Fitness-dependent recombination can be evolutionarily advantageous in diploids: a deterministic mutation–selection balance model

Sviatoslav R. Rybnikov[1], Zeev M. Frenkel[1] & Abraham B. Korol[1]*

[1]Department of Evolutionary and Environmental Biology and Institute of Evolution, University of Haifa

*corresponding author (korol@evo.haifa.ac.il)

Abstract

The omnipresence of recombination in nature is one of the most intriguing problem in evolutionary biology. The question of why recombination exhibits certain general features is no less interesting than that of why it exists at all. One such feature is recombination's dependence on genotype fitness. The evolution of fitness-dependent (FD) recombination in diploids remains theoretically unexplained, despite empirical evidence for this phenomenon coming mostly from diploids. Here, using numerical analysis of modifier models, we show that FD recombination can be evolutionarily advantageous in diploids under mutation–selection balance. This advantage is associated with the indirect effect of the modifier (benefits conferred on the selected system), rather than with the direct effect ('abandon-ship' mechanism) that is efficient in haploids but not diploids. Taken together with our analogous results for cyclical selection, we suggest that the evolutionary advantage of FD recombination based on an indirect effect can be universal in diploids.

Keywords: recombination, fitness dependence, diploids, mutation–selection balance

Introduction

Meiotic recombination is a process of reshuffling the parental genetic material, which takes place when a sexual organism produces its gametes. For about a century, recombination's omnipresence in nature has been a most intriguing question, given the evolutionary ambiguity of this process [1–4]. Indeed, the new allelic combinations generated in this process serve as the raw material to meet selection demands. On the other hand, it can also break down the existing combinations, including even the most successful ones. However, today, the question of why recombination exhibits certain general features has become no less interesting than the old question of why recombination exists at all [5]. One such feature is recombination's sensitivity to external and/or internal conditions affecting the proportion of recombinants in the progeny. Harold Plough was the first to show that recombination rates (RRs) can rise when the organism is exposed to an ecological stressor [6]. Empirical studies have provided accumulating evidence for the ecological plasticity of recombination (for recent reviews, see [7–9]). Earlier it was noticed that recombination ecological plasticity is genotype-specific [10–12], although the pattern of such specificity remained obscure. In 1986, Zhuchenko *et al*. demonstrated that stressor-induced changes in RRs can be modulated by genotype fitness in a negative-feedback manner [13], so that less stress-tolerant genotypes show more pronounced increases in RR. Moreover, genotype fitness can affect RRs even when no ecological stressors are imposed, i.e., when variation in fitness among individuals results from their differential genetic background (e.g., deleterious mutations) rather than from their differential stress tolerance [14]. In general, one can think of 'fitness-dependent'[13] or 'fitness-associated'[15] recombination; herein, we use the former term, abbreviated as FD recombination. Empirical evidence for this phenomenon is still very limited, both for stressor-induced [13,16–21] and mutation-induced [14,22] changes in RRs. Importantly, this evidence comes from diploids: mainly from fruit fly [14,16,17,19–22], but also from plants (tomato [13] and wheat [18]).

Within the adaptationist program, phenotypic traits (at least those that are heritable, affect reproductive success, and originate from earlier existing traits) are believed to evolve as adaptations [23]. Since FD recombination meets all of these criteria, it seems natural to consider it as an evolvable phenotype, or at least to test for this possibility. Theoretical models developed to date have clearly demonstrated the evolutionary advantage of FD recombination in haploids [15,24–27]. However, an attempt to extend these results to diploids failed, unless additional specific assumptions, such as cis/trans effects, were made [15]. In contrast, our recent study showed that FD recombination can also be evolutionarily advantageous in diploids under cyclical selection [28]. The same result was obtained for another type of condition dependence, i.e., ecological plasticity of recombination, again for diploids exposed to cyclical selection [28,29].

To address the discrepancy between the results obtained in the aforementioned diploid models, it was suggested that more complex selection regimes (such as cyclical selection) favor FD recombination more than less complex ones (such as directional selection or mutation–selection balance) [15]. Alternatively, as we discussed in our recent study [28], what may really affect the evolutionary advantage/disadvantage of FD recombination in the considered models is the presence or absence of variations in fitness among *recombination-responsive* genotypes, rather than the complexity of the selection regime. To further explore this assumption, here we test whether FD recombination can be evolutionarily advantageous in diploids under another mechanism, mutation–selection balance. As in our previous studies [28–30], here we compare different recombination strategies using a modifier approach [31,32], i.e., based on the dynamics of selectively neutral recombination-modifying alleles (*rec*-alleles). Also as in [28,30], we exploit a three-locus selected system: assuming no cis/trans effect, this is the minimal number of selected loci that ensures variation in fitness among recombination-responsive genotypes (double and triple heterozygotes).

Importantly, under the mathematically similar framework of mutation–selection balance, we consider two biologically different scenarios. The first one is *purifying selection*. In this scenario, the wild-type genotype is assumed to have the highest fitness, while mutations at any locus are deleterious. If mutations at different loci affect fitness in a purely multiplicative way, recombination is known to be neutral. However, this is not the case when the presence of a mutant allele(s) occurring simultaneously at several loci decreases fitness more markedly (synergistic, or negative, epistasis). Then, recombination can appear evolutionarily advantageous, since it facilitates purging mutant alleles from the population [33–39]. The second scenario implies a selective advantage of certain multilocus combinations of mutant alleles. Here again, each of the individual mutant alleles and each of the two-locus mutant combinations decrease fitness, whereas three-locus mutant combinations produce "progressive" genotypes with higher fitness compared to that expected under the assumption of purely multiplicative interlocus interaction. However, we limited our analysis to situations in which fitness of such "progressive" genotypes in the homozygous condition is still lower than that of the wild-type genotype. Herein, we refer to this scenario as *mixed selection*; formally, we model it by assuming two-locus epistasis to be synergistic (negative), and three-locus epistasis to be antagonistic (positive). In this case, recombination can be favored as well, since it enables assembling mutant alleles into relatively beneficial combinations [2,40]. Given the profound biological difference between the two described scenarios, we treat them separately.

Results

Comparisons between 'asexual reproduction' and 'sexual reproduction without recombination', on the one hand, and between 'sexual reproduction without recombination' and 'sexual reproduction with recombination', on the other, show that the effect of sex *per se* (i.e., of segregation) is much stronger than that of recombination [35]. Nonetheless, the latter is also of marked importance. Here, we study the evolution of recombination assuming obligate sexual reproduction with total panmixia, which seems realistic for many higher diploid eukaryotes.

