3.27pt

Multiple regression - information criteria for large data bases

Małgorzata Bogdan

University of Wroclaw

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Multiple regression model when $n > p$

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$$\hat{\sigma}^2 = s^2 = \frac{||Y - X\hat{\beta}_{LS}||^2}{n-p} = \frac{RSS}{n-p}$$

Selection of important variables

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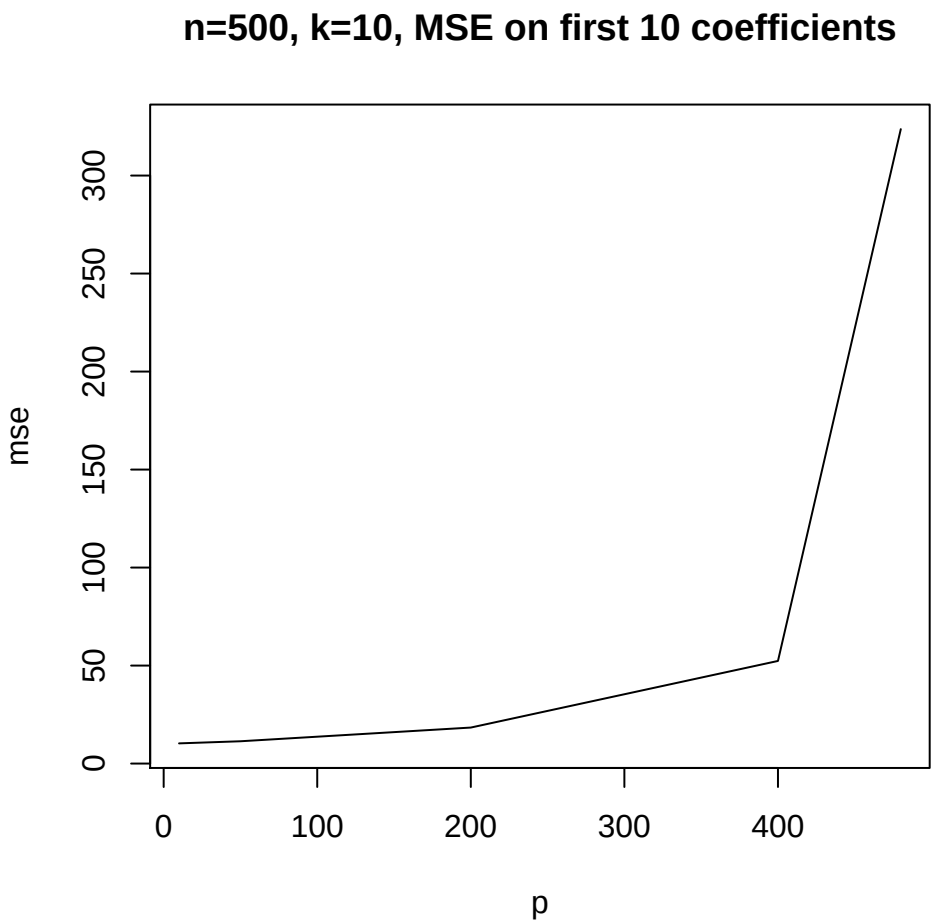
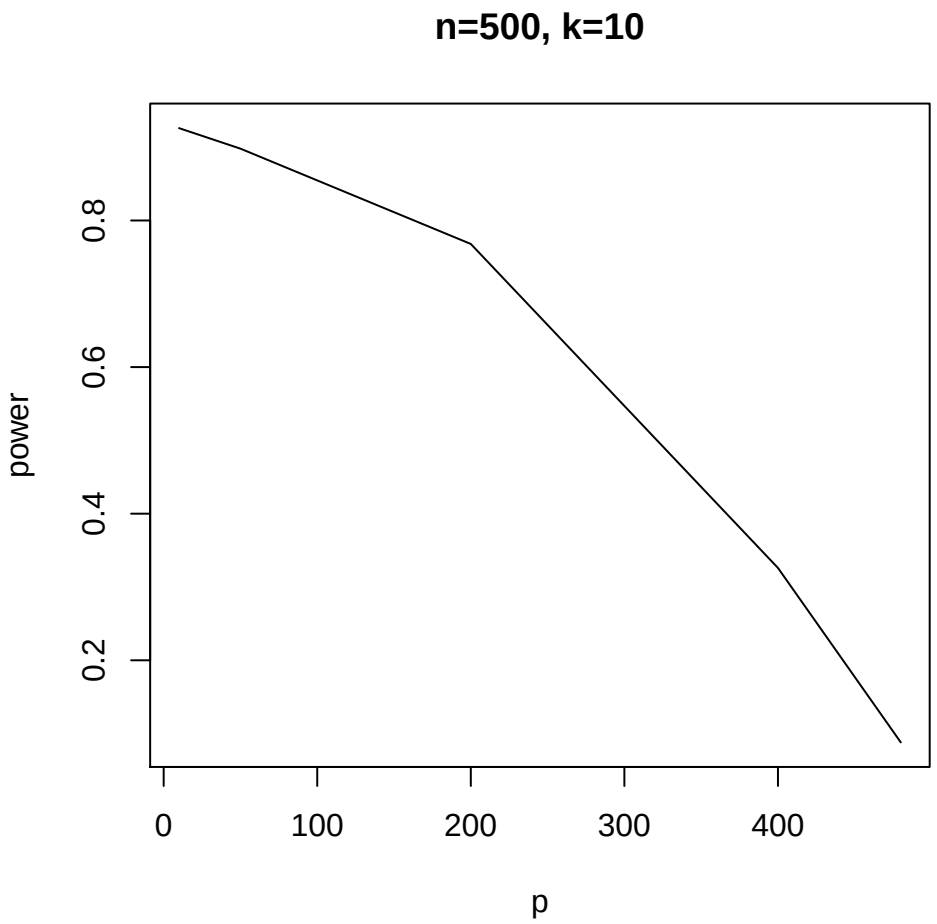
But $(X'X)^{-1}$ has the inverse Wishart distribution and the expected values of the elements on the diagonal are equal to $\frac{n}{n-p-1}$ and become very large as p approaches n.

Inflation of MSE



Loss of Power



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Also, RSS is not a good measure of the prediction error.

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RSS measures the fit within the training sample, i.e. it adjusts to the specific realization of the noise term ϵ - this is overfitting. PE measures the fit with respect to the true expected value of Y, which indeed is an indication of predictive properties (i.e. how well we can predict new observations with different noise terms).

