Does Crossover Interference Count in *Saccharomyces cerevisiae*?

Franklin W. Stahl,* 1 Henriette M. Foss,* Lisa S. Young,* Rhona H. Borts,† M. F. F. Abdullah‡ and Gregory P. Copenhaver§

*Institute of Molecular Biology, University of Oregon, Eugene, Oregon 97403-1229, †Department of Genetics, University of Leicester, Leicester LE1 7RH, United Kingdom, ‡Department of Microbiology, Mara University of Technology, 40450 Shah Alam, Malaysia and §Department of Biology and The Carolina Center for Genome Sciences, University of North Carolina, Chapel Hill, North Carolina 27599

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ABSTRACT

We previously proposed a “counting model” for meiotic crossover interference, in which double-strand breaks occur independently and a fixed number of noncrossovers occur between neighboring crossovers. Whereas in some organisms (group I) this simple model alone describes the crossover distribution, in other organisms (group II) an additional assumption—that some crossovers lack interference—improves the fit. Other differences exist between the groups: Group II needs double-strand breaks and some repair functions to achieve synapsis, while repair in group I generally occurs after synapsis is achieved; group II, but not group I, has recombination proteins Dmc1, Mnd1, and Hop2. Here we report experiments in *msh4* mutants that are designed to test predictions of the revised model in a group II organism. Further, we interpret these experiments, the above-mentioned differences between group I and II meiosis, and other data to yield the following proposal: Group II organisms use the repair of leptotene breaks to promote synapsis by generating double-Holliday-junction intermediates that lock homologs together (pairing pathway). The possible crossover or noncrossover resolution products of these structures lack interference. In contrast, for both group I and group II, repair during pachytene (disjunction pathway) is associated with interference and generates only two resolution types, whose structures suggest that the Holliday junctions of the repair intermediates are unligated. A crossover arises when such an intermediate is stabilized by a protein that prevents its default resolution to a noncrossover. The protein-binding pattern required for interference depends on clustering of sites that have received, or are normally about to receive, meiotic double-strand breaks.

A key feature of meiosis in most organisms is crossing over, the process in which homologous chromosomes exchange segments during the repair of programmed double-strand breaks (DSBs) in their DNA. The frequencies of crossing over provide the basis for genetic linkage mapping (*Sturtevant* 1913), in which the distance between genes (in morgans) is defined as the average number of points of crossing over in the interval that separates the genes (*Haldane* 1919). *Sturtevant* (1915) and *Muller* (1916) noted that crossovers occurring during *Drosophila melanogaster* oogenesis show a kind of territoriality—a relatively equitable, nonrandom distribution—among and within chromosomes. This property, which they called “interference,” is a widespread phenomenon, which may have been selected for its ability to encourage at least one crossover on each chromosome, without undue increase in the mean number of crossovers. Interference can act over great distances (e.g., about half the length of the Drosophila X linkage map) and still beguiles geneticists, microscopists, and mathematicians alike.

A mathematical model that effectively describes linkage data from the X chromosome of Drosophila (*McPeek* and *Speed* 1995; *Zhao et al.* 1995) was put forth by *Cobbs* (1978) and *Stam* (1979). Their model, notable for its simplicity and mathematical tractability, was foreshadowed by several others (reviewed in *Bailey* 1961). It describes the probability distribution for the linkage distances (in morgans) between adjacent crossovers as a scaled chi-square probability distribution with an even number of degrees of freedom. Such a distribution gained biological appeal from the suggestion that crossovers may be portrayed as successful outcomes of independently distributed attempts to cross over, and that adjacent crossovers are separated by a fixed number of failed outcomes. However, in the absence of an expressed view of what the “attempts” or “failures” might be, the model languished until *Foss et al.* (1993), elaborating a suggestion by *Mortimer* and *Fogel* (1974), proposed that the products of all programmed meiotic DSB repair (DSBR)—observable as gene conversions (see *Malkova et al.* 2004, accompanying article, this issue)—represent crossover attempts and that the gene
conversions unaccompanied by crossing over represent
the failures.

Evidence that attempts are, indeed, distributed inde-
pendently (i.e., at random with respect to each other)
is provided for Neurospora crassa by Stadler (1959) and
for (budding) yeast by Mortimer and Fogel (1974)
and Malkova et al. (2004). The most direct test of
independence would be a demonstration that conver-
sions (crossovers plus noncrossovers) manifest no inter-
ference with each other, either positive or negative. The
practical difficulty of obtaining adequate data for such
a test restricted those authors to asking whether conver-
sions unaccompanied by crossing over (failed attempts)
repress nearby crossovers, as do conversions that are
accompanied by crossing over. They did not.

A major implication of this “counting model” is that
the number of noncrossover gene conversions postu-
lated to lie between adjacent crossovers may be deter-
mimed experimentally as well as theoretically, and that
the two measurements should yield comparable values
(Foss et al. 1993). To test this prediction, published
interference data collected from Drosophila and Neu-
rospora were subjected to a best-fit analysis of the count-
ing model (McPeek and Speed 1995) to determine the
number of failures between adjacent “successes.” Foss
et al. (1993) compared these numbers with the experi-
mentally observed fraction of noncrossovers among
genome conversions. For Drosophila, the observed frac-
tion of noncrossovers is close to 0.80, as determined in a
Herculean analysis at one locus (Hilliker and Chov-
nick 1981; Hilliker et al. 1991). For Neurospora, the
observed fraction of noncrossovers is close to 0.67, based
on the average of numerous observations (Perkins et al.
1993). As predicted, both values are in agreement with
the optimal fits to the interference data determined by
McPeek and Speed (1995), who calculate the number
of obligate failures between adjacent crossovers to be
four for Drosophila and two for Neurospora.

