Hierarchical Generalized Linear Models Have A Great Potential in Genetics

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Definition of the h-likelihood

The hierarchical log-likelihood (**h-likelihood**): $h(\beta, \theta, u) = \log f(y|u) + \log f(u)$.

Example:
The log of the normal density function for n iid observations with mean 0 and variance σ^2 is: $log(f(\mathbf{y})) = -\frac{n}{2} log(\sigma^2) - \frac{1}{2\sigma^2}\mathbf{y}^T\mathbf{y}$

For a linear mixed model

$$h(\beta, \theta, \mathbf{u}) = \{-\frac{n}{2} log(\sigma_e^2) - \frac{1}{2\sigma_e^2}\mathbf{e}^T\mathbf{e}\} + \{-\frac{k}{2} log(\sigma_u^2) - \frac{1}{2\sigma_u^2}\mathbf{u}^T\mathbf{u}\}$$

where $\mathbf{e} = \mathbf{y} - \mathbf{X}\beta - \mathbf{Z}\mathbf{u}$

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h-likelihood estimation for HGLM

Estimating fixed and random effects: $\frac{\partial h}{\partial \beta} = 0$ and $\frac{\partial h}{\partial u} = 0$

Estimating variance components:

- MLE are biased. Solution: Adjusted profile likelihood

$$h_p = \left(h + \frac{1}{2} log|2\pi H^{-1}| \right)_{\beta=\hat{\beta}, u=\hat{u}}$$

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Why is this useful?

- Estimation and inference of generalized linear models with random effects
- Both **y** and **u** can come from a wide range of distributions.
- Approximate h-likelihood estimates can obtained by iterating between a relatively simple set of GLM
  - Implemented in the R package **hglm** (Rönnegård, Alam & Shen)
- Estimates can also be computed using iterative Newton-Raphson directly on the h-likelihood
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Double HGLM

- Easy to include predictors for the variance components in the h-likelihood
  $var(\mathbf{y}|\mathbf{u},\mathbf{u}_d) = \phi$ with $log(\phi) = \mathbf{X}_d b_d + \mathbf{Z}_d \mathbf{u}_d$

  $$h(\beta,\theta,u,u_d) = \log f(y|u,u_d) + \log f(u) + \log f(u_d)$$

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  - Double Hierarchical GLM (**DHGLM**)

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QTL analysis

Estimate effects of Single Nucleotide Polymorphic markers using a DHGLM

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

$$\mathbf{e} \sim \mathrm{N}(\mathbf{0}, \mathbf{I}_\mathrm{n}\sigma^2_\mathrm{e})$$

$$\mathrm{u_i} \sim \mathrm{N}(\mathbf{0}, \sigma^2_{\mathrm{u,i}}),\ log(\sigma^2_u) = \mu + \mathbf{Z}_\mathrm{d}\mathbf{u}_d$$

