Human meiotic interference

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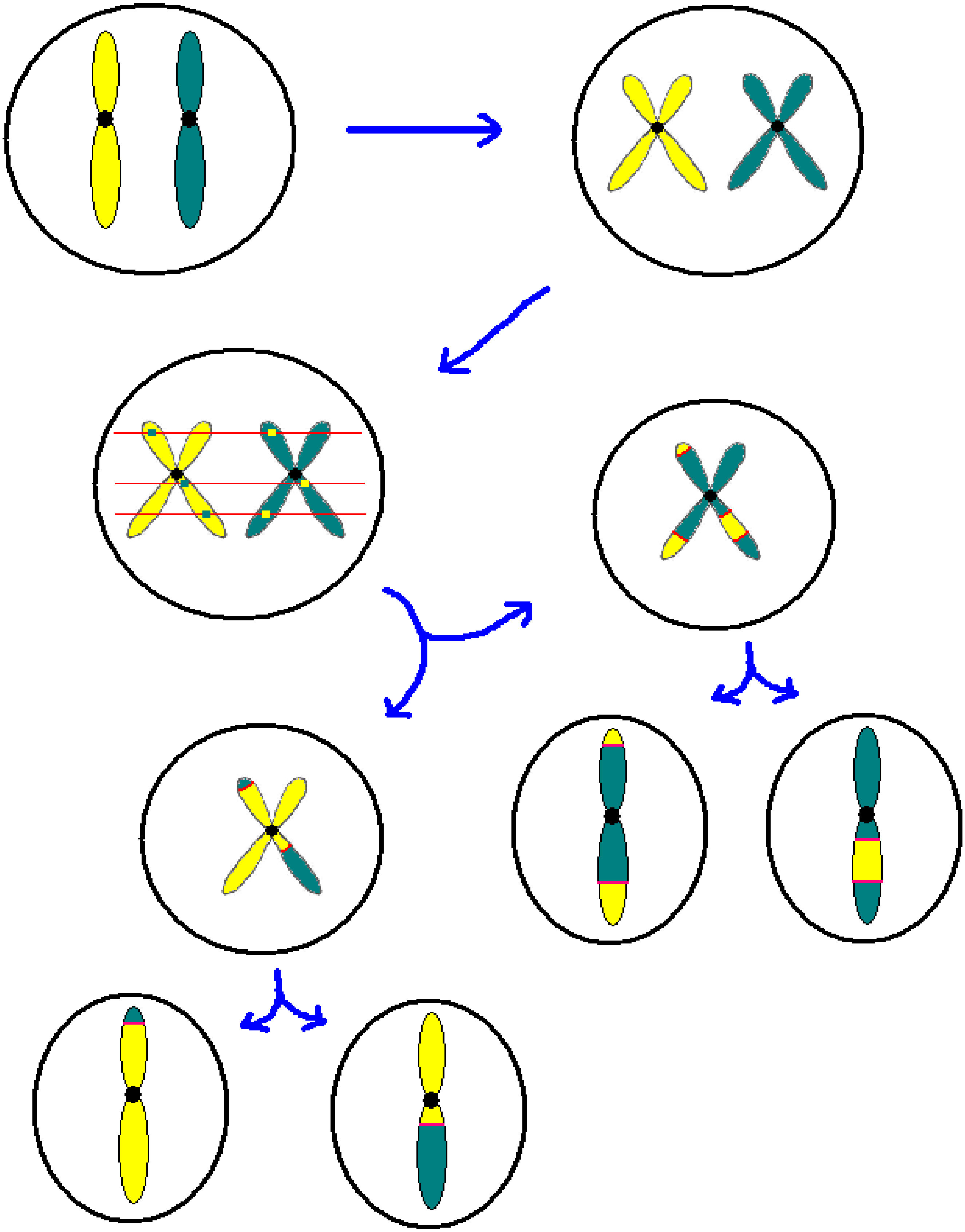
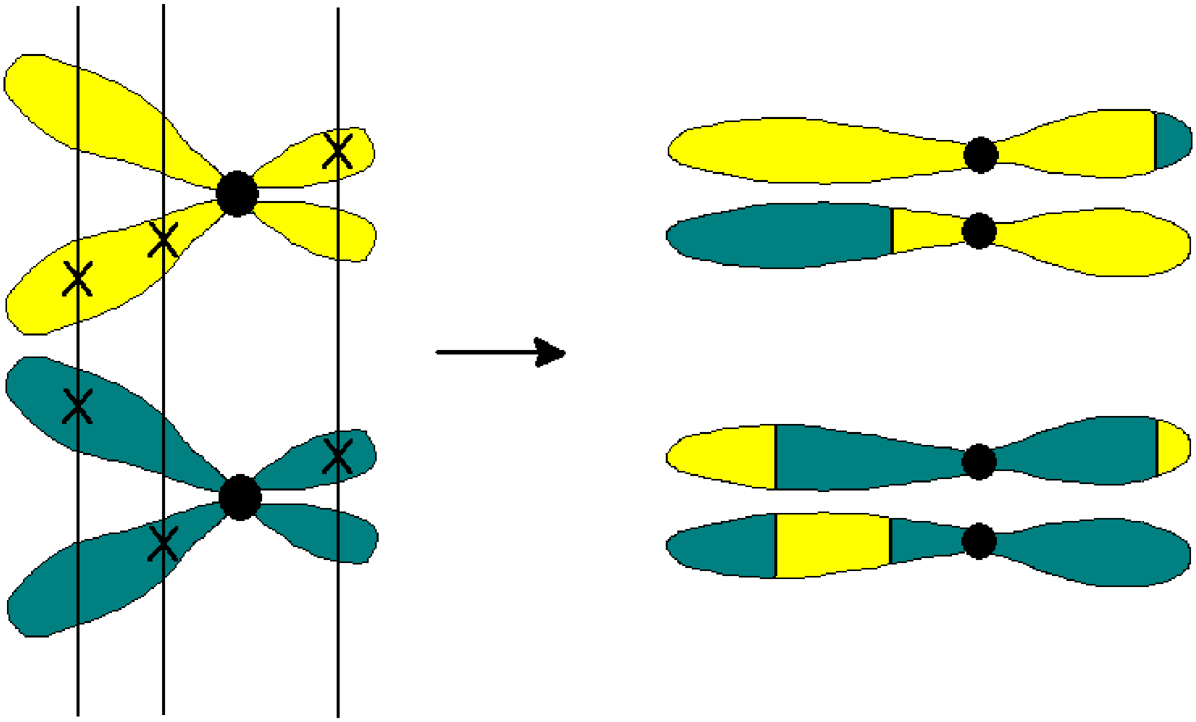
MARSHFIELD
MEDICAL
RESEARCH
FOUNDATION

