Genet. Res., Camb. (1991), **58**, *pp.* 157–165 *With 4 text-figures Printed in Great Britain*

A theoretical test of the DNA repair hypothesis for the maintenance of sex in eukaryotes

EÖRS SZATHMÁRY* AND SZILVIA KÖVÉR

Ecological Modelling Research Group, Department of Plant Taxonomy and Ecology, Eötvös University, H-1083 Budapest, Kun Béla tér 2, Hungary

(*Received 29 October 1990 and in revised form 24 April 1991*)

Summary

The DNA repair hypothesis for the maintenance of sex states that recombination is necessary for the repair of double-strand DNA damage. In a closed (mitotic) genetic system crossing-over generates homozygosity. This reduces fitness if deleterious recessive alleles become expressed. Thus, outcrossing is required to restore heterozygosity destroyed by recombination. The repair hypothesis is tested by comparing outcrossing sexuality with a hypothetical parthenogenic strategy (the Prudent Reparator) which destroys as little heterozygosity during repair as possible. In the Prudent Reparator, repair of double-strand DNA damage results in a small amount of homozygosity due to gene conversion only, since this process does not render outside markers homozygous. Diploidy, deleterious recessives, multiplicative fitness and linkage equilibrium in mutation–selection balance are assumed. The average fitness of this population increases, and complementation (i.e. masking of recessives in heterozygous form) decreases with the rate of damage per locus. The equilibrium fitness of the Prudent Reparator can be well above that of the sexual population. A lower complementation ability of parthenogens may not be an impenetrable barrier to their successful establishment if the invader's genome is relatively uncontaminated by mutant alleles: there are always such genotypes in the sexual population. Thus, the Prudent Reparator could solve the problem of repairing damage as well as that of invading an existing outcrossing population. As we do not see this strategy widely adopted instead of sexuality, the repair hypothesis is likely to miss some essential feature of the evolution of sex.

1. Introduction

The DNA repair hypothesis for the evolutionary maintenance of sex (Dougherty, 1955; Walker & Williams, 1976; Bernstein, 1977; Walker, 1978; Williams & Walker, 1978) states in its present form (Bernstein *et al.* 1981, 1985, 1988) that recombination is selected to repair double-strand DNA damage. In the presence of deleterious recessive mutations and recombination, outcrossing is selected, since this restores the heterozygosity destroyed by recombination through complementation. In contrast with mitotic recombination, meiotic recombination followed by syngamy gives a much lesser degree of homozygosity, so that a recessive bad allele is very likely complemented by a good one in the diploid. The primary function of sex is DNA repair and the complementation of mutations, and variation is only a by-product.

Comparing various diploid genetic systems Bernstein *et al.* (1985) conclude that the masking (complementation) ability is low for automixis and selfing, intermediate for outcrossing sex, and high for endomitosis, apomixis, and vegetative reproduction (see also Hopf *et al.* 1988). Hence there is a *transient* advantage in passing from the former to the latter systems, if we only consider the frequency of deleterious recessives. While both selfing and outcrossing can repair damage through recombination, the former is unstable against invasion by the latter if the mutation rate is high enough, despite the two-fold cost (Maynard Smith, 1978) paid by the latter. Inbreeding depression can well prohibit outcrossers from reverting to selfing. Outcrossing is, however, stable against invasion by endomitosis, apomixis, and vegetative reproduction, since in these systems recombinational repair is limited or thought to be negligible.

The statement that the genetic load is to a very good

* Present address: Laboratory of Mathematical Biology, MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK.

approximation independent of the genetic system (Hopf *et al.* 1988) is not completely true. Several authors (Ohta & Cockerham, 1974; Lande & Schemske, 1985; Charlesworth *et al.* 1990) have shown that mean fitness increases with the degree of selfing in a sexual population, or conversely, that the mutational load decreases. An analogous finding will be presented in connection with the establishment of an appropriate parthenogenic population.

Criticizing the repair hypothesis, Maynard Smith (1988) has raised the question: Why is not all recombination cryptic, i.e. channelled towards gene conversion without producing crossing over (i.e. allelic exchange)? (Note that the arguments in this paper always refer to diploids.) Bernstein *et al.* (1988) argue in their reply as follows:

(1) The frequency of crossing-over *versus* mere gene conversion is around fifty-fifty in various meiotic systems, although 1 to 0 would be required for generating as much variation as possible. Since this is not so, the variation hypothesis is not correct. A symmetric argument does not, however, apply to the repair hypothesis, since it seems impossible to design a system having 0% crossing-over in repair without excessive costs in time and/or energy.

(2) Even if such a system were possible, it would become functionally haploid in the long run through mutation followed by gene conversion at damaged sites.

(3) If such a system were possible, it could invade the sexual strategy only if *two* mutations occurred simultaneously: a shift to 0% allelic exchange, and apomixis. There would be no advantage for an outcrosser to adopt a 0% crossing-over mechanism alone since most mutations are masked anyway.

We consider these problems in turn.

2. The Prudent Reparator: cellular and molecular mechanisms

We shall present two versions of a closed, apogamous, essentially mitotic strategy which can repair double-strand DNA damage (for simplicity we shall refer to them as DSBs for double-strand breaks, conforming to common usage) through gene conversions only, avoiding crossing-over almost completely. We call such a strategy the Prudent Reparator.

A simple way to repair DSBs in a closed system without generating excessive homozygosity of deleterious recessives is to allow for any homologous recombination in phase G1 of the cell cycle while restricting these to proceed between sister chromatids in G2 (Figs. 1, 2).

