

Loss of complementation and the logic of two-step meiosis

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Abstract

Meiosis is usually a two-step process: two divisions preceded by a duplication. One-step meiosis, a single division without prior replication, is a more logical way to produce haploid gametes; moreover, one-step meiosis leads to higher variability in the progeny than two-step meiosis. Yet one-step meiosis is very rare in nature, and may not even exist at all. I suggest that this is because one-step meiosis, in contrast to two-step meiosis, can be easily invaded and replaced by asexual reproduction. I discuss why other existing peculiar forms of division leading to the production of haploid gametes, but not one-step meiosis, have the same effect as two-step meiosis.

The two problems of two-steps meiosis

The function of a normal meiosis is to produce haploid gametes, that is, to halve the genome size before mating. However meiosis begins with a duplication of chromosomes, which is followed by two divisions. Why is meiosis such a two-step process [$2n \rightarrow 4n \rightarrow 2(2n) \rightarrow 4(n)$] instead of a much simpler one-step division [$2n \rightarrow 2(n)$]?

It is possible that the two steps are just a relict of the mitosis from which meiosis originated, but there seems to be no compelling reason why the first duplication cannot be suppressed. In fact, some diploid protists appear to produce gametes by one-step meiosis (Raikov, 1982; Kondrashov, 1997), a single division without prior replication, producing two daughter cells with haploid sets of chromosomes. One-step meiosis has been reported for Pyrsonymphidae (Oxymonadida), Parabasalia (Hypermastigotes), Microsporidia, some Dinoflagellates, and Apicomplexa, though for all these cases there is uncertainty. In fact some researchers (Haig, 1993; Cavalier-Smith, 1995) have expressed doubts about the existence of one-step meiosis. Haig (1993) in particular suggests that Cleveland's observations (Cleveland, 1956) do not necessarily imply a one-step meiosis for some species.

The question of the evolutionary value of two-step meiosis is not just a trivial question of logic. There is another problem, not usually noticed. If the evolutionary

value of sex is the promotion of genetic variability, to combat coevolving parasites or to get rid of deleterious mutations (reviewed by Kondrashov, 1993; Barton & Charlesworth, 1998; Otto & Lenormand, 2002), then a one-step meiosis, and not a two-step meiosis, should be preferred, because a two-step meiosis may produce non-recombinant products that are useless for the production of variability, while a one-step meiosis does not (Figs 1 and 2). In other words, the same number of recombination events leads to a lower degree of variability with a two-step meiosis than with a one-step meiosis, because the formation of tetrads in a two-step meiosis allows only half the chromatids to recombine per crossing over, while in a one-step meiosis all of them recombine at each crossing over event.

Therefore there are two problems about two-step meiosis. The first is that a one-step meiosis would lead to the same, immediate result (the production of haploid gametes) in a much simpler way. The second is that a one-step meiosis would produce a higher degree of variation. So why is meiosis usually two-step?

Protection against sister-killers

Haig & Grafen (1991) proposed that the value of two-step meiosis is to prevent a kind of segregation distorters (sister-killers), as it creates uncertainty about the outcome of segregation, that is two-step meiosis does not allow sister-killer genes to evolve. One-step meiosis, on the other hand, can be exploited by sister-killer genes.

Haig and Grafen's theory is not, by its nature, a theory that is easily confirmed or dismissed: the failure to

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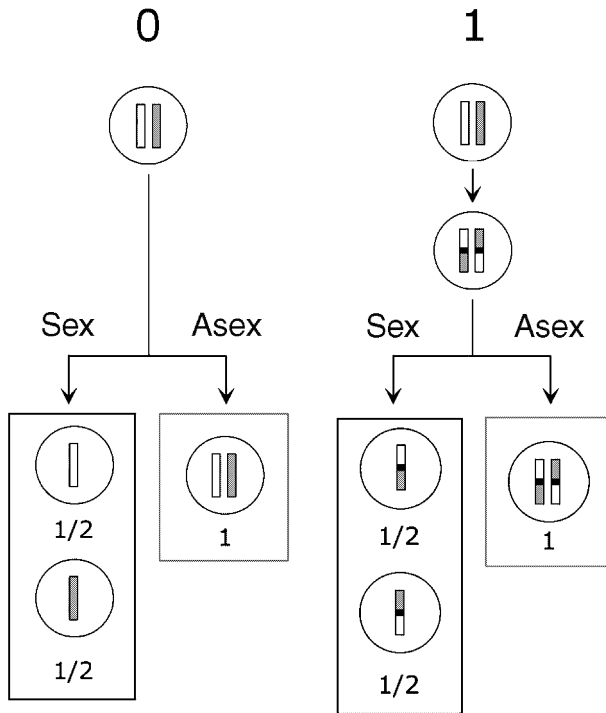


