Meiosis, recombination, and interference

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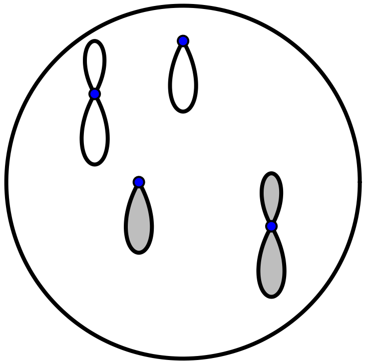
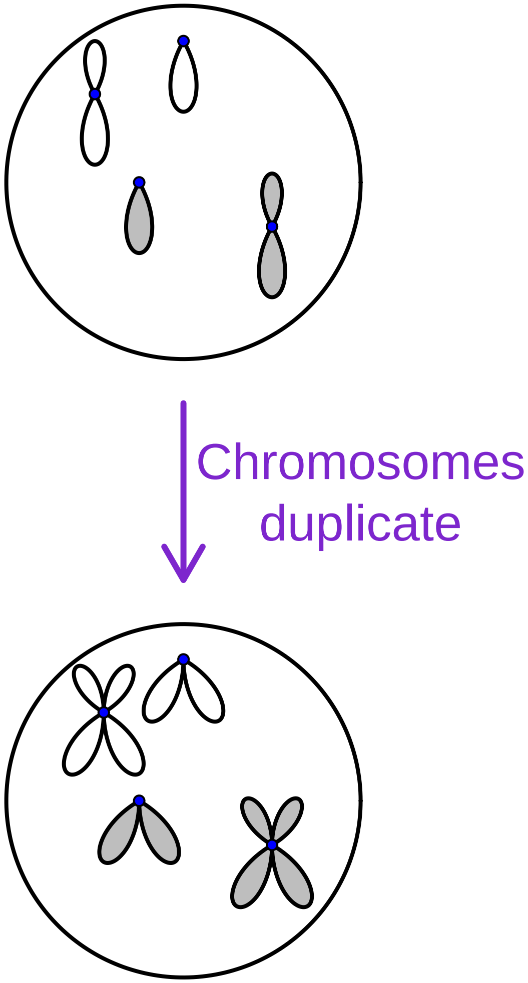
Outline

- Mitosis and meiosis
- Chiasmata, crossovers
- Genetic distance
- Genetic markers, recombination
- Chromatid and chiasma interference
- Mather's formula
- The count-location model
- The gamma model and the χ^2 model
- Data: humans and mice