The feasibility of this system can be judged on various grounds. For example, if we assume (in the

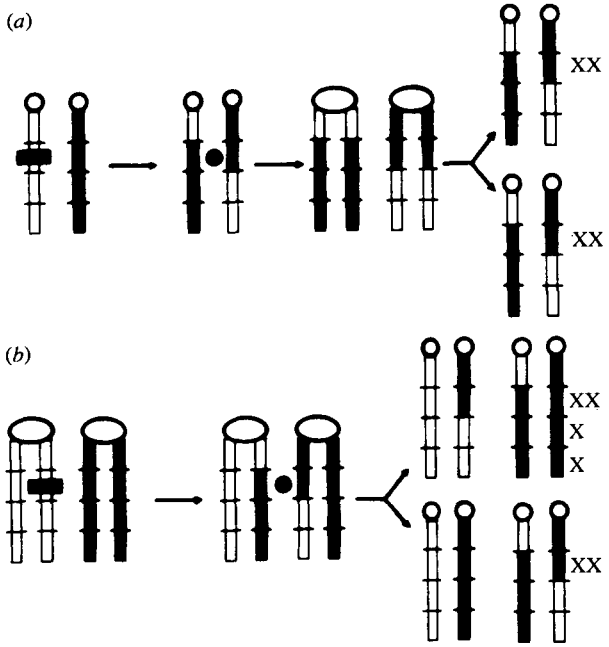

Fig. 1. Homozygosity generated in mitotic recombination. White and black distinguish between the maternal and paternal chromosomes. The hatched box indicates the site of damage. The black-filled circle shows the site of recombination. x and xx stand for homozygous loci (of exclusively paternal origin) arising from recombination and gene conversion, respectively. (*a*) Recombination in G1 does not lead to homozygosity except for the gene-converted loci. (*b*) Recombination in G2 between the homologs results in extensive homozygosity. [Note that in fact deleterious mutations will be scattered over both chromosomes, but this does not alter the conclusion.]

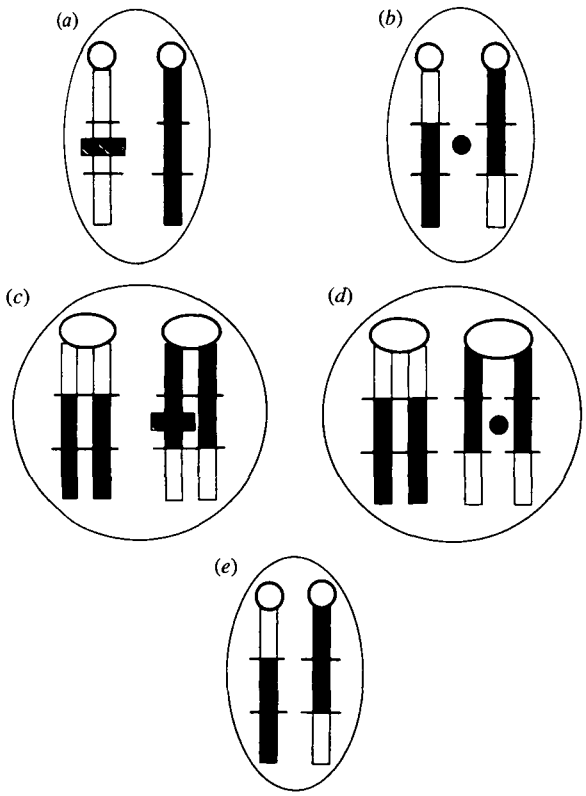

Fig. 2. One version of the Prudent Reparator. (*a*) Damage occurs at one locus (*b*) Recombination in G1. (*c*) Another damage occurs. (*d*) Recombination between the sister chromatids in G2. [Note that in (*a*) the damage could occur to the other chromosome with equal chance, resulting in a mutant allele converted to the wild type.]

https://doi.org/10.1017/S0016672300029815 Published online by Cambridge University Press

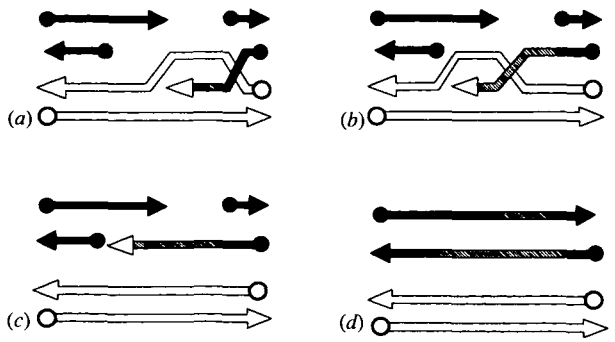

Fig. 3. A molecular mechanism for the Prudent Reparator. (*a*) Formation of a D loop by strand invasion. (*b*) Synthesis of new DNA by movement of the D loop. (*c*) Strand withdrawal. (*d*) Completion of repair.

spirit of the repair hypothesis) that the number of meiotic crossovers is a lower bound on the number of spontaneous DSBs in cells, then the fact that the frequency of mitotic recombination can be 1000-fold less than that of meiotic recombination (Orr-Weaver & Szostak, 1985), would indicate that normal mitotic cells deal with damage in a special way, and may be mechanistically close to the Prudent Reparator. Eighty per cent of mitotic gene conversions are induced in G1 in yeast, and 20% are induced in G2 (Roman & Ruzinski, 1990). Chemically induced DSBs induce sister chromatid exchange in the same organism (Fasullo & Davis, 1987). The molecular mechanism for channelling recombination towards sister-chromatic exchange may be that of mismatch repair (Rayssiguier *et al.* 1989).

An alternative model based on strictly molecular mechanisms is shown in Fig. 3. Here, the information of the intact DNA is copied, but recombination (allelic exchange) is avoided. The essence of this mechanism is a moving D loop in which synthesis on the intact template is taking place. Such an activity is in principle fully feasible: the uvsX protein of phage T4 mediates exactly such a process, linking recombination and DNA synthesis intimately (Alberts, 1987). The leading end of the D loop is opened by DNS synthesis, and the trailing end is continually reannealed through branch migration catalysed by the protein. If this process happens in a simple prokaryotic system, it could possibly be applied by an eukaryotic one as well if necessary.

