Title: Male mutation bias and possible long-term effects of human activities.
Authors: Cotton S., Wedekind C.

Journal: Conservation Biology
Year: 2010

Volume: 24(5)

Pages: 1190-1197

DOI: 10.1111/j.1523-1739.2010.01524.x

Implications of male mutation bias for conservation

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Keywords: conservation, evolutionary potential, life history, male mutation bias, mutation, sexual selection, population size

Abstract: The ability to adapt to changing environments depends critically on the amount and the kind of genetic variability within a population. Mutations are an important source of new genetic variability and may lead to new adaptations. However, slightly deleterious mutations typically accumulate in small populations leading to genomic deterioration. Population size and mutation rates are therefore two parameters that critically influence a population's long-term survival. Factors that affect mutation rates have received relatively little attention in the conservation genetics literature. However, mutation rates are extremely variable, and males usually have higher mutation rates. This male bias affects the overall mutation rate and is therefore important for conservation. Here, we review the various causes of male mutation bias, focusing on the effects of (i) classical life-history parameters such as the average age at reproduction, and (ii) elevated rates of sperm production in response to sexual selection and sperm competition. Human-induced changes in life-history and reproductive traits are predicted to affect the evolution of mutation rates, as a consequence of various kinds of management or conservation practices that change the strength and direction of natural and sexual selection. We argue that it is important to consider the evolution of mutation rates in order to understand the potential consequences of various population exploitation and management strategies.

Introduction

Genetic variability allows populations to adapt to future challenges. One of the main aims of conservation and management programs has therefore been to maintain existing levels of genetic variation (Ferrière et al. 2004). However, the evolutionary potential and persistence of a population depends not only on the variance depleting effects of selection, inbreeding and stochastic loss through drift, but also on the influx of new genetic variability created *de novo* by mutation. Whilst prevention of the loss of genetic variance has been well studied, factors that affect the ultimate source of genetic variance like, for example, mutations have received relatively little attention in the conservation genetics literature. In this article we consider some of the causes and consequences of variation in the mutation rate.

Mutation rates are highly variable, both between and within species and even within genomes or single chromosomes (Drake et al. 1998; Baer et al. 2007; Duret 2009; Hodgkinson et al. 2009). While mutations occur in all cell types, the most important for evolution are those that occur in the germline, as they are inherited by offspring. One of the most pervasive patterns to have emerged is that germline mutation rates are often much higher in males than females as a result of a greater number of cell replication events during spermatogenesis (Hurst & Ellegren 1998; Li et al. 2002; Ellegren 2007; Hedrick 2007; Ellegren 2009). Mutations are usually deleterious to fitness, so selection should lead to the evolution of lower mutation rates (Drake et al. 1998; Sniegowski et al. 2000; Baer et al. 2007). An elevated mutation rate in males is therefore likely to be maintained by some opposing force that is weaker or absent in females.

Selection can favour alleles that elevate mutation rates (Sniegowski et al. 1997; Taddei et al. 1997), but this may only occur in asexual populations (Johnson 1999) and may not yet explain why we observe different mutation rates in the sexes. An alternative, more pervasive, explanation for this sex difference is that there are physiological or mechanistic constraints to maintaining low mutation rates (Sniegowski et al. 2000; Agrawal & Wang 2008), with biased germline mutation rates being a consequence of higher per-gamete costs of DNA replication fidelity in males. If so, evolved mutation rates would reflect a balance between the costs of mutational repair and the negative fitness effects of mutation (Sniegowski et al. 2000; Baer et al. 2007), even if this balance cannot be fully optimized by natural selection (Pal et al. 2007; Clune et al. 2008).

Copying errors during cell replication are a major source of mutations. Anisogamy- the production of many small gametes by males and few large ova by females – leads to a disparity in germline cell division rates between the sexes. We expect germline mutation rates to be higher in males as a result of the greater number of cell divisions required for spermatogenesis relative to those of oogenesis. For instance, human females require 24 cell divisions to produce a mature ovum, whereas the male germline undergoes ~30 divisions prior to puberty with 23 additional replications per year(Crow 2006). Similarly, in birds female gametes undergo only 20 cell divisions, whereas sperm result from almost 90 cell divisions per generation (Kahn & Quinn 1999). Male-biased mutation rates have been reported in many higher metazoan taxa, e.g. mammals (Lawson & Hewitt 2002; Makova & Li 2002; Malcom et al. 2003; Makova et al. 2004; Lindblad-Toh et al. 2005; Sandstedt & Tucker 2005), birds (Ellegren & Fridolfsson 1997; Kahn & Quinn 1999; Fridolfsson & Ellegren 2000; Bartosch-Harlid et al. 2003; Axelsson et al. 2004), fish (Ellegren & Fridolfsson 2003; Zhang 2004), insects (Bachtrog 2008) but see (Bauer & Aquadro 1997), and plants (Filatov & Charlesworth 2002; Whittle & Johnston 2002).

