

Liberating genetic variance through sex

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Summary

Genetic variation in fitness is the fundamental prerequisite for adaptive evolutionary change. If there is no variation in survival and reproduction or if this variation has no genetic basis, then the composition of a population will not evolve over time. Consequently, the factors influencing genetic variation in fitness have received close attention from evolutionary biologists. One key factor is the mode of reproduction. Indeed, it has long been thought that sex enhances fitness variation and that this explains the ubiquity of sexual reproduction among eukaryotes. Nevertheless, theoretical studies have demonstrated that sex need not always increase genetic variation in fitness. In particular, if fitness interactions among beneficial alleles (epistasis) are positive, sex can reduce genetic variance in fitness. Empirical data have been sorely needed to settle the issue of whether sex does enhance fitness variation. A recent flurry of studies^(1–4) has demonstrated that sex and recombination do dramatically increase genetic variation in fitness and consequently the rate of adaptive evolution. Interpreted in light of evolutionary theory, these studies rule out positive in these experiments epistasis as a major source of genetic associations. Further studies are needed, however, to tease apart other possible sources. *BioEssays* 25:533–537, 2003.

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Introduction

Combinations of genes that are particularly fit rise in frequency over time as a result of natural selection. Breaking apart these gene combinations through sexual reproduction thus seems like a recipe for disaster. Indeed, theoretical models have demonstrated that sex and recombination, when they have any effect at all, typically reduce the average fitness of offspring in populations subject to selection (Fig. 1). This reduction in fitness, known as the recombination load, has been

shown to result whenever genetic associations among alleles result from a constant selective pressure, whether the populations are at equilibrium, changing in response to the selective pressure, or held at a balance between selection and mutation.

At first, we would expect that the recombination load would squelch any mutation that increases the frequency of sex or recombination. However, if such a mutation (known as a “modifier” allele) becomes associated with the fittest alleles within a population, it can escape the recombination load and “hitchhike” along with those fit alleles as they spread. How might such an association develop? If favorable alleles tend to be found on chromosomes that carry deleterious alleles at other loci (a pattern known as “negative linkage disequilibrium”), sex and recombination can bring together the good alleles from different chromosomes and generate much fitter individuals than could be produced without genetic mixing (Figs. 1, 2). Of course, sex and recombination will also bring together the bad alleles and generate much less fit offspring; this is the source of the recombination load (Fig. 1). Over evolutionary time, however, it will be the fittest individuals that survive, and these individuals will carry within their genomes those modifier alleles that helped bring together the favorable alleles. In other words, if genetic variance in fitness is lowered by negative genetic associations (“good alleles on bad backgrounds”), then modifier alleles that increase the frequency of sex and recombination will reduce these genetic associations, increase the genetic variation in fitness, and become associated with those individuals most likely to survive.

Overall, then, we can understand how the rates of sex and recombination should evolve by keeping track of two effects of sex and recombination: the immediate effect on mean fitness (the recombination load) and the effect on genetic variance in fitness.⁽⁵⁾ The recombination load is generally deleterious in the simplest models with constant selection. But the effect of sex and recombination on fitness variation depends on whether good alleles tend to be found on good or bad genetic backgrounds. If fitness rises faster the more good alleles there are within the genome (positive epistasis), then selection will be very effective at preserving those individuals carrying many good alleles. In this case, we would expect good alleles to be found more often with good alleles at other loci (Fig. 2A). Consequently, sex and recombination would mix loci from high fitness and low fitness chromosomes, making more combinations with intermediate fitness and reducing the genetic

