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# Discussion Draft v1

To place our results in the broader context of recombination rate variation we examine three modifier models and two functional and cell physiology models (table X). While there are challenges to fitting models built under different assumptions, we feel it’s a useful exercise to highlight any unifying patterns for our specific traits across exsisting models. The three modifier models were built to explain variation in genome wide recombination rates between sexes (heterochiasmy), while the chromosome ocillatory movement (COM) model was built to describe positive interference. This spindle based selection model was developed to explain the results resented in this manuscript. In cases where the models can’t be extended to predicting results, we list a ‘NA’ for the prediction.

### Evolution of reversed heterochiasmy direction

The direction of heterochiasmy under the two locus modifier model is dependent on female specific recombination modifier suppresses or increases recombination, if the modifier is linked to the driving locus, and the meiotic stage (reduction or equatorial division) when the driver acts (see Table 1 of Brandvain and Coop (2012)).

Under the spindle based model, faster male evolution of the genome wide recombination rate, is primarily driven by a more efficient spindle assembly checkpoint (SAC) acting on chromosome structures at metaphase I alignment. The SAC prevents anueploidy by ensuring all bivalents are correctly attached to the microtubulue, (bi-orientated) spindle before starting the metaphase-to-anaphase transition ((Lane and Kauppi 2019), subramanian and Hochwagen , J. Dumont and Desai (2012)).

A stable chromosome structure requires, i) kinetochores attached to opposite poles of the cells and ii) at least one crossover to create tension across a proportion of sister cohesion (Lane and Kauppi 2019). Unstable bivalents on the meiosis I spindle, cause the SAC to delay anaphase and allow time for the bivalent to stabilize on the microtubule spindle. If they fail to attach, the SAC triggers apoptosis. Genetic variants which increase the number of unstable bivalents (such as those affecting recombination rate or cohesion), will be selected against in favor for genetic variants causing faster stabilization of bivalents on the MI spindle. Multiple lines of evidence indicate that the effectiveness of SAC in spermatogenesis is greater compared to oogenesis ((Lane and Kauppi 2019), Subrahman). These differences in SAC strength have been connected to conserved features of gametogenesis; centrosome spindle (So et al. (2019), J. Dumont and Desai (2012)) and cell volume (Kyogoku and Kitajima 2017). This model nominates conserved differences in in the context of meiosis between males and females as the primary source of distinct evolutionary trajectories in genome wide recombination rates.

In our results and more generally in the literature, female biased heterochiasmy is the most common pattern, however male biased heterochiasmy is not especially rare (Brandvain and Coop 2012). Our results extend previous reports of male biased heterochiasmy (B. L. Dumont and Payseur 2011) to new subspecies of house mouse (*molossinus*) and emphasize the short evolutionary period. Whether these instances of evolution of genome-wide recombination rates are due to independent events or segregating genetic variation within house mouse subspecies requires further study. Regardless, the faster male evolution in genome-wide recombination rates suggests that even for species in female biased heterochiasmy species, selecting for higher male specific genome wide recombination rates may be the most effective way to increase the sex-averaged recombination rate for a genetic background. This insight could be important for animal breeding programs (Battagin et al. 2016).

### Conservation in sexual dimorphism in between cell variation in crossover number

In the spindle based selection model, the less efficient SAC in oocytes leads to relaxed selection on the metaphase I chromosome structure. This will result in increased variance in chromosome structure and crossover number per cell, not just across strains, but across cells within individuals. Oocytes at metaphase I, have an acentriolar spindle comprised of diffuse network of microtubules with multiple microtubule organizing centers (Schuh and Ellenberg 2007). Centrosomes spindles are in spermatogensis and mature sperm cells delivers centrioles (most mammals) or centrosome material (rodents and rabbits) to the egg during fertilization (Manandhar, Schatten, and Sutovsky (2005)). This is another way the spindle based selection model is linked to conserved sex differences in gametogenesis (Ross and Normark 2015).

