TARGET REVIEW

A pluralist approach to sex and recombination

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Abstract

One of the greatest challenges for evolutionary biology is explaining the widespread occurrence of sexual reproduction and the associated process of genetic recombination. A large number of theories have been developed that provide a sufficient short-term advantage for sex to offset its two-fold cost. These theories can be broadly classified into environmental (or ecological) and mutation-based models. Traditionally, the different theories have been viewed as competing, and empirical work has attempted to distinguish between them. Here we highlight the advantages that may be gained from considering that multiple mechanisms (environmental and mutational) may be at work, and that interactions between the theories may be very important.

Introduction

One of the greatest challenges for evolutionary biology is explaining the widespread occurrence of sexual reproduction, and the associated process of genetic recombination (Williams, 1975; Maynard Smith, 1978; Bell, 1982; Stearns, 1987; Michod & Levin, 1988; Hurst & Peck, 1996). Asexual females can potentially produce twice as many daughters as sexual females, so that the ratio of asexual to sexual females should initially double each generation, resulting in a 'two-fold cost of sex'. In addition, recombination breaks up favourable gene combinations that have increased in frequency under the action of natural selection. Given these costs, we would expect natural selection to favour asexual reproduction in wild populations. However, it generally does not: sexual reproduction is widespread throughout the animal and plant kingdoms.

In order to solve this apparent paradox, a considerable number (>20) of theoretical models have been developed which purport to show conditions under which there is a sufficiently large short-term advantage for sex to offset a two-fold cost (Kondrashov, 1993). In this paper we are concerned primarily with models that provide a deterministic advantage to sex and recombination through the production of genetically variable offspring (Weismann, 1889). This can increase the efficiency of selection, and hence accelerate the increase in mean fitness (Kondrashov, 1993; Barton, 1995; Feldman *et al.*, 1997). These models can be broadly classified into two groups: (1) environmental (or ecological) models and (2) mutation-based models (Kondrashov, 1988; Maynard Smith, 1988b).

Environmental models suggest that sex accelerates adaptation to a changing environment by creating new gene combinations (Bell, 1982). The biological basis of such varying selection pressures may involve a variety of biotic or abiotic mechanisms (Haldane, 1932; Bell, 1982). Currently the most popular environmental hypothesis, the Red Queen, states that sex provides an advantage in biotic interactions (Bell, 1982; Bell & Maynard Smith, 1987). Usually, parasites are assumed to provide the antagonistic driving force in this coevolutionary dance (Jaenike, 1978; Bremermann, 1980; Hamilton, 1980, 1993; Seger & Hamilton, 1988; Hamilton *et al.*, 1990), though host immune responses may also do so (Gemmill *et al.*, 1997). The 'dance' results from time-lagged selection by coevolving parasites against common host genotypes, leading to sustained oscillations in host and parasite gene frequencies (Hutson & Law, 1981; Bell, 1982).

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The population-genetic basis of environmental models such as the Red Queen are still not entirely clear (Barton, 1995; Otto & Michalakis, 1998). Two general types of deterministic population genetic model have been developed, both of which rely on epistasis (nonadditive genetic interactions) between beneficial alleles. These environmental models assume that either: (1) selection (epistasis) fluctuates, so as to sometimes favour one gene combination, and sometimes another (Sturtevant & Mather, 1938; Barton, 1995), or (2) there is directional selection (or stabilizing selection with a moving optimum) on a quantitative trait, and weak diminishing returns epistasis between favourable alleles (the fitness increase due to two favourable alleles is less than the product of their individual effects) (Maynard Smith, 1988a; Crow, 1992; Charlesworth, 1993; Barton, 1995; Kondrashov & Yampolsky, 1996). Importantly, theory suggests that fluctuating epistasis can only provide an advantage to sex and recombination when the fluctuations occur over just the right time-scale, making it unlikely to apply in response to physical variation in the environment (Charlesworth, 1976; Maynard Smith, 1978; Sasaki & Iwasa, 1987; Barton, 1995). However, it has been argued that biotic interactions such as host–parasite coevolution might tend to produce fluctuations on the right time-scale (Nee, 1989). It is not clear to what extent the simulation models of host–parasite coevolution (e.g. Hamilton, 1980, 1993; Bell & Maynard Smith, 1987; Hamilton *et al*., 1990; Howard & Lively, 1994) provide an advantage to sex and recombination because of fluctuating epistasis, directional selection, or another process such as allowing allele frequencies to change more rapidly or preventing the stochastic loss of temporarily bad alleles (Barton, 1995; Otto & Michalakis, 1998; but see Peters & Lively, in press).

