Ann. Zool. Fennici 40: 155–168 ISSN 0003-455X
Helsinki 30 April 2003

Genetic threats to population persistence

Oscar E. Gaggiotti

Metapopulation Research Group, Department of Ecology and Systematics, P.O. Box 65, FIN-00014 University of Helsinki, Finland (e-mail: oscar.gaggiotti@helsinki.fi)

Received 27 Nov. 2002, revised version received 20 Jan. 2003, accepted 20 Jan. 2003

Gaggiotti, O. E. 2003: Genetic threats to population persistence. — *Ann. Zool. Fennici* 40: 155–168.

Human activities are having a devastating effect on the survival of natural populations. The reduction in population size and changes in the connectivity of populations due to human disturbances enhance the effect of demographic and genetic factors that can lead to population extinction. This article provides an overview of our current understanding of the role of genetic factors in the extinction of populations. The three primary genetic factors are loss of genetic variability, inbreeding depression, and accumulation of mildly deleterious mutations. The effects of these factors are discussed in the context of three different scenarios: isolated populations, local populations with immigration, and metapopulations.

Introduction

Although the extinction of populations is a natural phenomenon, human induced habitat loss, pollution and overexploitation have increased extinction rates well above background levels and have lead to the mass extinction that we are experiencing at the moment (Jablonski 1986, Woodruff 2001). An increased awareness of the consequences of human activities on the fate of natural populations has brought about a strong interest in the study of the ecological and genetic factors that underlie population extinctions. A decade ago or so, genetic factors received most of the attention leading to a neglect of basic demography (Lande 1988). This bias lead to a protracted controversy (Lande 1988, Caro & Laurenson 1994, Caughley 1994, Lande 1995) over the relative importance of these two factors in the extinction of populations. The main impediment to the resolution of this controversy was a poor understanding of the interaction between demographic and genetic factors (Lande 1988). However, the last decade has witnessed much progress in this area and there is a general agreement that, although the most immediate causes of extinction are human predation, introduction of exotic species and habitat loss, genetic factors can still play an important role.

The purpose of this article is to provide an overview of our current understanding of the role of genetic factors in the extinction of populations. I begin by addressing the case of isolated populations, which is applicable to species that have been reduced to a few small and isolated populations or that are being maintained in captivity. I then consider to what extent migration can influence the effect of genetic factors on population persistence. A clear understanding of this problem is necessary to devise sensible management strategies aimed at maximizing population persistence. Finally, I describe the operation of genetic factors in a metapopulation context. This scenario is applicable to species that have

been less affected by human disturbance and that are still represented by many interconnected subpopulations.

Population extinction

Natural populations are subject to extinction due to genetic factors even in the absence of human intervention. Genetic threats are a function of the so-called effective population size, N_e. Strictly speaking, N_e is defined as the number of individuals in an ideal population that would give the same rate of random genetic drift as in the actual population (Wright 1931, Wright 1938). The ideal population consists of N individuals with non-overlapping generations that reproduce by random union of gametes. More intuitively, N_e can be defined as the number of individuals in a population that contribute genes to the following generation. This number can be much lower than the observed population size because of unequal sex ratios, variance in family size, temporal fluctuations in population size, etc. (Frankham 1995). Thus, apparently large populations may still be facing genetic problems. Small N_e can have multiple effects that include loss of genetic variability, inbreeding depression, and accumulation of deleterious mutations. The time scales at which these factors operate differ and determine to a large extent the risk of population extinction that they entail (Table 1).

Loss of genetic variability

Genetic variation is the essential material that allows natural populations to adapt to changes in the environment, to expand their ranges, and to reestablish after local extinctions (Hedrick & Miller 1992). The types of genetic variation considered most often are the heterozygosity of neutral markers, H, and the additive genetic variance, V_a, that underlies polygenic characters such as life-history traits, morphology, physiology, etc.

Table 1. Time scale at which genetic factors operate and their importance for population extinction.

Factor	Time scale	Extinction risk
Loss of genetic diversity	Long	Low
Inbreeding depression	Short	High
Mutational meltdown	Medium/Long	Unknown

In small populations, random genetic drift causes stochastic changes in gene frequencies, due to Mendelian segregation and variation in family size. In the absence of factors that replenish genetic variance such as mutation, migration or selection favouring heterozygotes, populations lose genetic variance according to

$$V_a(t+1) = V_a(t)\left(1 - \frac{1}{2N_e}\right), \qquad (1)$$

where $V_a(t)$ is the additive genetic variance in the tth generation (e.g. Hedrick & Miller 1992). A similar equation is obtained for heterozygosity by replacing V_a with H. Genetic variation is greatly reduced when populations are reduced to a small effective size, N_e, and maintained at that size for several generations. In fact, most genetic variation would be lost within about $2N_e$ generations (Wright 1969). Genetic variability can be replenished to its original level through mutation if the population grows back to its original size. The number of generations required for attaining the original level is of the order of the reciprocal of the mutation rate, m. Thus, for a nuclear marker with a mutation rate of 10^{-6}, genetic variation is restored after 10^6 generations but the genetic variation of quantitative characters is restored after only 1000 generations because their mutation rate is two orders of magnitude higher.

The maximum fraction of genetic variation lost during a bottleneck is a function of the population growth rate (Nei *et al*. 1975). Populations that recover quickly after the bottleneck lose little genetic variation even if the population was reduced to few individuals. For example, a growth rate of $r = 0.5$ ($l = e^r = 1.65$) allows a population that is reduced to only two individuals to retain 50% of its genetic variability (Fig. 1). If the population is reduced to 10 individuals, then a growth rate of $r = 0.1$ ($l = 1.10$) will allow it to retain 60% of its variability. Additionally, generation overlap can buffer the effect of environmental fluctuations

on population sizes. In general, reductions in population size are brought about by environmental changes that introduce fluctuations in vital rate parameters (e.g. survival, fecundity). The effect of these fluctuations on N_e depends on the life history of each species. The ratio of N_e to census size is directly proportional to the total reproductive value of a population but the sensitivity of this ratio to environmental fluctuations is proportional to the generation overlap (Gaggiotti & Vetter 1999). The larger the generation overlap, the smaller is the effect of environmental fluctuations on the level of genetic variability maintained by natural populations. Genetic variability is maintained through the "storage" of genotypes in long-lived stages. Adult individuals in these stages reproduce many times throughout their lives and, therefore, the genetic variability present in a given cohort is more likely to be transferred to future generations than in the case of organisms with discrete generations.

