Proportion of Non-zero Normal Means: Oracle Estimators and Applications to CGH Array

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Massive Data

- Massive investment in data collection/processing, many areas of science and business
- Massive datasets routinely generated:
  - Genomics and proteomics
  - Cosmology and astronomy
  - Financial tick-by-tick data
  - fMRI

High-dimensional Data Analysis

- Traditional statistical data
  - Sample: human being
  - Dimension: blood pressure, weight, height ....
  - Ex. 20 samples, 3 dimensions
- Modern statistical data
  - Sample: human being
  - Dimension: vectors, curves, spectra, images ...
  - Ex. 100 samples, $10,000$ dimensions

Large-scale multiple hypothesis testing

1. Many *null* hypotheses:

$$H_1, H_2, \ldots, H_n$$

2. Many test statistics (summary statistics, regression coefficients, transform coefficients):

$$X_1, X_2, \ldots, X_n$$

Terminology:

- If H_j is true, call X_j a null effect (noise, haystack)
- Otherwise, call X_j a non-null effect (signal, needle)

Two Types of Signal

1. Very strong signal:
   - stand out for themselves
   - relatively easier to tell "where", e.g. thresholding
   - relatively few in numbers
2. Moderately strong signal:
   - not strong enough to stand out
   - can't be isolated or detected **individually**
   - dominating in numbers

For Today

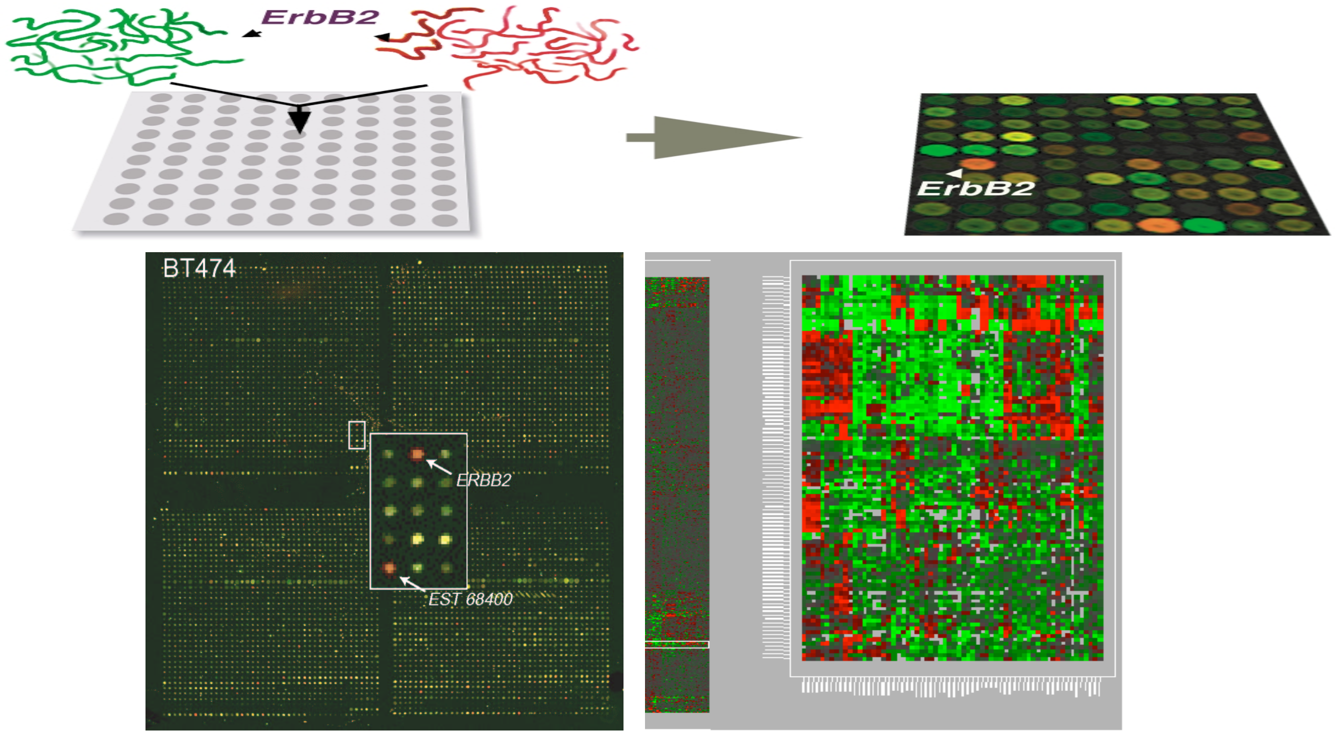
Estimating the **proportion of signals**:

$$\epsilon_n = \frac{\#\{j : H_j \text{ is untrue}\}}{n}$$

Focusing on **faint/moderately strong** signals:

- Signals not strong enough to be isolated *individually*
- Still possible to estimate the proportion