$$\mathbf{u}_\mathrm{d} \sim \mathrm{N}(0, \mathbf{I}\sigma^2_\mathrm{d})$$

Analysis of the QTLMAS 2009 data

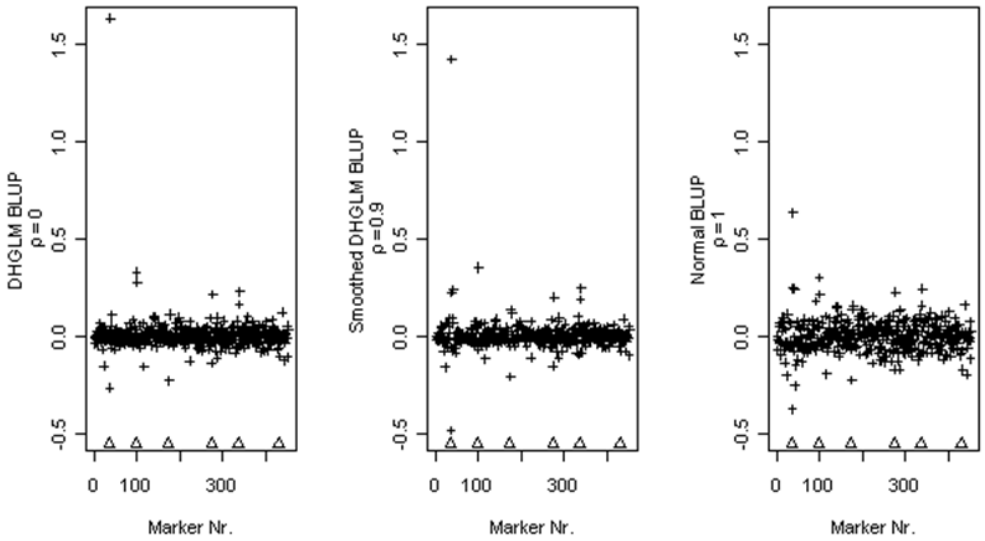

Figure 1: SNP-effects for the models: DHGLM, Smoothed DHGLM and a linear mixed model with constant variance. Simulated data from QTLMAS '09.

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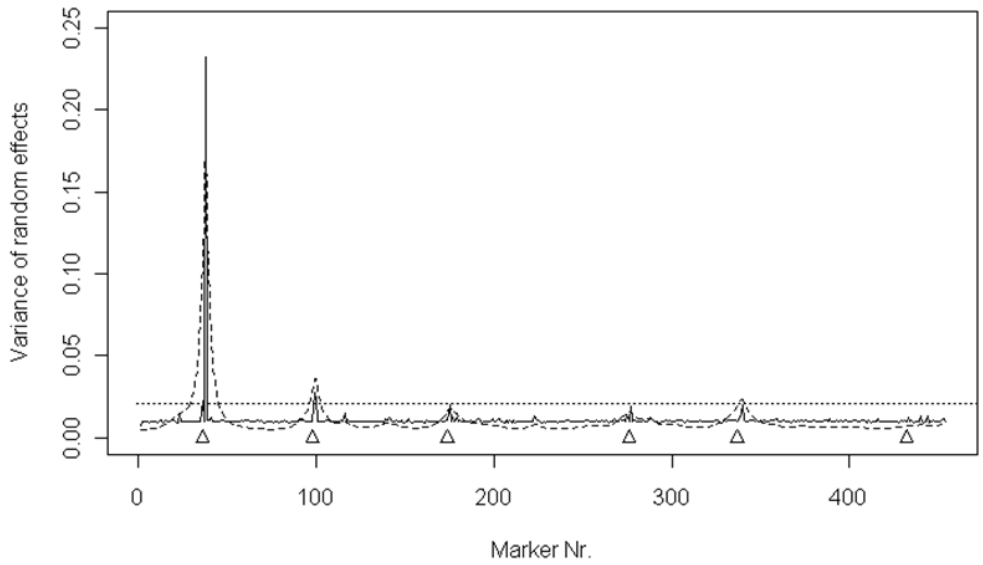

Figure 2: Estimated variance of random SNP-effects for QTLMAS '09 data.

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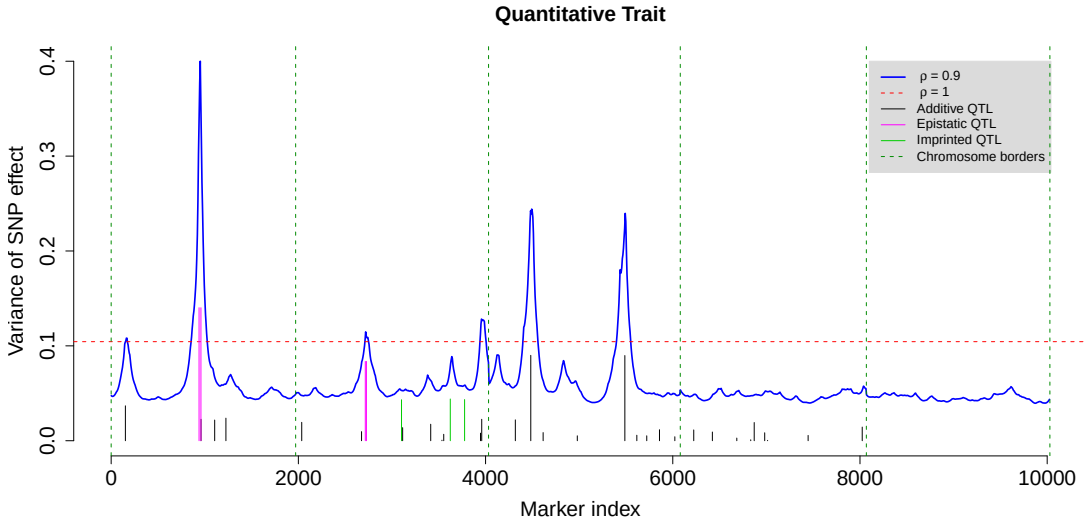

