Is sex in the details?

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The architect Mies van der Rohe is supposed to have said 'God is in the details'. I have always taken this to mean that life, substance and satisfaction are to be found (according to van der Rohe) in the concrete execution of a plan (that is, in the ways the particulars fit together and interact), rather than in the grand conception itself, which is necessarily abstract and therefore vague. Sex has been the grand problem of evolutionary biology for two decades. West, Lively and Read (1999) bring to full consciousness a long-standing tension in thinking about sex. This is not the familiar tension between ecological and mutational theories of sex. Instead, it is a tension between purist and integrationist approaches to the whole problem. West *et al*. propose to change the terms of the debate in ways that could have interesting and therapeutic consequences. Surely many of us have long accepted that the Red Queen and the Grim Mutator both seem likely to play significant roles in the maintenance of sex, yet we have also looked forward to a Decisive Answer in which one actor would prevail over the other. West *et al*. call attention to the inconsistency in this view.

Those who obsess about sex tend to be zoologists. We easily forget that plants defined the problem. Many angiosperms are self-compatible hermaphrodites that can self-fertilize a little, or a lot, or any level in between. In addition, many perennials can reproduce vegetatively. For such species there are no qualitative developmental or genetic barriers to incremental (and in the end, profound) retreats from sex (see Bell, 1982). Thus, many species that remain fairly sexy must do so in the face of easy access to greater asexuality. Their addiction to varying but significant levels of outcrossing should force even hopelessly unreconstructed zoocentrists to admit that ecology must explain some of the variance in rates of outcrossing and vegetative reproduction, and that for many species, sex isn't needed every generation (see Hurst & Peck, 1996). A smaller number of self-compatible hermaphroditic animals (West *et al*. mention the nematode *Caenorhabitis elegans*) illustrate the same point. This 'balance argument' (Williams, 1975; Maynard Smith, 1978) was advanced to show that sex must be advantageous in the short term. It also shows that ecology must be part of the explanation, because populations or closely related species that differ greatly in effective outcrossing rates, as some do, cannot plausibly do so (at least not in general) because they differ greatly in their underlying mutation rates, which must usually be similar.

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Unconditionally deleterious mutations must also be important, and West *et al*. review several lines of evidence that support this view. An additional line of evidence derives from well-established differences between the fixation probabilities of synonymous and nonsynonymous mutations (see Kondrashov & Crow, 1993; Crow, 1995; Drake *et al*., 1998; Eyre-Walker & Keightley, 1999). Synonymous nucleotide substitutions are typically about five times more likely to fix than nonsynonymous substitutions, on average, as estimated from comparisons between hundreds of orthologous genes in various taxa, especially rats and mice (e.g. Makalowski & Boguski, 1998). This implies that at least 4/5 of all mutations that change an amino acid must be deleterious. If mammals have about 50 000 genes averaging 2000 bp in length, then a typical mammal has around 10^8 functional base pairs. If even half of these nucleotides (5×10^7) were capable of mutating to deleterious states, and if the average mutation rate were around 4×10^{-9} per nucleotide per generation, then there would be $20 \times 10^{-2} = 0.2$ deleterious substitutions per haploid genome per generation. This number may substantially underestimate the overall deleterious mutation rate in most mammals because the per *generation* nucleotide substitution rate is undoubtedly larger than 4×10^{-9} in many species (Drake *et al*., 1998), especially those with long lifespans (e.g. Eyre-Walker & Keightley, 1999), and there are other classes of mutations (e.g. indels, including transposon hops). So deleterious mutations must go at least some distance toward supporting sex in many taxa, even if (perhaps) they do not do so, by themselves, in very many cases.

Given these well-known facts, how can anyone *not* be a pluralist? Why should West *et al*. feel compelled to argue the case? For one thing, it is necessary to establish that mutational and ecological factors may interact cooperatively to favour sex, and West *et al*. discuss this issue at length. At another level, it may also be necessary to relieve some physics envy. Simple, general, cleanly testable theories are beautiful. A universal process that could explain a pervasive pattern and that could be tested by a single decisive experiment would be a kind of

dream. Sex has seemed such a dream. But like many initially sweet dreams, this one could turn complicated, even ominous, and then wake us up. The real world may be messy, but fortunately, it may ultimately be more informative than what we would have been left with had the dream come true.