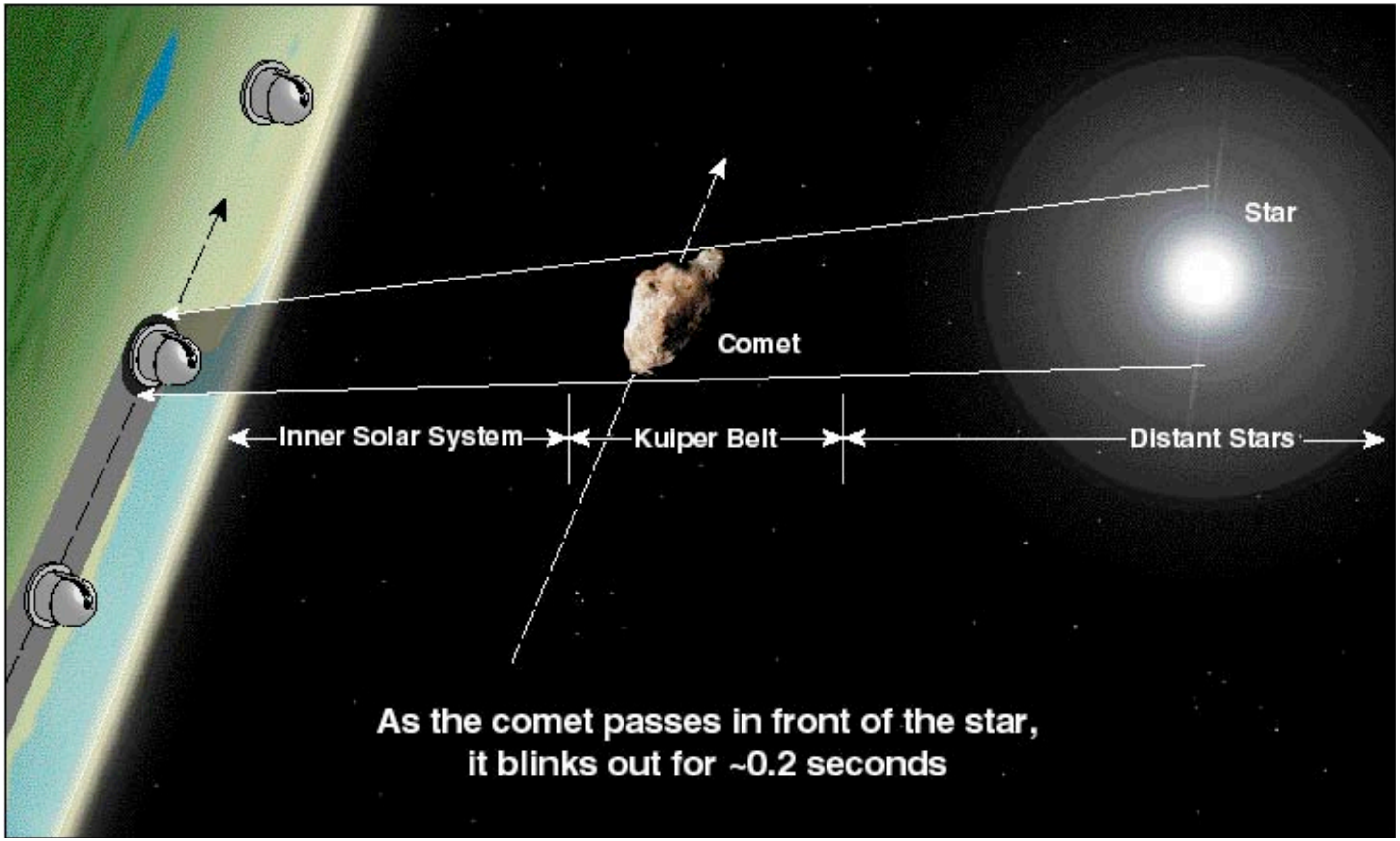
Example I: Lung Cancer CGH Array



Paired CGH profile (left) and mRNA profile (right)

CGH: Comparative Genomic Hybridization.

Example II: Kuiper Belt Object (KBO)



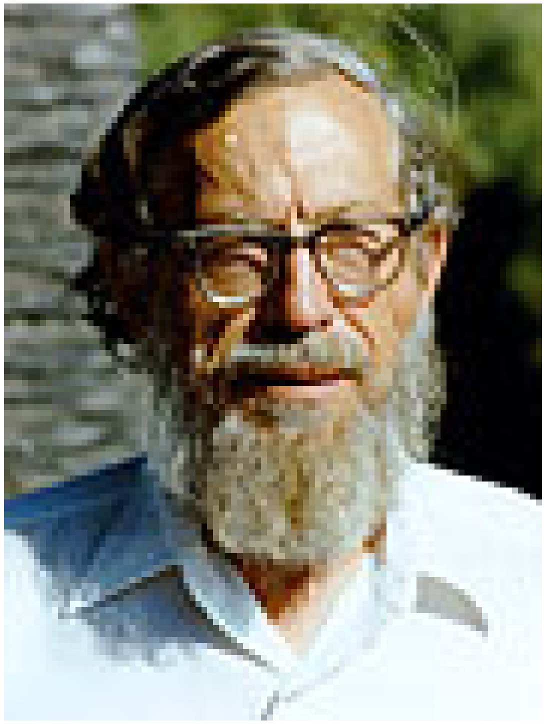
Taiwanese-American Occultation Survey (TAOS)