Fig. 1 One step meiosis. Sexual reproduction (sex) with one step meiosis, with one (1) or no (0) crossing over, and the corresponding asexual mutant (asex). Fractions indicate the frequency in the progeny.

observe sister-killer genes in two-step meiosis could be compatible both with the effect described by Haig and Grafen and, on the contrary, with the biological non-existence of sister killers (Hurst, 1993). Another possible difficulty is that it has been observed (Sharon & Simchen, 1990) that in yeast reproducing by a single meiotic division, the choice between reductional or equational segregation is made individually by each chromosome pair and is directed by sequences in the vicinity of the centromeres; therefore it could be possible for a sister-killer gene to evolve in linkage with these sequences to direct its own segregation. Haig and Grafen's theory is, however, the only plausible explanation of the evolutionary value of two-step meiosis.

A new explanation: loss of complementation

Another simple explanation is possible. Consider, in a species with a two-step meiosis, a mutant asexual, apomictic female (in which the first meiotic division is suppressed; see Archetti, 2004). Asexual reproduction has a twofold advantage in comparison with sexual reproduction (Maynard-Smith, 1971, 1978). This cost is not always actually twofold, especially in species with isogamous gametes, but there is in any case an

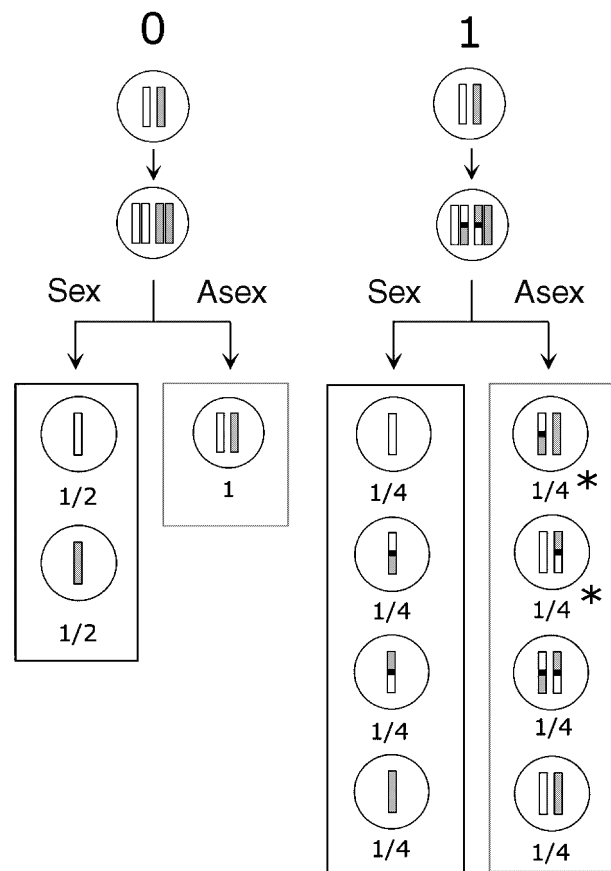


Fig. 2 Two step meiosis. Sexual reproduction (sex) with two step meiosis, with one (1) or no (0) crossing over, and the corresponding asexual (apomictic) mutant (asex). Fractions indicate the frequency in the progeny. Asterisks mark partial loss of complementation.

