Controlling the false discovery rate at detection of biological aberrations in -omics data

Djork-Arné Clevert, Andreas Mayr, Andreas Mitterecker, Günter Klambauer, and Sepp Hochreiter

Institute of Bioinformatics, JKU Linz

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Sources of -omics data

- Measurement techniques
  - Next generations sequencing
  - Mass Spec
  - Microarrays
- Application
  - mRNA and miRNA (gene expression profiling/transcriptomics)
  - Copy numbers (structural variant determination/genomics)
  - SNPs (genotyping/genomics)
  - Proteins and Metabolites (proteomics/metabolomics)
- Aberrations
  - Differentially expressed
  - Loss and gain of DNA segments, loss of heterozygosity
  - SNP frequencies
  - Different concentration

Characteristics of -omics data

- High-dimensional
  - # Genes, #miRNAs
  - # Loci
  - # SNPs
  - # Proteins
- Noisy
  - Measurement noise
  - Cross-hybridization, GC-content bias

Many falsely discovered aberrations or false positives (high FDR)

Problems caused by false discoveries

- FPs are not associated with an experimental condition
  while correction for multiple testing must take them into account
  - Decreases the study's discovery power
  - Decreases the significance of discoveries
- FPs misguide researchers

Demand for **methods with a low false discovery** rate at detection of biological aberrations in -omics data

Latent variable models

- Decompose observation into noise and signal by a generative model
  - Remove noise
    $\Rightarrow$ aberration detection in noise-free data
  - Decrease dimensionality
    $\Rightarrow$ signal variance for filtering (Informative/ Non-Informative calls)
- Model across samples for each gene, locus, SNP, or protein
- Use latent variable to represent the gene expression level, DNA copy number, genotype, or protein concentration

Our latent variable models

Next generations sequencing:

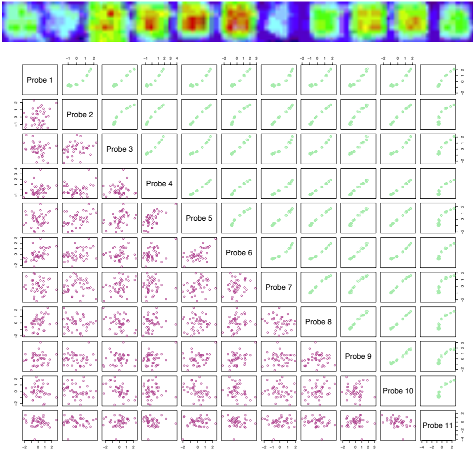
- cn.MOPS (Copy Number estimation by a Mixture Of PoissonS)
  $\longrightarrow$ DNA copy numbers

Microarray:

- FARMS (Factor Analysis for Robust Microarray Summarization)
  $\longrightarrow$ gene expression and miRNA
- cn.FARMS (Copy Number estimation by FARMS)
  $\longrightarrow$ DNA copy numbers

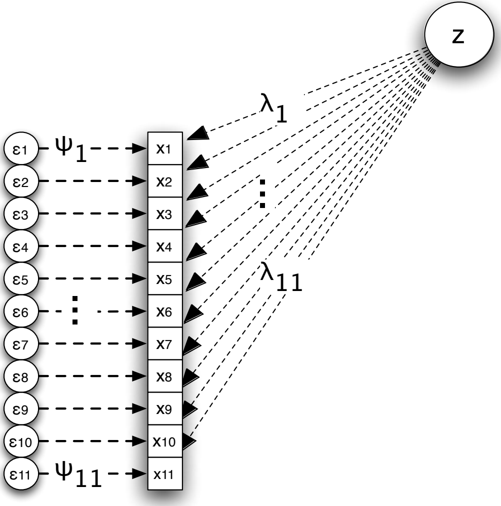
FARMS: Facts and assumptions

- Gene measured by different probes
- Goal: summarize probe intensities to an expression value
- Noise-free probes are positively correlated
    - Variable probe qualities
    - High quality probes are linear dependent
- Replicate probe intensities are Gaussian distributed

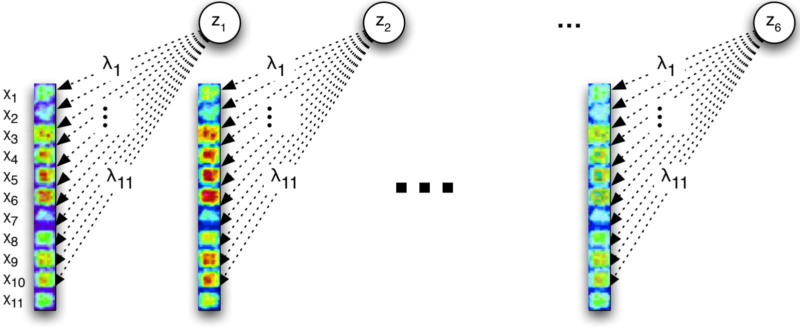


Higher mRNA concentration → larger intensities

FARMS: The idea



FARMS: The data



FARMS: The model

$$x = \boldsymbol{\lambda} \, z + \boldsymbol{\epsilon}$$

- $x, \boldsymbol{\lambda} \in \mathbb{R}^n$ and $z \sim \mathcal{N}(0,1)$, $\boldsymbol{\epsilon} \sim \mathcal{N}(0, \boldsymbol{\Psi})$.
- Probe intensities: $\{x\} = \{x_1, \ldots, x_N\}$ (log-transformed, standardized)
- Hidden factor z represents the gene expression level
- $\boldsymbol{\epsilon}$ accounts for the independent noise in the probes intensities
- $\boldsymbol{\epsilon}$ and z are independent

