ANNUAL REVIEWS

Annual Review of Genetics

Crossover Interference: Shedding Light on the Evolution of Recombination

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Annu. Rev. Genet. 2019. 53:19–44

First published as a Review in Advance on August 20, 2019

The *Annual Review of Genetics* is online at genet.annualreviews.org

https://doi.org/10.1146/annurev-genet-040119-093957

Keywords

interference, crossovers, recombination, evolution

Abstract

Through recombination, genes are freed to evolve more independently of one another, unleashing genetic variance hidden in the linkage disequilibrium that accumulates through selection combined with drift. Yet crossover numbers are evolutionarily constrained, with at least one and not many more than one crossover per bivalent in most taxa. Crossover interference, whereby a crossover reduces the probability of a neighboring crossover, contributes to this homogeneity. The mechanisms by which interference is achieved and crossovers are regulated are a major current subject of inquiry, facilitated by novel methods to visualize crossovers and to pinpoint recombination events. Here, we review patterns of crossover interference and the models built to describe this process. We then discuss the selective forces that have likely shaped interference and the regulation of crossover numbers.

How interference works remains one of the major unsolved problems of meiotic biology.

—Hughes et al. (57)

1. HISTORY

Few processes have played a role as fundamental as meiotic recombination in the history of genetics. In the first article published in *Genetics*, Bridges (22) used his observations of meiotic nondisjunction of X chromosomes that lacked crossovers to prove the chromosomal basis of heredity (22, 44). One early realization about recombination concerned the relative positions of crossovers. The first linkage map, constructed with visible markers in *Drosophila melanogaster*, revealed that the existence of a crossover in one chromosomal interval reduces the probability of another crossover occurring nearby (115), a phenomenon called interference (88, 116). Subsequent studies of *D. melanogaster* established that interference occurs between crossovers on the same chromosome (88) and that interference exerts its influence over large genetic distances (122).

For more than 100 years geneticists have been trying to understand how interference is achieved for two main reasons. First, interference is seen across a wide variety of organisms (16). Second, the existence of interference provides key insights about the mechanisms responsible for recombination. Namely, there is information transfer within chromosomes among the processes that lead to crossovers (68).

Recent methodological advances have generated considerable progress toward deciphering interference. Using immunofluorescent cytology, researchers have visualized biomarkers for crossovers in single meiotic cells, including the MLH1 mismatch repair protein, which localizes to sites of reciprocal crossing over (9). With this approach, causes of interference can be probed in mutants and estimates of interference can be extended beyond genetic model organisms. In addition, crossovers detected through transmission events from parents to offspring can be positioned with high resolution by genotyping large numbers of single nucleotide polymorphisms throughout the genome (e.g., 87). With this advance, distances between crossovers can be estimated with increasing accuracy. Finally, surveys of large pedigrees enable the examination of recombination in impressive numbers of meioses (e.g., 121). These advances have led to the identification of several genes encoding proteins that underlie crossover interference, including topoisomerase II [involved in chromosome disentanglement and release of topological stress (126)], Asy2/Mer2 [involved in the spatial juxtaposition of homologous chromosomes (117)], Mei-41/ATR (20) and Tel1/ATM (3, 45) (cell cycle checkpoint kinases), Blm/Sgs1 [involved in crossover patterning, the crossover/noncrossover decision, and determination of interfering or noninterfering crossover class (54)], and Mlh3 (25) and Msh2 (32) (involved in mismatch repair).

Evidence for interference comes chiefly from two types of data. A classic signature is that the numbers of crossovers per chromosome or per cell fail to follow a Poisson distribution, as would be expected if crossovers occur at a rate that is independent of other crossover events. As seen in rice (*Oryza sativa*) (120) (**Figure 1*a***), the variance in crossover numbers per cell is typically less than expected based on the Poisson distribution, indicating positive interference.

Another signature of interference can be found in the distribution of distances between crossover events. If each crossover occurs independently over the chromosome according to a Poisson process, the distances between events, the interevent distances, should be exponentially distributed. By contrast, with interference, interevent distances are more regularly spaced, leading to a hump-shaped distribution (120) (**Figure 1*b***). As discussed in Section 4.2, the shape parameter of the gamma distribution (υ) provides a statistical measure of interference (85), with $\upsilon = 1$ for independently distributed interevent distances (exponential with no interference) and $\upsilon > 1$ for more regularly spaced events (positive interference).

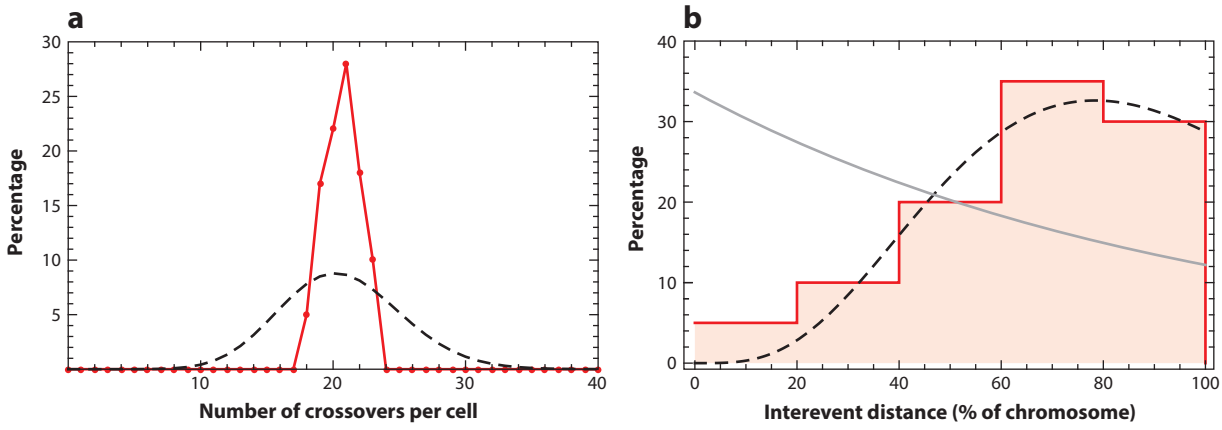

Figure 1

Distribution of crossovers in rice (*Oryza sativa*). (*a*) The number of crossovers per meiosis in *O. sativa* (*red dots*) is much less variable than expected if crossovers occurred independently of one another, which would generate a Poisson distribution with the same mean (*black dashed curve*). (*b*) The distance between crossover events measured as a percentage of the chromosome length is shown by the red histogram. A gamma distribution with shape parameter $\nu = 4.9$ (*black dashed curve*) better fits the data than an exponential distribution ($\nu = 1$; *light gray curve*), which would be expected if crossovers occurred independently at a constant rate across the chromosome. Data from Reference 120, using a least-squares fit to the interevent distribution assuming normally distributed errors (minimizing the total absolute differences to the gamma distribution gives instead $\nu = 8.39$, as reported in 120). Code used to generate all figures is supplied in the **Supplemental Appendix**.

Supplemental Material >

Interference imparts a remarkable regularity to the number of crossovers per chromosome across eukaryotes. Despite the fact that organisms vary tremendously in chromosome number, chromosome length, and genome size, the number of crossovers per bivalent hovers between one and three for most species (**Figure 2**) [based on data compilation by Stapley et al. (112)]. Particularly striking is the paucity of chromosomes with no crossovers, leading to the view that crossover regulation involves some mechanism ensuring that at least one crossover occurs (crossover assurance). Any such mechanism of crossover assurance would make crossover distributions less variable than Poisson distributions, contributing positively to interference.

The relative uniformity by which crossovers occur given the orders-of-magnitude variation in chromosome length puzzled geneticists for nearly a century and led them to favor models of interference that act on the scale of genetic maps rather than physical maps [e.g., the counting model of Foss & Stahl (42)]. More recent work has revealed the core structure of meiotic chromosomes to involve an axis of protein-bound DNA from which loops of DNA emanate, with the physical length relevant to crossovers being the axis length in microns rather than the chromosome length in nucleotides (129). Double-strand breaks (DSBs) leading to crossovers are thought to arise in the loops, with the axis serving as a DSB cold spot (43, 61). Species with larger genomes have longer loops of DNA anchored by proteins to the chromosomal axis, accounting for similar patterns of interference across chromosomes of vastly different sizes (43, 125). For example, loop length in mice (*Mus musculus*) has been estimated to be 50 times longer than that in budding yeast (*Saccharomyces cerevisiae*) (61), substantially reducing the difference in chromosome length (~1.25 Gb in mice but only ~0.75 Mb in budding yeast).

Crossovers originate as DSBs, raising the question of whether other events associated with recombination exhibit interference too. The evidence is mixed. In *D. melanogaster*, DSBs resolved as noncrossovers are randomly distributed throughout the genome (30, 87), as expected in the absence of interference, a finding in agreement with earlier inferences from *Neurospora crassa* (110).

