Hidden genetic variance and residual allogamy contribute to increase the adaptive potential of selfing populations

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Abstract: Standing genetic variation is considered a major contributor to the adaptive potential of species. The low heritable genetic variation observed in self-fertilising populations has led to the hypothesis that species with this mating system would be less likely to adapt. However, a non-negligible amount of cryptic genetic variation for polygenic traits, accumulated through negative linkage disequilibrium, could prove to be an important source of standing variation in self-fertilising species. To test this hypothesis we simulated populations under stabilizing selection subjected to an environmental change. We demonstrate that selfing populations are better able to store cryptic genetic variance than outcrossing populations, notably due to the reduced effective recombination rate associated with predominant selfing. Following an environmental shift, this diversity can be partially remobilized through residual allogamy, which increases the additive variance and adaptive potential of predominantly (but not completely) selfing populations. In such conditions, even though the process of adaptation itself is mating system dependant, selfing populations reach levels of fitness that are equal to or higher than outcrossing ones within a few generations. The population size and the mutation rate are the main parameters to consider, as they are the best predictors of the amount of cryptic diversity. Our results and their impact on our knowledge of adaptation under high selfing rates are discussed.

Keywords: self-fertilization, standing genetic variation, adaptation, linkage disequilibrium, residual allogamy.

INTRODUCTION

Natural populations harbour a significant amount of genetic variation, especially at loci governing polygenic traits (Mittell *et al.*, 2015; Wood *et al.*, 2016; Clo *et al.*, 2019). This variation, known as standing genetic variation, has been considered to be an important predictor for the adaptive potential of populations (Orr & Betancourt, 2001; Hermisson & Pennings, 2005; Barrett & Schluter, 2008; Pritchard *et al.*, 2010; Glémin & Ronfort, 2013; Matuszewski *et al.*, 2015). Indeed, standing variation represents an easily accessible and non-negligible source of genetic variation, that is readily available for adaptation to changing or heterogeneous conditions (Hermisson & Pennings, 2005; Barrett & Schluter, 2008). Contrary to adaptation from *de novo* mutations, the probability of adapting from standing variation is higher simply because mutations already segregating in a population are expected to be present at higher frequencies (Innan & Kim, 2004; Barrett & Schluter, 2008). It has also been suggested that populations adapting from standing genetic variation can cope with more severe and more rapid environmental change, as they are able to cross larger distances in phenotype space (Matuszewski *et al.*, 2015). The amount of heritable variation available in a population is thus expected to play a key role in adaptation, and any forces affecting it may greatly influence whether or not populations are able to survive new environments.

Mating system is a population characteristic that is known to greatly affect the amount and structure of genetic variance. For instance, both theoretical models (Charlesworth & Charlesworth, 1995; Lande & Porcher, 2015; Abu Awad & Roze, 2018) and empirical data (Charlesworth & Charlesworth, 1995; Geber & Griffen, 2003; Clo *et al.*, 2019) have shown that, compared to outcrossing populations, self-fertilization reduces, on average, the amount of additive genetic variance for polygenic or quantitative traits under stabilizing selection.

This diminution is due to more efficient purifying selection under selfing and to negative linkage disequilibria maintained between alleles at different loci: the so-called Bulmer effect (Lande & Porcher, 2015; Abu Awad & Roze, 2018). Due to this reduction in genetic variability, predominant selfing has been described as an evolutionary dead-end (Stebbins, 1957; Takebayashi & Morrell, 2001; Igic & Busch, 2013). However, recent theoretical work and empirical data have highlighted that cryptic genetic variability could contribute to the adaptive potential of natural populations. Cryptic genetic variation has been defined as the part of a population's standing genetic variation that has no effect on the phenotypic variation in a stable environment but can increase heritable variation in environmental conditions rarely experienced (Gibson & Dworkin, 2004; Paaby & Rockman, 2014). Such "hidden" variability has been detected in both outcrossing (in sticklebacks, McGuigan *et al.*, 2011, cavefish, Rohner *et al.*, 2013, dung flies, Berger *et al.*, 2011, gulls, Kim *et al.*, 2013 or spadefoot toads, Ledon-Rettig *et al.*, 2010) and selfing species (*Caenorhabditis elegans*, Milloz *et al.* 2008; *Arabidopsis thaliana*, Queitsch *et al.* 2002). Two main mechanisms could explain the accumulation and the release of such variance: interactions between loci (Badano & Katsanis, 2002; Shao *et al.*, 2008), and phenotypic plasticity (Anderson *et al.*, 2013). In this paper, we focus on interactions between loci maintained at stabilizing selection.

In maintaining the population close to the phenotypic optimum, stabilizing selection disfavors apparent genetic and phenotypic diversity (Lande & Porcher, 2015; Abu Awad & Roze, 2018). However, the structure of the additive variance also strongly depends on the trait mutation rate and the prevalence of pleiotropy (Charlesworth, 1990; Lande & Porcher, 2015; Abu Awad & Roze, 2018). When the per-trait mutation rate is weak, associations between loci are negligible (mutations of strong effect arise slowly and are easily purged), but when the rate increases, the creation and maintenance of co-adapted gene complexes structure the additive variance into positive within-loci components and negative among-loci components,

reducing the observed additive variance (Abu Awad & Roze, 2018). The remobilization through recombination of this last component of variance could boost the adaptability of populations undergoing a shift in the phenotypic optimum (Le Rouzic and Carlborg 2008). Indeed, if associations between loci are broken, segregating alleles could express some or all of their additive effects in new-genetic backgrounds. Such remobilization is only possible if residual allogamy occurs (*i.e.* if selfing rate is not equal to 1), which is expected to be common in natural plant populations (Kamran-Disfani & Agrawal, 2014; Clo *et al.*, 2019). Classical models analyzing the effect of selfing on adaptation from standing genetic variation have considered a single locus (Glémin & Ronfort, 2013), thus neglecting interactions among loci that could result in other forms of standing genetic variation. As self-fertilization reduces the effective recombination rate (Nordborg, 2000), allowing the maintenance of co-adapted gene complexes, the storage of hidden genetic diversity should be more prevalent in selfing populations (as suggested in Charlesworth, 1990; Lande & Porcher, 2015; Abu Awad & Roze, 2018).

In this paper, we explore this hypothesis, using a quantitative genetics framework. We describe and quantify how, to what degree, and under which conditions populations accumulate hidden genetic variation at polygenic traits. Because the development of tractable analytical predictions of the mean change of the means of phenotype and genetic variance is not trivial and often requires strong hypotheses to be made, notably random mating and considering the system to be at linkage equilibrium (Barton & Turelli, 1987; Keightley & Hill, 1989; Bürger, 1993), we chose to use a simulation approach. We showed that, in models allowing for hidden genetic diversity and when adaptation is only possible from pre-existing standing genetic variation, predominantly (but not obligatory) selfing populations are able to reach similar to higher fitness levels than their mixed-mating and outcrossing counterparts.