Model selection: maximize the likelihood $\left(x \sim \mathcal{N}\left(\boldsymbol{\lambda}\boldsymbol{\lambda}^T + \boldsymbol{\Psi}\right)\right)$ with respect to $\boldsymbol{\Psi}$ and $\boldsymbol{\lambda}$ by an EM algorithm

FARMS: Bayes framework

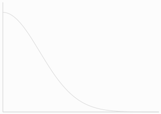
Posterior

$$p(\boldsymbol{\lambda}, \boldsymbol{\Psi} \mid \{x\}) \propto p(\{x\} \mid \boldsymbol{\lambda}, \boldsymbol{\Psi}) \; p(\boldsymbol{\lambda})$$

Prior knowledge

- Positive $\boldsymbol{\lambda}$ ensure positive probe correlation
- Most genes show no or small signal (large signals are of interest in a study)

Rectified Gaussian



$\lambda_j = \max\{y_j, 0\}$ with
$y_j \sim \mathcal{N}(\mu_\lambda, \sigma_\lambda)$

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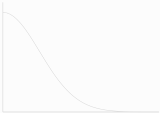

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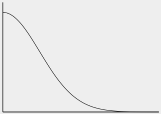


$\lambda_j = \max\{y_j, 0\}$ with

$y_j \sim \mathcal{N}\left(\mu_\lambda, \sigma_\lambda\right)$

FARMS: EM updates

E-step:

$$\mathrm{E}_{z_i|x_i}\left(z_i\right) = \mu_{z_i|x_i} \quad \text{and} \quad \mathrm{E}_{z_i|x_i}\left(z_i^2\right) = \mu_{z_i|x_i}^2 \; + \; \sigma_{z_i|x_i}^2$$

M-step:

$$\begin{aligned}
\lambda_j^{\mathrm{Gauss}} &= \left(\frac{1}{N}\sum_{i=1}^{N} x_{ij}\ \mathrm{E}_{z_i|x_i}\left(z_i\right) + \frac{1}{N}\,\frac{\mu_\lambda\ \Psi_{jj}^{\mathrm{old}}}{\sigma_\lambda^2}\right)\left(\frac{1}{N}\sum_{i=1}^{N}\mathrm{E}_{z_i|x_i}\left(z_i^2\right) + \frac{1}{N}\,\frac{\Psi_{jj}^{\mathrm{old}}}{\sigma_\lambda^2}\right)^{-1}\\
\lambda_j^{\mathrm{new}} &= \begin{cases} \lambda_j^{\mathrm{Gauss}} & \text{for} \quad \lambda_j^{\mathrm{Gauss}} \; > \; 0 \\ 0 & \text{for} \quad \lambda_j^{\mathrm{Gauss}} \; \leq \; 0 \end{cases} ,\\
\Psi_{jj}^{\mathrm{new}} &= \left[\mathrm{diagvect}\left(\frac{1}{N}\sum_{i=1}^{N} x_i x_i^T\right)\right]_j - \; \lambda_j^{\mathrm{new}}\left[\frac{1}{N}\sum_{i=1}^{N}\mathrm{E}_{z_i|x_i}\left(z_i\right) x_i\right]_j \; + \\
&\quad \frac{1}{N}\,\frac{\Psi_{jj}^{\mathrm{old}}}{\sigma_\lambda^2}\,\lambda_j^{\mathrm{new}}\left(\mu_\lambda \; - \; \lambda_j^{\mathrm{new}}\right)
\end{aligned}$$

FARMS: EM updates

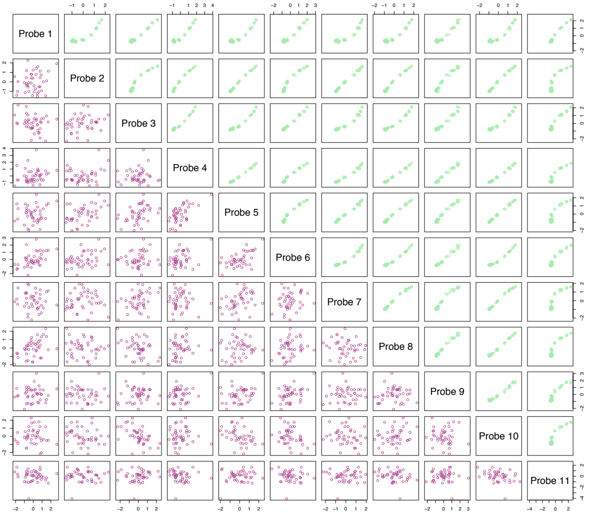
E-step:

$E_{z_i|x_i}(z_i) = \mu_{z_i|x_i}$ and $E_{z_i|x_i}(z_i^2) = \mu^2_{z_i|x_i} + \sigma^2_{z_i|x_i}$

