A Resolution of the Mutation Load Paradox in Humans

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ABSTRACT Current information on the rate of mutation and the fraction of sites in the genome that are subject to selection suggests that each human has received, on average, at least two new harmful mutations from its parents. These mutations were subsequently removed by natural selection through reduced survival or fertility. It has been argued that the mutation load, the proportional reduction in population mean fitness relative to the fitness of an idealized mutation-free individual, allows a theoretical prediction of the proportion of individuals in the population that fail to reproduce as a consequence of these harmful mutations. Application of this theory to humans implies that at least 88% of individuals should fail to reproduce and that each female would need to have more than 16 offspring to maintain population size. This prediction is clearly at odds with the low reproductive excess of human populations. Here, we derive expressions for the fraction of individuals that fail to reproduce as a consequence of recurrent deleterious mutation (φ) for a model in which selection occurs via differences in relative fitness, such as would occur through competition between individuals. We show that φ is much smaller than the value predicted by comparing fitness to that of a mutation-free genotype. Under the relative fitness model, we show that φ depends jointly on U and the selective effects of new deleterious mutations and that a species could tolerate 10's or even 100's of new deleterious mutations per genome each generation.

ALL organisms are subject to recurrent deleterious mutation, which cause some individuals to die or fail to reproduce. Deleterious mutations therefore impose a cost or load on the population. The evolutionary consequences of deleterious mutations were first studied by J. B. S. Haldane, who showed that the reduction in mean fitness in a diploid organism caused by recurrent semidominant deleterious mutation at a single locus is equal to twice the mutation rate (Haldane 1937). This led H. J. Muller to suggest that each new deleterious mutation ultimately leads to one genetic death, irrespective of the mutation's fitness effect (Muller 1950). Subsequently, the mutation load was more formally defined as the proportional reduction in mean fitness of a population relative to that of a mutation-free genotype, brought about by deleterious mutations (Crow 1970):

$$L = \frac{w_{\max} - \bar{w}}{w_{\max}}, \tag{1}$$

where $\bar{w}$ is the mean fitness of the population at equilibrium and $w_{\max}$ is the mean fitness of a deleterious mutation-free individual.

Under viability selection, the mutation load is equivalent to the proportion of individuals that fail to survive and hence leave no descendants in the next generation. For example, if an individual carries 10 mutations, each reducing the chance of surviving to reproductive age by 10%, then this individual is expected to survive with probability $(1–0.1)^{10} = 0.35$. If all individuals in the population have this genotype, then 65% of them would fail to have any descendants in the next generation. The load does not have such a simple interpretation under fertility selection, as we discuss below.

If the fitness effects of deleterious mutations are independent from one another, the mutation load across all loci subject to recurrent mutation is approximately

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$$L \approx 1 - e^{-U} \quad (2)$$

(Kimura and Maruyama 1966), where U is the overall rate of deleterious mutation per diploid genome per generation. This simple formula is a classic result of evolutionary genetics and appears in almost every textbook on the subject.

It has previously been estimated that U is considerably greater than one in humans (Kondrashov and Crow 1993; Eyre-Walker and Keightley 1999; Nachman and Crowell 2000) and may be as high as 10 (Reed *et al.* 2005). Under Crow's (1970) definition of the mutation load and a viability selection model, the fraction of individuals that fail to reproduce, φ, is predicted to be considerable; for example, if U is as high as 3, $\varphi = 1 - e^{-3} = 95\%$. However, previous estimates of U have relied on indirect estimates of the mutation rate, based on the neutral divergence between human and chimpanzee, and inaccurate estimates of the proportion of sites in the genome that are subject to natural selection (Kondrashov and Crow 1993; Eyre-Walker and Keightley 1999; Nachman and Crowell 2000). The mutation rate per nucleotide site in humans (μ) has recently been directly estimated by comparing the genome sequences of offspring and their parents. Three studies (Awadalla *et al.* 2010; Durbin *et al.* 2010; Roach *et al.* 2010) have yielded consistent estimates, with a mean of $\mu = 1.1 \times 10^{-8}$. Assuming a diploid genome of 6×10^9 nucleotides, each newborn therefore receives ~66 new single nucleotide mutations from its parents. To estimate U, we need to multiply this figure by the fraction of mutations that are deleterious (ζ) (Kondrashov and Crow 1993). Comparisons of the human and mouse genomes and the human and macaque genomes suggest that 5–6.5% of sites are subject to some degree of purifying selection (Meader *et al.* 2010; Lindblad-Toh *et al.* 2011; Mouse Genome sequencing Consortium 2002). However, the level of conservation, and hence ζ, was not explicitly estimated in these analyses, making it difficult to estimate U. A more formal analysis has estimated ζ by comparing the human–chimp nucleotide divergence for transposable element (TE) remnants, which appear to evolve largely neutrally (Lunter *et al.* 2006; Meader *et al.* 2010), with the divergence for the remainder of the genome (Eory *et al.* 2010). The non-TE fraction evolves at 94.3% the rate of the TE fraction, suggesting that 5.7% of non-TE mutations are deleterious and removed by natural selection. The non-TE fraction constitutes ~55% of the genome (Cordaux and Batzer 2009), so an estimate of $U = 66 \times 0.55 \times 0.057 = 2.1$. This is an underestimate, because some TEs are subject to selection (Brosius 2003) and we have disregarded insertion and deletion mutations, which occur at 0.05–0.1 the rate of single nucleotide mutations (Nachman and Crowell 2000; Kondrashov 2003) and are more likely to be deleterious. Furthermore, we have ignored adaptive mutations, which leads to an underestimate of the proportion of sites in genome that are subject to negative selection.

