



A selfish origin for recombination

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Received 21 November 2002; received in revised form 18 February 2003; accepted 27 February 2003

Abstract

Recent findings of molecular biology show that recombination is initiated by interactions between homologous chromosomes and that an allele can induce the initiation of recombination on the homolog. Since gene conversion at the site of initiation is strong enough to promote the transmission of that allele, recombination may be a way for a self-promoting element to spread, even if it gives no advantage to the individual or to the population. I develop a simple model and discuss available molecular evidence in support of this hypothesis. A consequent argument is that with asexual reproduction the evolution of recombination leads to an intragenomic conflict, and a possible outcome of this conflict may be the origin of sexual reproduction.

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Keywords: Recombination; Gene conversion; Evolution of sex; Intragenomic conflict

1. Introduction

Current explanations of the advantage of recombination derive, in different ways, from Weismann's idea (Burt, 2000) that recombination allows different combinations of alleles to be present in different individuals, that is to produce variability on which natural selection can act. Most theories (discussed in Kondrashov, 1993; Barton and Charlesworth, 1998) belong to one of two categories: either recombination increases the rate of adaptive evolution, by generating new allele combinations, or it prevents the accumulation of deleterious mutations.

In virtually all these theories recombination has been considered a mechanism that rearranges alleles elsewhere on the chromosome. Recombination, however, is a physical process of contact and exchange of DNA and this process affects also the very site where its initiation occurs. At this site, because of the molecular mechanism of initiation, one of the two alleles is transmitted with a higher probability than the other by gene conversion. Gene conversion is a very powerful force, comparable to meiotic drive, because it allows the preferential transmission of an allele even if this does not confer an advantage to the individual. Its effects, therefore, cannot be ignored.

But there is another reason to consider the evolution of recombination at the molecular level. Classical population genetics models have emphasized the role of modifier genes (for a review see Feldman et al., 1996) on the evolution of recombination, that is they have considered the evolution of recombination at a certain site as something imposed by another locus at a different position. This is of course appropriate to describe the action of the molecular machinery that induces the various steps of crossing over. However, recombination is influenced not only by this molecular machinery, but also by the very site where its initiation occurs: it is well known that some sequences are more likely than others to be sites for the initiation of recombination, that is some sequences are hotspots for recombination.

Therefore, not only can an allele at the site of initiation be subject to the effects of gene conversion, but it can also in some way influence the origin of crossing over, hence the probability of gene conversion at that locus. Thus it is possible that an allele induces crossing over just because in this way it is preferentially transmitted to the progeny through gene conversion, regardless of the effects of recombination on the rest of the genome. In this sense that allele could be considered a self-promoting element.

Self-promoting genetic elements are genetic sequences that promote their own transmission: they spread not because they increase the fitness of their carriers, but because they become over-represented in the genome.

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Examples of such elements include meiotic drive genes and cytoplasmic sex ratio distorters (Hurst et al., 1996).

2. The hypothesis of a self-promoting element

The main idea of this paper is that recombination is a consequence of a self-promoting element that promotes its own spread through gene conversion, acting as a site for the initiation of crossing over. The idea follows from these simple facts: (i) the initiation of recombination at one site can be induced by an allele at that site; (ii) at the site of initiation, gene conversion occurs in favor of that allele; (iii) gene conversion allows an allele to spread even if it does not confer any advantage to the organism.

I first discuss our current knowledge of the molecular biology of recombination about gene conversion and the mechanism of initiation. Then I develop a simple model to show that gene conversion alone can explain the evolution of recombination in a sexual population without any advantage at the individual level.

In the second part of the paper I discuss the possibility of a similar self-promoting element evolving in a clonal diploid organism. This may lead to an intragenomic conflict, because recombination, unmasks recessive deleterious mutations. One of the possible resolutions of this intragenomic conflict may be the evolution of sexual reproduction.

3. Gene conversion and recombination

Crossing over is due to many (at least 11) different genes (Paques and Haber, 1999), the products of which are necessary in the different steps of the process. These genes have also other functions, especially for DNA repair, indeed the molecular machinery is almost the same, and crossing over is widely believed to have evolved from the mechanism of DNA repair (see for example Devoret, 1988; Bernstein et al., 1985, 1988). A damage on one strand can be corrected using the sister chromatid as a template; if both strands are damaged instead the template must come from the homologous chromosome. In both cases the machinery for DNA repair induces invasion and replacement of the damaged sequence with the template (Devoret, 1988; Kowalczykowsky et al., 1994; Cox, 1997).

The existence of this machinery provides the opportunity for a self-promoting element to evolve. In a diploid organism, an allele that manages to exploit this machinery to invade the homologous chromosome and replace the homologous sequence will increase number of copies of itself in the genome. This is what actually happens in gene conversion (see for example Gutz and Leslie, 1976; Orr-Weaver and Szostak, 1985; Leach, 1996). Gene conversion occurs because at the initiation

of crossing over one strand is partially removed and replaced to allow the formation of a joint molecule (see Fig. 1). Two main molecular models have been proposed after Holliday (1964) to explain gene conversion and recombination (Fig. 1). In the Meselson–Radding model (MR, Meselson and Radding, 1975) crossing over begins with a single-strand nick on one homolog, after which one end of the broken strand invades the homologous duplex. In the double-strand break repair model (DSBR, Orr-Weaver and Szostak, 1985) instead, crossing over begins with a double-strand break (DSB) and the 5' of the broken strands is removed, allowing the invasion of one strand of the homologous sequence. I will call recombinogenic the allele that replaces the homologous sequence. In both cases the hybrid double strand (heteroduplex), with one strand from the A allele and one strand from the a allele, is corrected and becomes homoduplex of the original allele (restoration, that is the A:a ratio becomes 4:4) or of the recombinogenic allele (gene conversion, the A:a ratio

