

Limits to adaptation in partially selfing species

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Abstract

2 Single locus theory indicates that selfing species are more able than out-
crossing ones to fix emerging recessive beneficial mutations, as they are not
4 masked as heterozygotes. However, partially selfing organisms suffer from
relaxed recombination, which reduces overall selection efficiency. Although
6 the effect of linked deleterious alleles on adaptation has previously been
studied, the extent to which multiple adaptations interfere in partially self-
8 ing organisms is currently unknown. We derive branching-process models to
quantify the extent that emergence of a second beneficial allele is obstruc-
10 ted 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
12 sweep (the ‘stochastic interference effect’), and also the potential replace-
ment of the first sweep if the second mutant is fitter (‘replacement effect’).
14 Overall, the stochastic interference effect has a larger impact on preventing
fixation of both adaptive alleles in highly selfing organisms, but the replace-
16 ment effect can be stronger with multiple mutations. Interference has two
opposing effects on Haldane’s Sieve. First, recessive mutants are dispropor-
18 tionally likely to be lost, so it is more likely that only dominant mutations
will emerge in outcrossers. Second, with frequent rates of adaptive evolu-
20 tion, outcrossing organisms are more able to fix weak beneficial mutations
of any dominance value, contrary to the predictions of Haldane’s Sieve. Our
22 analysis shows that even under low rates of adaptive mutation, interference
can be sufficiently strong to greatly limit adaptation in selfing organisms.

24 Introduction

26 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 28 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 30 1955, 1967).

32 Hence self-fertilisation should be able to rapidly evolve, unless countered by high levels of inbreeding depression (LANDE and SCHEMSKE 1985). However, 34 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 36 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 38 addition, plenty of species display mixed-mating systems and even highly selfing species still outcross at a low rate, implying that even if selfing is beneficial 40 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 42 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 44 HILL 1992). Furthermore, recombination is reduced by a factor $1 - F$ (GOLDING and STROBECK 1980; NORDBORG 2000). This joint reduction in both diversity 46 and recombination can lead to a decrease in the efficacy of selection, so deleterious mutations accumulate more rapidly in selfing organisms, leading to population

48 extinction (HELLER and MAYNARD SMITH 1978; LYNCH *et al.* 1995).

Whether this mechanism is a major cause of extinction of self-fertilising species
50 is still under debate (reviewed in GLÉMIN and GALTIER (2012); IGIC and BUSCH
(2013)). Some sister-species comparisons of selfing-outcrossing taxa reveal evi-
52 dence of increased mutation accumulation in selfers, as demonstrated with either
increased nonsynonymous-to-synonymous polymorphism ratio (π_n/π_s) or weaker
54 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
56 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
58 for mutation accumulation to act.

Less investigated is the idea that selfing reduces the ability for a species to
60 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
62 likely than outcrossers to fix new recessive adaptive mutations (HALDANE 1927;
CHARLESWORTH 1992) but are generally less efficient in adapting from stand-
64 ing variation (GLÉMIN and RONFORT 2013). Yet the effect of adaptation across
multiple sites in partially selfing organisms has received much less attention. Of
66 particular interest is how the reduction in recombination in highly selfing organ-
isms impedes the overall rate of adaptation. A well-established phenomenon in
68 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
70 ROBERTSON 1966; CHARLESWORTH *et al.* 2009). Outcrossing can therefore break
down these effects and unite beneficial mutations from different individuals into
72 the same genome, greatly increasing the rate of adaptation (FISHER 1930; MULLER

1932; FELSENSTEIN 1974; OTTO and FELDMAN 1997).

74 Historically, the effect of advantageous mutations on mating-system evolution
has been neglected since most observable spontaneous mutations are deleterious in
76 partial selfers (SLOTTE 2014). Analysis using divergence data from the *Arabidopsis*
genome shows low number of genes acting under adaptive selection (BARRIER
78 *et al.* 2003; CLARK *et al.* 2007; SLOTTE *et al.* 2010, 2011), and only $\sim 1\%$ of
genes with signatures of positive selection in *Medicago truncatula* (PAAPE *et al.*
80 2013). These analyses reflect broader findings that the proportion of adaptive
substitutions in the coding regions of selfing plants are not significantly different
82 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;
84 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
86 can also increase once demography is accounted for (HUBER *et al.* 2014).

Finally, both outcrossing and selfing domesticated plant and crop species can
88 also be used to demonstrate recent adaptation. RONFORT and GLÉMIN (2013)
showed how adaptive traits obtained from quantitative trait loci, tended to be
90 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,
92 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
94 alleles should interfere with a greater region of the genome than in outcrossing
organisms.

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

98 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
100 selection interference at linked sites provided greater benefits to outcrossing and
mixed-mating systems over complete self-fertilisation. A multi-locus simulation
102 study by KAMRAN-DISFANI and AGRAWAL (2014) verified that background selection
impedes genome-wide adaptation rates in selfing organisms, but these costs
104 generally do not completely nullify the transmission advantage of selfing unless
pollen discounting is high, or beneficial mutations are strong and frequent. These
106 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
108 mutations interfere in highly selfing species.

This article will extend previous analyses to consider how linkage between
110 several beneficial mutations at linked sites affects their emergence in partially
selfing species. Classic two-locus analytical models of the Hill-Robertson effect
112 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
114 extension of the model of WEISSMAN and BARTON (2012) to determine the effect
of mating system when many sweeps are present.

116 **Outline of the problem**

General modelling approach

118 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

120 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
122 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
124 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
126 additive. Hence an individual composed of the two haplotypes 10 and 11 will have
fitness $1 + s_1 + h_2 s_2$.

128 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) condi-
130 tioned on escaping initial extinction (i.e. emergence) on a quasi-deterministic tra-
jectory until high frequency; (iii) a second stochastic phase at very high frequency
132 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
134 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
136 the other mutation. When considering only one mutation, once it has emerged its
ultimate fixation is certain (which corresponds to the branching process approx-
138 imation). The probability of fixation is thus equal to the probability of emergence.
However, when two (or more) mutations interfere, a mutation that has emerged
140 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).
142 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
144 account.

We assume that mutation 1 is the first to escape extinction by drift (although
146 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
148 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
150 simply equal to the single-locus probability of fixation of the second mutation,
given by:

$$P_{12}^* = P_2 = 2s_2 \frac{h_2 + F - h_2F}{1 + F} \quad (1)$$

152 (CABALLERO and HILL 1992; CHARLESWORTH 1992). Note that P_1 does not ap-
pear here because we conditioned on mutation 1 having emerged. Equation 1 leads
154 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
156 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
158 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
160 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
162 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
164 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
166 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.
168 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
170 to interference.