$10^{10} - 10^{12}$ tests, only tens or hundreds contain KBO

Agenda

1. Proportion of nonzero normal means:
   - Universal oracle equivalence
   - Uniformly consistent estimators
   - Extensions to heteroscedastic models
2. Comparison with other approaches
3. Applications to CGH array

Stein's n-normal Means Setting



Charles Stein

- n data points, n parameters:

$$X_j = \mu_j + \epsilon_j, \quad \epsilon_j \overset{iid}{\sim} N(0,1)$$

- A snapshot of an n-vector
- Caught a lot of enthusiasm
  - captures the essence of "high dimension" data
  - handle many applications
  - tractable

Estimating n-normal Means

Goal: Estimating μ_j's *simultaneously*

$$X_j \sim \mu_j + \epsilon_j, \qquad \epsilon_j \overset{iid}{\sim} N(0,1), \qquad j = 1, \dots, n$$

- MLE: $\hat{\mu}_j = X_j$
- Stein's shrinkage
- Wavelets and non-parametric estimation:
  - $Y(t) = f(t) + W(t), \;\; 0 < t < 1$
  - X_j: WC of $Y(t)$. WC: wavelet coefficients
  - μ_j: WC of $f(t)$
  - ϵ_j: WC of $W(t)$

Testing n-normal Means

- n test statistics

$$X_j \sim \mu_j + \epsilon_j, \qquad \epsilon_j \overset{iid}{\sim} N(0,1), \qquad j = 1, \ldots, n$$

- n hypotheses

$$\begin{aligned} \mu_j &= 0, \qquad \text{if } H_j \text{ is true} \\ \mu_j &\neq 0, \qquad \text{if } H_j \text{ is untrue} \end{aligned}$$

- An insurgence of research interest
  - Driven by development in multiple testing and microarray
  - Bridge for understanding more complicated models

Proportion of nonzero Normal Means

Jin (2006), under review

$$X_j \sim \mu_j + \epsilon_j, \qquad \epsilon_j \overset{iid}{\sim} N(0,1), \qquad j = 1, \ldots, n$$

Goal:

- Estimating the proportion of nonzero normal means

$$\epsilon_n(\mu) = \frac{\#\{j : \mu_j \neq 0\}}{n}$$

- Focusing on faint signals (i.e. μ_j are small)

Where is the Information?

1. Tukey's wisdom: which part of the data contains the information?

2. Where is the *information of the proportion?*

   - Surprisingly, not in the spatial domain (densities, cdfs, moments, data tails, etc.)

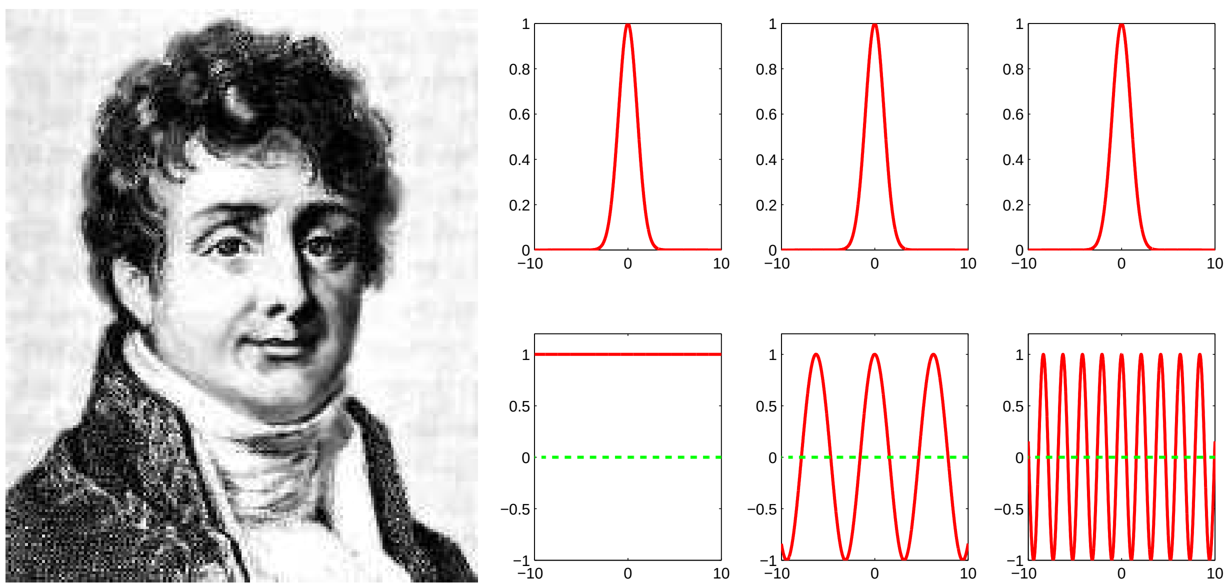
   - Reason: proportion is **scaling invariant**

$$X_j = \mu_j + \epsilon_j, \qquad \tilde{X}_j = \pm 3\mu_j + \epsilon_j, \qquad 1 \leq j \leq n$$

