The advantage of recombination when selection is acting at many genetic Loci

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\textbf{A R T I C L E   I N F O}

Article history:  
Received 4 September 2017  
Revised 16 January 2018  
Accepted 17 January 2018

Keywords:  
Evolution  
Adaptation  
Sex  
Linkage  
Evolution of sex

\textbf{A B S T R A C T}

Natural selection can act at many loci across the genome. But as the number of polymorphic loci increases linearly, the number of possible genotypic combinations increases exponentially. Consequently, a finite population – even a very large population – contains only a small sample of all possible multi-locus genotypes. In this paper, we revisit the classic Fisher-Muller models of recombination, taking into account the abundant standing variation that is commonly seen in natural populations. We show that the generation of new genotypic combinations through recombination is an important component of adaptive evolution based on multi-locus selection. Specifically, high-fitness genotypes are expected to be absent from the initial population when the frequencies of favorable alleles at the selected loci are low. But as the allele frequencies rise in response to selection the missing genotypes will be generated by recombination. Given recombination, if the average frequency of the favored alleles at the various selected loci is equal to \( p \), then the expected number of favorable alleles per chromosome will be equal to \( pL \), where \( L \) is the number of loci. As the value of \( p \) approaches unity at the selected loci, the number of favorable alleles per chromosome will approach a value of \( L \), i.e., at the end of the selection process a favorable allele will be found at all loci. In the absence of recombination, however, selection will be limited to the highest-fitness genotypes that are already present in the initial population. We point out that the fitness of such initial genotypes is far less than the theoretical maximum fitness because they contain a favorable allele at only a fraction of the loci. Consequently, recombination acts to unblock the adaptive response to multi-locus selection in finite populations. Using simulations, we show that the sexual population can withstand invasion by newly-arising asexual clones. These results help explain the maintenance of sexual reproduction in natural populations.

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1. Introduction

The evolutionary significance of sexual reproduction has been the subject of active debate among evolutionary geneticists since the early studies of Fisher (1930) and Muller (1932, 1964). Although sexual reproduction is ubiquitous among multicellular eukaryotes, we still lack a clear understanding of its adaptive function (see Felsenstein, 1974; Maynard Smith, 1978; Barton and Charlesworth, 1998; Hickey, 2000; Otto and Gerstein, 2006; Hartfield and Keightley, 2012 for reviews). There is, however, a general consensus that the function of sex relates to the production of genetic recombinants. Consequently, the “problem of sex” is often recast as the problem of explaining the adaptive significance of random genetic recombination. Previous investigations have either analyzed this problem in detail for small numbers of loci, or performed population simulations for many loci (see Crouch, 2017). Many of the detailed theoretical studies were limited to only two loci and they usually assumed infinite population sizes, whereas the simulations used finite populations (e.g., Otto and Barton, 2001; Roze, 2014). Felsenstein (1974) noted that only those studies which assumed a finite population size found an advantage for recombination. This is because recombination can break down the random negative linkage disequilibrium that tends to occur between favored alleles, especially when the individual allele frequencies are low. For example, if we consider a population of \( N \) haploid individuals where the frequencies of favored alleles at two loci are close to \( 1/N \), the expected frequency of genotypes carrying both favored alleles is \( 1/N^2 \). This means that we would expect only \( 1/N \) individuals to show this genotype. But since frac-
tional individuals do not exist, this combination would normally be absent from the population. Of course, if we assume either a larger population size or higher initial allele frequencies the problem goes away. In this paper, we extend this line of reasoning to more than just two loci. As the number of loci increases, recombination is favored over a wider range of population sizes and initial allele frequencies. In fact, given the levels of standing genetic variation that occur in natural populations, there is no reasonable adjustment in population size and/or allele frequencies that can solve the “problem” in the absence of recombination.

A few authors have already drawn attention to the fact that, as the number of polymorphic loci increases, the number of genotypic combinations increases exponentially (Iles et al., 2003; Neher et al., 2010; Albu et al., 2012; Edhan et al., 2017). For example, Iles et al. (2003) pointed out that 20 polymorphic loci would result in more than one million genotypic combinations and that this number is larger than many population sizes. Neher et al. (2010) echoed this statement when they stated that with selection acting at many loci, the number of possible genotypic combinations would dramatically exceed the population size and that population sizes for which each genotype is well sampled would be unattainably large. For instance, if we consider one hundred bi-allelic loci (which is still less than one per cent of all loci) there are approximately 10^20 possible genotypic combinations. Consequently, in most eukaryotic species the number of possible genotypes far exceeds the actual population size. The key point is that as the number of genotypes increases, the frequency of each genotype decreases. Thus, beyond a certain number of polymorphic loci, the expected frequency of the majority of multi-locus genotypes falls below the threshold value of 1/N. The result is that the actual genotypes that occur in a natural population are just a small sample of all possible genotypes.