If $s_1 < s_2$, then the second mutation can replace the first one if it arises on the
172 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
174 (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
176 Π_{rep} . In the general case, the degree of interference will be given by:

$$R = \Pi - \Pi_{rep} \quad (2)$$

In practice, R must be determined for mutation 2 arising when mutation 1 is at a
178 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).

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

182 Before deriving the full model, we can compare the two most extreme cases
that can be easily investigated. Under outcrossing and free recombination, the
184 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
186 probability of fixation given by Equation 1 with $F = 0$ (HALDANE 1927). At the
other extreme, with complete selfing recombination is suppressed and interference

188 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,
190 which is present at frequency p . Previous theory (HARTFIELD and OTTO 2011;
HARTFIELD and GLÉMIN 2014) on emergence in this scenario gives the probability
192 of fixation in the double mutant as:

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

See, for example, Equation 7 of HARTFIELD and GLÉMIN (2014) with $s_d = s_1$ and
194 $s_a = s_1 + s_2$. The probability of fixation of both alleles thus involves integrating
Equation 3 over the entire sweep, assuming that the second mutation arises at a
196 time that is uniformly distributed during the first sweep:

$$\overline{P_{2,self}} = \frac{1}{\tau} \int_0^\tau p P_{2,s}(p(t)) dt \quad (4)$$

where τ is the duration of the first sweep. We can also solve Equation 4 over p
198 from p_0 to $1 - p_0$; the term inside the integral is divided by $dp/dt = s_1p(1 - p)$
to remove time dependence. Solving in the limit of large population size (i.e.
200 $p_0 = 1/(2Ns_1) \rightarrow 0$) 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
202 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
204 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
206 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

208 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
210 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 $h_2 > 1/2$
212 without interference. However, the advantage to outcrossing may not be as high,
since the true degree of interference depends on the strength of both mutations and
214 the recombination rate. In addition, the degree of stochastic interference also
depends on the flow of beneficial mutations, which depends on the mating system.
216 We now turn to the full model to quantify exactly the stochastic interference effect.

Modelling Framework

218 Deriving the baseline reduction in emergence probability, Π

We first need to determine $\Pi(p)$, the reduction in the probability of emergence
220 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 mul-
222 tiple genetic backgrounds. In a seminal paper, BARTON (1995) outlined how to
calculate the emergence probability of a focal beneficial allele that changes between
224 different backgrounds in a haploid population. If the probability of switching
between backgrounds is of the same order as selection coefficients, s , and differ-
226 ence 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
228 at time t , Q_i , verifies the following differential equation:

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

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:

$$\frac{dp}{dt} = s_1 p(1-p)(F + h_1 - h_1 F + (1-F)(1-2h_1)p) + \mathcal{O}(s_1) \quad (6)$$

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):

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

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

248 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
250 follows:

$$-\frac{\partial Q_1}{\partial T} = -r(1 - F)(1 - p)(Q_1 - Q_2) + \theta_1(p)Q_1 - (1 + F)\frac{Q_1^2}{2}\quad (9)$$

$$-\frac{\partial Q_2}{\partial T} = -r(1 - F)p(Q_2 - Q_1) + \theta_2(p)Q_2 - (1 + F)\frac{Q_2^2}{2}\quad (10)$$

where p verifies Equation 6. Equations 9 and 10 reflects that selfing reduces
252 recombination by a factor $1 - F$ (GOLDING and STROBECK 1980; NORDBORG
2000) and increases drift by a factor $1/(1 + F)$ (POLLAK 1987; CHARLESWORTH
254 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
256 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,
258 $\Delta = Q_1 - Q_2$. 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
260 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

262 thus obtain:

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

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

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

264 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
266 numerically by, e.g., using the ‘NDSolve’ function in *Mathematica* (WOLFRAM RESEARCH, INC. 2014). Alternatively, to remove the time dependence (∂t) and
268 directly obtain $\Pi(p)$, we can divide both Equations 11 and 12 by dp/dt (Equation 6). Boundary conditions can be found by looking at the behaviour of the
270 system as $t \rightarrow \infty$ or $p \rightarrow 1$. In this case, we observe that $\Pi \rightarrow 1$, reflective of the fact that as the first sweep fixes, interference is not present as the second allele is
272 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
274 $\phi \ll 1$ (as used in BARTON (1995)) and $\partial\Delta/\partial T \rightarrow 0$ as $p \rightarrow 1$. In this case Δ tends to $(1-(1-F)h_1)/(1-(1-F)(h_1-\rho))$, which reflects the probability that the
276 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
278 condition assumes small ϕ , the system of equations appear to work well even with larger ϕ when compared to simulations.

280 Deriving the probability of sweep replacement, Π_{rep}

The previous analysis focussed primarily on the case where the second mutant
282 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
284 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
286 replacement occurring and subtract it from the baseline reduction Π . This prob-
ability can be calculated by altering the model of HARTFIELD and GLÉMIN (2014),
288 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'
290 allele the second fitter sweep. HARTFIELD and OTTO (2011) implemented a sim-
ilar rescaling for a haploid model, while YU and ETHERIDGE (2010) provided a
292 general stochastic algorithm for investigating this behaviour. By using the same
conditions under which the model of HARTFIELD and GLÉMIN (2014) is valid, we
294 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 $(1-(1-F)h_2)s_2 > (h_1 + F(1-h_1))s_1$;
- 296 2. The second mutation emerges on the wildtype background (with probability
 $1 - p$);
- 298 3. No 'successful' recombinant arises during the sweep of the second mutation
(‘successful’ meaning that the two beneficial alleles are placed together onto
300 the same genetic background and become fixed).

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

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

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

so

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

306 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
 308 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
 310 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 ,
 312 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 .
 314 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
 316 θ_3 are given in Supplementary Material 1, and are given as:

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

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

Following HARTFIELD and GLÉMIN (2014), the emergence probability of the re-
 318 combinant haplotype carrying both mutations were it to arise, P_d , is solution of:

$$\frac{dP_d}{dq} = \left(\theta_3(q)P_d(q) - \frac{1+F}{2}P_d(q)^2 \right) / \Delta q \quad (17)$$

Equation 6 of HARTFIELD and GLÉMIN (2014) is then used to calculate P_{HH} , for
 320 $\kappa(q) = q(1-q)r(1-F)P_d$:

$$P_{HH} = \exp \left(- \int_{p=0}^{p=1} \frac{2N\kappa(p)}{s_1 dp/dT} \right) dp \quad (18)$$

which can be inserted into Equation 14. Note that P_{HH} , hence $\Pi_{rep}(p)$, is not
 322 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 $s_2 \leq s_1$.

