The genomes of recombinant inbred lines

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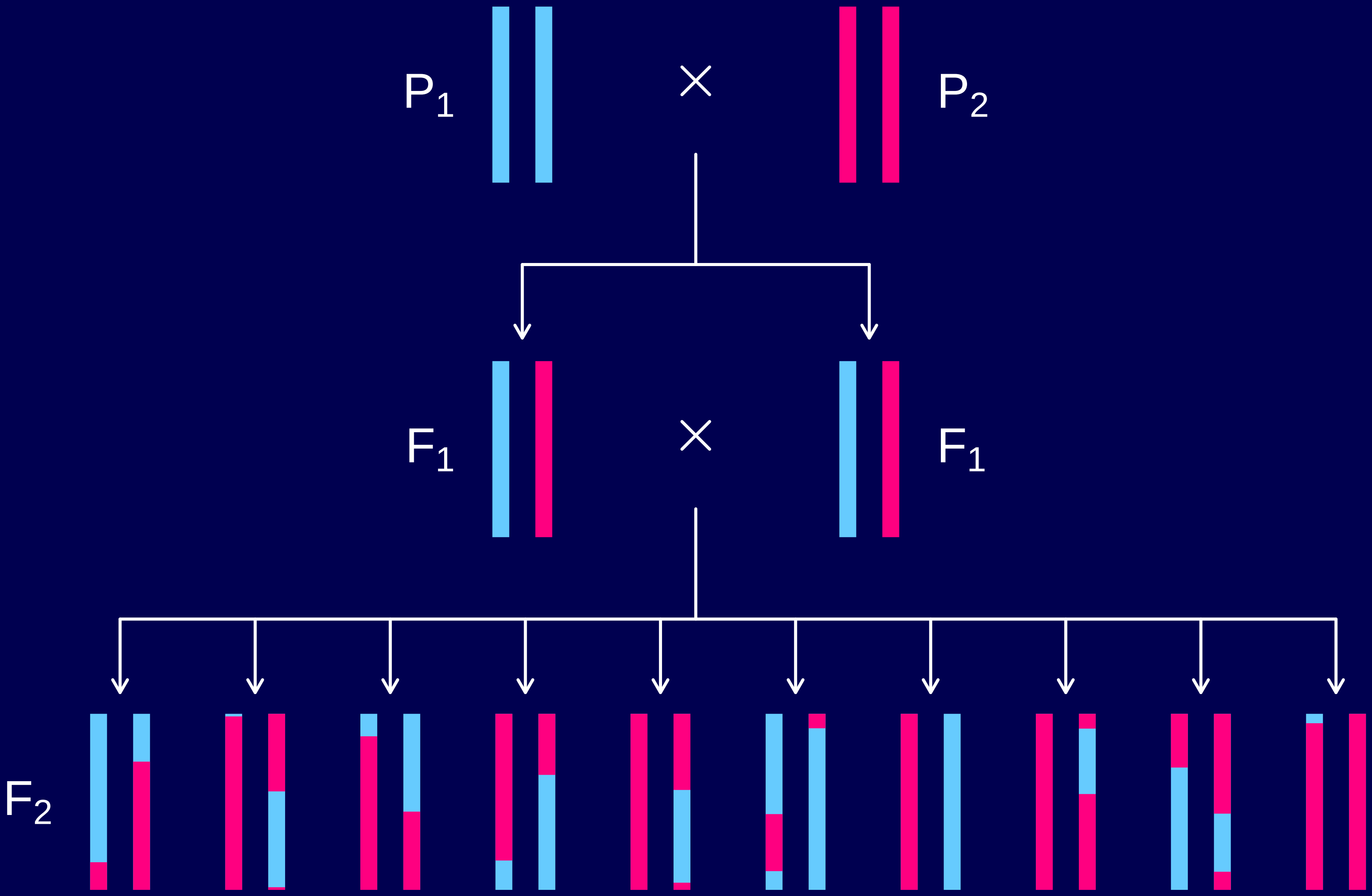
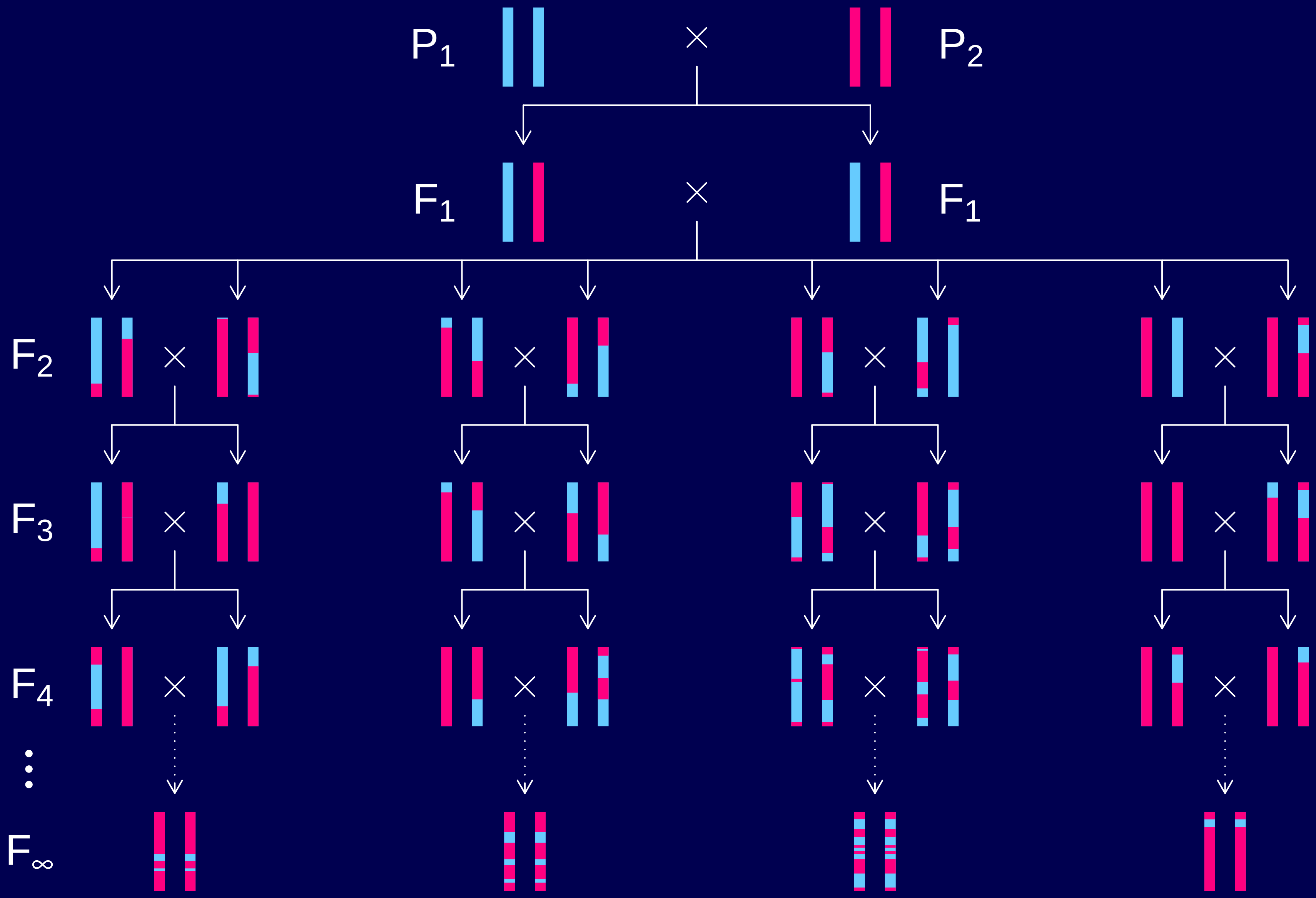
C57BL/6

Intercross

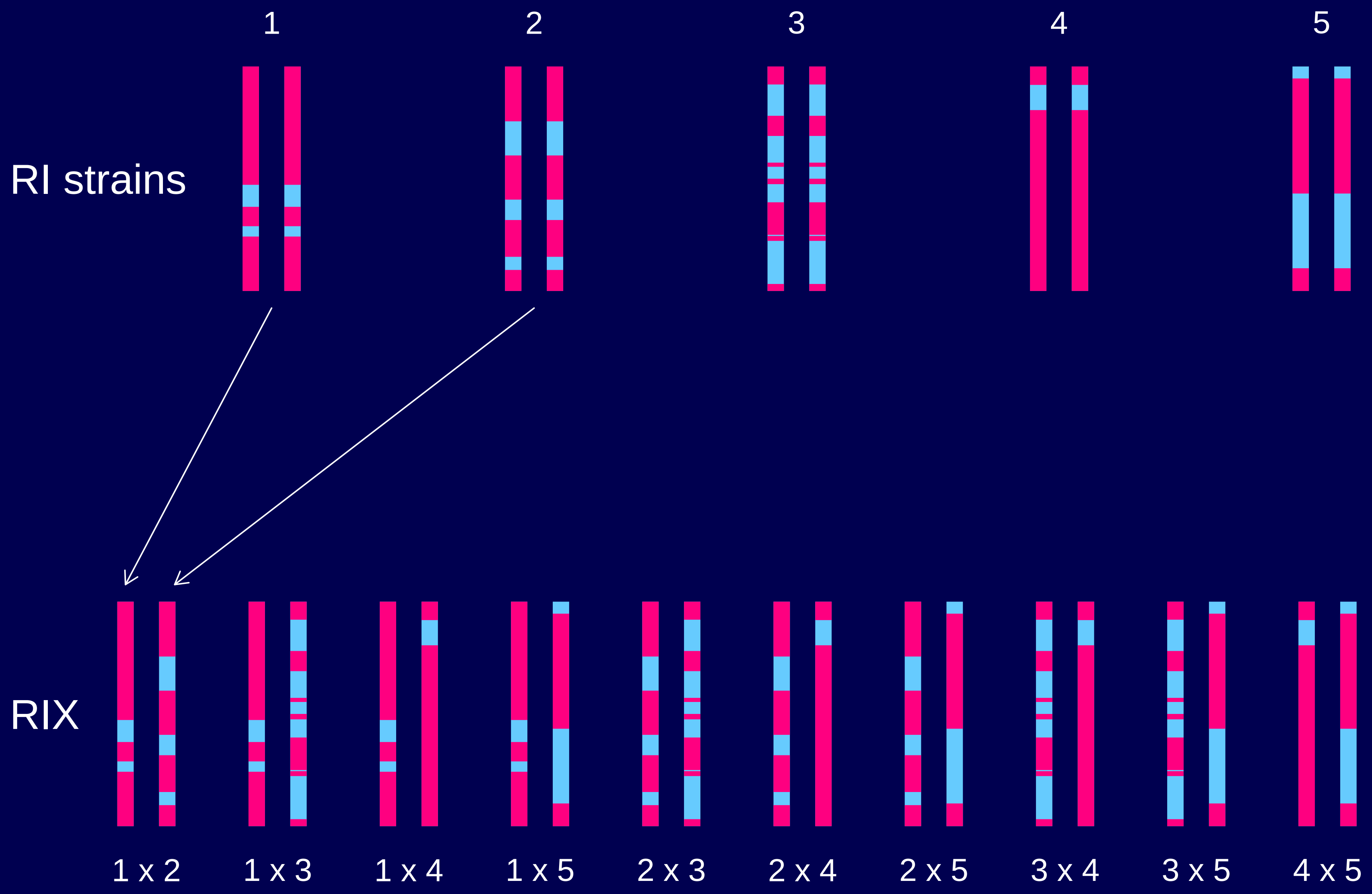


Recombinant inbred lines

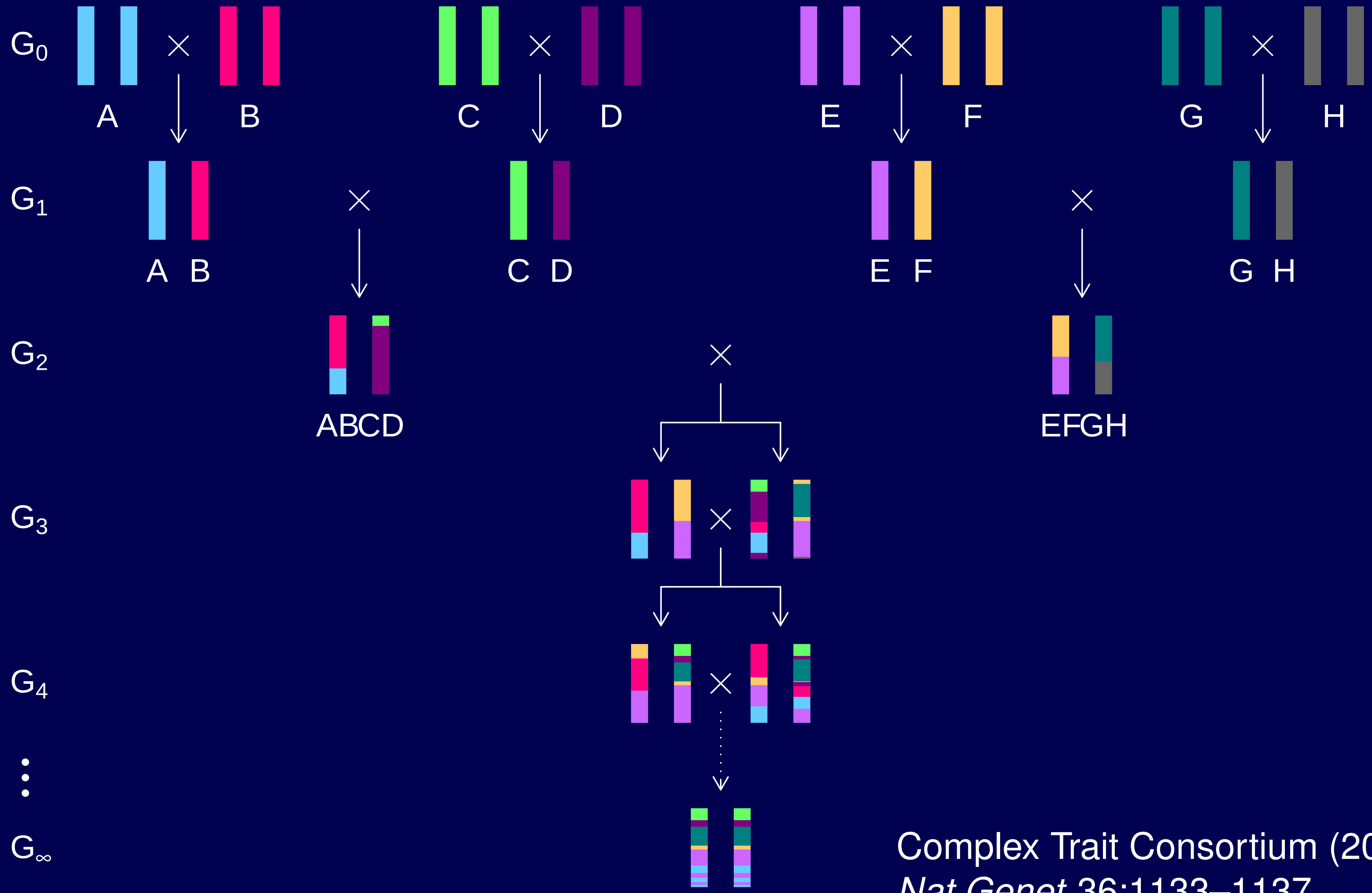
(by sibling mating)



The RIX design

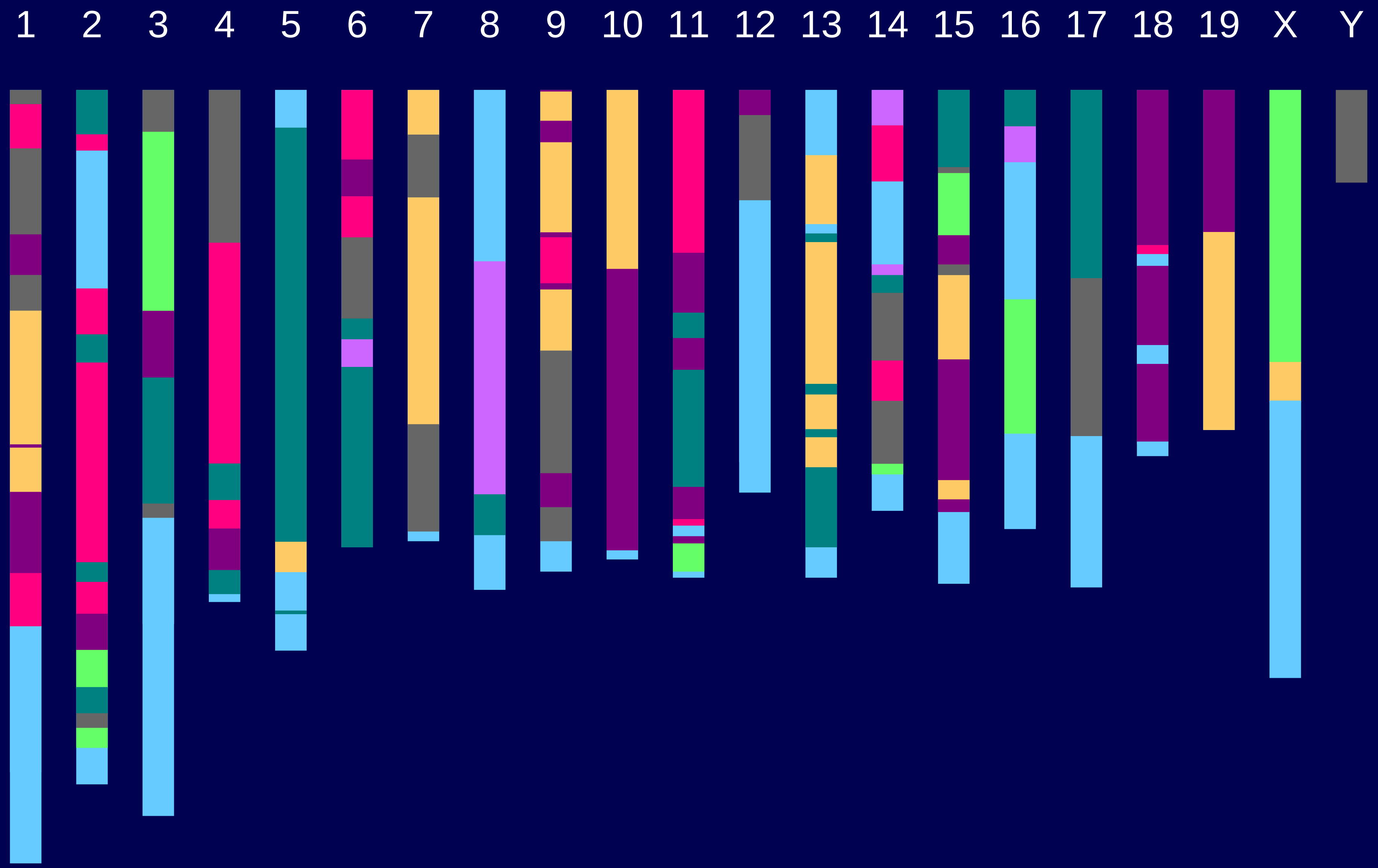


The “Collaborative Cross”

