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On the Maintenance of Sexually Antagonistic Genetic Variation

M.Sc. Thesis

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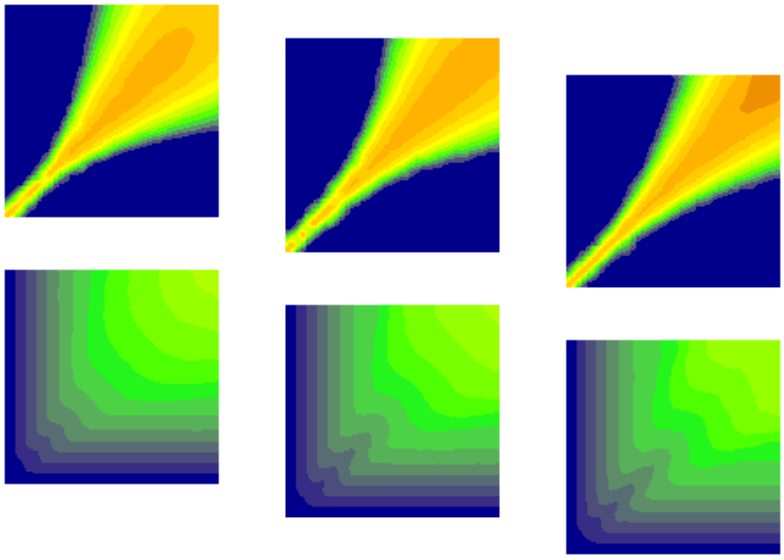

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Abstract

The presence of separate sexes and their different reproductive strategies often gives rise to sexual conflict. During intralocus conflict alleles at the same locus increase the fitness of one sex but decrease the fitness of the other. This form of disruptive selection can produce sexually antagonistic (SA) genetic variation. Current population genetic models predict that SA selection can maintain SA genetic variation only under quite restricted conditions which contradicts the ample empirical occurrence of SA genetic variation. By means of individual based simulations I test whether and how i) the number of loci that determine fitness, ii) recombination between them and iii) the dominance of allelic effects influence the protection conditions of SA genetic variation.

Evolution results in SA genetic variation under broader conditions when fitness is determined by several tightly linked loci with additive allelic effects. Even broader are the protection conditions for SA genetic variation when beneficial allelic effects are sex-specifically dominant, almost independent of the strength of selection. This effect is caused by heterozygous advantage when fitness is averaged across sexes. Therefore we can expect ample SA genetic variation in natural populations when allelic effects are sex-specifically dominant. I then conclude with a call for more theoretical and empirical research on the evolution of dominance under SA selection.

Introduction

The presence of separate sexes is a phenomenon occurring in a wide range of organisms. Because of anisogamy, and maternal investment usually being higher than paternal investment, female gametes are usually the limiting resource. Thus in general males experience intrasexual competition, while females exhibit choice of their mating partners (Bateman 1948; Trivers 1972). Because of these different reproductive strategies, selection in the two sexes often differs (Trivers 1972). This "conflict between the evolutionary interests of individuals of the two sexes" is called *sexual conflict* (Parker 1979) and can be separated into *intralocus* and *interlocus* sexual conflict. During intralocus conflict the target of selection is determined by alleles at one locus in the both sexes and different alleles are selected for in the two sexes (Rice 1984; Parker & Patridge 1998). In the case of interlocus conflict the target of selection is determined by alleles at different interacting loci in the two sexes (Parker & Patridge 1998). Interlocus conflict often occurs over interactions between the sexes, including mating rate, fertilization efficiency, relative parental effort, remating behavior and female reproductive rate, where the interacting traits are determined by different loci in the two sexes (Arnqvist & Rowe 2005). Therefore interlocus conflict is thought to be responsible for coevolutionary arms races between the sexes (Arnqvist & Rowe 2005; van Doorn 2009), in which males evolve 'persistence'

traits, females develop counter adaptations in form of 'resistance' traits to which males again adapt by evolving improved 'persistence' traits. Both the direct antagonistic interactions between the sexes (i.e., the interlocus component) and the accumulation of alleles favored in one sex despite counter selection in the other sex (i.e. the intralocus component) can cause 'gender load', a reduction in the average fitness of the sexes (and therefore that of the population) (Rice and Chippindale 2002; Connallon et al. 2010). Furthermore (and probably even more important for evolutionary dynamics), there will always be a fitness cost for SA alleles, because half the time they are expressed in the sex where they lead to low fitness.

While interlocus conflict has attracted considerable scientific attention (Arnqvist & Rowe 2005), intralocus conflict has not been studied to a greater extend until recently (reviewed in van Doorn 2009 and Bonduriansky & Chenoweth 2009). Furthermore, the evolutionary importance of intralocus conflict is debated, because the individual fitness costs seem to be quite easily resolved by the evolution of sexual dimorphism (e.g. by evolving of sex specific gene expression or by gene duplication and sex-specific cooption of paralogs, Connallon & Clark 2011). Still empirical findings suggest that intralocus conflict is important. For instance it is indicative for intralocus conflict that sexually antagonistic (henceforth, SA) selection has been demonstrated in many animal species (Cox & Calsbeek 2009; cf. Figure 1.). Robinson et al. 2006 for example showed that horn length in the soay sheep (*Ovis aries*) is positively selected in males but negatively selected in females. This pattern is probably caused by the function the horns play in male-male competition for mating in this species. Therefore longer horns are selected for in males, because it increases the number of mates, while the females have to carry the cost of producing such an expensive trait (Robinson et al. 2006). Direct empirical evidence for intralocus sexual conflict has been provided by three major approaches (see Bonduriansky & Chenoweth 2009 for a review). Firstly, *negative intersexual genetic correlation for fitness (components)* has been reported in some studies (Bilde et al. 2009; Brommer et al. 2007; Chippindale et al. 2001; Delcourt et al. 2009; Fedorka & Mousseau 2004; Foerster et al. 2007; Gibson et al. 2002; Innocenti & Morrow 2010; Pischedda & Chippindale 2006). Secondly, *SA selection and genetic constraints for shared traits* have been found (Delph et al. 2011; Long & Rice 2007; Maklakov et al. 2008; Merilä et al. 1997; Merilä et al. 2008; Price & Burley 1993; Price & Burley 1994) and finally, *sex-biased experimental evolution* has been used to show SA variation (Morrow et al. 2008; Prasad et al. 2007; Rice 1996; Rice 1998). Furthermore, SA genetic variation in fitness has several interesting implications for genome organization, sexual selection, aging and sex ratio allocation (van Doorn 2009). How can SA genetic variation (in fitness) be maintained in a population, despite the constant selection pressure to solve intralocus conflict by sexual dimorphism? To answer this question one needs to understand i) how much new SA variation is introduced due to mutation, ii) how this variation is maintained by different kinds of balancing selection and iii) how fast sexual

dimorphism can evolve which solves the intralocus conflict. In my thesis I focus on how SA genetic variation can be maintained through balancing selection.

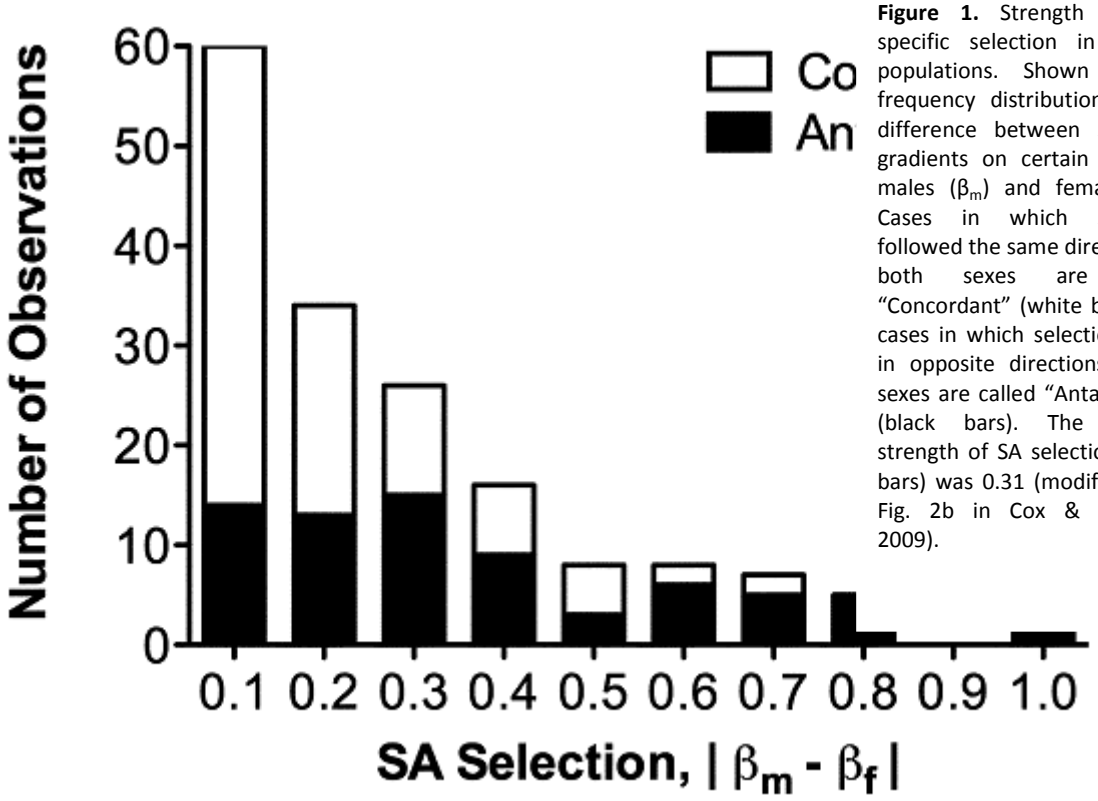

Figure 1. Strength of sex-specific selection in natural populations. Shown is the frequency distribution of the difference between selection gradients on certain traits in males (β_m) and females (β_f). Cases in which selection followed the same directions in both sexes are called "Concordant" (white bars) and cases in which selection acted in opposite directions in the sexes are called "Antagonistic" (black bars). The median strength of SA selection (black bars) was 0.31 (modified from Fig. 2b in Cox & Calsbeek 2009).

