

Unravelling the evolutionary advantage of sex: a commentary on ‘Mutation–selection balance and the evolutionary advantage of sex and recombination’ by Brian Charlesworth

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Delving into the literature on the evolution of sex is like picking up a dusty, old, unpromising book and discovering that a fascinating mystery novel lies within it. What makes this tome unpromising is that explaining the evolution of sex seems so trivial at first. Isn't it obvious that sex generates variation? The fact that nearly all eukaryotes engage in sex, at least occasionally, reinforces the view that the advantages of sex must be pervasive and strong. But cracks in this story appeared early on, when the first models were developed to investigate the fate of genes controlling the rate of sex and recombination (so-called ‘modifiers’).

The earliest work showed that genetic variants increasing recombination never spread when introduced into a population at equilibrium under selection (Kimura, 1956; Nei, 1967; Feldman *et al.*, 1983). While these papers focused on modifiers of recombination, similar results apply to modifiers that alter the frequency of sex (e.g. Dolgin & Otto, 2003). In short, when the only evolutionary process acting is viability selection (no mutation, no departures from random mating, no drift, etc.), evolutionary theory predicts that populations should evolve lower and lower rates of sex and recombination. That's a pretty big crack.

The underlying reason why evolution leads to reduced levels of sex and recombination in these models is that sex and recombination break apart the favourable gene combinations that have been built up by past selection. Consider the simplest case of a single selected locus, *A*, where selection favours heterozygotes. Modifiers that increase the frequency of sex increase the production of *AA* and *aa* offspring from heterozygous parents (who are more likely to have survived to reproduce). Sex therefore does produce more genetically variable offspring, but these offspring are less fit, and their deaths cause the demise of modifiers that promote sexual reproduction.

Metaphorically, we have come to the point in the mystery where the protagonist has been murdered. And as good detectives, evolutionary biologists have

been pursuing the culprit for decades in an attempt to find the real reason why sex and recombination have evolved and are so prevalent.

Enter Brian Charlesworth and his classic (1990) paper, ‘Mutation–selection balance and the evolutionary advantage of sex and recombination’ in *Genetical Research*. This paper explored whether deleterious mutations, added to a model of selection in an infinitely large diploid population, could favour sex and recombination. By producing more variable offspring, some of which carry more deleterious mutations than their parents and some of which carry fewer, sex and recombination could improve the efficiency of selection. As the fittest of these genomes spread by selection, so too could the modifier alleles that produced them through sex and recombination.

Previous work had found that mutation loads are lower in populations that engage in sex and recombination if fitness declines more rapidly as mutations accumulate (e.g. Kimura & Maruyama, 1966; Kondrashov, 1982, 1984). This form of fitness interaction was called ‘synergistic epistasis’, but I prefer the term negative epistasis (referring to the negative curvature of the fitness surface), because negative epistasis is also required for beneficial mutations to favour the evolution of sex and recombination (Barton, 1995). Whenever fitness surfaces are negatively curved (on a log-fitness scale), the fitness of extreme genotypes is lower than intermediate genotypes, and selection tends to narrow the array of genotypes present within the population. Sex and recombination can then regenerate this variation and improve the efficiency with which deleterious alleles are eliminated and beneficial alleles are preserved.

Previous work had also found that higher rates of recombination could be favoured when epistasis is negative, but the models were limited to two selected loci (Feldman *et al.*, 1980) or to numerical results with multiple loci (Kondrashov, 1984, with some analytical results for threshold selection).

Charlesworth (1990) pushed forward our understanding of the evolution of sex and recombination

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using an elegant trick. He employed the fitness function:

$$w(n) = \exp[-(\alpha n + \beta n^2/2)], \quad (1)$$

where α describes the linear decline in log-fitness with increasing numbers of mutations in the genome, n , and $-\beta$ describes the curvature of the log-fitness surface. This fitness function is special because, when applied to a population with a normally distributed number of mutations, the resulting distribution is still normal (Fig. 1). Charlesworth could then focus on the dynamics of the mean and the variance in n and how these differ for a resident population and, asymptotically, for individuals carrying a new modifier allele.

Charlesworth demonstrated that selection builds up negative disequilibria among mutant alleles when epistasis is negative (eqn 10b), resulting in less variation than one would expect if mutations were independently scattered across genomes. By mixing genomes together, sex and recombination increase variation in mutation number among offspring, allowing selection to act more efficiently. The result is that a sexual population has a lower number of mutations, on average, at equilibrium and a higher mean fitness than an asexual population. Charlesworth also discovered that most of this advantage comes from segregation, with recombination making a substantial difference only when there are few chromosomes.