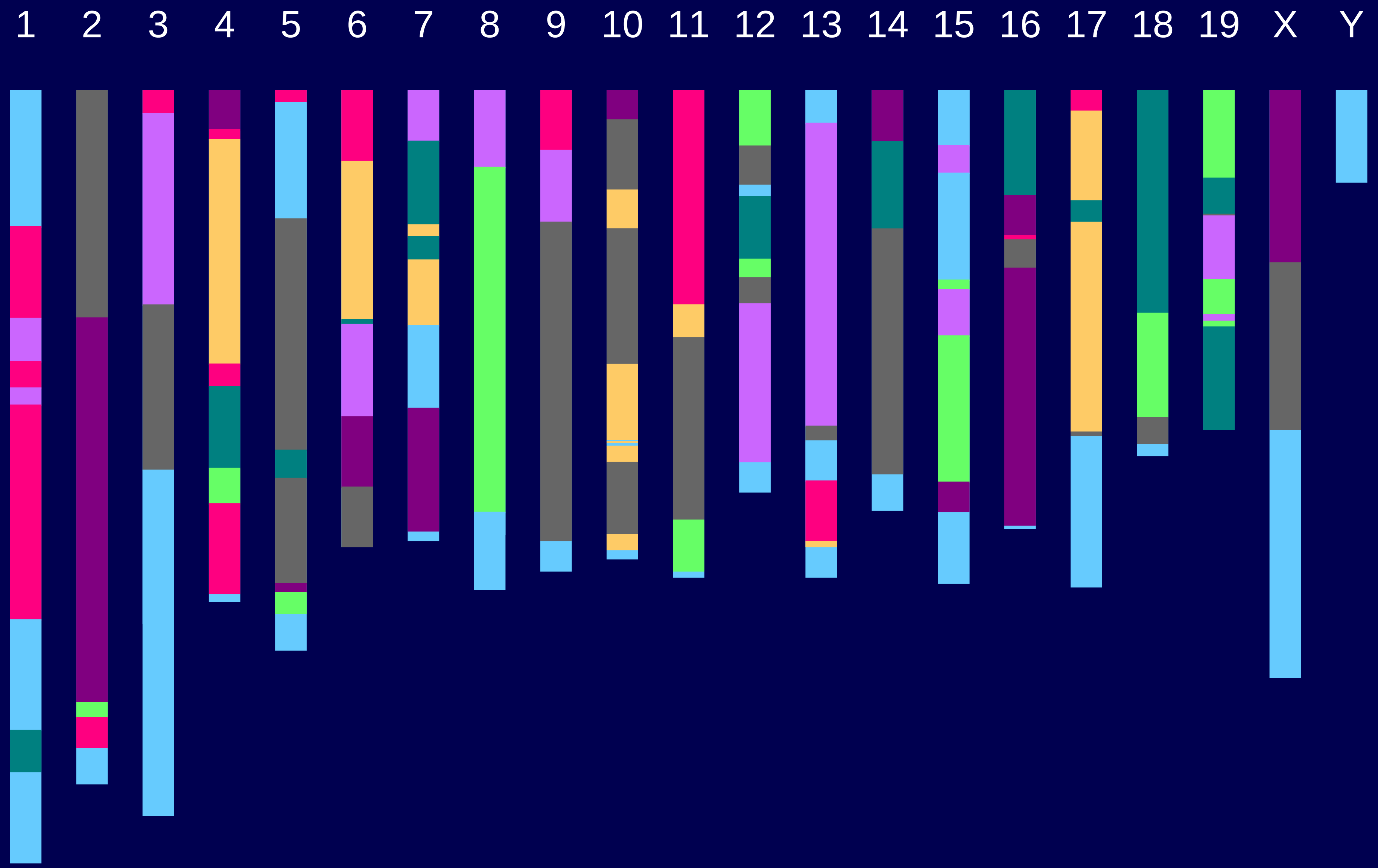


Complex Trait Consortium (2004)
Nat Genet 36:1133–1137

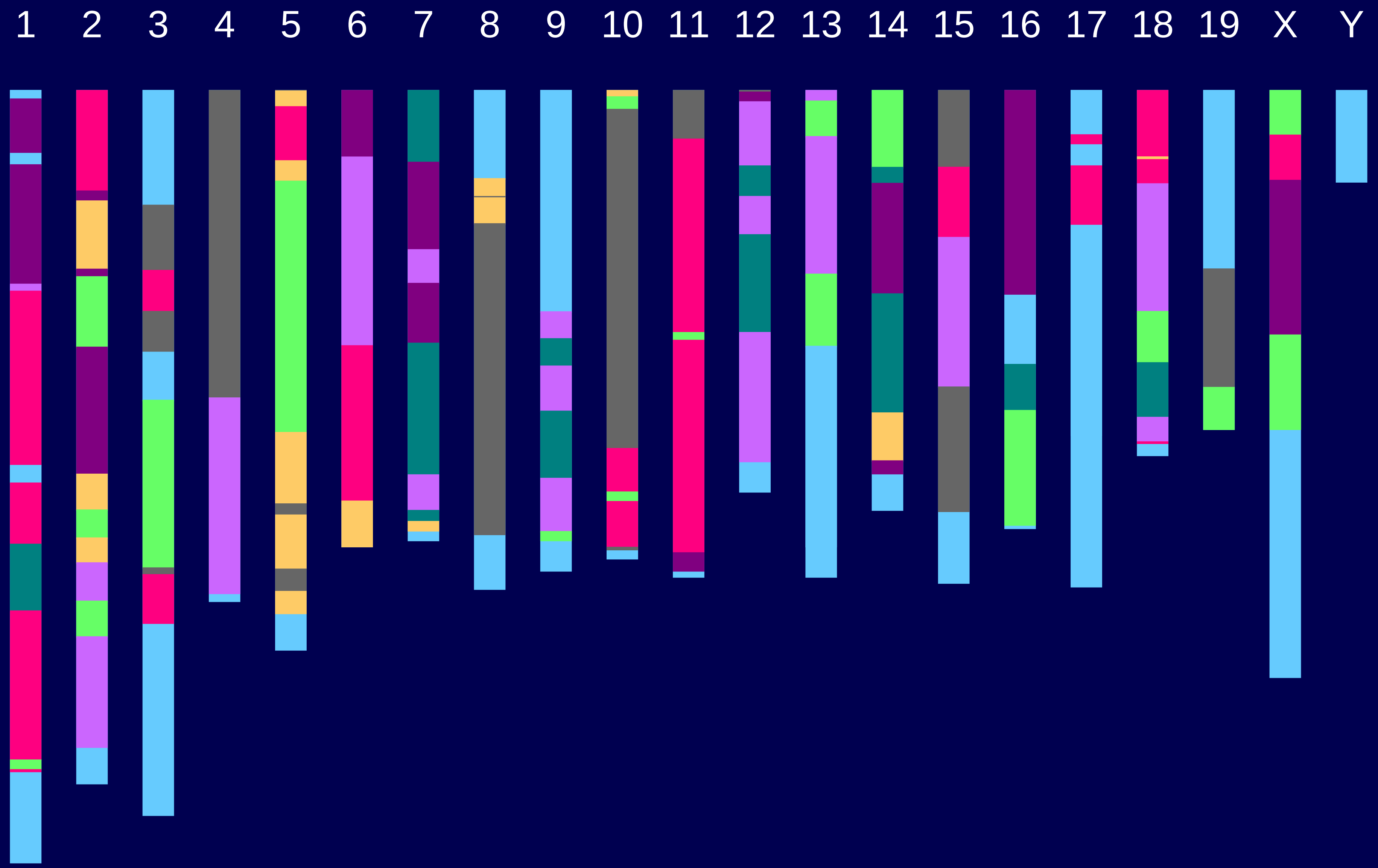
Genome of an 8-way RIL



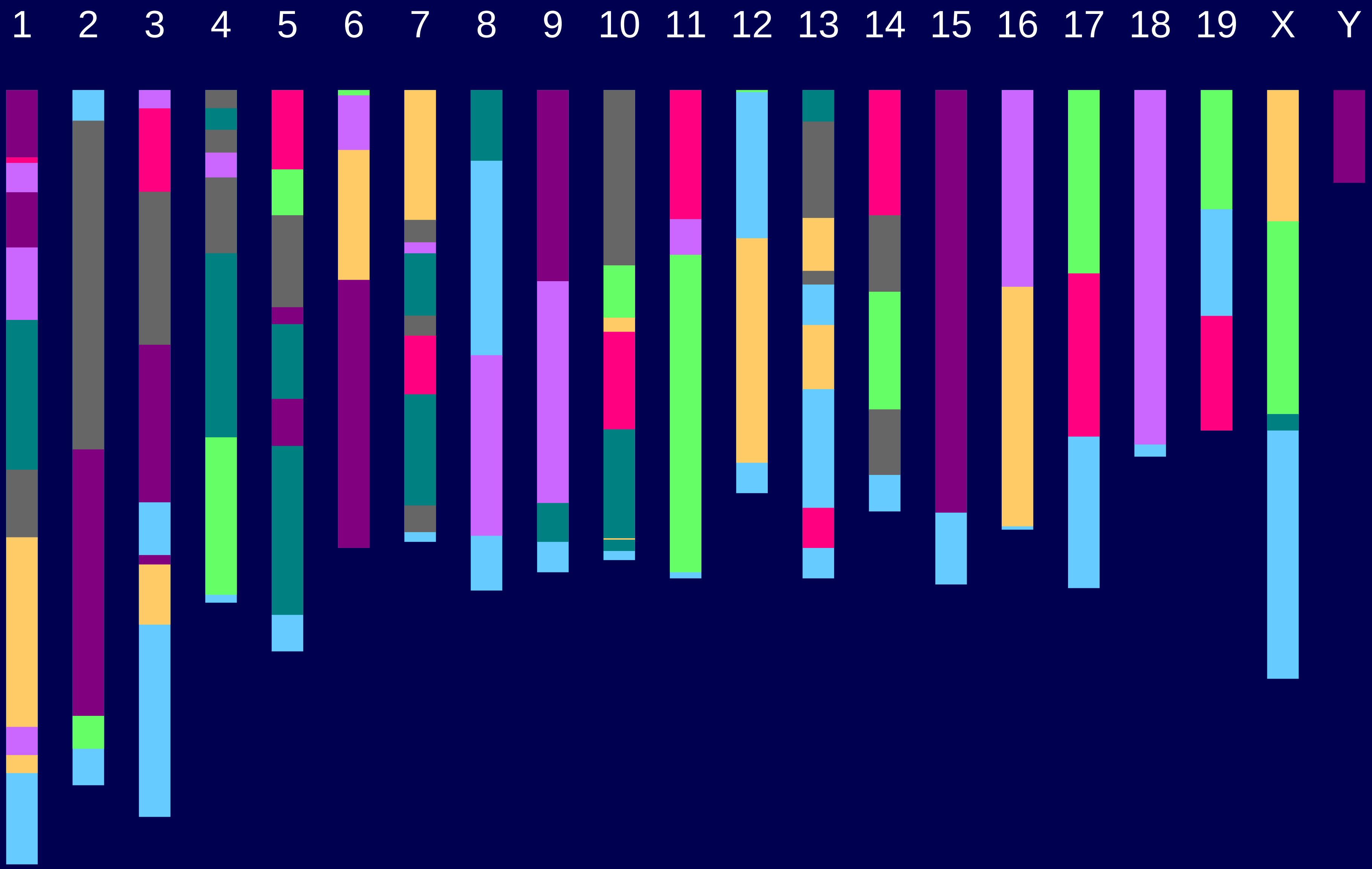
Genome of an 8-way RIL



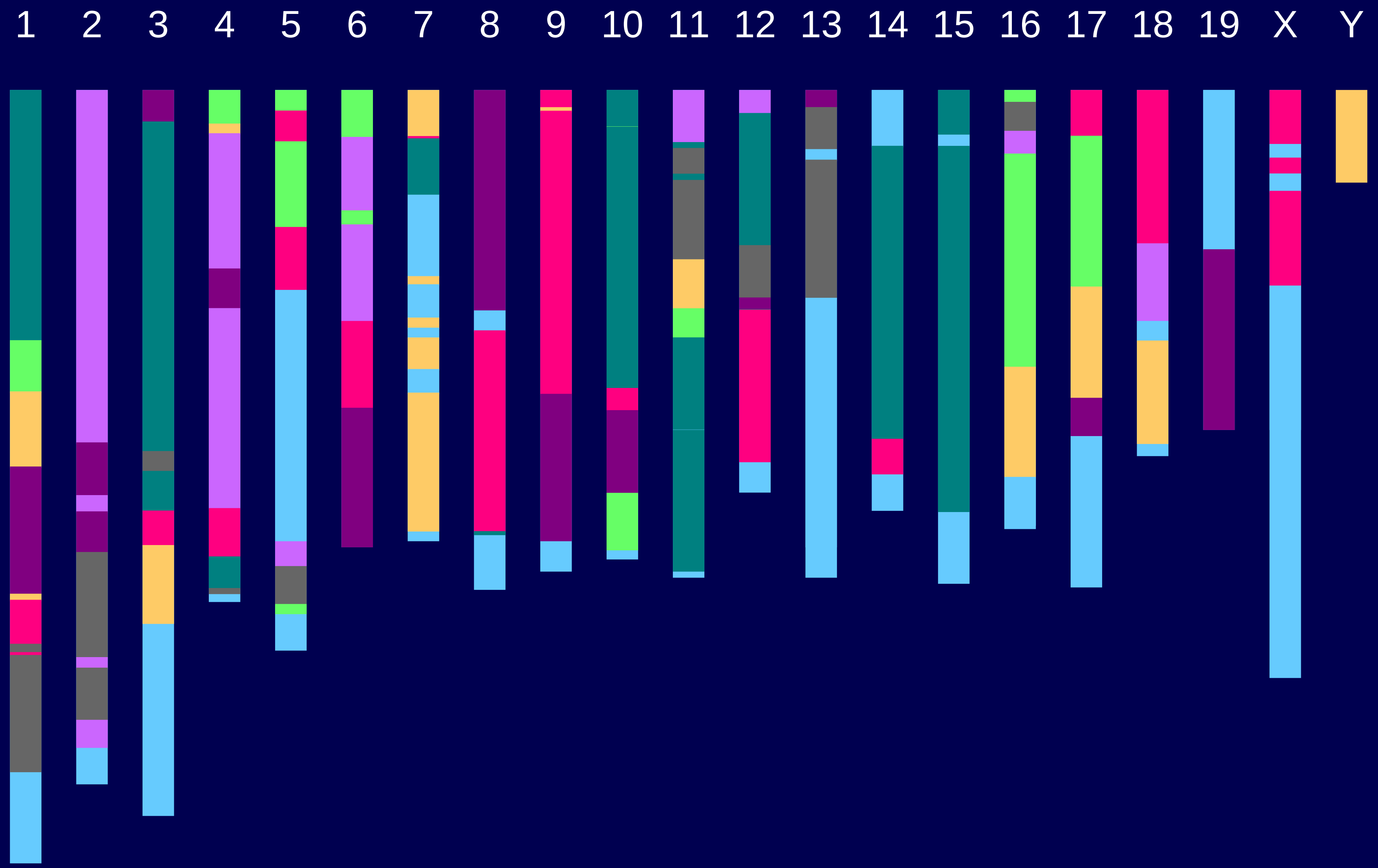
Genome of an 8-way RIL



Genome of an 8-way RIL



Genome of an 8-way RIL



The goal

(for the rest of this talk)

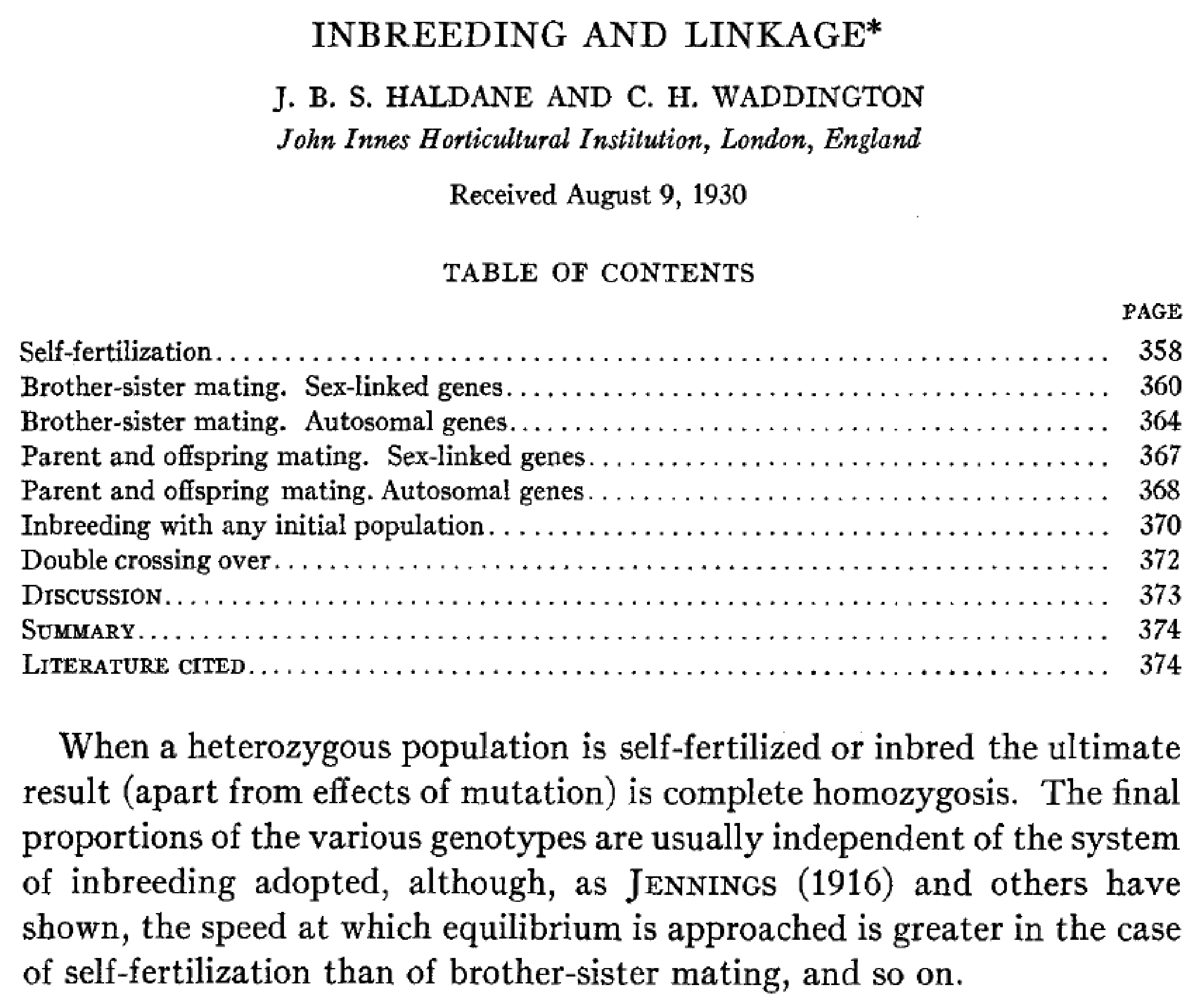
- Characterize the breakpoint process along a chromosome in 8-way RILs.
  - Understand the two-point haplotype probabilities.
  - Study the clustering of breakpoints, as a function of crossover interference in meiosis.

