Does Diploidy Increase the Rate of Adaptation?

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ABSTRACT

Explanations of the evolution of diploidy have focused on the advantages gained from masking deleterious alleles. Recent theory has shown, however, that masking does not always provide an advantage to diploidy and would never favor diploidy in predominantly asexual organisms. We explore a neglected alternative theory which posits that, by doubling the genome size, diploids double the rate at which favorable mutations arise. Consequently, the rate of adaptation in diploids is presumed to be faster than in haploids. The rate of adaptation, however, depends not only on the rate of appearance of new favorable mutations but also on the rate at which these mutations are incorporated (which depends on the population size and on the dominance of favorable mutations). We show that, in both asexuals and sexuals, doubling the mutation rate via diploidy often does not accelerate the rate of adaptation. Indeed, under many conditions, diploidy slows adaptation.

THERE has been a great deal of interest recently in the evolutionary advantages of diploidy (KONDRASHOV and CROW 1991; PERROT *et al.* 1991; CHARLESWORTH 1991; VALERO *et al.* 1992; OTTO and GOLDSTEIN 1992; BENGTSSON 1992; GOLDSTEIN 1992). Several genetic theories have been offered.

Perhaps the most popular emphasizes that diploids enjoy an advantage due to masking the deleterious effects of recessive mutations. This advantage does not, however, confer a higher mean fitness upon diploids at equilibrium since diploids suffer from the load of twice as many deleterious mutations (CROW and KIMURA 1965). Two recent variations on the masking hypothesis appear more promising. First, KONDRASHOV and CROW (1991) have shown that, with truncation selection, the mean fitness of a diploid population can exceed that of a haploid population. Further, PERROT *et al.* (1991), considering individual-level selection among interbreeding haploids and diploids, showed that an allele increasing the proportion of time spent as a diploid can invade despite a subsequent decrease in mean fitness at equilibrium.

Unfortunately, the latter result depends critically on the assumptions of random mating and free recombination between the locus controlling ploidy and the locus under selection. When asexuality, assortative mating, or selfing are common or when recombination is rare, alleles increasing the diploid phase of a life cycle do not invade while those increasing the haploid phase do invade (BENGTSSON 1992; OTTO and GOLDSTEIN 1992; S. P. OTTO and J. MARKS, unpublished results). Thus, in those many organisms having low rates of either recombination or outcrossing [*e.g.*, many taxa in the chlorophyta (BELL 1982), rhodophyta (HAWKES 1990), and bacillariophyta (WETZEL 1983)], the prevalence of diploidy is not satisfactorily explained by the masking hypothesis. Moreover, it is unclear whether diploidy evolved before or after high rates of recombination in the lineage leading to metazoans; if before, the masking hypothesis would also fail to explain diploidy among the higher animals.

A second hypothesis for the advantage of diploidy posits that diploids, who can produce heterozygotes, benefit from overdominance. However, in organisms having a brief diploid phase, overdominance cannot maintain a polymorphism (GOLDSTEIN 1992); without such a polymorphism, there is, of course, no benefit to diploidy. Thus this hypothesis fails to explain the initial expansion of the diploid phase.

There is, however, a third hypothesis that has been relatively ignored. This hypothesis emphasizes that, because diploids possess twice as many genes as haploids, twice as many favorable mutations arise per generation among diploids. As PAQUIN and ADAMS (1983) suggested, diploidy might, therefore, increase the rate of adaptive evolution over that in haploids, especially in asexual species that cannot rely upon recombination to assist in rapid adaptation (see also CHARLESWORTH 1983; VALERO *et al.* 1992). They further provide evidence that asexual lines of diploid yeast do in fact adapt faster than haploid yeast in chemostat experiments. PAQUIN and ADAMS conclude: "A higher rate of adaptive mutation for diploid cells should be common to all eukaryotes having an asexual diploid stage in the life cycle. Thus, it is tempting to suggest this as a general mechanism for the evolution of diploidy." Because the previous explanations of diploidy are not entirely satisfactory, especially in asexual organisms, we

have investigated this theory mathematically. At issue is whether a doubling of the genome generally accelerates the rate of adaptive evolution. We examine this question by first comparing rates of adaptive evolution in asexually reproducing haploids and diploids. Second, we examine adaptive evolution in a sexual population that undergoes an alternation of generations between haploid and diploid phases; here, the proportion of time spent in each phase is allowed to evolve.

