

An applied statistician does probability:

It's not pretty

Karl W Broman

Department of Biostatistics & Medical Informatics
University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

An applied statistician does probability:

Don't think—do!

Karl W Broman

Department of Biostatistics & Medical Informatics
University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

An applied statistician
does probability:
Don't think—simulate!

Karl W Broman

Department of Biostatistics & Medical Informatics
University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

Genotype probabilities in the pre-Collaborative Cross

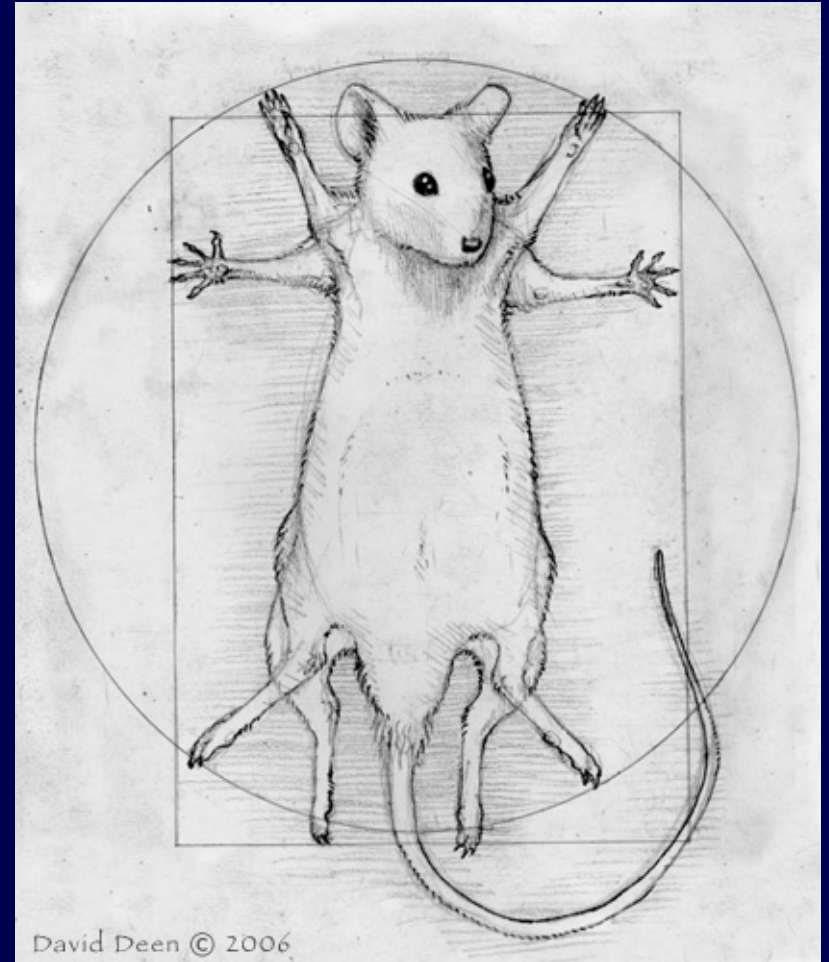
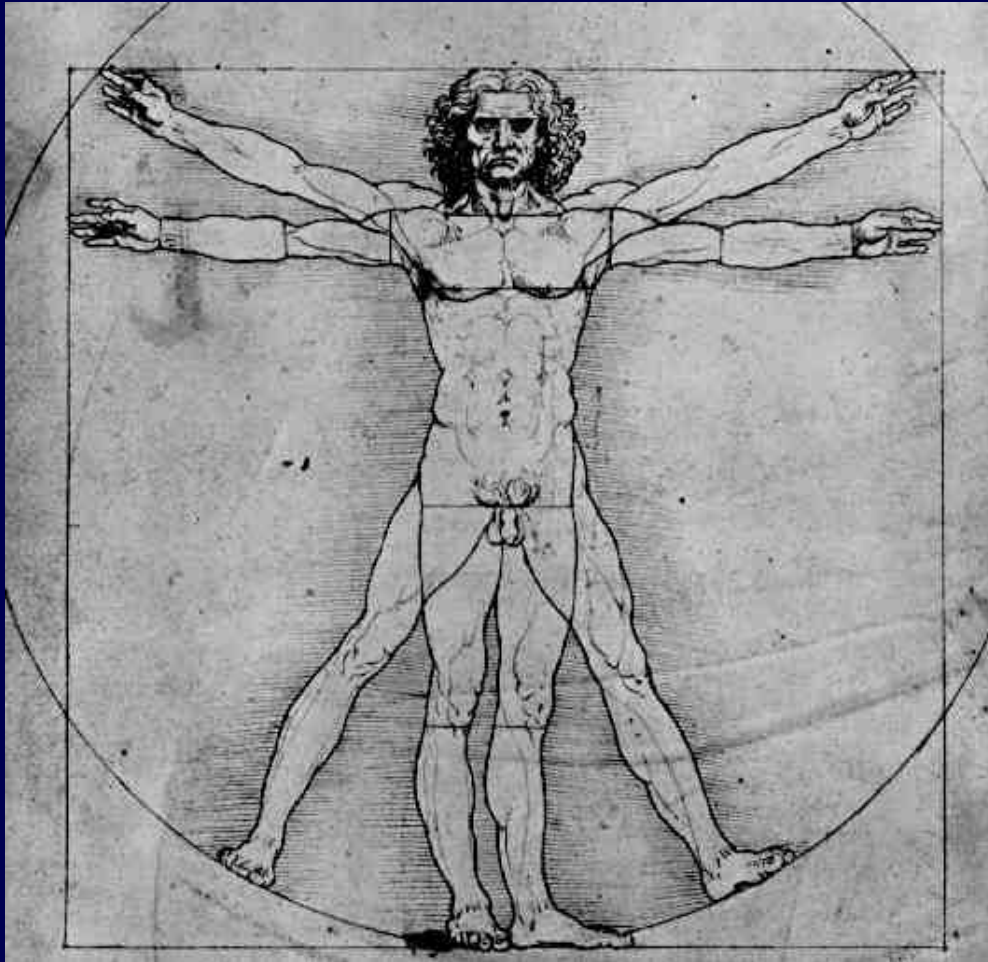
Karl W Broman

Department of Biostatistics & Medical Informatics
University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

