The distribution of crossovers, and the measure of total recombination

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Abstract

Comparisons of genetic recombination, whether across species, the sexes, individuals, or different chromosomes, require a measure of total recombination. Traditional measures, such as map length, crossover frequency, and the recombination index, are not influenced by the positions of crossovers along chromosomes. Intuitively, though, a crossover in the middle of a chromosome causes more recombination than a crossover at the tip. Similarly, two crossovers very close to each other cause less recombination than if they were evenly spaced. Here, we study a measure of total recombination that does account for crossover position: average r, the probability that a random pair of loci recombines in the production of a gamete. Consistent with intuition, average r is larger when crossovers are more evenly spaced. We show that average r can be decomposed into distinct components deriving from intra-chromosomal recombination (crossing over) and inter-chromosomal recombination (independent assortment of chromosomes), allowing separate analysis of these components. Average r can be calculated given knowledge of crossover positions either at meiosis I or in gametes/offspring. Technological advances in cytology and sequencing over the past two decades make calculation of average r possible, and we demonstrate its calculation for male and female humans using both kinds of data.

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1 Introduction

Recombination, the shuffling of maternally and paternally inherited genes in gamete formation, is an important process in sexual populations (Bell 1982). It improves the efficiency of adaptation by allowing natural selection to act separately on distinct mutations (Fisher 1930; Muller 1932, 1964; Hill and Robertson 1966; Felsenstein 1974; McDonald et al. 2016), and has been implicated in protecting populations from rapidly evolving parasites (Hamilton 1980; Hamilton et al. 1990) and from the harmful invasion of selfish genetic complexes (Haig and Grafen 1991; Burt and Trivers 2006; Haig 2010; Brandvain and Coop 2012).

The total amount of recombination that occurs in gamete formation is therefore a quantity of great interest. Total recombination has often been compared between species (Bell 1982; Burt and Bell 1987; True et al. 1996; Ross-Ibarra 2004; Dumont and Payseur 2008, 2011a; Segura et al. 2013; Brion et al. 2017), with implications ranging from distinguishing the evolutionary advantages of sex (Bell 1982; Burt and Bell 1987; Wilfert et al. 2007) to testing the genomic effects of domestication (Burt and Bell 1987; Ross-Ibarra 2004) to understanding the tempo of evolution of the recombination rate itself (Dumont and Payseur 2008; Segura et al. 2013). A large literature has also studied male/female differences in total recombination (Trivers 1988; Burt et al. 1991; Brandvain and Coop 2012), prompting several evolutionary theories for these differences (Trivers 1988; Lenormand 2003; Lenormand and Dutheil 2005; Haig 2010; Brandvain and Coop 2012), which could themselves be informative of the adaptive value of sex and recombination (Trivers 1988). There can also exist major differences in total recombination across individuals of the same sex (Kidwell 1972a,b; Broman et al. 1998; Lynn et al. 2002; Koehler et al. 2002; Sanchez-Moran et al. 2002; Kong et al. 2004, 2010; Cheng et al. 2009; Comeron et al. 2012; Ottolini et al. 2015), and across gametes produced by the same individual (Maudlin 1972; Lynn et al. 2002; Hassold et al. 2004; Lenzi et al. 2005; Cheng et al. 2009; Gruhn et al. 2013; Wang et al. 2017). Finally, comparisons have been made of the levels of total recombination of different chromosomes (Bojko 1985; Brooks and Marks 1986; Kong

et al. 2002), with implications for which chromosomes are most likely to be involved in aneuploidies (Hassold et al. 1980, 1995; Garcia-Cruz et al. 2010; Nagaoka et al. 2012), to be susceptible to harboring selfish genetic complexes (Haig 2010), and to be used as new sex chromosomes (Trivers 1988).

These quantitative comparisons naturally require a measure of total recombination. Two measures are most widely used, and are closely related: crossover frequency and map length. The crossover frequency is simply the number of crossovers at meiosis I. It can be observed cytologically in special preparations of meiotic nuclei (Tease and Jones 1978, Carpenter 1975, 1987, Anderson et al. 1999; reviewed in Jones 1987, Zickler and Kleckner 1999, 2015, Gruhn 2014), or estimated from sequencing data collected from gametes or offspring (Broman et al. 1998; Kong et al. 2002, 2010; Roach et al. 2010; Wang et al. 2012; Lu et al. 2012; Hou et al. 2013; Ottolini et al. 2015). Map length, whether of the genome or a single chromosome, is simply average crossover frequency multiplied by 50 centiMorgans (cM), 1 cM being the map distance between two linked loci that experience a crossover between them once every 50 meioses (Hartl and Ruvolo 2012). Another measure is Darlington's 'recombination index' (Darlington 1937, 1939; Bell 1982): the sum of the haploid chromosome number and the average crossover count. The recombination index is based on the observation that, given no chromatid interference in meiosis (Zhao et al. 1995; Hartl and Ruvolo 2012), two loci on segments of a bivalent chromosome that are separated by one or more crossovers recombine with probability 1/2 in the formation of a gamete, as if the loci were on separate chromosomes. The recombination index is therefore the average number of 'freely recombining' segments per meiosis. A final measure is the number of crossovers in excess of the haploid chromosome number (Burt and Bell 1987)—since each bivalent requires at least one crossover for its chromosomes to segregate properly (Darlington 1932), the 'excess crossover frequency' is the number of crossovers beyond this structurally-required minimum.

All of these measures of total recombination depend only on the average number of crossovers per meiosis (and the number of chromosomes, in the case of the recombination

index). None is affected by the *positions* of crossovers on the chromosomes. Intuitively, though, a crossover at the far tip of a pair of homologous chromosomes does very little work in shuffling the alleles of those chromosomes, while a crossover right in the middle shuffles many alleles (Figure 1). Similarly, two crossovers very close together may partially cancel each other's effect, causing less allelic shuffling than if they were more evenly spaced. Moreover, crossover count, map length, and excess crossover frequency do not directly take into account a major source of allelic shuffling, viz. the independent assortment of different chromosomes (inter-chromosomal recombination, in distinction to the intra-chromosomal recombination caused by crossovers), while the recombination index does not take into account variation in chromosome size. For all these reasons, crossover count, map length, the recombination index, and excess crossover frequency all fail to measure the total amount of recombination, instead serving as proxies for it.

This is not a trivial concern. On top of obvious karyotypic differences between species, there is significant heterogeneity in the chromosomal positioning of crossovers at all levels of comparison: between species (Levan 1935; True et al. 1996; Kauppi et al. 2004), populations within species (Levine and Levine 1954, 1955; Whitehouse et al. 1981; Hinch et al. 2011; Wegmann et al. 2011), the sexes (Callan and Perry 1977; Fletcher and Hewitt 1980; Trivers 1988; Brandvain and Coop 2012; Young 2014), individuals (King and Hayman 1978; Laurie and Jones 1981; Sun et al. 2006; Cheung et al. 2007; Ottolini et al. 2015), and different chromosomes (Bojko 1985; Froenicke et al. 2002; Sun et al. 2004). It is therefore crucial to consider a measure of recombination that accounts for the chromosomal positions of crossovers, according terminal crossovers less recombination, and central crossovers more recombination.

Here, we defend a simple, intuitive measure with these properties. *Average* r is the probability that a randomly chosen locus pair recombines in meiosis; i.e., the probability that the alleles at a random pair of loci in a gamete are of different grand-parental origin. The name we have chosen is suggestive: given two loci, the familiar population genetics quantity r is the recombination rate between these loci; average r is simply this

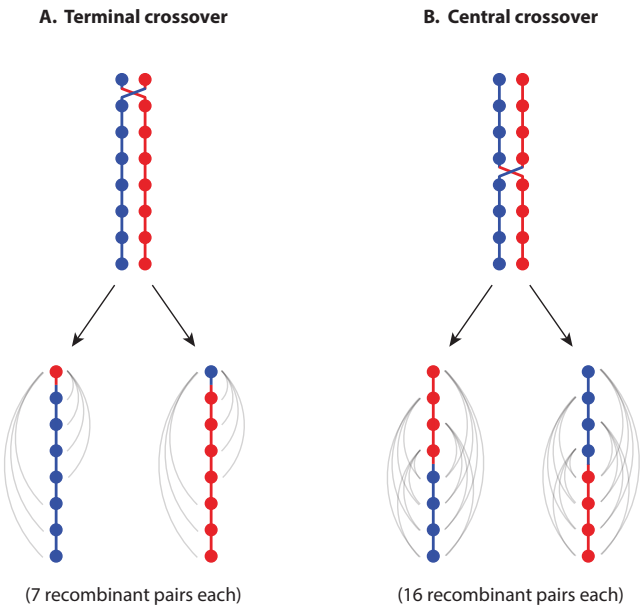

Figure 1: Crossover position affects the amount of recombination. The figure shows the number of recombinant locus pairs in gametes that result from crossing over between two chromatids in a one-step meiosis. The chromosome is arbitrarily divided into eight loci. (A) A crossover at the tip of the chromosome, between the seventh and eighth loci, causes 7 of the 28 locus pairs to be recombinant in each resulting gamete. (B) A crossover in the middle of the chromosome, between the fourth and fifth loci, causes 16 of the 28 locus pairs to be recombinant in each resulting gamete. The central crossover thus causes more recombination than the terminal crossover.

quantity averaged over all locus pairs. As we shall demonstrate, even spacing of crossovers increases average r, and terminal localization of crossovers decreases average r, consistent with our intuition. Average r also allows us to take into account recombination caused by independent assortment of different chromosomes, and in fact admits a simple partition into components deriving from intra- and inter-chromosomal recombination. Similar to the intuition for crossovers, greater variation in chromosome size decreases the inter-chromosomal component of average r.

We should note that we are not the first to propose this measure for total recombination. Burt et al. (1991), in a review of sex differences in recombination, give an explicit formula, identical to our Eq. (1), for 'the proportion of the genome which recombines'. They note, however, that this had yet to be measured in any species, and go on

to use crossover frequency in their comparative analysis. Colombo (1992) also gives an explicit characterization of what we call average r, phrased as a generalization of Darlington's recombination index. Finally, Haag et al. (in press), after noting that terminal crossovers cause little recombination and that map length is therefore an imperfect measure of genome-wide recombination, suggest a better measure to be 'the average likelihood that a [crossover] occurs between two randomly chosen genes'. To our knowledge, no study to date has carried out measurement of any of these quantities. [See also White (1973), Weissman (1976), Callan and Perry (1977), Bell (1982), Fletcher (1988), and Gorlov et al. (1994) for statements of the importance of crossover position for the amount of recombination.]

