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Epistasis, pleiotropy and the mutation load in sexual and asexual populations

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Running head: Fitness landscapes and the mutation load

ABSTRACT

Mutation may impose a substantial load on populations, which varies according to the reproductive mode of organisms. Over the last years, different authors used adaptive landscape models to predict the long term effect of mutation on mean fitness; however, many of these studies assumed very weak mutation rates, so that at most one mutation segregates in the population. In this paper we derive several simple approximations (confirmed by simulations) for the mutation load at high mutation rate (U), using a general model that allows us to play with the number of selected traits (n), the degree of pleiotropy of mutations and the shape of the fitness function (which affects the average sign and magnitude of epistasis among mutations). When mutations have strong fitness effects, the equilibrium fitness $\overline{W}$ of sexuals and asexuals is close to e^{-U} ; under weaker mutational effects, sexuals reach a different regime where $\overline{W}$ is a simple function of U and of a parameter describing the shape of the fitness function. Contrarily to weak-mutation results showing that $\overline{W}$ is an increasing function of population size and a decreasing function of n , these parameters may have opposite effects in sexual populations at high mutation rate.

Keywords: adaptive landscape, epistasis, evolutionary quantitative genetics, multi-locus models, mutation load, stabilizing selection

Although mutation represents the ultimate fuel for adaptation, it is also the source of a fitness cost for populations due to the production of sub-optimal genotypes. This “mutation load” may in turn affect many important evolutionary processes, such as the evolution of sex and recombination (Kondrashov, 1988; Barton, 1995; Keightley and Otto, 2006; Otto, 2009), inbreeding depression and the evolution of mating systems (Lande and Schemske, 1985; Charlesworth and Charlesworth, 1999; Charlesworth, 2006), mate choice (Rowe and Houle, 1996) or ploidy levels (Otto and Goldstein, 1992; Otto and Marks, 1996). Different types of models have explored the effect of recurrent mutation on the average fitness of populations. The simplest model assumes that each mutation decreases fitness by a fixed factor, independently of the genetic background (multiplicative model). In that case, the average fitness of a population at mutation-selection balance (relative to the maximal possible fitness) is approximately e^{-U} , where U is the genomic rate of deleterious mutation (e.g., Crow, 1970). This results holds for both sexual (randomly mating) and asexual populations, as long as stochastic effects can be neglected. However, it seems unlikely that most mutations have independent effects: for example, direct measures of fitness effects of mutations (alone and in combination) in microorganisms usually show a wide distribution of epistatic interactions among pairs of mutations (e.g., Martin et al., 2007). Kimura and Maruyama (1966) explored the effects of epistasis among deleterious alleles on mean fitness, assuming that epistasis is the same for all pairs of mutations. They showed that when interactions among mutations tend to reinforce their deleterious effect (negative epistasis) the mean fitness of sexual populations increases, while it

43 decreases when deleterious alleles tend to compensate each other (positive epistasis).
44 By contrast, the mean fitness of asexual populations is not affected by epistasis and
45 remains approximately e^{-U} .

46 In a different class of models, mutations affect a given number of phenotypic
47 traits which in turn influence fitness. Fisher (1930), Haldane (1932) and Wright (1935)
48 considered different models of stabilizing selection acting on a single quantitative trait
49 influenced by many genes. In particular, Haldane and Wright derived expressions for
50 equilibrium allele frequencies, from which mean fitness can be deduced; further de-
51 velopments (to which we will return below) were done in the sixties and seventies,
52 in particular by Kimura (1965), Bulmer (1971, 1972) and Lande (1976, 1977). Inter-
53 estingly, compensatory effects between mutations emerge naturally from this type of
54 model (a mutation that displaces from the optimum can be compensated by another
55 mutation bringing closer to the optimum), together with distributions of epistatic in-
56 teractions among mutations. In his *Genetical Theory of Natural Selection*, Fisher also
57 proposed a model involving multiple phenotypic traits in support of his idea that adap-
58 tation is mainly due to mutations of small effect: this geometrical model represents
59 an n -dimensional phenotypic space where each dimension corresponds to the value of
60 a quantitative trait, and where mutations correspond to random vectors displacing
61 individuals in phenotypic space. Fitness is assumed to decrease monotonously as the
62 Euclidean distance from a point corresponding to the optimal phenotype increases.
63 Although the initial goal of Fisher's geometrical model was to describe the dynamics
64 of adaptation (Fisher, 1930; Orr, 1998, 2000; Welch and Waxman, 2003), it has also
65 been used to explore the effects of various parameters (population size, number of
66 phenotypic traits under selection, shape of the fitness peak...) on the mean fitness

of populations in equilibrium situations. Several authors considered a weak-mutation
 limit ($NU \ll 1$, where N is population size and U the total rate of mutations affecting
 the traits under selection) so that at most one mutation segregates in the popula-
 tion at a given time (Hartl and Taubes, 1998; Poon and Otto, 2000; Sella and Hirsh,
 2005; Tenaillon et al., 2007; Sella, 2009): the population evolves away from the op-
 timum by fixing weakly deleterious alleles by random drift, and occasionally returns
 near the optimum by fixing a compensatory mutation. For example, using the fitness
 function $W = \exp(-d^Q)$, where d is the Euclidean distance from the optimum in
 phenotypic space and Q a parameter affecting the shape of the fitness peak, Tenaillon
 et al. (2007) showed that the equilibrium mean fitness of a haploid population is
 approximately $(1 - 1/(2N))^{\frac{n}{Q}}$, where n is the number of traits affecting fitness (often
 called “complexity”). Note that this result does not depend on the reproductive mode
 of organisms (sexual or asexual) since at most one locus is polymorphic in this low
 mutation limit.

It seems likely that in many organisms, however, $NU \gg 1$, in which case many
 of the loci affecting the traits under selection may be polymorphic at the same time.
 In this regime, and assuming that the position of the optimum remains constant over
 time, the population can be represented by a collection of points centered around the
 optimum, while mean fitness can usually be expressed in terms of the variance of the
 different trait values in the population. Since the original works of Haldane (1932)
 and Wright (1935), numerous models have been used to calculate the genetic variance
 of a quantitative trait (or a set of traits) maintained at mutation-selection balance,
 and different regimes have been described (e.g., Bulmer, 1989; Bürger, 2000; Johnson
 and Barton, 2005; Zhang and Hill, 2005). When mutations tend to have strong fitness

91 effects, the distribution of phenotypic values is often highly leptokurtic (with a sharp
 92 peak at the optimum) and may present a singularity (Waxman and Peck, 1998). In
 93 the limit of very strong selection, the expected contribution to future generations
 94 of individuals located away from the optimum becomes negligible; in this case, one
 95 expects that mean fitness, relative to the fitness of individuals at the optimum ($\bar{W}/W_0$)
 96 should be approximately e^{-U} when the number of new mutations per individual is
 97 Poisson-distributed, independently of the exact shape of the fitness peak. Indeed,
 98 a recursion for the frequency of individuals at the optimum (x_0) is given by $x_0' =$
 99 $e^{-U} x_0 W_0 / \bar{W}$ (e^{-U} being the probability that no mutation occurs), which yields the
 100 desired result when $x_0' = x_0$ (e.g., Kimura and Maruyama, 1966).