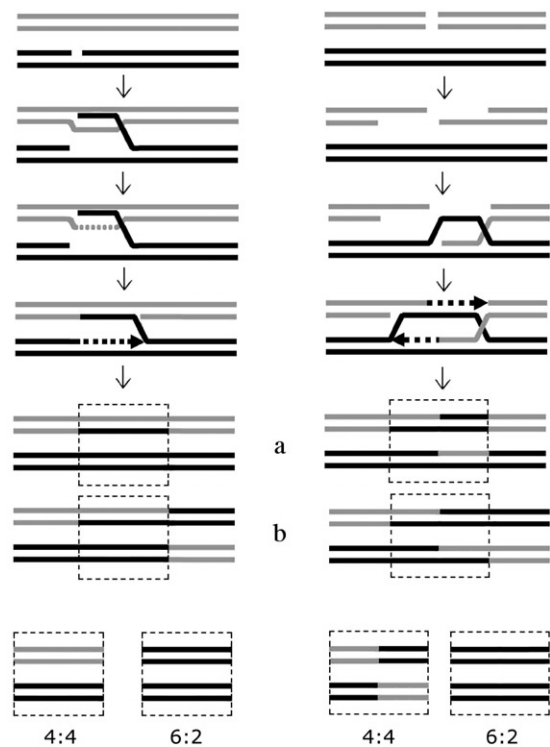


Fig. 1. Molecular models of gene conversion and recombination. Left: MR model. Right: DSBR model. The two double-stranded DNA molecules of the two chromatids (one in gray, the other in black) participating in crossing over are shown (note that each line is a single strand, therefore each double strand is a chromatid; the other two chromatids not participating in crossing over are not shown). The resolution of the joint molecule (the “Holliday junction”, not shown, see references in the text) produces non-recombinant (a) or recombinant (b) chromosomes with the same probability. In both cases the original allele in the heteroduplex (emphasized) will be then converted (yielding a 6:2 segregation in favor of the recombinogenic allele) or restored (yielding a normal 4:4 segregation).

becomes 6:2), but on average, if there is no bias, still 5:3. A heterozygote for a locus with two alleles A and a, therefore, will produce gametes with a ratio $A:a=5:3$ instead of the Mendelian 1:1, if the initiation of crossing over occurs at this locus and if the displaced strand belongs to allele a.

The resulting chromosomes will be recombinant or not with about the same probability because the intermediate joint molecule (the “Holliday junction”, see Fig. 1) can be cut and rejoined in two ways at random, yielding 50% recombinant and 50% non-recombinant products (Meselson and Radding, 1975; Szostak et al., 1983; Orr-Weaver and Szostak, 1985; Devoret, 1988; Kowalczykowsy et al., 1994; Leach, 1996; Paques and Haber, 1999). Throughout this discussion I will refer to the physical process of interaction and exchange between two DNA molecules as crossing over, and recombination will mean a possible outcome of crossing over (producing recombinant chromosomes), the other possible outcome being without recombination (producing non-recombinant chromosomes).

3.1. Molecular mechanism of the initiation

The logic of this paper is that crossing over is influenced by the recombinogenic site and not only by some other modifier genes. I am assuming only that a recombinogenic allele manages to exploit an existing molecule to induce a break on the homologous sequence. Once a break is present the machinery for DNA repair will process it as in Fig. 1. Therefore, such a molecule is supposed to be already present in the nucleus for another purpose, and to be able to induce a break. Before describing this molecule in detail, it is necessary to point out that there is a difference between the two models for the initiation of crossing over.

In the MR model the allele that promotes invasion is the same that invades and replaces the homolog and thus it is straightforward to see that it has the advantage of conversion. The MR model has been helpful to understand that crossing over is initiated by a single strand of only one homolog, and not by two single strands of the two homologs as in the original Holliday model. However, in spite of some recent discussions based on the MR model (see for example Leach, 1996; Wiuf and Hein, 2000), there is evidence that most crossing over events are initiated by DSBs, and the favorite molecular model for recombination, at least in eukaryotes, seems to be the DSB model (Paques and Haber, 1999).

The molecule that induces meiotic DSBs, and therefore the initiation of recombination, was for a long time supposed to be an endonuclease, though none of the genes involved in the initiation of recombination seemed to encode for a putative endonuclease (Haber, 1997).

In fact, successive discoveries in the molecular biology of recombination have not borne out this expectation: the protein that induces DSBs is not an endonuclease. It is a protein, called Spo11, which turns out to be a topoisomerase II-like protein (Bergerat et al., 1997; Haber, 1997; Keeney et al., 1997). This has several implications.

Already before the discovery of Spo11, there was evidence that interactions between homologs occur early during meiosis, prior to DSBs formation (Weiner and Kleckner, 1994; Xu and Kleckner, 1995; Keeney and Kleckner, 1996; Rocco and Nicolas, 1996). A topoisomerase II can interact simultaneously with two DNA duplexes (Roca et al., 1993) and this supports the idea that homologs interact before DSBs formation (Keeney et al., 1997). It has been suggested that Spo11 played initially a role in homolog pairing (Keeney et al., 1997; Haber, 1997), and type II topoisomerases are known to function in chromosome segregation, and to be able to induce transient cleavages.

Another important point, indeed, is the cleavage mechanism of a type II topoisomerase: a topoisomerase captures a DNA molecule and repeatedly cleaves and rejoins it, allowing direct reversal of the cleavage site to restore the integrity of the broken duplex. This cycle is interrupted to produce a non-reversible break only in the presence of the homologous sequence, which induces a conformational change in the structure of the topoisomerase (Berger et al., 1996; Haber, 1997; Keeney et al., 1997), and must therefore have some importance in inducing the break.

