Variance Component Models for Quantitative Traits

Biostatistics 666

Today

- Analysis of quantitative traits
- Kinship coefficients
  - measure of genetic similarity between two individuals
- Modeling covariance for pairs of individuals
  - estimating heritability
  - estimating locus-specific heritability
- Extending the model to larger pedigrees

Kinship Coefficients

- Summarize genetic similarity between pairs of individuals.

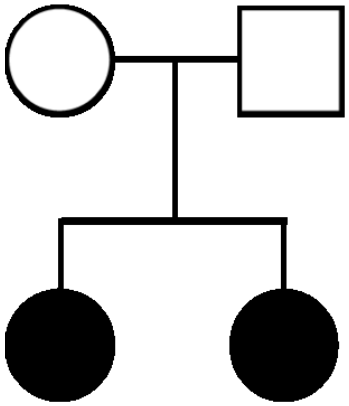
- In a variance components model, they predict the phenotypic similarity between individuals.

Kinship Coefficients – Definition

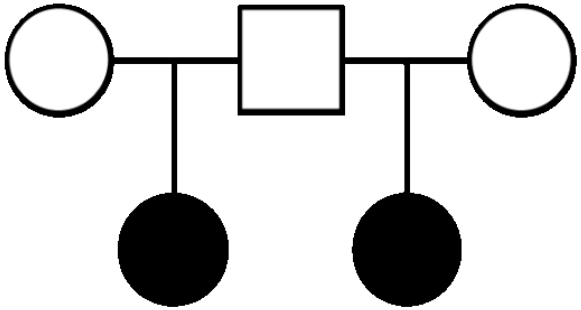
- Given two individuals
  - One with genes (g_i, g_j)
  - The other with genes (g_k, g_l)
- The kinship coefficient is:
  - $\frac{1}{4}P(g_i \equiv g_k) + \frac{1}{4}P(g_i \equiv g_l) + \frac{1}{4}P(g_j \equiv g_k) + \frac{1}{4}P(g_j \equiv g_l)$
  - where "$\equiv$" represents identity by descent (IBD)
- Probability that alleles sampled at random from each individual are (IBD)

Some kinship coefficients

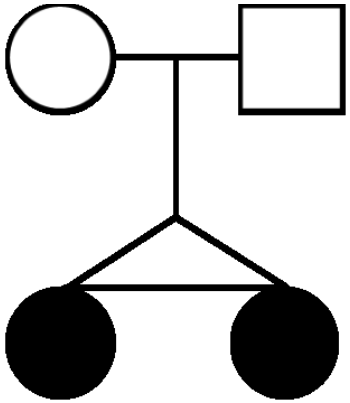
Siblings (φ=1/4)



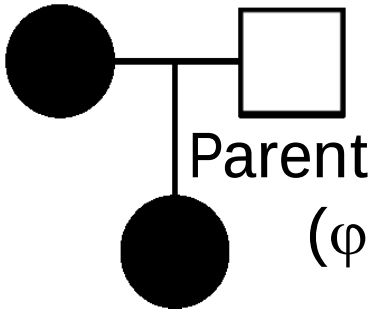
Half-Sibs (φ=1/8)



MZ Twins (φ=1/2)



Unrelated (φ=0)



Parent-Offspring (φ=1/4)

What about other relatives?

- For any two related individuals i and j …
- … use a recursive algorithm allows calculation of kinship coefficient
- Algorithm requires an order for individuals in the pedigree where ancestors precede descendants
  - That is where for any *i*>*j*, *i* is not ancestor of *j*
  - Such an order always exists!

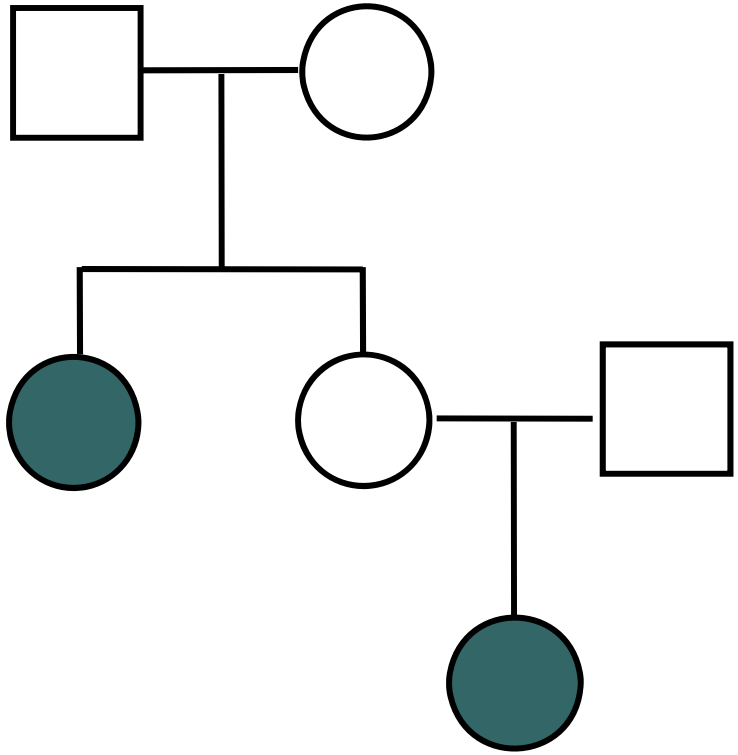
Computing Kinship Coefficients

- The recursive definition is then (for i ≥ j):

$$\varphi_{ij} = \begin{cases} 0 & i \text{ and } j \text{ are founders} \\ \frac{1}{2} & i = j, i \text{ is a founder} \\ \frac{1}{2}(\varphi_{mother(i)\,j} + \varphi_{father(i)\,j}) & i \neq j \\ \frac{1}{2}(1 + \varphi_{mother(i)\,father(i)}) & i = j \end{cases}$$

An example pedigree...