immediate cost associated with sexual reproduction (Lewis, 1987). However, apomixis has a cost too: because of the first meiotic duplication, the formation of tetrads occurs and recombination leads to loss of complementation in half the progeny of the asexual (the half produced by 'x segregation' according to the terminology of Stern, 1936; see Fig. 3 and Archetti, 2004). This means that deleterious recessive mutations (in the part of the chromosome opposite to the centromere – distal to the site of crossing over) are unmasked and lead to a reduction of fitness. Loss of complementation increases further after successive reproductive events, leading, after few generations, to almost complete unmasking of recessive mutations in the asexual. The same argument holds for automixis and endomitosis. Indeed in these cases loss of complementation is greater than with apomixis.

It is possible to calculate a quantitative measure of loss of complementation and its effects on fitness for each kind of asexual reproduction and for different numbers of crossing over events. The result (Archetti, 2004) is that

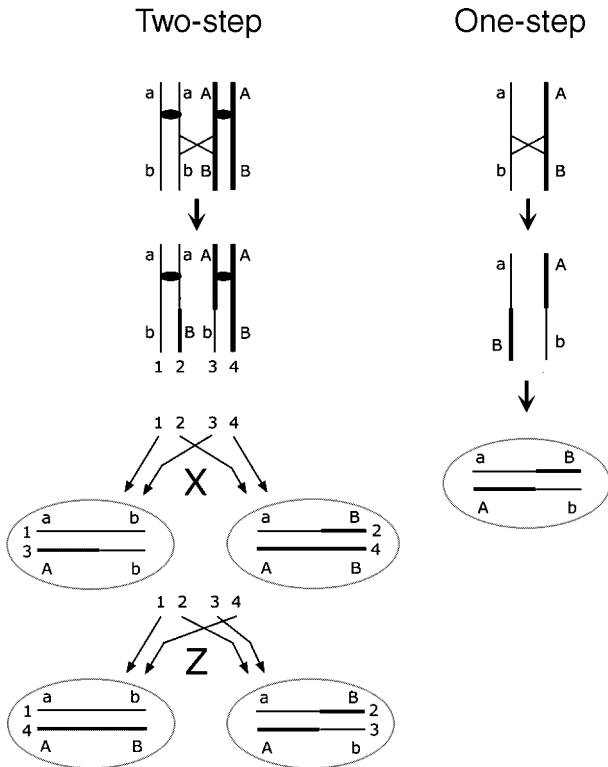


Fig. 3 Segregation with asexual reproduction. When recombination occurs with asexual reproduction and meiosis is two-step, segregation can be of two kinds (x and z); with x segregation, loss of complementation is lost on the part of the chromosome distal to the site of crossing over. If meiosis is one-step, whether recombination occurs or not, complementation is never lost.

loss of complementation in the asexual induces a cost that is greater than the twofold cost of meiosis in most cases. The only notable exception is apomixis associated with polyploidy – a case that indeed corresponds to most asexual species. Therefore, if meiosis is two-step, in most cases (polyploidy may be the exception) asexual reproduction cannot replace sexual reproduction because asexual reproduction leads to loss of complementation.

Consider, instead, a mutant asexual female in a species with a one-step meiosis (Fig. 1). In this case asexuality corresponds to automixis, a kind of automixis that does not lead to loss of complementation in any case, irrespective of recombination (which has not been reported for one-step meiosis but, in principle, can occur for diads of chromosomes as well as for tetrads). Note that one-step *endomitosis*, that is, a duplication followed by a one-step meiosis, would be the same as two-step apomixis. One-step *apomixis* (the suppression of one division in a one-step meiosis), on the other hand, cannot be maintained.

In the case of one-step meiosis there would be no loss of complementation in an asexual mutant. Therefore a one-step meiosis is easily invaded by asexual

reproduction. Sexual reproduction occurring by one-step meiosis is doomed to extinction because it has no 'protection' against invasion by asexual mutants, while two-step meiosis is 'protected' by the formation of tetrads – which would lead to loss of complementation in an eventual asexual mutant. The result is that, at any one time, we see most sexual species with a two-step meiosis, because species with one-step meiosis have become, in fact, asexual.

