Computer simulations

The genomes of recombinant inbred lines

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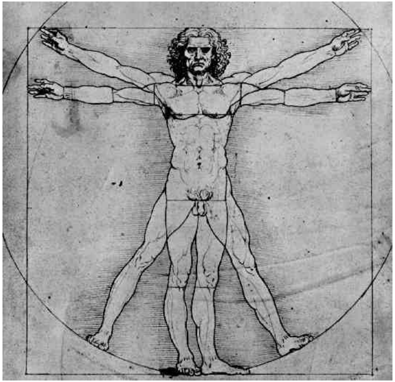
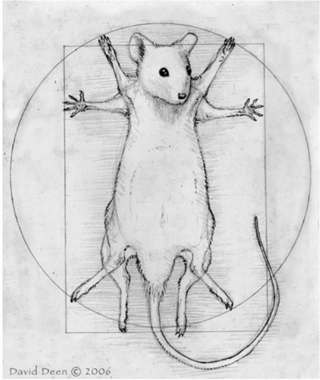
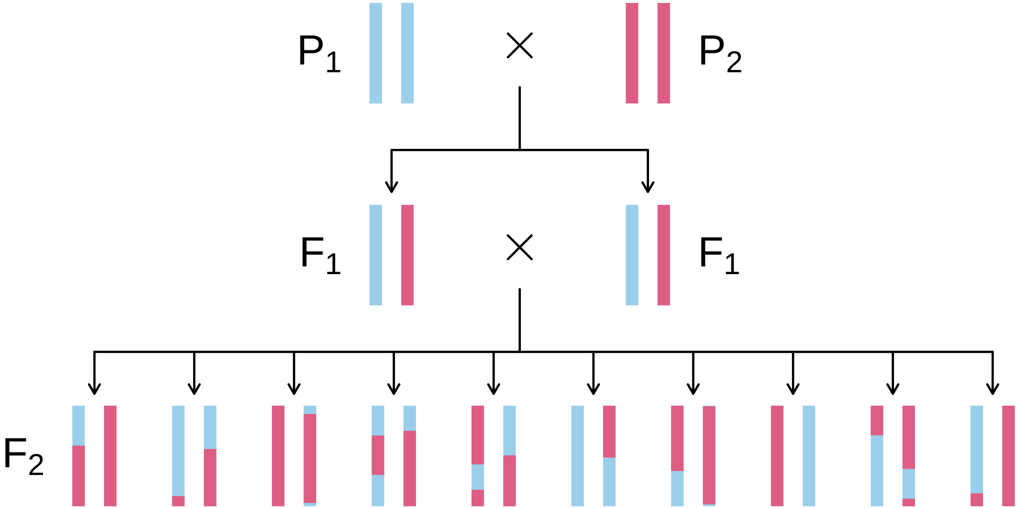


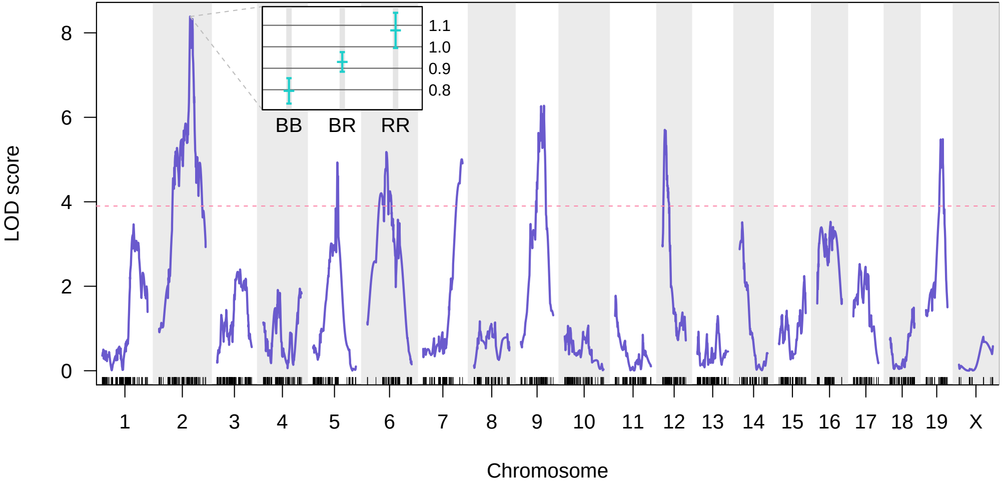


daviddeen.com

Intercross

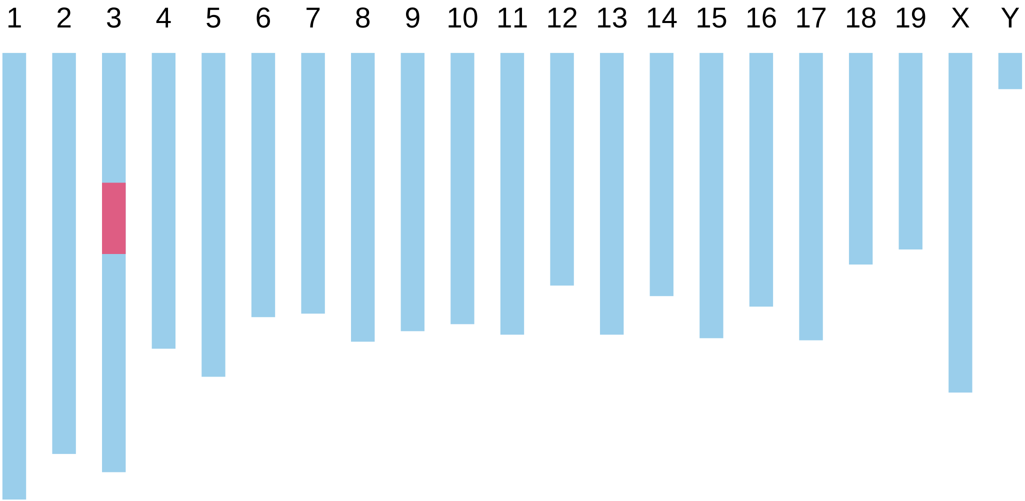


QTL mapping



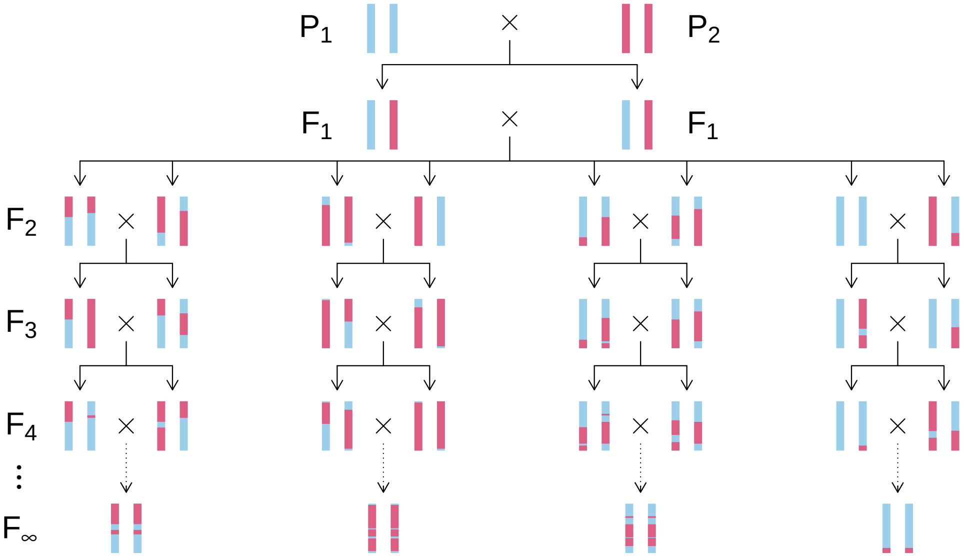
8
6
4
2
0
LOD score
1.1
1.0
0.9
0.8
BB
BR
RR
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