324 **Integration over the sweep trajectory**

To obtain the average effect of interference we need to consider all possible
 326 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:

$$\bar{R} = \frac{1}{T_1 - T_0} \int_{T_0}^{T_1} \Pi(T) - \Pi_{rep}(p(T)) dT \quad (19)$$

328 As previously showed by BARTON (1995), $\bar{\Pi}$ can be approximated by:

$$\bar{\Pi} \approx 1 - \frac{1}{T_1 - T_0} \int_{-\infty}^{\infty} (1 - \Pi(T)) dT = 1 - \frac{1}{T_1 - T_0} \int_0^1 \frac{(1 - \Pi(p))}{dp/dT} dp \quad (20)$$

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

330 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,
332 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 $p >$
334 $p_e \approx (1 + F) / [2Ns_1(h_1 + F - h_1F)]$. Note that this condition is a bit too restrictive
because we should also consider the case when mutation 1 arises after but emerge
336 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
338 (not shown) and as shown below, the reduction in the overall emergence probability
(Equation 19) can be written as:

$$\bar{R} \approx 1 - \frac{1}{T_1 - T_0} \left(\int_0^1 \frac{(1 - \Pi(p))}{dp/dT} dp + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{dp/dT} dp \right) \quad (21)$$

340 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
342 emerges after mutation 2 has occurred. Moreover, because selfing and dominance
affects the length of sweeps (GLÉMIN 2012), averaging over sweep length would
344 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
346 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
348 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
350 substitutions):

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

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

$$\bar{R} \approx 1 - \lambda_1 \left(\int_0^1 \frac{(1 - \Pi(p))}{dp/dT} dp + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{dp/dT} dp \right) \quad (23)$$

352 The justification is as follows. The waiting time between two sweeps is exponentially distributed with mean $1/\lambda_1$. If $T_1 - T_0 < 1/\lambda_1$, interference between
354 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:

$$(1 - \lambda_1(T_1 - T_0)) + \lambda_1(T_1 - T_0) \left(1 - \frac{1}{T_1 - T_0} \left(\int_0^1 \frac{(1 - \Pi(p))}{dp/dT} dp + \int_{p_e}^1 \frac{\Pi_{rep}(p)}{dp/dT} dp \right) \right) \quad (24)$$

356 leading to Equation 23.

Simulations

358 We tested the accuracy of the numerical solutions by comparing them to stochastic simulations written in R (R DEVELOPMENT CORE TEAM 2014); code
360 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
362 homozygotes, heterozygotes, and wild-type homozygotes were calculated based on standard equations with inbreeding (WRIGHT 1951). The second allele was subsequently
364 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/\bar{w} due
366 to selection, where w_i is the fitness of the genotype and \bar{w} is the population mean fitness. Recursion equations derived by HEDRICK (1980, Equation 3) then calculated
368 how genotype frequencies changed due to partial selfing. A life-cycle was

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

378 Results

Validity of the analytical/numerical approach

380 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
382 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
384 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
386 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
388 of recessive beneficial mutants are underestimated using the branching-process
solution without considering homozygotes genotypes (Equation 1, which holds
390 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
392 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
394 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 $s_2 > s_1$
396 and the first sweep is at frequency p . Generally, if the first mutation is not re-
cessive, recombination is low (and/or selfing high) and p is above $1/2$ then the
398 analytical solution matches up well with simulations. However, if recombination is
high ($2Nr$ approaches 1) and mutations are recessive then the actual replacement
400 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
402 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
404 not rapidly eliminated, so not all recombination occurs between the two selected
haplotypes. Hence Equation 18 would overestimate the effect of recombination,
406 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
408 the assumption that it will compete with the second sweep. This behaviour is also
observed if both mutants are dominant in outcrossing populations ($h_1 = h_2 = 0.8$;
410 see Supplementary Material 1). To calculate a more accurate replacement prob-
ability in this case, it would be necessary to explicitly account for the frequency
412 of the neutral class, or how recessive beneficial mutations drift at a low frequency.
Unfortunately it will probably be unfeasible to produce tractable analytical solu-
414 tions in either scenario. Hence in subsequent analyses when $\phi > 1$, we will focus
on additive or dominant mutations ($h \geq 1/2$).

416 Additive case

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

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

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

where $\rho_F = \rho(1 - F)/(1 + F)$. Equations 25, 26 are similar to BARTON'S (1995)
 422 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
 424 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
 426 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
 428 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
 430 BARTON (1995) with the appropriate rescaling:

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

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

Approximation for the replacement probability can also be obtained (see details
 432 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):

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

434 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 :

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

436 Integrating over the sweep trajectory we obtain:

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

Quantitative inspection of previous equations shows that the emergence effect
 438 (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
 440 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
 442 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
 444 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

446 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
448 chromosome tracts for high selfing rates.

In previous equations, the scaling factor $2/(1+F)$ arises because the length of
450 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
452 selfing: the reduction in effective recombination reduces the probability of emer-
gence, and also increases the probability of replacement but on a shorter period of
454 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
456 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).
458 When $4Nr < 1.386 \frac{(\phi-1)^2}{\phi \ln(\phi)}$, replacement is more likely under outcrossing than com-
plete selfing (see Supplementary Material 1). Emergence is also more likely under
460 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
462 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).

464 **Effect of dominance on interference**

For high selfing rates, the interference process is well approximated by the
466 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
468 outcrossing populations before considering the global effect of mating systems on

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

472 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
474 the length of the two stochastic phases. Because a mutation causes interference
mainly during its deterministic trajectory, which is similar for any dominance
476 level ($\mathcal{O}(1/2Ns_1)$ for any h_1 ; EWING *et al.* (2011)), the dominance level of muta-
tion 1 has thus only a weak effect on the probability of emergence of mutation
478 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
480 $\mathcal{O}(\frac{\ln(2Ns_2)}{2Nh_2s_2})$ (EWING *et al.* 2011). Recessive mutations are thus more sensitive to in-
terference than additive and dominant ones. Interference thus reinforces Haldane's
482 sieve, in the sense that recessive mutations are even less likely to emerge in out-
crossing populations, if tightly linked to the initial sweep. In the case of strong
484 interference, this effect can be substantial as illustrated in Figure 5. Interestingly,
this effect is not symmetrical since dominant mutations only exhibit slightly less
486 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
488 spectrum of fixed beneficial mutation should vary with recombination rate (Fig-
ure 6). The same pattern is observed for replacement but it is quantitatively
490 weaker (Supplementary Material 1) as already noted by HARTFIELD and GLÉMIN
(2014) for hitchhiking of deleterious mutations.