Within each of the two considered evolutionary scenarios (purifying and mixed selection), we examined 24,000 combinations of four selection parameters: deleterious effect of mutations (s), dominance of mutations (h), two-locus epistasis (ε_2), and three-locus epistasis (ε_3). For simplicity, deleterious effect and dominance were assumed to be equal for all three selected loci, and two-locus epistasis was assumed equal for all three pairs of selected loci. The deleterious effect was scanned from 0.05 (slightly deleterious mutation) to 1 (lethal mutation), with a step of 0.05. Dominance was scanned from 0.25 (partially recessive mutation) through 0.5 (co-dominant mutation) to 0.75 (partially dominant mutation). The two-locus epistasis was scanned from -0.05 to -1 with a step of 0.05; positive values were not considered, since they are expected to be incompatible with selection for non-zero RRs [35]. The three-locus epistasis was scanned from -0.05 to -1 for the purifying selection, and from 0.05 to 1 for the mixed selection, with a step of 0.05 for both. It should be noted that here, epistasis is modeled as a multiplier to the purely multiplicative fitness, rather than as an addend, as used in many other studies (see Methods). Thus, epistasis in fact varies across genotypes, although it is formally described by only two parameters. Such variable epistasis is known to facilitate selection for non-zero recombination [39]. Mutations were assumed to be unidirectional, with a rate of 10^{-4} per selected locus.

For each case, we first estimated the optimal constant RR (r^*). A RR was regarded as optimal if it appeared to be favored over both lower and higher RRs. Among two arbitrary RRs, one was considered to be favored over the other if the *rec*-allele conferring this rate succeeded in the following two tests: (i) invaded a population in which the *rec*-allele for the other RR prevailed, and (ii) resisted the backward invasion when it itself prevailed (protocol details are presented in Methods). Given that competition between different RRs is strongly affected by the *rec*-locus' linkage to the selected system (reviewed in [17,41]), we examined two situations separately: with linked (0.05) and unlinked (0.5) *rec*-locus.

Optimal constant recombination rates. The proportion of cases with non-zero optimal constant RR tended to increase with higher dominance of deleterious mutations; this held for both purifying and

mixed selection (Fig. 1, top and bottom, respectively), and for both linked and unlinked *rec*-locus (Fig. 1, left and right, respectively). For both purifying and mixed selection, cases with intermediate optimal constant RR ($0 < r^* < 0.5$) were observed only with linked *rec*-locus, where their proportion was higher under lower dominance of mutations (Fig. 1, left). For mixed selection, in some cases we observed outcomes of *rec*-allele competition tests that could be tentatively referred to as 'bistability', so that both minimal (0) and maximal (0.5) RRs appeared locally advantageous; such cases were observed for both linked and unlinked *rec*-locus (Fig. 1, bottom).

Evolutionary advantage of fitness-dependent recombination. Once the optimal constant RR was estimated for each case, we traced the competition between two strategies: (i) implying that all genotypes have the same RR, equal to r^* (OC-strategy), and (ii) implying that different genotypes have different RRs, varying around r^* according to genotype fitness (FD-strategy). We tested whether the *rec*-allele for the FD-strategy can displace that for the OC-strategy, or at least coexist with it in a steady state. We considered three types of FD-strategies. In all of them, RRs vary among genotypes according to their fitness, with the highest RR assigned to the least fit genotype and vice versa. However, the range of variation in RRs can differ. One type of FD-strategy is the two-sided, or 'fringe' FD-strategy[28], implying variation in RR *below* and *above* the optimal constant RR with a certain amplitude (Δr), i.e., from $r^*-\Delta r$ to $r^*+\Delta r$ (although in a more general situation, the amplitudes for downward and upward variation can be different). The two other types of FD-strategy are one-sided FD-strategies, implying variation in RRs either *below* the optimal constant RR, i.e., from $r^*-\Delta r$ to r^* (recombination-decreasing FD-strategy), or *above* it, i.e., from r^* to $r^*+\Delta r$ (recombination-increasing FD-strategy). Hereafter, we denote fringe, recombination-decreasing and recombination-increasing FD-strategies as '±FD-strategy', '–FD-strategy' and '+FD-strategy', respectively.

First and foremost, we were interested in cases with intermediate optimal constant RR ($0 < r^* < 0.5$). As already noted, such cases were observed only with linked *rec*-locus. We tried several values for the amplitude Δr, from 0.01 to 0.1. The results presented in Fig. 2 were obtained for amplitude 0.01, but they appeared quite robust in relation to higher amplitudes (not shown). Under purifying selection, the +FD-strategy was typically favored over the corresponding OC-strategy (~94–95% of cases), while the evolutionary advantage of the ±FD-strategy was much less pronounced, albeit still sound (~42–51% of cases). Selection for the –FD-strategy was never observed. Under mixed selection, the ±FD-strategy seemed to be the most successful (~95–96% of cases); –FD-strategy and +FD-strategy were favored, respectively, in ~70–81% and ~43% of cases.

For both evolutionary scenarios, a higher dominance of mutant allele *h* tended to slightly facilitate selection for RR plasticity.