Mutation-based models (the mutational deterministic hypothesis) suggest that sexual reproduction is advantageous because it allows individuals to eliminate deleterious mutations more efficiently (Kondrashov, 1988). The mutational deterministic hypothesis requires that each deleterious mutation leads to a greater decrease in log fitness than the previous mutation (synergistic epistasis between deleterious mutations) (Kondrashov, 1982). When this is the case sexual reproduction increases the variance in the number of deleterious mutations that will be carried by offspring. The low fitness of individuals carrying above average numbers of deleterious mutations will then lead to a larger number of deleterious mutations being eliminated (Kimura & Maruyama, 1966; Crow, 1970). If the mutation rate per genome per generation is sufficiently high, then this process can fully compensate for the two-fold cost of sex (Kondrashov, 1982, 1984; Charlesworth, 1990). In contrast to environmental models, the mutation-based models are able to work in an unchanging environment.

Unfortunately, data capable of discriminating between these models are almost nonexistent (Bell, 1985; Kondrashov, 1993, 1994b; Hurst & Peck, 1996). The majority of empirical work in this area has been correlational and focused on the ecological hypotheses. In these studies the occurrence of sex or rate of recombination is examined, either across or within species, with respect to key ecological variables (e.g. Glesener & Tilman, 1978; Bell, 1982; Burt & Bell, 1987; Lively, 1987, 1992; Koella, 1993; Schrag *et al*., 1994; Jokela & Lively, 1995). As such, these studies have taken a strong inference approach (Platt, 1964), with an emphasis on finding predictions that discriminate among different hypotheses. In our view these studies have played an important role in the rejection of some of the environmental models (e.g. the lottery model of Williams, 1975; Young, 1981). However, because these studies are correlational, they are open to multiple explanations, and *post hoc* scenarios can be developed which allow the results to be explained by environmental or mutation-based models (Charlesworth, 1987, 1990; Hamilton *et al*., 1990; Kondrashov, 1993; Hurst & Peck, 1996). With some ingenuity almost any hypothesis can explain any ecological correlation, and in a later section we shall discuss a particular example. It would at present seem that ecological correlations may be incapable of convincingly discriminating between the currently favoured models. These correlations are nonetheless important because any realistic model of sex should be able to account for the well-known patterns of sex and recombination.

In this commentary, we consider the advantages that may be gained from using a pluralistic framework to consider and test models of sexual reproduction. By this we mean that the different mechanisms may act simultaneously, that their relative importance may differ between species, and that they may interact synergistically in a number of ways. In particular, we aim to emphasize how environmental and mutational theories can complement each other, and cover each other's weaknesses. This is not the approach that has been taken in the majority of previous papers, and we believe there are a number of reasons for this: (1) the different hypotheses reflect different approaches (ecology vs. population genetics) and have been viewed as competing; (2) previous empirical work has concentrated on finding predictions that discriminate among the theories; and (3) at a first glance, pluralism seems to be a cop out – indeed, it has been specifically criticised for impeding useful empirical work (Kondrashov, 1993). Our purpose here is to argue that a pluralistic approach offers a useful framework with which to consider the maintenance of sexual reproduction, because it emphasizes the most useful empirical work and the importance of interactions between the theories.