This copy-choice mode of repair leading to gene conversion only is very similar to one of the earliest DSB-repair models by Resnick (1976): our mechanism (Fig. 3) differs from that shown in his Figs. 2 and 3 only in that a nicked strand of the undamaged DNA invades the damaged one in the latter whereas a strand from the damaged DNA goes to 'visit' the undamaged one in the former. We emphasize that our mechanism has been invented to demonstrate that it is possible to design easily a mode of repair avoiding allelic exchange altogether. Thus the first thesis of Bernstein *et al.* (1988; see Introduction) is not valid.

3. The Prudent Reparator: complementation and fitness

The question of functional haploidy and complementation can be discussed only in quantitative terms. We emphasize that we criticize the repair hypothesis under the assumptions made by its authors; i.e. we assume an infinite population, multiplicative fitness, and linkage equilibrium (cf. Hopf *et al.* 1988). Compelled by the nature of the problem, one has to consider many loci. Happily, a newly described principle (Szathmáry, in prep.) enables us to reduce the dynamics of genotype classes to that of the single-locus case. Two strategies are considered: the Prudent Reparator and outcrossing sex. We describe the single-locus dynamics of these two in turn.

There are two alleles: the wild type and the harmful mutant. The two strategies comprise the component processes as follows. The Prudent Reparator: mutation–damage/gene conversion–selection. The sexual strategy: mutation–meiosis–syngamy–selection. The single-locus equations are shown in the Appendix. Note that because of panmixis, the rate of gene conversion cancels from the equations of the latter since this process does not alter the allelic frequencies. The energetic cost of repair is assumed to be the same for both systems, and is thus neglected.

In order to pass from the single-locus case to the multilocus one we have to assume that there is linkage equilibrium. Considering that we are dealing with mutation-selection balance and multiplicative fitness this is justified (Felsenstein, 1974; Maynard Smith, 1978). Let us consider, following previous approaches (Haigh, 1978; Heller & Maynard Smith, 1979; Hopf *et al.* 1988), genotype (mutant) classes; if v_{ij} denotes the relative frequency of all genotypes with i mutant homozygous and j heterozygous loci, we obtain (Szathmáry, in prep.) from the single-locus dynamics (see Appendix):

$$v_{ij} = \frac{N!}{i!j!(N-i-j)!} x^{N-i-j} y^j z^i, \tag{1}$$

where x, y, z are the single-locus frequencies of wild-type homozygotes, heterozygotes, and mutant homozygotes, respectively. The population average fitness is, as a consequence of multiplicativeness, the Nth power of the single-locus average fitness, and the relative complementation of two genetic systems can also be judged from the single-locus equilibria.

If a genetic system harbours more recessives at equilibrium than another, then there is a transient gain in fitness when passing to it, due to the greater degree of complementation (Bernstein *et al.* 1985, 1988). Numerical results for the different genetic systems considered here are presented in Table 1. It is apparent that for certain parameter values, contrary to Bernstein *et al.*'s (1988) expectation, passing from outcrossing sexuality to the Prudent Reparator gives a transient advantage because of the higher degree of

Table 1. *Mutant allelic frequencies and fitnesses in equilibrium*

		q	w	System
$s = 10^{-3}$				
$\mu = 2 \times 10^{-6}$		0·0175	0·6870	S
	$\delta = 2 \times 10^{-6}$	0·0193	0·6730	P
	2×10^{-5}	0·0167	0·6934	P
	2×10^{-4}	0·0079	0·7662	P
	2×10^{-3}	0·0029	0·8109	P
$\mu = 2 \times 10^{-5}$		0·1075	0·0462	S
			(0·7535)	(S)
	$\delta = 2 \times 10^{-6}$	0·1692	0·01922	P
			(0·6735)	(P)
	2×10^{-5}	0·1464	0·0269	P
	2×10^{-4}	0·0736	0·0715	P
	2×10^{-3}	0·0282	0·1232	P
$s = 10^{-4}$				
$\mu = 2 \times 10^{-6}$		0·1075	0·7352	S
	$\delta = 2 \times 10^{-6}$	0·1464	0·6966	P
	2×10^{-5}	0·0736	0·7681	P
	2×10^{-4}	0·0283	0·8110	P

All values refer to $N = 10^5$ loci, except for those in parentheses referring to 10^4 loci. $h = 0{\cdot}1$ in all cases. q values displayed for the single-locus system, w values shown for the N-locus system. Fitness of sexuals does not include the two-fold cost of sex. P, Prudent Reparator; S, outcrossing sexual. Note that sexual systems are not affected by the value of δ since this does not alter the allelic frequencies in panmixis.

complementation in the latter. As explained in the Introduction, sex could be considered optimal in the sense that it has an intermediate degree of complementation, and a full capacity for recombinational repair. The Prudent Reparator is qualitatively similar: gene conversion corresponds to partial, rather than genome-wide, inbreeding (or automixis), since homozygosity is generated at only a few loci per generation in the former system.

Increase in the rate of gene conversion does reduce complementation below that of the sexual system, but the equilibrium fitness of the Prudent Reparator gets higher and higher. This situation is analogous to the gain in fitness (reduction of the mutation load) in sexual populations with inbreeding: it is more advantageous to remove the bad alleles in the homozygous form since in this case one genetic death results in the elimination of two mutant alleles at once (cf. Crow, 1970). This result is analogous to the finding that mean fitness increases with the rate of selfing in both inbred and outbred progeny (Ohta & Cockerham, 1974; Lande & Schemske, 1985; Charlesworth *et al.* 1990). Clearly, equilibrium fitnesses for the two systems are different, because gene conversion affects them differently (there is no free combination of alleles due to random mating in the Prudent Reparator). Discounting the two-fold cost of sex from the fitnesses in Table 1, we see that there is only one case where outcrossing sex is selectively superior to its rival.