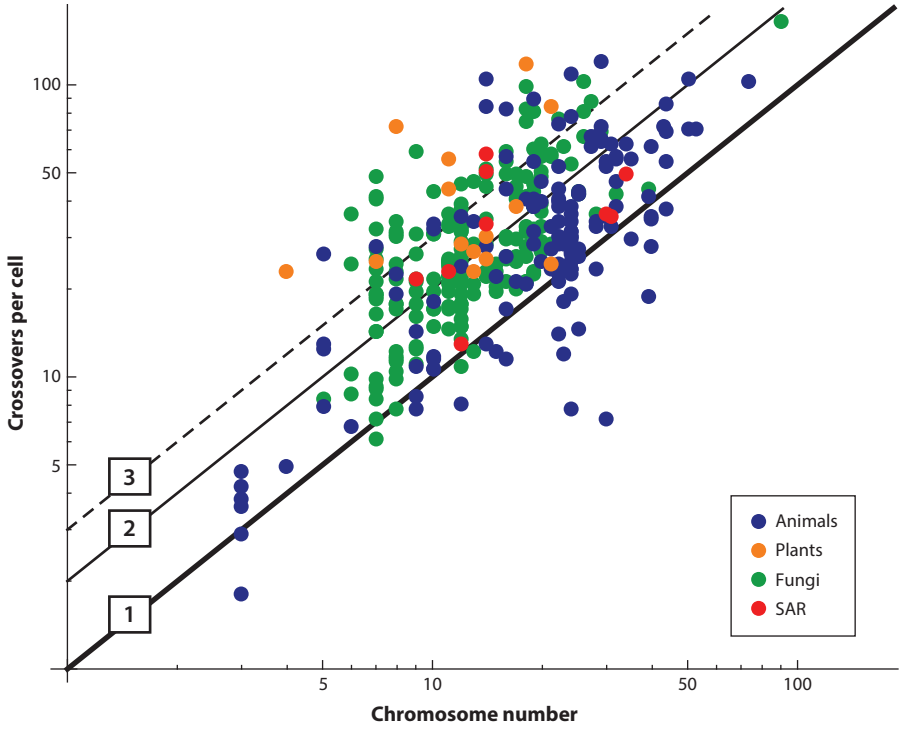

Figure 2

Crossovers per cell as a function of haploid chromosome number. Most species (73%) have between 1 and 3 crossovers per bivalent (between *thick* and *dashed lines*), with 48% falling between 1 and 2 crossovers (between *thick* and *thin lines*). Data from Stapley et al. (112). Crossover number was sex averaged and based on linkage maps using at least 50 markers, converting centiMorgans to crossover numbers by dividing by 100 (to convert to Morgans) and multiplying by 2 (for bivalents). Data for *Fusarium oxysporum* were based on a mitotic linkage map and were excluded, leaving 352 species of animals, plants, fungi, and protists (SAR). Crossover numbers are likely underestimated, depending on the marker density and distribution in the original study. Abbreviation: SAR, stramenopiles–alveolates–Rhizaria.

Modulation of DSB hot spot activity affects nearby DSB generation in *Schizosaccharomyces pombe* (43), although this species exhibits little to no crossover interference. In mice, Msh4 and Rpa foci that mark early intermediate stages of recombination (strand exchanges, not all of which are resolved as crossovers) also show interference, although to a weaker extent than crossover interference (35). Interference among early recombination nodules, thought to reflect DSBs, has also been observed in tomato (*Solanum lycopersicum*) (5, 6), although the scale of this interference is much shorter than the interference among crossovers (6). A recent study of *Saccharomyces cerevisiae* finds weak but significant interference between noncrossovers and crossovers (83). For an excellent discussion about different classes of interference, we refer the reader to Berchowitz & Copenhaver (16).

In this review, we focus on crossover interference. We assume no chromatid interference (16, 25) and use interference to stand for crossover interference along one chromatid (127). For clarity, we use crossover interference, or just interference, to describe positive crossover interference, in which observing a crossover in one region reduces the chance of observing a crossover in another, and crossover clustering to describe negative interference. We review interference patterns and

both mechanistic and statistical models of interference and then explore how evolution may have shaped interference.

2. PATTERNS

To look for patterns of crossover interference, we compiled empirical studies from the literature. Each study positioned crossovers using either marker transmission (in pedigrees or crosses) or immunolocalization of the MLH1 mismatch repair protein along the synaptonemal complex (in spermatocytes, oocytes, or both). We included articles that measured recombination across the genome (or at least across multiple chromosomes). For each species with multiple characterizations of interference, we focused on the survey with the largest number of meioses or the highest genomic coverage, which tended to be more recent.

We considered only studies that fit intercrossover distances to a gamma distribution and reported υ (the shape parameter) as an estimate of the strength of interference (85). This unitless value does not depend on the recombination rate, enabling direct comparisons across species. We also tabulated estimates of interference by fitting the gamma-sprinkling model (33, 56) (also known as the gamma-escape model). This model includes two types of crossovers: a proportion, $1 - p$, of class I events subject to interference ($\upsilon > 1$) and a proportion, p, of class II events that do not interfere ($\upsilon = 1$). The existence of these two classes of crossovers is supported by molecular evidence (36, 55, 124).

The distribution of υ confirms that crossover interference is taxonomically widespread (**Table 1**). Among the species surveyed, interference is uniformly positive, indicating that crossovers are spaced more evenly than expected under a Poisson process. Whenever directly compared [budding yeast and both sexes of human (*Homo sapiens*), dog (*Canis familiaris*), and *Arabidopsis thaliana*], the two-parameter gamma-sprinkling model fits significantly better than the one-parameter gamma model.

Extreme differences in crossover interference among species have long been recognized (16). *Caenorhabditis elegans* hermaphrodites produce exactly one crossover per bivalent (i.e., complete interference) (16, 81), whereas *S. pombe* and *Aspergillus nidulans* recombine with little or no interference (89, 114). Beyond these extremes, there exists substantial quantitative variation in interference strength (**Table 1**). Estimates for υ range widely, from $\upsilon = 2.9$ in tigers (*Panthera tigris*) to $\upsilon = 30.6$ in dogs. Although considerable uncertainty is often attached to υ estimates, it is clear that at least some of the differences in interference between species are robust. For example, estimates of υ from large pedigrees feature nonoverlapping confidence intervals for dogs and humans (23). We detected no significant difference in υ between plants and animals. Average υ for male mammals (11.3) is close to twice the average υ for male reptiles and male birds (5.7), a difference that is marginally significant (t-test; $P = 0.07$).

From the small subset of studies that have conducted direct statistical comparisons within species, there is compelling evidence that females and males have disparate interference landscapes. In *A. thaliana* and cattle (*Bos taurus*), υ is higher in females (13, 121). In contrast, males show stronger interference than females in humans (24), dogs (23), and gray geese (*Anser anser*) (118). Furthermore, a lower proportion of crossovers escape interference (p) in *A. thaliana* females versus males (13). Modulation of the length of the chromosome axis and the synaptonemal complex could explain differences in interference between the sexes (80, 96). That the form of sex differences depends on the species mirrors evolutionary patterns for recombination rate (heterochiasmy) (21, 76).

Natural variation in interference among individuals from the same sex has rarely been examined. In one study, point estimates of υ varied substantially among lines of maize (*Zea mays*) but

Table 1 Estimates of interference strength (v) and the proportion of crossovers that escape interference (p)