Meiosis



Interference



- Strand choice

  → Chromatid interference

- Spacing

  → Chiasma (crossover) interference

Model organisms

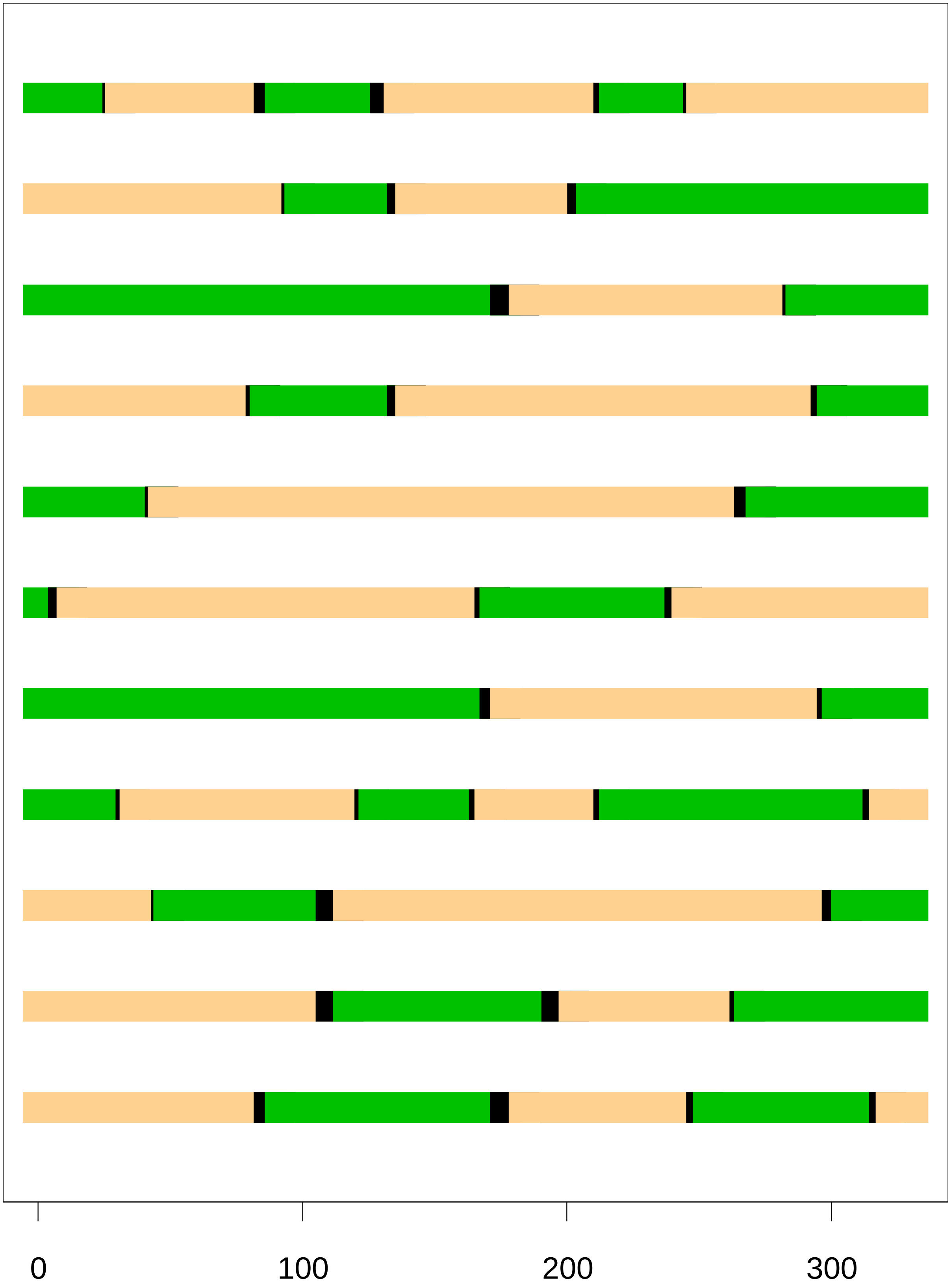
- Lots of meioses
- A few linked markers
- Look at frequency of rare multiple recombination events