These buffering mechanisms may explain why there are very few clear examples of populations that have lost a very large fraction of their genetic variability due to a bottleneck. One of the few cases is that of the Mauritius kestrel, which was reduced to a single pair in the 1950s. A comparison of microsatellite diversity present in museum specimens collected before the bottleneck and that present in extant individuals reveals that at least 50% of the heterozygosity was lost due to the bottleneck (Groombridge *et al*. 2000). Another example is the northern elephant seal, which was heavily exploited during the nineteenth century and reduced to a bottleneck population size estimated to be 10–30 individuals (Hoelzel *et al*. 2002). A comparison of genetic diversity in prebottleneck and postbottleneck samples shows a 50% reduction in mtDNA-haplotype diversity. The reduction in heterozygosity at microsatellite loci, however, was less pronounced.

An important caveat concerning the effect of population size reductions on genetic diversity is that although they may not have a very large effect on H, they will indeed have a large impact on allelic diversity (the mean number of alleles per locus) because random genetic drift will eliminate low frequency alleles very rapidly

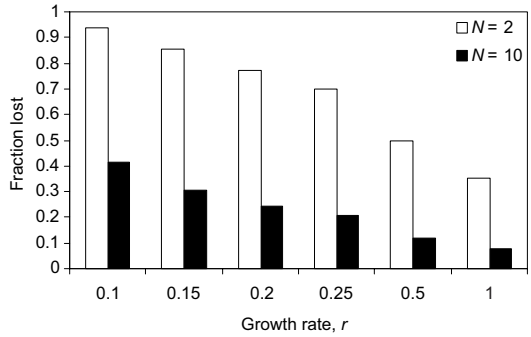

Fig. 1. Fraction of the heterozygosity lost during a population bottleneck that reduces population size to N = 2, 10 individuals. Calculated with eq. 8 in Nei *et al.* (1975).

(Nei *et al*. 1975). This is of particular concern because the long-term response of a population to selection is determined by the allelic diversity that remains after the bottleneck or that is gained through mutations (James 1971). A second caveat is that in the case of quantitative genetic characters, genetic variability may not be always beneficial. Using an overlapping generation model assuming weak stabilizing selection, Lande and Shannon (1996) showed that the effects of additive genetic variance on the average deviation of the mean phenotype from the optimum, and the corresponding "evolutionary" load depends on the pattern of environmental change. In an unpredictable (random) environment, additive genetic variance contributes to the evolutionary load because any response to selection increases the expected deviation between the mean phenotype and the optimum. However, when environmental changes are unidirectional, cyclic, or positively correlated (predictable), additive genetic variance allows the mean phenotype to track the optimum more closely, reducing the evolutionary load.

Most of the empirical studies of the effects of population bottlenecks on genetic diversity focus on heterozygosity of neutral markers. Although neutral genetic variation may become adaptive if the environment changes, the ability of a population to respond to novel selective pressures is proportional to the additive genetic variation underlying the traits that are the target of selection (Falconer & Mackay 1996). Unfortunately, direct quantification of the genetic

variation underlying polygenic traits is difficult and, therefore, heterozygosity of nuclear markers is used as an indicator of additive genetic variation (Pfrender *et al*. 2001). This practice is unwarranted because of the different rates at which genetic variation is replenished in neutral and quantitative markers (Lande 1988). Indeed, a recent study (Pfrender *et al*. 2001) detected no significant relationship between heritability and heterozygosity in natural populations of *Daphnia pulex* and *D. pulicaria*. Thus, the absence of genetic diversity in nuclear markers may not necessarily indicate an immediate genetic threat.

In general, the loss of genetic variation is detrimental for the long-term survival of populations. However, as pointed out by Allendorf and Ryman (2002) there is one case where a reduction in genetic variability can represent an imminent extinction threat. This is indeed the case for loci associated with disease resistance such as the major histocompatibility complex (MHC), which is one of the most important genetic systems for infectious disease resistance in vertebrates (Hedrick & Kim 2000). Allelic diversity at these loci is extremely high; for example, Parham (1996), and Parham and Ohta (1996) documented 179 alleles at the MHC class I locus in humans. However, species that have been through known bottlenecks have very low amounts of MCH variation. A study of the Arabian oryx found only three alleles present at the MHC class II DRB locus in samples from 57 individuals (Hedrick *et al*. 2000). Hunting pressure lead to the extinction of this species in the wild in 1972 and captive populations were susceptible to tuberculosis and foot-and-mouth disease, which is consistent with low genetic variability at MHC loci. Low genetic diversity at the MHC complex was also observed in bison, which went through a bottleneck at the end of the 19th century (Mikko *et al*. 1997). In the Przewalski's horse, in which the entire species is descended from 13 founders, Hedrick *et al*. (1999) observed four alleles at one locus and two alleles at a second locus. The northern elephant seal is another example of low MHC diversity, Hoelzel *et al*. (1999) found only two alleles at the MHC class II DQB gene in a sample of 69 individuals.

In general, it is possible to conclude that loss of genetic variation, as measured by heterozygosity and additive genetic, variance represents a long-term extinction threat. However, the loss of allelic diversity can have important consequences in the short-term if it occurs at loci associated with disease resistance.

Inbreeding depression

The decrease in fitness due to mating between related individuals is known as inbreeding depression, and results from the presence of partially recessive deleterious mutations maintained by the balance between selection and mutation. Deleterious mutations occur continuously in a population and most are at least partially recessive. In large populations, selection keeps these detrimental mutations at low equilibrium frequencies. Thus, under random mating, most copies of detrimental alleles are present in heterozygous state and their detrimental effects are partially masked. Mating between relatives, however, increases homozygosity and, therefore, the deleterious effects become fully expressed, decreasing the fitness of inbred individuals. Although it is generally agreed that increased expression of deleterious partially recessive alleles is the main cause of inbreeding depression, there is an additional mechanism that can contribute to inbreeding depression. If the fitness of a heterozygote is superior to that of both homozygotes (heterozygous advantage or overdominance), the reduced frequency of heterozygotes will reduce the opportunities to express this overdominance. This mechanism may be important for certain traits (e.g. sperm precedence in *Drosophila melanogaster*), and may contribute to the very high inbreeding depression for net fitness observed in *Drosophila* and outcrossing plants (Charlesworth & Charlesworth 1999).

The degree of inbreeding in a population is measured by the inbreeding coefficient F, which can be defined as the probability that the two alleles of a gene in an individual are identical by descent. The effect of inbreeding in a population with inbreeding coefficient F can be measured in terms of the logarithm of the ratio

of the mean fitness values for the outbred, W_O, and the inbred, W_I, populations (Charlesworth & Charlesworth 1999):

$$\ln\left(\frac{W_I}{W_O}\right) = BF \qquad (2)$$

The coefficient B can be interpreted as the reduction in log fitness associated with complete inbreeding (i.e. $F = 1$) and is widely used as a measure of inbreeding depression. B is also a good measure of the number of lethal equivalents per gamete, which is defined as the number of deleterious alleles whose cumulative effect equal that of one lethal (Cavalli-Sforza & Bodmer 1971).