Regardless of whether these hypotheses are true, our results further support the results of females having greater variation in the number of crossovers across cells in mice and humans (Lynn et al. 2002, Gruhn et al. (2013)). This feature of heterochiasmy supports evolutionary theories predicting distinct reproductive strategies between females (diversifying offspring) and males (maintain successful haplotypes) (Trivers and others 2002).

### Conservation in sex-specific recombination landscape

As reviewed in (Sardell and Kirkpatrick 2020), sexual dimorphism in the broad scale recombination landscape is a highly conserved trait. The two locus modifier and SACE models predict sexual dimorphism in the broad scale recombination landscape, for diminishing the effect of drive systems and maintaining larger chromosome blocks under linkage in males respectively. The COM model, predicts the sex differences in the recombination landscape via interference is due to a combination of the length of the axis and differing strengths of chromosome movements during the pairing process (Hultén 2011).

Under the spindle based model we hypothesize that the sexual dimorphism in the recombination landscapes hinges on sex differences on the requirements for chromosome cohesion in late meiosis I. The irreversible process of the metaphase to anaphase transition is initiated by the protyltic decay of the sister cohesion connecting homologs (Lane and Kauppi 2019), subramanian and Hochwagen , J. Dumont and Desai (2012)]. The number and placement of crossovers alter the distribution of sister cohesion and the resulting chromosome structure when bivalents are aligned and bi-oriented on the metaphase plate (Veen and Hawley 2003, Altendorfer et al. (2020)). Differences in timing of cell cycle between oogenesis and spermatogenesis imposes the the different selective pressures on how sister cohesion affects chromosome structure. Faster spermatogenesis may select for synchronization of the separation homologs (cite?). While in oogenesis, the slower cell cycle and multiple arrest stages may require chromosome structures with greater stability on the MI spindle, espicially for those with dicyate arrest (Lee 2019).

A consequence of the sexual dimorphism in broad scale recombination landscapes is that the male recombination pattern drives deviation from an uniform distribution in any sex averaged recombination landscape (Sardell and Kirkpatrick 2020). Elevation at the chromosome ends is a conserved trait across animals and plants and has a consequence of higher genetic diversity near chromosome ends (Haenel et al. 2018).

### Conservation of sex differences in chromatin structure

Our results from musculusMSM and musculusPWD demonstrate that chromatin compaction are uncoupled from the direction of heterochiasmy in house mice. These results slightly depart from predictions which nominate chromatin compaction as the primary driver of recombination rate variation (Petkov et al. 2007). Chromatin compaction could explain variation in heterochiasmy, which is driven by the disinct meiotic contexts across sexes but is a weak predictor for recombination rate variation within the sexes. Our results indicate the sexual dimorphism in chromatin compaction is conserved in house mouse (e.g. females have longer SC than males) and that the rapid male-specific evolution in crossover number per cell proceeded through another aspect of crossover regulation (see below).

Only the COM model predicts sexual dimorphism in chromatin structure and attributes the source to greater cell volume in oocytes. This prediction model might fit broader pattern such as in *Arabidopsis thalania* where pollen is the larger cell and has longer axis length (Cahoon and Libuda 2019).

As outlined in Haenel et al. (2018), sexual dimorphism in chromatin organization translates to interference strength measured in base pairs. Since more DNA is sequestered into the radial loops per unit of the central axis, chromatin organization with longer DNA loops (and shorter axis), as seen in males for mice (Petkov et al. 2007, Lynn et al. (2002)) and humans (Gruhn et al. 2013), interference strength measured in base pairs will be stronger compared to female linkage maps. The signal for interference is mediated though the chromosome axis (Zickler and Kleckner 2015), interference strength measured in micrometers of is conserved between sexes (Petkov et al. 2007). Stronger interference strength in base pairs for male specific linkage maps is indirect evidence that sexual dimorphism in chromatin organization however this has yet to be confirmed in cytological data from both sexes in species beyond mice and humans.

