Computational Genetics
Winter 2013
Lecture 10

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University of California, Los Angeles

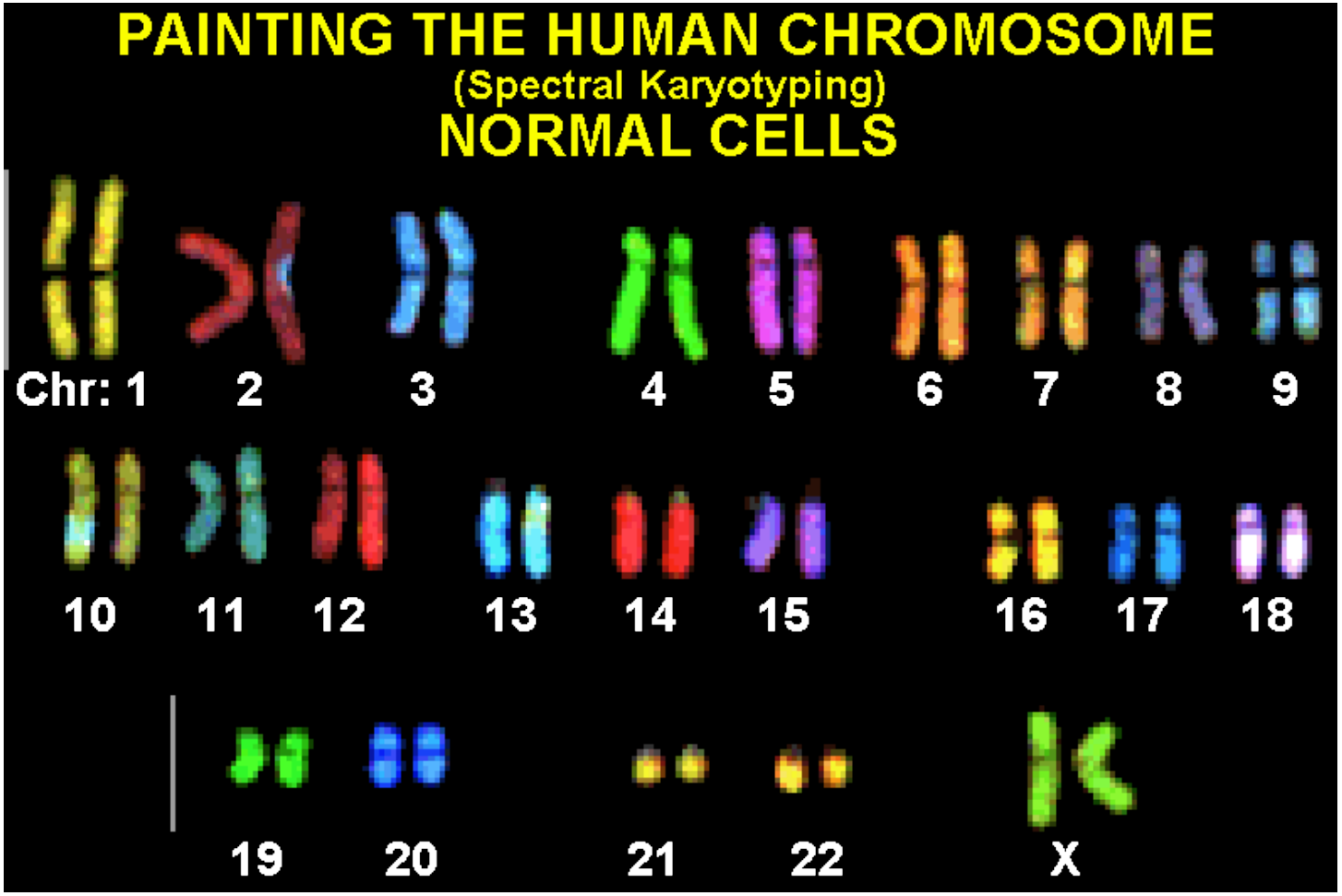
Pair End Sequencing

Lecture 10.

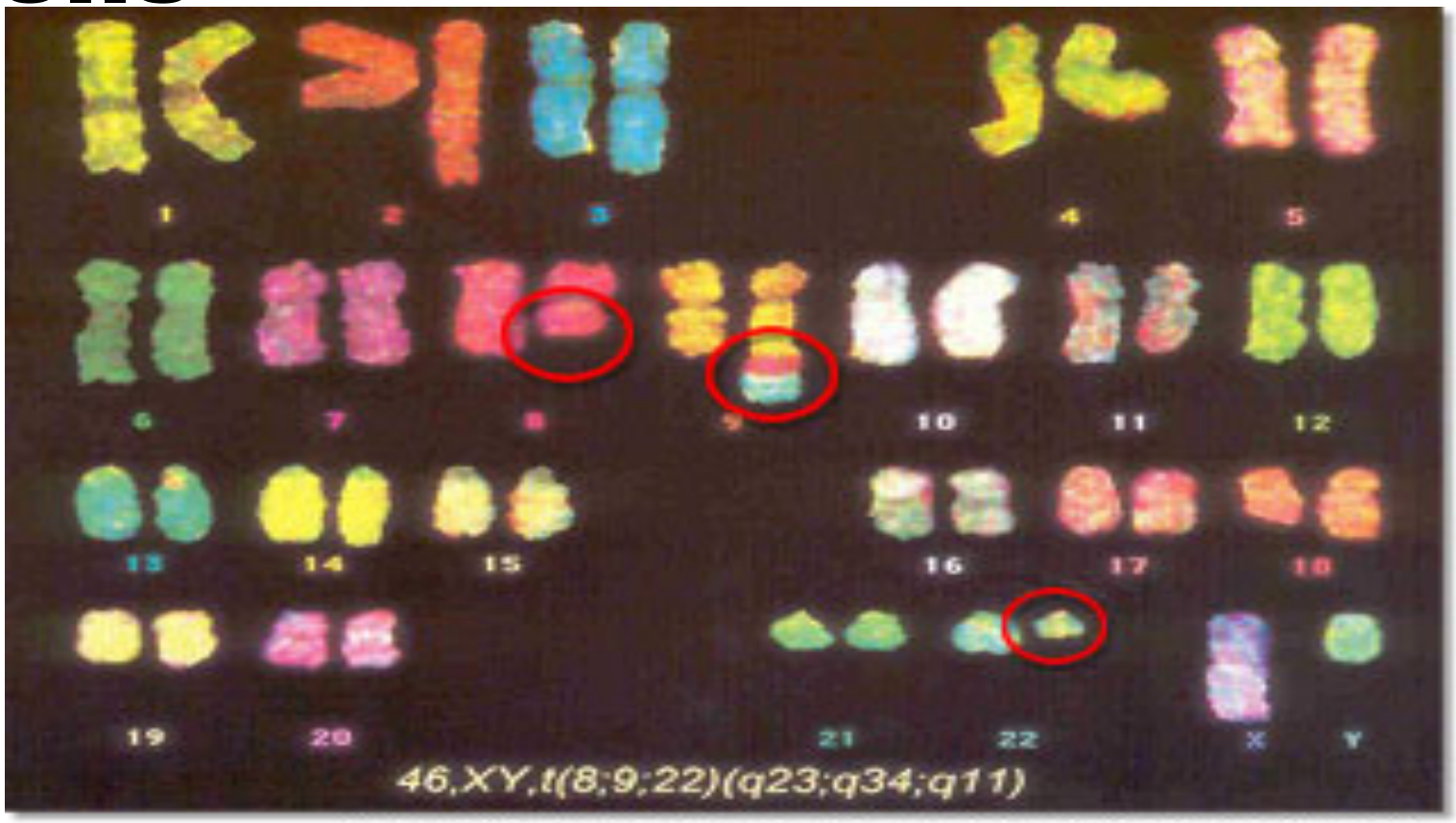
February 20th, 2013

(Slides from Ben Raphael)

