Robust Identification of Sparse Segments in Ultra-High Dimensional Data Analysis

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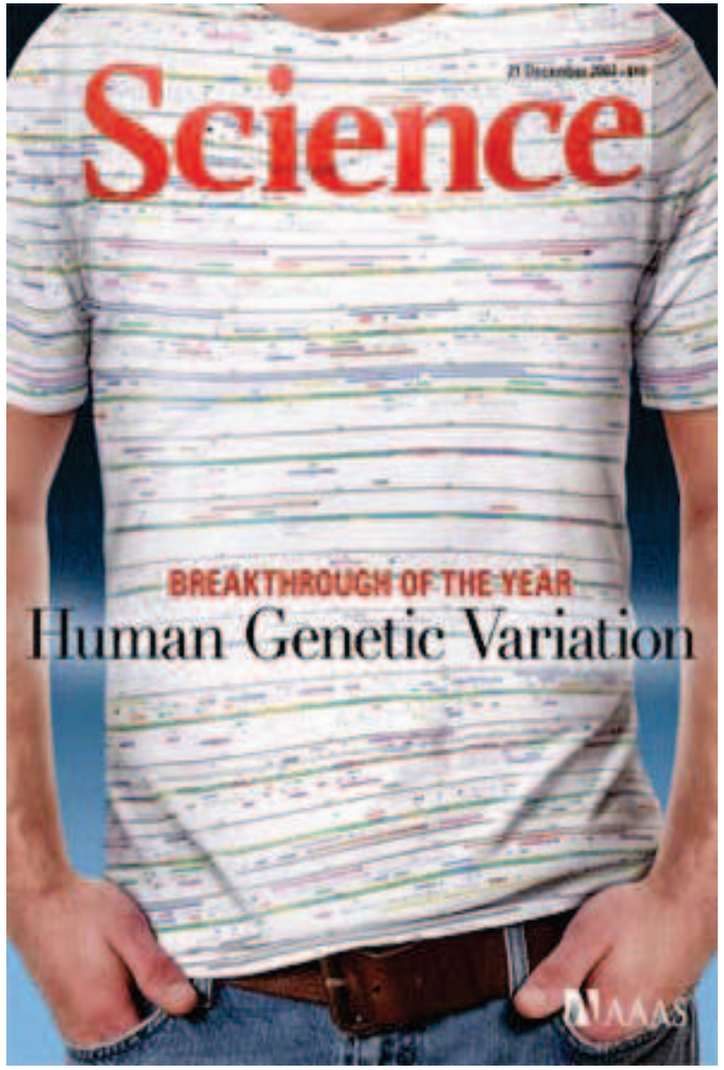
Joint work with Jessie Jeng and Tony Cai

Genetic variations and complex diseases



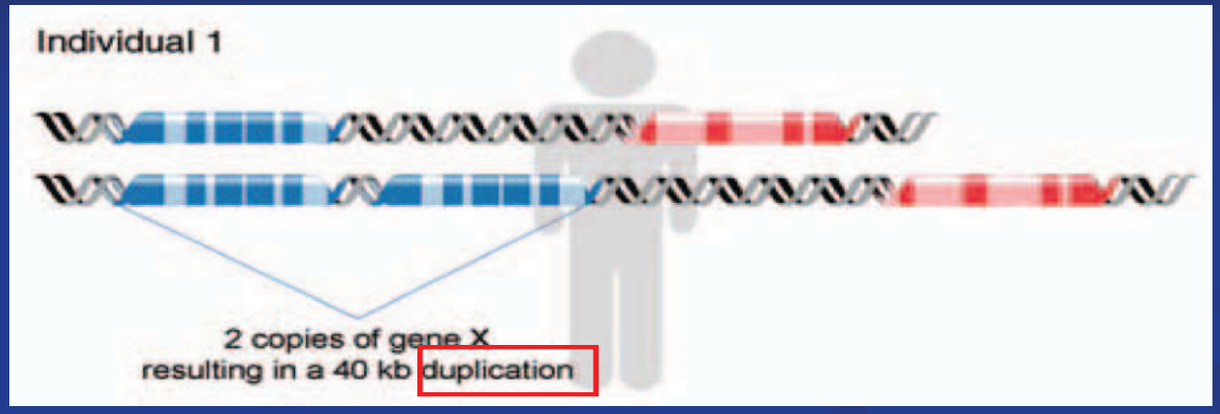
Commonly observed genetic variations:

- Single nucleotide polymorphisms (SNPs).
- Small insertions/deletions (InDels).
- Structure variations, including the copy number variations (CNVs).

All are associated with risk of complex diseases.

Copy number variants (CNVs)

Copy Number Variation



Many CNVs have functional consequences: alter gene dosage, disrupt genes, or uncover deleterious alleles.