101 When mutations tend to have weak fitness effects, different results can be ob-
 102 tained by assuming that equilibrium distributions of phenotypic values are Gaussian.
 103 Most models exploring this regime considered a single trait under selection and a
 104 Gaussian (or quadratic) fitness function, although multivariate models have also been
 105 proposed (Lande, 1980; Turelli, 1985). Different assumptions regarding the genetic ar-
 106 chitecture of traits (in particular the number of alleles per locus) have been explored.
 107 *Continuum-of-alleles* models assume that an infinite number of alleles (having different
 108 phenotypic effects) segregate at each locus; expressions for the genetic variance and
 109 mean fitness under this scenario have been obtained by assuming that the equilibrium
 110 distribution of allelic effects in the population is Gaussian at each locus (e.g., Kimura,
 111 1965; Lande, 1976). Lande (1980) generalized these models to the case where selection
 112 acts on multiple traits, assuming a multivariate Gaussian fitness function. Although
 113 the general expression for equilibrium genetic variances (and mean fitness) is cumber-
 114 some, it takes a simpler form when selection acts independently on each trait, and in

115 the absence of correlation of mutational effects across traits (p.294 in Bürger, 2000).
 116 Neglecting linkage disequilibria among loci, mean fitness can then be written as a sim-
 117 ple function that depends on the number of selected traits, number of loci, strength
 118 of selection and mutational variance (see Results section below). Other models con-
 119 sidered stabilizing selection (Gaussian fitness function) acting on a single trait coded
 120 by multiple biallelic loci (e.g., Bulmer, 1972, 1985; Barton, 1986, 1989). As shown by
 121 Barton (1986), multiple possible equilibria exist for allele frequencies at the different
 122 loci. Although the population mean phenotype may deviate from the optimum at
 123 some of these equilibria, Barton (1989) argues that perturbations generated for exam-
 124 ple by random drift should keep the population mean near the optimum. Neglecting
 125 linkage disequilibria, and as long as the effects of mutation and drift at each locus are
 126 weaker than selection, one obtains from the expression of the equilibrium genetic vari-
 127 ance that mean fitness should be close to e^{-U} . More recently, Zhang and Hill (2003)
 128 investigated the maintenance of genetic variation in multiple-trait models (including
 129 correlations among traits), assuming that the fitness function is multivariate Gaussian,
 130 and that selection at each locus is sufficiently strong so that mutations remain rare in
 131 the population (only one mutant allele segregates at each locus). Results for the case
 132 of a changing optimum have been derived by Zhang (2012). Finally, effects of linkage
 133 disequilibria have been explored in both continuum-of-alleles and biallelic models, for
 134 the case of a single trait under Gaussian stabilizing selection (Bulmer, 1974; Lande,
 135 1976; Turelli and Barton, 1990), and were shown to be minor as long as the total rate
 136 of mutation on loci affecting the trait remains small, and linkage is not too tight.

137 In this article, we derive several simple approximations for the mutation load in
 138 both sexual and asexual populations at high mutation rate, using a general model that

139 allows us to play with the shape of the fitness peak (which in turn affects the average
 140 sign and magnitude of epistasis among mutations), the number of traits under selection
 141 and the degree of pleiotropy of mutations. These results are tested by individual-
 142 based simulations representing stabilizing selection on traits coded by large numbers
 143 of loci. As we will see, two different regimes are observed in asexual populations: when
 144 mutations tend to have large fitness effects, mean fitness only depends on the mutation
 145 rate and is close to e^{-U} , while under weaker mutational effects mean fitness increases
 146 as mutational effects decreases, and can be expressed in terms of the mutation rate,
 147 the dimensionality of the landscape, the shape of the fitness peak and the average
 148 deleterious effect of mutations. By contrast, three regimes are observed in the case
 149 of sexual populations: under strong mutational effects, mean fitness is again close to
 150 e^{-U} , while it switches to a different value that only depends on the mutation rate
 151 and the shape of the fitness peak as mutational effects decrease. Interestingly, mean
 152 fitness is the same under these two regimes when the fitness function is Gaussian
 153 ($\bar{W} \approx e^{-U}$), while $\bar{W} > e^{-U}$ in the second regime when the fitness peak is flatter
 154 than a Gaussian around the optimum, and $\bar{W} < e^{-U}$ when the fitness peak is sharper.
 155 Finally, as mutational effects continue decreasing a third regime is entered, where allele
 156 frequency dynamics are dominated by mutation and drift. We also obtain expressions
 157 for linkage disequilibria and find that they can have a substantial effect on fitness, in
 158 particular when the mutation rate is high and the number of traits under selection is
 159 low.

161 **Multivariate stabilizing selection.** Parameters and variables are summarized in
 162 Table 1. The model represents an infinite haploid population with discrete generations,
 163 under stabilizing selection on n phenotypic traits; for each individual, trait values are
 164 given by the vector $\mathbf{z} = (z_0, z_1, \dots, z_n)$. Following others (Wilke and Adami, 2001;
 165 Tenaillon et al., 2007; Gros et al., 2009), we assume for simplicity that the fitness
 166 function is spherically symmetric, and is given by:

$$W = \exp \left[-\frac{d^Q}{2V_S} \right] \quad (1)$$

167 where $d = \sqrt{\sum_{i=1}^n z_i^2}$ is the Euclidean distance in phenotypic space from the optimal
 168 phenotype (located at $z_i = 0$ for each trait i), V_S measures the strength of selection,
 169 while the parameter Q determines the shape of the fitness peak: $Q = 2$ corresponds to
 170 a (multivariate) Gaussian fitness function, while $Q < 2$ (resp. $Q > 2$) leads to a sharper
 171 (resp. flatter) fitness peak. Traits are coded by L biallelic loci, each locus affecting
 172 a subset $m \leq n$ of phenotypic traits (sampled randomly and independently for each
 173 locus among the set of n traits). As in Lourenço et al. (2011), the parameter m thus
 174 measures the number of traits affected by a single mutation (“mutation pleiotropy”),
 175 while n is the total number of traits under selection (“complexity”): $m = n$ corresponds
 176 to maximal pleiotropy, where each mutation affects all selected traits (as in Fisher’s
 177 model). The genomic mutation rate is denoted U , so that each locus mutates at rate
 178 $u = U/L$. For simplicity, we assume additive effects of the different loci on phenotypic
 179 traits, and no environmental variance. Denoting 0 and 1 the two alleles at each locus,
 180 and X_j an indicator variable that equals 0 if an individual carries allele 0 at locus j ,

and 1 otherwise, the value of trait i in a given individual is given by:

$$z_i = \sum_{j=1}^L r_{ij} X_j \quad (2)$$

where r_{ij} measures the effect of allele 1 at locus j on trait i : an individual carrying alleles 0 at all loci is thus at the phenotypic optimum. For each locus j , the effect of allele 1 on each of the m traits affected by the locus is sampled in a Gaussian distribution with mean 0 and variance a^2 (therefore, r_{ij} can be positive or negative). Finally, we denote $\bar{s}$ the mean deleterious effect of mutations (measured on log-fitness) in a population at the optimum, given by Gros et al. (2009):

$$\bar{s} = \frac{(2a^2)^{\frac{Q}{2}}}{2V_S} \frac{\Gamma\left(\frac{m+Q}{2}\right)}{\Gamma\left(\frac{m}{2}\right)} \quad (3)$$