In small populations, the opportunities for mating are restricted, even under random mating patterns. Thus, mating among relatives is common and the proportion of individuals that are homozygous at many loci increases and results in inbreeding depression. The amount of inbreeding depression manifested by a population depends not only on F but also on the opportunity for selection to purge recessive lethal and sublethal mutations. Gradual inbreeding by incremental reductions in population size over many generations allows selection to eliminate the lethal and sublethal mutations when they become homozygous (Falconer & Mackay 1996). However, the component of inbreeding depression due to more nearly additive mutations of small effect are difficult to purge by inbreeding (Lande 1995). Despite this theoretical expectation, recent reviews indicate that purging is inefficient at reducing inbreeding depression in small and inbred populations (Allendorf & Ryman 2002, and references therein).

Most of the evidence for inbreeding depression comes from domesticated or captive populations. This together with the theoretical expectation that a large fraction of inbreeding depression can be purged in small populations and the numerous mechanisms of inbreeding avoidance observed in many species has led many researchers to question the importance of inbreeding depression for the persistence of wild populations (Keller & Waller 2002). However, evidence of inbreeding depression in natural populations of plants has existed for quite some time as documented by Charlesworth and Charlesworth (1987). A more recent review by Byers and Waller (1999) provides many more recent examples of inbreeding depression in plant populations and indicates that purging does not appear to act consistently as a major force in natural populations. In animals the situation is different but in the last decade there has been a rapid accumulation of evidence that indicates that many wild animal populations exhibit inbreeding depression. For example, Soay sheep on the island of Hirta (Saint Kilda archipelago, UK) suffer significant inbreeding depression in survival (Coltman *et al.* 1999). More homozygous sheep suffered higher rates of parasitism and, in turn, lower overwinter survival than did heterozygous sheep. Another example comes from song sparrows living on Mandarte Island (western Canada). In this case inbred birds died at a much higher rate during a severe storm than did outbred birds (Keller *et al.* 1994). A more recent study (Keller 1998) was able to quantify inbreeding depression in this population and estimated that inbreeding depression in progeny from a mating between first-degree relatives was 49%. The negative effect of inbreeding has also been documented in the red-cockaded woodpecker living in southeastern USA. Inbreeding reduced hatching rates, fledgling survival and recruitment to the breeding population (Daniels & Walters 2000). Extensive long-term data sets can help uncover inbreeding depression even in large populations with low inbreeding rates. An 18-year study of a large wild population of collared flycatchers revealed that inbreeding was rare but when it did occur it caused a significant reduction in the egg-hatching rate, in fledgling skeletal size and in post-fledging juvenile survival (Kruuk *et al.* 2002). This study also found that the probability of mating between close relatives ($f = 0.25$) increased throughout the breeding season, possibly reflecting increased costs of inbreeding avoidance.

There is also evidence that stressful environmental conditions can increase inbreeding depression. Crnokrak and Roff (1999) gathered and analyzed a data set that included seven bird species, nine mammal species, four species of poikilotherms and 15 plant species and showed that conditions experienced in the wild increase

the cost of inbreeding. A more recent study (Keller *et al*. 2002) shows that the magnitude of inbreeding depression in juvenile and adult survival of cactus finches living in Isla Daphne Major (Galápagos Archipelago) was strongly modified by two environmental conditions, food availability and number of competitors. In juveniles, inbreeding depression was present only in years with low food availability, and in adults inbreeding depression was five times more severe in years with low food availability and large population size.

Demonstrating the importance of inbreeding depression in the wild does not necessarily imply that it can cause wild populations to decline (Caro & Laurenson 1994). However, recent papers have demonstrated this connection. Saccheri *et al*. (1998) studied the effect of inbreeding on local extinction in a large metapopulation of the Glanville fritillary butterfly and found that extinction risk increased significantly with decreasing heterozygosity, even after accounting for the effects of ecological factors. Larval survival, adult longevity and egg-hatching rate all were adversely affected by inbreeding and seem to be the fitness component responsible for the relationship between inbreeding and extinction. More indirect evidence is provided by Newman and Pilson (1997). They established experimental populations of the annual plant *Clarkia pulchella* that differed in the relatedness of the founders. All populations were founded by the same number of individuals, but persistence time was much lower in those whose founders were related. Additional evidence comes from the study of an isolated population of adders in Sweden (Madsen *et al*. 1999) that declined dramatically around 35 years ago and was on the brink of extinction due to severe inbreeding depression. The introduction of twenty adult male adders from a large and genetically variable population led to a rapid population recovery due to a dramatic increase in recruitment.

All the evidence discussed above indicate that inbreeding depression is common in wild populations and can represent a short-term extinction threat specially if populations are subjected to environmental stress or to sharp population declines.

Accumulation of slightly deleterious mutations

Under more or less constant environments, mutations with phenotypic effects are usually deleterious because populations tend to be well adapted to the biotic and abiotic conditions of the environment they inhabit. Thus, a random mutation is likely to disrupt such adaptation. In populations with moderate or large effective sizes, selection is very efficient at eliminating detrimental mutations with large effects on fitness. However, mildly deleterious mutations with selection coefficient $s \leq 1/2N_e$ are difficult to remove because they behave as neutral mutations (Wright 1931). Thus, small population size hampers selection and increases the role of genetic drift in determining allele frequencies and fates. This increases the chance fixation of some of the deleterious alleles constantly supplied by mutation and result in the reduction of population mean fitness, which eventually leads to population extinction (Muller 1964). Initially this process was assumed to represent a threat only to asexual populations because in the absence of recombination, offspring carry all the mutations present in their parent as well as any newly arisen mutation (Muller 1964). Mathematical models of this process (Lynch & Gabriel 1990, Lynch *et al*. 1993) show that as mutations accumulate, there is a gradual reduction in population size. This increases the effect of random genetic drift, which enhances the chance fixation of future deleterious mutations, leading to further fitness decline and reduction in population size. Due to this positive-feedback mechanism (*see* Fig. 2), the final phase of population decline (when growth rate is negative) occurs at an accelerating rate, a process known as "mutational meltdown".

Although recombination can slow down the mutational meltdown to some extent, sexual populations are also at risk of extinction due to mutation accumulation (Lande 1994, Lynch *et al*. 1995). Lande (1994) studied this problem using a model of a randomly mating population with no demographic or environmental stochasticity. He considered only unconditionally deleterious mutations of additive effects and derived analytical approximations for the mean time until

extinction for two cases: (a) all mutations had the same selection coefficient s, and (b) there is variance in s. Lynch *et al*. (1995) provided a more detailed analysis of scenario (a) and check the analytical results using computer simulations. With constant s, the mean time to extinction, $\bar{t}_e$, is an approximately exponential function of effective population size. Since the mean time to extinction increases very rapidly with increasing N_e, the fixation of new mutations poses little risk of extinction for populations with a N_e of about 100 (Lande 1994). However, with variance in s, the mean time to extinction increases as a power of population size. If s is exponentially distributed, then $\bar{t}_e$ is asymptotically proportional to N_e^2. Since in this case the increase in $\bar{t}_e$ with population size is more gradual than for constant s, the risk of extinction is much greater. For reasonable variance in s (coefficient of variation of about 1) the mutational meltdown poses a considerable risk of extinction for populations with N_e as large as a few thousand individuals (Lande 1994). If, as generally agreed, the ratio of effective size to total population size is around 0.1–0.5, then moderately sized populations (several thousand individuals) may face extinction due to genetic stochasticity.

