The breakpoint process on RI chromosomes

(a work in progress)

Karl W Broman
Department of Biostatistics
Johns Hopkins University

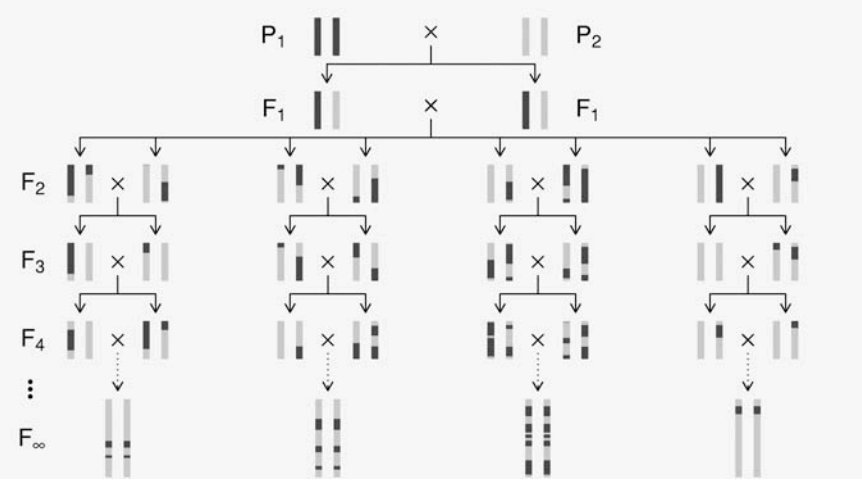
http://www.biostat.jhsph.edu/~kbroman

C57BL/6

2

Recombinant inbred lines

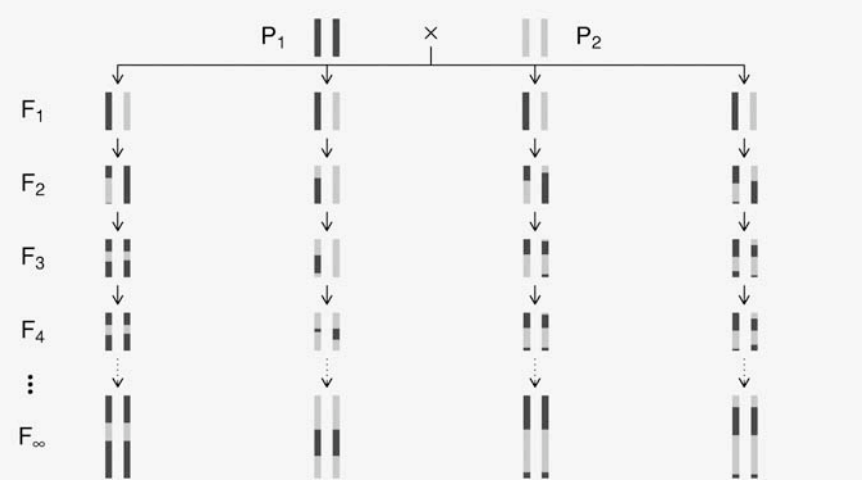
(by sibling matings)



3

Recombinant inbred lines

(by selfing)