Chromosome Painting: Normal Cells



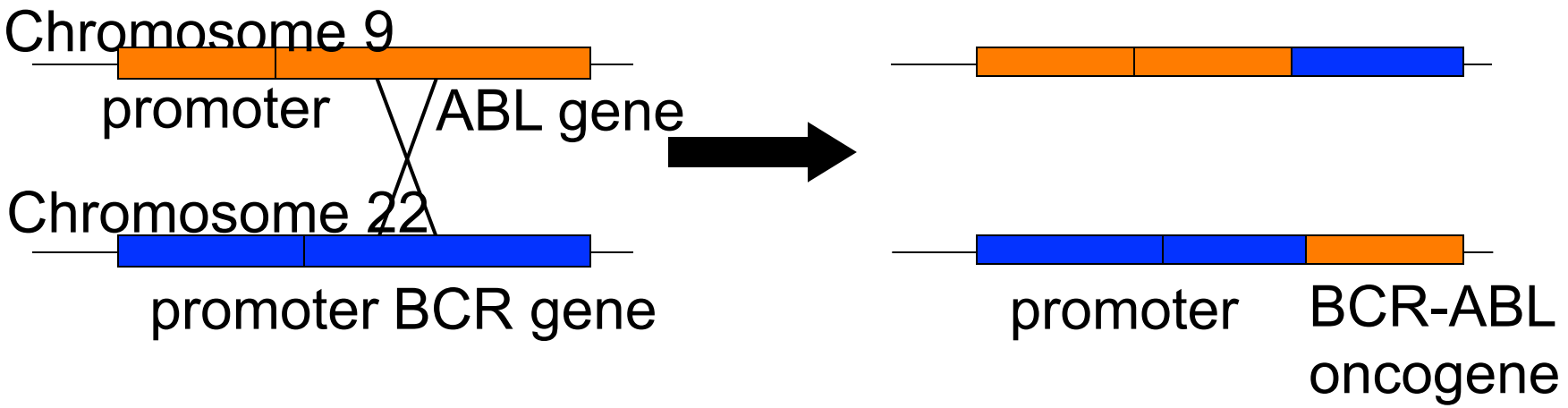
Chromosome Painting: Tumor Cells



Note: This karyotype was prepared using a FISH technique known as "chromosome painting". As well as having a translocation from chromosome 22, chromosome 9 also has translocated material from chromosome 8.

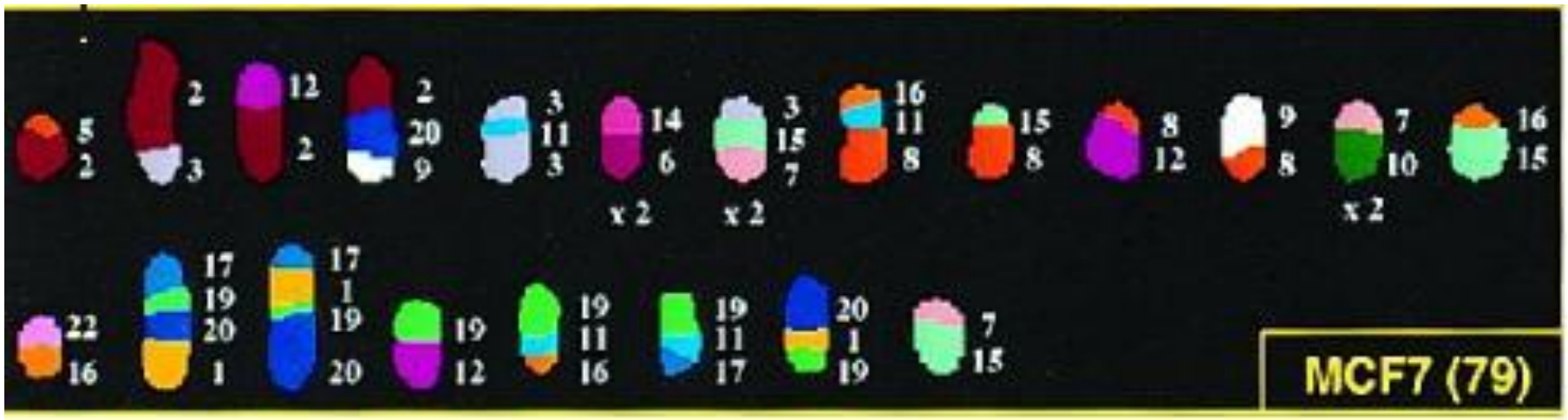
Rearrangements in Tumors

- Change gene structure and regulatory "wiring" of the genome.
- Create "bad" novel *fusion* genes and break "good" old genes.
- Example: translocation in leukemia.



- Gleevec™ (Novartis 2001) targets BCR-ABL oncogene.

Complex Tumor Genomes

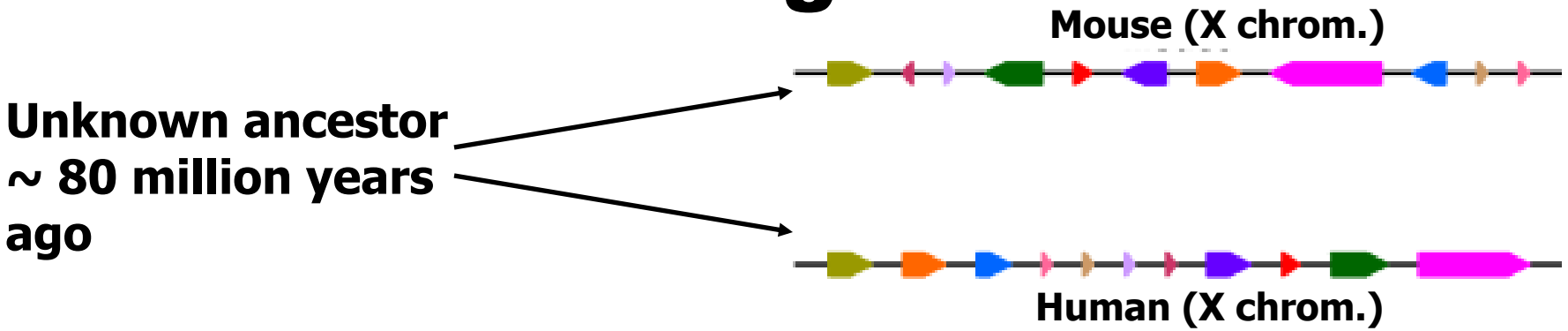


1) What are detailed architectures of tumor genomes?

2) What rearrangements/duplications produce these architectures and what is the order of these events?

