Detecting Copy Number Variations from Next-Generation Sequencing Data via a Bayesian Procedure

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- Sequencing Read Depths
- Bayesian Procedure
  - •Model
  - •RJMCMC
- NTUH data

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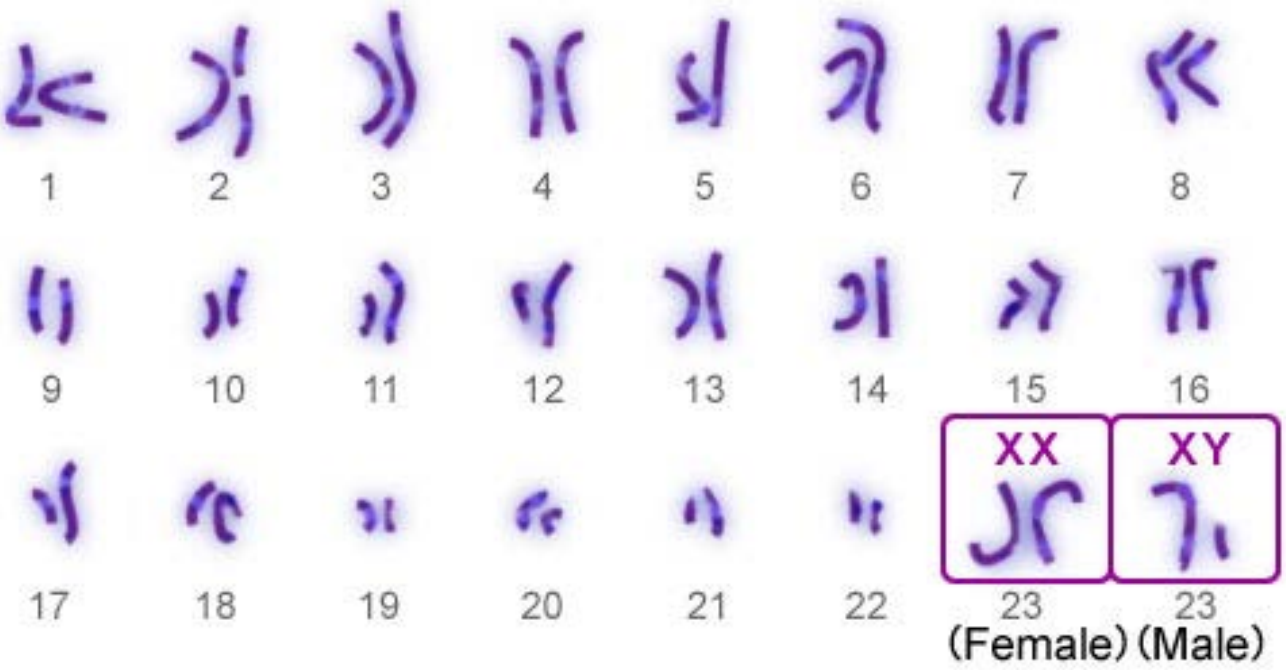

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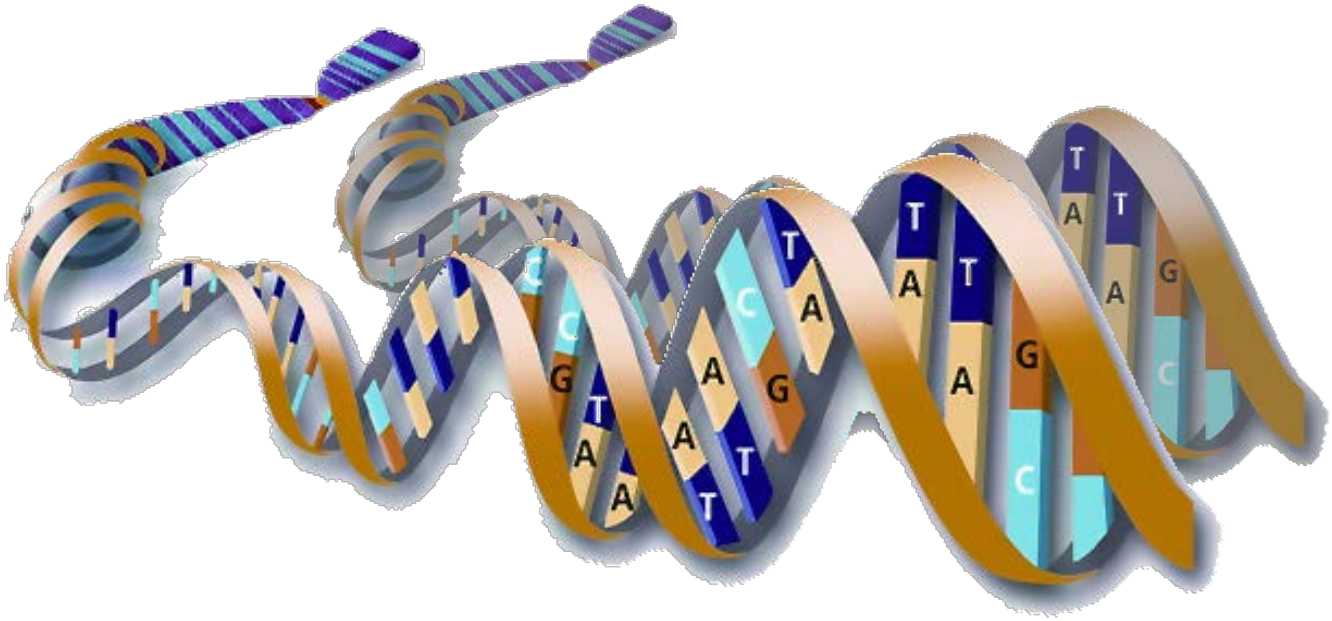

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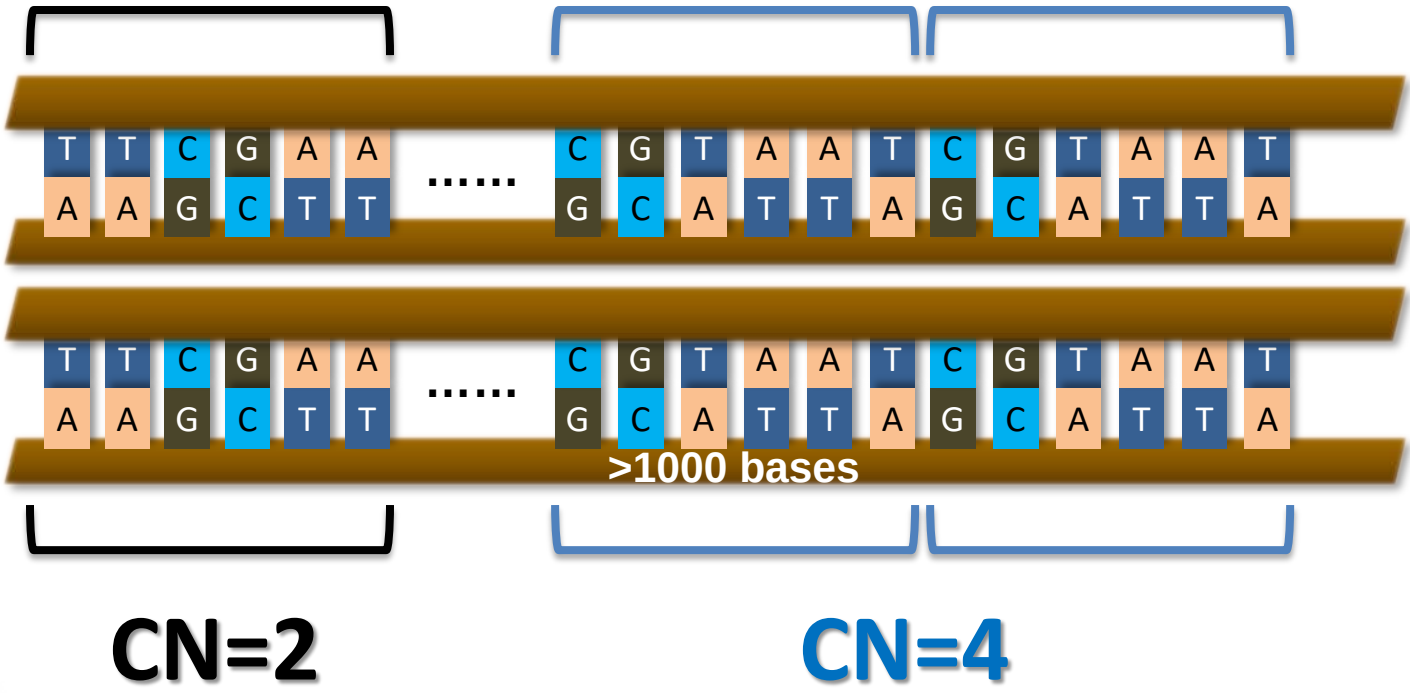

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Copy number variations (CNVs) and human genetic diseases

- CNVs account for roughly 12% of the human genome
- **Down syndrome**: a genetic disorder caused by the presence of a third copy of chromosome 21
- **Mental disorders**, including autism, schizophrenia: about 1% with rare DNA deletions in chromosome 15q13.3, 16p11.2, or 1q21.1