Previous theory

The maintenance of SA genetic variation in fitness is theoretically not well understood. Maintenance of this variation by SA selection is the result of a balance, in which selection an allele experiences in one sex is outbalanced by selection in the other sex such that selection does not drive any allele to fixation. There are only few models that try to delineate the conditions under which this happens. In apparent contradiction to the empirical findings, theory in general predicts SA genetic variation under constricted conditions. Kidwell et al. 1977 developed a one-locus model with SA selection and random mating, which showed stable polymorphism only for a restricted set of selection coefficients when allelic effects are additive. Selection intensities have to be approximately the same in the two sexes, especially when selection is weak (Figure 2). Since selection is rather weak most of the time in natural populations (Kingsolver 2001; Cox & Calsbeek 2009; cf. Figure 1), this makes it difficult to explain existing SA variation in fitness (Hedrick 1999). However, a broader parameter space of selection coefficients allows for polymorphism with sex specific partial dominance of the beneficial allele in each sex, which may be the more realistic case in natural populations. This is because although many major visible mutations (in domestic animals, Drosophila, etc.) are either recessive or

dominant irrespective of sex, the overall fitness effect of sexually antagonistic alleles is more likely to be partially dominant, because of the convexity of the fitness function (Fry 2010). Furthermore the model of Kidwell et al. makes several simplifying assumptions: random mating, fitness is determined by only one locus and frequency independence of selection.

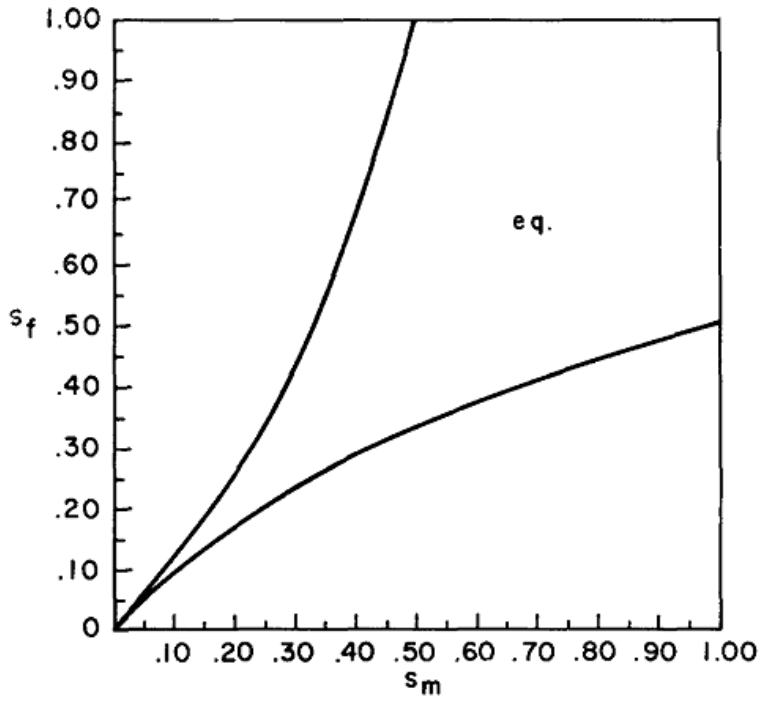

Figure 2. Proportion of parameter space allowing stable polymorphism (eq.) as a function of selection intensities in males (s_m) and females (s_f) for SA additive selection. Shown is the case of one locus with two alleles and random mating (modified from Fig. 1 in Kidwell et al. 1977).

Subsequent models relaxed some of these assumptions:

Arnqvist 2011 showed that assortative mating by fitness marginally increased the regions of parameter space showing protected polymorphism when alleles were partially dominant in each sex, while marginally decreasing regions of protected polymorphism when favored alleles were recessive (Figure 3). Furthermore assortative mating generally increased the proportion of heterozygotes. Assortative mating by fitness can be caused by different processes: Spatial as well as temporal distribution of individuals can lead to assortative mating when it makes individuals of the same fitness class more likely to meet each other (e.g. when high fitness individuals occupy the most profitable foraging patches). Furthermore, mutual mate choice (Parker 1983; McNamara & Collins 1990; Bergstrom & Real 2000) as well as conditions in which competition for mates is costly (Fawcett & Johnstone 2003) will lead to assortative mating. Since assortative mating by fitness is expected under these biologically realistic conditions, including assortative mating by fitness might contribute to explaining the maintenance of SA genetic variation.

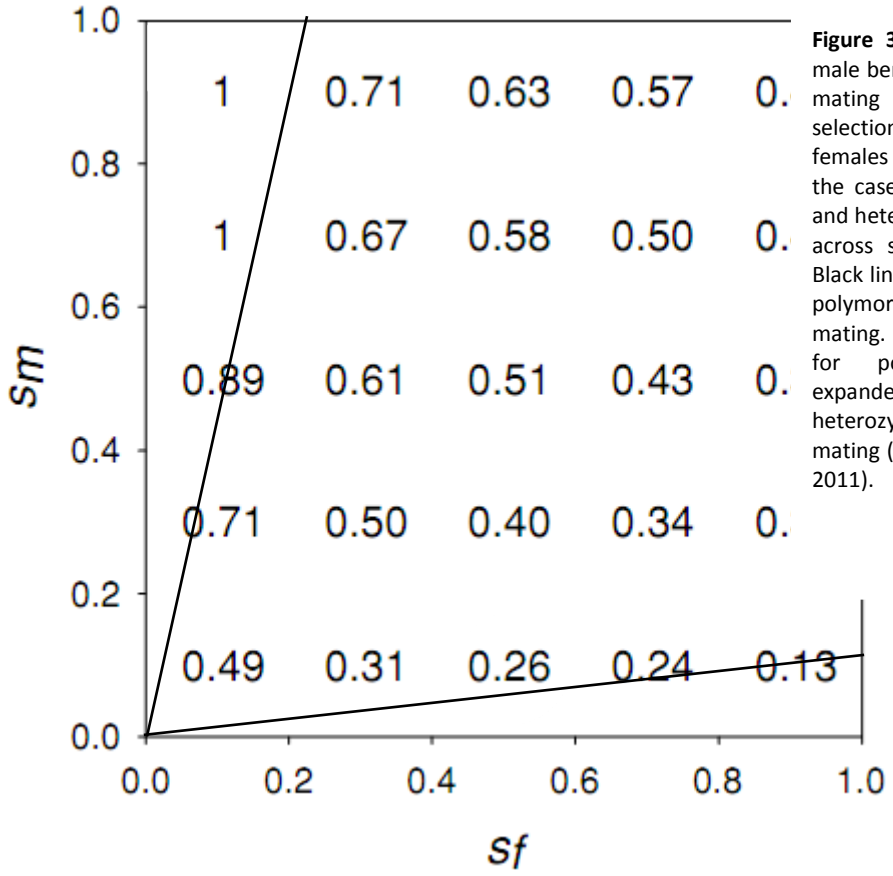

Figure 3. Equilibrium frequencies of a male benefit allele in case of assortative mating by fitness as a function of selection intensities in males (s_m) and females (s_f) for SA selection. Shown is the case of one locus with two alleles and heterozygous advantage on average across sexes (here h_f =0.1; h_m =0.2). Black lines indicate the regions of stable polymorphism in case of random mating. The parameter space allowing for polymorphism is marginally expanded and frequencies of heterozygotes are higher for assortative mating (modified from Fig. 1 in Arnqvist 2011).

When there are two loci involved SA selection will produce linkage disequilibrium (LD), the non-independence of alleles at two loci, especially under low recombination rates and strong selection (Úbeda et al. 2010). In the two-locus model lower recombination rates increase the opportunity for polymorphism, because linked loci can maintain gene variants that would be lost in a one locus model (Patten et al. 2010; cf. Figure 4). At any polymorphic equilibrium LD produces an excess of low- and high-fitness haplotypes. Increased opportunity for polymorphism and LD result in a higher fitness variance in a two-locus model compared to a single-locus model. Still LD between two loci cannot provide an explanation for SA fitness variation in the most meaningful parameter space with weak selection coefficients. Furthermore the two-locus model of Patten et al. assumes somewhat unrealistically only the case when allelic effects on fitness are additive.

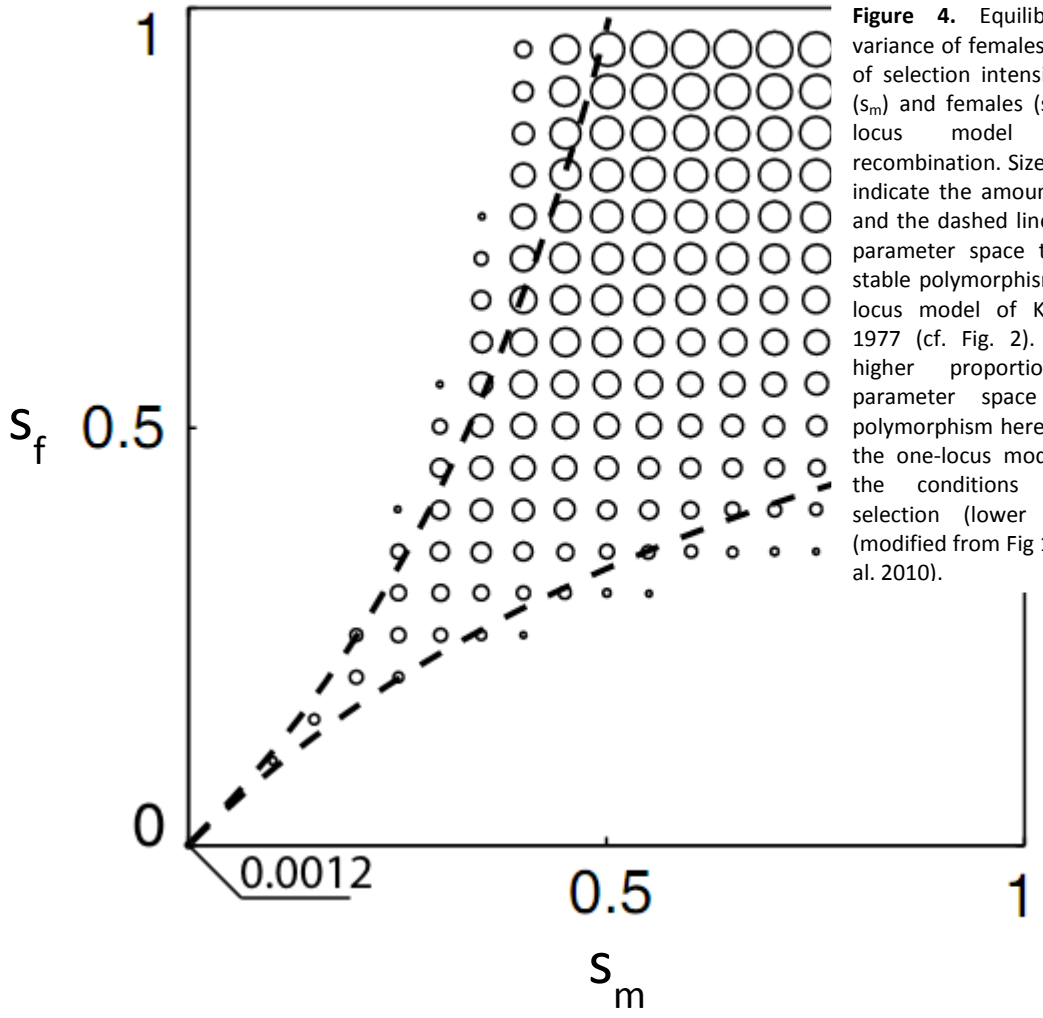

Figure 4. Equilibrium fitness variance of females as a function of selection intensities in males (s_m) and females (s_f) for a two-locus model with no recombination. Size of the circles indicate the amount of variance and the dashed line indicate the parameter space that leads to stable polymorphism in the one-locus model of Kidwell et al. 1977 (cf. Fig. 2). Note that a higher proportion of the parameter space allows for polymorphism here compared to the one-locus model, except in the conditions with weak selection (lower left corner) (modified from Fig 1. in Patten et al. 2010).