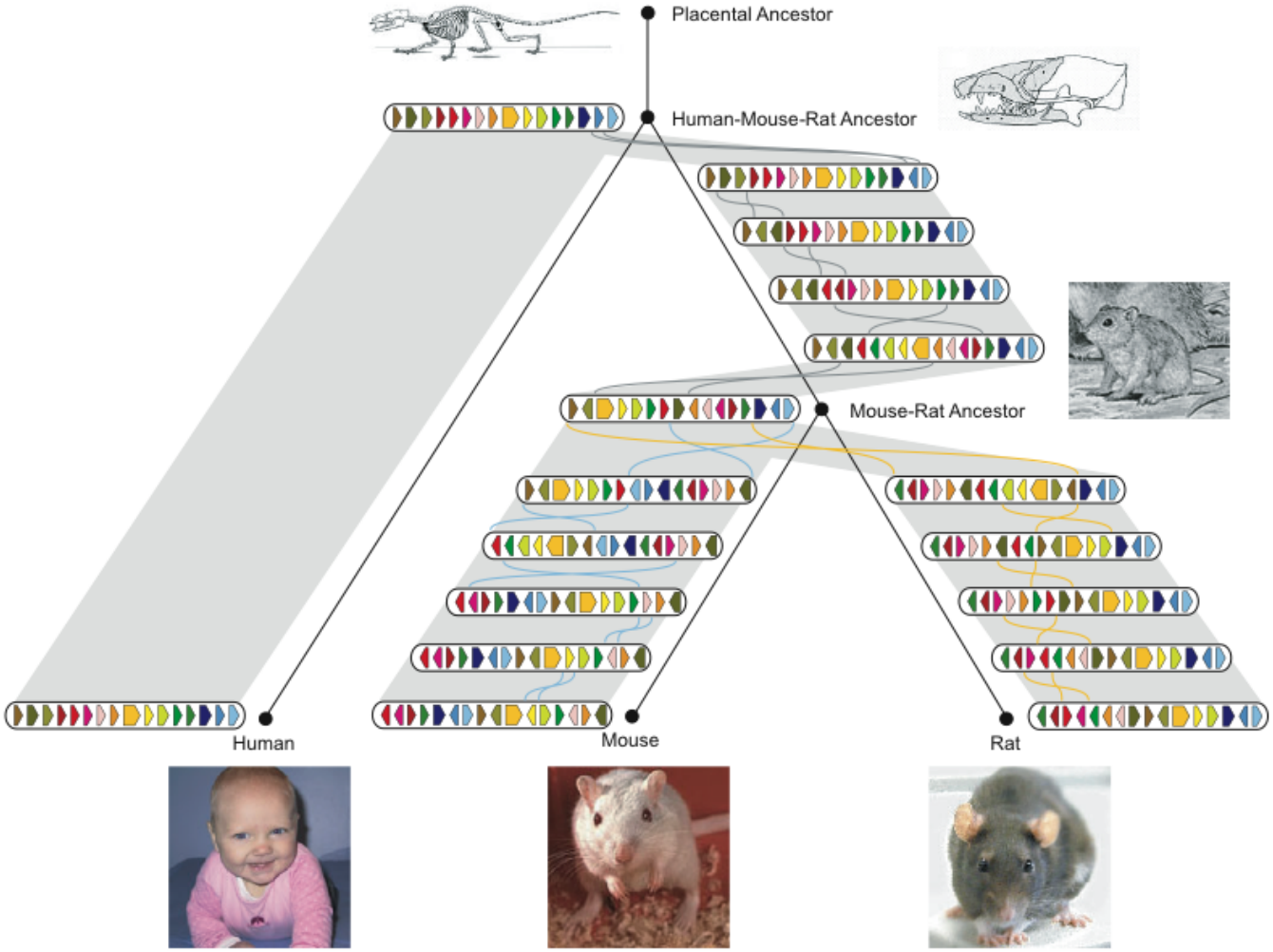
3) What are the novel fusion genes and old “broken” genes?

Genome rearrangements

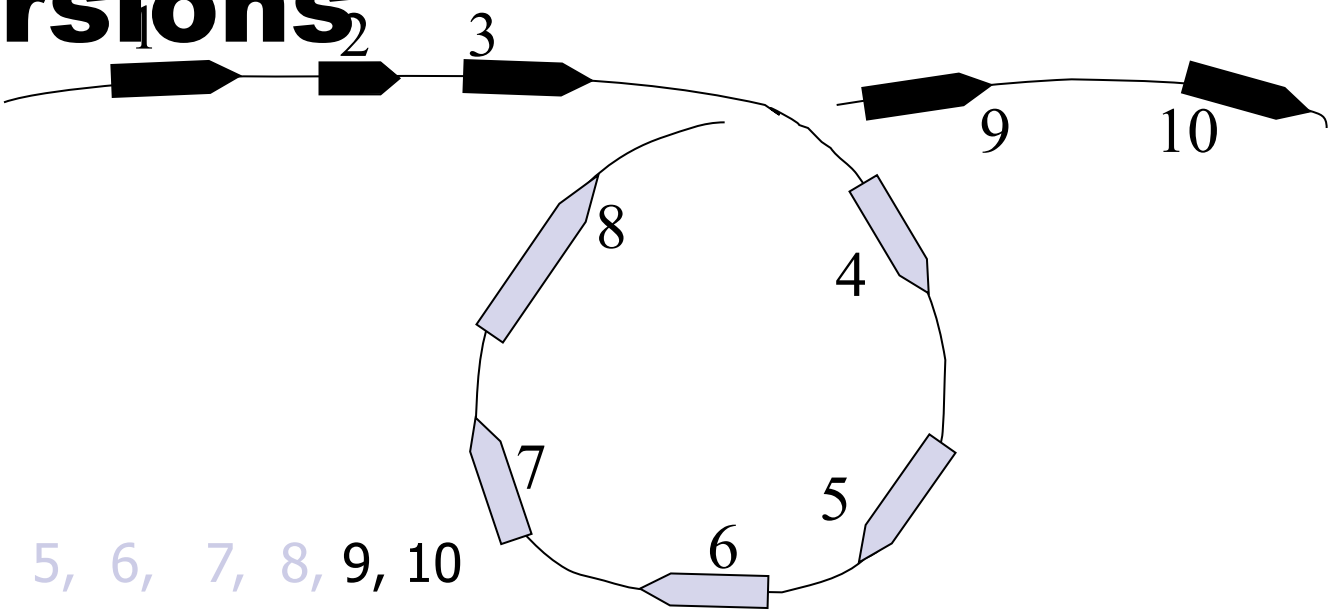


- What are the the “architectural blocks” forming the existing genomes and how to find them?
- What is the architecture of the ancestral genome?
- What is the evolutionary scenario for transforming one genome into the other?

History of Chromosome X



Inversions

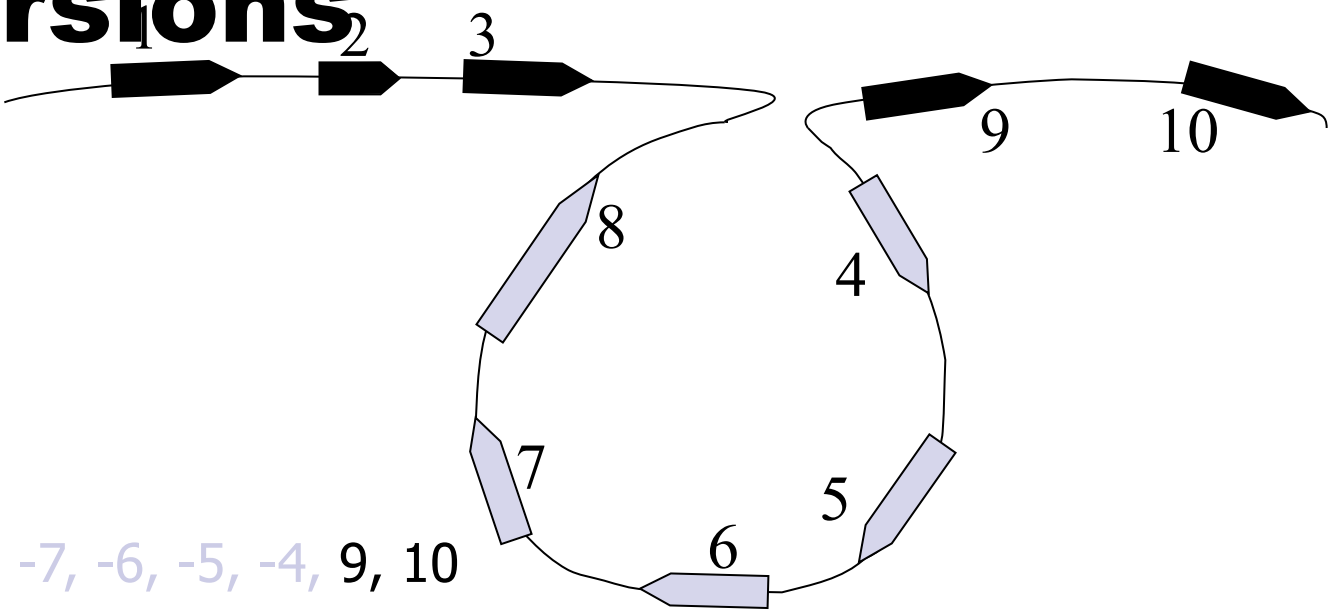


1, 2, 3, 4, 5, 6, 7, 8, 9, 10

- Blocks represent conserved genes.
- In the course of evolution or in a clinical context, blocks 1,2,…,10 could be misread as:

1, 2, 3, -8, -7, -6, -5, -4, 9, 10.

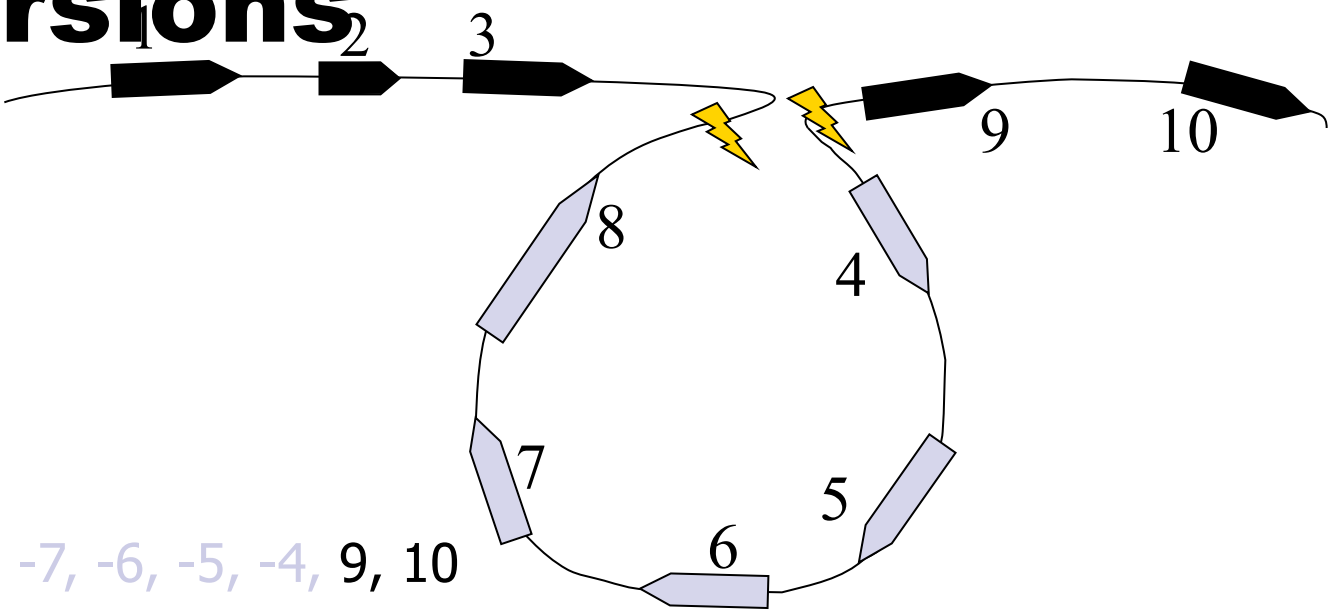
Inversions



1, 2, 3, -8, -7, -6, -5, -4, 9, 10

- Blocks represent conserved genes.
- In the course of evolution or in a clinical context, blocks 1,…,10 could be misread as 1, 2, 3, -8, -7, -6, -5, -4, 9, 10.
- **Evolution:** occurred one-two times every million years.
- **Cancer:** may occur every month.

Inversions

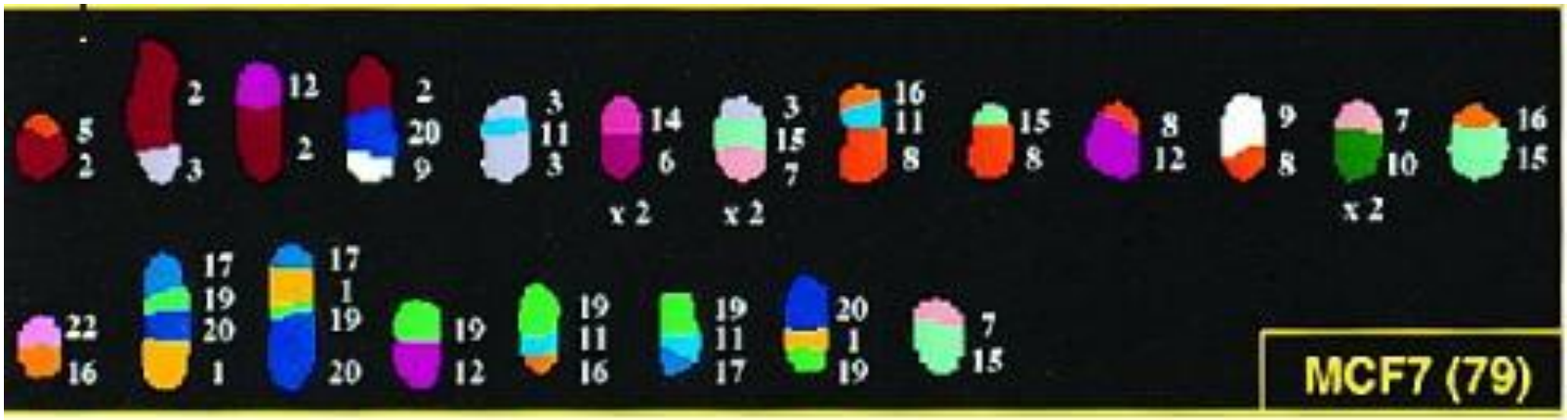


1, 2, 3, -8, -7, -6, -5, -4, 9, 10

The inversion introduced two *breakpoints* (disruptions in order).

Measuring Structural Changes in Tumors: Cytogenetics

- Directly visualize (fluorescently) labeled chromosomes.
  - Chromosome banding, mFISH, SKY