On the other hand, and this is the main point, there is evidence that DSBs frequencies on one chromosome can be increased by sequences at an allelic position on the homologous chromosome, i.e. in *trans* (Xu and Kleckner, 1995; Fan et al., 1995; Bullard et al., 1996; Keeney and Kleckner, 1996; Rocco and Nicolas, 1996; Keeney, 2001). Xu and Kleckner (1995) report that changes on one chromosome at a particular locus can influence the pattern of DSBs at the corresponding locus of the homologous chromosome, and at least in some cases the effect of a mutant allele is to *increase* DSBs in *trans*. Keeney and Kleckner (1996) further report that the chromatin structure at a certain site (chromatin structure influences the likelihood of DSBs) is influenced not only by the allele on that chromosome but also by the allele on the homologous chromosome, and suggest that such effects might be observed and be important even in cells that exhibit only partial or transient co-alignment of homologs (e.g. in mitosis). Bullard et al. (1996) also show that a mutation may act to stimulate DSBs in *trans*; they further suggest that certain sequences may act as hotspots only because of a more accessible conformation for the proteins involved in making the break, and not because they are preferentially recognized as sites for DSBs in *cis* (i.e. on that chromosome).

Further experimental studies could be performed to test in more details the capacity of mutant alleles to induce DSBs in *trans*, but the available data already provide unambiguous evidence that initiation of crossing over may be induced, or at least enhanced, through Spo11, by the allele that has the advantage of gene conversion.

The discovery that Spo11 (and not an endonuclease) induces the initiation of recombination, and the observations that an allele can stimulate DSBs in *trans* support the idea that recombination may be induced by a self-promoting element.

4. A model for the evolution of recombination in a sexual population

4.1. A self-promoting process

A recombinogenic allele will have an immediate advantage in a sexual population. If it is not deleterious it will quickly go to fixation even without any beneficial effect due to recombination for the individual. But it may spread in a sexual population even if its effect on the host genome is deleterious: if p is the frequency of gametes containing a recombinogenic allele and s is the coefficient of selection against it, then with complete dominance the mean fitness of the population is

$$W = [p^2 + 2p(1-p)](1-s) + (1-p)^2$$

and the change in frequency of the element after one generation is

$$\Delta p = [p^2 + (5/8)2p(1-p)](1-s)/W - p.$$

The frequency of the element increases if $\Delta p > 0$. Simple algebra shows that this is equivalent to $s < 1/(5 - 4p)$.

This means that the maximum value of s that allows the recombinogenic element to increase depends on the frequency of the element itself (Fig. 2). A similar result has been obtained for transposable elements by Hickey (1982). Since gene conversion is effective only in heterozygotes, the increase is slower towards fixation; moreover, the increase will be slower for recombinogenic mutants arising later, because when there are many recombinogenic loci (n) and still the same number of crossing over events ($m < n$), the effect of gene conversion is diluted because it occurs at only m of these n loci per replication (see Fig. 3).

Of course, there is no reason why a new recombinogenic element must arise only when the previous one has been fixed in the population, but the increase should be, in a similar way, slower for later recombinogenic mutants. Moreover, it is reasonable to think that when there are many recombinogenic loci in the chromosome and only one or few crossing over events per replication

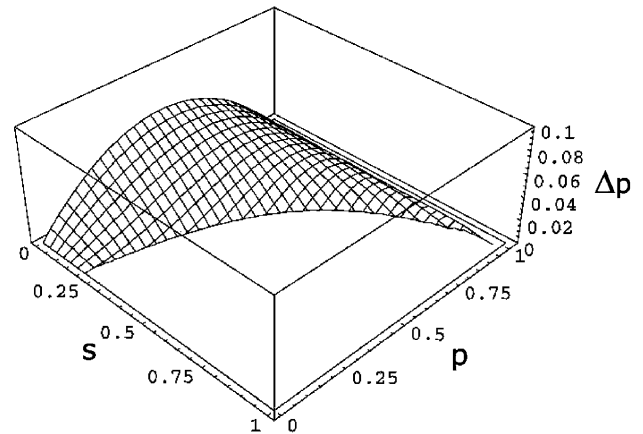


Fig. 2. Values of Δp depending on p and s (see text). Negative values are not shown for clarity.

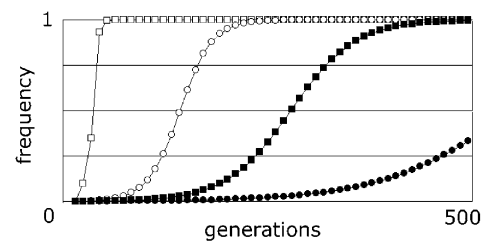


Fig. 3. Frequency of a recombinogenic allele, in a sexual population, when there are already x recombinogenic alleles fixed in the same chromosome; 1 crossing over event per replication; \square : $x = 0$; \circ : $x = 5$; \blacksquare : $x = 10$; \bullet : $x = 20$; plotted every ten generations.

the advantage of gene conversion will eventually become negligible and, in a finite population, the number of recombinogenic alleles will stop increasing. This can be investigated with a stochastic program that simulates the evolution of recombinogenic alleles in a finite population.

4.2. A simulation for a finite population

I use a computer program that creates a finite population of unicellular individuals with a haploid number of chromosomes = 1 (therefore one haploid genome is equivalent to one chromosome). A chromosome is made of a sequence of k loci and each locus can be recombinogenic or not; each locus can also be, independently, deleterious or not. Thus there are four possible alleles at each locus: neutral, non-recombinogenic (r); neutral, recombinogenic (R); deleterious, non-recombinogenic (r^*); deleterious, recombinogenic (R^*). I assume that the centromere is at one end of the chromosome and that at the opposite end there is a $(k + 1)$ th locus with two alleles, H and D , controlling reproduction, that can be diplontic (DD) or

haplodiplontic (HH); heterozygotes (HD) are either diplontic or haplodiplontic according to dominance. Haplodiplontic individuals go through a diploid phase and a haploid phase, while diplontic individuals are always diploid. Therefore, this stochastic model can be used to include asexual individuals in the population (this will be discussed later). For simplicity, I will use from now on the words asexual and sexual instead of diplontic and haplodiplontic, assuming that asexual individuals are always diploid. The sequence of events is the following.

Mutation: Possible mutations are $R \leftrightarrow r$, $R^* \leftrightarrow r^*$, with the same probability μ ; $R \rightarrow R^*$, $r \rightarrow r^*$, with the same probability ν (while I assume that the probability of mutations $R \leftarrow R^*$ and $r \leftarrow r^*$ is negligible); $D \leftrightarrow H$ with the same probability σ .

