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Recent advances in understanding of the evolution and maintenance of sex

Laurence D. Hurst and Joel R. Peck

The evolution of sex has been the focus of considerable attention during recent years. There is some consensus that the solution to the mystery is that sex either enables the creation and spread of advantageous traits (possibly parasite resistance) or helps to purge the genome of deleterious mutations. Recent experimental work has allowed testing of some of the assumptions underlying the theoretical models, most particularly whether interactions between genes are synergistic and whether the mutation rate is adequately high. However, although a variety of theories point out advantages to sex, most of them predict that a little sex and recombination can go a long way towards improving the fitness of a population, and it remains unclear why obligate sex is so common.

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Sex remains an enigma within a mystery. It is baffling for reasons other than the fact that, in a typical anisogamous species with no male investment in young, a female could have twice as many grandchildren were she asexual[1]. For example, it is curious that if one examines the phylogenetic distribution of sex, one finds that it seems to be quite the opposite of what one would predict with knowledge of the costs: in potentially isogamous groups (in which both sexes invest in offspring and hence where the costs of sex are much reduced) the frequency of asexuality seems higher than in anisogamous groups, where a much greater cost of sex is suffered. If sex is so great, then surely those organisms with a low cost should do it all the more frequently!

As has been the history of this debate for many years now, most of the work on the evolution of sex is theoretical, and the past 20 years have seen a veritable bloom of ideas and subsequent modifications of these. In general, however, from over 20 theories on sex[2] only two broad classes seem to predominate[3]. These are (1) that sex enables the spread/creation of advantageous traits, and (2) that sex enables the efficient removal of deleterious genes. This review will largely be restricted to consideration of these mainstream theories of sex.

Included within the first category is a general morass of theories (many of which have yet to be formally modelled) that suppose that sex is something to do with evading parasites (for references see Refs 2,4,5). These theories are unusual in so far as they are specific about the sorts of genes that are under selection (those affecting parasite resistance) and do not assume that the selective value of an allele is an intrinsic feature of that allele (i.e. what may be an advantageous allele at one moment may become deleterious when parasites have coevolved). Models incorporating both parasite effects and deleterious mutations provide (as might be expected) strong advantages to sex[6].

Despite our focus on the two categories of theories specified above, it is important to recognize that there is a variety of other ideas, many of which may deserve more attention than they are currently receiving. For example, meiosis seems to be important in resetting developmental programs and,

in ciliates, allows an escape from senescence (reviewed in Ref. 7). A sizeable body of ideas is centred on the notion that sex serves to enable genetic repair (e.g. see Ref. 8) but these have met theoretical[9] and empirical[10] difficulties. Theories about the initial evolution of sex and the possible role of selfish elements[11] have received a small but significant boost from genetic analyses in slime moulds[12] and yeast[13].

Sex and the advantageous allele

Many researchers have suggested that sex promotes the production and spread of advantageous traits. At least three different but related reasons are given for this. First, as pointed out by Weisman, Fisher and Müller, sex may be a means to create novel genotypes (putting mutant alleles that may have initially arisen in different individuals into one individual at the same or at different loci) (see Refs 14 and 15). A second and related advantage has to do with the observation that, in the absence of mutation, sexual populations have much potential phenotypic space that can be explored, while asexual ones are restricted to the minima and maxima present at any given time. By allowing the production of new combinations of genes, sex permits the population to explore space that was not represented in the previous generations. Thus, under some conditions, even if the direction of selection switches, a sexual population can respond effectively[16,17].

Thirdly, as pointed out by Fisher, sex may facilitate the spread of advantageous alleles simply because it allows these alleles to escape from the genetic surroundings in which they initially arose. For example, consider a situation where deleterious mutations arise repeatedly. Deleterious mutations can produce substantial variation in fitness; under asexuality, it turns out that this implies that only the fittest individuals (i.e. those with the fewest deleterious mutations) have any hope of having descendants in the population in the distant future. As a result, a beneficial mutation must arise among one of the fittest few, or it is likely to be dragged into oblivion by the deleterious mutations with which it was initially associated (for references see Ref. 18). This is not, however, the case under sexual reproduction. Recent calculations have shown that this effect can be very strong, and sex can decrease the probability of loss of a beneficial mutation by several orders of magnitude[18].