Mitosis: ordinary cell division

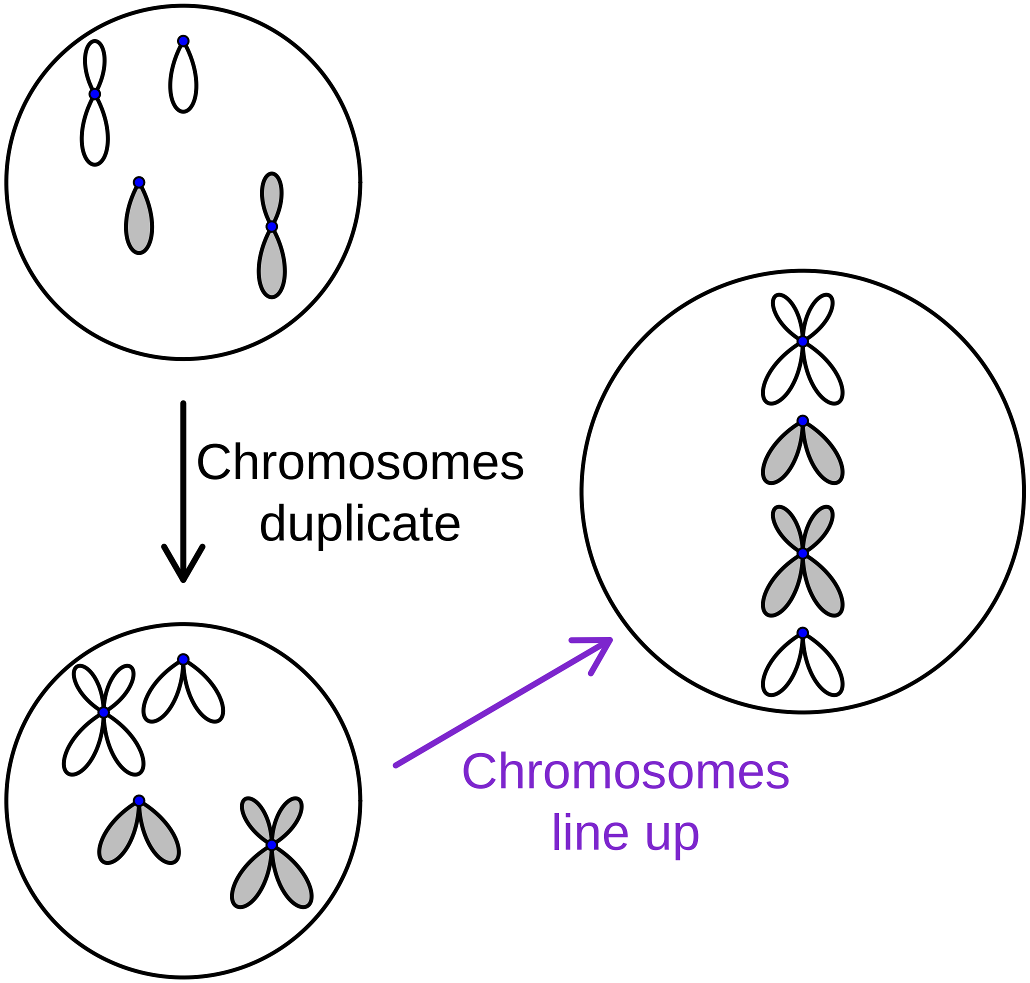


Mitosis: ordinary cell division



Chromosomes duplicate

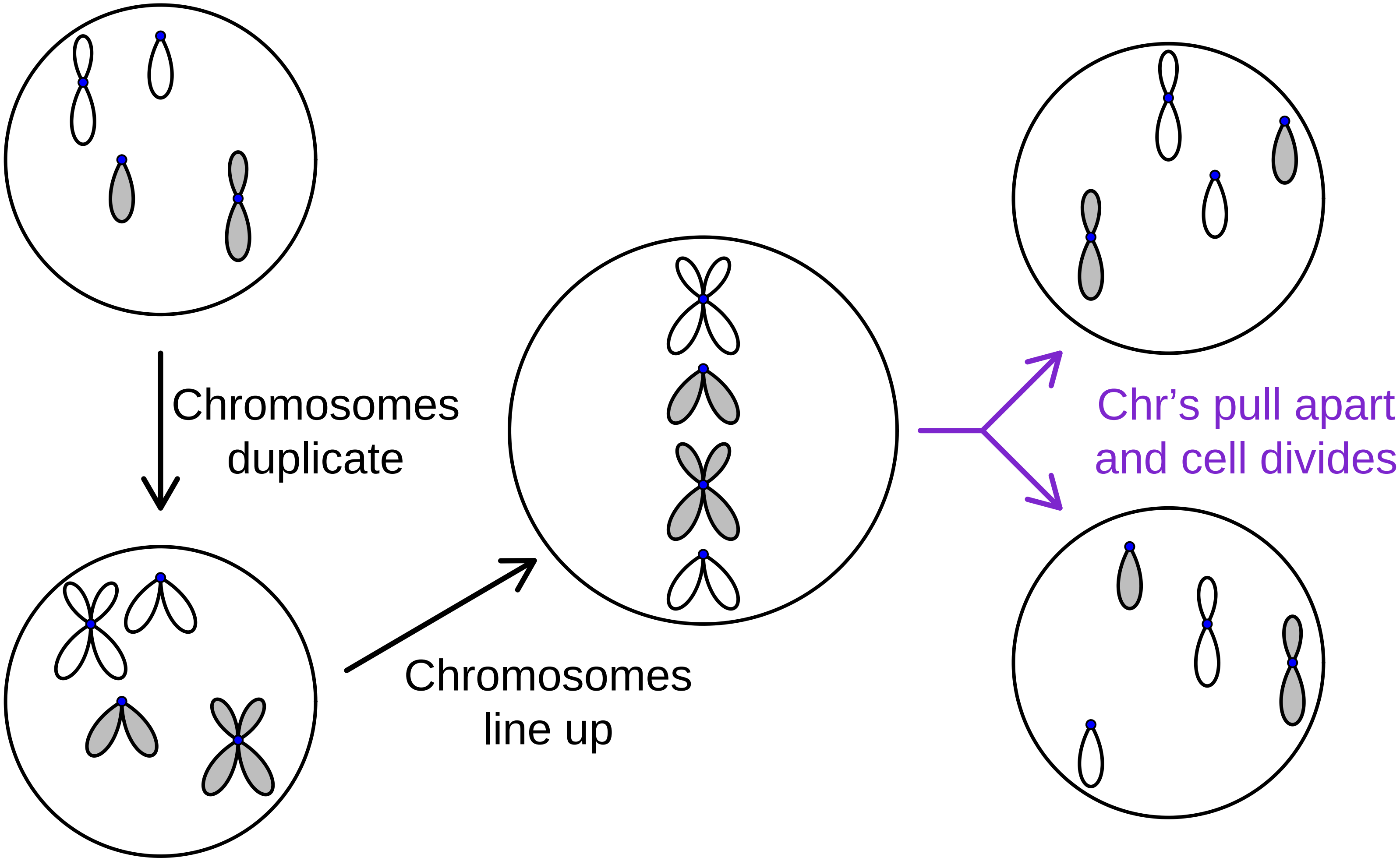
Mitosis: ordinary cell division



Chromosomes duplicate

Chromosomes line up

Mitosis: ordinary cell division

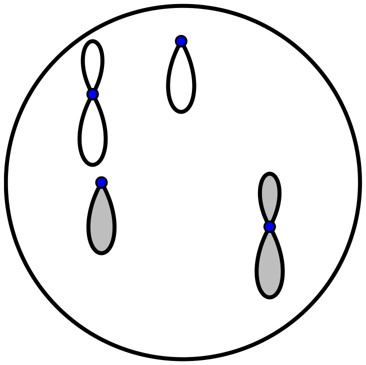


Chromosomes duplicate

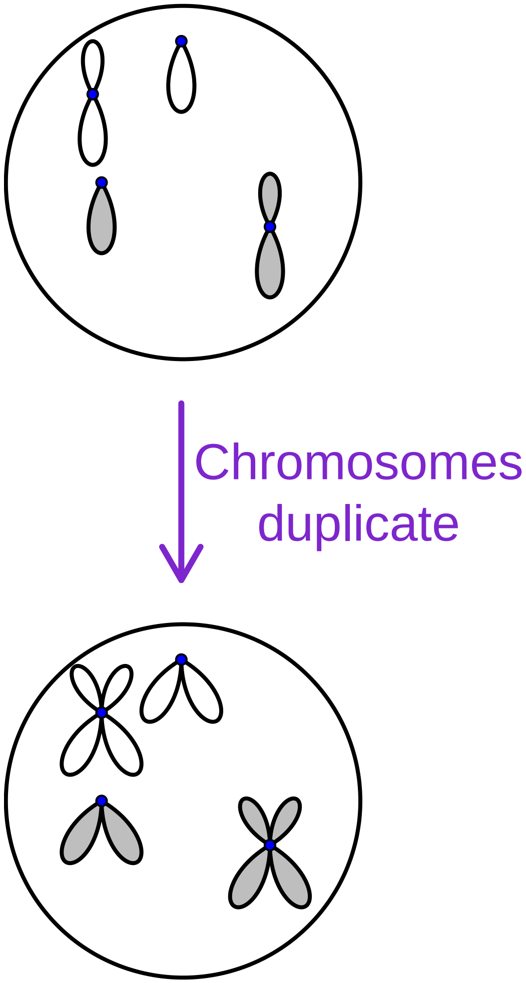
Chromosomes line up

Chr’s pull apart and cell divides

Meiosis: production of sex cells

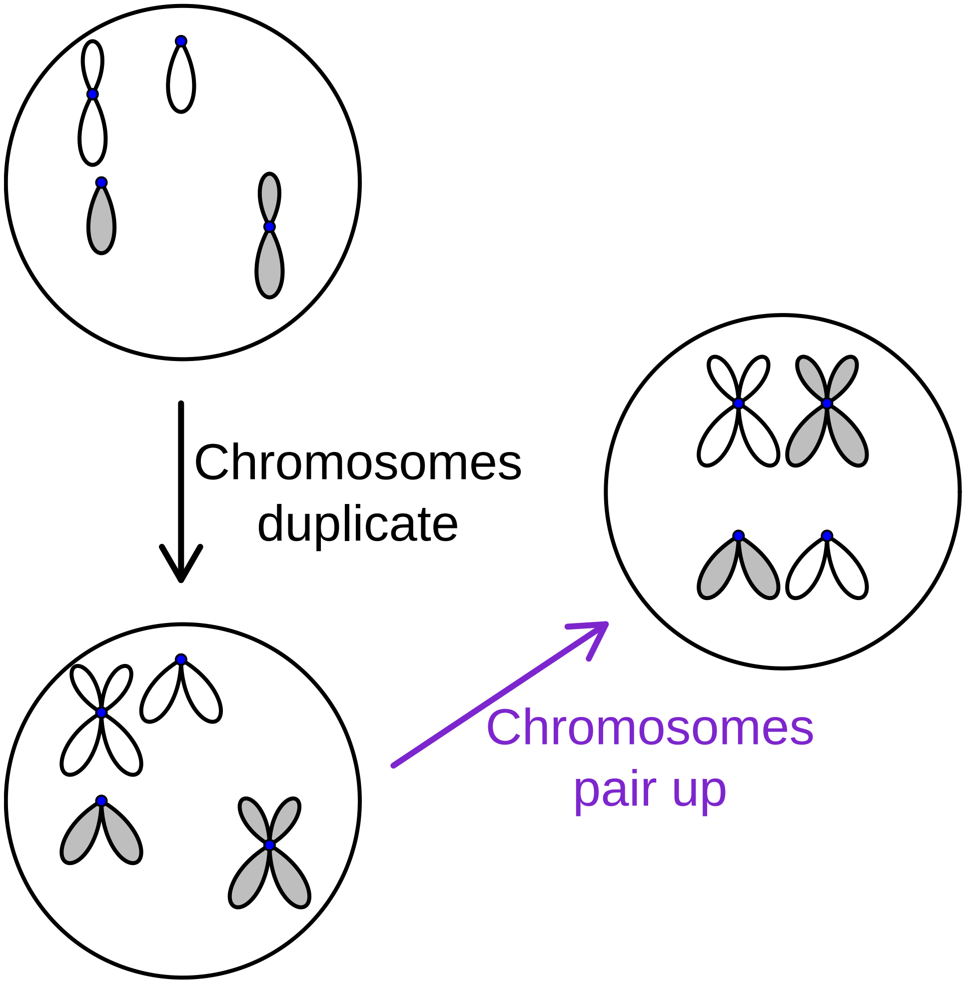


Meiosis: production of sex cells



Chromosomes duplicate

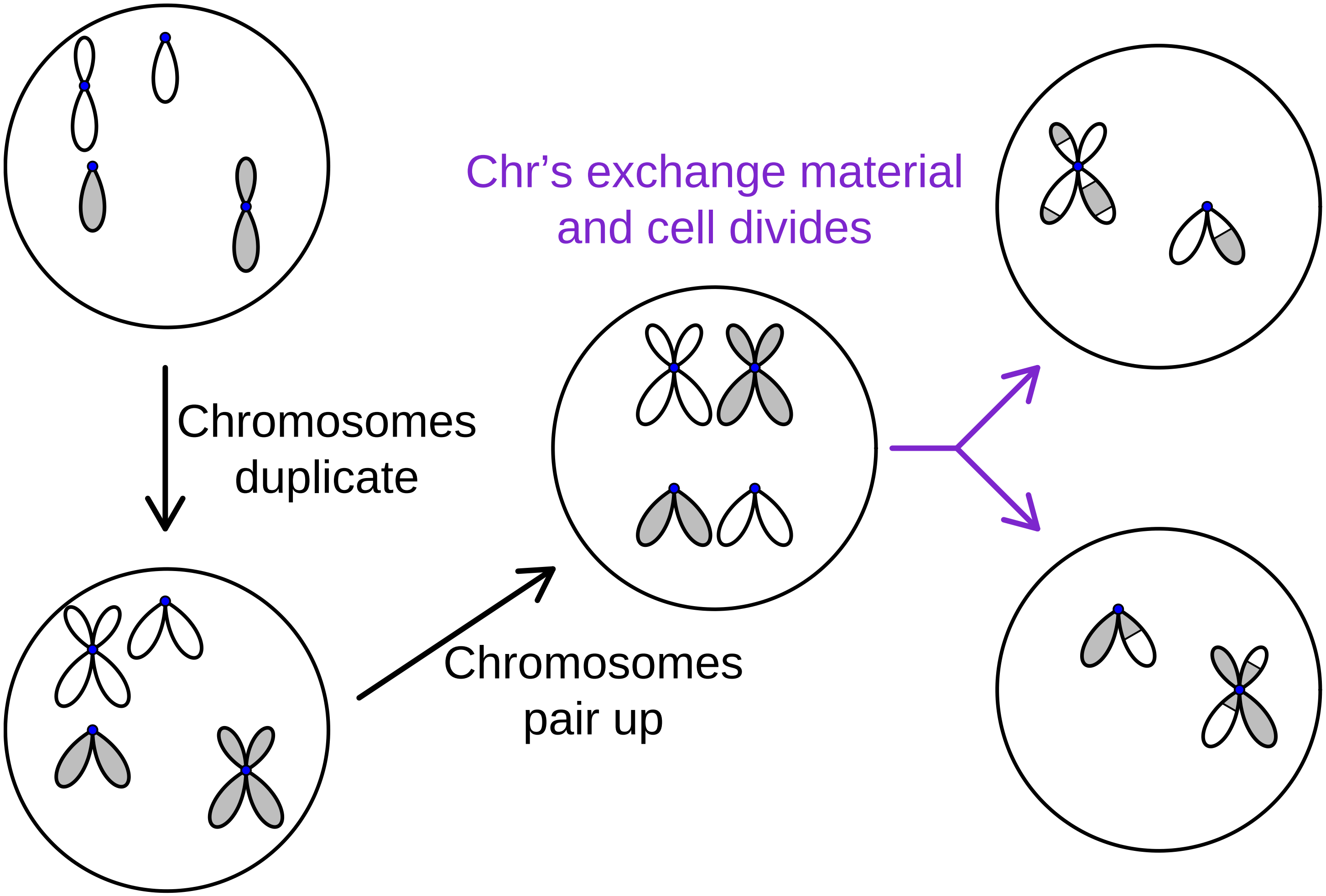
Meiosis: production of sex cells



Chromosomes duplicate

Chromosomes pair up

Meiosis: production of sex cells

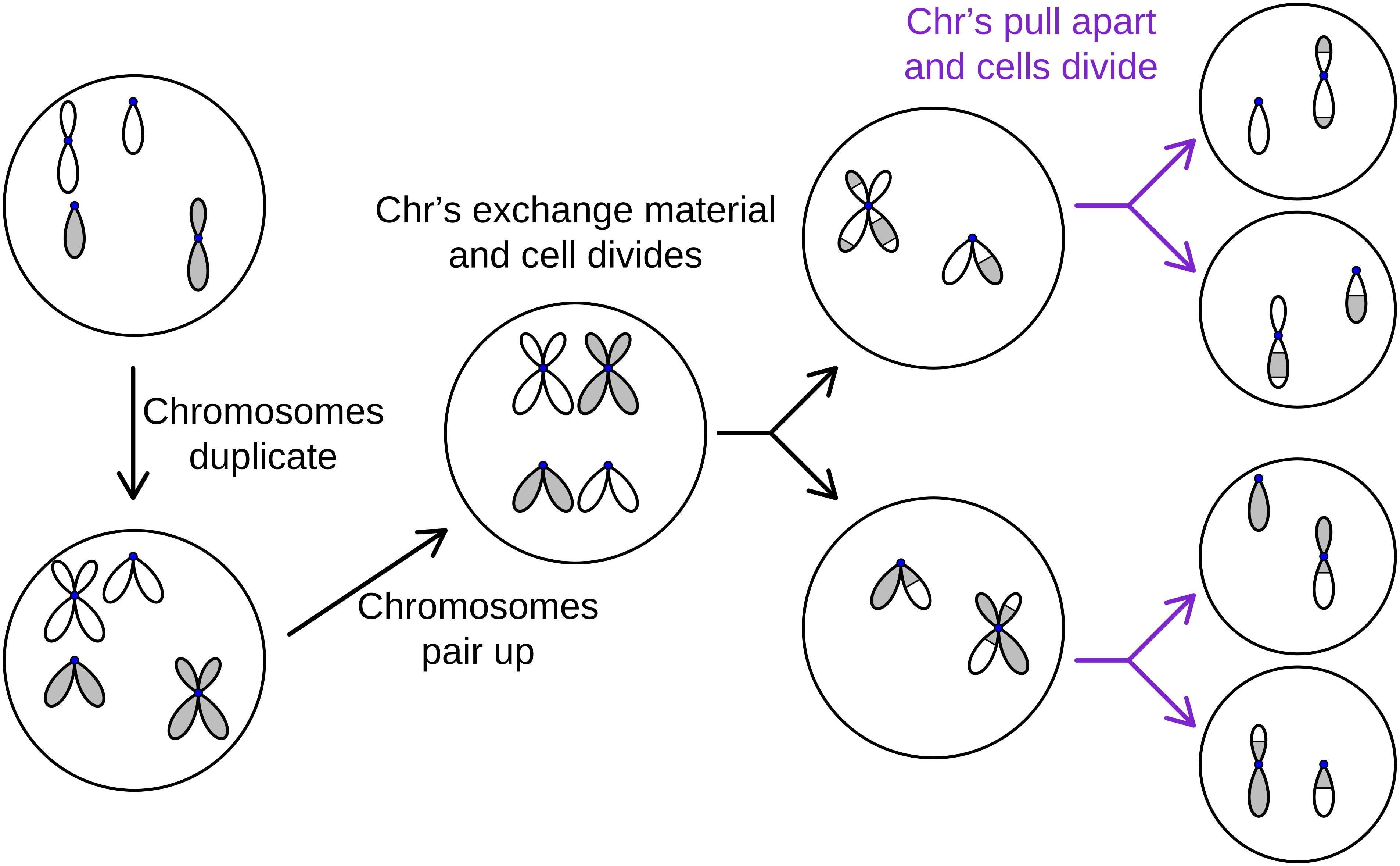


Chromosomes duplicate

Chromosomes pair up

Chr’s exchange material and cell divides

Meiosis: production of sex cells



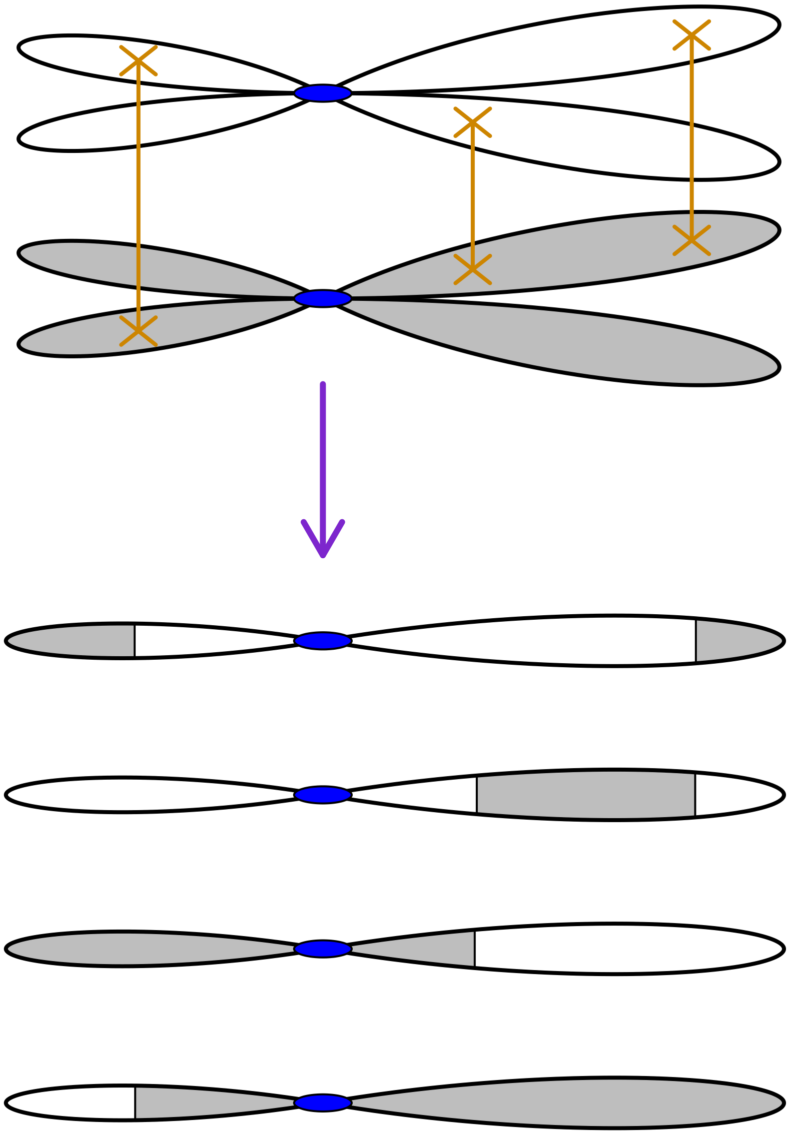
Chromosomes duplicate

Chromosomes pair up

Chr’s exchange material and cell divides

Chr’s pull apart and cells divide

The exchange process



Vocabulary

Four-strand bundle
Meiotic products

Sister chromatids
Non-sister chromatids

Chiasma, chiasmata
Crossovers

Obligate chiasma

Genetic distance

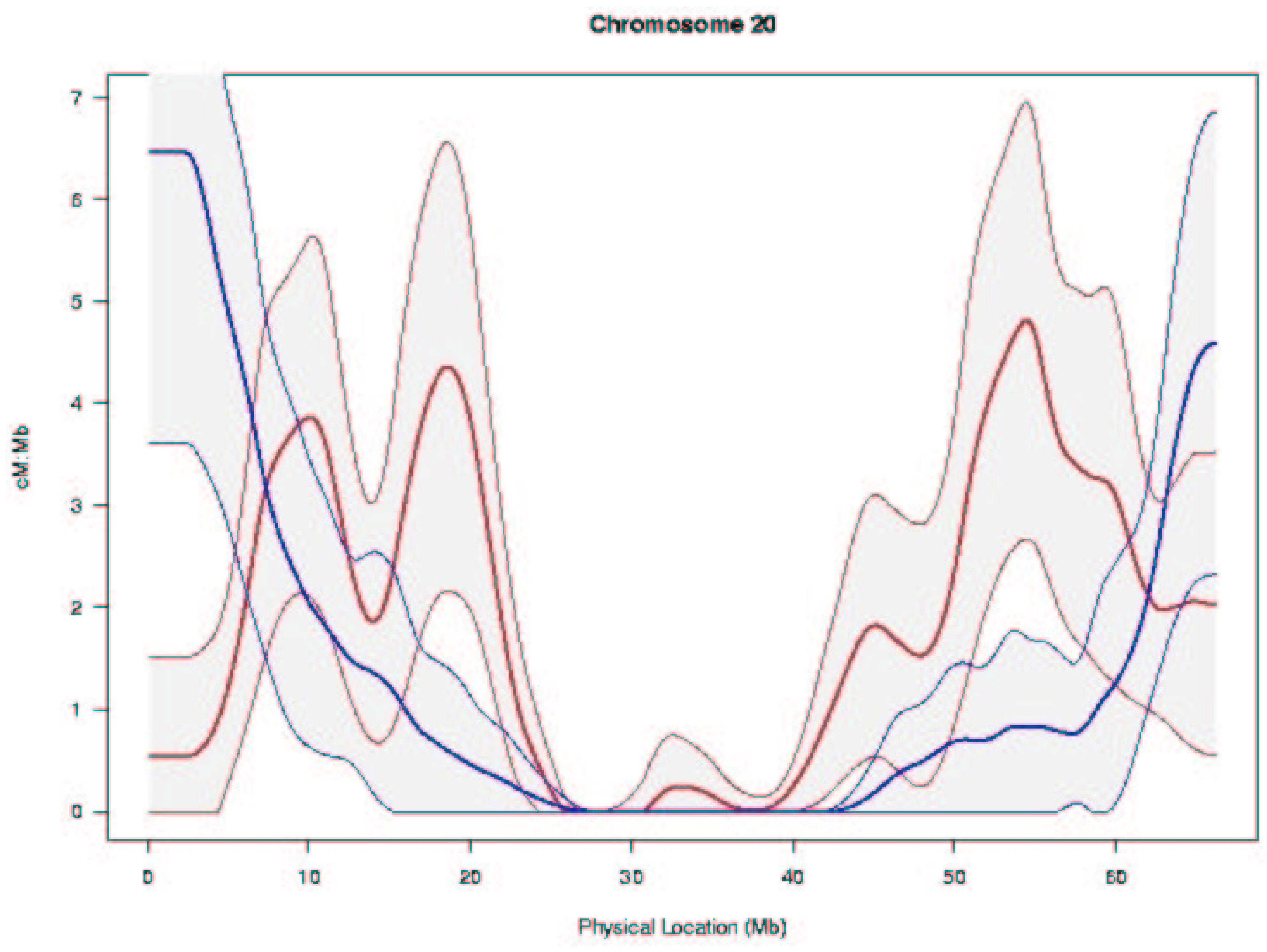
Two points are d Morgans apart if the average number of crossovers per meiotic product in the intervening interval is d.

Usual units: centiMorgan (cM); 100 cM = 1 Morgan

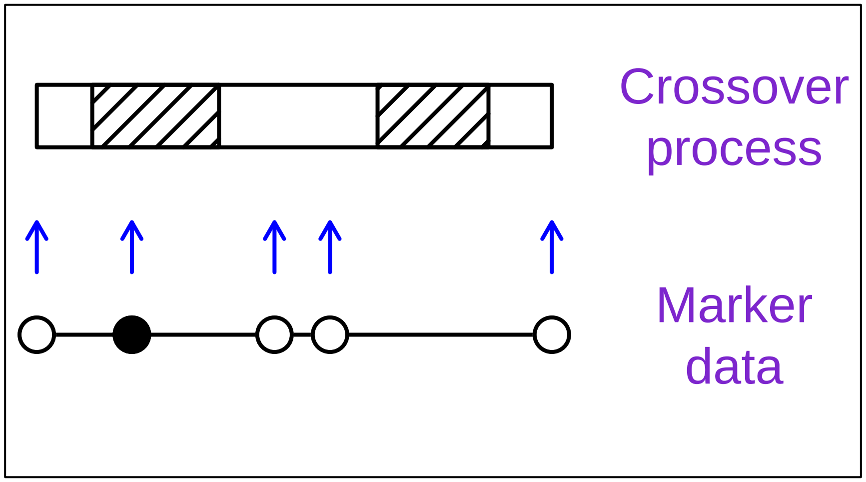
Genetic distance $\neq$ Physical distance

The intensity of the crossover process varies by

- Sex
- Individual
- Chromosome
- Position on chromosome
- Temperature


Chromosome 20
cM:Mb
0
1
2
3
4
5
6
7
Physical Location (Mb)
0
10
20
30
40
50
60

But we don’t observe crossovers



- Crossovers generally not observeable
- We instead observe the origin of DNA at marker loci.

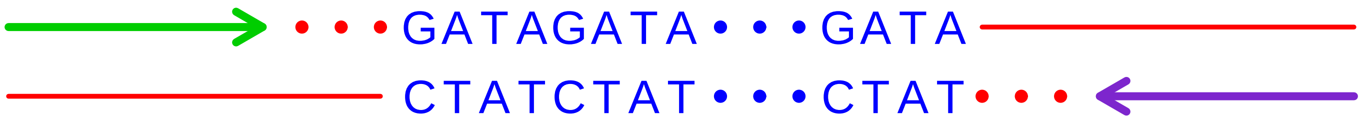
odd no. crossovers = recombination event

even no. crossovers = no recombination

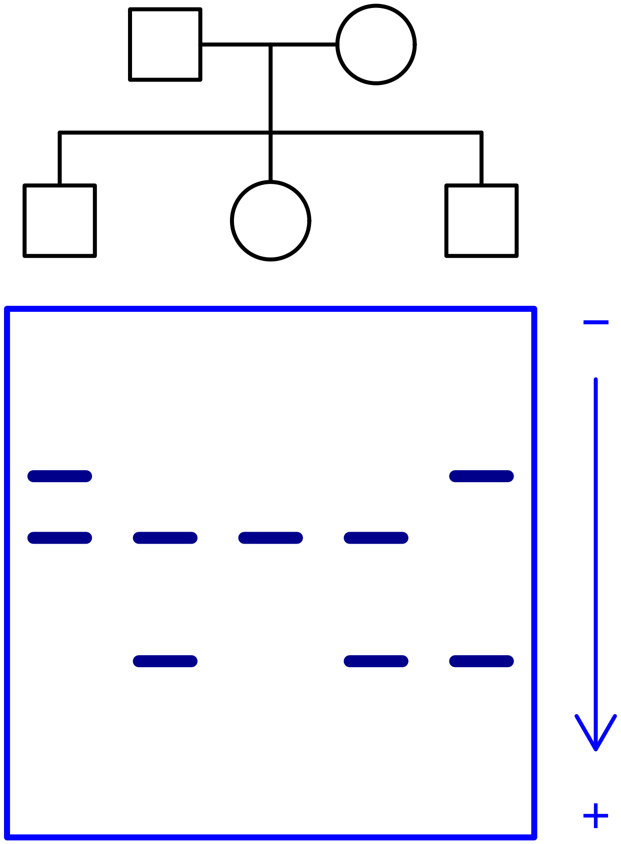
