ACGT Algorithms in Computational Genomics at Tau
Ron Shamir's group

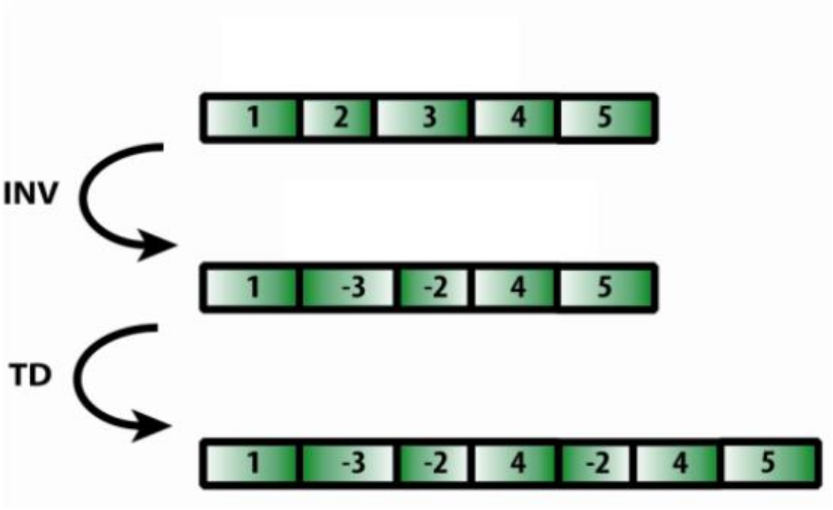
Reconstructing Cancer Karyotypes

Rami Eitan, Tel-Aviv University

13/8/14

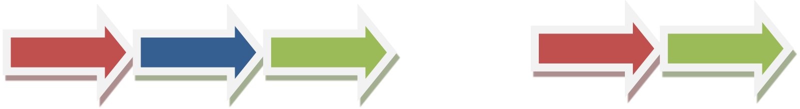
Driving mechanism of cancer

- Chromosomal rearrangements that gradually accumulate over time and create a complex cancer karyotype.



We consider 3 types of intra-chromosomal rearrangements:

- Deletion



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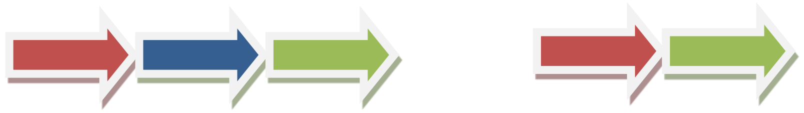

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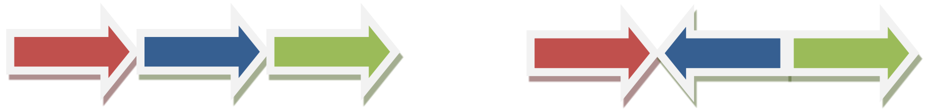

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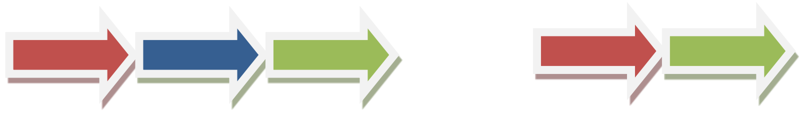

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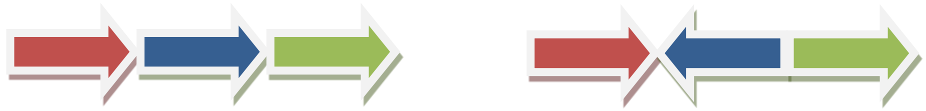
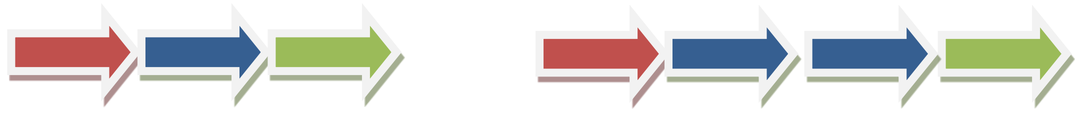
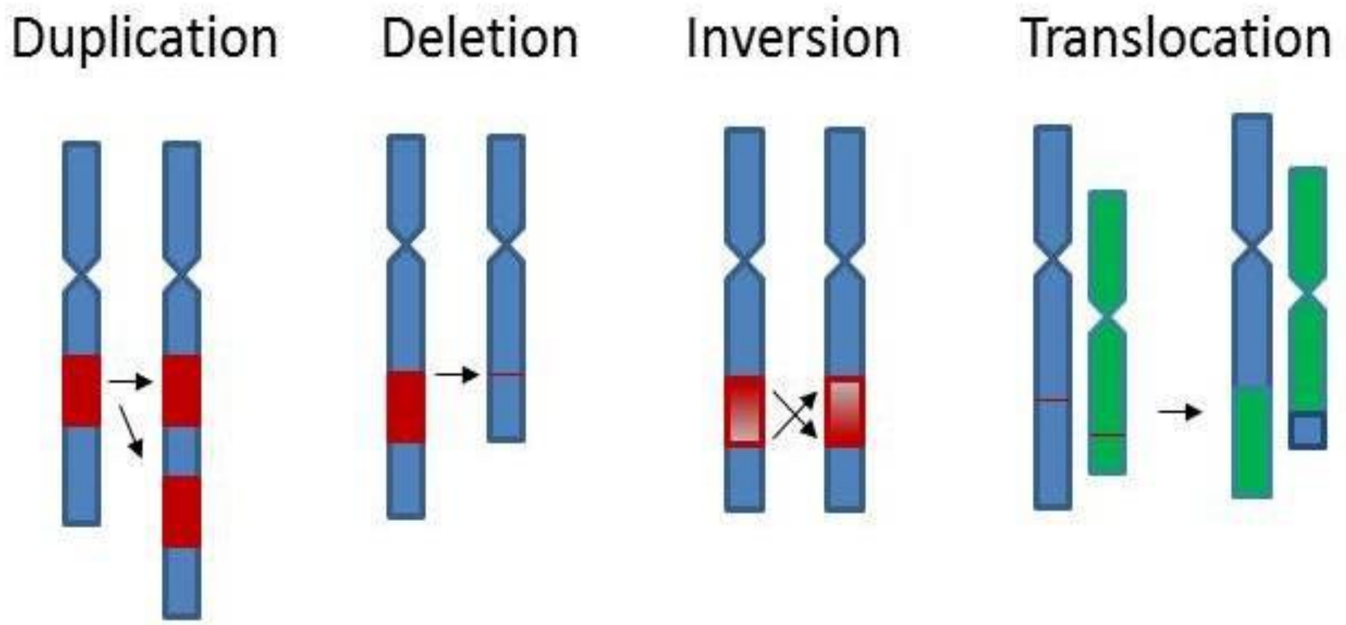


- Tandem Duplication



- In addition to duplication, inversion and deletion we also consider the inter-choromosomal variation of translocation.