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$PE = n\sigma^2 + E(SURE(\hat{\mu})) = n\sigma^2 + E(RSS) + 2\sigma^2 TrM - n\sigma^2$

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Leave-one-out cross-validation:

$$CV = \sum_{i=1}^{n} (Y_i - \hat{Y}[i])^2 = \sum_{i=1}^{n} \left(\frac{Y_i - \hat{Y}_i}{1 - M_{ii}} \right)^2$$

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Akaike Information Criterion in Linear Regression, σ known

$\epsilon_1 = Y_1 - X_1\beta, \ldots, \epsilon_n = Y_n - X_n\beta$ - iid from $N(0, \sigma^2)$, $\beta \in R^k$

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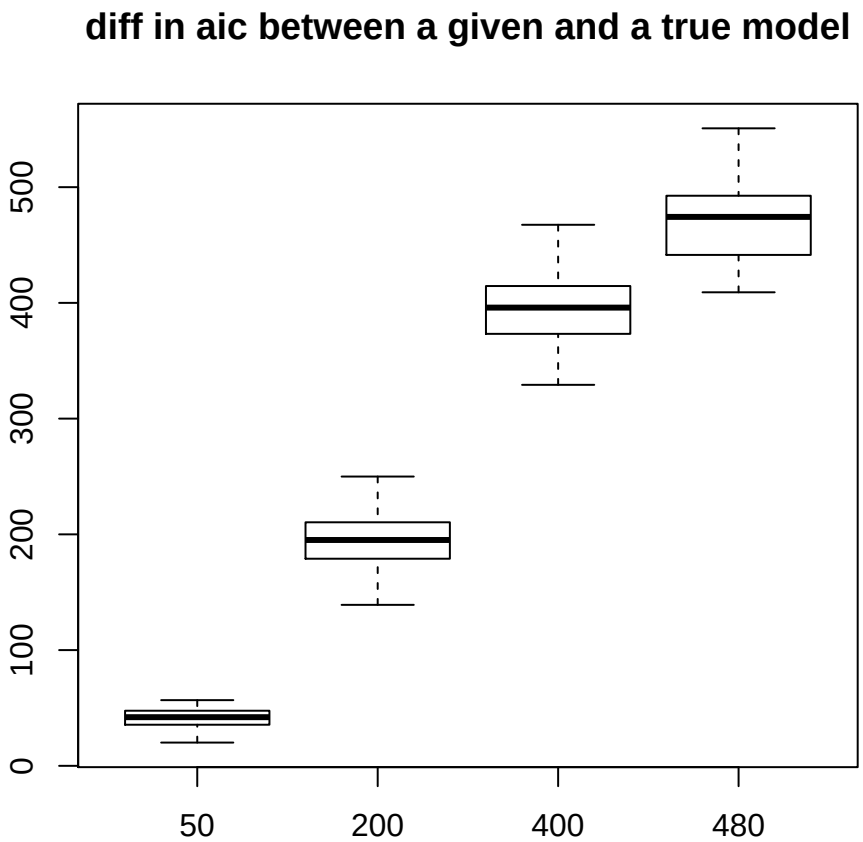
Properties of AIC (1)

In our example AIC identifies the true model among 5 models with different dimensions, $p = 500$, $k = 10$.



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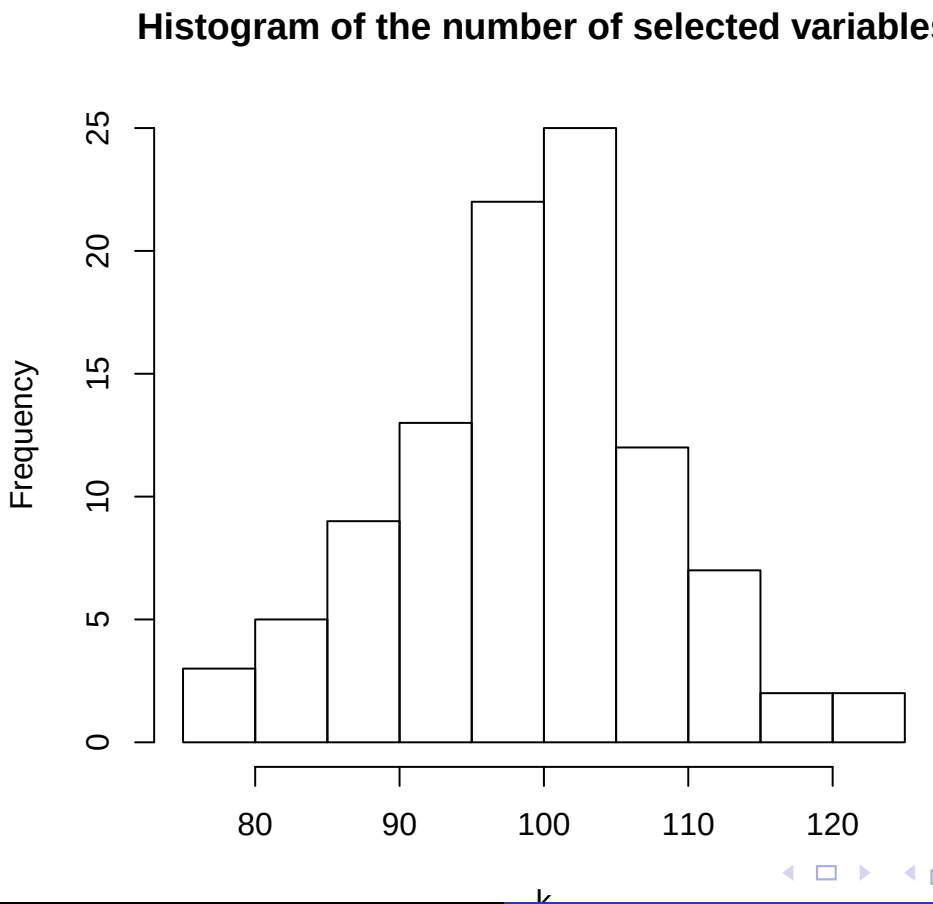
More complicated heuristics: genetic algorithms, simulated annealing etc.

Can we use AIC to select important variables in large data bases ?

bigstep - *R* library with many different search strategies, optimizing a variety of model selection criteria; $p = 500$, $k = 10$.



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In our simulations $\hat{k} \approx 100$ due to additional disturbance by the sample correlations between columns of the design matrix and using the form of AIC with unknown σ

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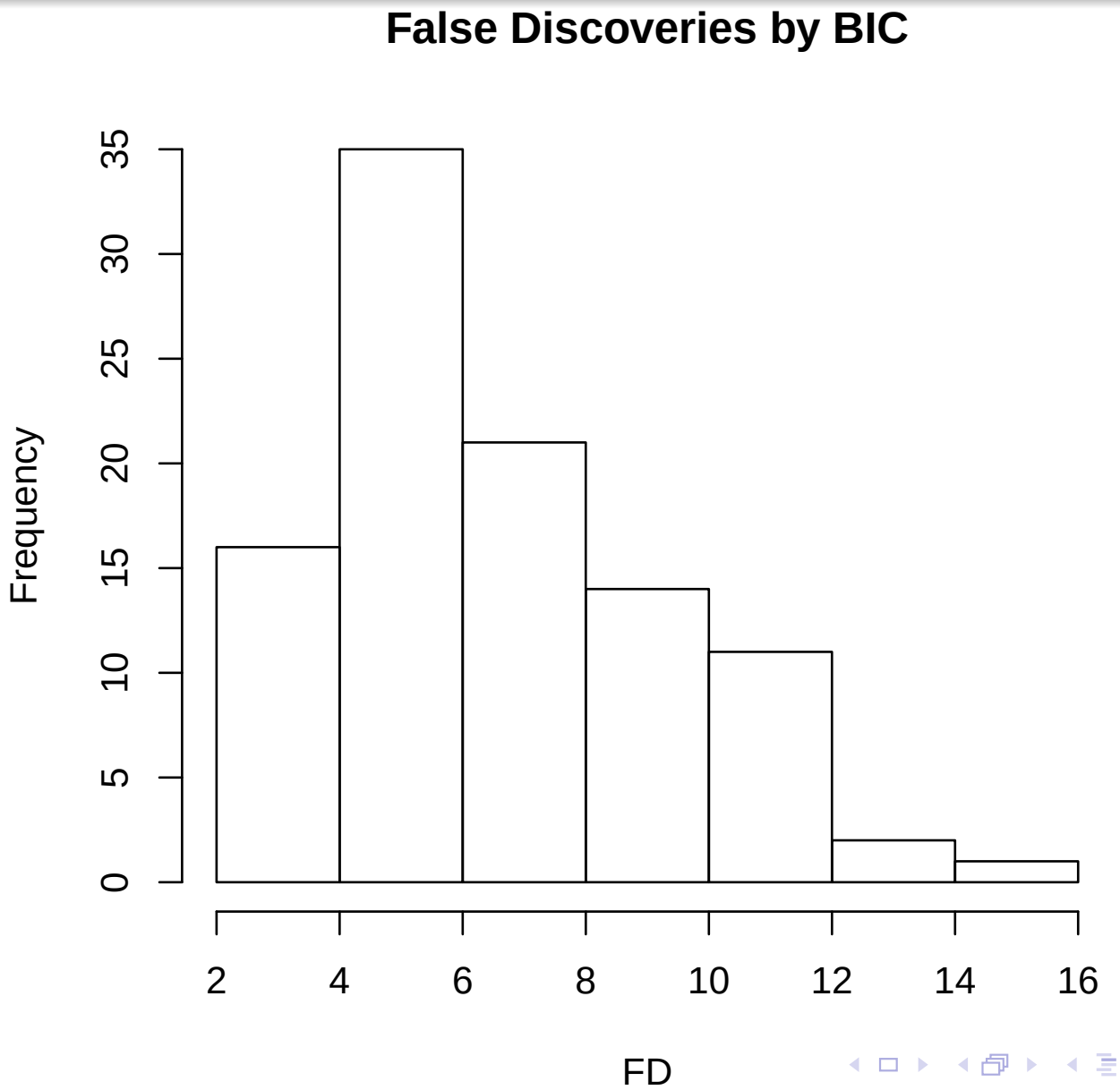
Thus we expect to see on average $p_0 * 0.013 = 490 * 0.013 \approx 6.5$ false discoveries

