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Research article

What drives the evolution of condition-dependent recombination in diploids? Some insights from simulation modelling

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Abstract. While the evolutionary advantages of non-zero recombination rates have prompted diverse theoretical explanations, the evolution of essential recombination features remains underexplored. We focused on one such feature, the condition dependence of recombination, viewed as the variation in within-generation sensitivity of recombination to external (environment) and/or internal (genotype) conditions. Limited empirical evidence for its existence comes mainly from diploids, whereas theoretical models show that it only easily evolves in haploids. The evolution of condition-dependent recombination can be explained by its advantage for the selected system (indirect effect), or by benefits to modifier alleles, ensuring this strategy regardless of effects on the selected system (direct effect). We considered infinite panmictic populations of diploids exposed to a cyclical two-state environment. Each organism had three selected loci. Examining allele dynamics at a fourth, selectively neutral recombination modifier locus, we frequently observed that a modifier allele conferring condition-dependent recombination between the selected loci displaced the allele conferring the optimal constant recombination rate. Our simulations also confirm the results of theoretical studies showing that condition-dependent recombination cannot evolve in diploids on the basis of direct fitness-dependent effects alone. Therefore, the evolution of condition-dependent recombination in diploids can be driven by indirect effects alone, i.e., by modifier effects on the selected system.

Keywords: recombination, condition dependence, diploid selection, fluctuating selection

1. Introduction

(a) Condition-dependent recombination: evidence and concepts

Recombination has long been known to vary substantially, both within and between generations, often with far-reaching micro- and macro-evolutionary consequences [1–6]. Although recombination is a complex phenomenon, the theory developed to date has focused mainly on the evolution of recombination rate (RR), namely on when and why non-zero RR is favoured. Indeed, given that recombination breaks apart existing haplotypes, including the most successful ones, its omnipresence in nature is intriguing (and recognised as a central evolutionary question) [7–9]. The suggested answers are well known (see for review [10–13]), and the matter seems to be more or less settled [14], although the extent to which the theory's assumptions hold in nature is still unclear [15]. However, recombination is obviously more than just a binary variable with "exists" and "does not exist" values. It displays certain essential features, such as crossover interference, sex dimorphism, dependence on environment and genotype, among others. The existence of recombination features is therefore also an evolutionary question, relatively new and certainly no less interesting. Raised in a series of original studies from the 1980s to 2000s [16–18], it still remains underexplored.

The present study focuses on one such feature, condition dependence of recombination. In general, this can be defined as variation in within-generation sensitivity of recombination to external (environment) and/or internal (genotype) conditions. A century ago, rearing fruit flies under different temperatures, Harold Plough demonstrated that RR, exactly like many other traits, varies between environments for *the same genotype*; in other words, recombination displays reaction-norm plasticity [19]. Specifically, by plotting RR against temperature, he obtained a clear-cut U-shaped curve, with the highest rates of recombination at very low and very high temperatures. Similar curves (or at least their parts) have been reported for many organisms and for different ecological factors (for recent reviews, see [20,21]). Usually, such U-shaped curves oppose bell-shaped curves for organisms' responses to ecological factors. This suggests that ecological factors affect recombination via the stress that they cause in an organism. Recently, this was tested directly by Jackson et al. [22]; their results inferred that RR is negatively associated with fitness. Importantly, they interpreted "fitness" *physiologically*, as a measure of an individual's being non-stressed in its "here-and-now" environment.

However, it seems no less interesting to interpret fitness *evolutionarily*, by considering a *set of genotypes* with respect to their differential success in passing alleles to subsequent generations. The first reviews on recombination plasticity in relation to ecological factors already noted that the reaction-norm curves differ between genotypes [23,24]. In 1986, Zhuchenko et al. [25] first

compared chiasma–temperature curves for tomato cultivars with different temperature preferences. Heat-resistant genotypes displayed less pronounced increases in RR when exposed to heat compared to cold-resistant ones, and vice versa, whereas their F_1 hybrids, being relatively tolerant to both cold and heat, showed no changes across the temperature range. Stress-induced changes in recombination have been shown, more or less convincingly, to be modulated by the genotype's stress tolerance in experiments with fruit flies exposed to alcohol intoxication [26], heat shock [1,27] and oxidative stress [28], and with wheat exposed to heat [29]. Although such between-genotype experiments remain extremely limited, their results suggest that RR plasticity is negatively correlated with genotype fitness.

Thus, the essence of the renowned "negative recombination–fitness association" strongly depends on whether fitness is considered physiologically or evolutionarily. The former implies that worse conditions lead to higher RR within the same genotype, whereas the latter implies that genotypes with lower fitness possess higher RR plasticity in relation to stressful environments. Unfortunately, this conceptual difference is often overlooked.

Finally, revelation of the evolutionary interplay between recombination and fitness does not necessarily need to consider a stressful environment, which naturally creates variation in fitness between genotypes according to their stress tolerance. Instead, the required variation in fitness may result from diversity of genetic backgrounds. In 1981, Tucić et al. [30] explored a panel of natural *Drosophila* lines differing in chromosome 2 and, consequently, in fitness components (viability, male fertility and female fecundity). The authors' initial hypothesis was that this variation in fitness would be positively associated with a variation in RR in the same chromosome, which could give an easy answer to the pressing question of why recombination exists. Surprisingly for themselves, they revealed a significant negative recombination–fecundity correlation. A quite strong negative correlation was also reported by Tedman-Aucoin and Agrawal [31], who used mutant lines with *a priori* known deleterious effects on fitness; however, the statistical significance of the revealed correlation was marginal.

Generalizing the studies of the two types of fitness variation, caused by either different stress tolerance or different genetic background, suggests that RRs are affected by stress *sensu lato*, both environmental [32,33] and genomic [34]. Furthermore, stress effects on recombination are likely to be modulated by both traditional Darwinian "fitting the environment" [35] and environment-free "fitting the organism's construction" [36].

(b) Condition-dependent recombination as an evolutionarily advantageous strategy

The question of whether recombination variation is adaptive has long been discussed [1,37]. As biophysical, biochemical, and physiological processes in meiosis become more transparent, condition dependence of recombination can be considered mechanistically, as an interplay between internal recombination-regulation pathways and external inputs (for recent reviews, see [21,38,39]). Stress can likely epigenetically mediate the level and spectrum of genetic variation in consecutive generations as well [1,40,41]. Obviously, this can be an additional argument for considering condition-dependent recombination as an evolutionarily advantageous strategy. Indeed, fitness-affecting processes such as recombination are not only *a factor for* but also *subject to* evolution [42]; nevertheless, explicit tests are required, via both experimentation and theoretical modelling.