MATERIAL AND METHODS

General assumptions

We consider the evolution of a quantitative trait Z in a population of size N, made of diploid individuals reproducing through partial self-fertilization, with a constant selfing rate σ. The phenotypic value z of an individual is determined by the additive action of L loci each with an infinite possible number of alleles and is given by

$$z = g + e, \quad (1)$$

where g is the genetic component of the individual's phenotype, and is given by $g = \sum_j^L (g_j^M + g_j^P)$, with $g^M{}_j$ (respectively $g^P{}_j$) the additive allelic effect at locus j inherited from the maternal (respectively paternal) gamete. The random environmental effect, e, is drawn from a Gaussian distribution of mean 0 and variance V_E, and is considered to be independent from the genetic components of fitness. The trait initially undergoes stabilizing selection around an optimal phenotypic value, denoted Z_{opt}. The fitness value W_Z of an individual with phenotype z is thus described by the Gaussian function:

$$W_Z = e^{-d^2/2\omega^2}, \quad (2)$$

where d is the distance between the individual's phenotype z and the optimum trait value and ω^2 is the width of the fitness function, and represents the strength of selection.

Simulation model

We implement the model described above into an individual based simulation model written in C++, a modified version of the "continuum of alleles" program provided in Abu Awad and Roze (2018) and is available in supplementary materials and online (https://github.com/dialaAbAw/SelfingAdaptation).

We consider a population of N diploid individuals, each represented by two linear chromosomes with L multi-allelic loci, coding for a single quantitative trait under selection. At the beginning of each simulation, all individuals are genetically identical and are at the phenotypic optimum (all loci carry alleles with effect 0 and $Z_{OPT} = 0$). The life cycle can be summarized by five successive events. First, there is a phenotype-dependent choice of the maternal parent (selection), followed by mating-type choice (selfing versus outcrossing at rates σ and (1- σ) respectively) and then, in the case of outcrossing, phenotype-dependent choice of the paternal parent. Once the two parents are chosen, they each contribute a gamete, produced through uniformly recombining the parental chromosomes. The number of cross-overs sampled from a Poisson distribution with parameter R, the map length. From Haldane's mapping function, the recombination rate between two adjacent loci is $r = \frac{1}{2}\left[1 - exp\left(\frac{-2R}{L-1}\right)\right]$, with $R = 50$ in our simulations so as to ensure that r remains at 0.5 and loci remain, at least physically, unlinked. This phase is then followed by the introduction of new mutations, the number of which is sampled from a Poisson distribution with parameter U (with $U = \mu L$, μ being the per locus mutation rate). The additive value of a new mutant allele is drawn from a Normal distribution of mean 0 and variance a^2.

Each simulation consists of two phases, the first being burn-in time to allow the population to attain Mutation-Selection-Drift equilibrium (M-S-D). The population is

considered to be at M-S-D equilibrium when the average fitness value calculated over the last thousand generations does not differ by more than one percent from the mean fitness calculated over the previous thousand generations. The second phase consists of following the population after a shift in the phenotypic optimum. After the shift, the haploid genomic mutation rate U is set to 0 so that the only source of genetic variability to reach the new optimum is the standing variation accumulated before the environmental change.

Simulation parameter values:

Simulations were run for several parameter sets in order to evaluate the effects of each parameter on both the equilibrium conditions and on the ability of populations to adapt after the environmental change. The values chosen for the mutation rate U range from 0.005 to 0.1, reflecting the *per*-trait haploid genomic mutation rate found in the literature (Keightley & Bataillon, 2000; Shaw *et al.*, 2002; Haag-Liautard *et al.*, 2007). We use parameter set values similar to those explored in Bürger *et al.*, (1989) and Ronce *et al.*, (2009), with the number of freely recombining loci under selection L = 50, and a^2 = 0.05, V_E =1, ω^2 = 1, 9 or 99 (so that $V_S = \omega^2 + V_E$ is equal to 2, 10 or 100 respectively). The mean deleterious effect of mutations $\bar{s}$ is therefore equal to 0.0125, 0.0025 or 0.00025 ($\bar{s} = a^2 / 2V_S$, Martin and Lenormand 2006).

Before the shift in the optimum, Z_{OPT} is set to 0, and after M-S-D equilibrium it is set to 2.5, so that the shift is of order $L.a^2$, and ensure that adaptation is due to genetic changes and not environmental variance (Ronce *et al.*, 2009). We follow populations only over 20 generations after the shift in the optimum, as we chose to follow the possibility of adaptation without any contribution from *de novo* mutations. After this time limit, genetic variation starts to erode, and the observed results are mainly due to the effects of loss of diversity due to drift and not to the selection process. We also assume that any population unable to adapt over this

period, is probably under high risk of extinction or replacement by another competing species. Although simulations were run over a large range of selfing rate values, throughout the manuscript we show results run principally for three rates of self-fertilization, σ = 0, 0.5 and 0.95, representing outcrossing, mixed-mating and predominantly selfing respectively. These three values were chosen because they were representative of the main patterns of adaptation we observed over the whole range of selfing rates (σ from 0 to 1). We also considered three population sizes N = 250, 1000 or 10000.

Analysis of the effect of selfing on the equilibrium genetic variance

Following Turelli & Barton (1990), we decompose the genetic variance of a polygenic trait using the following equation:

$$V_{\mathrm{A}} = 2\sum_{j}^{L}\left(C_{jj} + C_{j,j}\right) + 2\sum_{j\neq k}^{L}\left(C_{jk} + C_{j,k}\right), \quad (3)$$

with

$$C_{j\,j} = \frac{1}{2}E[\,(g^{\mathrm{M}}{}_{j} - \bar{g}_{j})^2 + (g^{\mathrm{P}}{}_{j} - \bar{g}_{j})^2] \quad (4)$$

and

$$C_{j\,,\,j} = E[\,(g^{\mathrm{M}}{}_{j} - \bar{g}_{j})\,.\,(g^{\mathrm{P}}{}_{j} - \bar{g}_{j})], \quad (5)$$

where $\bar{g}_j$ is the mean allelic effect on the phenotype at locus j and $g^{\mathrm{M}}{}_j$ (respectively $g^{\mathrm{P}}{}_j$) is the allelic effect at locus j inherited from the maternal (respectively paternal) gamete. The sum of of C_{jj} over loci represents the genic variance (noted V_{genic}, which is the genetic variance of a trait in a population harboring the same allelic frequencies as the population under study, but without any genetic associations between loci), and is computed from simulation outputs

following equation (4). The sum of all values of $C_{j,j}$ represents the covariance in allelic effects at locus j on the maternally and paternally inherited chromosomes, and represents the fraction of the genetic variance due to excess of homozygosity (noted V_{inbred}); we compute it following equation (5). This quantity represents $F.V_{\text{genic}}$, where F is the inbreeding coefficient of the population. The first term of equation (3) ($2\sum_{j}^{L}(C_{jj}+C_{j,j})$) represents the genetic variance due to within locus variation. The second term ($2\sum_{j\neq k}^{L}(C_{jk}+C_{j,k})$) represents the component of the variance due to associations between loci (noted COV_{LD}), and is obtained by subtracting V_{genic} and V_{inbred} from the total additive genetic variance. This component is proportional to linkage disequilibrium (LD), and tends to be negative under stabilizing selection due to associations between alleles at different loci with compensatory effects (*i.e.* the allele on one locus is positive, the other negative, their effects on the phenotype thus cancel out when both are present).