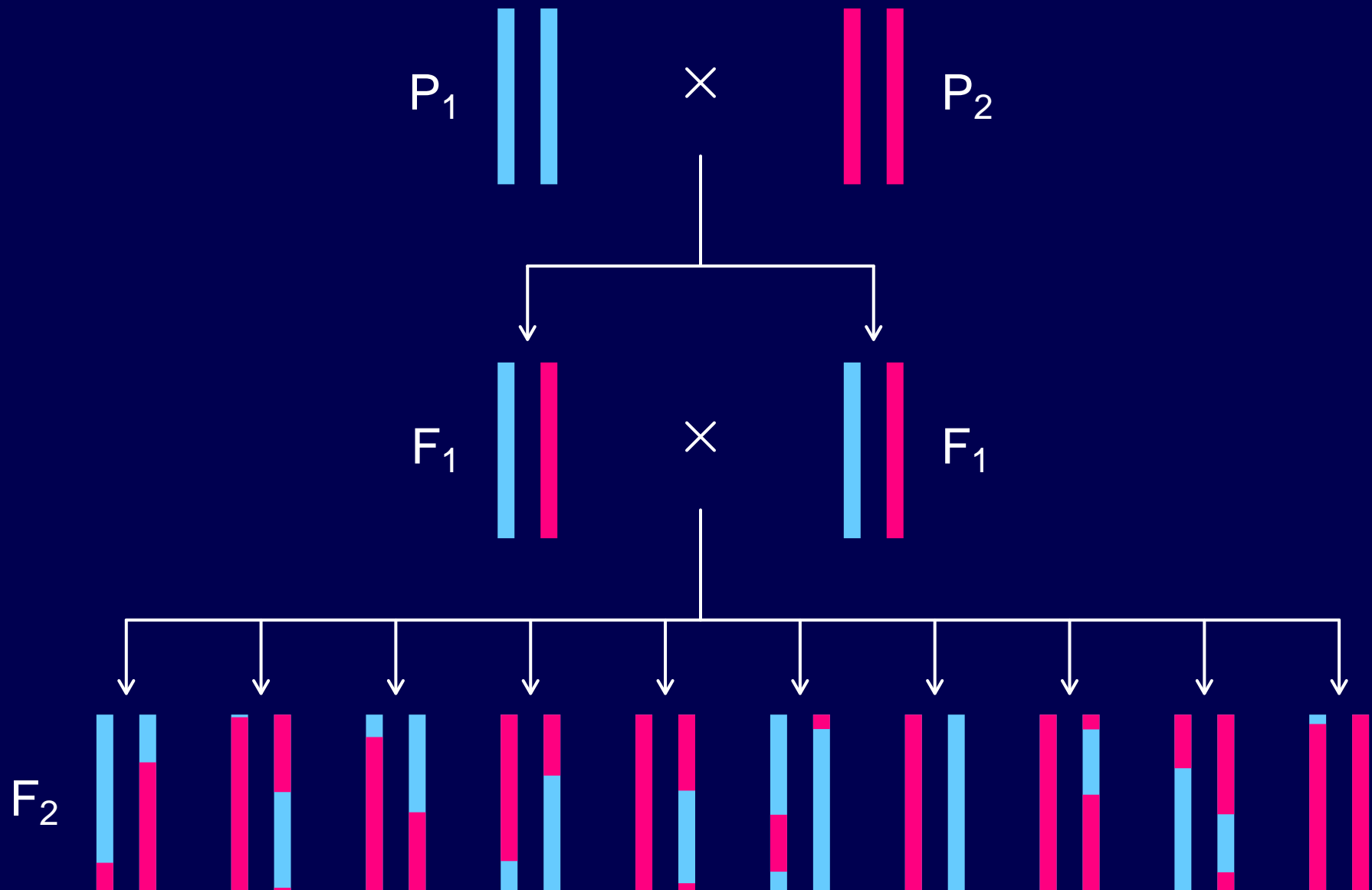


Human vs mouse

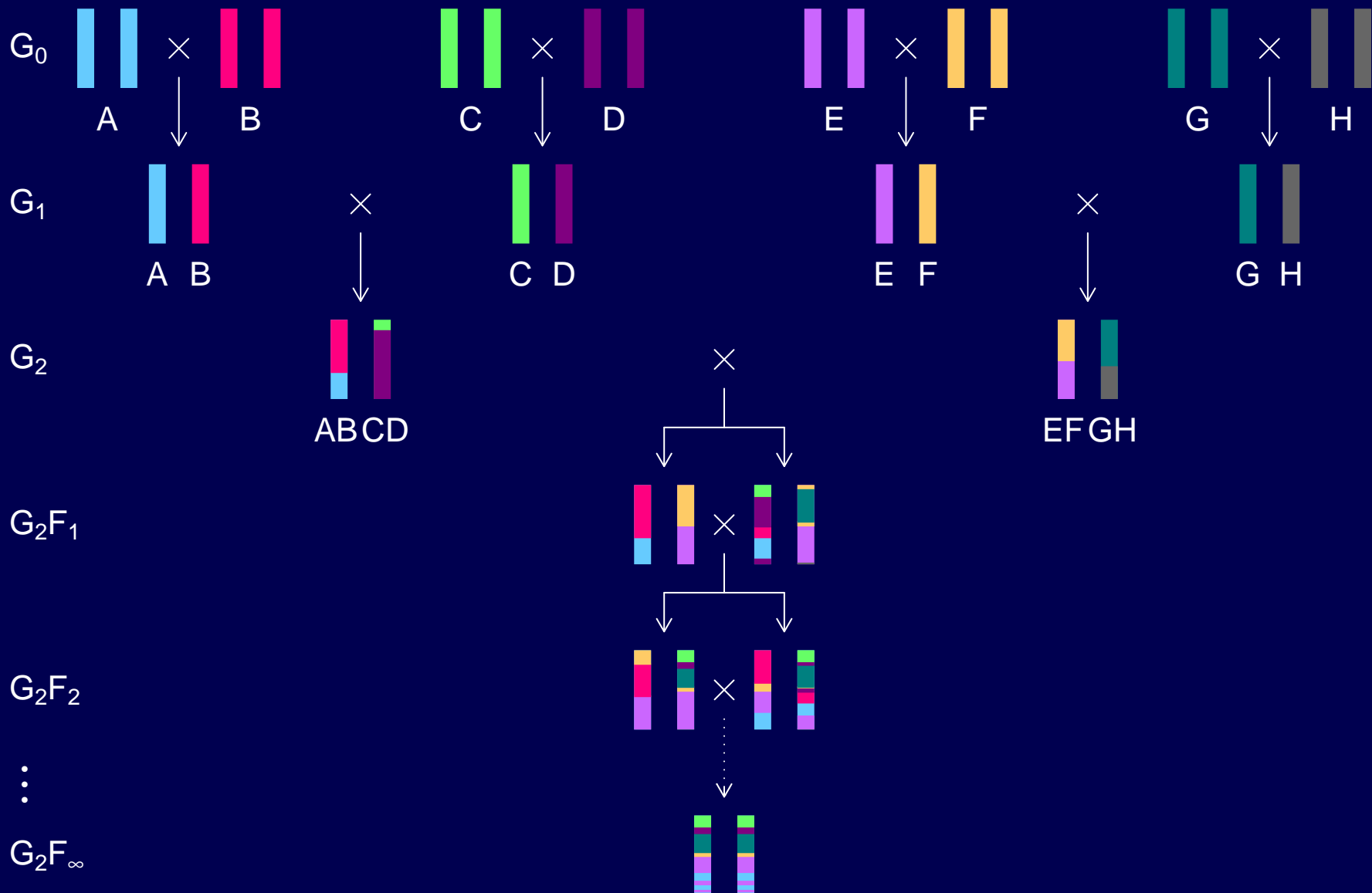


www.daviddeen.com

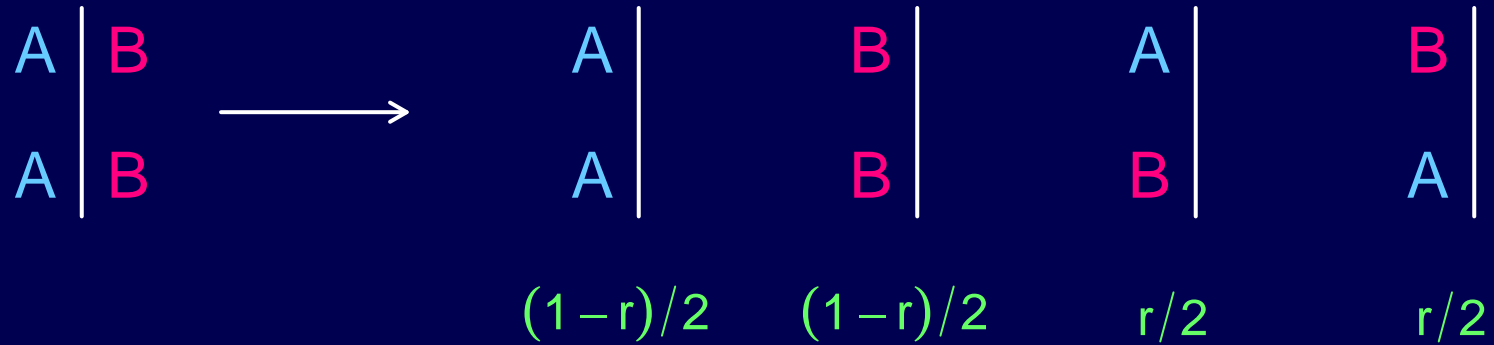
Intercross



The Collaborative Cross

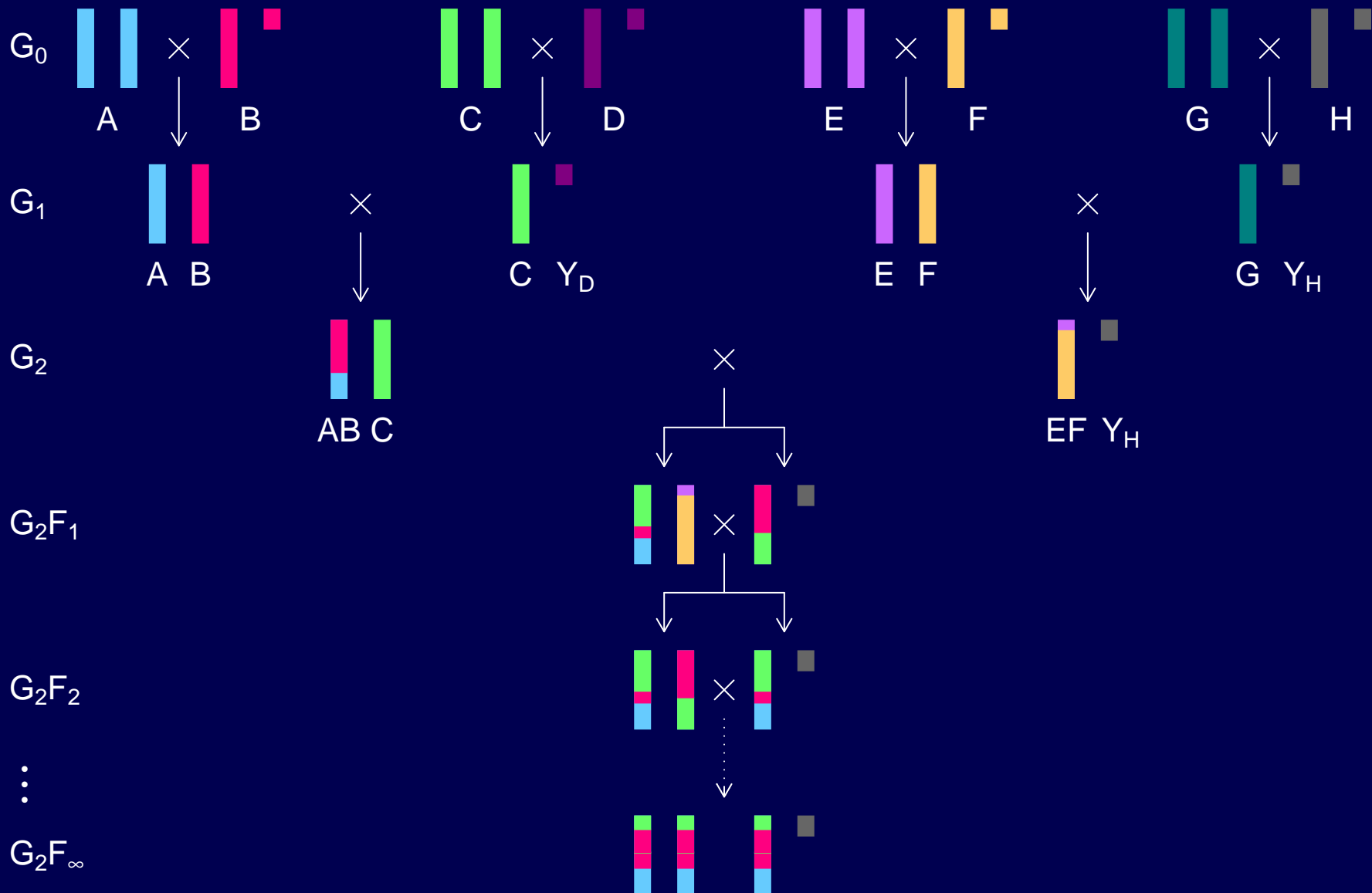


Recombination



r is the "recombination fraction"

