Scope for estimation of variances due to sex-linked, maternal and dominance effects in mixed model analyses

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Outline

Introduction

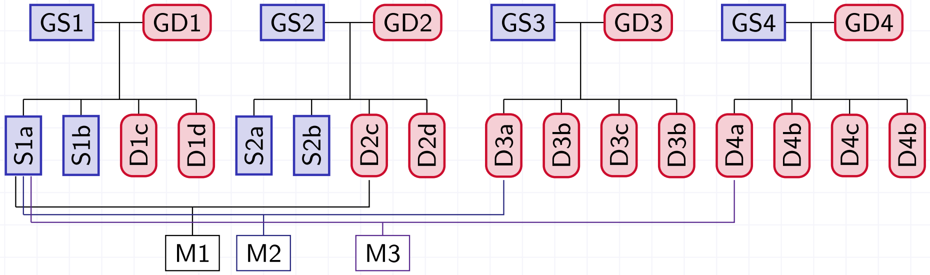
- Recent paper on sexual dimorphism & X-linked variation
  - Extended model with autosomal, sex-linked, dominance & maternal effects
  - New experimental design proposed
    - ⇒ full set of covariances among relatives
  - 'Animal model' analyses advocated
    - ⇒ no application for X-linked effects so far

Objectives

Examine scope for estimation for model & design suggested

Fairbairn D.J. and Roff D.A. (2006)
The quantitative genetics of sexual dimorphism : assessing the importance of sex-linkage. Heredity 97:319–328.

Experimental design



- Generate many types of relatives
- 3 generations
  - Generation 1: 4 unrelated pairs ⇒ 4 offspring/pair
    - ⇒ pairs 1 & 2: 1 ♂, 2 ♀; pairs 3 & 4: 4 ♀
  - Generation 2: 4 sires ⇒ each mated to 3 unrelated dams
  - Generation 3: 12 families
    - ⇒ Paternal half-sibs, full-sibs, single & double first cousins

Model

- Standard linear mixed model

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\left(\mathbf{a} + \mathbf{s} + \mathbf{da} + \mathbf{ds}\right) + \mathbf{W}\left(\mathbf{m} + \mathbf{c}\right) + \mathbf{e}$$

Term	Design M.	Variance	Effect
$\mathbf{y}$		$\mathbf{V}$	observations
β	$\mathbf{X}$	–	fixed
$\mathbf{a}$	$\mathbf{Z}$	$\sigma^2_A\mathbf{A}$	additive genetic; autosomal
$\mathbf{s}$	$\mathbf{Z}$	$\sigma^2_S\mathbf{S}$	additive genetic; sex-linked
$\mathbf{da}$	$\mathbf{Z}$	$\sigma^2_{DA}\mathbf{D_A}$	dominance; autosomal
$\mathbf{ds}$	$\mathbf{Z}$	$\sigma^2_{DS}\mathbf{D_S}$	dominance; sex-linked
$\mathbf{m}$	$\mathbf{W}$	$\sigma^2_M\mathbf{A}$	maternal genetic; autosomal
$\mathbf{c}$	$\mathbf{W}$	$\sigma^2_C\mathbf{I}$	maternal perm. environmental
$\mathbf{e}$	$\mathbf{I}$	$\sigma^2_E\mathbf{I}$	residual

Model (cont.)

- Variance of $\mathbf{y}$
  - allow for $Cov(\mathbf{a},\mathbf{m}') = \sigma_{AM}\mathbf{A}$

$$\mathbf{V} = \mathbf{Z}\left(\sigma^2_A\mathbf{A} + \sigma^2_S\mathbf{S} + \sigma^2_{DA}\mathbf{D_A} + \sigma^2_{DS}\mathbf{D_S}\right)\mathbf{Z}' + \sigma_{AM}\left(\mathbf{ZAW}' + \mathbf{WAZ}'\right) + \mathbf{W}\left(\sigma^2_M\mathbf{A} + \sigma^2_C\mathbf{I}\right)\mathbf{W}' + \sigma^2_E\mathbf{I}$$

➽ 8 (co)variance components to be estimated

Likelihood

- Unrelated families of equal structure: $\mathbf{V} = \mathbf{I} \otimes \mathbf{V}_0$
- No fixed effects
- Likelihood

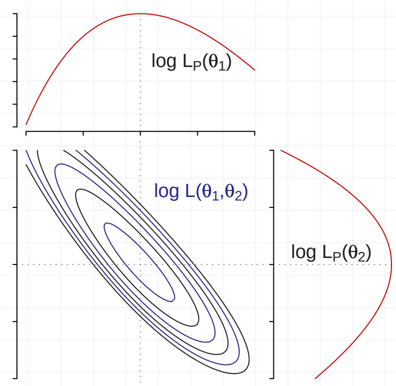
$$\log \mathcal{L} = const. - \frac{d}{2}\left(\log|\mathbf{V}_0| + \text{tr}\left(\mathbf{V}_0^{-1}\mathbf{M}\right)\right)$$