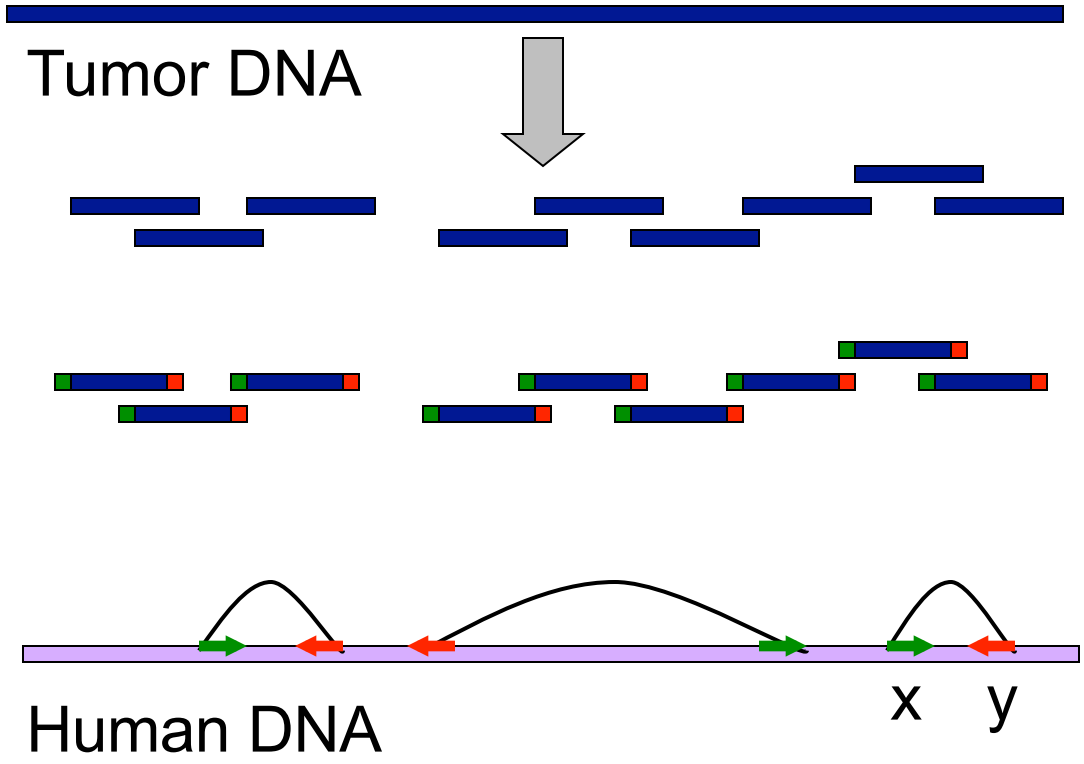


Weakness:

- Physical location of chromosomal junctions *not* revealed. Low resolution.
- No/little information about copy number changes.

Paired End Sequencing (PE)

C. Collins et al. (UCSF Cancer Center)



1) Pieces of tumor genome: clones (100-250kb).

2) Sequence ends of clones (500bp).

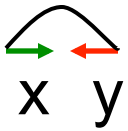
3) Map end sequences to human genome.

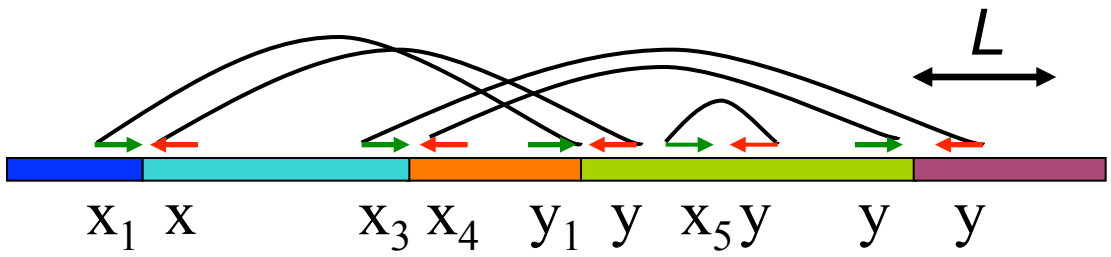
Each clone corresponds to pair of end sequences (***PE pair***) *(x,y).*

Typical Next Generation Sequencing read lengths are shorter.

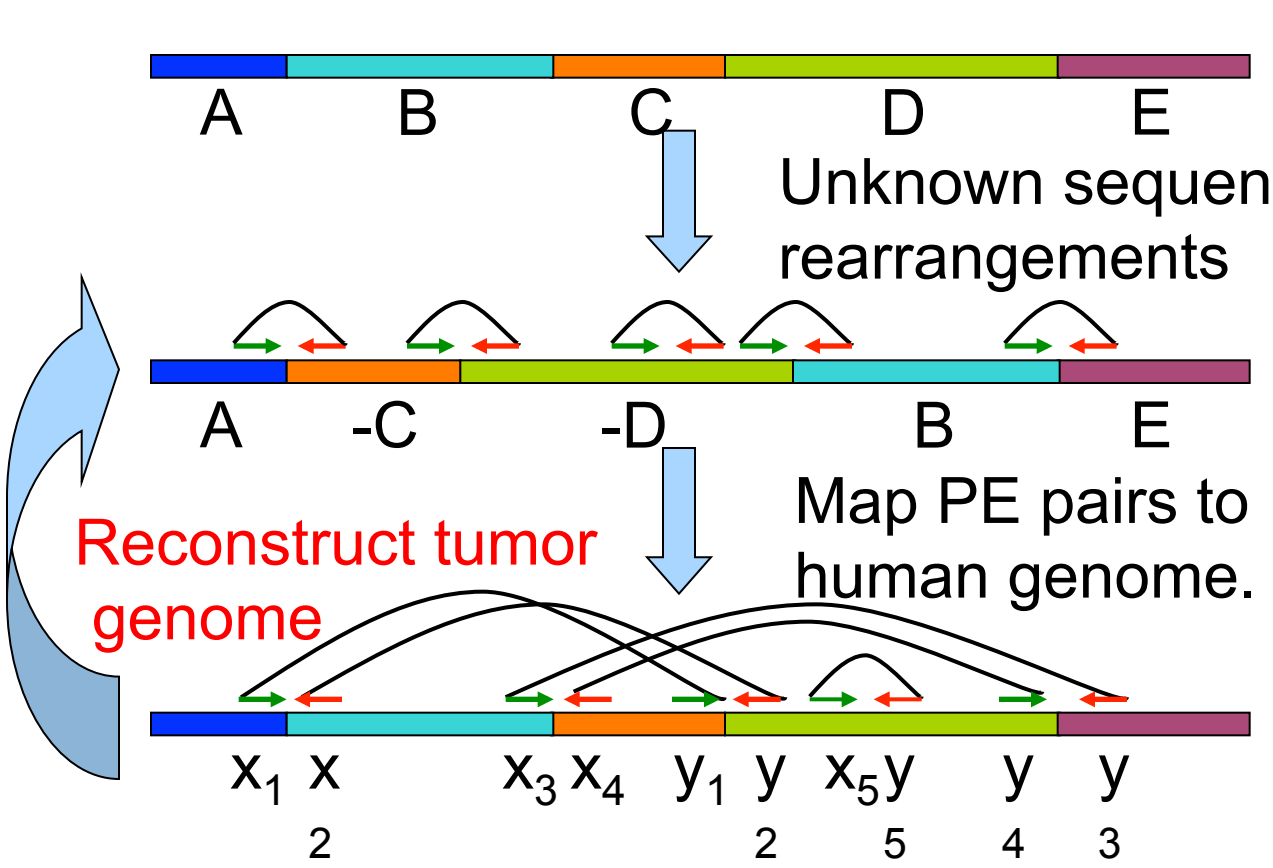
PE Pairs

- Order PE pair such that $x < y$.
- PE pair (x,y) is
  - ***valid*** if
    - x,y on same chromosome. and
    - $l \leq y - x \leq L$, min (max) size of clone.
    - x, y have opposite, convergent orientations
  - ***invalid,*** otherwise.
    - Results from rearrangement or experimental "noise".