Our estimate of U is similar to previous estimates, but this is largely coincidental, since those analyses generally considered only the rate of deleterious mutation in protein coding genes (Eyre-Walker and Keightley 1999; Nachman and Crowell 2000). If we calculate the deleterious mutation rate for protein-coding sequences using a recent estimate for the number of genes and the mutation rate we obtain a much smaller estimate. There are estimated to be ~20,000 genes in the human genome of average length 1500 bp; ~70% of mutations in protein coding genes are nonsynonymous and the mean level of constraint (*i.e.*, the proportion of the mutations that are deleterious) is estimated to be ~0.75 at nonsynonymous sites (Eory *et al.* 2010). This yields an estimate of 0.35 deleterious nonsynonymous mutations per diploid genome, which is substantially smaller than previous estimates (Eyre-Walker and Keightley 1999; Nachman and Crowell 2000), principally because recent estimates of the mutation rate and the number of protein coding loci are lower than previous estimates.

Our conservative estimate of $U = 2.1$, which includes mutations in coding and noncoding DNA, predicts that $\phi = 1 - e^{-2.1} = 88\%$ if mutations act independently; *i.e.*, 88% of the population is predicted to fail to reproduce as a consequence of recurrent deleterious mutation under a viability selection model (Equation 2). Furthermore, each individual would have to have an average of $1/(1 - 0.88) = 8.3$ offspring, and since there are two sexes in humans, each female would have to have at least 16 children to maintain the population size. Such a high frequency of genetic death is implausible in humans, particularly if many individuals fail to reproduce for nongenetic reasons. This is the mutation load paradox (Kondrashov and Crow 1993; Eyre-Walker and Keightley 1999; Nachman and Crowell 2000; Reed and Aquadro 2006; Barton *et al.* 2007; Charlesworth and Charlesworth 2010).

A number of factors can lead to a reduction in the mutation load (Agrawal and Whitlock 2012), two of which have been discussed in relation to the problem in humans. First, it has been suggested that many genetic deaths occur in the cell lineages leading to the gametes (Reed and Aquadro 2006) and prior to birth, since many pregnancies spontaneously abort at an early stage (Wang *et al.* 2004). However, this can explain only a small proportion of the mutation load, because the fraction of sites in the genome effectively selected in germ-line cell lineages is likely to be small, and most spontaneous abortions occur for nongenetic reasons or because of major genetic defects (Nagaishi *et al.* 2004), which are not included in our calculation of φ. Second, the mutation load can be reduced by synergistic epistasis, such that the combined effects of deleterious mutations are more severe than their independent effects (Kimura and Maruyama 1966; Crow and Kimura 1979). However, there is little empirical evidence that synergistic epistasis is more frequent than diminishing returns epistasis (Kouyos *et al.* 2007; Halligan and Keightley 2009), which has the opposite effect on the load.

It might also be argued that a load problem is unlikely to exist in humans if most selection acts on differences in

fertility. Under fertility selection, in which fitnesses are absolute, the load is the reduction in fertility relative to that of a mutation-free individual, not the proportion of individuals that fail to have descendants in the next generation. Defining x as the number of offspring that a deleterious mutation-free individual can produce, the average number of offspring per individual is $z = x\,e^{-U}$, since the mean fitness of the population is e^{-U}. Each offspring has two parents, so $z = 2$ when the population size is stationary. Hence, if $x > 2/e^{-U}$, the population is expanding and potentially at a rate such that $\varphi \approx 0$. On the other hand if $x < 2/e^{-U}$ the population is contracting and φ may approach 1 for small x. Therefore, the proportion of individuals that fail to have offspring depends both on the deleterious mutation rate and x. The rate of deleterious mutation that can be tolerated is therefore limited by x, but unfortunately, the value of x is not known with any degree of certainty. To prevent population decline x must be greater than 16 in humans if selection acts solely on absolute fertility differences. Agrawal and Whitlock (2012) have argued that x may substantially exceed 16, since human family sizes can be large in modern societies and males can potentially have many offspring by mating with multiple females. However, reproductive potential may have been much more limited in ancestral human populations. In hunter–gatherer societies, which may have reproductive patterns similar to ancient hominid populations, females breastfeed their offspring for several years; this suppresses ovulation and leads to an average interbirth interval of approximately 3 years (Eaton *et al.* 1994). Since hunter–gatherer females typically reach menarche at ~16 years and menopause at ~47 years (Eaton *et al.* 1994), they have the potential to produce only ~11 children, and actual average family size is ~6 live births per female (Eaton *et al.* 1994). Since the ages of menarche, menopause, and weaning are probably under stabilizing selection in such populations, and close to their optima, it is difficult to envisage how x could be much greater than 11 offspring for hunter–gatherer females. Fertility selection could potentially be stronger in males, if males can mate with several females. However, humans seem to have been largely monogamous, at least over the last million years (Labuda *et al.* 2010), and this trait is also likely to be under stabilizing selection. It therefore seems difficult to explain the mutation-load paradox in humans by assuming that selection acts largely on fertility, given what is known about human reproductive biology in extant populations.