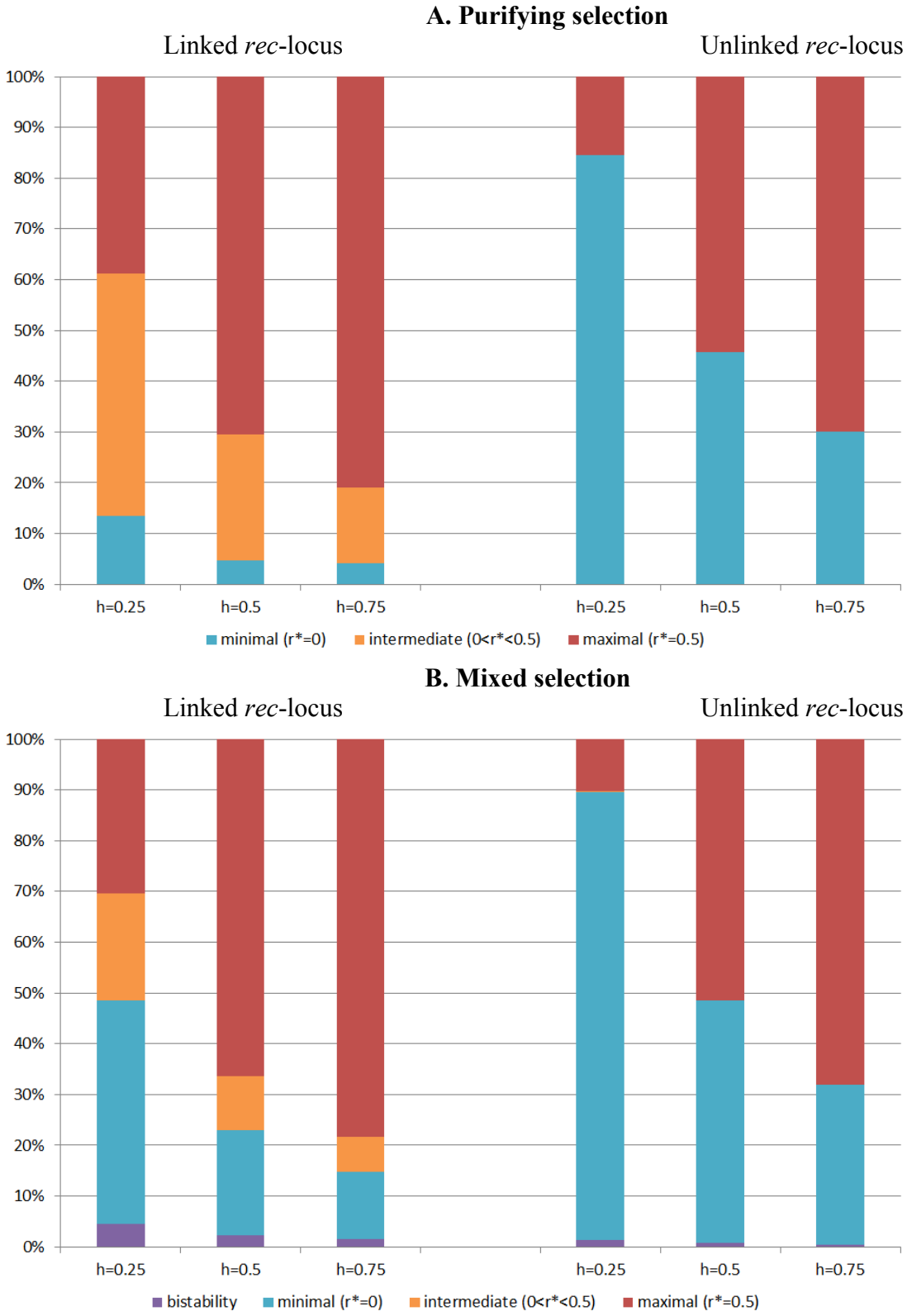

Fig. 1. Distribution of cases with respect to optimal constant recombination rate (r^*).

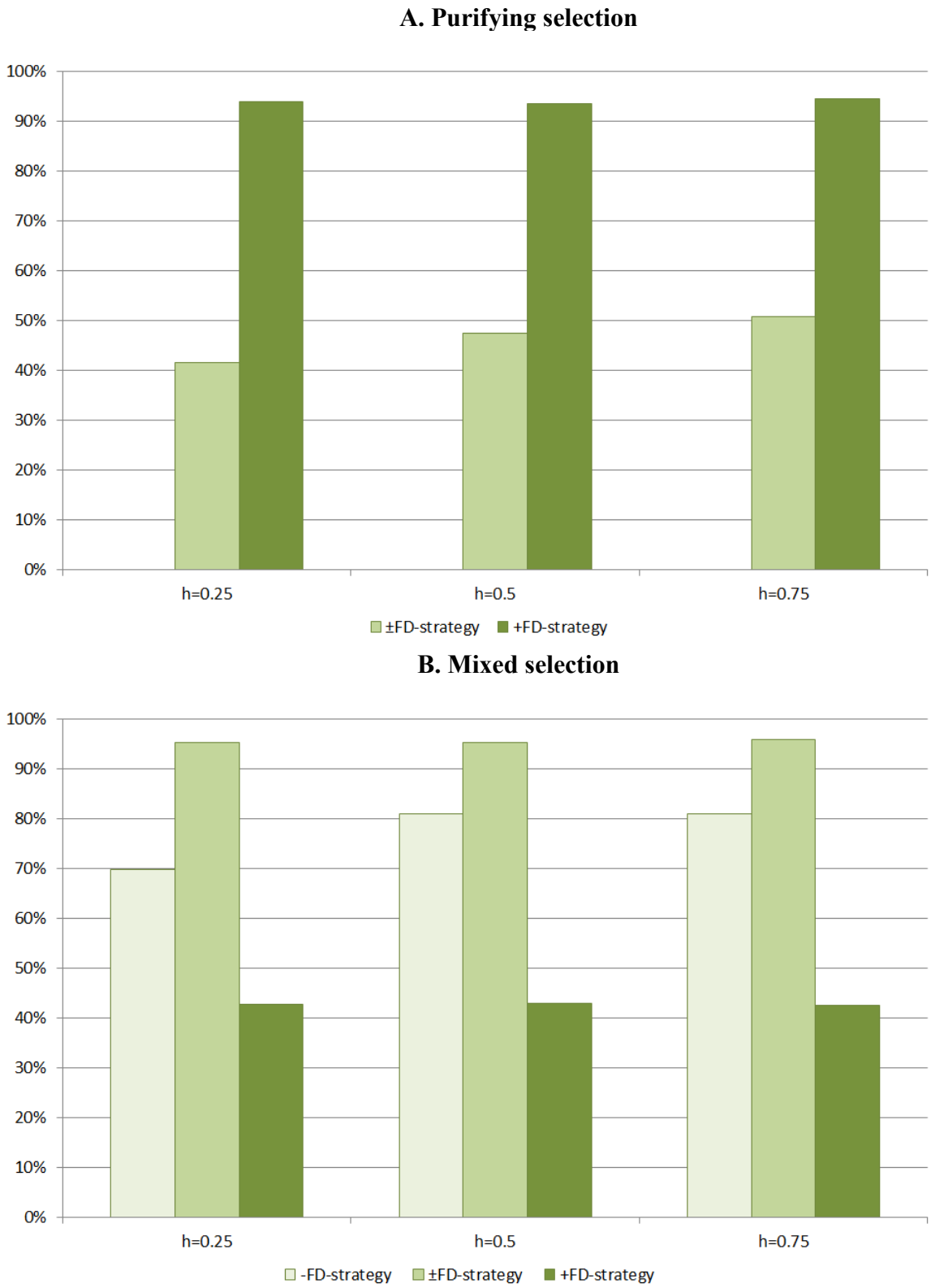

Fig. 2. Proportion of cases in which FD-strategy is favored over the corresponding OC-strategy (among cases with intermediate optimal constant recombination rates). The shown proportions represent cases with strict 'favoring', when the *rec*-allele for the FD-strategy displaces the *rec*-allele for the corresponding OC-strategy. Rare, though also existing, were cases in which the two *rec*-alleles coexist in a population, classified as 'non-favor'. Although (rare) cases with stable polymorphism at the *rec*-locus were also observed, they were considered to be a "failure" of the FD-strategy, i.e., showing its inability to displace the competitor.

The models presented herein are numerical, which does not allow strict inferences about conditions that favor or disfavor FD-strategy. Nevertheless, it is possible to discriminate parameter combinations leading to different outcomes using numerical classification, e.g., logit analysis. The most informative parameters discriminating cases with alternative outcomes were the two epistases (two-locus and three-locus) and absolute fitness of the best double heterozygote. Under purifying selection, the ±FD-strategy was typically favored over the corresponding OC-strategy when the three-locus epistasis was stronger that the two-locus one; higher fitness of the best double heterozygote tended to reduce the evolutionary advantage of RR plasticity. For the +FD-strategy, these constraints almost disappeared: cases of non-favor usually occurred only under very marginal combinations of two- and three-locus epistases, and under very high fitness of the best double heterozygote (Fig. 3).