Several theoretical studies, with diverse model assumptions, have shown that condition-dependent recombination can indeed evolve [16,43–46]. The evolutionary advantage of such a strategy is more apparent in models with haploid selection [43–46]; the results for diploid selection have been more modest [16,46], although empirical evidence for the existence of condition-dependent recombination comes mainly from diploids. Moreover, these results are not unequivocal. In numerical experiments by Zhuchenko et al. [16], ecological plasticity of recombination evolved markedly in a changing environment. In the mathematical model of directional selection analysed by Agrawal et al. [46], fitness-dependent recombination did not evolve readily and was due to incidental changes in mean RR rather than RR plasticity *per se*, unless cis–trans or maternal effects were additionally assumed. All of these discrepancies (between empirical evidence and theoretical models, haploid and diploid selection, different types of condition dependence and different selection regimes) prevent us from regarding the evolution of condition-dependent recombination as a solved question.

Regardless of ploidy, the evolution of condition-dependent recombination, considered through the dynamics of selectively neutral recombination modifier alleles (*rec*-alleles), can be explained in two mutually non-exclusive ways. First, the *rec*-allele that confers condition-dependent recombination *between the* rec-*locus and the selected system* may spread in the population, regardless of its effects on recombination within the selected system (referred to as the "abandon-ship" mechanism) [44,46]. Second, the *rec*-allele that confers condition-dependent recombination *within the selected system* may spread in the population as a result of association with the more favourable allele combinations that it creates [16,45,46]. Following these previous studies, we hereafter refer to these two effects of a *rec*-allele as "direct" and "indirect" [46]. Surprisingly, condition-dependent recombination is often thought to evolve only due to the "abandon-ship"

mechanism (see, e.g. [47,48]). However, it has also been shown to evolve in situations where the "abandon-ship" mechanism is expected to be inefficient, e.g., when the *rec*-locus is not linked to the selected system [44]. These findings indicate that the evolution of condition-dependent recombination may be driven, at least in some situations, by the indirect effect.

Here, we use simulation modelling to test whether condition-dependent recombination can be evolutionarily advantageous in diploids and if so, what drives this evolution. We consider genetic systems with three selected loci exposed to cyclical two-state environments. Unlike directional selection, or selection with a steadily moving optimum [49], cyclical selection does not favour a single RR all the time: along the cycle, the fitness effect of recombination changes from beneficial (when linkage disequilibria are negative) through neutral to deleterious (when linkage disequilibria become positive). As a result, a trade-off constant RR appears to be optimal, but it is natural to hypothesise that non-constant, condition-dependent recombination will be more favourable. Our setup with three selected loci and a two-state environment allows testing for the evolutionary advantage of both types of condition dependence: environment dependence, with RRs varying across environmental states (as in [16]), and fitness dependence, with RRs varying across genotypes (as in [43–46]). RRs depend on the conditions of the diploids in which meiosis occurs. We consider a modifier that affects RR but not the rate of sex (reproduction is assumed to be totally sexual). We do not use assumptions that might narrow the biological generality of the model, such as specific fitness matrices (as in [16]) or cis–trans or maternal effects (as in [46]). We found abundant situations in which condition-dependent recombination (both environment- and fitness-dependent) appeared more favourable than optimal constant RR, and emphasise that the revealed evolutionary advantage occurred under diploid selection due to the modifier effects on the selected system, rather than via its effects on its own linkage to the selected system.

In Box 1, we list and define the important abbreviations used in this paper.

Box 1. Abbreviations

"Direct" CD-strategy	Strategy with condition-dependent recombination rate between the *rec*-locus and the adjacent selected locus
"Indirect" CD-strategy	Strategy with condition-dependent recombination rates between the selected loci
"Universal" CD-strategy	Strategy with condition-dependent recombination rates between all pairs of adjacent loci
CD-strategy	Strategy with condition-dependent recombination rate
C-strategy	Strategy with a constant recombination rate
DOM-system	Selected system with non-zero dominance effect

ED-strategy	Strategy with environment-dependent recombination rate
FD-strategy	Strategy with fitness-dependent recombination rate
NEQ-system	Selected system with non-equal additive effects
OC-strategy	Strategy with the optimal constant recombination rate
RR	Recombination rate

2. Models and methods

(a) Life cycle

We consider an infinite population of obligate sexual diploids, with total panmixia and non-overlapping generations. The life cycle consists of fertilisation, maturation (during which selection acts), meiosis (during which recombination occurs), and random mating. Let $p(g_k)$ be the frequency of gamete with haplotype k. Let also $p(x_{ij})$ and $p'(x_{ij})$ be, respectively, the frequencies of an organism with genotype ij before selection (zygotes) and after selection (adults), and $w(x_{ij})$ its absolute fitness. Then, the adult frequencies can be obtained from the zygote frequencies as:

$$p'(x_{ij}) = \frac{p(x_{ij}) \cdot w(x_{ij})}{\sum_{ij} p(x_{ij}) \cdot w(x_{ij})} \quad (1)$$

Here, the denominator is population mean fitness in the given generation. Gamete frequencies in the pool of gametes produced by adults are:

$$p(g_k) = \sum_{ij} p'(x_{ij}) \cdot P_{ij \to k}, \quad (2)$$

where $P_{ij \to k}$ is the probability of obtaining gamete g_k from genotype x_{ij} (see, e.g., [14]). These gamete frequencies define zygote frequencies in the next generation:

$$p^{t+1}(x_{ij}) = p^t(g_i) \cdot p^t(g_j) \quad (3)$$

(b) Selected systems

We consider models with three linked bi-allelic selected loci, in order to provide variation in fitness among "recombination-responsive" genotypes (i.e., heterozygous for at least two selected loci). With only two loci, there exists only one "recombination-responsive" genotype ($A_1a_1A_2a_2$). Thus, variation in fitness would be possible only if a cis–trans effect is assumed (i.e., if coupling-phase variant A_1A_2/a_1a_2 and repulsion-phase variant A_1a_2/a_1A_2 of this genotype differ in fitness), an assumption which seems to be too specific (but see, e.g., [50]). The locus effect q_l includes two components: additive effect d_l and dominance effect h_l:

$$q_l = \begin{cases} 0, & a_l a_l \\ d_l + h_l, & A_l a_l \\ 2d_l, & A_l A_l \end{cases} \quad (4)$$

We conduct all simulations using two different selected systems: (i) with non-equal additive effects and zero dominance effects, $d_1 \neq d_2 \neq d_3$ and $h_1 = h_2 = h_3 = 0$ (NEQ-system), and (ii) with equal additive and non-zero dominance effects, $d_1 = d_2 = d_3$ and $h_1 = h_2 = h_3 \neq 0$ (DOM-system). Selected systems of these two types are known to be potentially compatible with polymorphism maintenance [51,52]. The three selected loci additively contribute to a quantitative fitness-related trait Q: $Q = \sum_l q_l$. Obviously, additive effects on the trait do not mean additive effects on fitness.