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 alleles at the two loci on a random RIL chromosome.

Haldane & Waddington 1931



INBREEDING AND LINKAGE*

J. B. S. HALDANE AND C. H. WADDINGTON
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Received August 9, 1930

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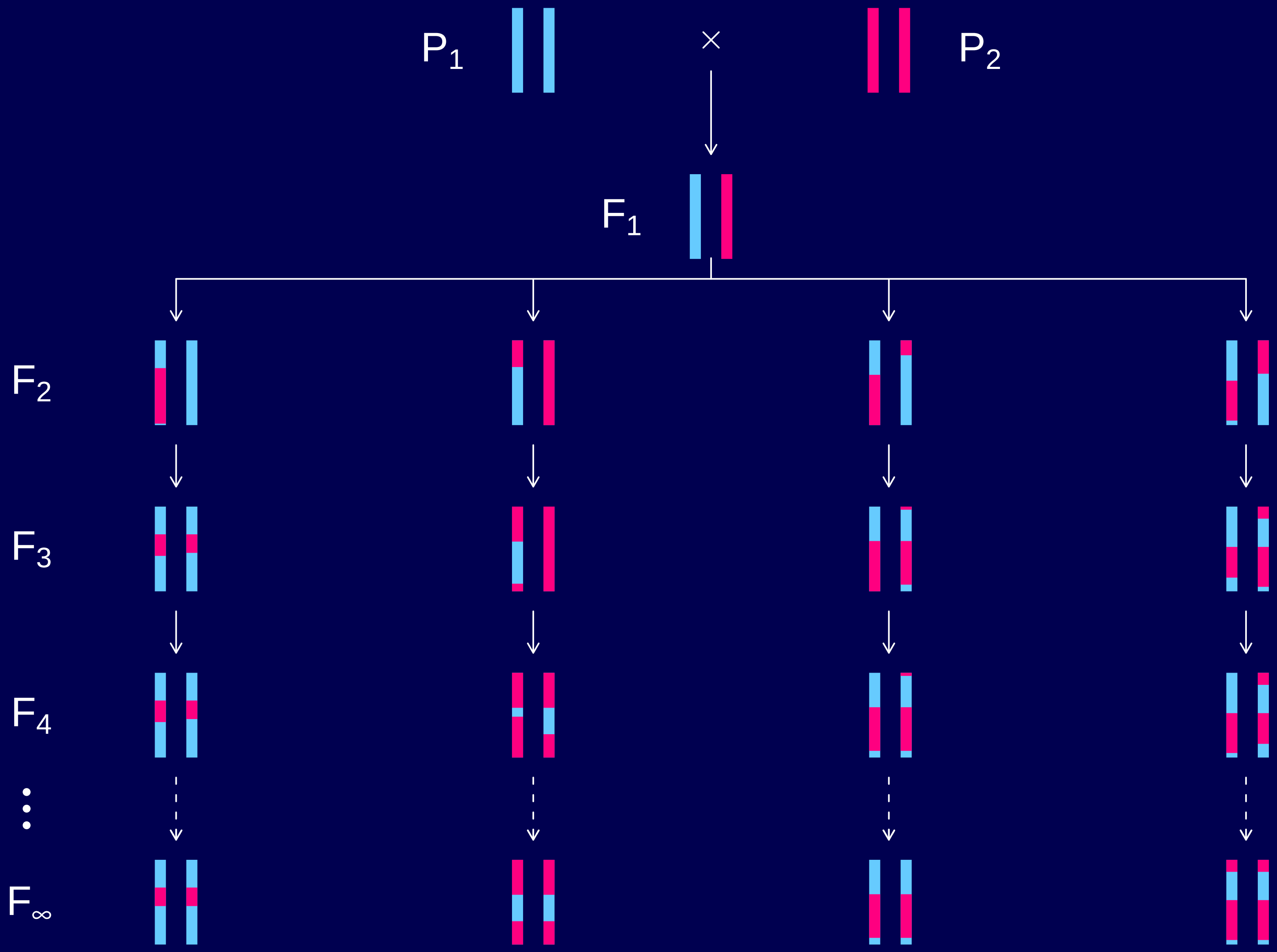
When a heterozygous population is self-fertilized or inbred the ultimate result (apart from effects of mutation) is complete homozygosis. The final proportions of the various genotypes are usually independent of the system of inbreeding adopted, although, as JENNINGS (1916) and others have shown, the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

Recombinant inbred lines

(by selfing)



Markov chain

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

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

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

- Here, X_n = "parental type" at generation n.

- We are interested in absorption probabilities

$$\Pr(X_n \longrightarrow j \mid X_0)$$

Absorption probabilities

Consider the case of absorption into the state $\begin{array}{c|c} A & A \\ A & A \end{array}$

(write this $AA|AA$)

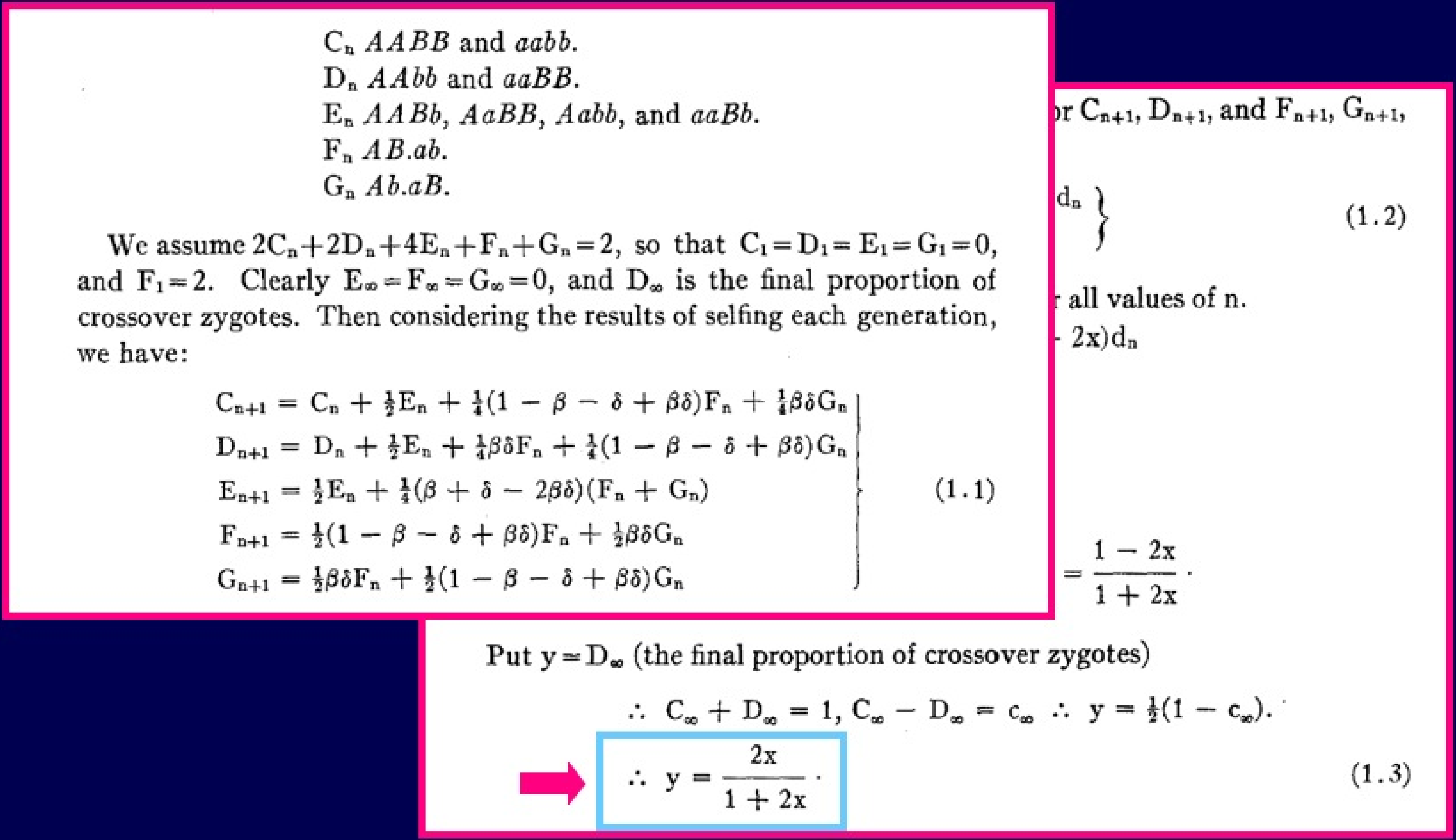
Let h_i = probability, starting at i, of being absorbed into $AA|AA$.

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.

$2x)d_n$

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

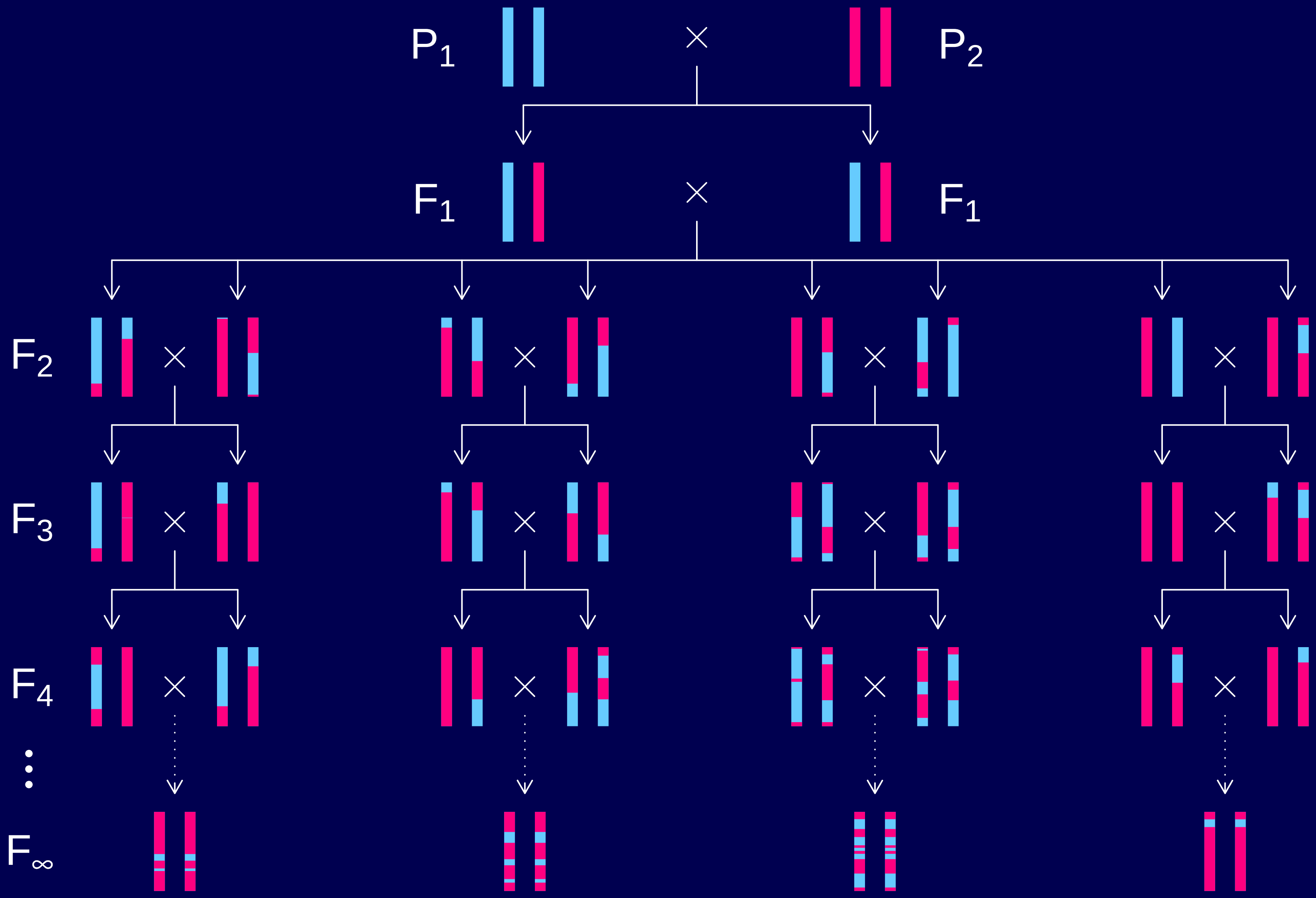
Put $y=D_\infty$ (the final proportion of crossover zygotes)

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

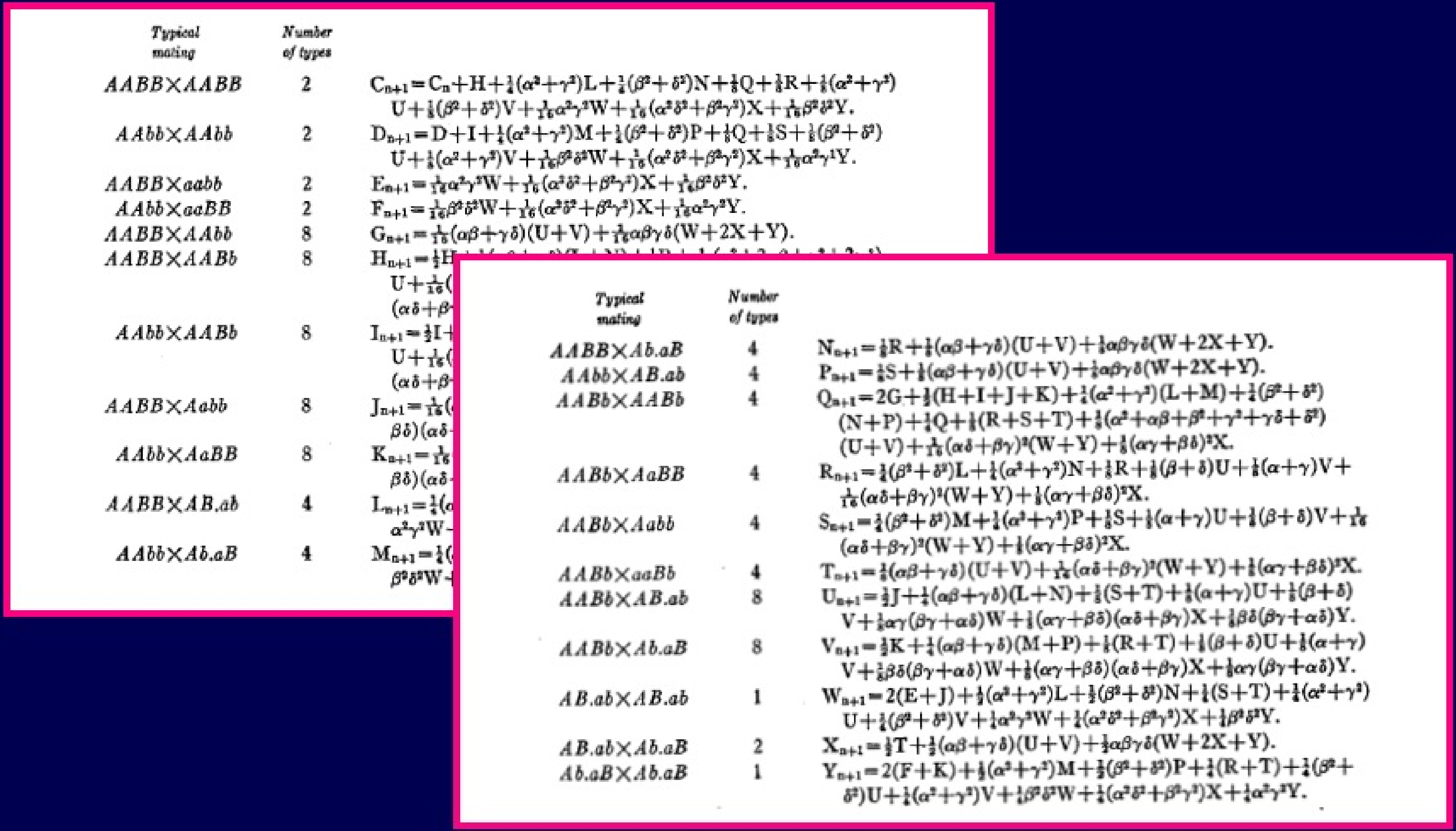
$$\boxed{\therefore\ y = \frac{2x}{1+2x}.} \quad (1.3)$$