The model

Purpose

Variance in fitness among individuals is probably determined by many more loci than considered in even the more complex population genetics model for SA selection (two loci in Patten et al. 2010 and Ubeda et al. 2011). The purpose of my model is to explore how SA genetic variation in fitness can be maintained when fitness is determined by a number of l autosomal loci for additivity and partial sex specific dominance (also called 'dominance reversal' in the literature). The number of loci was chosen as $l = 1, 2, 3, 4, 10$ to still allow reasonable tracking of allele (and haplotype) frequencies, yet introducing a more realistic number of loci. Forward time individual based simulations were used, since analytical solutions are very difficult for systems with such a complex interplay of several loci. This model is an attempt to extend the somewhat oversimplified one-locus and two-locus population genetic models on this subject in order to understand the conditions allowing for maintenance of SA genetic variation in a more comprehensible way.

Structure

The simulations were initiated with a population of fixed size (N=3000 individuals) with a diploid genotype. The genotype consisted of a number of l fitness determining, autosomal loci with two alleles each. Individuals were randomly assigned to be either male or female (primary sex ratio =0.5) and subsequently submitted to sex-specific viability selection in which their survival was proportional to their expected fitness value (i.e. viability selection during offspring stage). After selection adults were randomly paired and produced the offspring generation according to mendelian laws. This process was iterated until evolutionary equilibrium was reached (t =2000 for simulations with more than one locus and t=200 for simulations with one locus) (Fig. 5).

An expected fitness value for each diploid genotype (and therefore individual) was calculated according to an extension of the one-locus model (Kidwell et al. 1977). Fitness was first computed for each locus depending on which sex the individual belongs to. At each locus one allele (e.g. A_m) was favored in males while the other one was favored in females (e.g. A_f). The fitness at each locus depended on a sex-specific selection coefficient s (e.g. "s_m" for selection in males) and on a single dominance coefficient, h, for all loci. The most fit genotype was assigned a fitness of 1, the least fit genotype has the fitness of $1 - s_{Sex}$, where s_{sex} is the selection coefficient of a specific sex and the heterozygotes have the fitness of $1 - h\ s_{Sex}$, where h is the dominance coefficient (with the favored allele in each sex being completely dominant, when h=0 and being recessive, when h =1). The resulting sex specific fitness equations per locus for an example with three loci are given in Table 1. After calculating the genotype fitness at each locus, they were multiplied and the product was used as the total fitness of the individual (see Table 1), according to which it survived until reproductive age. Population statistics were extracted from the adult individuals after selection.

Table 1. Sex-specific relative fitness set for three loci (A, B, C) with two alleles (one favored in males and the other favored in females) each. The fitness values are first calculated per locus and then multiplicatively combined across loci (not shown in table). Parameter *s* is the selection coefficient and *h* is the dominance coefficient (h =0 [beneficial allele dominant], h =0.5 [additive], h =1 [beneficial allele recessive]). Subscripts for these parameters indicate to which sex (m =male, f =female) and locus (A, B, C) they belong. This model is easily extended to a number of ten loci.

	Genotypes								
	Locus A			Locus B			Locus C		
	A_mA_m	A_mA_f	A_fA_f	B_mB_m	B_mB_f	B_fB_f	C_mC_m	C_mC_f	C_fC_f
Males	1	$1-h\ s_m$	$1-s_m$	1	$1-h_m\ s_m$	$1-s_m$	1	$1-h_m\ s_m$	$1-s_m$
Females	$1-s_f$	$1-h\ s_f$	1	$1-s_f$	$1-h_m\ s_f$	1	$1-s_f$	$1-h_m\ s_f$	1

During the next step in the sequence of each generation mating took place. In case of random mating adult males and females were paired randomly (with replacement) and produced offspring with a genotype resulting from mendelian segregation with a recombination rate r, which was kept constant across all adjacent loci. In particular, the simulation program went along chromosomes and determined, between adjacent loci, whether a recombination event happens with probability r. Then the next reproducing parental pair was sampled and this process was repeated until the new generation reached the predefined constant population size of 3000 individuals. I also simulated a scenario in which there was assortative mating by fitness. For this purpose, adults were first sorted into quantiles of the fitness distribution (1-25, 26-50, 51-75 and 76-100%) separately for the two sexes at every generation. Randomly selected males were then paired with an adult female randomly drawn from the same fitness quantile (see Arnqvist 2011).

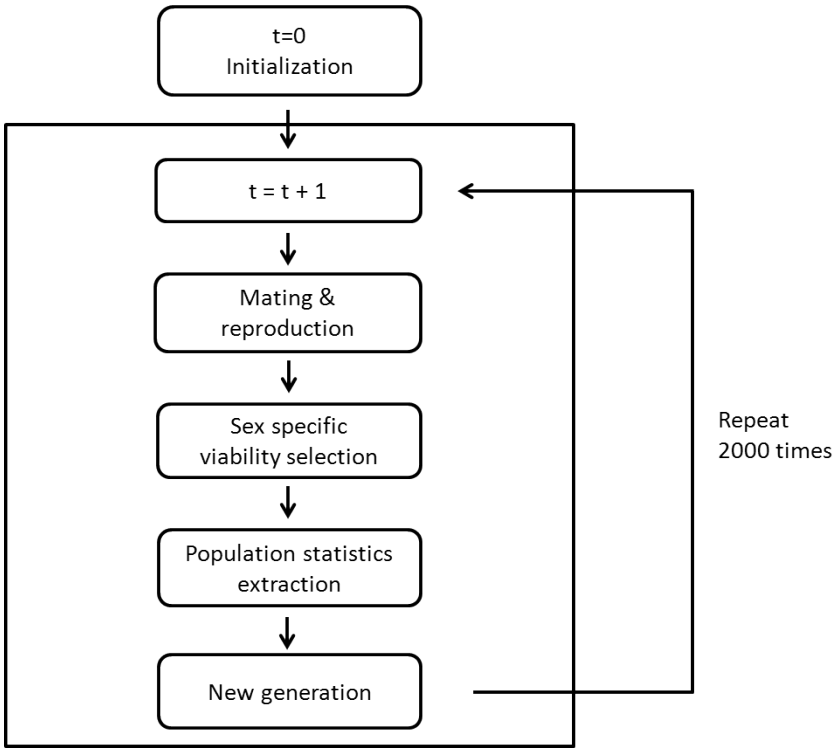

Figure 5. Flowchart of the model. After initialization the process is repeated for a number of t generations.

The simulations were initiated with allele frequencies of 0.5 at all loci. Preliminary runs with different population sizes (from N=500 to N=5000) were performed to explore what population size is optimal in the sense that it avoids genetic drift but simulations still take as less time as possible. The variance between independent replicates did not significantly decrease when the population size was increased above 3000, which was therefore used as the constant population size in all subsequent simulations. To explore the selection parameter space, each simulation was based on

values for the sex-specific selection coefficients drawn from a standard uniform distribution (with $0 \leq s_{Sex} \leq 1$). The simulations were repeated for different sets of dominance scenarios. For the one locus case partial recessivity (h= 0.8), additivity (h=0.5) and partial dominance (h=0.2) for the beneficial allele in each sex, were used and for the simulations with more than one locus only the more realistic scenarios of additivity (h=0.5) and dominance (h=0.2) were used (Manna et al 2011). During production of offspring genotypes, recombination between loci occurred with recombination rate r, which was varied from r=0.0 over r=0.1 to r=0.5. All these parameter values (except of course the allele frequencies) stayed constant during all generations in each simulation.

I used the simulation program simuPOP (version 1.0.6)(Peng & Kimmal 2005), which allows for forward-time modeling of advanced evolutionary processes, including non-random mating patterns and multilocus selection (Peng & Amos 2008), to simulate the different evolutionary scenarios.

For each scenario with a specific number of involved loci, dominance coefficient and recombination rate, evolution under at least 1000 sets of randomly drawn male and female selection coefficients was simulated to get a meaningful sample of the selection parameter space. For each of these sets of selection coefficients evolution of ten independent replicate populations was simulated. The same procedure was conducted with 1000 sets of randomly drawn male and female selection coefficients for weak selection (with $0 \leq s_{Sex} \leq 0.1$), which is more likely to reflect the conditions in natural populations (Kingsolver 2001; Cox & Calsbeek). Unfortunately, the simulations with ten loci and strong recombination often resulted in the loss of all members of one sex when selection was very high. Therefore no results for ten loci and strong recombination are presented for the case with the whole range of selection.

Extracted statistics

Since no deterministic analytical model was used some degree of stochastic variation is expected in the resulting allele frequencies. To account for this stochasticity the mean over the statistics of 10 independent replicate populations for each sample point in parameter space was calculated.

Realized heterozygosity (H) was used as a measurement of genetic polymorphism. For each locus the actual proportion of heterozygous individuals of the replicate population was used. First the heterozygosity was averaged across all loci within one replicate population. Then the mean of heterozygosity over the ten replicate populations was calculated and used as measurement of genetic polymorphism. To estimate the protection conditions for polymorphism the proportion of the over 1000 sets of selection coefficients that resulted in non-zero heterozygosity and therefore maintenance of allelic diversity (henceforth, P_H) was calculated. Subsequently, to get an estimate of the expected degree of genetic polymorphism for each evolutionary scenario, the mean heterozygosity of all the sample points of the parameter space where non-zero heterozygosity was

maintained (henceforth, mean H) was calculated. Means for other statistics were calculated the same way.

The coefficient of fitness variation in per cent was used as a measurement of fitness variation. The coefficient of variation was preferred over the fitness variance, because it allows for comparison among populations with different mean fitness. To estimate the expected phenotypic fitness variation for each evolutionary scenario, the mean coefficient of fitness variation over all 1000 sampled sets of selection coefficients (henceforth, CV_F) was used.

