Limits to adaptation in partially selfing species

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Running Head: Adaptation limits in partial selfers

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Abstract

Single locus theory indicates that selfing species are more able than outcrossing ones to fix emerging recessive beneficial mutations, as they are not masked as heterozygotes. However, partially selfing organisms suffer from relaxed recombination, which reduces overall selection efficiency. Although the effect of linked deleterious alleles on adaptation has previously been studied, the extent to which multiple adaptations interfere in partially selfing organisms is currently unknown. We derive branching-process models to quantify the extent that emergence of a second beneficial allele is obstructed by an existing selective sweep. We consider both the potential loss of the second beneficial mutation if it has a weaker advantage than the first sweep (the 'stochastic interference effect'), and also the potential replacement of the first sweep if the second mutant is fitter ('replacement effect'). Overall, the stochastic interference effect has a larger impact on preventing fixation of both adaptive alleles in highly selfing organisms, but the replacement effect can be stronger with multiple mutations. Interference has two opposing effects on Haldane's Sieve. First, recessive mutants are disproportionally likely to be lost, so it is more likely that only dominant mutations will emerge in outcrossers. Second, with frequent rates of adaptive evolution, outcrossing organisms are more able to fix weak beneficial mutations of any dominance value, contrary to the predictions of Haldane's Sieve. Our analysis shows that even under low rates of adaptive mutation, interference can be sufficiently strong to greatly limit adaptation in selfing organisms.

Introduction

Self-fertilisation - reproduction where both gametes arise from the same parent - has been one of the most frequently-observed transitions in nature. Self-fertilising species are widespread in angiosperms (Igic and Kohn 2006), some animals (Jarne and Auld 2006) and fungi (Billiard *et al.* 2011; Gioti *et al.* 2012). Selfing has immediate benefits, such as up to a two-fold transmission advantage (Fisher 1941) and reproductive assurance under mate limitation (Baker 1955, 1967).

Hence self-fertilisation should be able to rapidly evolve, unless countered by high levels of inbreeding depression (Lande and Schemske 1985). However, empirical studies usually find that selfing lineages are a 'dead end', since back-transitions to outcrossing are rare, and high extinction rates have been inferred from comparative studies of related selfing-outcrossing taxa (Igic *et al.* 2008; Goldberg *et al.* 2010; Wright and Barrett 2010; Wright *et al.* 2013). In addition, plenty of species display mixed-mating systems and even highly selfing species still outcrosse at a low rate, implying that even if selfing is beneficial overall, some outcrossing is desirable (Schemske and Lande 1985; Goodwillie *et al.* 2005). Self-fertilisation is posited to be detrimental in the long-term since the effective population size N_e is reduced at least by a factor $1/(1+F)$, for F the inbreeding coefficient (Pollak 1987; Charlesworth 1992; Caballero and Hill 1992). Furthermore, recombination is reduced by a factor $1-F$ (Golding and Strobeck 1980; Nordborg 2000). This joint reduction in both diversity and recombination can lead to a decrease in the efficacy of selection, so deleterious mutations accumulate more rapidly in selfing organisms, leading to population

extinction (Heller and Maynard Smith 1978; Lynch *et al.* 1995).

Whether this mechanism is a major cause of extinction of self-fertilising species is still under debate (reviewed in Glémin and Galtier (2012); Igic and Busch (2013)). Some sister-species comparisons of selfing-outcrossing taxa reveal evidence of increased mutation accumulation in selfers, as demonstrated with either increased nonsynonymous-to-synonymous polymorphism ratio (π_n/π_s) or weaker codon usage bias. Conversely, analyses of divergence rates generally do not show evidence for relaxed selection. Part of the reason for this lack of evidence could arise due to the recent transitions to selfing in most of these species, as explicitly demonstrated in *Capsella rubella* by Brandvain *et al.* (2013), leaving little time for mutation accumulation to act.

Less investigated is the idea that selfing reduces the ability for a species to adapt, especially in a new environment, though it was the one initially formulated by Stebbins (1957). For adaptation at a single locus, selfing organisms are more likely than outcrossers to fix new recessive adaptive mutations (Haldane 1927; Charlesworth 1992) but are generally less efficient in adapting from standing variation (Glémin and Ronfort 2013). Yet the effect of adaptation across multiple sites in partially selfing organisms has received much less attention. Of particular interest is how the reduction in recombination in highly selfing organisms impedes the overall rate of adaptation. A well-established phenomenon in low-recombining genomes is the 'Hill-Robertson effect', where selection at linked loci reduces the efficacy of selection acting on a specific mutation (Hill and Robertson 1966; Charlesworth *et al.* 2009). Outcrossing can therefore break down these effects and unite beneficial mutations from different individuals into the same genome, greatly increasing the rate of adaptation (Fisher 1930; Muller

1932; Felsenstein 1974; Otto and Feldman 1997).

Historically, the effect of advantageous mutations on mating-system evolution has been neglected since most observable spontaneous mutations are deleterious in partial selfers (Slotte 2014). Analysis using divergence data from the *Arabidopsis* genome shows low number of genes acting under adaptive selection (Barrier *et al.* 2003; Clark *et al.* 2007; Slotte *et al.* 2010, 2011), and only ∼1% of genes with signatures of positive selection in *Medicago truncatula* (Paape *et al.* 2013). These analyses reflect broader findings that the proportion of adaptive substitutions in the coding regions of selfing plants are not significantly different from zero (Gossmann *et al.* 2010; Hough *et al.* 2013). However, widespread local adaptation to climate in *Arabidopsis* is observed (Fournier-Level *et al.* 2011; Hancock *et al.* 2011; Ågren *et al.* 2013), which is expected to leave a weaker signature on the genome (Slotte 2014), and the power to detect local selection can also increase once demography is accounted for (Huber *et al.* 2014).

Finally, both outcrossing and selfing domesticated plant and crop species can also be used to demonstrate recent adaptation. Ronfort and Glémin (2013) showed how adaptive traits obtained from quantitative trait loci, tended to be dominant in outcrossers and recessive in selfers, in line with 'Haldane's sieve'. Hence while beneficial mutations may not be as frequent as deleterious alleles, it is clear that they arise often enough to impact on evolution of self-fertilising species. Furthermore, due to the reduced recombination rate in selfers, adaptive alleles should interfere with a greater region of the genome than in outcrossing organisms.

Recently, Hartfield and Glémin (2014) investigated the effect of a linked deleterious mutation on a selective sweep, and demonstrated how beneficial alleles

needed to be more recessive than 1/2 in order for selfing to be beneficial over obligate outcrossing. This model showed a clear example of how breaking apart selection interference at linked sites provided greater benefits to outcrossing and mixed-mating systems over complete self-fertilisation. A multi-locus simulation study by Kamran-Disfani and Agrawal (2014) verified that background selection impedes genome-wide adaptation rates in selfing organisms, but these costs generally do not completely nullify the transmission advantage of selfing unless pollen discounting is high, or beneficial mutations are strong and frequent. These studies clearly showed how linkage to deleterious mutations can limit adaptation in selfers, however it remains an open question as to what extent multiple beneficial mutations interfere in highly selfing species.

This article will extend previous analyses to consider how linkage between several beneficial mutations at linked sites affects their emergence in partially selfing species. Classic two-locus analytical models of the Hill-Robertson effect are altered to take dominance and selfing into account, then examined to quantify how adaptation is limited in partially selfing organisms. We also discuss a heuristic extension of the model of Weissman and Barton (2012) to determine the effect of mating system when many sweeps are present.

Outline of the problem

General modelling approach

The goal of this paper is to determine how the effect of existing beneficial mutations at linked loci impedes the emergence of novel adaptive alleles in partially

selfing organisms. We will mostly consider two locus models to ensure tractability. At a first locus, consider a beneficial mutation with selective coefficient s_1, so the fitness of individuals carrying it is $1 + h_1 s_1$ in heterozygote form, and $1 + s_1$ in homozygote form. Similarly at the second locus, the fitness of individuals carrying the beneficial mutation is $1 + h_2 s_2$ in heterozygotes and $1 + s_2$ in homozygotes. We denote the four haplotypes 00, 10, 01 and 11 and we assume that fitness is additive. Hence an individual composed of the two haplotypes 10 and 11 will have fitness $1 + s_1 + h_2 s_2$.

The trajectory of a beneficial mutation can be decomposed into (i) a initial stochastic phase at low frequency where extinction by drift is likely; (ii) conditioned on escaping initial extinction (i.e. emergence) on a quasi-deterministic trajectory until high frequency; (iii) a second stochastic phase at very high frequency where fixation is almost certain (Kaplan *et al.* 1989). If two mutations segregate simultaneously at low frequency in the stochastic zone they do not influence each other and their fates can be assumed to be independent. However, as soon as one mutant has emerged and start to sweep quasi-deterministically it affects the fate of the other mutation. When considering only one mutation, once it has emerged its ultimate fixation is certain (which corresponds to the branching process approximation). The probability of fixation is thus equal to the probability of emergence. However, when two (or more) mutations interfere, a mutation that has emerged can be replaced by a competing mutation and ultimately lost, which is well known in asexual species as the 'clonal interference' effect (Gerrish and Lenski 1998). If so, the probability of fixation can be lower than the probability of emergence. Under tight linkage, so under high selfing rate, this process has to be taken into account.

We assume that mutation 1 is the first to escape extinction by drift (although it could have been the second to arise), so is sweeping through the population. Its trajectory can be modelled using deterministic equations. The whole process is thus conditioned on mutation 1 having escaped extinction by drift initially. Without interference, the probability of fixation of the two mutations, P_{12}^*, is simply equal to the single-locus probability of fixation of the second mutation, given by:

$$P_{12}^* = P_2 = 2s_2 \frac{h_2 + F - h_2 F}{1 + F} \tag{1}$$

(Caballero and Hill 1992; Charlesworth 1992). Note that P_1 does not appear here because we conditioned on mutation 1 having emerged. Equation 1 leads to the classical result that the probability of fixation is higher under outcrossing than under selfing when $h_2 > 1/2$. However, more generally, the emergence of mutation 2 depends on the genetic background the mutation appears on and on the rate of switch between backgrounds through recombination, which is the cause of the 'Hill-Robertson' effects we wish to model (Hill and Robertson 1966). Denoting the actual fixation probability of both mutants as P_{12}, then the degree of interference R is the ratio P_{12}/P_{12}^*.