The Fourier Kingdom

- Function: nothing but superposition of waves
- A normal mixture is a mixture of waves

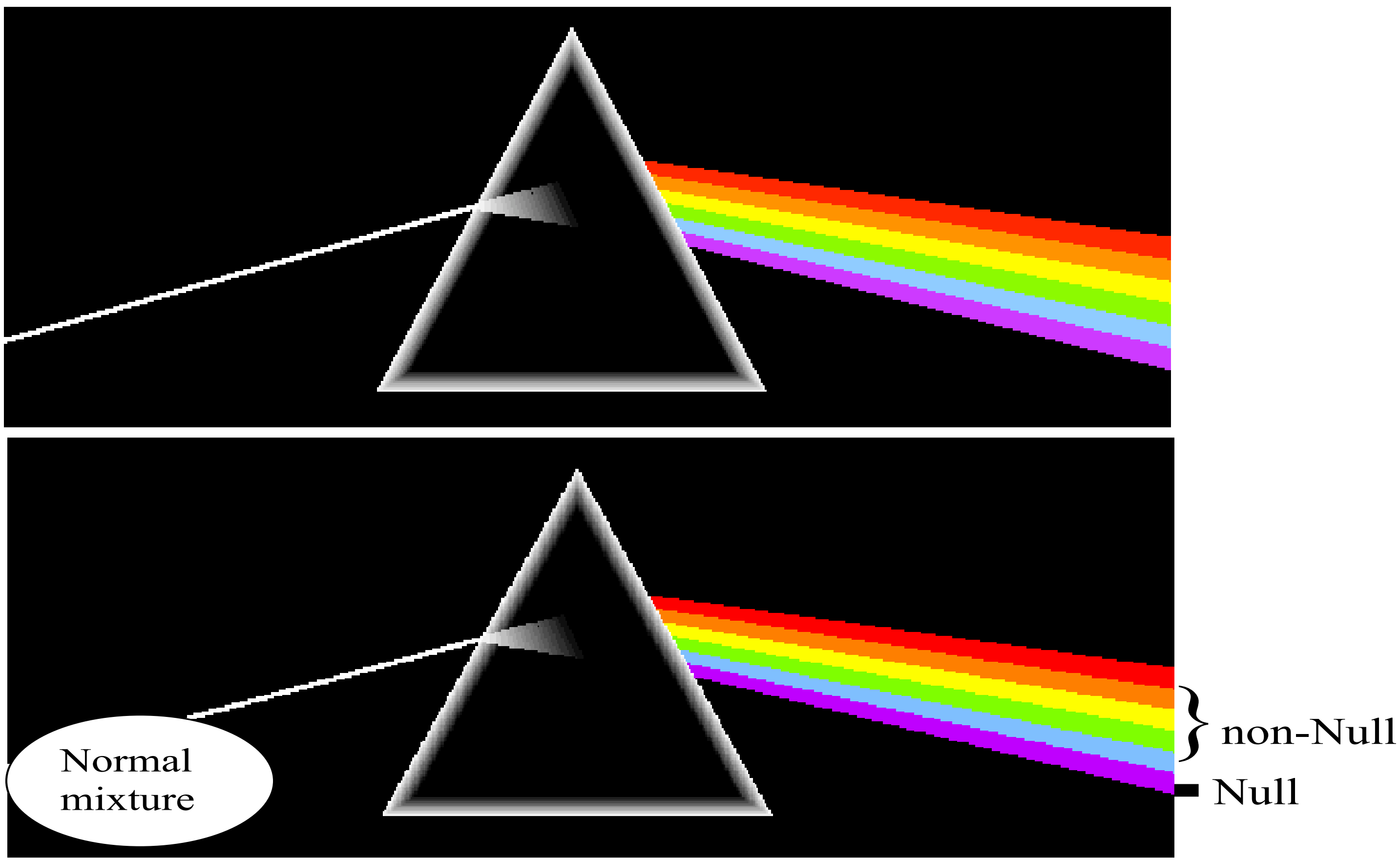
$$N(u,1) \quad \xrightarrow{FT} \quad e^{-\frac{t^2}{2}} \cdot e^{iut} \equiv \text{Amplitude} \cdot \text{Phase}$$