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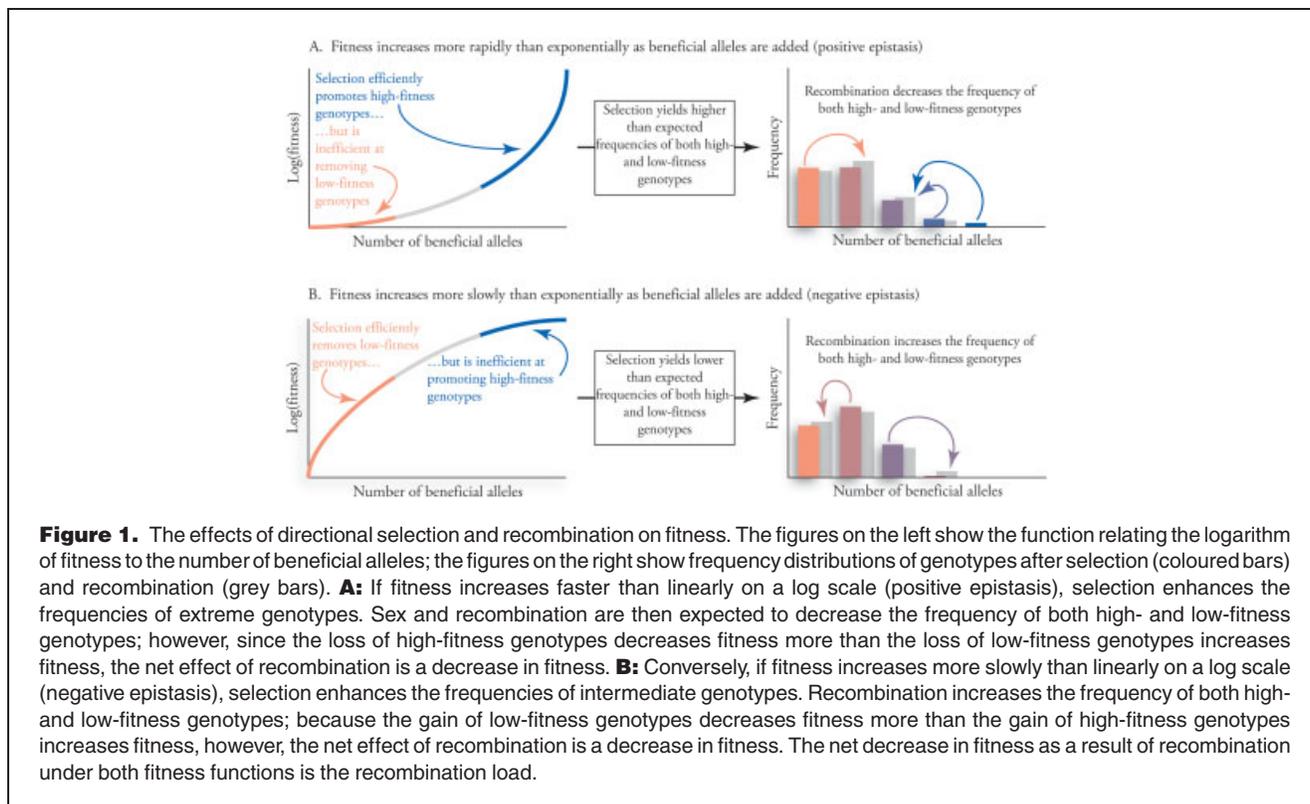
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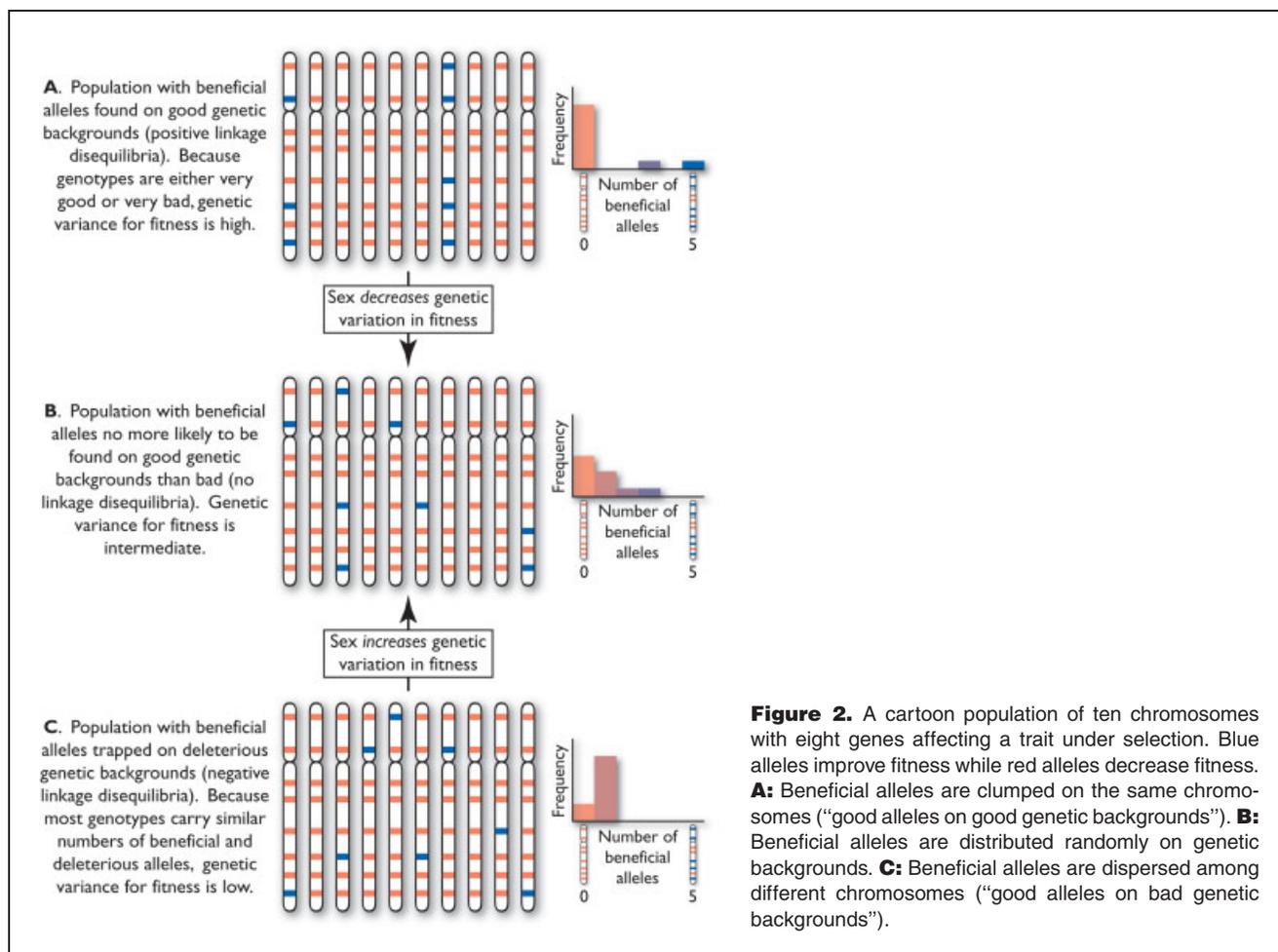