Breast cancer: 20-30% with HER-2 gene amplification and over-expression

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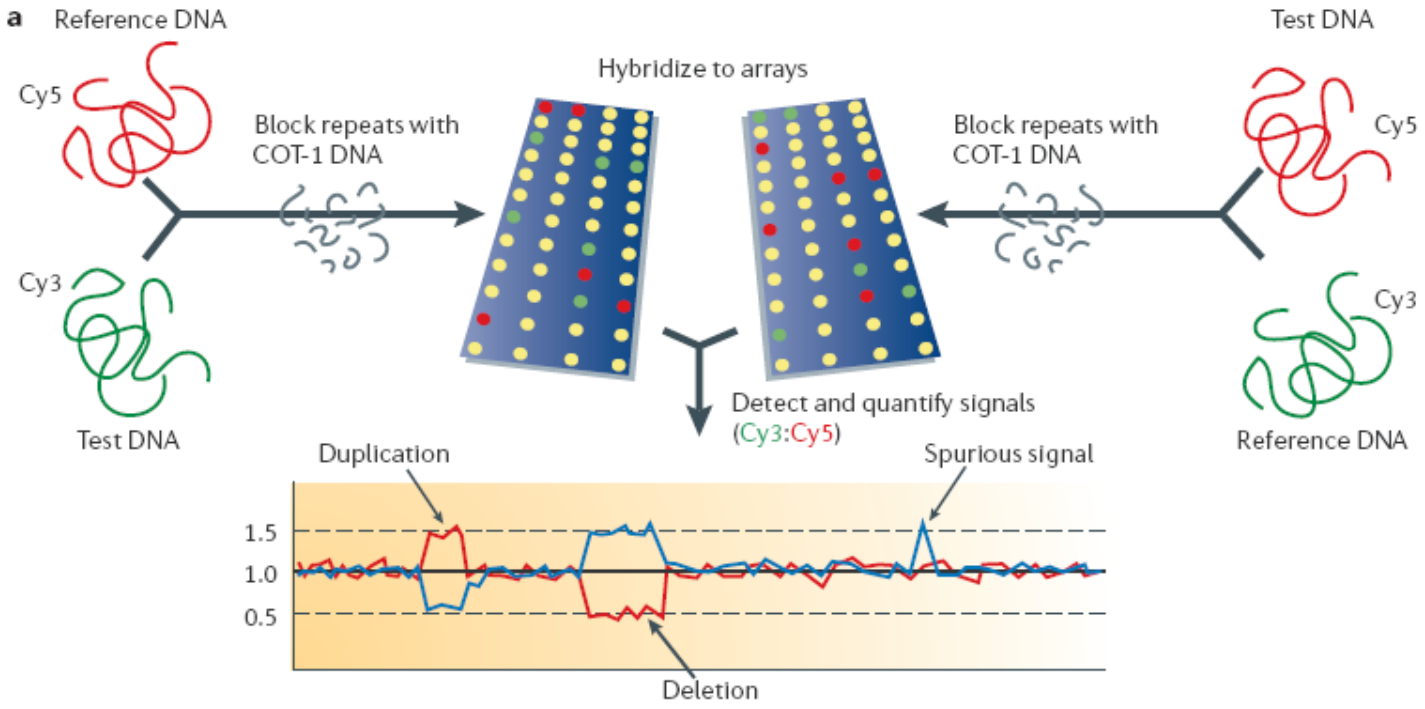
Detecting CNVs

Array-based comparative genome hybridization (array-CGH)



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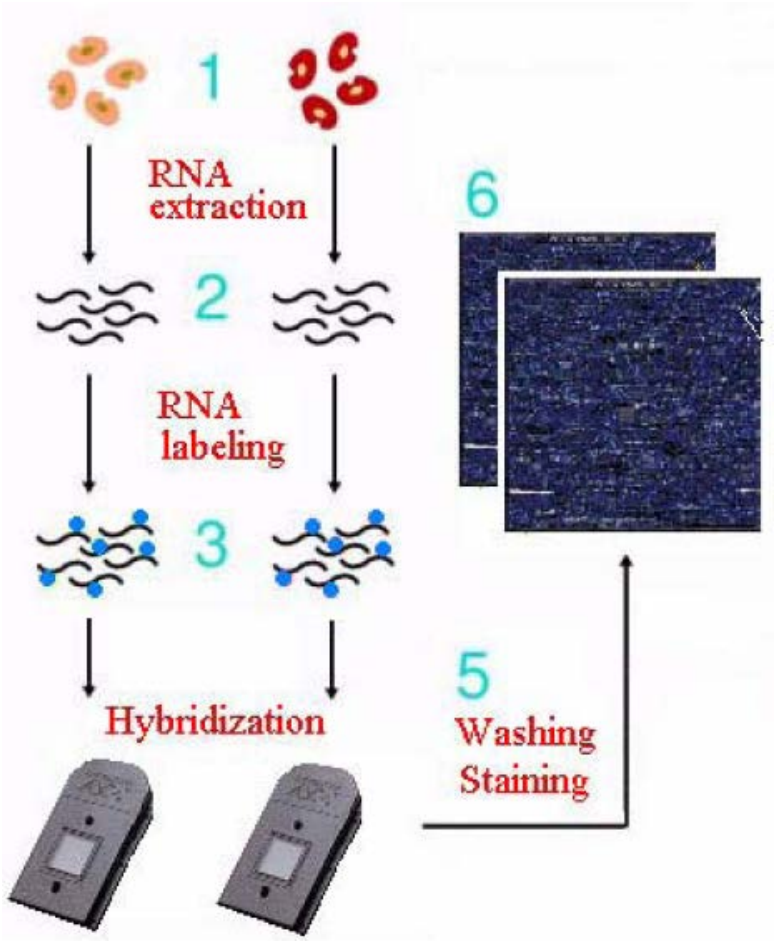
Detecting CNVs

Spotted oligonucleotides on Affymetrix SNP arrays



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Limitations of hybridization-based microarray approaches

- Hybridization-based microarray approaches: array-CGH and SNP arrays
- Microarrays are limited to
  - detect copy-number differences of sequences present in the reference assembly used to design the probes,
  - provide no information on the location of duplicated copies,
  - be generally unable to resolve breakpoints at the single-base-pair level

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Sequencing-based computational approaches

- The advent of next-generation sequencing (NGS) technologies promises to revolutionize copy number variation (CNV).
- NGS approaches can map CNVs with much greater accuracy than hybridization-based microarray approaches.
- However, NGS approaches present substantial computational and bioinformatics challenges.

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Sequencing-based computational approaches

- There are four general types of NGS strategy, all of which focus on mapping sequence reads to the reference genome and subsequently identifying CNVs:
  - read-pair (paired-end reads),
  - read-depth,
  - split-read,
  - sequence assembly.

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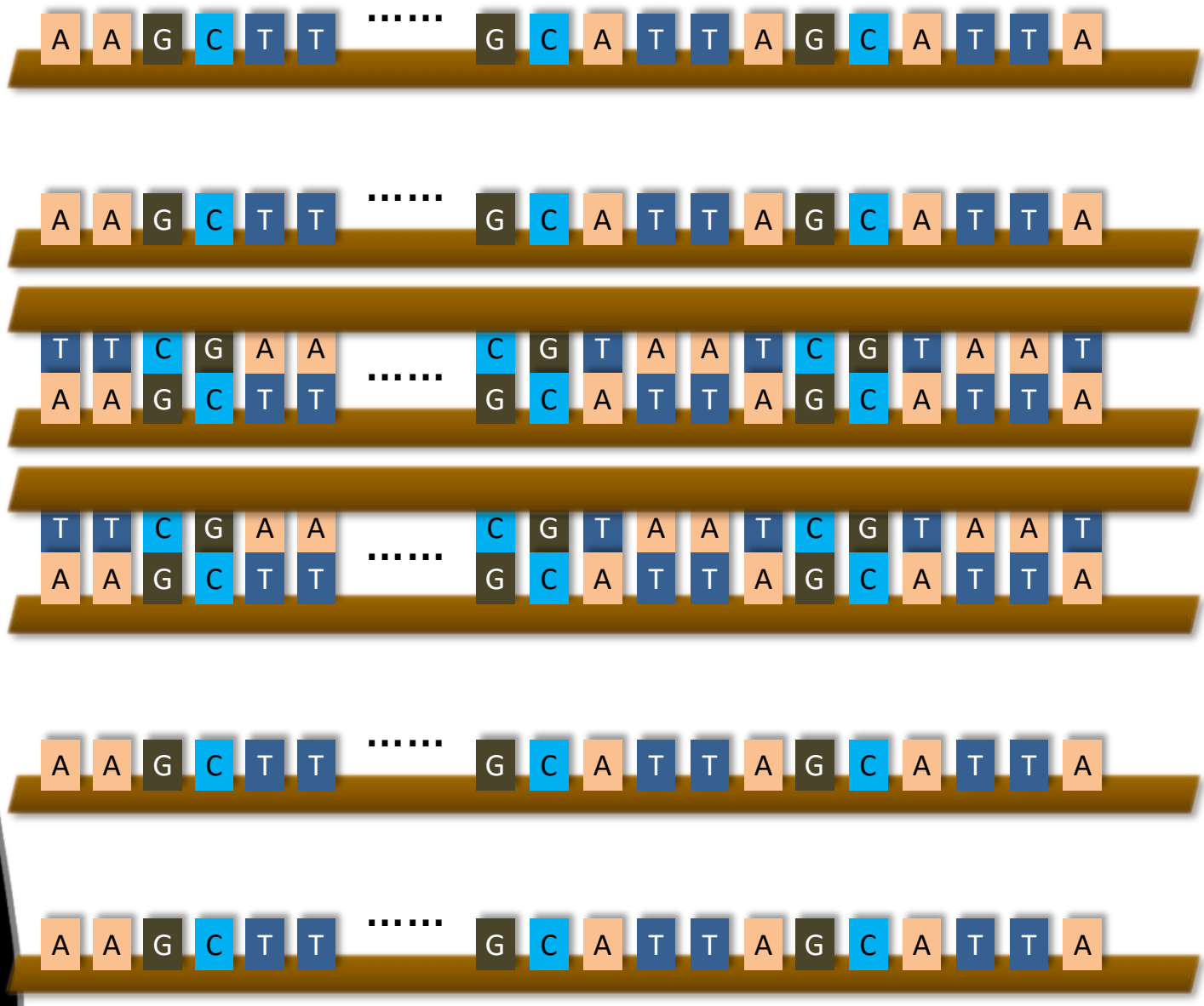