(where Γ is Euler's gamma function), which simplifies to $\bar{s} = \frac{m}{2} (a^2/V_S)$ in the case of a Gaussian fitness function ($Q = 2$, in agreement with Martin and Lenormand, 2006). As shown by Gros et al. (2009), the average epistasis among pairs of mutations (at the optimum, and measured on log-fitness) is given by $\bar{e} = (2 - 2^{Q/2}) \bar{s}$, which equals zero when $Q = 2$ (see also ref. Martin et al., 2007) but it positive for $Q < 2$, and negative for $Q > 2$.

Finally, we can note that the strength of selection V_S (equation 1) can be considered as a scaling parameter: using the scaled variables $z_{i,s} = z_i / (2V_S)^{\frac{1}{Q}}$ to measure phenotypic traits, fitness in terms of $z_{i,s}$ variables becomes independent of V_S , while the variance of the distribution of mutational effects on each $z_{i,s}$ equals $a_s^2 = a^2 / (2V_S)^{\frac{2}{Q}}$: therefore, a^2 and V_S affect the results only through the compound parameter a_s^2 . In the simulations (described next), we used $V_S = 1/2$ so that $a_s^2 = a^2$. As shown by equation 3, large (resp. small) values of a_s^2 imply that mutations have strong (resp. weak) fitness effects.

202 Simulations. Analytical predictions are tested using individual-based simulations.
 203 Our program (written in C++, and available upon request) represents a haploid pop-
 204 ulation of N individuals with discrete generations. The genome of each individual is
 205 represented by a sequence of L bits (0 or 1) corresponding to the different loci. Phe-
 206 notypic effects of mutation at each locus are sampled at the start of the simulation:
 207 the m traits affected by a given locus are sampled randomly (and independently for
 208 each locus) among the n selected traits, and the effect of mutation on each of these m
 209 traits is sampled from a Gaussian distribution with mean 0 and variance a^2 . At the
 210 start of a generation, phenotypic values are computed for each individual; from this,
 211 one obtains the fitness of the individual based on equation 1. For each individual of
 212 the next generation, two parents are sampled (the probability that an individual is
 213 sampled being proportional to its fitness); selfing is allowed if the same individual is
 214 sampled twice. To generate a recombinant chromosome, the number of cross-overs is
 215 sampled from a Poisson distribution with parameter R (genome map length), and the
 216 position of each cross-over along the chromosome is sampled from a uniform distribu-
 217 tion ($R = 0$ corresponds to the case of an asexual population). Finally, the number
 218 of new mutations occurring in each genome is sampled from a Poisson distribution
 219 with parameter U , and the positions of mutant loci are sampled randomly; alleles are
 220 switched at mutant loci, from 0 to 1 or from 1 to 0 (mutation and back mutation thus
 221 occur at the same rate). In order to gain execution speed, the program is parallelized
 222 (using the MPI library) to run on several processors, each processor dealing with a
 223 given segment of the genome, for all individuals; execution speed can be considerably
 224 increased when the number of processors is sufficiently large so that the probability
 225 that an event (mutation or cross-over) occurs in a given segment per generation is

low (in which case most genome segments stay unchanged from one generation to the next).

At the start of the simulation each genome contains only “0” alleles, which corresponds to the fitness optimum. Simulations run for 50000 generations, equilibrium being reached during the first 30000 generations for most parameter values tested. Every 1000 generations, the program records the mean fitness of the population and the first 6 moments of the distribution of each phenotypic trait in the population. The results shown in the different figures correspond to averages over the last 20000 generations. Error bars were calculated using Hastings’ (1970) batching method, dividing these 20000 generations into 4 batches of 5000 generations and calculating the standard error over these 4 batches; however, error bars were generally small relative to the size of symbols used in the figures and are thus not shown. All our simulation results (with the *Mathematica* commands used to generate the figures) can be found in the Supplementary Material.

RESULTS

Asexual population. Figure 1 shows the equilibrium mean fitness of an asexual population as a function of the variance of mutational effects (on scaled traits) a_s^2 (left) or of the mean deleterious effect of mutations $\bar{s}$ (right), and for different values of the shape parameter Q . As a_s^2 becomes large, mean fitness converges to e^{-U} (which is close to 0.6 for $U = 0.5$, dashed line). For smaller values of the scaled mutational variance, however, the population reaches a different regime where $\bar{W} > e^{-U}$. In this case, an approximation for mean fitness can be obtained by assuming that distributions

of phenotypic traits z_i are Gaussian at equilibrium. As explained in Supplementary File S1, Euclidean distances from the optimum (d) then follow a χ -distribution, which yields:

$$\overline{\ln W} = -\frac{(2V_G)^{\frac{Q}{2}}}{2V_S} \frac{\Gamma\left(\frac{n+Q}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} \quad (4)$$

where V_G is the genetic variance at equilibrium (the variance of z_i , which by symmetry should be the same for all traits i); for $Q = 2$ (Gaussian fitness function), this simplifies to $\overline{\ln W} = -(n/2)(V_G/V_S)$. An expression for V_G at equilibrium is derived in Supplementary File S1. Assuming that $\overline{\ln W} \approx \ln \overline{W}$, one obtains that when $m = n$ (that is, when each mutation affects all phenotypic traits):

$$\overline{W} \approx \exp \left[-\overline{s} \left(\frac{nU}{\overline{s}Q} \right)^{\frac{Q}{2+Q}} \right] \quad (5)$$

When $Q = 2$, equation 5 simplifies to $\exp \left[-\sqrt{\frac{n}{2}U\overline{s}} \right]$, in agreement with the result obtained from Lande's analysis (1980) when selection acts independently on the different traits, and in the absence of mutational covariances among traits (that is, when the variance-covariance matrices representing the effects of selection and mutation on the traits are diagonal). Indeed, in an asexual population the whole genome can be considered as a single locus with many alleles (provided that the number of loci is sufficiently large), in which case Lande's analysis of the continuum-of-alleles model yields $V_G = \sqrt{Ua^2V_S}$ when mutation and selection covariance matrices are diagonal (the equilibrium genetic variance for each trait is not affected by the other traits under selection, see also p. 294 in ref. Bürger, 2000). When $m < n$, equation 5 still holds when the fitness function is Gaussian ($Q = 2$), while $\overline{W}$ is given by a slightly more complicated expression when $Q \neq 2$ (Supplementary File S1). However, this expression only depends weakly on m (for fixed $\overline{s}$) and remains close to equation 5 in most

cases (unless Q is high and m is small). As shown by Figure 1, equation 5 provides accurate predictions for $\overline{W}$ as long as a_s^2 is not too high. Supplementary Figure S1 shows the genetic variance V_G at equilibrium, for the same parameter values as in Figure 1.

