How do self-fertilising and facultative sexual populations differ in mutation accumulation?

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Abstract

Self-fertilisation and asexual reproduction are both hypothesised to lead to long-term extinction due to inefficient selection acting against deleterious mutations. Self-fertilisation can counter these effects through creating homozygous genotypes and purging deleterious mutations. Although complete asexuality lacks meiotic gene exchange, mitotic gene conversion is a mechanism for creating homozygous regions that could limit deleterious mutation accumulation in a similar manner to self-fertilisation. Here, we compare mutation accumulation in self-fertilising and facultative sexual populations subject to mitotic gene conversion, to determine if the latter can purge deleterious mutations in an analogous manner to self-fertilisation. We first show analytically that this purging is most effective with high levels of asexuality and gene conversion, and when deleterious mutations are recessive. We further show using simulations that, when mitotic gene conversion becomes sufficiently high in obligate asexuals, there is a sudden reduction in the mutation count and a jump in homozygosity, reflecting mutation purging. However, this mechanism is not necessarily as efficient at purging compared to high levels of self-fertilisation, and elevated rates of mitotic gene conversion seem to be needed compared to empirical estimates. Hence, while mitotic gene conversion can remove recessive deleterious mutations, self-fertilisation seems to be a more effective mechanism for doing so.

Teaser Text

Asexuality has been argued to be an evolutionary ‘dead end’, due to a lack of gene exchange causing inefficient selection acting against deleterious mutations. It has been proposed that asexuals can counter these negative effects through mitotic gene conversion, which exposes mutations to selection within individual lineages. Here, we theoretically investigate how effective this mechanism is. We compare results to those obtained when individuals reproduce by self-fertilisation, which has similar effects on exposing deleterious variants. While mitotic gene conversion can be effective in removing recessive deleterious mutations, high rates are required and it is not always as effective as selfing.

Introduction

The generation of genetic variation is essential for biological evolution. Mutations are the ultimate source of genetic novelty in all organisms (Loewe and Hill 2010). Other processes responsible for the generation and/or maintenance of genetic variability (genotype combinations and their frequency) within eukaryotic populations are gene flow, selection, genetic drift (fluctuations of the frequency of variants due to 'randomness', i.e., independent of their fitness; Rice 2004, Charlesworth 2009), non-random mating (Sætre and Ravinet 2019), recombination (primarily as meiotic crossing-over) and independent chromosome assortment (Veller et al. 2019). However, the generation of variation is a double-edged sword; although favourable mutations may emerge that are crucial for long-term survival, it may also result in a burden of deleterious mutations, which are much more common than favourable ones (Eyre-Walker and Keightley 2007).

The reproductive system, which determines how offspring are generated in a population, has a profound impact on the prevalence of deleterious variation. Reproduction can be either with or without sex. Sex usually involves two phenomena (Hartfield and Keightley 2012): recombination (the exchange of genetic information between homologous DNA sequences, most commonly as meiotic crossing-over), and fusion of gametes (specialised cells with halved ploidy and DNA content). In the simplest case when asexuality is equivalent to clonal reproduction, the genotype of an offspring is identical to that of a parent (except for *de novo* mutations). Clonal reproduction encompasses diverse mechanisms, including fission or budding in unicellular eukaryotes, or budding (e.g., hydra, jellyfishes), fragmentation (e.g., corals) and whole-body fission (e.g., flatworms, starfish) in animals or many forms of vegetative propagation in plants (De Meeûs et al. 2007). Nevertheless, most eukaryotic organisms undergo some variant of sexual reproduction, at least occasionally (Speijer et al. 2015).

Gametes from which offspring originate may also be derived from the same individual, leading to self-fertilisation or selfing. The opposite of selfing is panmictic outcrossing, with

anyone in the population having an equal chance of being a mate of anyone else, with self-mating being rare or even prohibited (if, e.g., self-incompatibility mechanisms are in place to prevent self-fertilisation; Nettancourt 2001). Cloning and selfing are two types of uniparental reproduction, which forms a basis of their similarity (e.g., the lack of mate finding) and potential ecological advantages (e.g., reproductive assurance; Baker 1955, 1967; Theologidis et al. 2014; Mráz and Mrázová 2021).

Despite these apparent similarities, cloning and selfing differ in the manner in which they affect selection acting against deleterious mutations. Muller's ratchet is a model of a stochastic mutation accumulation in asexual populations due to the inability to generate offspring genomes that have fewer deleterious alleles than those of their ancestors (Muller 1964; Haigh 1978). This mechanism is a form of selection interference, which refers to the effect of strong genetic linkage on the dynamics of variants under selection (Felsenstein 1974). In completely clonal populations all sites are in absolute genetic linkage, therefore the presence of multiple deleterious alleles selectively interferes with one another having a strong impact on mutation accumulation (Hill and Robertson 1966; Roze and Barton 2006; Hartfield and Keightley 2012). Recombination breaks this linkage and allows the dynamics of variants to respond to selection independently, i.e., more efficient removal of deleterious mutations and restoration of the most-fit genotype. Another important consequence due to the lack of recombination and gamete fusion in diploid asexuals is the divergence of homologous chromosomes found within one individual. The two genome copies are always transmitted together across the lineage, gradually and independently accumulating mutations leading to a high level of heterozygosity (Butlin 2002).

In contrast to cloning, the main genetic consequence of selfing is genome homogenization. Under complete selfing, heterozygous genotypes *Aa* segregate into gamete carrying alleles *A* and *a* in equal proportion. Hence, the probability of the offspring of a homozygous parent losing heterozygosity is 50%, independently of the frequency of the alleles in the population. The probability that heterozygosity is retained decreases exponentially every generation, rapidly leading to overall genome homogenization. This homogenisation also

occurs, albeit at a lower rate, under partial selfing. As a consequence, the effective recombination rate is reduced since recombination creates variability only when heterozygosity is present (Nordborg et al. 1996; Nordborg 2000). An additional consequence of increased homozygosity is the exposure of recessive deleterious alleles to selection, giving rise to inbreeding depression (Charlesworth and Willis 2009). While this leads to an instant reduction in the fitness of selfers, the subsequent purging and removal of deleterious mutations from the population could eventually lead to elevated long-term fitness and persistence of the selfing population (Abu Awad and Billiard 2017). An outcome of selfing broadly shared with cloning is the removal of neutral variation through extensive linked selection acting against deleterious mutations, manifesting itself as a reduction in effective population size (Agrawal and Hartfield 2016).

From the phylogenetic distribution of cloning and selfing species, both reproductive systems have been called ‘dead-end’ strategies, meaning that species with them have an increased probability of extinction (Wright et al. 2013). In asexual populations, this phenomenon may be explained by mutational meltdown, i.e., the accumulation of deleterious mutations leading to extinction (Lynch et al. 1993; Olofsson et al. 2023). However, there are also models in which asexuality does not increase the extinction rate but can still generate this phylogenetic pattern (Janko et al. 2008; Schwander and Crespi 2009). For example, the rate of the transition from sexuality to asexuality may be low due to mechanical constraints associated with sexual reproduction, including the need for a haploid egg to become diploid or to get activated by a sperm. Rare events might thus be required to overcome these mechanical constraints, such as mutation to disable the requirement of activation by sperm (Engelstädter 2008). Furthermore, there exist ancient asexuals that have seemingly existed for long periods of time in the absence of sexual reproduction, including species of bdelloid rotifers (Flot et al. 2013), oribatid mites (Brandt et al. 2021), ostracods (Tran Van et al. 2021), and trypanosomes (Weir et al. 2016). The persistence of these ancient asexuals begs the question of whether there are underexplored mechanisms at play that could prevent these species from undergoing excessive accumulation of deleterious variants.