False Discoveries by BIC



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Here the expected number of false discoveries is smaller than 1 and decreases with p

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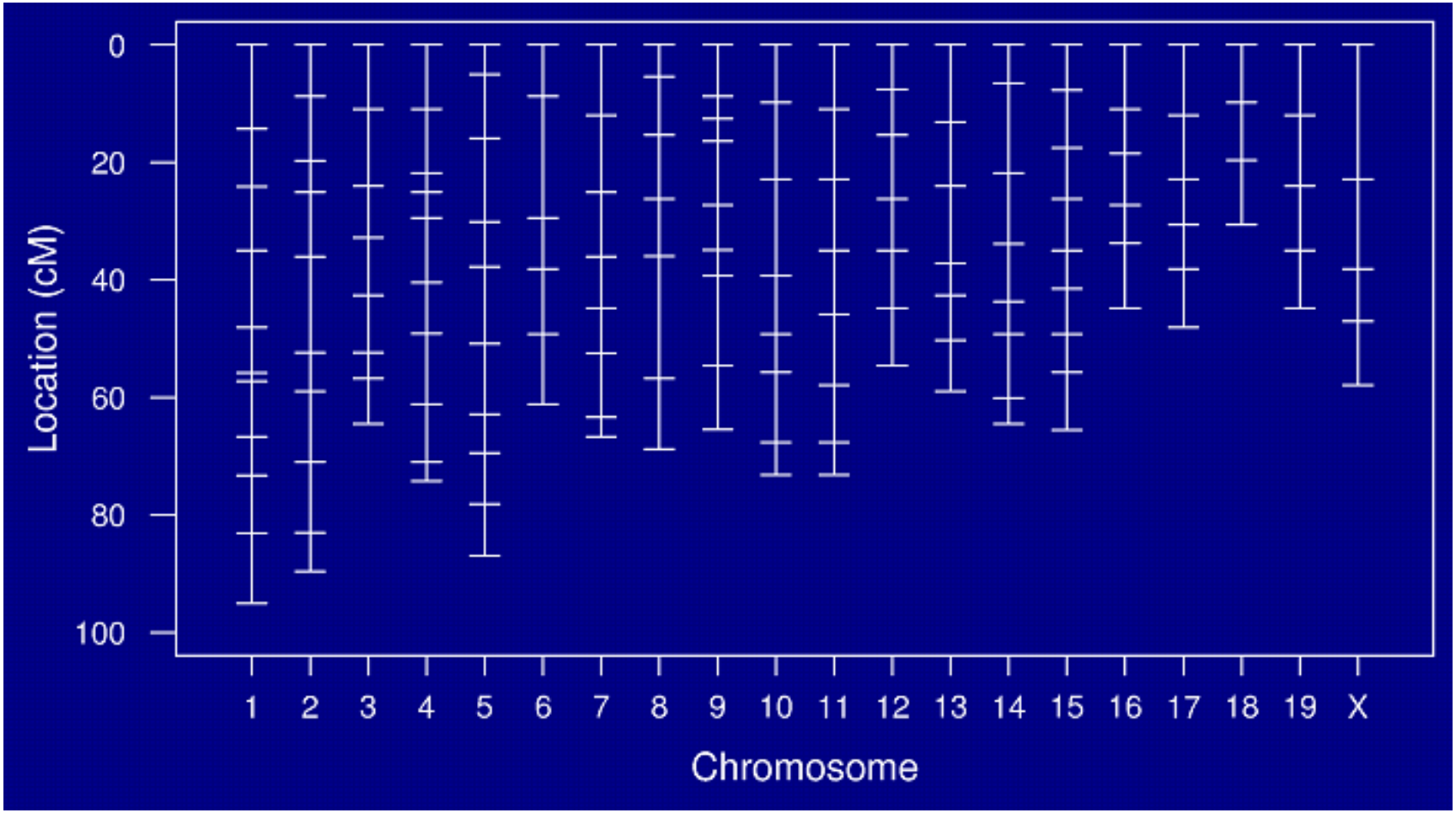
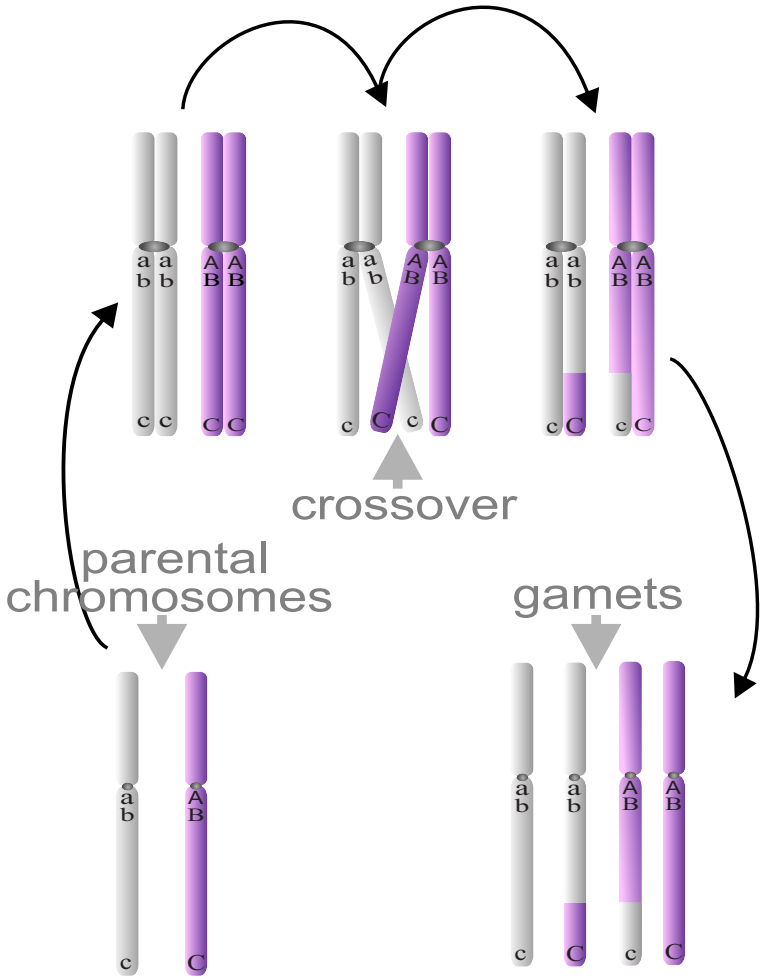
- Asymptotic Optimality and Consistency

