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

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ABSTRACT

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

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

INTRODUCTION

Deleterious mutations are constantly introduced into populations at relatively high rates (Keightley and Lynch, 2003). In spite of their deleterious effect, these alleles are not always immediately eliminated by selection from the genetic pool but can persist for several generations and, in the case of stochasticity, can even go to fixation. These mutations decrease mean population fitness by engendering a genetic or mutational load, and are responsible for inbreeding depression. In the field of population genetics, the evolution of load and inbreeding depression as a function of population size and structure has been greatly explored (Bataillon and Kirkpatrick, 2000; Roze and Rousset, 2004; Glémin, 2003). However, these models do not consider an explicit interaction between the two, as population size is considered to be a parameter. If and how these mutations affect population size remains unclear; while inbreeding depression is a major concern in conservation biology, whether the genetic load of populations affects population size and viability is debatable. In the case of very small populations, it is widely accepted that they can be at risk of a mutational meltdown (extinction due to the fixation of deleterious 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".

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

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

A limitation of the model proposed by Clarke (1973) is that it considers a genetic load that evolves independently of the demographic model and the timing of selection. The relative selective values he proposed were constructed so as to ensure that the genetic load remains equal to that expected from the fundamental model of population genetics (Gillespie, 1998, p.61). The genetic load is expected to directly affect a measure of individual or population fitness and fitness has been defined as being an individual's (or genotype's) mating success, fecundity or survival (Agrawal and Whitlock, 2012). While expected to be of great importance in demographic models (Haldane, 1957; Agrawal and Whitlock, 2012), the timing of selection is considered to be of no importance when calculating the genetic load or inbreeding depres-

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

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

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

ANALYTICAL MODEL

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

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

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

Model without selection

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

Table 1: **Notations.**

Λ, L, δ	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.
$V_t, \widetilde{V}_t$	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.
μ, μ_{fix}	The mutation rate from A to a and the threshold value of μ for which there is deterministic fixation of a.

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

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

$$\frac{dV_t}{dt} = R_t^V - M_t^V. \tag{1}$$

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

birth rate R_t^V is given by

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

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 μ. 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

$$M_t^V = d\frac{N_t}{K}V_t. \tag{2}$$

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)

$$N_{eq} = \frac{bK}{d}. \tag{3}$$

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

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

Timing of selection

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

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

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

Fecundity: When fecundity is affected by selection, an individual V contributes $\widetilde{V}_t$ female gametes and a proportion of $\frac{\widetilde{V}_t}{\widetilde{X}_t+\widetilde{Y}_t+\widetilde{Z}_t}$ 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

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

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

Selection on survival: Selection can also occur during the life cycle, independently of reproductive success, affecting either zygote or adult survival. Zygote survival can be translated as the proportion of germinating seeds, or, more generally, viable offspring. Selection on adult survival is considered to 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

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

The full equations for the change in the number of individuals of each genotype 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 $\widetilde{V}$, hence proportional to their fitness. As only surviving individuals reproduce and compete for resources, V is replaced by $\widetilde{V}$ 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

$$M_t^V = d\frac{\widetilde{X}_t + \widetilde{Y}_t + \widetilde{Z}_t}{K}qV_t. \tag{7}$$

The full equations for the change in the number of individuals of each genotype can be found in File S2.

Mutation-selection balance

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 Λ (the decrease of population size due to the presence of deleterious mutations), a term defined by Clarke (1973) and given by

$$\Lambda = \frac{N_{eq} - N_{mut}}{N_{eq}}, \tag{8}$$

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 δ, which we then compare We also compare the genetic load L and inbreeding depression δ 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

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

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):

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

Inbreeding depression δ 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):

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

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

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

RESULTS

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

Model	h	N_{mut}	Λ	L	δ	μ_{fix}
Mating success	0	$N_{eq}(1-\mu)^2$	$2\mu-\mu^2$	μ	$\frac{\sqrt{\mu s}-\mu}{2(1-\mu)}$	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	$N_{eq}(1-\mu)$	μ	μ	$\frac{\sqrt{\mu s}-\mu}{2(1-\mu)}$	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	μ	$\frac{\sqrt{\mu s}-\mu}{2(1-\mu)}$	s
	0.5	N_{eq}	0	$\frac{2\mu}{1+\mu}$	0	$\frac{s}{2-s}$
Zygote survival	0	$N_{eq}(1-\mu)$	μ	$\frac{\mu(1-s)}{1-\mu}$	$\frac{\sqrt{\mu s}-\mu}{2-2\mu(2-s)}$	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	$\frac{2}{2-s}$
Fundamental model	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 Λ, genetic load L, inbreeding depression δ and the threshold value of the mutation rate for deterministic fixation μ_{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.