variance in fitness. Conversely, if fitness rises more slowly the more good alleles are present within the genome (negative epistasis), chromosomes carrying an intermediate number of beneficial mutations will be reasonably well preserved by selection and will become fairly common within the population (Fig. 2C). It is in this situation, where good alleles are often found on bad genetic backgrounds, that sex and recombination can increase the genetic variance in fitness by mixing together good alleles carried by different individuals. Theoretical models tell us that, for sex and recombination to evolve under constant selection, epistasis must be negative (so that sex and recombination increase genetic variation) but not too negative (or else the recombination load is too onerous).⁽⁵⁾

The above discussion is incomplete, however, because constant selection is not the only force generating associations among alleles. Selection varying over time or space, or in combination with random genetic drift, may also create genetic associations (see Table 1). Theoretical models have been developed to incorporate many of these other forces,^(6–9) and we now have a fairly complete picture of how these forces might interact to influence the evolution of sex and recombination. But theory can only tell us what the influence of various forces could be, it can't tell us which forces are most important in the real world. One approach to assess the relative importance of the forces might be to measure all of the relevant quantities, such as the form of selection and the nature of

mutations. Table 1 suggests another approach, however. By asking whether the recombination load is or is not deleterious and whether sex does or does not increase the genetic variance in fitness, we can begin to cross off some of the possible forces affecting the evolution of sex and recombination and highlight others. Recent experiments have begun to do just this.^(1–4) Elegant experiments on the fruit fly *Drosophila melanogaster* and the unicellular alga *Chlamydomonas reinhardtii* have shown that recombining populations do respond to selection more quickly than non-recombining populations, indicating that genetic variance in fitness is increased by sex.

William Rice and Adam Chippindale⁽¹⁾ constructed effectively clonal haplotypes of *Drosophila melanogaster* using an ingenious combination of genetic manipulations to ensure that single X, second, and third chromosomes were passed from father to son without segregation or recombination. To assess the impact of sexual reproduction on selection, Rice and Chippindale produced 17 clonal populations. In each population, 80 white-eyed males were made clonal, each with a unique genetic composition “captured” from a genetically variable, laboratory-adapted stock. These were mixed with 20 clonal red-eyed males with the same genetic background. Rice and Chippindale then contrasted the effectiveness of selection against the white-eyed allele in these non-recombining populations to that in 17 recombining populations.