X in the CC



In the CC

Autosomes

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

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

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

X chromosome

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

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

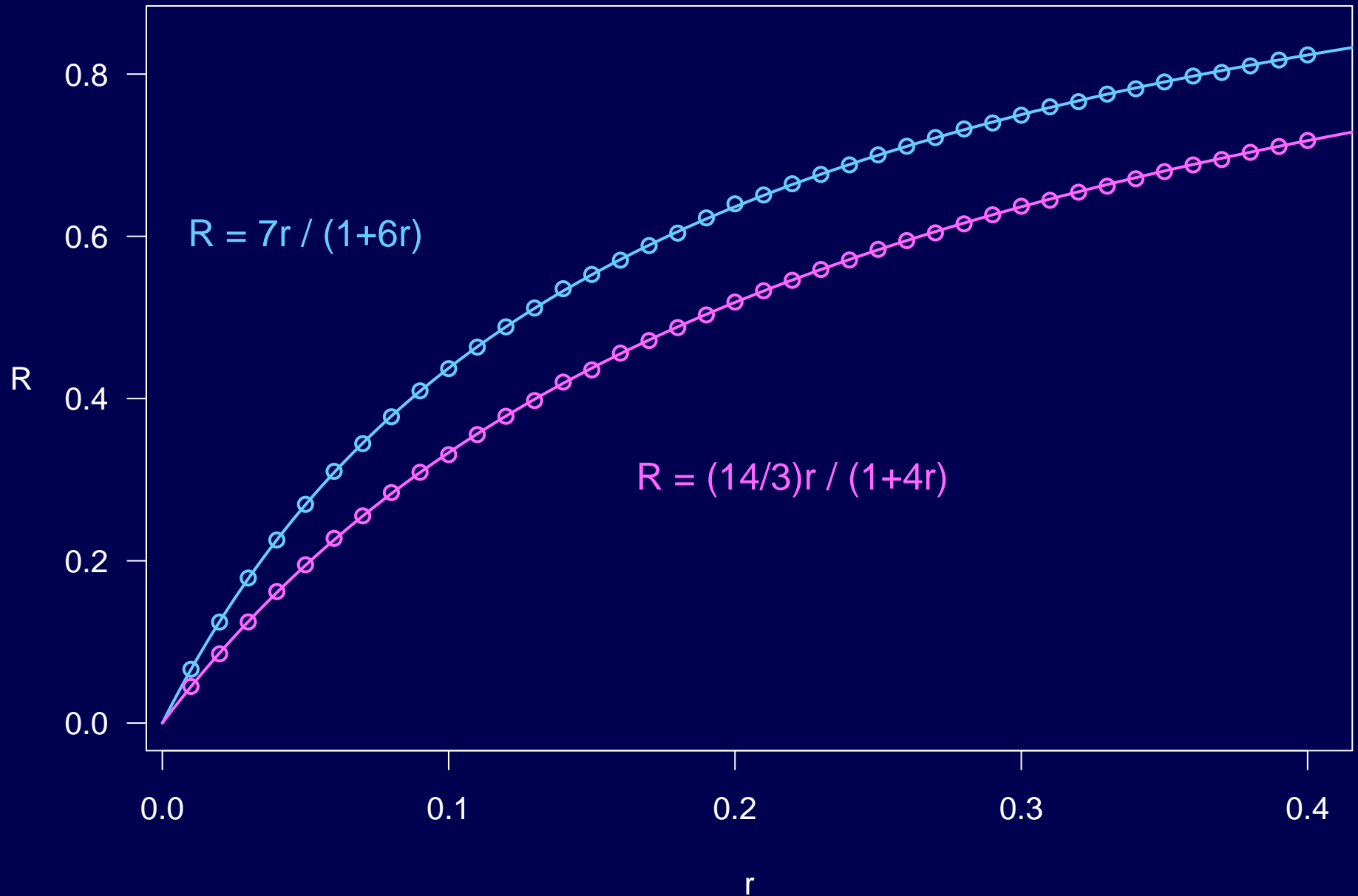
$$\Pr(G_2 = B \mid G_1 = A) = r/(1 + 4r)$$

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

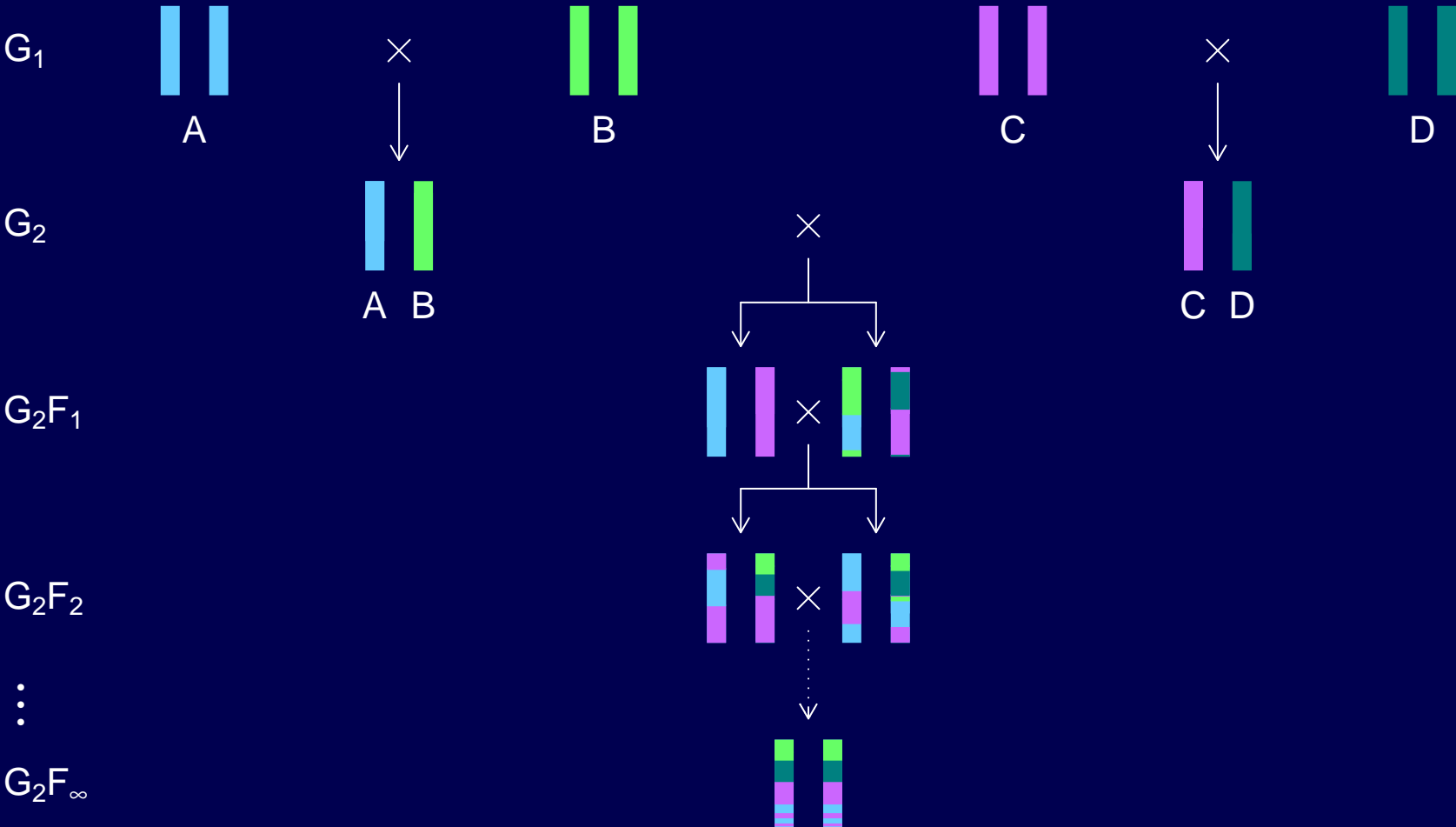
$$\Pr(G_2 = A \mid G_1 = C) = r/(1 + 4r)$$