Sex can have a similar salubrious effect on the spread of beneficial mutations when frequency-dependent selection is at work (for discussion and references see Ref. 19). For example, consider a haploid population where a stable polymorphism has been established at a particular locus as a result of frequency-dependent selection. Any beneficial allele that arises at another locus must inevitably be associated with one of the alleles subject to frequency-dependent selection. Therefore, spread of the advantageous allele will also force a change in the distribution of alleles at the frequency-dependent locus, and this forced change is bad for fitness. Sexuality allows the initial associations to be broken up, and so the difficulty does not arise[19].

In sum, the above results suggest that sex may be an important means to enhance the rate of adaptation. In severe contrast to this view, Eshel has argued that sex may be advantageous because it prevents rapid evolution[20]. It is argued that recombination breaks up favourable gene combinations more often than it creates them. Sexual populations can hence glide over short-term selective effects and be largely unaltered, whereas asexual populations tend to respond dramatically. The net effect is that sex stops the population from careering headlong in a direction forced by short-term selection that may be counter to long-term survival[20].

Eshel's argument depends on the assumptions that: (1) individuals with appropriate alleles exist in the asexual population; (2) that these alleles are not subject to frequency-dependent selection (which would limit an allele's spread); and (3) these alleles are not bogged down in a sea of deleterious mutations. The last two assumptions (particularly the last) seem especially restrictive to us and hence we would suggest that, typically, sex will tend to enhance the rate of adaptation.

Can we test this proposition? One test is to ask whether a reduced rate of recombination and/or outcrossing reduces the response to directional selection (and vice versa). Importantly, in *Drosophila*, a reduced recombination rate does indeed retard the response to selection[21]. In addition, there is phylogenetically limited evidence that the action of directional selection also acts to favour an increased recombination rate (as predicted[22]), in that domesticated mammals (effectively those under strong directional selection) apparently have unusually high recombination rates[23] (see also Ref. 24).

Escaping parasites

If a population lives in an environment that does not change for very long periods, we can expect that its rate of adaptation will eventually become very slow, whether the species is sexual or asexual. The above arguments hence typically require that the direction of selection must be changing.

Perhaps significantly, both those that hold that selection increases the rate of adaptation, and those that argue that it slows it, agree that, if the main source of mortality is short-term environmental change, sex is likely to be advantageous. While the 'rapid change' models emphasize the fact that sexual populations can respond to the alternating selection pressures by creating new genotypes, Eshel emphasizes that the change is not so fast as to leave the population unable to respond to changes in the near future.

One of the most popular mechanisms of environmental change that has been invoked by evolution-of-sex researchers concerns parasites. Parasites can produce pressures that favour a constant turnover of genotypes because they are thought to engage in 'evolutionary arms races' with host populations, which leads to the most common host genotypes becoming disfavoured, while rare host-genotypes become advantageous. These observations may explain the importance of sex as regards directional selection. In addition, they raise the point that parasites favour selection for fluctuating linkage disequilibrium, a state that can be facilitated by sex.

In general, support for the parasite model comes from many directions but is largely correlative and inferential[4,5]. For example, that there appears to be a North–South gradient in the variance of breeding values, with the more southerly populations showing a considerable excess in breeding value variance over the mutational prediction, is consistent with the theory because parasite prevalence also tends to be higher in the tropics[25]. There may, however, be alternative explanations and there are probably numerous exceptions (W.D. Hamilton, pers. commun.).

