0. This is how we are going to synthesize the results

We made a model and we will test hypothesis (if a number of traits can be produced following a number of models previously presented. We focus on models which make predictions for the evolution of heterochiasmy, since those are the primary results from this study.

1. Conserved heterochiasmy results

The genome wide recombination rates that is not the best characterization of heterochiasmy. The direction of heterochiasmy (or which sex has a greater genome wide recombination rate) is not conserved for the canonical pattern (female > male).

Instead we purpose that other chromosome and cell based traits which displayed **‘conserved patterns of sexual dimorphism’** are better indicators / descriptors of heterochiasmy.

1. Typical Landscape
2. Chromatin organization (interference strength is a consequence of DNA loop)
3. Between cell variance

Most all models we examined could predict the sexual dimorphism (for heterochiasmy)

(many of the models were built designed to primarily explain i) sex differences in genome wide recombination rates )

We

# Conserved Pattern, Heterochiasmy Results

The landscape aspects of heterochiasmy is more conserved than the genome wide rate differences. The conserved features are:

**1. Sexual dimorphism in broad scale recombination landscape**

The sexual dimorphism in broad scale crossover location (recombination landscape) is conserved in house mouse, with males having telomere bias and females having more uniform placement of crossovers along chromosomes. (Sardell Kirkpatrick 2019)

**2. Sexual dimorphism of within mouse variance for CO per cell**

We observe more between cell variance in females across all strains, beyond what is expected due to technical variance. The same pattern of sexual dimorphism for variance across crossover number per cell has been observed in humans (Lynn et al) and other inbred house mouse strains (Gruhn et al).

**2. Sexual dimorphism of chromatin configuration and interference strength**

This prediction combines the findings of chromatin compaction and interference differences which are intertwined by the transmission of interference along the chromosome axis and the inverse relationship chromatin compaction (axis length and DNA loop sizes).

Our results confirm those presented in Petkov et al 2004) …

In physical units (micro meters) (2D / SC length) the measures of interference are conserved across sexes in mouse, while the normalize measure of interfocal distances (IFD) suggest that males have stronger interference.

This is because the counting units are the BASES of DNA loops which is conserved along the 2D length of chromatin axis. When this space is transformed to account for all of the DNA base pairs which are sequestered into the DNA loops above the axis, the strength of interference will vary depending the on underlying chromatin structure.

The chromatin structure which has longer loops (and shorter axis) will have more DNA bps folded / sequestered into the DNA loops. Thus the strength of interference will be stronger because with each step (count) along the 2D axis,

more bases pairs are being skipped above the axis. (as outlined in Petkov 2004).

The conserved sexual dimorphism patterns above suggest there are distinct features of the recombination landscape in males and females (seen across many species and decoupled from the genome wide recombination rate. This in turn suggests distinct evolution trajectories for crossover counts per cell dependent on the cell being in spermatogenesis or oogenesis.

# Evolved Patterns, Predictors of Recombination rate evolution within (males)

A primary goal of this study was to identify additional meiotic traits which correlated with the faster evolution of genome wide recombination rate observed in males. We find that DSB number and interference strength were the strongest correlates to the increase in genome wide recombination rate evolution.

## A. Evolution of DSB number (and moderate support for SC length evolution)

<transition/ connection of conserved sexual dimorphism relationship for DSB #/ chromatin configuration (Lynn et al (female DSB estimates, Brick?)>

1. More DSBs in the high rec strains

2. The conserved ratios of DSB : CO implies that the increase in DSB numbers are accompanied by proportional increase in crossovers. This is evidence that shifts support away from the CO:NCO decision to an earlier prophase stage such as when the chromatin compaction is set up.

3. DSB number being driven by the number of chromatin loops which is positively correlated with axis length.

4. These results supported by the moderate support of longer SC length in the high rec males.

We have results that mirror those presented in Baier et al 2014, suggesting that the variation in MLH1 counts – across house mouse spermatocytes is due to the same mechanism, differences in chromatin configuration.

5. Reconcile the lack of stronger signal for SC length evolution in high and low rec male groups). The support is too weak due to the noise in our single bivalent data (no ability to track chromosomes across cells as in Baier et al). Even in the reduced bivalent dataset this is still a factor for our sample sizes.

## B. Evolution if interference strength, stronger inference observed in high recombining males

**I. Review results**

**1.** The strongest correlation with genome wide evolution in an increase in interference strength. The positive correlation is contrary to most expectations and empirical results, but we note that those are largely across longer time scales and genome wide averages.

2.The difference in interference patterns is driven by a paucity of short IFD observations in the high rec males. The short IFD drive down the mean IFDs in low rec strains, whereas the medians are similar.

3. Chromosome size effects are unlikely to cause this pattern since the IFD distributions show less variance in the high rec strains, which would have MORE Chromosomes (for example Chm1 to Chm9) compared to the low rec strains which have fewer 2Cos (presumably limited to large chromosomes (for example Chrm1 to Chrm5).