Additionally, we considered cases with marginal optimal constant RR (either $r^* = 0$ or $r^* = 0.5$). Obviously, we cannot consider fringe FD-strategy here; however, one-sided FD-strategies remain an interesting possibility: either +FD-strategy, with RRs varying from 0 to Δr (as a competitor for the OC-strategy with $r^* = 0$), or –FD-strategy, with RRs varying from $0.5–\Delta r$ to 0.5 (as a competitor for the OC-strategy with $r^* = 0.5$). Under purifying selection, +FD-strategy was still favored in a remarkably large proportion of cases with $r^* = 0$ (~47% with linked *rec*-locus and ~30% with unlinked *rec*-locus). Under mixed selection, this happened only episodically, if at all. However, under mixed selection, –FD-strategy was not rarely favored over the corresponding OC-strategy with $r^* = 0.5$. Again, the advantage appeared more pronounced with the linked *rec*-locus (~22%) versus unlinked *rec*-locus (~15%).

When applicable, we tested for associations between different criteria used to compare recombination strategies. Specifically, we compared changes in *rec*-allele frequencies (an individual-selection criterion, central to this study) with several group-selection criteria, such as population mean fitness, genetic dispersion, and time needed to reach mutation–selection balance, i.e., adaptation time (see Methods). Typically, when ±FD-strategies appeared to be favored over the corresponding OC-strategies, they also increased population mean fitness, improving it, on average, by about $\sim 10^{-8}$ (Fig. S1a), and simultaneously decreased genetic dispersion, by $\sim 10^{-7}–10^{-6}$ (Fig. S1b). However, such clear-cut associations were not always the case. For example, when the optimal constant RR was minimal ($r^* = 0$), +FD-strategies always increased population mean fitness and always decreased genetic dispersion, regardless of whether they succeeded or failed to spread. When +FD-strategies were rejected, the increase in population mean fitness and decrease in genetic dispersion were much more pronounced (by 3–4 orders of magnitude) compared to cases in which +FD-strategies were favored. On the other hand, when the optimal constant RR was maximal

($r^* = 0.5$), –FD-strategies often increased genetic dispersion, regardless of changes in both *rec*-allele frequencies and population mean fitness, although changes in all group-selection criteria were extremely small (10^{-14}–10^{-10}). Adaptation time did not appear to be affected by evolutionary advantage/disadvantage of FD-strategies.

In situations with linked *rec*-locus, in addition to the above described ±FD-strategy, we examined another type of FD-strategy, with fitness affecting RR only between the *rec*-locus and the selected system. RRs within the selected system were set equal to the optimal constant RR for all genotypes. We found that this 'selfish' FD-strategy does not compete with the corresponding OC-strategy at all, resulting in neutral polymorphism at the *rec*-locus (i.e., no changes in frequency of the *rec*-alleles, regardless of their initial frequencies).

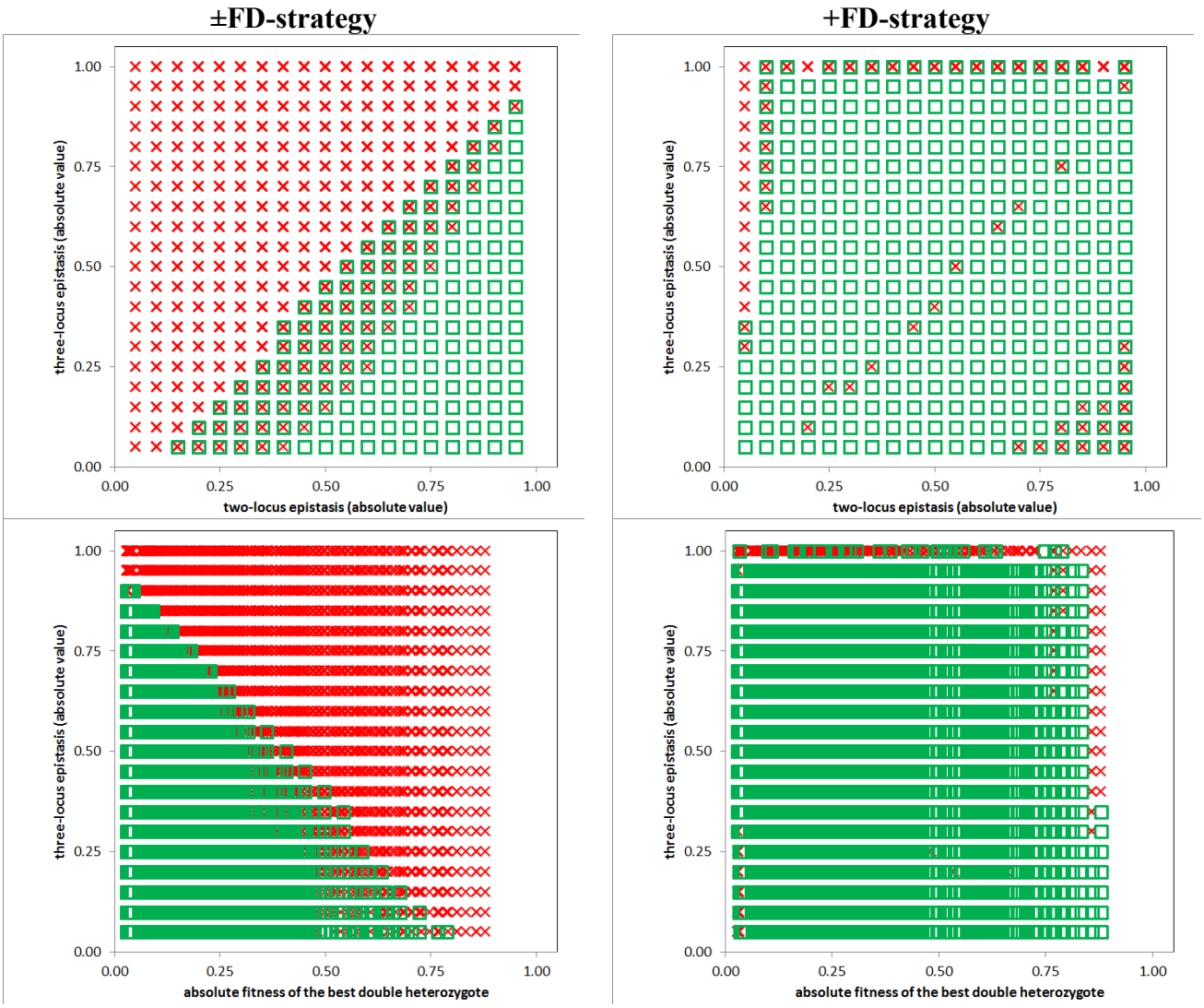

Fig. 3. Cases with different outcomes in space of different parameters. The data refers to purifying selection, cases with intermediate optimal constant recombination rate. Green squares and red crosses stand, respectively, for cases in which FD-strategy is and is not favored over the corresponding OC-strategy.