Support for the assumption that parasites are important as selective agents comes from comparative molecular evidence showing that components of the immune system are subject to natural selection (e.g. see Ref. 26). A comparison of the rate of evolution of two classes of protein (kinases and immunoglobulins) that both have brain-specific and immune-specific members, reveals for both classes of protein that immune system genes evolve faster[27]. An analysis of 363

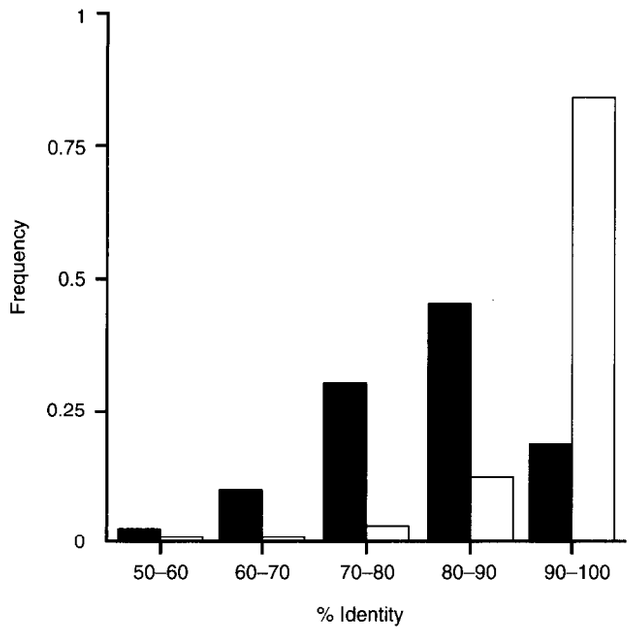

Fig. 1. The percentage protein identity of genes from the mouse–rat comparison. The genes are separated into those that are components of the immune system (black bars) ($N=46$) and those that are not (unshaded bars) ($N=317$). Included within the immune set are a broad variety of genes (number of each type in brackets), including the immunoglobulin family genes and the proteins that bind to them (12), components of complement (2), immune-related antigens (7), interleukins, their regulators and their receptors (7), lysosomal components (3), MHC components (1), interferon-related genes (3), inflammation-specific genes (3), T-cell receptors (3), platelet-related factors (2) and genes implicated in the control of opportunistic infections or with known resistance effects (3). Within the control set is a large variety of genes, from those coding for structural proteins to transcription factors, oncogenes and a variety of metabolic enzymes. The two distributions are highly significantly different (Mann–Whitney test: $P<0.0001$). In addition, the effect can be shown to be independent of differences in the mutation rate of immune and non-immune genes, despite the fact that immune genes tend to have a higher mutation rate. *Data from Ref. 60, analysis by L.D.H.*

proteins in the mouse–rat comparison suggests that rapid evolution of components of the immune system (not just kinases and immunoglobulins) is the rule and not the exception (Fig. 1). The same may be true of the antigens presented by parasites (see e.g. Ref. 28). Thus, it may well be that parasites produce much of the selection for novelty experienced by organisms, and thus they provide the environment necessary for the evolution and maintenance of sex.

A further means to test the parasite hypotheses is to enquire as to whether they can explain persistent asexuals. Asexuals should be common in situations in which they have no problems with parasites. But what species have no problems with parasites? Recent work has suggested that a correct answer might point to three sorts of organism. First, those organisms with relatively short generation times (when compared with their parasites), second, those that may be able to maintain heterozygosity without sex, and third, those species with particular dispersal forms in highly structured populations.

Fast-reproducing organisms, even if asexual, may be less vulnerable than slow reproducers to coevolution with parasites, because the extent to which the parasites can catch up with the hosts is reduced. That isogamous organisms tend to be unicellular and reproduce relatively quickly may go some way to explain why isogamous organisms tend to have more asexuality than expected. One further component of this escape is that the division of a single cell can result in one of the progeny cells inheriting all the parasites (owing to sampling), and hence the other cell can initiate a parasite-free lineage. The efficiency of lineage purification by this means should increase as the rate of host-cell division goes up.

It is unclear whether this rate-of-reproduction effect can explain the persistence of ancient multicellular asexuals (see Judson and Normark, this issue). One possible solution, that finds some empirical support[29], supposes that some asexual lineages may, at least in the relative short term, be able to maintain high levels of heterozygosity without having sex and may hence be able to maintain parasite resistance. Given the possibility of hybrid vigour, this sort of effect seems particularly effective at explaining incidences of asexuality associated with hybridization[29].