153 Although genome exchange is intrinsically part of sexual reproduction, gene
154 conversion (GC) is a mechanism of genome exchange that is also available to asexuals in the
155 form of mitotic recombination (Lee et al. 2009). GC results in homozygous tracts, akin to the
156 effect of selfing, and it has been shown to have an important impact on neutral diversity when
157 sex is rare (Hartfield et al. 2016; Hartfield 2021). Mitotic gene conversion has been argued to
158 affect deleterious mutation accumulation in asexual species, including the bdelloid rotifer
159 *Adenata vaga* (Flot et al. 2013; although see Vakhrusheva et al. (2020) who argue that these
160 species show evidence of inter-individual gene exchange), the crustacean *Daphnia pulex*
161 (Tucker et al. 2013) and the planarian worm *Schmidtea mediterranea* (Kershenbaum et al.
162 2023). Khakhlova and Bock (2006) also show experimental evidence of gene conversion
163 eliminating deleterious mutations in plastids of tobacco plants, which are uniparentally
164 inherited and are effectively asexual. However, there exist little theoretical predictions to
165 determine to what extent gene conversion can indeed purge deleterious mutations, and hence
166 maintain asexual populations, in an analogous manner to self-fertilisation. One exception is a
167 model in the supplement of Flot et al. (2013), showing how gene conversion slows down
168 Muller's Ratchet in asexual populations.

169 Here, we compare deleterious mutation prevalence and mutation purging in
170 populations that exhibit either self-fertilisation or facultative sex subject to mitotic gene
171 conversion. We use both single-locus analytical models and multi-locus simulations to
172 investigate what extent of genome homogenisation, either through selfing or mitotic gene
173 conversion, can reduce the frequency of deleterious mutations. Our principal goals are to
174 determine (i) if deleterious mutations can be removed from facultative sexual species under
175 realistic cases of gene conversion and fitness effects; (ii) what gene conversion and mutation
176 fitness parameters lead to purging; and (iii) if there is an equivalent level of selfing that leads
177 to a similar reduction in mutation prevalence, as compared to that observed under asexuality
178 with gene conversion.

Single-Locus Mathematical Model

To gain some insight into how mitotic gene conversion affects the purging of deleterious mutations, we investigate a single-locus model of deleterious allele frequencies in a diploid population subject to facultative sex, with asexuality occurring at frequency σ and gene conversion with frequency γ. We consider the frequency of a deleterious allele (denoted *A*) that arose from mutation from a wild-type allele *a* with frequency μ; heterozygous mutant genotypes have fitness 1–*hs* and homozygotes 1–*s*, for *h* the dominance coefficient and *s* the selection coefficient.

We can track the prevalence of deleterious mutations by creating numerical recursions of how the frequency is affected by selection, reproduction, mutation and gene conversion (following the methods of Agrawal and Hartfield (2016), Hartfield (2021); see Supplementary *Mathematica* file for the full recursion equations). Although these recursions calculate the change in genotype frequencies over time, we can convert these genotype frequencies to allele frequencies; specifically, if the frequency of the mutant allele is p_a, then the frequency of the mutant homozygote is $p_A^2 + Fp_A(1 - p_A)$ (with similar equations for the wild-type homozygote), and the heterozygote has frequency $2\,p_A\,(1 - p_A)\,(1 - F)$. Here, *F* denotes the reduction in homozygosity compared to Hardy-Weinberg expectations (Wright 1951), and shows to what extent gene conversion affects genotype composition by reducing heterozygote frequencies. After making these transformations, we linearise the equations assuming $\mu, p_A \ll 1$ to obtain steady-state values of p_A and *F* (see Otto (2003) for a similar approach).

After these algebraic calculations, the following steady-state for the deleterious mutation frequency is obtained:

$$\hat{p}_A = \frac{\mu}{s}\left(\frac{1 - \sigma(1 - s)\,(1 - \gamma)}{\gamma + h\,(1 - \gamma)\,(1 - \sigma(1 - s))}\right) \quad (1a)$$

$$\approx \frac{\mu}{s}\left(\frac{1 - \sigma}{\gamma + h\,(1 - \sigma)}\right) \quad (1b)$$

Equation 1b assumes that *s*, γ are small so 1 – s, 1 – γ both approximate to one. Both equations reduce to the classic mutation-selection balance result μ/hs if $\sigma = \gamma = 0$

(Wright 1931). We can see which factors have the greatest effect on reducing allele frequency by dividing Equation 1b by μ/hs and denoting $\varsigma = 1 - \sigma$ as the frequency of sex, to obtain:

$$\hat{p}_A \approx \frac{1}{1+\alpha} \quad (2)$$

where $\alpha = \gamma/h\varsigma$. Hence, the deleterious allele exhibits a lower relative reduction for higher α, which can either be caused by higher mitotic gene conversion γ, or lower dominance *h* and rates of sex ς. More specifically, both rare sex and gene conversion act together to not only expose mutations to selection, but ensure they stay exposed due to a lack of genetic segregation and are therefore subject to selection over several generations.

Mitotic gene conversion acts on deleterious mutations by increasing the frequency of homozygotes and reduce that of heterozygotes. We can also quantify the relative reduction of heterozygosity by calculating the steady-state value of *F*:

$$\hat{F} = \frac{\gamma}{1 - \sigma\,(1-s)\,(1-\gamma)} \quad (3)$$

Equation 3 demonstrates how a combination of gene conversion and rare sex both lead to higher homozygosity.

Figure 1 illustrates these calculations for different values of the rate of asexuality and mitotic gene conversion. If mutations are recessive (Figure 1a) then even small amounts of gene conversion can reduce the prevalence of deleterious mutations compared to outcrossing expectations, even for intermediate frequencies of sex. Conversely, the frequency of additive alleles are close to outcrossing expectations (Figure 1b). These results illustrate that mitotic gene conversion has the strongest effect on purging deleterious mutations if they are recessive, with the purging effect magnified as sex becomes rarer. Plots of $\hat{F}$ show that while this gene conversion effect leads to elevated homozygosity, the increase is mostly modest unless sex is rare and deleterious mutations have a weaker selection effect (compare Figure 1c with 1d). Note that dominance has no effect on $\hat{F}$, presumably because it measures the prevalence of homozygotes, whose fitness is not affected by the dominance coefficient.

To test the accuracy of these equations, we compared these values to exact values obtained from numerical recursions (Supplementary Figure S1, with code in Supplementary *Mathematica* file). Equation 1a for $\hat{p}_A$ and Equation 3 for $\hat{F}$ matches exact numerical recursions over a wide range of parameters, showing them to be broadly accurate. The simplified version of $\hat{p}_A$ (Equation 1b) is accurate as long as sex is frequent and selection is weak, but becomes inaccurate for rare sex and/or stronger deleterious mutation.

Multi-Locus Simulation Methods

Simulation Outline

While the single-locus model provides insight into how rare sex and gene conversion affect deleterious mutation frequencies, it does not show how gene conversion leads to mutation purging across the genome. Hence, we use simulations to compare how gene conversion leads to mutation removal in asexuals, compared to selfing species.