There is a paucity of empirical evidence for the mutational meltdown. Experimental evidence for the accumulation of deleterious mutations due to genetic drift exist but does not directly address the risk of extinction (Zeyl *et al*. 2001). As of today, only Zeyl *et al*. (2001) explicitly explored the plausibility of the mutational meltdown using an experimental approach. They established 12 replicate populations of *Saccharomyces cerevisiae* from two isogenic strains which genomewide mutation rates differed by approximately two orders of magnitude. They used a transfer protocol that resulted in an effective population size near 250 and after more than 100 daily bottlenecks, the yeast population with elevated mutation rates showed a tendency to decline in size, while the populations with wild-type mutation rates remained constant. Moreover, there were two extinctions among the mutator populations. These results provide support for mutational meltdown models.

Despite this preliminary empirical support there are a number of issues that remain unresolved. The first one is that there is a controversy about the estimates of per-genome mutation rates, U, and the average fitness cost per mutation, s, used in the meltdown models. These were based on mutation accumulation experiments using *Drosophila melanogaster* that resulted in $U = 1$ and a reduction in fitness of about 1%–2% (Lande 1994, Lynch *et al*. 1995). Recent studies (Garcia-Dorado *et al*. 1999; *see* also Zeyl & DeVisser 2001) that included *D. melanogaster* as well as *Caenorhabditis elegans* and *Saccharomyces cerevisiae*, resulted in U orders of magnitude less than one. Additionally, some mutation accumulation experiments (Keightley & Caballero 1997, Caballero *et al*. 2002) reported average fitness effects one order of magnitude higher than those reported previously. The assumption of additive effects is also questioned by Garcia-Dorado *et al*. (1999), who reported estimates of 0.1 for the average coefficient of dominance. The new estimates of U and s would lead to much lower rates of population decline making the mutational meltdown less likely. Caballero *et al*. (2002) used a combination of mutation accumulation experiments and computer simulations and concluded that a model based on few mutations of large effect was generally consistent with their empirical observations.

Finally, an additional criticism concerns the fact that mutational meltdown models ignore the effect of beneficial and back mutations. The inclusion of these types of mutations indicates that only very small populations would face the risk of extinction due to genetic stochasticity (Poon & Otto 2000, Whitlock 2000). Recent estimates of mutational effects using mutation

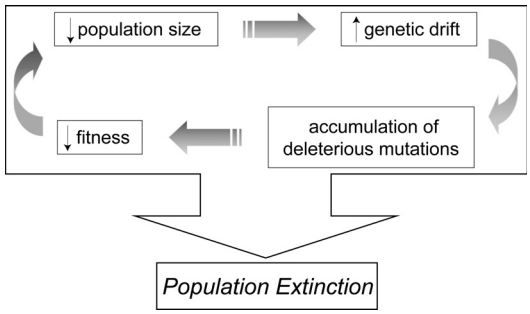

Fig. 2. Schematic showing the positive feedback loop that leads to a mutational meltdown.

accumulation experiments with *Arabidopsis thaliana* indicate that roughly half of the mutations reduce reproductive fitness (Shaw *et al*. 2002). Additionally, the per-generation, genomewide mutation rate is around 0.1–0.2. These new results suggest that the risk of extinction for small populations may be lower than initially thought. This issue is reviewed in more detail by Whitlock *et al*. (2003).

At the moment it is not possible to provide a clear evaluation of the importance of the mutational meltdown process. This will only be possible once the existing controversy over the properties of spontaneous mutations is resolved (Poon & Otto 2000). This in turn requires knowledge of the form of the distribution of mutational effects and the extent to which is modified by environmental and genetic background as well as the contribution of basic biological features such as generation length and genome size to interspecific differences in the genomic mutation rate (Lynch *et al*. 1999).

Local extinction in the presence of migration

Up to this point I have focused on the ecological and genetic factors that underlie the extinction of isolated populations. Although habitat fragmentation is leading to population isolation, under natural conditions few populations can be considered completely isolated. In most cases, they are connected to other populations through migration, a process that has important implications for population persistence.

Migration can have both positive and negative effects on the demography and genetics of local populations. The negative effects on the demography are related to the spread of disease and predators to populations where they were not present. The beneficial effect of migration arises because immigrants from surrounding populations might prevent the extinction of small populations, a process known as the 'rescue effect' (Gotelli 1991).

Migration also has both beneficial and detrimental genetic effects. Many populations experience gene flow at high enough rates to reintroduce genetic load quickly via immigrants; this can limit the purging of inbreeding depression. However, this negative effect is unlikely to offset the positive effects of increased mean population fitness due to heterosis and the arrival of immigrants with high fitness (outbred vigour). Heterosis refers to the increased fitness observed among offspring from crosses among populations. Different populations tend to fix different random subsets of deleterious alleles that mask each other when populations are crossed (Crow 1948, Whitlock *et al*. 2000). Thus, compared to resident genomes, initially rare immigrant genomes are at a fitness advantage because their descendants are more likely to be heterozygous for deleterious recessive mutations that cause inbreeding depression in the homozygous state (Ingvarsson & Whitlock 2000, Whitlock *et al*. 2000). Several recent studies have provided fairly conclusive evidence supporting this expectation. Saccheri and Brakefield (2002) carried out an experimental study with the butterfly *Bicyclus anynana*. They focused on the consequences of a single immigration event between pairs of equally inbred local populations. The experiment consisted in transferring a single virgin female from an inbred (donor) population to another equally inbred (recipient) population. The spread of the immigrant's and all the residents' genomes was monitored during four consecutive generations by keeping track of the pedigree of all individuals in the treatment populations. They replicated this experimental design and observed a rapid increase in the contribution of the initially rare immigrant genomes to the local populations gene pool. Additional strong support is provided by Ebert *et al*. (2002) who carried out experiments using a natural *Daphnia* metapopulation in which genetic bottlenecks and local inbreeding are common. Their results indicate that heterosis amplifies gene flow several times more than would be predicted from the nominal migration rate. Less conclusive evidence comes from experiments with the dioecious plant *Silene alba* (Richards 2000). Isolated populations of this plant suffer substantial inbreeding depression, presumably due to the absence of gene flow, and the resulting high degree of relatedness among individuals. Richards (2000) measured gene flow among experimental populations separated by 20 m and used paternity analysis to assign all

