Computer simulations

The genomes of recombinant inbred lines

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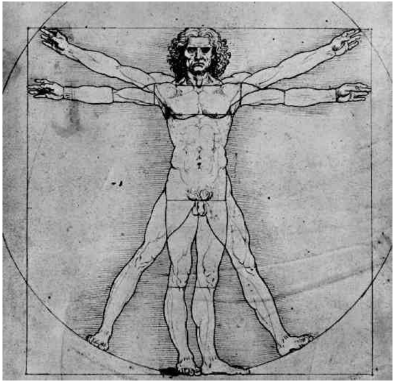
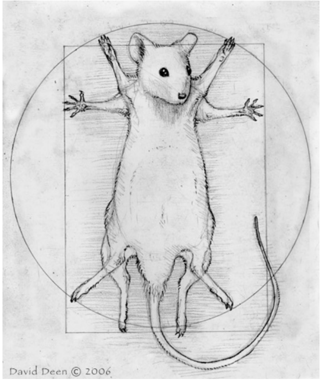
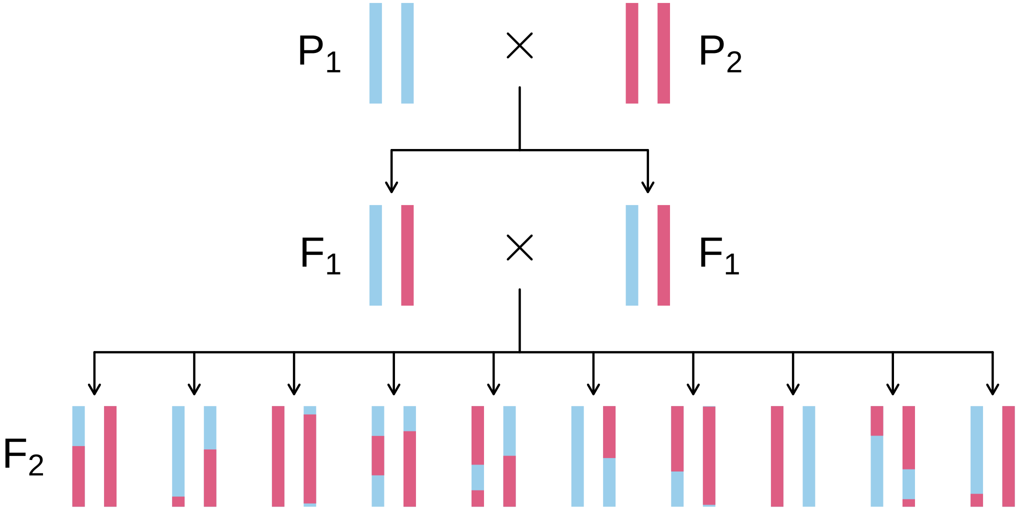


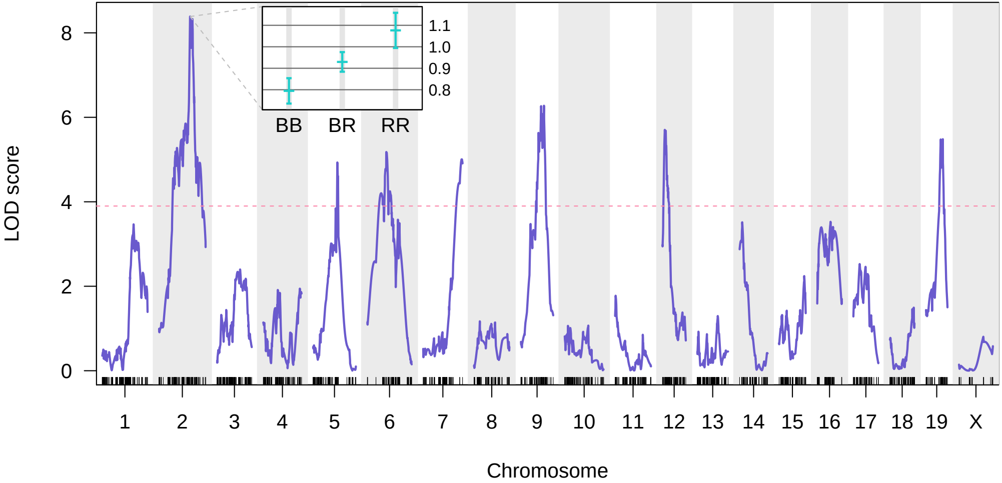


daviddeen.com

Intercross

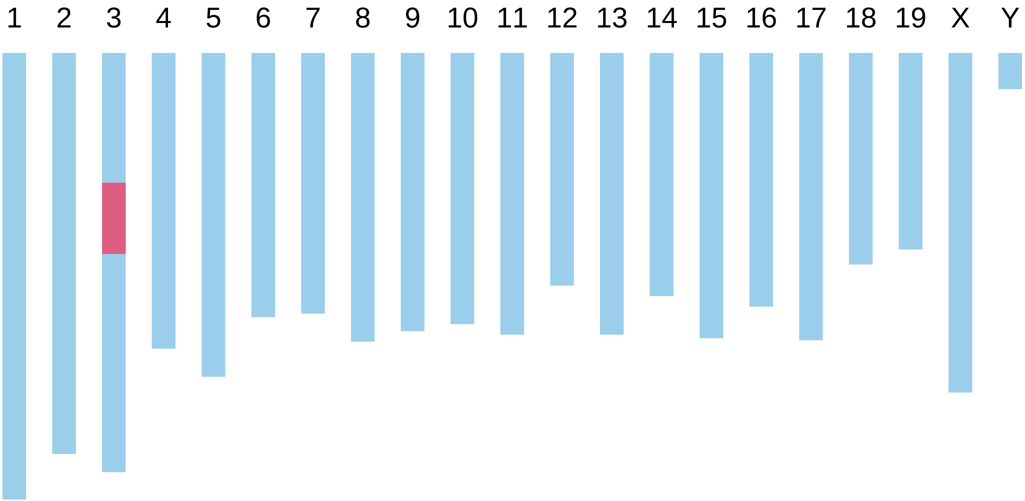


QTL mapping



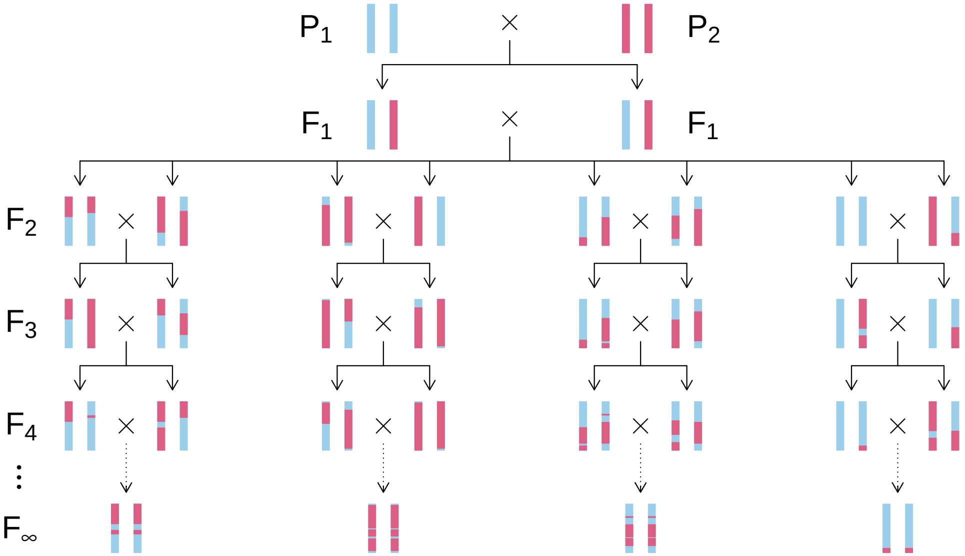
LOD score
8
6
4
2
0
1.1
1.0
0.9
0.8
BB
BR
RR
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