Male mutation bias α_m

Miyata *et al*. (1987) proposed that male mutation bias could be investigated evolutionarily by examining inter-specific nucleotide divergence at homologous DNA sequences on sex chromosomes and autosomes, assuming neutral sequence evolution and that substitution rates

reflect the true mutation rate. Each type of chromosome spends a differing amount of time in each sex; in male heterogametic systems Y chromosomes exist only in males, X chromosomes spend one third of their time in males, and autosomes inhabit each sex equally. Knowledge of the proportion of time spent in each sex for each chromosome type and the substitution rates on each chromosomal type therefore permits estimation of α_m, the ratio of male (μ_M) to female (μ_F) mutations. The average mutation rates on the Y, X and autosomes can be simplified to $\mu_Y = \mu_M$, $\mu_X = \frac{2}{3}\mu_F + \frac{1}{3}\mu_M$, and $\mu_A = \frac{1}{2}(\mu_F + \mu_M)$, respectively. Given that $\alpha_m = \mu_M / \mu_F$, the ratios of mutation rates on different chromosomes is then

$$\frac{\mu_Y}{\mu_X} = \frac{3\alpha_m}{(\alpha_m + 2)}, \frac{\mu_Y}{\mu_A} = \frac{2\alpha_m}{(\alpha_m + 1)}, \text{ and } \frac{\mu_X}{\mu_A} = \frac{2(\alpha_m + 2)}{3(\alpha_m + 1)}.$$

Rearranging allows α_m to be estimated for each chromosomal contrast as

$$\alpha_m = \frac{2\mu_Y}{(3\mu_X - \mu_Y)}, \alpha_m = \frac{\mu_Y}{(2\mu_A - \mu_Y)}, \text{ and } \alpha_m = \frac{(4\mu_A - 3\mu_X)}{(3\mu_X - 2\mu_A)},$$

respectively (Miyata et al. 1987; Ellegren 2007; Hedrick 2007; Ellegren 2009). Note that selection acts differently on sex chromosomes and autosomes because recessive mutations are directly exposed in the XY or, if one X chromosome is silenced (Chow et al. 2005), in the XX genotype. An evolutionarily reduced mutation rate on the X chromosomemay therefore lead to elevated α_m-values independent of higher male germline cell division rates (McVean & Hurst 1997). However, in species with female heterogamety (ZW/ZZ) where selection for reduced μ_Z should then lead to female, rather than male, mutation bias, α_m is usually still > 1 (Ellegren & Fridolfsson 1997; Bartosch-Harlid et al. 2003), suggesting that the relative rate of germ cell replication is the dominant factor influencing α_m.

Some variation in α_m has been attributed to the choice and nucleotide composition of the sequenced region(s) (Berlin et al. 2006; Taylor et al. 2006), and to the phylogenetic distance between species used in comparisons (Makova & Li 2002; Bartosch-Harlid et al. 2003; Sandstedt & Tucker 2005). However, two notable evolutionary associations with α_m have emerged.

First, while the number of cell divisions required to produce an ovum is similar across species and relatively unaffected by life history, the same is not true for spermatogenesis. Species are expected to have more cell divisions during spermatogenesis, and hence higher α_m values, if they have longer generation times or if they reproduce multiply over their life (Bartosch-Harlid et al. 2003; Goetting-Minesky & Makova 2006; Ellegren 2007 and references therein). For example, Bauer & Aquadro (1997) observed a female biased mutation rate in young *Drosophila* (α_m = 0.77 at 3 days) owing to more cell divisions being required to produce eggs from germline stem cells than sperm (18.5 *vs*. 16.5 respectively). However, the *rate* of stem cell division is twice as high in males, so gametes from older males originate from progenitor cells that have undergone more divisions than those from females. This leads to an increasingly male biased mutation rate in older flies (α_m = 1.33 at 21 days; Bauer & Aquadro 1997). Inter-specific support for the generation time hypothesis comes from the observation that generation times follow the order primates > dogs > mice and rats, taxa which have α_m-values of 4-6, ~3, and ~2, respectively (Li et al. 1996; Makova et al. 2004; Lindblad-Toh et al. 2005; Taylor et al. 2006). Similarly, Bartosch-Härlid et al. (2003) found a positive relationship between generation time and α_m among clades of birds.