In the simplifying case $h_1 = h_2$, the dynamics of how the second mutation emerges will differ depending on whether $s_1 < s_2$ or vice versa (see below for more general conditions). If $s_2 < s_1$, the dynamics of the first mutation is not influenced by the second and cannot be replaced. We thus only need to compute the probability of emergence of the second mutation. This second mutation is likely to go extinct unless it appears or recombines onto the first sweep background.

Barton (1995) outlined a general model to determine this effect for a haploid case. We will demonstrate how diploidy and selfing can be accounted for in that model and subsequently compute Π, the relative reduction in emergence probability due to interference.

If $s_1 < s_2$, then the second mutation can replace the first one if it arises on the wild-type background and if no successful recombinant occurs. We can calculate the probability of this effect, by adjusting the analysis of Hartfield and Glémin (2014) to consider two beneficial mutations. We thus need to subtract to Π the probability that mutation 2 replaces mutation 1 once it has emerged, denoted by Π_{rep}. In the general case, the degree of interference will be given by:

$$R = \Pi - \Pi_{rep} \tag{2}$$

In practice, R must be determined for mutation 2 arising when mutation 1 is at a given frequency p, and then averaged over the whole possible time of origin of the second mutation (see below for more formal definitions of these conditions).

A simple first analysis: complete selfing versus outcrossing with free recombination

Before deriving the full model, we can compare the two most extreme cases that can be easily investigated. Under outcrossing and free recombination, the fates of the two mutations are independent so that the probability of fixation of the second mutation, conditioned on the first having emerged, is simply the single locus probability of fixation given by Equation 1 with $F = 0$ (Haldane 1927). At the other extreme, with complete selfing recombination is suppressed and interference

is maximised. That is, if a second mutation appears in a selfing population, it can only fix if it appears on the same genetic background as the original selective sweep, which is present at frequency p. Previous theory (Hartfield and Otto 2011; Hartfield and Glémin 2014) on emergence in this scenario gives the probability of fixation in the double mutant as:

$$P_{2,self} = \frac{s_1(s_1 + s_2)}{ps_1 + s_2} \tag{3}$$

See, for example, Equation 7 of Hartfield and Glémin (2014) with $s_d = s_1$ and $s_a = s_1 + s_2$. The probability of fixation of both alleles thus involves integrating Equation 3 over the entire sweep, assuming that the second mutation arises at a time that is uniformly distributed during the first sweep:

$$\overline{P_{2,self}} = \frac{1}{\tau}\int_0^\tau pP_{2,s}(p(t))\mathrm{d}t \tag{4}$$

where τ is the duration of the first sweep. We can also solve Equation 4 over p from p_0 to $1 - p_0$; the term inside the integral is divided by $\mathrm{d}p/\mathrm{d}t = s_1p(1-p)$ to remove time dependence. Solving in the limit of large population size (i.e. $p_0 = 1/(2Ns_1) \to 0$) leads to $\overline{P_{2,self}} = s_2/2$ (see Supplementary Material 1): full linkage reduces the emergence probability by a half ($R = 1/2$). Intuitively, this can be explained by the fact that as population size increases, the deterministic phase of the first sweep becomes shorter compared to the initial and final stochastic phases ($\mathcal{O}(\frac{1}{s})$ vs $\mathcal{O}(\frac{\ln(2Ns)}{s})$; Ewing *et al.* (2011)). The second mutation thus occurs roughly half of the time during the initial stochastic phase where its probability of arising on the beneficial background, hence of emerging, is very low ($p \approx 0$ in Equation 4). Alternatively, it can appear half of the time during the last

stochastic phase were it almost always originates in the beneficial background and its probability of emerging is approximately s_2 ($p \approx 1$ in Equation 4). By comparing this result to that with outcrossing and free recombination ($2h_2s_2$), outcrossing is more able to fix both mutants if $h_2 > 1/4$, instead of $h_2 > 1/2$ without interference. However, the advantage to outcrossing may not be as high, since the true degree of inference depends on the strength of both mutations and the recombination rate. In addition, the degree of stochastic interference also depends on the flow of beneficial mutations, which depends on the mating system. We now turn to the full model to quantify exactly the stochastic interference effect.

Modelling Framework

Deriving the baseline reduction in emergence probability, Π

We first need to determine $\Pi(p)$, the reduction in the probability of emergence of the second mutation when it arises given the first is at frequency p. We use branching process methods for calculating mutation emergence if acting over multiple genetic backgrounds. In a seminal paper, Barton (1995) outlined how to calculate the emergence probability of a focal beneficial allele that changes between different backgrounds in a haploid population. If the probability of switching between backgrounds is of the same order as selection coefficients, s, and difference in emergence probability over background is of order s^2, Barton (1995) showed that the emergence probability of a novel beneficial allele in background i at time t, Q_i, verifies the following differential equation:

$$-\frac{\partial Q_i}{\partial t} = s_i Q_i + (\sum_j M_{i,j} Q_j - Q_i) - \frac{{Q_i}^2}{2} \tag{5}$$

where $M_{i,j}$ is the probability that offspring in background i moves to background j per generation. Barton (1995) subsequently used this framework to investigate the fixation probability of a second beneficial allele, given that it arises in close linkage to an existing sweep. In this case, the $M_{i.j}$ terms denote the probability that distinct haplotypes recombine to change the genetic background of the focal allele. We can modify these equations to determine the fixation probability of a novel beneficial allele, given that an existing sweep is present in frequency p, for a diploid partially-selfing population.

The first sweep arises and proceeds to increase in frequency over time according to classic population genetics theory. As in Barton (1995) its trajectory is assumed to be deterministic, and thus described by the following differential equation:

$$\frac{\mathrm{d}p}{\mathrm{d}t} = s_1 p(1-p)(F + h_1 - h_1 F + (1-F)(1-2h_1)p) + \mathcal{O}(s_1) \tag{6}$$

Furthermore, we can scale time by selection setting $T = s_1 t$ (Barton 1995).

Let $Q_1(p)$ denote the probability that the new allele fixes, given that it arises in linkage with the existing sweep (which is at frequency p), and $Q_2(p)$ if it appears on the wild-type (neutral) background. Furthermore, we denote the relative selective advantage of each haplotype (either containing both advantageous alleles, or the second allele only) by $\theta_1(p)$ and $\theta_2(p)$, which are given by (see Supplementary

Material 1 for the full calculation):

$$\begin{aligned}\theta_1(p) &= (F + h_2 - Fh_2)s_2 \\ &+ (1-p)(F + h_1 - Fh_1 + (1-F)(1-2h_1)p)s_1 \quad (7)\\ \theta_2(p) &= (F + h_2 - Fh_2)s_2 \\ &- p(F + h_1 - Fh_1 + (1-F)(1-2h_1)p)s_1 \quad (8)\end{aligned}$$

Equations 5 of Barton (1995), which gives the emergence probability of the new allele given it arises on a specific genetic background, can thus be modified as follows:

$$\begin{aligned}-\frac{\partial Q_1}{\partial T} &= -r(1-F)(1-p)(Q_1 - Q_2) + \theta_1(p)Q_1 - (1+F)\frac{Q_1^2}{2} \quad (9)\\ -\frac{\partial Q_2}{\partial T} &= -r(1-F)p(Q_2 - Q_1) + \theta_2(p)Q_2 - (1+F)\frac{Q_2^2}{2} \quad (10)\end{aligned}$$

where p verifies Equation 6. Equations 9 and 10 reflects that selfing reduces recombination by a factor $1-F$ (Golding and Strobeck 1980; Nordborg 2000) and increases drift by a factor $1/(1+F)$ (Pollak 1987; Charlesworth 1992; Caballero and Hill 1992). In order to simplify the analysis, we follow the approach of Barton (1995) and investigate the average fixation probability over haplotypes given the first sweep is at a certain frequency, defined as $\Pi = pQ_1 + (1-p)Q_2$, and the difference in emergence probability between the backgrounds, $\Delta = Q_1 - Q_2$. We also scale these terms by the probability of fixation of the second allele if unlinked, $(2s_2(F + h_2 - Fh_2))/(1+F)$, so Π lies between 0 and 1. We also introduce the rescaled parameters $\phi = s_2/s_1$ and $\rho = r/s_1$ to determine how the relative selective strengths and recombination rates affect allelic interference. We

thus obtain:

$$\frac{\partial \Pi}{\partial T} = H_2\phi(p(1-p)\Delta^2 - \Pi(1-\Pi)) \quad (11)$$

$$\frac{\partial \Delta}{\partial T} = \Delta(\rho(1-F) - K_1(1-2p) + H_2\phi(\Delta(1-2p) + 2\Pi - 1)) - K_1\Pi \quad (12)$$

where $H_2 = h_2 + F - h_2F$ and $K_1 = h_1 + F - h_1 + (1-F)(1-2h_1)p$.

For a given time of origin of the second mutation, t, the joint solution of this this system and Equation 6, 11 and 12 gives $\Pi(p(t))$. These equations must be solved numerically by, e.g., using the 'NDSolve' function in *Mathematica* (Wolfram Research, Inc. 2014). Alternatively, to remove the time dependence (∂t) and directly obtain $\Pi(p)$, we can divide both Equations 11 and 12 by $\mathrm{d}p/\mathrm{d}t$ (Equation 6). Boundary conditions can be found by looking at the behaviour of the system as $t \to \infty$ or $p \to 1$. In this case, we observe that $\Pi \to 1$, reflective of the fact that as the first sweep fixes, interference is not present as the second allele is certain to arise with the existing sweep. Hence the second allele's fixation probability is not reduced. Boundary conditions for Δ can be calculated by assuming $\phi \ll 1$ (as used in Barton (1995)) and $\partial\Delta/\partial T \to 0$ as $p \to 1$. In this case Δ tends to $(1-(1-F)h_1)/(1-(1-F)(h_1-\rho))$, which reflects the probability that the second allele can recombine onto the fitter background if appearing on a wild-type chromosome, otherwise it is guaranteed to be lost (Barton 1995). Although this condition assumes small ϕ, the system of equations appear to work well even with larger ϕ when compared to simulations.