Simulations were written using SLiM v4.0.1 (Haller and Messer 2023), and were implemented in either the Wright-Fisher framework (hereafter 'WF model') or in the non-Wright-Fisher framework (hereafter 'non-WF model'). Simulated populations consist of 5,000 diploid individuals, each with a genome size of L = 25 Mb that approximates the length of *Arabidopsis thaliana* chromosome 1 (The Arabidopsis Genome Initiative 2000). Individuals do not carry mutations at the start of the simulations. We let populations evolve for 60,000 generations, which is sufficient for the population variance to reach a steady-state (Supplementary Figure S2). After this time, 50 individuals are sampled and the number of mutations is calculated from SLiM's segregating mutations, as described in the 'Mutational Load Measurement' section below. The mutation rate was set to 4×10^{-9}, which is on the same order as that inferred from *Arabidopsis thaliana* (Ossowski et al. 2010). Per-base-position recombination rate was set to 4×10^{-8}, reflecting estimates obtained from crosses of *Arabidopsis thaliana* (Salome et al. 2012).

Simulated mutations were deleterious and mutation stacking is allowed by default. Two types of fitness models were investigated. They differ in whether selection and dominance coefficients were constant or drawn from a distribution (Table 1). In the first type, fixed values of deleterious mutations and dominance coefficients were chosen. In the second type, the selection and dominance coefficients were drawn from a distribution based on Spigler et al. (2017) (see Table 1). Selection coefficient is modelled by a gamma distribution with shape parameter α and mean $\underline{s}$. The dominance coefficient of a mutation with selection coefficient *s* is then drawn from a uniform distribution bounded by 0 and e^{-ks} , where *k* is a constant (see Table 1 for exact values). Free parameters in the model, *k*, $\underline{s}$, and α, were defined so $\underline{s}$ and $\underline{h}$ match with parameters in our main simulations (*s* = 0.01, *h* = 0.2) and the shape parameter was based on Chen *et al.* (2017). The general rationale behind this model is to reflect empirical observations that strongly deleterious mutations tend to be more recessive (Simmons and Crow 1977; Agrawal and Whitlock 2011).

Implementing mitotic gene conversion in asexual reproduction

By default, recombination in SLiM (including gene conversion) only acts exclusively when meiosis is involved. Therefore, the reproduction cycle was manually modified through a reproduction call-back (a SLiM function for governing reproduction), so that mitotic gene conversion in asexuals can be simulated. For simplicity, the model applies only to a completely asexual population. The development of the code was facilitated by a post on the SLiM discussion board (Dussert and Haller 2019) and was extended based on the gene conversion model under SLiM Wright-Fisher simulations (Haller and Messer 2016).

When an offspring is generated, then the number of gene conversion events that acts within it is drawn from a Poisson distribution with a mean $L\gamma$ where γ denotes the rate of GC initiating at a site. For each GC event, the central position is first drawn uniformly through the chromosome. Then, the tract is extended to the left and right independently by drawing each length from a geometric distribution with parameter *p:*

$$p = \frac{-\lambda + \sqrt{\lambda}\sqrt{8+\lambda}}{2\lambda} \quad (2)$$

where λ is the total mean tract length we want to use in simulations. This parameterization is used to account for the fact that GC tracts with length zero are discarded. This redefined value of *p* means that the mean tract length is λ after accounting for discarding these tracts (see Supplementary *Mathematica* notebook for further information). Gene conversion events that overlap with the chromosome ends are truncated so they stop at the chromosome edges.

After the GC start- and end-points are drawn, they are checked and potentially modified as follows: tracts of length 0 are removed; GC tracts may have the same start or end positions, in which case, the start (or end) of one of them is shifted to the right (left), so that GC tracts overlap; or two GC tracts overlap, in which case two interior GC positions are removed so that the resulting GC tract is a union of the two smaller ones. Since multiple GC tracts can overlap, this refinement process is repeated until all start and end positions are unique and alternate after sorting.

GC can occur on either of the homologous chromosomes with equal probability and results in the selected part of one chromosome being copied onto the same position at the other chromosome. Note that for each offspring-production event, all GC tracts are in the same direction, i.e., material is transferred solely from one strand to another during each reproduction event. Since the 'initiation' strand is randomly chosen for each reproduction event, then this effect should not lead to a major bias in results. The mean length of a GC event is set to 4,000 base pairs; this value accounts for the fact that empirical studies of mitotic gene conversion tends to find that GC tracts are bimodally distributed, with a combination of short (on the order of 1kb) and long tracts (on the order of 10kb) (Yim et al. 2014; Chumki et al. 2016; Jia et al. 2021). Using a mean length of 4,000bp will thus enable a wide distribution of tract lengths to be drawn that cover both these possibilities.

Further changes to the non-WF model were made so that it behaves as a standard Wright-Fisher model, based on section 16.15 in the SLiM Manual (Haller and Messer 2016). Briefly, survival callback limits the age of an individual to a single generation, reproduction callback samples constant number of parents with probability weighted by their fitness. By comparing measurements of population fitness (Supplementary Figure S3) and mutation count (Supplementary Figure S4) between the two simulations, we see that this new routine yields similar behaviour under low GC rates to the original WF model with complete asexuality.

100 replicate simulations were run if *s*, *h* were fixed; 20 replicate simulations were run for WF models where *s*, *h* are drawn from distributions; and 10 replicate simulations were run for non-WF models where *s*, *h* are drawn from distributions. Fewer simulations replicates were used in the latter two cases due to the much longer runtime of these simulations.

Mutational Load Measurement

Deleterious mutation load was assessed based on two measurements to reflect those used in empirical genomic studies (e.g., Laenen et al. (2018) in an analysis of *Arabis alpina*). Recessive load is defined as the number of homozygous mutant genotypes, while additive load is defined as the total number of mutations present in the population. Both of these population measures were estimated from 50 individuals' genomes sampled at the end of the simulation.. We also calculated the relative homozygosity for each simulation, defined as 2*(number of homozygous mutations)/(total number of mutations). This measurement can be interpreted as the proportion of deleterious mutations that are in homozygous state, across all sites and individuals. Simulation outputs were analysed in R (R Core Team 2024).

Results

Comparing self-fertilisation and facultative sex

We first compared the mean fitness and mutation loads with different levels of self-fertilisation or asexual reproduction, to determine how mutation accumulation differs between the two mating systems. These simulations were run using the WF model.

Figure 2 shows how the mean fitness changes over time. Under self-fertilisation (Figure 2a), while the mean fitness is fairly high overall, it is lowest when there is complete outcrossing. It generally increases with the selfing rate, reaching a maximum for around 95% self-fertilisation, but then drops for higher rates than this. In contrast, the mean fitness drops dramatically for highly asexual populations (Figure 2b).

