

# Fitness-associated recombination on rugged adaptive landscapes

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## Abstract

A negative correlation between fitness and recombination rates seems to exist in various organisms. In this article we suggest that a correlation of that kind may play an important role in the evolution of complex traits. We study the effects of such fitness-associated recombination (FAR) in a simple two-locus deterministic model, as well as in a multi-loci NK rugged adaptive landscape. In both models studied, FAR results in faster adaptation and higher average population fitness, compared with uniform-rate recombination.

## Introduction

Recombination affects adaptation in two opposite directions. On one hand, it creates new and possibly advantageous gene combinations. On the other hand, it also breaks down existing good combinations. If recombination does not discriminate between different gene combinations, its net effect is to reduce the overall linkage disequilibrium (Barton & Charlesworth, 1998). This effect can be positive in some scenarios, (Muller, 1964; Kondrashov, 1988), but negative in others (Eshel & Feldman, 1970). The effect of recombination is especially problematic for the evolution of complex traits, which are coded by more than one gene.

### The problem of evolving complex traits: adaptation on rugged landscapes

Natural genetic systems possess a high degree of interdependence. The effect of a single gene on the phenotype is affected both by regulation during transcription and translation and by protein–protein interactions (Lander & Schork, 1994; Moore & Nagle, 2000; Uetz *et al.*, 2000; Nadeau, 2001). This results in epistasis – inter-dependence between different loci along the genome, and in pleiotropy – the participation of one gene in determining several traits. Systems exhibiting these features may be

described by a rugged fitness landscape, in which ‘peaks’ of superior genetic combinations are separated by ‘valleys’ of inferior combinations (Wright, 1931). In such complex genetic systems, evolution by asexual reproduction is limited by the ability to create superior combinations.

Evolution by sexual reproduction, on the contrary, is limited because recently generated superior combinations are hard to maintain. They are likely to be lost because of recombination with other types. Several attempts have been made to explain evolution on such fitness landscapes, which requires shifts from one adaptive peak to another. These models have made assumptions about changes in the fitness landscape (Charlesworth, 1976; Grant, 1986; Milligan, 1986; Price *et al.*, 1993), heterogeneity of the environment (Hadany, 2003), or small population bottlenecks, usually associated with new founding groups (Barton & Charlesworth, 1984; Carson & Templeton, 1984).

One of the most prominent theories of adaptive peak shifts is Wright’s ‘Shifting Balance’ process (Wright, 1931, 1982). This theory suggests a three-stage mechanism: a small and partially isolated deme drifts away from its local peak; selection then takes it to a higher peak; migration can eventually allow the advantageous combination to fix in the entire population. Each of the three stages of the shifting balance requires a specific parameter range (Crow *et al.*, 1990; Barton & Rouhani, 1993; Wade & Goodnight, 1998), and there are conflicting demands to be met in order for all three of them to take place (Moore & Tonsor, 1994; Bergman *et al.*, 1995; Phillips, 1996). Specifically, the requirements of drift

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within demes and of spreading between them have opposite implications on the rate of migration. Similarly, random drift is reasonably strong only for small deme sizes, but demes should be large enough to produce favourable mutations at a satisfactory rate. These conflicts greatly reduce the applicable parameter range, and parameters found in nature seem to often lie outside this range [see Coyne *et al.* (1997) for a comprehensive review of these results, but also Goodnight & Wade (2000) for a contrasting view].

### Stress, fitness, and recombination

All the above theories share one implicit underlying assumption: that recombination is independent of individual fitness. However, there is some evidence pointing in the opposite direction: recombination and fitness may in fact be negatively correlated.

Evidence for the role of stress responses in regulating recombination rates exist in various taxa, ranging from bacteria to higher eukaryotes. Organisms that perform facultative sex supply an example of special interest. In these organisms stress responses are known to be correlated with an increased tendency for sexual reproduction and recombination (Fabre & Roman, 1977; several examples in Bell, 1982; Bernstein & Johns, 1989; Harris, 1989; West *et al.*, 2001).