Congenic line

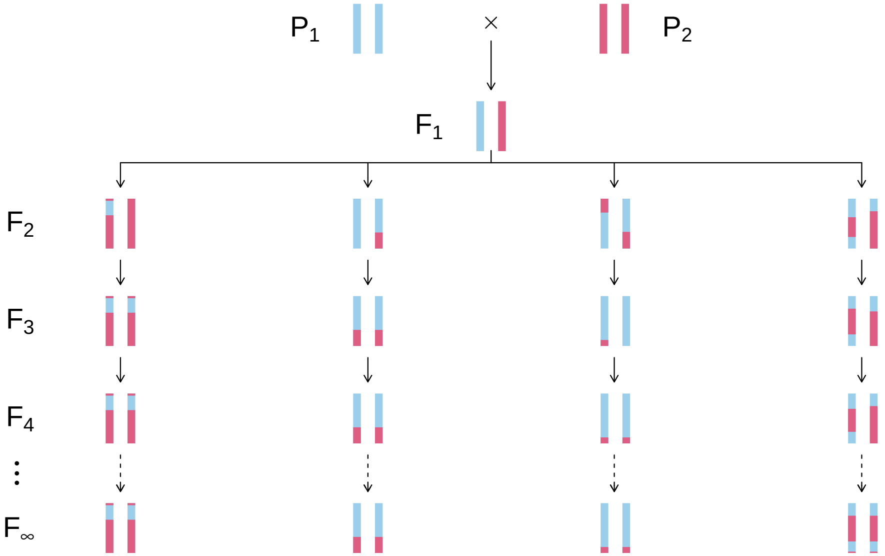


Advanced intercross lines

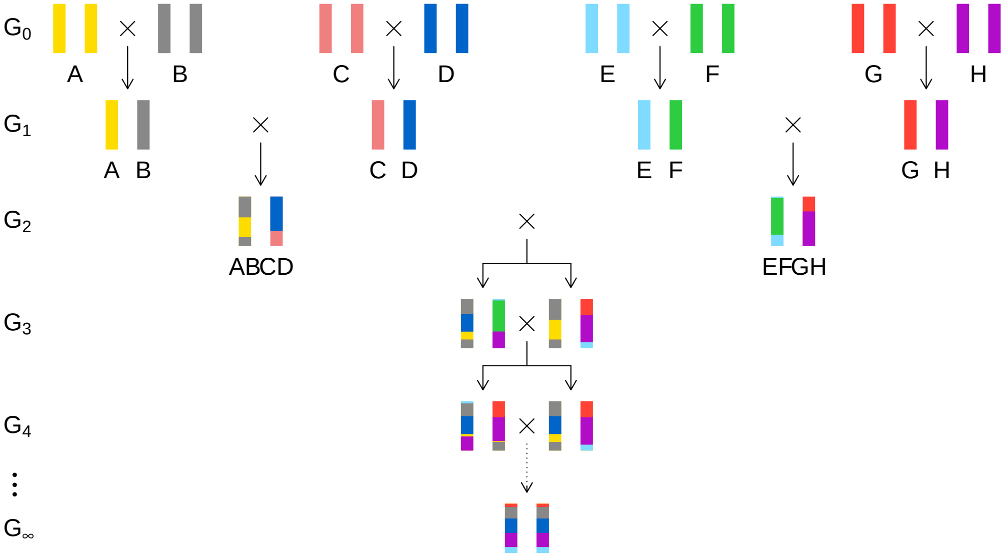
Recombinant inbred lines



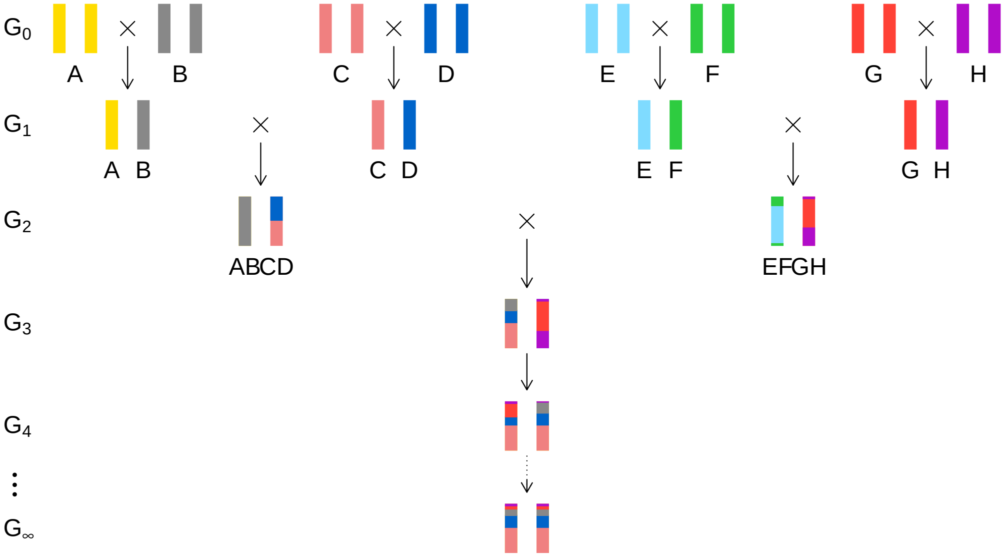
Recombinant inbred lines



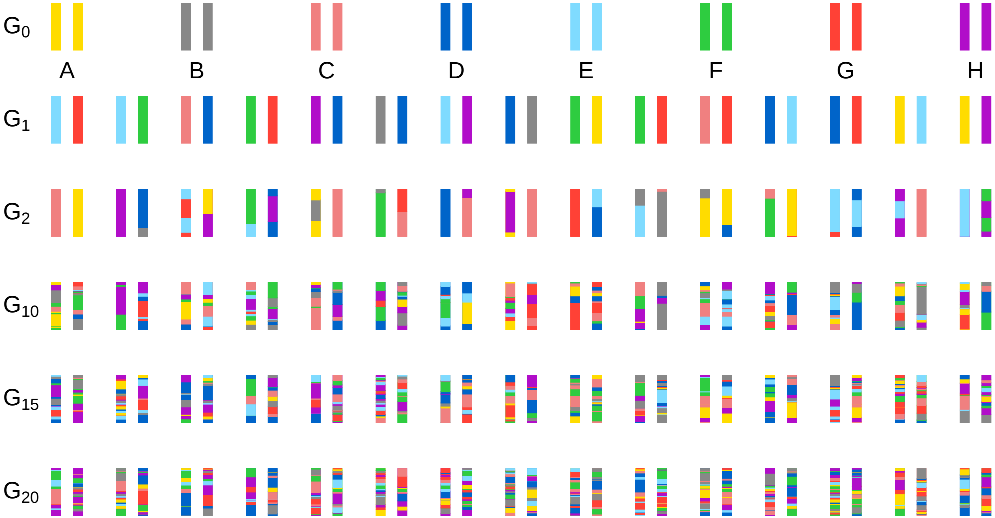
Collaborative Cross



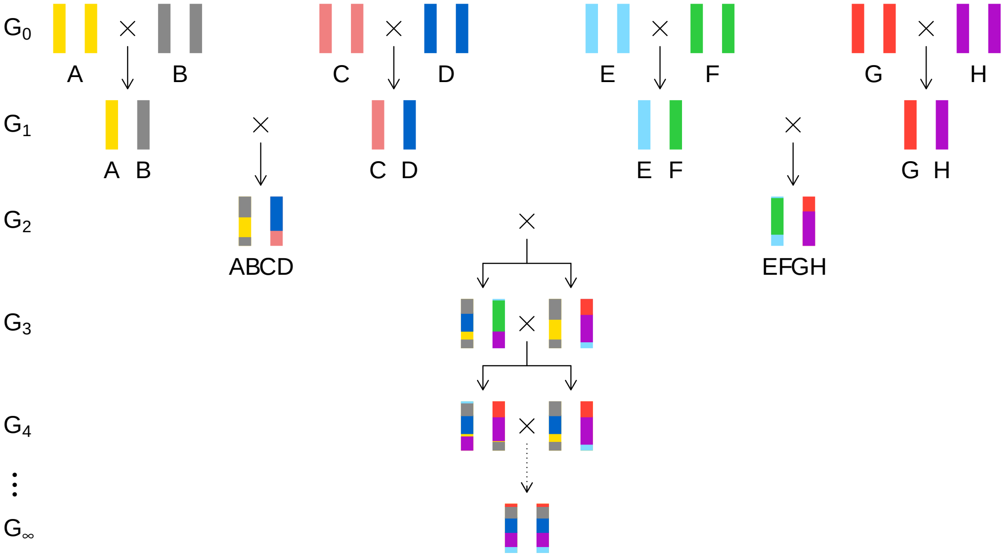
MAGIC



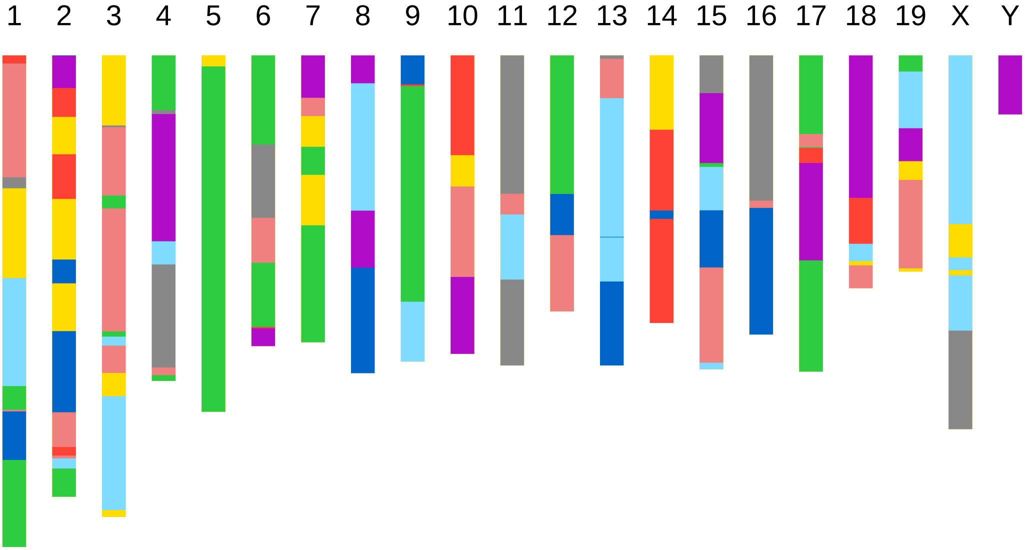
Heterogeneous stock



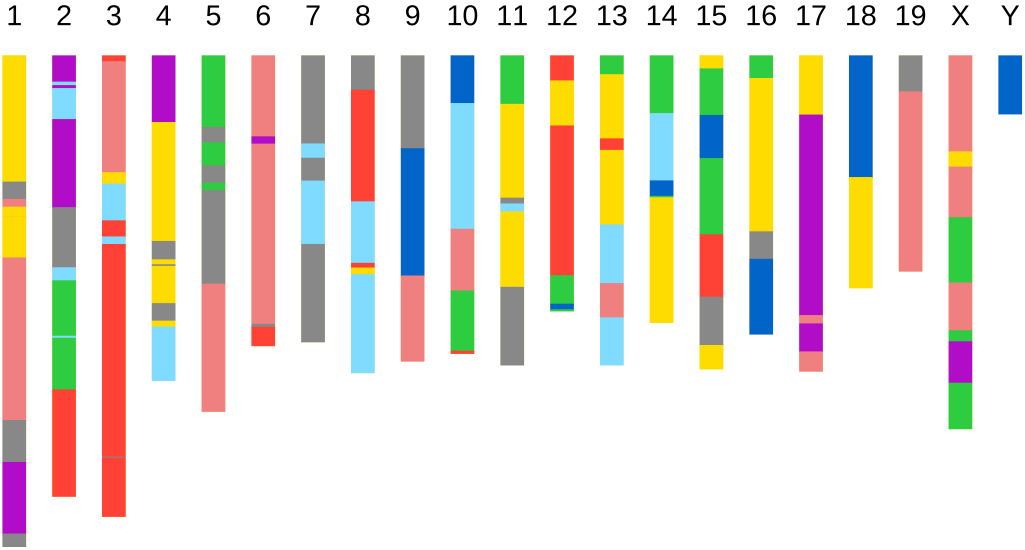
Collaborative Cross