A further novel solution that has recently been ventured is that dispersal may allow an escape from parasites. The logic is relatively simple: if I am an individual with parasites, and if I can disperse after having got rid of my parasites and go to a new sub-population in which the parasites have not co-adapted to me, then I do not need to have sex[30,31]. The model explicitly assumes that parasites do more harm if co-adapted with the host, which, though not generally true, is probably the case in some instances. So, are ancient asexuals dispersers, do they have means to rid themselves of parasites and are their populations structured?

The answers are unclear. Many asexuals have dispersal phases in which the dispersing form is resistant to some extreme character (e.g. heat, drought, and so on) that could be interpreted as the conditions under which parasites may be inhibited[30]. The data are, however, limited, and numerous counter-examples can be provided[32]. In support, at least one thorough analysis has found that in plants the rate of recombination (assayed by indirect means that are not necessarily accurate) goes down as dispersal distance goes up[33].

Sex and the mildly deleterious mutation

An alternative interpretation of the finding in Fig. 1 is that the majority of genes are under stabilizing selection most of the time (most genes have a low ratio of non-synonymous to synonymous substitutions and evolve slowly). This then would be consistent with those models for sex that see the main function of selection as a means to maintain the *status quo* (i.e. to purge the genome of deleterious mutations), rather than to promote novelty. Models of genomic purging may either be deterministic[34] (i.e. those in which sex is advantageous even in infinitely large populations) or stochastic (e.g. Müller's ratchet). Stochastic models require finite populations.

Several experimental observations of RNA viruses are consistent with the operation of Müller's ratchet (e.g. see Ref. 35). However, these observations may be heavily confounded by bottleneck effects. Furthermore, as these viruses have very high per-locus mutation rates and possibly a different form of epistasis, these demonstrations may not be very informative when extrapolating to DNA-based organisms.

Synergistic interactions – when Müller's ratchet stops and determinism starts?

Müller's ratchet proceeds if all individuals with the minimum number of deleterious alleles are randomly lost. Classical formulations of Müller's ratchet assume that the effect on fitness of a new mutation is independent of the number of mutations in the genome. Under this assumption, analysis has shown that the rate of genetic deterioration either remains constant, or grows if accumulation of mutations leads to the decline of the population size[36]. This

conclusion has, however, been shown to be sensitive to the assumption of independence of selective effects of alleles[37,38].

Interactions between deleterious mutations may be synergistic. At the extreme, this would be truncation selection: having a few mutations does not affect your fitness but have more than a critical number and you are dead (or infertile). If deleterious alleles have synergistic fitness effects, then, as the ratchet advances, the frequency of the best available genotype will necessarily increase, making its loss less and less probable. As a result, sufficiently strong synergistic epistasis can effectively halt the action of Müller's ratchet[37]. Instead of being driven extinct, a finite asexual population could then survive practically indefinitely, although with lower mean fitness than would be the case without random drift. The generality of this result is, however, unclear. The analysis, for example, ignores variation in the size of mutational effects. If very small mutations are allowed, then the ratchet need not be arrested under synergistic epistasis[39]. (For other recent work on Müller's ratchet see Judson and Normark, this issue.)

While synergistic epistasis may favour asexuality by slowing Müller's ratchet in finite populations, it can also provide an advantage to sex in the deterministic models (assuming an adequately high mutation rate). The key feature of sex in these models is that it is a means to maintain a high variance in mutation number and by so doing ensures that one death can remove numerous deleterious alleles[34]. This is so because sex allows the production of recombinants, some with many deleterious mutations, some with few. Selection may then remove those that have more than the critical numbers of mutations. However, with the high variance, many of these selective deaths remove a relatively large number of deleterious mutations. Selection reduces variance, but this is soon restored in the next round of sexual reproduction.