Of the facultative sexuals, yeast is perhaps the best studied. Regulation of recombination rate in yeast takes place at two levels. First, various types of stress induce a switch from asexual to sexual reproduction: starvation, DNA damage, and heat shock were all shown to increase the probability of that shift (Kassir *et al.*, 1988; Bernstein & Johns 1989; Davis & Smith, 2001). Another regulation of recombination rate occurs in the sexually reproducing yeast – stress is correlated with an increase in the frequency of recombination events at the sexual stage (Abdullah & Borts, 2001). This response is apparently mediated by activation of recombination hot spots (Kon *et al.*, 1997; Mizuno *et al.*, 2001). Moreover, it has been shown that the distribution of recombination rates across the population is far from uniform – there seem to be ‘hot cells’, in which recombination occurs much more often than in most of the population (Smith, 2001).

In bacteria, the phenomenon of transformation (genotype change following uptake of external DNA) can be considered as an early form of recombination. Starvation is known to trigger competence, the ability to take up external DNA, in *Bacillus subtilis* and *Haemophilus influenzae* (Dubnau, 1991; Redfield, 1993). Even under the recombination-inducing conditions, only a small part of the bacterial population becomes competent.

This type of correlations is not limited to unicellular organisms. *Drosophila melanogaster* shows an increase in recombination rate following stress induced by either starvation (Bergner, 1928; Neel, 1941; Parsons, 1988) or extreme temperatures (Grell, 1978; Tracey & Dempsey,

1981), and behavioural stress has been shown to increase recombination rates in the house mouse, *Mus musculus* (Belyaev & Borodin, 1982).

Most of the experiments discussed above involved extreme stress applied to a whole population, resulting in an increase in the average recombination rate, again measured in the population as a whole. In natural populations, different organisms are likely to experience varying amounts of stress, depending on how well they are adapted to their environment. Under such conditions, we would expect to find a negative correlation between the fitness of an individual and its tendency to perform recombination. The few works that directly studied this question indeed found such a negative correlation (Tucić *et al.*, 1981; Cvetković & Tucić, 1986; Korol *et al.*, 1994 and references therein; Nevo, 1997).

In this work we examine the effect that such a negative correlation between recombination and fitness (termed hereafter fitness-associated recombination, or FAR) would have on the evolution of complex traits.

### FAR and the peak shift problem

The problem of adaptive peak shift greatly depends on the reproductive strategy considered. For asexual populations the problem is reduced to the waiting time until a favourable combination of several mutations appears (Christiansen *et al.*, 1998). However, once such a combination appears it has a good chance to be retained and gradually take over the asexual population. In the case of sexual reproduction, moving to a new adaptive peak is not ensured even for an infinite population, since recombination acts against rare combinations that involve more than a single mutation.

If fitter individuals tend to have less recombination, as suggested by FAR, then the recombination pressure exerted on the rare favourable combinations is reduced, without reducing the rate of their production. This increases the capacity for adaptive peak shifts relative to models based on a uniform recombination rate. It may therefore extend the parameter range where current models of peak shift are effective.

### The models

FAR can be modelled in various ways. In this paper we model the recombination rate as a step function of the relative fitness. Individuals whose fitness falls below a certain percentile have recombination rate  $r$ , whereas the recombination rate of individuals whose fitness lies above this threshold is zero.

When individuals with different recombination rates meet, recombination between them occurs with probability equal to the average of their respective recombination rates. This model can be interpreted as describing either obligatory or facultative sex in haploids. In the former case the recombination rate  $r$  corresponds to the

average number of chiasmata during meiosis, whereas in the latter it describes the tendency for sexual reproduction, assuming one recombination event per sexual reproduction event.