Deriving the probability of sweep replacement, Π_{rep}

The previous analysis focussed primarily on the case where the second mutant is weaker than the first, hence not considering the possibility that the second sweep could replace the first. In that case, the probability of emergence is equal to the probability of fixation: $P_{12} = \Pi$. However, if selection acting on it is sufficiently strong then replacement is possible. We need to calculate the probability of such replacement occurring and subtract it from the baseline reduction Π. This probability can be calculated by altering the model of Hartfield and Glémin (2014), which investigated a deleterious allele hitchhiking with a sweep. In our case, the 'deleterious' allele is the wildtype allele at the first locus, and the 'advantageous' allele the second fitter sweep. Hartfield and Otto (2011) implemented a similar rescaling for a haploid model, while Yu and Etheridge (2010) provided a general stochastic algorithm for investigating this behaviour. By using the same conditions under which the model of Hartfield and Glémin (2014) is valid, we see that the second mutant can replace the first if:

1. $(h_2+F(1-h_2))s_2 > (1-(1-F)h_1)s_1$ and $(1-(1-F)h_2)s_2 > (h_1+F(1-h_1))s_1$;
2. The second mutation emerges on the wildtype background (with probability $1-p$);
3. No 'successful' recombinant arises during the sweep of the second mutation ('successful' meaning that the two beneficial alleles are placed together onto the same genetic background and become fixed).

Condition 1 ensures that no overdominance is present; if $h_1 = h_2 = 1/2$ both inequalities reduce to $s_2 > s_1$.

Noting P_{HH} the probability of hitchhiking of the wild allele at locus 1 by the beneficial mutation at locus 2, $P_{12}(p)$ can be written as:

$$\begin{aligned} P_{12} &= pQ_1(p) + (1-p)Q_2(p)(1-P_{HH}) \\ &= \Pi(p) - (1-p)(Q_2(p))P_{HH} \end{aligned} \tag{13}$$

so

$$\Pi_{rep}(p) = (1-p)(\Pi(p) - p\Delta(p))P_{HH} \tag{14}$$

where the relationship $Q_2(p) = \Pi(p) - p\Delta(p)$ is used in Equation 14.

$\Pi(p)$ and $\Delta(p)$ are given by Equations 11 and 12 but it is necessary to calculate P_{HH}. To do so we assume that the population is composed only of the haplotypes carrying just one sweep, 10 and 01, with the complete wild-type haplotype carrying no sweeps, 00, being quickly eliminated. We discuss when comparing the model to simulations when these assumptions are valid. We thus need to compute Δq, the change in frequency of the second sweep haplotype and the relative selective advantage of the recombinant haplotype carrying both sweeps, which we denote θ_3. We define q as the frequency of the second sweep haplotype to prevent confusion with p being the frequency of the first sweep haplotype. The derivation of Δq and θ_3 are given in Supplementary Material 1, and are given as:

$$\begin{aligned} \Delta q &= (1-q)q(((1-F)(q + h_1(1-2q)) - 1)s_1 \\ &+ (F + h_2 - Fh_2 + (1-F)(1-2h_2)q)s_2) \end{aligned} \tag{15}$$

$$\begin{aligned} \theta_3(q) &= q(1 - (1-F)q - h_1(1-F)(1-2q))s_1 \\ &+ (1-q)(F + h_2 - Fh_2 + (1-F)(1-2h_2)q)s_2 \end{aligned} \tag{16}$$

Following Hartfield and Glémin (2014), the emergence probability of the recombinant haplotype carrying both mutations were it to arise, P_d, is solution of:

$$\frac{\mathrm{d}P_d}{\mathrm{d}q} = \left(\theta_3(q)P_d(q) - \frac{1+F}{2}P_d(q)^2\right)/\Delta q \tag{17}$$

Equation 6 of Hartfield and Glémin (2014) is then used to calculate P_{HH}, for $\kappa(q) = q(1-q)r(1-F)P_d$:

$$P_{HH} = \exp\left(-\int_{p=0}^{p=1} \frac{2N\kappa(p)}{s_1 \mathrm{d}p/\mathrm{d}T}\right)\mathrm{d}p \tag{18}$$

which can be inserted into Equation 14. Note that P_{HH}, hence $\Pi_{rep}(p)$, is not defined for $s_2 \leq s_1$ and tends to 0 when s_2 tends to s_1. For completeness we can thus set $\Pi_{rep}(p) = 0$ for $s_2 \leq s_1$.

Integration over the sweep trajectory

To obtain the average effect of interference we need to consider all possible origins of the second mutation. The average R for mutation 2 arising uniformly in a long time interval $[T_0, T_1]$ spanning the sweep of mutation 1 is given by:

$$\overline{R} = \frac{1}{T_1 - T_0}\int_{T_0}^{T_1} \Pi(T) - \Pi_{rep}(p(T))\mathrm{d}T \tag{19}$$

As previously showed by Barton (1995), $\overline{\Pi}$ can be approximated by:

$$\overline{\Pi} \approx 1 - \frac{1}{T_1 - T_0}\int_{-\infty}^{\infty}(1-\Pi(T))\mathrm{d}T = 1 - \frac{1}{T_1 - T_0}\int_0^1 \frac{(1-\Pi(p))}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p \tag{20}$$

Integration from very ancient time (or equivalently frequency lower than $1/2N$)

reflects the fact that mutation 1 can affect the fate of mutation 2 even if it appears after it, when mutation 2 is still in low frequency in the stochastic zone. However, contrary to emergence, the replacement of mutation 1 by mutation 2 can occur only if mutation 2 arises when mutation 1 has already emerged, that is for $p > p_e \approx (1+F)/[2Ns_1(h_1+F-h_1F)]$. Note that this condition is a bit too restrictive because we should also consider the case when mutation 1 arises after but emerge before mutation 2. Moreover, the distribution of p_e should be used instead of the average value. However, these complications have only minor quantitative effects (not shown) and as shown below, the reduction in the overall emergence probability (Equation 19) can be written as:

$$\overline{R} \approx 1 - \frac{1}{T_1 - T_0}\left(\int_0^1 \frac{(1-\Pi(p))}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p\right) \tag{21}$$

A natural choice for $T_1 - T_0$ would be to use the length of the first sweep. However, as mentioned above, we must consider the effect of mutation 1 when it emerges after mutation 2 has occured. Moreover, because selfing and dominance affects the length of sweeps (Glémin 2012), averaging over sweep length would not allow direct comparison between different selfing rates and dominance levels. For example, the effect of a sweep is expected to be stronger under selfing than under outcrossing but the time interval when interference can occur is shorter. Finally, interference also depends on the rate of sweep at locus 1, which is also affected by selfing and dominance. All these effects can be taken into account by assuming a steady state of substitutions at a low rate at locus 1 (i.e. no multiple substitutions):

$$\lambda_1 = 4Nu\frac{h_1 + F - h_1F}{1+F} \tag{22}$$

where time is measured in $1/s_1$ generations. Following BARTON (1995) we use:

$$\overline{R} \approx 1 - \lambda_1 \left(\int_0^1 \frac{(1 - \Pi(p))}{\mathrm{d}p/\mathrm{d}T} \mathrm{d}p + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{\mathrm{d}p/\mathrm{d}T} \mathrm{d}p \right) \tag{23}$$

The justification is as follows. The waiting time between two sweeps is exponentially distributed with mean $1/\lambda_1$. If $T_1 - T_0 < 1/\lambda_1$, intereference between sweep 1 and sweep 2 thus occurs for a proportion of time $(T_1 - T_0)/(1/\lambda_1)$. On average, the effect of sweep 1 on sweep 2 is thus:

$$(1 - \lambda_1(T_1 - T_0)) + \lambda_1(T_1 - T_0) \left(1 - \frac{1}{T_1 - T_0} \left(\int_0^1 \frac{(1 - \Pi(p))}{\mathrm{d}p/\mathrm{d}T} \mathrm{d}p + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{\mathrm{d}p/\mathrm{d}T} \mathrm{d}p \right) \right) \tag{24}$$

leading to Equation 23.

Simulations

We tested the accuracy of the numerical solutions by comparing them to stochastic simulations written in R (R DEVELOPMENT CORE TEAM 2014); code will be deposited online. When measuring Π, the first allele was seeded at initial frequency p; given this frequency and selfing rate σ, the proportion of mutant homozygotes, heterozygotes, and wild-type homozygotes were calculated based on standard equations with inbreeding (WRIGHT 1951). The second allele was subsequently introduced onto a random background with frequency $1/2N$ (i.e. as a single copy). Frequencies of each genotype were altered deterministic by $w_i/\overline{w}$ due to selection, where w_i is the fitness of the genotype and $\overline{w}$ is the population mean fitness. Recursion equations derived by HEDRICK (1980, Equation 3) then calculated how genotype frequencies changed due to partial selfing. A life-cycle was

completed by resampling N genotypes from a multinomial distribution to implement random drift. The second allele was tracked until one haplotype fixed, with the simulation repeated until 5000 fixations of the second beneficial allele occurred. It was noted how often each haplotype fixed; from this data we subsequently calculated the frequency that the second allele fixed, relative to the expected result without interference. When measuring p_{HH} we instead measured how often the haplotype carrying solely the fitter mutant fixed. Confidence intervals were calculated using the Clopper-Pearson method for binomial sampling (Clopper and Pearson 1934).

Results

Validity of the analytical/numerical approach

We first tested the accuracy of Π, as given by Equation 11, with stochastic simulations. A subset of comparisons are shown in Figure 1; fuller comparisons are given in Supplementary Material 2. We see that on the whole, the analytical solutions provide an accurate match with simulations for a wide variety of selfing and dominance values. Inaccuracies tend to arise if $4Nr \gg 1$ so the assumption of tight linkage breaks down. Furthermore, if the second mutant is highly recessive where there is outcrossing ($h_2 = 0.1$), the simulated allele fixation probability is higher than in single-loci models. This is simply because the fixation probability of recessive beneficial mutants are underestimated using the branching-process solution without considering homozygotes genotypes (Equation 1, which holds for highly recessive alleles only in very large population sizes, i.e. at least $N =$

$100,000$). For smaller population sizes a diffusion-equation solution, P_{dif}, offers the correct baseline emergence probability (Caballero and Hill 1992). Hence rescaling the $h = 0.1$ simulations by this solution, $P_{dif}\Pi$ (instead of $P_2\Pi$ where P_2 is given by equation 1) offers realistic fixation probabilities that are less than one.