M-step:

$$
\begin{aligned}
\lambda_j^{\text{Gauss}} &= \left(\frac{1}{N} \sum_{i=1}^{N} x_{ij} \, E_{z_i|x_i}(z_i) + \frac{1}{N} \frac{\mu_\lambda \, \Psi_{jj}^{\text{old}}}{\sigma_\lambda^2} \right) \left(\frac{1}{N} \sum_{i=1}^{N} E_{z_i|x_i}(z_i^2) + \frac{1}{N} \frac{\Psi_{jj}^{\text{old}}}{\sigma_\lambda^2} \right)^{-1} \\
\lambda_j^{\text{new}} &= \begin{cases} \lambda_j^{\text{Gauss}} & \text{for} \quad \lambda_j^{\text{Gauss}} > 0 \\ 0 & \text{for} \quad \lambda_j^{\text{Gauss}} \leq 0 \end{cases} , \\
\Psi_{jj}^{\text{new}} &= \left[\text{diagvect} \left(\frac{1}{N} \sum_{i=1}^{N} x_i x_i^T \right) \right]_j - \lambda_j^{\text{new}} \left[\frac{1}{N} \sum_{i=1}^{N} E_{z_i|x_i}(z_i) \, x_i \right]_j + \\
& \frac{1}{N} \frac{\Psi_{jj}^{\text{old}}}{\sigma_\lambda^2} \lambda_j^{\text{new}} \left(\mu_\lambda - \lambda_j^{\text{new}} \right)
\end{aligned}
$$

FARMS: Filtering by signal variance



FARMS: *z*-posterior

Variance of $z \mid x$

Model

$$x \; = \; \boldsymbol{\lambda} \; z \; + \; \boldsymbol{\epsilon}$$

and Gaussian z-prior $\mathcal{N}\left(0,1\right)$ results in the z-posterior $p(z \mid x)$:

$$\begin{aligned} z \mid x \; &\sim \; \mathcal{N}\left(\mu_{z|x} \; , \; \sigma^2_{z|x}\right) \\ \mu_{z|x} \; &= \; (x)^T \; \boldsymbol{\Psi}^{-1} \boldsymbol{\lambda} \; \left(1 \; + \; \boldsymbol{\lambda}^T \boldsymbol{\Psi}^{-1} \boldsymbol{\lambda}\right)^{-1} \\ \sigma^2_{z|x} \; &= \; \left(1 \; + \; \boldsymbol{\lambda}^T \boldsymbol{\Psi}^{-1} \boldsymbol{\lambda}\right)^{-1} \end{aligned}$$

FARMS: The I/NI call

The variance of z is decomposed into a signal and a noise part:

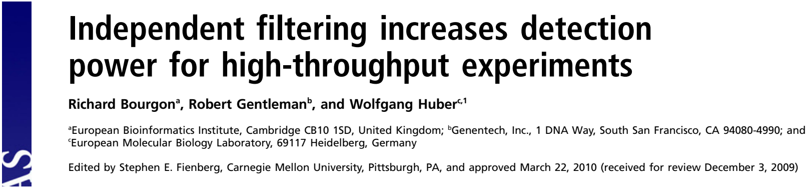
$$1 \; = \; \mathrm{var}(z) \; = \; \frac{1}{N} \sum_{i=1}^{N} \mathrm{E}_{z_i | x_i} \left(z_i^2 \right) \; = \; \frac{1}{N} \sum_{i=1}^{N} \left(\mu^2_{z_i|x_i} \; + \; \sigma^2_{z_i|x_i} \right)$$

$$\frac{1}{N} \sum_{i=1}^{N} \sigma^2_{z_i|x_i} \; = \; 1 \; - \; \frac{1}{N} \sum_{i=1}^{N} \mu^2_{z_i|x_i}$$

$$\sigma^2_{z|x} \; = \; 1 \; - \; \frac{1}{N} \sum_{i=1}^{N} \mu^2_{z_i|x_i} \; = \; \left(1 \; + \; \boldsymbol{\lambda}^T \boldsymbol{\Psi}^{-1} \boldsymbol{\lambda} \right)^{-1}$$

$\sigma^2_{z|x}$ is called the "Informative/NonInformative (I/NI) call" and is one minus the signal variance. We see that large $\boldsymbol{\lambda}$ (going with low noise $\boldsymbol{\Psi}$) leads to low variance of $z \mid x$ which means a precise conditional z.

FARMS: Independent I/NI calls filtering



Independent filtering increases detection power for high-throughput experiments

Richard Bourgon[a], Robert Gentleman[b], and Wolfgang Huber[c,1]

[a]European Bioinformatics Institute, Cambridge CB10 1SD, United Kingdom; [b]Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990; and [c]European Molecular Biology Laboratory, 69117 Heidelberg, Germany

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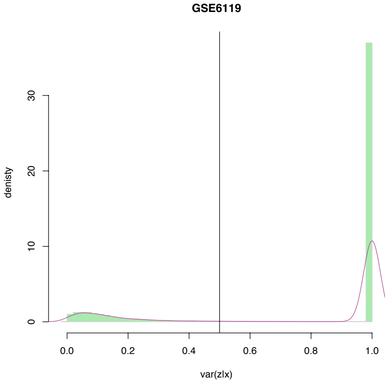
- For permutation invariant test statistics and for the t-test statistic T (only for Gaussian z-prior), the I/NI call filter applied to null hypotheses is independent of the statistic
- This guarantees type I error rate control if first filtering by I/NI calls, then using these statistics, and finally applying correction for multiple testing.
- http://www.bioinf.jku.at/software/cnfarms/proof_ini.pdf

FARMS: I/NI calls distribution



Bimodal distribution

- Enforced by the parameter prior
- Modes clearly separated (insensitive for filtering threshold)
- Works for unbalanced data (few samples contain a signal) in contrast to variance filtering (Bourgon et al. (2010))
- Works for few genes with a signal