Here we examine an alternative explanation for how humans can tolerate their high rate of harmful mutation. Wallace (1970) noted that the classic formulation of the load implicitly assumes that selection acts upon absolute fitness differences, such that the effect of a mutation in one individual is independent of the genotypes of other individuals in the population. Examples of mutations falling into this category are those that reduce cold tolerance or completely penetrant lethal mutations that knock out developmental pathways. However, Wallace argued that if selection occurs via competition between individuals within a species, then the proportion of individuals that fail to survive or reproduce depends on the variation in fitness between individuals, not the difference in fitness between the population mean and a deleterious mutation-free individual, as in Equation 1 (Crow 1970). The consequences of recurrent deleterious mutation for the magnitude of φ might therefore be much smaller than suggested by Equation 2 under a relative fitness model. Similar arguments have been made by Sved *et al.* (1967) in relation to the number of balanced polymorphisms that can be maintained in a population, and by Ewens (1970) in relation to the substitution load.

Wallace (1970) argued that the proportion of individuals failing to reproduce is significantly reduced under a relative fitness model compared to the prediction from the classic calculation of the load, but he did not demonstrate this either theoretically or empirically. Here, we calculate the proportion of individuals that fail to have an adult descendant in the next generation under a relative fitness model. We refer to the fraction of nonreproducing individuals under this model as φ_r, and under the old definition of load under a viability selection model (Equation 2), as φ_a.

Models

Consider a diploid organism with a genome containing M loci, each subject to deleterious mutation at rate u. Assume that mutations are not completely recessive and that their fitness effects in heterozygous individuals (s) are sufficiently strong that mutant alleles segregate only in heterozygous form. Assuming free recombination between loci, the average frequency of a deleterious mutation is expected to be u/s. An individual will therefore carry $2Mu/s = U/s$ deleterious mutations, on average. Information on the rate and distribution of fitness effects of deleterious mutations suggests that $U/s > 20$ (Lohmueller *et al.* 2008; Charlesworth and Charlesworth 2010), so the number of deleterious mutations per individual is expected to be approximately normally distributed with a variance equal to its mean. Assuming that the fitness effects of mutations are multiplicative, then the fitness of an individual carrying k mutations is $w(k) = (1 - s)^k$, and fitness is approximately lognormally distributed with a location parameter $\mu = U/s\ \mathrm{Log}(1 - s)$ and a squared scale parameter $\sigma^2 = U/s\ (\mathrm{Log}(1 - s))^2$.

Viability selection

To calculate φ_r under viability selection (*i.e.*, survival to reproductive age), assume that the population is censused at the zygote stage. Since, there is no selection on fertility, the proportion of individuals that survive viability selection is also the proportion of individuals that have descendants in the next generation, whether reproduction is monogamous or not. To enforce direct competition between individuals, we assume that the population size is stationary, as would be

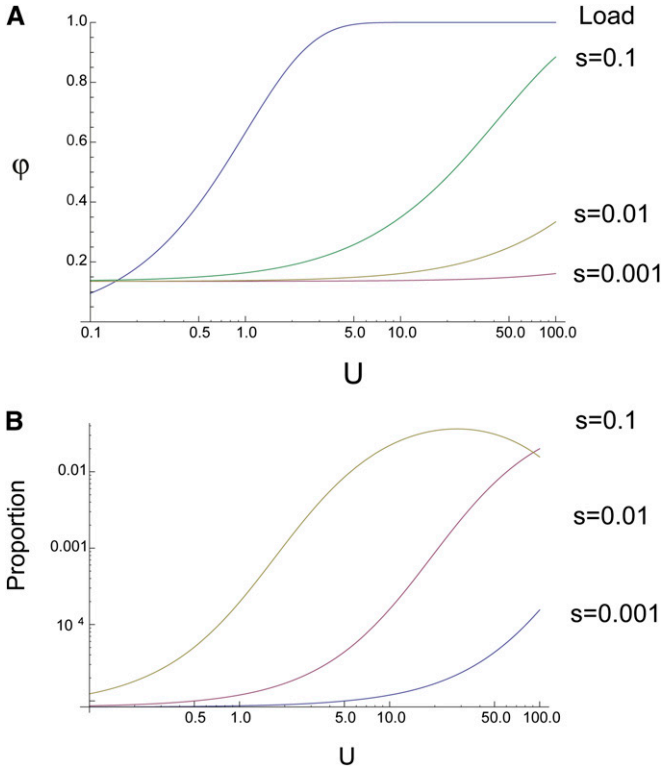

Figure 1 The fraction of nonreproducing individuals, φ_r, (A) and the proportion of couples that have more than 10 offspring (B) plotted as a function of the deleterious mutation rate (U) and the strength of selection against a deleterious mutation (s).

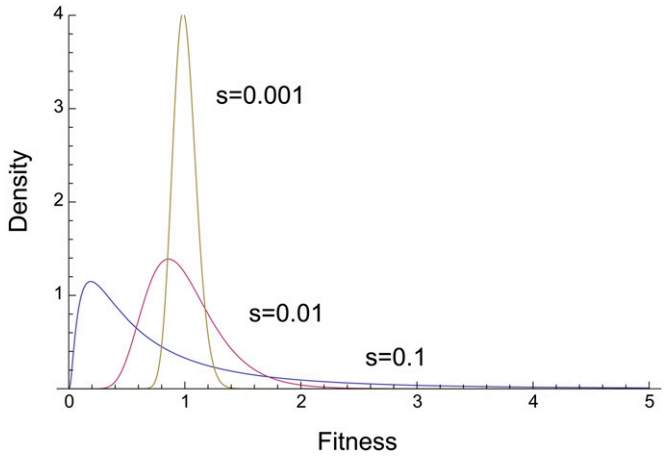

Figure 2 The density of fitness for $U = 10$. Fitness has been normalized such that the mean is 1.