Tumor Genome Reconstruction Puzzle

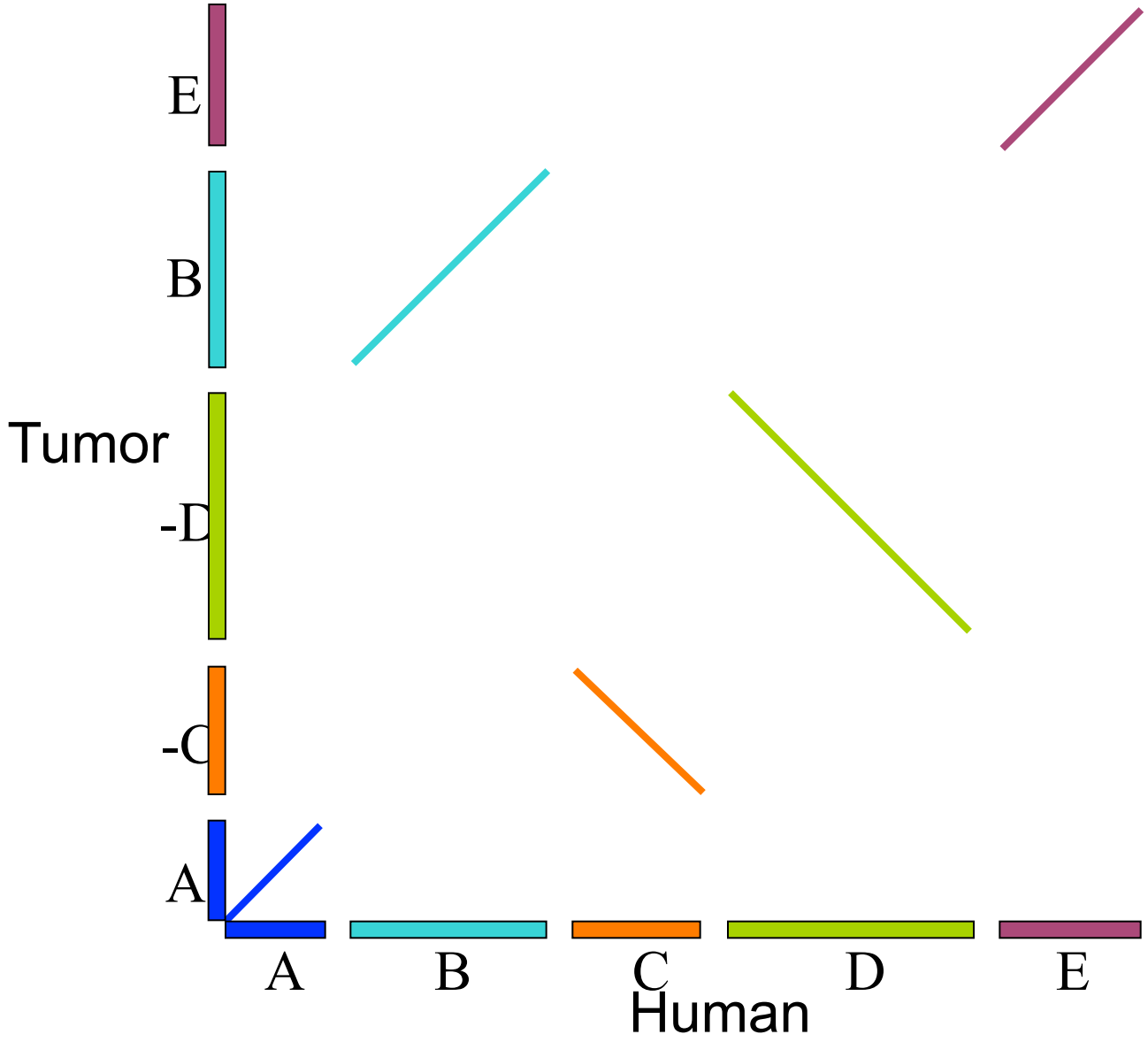


Human genome (known)

Tumor genome (unknown)

Location of PE pairs in human genome. (known)

Tumor Genome Reconstruction



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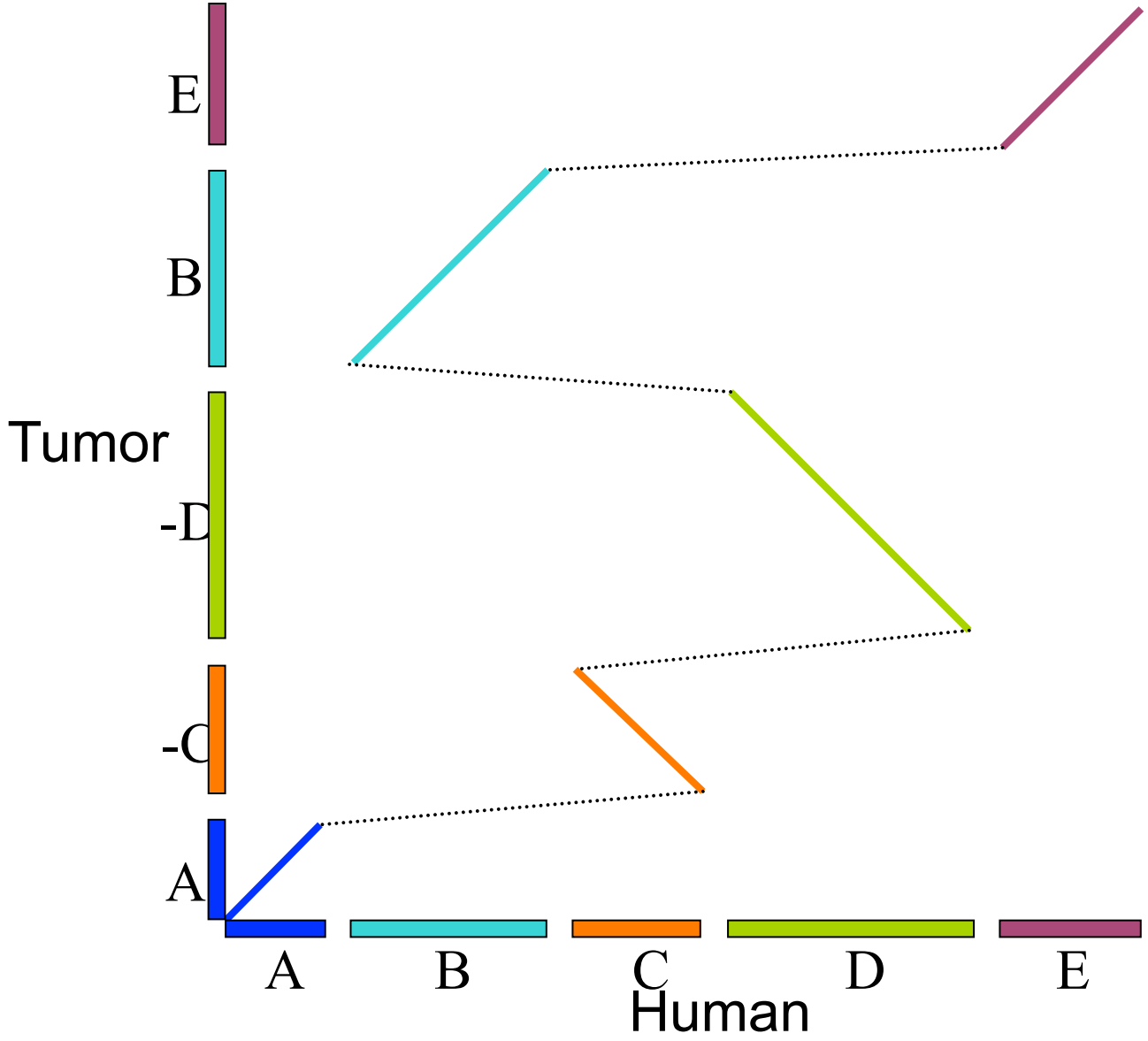