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

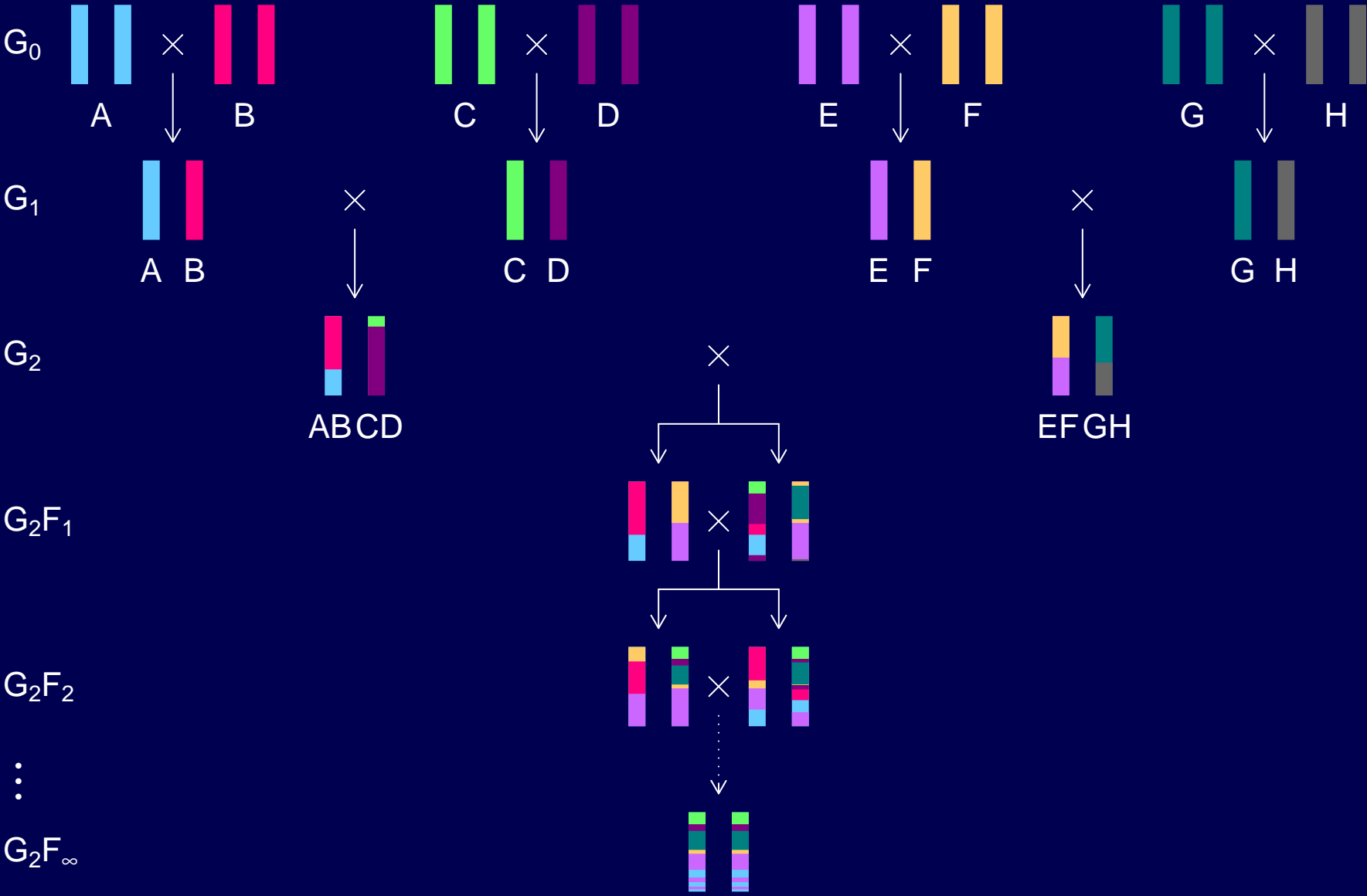
Computer simulations



4-way RIL



8-way RIL



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

...ideally, the **joint** probabilities for the **pair** of individuals.

...but, at least, for a **random** individual.

1 locus, X chr

G_2

AB|C

1 locus, X chr

G_2 AB|C

G_2F_1 AC|A AC|B BC|A BC|B

1 locus, X chr

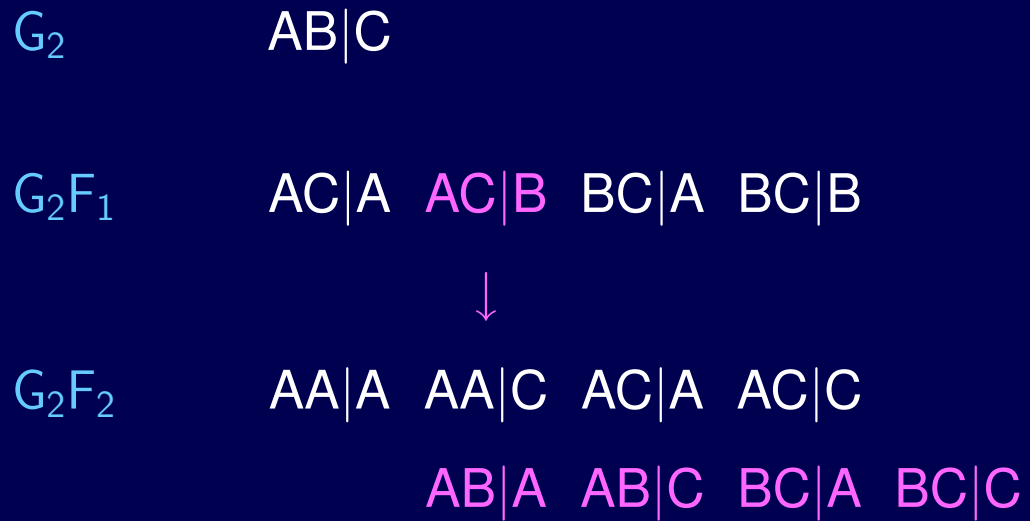
G_2 AB|C

G_2F_1 AC|A AC|B BC|A BC|B

↓

G_2F_2 AA|A AA|C AC|A AC|C

1 locus, X chr



1 locus, X chr

G_2 AB|C

G_2F_1 AC|A AC|B BC|A BC|B

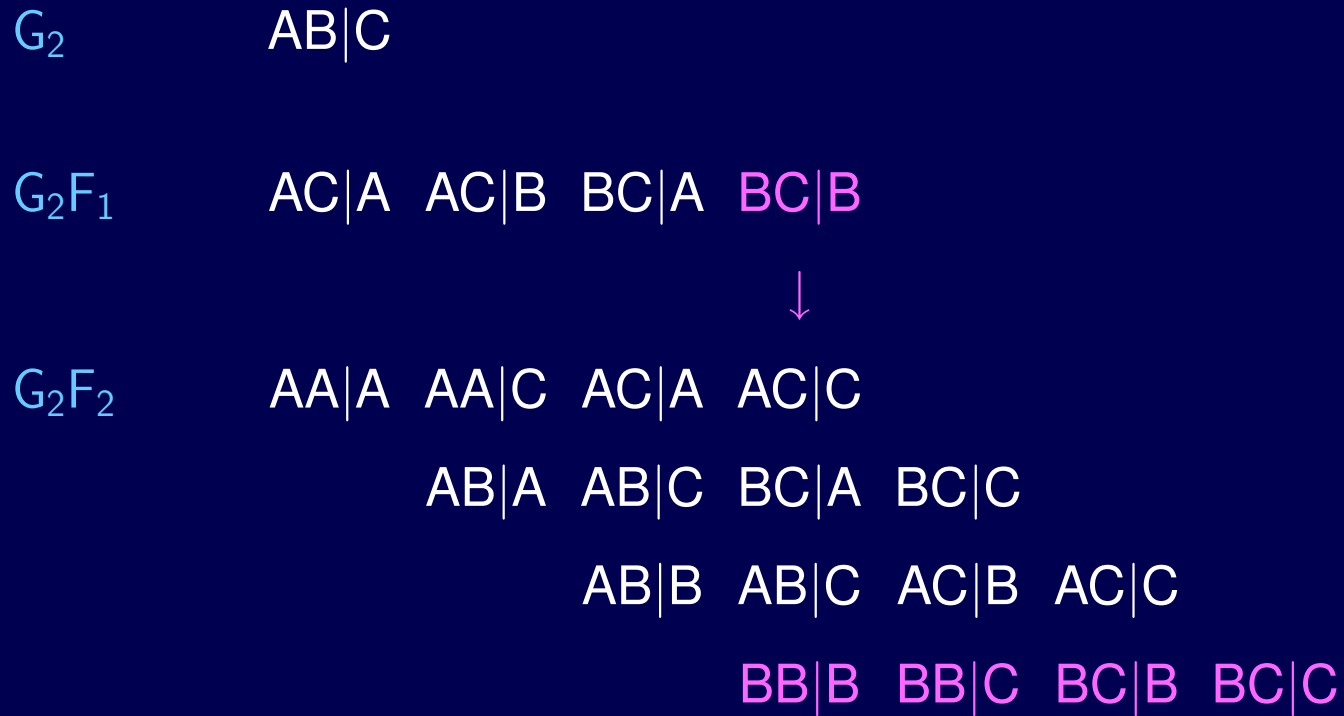


G_2F_2 AA|A AA|C AC|A AC|C

AB|A AB|C BC|A BC|C

AB|B AB|C AC|B AC|C

1 locus, X chr



1 locus, X chr

G_2 AB|C

G_2F_1 AC|A AC|B BC|A BC|B

G_2F_2 AA|A AA|C AC|A AC|C
AB|A AB|C BC|A BC|C
AB|B AB|C AC|B AC|C
BB|B BB|C BC|B BC|C

1 locus, X chr

G_2 AB|C

G_2F_1 AC|A AC|B BC|A BC|B

G_2F_2 AA|A AA|C AC|A AC|C
 AB|A AB|C BC|A BC|C
 AB|B AB|C AC|B AC|C
 BB|B BB|C BC|B BC|C

Females	AA, BB	1/8 each
	AC, BC	1/4 each
	AB	1/4 each

Males	A, B	1/4 each
	C	1/2

Markov chains

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

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

- Here, X_n = “parental type” at generation n .
- Transition probabilities $P_{ij} = \Pr(X_{n+1} = j \mid X_n = i)$
- If π_0 is the starting distribution (at G_2),
 $\pi_k = \pi_0 P^k$ is the distribution at $G_2 F_k$