492 **Conditions under which selection is more efficient under** 493 **outcrossing than under selfing**

494 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
496 factor increasing drift effects in selfers, selfing reduces (respectively increases) ad-
aptation from new dominant (respectively recessive) mutations (CHARLESWORTH
498 1992; CABALLERO and HILL 1992). How does interference affect this condition?
This question can be explored by considering a steady flow of mutations and ana-
500 lyzing $P_{12} = \bar{R}P_2$ where \bar{R} is given by Equation 23. As shown in Supplementary
Material 1, the total effect of interference on replacement will be no more than
502 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
504 case where $\phi < 1$.

Figure 7 illustrates how selfing can affect the probability of fixation of the
506 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
508 highly selfing species. This reduction is moderate and selfing species are still bet-
ter than outcrossing ones at fixing recessive mutations. Under strong adaptation
510 regime ($\theta = 0.2$), interference can be substantial even in mixed mating species and
adaptation can be fully impeded in highly selfing species if $\lambda_1 > 1 / \int_0^1 \frac{(1-\Pi(p))}{dp/dT} dp$
512 (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
514 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

522 Interference between beneficial mutations with partial self- 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 pos-
sibilities. First, given that an existing sweep is progressing through the population,
536 subsequent mutations confer a lower selective advantage and can only fix if recom-
bining 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

562 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
564 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
566 can be approximated by solving the following equation for λ (see Supplementary
Material 3):

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

568 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
570 that shows that for a moderate flow of beneficial mutation (where no interference
occurs under outcrossing) adaptation can be substantially reduced for very high
572 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
574 increases. While the two locus model suggests that only weak mutations should
be substantially affected by strong mutations, the multiple sweep model suggests
576 that mutations of similar effect can also interfere in highly selfing species.

Causes of limits to adaptation in selfing species

578 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 muta-
580 tions (HARTFIELD and GLÉMIN 2014), with KAMRAN-DISFANI and AGRAWAL
(2014) demonstrating that background selection can also greatly limit adaptation.
582 Hence the question arises as to whether deleterious mutations or multiple sweeps
are more likely to impede overall adaptation rates in selfing species.

584 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
586 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
588 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
590 fixed mutations. Similarly, adaptation from standing variation, which depends on
polymorphism level, is expected to be affected by the same proportion (GLÉMIN
592 and RONFORT 2013). Alternatively, interference between beneficial mutations is
mediated by ϕ , the ratio of the selection coefficients of the sweeps. Weak muta-
594 tions 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 BAR-
596 TON 2012). Because of selective interference, selfing is also expected to shift the
spectrum of fixed mutations towards towards those of strong effect. Interestingly,
598 WEISSMAN and BARTON (2012) showed that neutral polymorphism can be signi-
ficantly reduced by multiple sweeps even if sweeps do not interfere among them.
600 This suggests that in selfing species, adaptation from standing variation should be
more limited than predicted by single-locus theory (GLÉMIN and RONFORT 2013).
602 Selective interference could thus affect both the number and type of adaptations
observed in selfing species.

604 However, reflecting on this logic, both processes should interact and we there-
fore predict that background selection will have a diminishing-returns effect. As
606 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),
608 hence interference between beneficial mutations will subsequently be alleviated.

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

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

630 Empirical Implications

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

So far, few studies currently exist that directly compare adaptation rates and
640 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*
642 *flora* exhibited much higher adaptation rates (where $\alpha = 40\%$ of non-synonymous
substitutions were estimated to be driven by positive selection using the McDonald-
644 Kreitman statistic; SLOTTE *et al.* (2010)) than in the selfing related species *Arabidopsis thaliana*
(where α is not significantly different from zero). Similarly, the
646 outcrossing snail *Physa acuta* exhibited significant adaptation rates ($\alpha = 0.54$),
while no evidence for adaptation in the selfing snail was obtained (BURGARELLA
648 *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
650 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
652 species.

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

654 through selection interference, this result can explain why selective sweeps cover-
ing large tracts of a genome are commonly observed, as with *Arabidopsis thaliana*
655 (LONG *et al.* 2013) and *Caenorhabditis elegans* (ANDERSEN *et al.* 2012). Extended
sweep signatures can also be explained by reduced effective recombination rates in
658 selfing genomes. Finally, selection interference between beneficial mutations could
explain why maladaptive QTLs are observed as underlying fitness components,
660 as observed in *Arabidopsis thaliana* (ÅGREN *et al.* 2013). Direct QTL compar-
isons between selfing and outcrossing sister species would therefore be desirable to
662 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
\bar{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, $4NU_b$