As a check, estimates of additive genetic variance observed at M-S-D equilibrium in our simulations were compared to analytical predictions obtained by Bürger et al. (1989) (Stochastic House of Cards approximate) and by Abu Awad and Roze (2018) under similar assumptions. Comparisons and details are shown in Appendix A.

Analyses of the response to an environmental change

To analyse the population's response to an environmental change, we focus on the 20 first generations after the environmental change. We follow the temporal dynamics of the additive genetic variance of the trait and of its components. We also analyze changes through generations of the mean trait value and population fitness, as well as the dynamics of the

number of haplotypes and the proportion of new haplotypes generated after the environmental change.

In addition, and in order to determine if the remobilization of COV_{LD} plays a role in the adaptive process of a selfing population, we compute for each mutation rate, the slope of the trait mean variation shortly after the environmental change (during the first five generations) as a function of the amount of additive variance available at M-S-D equilibrium. If remobilization of COV_{LD} is involved in the adaptive process of selfing populations, the initial slope, for a similar amount of additive variance, should be higher in selfing populations than in mixed mating and outcrossing ones.

RESULTS

LEVEL AND STRUCTURE OF ADDITIVE GENETIC VARIANCE AT MUTATION SELECTION DRIFT EQUILIBRIUM

Figure 1 shows that, in agreement with expectations from previous works and due to the purging effect of selfing against deleterious mutations, the additive genetic variance present at M-S-D equilibrium in our simulations is overall negatively correlated with the selfing rate. This is especially true for strong selection ($V_S < 10$) and smaller populations sizes (N = 250 and 1000). The observed increase in V_A with selfing at high mutation rates for N = 10.000 and $V_S > 2$ can be explained by drift hindering the selection process (Abu Awad & Roze 2018, and Figure S1). In general, reducing the strength of selection increases the overall amount of additive variance, as mutations of small effect are not as easily purged from the

population (Figure 1), whereas change in population size has little qualitative effect on the relationship between selfing and V_A, as long as the mutation rate is not too high (Figure S1). As detailed in Appendix A, the values of V_A obtained from our simulations were compared to expectations from analytical expectations from Abu Awad & Roze (2018) and the Stochastic House of Cards approximation (SHC, Bürger *et al.*, 1989). We generally find a good agreement between our results and the SHC approximation for the smaller population sizes and outcrossing populations (σ = 0 or 0.5). Approximations from Abu Awad & Roze (2018) only hold for predominantly, considering the whole genome as a single locus (σ = 0.95, equation 44 in Abu Awad & Roze, 2018), or for all mating systems when population size is large (N=10.000) and the strength of selection weak (V_S=100, equation D23). The lack of fit between our results and approximations from Abu Awad & Roze (2018) is due to the small number of loci considered in our simulations (n = 50 in our parameter set) and considering only a single trait, parameters which violate the assumptions for these analytical approximations to hold.

By decomposing the observed additive variance V_A into the components described in the Methods above (V_{genic}, V_{inbred}, COV_{LD}), we find that for the range of parameters we chose to explore, the strong decrease in V_A observed under predominant selfing is not due to a strong decrease in V_{genic} but is mostly driven by a large but negative COV_{LD} (Figure 2). This confirms the expectation that recurrent selfing favours the maintenance of associations among loci. Under such associations the efficiency of purifying selection is reduced, which in turn contributes to increasing V_{genic} and V_{inbred} as observed in Figure 2 (see also Figures S2 – S9). The higher the mutation rate, the weaker the efficiency of purifying selection, leading to V_{genic} tending to be higher in selfers compared to outcrossers for high mutation rates. The increase of both V_{inbred} and V_{genic} can, in some cases, overcome the negative effect of COV_{LD}, as is the case for large populations (N=10.000), leading to selfing populations that have close to, and

sometimes even greater amounts of genetic variance than outcrossing or mixed mating populations (Figures S6 to S8). As can be expected from classical population genetics models, smaller population size leads to a decrease in V_A, whereas higher mutation rates tend to increase it (Figure S1).

PATTERNS OF ADAPTATION THROUGH STANDING GENETIC VARIATION:

After populations have reached mutation-selection-drift balance an environmental change is induced and no new mutations are introduced. Population dynamics are followed over 20 generations and, if during this time the population reaches a similar level of fitness as that observed before the environmental change, then we consider that the population is able to adapt to the new optimum. When the strength of selection is moderate to weak (V_S = 10 or 100), populations seem to harbour enough genetic variation to quickly and efficiently respond to an environmental change, independently of their selfing rate. As there were no observable dynamic changes in V_A and its components for these parameter values, the results for these simulations are only presented in Supplementary Figures S9 to S40. In the following sections we will only be concentrating on the case of V_S = 2.

DYNAMICS OF PHENOTYPE AND FITNESS DURING ADAPTATION:

As illustrated in Figure 3, when the mutation rate is small (U = 0.005), and hence the amount of cryptic diversity for selfing population is also small, none of the populations are

able to adapt, and population fitness remains low. In this case the amount of additive variance at equilibrium is the only source of diversity, and as outcrossing and mixed mating populations have higher V_A, they reach phenotypic values closer to the new optimum, and have a significantly higher fitness than their selfing counterparts (Figure 3 for U=0.005). For higher mutation rates (U > 0.005), dynamics of the phenotypic trait and fitness are extremely similar for all mating systems, despite lower genetic diversity for selfing populations. As shown in the following sections, when the mutation rate increases, the hidden additive variance stored in selfing populations through genetic associations is partially released, increasing the adaptive potential of these populations. In such cases, populations are able to reach (1) the new phenotypic optimum, and (2) level of fitness similar to those observed at M-S-D equilibrium (Figure 3).

The effect of the population size on the probability of adaptation stems from its effect on the level of additive genetic variance and hidden diversity. The greater the population size the greater the genetic diversity (express and hidden) for a given mutation rate, increasing the range of mutation rates for which selfing populations are at least as well, if not better, adapted as outcrossing and mixed mating populations (Figures S28 to S35).

DYNAMICS OF THE ADDITIVE VARIANCE AND OF ITS COMPONENTS

As the population undergoes directional selection, the dynamics of the observable additive variance and each of its components are telling of the processes driving adaptation to a new optimum. In small outcrossing populations (N = 250), the additive variance exhibits very small changes during the adaptation process, as do its components, whatever the strength of selection (Figures S9 to S11). For larger population sizes (N=1000 or 10.000), the additive

variance increases during the first generations when the mutation rate is small to medium ($U \leq 0.05$, Figure 4A for N=1000, see supplementary materials for N=10.000). This increase of V_A stems from an increase in V_{genic}, indicative of the change in the phenotype being driven by a few loci harbouring alleles of strong effect that may have been neutral or deleterious before the environmental change (Bürger 1993). For high mutation rates (U = 0.1), as for small populations, the additive genetic variance and its components remain constant through time (Figure 4). The fact that V_{inbred} does not vary in all cases indicates that there is no change in inbreeding coefficient during adaptation (Figure 4C). Overall patterns are similar for mixed mating populations.