Figure 2 shows the estimate of Π_{rep} compared to simulation data if $s_2 > s_1$ and the first sweep is at frequency p. Generally, if the first mutation is not recessive, recombination is low (and/or selfing high) and p is above $1/2$ then the analytical solution matches up well with simulations. However, if recombination is high ($2Nr$ approaches 1) and mutations are recessive then the actual replacement probability can be underestimated (for example, with $h_1 = h_2 = 0.2$; Figure 2(b)). By tracking the frequencies of individual haplotypes over time, we can determine that in cases where the model fails, it is because two key modelling assumptions are violated (Supplementary Material 2). In particular, the wild-type haplotype is not rapidly eliminated, so not all recombination occurs between the two selected haplotypes. Hence Equation 18 would overestimate the effect of recombination, although the error would not be large if net recombination is low. Furthermore the first sweep does not increase in frequency at the start of the process, also violating the assumption that it will compete with the second sweep. This behaviour is also observed if both mutants are dominant in outcrossing populations ($h_1 = h_2 = 0.8$; see Supplementary Material 1). To calculate a more accurate replacement probability in this case, it would be necessary to explicitly account for the frequency of the neutral class, or how recessive beneficial mutations drift at a low frequency. Unfortunately it will probably be unfeasible to produce tractable analytical solutions in either scenario. Hence in subsequent analyses when $\phi > 1$, we will focus on additive or dominant mutations ($h \geq 1/2$).

Additive case

Under additive selection ($h_1 = h_2 = 1/2$), selfing has no effect on the single probability of fixation. This case thus allows analyzing the effect of selfing on recombination only. Moreover, for this specific case, results can be obtained directly by rescaling haploid models. Equations 11 and 12 become:

$$\frac{\partial \Pi}{\partial p} = \frac{\phi((1-p)p\Delta(p)^2 - \Pi(p)(1-\Pi(p)))}{(1-p)p} \tag{25}$$

$$\frac{\partial \Delta}{\partial p} = \frac{\Delta(p)(2\rho_F + \phi(2\Pi(p)-1) + (1-2p)(\phi\Delta(p)-1)) - \Pi(p)}{(1-p)p} \tag{26}$$

where $\rho_F = \rho(1-F)/(1+F)$. Equations 25, 26 are similar to Barton's (1995) 6a and 6b for haploids, except with $p(1-p)$ terms in the denominator since our equations are as a function of the first sweep frequency, and that the recombination rate is decreased by $2(1-F)/(1+F)$. The latter scaling reflects how the population size is increased by a factor of 2 in diploids compared to haploids; how inbreeding magnifies drift by a factor $1/(1+F)$, increasing the speed at which the first sweep fixes and reducing the potential for recombination to act; and how the effective recombination rate is reduced by $1-F$ (Glémin 2012; Hartfield and Glémin 2014). Here, we can use the approximations given by Equations 8 and 9a of Barton (1995) with the appropriate rescaling:

$$\int_0^1 \frac{(1-\Pi(p))}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p \approx -\frac{2}{1+F}\frac{\ln(1-\phi^{2\rho_F})}{\phi} \quad \text{for small } \phi \tag{27}$$

$$\approx \frac{2}{1+F}\frac{1}{(\phi+2\rho_F)^2 - 1/4} \quad \text{for large } \phi+\rho_F \tag{28}$$

Approximation for the replacement probability can also be obtained (see details in Supplementary Material 1). P_{HH} can be obtained by replacing s_a by s_2 and s_d by s_1 in Equation 8 of Hartfield and Glémin (2014):

$$P_{HH} = \phi^{-4Nr\frac{1-F}{1+F}\frac{\phi}{(\phi-1)^2}} \tag{29}$$

Similarly, $Q_2(p)$ can be obtained by replacing s_a by s_2 and s_d by $s_2 - s_1$ in Equation 7 of Hartfield and Glémin (2014) and scaling by s_2:

$$Q_2(p) = \frac{\phi - 1}{\phi - 1 + p} \tag{30}$$

Integrating over the sweep trajectory we obtain:

$$\begin{aligned} \int_{p_e}^{1} \frac{\Pi_{rep}(p)}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p &= \phi^{-4Nr\frac{1-F}{1+F}\frac{\phi}{(\phi-1)^2}} \int_{1/Ns_1}^{1} \frac{2}{p(1+F)} \frac{\phi-1}{\phi-1+p}\mathrm{d}p \\ &= \frac{2\ln(Ns_1(1-1/\phi))}{1+F}\phi^{-4Nr\frac{1-F}{1+F}\frac{\phi}{(\phi-1)^2}} \end{aligned} \tag{31}$$

Quantitative inspection of previous equations shows that the emergence effect (or 'stochastic interference' effect) is more important than the replacement effect (Figure 3). The emergence effect is higher for low ϕ values, and can be very high; Equation 27 tends to ∞ when ϕ or ρ_F tend towards 0. On the contrary, Equation 31 tends towards $2\ln(Ns_1)/(1+F)$ as ϕ tends towards ∞. This difference can be explained because (i) mutations are more sensitive to interference in the stochastic zone than once they have emerged, and (ii) the effect of interference is longer on emergence than on replacement. Consequently, the effect of selfing is more important for low ϕ values when emergence is the most important process

than for high ϕ values when replacement predominates as illustrated on Figure 3). The same figure also illustrates how the effect of a sweep can extend across long chromosome tracts for high selfing rates.

In previous equations, the scaling factor $2/(1+F)$ arises because the length of the sweep is in $\mathcal{O}(\frac{1+F}{2s_1})$ but we scaled time by $1/s_1$ to conserve the same scaling for any selfing rate. Equations 27, 28 and 31 demonstrate the two opposite effects of selfing: the reduction in effective recombination reduces the probability of emergence, and also increases the probability of replacement but on a shorter period of time as sweeps are shorter (Glémin 2012). For loose linkage, the effect of selfing on recombination is the strongest so that selfing globally decreases the probability of fixation. However, for tight linkage interference occurs for any selfing rate, such that the dominant effect of selfing is the reduction in sweep length (Figure 4). When $4Nr < 1.386\frac{(\phi-1)^2}{\phi\ln(\phi)}$, replacement is more likely under outcrossing than complete selfing (see Supplementary Material 1). Emergence is also more likely under selfing than outcrossing when $\rho < 0.207\phi$ (but for $\phi > 1$ linkage only very weakly affects the probability of emergence). When $\phi < 1$, interference is stronger under outcrossing only for very tight linkage, that is for $\rho < -\epsilon/4\ln(\phi)$, where ϵ is the residual outcrossing rate under selfing (see Supplementary Material 1).

Effect of dominance on interference

For high selfing rates, the interference process is well approximated by the additive case. However, to get a complete picture of the effect of selfing we need to analyse how dominance affects the interference process. Here, we will consider fully outcrossing populations before considering the global effect of mating systems on

the rate of adaptation. When considering dominance, two questions arise: which kind of mutations cause the strongest interference and which ones are the most sensitive.

The effect of interference for different combinations of dominance levels are presented in Figure 5 for $\phi < 1$. The main difference in sweep dynamics is the length of the two stochastic phases. Because a mutation causes interference mainly during its deterministic trajectory, which is similar for any dominance level ($\mathcal{O}(1/2Ns_1)$ for any h_1; Ewing *et al.* (2011)), the dominance level of mutation 1 has thus only a weak effect on the probability of emergence of mutation 2. However, the sensitivity of mutation 2 to interference strongly depends on its dominance level, as it depends on the length of its initial stochastic phase, which is $\mathcal{O}(\frac{\ln(2Ns_2)}{2Nh_2s_2})$ (Ewing *et al.* 2011). Recessive mutations are thus more sensitive to interference than additive and dominant ones. Interference thus reinforces Haldane's sieve, in the sense that recessive mutations are even less likely to emerge in outcrossing populations, if tightly linked to the initial sweep. In the case of strong interference, this effect can be substantial as illustrated in Figure 5. Interestingly, this effect is not symmetrical since dominant mutations only exhibit slightly less interference than additive mutations. As far as we know this effect has not been described before and it leads to several predictions. For instance, the dominance spectrum of fixed beneficial mutation should vary with recombination rate (Figure 6). The same pattern is observed for replacement but it is quantitatively weaker (Supplementary Material 1) as already noted by Hartfield and Glémin (2014) for hitchhiking of deleterious mutations.

Conditions under which selection is more efficient under outcrossing than under selfing

We now have all the ingredients to study the range of conditions under which selfing reduces the rate of adaptation. Without interference, and without any other factor increasing drift effects in selfers, selfing reduces (respectively increases) adaptation from new dominant (respectively recessive) mutations (Charlesworth 1992; Caballero and Hill 1992). How does interference affect this condition? This question can be explored by considering a steady flow of mutations and analyzing $P_{12} = \overline{R}P_2$ where $\overline{R}$ is given by Equation 23. As shown in Supplementary Material 1, the total effect of interference on replacement will be no more than of the order of $\ln(2Ns_1)$ (which is always lower than few tens) while the effect on emergence can be much more important. In what follows we will thus focus on the case where $\phi < 1$.

Figure 7 illustrates how selfing can affect the probability of fixation of the second mutation compare to the single locus case. Under a low adaptation regime ($\theta = 0.02$) interference is weak and the probability of fixation is reduced only in highly selfing species. This reduction is moderate and selfing species are still better than outcrossing ones at fixing recessive mutations. Under strong adaptation regime ($\theta = 0.2$), interference can be substantial even in mixed mating species and adaptation can be fully impeded in highly selfing species if $\lambda_1 > 1/\int_0^1 \frac{(1-\Pi(p))}{\mathrm{d}p/\mathrm{d}T}\mathrm{d}p$ (see Barton (1995)). This threshold depends on ϕ, which means that, even under a low adaptation regime, weak mutations can be affected by interference in highly selfing species. Figure 8 shows the joined dominance and selection spectrum for which selection is more efficient in outcrossing than in highly selfing ($F = 0.95$)

516 species. Strongly beneficial mutations are very weakly affected by interference so only dominant mutations are more efficiently selected in outcrossing than in selfing
518 species. However, (very) weak beneficial mutations are better fixed in outcrossing populations, whatever their dominance level.