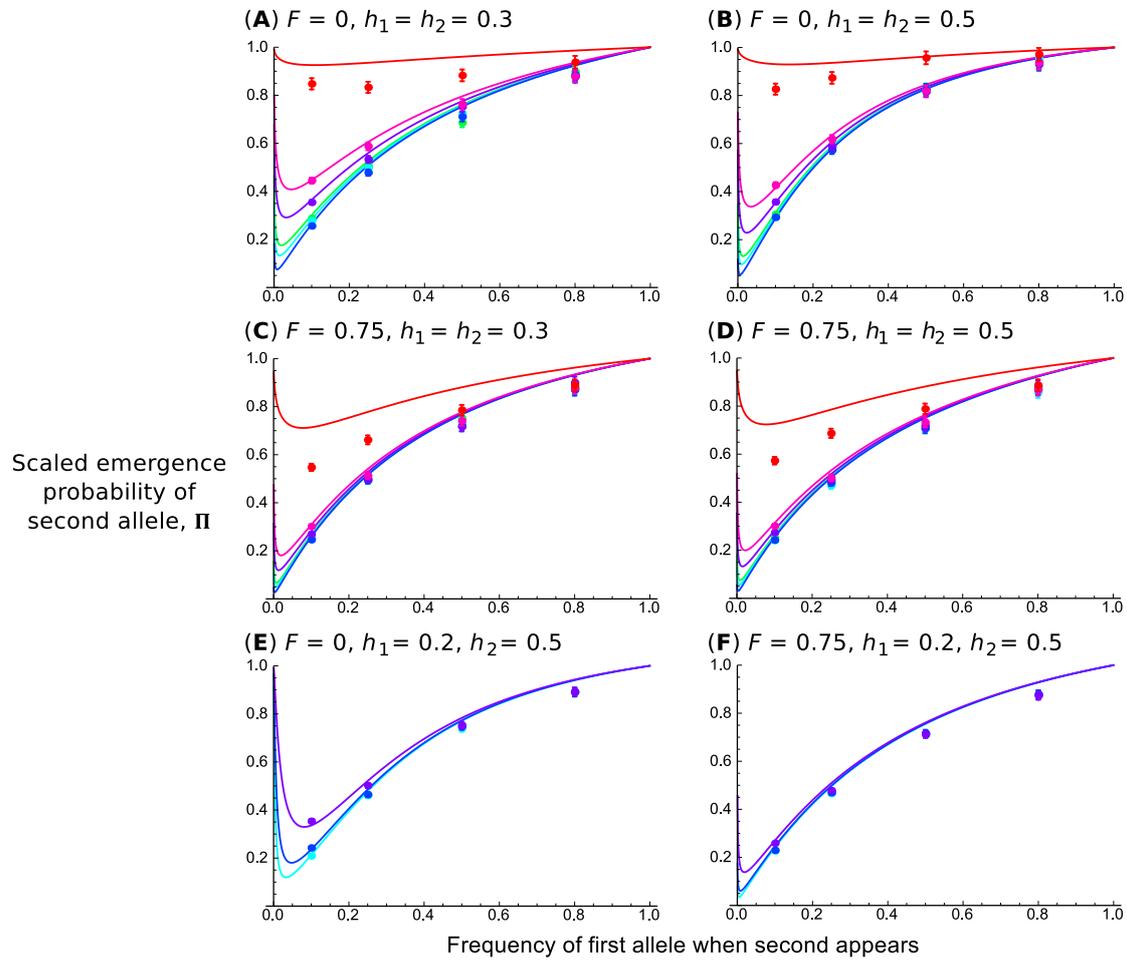


Figure 1: Probability of fixation of the second allele relative to the unlinked case, Π , as a function of the first allele frequency, p . $N = 2000$, $s_1 = 0.04$, $s_2 = 0.02$ (so $\theta = 0.5$), and from bottom to top in (a)–(d): $4Nr = 0.4, 1, 1.6, 4, 16, \text{ and } 80$ (corresponding to $\rho = 0.00125, 0.003125, 0.005, 0.0125, 0.025, \text{ and } 0.5$). 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.

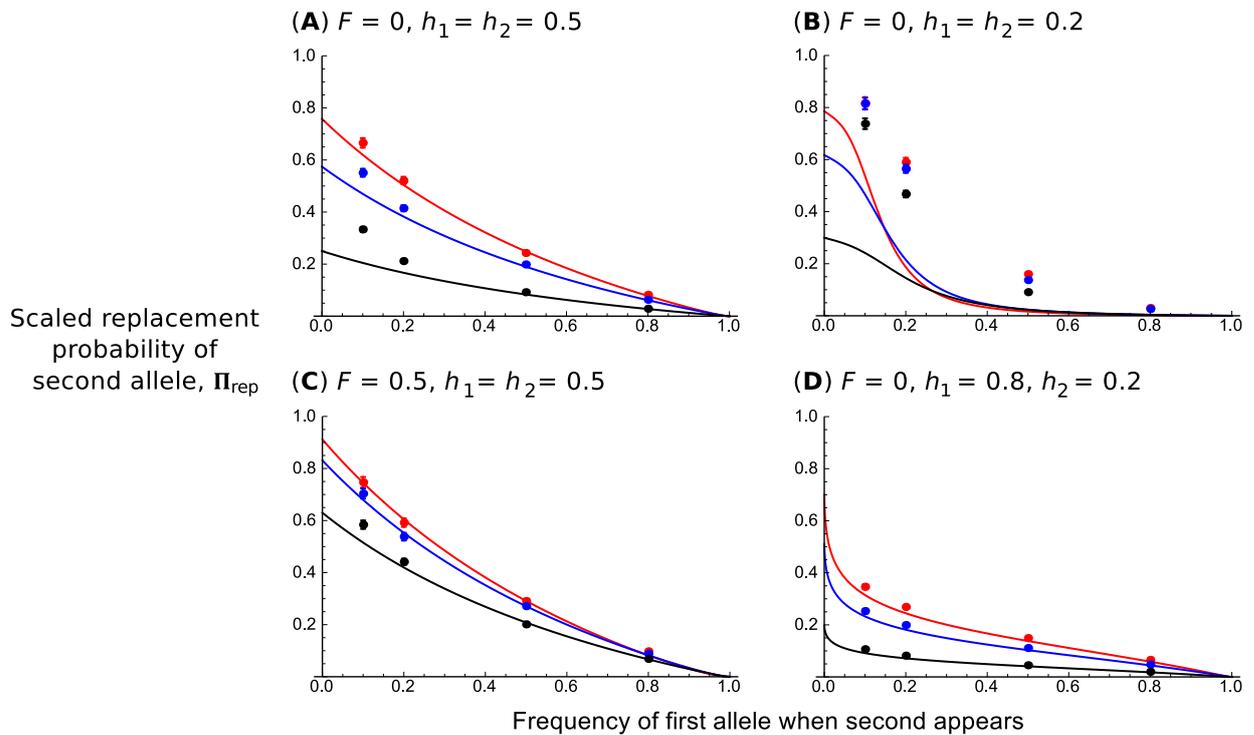


Figure 2: Probability Π_{rep} that a second beneficial allele with advantage s_2 replaces an existing sweep with selective advantage s_1 where $s_2 > s_1$, as a function of the first sweep frequency p when the second sweep appears. $N = 5,000$ and $2Nr = 0.1$ (red), 0.2 (blue) or 0.5 (black). Other parameters 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.