Figure 3 (and Supplementary Figure S5) shows mutation counts under these reproductive regimes. Selfing populations (Figure 3a) undergo mutation purging, as evidenced by a decreasing number of mutations in the population (approximately linearly with the selfing rate) and an increase in homozygous load reflecting higher inbreeding. In contrast, asexual populations (Figure 3b) have approximately the same mutation counts (both total and homozygote) as outcrossing populations, until the population becomes around 95% asexual. At this point, there is a spike in homozygosity that is then reduced with even higher levels of asexuality, while the total mutation count rapidly increases. The high mutation count reflects inefficient selection acting once asexuality becomes prevalent, as reflected in the drop in mean fitness (Figure 2). The spike in homozygosity likely reflects the fact that for high-but-incomplete asexuality, mutation accumulation starts acting but there is still sufficient segregation to create homozygous genotypes. In populations that become completely asexual (i.e., the level of clonal reproduction approaches 1), there is a lack of genetic segregation so genotypes only form as heterozygotes (also known as ‘allelic sequence divergence’ or the Meselson effect; Mark Welch and Meselson (2000); Butlin (2002); Hartfield (2016)). The relative homozygosity

(Supplementary Figure S6) also reflects these outcomes; it increases towards 1 with higher selfing, reflecting greater homozygosity due to inbreeding. In contrast, it stays constant with increased asexuality up to 95% asexual reproduction, but then decreases with higher rates. No apparent spike at 95% asexuality is observed using this measure.

Impact of mitotic gene conversion

Given this increased mutation load, we next investigated to what extent mitotic GC can reduce it. Here, we used the non-WF model with the new GC routine implemented. Figure 4 plots the mean fitness for different per-base-pair initiation rates of GC. For most values the mean fitness remains low, similar to results in the absence of GC (Figure 2b). However, once GC becomes sufficiently high (in this case, 10^{-7} and above) the mean fitness increases and starts reflecting that of outcrossing populations. These results imply that purging is indeed occurring, and this mechanism is validated when looking at mutation counts (Figure 5). At GC rates of 10^{-7} and above, the mutation count drops while the homozygosity increases (as reflected with heightened relative homozygosity; Supplementary Figure S7), in line with purging reducing the total mutation prevalence and increasing the mean fitness.

Comparing mitotic gene conversion to self-fertilisation

We next compare the effects of mitotic GC in asexuals to self-fertilisation, to determine to what extent the two effects are comparable. Figure 6 compares GC in asexuals against a range of selfing rates. When looking at homozygosity, it seems that asexuality with the highest gene conversion rates (10^{-5}) yield the same homozygous counts as complete selfing, implying that the two are equivalent. However, the total mutation count is lower under any level of self-fertilisation, compared to the highest gene conversion rate used. Hence, it seems that while GC in asexuals can purge mutations, it does not produce the same benefits in terms of reducing mutation load as observed under self-fertilisation.

Results where *s*, *h* are drawn from distributions

To test the generality of these results, we also investigate simulations where *s*, *h* are drawn from probability distributions, using the same mutation rate. In these cases the fitness variance also reaches a steady-state within 60,000 generations (Supplementary Figure S8). Mean fitness results are generally similar to the fixed *s*, *h* case, although if looking just at selfing populations, the highest fitness is realised for complete selfing (Supplementary Figure S9). Mutation accumulation in the absence of gene conversion acts slightly differently; while the highest mutation count occurs under high levels of sexual reproduction, the number of homozygous genotypes is reduced under both high levels of selfing and asexual reproduction (Supplementary Figures S10, S11). The relative homozygosity is higher than that for fixed *s*, *h* cases under low rates of sex, but drastically drops once the rate of asexuality reaches 95% and higher (Supplementary Figure S12). Gene conversion in asexuals restores population fitness in a similar manner to the fixed *h* simulations (Supplementary Figure S13), with similar levels of gene conversion needed to purge deleterious mutations (Supplementary Figure S14 – S16). Hence, it seems that the results found above do not strongly depend on the fitness model used.

Discussion

Summary of results

In this study, we theoretically explored to what extent mitotic gene conversion in facultative sexual species purge deleterious mutations. We additionally compared this process to self-fertilisation, as the latter mating-system is known to purge deleterious mutations so we can compare how effective the two are. Using a single-locus model (Figure 1), we first demonstrated that mitotic gene conversion has the greatest effect in reducing mutation frequency when asexuality is frequent, but also when mutations are recessive. We also show

404 that, while the process leads to elevated homozygosity (as measured by F_{IS}), it will not be
405 substantially elevated unless populations are fully asexual and gene conversion is high. We
406 subsequently used multi-locus simulations to explore the effect of mitotic gene conversion on
407 a genome-wide level. In the absence of gene conversion (Figures 2, 3), highly-asexual species
408 accumulate many mutations as heterozygotes, leading to a drastic drop in fitness. When gene
409 conversion is present in fully asexual populations (Figure 4), then we do see a purging effect:
410 once the gene conversion rate exceeds a critical value (generally an initialisation rate of 10^{-7}
411 per site) the total mutation count drops and more mutations are present as homozygotes.
412 These levels of gene conversion also dramatically increase the fitness of asexual populations
413 (Figure 5, Figure S13b). Despite these benefits of gene conversion, the total mutation count
414 is lowest still under any level of self-fertilisation (Figure 6), indicating that the benefits of gene
415 conversion do not fully counter the costs of inefficient selection under clonality.
416

417 Comparing mutation accumulation in self-fertilising and asexual 418 populations

419 One notable feature of the asexual-selfing comparison is the threshold behaviour of
420 the mutation load. In the absence of gene conversion, neutral genetic diversity in asexual
421 populations is similar to outcrossers unless the rate of sex is of the order $1/N$ (Bengtsson 2003;
422 Ceplitis 2003; Hartfield et al. 2016; Hartfield 2021); background selection also incurs
423 noticeable reductions in diversity in species with infrequent sex (Agrawal and Hartfield 2016).
424 We see similar results with regards to the mutation count in Figure 3; it stays fairly stable under
425 facultative sex unless populations become highly asexual. Conversely, under high selfing we
426 generally see a drop in the mutation count and heightened homozygosity, in line with mutation
427 purging. With very high levels of selfing, we see an elevation in both the homozygous mutation
428 count and in the total mutation number. These increases likely arise due to an additional
429 increase in mutation number due to genetic drift, as N_e can be dramatically reduced in selfing

430 populations due to background selection effects (Kamran-Disfani and Agrawal 2014; Roze
431 2016). Note that this behaviour can change with the fitness model assumptions; under a model
432 where *s* and *h* are drawn from distributions, we instead see a dramatic reduction in the
433 mutation count under high selfing, in line with a model where genetic variation is purged
434 (Charlesworth and Charlesworth 1995; Lande and Porcher 2015; Abu Awad and Roze 2018).
435

436 Effects of mitotic gene conversion, and comparison with 437 empirical estimates

438 Throughout this study, we compared purging via mitotic gene conversion in asexuals
439 to that via self-fertilisation. We showed that despite the benefits of mitotic gene conversion,
440 lower mutation counts were observed under any level of self-fertilisation (see, e.g., Figure 6).
441 These results indicate that self-fertilisation is a more efficient means of purging deleterious
442 mutations, likely because it affects the whole genome and homozygous regions can be formed
443 more rapidly. In contrast, mitotic gene conversion as employed here only affects a fraction of
444 the genome every generation, so purging acts in a piecemeal manner. This comparison seems
445 to hold over different mutation models, selfing and gene conversion rates; one caveat is that
446 there could be a specific, untested combination of mutation and recombination rates in selfers
447 that might lead to different results.