Syngamy: After mutation syngamy occurs, that is haploid cells (gametes) derived from sexual individuals merge to form the diploid stage, while asexual cells remain diploid. Mating of haploid cells is at random.

Selection: After syngamy cells undergo selection: individuals that reproduce are chosen at random, with a probability proportional to their fitness. Individuals that have already reproduced are not excluded. Fitness is $1-s(n/m)$, where s is the number of lethal equivalents per genome, m is the number (fixed) of genes with recessive deleterious alleles whose effects summed together make s lethal equivalents (one lethal equivalent is one gene or more genes whose effects summed together—when expressed—are lethal for their bearer) and n is the number of recessive deleterious alleles actually in homozygosis in that individual. If $s(n/m) > 1$, fitness is set to 0 (because of course an individual may have more than one lethal equivalent but not be killed more than one time).

Reproduction: Selected individuals produce either one diploid cell (if they are asexual) or two haploid gametes (if they are sexual). The process of selection continues until the total number of haploid genomes produced equals that of the previous generation (that is the population is stationary, there is always the same number of haploid genomes, N , but the ratio of sexual/asexual individuals may vary). The process of reproduction, for each individual, is the following:

- (i) Each chromosome duplicates to produce two chromatids, therefore, before recombination, two couples of chromatids are present.
- (ii) Two non-sister chromatids (that is, not generated by the same chromosome) are chosen at random for crossing over.
- (iii) A locus is chosen at random and starting from this locus the closer locus with at least one recombinogenic allele is searched in one direction at random; if there are no recombinogenic alleles on that direction the process starts again in the opposite

direction. If there are no recombinogenic alleles crossing over does not occur. If at the chosen locus a recombinogenic allele is present on both chromatids (homozygous), one of the two is chosen at random to act as the recombinogenic allele.

- (iv) The two chromatids participating in crossing over, exchange with each other all the part of chromosome distal to the recombinogenic locus (that is opposite to the centromere) in 50% of the cases (recombination) and do not exchange in the other 50% (no recombination). I assume one crossing over per replication. The two chromatids not participating in crossing over, of course, do not change.
- (v) Independently, gene conversion occurs in favor of the recombinogenic allele $\frac{1}{2}$ times (that is the recombinogenic allele replaces the original allele on the other chromatid), while restoration of the original allele occurs $\frac{1}{2}$ times. Therefore, the recombinogenic allele segregates with the normal ratio 5:3 due to a normal gene conversion (there is no biased gene conversion).
- (vi) Two non-sister chromatids are then chosen at random (not necessarily the two chromatids participating in crossing over) to produce either one diploid cell (if the individual is asexual) or two haploid gametes (if it is sexual). This is an assumption of isogamy, which is appropriate in this case since we are concerned with the origin of sexual reproduction and not with its maintenance.

4.3. Results: spread of recombinogenic alleles

As already discussed before, in a sexual population recombinogenic alleles arising later increase more slowly (Fig. 4). The dynamics does not change with different values of s , and even if $s = 0$ or if recombinogenic alleles arise only in the proximal half of the chromosome and deleterious alleles only in the distal half. This shows that, in this model, recombinogenic alleles do not increase because of their capacity to set the genome

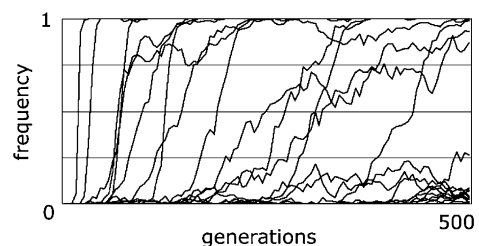


Fig. 4. Spread of recombinogenic alleles in a sexual population. Each trajectory is the frequency of a recombinogenic allele at a different locus, in a finite sexual population. $\mu = \nu = 1 \times 10^{-7}$ per locus per individual per generation; $\sigma = 0$; $s = 0.2$; $k = 100$; $N = 1000$; 1 crossing over event per replication.

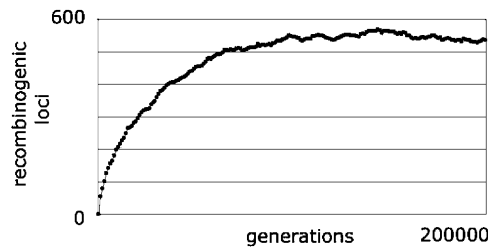


Fig. 5. The total number of recombinogenic alleles fixed in every individual of a sexual population during many generations. $\mu = \nu = 1 \times 10^{-7}$ per locus per individual per generation; $\sigma = 0$; $s = 0.2$; $k = 1000$; $N = 1000$; 1 crossing over event per replication.

free of deleterious mutations but really because of the intrinsic mechanism of gene conversion.

The number of recombinogenic alleles remains stable after about 100 000 generation, with some fluctuation due only to recurrent mutations (Fig. 5). The mean number of recombinogenic alleles in generations 150 000–200 000 has been (in 10 runs) 539.8, with a maximum of 551 and a minimum of 530. The result does not depend on the value of s , the number of loci k (unless of course $k \approx 550$ or less) or the mutation rate μ . These alleles are all fixed in the population, while only few alleles at low frequency are present because of recurrent mutations. Therefore, it is possible to expect that the number of recombinogenic loci per chromosome is about 540, if gene conversion is the only force operating and if recombinogenic alleles have all the same capacity to initiate crossing over, as assumed in the model. Of course, it will not be easy to compare this number with the number of sites for initiation of crossing over in a real chromosome, but with this in mind it is not surprising that there are regions of the chromosome where crossing over is less frequent or absent.

5. Intragenomic conflict in an asexual diploid

So far I have considered recombination in a sexual organism, but sexual reproduction is necessary only for the *spread* of the recombinogenic element to other individuals in the population, it is not necessary for its *origin*: what is required for its origin is only diploidy and the existence of the DNA repair machinery. Therefore, a recombinogenic element may arise even in an organism with asexual, apomictic, reproduction. Though recombination in mitosis is very rare, there is evidence (Kleckner, 1996) that in the evolution of meiosis from mitosis, crossing over appeared before the reductional cell division, therefore there was recombination in mitosis. Moreover, the action of a recombinogenic allele can be important even with partial or transient

co-alignment of homologs, as in mitosis (Keeney and Kleckner, 1996).