Left: Joseph Fourier (1768-1830). Right: $u = 0, 1, 3$

Reminiscent of Newton's Prism

Goal: Isolating the null component (and so an estimate of the proportion)



Phase Functions

Empirical phase function:

$$\varphi_n(t) = \varphi_n(t; X_1, \ldots, X_n) = \frac{1}{n} \sum_{j=1}^{n} e^{\frac{t^2}{2}} \cos(tX_j)$$

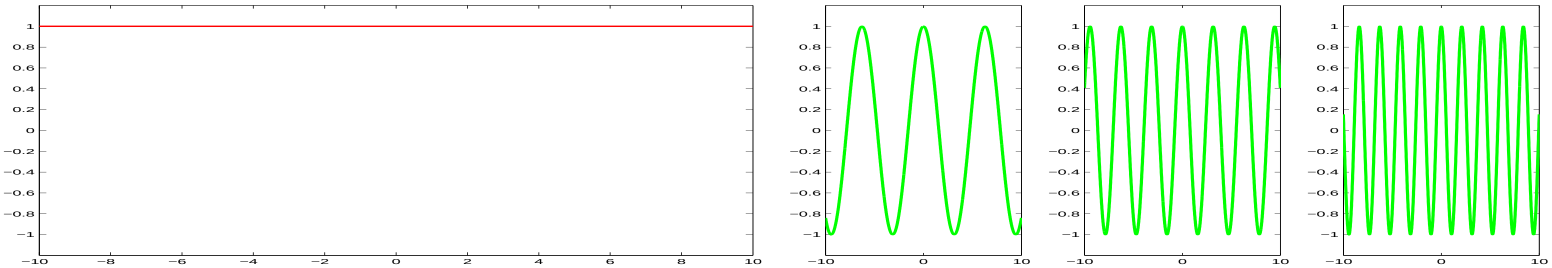
Underlying phase function:

$$\varphi(t) = \varphi(t; \mu, n) = \frac{1}{n} \sum_{j=1}^{n} \cos(t\mu_j)$$

Idea:

- Neglect stochastic fluctuations: $\varphi_n(t) \approx \varphi(t)$
- Use $\varphi(t)$ to construct an oracle estimator

Averaging: A Way to tell whether $\mu_j = 0$



$$\text{Phase}: \quad \varphi(t;\mu,n) = \frac{1}{n}\sum_{j=1}^{n}\cos(t\mu_j)$$

$$= [1-\epsilon_n(\mu)] + \frac{1}{n}\sum_{\{j:\mu_j\neq 0\}}\cos(t\mu_j)$$

Idea: average phase across a wide range of frequencies,

- the first term remains the same: $1-\epsilon_n(\mu)$
- the second term ≈ 0

Good Density: Choice of Weights

Call $\omega(\xi)$ *a good density* if

- a density function over $(-1, 1)$
- symmetric, continuous, and bounded
- $\omega(\xi) = g(1 - |\xi|)$; g: super-additive

Example: Triangle family with $\alpha \geq 1$

$$\omega(\xi) = \begin{cases} \frac{2}{\alpha+1}(1 - |\xi|)^{\alpha}, & |\xi| < 1 \\ 0, & \text{otherwise} \end{cases}$$

Universal Oracle Equivalence

Weighted empirical phase and underlying phase:

$$\psi_n(t;\omega) = \int_{-1}^{1} \omega(\xi)\varphi_n(t\xi)d\xi, \qquad \varphi_n(t) : \text{empirical phase}$$

$$\psi(t;\omega) = \int_{-1}^{1} \omega(\xi)\varphi(t\xi)d\xi, \qquad \varphi(t) : \text{underlying phase}$$

Theorem 1 (*Universal Oracle Equivalence*). If ω is good, then for any dimension n and normal means vector μ,

$$\epsilon_n(\mu) = \sup_t\{1 - \psi(t;\omega,\mu,n)\}$$

Interpretation

- Estimating the proportion reduces to estimating:

$$\sup_t \{1 - \psi(t;\omega)\} \equiv 1 - \lim_{t \to \infty} \psi(t;\omega)$$

- Where is the information?

Phase of high-frequency FT coefficients!

- Replacing $\psi(t;\omega)$ by $\psi_n(t;\omega)$ gives a *real estimator*:

$$1 - \psi_n(t;\omega) \approx 1 - \psi(t;\omega) \approx \epsilon_n(\mu)$$

- There is a trade-off in selecting t

Selecting t: Asymptotic Approach

- $t = \sqrt{2\gamma \log n}$: $\gamma \in (0, \frac{1}{2}]$
- $\psi_n(t;\omega)$: weighted empirical phase

Theorem 2 (*Uniform Consistency*). Suppose

1. (*summable*). $\frac{1}{n}\sum_{j=1}^{n} |\mu_j| \le r$
2. (*not very sparse*). true proportion $\ge n^{\gamma - 1/2}$
3. (*not very faint*). all nonzero means $\ge \frac{\log \log n}{\sqrt{\log n}}$