448 Our simulation model shows that a mitotic gene conversion *initiation rate* above 10^{-7}
449 per site can start facilitating the purging of deleterious mutations. This is in line with previous
450 theoretical work showing that, once gene conversion becomes sufficiently high, then it can
451 substantially reduce genetic variation in asexual populations (Hartfield et al. 2016; Hartfield
452 2021). However, note that this probability is not the same as the rate of a gene conversion
453 *event* per site; we have to multiply the initiation rate by 4,000 (the average length of each GC
454 event) to obtain this value, which gives a rate of around 10^{-4}. Although empirical estimates
455 are sparse, they are usually much lower than this value, ranging between 10^{-7} and 10^{-5}

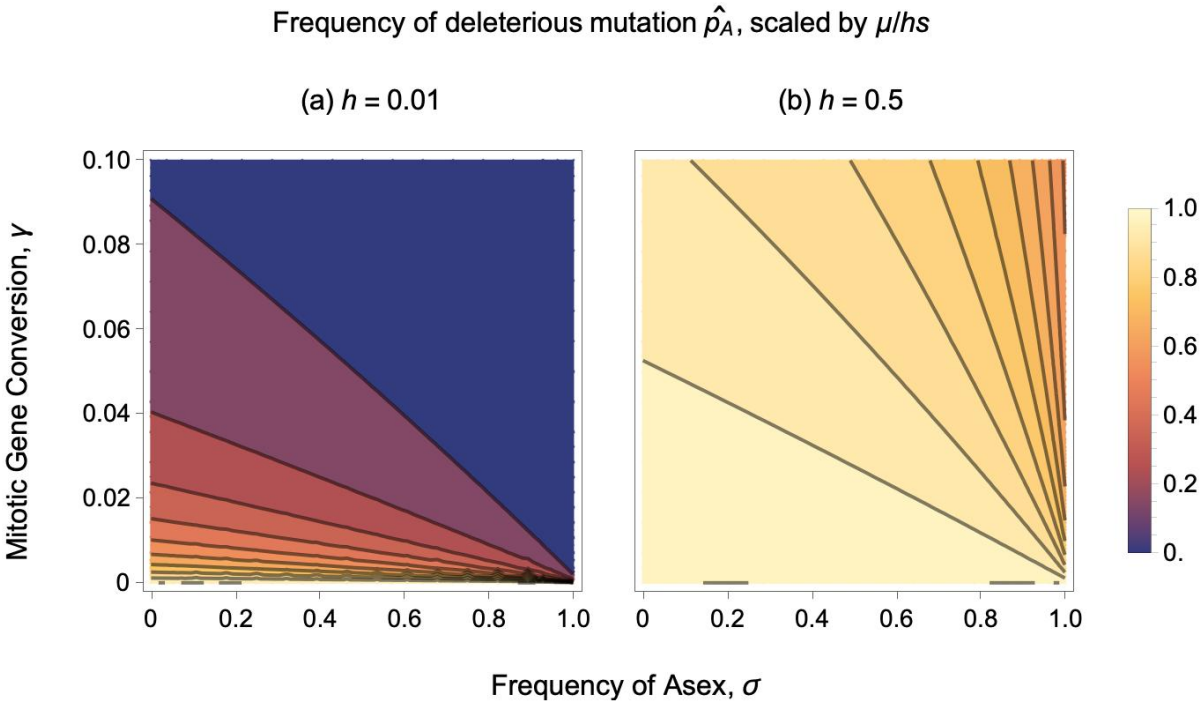
depending on the study organism (Mandegar and Otto 2007; Xu et al. 2011; Flot et al. 2013; Sharp and Agrawal 2016). Potentially higher rates were observed in rice; Jia et al. (2021) inferred a mitotic recombination rate of 10^{-6} with mean tract lengths ranging between 30-50kb, leading to a per-locus rate on the order of 10^{-2}. So it seems that while some larger empirical estimates are sufficiently high to cause extensive deleterious mutation purging, on the whole mitotic gene conversion is usually too weak a force to lead to extensive purging in nature. However, note that the estimates of Jia et al. (2021) consider all mitotic recombination events, both crossover and non-crossover events. Our simulation procedure only considers non-crossover events, which converts more localised genomic regions. Mitotic crossover events, in contrast, can convert much larger fractions of the genome (Jia et al. 2021). Even though the net conversion rate per site seems the most important parameter, longer conversion regions could have a stronger effect through affecting multiple sites at once, in a similar manner to self-fertilisation. Other forms of asexual reproduction that also create extensive heterozygous regions, such as terminal-fusion automixis (Mirzaghaderi and Hörandl 2016), could also affect enough of the genome to cause large levels of mutation purging. Future research can determine whether these different factors have a stronger effect on asexual fitness, especially when mutations interact with one another (i.e., if epistasis is present). Another factor not considered in our study are demographic feedbacks induced during the purging period, where mutation purging also causes a reduction in population size (Abu Awad and Billiard 2017). The presence of these feedbacks could increase the extinction probability of populations during gene-conversion induced purging.

An interesting case where gene conversion may be important in asexual organisms is tumour evolution. Here, cells reproduce asexually by mitosis and can potentially accumulate deleterious mutations due to a lack of recombination (Ní Leathlobhair and Lenski 2022). Hence, the gene conversion mechanisms investigated here may prevent transmissible cancers from experiencing mutation meltdown (Ní Leathlobhair and Lenski 2022), and also activate linked mutations that disable tumour-suppressing genes and enable carcinogenesis (Takahashi and Innan 2022).

Table 1. The summary of model parameters and values used for simulations

Parameter	Values for simulations with f. e.*	
	constant	**non-constant**
Genome	Diploid, L = 25 Mbp	
Per-base mutation rate	4×10^{-9}	
Per-position recombination rate	4×10^{-8}	
Population size	5 000	
Sample size	50	
Selection	s = 0.01	s ~ Gamma($\underline{s}$, α) mean $\underline{s}$ = 0.01 shape α = 0.2
Dominance	h = 0.2	h ~ U(0, e^{-ks}) k = 91.63
Mean GC tract length	λ = 4 000 bp	