The mutation rates are representative of a wide range of eukaryotes (Kondrashov, 1988; Maynard Smith, 1989). Available data seem to indicate that most deleterious mutations have only a slight effect on fitness (Simmons & Crow, 1977), and most of them are not completely recessive (Crumpacker, 1967). The crude estimate for DSBs is 0·1 per human cellular genome per day (Bernstein *et al.* 1985). A damage rate of 2×10^{-4} per locus per generation (Table 1) would imply 20 DSBs per genome per generation, counting only DSBs that occur at $\approx 10^5$ coding loci (note that the last figure is arguable). Given the fact that DSBs of only the last germ cell generation count (Bernstein *et al.* 1988), one would get 200 days as the duration of a generation from the estimated rate per day. Similarly, $\delta = 2 \times 10^{-3}$ implies 2000 days or 5·4 years. These time intervals for the last gametogenetic cell generation are of the right order of magnitude. We conclude that for humans, the Prudent Reparator would be selectively superior to sex. The conclusion is the same for *Drosophila* ($N = 10^4$). (The assumption that the rate of damage and subsequent gene conversion can be calculated on a per locus basis rests on the data on gene conversion tract lengths in Borts & Haber, 1989.) Thus the second thesis of Bernstein *et al.* (1988; see Introduction), that a closed repair system would become functionally haploid, is incorrect.

4. The Prudent Reparator: establishment and stability

The problem that complementation is lower than that maintained by sex is serious only with the extreme values $N = 10^5$, $\mu = 2 \times 10^{-5}$, $\delta = 2 \times 10^{-3}$, and $s = 10^{-3}$. Numerical solutions show that for the other parameter values, the transient population fitness after switching to the Prudent Reparator never gets below that of the sexual system, provided the two-fold cost of the latter is taken into account and the entire sexual population is thought to switch at once (although in fact, the parthenogenetic population consists of reproductively isolated clones). For the extreme values, however, the maladaptive transient lasts for over 2000 generations. Yet an infrequently occurring mutant allele which forces the organism to switch to prudent repair should be able to spread when rare if it arises in those genotypes of the sexual population which harbour relatively few bad alleles.

The last statement can be clarified through a model describing the dynamics of the individual genotypes. The essential elements of the numerical algorithm are as follows.

Mutation rates. Consider two genotypes i and j. Let the allelic mutation rate be μ and the back mutation rate be $\mu/10$. The reason why we assume non-zero back mutation rate in this particular case is that we would like to ensure that the same final mutant

https://doi.org/10.1017/S0016672300029815 Published online by Cambridge University Press

distribution be accessible from every invader type; and this needs back mutations for mutant homozygotes. In the course of mutation, both chromosomes of j can mutate to give either chromosome of genotype i. Thus first we have to calculate the probability that the first and second chromosome of genotype j mutate into the first and second chromosome of genotype i, respectively, then we calculate the probability for the first-$j \rightarrow$ second-i, second-$j \rightarrow$ first-i mutation. This double calculation is omitted whenever the two chromosomes of genotype i are identical (since then there is only one possible configuration).

Gene conversion. Let the gene conversion rate per diploid locus be δ. The single-locus dynamics are explained in the Appendix. For the multilocus case, there are some forbidden transition types. For any locus, the wild type homozygote cannot be converted to a mutant homozygote and vice versa. Neither homozygote can give rise to a heterozygote. If we fix genotypes i and j in a given arrangement, corresponding loci can be heterozygous but in the opposite configuration. If there are two or more such loci, gene conversion cannot convert these genotypes into one another. Whenever these particular problems are absent, genotype j can be converted into genotype i. Let the number of common heterozygous loci be m, and the number of excess homozygous loci in genotype i be n. Then the conversion rate from j to i is: $(\delta/2)^n(1-\delta)^m$.

Recombination. In linkage equilibrium, the only effect of recombination is to destroy heterozygosity (cf. Hopf *et al.* 1988). The probability that the ith locus from the centromere becomes homozygous depends on the number of crossovers between the locus and the centromere. This number k should be odd, assuming simply two single-chromatid chromosomes only. Then the overall probability for the ith locus is:

$$r_i = \sum_{k=1}^{i-1} \binom{i-1}{k} \delta^k (1-\delta)^{i-1-k} \tag{2}$$

and the genome-wide average for N loci is

$$\rho = \left(\sum_{i=1}^{N} r_i \right) / N. \tag{3}$$

We use this value for each locus throughout the genome. The probability of a crossover per locus equals the per locus damage rate, since in this model the repair of every damage results in allelic exchange; thus we are applying a worst-case approach to the problem.

Gamete production. The probability that the jth genotype gives the ith gamete is simply $g/2$, where g is the number of chromosomes in the diploid which are identical with the chromosome of the gamete ($g = 0, 1, 2$).

Zygote production. If the two chromosomes of the chosen diploid genotype are identical to those of the gametes, the probability of zygote formation from the latter is 1, otherwise it is zero.

Numerical results from this model are shown in Fig. 4, where the fitness dynamics of various parthenogenetic invaders (reproductively isolated clones) with mitotic recombination are displayed. It is apparent that if the genome of the invader is relatively uncontaminated, then the average fitness of the emerging mutant distribution never gets below that of the complete sexual population, despite the lesser complementation shown by the former in equilibrium. Note again that this is shown for the worst possible case. For the Prudent Reparator, the average complementation ability is higher anyway.

(Note that one can approximately determine the probability that a parthenogen will arise and be established in a sexual population, by calculating the chance that this individual will have a higher fitness than the average fitness of the N-locus sexual population, scaled down by the two-fold cost.)

The above finding is partly consistent with some results on selfing. It has been argued that the establishment of selfing should always be possible since if the rate of selfing is high, there is always some chance that the modifier allele for it will find itself in an uncontaminated genome (Campbell, 1986; Lande & Schemske, 1985).

The larger the relative selective advantage of the parthenogen, the higher is the probability of its final establishment (not forgetting that a whole mutant distribution emerges slowly during establishment, rendering the calculation of ultimate fixation very complicated).