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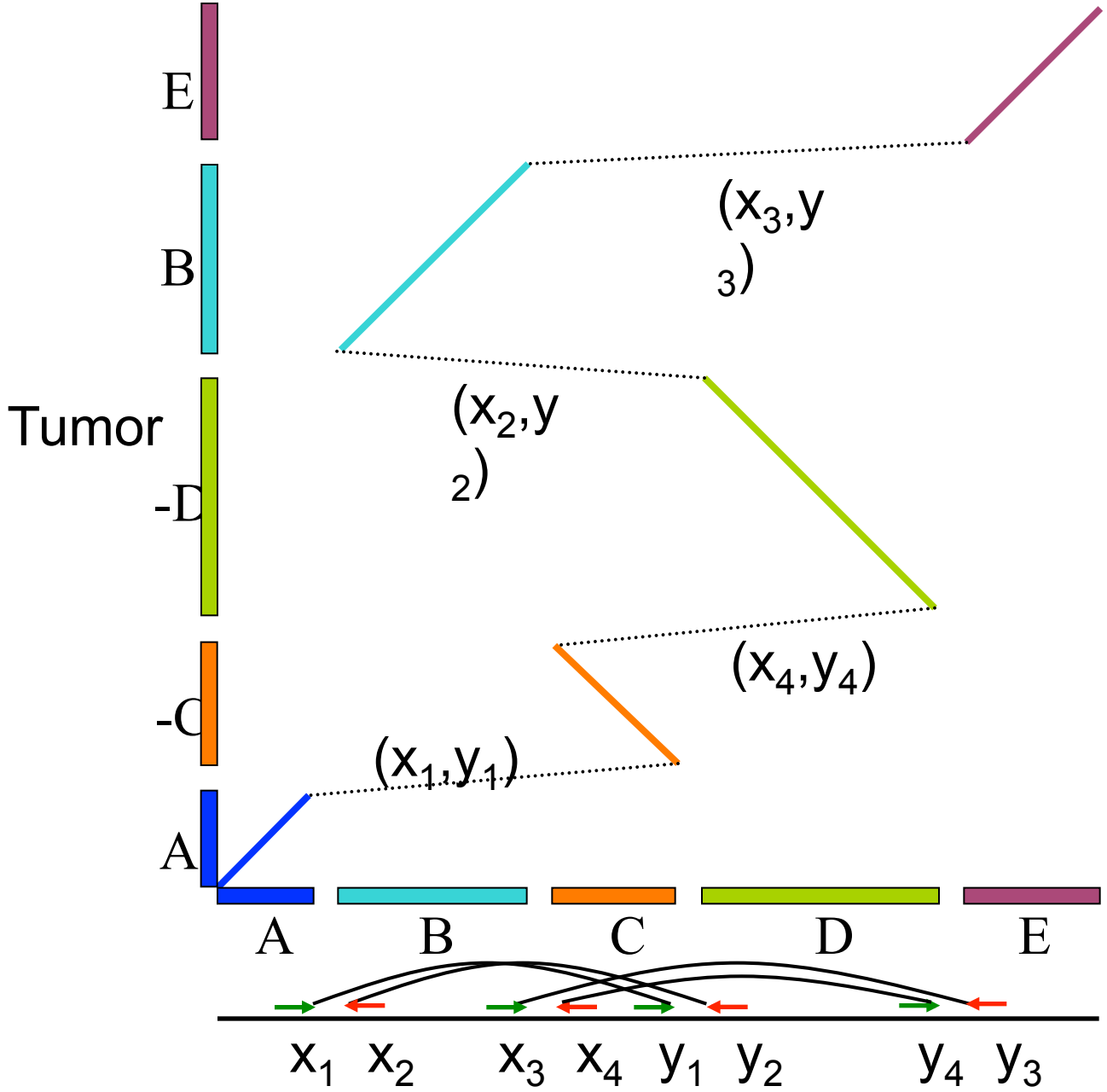
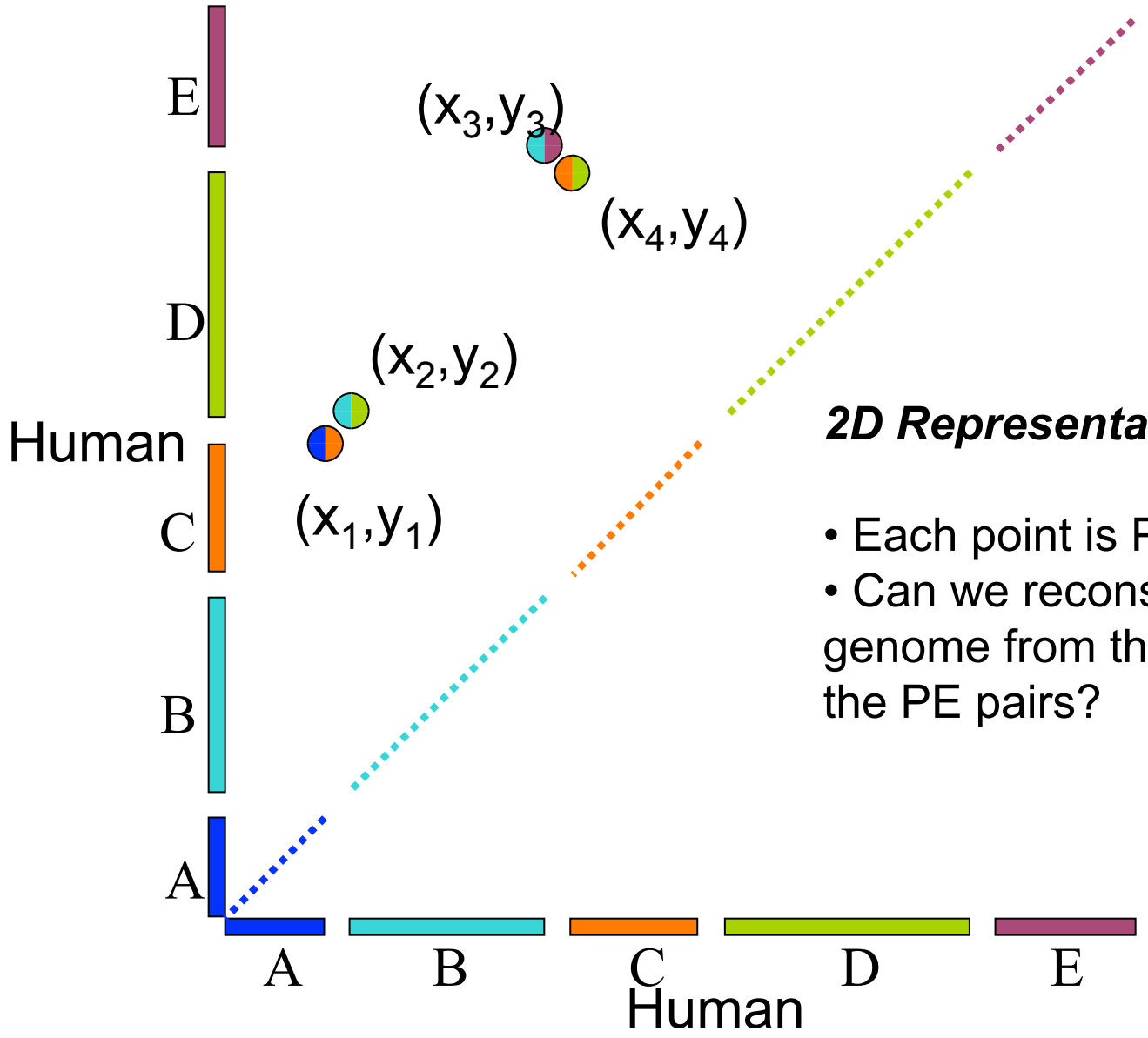
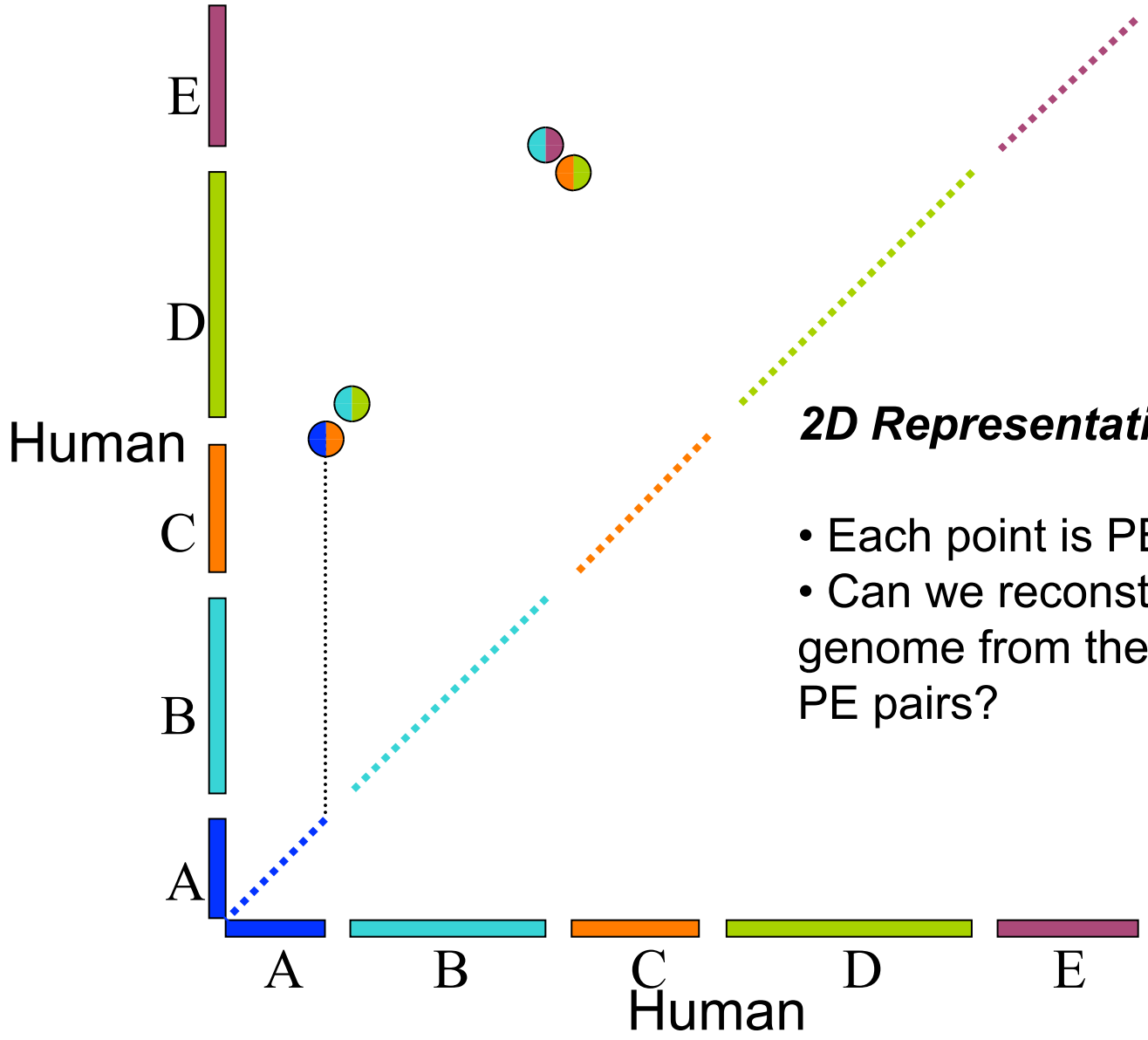