Alternatives to meiosis revisited and the odd case of Pyrsonymphida

Exceptions to the general rule may provide useful insights. Haig (1993) suggested that two peculiar genetic systems, possibly found in Microsporidia and red algae, are adaptations to resolve the same problem – the evolution of sister-killers – in a different way. However these genetic systems are compatible with the idea presented here too: they lead to loss of complementation in an asexual mutant.

Polyplodization – depolyplodization

Imagine an organism in which regular cycles of endomitosis are followed by cycles of division leading to the formation of haploid gametes or spores [$2n \rightarrow \dots \rightarrow (Xn/2) \rightarrow Xn \rightarrow 2(Xn/2) \rightarrow \dots \rightarrow X(n)$, see Fig. 4]. If this process stops before the formation of haploid products, that is if the progeny is produced asexually [$2n \rightarrow \dots \rightarrow (Xn/2) \rightarrow Xn \rightarrow 2(Xn/2) \rightarrow \dots \rightarrow (X/2)2n$], and if chromosomes assort independently, a binomial distribution of alleles arises at the end of the divisions. That is, with m rounds of endomitosis, the probability that a chromosome loses complementation at the final stage (diploid level, before gamete formation) is $[1 - 2^m / (2^{m+1} - 1)]$, which approaches 1/2 as m grows. Further reproductive events will increase loss of complementation.

Regular cycles of endomitosis followed by cycles of division occur in some unicellulars, for example *Entamoeba*, *Pelomixa* and *Phreatamoeba* (Afonkin, 1986), some red algae (Goff & Coleman, 1986), the brown alga *Ectocarpus siliculosus* (Mueller, 1967), and it is also possible in Radiolaria (Raikov, 1982), foraminiferans (Roettger *et al.*, 1989), dinoflagellates (Silva & Faust, 1995), Raphidophytes (Yamaguchi & Imai, 1994), *Physarum polycephalum* (Kubbies *et al.*, 1986), some pyrsonymphids and actinopods (Haig, 1993), and the charophyte alga *Coleochaete scutata* (Hopkins & McBride, 1976). In red algae the ploidy level (X) may be up to 128.

The microsporidian shuffle

Haig (1993) mentions a possible genetic system in Microsporidia in which it seems that nuclear fusion is followed by a diploid mitosis, after which a synaptonemal complex is formed and a second round of syngamy

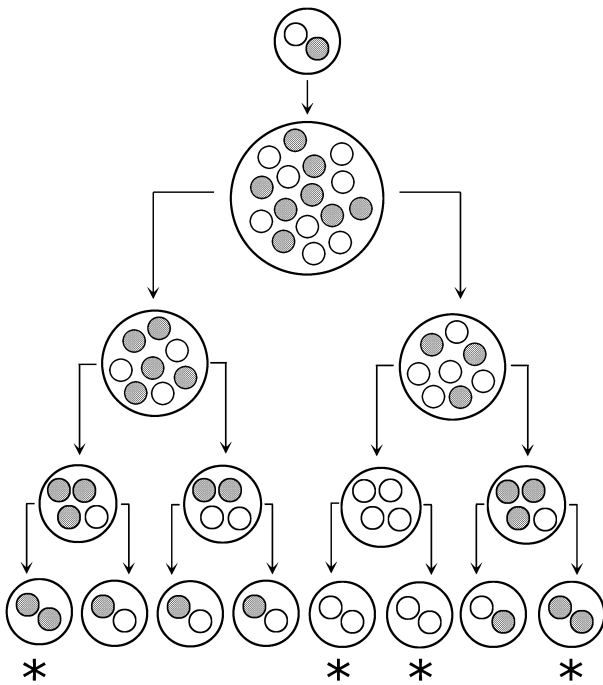


Fig. 4 Ploidy variation in red algae and others. Ploidy increases from two to 16 (three steps not shown) and then reduced from 16 to two in three steps. A further reduction would lead to gamete formation. Open and filled circles represent different chromosomes. Asterisks mark loss of complementation (modified from Haig, 1993).