Recombinant inbred lines

(by sibling mating)



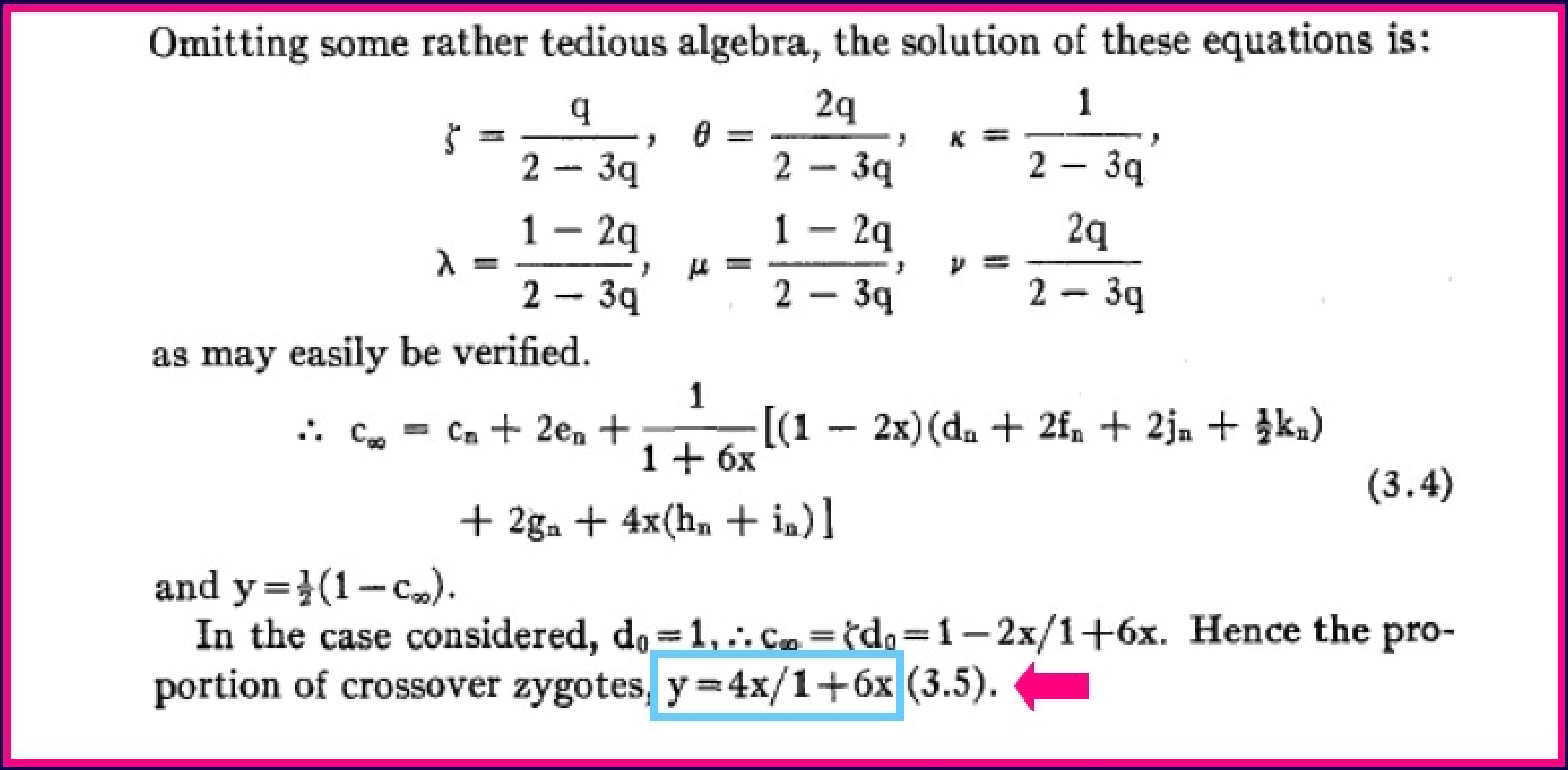
Equations for sib-mating



Typical mating	*Number of types*	
AABB×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×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×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×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×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×AABb	8	$H_{n+1}=\frac{1}{2}H$ $U+\frac{1}{16}($ $(\alpha\delta+\beta$
AAbb×AABb	8	$I_{n+1}=\frac{1}{2}I+$ $U+\frac{1}{16}($ $(\alpha\delta+\beta$
AABB×Aabb	8	$J_{n+1}=\frac{1}{16}($ $\beta\delta)(\alpha\delta$
AAbb×AaBB	8	$K_{n+1}=\frac{1}{16}$ $\beta\delta)(\alpha\delta$
AABB×AB.ab	4	$L_{n+1}=\frac{1}{4}($ $\alpha^2\gamma^2W$
AAbb×Ab.aB	4	$M_{n+1}=\frac{1}{4}($ $\beta^2\delta^2W$

Typical mating	*Number of types*	
AABB×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×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×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×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×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×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×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×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×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×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×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:

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

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

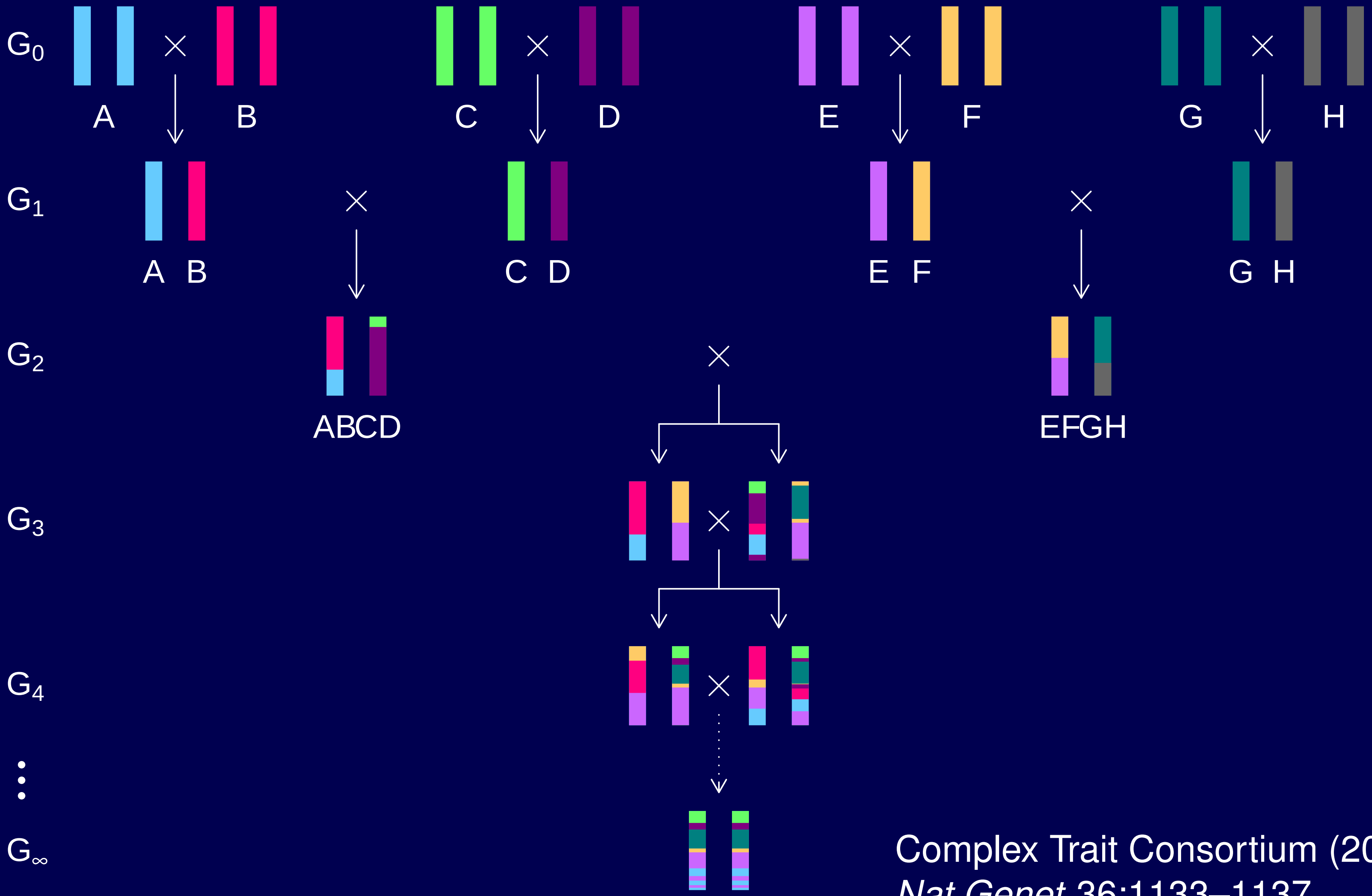
as may easily be verified.

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

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

The “Collaborative Cross”



Complex Trait Consortium (2004)
Nat Genet 36:1133–1137

8-way RILs

Autosomes

$\Pr(G_1 = i) = 1/8$
$\Pr(G_2 = j \mid G_1 = i) = r/(1+6r)$ for $i \neq j$

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

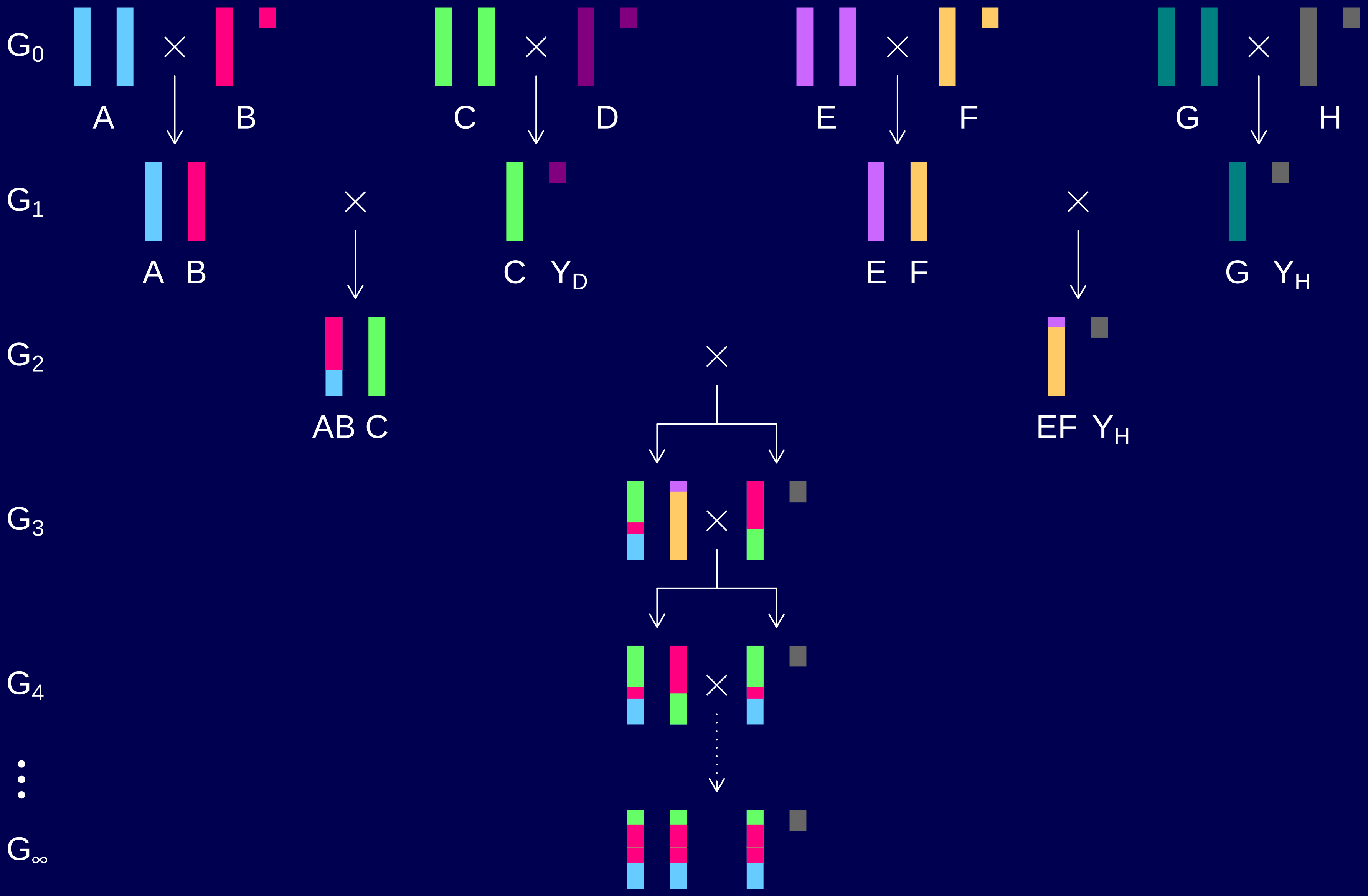
X chromosome

$\Pr(G_1 = A) = \Pr(G_1 = B) = \Pr(G_1 = E) = \Pr(G_1 = F) = 1/6$
$\Pr(G_1 = C) = 1/3$

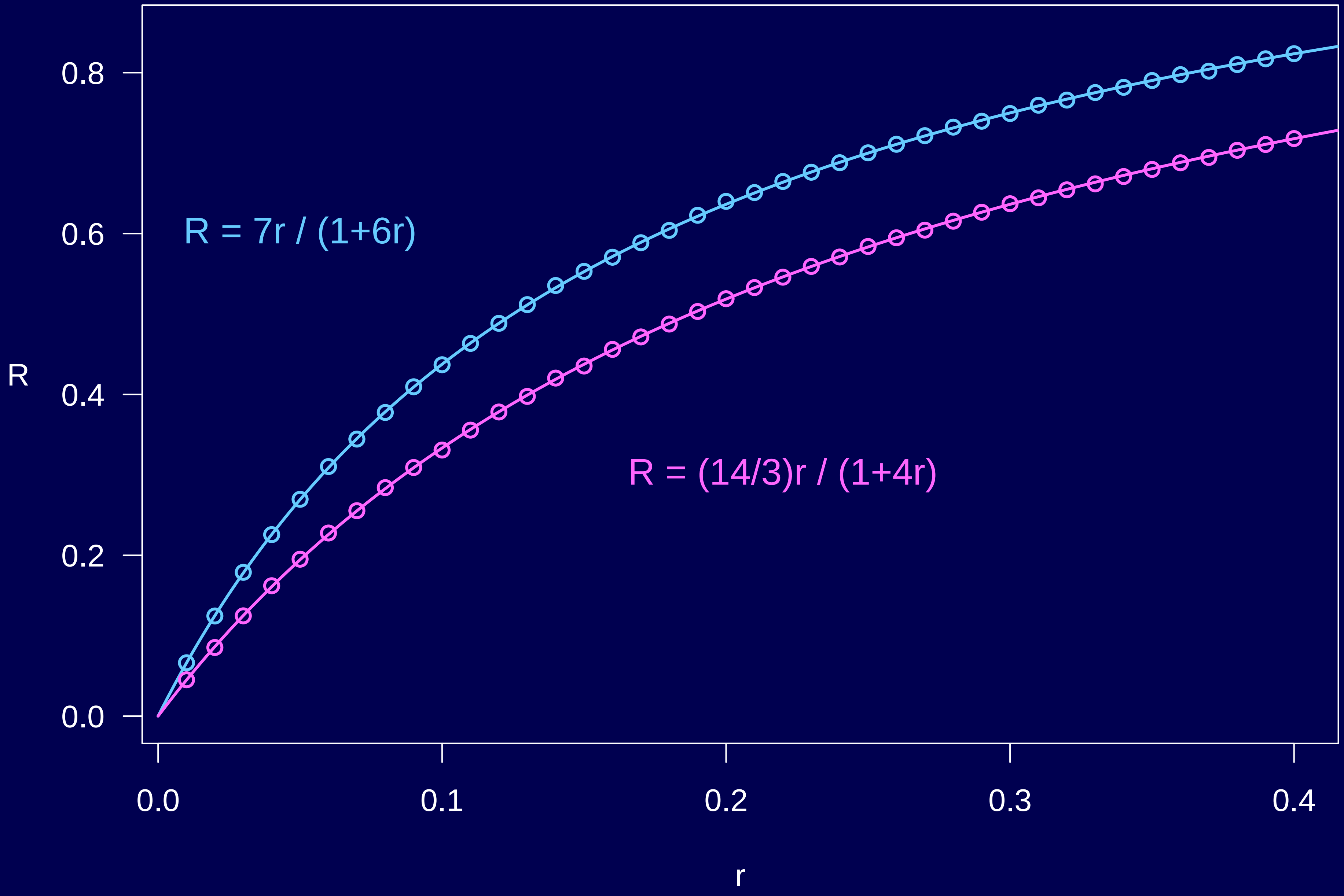
$\Pr(G_2 = B \mid G_1 = A) = r/(1+4r)$
$\Pr(G_2 = C \mid G_1 = A) = 2r/(1+4r)$
$\Pr(G_2 = A \mid G_1 = C) = r/(1+4r)$

$\Pr(G_2 \neq G_1) = (14/3)r/(1+6r)$

X chromosome



Computer simulations



3-point coincidence

- r_{ij} = recombination fraction for interval (i, j)
  Assume $r_{12} = r_{23} = r$.

