Conservation Genetics

Edited by V. Loeschcke
J. Tomiuk
S. K. Jain

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Editors

Dr. V. Loeschcke
Institute of Ecology and Genetics
University of Aarhus
Ny Munkegade, Building 540
DK-8000 Aarhus C
Denmark

Dr. J. Tomiuk
Section of Clinical Genetics
University of Tübingen
Wilhelmstr. 27
D-72074 Tübingen
Germany

Dr. S. K. Jain
Department of Agronomy
and Range Sciences
University of California
Davis, CA 95616
USA

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Extinction risk by mutational meltdown: Synergistic effects between population regulation and genetic drift

W. Gabriel[1] and R. Bürger[2]

[1]*Department of Physiological Ecology, Max Planck Institute for Limnology, Postfach 165 D-24302 Plön, Germany*
[2]*Institute of Mathematics, University of Vienna, Strudlhofgasse 4, A-1090 Vienna, Austria*

Summary. The accumulation of deleterious mutations reduces individual and mean population fitness. Therefore, in the long run, population size is affected. This facilitates further accumulation of mutations by enhanced genetic drift. Such synergistic interaction then drives the population to extinction.

This mutational meltdown process is studied primarily for asexual populations. Recombination cannot stop the meltdown in small sexual populations. Independent of the mode of reproduction, the asexual case is relevant for any paternally or maternally inherited trait and for mitochondria and chloroplasts that can be viewed as asexual populations inside cells.

The extinction risk is maximal for an intermediate value of the selection coefficient. Recombination does not destroy this effect, at least for small populations. In the asexual case, group selection is able to overpower individual selection to establish lineages with low repair capabilities, i.e., highly deleterious mutations.

If the expression of deleterious mutations is modified by the environment, changes in the environment can cause an unexpected increase or decrease in the extinction risk because of the pronounced maximum extinction risk at intermediate values of s. It may be that an environmental management treatment that improves individual fitness, counterintuitively enhances the extinction risk of a population.

Introduction

In addition to many ecological factors, e.g., random fluctuations of demographic parameters or externally forced perturbations of the environment, there are also well known genetic effects, e.g., inbreeding depression or loss of genetic variance that can contribute considerably to the extinction risk of populations. Besides these more classical problems of conservation genetics there is another source of genetic deterioration: the continuous input of slightly deleterious mutations. Lynch and Gabriel (1990) studied the consequences under asexual reproduction, and Gabriel et al. (1991) demonstrated that this mutation load considerably enhances the extinction risk for small sexual populations if it acts together with demographic stochasticity. Recent experiments (Houle et al., 1992) confirm the order of magnitude of the mutation load estimated from other data (see Lynch and Gabriel, 1990).

On average, each individual genome seems to incur one slightly deleterious mutation *per* generation. Mutation rate and mutational effect are hard to estimate and the mutation rate might even have been underestimated (Kondrashov, 1988). The consequences of the accumulation of deleterious mutations for asexual (or parthenogenetic) organisms are unquestionable, but for sexual species it is still debatable. For which population sizes is the mutational meltdown (Lynch and Gabriel, 1990) an important force if compared to other risks such as fluctuations in the environment? The smaller the population size, the more likely there is a synergistic interaction between many risk factors, i.e., the overall extinction risk might be much higher than expected from considering single risk factors.

To assess the impact of deleterious mutations for populations, classic population genetics is very helpful but can be misleading because most of this theory has been developed for constant (effective) population sizes. Historically, the main interest has been the change in relative gene frequencies. Complications arising from population dynamics have often been neglected. On the other hand, in ecological theory genetic influences have been ignored for a long time. Besides historical reasons, population genetics and theoretical ecology are already mathematically quite complex so that a combined treatment might often be hopeless with respect to mathematical tractability.

To investigate genetic effects in combination with population dynamics, a reference model without genetics is needed. For this reason, Gabriel and Bürger (1992) developed a purely demographic model. Studying the extinction risk by demographic stochasticity (random fluctuations of birth rate, death rate, and sex-ratio), they detected that the former theory, which has been developed with stochastic concepts that are valid only for large populations, often predicts extinction risks that are much too low for asexual and sexual populations. In addition, in sexual populations the influence of sex-ratio fluctuations has been ignored or drastically underestimated.