- Can you find …
- Suitable ordering for recursive calculation?
- Calculate kinship coefficient between shaded individuals?



So far ...

- Summarize genetic similarity between any two individuals …
- Next, we will proceed to build a simple model for their phenotypes

Simplest Data Structure

- Pairs of related individuals
  - Siblings (or twins!)
  - Parent-Offspring
- Corresponding phenotype measurements
  - $\mathbf{y} = (y_1, y_2)'$

Elements for a simple model …

- If the trait is normally distributed …
- Model mean and variance for $\mathbf{y_1}$ and $\mathbf{y_2}$
  - Mean and variance could be assumed equal …
  - … or they could depend on some covariates
- But we are also interested in covariance between the two …

Variance-Covariance Matrix

$$\Omega = \begin{bmatrix} V(y_1) & Cov(y_1, y_2) \\ Cov(y_1, y_2) & V(y_2) \end{bmatrix}$$

Model must describe not only variance of each observation but also covariance for pairs of observations

Bivariate density function

- Normal density function

$$L(y) = \frac{1}{\sqrt{2\pi}} \sigma^{-1} e^{-\frac{1}{2}(y-\mu)^2/\sigma^2}$$

- Bivariate normal density function

$$L(\mathbf{y}) = \frac{1}{2\pi} |\Omega|^{-1/2} \, e^{-\frac{1}{2}(\mathbf{y}-\boldsymbol{\mu})'\Omega^{-1}(\mathbf{y}-\boldsymbol{\mu})}$$

- Extends univariate density function

Intuition on Normal Densities

$$L(y) = (2\pi)^{-1/2}\sigma^{-1}e^{-1/2(y-\mu)^2/\sigma^2}$$

Scaling parameter, penalizes settings with large variances

Distance between observation and its expected value

Bivariate Normal Densities

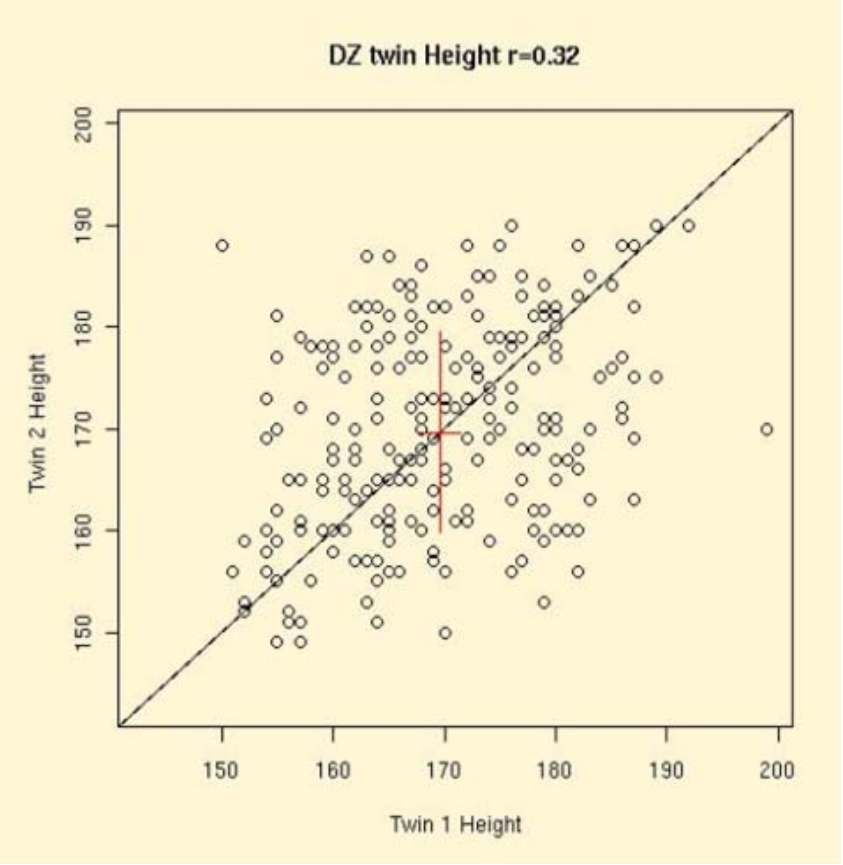
$$L(\mathbf{y}) = (2\pi)^{-1} |\boldsymbol{\Omega}|^{-\frac{1}{2}} e^{-\frac{1}{2}(\mathbf{y}-\boldsymbol{\mu})'\boldsymbol{\Omega}^{-1}(\mathbf{y}-\boldsymbol{\mu})}$$