In defending their use of a measure of total recombination that does not account for crossover positions, Burt et al. (1991) noted that, at the time of their writing, 'quantitative information on the position of chiasmata is available for very few species'. This is no longer the case. Cytological advances from the late 1990s have made possible efficient and accurate visualization of the positions of crossovers on pachytene bivalent chromosomes (Anderson et al. 1999; Lynn et al. 2002; Møens et al. 2002; Froenicke et al. 2002; Sun et al. 2004), while rapid technological advances in DNA sequencing have allowed crossovers to be determined at a fine genomic scale using sequence analysis of pedigrees (Broman et al. 1998; Shifman et al. 2006; Kong et al. 2010; Roach et al. 2010), individual gametes (Wang et al. 2012; Lu et al. 2012) and even meiotic triads/tetrads (Hou et al. 2013; Cole et al. 2014; Ottolini et al. 2015). These technological advances, as we shall demonstrate, allow simple estimation of average r.

The rest of the paper is structured as follows. In Section 2, we define average r, and provide formulas for average r given knowledge of crossover positions along bivalent chromosomes and given knowledge of realized crossovers in a gamete. We derive some properties of average r, and show how it can be decomposed into intra-chromosomal and inter-chromosomal components. In Section 3, we show how average r can be estimated from cytological data, arguing that the most appropriate data for the task are immunos-

tained pachytene nuclei. As an example, we provide a measurement of average r for male and female humans from such data. In Section 4, we show how to measure average r from sequence data, and measure it from gamete sequences of haplophased male and female humans. In Section 5, we discuss alternative measures of total recombination that are related to average r. Section 6 concludes.

2 Derivation of average r, and its properties

Average r can be calculated with knowledge either of where realized crossovers have occurred (e.g., given sequence data from gametes or offspring) or of where crossovers are positioned along bivalent chromosomes at meiosis I (e.g., from cytological data).

Average r is an 'average' in the sense that it is an average over all locus pairs. However, this measure itself can be averaged at various levels of aggregation, e.g., in a meiocyte nucleus at meiosis I, or across many gametes produced by an individual, or across gametes from many members of the same sex in a species, etc. In the first case, where we know where crossovers are situated along the bivalent chromosomes at meiosis I, the exact genomic content of a resulting gamete cannot be determined, because we do not know which chromatids are involved in the crossovers, and we do not know which centromeres will segregate to the chosen gamete; therefore, only an expected value, or average, of average r for that gamete can be calculated. We discuss this measurement in the following subsection. We discuss how to conduct higher-order averages across the meiocytes or gametes of an individual, or those of many individuals, in Section 2.4.

Some notes on terminology: First, we use the word 'recombination' in the population genetics sense to refer to allelic shuffling, caused either by crossing over (intra-chromosomal recombination) or independent assortment of different chromosomes (inter-chromosomal recombination). 'Recombination' has a different meaning in molecular and physical biology, where it refers to the physical breakage and rejoining of DNA molecules.

Second, there is some inconsistency across fields of study in the terminology used to describe various lengths of, or distances along, chromosomes. Here, we shall use 'genomic

length' or 'genomic distance' to describe lengths or distances in bp, as observed in sequence data, and 'physical length' or 'physical distance' to describe lengths or distances in μm, as observed in cytological micrographs. This usage is common in the physical biology literature. 'Physical length' has often been used in the genetics literature to describe lengths of DNA in bp, distinct in that usage from 'genetic length' measured in centiMorgans. That usage would become confusing in our case when we wish to describe, for example, the length of a chromosome axis, as when discussing the measurement of average r from cytological data.

Third, we shall refer to portions of DNA in a gametic genome or haploid portion of a diploid offspring's genome by their 'grand-parental' origin, grand-maternal when they derive from the mother of the individual who produced the gamete or haploid portion of the offspring's genome, or grand-paternal when from that individual's father. Thus, for clarity, when a male individual (call him Marcus) produces a sperm, we talk of that sperm's genome comprising a grand-paternal portion (derived from Marcus's father, the sperm's 'grandfather') and a grand-maternal portion (derived from Marcus's mother, the sperm's 'grandmother'). If that sperm fertilizes an egg to produce a diploid offspring, then the haploid complement of the offspring's genome that was furnished by Marcus's sperm similarly comprises a grand-paternal portion (from Marcus's father, i.e., the new offspring's grandfather) and a grand-maternal portion (from Marcus's mother, i.e., the new offspring's grandmother).

Finally, in what follows, 'loci' refers to distinct stretches of DNA of equal genomic length (measured in base pairs). It is assumed that the number of loci is large, so that sampling them with replacement closely approximates sampling them without replacement (the stylized example in Figure 1, with only eight loci, does not satisfy this requirement, for example).

2.1 Formulas for average r

If we have knowledge of crossover positions along bivalent chromosomes in a meiocyte at meiosis I, calculation of average r follows the formulas given in Burt et al. (1991) and Colombo (1992) (Figure 2A). If the haploid number of chromosomes is n, and there are a total of I crossovers, then these crossovers divide the bivalents into $n+I$ segments (= the recombination index). If there is no chromatid interference, loci on distinct segments of the same bivalent segregate as if unlinked (Darlington 1939; Hartl and Ruvolo 2012), as, of course, do loci on separate chromosomes. Label the segments in some order $1, 2, \ldots, n+I$, and suppose that the relative genomic length of segment i is l_i, so that $l_1+l_2+\ldots+l_{n+I} = 1$. For a random locus pair to recombine in the production of a gamete, the loci need to be situated on different segments, the probability of which is $1 - l_1^2 - l_2^2 - \ldots - l_{n+I}^2$ (this is one minus the probability that a random locus pair is on the same segment). If they are indeed situated on different segments, they recombine with probability 1/2. Therefore,

$$\text{Average } r = \frac{1}{2}\left(1 - \sum_{i=1}^{n+I} l_i^2\right), \tag{1}$$

as determined by Burt et al. (1991) and Colombo (1992). Eq. (1) is directly proportional to the Gini-Simpson index (Simpson 1949), a commonly used measure of diversity, especially in the field of ecology (Jost 2006).

If, rather than knowledge of crossover positions along bivalents in a nucleus at meiosis I, we instead have knowledge of crossover realizations in a gamete or haploid complement of an offspring, we may employ a more direct calculation of average r (Figure 2B). Suppose that we determine a proportion p of the loci in a gamete to be of grand-paternal origin (i.e., from the father of the individual producing the gamete). Then the probability that a random pair of loci has recombined in the production of that gamete is just the probability that the allele at one locus in the pair is of grand-paternal origin and the allele at the

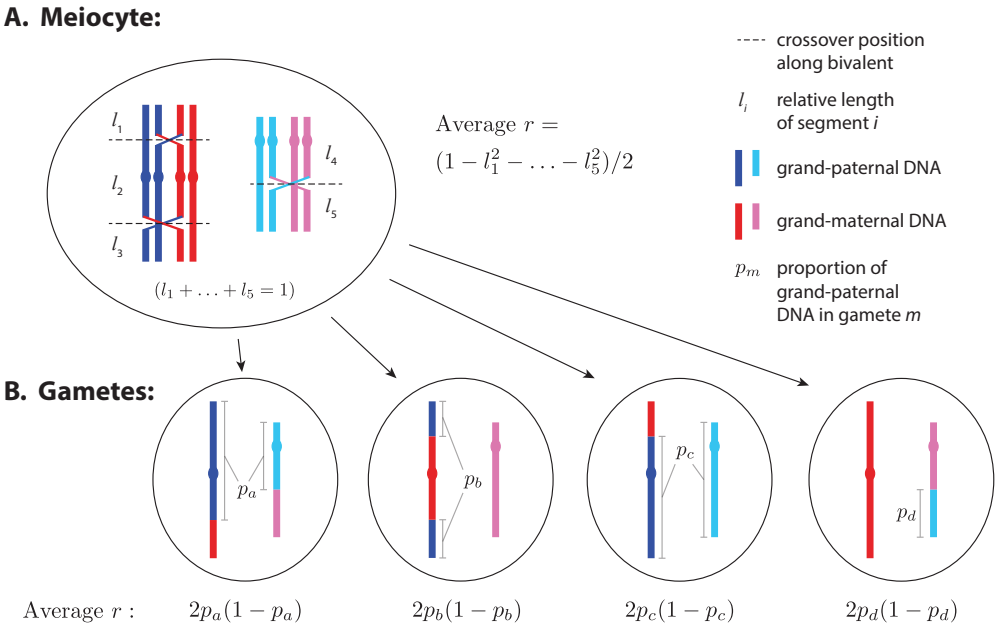

Figure 2: Calculating average r from a nucleus at meiosis I (A) and from individual gametes (B). Note that, at meiosis I, average r is an expectation for a random gamete resulting from the configuration of crossover positions, given no knowledge of which chromatids will be involved in the resolution of the observed crossovers, and assuming no chromatid interference. This expectation for average r at meiosis I is not necessarily the average value of average r among the four products that actually result from the meiosis, for reasons explained in the text.

other is of grand-maternal origin. This probability is simply

$$\text{Average } r = 2p(1-p). \tag{2}$$

The same measure obviously applies if we can determine, from an offspring's genotype, how much of one parentally-inherited complement is of grand-paternal origin, and how much of grand-maternal origin.

Note that the value for average r calculated for a given meiocyte at meiosis I [Eq. (1)] is the expected value of average r for a gamete resulting from that meiosis, though it is not necessarily the average value of average r among the four products that actually result from that gamete [for each product, calculated according to Eq. (2)]. This is easiest to see in an extreme example, a single acrocentric chromosome with two central crossovers

very close together. If the same two chromatids are involved in the resolution of these two crossovers, then very little recombination occurs, and the average value of average r across the four products of the meiosis will be small. On the other hand, if the chromatids are involved in the resolution of one crossover each, then much recombination occurs, and the average value of average r across the resulting gametes will be high.

It will often be the case that, although crossover positions can be determined from a haploid complement if the genotype of its producer is haplophased (that is, if the distinct sequences of the two chromosomes in each homolog pair are known), which of the sequences separated by these crossovers are grand-maternal and which are grand-paternal is not known without marker or sequence data from the producer's parents [e.g., Roach et al. (2010); Wang et al. (2012); Hou et al. (2013); Ottolini et al. (2015)]. Grand-paternal and grand-maternal sequences along a chromosome must alternate from crossover to crossover, of course, and so we will be able to determine for every chromosome i that a proportion p_i is of one grand-parental origin, and $1 - p_i$ of the other grand-parental origin, but which is grand-maternal and which is grand-paternal cannot be determined. In this case, we may nonetheless obtain an expected value for average r by averaging Eq. (2) over all possible combinations. The effect of this is simply to remove any gamete-specific information about recombination of loci on *separate* chromosomes, so that our best estimate that two loci on separate chromosomes have recombined is 1/2. In this case, if there are n chromosomes in the haploid set, and chromosome k accounts for a fraction L_k of the genome's length, and we determine a proportion p_k of chromosome k to be of one grand-parental origin and $1 - p_k$ to be of the other, then average r is estimated as

$$\sum_{k=1}^{n} 2p_k(1 - p_k)L_k^2 + \sum_{i \neq j} L_i L_j, \tag{3}$$

where the first term is the probability, summed over all chromosomes k, that two randomly chosen loci lie on chromosome k multiplied by the probability that they are of different grand-parental origin, and the second term is the probability that the two randomly chosen

loci lie on different chromosomes ($\sum_{i \neq j} 2L_i L_j$) multiplied by 1/2. This second term can also be written as $\sum_{k=1}^{n} \left(1 - L_k^2\right)/2$. Eq. (3) will show up again in Section 2.3, where we decompose average r into intra- and inter-chromosomal components.