(c) Selection regimes

We consider cyclically fluctuating selection, which is known to favour a non-zero RR [53–56]. The environment has two states; in both of them, selection is directional but acts in opposite directions. Absolute fitness is maximal under an optimal trait value Q^*, set equal to either minimal or maximal trait values (among the genotypes simulated according to equation 4), and gradually decreases as far as trait values deviate from it. Following Kimura and Crow [57], we model such fitness functions by an S-shaped curve. To further support polymorphism maintenance in the selected system, we assume multiplicative heterozygote advantage η (equal for all selected loci and all environmental states):

$$w(x_{ij}) = \exp\left\{-\frac{[Q(x_{ij}) - Q^*]^2}{2\sigma^2}\right\} \cdot \frac{\prod_l (1 + \eta \cdot \mathbf{1}\{A_l a_l\})}{\prod_l (1+\eta)} \quad (5)$$

The environmental states differ in duration and selection intensity: the state with shorter duration and higher selection intensity is referred to as stressful (e_s), the other as benign (e_b). Alternative selection regimes are therefore described by duration of benign and stressful states (τ_b and τ_s) and by selection intensity in these states (σ_b and σ_s).

(d) Recombination strategies

RR within the selected system is controlled by a selectively neutral modifier locus (*rec*-locus), either linked or unlinked to the selected system. For simplicity, RRs (r) in the two adjacent intervals within the selected system are equal. If not specified, *rec*-alleles are purely co-dominant. We consider two types of recombination strategies: with a constant RR (C-strategies), and with condition-dependent RR (CD-strategies). Under CD-strategies, RRs vary around a certain reference value r_0 with an amplitude Δr (such CD-strategies are referred to as "fringe" in relation to the C-strategy with RR r_0).

Further, we distinguish between two subtypes of CD-strategies: with fitness-dependent RR (FD-strategies) and with environment-dependent RR (ED-strategies). In these two cases, RR is determined by genotype fitness (w) and by environment (e), respectively. Thus, FD-strategies imply genotype-specific variation in RR according to genotype fitness, whereas under ED-strategies, RRs vary equally between environments for all genotypes. The consistent pattern is that "poor" conditions (either low fitness or stressful environment) increase RR, whereas "good" ones (either high fitness or benign environment) decrease it:

$$r(w)=\begin{cases} r_0+\Delta r, & w=w_{\min} \\ r_0+\Delta r\cdot\left(1-2\dfrac{w-w_{\min}}{w_{\max}-w_{\min}}\right), & w_{\min}<w<w_{\max} \\ r_0-\Delta r, & w=w_{\max} \end{cases} \quad (6a)$$

$$r(e)=\begin{cases} r_0+\Delta r, & e=e_s \\ r_0-\Delta r, & e=e_b \end{cases} \quad (6b)$$

Here, $w_{\min}$ and $w_{\max}$ stand, respectively, for minimal and maximal fitness among "recombination-responsive" genotypes, i.e., genotypes that are heterozygous for at least two selected loci in the concurrent generation. In addition to the above described "fringe" CD-strategies, we also consider CD-strategies which either increase RR compared to the reference level ($r\in[r_0;\ r_0+\Delta r]$), or decrease it ($r\in[r_0-\Delta r;\ r_0]$), in line with Agrawal et al. [46]. Such "one-sided" CD-strategies are used for more accurate analysis of the results obtained with "fringe" CD-strategies (see "Design of numerical experiments" below).

Further, since recombination regulation includes a hierarchy of genome-, chromosome- and segment-level mechanisms, we consider situations with *rec*-locus either unlinked or linked to the selected system (r_m = 0.5 or 0.05, respectively). In cases with a linked modifier, we consider three types of CD-strategies: (i) with condition-dependent RR between the *rec*-locus and the adjacent selected locus only, i.e., no effect on the selected system ("direct" CD-strategies); (ii) with condition-dependent RR between the selected loci only ("indirect" CD-strategies); and (iii) with condition-dependent RR between all pairs of adjacent loci ("universal" CD-strategies).

(e) Design of numerical experiments

In the model with fluctuating selection, we used two different selected systems: with non-equal additive effects (NEQ-system) and with non-zero dominance effects (DOM-system). The simulated effects of the selected loci were $\{d_1 = 0.75,\ d_2 = 1.00,\ d_3 = 1.25,\ h_1 = h_2 = h_3 = 0\}$ for the NEQ-system, and $\{d_1 = d_2 = d_3 = 1.00,\ h_1 = h_2 = h_3 = 0.25\}$ for the DOM-systems. These values were

chosen so that the quantitative fitness-related trait varied for both systems within the same range. For both systems, heterozygote advantage η was set equal to 0.05 per selected locus.

For each selected system, we scanned 63,000 different selection regimes (252,000 in total), by varying duration of the benign and stressful environmental states and selection intensity. Specifically, the period length varied from 2 to 40 generations, while the selection-describing scaling parameter σ varied from 1 to 5 (corresponding to variation in population mean fitness from 0.012 to 0.855). Naturally, in studying the evolution of recombination, polymorphism must be ensured within the selected system. For multi-locus selected systems subjected to fluctuating selection, polymorphism maintenance is a self-standing problem [58,59]; it is sensitive to various factors, including RR within the selected system, and may cause complex dynamics of *rec*-alleles [60,61]. Since neither polymorphism maintenance nor its effects on the evolution of recombination are the focus of the current study, we intentionally restricted the examined selection regimes to those with "good" polymorphism. Specifically, we chose selection regimes in which the selected system reaches central-like steady-state polymorphism regardless of initial allele frequencies at the selected loci and of RRs between them (electronic supplementary material, text 1*a*). By “steady-state”, we mean that after some transition time, all selected-genotype frequencies no longer change from period to period (so-called polymorphic steady-state cycle). By “central-like”, we mean that none of the selected-allele frequencies are too marginal. Overall, we chose >17,000 and >26,000 "good" selection regimes for the NEQ- and DOM-systems, respectively.

