Evolution, 2023, **77(2)**, 394–408
https://doi.org/10.1093/evolut/qpac013
Advance access publication 3 December 2022
Original Article

The efficacy of selection may increase or decrease with selfing depending upon the recombination environment

Shelley A. Sianta[1], Stephan Peischl[2,3], David A. Moeller[1], Yaniv Brandvain[1]

[1]Department of Plant and Microbial Biology, University of Minnesota, St. Paul, Minnesota, 55108, United States
[2]Swiss Institute of Bioinformatics, Lausanne, 1015, Switzerland
[3]Interfaculty Bioinformatics Unit, University of Bern, Bern, 3012, Switzerland
Corresponding author: Department of Plant and Microbial Biology, 1445 Gortner Avenue, Saint Paul, MN 55108, United States. Email: ssianta@umn.edu

Abstract

Much theory has focused on how a population's selfing rate affects the ability of natural selection to remove deleterious mutations from a population. However, most such theory has focused on mutations of a given dominance and fitness effect in isolation. It remains unclear how selfing affects the purging of deleterious mutations in a genome-wide context where mutations with different selection and dominance coefficients co-segregate. Here, we use individual-based forward simulations and analytical models to investigate how mutation, selection and recombination interact with selfing rate to shape genome-wide patterns of mutation accumulation and fitness. In addition to recovering previously described results for how selfing affects the efficacy of selection against mutations of a given dominance class, we find that the interaction of purifying selection against mutations of different dominance classes changes with selfing and recombination rates. In particular, when recombination is low and recessive deleterious mutations are common, outcrossing populations transition from purifying selection to pseudo-overdominance, dramatically reducing the efficacy of selection. At these parameter combinations, the efficacy of selection remains low until populations hit a threshold selfing rate, above which it increases. In contrast, selection is more effective in outcrossing than (partial) selfing populations when recombination rates are moderate to high and recessive deleterious mutations are rare.

Keywords: efficacy of selection, genetic load, mating systems, pseudo-overdominance, selective interference, selfing

The mating system, defined as the extent of mating with oneself (or close relatives), varies tremendously in plants, animals, fungi, protozoa and algae (Hanschen et al. 2018; Jarne and Auld, 2006). The shift from habitual outcrossing to self-fertilization is a very common evolutionary transition (Grant, 1981; Stebbins, 1974). Despite extensive theoretical efforts, e.g. (Charlesworth, 1992; Charlesworth and Wright, 2001; Glémin, 2007; Glémin and Galtier, 2012), *how* mating system affects the efficacy of natural selection (defined herein as the ability for selection to decrease and increase the frequency of deleterious and beneficial mutations, respectively) in a genome-wide context is unclear. Depending on model assumptions, and parameters/concepts explored, theory concludes that an increase in selfing can increase or decrease the efficacy of selection (Charlesworth, 1992; Glémin, 2007; Glémin and Galtier, 2012; Roze, 2016; Sachdeva, 2019). Because most theory has focused on one process at a time, it is unclear how the opposing population genetic consequences of the mating system interact to shape the efficacy of selection in a genome-wide context. We present whole genome simulations that make sense of these conflicting results.

Increased individual homozygosity upon selfing can decrease the efficacy of selection by decreasing the effective number of chromosomes (Pollak, 1987), or it can increase the efficacy of selection by increasing the variance in fitness (Uyenoyama & Waller, 1991). For additive mutations (h = 0.5), these effects cancel: the probability of fixation of such alleles is unaffected by the selfing rate (Caballero & Hill, 1992; e.g., Charlesworth, 1992; Glémin, 2007). However, the elevated homozygosity of selfers allows for the more efficient fixation of advantageous (Abu Awad & Roze, 2018), and removal of deleterious (Charlesworth, 1992), partially recessive ($h < 0.5$) mutations. As such, partially selfing populations can more effectively "purge" recessive (and likely highly deleterious mutations, as estimated in three model organisms; Agrawal & Whitlock, 2011; Crow, 1993; Huber *et al.*, 2018; Mukai *et al.*, 1972; Phadnis & Fry, 2005) mutations than can highly outcrossing populations (Lande & Schemske, 1985). So, all else equal, the selfing rate does not change the efficacy of selection on mutations with additive effect but facilitates the purging of (partially) recessive mutations.

However, all else is not equal. Ecological, demographic, and genomic features of selfing species modulate the effective population size, N_e, and thus, the efficacy of selection. These factors tend to make selection, and particularly selection on alleles with nearly additive effects on fitness, less effective as the selfing rate increases (Glémin, 2007; Wright *et al.*, 2008; Glémin & Galtier, 2012). Because recombination between homozygous sites does not generate new haplotypes, selfing decreases the effective recombination rate (Nordborg, 2000), potentially inducing Hill-Robertson interference between selected mutations (McVean & Charlesworth, 2000) and increasing the reach of background selection (Roze, 2016). By reducing N_e (Charlesworth *et al.*, 1993a), background selection

Received December 21, 2021; revisions received September 20, 2022; accepted November 10, 2022

both decreases diversity at linked neutral sites and limits selection's ability to affect linked mutations (Charlesworth & Wright, 2001). Moreover, near obligately selfing populations steadily increase their deleterious mutations by continual loss of the least loaded mutational class (a.k.a Muller's ratchet, Charlesworth *et al.*, 1993b) although rare beneficial mutations, can reverse this process (Goyal *et al.*, 2012). Thus, although selfing allows for effective selection on (partially) recessive mutations, the accompanying reduction in recombination decreases the efficacy of selection against additive mutations.

Theory examining how mating system impacts linked selection has largely focused on a single dominance coefficient, typically quite far from full recessivity (but see Arunkumar *et al.*, (2015) and Kim *et al.* (2018)). As such, our understanding of this topic is shaped by the impact of selection against rare mutations in the heterozygous state, and not dynamics that largely play out in only the homozygous state. However, selection occurs in real genomes with mutations spanning a range of dominance and selection coefficients, and thus, we must consider how, for example, purging recessive mutations in highly selfing populations mediates selection on linked deleterious mutations. By exposing rare deleterious recessive alleles, (partial) selfing will increase the equilibrium frequency of "unloaded" haplotypes with no such mutations (f_0, Charlesworth et al., 1993a), increasing N_e and decreasing the strength of selective interference (i.e., Hill–Robertson interference between deleterious alleles) induced by recessive mutations. Thus, selfing could either reduce the impact of selective interference by effectively purging rare recessive mutations or amplify the impact of selective interference on additive mutations by decreasing the effective recombination rate.

At the extreme, when recessive mutations arise faster than selection and recombination can remove them, obligately outcrossing populations will not be able to sustain a haplotype free of deleterious recessive mutations and will transition to a state known as pseudo-overdominance (Gilbert *et al.*, 2020; Ohta & Kimura, 1970). With pseudo-overdominance, partially recessive deleterious alleles at different loci are maintained on complimentary haplotypes under balancing selection (Charlesworth & Charlesworth, 1997; Charlesworth & Willis, 2009; Pálsson & Pamilo, 1999). Homozygosity for any such haplotype will expose its recessive mutations, likely with severe effects, favoring individuals heterozygous for complementary haplotypes. Gilbert *et al.* (2020) found that associative-overdominance – an apparent heterozygote fitness advantage which can be caused by numerous processes including pseudo-overdominance – occurs over a wider range of parameter space ($0.1 < Ns < 100$) than previously found with single locus models (Zhao & Charlesworth, 2016). Gilbert *et al.* (2020) attributed this associative overdominance to pseudo-overdominance, partly because genomes from populations showing associative overdominance consisted of a mosaic of long-diverged haplotypes. Because this study was restricted to randomly mating populations with a single dominance coefficient, it neither shows when and how selfing can prevent the emergence of pseudo-overdominance via purging, nor does it evaluate how pseudo-overdominance itself further influences the efficacy of selection.

We developed a series of individual-based forward simulations to explore how selfing affects the efficacy of selection in populations experiencing both recessive and additive mutations across a wide range of parameter space. To study how the transition from purifying selection to pseudo-overdominance interacts with the selfing rate to shape the accumulation of deleterious mutations, we extended analytical models from Gilbert *et al.* (2020) to formally derive when purifying selection transitions to pseudo-overdominance as a function of the mutation, recombination and selfing rates. In addition to recovering the known effects of partial selfing on the efficacy of direct and linked selection, including evidence of Mueller's ratchet with obligate selfing (Charlesworth *et al.*, 1993b) and a critical purging threshold attributable to genome-wide correlations in homozygosity under partial selfing (Lande *et al.*, 1994), we also found that by removing deleterious recessive variants, selfing can increase the efficacy of selection on linked additive mutations.

Methods

We developed simulations in SLiM v3.3.2 (Haller & Messer, 2019), and analytical theory to evaluate how linked selection, purging and inbreeding interact to affect the efficacy of purifying selection and the transition to pseudo-overdominance.

Simulations in SLiM

Fixed parameters:

Demography:

All simulations shown in the main text consisted of 10,000 diploid individuals for $6N$ non-overlapping generations.

Genome size and structure:

Genomes consisted of six 7.5Mb chromosomes, as in Gilbert *et al.* (2020), with uniform recombination rates across each chromosome, and free recombination among chromosomes. We modeled a uniform genome structure—i.e., each "mutation type" (see below) was independent of genomic position.

Mutational effects:

SLiM simulates genomes composed of specific mutation types, each characterized by a fixed dominance coefficient, h, and a (distribution of) selection coefficient(s), s. All simulations included four equally probable deleterious mutation types—one fully to partially recessive mutation ($0 \leq h < 0.5$) type (described in the variable parameter section below) and three additive mutation ($h = 0.5$) types. There were no neutral, beneficial or back mutations. As such, the genome-wide mutation rate, U, represented the deleterious genome-wide mutation rate, U_{del}. Because some of our results suggested that the recessive variation affected the efficacy of selection against the additive mutations, we also ran all parameter combinations with just the additive mutations, keeping the per-mutation-type mutation rate and relative recombination rate constant.

Individual fitness:

Fitness at each locus is 1, $1 - hs$, and $1 - s$ for genotypes homozygous for the wild-type allele, heterozygous for a deleterious mutation and homozygous for a deleterious mutation, respectively. Fitness was multiplicative across loci (i.e. the fitness of the i^{th} individual, $w_i = \prod w_{ij} = \prod(1 - h_{ij}\, s_{ij})$, where j indexes the locus).

Selection coefficients for mildly deleterious, additive mutations:

We chose selection coefficients of the three additive mutation types to slightly exceed the nearly neutral boundary ($4N_e s > 1$), which differentiates where natural selection can and cannot effectively remove deleterious mutations (Kondrashov, 1995) because this should expose differences in the efficacy of selection against additive mutations in selfers and outcrossers. The homozygote selection coefficients for these three mutation types were $s = 0.0005$ ($4Ns = 20$), $s = 0.00025$ ($4Ns=10$) to $s = 0.00005$ ($4Ns=2$). We chose these fixed selection coefficients, rather than the more biologically realistic distribution of fitness effects, because they provide theoretical insight into when and how selection becomes less effective.

Variable model parameters

We investigated all factorial combinations of five variables: (1) selfing rate, (2) deleterious mutation rate, (3) recombination rate, (4) fitness cost of strongly deleterious recessive mutations ($s_{recessive}$) and (5) recessivity of strongly deleterious mutations, with ten replicates for each parameter combination.