### Evolution of interference strength in males

Examples of evolution of interference strength are rare and may be complicated by changes in the underlying karyotype structure (Segura et al 2014). The general pattern of empirical measures of interference strength is that it has a negative correlation to the genome wide recombination rate (Otto and Payseur 2019). This fits the logic of the chromosome axis acting as the ‘real estate’ for DSBs and aligns with known molecular mechanisms (cite). Two examples of the opposite direction, a positive correlation of interference strength and genome-wide recombination rate, involve descriptions of observations at the single bivalent level; the between lab-raised and wild mice of *Peromyscus leucopus* from (Peterson, Miller, and Payseur 2019) or large effects on genome wide recombination rates across a short evolutionary differences; the within-sex comparison of two breeds of cattle with different genome wide recombination rates (Ma et al. 2015). We propose that there is a difference in resolution and power between these two groups of empirical results with the positive and negative relationship between genome wide recombination rates and interference strength.

We propose that the spindle based selection model can explain the positive correlation via selection on the amount of sister cohesion connecting homologs at metaphse. The evolution of genome wide recombination rates in our study is driven by a transition of the majority of bivalent having single crossovers to an enrichment of bivalents with two crossovers. All else being equal, interference strength would be expected to be equal or even weaker. Our results show that the two crossovers are spaced further apart when SC length is controlled for and chromosome size effects are minimized, in the strain enriched for two crossover bivalents. Assuming that chromatin compaction between pachtyene and metaphase is uniform along chromosomes, an outcome of this further spacing of two foci results in an increased area of sister cohesion connecting homologs (Figure X).

The COM model predicts that interference and the recombination landscape arises from known oscillatory movements during prophase, however it lacks a mechanism for a evolutionary based predictions. While the SACE modifier model does not explicitly model evolution of interference strength we note that a logical outcome of the main prediction of maintaining larger chromosome blocks in males, would be a recombination landscape with stronger interference strength.

We have focused on the model involving direct selection on the recombination pathway, which has an impact on the fitness of an individual, but we acknowledge connections to other models involving indirect selection on recombination rates which involve the fitness outcomes of offspring. A model from Goldstein et al, reviewed in (Otto and Payseur 2019) and Veller, Kleckner, and Nowak (2019), predict that interference strength evolves whenever increased recombination rates evolve. The simulations under this model indicate that the space across multiple loci or between multiple crossovers increases in a positive manner with the genome wide recombination rate. A distinguishing feature of this model from other modifer models is that the number of crossovers per chromosome is kept constant. Empiracally, the range of crossovers per chromosome is quite limited, 1-3, for the majority of chromosomes across most taxa (Otto and Payseur 2019, Stapley et al. (2017)). Constraining the number of crossovers per chromosome in models may fit empirical data better than those where recombination rate across an abstracted genetic space is unconstrained.

An expected consequence of our observed elevated genome-wide recombination rate is lower LD, which may increase the efficiency of selection and impact the dynamics of introgression. Given that the higher genome-wide recombination rates are paired with stronger interference these predicted pattern may have heterogeneous signal along chromosomes.

### Future steps

We make three suggestions for future steps in studying recombination variation. First consider the when comparing sex specific meiotic traits consider that evolutionary distinct trajectories due to the fundamental differences in gametogenesis. Second certain systems can be leveraged to overcome limitations inherent in some approached. For example, identifying chromosomes across cells in cytological data requires chromosome specific probes, (e.g. FISH) but chromosome specific data can be collected from organisms with diverse karyotypes (birds, peromyscus, humans) or backgrounds with Robertsonian trans-locations.

Third we encourage the cross-pollination of physiology based models and more abstract model such as population genetic models with testable hypotheses (Dapper Paysuer). A goal of such merging of models could be to connect empirical findings across scales.

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