The success with which the counting model describes
interference in Drosophila and Neurospora inspired
Foss and Stahl (1995) to test another powerful predic-
tion of the model—that, relative to the general popula-
tion, progeny with two close crossovers should show an
enhanced frequency of gene conversion unaccompa-
nied by crossing over in the interval between the two
crossovers. Testing the prediction in the only organism
in which such an experiment was feasible, Saccharomyces
cerevisiae, they obtained an unambiguously negative re-
sult and concluded that the counting model was either
wrong or not applicable to yeast.

The companion article to this work (Malkova et al.
2004), however, supports a third possibility—that inter-
ference in wild-type yeast, while approximating the rules
described by McPeek and Speed (1995), is better de-
scribed if that model includes a set of additional cross-
overs that are not subject to interference (and see de
los Santos et al. 2003). Moreover, for linkage data from
humans (Housworth and Stahl 2003) and Arabidopsis
thaliana (Copenhaver et al. 2002) too, the good fit of
the counting model is improved if a fraction of meiotic
crossovers is assumed to lack interference. In contrast,
the same analysis applied to data from Drosophila and
Neurospora suggests that all crossovers in these organ-
isms show interference (Copenhaver et al. 2002). Be-
low, we offer a context for these observations.

MATERIALS AND METHODS

Strains: Haploid S. cerevisiae strains carrying genetically
marked, bisected (JL51) and full-length (JL52) versions of
chromosome 1, diagrammed in Figure 1, are described by
Kaback et al. (1999). JL51 strains are MATα [FUN43-CEN1-URA3] fun43::
TRP1 his3 leu2 ura3 trp1 arg4, MATα [FUN43-CEN1-URA3] YAL067
HIS3 cdc24 fun30::LEU2 ade1 trp1 ura3 his3 arg4 leu2; JL52 strains
are MATα fun43::TRP1 his3 leu2 ura3 trp1 arg4, MATα YAL067:
HIS3 cdc24 fun30::LEU2 ade1 trp1 ura3 his3 arg4 leu2 (mating-
type designations were reversed in the original article; D. Kaback,
personal communication). In both JL51 haploids the 60-kb
(light gray) derivative of chromosome 1 carries a URA3 gene
that is not present in the 231-kb full-length chromosome
1-containing JL52 haploids. To avoid possible complicat-
ions resulting from differences in uracil auxotrophy, we trans-
formed both JL52 strains from ura3 to URA3 with a 1.1-kb
Smal fragment from plj242 (Jones and Prakash 1990) to
yield JL53 haploids. Results obtained with JL52 and JL53 dip-
loids were statistically indistinguishable and were pooled.

Strains precisely deleted for the MSH4 ORF were made with the
loxP-kanMX-loxP disruption cassette followed by excision
of the kanMX module by induction of the Cre recombinase
from plasmid pSH47 (Guldener et al. 1996). Oligonucleotides
used to effect MSH4 deletion were 5’-AGTTATAGCTGTAAGAAA
TCTGTAGCTGATCAACGCAAACTATATGCATCGACAACC
GTTAAATAACTGCGTTG-3’ and 5’-CAGAAATAATGGATTATA
GTAAAACTCAGCGGAAACCACTACCTAATAAC
TCTGTAGCTGTAAGAAA
TTTCAACACTCC-3’. The MSH4-targeted loxP-kanMX-loxP disruption cassette
was generated by polymerase chain reaction (PCR) using the
EXPAND high-fidelity kit (Roche Diagnostics, Indianapolis)
following the manufacturer’s directions. The following oligo-
nucleotides were used to verify MSH4 replacement with loxP-
TABLE 1

Two groups of eukaryotes

<table>
<thead>
<tr>
<th>Group</th>
<th>Candidates</th>
<th>Noninterfering crossovers</th>
<th>Evidence for two periods of DSBR</th>
<th>DMCI*&lt;sup&gt;a&lt;/sup&gt; (HOP2, MND1)</th>
<th>Resolution types</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: DSBR not required for synapsis&lt;sup&gt;a&lt;/sup&gt; (NA for N. crassa)</td>
<td>Drosophila</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>C. elegans</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>N. crassa</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
<td>No</td>
<td>Two types&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>II: DSBR required for synapsis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S. cerevisiae</td>
<td>Yes&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Yes</td>
<td>Five types&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Homo/Mus</td>
<td>Yes&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Green plants</td>
<td>Yes&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA, data not available.

<sup>a</sup>Reviewed in COPENHAVER et al. (2002).

<sup>b</sup>Foss et al. (1993); COPENHAVER et al. (2002).

<sup>c</sup>Zhao et al. (1995).

<sup>d</sup>Meneely et al. (2002).

<sup>e</sup>Malkova et al. (2004).

<sup>f</sup>Housworth and Stahl (2003).

<sup>g</sup>For Arabidopsis, COPENHAVER et al. (2002).

<sup>h</sup>Jang et al. (2003); PAGE and HAWLEY (2001); Liu et al. (2002).

<sup>i</sup>A. Villeneuve (personal communication).

<sup>j</sup>Xu et al. (1997) and see text.

<sup>k</sup>Moens et al. (2002).

<sup>l</sup>For Lilium, TERASAWA et al. (1995).


<sup>n</sup>Stadler and Towe (1963).

<sup)o</sup>e.g., Foss et al. (1999).

<sup>p</sup>kanMX<sub>loxP</sub> using standard PCR: 5′-GTATGATGGTATGGGATGA CATTGTTATCTGAGT-3′ (472 bp upstream of the MSH4 ORF) and 5′-CTCAAGCTGATTGAGGAGCCAGCGA-3′ (896 bp downstream of the MSH4 ORF).

**Media, diploid construction, sporulation, and tetrad analysis:** Media used were as described in McCusker and Haber (1988). To reduce the tendency of the 60-kb portion of bisected chromosome I to undergo duplication, it proved necessary to avoid applying selection for TRP1 or HIS3 when constructing the diploids. Thus, diploids were generated by micromanipulating appropriate haploids together, allowing colonies to grow up, and screening for nonmaters. All subsequent manipulations were at 25°C, except for detection of the CDC24 allele, which was at 37°C. Sporulation was induced on plates at 25°C (Malkova et al. 2004). Analysis of tetrad data was facilitated by MacTetrad 6.9.1, available by Gopher from merlot.welc.jhu.edu. Statistical analyses were carried out with the advice of Russell Lande. Online calculators are available at the Stahl Lab web site: http://groik.com/stahl/.

