GENOME-WIDE SCANS FOR QUANTITATIVE TRAIT LOCI IN EXPERIMENTAL POPULATIONS - ISSUES OF MULTIPLE TESTING AND MODEL SELECTION

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Multiple regression model:

$$Y_i = \mu + \sum_{j \in I} \beta_j X_{ij} + \sum_{(u,v) \in U} \gamma_{uv} X_{iu} X_{iv} + \varepsilon_i, \qquad (0.1)$$

I - a subset of $N = \{1, \ldots, m\}$, U - a subset of $N \times N$,

$\epsilon_i \sim N(0, \sigma^2)$

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$$L(Y|M_i, \theta_i) = \prod_{i=1}^{n} f_i(Y_i) = \frac{1}{(\sqrt{2\pi}\sigma)^n} exp\left(-\frac{RSS_{M_i,\theta_i}}{2\sigma^2}\right)$$

$$RSS_{M_i,\theta_i} = \sum_{i=1}^{n}(Y_i - \beta_0 - \sum_{j=1}^{k_i} \beta_j X_{ij} - \sum_{l=1}^{q_i} \gamma_j X_{iu(l)} X_{iv(l)})^2$$

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Surprise ? : - Broman and Speed (JRSS, 2002) report that BIC overestimates the number of regressors when applied to QTL mapping.

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BIC neglects $\pi(M_i)$ and uses Laplace approximation

$$\log m_i(Y) \approx \log L(Y|M_i,\hat{\theta}_i) - 1/2(k_i + q_i + 2)\log n + R_i,$$

where R_i is bounded in n.

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for $m = 400$ the prior distribution on K is almost entirely concentrated on $[160, 240]$

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$$\log L(Y|\hat{\theta}) - \frac{1}{2}(k+q)\log(n) - k\log\left(\frac{m}{c_1} - 1\right) - q\log\left(\frac{N_e}{c_2} - 1\right)$$

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The overall type I error is approximately equally divided between main and interaction effects.

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Orthogonal design: $X^T X = nI_{(m+1)\times(m+1)}, \quad (1)$

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It holds that for large values of n

$$\alpha_n = 2P(Z_j > \sqrt{\log n}) \approx \sqrt{\frac{2}{\pi n \log n}}.$$

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BIC is not consistent when $\frac{m}{\sqrt{n \log n}} \rightarrow \infty$

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$$c_{Bon} = 2\log\left(\frac{m}{\alpha_n}\right)(1 + o_{n,m}) = (\log n + 2\log m)(1 + o_{n,m}) \ ,$$

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$c_{mBIC} = \log n + 2\log\left(\frac{m}{c} - 1\right) \approx \log n + 2\log m - 2\log c$

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For larger K EBIC offers a substantially larger power then mBIC.

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Related to the Benjamini-Hochberg correction for multiple testing

Properties of mBIC and mBIC2

Consistency and Bayesian asymptotic optimality under sparsity and orthogonal designs (asymptotics when $m \to \infty$ and $n \to \infty$):

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Consistency of EBIC, mBIC and mBIC2, under more general designs and a fixed bound on the maximal number of effects - Chen and Chen (Biometrika, 2008)

Applications of mBIC for QTL mapping

1. Extending to intercross + a two-step version of mBIC : Baierl, Bogdan, Frommlet, Futschik *Genetics, 2006*

2. Robust versions based on M-estimates: Baierl, Futschik, Bogdan, Biecek *CSDA, 2007*

3. Rank version: Żak, Baierl, Bogdan, Futschik *Genetics, 2007*

4. Application for dense markers and interval mapping: Bogdan, Frommlet, Biecek, Cheng, Ghosh, Doerge, *Biometrics*, 2008

Intercross

Cockerham model (Kao and Zeng, Genetics, 2002):

Additive Effect for individual i: $X_{aij} = \begin{cases} 1 & \text{if } g_{ij} = AA, \\ 0 & \text{if } g_{ij} = aA, \\ -1 & \text{if } g_{ij} = aa. \end{cases}$

Dominance Effect for individual i: $X_{dij} = \begin{cases} 1/2 & \text{if } g_{ij} = Aa, \\ -1/2 & \text{otherwise} \quad . \end{cases}$

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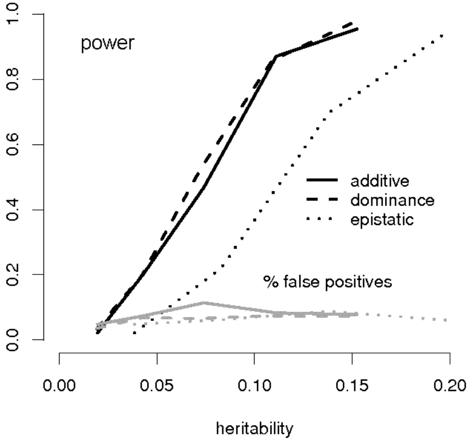
Four types of interaction effects: add-add $X_{aij}X_{aik}$, add-dom $X_{aij}X_{dik}$, dom-add $X_{dij}X_{aik}$ and dom-dom $X_{dij}X_{dik}$