Recombination fraction = Pr(recombination event in interval)

Microsatellite markers

aka Short Tandem Repeat Polymorphisms (STRPs)



- Tandem repeat of something like `GATA` at a specific position in the genome.
- Number of repeats varies
- Use PCR to “amplify” region
- Use gel electrophoresis to determine length of region



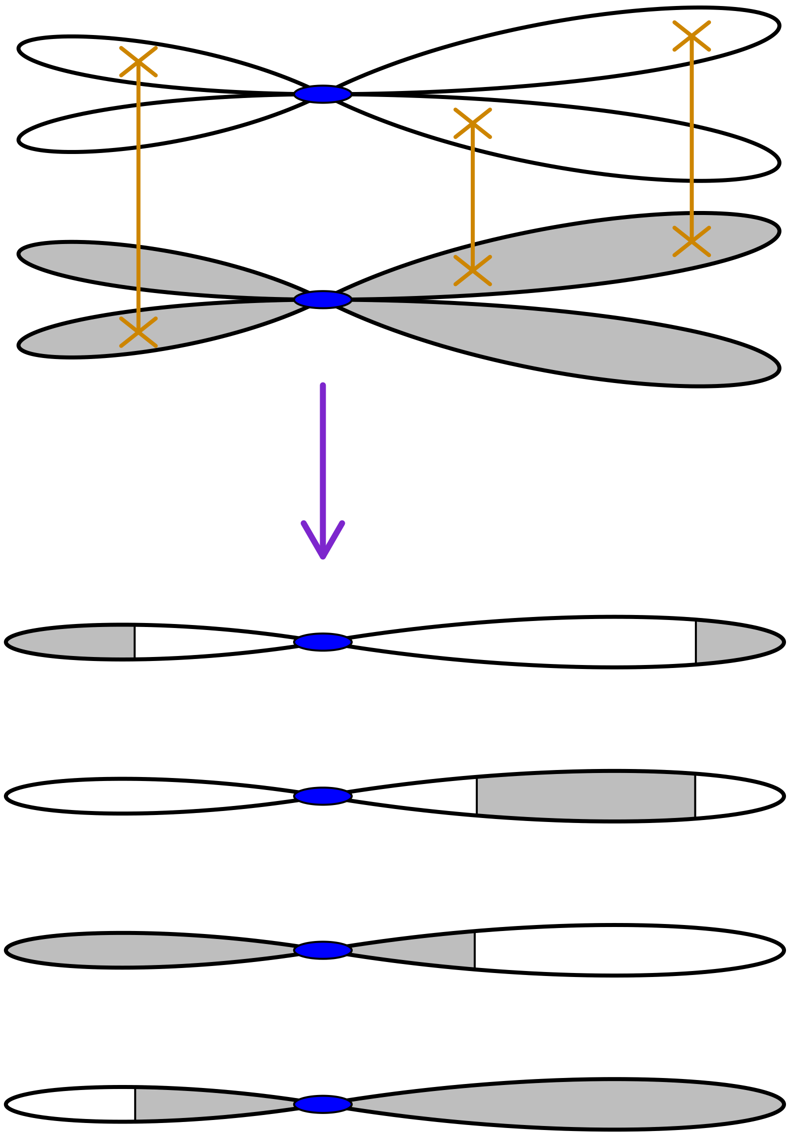
Map functions

Connect genetic distance (average no. crossovers)
to recombination fraction (chance of an odd no. crossovers).

$$r = \mathrm{M}(d) \qquad d = \mathrm{M}^{-1}(r)$$

We require a model for the crossover process.

Interference



Chromatid interference:

strand choice

Chiasma interference:

positions of chiasmata

Mather's formula

Assuming no chromatid interference (NCI):

$$\Pr(\text{no rec'n in interval}) = \tfrac{1}{2}\left\{ 1 - \Pr(\text{no chiasma in interval}) \right\}$$

↑ [in random meiotic product]

↑ [on 4-strand bundle]

Let n = no. chiasmata in interval on 4-strand bundle
and m = no. crossovers in interval on random meiotic product

Under NCI, $m \mid n \sim \text{Binomial}(n, 1/2)$

$$\text{Thus } \Pr(m \text{ is odd} \mid n) = \begin{cases} 0 & \text{if } n = 0 \\ 1/2 & \text{if } n \geq 1 \end{cases}$$

Haldane map function

Under no interference, the locations of chiasmata on the 4-strand bundle are according to a Poisson process (rate: 2 per Morgan).

Thus $n \sim \text{Poisson}(2\,d)$

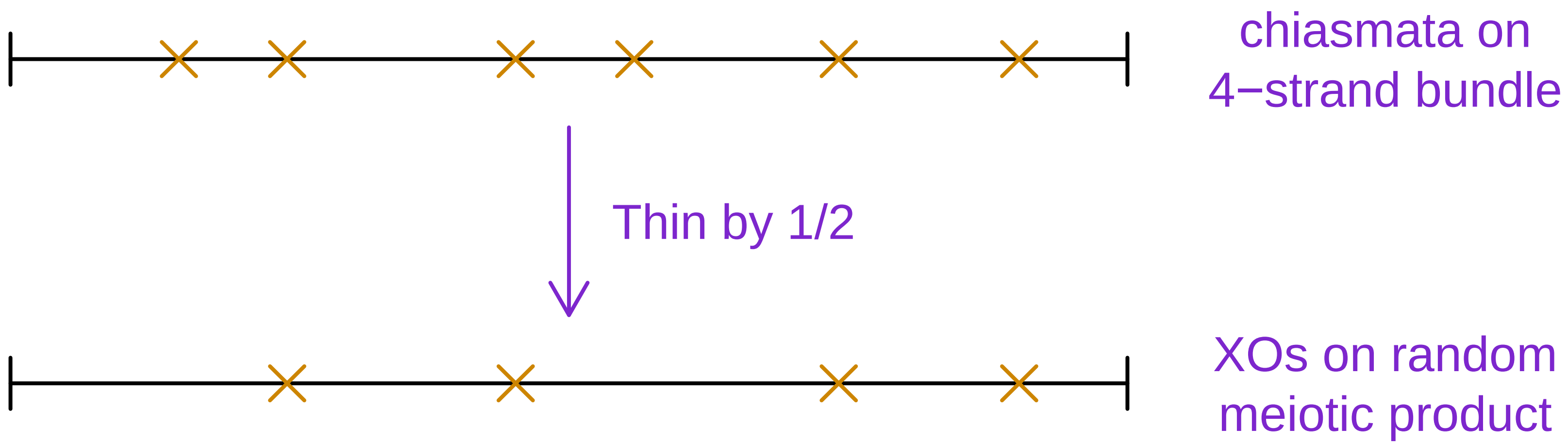
where d is the genetic length of the interval (in Morgans)

Thus $\Pr(n = 0) = \exp(-2\,d)$

Thus

$$r = \frac{1}{2}\,\{\,1 - \exp(-2\,d)\,\}$$

Models for recombination



- Assuming NCI, thin χ-process by 1/2, independently, to get the XO-process.
- Models:
  - Count-location model
  - Gamma model, χ^2 model

Count-location (CL) model

Let n = no. chiasmata on 4-strand bundle

Model: $n \sim \boldsymbol{p} = (p_0, p_1, p_2, \ldots)$

locations | $n \sim$ iid uniform(0,L)

Note: $\boldsymbol{p}$ = Poisson(2L) $\longrightarrow$ no interference

Under NCI, crossovers on random meiotic product will also follow a count-location model.

