Estimating Genome-wide Copy Number Using Allele Specific Mixture Models

Rafael A. Irizarry

Department of Biostatistics

Johns Hopkins Bloomberg School of Public Health

Ok Steve, I get it. I'll work harder on Copy Number.

Rafael A. Irizarry

Department of Biostatistics

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Affymetrix SNP chip terminology

Genomic DNA

SNP

A

TAGCCATCGGTANGTACTCAATGAT

G

Perfect Match probe for Allele A **ATCGGTAGCCATTCATGAGTTACTA**

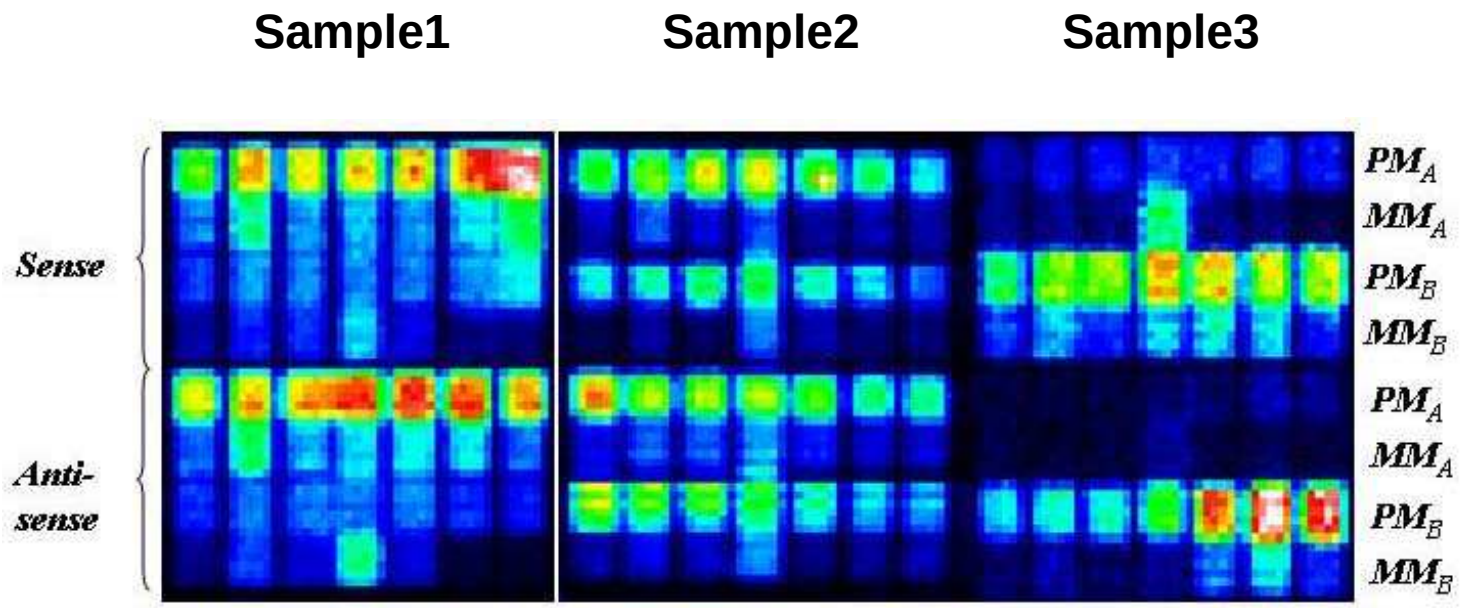
Perfect Match probe for Allele B **ATCGGTAGCCATCCATGAGTTACTA**

Genotyping: answering the question about the two copies of the chromosome on which the SNP is located:

Is a person **AA** , **AG** or **GG** at this Single Nucleotide Polymorphism?

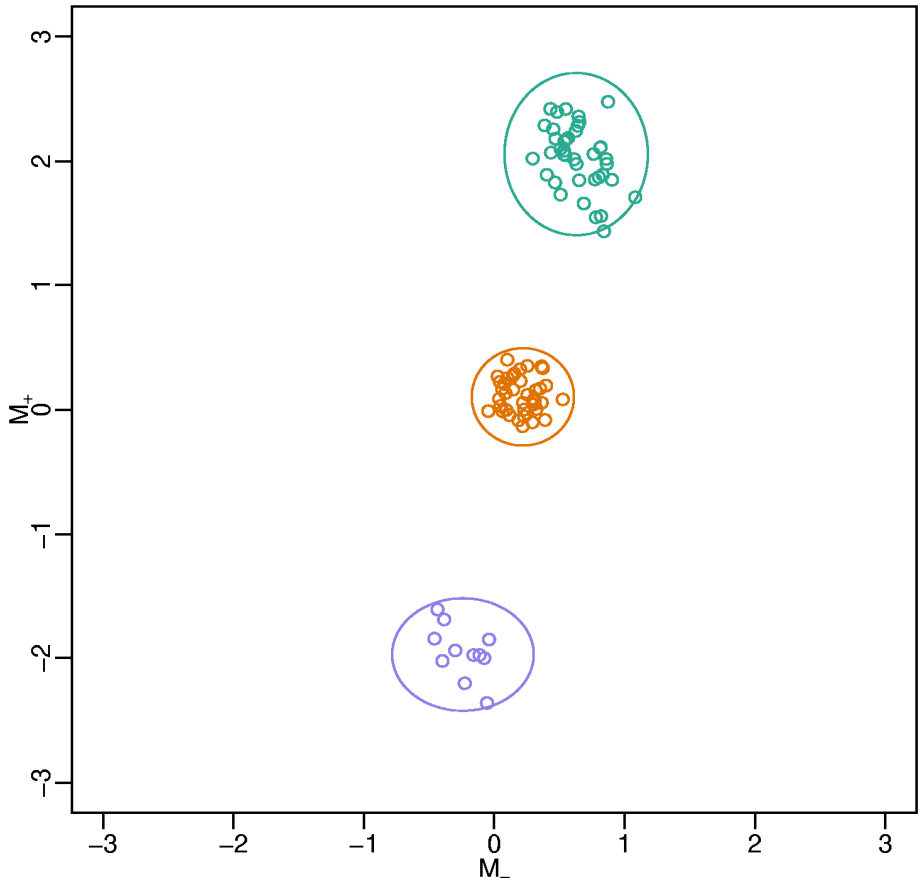
Probe Intensities

Fake (idealized) image for 3 samples on one SNP

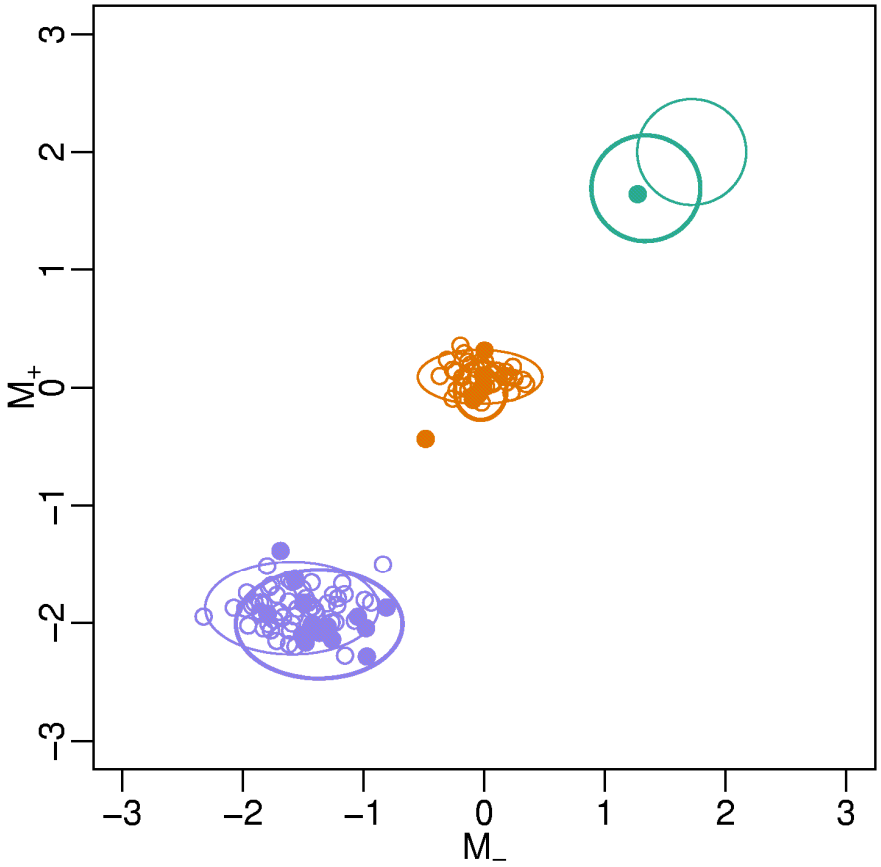


Fake, as the probes are not all adjacent on the chip
Idealized, as all the probes are high or low as they should be.