NEJM 2007, 356:1169-1171

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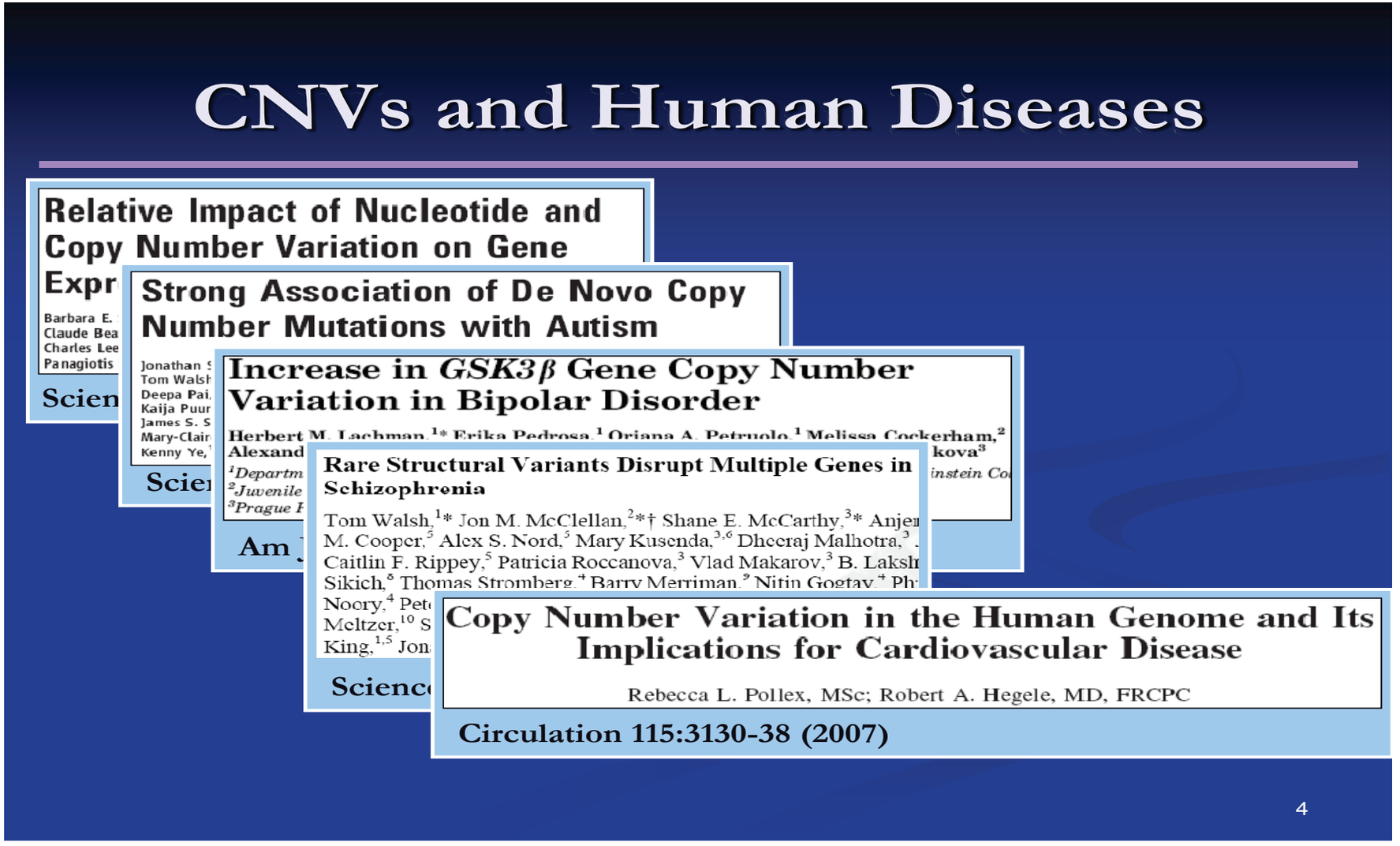
CNV Associations

