Selective interference among deleterious mutations favours sex and recombination in finite populations regardless of the nature of epistasis

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Sex and recombination are widespread, but explaining these phenomena has been one of the most difficult problems in evolutionary biology. Recombination is advantageous when different individuals in a population carry different advantageous alleles[1,2]. By bringing together advantageous alleles onto the same chromosome, recombination speeds up the process of adaptation[1,3,4,5] and opposes the fixation of harmful mutations via Muller's ratchet[4,5]. Nevertheless, adaptive substitutions favour sex and recombination only if the rate of adaptive mutation is high[1,6], and Muller's ratchet operates only in small or asexual populations[7]. Here, by tracking the fate of modifier alleles that alter the frequency of sex and recombination, we demonstrate that background selection against deleterious mutant alleles provides a stochastic advantage to sex and recombination that increases with population size. The advantage arises because, with low levels of recombination, selection at other loci severely reduces the effective population size and genetic variance in fitness at a focal locus[8] (the Hill-Robertson effect), making a population less able to respond to selection and to rid itself of deleterious mutations. Sex and recombination reveal the hidden genetic variance in fitness by combining chromosomes of intermediate fitness to create chromosomes that are relatively free of (or loaded with) deleterious mutations. This increase in genetic variance within finite populations improves the response to selection and generates a substantial advantage to sex and recombination that is fairly insensitive to the form of epistatic interactions among deleterious alleles. The mechanism supported by our results offers a robust and broadly applicable explanation for the evolutionary advantage of recombination and can explain the spread of costly sex.

Sex and recombination break apart co-adapted gene combinations, thereby reducing fitness.

Yet sexual reproduction is extremely widespread, and most eukaryotes have at least one chiasma per chromosome per meiosis[9]. One of the most promising evolutionary explanations for sex and recombination is that they break down associations between deleterious and beneficial alleles at different loci (negative disequilibria). By bringing together favourable alleles from different chromosomes, sex and recombination increase the additive genetic variance for fitness, and, by Fisher's Fundamental Theorem, can increase the rate of adaptation[1,3,4,10,11]. Nevertheless, current evolutionary models have difficulties explaining widespread sex and recombination by this mechanism. Directional selection in the presence of drift generates negative disequilibrium, on average, because selection rapidly eliminates positive disequilibrium whenever it arises by chance[6]. This negative disequilibrium favours the spread of a modifier allele that increases recombination, because the modifier allele is more likely to occur on chromosomes containing multiple beneficial alleles that have been brought together by past recombination[2,6]. This advantage to a recombination modifier can be substantial in small populations[12] or in large populations that are spatially structured[13] and/or subject to directional selection at multiple loci[14], but it requires a high rate of beneficial sweeps, for which evidence is equivocal[15,16]. Other mechanisms that can favour recombination in large populations require certain forms of epistasis or fluctuating epistasis. For these alternative mechanisms to work epistasis must be weak, synergistic, and similar among pairs of loci[17,18] or fluctuate rapidly[17,19]. There is currently little empirical support for such forms of epistasis[19,20].

Sex and recombination can also be favoured because they increase the rate of elimination of deleterious mutations. Deleterious mutations of small effect are a ubiquitous feature of living systems, and comparative molecular evolutionary analysis[21] and molecular analysis of

mutation accumulation experiments[22,23] suggest that there is at least one deleterious mutation per diploid per generation in taxa as diverse as *C. elegans*, *Drosophila*, mammals and birds. In the face of such recurrent deleterious mutations, sex and recombination can be advantageous for two distinct reasons. First, there is a deterministic advantage of recombination that eliminates the negative linkage disequilibrium generated by synergistic epistasis[17,18,24,25], but as mentioned above, there is little evidence for such epistasis[20]. Second, there is a stochastic advantage in that recombination can reduce the fixation of harmful mutations via Muller's ratchet[4]. Yet harmful mutations are unlikely to fix in sexual populations unless the effective population size is very small[7]. Even if harmful alleles do not fix, they can still reduce the efficacy of selection on neighbouring loci through a process called "Hill-Robertson interference"[8]. Hill-Robertson interference occurs because individuals bearing deleterious mutations are less likely to survive and reproduce, reducing the number of individuals that contribute genetically to the future population. This reduces the effective population size witnessed by a focal locus, thereby increasing the importance of random genetic drift at the locus relative to selection. The extent to which the Hill-Robertson effect favours the evolution of sex and recombination in the presence of recurrent deleterious mutations is not well understood. Although previous simulations[2,26] indicate that modifier alleles that increase the frequency of recombination can be favoured in small populations ($\leq$ 1000), whether this effect is appreciable in larger populations or in the presence of epistasis is unknown. To address this issue, we quantified rates of fixation of modifier alleles that increase recombination in chromosomes subject to recurrent deleterious mutations at many loci, exploring a range of population sizes and forms of epistasis.

