

# Computer simulations

The genomes of recombinant inbred lines

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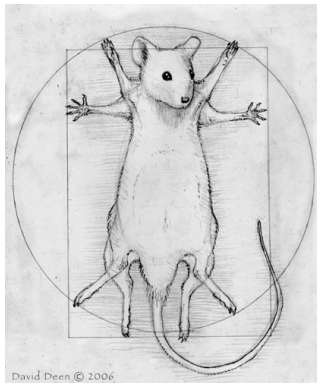
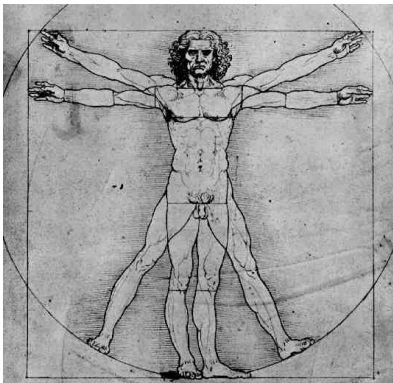
`kbroman.org`

`github.com/kbroman`

`@kwbroman`

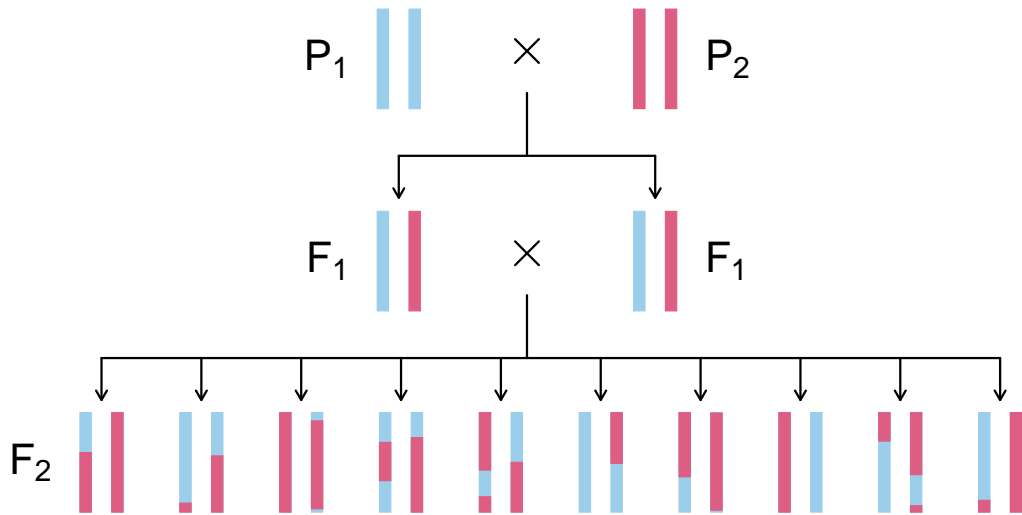
Course web: [kbroman.org/AdvData](https://kbroman.org/AdvData)