Alternative recombination strategies (constant recombination with different RR, environment- and fitness-dependent recombination) can be compared in terms of either group or individual selection, with either population mean fitness or *rec*-modifier dynamics as criteria (for review, see [62]). Here, we compared recombination strategies within the modifier approach introduced by Nei [63], i.e., based on frequencies of selectively neutral *rec*-alleles. Specifically, we regarded one strategy as more favourable than another if the corresponding *rec*-allele displaced its opponent (electronic supplementary material, text 1*b*). For each selection regime, we first compared alternative C-strategies, in order to find the optimal one (OC-strategy). Again, the optimality here was considered within the modifier approach, i.e., the *rec*-allele conferring the OC-strategy (with RR denoted as r^*) had to displace *rec*-alleles conferring all other C-strategies (electronic supplementary material, text 1*c*). Whenever the found OC-strategy had an intermediate RR ($0 < r^* < 0.5$), it was compared to "fringe" CD-strategies ($r \in [r^* - \Delta r; r^* + \Delta r]$), with the amplitude of RR plasticity $\Delta r = 0.01$.

If a tested CD-strategy appears more favourable than the corresponding OC-strategy, it is natural to conclude that this advantage results from RR plasticity. However, if OC-strategies are estimated with an accuracy comparable to the amplitude of RR plasticity under CD-strategies (as in our case), we cannot exclude that the mean RR of the tested CD-strategy will appear closer to the genuine optimal constant RR than the estimated RR of the OC-strategy. In such situations, it is impossible to guarantee that the CD-strategy is more favourable due to RR plasticity *per se*. To draw more accurate conclusions, we additionally used the so-called *two-reference* test offered by Agrawal et al. [46]. Specifically, the found OC-strategy ($r = r^*$) was compared to two "one-sided" CD-strategies: one with *a priori* lower mean RR ($r \in [r^* - \Delta r; r^*]$), and the other with *a priori* higher mean RR ($r \in [r^*; r^* + \Delta r]$). We ascribed the advantage to RR plasticity *per se* only if both "one-sided" CD-strategies proved more favourable than the OC-strategy.

3. Results

Numerical characteristics of all examined selection regimes and their outcomes are presented in electronic supplementary material, table S2. In general, the system with non-equal additive effects (NEQ-system) and the system with non-zero dominance effects (DOM-system) behaved similarly. With an unlinked *rec*-locus, "fringe" CD-strategies were more favourable than the corresponding OC-strategies in most cases (table 1). The two-reference test by Agrawal et al. [46] showed that in a small proportion of cases (<3%), the revealed evolutionary advantage indeed resulted from incidental changes in mean RR. Nevertheless, in most cases, CD-strategies outcompeted the corresponding OC-strategies due to RR plasticity *per se*. Specifically, for the FD-strategy, this held in 91% and 96% of the cases for the NEQ- and DOM-systems, respectively. For the ED-strategy, the corresponding numbers were slightly lower, 81% and 89%. Under the linked *rec*-locus, "indirect" and "universal" FD-strategies were almost always more favourable that the corresponding OC-strategies, whereas "indirect" and "universal" ED-strategies outcompeted in a smaller, though still sound, proportion of cases, up to 48% and 87% for the NEQ- and DOM-systems, respectively. As expected, we observed no allele frequency change at the *rec*-locus when *rec*-alleles conferring "direct" CD-strategies competed with those conferring the corresponding OC-strategies.

The obtained results appeared quite robust with respect to several parameters: amplitude of RR plasticity, dominance/recessiveness relations at the *rec*-locus, and heterozygote advantage (electronic supplementary material, text S3). The latter had the most pronounced effect because changes in this parameter affected the behaviour of the whole selected system, including RRs compatible with polymorphism maintenance, and the optimal RRs. Qualitatively and quantitatively similar results were obtained for another, slightly simplified selected system, where polymorphism

was kept due to heterozygote advantage alone. Here, FD- and ED-strategies outcompeted the corresponding OC-strategies in 91% and 62% of cases, respectively.

Table 1. Outcomes of competition between strategies with condition-dependent recombination rate (CD-strategies) and strategies with the optimal constant recombination rate (OC-strategies)

Type of CD-strategies	Outcomes of competition (% of cases)			
	NEQ-system		DOM-system	
	CD>OC	CD<OC	CD>OC	CD<OC
Unlinked *rec*-locus, FD-strategy	91.03	6.62	96.42	1.75
Unlinked *rec*-locus, ED-strategy	81.20	16.88	89.57	7.84
Linked *rec*-locus, "direct" FD-strategy	no allele frequency change at *rec*-locus			
Linked *rec*-locus, "indirect" FD-strategy	99.55	0.45	100.00	0.00
Linked *rec*-locus, "universal" FD-strategy	99.66	0.34	100.00	0.00
Linked *rec*-locus, "direct" ED-strategy	no allele frequency change at *rec*-locus			
Linked *rec*-locus, "indirect" ED-strategy	27.08	72.92	81.80	18.20
Linked *rec*-locus, "universal" ED-strategy	46.18	53.82	87.54	12.46

For "fringe" CD-strategies, the amplitude of RR plasticity was equal to 0.01.
CD>OC: CD-strategy is more favourable regardless of incidental changes in mean RR.
CD<OC: CD-strategy is less favourable regardless of incidental changes in mean RR.
CD>OC and CD<OC do not always add up to 100%; in some cases, CD-strategy appeared either more or less favourable depending on incidental changes in mean RR.