### A deterministic two locus model

Consider the simplest two-loci haploid landscape with two peaks, corresponding to genotypes  $AB$  and  $ab$ . The relative fitnesses are thus given by  $f_{AB} = 1$ ,  $f_{Ab} = f_{aB} = 1 - s$ ,  $f_{ab} = 1 - \theta s$  where  $0 < s$ ,  $\theta < 1$  (so that  $f_{Ab} = f_{aB} < f_{ab} < f_{AB}$ ). Assume that the population is initially fixed on genotype  $ab$  (the lower peak), and that a bi-directional mutation rate  $m$  acts on the two fitness-determining loci. Ignoring terms of order  $m^2$ , the effect of mutations on the four haplotype frequencies is given by

$$P_i^* = (1 - 2m)P_i + m(P_{Ab} + P_{aB}) \quad (i \in \{AB, ab\}) \quad (1)$$

$$P_i^* = (1 - 2m)P_i + m(P_{AB} + P_{ab}) \quad (i \in \{Ab, aB\}) \quad (2)$$

irrespective of the reproduction strategy.

In the case of a population with a uniform recombination rate  $r$  (UR population), the frequencies after recombination follow the equations

$$\omega P_i' = f_i(P_i^* - rD) \quad (i \in \{AB, ab\}) \quad (3)$$

$$\omega P_i' = f_i(P_i^* + rD) \quad (i \in \{Ab, aB\}) \quad (4)$$

where  $f_i$  stands for the fitness of type  $i$ ,  $\omega$  (the average fitness) is the sum of the right hand terms, and

$$D = P_{AB}^* P_{ab}^* - P_{Ab}^* P_{aB}^* \quad (5)$$

Let us now examine the case of an FAR population. For the sake of the analysis we assume that a fixed proportion  $\alpha$  consisting of the fittest individuals has recombination rate 0, while the rest of the population has recombination rate  $r > 0$  (if  $P_{AB} > \alpha$  the group would include only the  $AB$  type, whereas if  $P_{AB} < \alpha$ , other types would be included as well). After mutation, we subdivide the four major types to two sub-types, so that for type  $i$  ( $i \in \{AB, Ab, aB, ab\}$ ),  $P_i^0$  is the proportion of individuals of that type with recombination rate zero, and  $P_i^1$  is the proportion of individuals of the same type with recombination rate  $r$ . Thus  $P_i^0 + P_i^1 = P_i^*$ , and  $\sum_i P_i^0 = \alpha$ . This subdivision complicates analytical treatment of the equations, but is easy to implement in a computer program computing the haplotype frequencies at each generation. The frequencies of the four major types after recombination are then given by equations similar to (3)–(4), replacing  $D$  by  $D_v = D_1 - D_2$ , where

$$D_1 = P_{AB}^1 P_{ab}^1 + \frac{1}{2} (P_{AB}^0 P_{ab}^0 + P_{AB}^0 P_{ab}^1) \quad (6)$$

$$D_2 = P_{Ab}^1 P_{aB}^1 + \frac{1}{2} (P_{Ab}^0 P_{aB}^0 + P_{Ab}^0 P_{aB}^1) \quad (7)$$

Iterating these equations to equilibrium, from an initial population consisting of the genotype  $ab$  alone, we determine whether or not a given population would manage to make the shift from the lower peak to the

higher one. The criterion for a shift was that type  $AB$  constitutes at least 50% of the population after 30 000 generations. By this time the population has already reached a fixed point, as verified by comparing the genotype frequencies with the frequencies after 20 000 generations. We compared the dynamics of a UR population to that of an FAR population for various values of  $r$  and  $\alpha$ , and for values of the selection parameters  $\theta$  and  $s$  ranging from 0 to 1.

Lower recombination rates allow peak shifts to occur under a wider parameter range. FAR by definition dictates a lower average recombination rate, compared with a UR population with recombination rate  $r$ , possibly leading to a bias in favour of FAR. To eliminate this bias, we compared a UR population with recombination rate  $r = c$  to an FAR population with  $\bar{r} = c$ , where  $\bar{r}$  is the average recombination rate, defined as  $\bar{r} = r(1 - \alpha)$ . Under this definition, the two populations differ in the distribution of recombination events, but not in their expected total number per generation.