Based on the foregoing, there are basically two ways for the Prudent Reparator to arise: (1) to appear simultaneously with diploidy; (2) to invade an existing diploid population. We discuss these in turn.

Let us accept for the time being that outcrossing evolved in haploids to bring undamaged DNA into cells for recombinational repair (Bernstein *et al.* 1985). Because of the recombinational load (Wright, 1931; Charlesworth & Charlesworth, 1975), avoidance of the breaking up of coadapted gene complexes was useful, and this could have channelled repair towards the mechanism in Fig. 3, suppressing crossing-over. Diploidy, if it arose for whatever reason, could have led to the Prudent Reparator at once.

Invasion of a sexual system by a parthenogen is always difficult, but it has happened a number of times (Maynard Smith, 1978; Bell, 1982). Inbreeding depression can no doubt surpass the twofold cost of sex, which leads to highly unfit progeny in infrequently parthogenetic species, especially with automixis (Bell, 1982). It seems that parthenogenesis mostly arises by more direct 'macromutations', occurring infrequently but establishing themselves successfully in the short run (White, 1973, 1978; Maynard Smith, 1978).

A critical element in the appearance of parthenogens is the above finding that inbreeding depression is not

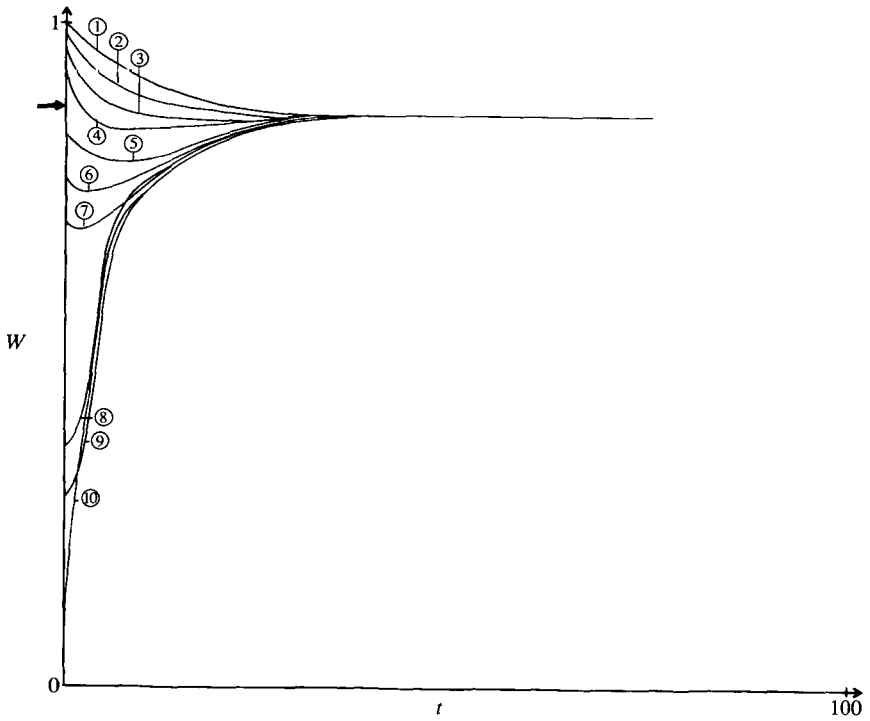

Fig. 4. Fitness dynamics of a switch from outcrossing sexuality to parthenogenesis with mitotic recombination for three loci and two alleles. It is assumed that a single type of sequence (as a macromutant) switches to parthenogenesis in each case, one from each of the 10 genotype classes. Each line represents an independent clone. For each parthenogen the same new mutant distribution is finally attained, but during the transition, the fitness of the mutant population can be lower as well as higher than that of the entire sexual population (indicated by an arrow on the w axis). The genotypes of the original invaders are as follows (the allelic sequences of the two chromosomes are presented as strings; w and m stand for the wild type and the mutant allele, respectively): 1, www and www; 2, mww and www; 3, mmw and www; 4, mmw and wwm; 5, wwm and wwm; 6, mmw and wmw; 7, mmw and mmw; 8, mmw and mwm; 9, mmm and mwm; 10, mmm and mmm. $s = 0{\cdot}4$, $h = 0{\cdot}1$, $\delta = 0{\cdot}05$, $\mu = 0{\cdot}05$.

necessarily manifested even for those practising mitotic recombination, provided the macromutant has a rather uncontaminated genome with a relatively high frequency of good alleles. It is apparent that in a large population such uncontaminated genotypes will always be present. Since there is no mating with an external partner, the establishing clone approaches mutation–selection balance rather slowly. (For the Prudent Reparator, as shown above, complementation may not be a problem at all.)

Let us, then, imagine a scenario following which the Prudent Reparator can easily establish itself. Imagine that some population of a species gets into an ecologically troubled habitat. Population size is likely to decrease, forcing inbreeding on the population as a whole. Harmful recessives begin to be unmasked. A parthenogen is likely to invade under such circumstances because it does not have to find a mate, does not have to produce males, and there is low complementation for the whole population anyway. Later, a mutant clone would take over with a greater masking ability: the Prudent Reparator establishes itself. Note that parthenogenesis is often associated with unfavourable habitats and low population densities (Bell, 1982).

Once the Prudent Reparator is established, it is stable against invasion by sexuals, primarily because the cost of finding a mate tends to infinity: quite unlike parthenogenetic macromutants in a sexual population, sexual ones in an asexual population are 'hopeless monsters' (Krieber & Rose, 1986).

Thus it is not true, contrary to Bernstein *et al.*'s third thesis (1988; see Introduction), that the mutations inducing parthenogenesis and 0% allelic exchange must occur at once; in fact, the latter can follow the former. Also, the Prudent Reparator can resist invasion by a sexual female. If the repair hypothesis were correct, and repair and complementation were the major forces relevant to sex, then we should see species adopting the Prudent Reparator strategy all over the biosphere. As this is not so, we conclude that the repair hypothesis is insufficient to explain the maintenance of outcrossing sex in diploids.