In a comparison of cases with opposite competition outcomes, several preliminary regularities could be noted (figure 1). A key factor seems to be environmental asymmetry, including asymmetry of duration (the ratio between durations of benign and stressful environmental states) and asymmetry of selection intensity (the ratio between selection intensities in benign and stressful environmental states). Its effect on outcomes of competition between recombination strategies was the same for the NEQ- and DOM-systems: typically, CD-strategies were more advantageous at small to moderate asymmetries, and less advantageous at very high asymmetries (figure 1*a,b*). However, in the DOM-system, in a small number of cases, the CD-strategy failed even at intermediate asymmetries, despite the fact that the total proportion of outcomes with fixation of the modifier allele conferring OC-strategy in the DOM-system was nearly four times lower that in the NEQ-system (see table 1). A similar pattern was observed when comparing ED- and OC-strategies, although the NEQ- and DOM-systems seemed to differ in the interplay between asymmetry of duration and asymmetry of selection intensity. Specifically, in the NEQ-system, a certain minimal asymmetry of duration was needed for the spread of CD-strategies whereas in the DOM-system, CD-strategies could spread due

solely to asymmetry of selection intensity, even in an environment with equally lasting states. Intermediate period lengths included a higher proportion of cases with CD-strategy advantage (figure 1*c,d*), although this conclusion may result from our early-stage filtering for systems with intermediate recombination rates ($r \neq 0$ and $r \neq 0.5$).

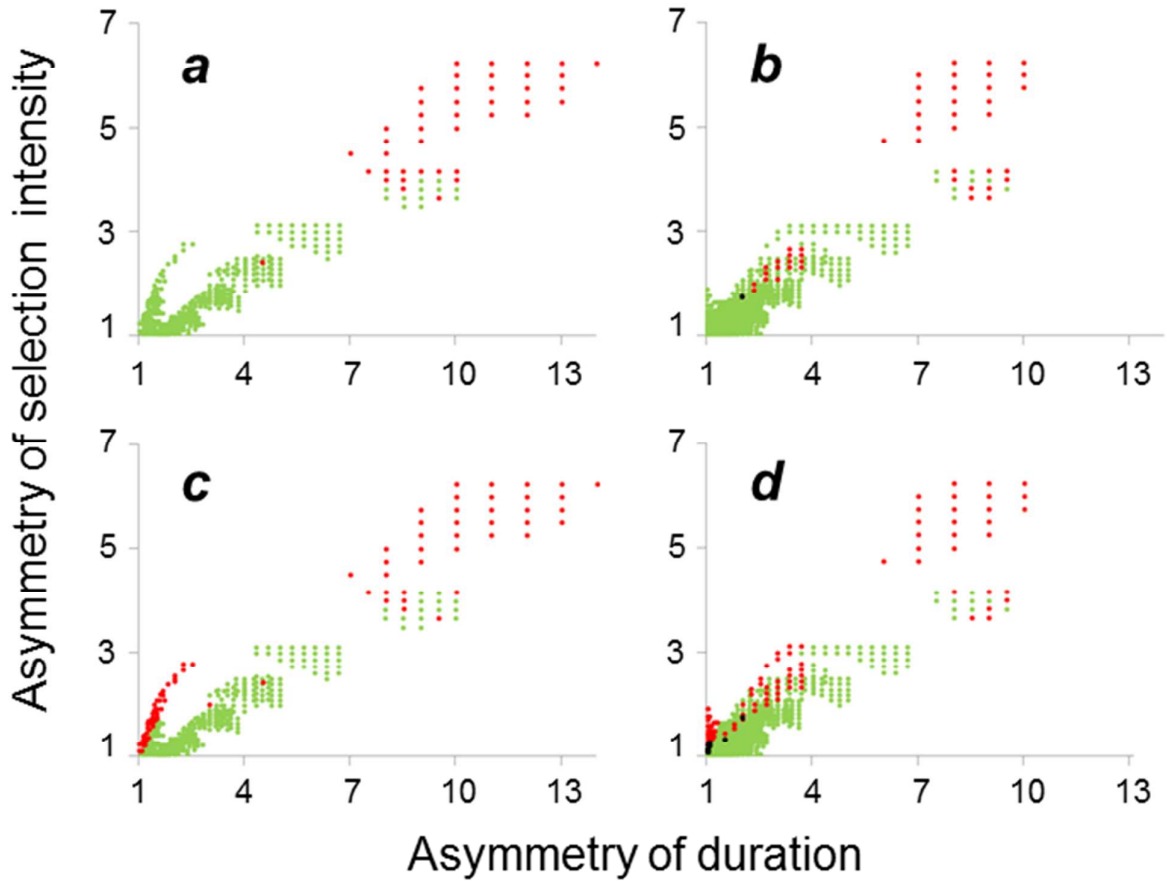

Figure 1. Effects of environmental asymmetry on the outcomes of competition between strategies with condition-dependent recombination rate (CD-strategies) and strategies with the optimal constant recombination rate (OC-strategies). Green and red points correspond, respectively, to cases where CD-strategies are more favourable ("CD>OC" in table 1) and less favourable ("CD<OC" in table 1); black points represent overlapping cases; unlinked modifier locus: (*a*) FD-strategy, NEQ-system. (*b*) FD-strategy, DOM-system. (*c*) ED-strategy, NEQ-system. (*d*) ED-strategy, DOM-system.

In addition to modifier dynamics, we also examined other characteristics of CD-strategies, such as the mean fitness of the population (measured as the geometric mean across the steady-state period) and average invasion speed (measured as the increase in frequency of the tested *rec*-allele per period). With the linked *rec*-locus, population mean fitness increased under CD-strategies regardless

of their success: the observed increase in population mean fitness ($\sim 10^{-4}$) was several orders higher than reported previously [44]. Yet, the increase was significantly higher in cases where CD-strategies were more favourable. With the unlinked *rec*-locus, population mean fitness decreased when CD-strategies were less favourable. However, when they were more favourable, population mean fitness did not necessarily increase. We also found that invasion speed of the *rec*-alleles was usually higher when CD-strategies were more favourable (electronic supplementary material, text S4).

The above results refer to situations in which OC-strategies had intermediate RRs. What if the optimal constant RR is zero? Intuitively, one would expect that CD-strategies have no chance when selection rejects recombination. However, Gessler and Xu [43] and Hadany and Beker [44] showed that CD-strategies could be favoured in haploids, even in such situations. We examined selection regimes with zero OC-strategies in our diploid-selection model (electronic supplementary material, table S5). Excitingly, under the unlinked *rec*-locus, CD-strategies appeared more favourable than the corresponding OC-strategies in a considerable proportion of the cases: FD-strategies outcompeted them in 22% and 23% of the cases for NEQ- and DOM-systems, respectively. The corresponding numbers for ED-strategies were 28% and 26%. In contrast, under a linked *rec*-locus, CD-strategies were only favoured extremely rarely.