In simulations, we allowed frequencies of deleterious mutant alleles and linkage disequilibria

among them to approach mutation-selection-drift balance in a population of N haploids. We then introduced, at a random position and in a single copy, a recombination modifier allele that uniformly stretched the genetic map length of a chromosome from an initial length L (L = 0, 0.1, or 1 Morgan) to L + 0.1 Morgan (M). The fixation probability, u, of the modifier allele was measured relative to the fixation probability, $u^* = 1/N$, of a neutral mutation. This quantity, when multiplied by the mutation rate to new modifier alleles, μ, also describes the expected rate of substitution (or "flux") at modifier loci ($N u \mu = u/u^* \mu$). The effect of population size on u/u^* is shown in Figure 1 for values of the chromosomal mutation rate, U, and deleterious mutational effect of single mutations, α, that span the range of empirical estimates for several eukaryotes[27]. We explored whether curvature in the fitness surface, as measured by the epistasis parameter β, had a major effect on the spread of the modifier (see methods). In all simulations in which recombination started at a low level (i.e. $L \leq 0.1$M), u/u^* was greater than one, implying that the recombination modifier is favoured. Even with chromosomes of 1M in length, the modifier of recombination tends to be favoured (Supplementary Table 1). Epistasis did not have a substantial effect on the outcome unless it was very strong and negative. For the cases considered in Figure 1, the input of mutational variation for fitness per generation ranges from $V_M \approx U\alpha^2 = 10^{-6}$ to 10^{-4}, assuming that each mutation has an independent effect on fitness ($\beta = 0$). These values are comparable to empirical estimates of V_M per chromosome in *Drosophila* - typically of the order of 2×10^{-5} (ref. 28). We also investigated simulations in which a modifier mutation arose at a random location in a genome containing 5 chromosomes. The advantage of the recombination modifier is only slightly smaller than that observed in a single chromosome genome (Supplementary Table 2).

Interestingly, the flux of modifier alleles increases with the population size over the range of parameters considered (Figure 1; Supplementary Figure 1), demonstrating that Hill-Robertson interference is relevant to the evolution of sex and recombination even in large populations (e.g., u/u^* can exceed 100 in populations of size 100,000). It is striking that the stochastic advantage to sex and recombination is stronger in populations of larger size; this surprising observation stems from the fact that populations of larger size maintain more polymorphic loci, increasing the strength of Hill-Robertson interference.

To investigate whether Hill-Robertson interference is strong enough to favour sexual reproduction, we asked whether sex could invade an asexual population, allowing for substantial costs of sex. After the allele frequency distribution reached steady-state in the asexual population, a mutation causing individuals to undergo sexual reproduction with probability p_{sex} was introduced into the population. The resulting zygotes had one recombination event, on average, per chromosome. We introduced a cost of sex, C, by the number of offspring per parent when reproduction is sexual rather than asexual, i.e., $w_{\text{sex}} = w_{\text{asex}}/C$; we explored values of C between 1 (no cost) and 2 (a two-fold cost of sex). The results (Figure 2) indicate that selection against deleterious mutations can favour costly sex (u/u^* exceeded 1 for C values ranging from 1 – 1.75), particularly when the modifier causes only a small increase in the probability of sexual reproduction. It is especially noteworthy that costly sex is more likely to spread in populations of large size.

Theory for infinite populations predicts no advantage to a modifier of recombination when genes independently affect fitness ($\beta = 0$), because such selection does not generate disequilibria[10]. Over the range of population sizes explored, however, our simulations show

that the relative fixation probability of a modifier of recombination increases with population size under a range of models of gene action, regardless of the presence or sign of epistasis. That the Hill-Robertson effect is behind this result was confirmed by a dramatic reduction in the effective population size (N_e) in our simulations compared to the actual population size. To estimate N_e, we measured the steady-state variance at a linked locus subject to recurrent neutral mutation (see Methods). The results (Figure 3; Supplementary Table 3) show that N_e remains far below the actual population size, especially when linkage is tight. For example, in the case of complete linkage, the effective population size remains below 200 even as the census size rises to 50,000 (Figure 3a). The reduction in effective population size observed in our simulations matched theoretical predictions (ref. 29; Supplementary Table 3), and the effect of recombination on N_e was a good predictor of the fixation probability of modifier alleles (Supplementary Figure 2). As a result of small effective population sizes, deleterious mutations fixed in several of the simulations (even in the presence of recombination). Such fixation events were not solely responsible for our results, however, as sex and recombination was also favoured in cases where deleterious mutations rarely, if ever, fixed (e.g., $L = 0.1$M, $U = 0.1$).

Although not directly under selection, modifiers increasing the amount of recombination experience substantial indirect selection through their association with favourable alleles at linked loci. The strength of selection, s, can be estimated from the fixation probability using the standard diffusion result[30]:

$$u \approx (1-\exp[-2sN_e/N])/(1-\exp[-2sN_e]).$$

For example, in Figure 1a ($L = 0$M, $U = 1$, $\alpha = 0.01$, no epistasis), selection acting on the modifier equals $s \approx 0.02$ when $N = 1{,}000$ and rises to $s \approx 0.5$ when $N = 50{,}000$, while in

Figure 1b (L = 0.1M), selection rises from $s \approx 0.004$ when N = 1,000 to $s \approx 0.008$ when N = 50,000 (using values of N_e estimated in our simulations). Drift hinders the fixation of even very beneficial modifier alleles because of the drastic reduction in the effective size relative to the census size of the population.