As soon as more than one locus is introduced in a model also the statistical association of alleles at two loci should be considered. This deviation from probabilistic independence between alleles at two different loci is most commonly called linkage disequilibrium (LD). Originally LD has been defined for the two-locus model as $D = x_{11} - p_1 \cdot q_1$, where x_{11} is the actual frequency of the haplotype A_1B_1 and $p_1 \cdot q_1$ is the expected frequency of this haplotype given the allele frequencies and independence of loci. One drawback of this measure is that changes in D reflect both real changes in the intensity of linkage correlation, but also changes in allele frequencies. Therefore Lewontin proposed to normalize D by the maximum D that is possible for specific allele frequencies to get $D' = \frac{D}{D_{max}}$ (Lewontin 1964). To facilitate comparison between linkage disequilibria of populations with different allele frequencies D' was used as a measure for linkage disequilibrium. For more than two loci calculation of LD is very complex, because correlations between different pairs of loci and correlations on several hierarchical levels have to be calculated. Therefore analysis of LD was only performed for the case of two loci.

Results

Confirmation of previous results

The results of the simulations with one fitness determining locus and random mating were congruent with previous theoretical models (Kidwell et al. 1977; Arnqvist 2011). Under partial recessivity of the sex specific beneficial allele (dominance coefficient of h=0.8) only quite restricted male and female selection coefficients allowed for polymorphism, namely when male and female selection coefficients were similar and either very low or very high (Fig. 6, upper row, on the left). The proportion of parameter space that maintained heterozygosity was P_H=0.085 and heterozygosity, when it was maintained, was on average H=0.162. Heterozygosity under additivity (h=0.5) was maintained under broader conditions, namely when male and female selection were approximately equal and when selection was strong (Fig. 6, upper row, in the middle). A proportion of P_H=0.538 of parameter space yielded polymorphism while the populations with polymorphism had on average a heterozygosity of H=0.295. Under dominance (h=0.2), heterozygosity was maintained in P_H=0.899

with an average heterozygosity of H=0.396 (Fig. 6, upper row, on the right). Naturally, almost all simulations resulted in phenotypic fitness variance. Only the ones with either zero selection on males or zero selection on females resulted in no fitness variance. The mean coefficient of fitness variation decreased with degree of dominance from CV_F=18.0 under recessivity to CV_F=16.9under additivity and to CV_F=13.0 under sex specific dominance of the beneficial allele (Tab. 2).

Just as in the literature assortative mating increased the impact the dominance coefficient has on maintenance of SA genetic variation (Arnqvist 2011). Therefore under recessivity heterozygosity is only maintained under P_H=0.072 with H=0.132. In case of additivity heterozygosity is maintained under P_H=0.514 with H=0.355 and under dominance P_H increases to 0.913 and to H=0.515 (Fig. 6, lower row). This means that assortative mating is able to increase the range of polymorphism by 1.6 per cent from 0.899 under random mating to 0.913 under assortative mating when allelic effects were dominant. As in case of random mating mean CV_F decreased with increasing dominance from CV_F=17.5 for recessivity to CV_F=16.3 for additivity to CV_F=11.5 under dominance (Tab. 2).

Table 2. Simulation results for *one locus* with the full range of selection coefficients ($0.0 \leq s \leq 1.0$). Shown are the proportion of parameter space that resulted in non-zero heterozygosity (P_H), the mean heterozygosity over all sets of selection coefficients that resulted in non-zero heterozygosity (Mean H) and the mean coefficient of fitness variation over all 1000 sets of selection coefficients (Mean CV_F). Note how the proportion of parameter space that results in polymorphism increases with dominance and how this effect changes from random to assortative mating.

Mating	P_H			Mean H			Mean CV_F		
	h=0.8	h=0.5	h=0.2	h=0.8	h=0.5	h=0.2	h=0.8	h=0.5	h=0.2
random	0.085	0.538	0.899	0.162	0.295	0.396	18.0	16.9	13.0
assortative	0.072	0.514	0.913	0.132	0.355	0.515	17.5	16.3	11.5

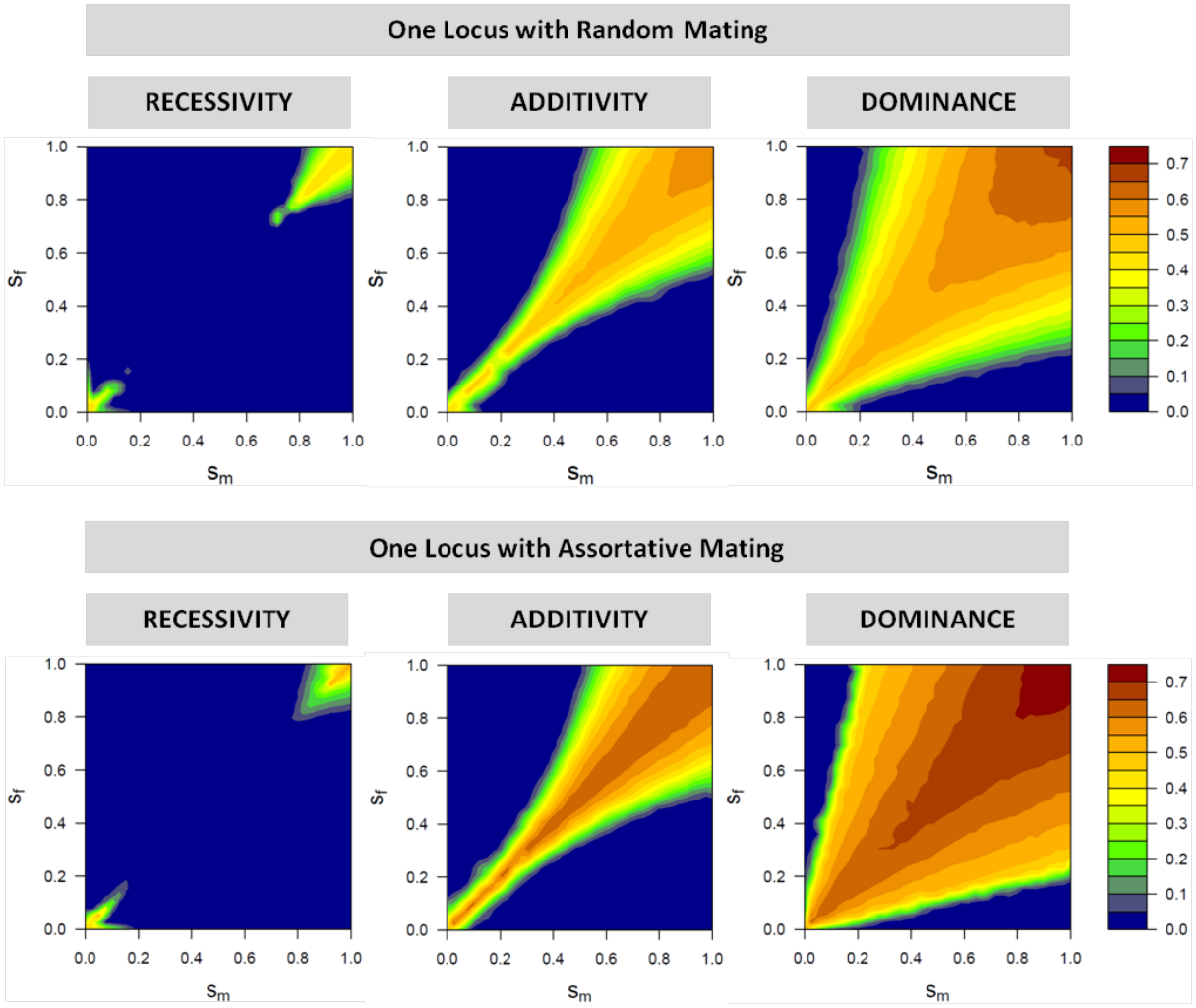

Figure 6. Realized heterozygosity as a function of male and female selection coefficients for sex specific recessivity, additivity and dominance of the beneficial allele for the *one locus* model. The color code shows the proportion of the population that is heterozygous for the fitness determining locus. The upper row shows the results for a random mating scheme and the lower row shows results for assortative mating scheme.

Additive allelic effects

When allelic effects are additive (h=0.5) the parameter space that results in heterozygosity increases as the result of the joint effect of linkage and number of involved loci (Fig. 7 & 8). When recombination between adjacent loci is high the number of loci involved has no effect on the protection conditions of polymorphism whose value lies around 0.36 (Fig. 8, right column; Table3). When there is no recombination or in other words complete linkage between adjacent loci the protection conditions increase with number of involved loci from P_H=0.504 for two, P_H=0.521 for three, 0.597 for four and 0.897 for ten loci (Fig. 7; Tab. 2).

While number of loci and linkage have a positive effect on P_H they have a negative effect on the average heterozygosity or in other words: when fitness is determined by many linked loci a broader range of selection coefficients will result in heterozygosity but the heterozygosity will be lower on average than in the case with few unlinked loci (Tab.2).

The mean coefficient of fitness variation is only influenced by the number of involved loci but not by recombination rate (Tab 2).

No joint effect of linkage and number of loci could be observed under weak selection (Tab. 3). Only when male and female selection coefficients are approximately the same can polymorphism be maintained under these conditions. The only exceptions are simulations with 10 loci have higher P_H when they are completely linked, although this could be an artifact from populations that did not reach equilibrium yet. In general the changes that the joint effect of linkage and polygenic inheritance causes are in the part of parameter space with high selection coefficients (see Fig. 8).

Table 2. Simulation results for *additive allelic effects* under the *full range of selection coefficients* ($0.0 \leq s \leq 1.0$). Shown are the proportion of parameter space that resulted in non-zero heterozygosity (P_H), the mean heterozygosity over all sets of selection coefficients that resulted in non-zero heterozygosity (Mean H) and the mean coefficient of fitness variation over all 1000 sets of selection coefficients (Mean CV_F).

# Loci	P_H			Mean H			Mean CV_F		
	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5
2	0.504	0.382	0.377	0.379	0.402	0.395	27.9	26.6	26.6
3	0.521	0.427	0.373	0.334	0.377	0.393	33.2	33.2	32.6
4	0.597	0.391	0.358	0.289	0.374	0.368	35.7	37.2	35.5
10	0.897	0.406	NA	0.115	0.275	NA	31.4	44.2	NA

Table 3. Simulation results for *additive allelic effects* under *weak selection* ($0.0 \leq s \leq 0.1$). Shown are the proportion of parameter space that resulted in non-zero heterozygosity (P_H), the mean heterozygosity over all sets of selection coefficients that resulted in non-zero heterozygosity (Mean H) and the mean coefficient of fitness variation over all 1000 sets of selection coefficients (Mean CV_F).