Congenic line/NIL

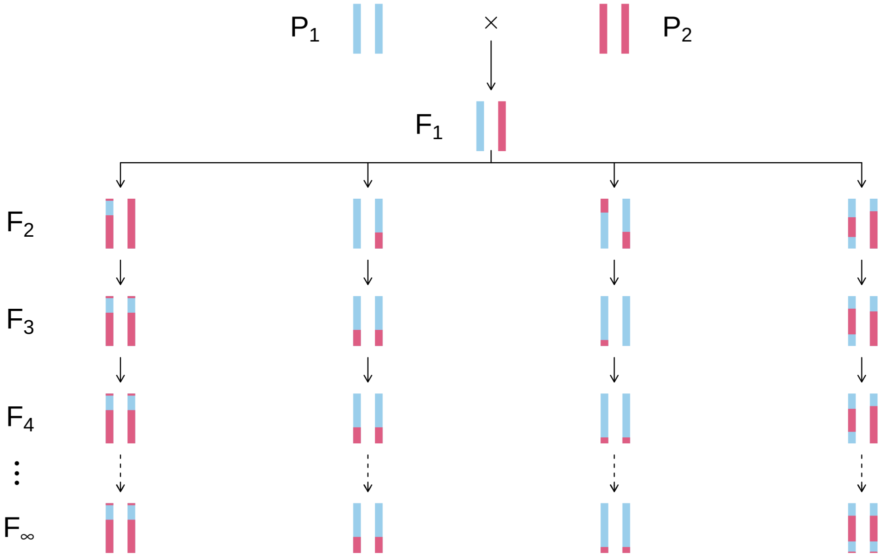


Advanced intercross lines

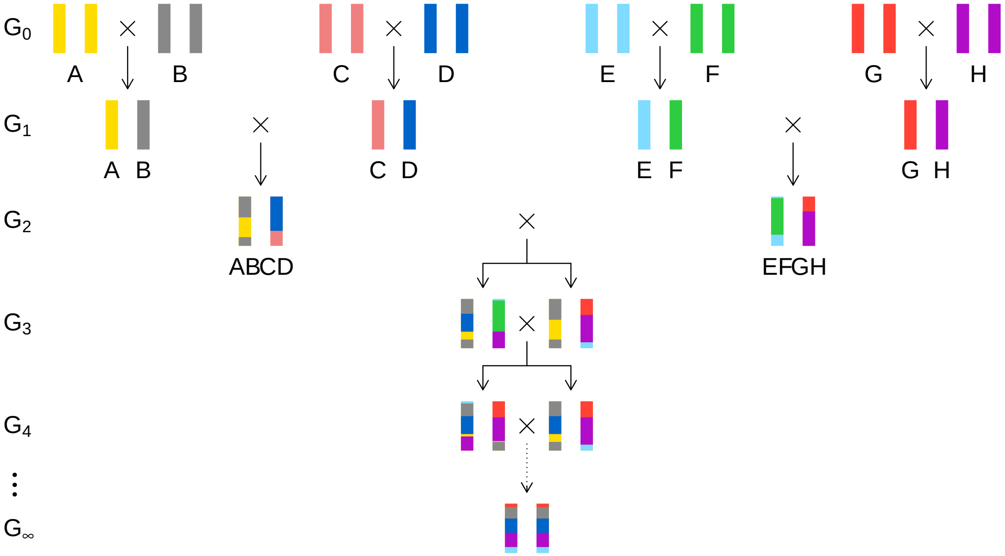
Recombinant inbred lines



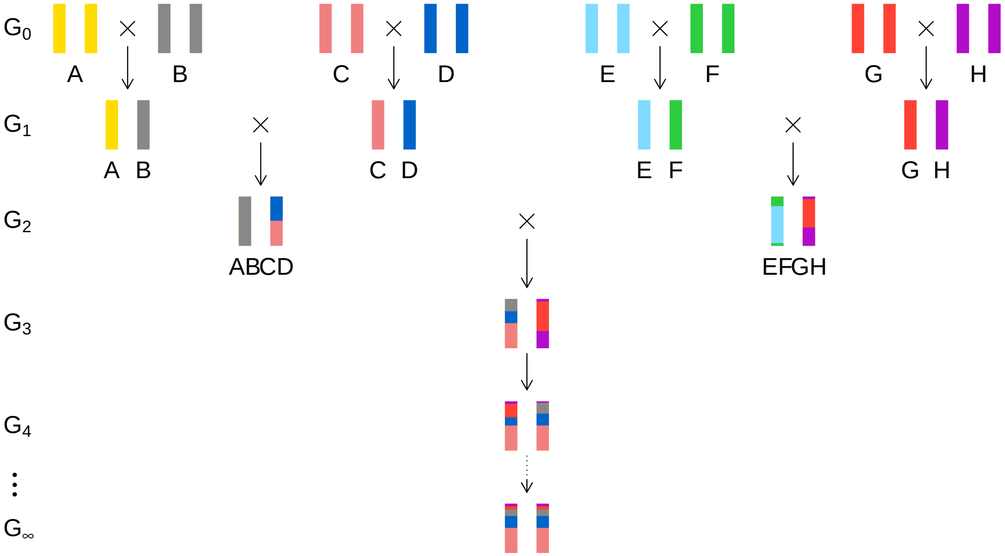
Recombinant inbred lines



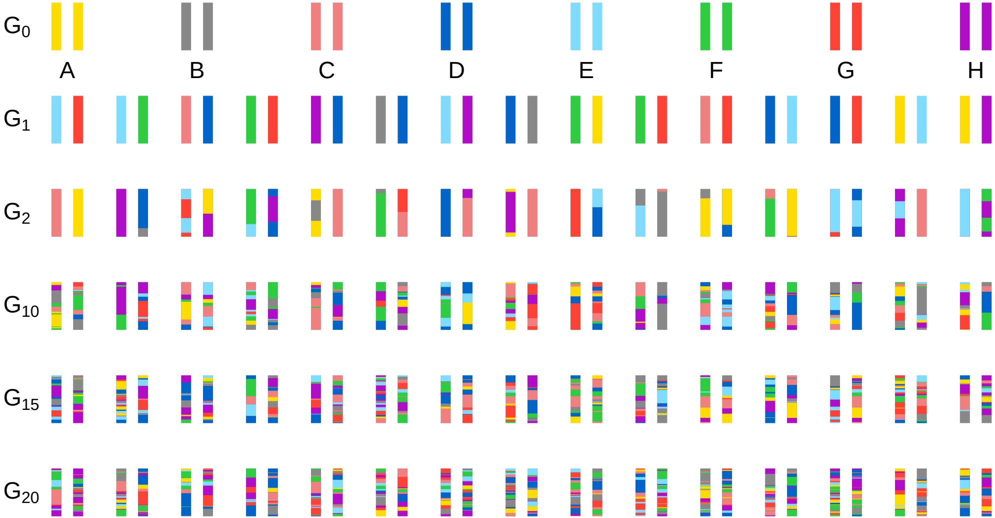
Collaborative Cross



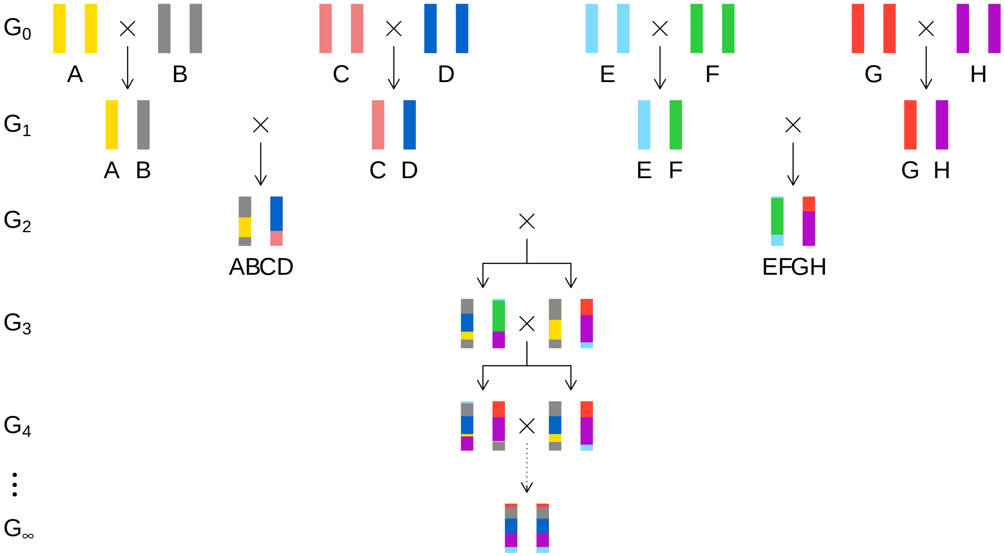
MAGIC



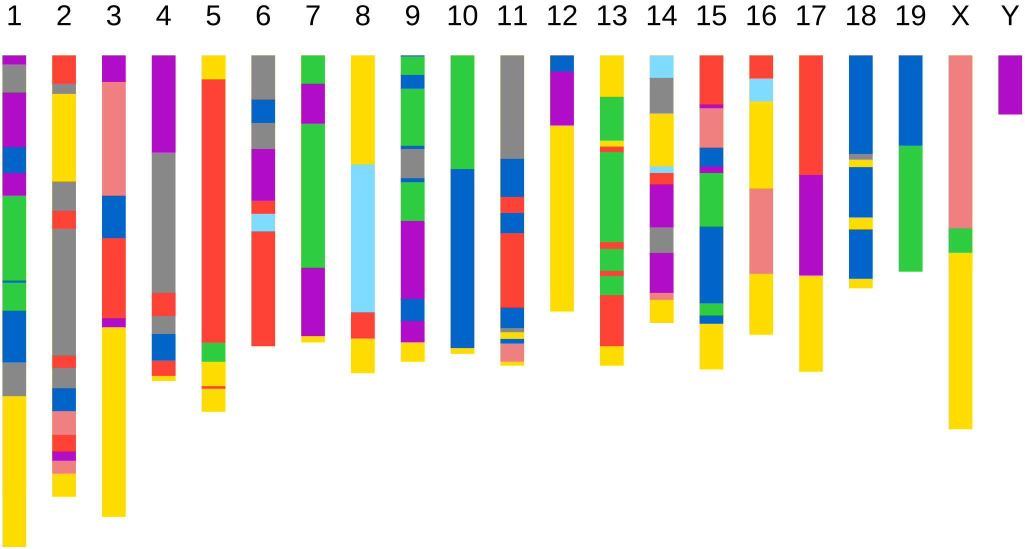
Heterogeneous stock



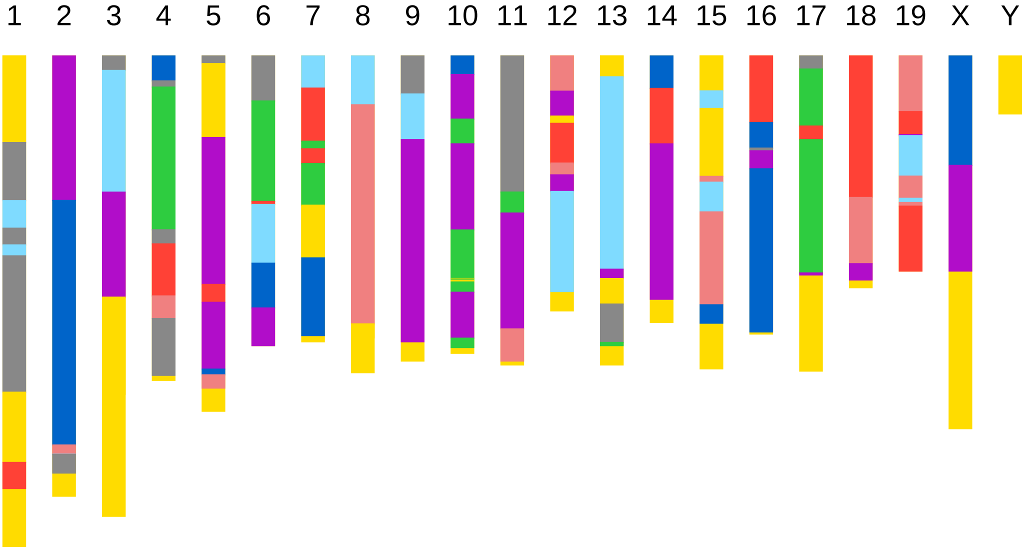
Collaborative Cross



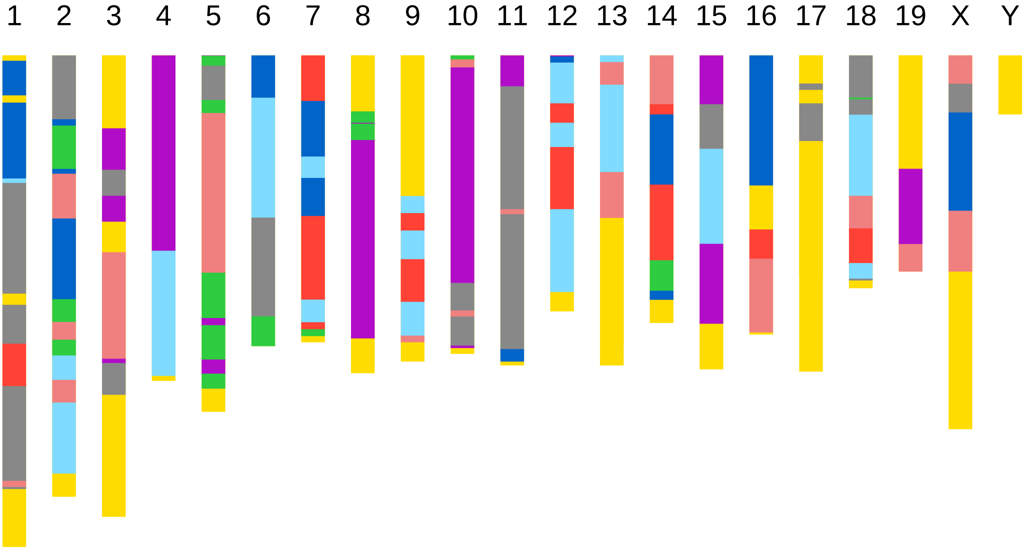
CC genome



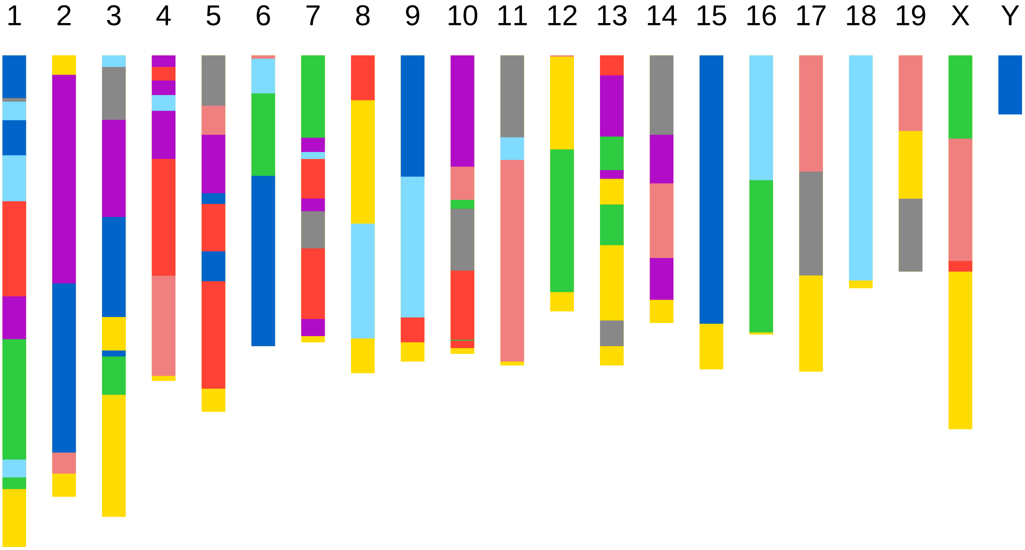
CC genome



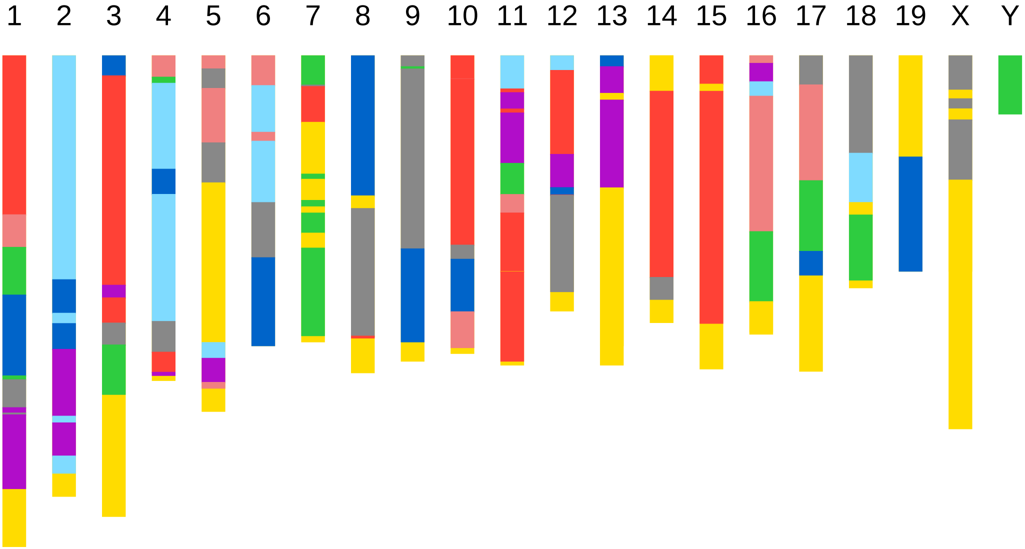
CC genome



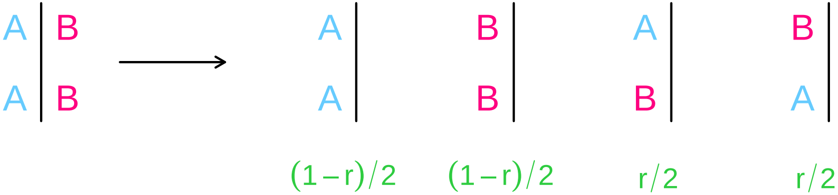
CC genome



CC genome

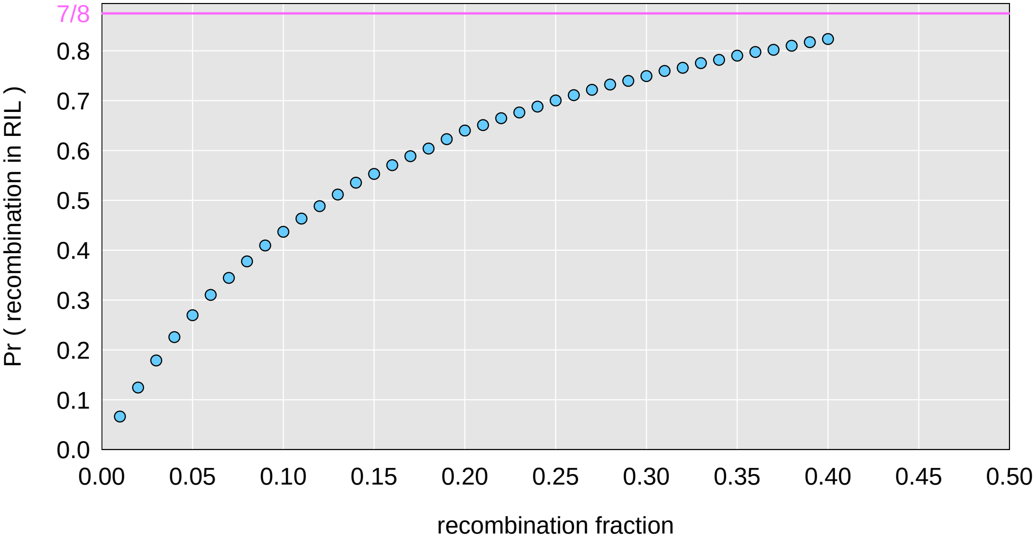


Recombination fraction



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)

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

$$\boxed{\therefore \ y = \frac{2x}{1+2x}.} \tag{1.3}$$

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.