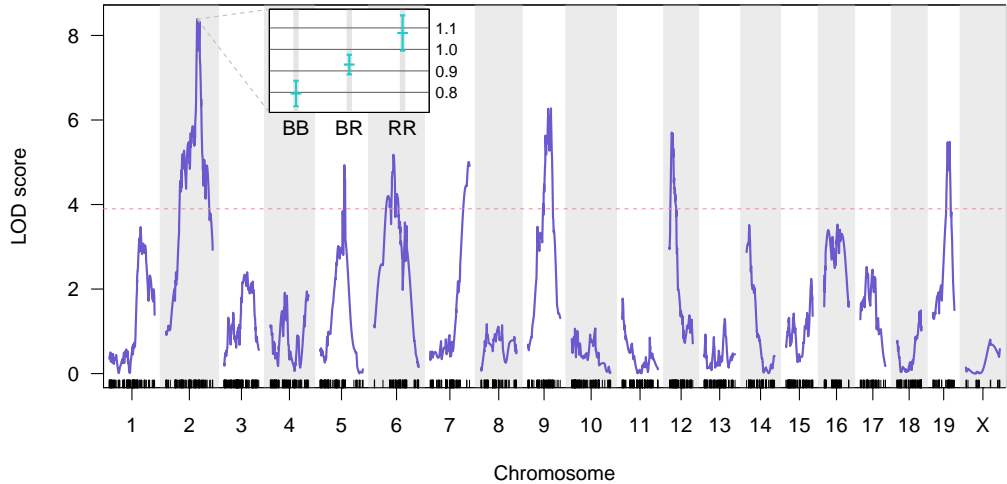


daviddeen.com

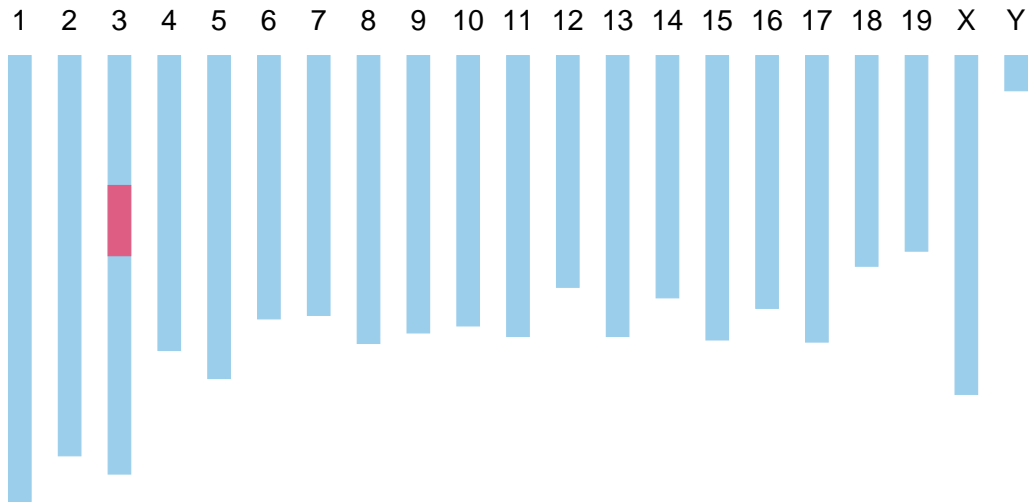
# Intercross



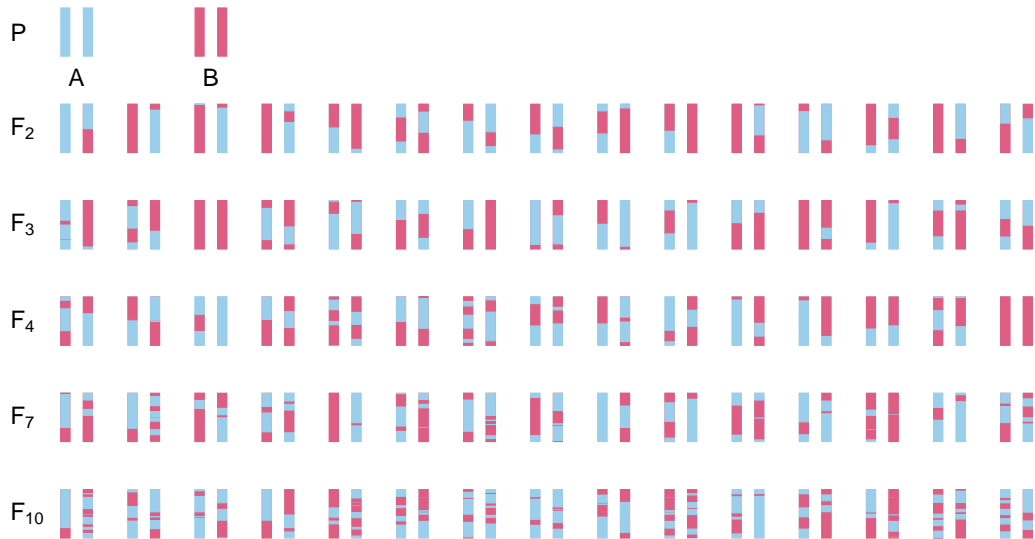
# QTL mapping



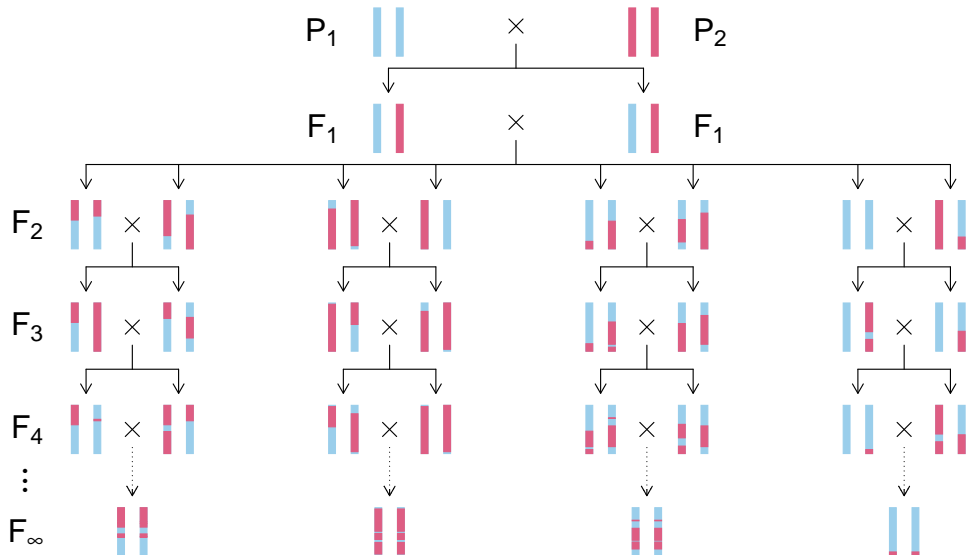
# Congenic line



# Advanced intercross lines

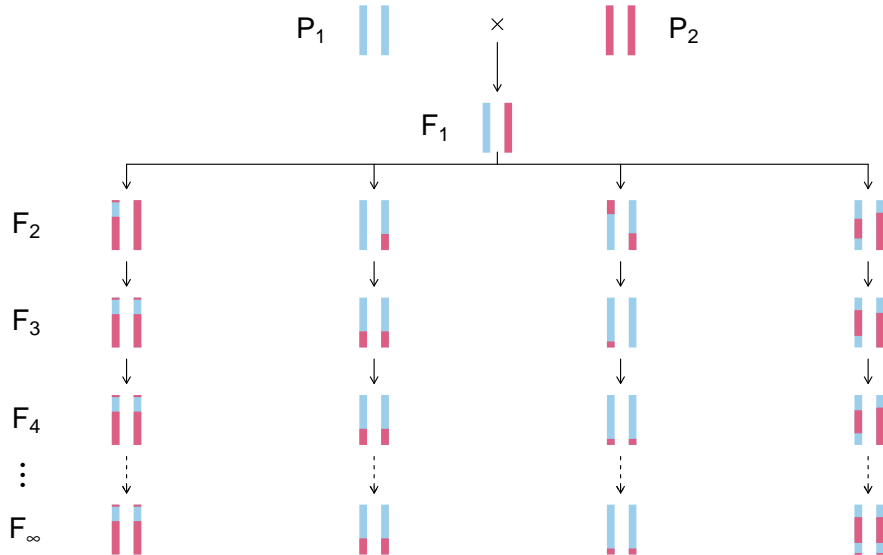


# Recombinant inbred lines

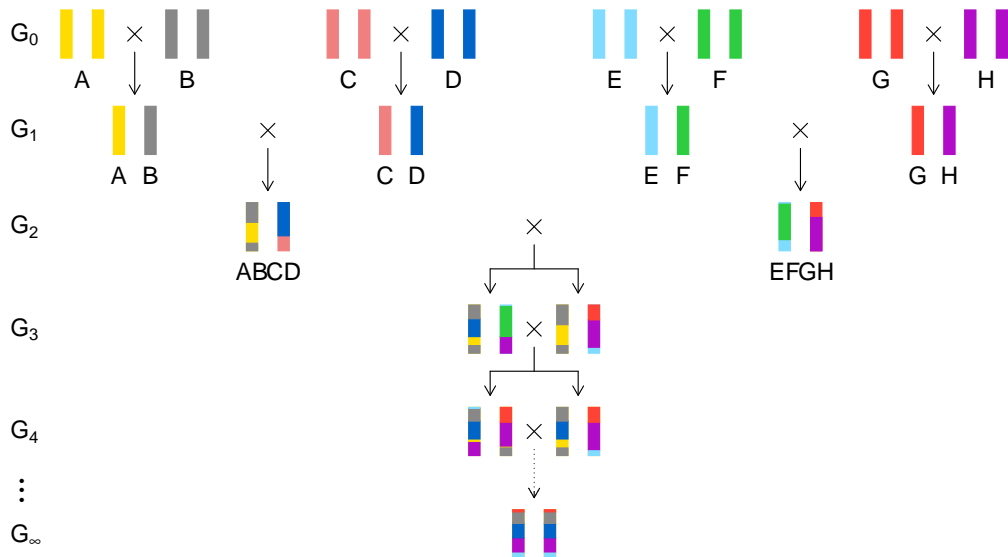




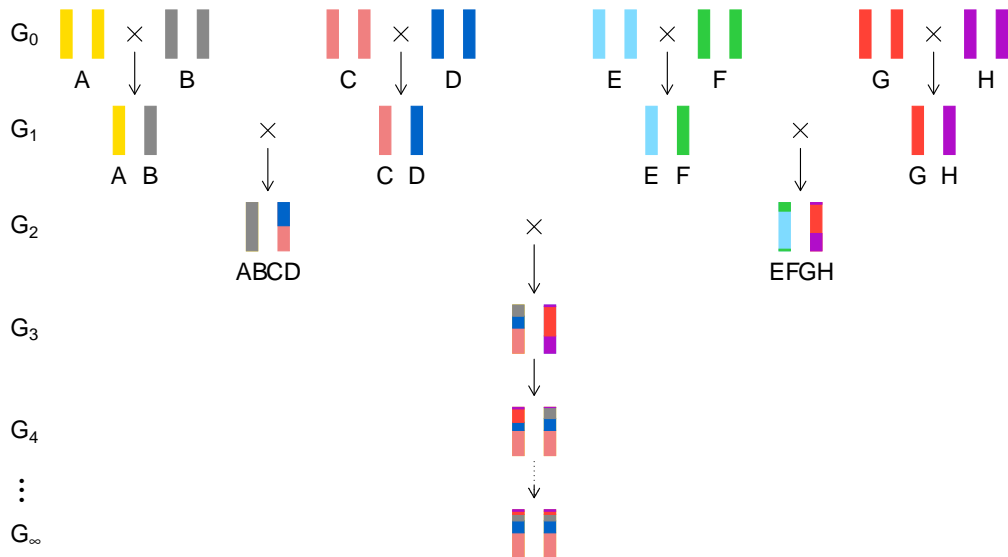
# Recombinant inbred lines



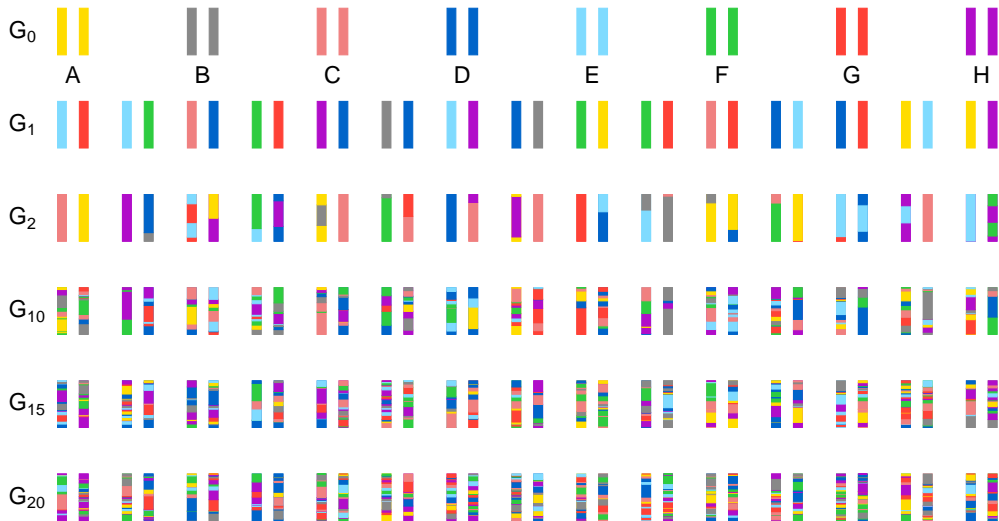
# Collaborative Cross



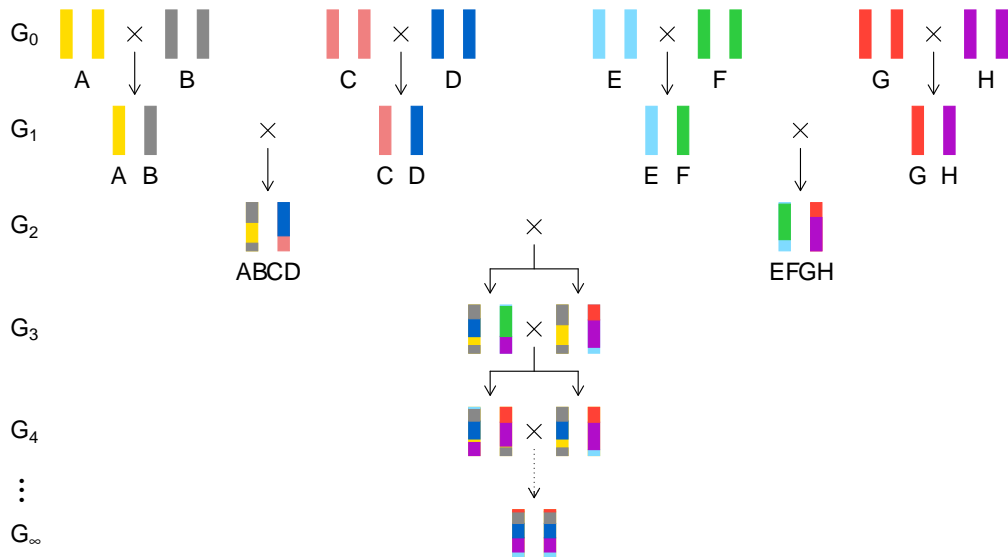
# MAGIC



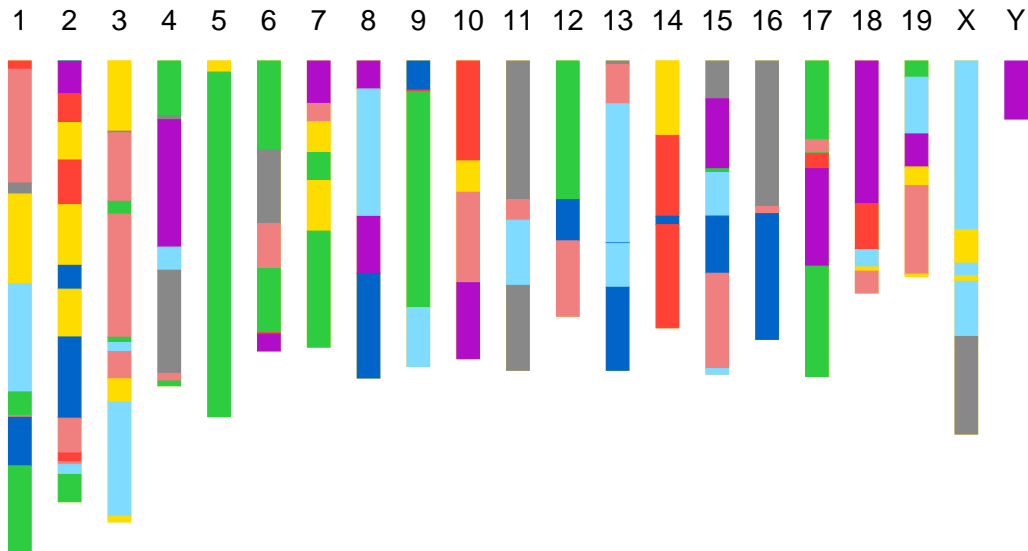
# Heterogeneous stock



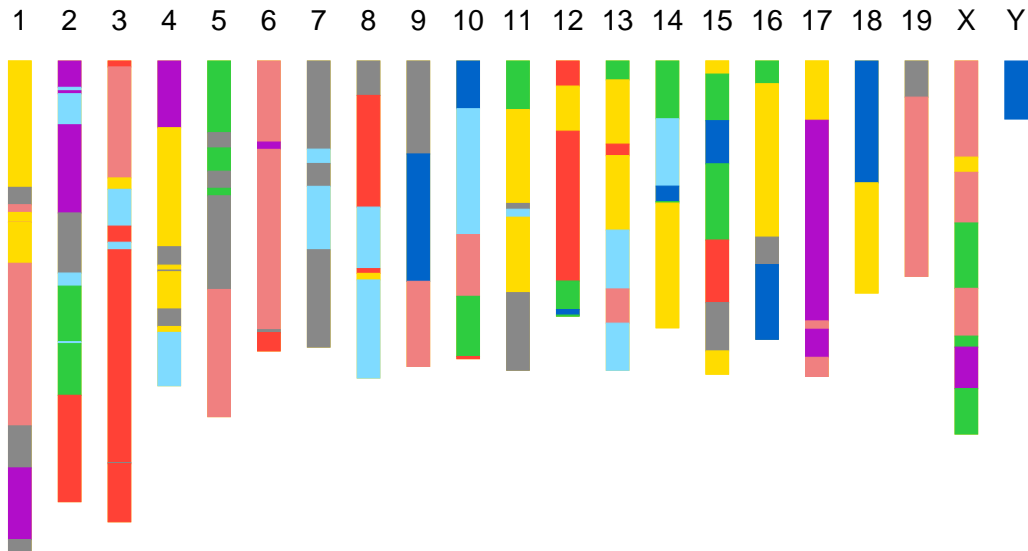
# Collaborative Cross



# CC genome



# CC genome

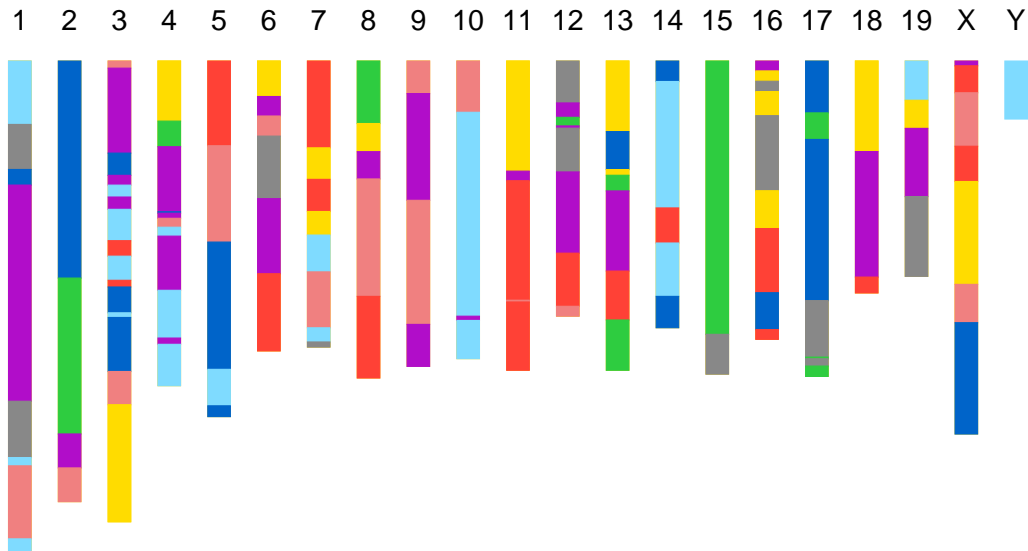


# CC genome

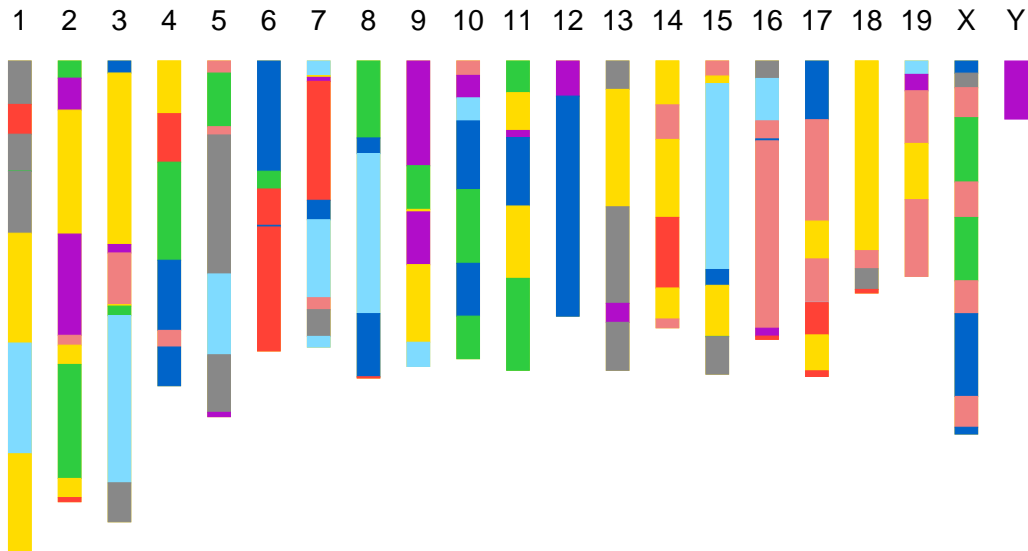




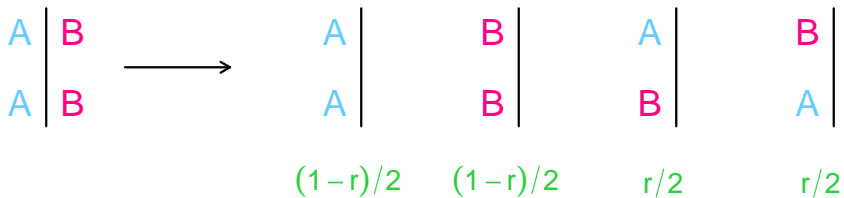
## CC genome



# CC genome

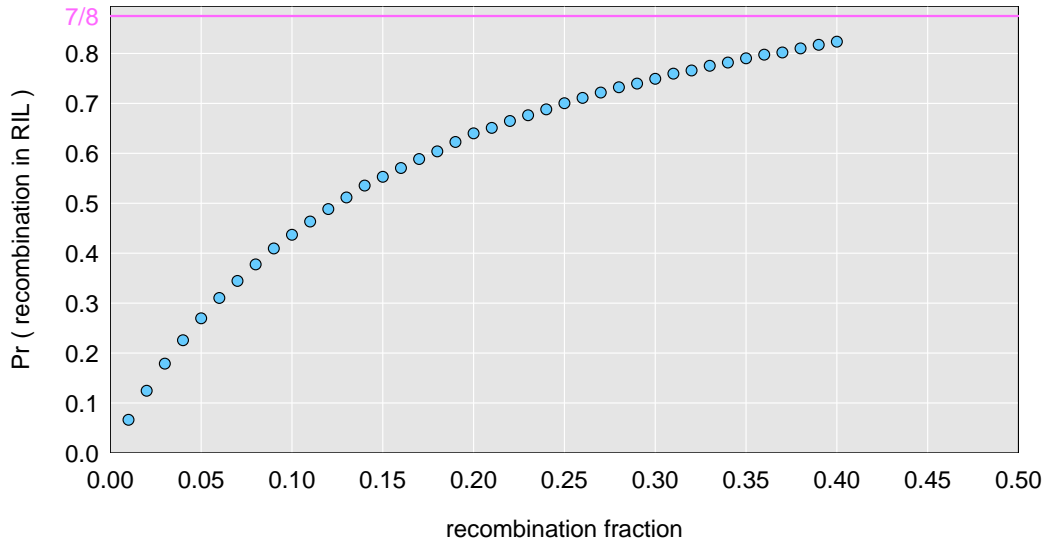


# Recombination fraction



$r$  is the "recombination fraction"

# Simulation results



# Haldane & Waddington 1931

## INBREEDING AND LINKAGE\*

J. B. S. HALDANE AND C. H. WADDINGTON

*John Innes Horticultural Institution, London, England*

Received August 9, 1930