520 Discussion

Interference between beneficial mutations with partial self-
522 ing and dominance

Multi-locus models of adaptation in partial self-fertilising species can inform on
524 how the interplay between homozygote creation, and reduction in recombination, both affect selection acting on multiple sites. It is already known that the presence
526 of linked deleterious variation means that mildly recessive beneficial mutations (h just less than $1/2$) are more able to fix in outcrossers by recombining away from the
528 deleterious allele, in contrast to Haldane's Sieve (Hartfield and Glémin 2014). More generally, genome wide background selection can substantially reduce adapt-
530 ation in highly selfing species (Kamran-Disfani and Agrawal 2014). Yet the extent that other linkage effects, especially between beneficial mutations, remain
532 unknown.

Here we extended several previous models of selection interference to consider
534 how adaptation is impeded in partially-selfing organisms. We considered two possibilities. First, given that an existing sweep is progressing through the population,
536 subsequent mutations confer a lower selective advantage and can only fix if recombining onto the fitter genetic background (the 'stochastic interference' effect). Al-

ternatively, a second mutant could be fitter and replace the existing sweep, unless recombination unites the two alleles (the 'replacement' effect). We found that the stochastic interference effect is generally stronger than the replacement effect, and is more likely to lead to loss of beneficial mutations (Figure 3).

Furthermore, selection interference leads to a reinforcement of Haldane's Sieve in outcrossing populations, as recessive mutations are more likely to be lost by drift when rare (Figure 5). Finally, interference can be substantial in selfing populations if there exists high rates of adaptive mutation (Figure 7). As a consequence, weakly-beneficial mutations are more likely to be fixed in outcrossers, irrespective of their dominance level (Figure 8). These findings thus contribute to a body of literature as to when the predictions of Haldane's Sieve should break down, or otherwise be weakened. Other examples include the fixation probability of mutations being independent of dominance if arising from previously deleterious variation (Orr and Betancourt 2001); more generally, outcrossers are more able to fix mutations with any dominance level compared to selfers if arising from standing variation, and when multiple linked deleterious variants are present (Glémin and Ronfort 2013). Conversely, dominant mutations can be lost in metapopulations due to strong drift effects (Pannell *et al.* 2005).

Heuristic extension to multiple sweeps

In our model we assumed that no more than two beneficial mutations can simultaneously interfere in the population. However, even if mutations occur rarely enough to lead to multiple mutations interfering under outcrossing, the presence of a few sweeping mutations throughout a genome can jointly interfere in highly selfing species, further reducing the rate of adaptation. Obtaining a general model

of multiple substitutions in a diploid partially selfing populations is a difficult task, but we can get a raw picture of the effect of selfing on adaptation at many loci by an heuristic extension of the haploid model of Weissman and Barton (2012). Assuming the same selective advantage for all mutations, s, the rate of adaptation can be approximated by solving the following equation for λ (see Supplementary Material 3):

$$\lambda = \Theta \frac{h + F - hF}{1 + F} \left(1 - \frac{2\lambda}{R_s(1-F)}\right) e^{-\frac{4\lambda}{(1-F)^2}} \tag{32}$$

where $\Theta = 4NU_b$ is the population genomic rate of beneficial mutations and R_s is the length of the genetic map scaled by s. Using this equation we can show that shows that for a moderate flow of beneficial mutation (where no interference occurs under outcrossing) adaptation can be substantially reduced for very high selfing rate (see Figure 1 in Supplementary Material 2). Moreover, for $s_1 = s_2$ the two-locus model (Equation 23) underestimates the effect of interference as Θ increases. While the two locus model suggests that only weak mutations should be substantially affected by strong mutations, the multiple sweep model suggests that mutations of similar effect can also interfere in highly selfing species.

Causes of limits to adaptation in selfing species

We have already shown in a previous paper how adaptation can be impeded in low-recombining selfing species due to the hitch-hiking of linked deleterious mutations (Hartfield and Glémin 2014), with Kamran-Disfani and Agrawal (2014) demonstrating that backround selection can also greatly limit adaptation. Hence the question arises as to whether deleterious mutations or multiple sweeps are more likely to impede overall adaptation rates in selfing species.

Background selection causes a general reduction in variation across the genome by reducing N_e (Nordborg *et al.* 1996); here the overall reduction in emergence probability is proportional to N_e/N, where N_e is mediated by the strength and rate of deleterious mutations (Barton 1995; Johnson and Barton 2002), and thus affects all mutations in the same way. Because of background selection, selfing is thus expected to globally reduce adaptation without affecting the spectrum of fixed mutations. Similarly, adaptation from standing variation, which depends on polymorphism level, is expected to be affected by the same proportion (Glémin and Ronfort 2013). Alternatively, interference between beneficial mutations is mediated by ϕ, the ratio of the selection coefficients of the sweeps. Weak mutations are thus more affected than stronger ones and the effect of interference cannot be summarised by a single change in N_e (Barton 1995; Weissman and Barton 2012). Because of selective interference, selfing is also expected to shift the spectrum of fixed mutations towards towards those of strong effect. Interestingly, Weissman and Barton (2012) showed that neutral polymorphism can be significantly reduced by multiple sweeps even if sweeps do not interfere among them. This suggests that in selfing species, adaptation from standing variation should be more limited than predicted by single-locus theory (Glémin and Ronfort 2013). Selective interference could thus affect both the number and type of adaptations observed in selfing species.

However, reflecting on this logic, both processes should interact and we therefore predict that background selection will have a diminishing-returns effect. As background selection lowers N_e then the substitution rate of beneficial mutations will be reduced (since it is proportional to $N_e\mu$ for μ the per-site mutation rate), hence interference between beneficial mutations will subsequently be alleviated.

No such respite will be available if the adaptive mutation rate increases; on the contrary, interference will increase (Figure 7). Hence interference between adaptive mutations should play a strong role in reducing the fitness of selfing species, causing them to be an evolutionary dead-end. Further theoretical work teasing apart these effects would be desirable. Given the complexity of such analyses, simulation studies similar to those of Kamran-Disfani and Agrawal (2014) would be a useful approach to answering this question.

In a recent study, Lande and Porcher (2015) demonstrated that once the selfing rate became critically high, selfing organisms then purged a large amount of quantitative trait variation, limiting their ability to respond to selection in a changing environment. This mechanism provides an alternative basis as to how selfing organisms are an evolutionary dead-end. However, they only consider populations at equilibrium and our results suggest that directional selection should further reduce quantitative genetic variation due to selective interference among mutations. Subsequent theoretical work is thus needed to determine the impact of interference via sweeps on the loss of quantitative variation. Furthermore, complex organisms (i.e. those where many loci underlie phenotypic selection) are less likely to adapt to a moving optimum compared to when only a few traits are under selection (Matuszewski *et al.* 2014), and can also purge genetic variance for lower selfing rates (Lande and Porcher 2015). Complex selfing organisms should be less able to adapt to environmental changes.

Empirical Implications

The models derived here lead to several testable predictions for the rate of adaptation between selfing and outcrossing sister-species. These include an overall reduction in the adaptive substitution rate in selfing populations; a shift in the distribution of fitness-effects in selfing organisms to only include strongly-selected mutations that escape interference; and a difference in the dominance spectrum of adaptive mutations in outcrossers compared to selfers, as already predicted by single-locus theory (Charlesworth 1992) and observed with quantitative trait loci (QTLs) for domesticated crops (Ronfort and Glémin 2013).

So far, few studies currently exist that directly compare adaptation rates and potential between related selfing and outcrossing species, but they are in agreement with the predictions of the model. In plants, the self-incompatible *Capsella grandiflora* exhibited much higher adaptation rates (where $\alpha = 40\%$ of non-synonymous substations were estimated to be driven by positive selection using the McDonald-Kreitman statistic; Slotte *et al.* (2010)) than in the selfing related species *Arabidopsis thaliana* (where α is not significantly different from zero). Similarly, the outcrossing snail *Physa acuta* exhibited significant adaptation rates ($\alpha = 0.54$), while no evidence for adaptation in the selfing snail was obtained (Burgarella *et al.* 2015); in fact, evidence suggests that deleterious mutations segregate due to drift ($\alpha = -0.19$). In agreement with the predicted inefficacy of selection on weak mutations, Qiu *et al.* (2011) also observed significantly lower selection on codon usage in the *Capsella* and *Arabidopsis* selfers than in their outcrossing sister species.

In addition, as only strong advantageous mutations are expected to escape loss

through selection interference, this result can explain why selective sweeps covering large tracts of a genome are commonly observed, as with *Arabidopsis thaliana* (Long *et al.* 2013) and *Caenorhabditis elegans* (Andersen *et al.* 2012). Extended sweep signatures can also be explained by reduced effective recombination rates in selfing genomes. Finally, selection interference between beneficial mutations could explain why maladaptive QTLs are observed as underlying fitness components, as observed in *Arabidopsis thaliana* (Ågren *et al.* 2013). Direct QTL comparisons between selfing and outcrossing sister species would therefore be desirable to determine to what extent selection interference leads to maladaptation in selfing species.

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Table 1: Glossary of Notation.

Symbol	Usage
$2N$	Overall (diploid) population size
s_1, s_2	Fitness coefficients of original and new advantageous alleles
h_1, h_2	Dominance coefficients of original and new advantageous alleles
p	Frequency of first advantageous allele at timepoint
σ	Proportion of matings that are self-fertilising
F	Wright's (1951) inbreeding coefficient, $\sigma/(2-\sigma)$
P_1, P_2	Fixation probability of original and new allele if unaffected by linkage (Equation 1)
P_{12}^*	Fixation probability of both mutants in absence of interference
P_{12}	Actual fixation probability of both mutants, after accounting for interference
R	Ratio of actual to non-interference double-allele fixation probability, P_{12}/P_{12}^*
$P_{2,self}$	Fixation probability of second allele with complete selfing (Equation 3)
$P_{2,w}$	Emergence probability of second allele if appearing on wildtype background
P_{HH}	Fixation probability of second allele with wildtype background
P_d	Fixation probability of haplotype carrying both sweeps
τ	Time taken for first sweep to reach frequency p
T	Scaled time, $s_1 t$
Π	Average fixation probability of second allele if it does not replace the first sweep
Π_{rep}	Probability that second sweep replaces first if $s_2 > s_1$
Q_1, Q_2	Fixation probability of novel allele if appearing on already beneficial or neutral genetic background
Δp	Change in first advantageous allele frequency over time
Δq	Change in second advantageous allele frequency over time (if first present)
w_1, w_2	Fitness of sweeping or neutral genetic background
$\overline{w}$	Population mean fitness, change in fitness following sweep
r	Recombination rate between two loci
θ_1, θ_2	Relative selective advantage of second allele, if residing on either beneficial or neutral background
θ_3	Relative selective advantage of recombinant haplotype carrying both alleles
Δ	Difference in fixation probability between different backgrounds
ϕ	Scaled advantage of new beneficial allele, s_2/s_1
ρ	Scaled recombination rate, r/s_1
λ_1	Rate of selected substitution with mutation
Θ	Population rate of beneficial mutation in multiple sweep case, $4NU_b$