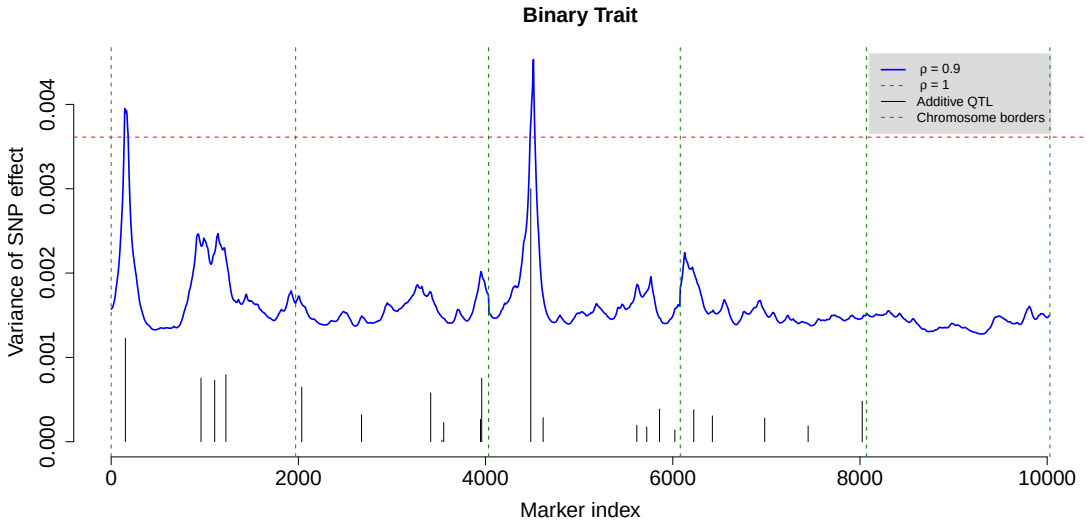

Using DHGLM for estimating genetic heterogeneity in residual variance

In Rönnegård et al. (2010 GSE 42:8) we fit a DHGLM for the pig litter size data previously studied in Sorensen and Waagepetersen (2003)

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

$$\mathbf{u} \sim \mathrm{N}(\mathbf{0}, \mathbf{A}\sigma^2_{\mathrm{u}})$$

$$\mathrm{e_i} \sim \mathrm{N}(\mathbf{0}, \sigma^2_{\mathrm{e,i}}),\ log(\sigma^2_e) = \mathbf{X}_d\beta_{\mathrm{d}} + \mathbf{Z}\mathbf{u}_d$$

$$\mathbf{u}_{\mathrm{d}} \sim \mathrm{N}(0, \mathbf{A}\sigma^2_{\mathrm{d}})$$

Data Description

Data from Danish Pig Production.

- Pig litter size from 4,149 sows
  - mean litter size 10.3
- The data includes 10,060 records from these 4,149 sows in 82 herds.
- Fixed effects: herd, season, type of insemination, parity

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Fitted Model and Estimates

Model Random animal and sow effects included in the model for the mean and also in the model for the residual variance.

Table 1 - Comparison between DHGLM estimates and the estimates obtained by Sorensen & Waagepetersen (2003 Genetics)

	Mean model		Model for residual variance					
			Fixed effects			Variances		
	σ^2_a	σ^2_p	b_0	b_{ins}	b_{par}	$\sigma^2_{a_d}$	$\sigma^2_{p_d}$	ρ
DHGLM	1.36	0.44	1.72	-0.17	0.32	0.09	0.06	
S&W 2003	1.62	0.60	1.77	-0.17	0.35	0.09	0.06	-0.62

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Summary

- The h-likelihood is an extension of Henderson's joint likelihood
- The h-likelihood can be used for estimation and inference for GLMs with random effects
- Estimation does not require MCMC nor numerical integration
- Random effects can be included in a model for the variance components (DHGLM)

Thank you!

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