

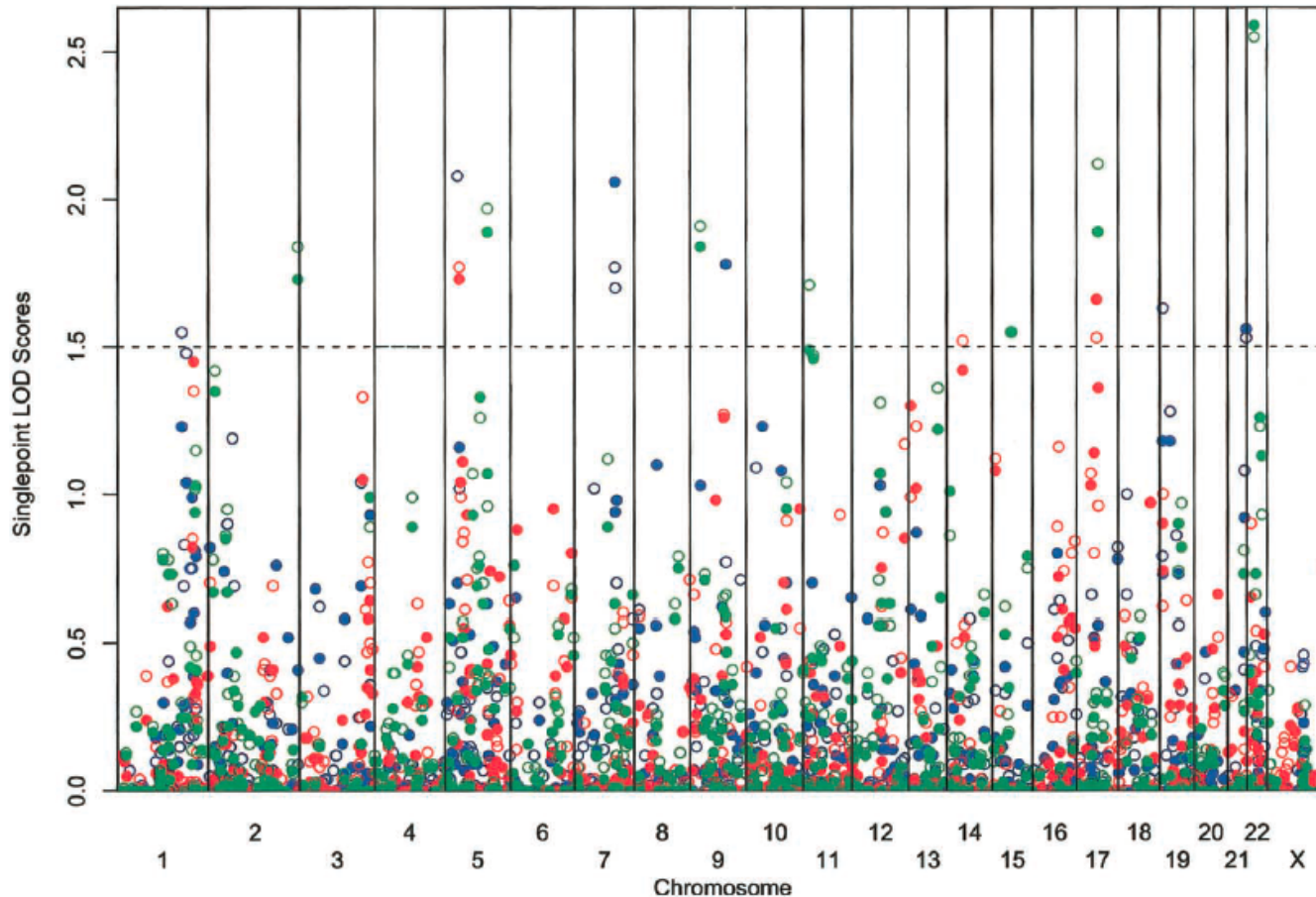
*Multipoint Analysis for
Sibling Pairs*

Biostatistics 666

Example of a Linkage Study

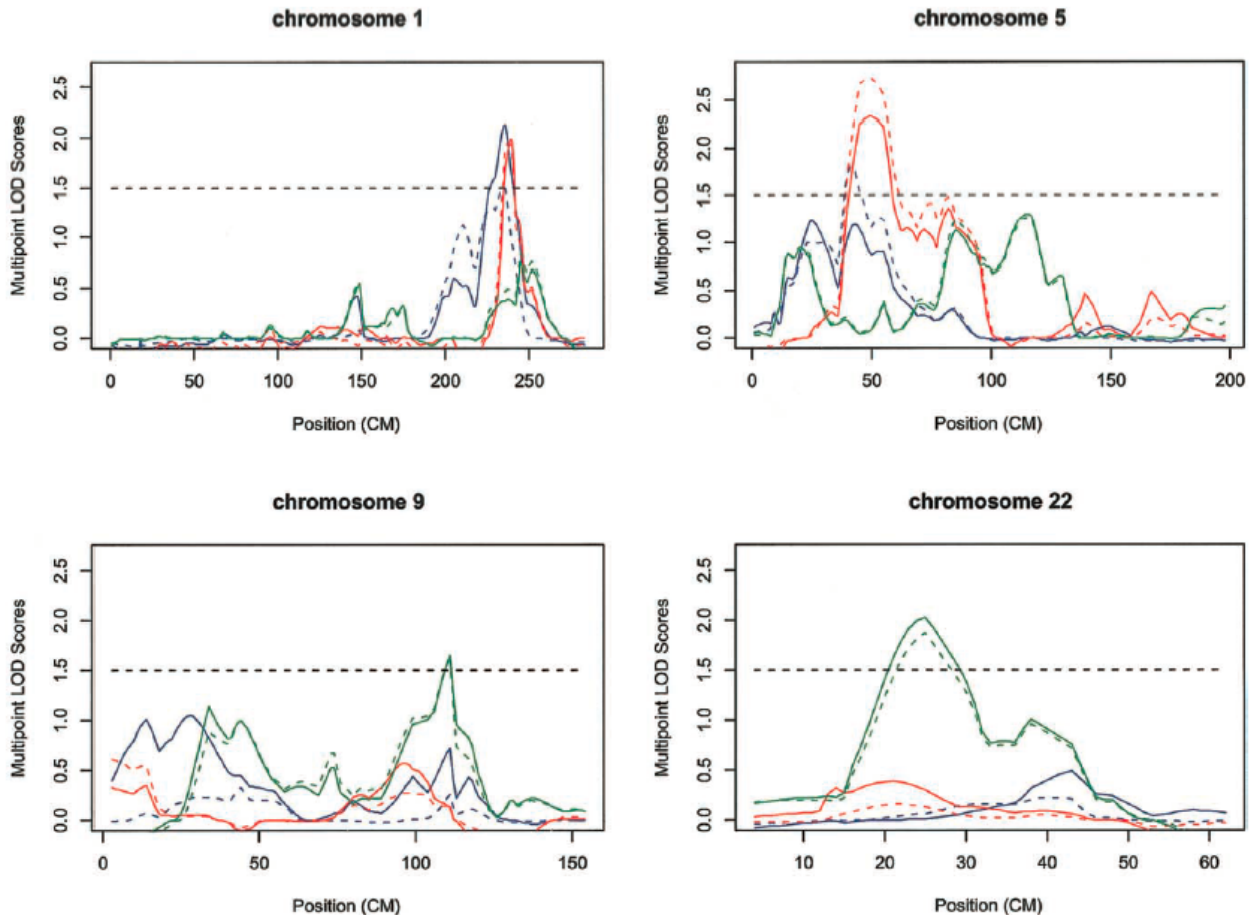
- In the US, age-related macular degeneration (AMD) is the most common cause of blindness in the elderly.
- Disease is heterogeneous, with two common forms of severe disease, termed “wet” and “dry” disease.
- Linkage study examined 734 genetic markers (~1 per 5Mb) in 412 affected relative pairs.