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

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, $\boxed{y = 4x/1 + 6x}$ (3.5).

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

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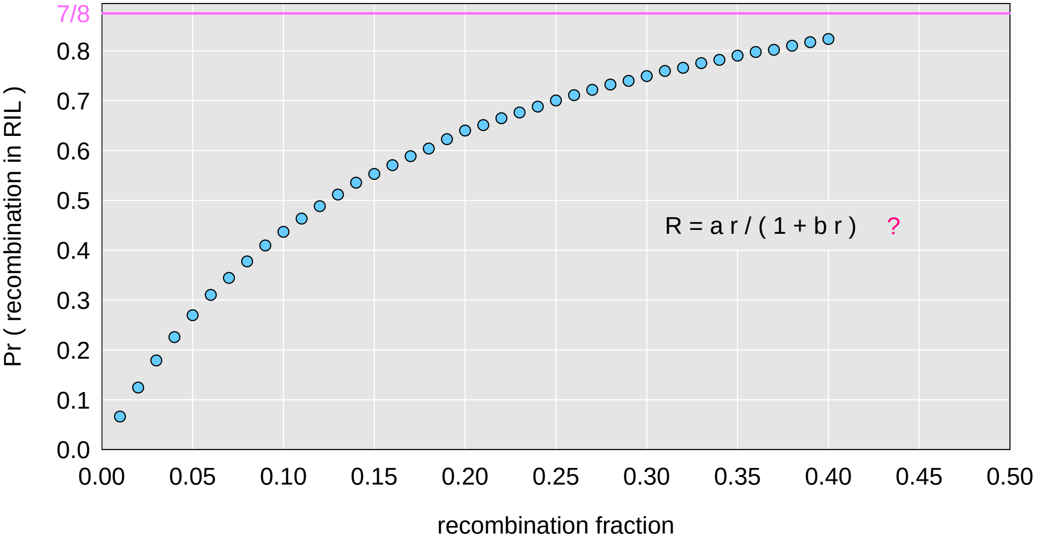
Simulation results



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

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```

	Estimate	Std. Error
a	7.016	0.011
b	6.023	0.016

Non-linear regression

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```
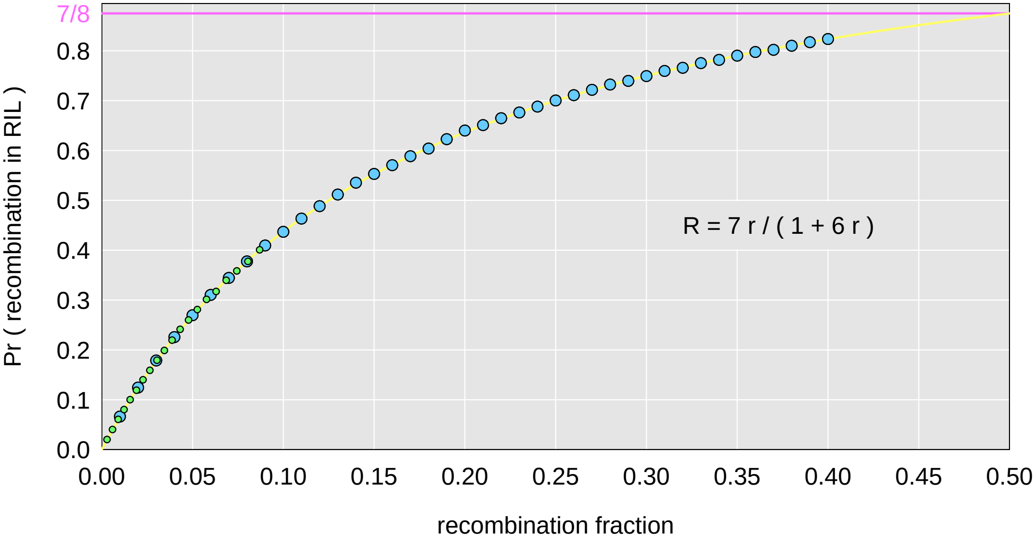

	Estimate	Std. Error
a	7.016	0.011
b	6.023	0.016

More data

	Estimate	Std. Error
a	7.003	0.008
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

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

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_∞ is the final proportion of crossover zygotes. Then considering the results of selfing each generation, we have:

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

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

d_n } (1.2)

all values of n.

2x)d_n

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

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

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

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

Equations for sib-mating

Typical mating	Number of types	
$AABB \times AABB$	2	$C_{n+1}=C_n+H+\frac{1}{4}(\alpha^2+\gamma^2)L+\frac{1}{4}(\beta^2+\delta^2)N+\frac{1}{8}Q+\frac{1}{8}R+\frac{1}{8}(\alpha^2+\gamma^2)U+\frac{1}{8}(\beta^2+\delta^2)V+\frac{1}{16}\alpha^2\gamma^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\beta^2\delta^2Y.$
$AAbb \times AAbb$	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	$M_{n+1}=\frac{1}{4}($ … $\beta^2\delta^2W+$ …

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

Result for sib-mating

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

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as may easily be verified.