The present paper focuses on asexual populations for which the accumulation of deleterious mutations is an irreversible process and concentrates on aspects not described in Gabriel et al. (1991). It should be stressed, especially in the context of conservation genetics, that all aspects studied for asexual species are also of importance for sexual species. In small sexual populations similar problems arise as in asexuals, but also there are several traits that are maternally or paternally inherited. Consequently, sexual species have to be treated as asexual populations with respect to these characters. Inside each cell there are (maternally or paternally inherited) asexual populations: mitochondria and additionally chloroplasts in plants. Therefore, the studies presented here are of general importance to the survival of all higher

organisms – and meant as stimuli for further experimental and theoretical investigations in the context of conservation genetics.

Accumulation of deleterious mutations in asexual populations under the assumption of constant population size

In finite populations, natural selection cannot efficiently remove mutants carrying deleterious mutations if fitness differences caused by mutations are small or the mutation rate is very high. In addition, random genetic drift can play an important role for the accumulation of deleterious mutations, especially under asexual reproduction. We use the following definitions:

s	selection coefficient = fractional reduction in viability caused by a single mutation;
$W_n = (1 - s)^n$	fitness of an individual carrying n mutations (which are assumed to act multiplicatively);
μ	mutation rate *per* genome and *per* generation;
mutational class	individuals carrying the same number of mutations (the loci at which mutations occur might differ between individuals).

An asexual population can be subdivided into mutational classes. Let us first consider the mutation-free class. The smaller this class, the higher the probability that by chance this class does not contribute to the survivors in the next generation. If this class is lost, it is lost forever because the present model neglects back mutations and compensatory mutations. (Backmutations are believed to occur at too low a rate, at least for population sizes below 10^8. However, compensatory, fitness increasing mutations may decrease the extinction risk considerably, cf. Lynch and Gabriel (1990).) Therefore, the mutation-free class cannot be re-established from the higher mutational classes. After the loss of the mutation-free class, the class carrying one mutation becomes the least loaded class and it will meet the same fate of being lost, and so on. With each loss of the actual least-loaded class, the population mean fitness declines. This ratchet-like process was first described by Muller (1964) and has been called Muller's ratchet (Felsenstein, 1974).

The speed of the ratchet critically depends on the size of the least loaded class C_0 in relation to population size N. For the order of events "reproduction-mutation-selection" the ratio C_0/N after selection is expected to be

$$\frac{C_0}{N} = e^{-\mu(1-s)/s}, \qquad (1)$$

if N is very large and μ is small (see Gabriel et al., 1993). Eq. (1) differs slightly from $\exp(-\mu/s)$, which is given by Haigh (1978), because of another life cycle. If s is small then the difference between the formulae is negligible. If the population is censured after selection, Haigh's formula cannot be appropriate for large s; this is obvious for $s = 1$ (lethal mutations) when only non-mutants survive selection. The proportion of the least loaded class must converge to one as the selection coefficient s approaches 1 as shown in Fig. 1.

This figure gives only a hint of the dynamics of the ratchet. If N individuals are drawn randomly after selection to constitute the next generation, then the probability of losing the least loaded class is approximately

$$p = \left(1 - \exp\left[-\frac{\mu(1-s)}{s}\right]\right)^N. \tag{2}$$

This probability can be used to calculate the speed of the ratchet in a deterministic fashion if one assumes that after each loss of the least loaded class (after each "turn" of the ratchet) the deterministic equilibrium distribution of mutation classes is the same as before apart from being shifted by one class. But to re-establish the equilibrium distribution takes time. If the ratchet turns too fast, the distribution of mutation classes will never correspond to the deterministic equilibrium distribution that is derived without taking into account an operating ratchet.

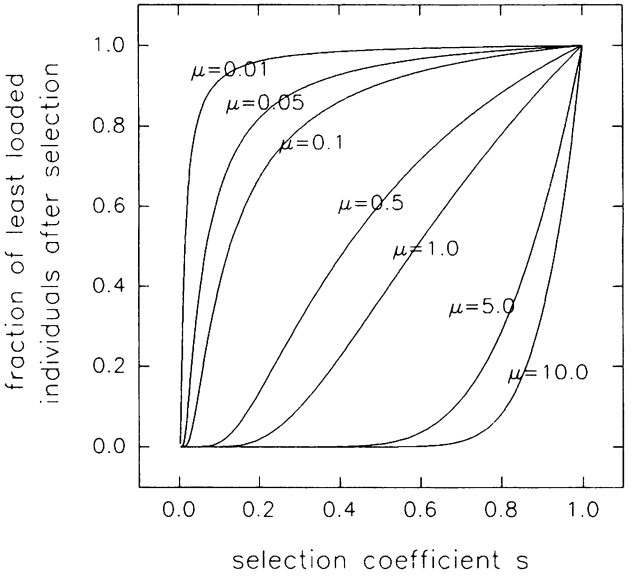

Fig. 1. Deterministic expectation of the proportion of the fittest (least loaded) mutational class as a function of the selection coefficient s, for various genomic mutation rates μ.