Then except an event with algebraically small prob.,

$$\lim_{n\to\infty}\left(\sup_{\{\mu \in \Theta_n(\gamma; r)\}} \left| \frac{[1-\psi_n(t;\omega)]}{\epsilon_n(\mu)} - 1 \right| \right) = 0$$

Selecting t: Adaptive Approach

1. Want: approaches adaptive for ω and small n
2. **Key**: the estimator $= \frac{1}{n}\sum_{j=1}^{n}[1 - g(X_j;\omega)]$; $g(X_j;\omega)$ has the largest 2^{nd} moment when $\mu_j = 0$
3. Adaptive selection of t:

$$t_n^*(\omega) = \max\{t : \left[s_0^2(t;\omega) + \frac{1}{n}\right] \leq \alpha_n\}$$

- α_n: specified tolerance for variance
- $s_0^2(t;\omega)$: variance when $\mu = 0$

Theorem 3 (*Adaptive Control on Variance*).

- For any n, ω, and normal means vector μ,

$$\mathrm{Var}(\psi(t_n^*(\omega);\omega)) \leq \alpha_n$$

- Theorem 2 continues to hold if $\alpha_n \to 0$ *slowly enough* (i.e. $t_n^*(\omega) \asymp \sqrt{\log n}$)

Advantage:

- $t_n^*(\omega)$ is non-stochastic, easy to calculate
- an adaptive control on variance (for n, ω, μ)

Extension to Heteroscedastic Gaussian Models

$$X_j \sim \begin{cases} N(0,1), & & H_j \text{ is true} \\ N(\mu_j, \sigma_j^2), & (\mu_j, \sigma_j) \neq (0,1), & \text{otherwise} \end{cases}$$

- found in many applications (e.g. microarray, CGH)
- handle many interesting situations
- proportion of non-null effects:

$$\epsilon_n = \frac{\#\{(\mu_j, \sigma_j) \neq (0,1)\}}{n}$$

Identifiability

1. Too broad to be identifiable: any density $\approx$ a Gaussian mixture (ℓ^1-metric)

2. Identifiable conditions

   - Elevated variances (Efron (2004))

$$\text{When } H_j \text{ is untrue :} \qquad \sigma_j \geq 1$$

   - Elevated means (CGH array):

$$\text{When } H_j \text{ is untrue :} \qquad \mu_j > 0$$

Main Results on Heteroscedastic Models

1. Elevated variances (Jin and Cai, JASA in press)
   - theoretic results successfully extended
   - applied to breast cancer microarray
2. Elevated means (Jin, Peng, and Wang, manuscript)
   - to accommodate heteroscedasticity, replace $i = \sqrt{-1}$ by $\sqrt{\sqrt{-1}}$

$$N(u, \sigma^2) \qquad \xrightarrow{FT} \qquad e^{-\frac{ut}{\sqrt{2}}} \cdot e^{i(\frac{\sigma^2}{2} + \frac{u}{\sqrt{2}} u)}$$

   - applied to lung cancer CGH array

- Empirical FT coefficients ≈ underlying FT coefficients
- In high-frequency underlying FT coefficients: null component sticks out

$$\left|\frac{1}{n}\sum_{j=1}^{n} e^{-\frac{\mu_j t}{\sqrt{2}}} e^{[i(\frac{\sigma_j^2 t^2}{2}+\frac{\mu_j t}{\sqrt{2}})]}\right|$$

$$=\left|e^{-\frac{it^2}{2}} \cdot \left\{[1-\epsilon_n] + \frac{1}{n}\sum_{\{j:\mu_j\neq 0\}} e^{-\frac{\mu_j t}{\sqrt{2}}} \cdot e^{i[\frac{(\sigma_j^2-1)t^2}{2}+\frac{\mu_j t}{\sqrt{2}}]}\right\}\right|$$

$$\approx[1-\epsilon_n]$$

Other Works on Estimating the Proportion

- Schweder (82), Storey (02), Genovese and Wasserman (04), Meinshausen and Rice (06)
- Langaas (05), Swanepoel (99)
- Only consistent under the *purity* condition