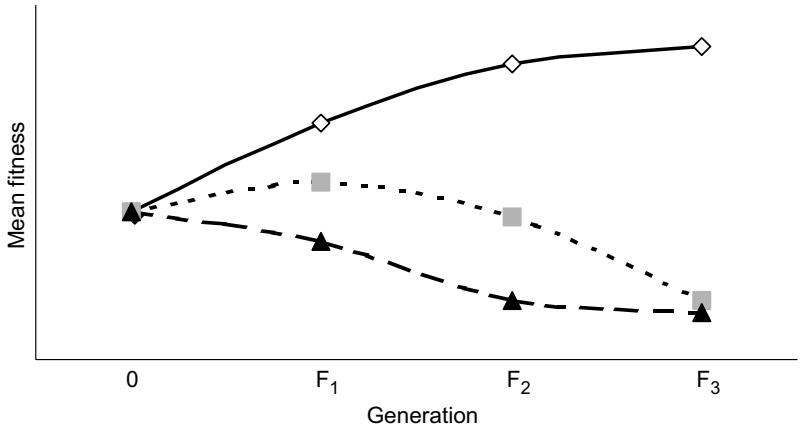

Fig. 3. Potential effects of migration on population fitness: heterosis increases fitness (solid line and diamonds), heterosis followed by outbreeding depression leads to a short lived fitness increase followed by a decline (dotted line and squares), outbreeding depression leads to steady decline in fitness (dashed line and triangles).

seeds to either local males or to gene flow from other nearby experimental population. When recipient populations were inbred, unrelated males from the experimental population 20 m away sired more offspring than expected under random mating. This can be due to some form of pollen discrimination that may be influenced by early acting inbreeding depression (Richards 2000) or to heterosis *per se*. More evidence comes from experiments with *Drosophila melanogaster* that measured the genetic contribution of single immigrants into inbred populations by measuring the relative frequency of immigrant marker alleles in the first and second generation (Ball *et al*. 2000). When immigrants were outbred, the mean frequency of the immigrant allele in the first and second generation after migration was significantly higher than its initial frequency. They attributed this result to the initial outbred vigour of immigrant males but the possibility that heterosis could have played a role was not completely excluded.

Outcrossing does not always enhance fitness (Fig. 3). The introduction of immigrant genomes from a highly divergent population can reduce mean population fitness if hybridization disrupts coadapted gene complexes or favourable epistatic interactions, this phenomenon is known as outbreeding depression. Outbreeding depression may not be expressed until the F_2 generation or later because F_1s carry a haploid set of chromosomes from each parental line, and segregation and recombination only begin to break apart coadapted genes from a single line in the F_2 generation (Dobzhansky 1950, 1970). Thus, outbreeding depression is demonstrated when the performance of F_2s is less than the average of immigrants and natives (Lynch & Walsh 1998: p. 225). However, few studies of natural populations track the contribution of immigrants beyond the F_1 generation (Marr *et al*. 2002). The few studies that go beyond the F_1 generation indicate that outbreeding depression may be common in the wild. Marr *et al*. (2002) showed that the same population of song sparrows in the Mandarte Islands (*see* above) that manifested heterosis among immigrant offspring, also show signs of outbreeding depression in the F_2 generation. Studies of the tidepool copepod *Tigriopus californicus* show that crosses between populations typically result in F_1 hybrid vigour and F_2 hybrid breakdown for a number of measures connected with fitness (Burton 1987, Burton 1990a, 1990b, Edmands & Burton 1998, Burton *et al*. 1999). Recent work (Edmands 1999) has shown that the detrimental effects of breaking up coadaptation are magnified by increasing genetic distance between populations. This same effect was shown for the shrub *Lotus scoparius* but in this case outbreeding depression was already present in the F_1 generation (Montalvo & Ellstrand 2001). Other plant species that show outbreeding depression are *Ipomopsis aggregata* (Waser *et al*. 2000) and *Silene diclinis* (Waldmann 1999).

Finally, the arrival of migrants from large populations can increase genetic variability, and, therefore, improve the evolutionary potential of the species as a whole. The extent to which migration can replenish genetic variability depends on the population dynamics and the pattern of migration into local populations. Populations with positive growth rates can rapidly recover lost genetic variability but sink populations will only be able to maintain genetic variability under migration patterns with low propagule size variance (Gaggiotti 1996, Gaggiotti & Smouse 1996). However, this long-term beneficial effect of migration may be offset by the introduction of maladapted genes, which could lead to a migrational meltdown (Ronce & Kirkpatrick 2001). Increased dispersal may lead to the loss of local adaptation in some populations, the appearance of source-sink dynamics, and the evolution of narrow niches (Kirkpatrick & Barton 1997, Ronce & Kirkpatrick 2001). This process, called migrational meltdown because small populations experience a downward spiral of maladaptation and shrinking size, is discussed in the next section.

Extinction in a metapopulation context

The same factors responsible for the genetic threats to the survival of isolated populations are operating at the metapopulation level but they have not been as well studied in this context. The best studied factor is the loss of genetic variability due to population turnover. Slatkin (1977) was the first to show that the extinction and recolonisation of local populations causes a major reduction in the genetic diversity maintained within demes and in the total metapopulation. The reduction in the total amount of genetic diversity is more pronounced when colonizing propagules are formed by individuals from the same deme ("propagule pool" model) than when they are formed by individuals coming from all extant demes ("migrant pool" model). Maruyama and Kimura (1980) demonstrated this same effect using a formulation that focused on the mutation effective size. Whitlock and Barton (1997) used a formulation based on the eigenvalue effective size (the number of individuals in an ideal population that would lose heterozygosity at the same rate as the actual population) of a metapopulation and concluded that the decrease in the effective size of the metapopulation is due to a sharp increase in the variance in reproductive success among individuals brought about by population turnover. Individuals that recolonise a habitat patch have an expected reproductive output of $N/k > 1$, where N is the local population size and k is the propagule size. On the other hand individuals in the demes that are about to go extinct fail to contribute progeny to the metapopulation. All the studies mentioned above considered a metapopulation composed of qualitatively similar demes (i.e. equal carrying capacities). If habitat patches differ in quality, which is typically the case for source-sink metapopulations, population turnover does not have a very large effect because genetic diversity is stored in the extinction resistant source populations. Moreover, sink populations can maintain a large fraction of the genetic variability present in the source population under migration patterns with a low variance in propagule size (Gaggiotti 1996).

The theoretical study of inbreeding depression in a metapopulation has received little attention but recently, Whitlock (2002) addressed this problem in some detail. When local populations contribute to the next generation in proportion to their average fitness (i.e. under hard selection), a metapopulation will respond more efficiently to selection than a panmictic population of equal size. This occurs because with local mating, recessive alleles are more likely to be expressed as homozygotes, thus the response to selection on recessive alleles is proportional to their homozygous effect rather than the weaker heterozygous effect. Under these circumstances, the purging of deleterious mutations is more pronounced and is not temporary because of persistent migration, which brings new variation into each local population. Thus, the equilibrium frequency of deleterious alleles is lower than in an undivided population of equal total size and results in reduced inbreeding depression.