RESULTS

The rate of adaptation in asexuals: Without mixis, two or more mutations can be incorporated into the same line only if subsequent mutations occur among the descendants of earlier mutations (MULLER 1932). This complicates calculation of the rate of adaptive substitution in asexual organisms (MULLER 1964; CROW and KIMURA 1965; MAYNARD SMITH 1971, 1978; KIMURA and OHTA 1971).

Fortunately, we can find the conditions under which diploid asexuals evolve faster than haploids by slightly modifying the approach of MULLER (1964). This approach [and its refinements by CROW and KIMURA (1965) and KIMURA and OHTA (1971)] allows one to estimate the adaptive substitution rate by calculating the waiting time, g, between the appearance of a favorable mutation and the appearance of another favorable mutation among the descendants of the first mutant. The rate of adaptive evolution is inversely proportional to g.

The calculations below involve trivial modifications of the approach taken by KIMURA and OHTA (1971). As in that model, we assume that adaptation is due to fixation of newly arising (or at least very rare) mutations that are definitely favorable. Only those favorable mutations that escape accidental loss when rare are considered. For simplicity, we assume that the effective population size is N for both haploids and diploids ($N_{dip} = N_{hap}$).

If U is the rate of occurrence per individual per generation of lucky favorable mutations (*i.e.*, those that escape stochastic loss when rare), the number of individuals who must on average be produced before a second favorable mutation arises among the descendants of the first is just $1/U$. We wish to find the average number of generations, g, that elapse before these $1/U$ individuals are produced. If p_t is the frequency of the original favorable mutation in the tth generation, then

$$1/U = \int_0^g N p_t \, dt. \tag{1}$$

We assume that the increase in frequency of an advantageous mutation takes the form of the logistic equation: $p_t = p_0/(p_0 + [1 - p_0]\, e^{-\sigma t})$, where σ is the selective advantage of the mutant asexual type (s in haploids and hs in diploids). Setting $p_0 = 1/N$ (*i.e.*, the mutation arose in one individual), and integrating (1), g may be found (CROW and KIMURA 1965):

$$g \approx \frac{1}{\sigma} \ln[N(e^{\sigma/(UN)} - 1)]. \tag{2}$$

In haploids, the rate of occurrence of lucky favorable mutations, U, is simply the product of the rate at which favorable alleles appear by mutation per haploid genome (v) and the probability that such a mutant escapes accidental loss, which is roughly $2s$ for weak selection (MORAN 1962, p. 116). Thus $U \approx 2vs$ and we can rewrite (2)

$$g_{hap} \approx \frac{1}{s} \ln[N(e^{1/(2Nv)} - 1)]. \tag{3}$$

In diploids, the rate of favorable mutations will equal the product of the mutation rate per diploid genome ($2v$) and the probability that such mutations escape loss ($2hs$), where h is the mean dominance coefficient for favorable mutations (mutations remain permanently heterozygous in asexual diploids). Now $U \approx 4vhs$ so that (2) becomes

$$g_{dip} \approx \frac{1}{hs} \ln[N(e^{1/(4Nv)} - 1)]. \tag{4}$$

Because the rate of adaptive evolution, K, is inversely proportional to g, the relative rate of adaptive evolution in diploids *vs.* haploids is just

$$\frac{K_{dip}}{K_{hap}} \approx h \frac{\ln[N(e^{1/(2Nv)} - 1)]}{\ln[N(e^{1/(4Nv)} - 1)]}, \tag{5}$$

which is independent of the strength of selection, s.

Equation 5 shows that, if populations are small enough that favorable mutations arise very rarely ($Nv \ll 1$), $K_{dip}/K_{hap} \approx 2h$. In this case, diploidy is favored if advantageous mutations are, on average, partially dominant ($h > 1/2$). If, on the other hand, populations are large enough that advantageous mutations appear fairly often somewhere in the population ($Nv \geq 1$), $K_{dip}/K_{hap} \approx h\ (\ln 2v/\ln 4v) \approx h$, where the last approximation assumes that v is small. Thus, in large populations, diploids actually evolve *slower* than haploids (as long as $h < 1$) even though twice as many favorable mutations appear in the diploid population.

Figure 1 shows how the dominance of favorable mutations and the product Nv interact to determine the ratio K_{dip}/K_{hap}. Obviously, over much of the parameter space, asexual diploids do not evolve faster than haploids.