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

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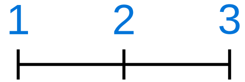
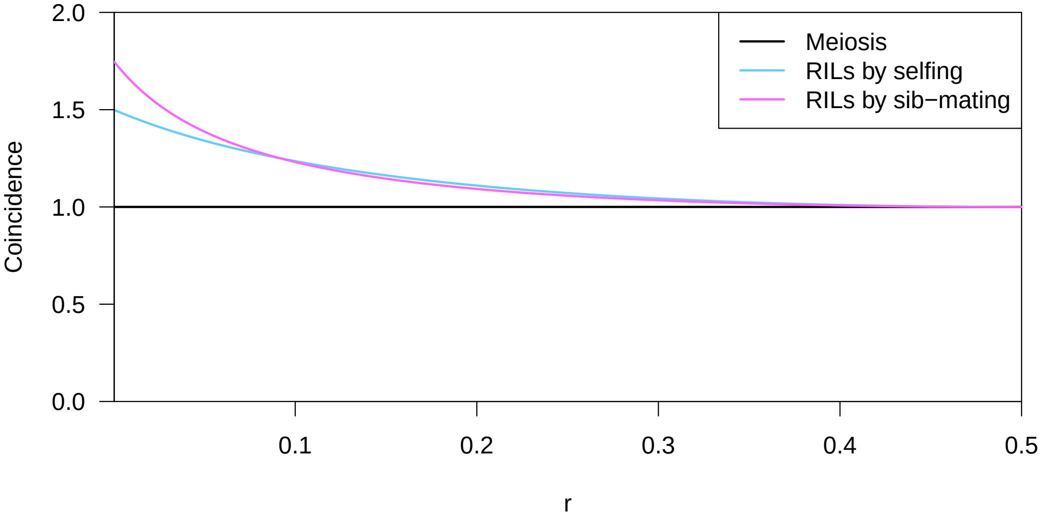
3-point coincidence

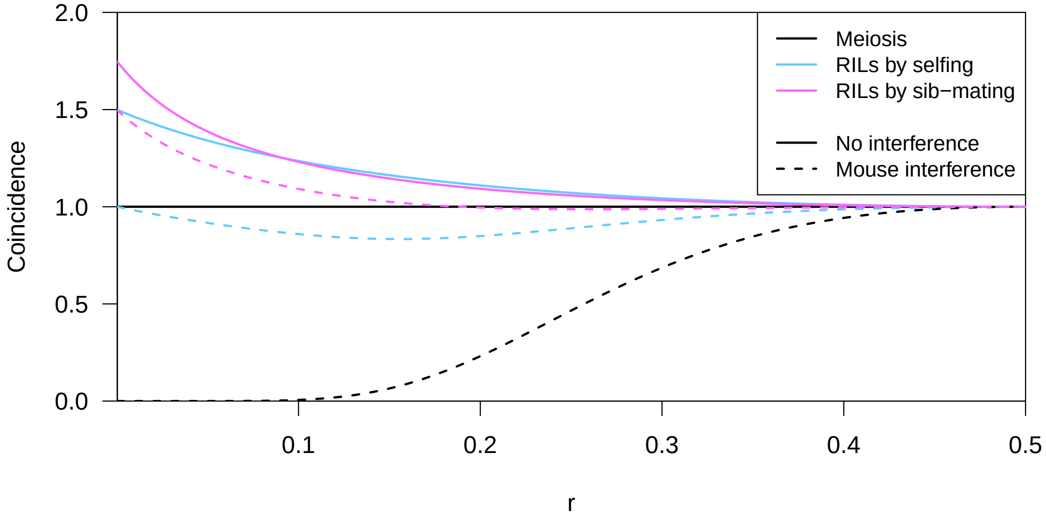


- r_{ij} = recombination fraction for interval (i, j)
  Assume $r_{12} = r_{23} = r$.
- Coincidence = c $=$ Pr(double recombinant)$/r^2$
  $= \Pr(\text{rec'n in 23} \mid \text{rec'n in 12}) / \Pr(\text{rec'n in 12})$
- No interference = 1
  Positive interference < 1
  Negative interference > 1
- Generally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

Coincidence



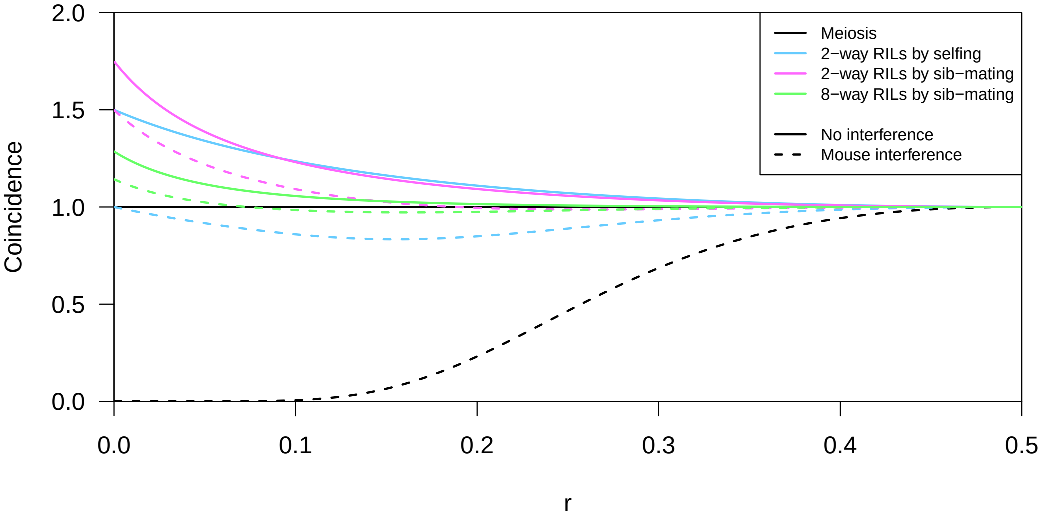
Coincidence



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 $\rightarrow$ 22 states by symmetry
  - 3 points in 4-way RILs by sib mating:
    2,164,240 parental types $\rightarrow$ 137,488 states by symmetry
- Even counting the states was difficult.