Consequently, even for a constant finite population size, the distribution of mutation classes can deviate drastically from the deterministic expectation if the time between successive losses of the least loaded class is of the same order of magnitude or shorter than the time needed to approximate a stable mutation class distribution.

There are only a few detailed studies on the dynamics of the ratchet that go beyond Haigh's (1978) analysis. Bell (1988) explored the dynamics of the ratchet process and the role of recombination in halting the ratchet. He predicted that the optimal class of size n_0 will be lost in approximately $10\,n_0$ generations, but recent numerical simulations (Charlesworth et al., 1993) yield quantitatively and qualitatively different results. Melzer and Koeslag (1991) studied possible effects of fertility selection. Stephan et al. (1993) derive two diffusion approximations for the speed of the ratchet in asexual populations that work for certain parameter combinations.

The classic models for Muller's ratchet (see Maynard Smith, 1978; and above) keep population size constant. This implicitly implies infinite fecundity, otherwise population size decreases if the ratchet operates and, therefore, mean fitness declines steadily. In reality, one can expect that mean population fitness will affect population size in the long run. Reduced population size, however, facilitates the operation of the ratchet. Therefore, especially in small populations, accumulation of deleterious mutations and extinction might occur much faster than estimated under the unrealistic assumption of constant population size and, eventually, the population will become extinct.

The first study of the ratchet without the assumption of constant population size was performed by Lynch and Gabriel (1990). Recent extensive simulation studies of the ratchet as well as mathematical treatments were performed by Gabriel et al. (1993) and Lynch et al. (1993). Some of their results are discussed later in this paper.

Muller's ratchet with density-dependent population regulation

The incorporation of finite fecundity of organisms into models of Muller's ratchet can be achieved by implementing a finite number of offspring *per* individual or by a density-dependent population regulation. Deleterious effects of mutations may show up in a complicated mixture of reduction in fertility and viability. We will restrict our analysis to viability selection.

Most of the following results have been obtained by means of a demographic model with Poisson-distributed number of offspring and non-overlapping generations. Various properties of this and related demographic models were studied in Gabriel and Bürger (1992). The extinction risk for small populations caused by the combined action of

demographic stochasticity and deleterious mutations is studied in Gabriel et al. (1991, 1993) and Lynch et al. (1993).

As a reference model, we will calculate the extinction risk with a "deterministic" null-model by removing all stochasticity. The time-course of the expected population size is then calculated without any noise. Family size is determined exactly by the assumed density dependence; fitness loss corresponds to the average mutation load when genetic drift is neglected. Therefore, in such a deterministic model, the ratchet cannot operate because the least loaded class will never be lost even if its frequency becomes very small. Starting from an unloaded population, the dynamics of the mutational classes can be calculated.

The formulae for the intrinsic growth rate $r = 0$, which corresponds to one surviving offspring *per* individual and implies a constant population size in the absence of other forces that could reduce offspring fitness, are given in Gabriel et al. (1993, Appendix D). This approach can be extended by including population regulation assuming that population regulation does not influence the distribution of mutational classes. Starting with a mutation-free population, the mutation load converges to $e^{-\mu}$ for $t \to \infty$. With the density dependent offspring production F the population size at each time step is then given by

$$N_{t+1} = F(N_t)\, e^{-\mu}\, e^{\mu(1-s)^{t+1}}, \tag{3a}$$

where

$$F(N_t) = \frac{e^r N_t}{(1 + aN_t)^\beta}, \qquad a = \frac{e^{r/\beta} - 1}{K}. \tag{3b}$$