A pipeline for gene expression analysis

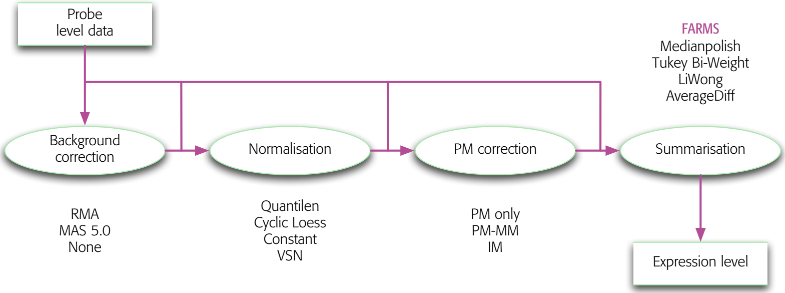


Figure: Probe-level modeling is a mandatory step

Receiver Operator Characteristics (ROC)

Affycomp II / GoldenSpike Benchmark (AUC - area under the curve):

	Intensity	FARMS	RMA	GCRMA	MAS 5.0	MBEI
HGU133	Low	**0.94**	0.51	0.62	0.07	0.21
	Med	**0.99**	0.91	0.94	0.00	0.43
	High	**1.00**	0.64	0.59	0.00	0.16
	Mean	**0.95**	0.60	0.69	0.05	0.26
HGU95	Low	**0.91**	0.57	0.45	0.09	-
	Med	**1.00**	0.91	0.91	0.00	-
	High	**0.98**	0.96	0.92	0.00	-
	Mean	**0.93**	0.65	0.57	0.06	-
GoldenSpike		**0.85**	0.76	0.78	0.28	0.39

Computational costs for processing 60 arrays

	FARMS	RMA	MAS 5.0	MBEI
Computational time [s]	**92**	384	851	591

Results I/NI call

- Leads on average to 84 (±1.5)% exclusion rate
  - Applied on 30 real life studies
  - A/P calls excluded only 33 (±1)%
- Validation was carried out on spiked-in data:

Exclusion rate on spiked-in data sets:

	Informative	Non-informative	Exclusion rate	Detected Spiked-ins	Detected Pseudo Spiked-ins
HGU133A	81	22219	99.63%	42/42	28/28*
HGU95_V2	56	12570	99.56%	14/14	5/5**
Hu. Gene 1.0 ST	40	19,753	99.80%	15/15***	-

*McGee et al. 2006; **Wolfinger and Chu 2002; Cope et al. 2004; ***long spiked-in fragments

I/NI call vs. A/P call

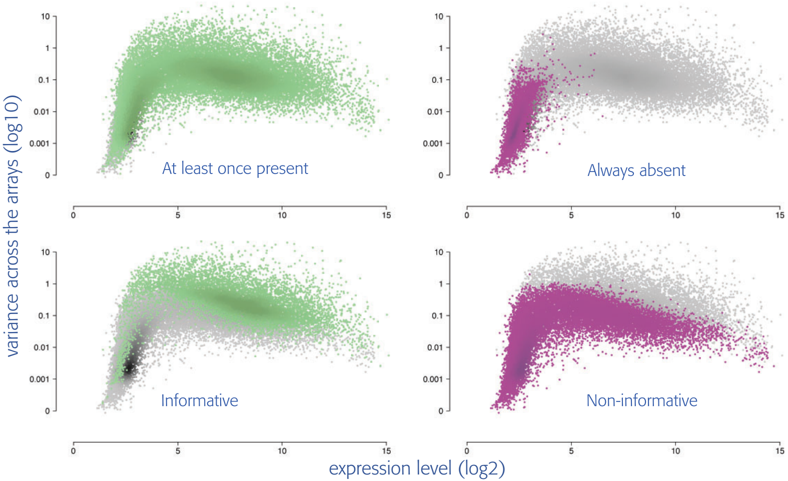


Figure: Variance and mean of genes selected by A/P calls and I/NI calls.

A pipeline for copy number analysis

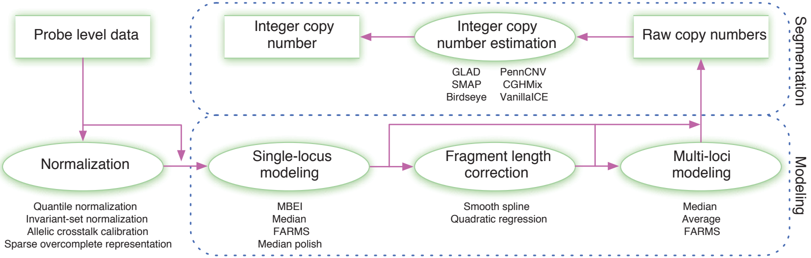


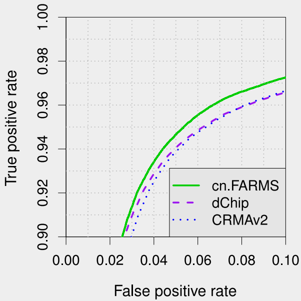
Figure: Copy number analysis for (Affymetrix) DNA genotyping arrays as a three-step pipeline: (1) Normalization, (2) Modeling, and (3) Segmentation.