Scaling parameter, penalizes settings with large variances

Distance between observation and its expected value

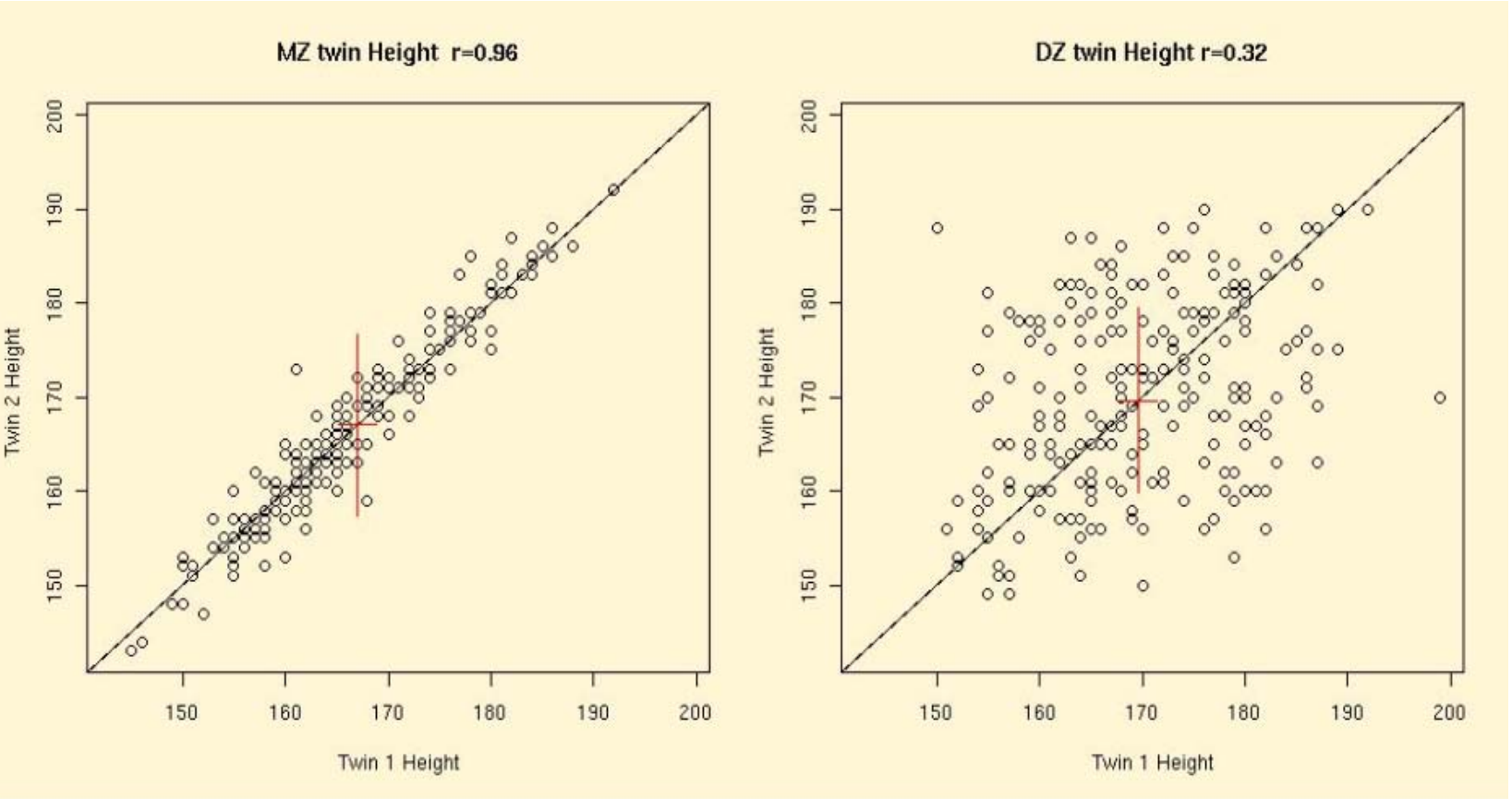
Possible Application…

In a sample of twin or sibling pairs, we could use all the data to estimate means, variances and even covariances…



(Data from David Duffy)

Height in DZ and MZ twins



(How would you interpret these data from David Duffy?)

Incorporating Kinship Coefficients

- If genes influence trait …
- Covariance will differ for each class of relative pair
- Instead of estimating covariance for each relationship, …
- Impose genetic model that incorporates kinship and relates covariance between different classes of relative pair

A Simple Model for the Variance-Covariance Matrix

$$\Omega = \begin{bmatrix} \sigma_g^2 + \sigma_e^2 & 2\varphi\sigma_g^2 \\ 2\varphi\sigma_g^2 & \sigma_g^2 + \sigma_e^2 \end{bmatrix}$$

Where,

φ is the kinship coefficient for the two individuals

Example...