There are two principal conclusions from our results. First, theory developed for infinite populations to predict the fate of a modifier does not apply, because random genetic drift in the presence of selection generates disequilibria that can favour a modifier, even in large populations. Second, over the range of parameters explored, Hill-Robertson effects overwhelm the effects of epistasis as a force generating disequilibria among alleles at different loci. Consequently, we find that the form of epistasis is not critical to the advantage of sex and recombination in finite populations, in contrast to theoretical predictions from infinite populations at mutation-selection balance[17,18,24,25]. These conclusions apply over a wide range of plausible values for the genomic deleterious mutation rate and mean effect of deleterious mutations.

While we have focused on the fixation probability of a single modifier mutation, simulations allowing recurrent modifier mutations show that chromosomal recombination rates can rise to the order of 1 Morgan (Figure 4). Multi-locus Hill-Robertson interference therefore provides a general and robust explanation for the evolution of recombination in any genome subject to recurrent deleterious mutations and can even contribute to the evolution of costly sex.

Methods

We simulated haploid populations of N individuals with genomes of c independently segregating chromosomes, each containing 100 equally spaced loci affecting fitness. Each generation, deleterious mutations affecting fitness occurred prior to mating and zygote formation. The number of mutations per generation per individual was sampled from a Poisson distribution with mean U. Each mutation was assigned to a random locus in the genome. We kept track of the number of mutations carried at each locus, so that we could allow for multiple mutations. The fitness of an individual i was $w_i = \mathrm{Exp}[-\alpha n_i + \beta n_i^2]$, where α is the independent fitness effect of a mutation, β is its epistatic effect, and n_i is the number of deleterious mutations carried by the individual. To ensure that mutations were always deleterious, we could explore only a narrow range of positive values of β. To form a mating pair, individuals were sampled with replacement with probability proportional to w_i. Having selected a mating pair, a zygote was formed by allowing n_c recombination events to occur between the pair's chromosomes, where n_c was sampled from a Poisson distribution with mean L to simulate a chromosome of initial map length L Morgans These n_c recombination events were then randomly and uniformly distributed between the 100 loci. This process was repeated until N offspring were produced, leading to a nearly Poisson distribution of offspring per parent.

To simulate the fate of a recombination modifier, the allele frequencies at the loci affecting fitness were allowed to approach their steady-state frequencies by allowing a long "burn-in" period of at least N generations of mutation, selection, drift and recombination. This burn-in period was set to many times the effective population size measured in the simulations (see below). After the burn-in, the state of the population was saved. A recombination modifier mutation was introduced to a random individual of the burn-in population at a random

position on a chromosome, coinciding with one of the fitness-altering mutations. The recombination modifier increased the expected number of recombination events in zygotes heterozygous (homozygous) for the modifier to L + 0.05 M (L + 0.1 M). For each burn-in population, the fates of between N and 5N modifier mutations were tracked. At least 5 replicate burn-in populations were simulated for each parameter combination. The fraction of recombination modifiers that fixed per burn-in population was recorded, and the mean and standard error of this fraction calculated over independent burn-ins.

The simulation of the fate of a modifier of sex was similar to that for a modifier of recombination. Asexual burn-in populations were simulated, then a mutation was introduced in a single copy that caused its haploid carrier to produce all of its offspring sexually with probability p_{sex} but at a cost, C.

To estimate effective population size (N_e) in the presence of deleterious mutations at linked loci, a neutral, linked locus was incorporated in the simulation. This locus was either telomeric or centrally located on the chromosome. Each generation, the value of each individual's neutral locus was altered by adding a normally distributed mutational effect of mean zero and variance $V_M = 1$. In the absence of selection, the equilibrium variance at the locus is expected to be NV_M, and this was confirmed in simulations. With selection at linked loci, the mean equilibrium variance at the neutral locus was then defined as the effective population size, N_e. A burn-in period of at least 7 times the equilibrium N_e computed from theory was allowed, then N_e was computed each generation for at least a further 10N generations. Average N_e estimates from independent burn-ins were used to calculate an overall estimate of the mean and standard error of N_e.

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Figure legends

Figure 1. The fixation probability, u, of a modifier mutation that increases the length of a chromosome by 0.1 Morgans, relative to that of a neutral locus, u^*, as a function of population size, N, for cases of chromosomes of initial map length 0 Morgans (a,c,e) or 0.1 Morgans (b,d,f). Results are shown for simulations with 5 different values of the epistasis parameter, β, ranging from 0.000001 (weak antagonistic epistasis) to -0.01 (very strong synergistic epistasis). We excluded cases in which antagonistic epistasis led to individuals with fitness > 1, implying that advantageous mutations were present. The chromosomal mutation rate and fitness parameters were U=1, α = 0.01 (a,b); U=0.1, α = 0.01 (c,d); U=1, α = 0.001 (e,f). The standard error of each point, measured as a percentage of the point's value, was less than or equal to 13%.