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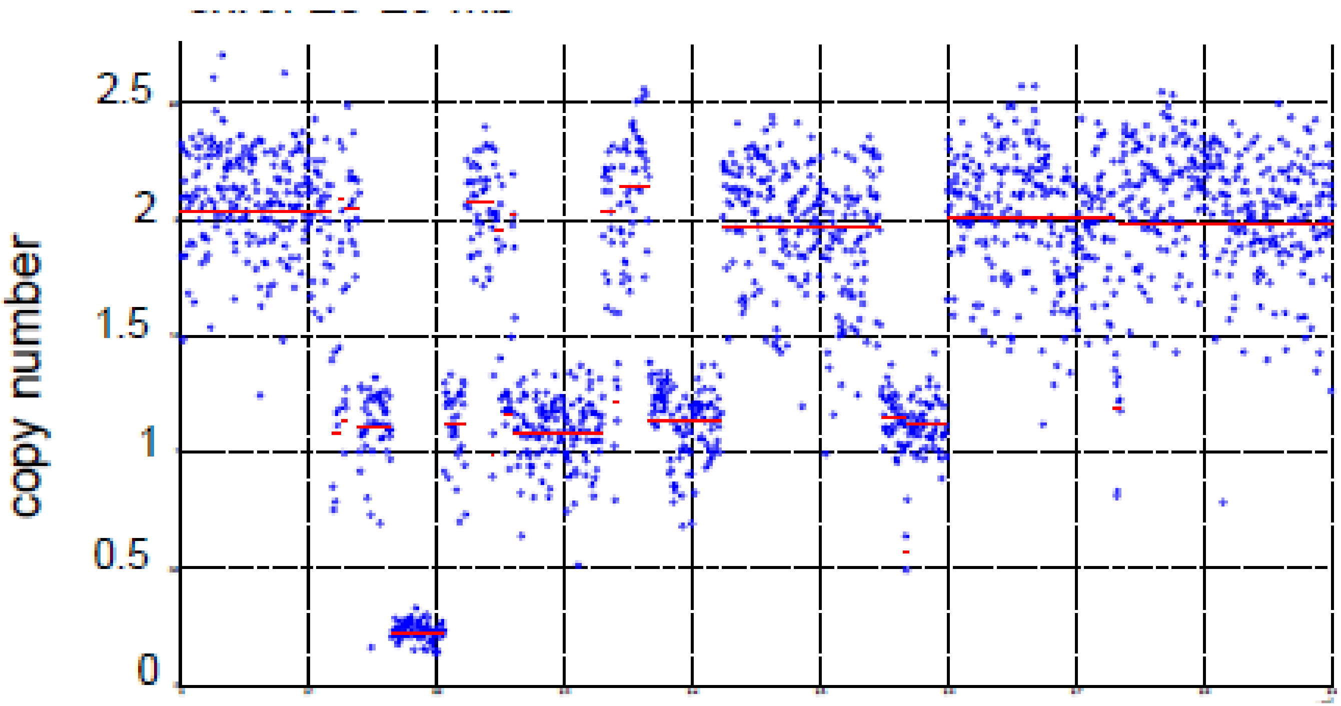
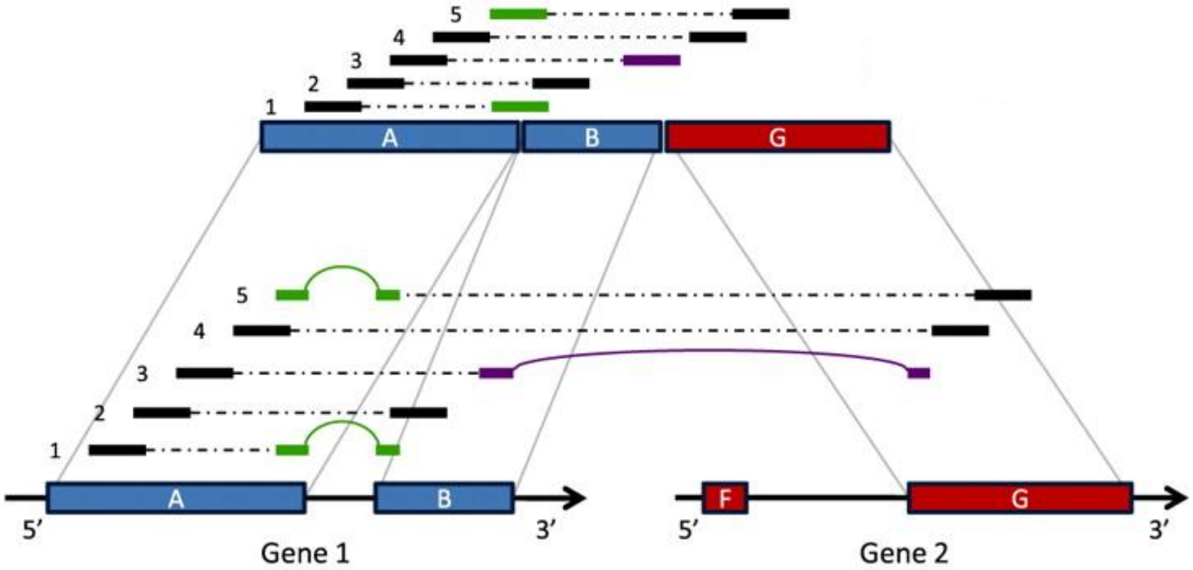
- CGH array – Detect Copy Number Variations (CNV), resolution as low as 100 Kilo bases.
- Paired Ends Reads – Detect novel adjacencies in the genome compared to the reference.

CGH Array



Paired-end reads

- Sample DNA sequence *S* is cut into small fragments (200-500 bp)
- Each end of the fragment (36 bp) is then aligned against a reference genome *R.*
- Concordant reads – both ends aligned to the same distance
- Discordant reads – ends are aligned to a different distance.



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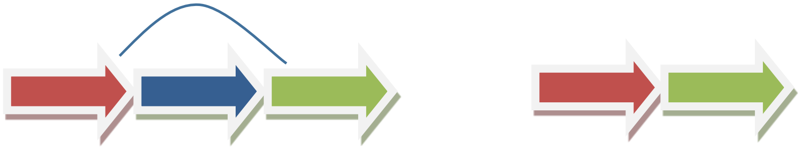

Orientation	Rearrangement
head-to-tail	Deletion

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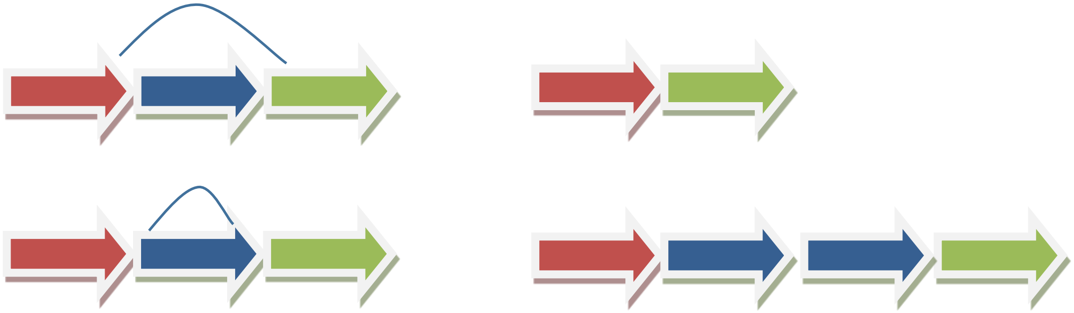

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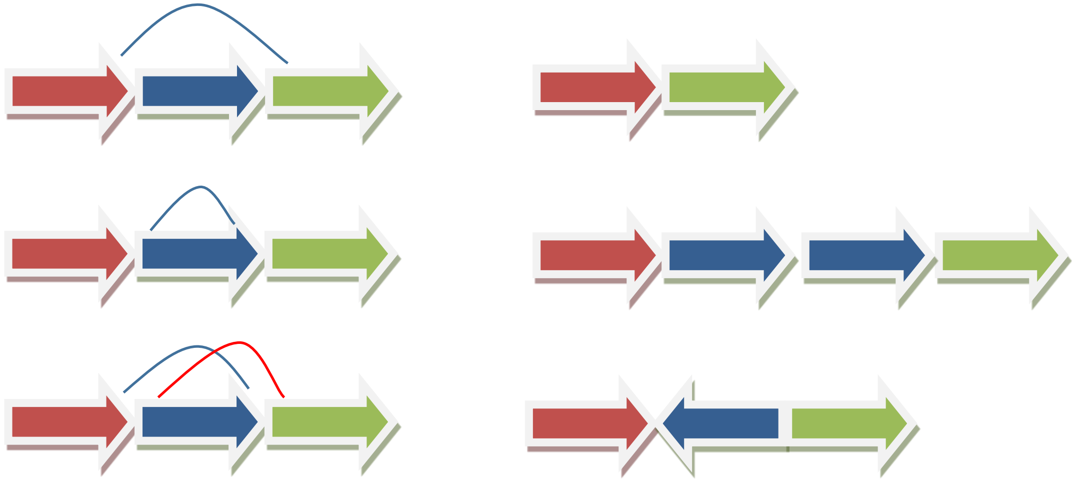