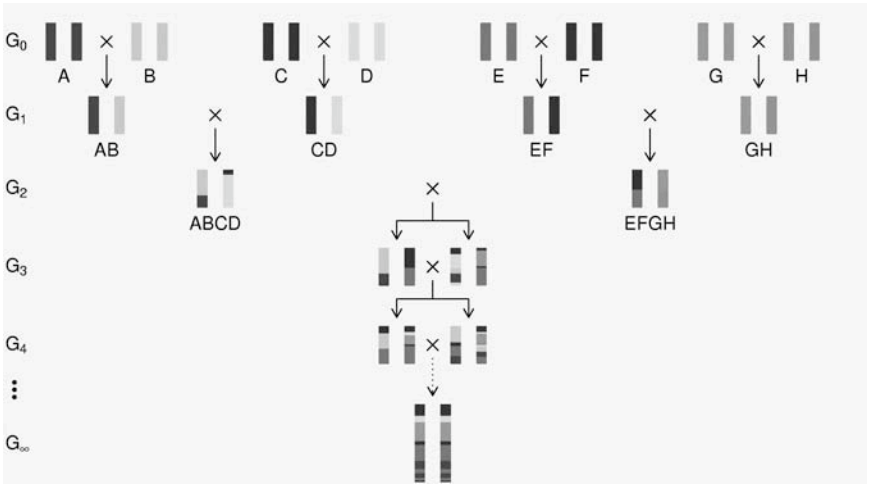
4

Advantages of RI lines

- Each strain is a eternal resource.
  - Only need to genotype once.
  - Reduce individual variation by phenotyping multiple individuals from each strain.
  - Study multiple phenotypes on the same genotype.
- Greater mapping precision.
  - More dense breakpoints on the RI chromosomes.

5

The “Collaborative Cross”



6

Genome of an 8-way RI

7

The goal

- Characterize the breakpoint process along a chromosome in 8-way RILs.
  - Understand the two-point transition matrix.
  - Study the clustering of the breakpoints, as a function of crossover interference in meiosis.

8

Why?

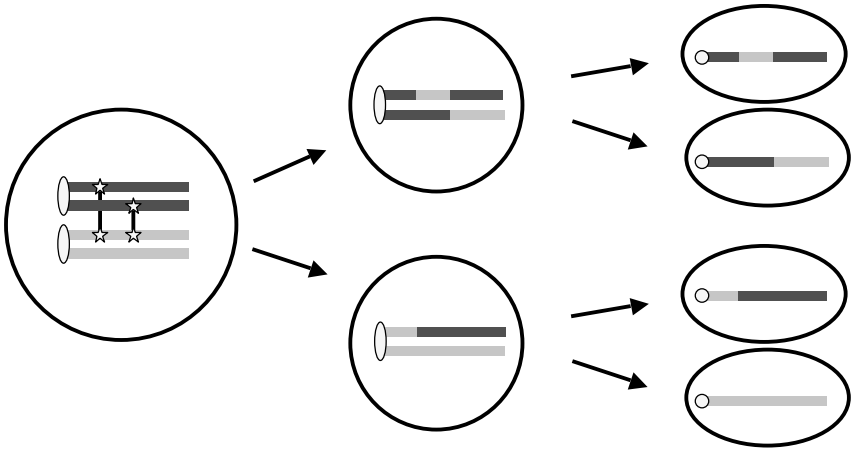
- It's interesting.
- Later statistical analyses will require:
  - The transition matrix.
  - A model for the whole process.

Actually, we'll probably just assume that:

- The breakpoints follow a Poisson process.
- The genotypes follow a Markov chain.

9

Meiosis



10

Crossover interference

- Most of the time we assume:
  - Crossovers occur according to a Poisson process, and so genotypes along a chromosome follow a Markov chain.
- In reality, crossovers tend not to occur too close together (positive crossover interference).
- Crossover interference is particularly strong in the mouse.

11

2 points in an RIL

- r = recombination fraction = probability of a recombination in the interval (in a random meiotic product).
- R = analogous thing for the RIL = probability of different genotypes at the two loci in a random RIL.

12

Haldane & Waddington 1931

INBREEDING AND LINKAGE*

J. B. S. HALDANE AND C. H. WADDINGTON
John Innes Horticultural Institution, London, England

Received August 9, 1930

Genetics 16:357-374

TABLE OF CONTENTS

When a heterozygous population is self-fertilized or inbred the ultimate result (apart from effects of mutation) is complete homozygosis. The final proportions of the various genotypes are usually independent of the system of inbreeding adopted, although, as JENNINGS (1916) and others have shown, the speed at which equilibrium is approached is greater in the case of self-fertilization than of brother-sister mating, and so on.

13

Equations for selfing

C_n *AABB* and *aabb*.
D_n *AAbb* and *aaBB*.
E_n *AABb*, *AaBB*, *Aabb*, and *aaBb*.
F_n *AB.ab*.
G_n *Ab.aB*.