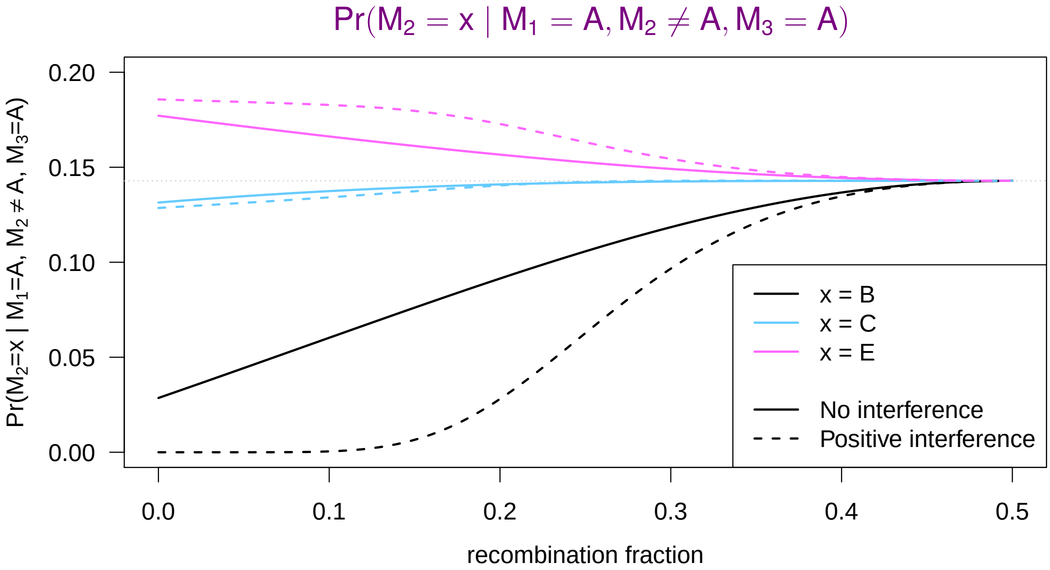
Coincidence



The formula

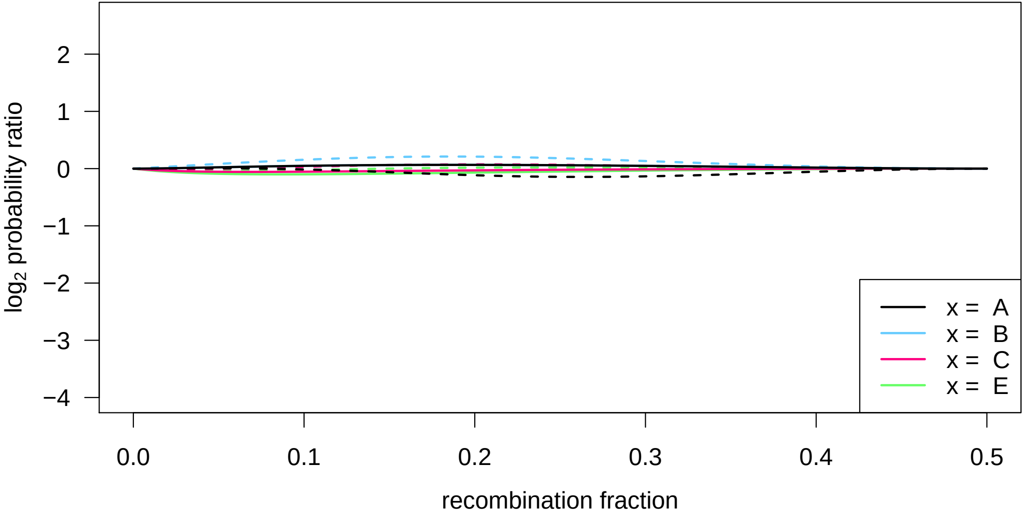
$$C = \frac{(1+6r)[280+1208r-848r^2+5c(7-28r-368r^2+344r^3)-2c^2(49-324r+452r^2)r^2-16c^3(1-2r)r^4]}{49(1+12r-12cr^2)[5+10r-4(2+c)r^2+8cr^3]}$$

3-point symmetry



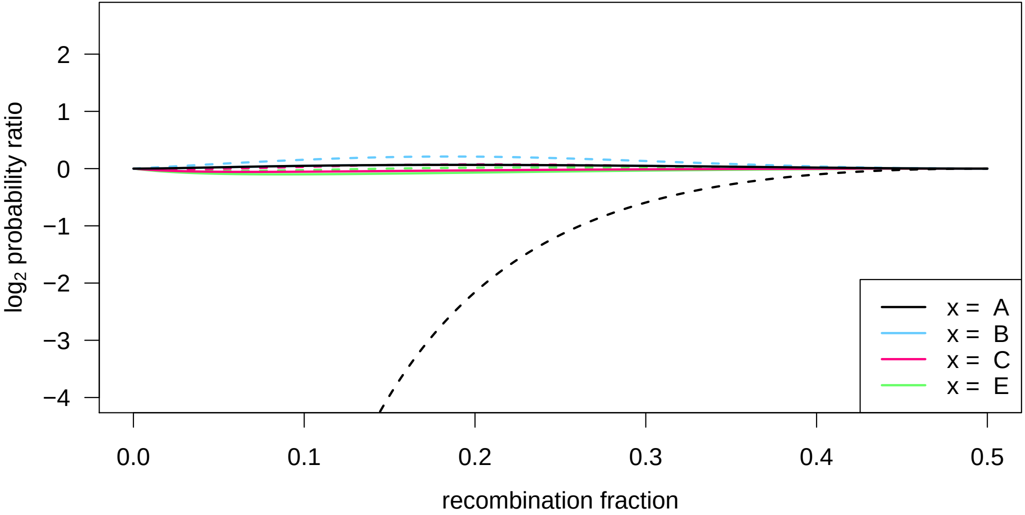
Markov property

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



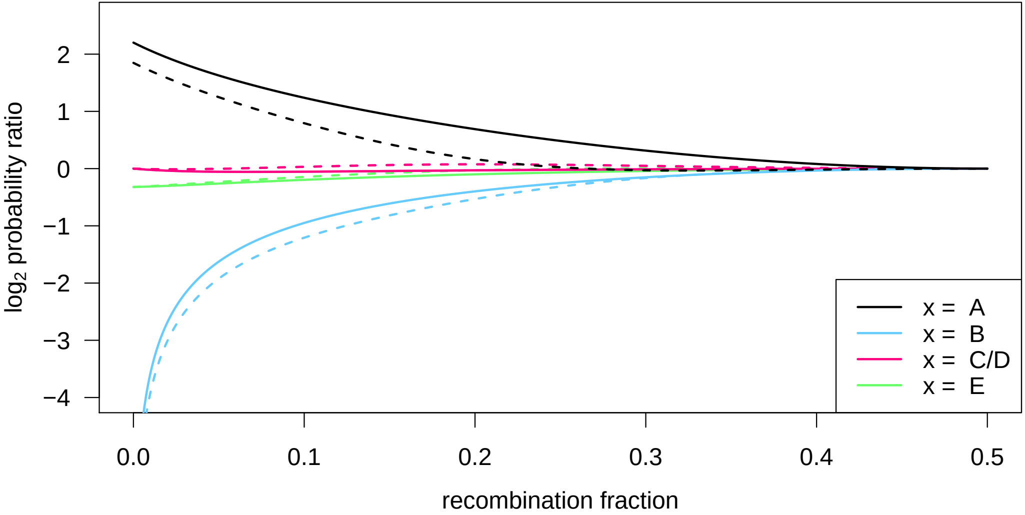
Markov property

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



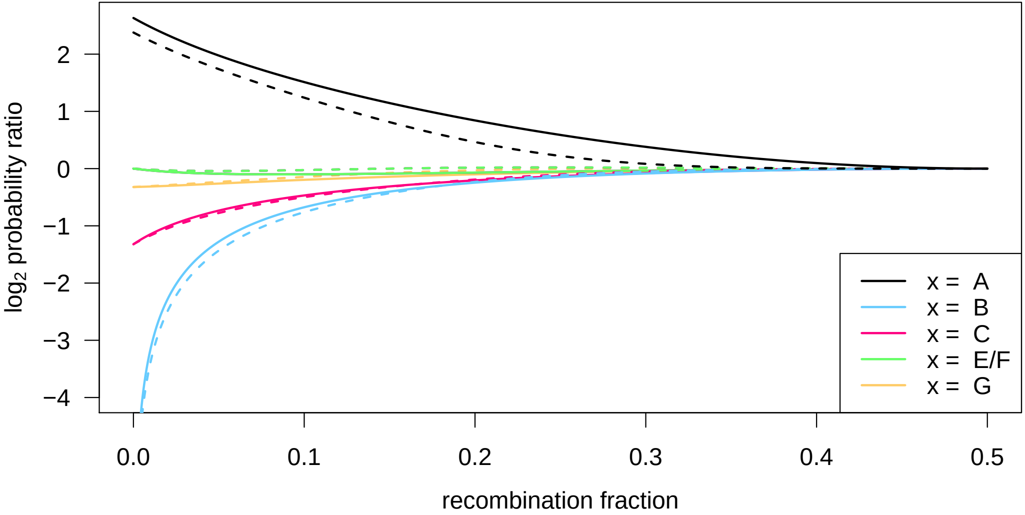
Markov property

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



Markov property

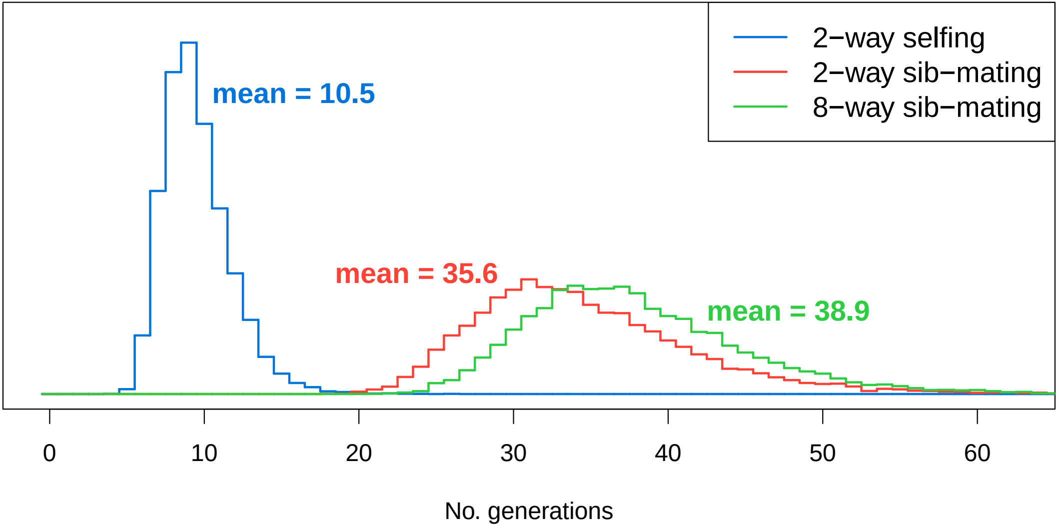
$$\log_2 \left\{ \frac{\Pr(M_3{=}A \mid M_2{=}E, M_1{=}x)}{\Pr(M_3{=}A \mid M_2{=}E)} \right\}$$