- Evidence for linkage to several regions, including chr1 (~240 cM) and chr22 (~25 cM). We now know these correspond to CFH and TIMP3 susceptibility alleles.
- American Journal of Human Genetics (2004) **74**:482-494

AMD Linkage Study, Results of Marker by Marker Analysis



Colors: All AMD, "Wet" Subtype, "Dry" Subtype

AMD Linkage Study, Results of Multipoint Analysis



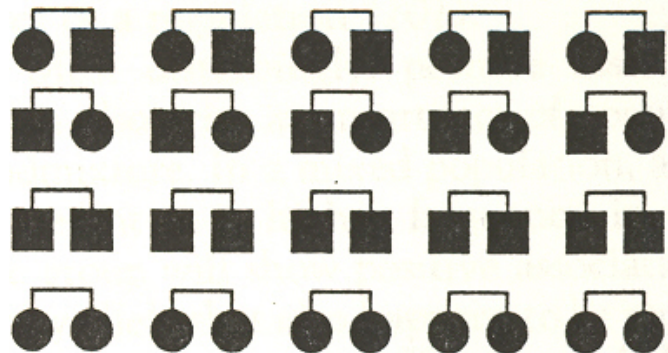
Colors: All AMD, “Wet” Subtype, “Dry” Subtype

Previously ...