4. Discussion

The evolutionary advantage of condition-dependent recombination has been shown for haploids [43–46]. In diploids, the situation appears to be more complicated. Agrawal et al. [46] showed analytically, using the simplest model with a single selected locus, that evolution of condition-dependent recombination in diploids cannot be driven by the direct effects of a *rec*-modifier. Our simulations confirmed this conclusion. Specifically, in situations with a linked modifier (where a direct effect is conceivable), there was no allele frequency change at the *rec*-locus when the alternative alleles conferred OC- and "direct" CD-strategies. We additionally compared "indirect" and "universal" CD-strategies, i.e., the other pair of strategies differing only in terms of modifier linkage to the selected system. Again, as expected, there was no allele frequency change at the *rec*-locus. However, the inefficacy of direct effects in diploids does not mean that condition-dependent recombination cannot evolve in these organisms at all. Theoretically, it can evolve due to an indirect effect. In haploids, this option was demonstrated by Hadany and Beker [44], who observed the evolution of FD-strategies in situations with a multi-locus-selected system and unlinked *rec*-locus. To test for indirect effects in diploids, Agrawal et al. [46] analysed a more complex model with two selected loci, where FD-strategies evolved if and only if their mean RR was selected for. Such results led the authors to ascribe the revealed evolutionary advantage to the incidental changes in mean RR,

rather than to RR plasticity *per se* [46]. In contrast, in our simulations, CD-strategies (both FD and ED) often appeared more favourable than the corresponding OC-strategies regardless of incidental changes in mean RR, suggesting that their evolutionary advantage was associated with RR plasticity *per se*. These results extend, in diploids, those of Hadany and Beker [44] who showed, in haploids, that the evolution of CD-recombination can be driven by indirect effects alone due to RR plasticity *per se* (since mean RRs under competing strategies were explicitly normalised in their simulations).

In an attempt to explain the difference between their results (no advantage of CD-strategies in diploids under directional selection) and those of Zhuchenko et al. [16] (clear advantage of CD-strategies in diploids under cyclical selection), Agrawal et al. [46], suggested that fluctuating selection may be more favourable in this respect. However, another, seemingly more important reason, related to the considered type of condition dependence, might explain the difference. Agrawal et al. [46] analysed FD-strategies, whereas Zhuchenko et al. [16] simulated ED-strategies. Naturally, to demonstrate an evolutionary advantage/disadvantage (if one exists at all) of FD-strategies, one needs to have *variation in fitness* in the model among "recombination-responsive" genotypes. Models with only two selected loci, such as those considered in Agrawal et al. [46], can provide such variation under specific additional assumptions, e.g., cis–trans effect. In contrast to FD-strategies, to assess the evolutionary advantage/disadvantage of ED-strategies, one needs to have *variation among environmental states* in the model. The model with two states considered in Zhuchenko et al. [16] meets this requirement even without variation in fitness among "recombination-responsive" genotypes. It is worth noting that the FD-strategies considered in our current study are not purely "environment-free": RRs here indeed explicitly depend only on fitness, but the latter varies among environmental states, which seems biologically reasonable. Our additional simulations showed that such FD-strategies could be evolutionarily advantageous even in models with two selected loci—precisely due to their implicit environmental dependence. However, as a self-control experiment, we also imagined "pure" FD-strategies, with RRs depending on mean fitness across the period, i.e. when each genotype has the same RR in different environmental states, but these RRs are different for different genotypes. The only source of variation for such FD-strategies (and, therefore, the very precondition to evolve) is variation in fitness among "recombination-responsive" genotypes. Our simulations showed that "pure" FD-strategies quite often (22% and 56% of cases for the DOM- and NEQ-system, respectively) appear more favourable in models with three selected loci, but never in models with two selected loci.

The evolutionary advantage of CD-strategies compared to the corresponding OC-strategies revealed herein for diploids can be explained as follows. A cyclical environment implies alternation

of two types of periods in terms of demands on recombination: shifts between opposite environmental states and further adaptation to new conditions favour higher RRs [64,49], but then these high RRs become unfavourable due to the excessive genetic load they produce [65]. As a result, intermediate RRs often appear optimal and evolutionarily stable [53,54] (as do intermediate rates of sex and outcrossing [66–69]). At the same time, CD-strategies allow for RRs which are both higher and lower than the level established under the OC-strategy, but only *when* and *where* these higher and lower RRs are favoured ("stressful environmental state and/or low-fitness genotypes" versus "benign environmental state or high-fitness genotypes", respectively). However, this explanation is simplified. In our simulations, the CD-strategies did not always outcompete the OC-strategies. A comparison of cases with opposite outcomes enabled suggesting that condition-dependent recombination is favoured when heterogeneity (either variation in fitness between genotypes or variation in selection intensity between environmental states) is lower than a certain threshold. This is consistent with Zhuchenko et al. [16], who failed to find an evolutionary advantage for plastic recombination in environments that were too asymmetric. In line with this, studies on the plasticity of other traits also argue for ambiguous effects of heterogeneity (recently reviewed in [70,71]).

The relative roles of direct and indirect effects in the evolution of condition-dependent recombination are not clear. In our opinion, the importance of indirect effects is underestimated. Perhaps the reason for this is that condition-dependent recombination almost never evolves under certain model assumptions in diploids [46]. Nevertheless, it may evolve under other assumptions (see [16], as well as results presented herein). Indirect effects alone can drive the evolution of condition-dependent recombination in haploids as well [44], which makes this mechanism less restricted than the "abandon-ship" one. The "abandon-ship" mechanism may play an important role in haploids. However, even in haploids, it needs a rather specific precondition to work (sensitivity of meiosis to fitness of the parental haploids). Moreover, since direct effects imply *rec*-locus linkage to a selected locus, the "sphere of their influence" is expected to be limited. Indeed, it is hard to assume that each cluster of linked fitness loci has its own local recombination modifier locus. In fact, recombination control is a hierarchical system involving many levels: the entire nucleus and cyto-nuclear interactions; chromosome size, centromere–telomere gradients and local variation of DNA sequence organisation; dependence on sex, age and environment; chromosome- and segment-specific effects of major *rec*-genes of the "coarse control system" affecting the basic steps in recombination mechanics; and segment-specific regulation of crossover rate by modifier genes of the "fine control system" with relatively small effects of individual components [72–77]. Indirect effects do not

necessarily imply *rec*-allele linkage to selected loci. This is a considerable advantage compared to the direct effect, since it enables "accumulating" evolutionary benefits of condition-dependent recombination from different genomic regions.