We assume $2C_n+2D_n+4E_n+F_n+G_n=2$, so that $C_1=D_1=E_1=G_1=0$, and $F_1=2$. Clearly $E_\infty=F_\infty=G_\infty=0$, and D_∞ is the final proportion of crossover zygotes. Then considering the results of selfing each generation, we have:

$$\left.\begin{aligned}
C_{n+1} &= C_n + \tfrac{1}{2}E_n + \tfrac{1}{4}(1-\beta-\delta+\beta\delta)F_n + \tfrac{1}{4}\beta\delta G_n \\
D_{n+1} &= D_n + \tfrac{1}{2}E_n + \tfrac{1}{4}\beta\delta F_n + \tfrac{1}{4}(1-\beta-\delta+\beta\delta)G_n \\
E_{n+1} &= \tfrac{1}{2}E_n + \tfrac{1}{4}(\beta+\delta-2\beta\delta)(F_n+G_n) \\
F_{n+1} &= \tfrac{1}{2}(1-\beta-\delta+\beta\delta)F_n + \tfrac{1}{2}\beta\delta G_n \\
G_{n+1} &= \tfrac{1}{2}\beta\delta F_n + \tfrac{1}{2}(1-\beta-\delta+\beta\delta)G_n
\end{aligned}\right\} \quad (1.1)$$

or C_{n+1}, D_{n+1}, and F_{n+1}, G_{n+1},

d_n } (1.2)

r all values of n.
$- 2x)d_n$

$= \dfrac{1-2x}{1+2x}$.

Put $y=D_\infty$ (the final proportion of crossover zygotes)

$\therefore\ C_\infty + D_\infty = 1,\ C_\infty - D_\infty = c_\infty\ \therefore\ y = \tfrac{1}{2}(1-c_\infty).$

$$\therefore\ y = \frac{2x}{1+2x}. \quad (1.3)$$

14

Equations for sib-matings

Typical mating	Number of types	
$AABB\times AABB$	2	$C_{n+1}=C_n+H+\frac{1}{4}(\alpha^2+\gamma^2)L+\frac{1}{4}(\beta^2+\delta^2)N+\frac{1}{8}Q+\frac{1}{8}R+\frac{1}{8}(\alpha^2+\gamma^2)$ $U+\frac{1}{8}(\beta^2+\delta^2)V+\frac{1}{16}\alpha^2\gamma^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\beta^2\delta^2Y.$
$AAbb\times AAbb$	2	$D_{n+1}=D+I+\frac{1}{4}(\alpha^2+\gamma^2)M+\frac{1}{4}(\beta^2+\delta^2)P+\frac{1}{8}Q+\frac{1}{8}S+\frac{1}{8}(\beta^2+\delta^2)$ $U+\frac{1}{8}(\alpha^2+\gamma^2)V+\frac{1}{16}\beta^2\delta^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\alpha^2\gamma^2Y.$
$AABB\times aabb$	2	$E_{n+1}=\frac{1}{16}\alpha^2\gamma^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\beta^2\delta^2Y.$
$AAbb\times aaBB$	2	$F_{n+1}=\frac{1}{16}\beta^2\delta^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\alpha^2\gamma^2Y.$
$AABB\times AAbb$	8	$G_{n+1}=\frac{1}{16}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{16}\alpha\beta\gamma\delta(W+2X+Y).$
$AABB\times AABb$	8	$H_{n+1}=\frac{1}{2}H+$ $U+\frac{1}{16}($ $(\alpha\delta+\beta$
$AAbb\times AABb$	8	$I_{n+1}=\frac{1}{2}I+$ $U+\frac{1}{16}($ $(\alpha\delta+\beta$
$AABB\times Aabb$	8	$J_{n+1}=\frac{1}{16}($ $\beta\delta)(\alpha\delta$
$AAbb\times AaBB$	8	$K_{n+1}=\frac{1}{16}$ $\beta\delta)(\alpha\delta$
$AABB\times AB.ab$	4	$L_{n+1}=\frac{1}{4}(\alpha$ $\alpha^2\gamma^2W$
$AAbb\times Ab.aB$	4	$M_{n+1}=\frac{1}{2}($ $\beta^2\delta^2W+$