2.2 Properties of average r

Turning to the properties of average r, we first note that the number of base pairs that constitute a 'locus', so long as it is constant for all loci (and small enough that there are many loci), does not affect the measure of average r, because it influences neither p (if we have data for realized crossovers) nor l_i (if we have data for crossover positions along bivalents).

Second, it can be seen from Eq. (2) that the maximum value of average r in a gamete is 1/2. This value can be obtained in a given gamete by chance, for example with no crossing over in meiosis but equal segregation of grand-maternal and grand-paternal chromosomes to the gamete. The maximum value of average r for a meiocyte at meiosis I is also 1/2, which can be noted from Eq. (1) or from the fact that a meiocyte's average r is the expected value of average r in a resulting gamete; this maximum is attained when every pair of loci are either on separate chromosomes or, if on the same chromosome, experience at least one crossover between them in every meiosis, with no chromatid interference. The minimum value of average r is zero, the general attainment of which requires both (i) crossing over to be completely absent [as in *Drosophila* males and *Lepidoptera* females (White 1973)], and (ii) a karyotype of only one chromosome or a meiotic process that causes multiple chromosomes to segregate as a single linkage group [as in some permanent translocation heterozygotes, such as several species in the evening primrose genus, *Oenothera* (Cleland 1972)].

Third, average r satisfies the intuitive property that a crossover at the tip of a chromosome causes less recombination than a crossover in the middle. This is easily seen in Eq. (1). Consider a bivalent chromosome upon which a single crossover will be placed. This will divide the chromosome into two segments of length l_1 and l_2, where $l_1 + l_2 = L$

is the proportion of base pairs in the genome accounted for by this chromosome. The contribution of this crossover to average r is easily seen from Eq. (1) to be $-(l_1^2 + l_2^2)/2$, which can be rewritten as $l_1 l_2 - (l_1 + l_2)^2/2$. Given the constraint that l_1 and l_2 must sum to the constant value L, the quantity $l_1 l_2 - (l_1 + l_2)^2/2$ is maximized when $l_1 = l_2 = L/2$, i.e., when the crossover is placed exactly in the middle of the bivalent. The quantity is minimized when $l_1 = 0$ and $l_2 = L$, or $l_1 = L$ and $l_2 = 0$, i.e., when the crossover is placed at one of the far ends of the bivalent. In general, as the crossover is moved further from the middle of the bivalent, average r steadily decreases. This is true regardless of the positions of the crossovers on other chromosomes, and also holds if, instead of considering where to place a single crossover on a whole bivalent, we consider where to place a new crossover on a segment already delimited by two crossovers (or by one crossover and a chromosome end). It is easy to show that this result extends to any number of crossovers: if we are to place some fixed number along a single chromosome, average r is increased if they are evenly spaced. This fact carries the interesting implication that positive crossover interference—a classical phenomenon (Sturtevant 1913; Muller 1916) where the presence of a crossover inhibits the formation of nearby crossovers—will tend to increase average r.

Fourth, average r will not covary in any simple way (for example, linearly) with the number of crossovers or the number of chromosomes. It is important to get a numerical sense of how average r depends on these factors, and so it is worth studying some simple examples.

In the case of crossover number, consider a diploid species with only a single chromosome in its haploid set, and consider the effect of placing either one or two crossovers along the single bivalent at meiosis I. In the case of one crossover, in line with the discussion above, average r is maximized by locating the crossover exactly in the middle of the chromosome, in which case we employ Eq. (1) to find that average $r = 1/4$. In the case of two crossovers, average r is maximized by locating the first crossover one third of the way and the second crossover two thirds of the way along the chromosome, in which case average $r = 1/3$. Doubling the number of crossovers has resulted in the maximum value

of average r increasing by a factor of only 4/3. In general, if there are I crossovers placed along the single bivalent, then the maximum value of average r is $I/[2(I+1)]$, so that the effect of increasing crossover number from I to $I+1$ is to increase the maximum value of average r by a factor $(I+1)^2/[I(I+2)] > 1$. This factor is a multiple $(I+1)/(I+2) < 1$ of the factor by which crossover number has increased, $(I+1)/I$. The general effect is that average r will increase sub-linearly with crossover frequency.

This effect, the sub-linear increase of average r with crossover frequency, is exacerbated when there are multiple chromosomes in the haploid set, because then a large, fixed component of average r is due to independent segregation of different chromosomes (inter-chromosomal recombination; see next section), which is not affected by changes in crossover frequency. The effect nonetheless persists when we restrict attention to that part of total recombination that is due to crossing over (intra-chromosomal recombination; see next section). This will have effect, for example, on differences in the total autosomal recombination rate of the two sexes in a species. Human female oocytes exhibit approximately 50% more crossovers than do human male spermatocytes (Kong et al. 2010; Gruhn et al. 2013); nonetheless, the increase in average r that this causes, restricting attention to the intra-chromosomal component, is substantially less than 50% (see Sections 3.2 and 4.1, Figures 5 and 7, and Table 1), even in spite of the tendency for crossovers to be more terminally situated in males (Broman et al. 1998; Gruhn et al. 2013).

In the case of chromosome number, suppose for simplicity that there is no crossing over, and that the haploid genome of a diploid species is divided into n equally sized chromosomes. Then average r is the same as if there were only a single chromosome and always $n-1$ evenly spaced crossovers along it; i.e., average r is simply $(n-1)/(2n)$. Increasing the haploid number of equally sized chromosomes from n to $n+1$, that is, by a factor $(n+1)/n$, therefore increases average r by a factor $n^2/[(n-1)(n+1)] > 1$. As with crossover number, the general effect is that average r will increase sub-linearly with haploid number. This conclusion is sensitive to the inclusion of crossovers, and specifically to how crossover number depends on chromosome number. If, for example, there is always at least

one crossover per bivalent, which in most species must be the case for structural reasons (Darlington 1932), then the effect of having an additional chromosome in the haploid set is to also have an additional crossover, situated somewhere on the extra bivalent chromosome. Thus, in the simplest case where each bivalent chromosome experiences one central crossover, the effect of increasing the haploid number from n to $n+1$ is to increase the number of freely recombining segments—the recombination index—from $2n$ to $2(n+1)$, and, since the segments are in each case of equal relative length (i.e., relative lengths $1/[2n]$ in the former case and $1/[2(n+1)]$ in the latter case), average r increases from $[2n-1]/4n$ to $[2(n+1)-1]/[4(n+1)]$, i.e., by a factor $[(2n+1)n]/[(2n-1)(n+1)]$.

The numerical effects of crossover number and position, and chromosome number and size, on average r are illustrated in Figure 3 for these and other examples.

2.3 Inter- and intra-chromosomal components of average r

It is often argued that the predominant source of recombination in sexual species is independent assortment of separate chromosomes, or, alternatively, that the most effective way for a species to increase genomic recombination in the long term is to increase karyotypic number, rather than to increase crossover frequency (Bell 1982; Crow 1988; though see Burt 2000 and Section 5). Our formulation of average r allows us to partition total recombination exactly into a component deriving from independent assortment of separate chromosomes (inter-chromosomal recombination) and a component deriving from crossovers (intra-chromosomal recombination). In terms of our broader goal of accounting for crossover positions in the measure of total recombination, this is useful because, in an organism with more than one chromosome in its haploid set, if all crossovers are terminal, then almost all recombination will be inter-chromosomal: any two sizable chromosomal segments that segregate randomly with respect to each other must be from separate chromosomes.

We first present this decomposition for average r given knowledge of crossover positions along bivalent chromosomes in a meiocyte. Suppose that the haploid number of chromo-

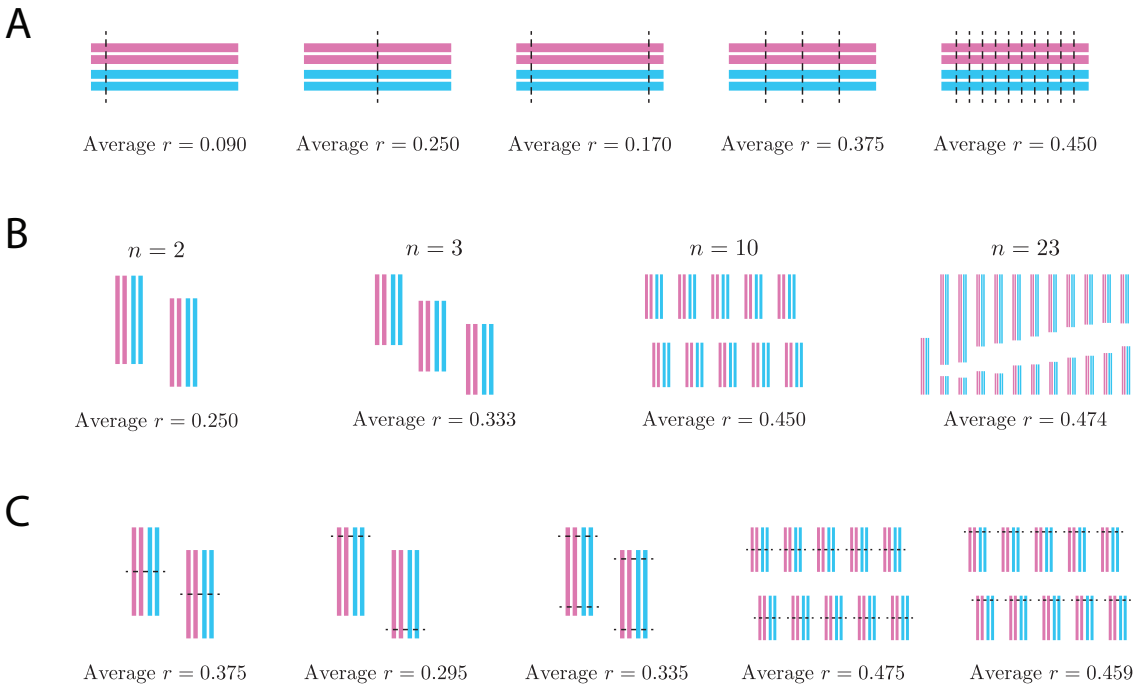

Figure 3: Example values of average r at meiosis I. In each case, average r is calculated according to Eq. (1). (A) Various crossover numbers and positions in a diploid organism with only one chromosome. Notice that average r increases sub-linearly with crossover number, even when crossovers are evenly spaced (which maximizes average r). (B) Various chromosome numbers for a diploid organism without crossing over. Notice that average r increases sub-linearly with chromosome number, even when chromosomes are evenly sized (which maximizes average r). Notice too that, when the number of chromosomes is not small, average r is close to its maximum value of 1/2. The rightmost panel represents a crossover-less meiosis in a human female, in which case average r is 0.474, close to its maximum value of 1/2. (C) Various configurations of crossovers in a diploid organism with multiple chromosomes.