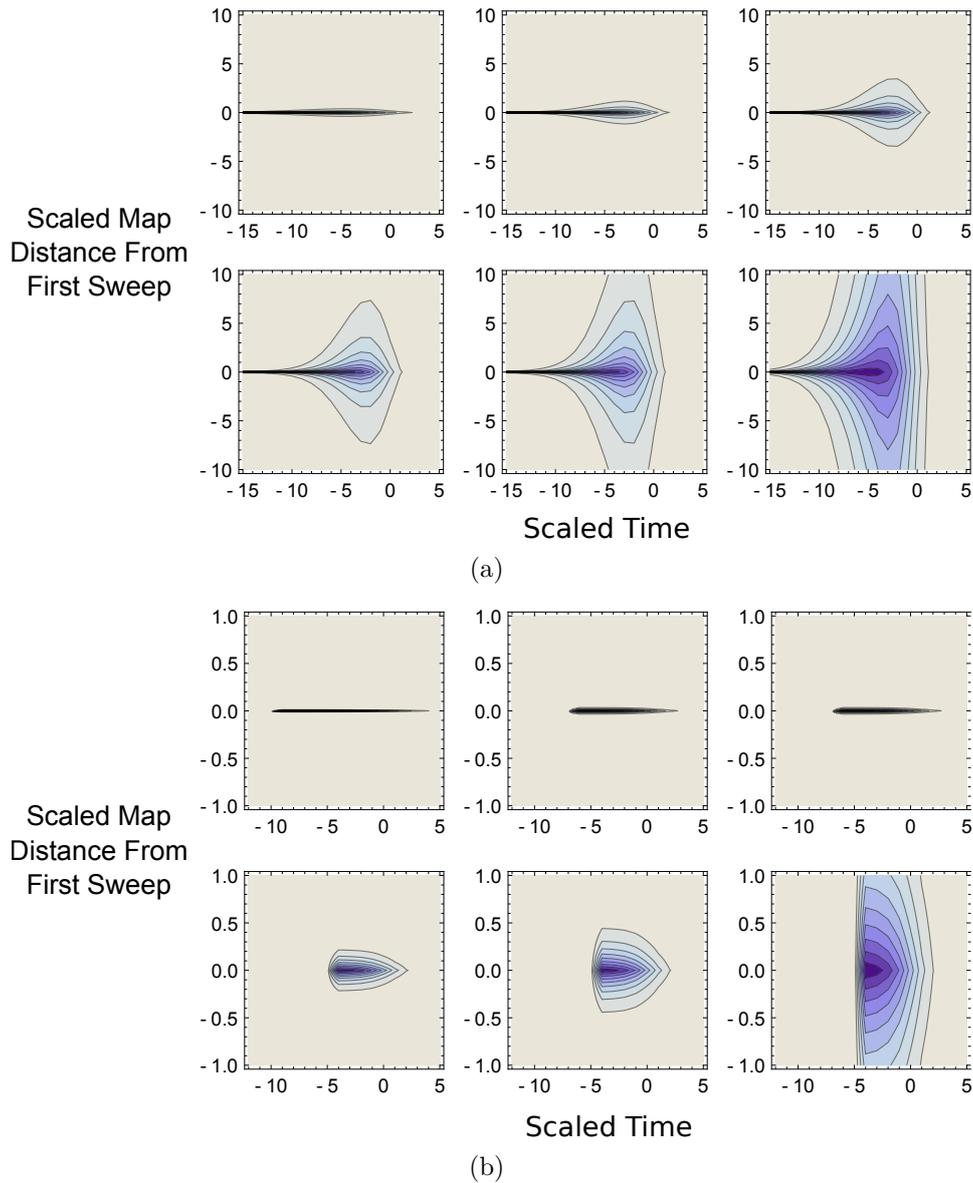


Figure 3: Contour plots showing degree of interference, as measured by Equation 2 with Π defined by Equation 25 (for $\phi < 1$) and Π_{ref} defined with Equation 31 (for $\phi > 1$), when both mutations are additive ($h_1 = h_2 = 1/2$). In both panels, darker colours indicate higher degree of interference (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 $\phi = 5$.

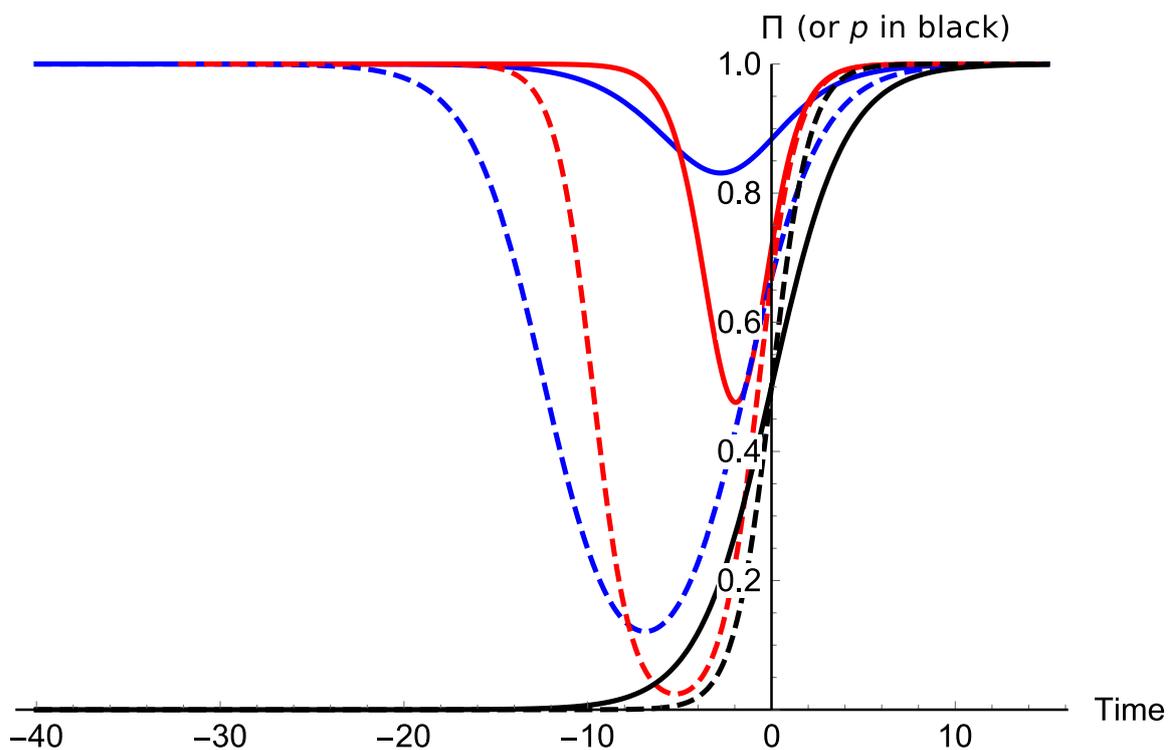


Figure 4: Profile of how Π changes over the course of the first sweep, as a function of time T . $h_1 = h_2 = 0.5$, $\phi = 1$ and ρ equals 0.1 (coloured solid lines) or 0.0001 (coloured dashed lines). Results are compared for $F = 0$ (blue lines) or $F = 0.95$ (red lines). For comparison, the underlying 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 $T = 0$.

