

Consequences of genetic linkage for the maintenance of sexually antagonistic polymorphism in hermaphrodites

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When selection differs between males and females, pleiotropic effects among genes expressed by both sexes can result in sexually antagonistic selection (SA), where beneficial alleles for one sex are deleterious for the other. For hermaphrodites, alleles with opposing fitness effects through each sex function represent analogous genetic constraints on fitness. Recent theory based on single-locus models predicts that the maintenance of SA genetic variation should be greatly reduced in partially selfing populations. However, selfing also reduces the effective rate of recombination, which should facilitate selection on linked allelic combinations and expand opportunities for balancing selection in a multilocus context. Here, I develop a two-locus model of SA selection for simultaneous hermaphrodites, and explore the joint influence of linkage, self-fertilization, and dominance on the maintenance of SA polymorphism. I find that the effective reduction in recombination caused by selfing significantly expands the parameter space where SA polymorphism can be maintained relative to single-locus models. In particular, linkage facilitates the invasion of male-beneficial alleles, partially compensating for the “female-bias” in the net direction of selection created by selfing. I discuss the implications of accounting for linkage among SA loci for the maintenance of SA genetic variation and mixed mating systems in hermaphrodites.

KEY WORDS: Balancing selection, genetic linkage, intralocus sexual conflict, mixed mating systems, recombination, two-locus model.

Due to fundamental differences in their reproductive biology, males, and females rarely share the same optimal phenotype (Parker 1979; Kokko and Jennions 2008). When phenotypic optima differ between males and females, pleiotropic effects among genes expressed by both sexes can result in sexually antagonistic selection (SA hereafter), where beneficial alleles for one sex have deleterious fitness effects in the other (Kidwell et al. 1977; Rice 1992; Connallon and Clark 2012). SA alleles have been shown to play an important role in the maintenance of genetic variation in fitness, the evolution of reproductive and life-history traits, and genome evolution in a variety of theoretical and empirical contexts (Rice 1992; Prout 2000; Rice and Chippindale 2001; Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2010; Fry 2010; Connallon and Clark 2012; Barson et al. 2015).

The existence of physically separate sexes makes the relevance of SA selection to dioecious species intuitive, and this is reflected in the traditional emphasis on SA polymorphism in this

group (e.g., Kidwell et al. 1977; Rice 1992; Prout 2000; Connallon and Clark 2012). However, alleles with opposing fitness effects through male and female sex functions represent analogous genetic constraints on fitness for hermaphrodites (Abbott 2011; Jordan and Connallon 2014; Tazzyman and Abbott 2015). For hermaphroditic individuals, both the male and female sex functions must be accommodated by a single phenotype, and there is ample scope for traits with a shared genetic basis to constrain fitness through each sex function (Barrett 2002; Conner 2006; Abbott 2011; Sicard and Lenhard 2011). Furthermore, fitness trade-offs between sex functions, and thus SA alleles, can have diverse consequences for the evolution of reproductive traits (e.g., floral and inflorescence morphology) as well as sexual and mating systems in hermaphrodites (Charlesworth and Charlesworth 1978; Lloyd and Webb 1986; Webb and Lloyd 1986; Barrett 2002; Goodwillie et al. 2005; Harder and Barrett 2006; Abbott 2011).



The fate of SA alleles in hermaphrodites is complicated by the fact that individuals may pass on genes to subsequent generations through a combination of outcrossing and self-fertilization (Goodwillie et al. 2005; Igic and Kohn 2005; Jarne and Auld 2006; Jordan and Connallon 2014). Self-fertilization has several important theoretical consequences for the maintenance of SA genetic variation (Kimura and Ohta 1971; Jordan and Connallon 2014). Selfing diminishes the opportunity for balancing selection to maintain SA polymorphism, and thereby reduces the sensitivity of SA polymorphism to dominance (Jordan and Connallon 2014; Tazzyman and Abbott 2015). If SA alleles influence gamete production and/or gamete quality or performance, selfing also creates a “female-bias” in the net direction of selection because there is reduced opportunity for selection to act via the male sex function (Charlesworth and Charlesworth 1978; Jordan and Connallon 2014; but see Tazzyman and Abbott 2015 for alternative assumptions regarding selection on selfed gametes). This skews the parameter space where SA polymorphism can be maintained toward female-beneficial alleles (Jordan and Connallon 2014).