Higgins and Lynch (2001) extended the mutational meltdown theory described above to cover the case of metapopulations using an

individual-based model that includes stochastic, demographic, environmental, and genetic mechanisms. The metapopulation structure is modelled as a linear array of patches connected by either nearest-neighbour (stepping-stone), global (island), or intermediate dispersal. The mutational effect is modelled in such a way that mutations of large effect are almost recessive, whereas those of small effect are almost additive. The results show that for metapopulations with more than a few patches, mutational accumulation is expected to accelerate extinction time by many orders of magnitude, compared to a globally dispersing metapopulation without mutation accumulation. Moreover, extinction because of mutation accumulation can be quite rapid, on the order of tens of generations. In general, the results indicate that the mutational meltdown may be a significant threat to large metapopulations and would exacerbate the effects of habitat loss or fragmentation on metapopulation viability. These conclusions, however, where reached under the assumptions of an expected per-generation genome wide mutation rates of 1 and unconditionally deleterious mutational effects. As mentioned before, these two assumptions have been put under close scrutiny and preliminary evidence indicates that they may not be of general applicability.

An additional mechanism for extinction in a metapopulation context is motivated by the idea that peripheral populations receive gene flow from the center of the species' range. These immigrant genes will typically be adapted to the conditions at the range center and could inhibit adaptation at the periphery (Mayr 1963). Kirpatrick and Barton (1997) used a quantitative genetic model to study the evolution of a species range in a linear habitat with local migration. The model tracks evolutionary and demographic changes across space and time and assumes that variation in the environment generates patterns of selection that change in space but are constant in time. Among other things, the results show that a species' range can contract as the dispersal rate increases and extinction can result if conditions change too rapidly as one moves across the habitat, even if the species remains perfectly adapted to the habitat at the range center. Ronce and Kirpatrick (2001) also studied the maladaptive effect of migration but they considered a model with two discrete habitat types connected by migration. In this case, increasing migration rate above some threshold value results in the collapse of the total population size and the complete loss of one of the two habitats. As opposed to Kirpatrick and Barton analysis, there is no metapopulation extinction. Ronce and Kirpatrick (2001) attributed this disagreement between the two models to the assumption of infinite space made by Kirpatrick and Barton's model: the distance traveled by migrants and thus the maladaptation of such migrants to local conditions increase indefinitely with the migration rate. This indicates that the migrational meltdown is unlikely to cause metapopulation extinction but it can lead to the extinction of local populations.

Discussion

Much progress has been made towards gaining a better understanding of the interaction between demographic and genetic factors in the extinction of populations. For example, it is now clear that their interaction can lead to positive feedback loops involving ever decreasing population sizes and eventual extinction (e.g. mutational meltdown). A substantial amount of empirical evidence has been gathered supporting the importance of genetic threats. This is particularly the case for inbreeding depression, which is the most immediate genetic threat to the survival of small populations. Theoretical work indicates that the accumulation of mildly deleterious mutations could be potentially important in the short term while the loss of genetic variability is important in the long term.

Despite this progress, there are still some few unresolved issues that need to be clarified before being able to fully evaluate the importance of genetic threats. In particular, the current controversy (Garcia-Dorado *et al*. 1999, Lynch *et al*. 1999, Caballero *et al*. 2002) surrounding the genome-wide mutation rates and their average effect makes it difficult to have a clear sense of the importance of the mutational meltdown for the extinction of local populations and whole metapopulations. More research on the mutation

process underlying the mutational meltdown and more empirical demonstration of the feasibility of this phenomenon are needed. Additionally, models such as that of Higgins and Lynch (2001) should be extended to include beneficial mutations.

Additional work has to be carried out in order to evaluate the importance of the genetic rescue effect due to heterosis and, in particular, to understand how outbreeding influences the mean fitness of natural populations. This will require carrying out experiments that follow the fate of descendants from immigrants beyond the F_2 generation. It is possible that the results of the experiments will depend on the degree of inbreeding depression in the experimental populations. Highly inbred populations whose fitness is very low may react positively to the influx of migrants and show no signs of outbreeding depression at all. However, less inbred populations whose fitness has not been dramatically impaired may show heterosis in the F_1 but outbreeding depression in the F_2 and subsequent generations. Thus, unraveling the effect of immigration on fitness will require controlling for the inbreeding level using lines whose pedigree is known.

Recent theoretical work has shown that metapopulations can be subject to extinction due to genetic factors, but there is little empirical evidence supporting their predictions and special efforts are needed to address this issue.

The multidisciplinary research carried out in the last decade or so clearly indicates that the dichotomy between demographic and genetic factors is artificial since extinction processes can involve both of them. This is particularly the case for populations of intermediate sizes that were previously thought to be under no risk of extinction. In the case of populations that have declined to very low numbers, the risk of extinction is more likely to be influenced by demographic and ecological stochasticity. Finally, it is important to note that neither demographic nor genetic factors *per se* are responsible for the large number of population declines that we are witnessing today. They only become important once human intervention has driven initially healthy and sustainable populations to critically low levels.

Acknowledgements

This work was supported by the Academy of Finland through its Finnish Centre of Excellence Programme (2000–2005). The original manuscript benefited from the comments of a reviewer and the editor.

References

Allendorf, F. W. & Ryman, N. 2002: The role of genetics in population viability analysis. — In: Beissinger, S. R. & McCullough, D. R. (eds.), *Population viability analysis*: 50–85. University of Chicago Press, Chicago.

Ball, S. J., Adams, M., Possingham, H. P. & Keller, M. A. 2000: The genetic contribution of single male immigrants to small, inbred populations: a laboratory study using *Drosophila melanogaster*. — *Heredity* 84: 677–684.

Burton, R. S. 1987: Differentiation and integration in the genome of the marine copepod, *Tigriopus californicus*. — *Evolution* 41: 504–513.

Burton, R. S. 1990a: Hybrid breakdown in physiological-response — a mechanistic approach. — *Evolution* 44: 1806–1813.

Burton, R. S. 1990b: Hybrid breakdown in developmental time in the copepod *Tigriopus californicus*. — *Evolution* 44: 1814–1822.

Burton, R. S., Rawson, P. D. & Edmands, S. 1999: Genetic architecture of physiological phenotypes: Empirical evidence for coadapted gene complexes. — *American Zoologist* 39: 451–462.

Byers, D. L. & Waller, D. M. 1999: Do plant populations purge their genetic load? Effects of population size and mating history on inbreeding depression. — *Annual Review of Ecology and Systematics* 30: 479–513.