Benchmark data sets

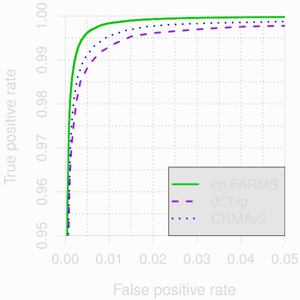
- 30 male and 30 female CEU founders
  - SNP 6.0 and 250K NSP Arrays
  - Classification task: distinguish males from females by their copy number on the X chromosome
- Evaluation on:
  - Single-locus / multi-loci classification (window mode)
  - Multi-loci summarization with
    - cn.FARMS
    - Median locus for dChip and CRMA_v2

ROC-Curve (250K arrays)

single-locus



multi-loci, 3 markers



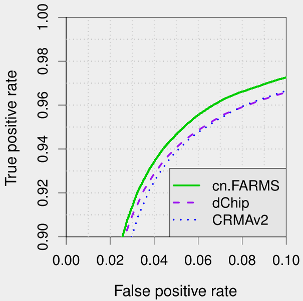
TPR / FPR

True positive rate (TPR) = TP/(TP+FN)

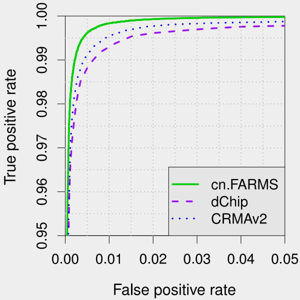
False positive rate (FPR) = FP/(FP+TN)

ROC-Curve (250K arrays)

single-locus



multi-loci, 3 markers



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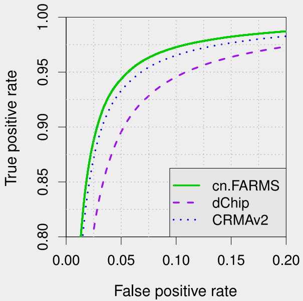
ROC-Curve (SNP 6.0 arrays)

single-locus



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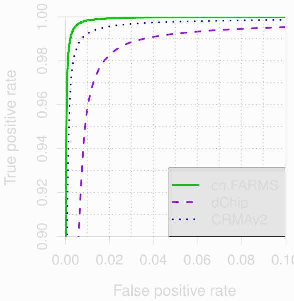

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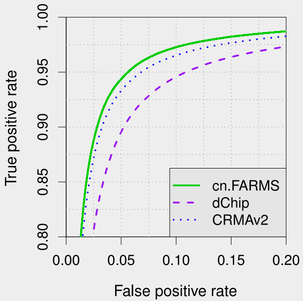

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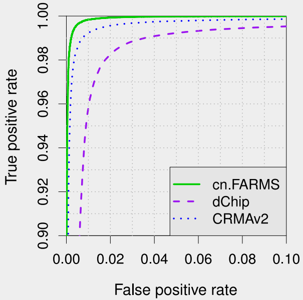

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True positive rate (TPR) = TP/(TP+FN)

False positive rate (FPR) = FP/(FP+TN)

Results cn.FARMS

		Affymetrix Mapping250K_NSP			Affymetrix SNP 6.0		
Loci	Criteria	**cn.FARMS**	CRMA_v2	dChip	**cn.FARMS**	CRMA_v2	dChip
1	AUC	**0.9852**	0.9820	0.9819	0.9838	0.9807	0.9721
	FP	**8472**	9106	9018	56145	68593	77438
	p-value	–	1.8e-65	3.1e-26	–	1e-1160	1e-6049
2	AUC	**0.9983**	0.9974	0.9969	0.9983	0.9963	0.9894
	FP	**1375**	1449	1611	9777	11705	18039
	p-value	–	2.7e-4	2.5e-12	–	1e-317	1e-3713
3	AUC	**0.9998**	0.9995	0.9992	0.9998	0.9990	0.9953
	FP	**240**	366	440	1573	3462	6625
	p-value	–	2.6e-38	7.2e-58	–	1e-896	1e-3455

Table: AUC values at the sex classification task for 59 HapMap CEU founders based on the X chromosome copy numbers:

CNV detection benchmark

- "The International HapMap Project" phase 2 data set with Affymetrix SNP 6.0 arrays
  - Goal is to identify true rare CNV regions with a low FDR
  - "True CNV regions" are those regions which were detected and verified by different bio-technologies
    - NimbleGen tiling arrays, Agilent CGH arrays, Illumina Infinium genotyping (Human660W)
  - 2,515 true CNV regions as reference
- CNV calling criteria:
  - I/NI call for cn.FARMS
  - Variance of the raw copy numbers on the samples for dChip and CRMA_v2

CNV detection plot

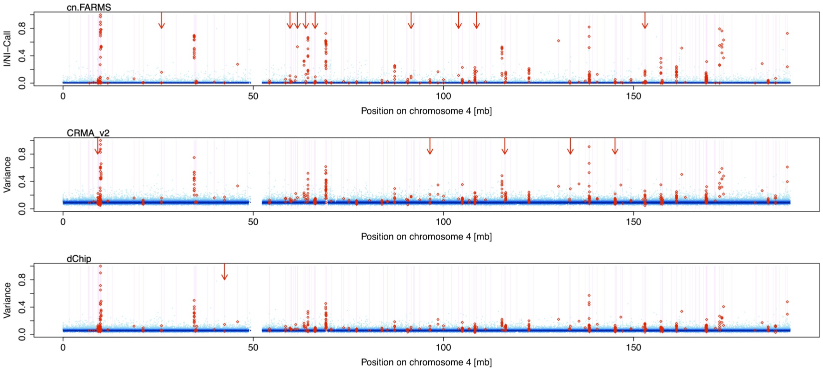
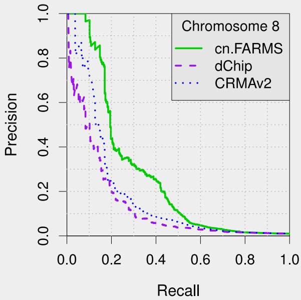


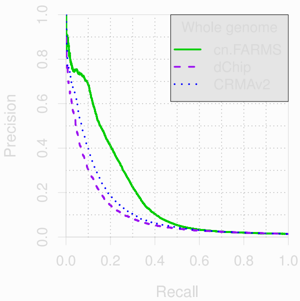
Figure: CNV calling plots across chromosome 4 for 3-loci regions (each point in the plot summarizes 3 loci).