In an asexual population, on the other hand, theory predicts that, unless the rate of mutation is very high, the variance in the number of mutations will be very low, and that most individuals who are eliminated by selection will have only one mutation in excess of the critical number. As a result, more individuals will have to die than in a sexual population to eliminate the same number of deleterious mutations. This implies that sexual populations will be more fit than asexual populations. To compensate for the twofold cost of sex, this deterministic model requires that the per-genome mutation rate be sufficiently high. The usual value cited is one mutation per-genome per generation[34]. The relevance of this precise value is unclear, however, as relaxation of some of the assumptions of the derivation leads to the necessary value being significantly higher[40]. We may perhaps conclude that if the mutation rate of obligate asexuals is <1 the deterministic deleterious mutation argument should be rejected as an explanation for sexual reproduction (though, as we shall see, this condition may be too weak).

But are interactions synergistic and is the mutation rate sufficiently high? The first problem has very recently been ingeniously addressed by de Visser and colleagues[41]. They reasoned thus: if sex is randomizing, then cross two strains and the number of mutations should be normally distributed. However, add on the effect of epistasis and the distribution of log-fitness should be skewed. If the epistasis is synergistic then the fitness distribution will be skewed in the direction of low fitness (negative skew). So if one can investigate the distribution of fitness of the progeny of a cross then one can assess the nature of interactions between genes.

De Visser *et al.* have applied this methodology to two strains of *Chlamydomonas* that have been kept in the laboratory without sex for over 60 years (and are hence expected to have accumulated mutations). Crosses were made and the growth parameters r and K were examined as measures of fitness. The results were, perhaps, not as cut and dried as might be liked, but reveal that log K is negatively skewed (consistent with synergism). It is unclear whether log r is skewed (there is a tendency to a negative skew). Given the ambiguity of the results produced by de Visser *et al.* and by other researchers (for an example and discussion see Ref. 42), we feel that the evidence for synergistic epistasis is inconclusive and certainly warrants further investigation.

Mutations in males and microbes

And what of the mutation rate? Is it sufficiently high? And how deleterious are they? Do the ancient asexuals have particularly low mutation rates? Unfortunately we have no good answers to these questions[43]. In *Drosophila*, the genomic mutation rate is probably >1 (for discussion, see Ref. 3). Recent analysis in two species of largely self-fertilizing annual plants provided minimal estimates of mutation rates of 0.24–0.87 per sporophyte genome per generation, but confidence intervals exceeded 1.0 in each of the four populations[44]. Other recent estimates from plants[45] put the value as being not less than about 0.5. These values are all very close to the margin at which obligate sexual reproduction becomes advantageous (in comparison with obligate asexuality), according to Kondrashov's formulation of the 'mutational deterministic' hypothesis[2].

Perhaps more troublesome to this latter argument is the finding that in a variety of organisms[46] (*Neurospora*, yeast, phage and bacteria) there appears to be an almost constant per genome per DNA replication mutation rate (between 10^{-2}–10^{-3}) (see Fig. 2). These organisms, however, most probably differ in the rate at which they recombine. Given that they have the same mutation rate, rates of recombination appear then not to be determined by mutation rate alone. This is contrary to expectations of the mutational deterministic hypothesis. But this finding should not be overstated. If the outliers to the distribution are included, the data (Fig. 2) could alternatively be interpreted as showing that the more sexual species (*Neurospora* and yeast) have a higher mutation rate. Were this correct then these data may be more or less consistent with theory.