Here, K is the carrying capacity and r the intrinsic growth rate (on the time scale of generations^{-1}) so that (in the limit $K \to \infty$) e^r is the maximal reproductive rate (offspring *per* individual). The strength of population regulation is parameterized by β; for example, with $\beta = 1$ the density dependence is equivalent to the classic Verhulst model. (This is a discrete version of the usual logistic growth equation that does not lead to complicated dynamics like chaos; for details see Gabriel and Bürger (1992).) The population becomes extinct if N falls below 1. Survival is possible only if $N(t+1) \geq 1$ for $N(t) = 1$. In the limit $t \to \infty$, this leads to the condition:

$$K \frac{e^{(r-\mu)/\beta} - 1}{e^{r/\beta} - 1} > 1. \tag{4}$$

Therefore, necessary conditions for population survival are

$$\begin{aligned} r &> \mu \\ K &> e^{\mu/\beta}. \end{aligned} \tag{5}$$

The lower limit of K is obtained by allowing infinite growth rates $r \to \infty$. Only if the conditions of Eqs (4) and (5) are fulfilled can the population compensate for the loss due to mutational load, otherwise it becomes extinct even without demographic stochasticity and without genetic drift. The mean time to extinction decreases with random variation in demography and genetic drift. Therefore, this deterministic expectation imposes only a lower limit on the extinction risk. Simulations that include drift and demographic stochasticity are expected to agree with the deterministic model only if the growth rate is small $r \ll \mu$ (if $r > \mu$ the time to extinction becomes infinite for the deterministic model) and for at least moderately large carrying capacity K (increasing K slows down the speed of the ratchet and reduces noise from family size variation).

Fig. 2 shows how the mean time to extinction increases and how extinction risk decreases as growth rate increases. The extinction risk for $s = 0.01$ is much smaller than for $s = 0.1$ although the ratchet turns much faster at the lower s value. The approximate probability that none of the K offspring are drawn from the least loaded class is given by Eq.

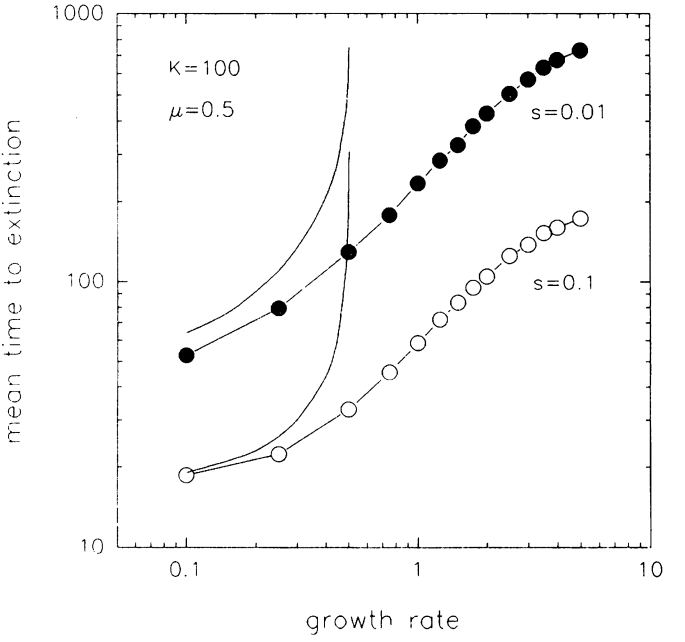

Fig. 2. Mean time to extinction as a function of the intrinsic population growth rate r for the selection coefficients $s = 0.01$ and $s = 0.1$ with a genomic mutation rate $\mu = 0.5$ *per* generation (strength of density dependence of $\beta = 1$). The connected data points show simulation results allowing for genetic drift (Muller's ratchet can operate). For comparison, the "deterministic" solutions without genetic drift and without noise in family size are shown; they become infinite as r approaches μ.

(2). Even if the actual population size is smaller than K, K offspring are always drawn if fecundity is high enough to compensate for the reduced mean fitness caused by the ratchet. For $\mu = 0.5$ and $K = 100$, this probability of losing the least loaded class is $p \approx 1$ for $s = 0.01$ and $p = 0.327$ for $s = 0.1$. Therefore, although the ratchet turns more than three times faster, the time to extinction is larger at the lower s value; this contrasts with the usual view of Muller's ratchet. This effect has been demonstrated already by Lynch and Gabriel (1990) in a model with a very simple population regulation. There it was shown that a lowered speed of the ratchet as s increases can be more than compensated for by the population fitness reduction *per* each turn of the ratchet.

The deterministic model converges to the stochastic simulation model as r becomes very small but gives zero extinction risk when $r > \mu$ as predicted by Eq. (5). The stochastic simulations show a considerable extinction risk even for $r > \mu$. This nicely demonstrates the effect of genetic drift that causes continuous accumulation of deleterious mutations. The extinction risk due to demographic stochasticity alone is negligible for $K \geq 100$ unless r is in the order of zero or below (see Gabriel and Bürger, 1992).

