Human meiotic interference

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Abstract

While there exists strong evidence for the presence of positive crossover interference in humans, little work has been done to further measure the strength of this interference. Investigations of interference in experimental organisms, such as *Drosophila* and mice, have used the observed frequencies of rare multiple recombination events in sets of adjacent intervals. Such an approach requires many thousands of meioses, each informative for the same set of markers, a resource which is not readily available in humans.

We recently constructed new comprehensive human genetic maps, based upon nearly one million genotypes from eight CEPH families and incorporating over 8,000 STRP markers from several laboratories. These data are the best available resource to date for the study of interference in humans; they not only provide evidence for the presence of interference genome-wide, but also allow a characterization of the extent of human crossover interference and the derivation of an empirical map function.

Using these data, the number and locations of the recombination events on each chromosome may be estimated. The difference between the distribution of the number of recombination events per chromosome and that expected under no interference provides strong evidence for the presence of positive crossover interference in humans. In order to further characterize the strength of interference, we estimate the distribution of distances between recombination events by fitting a gamma renewal model to the underlying chiasma process. The results suggest that the level of interference in human meiosis is stronger than that corresponding to the commonly used Kosambi map function.

Why study interference?

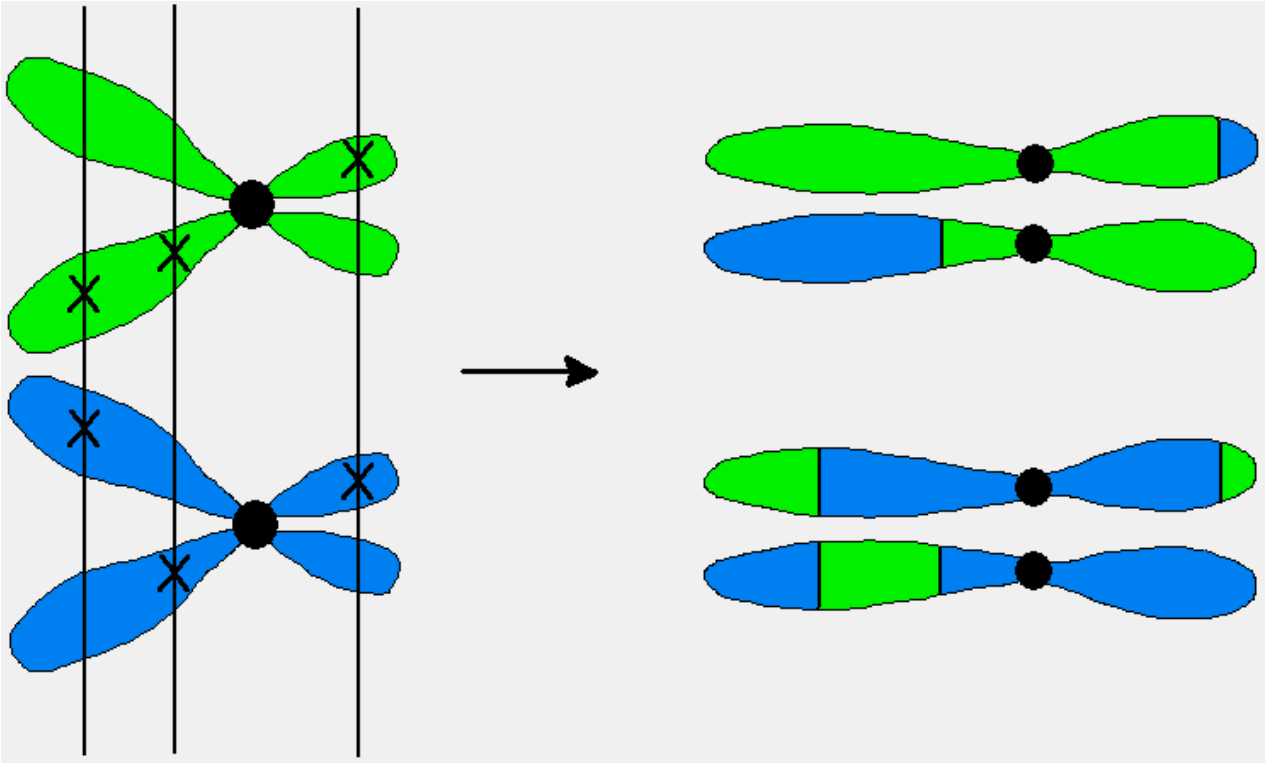
- Estimate the probability of a double crossover in a small interval
- Obtain a model of meiosis for simulation and analysis
- Compare human meiosis to that of other organisms