	N	r
MZ males	292	.80
MZ females	380	.80
DZ males	179	.47
DZ females	184	.55
DZ male-female	284	.41

(Reading ability scores from Eaves et al., 1997)

Interpretation…

- Fitting a maximum likelihood model…
  - Eaves et. al estimated
    - $\sigma_g^2 = .81$
    - $\sigma_e^2 = .19$
  - Found no evidence for sex differences
  - Saturated model did not improve fit

So far ...

- Model allows us to estimate the genetic contribution to the variation in any trait
- Incorporates different relative pairs …
- But it doesn't always fit…
  - Fortunately, the model can be easily refined

Another Example...

	N	r
MZ males	271	.56
MZ females	353	.52
DZ males	167	.33
DZ females	165	.45
DZ male-female	260	.41

(Psychomotor retardation scores from Eaves et al., 1997)

Refined Matrix

$$\Omega = \begin{bmatrix} \sigma_g^2 + \sigma_c^2 + \sigma_e^2 & 2\varphi\sigma_g^2 + \sigma_c^2 \\ 2\varphi\sigma_g^2 + \sigma_c^2 & \sigma_g^2 + \sigma_c^2 + \sigma_e^2 \end{bmatrix}$$

Where,

φ **is the kinship coefficient for the two individuals**

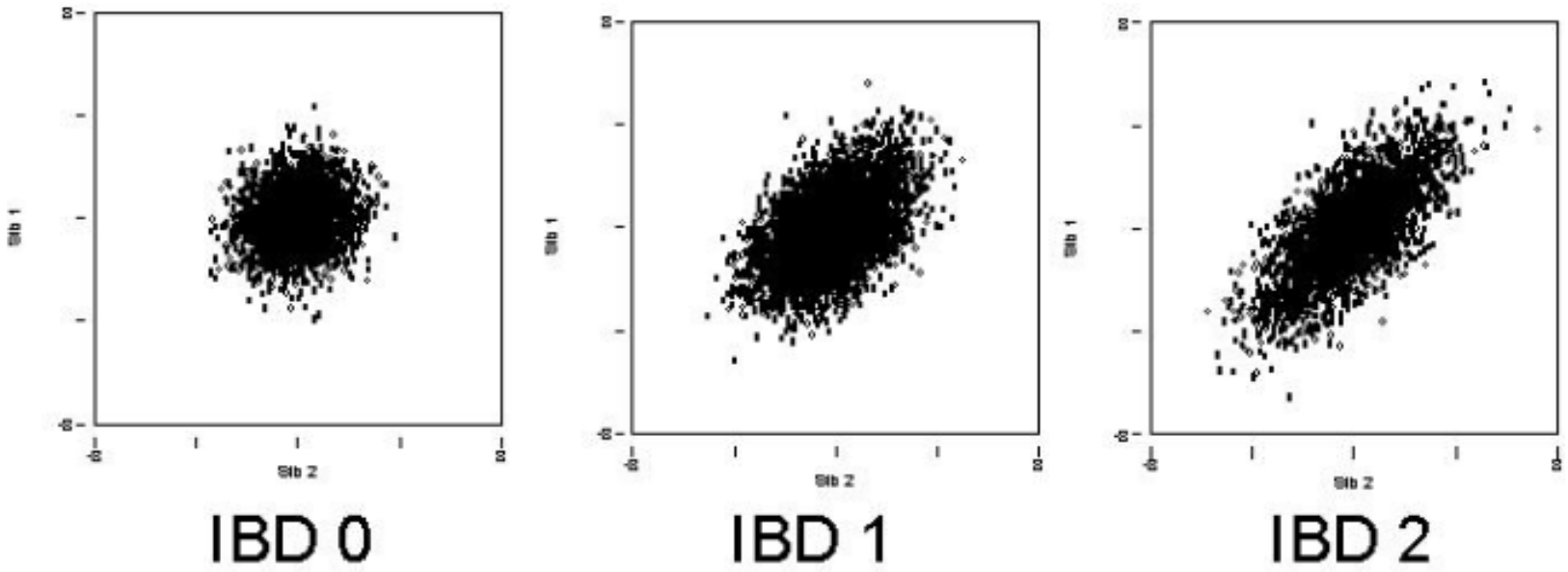
Interpretation…

- Fitting a maximum likelihood model…
  - Eaves et. al estimated (for males)
    - $\sigma_g^2 = .29$
    - $\sigma_c^2 = .24$
    - $\sigma_e^2 = .46$
  - Additive genetic effects could not explain similarities. Any idea why?