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

The numerical load

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

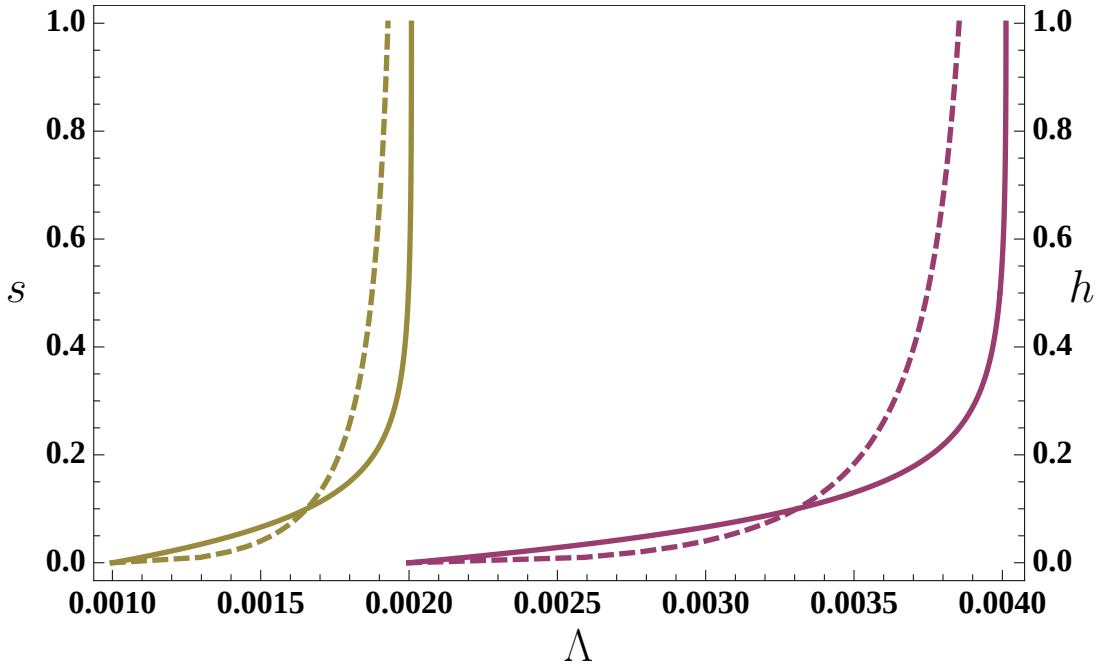

Figure 1: Numerical load Λ at mutation-selection balance as a function of the coefficient of selection s (dashed lines, for $h = 0.1$ and $\mu = 10^{-3}$) and as a function of dominance h (full lines,with $s = 0.1$ and $\mu = 10^{-3}$). Selection on mating success is represented in red, whereas selection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

The timing of selection and the genetic load

The timing of selection affects the genetic load L at mutation-selection balance both quantitatively and qualitatively (Figure 2). We find the same expressions for L when selection is on mating success, fecundity and on adult survival. For these three models L increases with the coefficient of selection s (Figure 2) and with dominance h (Figure 2). When selection affects zygote survival, there is a non-monotonic effect of both s and h on L (this effect becomes smaller with increasing mutation rates μ, results not shown); L is therefore maximal for intermediate values of s and/or h.

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

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

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

The timing of selection not only affects the numerical load Λ and the genetic load L, but also the interaction between the two at mutation-selection balance. When plotting Λ as a function of L (see Figure 3), selection on