Self-fertilization carries with it a variety of other genomic consequences for hermaphrodites, including a reduction in the effective rate of recombination among neighboring loci (reviewed in Wright et al. 2008). The effect of selfing on effective recombination is of particular interest because this should drive selection on linked allelic combinations, potentially preserving polymorphisms that would otherwise experience purifying selection at a single locus (Fisher 1930). For dioecious species, tight linkage between SA loci is predicted to expand the parameter space where SA polymorphism is maintained (Patten et al. 2010). Thus, for hermaphrodites there is the potential for reduced recombination to compensate for the loss in SA polymorphism due to increased selfing. However, the conditions under which each of these two countervailing effects of self-fertilization will be more influential in maintaining SA polymorphism have yet to be explored.

Here, I use a two-locus model of SA selection with partial selfing to investigate the joint influence of linkage, self-fertilization, and dominance on the maintenance of SA polymorphism in hermaphroditic species. In the two-locus context, reduced effective recombination caused by selfing significantly increases the parameter space where balancing selection is predicted to maintain SA polymorphism relative to single-locus models. In particular, linkage expands the conditions where male-beneficial alleles are able to invade, partially compensating for the “female-bias” in selection introduced by selfing.

Model

Consider a genetic system involving two diallelic autosomal loci **A** (with alleles A, a) and **B** (with alleles B, b), that recombine at a rate r in a large population of simultaneous hermaphrodites. The

rate of self-fertilization (C) in the population is independent of the genotype at the loci in question (a “fixed” selfing model *sensu* Holden 1979; Caballero and Hill 1992; Jordan and Connallon 2014). Generations are assumed to be discrete and nonoverlapping, with selection occurring on diploid adults before fertilization. Let x_i and y_i denote the frequencies of the four possible haplotypes [AB, Ab, aB, ab] among male and female gametes, respectively. Both loci are under sexually antagonistic selection such that A and B represent male-beneficial alleles, while a and b represent female-beneficial alleles (Kidwell et al. 1977). The fitness of offspring formed by the union of the i th female and j th male gametic haplotypes, $w_{k,ij}$ (where $k \in [m, f]$), is assumed to equal the product of the fitnesses at **A** and **B** (Table 1; parameterization follows Patten et al. 2010). Following convention for SA models, sex-specific selection coefficients are constrained to be $0 < s_k < 1$ (e.g., Kidwell et al. 1977).

The evolutionary trajectory of genotype frequencies in this scenario is described by a system of 10 recursion equations (Holden 1979; Jordan and Connallon 2014). However, it is possible to approximate the evolutionary trajectories of haplotypes in this system under weak selection (See Appendix A in the Supporting Information). For partially selfing populations under weak selection, the rate of allele frequency change due to selection should be slow relative to the rate at which genotypes approach equilibrium under nonrandom mating (Nagylaki 1997). Under this assumption, it may be appropriate to use a separation of timescales (Otto and Day 2007), and calculate the quasi-equilibrium (QE) genotypic frequencies in the absence of selection. The genotypic recursions for allele frequency change across generations can then be approximated by substituting into them the QE frequencies, yielding a reduced system of four haplotype recursions.

Using this approach, I model the evolution of the four-haplotype system $q_i = [AB, Ab, aB, ab]$, where the QE adult genotypic frequencies are denoted by ϕ_{ij} . The recursions giving the haplotype frequencies in the next generation are then