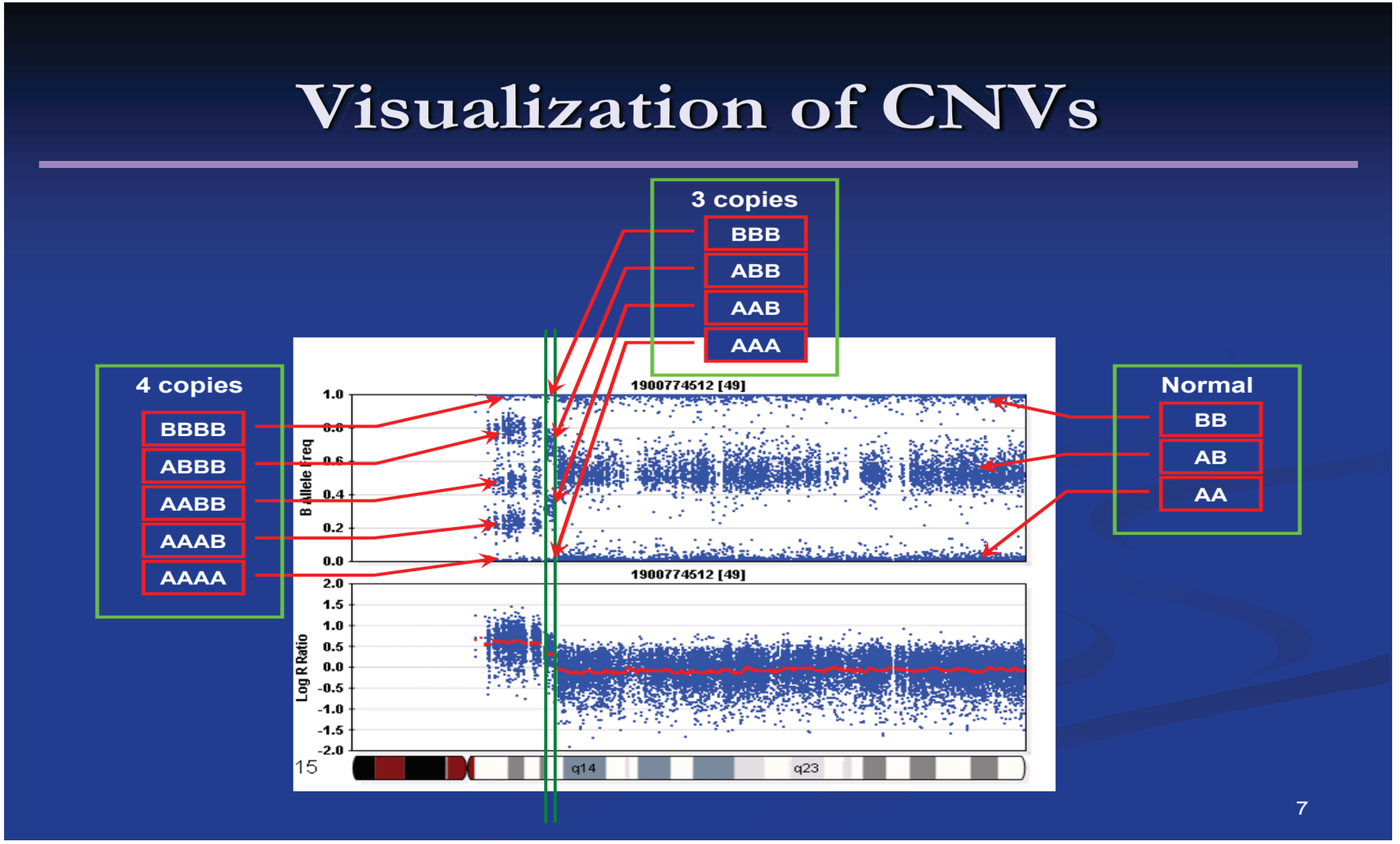


Data available for CNV Analysis, literature

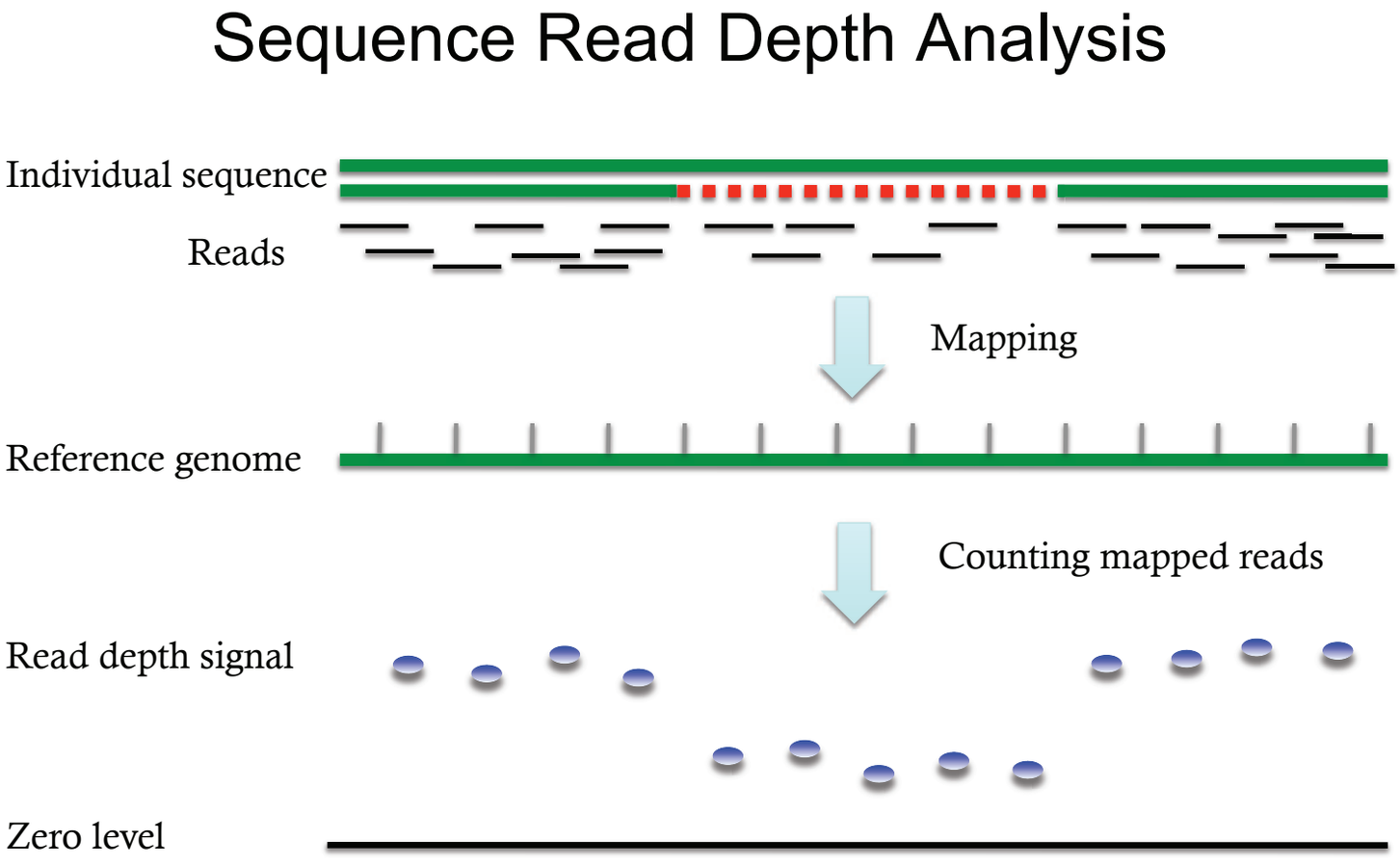
Two types of data can be used for CNV analysis for germline DNA.

- SNP chip data for GWAS - high dimensional continuous data. Sebat et al. 2004; McCarrol and Altshuler 2007; Wellcome trust (Nature 2010).
- Next generation sequencing data (NGS) - ultra high dimensional discrete data; Medvedev et al., 2009 (Nat. Meth).
- Methods available:
  - GWAS SNP data: circular binary segmentation (CBS) (Olshen et al, 2004); HMM based method (PennCNV, Wang et al 2007); scanning-based methods (Zhang and Siegmund 2010); Likelihood ratio selection (Jeng, Cai and Li, 2010).
  - NGS data: Most methods are computational.

CNV analysis based on SNP Chip data



CNV Analysis and Next Generation Sequence Data



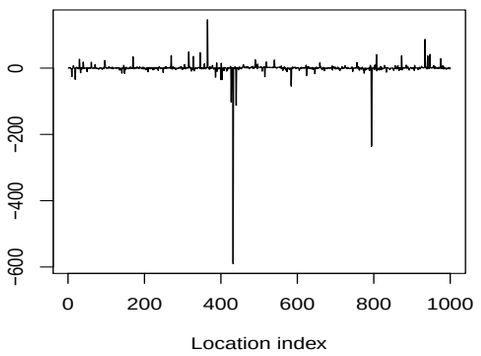
Statistical challenges

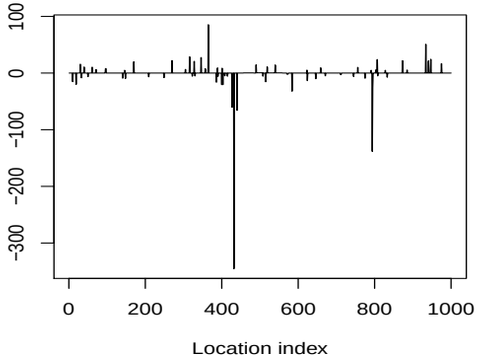
Y_i: # of read counts covering location i, $i = 1, \cdots, n$; or
Y_i: # of read counts in 100bp intervals.