The logistic equation used in the above theory naively assumes that only one favorable mutation segregates in a population at any given time; this clearly becomes less realistic as Nv increases. To check the accuracy of Equation 5 under more realistic assumptions, we performed simulations comparing the rate of adaptation in diploids

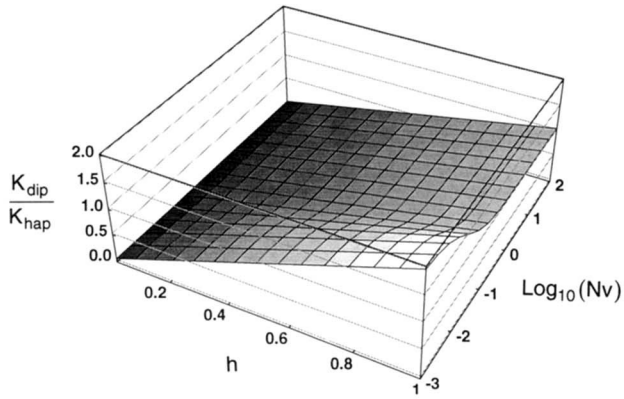

FIGURE 1.—Rate of adaptation in diploid *vs.* haploid asexuals. The ratio, K_{dip}/K_{hap}, of adaptive substitution rates (from Equation 5) in diploids *vs.* haploids plotted as a function of both the dominance coefficient, h, and the product of population size and genomic mutation rate to favorable alleles (expressed as $\log_{10}(Nv)$). $v = 10^{-6}$, although other small values yield nearly identical results. Diploidy is favored only when h is large and Nv is small.

vs. haploids when several favorable mutants were allowed to segregate simultaneously. The mechanics of the simulations were similar to those in MAYNARD SMITH (1971). Mutations were introduced at a frequency of $1/N$, where the effective mutation rate to "lucky" favorable alleles was $2vs$ for haploids and $4vhs$ for diploids. The change in frequency of asexual types was deterministic, where the fitness of an individual was a multiplicative function of the number of favorable mutations (n) that the individual carried compared to the least fit individuals currently in the population. When the class of least fit individuals ($n = 0$) reached a frequency of 10^{-4}, they were pooled with the class carrying only one additional favorable mutation ($n = 1$). This pooled class was then considered the wild type.

The results showed that our approximate analytic results are quite robust; indeed the plot of K_{dip}/K_{hap} *vs.* h and $\log_{10}(Nv)$ obtained from the simulations is almost identical to that given in Figure 1 (not shown).

The above theory also assumes separate populations of haploids and diploids that are equal in size and that do not directly compete (*i.e.*, N_{dip} always equals N_{hap} and both are constant). Since diploid cells are often larger and require more nutrients, one might wish instead to assume that N_{dip} is less than N_{hap}, an assumption that restricts the advantage of diploidy even further than described above (proof not shown). Alternatively, one might consider the case where diploids and haploids compete against one another for limited resources. Imagine a single asexual population of constant size N with a variable fraction, f, of diploids and a fraction, $(1-f)$, of haploids. If mutations are very rare, whichever ploidy-type happens to carry a single new advantageous mutation will sweep to fixation. The fraction of rare mutations that appear within a diploid individual, survive random sampling, and hence spread to fixation together with diploidy is

$$\frac{2Nf(2hs)}{2Nf(2hs) + N(1-f)(2s)}, \tag{6}$$

while the analogous fraction for haploids is

$$\frac{N(1-f)(2s)}{2Nf(2hs) + N(1-f)(2s)}. \tag{7}$$

Thus, Equations 6 and 7 show that, when $h > 1/2$, mutations are more likely to fix the diploidy-type than expected given their initial frequency in the population. A very different result obtains, however, if mutations are common enough (or the population is large enough) that mutations appear in both haploid and diploid individuals. In this case, haploid mutants will have the highest fitness (when $h < 1$) and will generally displace the diploids, since mean fitness is maximized in asexual populations.

Qualitatively, then, one obtains the same result whether considering separate populations of haploids and diploids or a single population in which the two types compete: diploidy is favored if favorable mutations are both dominant and rare (*e.g.*, when populations are small). Haploidy, however, is favored whenever mutations are fairly common (*e.g.*, when populations are large).