Mutational meltdown in asexual populations

As a consequence of finite fecundity, in the long run the population size N will be affected by the accumulation of deleterious mutations for almost any kind of demographic model. If accumulation of deleterious mutations reduces the actual population size, then subsequent mutations accumulate faster because the chance of losing the least-loaded mutation class is enhanced at reduced population size. Each loss of the actual fittest mutation class further reduces population size. This again speeds up the ratchet. Therefore, mutation accumulation and random genetic drift synergistically intensify each other and drive populations to extinction. This positive feedback mechanism was first described by Lynch and Gabriel (1990) and denoted as "mutational meltdown".

The meltdown has been studied using two different demographic models. In the first model, it is assumed that the maximal number of adults is bounded by the carrying capacity K, and the number of offspring produced *per* individual (fecundity rate) is independent of population size. At high fecundity, the total number of offspring might be much higher than K. If the new generation of adults ($N \leq K$) is drawn from the surviving offspring after selection, then population size N is not reduced immediately by the mutational load. But if the load continues to increase, after a sufficiently long time-span the total number of surviving offspring will fall below K and the number of adults

becomes smaller than K. Such a population regulation is studied in detail in Lynch et al. (1993). These models put upper limits on the mean extinction time (especially with high fecundity) because all other additional effects will further increase the extinction risk.

For a second demographic model, let us assume that carrying capacity acts for the number of offspring produced and selection occurs after density-dependent population regulation. Then the number of reproducing adults can be reduced immediately by deleterious mutations (without mutation load the number of offspring and adults would both stay near K). The number of reproducing adults decreases as the accumulation of mutations proceeds. Thereby, the number of offspring *per* individual increases towards the maximum reproductive rate (studied in Gabriel et al., 1993 and Lynch and Gabriel, 1990). The disadvantage is that this model – like all specific demographic models – assumes a more or less arbitrary population regulation. In reality, deleterious mutations might affect fecundity, viability, and population regulation in a complicated manner. Nevertheless, it is helpful to have a model formulated with the parameters r and K which are used widely in ecology. Of course, one has to be careful when applying these parameters. But as an analogy to "effective population size" in population genetics, this model can be used as a null-model with "effective r and K" values.

The meltdown effect is independent of the kind of population regulation and the order of events (Lynch et al., 1993). The time at which the meltdown becomes the dominant force might depend on the demographic model. Also, if the fitness reduction s varies between mutations and some mutations are beneficial, the meltdown effect still occurs (Lynch and Gabriel, 1990). Epistatic fitness effects between single mutations are unlikely to prevent the meltdown (Lynch et al., 1993; Butcher, personal communication).

Fig. 3 gives an example of mean times to extinction for a density-dependent population regulation according to Eq. (1). The striking feature that an intermediate s value minimizes the mean time to extinction is discussed in detail in Gabriel et al. (1993). The position of the minimum can be predicted roughly for moderate and large K values. The position of the minimum shifts to higher s values if the genomic mutation rate increases; but the minimum appears at lower s values if K (see Fig. 3) or r increase (see Gabriel et al., 1993, where approximate formulae to estimate the position of the minimum can be found). With this demographic model, the extinction times for $s = 0$ and $s = 1$ can be calculated (see Gabriel and Bürger, 1992; Gabriel et al., 1993). A useful substitution formula (see Gabriel et al., 1993) to estimate the effect of lethal ($s = 1$) mutations is

$$\begin{aligned} r_{s=1} &= r - \mu \\ K_{s=1} &= K \frac{e^{r-\mu} - 1}{e^r - 1}. \end{aligned} \tag{6}$$

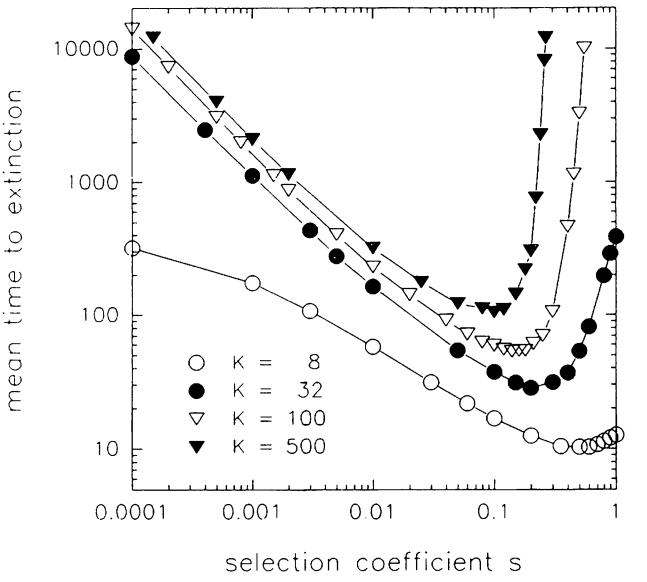

Fig. 3. Mean time to extinction shows a minimum for intermediate selection coefficients. Genomic mutation rate $\mu = 0.5$, r = 1, K = 8, 32, 100, 500.