5. Outlook

The possibility that the rate of DSB occurrence in mitotic cells is much less than that assumed by the repair hypothesis, and that meiotic recombination is initiated by enzymatically produced recombinogenic lesions (Orr-Weaver & Szostak, 1985), is open. The fact that DSBs can be the initiation sites for meiotic recombination (Sun *et al.* 1989) is only consistent with the repair hypothesis but does not prove it; it ought to

be demonstrated at least that the breaks are spontaneous rather than enzymatically induced; the data are insufficient to decide on this.

Let us assume, in the spirit of the repair hypothesis, that recombinogenic DSBs that occur in meiosis arise spontaneously. In the light of the present model even this would be insufficient for sex to be superior. Dropping the assumption of multiplicative fitness may change the conclusion dramatically. There is evidence that harmful mutations act synergistically, and that this selects for outcrossing sexual recombination (reviewed by Kondrashov, 1988). The snag is that it would do so without spontaneous DSBs as well. So, if it turns out that meiotic recombination is initiated by spontaneous DSBs (as required by the repair hypothesis), and mutations act synergistically (as required by the mutation theory), this should be evidence more for the latter than the former (Kövér & Szathmáry, in prep.). Note that the repair hypothesis as applied to eukaryotic diploids cannot be substantiated by experiments on bacteria (Michod *et al.* 1988) or haploid yeast (Bernstein & Johns, 1989).

Finally, three interesting aspects of the Prudent Reparator may be noted. First, depending on the rate of gene conversion, it can maintain functional diploidy without outcrossing sex (cf. Lewis & Wolpert, 1979). Second, with a certain efficiency, it can resist the effect of Muller's ratchet (Muller, 1964; Maynard Smith, 1978; Haigh, 1978), since unbiased gene conversion mimics frequent back mutation, thus restoring the optimal genotype lost by chance from a finite population (Szathmáry & Kövér, in prep.). Third, whether the Prudent Reparator is important in the genetics of such long-lasting parthenogenetic taxa such as the bdelloid rotifers (Maynard Smith, 1978) or not, remains to be seen.

We thank for useful discussions for (F. Hopf and R. Michod) and against (J. Maynard Smith) the repair hypothesis, and an anonymous referee for helpful comments. This work was partly supported by the SOROS Foundation and the Hungarian National Research Fund (OTKA).

Appendix

(A) *Dynamics of the Prudent Reparator*

Let the frequency of the wild-type homozygote, the heterozygote and the mutant homozygote be x, y, and z, respectively. After mutation we have:

$$x_1 = x(1-\mu)^2, \quad \text{(A 1}a\text{)}$$
$$y_1 = 2x\mu(1-\mu)+y(1-\mu), \quad \text{(A 1}b\text{)}$$
$$z_1 = z+x\mu^2+y\mu \quad \text{(A 1}c\text{)}$$

where μ is the allelic mutation rate per haploid locus.

After damage and gene conversion:

$$x_2 = x_1+y_1\delta/2, \quad \text{(A 2}a\text{)}$$
$$y_2 = y_1(1-\delta), \quad \text{(A 2}b\text{)}$$
$$z_2 = z_1+y_1\delta/2, \quad \text{(A 2}c\text{)}$$

where δ is the rate of damage per diploid locus. It is assumed that damage occurs to either chromosome with a probability of $\delta/2$ per locus; the net consequence of repair is thus unbiased gene conversion. Obviously, this process does not alter homozygous loci, but converts heterozygous ones into either homozygote. Mutations occurring during gene conversion and DSBs damaging both chromosomes at the same locus are deliberately neglected since they occur on the order of $\delta\mu$ and δ^2, respectively.

After selection we have:

$$x' = x_2/w, \quad \text{(A 3}a\text{)}$$
$$y' = y_2(1-hs)/w, \quad \text{(A 3}b\text{)}$$
$$z' = z_2(1-s)/w, \quad \text{(A 3}c\text{)}$$

where the average fitness w is:

$$w = 1-hsy_2-sz_2, \quad \text{(A 4)}$$

and $1-h$ is the degree of dominance, and s is the per locus selective disadvantage for the mutant homozygote.

In order to find the equilibrium frequencies we put system (A 1)–(A 3) in a different form:

$$x' = [x(1-b-c)+ay]/w, \quad \text{(A 5}a\text{)}$$
$$y' = [y(1-a-d)+bx](1-hs)/w, \quad \text{(A 5}b\text{)}$$
$$z' = (cx+dy+z)(1-s)/w, \quad \text{(A 5}c\text{)}$$

where a, b, c and d are overall dynamical coupling constants, i.e.:

$$a = \delta(1-\mu)/2, \quad \text{(A 5}d\text{)}$$
$$b = 2\mu(1-\delta)(1-\mu), \quad \text{(A 5}e\text{)}$$
$$c = \mu[\mu(1-\delta)+\delta], \quad \text{(A 5}f\text{)}$$
$$d = [\mu(2-\delta)+\delta]/2. \quad \text{(A 5}g\text{)}$$

We seek the equilibrium solutions when in system (A 5) $x' = x$, $y' = y$, and $z' = z$. Note that because z does not explicitly show up in (A 5a, b), the ratio of the frequencies of X and Y (capital letters designate equilibrium values) can be calculated from these two equations alone:

$$(1-hs)(bX-Y(a+d-1))/Y = -(X(b+c-1)-aY)/X, \quad \text{(A 6)}$$

thus we have two roots [substituting the parameters (A 5d–g)]:

$$X = \pm Y[H+(\mu(\delta-1)+\delta)-hs(\delta-1)]/[4\mu(1-hs)(1-\delta)], \quad \text{(A 7)}$$

where

$$H = \sqrt{[h^2s^2(1-\delta)^2+2hs(\mu[\delta^2-1]-\delta^2+\delta)+\mu^2(1-\delta)^2-2\mu\delta(\delta-1)+\delta^2]}. \quad \text{(A 8)}$$

It can be proved that the numerator of eqn (A 7) with the positive sign is always positive provided $\mu\delta(1-\delta)(1-hs) > 0$, which is obviously satisfied. Therefore, we have one positive and one negative root in (A 7), if $Y > 0$ holds (which must be true). As only the root $X > 0$ is feasible, we conclude that there is only one fixed point in the interior of the simplex. It can be seen

directly that $X = Y = 0$, $Z = 1$ is another fixed point.