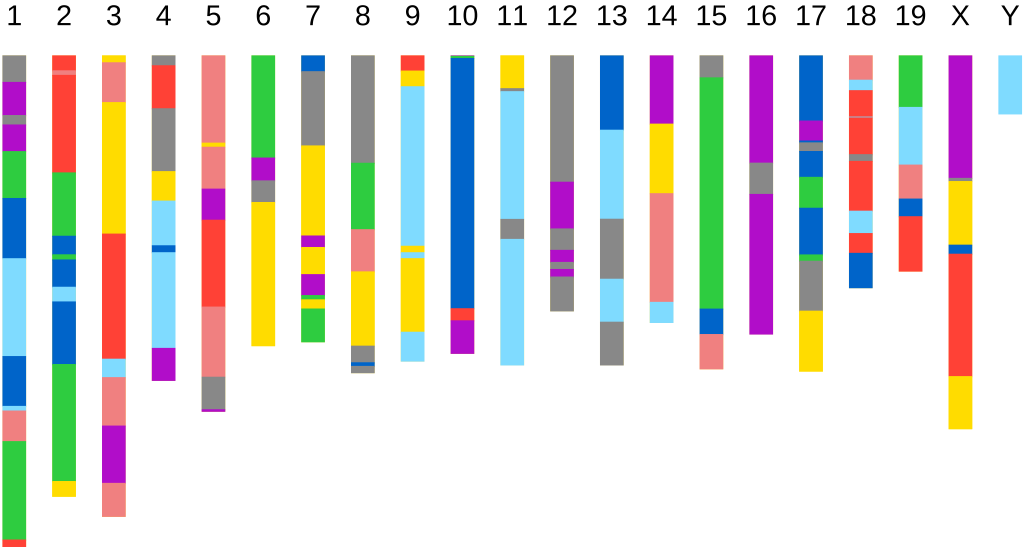
CC genome



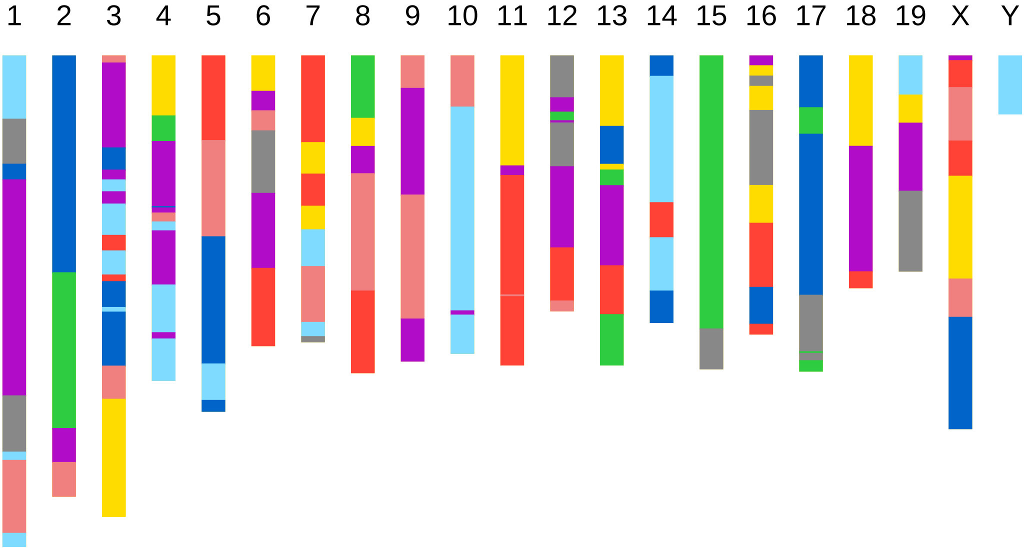
CC genome



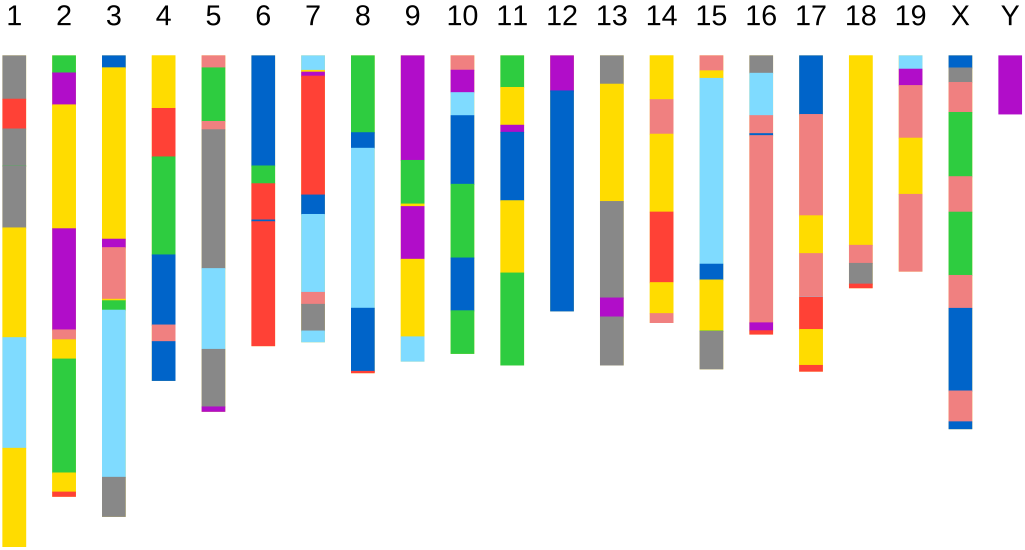
CC genome



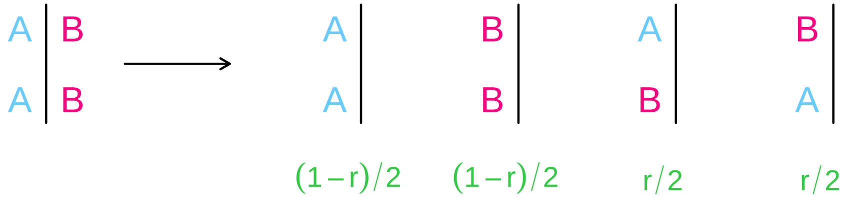
CC genome



CC genome

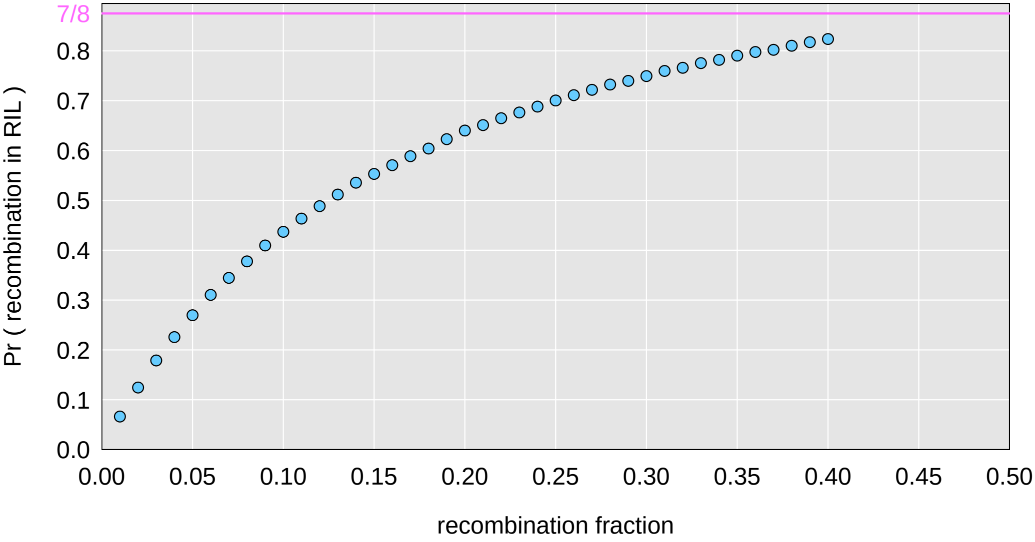


Recombination fraction



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)

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

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