between the products of mitosis occurs, followed by two divisions: $[2n \rightarrow 2(2n) \rightarrow 4n \rightarrow 2(2n) \rightarrow 4(n)]$, see Fig. 5]. However the view that Microsporidia have this atypical meiosis (the *microsporidian shuffle*, Canning, 1988; Haig, 1993) has been questioned (Flegel & Pasharawipas, 1995), and it is probable that Microsporidia have, in fact, a typical meiosis. When Haig (1993) discussed the *microsporidian shuffle*, Microsporidia were believed to be very early diverging eukaryotes, so they were plausible candidates for having a highly-diverged form of meiosis (Haig, personal communication). Microsporidia are now known to be closely related to Fungi and therefore more likely to have a conventional form of meiosis as proposed by Flegel & Pasharawipas (1995).

In any case, if the *microsporidian shuffle* actually exists, if the chromatids of the two bivalents assort independently in the first division, then there is only 50% probability that segregation occurs after the first division, and therefore 50% probability that an eventual asexual mutant, suppressing the second division, has loss of complementation. After one replication, loss of complementation is on the whole chromosome, if there is no crossing over, or in half the chromosome (on average), if there is one crossing over (see Fig. 5), but it will increase more and more after further reproductive events of this kind.

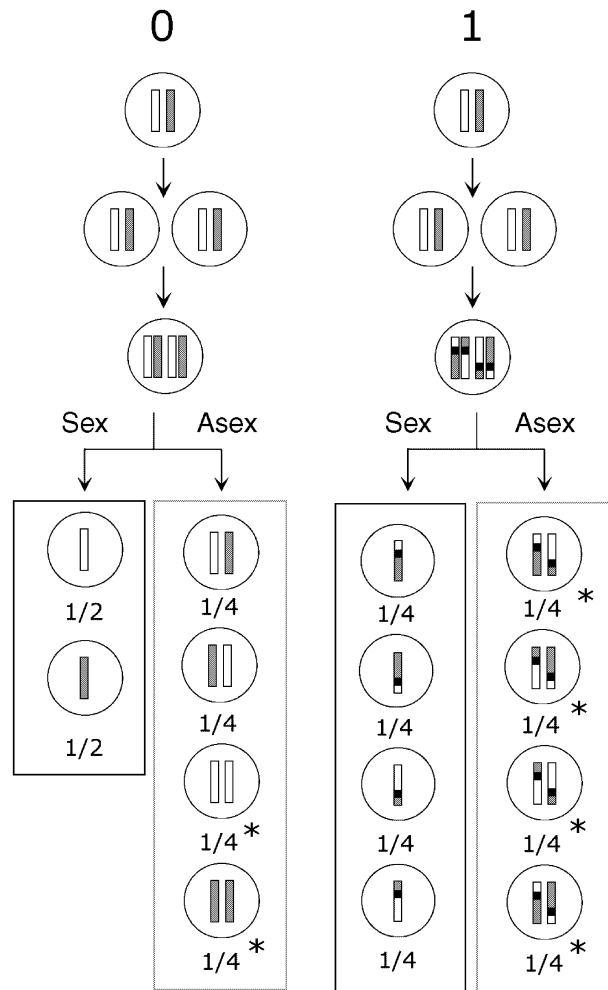


Fig. 5 Meiosis in Microsporidia. Sexual reproduction (sex) with the possible microsporidian form of meiosis, with one (1) or no (0) crossing over, and the corresponding asexual mutant (asex). Fractions indicate the frequency of each pattern of complementation in the progeny. Asterisks mark partial loss of complementation.

One-step meiosis with conjugation

In ciliates, syngamy is replaced by conjugation of two individuals, each of which undergoes meiosis and a mitotic division of one of the four meiotic nuclei (the other three degenerate), after which one nucleus from each cell moves to the other cell and two identical individuals are produced by nuclear fusion. Ciliate conjugation is a complex kind of genetic system, though meiosis is a typical two-step meiosis.

