

COMMENTARY

An even broader perspective on sex and recombination

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An historical note: why we needed the paper of WLR

Understanding why sexual reproduction in eukaryotes is so prevalent is a hard problem, and it has gone through a progression of stages that are typical for work on hard biological problems. First, a pioneer suggests a plausible solution, usually very general and not rigorously defined because the theory surrounding the problem has not been fully developed. Other pioneers may add competing but similarly broad and fuzzy theories. As interest in the problem spreads and the theory in which it is embedded matures, more detailed theories about more specific mechanisms are proposed; these are often presented as alternatives because of scientists' desire to be the one who solved the problem ... the only one. The new theories become more and more detailed as the available theory space is used up. Occasionally, someone sits back and looks for a more general solution that includes all the detailed models as special cases. And often someone else comes forward and points out that many, if not most, of the models may be operating in nature, in different species or even in the same one.

So it has been with the question of why sexual reproduction is so prevalent among eukaryotes (Mooney, 1992). Early hypotheses, such as Weismann's (1891) that sex facilitates evolution by increasing genetic diversity, were necessarily vague and difficult

to evaluate because they were devised in the absence of any real understanding of transmission genetics or population and evolutionary genetics. More sophisticated hypotheses appeared after the development of Mendelian genetics and population genetics. An important example is the hypothesis of Fisher (1930) and Muller (1932) that sex facilitates natural selection for advantageous mutations, extended to selection against detrimental mutations by Muller in 1964. This was followed in the 1970s and 1980s by a proliferation of models with increasing sophistication and detail, but of decreasing generality. The books of Williams (1975), Maynard Smith (1978) and Bell (1982) contributed to the proliferation of models directly and also indirectly by making the field more popular. We now have models for organisms with many different permutations of finite or infinite population size, advantageous or detrimental mutations, positive or negative epistasis or no epistasis, and a variety of different reproductive patterns and ecological niches. Unfortunately, the numerous models are often presented as mutually exclusive and individually sufficient to explain the prevalence of sex in most or all organisms.

Few authors have asked if there might be a more generally applicable model that subsumes most or all of the detailed models as special cases (for two exceptions, see Felsenstein (1974) and the review by Barton & Charlesworth (1998)). Even fewer have combined the detailed models to see what happens when two or more are operating simultaneously. West, Lively and Read (1999) (WLR hereafter) have done that. They are to be applauded for emphasizing that at least some of these competing hypotheses are not mutually exclusive, and for showing that they may be more powerful, as well as more realistic, when combined.

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The contribution of MR

WLR focus on population genetic models that give sexually reproducing individuals a selective advantage over asexual individuals that is sufficient to overcome the two-fold cost of sex. They initially say that they will focus on deterministic models, because they believe that the inclusion of stochastic processes restricts the generality of a model. They divide deterministic models into two classes, mutational and environmental, and say they will look at interactions between the mutational deterministic and parasite-driven Red Queen hypotheses as representatives of the mutational and environmental classes. I am dubious about their reasons for choosing these models, but it does not matter because the models they actually consider (Howard & Lively, 1994, 1998) combine host-parasite interactions with stochastic processes such as Muller's ratchet in finite populations. This is unfortunate from a truth-in-advertising standpoint, but it is probably wise scientifically. Many organisms with very large populations lead very uncertain lives and have a high variance in offspring number; moreover, the ratio of effective population size to the actual size (N_e/N) decreases as N increases (Pray *et al.*, 1996). I doubt that any approach to the evolution of sex that ignores stochastic effects of population size can be very general.

WLR's combined models give a larger advantage to sex than either model alone in many conditions. The advantage can be greater than two-fold, sufficient to overcome the cost of sex. WLR argue that the analysis of multiple models is important because it may be necessary to explain the maintenance of sex. I agree; it seems extremely unlikely that any of the existing detailed models can explain the maintenance of sex in all eukaryotes. Suppose, for example, that we had enough information about the rates, fitnesses and epistatic interactions of mutations in many different organisms to convince ourselves that the mutational deterministic model could in principle explain the maintenance of sex everywhere. This would not prove that it is the only factor involved; it would not prove that Red Queen interactions with parasites made no significant contribution to the maintenance of sex, or that Muller's ratchet did not routinely extinguish small asexual populations. It would not even prove that these models were less important than mutation accumulation; they might contribute more to the fitness differential between sexuals and asexuals than deterministic mutation accumulation. Moreover, it ignores the fact that these models might interact so as to change the parameter space in which they are effective.