Let m = no. crossovers on random meiotic product

Then $m \mid n \sim$ Binomial(n, 1/2) and

$$\Pr(m = i) = \sum_{n=0}^{\infty} p_n \binom{n}{i} \left(\tfrac{1}{2}\right)^n$$

The CL model stinks

Advantage: Can easily incorporate obligate chiasma

Disadvantage: Fits data poorly!

⟶ Allows crossovers to be too close together.

Gamma model

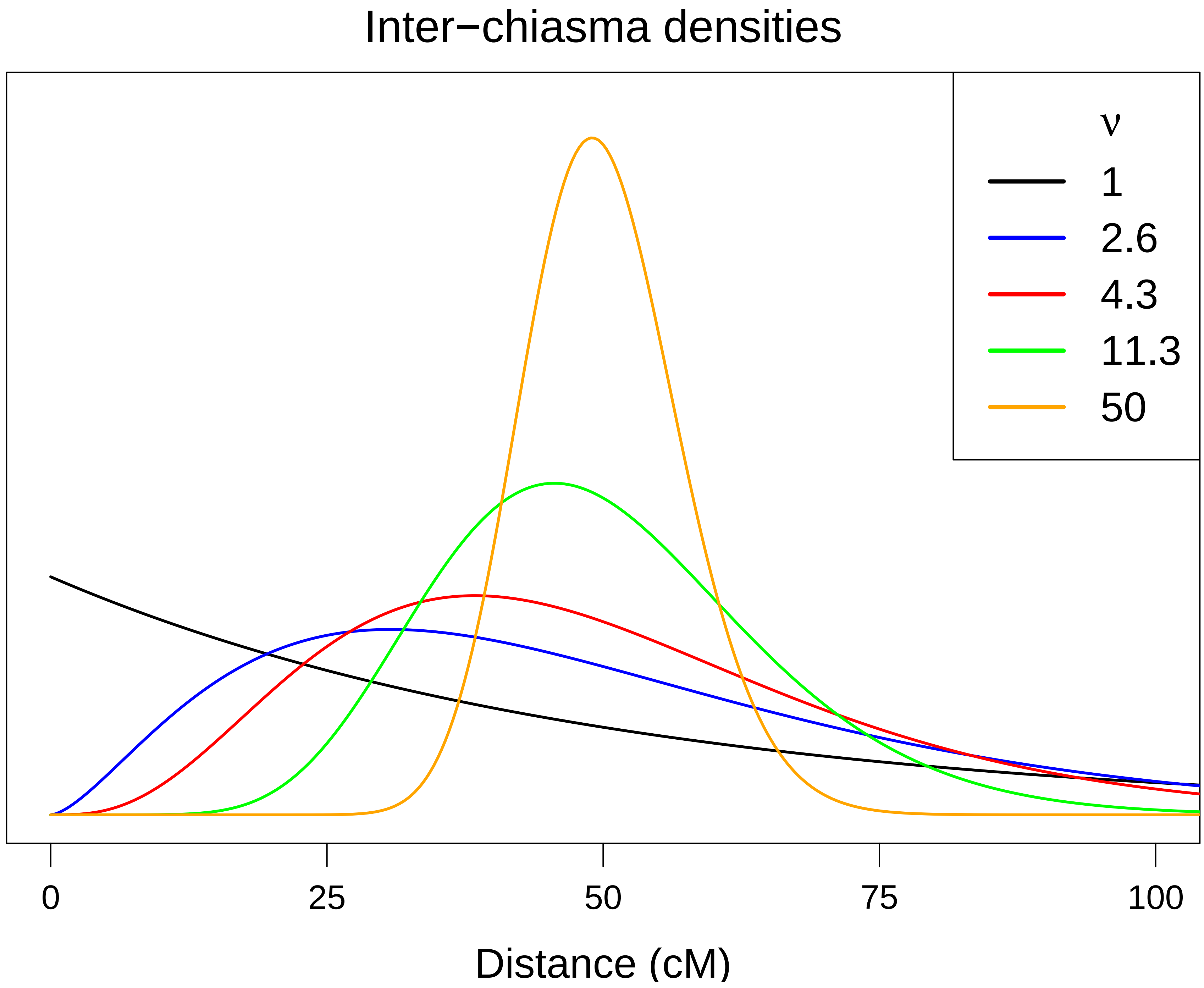
Locations of chiasmata according to a stationary gamma renewal process.

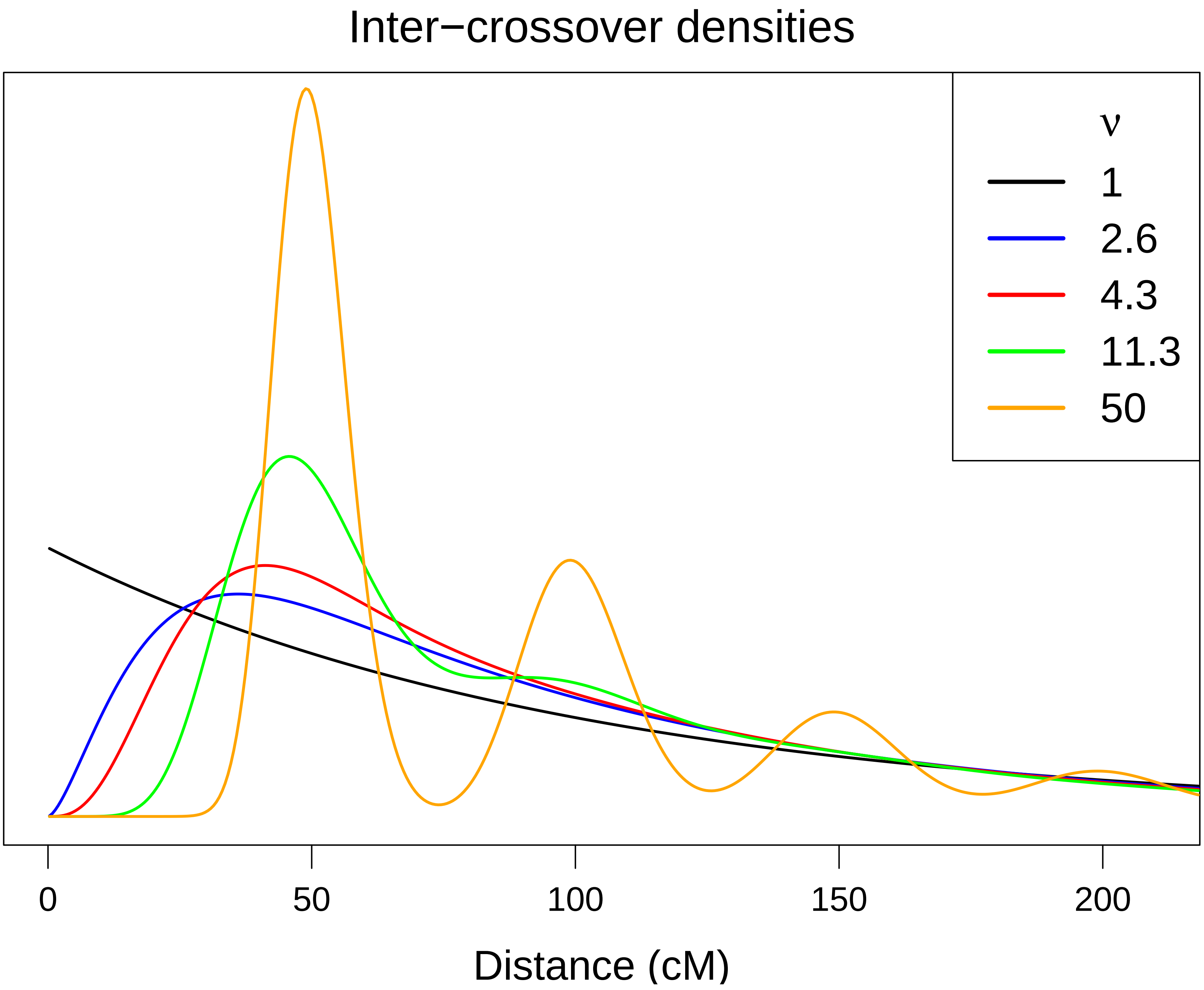
Increments are iid gamma(shape = ν, rate = 2ν)
(Constrained to have mean 1/2 Morgan.)

$$\nu \begin{cases} = 1 & \text{no interference} \\ > 1 & \text{positive chiasma interference} \end{cases}$$

Locations of crossovers on random meiotic product also a stationary renewal process.

Inter-arrival distribution is a mixture of gammas


Inter−chiasma densities
ν
1
2.6
4.3
11.3
50
0
25
50
75
100
Distance (cM)


Inter−crossover densities
ν
1
2.6
4.3
11.3
50
0
50
100
150
200
Distance (cM)

Chi-square model

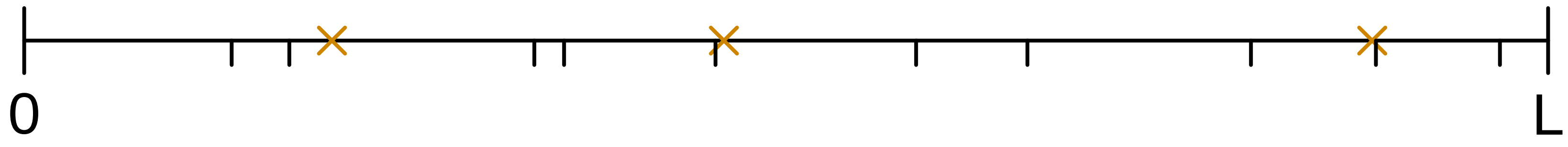
Special case of the gamma model when the parameter is a non-negative integer (take $m = \nu - 1$).

Computer simulations and many calculations are easier.

Chiasmata on the 4-strand bundle: take every *m*th point from a Poisson process with rate 2*m* per Morgan.

Inter-arrival distribution is a scaled version of a χ^2 distribution.

Example: (m = 4)



The gamma model

Advantage: Fits data reasonably well

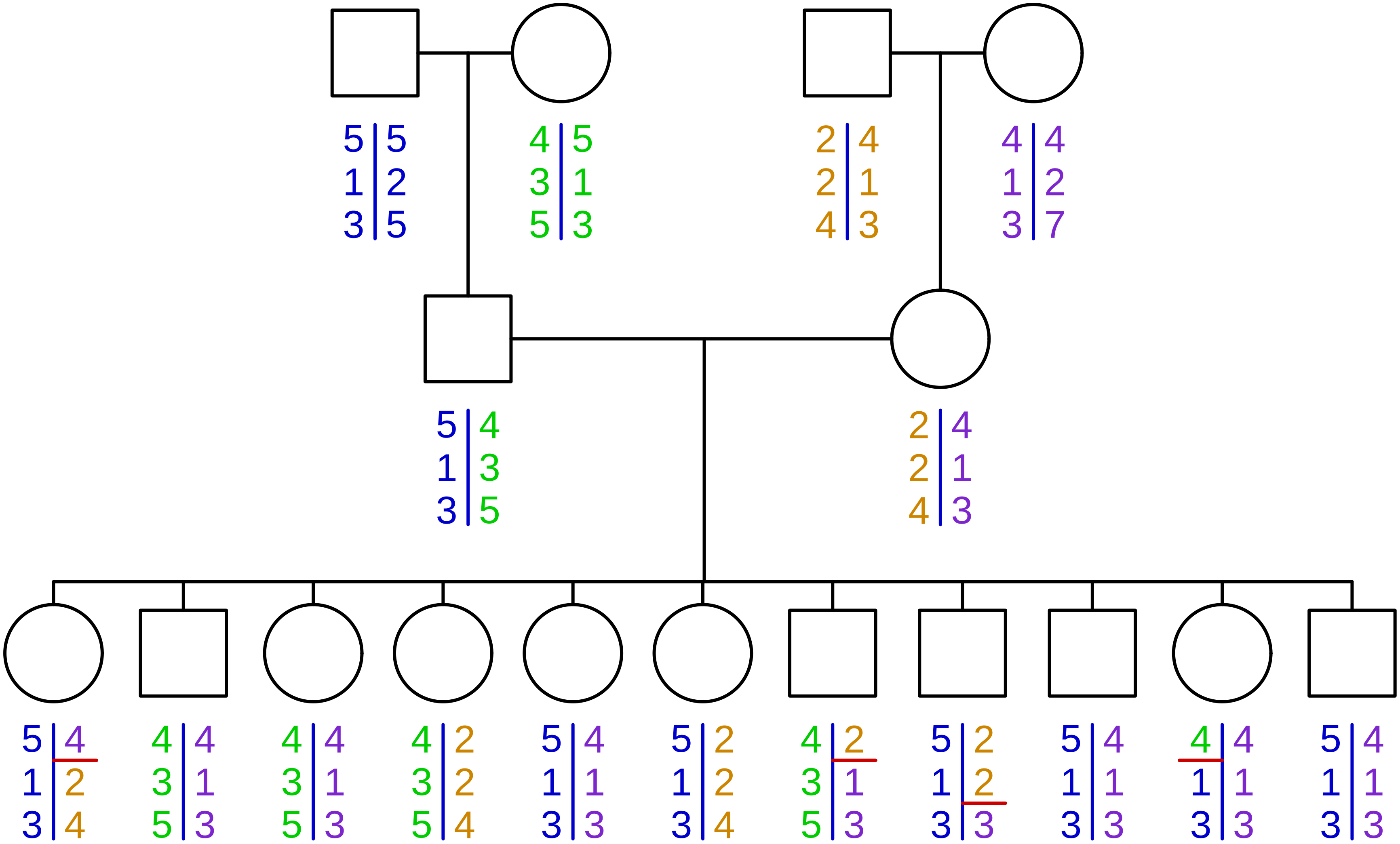
Disadvantage: Doesn’t account for obligate chiasma

Human data

- `http://research.marshfieldclinic.org/genetics`
- 8 CEPH families
  - three generations
  - 11 to 15 progeny
  - 92 meioses, total
- ∼8000 STRP markers (∼90% typed)
- Average spacing:
  - Female: 0.6 ± 1.2 cM
  - Male: 0.4 ± 1.0 cM
- Data cleaning
  - Removed 764/954,425 (∼0.08%) genotypes resulting in tight double recombinants