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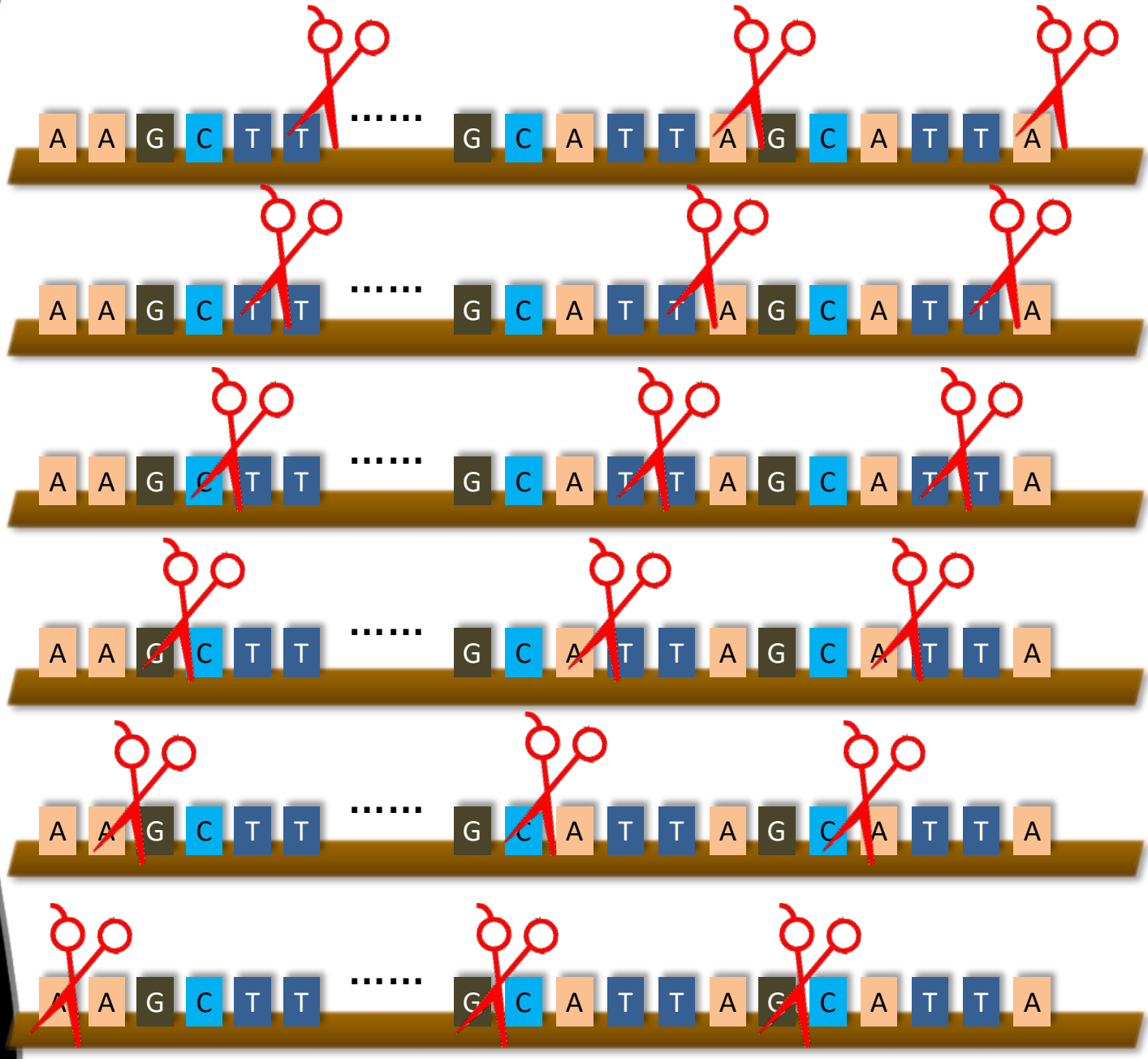

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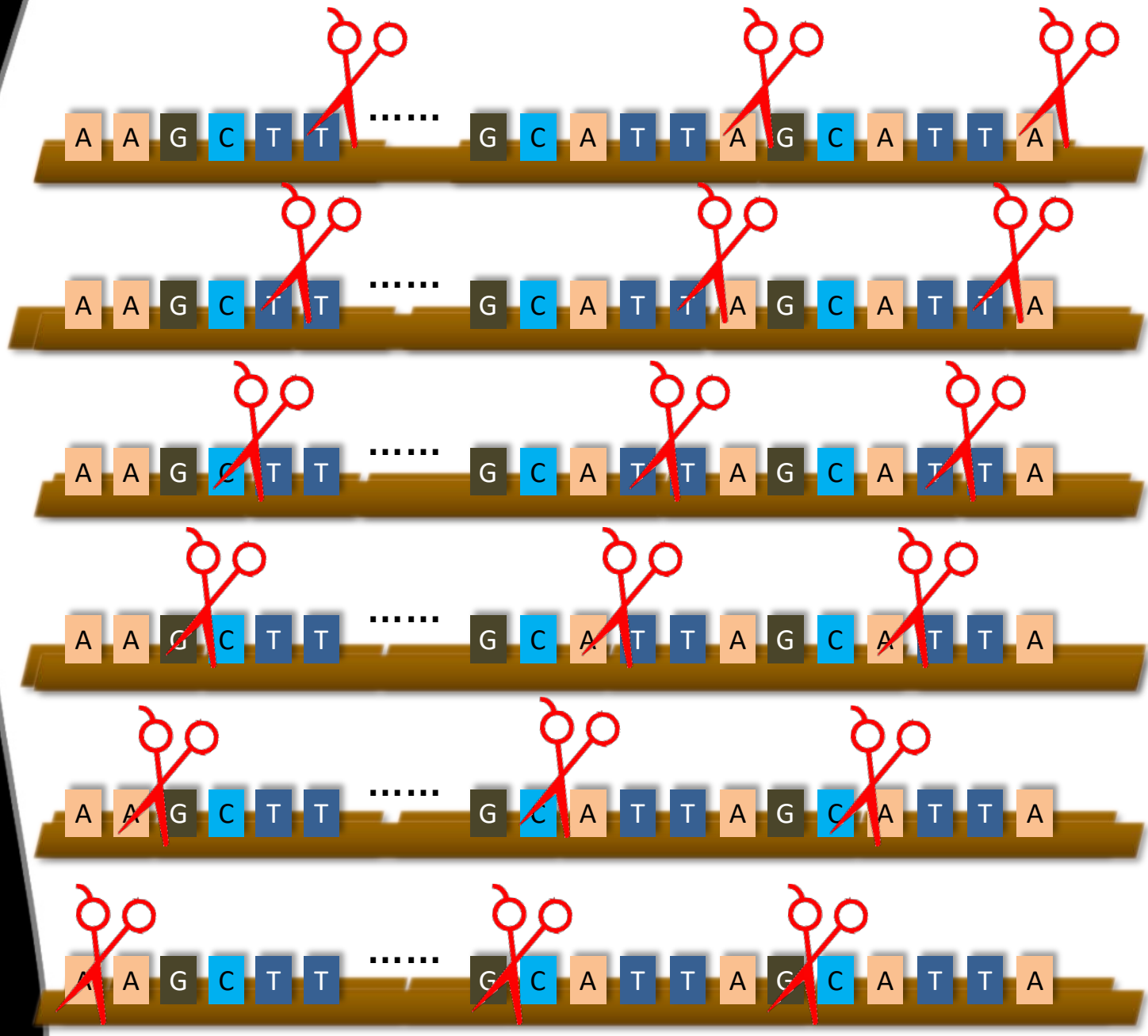