Caballero, A., Cusi, E., Garcia, C. & Garcia-Dorado, A. 2002: Accumulation of deleterious mutations: Additional *Drosophila melanogaster* estimates and a simulation of the effects of selection. — *Evolution* 56: 1150–1159.

Caro, T. M. & Laurenson, M. K. 1994: Ecological and genetic factors in conservation: a cautionary tale. — *Science* 263: 485–486.

Caughley, G. 1994: Directions in conservation biology. — *Journal of Animal Ecology* 63: 215–244.

Cavalli-Sforza, L. L. & Bodmer, W. F. 1971: *The genetics of human populations*. — W.H. Freeman and Co., San Francisco.

Charlesworth, B. & Charlesworth, D. 1999: The genetic basis of inbreeding depression. — *Genetical Research* 74: 329–340.

Charlesworth, D. & Charlesworth, B. 1987: Inbreeding depression and its evolutionary consequences. — *Annual Review of Ecology and Systematics* 18: 237–268.

Coltman, D. W., Pilkington, J. G., Smith, J. A. & Pemberton, J. M. 1999: Parasite-mediated selection against inbred Soay sheep in a free-living, island population. — *Evolution* 53: 1259–1267.

Crnokrak, P. & Roff, D. A. 1999: Inbreeding depression in the wild. — *Heredity* 83: 260–270.

Crow, J. F. 1948: Alternative hypotheses of hybrid vigor. — *Genetics* 477–487.

Daniels, S. J. & Walters, J. R. 2000: Inbreeding depression and its effects on natal dispersal in red-cockaded woodpeckers. — *Condor* 102: 482–491.

Dobzhansky, T. 1950: Genetics of natural populations. 19. Origin of heterosis through natural selection in populations of *Drosophila pseudoobscura*. — *Genetics* 35: 288–302.

Dobzhansky, T. 1970: *Genetics of the evolutionary process*. — Columbia University Press, New York.

Ebert, D., Haag, C., Kirkpatrick, M., Riek, M., Hottinger, J. W. & Pajunen, V. I. 2002: A selective advantage to immigrant genes in a *Daphnia* metapopulation. — *Science* 295: 485–488.

Edmands, S. & Burton, R. 1998: Variation in cytochrome-C oxidase activity is not maternally inherited in the copepod *Tigriopus californicus*. — *Heredity* 80: 668–674.

Edmands, S. 1999: Heterosis and outbreeding depression in interpopulation crosses spanning a wide range of divergence. — *Evolution* 53: 1757–1768.

Falconer, D. S. & Mackay, T. F. C. 1996: *Introduction to quantitative genetics*. — Longman, Harlow.

Frankham, R. 1995: Effective population size/adult population size ratios in wildlife: a review. — *Genetic Research* 66: 95–107.

Gaggiotti, O. E. 1996: Population genetic models of source-sink metapopulations. — *Theoretical Population Biology* 50: 178–208.

Gaggiotti, O. E. & Smouse, P. E. 1996: Stochastic migration and maintenance of genetic variation in sink populations. — *American Naturalist* 147: 919–945.

Gaggiotti, O. E. & Vetter, R. D. 1999: Effect of life history strategy, environmental variability, and overexploitation on the genetic diversity of pelagic fish populations. — *Canadian Journal of Fisheries and Aquatic Sciences* 56: 1376–1388.

Garcia-Dorado, A., Lopez-Fanjul, C. & Caballero, A. 1999: Properties of spontaneous mutations affecting quantitative traits. — *Genetical Research* 74: 341–350.

Gotelli, N. J. 1991: Metapopulation models — the rescue effect, the propagule rain, and the core-satellite hypothesis. — *American Naturalist* 138: 768–776.

Groombridge, J. J., Jones, C. G., Bruford, M. W. & Nichols, R. A. 2000: 'Ghost' alleles of the Mauritius kestrel. — *Nature* 403: 616.

Hedrick, P. N. & Kim, T. J. 2000: Genetics of complex polymorphisms: parasites and maintenance of the major histocompatibility complex variation. — In: Sing, S. R. & Krimbas, C. B. (eds.), *Evolutionary genetics: from molecules to morphology*: 204–234. Cambridge University Press, Cambridge.

Hedrick, P. N., Parker, K. M., Gutierrez-Espeleta, G. A., Rattink, A. & Lievers, K. 2000: Major histocompatibility complex variation in the Arabian orix. — *Evolution* 54: 2145–2151.

Hedrick, P. W. & Miller, P. S. 1992: Conservation genetics — techniques and fundamentals. — *Ecological Applications* 2: 30–46.

Hedrick, P. W., Parker, K. M., Miller, E. L. & Miller, P. S. 1999: Major histocompatibility complex variation in the endangered Przewalski's horse. — *Genetics* 152: 1701–1710.

Higgins, K. & Lynch, M. 2001: Metapopulation extinction caused by mutation accumulation. — *Proceedings of the National Academy of Sciences of the United States of America* 98: 2928–2933.

Hoelzel, A. R., Stephens, J. C. & O'Brien, S. J. 1999: Molecular genetic diversity and evolution at the MHC DQB locus in four species of pinnipeds. — *Molecular Biology and Evolution* 16: 611–618.

Hoelzel, A. R., Fleischer, R. C., Campagna, C., Le Boeuf, B. J. & Alvord, G. 2002: Impact of a population bottleneck on symmetry and genetic diversity in the northern elephant seal. — *Journal of Evolutionary Biology* 15: 567–575.

Ingvarsson, P. K. & Whitlock, M. C. 2000: Heterosis increases the effective migration rate. — *Proceedings of the Royal Society of London Series B* 267: 1321–1326.

Jablonski, D. 1986: Background and mass extinctions — the alternation of macroevolutionary regimes. — *Science* 231: 129–133.

James, J. W. 1971: The founder effect and response to artificial selection. — *Genetical Research* 12: 249–266.

Keightley, P. D. & Caballero, A. 1997: Genomic mutation rates for lifetime reproductive output and lifespan in *Caenorhabditis elegans*. — *Proceedings of the National Academy of Sciences of the United States of America* 94: 3823–3827.

Keller, L. F., Arcese, P., Smith, J. N. M., Hochachka, W. M. & Stearns, S. C. 1994: Selection against inbred song sparrows during a natural population bottleneck. — *Nature* 372: 356–357.

Keller, L. F. 1998: Inbreeding and its fitness effects in an insular population of song sparrows (*Melospiza melodia*). — *Evolution* 52: 240–250.

Keller, L. F., Grant, P. R., Grant, B. R. & Petren, K. 2002: Environmental conditions affect the magnitude of inbreeding depression in survival of Darwin's finches. — *Evolution* 56: 1229–1239.

Keller, L. F. & Waller, D. M. 2002: Inbreeding effects in wild populations. — *Trends in Ecology and Evolution* 17: 230–241.