Common name	Species	Sex	v	p	Model	Data	Reference
Anole	*Anolis carolinensis*	Male	5.6	Not estimated	Gamma	Cytology: MLH1	79
Anole	*Deiroptyx coelestinus*	Male	5	Not estimated	Gamma	Cytology: MLH1	79
Antelope	*Tragelaphus spekii*	Male	20	Not estimated	Gamma	Cytology: MLH1	105
Barley	*Hordeum vulgare*	Male	3.02	Not estimated	Gamma	Linkage	37
Cat (domestic)	*Felis silvestris catus*	Male	3.71	Not estimated	Gamma	Cytology: MLH1	19
Gray goose	*Anser anser*	Female	4.34	Not estimated	Gamma	Cytology: MLH1	118
Gray goose	*Anser anser*	Male	5.84	Not estimated	Gamma	Cytology: MLH1	118
Mink	*Mustela vison*	Male	5.7	Not estimated	Gamma	Cytology: MLH1	17
Mouse	*Mus musculus*	Female	8.85	Not estimated	Gamma	Cytology: MLH1	35
Mouse	*Mus musculus*	Male	11.65	Not estimated	Gamma	Cytology: MLH1	35
Sheep	*Ovis aries*	Male	7.23	Not estimated	Gamma	Cytology: MLH1	105
Shrew	*Sorex araneus*	Male	13.35	Not estimated	Gamma	Cytology: MLH1	18
Steppe agama	*Trapelus sanguinolentus*	Male	6.5	Not estimated	Gamma	Cytology: MLH1	78
Tiger	*Panthera tigris*	Male	2.9	Not estimated	Gamma	Cytology: MLH1	106
Tomato	*Solanum lycopersicum*	Male	7	Not estimated	Gamma	Cytology: MLH1, RecNod	6
Budding yeast	*Saccharomyces cerevisiae*	N/A	3.1	0.41	Gamma-sprinkling	Linkage	25
Cattle (Holstein)	*Bos taurus*	Female	9.96	0.100	Gamma-sprinkling	Linkage	121
Cattle (Holstein)	*Bos taurus*	Male	8.7	0.083	Gamma-sprinkling	Linkage	121
Cattle (Jersey)	*Bos taurus*	Female	7.55	0.029	Gamma-sprinkling	Linkage	121
Cattle (Jersey)	*Bos taurus*	Male	6.7	0.022	Gamma-sprinkling	Linkage	121
Corn	*Zea mays*	Female	5.25	0.1	Gamma-sprinkling	Linkage	14
Corn	*Zea mays*	Male	5.2	0.15	Gamma-sprinkling	Cytology: RecNod	39
Dog	*Canis familiaris*	Female	14.05	0.035	Gamma-sprinkling	Linkage	23
Dog	*Canis familiaris*	Male	30.64	0.055	Gamma-sprinkling	Linkage	23
Human	*Homo sapiens*	Female	7.19	0.078	Gamma-sprinkling	Linkage	24
Human	*Homo sapiens*	Male	8.93	0.067	Gamma-sprinkling	Linkage	24
Mustard	*Arabidopsis thaliana*	Female	25	0.09	Gamma-sprinkling	Linkage	13
Mustard	*Arabidopsis thaliana*	Male	11.5	0.155	Gamma-sprinkling	Linkage	13
Sockeye salmon	*Oncorhynchus nerka*	Female	7.3	0.08	Gamma-sprinkling	Linkage	77

Abbreviation: RecNod, recombination nodule.

with wide confidence intervals (14). v is associated with variants in the *Nek9* gene in male cattle (121), which implies the existence of heritable variation in interference strength (at least in males) and identifies a gene involved in spindle formation as a strong candidate.

v is often estimated by pooling intercrossover distances across chromosomes. Nevertheless, multiple species show significant interchromosomal variation in v and p (13, 24, 121). Both parameters are negatively correlated with chromosome length in cattle (121), a result that is consistent with the view that crossover assurance and interference are particularly critical for segregation of short chromosomes (40). Although it is difficult to detect, there is also evidence for regional variation in interference along chromosomes (13).

We might expect the strength of crossover interference to be connected to recombination rate itself. To begin to assess this prediction, we compared v (**Table 1**) to estimates of crossover number from across the subset of species for which data were available (crossover data were based on counts of MLH1 foci from 4, 6, 12, 17–19, 24, 25, 37, 46, 71, 78, 105, 106, 118). v negatively correlates with the average number of crossovers per chromosome in males (plus budding yeast) (Spearman's $\rho = -0.52$; $P = 0.03$; $n = 19$ species). The negative correlation persists in the more homogeneous group of male mammals ($\rho = -0.63$; $P = 0.05$; $n = 10$ species). The number of DSBs per chromosome (data from 7, 12, 28, 49, 83, 105, 108) also correlates negatively with v in males (plus budding yeast) but not significantly ($\rho = -0.52$; $P = 0.13$; $n = 10$ species). v is not correlated with total crossover count across all chromosomes, total DSB count, or chromosome number. Unfortunately, there are not enough data for females to make similar comparisons. Although these preliminary analyses are based on small sample sizes, are restricted to males, and do not account for phylogenetic nonindependence, they raise the prospect that species with less recombination per chromosome have higher interference, again consistent with crossover regulation being particularly important for short chromosomes. This negative relationship is also consistent with comparisons between v and recombination rate among strains of maize (14, but see Reference 98 for yeast).

Examination of potential determinants of p in a comparative context awaits estimates from more species. But two studies suggest that age is an important factor in mammals. Noninterfering crossovers, p, increase with maternal (but not paternal) age in humans (24) but decrease with maternal age in cattle (121). These divergent patterns suggest that species differ in how the balance of interfering versus noninterfering crossovers is determined. Another factor that affects p is the degree of sequence divergence between chromosomes. Where homologs differ in sequence, mismatched base-pairing after strand invasion triggers the mismatch repair system, suppressing noninterfering crossovers but not interfering crossovers in budding yeast, leading to a higher value of p when mismatch repair is active (32). Thus, the genetic distance between the parents of a diploid strain of yeast is predicted to alter patterns of crossover interference (32).

Our empirical survey points to several recommendations for future research on crossover interference. First, the statistical models we fit should match existing knowledge about interference. For example, the demonstration that meiotic cells from most species generate both interfering and noninterfering crossovers should favor application of the gamma-sprinkling model over the gamma model for linkage data (but not for MLH1 foci, which are associated only with interfering crossovers). In *A. thaliana*, differences in v between females and males detected with a gamma-sprinkling model (13) were invisible when a gamma model was applied to the same data set (46).

Second, when measuring interference, other factors (e.g., sex, chromosome, strain) should be controlled as much as possible. Mixing interevent distributions, across sexes or chromosomes or any other feature that varies in the rate of crossovers, will cause v to be underestimated. For example, if two exponential distributions are mixed, in which each has $v = 1$ but with a twofold

Supplemental Material >

difference in mean crossover rate, the mixed distribution will have $v = 0.82$ (see the general proof in the **Supplemental Appendix**).

Third, we need estimates of interference for more wild-derived organisms. Although the list of species in which interference has been profiled continues to grow, it is biased toward domesticated animals and plants. For organisms that can be bred in the laboratory, crosses could help fill this gap; for others, immunocytology might be applicable.

Finally, the field should prioritize quantitative comparisons of interference within and between closely related species. Such comparisons would bring the empirical study of crossover interference into the realms of population and quantitative genetics, which would aid the evolutionary interpretation of patterns and clarify the selective forces acting on interference.

3. MECHANISMS OF INTERFERENCE

Models can generally be divided into two categories: mechanistic and phenomenological (94). Mechanistic models attempt to accurately describe a process by modeling the precise mechanisms by which interactions occur among potential crossover sites. By contrast, phenomenological models aim to describe observations at a statistical level, with sufficient complexity to capture the phenomena but no more.

In this section, we discuss hypotheses for the mechanistic basis of interference and the types of models that they would generate (for further review, see 16). We then turn in Section 4 to phenomenological models that fit data on interference among loci, starting with the earliest model by Haldane (51) in 1919.

Unfortunately, a current challenge to developing a mechanistic model is that the precise mechanisms yielding crossover interference remain unknown. Determining the mechanisms is hindered by the fact that the phenomenon is itself statistical, requiring sufficient data to infer the nonindependence of DSBs, crossovers, or both. An additional challenge is that organisms likely vary in the way that interference is accomplished, and even whether it is, making it difficult to infer a complete mechanistic picture with pieces from different puzzles.

3.1. Polymerization Model

An early mechanistic model of interference hypothesized that there are many potential crossover sites and that when recombination is initiated at one of these sites, it triggers a polymerization reaction that inhibits crossovers at neighboring sites in both directions (67). A model of this process would start at the first initiating site, inhibit recombination regionally, and continue to add crossovers with an acceptance probability that decreases with the degree of inhibition experienced at each site until a stopping rule is reached (e.g., that a certain amount of time or number of attempts have passed). **Figure 3** illustrates such a model, assuming that the extent of inhibition follows a reflected exponential decay curve away from sites where crossovers have occurred [the original model of King & Mortimer (67) was dynamic, with growing polymers stopping if they encountered one another].

While evidence is generally lacking for a reaction that proceeds from crossover initiation sites (16), stabilization of the synaptonemal complex in *C. elegans* following a crossover acts to inhibit further DSBs and crossovers (81), causing complete interference in a manner reminiscent of the polymerization model.

3.2. Beam-Film Model

Another mechanistic model is the beam-film model of Kleckner et al. (69). This model focuses on the mechanical stresses imposed on chromosomes as they compress and expand during meiosis.