CNV detection on HapMap (multi-loci 3)

Chromosome 8



Whole genome



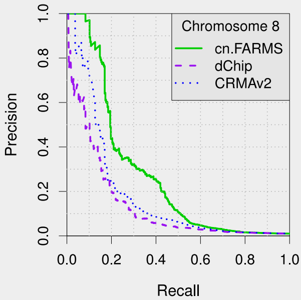
Precision / Recall

Recall = TP/(TP+FN)

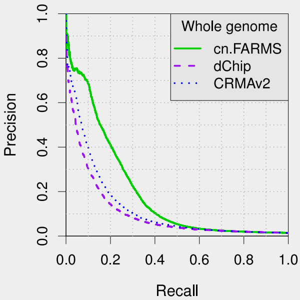
Precision = TP/(TP+FP) = 1 - FDR

CNV detection on HapMap (multi-loci 3)

Chromosome 8



Whole genome



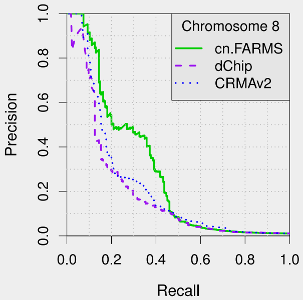
Precision / Recall

Recall = TP/(TP+FN)

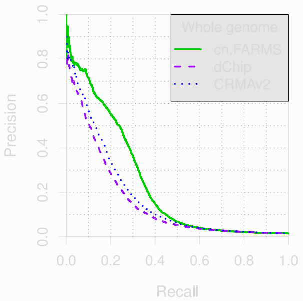
Precision = TP/(TP+FP) = 1 - FDR

CNV detection on HapMap (multi-loci 5)

Chromosome 8



Whole genome



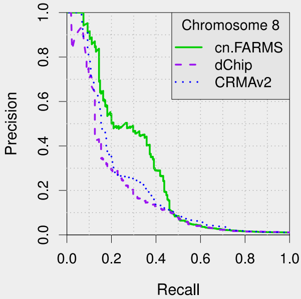
Precision / Recall

Recall = TP/(TP+FN)

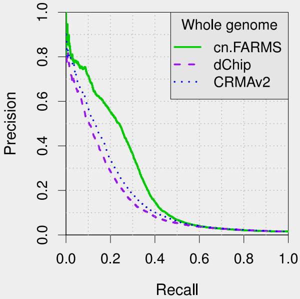
Precision = TP/(TP+FP) = 1 - FDR

CNV detection on HapMap (multi-loci 5)

Chromosome 8



Whole genome



Precision / Recall

Recall = TP/(TP+FN)

Precision = TP/(TP+FP) = 1 - FDR

Interim results

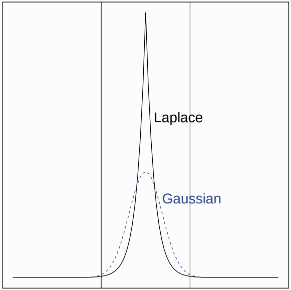
- cn.FARMS outperforms aroma.affymetrix, *dChip*, *CNAG* and *CNAT* in terms of sensitivity and specificity
  - Shows good signal detection while being robust against measurement noise
- I/NI call correctly prioritizes CNV regions of interest
  - Reduces the FDR at CNV detection

Rare CNV events

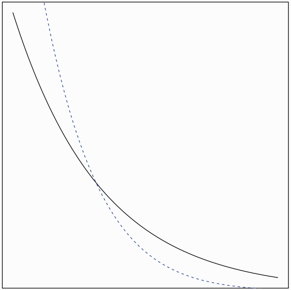
Sparse data

CNV data is sparse with an kurtosis larger than 30 → change the model assumption to a Laplacian distributed hidden variable z.

Gauss vs. Laplace



Close up Gauss vs. Laplace



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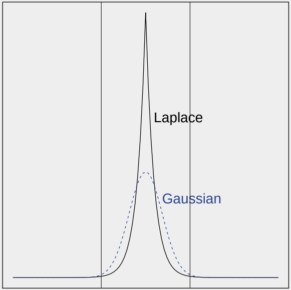
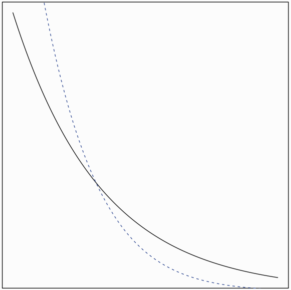


Close up Gauss vs. Laplace



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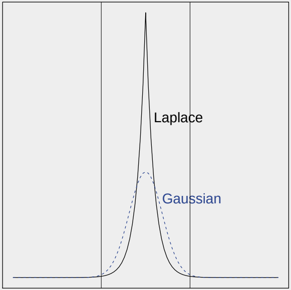
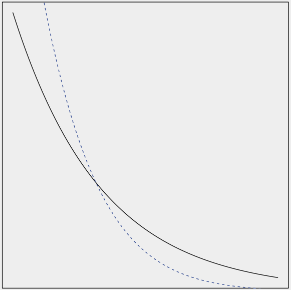


Close up Gauss vs. Laplace



Laplacian FARMS

Data likelihood

$$p\left(\{x\} \mid \boldsymbol{\lambda}, \boldsymbol{\Psi}\right) \;=\; \int p\left(\{x\} \mid z, \boldsymbol{\lambda}, \boldsymbol{\Psi}\right)\; p(z)\; dz$$