This means that a population with s = 1 behaves like a population with s = 0 if r and K are reduced according to Eq. (6). Note that the minimum time to extinction, at $s = s^*$, is many orders of magnitude lower than the extinction time at s = 1, unless K is very small. This minimum is not a consequence of the particular demographic model (compare with Fig. 5 where another demography was used).

For conservation genetics, this pronounced minimum may have severe consequences. The selection coefficient of slightly deleterious mutations might differ between species and between habitats. In a real population with genetic diversity the s-values will differ between individuals so that one has to consider a distribution of selection coefficients rather than a single s value. External forces might shift this distribution. This can produce unpredictable changes in the extinction risk. To illustrate the possible effect, let us consider the simplified case of equal s values for all individuals of a population. Imagine that in such a locally adapted population, deleterious mutations cause a fitness reduction that corresponds to s values above s^*, the value at which the extinction time shows the minimum. After a change in the environment – or a management treatment to improve individual fitness – the selection coefficient might decrease. The unexpected consequence would be a dramatic increase in extinction risk.

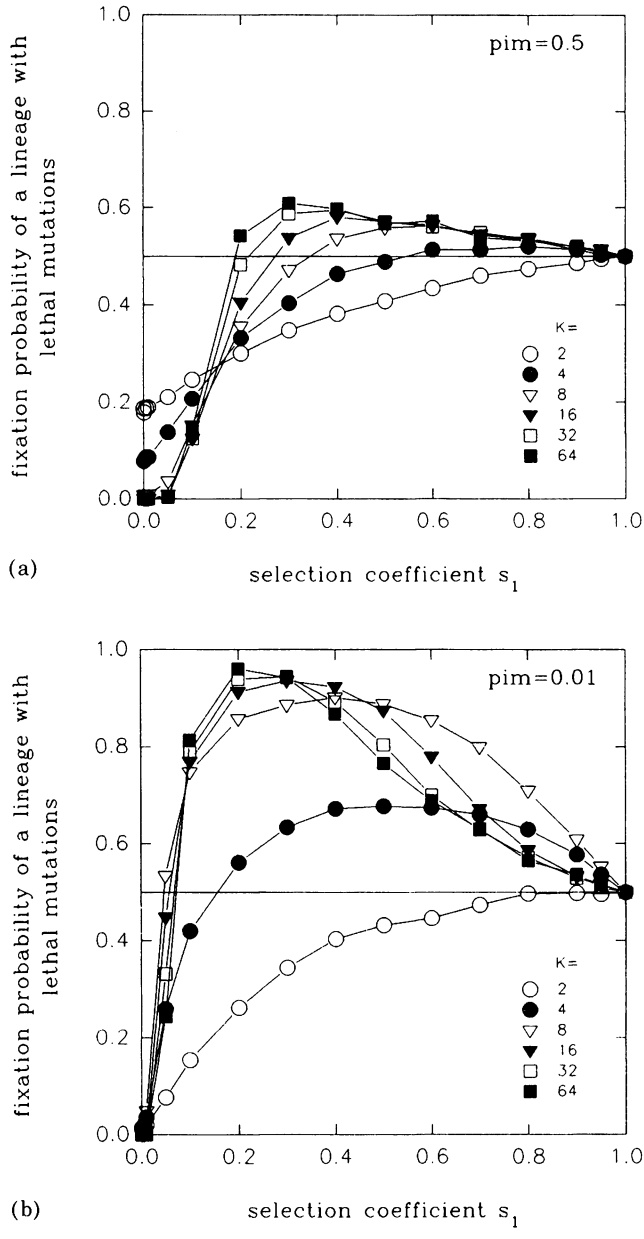

Fig. 4. Group selection overpowers individual selection. At start, two lineages with different selection coefficients are separated into two demes in a simple metapopulation that allows reciprocal immigration with probability pim. The fixation probability of the lineage with s = 1 is shown as a function of the selection coefficient of the second lineage for different K values. Immigration probabilities are a) pim = 0.5 b) pim = 0.01.