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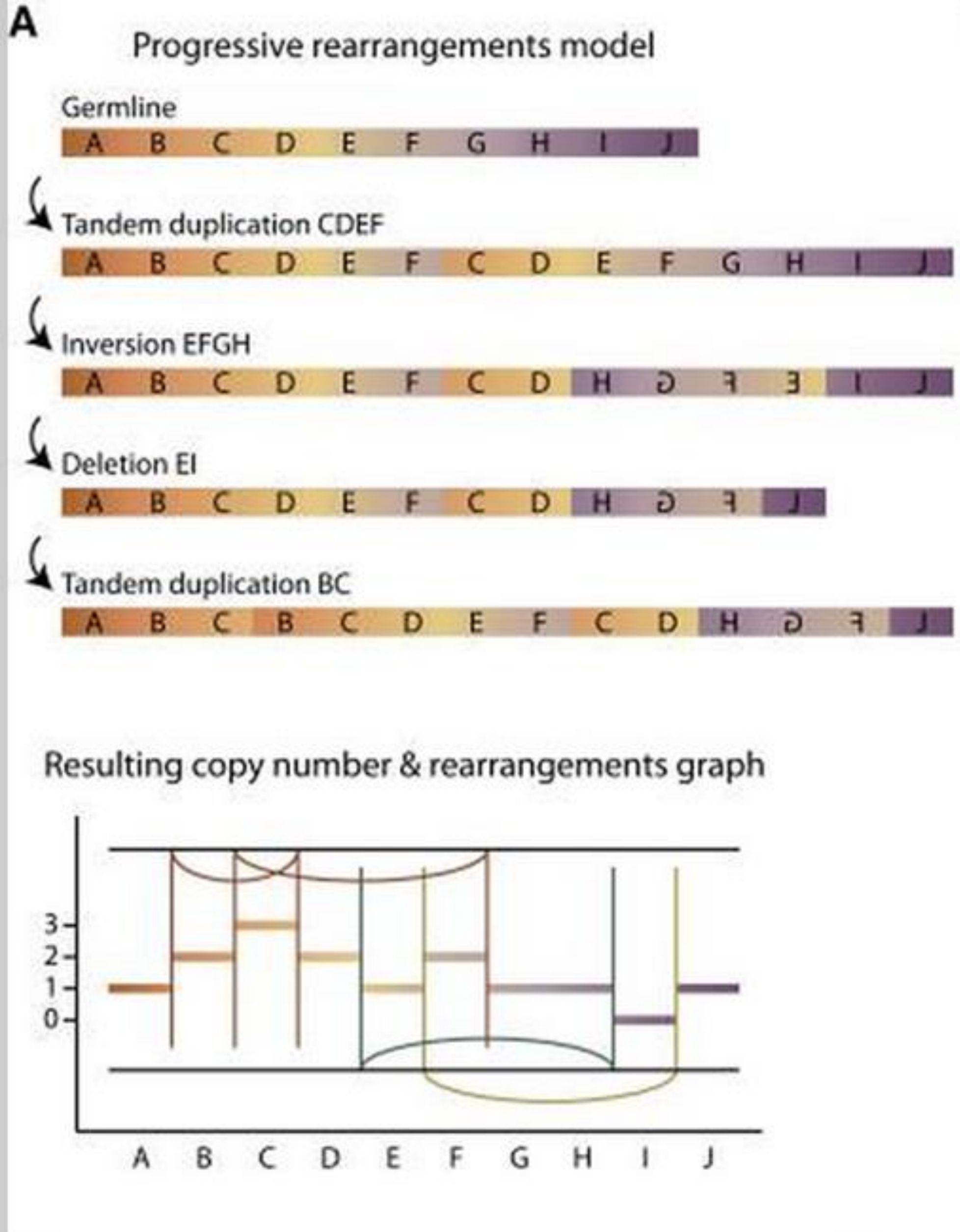
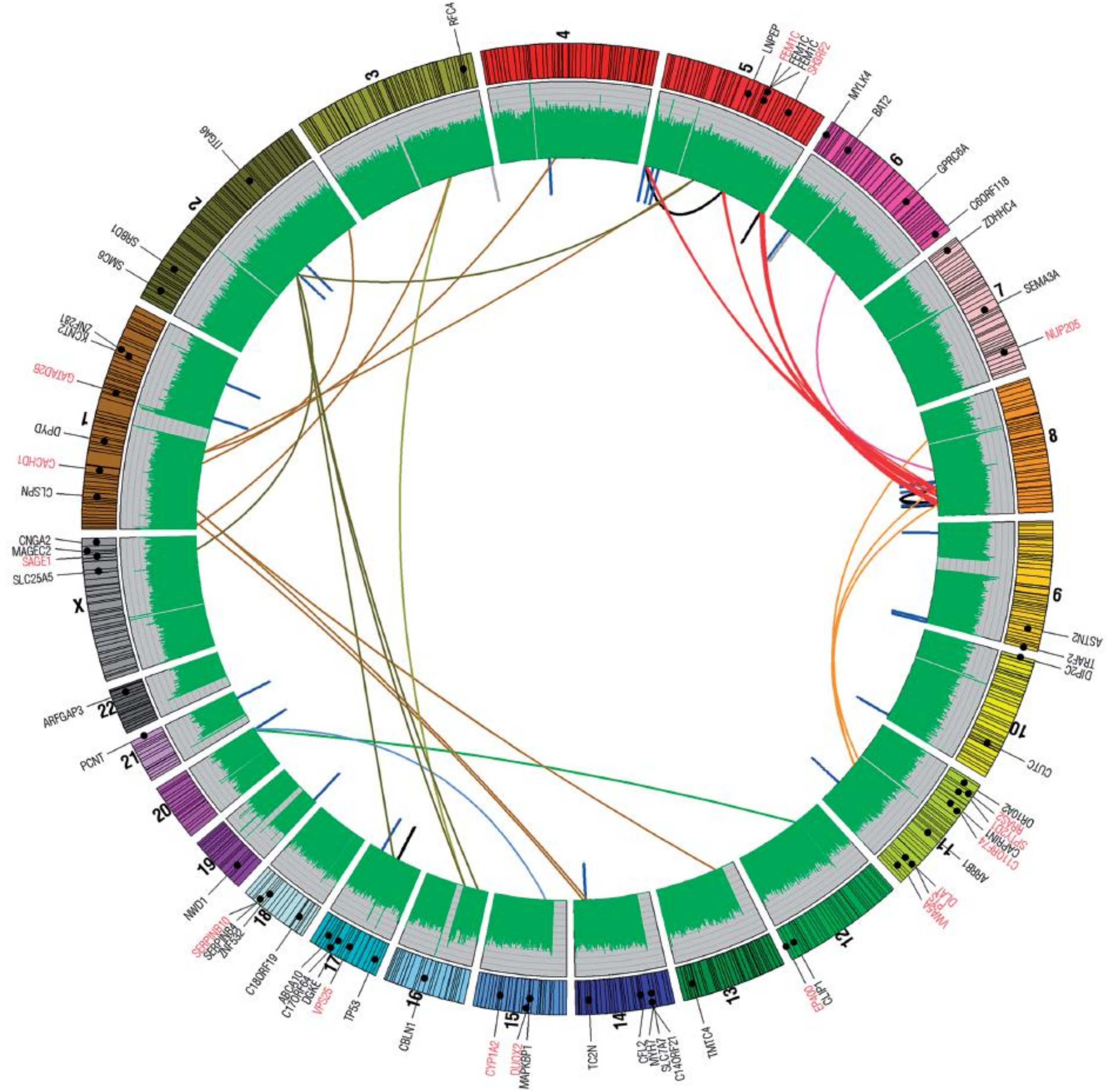