5. Conclusions

Empirical evidence suggests that recombination depends, to a certain extent, on external and internal conditions. Specifically, environmental stressors may increase RR (environment dependence) with genotype fitness modulating this increase (fitness dependence). The recombination–fitness association is negative, i.e., "bad" conditions result in higher RRs and vice versa. This form of condition dependence may have important evolutionary consequences (figure 2). Recombination, by definition, destroys existing haplotypes, including the most successful ones. Certainly, it creates new haplotypes, which have a chance to be successful as well. However, if recombination is random relative to the conditions, its effect on the fate of the most successful haplotypes is likely to be negative. In contrast, upon non-random, condition-dependent recombination, higher-fitness haplotypes have a reduced chance of being destroyed, while recombination trials to build up new haplotypes occur with a higher probability at the expense of lower-fitness ones. Remarkably, empirical studies also provide evidence of condition dependence for mutation, sex and outcrossing [78–80], suggesting that it may be an important feature of variation-effecting mechanisms. The results presented herein suggest that condition-dependent recombination can be evolutionarily advantageous in diploids, and can therefore emerge as an adaptive trait. This is consistent with the results of other theoretical studies, which confirm that condition-dependent sex, mutation or dispersal can also be considered evolutionarily advantageous strategies [81–85].

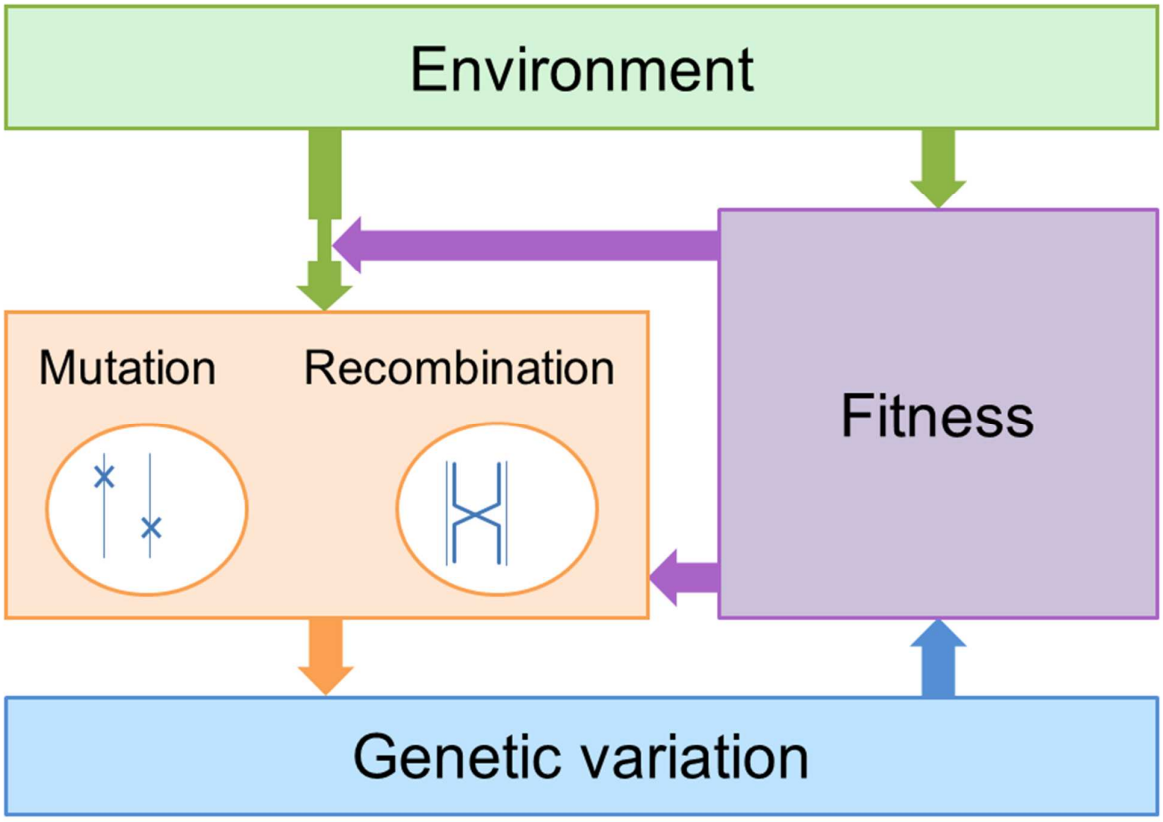

Figure 2. Suggested evolutionary interplay among recombination, fitness and environment ([1], with modifications). Environment not only favours/disfavours genotypes according to their fitness (selection); it also affects the main processes involved in *de novo* generation of genetic variation (recombination, mutation and transposition of mobile genetic elements). These environment-induced changes are modulated by genotype fitness in a negative-feedback way, with lower fitness leading to greater recombination and mutation in the progeny. In addition, fitness may affect recombination and mutation directly, regardless of the environment [86].

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Competing Interests. We declare no competing interests.