In contrast, a genetic system with some resemblance to ciliate conjugation, but with one-step meiosis, may exist in Pyrsonymphida (Oxymonadida; Cleveland, 1947; Raikov, 1982, 1995): two individuals copulate and each produces two haploid nuclei; conjugation leads to the exchange of nuclei and to an individual with two

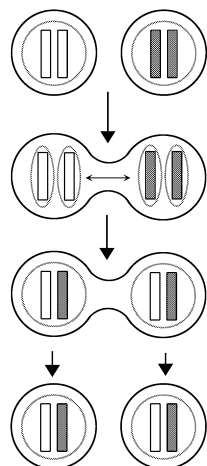


Fig. 6 One-step meiosis in Pyrsonymphida. One step meiosis is followed by conjugation with exchange of haploid nuclei, after which two new diploid nuclei are formed.

diploid nuclei, which divide into two single zygotes (see Fig. 6).

It is hard to classify this genetic system. Conjugation allows the exchange of genetic material between two individuals, and for this reason it could be classified as a form of sexuality. However, in this case the twofold cost of sex clearly does not apply. As there is no formation of a haploid stage, in the absence of conjugation it would be classified as a one-step automixis and no loss of complementation would occur. The case of Pyrsonymphida shows that there is nothing intrinsically impossible in one-step meiosis.

Note that the formation of haploid nuclei without the formation of tetrads would allow the evolution of a sister-killer as in a normal one-step meiosis. In principle a gene located in one chromosome could damage the homologous chromosome *after* it has been transferred to the other nucleus by conjugation, and lead to the death of the resulting sister diploid zygote. In the presence of recombination, however, this could result in a suicide effect.

Green frogs

In the green frog complex (*Rana esculenta*, *Rana lessonae* and *Rana ridibunda*) and in some fish (*Poeciliops*) one parental genome is entirely eliminated during meiosis {hybridogenesis or hemiclinal reproduction, $[2n \rightarrow 4n \rightarrow 2(2n) \rightarrow 2(n)]$; Dawley & Bogart, 1989}. For example, in the hybrid *R. esculenta* and *R. lessonae*, the *lessonae* genome is excluded from the gonads and the *ridibunda* genome is endoreduplicated. As a result the genotype of every gamete of *R. esculenta* is identical to that of the *R. lessonae* gamete. The *R. lessonae* genome persists as a sort of genomic parasite of *R. esculenta*.

Hybridogenesis would lead to complete loss of complementation in a mutant asexual, because it would be entirely homozygous and may therefore be an extreme version of the 'protection' effect conferred by two step meiosis. However, it is probably easier to consider this peculiar genetic system as an extreme form of meiotic drive that involves a whole genome.

The logic of meioses

It seems that, while some very diverse alternatives to meiosis exist, even more complicated and bizarre than the common two-step meiosis, the simplest possible alternative, one-step meiosis, is very rare or may not exist at all.

I have suggested that the reason is that all the cases described above except one-step meiosis prevent the replacement of sexual reproduction by asexual mutants, because asexual mutants would incur the cost of loss of complementation, like asexual mutants arising from a typical two-step meiosis. This does not mean that asexual mutants cannot evolve in these cases, but that they are doomed to extinction in few generations (Archetti, 2004). Asexual mutants deriving from one-step meiosis, instead, do not incur the cost of loss of complementation. Therefore sexual reproduction, if meiosis is one-step, can be invaded by asexual reproduction, and eventually goes extinct because of the deleterious effects of loss of complementation.

There is an analogy between Haig and Grafen's theory and the theory presented in this paper: the production of homozygosity. In Haig and Grafen's theory, transient homozygosity (no segregation) during the two steps of meiosis produces uncertainty about the outcome of a meiotic drive gene, which could result in a 'suicide' effect. This will not be the case with one-step meiosis: sister-killers could evolve and affect negatively the fitness of the sexual. In the theory presented here, instead, homozygosity will affect the fitness of an asexual mutant that eventually arises: loss of complementation will lead to the elimination of the asexual progeny. This will not be the case with one-step meiosis, with the result that in that case asexual reproduction can replace sexual reproduction.