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.

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

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).

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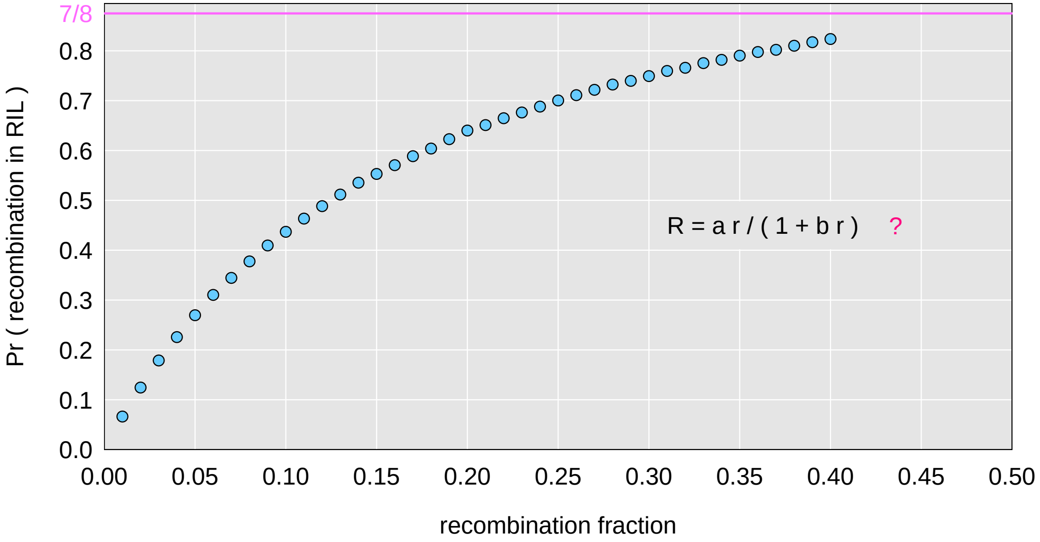
Simulation results



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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out <- nls( R ~ a*r/(1 + b*r),
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```