Goals

- Demonstrate the presence of interference in human meiosis
- Obtain an empirical map function
- Find a good model

New human genetic maps

- www.marshmed.org/genetics
- 8 CEPH families (92 progeny total)
- ~8,000 STRP markers
  - from Généthon, CHLC, Utah and others
  - removed “cryptic duplicates” (same polymorphism, different primers)
- Average spacing
  - female: 1.8 ± 1.5 cM
  - male: 1.5 ± 1.5 cM
  - sex-ave: 1.3 ± 1.0 cM
- Data cleaning
  - Removed 764/964,425 (~0.08%) genotypes resulting in tight double recombinants

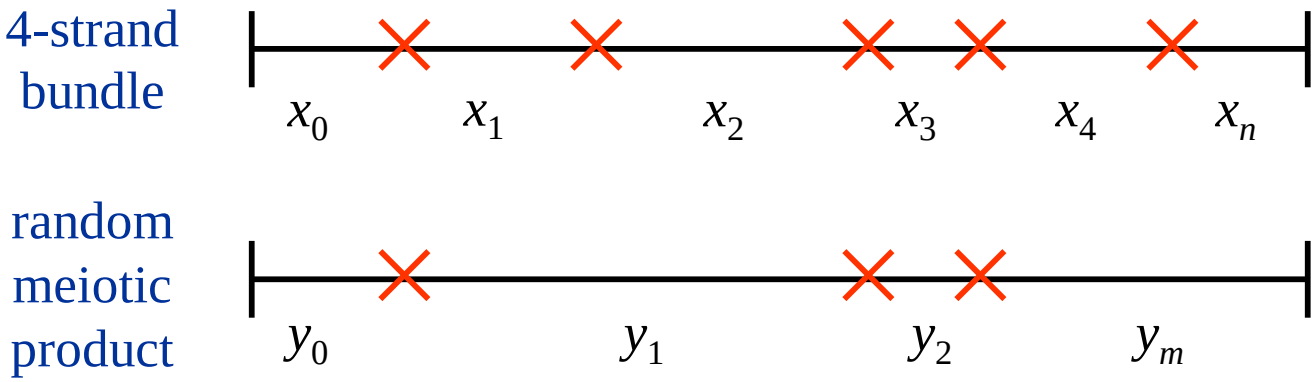


Chromatid interference:

The choice of strands involved in one chiasma depends on the strand choice in nearby chiasmata.

Crossover interference:

Chiasmata (and hence crossovers) tend not to be too close together.



No chromatid interference:

The crossover process is obtained by "thinning" the chiasma process: chiasmata are retained as crossovers independently with probability 1/2.

Count-location model:

The number of chiasmata, n, follows some distribution p. Given n, the locations of the chiasmata are iid uniform (with respect to genetic distance). **Under no interference, p = Poisson(λ).**

Gamma model:

The chiasmata positions follow a stationary gamma renewal process:

$x_1, x_2, \ldots \sim$ Gamma(shape = υ,rate = 2υ)

$x_0 \sim$ density $g = 2\,(1 - \mathrm{F})$
where F = cdf of Gamma(υ, 2υ)

$x_0, x_1, x_2, \ldots$ are independent

$y_1, y_2, \ldots \sim$ mixture of Gammas

$y_0 \sim$ mixture of g and Gammas

$y_0, y_1, y_2, \ldots$ are independent

$\upsilon = 1 \quad \Rightarrow$ no interference
$\upsilon > 1 \quad \Rightarrow$ positive interference
$\upsilon \approx 2.6 \quad \Rightarrow$ Kosambi map function