Locating Quantitative Trait Loci in experimental populations

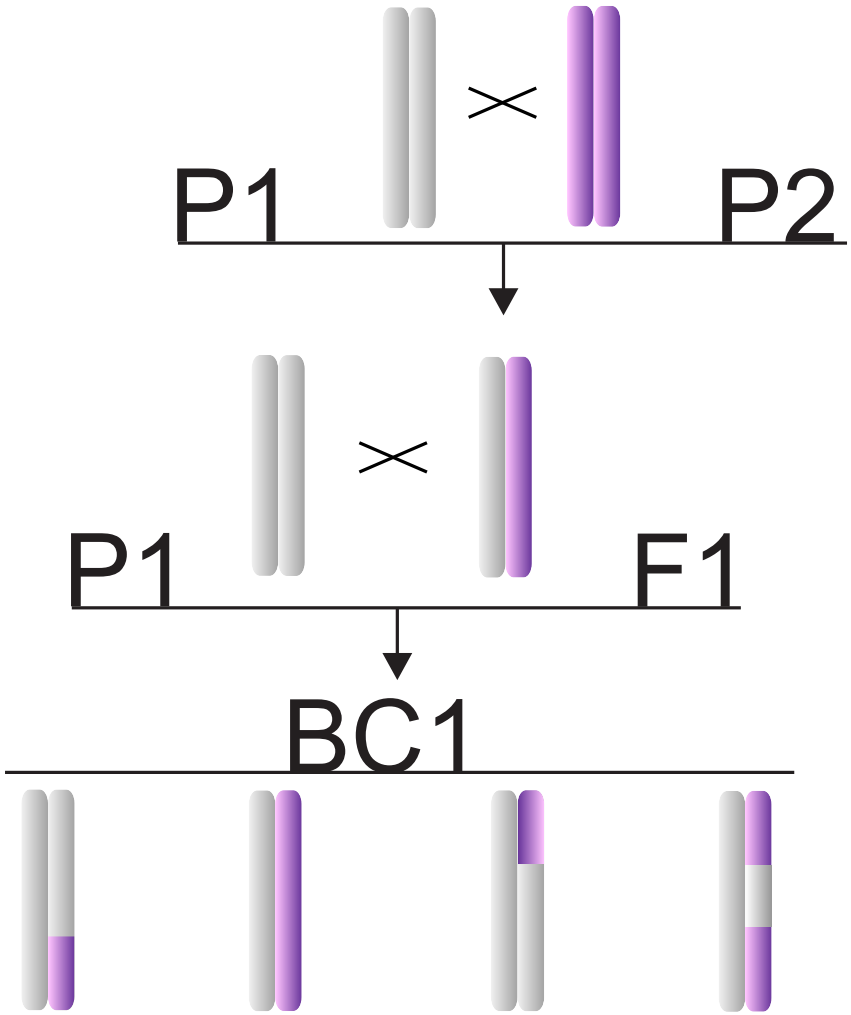


Meiosis

1 M= 1 Morgan - unit of distance - expected number of cross-overs in one meiosis, Average length of the chromosome: 120 cM=1.2 M



Back-cross experiment



Data for QTL mapping in backcross population and recombinant inbred lines

Y_i, $1 \leq i \leq n$ - trait values

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Strong correlation between neigboring loci: backcross

d - distance in M , $\rho = e^{-2d}$

$d = 0.1M$, $\rho = 0.82$

$d = 1M$, $\rho = 0.14$

Usually around 10-15 markers on each chromose

$p \approx 300$, $n > 200$

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Weak and non-regular correlation between neigboring loci

Usually $n \approx k \times 100$ or $k \times 1000$, $p \approx k \times 100,000$

Multiple regression model

$$Y_i = \mu + \sum_{j \in I} \beta_j X_{ij} + \sum_{(u,v) \in U} \gamma_{uv} X_{iu} X_{iv} + \varepsilon_i, \qquad (1)$$

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

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Task : estimation of the number of influential genes and interaction effects

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M_i - i-th linear model

k_i - number of main effects, q_i - number of interactions

$k_i + q_i < n$

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maximize $BIC = \log L(Y|M_i, \hat{\theta}_i) - \frac{1}{2}(k_i + q_i) \log n$

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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 approximation

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

R_i is bounded in n.

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

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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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Corollary: BIC is not consistent when $\frac{p}{\sqrt{n \log n}} \to \infty$

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

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*

5. Application for the count data, based on the Zero-Inflated Generalized Poisson Regression: Earhardt, Bogdan, Czado *SAGMB, 2010*

Computer simulations(1)

Setting : $n = 200$, $p = 300$, entries of $X \sim N(0, \sigma = 0.5)$,

$k \sim Binomial(p, u)$, with $u = \frac{1}{30}$ $(pu = 10)$, $\beta_i \sim N(0, \sigma = 1.5)$,

$\varepsilon \sim N(0, 1)$ and Tukey's gross error model:
$\varepsilon \sim Tukey(0.95, 100, 1) = 0.95 * N(0, 1) + 0.05 * N(0, 10)$.

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Characteristics : Power, $FDR = \frac{FP}{AP}$, $MR = FP + FN$,
$l_2 = \sum_{j=1}^{m} (\beta_j - \hat{\beta}_j)^2$
mean value of the absolute prediction error based on 50 additional observations, d

Computer simulations, Bogdan et al. (QREI, 2008)

Table: **Results for 1000 replications.**

noise	N(0,1)			Tukey(0.95, 100, 1)		
citerion	BIC	mBIC	rBIC	BIC	mBIC	rBIC
FP	13.3	0.073	0.08	12.5	0.08	0.1
FN	1.84	2.97	3.45	3.95	6.11	4.29
Power	0.8155	0.7030	0.6586	0.6087	0.3923	0.5806
FDR	0.5889	0.0107	0.0116	0.6487	0.0210	0.0162
MR	15.1480	3.0410	3.5310	16.4440	6.1910	4.3910
l_2	2.3610	0.6025	0.8500	13.51	4.732	1.597
d	0.9460	0.8505	0.8687	1.714	1.503	1.298

$E|\varepsilon_1| \approx 0.8 \qquad , E|\varepsilon_2| \approx 1.16$

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Benjamini and Hochberg procedure:
sorted p-values: $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(p)}$

$$k_F = argmax_j \left\{ p_{(j)} \leq \frac{j\alpha}{p} \right\} . \qquad (2)$$

BH rejects the hypothesis with p-values smaller or equal than $p_{(k_F)}$.