- Hessian matrix

$$\mathbf{H} = -E\left[\frac{\partial^2 \log \mathcal{L}}{\partial\theta_k\partial\theta_m}\right] = \frac{d}{2}\,\text{tr}\left(\mathbf{V}_0^{-1}\frac{\partial\mathbf{V}_0}{\partial\theta_k}\mathbf{V}_0^{-1}\frac{\partial\mathbf{V}_0}{\partial\theta_m}\right)$$

d degrees of freedom
$\mathbf{M}$ Matrix of mean SQ/CP (across families)
θ_k k−th parameter to be estimated

Profile likelihood



- Vector of parameters $\boldsymbol{\theta}$
- Partition into:
  - $\theta_k \Rightarrow$ parameter of interest
  - $\boldsymbol{\theta}_{\neq k} \Rightarrow$ remaining parameters
- Profile likelihood: $\log \mathcal{L}_P\left(\theta_k\right)$
  - maximize $\log \mathcal{L}\left(\boldsymbol{\theta}_{\neq k}|\theta_k = \mathbf{t}\right)$
  - gives likelihood ratio test of $\text{H}_0 : \theta_k = \mathbf{t}$
  - projection of likelihood surface on axis for θ_k
  - curvature (2nd derivatives) preserved

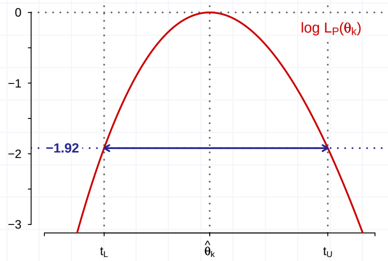
Confidence interval

1. Hessian matrix:
   - Inverse $\mathbf{H}^{-1} = \{h^{km}\}$
     - ➼ asymptotic, lower bound sampling covariances of $\hat{\boldsymbol{\theta}}$
   - Normal approximation: 95% confidence interval for $\hat{\theta}_k$

$$[t_L, t_U] = \left[\hat{\theta}_k - 1.96\sqrt{h^{kk}}, \hat{\theta}_k + 1.96\sqrt{h^{kk}}\right]$$

2. Profile $\log \mathcal{L}$
   - Find values t_L, t_U for

$$\log \mathcal{L}_P - \log \mathcal{L}^m = -\frac{1}{2}\chi^2_{1,95\%} = -1.92$$

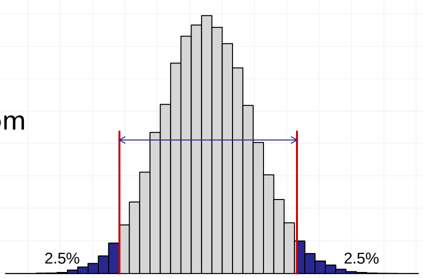


Simulaton study

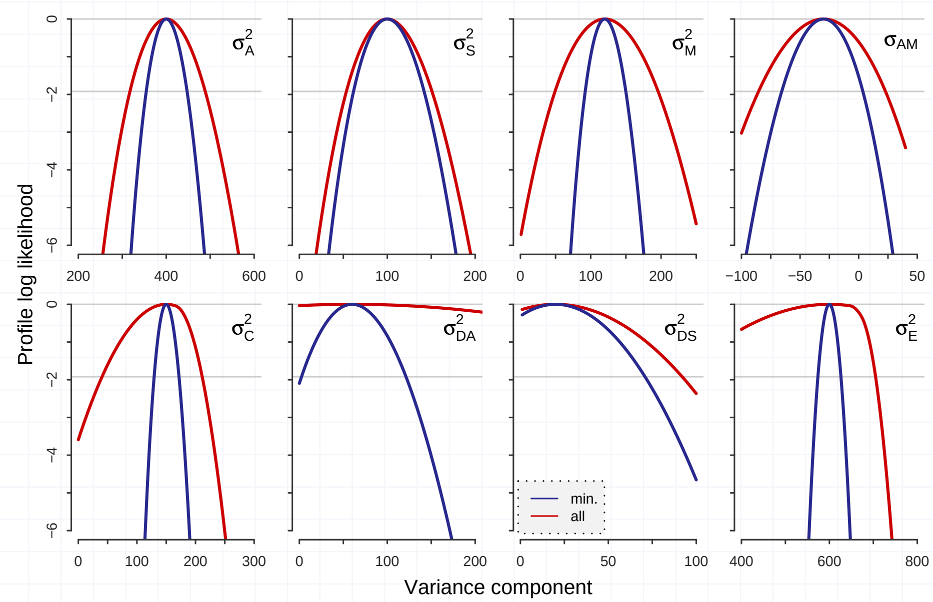
- Design suggested by Fairbairn & Roff (2006)
  - 4 offspring/mating in generation 3 (2 ♂, 2 ♀)
  - 72 records per family + 8 dams w/out records
  - 200 unrelated families ➼ 14 400 records
- Sample **M** from Wishart distribution
- Population values
  - $\sigma^2_A = 400$, $\sigma^2_S = 100$, $\sigma^2_M = 120$, $\sigma_{AM} = -30$, $\sigma^2_C = 150$, $\sigma^2_{DA} = 60$, $\sigma^2_{DS} = 20$ and $\sigma^2_E = 600$.
- Consider full model & models with subsets of effects
- 50 000 replicates per analysis
- REML estimation using Method of Scoring

Simulaton study (cont.)