The equilibrium in the interior can be calculated as follows. We substitute the positive root X under (A 7) and $Z = 1-X-Y$ into (A 5c), and we solve for Y. The root is:

$$Y = \frac{ahs-[bfhs+cf-(d[hs-1]+s[f+1-h])]}{s[ah-(bfh+cf-[d(h-1)+f-h+1])](f+1)}, \quad \text{(A 9)}$$

where f stands for the coefficient of Y in (A 7). Expanding the overall parameters by (A 5) results in a surprisingly complex (one page long) expression for Y, which can only be evaluated numerically. However, knowing relation (A 7) and the constraint that the system is confined to the simplex, the equilibrium solution is in principle available.

The asymptotic stability of the equilibria can be calculated by local analysis following the standard procedure (Roughgarden, 1979). First we substitute the values of (5d–g) into eqns (5a–c). Then (5c) and the variable z can be omitted using the constraint $z = 1-x-y$. (There are 2 degrees of freedom since the variables move on a triangular simplex.) We calculate the Jacobian matrix of the system, and substitute $x = 0$, $y = 0$. The entries then look as follows:

$$j_{xx} = (\mu(\delta-1)+1)(\mu-1)/(s-1), \quad \text{(A 10}a\text{)}$$
$$j_{xy} = \delta(\mu-1)/(2(s-1)), \quad \text{(A 10}b\text{)}$$
$$j_{yx} = 2\mu(\delta-1)(\mu-1)(hs-1)/(s-1), \quad \text{(A 10}c\text{)}$$
$$j_{yy} = (\delta-1)(\mu-1)(hs-1)/(s-1). \quad \text{(A 10}d\text{)}$$

From the matrix (A 10) we can calculate the eigenvalues:

$$\lambda_{1,2} = \frac{(\mu-1)[\pm H+hs(\delta-1)+\mu(\delta-1)+2-\delta]}{2(s-1)}. \quad \text{(A 11)}$$

The above eigenvalues can be evaluated numerically for all the parameter values in Table 1 (data not shown). The fixed-point $Z = 1$ is unstable in all cases investigated, since stability would require that both eigenvalues lie between -1 and $+1$, and this is not the case.

Calculation of the stability of the interior fixed-point [(A 7), (A 9)] is much more difficult. We give the entries of the Jacobian matrix in the general form in the order of (A 10):

$$-4(\mu-1)(sy(\delta-1)(\mu-1)^2(h-1)+(1-s)(\mu(\delta-1)+1))/U, \quad \text{(A 12}a\text{)}$$
$$2(\mu-1)(2sx(\delta-1)(\mu-1)^2(h-1)+\delta(s-1))/U, \quad \text{(A 12}b\text{)}$$
$$4(\delta-1)(\mu-1)(hs-1)(sy(\mu-1)^2+2\mu(s-1))/U, \quad \text{(A 12}c\text{)}$$
$$-4(\delta-1)(\mu-1)(hs-1)(sx(\mu-1)^2+1-s)/U, \quad \text{(A 12}d\text{)}$$

where U is:

$$[2sx(\mu-1)[2h\mu(\delta-1)+1-\mu(\delta-1)]+sy(\mu-1)[2h(\delta-1)+2-\delta]+2(s-1)]^2. \quad \text{(A 13)}$$

Again, the eigenvalues can be numerically calculated to give the result that for all parameter values in Table 1. The interior fixed-point is stable since the eigenvalues are positive and smaller than 1.

(B) *Dynamics of the sexual outcrosser*

Let the frequency of the recessive allele be q. Equilibrium q in selection–mutation balance (Crow, 1970, p. 137):

$$Q = \frac{-hs(1+\mu)+\sqrt{[(hs)^2(1+\mu)^2+4s(1-2h)\mu]}}{2s(1-2h)}. \quad \text{(B 1)}$$

The equilibrium fitness is (Crow, 1970, p. 137):

$$w = 1-\mu-Qhs(1-\mu) \quad \text{(B 2)}$$

The equilibrium frequency in mutation–selection balance is:

$$-\frac{F(h-1)G-[h^2s(\mu-3)+h[4-s(\mu-1)]-2][G-hF(\mu+1)]}{2F[hFG-(h^2(\mu+1)-4h+2)](2h-1)(\mu-1)} \quad \text{(B 3)}$$

where

$$F = \sqrt{s};\ G = \sqrt{[h^2s(\mu+1)+8h\mu+4\mu]}. \quad \text{(B 3}a\text{)}$$

References

Alberts, B. M. (1987). Prokaryotic DNA replication mechanisms. *Philosophical Transactions of the Royal Society of London* B**317**, 395–420.

Bell, G. (1982). *The Masterpiece of Nature*. London: Croom Helm.

Bernstein, H. (1977). Germ line recombination may be primarily a manifestation of DNA repair processes. *Journal of Theoretical Biology* **69**, 371–380.

Bernstein, H., Byerly, H. C., Hopf, F. A. & Michod, R. (1985). Genetic damage, mutation, and the evolution of sex. *Science* **229**, 1277–1281.

Bernstein, H., Byers, G. S. & Michod, R. (1981). Evolution of sexual reproduction: importance of DNA repair, complementation, and variation. *American Naturalist* **117**, 537–549.