1 locus, X chr, male

	A	B	C
G_2	0	0	1
G_2F_1	1/2	1/2	0
G_2F_2	1/4	1/4	1/2
G_2F_3	.	.	1/4
G_2F_4	.	.	3/8
G_2F_5	.	.	5/16
G_2F_6	.	.	11/32
G_2F_7	.	.	21/64
G_2F_8	.	.	43/128
G_2F_9	.	.	85/256

1 locus, X chr, male

	A	B	C
G_2	0	0	1
G_2F_1	1/2	1/2	0
G_2F_2	1/4	1/4	1/2
G_2F_3	.	.	1/4
G_2F_4	.	.	3/8
G_2F_5	.	.	5/16
G_2F_6	.	.	11/32
G_2F_7	.	.	21/64
G_2F_8	.	.	43/128
G_2F_9	.	.	85/256

G_2F_k (for $k \geq 1$): $\Pr(C) = 1 - \sum_{i=0}^{k-1} \left(-\frac{1}{2}\right)^i$

1 locus, X chr, female

	AA, BB	AC, BC	AB	CC
G_2	0	0	1	0
G_2F_1	0	1/2	0	0
G_2F_2	1/8	2/8	2/8	0
G_2F_3	1/8	2/8	1/8	1/8
G_2F_4	3/16	3/16	2/16	2/16
G_2F_5	13/64	10/64	6/64	12/64
G_2F_6	15/64	8/64	5/64	13/64
G_2F_7	32/128	13/128	8/128	30/128
G_2F_8	137/512	42/512	26/512	128/512
G_2F_9	143/512	34/512	21/512	137/512

1 locus, autosome, 1 ind'l

	AA, BB, CC, DD	AB, CD	AC, AD, BC, BD
G_2	0	$1/2$	0
G_2F_1	0	0	$1/4$
G_2F_2	$1/16$	$2/16$	$2/16$
G_2F_3	$3/32$	$2/32$	$4/32$
G_2F_4	$4/32$	$2/32$	$3/32$
G_2F_5	$19/128$	$6/128$	$10/128$
G_2F_6	$43/256$	$10/256$	$16/256$
G_2F_7	$47/256$	$8/256$	$13/256$
G_2F_8	$201/1024$	$26/1024$	$42/1024$
G_2F_9	$423/2048$	$42/2048$	$68/2048$

Summary

		1 locus	2 loc, hap	2 loc, gen
X chr	Male	✓	✓	—
	Female	✓	✓	×
	Pair	✓	—	×
Autosome	Ind'l	✓	✓	×
	Pair	✓	—	×

Kinship coefficients

$\Phi_{11}^{(k)}$ = kinship coefficient of ind'l w/ itself at G_2F_k

$\Phi_{12}^{(k)}$ = kinship coefficient of sibs at G_2F_k

$$\Phi_{11}^{(0)} = \frac{1}{2}, \Phi_{12}^{(0)} = 0$$

$$\Phi_{11}^{(k+1)} = \frac{1}{2} + \frac{1}{2}\Phi_{12}^{(k)}$$

$$\Phi_{12}^{(k+1)} = \frac{1}{2}\Phi_{11}^{(k)} + \frac{1}{2}\Phi_{12}^{(k)}$$

$$\Phi_{12}^{(k+2)} = \frac{1}{2}\Phi_{12}^{(k+1)} + \frac{1}{4}\Phi_{12}^{(k)} + \frac{1}{4}$$

$$\Phi_{12}^{(k+3)} = \frac{3}{2}\Phi_{12}^{(k+2)} - \frac{1}{4}\Phi_{12}^{(k+1)} - \frac{1}{4}\Phi_{12}^{(k)}$$

Fibonacci numbers

0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, 233, 377, 610, 987, ...

$$x_k = x_{k-1} + x_{k-2}, \text{ where } x_0 = 0, x_1 = 1$$

Characteristic polynomial: $x^2 - x - 1$

$$\text{Roots: } \varphi = \frac{1+\sqrt{5}}{2}, 1 - \varphi = \frac{1-\sqrt{5}}{2}$$

φ is the “golden ratio”

$$x_k = A\varphi^k + B(1 - \varphi)^k = \dots = \frac{\varphi^k - (1-\varphi)^k}{\sqrt{5}}$$

1 locus, X chr, female

	AA, BB	AC, BC	AB	CC
G_2	0	0	1	0
G_2F_1	0	1/2	0	0
G_2F_2	1/8	2/8	2/8	0
G_2F_3	1/8	2/8	1/8	1/8
G_2F_4	3/16	3/16	2/16	2/16
G_2F_5	13/64	10/64	6/64	12/64
G_2F_6	15/64	8/64	5/64	13/64
G_2F_7	32/128	13/128	8/128	30/128
G_2F_8	137/512	42/512	26/512	128/512
G_2F_9	143/512	34/512	21/512	137/512

1 locus, X chr, female

Pr(AC) satisfies $a_{k+2} = \frac{1}{2}a_{k+1} + \frac{1}{4}a_k$ with $a_0 = 0, a_1 = \frac{1}{2}$

$$a_k = \frac{\sqrt{5}}{5} \left[\left(\frac{1+\sqrt{5}}{4} \right)^k - \left(\frac{1-\sqrt{5}}{4} \right)^k \right]$$

Pr(AB) satisfies $a_{k+2} = \frac{1}{2}a_{k+1} + \frac{1}{4}a_k$ with $a_0 = 1, a_1 = 0$

$$a_k = \left(\frac{5-\sqrt{5}}{10} \right) \left(\frac{1+\sqrt{5}}{4} \right)^k + \left(\frac{5+\sqrt{5}}{10} \right) \left(\frac{1-\sqrt{5}}{4} \right)^k$$

Pr(AA)

$$a_k = \frac{1}{3} + \left(\frac{1}{6} \right) \left(-\frac{1}{2} \right)^k - \left(\frac{5+\sqrt{5}}{20} \right) \left(\frac{1+\sqrt{5}}{4} \right)^k - \left(\frac{5-\sqrt{5}}{20} \right) \left(\frac{1-\sqrt{5}}{4} \right)^k$$

Pr(CC)

$$a_k = \frac{1}{3} + \left(\frac{1}{6} \right) \left(-\frac{1}{2} \right)^{k-1} - \left(\frac{5+\sqrt{5}}{20} \right) \left(\frac{1+\sqrt{5}}{4} \right)^{k-1} - \left(\frac{5-\sqrt{5}}{20} \right) \left(\frac{1-\sqrt{5}}{4} \right)^{k-1}$$

1 locus, autosome, 1 ind'l

	AA, BB, CC, DD	AB, CD	AC, AD, BC, BD
G_2	0	$1/2$	0
G_2F_1	0	0	$1/4$
G_2F_2	$1/16$	$2/16$	$2/16$
G_2F_3	$3/32$	$2/32$	$4/32$
G_2F_4	$4/32$	$2/32$	$3/32$
G_2F_5	$19/128$	$6/128$	$10/128$
G_2F_6	$43/256$	$10/256$	$16/256$
G_2F_7	$47/256$	$8/256$	$13/256$
G_2F_8	$201/1024$	$26/1024$	$42/1024$
G_2F_9	$423/2048$	$42/2048$	$68/2048$

1 locus, autosome, 1 ind'l

Pr(AC) satisfies $a_{k+2} = \frac{1}{2}a_{k+1} + \frac{1}{4}a_k$ with $a_0 = 0, a_1 = \frac{1}{4}$

$$a_k = \frac{\sqrt{5}}{10} \left[\left(\frac{1+\sqrt{5}}{4} \right)^k - \left(\frac{1-\sqrt{5}}{4} \right)^k \right]$$

Pr(AB) satisfies $a_{k+2} = \frac{1}{2}a_{k+1} + \frac{1}{4}a_k$ with $a_0 = \frac{1}{2}, a_1 = 0$

$$a_k = \left(\frac{5-\sqrt{5}}{20} \right) \left(\frac{1+\sqrt{5}}{4} \right)^k + \left(\frac{5+\sqrt{5}}{20} \right) \left(\frac{1-\sqrt{5}}{4} \right)^k$$

Pr(AA)

$$a_k = \frac{1}{4} - \left(\frac{5+2\sqrt{5}}{40} \right) \left(\frac{1+\sqrt{5}}{4} \right)^{k-1} - \left(\frac{5-2\sqrt{5}}{40} \right) \left(\frac{1-\sqrt{5}}{4} \right)^{k-1}$$

2-locus hap, X chr, male

For Pr(CC):

$$r = 0.01 \quad a_{k+4} = \frac{199}{200}a_{k+3} + \frac{199}{400}a_{k+2} - \frac{74}{200}a_{k+1} - \frac{49}{400}a_k$$

$$r = 0.02 \quad a_{k+4} = \frac{198}{200}a_{k+3} + \frac{198}{400}a_{k+2} - \frac{73}{200}a_{k+1} - \frac{48}{400}a_k$$

$$r = 0.03 \quad a_{k+4} = \frac{197}{200}a_{k+3} + \frac{197}{400}a_{k+2} - \frac{72}{200}a_{k+1} - \frac{47}{400}a_k$$

$$a_{k+4} = \left(\frac{2-r}{r}\right) a_{k+3} + \left(\frac{2-r}{4}\right) a_{k+2} - \left(\frac{3-4r}{8}\right) a_{k+1} - \left(\frac{1-2r}{8}\right) a_k$$

$$\Pr(\text{CC}) = \frac{1}{12r+3} + \frac{2}{3r+3} \left(-\frac{1}{2}\right)^k + \alpha \left(\frac{1-r+\sqrt{r^2-10r+5}}{4}\right)^k + \beta \left(\frac{1-r-\sqrt{r^2-10r+5}}{4}\right)^k$$

$$\text{where } \alpha = \frac{2r^4+(2r^3-r^2+r)\sqrt{r^2-10r+5}-19r^3+5r}{4r^4-35r^3-29r^2+15r+5}$$

$$\beta = \frac{2r^4-(2r^3-r^2+r)\sqrt{r^2-10r+5}-19r^3+5r}{4r^4-35r^3-29r^2+15r+5}$$

Pr(AC), Pr(AB), Pr(AA) similarly obnoxious

Fixation probability

Consider the two individuals at a single autosomal locus.