The advantages of a pluralistic approach

There are at least four advantages to be gained from taking a pluralistic approach. First, it is entirely plausible

that multiple mechanisms may be providing an advantage to sex, and/or that the different mechanisms may be important in different species or environments. Indeed, many (most?) traits that apparently arose once have been put to several different uses, or lost (e.g. gill arches, mammalian forelimbs). The factors maintaining sexual reproduction may be different from those which led to its evolution. Multiple selection pressures are the norm in evolutionary biology: for instance, we do not expect, nor do we find, that the same selection pressure is responsible for female-biased sex ratios in widely divergent taxa (Charnov, 1982). Widespread traits are often not adaptations with just a single function. In the discussion we consider the possibility that different mechanisms may be working even at different levels within the same species (e.g. the maintenance of sex and clonal diversity).

Second, more than one mechanism may be required to fully balance the two-fold cost of sex. Acting alone, each of the various theories requires extreme, and possibly unreasonable, assumptions in order to be able to fully explain the maintenance of sex. The mutation-accumulation theory requires that mutation rates are high (at least >1 per genome per generation; Kondrashov, 1988; Charlesworth, 1990; Redfield, 1994), that each deleterious mutation leads to a greater decrease in log fitness than the previous mutation (synergistic epistasis; Kondrashov, 1982), that the variation between loci in the extent of epistasis is not too great (Otto & Feldman, 1997) and that population sizes are large (Kondrashov, 1982; Charlesworth, 1990; Howard, 1994). The most popular environmental model, the Red Queen, requires that parasites have severe fitness effects on their hosts (May & Anderson, 1983; Howard & Lively, 1994) or that only the most healthy hosts are able to reproduce (termed rank-order truncation selection; Hamilton *et al.*, 1990). However, even if a model is not fully able to explain the two-fold cost of sex, it may play an important role. The pluralist approach emphasizes that it is just as important to determine the magnitude of the advantage of sex due to a particular mechanism, even if it does not balance the two-fold cost. Indeed, in some cases, such as when there is a cost to finding mates, the cost of sex may be substantially greater (or less) than two-fold (Bierzychudek, 1987; Jokela *et al.*, 1997). In a later section we discuss a specific example, showing how current data from plants are consistent with the importance of more than one mechanism.

Third, a pluralist approach shifts the emphasis of empirical work from the search for a discriminating prediction to parameter estimation. Given the pluralist assumption, the major task is to estimate the relative importance of the various mechanisms. This can only be done by testing assumptions of the different models, and estimating relevant parameters. Crucially, this approach does not exclude the possible conclusion that only one mechanism is responsible for the maintenance of sex.

Finally, different mechanisms may interact not only simultaneously, but synergistically (Manning & Thompson, 1984; Howard & Lively, 1994, 1998; Lively & Howard, 1994; Peck, 1994). This possibility can only be considered from a pluralistic framework. Given such interactions, the maintenance of sexual reproduction can be explained with much more reasonable assumptions than each of the theories acting alone (Howard & Lively, 1994). This possibility has only recently been seriously considered and we believe that it may be very important. In the next section we discuss some possibilities in detail.

An important point to note here is that we are not suggesting that all possible mechanisms and their interactions should be considered equally – over 20 theories have been proposed to explain sexual reproduction (Kondrashov, 1993). Many mechanisms require restrictive assumptions such as small populations or certain population structures, and so are likely to be of limited applicability (Maynard Smith, 1988b; Kondrashov, 1993). Others, such as the genetic repair hypothesis (reviewed by Bernstein *et al.*, 1987), have been argued against on both theoretical and empirical grounds (Maynard Smith, 1988b; Charlesworth, 1989; Szathmary & Kover, 1991; Mongold, 1992; Kondrashov, 1993). Our emphasis is on the types of deterministic mechanisms (environmental and mutation-based) that are able to work even in large panmictic populations, are most likely to be widely applicable and are generally believed on theoretical and empirical grounds to be the most feasible. In particular, we discuss how environmental and mutation-based mechanisms are particularly suited to interacting synergistically, and how they can cover each other's weaknesses.