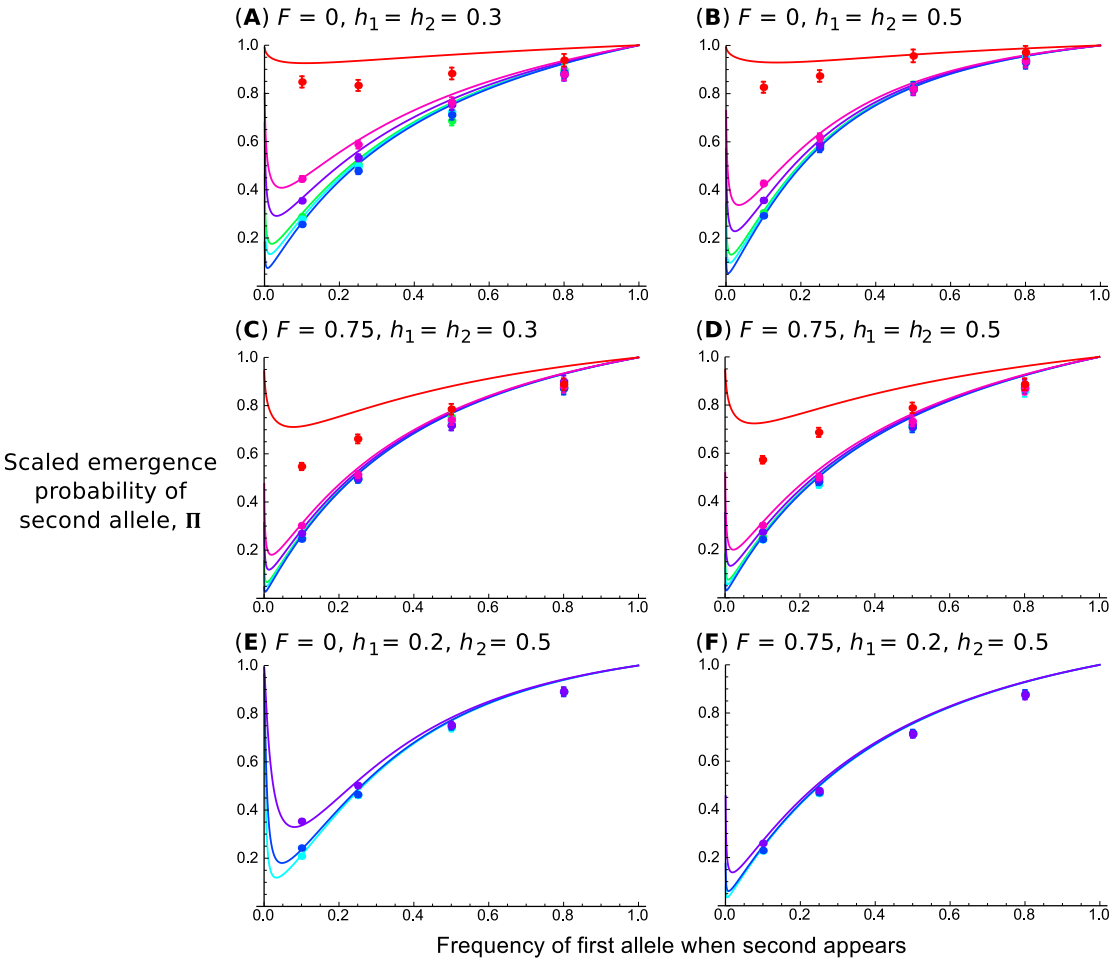


Figure 1: Probability of fixation of the second allele relative to the unlinked case, Π, as a function of the first allele frequency, p. $N = 2000$, $s_1 = 0.04$, $s_2 = 0.02$ (so $\theta = 0.5$), and from bottom to top in (a)–(d): $4Nr = 0.4$, 1, 1.6, 4, 16, and 80 (corresponding to $\rho = 0.00125$, 0.003125, 0.005, 0.0125, 0.025, and 0.5). In (e) and (f), from bottom to top: $4Nr = 0.4$, 1, 4 (corresponding to $\rho = 0.00125$, 0.003125, 0.0125). Parameters used are $F = 0$, $h_1 = h_2 = 0.3$ (a); $F = 0$, $h_1 = h_2 = 0.5$ (b); $F = 0.75$, $h_1 = h_2 = 0.3$ (c); $F = 0.75$, $h_1 = h_2 = 0.5$ (d); $F = 0$, $h_1 = 0.2$, $h_2 = 0.5$ (e); and $F = 0.75$, $h_1 = 0.2$, $h_2 = 0.5$ (f). Curves correspond to solutions provided by analytical system of differential equations, 11, rescaled so it is a function of p instead. Points corresponds to 5000 stochastic simulations for which the second beneficial allele has fixed.

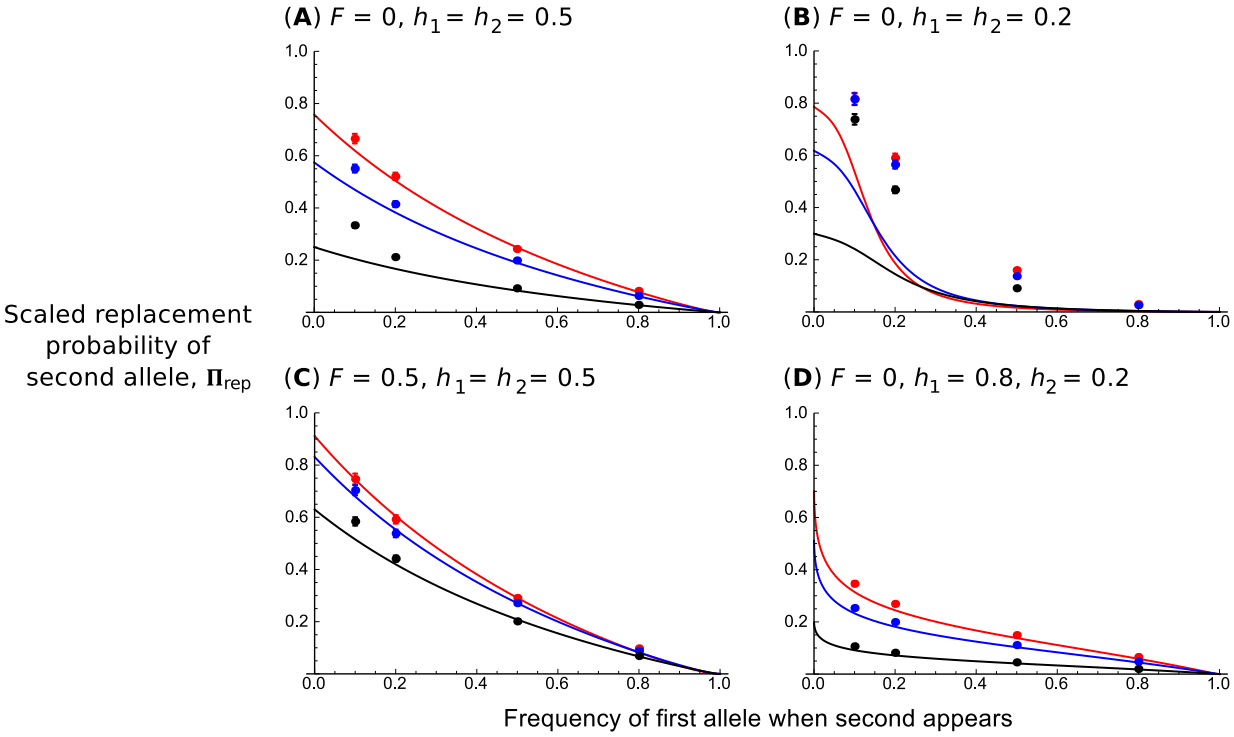
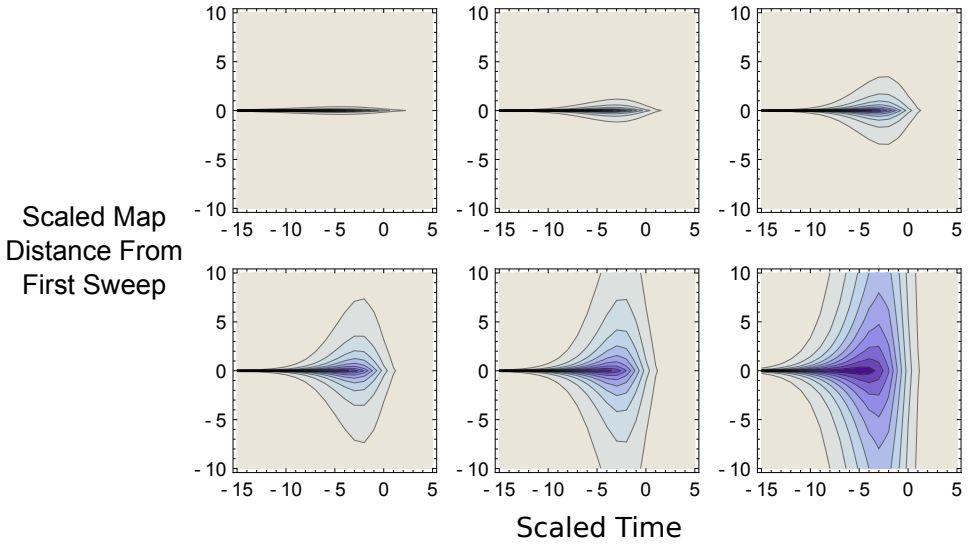
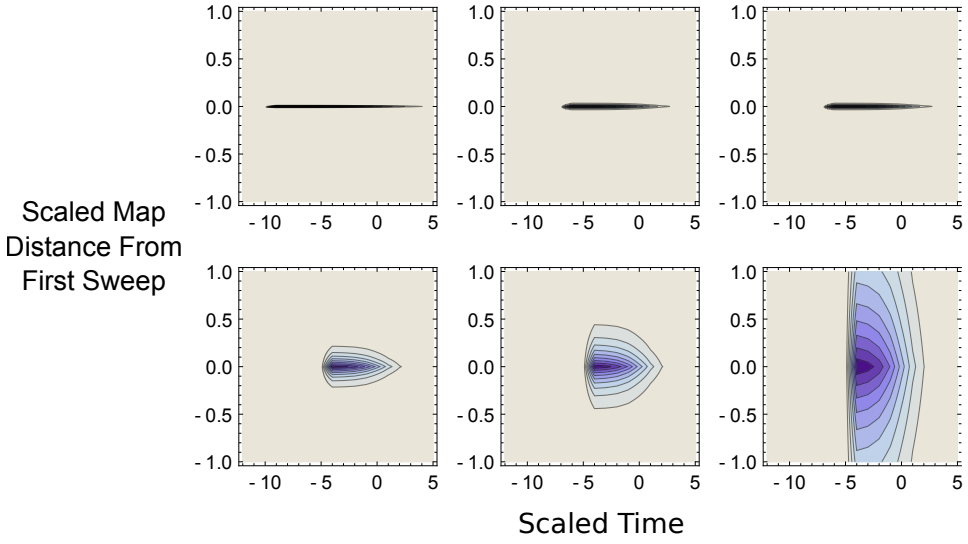