**Estimation of interference:** The chi-square probability distribution, or its gamma variation, has been shown to provide a good description of interference in a variety of organisms (e.g., Foss et al. 1993; Lande and Stahl 1993; McPeek and Speed 1995; Broman and Weber 2000). The chi-square distribution is fully determined by the value of a single parameter, which Foss et al. (1993) called m. When m = 0, the chi-square distribution is exponential (i.e., no interference). m-values were determined from tetrad data as described in Stahl and Lande (1995) with the aid of the online calculator at http://www.molbio.uoregon.edu/%7Egraham/tetrad.html.

A widely used measure of interference in two-factor tetrad data, the “NPD ratio” (Papazian 1952), measures a consequence of interference that necessarily changes value when the map distance changes. For data that approximate the chi-square distribution, the m-value, calculated from the frequencies of tetrad types, increases with increasing interference and is independent of map distance.

**RESULTS AND DISCUSSION**

**Two groups of eukaryotes:** Some eukaryotes are known to depend on some meiotic DSBR functions for intimate pairing and synapsis, as well as for proper disjunction of homologous chromosomes (for reviews see Kleckner 1996; Roeder 1997; Zalevsky et al. 1999; Walker and Hawley 2000; Copenhaver et al. 2002; Viera et al. 2004). Other eukaryotes, including Drosophila and Caenorhabditis elegans, achieve synapsis via cis-acting “homolog recognition centers” or “pairing centers” (Villeneuve 1994; Dernburg et al. 1998; McKim et al. 1998; Page and Hawley 2001; Liu et al. 2002). Eukaryotes requiring DSBR functions for synapsis share a set of additional meiotic features, including the prediction of noninterfering crossovers (Table 1). Thus, it is economical to hypothesize (1) that, together, these features characterize a process that potentiates synapsis and (2) that noninterfering crossovers are a (by)product of this process.

**Additional evidence for the existence of noninterfering crossovers in wild-type S. cerevisiae:** Zalevsky et al. (1999) raised the possibility that, in wild-type yeast but
Figure 2.—Relationships among chromosome length, crossover density, and msh4 phenotype. (a) Chromosome length in centimorgans as a function of length in kilobases with the least-squares regression of the data for S. cerevisiae. The y-axis intercept is above zero, indicating that crossover density is higher on short than on long chromosomes. Data are from Saccharomyces Genome Database: http://db.yeastgenome.org/cgi-bin/SGD/GMAP/pgMap. Data for chromosomes of special interest in this article are indicated by solid points. (b) Bisection of chromosome I into a longer and a shorter derivative (see Figure 1) confirms the observation of Kaback et al. (1992) that, in MSH4 (wild-type) cells, a defined interval is genetically longer when it resides on a shorter chromosome. For the HIS3-TRP1 interval on the shorter derivative (60 kb), the increase in map length resulting from the bisection is significant. (c) Deletion of MSH4 (which abolishes interference and reduces the map length of all intervals) enhances, rather than eliminates, the influence of chromosome length on crossover density. The relatively greater influence of chromosome length on the density of crossovers in the msh4 mutant (significant for all intervals tested) suggests that chromosome-length dependence is a feature of the Msh4-independent crossovers. Solid bar, full-length chromosome (231 kb); shaded bar, shorter derivative (60 kb); hatched bar, longer derivative (180 kb). Figure 2, b and c, is based on the tetrad data tabulated in Table 2.

not in C. elegans, DSBR functions aiding in the establishment of noninterfering crossovers. These workers called attention to mutant phenotypes of the meiosis-specific HIM-14 gene in C. elegans and those of its S. cerevisiae homolog, MSH4. In both yeast and C. elegans, msh4/him-14 mutations reduce crossover over, apparently without affecting the formation or final level of repair of DSBs (Ross-Macdonald and Roeder 1994; Novak et al. 2001; Colaiácovo et al. 2003). In C. elegans, however, him-14 mutations completely eliminate crossing over, while msh4 mutations in yeast allow a conspicuous residuum of crossovers, and these crossovers lack interference. One interpretation of these data is that yeast, but not C. elegans, has a pathway of DSBR that promotes homolog pairing and produces noninterfering crossovers (and noncrossovers). Intermediates in this pathway do not depend on Msh4 for crossover resolution, although Msh4 may aid in stabilizing the intermediate during its formation as suggested (to us) by the delayed synapsis observed in msh4 mutants (Novak et al. 2001; see also Moens et al. 2002; Santucci-Darmann et al. 2000; reviewed in Hoffman and Borts 2004).

An alternative hypothesis, proposed by Storlazzi et al. (1996; and see Sym and Roeder 1994), was based on mutant phenotypes of ZIP1, a member of the yeast epistasis group that includes MSH4 and, presumably, its partner MSH5 (Novak et al. 2001). ZIP1 is responsible for making the transverse elements of the synaptonemal complex, and zip1 mutations, like msh4 mutations, reduce crossing over and eliminate interference without affecting the frequency of gene conversion. Storlazzi et al. (1996, p. 9047) proposed that all crossovers in wild-type yeast are subject to interference and that in a zip1 mutant “precrossover intermediates lacking their special epistatic factors mature aberrantly and also, via randomization at the resolution stage, into both crossovers and noncrossovers.” Although the model of Storlazzi et al. accounts for the observed residual crossovers and their lack of interference, it does not predict the difference between the mutant phenotypes of msh4 in yeast and those of him-14 in C. elegans.