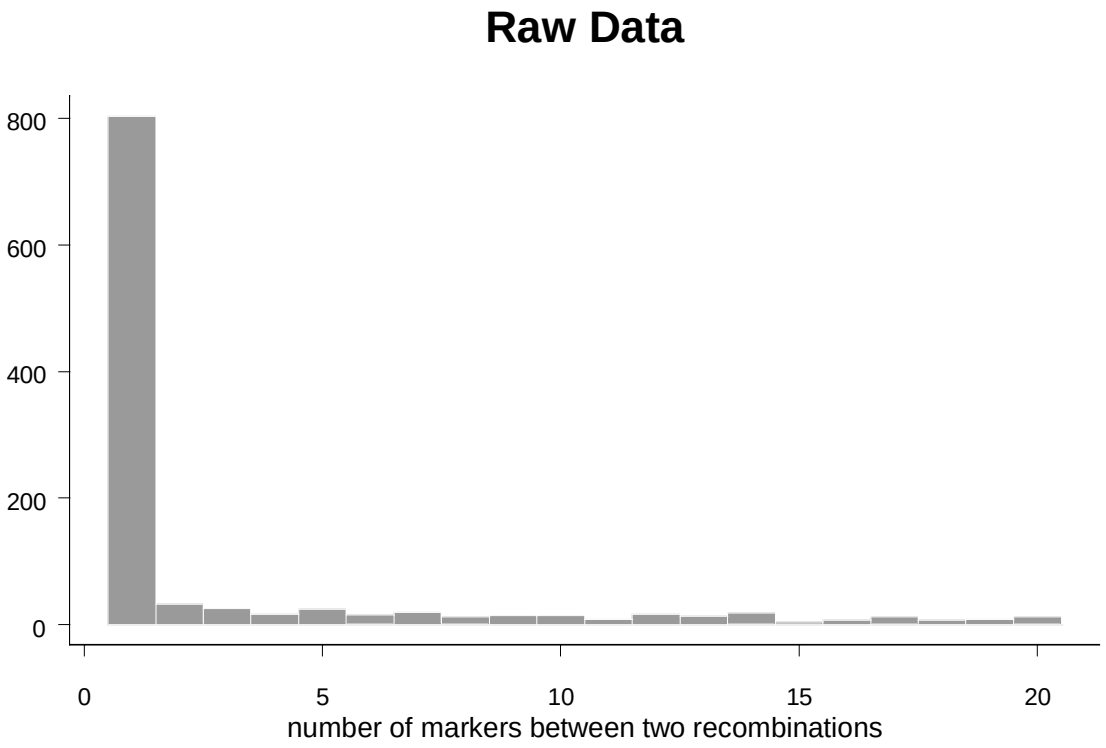
CRI-MAP chrompic output

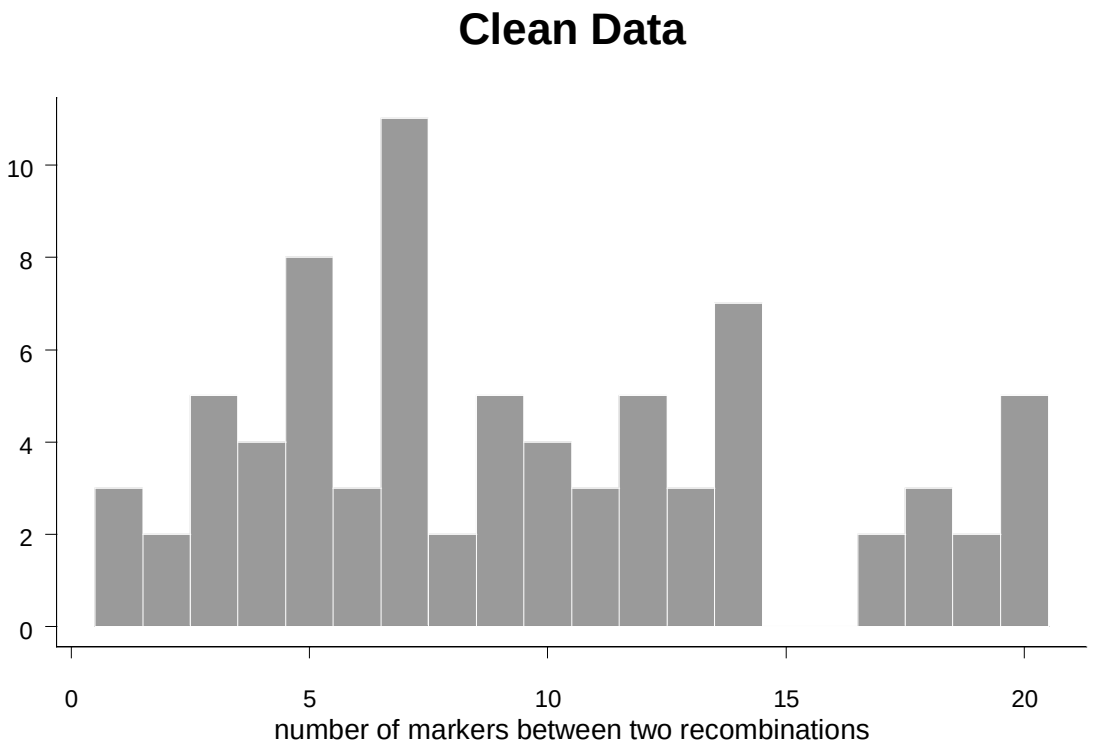
CEPH individual 1331–11

maternal chromosome 10

```
1111111--- 11-111-11- --11--111i
1-11---11- 111111--i- 11-1111-11
--11111-11 1111-11111 11--111111
111-111i-i 1111111111 10000-0-00
0--o00-000 0000-00000 0000--0000
0000--0000 0000-00000 o00-0--0--
--0-11-11- -111ii1i-1 ---1-i-1-i
1111-i--11 11111-11i1 -11i-11111
-1----i111 1i1111-111 -11i1-111-
11-111111i 111-i111i- 1111111-i-
1111111-1i 1i-111i11- 1i--1-11-1
111-1i-1-1 1-1----1-1 1i-1ii1i11
1i--1--1i- 11i11--111 11--1i111i
1i1i-11111 i-0---0000 00000-000o
o0-00o
```

Left tail of the distribution of # markers between recombinations





Distributions of # XOs / chr

Maternal chromosome 1

	0	1	2	3	4	5	> 5	X^2
observed	2	7	12	24	23	14	10	
Poisson	3	9	17	20	17	12	14	**9.2**
Count-location	2	7	14	22	23	16	9	0.8
Gamma	1	5	14	23	23	16	10	1.2

Maternal chromosome 4

	0	1	2	3	4	5	> 5	X^2
observed	1	16	**36**	15	15	9	0	
Poisson	7	18	23	20	13	7	4	**14.4**
Count-location	4	16	26	25	15	6	1	**12.8**
Gamma	4	15	26	24	15	6	1	**7.1**