4. These results are different from the sex differences since the inferences measures are significantly different in both the raw and normalized IFD.

**II. Review the assumptions for measuring CO interference**

1. The logical model: Crossover interference is a mechanism of suppressing crossovers, negative relationship between interference strength and gwRR. More crossovers can fit along the chromosomes and results in more crossovers overall.
   1. Examples of empirical results supporting this pattern; Otto Payseur, gamma
   2. Caveats for gamma estimates, The assumptions for infinite space and (no upper and lower bounds for number of crossovers don’t fit realities of meiotic chromosomes and recombination landscape: i) finite chromosome length and ii) limited range of crossovers per chromosomes and crossover assurance.
2. Alternative interference characterization: i) the number of crossovers are held constant or prioritize crossover assurance and ii) generalize the rec landscape, (focus on how the rec landscape would change instead of the genome wide rate).

-The Goldstein et al results (reviewed in Otto and Payseur 2019), predict a positive correlation with interference strength and higher recombination rate. A modifier which changes the probability of the recombination landscape having 0 crossovers or 2 crossovers, (largely driven by crossover assurance).

3. Examples of empirical results which show this positive correlation

- cattle pedigree paper, comparison WITHIN sexes (Jersey to Holstein)

- Beth’s (PWD - CAST) F2 cross (Hannah’s IFD measures)

- Peromyscus Chromosome 1 (Peterson et al 2019)

# Model review for explaining results

(reference matrix of models by results)

**Two-locus (protect for drivers) (Brandvain and Coop)**

Asymmetric division of egg opens them up to meiotic drivers. Recombination modifiers for sex specific female landscape will decrease the chances of driving centromeres to segregate to the egg by increasing the number of crossovers and placing them across a larger area of the genome (uniform placement).

**Gamete selection (or haploid selection) (Lenormand 2003, Lenormand and Duthiel 2005)**

The sex with more variance in reproductive fitness will have lower overall recombination rate.

**SACE (Sardell Kirkpatrick 2019)**

Extension of gamete selection. Assumes sex difference in strength and direction of epistasis. Results in large blocks of genetic areas/chromosomes being kept together in male meiosis. Reduce recombination between coding regions and regulatory elements.

**Sexual dimorphism in spindle and checkpoints for MI**

A fundamental difference in meiosis (MI) for males and females is the presence of the centrosome which serves as a nucleation site for MT at each pole and influences the shape of the spindle. My hypothesis for this model leading to distinct evolutionary trajectories for the gwRR in sperm and egg is that the tension in a centrosome spindle is stronger (or more uniform) since all MT-KT are anchored at single points at the cell poles.

This will also makes the spindle assembly checkpoint (SAC) stricter in smaller gametes with centrosomes during meiosis (sperm) and more sensitive to achiasmate bivalents on the spindle (correcting MT-KT attachments or triggering apoptosis). Whereas in the acentrosome spindle is more diffuse (multiple aMTOCs diffused across a larger area) resulting in less effective SAC, that is more achiasmate bivalents are required to trigger the SAC to stop division entry into anaphase. This is supported by the higher rates of aneuploidy in oocytes.

These physiology differences in meiocytes results in stronger selection on the recombination landscape in males compared to females. Which can produce directional pattern in male and relaxed selection on the gwRR (and recombination landscape) in males and females respectively.

1. Female have more random landscape (broad scale placement, weaker interference and greater between cell variance in crossover number) compared to males (telomere bias and stronger interference are less random). While the telomere bias in males may have evolved due to directional selection via the SAC towards an uniform tetrad structure across all of the bivalent pairs within a cell.

could be connected to the amount of sister cohesion – the tetrad structure at metaphase

1. Exceptions for canonical heterochiasmy landscape such as higher telomeric crossover positioning in females in marsupial could be connected to chromosome chains during meiosis (Gruetzner et al 2006).

A consequence of the stronger interference strength in the high rec males is that there is a greater amount proportion of the chromosomes/bivalents with sister cohesion under tension.

The bivalent /tetrad 3D structure at metaphase (spindle with tension) can be estimated based on the proportion of chromosome area predicted to be connected to a new centromere (DNA molecule) and has cohesion connecting it to its sister strand and original centromere from the number and placement of crossovers along the pachtyene chromosome.

Still unanswered questions regarding this model:

-What would drive the evolution between the groups of males?

-The high rec mice will have a mice of tetrad structures (single crossover and double crossover bivalents) what would cause this?

-Are there differences in segregation success for the two crossover bivalents with short IFD (in the low rec strains) and the two crossover bivalents with longer IFDs (in the high rec strains).

**Conclusion**

Spindle differences model is most parsimonious model given our results.

SACE is runner up, since it would always predict female biased heterochiasmy, but the positive correlation with gwRR and interference strength fits with maintaining larger chunks of chromosomes together in males.

# Future steps

* Sex average measures data can obscure distinct sex specific patterns
* Rethink how interference is measured