somes is n, and that bivalent k exhibits $S_k - 1$ crossovers, partitioning it into segments $s = 1, \ldots, S_k$, the genomic lengths of which (relative to total genomic length) are $l_{k,s}$. The relative genomic length of chromosome k is then $L_k = l_{k,1} + l_{k,2} + \ldots + l_{k,S_k}$, and $L_1 + L_2 + \ldots + L_n = 1$. We may then partition the expression for average r, Eq. (1), into an inter-chromosomal component—the probability that two randomly chosen loci are on separate chromosomes and recombine—and an intra-chromosomal component—the prob-

ability that two loci are on the same chromosome and recombine:

$$\begin{aligned}\text{Average } r = & \underbrace{\frac{1}{2}\left(1-\sum_{k=1}^{n} L_k^2\right)}_{\text{Inter-chromosomal component}} + \underbrace{\frac{1}{2}\sum_{k=1}^{n}\left(L_k^2\left[1-\sum_{s=1}^{S_k}\left(\frac{l_{k,s}}{L_k}\right)^2\right]\right)}_{\text{Intra-chromosomal component}} \\ = & \underbrace{\frac{1}{2}\left(1-\sum_{k=1}^{n} L_k^2\right)}_{\text{Inter-chromosomal component}} + \underbrace{\frac{1}{2}\sum_{k=1}^{n}\left(L_k^2-\sum_{s=1}^{S_k} l_{k,s}^2\right)}_{\text{Intra-chromosomal component}} . \end{aligned} \tag{4}$$

We now turn to a similar decomposition given knowledge of crossover realizations in a gamete or haploid complement of an offspring. If chromosome k contains a proportion p_k of grand-paternal content, then the appropriate decomposition is

$$\text{Average } r = \underbrace{\sum_{i\neq j}[2p_i(1-p_j)+2(1-p_i)p_j]L_iL_j}_{\text{Inter-chromosomal component}} + \underbrace{\sum_{k=1}^{n} 2p_k(1-p_k)L_k^2}_{\text{Intra-chromosomal component}} . \tag{5}$$

If we know crossover realizations in a haploid complement, but we do not know whether the segments they delimit are of grand-paternal or grand-maternal origin, then, assuming that we know a proportion p_k of chromosome k to be of one grand-parental origin and $1-p_k$ to be of the other (but not knowing which is which), we retain the second term in Eq. (5), but lose information about the first term, so that the appropriate partition is

$$\text{Average } r = \underbrace{\sum_{i\neq j} L_iL_j}_{\text{Inter-chromosomal component}} + \underbrace{\sum_{k=1}^{n} 2p_k(1-p_k)L_k^2}_{\text{Intra-chromosomal component}} , \tag{6}$$

which is the same as Eq. (3). Notice that the first term in Eq. (6) could also be written $\left(1-\sum_{k=1}^{n} L_k^2\right)/2$.

2.4 Averaging average r

As noted at the beginning of this section, the measurement of average r can be carried out at various levels of aggregation. It can be measured in an individual gamete, as per

Eq. (2), or it can be calculated for a meiocyte at meiosis I, as per Eq. (1). This latter measure is the expectation of average r for a randomly chosen gamete resulting from the configuration of crossover positions observed at meiosis I.

These measures can be aggregated to obtain the average value of average r for, e.g., the gametes produced by a single individual, or the gametes produced by one sex in a species, or any other level of aggregation.

To average average r given data of crossover positions along bivalent chromosomes in many meiocytes, it is easiest to use Eq. (4). Notice that

$$\begin{aligned}\mathbb{E}\left[\text{Average } r\right] &= \mathbb{E}\left[\frac{1}{2}\left(1-\sum_{k=1}^{n} L_k^2\right)+\frac{1}{2}\left(\sum_{k=1}^{n}\left[L_k^2-\sum_{s=1}^{S_k} l_{k,s}^2\right]\right)\right] \\ &= \frac{1}{2}\left(1-\sum_{k=1}^{n} L_k^2\right)+\frac{1}{2}\left(\sum_{k=1}^{n}\left[L_k^2-\mathbb{E}\left[\sum_{s=1}^{S_k} l_{k,s}^2\right]\right]\right), \qquad (7)\end{aligned}$$

where the second step follows because the genomic lengths of the chromosomes, L_k, are constant across meiocytes.

To average average r given sequence data from, say, many gametes of a haplophased individual, and supposing that we cannot distinguish which sequences are grand-paternal and which are grand-maternal, we use Eq. (6):

$$\begin{aligned}\mathbb{E}\left[\text{Average } r\right] &= \mathbb{E}\left[\sum_{i\neq j} L_i L_j + \sum_{k=1}^{n} 2p_k(1-p_k)L_k^2\right] \\ &= \sum_{i\neq j} L_i L_j + \sum_{k=1}^{n} \mathbb{E}\left[2p_k(1-p_k)\right] L_k^2, \qquad (8)\end{aligned}$$

Eqs. (7) and (8) mean that we can estimate the average intra-chromosomal contribution to average r separately for each chromosome, possibly from different sets of data, and then combine these averages into a final measure of average r. This is very useful, because often in cytological and sequencing studies of large numbers of meiosis I nuclei or gametes, it is possible (or desired) only to obtain accurate measurements for a subset of the chromosomes in each cell, so that the sets of cells from which measurements are

taken for two chromosomes will in general not overlap. This is the case, for example, in the very rich cytological data from human pachytene nuclei in Gruhn et al. (2013). In such cases, Eqs. (7) and (8) state that the average intra-chromosomal contribution of the one chromosome can be estimated from the set of cells from which measurements of that chromosome were possible, while the contribution of the other chromosome can be estimated from the set of cells from which measurements of that chromosome were possible (possibly from different sets of data); these two separate estimates can then be combined in Eq. (7) or Eq. (8).

3 Estimation of average r from cytological data

In this section, we describe how to measure average r from cytological data. Only physical distances (i.e., measured in μm) along chromosomes can be directly inferred from cytological data, and so the measurement of average r from such data requires a way to convert relative physical distances into relative genomic distances (in bp). Because of this requirement, we advocate for the use of pachytene-stage chromosomes in the measurement of average r, owing to several fortuitous features of their structural organization, which we shall discuss below. Spread pachytene nuclei immuno-stained for visualization of crossover positions are now very common in the literature, and are easily generated. We shall provide some examples of the measurement of average r from such spreads.

3.1 The structural organization of pachytene chromosomes

For context, we summarize the events leading up to the pachytene stage of meiosis, as they are currently understood [reviewed in Kleckner et al. (2012); Hunter (2015)]: During S-phase, the chromosomes replicate to form conjoined pairs of sister chromatids. At G2/leptotene, double strand breaks (DSBs) occur at many positions along the chromatids, releasing $3'$ single strand DNA tails as 'tentacles' to search for homologous double strand sequences (on homolog chromatids, not sister chromatids). The interactions between the searching single strands and their double strand homologs enable homologous chromosome

pairing: homologs will be co-aligned by late leptotene. In addition, each interaction results in a structure (a 'nascent D-loop') that will be processed at the leptotene/zygotene transition either as a crossover-designated interaction (via formation of a double Holliday junction [dHJ], all of which are crossover-designated, in contrast to classical models) or, more commonly, as a non-crossover-designated interaction (via release of the $3'$ searching strand, which then anneals to the $3'$ tail of the second end of the DSB from which it came). Crossover-designated interactions mature to 'type I' crossovers [though see Wang et al. (2017); Zelazowski et al. (in press)]. In some organisms, it has been reported that a subset of non-dHJ interactions mature to crossovers, which are then called 'type II' crossovers (de los Santos et al. 2003; Berchowitz et al. 2007; Anderson et al. 2014). All crossovers are type I or type II, and in most studied organisms, type I crossovers account for the majority [$\sim$ 75-95% (Hunter 2015)]. Type I crossovers exhibit among themselves the classical phenomenon of crossover interference (Sturtevant 1913; Muller 1916), while type II crossovers do not interfere with each other (Copenhaver et al. 2002; de los Santos et al. 2003; Higgins et al. 2004; Berchowitz et al. 2007; Anderson et al. 2014); interference between type I and II crossovers has been reported (Anderson et al. 2014). At zygotene, a proteinaceous structural complex, the synaptonemal complex (SC), begins to form between coaligned homologs; at pachytene, the SC has extended fully along the axis lengths of the chromosomes, at which point the homologs are said to be 'synapsed'.

The physical structure of pachytene chromosomes is highly regular: The chromatin of each chromatid is arranged in a linear array of loops, the bases of which lie at regular intervals (with an evolutionarily conserved physical spacing of $\sim 20/\mu$m) along the axis demarcated by the SC [reviewed in Møens and Pearlman (1988); Zickler and Kleckner (1999); Kleckner (2006)]. In addition, almost all of the DNA is accommodated in the loops, with very little in the axis between loop bases (Li et al. 1983; Møens and Pearlman 1988; Zickler and Kleckner 1999). These two facts—the regular physical spacing of loop bases and the fact that the loops contain almost all of the DNA—imply that the genomic lengths of the loops determine (i) the physical length of the axes, in an inverse relationship,

or, equivalently, (ii) the genomic distance per unit of physical distance along a pachytene bivalent axis (the local 'packing ratio'), in a direct relationship (Zickler and Kleckner 1999; Kleckner et al. 2003; Novak et al. 2008).

The physical position of crossovers along the axes of pachytene chromosomes can be determined reliably in spread pachytene nuclei (or in 3D reconstructions from serial sectioning), either with electron microscopy by direct visualization of late recombination nodules [which mark all crossovers (Sherman and Stack 1995; Zickler and Kleckner 1999; Anderson et al. 2014)], or with light microscopy using immunofluorescent staining techniques to detect type I crossovers [reviewed in Hassold et al. (2000); see Figure 5].