- Linkage analysis with sibling pairs
- Risch's Maximum LOD Score approach
- Holman's Possible Triangle Constraint
- Distribution of IBD in affected sibling pairs

Affected Sib Pair Linkage Tests

- Consider affected sibling pairs
 - Pairs selected to have similar phenotypes ...
 - ... show increased similarity at loci that change disease risk
- Scan the genome and test whether pair genotypes are more similar than expected ...



Likelihood for a Single ASP

$$L_i = \sum_{j=0}^2 P(IBD = j | ASP) P(Genotypes | IBD = j) = \sum_{j=0}^2 z_j w_{ij}$$

Risch (1990) defines

$$w_{ij} = P(Genotypes_i | IBD = j)$$

We only need proportionate w_{ij}

w_{ij} for single marker analyses

Relative		IBD		
I	II	0	1	2
(a,b)	(c,d)	$4p_a p_b p_c p_d$	0	0
(a,a)	(b,c)	$2p_a^2 p_b p_c$	0	0
(a,a)	(b,b)	$p_a^2 p_b^2$	0	0
(a,b)	(a,c)	$4p_a^2 p_b p_c$	$p_a p_b p_c$	0
(a,a)	(a,b)	$2p_a^3 p_b$	$p_a^2 p_b$	0
(a,b)	(a,b)	$4p_a^2 p_b^2$	$(p_a p_b^2 + p_a^2 p_b)$	$2p_a p_b$
(a,a)	(a,a)	p_a^4	p_a^3	p_a^2
Prior Probability		$1/4$	$1/2$	$1/4$

These probabilities apply to pair of individuals, when no other genotypes in the family are known.

MLS Linkage Test

$$L(z_0, z_1, z_2) = \prod_i \sum_j z_j w_{ij}$$

$$LOD = \log_{10} \prod_i \frac{z_0 w_{i0} + z_1 w_{i1} + z_2 w_{i2}}{\frac{1}{4} w_{i0} + \frac{1}{2} w_{i1} + \frac{1}{4} w_{i2}}$$

The MLS statistic is the LOD evaluated at the MLEs of z_0, z_1, z_2

These MLEs can be calculated using an EM algorithm

P(Affected Pair|IBD=j)

$$\bullet P(\text{affected pair}|IBD = 0) = (p^2 f_{11} + 2p(1-p)f_{12} + (1-p)^2 f_{22})^2 = K^2$$

$$P(\text{affected pair}|IBD = 1) = p^3 f_{11}^2 + 2p^2(1-p)f_{11}f_{12} + p(1-p)f_{12}^2 + 2p(1-p)^2 f_{12}f_{22} + (1-p)^3 f_{22}^2 = \lambda_o K^2$$

$$P(\text{affected pair}|IBD = 2) = p^2 f_{11}^2 + 2p(1-p)f_{12}^2 + (1-p)^2 f_{22}^2 = \lambda_{MZ} K^2$$