A
Progressive rearrangements model
Germline
A B C D E F G H I J
Tandem duplication CDEF
A B C D E F C D E F G H I J
Inversion EFGH
A B C D E F C D H G F E I J
Deletion EI
A B C D E F C D H G F J
Tandem duplication BC
A B C B C D E F C D H G F J
Resulting copy number & rearrangements graph
3
2
1
0
A B C D E F G H I J



Breast tumor HCC1954

Galante 2011

Genome reconstruction

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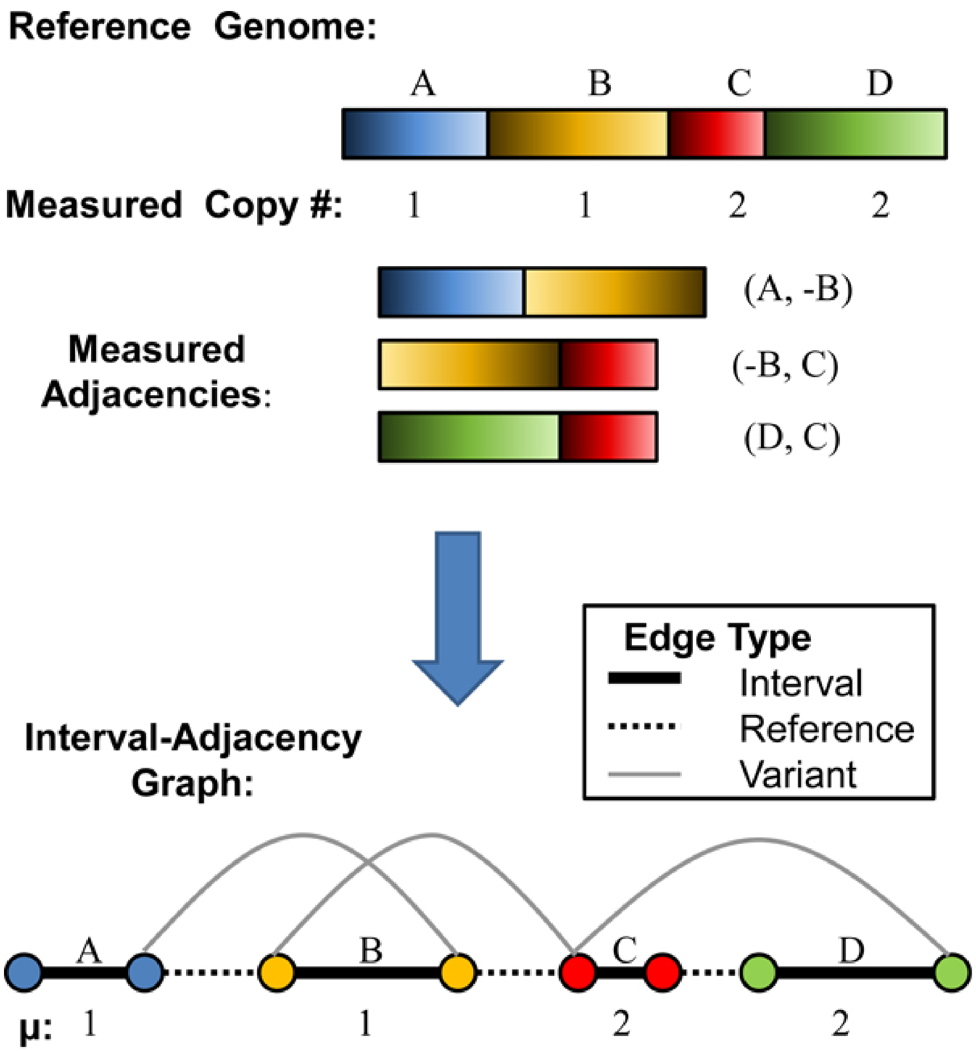
- From CGH array: CNV data - $c: I \rightarrow R$

Copy number and adjacency genome reconstruction problem

Given an interval vector I*, a set* A *of cancer adjacencies, and a copy number vector derived from a cancer sample* S*, find the cancer genomes that are most consistent with the data.*

Interval-adjacency graph



Reference Genome:

A B C D

Measured Copy #: 1 1 2 2

Measured Adjacencies:

(A, -B)

(-B, C)

(D, C)

Edge Type

Interval

Reference

Variant

Interval-Adjacency Graph:

A B C D

μ: 1 1 2 2

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- *Interval edges*
- *Reference Edges*
- *Variant edges*

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$$E_R = \{(t_j, s_{j+1})\}$$

$$E_V = \{(t_i/s_i, s_j/t_j) | [I_{i/-i}, I_{j/-j}] \in A\}$$

A block organization of the cancer genome corresponds to a path along the graph that:

1. *Starts at* s_1 *and ends at* t_n
2. *Alternates between interval edges and non-interval edges.*
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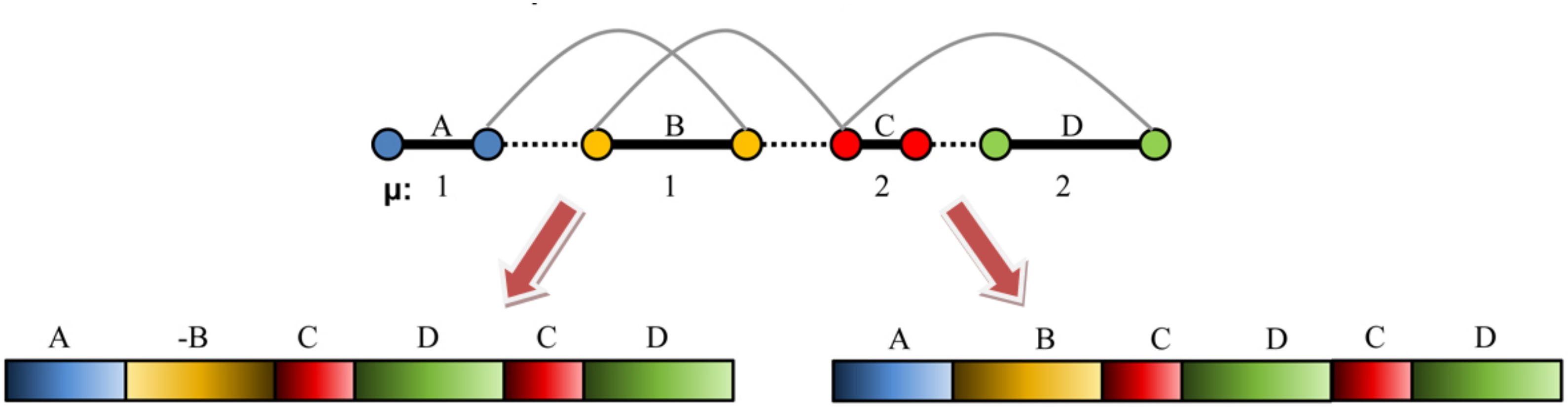
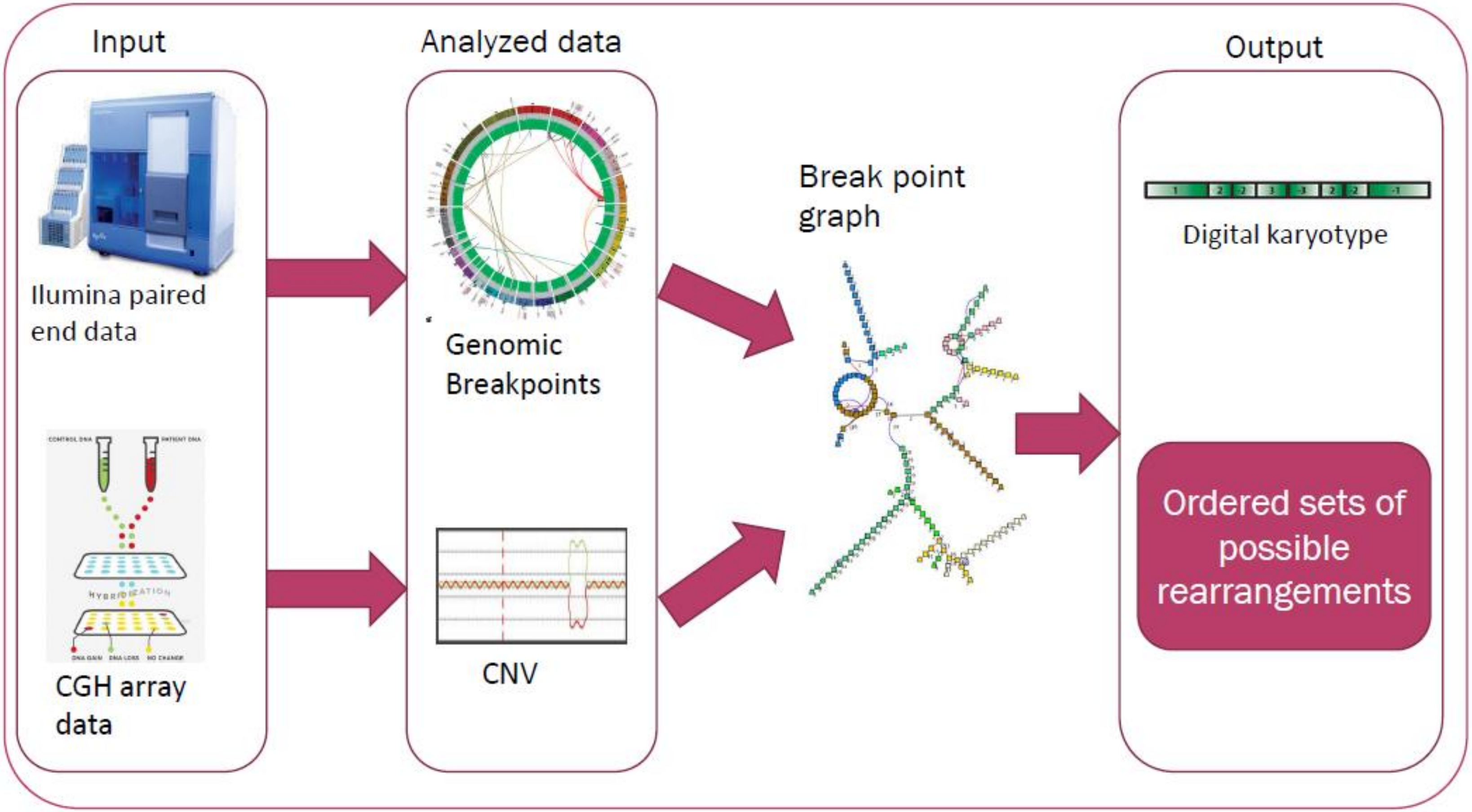


Reconstruction pipeline



Input

Ilumina paired end data

CGH array data

Analyzed data

Genomic Breakpoints

CNV

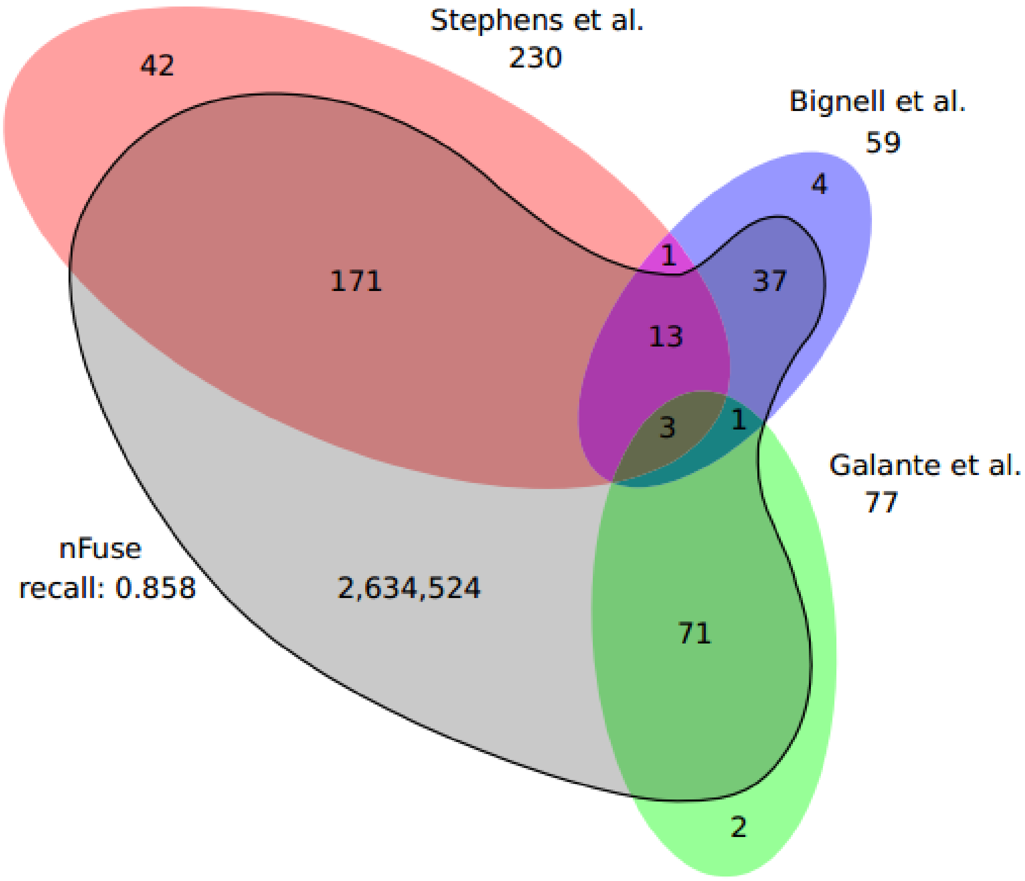
Break point graph

Output

Digital karyotype

Ordered sets of possible rearrangements

Intersection of discovered BPs



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    - Derive breakpoints and intervals from the data
    - Use a maximum likelihood function to estimate the copy number from the concordant reads.