the case, for example, if individuals compete for some finite resource that limits population size. An individual's fitness is then determined both by its own genotype and the genotypes of other individuals. If all individuals have the same fitness then individuals can fail to reproduce by chance. However, φ_r increases if there is variation in fitness, because some individuals will have greater reproductive success than average, and others will have few or no surviving offspring. The fraction of nonreproducing individuals in this model can be calculated as follows. The proportion of offspring in the next generation contributed by a zygote with k mutations is $w'(k) = w(k)/\bar{w}$, where $\bar{w}$ is the mean of $w(k)$, and the distribution of w' is lognormal with $\sigma^2 = U/s\ (\mathrm{Log}(1-s))^2$. We assume that the population size is stationary, so the number of offspring to which an individual contributes is Poisson distributed with a mean of 2. The proportion of individuals leaving x descendants is therefore

$$Q(x) = \int_0^\infty D(w')P(2w', x)dw, \qquad (3)$$

where $P(m, x)$ is the Poisson distribution with a mean of m and $D(w')$ is the distribution of w'. The probability of a couple producing no offspring is $\varphi_r = Q(0)$.

Evaluation of Equation 3 shows that φ_r increases as both the genomic deleterious mutation rate and the strength of selection on a new mutation increase (Figure 1A). However, φ_r is generally substantially lower than φ_a (calculated using Equation 2), and approaches φ_a only if selection is very strong and the deleterious mutation rate very high. For example, if we assume, unrealistically, that every new mutation in the human genome is deleterious (*i.e.*, $U = 66$) and $s = 1\%$ φ_r is only 28% whereas φ_a is close to 100%.

The fraction of nonreproducing individuals has a minimum value, which represents the probability that an individual has no offspring by chance alone. We assume a stationary population size, so the mean number of offspring per individual is 2, and therefore the chance of an individual having no offspring is $e^{-2} = 0.14$. This component is not included in φ_a. The proportion of nonreproducing individuals explained by selection alone is $(\varphi_r - e^{-2})/(1 - e^{-2})$, which is lower than φ_r and hence even lower than φ_a (see below).

Although the predicted proportion of nonreproducing individuals is small under a relative fitness model, it is important to check that the model does not predict the existence of super-fit individuals, since even the most successful individuals have limited reproductive potential. We investigated this by estimating the proportion of individuals that have >10 offspring by evaluating Equation 3 for a range of U and s values, summing the result for $x > 10$. It is evident that the proportion is generally small and consistent with levels of reproduction seen in humans (Figure 1B).

The proportion of individuals having no descendants in the next generation is smaller under a relative than absolute fitness model because φ_r is determined by the variance in fitness among individuals, and this is generally small. Unless the deleterious mutation rate is very high and the selection strength against each deleterious mutation very strong, the model predicts that the fittest individuals (or couples) are not much fitter than the least fit individuals (Figure 2). For example, if $U = 10$ and $s = 0.01$ and we scale fitness to a mean of 1, then 97% of individuals have relative fitnesses between 0.5 and 2.

Other models of selection

In the model described above, we calculated φ_r assuming viability selection since φ_a is equal to the mutation load under this model, and the consequences of recurrent deleterious mutation are therefore comparable under relative and absolute fitness models. However, it is also of interest to calculate φ_r under a fertility selection model. If individuals are free to interbreed, rather than forming monogamous relationships, then the proportion of offspring produced by an individual with k mutations is $w'(k) = w(k)/\bar{w}$ and relative fitness is lognormally distributed with a mean of 1 and a squared scale parameter of $\sigma^2 = U/s$ $(\mathrm{Log}(1 - s))^2$. Since we assume that the population size is stationary each individual will contribute to an average of two offspring in the next generation, so an individual with k mutations will contribute to a Poisson distributed number of offspring with a mean of $2w'(k)$. The proportion of the population leaving x offspring is therefore as given by Equation 3.

To investigate the consequences of monogamy let us assume that there is random mating and that the fertility of a couple is a function of the total number of deleterious mutations carried by the couple. In this case the proportion of offspring contributed by a couple to the next generation is $w'(k) = w(k)/\bar{w}$, which is lognormally distributed with a squared scale parameter $\sigma^2 = 2U/s$ $(\mathrm{Log}(1 - s))^2$. Since we assume that the population is stationary each couple is expected to have two offspring. The proportion of couples leaving x offspring is therefore given by Equation 3, but $D(w')$ has a squared scale parameter of $\sigma^2 = 2U/s$ $(\mathrm{Log}(1 - s))^2$ rather than $\sigma^2 = U/s$ $(\mathrm{Log}(1 - s))^2$; *i.e.*, the mutation rate is effectively doubled by considering couples rather individuals.