***Drosophila* data (Morgan et al 1935)**

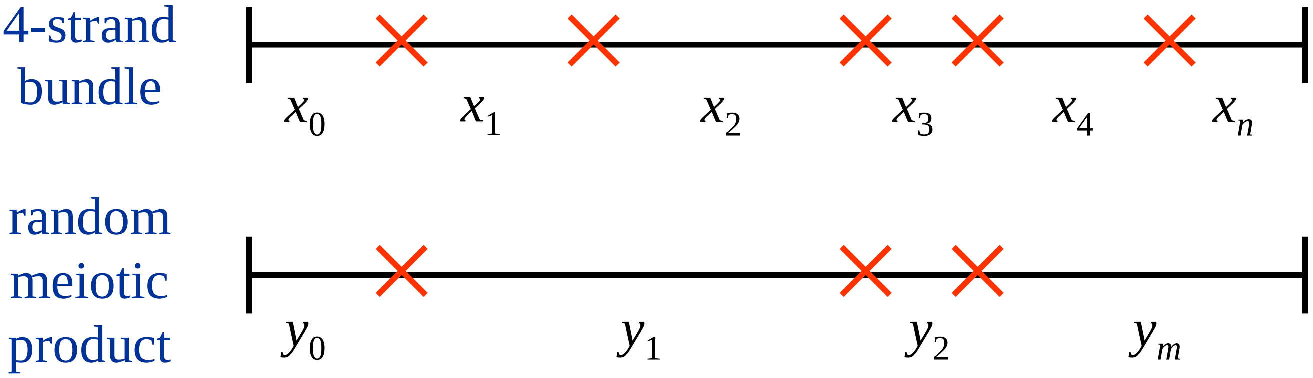
Event	Count	Event	Count
0000	10,431	1001	46
1000	771	0101	53
0100	1,579	0011	25
0010	1,221	1110	1
0001	1,994	1101	1
1100	4	1011	1
1010	7	0111	1
0110	4	1111	1

Human data

- www.marshmed.org/genetics
- 8 CEPH families
  - three generations
  - 11 to 15 progeny
  - 92 meioses
- ~8,000 STRP markers
  - 90 ± 7 % typed
- Average spacing
  - female: 0.6 ± 1.2 cM
  - male: 0.4 ± 1.0 cM
  - sex-ave: 0.5 ± 0.9 cM
- Data cleaning
  - Removed 764/964,425 (~0.08%) genotypes resulting in tight double recombinants