Second, sperm competition frequently leads to larger testes and increased sperm production (Hosken et al. 2001; Pitnick et al. 2001; Ramm & Stockley 2009) If we assume that elevated sperm production increases the number of cell divisions in the male germline, then sperm competition will lead to heightened α_m (Bartosch-Harlid et al. 2003; Blumenstiel 2007; Ellegren 2007). When males face a trade-off between increased sperm production and investment (in terms of DNA replication fidelity) per gamete, even moderate levels of sperm

competition were found to cause a shift in the evolutionarily optimal mutation rate towards higher α_m-values (Blumenstiel 2007). Under such circumstances the immediate fitness gained by males though success in sperm competition is greater than that lost in the next generation through the deleterious effects of the extra, male derived, mutations on offspring fitness (Blumenstiel 2007). Empirical support for this model comes from the finding that α_m-values are higher in clades of birds with more intense sperm competition, measured as the frequency of extra-pair paternity (EPP) (Bartosch-Harlid et al. 2003). For example, the mean frequency of EPP in three passerine clades was 27.8, 22.9 and 13.6, which had respective α_m-values of 3.48, 2.42 and 1.70 (Bartosch-Harlid et al. 2003). Are the evolutionary ramifications of male-biased mutation rates important for conservation biology? We argue that they are, and suggest that they may have both destructive yin and creative yang consequences, depending on the kind and strength of selection and on the effective size (N_e) of the population, especially on the respective N_e of males and females.

Mutation consequences and N_e:

In a highly adapted and complex organism, the introduction of random mutations is likely to be deleterious to fitness, and hence selection tends to remove such mutations from the population. In large populations, the frequency of a deleterious allele at equilibrium (q_{eq}) increases with its rate of mutation (μ) from the wildtype allele and decreases with the selection coefficient (s) acting against the allele in its heterozygous state ($q_{eq} = \mu/s$) (Whitlock 2000). The average reduction in population fitness due to standing mutations is the mutation load, L. In large diploid populations, $L = 2sq_{eq} = 2\mu$, assuming incomplete dominance, meaning that the deleterious effects of mutation load scales in proportion to the mutation rate (Haldane 1937; Whitlock & Agrawal 2009).

The efficiency of selection at removing deleterious mutant alleles is contingent on N_e. When N_e is small, selection is rendered less effective at driving changes in allele frequency compared to stochastic factors such as drift (Lande 1994, 1995). In large populations, drift plays only a minor role with selection being the predominant evolutionary force. Selective neutrality of mutations occurs when changes in allele frequency due to selection are less than or equal those due to drift, and is reached when $s = 1/2N_e$ (Wright 1931). Population size therefore influences the margins of selective neutrality and thus selection can only act in small populations against mutations of increasingly large deleterious effects; mutations causing deleterious effects on fitness of $\leq 1/2N_e$ are unable to be selectively removed from populations of effective size N_e.

Once mutations have arisen in a diploid population with census and effective population sizes of N and N_e, respectively, the probability that they become fixed is,

$$u(s) = \frac{2s(N_e/N)}{1 - e^{-4N_e s}}$$

(Crow & Kimura 1970; Whitlock 2000). Since most mutations are of small effect and selection is unable to purge these from small populations, then such populations are most at risk from the fixation of nearly-neutral mutations (i.e. mutations with $s \approx 1/2N_e$ (Lande 1995). The accumulation of fixed nearly-neutral deleterious alleles in the gene pool of small populations may lead to mutational meltdown, which threatens the long-term population viability (Lande 1994, 1995). For example, Lande (1994) showed that the maximum risk of extinction due to mutation accumulation in small populations occurred when $s \approx 0.4/N_e$, which is close to the margins of selective neutrality.