Problem

- The **likelihood is analytically intractable** for the non-Gaussian prior

Solution

- Variational EM approach
- Based on a local Gaussian approximation to the mode

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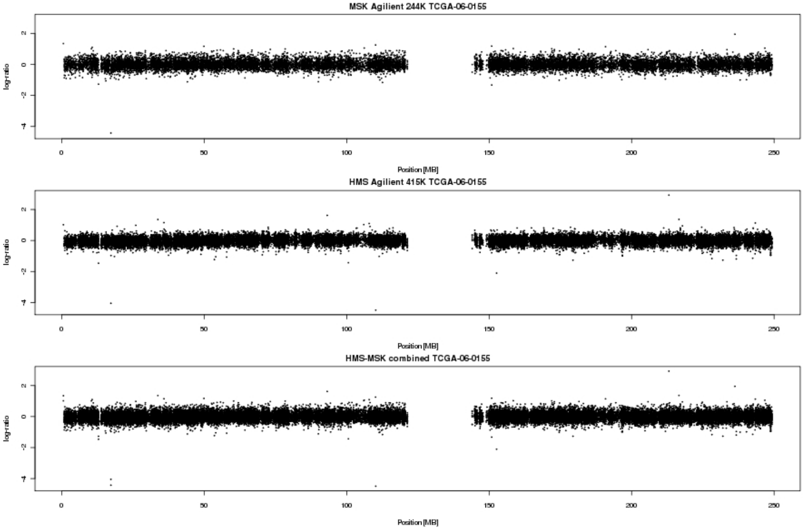
CAMDA copy number data sets

- Glioblastoma multiforme data sets
    - 167 Agilent 415K CGH arrays from Harvard
    - 262 Agilent 244A CGH arrays from Harvard
    - 461 Agilent 244A CGH arrays from MSKCC
    - 533 Affymetrix SNP 6.0 arrays from Broad
    - 432 Illumina HumanHap 550 from Stanford
- CN data for SNP 6.0 and HumanHap 550 were not available
- 167 matched arrays HMS 415K and MSKCC 244A remain

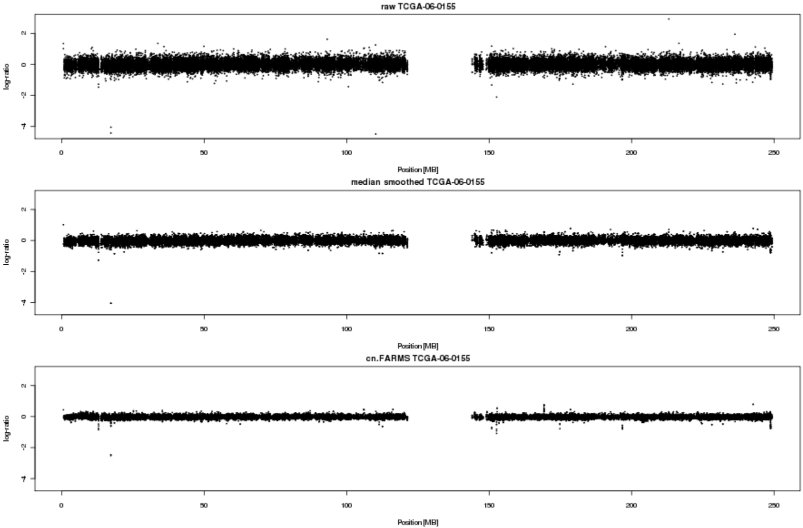
Merged raw data (Chromosome 1)