$$\begin{aligned} q'_1 &= (1 - C) \frac{(x_1 + y_1)}{2} + C \left(\frac{x_1 - r(\phi_{14} - \phi_{23})}{2\bar{w}_f} \right) \\ q'_2 &= (1 - C) \frac{(x_2 + y_2)}{2} + C \left(\frac{x_2 + r(\phi_{14} - \phi_{23})}{2\bar{w}_f} \right) \\ q'_3 &= (1 - C) \frac{(x_3 + y_3)}{2} + C \left(\frac{x_3 + r(\phi_{14} - \phi_{23})}{2\bar{w}_f} \right) \\ q'_4 &= (1 - C) \frac{(x_4 + y_4)}{2} + C \left(\frac{x_4 - r(\phi_{14} - \phi_{23})}{2\bar{w}_f} \right), \quad (1) \end{aligned}$$

where x_i and y_i are functions $f(C, s_k, h_k, \phi_{ij})$ describing the haplotype frequencies in male and female gametes, and \bar{w}_f is the population average fitness through female function (see Appendix A in the Supporting Information for a full development of the recursions). The QE haplotype recursions approximated

Table 1. Two-locus fitness expressions for the adult female sex function ($w_{f,ij}$) and male sex function ($w_{m,ij}$).

Haplotype	$y_1 = AB$	$y_2 = Ab$	$y_3 = aB$	$y_4 = ab$
Females				
$x_1 = AB$	$(1 - s_f)^2$	$(1 - s_f)(1 - h_f s_f)$	$(1 - s_f)(1 - h_f s_f)$	$(1 - h_f s_f)^2$
$x_2 = Ab$	$(1 - s_f)(1 - h_f s_f)$	$(1 - s_f)$	$(1 - h_f s_f)^2$	$(1 - h_f s_f)$
$x_3 = aB$	$(1 - s_f)(1 - h_f s_f)$	$(1 - h_f s_f)^2$	$(1 - s_f)$	$(1 - h_f s_f)$
$x_4 = ab$	$(1 - h_f s_f)^2$	$(1 - h_f s_f)$	$(1 - h_f s_f)$	1
Males				
$x_1 = AB$	1	$(1 - h_m s_m)$	$(1 - h_m s_m)$	$(1 - h_m s_m)^2$
$x_2 = Ab$	$(1 - h_m s_m)$	$(1 - s_m)$	$(1 - h_m s_m)^2$	$(1 - s_m)(1 - h_m s_m)$
$x_3 = aB$	$(1 - h_m s_m)$	$(1 - h_m s_m)^2$	$(1 - s_m)$	$(1 - s_m)(1 - h_f s_f)$
$x_4 = ab$	$(1 - h_m s_m)^2$	$(1 - s_m)(1 - h_m s_m)$	$(1 - s_m)(1 - h_m s_m)$	$(1 - s_m)^2$

Rows and columns indicate the haplotype inherited from mothers and fathers, respectively.

deterministic simulations of the genotypic recursions very well, even under strong selection (Figs. B1 and B2; the full set of exact recursions can be found in Appendix A in the Supporting Information); I therefore focus the analysis on the analytic QE results.

To identify the parameter conditions under which balancing selection is predicted to maintain SA polymorphism, I evaluate the stability of the system of haplotype recursions, equation (1), for populations initially fixed for male-beneficial or female-beneficial alleles (i.e., stability was assessed at the boundary haplotype frequencies $[AB] = 1$ and $[ab] = 1$). For these boundary equilibria, one minus the leading eigenvalue of the Jacobian matrix, $1 - \lambda_L$, approximates the rate of change of the frequencies of rare haplotypes, and therefore whether new mutations will be able to invade (Otto and Day 2007). Balancing selection is predicted to maintain SA polymorphism when $\lambda_L > 1$ for both boundary equilibria (Prout 1968). Three candidate leading eigenvalues emerge from the analysis (See Appendix C in the Supporting Information). The first two describe invasion at each locus individually, and are identical functions of the sex-specific selection parameters (s_k, h_k) and the selfing rate (C). Balancing selection at both loci occurs whenever single-locus criteria for balancing selection are met because the selection parameters are identical for both loci (if invasion can occur at one locus, it can also occur at the other). If the two SA loci are physically linked, the conditions for balancing selection differ from the single-locus expectation. This condition is described by the third candidate leading eigenvalue, which involves the recombination rate, r , in addition to s_k, h_k , and C .