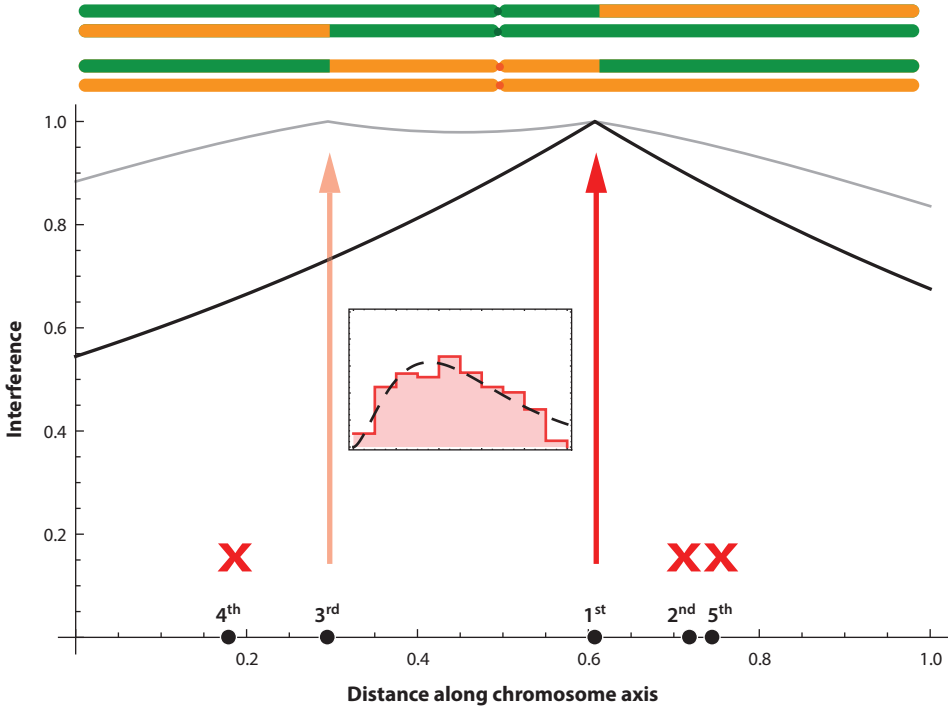

Figure 3

Exponential decay of interference. In the polymerization model (67), a series of crossovers are attempted (*black dots*). After the first event, a reaction emanates from that site along the chromosome and interferes according to a decaying function (*black curve*). Further crossover attempts then fail with a probability given by the height of the interference curve. In this example, the second event failed by chance but the third attempt was successful, further contributing to interference (*gray curve*). The last two attempts also failed, leading to two successful crossover events as illustrated in the bivalent above the graph. Interference after the nth crossover event is modeled as $1 - \prod_{i=1}^{n} (1 - e^{-\delta|x-x_i|})$, where $\delta = 1$ measures the exponential decay of interference and x_i is the position of the ith crossover. The x-axis represents distance along the chromosomal axis, measured in terms of the cumulative probability of recombination to account for hot and cold spots. Simulating this process repeatedly with these parameter choices leads to positive interference, with $\nu = 2.68$ among cases with two crossovers (*inset* shows interevent distribution, as in **Figure 1*b***).

These stresses could lead to conformational changes in proteins or RNAs associated with the DNA, which could increase the likelihood of crossovers. According to this model, various steps in the pathway leading to a crossover—DSB production, strand invasion, and resolution of a Holliday junction—may each relieve stress and are all associated with periods of chromatin expansion and contraction. Any such event that relieves mechanical stress at one point in the genome would then propagate this release of stress up and down the chromosome, inhibiting crossovers in the surrounding region and leading to crossover interference.

At first glance, it seems unlikely that such stresses would account for similar crossover levels per chromosome across a wide variety of species (**Figure 2**), given their tremendous variation in chromosome size, degree of interference, and the exact choreography of meiosis (e.g., whether synaptonemal complex formation follows DSBs, as in budding yeast and mammals, or proceeds without it, as in nematodes and *D. melanogaster* females) (48). Kleckner et al. (69) note, however, that several other aspects of chromosomal organization, including nucleosomes, chromatin loops,

and axial chromosome coils, reduce this variation and translate mechanical stresses to the scale of the chromosome.

A beam-film program has been developed to address many empirical aspects of crossing over, including crossover assurance and interference (125). The model is parameter rich, with 10 parameters as well as the ability to fine-tune the distribution of crossover precursors (e.g., hot spots). While initially intended to capture aspects of the beam-film hypothesis, mechanical stress is not directly modeled but is assumed to be released locally by crossing over, with this relief spreading to the surrounding chromosomal region via an exponentially decaying function with parameter L_{BM} (similar to **Figure 3**). Thus, a good fit of the model to interference data may reflect the statistical appropriateness of a local process of interference, controlled largely by the parameter L_{BM}, rather than providing proof of the beam-film mechanism, as acknowledged by Zhang et al. (126). When the model is fit to data, some aspects appear to conflict with a stress-based mechanism; for example, one might predict that stress would be minimized at the telomeres (125), but model fits to data from a variety of organisms imply strong levels of stress at chromosome ends (high clamping parameters). One mechanical explanation is that the tethering of telomeres to the nuclear envelope acts to prevent the release of mechanical stress (38). Nevertheless, it remains unclear whether the beam-film model fits data well because it is mechanistically correct or because it is parameter rich and able to capture the main phenomena associated with crossing over. That the model does capture underlying processes (whether due to mechanical stresses or not) is demonstrated by the excellent match to data not used to fit the model, such as crossover data from mutant strains (125).

3.3. Telomere-Initiated Model

Another potential mechanism focuses on the observation that telomeres aggregate at the nuclear membrane early in meiosis and that synapsis of the homologs and DSB production, as well as resolution of DSBs as crossovers, occur in a telomere-guided fashion (50 and references therein). According to this suggestion, the machinery involved in recombination (either in the placement of DSBs or in the resolution of them) begins at the telomere and proceeds inward. Mechanistically, this might be achieved by the transmission of cytoskeletal forces from microtubules to the tethered telomeres, causing a whip-like movement of chromosomes that brings chromosomes together until homologs are found and stabilized by crossovers (38, figure 1). In support of a telomere-initiated mechanism, Haenel et al. (50) present evidence that recombination rates are lower near the middle of chromosomes in animals and plants regardless of where the centromere lies. This finding is consistent with a model whereby the likelihood of a crossover decreases with distance from the telomere. Interference would arise if the machinery required conformational change or recruitment of additional elements before it can reengage or became inactivated after inducing an event (e.g., if a crossover physically stabilizes the homologs). **Figure 4** illustrates the latter model, assuming that the machinery follows a Poisson process beginning at the telomere until an event is induced.

3.4. Spatial Cluster Model

Another mechanistic model highlights spatial clusters of recombinational machinery within the nucleus, where each cluster interacts with DNA located within a certain distance and induces a single event. Using a chromosome-conformation-capture technique, Fowler et al. (43) found evidence for three-dimensional clustering of DSB hot spots associated with LinE proteins within *S. pombe*. These clusters caused hot spots within a region of approximately 200 kb to compete for DSB formation, leading to low but significant levels of crossover interference. This interference

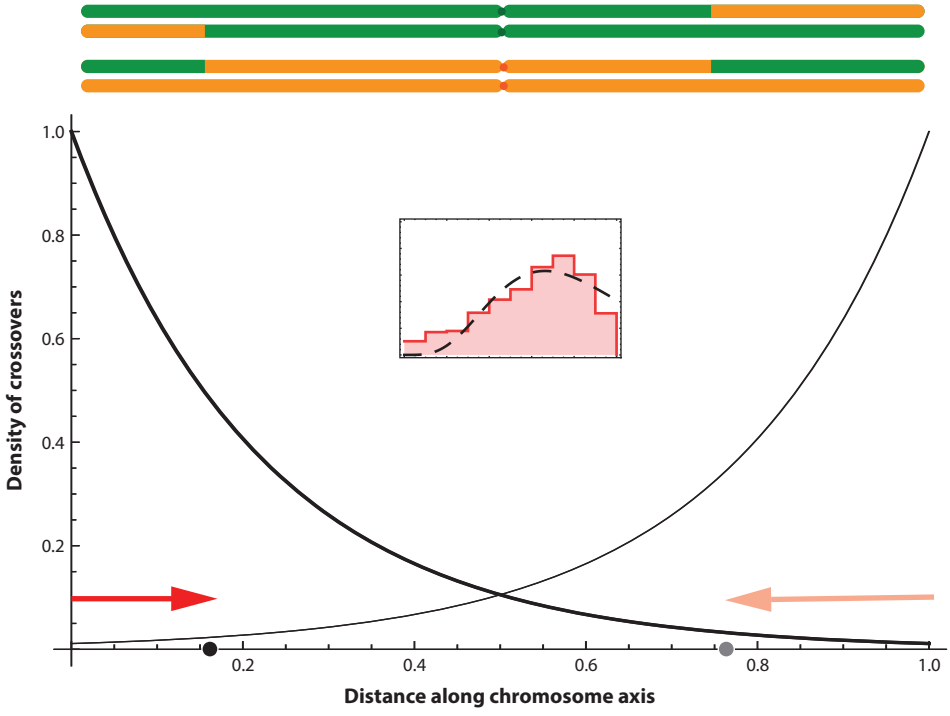

Figure 4

A telomere-initiated interference process (50). Crossover initiation is modeled as a Poisson process starting at either end of the chromosome, here using a rate parameter of 4.5. The black curves give the probability density function of crossover events (*thick curve*, left initiated; *thin curve*, right initiated), a random outcome of which is shown as red arrows, leading to the crossovers located at the black dots (resulting bivalent above the graph). Simulating this process repeatedly with these parameter choices and assuming that the Poisson process is terminated if it hits a crossover initiated from the other telomere lead to positive interference, with $\nu = 5.4$ (*inset* shows interevent distribution, as in **Figure 1*b***).