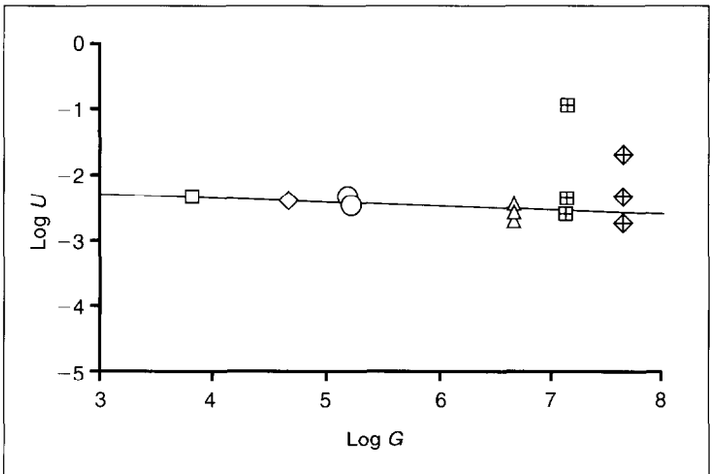

Fig. 2. The relationship between the log of the genome size in base pairs (log G) and the log of the per genome mutation rate per DNA replication (log U). The two high points (one each from *Neurospora* and *Saccharomyces*) are claimed to be outliers. The slope of the line, omitting the outliers is slightly negative (−0.05). Species (left to right): phage M13 (square), phage I (diamond), phages T2 and T4 (circle), *Escherichia coli* (triangle), *Saccharomyces cerevisiae* (square with cross), *Neurospora crassa* (diamond with cross). *Data from Ref. 46.*

What we can say with more certainty is that, in a number of species [particularly in mammals (e.g. see Ref. 47)], the mutation rate appears to be higher in males than it is in females. For those theories that see sex as a means to get rid of deleterious mutations this may be a problem[48]. If most mutations are in males, then why do females not simply give up mating with males and reproduce asexually? The arguments centred on the idea that sex is a means to enhance the spread of advantageous alleles have fewer problems with the finding.

The extent to which enhanced male-mutation rates is a problem to the deleterious-mutation arguments is unclear. First, it may be the case that even with a high male mutation rate, the mutation rate in females may still be too high to allow asexuality to be permissive. Indeed, if the option of asexuality is not viable, it might actually be the case that, because males have a high mutation rate, regular sex becomes an absolute necessity. Second, the generality of higher mutation rates in males is uncertain. There is little or no effect in *Drosophila*[49], and in general, we know of no supportive data outside of mammals. Perhaps, then, this problem should not be overstated.

More particularly, the debate should not be centred around mammals, as mammals do not really have the option of being asexual. This restriction is probably a consequence of genomic imprinting (a system in which certain genes switch on only if inherited from a particular sex). Necessary genes expressed from the paternally derived chromosomes will not be expressed in parthenogenetically derived offspring. Thus, asexuality is apparently not possible for mammalian species.

A little sex may go a long way

If imprinting really does prevent the creation of an asexual mammal, then to ask why mammals are sexual when there is a twofold cost to sex is to pose the wrong question. Is this the only case within the debate in which the question has not been properly cast? Possibly not. Most of the published theoretical work on the evolution of sex compares an obligately sexual population with a population that is wholly asexual (for exceptions see Refs 15, 18 and 50). The two populations are typically assumed to be reproductively isolated. If, after taking the twofold cost of sex into consideration, the obligately sexual population is more fit than an entirely asexual population, then the model is considered to have explained obligate sexuality. However, obligate sex and obligate asexuality are not necessarily the only possible options. In several species, reproduction is sexual and asexual (reviewed in Ref. 32).

The dearth of models to explain the existence of such species is all the more remarkable when one considers that these species' very existence has been central to Williams' 'balance' argument. Williams suggested that the stable maintenance of sex and asex within a species implies that sex must have short-term benefits for sexual reproduction, and hence that group-selection models of the evolution of sex were invalid[51].

As the cost of sex can be expected to increase approximately linearly with the proportion of progeny that is produced sexually, we should ask how much sex is optimal? Will a little sex go a long way? Only a few models suggest that frequent sex and recombination is beneficial. The advantages of recombination in freeing a beneficial mutation from its deleterious surround may be one example[18]. For the most part, however, analysis of typical evolution-of-sex theories suggests that most of the benefits of sex accrue when only a small fraction of the offspring are produced sexually.