Figure 2: Probability Π_{rep} that a second beneficial allele with advantage s_2 replaces an existing sweep with selective advantage s_1 where $s_2 > s_1$, as a function of the first sweep frequency p when the second sweep appears. $N = 5,000$ and $2Nr = 0.1$ (red), 0.2 (blue) or 0.5 (black). Other parameters are (a) $F = 0$, $s_1 = 0.02$, $s_2 = 0.04$ and $h_1 = h_2 = 0.5$; (b) $F = 0$, $s_1 = 0.01$, $s_2 = 0.04$, and $h_1 = h_2 = 0.2$; (c) $F = 0.5$, $s_1 = 0.02$, $s_2 = 0.04$, and $h_1 = h_2 = 0.5$; or (d) $F = 0$, $s_1 = 0.005$, $s_2 = 0.02$, $h_1 = 0.8$ and $h_2 = 0.2$. Points corresponds to 5,000 stochastic simulations for which the second beneficial allele has fixed.



(a)



(b)

Figure 3: Contour plots showing degree of interference, as measured by Equation 2 with Π defined by Equation 25 (for $\phi < 1$) and Π_{ref} defined with Equation 31 (for $\phi > 1$), when both mutations are additive ($h_1 = h_2 = 1/2$). In both panels, darker colours indicate higher degree of interference (with the darkest representing R approaching 0); x-axis denotes time of the sweep (with the sweep reaching 50% frequency at $T = 0$); y-axis is the map distance from the first sweep (scaled to $10^{-2}/s_1$). Top panels of plots are for F values of 0, 0.5, and 0.8 respectively; bottom row are F values of 0.9, 0.95, 0.99. Other parameters are $N = 10,000$, and (a) $s_1 = 0.01$, $s_2 = 0.005$ so $\phi = 0.5$; or (b) $s_1 = 0.01$, $s_2 = 0.05$ so $\phi = 5$.

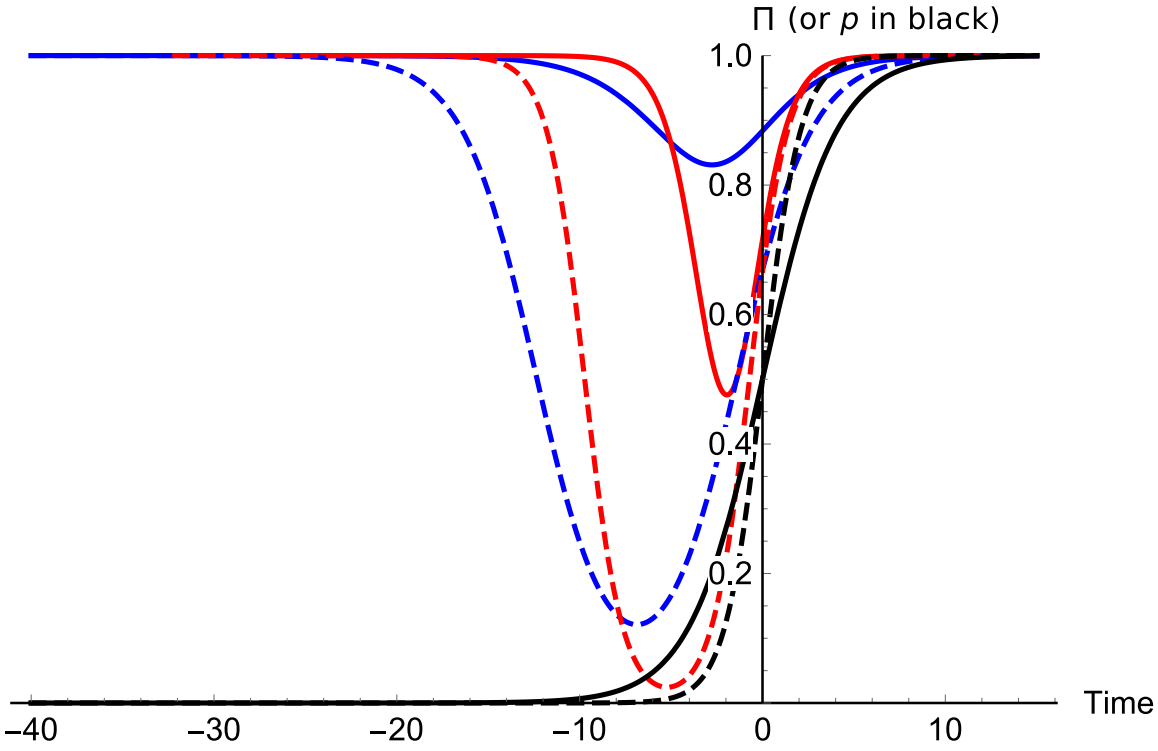


Figure 4: Profile of how Π changes over the course of the first sweep, as a function of time T. $h_1 = h_2 = 0.5$, $\phi = 1$ and ρ equals 0.1 (coloured solid lines) or 0.0001 (coloured dashed lines). Results are compared for $F = 0$ (blue lines) or $F = 0.95$ (red lines). For comparison, the underlying first sweep is also plotted, for $F = 0$ (solid black line) or $F = 1$ (dashed black line). Note that time is scaled so both sweeps reach a frequency of 50% at time $T = 0$.

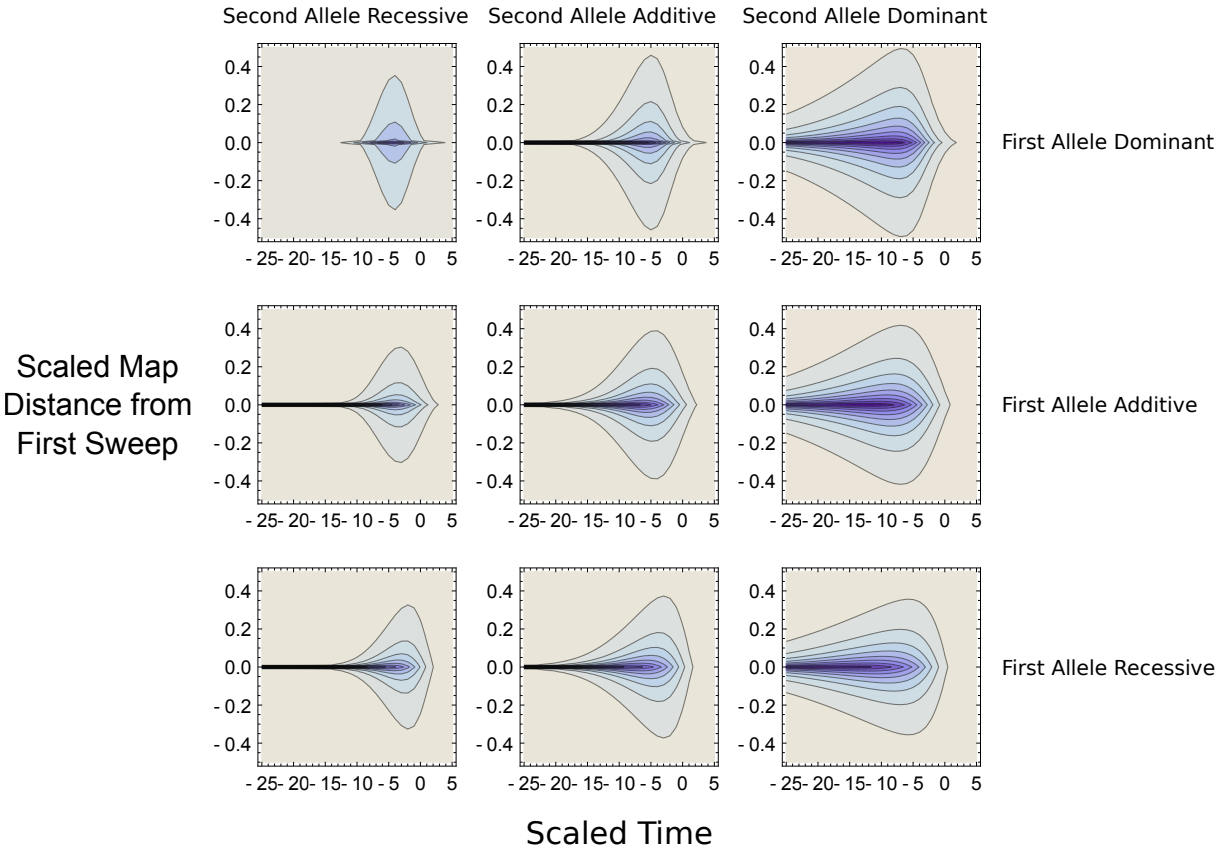


Figure 5: Contour plots showing degree of interference, as measured by Equation 2 with Π defined by Equation 25 and $\Pi_{rep} = 0$ (as $\phi < 1$), for different dominance values. In both panels, darker colours indicate higher degree of interference (R approaching 0); x-axis denotes time of the sweep (with the sweep reaching 50% frequency at $T = 0$); y-axis is the map distance from the first sweep (scaled to $10^{-2}/s_1$). Labels denote the dominance value of the first and second mutation, with recessive mutants having $h = 0.2$; additive mutations $h = 0.5$; dominant mutations $h = 0.8$. Other parameters are $N = 10,000$, and $s_1 = 0.01$, $s_2 = 0.005$ so $\phi = 0.5$.