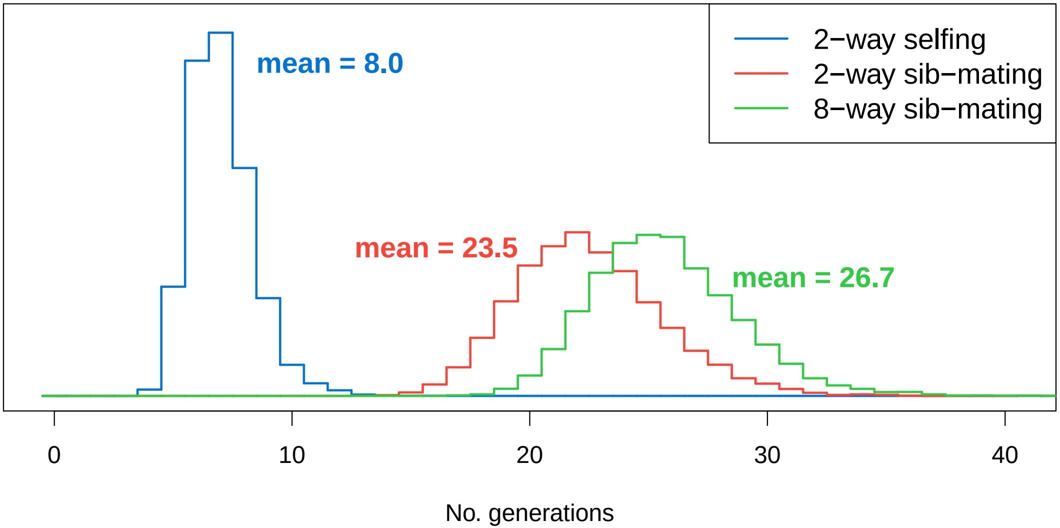
Whole genome simulations

- 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

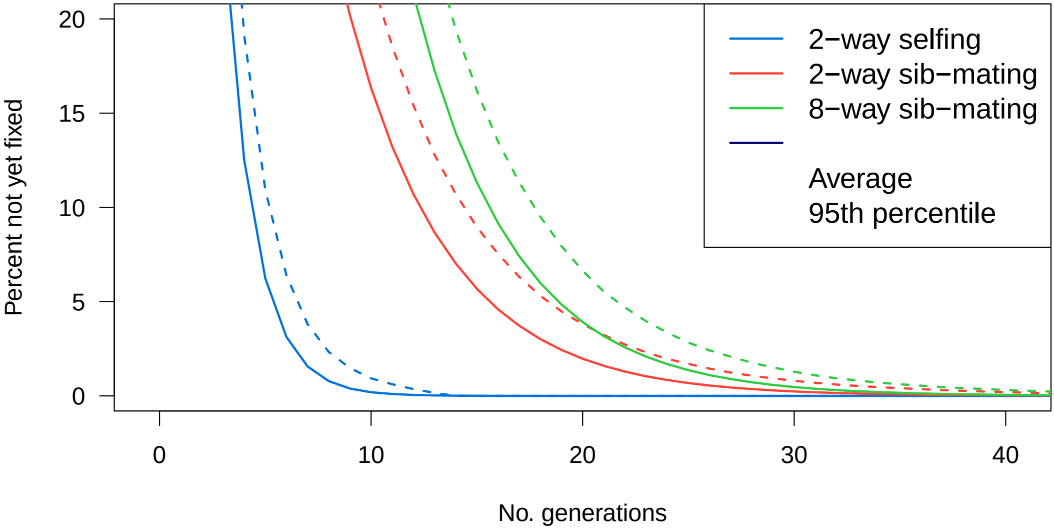
No. generations to fixation



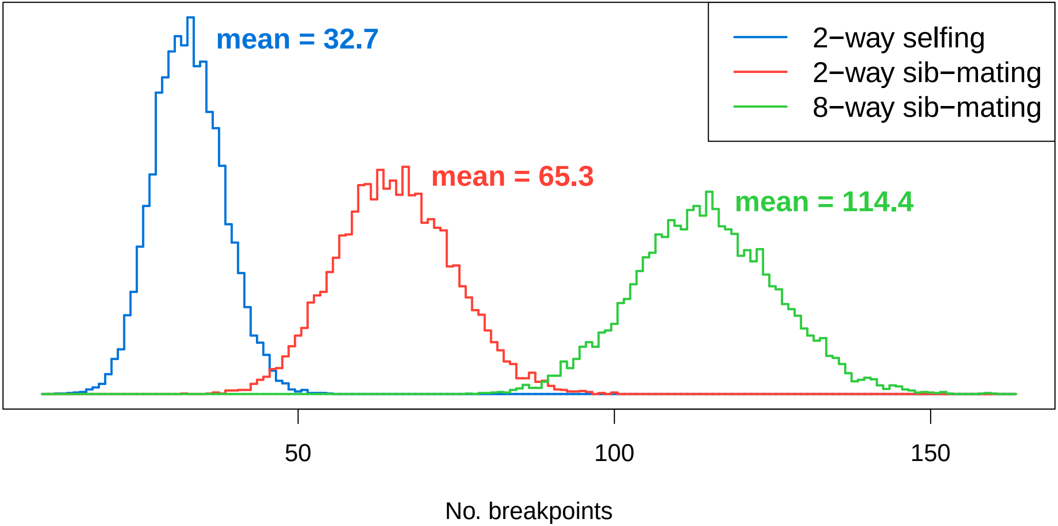
No. generations to 99% fixation



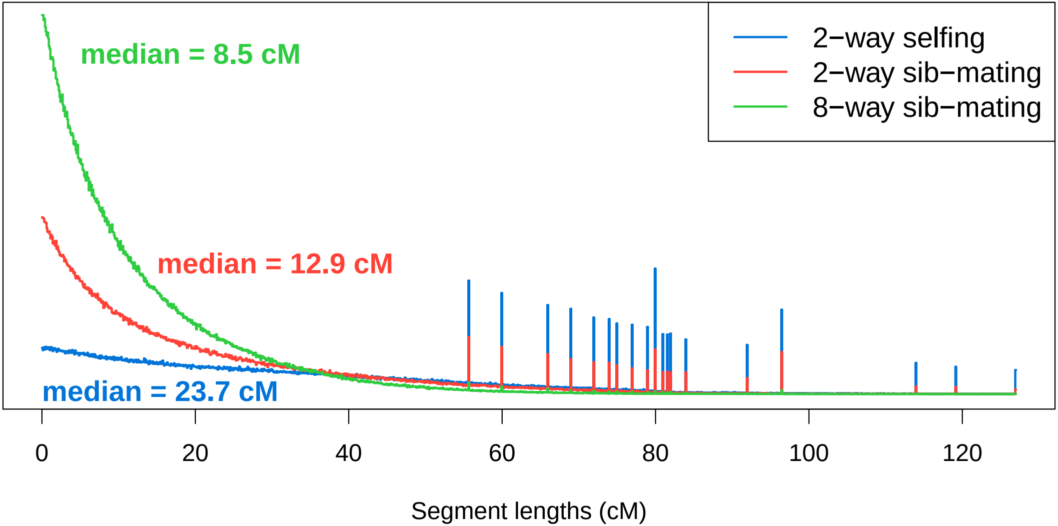
Percent genome not fixed



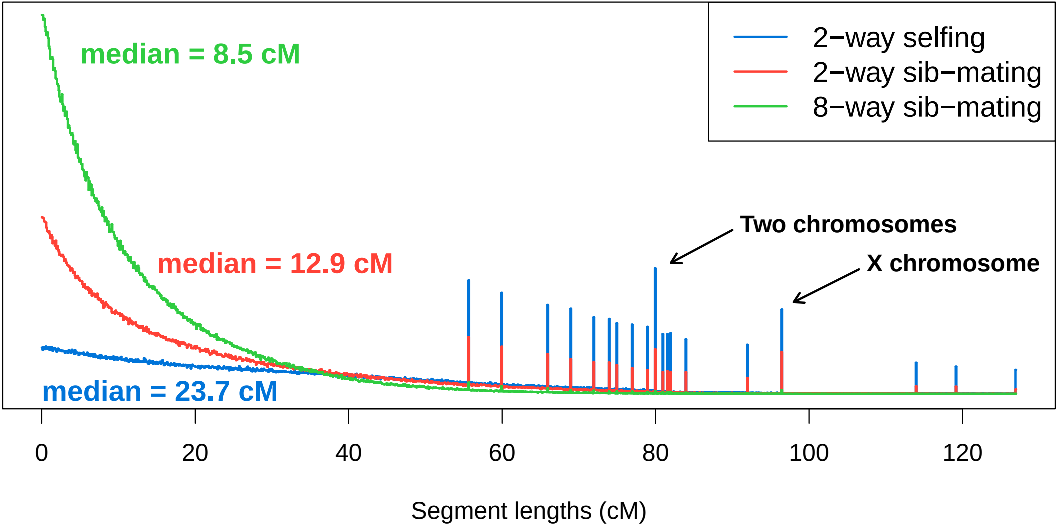
No. breakpoints