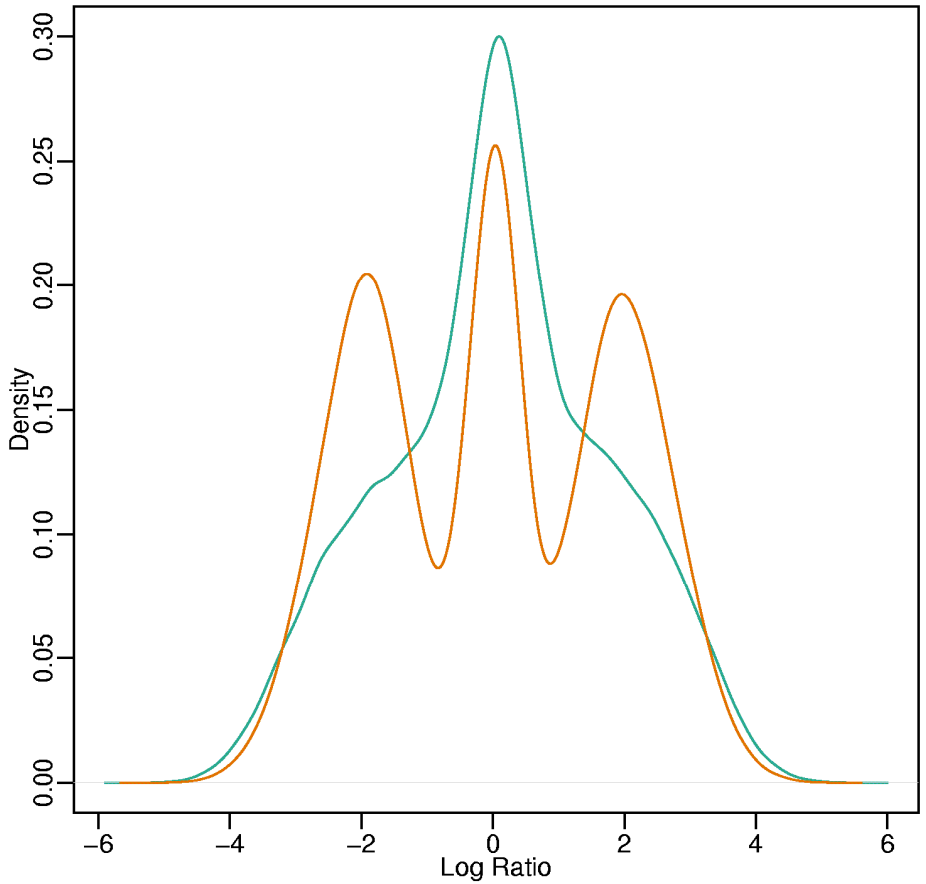
Fit model: define genotype regions and confidence measure



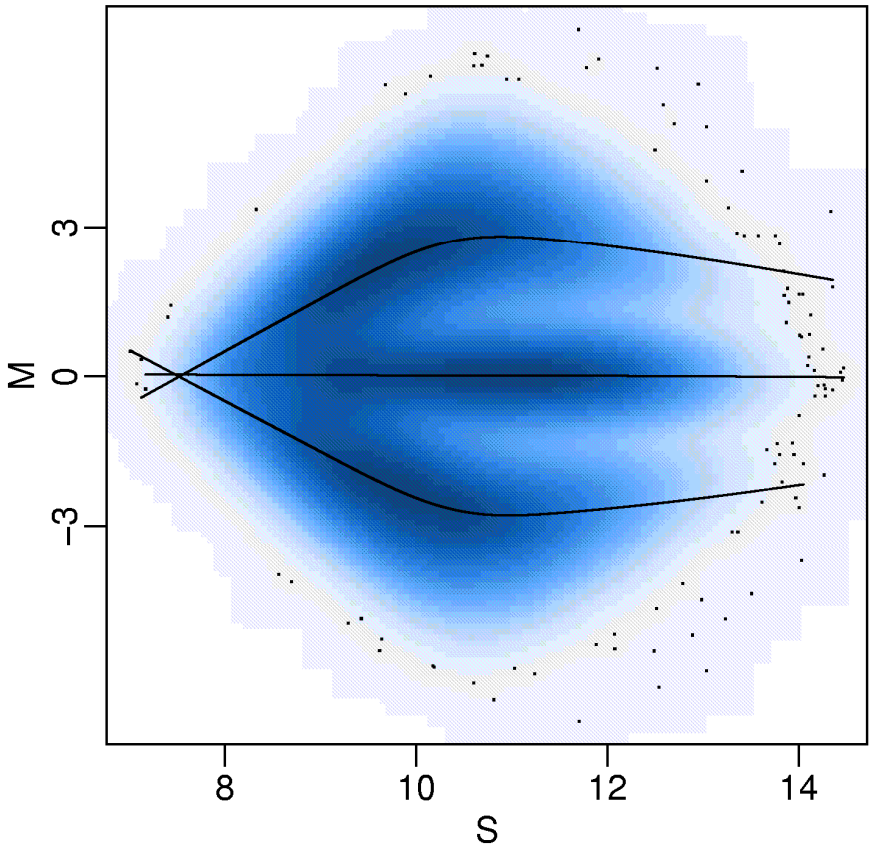
Low frequency alleles?



Different quality hybes



Intensity effect on M



Confidence measures

Figure 2A

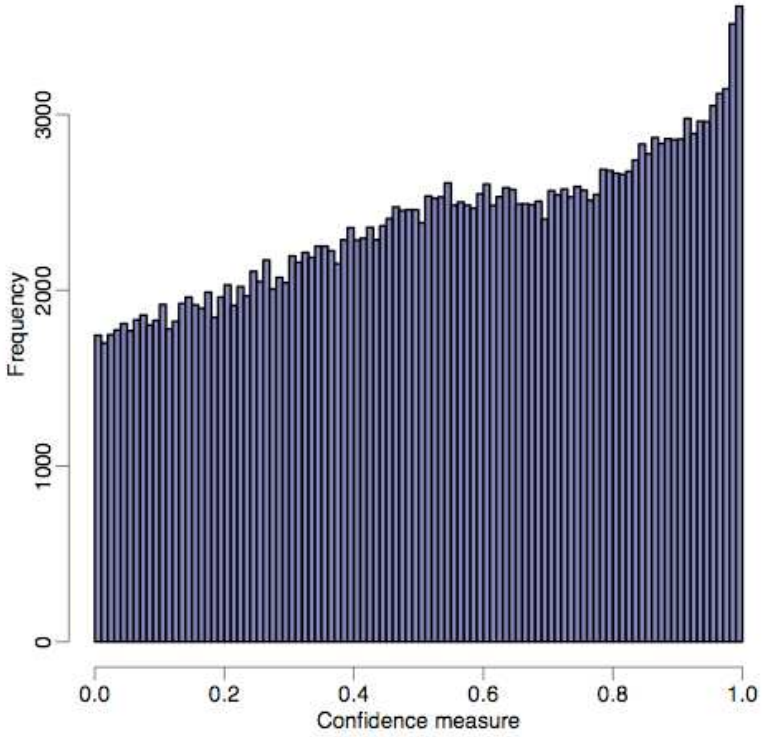
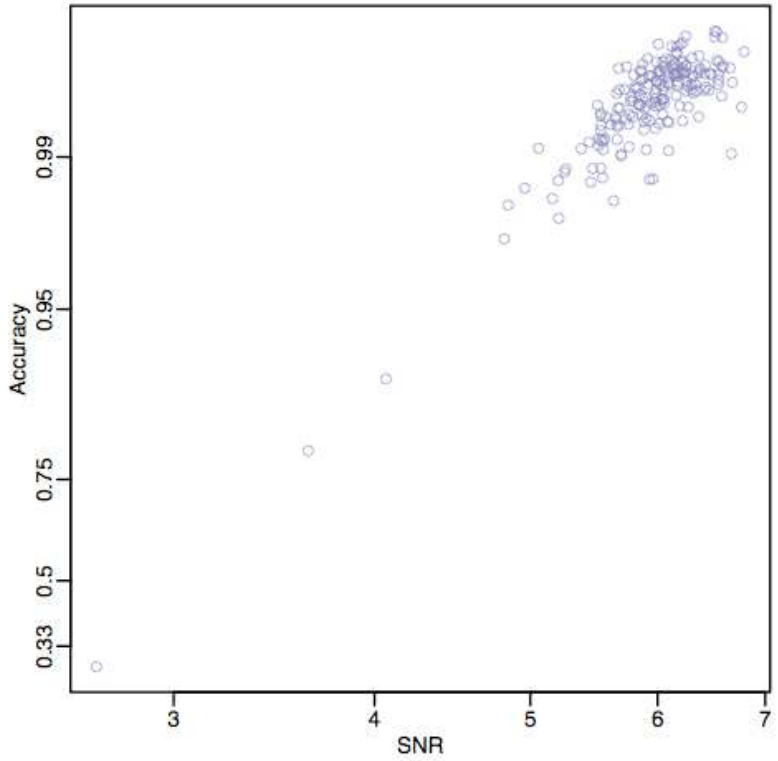
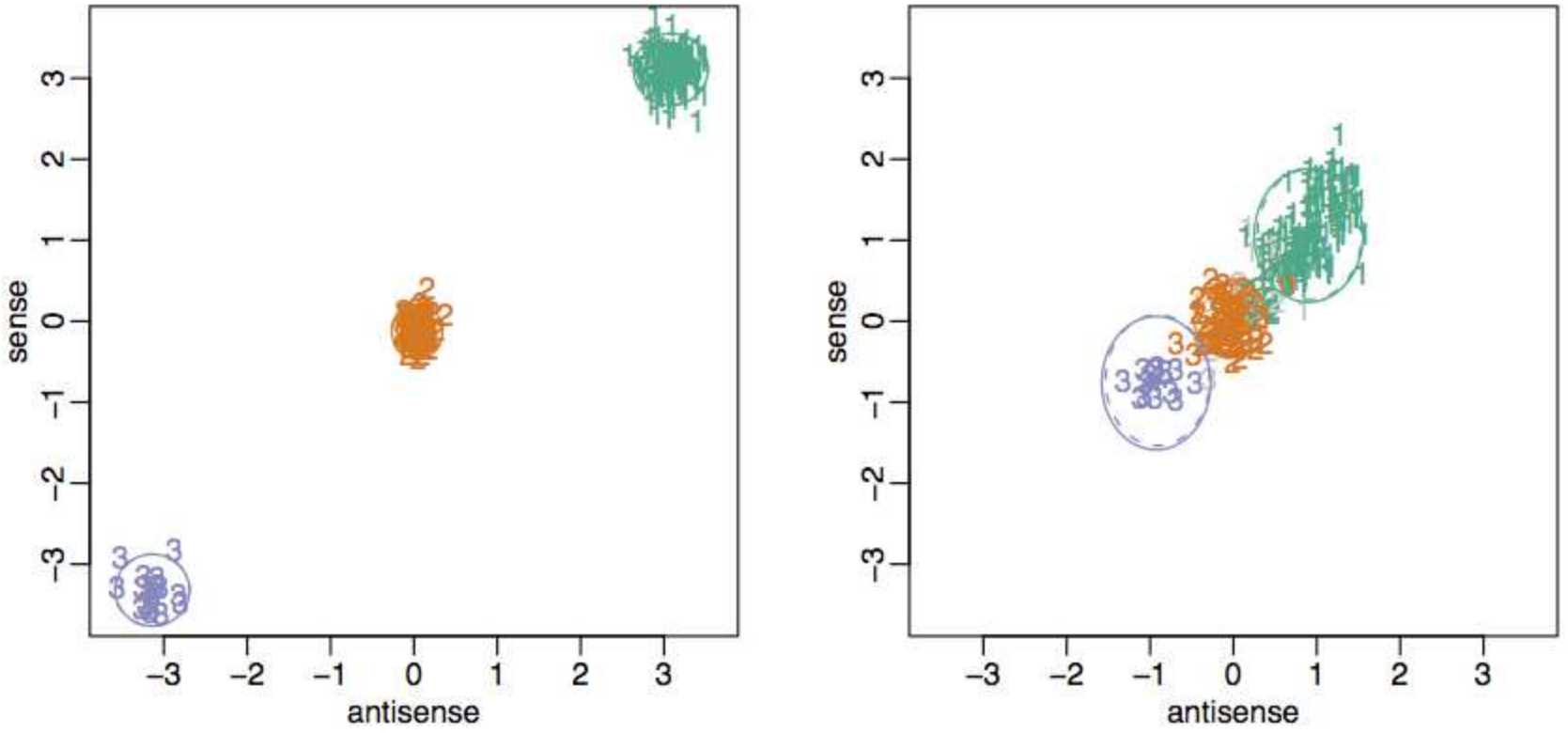