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Abramovich, Benjamini, Donoho and Johnstone, Ann.Statist. 2006 - asymptotic minimax properties with respect to estimation loss $||\hat{\beta} - \beta||$, when $\epsilon_p \geq \frac{log^5 p}{p}$

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Bonferroni correction at the FWER $\alpha \propto 1/\sqrt{n}$ is ABOS if $p \approx \frac{1}{m}$

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$\beta_j \sim (1-\epsilon)\delta_0 + \epsilon F_A$, where F_A has a positive density at 0.

Bayes oracle $\rightarrow$ Bayes classifier

The rule is Asymptotically Bayes Optimal under Sparsity (ABOS) if $\lim \frac{R}{R_{opt}} \rightarrow 1$ (as $m \rightarrow \infty$)

Bonferroni correction at the FWER $\alpha \propto 1/\sqrt{n}$ is ABOS if $p \approx \frac{1}{m}$

BH at FDR $\alpha \propto 1/\sqrt{n}$ is ABOS if $p \rightarrow 0$ and $mp \rightarrow (0, \infty]$

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Simulation results for GWAS (Frommlet, Ruhaltinger, Twarog and Bogdan, 2011, CSDA)

Population reference sample POPRES from dbGaP

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- Simulation scenario:
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Search strategy

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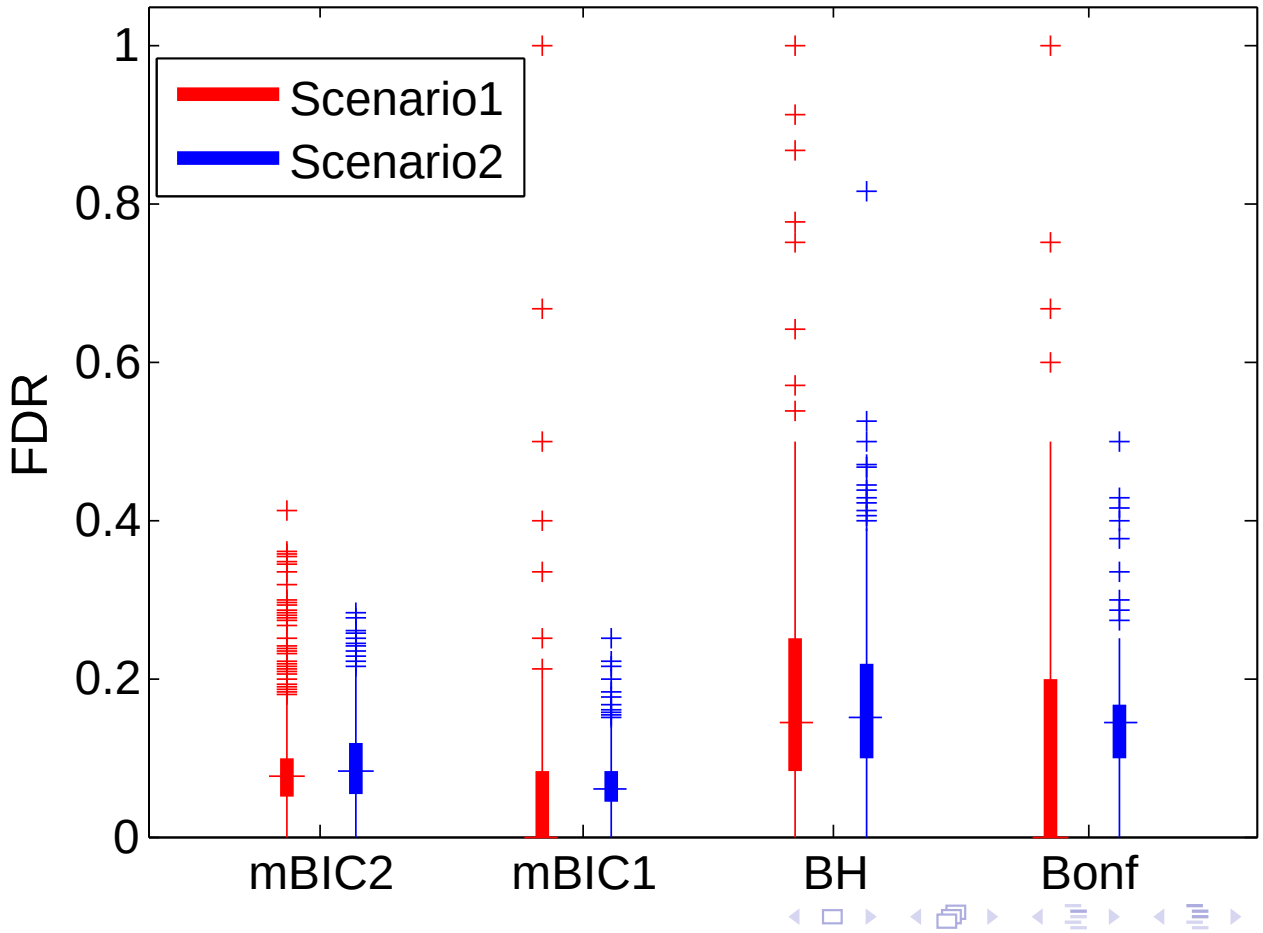
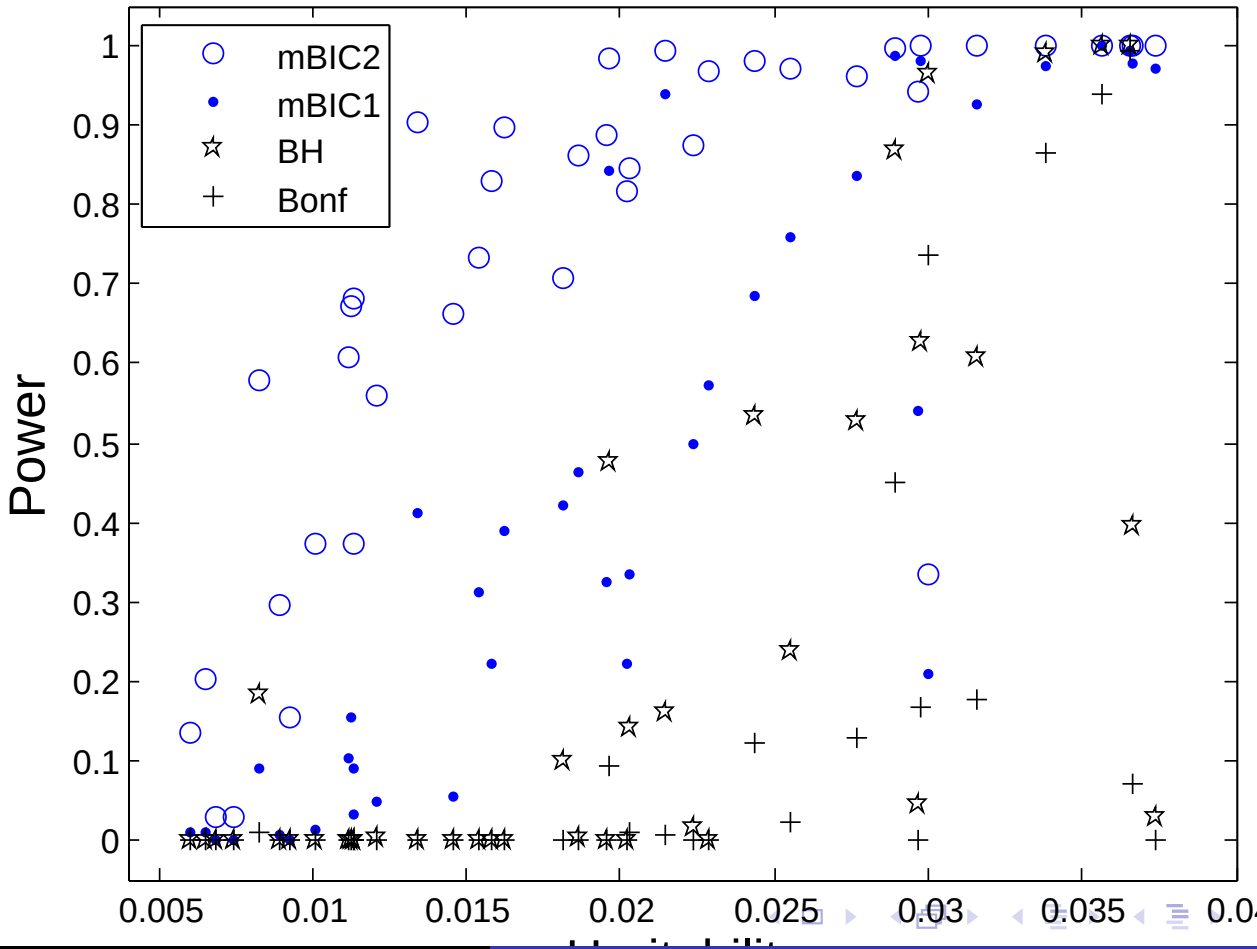
4. False positive - correlation with a causal SNP$<$0.9