I do worry about one aspect of interacting models. WLR note that 'it may be easier to accept the pluralist approach with empirical data than to reject the theoretically simpler models' and appear to see this as an advantage. The flip side of this is that multiple interacting

mechanisms may be difficult to reject. There may be no way around this; I suspect that so many biological and ecological variables affect the selective value of sex that it will require an immense amount of work to identify the important ones and show which detailed model(s) are operative for any one group of organisms.

A broader perspective

WLR's work should broaden our perspective on the evolution of sex to include interactions between the various detailed models, but I believe that we need to extend the perspective in at least two more dimensions.

Not all organisms are animals or plants

The majority of theory and observation on evolution in general, and on the evolution of sex in particular, deals with vertebrates, insects and plants. This is perhaps understandable, because these organisms have both aesthetic and economic impact on humans. Nevertheless, any general theory of the advantage of sex requires a broader phylogenetic perspective. Invertebrates, fungi and eukaryotic micro-organisms have very different and diverse life styles, and the differences may provide insights into the advantages and disadvantages of sex. Many do not have a two-fold cost of sex. Nevertheless, asexual reproduction is common among these groups, and the amount and effectiveness of sex varies greatly. Many of them alternate long periods of asexual reproduction with bouts of sex. Some are basically clonal in spite of obligate sexual reproduction, suggesting that they show extreme inbreeding (e.g. Rich *et al.*, 1997). Many appear to be strictly asexual, although it is difficult to rule out sex entirely. No theory or combination of theories can claim to be a general explanation of the prevalence of sex unless it applies to these organisms. I strongly suspect that a general theory must explain not only obligate sexual and obligate asexual reproduction, but also sexual reproduction of varying degrees of effectiveness.

Interactions between selection on individuals, groups and species

In principle, selection can act on individuals within a population or species; on partially isolated populations within a species; and on species. There is some confusion about these levels of selection in the literature on sex. It is important to keep in mind that what we are trying to explain is why so many species reproduce sexually. Sexual reproduction evolved early in the eukaryotic lineage and is the ancestral state for most eukaryotes. What we have to explain is why it has been retained in lineages where asexual mutants can occur. These mutants can potentially give rise to asexual species; to do this they must go through at least two steps involving

selection at the individual and species levels, and possibly at the group level.

1 First, the mutant must be fixed: it must increase in frequency in the species, by the operation of random drift and/or selection, until the entire species is asexual. Here, asexual mutants may automatically enjoy as much as a two-fold advantage over the sexual genotype. By itself, this advantage would guarantee the fixation of the majority of asexual mutants if the sexual genotype did not have some compensating advantage. It is important to keep in mind that the two-fold advantage of asexual reproduction, and any compensating advantage of sexual reproduction, is basically a matter of individual selection. The two-fold advantage works only because the asexual and sexual genotypes are adapted to the same niche and thus subject to the same limitations on population size (the carrying capacity of the niche). Although they are reproductively isolated from each other, this does not automatically make them different groups in the classic and customary sense of group selection, which requires that the groups evolve with a high degree of independence.

Although the fate of an asexual mutant depends at least partly on individual selection, group selection might also be important if the mutant is first fixed in a subpopulation or colony that is partially isolated from the rest of the species. (Note that stochastic effects are likely to be especially effective here because the subpopulation may be small.) It can also disperse to an unoccupied habitat and found a new colony which is completely asexual. In either case the asexual subpopulation can potentially replace the sexual subpopulations, or go extinct. This is group selection in the sense that the subpopulations or colonies still occupy the same niche and can potentially exchange migrants with the rest of the species, but do so at a low rate and so show some degree of evolutionary independence. In what follows I will ignore group selection but it may not be safe to ignore it in many organisms. *A priori* arguments that group selection is weak compared with individual selection because individuals have shorter life spans than groups are compelling but probably do not apply to all organisms, and in any event we need to find ways to actually measure the relative roles of these two kinds of selection in nature.