Kirkpatrick, M. & Barton, N. H. 1997: Evolution of a species' range. — *American Naturalist* 150: 1–23.

Kruuk, L., Sheldon, B. & Merilä, J. 2002: Severe inbreeding depression in collared flycatchers (*Ficedula albicollis*). — *Proceedings of the Royal Society of London Series* B 269: 1581–1589.

Lande, R. 1988: Genetics and demography in biological conservation. — *Science* 241: 1455–1460.

Lande, R. 1994: Risk of population extinction from fixation of new deleterious mutations. — *Evolution* 48: 1460–1469.

Lande, R. 1995: Mutation and conservation. — *Conservation Biology* 9: 782–791.

Lande, R. & Shannon, S. 1996: The role of genetic variation in adaptation and population persistence in a changing environment. — *Evolution* 50: 434–437.

Lynch, M. & Gabriel, W. 1990: Mutation load and the sur-

vival of small populations. — *Evolution* 44: 1725–1737.

Lynch, M., Burger, R., Butcher, D. & Gabriel, W. 1993: The mutational meltdown in asexual populations. — *Journal of Heredity* 84: 339–344.

Lynch, M., Conery, J. & Burger, R. 1995: Mutational meltdowns in sexual populations. — *Evolution* 49: 1067–1080.

Lynch, M. & Walsh, B. 1998: *Genetics and analysis of quantitative traits*. — Sinauer Associates, Sunderland, MA.

Lynch, M., Blanchard, J., Houle, D., Kibota, T., Schultz, S., Vassilieva, L. & Willis, J. 1999: Perspective: spontaneous deleterious mutation. — *Evolution* 53: 645–663.

Madsen, T., Shine, R., Olsson, M. & Wittzell, H. 1999: Conservation biology — restoration of an inbred adder population. — *Nature* 402: 34–35.

Marr, A. B., Keller, L. F. & Arcese, P. 2002: Heterosis and outbreeding depression in descendants of natural immigrants to an inbred population of song sparrows (*Melospiza melodia*). — *Evolution* 56: 131–142.

Maruyama, T. & Kimura, M. 1980: Genetic variability and effective population size when local extinction and recolonization of subpopulations are frequent. — *Proceedings of the National Academy of Sciences, USA* 77: 6710–6714.

Mayr, E. 1963: *Animal species and evolution*. — Harvard University Press.

Mikko, S., Spencer, M., Morris, B., Stabile, S., Basu, T., Stormont, C. & Andersson, L. 1997: A comparative analysis of Mhc DRB3 polymorphism in the American bison (*Bison bison*). — *Journal of Heredity* 88: 499–503.

Montalvo, A. M. & Ellstrand, N. C. 2001: Nonlocal transplantation and outbreeding depression in the subshrub *Lotus scoparius* (Fabaceae). — *American Journal of Botany* 88: 258–269.

Muller, H. J. 1964: The relation of recombination to mutational advance. — *Mutation Research* 1: 2–9.

Nei, M., Maruyama, T. & Chakraborty, R. 1975: The bottleneck effect and genetic variability in populations. — *Evolution* 29: 1–10.

Newman, D. & Pilson, D. 1997: Increased probability of extinction due to decreased genetic effective population size: Experimental populations of *Clarkia pulchella*. — *Evolution* 51: 354–362.

Parham, P. 1996: Pictures of MHC restriction. — *Nature* 384: 109–110.

Parham, P. & Ohta, T. 1996: Population biology of antigen presentation by MHC class I molecules. — *Science* 272: 67–74.

Pfrender, M., Spitze, K., Hicks, J., Morgan, K., Latta, L. & Lynch, M. 2001: Lack of concordance between genetic diversity estimates at the molecular and quantitative-trait levels. — *Conservation Genetics* 1: 263–269.

Poon, A. & Otto, S. P. 2000: Compensating for our load of mutations: Freezing the meltdown of small populations. — *Evolution* 54: 1467–1479.

Richards, C. M. 2000: Inbreeding depression and genetic rescue in a plant metapopulation. — *American Naturalist* 155: 383–394.

Ronce, O. & Kirkpatrick, M. 2001: When sources become sinks: Migrational meltdown in heterogeneous habitats. — *Evolution* 55: 1520–1531.

Saccheri, I., Kuussaari, M., Kankare, M., Vikman, P., Fortelius, W. & Hanski, I. 1998: Inbreeding and extinction in a butterfly metapopulation. — *Nature* 392: 491–494.

Shaw, F. H., Geyer, C. J. & Shaw, R. J. 2002: A comprehensive model of mutations affecting fitness and inferences from *Arabidopsis thaliana*. — *Evolution* 56: 453–463.

Slatkin, M. 1977: Gene flow and genetic drift in a species subject to frequent local extinctions. — *Theoretical Population Biology* 12: 253–262.

Waldmann, P. 1999: The effect of inbreeding and population hybridization on developmental instability in petals and leaves of the rare plant *Silene diclinis* (Caryophyllaceae). — *Heredity* 83: 138–144.

Waser, N. M., Price, M. V. & Shaw, R. G. 2000: Outbreeding depression varies among cohorts of *Ipomopsis aggregata* planted in nature. — *Evolution* 54: 485–491.

Whitlock, M. C. & Barton, N. H. 1997: The effective size of a subdivided population. — *Genetics* 146: 427–441.

Whitlock, M. C. 2000: Fixation of new alleles and the extinction of small populations: Drift load, beneficial alleles, and sexual selection. — *Evolution* 54: 1855–1861.

Whitlock, M. C., Ingvarsson, P. K. & Hatfield, T. 2000: Local drift load and the heterosis of interconnected populations. — *Heredity* 84: 452–457.

Whitlock, M. C. 2002: Selection, load and inbreeding depression in a large metapopullation. — *Genetics* 160: 1191–1202.

Whitlock, M. C., Griswold, C. K. & Peters, A. D. 2003: Compensating for the meltdown: The critical effective size of a population with deleterious and compensatory mutations. — *Annales Zoologici Fennici* 40: 169–183.

Woodruff, D. S. 2001: Declines of biomes and biotas and the future of evolution. — *Proceedings of the National Academy of Sciences of the United States of America* 98: 5471–5476.

Wright 1931: Evolution in mendelian populations. — *Genetics* 16: 97–159.

Wright, S. 1938: Size of population and breeding structure in relation to evolution. — *Science* 87: 430–431.

Wright, S. 1969: *The theory of gene frequencies*. — The University of Chicago Press, Chicago, IL.

Zeyl, C. & DeVisser, J. 2001: Estimates of the rate and distribution of fitness effects of spontaneous mutation in *Saccharomyces cerevisiae*. — *Genetics* 157: 53–61.

Zeyl, C., Mizesko, M. & de Visser, J. 2001: Mutational meltdown in laboratory yeast populations. — *Evolution* 55: 909–917.