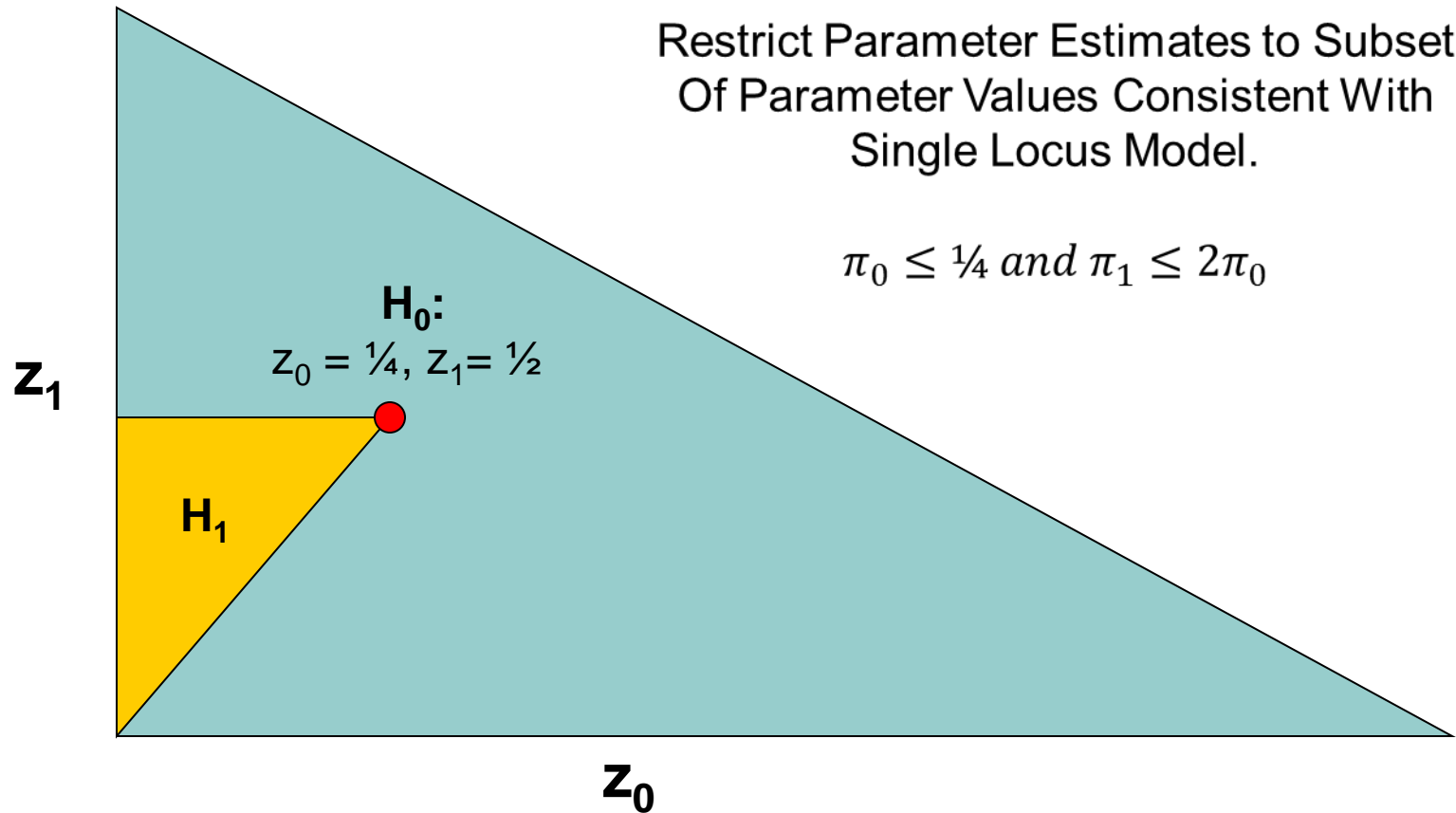
P(Affected Sibling Pair), P(IBD = j | Affected Sibling Pair)

- $P(ASP) = \sum P(IBD = j)P(ASP|IBD = j)$
● $= (\frac{1}{4} + \frac{1}{2}\lambda_0 + \frac{1}{4}\lambda_{MZ})K^2$
- $P(IBD = j|ASP) = \frac{P(IBD=j)P(ASP|IBD=j)}{P(ASP)}$
- $P(IBD = 0|ASP) = 0.25 \frac{1}{\lambda_{sib}}$
- $P(IBD = 1|ASP) = 0.50 \frac{\lambda_0}{\lambda_{sib}}$
- $P(IBD = 2|ASP) = 0.25 \frac{\lambda_{MZ}}{\lambda_{sib}}$
- $1 \leq \lambda_0 \leq \lambda_{sib} \leq \lambda_{MZ}$

Possible Triangle Constraint

Restrict Parameter Estimates to Subset
Of Parameter Values Consistent With
Single Locus Model.

$$\pi_0 \leq \frac{1}{4} \text{ and } \pi_1 \leq 2\pi_0$$



Important Limitation

- A major limitation of our approach so far is that it considers one marker at a time
- This may not allow us to extract all available information about IBD...

Today ...