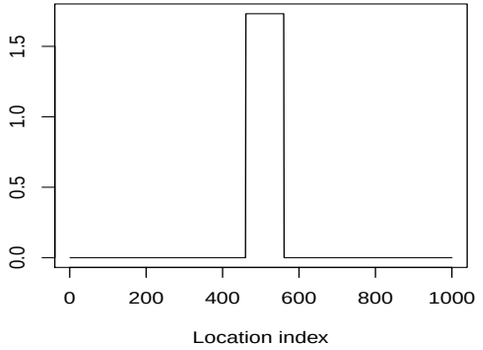
- n is ultra-high, computational challenge.

- Y_i usually does not follow a normal distribution, outliers Existing methods do not work well when noise distribution is non-Gaussian and hard to be estimated.

Cauchy distribution: data, LRS, RSI.







Statistical model for read depth data - one sample

For a given individual, observe read counts $\{Y_i, i = 1, ..., n\}$ with

$$Y_i = \mu_1 1_{\{i \in I_1\}} + \ldots + \mu_q 1_{\{i \in I_q\}} + \xi_i, \qquad 1 \le i \le n. \tag{1}$$

n: length of genome (billions);

$q = q_n$: unknown number of the signal segments;

$\mathbb{I} = \{I_1, \ldots I_q\}$: disjoint intervals representing signal segments with unknown locations;

$\mu_1, \ldots \mu_q$ are unknown means

ξ_i is symmetric at 0 and density function h s.t.

$$h(0) > 0, \quad |h(y) - h(0)| \le Cy^2 \text{ in an open nbhd of } 0.$$

We want to

(a) (detection) test $H_0 : \quad \mathbb{I} = \emptyset \qquad$ against $\qquad H_1 : \quad \mathbb{I} \neq \emptyset,$

(b) (identification) if the alternative is true, identify each $I_j \in \mathbb{I}$.

Methods Assuming Gaussian Noise

- Methods for detecting the presence of segments assuming Gaussian noise: Arias-Castro, Donoho and Huo (2005)
- Identification methods assuming Gaussian noise:
  likelihood ratio selector (LRS) (Jeng, Cai and Li 2010 JASA).

Key of the LRS:

(1) For any given interval $\tilde{I} \subseteq \{1, 2, ..., n\}$, define its likelihood ratio statistic as

$$Y(\tilde{I}) = \sum_{i \in \tilde{I}} Y_i / \sqrt{|\tilde{I}|}.$$

(2) Scan the genome with intervals of length $\leq L$, threshold $\sqrt{2 \log(nL)}$.

(3) Identify local maximums.

Detection boundaries and optimality results are established.

Data Transformation - local median

- Equally divide the n observations (e.g., counts at each bp) into $T = T_n$ groups with $m = m_n$ observations in each group.
- Define jth interval $J_k = \{i : (k-1)m + 1 \le i \le km\}$ and take median: $X_k = \text{median}(Y_i : i \in J_k)$, $\eta_k = \text{median}\{\xi_i : i \in J_k\}$, $\quad 1 \le k \le T$.
- We have

$$X_k = \theta_k + \eta_k, \qquad 1 \le k \le T,$$

$$\theta_k \begin{cases} = \mu_j, & J_k \subseteq I_j \text{ for some } I_j, \\ \in [0, \mu_j], & J_k \cap I_j \neq \emptyset \text{ for some } I_j \text{ and } J_k \not\subseteq I_j, \\ = 0, & \text{otherwise.} \end{cases}$$

Key point: $\sqrt{m}\eta_k = \frac{1}{2h(0)} Z_k + \zeta_k, \quad Z_k \sim N(0,1), \zeta_k \to_D 0$ fast
$\Rightarrow \eta_k \sim N(0, 1/(4h^2(0)m))$.
(Brown, Cai and Zhou: AoS 08).

Robust Segment Detection (RSD)

Segment detection: test $H_0 : \mathbb{I} = \emptyset$ vs $H_1 : \mathbb{I} \neq \emptyset$.

For any interval $\tilde{I}$, define

$$X(\tilde{I}) = \sum_{k \in \tilde{I}} X_k / \sqrt{|\tilde{I}|},$$

and threshold

$$\lambda_n = \sqrt{2 \log n}/(2h(0)\sqrt{m}).$$

The RSD rejects H_0 when $\max_{\tilde{I} \in \mathbb{J}_T} X(\tilde{I}) > \lambda_n$, where $\mathbb{J}_T$ is the collection of all possible intervals in $\{1, \ldots, T\}$.

Robust Segment Detection - Type 1 error and power

Under the assumed model and median transformation with $m = \log^{1+b} n$ for some $b > 0$.

Type 1 error: For the collection $\mathbb{J}_T$ of all the possible intervals in $\{1, \ldots, T\}$,

$$P_{H_0}(\max_{\tilde{I} \in \mathbb{J}_T} X(\tilde{I}) > \lambda_n) \leq \frac{C}{\sqrt{\log T}} \to 0, \qquad T \to \infty.$$

Power: If there exists some segment $I_j \in \mathbb{I}$ that satisfies

$$|I_j|/m \to \infty$$

and

$$\mu_j \sqrt{|I_j|} \geq \sqrt{2(1+\epsilon)\log n}/(2h(0))$$

for some $\epsilon > 0$, then RSD has the sum of the probabilities of type I and type II errors going to 0.

Robust Segment Identifier (RSI)

- Perform local median transformation with bin size m, get $X_k = \theta_k + \eta_k$, $1 \leq k \leq T$.
- Set data-driven threshold at

$$\lambda_n^* = \hat{\sigma}\sqrt{2\log n}, \qquad \hat{\sigma}^2 : \text{estimate of } Var(\eta_k)(e.g., MAD)$$

- Apply LRS on X_k:
  - select intervals with their likelihood ratio statistics $> \lambda_n^*$ and achieve local maximums.
  - only consider short intervals with length $\leq L/m$, L: max CNV size. (Jeng, Cai and Li, JASA 2010.)
- Conditions on m and L: $m = \log^{1+b} n$, $\qquad \bar{s} \leq L < \underline{d}$, $b > 0$, $\bar{s}$ =length of the longest segment, $\underline{d}$ =shortest distance between two adjacent segments.