Moreover, Charlesworth demonstrated that modifiers increasing the frequency of recombination tend to spread when epistasis is negative, but not always. In particular, Charlesworth found that recombination rates would increase only up to an intermediate level when the mutation rate was low ($U \leq 0.1$). In light of later work on the evolution of recombination (Barton, 1995), this is because the fitness function (1) is characterized by a great deal more epistasis (curvature) relative to the strength of selection (slope) when there are few mutations than when there are several. The more curved the fitness function, the more that recombination tends to create low fitness genotypes by breaking apart linkage disequilibrium, which hinders the spread of modifiers of recombination. Of course, only when the mutation rate is high would selection favouring modifiers of sex and recombination be strong enough to overcome anything but trivial costs associated with these processes.

It is also worth pointing out that sex and recombination are never favoured when log-fitness surfaces exhibit positive curvature. Selection then builds more variation in mutation number than expected from randomly distributed mutations, sex and recombination reduce variation in mutation number (thereby hindering selection), and modifiers that increase the rate of sex and recombination never spread.

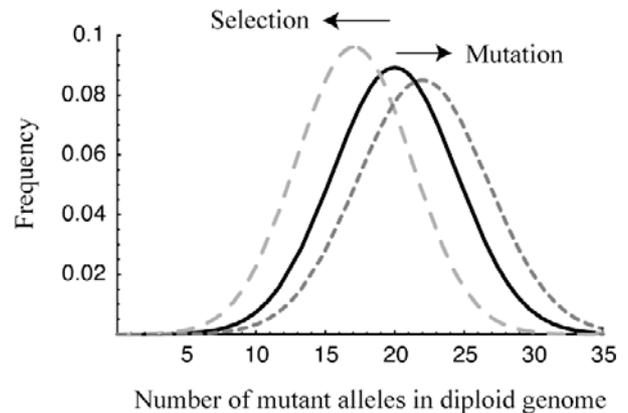


Fig. 1. Selection and mutation in Charlesworth's (1990) model. If the number of heterozygous mutant alleles per diploid genome, n , is normally distributed (black curve), then selection acting according to eqn (1) preserves normality. This is because both the normal distribution, $f(n) = \exp[-(n - \bar{n})^2/2V]/\sqrt{2\pi V}$, and $w(n)$ are quadratic functions of n in the exponent, and their product $f(n)w(n)$ remains so. Dividing by the mean fitness, the distribution after selection is a normal distribution (long dashed curve) with a new mean, $\bar{n}^s = (\bar{n} - V\alpha)/(1 + 2V\beta)$, and variance $V^s = V/(1 + 2V\beta)$. Notice that selection reduces variability whenever there is negative epistasis ($\beta > 0$). Mutations, on the other hand, are Poisson-distributed, not normally distributed, and so introduce some skew. This skew is relatively minor as long as selection is weak, because the sum of several generations of mutations that are relatively unhindered by selection is approximately normally distributed. Accordingly, the distribution resulting from mutation is approximately normal (short dashed curve) with a new mean, $\bar{n}^m = \bar{n} + U$, and variance $V^m = V + U$, where U is the diploid genome-wide deleterious mutation rate.

Perhaps the most important outcome of Charlesworth's (1990) paper, along with those of Kondrashov (1982, 1984), is that it inspired a great deal of effort to measure genome-wide deleterious mutation rates and to assess the nature of epistasis. The ensuing empirical results have been mixed. While long-lived organisms do exhibit sufficiently high mutation rates that sex and recombination could be favoured according to mutation–selection balance models (say $U > 0.1$), short-lived organisms do not (Keightley & Eyre-Walker, 2000). In particular, single-celled organisms, in which sex presumably first arose, are generally characterized by very low values of U (de Visser & Elena, 2007; Table 2 in Hill & Otto, 2007). Furthermore, where estimated, positive epistasis is almost as prevalent as negative epistasis (de Visser & Elena, 2007), and this variability in the form of epistasis tends to select more strongly against recombination than in its favour (Otto & Feldman, 1997).

While I wouldn't go so far as to say that this closes the book on mutation–selection balance in infinite populations as a major player in the evolution of sex and recombination, the empirical work does restrict

its applicability to the subset of multicellular species with high genome-wide mutation rates and with a predominance of negative epistatic interactions. While this might seem like a disappointing ending, it really illustrates the best kind of evolutionary story: where theory clarifies what must be true for a hypothesis to work, and empirical data are brought to bear on these predictions. It is thus fitting that Charlesworth's paper be highlighted in this, the final issue of *Genetical Research* before its rebirth as *Genetics Research*.

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