For predominantly selfing populations, the dynamics strongly depend on "how much" cryptic diversity (COV_{LD}) the population has stored while undergoing stabilising selection and at M-S-D equilibrium. In all cases, additive genetic variance increases during the adaptation process (Figure 5A). When genetic associations are rare (Figure 5, U = 0.005), adaptation is driven solely through the fixation of beneficial alleles, leading to an increase of the genic variance and inbred variance (Figures 5B and C). In this case, COV_{LD} does not vary (Figure 5D). When among-loci associations matter (U > 0.005), the dynamics observed are qualitatively different, and reflect another process of adaptation. The increase in additive variance is due to the "release" of genetic diversity (COV_{LD} increases, figure 5D), whereby the genic and inbred variances remain constant or decrease (Figure 5B and C). The variation of V_{inbred} remains equal to $F.V_{genic}$, indicating that, as observed for outcrossing populations, the inbreeding coefficient does not vary during adaptation.

This release of diversity leads to a stronger initial response of the phenotypic trait (computed as the slope of increase of the phenotypic trait for the 5 first generations) for selfing populations, compared to more allogamous ones, for an equal amount of additive variance at equilibrium (Figure 6). The larger the population size, the more the pattern

observed for selfing populations differs from that observed in outcrossing and mixed mating ones (Figure 6). When selection is moderate to weak, the release of hidden variability is not necessary for selfing populations to adapt, thus this increase in the strength of adaptation for selfers is no longer observed (Figure S26 to S28). It is important to note though, that in the range of parameters that we have explored, genetic variation in selfing populations is not often maintained at levels as high as those observed in outcrossing and mixed mating populations. Thus for similar population properties (mutation rate, population size), outcrossing and mixed mating can lead to a much stronger responses to selection.

During this process, the mean number of haplotypes in the population remains relatively stable and as the population evolves to the new phenotypic optimum, all haplotypes that were initially present in the population are replaced by new haplotypes, whatever the mating system of the population. The effect of the mating system is mainly on the rate of change observed, it being faster in outcrossing populations due to the higher rates of recombination (Figure S29 to S41).

DISCUSSION

In accordance with Stebbins' definition of the dead-end hypothesis (Stebbins, 1957), single-locus models predict that adaptation from standing genetic variation is less likely in selfing populations compared to outcrossing ones, notably due to the reduced genetic variation resulting from purging (Glémin & Ronfort, 2013). Considering a polygenic trait, and among loci associations, we find that this is not always the case. Previous works have highlighted that stabilizing selection favours the build-up of associations between loci and, through this, favours the storage of hidden genetic diversity especially in self-fertilising

populations (Charlesworth, 1990; Lande & Porcher, 2015; Abu Awad & Roze, 2018). If the selective regime were to change from stabilising to directional selection, due to a strong environmental effect for example, our simulations show that some of this variance can be released through residual allogamy. Although the strength of the response to selection is positively correlated with the amount of observable standing genetic variation, despite less additive genetic variance at equilibrium, it is possible to observe similar or better levels of adaptation in selfing compared to outcrossing or mixed mating populations. When the strength of selection is moderate to weak (V_S = 10 or 100), populations seem to harbour enough genetic variation to quickly and efficiently respond to an environmental change, independently of the self-fertilization rate, and thus without remobilizing any hidden diversity.

Genetic variance dynamics under directional selection: the role of genetic associations

Few theoretical studies try to predict the dynamic of the additive variance for a trait under directional directions (Barton & Turelli, 1987; Keightley & Hill 1989; Bürger, 1993). From these works, under the assumption of random mating and no associations between loci, it is predicted that V_A remains unchanged, if population size is small (N < 500, Bürger, 1993) and/or if the inverse of the strength of selection, given by the term V_S, is large compared to the amount of available genetic variance (Barton & Turelli, 1987). This prediction is supported by our results for obligate outcrossing populations (Figures S9 to S16), even when some negative linkage disequilibrium contributes significantly to additive variance (Figures 2 & 4). For selfing populations, the hypothesis of linkage equilibrium is no longer valid. As shown in our analysis, genetic associations between loci are significant for

those populations, notably when the mutation is high. In such case, the remobilization of genetic variance is necessary to adapt when most of the genetic variance is hidden in among-loci associations, leading to the increase of additive variance. The mutation rates for which such associations contribute significantly to the genetic additive variance are in the range of mutation rates observed for phenotypic traits in literature (Keightley & Bataillon, 2000; Shaw *et al.*, 2002; Haag-Liautard *et al.*, 2007), which allows to make the assumption that these associations are probably common in natural populations. This assumption is further supported by empirical observations of more frequent transgressive segregation (progeny of a cross being outside the parental phenotypic range) in inbred compared to outbred species (Rieseberg *et al.*, 1999; Johansen-Morris & Latta, 2006).

***De novo* mutations *vs.* standing genetic variation: rethinking adaptation in selfing species?**

It has been a long accepted paradigm that the advantage procured by selfing is the more rapid fixation of *de novo* mutations, independently of their dominance coefficient, compared to outcrossing populations, where recessive beneficial mutations can be lost through drift before selection drives them to fixation, a process known has “Haldane’s sieve” (Haldane, 1927). From single locus theory, it is expected that adaptation through new mutations should be more likely in selfing species, and should be more likely than adaptation from standing genetic variation (Glémin & Ronfort, 2013). However, recent works have suggested that the reduced effective recombination rate in selfing populations adds a disadvantage even when it comes to the fixation of new mutations. Unlike what is expected in outcrossing populations, the fixation of beneficial mutations in selfing populations can be

hindered if they appear during a selective sweep triggered by a beneficial allele at another locus (Hartfield & Glémin, 2016). This observation, as well as the results presented here, show that considering interactions between loci can strongly modify the expectations from single-locus models. The mutation rate seems to be the major parameter to consider when considering adaptation from a polygenic point of view, independently of whether adaptation occurs from *de novo* mutations (Hartfield & Glémin, 2016) or standing genetic variation.

In our simulations, we have considered a quantitative trait with a simple architecture, assuming pure additivity of genetic effects on the phenotype. Epistasis, and notably its directionality, is known to play a key role in adaptation (Hansen, 2013). Positive epistasis (several loci reinforcing each other's effects in the direction of selection), inflates the additive variance and thus the ability of a population to adapt to an environmental change (Carter *et al.*, 2005; Monnahan & Kelly, 2015). On the contrary, negative epistasis (loci suppressing effects at other loci), reduces the additive variance of the character, thus limiting adaptive potential (Carter *et al.*, 2005). Few empirical estimations of the directionality of epistasis are available in the literature (Le Rouzic 2014; Monnahan and Kelly 2015; Oakley *et al.* 2015, all detecting positive epistatic interactions), despite numerous methods and the diversity of data used to infer it (Le Rouzic, 2014). How the directionality of epistatic interactions varies in relation to the mating system remains unknown in natural populations. Knowledge on this relationship may bring us closer to the understanding of the differences in patterns of adaptation observed between selfing and outcrossing populations.