depended on the presence of the protein kinase Tel1 (an ATM ortholog), which the authors suggest modifies the cluster following DSB formation to prevent further breaks. Only interference within a homolog was inferred for *S. pombe* (*cis* interference), in contrast to a previous finding that DSB interference occurs both in *cis* and in *trans* in *S. cerevisiae* (43). Fowler et al. (43) suggested that differences between these yeasts in synaptonemal complex formation and the spatial proximity of homologs may alter the strength of *cis* versus *trans* interference. An accurate model of this mechanism would involve a spatial model of cluster distributions throughout the nucleus as well as information about the spatial scale of hot spot attraction to a cluster and the chromosomal territories (homologous and potentially nonhomologous) within the nucleus early in meiosis. A more abstract model of this mechanism would group hot spots into clusters along the chromosome, within which one and only one DSB is induced. The spacing between clusters thus generates interference (**Figure 5**).

The above mechanistic models are not an exhaustive list nor are they mutually exclusive. Different mechanisms may act simultaneously in the same species and may play more or less dominant roles in different species. The cellular basis of crossover positioning and interference is an active area of research and undoubtedly more mechanistic details will be revealed in the years to come, allowing more accurate mechanistic models to be developed.

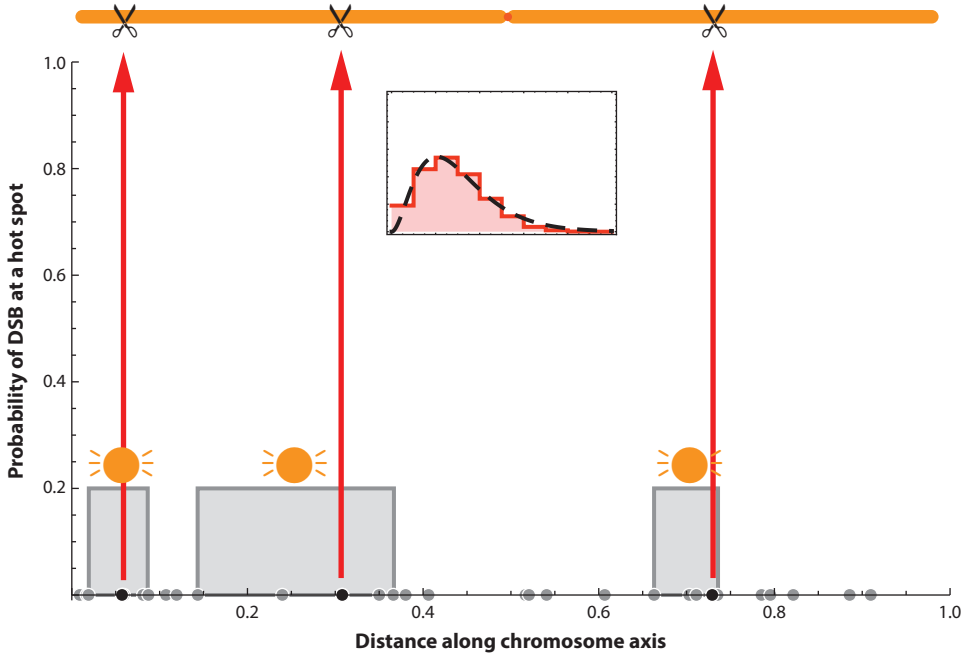

Figure 5

A spatial cluster process of interference. Clusters of hot spot–binding proteins (*orange suns*) attract and bind hot spots (*gray dots*, $n = 30$), initiating a double-strand break (DSB) at one of these spots (*black dots*, illustrated by the scissors cutting a chromatid above the graph), after which no further breaks occur in the cluster (data based on 43). Here, we assume each cluster binds five hot spots, each of which has an equal probability of being cut (*gray-shaded histograms*). We allow the formation of three clusters, which can be adjacent but cannot overlap (i.e., cannot contain the same hot spot). Simulating this process repeatedly with these parameter choices leads to positive interference, with $\nu = 3.03$ between the three DSBs that form (*inset* shows interevent distribution, as in **Figure 1*b***).

4. STATISTICAL MODELS OF INTERFERENCE

The above models mechanistically describe how crossovers arise and generate interference. While these models can be used to fit data (e.g., 125), there is a long history of fitting statistical models that are not mechanistic but phenomenological (i.e., describing the phenomenon of recombination and interference in statistical terms). Such statistical models can strip out details typical of mechanistic models and can facilitate more complete statistical inference (e.g., confidence intervals), particularly when the likelihood of observing the data can be computed (39). The earliest such statistical descriptions were developed by Haldane (51), who compared the probability of a double recombination event $r_{AB\&BC}$ between three markers, A, B, and C, with its expected value on the basis of the recombination rates in the two intervals, r_{AC} times r_{BC}, using the coefficient of coincidence,

$$c.o.c. = r_{AB\&BC}/(r_{AC}r_{BC}), \qquad 1.$$

and a related measure of interference, $I = 1 - c.o.c.$ Applying this measure to marker data from *D. melanogaster*, Haldane (51) found fewer double crossovers than expected ($I > 0$). Although useful for detecting interference statistically, the coefficient of coincidence cannot be easily compared across different sets of loci or species, as the measure depends on how recombination rates and

interference covary across chromosomes. Furthermore, the coefficient of coincidence between three loci cannot be used to distinguish among the mechanistic models of interference described above, as they all can generate a range of interference, from none to complete.

Haldane (51) went on to introduce the concept of a mapping function, $M(x) = r$, relating genetic distance between two loci in Morgans, x, to the chance that they would recombine, r. In the absence of interference, the resulting relationship is described by Haldane's mapping function,

$$r = \frac{1}{2}(1 - e^{-2x}). \quad 2.$$

Haldane demonstrated that this mapping function underestimates recombination rates between distant loci in *D. melanogaster* owing to interference and the paucity of double crossover events. Kosambi (73) introduced a better-fitting mapping function,

$$r = \frac{1}{2}\tanh(2x). \quad 3.$$

Mapping functions are limited, however, in that they treat interference as a homogenous process dependent only on the genetic distance, x. Importantly, this statistical treatment fails to specify whether recombination between two loci is the outcome of one, three, or any odd number of crossovers. Mapping functions do not describe the joint distribution of the number and location of crossover events. The same mapping function can be generated by different underlying distributions of recombination across the chromosome (127).

4.1. Counting Model

Motivated by the observation that interference appeared to scale not with base pairs but with genetic distance, Foss et al. (41) formulated a counting model, whereby recombination intermediates (*C*) could be resolved either with crossovers (*Cx*) or without crossovers (*Co*). The authors modeled the probability of a given recombination rate within an interval based on a Poisson distribution of *C* initial events that arise independently, from which an alternating series of *m Co* events and one *Cx* crossover event occur.

The counting model was proposed largely for its statistical properties: explaining why interference scales with genetic distance, as this scale is set by the *C* recombination intermediates (e.g., DSBs). Nevertheless, it could also be considered a mechanistic model if there were machinery that effectively counted and allowed crossovers at every $m + 1$ intermediates along a chromosome. Indeed, two of the mechanistic models considered above have related features. Closely related is the spatial cluster model, whereby hot spots are the intermediates (*C*) and the number that fits within and between one DSB-initiating cluster gives the value of $m + 1$, where +1 indicates the site that obtains the DSB (43), although the mathematics is slightly different because there need not be a regular alteration of *Cx* and *Co* events unless DSBs always occur in a particular position in the cluster (e.g., in the most central loop). Counting also results from the feedback mechanism described for *C. elegans*, in which a single crossover event is sufficient to stabilize the synaptonemal complex and in which meiosis is prolonged if no crossovers have occurred to allow subsequent crossover attempts. This effectively implies a large value of *C* (e.g., all potential DSB sites on a chromosome) and a large value of *m* (i.e., $C - 1$) such that the occurrence of one *Cx* event prevents all others from resulting in a crossover.