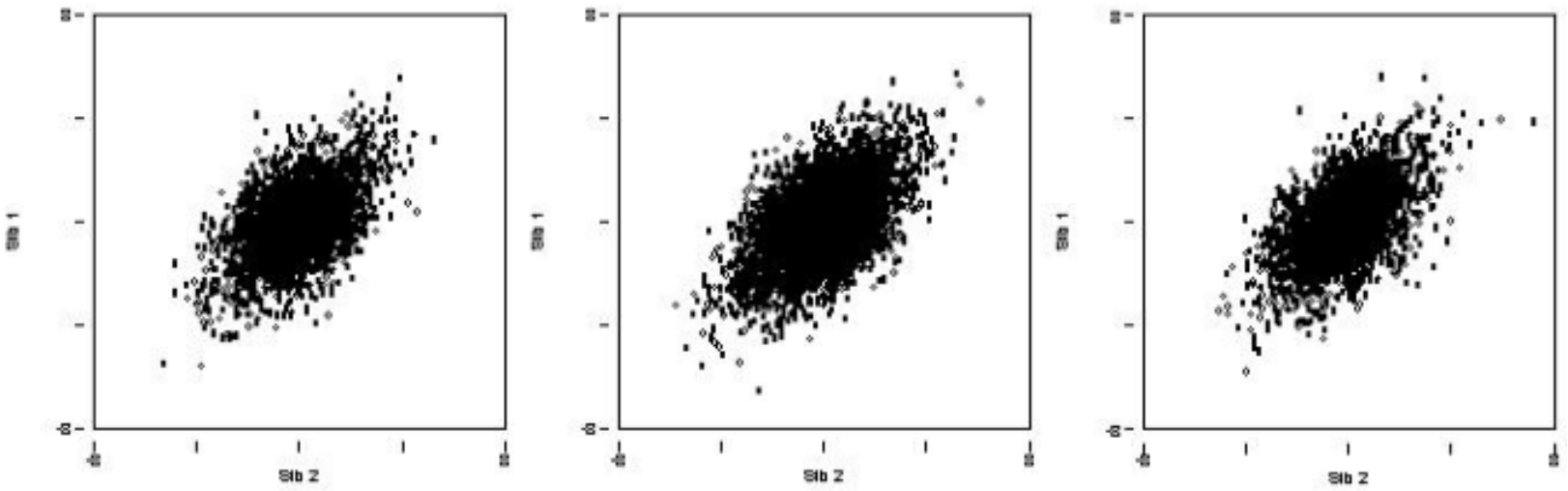
Incorporating IBD Coefficients

- Covariance might differ according to sharing at a particular locus
  - If locus contains genes that influence the trait
- Again, impose a genetic model and estimate model parameters

Linkage



No Linkage



IBD 0 IBD 1 IBD 2

Relationship to IBD probabilities

- For non-inbred pair of relatives, marker or locus-specific kinship coefficients can be derived from IBD probabilities:

$$\varphi_{marker} = \tfrac{1}{4} P(IBD_{marker} = 1) + \tfrac{1}{2} P(IBD_{marker} = 2)$$

Variance-Covariance Matrix

$$\Omega = \begin{bmatrix} \sigma_a^2 + \sigma_g^2 + \sigma_e^2 & 2\varphi_{marker}\sigma_a^2 + 2\varphi\sigma_g^2 \\ 2\varphi_{marker}\sigma_a^2 + 2\varphi\sigma_g^2 & \sigma_a^2 + \sigma_g^2 + \sigma_e^2 \end{bmatrix}$$

Where,

φ is the kinship coefficient for the two individuals

φ_{marker} depends on the number of alleles shared IBD

Likelihood function, Incorporating Uncertain IBD

$$L = \prod_i \sum_{j=0,1,2} Z_{ij} (2\pi)^{-1} |\Omega_{IBD=j}|^{-\frac{1}{2}} e^{-\frac{1}{2}(\mathbf{y}-\boldsymbol{\mu})' \Omega_{IBD=j}^{-1} (\mathbf{y}-\boldsymbol{\mu})}$$

$$\approx \prod_i (2\pi)^{-1} |\Omega^*|^{-\frac{1}{2}} e^{-\frac{1}{2}(\mathbf{y}-\boldsymbol{\mu})' \Omega^{*-1} (\mathbf{y}-\boldsymbol{\mu})}$$