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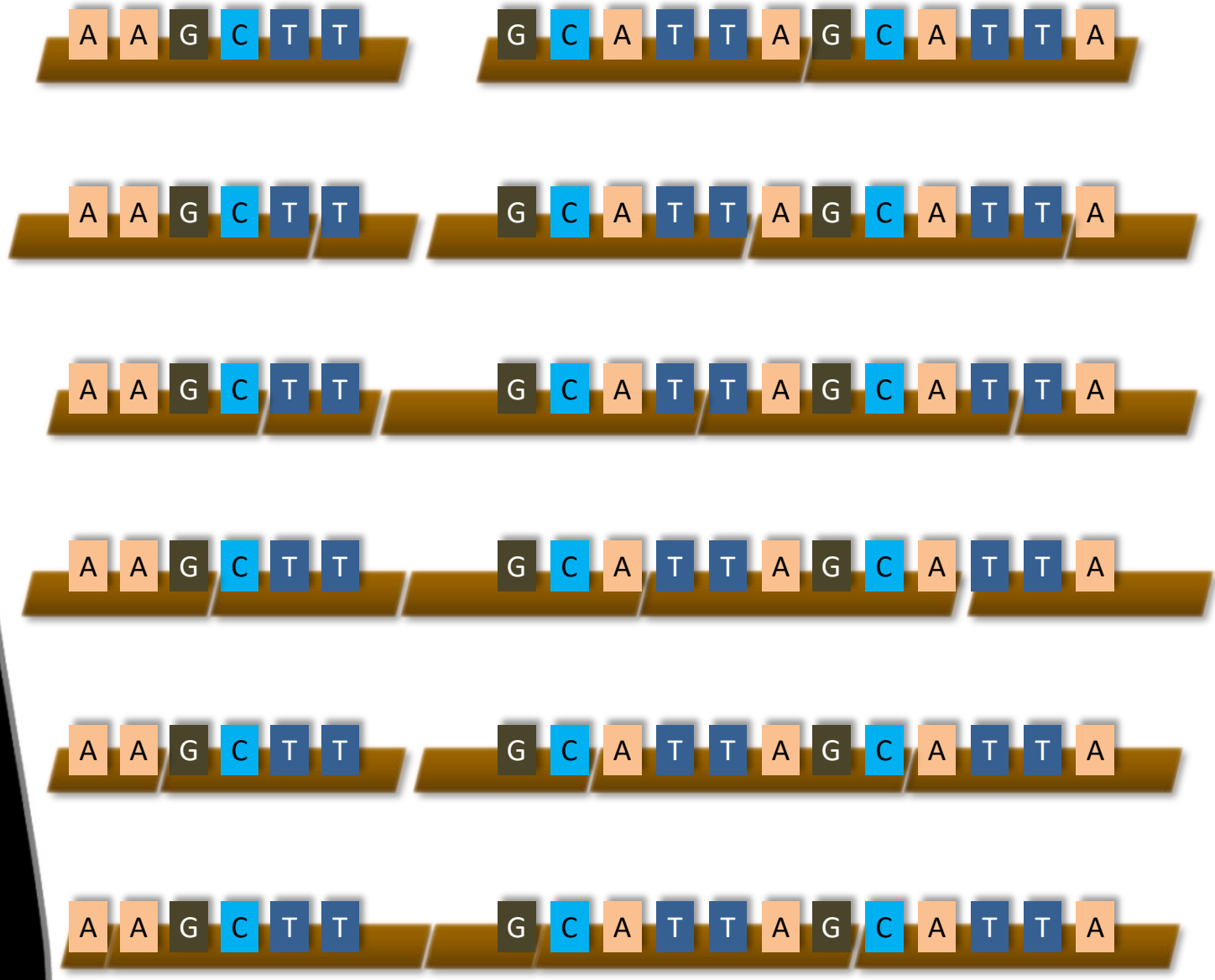

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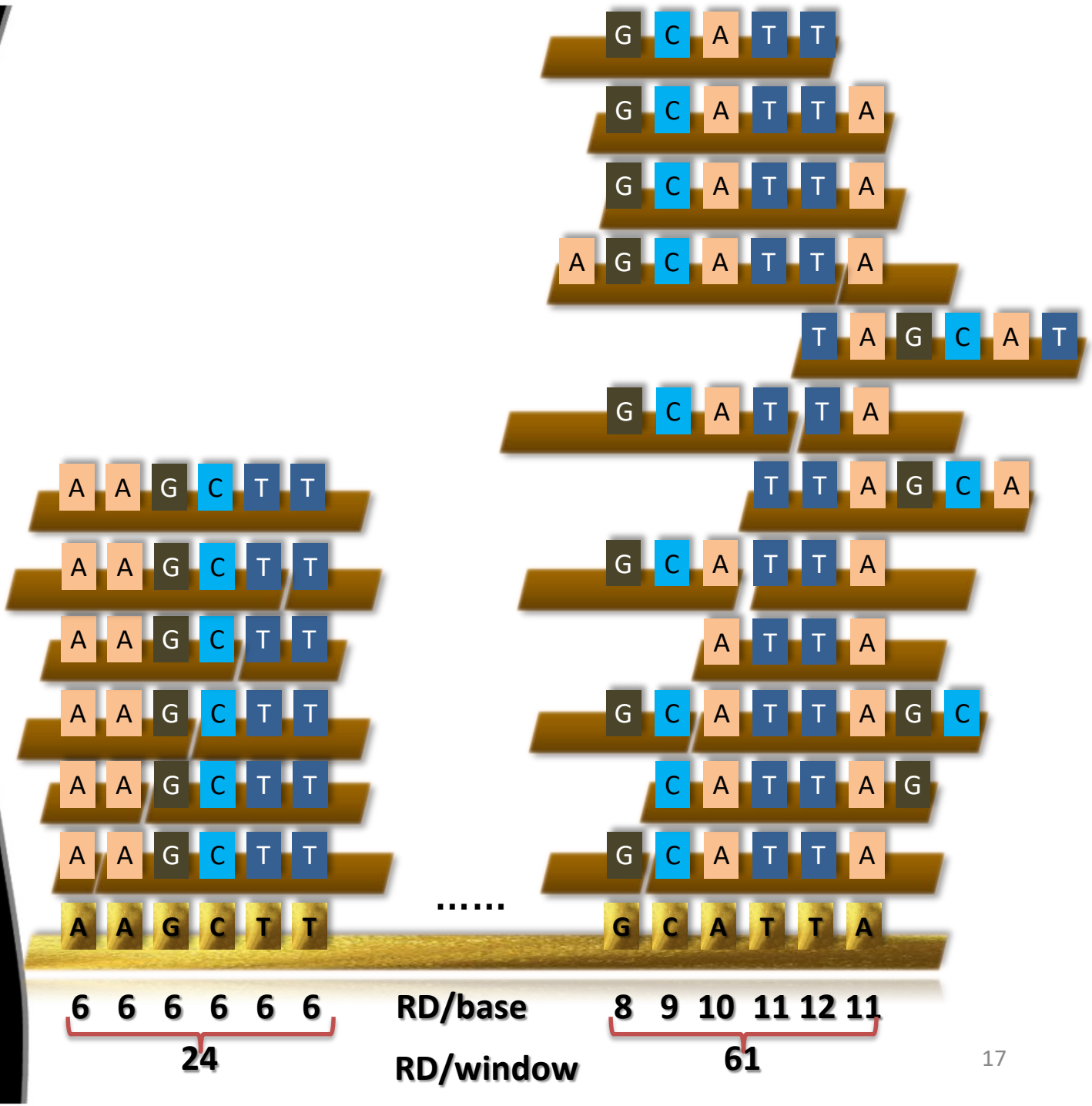