The counting model has also been supplemented to force an initial crossover event from which *m Co* events are counted outward in both directions before the next crossover is allowed [the forced-initial counting model (FIC)] (40). Even when the first crossover is uniformly placed on the chromosome, the FIC model generates a smile distribution of crossovers along the chromosome,

with a lower density toward the center of a chromosome as observed empirically (50). This occurs because a first crossover arising more distally on a chromosome, by chance, leaves enough room to fit a second according to the FIC model, so that more crossovers are expected near the telomeres (as with **Figure 4**). Because the FIC model enforces crossover assurance, it provides a better fit to some data, particularly with short chromosomes (40).

4.2. Renewal Processes and the Gamma Model

The counting model is an example of a renewal process, which describes the probability distribution of events that occur across an axis (over time or over space) that is reset whenever an event happens. Foss et al.'s (41) counting model, for example, matches a renewal process considered for recombination in the 1970s by Cobbs (27) and Stam (111). Indeed, conceptualizing recombination events across the chromosome as a renewal process harkens back to the early days of genetics [see overviews by McPeek & Speed (85) and Zhao & Speed (127)], starting with Haldane (51), who considered the simplest renewal process in which events occur homogenously at constant rate (the Poisson process).

In the counting model, if each of the $m + 1$ distances between potential crossover events is exponentially distributed with mean distance δ, the sum of these distances would be gamma distributed, with a mean total distance of $(m + 1)\delta$ and a squared coefficient of variation equal to $1/(m + 1)$. As m is an integer in the counting model, this gamma distribution is also equal to a χ^2-distribution with degrees of freedom set to $2(m + 1)$.

More generally, the gamma model can be used to describe the distribution of interevent distances, regardless of whether m is an integer, providing a flexible statistical description of crossover events (85, 111). In the gamma model, the shape parameter v describes whether the distribution is L-shaped ($v < 1$; crossover clumping), exponential ($v = 1$), or humped with a mode at some positive distance ($v > 1$; crossover interference). Specifically, v describes the inverse of the squared coefficient of variation and so equals $m + 1$ in the counting model.

The shape of the gamma model provides a convenient summary statistic, allowing data on interference to be compared across strains and species (**Table 1**). The flexibility of the shape of the gamma when fitting data, however, makes it challenging to infer the underlying mechanisms. Zhang et al. (125), for example, described how changing four different parameters in the beam-film model would affect the shape of the interevent distribution. Considering also the mean number of crossovers and the decay in the coefficient of coincidence with distance provides additional information to determine how the process of interference varies among strains and species.

Many other variants of renewal processes have been considered (85). For example, in the hard-core model, events occur according to a Poisson process but are eliminated if they occur too close to a previous event (85), as arises when the recombination machinery is spatially clustered and allows only one event per cluster (43).

As mentioned above, the gamma-sprinkling model is a commonly applied variant that incorporates a proportion, p, of noninterfering crossovers alongside a fraction $1 - p$ of interfering crossovers (33, 56). The gamma-sprinkling model has an advantage over many mechanistic models in that the likelihood can be calculated given data on crossover locations (39). It also provides a better fit to crossover data than the gamma model alone for some species by allowing for the possibility of closely spaced crossovers, even if most crossovers are distantly spaced (13, 39). The gamma-sprinkling model also fits some data better than the beam-film model because the latter tends not to fit interevent distributions with narrow peaks (39).

As the mechanisms of interference become increasingly revealed experimentally, we will gain a clearer picture of which models—both mechanistic and phenomenological—best match the underlying biology of different species.

5. SELECTIVE FORCES ACTING ON INTERFERENCE

That crossover interference varies in strength across taxa (Section 2) raises the question of how it evolves over time. Three main selective forces have been invoked in discussions of the evolution of interference: the benefits of proper segregation, the costs of DSBs, and the indirect selection arising from altering patterns of recombination among selected loci. We briefly summarize these selective forces and then describe how they may together shape the long-term evolution of interference.

5.1. Benefits of Proper Segregation

For many species, crossovers are thought to provide crucial tension as homologous chromosomes align on the metaphase plate and are pulled to opposite poles by microtubules. Aneuploidy can result when the number or location of crossovers causes premature separation of sister chromatids or of homologs or causes entanglement and failure to separate during meiosis. Problems with segregation are thought to contribute substantially to failed pregnancies and to infertility in humans, both in men (60) and in women (72, 90). At least 10% and potentially as many as 50% (at later maternal age) of human embryos may be aneuploid, with many originating from segregation errors in meiosis (53, 90).

Studies of aneuploid events in several species, including budding yeast, *D. melanogaster*, and humans, have found an association between homologs without any crossovers (achiasmate) and aneuploidy (53, 72). Analyzing missegregation events involving the X chromosome in *D. melanogaster* females, Koehler et al. (70) found that more than 76% of errors attributed to meiosis I involved achiasmate bivalents. Chromosomes that normally only have one crossover in human males, chromosomes 21, 22, X, and Y, are particularly prone to having none and to exhibiting aneuploidy (60). Achiasmy is associated with 40% of cases of trisomy 21 (Down syndrome) that originate from meiosis I missegregation in eggs (53).

Premature separation of sister chromatids rather than homologs is a frequent source of missegregation during oogenesis in humans, especially for nonrecombinant chromatids, which exhibit unusual segregation at five times the rate of recombinant chromatids (~12.5% versus 2.5%) (95). Furthermore, these nonrecombinant chromatids are more likely to segregate to the polar body than to the oocyte, a meiotic drive mechanism that contributes to the crossover assurance and interference observed among offspring (95).

In budding yeast, sequence differences between strains disrupt recombination, leading to an increased frequency of chromosome pairs lacking crossovers and a corresponding increase in the frequency of nondisjunction (102). The frequency of nonexchange chromosomes among distantly related crosses may be further increased by the shift toward noninterfering (class II) crossovers when mismatch repair is activated (32). At the extreme, in hybrids between *Saccharomyces paradoxus* and *S. cerevisiae*, nearly all homologous pairs lack a crossover and chromosome segregation is nearly random, leading to a large fraction of spores that lack one of the 16 chromosomes and are inviable ($99\% = 1 - 0.75^{16}$). With every 0.1% increase in parental sequence divergence, spore viability declines by approximately 1.25%, a direct cost of the failure to recombine.

To the extent that interference supports crossover assurance, genes contributing to interference would benefit from reduced costs of aneuploidy. For example, the proportion of bivalents without crossovers is increased and matches a Poisson expectation in an *msh4* mutant of *S. cerevisiae*—one line of evidence for a mechanistic connection between interference and crossover assurance (74). Selection to avoid aneuploidy would thus contribute to the maintenance of MSH4 functioning.

There is some evidence that too many crossovers also lead to aneuploidy. In humans, 24% of trisomy 21 cases of maternal origin are attributed to meiosis II errors (with identical centromeric

sequences) and exhibit an increase in map length of approximately 50% (72). Koehler et al. (72) note that this attribution to meiosis II may reflect a failure of bivalents to separate during meiosis I, followed by the separation of homologs at meiosis II, creating an error in which the disomic chromosomes carry the same centromeric region. The authors also postulate that this entanglement may arise when additional crossover events occur in response to breaks during the extended arrest at meiosis I in mammalian oogenesis. In budding yeast, evidence that missegregation may result from too many crossovers is provided by mutations in *SGS1*, which exhibit both higher crossover rates and reduced spore viability (101), although this result appears to be strain specific as *sgs1* mutants do not strongly elevate crossover rates in other backgrounds (63, 84) and missegregation may result from disruption of crossover patterning rather than crossover number (54, 63).

The location of crossovers can also influence nondisjunction rates, with evidence from budding yeast, *D. melanogaster*, and humans that single exchanges too near or too far from the centromere can result in aneuploidy (53, 72). A physical argument has been made that crossovers that are too close to one another may uncouple the homologs and fail to provide cohesiveness to the bivalent (82, 91). Nevertheless, whether interference effectively positions multiple crossovers along a chromosome to maximize the fidelity of segregation remains unclear.

Altogether, proper alignment and segregation of homologous chromosomes are facilitated by the tight regulation of recombination, generally assuring at least one crossover per chromosome and with interference preventing crossovers that are too numerous (entangling the homologs) (72), too close (freeing the homologs from one another) (82, 91), or too weak (binding ineffectively with a single telomeric exchange) (72). The fitness disadvantage of missegregation is thus thought to induce stabilizing selection on crossover numbers—selecting strongly against no crossovers and weakly against too many—favoring the evolution of positive interference.