Consider a particular allele (say A).

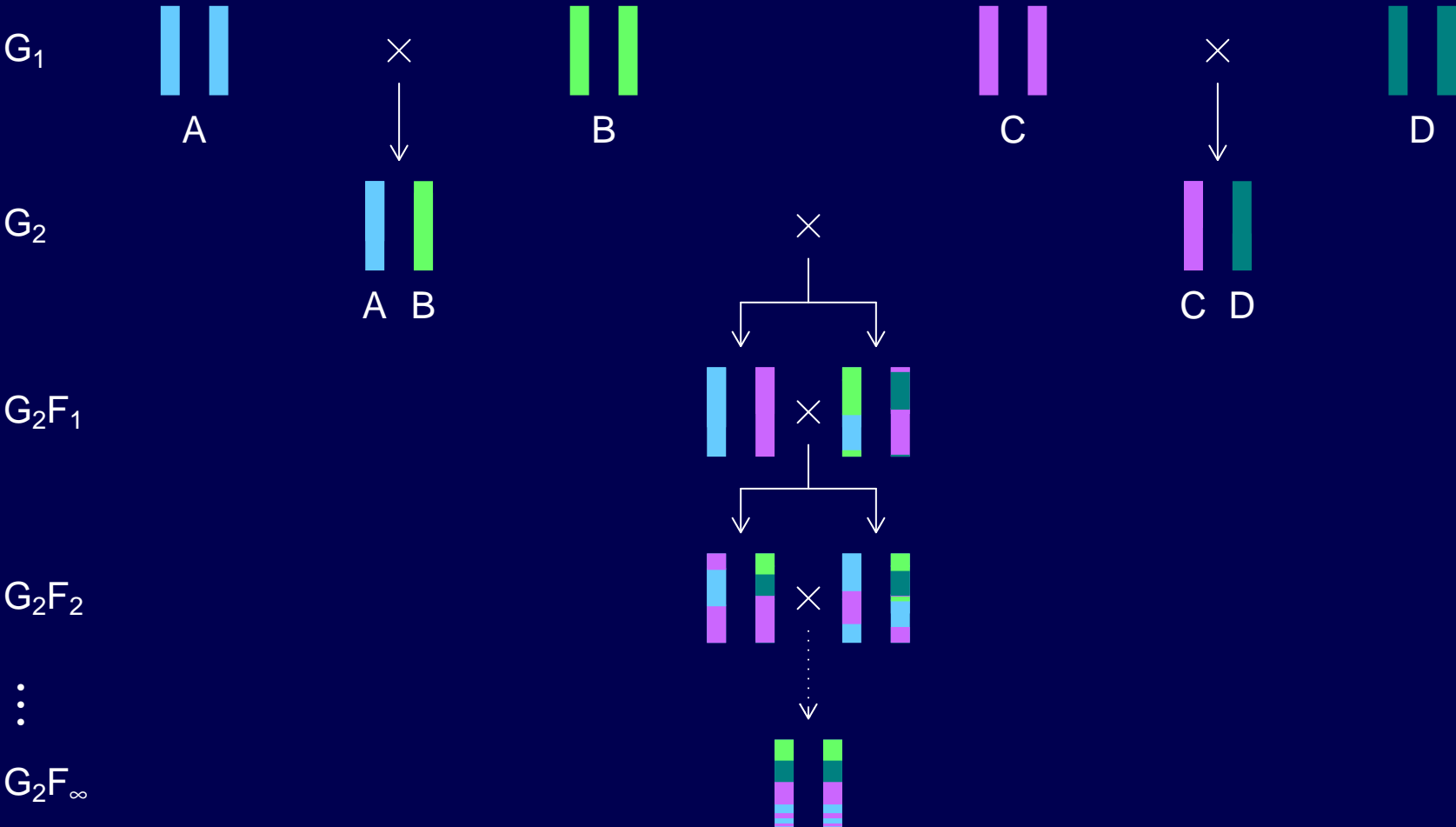
Pool others into a single allele (B).

We want $\Pr(X_k = AA \times AA)$ [or really $4 \times$ that]

Transition matrix, P:

	AA×BB	AA×AB	AB×AB	AB×BB	AA×AA	BB×BB
AA×BB	0	0	1	0	0	0
AA×AB	0	$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{4}$	0
AB×AB	$\frac{1}{8}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{1}{16}$
AB×BB	0	0	$\frac{1}{4}$	$\frac{1}{2}$	0	$\frac{1}{4}$
AA×AA	0	0	0	0	1	0
BB×BB	0	0	0	0	0	1

4-way RIL



Fixation probability

We seek $\pi_k = \pi_0 P^k$ where $\pi_0 = (0 \ 0 \ 0 \ 1 \ 0 \ 0)$ [start at AB×BB].

Write $P = V D V^{-1}$

where $D =$ diagonal matrix of eigenvalues, $V =$ eigenvectors

So $P^k = V D^k V^{-1}$, and so $\pi_k = \pi_0 V D^k V^{-1}$.

Thus, the fixation probability for 4- and 8-way RIL is

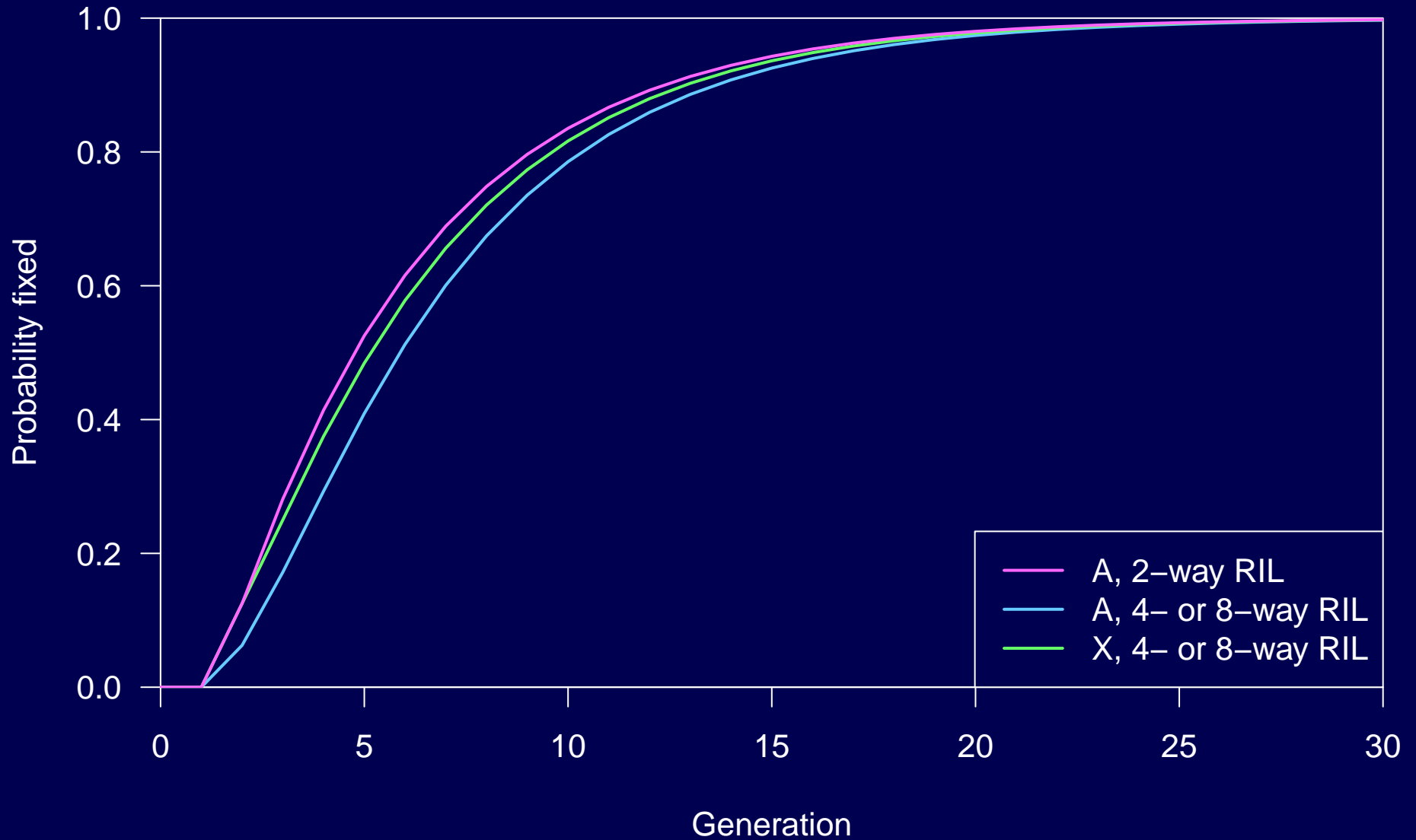
$$1 + \left(\frac{1}{2}\right)^k - \frac{1}{5} \left(\frac{1}{4}\right)^k - \left(\frac{9-4\sqrt{5}}{10}\right) \left(\frac{1-\sqrt{5}}{4}\right)^k - \left(\frac{9+4\sqrt{5}}{10}\right) \left(\frac{1+\sqrt{5}}{4}\right)^k$$