Asexual (apomictic) reproduction with recombination was first observed by Darlington (Darlington, 1937; Darlington and Mather, 1952) who called it “subsexual reproduction”, to describe some aberrant offspring in cultivation experiments of apomictic lineages. Aberrations were due to homozygosity of genes distal to the site of crossing over. This name is not well known probably because it is actually a very uncommon way of reproduction. It was a recent discovery (van Baarlen et al., 2000) even for a well-known apomictic species like the dandelion *Taraxacum officinale*. Indeed, up to few years ago recombination in polyploid obligate apomictic species (like dandelion) was considered impossible even from a theoretical point of view and its eventual discovery a possibly very interesting surprise (Kondrashov, 1997). From the point of view of the present hypothesis instead this is not surprising. I will discuss later the case of *Taraxacum*, which is interesting and consistent with the hypothesis.

Imagine that a recombinogenic allele arises in a diploid asexual (apomictic) organism. An immediate effect of the recombinogenic element in this case is to abolish complementation in the part of the chromosome distal to the site of crossing over in one-quarter of the progeny (the cases with recombination and adjacent segregation, see Fig. 6), that is to unmask recessive mutations that in the heterozygous state were not deleterious. Inducing crossing over for a recombinogenic allele is advantageous because, by gene conversion, it replaces the homologous allele; on the other hand it is disadvantageous because it unmasks recessive deleterious mutations on the chromosome where it happens to be.

This can result in a version of the Prisoner’s Dilemma (Axelrod and Hamilton, 1981) played by the two alleles of the same locus, where the strategies “cooperation” and “defection” correspond respectively to “non-recombinogenic” and “recombinogenic” alleles (Fig. 7). The “ $\frac{5}{4}$ ” and “ $\frac{3}{4}$ ” values on the main diagonal of the payoff matrix are due to gene conversion in all the four different possible segregations (see Fig. 6). Therefore the “4” here is related to the number of chromatids (not to the four kinds of segregation) and “ $\frac{5}{4}$ ” and “ $\frac{3}{4}$ ” are the deviations (due to gene conversion) from the normal ($\frac{4}{4}$) segregation. The value “1” ($\frac{4}{4}$) for the combination non-rec–non-rec corresponds to the absence of gene conversion and the value “1” for rec–rec corresponds to $(\frac{1}{2})(\frac{3}{4}) + (\frac{1}{2})(\frac{5}{4})$ in which “ $\frac{1}{2}$ ” is the probability that one of the two alleles act as the recombinogenic elements (they are assumed to be equivalent in strength). The cost for loss of complementation in the distal part of the chromosome (c) is not related to the number of copies of the recombinogenic allele, but occurs only, and only if, when there is *recombination with adjacent segregation*,

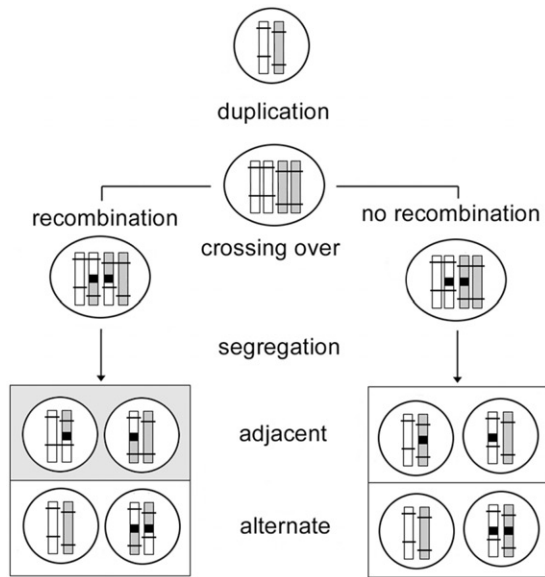


Fig. 6. Asexual reproduction with recombination. Two homologous chromosomes (white and grey) with a single recombinogenic locus in the middle and two recessive deleterious mutations each (horizontal lines). Gene conversion occurs at the recombinogenic locus (black square). Segregation can be of two types: “alternate” or “adjacent”. In the case of recombination followed by adjacent segregation (with no bias in the resolution of crossing over and segregation this occurs in $\frac{1}{4}$ cases), complementation is lost in the part of the chromosome distal to the recombinogenic locus.

payoff to:	against:	
	non rec	rec
non rec	$R = 1$	$Q = \frac{3}{4} - \frac{c}{4}$
rec	$T = \frac{5}{4} - \frac{c}{4}$	$P = 1 - \frac{c}{4}$

Fig. 7. Recombination as a Prisoner’s Dilemma. Payoff matrix for the two possible alleles in a diploid individual with asexual reproduction. If one allele is recombinogenic (rec) and the other is not, the former has a net advantage due to gene conversion ($\frac{3}{4}$ against $\frac{3}{4}$); if one or both are recombinogenic, both have a reduction of fitness c ($1 - c$ is the fitness with loss of complementation in $\frac{1}{2}$ of the chromosome) in $\frac{1}{4}$ of the progeny, where recombination unmasks distal recessive deleterious mutations.

which occurs, on average, $\frac{1}{4}$ of the times (this “4”, therefore, is related to the number of possible kinds of segregation) in the presence of *at least* one recombinogenic element.

This is a version of the Prisoner’s Dilemma (if $0 < c < 1$) because $R > P$, $T > R$, $P > Q$, and $R > Q/2 + T/2$ (see Fig. 7). As in the classical game, defection is the only stable strategy, even if it lowers the fitness of the

players. Therefore, even in an asexual organism a DNA sequence has an advantage in becoming recombinogenic, not because it spreads through the population (this of course requires sexual reproduction and out-crossing) but simply because if two alleles exist, recombinogenic and not recombinogenic, the former is more likely to survive and to go on to the next generation. In a diploid asexual population there will be recurrent invasions of recombinogenic elements but they will not spread as in a sexual population, indeed their carriers will go extinct because recombination unmasks deleterious recessive mutations. A recombinogenic element is a self-promoting element: it is “short-sighted”, it evolves because it has a short-term advantage, but it leads to a conflict with the rest of the genome. This should promote the evolution of another gene that suppresses (see Hurst et al., 1996) the deleterious effects of recombination.