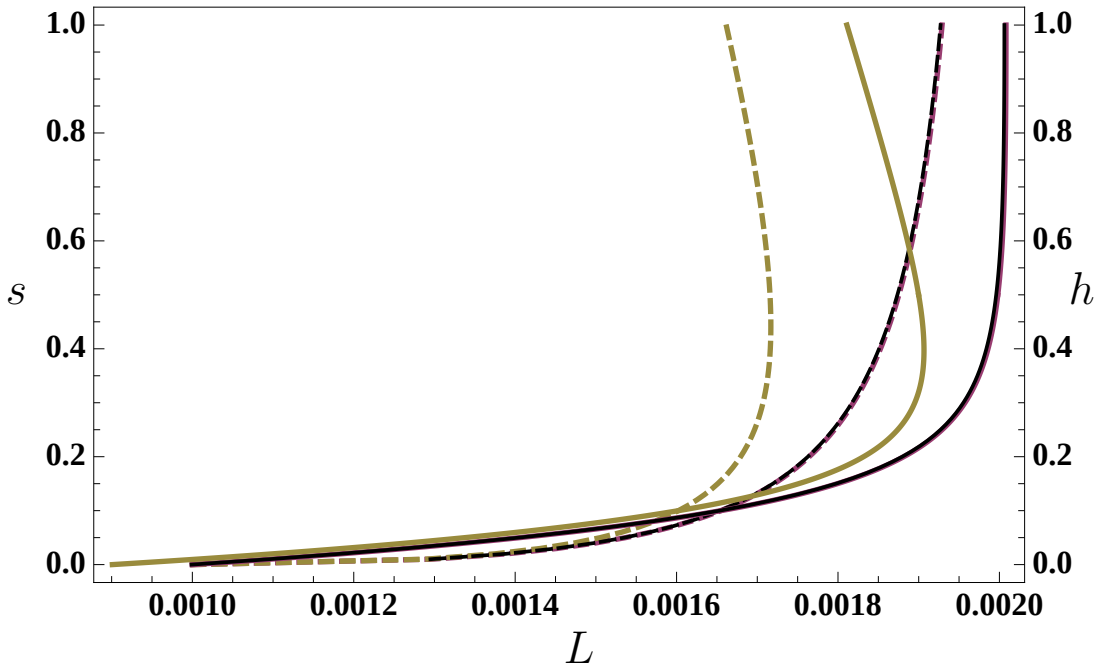

Figure 2: Genetic load L at mutation-selection balance at mutation-selection balance as a function of the coefficient of selection s (dashed lines, for $h = 0.1$ and $\mu = 10^{-3}$) and as a function of dominance h (full lines,with $s = 0.1$ and $\mu = 10^{-3}$). Selection on mating success, fecundity 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.

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

Inbreeding depression

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

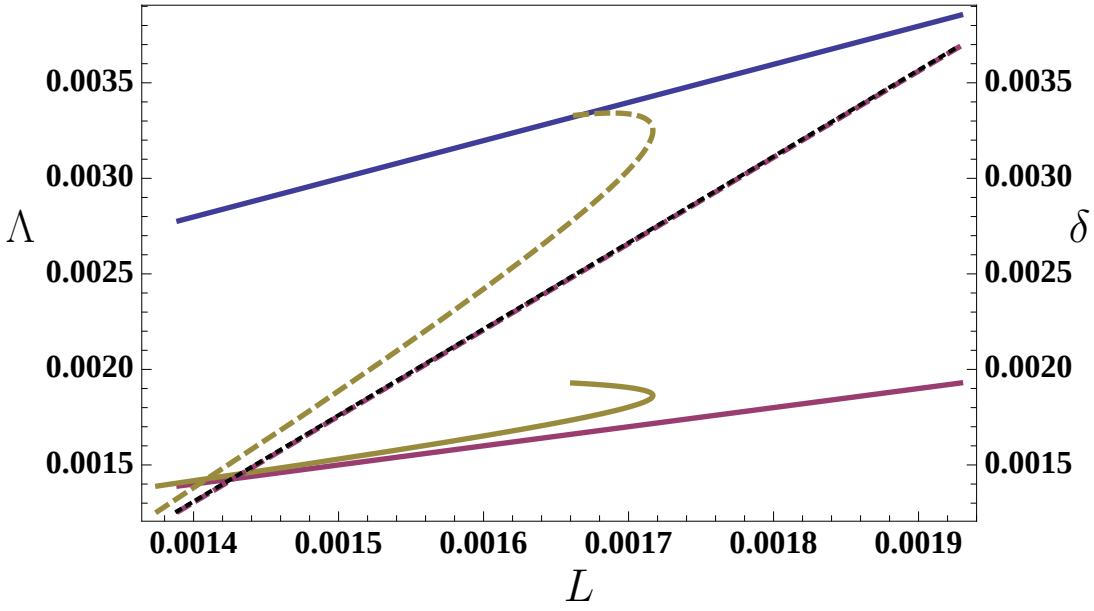

Figure 3: The numerical load Λ (full lines) and inbreeding depression δ (dashed lines) as a function of the genetic load L at mutation-selection balance, for $h = 0.1$, $\mu = 10^{-3}$ and s between 0 and 1. Λ for selection on mating success, fecundity and zygote survival is represented in red, blue and yellow respectively. δ 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.