Sexual population. Figure 2 shows the equilibrium mean fitness of a sexual population as a function of a_s^2 and $\bar{s}$. When mutations have strong effects on fitness, one obtains again that $\overline{W} \approx e^{-U}$ (right-most points on Figure 2). As a_s^2 decreases, a second regime is entered where $\overline{W}$ reaches a new value which is independent of a_s^2 , but depends on the shape parameter Q (roughly for $-4 < \log_{10}(a_s^2) < -2$). Finally, as a_s^2 continues decreasing a third regime is entered where $\overline{W}$ increases up to $\overline{W} \approx 1$ as a_s^2 decreases. In Supplementary File S2, we show that approximations for mean fitness under these last two regimes (a_s^2 small) can be obtained by assuming that distributions of phenotypic values in the population are Gaussian. As in previous models (e.g., Bulmer, 1972; Barton, 1986) one obtains that the equilibrium frequency of allele 1 at locus j (p_j) is either (i) at $p_j = 1/2$ (when selection at locus j is weak relative to mutation) or (ii) at one of the two symmetric equilibria where $p_j(1 - p_j) = X < 1/4$ (where X is a function of the model's parameters), the locus being closer to fixation (for allele 0 or 1) as selection increases. Assuming that all loci are at equilibrium (ii) and neglecting linkage disequilibria among loci, one obtains the following approximation for mean fitness:

$$\overline{W} \approx \exp \left[-\frac{2U}{Q} \right] \quad (6)$$

Figure 2 shows that this expression does indeed provide a correct prediction of $\overline{W}$ for intermediate values of a_s^2 (dashed lines). A better approximation can be obtained by

292 taking into account effects of the linkage disequilibria, which is done in Supplementary
 293 File S2 using the methods developed by Turelli and Barton (1990). As described before
 294 (Bulmer, 1971, 1974; Lande, 1976; Turelli and Barton, 1990), stabilizing selection tends
 295 to generate negative covariances among loci, which affect $\overline{W}$ through two effects: a
 296 reduction of the genetic variance V_G which directly increases $\overline{W}$, and an effect on
 297 equilibrium allele frequencies and thus on the *genic* variance V_g (see Appendix A)
 298 which has the opposite effect on $\overline{W}$. As long as linkage disequilibria remain small
 299 the second effect predominates, and one obtains the following approximation for $\overline{W}$
 300 (assuming that the number of loci L is large):

$$\overline{W} \approx \exp \left[-\frac{2U}{Q} \left(1 + \frac{2U}{n} \left(\frac{1}{r_H} - 1 \right) \right) \right] \quad (7)$$

301 where r_H is the harmonic mean recombination rate between all pairs of loci (derived in
 302 Appendix B under our simulated genetic architecture). Figure 2 shows that equation
 303 7 does indeed provide a slightly better approximation than equation 6 for intermediate
 304 values of a_s^2 (horizontal solid lines). Interestingly, Supplementary Figure S1 shows that
 305 Q has only a weak effect on the equilibrium genetic variance V_G in this intermediate
 306 regime, which remains close to the value obtained for $Q = 2$, neglecting linkage dise-
 307 quilibria: $V_G = 2UV_S/n$ (which is also obtained from *house-of-cards* models assuming
 308 a Gaussian fitness function, e.g. Turelli, 1985; Bürger, 2000). Finally, when a_s^2 is very
 309 small (so that mutations have very weak fitness effects) one predicts that most loci
 310 should be at the equilibrium where $p_j = 1/2$, in which case $\overline{W} \approx \exp \left[-\overline{s} (L/4)^{\frac{Q}{2}} \right]$
 311 where L is the total number of loci. However, in this regime we expect that the
 312 relative effect of genetic drift on allele frequency dynamics could be important. In
 313 Supplementary File S4, we show that when selection at each locus becomes weaker

than mutation and drift, an approximation for mean fitness is given by:

$$\overline{W} \approx \exp \left[-\overline{s} \left(\frac{NU}{1 + 4Nu} \right)^{\frac{Q}{2}} \right] \quad (8)$$

where N is population size. Figure 2 shows that equation 8 provides accurate predictions when a_s^2 is very small (left part of the figures). Furthermore, combining equations 7 and 8 (solid curves) gives good predictions for all values of a_s^2 as long as they remain small (roughly, $< 10^{-2}$ for the parameter values of Figure 2) so that the Gaussian approximation holds. For higher values of a_s^2 , simulations indicate that distributions of phenotypic values depart from Gaussian distributions: in particular, the fourth and sixth cumulants K_4 and K_6 are positive and increase as a^2 increases (while the third and fifth cumulants stay close to zero), for all values of Q (results not shown). In Supplementary File S3, we show that using a Gram-Charlier expansion to approximate the distribution of phenotypic effects yields an expression for $\overline{W}$ in terms of the genetic variance V_G and of higher cumulants (K_4 , K_6). Furthermore, these higher cumulants can in turn be expressed in terms of the genetic variance, assuming that $p_j q_j$ is small at each locus (*rare-alleles approximation*, e.g. Barton and Turelli, 1987; Turelli and Barton, 1990): one obtains in particular $K_4 \approx a^2 V_G [3m / (2 + m)]$, $K_6 \approx a^4 V_G [15m / (4 + m)]$, which fits well with the simulation results (see Figure 1 in Supplementary File S3). Finally, the methods developed by Turelli and Barton (1994) can be used to calculate V_G at equilibrium in this non-Gaussian regime. As shown in Supplementary File S3, the result (which has to be obtained numerically) fits well with the simulation results as long as a_s^2 is not too large, and $Q \geq 2$; however, we could not find any simple analytical expression for $\overline{W}$ in this non-Gaussian regime. From the expressions of K_4 and K_6 above, one predicts that the Gaussian regime should be left

more rapidly (as a^2 increases) for larger m , since K_4 and K_6 are increasing functions of m ; Figure 3 (left) confirms that this is indeed the case. However, Figure 3 right indicates that for a fixed $\bar{s}$, $\bar{W}$ is relatively insensitive to m .