MSK Agilient 244K TCGA-06-0155

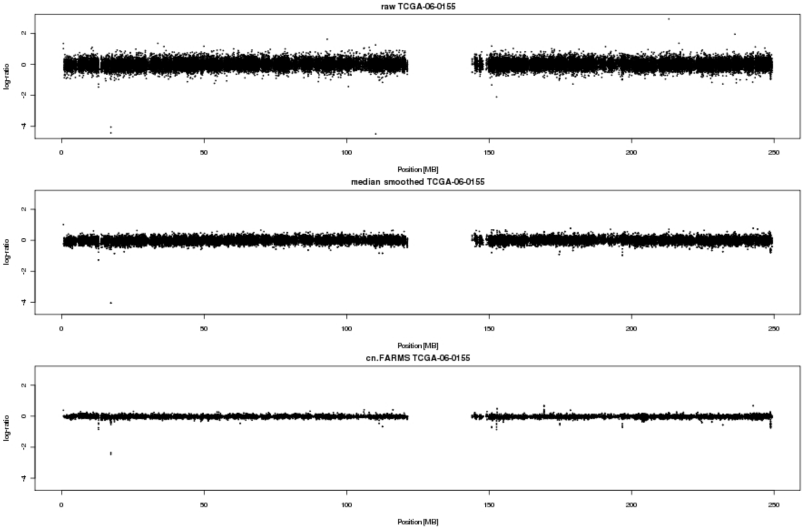
HMS Agilient 415K TCGA-06-0155

HMS-MSK combined TCGA-06-0155

Prior weight 0.5



Prior weight 1.5

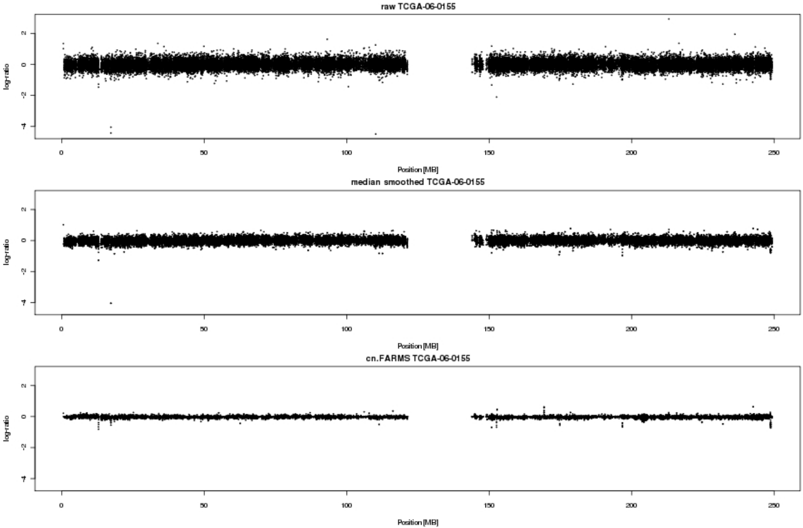


raw TCGA-06-0155

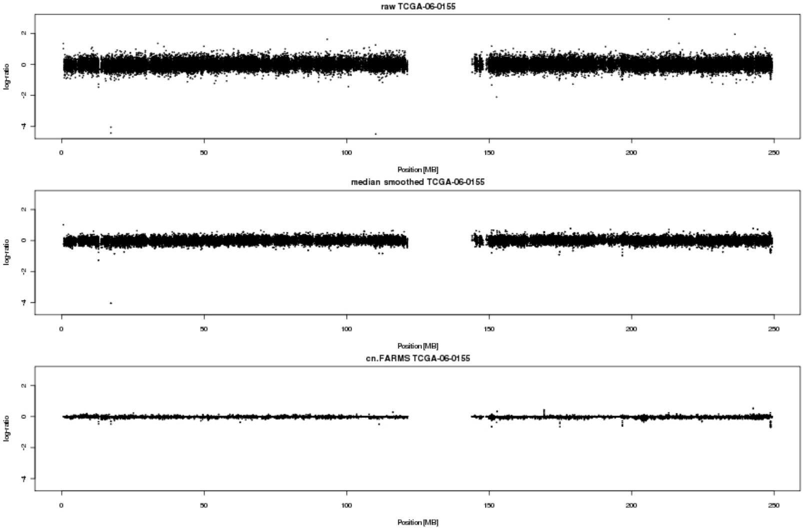
median smoothed TCGA-06-0155

cn.FARMS TCGA-06-0155

Prior weight 2.0



Prior weight 2.5



Conclusion

- Latent variable models decompose observation into noise and signal
- Remove noise so that aberration detection take place in noise-free data
- Reduce dimensionality by filtering for signal variance

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Further information

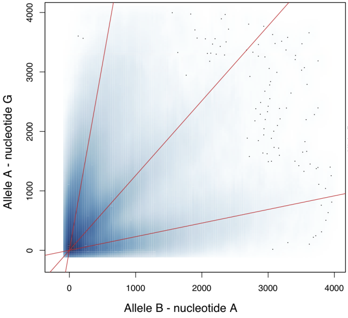
- Clevert DA, Mitterecker A, Mayr A, Klambauer G, Tuefferd M, De Bondt A, Talloen W, Göhlmann H, and Hochreiter S: *cn.FARMS: a latent variable model to detect copy number variations in microarray data with a low false discovery rate* **Nucl. Acids Res.** (2011) 39: e79
- Talloen W, Hochreiter S, Bijnens L, Kasim A, Shkedy Z, Amaratunga D, and Göhlmann H: *Filtering data from high-throughput experiments based on measurement reliability* **PNAS** (2010) 107 (46) E173-E174
- Hochreiter S, Clevert DA, and Obermayer K: *A new summarization method for Affymetrix probe level data*. **Bioinformatics** (2006), 22: 943-949.
- Talloen W, Clevert DA, Hochreiter S, Amaratunga D, Bijnens L, Kass S and Göhlmann H: *I/NI-calls for the exclusion of non-informative genes: a highly effective filtering tool for microarray data*. **Bioinformatics** (2007) 23(21): 2897-2902

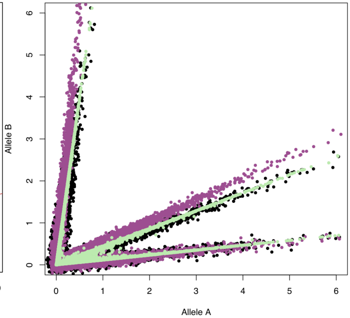
Open source software

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

- FARMS, I/NI call and cn.FARMS are publicly available as Bioconductor R packages
- Software homepages:
  - http://www.bioinf.jku.at/software/farms/farms.html
  - http://www.bioinf.jku.at/software/cnfarms/cnfarms.html

Sparse overcomplete representation





A sparse overcomplete representation of two-dimensional data $x_s \in \mathbb{R}^2$ can be modeled as: $x_s = \boldsymbol{\lambda}_s \, z_s + \boldsymbol{\epsilon}_s$ where $z_s \in \mathbb{R}^3$, $\boldsymbol{\lambda}_s \in \mathbb{R}^{2\times3}$. Sparseness is enforced by assuming a Laplacian prior for z_s:

$$p\left(z_s\right) = (2)^{-\frac{3}{2}} \prod_{l=1}^{3} \exp\left(\sqrt{2}\,|z_{sl}|\right)$$