 introduction of individuals carrying  $a$  depends only on the mutation rate  $\mu$   
393 when selection is on fecundity. However, when selection is on zygote survival,  
394 this rate depends on  $\mu$ ,  $s$  and  $h$  as the birth rate  $R_t$  for zygote survival directly  
395 depends on these parameters (equation 6 and File S2). The birth rate of  $aa$   
396 and  $Aa$  individuals is therefore lower when selection is on zygote survival  
397 than when it affects fecundity. We would therefore expect that if  $a$  affects  
398 zygote survival it would segregate at lower frequencies at mutation selection  
399 balance than if  $a$  affects fecundity. As the rate of introduction of individuals  
400 carrying  $a$  also depends on  $s$  and  $h$ , we would also expect that of the muta-  
401 tions affecting zygote survival strongly deleterious mutations would tend to  
402 be recessive, and slightly deleterious mutations would have a larger variance  
403 of dominance associated. On the other had, if selection affects fecundity,  
404 then we should observe a more random association between the coefficient  
405 of selection and the dominance of  $a$ . This reasoning is also applicable to the  
406 estimation of the levels of inbreeding depression  $\delta$  within populations, as our  
407 results agree with the empirical observation that levels of  $\delta$  vary between  
408 traits (Frankham et al. 2010, Chapter 13; Angeloni et al. 2014). In our  
409 model, we find that inbreeding depression is lower for zygote survival than

410 for fecundity. A better understanding of how  $\delta$  evolves in populations is key  
411 for the understanding of evolutionary processes (e.g. the transition between  
412 outcrossing and self-fertilization in plants (Charlesworth and Charlesworth,  
413 1987; Porcher and Lande, 2005) and for conservation efforts.

#### 414 **How considering the life cycle affects predictions compared to the** 415 **fundamental model**

416 When considering neutral alleles, we find that whether the life cycle is taken  
417 into account or not, the genotypic frequencies will be at Hardy-Weinberg  
418 equilibrium. However, in the case of deleterious mutations, explicitly con-  
419 sidering the life-cycle and the timing of selection can have an effect on the  
420 fate of such alleles. The genetic load  $L$  and the amplitude of inbreeding  
421 depression are both affected by how selection acts against deleterious muta-  
422 tions. Historically,  $L$  has been estimated ignoring the potential effects of the  
423 life cycle, which can be relatively (numerically) small when selection affects  
424 reproductive success, fecundity and adult survival or relatively important as  
425 is the case when the deleterious allele  $a$  affects zygote survival. Selection  
426 on zygote survival leads to an unexpected non-monotonic relationship be-  
427 tween the effects of the deleterious mutations (its coefficient of selection  $s$

428 and dominance  $h$ ) which has never been observed, to our knowledge, in mod-  
429 els that have estimated load using the fundamental model, not even when  
430 taking stochasticity into account (Bataillon and Kirkpatrick, 2000; Roze and  
431 Rousset, 2004; Glémin, 2003). The predictions of the fundamental model  
432 imply that all mutations, independently of their properties ( $s$  and  $h$ ) lead to  
433  $L$  proportional to the rate at which they are introduced, the mutation rate  $\mu$ .  
434 This is not the case when selection affects zygote survival: very deleterious  
435 mutations that are observed in the population have to be recessive. If they  
436 are not recessive, the zygotes carrying them never survive to become a part  
437 of the population, and hence such mutations (that are both very deleterious  
438 and dominant) cannot be detected. Considering the life cycle can therefore  
439 provide further insight into how selection can affect the fate of newly intro-  
440 duced mutations, as well as perhaps understanding the distribution of their  
441 dominance and selective coefficient as well as the interaction between the  
442 two.

#### 443 **Towards more accurate models**

444 The timing of selection is not the only demographic factor with a potential  
445 effect on the numerical load, the genetic load and inbreeding depression; the

446 intrinsic birth and death rates could also play an important role. In our  
447 deterministic model these parameters have no effect, as we find neither the  
448 intrinsic birth nor death rates ( $b$  and  $d$ ) in the equations for the numerical  
449 load, the genetic load or inbreeding depression. Results of demographically  
450 explicit and stochastic models have suggested that  $b$  and  $d$  can affect the fate  
451 of a deleterious allele, or more specifically its probability of fixation Coron  
452 et al. (2013). Developing a stochastic version of this model would allow us to  
453 evaluate the importance of these parameters; as we could imagine that higher  
454 birth rates lead to less efficient selection against deleterious mutations and  
455 a higher genetic load at mutation-selection balance, without necessarily in-  
456 creasing the numerical load. In this paper, we consider a specific demographic  
457 model; other demographic models may lead to different relationships between  
458 the genetic and numerical loads. Considering density and/or frequency de-  
459 pendent selection ((Wallace, 1970); (Charlesworth, 1971)) may also modify  
460 the present predictions. Our results highlight the importance of considering  
461 the interaction between selection against deleterious mutations and the de-  
462 mographic evolution of populations. The modern tools that are now available  
463 allow us to find explicit, and in some cases simple, equations for calculating  
464 load and inbreeding depression while considering demography. Using these



465 tools could provide us with more accurate and detailed predictions of how  
466 these two aspects (demography and genetics) that have often been considered  
467 as separate things, both affect the evolution of populations.

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