Our attempt

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- Use available breakpoint and CNV data
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- Consider multi ploidity – find the set of paths that are closest to the observed data

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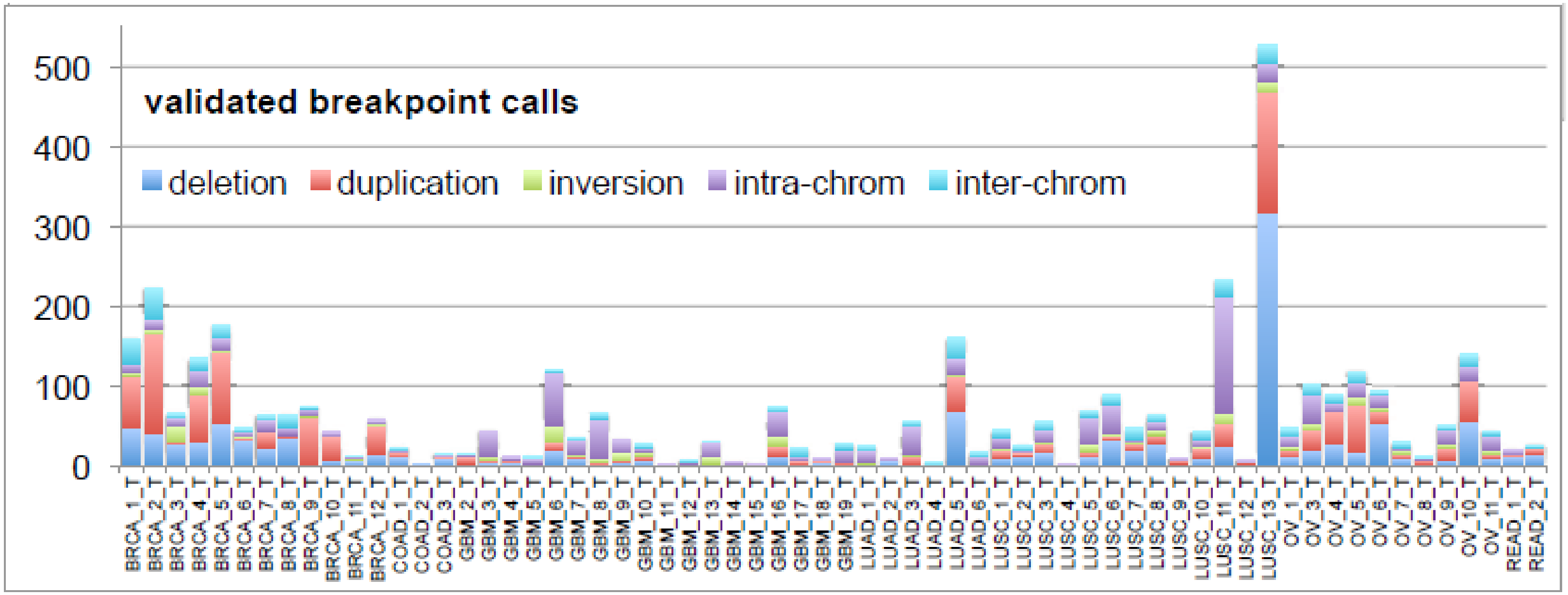
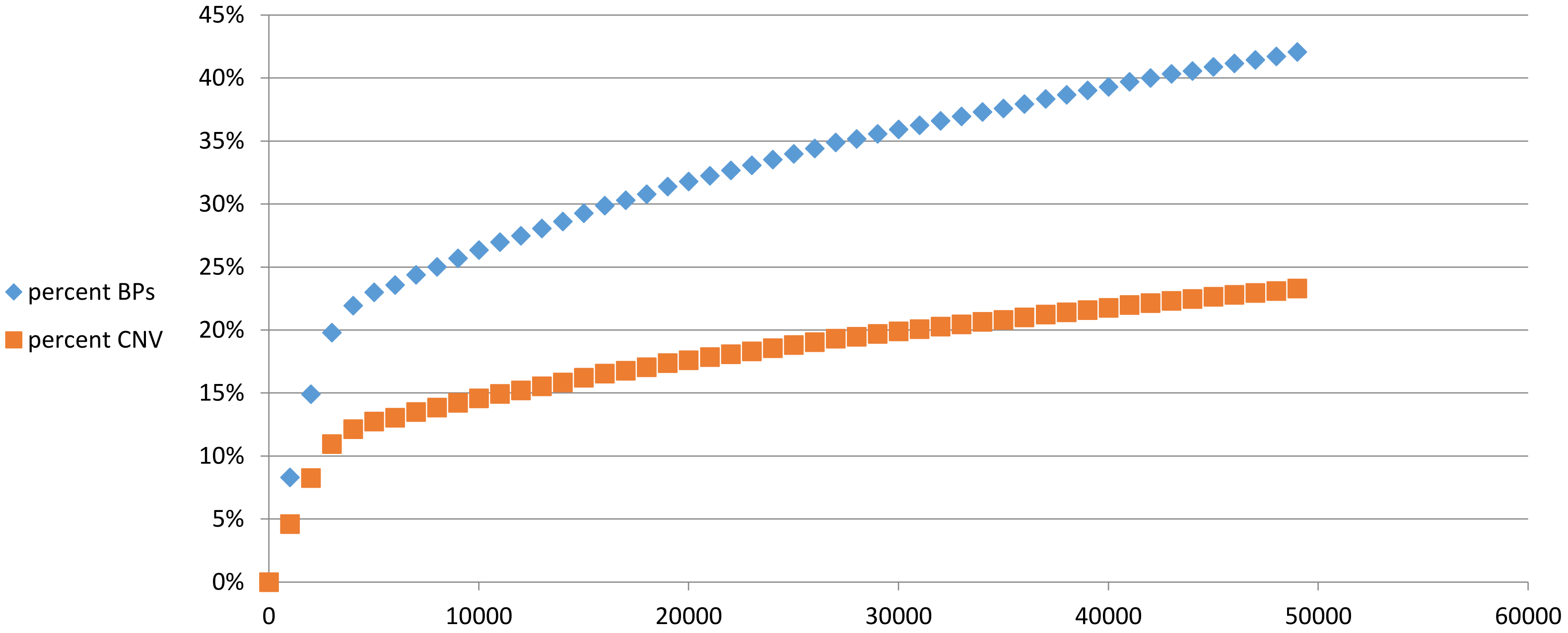


CNV to BP agreement rate



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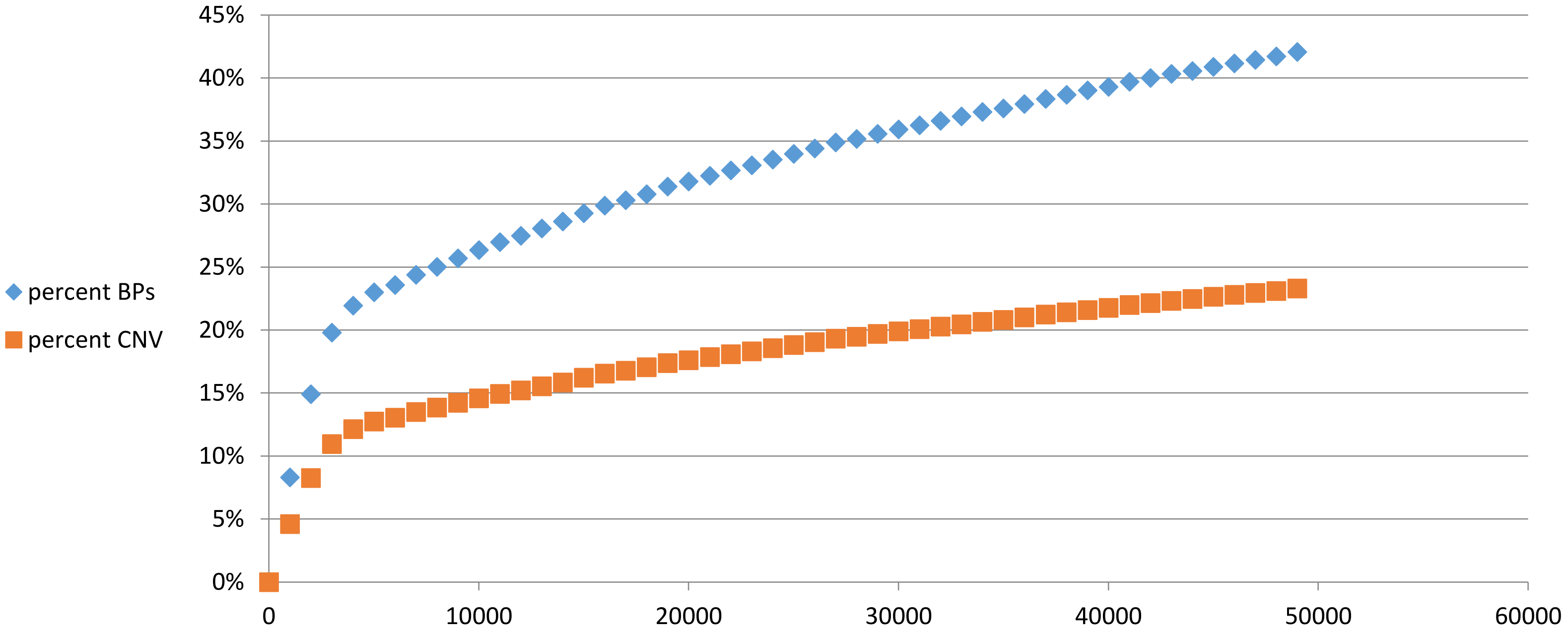