0
100
200
300

Models



- Count-location model

  $n \sim (p_0, p_1, p_2, \ldots)$

  locations | n ~ iid uniform

- Gamma model

  x_i's ~ stationary gamma renewal process (shape = υ, rate = 2υ)

  y_i's ~ mixtures of gammas

Model fitting

- Count-location model

m_i = # crossovers
n_i = underlying # chiasmata

$n_i \sim (p_0, p_1, p_2, \ldots)$
$m_i \mid n_i \sim \text{binomial}(n_i, 1/2)$

MLEs via a version of the EM algorithm

Model fitting

- Gamma model

$x_1, x_2, \ldots \sim f(\upsilon, 2\upsilon)$
$x_0 \sim g = 2[1 - F(\upsilon, 2\upsilon)]$
x_i's independent

$y_1, y_2, \ldots \sim \Sigma\, (½)^k f(k\upsilon, 2\upsilon)$
$y_0 \sim ½\, g + \Sigma\, (½)^{(k+1)}\, g * f(k\upsilon, 2\upsilon)$
y_i's independent

- MLE of υ using y_i's
- g calculated numerically
- Convolutions calculated numerically
- Maximization performed using a quasi-Newton method

Distributions of # XOs / chr

Maternal chromosome 1

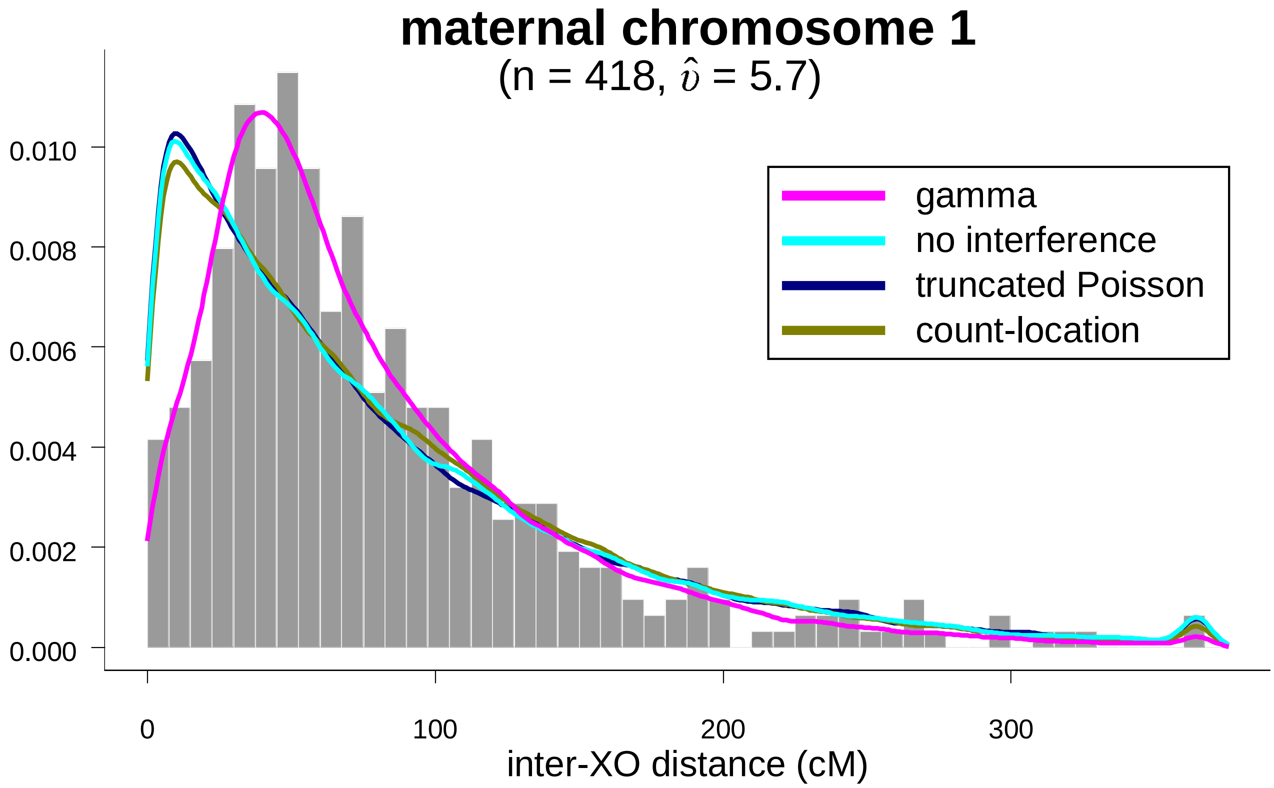
	0	**1**	**2**	**3**	**4**	**5**	**> 5**	**X^2**
Obs.	2	7	12	24	23	14	10	
Pois.	3	9	17	20	17	12	14	**9.2**
C-L	2	7	14	22	23	16	9	0.8
Gamma	1	5	14	23	23	16	10	1.2