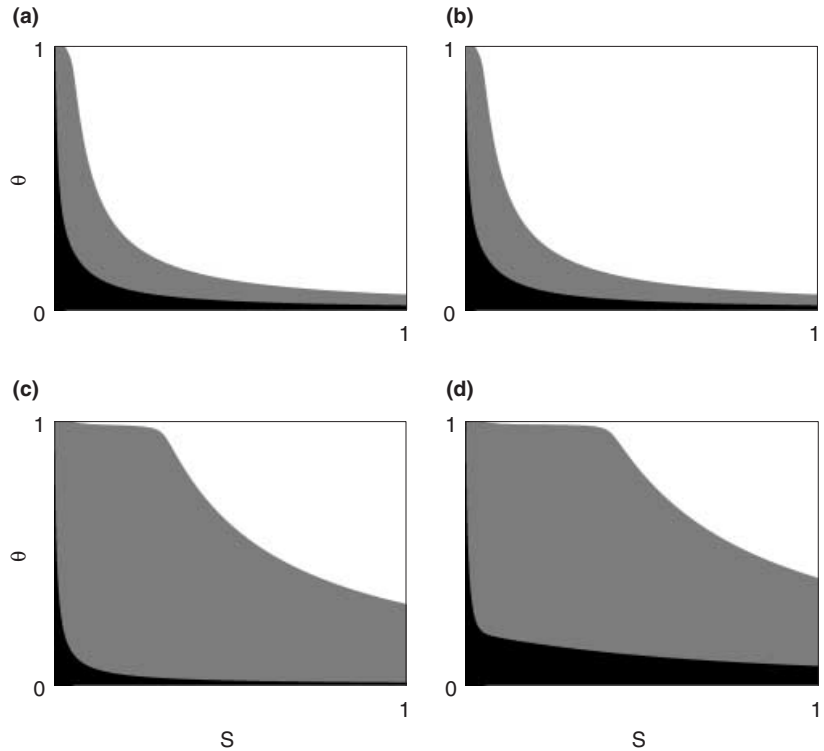
The comparison of the two populations, for three different recombination rates and four values of  $\alpha$ , is summarized in Fig. 1. The parameter range where UR managed to cross the adaptive valley was in all cases strictly contained within the range where FAR managed to cross the valley. It is notable that even when operating on the background of a high recombination rate, the parameter range where FAR populations crossed the adaptive barrier (Fig. 1 c,d – area II) was larger than the corresponding area for a UR population with a low recombination rate (Fig. 1 a,b – area I).

### A multiple loci model

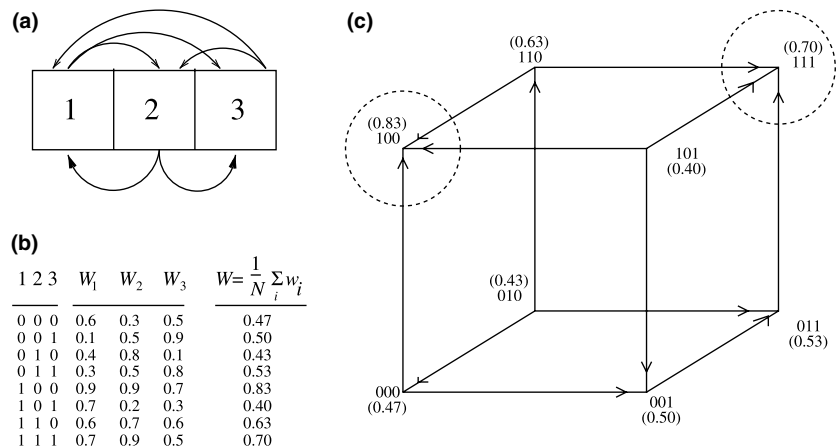
A standard model for rugged fitness landscapes is the  $NK$  model formulated by Kauffman (Kauffman & Levin, 1987; Kauffman, 1993) and later applied to modeling adaptation on complex landscapes (Bergman *et al.*, 1995; Lehman *et al.*, 2000; Taylor & Higgs, 2000). In this model,  $N$  is the number of haploid loci, and the contribution of each locus to the fitness is affected by  $K$  other loci, each having two possible alleles. An  $NK$  landscape is constructed by assigning a random value drawn uniformly between 0 and 1 to each of the  $2^{K+1}N$  possible combinations. The fitness of a given haplotype is then computed as the sum of the contributions of the  $N$  loci. In the calculation of fitness, we normalized the individual fitness values by the global maximum of the corresponding landscape, to obtain a unified measure of fitness across varying landscapes. The construction of  $NK$  fitness landscapes is illustrated in Fig. 2.