Accelerated mutation accumulation in small populations:

Male biased mutation rates may evolve when populations experience elevated μ_M and/or reduced μ_F. The latter cannot be ignored (McVean & Hurst 1997; Whitlock & Agrawal 2009),

but it seems reasonable to assume that $\alpha_m > 1$ is caused primarily by increased μ_M owing to higher male germline cell division rates (Hedrick 2007; Ellegren 2009). When male and female mutation rates differ, the overall mutation rate is equal to the sex-averaged rate, which increases with the degree of male bias, $\mu = 0.5\mu_F(\alpha_M + 1)$. Thus when μ_F is static, populations with $\alpha_m = 3$ have mutation rates (and hence mutation loads) twice as high as those whose $\alpha_m = 1$. So while the *probability* of fixation, $u(s)$, is independent of α_m and μ (see above), the *rate* of fixation of deleterious alleles increases with male-biased mutation, owing to the elevated influx of mutations in such populations.

Small populations of long-lived species and/or those with strong sperm competition may therefore be disproportionately prone to mutation accumulation and the problem of genomic deterioration. Redfield (1994) provides partial support for this in the context of the evolution of sexual reproduction, as simulated populations with an elevated male mutation rate produced offspring with more mutations than sex and recombination were able to eliminate. Consequently, populations with high α_m-values had lower fitness than those whose sexes contributed equivalent numbers of mutations. Lynch *et al*. (1995) estimated that a doubling of the influx of mildly deleterious mutations reduces the expected persistence time of a (small) population by 50%. An elevated mutation rate of this magnitude might be easily achievable in high α_m-value, long-lived species with a high prevalence of sperm competition (relative to more short lived and monogamous relatives: e.g. Bartosch-Harlid et al. 2003).

N_e in species with harem-based mating systems and/or strong sperm competition is likely to be much lower than those of monogamous populations, because $N_e = (4N\text{-}2)/(V_k+2)$, with V_k being the variation in family sizes, i.e. N_e declines as variance in reproductive success increases (Nomura 2002).. So the process of sexual selection may itself exacerbate the mutational problems created by the high α_m-values associated with it.

Poon & Otto (2000) showed that mutational meltdowns are less likely when beneficial mutations are considered, an idea supported by Silander et al. (2007), who observed fitness of small populations declining to a plateau rather than decreasing inexorably as expected under the mutational meltdown hypothesis. Furthermore, work by Gillespie (2001) suggests that a species' mutational characteristics may be rather insensitive to population size, at least in areas of low recombination. Such processes may mitigate, to varying degrees, our proposed consequence of N_e and α_m for a population's evolution. Nonetheless, given that high α_m populations have higher mutation rates, this alone makes male mutation bias an important consideration for evolutionary-based conservation decisions.

Male mutation bias, genetic variance and sexual selection

The response of a trait to selection, and hence the ability to adapt, is contingent upon the level of standing genetic variance (V_G), which ultimately depends on the input of new genetic variance each generation through mutation (V_M). The level of standing genetic variance is also sensitive to N_e and can be expressed as,

$$V_G = \frac{(2V_M N_e)}{(1 + 2N_e s)},$$

where s is the selection coefficient against the average mutant phenotype (derived from (Houle et al. 1996). $V_M = 2\sum_{i=1}^{n} \mu_i \overline{a_i^2}$, where μ_i is the mutation rate at the ith locus in a genome with n loci, and a_i^2 is the variance of the mutational effect at the ith locus (Roff 1997). All other things being equal, standing genetic variance increases with mutation rate and is greater in larger (effective) populations. Populations with male-biased mutation rates may therefore be subject to conflicting evolutionary genetic processes. On one hand they suffer from a decrease in mean fitness owing to the increased deleterious load that results from the elevated mutation rate. And on the other, they may benefit in the longer term from