The latter method is now most commonly used, being more efficient because only light microscopy is required. Visualization of the chromosome axes can be achieved by staining using antibodies against proteins in the SC, such as SYCP1-3. Crossover positions along the axes can be visualized using antibodies against the mismatch repair protein MLH1 (Barlow and Hultén 1998a; Anderson et al. 1999), which is part of a protein complex involved in the maturation of type I crossovers (Baker et al. 1996; Hunter and Borts 1997; Zhang et al. 2014; Hunter 2015). If desired, the positions of centromeres along the axes can be visualized by staining for centromeric proteins, such as CEN3. If it is desired that individual chromosomes be identified, this can be achieved concurrently by fluorescence in situ hybridization (FISH) of chromosome-specific probes [e.g., Froenicke et al. (2002); Sun et al. (2004); Cheng et al. (2009); Gruhn et al. (2013); Mary et al. (2014)].

Average r takes as inputs the relative genomic lengths of the segments separated by crossovers. But cytological observation can yield only physical distances. To measure average r from cytological data therefore requires inferring, from observed physical crossover positions along chromosome axes, the relative genomic lengths of the segments that they demarcate. This requires knowledge of the average packing ratios (bp/μm) of the different segments, which depends on the genomic lengths of the chromatin loops in these segments, as noted above. The simplest condition for relative genomic lengths to be accurately inferred from physical lengths at the resolution of the distance between crossovers

would be that the average genomic length of loops is, per nucleus, approximately constant at this crude resolution. In principle, this could be assayed directly at pachytene using high-resolution FISH (Beliveau et al. 2012, 2015; Wang et al. 2016) at multiple genomic points. We are not aware of such an exercise having been carried out, and so we must rely on more circumstantial evidence, which we describe below. Fortunately for our purposes, this evidence suggests that loop lengths do not differ substantially within each nucleus, at least in mammals.

Loop lengths can be inferred in two ways. First, by measurement of physical loop lengths, either by direct observation of hypotonically decondensed chromosomes (Møens and Pearlman 1988; Zickler and Kleckner 1999) or by measuring the distance of hybridizing probes from the SC axis (Barlow and Hultén 1996; Tease and Hultén 2004; Novak et al. 2008; Gruhn et al. 2013). Measurements of physical loop lengths have revealed substantial differences in average loop length between species (Møens and Pearlman 1988; Zickler and Kleckner 1999; Kleckner 2006), the sexes (Tease and Hultén 2004; Gruhn et al. 2013; Wang et al. 2017), and meiotic nuclei across and within individuals (Wang et al. 2017). However, these measurements have also revealed that loop lengths *within* individual meiotic nuclei are remarkably uniform (e.g., Keyl 1975; Pukkila and Lu 1985; Møens and Pearlman 1988; Lu 1993; Novak et al. 2008; reviewed in Zickler and Kleckner 1999). For example, Novak et al. (2008) used FISH probes to measure physical loop lengths along chromosome 1 in mouse pachytene oocytes and report that, while the average loop length for this chromosome in wild-type oocytes is about 6μm, the longest loops along the chromosome are typically only $\sim 0.5\mu$m longer than this. Average physical loop lengths do not appear to vary systematically across chromosomes either (though see discussion below of euchromatin vs. heterochromatin, and telomeres). Using the distance of FISH probes from the SC axis as a proxy for loop length, Gruhn et al. (2013) find for human chromosomes 1, 16, and 21 that average physical loop lengths are approximately equal for these chromosomes within each sex (though they differ substantially between the sexes).

Second, the average genomic length of loops can be deduced given observation of axis

lengths and knowledge of the genomic length of the DNA packed along them (this is a more direct measurement of the average packing ratio). This will typically give a measurement of average loop length at a cruder resolution than direct observation of physical loop length, but since for our purposes we are only interested in average loop lengths at the resolution of inter-crossover intervals, this is no problem. This method also avoids the possible objection that, while *physical* loop lengths may be approximately constant within a nucleus, there could be variation across loops in how the chromatin is packed within loops, leading to different *genomic* loop lengths (Zickler and Kleckner 1999). In general, we may argue that, if it could be shown by this method that the packing ratio within a nucleus does not vary systematically from chromosome to chromosome, then it should also not vary much from inter-crossover segment to inter-crossover segment, because the sizes of the segments and of the whole chromosomes are of the same order (this may not be true of small segments between terminal crossovers and chromosome tips, but these segments contribute negligibly to average r, and so unless the packing ratio in these small segments is much larger than in other segments—which is unlikely owing to the physical observations cited above—our approximation that the packing ratios are in fact about the same will scarcely alter our measurement of average r).

Evidence that this is indeed the case can be found in humans. Figure 4 uses SC length data from Gruhn et al. (2013) to plot, separately for males and females, the average SC length of ten chromosomes against their genomic lengths. The SC lengths are averaged across many nuclei, though the sets of nuclei used to measure the various chromosomes' average SC lengths do not exactly coincide. In each case, a straight line through the origin provides an excellent fit to the data, suggesting that the average packing ratio of each chromosome, averaged across many nuclei, is about the same. While the aggregate pattern in Figure 4 could in principle still be generated if there are systematic differences in the average packing ratios of chromosomes within individual nuclei—for example, if these systematic differences take the form of negative correlations between SC lengths of certain chromosome pairs within nuclei—this seems unlikely given that SC lengths of

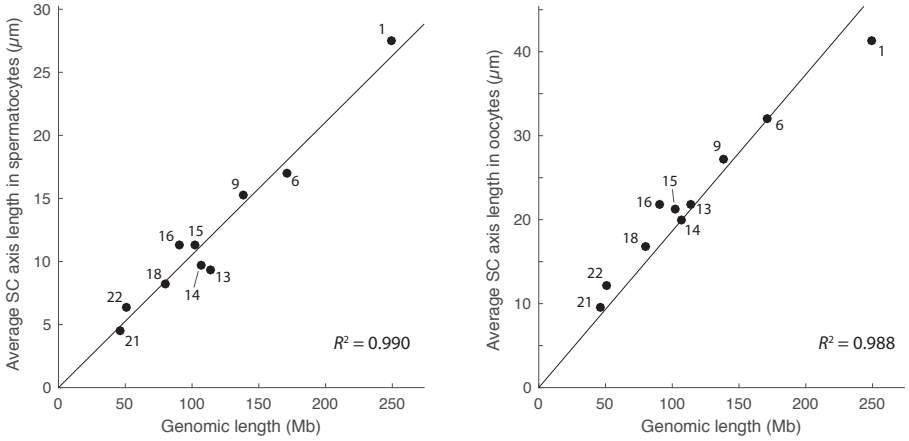

Figure 4: Average synaptonemal complex (SC) length of several human chromosomes plotted against their genomic length, separately for male and female pachytene meiotic nuclei. In each case, a straight line forced through the origin provides an excellent fit, suggesting that the average packing ratios (bp/μm) of the various chromosomes are approximately equal within each sex. We extrapolate this to infer that, in a given meiotic nucleus (male or female), the average packing ratios of inter-crossover segments are approximately equal. Since we have forced the regression through the origin, R^2 values are calculated as the sum of squares of fitted SC lengths divided by the sum of squares of observed SC lengths. Average SC length data are from Gruhn et al. (2013); genomic lengths of chromosomes are as reported in assembly GRCh38.p11 of the human reference genome (available online at www.ncbi.nlm.nih.gov/grc/human/data).

chromosomes within nuclei have been shown to be strongly *positively* correlated, an effect attributed to global per-nucleus modulation of loop lengths (Wang et al. 2017).

It has been reported from physical measurement that loops are more tightly associated with the SC, and therefore possibly shorter, in telomeric regions in some rodent spermatocytes (Heng et al. 1996), with this pattern also observed in human spermatocytes (Barlow and Hultén 1996) and oocytes (Barlow and Hultén 1998b). It has also been reported from DNA density measurement that loop lengths differ in heterochromatin and euchromatin, with loops in heterochromatic regions being two to four times longer (genomically) than those in euchromatin, at least in some plants (Zickler and Kleckner 1999), though this pattern was not observed among physical loop lengths in human spermatocytes (Barlow and Hultén 1996). The claim that loop lengths differ in heterochromatin and euchromatin is testable with aggregate data such as those displayed in Figure 4. If heterochromatin

at pachytene is indeed accommodated in loops with a greater average genomic length than is euchromatin, then the average SC length of the chromosomes should covary in a predictable way with their proportions of heterochromatin. Given the high degree of variation in heterochromatic content across human chromosomes, Figure 4 suggests that average pachytene loop lengths do not in fact vary greatly between euchromatin and heterochromatin in human spermatocytes and oocytes. A more formal analysis, for humans and other species, is in progress.

3.2 Examples of the measurement of average r from cytological data

Figure 5 shows the calculation of average r from cytological data, viz. spread immunostained pachytene chromosomes of a human spermatocyte (from Hassold et al. 2000) and a human oocyte (from Cheng et al. 2009).

For both males and females, average r is close to its maximum value of 1/2. This is due almost entirely to the independent assortment of different chromosomes: the inter-chromosomal component of average r is itself close to 1/2 in each case. In both cases, the intra-chromosomal component is dwarfed by the inter-chromosomal component: the portion of recombination that is due to independent assortment of chromosomes is greater than that due to crossing over by a factor of about 35 in the male and about 27 in the female. This reinforces the view that, in species with large haploid numbers, almost all genetic shuffling occurs according to Mendel's Second Law.

Because the X chromosome is included in the calculation for the oocyte, the inter-chromosomal components of average r for the spermatocyte and oocyte are not expected to be equal. In fact, their expected values can be calculated exactly from known genomic lengths of the chromosomes. Substituting the chromosome lengths reported in assembly GRCh38.p11 of the human reference genome (available online at www.ncbi.nlm.nih.gov/grc/human/data) into the first term in Eq. (4), we find that the value for the spermatocyte—i.e., just the autosomes—should be 0.4730, close to the value of 0.4744 calculated in Figure 5A, and the value for the oocyte—i.e., including the X chromosome—should be 0.4744, close to the