- Coincidence = $c = \Pr(\text{double recombinant})/r^2$
  $= \Pr(\text{rec'n in 23} \mid \text{rec'n in 12})/\Pr(\text{rec'n in 12})$

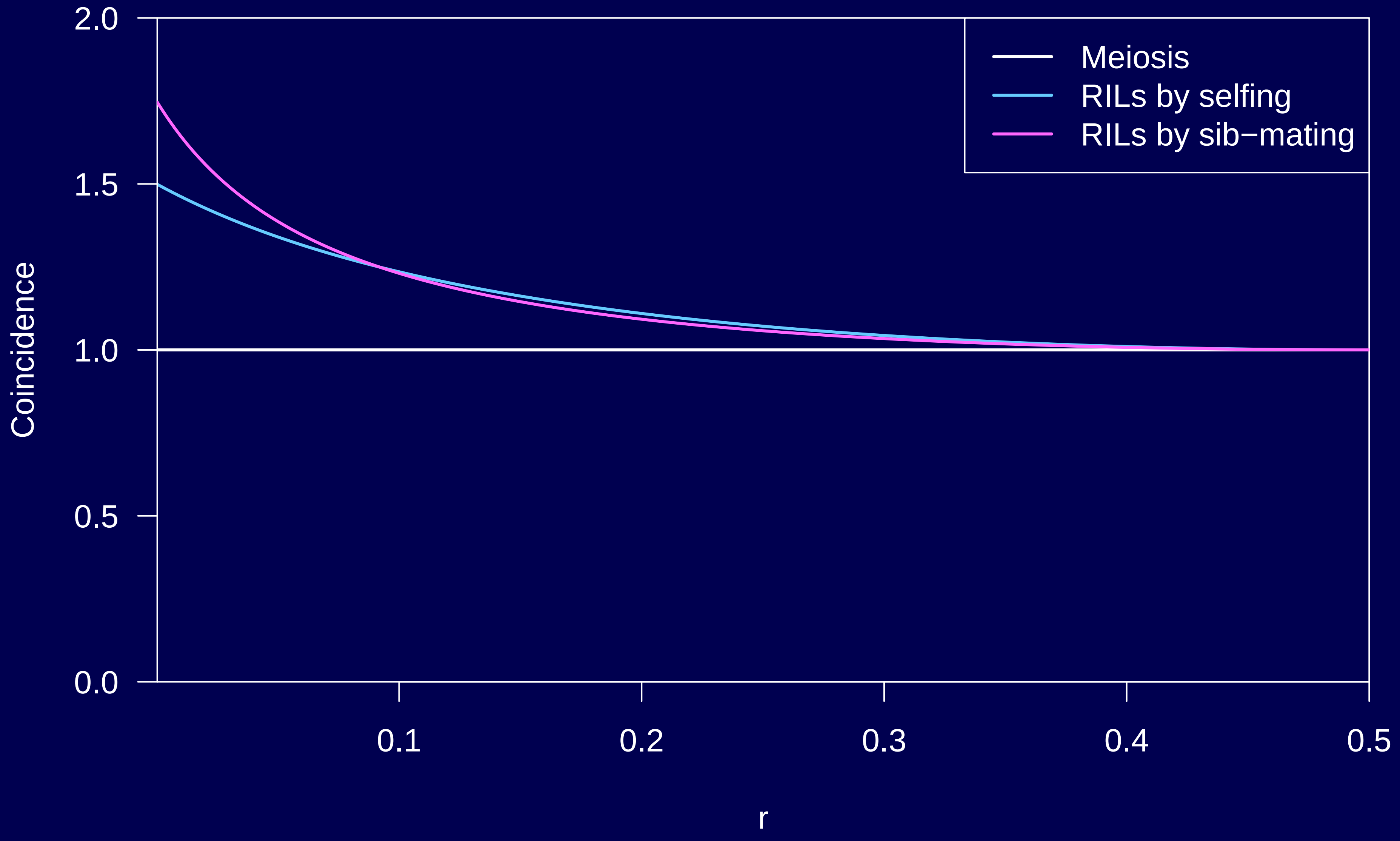
- No interference $= 1$
  Positive interference < 1
  Negative interference > 1

- Generally c is a function of r

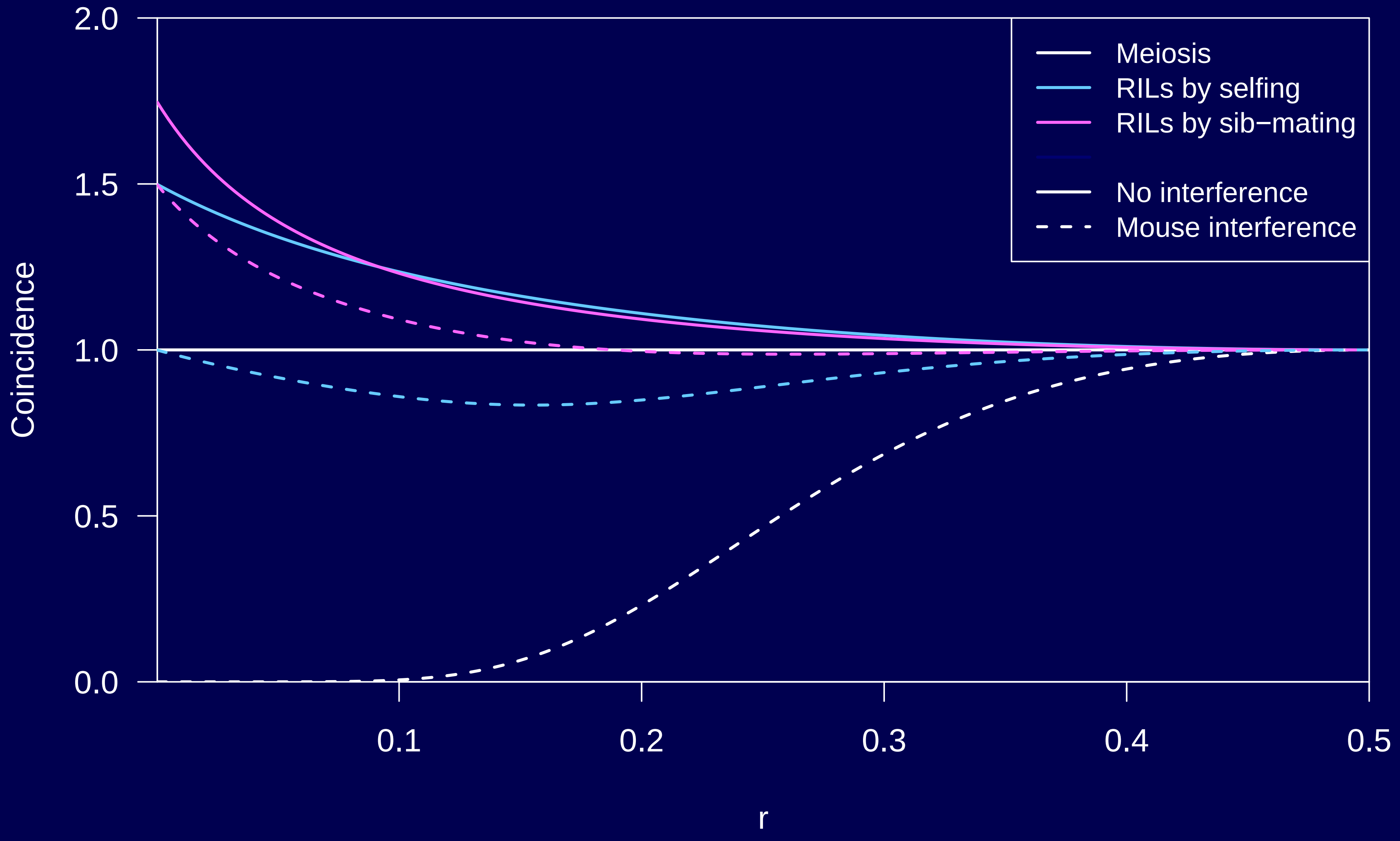
3 points in 2-way RILs

- $r_{13} = 2r(1 - cr)$
- $R = f(r); \qquad R_{13} = f(r_{13})$
- Pr(double “recombinant” in RIL) = $\{R + R - R_{13}\}/2$
- Coincidence (in 2-way RIL) = $\{2R - R_{13}\}/\{2R^2\}$

Coincidence



Coincidence



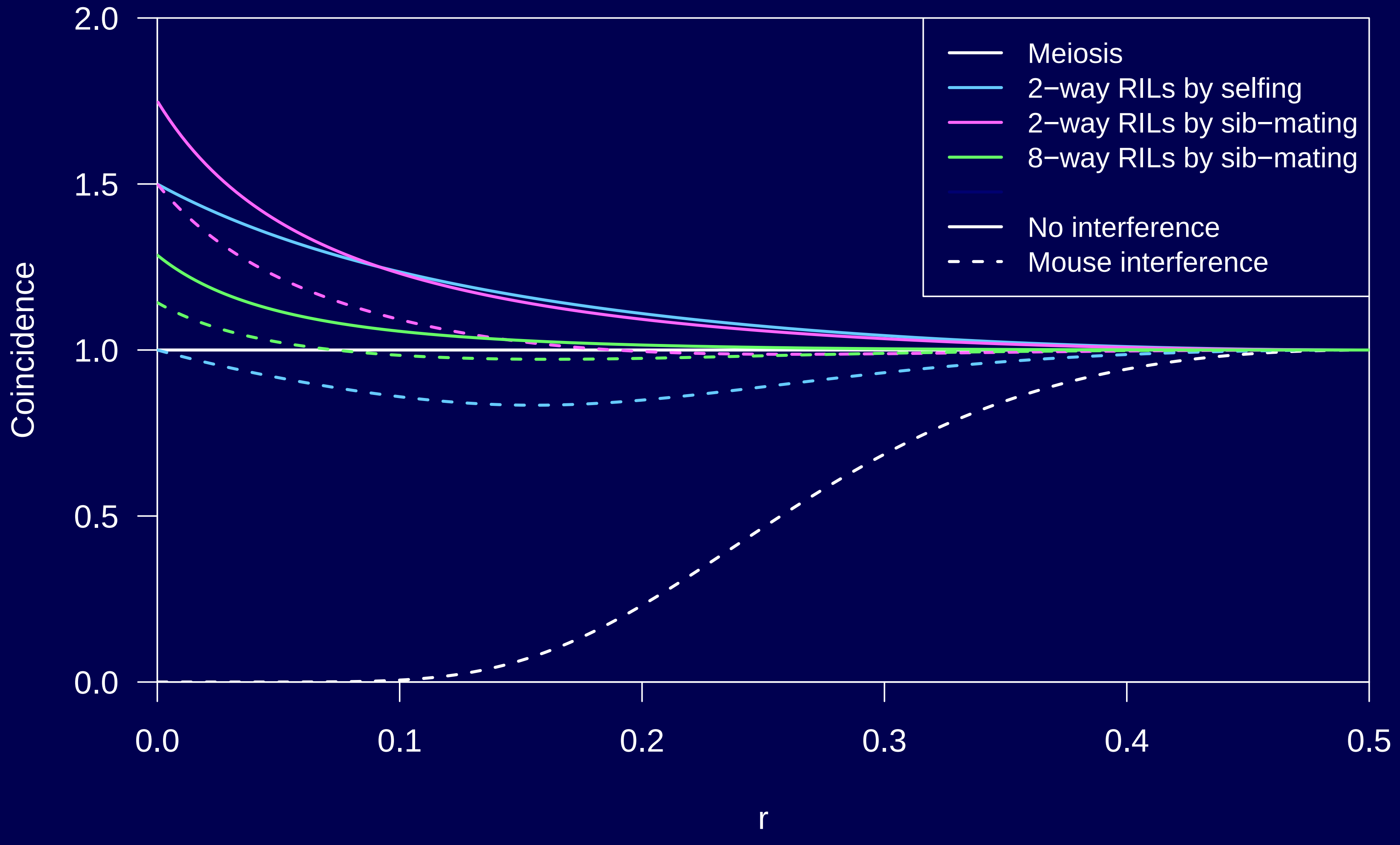
Why the clustering of breakpoints?

- The really close breakpoint occur in different generations.
- Breakpoints in later generations can occur only in regions that are not yet fixed.
- These regions of heterozygosity are surrounding by breakpoints.

Coincidence in 8-way RILs

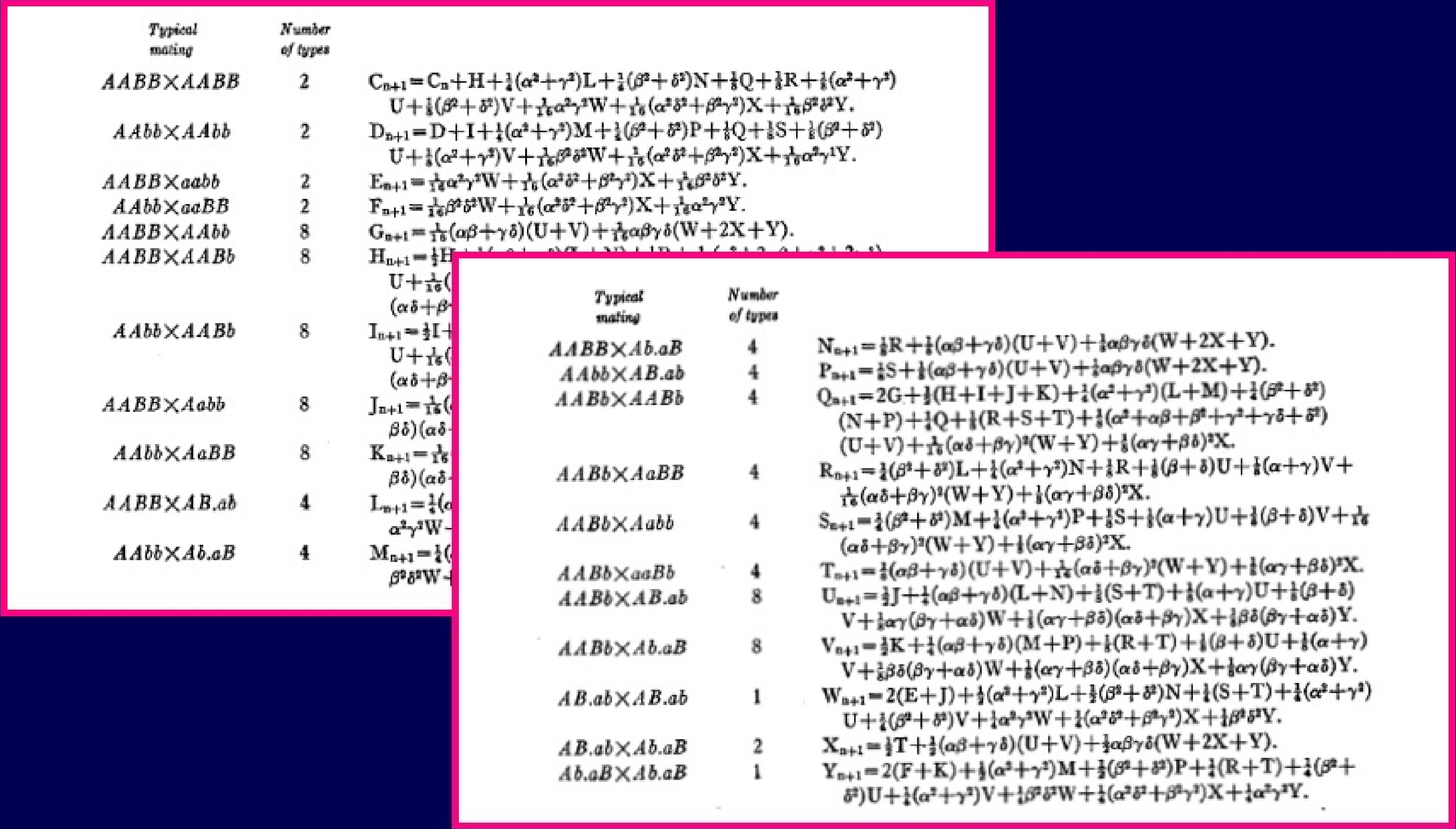
- The trick that allowed us to get the coincidence for 2-way RILs doesn't work for 8-way RILs.
- It's sufficient to consider 4-way RILs.
- Calculations for 3 points in 4-way RILs is still astoundingly complex.
  - 2 points in 2-way RILs by sib mating:
    55 parental types → 22 states by symmetry
  -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



But there is an easier way...

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	$L_{n+1}=\frac{1}{4}($ $\alpha^2\gamma^2W$
$AAbb \times Ab.aB$	4	$M_{n+1}=\frac{1}{4}($ $\beta^2\delta^2W$

Typical mating	*Number of types*	
$AABB \times Ab.aB$	4	$N_{n+1}=\frac{1}{8}R+\frac{1}{8}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{4}\alpha\beta\gamma\delta(W+2X+Y).$
$AAbb \times AB.ab$	4	$P_{n+1}=\frac{1}{8}S+\frac{1}{8}(\alpha\beta+\gamma\delta)(U+V)+\frac{1}{4}\alpha\beta\gamma\delta(W+2X+Y).$
$AABb \times AABb$	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	$Y_{n+1}=2(F+K)+\frac{1}{2}(\alpha^2+\gamma^2)M+\frac{1}{2}(\beta^2+\delta^2)P+\frac{1}{4}(R+T)+\frac{1}{4}(\beta^2+\delta^2)U+\frac{1}{4}(\alpha^2+\gamma^2)V+\frac{1}{4}\beta^2\delta^2W+\frac{1}{4}(\alpha^2\delta^2+\beta^2\gamma^2)X+\frac{1}{4}\alpha^2\gamma^2Y.$

The simpler method

Consider the cross $W_1W_2|X_1X_2 \times Y_1Y_2|Z_1Z_2$

Let
$$\begin{aligned} q_1 &= \Pr(W_1W_2 \text{ fixed}) \\ q_2 &= \Pr(W_1X_2 \text{ fixed}) \\ q_3 &= \Pr(W_1Y_2 \text{ fixed}) \end{aligned}$$

First generation: $W_i \equiv X_i \equiv A$, $Y_i \equiv Z_i \equiv B$

$$\begin{aligned} \text{Then } \Pr(\text{AA fixed}) &= 2(q_1 + q_2) \\ \Pr(\text{AB fixed}) &= 4q_3 \end{aligned}$$

The simpler method

$W_1W_2|X_1X_2 \times Y_1Y_2|Z_1Z_2$

$q_1 = \Pr(W_1W_2 \text{ fixed}) \qquad q_2 = \Pr(W_1X_2 \text{ fixed}) \qquad q_3 = \Pr(W_1Y_2 \text{ fixed})$

Second generation: $W_i \equiv Y_i \equiv A$, $X_i \equiv Z_i \equiv B$

Then Pr(AA fixed) = $2(q_1 + q_3)$

Thus $q_2 = q_3$

The simpler method

$W_1W_2|X_1X_2 \times Y_1Y_2|Z_1Z_2$

$q_1 = \Pr(W_1W_2 \text{ fixed}) \qquad q_2 = \Pr(W_1X_2 \text{ fixed}) \qquad q_3 = \Pr(W_1Y_2 \text{ fixed})$