Selfing rate:

Selfing rates ranged from obligate outcrossing ($\alpha = 0$) to near obligate selfing ($\alpha = 0.99$) and values between ($\alpha = 0.05$, 0.1, 0.25, 0.5, 0.75, or 0.9). Because we do not model an evolutionary transition between selfing rates, we do not consider the initial purging, or lack thereof required for the transition to selfing (see Bataillon & Kirkpatrick, 2000; Waller, 2021; Wang *et al.*, 1999).

Deleterious mutation rate:

We varied the genome-wide deleterious mutation rate $U_{del} = \mu_{del}$ x genome size. We chose U_{del} values of 0.04, 0.16, and 0.48 to span a range of U_{del} values estimated from multicellular eukaryotes (Cutter & Payseur, 2003; Haag-Liautard *et al.*, 2007; Lynch, 2010; Schultz *et al.*, 1999; Slotte, 2014; Willis, 1999).

Recombination rate:

To probe how linked selection interacts with the selfing rate to modulate the efficacy of selection, we varied the recombination rate. We report this as the Relative Recombination Rate (RRR)—the per-base-pair recombination rate divided by the per-base-pair mutation rate. We examined RRR values of 0.01, 0.1, 1 and 10, corresponding to per-base-pair recombination rates ranging from 8.89×10^{-12} to 1.07×10^{-7} across all mutation rates (see Table S1 for per-base pair mutation and recombination rates for each parameter combination). We chose this composite measure, which does not quantitatively predict outcomes in our simulations, because it explains major qualitative differences in our results.

Selection and recessivity of (partially) recessive deleterious mutations:

We varied the intensity of selection against strongly deleterious (partially) recessive mutations from $s_{recessive} = 0.015$, $s_{recessive} = 0.3$, and $s_{recessive} = 0.9$. These mutations could be nearly additive ($h = 0.25$), largely recessive ($h = 0.1$), or fully recessive ($h = 0$). We assume that recessivity is a property of a mutation, not a gene, and as such we ignore the possibility of "compound heterozygotes." Such compound heterozygotes, when they occur will increase selection's ability to remove alleles that are recessive otherwise.

Quantifying the consequences of selection

Quantifying the efficacy of selection:

We examined the accumulation of recessive and additive mutations separately by quantifying their prevalence, which we define as the average number of mutations per diploid individual, for each of the four mutation types. Prevalence is meant to capture common genomic summaries of the number of derived deleterious mutations, and is comparable to "mutation burden" (Valluru *et al.*, 2019). Because the translation of prevalence to fitness depends on dominance coefficients, inbreeding coefficients and the frequency of mutations (Do *et al.*, 2015; Lohmueller, 2014), we also quantify overall population fitness. Along with total population fitness, we quantify fitness in the same way for only sites that contain recessive mutations (the "recessive contribution to fitness" or "recessive load") and only sites that contain additive mutations (the "additive contribution to fitness" or "additive load"). Our measures of population fitness equal one minus the genetic load (Gravel, 2016) and incorporate the consequences of both derived mutations (the mutation load) and inbreeding (the inbreeding load) (Henn *et al.*, 2015).

For computational efficiency, we had SLiM only track segregating mutations and use them in real time fitness calculations during the simulation, and additionally outputted all fixed mutations at the end of the simulation. We used custom R scripts to calculate derived mutation prevalence and frequency, and population mean fitness from segregating and fixed mutations combined in all simulations. R scripts are available at Dryad (doi: https://doi.org/10.7291/D16D6W)

Summarizing neutral genetic variation:

We quantified neutral diversity (π) and an unfolded allele frequency spectrum (AFS), in eight replicate runs per simulation using tskit (https://tskit.dev/tskit/docs/stable/). We generated these neutral mutations by recording the tree sequence (Haller *et al.*, 2019) of each simulation, and overlying neutral mutations (μ = 1e-7) in msprime (Kelleher *et al.*, 2016). To ensure that chromosomes where independent, we sampled one genome from 200 individuals rather than 100 diploid individuals to calculate diversity statistics.

Identifying pseudo-overdominance:

We qualitatively characterized a simulation as one in which pseudo-overdominance evolved if the population meets three criteria: 1) There was an increase in π, above neutral expectations, 2) there was a visible shift in the AFS towards more intermediate frequencies, and 3) there was an increase in the prevalence of recessive mutations. We labelled these deviations as pseudo-overdominance rather than the broader term, "associative-overdominance," because the alternative processes generating such patterns were unlikely in our simulation (Text S1).

Analytical model for the transition to pseudo-overdominance

To analytically derive how partial selfing prevents the transition from purifying selection to pseudo-overdominance, we extended the multi-locus model of Gilbert *et al.* (2020) (Appendix). We considered n biallelic loci, each with a

wild-type or fully recessive deleterious derived mutation with fitness 1–*s* when homozygous for the derived mutation and 1 otherwise, and multiplicative fitness effects across loci. To determine if there had been a transition to pseudo-overdominance, we derived the frequency of the zero-mutation haplotype, i.e., the haplotype without a deleterious recessive mutation, at mutation-selection balance. Loss of the zero-mutation haplotype is necessary for pseudo-overdominance (Gilbert *et al.,* 2020; Ohta and Kimura, 1970) because then individuals that are heterozygous at all deleterious loci have the highest fitness (Appendix). We assumed that haplotypes with more than one deleterious mutation are vanishingly rare at equilibrium and hence ignored them, meaning that any genotype could be polymorphic at most at two deleterious loci and we only considered homozygotes at a single locus. This simplifies the mathematical analysis of recombination considerably because then recombination mainly re-introduces the unloaded haplotype, which is the most relevant aspect of recombination for preventing the occurrence of pseudo-overdominance. This assumption is quite different from our SLiMulations, given that we simulated large genomes, but provides a reasonable guide to our major qualitative results.

Results

Selfing rate can increase or decrease the efficacy of selection in multilocus simulations

We aimed to determine when and how an increase in selfing increases or decreases the efficacy of purifying selection in genomes experiencing both recessive and additive mutations. To do so, we varied recombination and mutation rates and the dominance and selective coefficients of (partially) recessive mutations. We report how different parameter combinations modulate how the selfing rate impacts the accumulation of strongly deleterious ($Ns > 150$) recessive mutations, then mildly deleterious ($Ns < 5$) additive mutations, and overall population fitness, below.

Selfing prevents the accumulation of recessive mutations and impedes the transition to pseudo-overdominance

We observed different phenomena affecting the accumulation of fully recessive mutations as a function of selfing rate in relatively high recombination (RRR ≥ 1) vs. low recombination (RRR < 1) simulations. Thus, we present our results of fully recessive mutations in simulations with relatively high and then with relatively low recombination rates. We close this section with an overview of how partial recessivity affects the accumulation of recessive mutations across all recombination rates. We remind readers that, although we focus on the dynamics of recessive mutations, these simulations also contain mildly deleterious additive mutations, which will slightly affect the quantitative, but not qualitative, outcomes of selection against recessive mutations.

Complete recessivity and relatively high recombination rates

Highly selfing populations maintain both a lower prevalence and frequency of recessive mutations than do outcrossing populations (Figure 1). With high recombination rates (RRR ≥ 1), the number of recessive deleterious mutations per individual generally declines with an increase in the selfing rate. This decay is rapid and steep when mutations are strongly deleterious. That is, populations with mixed mating systems effectively purge extremely deleterious mutations ($s_{recessive}$ = 0.3 or $s_{recessive}$ = 0.9) but maintain a larger number of less deleterious mutations ($s_{recessive}$ = 0.015, Figure 1A). These results are consistent with both our analytical derivations and those by Roze and Rousset (2004) (see equation A1 and compare Figures 1B and Figure A1 in the Appendix).

The frequency of derived recessive mutations drops dramatically between selfing rates of 0.25 and 0.5 when the mutation rate is high and mutations are severe ($U_{recessive}$ = 0.12, $s_{recessive}$ = 0.9 or $s_{recessive}$ = 0.3), and shows a similarly drastic shift as the selfing rate increases from 0.05 to 0.10 for the most deleterious mutations at intermediate mutation rates ($U_{recessive}$ = 0.04 $s_{recessive}$ = 0.9, Figure 1B). We interpret these shifts as a "purging threshold" which differentiates selfing rates that can and cannot effectively purge their recessive mutations (Lande *et al.,* 1994). Given the high recombination rate in these simulations (this effect is strongest with an RRR of 10), we attribute this purging threshold—which exceeds single locus expectations—to the near-lethal inbreeding depression that occurs when selfed individuals in partially selfing populations expose numerous unlinked recessive mutations in the homozygous state. This correlated homozygosity across unlinked loci, is a form of identity disequilibrium (Weir and Cockerham, 1973), is greatest with partial selfing, and can hinder the purging of recessive mutations because selfing events do not generate living offspring (Kelly, 2007; Lande *et al.,* 1994). Although our simulations contain mildly deleterious additive mutations, similar identity disequilibrium-driven thresholds occur in models without additive mutations (Kelly, 2007; Lande *et al.,* 1994). The fit between multi-locus simulation results and analytical single locus derivations is qualitatively tighter with weaker selection, lower mutation rates and lower selfing rates, likely because multilocus interactions due to linked selection in predominant selfers are greater with stronger selection (Charlesworth *et al.,* 1993a) and because analytical derivations assume weak selection and low mutation (i.e., $u << s << 1$).

Complete recessivity and relatively low recombination rates

When recombination rates are greater than mutation rates (RRR ≥ 1), the prevalence of recessive mutations declines smoothly with an increase in the selfing rate (yellow and red lines in Figure 2A). In contrast, when recombination is much rarer than mutation (RRR < 1, in Figure 2A) the prevalence of recessive mutations is exceptionally high in largely outcrossing populations. At some threshold selfing rate, which we call another "purging threshold", the prevalence of recessive mutations sharply decreases. At selfing rates above the purging threshold, the prevalence of deleterious recessive mutations smoothly declines with an increase in the selfing rate as seen at higher relative recombination rates.