With a window of 3000 bases – 20% of breakpoints and 11% of CNV agree.

Why is the support rate so low?

- Data is noisy
- Diploidity
- Not all breakpoints cause changes in CN
- Complex rearrangements (eg chromotripsis)

Some samples have higher agreement rate and are non trivial.

Example: COAD_1, chr 3

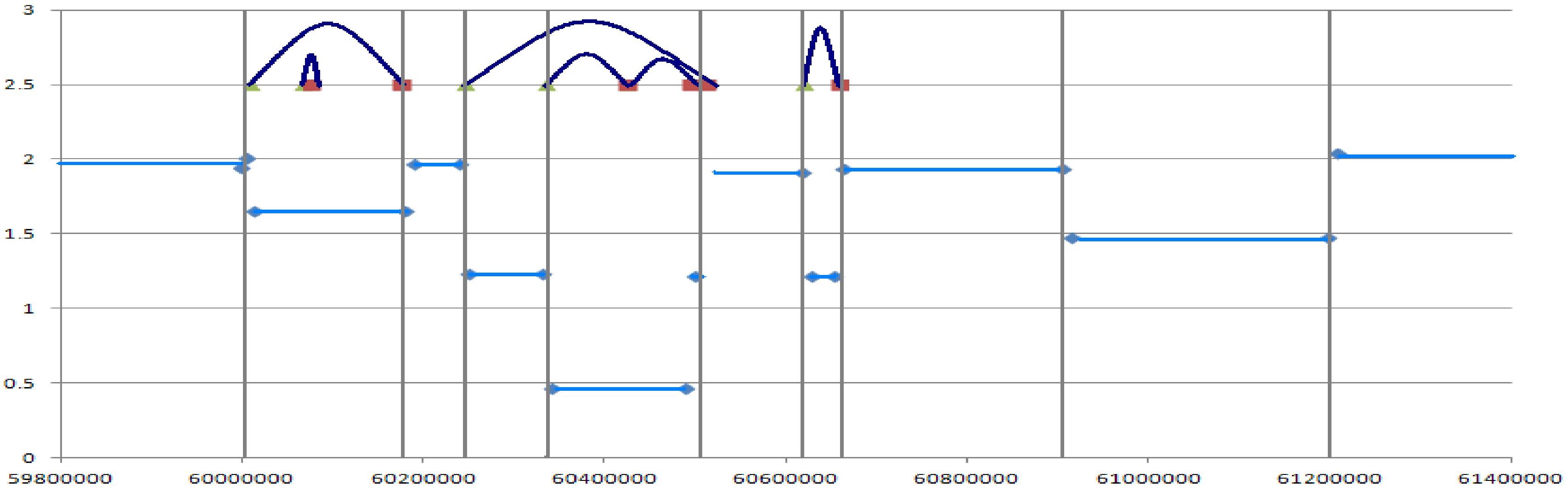
Breakpoints:

chrom	pos1	pos2	chrom2	pos3	pos4	support	strand1	strand2	variantClass
3	60009834	60009999	3	60174480	60174642	4	+	-	DEL
3	60067795	60067974	3	60076102	60076309	4	+	-	DEL
3	60246396	60246538	3	60510688	60510817	4	+	-	DEL
3	60335087	60335302	3	60423401	60423651	7	+	-	DEL
3	60424798	60424924	3	60494986	60495132	6	+	-	DEL
3	60619732	60619892	3	60658637	60658840	4	+	-	DEL

CNV:

Chromosome	Start	End	Left Segment Copy Number	Right Segment Copy Number
3	4406420	4416420	1.95265	2.49525
3	60004169	60014169	2.01003	1.65659
3	60180509	60190509	1.65659	1.96985
3	60240613	60250613	1.96985	1.23601
3	60330752	60340752	1.23601	0.467678
3	60489487	60499487	0.467678	1.21906
3	60618204	60628204	1.91301	1.225
3	60653678	60663678	1.225	1.94135
3	60904531	60914531	1.94135	1.47669
3	61198109	61208109	1.47669	2.04196
3	100439625	100449625	2.98631	2.01899

COAD_1, Chr 3



3
2.5
2
1.5
1
0.5
0
59800000
60000000
60200000
60400000
60600000
60800000
61000000
61200000
61400000