Now we use the usual trick, condition on the first step:

$$q_1 = [(1-r)/2 \times q_1 \times 4] \;+\; [1/2 \times 1/2 \times q_2 \times 12]$$

Combined with the previous results, we obtain

$$q_2 = r/[2(1+6r)]$$

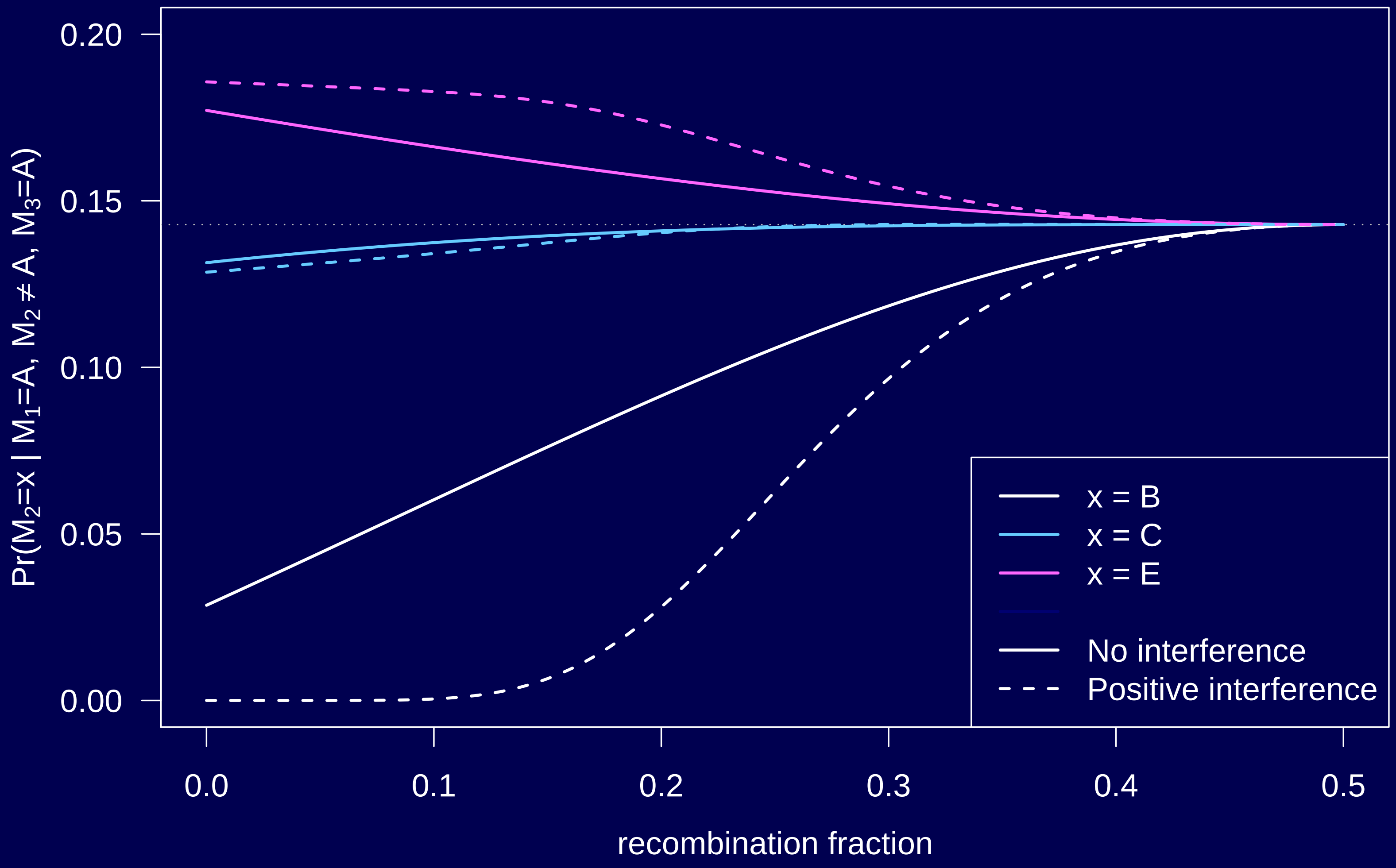
And so Pr(AB fixed) = $4q_3 = 4r/(1+6r)$