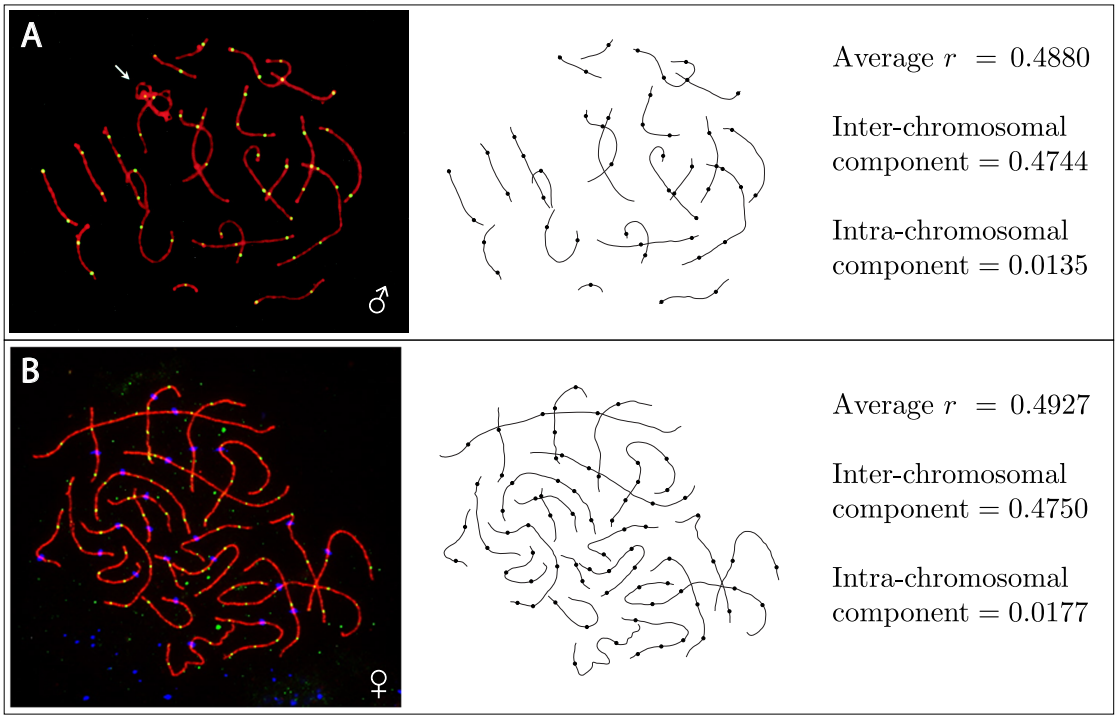

Figure 5: Calculation of average r from crossover patterns at meiosis I in humans. The left panels are micrographs of immunostained spreads of a pachytene spermatocyte (A) and a pachytene oocyte (B). The red lines show localization of synaptonemal complex protein SYCP3, and demarcate the structural axes of the chromosomes. The green dots show foci of the protein MLH1, and demarcate the positions of crossover associations along the axes. The white arrow in (A) points to the paired X and Y chromosomes (the 'sex body'). In (B), the blue dots along the chromosome axes mark the centromeres. The paired X chromosomes in (B) have not been identified, and are included in the calculation of average r. The central panels show the traced axes and crossover positions from the spreads. From these, the relative physical lengths of the segments separated by the crossovers can be measured (these measurements can be found in Supplement File S1). These relative physical lengths can be taken to be approximately equal to relative genomic lengths, from the arguments given in Section 3.1. With these relative genomic lengths, average r may be calculated for each spread according to Eq. (1), and its inter- and intra-chromosomal components determined according to Eq. (4). The results of these calculations are given in the right panels. The left panels of (A) and (B) are modified, with permission, from Hassold et al. (2000) and Cheng et al. (2009) respectively.

value of 0.4750 calculated in Figure 5B. This concordance between the exact values and those deduced from the cytological spreads is not unexpected, given the general arguments in Section 3.1 and the data displayed in Figure 4.

Though the female spread exhibits about 50% more crossovers than the male spread (74

vs. 48), the intra-chromosomal component of average r for the female spread is only about 30% larger than that of the male spread. This is expected from the general arguments given in Section 2.2.

Gruhn et al. (2013) generate a rich data set of the positions of MLH1 foci along pachytene synaptonemal complexes in human oocytes and spermatocytes, focusing on chromosomes 1, 6, 9, 13, 14, 15, 16, 18, 21, and 22. These data can be accessed at the *Cell* website for the paper of Wang et al. (2017). Since data were not collected for all chromosomes, we cannot use these data to calculate a genome-wide measure of average r. However, we can calculate average values for the individual intra-chromosomal contributions to average r of these particular chromosomes, and compare the values for oocytes and spermatocytes. The results of these calculations are given in Table 1 (MATLAB code for these calculations is given in Supplement File S2).

The average intra-chromosomal contribution to average r of each chromosome is greater in oocytes than in spermatocytes, as is the average number of crossovers. Chromosomes 14 and 15 show the smallest male-female difference in intra-chromosomal recombination, with the value in oocytes exceeding that in spermatocytes by 11% and 7% respectively. Sensibly, these chromosomes also exhibit some of the smallest differences in average crossover numbers between the sexes: the average number of crossovers on chromosomes 14 and 15 in oocytes exceeds the values in spermatocytes by 15% and 17% respectively. Curiously, chromosome 1 shows a similarly small difference between the sexes in its intra-chromosomal contribution to average r (12% higher in oocytes), despite also showing the greatest difference between the sexes in average crossover number (57% higher in oocytes). This is presumably due, in part, to the sub-linear increase of the intra-chromosomal contribution to average r with crossover number, as explained in Section 2.2: chromosome 1, being the longest chromosome, also has the greatest average number of crossovers in both sexes.

Table 1: Average crossover frequencies and contributions to the intra-chromosomal component of average r for ten chromosomes, in both human female and male meiocytes. Values are calculated from data from cytological observation of MLH1 foci in pachytene oocytes and spermatocytes, collected by Gruhn et al. (2013).

	# meiocytes		Average # crossovers			Average contribution to intra-chromosomal average r		
Chrom.	♀	♂	♀	♂	♀/♂	♀ ($\times 10^4$)	♂ ($\times 10^4$)	♀/♂
1	83	139	5.87	3.75	1.57	28.32	25.36	1.12
6	30	174	3.67	2.56	1.43	11.77	9.14	1.29
9	34	58	2.82	2.50	1.13	6.95	6.08	1.14
13	109	139	2.74	1.90	1.44	4.98	4.10	1.21
14	70	142	2.19	1.89	1.15	4.00	3.61	1.11
15	45	130	2.31	1.97	1.17	3.48	3.26	1.07
16	63	204	2.56	1.99	1.29	2.85	2.36	1.21
18	100	187	2.53	1.80	1.41	2.37	1.76	1.34
21	218	302	1.32	1.03	1.27	0.63	0.53	1.19
22	161	313	1.52	1.24	1.22	0.81	0.63	1.29

4 Estimation of average r from sequence data

The genomic positions of crossovers in an individual's meioses can be inferred at a high resolution by sequencing the products of those meioses—either by directly sequencing gametes or polar bodies, or inferring gametic genomes by sequencing diploid offspring—provided the individual's diploid genome has been haplophased. This haplophasing can be achieved either by sequencing an extended pedigree involving the individual (Broman et al. 1998; Cheung et al. 2007; Handyside et al. 2010), by sequencing multiple offspring, gametes, and/or polar bodies of the individual (Kong et al. 2002; Coop et al. 2008; Chowdhury et al. 2009; Lu et al. 2012; Hou et al. 2013; Ottolini et al. 2015), or by isolating individual chromosomes from a somatic cell and sequencing them separately (Fan et al. 2011; Wang et al. 2012).

Below, we provide examples of calculation of average r from such data. Before then, it is important to note that crossover distributions derived from pooled sequencing data cannot be used to calculate average r. Such distributions have been obtained, for ex-

ample, from pooled sperm samples [reviewed in Jeffreys et al. (2004)] and from patterns of linkage disequilibrium in population sequence data [reviewed in Coop and Przeworski (2007)]. Data generated in this way have been very useful, for example in identifying recombination hotspots at a high genomic resolution [e.g., Myers et al. (2005)], but cannot be used to calculate average r. This is because different distributions of crossovers at the individual level, each associated with a different value of average r, can give rise to the same population-level aggregate distribution (a simple example is given in Figure 6). Therefore, average r is not well-defined in aggregate crossover distribution data. This problem arises because pooled distributions do not retain information about the dependence of crossover positions on one another within individual meioses (i.e., the effect of crossover interference).

4.1 Examples of the measurement of average r from sequencing data

Lu et al. (2012) sequenced 99 individual sperm cells of a healthy Asian male, in his late forties and with children. They used an algorithm to haplophase the individual directly from the gametic sequences (based on the fact that a crossover between adjacent heterozygous markers is unlikely to occur in many gametes in their sample), and validated this by sequencing the individual's parents (which also allows the grand-parental origin of the various parts of the gametic sequences to be discerned). Figure 7A is a modified version of Figure 2A from Lu et al. (2012), showing the grand-maternal and grand-paternal regions of the genome of a single sequenced sperm cell, and allowing us to measure the proportions of each directly. Carrying out this measurement reveals a proportion $p = 0.5295$ of the sperm's autosomal genome to be grand-paternal in origin, which value we substitute into Eq. (2) to yield a measure of average $r = 0.4983$ for this particular sperm cell (all calculations for this cell are detailed in Supplement File S3).

We may further determine the grand-paternal portion of each autosome in the sperm cell, and substitute these proportions into Eq. (5) to determine the inter- and intra-chromosomal components of average r for the sperm cell. Carrying out this calculation

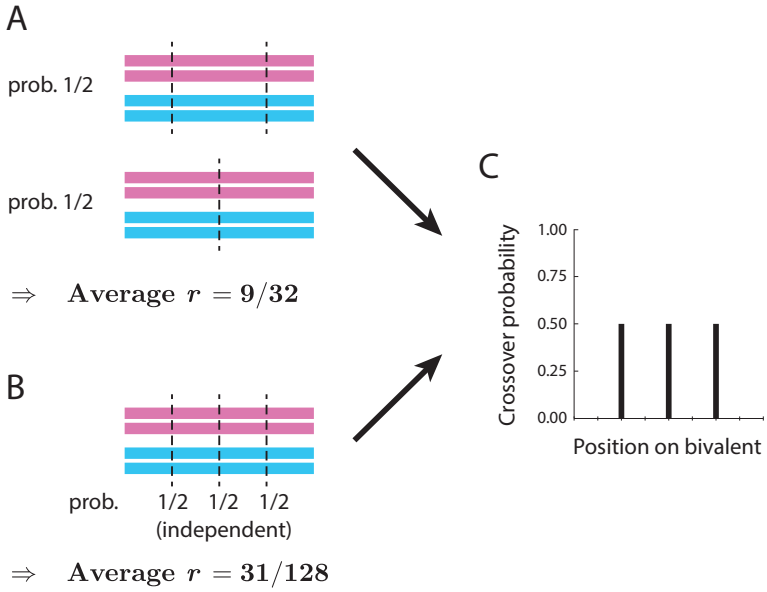

Figure 6: Average r is not well defined in aggregate crossover distributions generated from pooled sequencing data. The individual crossover distributions at meiosis I in (A) and (B) are associated with different values of average r, but give rise to the same aggregate crossover distribution, displayed in (C). The individual distribution in (A) is reminiscent of the effect of crossover interference: two crossovers can occur along the bivalent only if they are both terminally located; a central crossover 'crowds out' other crossovers along the bivalent. Notice that, in (A), the ends of the chromosome are always separated by at least one crossover, so that they recombine in a gamete with probability 1/2. In (B), on the other hand, there is a probability of 1/8 that no crossover separates the ends of the chromosome, so that they recombine in a gamete with probability less than 1/2. The recombination rate of loci at opposite ends of the chromosome therefore cannot be deduced from the pooled distribution in (C).