It appears, for example, that the difficulties created for asexual species by Müller's ratchet can be largely alleviated with a very low rate of sex-induced-recombination[15,38]. The same is true for the problem of interference between beneficial mutations[15]. Similarly, a little sex should alleviate the problems associated with asexuality under frequency dependence[19]. A little sex is very efficient at increasing the rate of incorporation of beneficial homozygotes[52] and in bringing together advantageous alleles at different loci[52]. In addition, calculations by Joel Peck suggest that, in the absence of very high rates of mutation, most of the benefits of sex described by the mutational deterministic hypothesis can be obtained if only a small fraction of the population reproduces sexually. Even if both the expression of deleterious mutations and the effects of parasites are included, partial outcrossing is stable over a large region of parameter space[53]. The best strategy in a between-species ecological contest appears then for a species to produce just a small fraction of offspring sexually, and the rest asexually. It is also not understood why crossing-over is so frequent, particularly in organisms with very many chromosomes.

Even more rare than models that consider competition between partially asexual species and obligately sexual species are studies that allow for within-species variation in the tendency to reproduce sexually, with some types producing some offspring asexually and others sexually, while others are obligately sexual. We are only aware of one example of this sort of study[50] and it is another case where obligate sex appears unlikely in the absence of extreme conditions.

Is sex a one-way street?

Despite the foregoing considerations, the problem of partial sex may be more apparent than real. It may be that there are mechanisms that make a simultaneous mixture of sexual and asexual reproduction very unstable. If this is so, then we need not be worried by the Williams' 'balance' argument – a little sex may tend to lead to obligate sex.

For example, if sex makes the removal of deleterious mutations more efficient, then an increment in the rate of sex may lead to the evolution of a diminished proof-reading activity during replication or for reduced accuracy of repair. Hence, a little sex may lead to a higher mutation rate, making the reversion to asexuality harder (for related hypotheses see Refs 4, 54). Note also that a modifier associated with the above features is not only associated with higher fitness owing to the removal of some of the costs of fidelity but, because of recombination, it need not remain as closely associated with the resulting new mutations as would be the case under asexuality.

An alternative possibility is that evolutionary processes give a selective advantage to individuals or groups in which viable asexual mutants are extremely unlikely. Such a process has been outlined by Nunney[55]. He assumes that asexuals are more likely to arise in some sexual lineages than in others and that asexual lineages are subject to a higher rate of extinction or to a lower rate of speciation than sexual species. As a result, sexual lineages that have a relatively low probability of giving rise to asexual mutants are favoured by evolution over the long term. Nunney also uses models to examine the idea that sex can be maintained by group selection, and his conclusions are more favourable to this possibility than previous discussions[51].

That there are blocks to asexuality is increasingly being realized, and their mechanistic basis becoming better understood. The mechanisms are diverse and come down to quirky details of biology. The evolution of imprinting in mammals, touched on briefly above, would be one example. It

seems probable also that the absence of parthenogenesis in gymnosperms is a result of the need for paternally derived organelles in this taxonomic group.

Likewise, incidences of cytoplasmic bacteria that manipulate reproduction in various wasps, forcing the production of parthenogenetically derived females, are largely restricted to inbred wasps, not the outbred ones. Being haplodiploid, wasp eggs can typically develop without fertilization into haploid males. The bacteria act by preventing the first cleavage division of a haploid egg so rendering the zygote diploid. In inbred wasps diploidy *per se* is adequate to make a female. In contrast, in outbred wasps heterozygosity is required to make a female, hence, the strategy of blocking first cleavage would result in a diploid male.

In some cases, there appears to be a partial block to asexuality, but the reason is obscure. For example, it has been estimated that in many insect species, for some unknown reason, parthenogens produce only about 60% of the progeny of sexuals[56]. If this is generally true then, brooding, and the ability to replace unfit progeny with fit ones, might well be a predisposing factor to the invasion of parthenogenesis, as appears to be the case in various aquatic invertebrates[57]. It is most probably the case that reproductive compensation in general provides the conditions for the invasion of parthenogenesis.