Discussion

Under both considered evolutionary scenarios, cases with non-zero optimal constant RR were quite numerous. Their proportion was higher under higher dominance of mutant alleles. In contrast, the proportion of cases with intermediate optimal constant RR was higher under lower dominance. Nevertheless, both results reflect the same pattern, discovered by Roze: mutation dominance facilitates selection for recombination [42]. Moreover, the proportion was higher when the *rec*-locus was linked to the selected system. It may be that in this case, *rec*-alleles remain associated with the selected-system haplotypes for a longer time, mitigating the constraints imposed on epistasis, as happens when a population practices less sex compared to panmixia [41].

Several experiments with diploid organisms demonstrated that variation in fitness among genotypes can affect RRs, including situations when such variation originated from different genetic background of population members caused by deleterious mutations [14,22]. Our results indicate that FD recombination can be favored in diploids under mutation–selection balance. We previously showed the same for cyclical selection[28], and for Red Queen dynamics (for preliminary results, see ref [30]). Naturally, the proportion of cases favoring FD-strategies differs for different selection regimes; nevertheless, their evolutionary advantage seems to be general, rather than associated with a certain type of selection mechanism (e.g., environmental variation, antagonistic interspecific interaction, or mutation–selection balance).

The evolutionary advantage of FD recombination can be explained by two different, albeit non-exclusive mechanisms. The first appeals to benefits from modifying RR between the *rec*-locus and the selected system (direct effect), while the second, from modifying RRs within the selected system (indirect effect). The former is commonly referred to as the 'abandon-ship' mechanism [15]. It is even sometimes viewed as the only explanation (e.g., in ref [43]), perhaps due to its self-evidence. Indeed, if a *rec*-allele is capable of somehow 'evaluating' its current genetic environment and tends to recombine from the low-fitness chromosome, it will apparently increase its chances of surviving and spreading. Such 'selfish' *rec*-alleles have been shown to be favored, even if they do not affect RRs within the selected system at all, and moreover, even if the selected system consists of only a single locus [15,25]. However, the 'abandon-ship' mechanism can be efficient only in haploids. In diploids, *rec*-alleles cannot 'recognize' which of the two homologous chromosomes causes lower fitness, unless a cis/trans effect (a rather specific phenomenon) is assumed. Thus, *rec*-alleles make 'right' and 'wrong' decisions with equal probabilities and, therefore, with no effect on their own frequencies in the next generation. The inefficiency of the 'abandon-ship' mechanism in diploids was shown analytically under directional selection [15], and numerically under cyclical selection[28]. The results obtained herein confirm that the 'abandon-ship' mechanism is also inefficient in diploids

under mutation–selection balance: the 'selfish' FD-strategy (i.e., with effect of fitness only on RR between the *rec*-locus and the selected system, with no effect on RRs within the selected system) did not compete with the corresponding OC-strategy at all.

Thus, whenever our numerical experiments revealed the evolutionary advantage of a FD-strategy, this advantage originated from benefits being conferred on the selected system. Such benefits come from RR plasticity. Indeed, recombination is inherently evolutionarily ambiguous: it creates new haplotypes, but it also breaks apart existing, including the most successful, ones. FD-strategy, which by definition tends to protect more fit genotypes while generating novelties utilizing less fit genotypes, allows discriminating between these two opposite effects. However, the advantage of FD-strategy over the corresponding OC-strategies is not absolute. This is because practicing a FD-strategy can move the population's mean RR to a new value, which is *a priori* worse than that under the OC-strategy. Thus, there emerges a kind of tradeoff between the positive effect caused by RR plasticity, and the negative effect caused by deviation from the optimal RR. Therefore, the evolutionary advantage/disadvantage of a FD-strategy seems to depend on which of the two effects appears stronger. This is elucidated by comparing the evolutionary advantage of different FD-strategies under purifying selection. Under this mode of selection, most of the population is represented by the wild-type genotype, while mutant genotypes exist at extremely low frequencies (in our numerical experiments, mutant allele frequencies never exceeded 0.2%). Thus, ±FD-strategy, which by definition decreases RRs in more fit genotypes and increases RRs in less fit ones, inevitably moves the population's mean RR strongly downward. This shift appears to be critical, resulting in a relatively modest (~42–51%) proportion of cases favoring the ±FD-strategy. Mitigating the 'punishment' imposed upon more fit genotypes immediately improved the picture. Indeed, in the marginal situation, when FD recombination was presented in the form of +FD-strategy (which does not affect the predominant fitter genotypes at all and only increases RRs in less fit ones), its success became much more pronounced (in ~94–95% of cases). In contrast, under mixed selection, the evolutionary advantage of the ±FD-strategy was observed in a larger proportion of cases compared to each of the one-sided FD-strategies. Our intuitive speculation is that the oppositely directed two- and three-locus epistases assumed in the mixed-selection model complicate 'interrelations' between recombination-responsive genotypes.

An interesting additional manifestation of the evolutionary advantage of RR plasticity can be obtained by comparing +FD-strategies with different amplitudes. Apparently, as the amplitude grows, population's mean RR stronger deviates from the optimal RR. Theoretically, this can make larger-amplitude +FD-strategies less advantageous. However, in all our simulations, large-amplitude +FD-strategies were still favored over the corresponding OC-strategy. This indicates that the

negative effect of large amplitude, caused by deviation from the optimal RR, was always compensated by its positive effect, caused by higher RR plasticity. Yet, in some cases, larger-amplitude +FD-strategies indeed demonstrated a tendency towards a decline in invasion speed (Fig. S2).

The results presented herein confirm that FD recombination can be evolutionarily advantageous in diploids under mutation–selection balance. Together with previously obtained results, which confirmed the same for diploids exposed to other selection regimes (cyclical abiotic selection and Red Queen dynamics), this indicates that selection regime is not a crucial precondition for the advantage of FD recombination. Importantly, in all of these situations, the advantage of FD recombination was associated with the *rec*-modifier's indirect effect, i.e., with benefits conferred by the modifier to the selected system, since the 'abandon-ship' mechanism (direct effect) is inefficient in diploids. In haploids, the latter is efficient. Yet, even there, the indirect effect alone can drive the evolution of FD recombination, as was clearly demonstrated in models with an unlined *rec*-locus [25]. All this allows us to suggest that benefits for the selected system can be considered as a more universal mechanism compared to the 'abandon-ship' one. However, it is likely that FD recombination first appeared in haploids. There, it could indeed have been invented by some 'selfish' genes, which spread by exploiting the 'abandon-ship' benefits. Later, such genes probably expanded this feature to other genome regions, becoming recombination-modifying genes *per se*. Once this happened, FD recombination stopped being entirely dependent on the 'abandon-ship' benefits, and could also evolve in diploids, where 'abandon-ship' mechanisms do not work [24,41].