We attribute this drastic difference in the prevalence of recessive mutations in populations above and below the purging threshold to a transition from classic purifying selection (selection against single deleterious mutations) to pseudo-overdominance (selection for complementary heterozygous haplotypes that can hide recessive deleterious mutations). This spike in the prevalence of recessive mutations only occurs in relatively low recombination simulations (e.g., compare dark blue vs all other lines in Figure 2A), and is also associated with a concomitant spike in neutral diversity (Figure 2B, Figure S3A) and a shift in the allele frequency spectrum (Figure 2C, Figure S4). We also see a structuring of

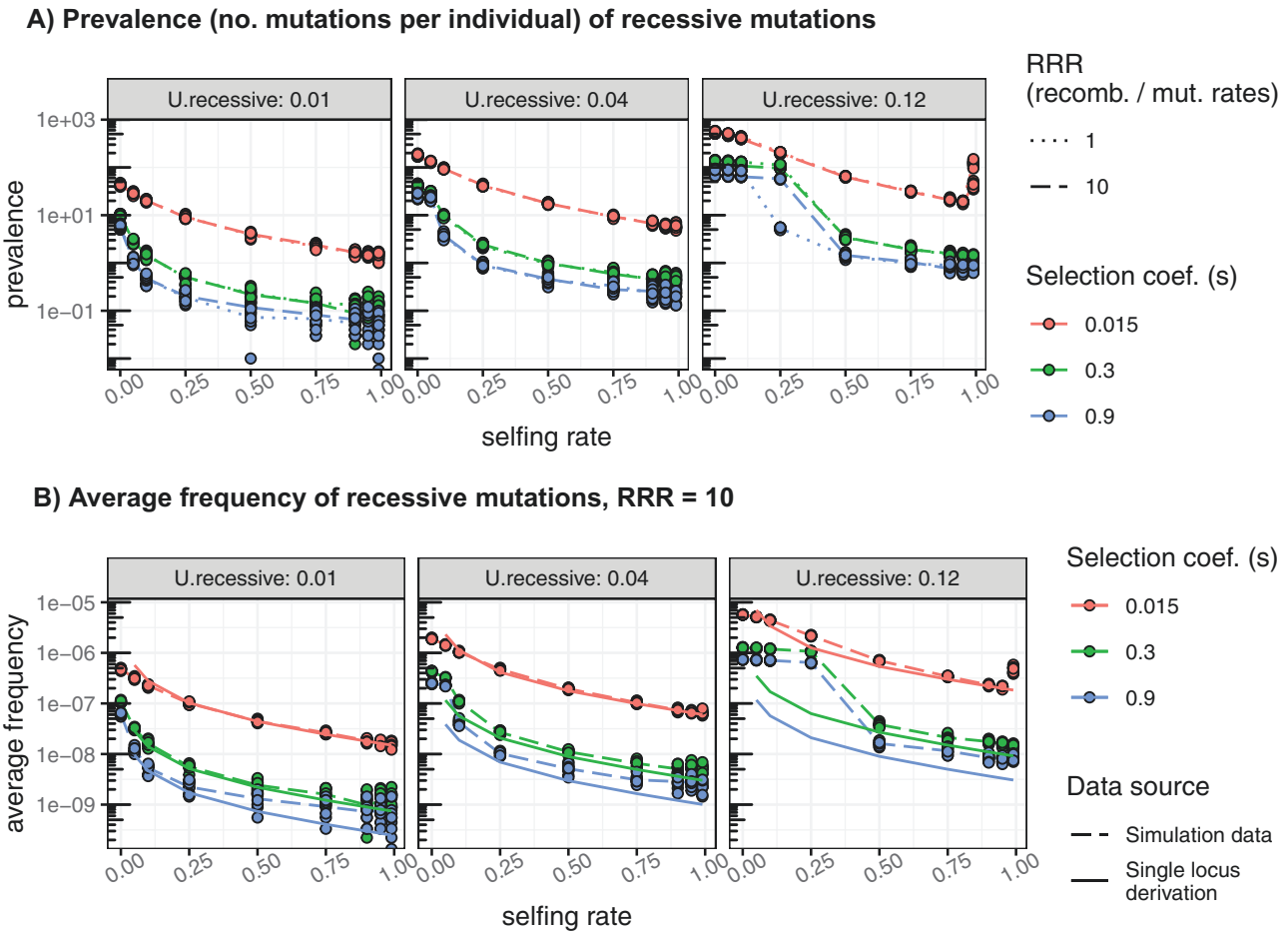

Figure 1: Purging dynamics of fully recessive (h = 0) mutations when per base-pair recombination rates are equal to (relative recombination rate, RRR, = 1) or greater than (RRR >1) per base-pair deleterious mutation rates. (A) Prevalence (i.e., the mean number of mutations per diploid genome) of recessive mutations. The tick marks on the y-axis highlight the $\log_{10}$ scale. (B) Results from multilocus simulations tend to fit analytical expectations derived from single locus models better with weaker selection coefficients and lower mutation rates than with large selection coefficients and higher mutation rates. This likely reflects cases in which identity disequilibria generated by partial selfing hinders the purging process (at $U_{recessive}$ = 0.12 and $s_{recessive}$ = 0.3 and 0.9), and follows from the assumption made in our analytical derivation that mutation rates are much smaller than selection coefficients.

pseudo-overdominant haplotypes by complementary sets of deleterious recessive mutations in genomes from populations below this purging threshold, but not in populations that can more effectively purge (Figure S2).

Partial (5% to 50%) selfing can prevent the shift to pseudo-overdominance by purging rare recessive mutations (Figure 2D). The amount of selfing required to prevent the emergence of pseudo-overdominance depends on how rapidly deleterious recessive mutations are removed by selection before mutation-free haplotypes are eliminated. That is, less selfing is required to prevent pseudo-overdominance when deleterious mutations become easier to purge before they accumulate (as occurs with strong selection coefficients, low mutation, and high recombination rates, Figure 2D).

Partial recessivity across recombination rates

Because partial (as compared to complete) recessivity facilitates purging in predominantly outcrossing populations, we evaluated when intermediate dominance (h = 0.1 and h = 0.25) prevents the emergence of pseudo-overdominance. Like Gilbert *et al.* (2020), we find that partial recessivity substantially decreases the parameter space under which pseudo-overdominance occurs (Figure S5-S8). When h= 0.1, pseudo-overdominance occurs when $s_{recessive}$ is relatively modest ($s_{recessive}$= 0.015; $Nhs_{recessive}$ = 15) and mutation rates are high (U_{del}=0.48) at selfing rates of 0, 0.05, 0.1 and 0.25, but not when partially deleterious mutations have larger fitness consequences (because these mutations are effectively removed when heterozygous). When h = 0.25, partially recessive mutations accumulate in predominantly outcrossing populations at the highest mutation rate and lowest selection coefficient ($s_{recessive}$= 0.015; $Nhs_{recessive}$ = 37.5; Figure S1-C), but this does not cause the switch to pseudo-overdominance, i.e., there is no increase in diversity (Figure S3-C) nor a shift in the allele frequency spectrum (Figure S8). Thus, partial recessivity limits but does not eliminate the potential for pseudo-overdominance.

For lower mutation rates, higher relative recombination rates, and/or more deleterious mutations, increasing the dominance coefficient of partially recessive mutations decreases their prevalence in primarily outcrossing populations because selection becomes more efficient in the heterozygous state with larger dominance coefficients. Thus, the prevalence of recessive mutations in outcrossers becomes closer to that of selfers (Figure S6).

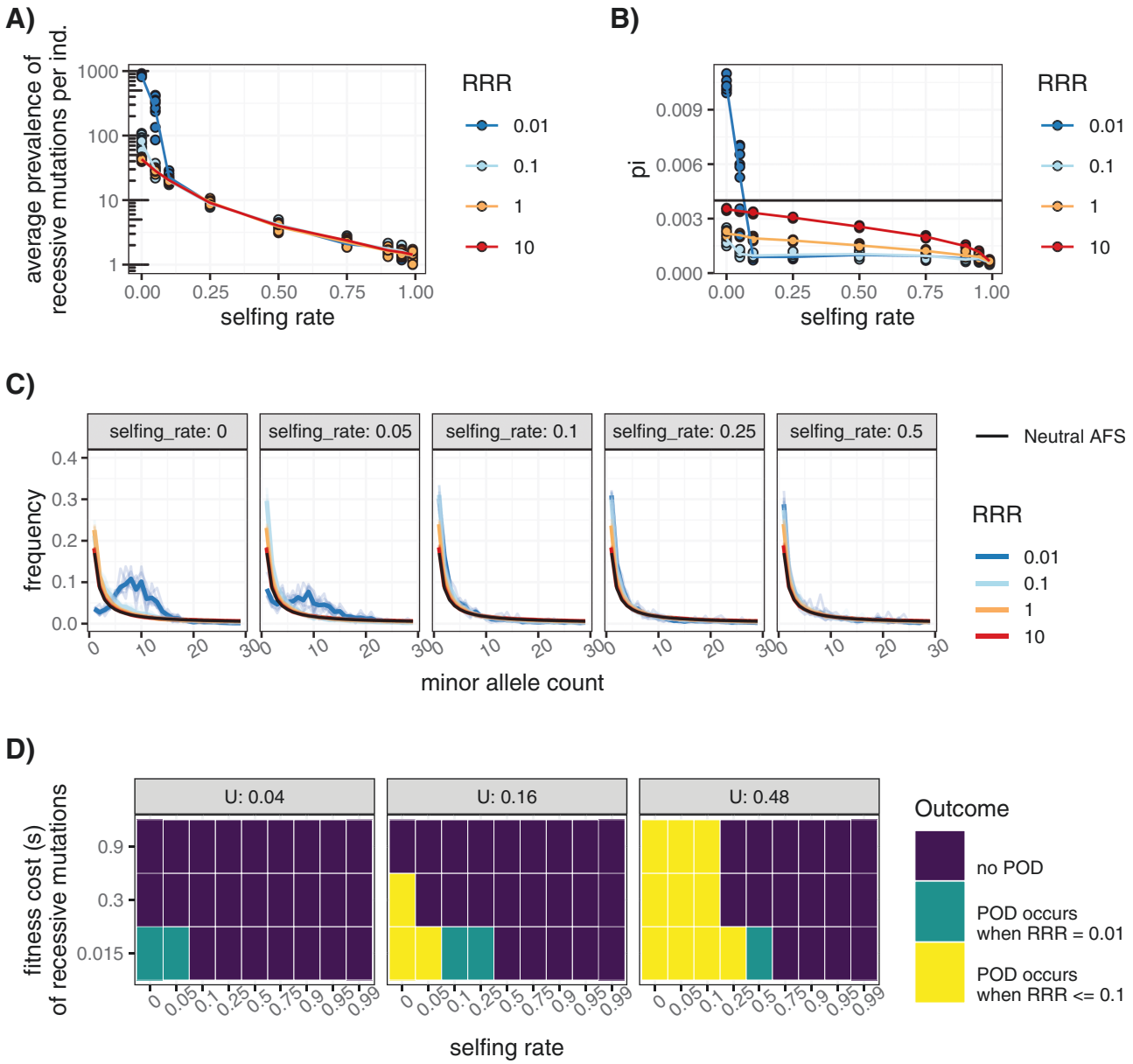

Figure 2: Pseudo-overdominance (POD) occurs in low recombination environments (relative recombination rate, RRR, < 1). (A-C) Genome-wide deleterious mutation rate U_{del} = 0.04, $s_{recessive}$ = 0.015, and h= 0 for the recessive mutation type. (A) POD leads to a spike in the prevalence of recessive mutations in predominantly outcrossing populations. Points are simulation replicates and lines connect mean values. (B) POD also leads to a spike in neutral diversity, driven by heterozygosity at linked neutral sites. Expected neutral diversity ($4N\mu$) is shown by the black horizontal line. (C) Allele frequency spectra (AFS) at a subset of selfing rates (different facets). POD shifts the AFS to more intermediate frequency alleles. Mean AFS are in bold lines, and individual simulation replicates are in faint lines. Black lines correspond to the neutral AFS. (D) Outcome plot of POD occurrence when h= 0 for the recessive mutation type. Green blocks indicate POD occurs at only the lowest relative recombination rate (RRR; RRR = 0.01); yellow blocks indicate POD occurs at the two lowest RRR (0.01, 0.1). Data in panels A-C correspond to the bottom row of the U_{del} = 0.04 outcome plot.

An analytical model for the transition to pseudo-overdominance with partial selfing

Our SliMulations revealed that (partial) selfing can prevent the emergence of pseudo-overdominance. However, without a computationally intense search of parameters space, it does not allow us to quantitatively characterize this threshold. To do so, we present results of our analytical model which approximates the frequency of the unloaded haplotype (i.e., the haplotype with no derived deleterious mutations) under the assumption of weak selfing and weak recombination (equation (2) in the Appendix). Roughly, this assumes that $F, r, u < 1/N < s$, (where F is the inbreeding coefficient) but the exact conditions for when this approximation is unreliable are difficult to derive (see Appendix for more details). Reassuringly, when reduced to a single locus, our model recovers the results of Roze and Rousset (2004). Because comparable two-locus results have not been derived previously, we check our approximation against results obtained by numerical iteration of the difference equation (see Appendix Figure A1 and A2). Importantly, the selfing rate needed for loss of the zero-mutation haplotype in two-locus simulations is accurately predicted by our model (see Appendix Figure A2).