I focus the analysis on representative, and biologically plausible, dominance scenarios that have been recently explored in the single-locus context (Kidwell et al. 1977; Prout 2000; Fry 2010; Jordan and Connallon 2014). These correspond to: (1) additive fitness effects ($h_f = h_m = 1/2$), as is commonly observed for small to intermediate effect alleles (Agrawal and Whitlock 2011);

and (2) partially recessive fitness effects yielding a “dominance reversal” ($h_f = h_m = 1/4$), which are commonly predicted by a variety of fitness landscape models (Manna et al. 2011; Connallon and Clark 2014), and are predicted to evolve under some conditions for SA alleles (Spencer and Priest 2016).

Results

Consideration of invasion at a single locus provides a useful baseline for comparison with the two-locus case. Analysis of the first candidate leading eigenvalue yields the general invasion criteria at a single locus, where balancing selection requires that

$$\frac{s_m (C - 1)(2h_m (C - 1) - C)}{s_m (C - 1)(2h_m (C - 1) - C) + (C + 1)(2 - C + 2h_f (C - 1))} < s_f < \frac{s_m (1 - C)(2 - C + 2h_m (C - 1))}{(C + 1)(2h_f (C - 1) - C)(s_m - 1)}. \quad (2)$$

Under additive fitness effects ($h_f = h_m = 1/2$), equation (2) reduces to the single-locus invasion criteria given by Jordan and Connallon (2014); and reduces further under obligate outcrossing ($C = 0$) to the classic dioecious result of $s_m/(1 + s_m) < s_f < s_m/(1 - s_m)$ (Kidwell et al. 1977; Patten et al. 2010; Tazzyman and Abbott 2015). The corresponding funnel-shaped parameter space where balancing selection at a single locus is predicted to maintain SA polymorphism is shown in Fig. 1 by the shaded regions bounded by black solid lines.

Increased self-fertilization broadens the scope for linkage to maintain SA polymorphism that would otherwise be lost in a single-locus model. Analysis of the third candidate leading eigenvalue yields invasion criteria involving both loci that are more complex than the single-locus case. However, under the simplifying assumptions of complete linkage ($r = 0$) and obligate outcrossing ($C = 0$), the third candidate leading eigenvalue yields invasion criteria that are algebraically equivalent to the two-locus dioecious case (eq. 11 in Patten et al. (2010); see Appendix C