# Loci	P_H			Mean H			Mean CV_F		
	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5
2	0.299	0.324	0.319	0.146	0.142	0.137	3.16	3.18	3.07
3	0.291	0.318	0.304	0.154	0.134	0.125	4.58	4.67	4.63
4	0.317	0.341	0.329	0.158	0.127	0.119	6.07	6.31	6.00
10	0.996	0.345	0.335	0.109	0.123	0.113	12.11	13.78	13.62

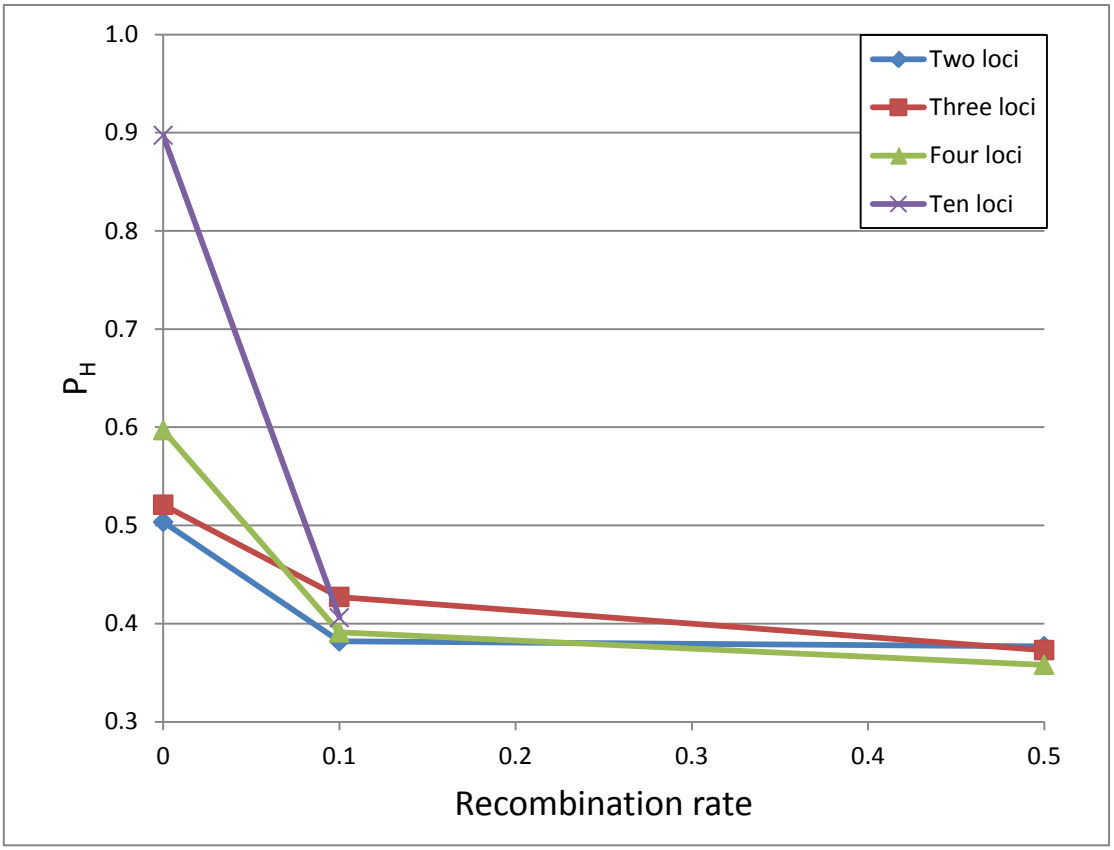

Figure 7. Protection conditions for genetic polymorphism under *additive allelic effects* as a function of recombination rate for simulations with different numbers of involved loci. Note how the proportion of parameter space that results in heterozygosity (P_H) decreases with increasing recombination rate.

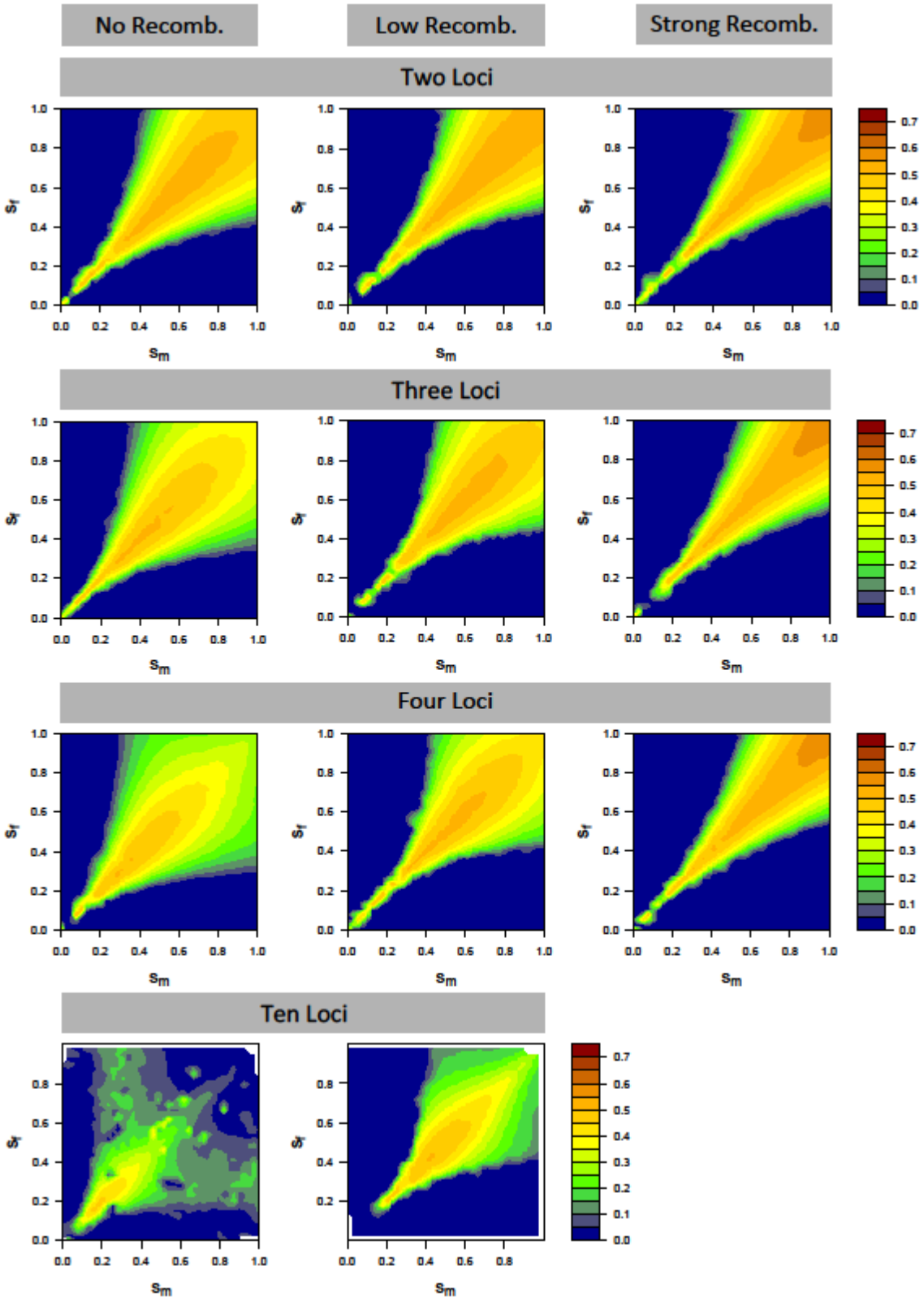

Figure 8. Realized heterozygosity as a function of male and female selection coefficients under *additive allelic effects* for no recombination (r=0.0; first column), low recombination (r=0.1; second column) and strong recombination (r=0.5; third column) between neighboring loci. The color code shows the proportion of the population that is heterozygous for the fitness determining loci. The four rows show results for two, three, four and ten fitness determining loci. Note, in particular, how the protection conditions for heterozygosity change with number of loci for no recombination (left column).

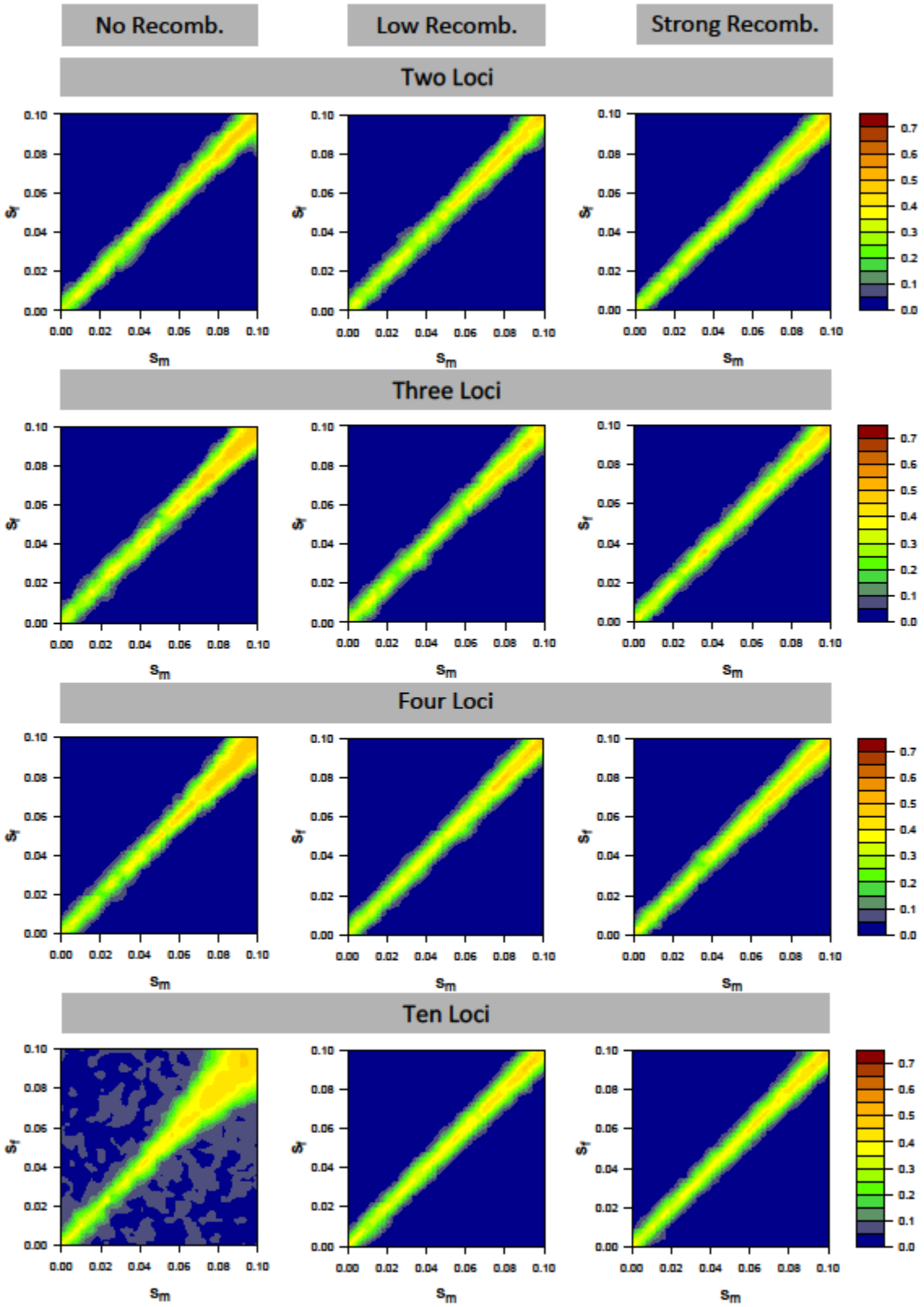

Figure 9. Simulation results for *weak selection* ($0.0 \leq s \leq 0.1$). Shown is realized heterozygosity as a function of male and female selection coefficients under *additive allelic effects* for no recombination (r=0.0; first column), low recombination (r=0.1; second column) and strong recombination (r=0.5; third column) between neighboring loci. The color code shows the proportion of the population that is heterozygous for the fitness determining loci. The four rows show results for two, three, four and ten fitness determining loci.