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## Result for selfing

Then  $c_n + \lambda d_n \equiv c_n + \frac{1}{4}(1 - 2x)d_n + \frac{1}{2}\lambda(1 - 2x)d_n$

$$\therefore \lambda = \frac{1 - 2x}{2 + 4x}.$$

Then since  $d_\infty = 0$ , and  $c_1 = 0$ ,  $d_1 = 2$ ,

$$c_\infty = c_\infty + \lambda d_\infty = c_1 + \lambda d_1 = \frac{1 - 2x}{1 + 2x}.$$

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

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

$$\therefore y = \frac{2x}{1 + 2x}.$$

(1.3)

# Result for sib-mating

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.

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

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).

# Result for sib-mating

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

$$\zeta = \frac{q}{2-3q}, \quad \theta = \frac{2q}{2-3q}, \quad \kappa = \frac{1}{2-3q},$$
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as may easily be verified.

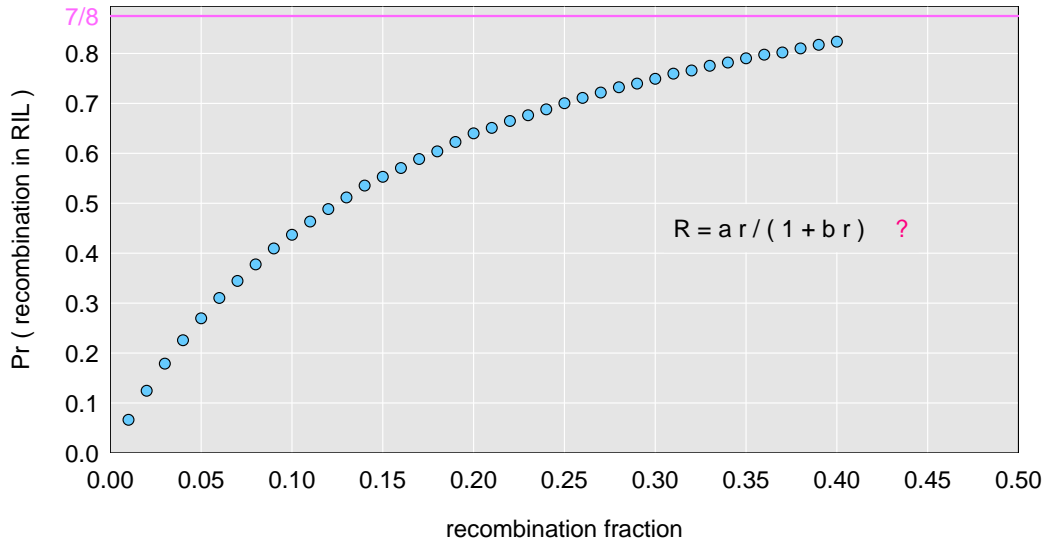
$$\begin{aligned} \therefore c_{\infty} = c_n + 2e_n + \frac{1}{1+6x} & [(1-2x)(d_n + 2f_n + 2j_n + \tfrac{1}{2}k_n) \\ & + 2g_n + 4x(h_n + i_n)] \end{aligned} \quad (3.4)$$

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).