Remarkably, +FD-strategy appeared to be favored over the corresponding OC-strategy in a considerable proportion of cases with zero optimal constant RR. In other words, non-zero RRs can be favored even where recombination seems to be evolutionarily unfavorable; the 'recipe' is to allow recombination to occur only in less fit genotypes. Thus, FD-strategy can serve as an evolutionary rescue mechanism for recombination *per se*. This amazing property of FD recombination was first demonstrated by Gessler & Xu [24] in their pioneering study with haploids, and then extended to diploids (under cyclical selection) [28]. Moreover, the same pattern was also shown for the rate of sex, which has long been known to exhibit fitness dependence (for recent review, see [44]). Under Red Queen dynamics, FD sex seemed to be often favored in cases where any positive constant rate of sex was rejected [45]. Again, we explored +FD-strategies with different amplitude of RR plasticity, up to maximal possible amplitude ($\Delta r = 0.5$). Typically, when +FD-strategies were favored over the corresponding OC-strategy with $r^* = 0$, this happened under all values of amplitude, suggesting that the positive effect of large amplitude (i.e., higher RR plasticity) appears stronger that its negative effect (i.e., higher deviation from the optimal RR). However, we found several remarkable cases in

which large-amplitude +FD-strategies were less successful (compared to the OC-strategy) than small-amplitude +FD-strategies. This gave rise to a natural question of whether there exists an *optimal amplitude* of RR plasticity. To address it, we let +FD-strategies with different amplitudes compete one with another. We found that *rec*-allele for a certain intermediate amplitude of RR plasticity displaces *rec*-alleles for both smaller and larger amplitudes (Fig. S3). This further confirms that the evolutionary advantage of FD recombination is a trade-off between mean RR and RR plasticity.

Methods

Life cycle. We consider an infinite population of obligate sexual diploids with total panmixia. The life cycle includes random mating, selection at the diploid level, and meiosis resulting in gametes of the next generation. The generations do not overlap. Let x_{ij} be a diploid genotype made up of haplotypes i and j. Its frequency p^s after selection (as adult) can be calculated based on its frequency p before selection (as zygote) and its absolute fitness W:

$$p^s(x_{ij}) = \frac{p(x_{ij}) \cdot W(x_{ij})}{\sum_{ij} p(x_{ij}) \cdot W(x_{ij})} \tag{1}$$

Then let g_k be gamete of haplotype k. Its frequency p in the gamete pool can be calculated based on frequencies of adults and probabilities of recombination events:

$$p(g_k) = \sum_{ij} p^s(x_{ij}) \cdot P^r_{ij \to k}\ , \tag{2}$$

where $P^r_{ij \to k}$ is the probability of obtaining gamete g_k from genotype x_{ij} via recombination[37].

Frequency p^m of a given gamete after mutation can be calculated based on probabilities of mutation events:

$$p^m(g_k) = \sum_{l} p(g_l) \cdot P^m_{l \to k}\ , \tag{3}$$

where $P^m_{l \to k}$ is the probability of obtaining gamete g_k from gamete g_l via mutations.

Finally, frequencies of zygotes in the next generation can be calculated based on frequencies of the corresponding gametes, given the random mating:

$$p_{t+}(x_{ij}) = p^m_t(g_i) \cdot p^m_t(g_j) \tag{4}$$

Selected system. Each genotype has $n = 3$ linked selected loci, each with two possible alleles, wild-type (A_n) and mutant (a_n). The locus-associated component of fitness (W_n) depends on the number of mutant alleles at this locus:

$$W_n = \begin{cases} 1, & \text{for} \quad A_n A_n \\ 1 - hs, & \text{for} \quad A_n a_n \\ 1 - s, & \text{for} \quad a_n a_n \end{cases} \tag{5}$$

Here, s and h represent the deleterious effect of mutations in the homozygous state and the dominance of mutations, respectively.

The whole-genotype fitness (W) deviates from a purely multiplicative one, due to interlocus epistasis (ε):

$$W = \prod_n W_n \cdot (1 + \varepsilon) \tag{6}$$

The effect of epistasis is defined by the number of mutant loci (a locus is regarded as 'mutant' if it bears at least one mutant allele):

$$\varepsilon(n_M) = \begin{cases} 1, & \text{for} \quad n_M \le 1 \\ \varepsilon_2, & \text{for} \quad n_M = 2 \\ \varepsilon_3, & \text{for} \quad n_M = 3 \end{cases} \tag{7}$$

Here, ε_2 and ε_3 represent two-locus epistasis and three-locus epistasis, respectively.

Recombination strategies. RRs between the selected loci are assumed to be defined by genotype at a separate, selectively neutral *modifier* locus (*rec*-locus). The modifier locus can be either linked or unlinked to the selected system. For simplicity, RRs between two pairs of adjacent selected loci are assumed to be equal. No crossover interference is assumed. We consider two types of recombination strategy: (i) constant recombination, implying equal RRs for all genotypes (C-strategy), and (ii) FD recombination, implying varying RRs among genotypes according to their fitness (FD-strategy). Under the FD-strategy, RR (r) negatively depends on genotype absolute fitness (W). Specifically, the genotype with the highest fitness ($W_{\max}$) has the lowest recombination rate ($r_{\min}$) and vice versa. For genotypes with intermediate fitness values, RR is obtained by linear interpolation:

$$r(W) = \begin{cases} r_{\min}, & \text{for} \quad W = W_{\max} \\ r_{\min} + (r_{\max} - r_{\min}) \cdot \dfrac{W_{\max} - W}{W_{\max} - W_{\min}}, & \text{for} \quad W_{\min} < W < W_{\max} \\ r_{\max}, & \text{for} \quad W = W_{\min} \end{cases} \tag{8}$$

Importantly, when estimating the lowest and highest fitness values, we took into account only those genotypes where recombination has an effect, i.e., only double and triple heterozygotes

('recombination-responsive genotypes'). The relations between alleles at the *rec*-locus are assumed to be purely co-dominant.