Figure 4 explores the effect of linkage on mean fitness: for $U = 0.5$ and $n = 50$, the effect of linkage disequilibria on $\bar{W}$ remains small as long as the harmonic mean recombination rate r_H is not too small (with $L = 10000$ loci, $r_H \approx 0.053$ for a map length of 1 Morgan, while $r_H \approx 0.3$ for a map length of 10 Morgans — see Appendix B). In this regime, increasing linkage tends to reduce mean fitness (through an increase in genic variance V_g), and equation 7 matches well with the simulation results (except for $Q = 1$ where the fit is less good). For tighter linkage, however (roughly, $R < 1$) simulations results depart from the prediction from equation 7 (which assumes that the contribution of linkage disequilibria to the genetic variance remains small) and show that $\bar{W}$ increases as recombination decreases: overall, linkage thus has a non-monotonic effect on mean fitness. Interestingly, equation 7 indicates that the contribution of linkage disequilibria becomes more important when the number of traits under selection (n) is small. Figure 5 confirms this result, showing that lower values of n lead to a stronger decrease in $\bar{W}$ for both $\bar{s} = 0.01$ and $\bar{s} = 0.1$, while the effect is less marked (and may even be reversed) when $\bar{s} = 0.001$. This effect of n can be understood as follows: mean fitness decreases when the sum of genetic variances for the different traits $\sum_{i=1}^n V_{G,i}$ increases. Due to the symmetry of our model, the two components of the genetic variance (the genic variance $V_{g,i}$, and the contribution of linkage disequilibria d_i , see Appendix A) should be the same for all traits. As shown in Supplementary File S2 (see also Turelli, 1985; Bürger, 2000), when the effects of linkage disequilibria are neglected the genetic variance for each trait at equilibrium is

proportional to $1/n$ (roughly, $p_j q_j$ at each locus scales with $1/m$, since the strength of selection at each locus increases with m ; however, a proportion m/n only of loci contribute to trait i : therefore, the effect of m cancels and $V_{g,i}$ scales with $1/n$). As a consequence $\overline{W}$ (which depends on the product nV_G) is independent of n . The contribution of associations between loci depends on all pairwise linkage disequilibria and is proportional to V_g^2 (see Supplementary File S2) and therefore to $1/n^2$. As a consequence, the overall contribution of linkage disequilibria to mean fitness is proportional to $1/n$. However, pairwise linkage disequilibria may not be the only cause of the strong reduction of $\overline{W}$ shown on Figure 5 at low values of n (for $\bar{s} = 0.01$ and 0.1): indeed, simulations indicate that for these low values of n , distributions of phenotypic traits in the population depart from Gaussian distributions (fourth and sixth cumulants become significantly different from zero), in which case the results derived in Supplementary File S2 (which assume Gaussian distributions of phenotypic traits) do not hold.

Effects of population size and number of loci. Many of the results shown above assume a large population size and large number of loci. Figure 6 explores the effects of varying population size: in the case of a sexual population (Figure 6A), smaller population sizes tend to decrease $\overline{W}$ when the average fitness effect of mutations is sufficiently strong (right part of the figure). However, for lower values of $\bar{s}$ one observes the opposite effect, with higher values of mean fitness for lower population sizes. With a Gaussian fitness function ($Q = 2$, as in Figure 6), a diffusion model can be used to predict the equilibrium genetic variance under selection, mutation and drift, assuming that mean phenotypes stay at the optimum (Bulmer, 1972). In Supplementary File S4,

we obtain an approximation for mean fitness (in terms of hypergeometric functions) valid for $Nu \ll 1$, which fits well with simulation results for $N = 500$ (dotted curve in Figure 6A). In contrast to the sexual case, the effects of population size are less marked in the case of asexual organisms (Figure 6B), and $\overline{W}$ always decreases as N decreases. These effects of finite population size can be understood as follows. Genetic drift affects mean fitness through two different effects: an effect on the genetic variance maintained at equilibrium, which is usually (but not always) lower in smaller populations, and an effect on mean phenotypes, which may be displaced from the optimum due to drift. In the case of a Gaussian fitness function ($Q = 2$), these two effects can easily be separated: indeed, log-fitness equals $-\sum_{i=1}^n (z_i - z_i^*)^2 / (2V_S)$, where z_i is the value of phenotype i and z_i^* the optimal value for this phenotype (fixed to zero in our model). Therefore, the average log-fitness is given by $-\sum_{i=1}^n (V_{G,i} + (\overline{z}_i - z_i^*)^2) / (2V_S)$, where $V_{G,i}$ is the genetic variance for trait i and $\overline{z}_i$ the average value of trait i (see also Charlesworth, 2013). Assuming that $\overline{\ln W} \approx \ln \overline{W}$, mean fitness can thus be written as a product of two terms:

$$\overline{W} \approx \exp \left[-\frac{\sum_{i=1}^n V_{G,i}}{2V_S} \right] \exp \left[-\frac{\sum_{i=1}^n (\overline{z}_i - z_i^*)^2}{2V_S} \right]. \quad (9)$$

The first term (denoted hereafter $\overline{W}_{V_G}$) shows that increasing the variance of phenotypic traits tends to decrease mean fitness, while the second term (denoted hereafter $\overline{W}_{\overline{z}}$) shows that displacing mean phenotypes from the optimum also decreases $\overline{W}$. Simulations show that injecting equilibrium values of genetic variances $V_{G,i}$ and mean phenotypes $\overline{z}_i$ (measured in the simulations) into equation 9 accurately predict $\overline{W}$ for all parameters tried with $Q = 2$, as long as $\log_{10}(\overline{s}) \leq -1$ (results not shown). Note that all the mathematical derivations performed in the different Supplementary Files

406 assume that mean phenotypes are at the optimum, and therefore that $\overline{W}_{\bar{z}} = 1$. Sup-
 407 plementary Figure S2 shows measures of $\overline{W}_{V_G}$ and $\overline{W}_{\bar{z}}$ for the different values of N
 408 and $\bar{s}$ explored in Figure 6. These results can be summarized as follows: in a sexual
 409 population (Figure 6A), $\overline{W}_{\bar{z}}$ stays close to 1 in most cases, but may be slightly less
 410 than 1 (around 0.97 - 0.98) for $N = 500$: mean phenotypes thus generally stay close
 411 to their optimal values, and the mutation load is mainly generated by the term $\overline{W}_{V_G}$.
 412 When mutations tend to have strong fitness effects ($\log_{10}(\bar{s}) \geq -2$), drift tends to
 413 increase genetic variances $V_{G,i}$ (by increasing $\overline{p_j q_j}$ at each locus j above its value at
 414 mutation-selection balance), and thus decreases $\overline{W}_{V_G}$ — note that this effect is taken
 415 into account by the diffusion model (equation 6 in Supplementary File S4). When
 416 mutations tend to have weak fitness effects ($\log_{10}(\bar{s}) \leq -3$) however, drift tends to
 417 reduce $V_{G,i}$ by bringing the different loci closer to fixation, thereby increasing $\overline{W}_{V_G}$
 418 (and hence $\overline{W}$). By contrast, in an asexual population drift always reduce the genetic
 419 variance ($\overline{W}_{V_G}$ increases as N decreases), but also has a substantial effect on mean
 420 phenotypes ($\overline{W}_{\bar{z}}$ decreases as N decreases). Because the second effect is stronger than
 421 the first, the overall effect of drift is to reduce the mean fitness of asexuals.