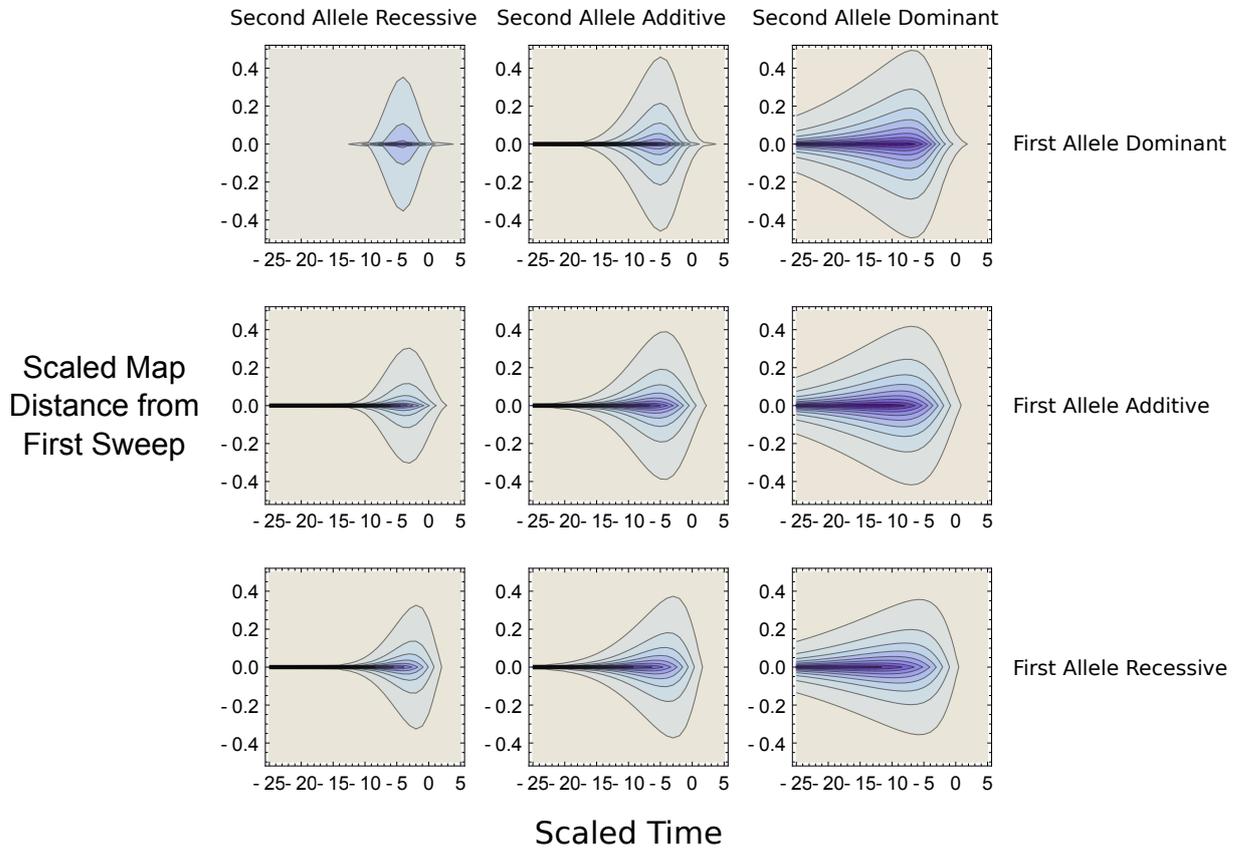


Figure 5: Contour plots showing degree of interference, as measured by Equation 2 with Π defined by Equation 25 and $\Pi_{rep} = 0$ (as $\phi < 1$), for different dominance values. In both panels, darker colours indicate higher degree of interference (R approaching 0); x-axis denotes time of the sweep (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 $\phi = 0.5$.

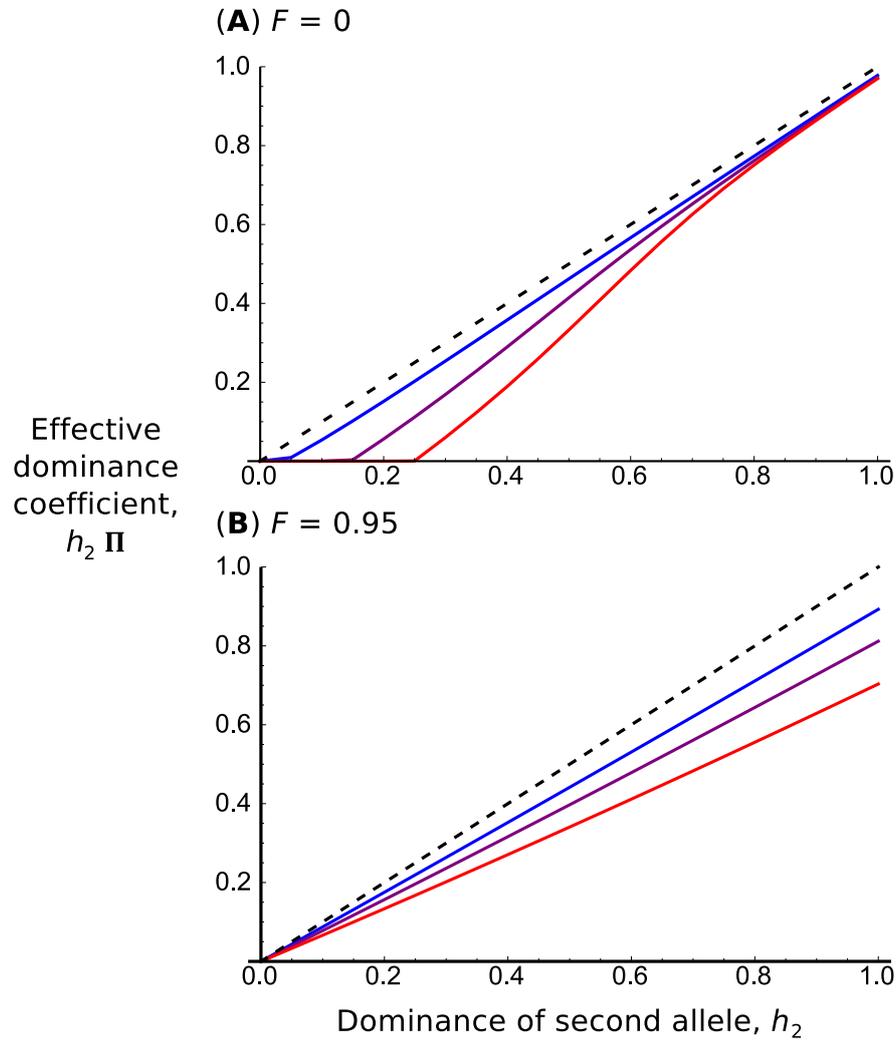


Figure 6: Plots of the effective distribution of dominance effects in either an outcrossing population ($F = 0$, (a)), or a selfing population ($F = 0.95$, (b)), defined by $h_2 \cdot \bar{\Pi}$ (Equation 20), as a function of h_2 . $N = 10,000$, $h_1 = 0.5$, $s_1 = s_2 = 0.01$ ($\phi = 1$), $\theta = 4Nu = 0.1$ 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.