Figure 2B

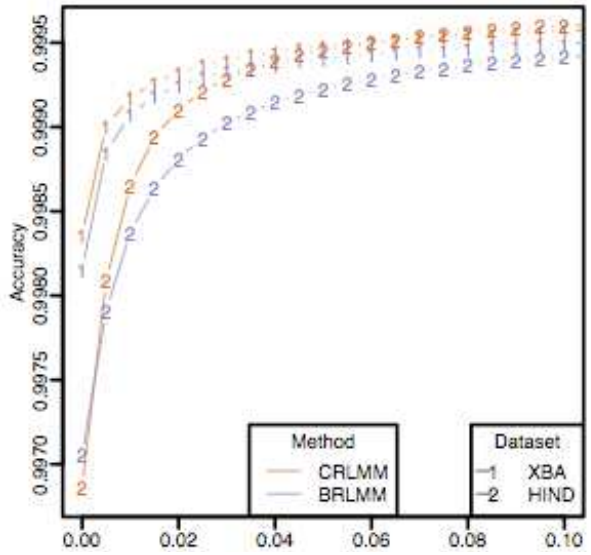


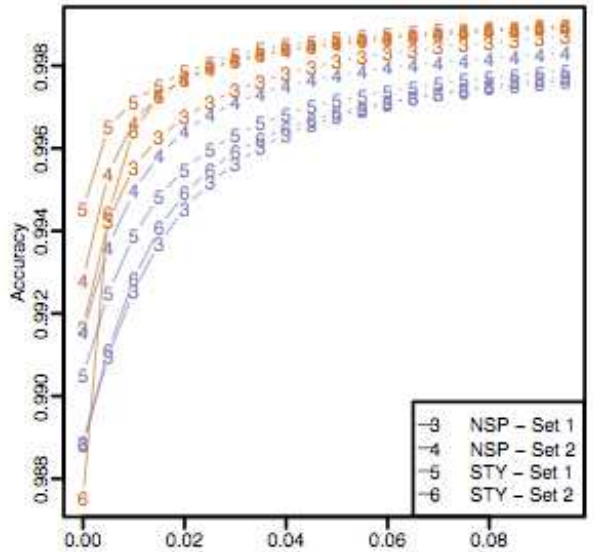
All arrays not equal!