5.1. Possible resolutions of the conflict

I envisage the following possibilities: endomitosis; suppression of recombination; suppression of crossing over; sexual reproduction. These four possibilities are likely to occur under different conditions.

5.1.1. Endomitosis

With endomitosis, a duplication of the chromosomes before a reductional division, pairing would not be between homologs, but between sister chromosomes produced by that duplication. In this way a recombinogenic element could evolve without causing loss of complementation.

The problem with endomitosis is that, since pairing is not between homologs but between sister chromosomes produced by the first duplication, DSBs naturally occurring before this duplication cannot be repaired. This is the probable reason why this kind of reproduction is so rare (Bernstein et al., 1988). Endomitosis is possible only if damages to DNA, and in particular DSBs, are not a problem for the organism or can be repaired in some other way, and this seems uncommon. It would be interesting to know how the few organisms reproducing by endomitosis can respond to DSBs. These include, for example, some lizards (*Cnemidophorus*), some amphibians (*Ambystoma*) and some fish (*Poeciliopsis*) (Parker and Selander, 1976; Maynard-Smith, 1978).

5.1.2. Suppression of crossing over

The proteins that induce crossing over could be suppressed: in this case there would be no recombination at all and therefore no loss of complementation, however DNA repair would also be suppressed.

Spo11 may not be considered actually a protein of the repair machinery, indeed it induces DSBs, however, as

noted by Bernstein (1988 and references therein), naturally occurring damages to DNA are of many different kinds, and many single-strand damages do not have specific enzymes that recognize them, but are converted into gaps that induce repair via the DSBR model, and Spo11 might play a role on this. Moreover Spo11 has different functions in homolog pairing, formation of the axial cores of the synaptonemal complex and cell cycle progression (Keeney et al., 1997). Suppression of crossing over through suppression of Spo11 or other molecules of the machinery for DNA repair therefore would be associated with high costs.

The frequency of crossing over in mitosis is several orders of magnitude lower than in meiosis, but DNA repair in mitosis is not essential as in meiosis: in multicellular organisms some damages to DNA are not repaired and may be discarded through cellular selection. On the other hand, most importantly, damages to DNA accumulate in the soma, ultimately leading to senescence, because the soma is “disposable”. Mitotic crossing over is in fact more similar to mating type switching (see the following discussion) than to meiotic recombination, in that it is induced by an endonuclease and not by Spo11, it goes probably via a different pathway and the resolution is biased towards non-recombinant products (Paques and Haber, 1999).

5.1.3. Suppression of recombination

Recombinant and non-recombinant chromosomes are produced usually with the same frequency because the intermediate joint molecule (the “Holliday junction”) exists at equilibrium in two isomeric forms and it can be cut and rejoined in two ways at random, producing recombinant or non-recombinant chromosomes. The recombinogenic element could be allowed to evolve but to induce only gene conversion without recombination. In this way the recombinogenic element would not produce loss of complementation.

However, as noted by Bernstein et al. (1988), while the production of non-recombinant chromosomes could be easily avoided (eliminating a step which is costly and more complex than need be) recombinant products cannot be completely eliminated. This would be possible only by cutting and rejoining the Holliday junction quickly before the equilibrium between the two isomeric forms is reached. The actual time is not known, but it is likely to be very short, and this possibility would be in any case associated with high costs, due to higher energetic requirements and higher probability of errors. However, the regulation of the production of recombinant or non-recombinant chromosomes is not yet well understood, and it has also been proposed that the regulation is not at the step of Holliday junction resolution but before its formation, or that the two kind of products go via two different pathways (Zickler and Kleckner, 1998; Paques and Haber, 1999).

Suppression of recombinant products after crossing over therefore seems to be associated with high costs, and it is likely to evolve only when the benefits of reducing recombination exceed these costs. A well known case exists of crossing over associated with 0% recombination, the case of mating type switching in yeast. In yeast the expressed mating type allele is at locus MAT on chromosome III, and two unexpressed alleles are at loci HML and HMR on the same chromosome: during switching the allele from one of the silent loci is copied to the MAT locus by gene conversion (Orr-Weaver and Szostak, 1985; Haber, 1998) and this process is never associated with recombination of flanking markers. Mating type switching has been used as a model to study mitotic recombination, but it differs from meiotic recombination in several respects: it is unidirectional (the MAT locus is always the recipient); it occurs in haploid cells, at the G1 phase of the cell cycle; it is a very slow process, requiring about 1 h to complete; DSBs are not produced by a topoisomerase but by an endonuclease. It is important to notice that, occurring between loci of the same chromosome, a resolution producing recombination would generate either a large deletion or a circular chromosome (Paques and Haber, 1999) that would be easily lethal. Therefore, this may be a case where the cost of producing 0% recombinant chromosomes previously discussed is smaller than the cost of allowing recombination, and that the problem has been resolved with a very slow process, which probably goes via a pathway that differs from the DSBR model (Paques and Haber, 1999).

The cases of mitotic recombination and mating type switching suggest that recombinant products can be eliminated only in the absence of Spo11 (Malkova et al., 2000), therefore the suppression of recombination, as in mating type switching, seems impossible if Spo11 cannot be suppressed. In any case, even if it was possible to retain Spo11 and to suppress recombination, this would be associated with the high costs already described to reduce recombination. Finally, even if it was possible to suppress recombinant products gene conversion would still generate homozygosity at sites of initiation, and in such a closed system, without outcrossing, this would lead to loss of complementation as well (Bernstein et al., 1988).