	Estimate	Std. Error
a	7.016	0.011
b	6.023	0.016

Non-linear regression

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out <- nls( R ~ a*r/(1 + b*r),
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summary(out)
```
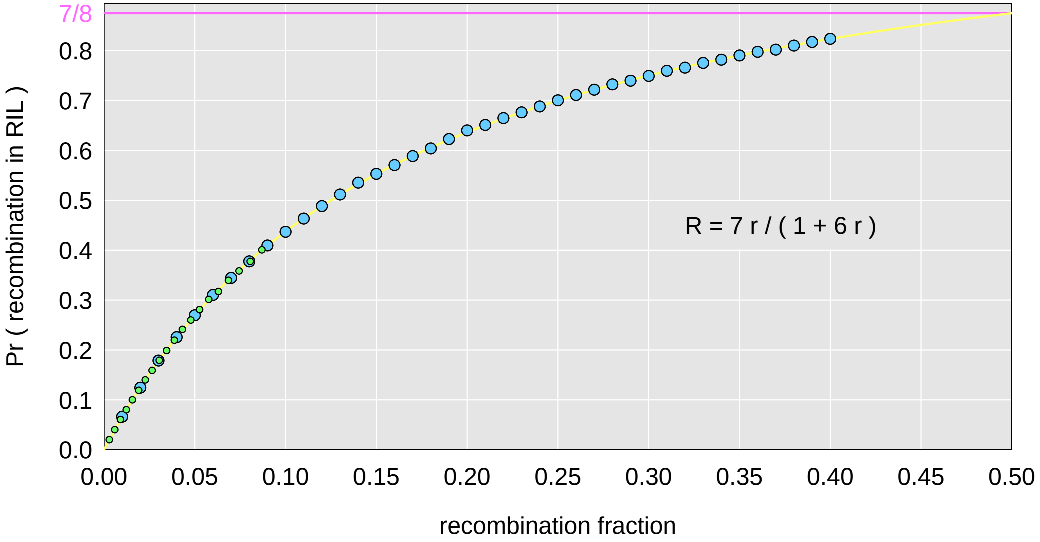

	Estimate	Std. Error
a	7.016	0.011
b	6.023	0.016

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:

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

...r 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)

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

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

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	$D_{n+1}=D+I+\frac{1}{4}(\alpha^2+\gamma^2)M+\frac{1}{4}(\beta^2+\delta^2)P+\frac{1}{8}Q+\frac{1}{8}S+\frac{1}{8}(\beta^2+\delta^2)U+\frac{1}{8}(\alpha^2+\gamma^2)V+\frac{1}{16}\beta^2\delta^2W+\frac{1}{16}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{16}\alpha^2\gamma^1Y.$