# Simulation results



# Non-linear regression

```
out <- nls(R ~ a*r/(1 + b*r),  
           data = data.frame(r=r, R=R),  
           start = list(a=4, b=6))  
summary(out)
```

# Non-linear regression

```
out <- nls(R ~ a*r/(1 + b*r),  
           data = data.frame(r=r, R=R),  
           start = list(a=4, b=6))  
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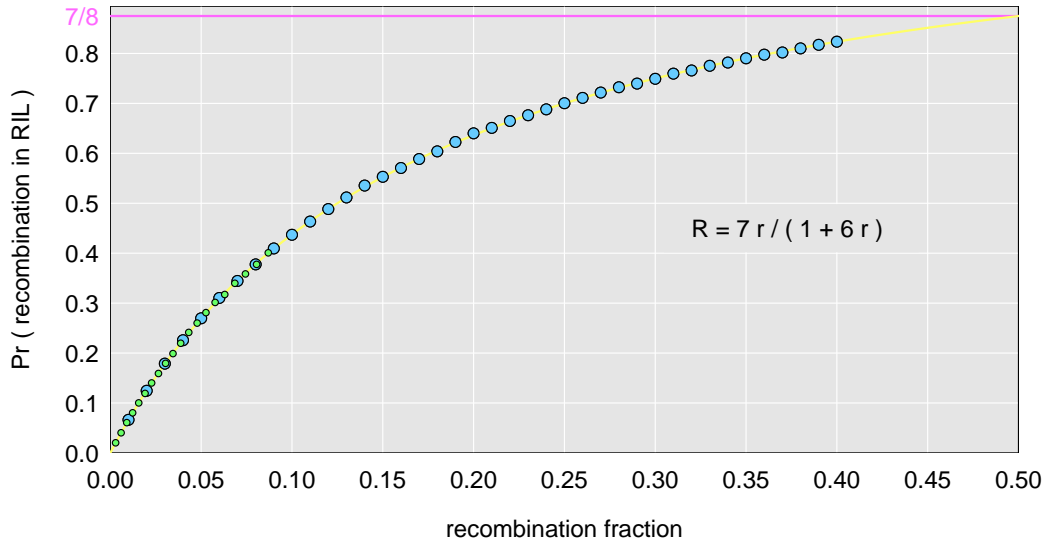
	Estimate	Std. Error
a	7.016	0.011
b	6.023	0.016

# Non-linear regression