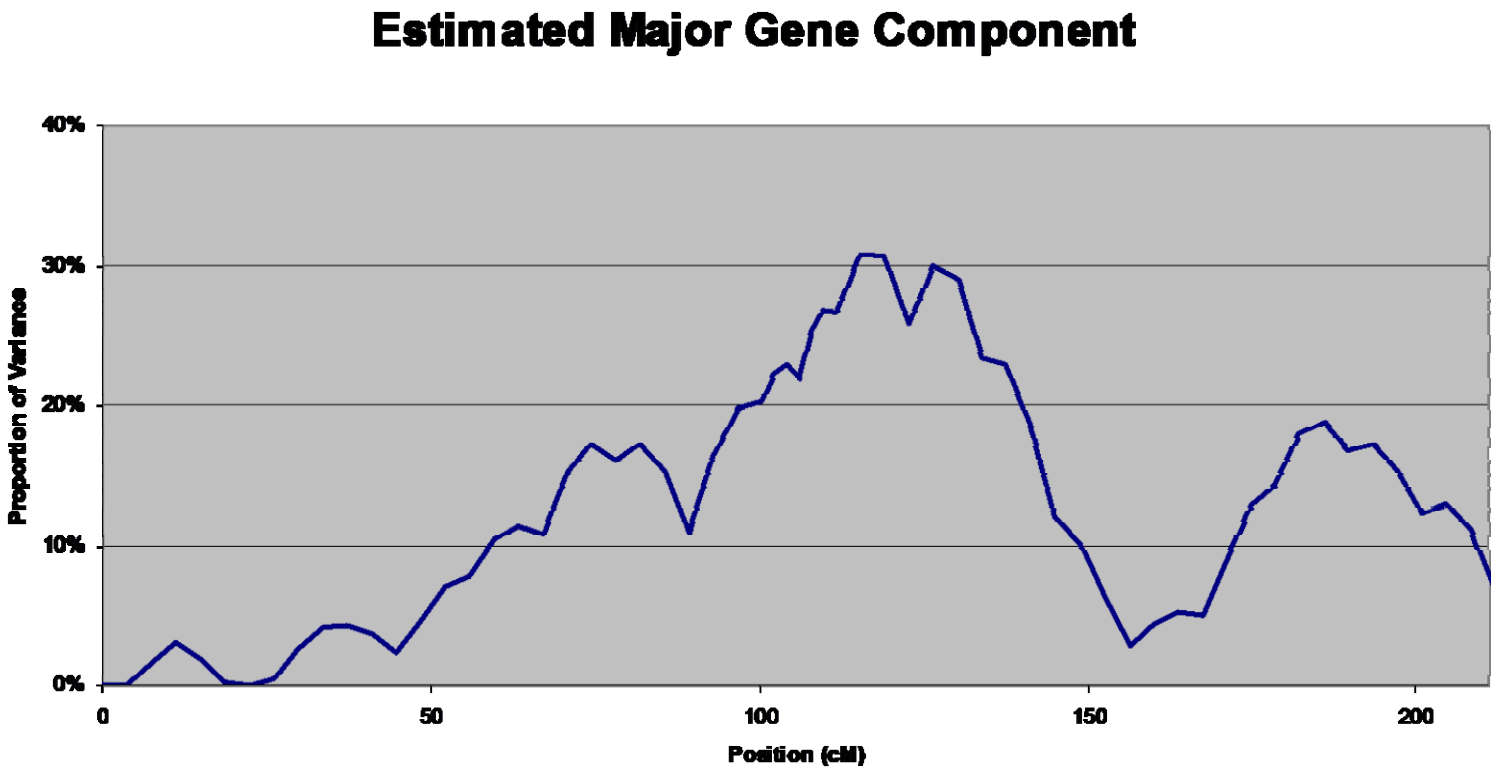
$Z_{ij} = P(IBD_i = j \mid \text{marker data})$ IBD sharing probabilities