The importance of interactions between theories

Interactions between mechanisms may greatly increase the advantage of sexual reproduction. In this section we present some possibilities, whilst noting that this is a largely unexplored area, both theoretically and empirically. In particular, we will show how environmental and mutational mechanisms may complement each other, covering each other's weaknesses. Such interactions suggest that the combined effects of the two mechanisms are likely to be greater than the sum of their parts, which would relax greatly the conditions under which sex is favoured. When we discuss interactions between environmental and mutational mechanisms we shall do so in terms of the parasite (or Red Queen) hypothesis for sex. We do this because it is the most favoured environmental hypothesis (Hamilton *et al.*, 1990; Ladle, 1992), and because previous theoretical work looking at interactions has been based upon this (Howard & Lively, 1994, 1998). However, most of the scenarios which we consider would also apply to other environmental hypotheses, such as other forms of fluctuating selection, and there are other

possible interactions (e.g. Manning & Thompson, 1984; Peck, 1994).

Mutations aid the Red Queen

As we have pointed out above, one problem of the Red Queen hypothesis is that it requires that parasites have severe fitness effects on their hosts (May & Anderson, 1983; Howard & Lively, 1994) or that only the most healthy hosts are able to reproduce (Hamilton *et al*., 1990). Another problem is that it does not select for sex *per se*, but for diversity, however it is generated (Lively & Howard, 1994). Consequently, clonal diversity is able to erode any advantage that sexual reproduction gains through the production of variable progeny. Clonal diversity could arise from repeated mutation of sexual individuals to asexual reproduction, or through mutation in asexual individuals.

One possible solution to these two problems is that mutation accumulation also occurs. Howard & Lively (1994) constructed a simulation model which allowed both host–parasite interactions and mutation accumulation to occur. Their model assumed that the fitness consequences of deleterious mutations were multiplicative, and so the Mutational Deterministic process was not operating. Instead, mutation accumulation occurred through Muller's ratchet, the irreversible decrease in fitness that can occur through the stochastic accumulation of deleterious mutations in finite asexual populations (Muller, 1964; Lynch *et al*., 1993). Acting alone, Muller's ratchet operates too slowly to provide a significant short-term advantage to sex (Maynard Smith, 1978). Howard & Lively (1994) showed that moderate effects of parasites combined with reasonable rates of mutation could more than balance the two-fold cost of sex. In the short term, parasites prevented the fixation of clones and the elimination of sex. In the long term, mutation accumulation led to the eventual extinction of clones. The accumulation of mutations in clonal lineages is enormously aided by parasite-driven oscillations, because the rate of mutation accumulation is enhanced during periods in which the clone is driven to low numbers by the parasite.

The model has recently been extended to allow for synergistic epistasis between deleterious mutations (Howard & Lively, 1998). The results showed that adding synergistic epistasis increased the advantage of sex at relatively high mutation rates ($U = 1.5$; where U is the genomic deleterious mutation rate per generation), made negligible difference at intermediate mutation rates ($U = 1.0$) and decreased the advantage of sex at relatively low mutation rates ($U = 0.5$). These results can be explained by the two consequences of adding synergistic epistasis: (1) by increasing the fitness cost of deleterious mutations it slows down and can even halt Muller's ratchet (Kondrashov, 1994a), and (2) it provides a purely deterministic advantage to sexual reproduction (Mutational Deterministic hypothesis). The first of these consequences decreases the advantage of sexual reproduction, while the second increases it. The relative importance of these two mechanisms will be determined by the mutation rate. At relatively low mutation rates (e.g. $U = 0.5$) the deterministic advantage will be small and so the most important consequence will be the slowing down of Muller's ratchet. In contrast, at high mutation rates (e.g. $U = 1.5$) the deterministic advantage will become large and so have a much greater effect than the slowing down of Muller's ratchet.