Theory - consistency and optimality

- Result 1: Assume the general condition on the background noise ξ_i and some sparsity conditions on the signal segments. If all $I_j \in \mathbb{I}$ satisfies $|I_j|/m \to \infty$ and

$$\mu_j \sqrt{|I_j|} \geq \sqrt{2(1+\epsilon)\log n}/(2h(0))$$

for some $\epsilon > 0$, then the RSI with $m = \log^{1+b} n$ for $b > 0$ and $\bar{s} \leq L < \underline{d}$, is consistent for $\mathbb{I}$, i.e., for some $\delta_n = o(1)$,

$$P_{H_0}(|\hat{\mathbb{I}}| > 0) + P_{H_1}(\max_{I_j \in \mathbb{I}} \min_{\hat{I}_j \in \hat{\mathbb{I}}} D(\hat{I}_j, I_j) > \delta_n) \to 0$$

$$D(\hat{I}, I) = 1 - |\hat{I} \cap I|/\sqrt{|\hat{I}||I|}$$

- Result 2: If for all $I_j \in \mathbb{I}$,

$$\mu_j \sqrt{|I_j|} \leq \sqrt{2(1-\epsilon)\log n}/(2h(0)),$$

then no method constructed on X_k with $m \to \infty$ is consistent.

Comparison with Gaussian noises

- Compare to the case with Gaussian noise:
  - Assume $\xi_i \sim N(0,1)$, then the original GLRT based on Y_i is optimal.
  - Further, if $\exists I_j \in \mathbb{I}$ s.t.

$$\mu_j \sqrt{|I_j|} \geq \sqrt{2(1+\epsilon_n)\log n},$$

    then the original GLRT is consistent.

Possible price for robustness:

$\sqrt{2(1+\epsilon_n)\log n}/(2h(0)) \approx 1.25 \times \sqrt{2(1+\epsilon_n)\log n}$

Simulation results - robustness

$n = 5 \times 10^4$, $|\mathbb{I}| = 3$. Noise is generated from $t(1), t(3), t(30)$.

Estimation error for I_j: $D_j = \min_{\hat{I}_k \in \hat{\mathbb{I}}} \left\{1 - |I_j \cap \hat{I}_k| / \sqrt{|I_j||\hat{I}_k|}\right\} \in [0, 1]$.

Number of over-selections: $\#O$.

Medians of D_j and $\#O$ for RSI with $m = 20$ and $L = 6$.

		$D_{1(\lvert I_1\rvert=100)}$	$D_{2(\lvert I_2\rvert=40)}$	$D_{3(\lvert I_3\rvert=20)}$	$\#O$
$t(1)$	$\mu = 1.0$	0.080(0.015)	1.000(0.026)	1.000(0.000)	2(0.33)
	$\mu = 1.5$	0.087(0.003)	0.184(0.017)	1.000(0.000)	2(0.26)
	$\mu = 2.0$	0.087(0.009)	0.150(0.020)	0.423(0.220)	2(0.14)
t(3)	$\mu = 1.0$	0.087(0.005)	1.000(0.270)	1.000(0.000)	0(0.00)
	$\mu = 1.5$	0.060(0.009)	0.175(0.029)	1.000(0.000)	0(0.00)
	$\mu = 2.0$	0.050(0.008)	0.150(0.016)	0.293(0.019)	0(0.00)
t(30)	$\mu = 1.0$	0.070(0.014)	1.000(0.320)	1.000(0.000)	0(0.00)
	$\mu = 1.5$	0.065(0.012)	0.175(0.021)	1.000(0.245)	0(0.00)
	$\mu = 2.0$	0.050(0.010)	0.175 (0.019)	0.250(0.028)	0(0.00)

Simulation results - comparison with LRS and CBS

Table 1: Both homogeneous and heterogeneous noises are considered. Homogenous noise is generated from the t-distribution with degrees of freedom 1, 3, and 30. Heterogeneous noise is generated from a mixture of $N(0,1)$ and $N(0,\sigma^2)$, where $\sigma \sim Gamma(2,\tau)$. μ is fixed at 2.0.

	RSI		LRS		CBS	
	$D_{2(\lvert I_2\rvert=40)}$	$\#O$	$D_{2(\lvert I_2\rvert=40)}$	$\#O$	$D_{2(\lvert I_2\rvert=40)}$	$\#O$
$t(1)$	0.163(0.024)	2(0.2)	0.340(0.054)	3882(7)	1.000(0.000)	0(0.0)
$t(3)$	0.125(0.028)	0(0.0)	0.025(0.006)	467(4)	1.000(0.000)	0(0.0)
$t(30)$	0.125(0.018)	0(0.0)	0.000(0.001)	2(0)	0.006(0.006)	0(0.0)
$\tau = 0.5$	0.125(0.015)	2(0.4)	0.013(0.005)	37(3)	0.180(0.006)	4(0.6)
$\tau = 1.0$	0.113(0.022)	12(0.6)	0.000(0.006)	227(6)	1.000(0.010)	10(1.1)
$\tau = 1.5$	0.125(0.016)	26(0.8)	0.000(0.006)	461(11)	1.000(0.000)	8(1.1)

Simulation results - effect of m

Table 2: Effect of bin size m on the performance of RSI. μ is fixed at 2.

		$D_{1(\|I_1\|=100)}$	$D_{2(\|I_2\|=40)}$	$D_{3(\|I_3\|=20)}$	$\#O$
$t(1)$	$m = 10$	0.035(0.009)	0.10(0.018)	0.184(0.033)	19(0.85)
	$m = 20$	0.087(0.009)	0.15(0.020)	0.423(0.220)	2(0.14)
	$m = 40$	0.101(0.006)	0.25(0.056)	1.000(0.024)	0(0.00)
$t(3)$	$m = 10$	0.030(0.004)	0.088(0.015)	0.150(0.033)	1(0.22)
	$m = 20$	0.050(0.008)	0.150(0.016)	0.293(0.019)	0(0.00)
	$m = 40$	0.087(0.006)	0.293(0.041)	1.000(0.250)	0(0.00)
$t(30)$	$m = 10$	0.020(0.007)	0.075(0.008)	0.150(0.018)	0(0.00)
	$m = 20$	0.050(0.010)	0.175(0.019)	0.250(0.028)	0(0.00)
	$m = 40$	0.105(0.008)	0.293(0.035)	1.000(0.094)	0(0.00)