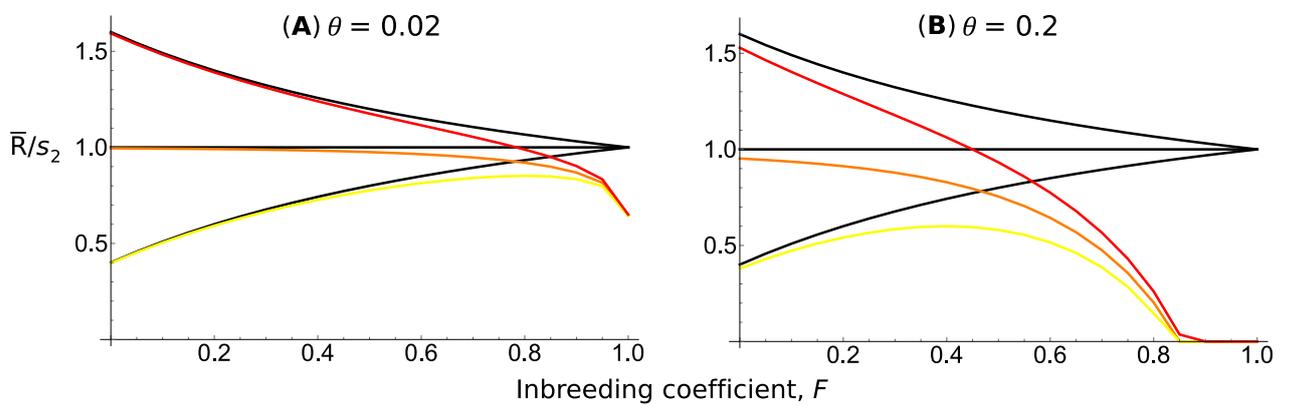


Figure 7: Plots of the total effect of interference, \bar{R} , as defined using Equation 23, as a function of F . The y -axis is the probability of emergence scaled to s_2 , the expected emergence probability with $F = 1$. There is a continual rate of mutation $\theta = 4Nu = 0.02$ (left) or 0.2 (right). $N = 10,000$, $r = 0.01$, $h_1 = 0.5$, $s_1 = 0.01$, $s_2 = 0.001$ ($\phi = 0.1$), 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.

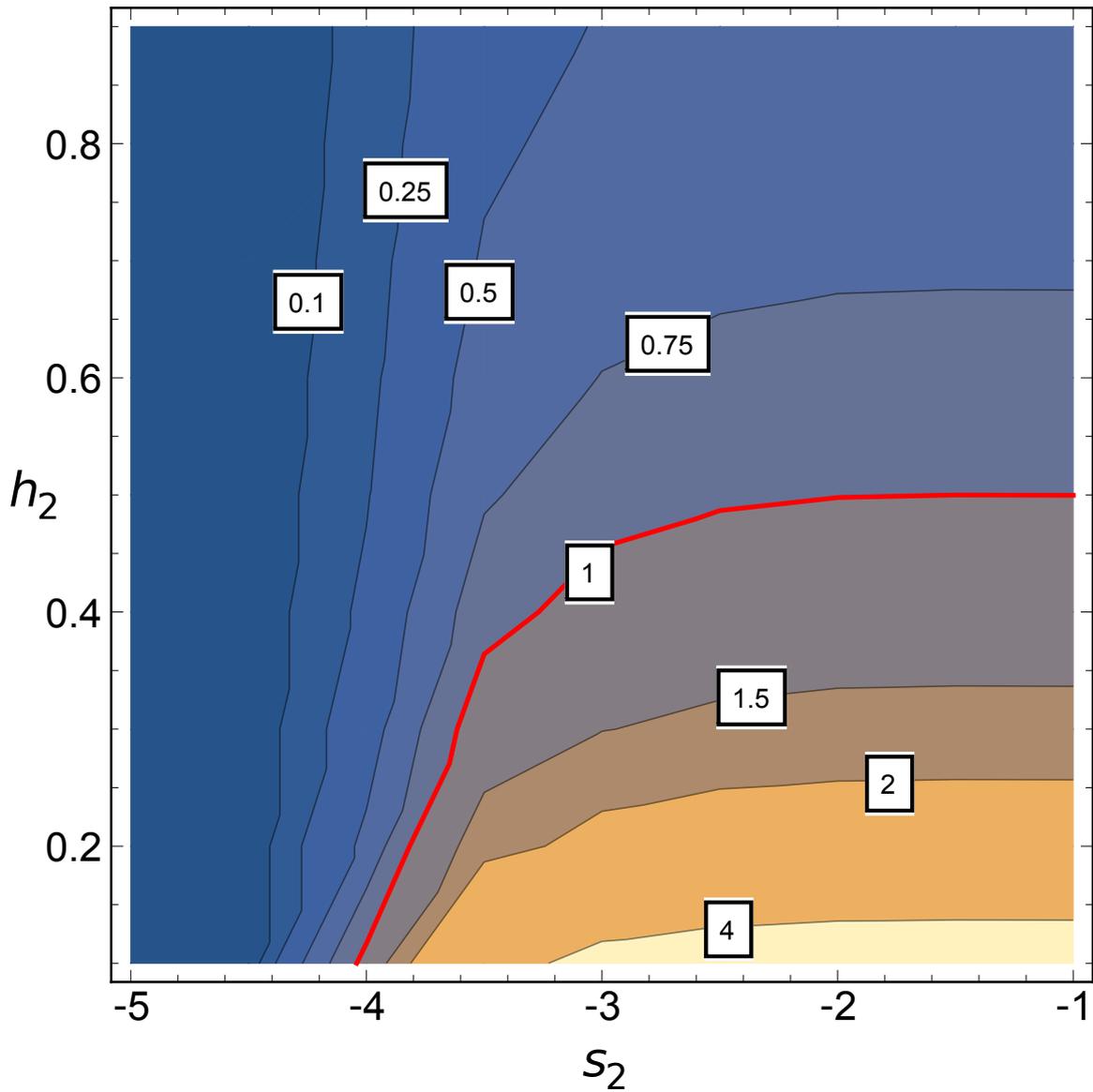


Figure 8: Contour plot of the ratio of \bar{R} (Equation 23) for $F = 0$ and $F = 0.95$, as a function of s_2 and h_2 . Values less than one indicate that outcrossers has the higher fixation probability, and values greater than one indicate that $F = 0.95$ populations have the higher probability. Other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