The formula

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

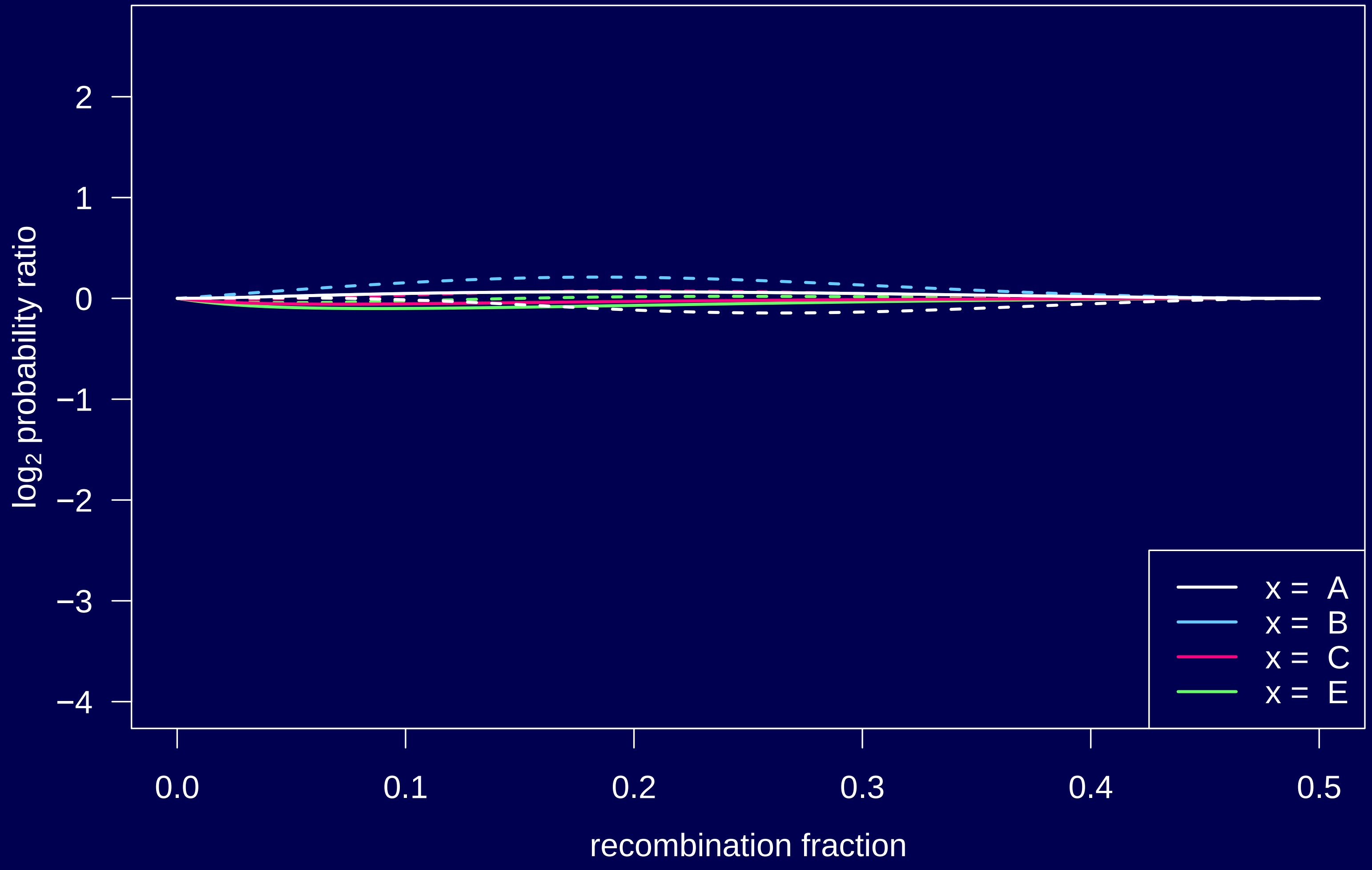
3-point symmetry

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



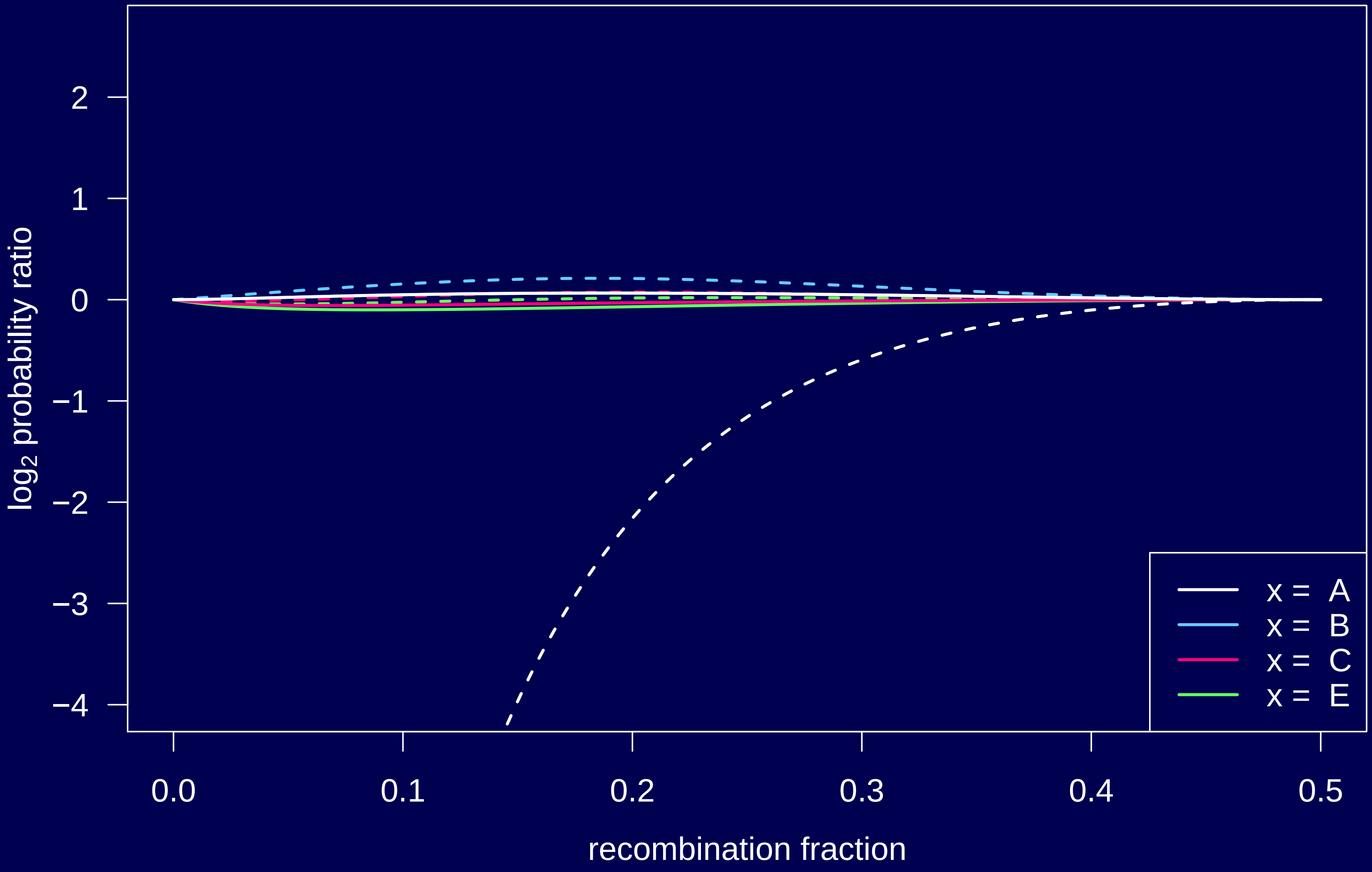
Markov property

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



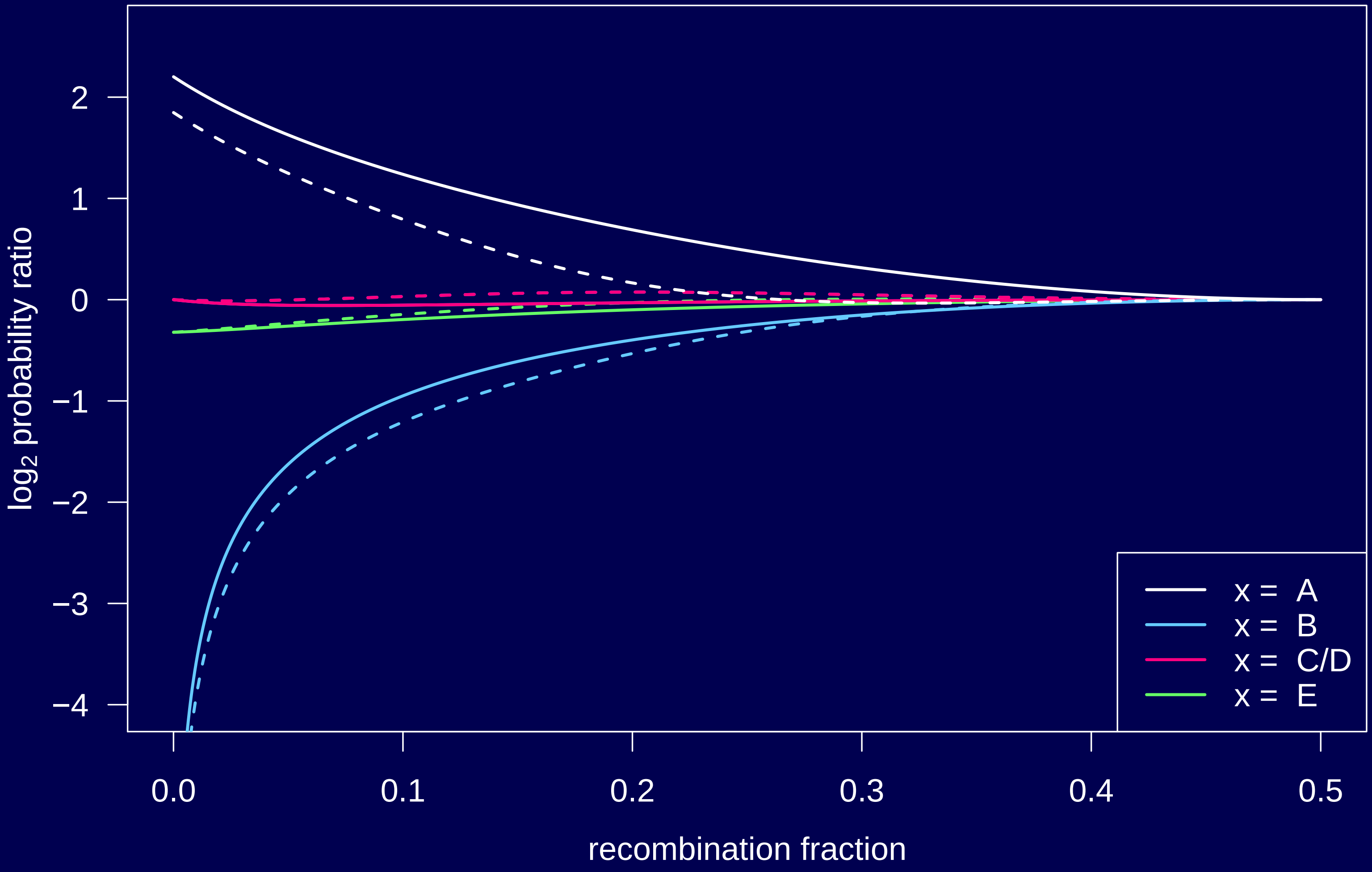
Markov property

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



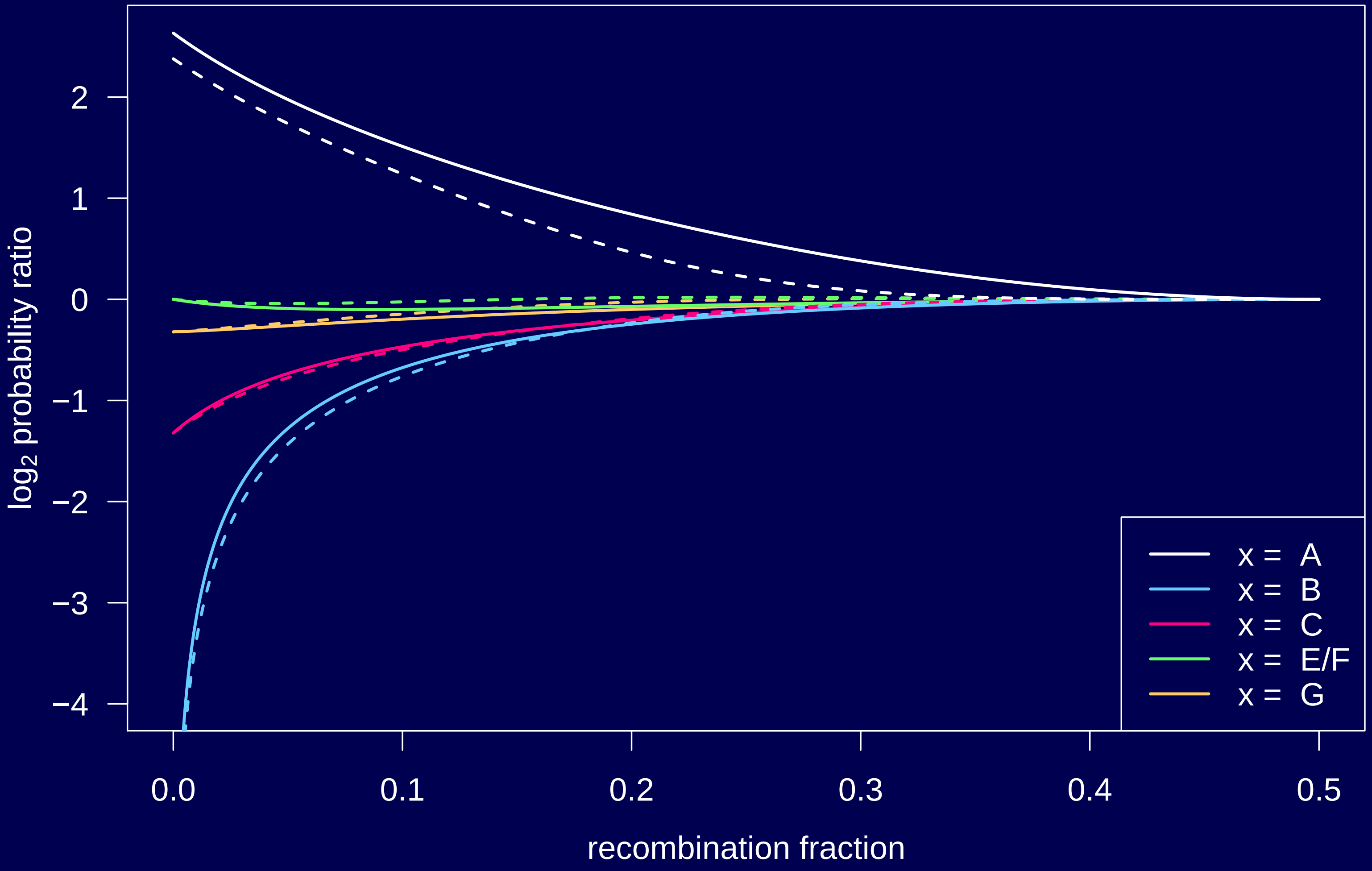
Markov property

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



Markov property

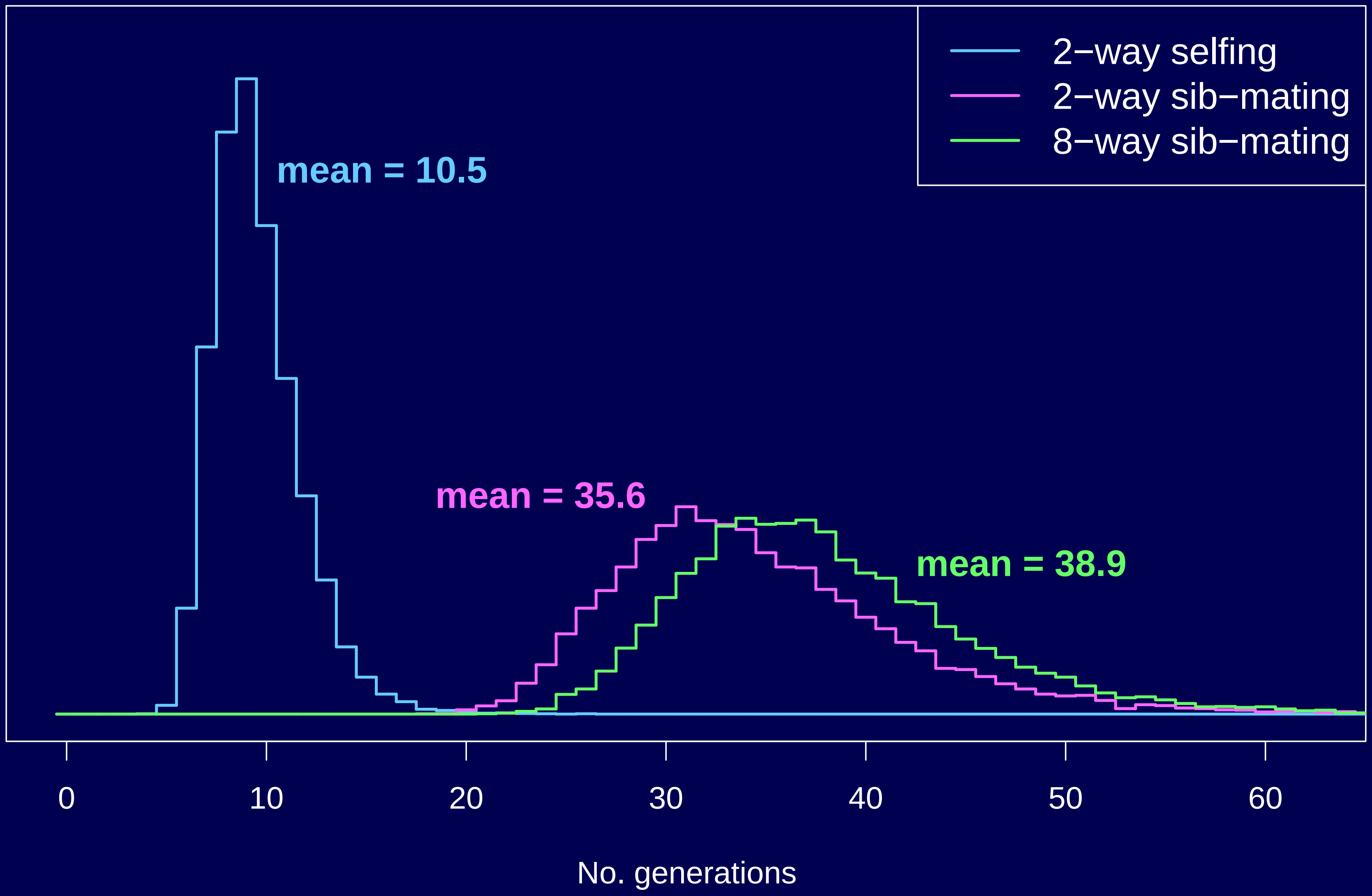
$$\log_2 \left\{ \frac{\Pr(M_3 = A \mid M_2 = E, M_1 = x)}{\Pr(M_3 = A \mid M_2 = E)} \right\}$$