A population-level advantage for highly deleterious mutations

On an evolutionary time scale, the minimum of the extinction time as a function of s evokes other questions. In relation to the problems mentioned above, one might ask which value of slightly deleterious mutations would be favored during evolution – assuming that the deleterious effect cannot be removed, e.g., by perfect repair mechanisms. On the level of individual selection, any decrease in s would be favored, but on the population level there is a critical amount of repair. For example, compared to accepting a mutation as lethal, one would have to repair until s values are small enough so that the extinction time is larger than for $s = 1$. In one step, the repair would have to cross a very deep valley of selection coefficients that would otherwise lead to increased extinction risk. This argument, of course, is only valid if selection on the population level (i.e., group selection) is fast or efficient enough to overpower individual selection which favors any reduction in s.

This problem can be evaluated by a simple metapopulation approach. We start with two demes. Initially, each deme consists of a single lineage, but the lineages differ between demes with respect to s; for example, in one lineage any mutation is lethal ($s = 1$), for the other lineage we assume $s < 1$. Further, we allow reciprocal immigration between demes with probability p_{im} after successful reproduction. Then, we let both lineages in the metapopulation reproduce until one lineage becomes fixed, i.e., the other lineage is removed from the metapopulation. (The time to fixation is short compared to the extinction time of the metapopulation.) Simulating many such experiments, we then calculate the fixation probability. Fig. 4 shows that, indeed, group selection can overpower individual selection.

As an evolutionary consequence, in many cases it seems to be advantageous not to repair damaged DNA if the repair does not guarantee that the valley of critical s-values will be crossed.

Because of its maternal inheritance, mitochondria (and also chloroplasts) can be viewed as small asexual populations within a cell. Mitochondria do not have genes for gene repair. Therefore, the minimum in s could explain this absence of repair mechanisms. One must carefully determine whether mutations in mtDNA influence replication efficiency of the mtDNA itself or only influence the fitness of the host cell (for discussion see Gabriel et al., 1993).

Does meltdown occur in spite of segregation and recombination?

Even if the mutation-free class is empty, recombination can produce mutation-free individuals as long as the loci, at which the mutations occurred, differ between the individuals, i.e., before specific mutations

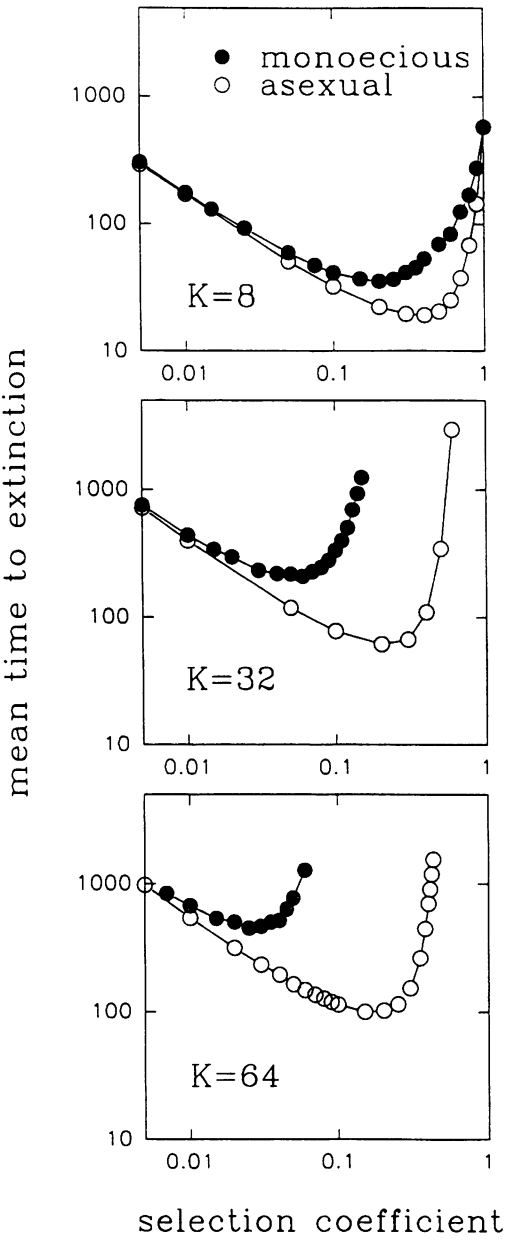

Fig. 5. Comparison of extinction times for asexual and monoecious populations with simple density dependence and reduced demographic stochasticity for carrying capacities K = 8, 32 and 64. A genomic mutation rate of $\mu = 0.6$ is assumed. In the diploid case fitness is multiplicative within and between loci.

are fixed in the population. Recombination should in principle be able to stop Muller's ratchet, but it is debatable how effective and under which conditions this occurs. Bell (1988) predicts that the ratchet cannot be stopped by recombination, but Charlesworth et al. (1993) arrive at different conclusions.