yields an inter-chromosomal component of 0.4785 and an intra-chromosomal component of 0.0197. The value for the inter-chromosomal component is high relative to the expectation that we may calculate from the known genomic lengths of the human autosomes (e.g., the value of 0.4730 that we calculated in Section 3 using autosome lengths from the human reference genome), which is a result of a very even segregation of grand-maternal and grand-paternal genetic material to this particular sperm cell. The value of the intra-chromosomal component of average r for this sperm cell is also unusually high, relative, for example, to the value calculated for the spermatocyte spread in Figure 5A, and to the maximum value among 91 sequenced sperm cells of the male described in the next

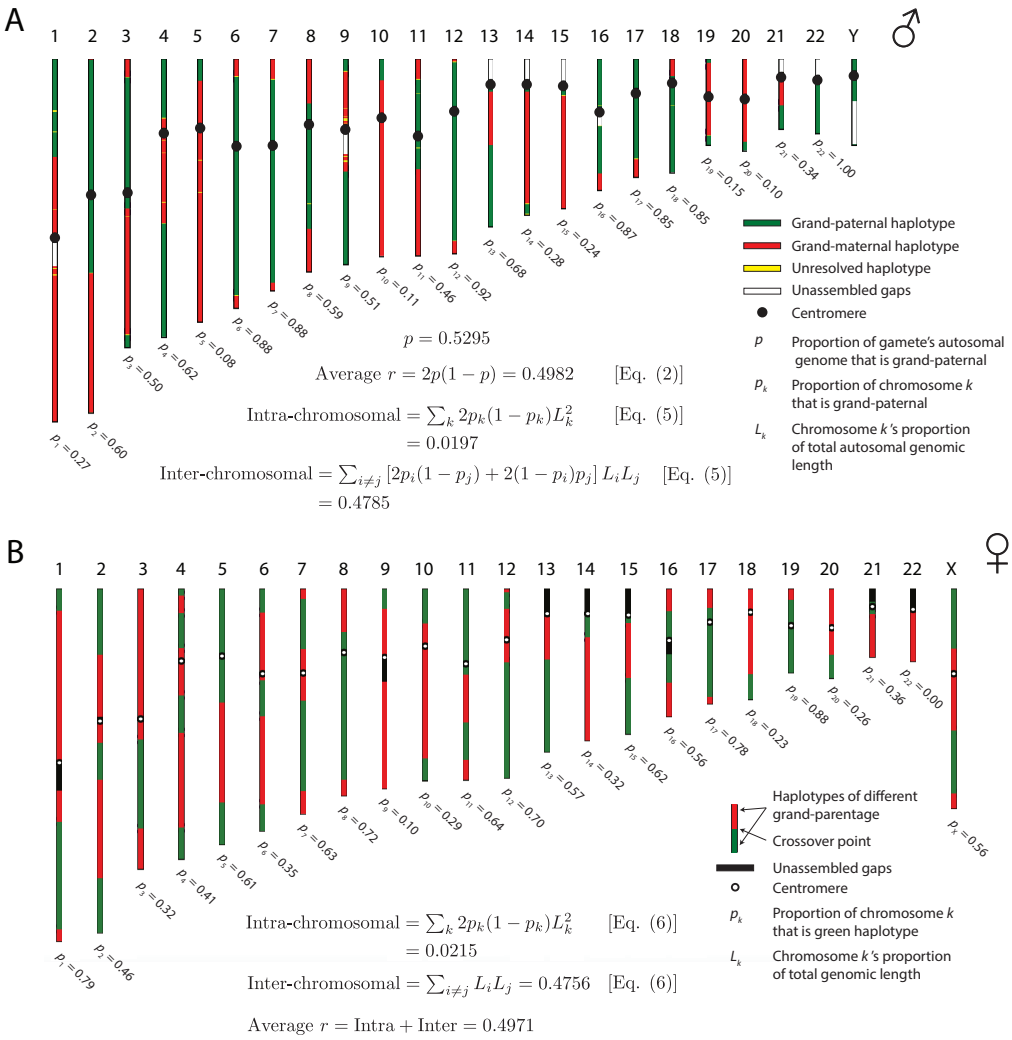

Figure 7: Calculation of average r from individual gamete sequences obtained from haplophased individuals. (A) Points of recombination in the sequence of a sperm cell from a haplophased human male. The individual's parents have also been sequenced, and so the haplotypes separated by the recombination points can be identified as grand-paternal (green) or grand-maternal (red). Thus, we can calculate exactly what proportion of the sperm's autosomal sequence is grand-paternal (p), allowing us to use Eq. (2) to calculate average r. (B) Points of recombination in the sequence of an egg from a haplophased human female. With no sequencing of an extended pedigree, we cannot tell which of the haplotypes separated by recombination points are grand-maternal, and which are grand-paternal. Therefore, we cannot directly calculate p, the proportion of the egg's sequence that is grand-paternal. We can, however, for each chromosome k find the proportion p_k that is of one grand-parental origin (without knowing which), and then use Eq. (6) to calculate average r and its components. (A) and (B) are modified, with permission, from Lu et al. (2012) and Hou et al. (2013) respectively.

paragraph (though that male's average value is expected to be unusually low—see below). The unusually high value of the intra-chromosomal component of average r for the sperm cell displayed in Figure 7A derives in part from its large number of crossovers [34, compared, for example, to an average of 25.9 in Icelandic males (Kong et al. 2002) and 26.2 in Hutterite males (Coop et al. 2008)], but also from an unusually large number of centrally-placed crossovers, especially on the largest chromosomes (e.g., chromosomes 1, 2, and 3, compared with chromosomes 5, 6, and 7, whose crossover placements are more typical for human males).

Fan et al. (2011) haplophased a healthy, forty year-old Caucasian male with children by using microfluidic techniques to isolate his various chromosomes from somatic cells at mitotic metaphase, thus allowing homologs to be sequenced separately. Wang et al. (2012) sequenced 91 individual sperm cells from this individual, and used the haplophasing from Fan et al. (2011) to determine the points of recombination in each gametic sequence. The points of recombination for each gamete are given in Table S2 of Wang et al. (2012). Though the grand-parental origin of each segment separated by these recombination events cannot be determined, we may nonetheless use Eq. (6) to calculate average r and its components for the autosomal genome of each gamete, and then average this measure for all of the individual's sequenced gametes [or, more directly, we may use Eq. (8)].

Carrying out this calculation yields a value for average r, averaged across the individual's gametes, of 0.4856, with an average inter-chromosomal component of 0.4729, and an average intra-chromosomal component of 0.0127 (MATLAB code for these and the following calculations is provided in Supplement File S4). In calculating the inter-chromosomal component of average r, because some recombinant SNP positions for this individual exceeded the chromosome lengths of the human reference genome, we used the position of the last SNP on each chromosome [as reported by Fan et al. (2011) in their Supplemental Data Set 2] as our measure of that chromosome's genomic length in this individual. Because there is no information about the grand-parental origin of the sequences in each sperm, the inter-chromosomal component that we calculate is an average one, deduced

from the fixed genomic lengths of the individual's chromosomes [using Eq. (6)]. There is therefore no variance across gametes in this component. The estimated standard deviation of the intra-chromosomal component of average r across gametes is 0.0026, resulting in a coefficient of variation of about 0.2. The minimum value of the intra-chromosomal component across all 91 sperm is 0.0058; the maximum value is 0.0178. The intra-chromosomal component of this individual is expected to be lower than that for the population as a whole, as he is homozygous for a variant of the *RNF212* gene that, in homozygous form, is associated with a reduction of about 5-7.5% in crossover numbers in males (Kong et al. 2008; Chowdhury et al. 2009). Indeed, the 91 sperm show, on average, 22.8 crossovers each (minimum 12; maximum 32), as compared to the previously cited averages of 25.9 for Icelandic males (Kong et al. 2002) and 26.2 for Hutterite males (Coop et al. 2008).

Hou et al. (2013) sequenced the products (first polar bodies, second polar bodies, and ova) of several meioses of eight Asian females, all between twenty-five and thirty-five years old, healthy, and having had children from normal pregnancies. The individuals were all haplophased directly from the sequences of the products of their meioses, allowing the crossover points in those products to be determined. Figure 7B is a modified version of Figure S2 from Hou et al. (2013), showing the crossover points along the chromosomes of an egg cell from one of the individuals. Because relatives of the individual were not sequenced, the grand-paternal and grand-maternal sequences cannot be discerned [contrary to the legend of the figure as it appears in Hou et al. (2013)]. Therefore, calculation of average r proceeds according to Eq. (3), with its inter- and intra-chromosomal components determined according to Eq. (6). Carrying out this calculation for all chromosomes, including the X, reveals a value of average $r = 0.4971$, with an inter-chromosomal component of 0.4756 (calculated using relative chromosome lengths as they appear in Figure 7B) and an intra-chromosomal component of 0.0215 (all details in Supplement File S3). If we instead restrict attention to the autosomes, we find average $r = 0.4965$, with an inter-chromosomal component of 0.4735, and an intra-chromosomal component of 0.0230.

5 Related measures of total recombination

In the calculations above, we have focused on the average rate of recombination across locus pairs, average r. This is clearly a suitable measure of the total amount of genetic shuffling caused by recombination, aggregating, in a linear fashion, the rates of recombination between different locus pairs. However, certain population genetic properties exhibit non-linear dependence on the rates of recombination between loci. In quantifying these properties at an aggregate level, alternative measures may be more appropriate.

For example, theoretical studies have determined that certain allelic associations across loci can jointly increase in frequency only if their constituent loci recombine at a rate below a critical threshold value. For example, this has been shown for co-adapted gene complexes exhibiting positive fitness epistasis (Crow and Kimura 1965; Weinreich and Chao 2005; Neher and Shraiman 2009), for genetic complexes causing reproductive incompatibilities and reproductive isolation between populations (Felsenstein 1981; Barton and De Cara 2009), for selfish genetic complexes such as 'poison-antidote' gamete-killing haplotypes involved in meiotic drive (Hartl 1975; Liberman 1976; Charlesworth and Hartl 1978; Haig and Grafen 1991), and for associations between sex-determining genes and genes with sexually antagonistic fitness effects (Rice 1986; van Doorn and Kirkpatrick 2007, 2010).

For these cases, a more suitable measure of recombination would be the proportion of locus pairs that recombine below the critical threshold value. This would obviously require more data than the minimum required to calculate average r. For example, while average r, as we have shown, can be calculated from a single meiocyte in which crossover positions are known, to determine the average rate of recombination for specific locus pairs (so that, for each locus pair, this average can be compared to the threshold rate) requires observation of many meioses. Again, aggregate distributions of crossover positions from pooled population data are problematic here, since by not retaining information about the correlation of crossover positions in individual meioses (i.e., crossover interference), they cannot be used to calculate the proportion of meioses in which a given locus pair

recombines (Figure 6).