Typical mating	Number of types	
$AABB\times Ab.aB$	4	$N_{n+1}=\frac{1}{2}R+\frac{1}{4}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{8}\alpha\beta\gamma\delta(W+2X+Y).$
$AAbb\times AB.ab$	4	$P_{n+1}=\frac{1}{2}S+\frac{1}{4}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{8}\alpha\beta\gamma\delta(W+2X+Y).$
$AABb\times AABb$	4	$Q_{n+1}=2G+\frac{1}{2}(H+I+J+K)+\frac{1}{4}(\alpha^2+\gamma^2)(L+M)+\frac{1}{4}(\beta^2+\delta^2)$ $(N+P)+\frac{1}{8}Q+\frac{1}{8}(R+S+T)+\frac{1}{16}(\alpha^2+\alpha\beta+\beta^2+\gamma^2+\gamma\delta+\delta^2)$ $(U+V)+\frac{1}{16}(\alpha\delta+\beta\gamma)^2(W+Y)+\frac{1}{8}(\alpha\gamma+\beta\delta)^2X.$
$AABb\times AaBB$	4	$R_{n+1}=\frac{1}{4}(\beta^2+\delta^2)L+\frac{1}{4}(\alpha^2+\gamma^2)N+\frac{1}{8}R+\frac{1}{8}(\beta+\delta)U+\frac{1}{8}(\alpha+\gamma)V+$ $\frac{1}{16}(\alpha\delta+\beta\gamma)^2(W+Y)+\frac{1}{8}(\alpha\gamma+\beta\delta)^2X.$
$AABb\times Aabb$	4	$S_{n+1}=\frac{1}{4}(\beta^2+\delta^2)M+\frac{1}{4}(\alpha^2+\gamma^2)P+\frac{1}{8}S+\frac{1}{8}(\alpha+\gamma)U+\frac{1}{8}(\beta+\delta)V+\frac{1}{16}$ $(\alpha\delta+\beta\gamma)^2(W+Y)+\frac{1}{8}(\alpha\gamma+\beta\delta)^2X.$
$AABb\times aaBb$	4	$T_{n+1}=\frac{1}{8}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{16}(\alpha\delta+\beta\gamma)^2(W+Y)+\frac{1}{8}(\alpha\gamma+\beta\delta)^2X.$
$AABb\times AB.ab$	8	$U_{n+1}=\frac{1}{2}J+\frac{1}{4}(\alpha\beta+\gamma\delta)(L+N)+\frac{1}{8}(S+T)+\frac{1}{8}(\alpha+\gamma)U+\frac{1}{8}(\beta+\delta)$ $V+\frac{1}{8}\alpha\gamma(\beta\gamma+\alpha\delta)W+\frac{1}{8}(\alpha\gamma+\beta\delta)(\alpha\delta+\beta\gamma)X+\frac{1}{8}\beta\delta(\beta\gamma+\alpha\delta)Y.$
$AABb\times Ab.aB$	8	$V_{n+1}=\frac{1}{2}K+\frac{1}{4}(\alpha\beta+\gamma\delta)(M+P)+\frac{1}{8}(R+T)+\frac{1}{8}(\beta+\delta)U+\frac{1}{8}(\alpha+\gamma)$ $V+\frac{1}{8}\beta\delta(\beta\gamma+\alpha\delta)W+\frac{1}{8}(\alpha\gamma+\beta\delta)(\alpha\delta+\beta\gamma)X+\frac{1}{8}\alpha\gamma(\beta\gamma+\alpha\delta)Y.$
$AB.ab\times AB.ab$	1	$W_{n+1}=2(E+J)+\frac{1}{4}(\alpha^2+\gamma^2)L+\frac{1}{4}(\beta^2+\delta^2)N+\frac{1}{8}(S+T)+\frac{1}{8}(\alpha^2+\gamma^2)$ $U+\frac{1}{8}(\beta^2+\delta^2)V+\frac{1}{16}\alpha^2\gamma^2W+\frac{1}{8}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{8}\beta^2\delta^2Y.$
$AB.ab\times Ab.aB$	2	$X_{n+1}=\frac{1}{2}T+\frac{1}{4}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{8}\alpha\beta\gamma\delta(W+2X+Y).$
$Ab.aB\times Ab.aB$	1	$Y_{n+1}=2(F+K)+\frac{1}{4}(\alpha^2+\gamma^2)M+\frac{1}{4}(\beta^2+\delta^2)P+\frac{1}{8}(R+T)+\frac{1}{8}(\beta^2+$ $\delta^2)U+\frac{1}{8}(\alpha^2+\gamma^2)V+\frac{1}{16}\beta^2\delta^2W+\frac{1}{8}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{8}\alpha^2\gamma^2Y.$