We find that the frequency of the unloaded haplotype approaches zero (i.e., when we expect pseudo-overdominance)

when selection coefficients are small, selfing is rare, and recombination rates are low (Figure 3). When recombination is much rarer than the rate of recessive mutation (RRR = 0.01, Figure 3A), frequent selfing is required to prevent the transition to pseudo-overdominance when selection coefficients are small. By contrast, lower selfing rates can prevent the transition to pseudo-overdominance as the relative recombination rate increases (RRR = 0.1, Figure 3B). Additionally, with very weak selection, recombination can generate new mutation-free haplotypes and prevent pseudo-overdominance. This result, which is most obvious in Figure 3B, was also seen in Gilbert (2020). This synergistic effect of recombination and selfing on the efficacy of purging recessive mutations and preventing pseudo-overdominance is mostly observed for small selection coefficients, simply because pseudo-overdominance is unlikely if selection is strong and hence there is no opportunity for recombination to prevent it. The synergistic effect of recombination and selfing is quite general in our model (Appendix Figure A3) and is consistent with results from our whole genome SliMulations (Figures 2D and 3).

The analytical model is not designed for direct comparison with genome-wide simulations of thousands of loci in regions of low recombination. Nevertheless, we expect that our model should capture the qualitative nature of how recombination, mutation, and selection interact in regions of low recombination and therefore can provide valuable insights for the interpretation of simulation results. Indeed, our analytical predictions are qualitatively consistent with the SliMulation results (Figure 3). Note that the parameters used for simulations and the analytical model in Figure 3 are not directly comparable (specifically, we assumed a much smaller number of loci and larger per locus mutation rate in the analytical model as compared to the simulations).

The number of deleterious additive mutations does not necessarily increase with selfing

When modelling both additive and recessive deleterious mutations, increasing the selfing rate can have no effect, increase, or decrease the prevalence of additive mutations (Figure 4). These different outcomes are determined by whether Hill-Robertson interference is stronger in selfers (due to their reduced effective recombination rate) or outcrossers (due to their inefficiency in purging recessive mutations).

Below, we show results for the most deleterious of the three additive mutation types. As the selection coefficient of our additive mutation types gets smaller, mutations of that type behave more like neutral mutations. Therefore, patterns of prevalence of additive mutations that are driven by selfing rate, mutation rate, and relative recombination rate become more dilute. They show similar patterns as those reported for the most deleterious additive mutation type but with more variation among replicates in simulations with less deleterious mutations (Figures S9-11).

Selfers accumulate more additive deleterious mutations than outcrossers when recombination rates are high

Predominant selfers accumulate more additive mutations with high recombination than do predominant outcrossers (when recombination rate is greater than (red) or equal to (yellow) the mutation rate, Figures 4A, S9-S11). At the highest relative recombination rates (RRR = 10), selfing rates greater than 0.95 are required for an increase in the prevalence of additive mutations, as the local effective recombination rate in partially selfing populations is large enough to allow most mutations to escape selective interference otherwise. In between full outcrossing and near obligate selfing, the prevalence of additive deleterious mutations subtly decreases with an increase in the selfing rate until the selfing rate becomes high enough to experience selective interference (~ 0.75-0.9). We revisit this result, which was also observed in Roze (2015), in our low recombination rate results below. We find a similar pattern when the recombination rate equals the mutation rate; however, in this case, the increase in additive mutations begins to increase at a lower selfing rate.

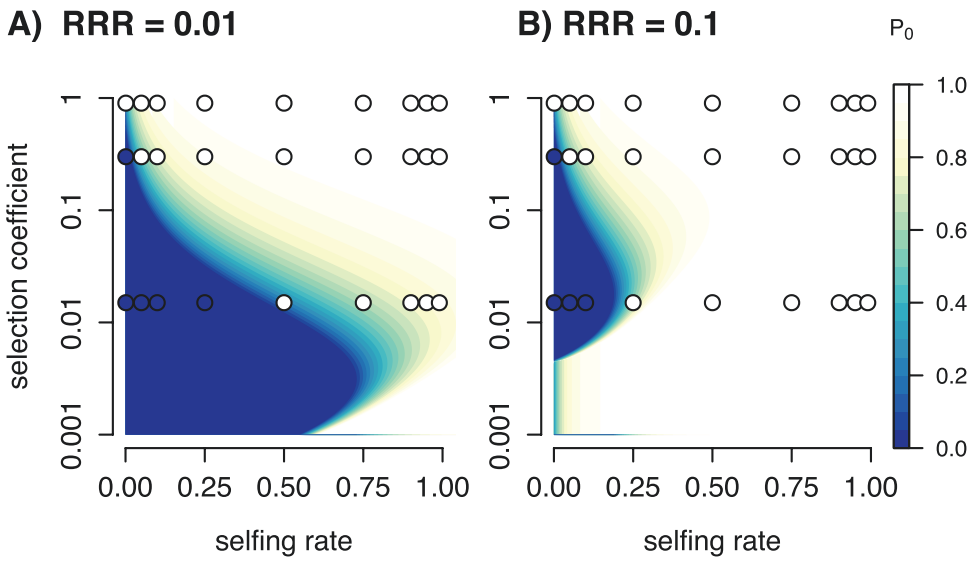

Figure 3: Qualitative comparison between analytical predictions and simulation results. Shaded areas indicate the analytical predictions for pseudo-overdominance (POD), specifically the frequency of the zero-mutation haplotype (P_0) (based on equation 2; see Appendix), for two relative recombination rates. For the analytical model, we assumed a total of n = 100 loci equidistantly spaced on a chromosome with a total mutation rate of U_{del} = 0.005 and relative recombination rate RRR = 0.01 (A) and 0.1 (B). Circles show results from simulations when U_{del} = 0.16: filled circles indicate simulations where we observed POD and white circles indicate no POD.

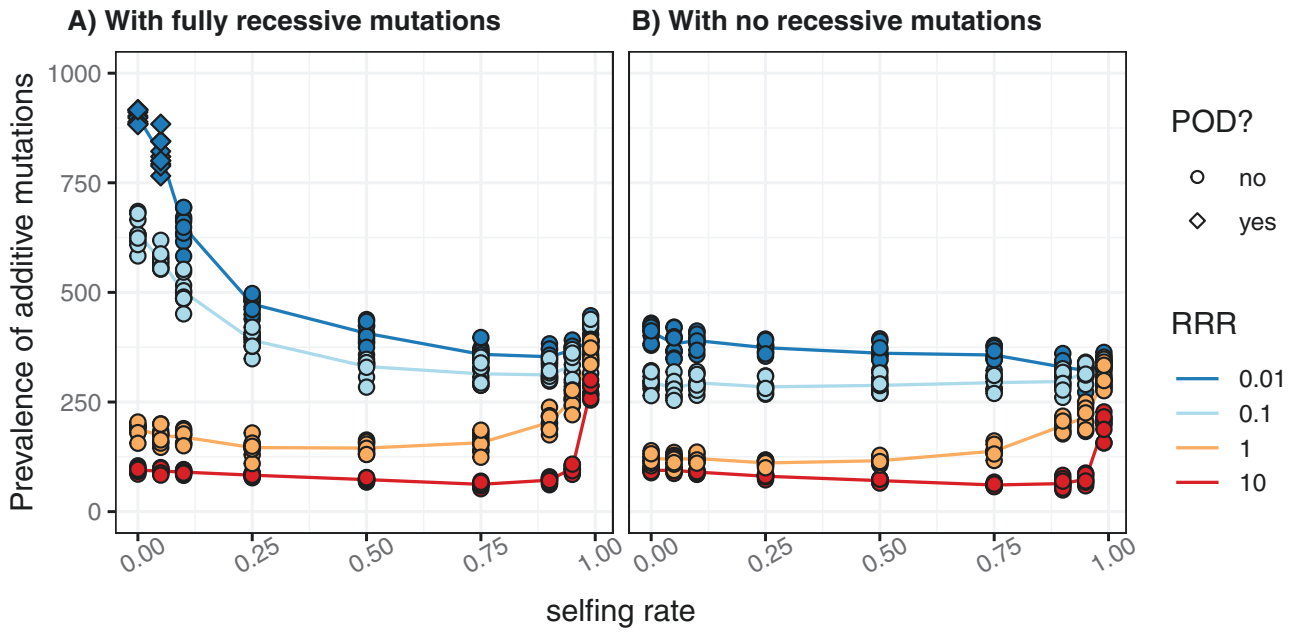

Figure 4: The accumulation of additive mutations as a function of selfing rate is heavily influenced by the relative recombination rate (RRR) and whether pseudo-overdominance (POD) occurs. Facets contrast simulations with fully recessive mutations (A) and with only additive mutations (B). U_{del} = 0.04 and $s_{recessive}$ = 0.015.

With low recombination, selfers do not accumulate more deleterious additive mutations than outcrossers

When recombination is less frequent than mutation, the prevalence of additive mutations sharply declines with an increase in the selfing rate – a pattern most pronounced at the lowest relative recombination rate (light blue versus dark blue lines, Figure 4A). This pattern is driven by an increase in prevalence in primarily outcrossing populations (i.e., prevalence does not change in obligate selfing populations across relative recombination rates, Figure 4A). The increase in prevalence of additive mutations is particularly large in primarily outcrossing populations that have transitioned from purifying selection to pseudo-overdominance (diamonds in Figure 4A), however, it also occurs without pseudo-overdominance. These results suggest that purging of recessive mutations under partial selfing can increase the efficacy of selection against (i.e., decrease the prevalence of) linked mildly deleterious additive mutations.

To determine how selection on recessive mutations affect the efficacy of selection on additive mutations, we ran a small set of simulations without recessive mutations, keeping the per-mutation-type mutation rate and relative recombination rate constant. In Figure 4, we contrast the same set of parameter conditions (U_{del} = 0.04 and $s_{recessive}$ = 0.015) between simulations with fully recessive mutations (h = 0; Figure 4A) to those with no recessive mutations (Figure 4B). The presence of recessive mutations does not have a large effect on the prevalence of additive mutations in high relative recombination rate (RRR ≥ 1) simulations (yellow and red lines). However, the presence of recessive mutations greatly increases the prevalence of additive mutations in low relative recombination rate (RRR < 1) simulations (dark and light blue lines), particularly in primarily outcrossing populations. Notably, this result does not require complete recessivity – simulations with h = 0.1 can also generate a similarly dramatic spike in the prevalence of additive mutations at high outcrossing rates (Figure S9). A sufficiently large dominance coefficient (h = 0.25, Figure S9) prevents the accumulations of linked additive mutations, as this uptick in the number of deleterious additive mutations is not observed in comparable simulations for higher levels of dominance.