For completeness, let us consider an asexual organism with discrete generations. Each generation, an individual can have several offspring, but the carrying capacity of the environment is such that the population is reduced to its former size before the next round of reproduction. Although asexual, we ignore the complication of Hill–Robertson interference, so the average frequency of a deleterious mutation is expected to be u/s as above. As before, the contribution of an individual with k mutations to the next generation is $w'(k) = w(k)/\bar{w}$. Hence relative fitness, w', is lognormally distributed with a mean of one and a squared scale parameter $\sigma^2 = U/s$ $(\mathrm{Log}(1 - s))^2$. However, because there is no sex, an individual is expected to have only one adult descendent, on average, in the next generation rather than two if population size is stationary. The proportion of the population leaving x offspring is therefore:

$$Q(x) = \int_0^\infty D(w')P(w', x)dw. \qquad (4)$$

Let us refer to the three models above as MF (monogamy with fertility selection), SEX (all models involving sex except MF) and ASEX (asexual). The proportion of nonreproducing individuals, $\varphi_r = Q(0)$, under these three models is shown in Figure 3. As expected, given the difference in the effective mutation rate between the two models, φ_r under SEX is always lower than that under MF. The value of φ_r under the ASEX model is generally higher than under either MF or SEX; this is largely due to the greater proportion of individuals having no offspring at low mutation rates under the ASEX model, since each individual is expected to have only one descendant, not two as under the SEX models. If we remove the effect of chance by calculating φ_r attributable to selection alone as $(\varphi_r - e^{-2})/(1 - e^{-2})$ for the MF and SEX models and $(\varphi_r - e^{-1})/(1 - e^{-1})$ for the ASEX model, then we find φ_r explained by selection is identical for the SEX and ASEX models and consistently lower than for the MF model (Figure 4).

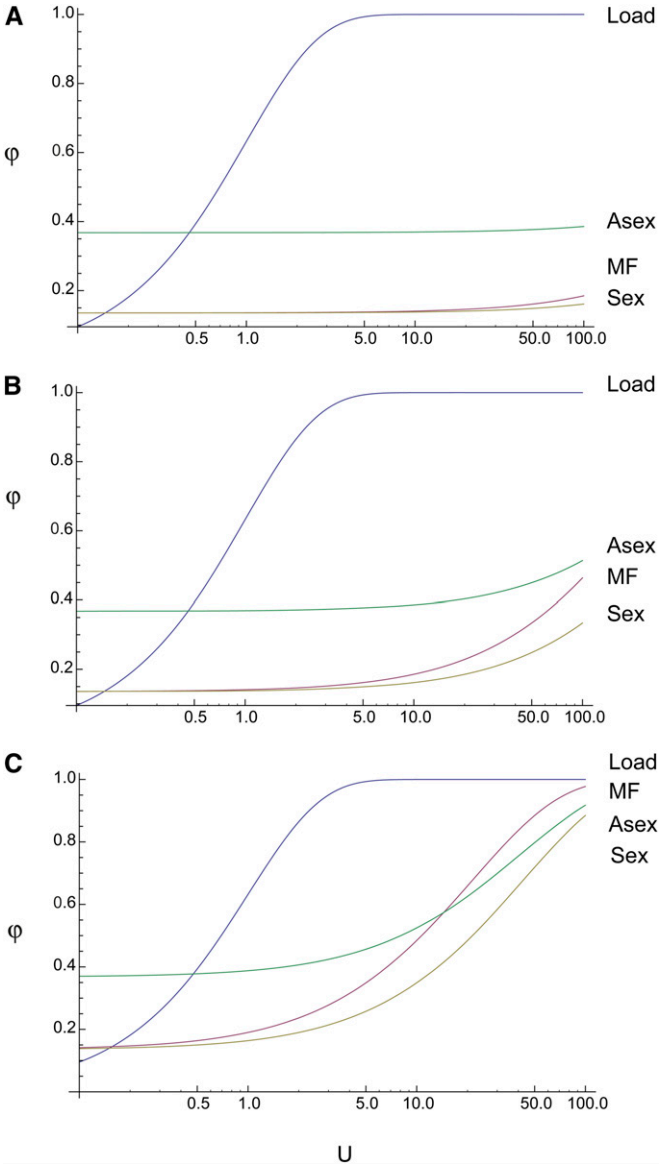

Figure 3 The fraction of nonreproducing individuals, φ_r, under various models assuming strengths of selection: (A) $s = 0.001$, (B) $s = 0.01$, (C) $s = 0.1$.

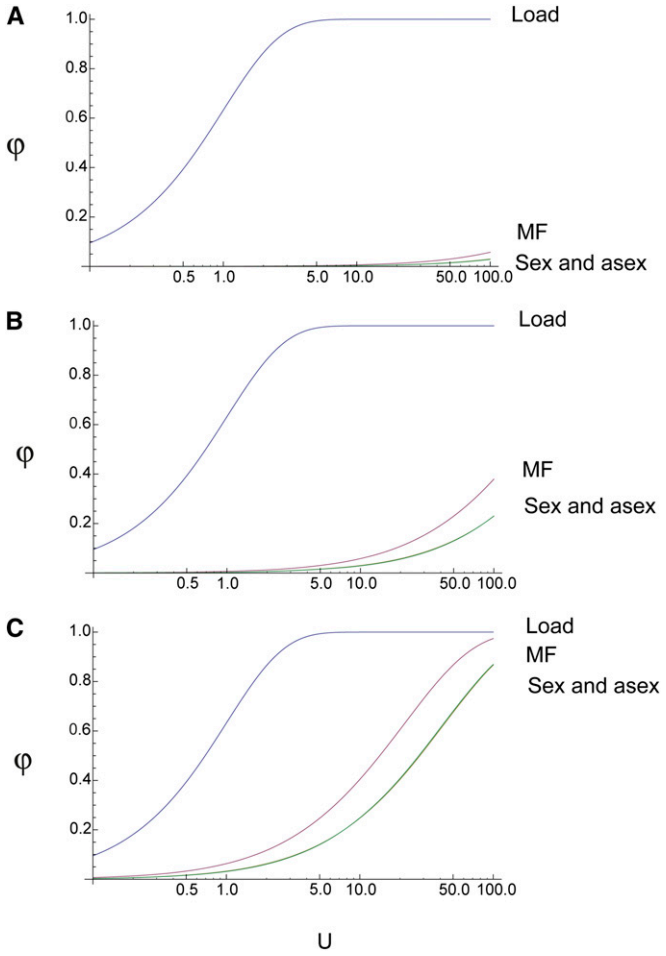

Figure 4 The fraction of nonreproducing individuals, φ_r, with the effect of chance removed: (A) $s = 0.001$, (B) $s = 0.01$, (C) $s = 0.1$.