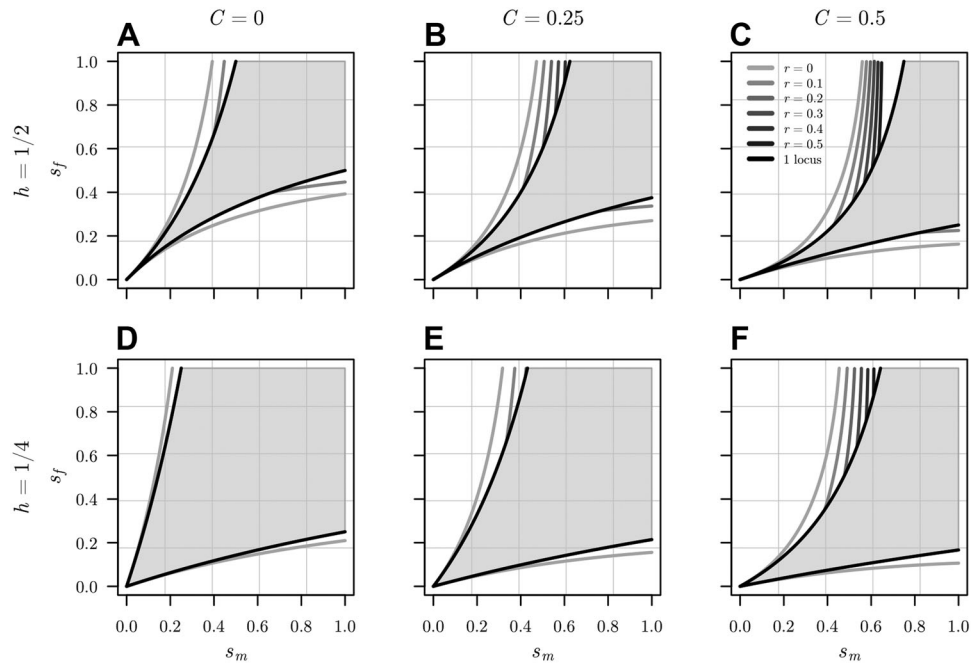


Figure 1. Self-fertilization increases the scope for genetic linkage to expand the parameter space where balancing selection can maintain SA polymorphism. Results are shown for the conditions of additive allelic effects ($h_i = 1/2$; panels A–C), and dominance reversal ($h_i = 1/4$; panels D–F). In each panel, the shaded region between the black lines indicates the region of sexually antagonistic polymorphism for the single locus case; grayscale lines indicate the thresholds for invasion for female-beneficial (lower lines) and male-beneficial (upper lines) alleles at different recombination rates for the two-locus model.

in the Supporting Information). As in Patten et al. (2010), under perfect linkage ($r = 0$), the two-locus invasion criteria expands the parameter space conducive to balancing selection, describing a funnel-shaped region that subsumes the region described by the single-locus criteria. With weaker linkage ($0 \leq r \leq 0.5$), stronger selection is required for the two-locus invasion criteria to expand the parameter space conducive to balancing selection (Fig. 1, grayscale lines). This is most restrictive under obligate outcrossing, where linkage must be tight ($r < 0.2$ for additive effects, $r < 0.1$ for dominance reversal), for the two-locus invasion criteria to increase SA polymorphism beyond the single-locus case (Fig. 1A, D; Patten et al. 2010). If selection on individual SA loci is weak ($s_f, s_m < 0.1$), tight linkage is required to significantly expand the parameter space where balancing selection is predicted beyond that of single-locus models (Figs. B3, B4 in the Supporting Information). However, the magnitude of the increase is still substantial under tight linkage, particularly for additive fitness effects.

Increased selfing has two important consequences in the two-locus context. As predicted for the single-locus case, selfing biases the net direction of selection toward female interests, reducing the opportunity for male-beneficial alleles to invade at a single locus (Fig. 1B, C, E, F; Charlesworth and Charlesworth 1978; Jordan and Connallon 2014; but see Tazzyman and Abbott 2015). However, the concomitant decrease in effective recom-

bination among double heterozygotes partially compensates for this “female-bias” in selection in several ways. Overall, linkage increases the effective strength of selection at both loci, which is more permissive of balancing selection (Patten et al. 2010). Reduced recombination also slows the break-up of haplotypes pairing male-beneficial with male-beneficial (and female-beneficial with female-beneficial) alleles at both loci, increasing the likelihood that male-beneficial alleles at each locus are paternally inherited (and female-beneficial alleles are maternally inherited) (Patten et al. 2010; Úbeda et al. 2010). With higher selfing, this effectively shelters male-beneficial alleles from increased selection through the female sex function. The net effect is to expand the parameter space where balancing selection is predicted to maintain SA polymorphism, particularly for male-beneficial alleles (Fig. 1, upper grayscale lines). The effect of reduced recombination is strongest at higher selfing rates ($C > 0.5$), where interaction between SA loci expands the parameter space where male-beneficial alleles can invade beyond the single-locus case, even under free recombination (Fig. 1B, C, E, F, Fig. 2B, D).

Under additive fitness effects, the increase in SA polymorphism due to linkage can offset the loss in parameter space attributable to invasion at a single locus up to a selfing rate of about $C = 0.5$ (Fig. 2A). At higher selfing rates ($C > 0.5$), the total parameter space where balancing selection can occur declines, but the relative increase in SA polymorphism predicted by the