Pseudo-overdominance decreases the efficacy of selection on linked mutations with additive effects

We propose that pseudo-overdominance limits the efficacy of selection against additive mutations by effectively subdividing the population into haplotypic classes of complementary recessive mutations. We show that when an additive deleterious (or beneficial) mutation falls on a haplotype maintained at equilibrium by pseudo-overdominance, selection against (or for) the new mutation will be limited by the recessive load at linked sites. Specifically, the Appendix shows that in a two-locus model for pseudo-overdominance the efficacy of selection is reduced by a factor of 1-s/2 for outcrossing populations, where s is the fitness effect of recessive mutations. Intuitively speaking, in our two-locus model a new additive mutation will have a 50% chance to be in a heterozygous genotype where the recessive load is masked, effectively reducing the strength of selection against (or for) the additive mutation by (1-s) in half of the genotypes. These results resemble Assaf *et al.*'s (2015) "staggered sweep" model, in which the spread of adaptive mutations is slowed by the exposure of linked recessive mutations that occurs when they become common.

The effect of mating system on mean population fitness

When recombination rates are high relative to mutation rates, mean population fitness is generally greatest in outcrossers and lowest in near obligate selfers (Figure 5A, Figures S12-S13), reflecting the elevated number of additive mutations accumulated by full selfers (Figure 4A) and their effect on

fitness (Figure 5B). Exceptions are at the highest recombination rates, when fitness is maximized in populations with intermediate selfing rates (corresponding to selfing rates of 0.75 in Figures 5, S12-S13). By contrast, when recombination rates are lower than mutation rates, mean population fitness either does not vary (when selection on recessive variants does not interfere with selection on additive variants), or increases with an increase in the selfing rate.

Comparing the contribution of additive and recessive mutations to overall population fitness (Figure 5B and 5C, respectively) shows that total population fitness is primarily affected by additive mutations, regardless of selfing rate, because recessive mutations are masked in the heterozygous state in primarily outcrossing populations and purged in partially selfing populations. The exception is when primarily outcrossing populations transition to pseudo-overdominance (top right graph, dark blue line, Figure 5C). Here, the population is not crystallized into complementary haplotypes, resulting in a decrease in fitness because of the high prevalence of recessive mutations. At higher mutation rates (Figure S14), we see complex fitness effects of recessive mutations across simulations where pseudo-overdominance occurs. For example, at the highest mutation rate (Figure S14C, top panel), fitness due to recessive mutations is lowest at higher selfing rates or higher recombination rates, as recombination creates more non-complementary haplotypes and/or as selfing exposes more haplotypes in the homozygous state (Figure S14).

The general patterns seen in Figure 5 are consistent across most of parameter space (Figures S12, S13), except for cases where there are identity disequilibrium-driven purging thresholds (high RRR, h=0, $s_{recessive}$=0.3 or 0.9 and U_{del} = 0.48). In this regime of parameter space, additive mutations accumulate as populations move from outcrossing to the selfing rate required to purge (Figures S9-S11), causing extreme non-monotonicity in fitness (Figure S13).

Discussion

The common evolutionary transition to predominant self-fertilization (Grant 1981; Stebbins 1974; Wright *et al.* 2013) provides the opportunity to test if and how numerous simultaneous population genomic processes affect the efficacy of selection. The lack of consistent empirical evidence for reduced efficacy of selection in selfers (Brandvain *et al.*, 2014; Escobar *et al.*, 2010; Gioti *et al.*, 2013; Haudry *et al.*, 2008; Hazzouri *et al.*, 2012; Ness *et al.*, 2012; Qiu *et al.*, 2011; Slotte et al., 2010, 2013) is often attributed to factors not directly related to mating system and/or the recency of most selfing lineages (Glémin & Galtier, 2012; Haudry *et al.*, 2008). These explanations may be true; however, our results highlight a limitation of narrowly focusing on one hypothesized consequence of selfing, as self-fertilization has numerous genomic consequences with different predicted effects contributing to the efficacy of selection. Specifically, we discover that selection is more effective in outcrossing than selfing populations when

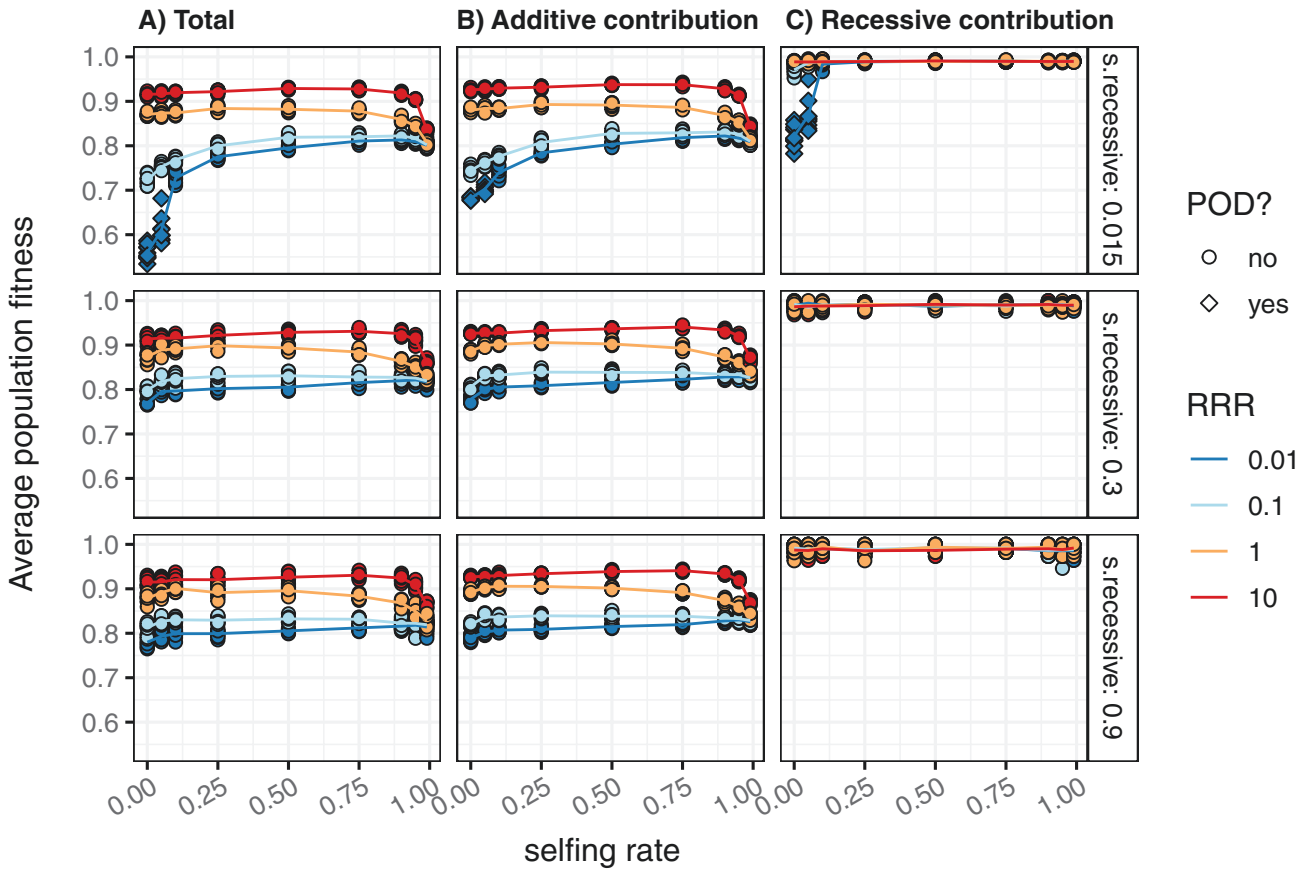

Figure 5: The relationship between mean population fitness and the selfing rate varies as a function of the recombination rate and the presence of pseudo-overdominance (POD), and is largely driven by the fitness consequences of additive mutations. U_{del} = 0.04, h = 0. (A) Average population fitness across all loci. (B) Average population fitness at loci that have additive mutations. (C) Average population fitness at loci that have recessive mutations.

recombination rates are not too low and recessive deleterious mutations are rare, but when recombination rates are low and highly recessive deleterious mutations are common, selection is more effective in (partial) selfers than outcrossers.

Effects of selfing rate on the efficacy of selection against deleterious mutations

By jointly simulating deleterious recessive and additive mutations across a broad slice of parameter space, we found that increases in selfing rate can have positive, neutral or negative effects on the accumulation of deleterious mutations (see Figures 5, S12, S13).

Selection on unlinked recessive mutations:

When recombination rates are exceptionally high, the fate of mutations in nearly all populations (save near obligate selfers experiencing Muller's ratchet) is independent of linked deleterious mutations because recombination rapidly dissociates mutations from one another. With these high recombination rates (RRR ≥ 1), some threshold selfing rate is required to purge the genetic load when mutation rates are high ($U_{recessive}$ = 0.12) and mutations are severe (as in Kelly, 2007; Lande *et al.*, 1994). Below this threshold, the prevalence of recessive mutations exceeds predictions from single locus theory. This is because partial selfing generates correlations in homozygosity at unlinked loci, which prevents purging when multi-locus inbreeding depression is nearly lethal (i.e., the load cannot be purged when all selfed offspring die).

We find that partially selfing populations that cannot purge recessive mutations because of identity disequilibrium also experience a lower efficacy of selection against additive mutations. That is, when recombination rates are high (RRR ≥ 1) and highly deleterious recessive mutations are common ($U_{recessive}$ = 0.12, $s_{recessive}$ =0.3 or 0.9) the prevalence of additive mutations increases with an increase in selfing rate until populations can purge their load (red and orange lines in the two lower left panels of Figures S10C and S11C). Once the selfing rate exceeds this purging threshold, the prevalence of additive mutations begins decreasing with an increase in selfing rate, until Muller's Ratchet occurs in near obligate selfers. Sachdeva (2019) similarly found a greater increase in the unlinked additive load in partially selfing populations in the presence of highly deleterious recessive mutations than in cases without these recessive mutations.

There are two key differences between the purging thresholds caused by correlations in homozygosity (i.e., identity disequilibrium) with *high* recombination rates and those caused by pseudo-overdominance with *low* recombination rates. First, the difference in the prevalence of recessive mutations on either side of the purging threshold is much larger when thresholds are driven by pseudo-overdominance than by identity disequilibrium (right panel of Figure S1A). Second, identity disequilibrium-driven thresholds only occur at the highest mutation rate when the fitness effects of deleterious mutations are high, whereas pseudo-overdominance-driven thresholds occur over all mutation rates and more frequently when the fitness effects of deleterious mutations are relatively low ($s_{recessive}$=0.015).

A little outcrossing goes a long way when recombination is common

At intermediate recombination rates (RRR ≥ 1), mildly deleterious mutations accumulate in near-obligate selfers but are removed by selection in outcrossers and mixed maters. The low effective recombination rate in predominant selfers causes selection against additive mutations at one site to both limit the efficacy of selection against other additive mutations and decrease neutral diversity at linked sites (i.e., increase background selection; Figures 2B, S3). By contrast, in mixed mating and outcrossing populations mutations rapidly recombine away from linked deleterious mutations, increasing the efficacy of selection (as seen in Charlesworth *et al.*, 1993a; Glémin, 2007; Glémin and Ronfort, 2013; Kamran-Disfani & Agrawal, 2014). Therefore, the weak empirical evidence for a decrease in the efficacy of selection in selfing populations may be partially attributable to the paucity of near obligate selfing in nature (Goodwillie *et al.*, 2005; Moeller *et al.*, 2017); that is, the outcrossing rate of "predominant selfers" may be large enough to maintain an efficacy of selection comparable to their outcrossing relatives.