* f. e. - fitness effects; selection and dominance coefficients



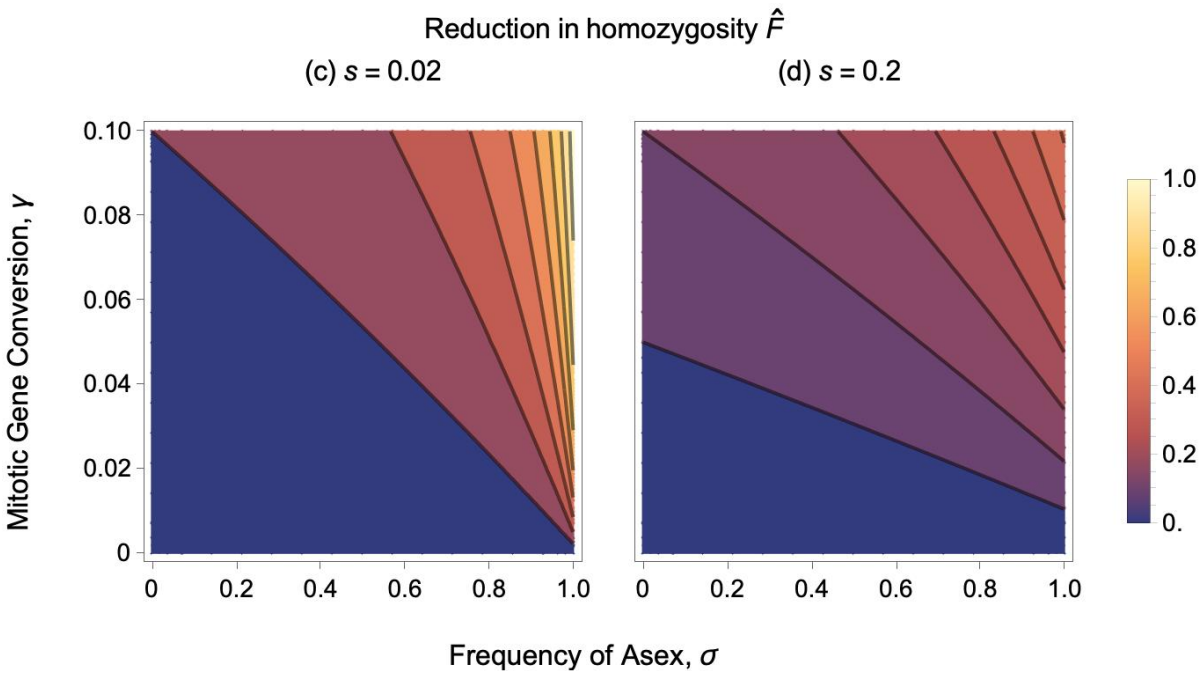


Figure 1: Plots of single-locus analytical results. *Panels (a), (b) show the steady-state frequency of the deleterious mutation (Equation 1a), scaled to that expected under outcrossing (μ/hs), for different dominance values. Note that μ, s are not present in this scaled equation. Panels (c), (d) show $\hat{F}$ (Equation 3) for different selection coefficients.*

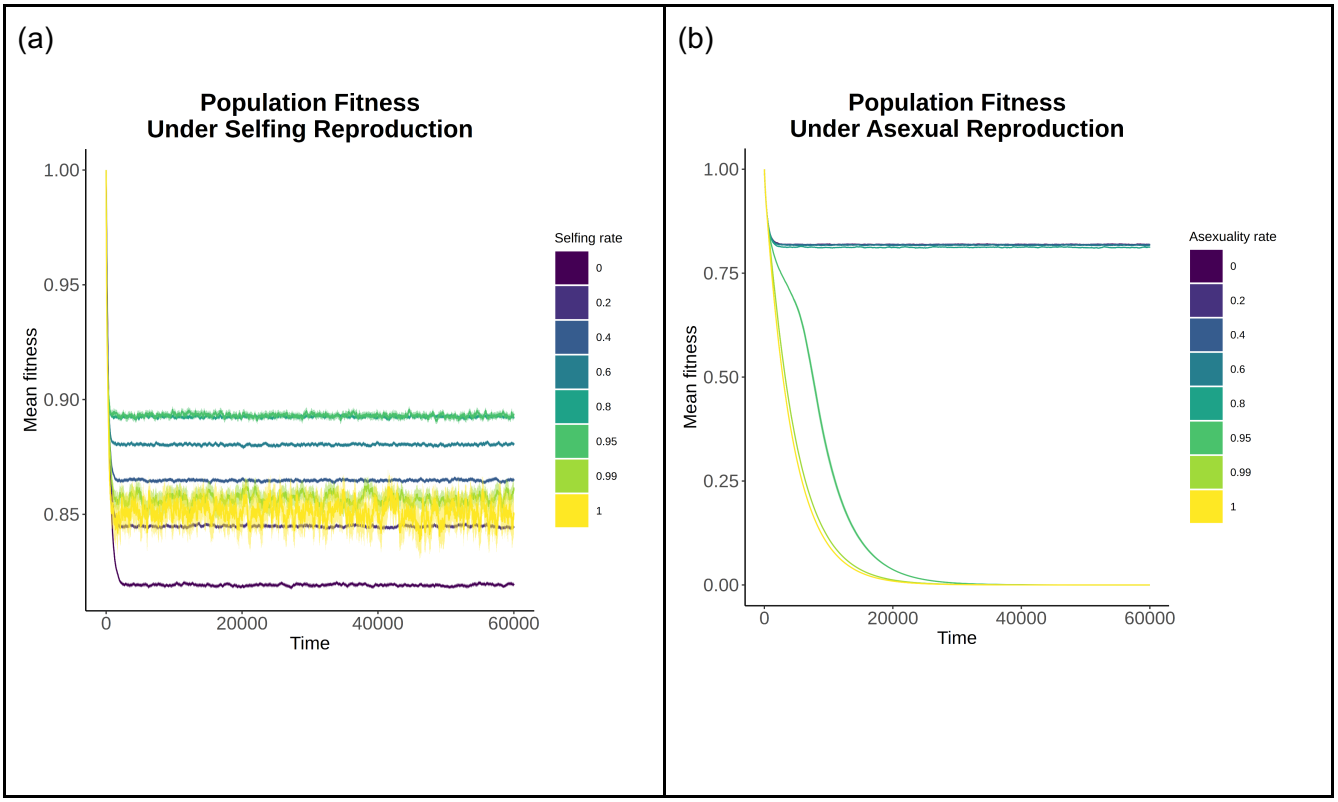


Figure 2: Mean fitness for different modes of uniparental reproduction. *Results are shown as a function of time, for (a) different rates of self-fertilisation or (b) asexual reproduction. Thick lines are mean values, while thinner shading around lines show 95% confidence intervals. Notice the change of scale on the y-axis between (a) and (b).*