It should, however, be noted that the results of the model are likely to depend upon the assumption of a single class of mutations. In reality the fitness consequences of deleterious mutations are likely to vary (Keightley, 1994, 1996; Elena & Lenski, 1997; Keightley & Ohnishi, 1998). If, instead, a distribution of mutation effects is used, then Muller's ratchet continues to operate even with synergistic epistasis (Butcher, 1995). In this case we might expect synergistic epistasis to increase the advantage of sex over the whole range of mutation rates.

Perhaps ironically, this reasoning suggests that mutation accumulation is best able to aid the Red Queen hypothesis, and therefore the Red Queen works best when there is synergistic epistasis between deleterious mutations. We have argued above that, given a distribution of mutation effects, Howard & Lively's (1998) model would generally provide the greatest advantage to sex when there is synergistic epistasis between deleterious mutations. However, this model assumed a finite population that was small enough (10^3) for Muller's ratchet to operate. At very large population sizes the importance of Muller's ratchet will decrease, and so mutation accumulation will only help provide an advantage deterministically. This will only occur if deleterious mutations exhibit synergistic epistasis.

The Red Queen aids the Mutational Deterministic hypothesis

The Mutational Deterministic hypothesis has been shown to require high rates of deleterious mutation, at least greater than approximately 1 per genome per generation (Kondrashov, 1988; Charlesworth, 1990). However, most of the relevant models have assumed infinite populations and considered populations at equilibrium in mutation-selection balance, ignoring the dynamics of reaching this situation. Relaxing these assumptions can cause problems for the hypothesis. In particular, the initial number of deleterious mutations in a new asexual lineage is always likely to be lower than the equilibrium number, and will occasionally be much lower (Charlesworth, 1990). This becomes important at finite population sizes because an asexual lineage may be able to replace the resident sexual population before it accumulates enough deleterious mutations to balance the cost of sex (Kondrashov, 1982; Charlesworth, 1990; Howard, 1994). This possibility is further increased if

stochasticity is introduced in the rate at which populations grow and accumulate mutations (Howard, 1994). A consequence of these factors is that greater genomic deleterious mutation rates are required to be able to balance the two-fold cost of sex. For example, with moderate synergistic epistasis between deleterious mutations, a deleterious mutation rate of 2 is required for a population of size 10^4; a greater rate is required for smaller populations (Howard, 1994).

An ecological mechanism, such as the Red Queen, provides a number of possible solutions to these problems. First, it produces frequency-dependent selection and so slows down the spread of asexual clones, allowing more time for mutation-selection balance to be reached (Howard & Lively, 1994). Second, it reduces the fitness advantage of asexuals and so reduces the number of deleterious mutations required to reduce the fitness of the asexuals below that of sexuals. Third, it may speed up the rate at which an asexual lineage accumulates mutations, leading to a faster decline in fitness, and allowing mutation-selection balance to be reached more quickly. This will happen because frequency-dependent selection will drive a clonal lineage through population cycles, and the accumulation of deleterious mutations will be increased by the stochastic process of Muller's ratchet at the low points of these cycles (Howard & Lively, 1994, 1998). Fourth, by increasing the stochastic accumulation of deleterious mutations, mutation-selection balance may be reached at a higher number of deleterious mutations, and so a lower fitness. This is analogous to the fact that the equilibrium number of deleterious mutations in an asexual lineage increases with the number of deleterious mutations in the individual in which the lineage arose (Kimura & Maruyama, 1966; Charlesworth, 1990).

Moreover, a combination of both hypotheses may resolve another important challenge to the Mutational Deterministic hypothesis: explaining the ecological correlates of sex. The Mutational Deterministic hypothesis does not readily explain why, for example, there is more sex where parasites are more common (e.g. Lively, 1987, 1992; Schrag *et al*., 1994; Jokela & Lively, 1995). With *post hoc* modifications it may be able to address the correlates, perhaps by arguing that parasites are the factor that causes truncation selection against high mutation loads, but such patterns do not flow as straightforward predictions from the model. This is, however, a straightforward prediction of Red Queen models. As far as we are aware, the parasite models predict the majority of within- and between-host patterns of sexuality.