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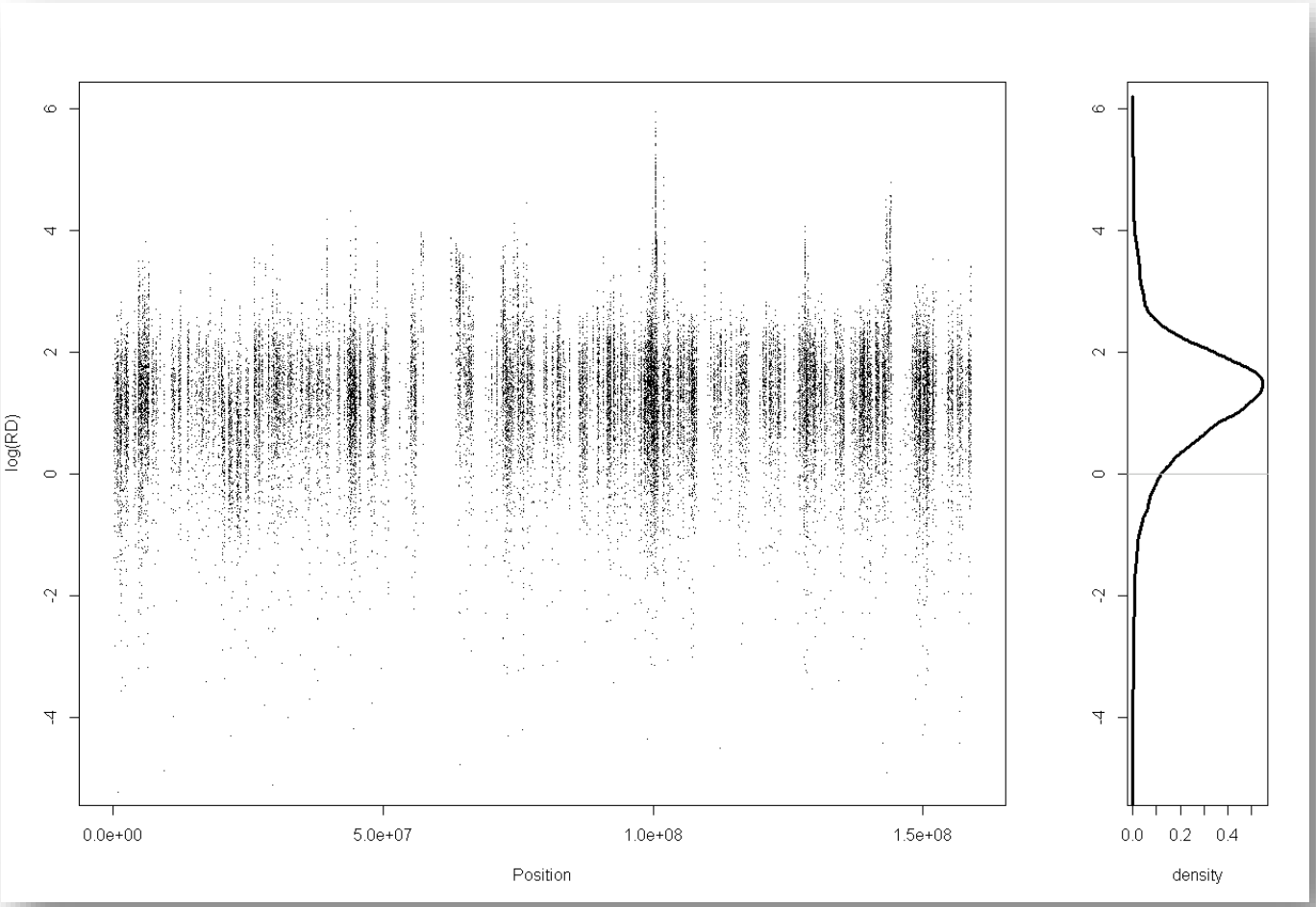

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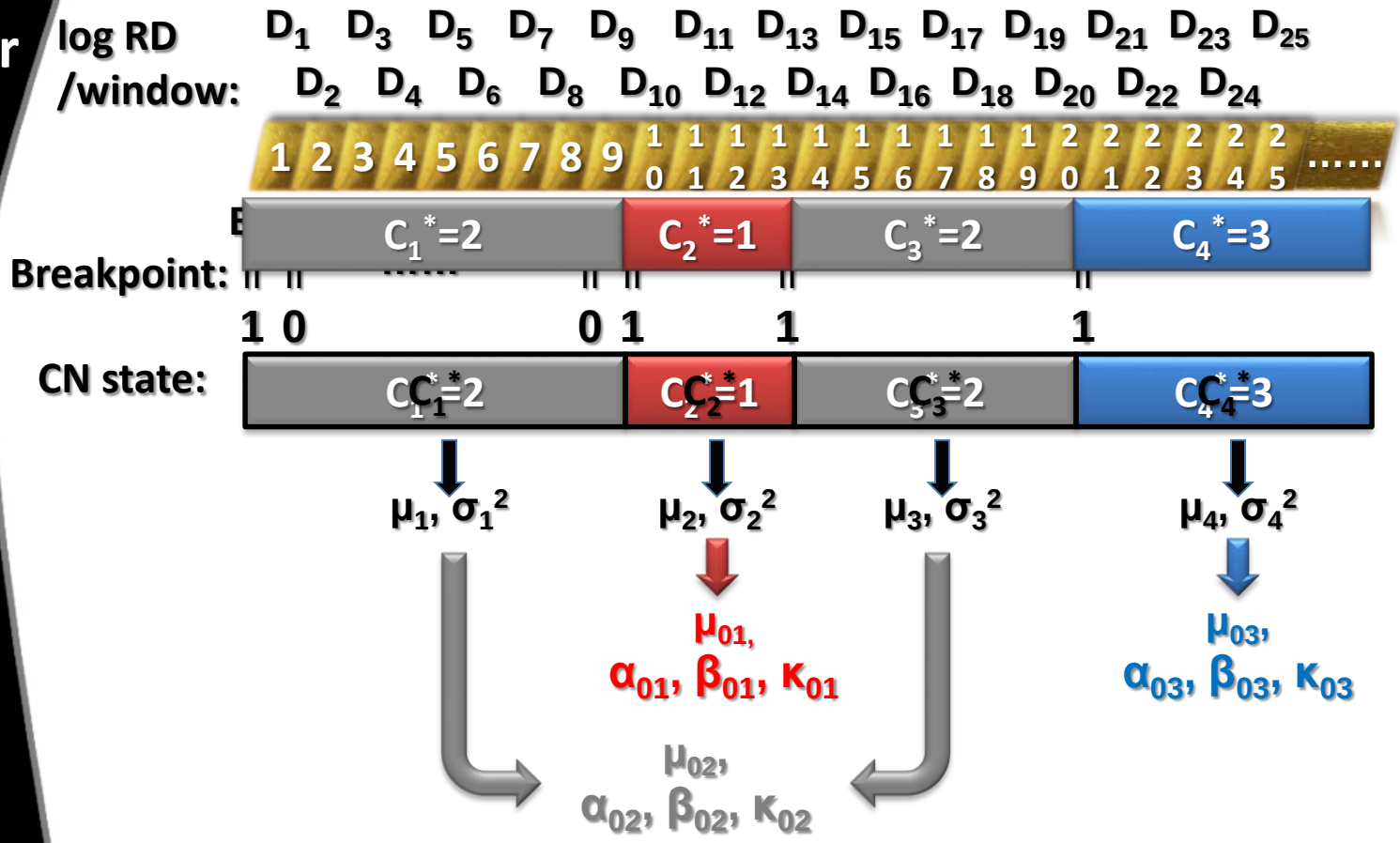

$$P(\underset{\sim}{C},\underset{\sim}{B}|\underset{\sim}{D})$$

$$\propto P(\underset{\sim}{D}|\underset{\sim}{C},\underset{\sim}{B})\times P(\underset{\sim}{C},|\underset{\sim}{B})\times P(\underset{\sim}{B})$$

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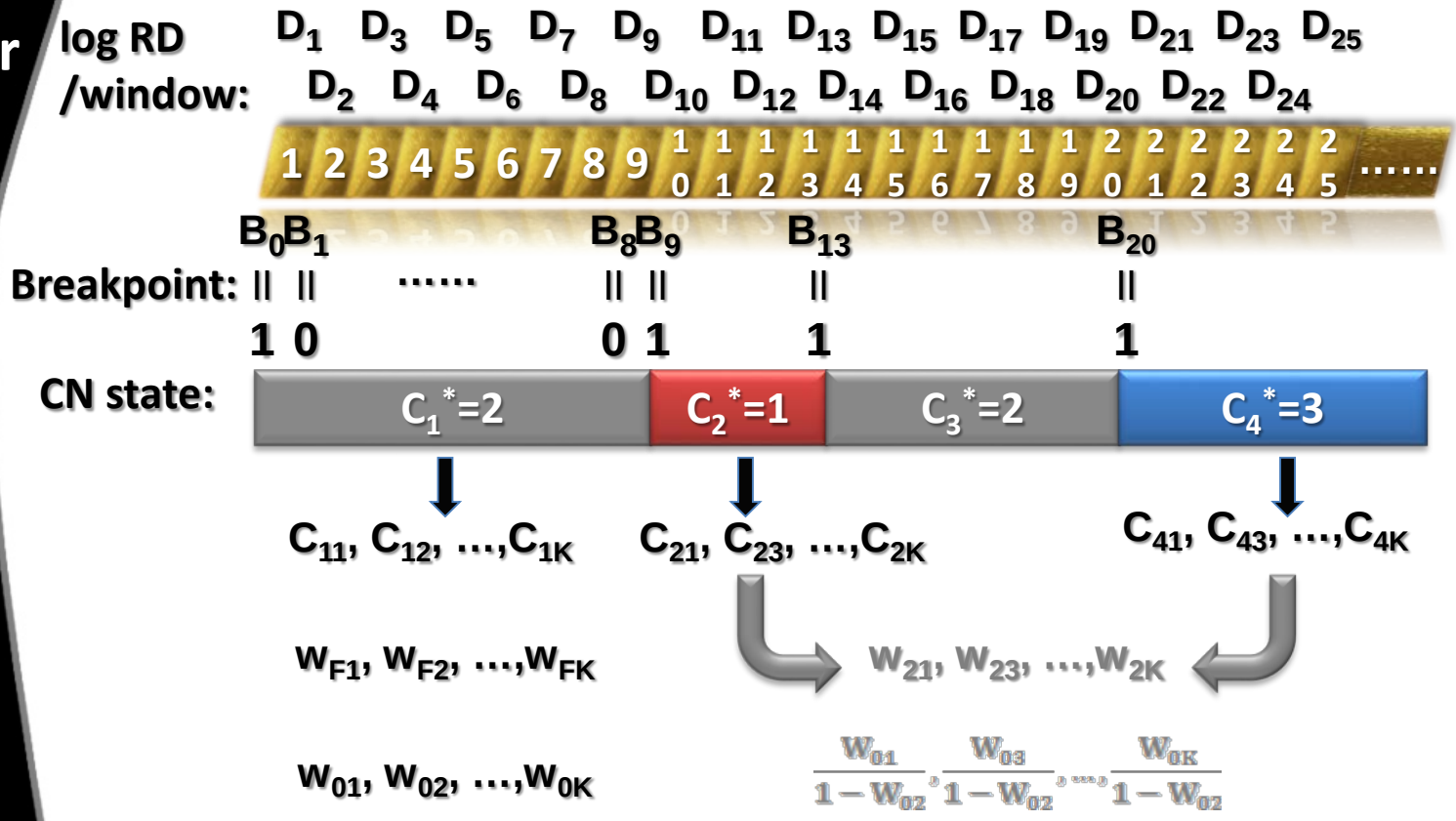

$$P\left(\underset{\sim}{C},\underset{\sim}{B}\middle|\underset{\sim}{D}\right)$$

$$\propto P\left(\underset{\sim}{D}\middle|\underset{\sim}{C},\underset{\sim}{B}\right)\times P\left(\underset{\sim}{C}\middle|\underset{\sim}{B}\right)\times P\left(\underset{\sim}{B}\right)$$