It is hard to imagine any other explanation beyond such stabilizing selection to account for the limited range of crossovers per chromosome observed among species (**Figure 2**) despite immense variation in their selective environments, life histories, and genome sizes. Yet such stabilizing selection is not universal, with at least 26 independent losses of recombination from one sex or the other (112), including the plant *Fritillaria*, the flatworm *Dugesia*, many species of oligochaete worms, *Tigriopus* copepods, *Tityus* scorpions, 14 genera of mantises, all Lepidoptera, many Diptera, and *Gyropus* chewing lice (15). Clearly, effective segregation can evolve without crossovers, pointing to other mechanisms that ensure proper segregation (e.g., distributive segregation, spindle checkpoints, centromere pairing) (25, 75).

Even in species in which segregation relies on having the appropriate number and distribution of crossover events, segregation problems are not always found in studies of mutant strains that reduce interference. One reason is that mutations that affect interference typically also affect the average number of crossovers, but this relationship is complex and dependent on the precise genes affected. In the *S. cerevisiae* mutants studied by Zhang et al. (126), reduced interference was accompanied by an increase in crossover number, with no major effect on the number of chromosome pairs lacking an exchange (126). By contrast, a *mlh3Δ* mutant in *S. cerevisiae* both impaired interference and reduced the number of crossovers, the combination of which increased nonexchange pairs (25). This mutant did not, however, suffer from missegregation of the achiasmate chromosomes or reduced spore viability, again pointing to other mechanisms that facilitated segregation (25, 75).

5.2. Cost of Double-Strand Breaks

DSBs both occur naturally and are induced in cells undergoing meiosis. DSBs can be repaired either by nonhomologous end joining, which is independent of the homologous chromatids, or by homology-dependent repair (HDR), whereby breaks are repaired by strand invasion of

a homologous chromosome (sister or nonsister) and synthesis from the homologous template, leading to either gene conversion or a crossover. Both the beam-film model (Section 3.2) and the counting model (Section 4.1) of crossover interference involve the production of more DSBs than are resolved as crossovers. Indeed, only approximately 10% of DSBs in mammals (29) and approximately 5% of DSBs in humans (calculated from figure *6D* in 97) lead to crossovers. Because DSB repair is inherently more mutagenic than ordinary DNA synthesis (113), these models of interference imply a mutational cost to interference relative to systems that would achieve the same number of crossovers with fewer DSBs.

Experiments in *S. cerevisiae* have found a 300-fold-higher rate of mutation at sites during HDR (113); this higher mutation rate is thought to span the tract undergoing template repair (100, 113). We can make a quantitative comparison as follows. With g DSBs per genome and an average tract length of l bp synthesized from the template, the mutational burden of DSBs is expected to be $300\ g\ l\ \mu/4$ (divided by 4 because the mutations occur on only one of the four chromatids), compared to the remainder of the genome ($G\ \mu$), where G is the haploid genome size and μ is the base pair mutation rate. For compact genomes such as *S. cerevisiae*, the burden of DSBs can thus be a substantial proportion, approximately 65%, of the mutations that arise during meiosis [$\frac{300 g l \mu/4}{G\mu+300 g l \mu/4}$ with $g \sim 150$ (83), $l \sim 2{,}000$ bp (83), and $G = 12 \times 10^6$ bp (123)]. Empirically, the meiotic mutation rate in a *CAN1* insert was 6.5 times higher in wild-type yeast than in yeast lacking the protein (Spo11) responsible for DSBs, suggesting that an even higher fraction (87%) of mutations that arise during meiosis are DSB related (100). This empirical study implies that DSBs and their repair account for $0.038\ [= (6.5 - 1) \times 2\ G\ \mu]$ additional mutations per meiosis in diploid progeny, using 2.89×10^{-10} as the baseline mitotic mutation rate in diploid yeast (107). This input of mutations must be balanced by selective deaths (the diploid mutation load) (34), which suggests a moderate reduction in fitness for diploid yeast of a few percent per meiosis due to the induction of large numbers of DSBs that are subsequently thinned by crossover interference.

In larger genomes, DSBs affect a much smaller proportion of sites, but the total DSB burden may be similar if the mutability of HDR scales with the background rate of mutation. That is, if HDR is again 300-fold-more mutable than the background rate of mutation in humans, we would predict that only approximately 0.075% of the mutations that arise during meiosis would be due to DSBs [$\frac{300 g l \mu/4}{G\mu+300 g l \mu/4}$ with $g \sim 150$ (8), $l \sim 200$ bp (62), and $G = 3 \times 10^9$ bp (59)]. The genome is so large, however, that we estimate a genome-wide diploid meiotic mutation rate of 30 [using the germline mutation rate in females of 0.5×10^{-8} per base pair (31) multiplied by $2G$ to scale up to the genome]. The diploid mutation load due to DSBs would then again be a few percent in humans (0.022, i.e., 0.075% of 30). Pratto et al. (97) indeed found higher genetic diversity around DSB hot spots, consistent with a mutagenic effect of DSBs, as well as evidence for a heightened frequency of disease-causing structural variants. In addition, mutation rates are elevated 50-fold within 1 kb of crossovers in humans (52).

These calculations are coarse, but they suggest that the fitness burden of mutations caused by the production of a large number of DSBs that then interfere with one another to enable a much smaller number of crossovers is nonnegligible and would select for meiotic machinery that induced fewer DSBs, all else being equal.

All else need not be equal, however. In a variety of species including plants, mammals, and yeast, DSBs have proven important in homolog recognition and pairing, regardless of whether they mature into a crossover (16, 128). Kauppi et al. (64), for example, found severely impaired homolog pairing and synapsis formation in mice carrying a *Spo11* mutation that halved the number of DSBs; small chromosomes and X and Y pairing were particularly affected. In other species, such as *C. elegans* and *D. melanogaster* females, however, homolog pairing and synapsis initiate without DSB formation (16, 128), although crossovers may stabilize the synaptonemal complex

(81). Species with other mechanisms for chromosome pairing have dramatically fewer DSBs per genome [*D. melanogaster* has 20–24 (86); *C. elegans* typically has fewer than 10 (103)] relative to approximately 150–2,000 DSBs in species in which DSBs followed by single-strand invasions are key to pairing and synapsis (65). It is thus tempting to suggest that the mutation load caused by high ratios of DSBs to crossovers is maintained primarily to ensure pairing of homologs in taxa lacking other means of pairing rather than to facilitate crossover interference.

5.3. Indirect Selection on Genetic Modifiers of Interference

As noted by Veller et al. (119), interference increases the average rate of recombination between pairs of loci for a given number of crossovers. Consequently, genes that modify the strength of interference alter the recombination landscape between selected loci, thereby altering the distribution of offspring and their survival probabilities in a manner that can shift the frequency of genes modifying interference. This indirect selective effect, which acts through impacts on linkage disequilibria between selected loci, can lead to the evolution of interference.

Goldstein et al. (47) explicitly modeled the evolution of interference in a model with a gene (**M**) that modifies interference between three selected loci (**A**, **B**, **C**). In this model, the frequency of crossover events between the selected loci depends on the recombination rate between adjacent loci (r) and the strength of interference χ_{ij}, as determined by the diploid genotype ij at the modifier locus,

$$\begin{aligned}
(1-r)^2 - \chi_{ij} &= \text{probability of no crossover} \\
r(1-r) + \chi_{ij} &= \text{probability of crossover in } \mathbf{AB} \text{ interval only} \\
r(1-r) + \chi_{ij} &= \text{probability of crossover in } \mathbf{BC} \text{ interval only} \\
r^2 - \chi_{ij} &= \text{probability of crossover between } \mathbf{AB} \text{ and } \mathbf{BC}
\end{aligned} \quad . \qquad 4.$$

[For clarity we have used χ_{ij} instead of $\delta_{ij} = -\chi_{ij}$ as used by Goldstein et al. (47), so that positive values of χ_{ij} refer to positive interference. We also continue to use their simplifying assumption that r is the same for both adjacent intervals, but this is only for clarity and is not necessary in the model.]

By construction, the average recombination rate between adjacent selected loci remains constant at r (summing, for example, the second and fourth probabilities for interval **AB**), as does the average number of crossovers in the region ($2r$, assuming that there is at most one crossover in each interval). The average probability of recombination between the outermost loci (**A** and **C**), however, does depend on the strength of interference and equals $2r(1-r) + 2\chi_{ij}$. As a consequence of the impact of interference on crossovers in the **AC** interval, Goldstein et al. (47) found that interference levels evolved through changes in allele frequencies at the **M** locus. More clustering evolved (more negative χ_{ij}) when simulating circumstances in which reduced recombination was favored, such as populations in a constant environment under overdominant selection. This result reflects the reduction principle (2): When populations are at equilibrium under selection, genetic systems evolve to transmit the parental genotypes more faithfully, basically because the genetic associations built up by past selection helped the parents survive. In this case, more faithful transmission evolved via negative interference.