FDR



Power


mBIC2
mBIC1
BH
Bonf
Power
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04

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Caution - in EBIC $E(K) = \frac{m}{2}$.

Relationship between mBIC, mBIC2 and EBIC

If $\frac{\log k_{max}}{\log m} \to 0$ then $\frac{pen(EBIC(k))}{pen(mBIC(k))} \to 1$ uniformly for $k \in \{1, \ldots, k_{max}\}$

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mBIC2 is asymptotically equivalent to the Bayes rule based on the uniform prior on $\{0, \ldots, k_{max}\}$, where $\frac{k_{max}}{m} \to 0$.

Consistency (1)

Chen and Chen, 2008 - fixed true model dimension p_0, fixed maximal size of the model to search K

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Identifiability condition: $\mu = EY$,
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Foygel and Drton, 2012 - random covariates,
There exists positive constants $a_1 < a_2$ such that for all $|J| \leq 2K$ the eigenvalues of $E[X_J X_J^T]$ are within $[a1, a2]$. The small true coefficients have bounded decay.

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Open problem - asympotic optimality under non-orthogonal designs

Dense markers - Bogdan et al. (Biometrics, 2008)

Feingold, Brown and Siegmund, Genetics, 1993 - backcross

$$\begin{aligned} \alpha &= P_{H_0}\left(max_{j\in\{1,\ldots,p\}} LRT_j > c\right) \\ &\approx 1 - exp(-2[1-\Phi(\sqrt{c})]) - 0.04L\sqrt{c}\nu\left(\sqrt{0.04\delta}\right) \quad , \end{aligned}$$

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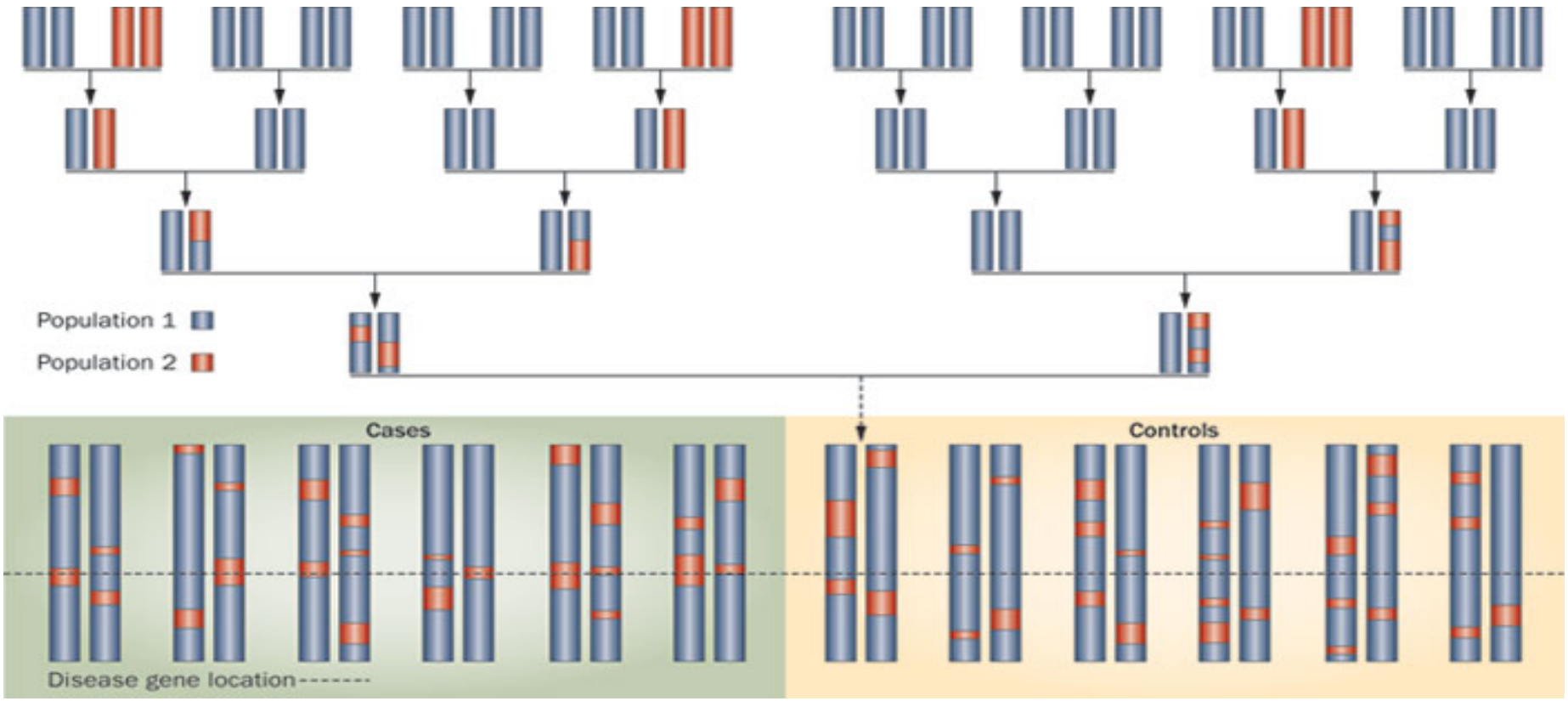
$$p^{eff} = \log(1-\alpha)/\log\left(2\Phi(\sqrt{c})-1\right) \quad .$$

Admixtures, Szulc, B,Frommlet, Tang (2017)

Picture from Rosset, Tzur, Behar, Wasser and Karl Skorecki, Nature Reviews Nephrology 7, 313-326 (June 2011)



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Locus-specific ancestry can be accurately estimated based on the genotype data from standard genotyping platforms and distribution of haplotypes in ancestral population (see e.g. methods based on Hidden Markov models in Tang et al. (2006, Am. J. Hum. Gen.) or Price et al. (2009, PLOS Genet.)).