However, we know of no evidence to suggest that the evolution of these blocks (absolute or otherwise) to asexuality were the consequence of selection in favour of sexuality. They are probably better interpreted as side products of selection on something else. It is also unclear whether, as Nunney hypothesized, those lineages for which the reversion to asexuality is problematic are more successful lineages (but this should be amenable to comparative analysis).

In sum, it remains unclear as to whether partial sex will tend to lead to obligate sex. Perhaps then it is still necessary to consider the invasion of obligate sexuality by partial sexuality. However, it should be possible to resolve this matter in a relatively straightforward manner. One needs to determine whether substantial within-species heritable variation for the proportion of sexually-reproduced offspring is common, and whether such variation allows for selection to increase the proportion of asexually-produced offspring without immediately incurring deleterious pleiotropic effects. If one can answer both questions in the affirmative, then Williams is right, and any theory that cannot show how obligate sex can win in the face of within-species competition from partial asexuals is flawed. Similarly, if one can show that competition between partially sexual and obligately sexual species is common, then the value of models that fail to consider such competition must be questioned.

The search for the discriminating prediction

One of the great struggles in the evolution-of-sex literature is to find a prediction that is truly discriminating between hypotheses. As Hamilton *et al.* note, most of the conditions required by the parasite hypotheses are those required by the mutation–purification hypotheses[4]. Similarly, the two sets of theories provide alternative explanations for the high frequency of isogamous asexuals: this may be explained in terms of the ability to be rid of parasites, the reduced probability of the click of Müller's ratchet in larger populations (which *r*-selected/small organisms tend to have) or by evoking the idea that much sex may be covert in these populations or that, for some reason, the per-genome mutation rate may be low (see Fig. 2). Likewise, the data on the tropical tendencies of sex may be a mutation rate effect if this is affected by temperature. Is then the prediction that asexuality and dispersal should be correlated a prediction that is unique to the parasite hypothesis? Unfortunately not.

Recent work suggests that, when dispersal is limited, populations may suffer from an increased frequency of deleterious mutations[58]. This is because low dispersal leads to competition between siblings, and siblings tend to be similar in competitive ability. Similarity among competitors makes competition inefficient at removing deleterious mutations. This problem is worse under asexuality, as the offspring of an asexual mother will be clones, and thus more similar to each other than the offspring of a sexual mother. When dispersal is strong, on the other hand, the problem disappears, as siblings rarely compete. Thus, we have a second, and quite different reason to expect a correlation between dispersal and asexuality.

The lack of discriminating predictions is one of the great problems with the evolution-of-sex literature. Perhaps progress can be made most quickly by focusing on the assumptions of the various theories, rather than on the predictions of the ecological correlates of sexuality. Thus, for example, it may be more fruitful to study mutation rates, epistasis, and the details of host–parasite relations than to try to use simple models to predict the geographic distributions of sexual and asexual species in a complex world.

It is perhaps worth noting that, to a large extent, the debate between the hypotheses based on genomic purging arguments and those centred on adaptive evolution is no different from the debate on whether selection's main activity is to maintain the *status quo* or to promote novelty. It may be that there are lessons to be learned from the latter debate.

The future

The big theoretical problem seems to be to understand, not why organisms have sex, but rather why they have sex and recombination so very often. That is to say, why don't more species reproduce asexually most of the time, with only occasional bouts of sex? Experimentally, the clearest hope for the future lies in testing existing models. Investigation of the prevalence of synergistic epistasis should be a priority and the methodology of de Visser and colleagues opens a new avenue in this regard. Similarly, measures of mutation rate may provide the data by which the mutational deterministic hypothesis may live or die. Measures of mutation rate are hence another clear priority, and a novel protocol has been outlined by Kondrashov and Crow[59].

What of the parasite hypotheses? The real weakness of these ideas is that they seem to make no unambiguous predictions upon which the theory may fail. Nevertheless, we find the comparative evidence in favour of these hypotheses moderately compelling (and often the mutational hypotheses struggle to explain the results). The evidence for rapid evolution of immune system genes lends credence to some of the underlying assumptions of some formulations of the parasite hypothesis. The development of strong and unambiguous predictions of the model would be an important next step.

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