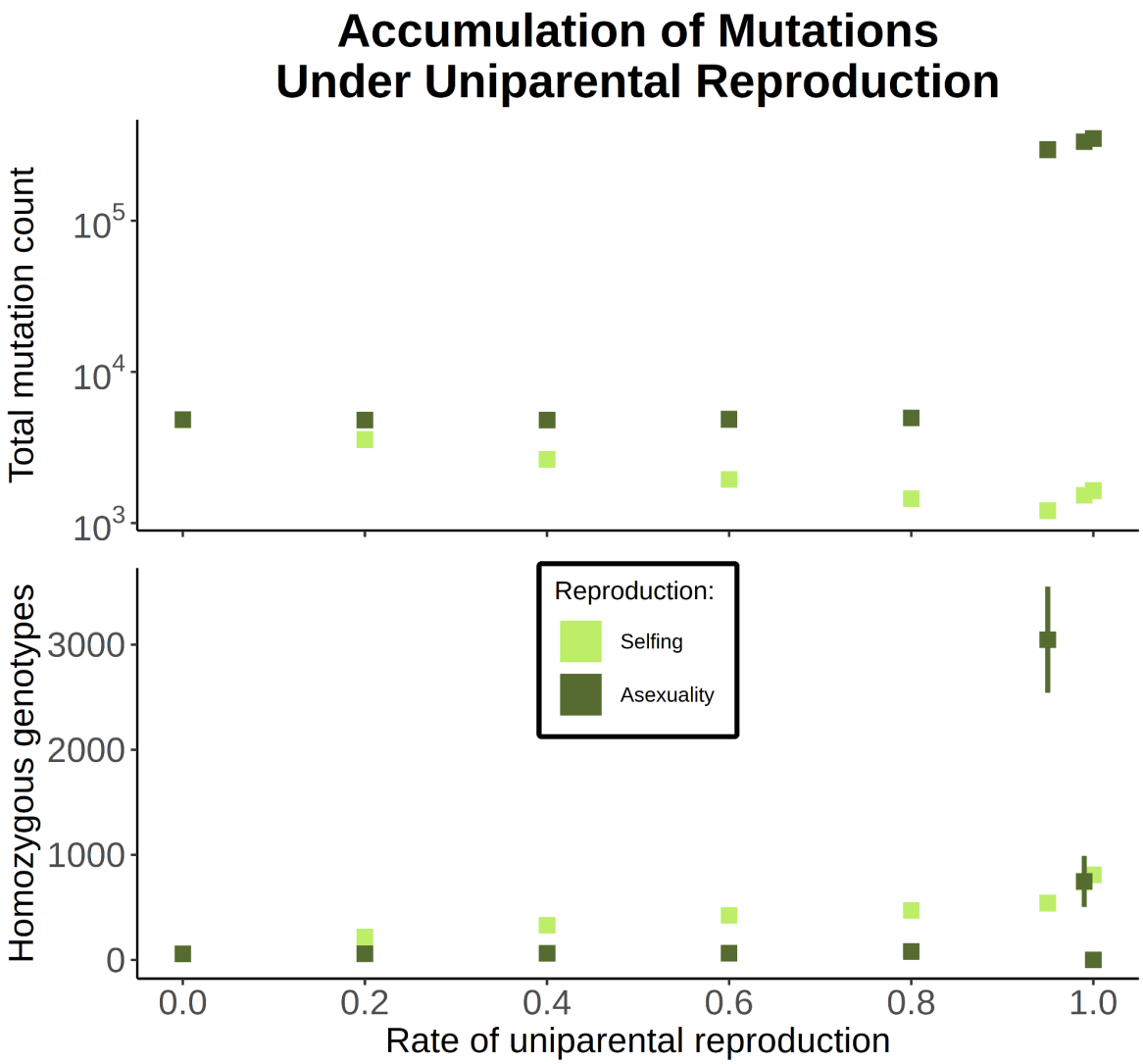


Figure 3: Deleterious mutation counts under different uniparental reproductive modes. *As a function of the rate of uniparental reproduction (either selfing or asexual reproduction), these plots show (top) the total mutation count present in the sample of 50 individuals, and (bottom) the number of homozygous genotypes present in the sample. Error bars represent 95% confidence intervals; if they are not shown then they lie within a point. See Supplementary Figure S5 for the total count on a linear scale.*

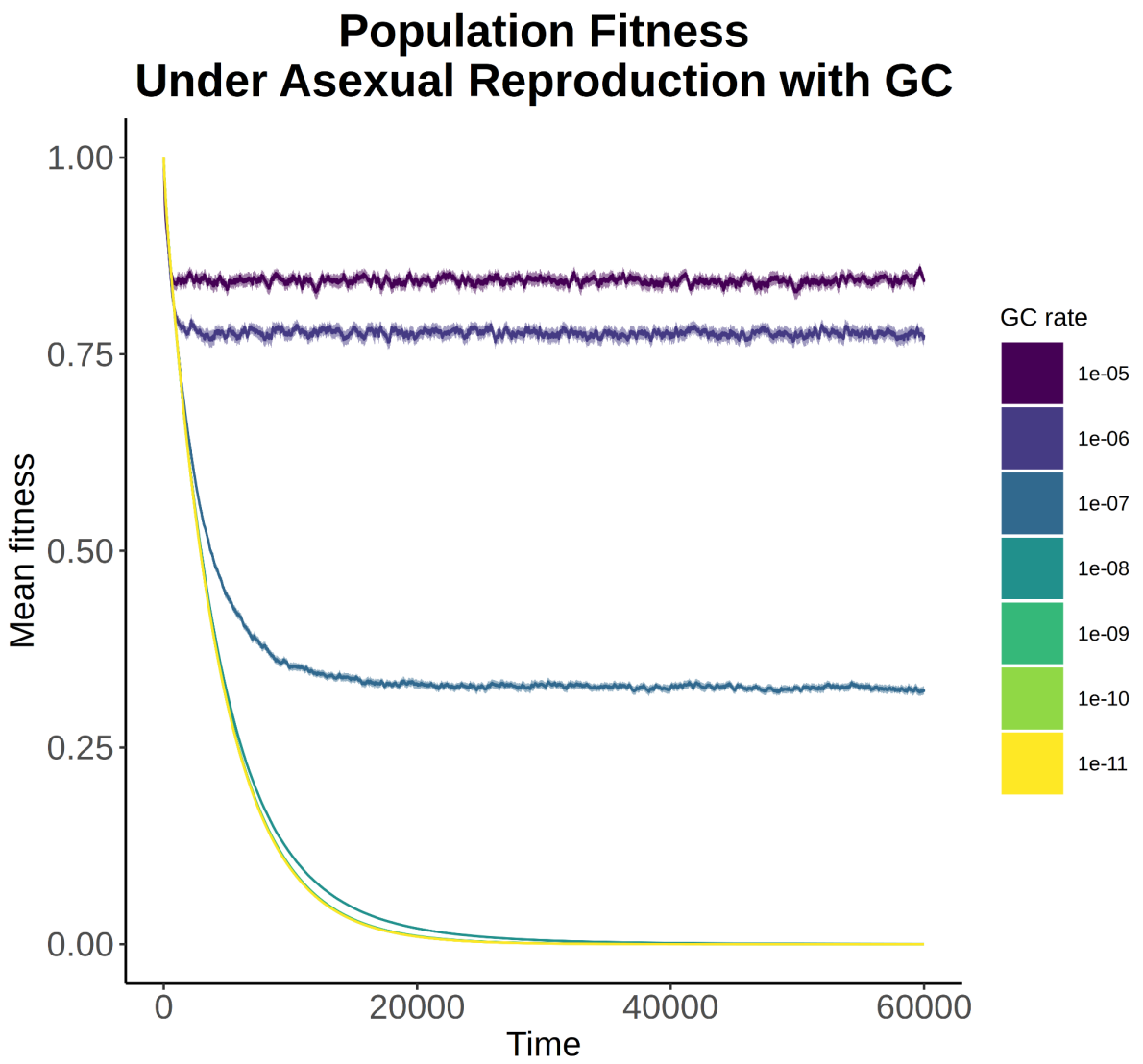


Figure 4: Mean fitness for obligately asexual populations when mitotic GC is present at different rates. *Results are shown as a function of time. Thick lines are mean values, while thinner shading around lines show 95% confidence intervals.*