As the recombination and mutation rates become more similar, the efficacy of selection decreases continuously with an increase in selfing rate. This is because, at these lower recombination rates, mixed maters, but not outcrossers, experience increased selective interference and background selection (Glémin, 2007; Glémin & Ronfort, 2013; Kamran-Disfani & Agrawal, 2014). Consistent with our results and others, Laenen *et al.* (2018) found that highly selfing (~0.9 selfing rate), but not mixed-mating (~0.8 selfing rate) populations of *Arabis alpina* have higher genetic load than outcrossing populations.

Selection against alleles linked to deleterious recessive mutations is more effective in partially selfing populations

The equilibrium frequency of haplotypes without a deleterious mutation, f_0, determines the strength of background selection and selective interference among linked deleterious mutations (Charlesworth *et al.*, 1993a). By removing rare recessive mutations, partial selfing increases f_0 and decreases the extent of background selection and selective interference. In contrast, the accumulation of many recessive mutations in outcrossers decreases f_0, lowering the efficacy of selection against linked deleterious mutations. This explains why outcrossers can accumulate more deleterious additive variants than selfers (Figure 4A), even without a transition to pseudo-overdominance. In other words, when the decrease in N_e due to segregating haplotypes with recessive deleterious variants in outcrossers exceeds the reduction in N_e due to the greater extent of background selection in selfers, selection is less effective in outcrossers.

The shift to pseudo-overdominance weakens the efficacy of selection

Despite increasing diversity at linked neutral sites (Gilbert *et al.*, 2020; Ohta and Kimura, 1970), pseudo-overdominance substantially decreases the efficacy of selection (Figures 4 and 5). We propose that, by sub-structuring a population into complementary haplotypes in repulsion, pseudo-overdominance effectively decreases the N_e that affects the efficacy of selection, as is generally predicted in subdivided populations (Whitlock, 2003). Because the pseudo-overdominant haplotypes form in low recombination regions, there is effectively no 'migration' of alleles between haplotypes (Charlesworth *et al.*, 2003; Charlesworth, 2006). Consequently, the N_e that determines the efficacy of selection against mildly deleterious additive mutations is a function of the number of genomes *within* a haplotype class. Although the frequency

of pseudo-overdominance in nature is unknown, a recent genome scan (Becher *et al.*, 2020) identified numerous genomic regions displaying signatures of associative overdominance (which can be caused by pseudo-overdominance) in flies and humans, and a recent review (Waller, 2021) compiled numerous lines of evidence suggesting pseudo-overdominance is common in plants.

Once pseudo-overdominant haplotypes emerge, additional recessive mutations are sheltered from selection and continue to accumulate, as is known for other cases of heterozygote advantage (Glémin *et al.*, 2001; Jay *et al.*, 2021; Mather & de Winton, 1941; van Oosterhout, 2009). This sheltered load can reinforce pseudo-overdominance because genomic regions which are rarely homozygous are free to accumulate additional recessive variants (Llaurens *et al.*, 2017), further increasing the strength of selection against individuals homozygous in these regions. Such a pattern has been shown for certain types of polymorphic inversions (Berdan *et al.*, 2021).

Selfing prevents the shift from background selection to pseudo-overdominance

The analytical theory derived here qualitatively matches results from our individual-based simulations and shows that by purging recessive mutations, partial selfing prevents a shift from purifying selection to pseudo-overdominance, and that recombination amplifies the effects of partial selfing on preventing the transition to pseudo-overdominance (Figure 2E). At a given partial selfing rate (i.e., selfing rate < 0.5), pseudo-overdominance becomes more likely when U_{del} is high and $s_{recessive}$ is low, as these parameter combinations make it harder to purge recessive mutations (Wang *et al.*, 1999). As populations experience a greater influx of deleterious recessive mutations, a higher selfing rate is needed to purge recessive mutations before pseudo-overdominant haplotypes emerge.

Caveats and future directions

The joint distribution of dominance and fitness effects

Mutations take selective and dominance coefficients from a poorly understood two-dimensional density function. The best methods to infer the distribution of fitness effects from polymorphism data (Keightley & Eyre-Walker, 2007) provide only crude estimates of this distribution. However, two of the best studies on the topic show that more recessive mutations are more deleterious (*Saccharomyces*, Agrawal & Whitlock, 2011; *Arabidopsis*, Huber *et al.*, 2018). Our chosen parameters, consisting of recessive mutations with selection coefficients much larger than $4Ns$=1, and additive mutations with selection coefficients closer to $4Ns$=1, capture the spirit of this result. Although, highly deleterious mutations are unlikely to be fully recessive (Crow, 1993; Mukai *et al.*, 1972; Phadnis and Fry, 2005), we note that most qualitative results found with complete recessivity, including the emergence of pseudo-overdominance, are also found when h = 0.1 (Figures S2B and S5A).

Where does empirical reality fall in our simulated parameter space?

An increase in the selfing rate can increase, decrease, or not affect the accumulation of mildly deleterious mutations, depending on recombination and mutation rates, as well as the joint distribution of dominance and fitness effects of new mutations. So, where in parameter space are organisms in the natural world?

In many taxa, the genome-wide per base-pair recombination and mutation rates are similar (i.e., the genome-wide relative recombination rate is approximately one or somewhat higher for most taxa). For example, the relative recombination rate from genome-wide estimates of mutation and recombination rates is approximately 0.85 in humans (Kong *et al.*, 2002; Tian *et al.*, 2019), 2.75 in *Drosophila melanogaster* (Comeron *et al.*, 2012; Keightley *et al.*, 2014), and 4.5 in *Arabidopsis thaliana* (Singer *et al.*, 2006; Weng *et al.*, 2019; Text S2). Thus, at first glance, parameters explored by our model likely straddle what is true in nature. However, these gross estimates, although instructive, do not map particularly cleanly onto our model. First, we model a deleterious mutation rate, while genome-wide estimates include neutral mutations, so this crude estimate of the relative recombination rate is likely an underestimate. Additionally, we assume a very specific distribution of dominance and selection coefficients that is unlikely to map well onto the actual 2D distribution of dominance and fitness effects of new mutations in a given species. Finally, both the deleterious mutation rate and the recombination rate can vary tremendously across the genome. As such, it is likely that different regions of the genome will experience different selective consequences of the shift to selfing.

Realistic genomic architecture

We assumed that recombination and mutation rates did not vary across the genome. In reality, however, genomes have heterogenous recombination and deleterious mutation rates (Gaut *et al.*, 2007; McVicker *et al.*, 2009; Slotte, 2014), and intragenomic variation in rates likely differs substantially across species. For example, recombination rates in the gene-rich center of the genome of the selfing nematode, *Caenorhabditis elegans*, are very low, with recombination events roughly evenly spread across the gene poor regions away from these gene clusters.

This negative covariation between gene density and recombination rate likely results in a low recombination rate relative to the deleterious mutation rate in functional genomic regions (Rockman & Kruglyak, 2009). As such, we may expect *C. elegans* to have a lower burden of deleterious mutations than its outcrossing relatives, all else equal. In contrast, many other organisms (e.g., rice, *Arabidopsis thaliana*, *Mimulus guttatus*; International Rice Project and Sasaki, 2005; Giraut *et al.*, 2011; Aeschbacher *et al.*, 2017) tend to recombine more in regions of high gene density, and therefore may functionally have a higher relative recombination rate than inferred from genome-wide estimates. In such taxa, selfing will likely result in an increased number of additive mildly deleterious mutations throughout the genome.

Demographic history

Beyond the genomic consequences of selfing *per se*, shifts to selfing can lower N_e due to associated shifts in demography. For example, selfing is often associated with colonization of and rapid expansion in islands, disturbed, or other marginal habitats (Baker, 1955). As such, selfers may suffer a more severe expansion load (Peischl et al., 2013, 2015) than outcrossers. However, demographic changes such as population expansion and contraction have more influence on recessive than additive mutations, making their effects on (partially) selfing populations likely limited (Balick *et al.*, 2015;

Kirkpatrick & Jarne, 2000; Peischl *et al.*, 2015). Integration of both the genetic and demographic consequences of the mating system would better predict differences in the genetic load across mating systems.

Conclusions

We highlight the multifaceted ways selfing affects the efficacy of selection, and show it to be driven by interactions among dominance coefficients and the rates of selfing, recombination and mutation. We find that selection is more effective in the mating system that minimizes Hill-Robertson interference under the specified parameters. That is, selection is more effective in selfers (relative to outcrossers) when their purging of recessive mutations decreases Hill-Robertson interference more than the reduction in effective recombination increases it.

Data availability

All SLiM scripts, scripts for analysis and figures, and seeds used to run simulations are available on Dryad at doi: https://doi.org/10.7291/D16D6W

Author contributions

S.A.S. and Y.B. conceived the project. S.A.S. wrote, ran and analyzed simulations. S.P. derived the analytical models. S.A.S. wrote the first manuscript draft, and S.A.S., S.P., D.M., and Y.B. contributed to the final version.

Funding statement

This project was funded by National Science Foundation DEB #1754246 awarded to D.M. and Y.B.

Conflict of interest: The authors declare no conflict of interest.

Acknowledgments

We would like to thank Stephen Wright, Kimberly Gilbert, and members of the Brandvain and McGaugh labs at the University of Minnesota for comments on early drafts.

References

Abu Awad, D., & Roze, D. (2018). Effects of partial selfing on the equilibrium genetic variance, mutation load, and inbreeding depression under stabilizing selection. *Evolution*, 72, 751–769. https://doi.org/10.1111/evo.13449

Aeschbacher, S., Selby, J. P., Willis, J. H., & Coop, G. (2017). Population-genomic inference of the strength and timing of selection against gene flow. *Proceedings of the National Academy of Sciences*, 114, 7061–7066. https://doi.org/10.1073/pnas.1616755114

Agrawal, A. F., & Whitlock, M. C. (2011). Inferences about the distribution of dominance drawn from yeast gene knockout data. *Genetics*, 187, 553–566. https://doi.org/10.1534/genetics.110.124560

Arunkumar, R., Ness, R. W., Wright, S. I., & Barrett, S. C. H. (2015). The evolution of selfing is accompanied by reduced efficacy of selection and purging of deleterious mutations. *Genetics*, 199, 817–829. https://doi.org/10.1534/genetics.114.172809

Assaf, Z. J., Petrov, D. A., & Blundell, J. R. (2015). Obstruction of adaptation in diploids by recessive, strongly deleterious alleles. *Proceedings of the National Academy of Sciences*, 112, E2658–66. https://doi.org/10.1073/pnas.1424949112

Baker, H. G. (1955). Self-compatibility and establishment after "long-distance" dispersal. *Evolution*, 9, 347. https://doi.org/10.2307/2405656

Balick, D. J., Do, R., Cassa, C. A., Reich, D., & Sunyaev, S. R. (2015). Dominance of deleterious alleles controls the response to a population bottleneck. *PLoS Genetics*, 11, e1005436. https://doi.org/10.1371/journal.pgen.1005436

Bataillon, T., & Kirkpatrick, M. (2000). Inbreeding depression due to mildly deleterious mutations in finite populations: size does matter. *Genetical Research*, 75, 75–81. https://doi.org/10.1017/S0016672399004048

Becher, H., Jackson, B. C., & Charlesworth, B. (2020). Patterns of genetic variability in genomic regions with low rates of recombination. *Current Biology*, 30, 94–100.e3. https://doi.org/10.1016/j.cub.2019.10.047

Berdan, E. L., Blanckaert, A., Butlin, R. K., & Bank, C. (2021). Deleterious mutation accumulation and the long-term fate of chromosomal inversions. *PLoS Genetics*, 17, e1009411. https://doi.org/10.1371/journal.pgen.1009411