The population was initialized with all its members having an all-zero genotype. Bi-directional point mutations occurred at each locus with probability  $m = 10^{-5}$ . The recombination rate of the UR population was fixed at  $r = 0.4$ . In the FAR population, recombination rates were determined after fitness evaluation, so that the

**Fig. 1** The ability to cross the adaptive valley as a function of the two selection parameters,  $s$  and  $\theta$ . Area I (white) is the parameter range where both strategies succeed, in area II (grey) fitness-associated recombination (FAR) succeeds but uniform recombination (UR) fails, and in area III (black) none succeeds. (a)  $\bar{r} = 0.05$ ,  $\alpha = 0.1$  (b)  $\bar{r} = 0.05$ ,  $\alpha = 0.9$  (c)  $\bar{r} = 0.3$ ,  $\alpha = 0.4$  (d)  $\bar{r} = 0.4$ ,  $\alpha = 0.2$ . In all four cases,  $m = 10^{-5}$ . The average recombination rates are equal in the FAR and UR populations, but the distribution is different. Whereas in the UR population each individual has recombination rate  $\bar{r}$ , in the FAR population a proportion  $\alpha$  consisting of the fittest individuals has recombination rate zero, and the rest have recombination rate  $\bar{r}/(1 - \alpha)$ . For each reproduction strategy, the parameter range allowing a shift becomes narrower as  $\bar{r}$  increases. The value of  $\alpha$ , on the contrary, does not have a dramatic effect on the success of FAR, as long as  $0 < \alpha < 1$  (compare a and b). In all four figures, a large part of area I lies within a range of extreme selection intensity, which would be very rare in reality.



**Fig. 2** Constructing an NK fitness landscape: an example with  $N = 3$  and  $K = 2$ . (a) Each of the  $N$  sites is assigned  $K$  epistatic inputs. (b) Random assignment of values to each gene in each of the  $2^{K+1}$  possible backgrounds yields the fitness for each genotype. (c) The resulting fitness landscape is illustrated on the three dimensional cube. The two local peaks are indicated by dashed circles (after Kauffman, 1993).