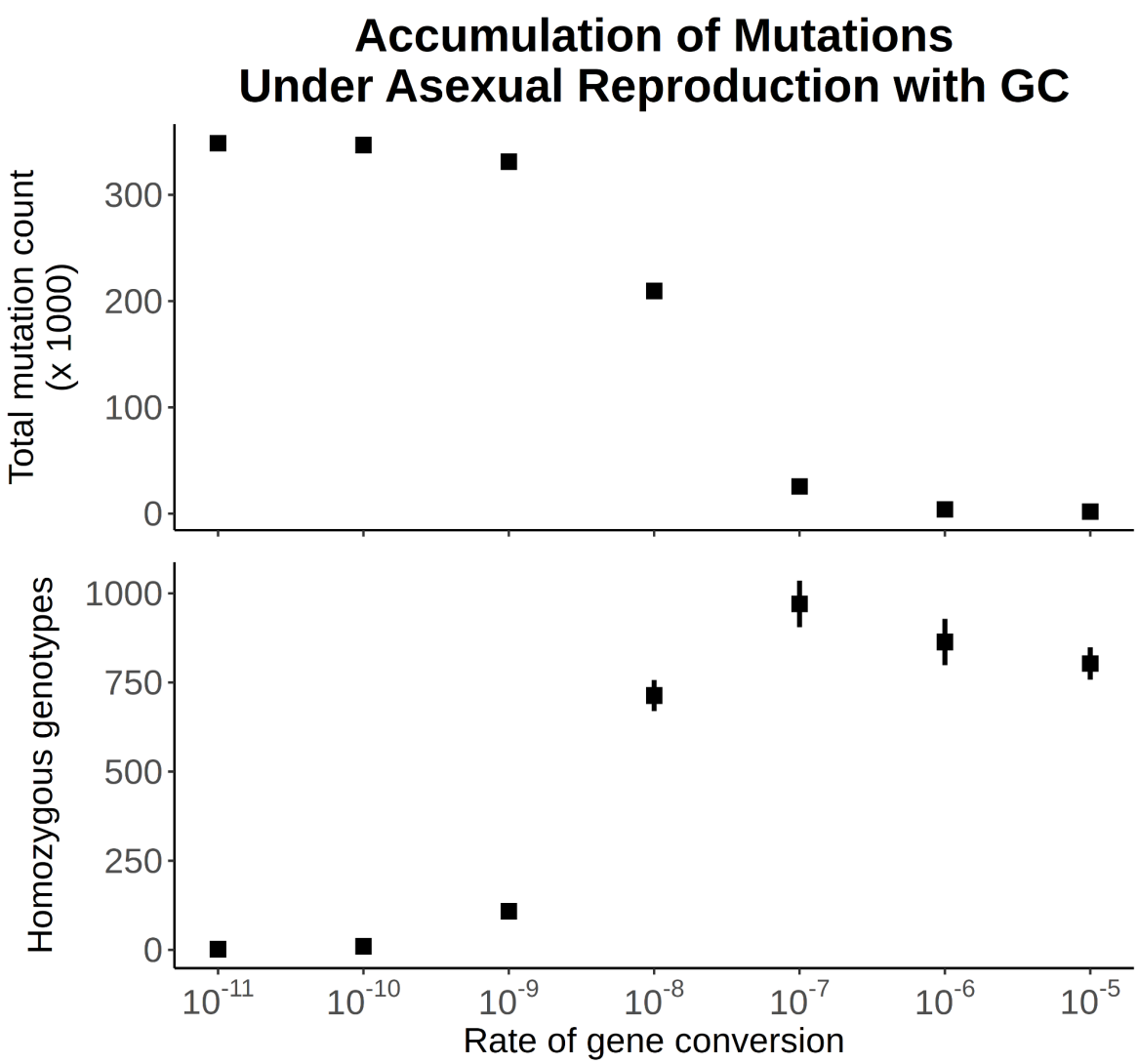


Figure 5: Deleterious mutation counts for obligate asexual populations with mitotic GC present. *Results are shown as a function of the rate of gene conversion initiation at a single site. Plots show (top) the total mutation count present in the sample of 50 individuals, and (bottom) the number of homozygous genotypes present in the sample. Error bars represent 95% confidence intervals; if they are not shown then they lie within a point.*

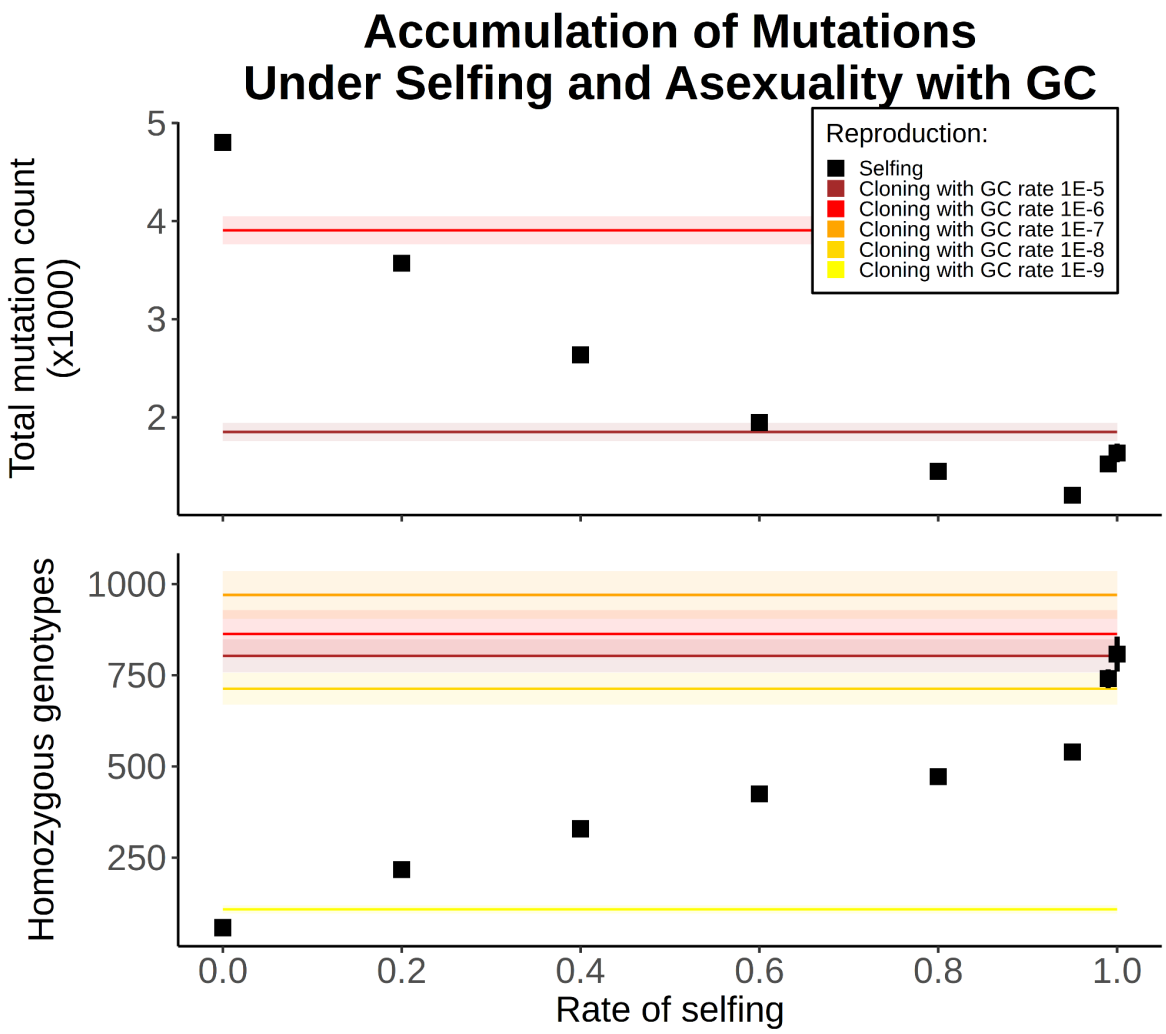


Figure 6: Comparing mutation counts under different levels of self-fertilisation to asexual populations subject to mitotic GC. *Plots show (top) the total mutation count present in the sample of 50 individuals, and (bottom) the number of homozygous genotypes present in the sample. Note that only GC rates of 10^{-5} and 10^{-6} are shown in the top panel. The points show results under different levels of self-fertilisation; error bars represent 95% confidence intervals, and if they are not shown then they lie within a point. Coloured lines are results for asexuality with different levels of mitotic GC, as indicated by the legend; shaded bands around lines indicate 95% confidence intervals.*

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