Synergism at the empirical level

Different mechanisms may also interact in their direct fitness consequences. For example, individuals with high mutational loads might be considerably sicker when infected with coevolved parasites than individuals with low mutational loads (Lively & Howard, 1994). Although it has yet to be formally modelled, such synergistic interactions are likely to provide a substantial advantage to sexual reproduction. In addition, this point illustrates how the different underlying mechanisms may interact to increase the extent of truncation selection. This is important because both the Mutational Deterministic and the Red Queen models work best under truncation selection, against deleterious mutations and parasite infection, respectively. Parasites may increase the form of truncation selection against mutations, and mutations may increase the extent of truncation selection against individuals infected by coevolved parasites.

Empirical evidence for the pluralist approach

Do we have any empirical evidence for more than one mechanism acting in a species? It seems reasonable that more than one mechanism is likely to be acting in a species: parasites are prevalent; they can have large effects on the fitness and population dynamics of their hosts; and host–parasite coevolution undoubtedly does take place (e.g. Toft *et al*., 1991; Grenfell & Dobson, 1995; Clayton & Moore, 1997; Dybdahl & Lively, 1998). In addition, mutations are ubiquitous, and are far more likely to be deleterious than they are beneficial (Crow & Simmons, 1983; Keightley & Ohnishi, 1998; see also Gillespie, 1991). However, there are few data measuring the importance of the different mechanisms in any species, let alone quantifying the importance of the different mechanisms in the same species.

The possible importance of more than one mechanism working simultaneously can be demonstrated, and speculatively quantified, by available data on plants. Kelley *et al*. (1988) and Kelley (1994) studied the perennial grass *Anthoxanthum odouratum* and demonstrated that the fitness of sexual progeny was 1.55 times greater than that of asexual progeny. This immediate fitness difference cannot be explained by the Mutational Deterministic hypothesis (Charlesworth, 1990) and so is likely to represent an environmental mechanism. Evidence suggests a role of viral pathogens transmitted by aphids (Kelley, 1993, 1994). Importantly, Kelley (1993) also determined whether parental clones were infected at the beginning of the experiment, and so showed that asexual progeny were more likely to acquire new infections. In order to balance a two-fold cost of sex, a further $2/1.55 = 1.29$ advantage to sexually produced offspring is required.

This remaining advantage can be supplied by the Mutational Deterministic hypothesis, given existing estimates of the genomic deleterious mutation rate in plants. Considering only the effects of deleterious mutations, the equilibrium fitness of an asexual population/lineage is

independent of the form of selection and equal to e^{-U}, where U is the genomic deleterious mutation rate per generation (Kimura & Maruyama, 1966). Given intermediate levels of synergistic epistasis between deleterious mutations, the equilibrium fitness of a sexual population is approximately $e^{-U/2}$ (Charlesworth, 1990). Consequently, the advantage to sexually produced offspring supplied by the Mutational Deterministic hypothesis is equal to $e^{-U/2}/e^{-U} = e^{U/2}$ (Fig. 1), and the deleterious mutation rate required to provide a fitness advantage a is equal to $2\ln(a)$. An advantage to sexual reproduction equal to 1.29 is therefore supplied by a deleterious mutation rate (U) of 0.51. Indirect estimates of the deleterious mutation rate from highly inbred plant populations suggest values in the range of 0.5–1.0 (Charlesworth *et al*., 1990, 1994; Johnston & Schoen, 1995), and so provide the required value. Other empirical investigations of possible multiple mechanisms are provided by McVean & Hurst (1997) and Zeyl & Bell (1997).

This section illustrates how, in practice, it may be easier to accept the pluralist approach with empirical data than to reject the theoretically simpler models such as the Mutational Deterministic or Red Queen hypotheses. This is particularly true because of the large confidence limits that must be placed on estimates of parameters such as the mutation rate, a subject that we shall return to in the discussion. Given this, as well as the additional insights that the pluralist approach provides (e.g. synergistic interactions between mechanisms and different mechanisms working at different levels), we believe that it does more than just make things more complicated in defiance of Occam's razor.