Dominant allelic effects

When sex specific allelic effects were partially dominant polymorphism was maintained under broader conditions than when allelic effects were additive (Fig. 10 & 11). Again recombination and number of loci had a joint effect with many, completely linked loci resulting in a broader parameter space with polymorphism (Fig. 10; Tab. 4). While the increase of polymorphic populations was very slight from 0.778 under strong recombination, over 0.779 under low recombination to 0.787 under no recombination, for four loci the increase was stronger from 0.762 under strong recombination, over 0.782 under low recombination to 0.819 under no recombination (Fig. 10; Tab. 4). Still the increase is not as strong as under additivity. Contrary to the case of additivity under dominance also the average heterozygosity over polymorphic populations increases with linkage and number of loci, although this effect does not hold for simulations with ten loci anymore (Tab. 4). In fact, in simulations with ten loci and complete linkage, regions with very strong selection show a reduced heterozygosity again (Fig. 11, lower left graph). Under dominance the mean coefficient of variation increases with number of loci, as under additivity, but decreases with linkage (Tab. 4).

For weak selection and dominance there is no effect of linkage and number of loci neither on the range of polymorphism nor on the mean heterozygosity (Fig. 12; Tab. 5). Interestingly, there is a positive effect of number of loci on mean CV_F , but unlike under the whole range of selection coefficients under weak selection simulations with strong recombination have a higher fitness variance (Tab. 5)

Table 4. Simulation results for *dominant allelic effects* under the *full range of selection coefficients* ($0.0 \leq s \leq 1.0$). Shown are the proportion of parameter space that resulted in non-zero heterozygosity (P_H), the mean heterozygosity over all sets of selection coefficients that resulted in non-zero heterozygosity (Mean H) and the mean coefficient of fitness variation over all 1000 sets of selection coefficients (Mean CV_F).

# Loci	P_H			Mean H			Mean CV_F		
	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5
2	0.787	0.779	0.778	0.481	0.444	0.436	17.3	19.3	19.5
3	0.818	0.788	0.774	0.499	0.451	0.442	21.6	24.2	25.2
4	0.819	0.782	0.762	0.509	0.452	0.443	25.3	27.6	29.1
10	0.930	0.761	NA	0.406	0.439	NA	40.9	44.5	NA

Table 5. Simulation results for *dominant allelic effects* under *weak selection* ($0.0 \leq s \leq 0.1$). Shown are the proportion of parameter space that resulted in non-zero heterozygosity (P_H), the mean heterozygosity over all sets of selection coefficients that resulted in non-zero heterozygosity (Mean H) and the mean coefficient of fitness variation over all 1000 sets of selection coefficients (Mean CV_F).

# Loci	P_H			Mean H			Mean CV_F		
	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5	r=0	r=0.1	r=0.5
2	0.823	0.839	0.834	0.332	0.333	0.325	2.54	2.39	2.27
3	0.832	0.841	0.845	0.341	0.319	0.331	3.69	3.04	3.12
4	0.855	0.835	0.847	0.331	0.332	0.323	4.72	3.67	3.76
10	1	0.863	0.874	0.325	0.310	0.308	8.90	7.47	7.27

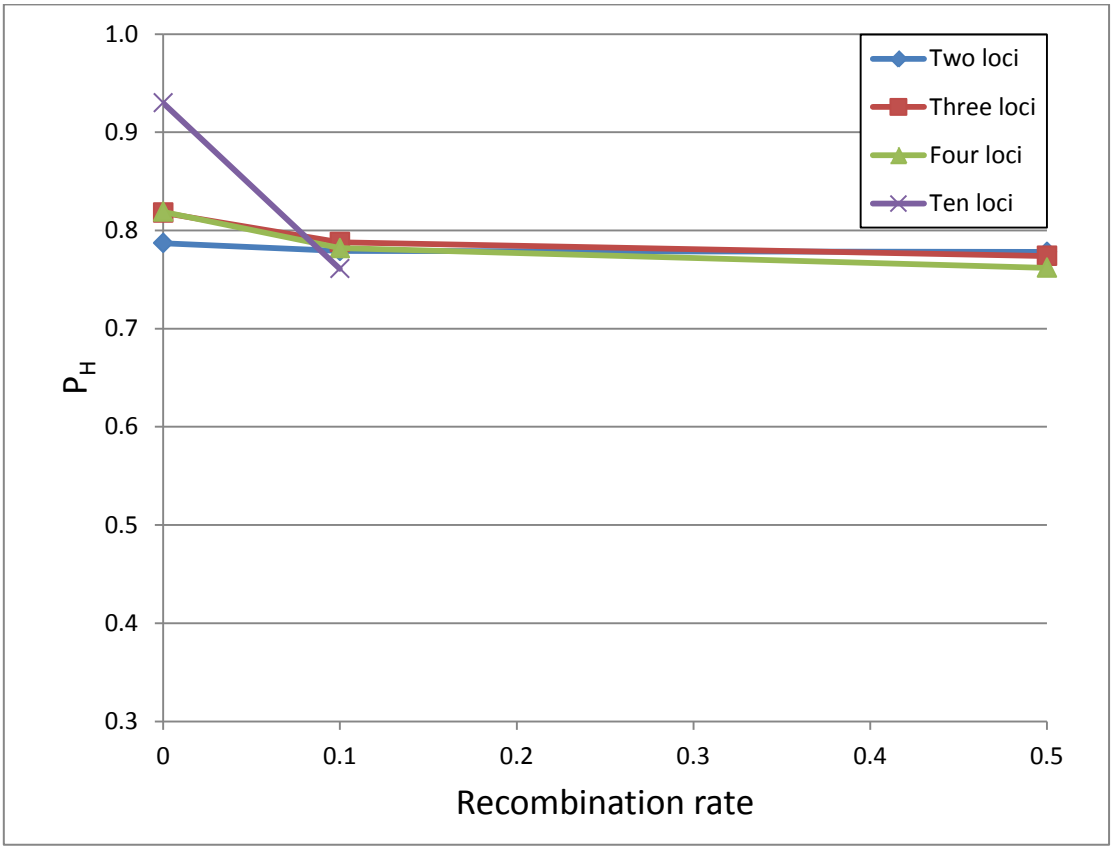

Figure 10. Protection conditions for genetic polymorphism under *dominance* as a function of recombination rate for simulations with different numbers of involved loci. Note how the proportion of parameter space that results in heterozygosity (P_H) decreases only slightly with increasing recombination rate.

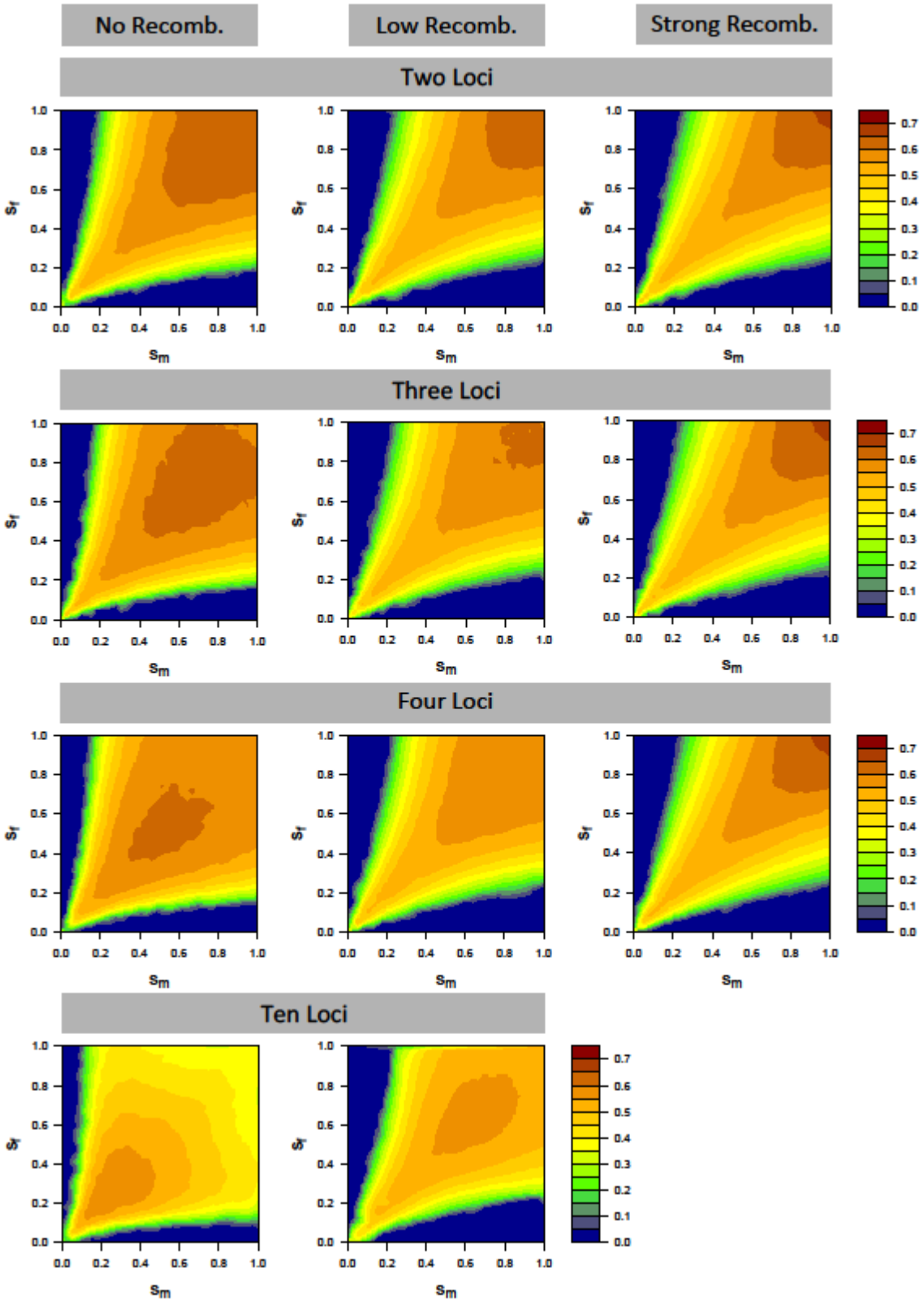

Figure 11. Simulation results for *dominant allelic effects* and the *whole range of selection coefficients* ($0.0 \leq s \leq 1.0$). Shown is realized heterozygosity as a function of male and female selection coefficients for no recombination (r=0.0; first column), low recombination (r=0.1; second column) and strong recombination (r=0.5; third column) between neighboring loci. The color code shows the proportion of the population that is heterozygous for the fitness determining loci. The four rows show results for two, three, four and ten fitness determining loci. Note, in particular, how the protection conditions for heterozygosity change with number of loci for no recombination (left column).