Selection against the white-eyed allele was enhanced by adding an extra 10% red-eyed males every generation, conferring a 10% selective advantage upon red eye color (natural selection also favors red eyes, but this effect was minimized in the experimental design). After 11 generations, the frequency of red eyes had increased from 20% to an average of ~40% across recombining populations but only to ~30% across non-recombining populations. At this point, the response to selection in the non-recombining populations appeared to be slowing down, while that in the recombining populations was continuing at an approximately constant rate. These results suggest that recombination does indeed increase genetic variance in fitness. There is one aspect of the experimental design that complicates this conclusion, however. The recombining populations were constructed with more initial genetic variance to mimic a history of recombination (with the 20 red-eyed males coming from different genetic backgrounds).⁽¹⁰⁾ It can be shown that this increase in background variation is sufficient to explain the observations and that the additional benefits of recombination during the course of the experiment would have been negligible.

In a series of experiments on the unicellular alga, *Chlamydomonas reinhardtii*, Nick Colegrave, Oliver Kaltz, and Graham Bell^(2–4) used a different approach to address the same question. *Chlamydomonas* reproduces asexually under normal laboratory conditions but can be coaxed into reproducing sexually under conditions of nitrogen starvation. The basic experimental strategy involved exposing populations of *Chlamydomonas* to a novel environment, allowing them to have zero, one, or several bouts of sex, and comparing the fitness trajectories of populations with different sexual histories. In the first two experiments, the focus was on the average degree of adaptation to several novel carbon sources holding population size constant. The first experiment⁽²⁾ imposed a single bout of sex, while the second⁽³⁾ imposed three bouts of sex separated by 50–70 generations. In the third experiment, Colegrave⁽⁴⁾ quantified the ability of populations that had undergone a single bout of sex to adapt to the presence of sodium bicarbonate at a variety of effective population sizes ranging from 15,000 to 5,500,000 individuals. Despite the differences in experimental design, one consistent result emerged: the rate of adaptation, measured as

Table 1. The forces that generate genetic associations among alleles and the effects of breaking down these associations via sex and recombination

Source of genetic associations	Effect of sex and recombination on:	
	Mean offspring fitness (recombination load)	Genetic variance in fitness
(1) Selection alone (at equilibrium)	Detrimental	Negligible
(2) Directional selection or mutation-selection balance with: ⁽⁵⁾		
Positive Epistasis	Detrimental	Detrimental
Negative Epistasis	Detrimental ^a	Beneficial
(3) Dominance with: ⁽⁶⁾		
Random Mating	Negligible	Negligible
Inbreeding	Beneficial ^b	Detrimental ^b
(4) Fitness differences over time: ⁽⁷⁾		
Slow Fluctuations	Detrimental	Similar to case (2)
Rapid Fluctuations	Beneficial	
(5) Fitness differences over space with: ⁽⁸⁾		
Positive Covariance	Beneficial if epistasis < 0 ^c	Detrimental
Negative Covariance	Beneficial if epistasis > 0 ^c	Beneficial
(6) Random genetic drift: ⁽⁹⁾		
Without Selection	Neutral	Neutral
With Positive Epistasis	Beneficial ^d	Beneficial ^d
With Negative Epistasis	Detrimental ^d	Beneficial ^d

^aThe recombination load is beneficial in a very small region of the parameter space, when epistasis is negative on a multiplicative scale but positive on an additive scale.

^bAssuming that deleterious alleles are partially recessive and weakly selected.

^cAssuming that spatial variation in selection rather than epistasis determines the sign of the genetic associations.

^dAssuming that drift rather than epistasis determines the sign of the genetic associations.

the population growth rate of evolved lines relative to the ancestral line, was greater in populations that had undergone sexual reproduction than in those that had not. In addition, the first two experiments showed an increase in fitness variance immediately following each sexual episode.