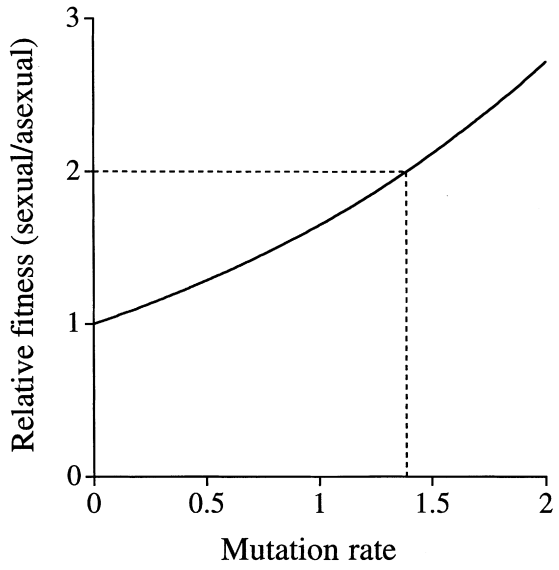

Fig. 1 The fitness advantage provided for sexual reproduction by the mutational deterministic hypothesis. Plotted is the relative fitness (at equilibrium) of a sexual population/lineage (with no cost of sex) divided by that of an asexual population/lineage against the deleterious mutation rate per genome per generation. The dashed lines show at what point this fitness advantage is able to account for a 'two-fold' cost of sex. Moderate synergistic epistasis between deleterious mutations is assumed (Charlesworth, 1990).

Discussion

Is a pluralistic approach a cop out? We believe that it is the most logically defensible approach, and have suggested a number of reasons why it is also likely to be the most useful approach. It may be required to explain the maintenance of sex, and it shifts the emphasis of empirical work away from the search for discriminating predictions to parameter estimation. Moreover, it emphasizes that the environmental and mutational mechanisms may interact synergistically in a number of ways and cover each other's potential weaknesses.

We have also suggested that, on a broader level, different mechanisms may work at different levels on related questions. For example, there are several studies that show apparent partitioning of resources among asexual clones (e.g. Vrijenhoek, 1979; Bolger & Case, 1994; Fox *et al*., 1996; Semlitsch *et al*., 1997), and it could be argued that these studies provide support for the tangled bank hypothesis, with different genotypes doing better in different environments. However, clonal coexistence and the maintenance of sex are somewhat separate issues. Consider a species such as the freshwater snail *Potamopyrgus antipodarum* that undergoes predominantly sexual reproduction in some areas, and asexual reproduction in other areas (Dybdahl & Lively, 1995; Fox *et al*., 1996). Where it occurs, sex may explained in part by the presence of coevolving parasites (e.g. Lively, 1987; Dybdahl & Lively, 1998). In areas where parasites are not present, clonal diversity may be maintained across different habitats by resource partitioning. If this is correct, then the answer depends on the question. If the question is: how do we explain the distribution of sex and the maintenance of clonal diversity across niches, then the answer almost certainly requires multiple mechanisms.

What needs to be done? Direct quantitative estimates of relevant parameters are vital. But this is not necessarily for the reason – popular in some quarters – that parameter estimates may enable particular models to be eliminated. A pluralist perspective suggests this is an overly optimistic view, true only for extreme values. For instance, Kondrashov (1993) has argued that an advantage of the Mutational Deterministic hypothesis is that it is easily falsifiable: if the genomic deleterious mutation rate is too low, the model cannot work. But unless it is extremely low (e.g. $\ll 0.1$), the crucial question is a quantitative one: how important is mutation pressure? Several estimates have placed a lower limit on the mutation rate in the range of 0.4–1.0 (Mukai, 1964;

Mukai *et al*., 1972; Ohnishi, 1977; Charlesworth *et al*., 1990; Charlesworth *et al*., 1994; Keightley, 1994; Johnston & Schoen, 1995; Deng & Lynch, 1997; Drake *et al*., 1998). This happens to be the range where the mutation rate would not fully balance the two-fold cost of sex, but would still provide a considerable advantage (Fig. 1). Moreover, empirical estimates of the mutation rate generally provide lower limits and have large confidence intervals (Keightley, 1998). Consequently, if the mutation rate is in the range of 0.4–1.0 then current empirical methodologies would not allow the Mutational Deterministic hypothesis to be easily falsified.