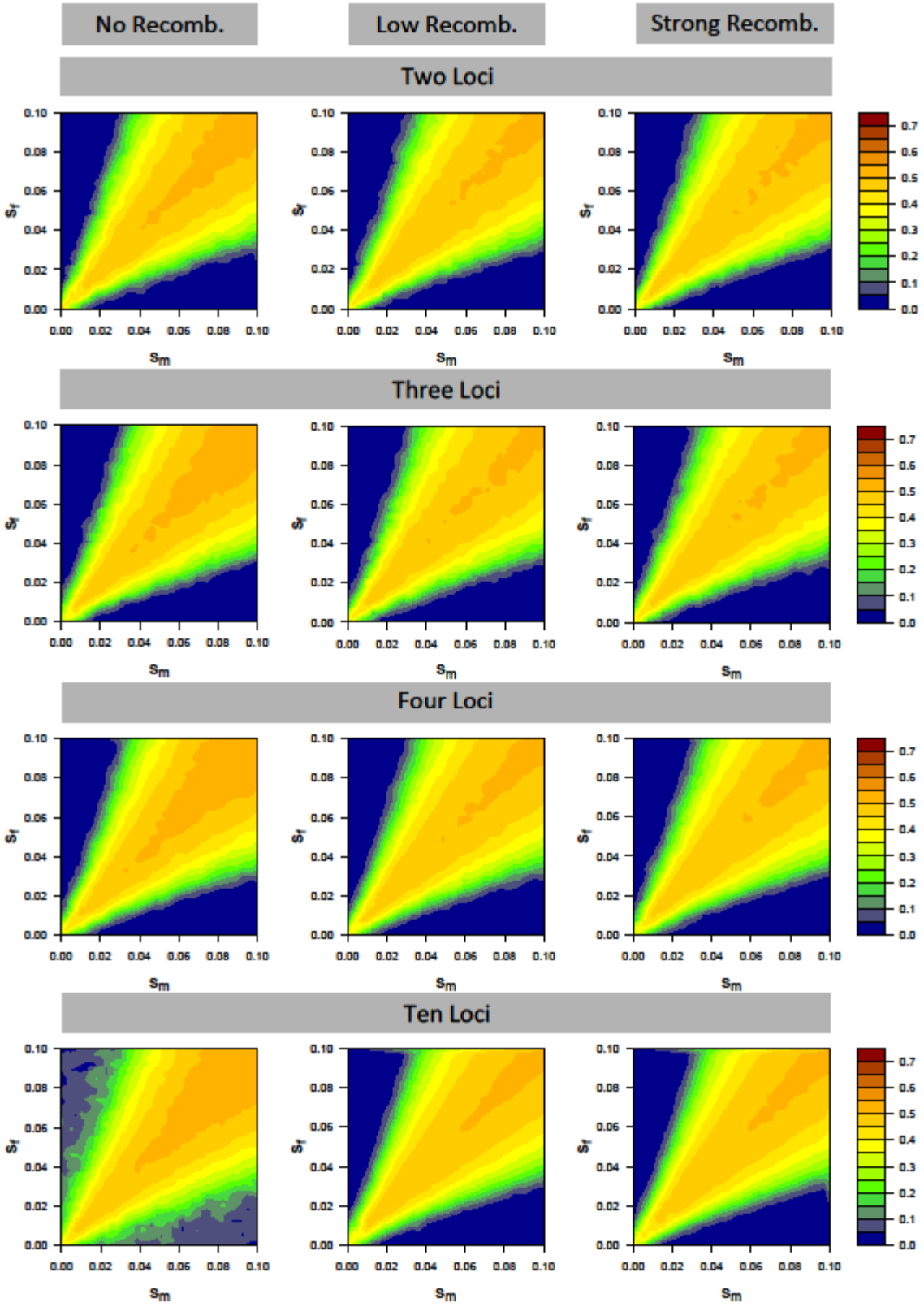

Figure 12. Simulation results for allelic *dominance* and *weak selection* ($0.0 \leq s \leq 0.1$). Shown is realized heterozygosity as a function of male and female selection coefficients for no recombination (r=0.0; first column), low recombination (r=0.1; second column) and strong recombination (r=0.5; third column) between neighboring loci. The color code shows the proportion of the population that is heterozygous for the fitness determining loci. The four rows show results for two, three, four and ten fitness determining loci.

Linkage disequilibrium for the two locus case

Under complete linkage almost all simulations that resulted in polymorphism also resulted in the highest possible linkage disequilibrium (red area in Fig. 13, left column). Therefore, as an example, the value for P_H for additive allelic effects is almost the same and just a little bit higher than the proportion of parameter space that resulted in LD (P_H=0.504 and P_{LD}=0.449). In fact, all populations for simulations with additive allelic effects and no recombination ended up having either a D'-value of zero or one. The values of intermediate D' (yellow areas in the upper left graph of Fig. 13) emerged when some of the ten replicate populations for the same selection coefficients reached D'-values of one and some ended up with zero D'. The stronger recombination gets, the stronger the selection coefficients have to be in order for selection to build up LD. Under strong recombination only unrealistically high selection coefficients can result in the build-up of LD of intermediate strength (Fig. 13, upper right graph).

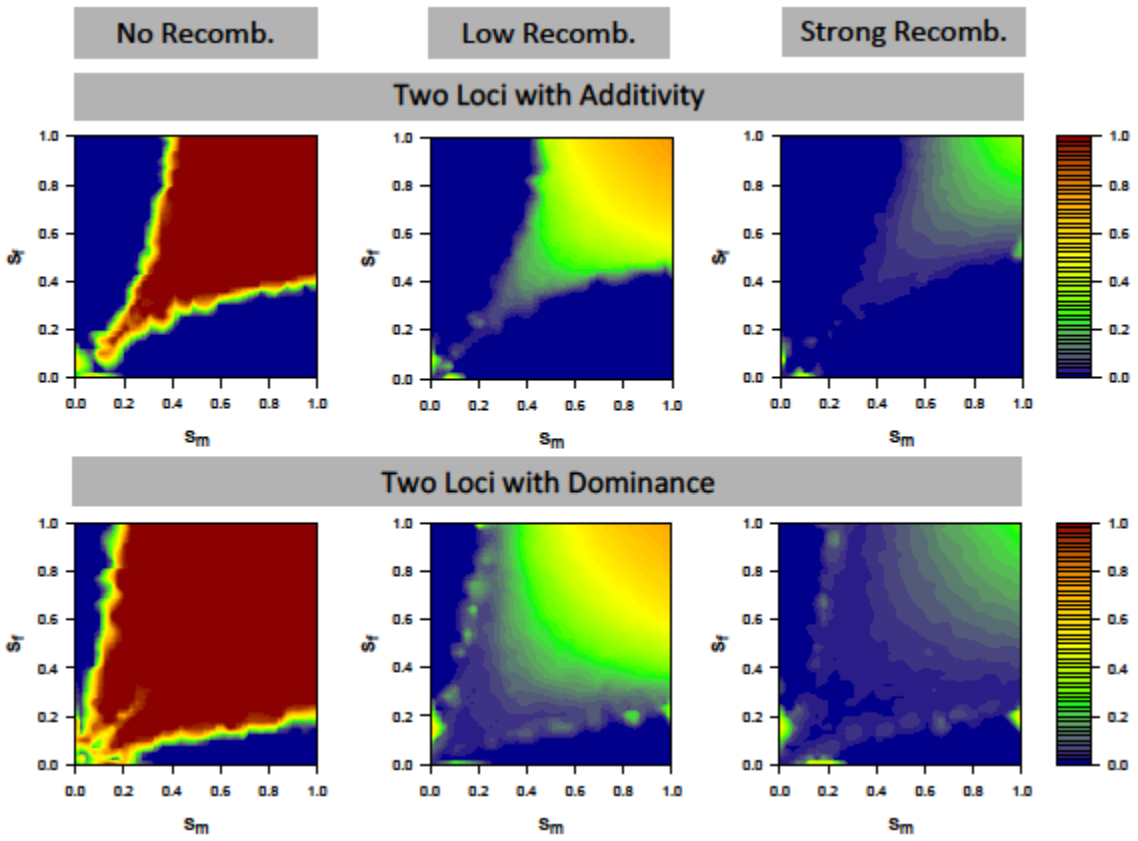

Figure 13. Normalized linkage disequilibrium (D') as a function of male and female selection coefficients. Shown are the results for simulations with *two loci* and either additive (upper row) or dominant (second row) allelic effects. Simulations with the highest possible LD have a D'-value of one (red area) and simulations which resulted in no linkage have a value of zero (dark blue areas).

Discussion

The results of the simulations show that we can expect widespread SA genetic variation when sex specific allele effects on fitness are dominant in natural populations. If allele effects are additive we can expect SA genetic variation under reasonable assumptions about natural populations like polygenic inheritance and linkage.