422 Our model is somehow artificial, however, as we assumed that the fitness opti-
 423 mum is located at the origin ($z_i^* = 0$ for all i). Due to the symmetry of the model, one
 424 expects that mean phenotypes should be at the origin (and thus at the optimum) in
 425 the regime where dynamics are mainly driven by mutation and drift (low $\bar{s}$), when the
 426 number of loci is large: for example if a large, random proportion of loci are fixed for
 427 allele 1 and the other loci fixed for allele 0, mean phenotypes should be close to zero
 428 since the sum of all mutational effects (corresponding to the effects of fixed alleles 1)
 429 converges to the average effect of mutations, which is zero. It seems artificial, however,

430 to assume that optimal trait values are precisely the values towards which the pop-
 431 ulation should converge at mutation-drift equilibrium, and it seems more likely that
 432 in many cases, mean phenotypes at mutation-drift equilibrium should be far from the
 433 optimal values (decreasing the value of $\overline{W}_z$ in the mutation-drift regime). In order to
 434 explore that, we modified our simulation program so that the fitness optimum is not
 435 located at the origin of the phenotypic space ($z_i = 0$ for all i). To do this, we select a
 436 genotype sufficiently distant from the origin (in phenotypic space) so that when setting
 437 optimal phenotypic values z_i^* to the values coded by this genotype, fitness at the origin
 438 is less than 0.1. At the start of the simulation, the population is fixed for the genotype
 439 corresponding to the fitness optimum. At mutation-drift balance, the population is
 440 still expected to converge to the origin (due to the symmetry of the distribution of
 441 mutational effects), where fitness is lower than 0.1. Results are shown on Figures 6C
 442 and 6D in the case of a sexual and asexual population, respectively. As can be seen
 443 on these Figures, the position of the fitness optimum has little effect as long as selec-
 444 tion is sufficiently strong ($\log_{10}(\bar{s}) \geq -3$), since in this case selection maintains the
 445 population near the optimum. For lower $\bar{s}$, however, mutation and drift tend to bring
 446 populations away from the optimum (and closer to the origin), which decreases $\overline{W}_z$
 447 and thus decreases mean fitness (see also Supplementary Figure S2), this effect being
 448 more pronounced in asexual than in sexual populations (in sexuals, this effect becomes
 449 important only for $\bar{s} = 10^{-5}$). Note that we could not obtain results for $\bar{s} = 10^{-6}$,
 450 because with such low mutational effects (and with 10000 loci) it was not possible to
 451 find a genotype sufficiently distant from the origin so that fitness at the origin is lower
 452 than 0.1 when setting the optimum to the phenotypic values coded by this genotype.
 453 Interestingly, in the sexual case (Figure 6C) one still observes an intermediate range

454 of $\bar{s}$ ($\bar{s} = 10^{-4}, 10^{-3}$) where decreasing population size increases mean fitness: in this
455 regime, drift tends to bring each locus closer to fixation (thus reducing $V_{G,i}$), but se-
456 lection still maintains mean phenotypes $\bar{z}_i$ close to the optimum. Decreasing $\bar{s}$ (or
457 decreasing N further, as shown in Supplementary Figure S2 for $N = 100$) generates
458 departures of mean phenotypes from the optimum, decreasing $\overline{W}_{\bar{z}}$ (and thus $\overline{W}$).

459 Finally, Supplementary Figure S3 shows that changing the number of loci L
460 (for a fixed U) has generally stronger effects in the case of sexual populations, where
461 in the low $\bar{s}$ regime, decreasing the number of loci decreases the genetic variance (and
462 thus increases $\overline{W}$).

463 DISCUSSION

464 As we have seen in introduction, different forms of models have been proposed
465 to predict the overall effect of recurrent mutation on the mean fitness of populations.
466 Typically, models representing deleterious mutations (without including a phenotypic
467 dimension) do not consider possible compensatory effects among mutations, and as-
468 sume that epistasis is the same for all pairs of mutations (Kimura and Maruyama,
469 1966; Charlesworth, 1990). Using this type of model, Kimura and Maruyama (1966)
470 predicted that epistasis should have no effect on the mean fitness of asexuals (which
471 should remain close to e^{-U}), while it should increase the fitness of sexuals if it is
472 negative, and decrease $\overline{W}$ if it is positive. On the other hand, models representing sta-
473 bilizing selection on a set of quantitative phenotypic traits (such as Fisher’s geometric
474 model) provide a natural way of incorporating compensatory effects among mutations
475 and distributions of selection coefficients and epistatic effects. In this paper, we used a

general model that allows us to play with the number of traits under selection (n), the number of traits affected by a given mutation (m) and the shape of the fitness peak (Q). Interestingly, this last parameter was already shown by others to affect the average sign of epistasis among pairs of mutations: epistasis is positive on average when the fitness peak is sharper than a Gaussian function ($Q < 2$), while it is negative when the fitness peak is flatter than a Gaussian ($Q > 2$), and equal to zero when fitness is exactly Gaussian (Martin et al., 2007; Gros et al., 2009). Furthermore, the average deleterious effect of mutations at the optimum $\bar{s}$ can be expressed as a simple function of the variance of scaled phenotypic effects of mutations a_s^2 and the parameters m and Q (equation 3).

In the case of an asexual population, we found that mean fitness stays indeed close to e^{-U} when mutations tend to have strong fitness effects; however, $\bar{W} > e^{-U}$ under weaker fitness effects of mutations (Gaussian regime), due to the possibility of compensatory effects among mutations at different loci. For a fixed $\bar{s}$, mean fitness is higher under positive epistasis ($Q < 2$) than under negative epistasis ($Q > 2$); this is probably due to the fact that selection for compensatory mutations is stronger when the fitness peak is sharp, keeping the population closer to the fitness optimum. In contrast, under negative epistasis the fitness landscape presents a plateau around the optimum, and at equilibrium many genotypes are located near the edge of this plateau, where the effect of deleterious mutations tends to be strong. Finally, we showed that under this regime mean fitness can be expressed as a simple function of U , $\bar{s}$, n and Q (equation 5), which indicates that $\bar{W}$ decreases as the number of traits under selection n increases.