New insights into the role of standing genetic variation in the adaptation dynamics of selfing populations

The overwhelming success of selfing species in the domestication process and as invasive species has been attributed to mechanisms other than their adaptive ability from standing genetic variation. For instance, the invasive success of selfing populations is attributed to the reproductive assurance of selfing species, since a single individual is able to colonize a new environment (Rambuda & Johnson, 2004; van Kleunen *et al.*, 2008), and to reduced gene flow, which is expected to limit maladapted gene exchanges between populations (Levin, 2010). Regarding domestication as an adaptation process, it has been suggested that domestication in selfing populations most probably relied on new mutations, due to the initially low genetic variance that would have been further reduced due to the bottleneck effect of domestication (Glémin & Bataillon, 2009). This idea is reinforced by the fact that selfing species are expected to quickly fix a rare beneficial mutation, independently of its dominance level (Ross-Ibarra, 2005). In their review on mating system variation in domesticated plant species, Glémin and Bataillon (2009) have suggested that the high frequency of self-fertilizing crop species could be related to an increase in the amount of additive variance during the domestication process of selection. This idea has, however, never been tested theoretically or empirically. Here we show that this increase in additive variance could indeed be an advantage when selfing species are faced with strong directional selection. However, our results hold true only if the bottleneck related to domestication (or other invasion processes) is not too strong and if mutation rates are high enough to maintain enough hidden diversity that can promote adaptation to new conditions.

CONCLUSION AND PERSPECTIVES

In this work, we argue that under stabilizing selection, selfing populations are able to accumulate hidden genetic variation through negative linkage disequilibrium and thanks to this hidden genetic variability, adaptation under high self-fertilisation rates is no longer constrained by the reduced observable additive genetic variance due to purging. In our simulations, the key parameters determining the amount of hidden variation are the mutation rate and the population size. Our analysis thus shows that measuring the amount of additive variance available for quantitative traits is not sufficient to make predictions about the adaptive potential of a population. Complementary analyses should be carried out when quantifying the short-term adaptability of a population. Such analyses could include looking for transgressive segregations or carrying out experimental evolutionary experiments in which directional selection is induced, and follow the dynamic of additive genetic variance. Follow the components of additive variance is complicated, as it necessitates knowing thoroughly the genetic architecture of the quantitative trait under study (number of loci underlying phenotypic variation, their frequency, the linkage disequilibrium…), which is complicated for non-model species. More empirical evidence is required to determine how frequent cryptic diversity occurs in natural populations of selfing species, and whether or not this property is sufficient to allow selfing species to adapt to a changing environment.

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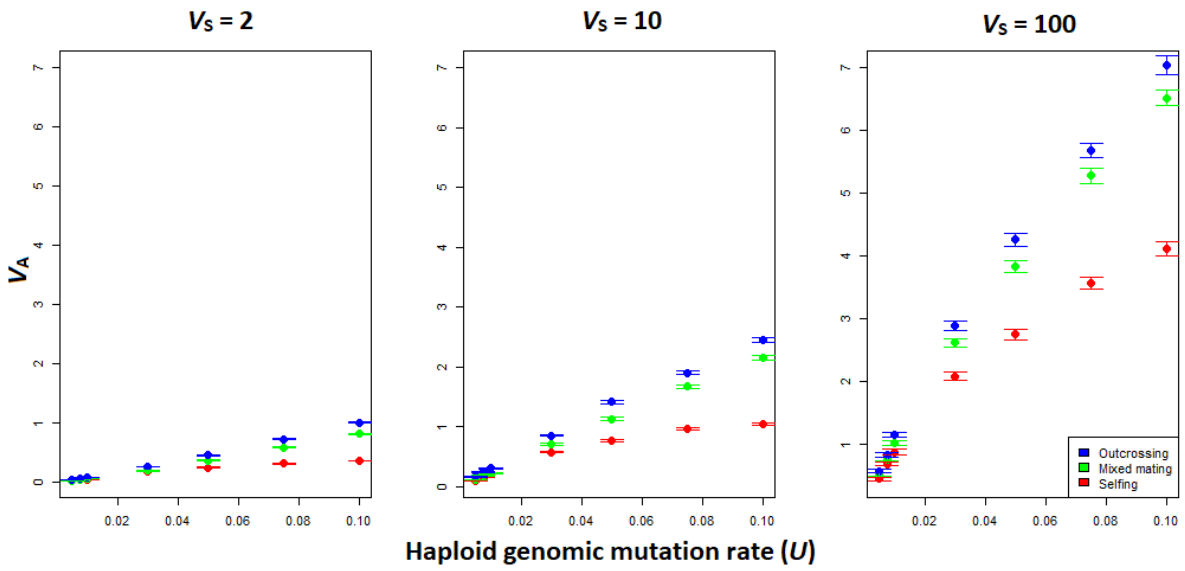

Figure 1. Additive genetic variance observed at mutation-selection-drift equilibrium in the simulated populations, for different mating systems, N=1000, and different strengths of selection (from V_S=2 to V_S=100, from the left to the right). Error bars stand for the 95% confidence interval (n = 100 simulations).