$AABB \times aabb$	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	$Y_{n+1}=2(F+K)+\frac{1}{2}(\alpha^2+\gamma^2)M+\frac{1}{2}(\beta^2+\delta^2)P+\frac{1}{4}(R+T)+\frac{1}{4}(\beta^2+\delta^2)U+\frac{1}{4}(\alpha^2+\gamma^2)V+\frac{1}{4}\beta^2\delta^2W+\frac{1}{4}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{4}\alpha^2\gamma^2Y.$

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as may easily be verified.

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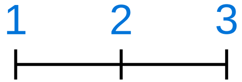
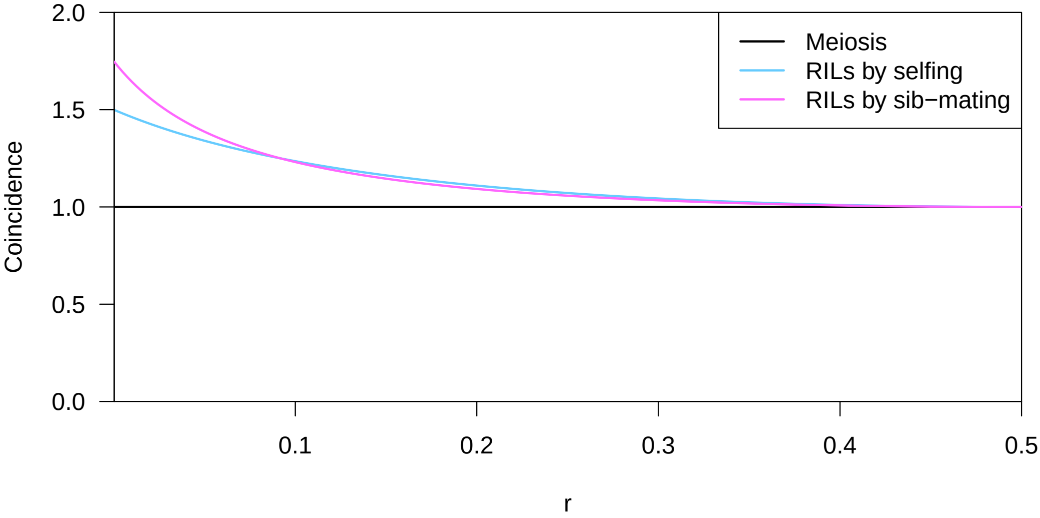
3-point coincidence

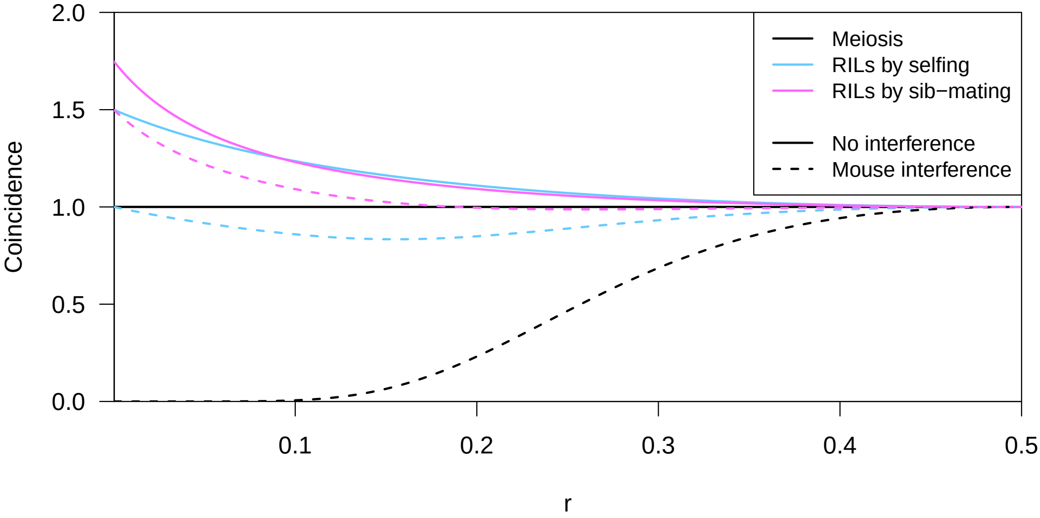


- r_{ij} = recombination fraction for interval (i, j)
  Assume $r_{12} = r_{23} = r$.
- Coincidence = $c = \Pr(\text{double recombinant})/r^2$
  $= \Pr(\text{rec'n in 23} \mid \text{rec'n in 12})/\Pr(\text{rec'n in 23})$
- No interference = 1
  Positive interference < 1