For 2-way RIL, we use $\pi_0 = (1 \ 0 \ 0 \ 0 \ 0 \ 0)$ [start at AA×BB], and obtain

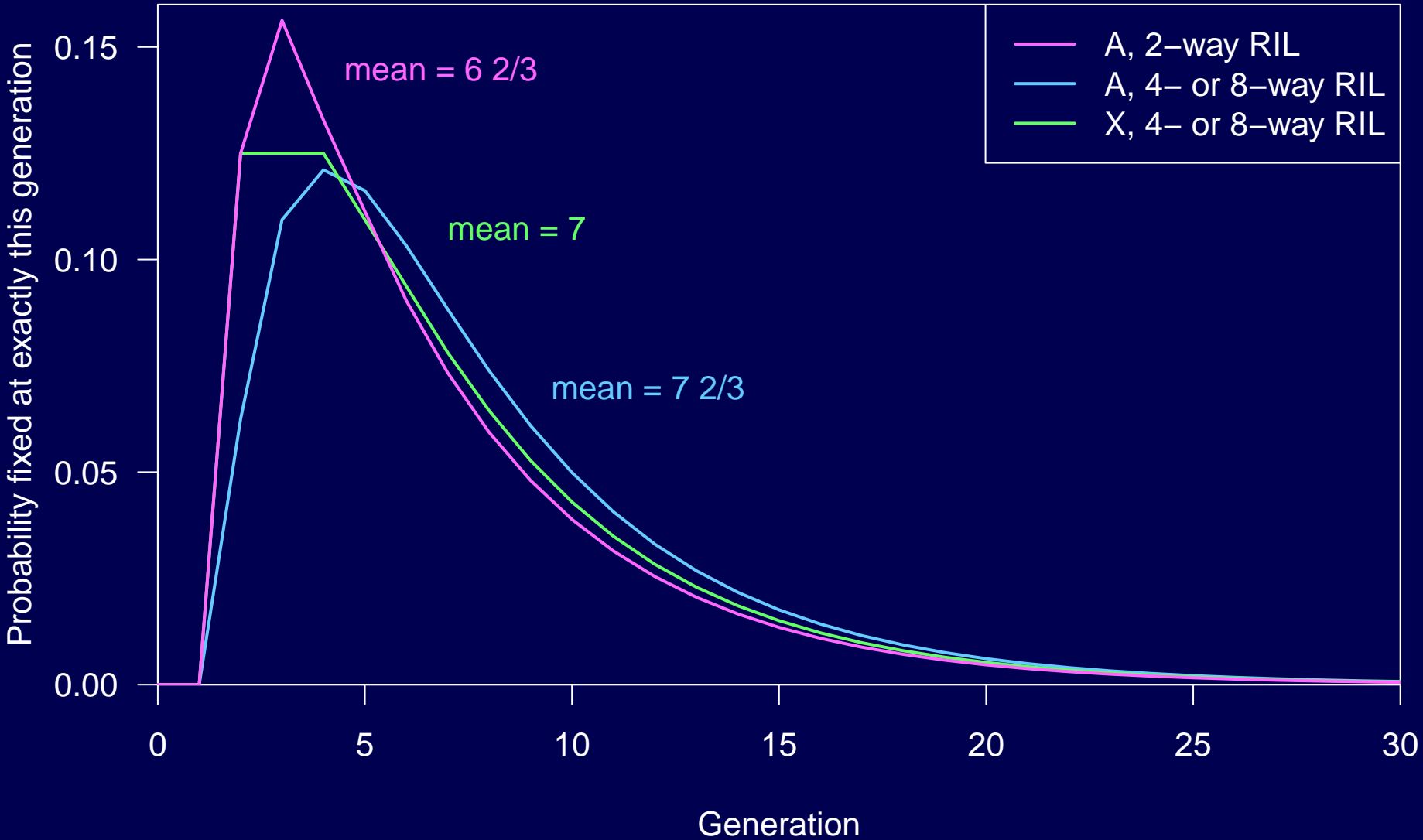
$$1 + \left(\frac{2}{5}\right) \left(\frac{1}{4}\right)^k - \left(\frac{7-3\sqrt{5}}{10}\right) \left(\frac{1-\sqrt{5}}{4}\right)^k - \left(\frac{7+3\sqrt{5}}{10}\right) \left(\frac{1+\sqrt{5}}{4}\right)^k$$

[Caveat: meaning of generation k somewhat different in 2-, 4-, and 8-way RIL]

Fixation probability



Time of fixation



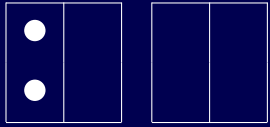
Kimura (1963)

$C_k(xy)$ = Pr(random chr from gen k has x at locus 1 and y at locus 2)

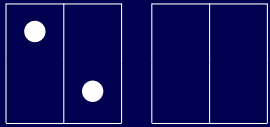
$S_k(xy)$ = Pr(random chr from gen k has x at locus 1 and opposite chr in that ind'l has y at locus 2)

$T_k(xy)$ = Pr(random chr from gen k has x at locus 1 and random chr from other individual has y at locus 2)

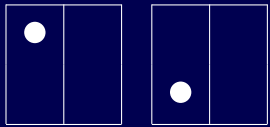
Kimura (1963)



$C_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and } y \text{ at locus 2})$

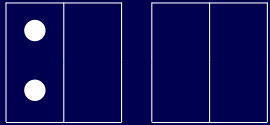


$S_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and opposite chr in that ind'l has } y \text{ at locus 2})$

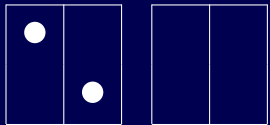


$T_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and random chr from other individual has } y \text{ at locus 2})$

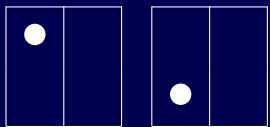
Kimura (1963)



$C_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and } y \text{ at locus 2})$



$S_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and opposite chr in that ind'l has } y \text{ at locus 2})$



$T_k(xy) = \text{Pr}(\text{random chr from gen } k \text{ has } x \text{ at locus 1 and random chr from other individual has } y \text{ at locus 2})$

$$C_{k+1} = (1 - r)C_k + rS_k$$

$$S_{k+1} = T_k$$

$$T_{k+1} = \frac{1}{4}C_k + \frac{1}{4}S_k + \frac{1}{2}T_k$$

2-locus hap, autosome

$$\Pr(\text{AA}) = \frac{1}{4} \left\{ \frac{1}{1+6r} + \left[\frac{1-2r-z}{4} \right]^k \left[\frac{6r^2-7r+3rz}{(1+6r)z} \right] - \left[\frac{1-2r+z}{4} \right]^k \left[\frac{6r^2-7r-3rz}{(1+6r)z} \right] \right\}$$

