Sex may need more than one

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The positive replies to our original paper (West *et al.*, 1999) leave us in the pleasurable position of being able to keep our final comments short.

Kondrashov (1999) demonstrates what Seger (1999) called 'physics envy'. The idea that the Mutational Deterministic hypothesis can be easily validated or rejected, once the minimum rate of deleterious mutations per genome per generation (U) is known, sounds great, especially if the magical number is $U > 1$. However, quantitative predictions (and assumptions) are almost always model-specific, so that there is unlikely to be a single, uncontroversial value, even if we ignore the large confidence limits that are placed on estimates of U (see West *et al.*, 1999). For instance, with reasonable levels of epistasis, a value of $U > 1.5$ is required (Charlesworth, 1990). If stochastic effects (which are unavoidable during the early phases of any clonal invasion) or variation in the extent of epistasis are included, then $U > 2.0$ is required (Howard, 1994; Otto & Feldman, 1997). In addition, irrespective of the value of U, the Mutational Deterministic hypothesis absolutely requires synergistic epistasis between deleterious mutations (Kondrashov, 1982). The idea that a single value of U will resolve the issue seems to us somewhat optimistic.

We agree with Kondrashov (1999) that our particular form of pluralist explanation is required for only a small fraction ($\approx 0.2 < U < \approx 2.0$) of the *entire* parameter space ($0 < U < \infty$). However, that 'small fraction' is the *relevant* parameter space: it is where the majority of estimates of the mutation rate in sexual species fall (West *et al.*, 1999). A pressing goal now is to determine the virulence of parasites in the wild, and whether they in fact evolve to infect locally common host genotypes. If the latter is not true, or if parasites are not sufficiently virulent to drive host gene frequency dynamics, then both the parasite-driven Red Queen and our particular form of pluralism are falsified.

We agree with Lenski (1999) that different factors may be responsible for the evolutionary origin and maintenance of sex. As we said, our discussion concerned the maintenance of sex. We also agree that experiments with *Escherichia coli* offer an exceptional opportunity to test for 'a general tendency for genetic structures to exhibit synergistic epistasis among deleterious mutations' (Elena & Lenski, 1997). We note, however, that such experiments cannot test whether synergistic epistasis occurs in a type of organism where sexual reproduction predominates. Do larger, more complex genomes with higher mutation rates lead to synergistic epistasis (Szathmary, 1993; Falush, 1998; Hurst & Smith, 1998)? Do the higher numbers of parasites in larger species help cause truncation selection against individuals with large numbers of mutations? Estimating relevant parameters can be much harder in more complex and sexual species (West *et al.*, 1998), but such results are crucial. We hope eventually to have a range of estimates of the mutation rate and the extent of epistasis from a number of sexual and asexual species, so that a whole slew of more subtle questions can be addressed.

Redfield's (1999) comments give us the opportunity to make the following points, orthogonal to our discussion of plurality. (1) Theoretical models suggest that the rate of crossing over is far more important than chromosome number in determining the effective amount of recombination (Burt, unpublished observations). (2) Variation in recombination rates across species are consistent with Red Queen and mutational models (Burt & Bell, 1987;

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Charlesworth, 1987). (3) Recombination 'hot-spots' could be maintained if: (a) they have some other function which helps maintain them, or (b) the use of the sequence as a recognition site is recent and temporary, with intragenomic conflict leading to a form of coevolution between recombination sites (cis) and recombination machinery (trans) (Burt, unpublished observations). (4) It is not surprising that sex occurs more often in the higher eukaryotes, where species are bigger (more parasites) and have larger genomes (more mutations). (5) We need to know whether asexuals are derived from sexual ancestors, and in many cases the phylogeny of a genus is enough, rather than a complete phylogeny of the eukaryotes. Finally, (6) Redfield appears to be advocating a basic philosophy that complex adaptations can be understood by extrapolating from mechanism. We see no precedent for this. For example, the adaptationist theory of sex allocation is perhaps the most qualitatively and quantitatively successful area in evolutionary biology; here, most insight has come from studying evolutionary ecology (population structure, male & female fitness functions) rather than sex chromosomes and eukaryote phylogeny (Charnov, 1982; Godfray & Werren, 1996).

Prompted by Butlin *et al*. (1999), we reiterate the following. First, we did not 'ignore the variety of reproductive modes found in nature.' We said that: (a) correlational studies will not be able to tell us the relative importance of mutations and environmental factors, and that (b) different mechanisms may work at different levels (see also Gouyon, 1999; Birky, 1999). Second, we did not restrict the Red Queen hypothesis to parasites. We said that: (a) the Red Queen works best through biotic interactions – abiotic changes are unlikely to lead to fluctuating epistasis on the correct time-scale (Charlesworth, 1976; Barton, 1995; Peters & Lively, in press); (b) usually parasites are assumed to be the biotic factor, but there are other possibilities such as host immune response (Gemmill *et al*., 1997); and (c) parasite models predict the majority of observed within- and between-host patterns of sexuality (the references of some of the large number of relevant correlational studies were given in the sixth paragraph of our introduction). Third, we agree wholeheartedly that there are many empirical issues that need to be addressed and parameterized, such as the diversity and turnover rates of clones and the apparent persistence of 'ancient asexuals'. Some of these need to be accounted for by any complete theory of the evolutionary maintenance of sex. We suggest that pluralism provides the most productive route to such a theory.

In fact, as we pointed out, searching for a single mechanism could be counterproductive (see also Crow, 1999; Gouyon, 1999; and for the general case, Hilborn & Stearns, 1982). We acknowledge that pluralism is not an easy approach and, like Kondrashov (1999) and physicists, we prefer simple answers. But a pluralistic approach, with explicit theory and data that at least consider the joint action of ecology and mutations, should provide the most useful advances. Crucially, such an approach does not rule out the possibility that one theory might prove sufficient.

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