15

Result for sib-matings

Omitting some rather tedious algebra, the solution of these equations is:

$$\zeta=\frac{q}{2-3q},\quad \theta=\frac{2q}{2-3q},\quad \kappa=\frac{1}{2-3q},$$

$$\lambda=\frac{1-2q}{2-3q},\quad \mu=\frac{1-2q}{2-3q},\quad \nu=\frac{2q}{2-3q}$$

as may easily be verified.

$$\therefore\ c_\infty=c_n+2e_n+\frac{1}{1+6x}[(1-2x)(d_n+2f_n+2j_n+\tfrac{1}{2}k_n)+2g_n+4x(h_n+i_n)] \qquad (3.4)$$

and $y=\frac{1}{2}(1-c_\infty)$.

In the case considered, $d_0=1, \therefore c_\infty=\zeta d_0=1-2x/1+6x$. Hence the proportion of crossover zygotes, $y=4x/1+6x$ (3.5).

16

Haldane & Waddington 1931

r = recombination fraction per meiosis between two loci
G_i = allele at marker i in a random RIL.

Autosomes

$Pr(G_1=A) = Pr(G_1=B) = 1/2$

$Pr(G_2=B \mid G_1=A) = Pr(G_2=A \mid G_1=B) = 4r / (1+6r)$

X chromosome

$Pr(G_1=A) = 2/3 \qquad Pr(G_1=B) = 1/3$

$Pr(G_2=B \mid G_1=A) = 2r / (1+4r)$

$Pr(G_2=A \mid G_1=B) = 4r / (1+4r)$

$Pr(G_2 \neq G_1) = (8/3)\, r / (1+4r)$

17

8-way RILs

Autosomes

$Pr(G_1 = i) = 1/8$

$Pr(G_2 = j \mid G_1 = i) = r / (1+6r) \quad \text{for } i \neq j$