CEPH pedigree

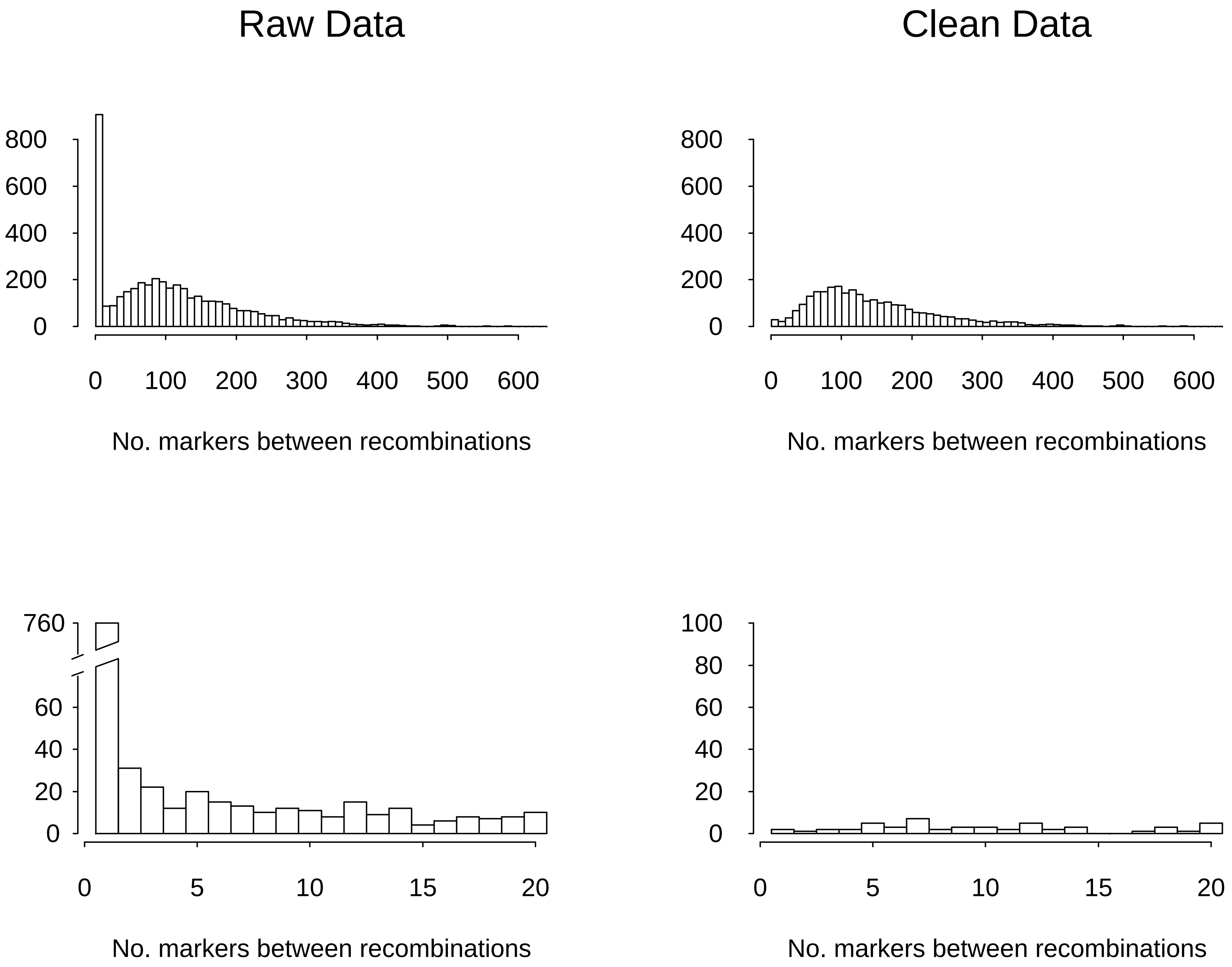
(data on 3 markers)



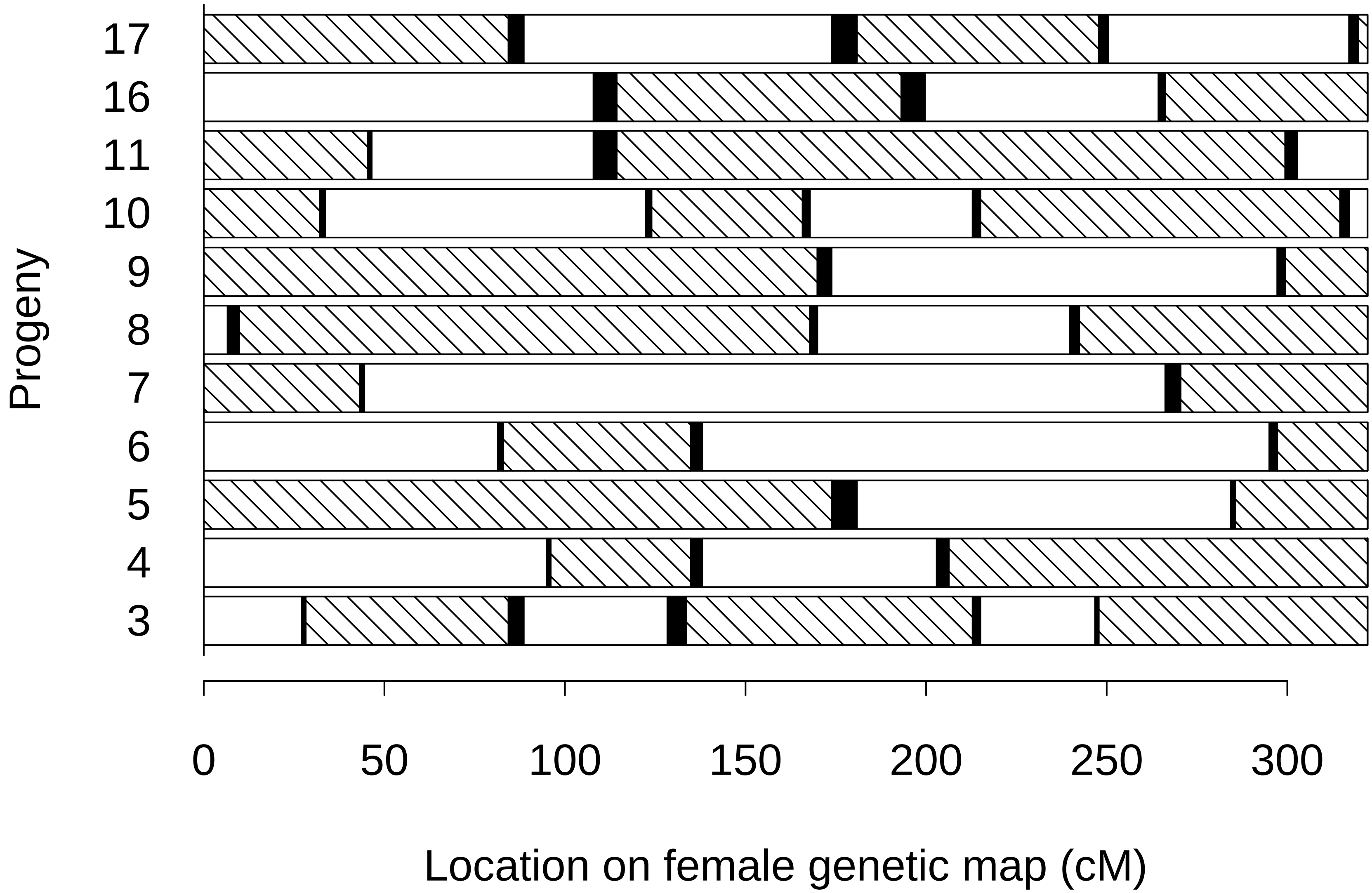
CEPH individual 1331–11

maternal chr 10 haplotype

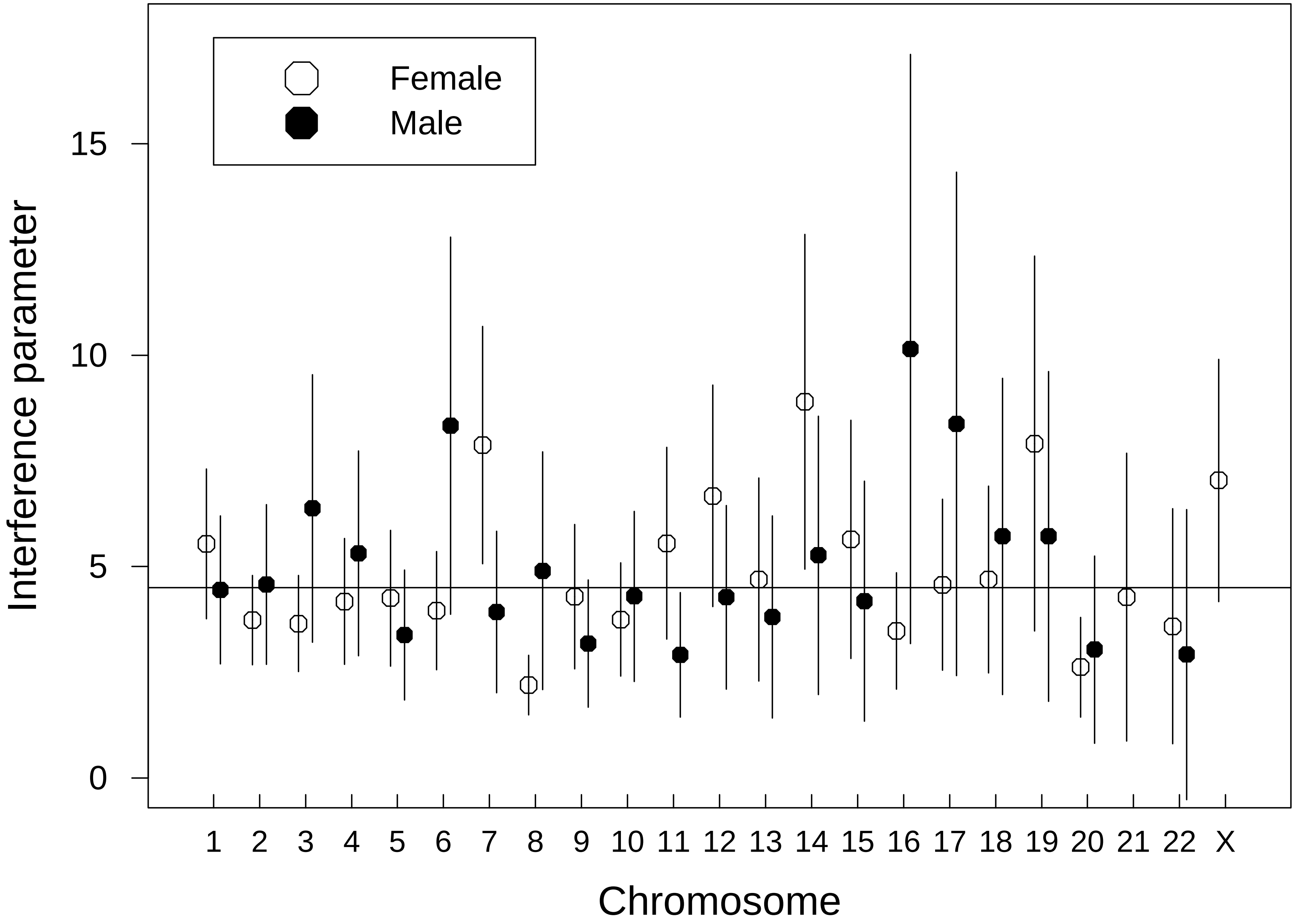
```
1111111--- 11-111-11- --11--1111 1-11---11-
111111--1- 11-1111-11 --11111-11 1111-11111
11--111111 111-1111-1 1111111111 10000-0-00
0--000-000 0000-00000 0000--0000 0000--0000
0000-00000 000-0--0-- --0-11-11- -1111111-1
---1-1-1-1 1111-1--11 11111-1111 -111-11111
-1----1111 111111-111 -1111-111- 11-1111111
111-11111- 1111111-1- 1111111-11 11-111111-
11--1-11-1 111-11-1-1 1-1----1-1 11-1111111
11--1--11- 11111--111 11--111111 1111-11111
1-0---0000 00000-0000 00-000
```


Raw Data
Clean Data
800
600
400
200
0
0
100
200
300
400
500
600
No. markers between recombinations
760
60
40
20
0
5
10
15
20
100
80
No. markers between recombinations