The presence of noninterfering crossovers could account for a phenomenon described by Zhao et al. (1995). These workers demonstrated that the strength of interference in wild-type yeast varies significantly among different parts of the genome. We suggest that the weaker interference in some genomic regions simply reflects a relatively higher density of noninterfering crossovers in these regions. Conversely, regions of stronger interference would signal a relatively higher concentration of interfering crossovers. Since crossover interference is strictly dependent on genes in the MSH4-MSH5-ZIP1 epistasis group, this hypothesis predicts that mutations in these genes should cause a greater reduction in crossing over in genomic segments with normally strong interference than in segments with weak interference in wild-type yeast. Several sets of data indicate that this is, indeed, the case (Sym and Roeder 1994; Novak et al. 2001; Figure 3). The hypothesis that the lack of interference in msh4 or zip1 mutants was created by the relevant mutations (Storlazzi et al. 1996) makes no predictions...
TABLE 2
Tetrad data for Figure 2, b and c

<table>
<thead>
<tr>
<th>Genetic interval</th>
<th>Chromosome size (kb)</th>
<th>Genotype</th>
<th>Tetrad type</th>
<th>Map distance (cM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PD</td>
<td>NPD</td>
</tr>
<tr>
<td>CDC24-LEU2 (44 kb)</td>
<td>180</td>
<td>MSH4</td>
<td>201</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>msh4</td>
<td>255</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>231</td>
<td>MSH4</td>
<td>202</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>msh4</td>
<td>243</td>
<td>0</td>
</tr>
<tr>
<td>CDC24-ADE1 (97 kb)</td>
<td>180</td>
<td>MSH4</td>
<td>83</td>
<td>46</td>
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<td></td>
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<td></td>
<td></td>
<td>msh4</td>
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<td>1</td>
</tr>
<tr>
<td>LEU2-ADE1 (53 kb)</td>
<td>180</td>
<td>MSH4</td>
<td>375</td>
<td>9</td>
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<td>280</td>
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<td>MSH4</td>
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<td>6</td>
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<tr>
<td></td>
<td></td>
<td>msh4</td>
<td>259</td>
<td>0</td>
</tr>
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<td>HIS3-TRP1 (43 kb)</td>
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<td>MSH4</td>
<td>163</td>
<td>19</td>
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<td>msh4</td>
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<td></td>
<td></td>
<td>msh4</td>
<td>264</td>
<td>0</td>
</tr>
</tbody>
</table>

regarding the relationship between the density of Msh4-dependent crossovers and strength of interference.

Another phenomenon, illuminated by Kaback et al. (1999), may also be explained by the presence of noninterfering crossovers. These workers started with the observation that, in yeast, the shorter chromosomes have a higher crossover density than the longer ones (Figure 2a) and demonstrated that chromosome length per se affects both crossover density and interference. Specifically, they showed that, within a defined chromosome segment, crossover density is higher, and interference weaker, when that segment is embedded in a short chromosome than when it resides in a long chromosome.

Kaback et al. (1999) hypothesized that longer chromosomes are more susceptible to interference, and that interference suppresses crossover density. This interpretation predicts that the elimination of interference, e.g., via deletion of MSH4, should remove the differential crossover suppression and, hence, abolish the chromosome-length dependence of crossover density. We tested this prediction. Using strains generously provided by D. Kaback, we examined four intervals (one of which is the sum of two smaller, adjacent intervals) embedded in full-length chromosome 1 (~231 kb) and in shorter derivatives of chromosome 1 (60 and 180 kb), created by bisection (Figure 1; MATERIALS AND METHODS). Crossover densities for each interval were measured in MSH4 and msh4 backgrounds. In wild-type cells (MSH4), all four intervals examined showed a greater crossover density on the shorter chromosomes. The increase was significant for the HIS3-TRP1 interval on the shorter derivative of chromosome 1 (Figure 2b). However, instead of abolishing the chromosome-length dependence of crossover density observed in wild-type strains, the msh4 defect appeared to significantly enhance the length dependence in each case (Figure 2, b and c, and Table 2).

Only tetrads with four viable spores were used for the data presented in Figure 2. Such tetrads constituted 72% of the total in the MSH4 diploid, but only 11–13% in the msh4 diploid. To guard against the possibility that this small subclass misrepresented the total msh4 tetrad population, we measured the effect of chromosome length on crossover density in MSH4 and msh4 tetrads with fewer than four viable spores and in MSH4 and msh4 tetrads with four viable spores. The fraction of tetrads with at least one spore recombinant for HIS3 and TRP1 was used as a relative measure of recombination activity. In each case, deletion of MSH4 resulted in a relative increase in the observed chromosome length dependence of such activity (data not shown), arguing that the poor spore viability of the msh4 diploid did not affect our results. Together, our results argue against the notion that suppression of crossing over by interference accounts for the lower density of crossing over on longer chromosomes.

On the other hand, the notion that yeast has two kinds
Msh4-Msh5-independent crossovers. It is not obvious that msh4 mutants show interference, and is distributed at a roughly constant number per chromosome.

As proposed by the authors, these results suggest that there are crossovers of (at least) two types: those that depend on Msh4-Msh5 and exhibit interference and those that depend on Mms4-Mus81, lack interference, and occur at a higher density on shorter chromosomes.

The data described above argue that the overall distribution of crossovers may be expressed as $X = aL + b$, where $X$ equals map length (in morgans), $L$ equals chromosome length (in base pairs), $aL$ represents the component of crossovers (hypothesized to be interfering) whose number increases with chromosome length, and $b$ represents the crossovers (hypothesized to be non-interfering) whose number per chromosome is insensitive to chromosome length. Figure 2a estimates $b$ at 62 cM and implies that the fractions of length-insensitive crossovers on chromosomes VII and III are 0.16 and 0.43, respectively. These values are compatible with the independently derived averages of 0.21 and 0.48 (Figure 3) for the fractions of Msh4-independent (hence, noninterfering) crossovers on chromosomes VII and III, respectively. Presumably, the frequencies of Mms4-dependent crossovers reported by de los Santos et al. (2003) also represent the frequencies of Msh4-independent crossovers. Their values were 0.11 and 0.34 for VII and III, respectively. Moreover, a fourth independent method of analysis, described in the companion article (Malkova et al. 2004), yields values of 0.08–0.12 as the fraction of noninterfering crossovers on chromosome VII. These numbers, arrived at by very different routes, are compatible with the hypothesis that wild-type S. cerevisiae meioses generate two populations of crossovers, one of which occurs independently of Msh4, lacks interference, and is distributed at a roughly constant number per chromosome.