Joint effect of polygenic inheritance and linkage

Under additivity the joint effect of polygenic inheritance and linkage facilitates the maintenance of SA variation. Maintenance of genetic variation by SA selection is the result of a balance, in which selection an allele experiences in one sex is outbalanced by selection in the other sex such that selection does not drive any allele to fixation. In case of polygenic inheritance linkage effectively increases selection on the involved loci. Each locus then experiences also selection from neighboring loci and thereby equilibrium allele frequencies are increased. This way alleles can be maintained even under conditions where they would be lost in the case of the one locus model (Patten et al. 2010). The more linked loci are involved, the stronger the combined selection on each locus and the broader the conditions in which polymorphism is maintained (Fig. 7). Therefore we can expect more SA genetic variation in fitness on autosomes when fitness is determined by many tightly linked loci, even under pure additivity.

Effect of dominance

Dominance facilitates the maintenance of SA variation independently from the effect of linkage and polygenic inheritance. The effect of dominance under polygenic inheritance is very similar to the dominance effect in the one locus model as discussed in Kidwell et al. 1977 or Fry 2010. As long as selection coefficients in males and females are not too different, partial dominance of the beneficial allele will result in heterozygote advantage when fitness is averaged across sexes (Fry 2010). This is because each genotype is equally likely to be expressed in a male or a female body, so that heterozygotes will on average have higher fitness than homozygotes when there is partial dominance. Heterozygote advantage is long known in population genetics to be able to maintain genetic variation (e.g. Hedrick 1983). For that reason genetic polymorphism will also be maintained under SA selection and partial dominance.

Linkage disequilibrium

Genetic polymorphism is not the only source of phenotypic fitness variation. Also linkage disequilibrium influences fitness variance. Linkage disequilibrium builds up in about 40 per cent of the parameter space when allelic effects are additive and in almost 75 per cent of the parameter

space when allelic effects are dominant (Fig. 13). These values were little influenced by the degree of recombination under dominance although under additivity linkage increased parameter space resulting in LD' in almost the same way as it did increase parameter space resulting in heterozygosity. Linkage causes an excess of haplotypes with high sex specific fitness (i.e. the A_mB_m and the A_fB_f haplotypes) and low frequencies of the haplotypes with low sex specific fitness (Fig. 14, a and c). When selection in males and females is the same also the frequencies of the sex specific beneficial haplotypes are the same (Fig. 14. a and b), while when one sex experiences stronger selection (but not enough to drive any allele to fixation) the haplotype which is beneficial for that sex will increase to higher frequency (Fig. 14, c and d). Strong recombination will counteract against the buildup of those excesses of beneficial haplotypes, so that frequencies of all haplotype tend towards 0.25 when selection in both sexes is equal (Fig. 14 b). Therefore LD is lower when recombination is high (Fig. 13, right column). Interestingly, under conditions that maintain the highest degree of allelic variation, i.e. when selection on males and females are the same, variation in haplotypes is in general lower, so that also fitness variation is lower under these conditions (Fig. 14 a and b).

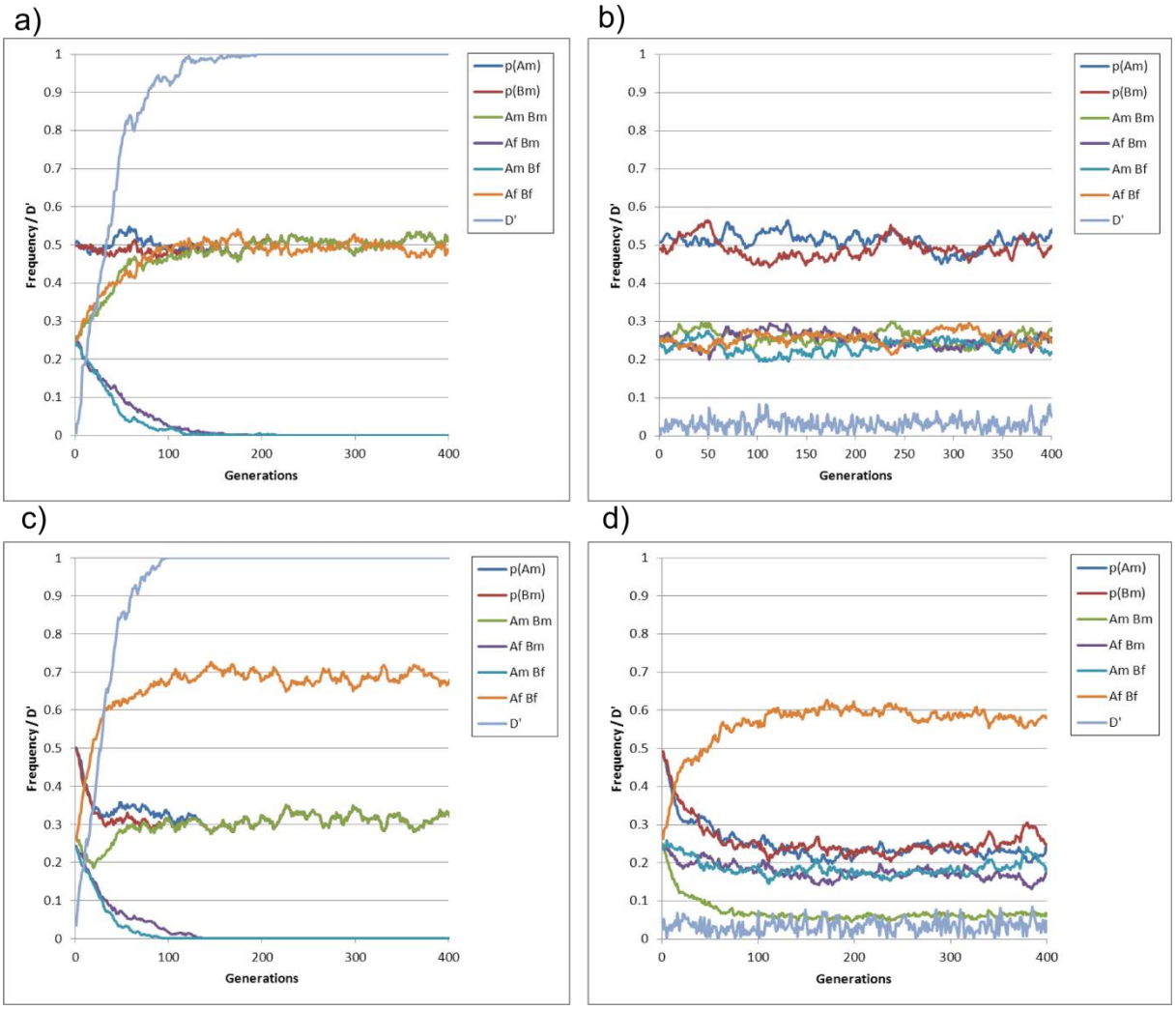

Figure 14. Frequencies of alleles, haplotypes and the normalized linkage disequilibrium (D') over time. Shown is the case of *two loci* with a) no recombination and equal selection in the sexes (s_m=0.4; s_f=0.4), b) strong recombination and equal selection in the sexes (s_m=0.4; s_f=0.4), c) no recombination and unequal selection in the sexes (s_m=0.4; s_f=0.5) and d) strong recombination and unequal selection in the sexes (s_m=0.4; s_f=0.5). For more explanations see the text.

Critical review of model assumptions

There are several reasons why too strong conclusions from the results of the simulations may be misleading:

For instance, the joint effect of linkage and polygenic inheritance under additivity is only able to predict an increase in protection conditions for polymorphism when the whole range of selection coefficients is considered. But for the more interesting parameter space of weak selection, that resembles natural conditions more closely (Kingsolver 2001; Cox & Calsbeek), this effect does not hold. In fact the only parameter in my simulations that influenced P_H under weak selection was the dominance coefficient.

Therefore the assumption of sex specific partial dominance of the beneficial allele is a crucial one, when trying to explain the maintenance of SA variation. To my knowledge there is no empirical

study about the distribution of dominance for fitness for sexually antagonistic alleles. In fact even the distribution of dominance for fitness for sexually non-antagonistic alleles is not well understood empirically and still much under debate although there are reasons to believe that selection will lead to dominance modifier loci that make beneficial alleles more dominant (Bourguet 1999). For instance, even the results of the very comprehensive yeast gene deletion project are thought to be not good enough to allow for inferences of dominance for the most important part of slightly deleterious mutations (Manna et al. 2012). Therefore how sex-specific dominance values are distributed empirically remains an open question. There are, however, authors who point out that sex specific partial dominance should emerge when fitness functions are non-linear and convex (Rice & Chippindale 2001; Fry 2010). Furthermore, there are reasons to believe that selection will lead to sex specific partial dominance, because dominance modifier that decrease h_m and h_f respectively can invade (Connallon & Clark 2011). For example, is has been shown that in a heterogeneous environment a dominance modifier, that increases the weighted average heterozygote fitness across patches, can invade (see "small-scale patchiness" model of Otto & Bourguet 1999). This is mathematically a quite similar case to the sexually antagonistic selection models and should therefore apply here as well.

Another assumption in the model which might have an important impact on the maintenance of SA variation is the one about multiplicativity between loci. Since fitness values of each locus are smaller than one, the total fitness, which is the product of those values, will be even smaller. Therefore selection will be stronger the more loci are involved. And because stronger SA selection results in more polymorphism (Kidwell et al. 1977), more polymorphism could be caused as an artifact of multiplicatively combining fitness of each loci. Since there is no a priori biological reason why fitness values of different loci should be multiplied and not added for example, but it is a mere convention in many population genetic models, the effect of this assumption should be examined in the future. Conclusions made by Patten et al. 2010 about the increased protection conditions for polymorphism in their two locus model with multiplicatively loci effects should also be viewed with caution for the same reason.

The next assumption which has to be considered having a potential impact on maintenance of SA variation is that selection coefficients at different loci are the same. It is very likely that selection, which different loci experience, varies. In that case it is not too improbable for at least one of those loci to have a selection coefficient of sufficient degree to maintain genetic variance and thereby pulling alleles at other loci with them and maintaining polymorphism at those as well.

And finally, much of SA selection can be expected to take place in the context of sexual selection. Sexual selection is by definition fecundity selection and often frequency-dependent.

Therefore the assumptions in this model of constant viability selection should also be relaxed in order to predict the amount of SA genetic variation in nature.

Conclusion

In conclusion, the most important factor influencing the maintenance of SA selection is dominance. It will be an important task to examine empirically whether dominance coefficients at SA loci are sex-specific and if the beneficial alleles are dominant. There are good theoretical reasons why this should be the case, although theoretical models that explicitly address the evolution of dominance under SA selection are lacking. Therefore extending theoretical and empirical knowledge about the distribution of dominance will be important. The influence of polygenic inheritance of fitness and recombination on the maintenance of SA genetic variation in natural conditions (i.e. under weak selection) remains equivocal. To examine the effect of polygenic inheritance and linkage the assumption of multiplicatively combining fitness from different loci and the assumption of constant selection at all loci should be relaxed.

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