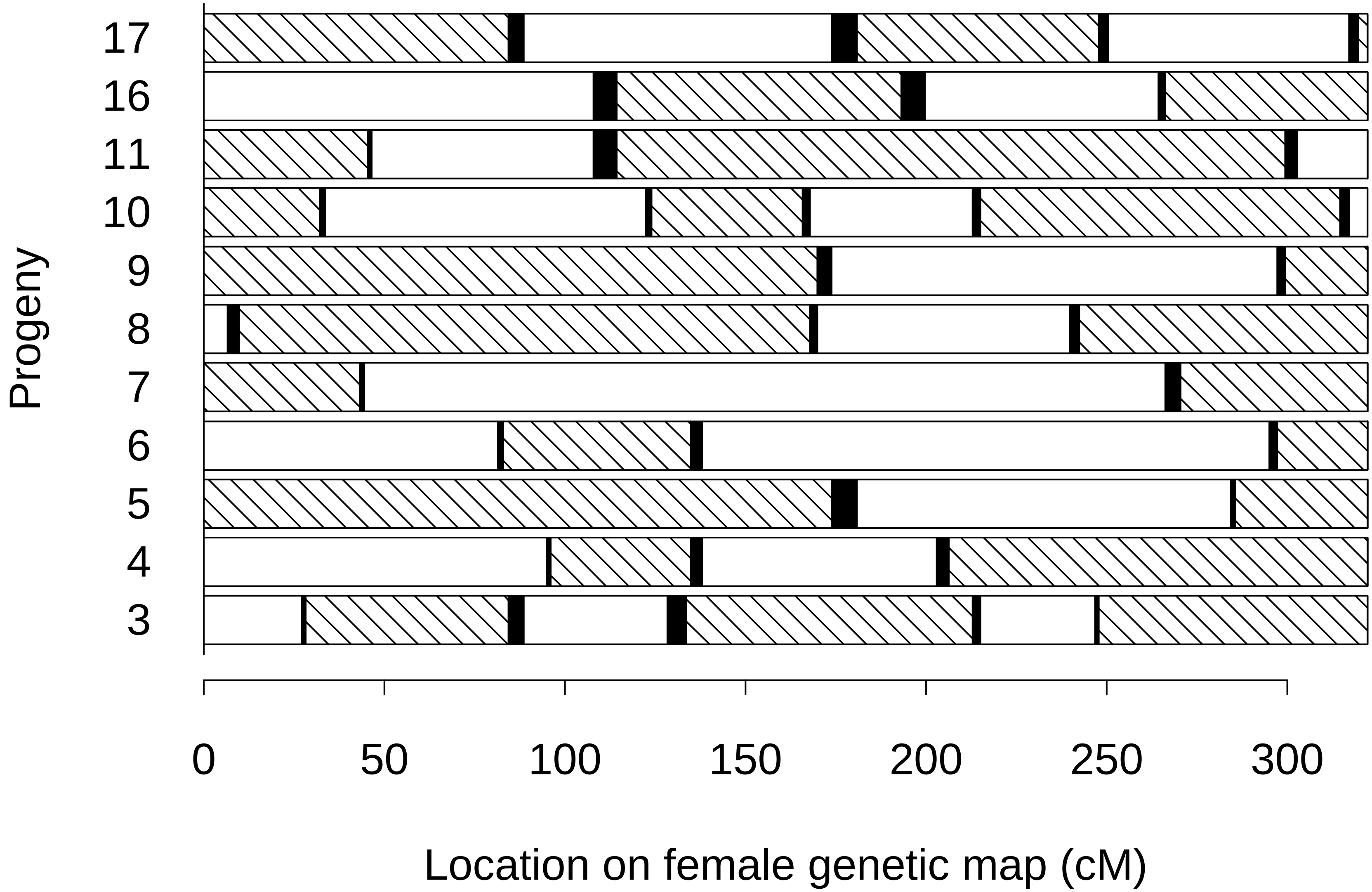
The data


Progeny
17
16
11
10
9
8
7
6
5
4
3
0
50
100
150
200
250
300
Location on female genetic map (cM)

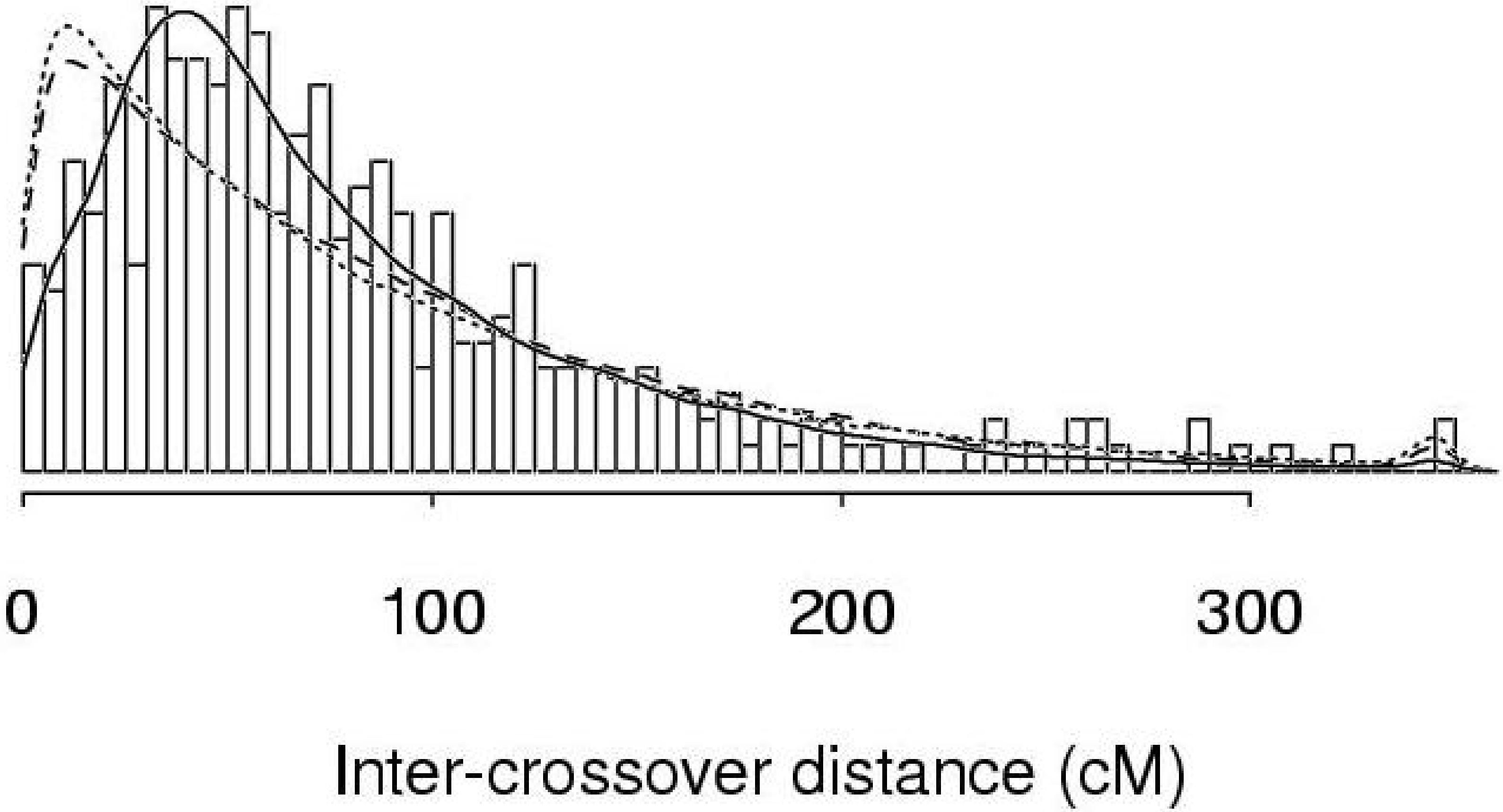
MLEs of interference parameter



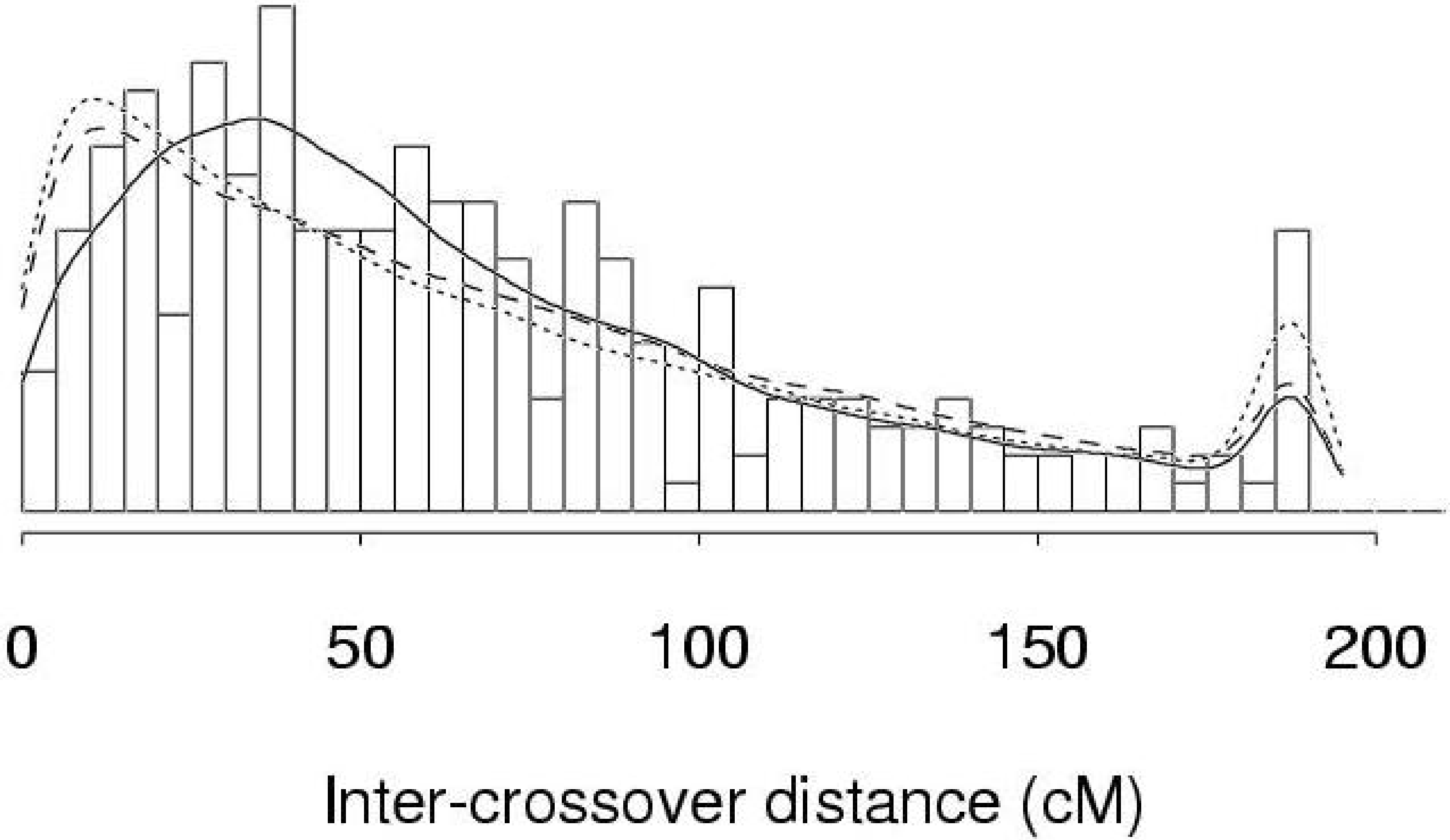
Goodness of fit?