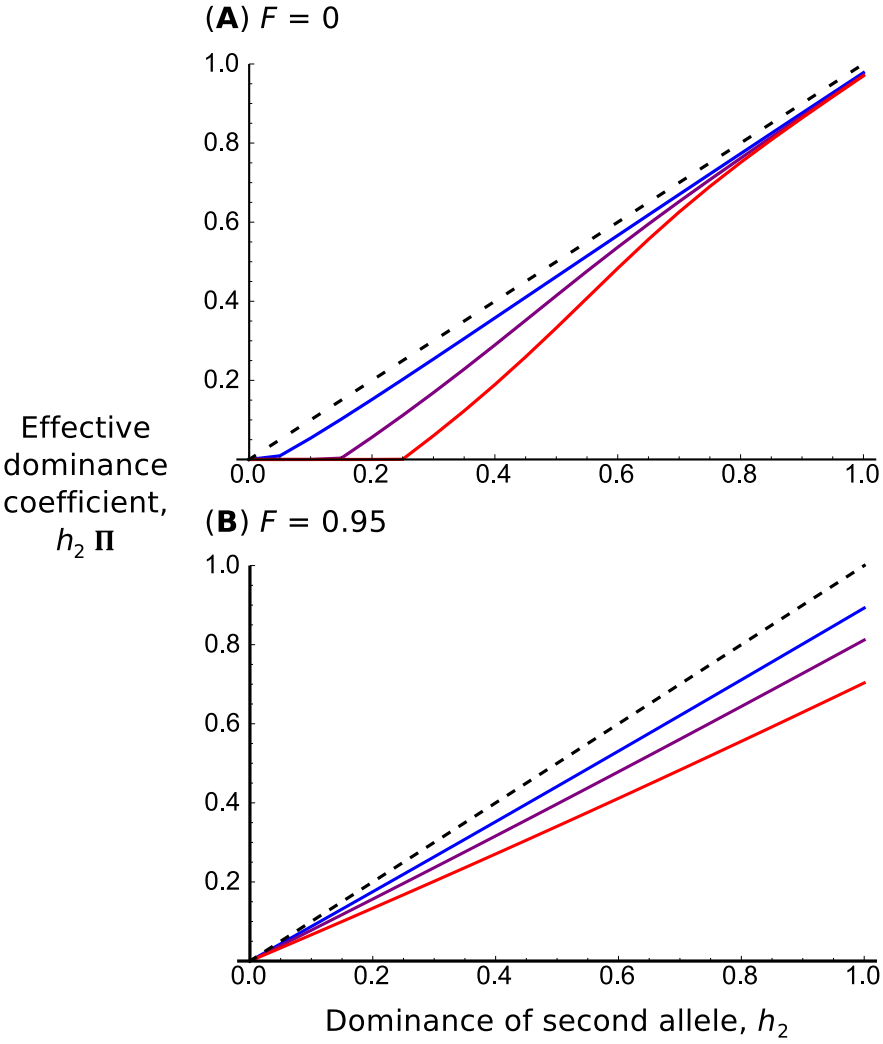


Figure 6: Plots of the effective distribution of dominance effects in either an outcrossing population ($F = 0$, (a)), or a selfing population ($F = 0.95$, (b)), defined by $h_2 \cdot \overline{\Pi}$ (Equation 20), as a function of h_2. $N = 10,000$, $h_1 = 0.5$, $s_1 = s_2 = 0.01$ ($\phi = 1$), $\theta = 4Nu = 0.1$ and $r = 0.001$ (blue line), 0.0001 (purple line), or 0.00001 (red line). The dashed line shows the $y = x$ line, as expected without interference.

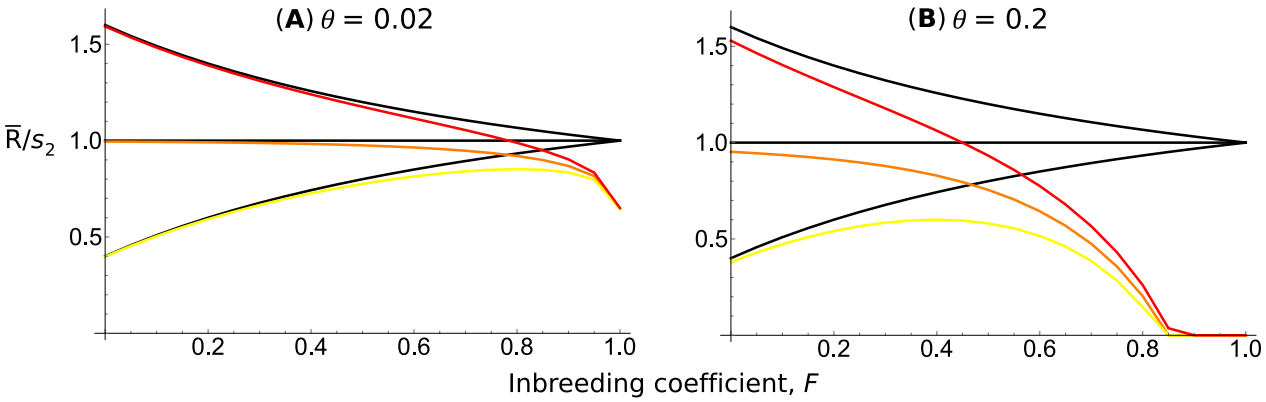


Figure 7: Plots of the total effect of interference, $\overline{R}$, as defined using Equation 23, as a function of F. The y–axis is the probability of emergence scaled to s_2, the expected emergence probability with $F = 1$. There is a continual rate of mutation $\theta = 4Nu = 0.02$ (left) or 0.2 (right). $N = 10,000$, $r = 0.01$, $h_1 = 0.5$, $s_1 = 0.01$, $s_2 = 0.001$ ($\phi = 0.1$), and $h_2 = 0.2$ (yellow line), 0.5 (orange line), or 0.8 (red). Black lines show expected fixation probability in the absence of interference.

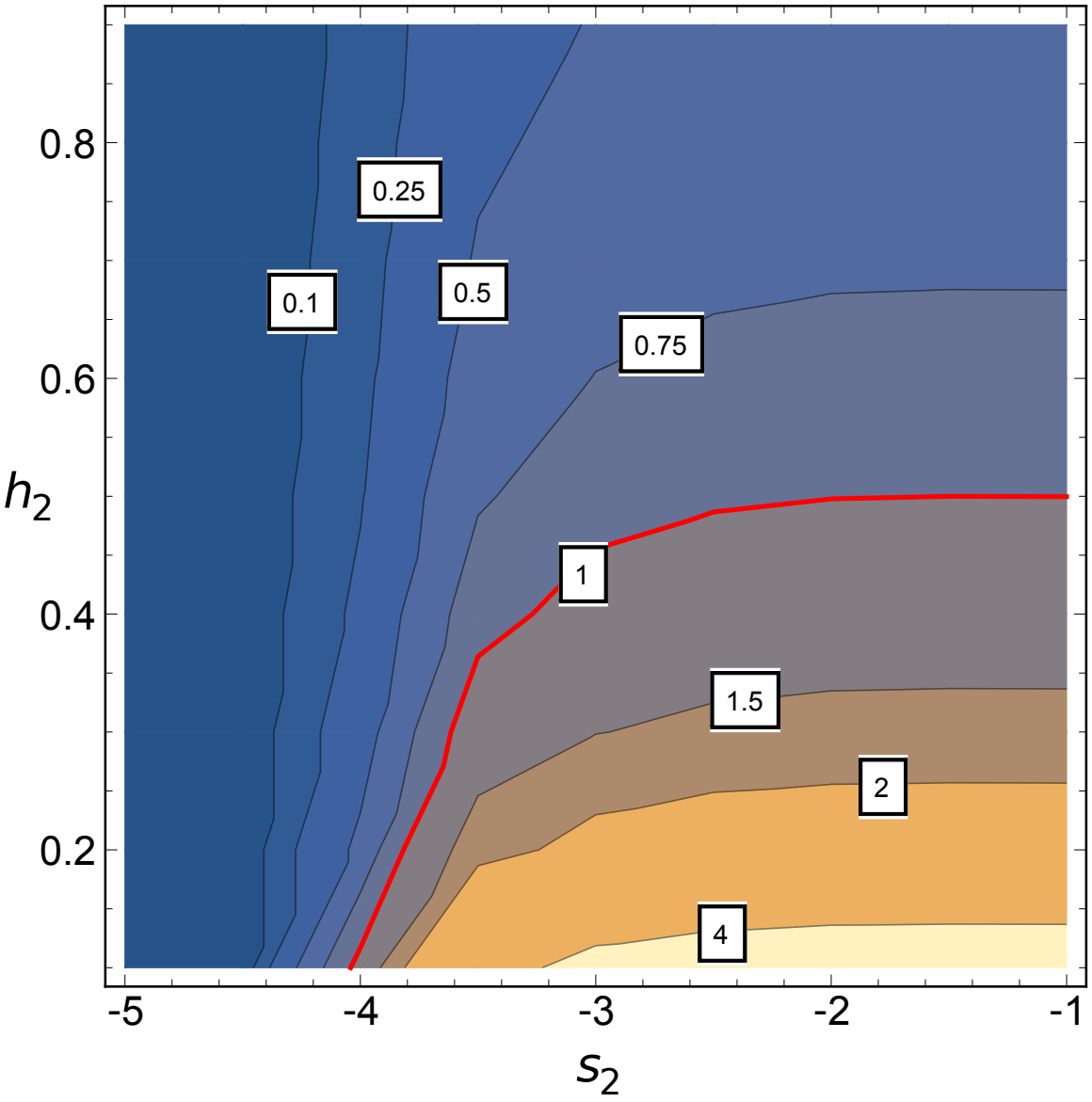


Figure 8: Contour plot of the ratio of $\overline{R}$ (Equation 23) for $F = 0$ and $F = 0.95$, as a function of s_2 and h_2. Values less than one indicate that outcrossers has the higher fixation probability, and values greater than one indicate that $F = 0.95$ populations have the higher probability. Other parameters are $\theta = 0.1$, $N = 10,000$, $r = 0.01$, $h_1 = 0.5$, and $s_1 = 0.01$.