```
out <- nls(R ~ a*r/(1 + b*r),  
           data = data.frame(r=r, R=R),  
           start = list(a=4, b=6))  
summary(out)
```

				More data	
	Estimate	Std. Error		Estimate	Std. Error
a	7.016	0.011	a	7.003	0.008
b	6.023	0.016	b	6.005	0.012

# Simulation results



# Markov chain

- ▶ Sequence of random variables  $\{X_0, X_1, X_2, \dots\}$  satisfying

$$\Pr(X_{n+1} \mid X_0, X_1, \dots, X_n) = \Pr(X_{n+1} \mid X_n)$$

- ▶ Transition probabilities  $P_{ij} = \Pr(X_{n+1} = j \mid X_n = i)$

- ▶ Here,  $X_n$  = “parental type” at generation  $n$ .

- ▶ We are interested in **absorption probabilities**

$$\pi_j = \Pr(X_n \rightarrow j \mid X_0)$$

# Absorption probabilities

Consider the case of **absorption** into the state  $\begin{array}{c|c} A & A \\ A & A \end{array}$   
(write this  $AA|AA$ )

Let  $h_i$  = probability, starting at  $i$ , of being absorbed into  $AA|AA$ .

Then  $h_{AA|AA} = 1$  and  $h_{AB|AB} = 0$ .

**Condition on the first step:**  $h_i = \sum_k P_{ik} h_k$

For selfing, this gives a system of 3 linear equations.

# 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  $D_\infty$  is the final proportion of crossover zygotes. Then considering the results of selfing each generation, we have:

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

for  $C_{n+1}$ ,  $D_{n+1}$ , and  $F_{n+1}$ ,  $G_{n+1}$ ,

$$\left. \begin{aligned} & \\ & \end{aligned} \right\} \quad (1.2)$$

for all values of  $n$ .

$$- 2x)d_n$$

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

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

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



$$\therefore y = \frac{2x}{1 + 2x}.$$

$$(1.3)$$



# Equations for sib-mating

Typical mating	Number of types	
$AABB \times AABB$	2	$C_{n+1} = C_n + H + \frac{1}{4}(\alpha^2 + \gamma^2)L + \frac{1}{4}(\beta^2 + \delta^2)N + \frac{1}{4}Q + \frac{1}{4}R + \frac{1}{4}(\alpha^2 + \gamma^2)U + \frac{1}{4}(\beta^2 + \delta^2)V + \frac{1}{4}\alpha^2\gamma^2W + \frac{1}{4}\beta^2\delta^2X + \frac{1}{4}\alpha^2\beta^2Y + \frac{1}{4}\gamma^2\delta^2Z$
$AAbb \times AAbb$	2	$D_{n+1} = D + I + \frac{1}{4}(\alpha^2 + \gamma^2)M + \frac{1}{4}(\beta^2 + \delta^2)P + \frac{1}{4}Q + \frac{1}{4}S + \frac{1}{4}(\beta^2 + \delta^2)U + \frac{1}{4}(\alpha^2 + \gamma^2)V + \frac{1}{4}\alpha^2\beta^2W + \frac{1}{4}\gamma^2\delta^2X + \frac{1}{4}\alpha^2\gamma^2Y + \frac{1}{4}\beta^2\delta^2Z$
$AABB \times aabb$	2	$E_{n+1} = \frac{1}{4}\alpha^2\gamma^2W + \frac{1}{4}\beta^2\delta^2X + \frac{1}{4}\alpha^2\beta^2Y + \frac{1}{4}\gamma^2\delta^2Z$
$AAbb \times aaBB$	2	$F_{n+1} = \frac{1}{4}\alpha^2\beta^2W + \frac{1}{4}\gamma^2\delta^2X + \frac{1}{4}\alpha^2\gamma^2Y + \frac{1}{4}\beta^2\delta^2Z$
$AABB \times AAbb$	8	$G_{n+1} = \frac{1}{4}(\alpha\beta + \gamma\delta)(U + V) + \frac{1}{4}\alpha\beta\gamma\delta(W + 2X + Y)$
$AAbb \times AABB$	8	$H_{n+1} = \frac{1}{4}(\alpha\delta + \beta\gamma)(U + V) + \frac{1}{4}\alpha\delta\beta\gamma(W + 2X + Y)$
$AAbb \times AAbb$	8	$I_{n+1} = \frac{1}{4}I + \frac{1}{4}(\alpha\delta + \beta\gamma)(U + V) + \frac{1}{4}\alpha\delta\beta\gamma(W + 2X + Y)$
$AABB \times Aabb$	8	$J_{n+1} = \frac{1}{4}J + \frac{1}{4}(\alpha\delta + \beta\gamma)(U + V) + \frac{1}{4}\alpha\delta\beta\gamma(W + 2X + Y)$
$AAbb \times AaBB$	8	$K_{n+1} = \frac{1}{4}K + \frac{1}{4}(\alpha\delta + \beta\gamma)(U + V) + \frac{1}{4}\alpha\delta\beta\gamma(W + 2X + Y)$