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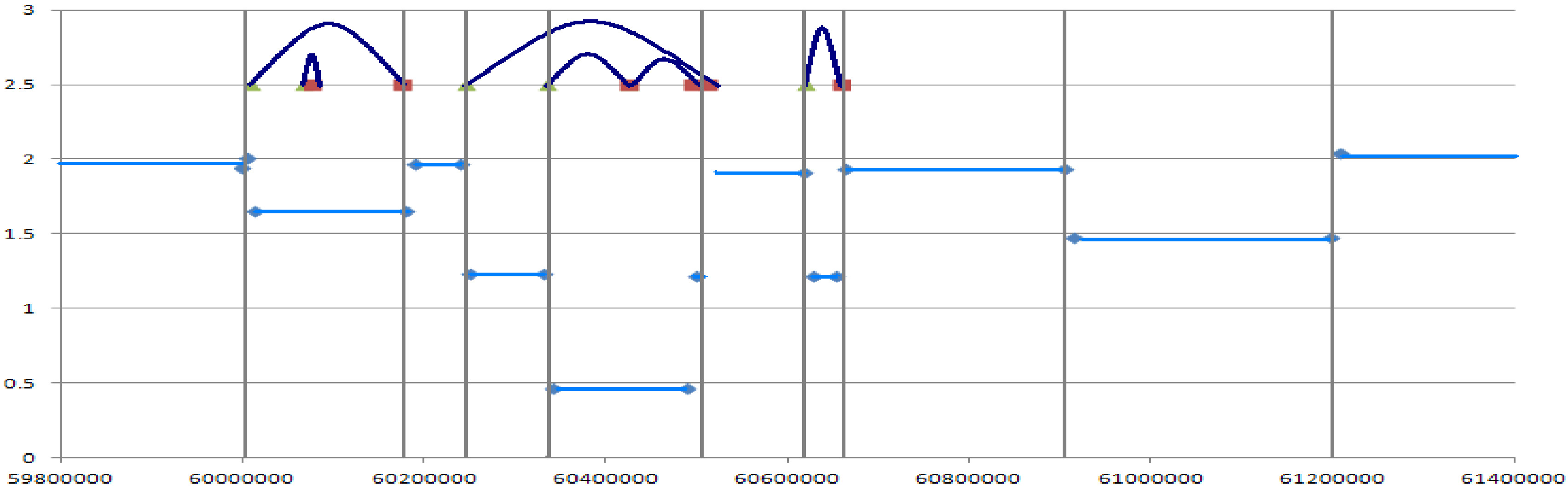
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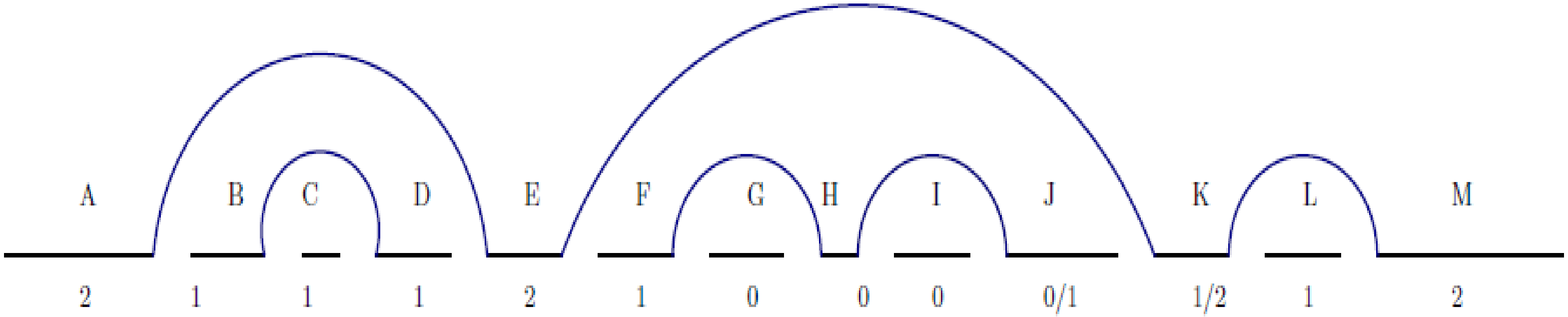
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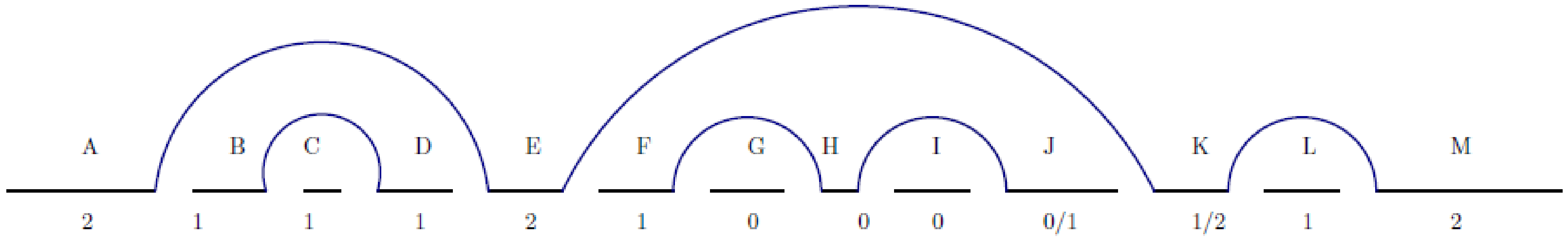
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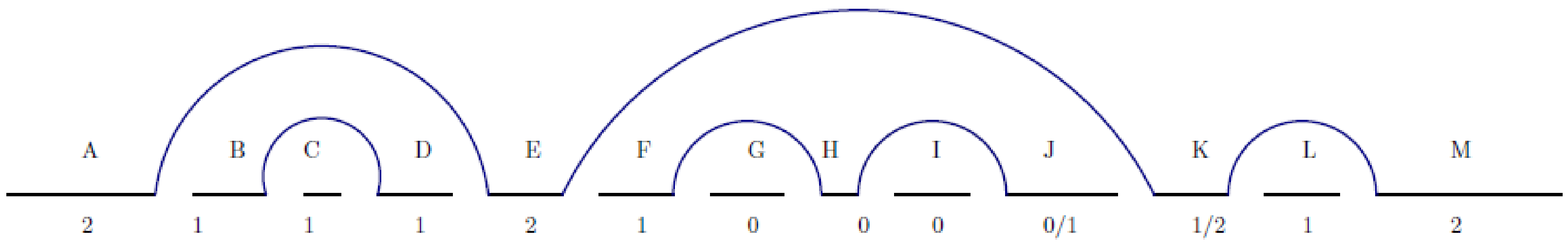
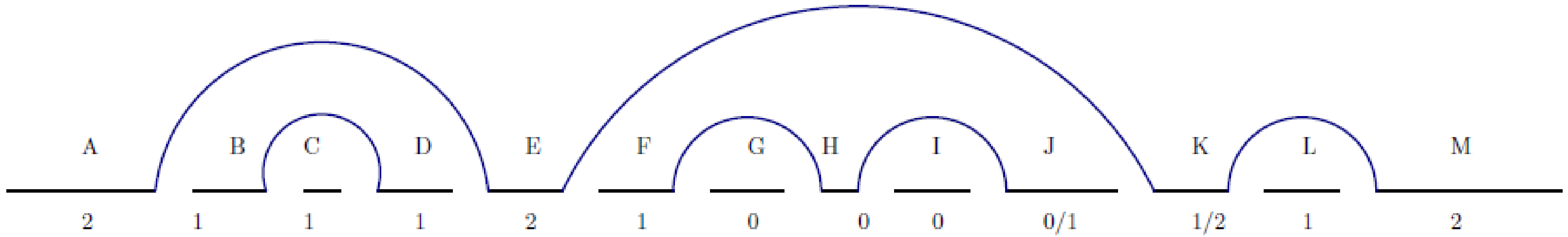


- This can be represented by the following directed graph:



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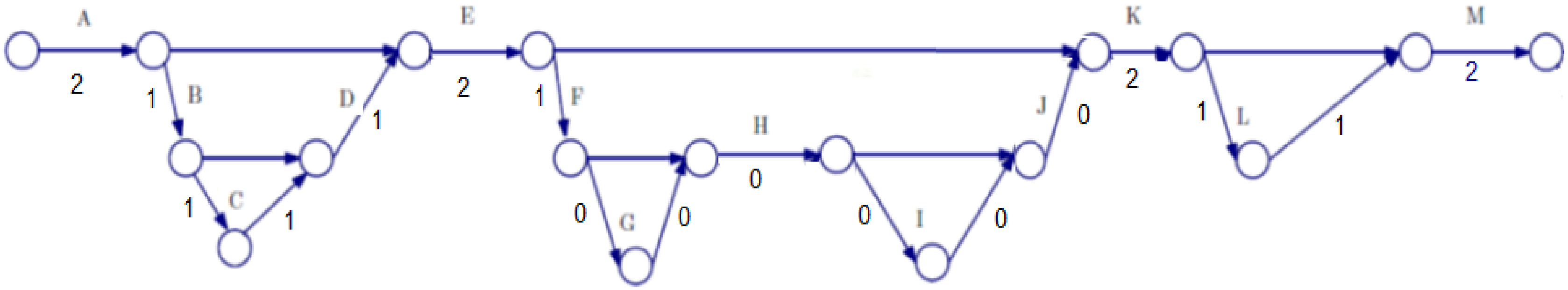

Formally

Let G=(V,E) be a directed graph constructed from the data as follows:

- Each adjoining of two reference segments on the breakpoint graph is represented by a node in V.
- $E = E_I \cup E_v$ is the union of both interval (segments) and variant (breakpoint) edges on the breakpoint graph.

Let $f: E \rightarrow R$ be a copy number function derived from the data.

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- Linearize the target function using discretization and a truth table.

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2. Minimize:
   $$\sum_e \left| f(e) - \sum_p C_p(e) \right|^2 \cdot w(e)$$

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- Copy number for reference edges as well (nodes in the graph)