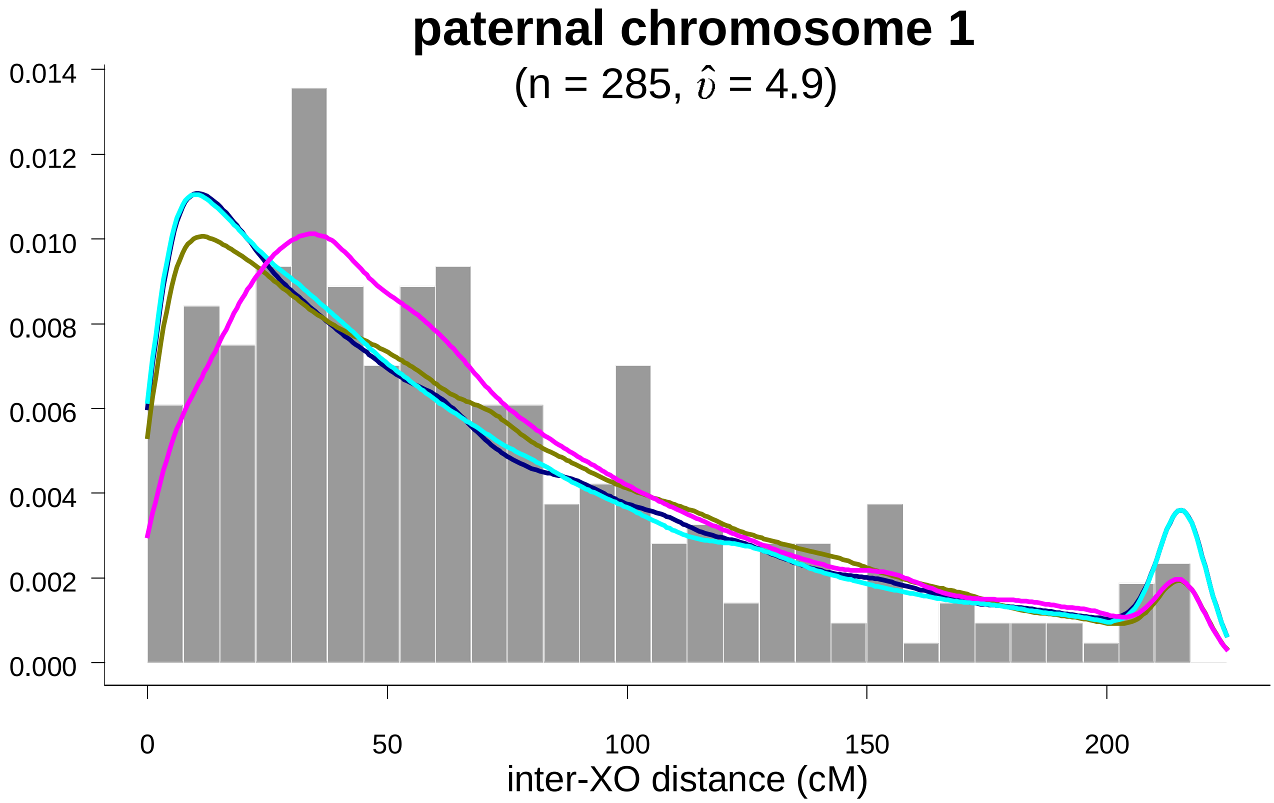
Maternal chromosome 4

	0	**1**	**2**	**3**	**4**	**5**	**> 5**	**X^2**
Obs.	1	16	**36**	15	15	9	0	
Pois.	7	18	23	20	13	7	4	**14.4**
C-L	4	16	26	25	15	6	1	**12.8**
Gamma	4	15	26	24	15	6	1	**7.1**

Evidence for interference:

maternal 3, 9, 12, 14, 15, 17
paternal 1, 4, 5, 9, 14


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


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)

Discussion

- Approximations
  - Correct marker order
  - Correct genetic distances
  - All crossovers observed
  - Interval censoring unimportant
  - No individual variation in recombination
  - Interference constant across chromosome
- Conclusions
  - Gamma model fits well
  - Count-location model fits poorly
  - Gamma parameter, $\hat{\upsilon} \approx 3$–5
    (stronger than Kosambi, $\upsilon \approx 2.6$)
- Further work
  - Interference across the centromere
  - Variation between chromosomes