  Negative interference > 1
-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

Coincidence



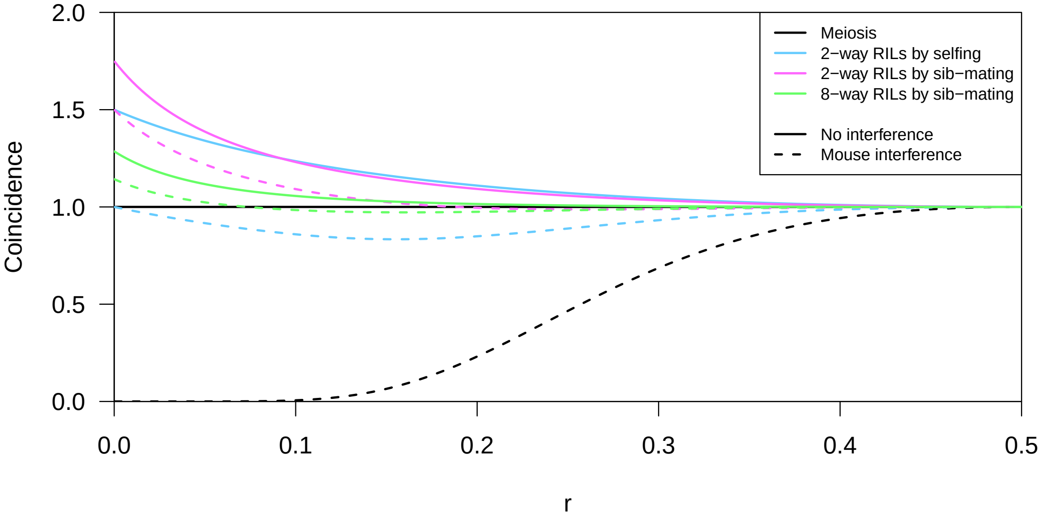
Coincidence



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 $\rightarrow$ 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.

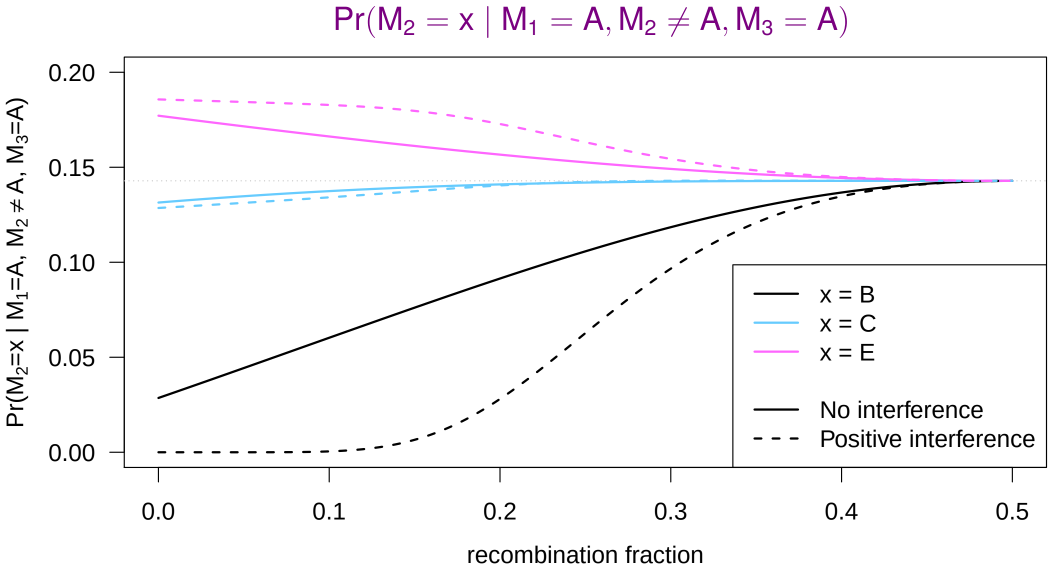
Coincidence



The formula

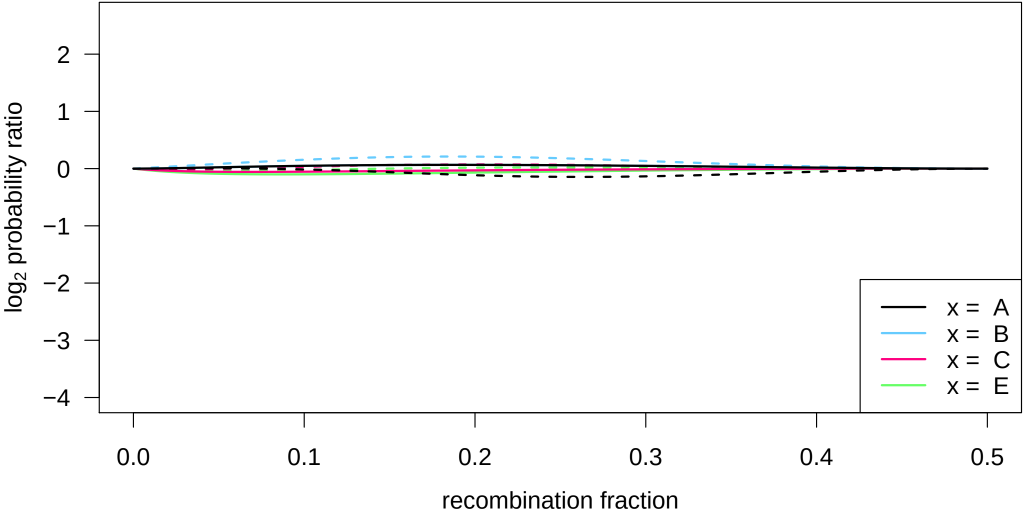
$$C = \frac{(1+6r)[280+1208r-848r^2+5c(7-28r-368r^2+344r^3)-2c^2(49-324r+452r^2)r^2-16c^3(1-2r)r^4]}{49(1+12r-12cr^2)[5+10r-4(2+c)r^2+8cr^3]}$$

3-point symmetry



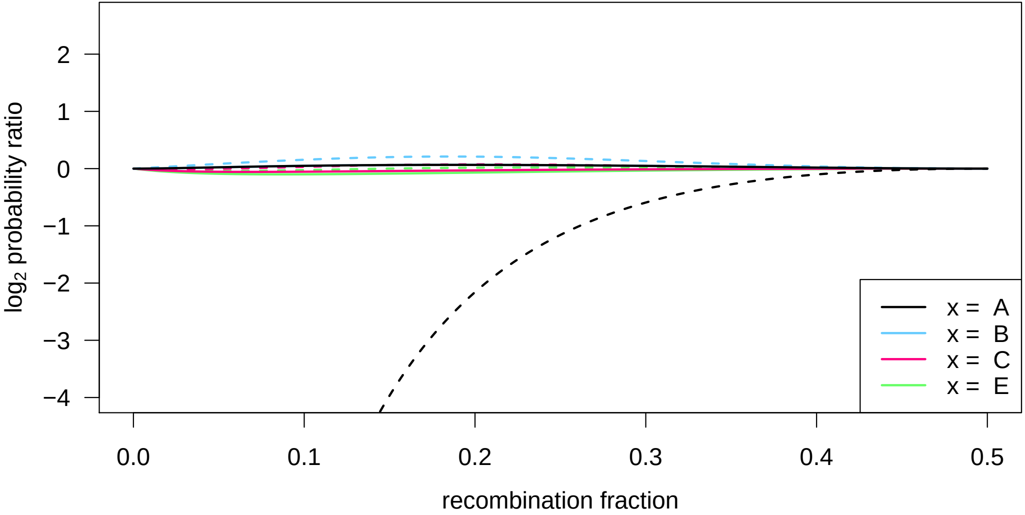
Markov property

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



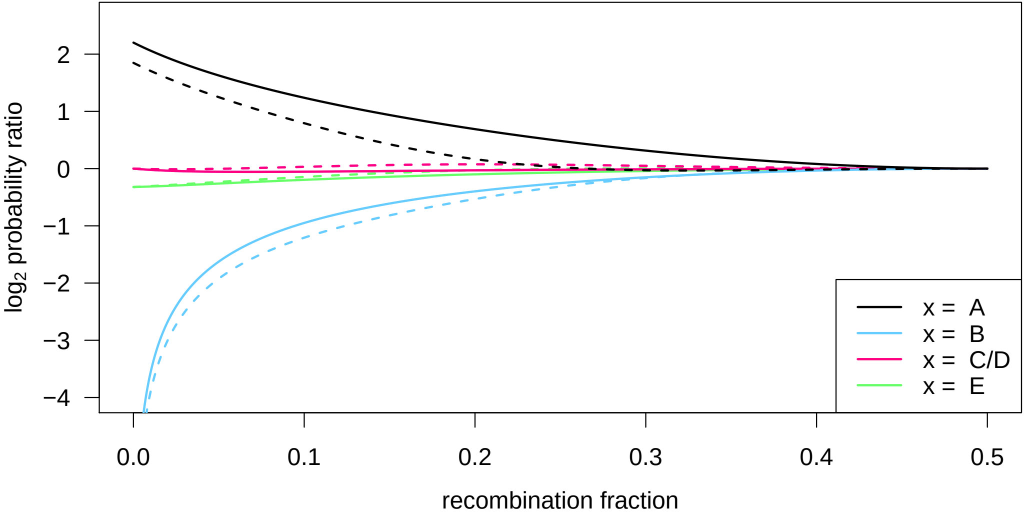
Markov property

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



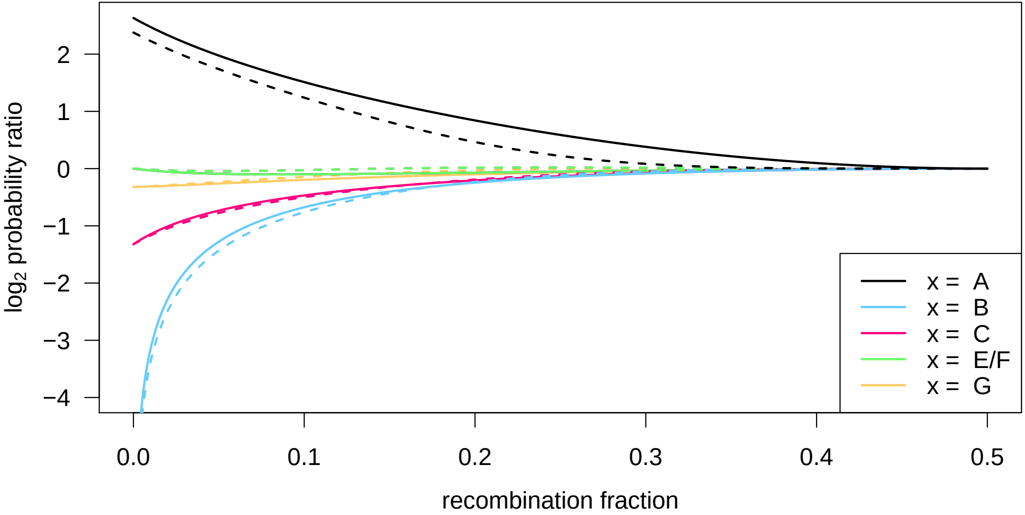
Markov property

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



Markov property