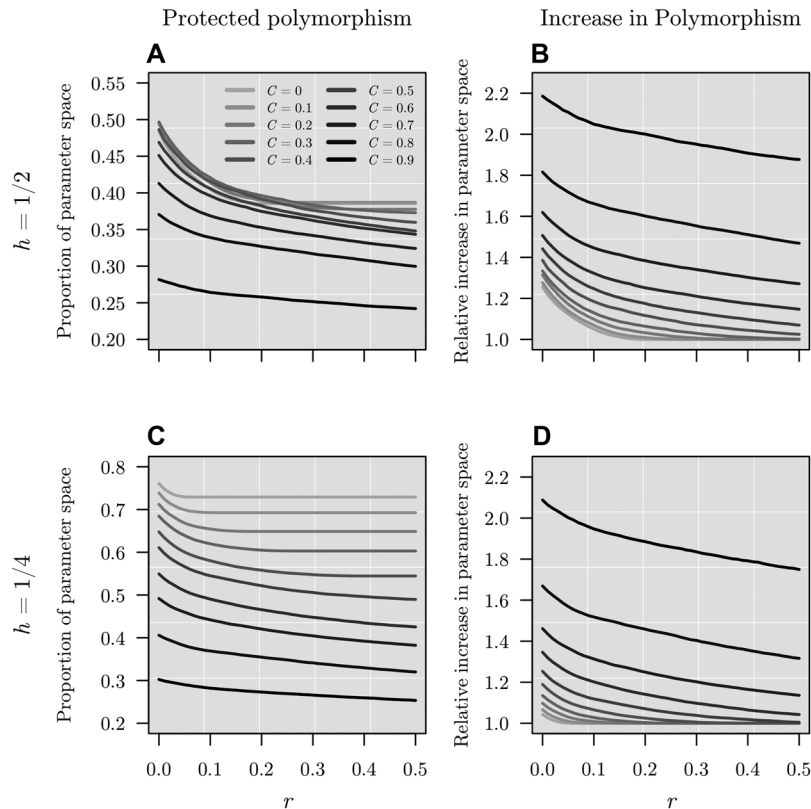


Figure 2. The proportion of parameter space where SA polymorphism is maintained declines with increased recombination and self-fertilization (panels A, C). The increase in SA polymorphism in the two-locus model relative to the single-locus case also declines with the recombination rate, but increases with the rate of self-fertilization (panels B, D). Results are shown for the conditions of additive allelic effects ($h_i = 1/2$; panels A–B), and dominance reversal ($h_i = 1/4$; panels C–D). Results were obtained by evaluating the leading eigenvalue of the Jacobian matrix of the haplotype recursions for populations initially fixed for the haplotypes $[AB]$ and $[ab]$ at 30,000 points distributed uniformly throughout parameter space defined by $s_m \times s_f$.

two-locus model relative to the single-locus case becomes increasingly pronounced, even under free recombination (Fig. 2A, B). Under dominance reversal conditions ($h_f, h_m < 1/2$) the sex-specific fitness costs of SA alleles are partially masked, and balancing selection can maintain SA polymorphism over a broader range of parameter conditions due to net overdominance in fitness (Connallon and Clark 2012, 2014). As a consequence, the effect of linkage is somewhat dampened, and increased selfing always results in a decrease in the total parameter space where SA polymorphism is predicted (Fig. 2C). However, the relative increase in the two-locus relative to the single-locus case remains for higher selfing rates ($C > 0.5$), even under free recombination (Fig. 2D).

Discussion

Accounting for linkage between SA loci yields several theoretical insights regarding the maintenance of SA polymorphism in hermaphroditic organisms. Provided that either linkage is tight or selection is strong, the reduction in the effective recombination rate due to selfing significantly expands the parameter space

where balancing selection is predicted to maintain SA polymorphism beyond that of single-locus models (doubling the parameter space under some conditions). When the sex-specific fitness costs of SA alleles are partially recessive, net overdominance of heterozygotes across both sex functions allows polymorphism to be maintained over a broader range of parameter space than when fitness costs are additive. This alters relative importance of recombination and net overdominance as proximal mechanisms underlying balancing selection at multiple SA loci. However, this does not dramatically influence the role of linkage between SA loci in expanding SA polymorphism relative to single-locus models. Thus, although balancing selection at SA loci is least likely in highly selfing species, it may still provide a plausible mechanism, along with recurrent mutation (Jordan and Connallon 2014), for the maintenance of genetic variation at linked SA loci in populations with intermediate to high selfing rates.