an increased ability to adapt owing to the greater input of mutational variance upon which selection can act.Male ornamental traits, such as song, courtship and displays, are thought to reflect aspects of male genetic quality, allowing females to derive indirect benefits for their offspring by choosing such males as mates (Iwasa & Pomiankowski 1994). However, strong sexual selection will deplete genetic variation in male fitness, and hence female mate choice seems unlikely to confer genetic benefits to offspring. The dominant resolution for this evolutionary problem is provided by the prediction (Rowe & Houle 1996) and observation (Cotton et al. 2004) that sexual ornaments display condition-dependent expression; only high quality individuals are able to afford the costs of such traits. Condition is defined as a trait showing strong positive covariance with general viability (Rowe & Houle 1996; Cotton et al. 2004). Many loci are expected to influence condition, and so condition is a broad target for internal (i.e. mutations) and external (i.e. parasites, stress, environmental) factors that create or maintain genetic variance (Pomiankowski & Møller 1995; Rowe & Houle 1996). Mutational variance (V_M) in life-history traits such as condition is high (Houle et al. 1996), so genetic advantages of sexual selection are likely to increase with mutation rate,(Kirkpatrick 1996). If the strength of sexual selection shows positive covariance with α_m (Table 1), then the additional influx of mutation derived from males may provide additional genetic variation in fitness to maintain female mate choice.

Ornament costs may also influence mutation rates and α_m (Cotton 2009). Stress is known to induce higher mutation rates (Goho & Bell 2000), and individuals in poor condition contribute more mutations to their offspring (Agrawal & Wang 2008), presumably because the relative costs of DNA fidelity are higher under stress and in low-quality individuals (Sniegowski et al. 2000; Agrawal & Wang 2008). Costly sexual ornaments may therefore evolve at the expense of DNA replication and repair (Cotton 2009), and hence elevate α_m (Table 1). However, relationships between ornaments and (biased) mutation rates have not been explored empirically.

Lorch et al. (2003) have shown that conditiondependent ornaments allow both natural and sexual selection to act on condition, leading to elevated equilibrium mean fitness and an increased speed of adaptation. With respect to elevated evolutionary potential of populations with male biased mutation, we predict adaptation will occur more quickly with increasing α_m. Such an effect could mitigate the positive relationship between male mutation bias and mutation accumulation (Redfield 1994); Siller (2001) suggested that sexual selection for condition-dependent ornaments in populations with male-biased mutation rates will cause males to undergo stronger viability selection than females, and that this will reduce the mutation load.

We would like to stress that even if somewhat increased mutation rates may allow especially large populations to adapt more quickly and hence persist for longer, selection almost always acts in the short-term to reduce the mutation rate (Johnson 1999), so any relationship between α_m and increased evolutionary potential is unlikely to be under natural selection. Nevertheless, α_m and its effect on the evolutionary potential of populations can, to some degree, still be managed.

Effects of management and exploitation

Populations subject to human intervention, either through conservation or management practices, or through exploitation frequently demonstrate human-induced rapid evolution (Haugen & Vøllestad 2001; Coltman et al. 2003; Olsen et al. 2004; Nusslé et al. 2009). For example, fishing pressure shifted the life history towards maturation at earlier ages and smaller sizes in northern populations of Atlantic cod (*Gadus morhua*) (Olsen et al. 2004). Similar patterns have been observed in the European grayling (*Thymallus thymallus,* Haugen & Vøllestad 2001).

If human-induced changes in life history and reproductive traits influence the rate or frequency of cell division in the male germline, then affected populations will also likely

exhibit changed α_m. For instance, if the number of cell divisions during spermatogenesis increases when individuals reproduce at an older age (Bartosch-Harlid et al. 2003; Goetting-Minesky & Makova 2006; Ellegren 2007), then fisheries-derived selection for earlier age at maturity will lead to lowered α_m-values. A higher reproductive success of young males, for instance as a result of harvesting of older, larger individuals, will also result in a decreased mutational input (Table 2).

Sperm numbers adapt rapidly when the strength of sperm competition is manipulated; they show an evolutionary decrease when populations shift from polygamy to monogamy (Hosken & Ward 2001; Pitnick et al. 2001). Similar effects are expected in wild or captive populations when natural patterns of matings and reproductive success are altered, for instance through equalisation of reproductive success of males, randomisation of matings and/or artificial insemination (Table 2).

If sexual selection is disrupted or modified, or if anthropogenic selection causes evolutionary decreases in male longevity and/or sperm production, then the consequent reduction in α_m may reduce the amount of genetic variation below the critical level required for sustaining adaptive female mate choice, i.e. diminishing the efficacy of sexual selection, one of the most potent generators of biodiversity and genetic quality (Neff & Pitcher 2005). However, any long-term fitness consequences of the reduction in mutation load due to reduced α_m needs to be contrasted with the increase in N_e that could result from the removal of sexual selection (Nomura 2002); the relative importance of these two forces requires further investigation.. Anthropogenic selection may therefore have long-term consequences for evolutionary potential and adaptability, even in large populations (Table 2).