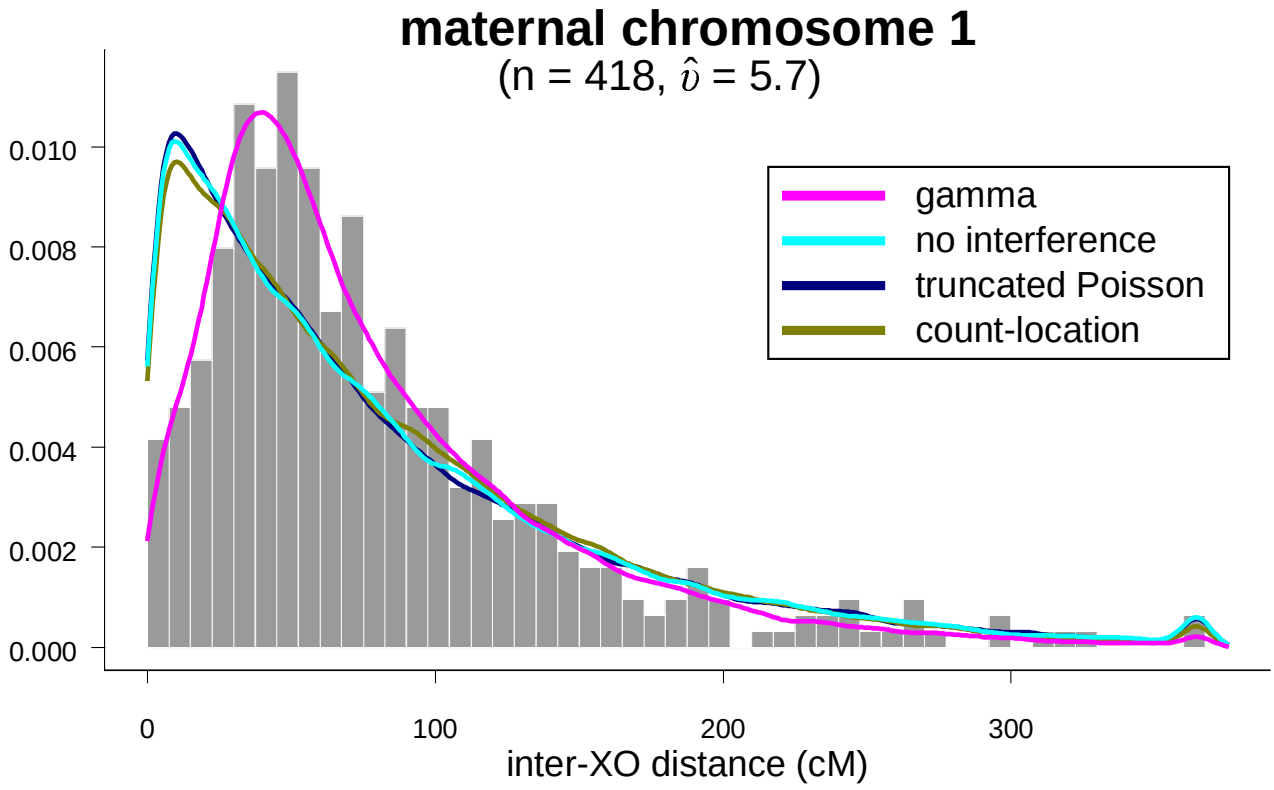
Paternal chromosome 1

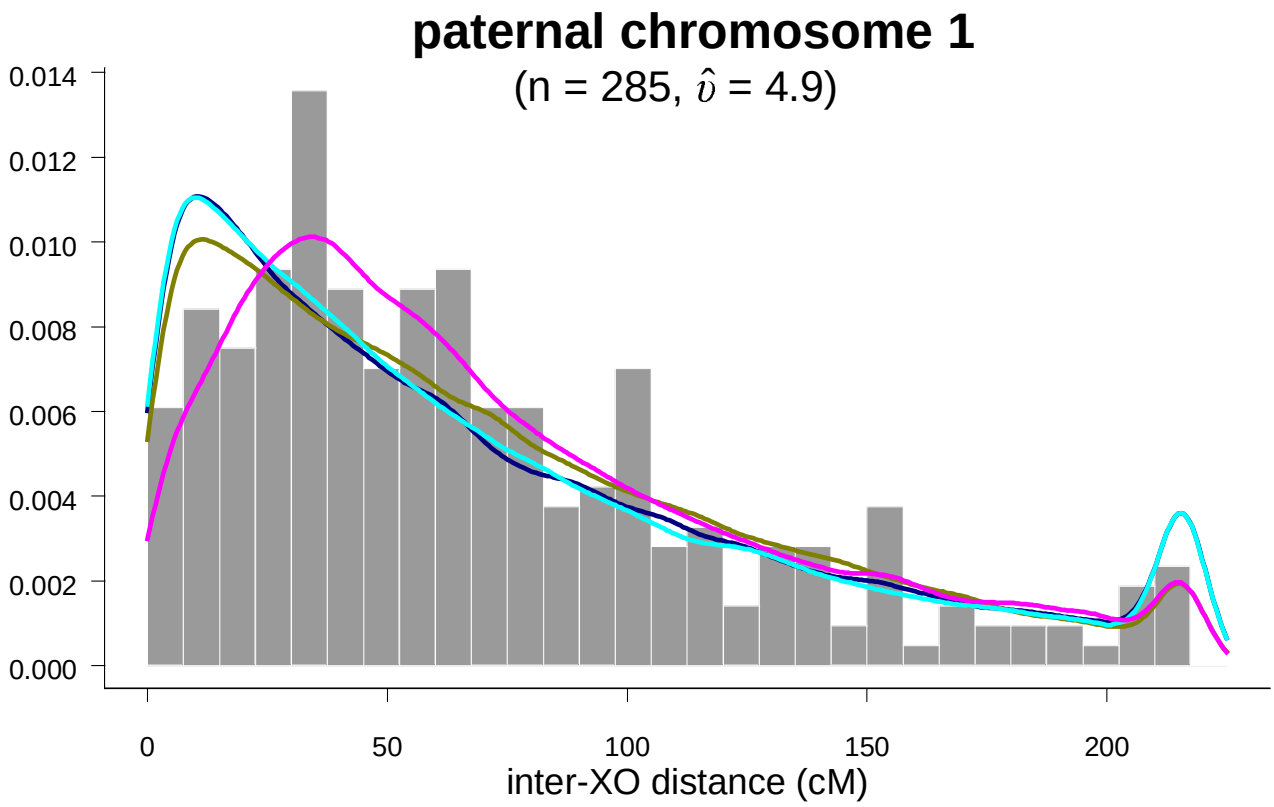
	0	1	2	3	4	5	> 5	X^2
observed	5	23	31	25	7	1	0	
Poisson	11	24	25	17	9	4	1	**12.8**
Count-location	6	22	33	23	8	1	0	0.4
Gamma	6	21	31	22	10	2	0	1.9