Criteria for comparison of recombination strategies. First and foremost, we compared alternative recombination strategies in terms of *individual selection*, based on frequencies of alleles at the modifier *rec*-locus[31,32]. Specifically, strategy S_1 is regarded as evolutionarily more advantageous than strategy S_2 if the *rec*-allele for S_1 succeeds in the two following tests. First, it should invade populations in which the *rec*-allele for S_2 prevails. Second, it should resist, when it itself prevails, backward invasion by the *rec*-allele for S_2. In our tests, 'prevailing' means an allele frequency 0.95. In both tests, *rec*-alleles are allowed to compete for 10,000 generations. Before the competition starts, the selected system is allowed to evolve with a monomorphic *rec*-locus, until it reaches mutation–selection balance. The latter is diagnosed when allele frequencies at each selected locus change by less than 10^{-12} per generation.

Besides *rec*-allele dynamics, we also used additional criteria to compare recombination strategies, appealing to *group selection*; they include the population's mean fitness, genetic dispersion, and adaptation time. Mean population fitness was calculated as fitness of all genotypes weighted by their frequencies. Genetic dispersion V was calculated as mean standard deviation of allele frequencies within the selected system:

$$V = \frac{1}{n}\sum_i \sqrt{p_i(1-p_i)}, \qquad (9)$$

where p_i is allele frequency at the i-th selected locus, and n is number of selected loci.

Adaptation time was considered as the number of generations needed for the selected system to reach mutation–selection balance.

Statistical analysis. Statistical analysis was performed in Statistica V 10.0 (Dell Software, Round Rock, USA).

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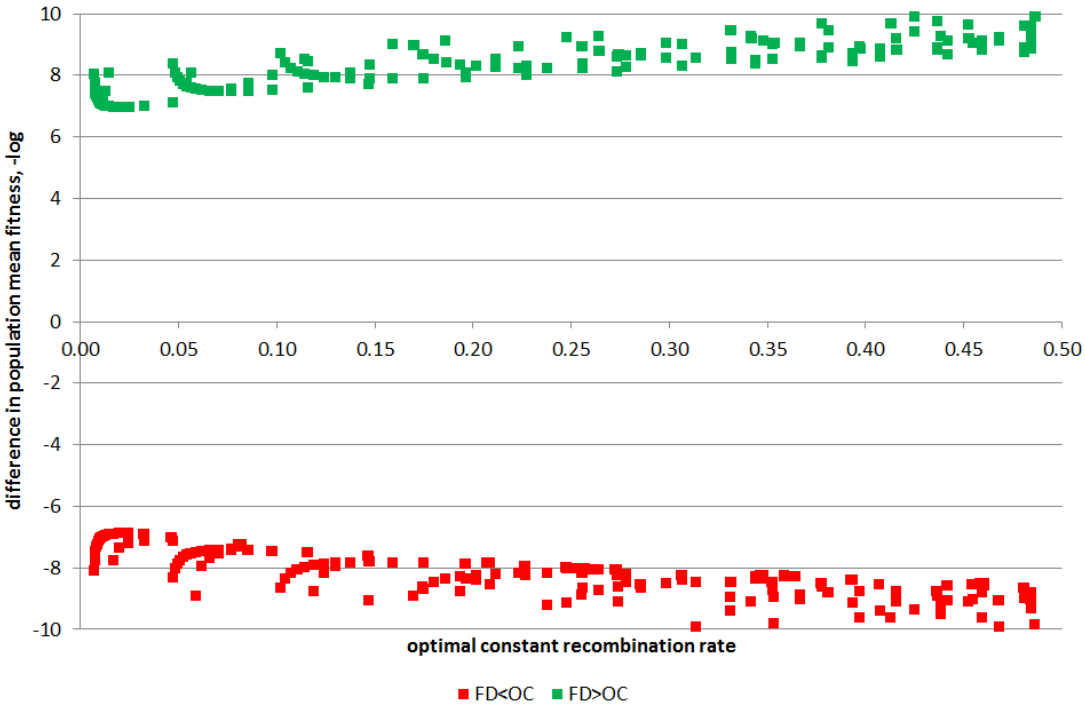
Supplementary materials

A. Difference in terms of population mean fitness



B. Difference in terms of population genetic dispersion

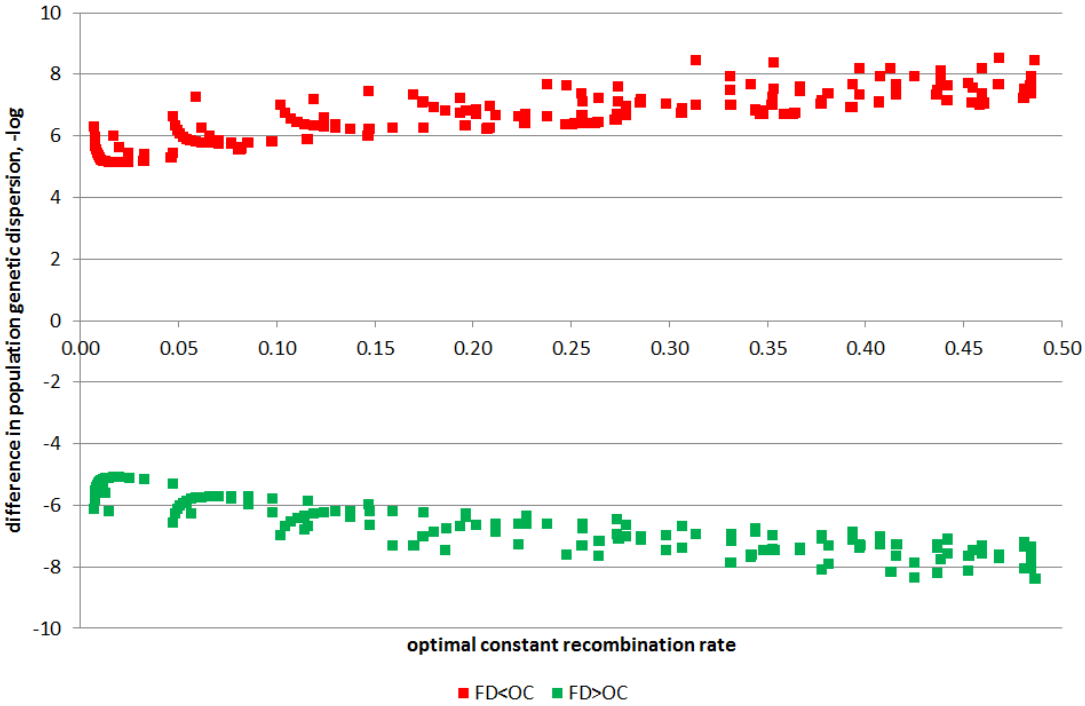


Fig. S1. Changes in population mean fitness (a) and population genetic dispersion (b) in cases with the opposite outcomes (favor/non-favor of FD recombination). Values on the ordinate axes represent –log of absolute difference when this difference is positive, and log of absolute difference when this difference is negative. The data refer to purifying selection, cases with intermediate optimal constant RR, and ±FD-strategy.