It is not strange, therefore, that the 'alternatives' to meiosis presented here and in Haig (1993) can be explained by both the 'sister-killer effect' (protection against meiotic drive, Haig & Grafen, 1991) and the 'loss of complementation' effect (protection against invasion by asexuals, the idea presented here). Both rely on the creation of homozygosity at a certain stage, though the level of explanation is different.

The two hypotheses are not incompatible and possibly both effects are important in the maintenance of two-step meiosis. Before one can decide about their relative importance it is necessary to gather more data on the alleged cases of one-step meiosis; Pyrsonymphida with

their peculiar genetic system may provide useful insights. In particular, it would be interesting to know if there is recombination before conjugation. If this is not the case, the genetic system of *Pyronymphida* might be a challenge to Haig and Grafen's theory, because, as I have explained, a sister-killer could evolve in that case.

Mechanistic problems during meiosis

There are, in principle, some mechanistic problems that meiosis could face. The main problem is correct segregation of the chromatids to each pole. In the first division of a two-step meiosis, the two homologous chromosomes segregate from each other while the sister centromeres are held together and migrate to the same pole; in the second division, the sister centromeres segregate from each other, pulling the chromatids to opposite poles. Therefore, in the first division centromeres segregate reductionally, and in the second divide equationally (Kleckner, 1996; Page & Hawley, 2003).

It is possible, in principle, that a successful equational (second) division requires a prior reductional division, that is, gamete (spore) formation is possible only if homologs are separated.

Moreover, some form of coordination is necessary at the stage of migration of the centromeres to the poles of the meiotic spindle to ensure correct segregation of the chromatids that would, otherwise, produce aneuploidy. Therefore cohesion between sister chromatids must assure correct segregation.

Finally, crossing over is initiated by double-strand breaks (DSBs), followed by the formation of a joint molecule (double Holliday junction) and conformational changes in the chromatids involved in crossing over (Keeney, 2001). In the absence of stability the DSBs would be disastrous for the chromosome.

To summarize, there are at least three main, possible mechanistic problems. (1) Equational segregation might require a prior reductional segregation. (2) Ordered segregation of the four chromatids must be assured to prevent aneuploidy. (3) Crossing over requires some mechanism to assure stability after the formation of DSBs.

Can two-step meiosis be a necessary consequence of these mechanistic problems? A definitive answer to this question is difficult, because some details of the mechanism of meiosis are not yet known (for example the functions of the synaptonemal complex are still under study); it would require analysis of a mutant that induced a one-step meiosis or, even better, of a natural one-step meiosis. One-step meiosis may in fact exist in some taxa, showing that it is not mechanistically impossible. However I think it is possible to provide a tentative answer to these questions.

1 *A successful equational division does not require a prior reductional division.* In some mutant yeast (*Saccharomyces cerevisiae*) strains, only a single division occurs in meiosis,

instead of the usual two, forming two-spored asci, that is two diploid products instead of four haploid products. In some strains, spores are produced by a first-division (reductional) segregation, while in other strains spores are produced by a second-division (equational) segregation (Sharon & Simchen, 1990). In all of these mutants, meiotic events known to precede and follow the divisions are normal.

Therefore it seems that a successful reductional division is not essential for the equational division and for spore formation and maturation.

2 *Sister chromatid cohesion assures correct segregation of the four chromatids, but it would not be necessary for a two-chromatids meiosis.* Sister chromatid cohesion during meiosis is produced by specific proteins (cohesin complex proteins) deposited along the chromosome, and assures correct chiasma function, preventing premature migration of the centromeres to the poles of the meiotic spindle (Nasmyth, 2001). It has been observed that mutants for certain genes in maize, *Drosophila* and yeast, show precocious sister chromatid separation or fail to disjoin (Page & Hawley, 2003).