2 Once a sexual species has become asexual as the result of fixing a mutation, selection at the species level becomes important. The fate of a species is determined by the ratio of (or difference between) its probabilities of speciation and extinction. We ignore species selection at our peril, as indicated by the following simple argument.

First, asexual mutations quickly become irreversible. This is because sex is a complex process that depends on a number of genes for its successful completion, and after one gene is inactivated by mutation, additional mutations can inactivate other genes; after two or three are inactivated, the probability of restoring all of them to

functionality is effectively zero. Second, asexual mutants can be fixed by drift, even if they have a net selective disadvantage. Given these two facts, simple mathematical treatments (Van Valen, 1975; Nunney, 1989) verify what is intuitively obvious: even if asexual mutants are rarely fixed, eventually all sexual lineages will be replaced by asexuals. This will happen unless there are no viable asexual mutants, or there is species-level selection. The first possibility is probably true in mammals and possibly in some other groups, but cannot be the case in clades that contain at least one asexual lineage. The important lesson is that selection at the level of species is required to maintain sexual reproduction in most groups of eukaryotes.

Moreover, it is absolutely necessary to consider the interaction between selection at the individual and species levels. It is possible, for example, that the two-fold advantage of asexual reproduction can be completely compensated by a disadvantage of asexual reproduction in species. The relative importance of selection at the level of individuals and species is, in the final analysis, an empirical question, to be decided by observation rather than by *a priori* arguments. The answer is probably different for different taxa. Again a reminder: group selection is ignored in this treatment but might actually be important in some cases.

What is needed?

I applaud WLR's emphasis on the need for good estimates of all of the relevant parameters, such as mutation rate and parasite-induced frequency dependence, from the same organisms. I also heartily agree that we need estimates of these parameters from sexual species. I would add that we need to know the frequency and effectiveness of sexual reproduction in species that reproduce sexually part or all of the time, as well as estimates of real and effective population sizes. Besides these population genetic parameters, we need some even more fundamental information of at least three kinds.

First, we need more work on organisms other than vertebrates, insects and plants. We cannot hope to look at all groups of organisms, but granting agencies and thesis advisers should encourage people to identify representative taxa, i.e. whose life styles differ in ways that may affect the ratio of asexual to sexual species. It is important to include groups in which the sexual species have different amounts of sexual reproduction with outcrossing. Then we need to do detailed studies of these groups. Not only do we need to measure all relevant parameters in each group, but we need to test multiple hypotheses in each group, even if we believe they are mutually exclusive.

Second, we need more data on how much sex there really is. We need to know what taxa are truly obligately asexual. This is not trivial, because it is difficult to prove that an organism in which sex has never been observed is

not having sex that is rare (and thus not yet seen), or furtive (doing it under conditions in which we have not looked for it), or cryptic (sexual reproduction by a mode which we can see but do not recognize) (Judson & Normark, 1996). In taxa that are sexual, how much sex are they having, and how effective is it? It is not clear what parameters should be used to measure the amount and effectiveness of sex, although linkage disequilibrium is almost certainly one of them.

Third, we need some way to separate and measure the roles of individual, group and species selection. Measuring species selection should have high priority, and it may be possible to do this by comparing diversification in asexual and sexual clades in phylogenetic trees (for examples, see Sanderson & Donoghue, 1996).

Finally, I think it would be useful to look again for a general explanation of the prevalence of sex that applies to all eukaryotes and subsumes the detailed models such as those discussed by WLR. It is very unlikely that any of the detailed models will suffice to explain the maintenance of sex in all organisms. We need a really general model to guide our experimentation, and of course to put in general biology or genetics textbooks and explain to the public. 'Sex facilitates selection by breaking down negative linkage disequilibria' seems like a good candidate (see also Barton & Charlesworth, 1998). It can operate at the levels of both species and individuals, and probably groups as well. It may be the most specific statement that applies to all eukaryotes, or even to most eukaryotes. Happily, it also has the virtue of being relatively easy to understand and explain.

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