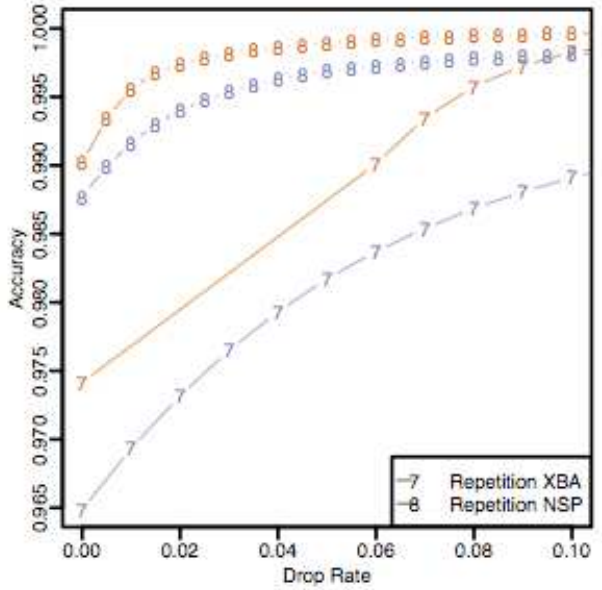
All SNPs not equal

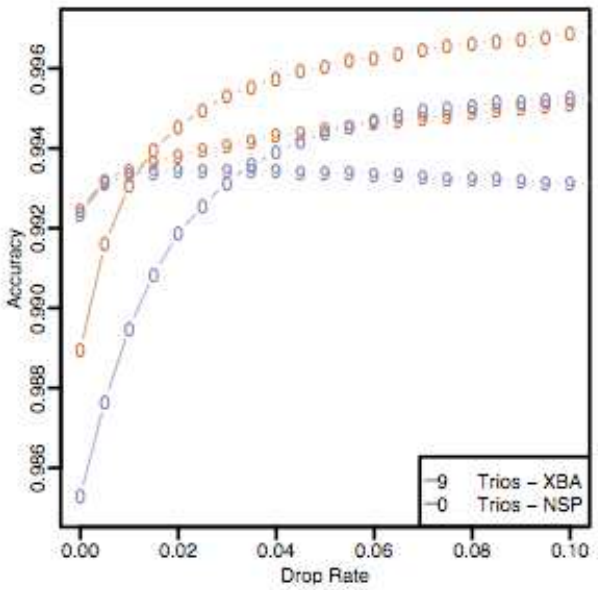


Accuracy versus Drop Rate

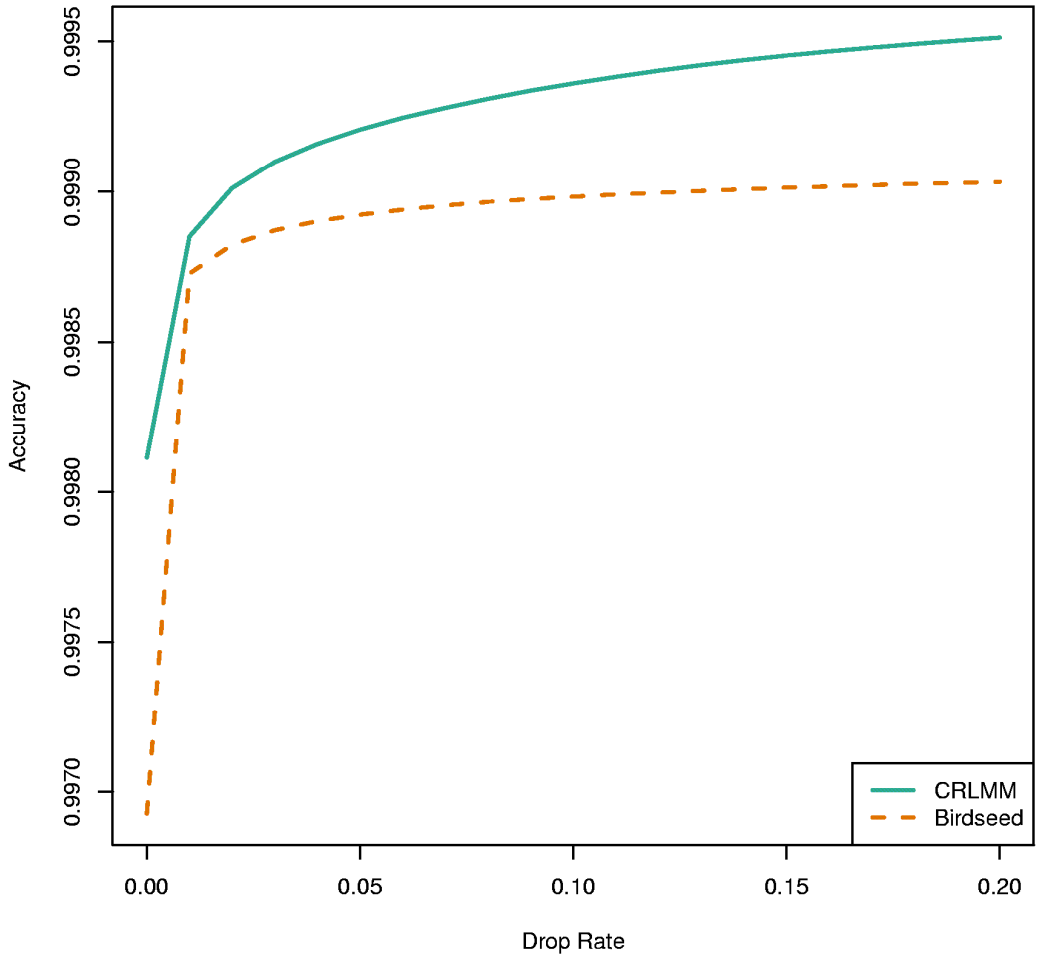








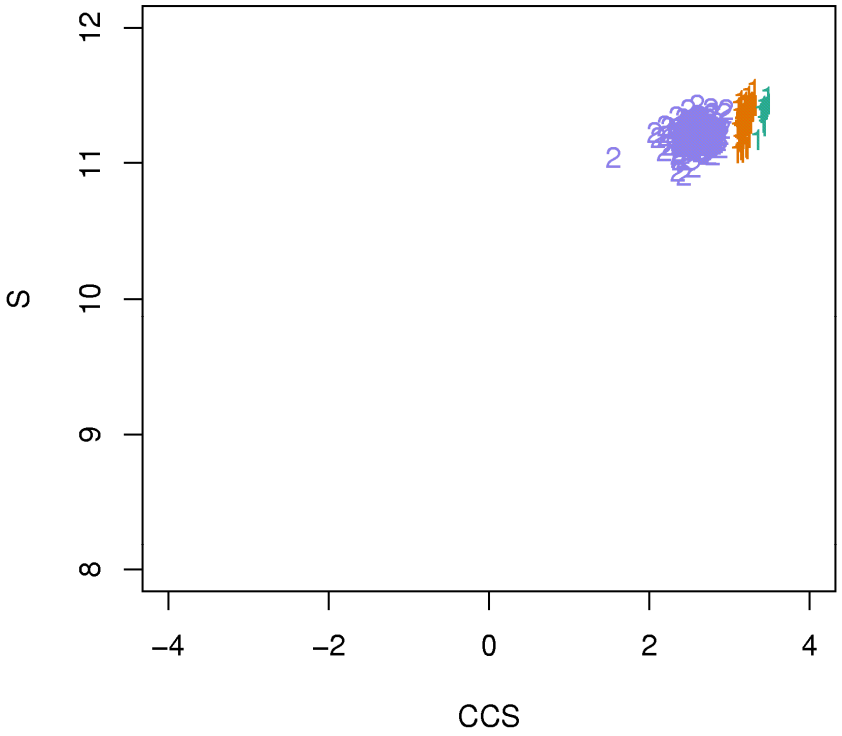
CRLMM v birdseed



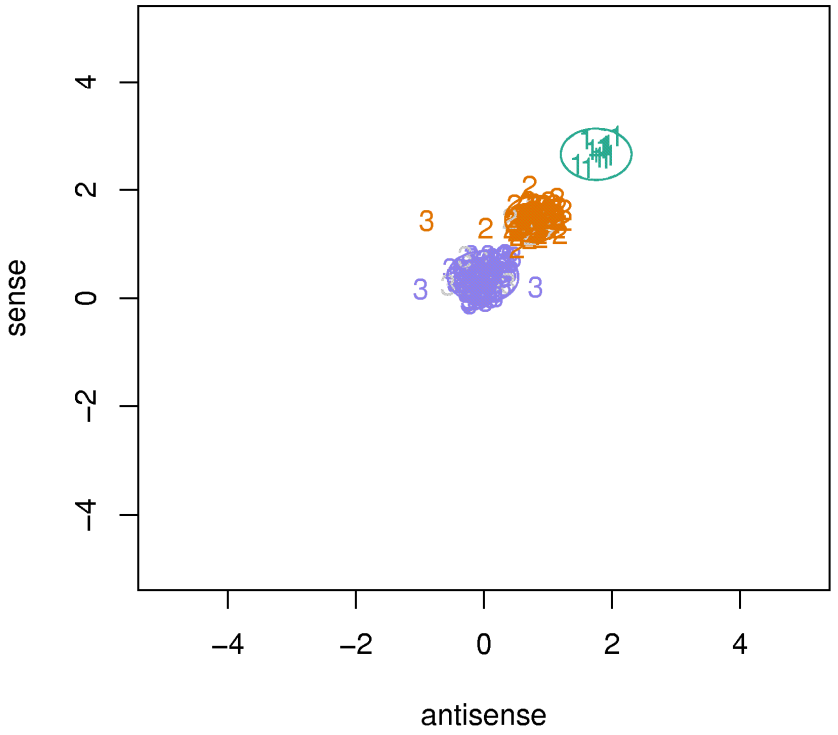
Why CRLMM better?