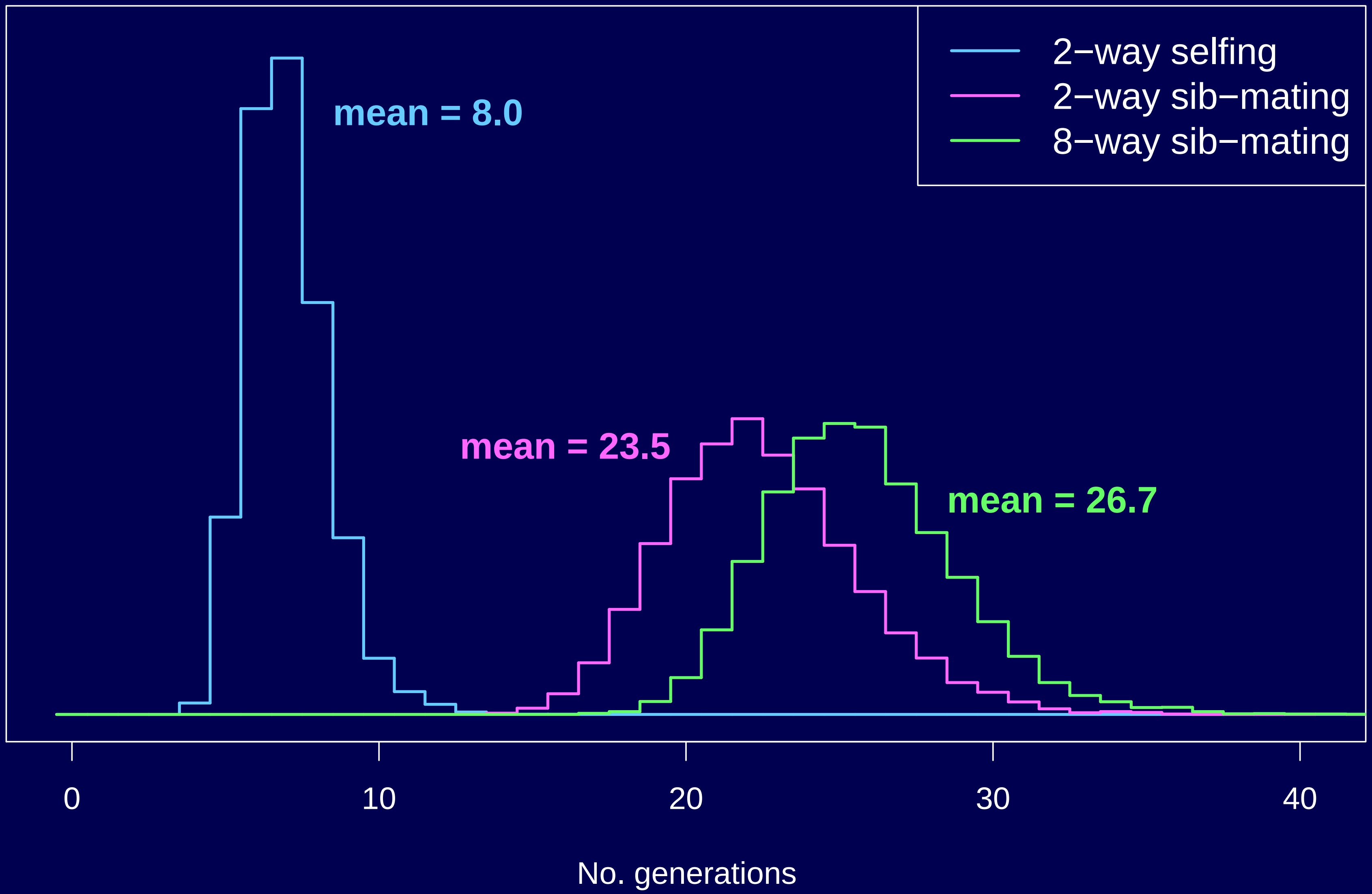
Whole genome simulations

- 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

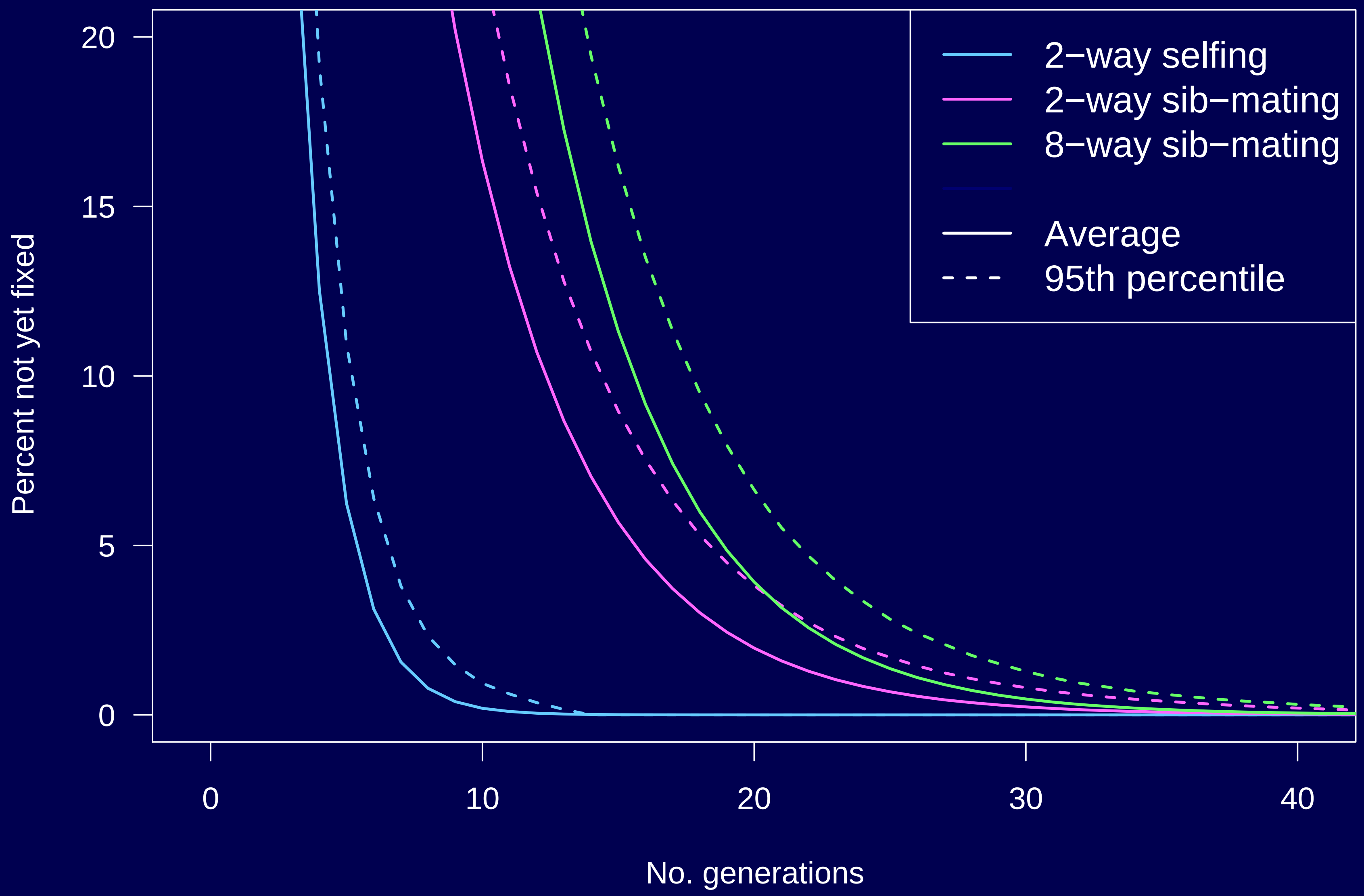
No. generations to fixation



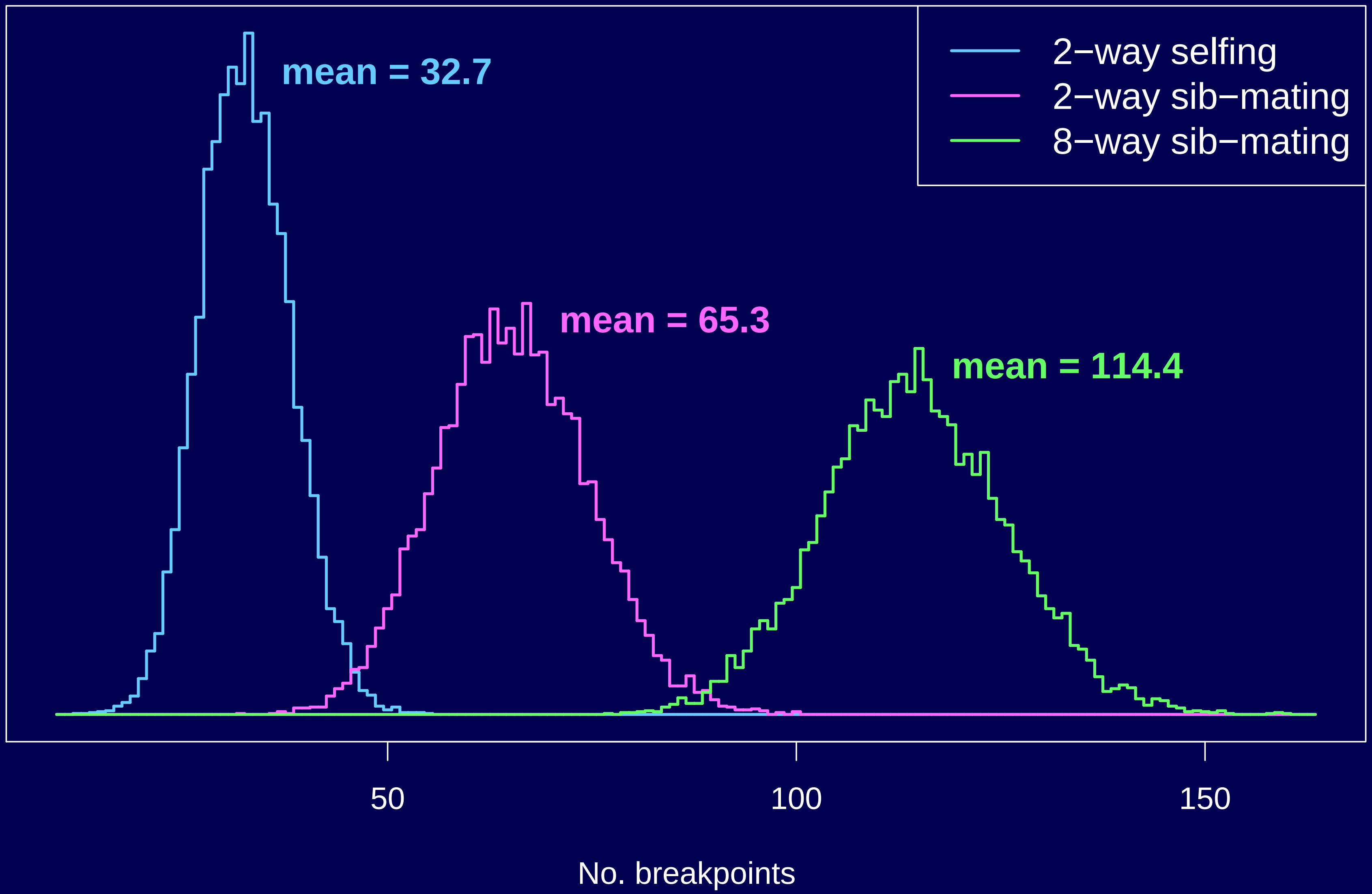
No. generations to 99% fixation



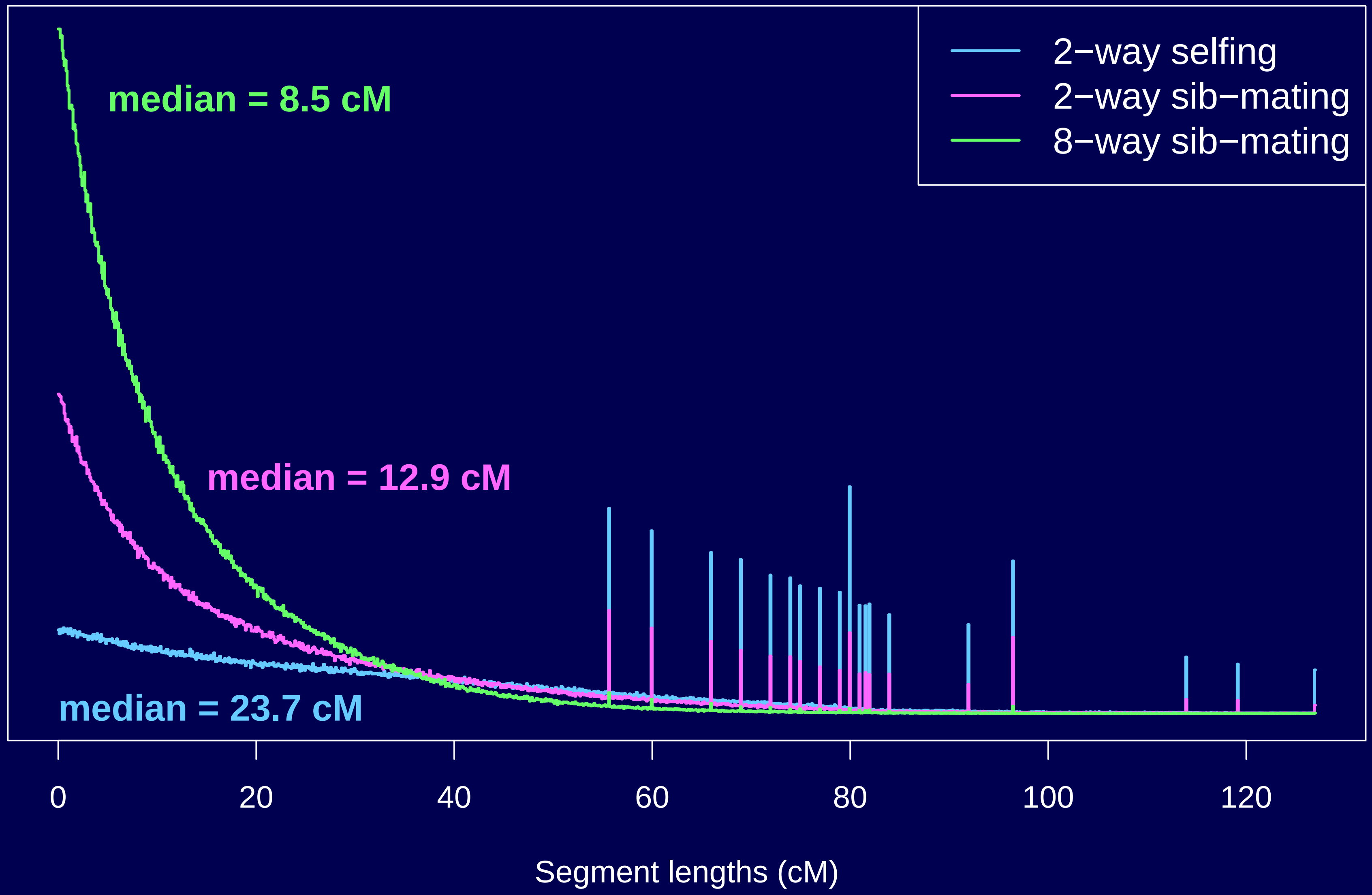
Percent genome not fixed



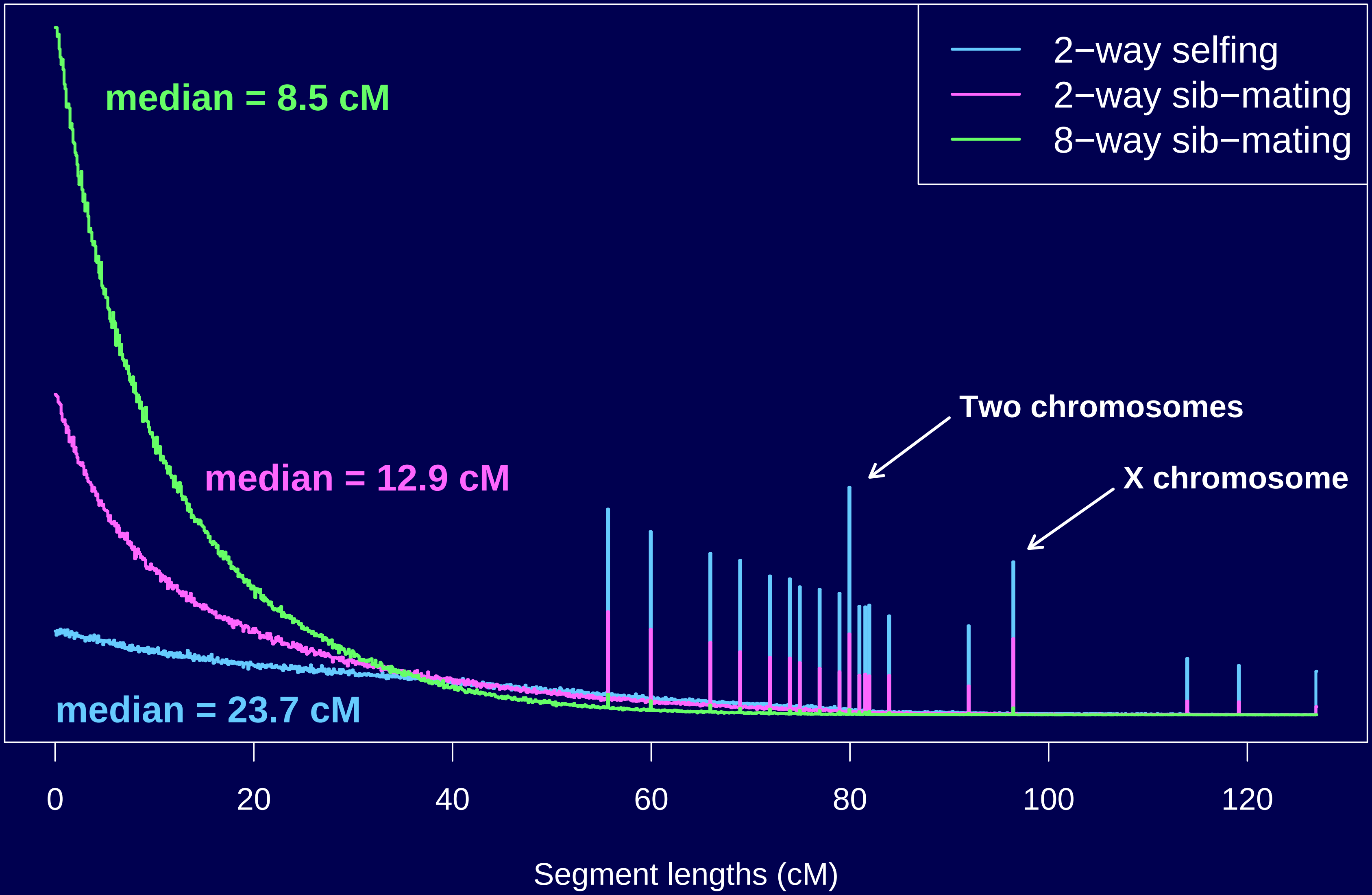
No. breakpoints



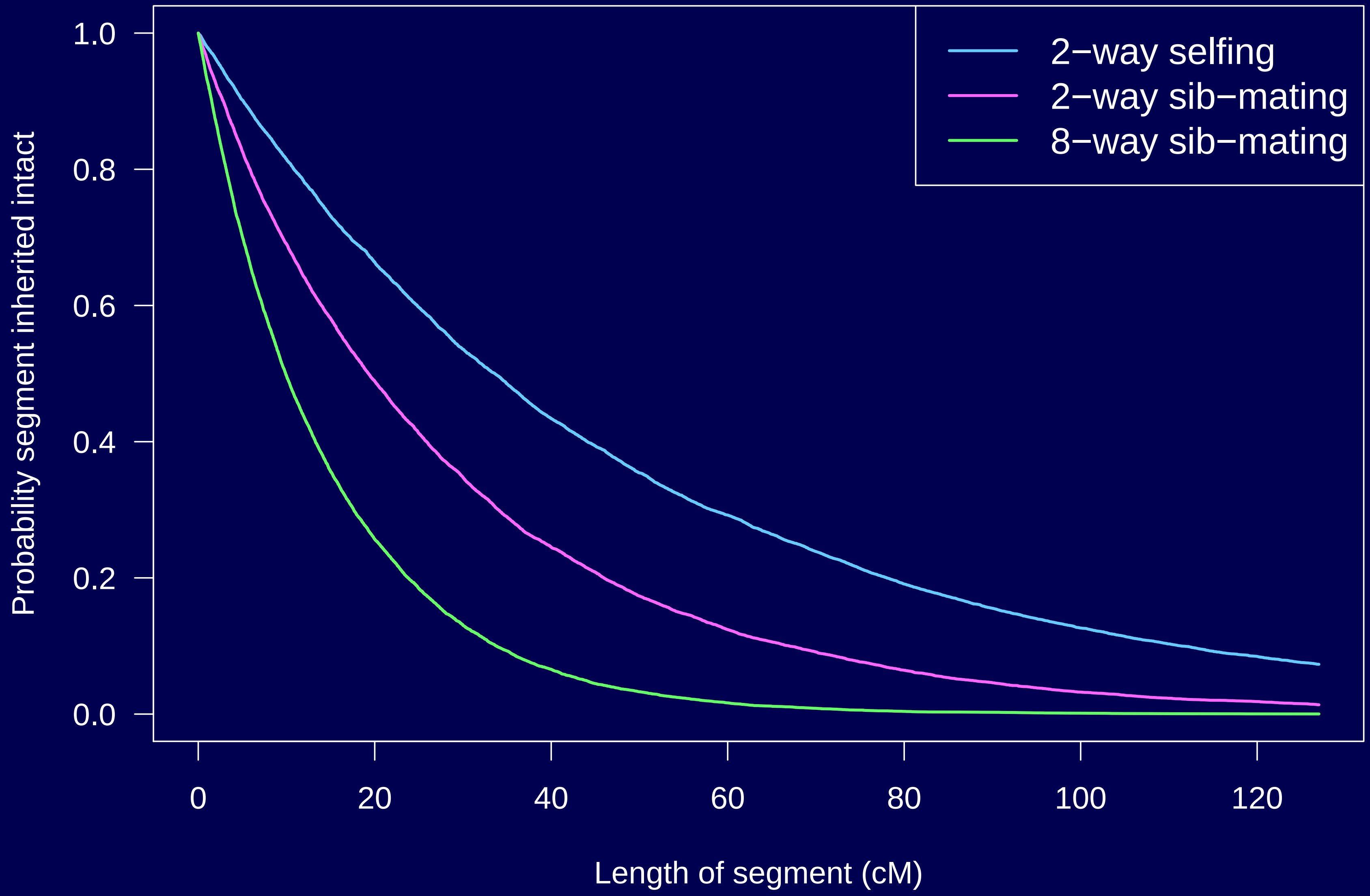
Segment lengths



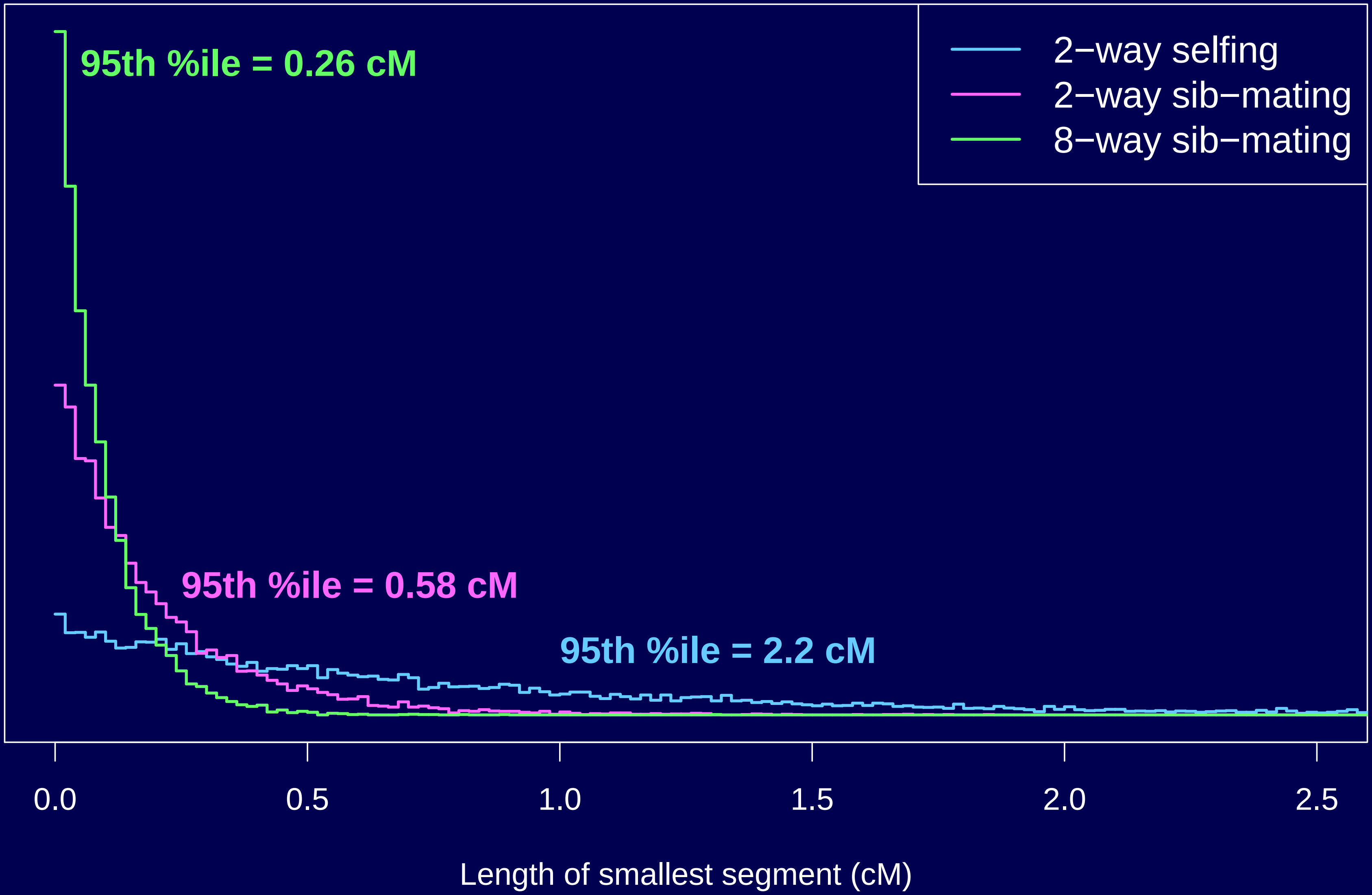
Segment lengths



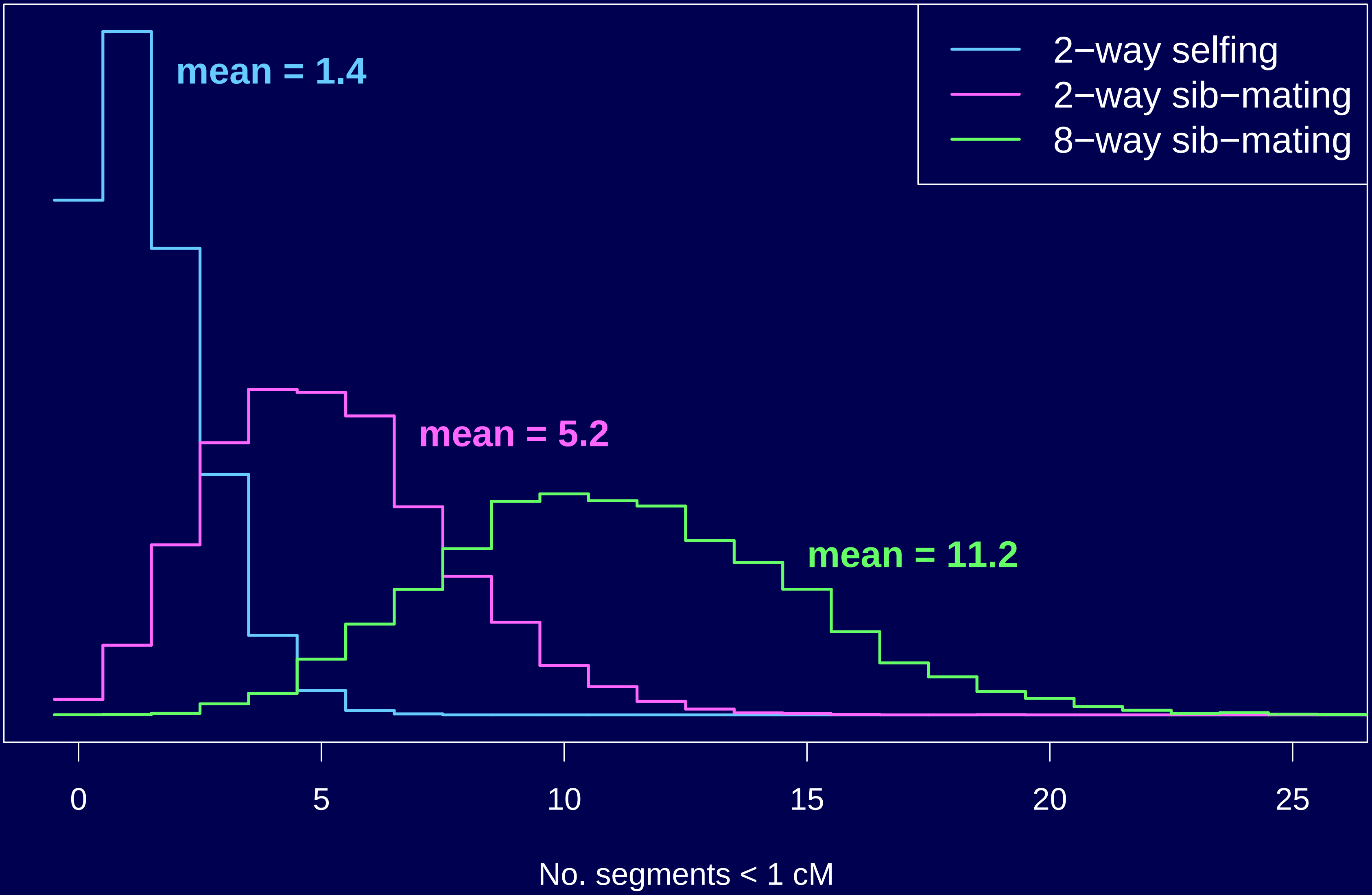
Probability a segment is inherited intact



Length of smallest segment



No. segments $<$ 1 cM



Summary

- The Collaborative Cross could provide “one-stop shopping” for gene mapping in the mouse.

- Use of such 8-way RILs requires an understanding of the breakpoint process.

- We’ve extended Haldane & Waddington’s results to the case of 8-way RILs: $R = 7r/(1+6r)$

- We’ve shown clustering of breakpoints in RILs by sib-mating, even in the presence of strong crossover interference.

- Broman KW (2005) The genomes of recombinant inbred lines. *Genetics* 169:1133–1146

Acknowledgement

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