Purity Condition

- Introduced in Genovese and Wasserman (2004)
- $X_j \overset{iid}{\sim} (1-\epsilon_n) f_0 + \epsilon_n f$
  - f_0: $N(0,1)$, marginal density of null effects
  - f: marginal density of non-null effects
- Purity condition

$$\inf_{-\infty < x < \infty} \left\{ \frac{f(x)}{f_0(x)} \right\} = 0$$

- For the sake of *identifiability*

Comparisons

Meinshausen and Rice type approaches

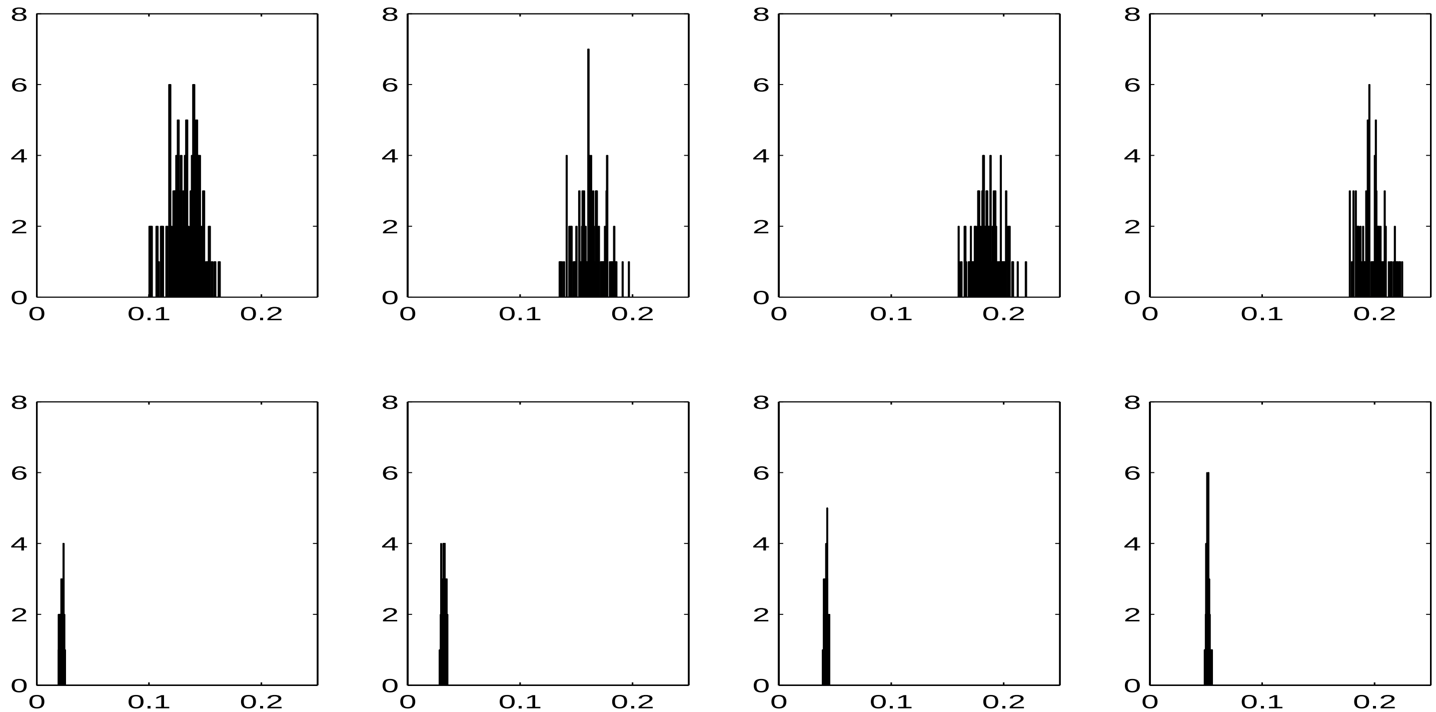
- Use fully non-parametric models
- Consistent only in the *purity* regime

Our approaches:

- Use Gaussian models
- Remove the hurdle of identifiability
- Successful beyond the *purity* regime

Comparisons Using Simulated Data

- Fix $n = 10^5$ and $\epsilon_n = 0.2$
- Pick $a = \frac{1}{4} \times 2, 3, 4, 5$
- Conduct 100 simulation cycles
  1. Generate $n(1 - \epsilon_n)$ null effects $X_j \sim N(0, 1)$
  2. Generate $n\epsilon_n$ non-null effects $X_j \sim N(\mu_j, 1)$
     - $|\mu_j| \overset{iid}{\sim} \text{Uniform}(a, a + 1)$
     - $\text{sgn}(\mu_j) \overset{iid}{\sim} \{-1, 1\}$
  3. Implement our adaptive approach with $\alpha = 0.015$ (ω: triangle density)
  4. Implement Meinshausen and Rice's approach