The rate of adaptation in sexuals: Because diploids produce more favorable mutations than haploids, we might expect the diploid phase of a sexual organism to increase over evolutionary time. This advantage of diploidy, however, may be offset by the incomplete dominance of favorable mutations in diploids. To see how these two effects balance, we can begin by taking an optimality approach and determining how mean fitness depends on the life cycle. We calculate a measure of mean fitness for a sexual population having both a haploid and a diploid phase: let p equal the frequency of a beneficial allele with selective advantage of s when haploid or homozygous and an advantage of hs when heterozygous. Let selection occur among diploids after syngamy for a proportion of time, t, followed by meiosis and selection in haploids (Figure 2). Multiplying the mean fitness in the diploid phase by that in the haploid phase, we get

$$W = (1+s)\,p^2 + (1+hs)^t[(1+s)^{(1-t)} + 1] \cdot p(1-p) + (1-p)^2. \tag{8}$$

For weak selection, mean fitness increases with the time spent in the diploid phase for dominant beneficial mutations ($h > 1/2$), but decreases for recessive mutations ($h < 1/2$). We might expect, therefore, that selection would favor increases in t for dominant mutations and decreases in t for recessive mutations. Unfortunately,

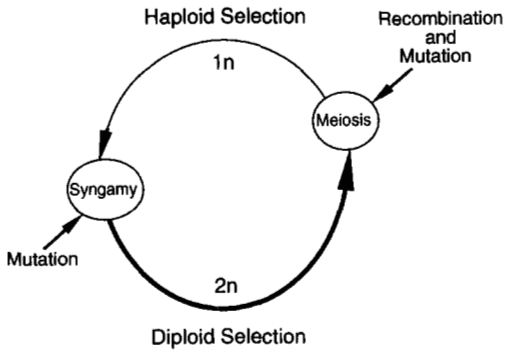

FIGURE 2.—The life cycle of the sexual species considered. Mating of haploid gametes occurs randomly to produce diploid zygotes. These diploids experience selection according to the amount of time spent in this phase, which is under the control of the ploidy locus. Once meiosis occurs, the haploids produced experience selection for the remainder of the cycle. These haploids then produce gametes and the cycle repeats.

this simple argument ignores potentially important associations between fitness loci and genes controlling ploidy levels.

To assess the effects of these associations, we performed simulations with one to three fitness loci and one "ploidy" locus governing the timing of meiosis (Figure 2; for more details see OTTO 1994). A population began with variation at the ploidy locus such that some genotypes had a longer and others a shorter diploid phase. Favorable mutations were introduced at the fitness loci and were assumed to be in linkage equilibrium with alleles at the ploidy locus. This assumption is more likely to be met when the product Nv is fairly large and when the timing of meiosis does not vary dramatically between alleles. Mutations were allowed to increase in frequency deterministically. A particular ploidy level was said to be favored when alleles causing individuals to spend more time in that phase increased in frequency during the sweeps of beneficial mutations.

These simulations were repeated with different rates of recombination between the ploidy and fitness loci. For a given rate of recombination, the critical level of dominance for beneficial mutations, h^*, was found above which increases in the diploid phase occurred and below which increases in the haploid phase occurred. The results (Figure 3) clearly show that partial dominance of favorable mutations ($h > 1/2$) is *not* sufficient to ensure that diploidy will be favored. As expected, dominance is less of a guarantee of the advantage of diploidy as the recombination rate falls. Indeed—just as with deleterious mutations (OTTO and GOLDSTEIN 1992)—haploidy is almost always favored when there is little recombination between the fitness and ploidy loci.

Last, it is worth noting that, in a sexual population, favorable mutations are likely to arise in linkage disequilibrium with the ploidy locus, especially when mutations are rare. Whichever ploidy allele happens to be coupled