Big Shifts

BRLMM

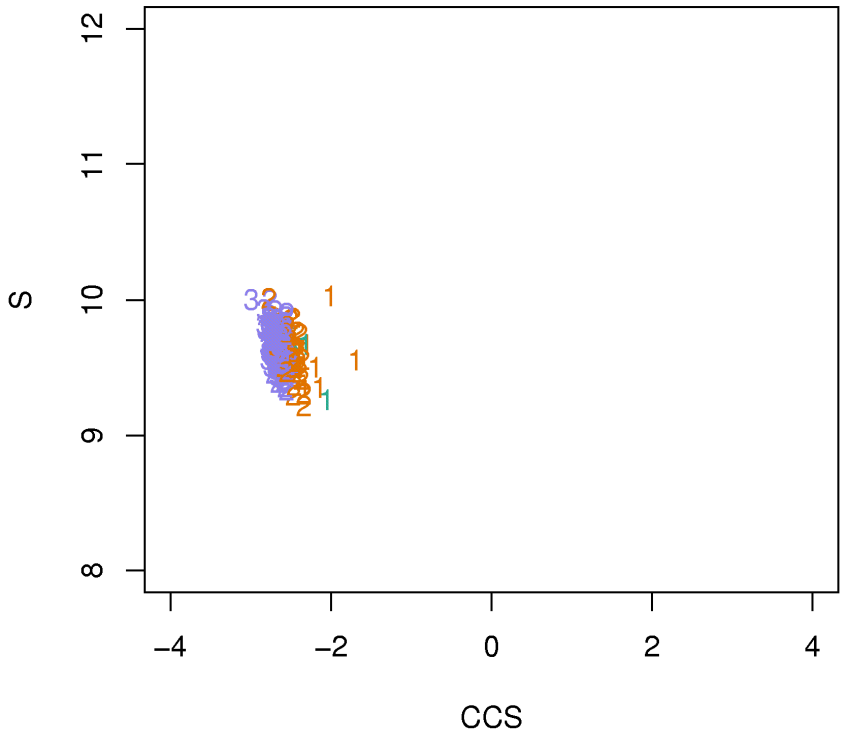


CRLMM

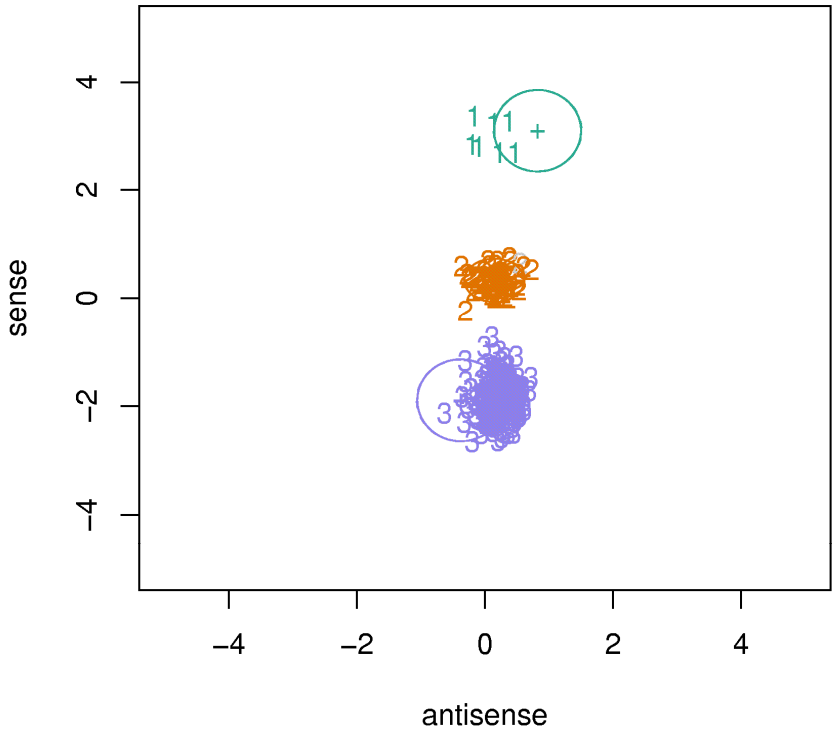


“Room for improvement” Probes

BRLMM



CRLMM



Improved Accuracy Prediction

Figure 3A

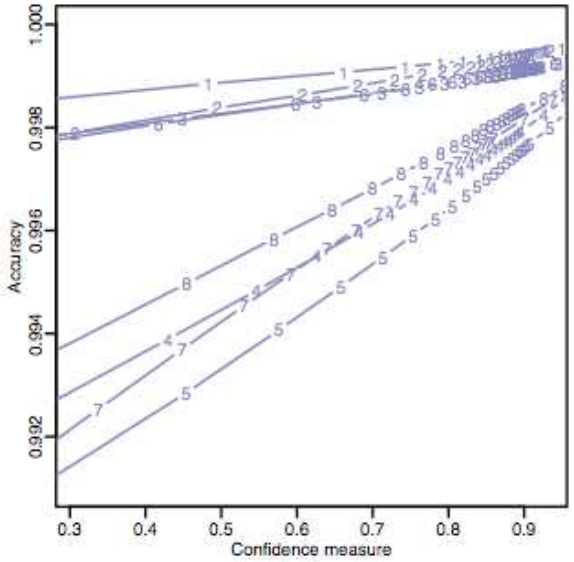


Figure 3B

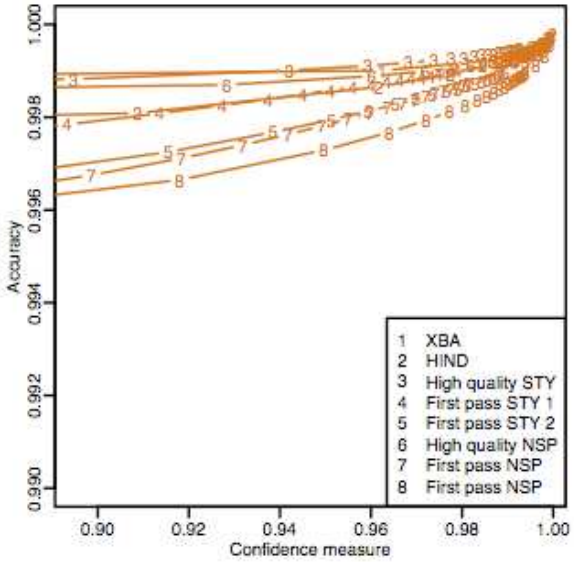
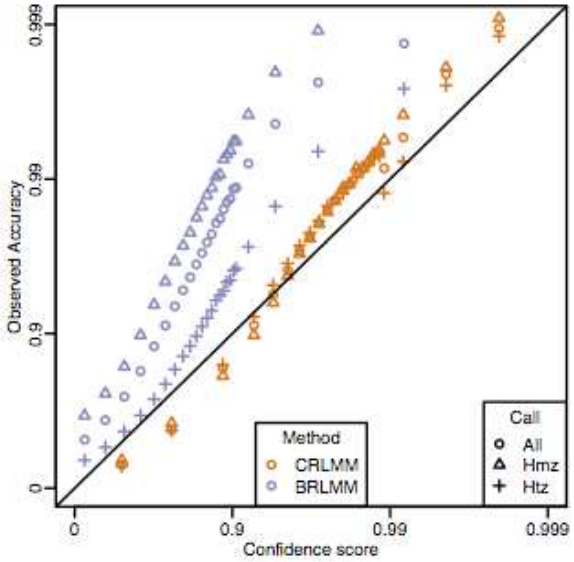
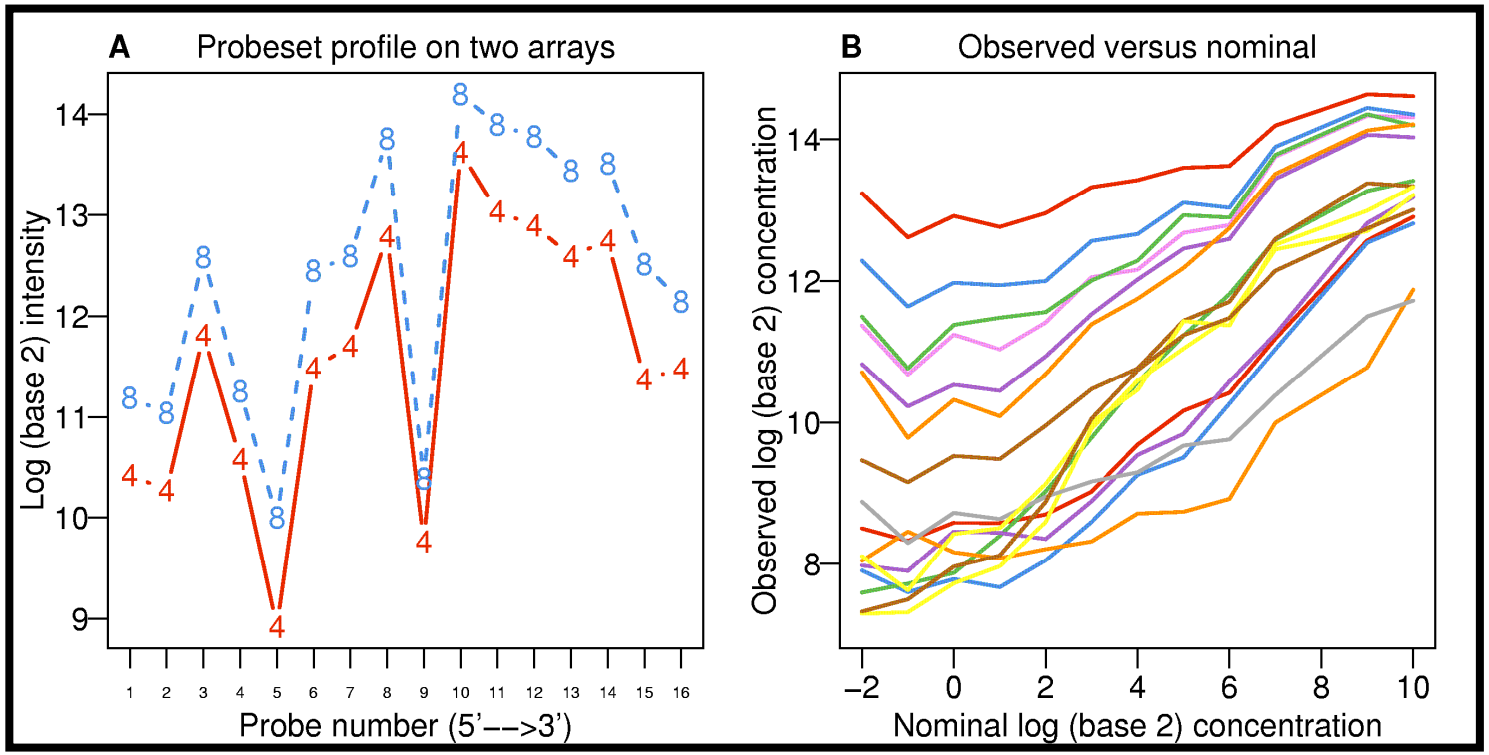