Figure 2. Fixation probability of a modifier that causes an individual to undergo sexual reproduction with probability p_{sex} plotted against the cost of sex, C, relative to the case of a mutation that has no effect on sex. The advantages of sex are greater than the costs for points above the horizontal thin line. Results for two values of p_{sex} are shown: 0.05 (a) and 0.01 (b). Each simulated individual carried a single chromosome of map length 1M with U = 1, α = 0.01, no epistasis, and no sex among the remaining individuals. The standard error of each point, measured as a percentage of the point's value, was less than or equal to 14% in panel (a) and 9% in panel (b).

Figure 3. Effective population size estimated in our simulations with (a) U = 1 and (b) U = 0.1, both with α = 0.01 and β = 0 (no epistasis). Individuals carried only one chromosome,

with the neutral locus situated at the very end. Even greater reductions in N_e are observed at centrally located neutral loci (see Supplementary Table 3). The standard error of each point, measured as a percentage of the point's value, was less than or equal to 7% in panel (a) and 21% in panel (b).

Figure 4. The long-term evolution of recombination allowing recurrent mutation at modifier loci. The mean map length from 10 replicate simulations is plotted against generation number. Background selection was simulated on a single chromosome without epistasis ($U = 1$, $\alpha = 0.01$, $\beta = 0$). Recurrent recombination modifier mutations arose at 100 random loci on the chromosome at a rate of 0.001 per chromosome. Their effects were +0.1M or –0.1M, with equal probability. The population size was 1,000.

Figure 1:

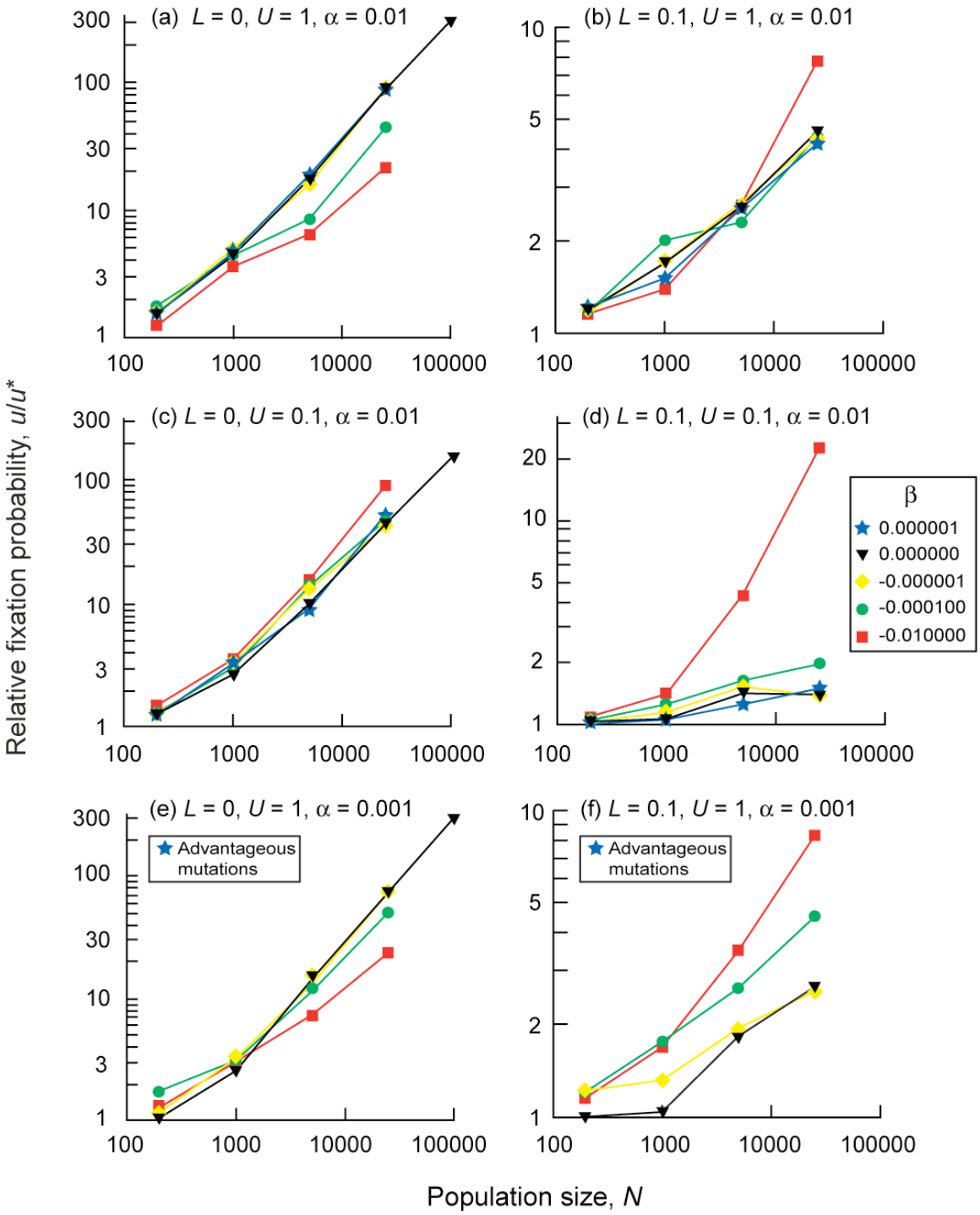

(a) L = 0, U = 1, α = 0.01
(b) L = 0.1, U = 1, α = 0.01
(c) L = 0, U = 0.1, α = 0.01
(d) L = 0.1, U = 0.1, α = 0.01
(e) L = 0, U = 1, α = 0.001
(f) L = 0.1, U = 1, α = 0.001
Advantageous mutations
β
0.000001
0.000000
-0.000001
-0.000100
-0.010000
Relative fixation probability, u/u*
Population size, N

Figure 2:

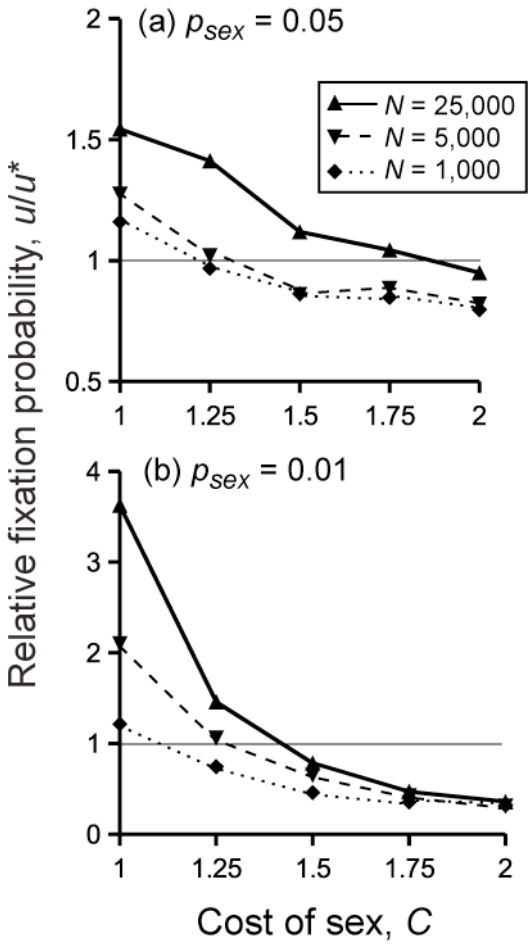

(a) p_{sex} = 0.05
N = 25,000
N = 5,000
N = 1,000
(b) p_{sex} = 0.01
Relative fixation probability, u/u^*
Cost of sex, C

Figure 3:

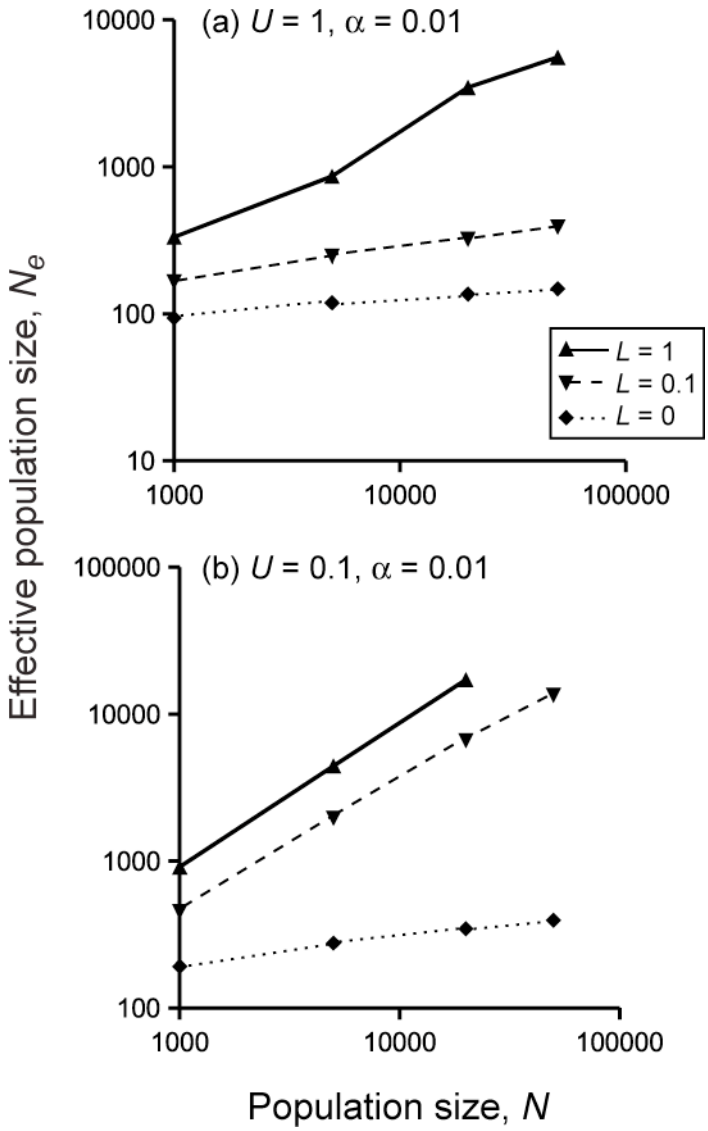
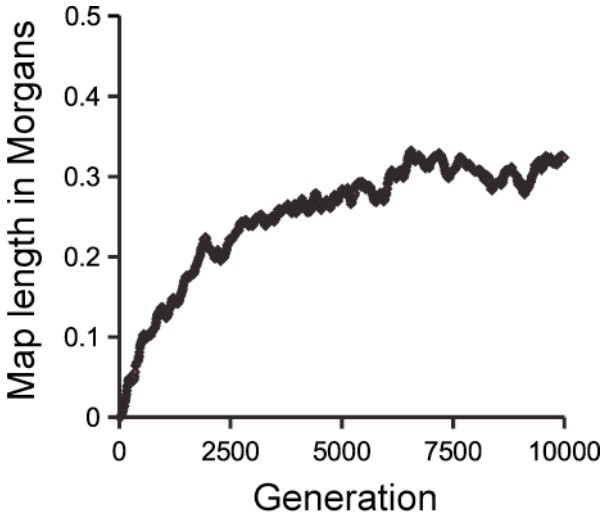
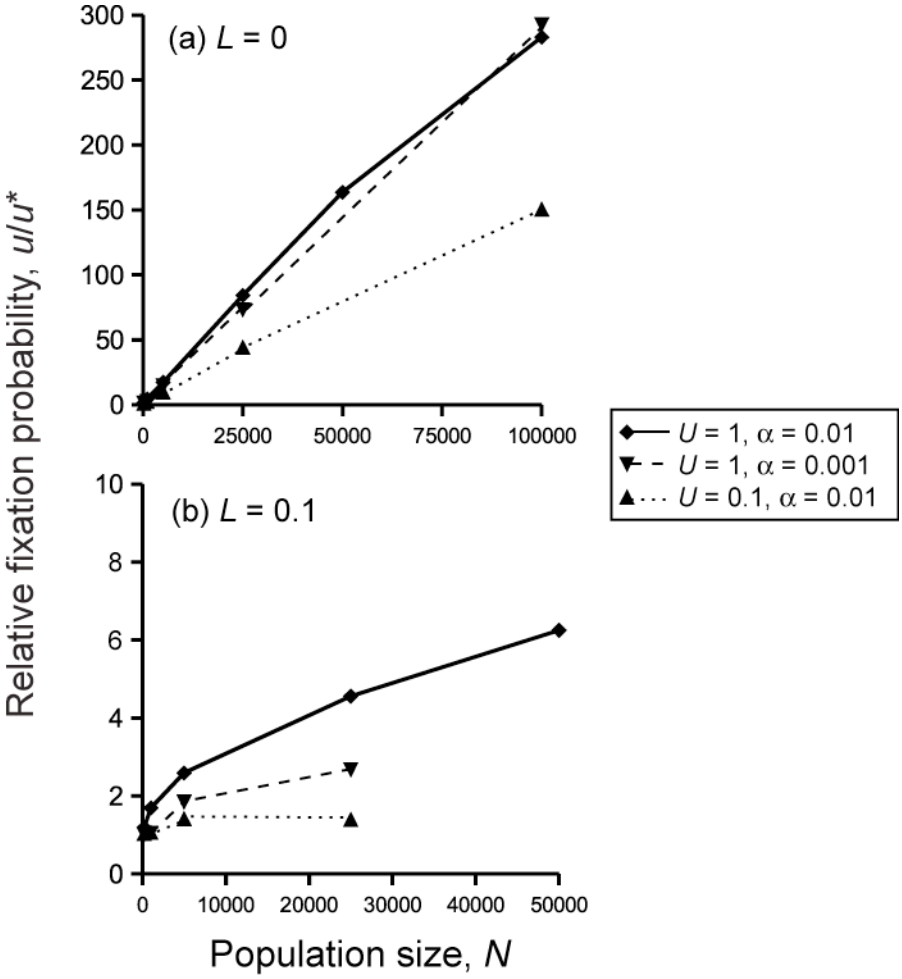

(a) U = 1, α = 0.01
10000
1000
100
10
1000
10000
100000
L = 1
L = 0.1
L = 0
(b) U = 0.1, α = 0.01
100000
10000
1000
100
1000
10000
100000
Effective population size, Ne
Population size, N