- Refresher on IBD probabilities
- Intuition behind multipoint calculations
- Framework for multipoint calculations
- Using a Markov Chain to speed analyses

IBD Probabilities

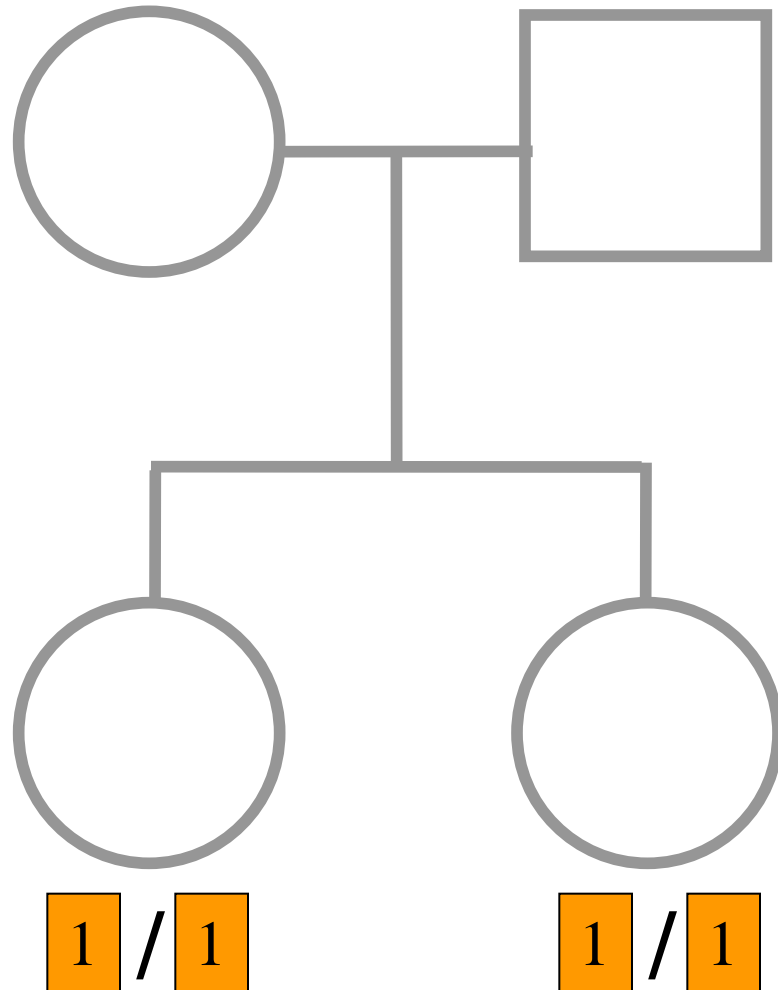
- Number of alleles identical by descent
- For sibling pairs, must be:
 - 0
 - 1
 - 2
- Often, remains ambiguous given genotype

Refresher ...

Bayes Theorem for IBD Probabilities

$$\begin{aligned}P(IBD = i | X) &= \frac{P(IBD = i, X)}{P(X)} \\&= \frac{P(IBD = i)P(X | IBD = i)}{P(X)} \\&= \frac{P(IBD = i)P(X | IBD = i)}{\sum_j P(IBD = j)P(X | IBD = j)}\end{aligned}$$

Worked Example



$$p_1 = 0.5$$

$$P(X | IBD = 0) = p_1^4 = \frac{1}{16}$$

$$P(X | IBD = 1) = p_1^3 = \frac{1}{8}$$

$$P(X | IBD = 2) = p_1^2 = \frac{1}{4}$$

$$P(X) = \frac{1}{4} p_1^4 + \frac{1}{2} p_1^3 + \frac{1}{4} p_1^2 = \frac{9}{64}$$

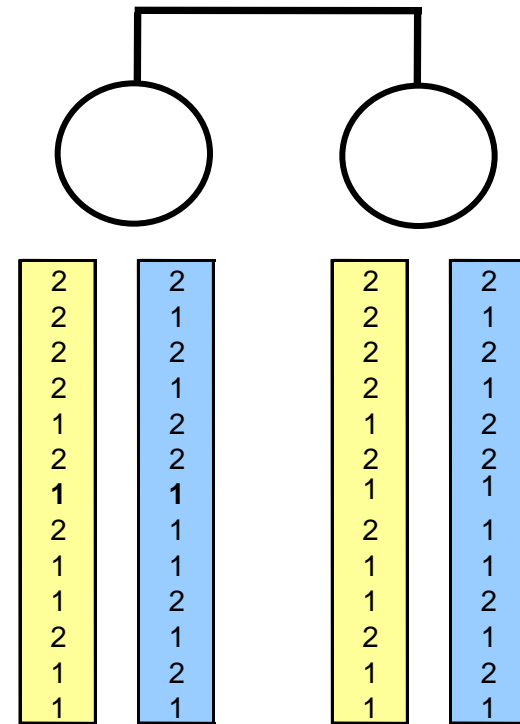
$$P(IBD = 0 | X) = \frac{\frac{1}{4} p_1^4}{P(X)} = \frac{1}{9}$$