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$$Z_{ij} = \begin{cases} 0 & \text{if} \quad A_{ij} = bb \\ 1 & \text{if} \quad A_{ij} = bB \\ 2 & \text{if} \quad Z_{ij} = BB \end{cases}$$

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Admixture mapping - looking for association between the ancestry and the trait

When is ancestry information useful ? (1)

Assumption - the trait is determined by the genotype at “causal" loci X_j, $j \in \{1, \ldots, k\}$.

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Corollary : Admixture mapping can detect only those "causal" loci, for which the allelic distribution differs between admixing population.

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Admixture mapping can help to detect genes in the regions of a low linkage disequilibrium and such that their allelic frequencies differ between parental populations.

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Solution - conditioning on Q - genomewide ancestry for i-th individual

Statistical models for single marker tests:

$$Y_i = \beta_0 + \beta_Q Q_i + \beta_j X_{ij} + \epsilon_i, \quad \epsilon_i \sim N(0, \sigma^2)$$

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In the context of regression one could consider a joint test for:

$$H_0 : \beta_{Xj} = \beta_{Zj} = 0$$

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In many cases one of these variables would be sufficient to detect a gene. Two degrees of freedom - unnecessary inflation of critical values - loss of power.

mBIC2

$$Y_i = \beta_0 + \beta_Q Q_i + \sum_{j \in I} \beta_{Xj} X_{ij} + \sum_{j \in J} \beta_{Zj} Z_{ij} + \varepsilon_i, \qquad (3)$$

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Derived by the analogy to BH

Ancestry dummy variables - adjustment for correlation, Bogdan et al. (Biometrics, 2008)

Hybrid isolation model: $\rho = Corr(Z_j, Z_{j+1}|Q = q) = exp(-t\Delta)$, where t is the time from the admixing event and Δ is the distance between loci (in Morgans).

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Feingold, Brown and Siegmund, Genetics, 1993 - Modelling the distribution of the t-test statistics by the Gaussian process

$$P_{H_0}\left(max_j LRT_j > c\right) \approx 1 - exp(-2[1-\Phi(\sqrt{c})]) - 0.02mt\Delta\sqrt{c}\nu\left(\sqrt{0.02t\Delta}\right.$$

where

$$\nu(t) \approx \frac{(2/t)(\Phi(t/2) - 0.5)}{(t/2)\Phi(t/2) + \phi(t/2)}.$$

Effective number of tests (1)

Alternatively, FWER resulting from performing m^{eff} independent test is

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m_{eff} may be also calculated based on the simulations/permutations

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m_{eff} may be also calculated based on the simulations/permutations

Effective number of tests (1)

Alternatively, FWER resulting from performing m^{eff} independent test is

$$\alpha = P_{H_0}\left(\max_{i\in\{1,\ldots,m^{eff}\}} LRT_j > c\right) \approx 1-\left[1-2\left(1-\Phi(\sqrt{(c)})\right)\right]^{m^{eff}} \quad .$$

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$t\Delta := -\overline{\log \rho}$

m_{eff} may be also calculated based on the simulations/permutations

Effective number of tests (2)

Table: Effective number of tests for 22 chromosomes.

Chr	L_{tot}	$\bar{L}$	m	m_{eff}
1	278.09	0.0075	37173	397
2	263.45	0.0066	39958	376
3	224.62	0.0067	33385	314
4	213.19	0.0073	29290	295
5	203.98	0.0067	30587	281
6	193.02	0.0060	32204	266

Model selection for admixtures:

$$\text{mBIC2:} n \log RSS \quad + \quad k_{\mathbf{j}}(\log n + 2\log(m/4)) - 2\log(k_{\mathbf{j}}!) \qquad (4)$$

$$+ \quad \tilde{k}_{\mathbf{j}}(\log n + 2\log(m^{eff}/4)) - 2\log(\tilde{k}_{\mathbf{j}}!)\ , \qquad (5)$$

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3. Threshold for stepwise selection is determined by *mBIC*2.

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"Recombination" points are generated according to $d \sim Exp(\lambda = T)$ distribution. At recombination points ancestry is randomly generated as a Bernoulli variable, P(A)=Q. Block genotypes are randomly sampled from the HapMap data for the given population.

Scenario 1

Table: SNPs selected for Scenario 1

	SNP's name	AF	MAF	LD
1	ch01_27796	0.000	0.455	0.994
2	ch03_10846	0.000	0.418	0.990
3	ch05_07371	0.000	0.414	0.991
4	ch10_00444	0.000	0.488	0.990
5	ch02_39189	0.000	0.432	0.943
6	ch17_04306	0.000	0.495	0.942
7	ch19_06378	0.000	0.466	0.991
8	ch22_00033	0.000	0.485	0.947
9	ch01_32763	0.803	0.430	0.872
10	ch04_05127	0.765	0.461	0.993
11	ch06_25838	0.743	0.428	0.895
12	ch11_12611	0.719	0.491	0.807
13	ch12_03421	0.808	0.419	0.977
14	ch14_06999	0.821	0.414	0.996
15	ch15_03859	0.785	0.401	0.932
16	ch16_04525	0.720	0.426	0.868
17	ch01_19810	0.715	0.497	0.363
18	ch08_15190	0.583	0.400	0.377
19	ch02_22034	0.634	0.456	0.379
20	ch10_08265	0.646	0.492	0.377
21	ch11_20057	0.718	0.447	0.358
22	ch18_01031	0.650	0.431	0.382
23	ch19_01377	0.656	0.499	0.376
24	ch03_02703	0.654	0.497	0.460

Scenario 2

Table: SNPs selected for Scenario 2

SNP's no.	SNP's name	AF	MAF	LD
1	ch01_00531	0.674	0.483	0.347
2	ch01_19810	0.715	0.497	0.364
3	ch04_22846	0.745	0.500	0.505
4	ch08_12075	0.812	0.407	0.624
5	ch02_16712	0.755	0.409	0.650
6	ch11_20899	0.779	0.428	0.682
7	ch03_26157	0.769	0.425	0.691
8	ch05_16192	0.741	0.433	0.899
9	ch15_03859	0.785	0.401	0.931
10	ch07_05936	0.824	0.404	0.954
11	ch12_03421	0.808	0.419	0.977
12	ch14_06999	0.821	0.415	0.996
13	ch13_05394	0.458	0.410	0.396
14	ch20_12128	0.450	0.401	0.429
15	ch19_00410	0.467	0.411	0.499
16	ch21_02904	0.453	0.419	0.599
17	ch18_01592	0.447	0.421	0.698
18	ch16_06363	0.446	0.451	0.904
19	ch22_03194	0.458	0.486	0.912
20	ch17_11568	0.458	0.459	0.996

Simulation Study (3)

Statistical model:

$$Y_i = 0.5 \sum_{j=1}^{k} X_j + \epsilon_j \quad ,$$

where $\epsilon_j \sim N(0, 1)$.

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"Causal" SNPs are removed from the data set used to locate them.

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100 simulation runs

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We used the 0.5 correlation cutoff for [X,causal X] or [Z, causal Z].

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Multiple testing procedures - concept of scan statistics (Siegmund, Biometrika 2010). Detected SNP + its 0.5 correlation neigborhood are classified as a one (true or false) discovery.

FWER

Table: Familywise Error Rate, 1000 simulations (no differences between mBIC and mBIC2).