Both the *Drosophila* and the *Chlamydomonas* experiments provide convincing evidence that sex and recombination increased genetic variance for fitness, which in turn improved the response of these populations to selection. These results suggest that negative associations among loci (“good alleles on bad backgrounds”), which impede selection, may be a general phenomenon. These results also rule out positive epistasis as a major source of genetic associations (Table 1), because recombination would then be expected to reduce genetic variance for fitness. There are, however, two potential sources for the negative associations inferred in these experiments: negative epistasis and drift. Negative associations arising by chance in finite populations slow down selection, so they tend to be preserved longer than positive associations.⁽¹¹⁾ Unfortunately, we still require experiments to determine the relative importance of drift versus epistasis in the evolution of sex. The Rice and Chippindale experiment was designed to maximize the importance of drift; indeed, in the non-recombining populations, the fate of the beneficial (red-eyed) mutation was almost entirely dependent on the fitness of the single genetic background within which it was placed by

chance. Thus, this experiment cannot resolve the relative importance of drift and epistasis under more natural conditions. In two of the *Chlamydomonas* experiments,^(2,3) the presence of negative epistasis is suggested by the observation that fitness declined immediately following sex (Table 1). But this fitness decline could have resulted from other costs of sex (e.g., costs of switching between mitotic and meiotic processes) besides a recombination load.⁽¹²⁾ Colegrave⁽⁴⁾ assessed the relative importance of drift versus epistasis by adapting *Chlamydomonas* in populations of varying size. He found that the greatest benefit of sex occurred in the largest populations. Colegrave argued that this result is unlikely to be explained by epistasis, which should be present in populations of any size, or by on-going drift, which should be stronger in smaller populations. He thus concluded that the main source of the negative genetic associations was the chance placement of mutations on specific backgrounds (a form of drift that occurs in populations of any size). Unfortunately, this line of reasoning assumes that the same polymorphisms are present in the different populations, but it is likely that fewer beneficial mutations arose in smaller populations and that consequently there was less to recombine.

The challenge for future experiments is to assess the importance of drift and epistasis in generating associations among alleles. The ideal experiment to test for the existence of negative epistasis would quantify the recombination load in a

way that controls for other costs of sex. For example, in experiments akin to those of Colegrave et al.⁽²⁾ and Kaltz & Bell,⁽³⁾ the effects of sex on fitness in genetically variable populations could be measured in parallel with the effects in genetically uniform populations: the difference would be an estimate of the recombination load. An alternative experiment, akin to that of Colegrave,⁽⁴⁾ would evolve populations of different size, but starting with substantial levels of genetic variance in fitness; this would decouple the effects of population size on the number of segregating mutations from the effects of population size on the impact of recombination. Such experiments, in combination with theoretical predictions, would allow us to quantify the relative importance of drift and epistasis and provide us with a better understanding of the evolution of sex.

References

1. Rice WR, Chippindale AK. Sexual recombination and the power of natural selection. *Science* 2001;294:555–559.
2. Colegrave N, Kaltz O, Bell G. The ecology and genetics of fitness in *Chlamydomonas*. VIII. The dynamics of adaptation to novel environments after a single episode of sex. *Evolution* 2002;56:14–21.
3. Kaltz O, Bell G. The ecology and genetics of fitness in *Chlamydomonas*. XII. Repeated sexual episodes increase rates of adaptation to novel environments. *Evolution* 2002;56:1743–1753.
4. Colegrave N. Sex releases the speed limit on evolution. *Nature* 2002;420:664–666.
5. Barton NH. A general model for the evolution of recombination. *Genet Res* 1995;65:123–144.
6. Otto SP. The advantages of segregation and the evolution of sex. *Genetics* 2003; in press.
7. Peters AD, Lively CM. The Red Queen and fluctuating epistasis: A population genetic analysis of antagonistic coevolution. *Am Nat* 1999;54:393–405.
8. Lenormand T, Otto SP. The evolution of recombination in a heterogeneous environment. *Genetics* 2000;156:423–438.
9. Otto SP, Barton N. Selection for recombination in small populations. *Evolution* 2001;55:1921–1931.
10. Charlesworth B. The evils of abstinence from sex. *Current Biology* 2002;12:R56–R58.
11. Hill WG, Robertson A. The effect of linkage on limits to artificial selection. *Genet Res Cambridge* 1966;8:269–294.
12. Greig D, Borts RH, Louis EJ. The effect of sex on adaptation to high temperature in heterozygous and homozygous yeast. *Proc R Soc Lond B* 1998;265:1017–1023.