$\Omega^* = \sum_{j=0,1,2} Z_{ij} \Omega_{IBD=j}$ "Expected" Ω

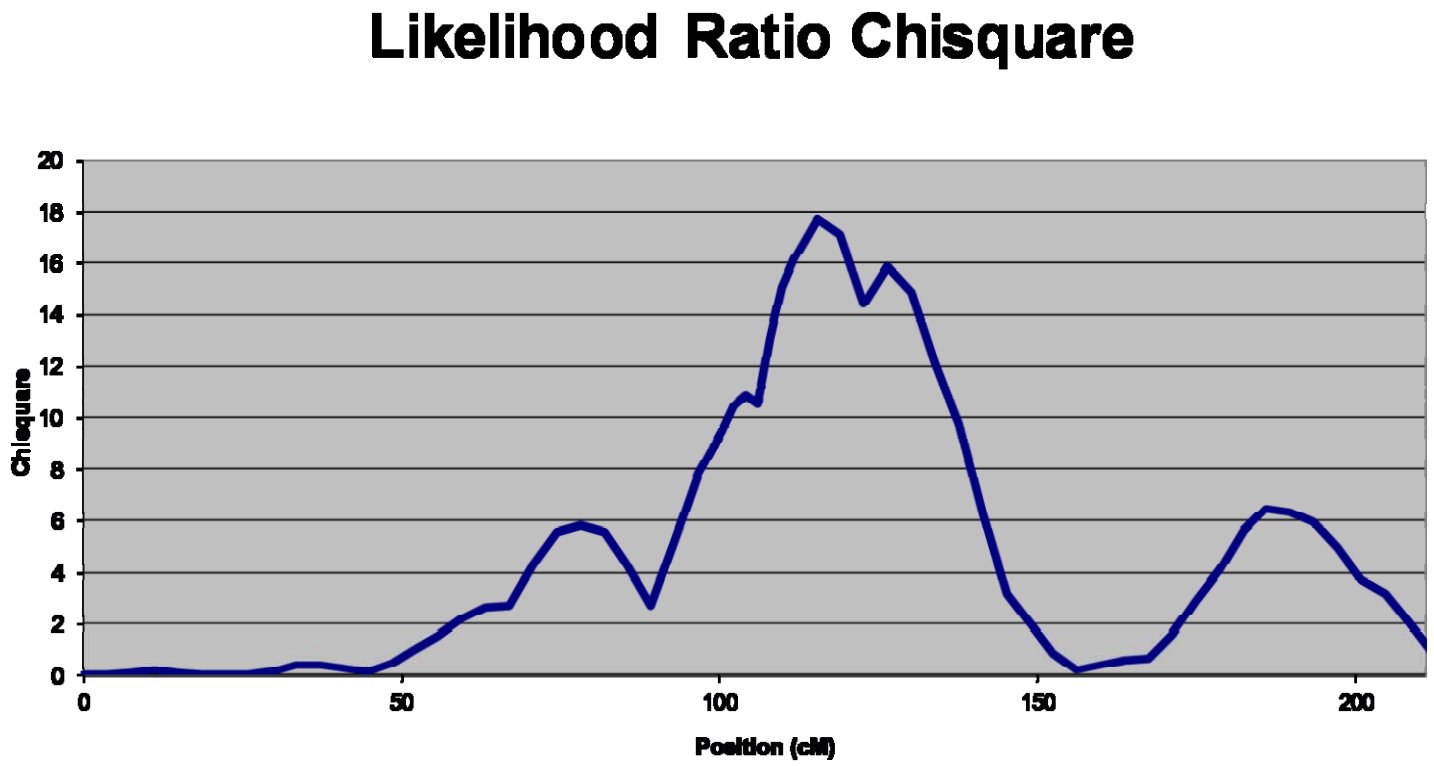
How it works …

- To find linkage to a particular trait…
- Collect sibling pair sample
- Calculate IBD for multiple points along genome
- Model covariance as a function of IBD sharing at each point

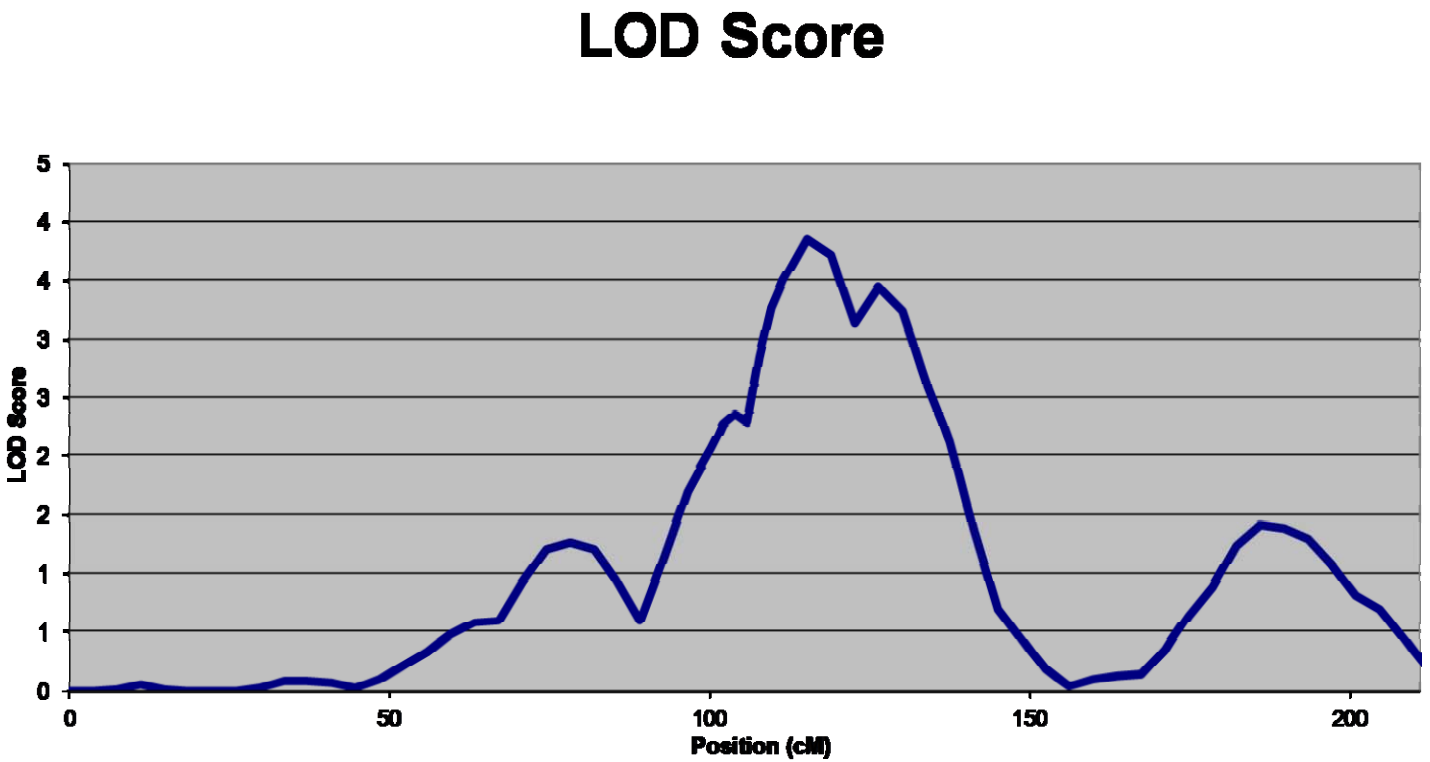
Example...


Estimated Major Gene Component
40%
30%
20%
10%
0%
Proportion of Variance
0
50
100
150
200
Position (cM)

Example...


Likelihood Ratio Chisquare
Chisquare
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
Position (cM)

Example...



So far ...