Figure 3C



Copy Number

Probe effect



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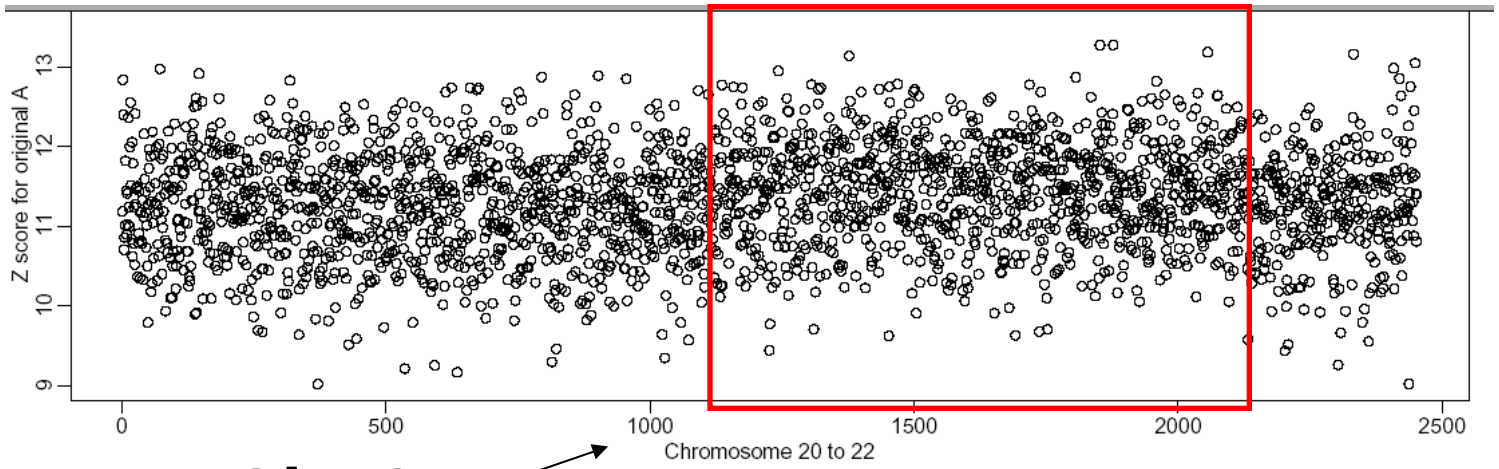
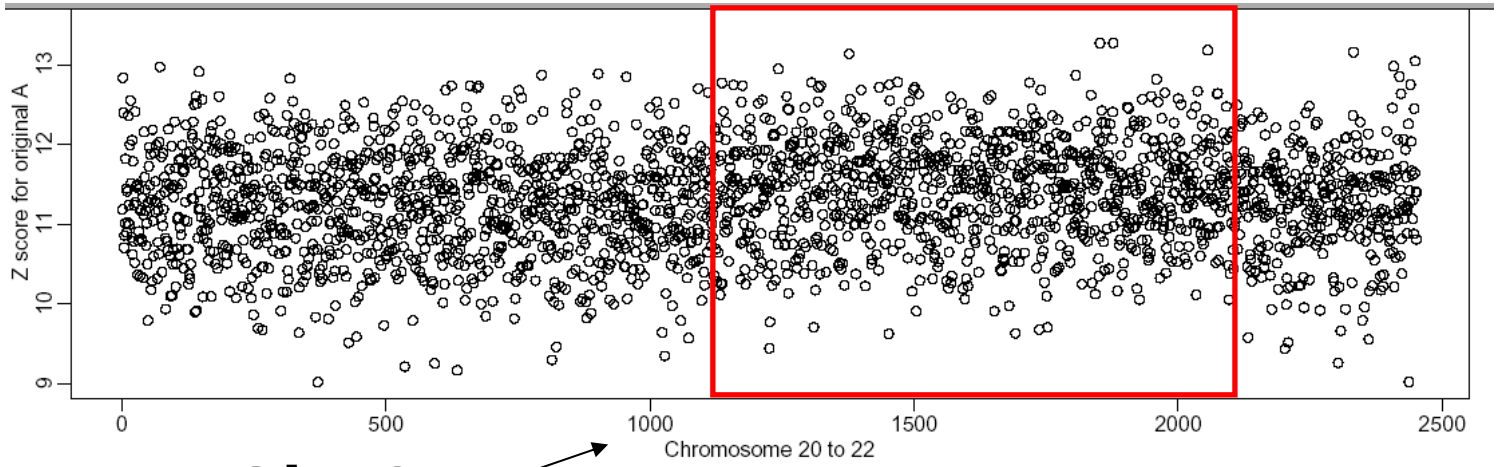


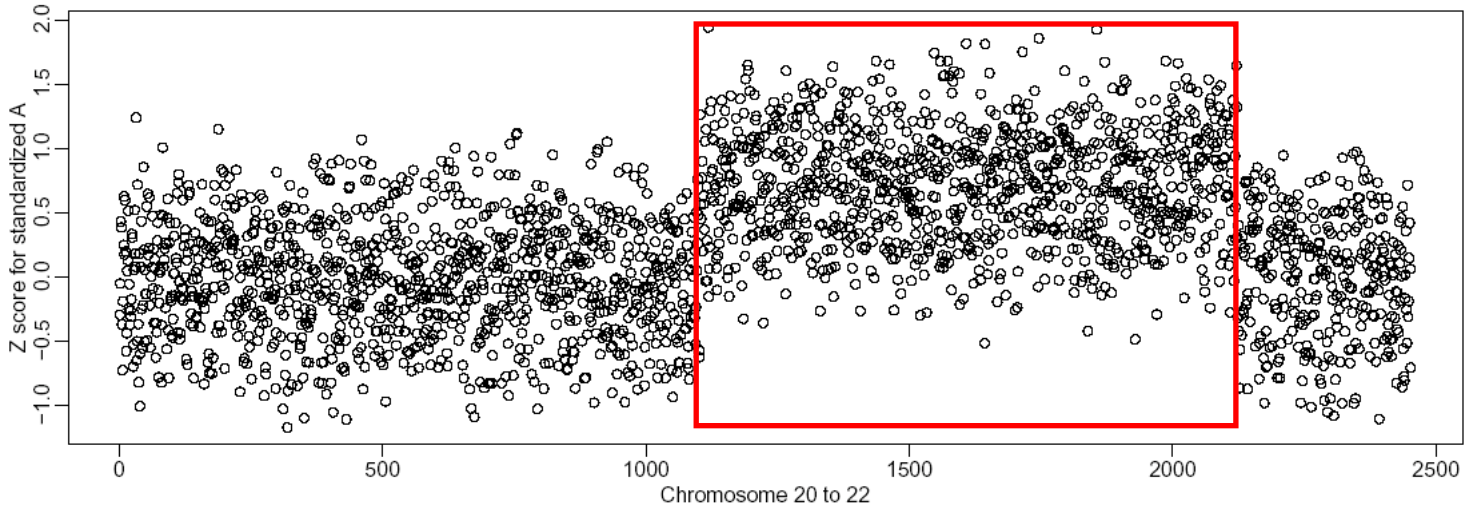
Chr 21

Now we want absolutes:
Probe effect a problem!

Copy Number



Chr 21



Statistical Problem

- A first step is to summarize probe intensities into single point estimates
- Regional (contiguous-point) copy number estimation
- Comparison across individuals

Model for Microarray Data

With expression arrays we see:

- Probe specific additive background noise
- Multiplicative probe effect
- Multiplicative measurement error

Wu et al., JASA (2004)

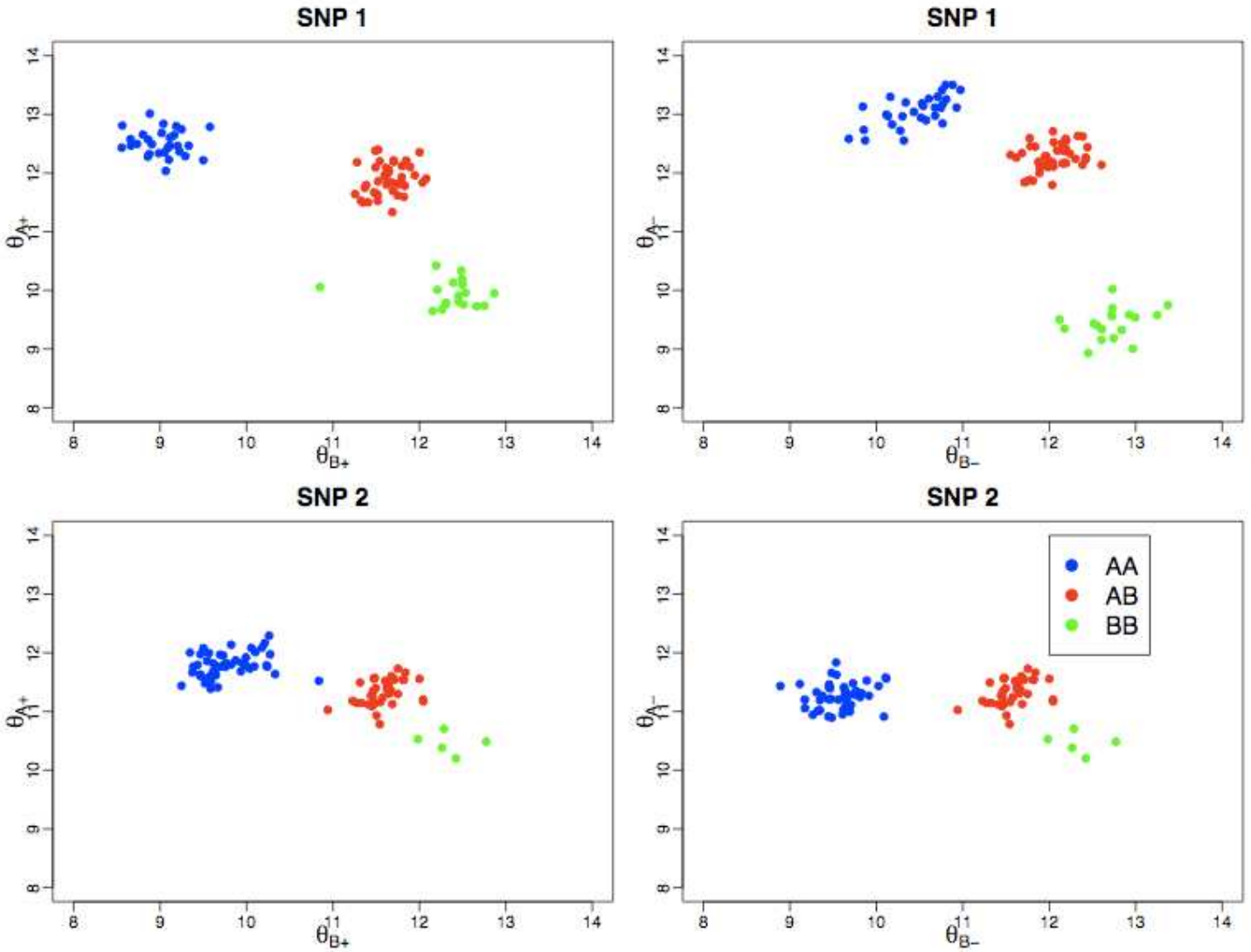
Model adapted for copy number applications:

$$I_{p,j} = \beta_p + C_p \exp(\phi_p + \varepsilon_{p,j})$$

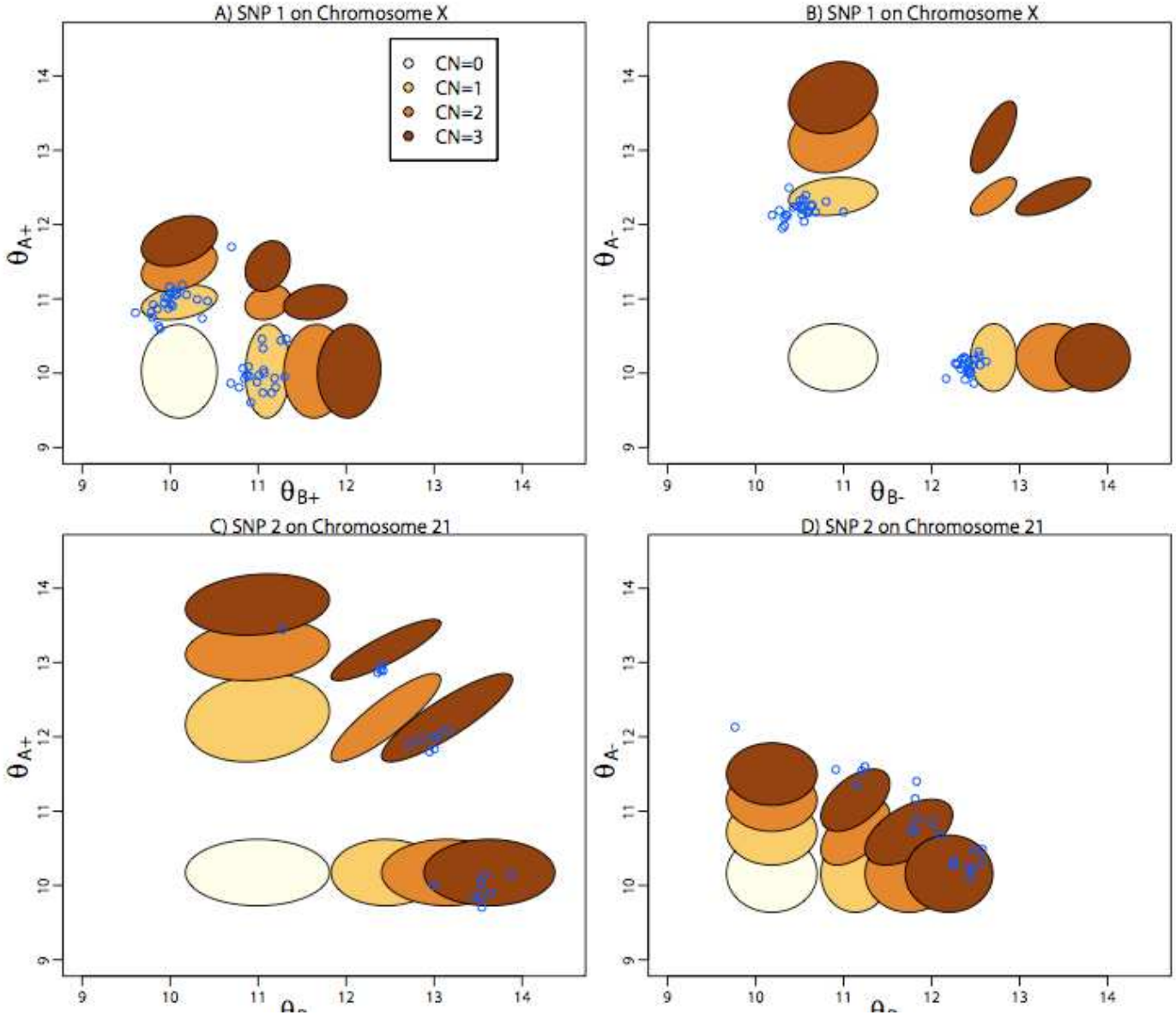
Some Current Approaches

- CNAT: Huang et al. Human Genomics (2004)
- CGAG: Nannya et al. Cancer Research (2005)
- GIM: Ishiwaka et al. Biochem Biophys Res Commun (2005)
- PLASQ: Laframboise et al. Biostatistics (2006)
- CARAT: Huang et al. BMC Bioinformatics (2006)

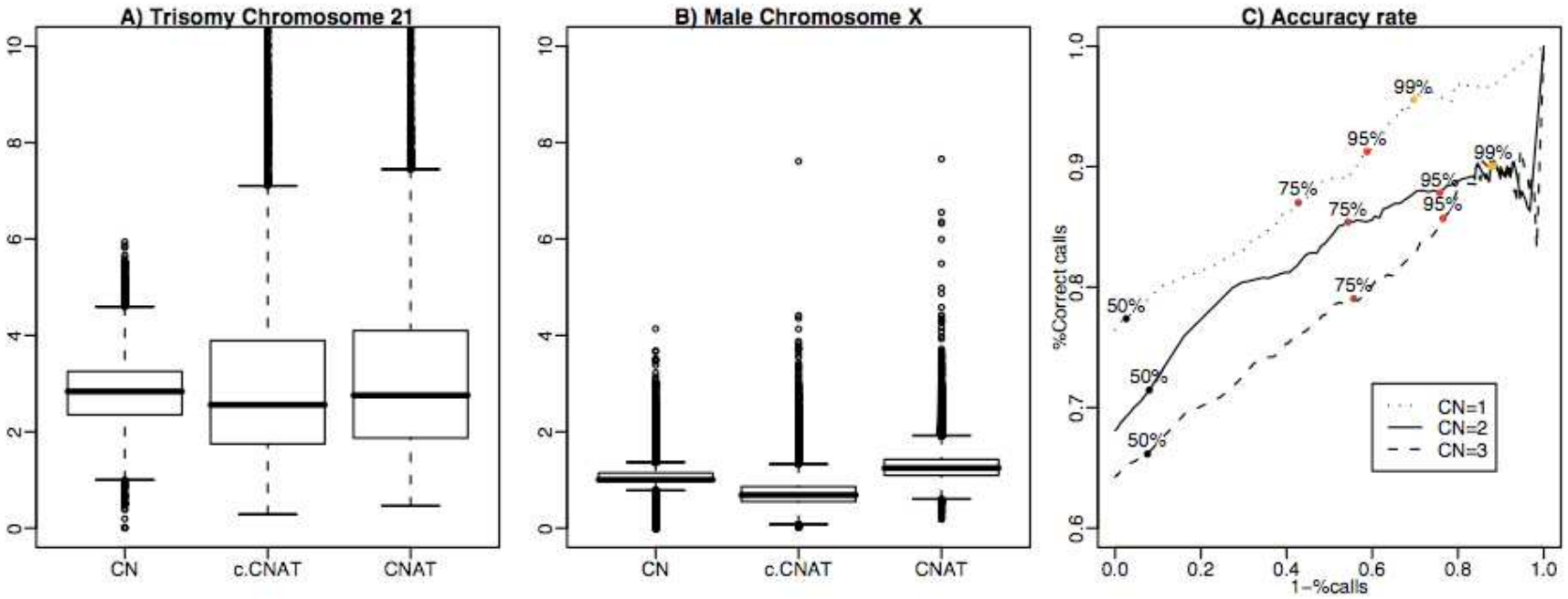
We use genotype calls?