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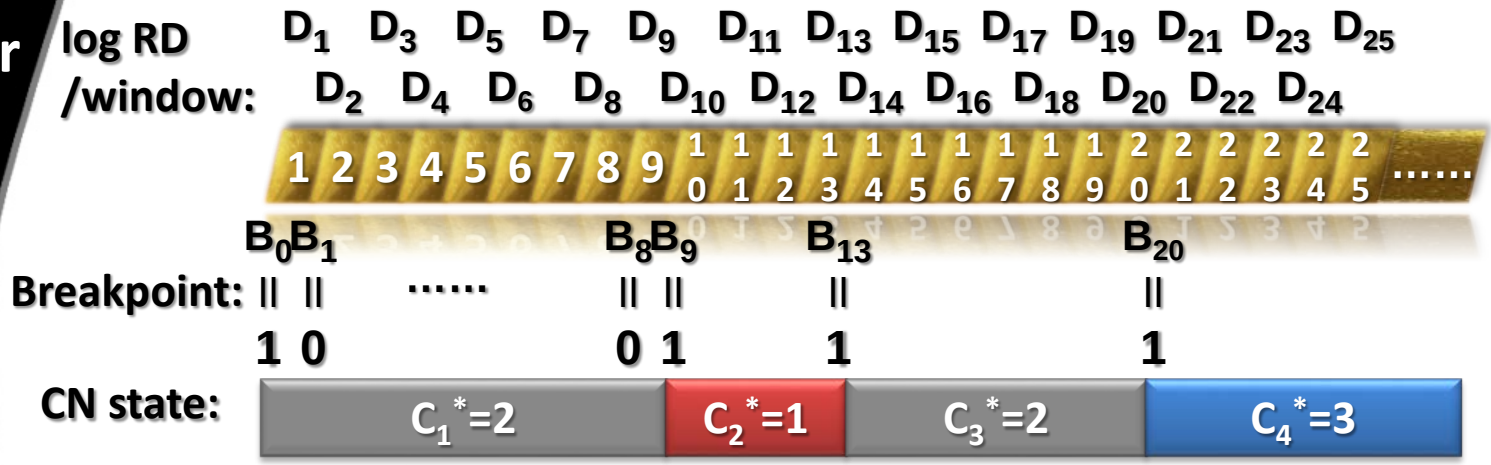

$$B_i \sim \text{Binomial}(\lambda)$$

$$P(\underset{\sim}{C}, \underset{\sim}{B} \mid \underset{\sim}{D})$$

$$\propto P(\underset{\sim}{D} \mid \underset{\sim}{C}, \underset{\sim}{B}) \times P(\underset{\sim}{C} \mid \underset{\sim}{B}) \times P(\underset{\sim}{B})$$

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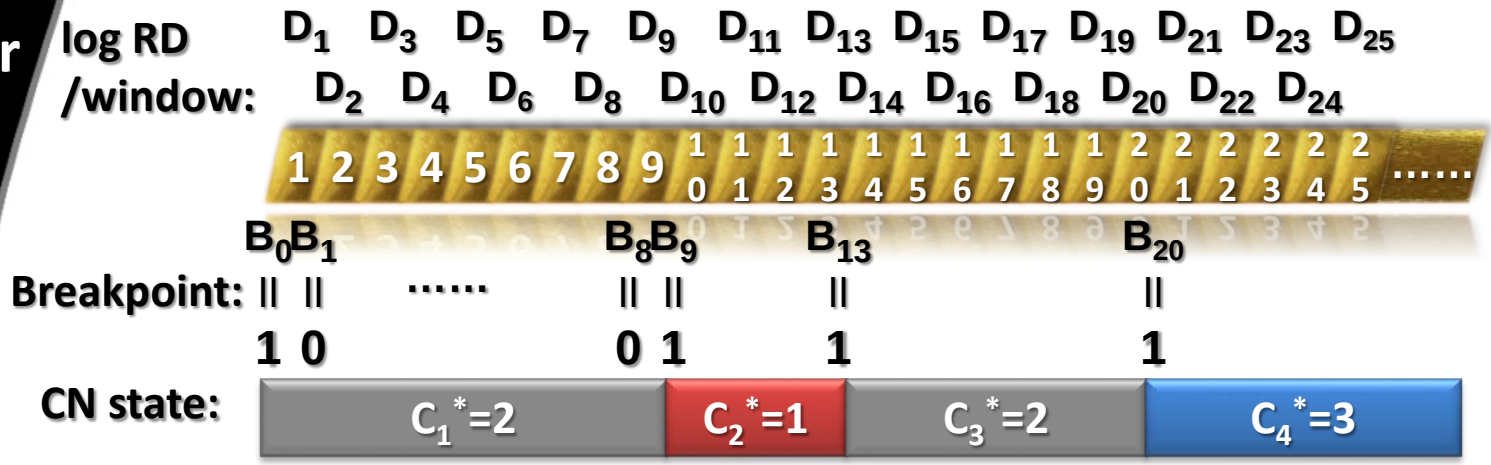

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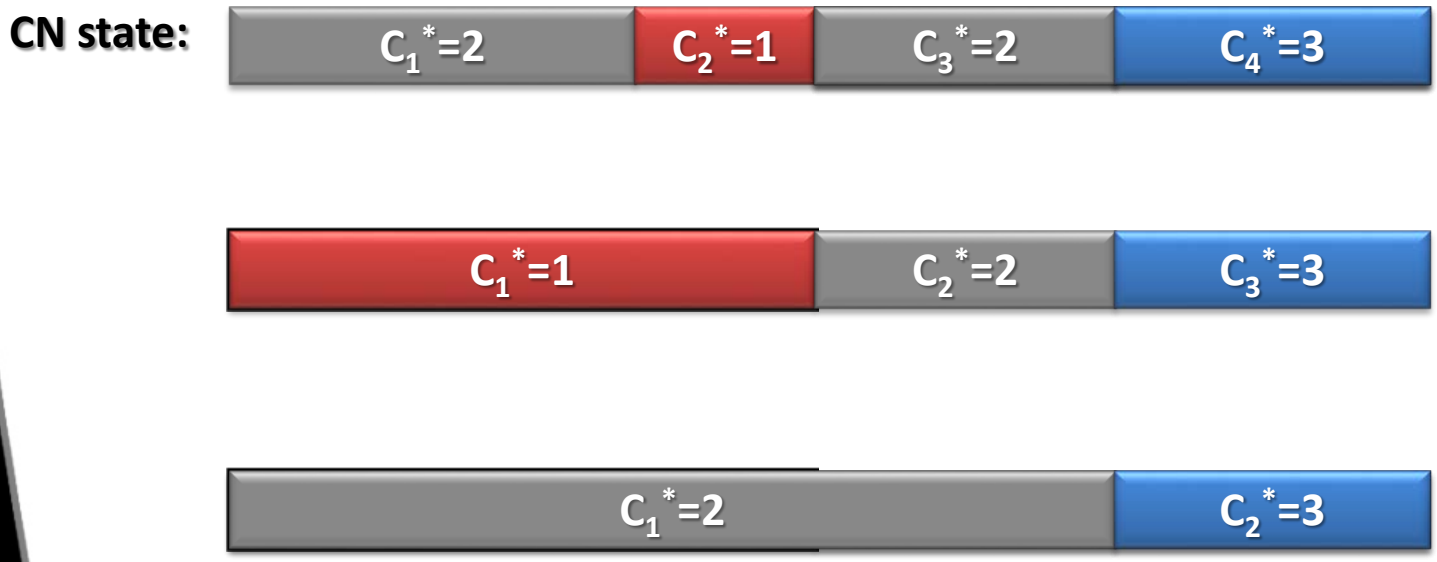
1. Merge