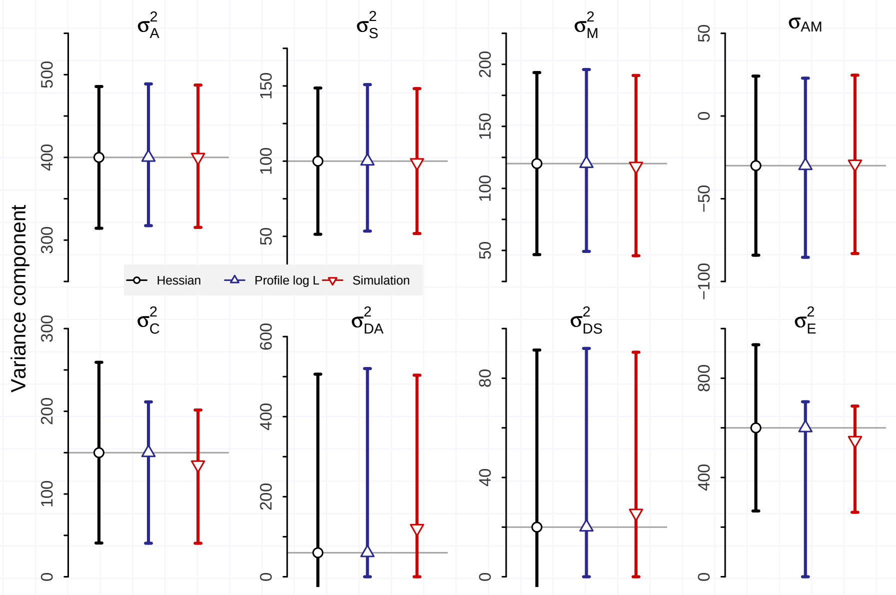
- Constrain parameters
  - variance components $\geq 10^{-8}$
  - $\sigma_{AM}/\sqrt{\sigma^2_A\,\sigma^2_M} \in [-1, 1]$
- Obtain **A** and **S** from pedigree (tabular method)
- Construct $\mathbf{D_A}$ and $\mathbf{D_S}$ from coefficients in E[Cov(relatives)] given by F & R (2006).
- Empirical 95% confidence limits
  - values truncating top & bottom 2.5% of estimates



Profile likelihood



Confidence intervals



Sampling correlations ($\times$100)

	σ^2_A	σ^2_S	σ^2_M	σ_{AM}	σ^2_C	σ^2_{DA}	σ^2_{DS}	σ^2_E
σ^2_A		-29	28	**-63**	-10	-3	6	-15
σ^2_S	-30		-9	-5	6	2	-21	1
σ^2_M	28	-9		**-65**	-33	-16	1	10
σ_{AM}	**-63**	-5	**-66**		16	8	2	4
σ^2_C	-6	3	-14	7		**-80**	-5	**80**
σ^2_{DA}	-4	4	-22	11	**-90**		-5	**-96**
σ^2_{DS}	8	-28	3	2	1	-12		-14
σ^2_E	-9	0	18	-3	**90**	**-97**	-6	

- Below diagonal: values from Hessian matrix
- Above diagonal: empirical values from simulation

Expectation Cov(Relatives)

		σ^2_A	σ^2_S	σ^2_M	σ_{AM}	σ^2_C	σ^2_{DA}	σ^2_{DS}
PHS	♂	¼						
	♀	¼	½					
FS	♂	½	½	1	1	1	¼	
	♀	½	¾	1	1	1	¼	½
SFC	♂	⅛	⅜	½	½			
	♀	⅛	3⁄16	½	½			
DFC	♂	¼	⅜	½	½		1⁄16	
	♀	¼	7⁄16	½	½		1⁄16	3⁄16

- SFC : Dams full sisters
- DFC : Sires full brothers, dams full sisters

Conclusions

- Design suggested provides many types of covariances between relatives
- But: unlikely to support accurate estimation of all 8 (co)variance components
  - Embryo transfer ?
- 'Animal model' analysis not a magic bullet
- Inspection of E[Cov(relatives)] $\Rightarrow$ incomplete information
- Profile (log) likelihood calculations recommended
  - Provide additional insights
  - Good agreement with simulation results
  - Straightforward & computationally undemanding
  - Should be part of planning experiments