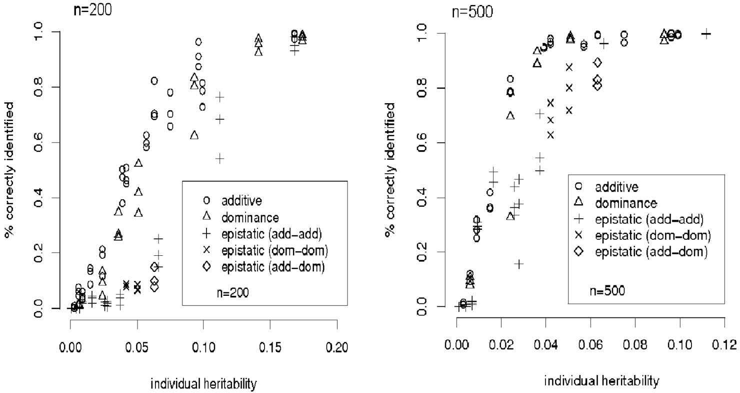
Simulations (1)

A. Baierl, M. Bogdan, F.Frommlet, A. Futschik, *Genetics* (2006) - intercross design

Simple models - one or two effects, n=200



Simulations (2)



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Generalized Poisson Regression:

$$P(Y = k) = \frac{\mu(\mu + (\varphi - 1)k)^{k-1}}{k!} \varphi^{-k} e^{-\frac{1}{\varphi}(\mu + (\varphi - 1)k)}$$

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$E(Y) = \mu$ and $Var(Y) = \varphi^2 \mu$

Zero Inflated Generalized Poisson Regression

Zero Inflated Generalized Poisson Distribution :

$$ZIGP(\mu,\varphi,\omega) = \omega\delta_0 + (1-\omega)GP(\mu,\varphi) \quad ,$$

where $\omega \in [0,1]$ is the zero-inflation parameter.

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Zero Inflated Generalized Poisson Regression: $\omega = const$,

$$\log \mu_i = \beta_0 + \sum_{j \in I} \beta_j X_{ij} + \sum_{(u,v) \in U} \gamma_{uv} X_{iu} X_{iv}$$

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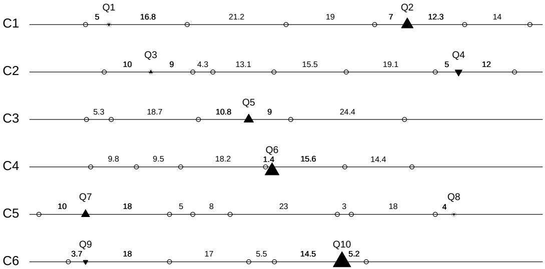
Vinzenz Erhardt - implementation in R, available in CRAN (The Comprehensive R Archive Network)

Simulations

Lyons, M. A., H. Wittenburg, R. Li, K. A. Walsh, M. R. Leonard, G. A. Churchill, M. C. Carey, and B. Paigen (2003). New quantitative trait loci that contribute to cholesterol gallstone formation detected in an intercross of CAST/Ei and 129S1/SvImJ inbred mice. *Physiol. Genomics 14*(3), 225–239.

20 chromosomes, 100 markers, 10 QTL on 6 chromosomes



Characteristics

- true positives (TP): number of selected effects whose distance to the simulated QTL's was less or equal 20 cM; if more than one effect was caught in the interval around a certain QTL only one of them was counted
- false positives (FP): number of selected effects whose distance to the simulated QTL's was higher than 20 cM
- misclassification error, ME = false positives (FP) + false negatives (FN), where $FN = 10 - TP$
- power: $TP/10$
- observed false discovery rate : $FDR = FP/(FP + TP)$

Results (1)

	$\mathbf{n} = \mathbf{500}$, $\varphi = 2$, $\omega = 40\%$				
	mBIC				
	LM	PoiR	ZIPR	GPR	ZIGPR
FP	0.117	30.817	13.813	0.405	0.234
ME	5.949	31.847	15.088	8.381	4.047
Power	0.417	0.897	0.873	0.202	0.619
FDR	0.025	0.770	0.599	0.142	0.033
	EBIC				
FP	0.120	48.520	23.765	0.465	0.435
ME	5.815	49.110	24.665	8.490	3.940
Power	0.430	0.941	0.910	0.198	0.649
FDR	0.024	0.835	0.708	0.154	0.057

Results (2)

Data generated according to the Poisson Regression.

	$\mathbf{n = 200}$, mBIC				
	LM	PoiR	ZIPR	GPR	ZIGPR
FP	0.095	8.200	8.150	0.405	0.410
FP+FN	5.285	9.830	9.810	3.920	3.930
Power	0.481	0.837	0.834	0.648	0.648
FDR	0.018	0.476	0.475	0.053	0.053

Conclusion - Poisson Regression has a tendency to include spurious QTL to explain an increased data heterogeneity

Real Data Analysis (1)

Lyons, M. A., H. Wittenburg, R. Li, K. A. Walsh, M. R. Leonard, G. A. Churchill, M. C. Carey, and B. Paigen (2003). New quantitative trait loci that contribute to cholesterol gallstone formation detected in an intercross of CAST/Ei and 129S1/SvImJ inbred mice. *Physiol. Genomics 14*(3), 225–239.