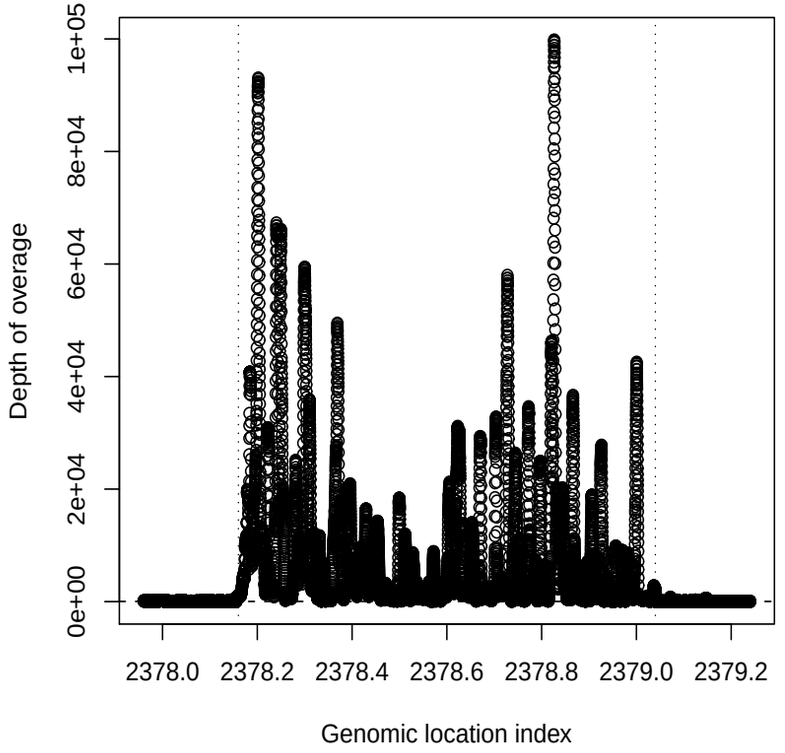
1000 Genomes Project - NA19240, Chr 19

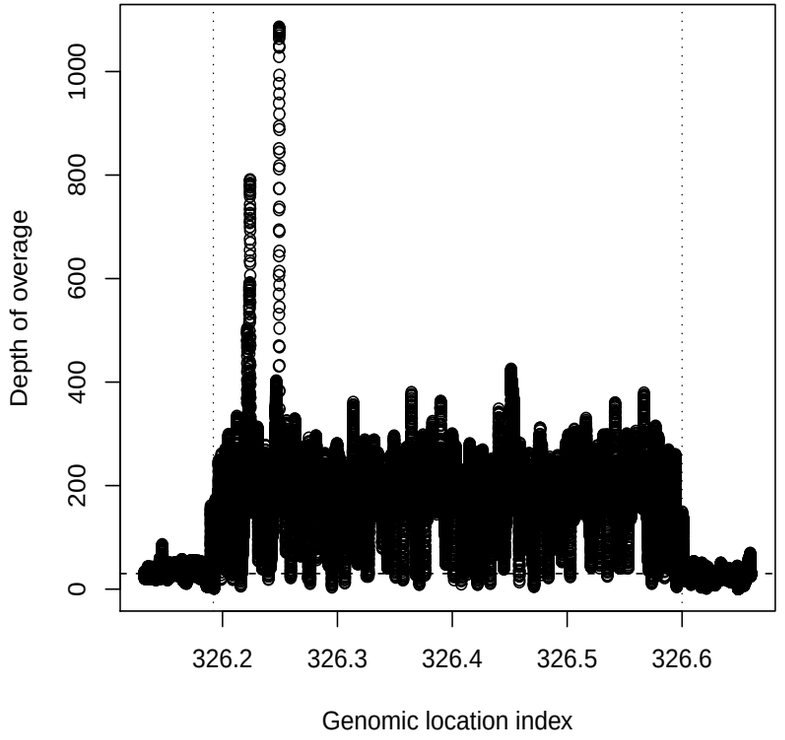
NA19240: an International HapMap project Yoruban female sample and parents.
42x, SOLiD, map to the human reference genome.

$n = 54,361,060$ read counts for Chr 19.
Apply RSI with $m = 400$, $L = 60,000$. Identify 101 CNVs.
Take less than 3 mins.

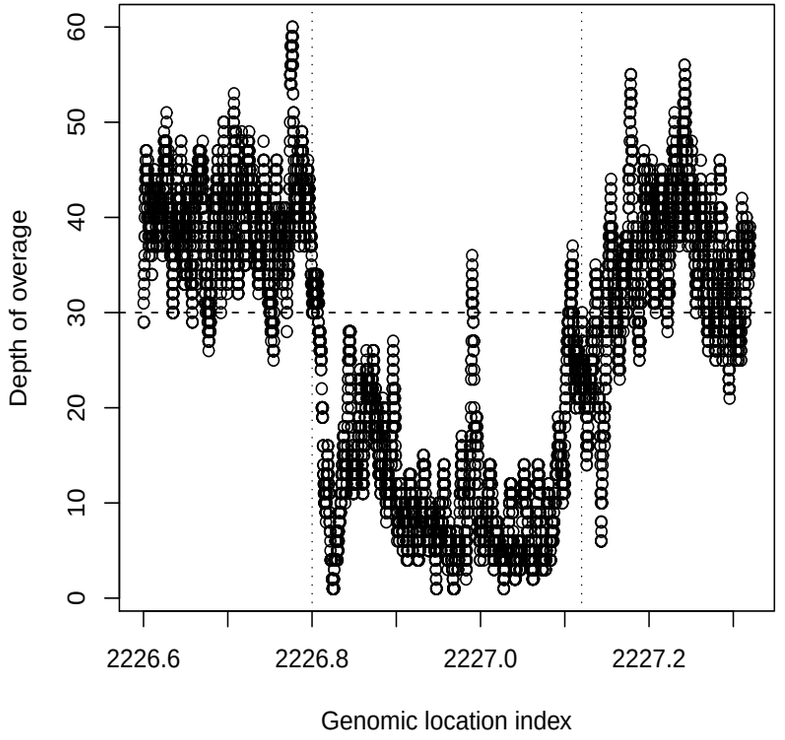
Compare with the CNV map from 1000 Genomes Project based on 185 samples (Mills et al. 2011), 76 overlap with the reported CNVs based on 185 low-coverage samples and three methods (438, 332 and 615 CNVs).