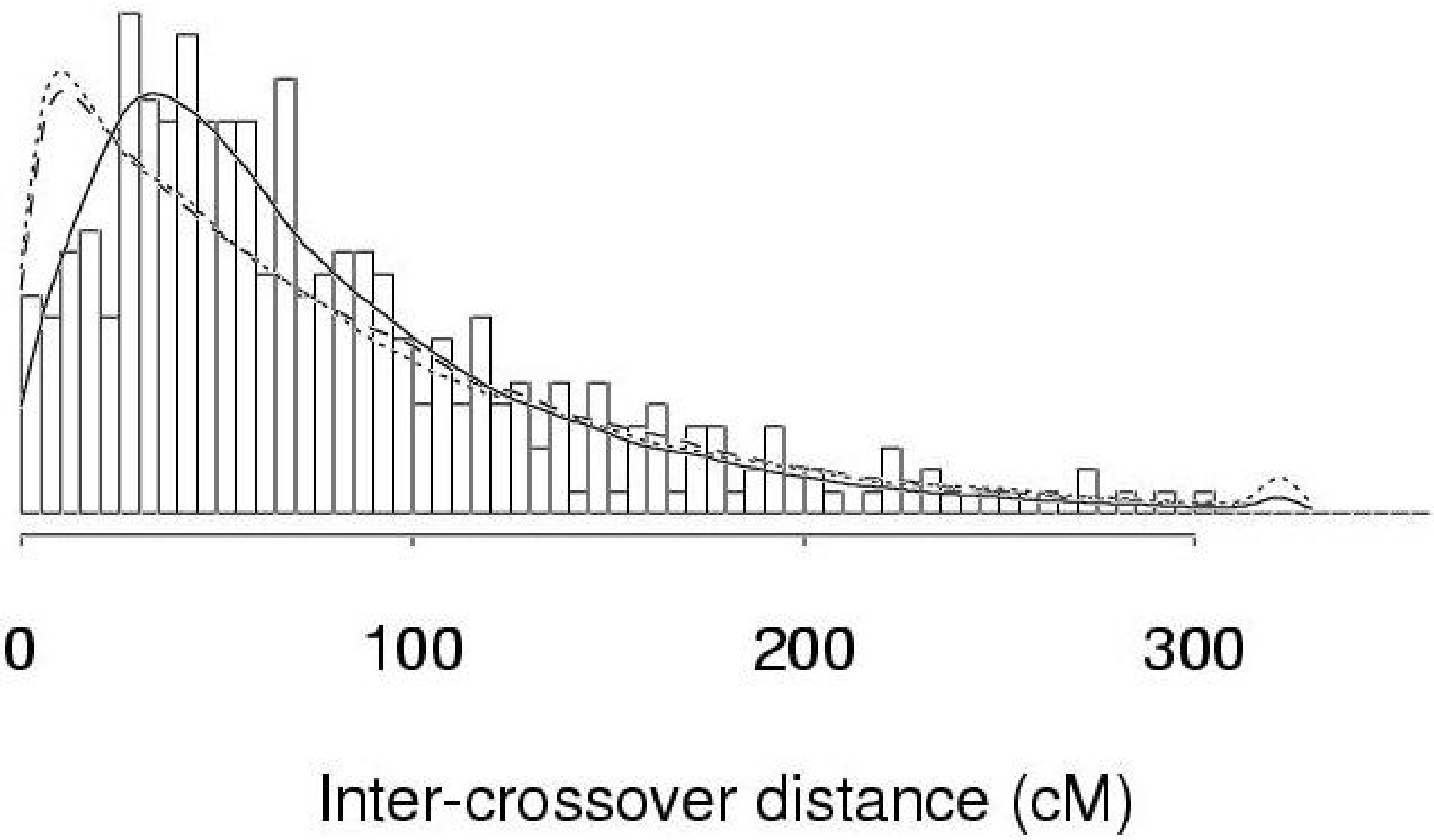
Maternal chromosome 1



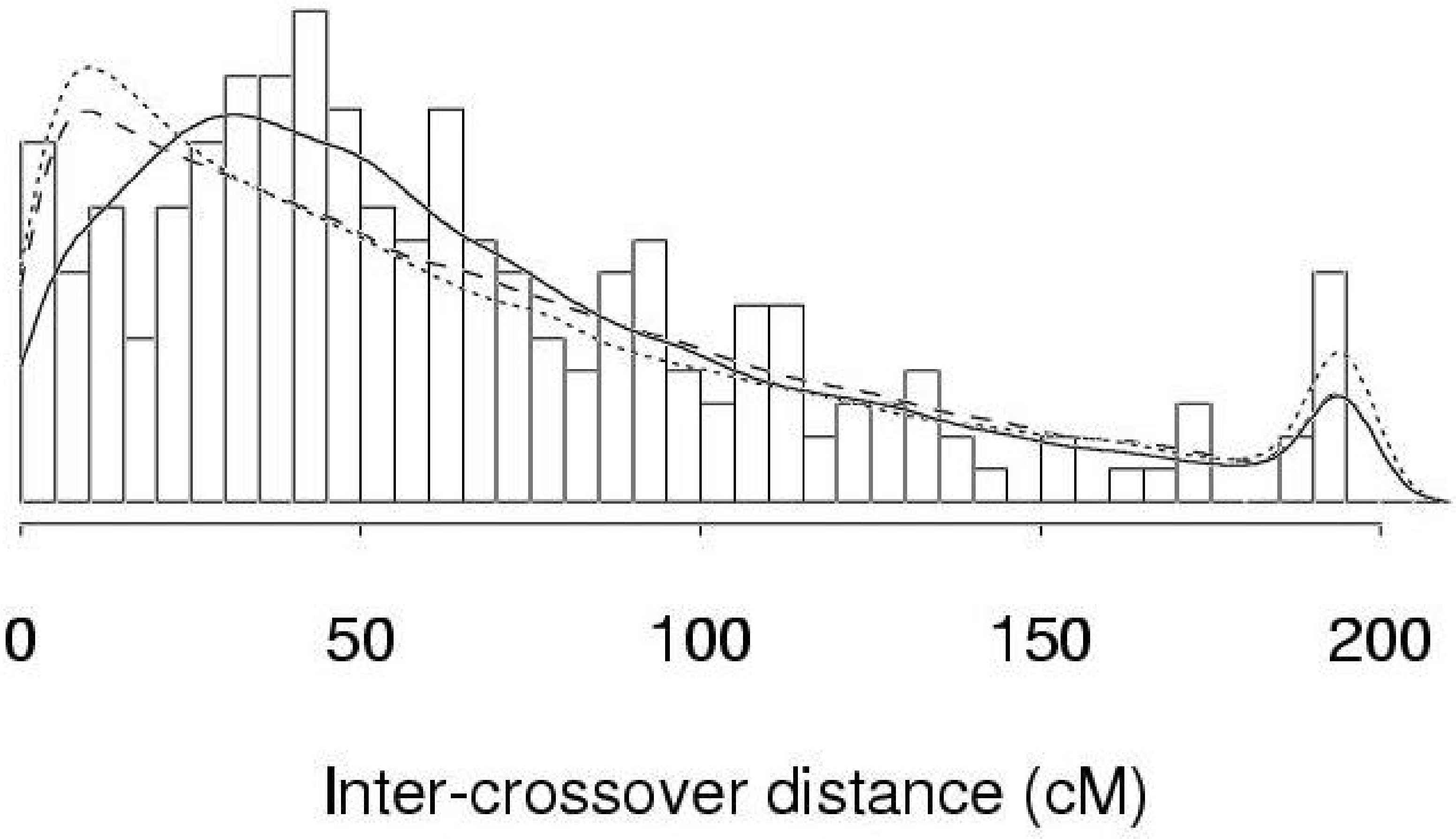
Paternal chromosome 1



Maternal chromosome 2



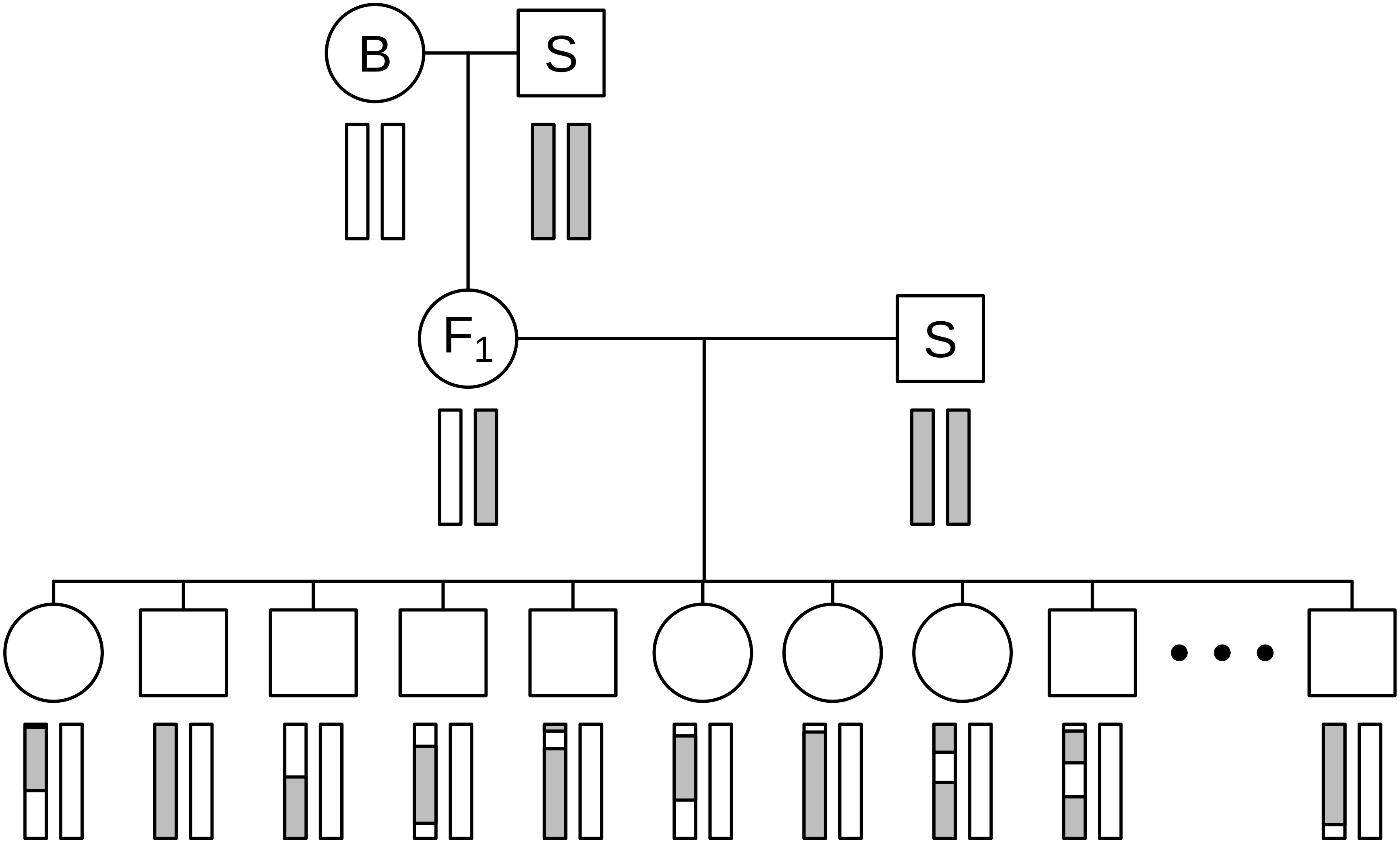
Paternal chromosome 2



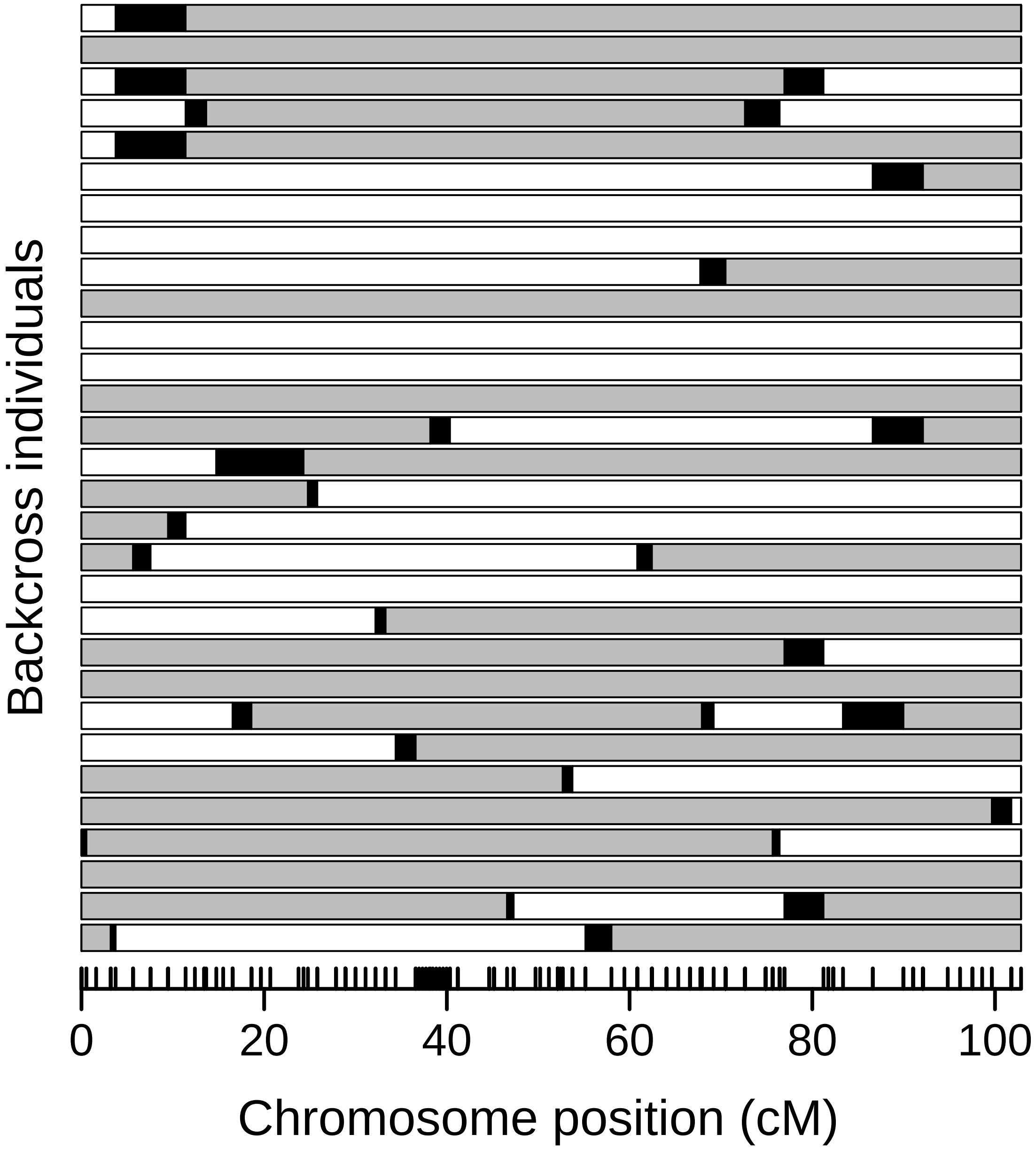
Mouse data

- `http://www.jax.org/resources/documents/cmdata/ftp.html`
- Two interspecific backcrosses with common F_1 parent
  - BSB: (C57BL/6J × M. spretus) × C57BL/6J
  - BSS: (C57BL/6J × SPRET/Ei) × SPRET/Ei
  - 94 individuals from each cross
- High-density STRP markers
  - BSB: 1372 markers
  - BSS: 4913 markers
- Average spacing:
  - BSB: 1.0 cM
  - BSS: 0.3 cM