5.1.4. Sexual reproduction

A further cell division (meiosis) followed by random mating of the resulting haploid products (outcrossing) could restore complementation because it is unlikely that mating, if random, will be with a gamete with deleterious mutations exactly at the same loci. In this way the deleterious effect of the recombinogenic element would be suppressed without suppressing the element itself.

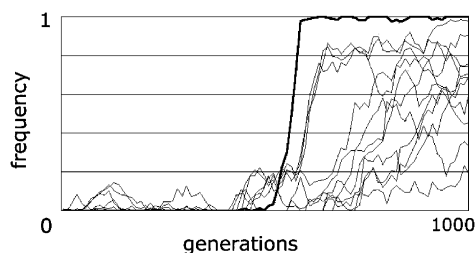


Fig. 8. Evolution of sexual reproduction and recombination. The bold line is the frequency of sexual individuals, other lines are the frequency of recombinogenic alleles at some different loci. $\mu = 1 \times 10^{-7}$ per locus per individual per generation; $\sigma = 1 \times 10^{-6}$ per individual per generation; $\nu = 1 \times 10^{-5}$ per locus per individual per generation; starting with 4 deleterious recessive mutations; $m = 4$; $s = 0.2$; $k = 100$; $N = 1000$; 1 crossing over event per replication; H dominant. The model is the same used for Figs. 4 and 5, but starting from an asexual population.

With asexual reproduction, recombinogenic alleles arise because they have a very short-term advantage due to gene conversion (see the discussion about the Prisoner's Dilemma), but go extinct because of the deleterious effects due to loss of complementation. If sexual reproduction evolves, instead, they begin to increase in frequency, because outcrossing allows the restoration of complementation (Fig. 8). Therefore, sexual reproduction may evolve as a response to the genetic conflict produced by recurrent recombinogenic elements. When sexual reproduction evolves, however, it does not eliminate the recombinogenic elements, indeed it allows their spread in the population. This is a case where the intragenomic conflict promoted by a selfish element induces the evolution of a suppressor (the gene for sexual reproduction) that, while suppressing the deleterious effect of the element, does not suppress the element itself, and indeed allows its spread to different individuals.

Fig. 8 shows an episode of invasion of a mutation for sexual reproduction but in many cases sexual mutants do not invade. In fact in a population of diploid individuals, if only one sexual mutant individual exists, it will not have an immediate advantage because, as in selfing, its gametes will merge among themselves, deleterious alleles will be at the same positions in all gametes, therefore complementation will not be restored. If the number of sexual individuals increases even slightly, however, outcrossing becomes possible: each gamete can merge with a different one with deleterious alleles at different positions, allowing the restoration of complementation; in this case, the asexual population is easily replaced by the sexual individuals (see Table 1). Note that this problem is a common problem for all the theories on the origin of sex (unless one assumes that a pool of haploid cells exists continuously in the population). In the case of the present hypothesis, however, the problem is weakened because also in diploid individuals there is loss of

Table 1
Replacement of an asexual population with a sexual population

x	S				
	0*	0.1	0.2	0.5	1
1	0 (0)	6 (4)	8 (6)	4 (1)	1 (0)
2	0 (0)	31 (19)	71 (41)	42 (20)	3 (2)
5	0 (0)	113 (60)	192 (147)	141 (94)	16 (3)
10	0 (0)	298 (236)	531 (429)	502 (405)	174 (84)

Each entry is the number of times in 1000 runs that an asexual population is replaced by a sexual population when there is recombination (one crossing over event per replication). $N = 1000$; $n = 4$; $m = 4$ (as defined in the text). The initial number of H alleles is x . Entries are for H dominant (values in parentheses are for H recessive). Results for $s > 0$ without crossing over (*) and for the case $s = 0$ are the same.

complementation (distal to crossing over), not because of inbreeding but because of recombination. The data in Table 1, while still showing the problem of the origin (especially with high values of s), show that nevertheless sexual reproduction can invade and replace asexual reproduction; on the contrary sexual reproduction never replaced asexual reproduction assuming no crossing over in the diploids.

Diploidy allows recessive deleterious mutations to accumulate in the genome, because they are masked in the heterozygous state, and for many living organisms the number of lethal equivalents is probably > 1 ; for example, in vertebrates it is estimated to be among 1 and 6 (Lynch and Walsh, 1998), but at the origin of diploidy, when the first haploid unicellular organisms merged, it was probably much lower. This seems reasonable because haploid genomes are obviously unmasked for all their deleterious mutations and therefore exposed to selection against these mutations, which will be maintained at lower frequency.

If DNA repair is necessary for the organism and recombination cannot be suppressed, therefore, the best possible solution to avoid loss of complementation may be sexual reproduction. However, apomixis is common, for example in plants, though it is almost always facultative. Cases of obligate apomixis in plants are less common, but very interesting. The dandelion (*Taraxacum officinale*) is one of the best known obligate apomictic species. As obligate apomicts dandelions were predicted to have low levels of genetic variation, yet recent studies reveal large variation. Van Baarlen et al. (2000) have shown that this is a result of recombination and that chromosome pairing and chiasma formation occur even though at lower levels than in sexual diploids. *Taraxacum* apomicts are triploid and avoid formation of unbalanced gametes and sterility by circumvention of the first meiotic (reductional) division. Therefore, the first meiotic prophase is initiated so that recombination can occur, though the first reductional

division does not take place (this is an example of “subsexual reproduction” sensu Darlington).

It is interesting that virtually all other apomictic plants that undergo recombination like *Taraxacum* (e.g., *Chondrilla*, *Arabis*; Van Baarlen et al., 2000) are triploid and that also most vertebrate apomicts are triploid of presumably recent hybrid origin (Kondrashov, 1997). Having three copies of each gene prevents loss of complementation because recombination (and the consequent homozygosis of distal loci) occurs only between two of the three homologs. This might be the reason why triploidy is so common in apomictic species.