Is it possible that the presence of four chromatids (that is the two steps of meiosis) is necessary only for the mechanistic purpose of a correct segregation? I believe this cannot be the complete answer, because sister chromatid cohesion is necessary for a two-step (four-chromatid) meiosis, but this does not necessarily mean that a one-step (two-chromatid) meiosis would face the same problems. Sister chromatid cohesion (the cohesin complex proteins) is necessary because of the very presence of two pairs of chromatids that would otherwise segregate in a disordered way (while in this way they migrate together to the same pole at the same time); but with unreplicated chromosomes this would not be necessary because only single chromosomes, and not pairs of chromatids, must migrate to each pole.

In other words, the fact that in a two-step meiosis a mechanism for sister chromatid cohesion has evolved to ensure correct segregation of the four chromatids, does not mean that the very reason for the presence of four chromatids is to ensure correct segregation, and does not mean that two unreplicated chromosomes could not segregate correctly.

3 *Stability of crossing over requires homolog pairing but not necessarily sister chromatid cohesion.* The pairing of chromosomes in most species is stabilized by synapsis, in which the homologs are brought into an intimate alignment by the formation of the synaptonemal complex (SC). The SC assures stability to the joint molecule that is formed after DSB. [However, meiosis with normal levels of recombination is still possible in the absence of synapsis, which is in fact not observed, for example, in *Saccharomyces pombe*, where a canonical SC does not assemble at all and its function is substituted by discontinuous structures called linear elements (Page & Hawley, 2003)]. DSBs conversion to double Holliday junctions is

approximately concomitant with SC formation; the SC disappears immediately before, or concomitant with, the formation of crossover or noncrossover products of recombination, that is with Holliday junction resolution (Kleckner, 1996). Defects in the SC almost invariably lead to defects in recombination (Zickler & Kleckner, 1999).

Stability after DSBs and during crossing over is assured by the SC between homologs, not by sister chromatid cohesion. Sister chromatid cohesion does help at this stage, but essentially because it reduces a 'four-body' problem to a 'two-body' problem (Kleckner, 1996).

Moreover, this problem arises only with recombination. It is not necessarily true that recombination is the main purpose of meiosis (Archetti, 2004) and, in fact, in all the reported cases of one-step meiosis recombination has not been observed.

Therefore, I believe it is not out of place to look for an adaptive explanation of two-step meiosis that goes beyond the purely mechanistic problems of segregation, given that two-step meiosis, in contrast with one-step meiosis, raises the problems of the evolution of sister-killers, of invasibility by asexual mutants, and of the reduction of variability in the progeny.

Implications for the evolution of sexual reproduction

The evolutionary advantage of sexual reproduction is usually considered to be the production of variability on which selection can act (Burt, 2000), either to adapt to changing biotic interactions, with parasites being especially likely to provide the driving coevolutionary force (Jaenike, 1978; Bremermann, 1980; Hamilton, 1982; 1993; Seger & Hamilton, 1998; Hamilton *et al.*, 1990), or to get rid of deleterious mutations more efficiently (Kondrashov, 1982; 1988; 1994). However, if the evolutionary advantage of sexual reproduction is primarily the creation of variability, then the existence of two-step meiosis is a problem, because one-step meiosis produces more variability with the same frequency of recombination. This observation is a difficulty for the theories according to which the value of sexual reproduction is the production of variability, but does not affect Haig & Grafen's (1991) theory, nor the idea presented here. Indeed both the idea presented here and Haig and Grafen's idea may provide an explanation to this difficulty that is a short-term advantage for two-step meiosis that counterbalances the production of reduced variability.

While the evolutionary value of sexual reproduction has received considerable attention, the evolutionary value of the very mechanism by which sexual reproduction usually occurs, two-step meiosis, has not. The effect described here may provide an alternative or complementary explanation to Haig and Grafen's. As Haig & Grafen (1991) pointed out, an explanation for the prevalence of two-step meiosis does not mean that the

same explanation is responsible for the maintenance of sexual reproduction. However, theories that explain the advantage of sexual reproduction with the creation of variability neither readily explain the value of alternative forms of meiosis, nor the very existence of the common two-step meiosis, because they all produce less variation than one-step meiosis.

A comprehensive theory for the evolution of sexual reproduction must not only explain how it outweighs the twofold cost of meiosis, but also why its very mechanism proceeds in two steps instead of just one.

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