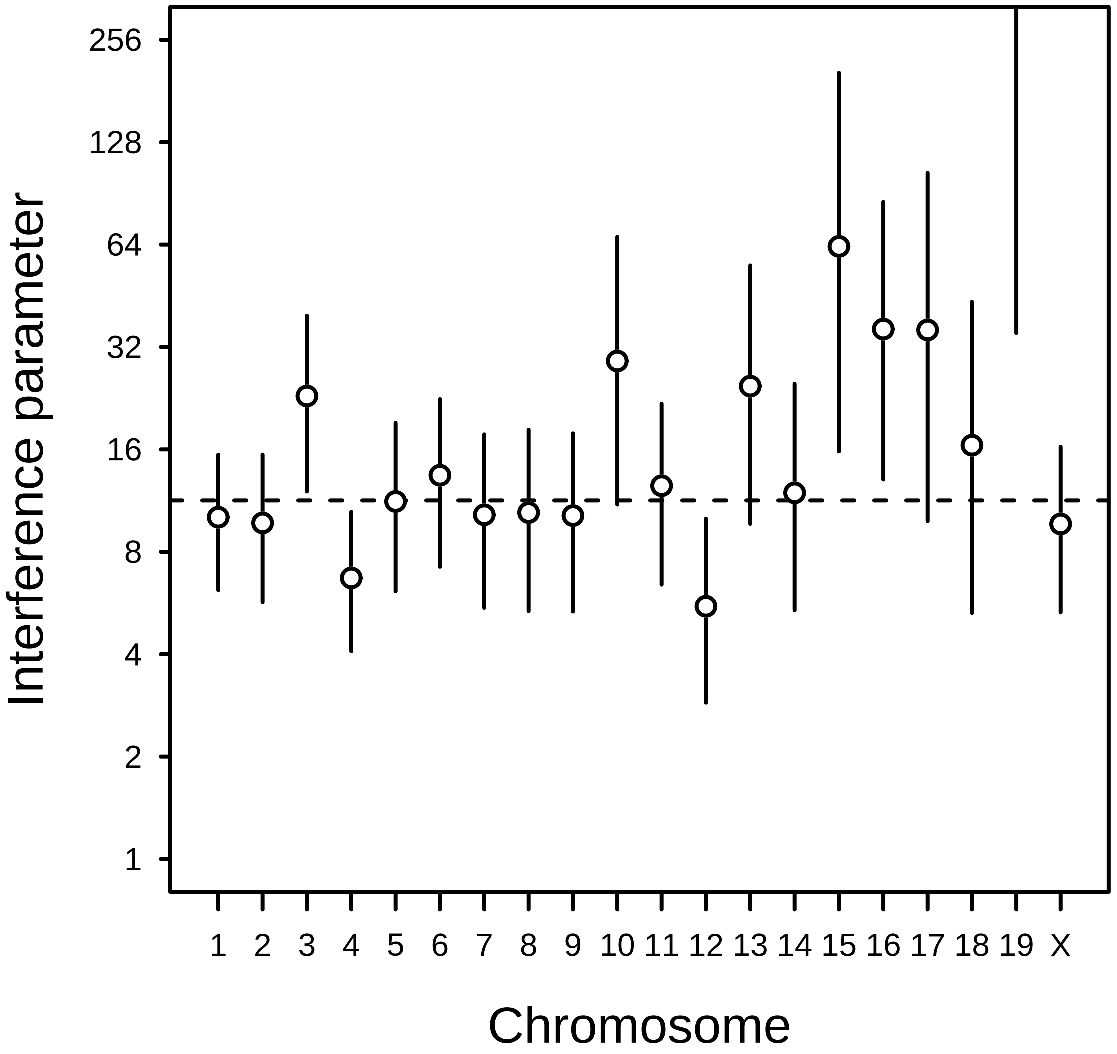
Backcross pedigree



Mouse data

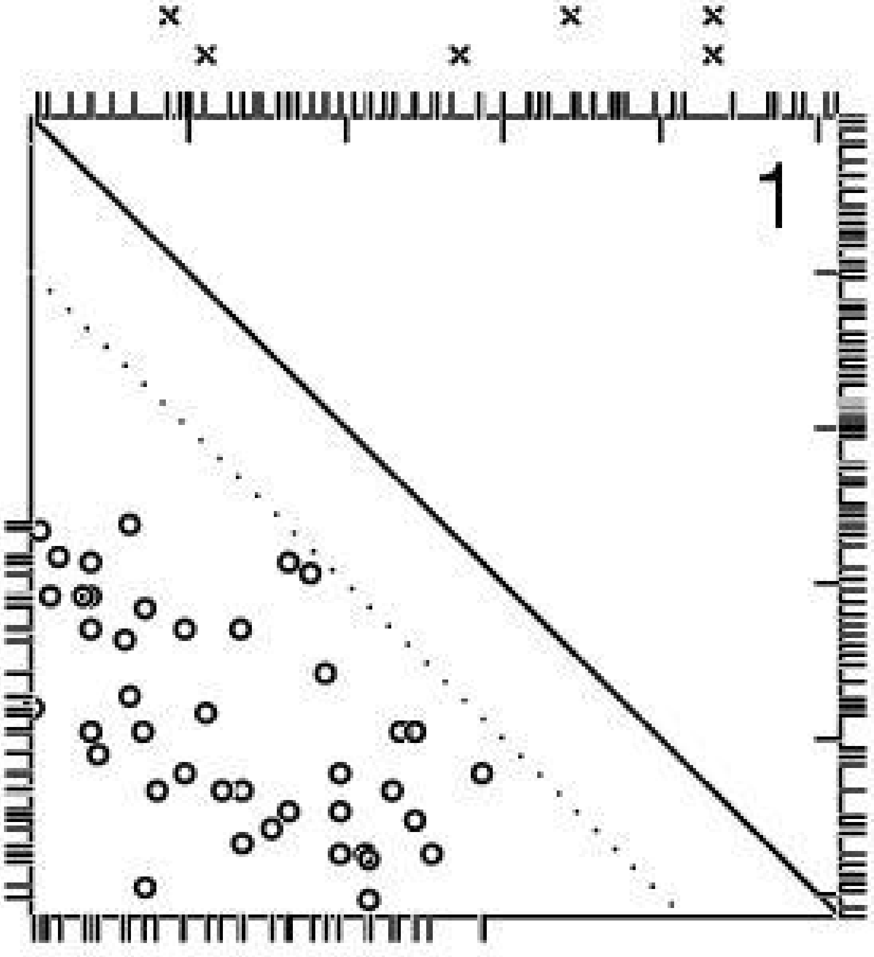

Backcross individuals
0
20
40
60
80
100
Chromosome position (cM)

MLEs: mouse

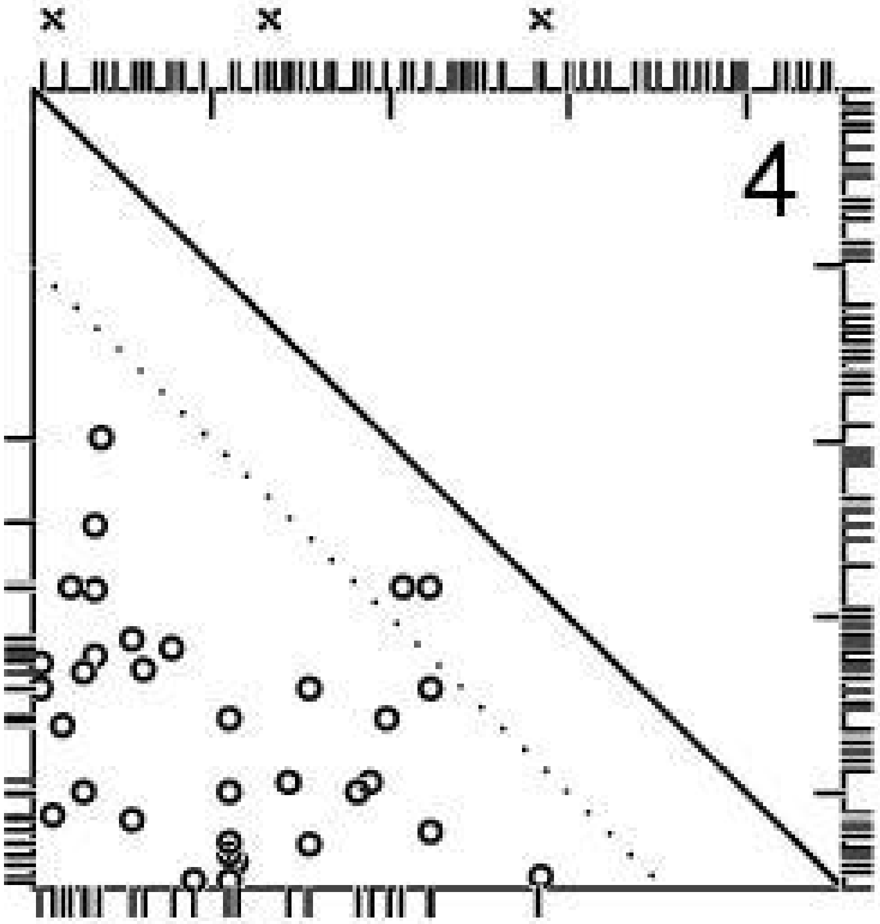


Interference parameter
256
128
64
32
16
8
4
2
1
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

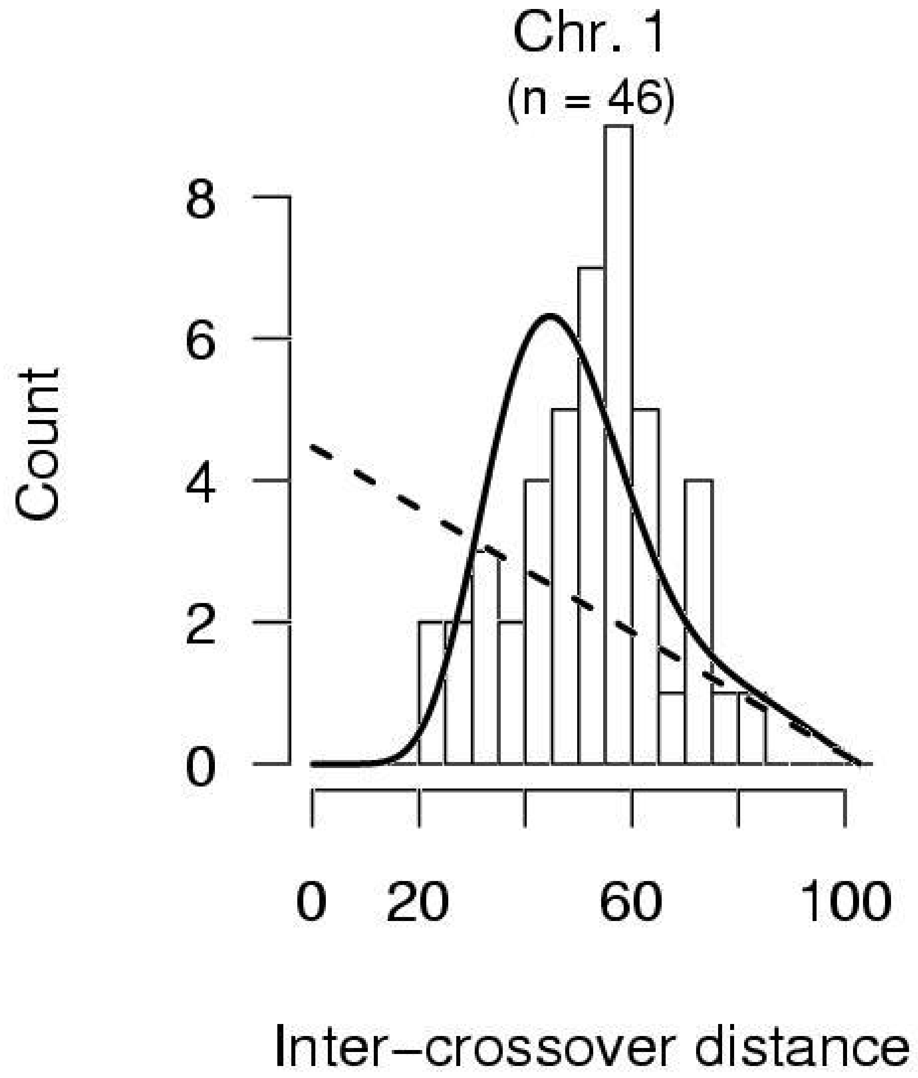
Crossover locations: Chr 1



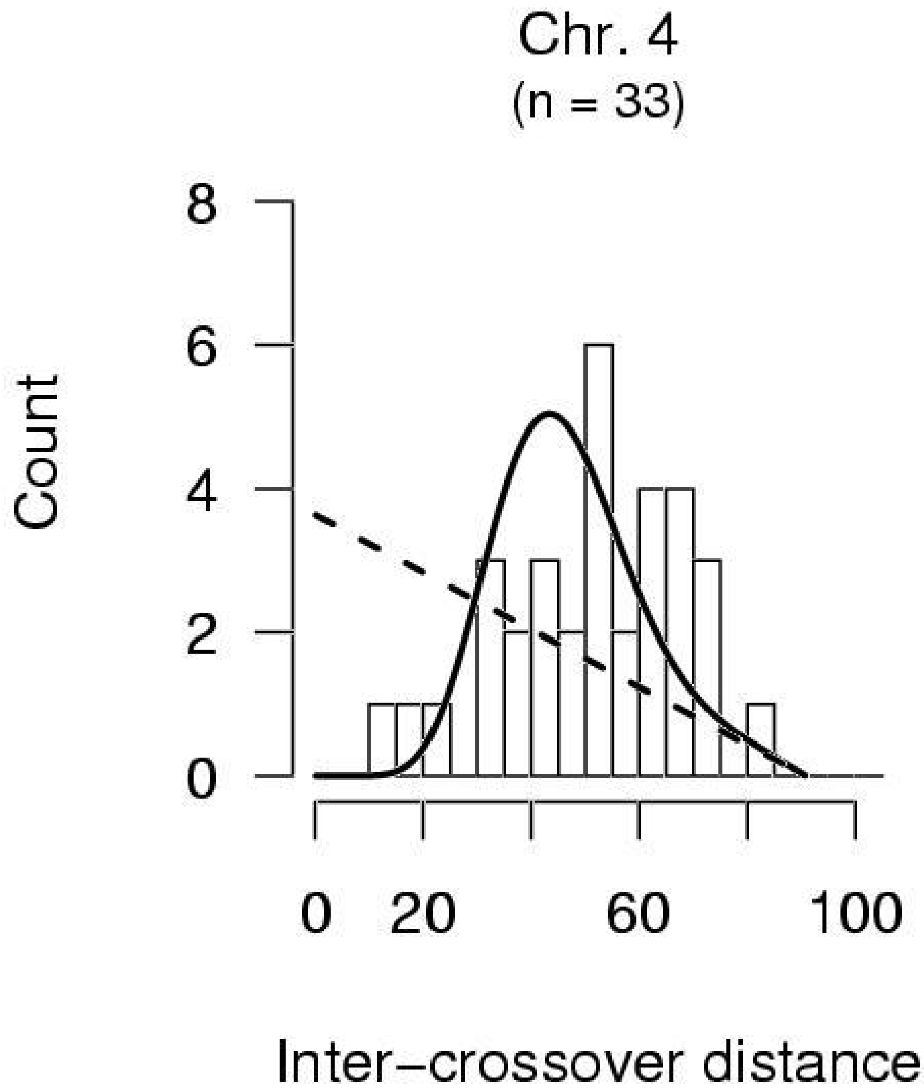
Crossover locations: Chr 4



Inter-XO distances: Chr 1



Inter-XO distances: Chr 4



Acknowledgements

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