For humans, as for Arabidopsis (Copenhaver et al. 2002) and for the yeast chromosome analyzed by Malkova et al. (2004), the frequency distributions of intercrossover distances were significantly better described when crossovers assumed to be free of the interference were added to the chi-square distribution (Housworth and Stahl 2003). Most of the exceptional chromosomes (i.e., those for which the fit of the data was not improved by assuming a fraction of noninterfering crossovers) in the human and Arabidopsis data sets share an architectural feature: the presence of large rDNA arrays, which are thought to aid pairing and synapsis of homologous chromosomes (Copenhaver et al. 2002). This feature may allow these exceptional chromosomes to achieve synapsis with a minimum of DSBR. It is not obvious that chromosome 1 has a synapsis-promoting feature that could account for our observation that the implied value of ~0.30 Msh4-independent crossovers falls short of the ~0.56 predicted by the data shown in Figure 2a (but see Clustered intermediates, below).

As with yeast, the best estimates for the frequencies of the interference-free crossovers in humans, which differed for the two sexes, were compatible with the values
CROSSOVER INTERFERENCE

Figure 4—Double-strand-break repair pathways. We propose that DSBs occurring in the pairing pathway give rise to noncrossovers (h and i) and noninterfering crossovers (f and g) via the cutting of fully ligated double Holliday junctions of joint-molecule intermediates (e). These breaks could also give rise to noncrossovers of type j via helicase-dependent unwinding of either ligated (e) or as yet unligated (d) intermediates. DSBR in the disjunction pathway involves only joint-molecule intermediates with unligated Holliday junctions that are either unwound, to form noncrossovers (j), or cut, to form interfering crossovers (f). Lowercase alphabetic designations of resolution products are after Hillers and Stahl (1999). Uppercase designations indicate the implied mode of resolution of the intermediates. U indicates unwinding.

**PAIRING PATHWAY**

Unwind

**DISJUNCTION PATHWAY**

Cut

**PAIRING PATHWAY**

Unwind

**DISJUNCTION PATHWAY**

Cut

(with or without the aid of a topoisomerase), as deduced from the presence of a heteroduplex on only one of the participating duplexes. The letters S or N (ordered from left to right) refer to the mode of resolution cutting at the left and right junctions, respectively. S, cutting of the strand that has newly synthesized DNA at the junction and/or the co-polar strand; N, cutting of the pair of co-polar strands that includes no newly synthesized DNA at the junction. Additional repair products (not shown) that could have resulted from “synthesis-dependent strand annealing” or “single-end invasion” are discussed in Paques and Haber (1999) and Hunter and Kleckner (2001), respectively.

**Two periods of DSBR:** In group I organisms such as Drosophila and C. elegans, evidence of repair of meiotic DSBs is seen primarily in pachytene cells, i.e., those in which synopsis of homologous chromosomes is complete (Page and Hawley 2001; Liu et al. 2002; Jang et al. 2003; Golalácido et al. 2003). In contrast, group II organisms depend on DSBR functions to establish synopsis. During leptotene these organisms enjoy programmed DSBs, the repair of which may have reached the stage of “double Holliday junctions” (Figure 4e) before pachytene (reviewed in Zickler and Kleckner 1998) or not (Hunter and Kleckner 2001).

Reports (Atcheson et al. 1987; Chu et al. 1998) that the yeast transcript of SPO11, a gene conserved among eukaryotes and required for DSB formation, reaches its highest level in pachytene lends credibility to the possibility of a round of DSBs at that stage. As in yeast, SPO11 transcription in mouse occurs from leptotene through pachytene with its maximum level in pachytene (Shannon et al. 1999). This led Shannon et al. (1999, p. 334) to write, “One possibility is that SPO11 acts in both the early and middle stages of meiotic prophase,” with the implication that its role at both stages was to make DSBs. The observation by Romanienko and Camerini-Otero (2000) that Spo11 is localized on pachytene chromosomes supports the view that it has a role, although the authors, in the absence of evidence, eschewed the possibility that the pachytene role of Spo11 is to make DSBs. In a different interpretation of a similar experiment, Liu et al. (2002), working with the Drosophila protein MEI-P22 (which they demonstrated to be required for meiotic DSB formation), took the appearance of MEI-P22 foci on synapsed chromosomes as evidence that, in flies, DSBs are formed after synopsis. The appearance of γH2AX, indicative of DSBs, only in the pachytene stage of Drosophila supports that conclusion (Jang et al. 2003; and see Viera et al. 2004).

Whether or not group II organisms produce DSBs at pachytene, observations made on non-yeast group II organisms suggest that they, like those of group I, engage in a round of DSBR during pachytene. Hotta and Stern (1971) used DNA-DNA hybridization, density label substitutions, and sensitivity of DNA synthesis to hydroxyurea to demonstrate that “repair synthesis” occurs during pachytene in meioses of lily. Other workers used microscopy to detect the presence of labeled proteins involved in early stages of meiotic DSBR (e.g., the strand-exchange proteins Rad51 and/or Dmc1). These proteins may appear as “foci” or “painted regions” on independently labeled chromosomes, indicating the occurrence of DSBR (see Roeder 1997 for review). Such methods applied to lily (Terasawa et al. 1995) and...
Dmc1p appears to be a group II-specific protein: The hypothesis summarized in Table 1 correlates presynaptic DSBR with a special set of proteins that include Dmc1 and Mnd1. These meiosis-specific proteins have been identified in protists, several yeasts, Arabidopsis, mice, and humans; in Drosophila and C. elegans (Takanami et al. 2000; Gerton and DeRisi 2002; Rinaldo et al. 2002) and in Neurospora (Borkovich et al. 2004) they were looked for but not found. Mnd1’s meiosis-specific partner, Hop2, which appears to form a complex with Mnd1 (Tsubouchi and Roeder 2002), is another candidate for a protein that occurs uniquely in group II organisms. Only the strand-exchange protein Dmc1, however, has been studied widely enough to inspire a hypothesis as to its function in promoting synopsis. Dmc1 (Lim15 in lily) and its relative Rad51 are eukaryotic homologs of the bacterial protein RecA, which catalyzes homology-dependent exchange between DNA segments (West 1992). While Rad51 functions in both vegetative and meiotic cells of all eukaryotes examined, Dmc1 is meio-tene (see Copenhaver et al. 2002 for review).