$$P(IBD = 1 | X) = \frac{\frac{1}{2} p_1^3}{P(X)} = \frac{4}{9}$$

$$P(IBD = 2 | X) = \frac{\frac{1}{4} p_1^2}{P(X)} = \frac{4}{9}$$

Intuition For Multipoint Analysis

- IBD changes infrequently along the chromosome
- Neighboring markers can help resolve ambiguities about IBD sharing
- In the Risch approach, they might ensure that only one w is *effectively* non-zero



Ingredients for Multipoint Model

- Probability of observed genotypes at each marker conditional on IBD state
- Probability of changes in IBD state along chromosome
- Hidden Markov Model

Ingredients

X_1

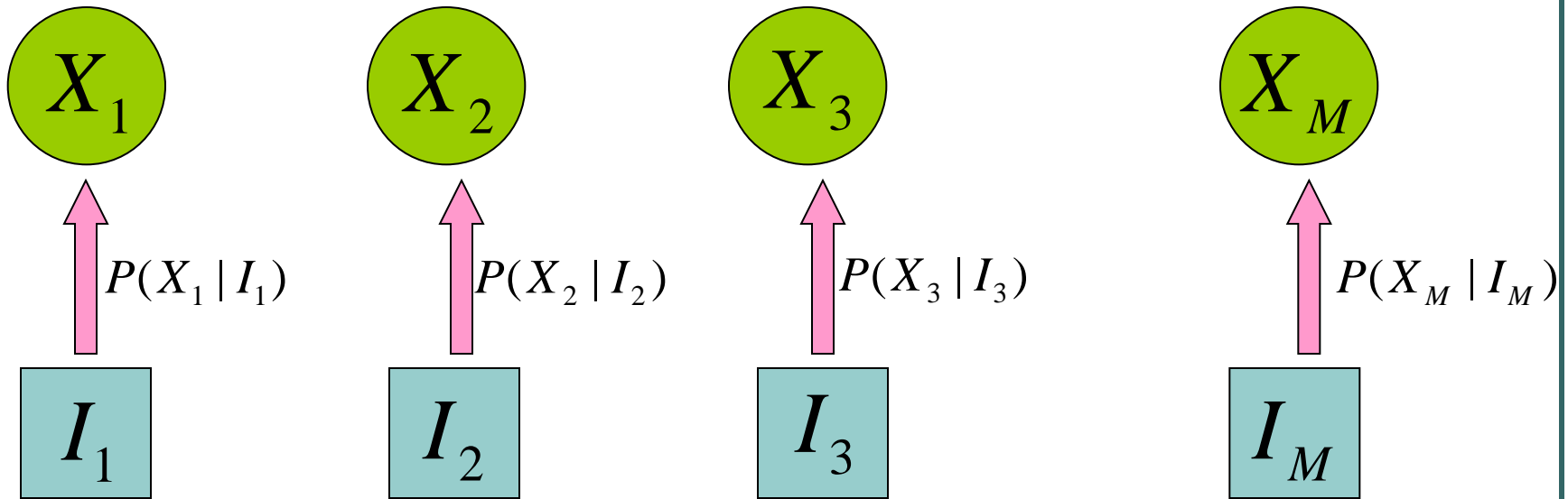
X_2

X_3

X_M

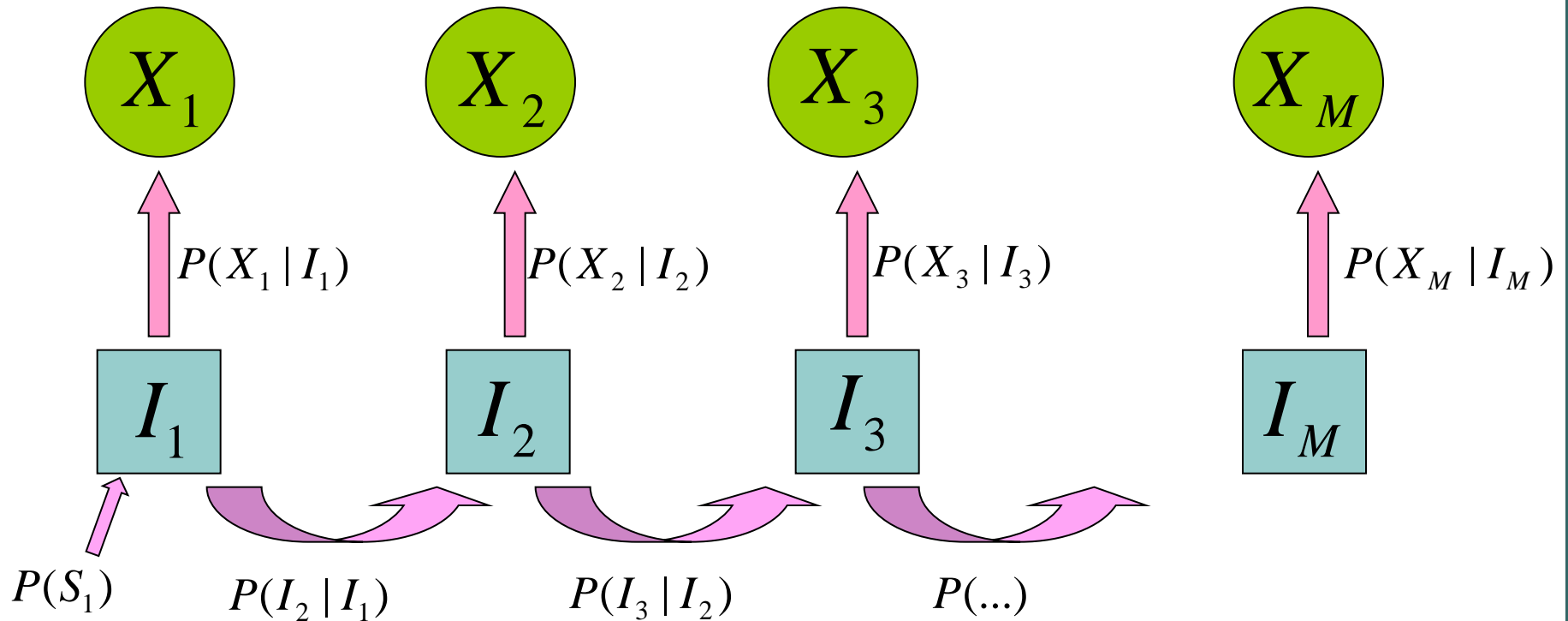
One ingredient will be the observed genotypes at each marker ...

Ingredients



Another ingredient will be the possible IBD states at each marker ...