By contrast, when populations are shifted away from an equilibrium by mutation, drift, or a changing environment, increased recombination can evolve (92). At mutation–selection balance, for example, Goldstein et al. (47) found that interference (more positive χ_{ij}) could evolve under the same circumstances that increased recombination could evolve, that is, when epistasis was weak and negative and when the modifier was sufficiently tightly linked to the selected loci.

As Goldstein et al. (47) conclude, modifiers of interference are simply special cases of modifiers of recombination, affecting genetic intervals differently than would a locally acting modifier (e.g., a recombination hot spot) or a broadly acting modifier (e.g., a PRDM9 variant) (97). This realization allows the many theoretical results for recombination modifiers to be applied directly to inform our expectations of how interference should evolve.

In particular, from Barton (10), we learn that increased interference should evolve, like increased recombination, when epistasis is negative and weak and when modifiers are tightly linked, whether populations are at mutation–selection balance or subject to directional selection. From a series of papers (e.g., 11, 66, 104), we learn that crossover interference, like recombination, is more likely to evolve in finite populations to reduce selective interference among loci (including Hill–Robertson effects, clonal interference, and Muller's ratchet), which occurs because the variation that remains after periods of selection in finite populations tends to involve chromosomes containing mixtures of beneficial and deleterious alleles, which can be uncoupled by recombination. Furthermore, periods of intense directional selection, for example, associated with domestication, may lead to increased interference as a means to reduce these Hill–Robertson effects and increase genetic shuffling (93).

Importantly, the above discussion assumes that modifiers increasing the extent of crossover interference have no impact on the total number of crossovers. As mentioned above, however, mutations in genes affecting interference also commonly affect the rate of crossing over. Consider instead a modifier of interference that acts in a checkpoint pathway preventing meiosis from proceeding when chromosomes lack a crossover until one forms. In this case, modifiers would convert achiasmate chromosomes to ones bearing a single crossover, without having a substantial effect on the probability of two or more crossovers,

$$\begin{aligned}
(1-r)^2 - \chi_{ij} &= \text{probability of no crossover} \\
r(1-r) + \chi_{ij}/2 &= \text{probability of crossover in } \mathbf{AB} \text{ interval only} \\
r(1-r) + \chi_{ij}/2 &= \text{probability of crossover in } \mathbf{BC} \text{ interval only} \\
r^2 &= \text{probability of crossover between } \mathbf{AB} \text{ and } \mathbf{BC}
\end{aligned} \quad . \qquad 5.$$

Evolution of crossover interference via such modifier genes would generate a positive correlation between interference and number of crossovers, as seen with *mlh3Δ* mutants in *S. cerevisiae* (25) and across strains of yeast (99). Furthermore, mechanisms that act in this way—enforcing an obligate crossover (e.g., 40)—cause recombination between all pairs of loci to rise with the degree of interference [recombination rate between **AB** or **BC**, $r + \chi_{ij}/2$; and between **AC**, $2r(1 - r) + \chi_{ij}$]. Hence, theory predicts that crossover interference would again evolve whenever increased recombination is favored.

By contrast, if genes modify interference by preventing recombination in adjacent intervals, eliminating cases with multiple crossovers, then the resulting recombination rates may follow,

$$\begin{aligned}
(1-r)^2 &= \text{probability of no crossover} \\
r(1-r) + \chi_{ij}/2 &= \text{probability of crossover in } \mathbf{AB} \text{ interval only} \\
r(1-r) + \chi_{ij}/2 &= \text{probability of crossover in } \mathbf{BC} \text{ interval only} \\
r^2 - \chi_{ij} &= \text{probability of crossover between } \mathbf{AB} \text{ and } \mathbf{BC}
\end{aligned} \quad . \qquad 6.$$

Interference evolving via such modifier genes, those preventing supernumerary crossovers, would generate a negative correlation between interference and number of crossovers, as seen with topoisomerase II mutants in *S. cerevisiae* (126) and across strains of maize (14) and across species (see Section 2). Interference of this form causes adjacent loci to exhibit lower rates of recombination (**AB** or **BC**: $r - \chi_{ij}/2$) and distant loci to exhibit higher rates [**AC**: $r(1 - r) + \chi_{ij}$]. Consequently, it is harder to predict exactly what circumstances would favor the evolution of interference, because this would depend on the net effect across all intervals (e.g., calculated using equation 12 in Reference 10). As the most tightly linked selected loci tend to dominate in modifier models of recombination, we might predict that increased interference would evolve whenever decreased recombination is evolutionarily favored (e.g., in more stable environments) (92), exactly the opposite of the result of Goldstein et al. (47). There is some empirical evidence for the evolution of modifiers of this sort; Aggarwal et al. (1) observed reductions in interference and increases in recombination in some genomic intervals in *D. melanogaster* subjected to directional selection for survival under three different experimental conditions (desiccation, hypoxia, and hyperoxia).

In summary, the indirect selective forces acting on genes that alter interference will be mediated by their impact on recombination rates between selected loci. We cannot predict, in general, how indirect selective forces will act to shape the evolution of interference, except to say that—if we did hold the genetic map constant [i.e., changing v only in the gamma model, as assumed by Goldstein et al. (47)] or if modifier mutations tended to positively impact both interference and crossover rates—positive crossover interference (higher v) would evolve whenever recombination is favored.

6. DISCUSSION

Across eukaryotes the number of crossovers per chromosome is remarkably consistent (**Figure 2**), with typically more than one crossover per chromosome but rarely many more, despite orders of magnitude differences in genome size, chromosome numbers, population size, body size, and other characteristics. Crossover interference is integral to this pattern. Yet despite this homogeneity, there are substantial differences in how crossovers are achieved: with different hot spot motifs, with or without homolog pairing prior to DSB production, and with a range of contributions from class I and class II crossovers (16, 58, 112). Furthermore, map length can respond over short time periods to either direct selection on recombination (26) or indirect selection on other traits (93) and differs substantially among closely related species (109). This variability indicates that the underlying processes involved in generating crossovers and regulating their numbers are dynamic and have evolved over time.

The evolutionary lability of the recombination process, including interference, is inconsistent with the view that crossover interference evolved and has been constrained ever since by a requirement to achieve proper segregation. Evidence that homologous chromosomes pair prior to recombination in some species (e.g., *D. melanogaster* and *C. elegans*), that a variety of taxa lack crossovers in males or in females (15), and that interference is weak or absent in some species (89, 114) demonstrates that neither recombination nor interference is essential for proper segregation.

How do we reconcile rapid evolutionary responses in the recombinational landscape with relative stasis in the number of crossovers per bivalent? How do we reconcile the common role that crossovers play in ensuring proper segregation with the recurrent evolution of taxa that successfully segregate their chromosomes without recombination in one sex?

We hypothesize that the advantages of recombination—releasing hidden variation (negative linkage disequilibria) resulting from past epistatic selection (10) or past selection with drift (11, 66, 104)—constrain meiotic systems from evolving means of segregating chromosomes that lack functional recombination (e.g., achiasmy in both sexes or strictly telomeric recombination). These

indirect selective forces thereby generate a reflecting boundary that keeps meiotic systems away from the complete loss of recombination on a chromosome. In this context, meiosis may have coevolved with recombination to rely on the crossovers that do occur and co-opt them to bind together homologs and ensure their accurate segregation. Similarly, strand invasion following DSBs serves a dual role in many species, facilitating meiotic recombination but also physically finding and drawing together homologs. By contrast, too many crossovers per bivalent may be counterselected owing to a combination of indirect and direct selection. Theoretical models of recombination often find that indirect selection, although favoring recombination when rare, weakens and selects against recombination when frequent because of the increasing recombination load (e.g., 10, 66). In this context, mechanisms of homeostatic regulation that prevent too many crossovers may simultaneously benefit from this indirect selection and direct selection to avoid entanglement during meiosis and to reduce the mutations that frequently occur with DSBs. This perspective of mutually reinforcing selection away from both too few and too many crossovers to allow both effective selection and effective segregation in eukaryotic genomes may help account for the remarkable stasis in crossover numbers per bivalent despite the evolutionarily dynamic nature by which recombination is accomplished.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors wish to thank Andy Clark, Michael Lichten, and Nadia Singh for their helpful suggestions and insights, as well as April Peterson and Karl Broman for useful discussions. S.P.O. was supported by a Natural Sciences and Engineering Research Council of Canada grant (RGPIN-2016-03711). B.A.P. was supported by National Institutes of Health grants R01GM120051 and R01GM100426.

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