The phenotypes of dmc1 mutants in S. cerevisiae and other group II organisms suggest that Dmc1 promotes synopsis by allowing early DSBs to be processed into intermediates that topologically bind homologous chromatin together. Such intermediates were isolated by Schwacha and Kleckner (1995) and were shown to have the joint-molecule structure diagrammed in Figure 4e. In meioses of “SKI” strains of S. cerevisiae, dmc1 mutants fail to form these double-Holliday-junction intermediates, except under special circumstances discussed below (Schwacha and Kleckner 1997; Hunter and Kleckner 2001). Instead, these dmc1 mutants accumulate unrepai-versed DSBs, and their progress through meiosis is arrested.

“BR” strains of yeast have also been used to examine dmc1 phenotypes. In these strains the dmc1 mutations allow significant DSBR and recombination. Rockmill et al. (1995) demonstrated that BR dmc1 (and rad51) mutants are deficient in chromosome pairing as measured by fluorescence in situ hybridization (FISH). Moreover, electron micrographs of silver-stained dmc1 chromosomes failed to show “axial associations,” the intimate connections between homologous chromosomes visible in zip1 single mutants. Thus, in group II, presynaptic pairing and subsequent progress through meiosis are normally dependent on Dmc1-mediated DSBR.

Two conditions, identified by Schwacha and Kleckner (1997), allow dmc1 yeast mutants to undergo DSBR and form joint-molecule intermediates: (1) the absence of the meiosis-specific protein Red1 (and, perhaps, other members of the RED1 epistasis group) and (2)—possibly a special case of (1)—the return of meiotic cells to growth in rich medium. The following section includes a proposal for the significance of these observations.

Issues of special concern to group II: The transition from mitosis to meiosis includes a change in repair templates used for homology-based DSBR—sister chromatids are the preferred templates in mitosis, whereas homologs serve predominantly as templates in meiosis. In yeast, and possibly all group II organisms, DSBs follow promptly upon chromosome replication, at which time homologs are unpaired. In due course, homologous chromosomes realign themselves in a process that is independent of DSBR formation or repair (reviewed in Burgess et al. 1999). Until then, however, homologous sequences on sister chromatids (acting as in meiosis) or in nonallelic (ectopic) positions could be serious competitors to allelic homologies as templates for DSBR (Goldman and Lichter 2000; Walker and Hawley 2000). Thus, since synopsis depends on allelic inter-homolog interactions, it would appear to be important that group II organisms, especially, have a mechanism for avoiding DSBR until the homologs are the primary candidates for repair template. In pursuit of that possibility, we ask whether extant data in yeast are subject to an interpretation that might solve that problem. In doing so, we do not claim that our interpretation is driven by the data, and we recognize that others will interpret these data differently.

Some phenotypes of mutants in the yeast RED1-MEK1-HOP1 epistasis group suggest that these genes play a role in preventing premature DSBR. That Red1 prevents
DSBR is readily discernible in \textit{dmc1} mutants, which normally arrest in meiotic prophase with an accumulation of unrepaird DSBs (Schwacha and Kleckner 1997). The absence of Red1 allows \textit{dmc1} mutants to repair their DSBs and progress through meiosis (Schwacha and Kleckner 1997; Xu et al. 1997). In a \textit{Dmc1} background, too, Red1 may delay DSBR as suggested by the RED1-dependent preference for DSBR involving the homolog as opposed to the sister chromatid (Schwacha and Kleckner 1997).

Of course, even in \textit{Red1} cells, the early DSBs need to be repaired in due time. The mutant \textit{red1} and \textit{dmc1} phenotypes suggest that the accumulation of the meiosis-specific protein Dmc1 is required for alleviating the postulated Red1-induced block to DSBR. Presumably, by the time Dmc1 has accumulated sufficiently to overcome the block to repair, the homologs will be closely aligned so that interhomolog, rather than intersister or ectopic, interactions are predominant. In the context of Table 1, the dependence on Dmc1 of timely DSBR implies that the Dmc1-facilitated joint-molecule intermediates (Figure 4e) yield noninterfering crossovers. Suppression of the recombination phenotype in \textit{dmc1} mutants by overexpression of Rad51 (Tsoubouchi and Roeder 2003) or Rad54 (Shinohara et al. 2003) suggests that the mechanism by which Dmc1 overcomes the Red1-imposed barrier is to empower strand invasion by Rad51 with the help of Rad54.

\textbf{Ligated and unligated DSBR intermediates?} The “canonical” DSBR model (Szostak et al. 1983, as modified by Sun et al. 1991) has served as a useful basis for studies of meiotic recombination. Molecular and genetic studies of yeast meiosis have provided evidence in support of the major features of the model: (1) DSBs, (2) 5’-3’ resection of the broken DNA ends, (3) the bimolecular, ligated intermediate (Figure 4e), and (4) the predicted resolution products (Figure 4, f, g, h, and i) (Sun et al. 1989, 1991; Schwacha and Kleckner 1995; Gilbertson and Stahl 1996; Hillers and Stahl 1999; for reviews see Roeder 1997; Zickler and Kleckner 1998).