In a sexual population, mean fitness is also at e^{-U} when mutations have very

500 strong fitness effects: this is expected, as mutations stay at very low frequency and
 501 epistatic interactions among mutations have thus little effect. For weaker mutational
 502 effects, Kimura and Maruyama (1966)’s prediction is verified: positive epistasis de-
 503 creases $\overline{W}$, while negative epistasis increases it; furthermore, we showed that $\overline{W}$ con-
 504 verges to a very simple expression ($e^{-\frac{2U}{Q}}$) when the phenotypic effect of mutations
 505 is sufficiently weak, so that distributions of phenotypic values in the population are
 506 nearly Gaussian. Although this expression assumes that linkage disequilibria among
 507 loci can be neglected, effects of genetic associations can be computed, showing that
 508 linkage disequilibria tend to reduce $\overline{W}$ as long as they remain weak, the importance of
 509 this effect increasing as the number of selected traits n decreases. Contrarily to results
 510 obtained previously assuming $NU \ll 1$ (Hartl and Taubes, 1998; Poon and Otto, 2000;
 511 Tenaillon et al., 2007; Lourenço et al., 2011), our model predicts a higher mean fitness
 512 when the number of traits is large, through this effect on linkage disequilibrium. Figure
 513 5 indeed shows important reductions in fitness when the number of traits decreases
 514 (for moderate to strong fitness effects of mutations, of the order 0.01 to 0.1), which
 515 may also involve higher-order genetic associations (since distributions of phenotypic
 516 values depart from Gaussian distributions for very low values of n). Rather than the
 517 “cost of complexity” often described at low mutation rate, we thus predict a “cost of
 518 simplicity” when the overall mutation rate is large (as shown by equation 7, this effect
 519 is proportional to U^2 and should thus become negligible when the overall mutation
 520 rate is small). Note that this cost does not depend on the degree of pleiotropy (m) of
 521 individual mutations, but only on the total number of traits under selection. Interest-
 522 ingly, these results do not depend on the precise shape of the distribution of mutational
 523 effects (which was Gaussian in the simulations), since the derivation of equations 6 and

7 in Supplementary File S2 makes no assumption on this distribution. It does assume uncorrelated mutational effects on the different traits, however, and it would be interesting to extend our analysis by incorporating mutational and/or selective correlations among traits — as shown by Martin and Lenormand (2006), the overall effect of such correlations is to reduce the effective number of phenotypic traits (see also Zhang and Hill, 2003 for an analysis of the effects of correlations among traits). Furthermore, different ways of incorporating restricted pleiotropy could be considered: in particular, Welch and Waxman (2003) proposed a model in which different sets of traits are affected by different subsets of loci (modular pleiotropy), and it would be interesting to explore how this form of modularity would affect our results.

Regarding genetic architecture, an important assumption of our model is the fact that loci are biallelic. By contrast, Lande (1980)’s analysis considered an infinite number of alleles per locus (continuum-of-alleles model); in that case, assuming diagonal mutation and selection matrices (no mutational or selective covariance among traits) and neglecting linkage disequilibria, one obtains that the mean log-fitness should be $-\sqrt{\frac{n}{2}LU\bar{s}}$ (where L is the number of loci) in the case of a Gaussian fitness function (this stems from the fact that the contribution of each locus to the genetic variance is $\sqrt{u a^2 V_S}$, where u is the per-locus mutation rate). This contrasts with the result that mean log-fitness should be $\approx -U$ when $Q = 2$ in biallelic models, and indicates that assumptions about the number of alleles per locus may have important effects. However, a key assumption of Lande’s analysis is the fact that distributions of allelic effects in the population are Gaussian *at each locus*, which is much stronger than the assumption that distributions of overall phenotypes are Gaussian, and may not hold for realistic values of per-locus mutation rates and mutational variances (e.g., Turelli,

1984). It would thus be interesting to explore how sensitive are our results to assumptions regarding the number of alleles per locus. In particular, our assumption of biallelic loci should not hold when $Nu \sim 1$ (in which case many alleles may segregate at the same locus).

Finally, we found that the degree of pleiotropy of mutations (m) affects mean fitness mostly through its effect on $\bar{s}$, in regimes where $\bar{W}$ is affected by $\bar{s}$: in particular the Gaussian regime in asexual populations (equation 5), and the regime where selection at each locus is weaker than mutation and drift in sexual populations (equation 8). This contrasts with the result obtained by Lourenço et al. (2011) in the low mutation limit ($NU \ll 1$), showing that the average fitness at equilibrium depends on the total number of selected traits but not on the degree of mutational pleiotropy. Another difference concerns the effect of population size: although the load always increases as population size decreases when $NU \ll 1$ (Hartl and Taubes, 1998; Poon and Otto, 2000; Tenaillon et al., 2007; Lourenço et al., 2011), we found that in sexuals, the mutation load may actually be lower at smaller population sizes in the weak selection regime (Figure 6). As we have seen, this occurs whenever the fitness effect of mutations is small ($\bar{s} = 10^{-4}, 10^{-3}$ in the case of Figure 6), so that diversity at each locus ($p_j q_j$) at mutation-selection balance is substantial, in which case drift tends to reduce this diversity and therefore reduces the genetic variance V_G — the same effect has also recently been discussed by Charlesworth (2013) in a 1-trait model. For very low fitness effects of mutations, however, mutation and drift may displace mean phenotypes away from the optimum and substantially reduce mean fitness (Figures 6C and D). This last effect may only occur for a restricted range of parameters, since when $\bar{s}$ becomes very low, very large numbers of loci are required for fitness to decrease

significantly (see also Charlesworth, 2013).

In general, we found that asexual populations have a higher mean fitness than sexual populations, in agreement with previous models of stabilizing selection with a constant optimum (e.g., Charlesworth, 1993): this is due to the fact that genotypes coding for optimal trait values are preserved by asexual reproduction, but broken by recombination. Nevertheless, sexuals may have a higher mean fitness than asexuals when epistasis among mutations is negative on average ($Q > 2$), as long as $\bar{s}$ is not too small (so that $\bar{W}$ stays close to e^{-U} in asexuals, but reach higher values in sexuals); this occurs for example for $Q = 6$, when $\bar{s} \geq 10^{-4}$ (for the parameter values used in Figures 1 and 2). Sexuals may also have a higher mean fitness when the effects of drift are important: in particular, Figure 6C and 6D show that deviations of mean phenotypes from their optimal values caused by drift are generally more important in asexual than in sexual populations (for low $\bar{s}$). Although we only observed this last effect for restricted ranges of parameters, it may become more important in the case of populations subdivided into many small demes. Previous models explored the evolution of recombination modifiers under stabilizing selection (Charlesworth, 1993; Barton, 1995), but ignored the effects of genetic drift: it would thus be interesting to extend these models to the case of finite (or spatially structured) populations. Exploring the effects of diploidy and of the mating system would be other possible extensions of the present work.