$AABB \times AB.ab$	4	$L_{n+1} = \frac{1}{4}L + \frac{1}{4}(\alpha^2 + \gamma^2)M + \frac{1}{4}(\beta^2 + \delta^2)P + \frac{1}{4}Q + \frac{1}{4}S + \frac{1}{4}(\beta^2 + \delta^2)U + \frac{1}{4}(\alpha^2 + \gamma^2)V + \frac{1}{4}\alpha^2\gamma^2W + \frac{1}{4}\beta^2\delta^2X + \frac{1}{4}\alpha^2\beta^2Y + \frac{1}{4}\gamma^2\delta^2Z$
$AAbb \times Ab.aB$	4	$M_{n+1} = \frac{1}{4}M + \frac{1}{4}(\alpha^2 + \gamma^2)N + \frac{1}{4}(\beta^2 + \delta^2)P + \frac{1}{4}Q + \frac{1}{4}S + \frac{1}{4}(\beta^2 + \delta^2)U + \frac{1}{4}(\alpha^2 + \gamma^2)V + \frac{1}{4}\alpha^2\gamma^2W + \frac{1}{4}\beta^2\delta^2X + \frac{1}{4}\alpha^2\beta^2Y + \frac{1}{4}\gamma^2\delta^2Z$
$AABB \times Ab.aB$	4	$N_{n+1} = \frac{1}{4}N + \frac{1}{4}(\alpha\beta + \gamma\delta)(U + V) + \frac{1}{4}\alpha\beta\gamma\delta(W + 2X + Y)$
$AAbb \times AB.ab$	4	$P_{n+1} = \frac{1}{4}P + \frac{1}{4}(\alpha\beta + \gamma\delta)(U + V) + \frac{1}{4}\alpha\delta\beta\gamma(W + 2X + Y)$
$AAbb \times AABB$	4	$Q_{n+1} = 2G + \frac{1}{4}(H + I + J + K) + \frac{1}{4}(\alpha^2 + \gamma^2)(L + M) + \frac{1}{4}(\beta^2 + \delta^2)(N + P) + \frac{1}{4}Q + \frac{1}{4}(R + S + T) + \frac{1}{4}(\alpha^2 + \alpha\beta + \beta^2 + \gamma^2 + \gamma\delta + \delta^2)(U + V) + \frac{1}{4}(\alpha\delta + \beta\gamma)(W + Y) + \frac{1}{4}(\alpha\gamma + \beta\delta)^2X$
$AAbb \times AaBB$	4	$R_{n+1} = \frac{1}{4}(\beta^2 + \delta^2)L + \frac{1}{4}(\alpha^2 + \gamma^2)N + \frac{1}{4}R + \frac{1}{4}(\beta + \delta)U + \frac{1}{4}(\alpha + \gamma)V + \frac{1}{4}(\alpha\delta + \beta\gamma)(W + Y) + \frac{1}{4}(\alpha\gamma + \beta\delta)^2X$
$AAbb \times Aabb$	4	$S_{n+1} = \frac{1}{4}(\beta^2 + \delta^2)M + \frac{1}{4}(\alpha^2 + \gamma^2)P + \frac{1}{4}S + \frac{1}{4}(\alpha + \gamma)U + \frac{1}{4}(\beta + \delta)V + \frac{1}{4}(\alpha\delta + \beta\gamma)(W + Y) + \frac{1}{4}(\alpha\gamma + \beta\delta)^2X$
$AAbb \times aaBB$	4	$T_{n+1} = \frac{1}{4}(\alpha\beta + \gamma\delta)(U + V) + \frac{1}{4}(\alpha\delta + \beta\gamma)(W + Y) + \frac{1}{4}(\alpha\gamma + \beta\delta)^2X$
$AAbb \times AB.ab$	8	$U_{n+1} = \frac{1}{4}J + \frac{1}{4}(\alpha\beta + \gamma\delta)(L + N) + \frac{1}{4}(S + T) + \frac{1}{4}(\alpha + \gamma)U + \frac{1}{4}(\beta + \delta)V + \frac{1}{4}\alpha\gamma(\beta\gamma + \alpha\delta)W + \frac{1}{4}(\alpha\gamma + \beta\delta)(\alpha\delta + \beta\gamma)X + \frac{1}{4}\beta\delta(\beta\gamma + \alpha\delta)Y$
$AAbb \times Ab.aB$	8	$V_{n+1} = \frac{1}{4}K + \frac{1}{4}(\alpha\beta + \gamma\delta)(M + P) + \frac{1}{4}(R + T) + \frac{1}{4}(\beta + \delta)U + \frac{1}{4}(\alpha + \gamma)V + \frac{1}{4}\beta\delta(\beta\gamma + \alpha\delta)W + \frac{1}{4}(\alpha\gamma + \beta\delta)(\alpha\delta + \beta\gamma)X + \frac{1}{4}\alpha\gamma(\beta\gamma + \alpha\delta)Y$
$AB.ab \times AB.ab$	1	$W_{n+1} = 2(E + J) + \frac{1}{4}(\alpha^2 + \gamma^2)L + \frac{1}{4}(\beta^2 + \delta^2)N + \frac{1}{4}(S + T) + \frac{1}{4}(\alpha^2 + \gamma^2)U + \frac{1}{4}(\beta^2 + \delta^2)V + \frac{1}{4}\alpha^2\gamma^2W + \frac{1}{4}(\alpha^2\beta^2 + \beta^2\gamma^2)X + \frac{1}{4}\beta^2\delta^2Y$
$AB.ab \times Ab.aB$	2	$X_{n+1} = \frac{1}{4}T + \frac{1}{4}(\alpha\beta + \gamma\delta)(U + V) + \frac{1}{4}\alpha\beta\gamma\delta(W + 2X + Y)$
$Ab.aB \times Ab.aB$	1	$Y_{n+1} = 2(F + K) + \frac{1}{4}(\alpha^2 + \gamma^2)M + \frac{1}{4}(\beta^2 + \delta^2)P + \frac{1}{4}(R + T) + \frac{1}{4}(\beta^2 + \delta^2)U + \frac{1}{4}(\alpha^2 + \gamma^2)V + \frac{1}{4}\beta^2\delta^2W + \frac{1}{4}(\alpha^2\delta^2 + \delta^2\gamma^2)X + \frac{1}{4}\alpha^2\gamma^2Y$