Similarly, if mutational effects turn out to be independent, the Mutational Deterministic hypothesis is dead. But if there is some synergism, the issue again becomes quantitative: given observed mutation rates and levels of synergism, how big is the role played by the Mutational Deterministic hypothesis? It could be argued that, in principle, parasite models could also be falsified, for example, if selection does not fluctuate. But if there is some fluctuation in selection, quantitative estimates are needed to determine the extent to which parasite pressure could, on its own or in combination with other factors, favour sexuality. Thus, while it may be relatively easy to rule out a model as a sufficient explanation of sex, it will require substantial amount of work to eliminate it as part of the explanation.

As well as parameter estimation it is also important to test the assumptions of the different models. For example, there is considerable experimental evidence showing that the amount of recombination both influences the response to selection and increases as a correlated response to selection (McPhee & Robertson, 1970; Flexon & Rodell, 1982; Burt & Bell, 1987; Korol & Iliadi, 1994). Similar work on deleterious mutations would be extremely useful. However, it should be noted that while these studies demonstrate that a certain mechanism can work, they do not quantify its importance under natural conditions.

There are several other general points that arise naturally from the pluralist standpoint. First, the importance of measuring fitness under as realistic conditions as possible cannot be overstated. The influence of any factors affecting fitness such as deleterious mutation or parasite loads are likely to vary enormously with the conditions under which fitness is measured (Dudash, 1990; Kondrashov & Houle, 1994; West *et al*., 1996). The relative contribution of different models, and of any interaction between them, is likely to similarly vary.

Second, to be of value in considering the relative importance of particular models, and any synergism between them, parameter estimates need to be derived from the same biological system. While we accept the desirability of being able to generalize, and agree that will only be possible once many different systems have been investigated, little progress will be made if we have estimates of mutation rates in a nematode, for example, and parasite-induced frequency dependence in a plant.

We also consider it highly important to estimate relevant parameters in sexual species. The form of selection must be different in sexual species than in species which are asexual or only occasionally undergo a sexual cycle. The mutation rate, for example, is generally selected to be lower in asexual species (Leigh, 1970; Kondrashov, 1995), and asexual lineages would not persist with a rate above 1.0–2.0 (Kondrashov, 1993). It is perhaps not surprising that the lowest estimates of the deleterious mutation rate have been obtained from largely nonsexual species (Kibota & Lynch, 1996; Keightley & Caballero, 1997). Similar arguments could be made that the form of epistasis between deleterious mutations is likely to differ between sexual and asexual species (Malmberg, 1977; Falush, 1998; Hurst & Smith, 1998; see also Szathmary, 1993), especially when asexuality is coupled with polyploidy, which is common in plants and animals (Bell, 1982). Environmental mechanisms could also be argued to differ between sexual and asexual species for similar reasons. Indeed, we have already suggested that even in a single species such as *P. antipodarum*, different environmental mechanisms may be responsible for the maintenance of sex and clonal diversity.

Finally, work on testing for synergistic epistasis between deleterious mutations has demonstrated the importance of developing theory for how experiments should be carried out (West *et al*., 1998). There is enormous scope for further work in this area, particularly with regards to the environmental models. In many cases, multigenerational experiments may be vital: one round of sex is often predicted to decrease mean fitness but increase its variance (Charlesworth & Barton, 1996; West *et al*., 1998). But as well as assisting in the development of effective experimental protocols, we see an important role for theory in assessing the conditions under which synergistic interaction between existing models can be most powerful. This may go a long way towards explaining the currently embarrassing existence of biparental sex, especially where the costs may be substantially more than two-fold.

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