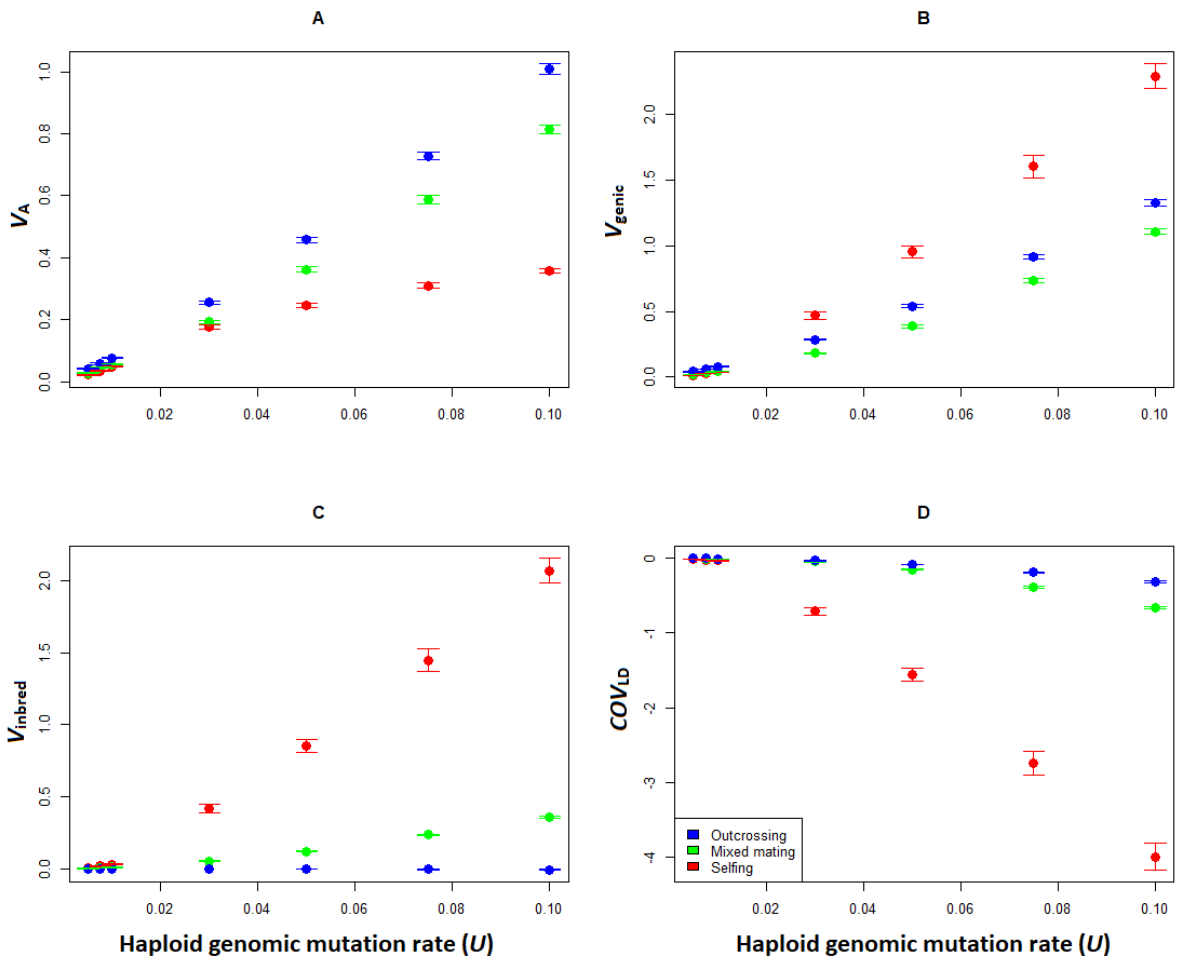

Figure 2. Total additive genetic variance and its three components estimated at MSD equilibrium, for different genomic mutation rates and mating systems, for N=1000 and V_S=2. **A.** Total additive variance of the phenotypic trait. **B.** Genic variance for the phenotypic trait (V_{genic}). **C.** Genetic variance due to inbreeding (V_{inbred}). **D.** Genetic covariance due to linkage disequilibrium (COV_{LD}). Error bars stand for 95% confidence interval (n = 100).

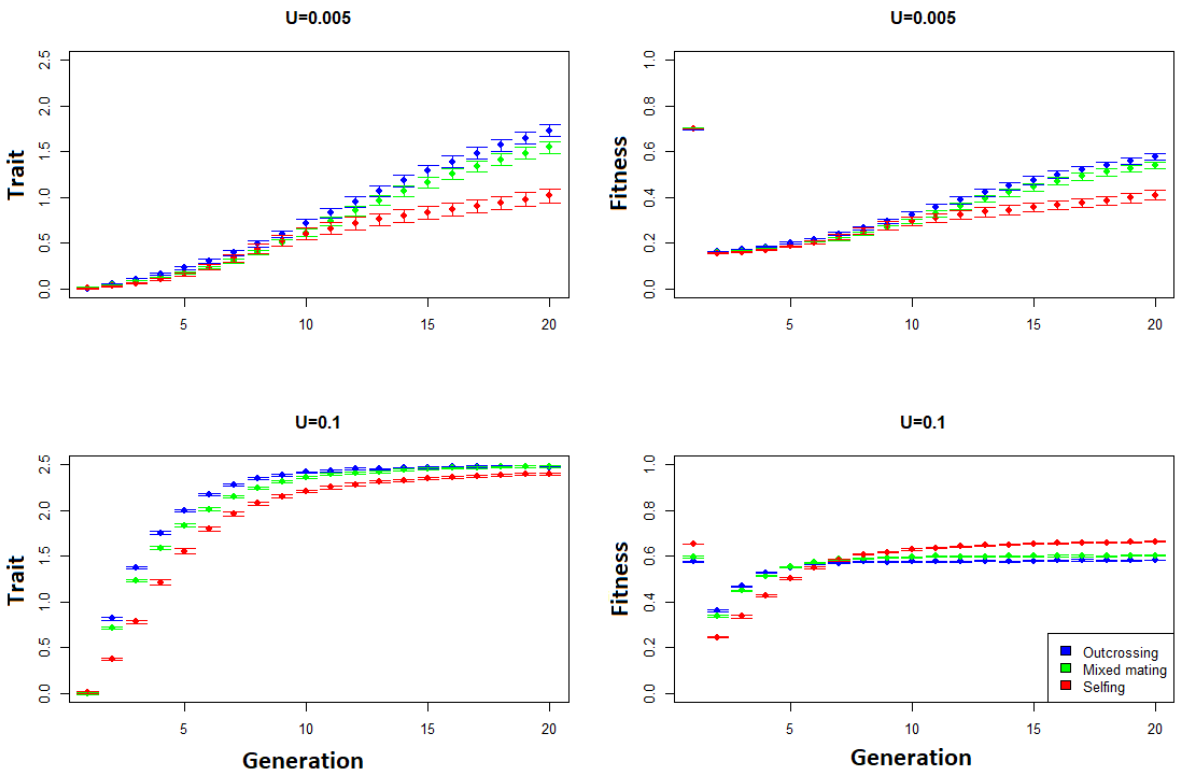

Figure 3. Dynamics of the mean trait value and of the mean fitness value of the population during the 20 generations following the environmental change, for different haploid mutation rates (Top-down: U=0.005; U=0.1) and as a function of the mating systems. Other parameter values are N=1000 and V_S=2. Error bars stand for 95% confidence interval (n=100).