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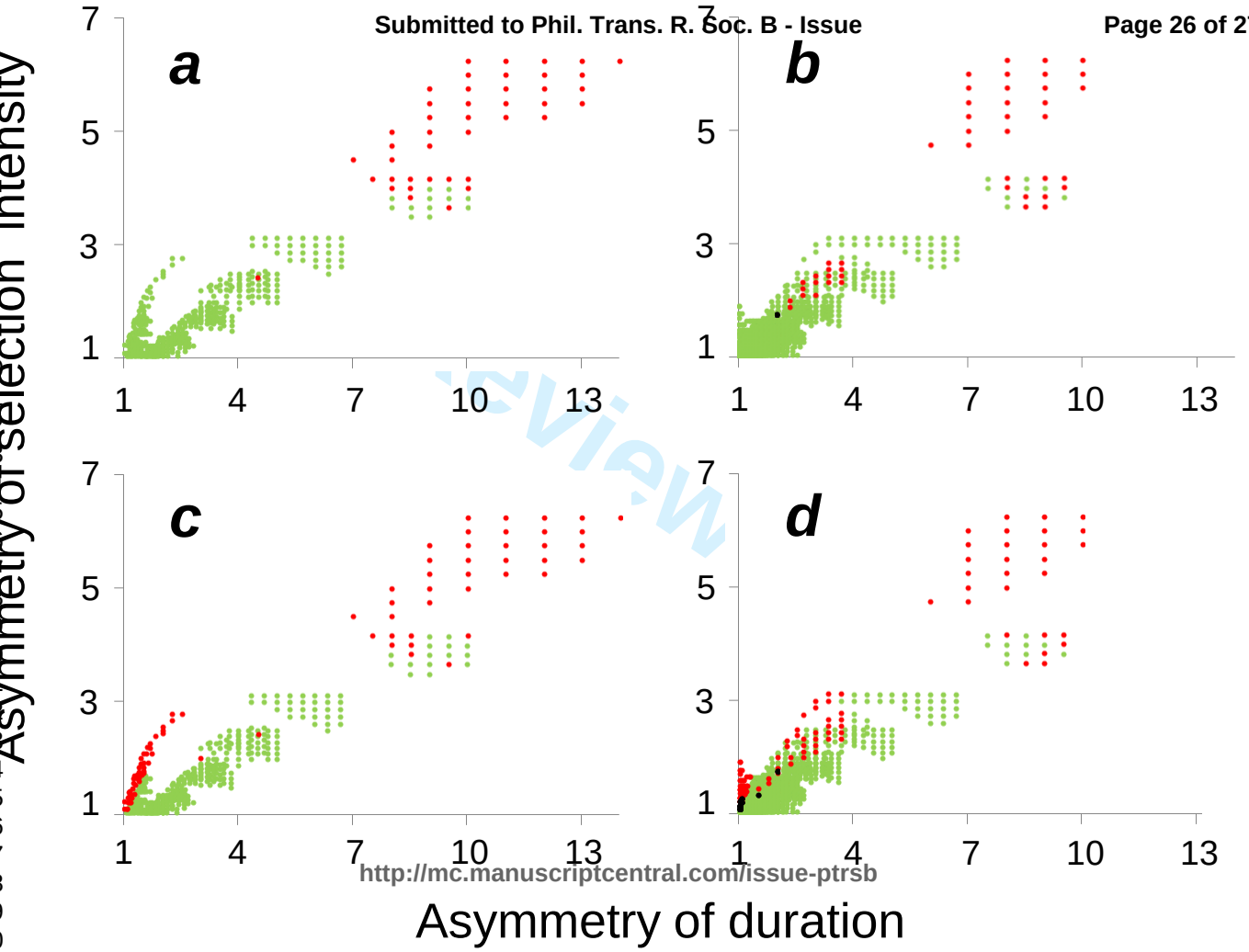

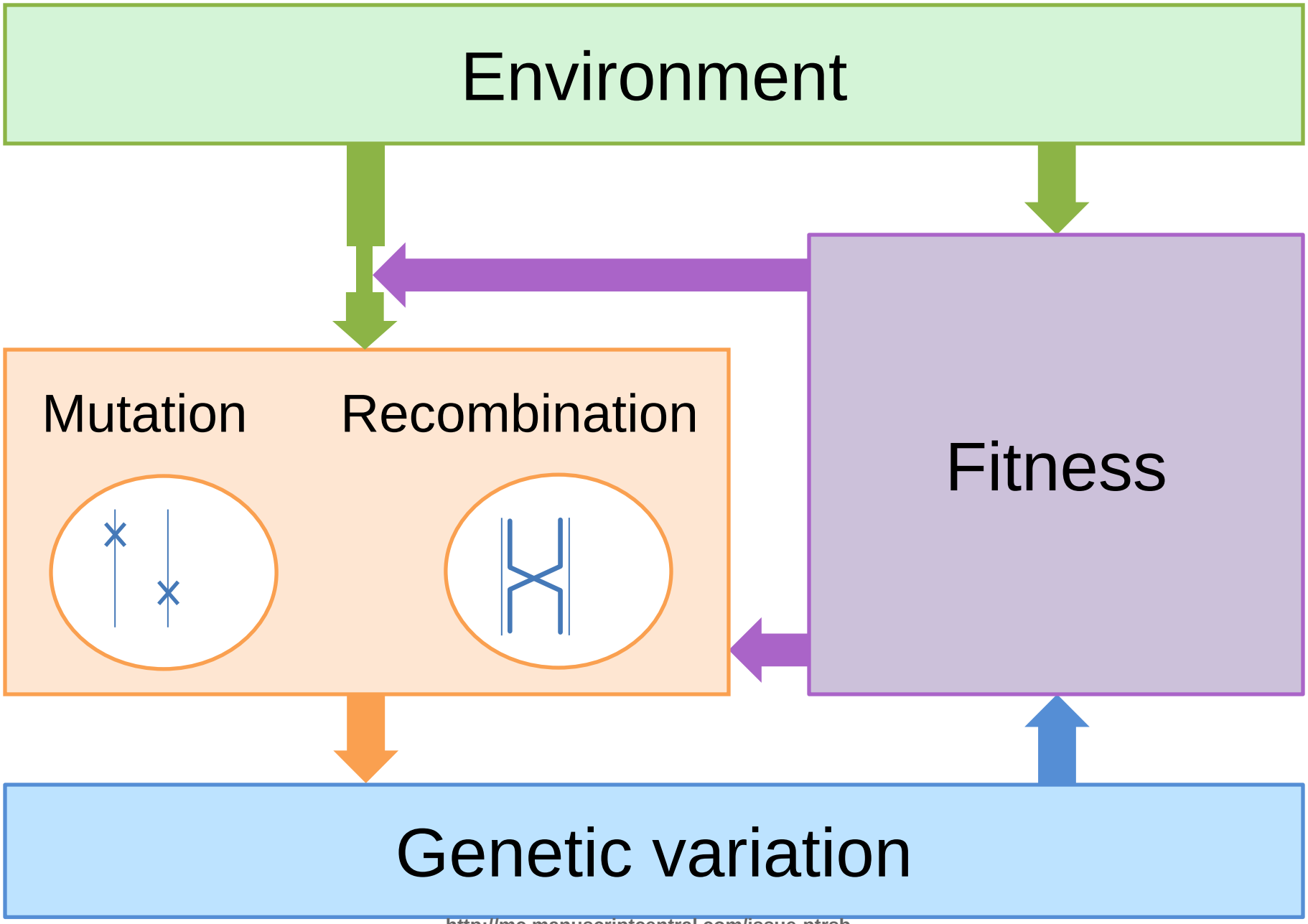
Environment
Mutation
Recombination
Fitness
Genetic variation