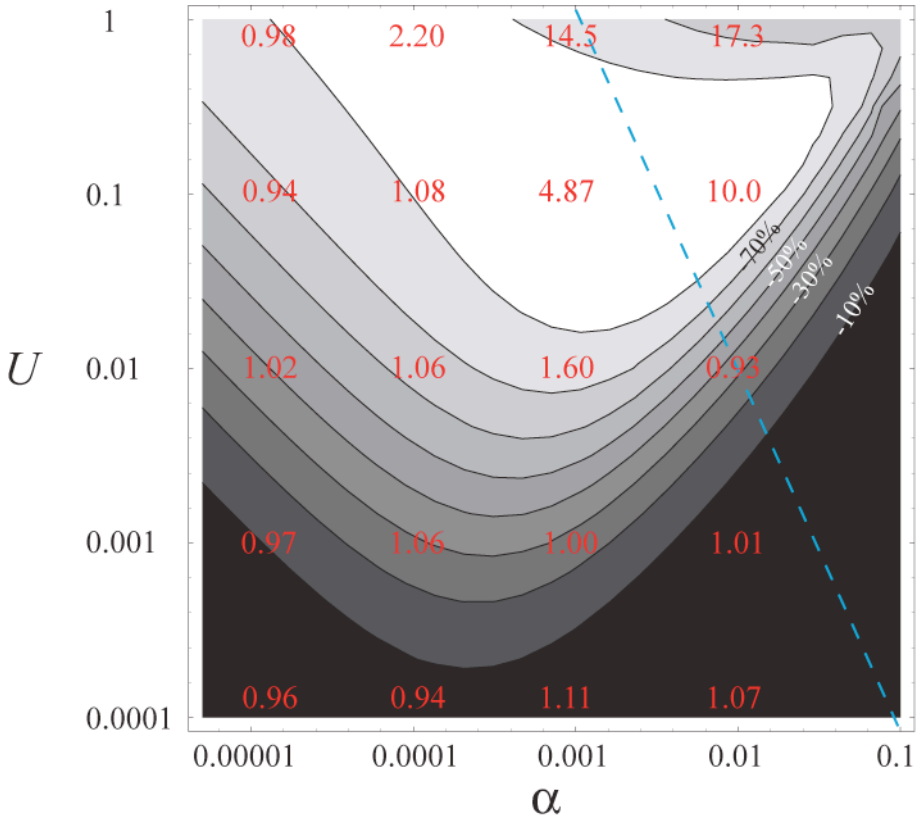
Figure 4:


Map length in Morgans
0.5
0.4
0.3
0.2
0.1
0
0
2500
5000
7500
10000
Generation

Legend to Supplementary Figure 1: Relative fixation probability of a modifier of recombination that increased recombination uniformly across a chromosome by 0.1 Morgan plotted against population size.. The flux of modifier alleles (a) increases approximately linearly with population size with initial map length L = 0M and (b) shows a concave downward relationship with initial map length L = 0.1M. Mutant effects on fitness were independent (i.e., $\beta = 0$); as a consequence, the relative fixation probability must return to $u/u^* = 1$ for populations of infinite size (Barton 1995; ref. 17).



Legend to Supplementary Figure 2. Contour plot illustrates the effect of recombination on the strength of the Hill-Robertson effect. Based on the theory of Santiago and Caballero (1998) (ref. 29), we calculated the strength of drift, $1/N_e$, when recombination was present (L = 0.1M) and compared this to $1/N_e$ when recombination was absent (L = 0M). The –50% contour, for example, describes cases where recombination halved the amount of drift (i.e., doubled N_e). Superimposed upon the contour plot is the relative fixation probability of a modifier allele that increased the map length from 0M to 0.1M from simulations (red). Although the correspondence is not perfect, the figure indicates that the change to the amount of drift is a good predictor of the fate of the modifier (t-test of the significance of the slope: p = 0.057; coefficient of determination: R^2 = 0.19). Data from metazoans (Caballero and Keightley 1994; ref. 28) suggest that the mutational variance, V_m, for fitness is greater than $\approx 10^{-6}$, suggesting that realistic parameter combinations fall to the right of the dashed blue line. The population size was 5,000, epistasis was absent, and N_e was calculated as in Supplementary Table 3 (the focal locus was placed at each of the 100 possible loci, and the average of these N_e values was used). The standard error of each fixation probability was less than or equal to 10% of the fixation probability.


1
0.1
0.01
0.001
0.0001
U
0.98
2.20
14.5
17.3
0.94
1.08
4.87
10.0
1.02
1.06
1.60
0.93
0.97
1.06
1.00
1.01
0.96
0.94
1.11
1.07
70%
50%
30%
10%
0.00001
0.0001
0.001
0.01
0.1
α

Supplementary Table 1. Relative fixation probabilities of a modifier of recombination with an effect of +0.1M on a chromosome that was initially 1M in length. We excluded cases in which antagonistic epistasis led to individuals with fitness > 1, implying that advantageous mutations were present.