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599 We call $V_{G,i}$ the variance of the value of trait i in the population: $V_{G,i} =$
 600 $\text{Var}[z_i]$. Because we assume additive effects of the different loci on phenotypic traits
 601 ($z_i = \sum_j r_{ij} X_j$, where the sum is over all loci j), $V_{G,i}$ can be decomposed into two
 602 terms (e.g., Lynch and Walsh, 1998): $V_{G,i} = V_{g,i} + d_i$, where $V_{g,i} = \sum_j r_{ij}^2 p_j (1 - p_j)$
 603 is the genic variance (p_j being the frequency of allele 1 at locus j in the population),
 604 and $d_i = \sum_{j \neq k} r_{ij} r_{ik} D_{jk}$ the effect of linkage disequilibria on the genetic variance
 605 ($D_{jk} = \text{Cov}[X_j, X_k]$ being the linkage disequilibrium between loci j and k). In the
 606 case of an asexual population, the genetic variance at equilibrium can be calculated
 607 by considering the whole genome as a single locus with a large number of alleles
 608 (Supplementary File S1). In the sexual case, $V_{g,i}$ and d_i at equilibrium can be computed
 609 using the methods developed by Turelli and Barton (1990), extended to deal with
 610 multiple traits under selection (Supplementary File S2). Due to the symmetry of the
 611 model we expect that $V_{G,i}$ and $V_{g,i}$ should be the same for all traits at equilibrium,
 612 and are thus simply denoted V_G and V_g in the text.

Under the genetic setting described above, the harmonic mean recombination rate among pairs of loci r_H (that appears in equation 7) can be computed as follows. The genetic distance between adjacent loci (in Morgans) is $R/(L-1)$, and therefore the distance between two loci separated by i between-locus intervals is $iR/(L-1)$. Furthermore, the number of different pairs of loci separated by i intervals is $L-i$. Finally, the rate of recombination between two loci at genetic distance x (probability that an odd number of cross-overs occurs within the interval) is given by Haldane's mapping function: $r(x) = \frac{1}{2}(1 - e^{-2x})$, yielding:

$$\frac{1}{r_H} = \frac{1}{\frac{1}{2}L(L-1)} \sum_{i=1}^{L-1} \frac{L-i}{\frac{1}{2} [1 - \exp(-2i\frac{R}{L-1})]} \quad (10)$$

which has to be evaluated numerically. For $L = 10000$ and $R = 10$, one obtains $r_H \approx 0.3$.

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Figure 1. Mean fitness of an asexual population as a function of a_s^2 and $\bar{s}$. X-axes correspond to the mutational variance on scaled traits $a_s^2 = a^2 / (2V_S)^{\frac{2}{Q}}$ (left) and the average deleterious effect of mutations (on log-fitness) at the optimum $\bar{s}$ (right). The different colors correspond to different shapes of the fitness function, controlled by the parameter Q : $Q = 1, 2, 3, 4, 5, 6$ from red to purple. The dashed horizontal line corresponds to e^{-U} , while colored curves are predictions from equation 5, and dots are simulation results. Parameter values are $U = 0.5$, $n = 50$, $m = 5$; in the simulations $V_S = 0.5$, population size is set to $N = 50000$ and the number of loci to $L = 10000$.

Figure 2. Mean fitness of a sexual population as a function of a_s^2 and $\bar{s}$ (defined as the average effect of mutations on log-fitness at the optimum). Parameter values are the same as in Figure 1, with genome map length $R = 10$ Morgans (which leads to $r_H \approx 0.3$, see Appendix B). Dots correspond to simulation results, and curves to different approximations obtained assuming Gaussian distributions of phenotypic traits in the population: equations 6 (dashed lines), 7 (horizontal solid lines) and 8 (solid curves on the left). Note that in the left figure all points are superposed for $\log_{10}(a_s^2) = 0$.

Figure 3. Mean fitness of a sexual population: effect of the degree of pleiotropy m . Squares: simulation results for $Q = 6$, $m = 5$ (white) and $m = 50$ (black); other parameters are as in Figure 2. The solid line corresponds to the prediction from equation 7 (Gaussian regime), and the dashed line to e^{-U} .

Figure 4. Mean fitness as a function of map length R in Morgans. R corresponds to the mean number of cross-overs per meiosis within the genome; note that $R = 0$ corresponds to asexual reproduction. Parameter values are the same as in Figures 1 and 2, with $a^2 = 0.0002$ in the simulations (so that $\bar{s} = 0.001$ for $Q = 2$). Dots correspond to simulation results, and curves to the prediction from equation 7.

Figure 5. Mean fitness of a sexual population as a function of the number selected traits n . The fitness function is Gaussian ($Q = 2$). Curve: prediction from equation 7; dots: simulation results with $\bar{s} = 0.001$ (empty circles), $\bar{s} = 0.01$ (filled circles) and $\bar{s} = 0.1$ (filled squares). Other parameters are as in Figure 2.

Figure 6. Mean fitness of a sexual (A, C) and asexual (B, D) populations: effects of population size. Dots correspond to simulation results for to $N = 50000$ (empty circles), 5000 (empty squares), 500 (filled circles). Other parameters are as in Figure 1 and 2, with $Q = 2$. A, B: the optimum is located at the origin (in phenotypic space), that is, in $z_i = 0$ for all traits i ; C, D: the optimum is located away from the origin, so that the fitness of an individual at the origin is less than 0.1 (see text for more explanations). Solid curves on the left figures (sexual populations) correspond to the predictions from equation 8 for $N = 50000$, 5000 and 500 from left to right, while the dotted curves corresponds to equation 6 in Supplementary File S4 (for $N = 500$). Curves on the right figures (asexual populations) correspond to equation 5. Finally, the dashed horizontal lines correspond to e^{-U} .

Table 1: Parameters and variables of the model.

n	number of phenotypic traits under selection
m	number of traits affected by a single mutation
Q	shape of the fitness peak (see equation 1)
V_S	strength of selection (see equation 1)
a^2	variance of phenotypic effects of mutations
$a_s^2 = a^2 / (2V_S)^{\frac{2}{Q}}$	variance of mutational effects on scaled traits
L	number of loci affecting selected traits
U	total rate of mutation per generation on selected loci
$u = U/L$	mutation rate per locus
$\bar{s}$	mean deleterious effect of mutations (on log-fitness) at the fitness optimum (given by equation 3)
R	genome map length (in Morgans)
r_H	harmonic mean recombination rate among pairs of loci
N	population size
z_i	value of trait i in a given individual
r_{ij}	effect of mutation at locus j on trait i
p_j	frequency of allele 1 at locus j in the population
D_{jk}	linkage disequilibrium between loci j and k
V_G	genetic variance (variance of z_i among individuals, which at equilibrium should be the same for all traits i)
V_g	genic variance (see Appendix A)