Measuring this quantity—the proportion of locus pairs that recombine below some critical rate—could be useful in a number of fields. In the case of meiotic drive, given some threshold recombination rate for the invasion of a gamete-killing complex, calculating the proportion of locus pairs that recombine below the threshold for a given species would be informative of how susceptible that species is to the invasion of such complexes. Measuring the quantity across chromosomes, or smaller genomic regions, would be informative of where such complexes are most likely to arise [for example, this could quantify the argument that two-locus meiotic drive complexes are more likely to be found near centromeres, where recombination is usually low (Burt and Trivers 2006)]. Similarly, transitions to or between heterogametic sex determining systems have been hypothesized to involve genetic complexes comprising sexually antagonistic genes and new sex determining genes, with these complexes required to recombine below some threshold rate to invade (Rice 1986; van Doorn and Kirkpatrick 2010). In a given species, measuring which chromosomes have the most locus pairs that recombine below this critical threshold value would tell us which, all else equal, are most likely to be co-opted as new sex chromosomes [a similar logic was articulated by Trivers (1988) for which of the sexes is more likely to bear the sex-specific chromosome in a heterogametic species].

Of course, more nuanced measures than this are possible. It is not the case, for example, that every complex formed by a new gene of major sex determining effect and a sexually antagonistic gene has the same threshold recombination rate below which it can invade; instead, the threshold recombination rate depends on the nature and degree of the sexual antagonism (Rice 1986; van Doorn and Kirkpatrick 2007, 2010). Similarly, the threshold recombination rate for a gamete-killing meiotic drive complex depends on the strength of the drive and other fitness effects associated with the complex (Hartl 1975; Charlesworth and Hartl 1978; Haig and Grafen 1991). Moreover, the binary outcomes of 'invasion' and 'no invasion' are peculiar to deterministic models of infinite populations. In reality, the relevant outcome to be quantified is the probability of establishment or fixation

of the complex—this is expected to be a continuous function of the rate of recombination within the complex as well as the various parameters associated with the complex. In this case, the most appropriate measure would involve finding the average of this probability of establishment or fixation, with this average taken across all locus pairs, and across an expected distribution of the parameters associated with the complex. We are, of course, not unaware of the potential difficulty of such calculations, but we suggest that their importance would justify the efforts required.

6 Discussion

Both the number and distribution of crossovers are known to differ systematically at all levels of comparison: between species, between the sexes, between individuals, and between different chromosomes. In the extensive literature that measures the amount of recombination that crossovers cause, usually only their number is taken into account. This is despite the fact that the distribution of crossovers also influences the amount of recombination that they cause, with terminal crossovers contributing little and central crossovers contributing much. Nor do standard measures (with the exception of the recombination index) take into account recombination caused by independent assortment of different chromosomes, despite chromosome number (and heterogeneity in their size) differing widely across species. We have studied a measure of total recombination that takes into account both the number of crossovers and their positions, as well as the independent assortment of different chromosomes: average r, the probability that a randomly chosen locus pair recombines in the formation of a gamete. We have demonstrated that average r can easily be calculated from cytological and sequencing data, enabled by recent methodological advances in both of these fields.

As a general measure of total recombination, average r obviously has wide applicability. One field where the dependence of total recombination on crossover position is especially relevant is that studying quantitative sex differences in recombination ('heterochiasmy'). In many species, both the number and distribution of crossovers differ between the sexes

[reviewed in Brandvain and Coop (2012)]. Separate evolutionary explanations have been offered for both facts [e.g., Trivers (1988), Lenormand (2003), and Lenormand and Dutheil (2005) for crossover number; Haig (2010) and Brandvain and Coop (2012) for crossover distribution]. A review of the empirical literature reveals that the sex with fewer crossovers often also tends to situate them terminally on chromosomes. For example, in many placental mammals, there are fewer crossovers in spermatogenesis than in oogenesis, and the distribution of crossovers in spermatogenesis is concentrated near the ends of the chromosomes, with a more even distribution in oogenesis [this pattern is well illustrated by humans (Broman et al. 1998) and mice (Liu et al. 2014)]. In several marsupials, however, this pattern is reversed: there are fewer crossovers in oogenesis than in spermatogenesis, and those in oogenesis tend to be terminally located, compared to a more uniform distribution in spermatogenesis (Bennett et al. 1986; Hayman et al. 1988). If this pattern is indeed a general one (and we should note that this awaits a thorough review), then it suggests that both crossover number and distribution work synergistically to reduce average r in one sex relative to the other. If so, separate evolutionary explanations for sex differences in crossover number and distribution might not be required. All of this is consistent with both phenomena having a common, conserved mechanistic basis, viz. shorter chromosome axis length at meiotic prophase in the sex with both reduced crossover number and terminal crossover distribution (Kleckner et al. 2003; Petkov et al. 2007). [This pattern has been suggested possibly to hold across species too: species with few crossovers also tend to situate them at the ends of chromosomes (Haag et al. in press). If so, then similar to the discussion above for heterochiasmy, both reduced number of crossovers and their terminal localization could be explained by common selection for reducing average r.]

Another field where average r could find use is that around the evolutionary advantages of recombination and sex. Comparative studies in this field often seek ecological, morphological, or life history correlates of total recombination. For example, Bell (1982) studies correlates of haploid chromosome number within the plant genus *Carex*, finding, among other things, that chromosome number shows a strong positive correlation with allocation

of resources to reproduction, specifically in terms of number, not size, of propagules. Burt and Bell (1987) show that excess crossover frequency (the number of crossovers in excess of the haploid number) correlates positively with (the logarithm of) generation time in non-domesticated mammals, and interpret this pattern as evidence in favor of the Red Queen theory of recombination, that it serves to combat rapidly evolving parasites (who, in a longer-lived host, have more generations to evolve resistance to the host's defenses). These measures of total recombination, haploid chromosome number (as a measure of inter-chromosomal recombination) and excess crossover frequency, were used because of the availability of such data at the time. However, as we have argued, these measures can at best be thought of as proxies for total recombination. With the growing availability of data such as those used to calculate average r in Sections 3 and 4, carrying out comparative studies using average r as the measure of total recombination will become possible.

Especially interesting in this regard would be to study, given a potential biological correlate of recombination rate, whether the inter- or intra-chromosomal component of total recombination is a stronger correlate [we have formulated these components in Eqs. (4) and (5)]. It has often been argued that inter-chromosomal recombination contributes more to total recombination (Bell 1982; Crow 1988), but chromosome number exhibits a high degree of evolutionary inertia (Burt and Bell 1987; but see de Villena and Sapienza 2001), while the number and location of crossovers have been shown to change on relatively short evolutionary timescales [e.g., Watson and Callan (1963); Weissman (1976); Dumont and Payseur (2011a,b)], implying that the intra-chromosomal component of total recombination is able to evolve more rapidly. Moreover, as Burt (2000) has argued, while inter-chromosomal recombination is the dominant source of total recombination, intra-chromosomal recombination is more important for reducing allelic correlations across loci over many generations. Some theories of the adaptive purpose of sex and recombination involve the 'raw' recombination rate, of which average r is the appropriate measure, and to which inter-chromosomal recombination contributes most—the Tangled Bank (Ghiselin

1974; Bell 1982) and sib-competition (Williams 1975; Maynard Smith 1976) theories would seem to be in this category (generally speaking, those theories that posit a short-term advantage to sex). Other theories, such as those of the Fisher-Muller variety (Fisher 1930; Muller 1932, 1964; Felsenstein 1974) and those involving low-frequency fluctuations in the selective environment (Sasaki and Iwasa 1987) [including some models of the Red Queen hypothesis (Hamilton et al. 1990)], require only small rates of recombination between loci for recombination to have its full adaptive effect, and so intra-chromosomal recombination might be more important (Burt 2000). These latter theories involve medium- or long-term advantages to sex. In comparative studies, we might therefore expect inter-chromosomal recombination to be a stronger correlate of whichever biological variable we are studying if one of the short-term-advantage theories is true, while intra-chromosomal recombination should be a stronger correlate under theories of a medium- or long-term advantage. Alternatively, we should expect average r to be a stronger correlate under the short-term theories, and a threshold-based measure (as described in Section 5) to be a stronger correlate under the medium- and long-term theories.

Average r, as we have defined it, treats all regions of equal genomic length as of the same importance in the calculation. However, the quantity we are trying to measure is really the amount of shuffling of functional genetic elements—it is for most purposes irrelevant if two functionless pseudogenes recombine, for example. Therefore, correcting the calculation of average r to account for gene density is an important extension, a point already noted by Burt et al. (1991). This is especially so if the distribution of genes is non-random along or across chromosomes. Accounting for the gene densities of different genomic regions would be easiest with sequencing data, especially in species with well-annotated genomes. For species without well-annotated genomes, proxies of the gene density of genomic regions, such as euchromatin content or GC-richness, could be used. Accounting for gene density with cytological data would be more complicated, since it requires knowledge of the identity and orientation of the various chromosomes. At a crude resolution, this can be achieved with chromosome-specific FISH probes (and, if required,

centromere immunolocalization). Finer-scale identification of different genomic regions in cytological spreads could be achieved using high-resolution FISH (Beliveau et al. 2012, 2015; Wang et al. 2016). In any case, the usual problems would arise in deciding which parts of the genome are 'functional' [see Eddy (2012, 2013) for reviews of recent debates on this topic].

One potential drawback of measuring average r is that the data required, such as the cytological spreads described in Section 3 and the gametic genome sequences described in Section 4, are often laborious or expensive to obtain in large quantities. This will limit the sample sizes available, especially in non-model organisms on which smaller numbers of researchers work. The beam-film model (Kleckner et al. 2004) is a physical model of crossing over that, when computationally calibrated (White et al. 2016), has been shown to accurately reproduce crossover distributions in various taxa and across the sexes (Zhang et al. 2014; Wang et al. 2017). The model can be calibrated given limited input data, after which large data sets of crossovers can be simulated; from these, average r and its components can be calculated. Tweaking various parameters in the model, such as the strength of crossover interference, would also allow study of how these parameters influence average r. The large data sets that could be generated with the beam-film model would be especially useful in estimating the threshold-based measures of total recombination discussed in Section 5. The beam-film model can also be used in other ways in the calculation of average r. We have suggested that, among cytological data, pachytene meiocytes stained for foci of the protein MLH1 be used in calculating average r. As we have noted, MLH1 foci mark the sites of type I (interfering) crossovers, but not type II (non-interfering) crossovers. In cases where MLH1 foci are used to calculate average r, the beam-film model can be used to 'sprinkle' type II crossovers onto the pachytene spreads (Zhang et al. 2014; White et al. 2016) [for which purpose the incidence and properties of type II crossovers can be inferred using genetic (Mancera et al. 2008; Stahl and Foss 2010) or cytological (Anderson et al. 2014) methods].

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