Brandvain, Y., Kenney, A. M., Flagel, L., Coop, G., & Sweigart, A. L. (2014). Speciation and introgression between Mimulus nasutus and Mimulus guttatus. *PLoS Genetics*, 10, e1004410. https://doi.org/10.1371/journal.pgen.1004410

Caballero, A., & Hill, W. G. (1992). Effects of partial inbreeding on fixation rates and variation of mutant genes. *Genetics*, 131, 493–507. https://doi.org/10.1093/genetics/131.2.493

Charlesworth, B. (1992). Evolutionary rates in partially self-fertilizing species. *American Naturalist*, 140, 126–148. https://doi.org/10.1086/285406

Charlesworth, D. (2006). Balancing selection and its effects on sequences in nearby genome regions. *PLoS Genetics*, 2, e64. https://doi.org/10.1371/journal.pgen.0020064

Charlesworth, B., & Charlesworth, D. (1997). Rapid fixation of deleterious alleles can be caused by Muller's ratchet. *Genetical Research*, 70, 63–73. https://doi.org/10.1017/S0016672397002899

Charlesworth, B., Charlesworth, D., & Barton, N. H. (2003). The effects of genetic and geographic structure on neutral variation. *Annual Review of Ecology, Evolution, and Systematics*, 34, 99–125. https://doi.org/10.1146/annurev.ecolsys.34.011802.132359

Charlesworth, B., Morgan, M. T., & Charlesworth, D. (1993a). The effect of deleterious mutations on neutral molecular variation. *Genetics*, 134, 1289–1303. https://doi.org/10.1093/genetics/134.4.1289

Charlesworth, D., Morgan, M. T., & Charlesworth, B. (1993b). Mutation accumulation in finite populations. *Journal of Heredity*, 84, 321–325. https://doi.org/10.1093/oxfordjournals.jhered.a111351

Charlesworth, D., & Willis, J. H. (2009). The genetics of inbreeding depression. *Nature Reviews Genetics*, 10, 783–796. https://doi.org/10.1038/nrg2664

Charlesworth, D., & Wright, S. I. (2001). Breeding systems and genome evolution. *Current Opinion in Genetics and Development*, 11, 685–690. https://doi.org/10.1016/S0959-437X(00)00254-9

Comeron, J. M., Ratnappan, R., & Bailin, S. (2012). The many landscapes of recombination in Drosophila melanogaster. *PLoS Genetics*, 8, e1002905. https://doi.org/10.1371/journal.pgen.1002905

Crow, J. F. (1993). Mutation, mean fitness, and genetic load. Oxford Surv. *Evolutionary Biology*, 9, 3–42.

Cutter, A. D., & Payseur, B. A. (2003). Rates of deleterious mutation and the evolution of sex in Caenorhabditis. *Journal of Evolutionary Biology*, 16, 812–822. https://doi.org/10.1046/j.1420-9101.2003.00596.x

Do, R., Balick, D., Li, H., Adzhubei, I., Sunyaev, S., & Reich, D. (2015). No evidence that selection has been less effective at removing deleterious mutations in Europeans than in Africans. *Nature Genetics*, 47, 126–131. https://doi.org/10.1038/ng.3186

Escobar, J. S., Cenci, A., Bolognini, J., Haudry, A., Laurent, S., David, J., & Glémin, S. (2010). An integrative test of the dead-end hypothesis of selfing evolution in Triticeae (Poaceae). *Evolution*, 64, 2855–2872. https://doi.org/10.1111/j.1558-5646.2010.01045.x

Gaut, B. S., Wright, S. I., Rizzon, C., Dvorak, J., & Anderson, L. K. (2007). Recombination: an underappreciated factor in the evolution of plant genomes. *Nature Reviews Genetics*, 8, 77–84. https://doi.org/10.1038/nrg1970

Gilbert, K. J., Pouyet, F., Excoffier, L., & Peischl, S. (2020). Transition from background selection to associative overdominance promotes diversity in regions of low recombination. *Current Biology*, 30, 101–107. https://doi.org/10.1016/j.cub.2019.11.063

Gioti, A., Stajich, J. E., & Johannesson, H. (2013). Neurospora and the dead-end hypothesis: genomic consequences of selfing in the model genus. *Evolution*, 67, 3600–3616. https://doi.org/10.1111/evo.12206

Giraut, L., Falque, M., Drouaud, J., Pereira, L., Martin, O. C., & Mézard C. (2011). Genome-wide crossover distribution in Arabidopsis thaliana meiosis reveals sex-specific patterns along chromosomes. *PLoS Genetics*, 7, e1002354. https://doi.org/10.1371/journal.pgen.1002354

Glémin, S. (2007). Mating systems and the efficacy of selection at the molecular level. *Genetics*, 177, 905–916. https://doi.org/10.1534/genetics.107.073601

Glémin, S., Bataillon, T., Ronfort, J., Mignot, A., & Olivieri, I. (2001). Inbreeding depression in small populations of self-incompatible plants. *Genetics*, 159, 1217–1229. https://doi.org/10.1093/genetics/159.3.1217

Glémin, S., and N. Galtier. (2012). Genome evolution in outcrossing versus selfing versus asexual species. Pp. 311–335 *in* M. Anisimova, ed. *Evolutionary Genomics: Methods in Molecular biology (Methods and Protocols)*, vol 855. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-61779-582-4_11

Glémin, S., & Ronfort, J. (2013). Adaptation and maladaptation in selfing and outcrossing species: new mutations versus standing variation. *Evolution*, 67, 225–240. https://doi.org/10.1111/j.1558-5646.2012.01778.x

Goodwillie, C., Kalisz, S., & Eckert, C. G. (2005). The evolutionary enigma of mixed mating systems in plants: Occurrence, theoretical explanations, and empirical evidence. *Annual Review of Ecology, Evolution, and Systematics*, 36, 47–79. https://doi.org/10.1146/annurev.ecolsys.36.091704.175539

Goyal, S., Balick, D. J., Jerison, E. R., Neher, R. A., Shraiman, B. I., & Desai, M. M. (2012). Dynamic mutation–selection balance as an evolutionary attractor. *Genetics*, 191, 1309–1319. https://doi.org/10.1534/genetics.112.141291

Grant, V. (1981). *Plant Speciation*. Columbia University Press, New York, NY. https://doi.org/10.7312/gran92318

Gravel, S. (2016). When is selection effective?. *Genetics*, 203, 451–462. https://doi.org/10.1534/genetics.115.184630

Haag-Liautard, C., Dorris, M., Maside, X., Macaskill, S., Halligan, D. L., Houle, D., Charlesworth, B., & Keightley, P. D. (2007). Direct estimation of per nucleotide and genomic deleterious mutation rates in Drosophila. *Nature*, 445, 82–85. https://doi.org/10.1038/nature05388

Haller, B. C., Galloway, J., & Kelleher, J. (2019). Tree-sequence recording in SLiM opens new horizons for forward-time simulation of whole genomes. *Molecular Ecology*, 19, 552–566. https://doi.org/10.1111/1755-0998.12968

Haller, B. C., & Messer, P. W. (2019). SLiM 3: Forward genetic simulations beyond the Wright-Fisher model. *Molecular Biology and Evolution*, 36, 632–637. https://doi.org/10.1093/molbev/msy228

Hanschen, E. R., Herron, M. D., Wiens, J. J., Nozaki, H., & Michod, R. E. (2018). Repeated evolution and reversibility of self-fertilization in the volvocine green algae. *Evolution*, 72, 386–398. https://doi.org/10.1111/evo.13394

Haudry, A., Cenci, A., Guilhaumon, C., Paux, E., Poirier, S., Santoni, S., David, J., & Glémin S. (2008). Mating system and recombination affect molecular evolution in four Triticeae species. *Genetical Research*, 90, 97–109. https://doi.org/10.1017/S0016672307009032

Hazzouri, K. M., Escobar, J. S., Ness, R. W., Killian Newman, L., Randle, A. M., Kalisz, S., & Wright, S. I. (2012). Comparative population genomics in Collinsia sister species reveals evidence for reduced effective population size, relaxed selection, and evolution of biased gene conversion with an ongoing mating system shift. *Evolution*, 67(5), 1263–1278. https://doi.org/10.1111/evo.12027

Henn, B. M., Botigué L. R., Bustamante, C. D., Clark, A. G., & Gravel, S. (2015). Estimating the mutation load in human genomes. *Nature Reviews Genetics*, 16, 333–343. https://doi.org/10.1017/S0016672307009032

Huber, C. D., Durvasula, A., Hancock, A. M., & Lohmueller, K. E. (2018). Gene expression drives the evolution of dominance. *Nature Communications*, 9, 2750. https://doi.org/10.1017/S0016672307009032

International Rice Genome Sequencing Project, & Sasaki, T. (2005). The map-based sequence of the rice genome. *Nature*, 436, 793–800. https://doi.org/10.1038/nature03895

Jarne, P., & Auld, J. R. (2006). Animals mix it up too: The distribution of self-fertilization among hermaphroditic animals. *Evolution*, 60, 1816–1824. https://doi.org/10.1111/j.0014-3820.2006.tb00525.x

Jay, P., Chouteau, M., Whibley, A., Bastide, H., Parrinello, H., Llaurens, V., & Joron, M. (2021). Mutation load at a mimicry supergene sheds new light on the evolution of inversion polymorphisms. *Nature Genetics*, 53, 288–293. https://doi.org/10.1111/j.0014-3820.2006.tb00525.x

Kamran-Disfani, A., & Agrawal, A. F. (2014). Selfing, adaptation and background selection in finite populations. *Journal of Evolutionary Biology*, 27, 1360–1371. https://doi.org/10.1111/jeb.12343

Keightley, P. D., & Eyre-Walker, A. (2007). Joint inference of the distribution of fitness effects of deleterious mutations and population demography based on nucleotide polymorphism frequencies. *Genetics*, 177, 2251–2261. https://doi.org/10.1534/genetics.107.080663

Keightley, P. D., Ness, R. W., Halligan, D. L., & Haddrill, P. R. (2014). Estimation of the spontaneous mutation rate per nucleotide site in a Drosophila melanogaster full-sib family. *Genetics*, 196, 313–320. https://doi.org/10.1534/genetics.113.158758

Kelleher, J., Etheridge, A. M., & McVean, G. (2016). Efficient coalescent simulation and genealogical analysis for large sample sizes. *PLoS Computational Biology*, 12, e1004842. https://doi.org/10.1371/journal.pcbi.1004842

Kelly, J. K. (2007). Mutation–selection balance in mixed mating populations. *Journal of Theoretical Biology*, 246, 355–365. https://doi.org/10.1016/j.jtbi.2006.12.030

Kim, B. Y., Huber, C. D., & Lohmueller, K. E. (2018). Deleterious variation shapes the genomic landscape of introgression. *PLoS Genetics*, 14, e1007741. https://doi.org/10.1371/journal.pgen.1007741

Kirkpatrick, M., & Jarne, P. (2000). The effects of a bottleneck on inbreeding depression and the genetic load. *American Naturalist*, 155, 154–167. https://doi.org/10.1086/303312

Kondrashov, A. S. (1995). Contamination of the genome by very slightly deleterious mutations: why have we not died 100 times over?. *Journal of Theoretical Biology*, 175, 583–594. https://doi.org/10.1006/jtbi.1995.0167