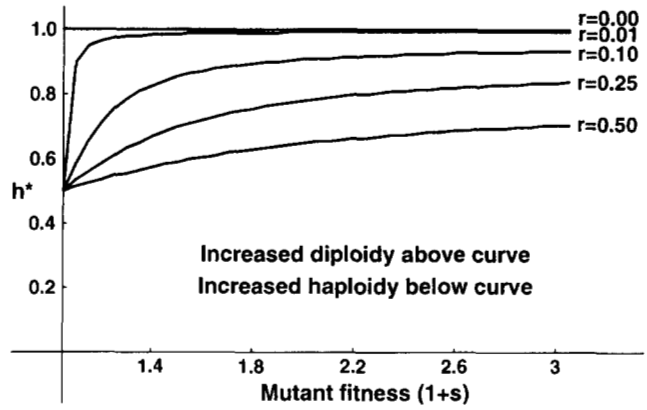

FIGURE 3.—Conditions favoring haploid *vs.* diploid sexuals. Simulations were run with one ploidy locus and one viability locus to find the critical value of dominance (h^*) above which ploidy alleles extending the diploid phase increase in frequency and below which alleles extending the haploid phase are favored. The population began with two alleles at the ploidy locus (in equal frequencies) and a favorable mutation at a frequency of 0.002 (in linkage equilibrium). Depending on the diploid genotype at the ploidy locus, an individual spent 49.9, 50 or 50.1% of the generation in the diploid phase. h^* clearly depends on s and r, but is fairly insensitive to the exact ploidy alleles compared, to the starting conditions when in linkage equilibrium, and to the co-segregation of favorable alleles at more than one viability locus (results not shown). However, the curves are quite sensitive to the initial linkage disequilibrium between the viability and ploidy loci: if the population starts with disequilibrium coupling the more haploid allele with the beneficial allele, all the curves are shifted up (haploidy more favored) and vice versa (see OTTO 1994). The size of this shift is greatest with low rates of recombination and smallest with high rates.

with a new mutation enjoys an obvious advantage. Because the probability that a mutation escapes stochastic loss ($= 2\,[(1 + h\,s)^t\,(1 + s)^{(1-t)} - 1\,]$) *decreases* with the amount of time spent in the diploid phase, the number of mutations that survive random sampling will be larger per gene for more haploid individuals. This suggests that any initial linkage disequilibria should, on average, favor haploidy.

DISCUSSION

Because diploidy doubles the rate at which favorable mutations appear, one might intuitively expect diploids to enjoy a faster rate of adaptation than haploids. This could, in turn, explain the prevalence of diploidy (PAQUIN and ADAMS 1983). The present work shows, however, that under many conditions this verbal argument fails: among both asexuals and sexuals, diploidy often does not increase the rate of adaptive evolution.

In asexual species, where adaptation requires the incorporation of favorable mutations among the direct descendants of earlier mutations, we find that the effect of diploidy on this rate of incorporation depends both on the dominance of advantageous mutations (h) and

on the number of favorable mutations that appear per generation (Nv). The effect of dominance enters in two ways. First, the fact that not all mutations act as complete dominants among diploids increases the chances that favorable mutations will be accidentally lost when rare in diploids. Second, even if a mutant does escape random loss, its rate of increase is slower among asexual diploids than haploids (unless $h = 1$), since the selective advantage of the mutation would be smaller (hs compared to s). This, in turn, means that a smaller proportion of subsequent favorable mutations arise among the descendants of previous ones, lowering the rate of incorporation of mutations in diploid asexuals.

Perhaps more importantly, diploidy is favored in asexuals only when the product Nv is small. This effect has a straightforward explanation. If advantageous mutations appear very rarely, a mutation will almost always be fixed long before a second appears. Thus almost all favorable mutations arise among descendants of previous ones and so almost all mutants that escape stochastic loss when rare ultimately become incorporated. In this case, the speed of adaptation is limited by the advantageous mutation rate and doubling this rate (*e.g.*, by diploidy) can speed adaptation (when $h > 1/2$). If, however, haploid populations are large enough that, on average, at least one favorable mutation appears each generation ($Nv \geq 1$), many advantageous mutations fail to get incorporated because they arise before the fixation of previous mutants. In this case, the rate of adaptation is not limited by the rate of appearance of favorable mutants, but by their rate of spread, and so doubling the mutation rate (by diploidy) does little or nothing to help. In fact, if $h < 1$ in a large population, diploidy actually *slows* the rate of adaptation below that in haploids because diploids merely suffer the disadvantages of incomplete dominance (lower probabilities of fixation and slower increases in allele frequency).

Although there are some metabolic reasons for expecting that $h > 1/2$ for favorable mutations (KACSER and BURNS 1981; but see CHARLESWORTH *et al.* 1987), we have very little direct evidence on this point. Even less, of course, is known about the magnitude of Nv. It would certainly seem, however, that population sizes are extremely large in many of the taxa in which diploid asexuality is common (*e.g.*, diatoms). The doubling-of-mutation-rate hypothesis would not, therefore, seem to offer a very satisfactory explanation of diploidy in such groups.