Future considerations

The significance of mutation rates and hence of α_m depends on various factors. The timescale is certainly crucial. High mutation rates immediately reduce the average viability of individuals. On the long term, however, they may allow populations to adapt to changing environments. Management of long-lived and/or sexually selected populations therefore needs to be sensitive to factors that affect α_m.

In small populations, the primary concern is often to increase N_e to above-critical levels, which might mean over-riding natural mating systems (Wedekind 2002). Circumventing sexual selection or encouraging reproduction at ages younger than normally seen in nature may elevate N_e but diminish α_m. Analogously, if harvesting or even assisted breeding of large populations (which is common for many fish) disrupts sexual selection and/or reproductive scheduling, then α_m and the evolutionary potential of the populations may decrease.

At present the data available on male-biased mutation rates are crude and, owing to high errors, unable to tell us anything more than basic patterns and trends. However, as the genomic era unfolds and a greater amount of sequence data from more species becomes available to study, investigations of male-biased mutations should become increasingly feasible and their conclusions more precise. It is now feasible to directly measure mutation rates by high-throughput sequencing technologies (Nishant et al. 2009). So far, these techniques have been used in few organisms (Denver et al. 2004; Haag-Liautard et al. 2008; Lynch et al. 2008), but it seems clear that our estimates of male mutation bias in other species can only improve. This should lead to more, and higher quality, data to test our predictions. We hope that this paper will stimulate more research into this important area of conservation biology.

Acknowledgments

This work was supported by a UK NERC Fellowship (to SC) and the Swiss National Science Foundation (CW). We thank two anonymous referees and D. Couvet, whose comments improved this manuscript considerably.

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Table 1 Factors linked to sexual selection that potentially influence the overall mutation rate μ and the male mutation bias α_m. Changes in evolutionary potential are considered relative to a population of similar N_e without sexual selection.

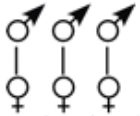
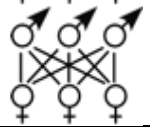
Factor affecting α_m	Increased by	Recent examples	Expected effect on α_m	Expected effect on μ	Evolutionary potential
Sperm production	Sperm competition or multiple mating	(Preston & Stockley 2006)	+, - [a]	+, - [a]	Increased, Reduced [a]
Sexual selection on condition	Male dominance fights	(Hudman & Gotelli 2007; McGhee et al. 2007)	+ [b], - [c]	+ [b], - [c]	Increased, Reduced [a]
Sexual selection on condition	Female choice	(Hudman & Gotelli 2007; Siitari et al. 2007)	+ [b]	+ [b]	Increased
Sexual selection on high age at reproduction	Male dominance fights	(Hollister-Smith et al. 2007; Jacob et al. 2007; Rasmussen et al. 2008)	+	+	Increased
Sexual selection on high age at reproduction	Female choice	(Bitton et al. 2007)	+	+	Increased

[a] If deleterious mutations specifically reduce sperm function then gametic α_m may be decreased owing to (natural) selection on sperm.

[b] If sexual selection induces stress that increases α_m.

[c] Negative, if investment into sperm production is correlated negatively to male dominance and condition, as within many fish populations (Ball & Parker 1996, 2000; Rudolfsen et al. 2006).

Table 2 Typical management procedures in fish management and their likely effects on μ and the evolution of α_m. Changes in evolutionary potential are considered relative to an unmanaged population at same N_e.

	Procedure	Breeding regime	Expected effect on α_m	Expected effect on μ	Evolutionary potential
Fishing	Size-selective, selecting against large, old, and fast-growing individuals		-	-	Reduced
Supportive breeding	Random mating		-	-	Reduced
Supportive breeding	Random mating, using maximal sperm volume		+	+	? [a]
Supportive breeding	Random mating, equalizing sperm volume		- [b]	- [b]	Reduced

[a] Reduced by the lack of sexual selection that may promote beneficial mutations, and increased or reduced by the effects of sperm competition on α_m (Wedekind et al. 2007)
[b] Negative, if older males would normally be more successful at natural spawning (Jacob et al. 2007; Wedekind et al. 2007; Rudolfsen et al. 2008; Jacob et al. 2009).