Ingredients



The final ingredient connects IBD states along the chromosome ...

The Likelihood of Marker Data

$$L = \sum_{I_1} \sum_{I_2} \dots \sum_{I_M} P(I_1) \prod_{i=2}^M P(I_i | I_{i-1}) \prod_{i=1}^M P(X_i | I_i)$$

- General formulation, allows for any number of markers.
- Combined with Bayes' Theorem can estimate probability of each IBD state at any marker.
- This is not a linkage test yet!

$$P(X_m | I_m)$$

Sib	CoSib	IBD		
		0	1	2
(a,b)	(c,d)	$4p_a p_b p_c p_d$	0	0
(a,a)	(b,c)	$2p_a^2 p_b p_c$	0	0
(a,a)	(b,b)	$p_a^2 p_b^2$	0	0
(a,b)	(a,c)	$4p_a^2 p_b p_c$	$p_a p_b p_c$	0
(a,a)	(a,b)	$2p_a^3 p_b$	$p_a^2 p_b$	0
(a,b)	(a,b)	$4p_a^2 p_b^2$	$(p_a p_b^2 + p_a^2 p_b)$	$2p_a p_b$
(a,a)	(a,a)	p_a^4	p_a^3	p_a^2
Prior Probability		$1/4$	$1/2$	$1/4$

Question:

What to do about missing data?