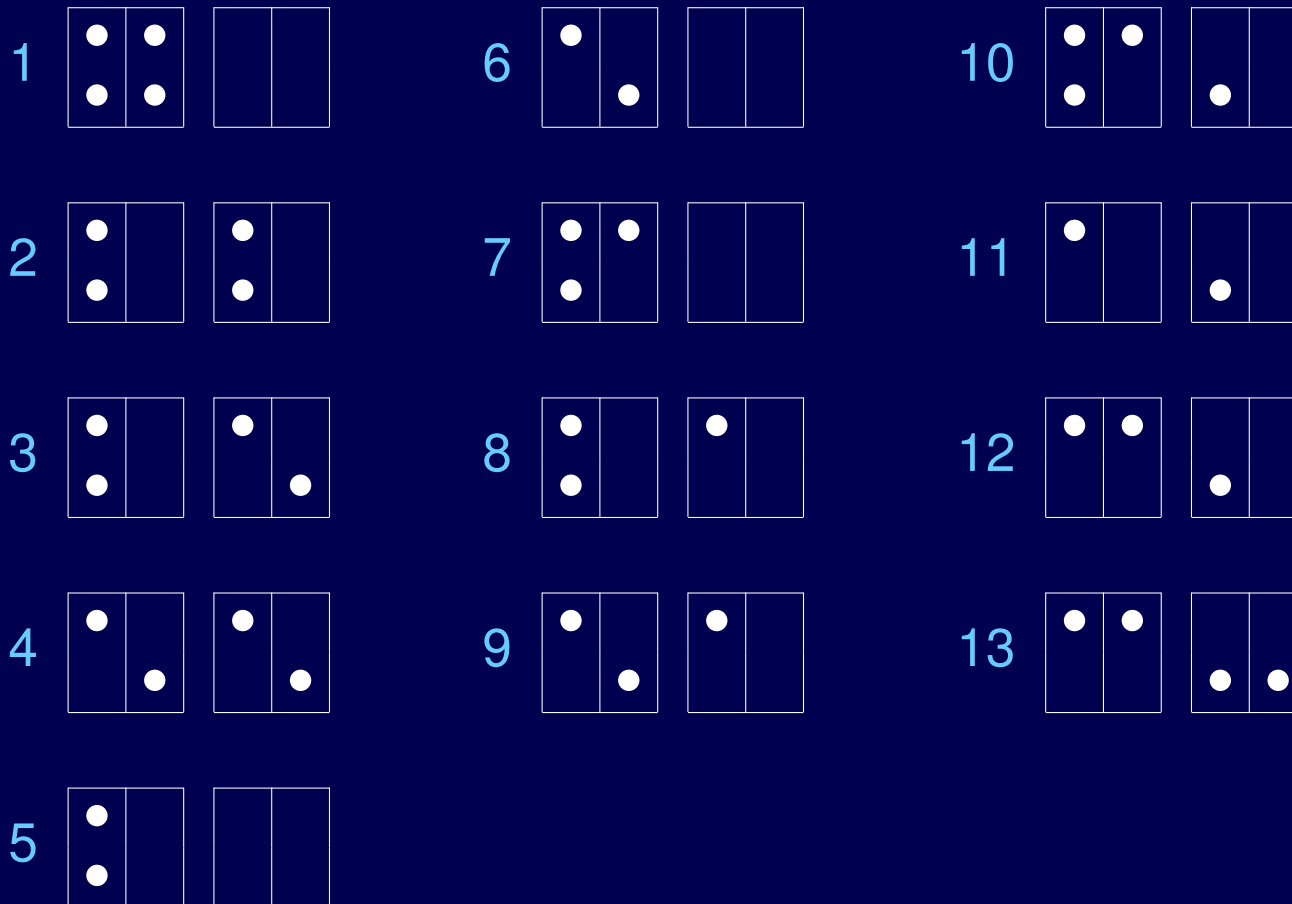
$$\Pr(\text{AB}) = \frac{1}{4} \left\{ \frac{2r}{1+6r} - \left[\frac{1-2r-z}{4} \right]^k \left[\frac{10r^2-r+rz}{(1+6r)z} \right] + \left[\frac{1-2r+z}{4} \right]^k \left[\frac{10r^2-r-rz}{(1+6r)z} \right] \right\}$$

$$\Pr(\text{AC}) = \frac{1}{8} \left\{ \frac{4r}{1+6r} + \left[\frac{1-2r-z}{4} \right]^k \left[\frac{4r^2+6r-2rz}{(1+6r)z} \right] - \left[\frac{1-2r+z}{4} \right]^k \left[\frac{4r^2+6r+2rz}{(1+6r)z} \right] \right\}$$

where $z = \sqrt{(1-2r)(5-2r)}$

2-locus gen, autosome

We seek to extend the idea from Kimura (1963) to get probabilities at G_2F_k for patterns like $\begin{array}{c|c} A & A \\ \hline A & A \end{array}$, $\begin{array}{c|c} A & A \\ \hline B & B \end{array}$, $\begin{array}{c|c} A & A \\ \hline C & C \end{array}$



2-locus gen, autosome

The “transition” matrix (really, the matrix that defines the recursion):

	1	2	3	4	5	6	7	8	9	10	11	12	13
1		$(1-r)^2$	$2r(1-r)$	r^2									
2	$\frac{r^2+(1-r)^2}{4}$	$\frac{(1-r)^2}{2}$	$r(1-r)$	$\frac{r^2}{2}$	$\frac{(1-r)^2}{4}$	$\frac{r^2}{4}$	$r(1-r)$						
3								$\frac{1-r}{2}$	$\frac{r}{2}$	$\frac{1}{2}$			
4		$\frac{1}{8}$	$\frac{1}{4}$	$\frac{1}{8}$							$\frac{1}{8}$	$\frac{1}{4}$	$\frac{1}{8}$
5					$(1-r)$	r							
6											1		
7							$(1-r)$	r					
8					$\frac{1-r}{4}$	$\frac{r}{4}$	$\frac{1}{4}$	$\frac{1-r}{2}$	$\frac{r}{2}$				
9								$\frac{1}{4}$	$\frac{1}{4}$		$\frac{1}{4}$	$\frac{1}{4}$	
10		$\frac{1-r}{4}$	$\frac{1}{4}$	$\frac{r}{4}$				$\frac{1-r}{4}$	$\frac{r}{4}$	$\frac{1}{4}$			
11					$\frac{1}{4}$	$\frac{1}{4}$					$\frac{1}{2}$		
12								$\frac{1}{2}$	$\frac{1}{2}$				
13		$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$									

What are we doing?

We have a Markov chain with many states (say n)

Transition matrix P ; starting distribution π_0

We want to calculate $\pi_k = \pi_0 P^k$

Really, we just need $\pi_k b = \pi_0 P^k b$ for some $n \times 1$ vector b

Suppose we can expand b to an $n \times m$ matrix B in a way that $PB = BA$
for some $m \times m$ matrix A

Then $P^k B = P^{k-1}(PB) = P^{k-1}(BA) = \dots = BA^k$

And so $\pi_0 P^k B = \pi_0 BA^k$

→ work with $A [m \times m]$ in place of $P [n \times n]$

Counting states

Two loci, X chromosome

3 alleles: $3^6 = 729$ types

Swap $A \leftrightarrow B$, two hapl in female, 2 loci \rightarrow 116 types

To get at $\Pr(AA|AA)$ in females, consider just 2 alleles ($2^6 = 64$ types)

After symmetries: 24 types

Two loci, autosome

4 alleles: $4^8 = 65,536$ types

After symmetries: 700 types

To get at $\Pr(AA|AA)$, consider just 2 alleles ($2^8 = 256$ types)

After symmetries: 34 types

2-locus gen, autosome

Returning to that 13×13 matrix, we need the eigenvalues and eigenvectors.

The first 7 eigenvalues:

$$1$$

$$\frac{1 \pm \sqrt{5}}{4}$$

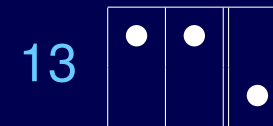
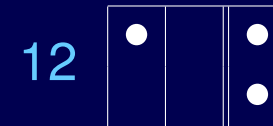
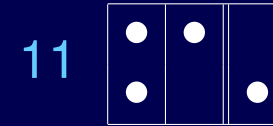
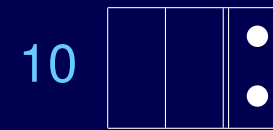
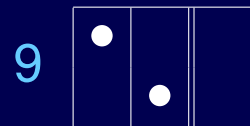
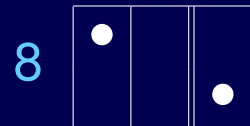
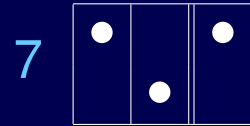
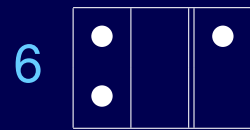
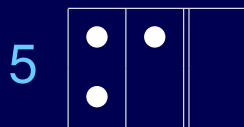
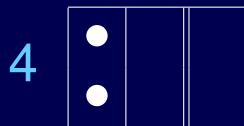
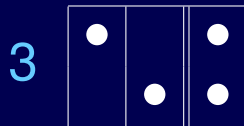
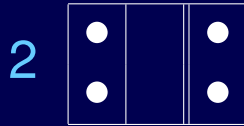
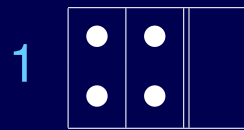
$$\frac{1 - 2r \pm \sqrt{4r^2 - 12r + 5}}{4}$$

$$\frac{1 - 2r \pm \sqrt{(1 - 2r)(9 - 2r)}}{8}$$

The other 6 eigenvalues are the roots of

$$\begin{aligned} 1026x^6 &- 128(4r^2 - 8r + 7)x^5 - 64(8r^4 - 24r^3 + 26r^2 - 10r + 3)x^4 \\ &+ 8(16r^4 - 80r^3 + 120r^2 - 84r + 23)x^3 - 8(16r^5 - 56r^4 + 72r^3 - 48r^2 + 18r - 3)x^2 \\ &+ 4(16r^5 - 40r^4 + 50r^3 - 35r^2 + 13r - 2)x + (16r^5 - 40r^4 + 44r^3 - 26r^2 + 8r - 1) \end{aligned}$$

2-locus gen, X chr



2-locus gen, X chr

The first 6 eigenvalues:

$$1, -\frac{1}{2}$$

$$\frac{1 \pm \sqrt{5}}{4}$$

$$\frac{1 - r \pm \sqrt{r^2 - 10r + 5}}{4}$$

The other 7 eigenvalues are the roots of

$$16x^3 + 4x^2 - (6r + 4)x + 2r - 1$$

and

$$\begin{aligned} &32x^4 + (16r - 24)x^3 + (16r^3 - 32r^2 + 20r - 8)x^2 \\ &- (4r^3 - 8r^2 + 10r - 4)x - (4r^3 - 6r^2 + 4r - 1) \end{aligned}$$

Summary

		1 locus	2 loc, hap	2 loc, gen
X chr	Male	✓	✓	—
	Female	✓	✓	×
	Pair	✓	—	×
Autosome	Ind'l	✓	✓	×
	Pair	✓	—	×

Acknowledgments

Timo Seppäläinen

Mathematics, UW–Madison

Bret Larget

Statistics & Botany, UW–Madison