Example: Mixture Models



Results



MSE	CN	c.CNAT	CNAT
CN= 3	0.66	3.68	3.55
CN= 1	0.10	0.16	0.19

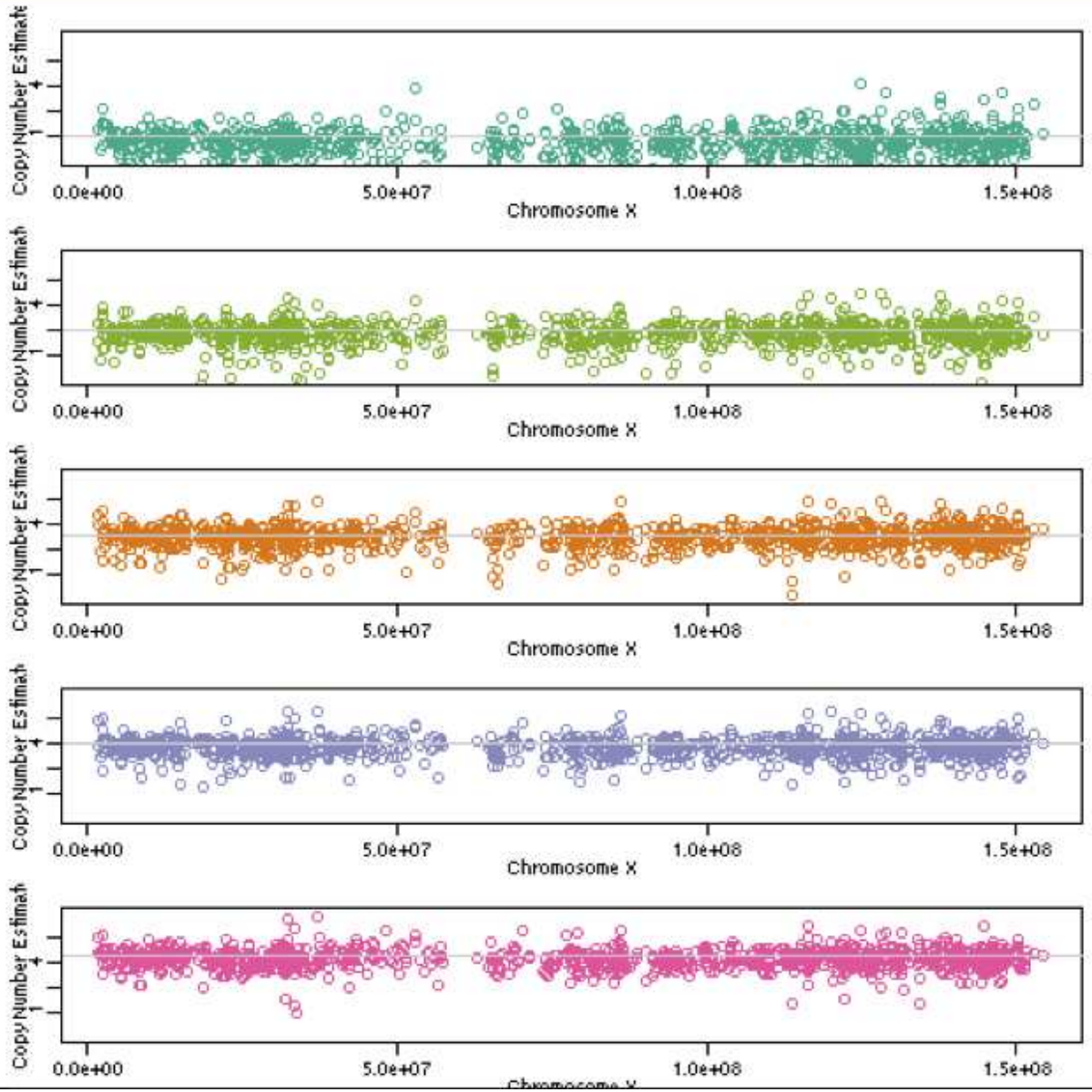
Inverse Regression

- Our model – SNP i, probe p

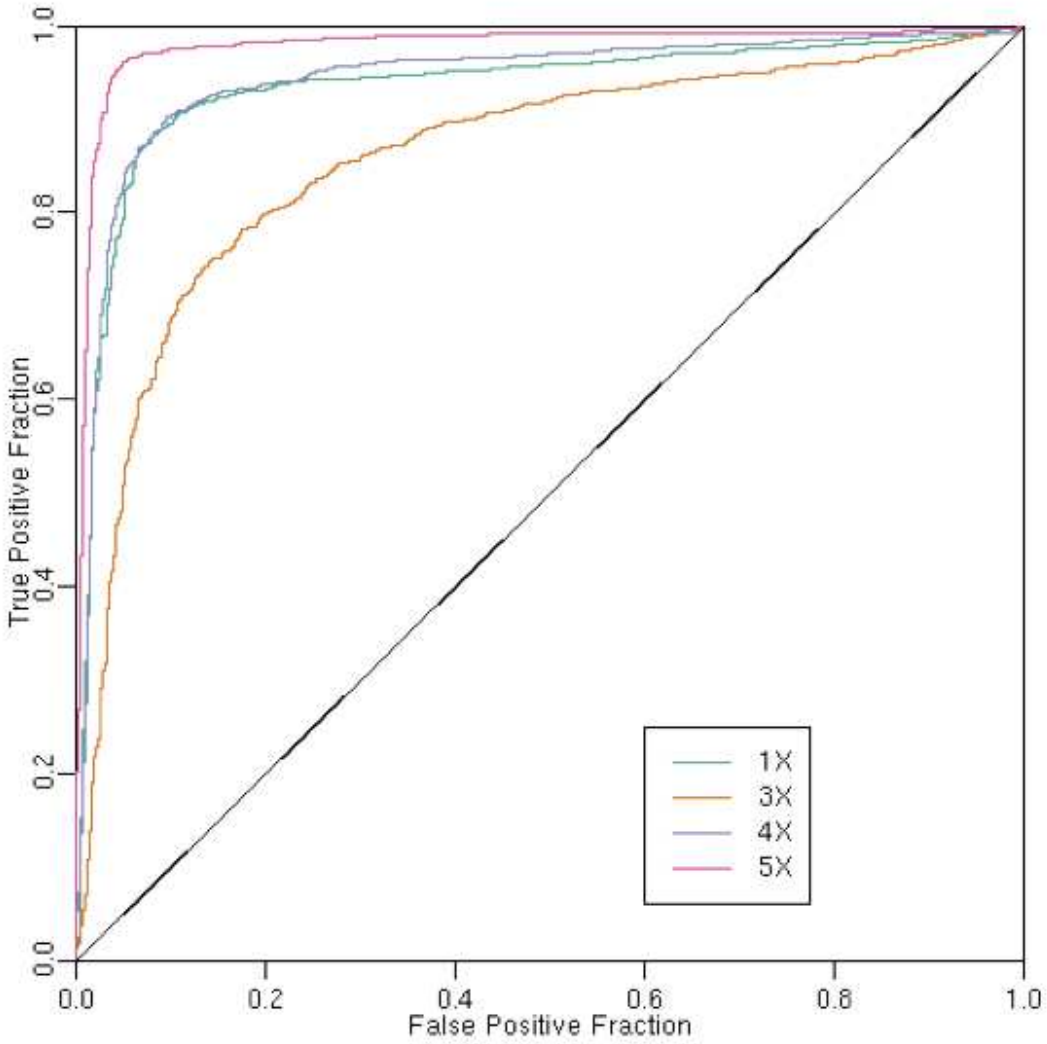
$$\begin{aligned} I_{A,j} &= \beta_A + \varepsilon_{1,A,j} + C_{A,j} \exp(\phi_A + \varepsilon_{2,A,j}) \\ I_{B,j} &= \beta_B + \varepsilon_{1,B,j} + C_{B,j} \exp(\phi_B + \varepsilon_{2,B,j}) \end{aligned}$$

- If $\log(I - \beta) < 1.96 * \sigma_{\varepsilon_1}$, then $C = 0$
- Else, $\log(C) = \log(I - \beta) - \phi \pm 1.96 * \sigma_{\varepsilon_2}$

Results – Chromosome X 1 – 5

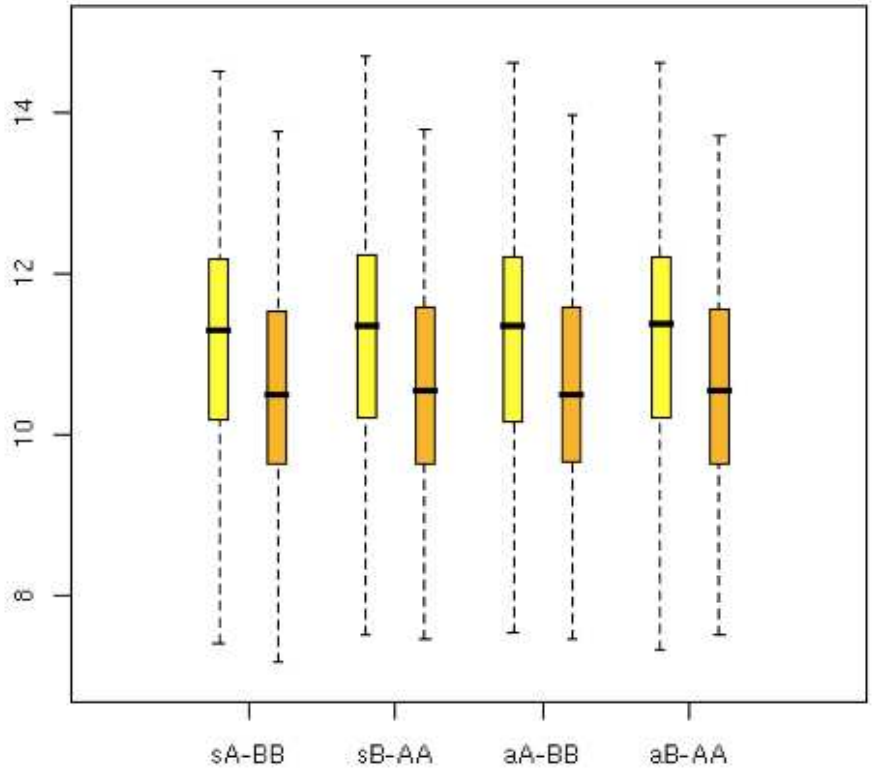


Results – Chromosome X 1 – 5



Cross-hybridizaton

- Assumption
  - Parameters for allele A only depend on C_A except for the correlation, and vice versa



Where is the gratuitous picture of Wolfgang?