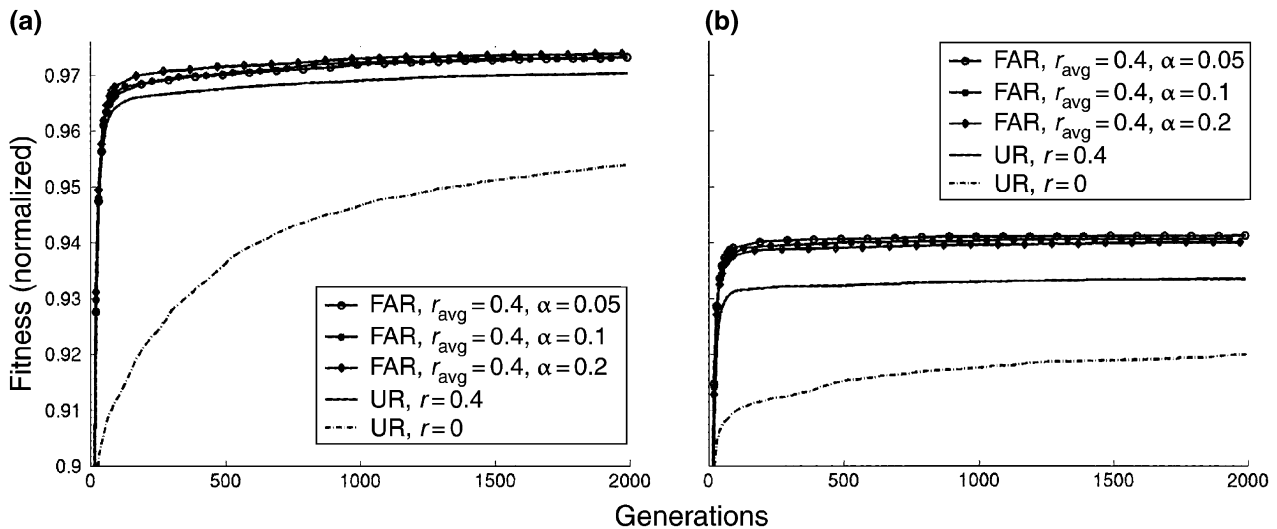


average recombination rate was also  $\bar{r} = 0.5$ . The fittest  $500 \cdot \alpha$  individuals had a zero recombination rate, whereas the  $500 \cdot (1 - \alpha)$  less fit ones had  $r = 0.4 / (1 - \alpha)$ , with values of  $\alpha$  ranging from 0.05 to 0.2.

Because of the stochasticity of the NK model, averaging over many randomly generated landscapes is required in order to obtain statistically significant results. We performed simulations with asexual, sexual UR and sexual FAR populations of 500 individuals each, for landscapes with  $N = 10$  and  $K = 2, 6$ . For each of these two settings, we averaged the results of 1000 runs with different landscapes. Each of the randomly generated landscapes

was used five times – once with an asexual population, once with a sexual UR population, and three times with FAR populations having different values of  $\alpha$ .

Figure 3 summarizes the results of these simulations. On average, the FAR populations maintain a higher average fitness than both the asexual populations and the ones with a fixed recombination rate throughout the simulation. The benefit of FAR is especially noticeable in the case  $K = 6$ , where the fitness landscape is more rugged. In this case, FAR has a bigger advantage than in the case  $K = 2$  in absolute terms. The relative advantage of FAR in the case  $K = 6$  (compared with the average



**Fig. 3** Average population fitness across generations, in an  $NK$  fitness landscape with  $N = 10$ . (a)  $K = 2$ . (b)  $K = 6$ . Five different populations are compared in each graph: an asexual population, a sexual population with uniform recombination rate 0.4, and three FAR populations. The three FAR populations have the same average recombination rate of 0.4, but three different values of  $\alpha$ :  $\alpha = 0.05, 0.1, 0.2$ . When  $\alpha = 0.2$ , for example, the top 20% of the population have recombination rate 0, and the rest have rate 0.5. Each line presents the average of 1000 runs with randomly created landscapes.

fitness obtained by the other two strategies) is even larger. For  $K = 2$  the effect is smaller, but still statistically significant ( $P < 0.001$ ).

## Discussion

The problem of evolving complex traits, also characterized as the problem of adaptation on rugged fitness landscapes (Wright, 1931) has bothered theoreticians for a long time. Many models have been put forward in an attempt to suggest conditions under which complex traits may efficiently evolve. These models involve temporal or spatial variation in the fitness landscape (Kirkpatrick, 1982; Milligan, 1986; Whitlock, 1997; Hadany, 2003), drift in the course of population founding events (Mayr, 1963; Barton & Charlesworth, 1984; Carson & Templeton, 1984), or assumptions about the spatial structure of the population (Wright, 1931, 1982). The work presented here attacks the problem from a somewhat different angle, suggesting a change in one of the basic assumptions common to most current models, which may allow more efficient evolution of complex traits. This change complements the current theories rather than contradicting them.