Matrix X	Matrix X+Z
0.016	0.037

Results

BMIX - Shriner et al (PLOS Comput. Biol., 2011)

Table: Summary results: TP, FP and FDR

	Bonf		B-H		BMIX	mBIC2		
	X	Z	X	Z	X+Z	X	Z	X+Z
	Scenario1							
TP	8.04	4.68	11.95	8.26	6.65	15.41	9.43	20.81
FP	0.21	0.23	2.31	1.01	0.29	2.18	0.51	0.69
FDR	0.03	0.16	0.05	0.11	0.04	0.12	0.05	0.03
	Scenario2							
TP	5.56	6.30	7.32	9.90	9.74	9.82	8.54	15.14
FP	0.52	0.44	2.72	1.83	0.69	1.98	0.68	0.63
FDR	0.08	0.07	0.27	0.16	0.07	0.17	0.07	0.04

	Bonf		BH		mBIC2		
	X	Z	X	Z	X	Z	X+Z
1	0.99	0.00	1.00	0.00	1.00	0.00	1.00 (Z: 0.00)
2	0.73	0.00	0.94	0.00	0.99	0.00	1.00 (Z: 0.00)
3	1.00	0.00	1.00	0.00	1.00	0.00	1.00 (Z: 0.00)
4	0.50	0.00	0.82	0.00	1.00	0.00	0.97 (Z: 0.00)
5	1.00	0.00	1.00	0.00	1.00	0.00	1.00 (Z: 0.00)
6	0.34	0.00	0.66	0.00	1.00	0.00	0.99 (Z: 0.00)
7	0.65	0.00	0.88	0.00	1.00	0.00	1.00 (Z: 0.00)
8	0.29	0.00	0.68	0.00	1.00	0.00	1.00 (Z: 0.00)
9	0.18	0.52	0.59	0.85	0.72	0.92	0.92 (Z: 0.63)
10	0.67	0.56	0.95	0.85	1.00	0.66	0.99 (Z: 0.03)
11	0.21	0.20	0.63	0.54	1.00	0.62	0.99 (Z: 0.21)
12	0.00	0.00	0.02	0.10	0.87	0.09	0.76 (Z: 0.23)
13	0.62	0.79	0.86	0.95	1.00	0.88	1.00 (Z: 0.14)
14	0.11	0.30	0.42	0.68	0.96	0.91	0.92 (Z: 0.15)
15	0.23	0.10	0.58	0.48	0.87	0.73	0.94 (Z: 0.21)
16	0.52	0.85	0.92	0.98	1.00	0.99	1.00 (Z: 0.03)
17	0.00	0.29	0.00	0.55	0.00	0.59	0.89 (Z: 0.89)
18	0.00	0.00	0.00	0.04	0.00	0.07	0.17 (Z: 0.17)
19	0.00	0.00	0.00	0.03	0.00	0.34	0.54 (Z: 0.54)
20	0.00	0.56	0.00	0.89	0.00	0.69	0.85 (Z: 0.85)
21	0.00	0.21	0.00	0.51	0.00	0.55	0.95 (Z: 0.95)
22	0.00	0.23	0.00	0.61	0.00	0.83	0.85 (Z: 0.85)

	Bonf		BH		mBIC2		
	X	Z	X	Z	X	Z	X+Z
1	0.00	0.53	0.00	0.85	0.00	0.75	0.95 (Z: 0.95)
2	0.00	0.60	0.00	0.87	0.00	0.78	0.89 (Z: 0.89)
3	0.00	0.05	0.00	0.23	0.00	0.45	0.88 (Z: 0.88)
4	0.06	0.96	0.15	1.00	0.40	0.95	0.98 (Z: 0.98)
5	0.02	0.80	0.07	0.97	0.63	0.89	0.95 (Z: 0.91)
6	0.00	0.15	0.03	0.55	0.07	0.44	0.48 (Z: 0.34)
7	0.00	0.30	0.08	0.73	0.23	0.64	0.86 (Z: 0.72)
8	0.08	0.08	0.27	0.24	0.81	0.21	0.78 (Z: 0.06)
9	0.58	0.16	0.79	0.34	0.98	0.16	0.99 (Z: 0.00)
10	0.53	0.62	0.8	0.92	0.97	0.44	0.98 (Z: 0.29)
11	0.79	0.84	0.95	0.99	1.00	0.96	0.99 (Z: 0.09)
12	1.00	1.00	1.00	1.00	1.00	1.00	0.99 (Z: 0.02)
13	0.00	0.00	0.00	0.00	0.00	0.00	0.01 (Z: 0.01)
14	0.00	0.01	0.00	0.09	0.00	0.12	0.32 (Z: 0.32)
15	0.00	0.01	0.00	0.04	0.00	0.06	0.02 (Z: 0.02)
16	0.03	0.05	0.15	0.25	0.42	0.11	0.62 (Z: 0.16)
17	0.00	0.25	0.01	0.71	0.34	0.23	0.49 (Z: 0.12)
18	0.78	0.06	0.93	0.45	1.00	0.36	0.96 (Z: 0.00)
19	0.85	0.00	0.98	0.01	1.00	0.00	1.00 (Z: 0.00)
20	0.54	0.00	0.85	0.00	0.96	0.00	1.00 (Z: 0.00)

Multiple regression vs Single marker tests

$$\hat{\beta} \approx \frac{Cov(Y-\beta_Q Q, X)}{VarX}$$

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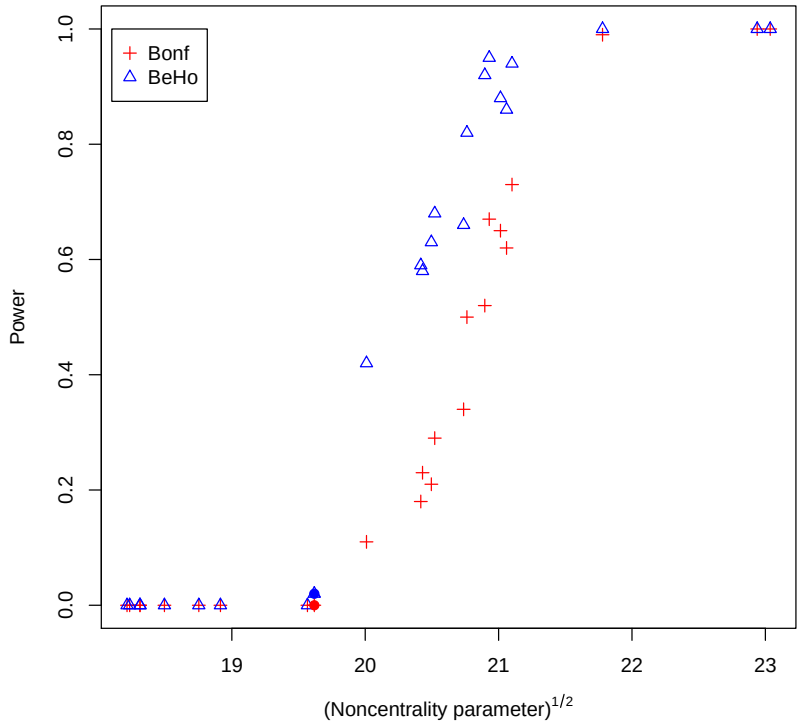
$$E \sum_{i=2}^{k} \beta_i Cov(X_1, X_i) = 0$$

$$Var(\sum_{i=2}^{k} \beta_i Cov(X_1, X_i)) \approx \sum_{i=2}^{k} \beta_i^2 \sigma_c^2$$

Power vs noncentrality parameter



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