Several observations, however, suggest that the canonical DSBR model describes the DSBR required for synapsis in group II organisms, rather than the type of DSBR that results in crossover interference. For example, the observed ligated bimolecular intermediate is normally dependent on Dmc1, a protein apparently lacking in group I organisms. Moreover, three of the four canonical resolution products are underrepresented in yeast and may be lacking altogether in Neurospora, a group I candidate (Table 1, and see below). Conversely, at least two features documented for DSBR in yeast as well as in Neurospora were not predicted by the model: (1) the predominance among noncrossovers of resolutions of the type labeled j in Figure 4 and (2) the predominance among crossovers of type f resolutions (Figures 4 and 5; Stadler and Towe 1963; Gilbertson and Stahl 1996; Foss et al. 1999; also see data, if not text, from Merker et al. 2003). Below, we discuss these “noncanonical” features and the mechanism for crossover interference suggested by their presence.

An early hint of noncanonical DSBR comes from an analysis by Stadler and Towe (1963) of the four haploid products from individual acts of meiosis in Neurospora. If we grant the order of markers proposed by the authors, their data are simply interpreted as indicative of only two resolution types—essentially all of the crossover resolutions that could be typed were of type f, and none of the noncrossovers showed any sign of reciprocal transfer of markers between the participating chromosomes (as in h’s or i). Instead, all appeared to be of type j, as if the two participants in the intermediate had simply slid apart from each other (Figure 5; h’s would not have been detected in this study because the markers monitoring the conversion were only on the right side of the DSB; their absence is inferred from the absence of i’s with which they share molecular symmetry).

The notion that participants can slide apart suggests that the Holliday junctions, instead of being fully formed as in the canonical model (Figure 4e), have failed to execute the final, ligation, step. Such a failure would mean that the participants are not topologically locked together (Figure 4d) and so could be separated without the involvement of either a topoisomerase or a junction-cutting “resolvase.” If, however, the bimolecular intermediate were stabilized so as to prevent its members from sliding apart, it would become a substrate for a junction-cutting resolvase. As elaborated below, a feature that appears typical of resolvases clarifies how the concept of nonligation of the bimolecular intermediate can account for the possible absence in Neurospora (and paucity in yeast) of three out of the four canonical resolution types and suggests a mechanism for interference.

When presented, \textit{in vitro}, with a fully ligated Holliday junction, the most thoroughly characterized resolvases, RuvC from \textit{Escherichia coli} and endonuclease VII from phage T4, are equally likely to cut the two “Watson” or the two “Crick” strands (see, for example, Schwacha and Kleckner 1995). However, when presented with a junction that is nicked (unligated or precut) on one strand, the resolvases always cut the intact strand of corresponding polarity (Fogg and Lilley 2000; Birkenbhl and Kemper 2002). The same principle appears to govern the action of the Mus81-Eme1 complex in fission yeast (Gaillard et al. 2003). In a stabilized, unligated intermediate (Figure 4d), the “nick” to be recognized by the resolvase is necessarily adjacent to the 3’ end of the newly synthesized DNA at each junction. This limits, at each junction, the resolvase’s substrate to the strand of the same polarity as that carrying the newly synthesized DNA (S in Figure 4) and dictates that the outcome is, inevitably, a crossover of type f (SS). Candidates for proteins to stabilize bimolecular recombination intermediates include Msh4 and Msh5 (Zalev-
Figure 5.—Conversion and crossing over in the cys gene of Neurospora. The example, which shows only the two interacting chromatids, is for cys\(^+\) arising by conversion at a right-hand site in cys. That results when the white (cys\(^2\)) parent is cut, at the hotspot left of cys, and resection extends rightward beyond cys\(^2\). Junction cutting is directed by the strand discontinuities, so that in common parlance, “the crossover is always to the left of the gene” (f, Figure 4). In noncrossovers, the participants slide apart (j, Figure 4). In these studies, postmeiotic segregation was rare, so cys\(^+/H11001\) is generally the result of mismatch repair to /H11001 at both sites. For both crossovers and noncrossovers, these rules account for “Reciprocal crossing over accompanying cysteine recombination nearly always results from an exchange at the left of the cysteine locus” (p. 1323), and “The striking result that [in the /H11001/H11001 spore pair] the right-hand marker (ylo locus) almost always identifies the cys mutant which has segregated 3:1” (STADLER and TOWE 1963, p. 1332). (These rules apply as well when the red parent is cut and conversion to /H11001 occurs at the cys\(^1\) site.) [Note that in the filamentous fungi examined, unlike in S. cerevisiae, meiotic mismatch repair is not directed by strand discontinuities, as revealed by the strong conversion disparities demonstrated for frameshift markers by ROSSIGNOL and PAQUETTE (1979).]

Resolution types: If the in vivo behavior of resolvases mimics their in vitro behavior, the resolution of an unligated intermediate must yield a crossover of type f (SS) if the intermediate is stabilized or a noncrossover of type j (U) if it is not (Figure 4). In contrast, the resolution of a ligated intermediate has no such limitations. The ligation serves both to stabilize the intermediate and to abolish the nick that would have directed the resolvase to one substrate only. Thus, the newly synthesized DNA in ligated intermediates does not signal a substrate for resolvase, allowing indiscriminate (though not necessarily equal) resolution into types SS, SN, NS, or NN, as expected of the canonical DSBR model (Figure 4).

If resolution products g (NN), h (NS), and i (SN) are unique to the postulated canonical, leptotene/zygotene DSBR, genomic regions or loci that normally show relatively weaker interference should coincide with a rela-
tively higher incidence of such products. Support for this prediction comes from studies in yeast of the ARG4 locus on chromosome VIII, where interference is strong, and the HIS4 locus or neighborhood on chromosome III, where interference is weak (King and Mortimer 1991; Hoffmann 2002). At ARG4, Gilbertson and Stahl (1996) found a strong predominance of resolution types f and j, reminiscent of Neurospora. At HIS4, in contrast, Hillers and Stahl (1999) and Hoffmann (2002) found a relatively greater fraction of the products predicted by the canonical DSBR model.