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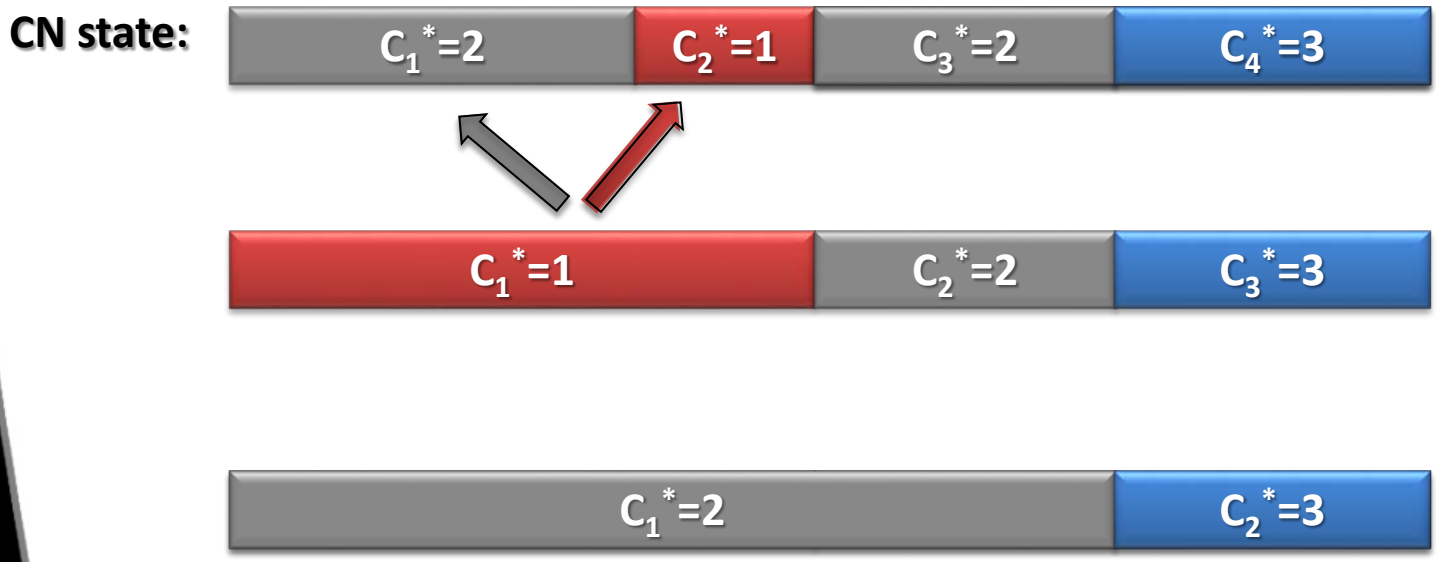
2. Split



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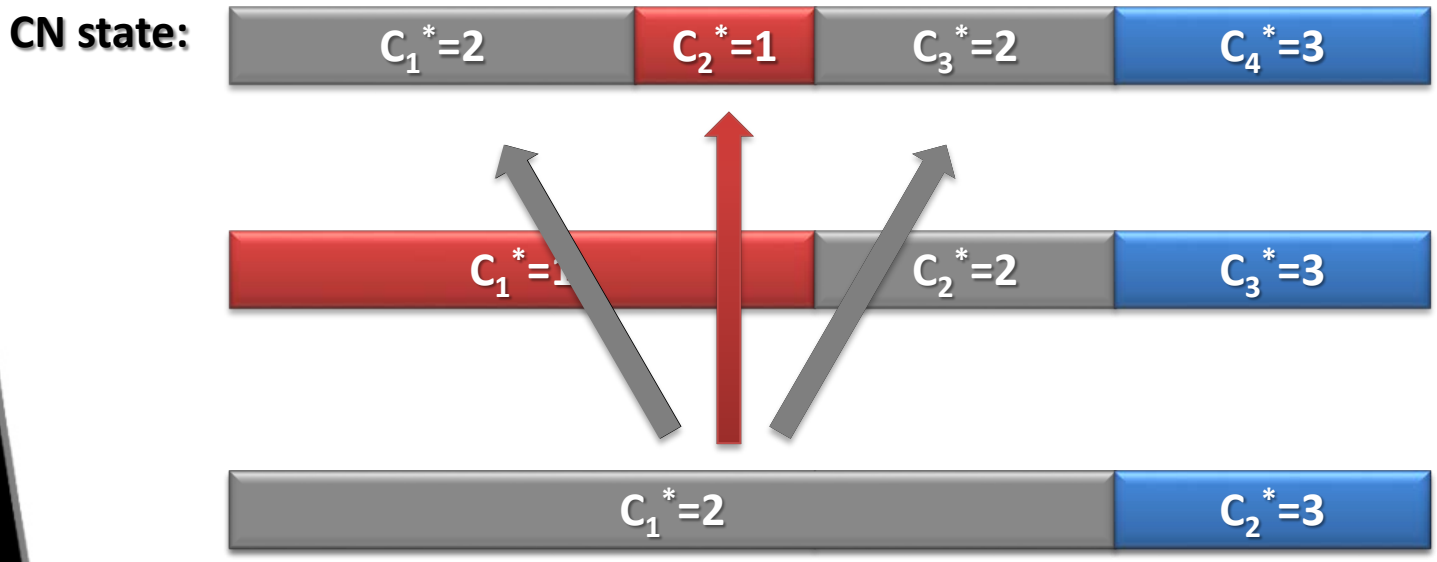
3. Trifid



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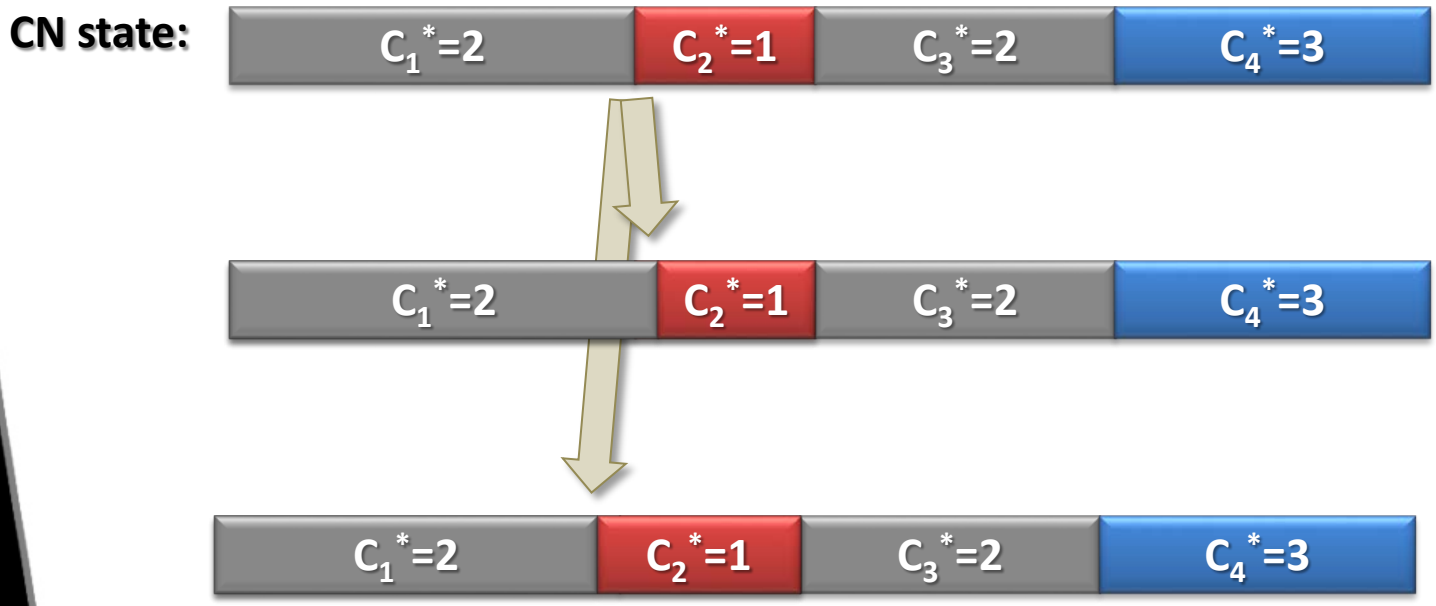
4. Boundary Change



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NTUH Department of OB/GYN

- **Silver-Russell syndrome**: a growth disorder, have a small, triangular face with distinctive facial features
- Illumina/Solexa (NGS technology)
- Targeted exon region (protein coding regions)
- Chromosome 7
- 32387 windows