- Models for similarity between relative pairs
- Kinship coefficient used to estimate overall genetic effect
- Locus-specific coefficients used to detect genetic linkage

Extensions ...

- The model extends gracefully to other settings:
- For larger pedigrees, we extend the covariance matrix
- To model genetic association, we model specific means for each individual

Larger Pedigrees...

$$\Omega_{jk} = \begin{cases} \sigma_a^2 + \sigma_g^2 + \sigma_e^2 & \text{if } j = k \\ 2\varphi_{marker}\sigma_a^2 + 2\varphi\sigma_g^2 & \text{if } j \neq k \end{cases}$$

Where,

φ is the kinship coefficient for the two individuals

φ_{marker} depends on the number of alleles shared IBD

j and k index different individuals in the family

Multivariate density function

- Normal density function

$$L(y) = (2\pi)^{-½}\sigma^{-1}e^{-½(y-\mu)^2/\sigma^2}$$

- Multivariate normal density function

$$L(\mathbf{y}) = 2\pi^{-n/2}\,|\,\Omega\,|^{-½}\;e^{-½(\mathbf{y}-\boldsymbol{\mu})'\Omega^{-1}(\mathbf{y}-\boldsymbol{\mu})}$$

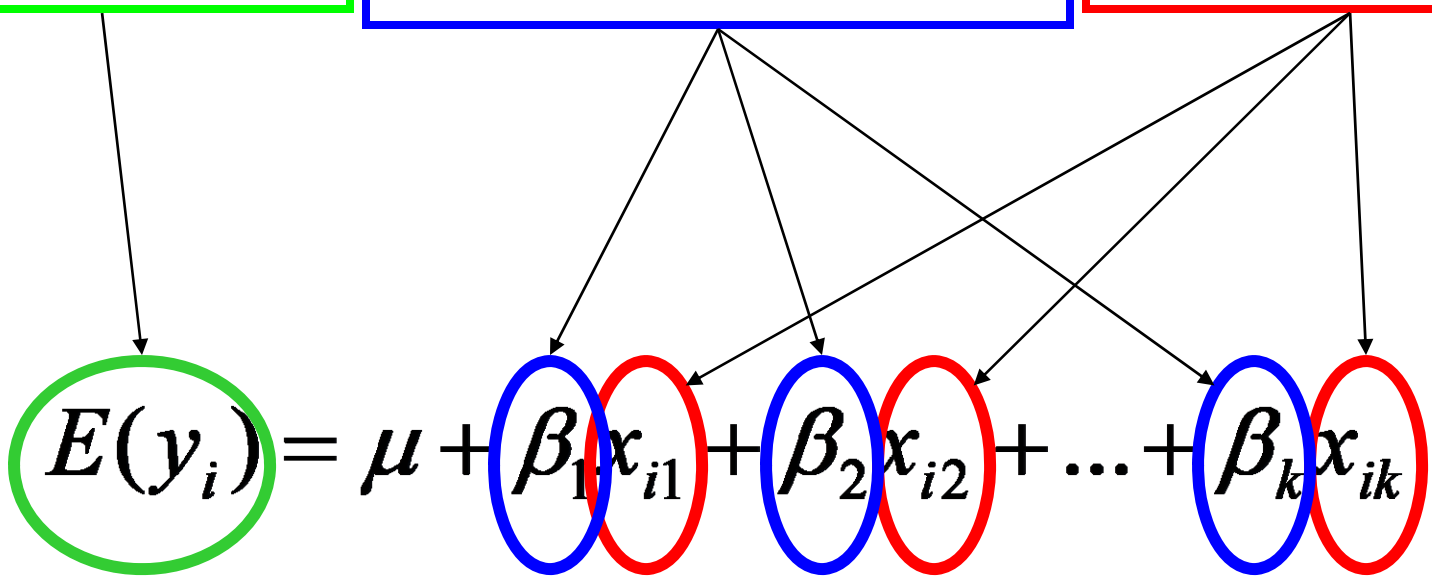
- Extends univariate density function

Means Model

Expected Phenotype for Individual i (e.g. expected weight)

Estimated effects for covariates (e.g. expected weight increases 1kg/year with age)

Measured Covariates for Individual i (e.g. age, sex, …)



$$E(y_i) = \mu + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik}$$

In addition to modeling variances and covariances, we can model the means

Simple Association Model

- Each copy of allele changes trait by a fixed amount
  - Include covariate counting copies for allele of interest
- Evidence for association when a $\neq 0$

$$E(y_i) = \mu + a*[\text{number of copies of mutant allele}]$$

$$E(y_i) = \mu + \beta_X X_i$$

X is the number of copies for allele of interest.
β_x is the estimated effect of each copy (the additive genetic value).

Today

- Analysis of quantitative traits
- Kinship coefficients
  - Measure of genetic similarity between two individuals
- Modeling covariance for pairs of individuals
  - estimating heritability
  - estimating locus-specific heritability
- Extending the model to larger pedigrees

Useful References

- Amos (1994)

  Am J Hum Genet **54:**535-543

- Hopper and Matthews (1982)

  Ann Hum Genet **46**:373–383

- Lange and Boehnke (1983)

  Am J Med Genet **14**:513-24