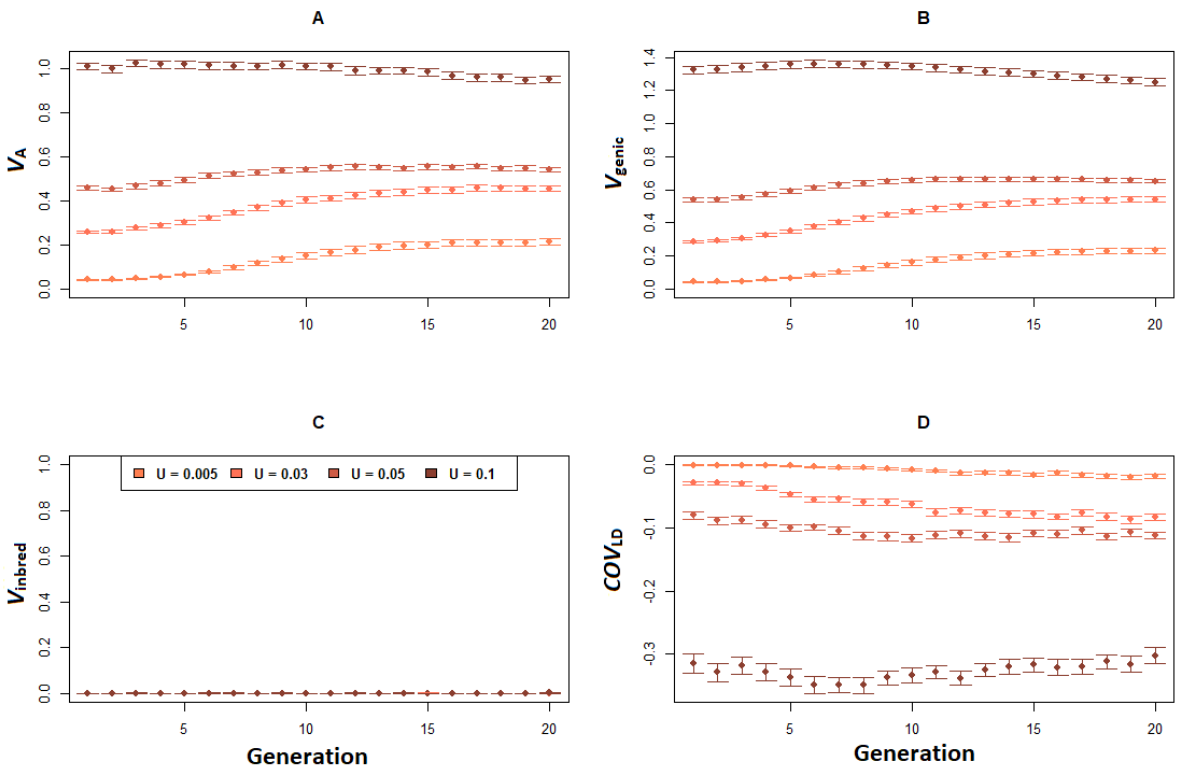

Figure 4. Dynamics of the additive genetic variance and its components in outcrossing populations (σ=0). **A.** Observed additive variance for the phenotypic trait. **B.** Genic variance for the phenotypic trait (V_{genic}). **C.** Genetic variance due to inbreeding (V_{inbred}). **D.** Genetic covariance due to linkage disequilibrium (COV_{LD}), for different mutation rates (U=0.005; U=0.03; U=0.05; U=0.1). Error bars stand for 95% confidence interval (n = 100). Other parameter values are N=1000 and V_S=2.

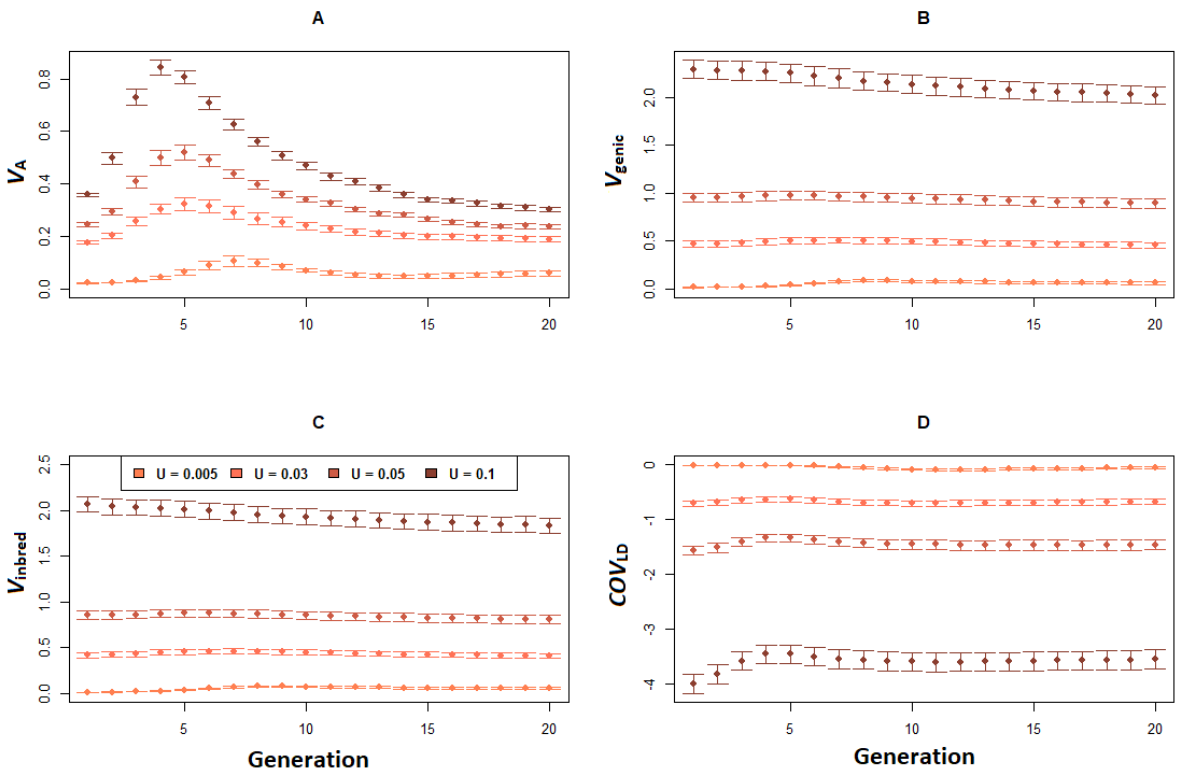

Figure 5. Dynamics of the additive genetic variance and its components in selfing populations (σ=0.95). **A.** Observed additive variance for the phenotypic trait. **B.** Genic variance for the phenotypic trait (V_{genic}). **C.** Genetic variance due to inbreeding (V_{inbred}). **D.** Genetic covariance due to linkage disequilibrium (COV_{LD}), for different mutation rates (U=0.005; U=0.03; U=0.05; U=0.1). Error bars stand for 95% confidence interval (n = 100). Other parameter values are N=1000 and V_S=2.