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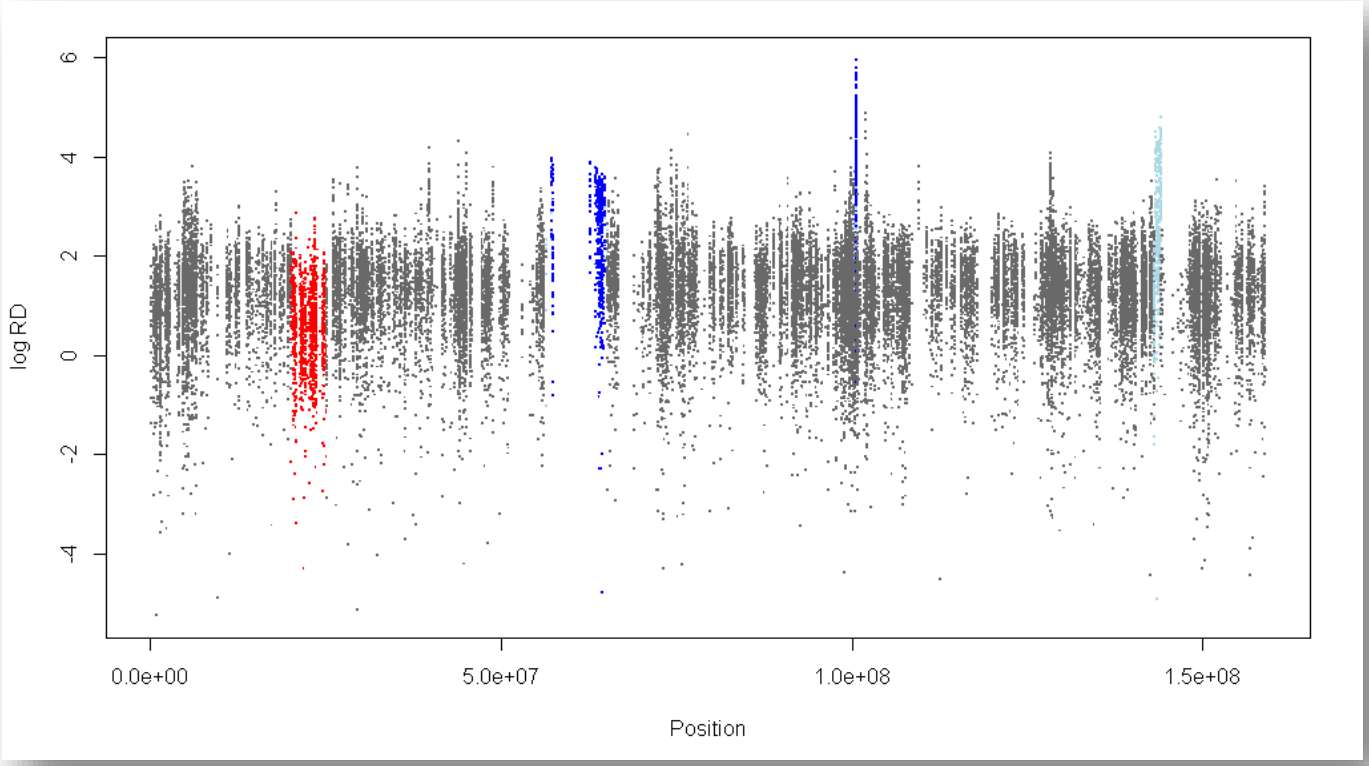
Sample 1:



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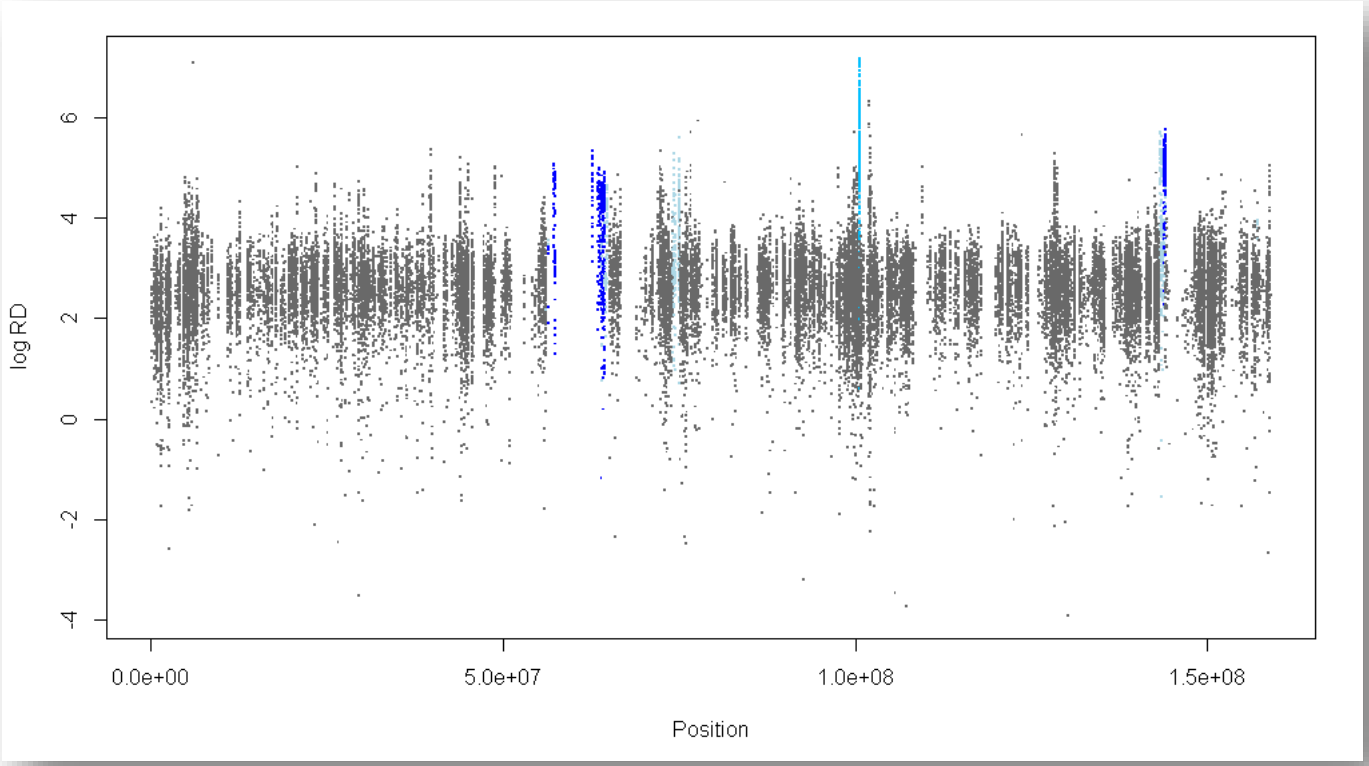
Sample 2:



● :CN1 ● :CN2 ● :CN3 ● :CN4 ● :CN5

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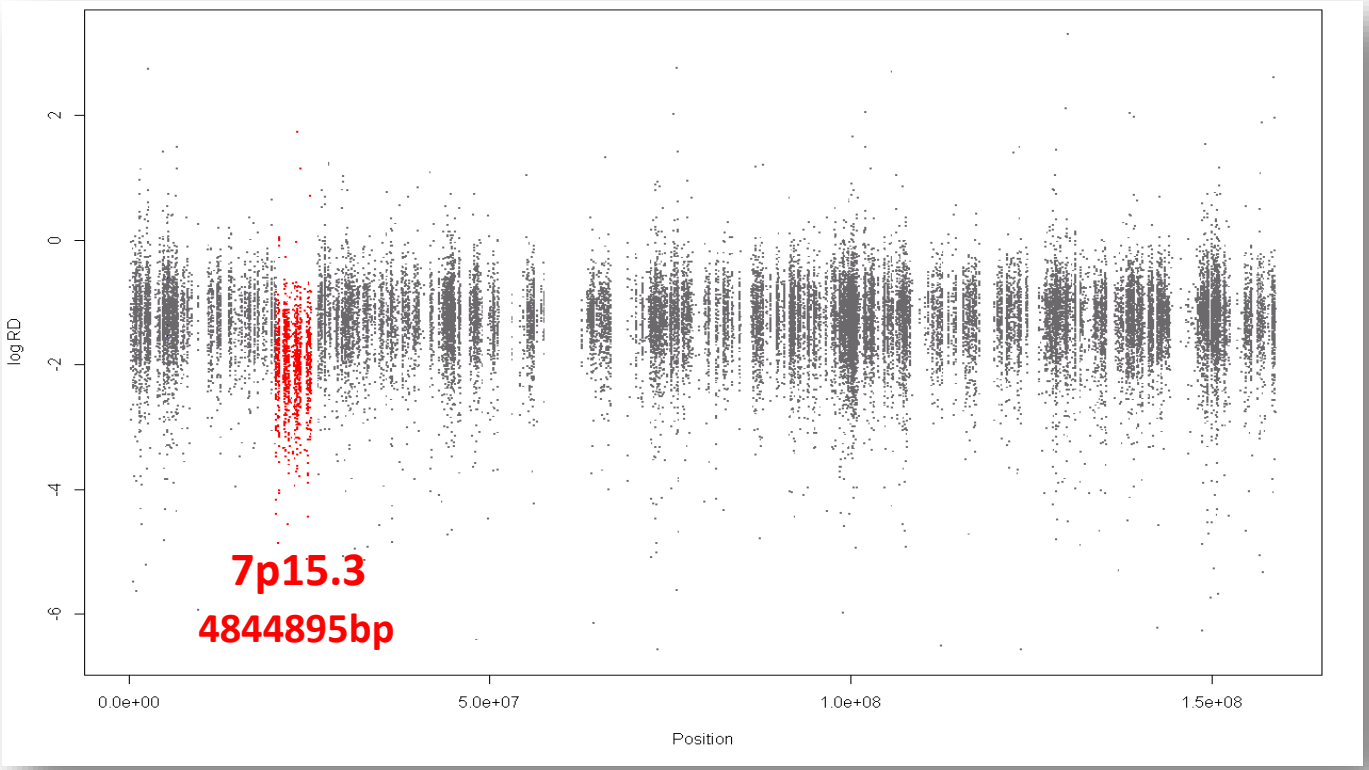
Sample 1 vs. 2:



● :Deletion ● :Normal ● :Duplication