Evidence for the impact of slightly deleterious mutations for small sexual populations is given by Gabriel et al. (1991). In that model, demographic and sex-ratio fluctuations are the dominant sources for extinction if population sizes are very small; at population sizes above 20, however, the genetic effects become quite influential. It is not yet known how large a sexual population has to be in order to effectively purge the mutation load in comparison to an asexual population.

In the study of Gabriel et al. (1991), the extinction process is heavily determined by sex-ratio fluctuations. There is a high risk that no male or no female is left, especially after temporary bottlenecks. In addition, sex-ratio fluctuations reduce effective population size drastically and this implies large effects of genetic drift.

To study the influence of segregation and recombination with a minimum of non-genetic stochasticity, we have performed simulations for small (monoecious) sexual and asexual populations with reduced demographic stochasticity by using the simple population-regulation model of Lynch and Gabriel (1990). (The order of events was: (1) zygotes; (2) mutation; (3) selective mortality; (4) check for extinction; (5) next generation by drawing randomly K zygotes, in the monoecious population, by random mating and free recombination.) There is again an intermediate value of s^* that minimizes the expected time to extinction (see Fig. 5). The critical value s^* is substantially smaller for sexual than for asexual populations of the same size. The expected time to extinction due to mutation accumulation in sexual populations is higher than in asexuals, but not greatly so for small K or small s. In the neutral ($s = 0$) and lethal ($s = 1$) case the mean time to extinction is the same for sexual and asexual populations.

These preliminary results show that for small populations, the mutational meltdown cannot be stopped by recombination. Further investigations with larger population sizes have to be performed to study the general impact of the meltdown on sexual species. Such investigations are currently in progress (Lande; Lynch et al., personal communications).

Conclusions

In this paper, mutations are considered as unconditionally deleterious. There are other kinds of mutational effects that cannot be treated in this way, e.g., a different approach is necessary if fitness is determined by

Table 1. Main effects of the model parameters

s	selection coefficient; fitness reduction *per* mutation: the extinction risk is maximal at intermediate levels of s. The influence on extinction risk is strong. The ratchet turns more slowly when s increases. The damage to the population per turn of the ratchet increases with s and this can overcompensate for the reduction in the speed of the ratchet.
s*	s value that maximizes the extinction risk, resp. minimizes the mean time to extinction.
μ	genomic mutation rate *per* generation: it strongly enhances the speed of the ratchet and drastically increases the extinction risk. Increased μ moves s* to higher values.
K	carrying capacity, related to population size N: extinction occurs if $K < e^{\mu}$ for any $s > 0$. Larger K reduces the speed of the ratchet and shifts s* to lower values.
r	growth rate, fecundity: If r is too small ($r < \mu$) then extinction is unavoidable for any $s > 0$. It has strong impact on the onset of the meltdown process. An increase if fecundity above a medium sized number of offspring ($e^r > 10$) has little further effect. Increased r shifts s* to lower values.

several quantitative traits under stabilizing selection. Gabriel and Wagner (1988) and Wagner and Gabriel (1990) studied conditionally deleterious mutations by allowing mutations to compensate phenotypic effects of deleterious mutations. Such compensatory mutations for quantitative characters are as effective as recombination in halting the decline of mean fitness otherwise caused by Muller's ratchet. Extinction was not studied in these papers but it would be interesting to look at how these mutations interact with extinction.

Even if many details still have to be worked out, the importance of the meltdown process for extinction is unquestionable. Tab. 1 summarizes some of the effects of the different model parameters. There remains a large field of necessary theoretical and experimental investigations, for example, we assumed that mutations act multiplicatively and we did not allow for epistatic interactions. Further, there is not enough information on mutation rates and selection coefficients for different species and little is known about how a selection coefficient measured in the laboratory transforms into fitness reduction in the field. The expression of deleterious mutations – even if independent of the genetic background – could be strongly dependent on the environmental conditions. Studies like this paper intend to estimate minimum levels of extinction risk. Additional effects like environmental stochasticity (cf. Lande, 1993) that might themselves synergistically interact with the processes described in this chapter would increase the extinction risk considerably. Hopefully, this study stimulates further experimental and theoretical investigations and increases the awareness of interaction between environmental and genetic problems that we have to deal with in conservation biology.

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