Our focus is on the distribution of genotypes within the population. Albu et al. (2012) noted that, for intermediate allele frequencies, the genotypic distribution does not normally contain the highest fitness genotypes (or the lowest fitness genotypes). We use classical population genetics theory to predict how the distribution of genotypes would change as the allele frequencies increased at many loci in response to selection. We then use numerical simulations to verify our predictions and to monitor the fate of a newly-arising asexual mutant within a sexual population.

2. The model

Our simple statistical model can be illustrated by using a numerical example. Let’s assume a large, diploid, finite population. Rather than considering all polymorphic loci within the genome, we focus on just 100 bi-allelic loci. Despite the simplicity of this “toy model” it does reveal the main features of the process. Now, let’s assume that the frequency of a favored allele at a given locus is equal to 0.05; that means that five percent of the chromosomes in the population will contain that particular favored allele. We can apply the same logic to the entire set of 100 loci with similar allele frequencies: at any given locus, five per cent of the chromosomes will contain the favored allele at that locus. From this it follows that the expected number of favorable alleles per chromosome (across all 100 loci) is equal to 5. In general, if the average frequency of the favored alleles at the various selected loci is equal to p, then we expect that the average number of favorable alleles per chromosome will be equal to np, where p is the number of loci.

In a sexual population undergoing random mating, the distribution of favorable alleles per haplotype (i.e., per chromosome) will form a binomial distribution around the expected mean. This allows us to estimate the expected frequency of chromosomes that carry higher than average numbers of favorable alleles. We find that this frequency drops off surprisingly rapidly for higher numbers of favorable alleles per chromosome. For example, the probability that a given randomly chosen chromosome will contain a favored allele at even 25% of the loci is very small, less than one in a billion. What this means in practice is that in a population that is even as large as a million individuals, the expected number of chromosomes containing a favorable allele at 25 or more out of the 100 loci is much less than unity. And since fractional individuals do not exist, this means that such chromosomes are normally absent from the population. In other words, all of the chromosomes in the actual population will have less than a quarter of the maximum number of favorable alleles. This, in turn, means that the diploid individuals containing these chromosomes span a fitness range that falls far below the maximum theoretical fitness. We will argue that the key role of recombination in a finite population is to generate chromosomes containing higher numbers of favorable alleles as the allele frequencies at individual loci increase in response to selection.

We assume a selective advantage, s = 0.05, for each favored allele. We also assume that the fitness interactions between loci are purely multiplicative. Based on infinite population models (Felsenstein, 1965), this selection scheme should not generate any negative linkage disequilibrium. But, as we shall argue below, this is not true for finite populations; in a finite population, even a purely multiplicative fitness function results in the build up of significant levels of negative linkage disequilibrium in the absence of recombination.

In Fig. 1 we show the predicted outcome of selection acting at 100 freely recombining loci. We assume that the frequency of the favored allele at each of the hundred loci will rise at approximately the rate predicted by classical population genetics models for selection at a single locus (see Li, 1955 page 238). We also assume that recombination will translate the rise in allele frequency at the various loci into increased numbers of favorable alleles per chromosome, as outlined above. The fitness is then calculated based on the expected number of favorable alleles per diploid genotype. The graph shows the rise in the average fitness of an outbreeding sexual population. For comparison, we also show the predicted fitness of a newly-arising asexual clone. As can be seen in the Figure, the asexual clone has an initial two-fold replication advantage, but its lack of recombination prevents it from maintaining this two-fold advantage relative to the sexual population. This is because it cannot replace its current genotype with a new genotype of higher fitness. Indeed, the clonal advantage is completely lost after twenty generations of selection. At that point, the expected number of favorable alleles per chromosome has doubled among the sexual individuals, thus offsetting the initial two-fold replication advantage of the asexual clone. Thus, one sees a typical “tortoise and hare"
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