N	***U* / chromosome**	**α**	**β**	***u/u* (SE)***
200	1	0.01	0.000001	1.00 (0.033)
			0.000000	1.04 (0.030)
			-0.000001	1.03 (0.033)
			-0.000100	1.01 (0.031)
			-0.010000	1.07 (0.037)
1,000	1	0.01	0.000001	1.01 (0.029)
			0.000000	1.03 (0.031)
			-0.000001	0.97 (0.029)
			-0.000100	1.10 (0.036)
			-0.010000	1.24 (0.036)
5,000	1	0.01	0.000001	1.06 (0.057)
			0.000000	1.04 (0.043)
			-0.000001	1.03 (0.059)
			-0.000100	1.03 (0.052)
			-0.010000	1.90 (0.074)
200	0.1	0.01	0.000001	0.97 (0.028)
			0.000000	1.05 (0.032)
			-0.000001	0.95 (0.029)
			-0.000100	1.04 (0.032)
			-0.010000	0.99 (0.028)
1,000	0.1	0.01	0.000001	1.01 (0.034)

N	*U* / chromosome	α	β	*u/u* (SE)*
			0.000000	1.01 (0.034)
			-0.000001	1.01 (0.028)
			-0.000100	1.03 (0.032)
			-0.010000	1.00 (0.031)
5,000	0.1	0.01	0.000001	0.97 (0.056)
			0.000000	1.04 (0.062)
			-0.000001	1.08 (0.053)
			-0.000100	0.96 (0.047)
			-0.010000	1.11 (0.057)
200	1	0.001	0.000001	Adv. mutants
			0.000000	0.96 (0.032)
			-0.000001	1.03 (0.033)
			-0.000100	1.03 (0.033)
			-0.010000	1.06 (0.036)
1,000	1	0.001	0.000001	Adv. mutants
			0.000000	0.99 (0.032)
			-0.000001	1.09 (0.037)
			-0.000100	1.09 (0.036)
			-0.010000	1.21 (0.034)
5,000	1	0.001	0.000001	Adv. mutants
			0.000000	1.01 (0.062)
			-0.000001	1.12 (0.053)
			-0.000100	1.27 (0.053)
			-0.010000	2.00 (0.075)

Supplementary Table 2. Relative fixation probabilities of a modifier of recombination arising at a random locus in a genome containing either 1 or 5 chromosomes, each with initial length 0 or 0.1M. The population size was 5,000, and there were 100 loci affecting fitness per genome. The genomic mutation rate was 1 (*i.e.*, for the case of 5 chromosomes, the chromosomal mutation rate was 0.2), and α was 0.01.

		u/u* (SE)	
β	***L***	**1 chromosome**	**5 chromosomes**
0.000001	0	18.5 (0.99)	12.7 (0.49)
	0.1	2.5 (0.17)	1.8 (0.10)
0.000000	0	17.3 (0.76)	15.5 (1.0)
	0.1	2.6 (0.071)	1.7 0.17)
-0.000001	0	15.5 (0.90)	14.8 (0.59)
	0.1	2.7 (0.16)	1.6 (0.12)
-0.000100	0	10.4 (1.2)	6.6 (0.37)
	0.1	2.3 (0.14)	2.0 (0.092)
-0.010000	0	6.4 (0.48)	2.5 (0.16)
	0.1	2.6 (0.14)	2.1 (0.14)

Supplementary Table 3. The effective population size estimated in our simulations (Sim) is compared to the theoretical results of Santiago and Caballero (1998; Theory). A numerical evaluation of N_e was obtained from the first part of their equation (4a) using equation (1), modified for haploids (details available upon request). In the simulations and theoretical evaluations, N_e was estimated at one telomeric (T) or centrally (C) located neutral locus, assuming one chromosome carrying 100 equidistant loci subject to deleterious mutations. The order of magnitude of N_e, but not the exact value, is accurately predicted by the theory; discrepancies arise, in part, because the theory does not account for disequilibria among the selected loci. ("na": Not available due to length of simulation runs.)

(a) $U = 1$, $\alpha = 0.01$, $\beta = 0$

		Map Length					
		0 M		0.1 M		1 M	
N	*Location*	Sim	Theory	Sim	Theory	Sim	Theory
1,000	T	94	35	165	105	333	538
1,000	C			126	67	261	421
5,000	T	119	45	246	224	862	2,435
5,000	C			181	111	600	1,815
25,000	T	131	55	348	547	4,223	11,858
25,000	C			244	187	2,068	8,700
50,000	T	148	59	389	868	5,568	23,633
50,000	C			368	238	3,654	17,298
100,000	T	na	64	na	1,459	na	47,182
100,000	C			na	309	na	34,494
1,000,000	T	na	79	na	11,432	na	471,055

			Map Length			
1,000,000	C		na	923	na	344,015

Supplementary Table 3. (cont)

(b) $U = 0.1$, $\alpha = 0.01$, $\beta = 0$

		Map Length					
		0 M		0.1 M		1 M	
N	*Location*	Sim	Theory	Sim	Theory	Sim	Theory
1,000	T	192	156	452	659	911	929
1,000	C			338	505	656	902
5,000	T	277	303	1,952	3,125	4,434	4,606
5,000	C			1,130	2,249	3,583	4,462
25,000	T	366	635	8,361	15,422	18,503	22,987
25,000	C			3,994	10,895	19,352	22,258
50,000	T	395	920	13,409	30,791	na	45,963
50,000	C			7,371	21,697	na	44,503
100,000	T	na	1,400	na	61,529	na	91,915
100,000	C			na	43,300	na	88,993
1,000,000	T	na	8,483	na	614,808	na	919,045
1,000,000	C			na	432,150	na	889,806