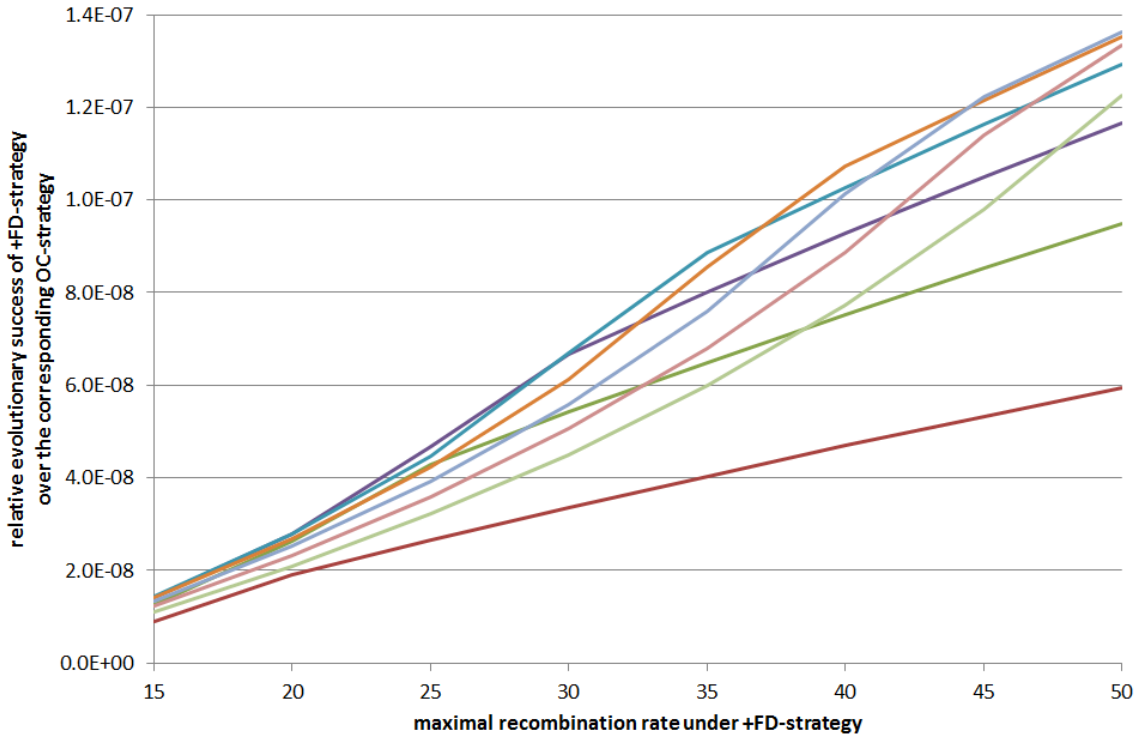


Fig. S2. Effect of amplitude of RR plasticity on the evolutionary advantage of +FD-strategies (purifying selection, cases with intermediate optimal constant RR). The ordinate axis represents relative evolutionary advantage of a given +FD-strategy over the corresponding OC-strategy (the advantage is expressed as the difference between speed of direct invasion and speed of backward invasion, per 10,000 generations. The colored curves refer to several arbitrary chosen cases. Note that in some cases the curves show a non-smooth pattern of increase in the evolutionary advantage of +FD-strategy displayed as a clear-cut local switch (decrease) of the derivative.

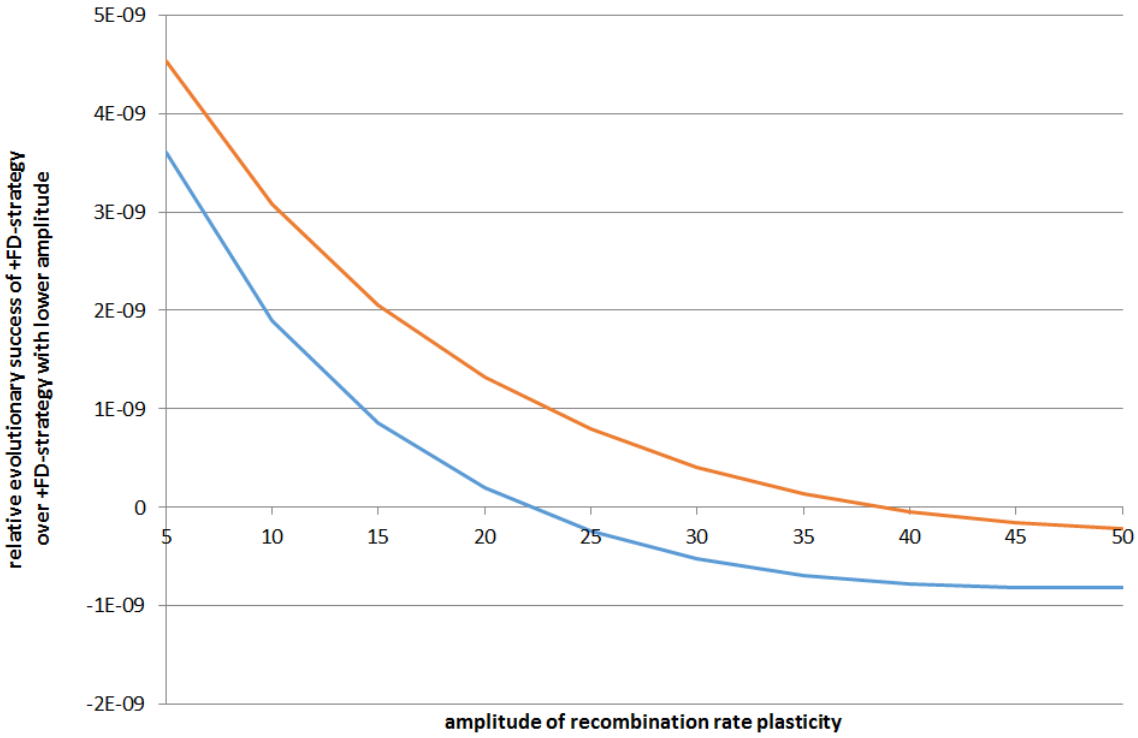


Fig. S3. Results of competition between +FD-strategies with different amplitudes of RR plasticity (purifying selection, cases with zero optimal constant RR). The ordinate axis represents relative evolutionary advantage of +FD-strategy with a given amplitude over +FD-strategy with one-step (0.05) smaller amplitude (the advantage is expressed as the difference between speed of direct invasion and speed of backward invasion, per 10,000 generations). Note that below certain value of amplitude, the advantage is positive (i.e., +FD-strategy with a given amplitude is *better* than +FD-strategy with a smaller amplitude), whereas above such value the advantage becomes negative (i.e., +FD-strategy with a given amplitude is *worse* than +FD-strategy with a smaller amplitude). This critical value of amplitude (~0.22 and ~0.38 for cases depicted by the blue and the orange curves, respectively) corresponds to the *optimal* amplitude of RR plasticity.