It is often assumed, both in theoretical models and in experimental works, that recombination rates are independent of other parameters. In other words, the probability of recombination between two specific loci is assumed to be the same for the whole population [but see Korol *et al.* (1994) and Gessler & Xu (2000) for counter-examples]. While this is a reasonable first-order approximation, it is probably not a precise description of

biological reality. In this article we examined how the evolution of complex traits is affected by an alternative assumption, namely that recombination rates are negatively correlated with fitness.

We concentrated on FAR acting in an epistatic fitness landscape. The possible advantage of FAR in this scenario can be intuitively understood. It utilizes the ability of recombination to produce favourable gene combinations, which would take a long time to reach by way of mutations alone. On the contrary, it does not easily sacrifice such rare combinations, once they appear: if they are fitter than most of the population their chances to be broken down by recombination are considerably reduced. In a deterministic two-locus model, assuming infinite population size and approximating infinite time, FAR expands the parameter range allowing a peak shift to occur in a sexual population (Fig. 1). This corresponds to elimination of the valley in the average population fitness landscape (Coyne *et al.*, 1997). A similar result was obtained using a more realistic model of rugged fitness landscape, representing adaptation in multiple loci over a finite time. In this model FAR resulted in higher average population fitness compared with asexual populations, as well as with sexual populations with fitness-independent recombination (Fig. 3).

It should be noted that this work concentrates on the variation in recombination rates within a population, and does not deal with the optimal value of the average recombination rate. This optimal value can be lower in some situations and higher in others (e.g. changing or heterogeneous environments – see Charlesworth, 1993; Otto & Michalakis, 1998; Lenormand & Otto, 2000).

Whatever this value is, our results suggest that fitness-associated distribution of the recombination events is beneficial for adaptation on rugged landscapes, compared with uniform distribution.

The choice of the modelling assumptions we made in this article was primarily motivated by the need to present a clear comparison with fitness-independent recombination models. However, examination of alternative models indicates that the behaviour is robust, and many of these assumptions could be relaxed without changing the fundamental properties of the model. One example is the use of relative fitness to determine the recombination rate. In reality, we would expect a combination of absolute and relative fitness to determine it, and therefore, the proportion of highly recombining individuals would not be kept constant. Following an extreme environmental change, a large part of the population would have high recombination rates, whereas in well-adapted populations the large majority of the population will have low recombination rates. Another example is the use of a step function – the assumption that only two possible recombination rates exist. Limited-scale experiments with different modelling assumptions yielded qualitatively similar results. More generally, the advantages of FAR are not restricted to rugged fitness landscapes or to an adaptation scenario. A similar advantage was demonstrated on unimodal fitness landscapes, and in models where the population had to cope with accumulation of slightly deleterious mutations in a constant environment (Hadany & Beker, in press).

There is plenty of evidence for increase in recombination rates as a result of severe environmental stress. This phenomenon was observed in many experiments, spanning organisms from bacteria (where transformation with external DNA can be regarded as an early form of recombination) to mammals. A partial list would include the bacteria *H. influenza* and *B. subtilis* (Dubnau, 1991; Redfield, 1993; Jarmer *et al.*, 2002), the haploid unicellular chlorophyte *Chlamydomonas reinhardtii* (Harris, 1989), yeast (Kassir *et al.*, 1988; Bernstein & Johns, 1989; Abdullah & Borts, 2001; Davis & Smith, 2001), soil microfungi (Grishkan *et al.*, 2002), plants and nematodes (Bell, 1982; Hoffman & Parsons, 1991 and references therein), *Drosophila melanogaster* (Plough, 1917; Bergner, 1928; Neel, 1941; Chandley, 1968; Grell, 1978; Tracey & Dempsey, 1981; Parsons, 1988), and *Mus musculus* (Belyaev & Borodin, 1982). The types of stress used in these experiments were also quite variable and included heat, starvation, aridity, excessive salinity, irradiation, and even behavioural stress.