The situation in sexuals is somewhat more favorable to diploidy. As Figure 3 shows, diploidy can be favored if advantageous mutations are quite dominant and if recombination is frequent. However, as Figure 3 also shows, diploidy is *not* invariably favored whenever $h > 1/2$ as mean fitness arguments (Equation 8) would suggest. Instead, the critical level of dominance above which diploidy is favored rises far above $h = 1/2$ as recombination rates decrease. The reason is that, as beneficial mutations sweep through a population, associations develop coupling these mutations with alleles extending the haploid phase. This occurs because the efficiency of selection increases with the extent of the haploid phase, such that less fit alleles are more often removed and beneficial mutations are more often preserved during haploid selection. The net result is that organisms with longer haploid phases tend to have more beneficial alleles than expected and are thus favored more often than expected from mean fitness arguments that ignore these associations. Mechanisms that maintain genetic associations (such as linkage) strengthen this coupling and hence favor the evolution of haploidy.

In sum, despite its intuitive appeal, a doubling of the favorable mutation rate often confers no advantage on diploidy. Unfortunately, this hypothesis fails under roughly the same conditions as the masking of deleterious recessives hypothesis; whenever recombination rates are low (either due to asexuality *per se* or to restricted recombination in sexual diploids), diploidy is typically not favored. Thus, in those taxa showing little sex or in which diploidy evolved *before* frequent recombination, we are left with no clear explanation of the prevalence of diploidy.

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LITERATURE CITED

BELL, G., 1982 *The Masterpiece of Nature: The Evolution and Genetics of Sexuality*. University of California Press, Berkeley.

BENGTSSON, B., 1992 Deleterious mutations and the origin of the meiotic ploidy cycle. Genetics **131:** 741–744.

CHARLESWORTH, B., 1983 Adaptive evolution in the laboratory. Nature **302:** 479–480.

CHARLESWORTH, B., 1991 When to be diploid. Nature **351:** 273–274.

CHARLESWORTH, B., J. A. COYNE and N. H. BARTON, 1987 The relative rates of evolution of sex chromosomes and autosomes. Am. Nat. **130:** 113–146.

CROW, J. F., and M. KIMURA, 1965 Evolution in sexual and asexual populations. Am. Nat. **99:** 439–450.

GOLDSTEIN, D. B., 1992 Heterozygote advantage and the evolution of a dominant diploid phase. Genetics **132:** 1195–1198.

HAWKES, M. W., 1990 Reproductive strategies, pp. 455–476, in *Biology of the Red Algae*, edited by K. M. COLE and R. G. SHEATH. Cambridge University Press, Cambridge.

KACSER, H., and J. A. BURNS, 1981 The molecular basis of dominance. Genetics **97:** 639–666.

KIMURA, M., and T. OHTA, 1971 *Theoretical Aspects of Population Genetics*. Princeton University Press, Princeton, N.J.

KONDRASHOV, A. S., and J. CROW, 1991 Haploidy or diploidy: which is better? Nature **351:** 314–315.

MAYNARD SMITH, J., 1971 What use is sex? J. Theor. Biol. **30:** 319–335.

MAYNARD SMITH, J., 1978 *The Evolution of Sex*. Cambridge University Press, New York.

MORAN, P. A. P., 1962 *The Statistical Processes of Evolutionary Theory*. Oxford University Press, Oxford.

MULLER, H. J., 1932 Some genetic aspects of sex. Am. Nat. **64:** 118–138.

MULLER, H. J., 1964 The relation of recombination to mutational advance. Mutat. Res. **1:** 2–9.

OTTO, S. P., and D. B. GOLDSTEIN, 1992 Recombination and the evolution of diploidy. Genetics **131:** 745–751.

OTTO, S. P., 1994 The role of deleterious and beneficial mutations in the evolution of ploidy levels, in press, in *Theories for the Evolution of Haploid-diploid Life Cycles*, edited by M. KIRKPATRICK. American Mathematical Society.

PAQUIN, C., and J. ADAMS, 1983 Frequency of fixation of adaptive mutations is higher in evolving diploid than haploid yeast populations. Nature **302:** 495–500.

PERROT, V., S. RICHERD and M. VALERO, 1991 Transition from haploidy to diploidy. Nature **351:** 315–317.

VALERO, M., S. RICHERD, V. PERROT and C. DESTOMBE, 1992 Evolution of alternation of haploid and diploid phases in life cycles. Trends Ecol. Evol. **7:** 25–29.

WETZEL, R. G., 1983 *Limnology*, Ed. 2. Saunders College Publishing, Philadelphia.

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