**Clustered intermediates**: While the presence or absence of Msh4-Msh5 binding may guide the resolution fate of a DSBR intermediate (Zalevsky et al. 1999), crossover interference according to the counting model will result only if the bound intermediates routinely flank a quasi-constant number of unstabilized intermediates. How might such a pattern be created? Perhaps (as part of the process of chromosome condensation?) neighboring intermediates (to-be) are gathered into clusters of more or less fixed size (Stahl 1993) in which one member, in a favored position, competitively commands the multiple Msh4-Msh5 heterodimers needed for stabilization. Then, only that member, for instance the middle one, becomes a crossover.

Direct evidence for clustering of sites of DSBR in yeast comes from experiments that address the relationship between meiotic DSBR and “synapsis initiation complexes” (SICs—colocalizations of Zip3 and Zip2 and other proteins required for normal frequencies of crossing over; Fung et al. 2004). Henderson and Keeney (2004) measured the fate of SICs, presumed sites of crossing over, as a function of decreasing frequencies of DSBs achieved through the use of Spo11 hypomorphs. They found that loss of DSBs down to ~40–20% of wild type had little or no effect on the survival of Zip3 foci. DSB frequencies of <20%, however, caused a steep decline in Zip3 foci. They report that crossovers were lost with similar kinetics. Such kinetics imply that each wild-type SIC has multiple DSB sites and that a mutant SIC, and its associated crossover, will be lost only if every site in that SIC fails to receive a DSB. The equation for this model fits the data of Henderson and Keeney (2004) if its single adjustable parameter—cluster size of one crossover plus m noncrossovers—is set at five (Figure 6). Those authors suggest (K. A. Henderson and S. Keeney, personal communication) that their data are better described as compatible with a range of N values from 4 to 9. Using the two-pathway model to analyze crossover interference in tetrad data from yeast chromosome VII, Malkova et al. (2004) estimated $m + 1 = 4$. Uncertainties in the two methods of calculating m are such that the estimates appear compatible with each other.

This view of SICs, provoked by the data of Henderson and Keeney (2004), demands that, in wild-type strains, the items clustered are guaranteed to receive a DSB without regard to whether the DSBs occur prior to or following the clustering. The SICs, which we take to be clusters of “attempts”, manifest nonrandom spacing characteristic of chiasma interference and occur at a frequency of about two-thirds the overall frequency of crossing over (Rockmill et al. 2003; Fung et al. 2004), making them eligible candidates for sites of crossing over in the disjunction pathway. Fung et al. (2004) observed that the spacing of SICs is unaffected by zip1 mutations, which eliminate crossover interference, suggesting that the absence of Zip1, and hence of Msh4-Msh5 proteins (Novak et al. 2001), causes all DSBR intermediates in each SIC to be resolved, by default, as noncrossovers (j’s, Figure 4). The concept of clustering is further boosted by the demonstration that “late recombination nodules,” each of which, in group I organisms, demonstrably corresponds to a single crossover, can be seen by electron microscopy (in pachytene of pigeon meiosis) to be composed of four to five morphologically equivalent subunits (Pigozzi and Solari 1998). Each such subunit may represent a recombination intermediate with associated proteins.

A cluster version of the counting model raises concerns regarding “end effects.” Clusters at one end of the chromosome (or the other, or both) are apt to fall shy of the normal number of attempts. Crossovers in such shorted clusters would manifest reduced interference and would occur at increased density. This effect, which would have a greater impact on the analysis of interference in short chromosomes than in long ones, will be assessed in subsequent analyses. At this point we note that such an end effect could contribute to the
inverse relationship between crossover density and chromosome length (e.g., Figure 2a) and might account for the quantitative discrepancy noted above between the observed and “expected” frequency of Msh4-independent crossovers on the very short chromosome I.

Implications and ramifications: An implication of the perspective presented here is that mitotic Rad51-dependent DSBR resembles the DSBR of the disjunction pathway, and that such repair occurs via an unligated joint-molecule intermediate. In the apparent absence of proteins to stabilize this intermediate, most mitotic products would be noncrossovers, as observed (for review, see Ira et al. 2003). Furthermore, crossovers should be resolution type f, as was observed by Baker and Birmingham (2001) in their studies of in vivo homologous recombination between a linearized transfer vector and a mammalian chromosome. That no direct identification of joint-molecule intermediates has been reported for mitotic DSBR may reflect a short life span for such intermediates as compared with those detected in meiotic prophase.

The proposal summarized in Table 1 rests on the premise that the unique attributes of group II organisms all serve to promote synopsis between homologous chromosomes. It may be distilled into the following set of related hypotheses: (1) Interference, wherever it occurs, is governed by the rules of the counting model and is based on the patterning and resolution of repair intermediates; (2) the noncrossovers and the interfering crossovers arising from the disjunction pathway of DSBR represent the sole alternative resolution modes of intermediates with properties such as those of the unligated joint molecules pictured in Figure 4d (see also Figure 5); (3) crossover resolution of such intermediates requires proteins such as Msh4-Msh5 to stabilize the intermediate until its junctions are cleaved by a resolvase; (4) the pattern of Msh4-Msh5 binding required for interference is achieved through competition within clusters (the size of the clusters determines the intensity of interference (m in the counting model)); (5) those creatures (group II) that use DSBR to promote synopsis are a subclass of organisms that have crossover interference; (6) synopsis-promoting DSBR generates canonical DSBR intermediates (which tie the homologs together), yielding noninterfering crossovers of types g and f and noncrossovers of types h, i, and, possibly, j (Figure 4); (7) the noninterfering crossovers found in mutants such as msh4 in S. cerevisiae represent these noninterfering crossovers present in wild-type organisms; (8) chromosomes without pairing centers have a roughly fixed average number of Msh4-independent, noninterfering crossovers, regardless of chromosome length; and (9) genes in the RED1 epistasis group prevent premature repair of DSBS.

The body of this article exposes the rationale leading to these interrelated postulates. We present our view for its explanatory, predictive, and iconoclastic value and for its vulnerability to experimental test.

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