- What happens when some genotype data is unavailable?

$$P(I_{m+1} | I_m)$$

- Depends on recombination fraction θ
 - This is a measure of distance between two loci
 - Probability grand-parental origin of alleles changes between loci
- Leads to probability of a change in IBD:

$$\psi = 2\theta(1 - \theta)$$

$$P(I_{m+1} \mid I_m)$$

		IBD State at m + 1		
		0	1	2
IBD state at marker m	0	$(1-\psi)^2$	$2\psi(1-\psi)$	ψ^2
	1	$\psi(1-\psi)$	$(1-\psi)^2 + \psi^2$	$\psi(1-\psi)$
	2	ψ^2	$2\psi(1-\psi)$	$(1-\psi)^2$

$$\psi = 2\theta(1 - \theta)$$

Example

- Consider two loci separated by $\theta = 0.1$
- Each loci has two alleles, each with frequency .50
- If two siblings are homozygous for the first allele at both loci, what is the probability that $IBD = 2$ at the first locus?

The Likelihood of Marker Data

$$L = \sum_{I_1} \sum_{I_2} \dots \sum_{I_M} P(I_1) \prod_{i=2}^M P(I_i | I_{i-1}) \prod_{i=1}^M P(X_i | I_i)$$

- General, but slow unless there are only a few markers.
- How do we speed things up?

A Markov Model

- Re-organize the computation slightly, to avoid evaluating nested sum directly
- Three components:
 - Probability considering a single location
 - Probability including left flanking markers
 - Probability including right flanking markers
- Scale of computation increases linearly with number of markers

The Likelihood of Marker Data

$$\begin{aligned} L &= \sum_{I_j} P(I_j) P(X_j | I_j) P(X_1 \dots X_{j-1} | I_j) P(X_{j+1} \dots X_M | I_j) \\ &= \sum_{I_j} P(I_j) P(X_j | I_j) L_j(I_j) R_j(I_j) \end{aligned}$$

- A different arrangement of the same likelihood
- The nested summations are now hidden inside the L_j and R_j functions...

Left-Chain Probabilities

$$\begin{aligned} L_m(I_m) &= P(X_1, \dots, X_{m-1} | I_m) \\ &= \sum_{I_{m-1}} L_{m-1}(I_{m-1}) P(X_{m-1} | I_{m-1}) P(I_{m-1} | I_m) \end{aligned}$$

$$L_1(I_1) = 1$$

- Proceed one marker at a time.
- Computation cost increases linearly with number of markers.

Right-Chain Probabilities

$$\begin{aligned} R_m(I_m) &= P(X_{m+1}, \dots, X_M | I_m) \\ &= \sum_{I_{m+1}} R_{m+1}(I_{m+1}) P(X_{m+1} | I_{m+1}) P(I_{m+1} | I_m) \end{aligned}$$

$$R_M(I_M) = 1$$

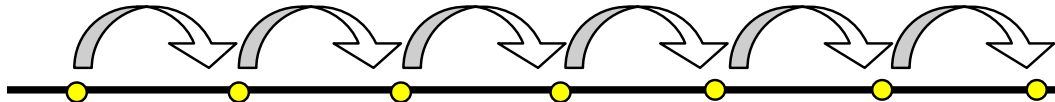
- Proceed one marker at a time.
- Computation cost increases linearly with number of markers.

Pictorial Representation

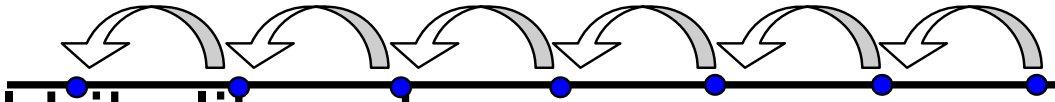
- Single Marker



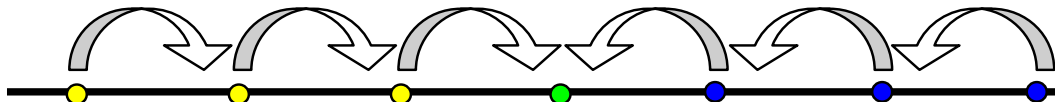
- Left Conditional



- Right Conditional



- Full Likelihood



Extending the MLS Method ...

$$\begin{aligned}w_j &= P(X_j | I_j)P(X_1 \dots X_{j-1} | I_j)P(X_{j+1} \dots X_M | I_j) \\ &= P(X_j | I_j)L_j(I_j)R_j(I_j)\end{aligned}$$

- We just change the definition for the “weights” given to each configuration!

Possible Further Extensions

- Modeling error
 - What components might have to change?
- Modeling other types of relatives
 - What components might have to change?
- Modeling larger pedigrees
 - What components might have to change?

Today

- Efficient computational framework for multipoint analysis of sibling pairs