Recessive mutations

The analysis above has assumed that mutations are not completely recessive and sufficiently strongly selected that we need consider only the selection against them when they are heterozygous. Let us now consider the value of φ_r predicted under a model of recessive mutations. We consider a model in which selection is due to viability, or equivalently, fertility with free interbreeding. If the fitness of the three genotypes are 1, $1 - 2hs$, and $1 - 2s$ then Kimura (1964) has shown that the time that a new mutation spends at frequency x is

$$f(x;S,h) = \frac{e^{-2Shx-S(1-2h)x^2}}{x(1-x)} \frac{\int_x^1 e^{2Shq+S(1-2h)q^2}dq}{\int_0^1 e^{2Shq+S(1-2h)q^2}dq}, \qquad (5)$$

where $S = 4N_e s$ and N_e is the effective population size. To estimate φ_r, we need to know the expected number of loci for which an individual is homozygous for the recessive allele. This is

$$R_r(S,\Theta) = \Theta \int_{x=0}^{1} f(x;S,0)\, x^2 dx, \qquad (6)$$

where $\Theta = 4MN_e u$ and M is the number of loci.

The expected number of loci that are expected to be heterozygous for a semidominant mutation is

$$R_s(S,\Theta) = \Theta \int_{x=0}^{1} f(x;S,1/2)2x(1-x)\, dx, \qquad (7)$$

which is approximately $2U/s = 2\Theta/S$. Evaluation of Equations 6 and 7 suggests that the average number of homozygous recessive loci is between 25% and 50% of the number of heterozygous semidominant loci (assuming equal numbers of loci and mutation rates) (Table 1). This can also be seen by an analytical approximation. The average frequency of a deleterious recessive mutation is approximately $u\sqrt{\pi N_e/s} = \theta\sqrt{\pi}/2\sqrt{S}$, where $\theta = 4N_e u$ and $S = 4N_e s$, if $\theta \ll 1$ (Nei 1968) (note the classic formula $\sqrt{u/s}$ applies only in infinite populations). Hence the average frequency of each deleterious mutation introduced into the population is $\sqrt{\pi}/2\sqrt{S}$, so the expected frequency of the homozygous genotype for each of these mutations is approximately $\pi/4S$ and the expected number of loci that are homozygous is

$$R_r'(S,\Theta) = \Theta\pi/4S. \qquad (8)$$

Comparing this against the expected number of semidominant loci that are heterozygous suggests that we expect approximately $8/\pi = 2.5$ times more sites to be heterozygous for semidominant mutations than homozygous for recessive mutations (Table 1).

The contribution of an individual with z loci that are homozygous for a deleterious recessive to the next generation is $w'(z) = w(z)/\bar{w}$. Hence the relative fitness, w', is lognormally distributed with a mean of one and a squared scale parameter $\sigma^2 = R_r(\Theta,S)\ (\mathrm{Log}(1 - 2s))^2$. Since we assume that the population size is stationary, each individual will

Table 1 The expected number of homozygous and heterozygous loci, when $\Theta = 1$, for recessive and semidominant mutations respectively

S	No. of homozygous recessive loci (Equation 6)	Approximate no. of homozygous recessive loci (Equation 8)	No. of heterozygous semidominant loci (Equation 7)	Ratio (column 2/4)
0.01	0.50	79.0	1.0	0.50
0.1	0.49	7.9	0.98	0.50
1	0.44	0.78	0.84	0.52
10	0.073	0.078	0.20	0.37
100	0.0055	0.0079	0.020	0.28
1000	0.00051	0.00078	0.0020	0.26