$Pr(G_2 \neq G_1) = 7r / (1+6r)$

X chromosome

$Pr(G_1=A) = Pr(G_1=B) = Pr(G_1=E) = Pr(G_1=F) = 1/6$

$Pr(G_1=C) = 1/3$

$Pr(G_2=B \mid G_1=A) = r / (1+4r)$

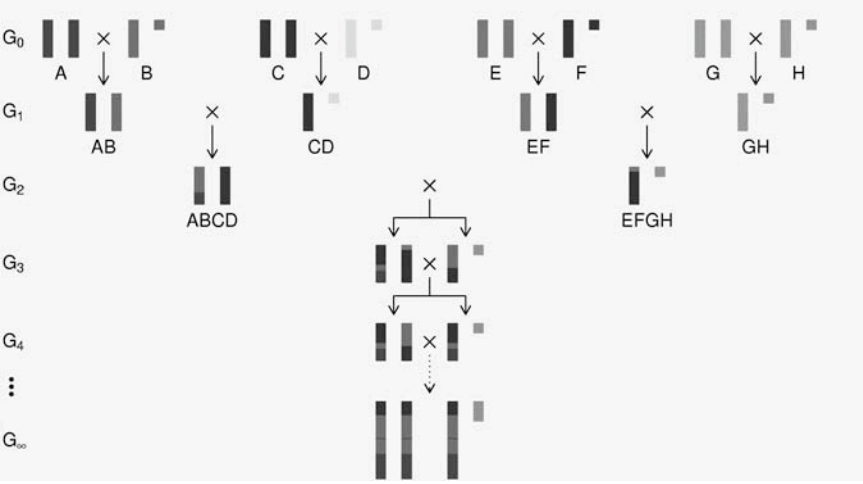
$Pr(G_2=C \mid G_1=A) = 2r / (1+4r)$

$Pr(G_2=A \mid G_1=C) = r / (1+4r)$

$Pr(G_2 \neq G_1) = (14/3)\, r / (1+4r)$

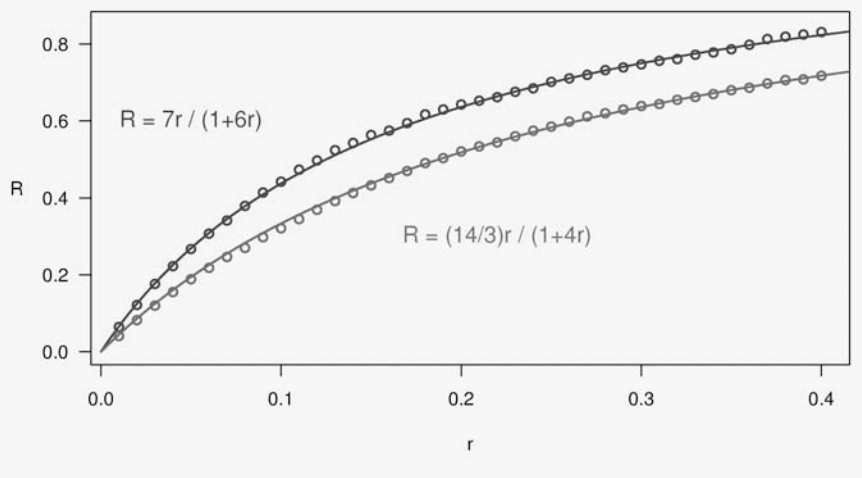
18

The X chromosome



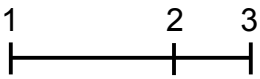
19

Computer simulations



20

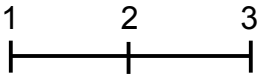
Coincidence



- r_{ij} = recombination fraction for interval i,j
- Coincidence = Pr(rec'n in both intervals) / (r_{12} r_{23})
  = (r_{12} + r_{23} – r_{13}) / (2 r_{12} r_{23})
- No interference = 1
- Positive interference < 1
- Negative interference > 1

21

3 points in 2-way RILs

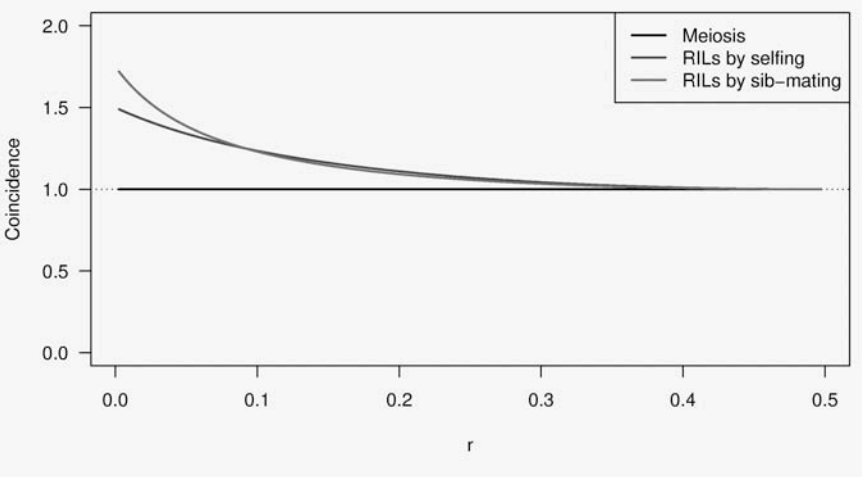


- M = map function; r = M(d)
- $r_{13} = M^{-1}[\, M(r_{12}) + M(r_{23}) \,]$
- Combine this with the result of H&W, and we can get the equivalent coincidence type thing for the RIL chromosome.
- Here we assume $r_{12} = r_{23} = r$.