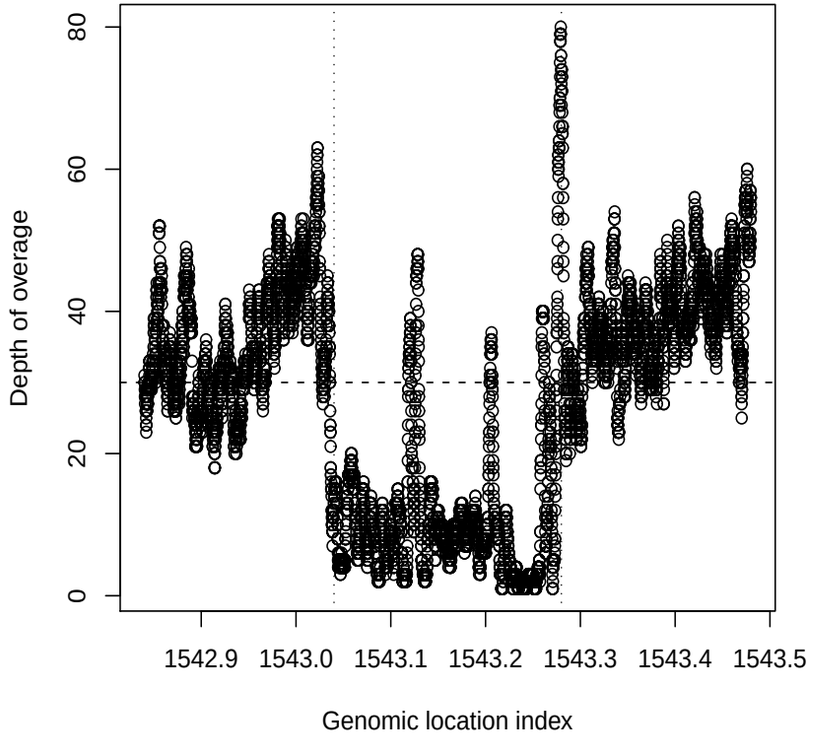
Chr 19 sequence data - NA19240



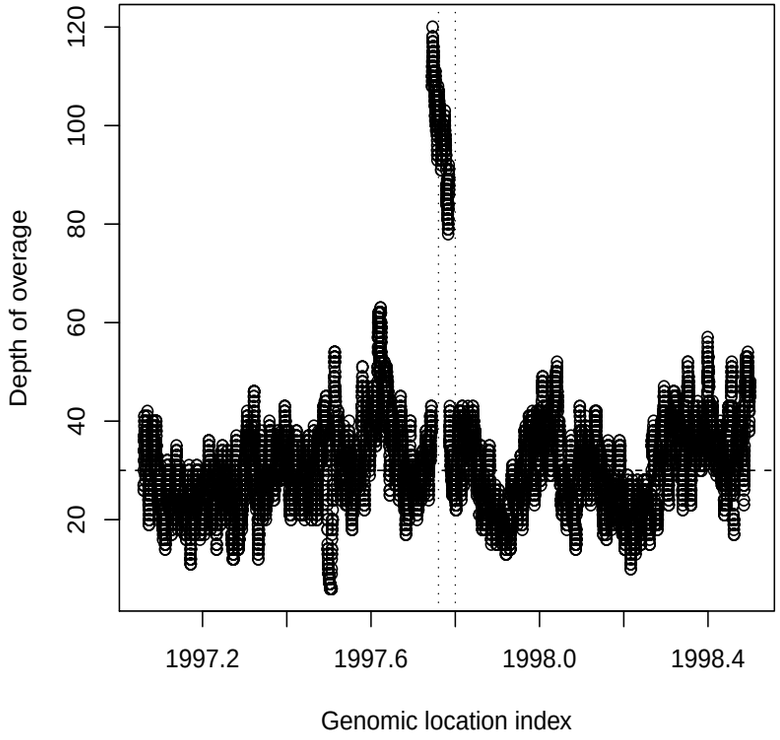


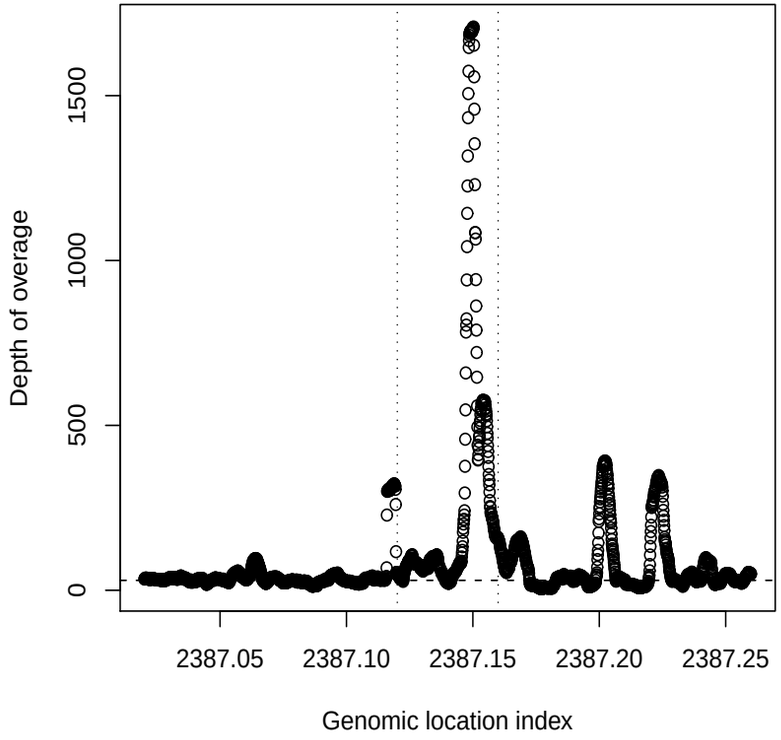
Chr 19 sequence data - NA19240





Chr 19 sequence data - NA19240





Alternative Approach -Negative Binomial Counts

NB model:

$$X_i \sim \text{Negative Binomial}(r, p_i), \qquad p_i = p_0 + \sum_{j=1}^{q} d_j 1_{(i \in I_j)}.$$