6. Discussion

I have argued that recombination can be explained as a secondary consequence of gene conversion, and therefore as a consequence of the evolution of a self-promoting element. I want to point out briefly the differences from two mechanisms that may superficially resemble this hypothesis: homing endonucleases and biased gene conversion. Homing endonuclease genes are copied to chromosomes that lack them by a gene conversion process initiated by site-specific endonucleases that are encoded by the mobile elements themselves (see for example Jurica and Stoddard, 1999). Homing endonucleases can be considered self-promoting elements, but they have no connection with the process of crossing over and gene conversion described here. Bengtsson (1985) proposed instead that the primary function of crossing over is gene conversion because, if it is biased, it may reduce the mutation load. This explanation considers the advantages of gene conversion for the individual, and is very different from the one discussed here.

Haig and Grafen (1991) proposed that recombination may confer an advantage because it may prevent the evolution of meiotic drive systems, which are usually deleterious for the organism. In their case a system of selfish elements promotes recombination, but recombination confers a protection to the individual against the deleterious effects of the selfish element, and not an advantage to the element itself. Again, the advantage is for the individual, and it is different from the idea discussed here.

Boulton et al. (1997) have modeled the evolution of recombination with the assumption that crossing over is initiated at DSBs and that DSBs are formed at precise sites by an endonuclease. According to these authors, therefore, the persistence of these sites, and hence of recombination, is a paradox because the endonuclease breaks the specific target sequences necessary for the initiation of recombination, and these sequences are lost as a result of gene conversion. As I have discussed, the assumption of an endonuclease was considered reason-

able at the time, and since endonucleases recognize and cut specific sequences in *cis* the persistence of recombination seemed really a paradox. The discovery that the initiation of recombination is due to a topoisomerase and not to an endonuclease resolves the paradox, and is consistent with previous and recent data I have discussed.

The idea discussed here is that if an allele can induce or enhance the initiation of crossing over it will have an advantage because of gene conversion. As a consequence, recombination is not necessarily an advantage for the individual. Indeed, if it occurs in a diploid asexual organism, it can be deleterious because it induces loss of complementation, and it can create a selective pressure for the evolution of sexual reproduction.

The main reason why this simple idea has been so far ignored is probably that most evolutionary models have assumed (see Crow, 1988) that recombination is the evolutionary value of sex, and that it must therefore give some advantage to the individual or to the population. Moreover, population genetics models for the evolution of recombination have usually ignored gene conversion and assumed that the rate of crossing over depends only on a neutral modifier at another locus, ignoring the features of the very site where crossing over occurs (the recombinogenic locus). Finally, only the discovery of the Spo11 protein provided that change in our current view of the initiation of crossing over advocated by Boulton et al. (1997) to resolve the paradox of initiation. Gene conversion is a very powerful force, and provides a resolution in terms of intragenomic conflict. This hypothesis can be dismissed if it is found that there are no effects in *trans* on the formation of DSBs and gene conversion. So far there is evidence that these effects do exist, as I have discussed.

I have discussed the possibility that crossing over evolved before the production of haploid gametes and therefore before the alternation of haploid a diploid generations. The alternative possibility is that the haplodiplontic cycle arose before the evolution of crossing over, but mechanistic considerations suggest that crossing over appeared first (Kleckner, 1996). The sequence of events is probably the following. As the haploid genome expands during evolution, increasing the information content of the genotype and the complexity of the phenotype, it becomes more and more vulnerable to deleterious mutations because of the increased number of vital genes. Therefore if two haploid genomes, with deleterious mutations at different loci, merge to form a common cell (syngamy), deficiencies in one can be compensated for by the other (complementation). It has been noted (Muller, 1932; Crow and Kimura, 1965) that in the long term, if the deleterious alleles are not completely recessive, the mutation load for a diploid is twice that of an haploid,

and that therefore the advantage of diploidy is only transient. Of course, however, the event is irreversible because a shift back to haploidy would express all the deleterious alleles. In a diploid genome DNA recombinational repair can now occur and eventually recombinogenic alleles may exploit the machinery for DNA repair and evolve (but not spread in the population). Loss of complementation due to recombination in an asexual organism promotes the evolution of suppressor genes. I have discussed different possibilities for suppression: I have proposed that the most likely resolution is the evolution of sexual reproduction, except for the cases of mating type switching in yeast and somatic recombination, where reduction of recombination rates and of crossing over rates, respectively, may be the only solutions.

The argument I have presented for the origin of sex, unmasking of deleterious mutations due to loss of complementation, is similar to that proposed by Bernstein et al. (Bernstein et al., 1985, 1988; see also the discussion in Maynard-Smith, 1988) in that recombination is an unavoidable process and sex evolved as a way to suppress deleterious effects of this process. A difficulty with the hypothesis of Bernstein et al., however, is that it cannot explain why the evolutionary value of recombination is to repair DNA if DSBs are actively induced to promote the initiation of recombination. In the idea of Bernstein et al. recombination confers an advantage to the individual in that it allows DNA repair, while in the idea discussed here recombination confers an advantage to the recombinogenic element.

Hickey (1982), also suggested that the origin of sex was induced by a self-promoting element, but in the original idea of Hickey the self-promoting element was a transposable element and sexual reproduction was induced by that element itself to spread into the population, whereas in this case the self-promoting element is just an existing sequence that exploits the machinery for DNA repair and sexual reproduction is the effect of another, different, suppressor gene.

I have not considered possible long-term benefits or disadvantages of recombination, and I want to point out that I am not claiming that other hypotheses on the evolution of sex are wrong or incompatible with the one presented here. In the long-term recombination associated with sex can undergo all the positive or negative selective pressures that have been proposed (for a review see for example Kondrashov, 1993; Barton and Charlesworth, 1998), but in the short term its origin may have been the effect of a self-promoting element. In this sense the evolutionary value of sex is not the promotion of recombination but instead recombination is a self-promoting process and sexual reproduction the resolution of the consequent genetic conflict.

Acknowledgements

The final version of this manuscript was considerably improved by comments and corrections suggested by Alan Grafen, Carlo Matessi, Dieter Ebert, Steven Frank and Mark Ridley. Thanks for suggestions are also due to Austin Burt, Rosemary Redfield and especially Nancy Kleckner.

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