# Result for sib-mating

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.

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

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

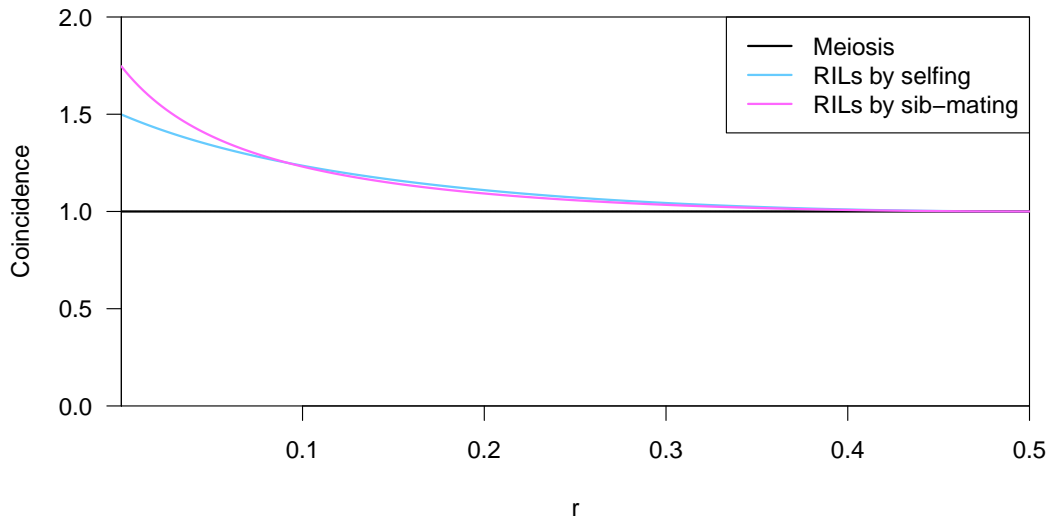
In the case considered,  $d_0 = 1$ ,  $\therefore c_{\infty} = \zeta d_0 = 1 - 2x/1 + 6x$ . Hence the proportion of crossover zygotes,  $y = 4x/1 + 6x$  (3.5).

# 3-point coincidence

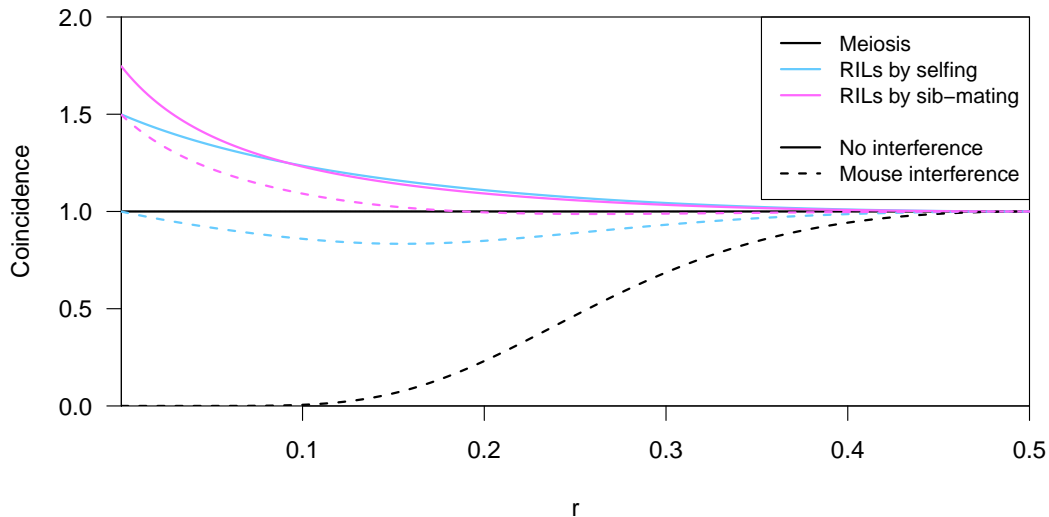


- ▶  $r_{ij}$  = recombination fraction for interval (i, j)  
Assume  $r_{12} = r_{23} = r$ .
- ▶ **Coincidence** =  $c = \Pr(\text{double recombinant})/r^2$   
=  $\Pr(\text{rec'n in 23} \mid \text{rec'n in 12})/\Pr(\text{rec'n in 23})$
- ▶ No interference = 1  
Positive interference < 1  
Negative interference > 1
- ▶ Generally  $c$  is a function of  $r$

# Coincidence



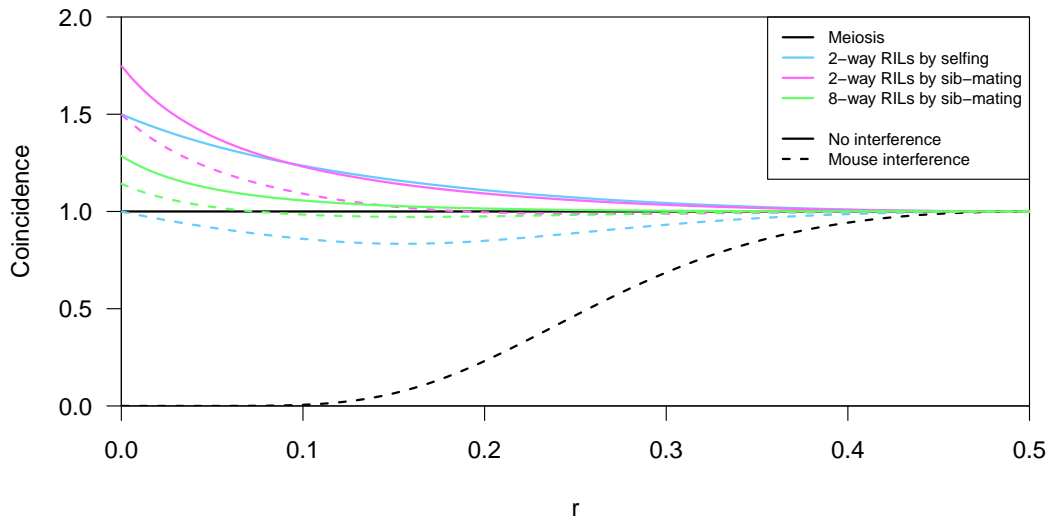
# Coincidence



# Coincidence in 8-way RILs

- ▶ The trick that allowed us to get the coincidence for 2-way RILs doesn't work for 8-way RILs.
- ▶ It's sufficient to consider 4-way RILs.
- ▶ Calculations for 3 points in 4-way RILs is still **astoundingly complex**.
  - 2 points in 2-way RILs by sib mating:  
55 parental types → **22 states** by symmetry
  - 3 points in 4-way RILs by sib mating:  
2,164,240 parental types → **137,488 states** by symmetry
- ▶ Even **counting** the states was difficult.

# Coincidence



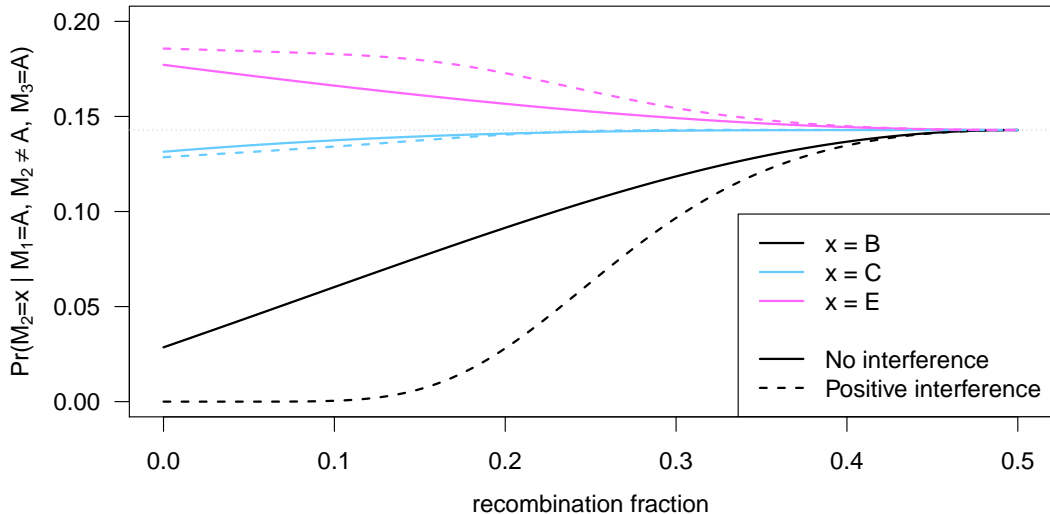
# The formula

$$C = \frac{(1 + 6r)[280 + 1208r - 848r^2 + 5c(7 - 28r - 368r^2 + 344r^3) - 2c^2(49 - 324r + 452r^2)r^2 - 16c^3(1 - 2r)r^4]}{49(1 + 12r - 12cr^2)[5 + 10r - 4(2 + c)r^2 + 8cr^3]}$$



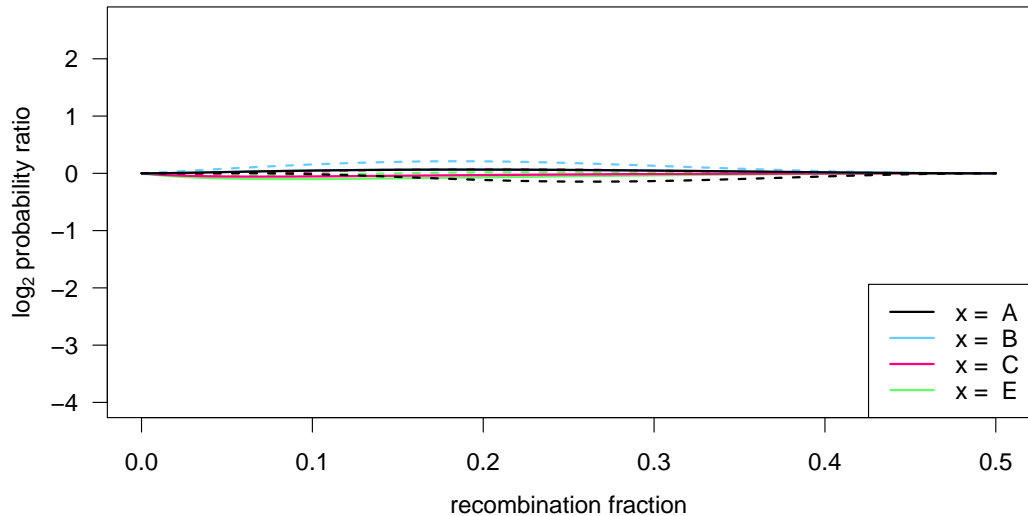
# 3-point symmetry

$$\Pr(M_2 = x \mid M_1 = A, M_2 \neq A, M_3 = A)$$



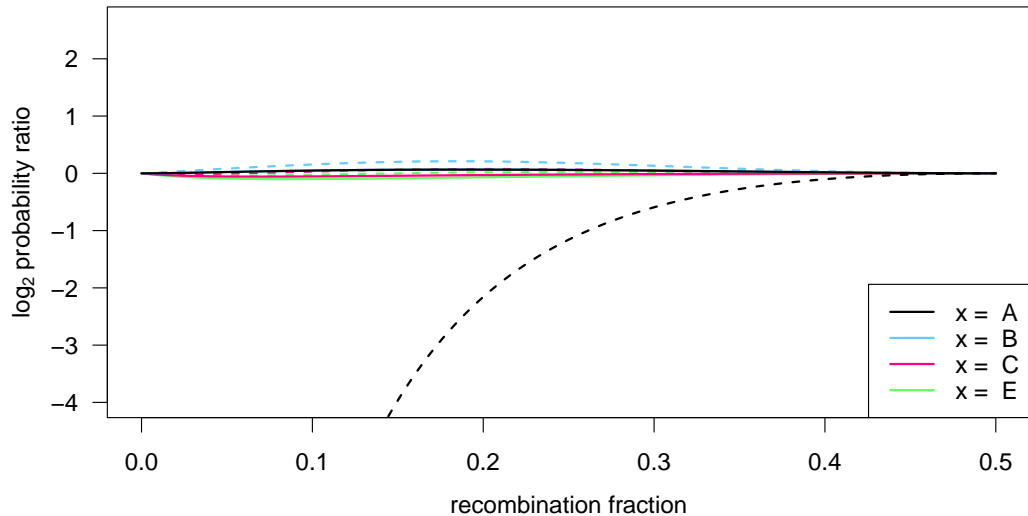
# Markov property

$$\log_2 \left\{ \frac{\Pr(M_3=A \mid M_2=A, M_1=x)}{\Pr(M_3=A \mid M_2=A)} \right\}$$



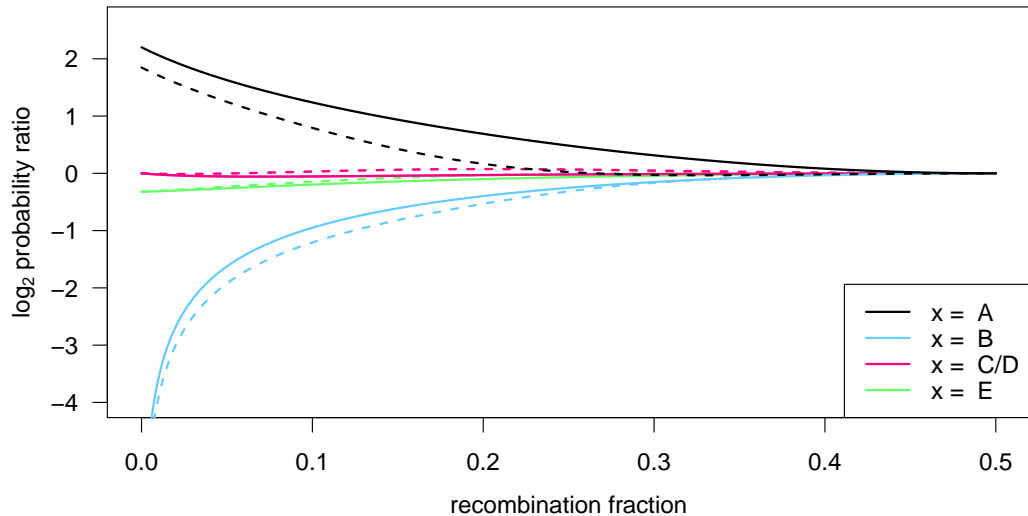
# Markov property

$$\log_2 \left\{ \frac{\Pr(M_3=A \mid M_2=B, M_1=x)}{\Pr(M_3=A \mid M_2=B)} \right\}$$



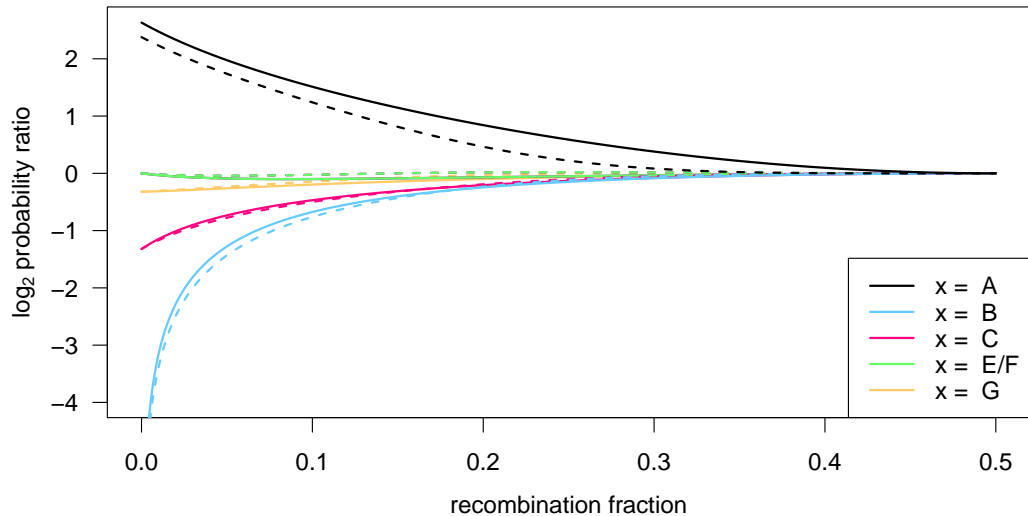
# Markov property

$$\log_2 \left\{ \frac{\Pr(M_3=A \mid M_2=\text{C}, M_1=x)}{\Pr(M_3=A \mid M_2=\text{C})} \right\}$$



# Markov property

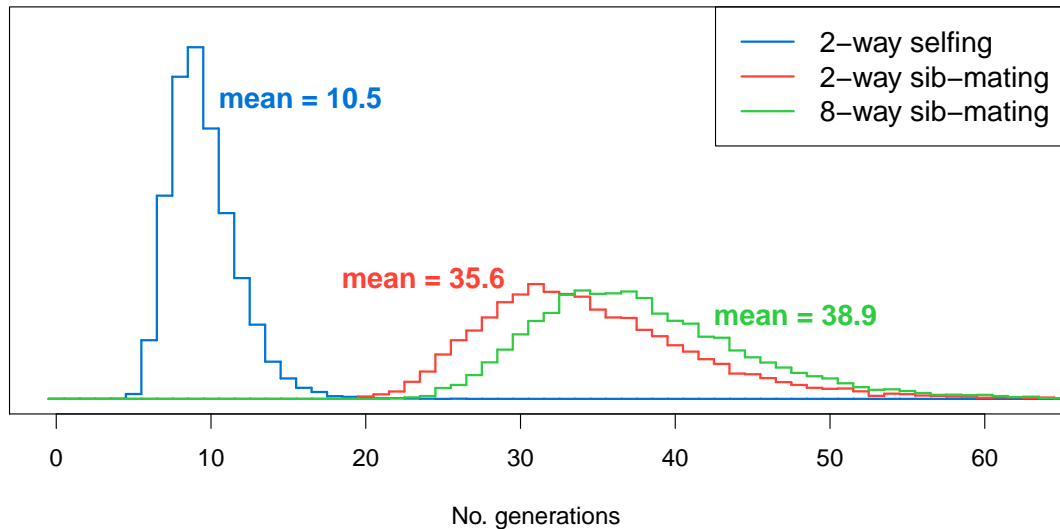
$$\log_2 \left\{ \frac{\Pr(M_3=A \mid M_2=E, M_1=x)}{\Pr(M_3=A \mid M_2=E)} \right\}$$



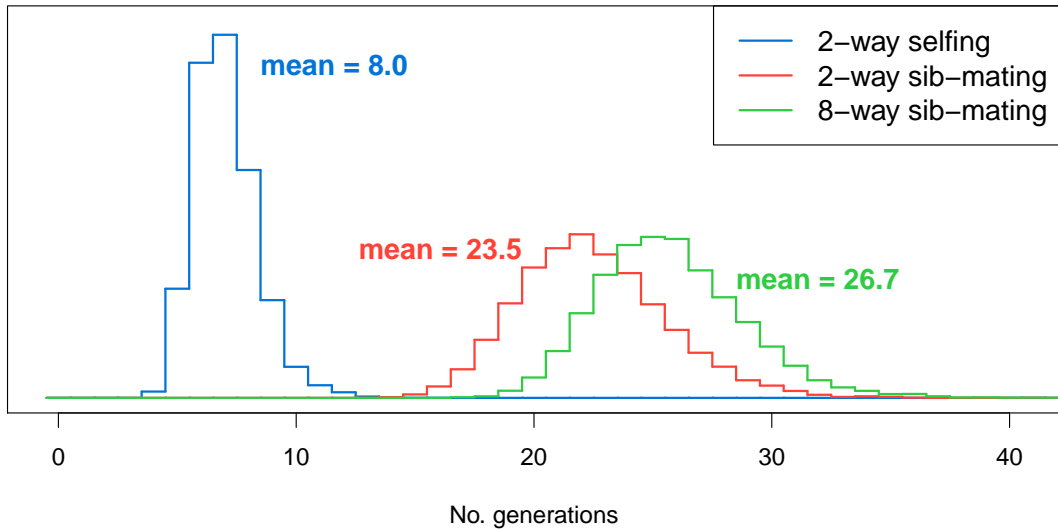
# Whole genome simulations

- ▶ 2-way selfing, 2-way sib-mating, 8-way sib-mating
- ▶ Mouse-like genome, 1665 cM
- ▶ Strong positive crossover interference
- ▶ Inbreed to complex fixation
- ▶ 10,000 simulation replicates

# No. generations to fixation

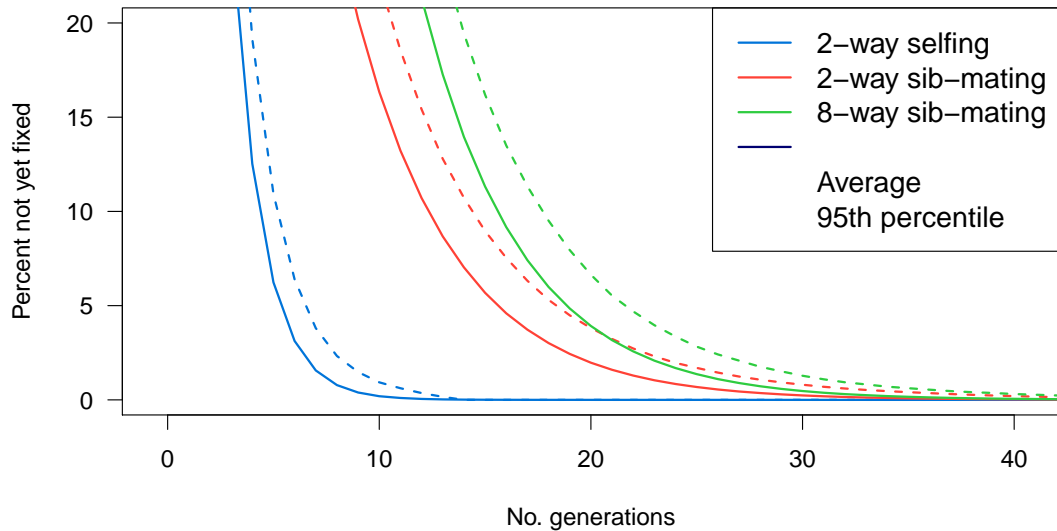


# No. generations to 99% fixation

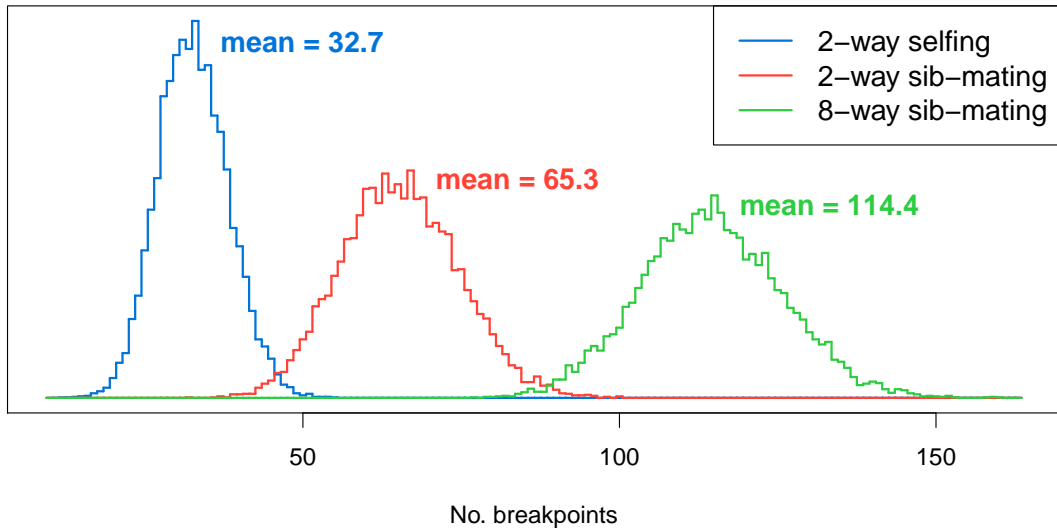




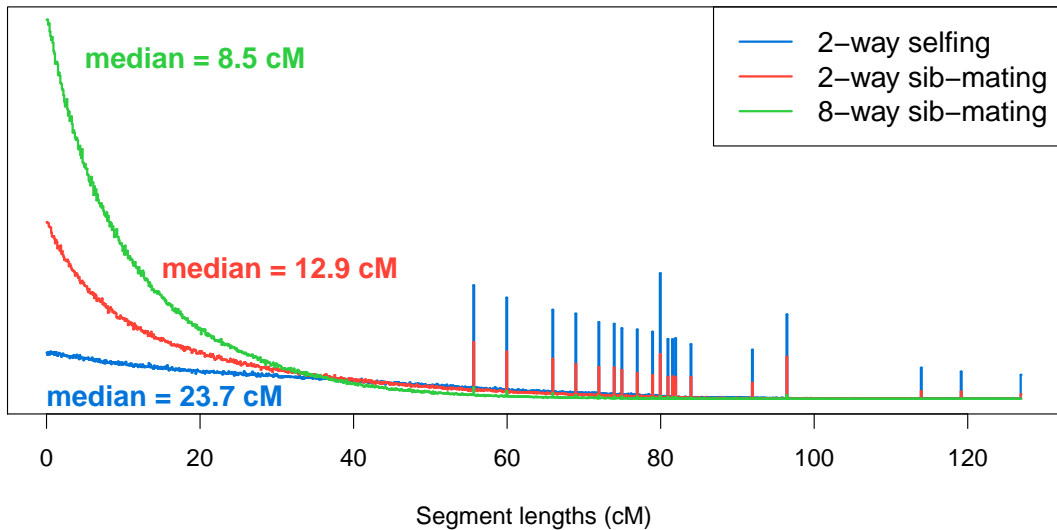
# Percent genome not fixed



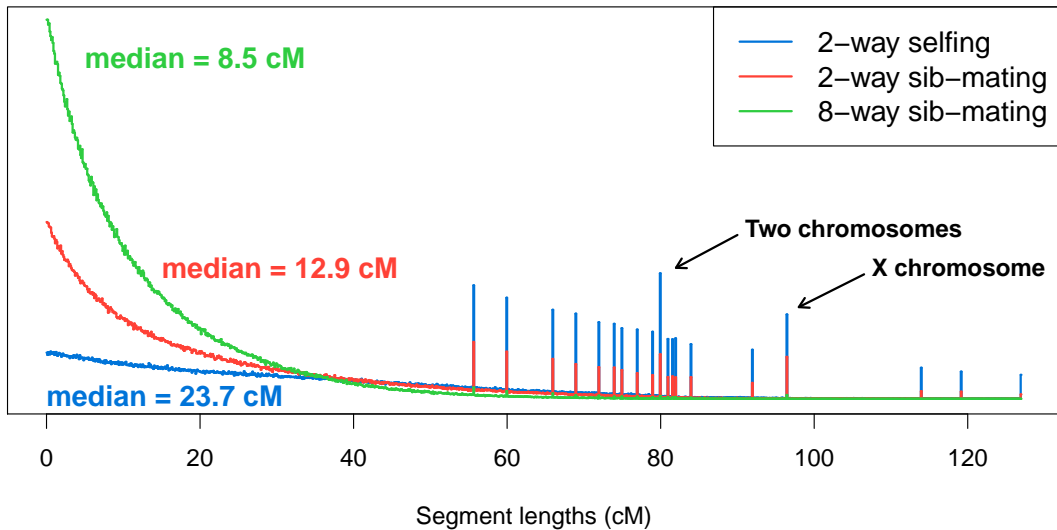
# No. breakpoints



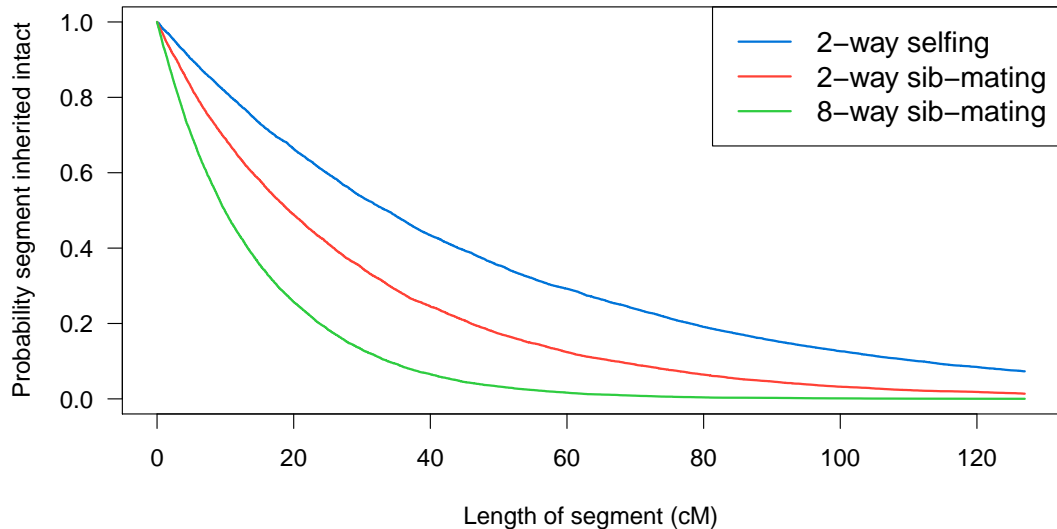
# Segment lengths



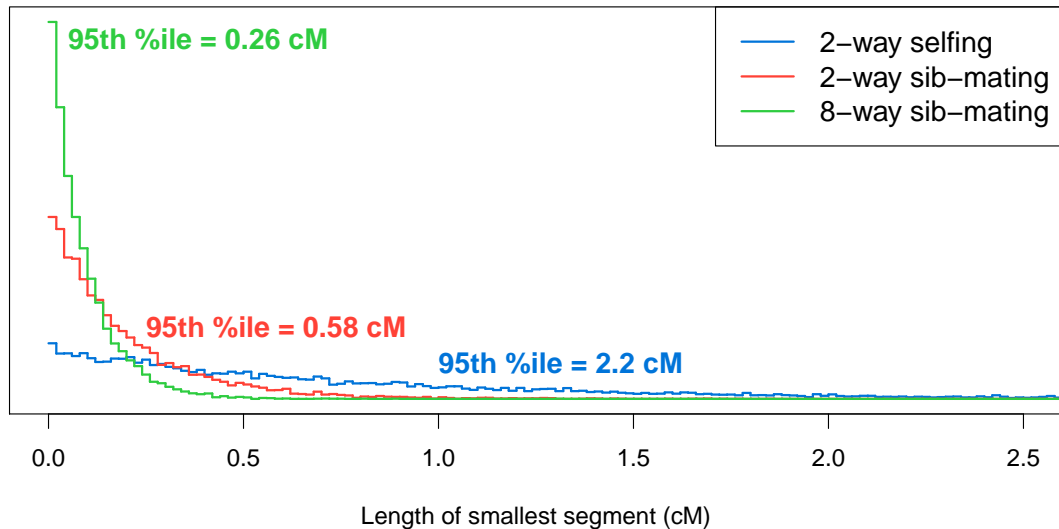
# Segment lengths



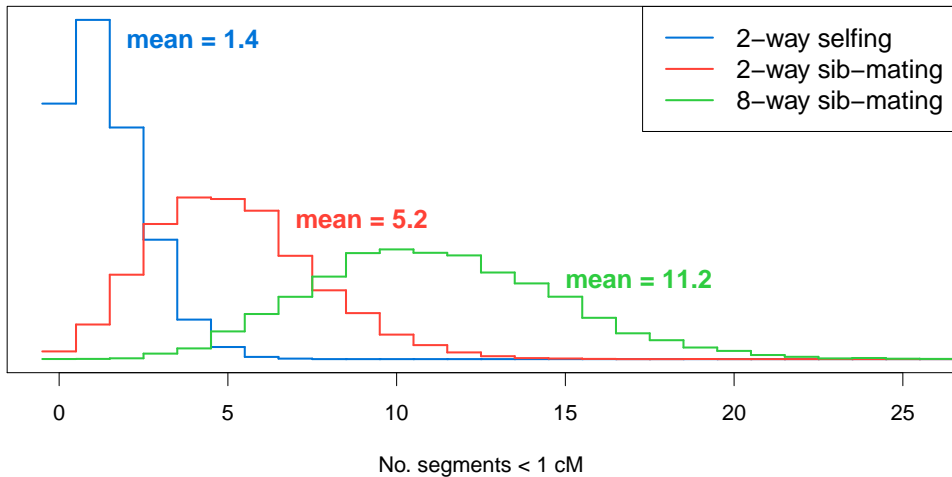
# Probability a segment is inherited intact



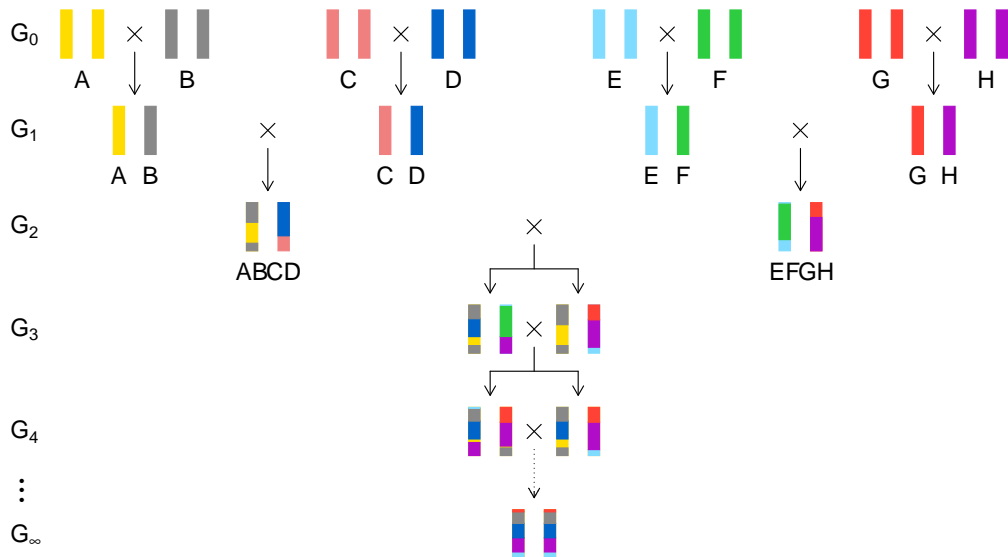
# Length of smallest segment



# No. segments $< 1$ cM



# Collaborative Cross





# The PreCC

What happens at  $G_2F_k$ ?

$\Pr(g_1 = i)$  as a function of  $k$

$\Pr(g_1 = i, g_2 = j)$  as a function of  $k$  and the recombination fraction