Kong, A., Gudbjartsson, D. F., Sainz, J., Jonsdottir, G. M., Gudjonsson, S. A., Richardsson, B., Sigurdardottir, S., Barnard, J., Hallbeck, B., Masson, G., Shlien, A., Palsson, S. T., Frigge, M. L., Thorgeirsson, T. E., Gulcher, J. R., & Stefansson, K. (2002). A high-resolution recombination map of the human genome. *Nature Genetics*, 31, 241–247. https://doi.org/10.1006/jtbi.1995.0167

Laenen, B., Tedder, A., Nowak, M. D., Toräng P., Wunder, J., Wötzel S., Steige, K. A., Kourmpetis, Y., Odong, T., Drouzas, A. D., Bink, M. C. A. M., Ågren J., Coupland, G., & Slotte, T. (2018). Demography and mating system shape the genome-wide impact of purifying selection in Arabis alpina. *Proceedings of the National Academy of Sciences*, 115, 816–821. https://doi.org/10.1073/pnas.1707492115

Lande, R., & Schemske, D. W. (1985). The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. *Evolution*, 39, 24. https://doi.org/10.2307/2408514

Lande, R., Schemske, D. W., & Schultz, S. T. (1994). High inbreeding depression, selective interference among loci, and the threshold selfing rate for purging recessive lethal mutations. *Evolution*, 48, 965–978. https://doi.org/10.1111/j.1558-5646.1994.tb05286.x

Llaurens, V., Whibley, A., & Joron, M. (2017). Genetic architecture and balancing selection: the life and death of differentiated variants. *Molecular Ecology*, 26, 2430–2448. https://doi.org/10.1111/mec.14051

Lohmueller, K. E. (2014). The distribution of deleterious genetic variation in human populations. *Current Opinion in Genetics and Development*, 29, 139–146. https://doi.org/10.1016/j.gde.2014.09.005

Lynch, M. (2010). Evolution of the mutation rate. *Trends in Genetics*, 26, 345–352. https://doi.org/10.1016/j.tig.2010.05.003

Mather, K., & de Winton, D. (1941). Adaptation and counter-adaptation of the breeding system in Primula. *Ann. Bot*, 5, 297–311

McVean, G. A., & Charlesworth, B. (2000). The effects of Hill-Robertson interference between weakly selected mutations on patterns of molecular evolution and variation. *Genetics*, 155, 929–944. https://doi.org/10.1093/genetics/155.2.929

McVicker, G., Gordon, D., Davis, C., & Green, P. (2009). Widespread genomic signatures of natural selection in hominid evolution. *PLoS Genetics*, 5, e1000471. https://doi.org/10.1371/journal.pgen.1000471

Moeller, D. A., Briscoe Runquist, R. D., Moe, A. M., Geber, M. A., Goodwillie, C., Cheptou, P. -O., Eckert, C. G., Elle, E., Johnston, M. O., Kalisz, S., Ree, R. H., Sargent, R. D., Vallejo-Marin, M., & Winn, A. A. (2017). Global biogeography of mating system variation in seed plants. *Ecol. Lett*, 20, 375–384. https://doi.org/10.1111/ele.12738

Mukai, T., Chigusa, S. I., Mettler, L. E., & Crow, J. F. (1972). Mutation rate and dominance of genes affecting viability in Drosophila melanogaster. *Genetics*, 72, 335–355. https://doi.org/10.1093/genetics/72.2.335

Ness, R. W., Siol, M., & Barrett, S. C. H. (2012). Genomic consequences of transitions from cross- to self-fertilization on the efficacy of selection in three independently derived selfing plants. *BMC Genomics*, 13, 611. https://doi.org/10.1186/1471-2164-13-611

Nordborg, M. (2000). Linkage disequilibrium, gene trees and selfing: an ancestral recombination graph with partial self-fertilization. *Genetics*, 154, 923–929. https://doi.org/10.1093/genetics/154.2.923

Ohta, T., & Kimura, M. (1970). Development of associative overdominance through linkage disequilibrium in finite populations. *Genetical Research*, 16, 165–177. https://doi.org/10.1017/S0016672300002391

Pálsson, S., & Pamilo, P. (1999). The effects of deleterious mutations on linked, neutral variation in small populations. *Genetics*, 153, 475–483. https://doi.org/10.1093/genetics/153.1.475

Peischl, S., Dupanloup, I., Kirkpatrick, M., & Excoffier, L. (2013). On the accumulation of deleterious mutations during range expansions. *Molecular Ecology*, 22, 5972–5982. https://doi.org/10.1111/mec.12524

Peischl, S., Kirkpatrick, M., & Excoffier, L. (2015). Expansion load and the evolutionary dynamics of a species range. *American Naturalist*, 185, E81–93. https://doi.org/10.1086/680220

Phadnis, N., & Fry, J. D. (2005). Widespread correlations between dominance and homozygous effects of mutations: implications for theories of dominance. *Genetics*, 171, 385–392. https://doi.org/10.1534/genetics.104.039016

Pollak, E. (1987). On the theory of partially inbreeding finite populations. I. Partial selfing. *Genetics*, 117, 353–360. https://doi.org/10.1093/genetics/117.2.353

Qiu, S., Zeng, K., Slotte, T., Wright, S., & Charlesworth, D. (2011). Reduced efficacy of natural selection on codon usage bias in selfing Arabidopsis and Capsella species. *Genome Biol. Evol*, 3, 868–880. https://doi.org/10.1093/gbe/evr085

Rockman, M. V., & Kruglyak, L. (2009). Recombinational landscape and population genomics of Caenorhabditis elegans. *PLoS Genetics*, 5, e1000419. https://doi.org/10.1371/journal.pgen.1000419

Roze, D. (2015). Effects of Interference Between Selected Loci on the Mutation Load, Inbreeding Depression, and Heterosis. *Genetics*, 201, 745–757. https://doi.org/10.1534/genetics.115.178533

Roze, D. (2016). Background selection in partially selfing populations. *Genetics*, 203, 937–957. https://doi.org/10.1534/genetics.116.187955

Roze, D., & Rousset, F. (2004). Joint effects of self-fertilization and population structure on mutation load, inbreeding depression and heterosis. *Genetics*, 167, 1001–1015. https://doi.org/10.1534/genetics.103.025148

Sachdeva, H. (2019). Effect of partial selfing and polygenic selection on establishment in a new habitat. *Evolution*, 73, 1729–1745. https://doi.org/10.1111/evo.13812

Schultz, S. T., Lynch, M., & Willis, J. H. (1999). Spontaneous deleterious mutation in Arabidopsis thaliana. *Proceedings of the National Academy of Sciences*, 96, 11393–11398. https://doi.org/10.1073/pnas.96.20.11393

Singer, T., Fan, Y., Chang, H. -S., Zhu, T., Hazen, S. P., & Briggs, S. P. (2006). A high-resolution map of Arabidopsis recombinant inbred lines by whole-genome exon array hybridization. *PLoS Genetics*, 2, e144. https://doi.org/10.1371/journal.pgen.0020144

Slotte, T. (2014). The impact of linked selection on plant genomic variation. *Brief. Funct. Genomics*, 13, 268–275. https://doi.org/10.1093/bfgp/elu009

Slotte, T., Foxe, J. P., Hazzouri, K. M., & Wright, S. I. (2010). Genome-wide evidence for efficient positive and purifying selection in Capsella grandiflora, a plant species with a large effective population size. *Molecular Biology and Evolution*, 27, 1813–1821. https://doi.org/10.1093/molbev/msq062

Slotte, T., Hazzouri, K. M., ÅgrenJ. A.J. A., Koenig, D., Maumus, F., Guo, Y. -L., Steige, K., Platts, A. E., Escobar, J. S., Newman, L. K., Wang, W., Mandáková T.T., Vello, E., Smith, L. M., Henz, S. R., Steffen, J., Takuno, S., Brandvain, Y., Coop, G., … Wright, S. I. (2013). The Capsella rubella genome and the genomic consequences of rapid mating system evolution. *Nature Genetics*, 45, 831–835. https://doi.org/10.1038/ng.2669

Stebbins, G. L. 1974. *Flowering plants: evolution above the species level*. Harvard University Press, Cambridge, MA. https://doi.org/10.4159/harvard.9780674864856

Tian, X., Browning, B. L., & Browning, S. R. (2019). Estimating the Genome-wide Mutation Rate with Three-Way Identity by Descent. *American Journal of Human Genetics*, 105, 883–893. https://doi.org/10.1016/j.ajhg.2019.09.012

Uyenoyama, M. K., & Waller, D. M. (1991). Coevolution of self-fertilization and inbreeding depression. I. Mutation-selection balance at one and two loci. *Theoretical Population Biology*, 40, 14–46. https://doi.org/10.1016/0040-5809(91)90045-H

Valluru, R., Gazave, E. E., Fernandes, S. B., Ferguson, J. N., Lozano, R., Hirannaiah, P., Zuo, T., Brown, P. J., Leakey, A. D. B., Gore, M. A., Buckler, E. S., & Bandillo, N. (2019). Deleterious Mutation Burden and Its Association with Complex Traits in Sorghum (Sorghum bicolor). *Genetics*, 211, 1075–1087. https://doi.org/10.1534/genetics.118.301742

van Oosterhout, C. (2009). A new theory of MHC evolution: beyond selection on the immune genes. *Proceedings Biological Sciences*, 276, 657–665. https://doi.org/10.1098/rspb.2008.1299

Waller, D. M. (2021). Addressing Darwin's dilemma: Can pseudo-overdominance explain persistent inbreeding depression and load?. *Evolution*, 75, 779–793. https://doi.org/10.1111/evo.14189

Wang, J., Hill, W. G., Charlesworth, D., & Charlesworth, B. (1999). Dynamics of inbreeding depression due to deleterious mutations in small populations: mutation parameters and inbreeding rate. *Genetical Research*, 74, 165–178. https://doi.org/10.1017/S0016672399003900

Weir, B. S., & Cockerham, C. C. (1973). Mixed self and random mating at two loci. *Genetical Research*, 21, 247–262. https://doi.org/10.1017/S0016672300013446

Weng, M. -L., Becker, C., Hildebrandt, J., Neumann, M., Rutter, M. T., Shaw, R. G., Weigel, D., & Fenster, C. B. (2019). Fine-grained analysis of spontaneous mutation spectrum and frequency in *Arabidopsis thaliana*. *Genetics*, 211, 703–714. https://doi.org/10.1534/genetics.118.301721

Whitlock, M. C. (2003). Fixation probability and time in subdivided populations. *Genetics*, 164, 767–779. https://doi.org/10.1093/genetics/164.2.767

Willis, J. H. (1999). Inbreeding load, average dominance and the mutation rate for mildly deleterious alleles in *Mimulus guttatus*. *Genetics*, 153, 1885–1898. https://doi.org/10.1093/genetics/153.4.1885

Wright, S. I., Kalisz, S., & Slotte, T. (2013). Evolutionary consequences of self-fertilization in plants. *Proceedings Biological Sciences*, 280, 20130133. https://doi.org/10.1098/rspb.2013.0133

Wright, S. I., Ness, R. W., Foxe, J. P., & Barrett, S. C. H. (2008). Genomic consequences of outcrossing and selfing in plants. *International Journal of Plant Sciences*, 169, 105–118. https://doi.org/10.1086/523366

Zhao, L., & Charlesworth, B. (2016). Resolving the conflict between associative overdominance and background selection. *Genetics*, 203, 1315–1334. https://doi.org/10.1534/genetics.116.188912