Data transformation: divide the n obs into $T = T_n$ groups of $m = m_n$ obs.

$$Y_k = 2\sqrt{\hat{r}} \ln \left(\sqrt{\frac{\sum_{i \in J_k} X_i + 1/4}{m\hat{r} - 1/2}} + \sqrt{1 + \frac{\sum_{i \in J_k} X_i + 1/4}{m\hat{r} - 1/2}} \right), \qquad 1 \le k \le T,$$

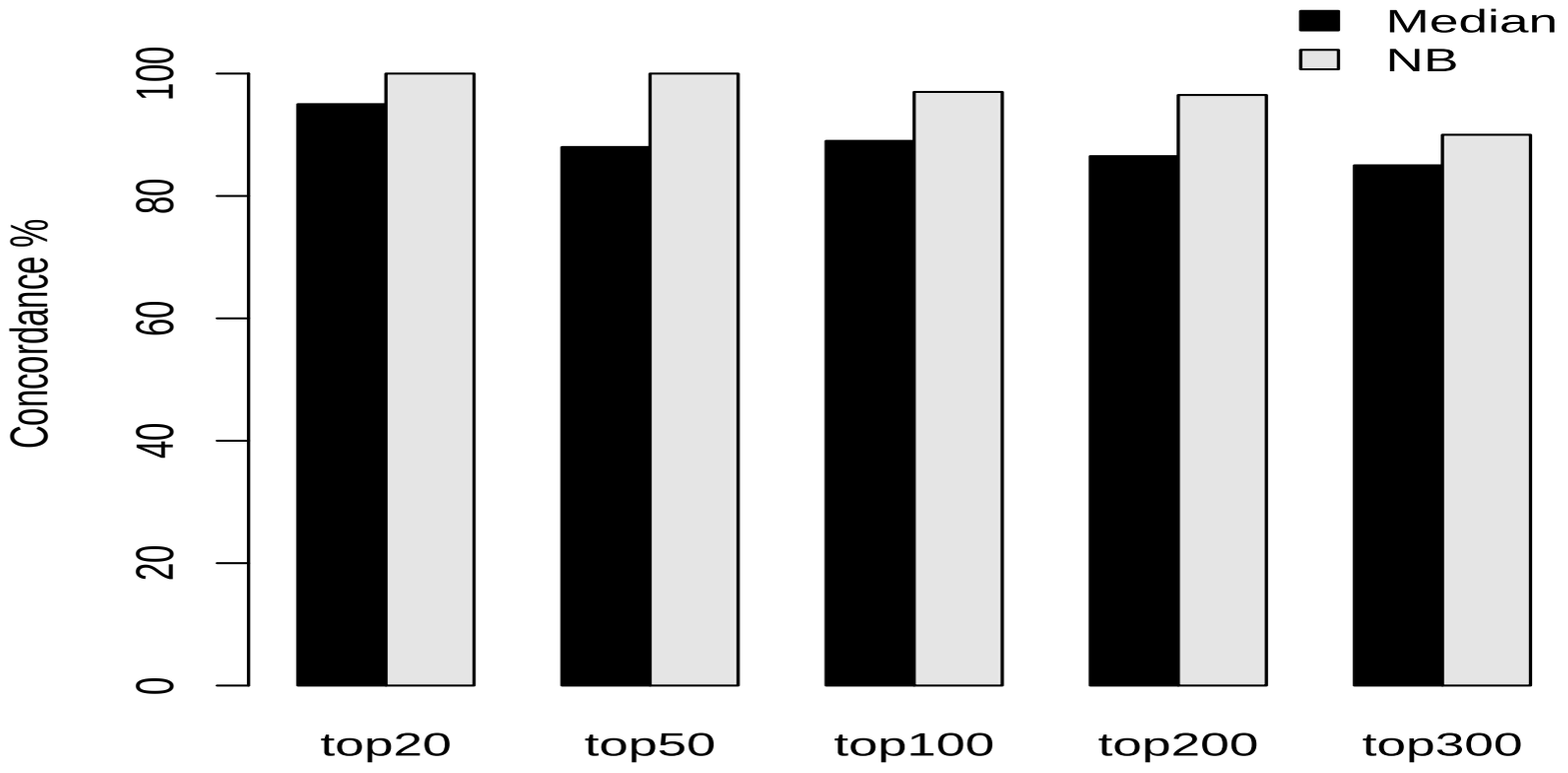
$$Y_k = 2 \ln(\sqrt{\theta_k} + \sqrt{r + \theta_k}) + \epsilon_k + m^{-1/2} Z_k + \xi_k,$$

$$\theta_k \begin{cases} = r(p_0 + d_j)/(1 - p_0 - d_j), & J_k \subseteq I_j \text{ for some } I_j, \\ \in [rp_0/(1-p_0),\ r(p_0 + d_j)/(1 - p_0 - d_j)], & J_k \cap I_j \neq \emptyset \text{ for some } I_j \text{ and } J_k \not\subseteq I_j, \\ = rp_0/(1-p_0), & \text{otherwise}, \end{cases}$$

ϵ_k and ξ_k are stochastically small, $Z_k \sim N(0, 1)$.

Concordant of the Yoruba trio

CNVs are inheritable - concordant rates, ranked by $\mu\sqrt{|\hat{I}|}$.



Comments and extensions

Cai, Jeng and Li (2011): JRSS(B), in press.

Many other complicated factors: repeated regions, complex rearrangments, highly repetitive elements.

Read depths data: difficulty in finding high repetitive CNVs (LINE, SINE), uncertain in CNV location, but can ba applied to paired-end, single-end and mixed data;

Paired-end whole genome sequencing data: statistical modeling of anomalous read pairs, can detect highly repetitive CNVs (LINE and SINE), precise location of CNVs; but span distances have effects on resolution.

Detection of other structure variants and precise breakpoints estimation.

THANKS!

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Tony Cai - Statistics Dept
John Maris - CHOP.

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