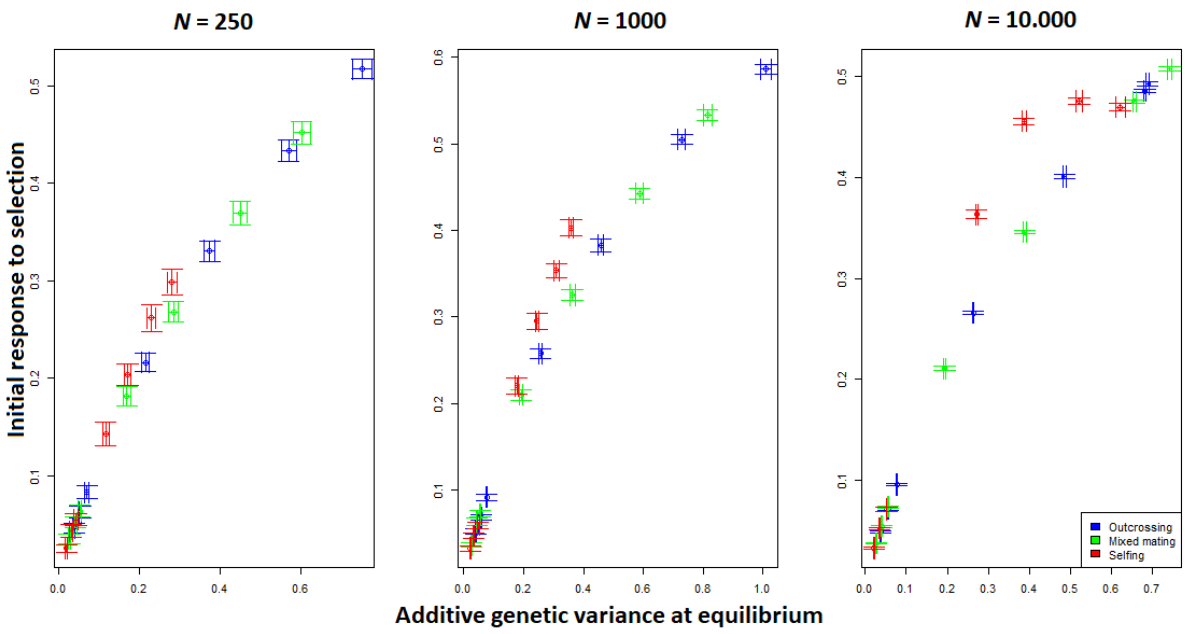

Figure 6. Initial response to selection in function of the amount of additive variance at equilibrium, as a function of the mating system, each point correspond to a haplotypic mutation rate (*U* ranging from 0.005 to 0.1, from the left to the right), and for the three population sizes, when selection is strong (V_S=2). Error bars stand for 95% confidence interval (n = 100).

Appendix A: Impact of the mating system on genetic variance at mutation-selection-drift equilibrium: comparison of simulation results with analytic predictions

Several theoretical works have been developed to explicitly quantify the effect of selfing on the amount of additive genetic variance maintained in a population (Lande, 1977; Charlesworth & Charlesworth, 1995; Lande & Porcher, 2015; Abu Awad & Roze, 2018). However, these approaches often do not take the effects of genetic drift due to small population sizes into account. The Stochastic House of Cards approximation (SHC) provided in Bürger *et al.*, (1989), an extension to Turelli's (1984) House of Cards, explicitly considers the effective population size N_E, which can be chosen so as to reflect the population's reproductive strategy (see Bürger *et al.*, 1989, for the case of dieocious reproduction). Considering these different constructions of models, we briefly compare the analytical expectations of some of the above-mentioned works to our simulation results at mutation-selection-drift equilibrium.

In the SHC framework (Bürger *et al.* 1989), the amount of additive variance at equilibrium is given by:

$$V_{A-SHC} = \frac{4UV_S}{1+\frac{V_S}{N_E\alpha^2}}. \qquad \text{(A.1)}$$

Where U, V_S and α are the haploid mutation rate, the strength of selection and the variance in mutational effects, respectively. Following Caballero & Hill (1992), and ignoring background selection and linkage disequilibrium, the effective population size of an inbreeding population is $N_E = N/(1+F)$. F is the inbreeding coefficient, which, for a given selfing rate σ, is equal to σ/(2- σ). As mentioned above, this approximation takes into account the population and the strength of selection. However the inbreeding coefficient F does not account for consequences of background selection on N_E, which are not known in this specific class of population genetics

models (i.e. quantitative traits and stabilising selection) and could thus limit the accuracy of the SHC approximation.

Abu Awad & Roze (2018) provided approximations for the expected level of V_A under the continuum of alleles model, neglecting genetic drift and associations between loci:

$$V_{A-CA} = 4V_S\sqrt{\frac{\bar{s}UL}{2n}\frac{2}{2+\sigma(1-\sigma)}}\,. \qquad \text{(A.2)}$$

n is the number of quantitative traits under consideration (n = 1 in our case). In order to account for cases in which linkage is complete (i.e. for very high self-fertilisation rates), setting the number of loci L to 1 gives

$$V_{A-DL} = 4V_S\sqrt{\frac{\bar{s}U}{2n}\frac{2}{2+\sigma(1-\sigma)}}\,. \qquad \text{(A.3)}$$

This whole genome is thus modelled as a single locus, with a large number of possible alleles, whose effects follow a Gaussian distribution (Lande, 1977).

To determine the accuracy of these equations under our model conditions, we ran one hundred repetitions per parameter set for three selfing rate values (σ = 0, 0.5 and 1), as well as for the seven mutation rates tested in the main text. The mean additive variance from the simulation runs are then compared to the expectations from equations A.1, A.2 and A.3, by using the sum of absolute values of the differences between observations and expectations over the seven mutation rates. Results are presented in Table A1.

Table A1. Comparison of analytical predictions for the amount of V_A under different quantitative genetics models and results obtained in our simulations at MSD equilibrium, for different sets of parameters. The best model for the prediction of V_A (i.e. closest to our simulation results) is highlighted in green for each parameter set.

Parameters		N = 250 V_S			N = 1000 V_S			N= 10 000 V_S		
		1	9	99	1	9	99	1	9	99
$V_{A\text{-}SHC}$	σ=0	0.16	0.89	1.56	0.49	1.92	14.58	0.31	4.38	67.81
	σ=0.5	0.11	0.28	2.81	0.18	2.05	4.71	0.22	4.65	57.87
	σ=0.95	0.80	1.76	1.13	0.86	4.10	8.10	0.36	4.93	56.71
$V_{A\text{-}CA}$	σ=0	3.49	7.16	28.57	2.94	5.11	16.93	3.28	5.95	14.66
	σ=0.5	3.92	7.34	26.89	3.16	5.55	16.53	3.14	5.65	12.74
	σ=0.95	4.61	9.79	31.77	4.30	8.47	24.37	3.59	6.55	16.29
$V_{A\text{-}DL}$	σ=0	1.30	3.52	5.57	1.85	5.57	16.85	1.51	4.74	19.12
	σ=0.5	0.95	2.75	5.21	1.39	4.52	15.31	1.42	4.42	19.06
	σ=0.95	0.25	0.86	2.17	0.53	2.09	9.02	1.23	4.01	17.01

From Table 1, we find that for outcrossing and mixed-mating populations, the Stochastic House of Cars approximation (equation A.1) is the best predictor of the mean additive genetic variance for a wide range of parameters for outcrossing and mixed mating populations. The continuum of alleles approximation (equation A.2) is accurate only for very large population sizes and weak selection, conditions for which the underlying assumptions made when deriving this approximation are met (low allelic frequencies, weak genetic drift and few among-loci associations). For predominantly selfing populations, the approximation considering full linkage (equation A.3) is accurate in conditions where strong genetic associations are maintained throughout the genome *i.e.* selection is strong or moderate (table A1).

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