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$n = 277$, intercross, Y - number of gallstones

Real Data Analysis (2)

Additive effect at D5Mit183 (QTL previously identified at Lyons et al. (2003))

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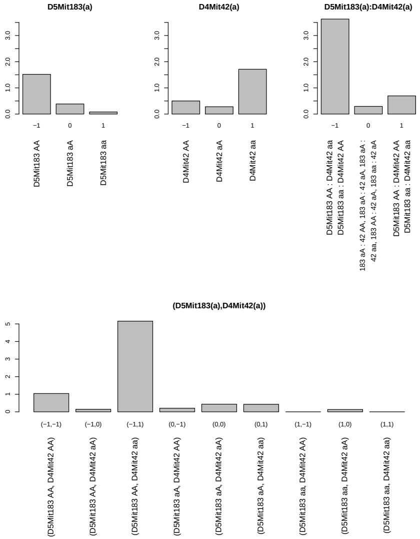
Interaction with a novel QTL at D4Mit42

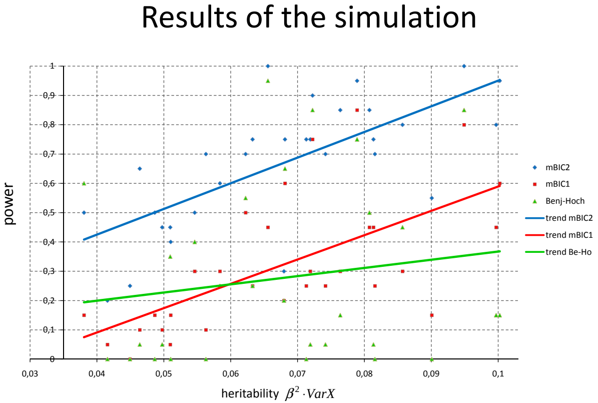
	Estimate	Std. Error	z value	$Pr(>\|z\|)$
Intercept	-0.864	0.573	-1.510	0.131
D5Mit183(a)	-1.244	0.442	-2.817	0.005
D4Mit42(a)	-0.215	0.476	-0.451	0.652
D5Mit183(a):D4Mit42(a)	-2.177	0.548	-3.973	$7.1 \cdot 10^{-5}$
φ	5.387	2.185	2.466	0.014
ω	0.458	0.163	2.809	0.005

Real Data Analysis (2)



Current research

Application for GWAS: Frommlet, Twaróg, Bogdan - in preparation $m \approx 200000$, 30 QTL, total heritability $= 66\%$, individual heritability $[1.3\%, 3.4\%]$



Explanation

$$\hat{\beta} = \frac{Cov(Y,X)}{VarX}$$

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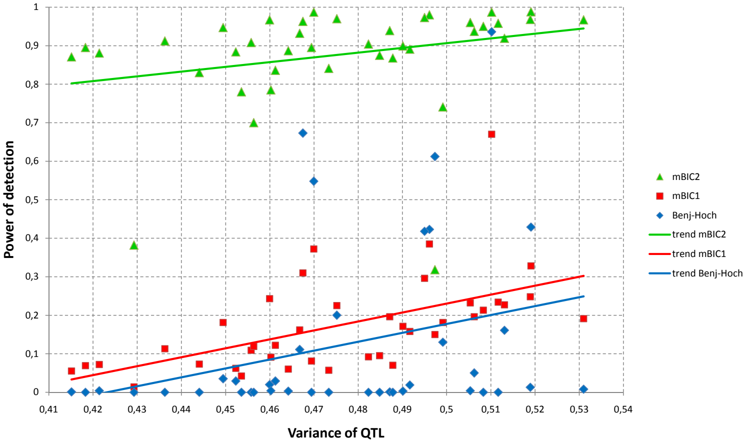
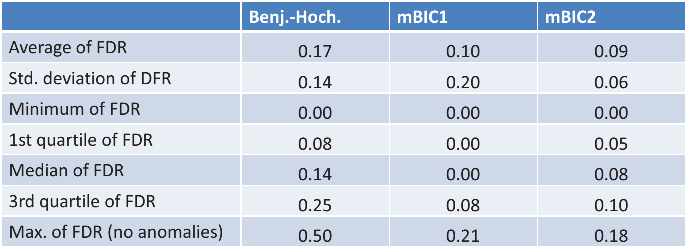
$Var[Cov(Y, X_1)] \approx \sum_{j=2}^{k} \beta_j \sigma^2$

Results

$h^2 \approx 80\%$



Results



	Benj.-Hoch.	mBIC1	mBIC2
Average of FDR	0.17	0.10	0.09
Std. deviation of DFR	0.14	0.20	0.06
Minimum of FDR	0.00	0.00	0.00
1st quartile of FDR	0.08	0.00	0.05
Median of FDR	0.14	0.00	0.08
3rd quartile of FDR	0.25	0.08	0.10
Max. of FDR (no anomalies)	0.50	0.21	0.18

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