In adopting a pluralist stance we are encouraged to see more than just a qualitative contrast between sex and asex (distributed taxonomically in patterns influenced, perhaps, by several factors including ecology and mutations, and shaded, perhaps, by partial retreats such as selfing, cloning, and cyclical parthenogenesis). We are also encouraged to see (and to need to explain) continuously varying degrees of sexiness *within* species that practice sex in every generation. For example, rates of mutation and rates of recombination both appear to vary by an order of magnitude on individual mammalian chromosomes (Wolfe *et al.*, 1989; Nachman & Churchill, 1996; McVean & Hurst, 1997; Makalowski & Boguski, 1998; Nachman *et al.*, 1998). Interestingly, genes that seem to experience relatively high mutation rates (high-K_S genes) fix *disproportionately* more amino-acid substitutions, on average, than those with relatively low mutation rates (Fig. 1). This pattern would seem to suggest that many high-K_A genes may be located in chromosomal regions where high rates of mutation and low rates of recombination lead to greater than average numbers of slightly deleterious fixations for genes throughout the region, owing to background selection or to hitchhiking with linked adaptive mutations (see Barton & Charlesworth, 1998; Charlesworth & Charlesworth, 1998a,b). Alternatively, if the variation in K_S is *not* caused largely by regional variation of the mutation rate, then it must be caused by variation in the coalescence times of rat and mouse orthologs. But this would seem to require that there be strongly protected polymorphisms at an implausibly large proportion of all loci (or that most 'orthologs' are really paralogs). The various possibilities could be investigated by comparing levels of polymorphism, divergence and local recombination for genes from different parts of the joint distribution of K_S and K_A, and for chromosomal neighbours of those genes.

Why does such variation occur? If mutation is bad and sex is good, then why are they not equally bad and good for all genes in a genome? As always, the answer must be 'tradeoffs' (see McVean & Hurst, 1997; Drake *et al.*, 1998). But tradeoffs between what, balanced by what mechanisms, and in whose interests? These and other, more general questions might be illuminated by studies of quantitative variation in sexiness within genomes, where the differences occur on backgrounds well controlled for population and phylogenetic history. If such approaches prove successful, then the goddess of sex may turn out to speak less through oracles than through storytellers.

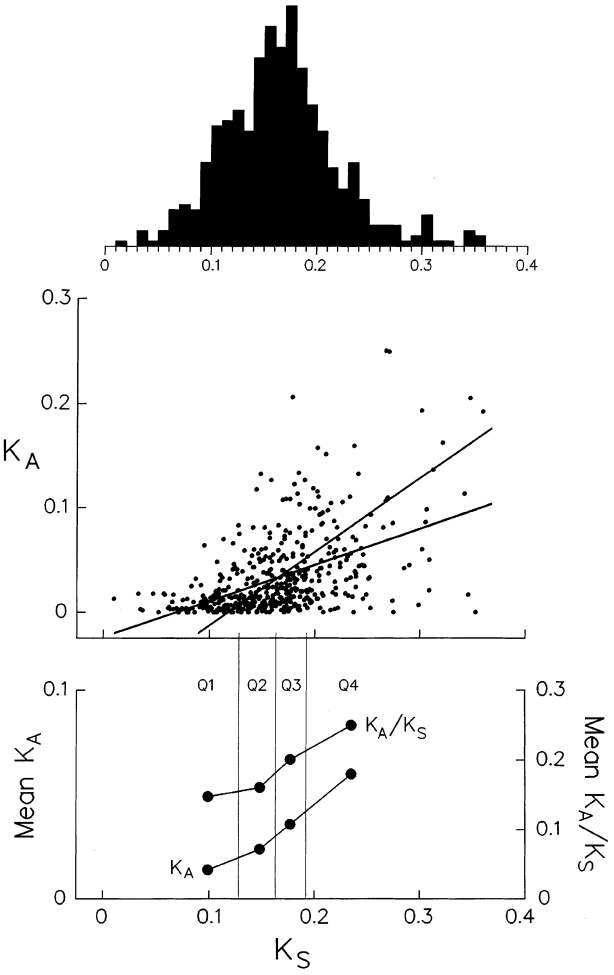

Fig. 1 The distribution of synonymous nucleotide substitutions (K_S) and the joint distribution of synonymous and nonsynonymous (K_A) substitutions for 465 orthologous gene pairs in rat and mouse. Substitutions were estimated by Makalowski & Boguski (1998) as part of a comprehensive survey of orthologous sequences from humans and rodents. The scatterplot shows K_A as a function of K_S. The linear regression (shallower slope) and reduced major axis (steeper slope) both pass below the origin, indicating that genes with high values of K_S tend to have disproportionately high K_A. This accelerating relationship between K_A and K_S is shown more clearly in the lower panel, where mean values of K_A and of the ratio K_A/K_S are shown for each of the four quartiles in K_S. On the null hypothesis, average K_A/K_S ratios would be expected to decline with increasing values of K_S because K_S and K_A are measured with error and K_S appears in the denominator of the ratio. Thus the observed positive relationship underestimates the real relationship, because it is contaminated by an artifactual negative correlation. Even so, the observed increase is formally significant by various criteria. For example, the mean $\log(K_A/K_S)$ values for nonadjacent quartiles differ significantly by two-tailed *t*-tests, as do those for Q3 vs. Q4, and for the combined upper and lower halves of the distribution (Q1 + Q2 vs. Q3 + Q4, $P < 0.00002$).

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