22

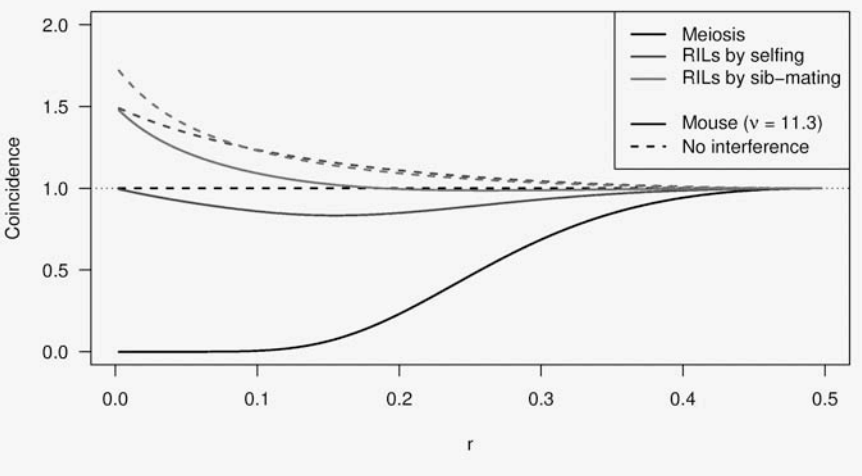
Coincidence

No interference



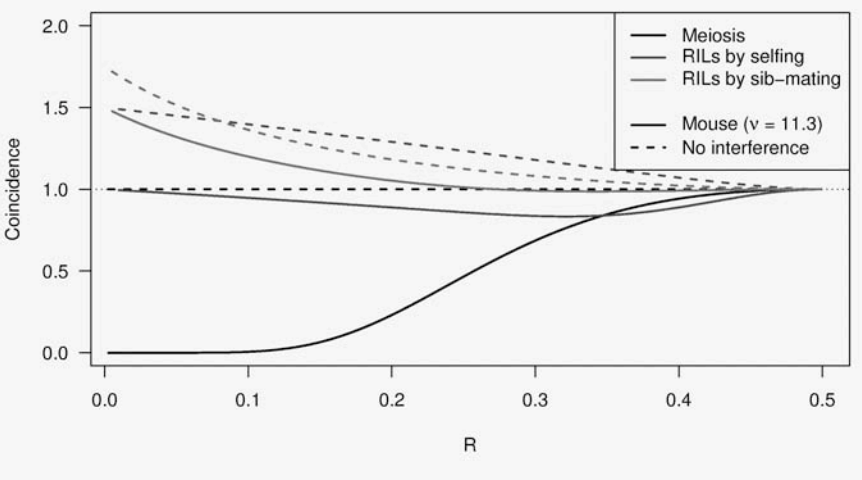
23

Coincidence



24

Coincidence



25

Why the clustering of breakpoints?

- The really close breakpoints occur in different generations.
- Breakpoints in later generations can occur only if there is heterozygosity (i.e., the region is not yet fixed).
- The regions of heterozygosity are, of course, surrounded by breakpoints.

26

Summary

- RILs are useful.
- The Collaborative Cross could provide “one-stop shopping” for gene mapping.
- Use of 8-way RILs requires an understanding of the breakpoint process.
- We’ve extended Haldane & Waddington’s results on 2-way RILs, but need to prove our results.
- We’ve come to understand 3 points in 2-way RILs, but need to extend this to the 8-way RILs.
- We’d like to:
  - Fully characterize the breakpoint process.
  - Study data (e.g., on 2-way RILs via selfing in Arabidopsis).

27