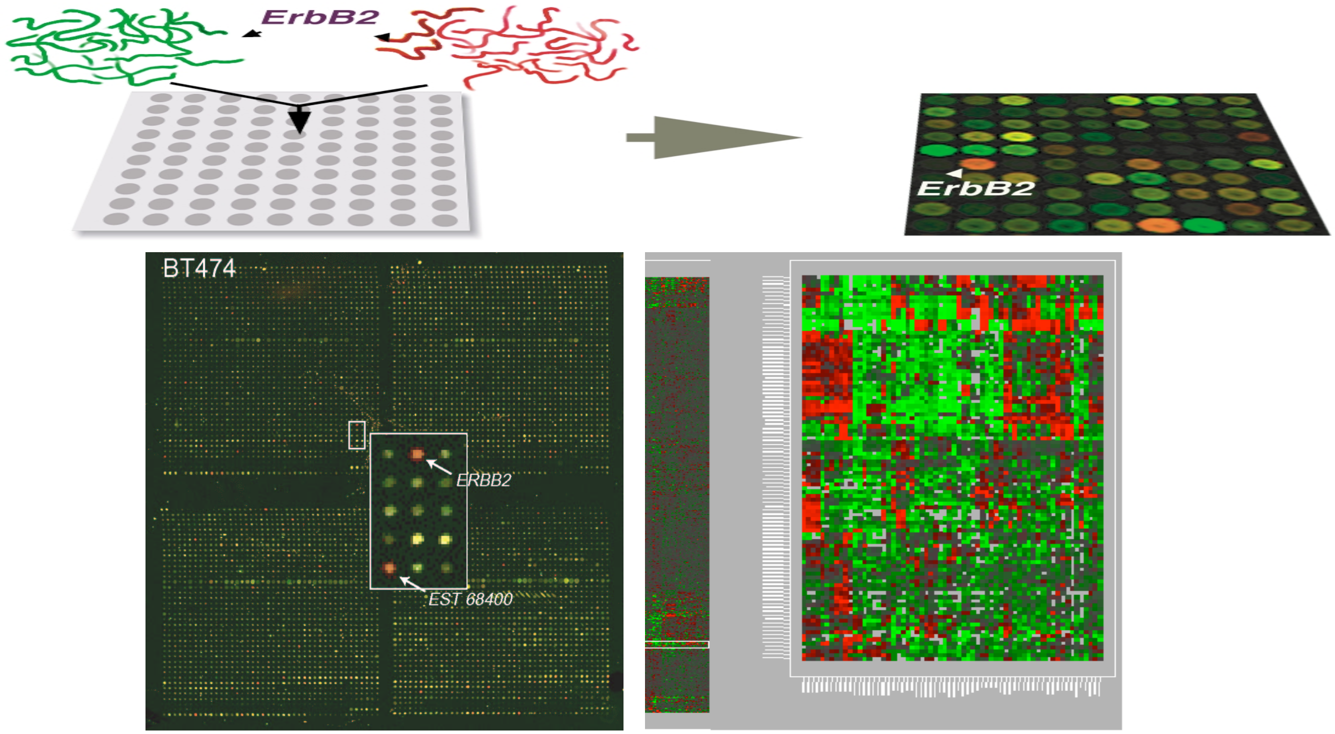


- $n = 10^5$, $\epsilon_n = 0.2$, $a = \frac{1}{4} \times 2, 3, 4, 5$
- Each cycle: $\quad n(1-\epsilon_n)$ null effects $X_j \sim N(0,1)$

  $n\epsilon_n$ non-null effects $X_j \sim N(\mu_j, 1)$

  $$|\mu_j| \overset{iid}{\sim} \text{Uniform}(a, a+1), \quad \text{sgn}(\mu_j) \overset{iid}{\sim} \{-1, 1\}$$

Applications to Lung Cancer CGH array



Paired CGH profile (left) and mRNA profile (right)

CGH: Comparative Genomic Hybridization.

Abstraction

- 23 tumor cells, same set of 25736 genes
- N_j: log-intensity of CGH profile, measures DNA copy number alternation; j: j-th gene
- R_j: log-intensity of mRNA profile, measures RNA expression level

Interested in:

- proportion of genes where N_j and R_j are correlated
- conjectured to be large (2/3)

Amplification and Deletion

Terminology:

- N_j: DNA copy number alternation of j-th gene
- Call DNA copy number *amplification*, *deletion*, or *no alternation* if $N_j > 0$, < 0, or $= 0$

Accordingly, genes split into two groups:

- *Amplification (13356 genes).* ≥ 1 amplifications across 23 cells
- *Deletion (11283 genes).* ≥ 1 deletion across 23 cells

Multiple Testing Setup (Amplification)

- n hypotheses:

$$H_j : \qquad N_j \text{ and } R_j \text{ not correlated}$$

  equivalent to (roughly)

$$H_j : \qquad (R_j | N_j > 0) \;\; =_d \;\; (R_j | N_j = 0)$$

- n test statistics:

$$X_j = \bar{\Phi}^{-1}(p_j) \qquad p_j\text{:} \quad \text{p-value based on rank test}$$

- (*Elevated mean*). If H_j is true: $X_j \sim N(0,1)$
  Otherwise: $\quad X_j \sim N(\mu_j, \sigma_j^2), \quad \mu_j > 0$

	Jin, Peng, Wang	MR	Efron/GR/Storey
Amplificatioin	0.585	0.466	0.406
Deletion	0.539	0.464	0.418

Take Home Messages

1. Constructed universal oracle equivalence of the proportion
2. Developed estimators which are uniformly consistent over a wide class of parameters.
3. Applied to lung cancer CGH array

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