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

Deterministic fixation

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

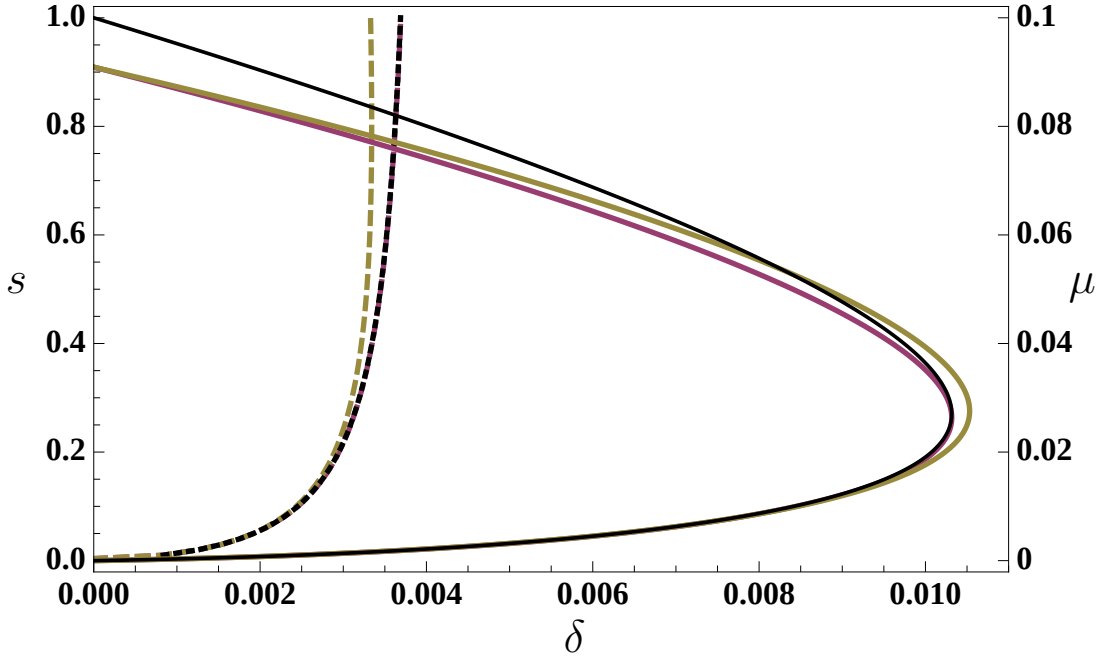

Figure 4: Inbreeding depression δ at mutation-selection balance as a function of the coefficient of selection s (dashed lines, for $h = 0.1$ and $\mu = 10^{-3}$) and as a function of the mutation rate μ (full lines, with $s = 0.1$ and $h = 0.1$. Selection on mating success, fecundity or adult survival 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.

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

DISCUSSION

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

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

Population size as a consequence of selection

If not all individuals in a population have the optimal reproductive capacity, all the while consuming the same amount of resources, then this automatically decreases the population's mean reproductive capacity. For the

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

probability of viable gametes meeting and engendering an offspring.

The importance of the timing of selection

When comparing our four models of selection we observe two distinct behaviors concerning the frequency and state (homozygous or heterozygous) of the deleterious allele a, and consequently the genetic load L and amplitude of inbreeding depression δ at mutation-selection balance. Even though we find different numerical loads when selection affects mating success, fecundity or adult survival, these models all lead to the same frequency of AA, Aa and aa individuals, and hence the same expressions for L and δ, at mutation selection balance, whereas selection on zygote survival leads to different behaviors for these variables. For simplicity, we will refer solely to selection on fecundity and not to all three models in order to facilitate the comparison between these three model and selection on zygote survival. The expressions for both L and δ when selection is on zygote survival lead to a non-monotonic effect of the coefficient of selection s on these variables, as well as a non-monotonic effect of dominance h on L, something which is not observed for selection on fecundity. This non-monotonic effect is due to differences between both the 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 μ
393 when selection is on fecundity. However, when selection is on zygote survival,
394 this rate depends on μ, 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 δ within populations, as our
407 results agree with the empirical observation that levels of δ 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

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

How considering the life cycle affects predictions compared to the fundamental model

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

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

Towards more accurate models

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

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

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

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