Bernstein, H., Hopf, F. A. & Michod, R. E. (1988). Is meiotic recombination an adaptation for repairing DNA, producing genetic variation, or both? In *The Evolution of Sex: and Examination of Current Ideas* (ed. R. E. Michod and B. R. Levin), pp. 139–160. Sunderland: Sinauer.

Bernstein, C. & Johns, V. (1989). Sexual reproduction as a response to H_2O_2 damage in *Schizosaccharomyces pombe*. *Journal of Bacteriology* **171**, 1893–1897.

Borts, R. H. & Haber, J. E. (1989). Length and distribution of meiotic gene conversion tracts and crossovers in *Saccharomyces cerevisiae*. *Genetics* **123**, 69–80.

Campbell, R. B. (1986). The interdependence of mating structure and inbreeding depression. *Theoretical Population Biology* **30**, 232–244.

Charlesworth, B. & Charlesworth, D. (1975). An experiment on recombination load in *Drosophila melanogaster*. *Genetical Research* **25**, 267–274.

Charlesworth, D., Morgan, M. T. & Charlesworth, B. (1990). Inbreeding depression, genetic load, and the evolution of outcrossing rates in a multilocus system with no linkage. *Evolution* **44**, 1469–1489.

Crow, J. F. (1970). Genetic loads and the cost of natural selection. In *Mathematical Topics in Population Genetics* (ed. K. Kojima), pp. 128–177. Berlin: Springer-Verlag.

Crumpacker, D. W. (1967). Genetic loads in maize (*Zea mays* L.) and other cross-fertilized plants and animals. *Evolutionary Biology* **1**, 306–423.

Dougherty, E. C. (1955). Comparative evolution and the origin of sexuality. *Systemaic Zoology* **4**, 149–169.

Fasullo, M. T. & Davis, R. V. (1987). Recombinational substrates designed to study recombination between unique and repetitive sequences *in vivo*. *Proceedings of the National Academy of Sciences of the USA* **84**, 6215–6219.

Haigh, J. (1978). The accumulation of deleterious genes in a population – Muller's ratchet. *Theoretical Population Biology* **14**, 251–267.

Heller, R. & Maynard Smith, J. (1979). Does Muller's ratchet work with selfing? *Genetical Research* **32**, 289–293.

Hopf, F. A., Michod, R. E. & Sanderson, M. J. (1988). The effect of the reproductive system on mutation load. *Theoretical Population Biology* **33**, 243–265.

Kondrashov, A. S. (1988). Deleterious mutations and the evolution of sexual reproduction. *Nature* **336**, 435–440.

Krieber, M. & Rose, M. R. (1986). Males, parthenogenesis, and the maintenance of anisogamous sex. *Journal of Theoretical Biology* **122**, 421–440.

Lande, R. & Schemske, D. W. (1985). The evolution of self-fertilization and inbreeding depression in plants I. Genetic models. *Evolution* **39**, 24–40.

Lewis, J. & Wolpert, L. (1979). Diploidy, evolution and sex. *Journal of Theoretical Biology* **78**, 425–438.

Maynard Smith, J. (1978). *The Evolution of Sex*. Cambridge: Cambridge University Press.

Maynard Smith, J. (1988). The evolution of recombination. In *The Evolution of Sex*: *an Examination of Current Ideas* (ed. R. E. Michod and B. R. Levin), pp. 106–125. Sunderland: Sinauer.

Maynard Smith, J. (1989). *Evolutionary Genetics*. Oxford: Oxford University Press.

Michod, R. E., Wojciechowski, M. F. & Hoelzer, M. A. (1988). DNA repair and the evolution of transformation in the bacterium *Bacillus subtilis*. *Genetics* **118**, 31–39.

Moran, P. A. P. (1962). *The Statistical Processes of Evolutionary Theory*. Oxford: Oxford University Press.

Muller, H. J. (1964). The relation of recombination to mutational advance. *Mutation Research* **1**, 2–9.

Ohta, T. & Cockerham, C. C. (1974). Detrimental genes with partial selfing and effects on a neutral locus. *Genetical Research* **23**, 191–200.

Orr-Weaver, T. L. & Szostak, J. W. (1985). Fungal recombination. *Microbiological Reviews* **49**, 33–58.

Rayssiguier, C., Thaler, D. S. & Radman, M. (1989). The barrier to recombination between *Escherichia coli* and *Salmonella typhimurium* is disrupted in mismatch-repair mutants. *Nature* **342**, 396–401.

Resnick, M. A. (1976). The repair of double-strand breaks in DNA: a model involving recombination. *Journal of Theoretical Biology* **59**, 97–106.

Roman, H. & Ruzinski, M. M. (1990). Mechanisms of gene conversion in *Saccharomyces cerevisiae*. *Genetics* **124**, 7–25.

Roughgarden, J. (1979). *Theory of Population Genetics and Evolutionary Ecology*: *an Introduction*. New York: Macmillan.

Simmons, M. J. & Crow, J. F. (1977). Mutations affecting fitness in *Drosophila* populations. *Annual Reviews in Genetics* **11**, 49–78.

Sun, H., Treco, D., Schultes, N. P. & Szostak, J. W. (1989). Double-strand breaks at an initiation site for meiotic gene conversion. *Nature* **338**, 87–90.

Walker, I. (1978). The evolution of sexual reproduction as a repair mechanism. Part I A model for self-repair and its biological implications. *Acta Biotheoretica* **27**, 133–158.

Walker, I. & Williams, R. M. (1976). The evolution of the cooperative group. *Acta Biotheoretica* **25**, 1–43.

White, M. J. D. (1973). *Animal Cytology and Evolution*. Cambridge: Cambridge University Press.

White, M. J. D. (1978). *Modes of Speciation*. San Francisco: Freeman.

Williams, R. M. & Walker, I. (1978). The evolution of sexual reproduction as a repair mechanism. Part II. Mathematical treatment of the wheel model and its significance for real systems. *Acta Biotheoretica* **27**, 159–184.

Wright, S. (1931). Evolution in Mendelian populations. *Genetics* **16**, 97–159.