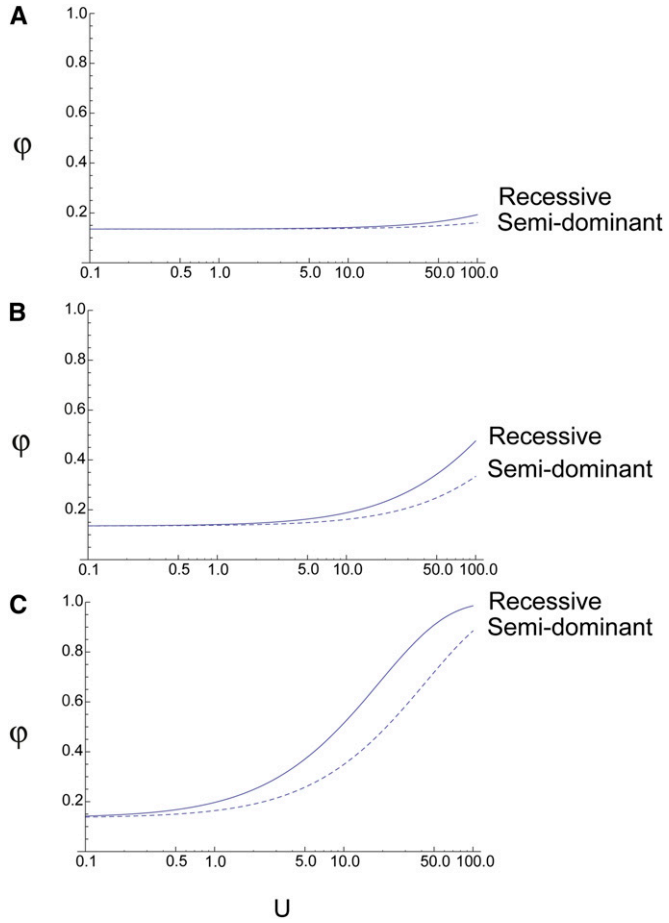

Figure 5 The fraction of nonreproducing individuals, φ_r, under models with semidominant and completely recessive mutations for N_e = 10,000. (A) s = 0.001, (B) s = 0.01, (C) s = 0.1.

contribute to two offspring in the next generation and so the proportion of the population leaving x offspring is

$$Q(x) = \int_0^\infty D(w')P(2w', x)\,dw, \qquad (9)$$

where $P(m, x)$ is the Poisson distribution with a mean of m and $D(w')$ is the distribution of w'.

The value of φ_r, predicted under a model of recessive mutations (Equation 9), is compared to φ_D under a model of semidominant mutations (Equation 3), in Figure 5. From this it can seen that with recessive mutations φ_r is somewhat higher than under a model with semidominant mutations for the same rate of mutation for N_e = 10,000. The situation can be reversed if N_e is much smaller, but the φ_r is always quite similar.

Simulations

We ran a series of simulations to check our analytical approach. A population of N diploid individuals with M independent loci was subject to recurrent deleterious mutation at a rate u per locus, such that $2Mu = U$. The fitness of each individual with k mutations was calculated as $(1 - s)^k$. In each generation we randomly selected pairs of individuals in proportion to their relative fitnesses (*e.g.*, if we had four individuals with absolute fitnesses of 0.1, 0.2, 0.3, and 0.2 we would select the first individual on average 0.1/(0.1 + 0.2 + 0.3 + 0.2) = 0.125 of the time to mate). Each mating produced one offspring, with alleles drawn at random from the parental genomes (*i.e.*, assuming free recombination). This process of selecting individuals to form pairs was repeated until N offspring had been produced; individuals could contribute to multiple matings. The value of φ_r in the simulations was very close to that expected from Equation 3 suggesting that our analytical derivation of φ_r was satisfactory (Table 2).

Discussion

We have shown that the proportion of individuals that fail to have descendants in the next generation under a relative fitness model is substantially lower than that predicted under an absolute viability fitness model and that species could potentially survive a mutation rate of 10's if not 100's of deleterious mutations per genome per generation if selection was largely mediated through competition.

The fraction of nonreproducing individuals (φ) depends on both the rate of deleterious mutation and the strength of

Table 2 Simulations under a relative fitness model

S	U	ϕ_r (theory)	ϕ_r (simulated)(SE)	Observed average frequency over expected (SE)
0.01	0.1	0.136	0.135 (0.000)	1.03 (0.00)
	1	0.138	0.138 (0.000)	1.03 (0.00)
	2	0.141	0.141 (0.000)	1.03 (0.00)
	5	0.149	0.148 (0.000)	1.03 (0.00)
	10	0.161	0.161 (0.000)	1.04 (0.00)
0.1	0.1	0.138	0.138 (0.000)	1.00 (0.00)
	1	0.164	0.163 (0.000)	1.00 (0.00)
	2	0.190	0.188 (0.000)	1.01 (0.00)
	5	0.258	0.254 (0.000)	1.02 (0.00)
	10	0.349	0.342 (0.000)	1.06 (0.00)

The table gives the fraction of nonreproducing individuals, φ_r , along with its theoretical prediction, and the average frequency of a deleterious mutations divided by its expected value under an absolute fitness model (*i.e.*, *u*/*s*). The simulations were run with a population size of 1000 and 100,000 sites.

selection acting on deleterious mutations. The mean fitness effect of a deleterious mutation in humans is unknown, but mutation accumulation experiments in other animals and plants suggest that nonlethal mutations have fitness effects of at most 1–20% (Keightley and Halligan 2009). However, such estimates are upwardly biased because they are generally made under the unrealistic assumption that mutations have equal selective effects, implying that the true mean value of s is likely to be substantially lower. Even assuming s as high as 20%, φ_r would be only 51% if $U = 5$. The load from lethal mutation is expected to be much lower than that for nonlethals, since lethal mutations have been estimated to occur at about one-hundredth the rate of nonlethals (Crow and Simmons 1983).

The extent to which selection is mediated through competition between conspecifics is unknown. If individuals compete for resources or mates, and competitive ability is genetically determined, then the success of an individual will depend both on its own genotype and the genotypes of its competitors. This might suggest that there is epistasis generated in a relative fitness model, and it has been shown that the mutation load can be substantially reduced if there is synergistic epistasis (Kimura and Maruyama 1966). However, synergistic epistasis is not expected to be a feature of our model, since the contribution of a genotype with k mutations to the next generation is $w'(k) = w(k)/\bar{w}$, so $\log(w'(k))$ is linear with respect to k. To check that epistasis is not an emergent property of our model we tabulated the number of offspring produced in our simulation (see above). As expected, the log of the mean number of offspring produced by individuals with k mutations is linearly related to k (Figure 6A), demonstrating that epistasis does not emerge within this model. We also kept track of the mean absolute fitness of the population within the simulation. As expected, the mean absolute fitness is e^{-U}. If synergistic epistasis had been present then we would expect the mean absolute fitness to be higher than this expected value (Figure 6B).