While these results are all in accordance with the assumption of FAR, some of them can be subject to an alternative interpretation. Namely, one could argue that the observed phenomena occur at the level of the whole population: an increased frequency of recombination would occur simultaneously in all organisms within the

same population, or in none of them. For such a process to occur, however, two requirements should be met. The first is some regulation of recombination rate at the level of the individual organism, and the second is synchronization of the process within the whole population. The hypothesis of FAR is in fact simpler, requiring only the first of these two elements. It is important to note that under artificial stress conditions, the whole population can present an almost identical response even in the absence of a synchronizing factor. Assume, for example, that recombination rates tend to increase under prolonged starvation. Under normal conditions, the worst individual in the population is likely to feel much more stressed than the best one, as it is competing for resources with fitter individuals. However, if the environment deteriorates very drastically, as in the case of transfer to a minimal medium, all individuals would cross the starvation threshold almost simultaneously, and the reaction would seem like a whole population effect. While some works did study the variation in recombination rates within a single population and found that they were negatively correlated with individual fitness (Tucic *et al.*, 1981; Hoffman & Parsons, 1991; Korol *et al.*, 1994), more experimental work is needed in order to ascertain the generality of this phenomenon.

Interesting supportive evidence can be obtained from examination of the correlation between age and recombination rates in higher eukaryotes. Age is a good indicator of survivorship, and is thus positively correlated with fitness, to the extent that lifespan is a component of fitness. This argument was originally suggested to account for the common observation that females prefer to mate with older males (Trivers, 1972; Manning, 1985). The positive correlation between age and fitness is, however, imperfect. If there is a trade-off between lifespan and fertility or between adult lifespan and early-age viability, this correlation may be weakened (Kokko, 1998), and in extreme cases even become negative (Hansen & Price, 1995). Furthermore, the quality of genes passed on to the next generation is also affected by accumulation of germline mutations, and thus deteriorates with age (Crow, 1993). A natural prediction about FAR would be that the average recombination rate would initially decrease with age, but may start increasing again at a late stage of life. A decrease of recombination rates with age has indeed been demonstrated in plants (Griffing & Langridge, 1963). In mammals, a fall in recombination with maternal age has been found in *Mus musculus*, although correlation with paternal age has been inconsistent (Bodmer, 1961; Reid & Parsons, 1963). In *Drosophila*, both an initial decrease and a later increase in recombination frequency have been shown (Hayman & Parsons, 1960; Redfield, 1966; Ashburner, 1989). It is interesting to note that examination of female mate-choice in lekking flies has indicated a preference for middle-aged males over young and old males (Jones *et al.*, 2000), hinting at a similar correlation with male fitness.

FAR might be just a part of a broader picture. It is possible that mutation is also associated with fitness to some extent. In *Escherichia coli*, there is evidence for a stress-induced hyper-mutation state, regulated by the SOS response (Foster, 1999; McKenzie *et al.*, 2000). In *Chlamydomonas*, increased mutation was demonstrated as a result of various stress factors including starvation, toxicity, high osmolarity, or extreme temperatures (Goho & Bell, 2000). Transposition of transposable elements is highly mutagenic, and is often activated by stress (McClintock, 1984; Strand & McDonald, 1985; Grandbastien, 1998). It is possible to see both FAR and stress-induced mutation as two instances of a more general principle. Plastic variation, occurring more often when the individual is less adapted to its environment, can be more beneficial than uniform variation.

With the growing understanding of genome structure and function, it becomes more and more evident that complex interactions between different loci in the genome are the rule rather than the exception. The question of evolution on rugged adaptive landscapes may therefore apply to many of the adaptation scenarios encountered in nature. If recombination in nature is indeed fitness-associated to a significant extent, as suggested by accumulating experimental evidence, it may constitute a key element in our understanding of this fundamental question.

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