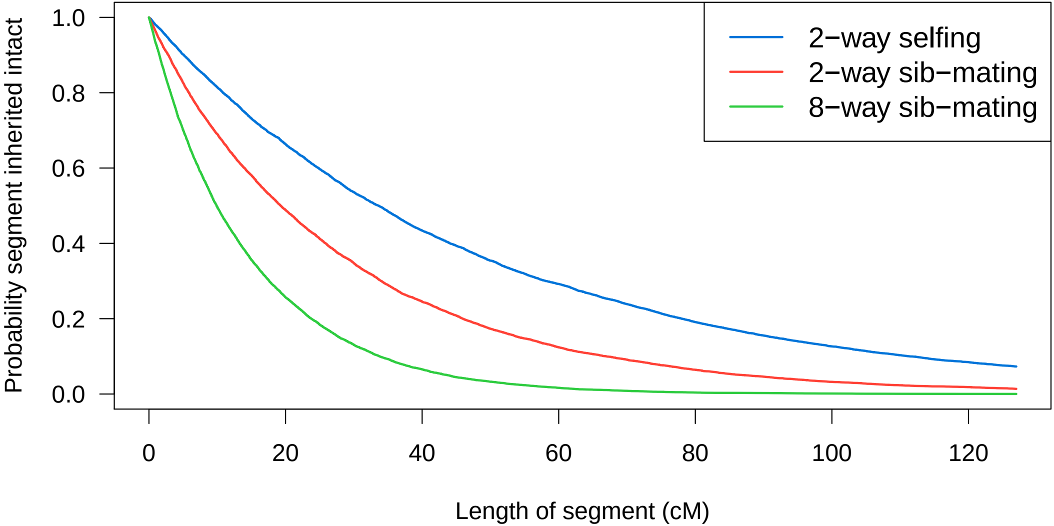
Segment lengths



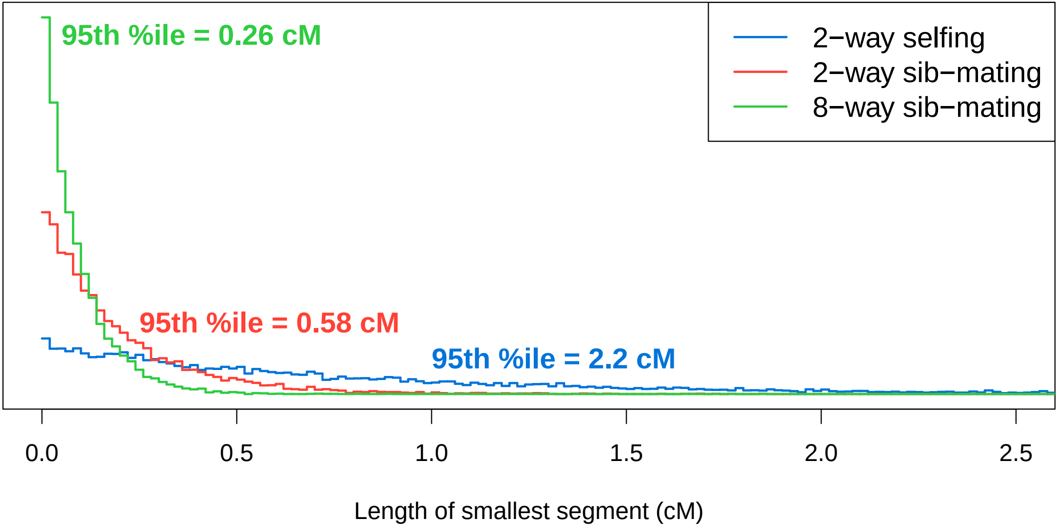
Segment lengths



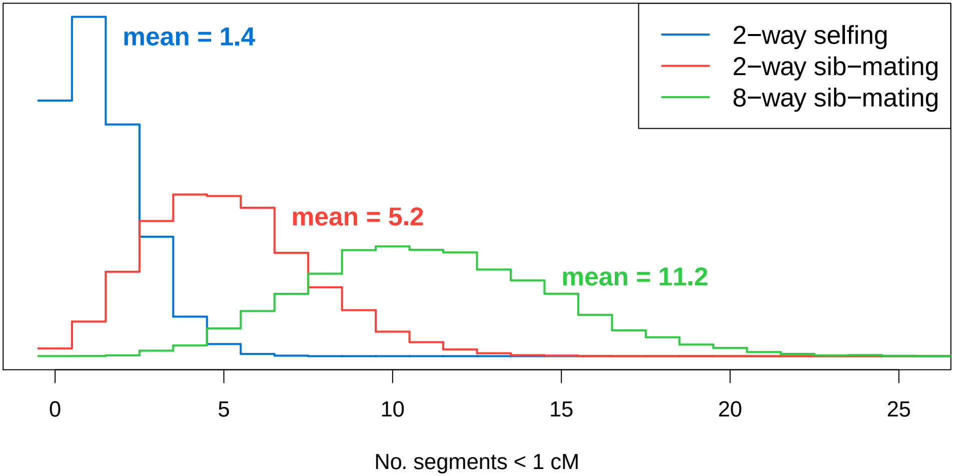
Probability a segment is inherited intact



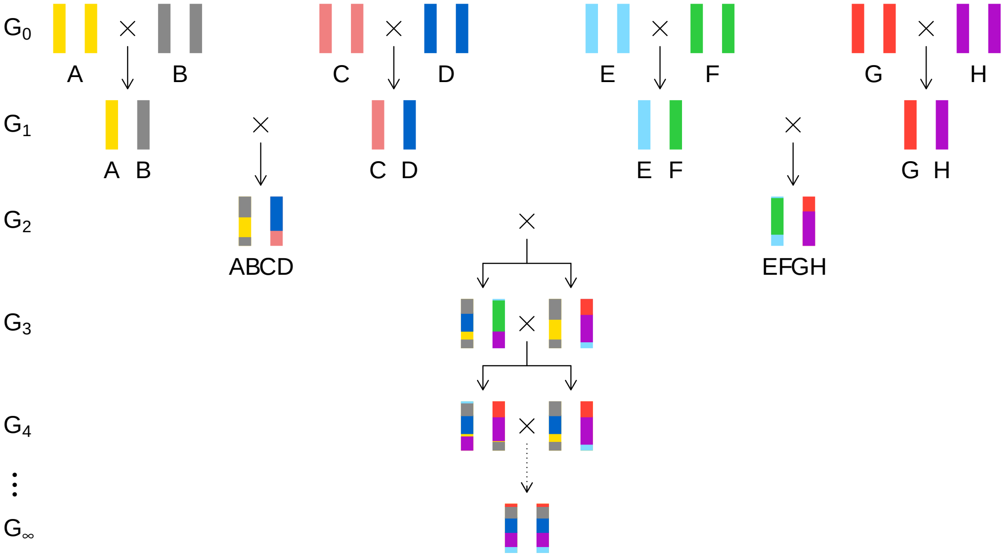
Length of smallest segment



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

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