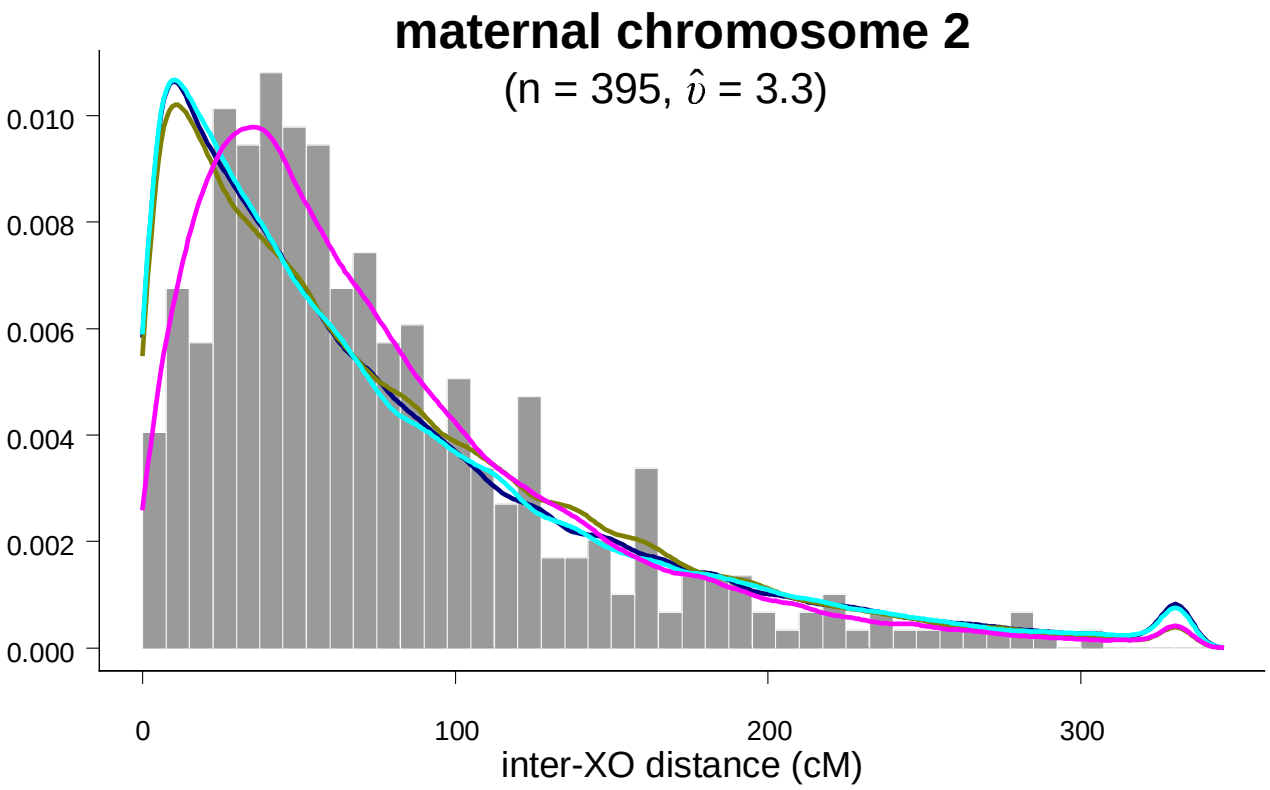
Evidence for interference:

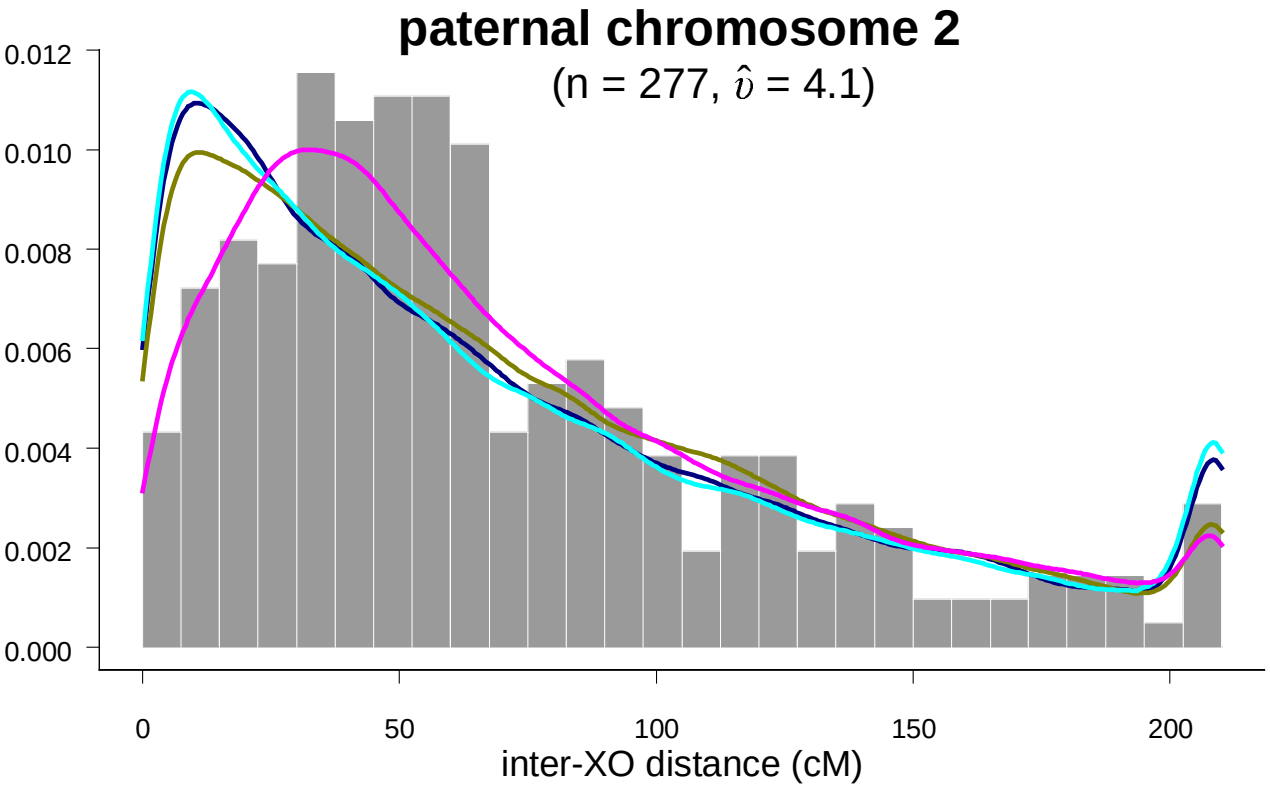
maternal chr 3, 9, 12, 14, 15, 17

paternal chr 1, 4, 5, 9, 14


maternal chromosome 1
(n = 418, $\hat{\upsilon}$ = 5.7)
gamma
no interference
truncated Poisson
count-location
0.010
0.008
0.006
0.004
0.002
0.000
0
100
200
300
inter-XO distance (cM)


paternal chromosome 1
(n = 285, $\hat{\upsilon}$ = 4.9)
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
50
100
150
200
inter-XO distance (cM)





Notes: The histograms contain XO-to-end lengths. The bumps at the far right correspond to whole chromosomes. The fitted distributions are obtained from 9200 simulated chromosomes.

Discussion

- A number of approximations
  - marker order is correct
  - genetic distances are correct
  - all crossovers observed
  - interval censoring of crossover locations is unimportant
  - no individual variation in recombination
- Gamma model fits well;
  Count-location model fits poorly
- Gamma parameter, $\hat{\upsilon} \approx 3–5$;
  Stronger interference than Kosambi