It has been suggested that sexual reproduction might be maintained because sexual species can have substantially lower mutation loads than asexual species if there is synergistic epistasis (Kimura and Maruyama 1966). If $U > 1$ this can be sufficient to offset the twofold cost of sex (Kondrashov 1982; Kondrashov 1988). This is known as the deterministic mutation hypothesis. However, since the overall effect of recurrent deleterious mutation on population fitness is considerably reduced, if selection is mediated by competition, it is likely that the conditions under which sexual species have an advantage will also be greatly reduced.

The consequences of recurrent deleterious mutation for the proportion of the population that fails to reproduce is less extreme under a relative compared to an absolute fitness model. One might therefore expect natural selection to be weaker under a relative fitness model and that deleterious mutations would accumulate in the population. However, this is not the case: in our simulation the average

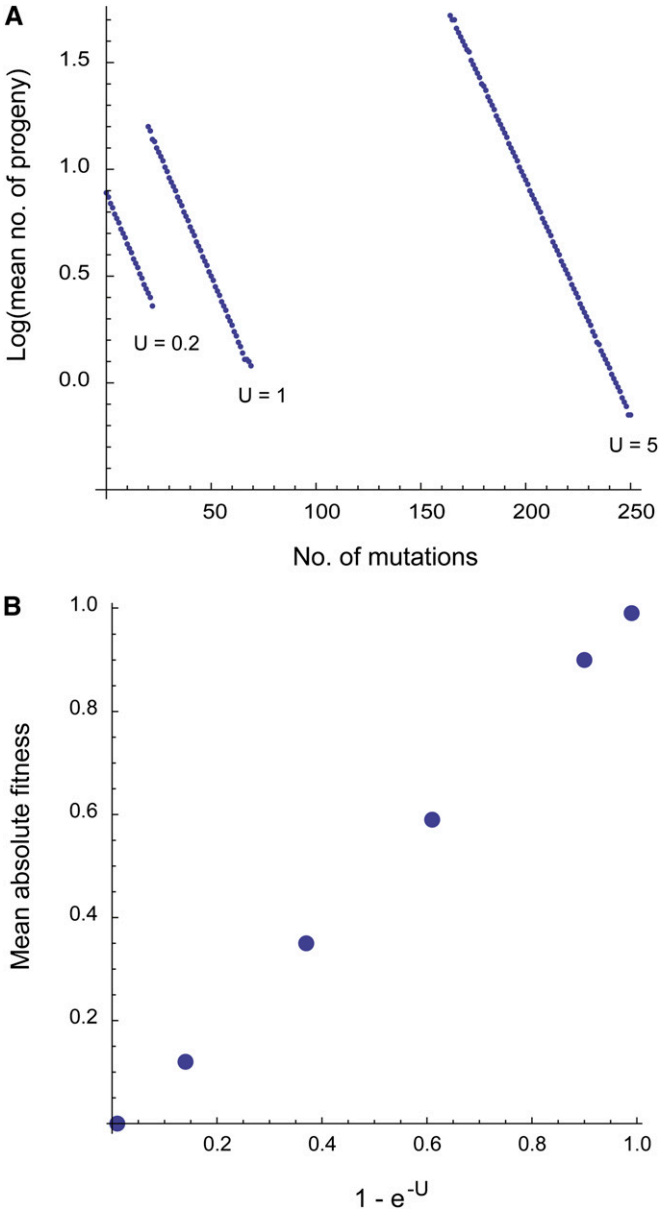

Figure 6 Individual and population fitness in a simulated population under a relative fitness model. (A) The relationship between the log mean progeny number and the number of mutations for three populations subject to genomic deleterious mutation rates of 1, 2, and 5. (B) The relationship between the mean absolute fitness of a population and the expected absolute fitness, e^{-U} for different values of U.

frequency of a deleterious mutation is close to the value expected under an absolute fitness model (Table 2). The average frequency of a deleterious mutation is very slightly higher than we expect, but this is likely to be due to Hill–Robertson interference.

Following Wallace (1970), we have shown that the fraction of individuals that fail to reproduce as a consequence of recurrent deleterious mutation depends on whether selection is mediated via absolute or relative differences between individuals. The classic definition of the mutation load equates

to the fraction of nonreproducing individuals if selection acts on absolute differences under a viability selection model, as would be the case if the fitness of a genotype were independent of the genotypes of conspecifics. If fitness depends on the genotypes of conspecifics, then the proportion of nonreproducing individuals depends on the distribution of fitness among individuals and tends to be much lower than predicted by the absolute mutation load. Evaluation of our model, assuming plausible values for the genomic deleterious mutation rate and strength of selection against a new mutation, suggests that the proportion of individuals that fail to reproduce is much lower than predicted by the classic formula for the absolute load, and there is no requirement for some individuals to be unrealistically fecund. Our analytical results and simulations suggest a resolution of the mutation load paradox by showing that a very high number of deleterious mutations can be eliminated from the population each generation and that the population can still be viable. Our results also demonstrate that one mutation does not necessarily result in one genetic death.

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