# Crazy table

**Table 4 Two-locus haplotype probabilities at generation  $F_k$  in the formation of four-way RIL by sibling mating**

Chr.	Individual	Prototype	No. states	Probability of each
A	Random	AA	4	$\frac{1}{4(1+6r)} - \left[ \frac{6r^2-7r-3rs}{4(1+6r)s} \right] \left( \frac{1-2r+s}{4} \right)^k + \left[ \frac{6r^2-7r+3rs}{4(1+6r)s} \right] \left( \frac{1-2r-s}{4} \right)^k$
		AB	4	$\frac{r}{2(1+6r)} + \left[ \frac{10r^2-r-rs}{4(1+6r)s} \right] \left( \frac{1-2r+s}{4} \right)^k - \left[ \frac{10r^2-r+rs}{4(1+6r)s} \right] \left( \frac{1-2r-s}{4} \right)^k$
		AC	8	$\frac{r}{2(1+6r)} - \left[ \frac{2r^2+3r+rs}{4(1+6r)s} \right] \left( \frac{1-2r+s}{4} \right)^k + \left[ \frac{2r^2+3r-rs}{4(1+6r)s} \right] \left( \frac{1-2r-s}{4} \right)^k$
X	Female	AA	2	$\frac{1}{3(1+4r)} + \frac{1}{6(1+r)} \left( -\frac{1}{2} \right)^k - \left[ \frac{4r^3-(4r^2+3r)t+3r^2-5r}{4(4r^2+5r+1)t} \right] \left( \frac{1-r+t}{4} \right)^k + \left[ \frac{4r^3+(4r^2+3r)t+3r^2-5r}{4(4r^2+5r+1)t} \right] \left( \frac{1-r-t}{4} \right)^k$
		AB	2	$\frac{2r}{3(1+4r)} + \frac{r}{3(1+r)} \left( -\frac{1}{2} \right)^k + \left[ \frac{2r^3+6r^2-(2r^2+r)t}{2(4r^2+5r+1)t} \right] \left( \frac{1-r+t}{4} \right)^k - \left[ \frac{2r^3+6r^2+(2r^2+r)t}{2(4r^2+5r+1)t} \right] \left( \frac{1-r-t}{4} \right)^k$
		AC	4	$\frac{2r}{3(1+4r)} - \frac{r}{6(1+r)} \left( -\frac{1}{2} \right)^k - \left[ \frac{9r^2+5r+rt}{4(4r^2+5r+1)t} \right] \left( \frac{1-r+t}{4} \right)^k + \left[ \frac{9r^2+5r-rt}{4(4r^2+5r+1)t} \right] \left( \frac{1-r-t}{4} \right)^k$
		CC	1	$\frac{1}{3(1+4r)} - \frac{1}{3(1+r)} \left( \frac{1}{2} \right)^k + \left[ \frac{9r^2+5r+rt}{2(4r^2+5r+1)t} \right] \left( \frac{1-r+t}{4} \right)^k - \left[ \frac{9r^2+5r-rt}{2(4r^2+5r+1)t} \right] \left( \frac{1-r-t}{4} \right)^k$
X	Male	AA	2	$\frac{1}{3(1+4r)} - \frac{1}{3(1+r)} \left( -\frac{1}{2} \right)^k + \left[ \frac{r^3-(8r^3+r^2-3r)t-10r^2+5r}{2(4r^4-35r^3-29r^2+15r+5)} \right] \left( \frac{1-r+t}{4} \right)^k + \left[ \frac{r^3+(8r^3+r^2-3r)t-10r^2+5r}{2(4r^4-35r^3-29r^2+15r+5)} \right] \left( \frac{1-r-t}{4} \right)^k$
		AB	2	$\frac{2r}{3(1+4r)} - \frac{2r}{3(1+r)} \left( -\frac{1}{2} \right)^k + \left[ \frac{r^4+(5r^3-r)t-10r^3+5r^2}{4r^4-35r^3-29r^2+15r+5} \right] \left( \frac{1-r+t}{4} \right)^k + \left[ \frac{r^4-(5r^3-r)t-10r^3+5r^2}{4r^4-35r^3-29r^2+15r+5} \right] \left( \frac{1-r-t}{4} \right)^k$
		AC	4	$\frac{2r}{3(1+4r)} + \frac{r}{3(1+r)} \left( -\frac{1}{2} \right)^k - \left[ \frac{2r^4+(2r^3-r^2+r)t-19r^3+5r}{2(4r^4-35r^3-29r^2+15r+5)} \right] \left( \frac{1-r+t}{4} \right)^k - \left[ \frac{2r^4-(2r^3-r^2+r)t-19r^3+5r}{2(4r^4-35r^3-29r^2+15r+5)} \right] \left( \frac{1-r-t}{4} \right)^k$
		CC	1	$\frac{1}{3(1+4r)} + \frac{2}{3(1+r)} \left( -\frac{1}{2} \right)^k + \left[ \frac{2r^4+(2r^3-r^2+r)t-19r^3+5r}{4r^4-35r^3-29r^2+15r+5} \right] \left( \frac{1-r+t}{4} \right)^k + \left[ \frac{2r^4-(2r^3-r^2+r)t-19r^3+5r}{4r^4-35r^3-29r^2+15r+5} \right] \left( \frac{1-r-t}{4} \right)^k$

$s = \sqrt{4r^2-12r+5}$  and  $t = \sqrt{r^2-10r+5}$ ; the autosomal haplotype probabilities are valid for  $r < \frac{1}{2}$ .

# Lesson

Computer simulations are hugely valuable.

# Uses of simulations

- ▶ Study probabilities
- ▶ Estimate power/sample size
- ▶ Evaluate performance of a method
- ▶ Evaluate sensitivity/robustness of a method

# Relative advantages?

- ▶ Simulations
- ▶ Numerical calculations
- ▶ Analytic calculations

# References

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