The joint influence of linkage and self-fertilization on SA polymorphism may have interesting implications for the genomic location of SA loci in hermaphrodites. On one hand, polymorphic SA genes are predicted to be more tightly clustered in the genome

than expected at random because linkage facilitates SA polymorphism (Patten et al. 2010; Jordan and Charlesworth 2011). The current results predict that the effect of linkage on the maintenance of SA polymorphism should be stronger in partially selfing species relative to obligately outcrossing ones. This could facilitate increased clustering of polymorphic SA genes in the genomes of partial selfers relative to outcrossers. On the other hand, the reduction in effective rates of recombination due to selfing may have the opposite effect, where interactions between more distant loci are increasingly able to facilitate balancing selection on SA alleles in selfing species. A comparison of the genomic location of SA loci in species with varying rates of self-fertilization would be an interesting direction for future empirical work, particularly given the past emphasis on dioecious species (Bonduriansky and Chenoweth 2009; Abbott 2011).

As the frequency of self-fertilization increases, linkage among SA loci compensates for the increasing “female-bias” in selection and associated decrease in SA polymorphism predicted by single-locus models (Charlesworth and Charlesworth 1978; Jordan and Connallon 2014; but see discussion of model assumptions below). This occurs primarily through an expansion of the parameter space where male-beneficial alleles are able to invade. In this way, linkage among SA loci may have bearing on the prevalence of mixed mating systems. Although many hermaphroditic plants and animals reproduce primarily through either outcrossing or selfing, a large fraction reproduce through a combination of the two (Goodwillie et al. 2005; Igic and Kohn 2005; Jarne and Auld 2006). Various theoretical explanations have been proposed for mixed mating strategies, including (but not limited to) reproductive assurance (Lloyd 1979), purging of deleterious alleles and reduced inbreeding depression (Lande and Schemske 1985), reproductive compensation (Porcher and Lande 2005; Harder et al. 2007), and frequency dependence (Holsinger 1991) (reviewed in Goodwillie et al. 2005; Harder and Barrett 2006). The female-bias in selection caused by increased selfing is consistent with the evolution of “selfing syndromes” (Sicard and Lenhard 2011; Jordan and Connallon 2014). However, the concomitant increase in the parameter space where male-beneficial alleles can invade relative to the single-locus case provides an additional mechanism for the persistence of traits promoting male gamete dispersal and performance in partially selfing populations, provided these traits are under SA selection (Barrett 2002; Goodwillie et al. 2005; Harder and Barrett 2006). Given that change in SA allele frequencies is often predicted to be slow and dominated by drift (Connallon and Clark 2011, 2012, 2014), the loss of male-beneficial alleles may also be slow and stochastic in partially selfing species with linked SA loci, regardless of whether mixed mating is an evolutionary stable strategy.

It should be noted that the increased invasion of male-beneficial alleles predicted by this model is sensitive to the as-

sumption that selection on SA alleles influences the performance of selfed female gametes (Tazzyman and Abbott 2015). The appropriateness of this assumption depends on whether SA fitness costs are incurred primarily through differential gamete production and/or quality and performance of male and female gametes, or external factors such as conflict with mates (Tazzyman and Abbott 2015). In the absence of selection influencing the performance of selfed female gametes, there is no asymmetry in the net direction of selection, and thus no bias toward the increased invasion of male-beneficial alleles. The scope for linkage to increase SA polymorphism beyond single-locus predictions is also greatly reduced when selection does not influence the performance of selfed gametes (no expansion occurs beyond $r \approx 1/4$, even under strong selfing and additive fitness effects; Appendix C in the Supporting Information). Thus, the mechanisms underlying SA fitness costs can be very important in determining the effect of linkage on the maintenance of SA polymorphism in hermaphrodites.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix A: Development of recursions, quasi-equilibrium approximations.

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Appendix B: Supplementary Figures B1-B4.

Appendix C: Mathematica notebook (.nb) file.