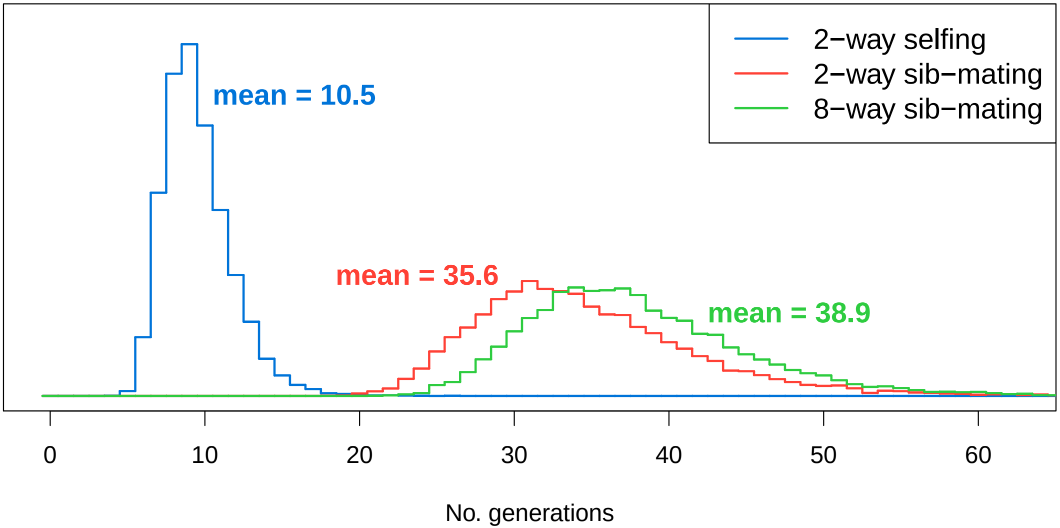
$$\log_2 \left\{ \frac{\Pr(M_3{=}A \mid M_2{=}E, M_1{=}x)}{\Pr(M_3{=}A \mid M_2{=}E)} \right\}$$



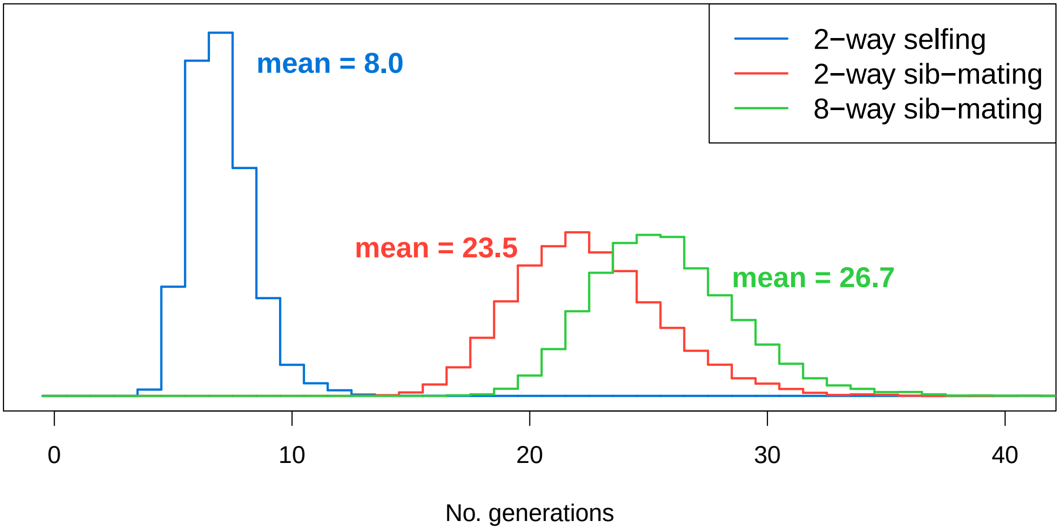
Whole genome simulations

- 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

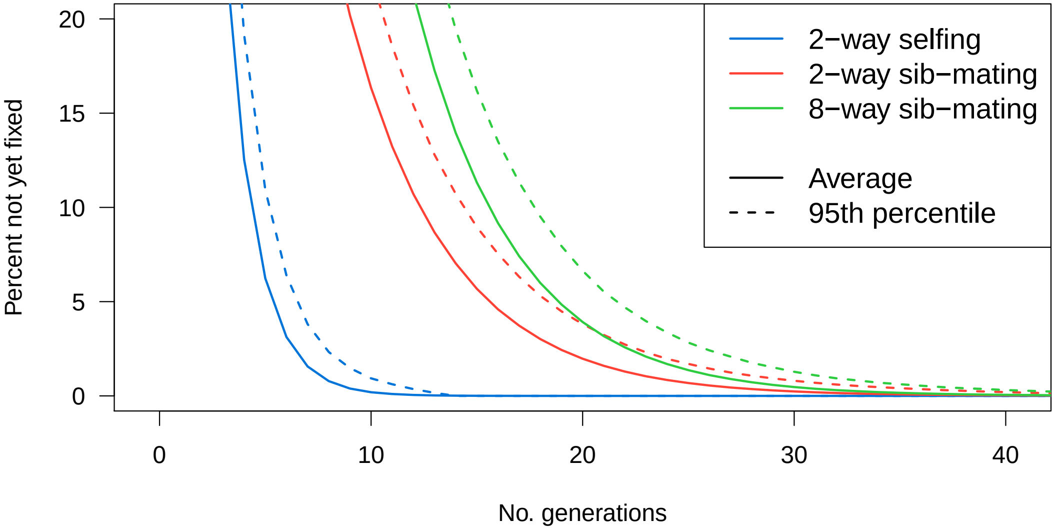
No. generations to fixation



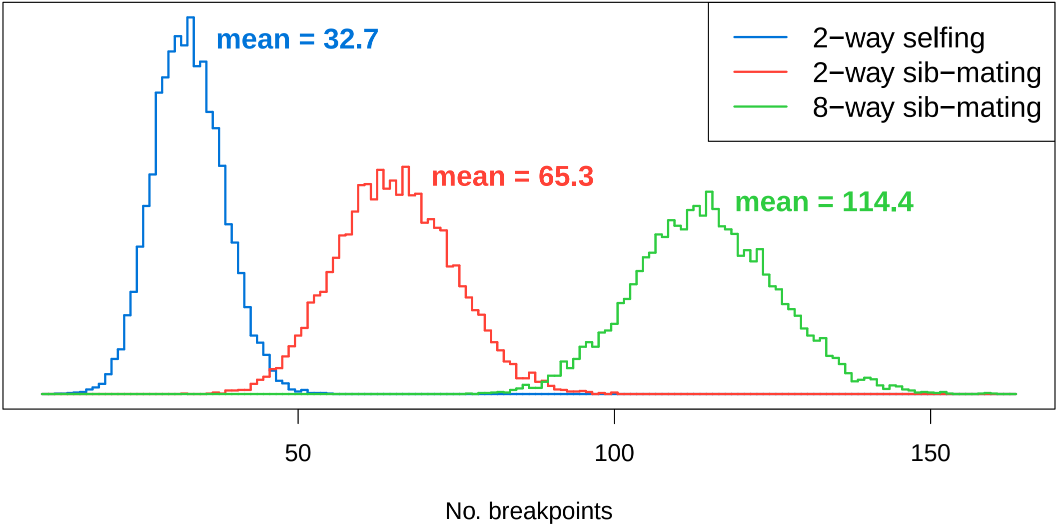
No. generations to 99% fixation



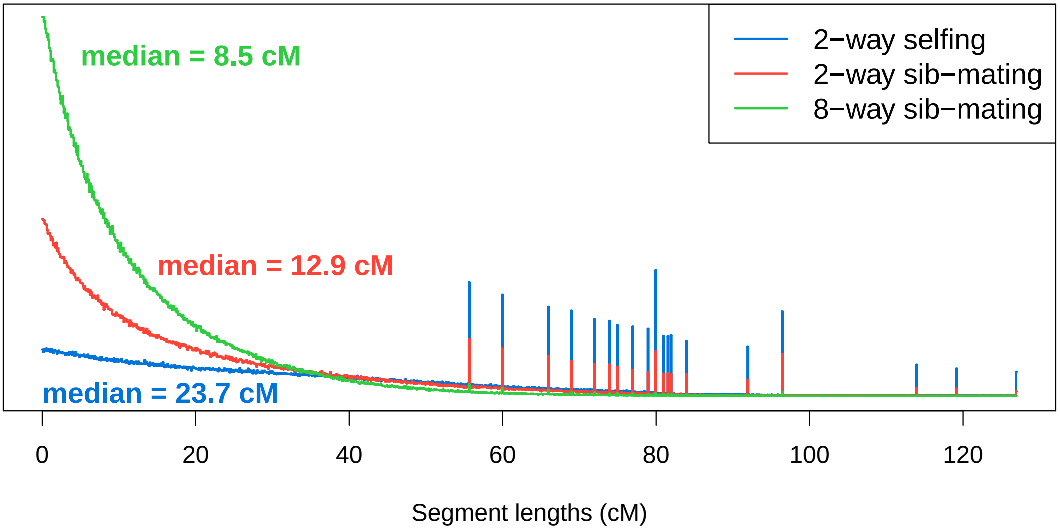
Percent genome not fixed



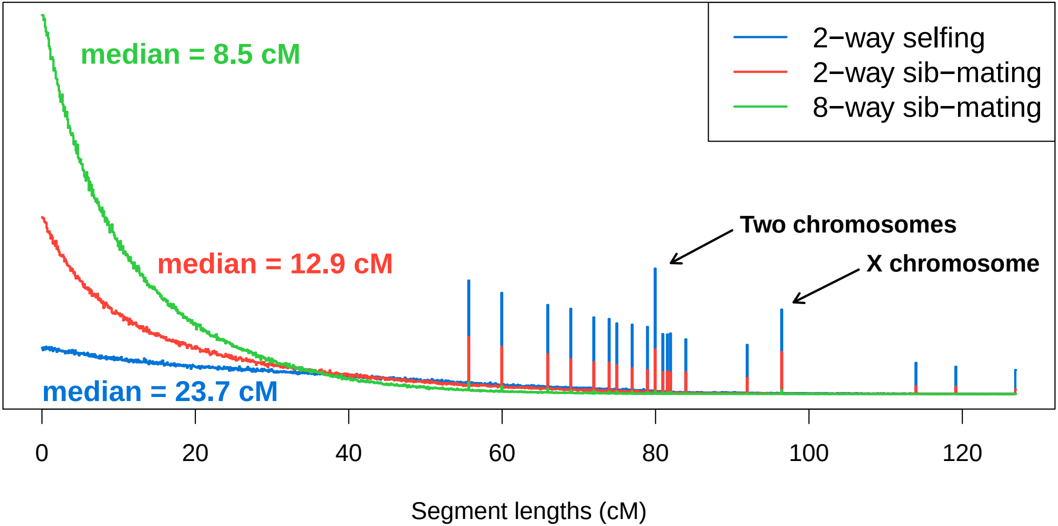
No. breakpoints



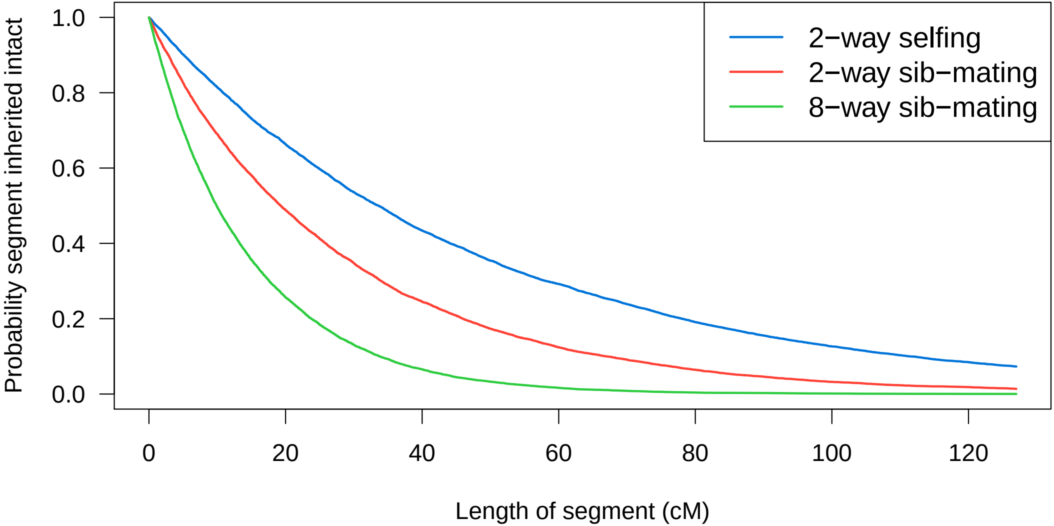
Segment lengths



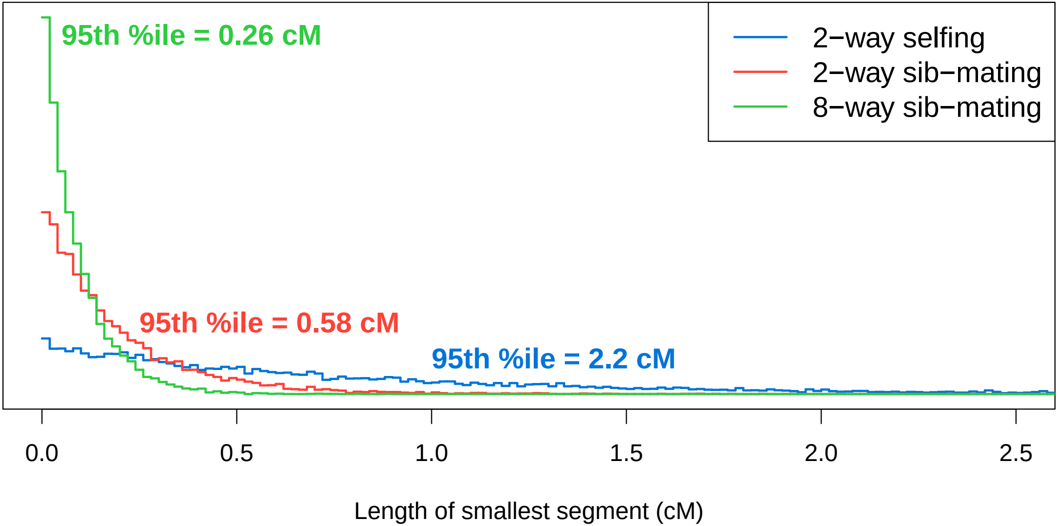
Segment lengths



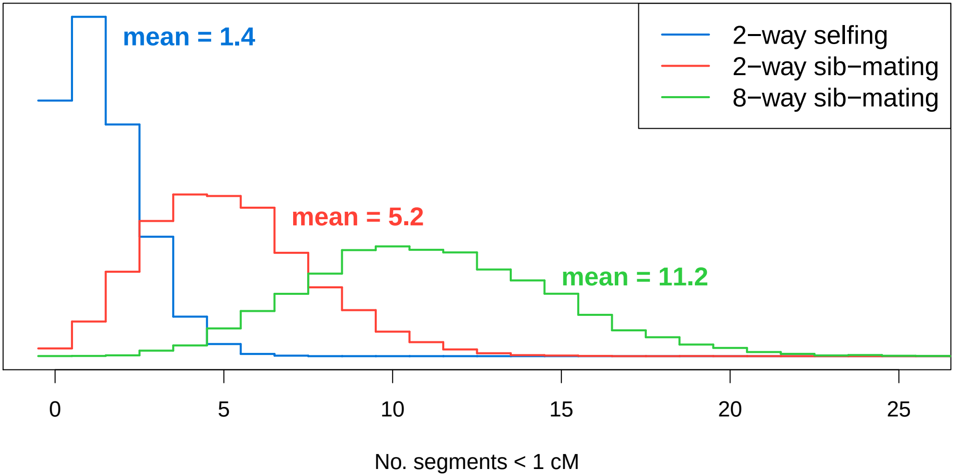
Probability a segment is inherited intact



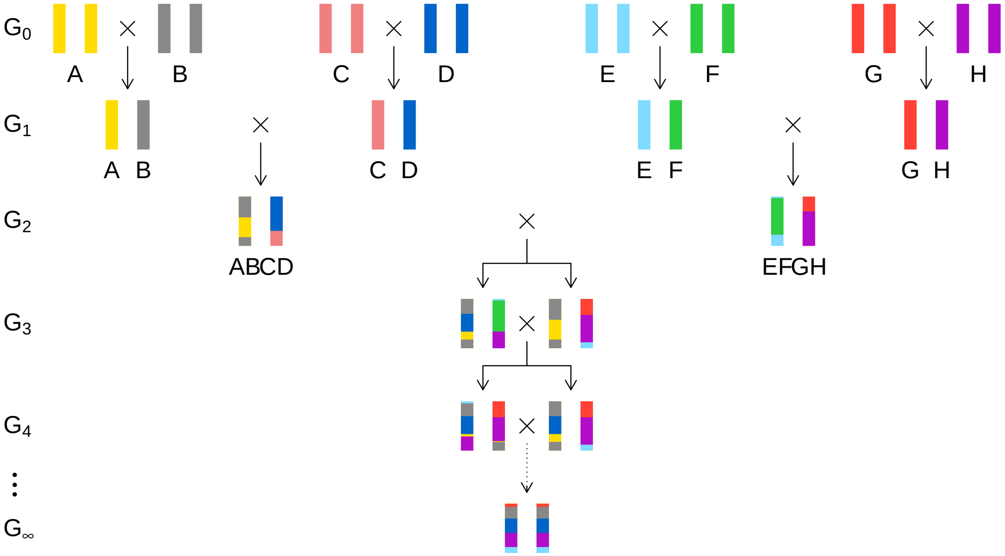
Length of smallest segment



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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