PE Plot



2D Representation of PE Data

- Each point is PE pair.
- Can we reconstruct the tumor genome from the positions of the PE pairs?



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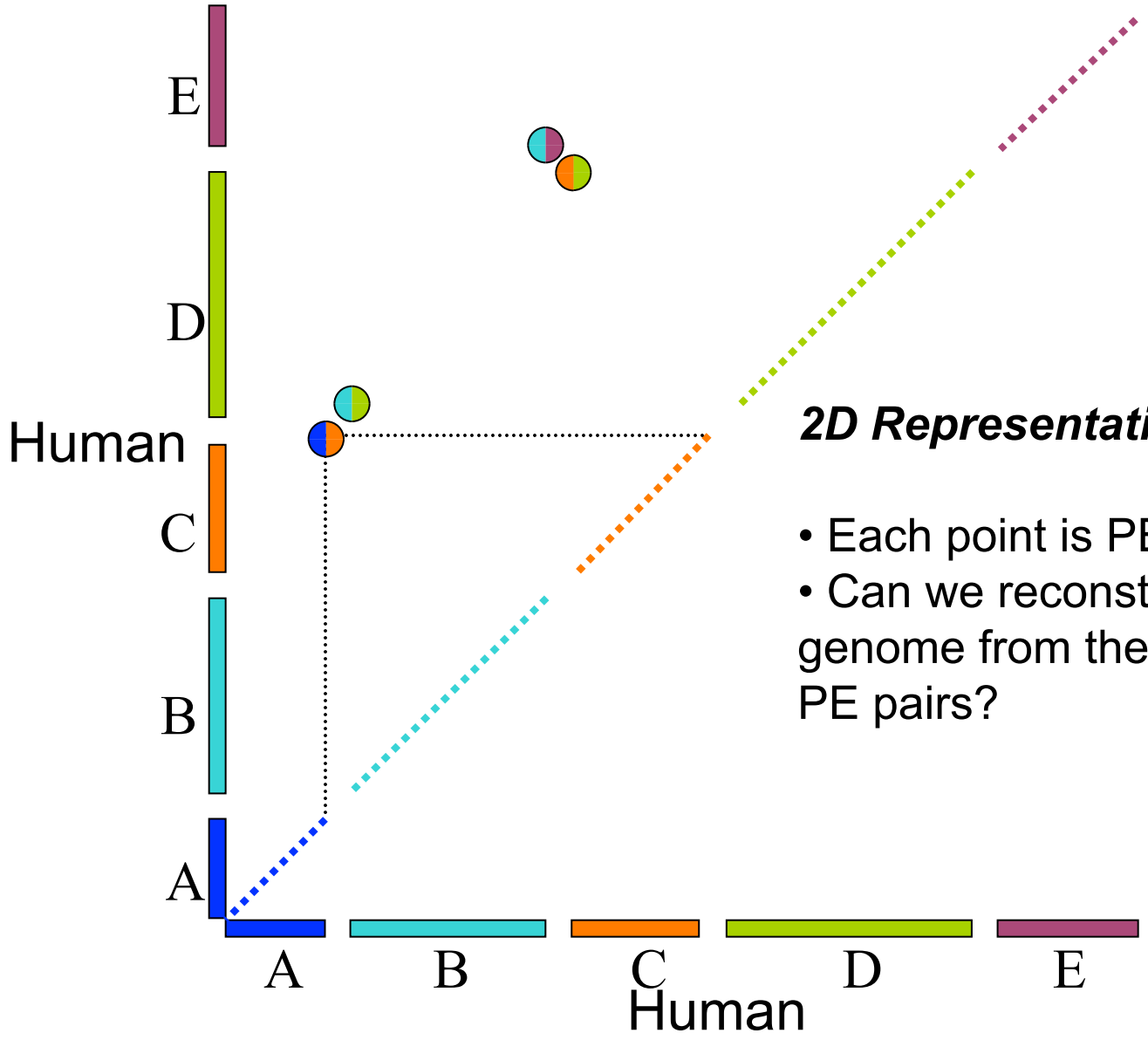

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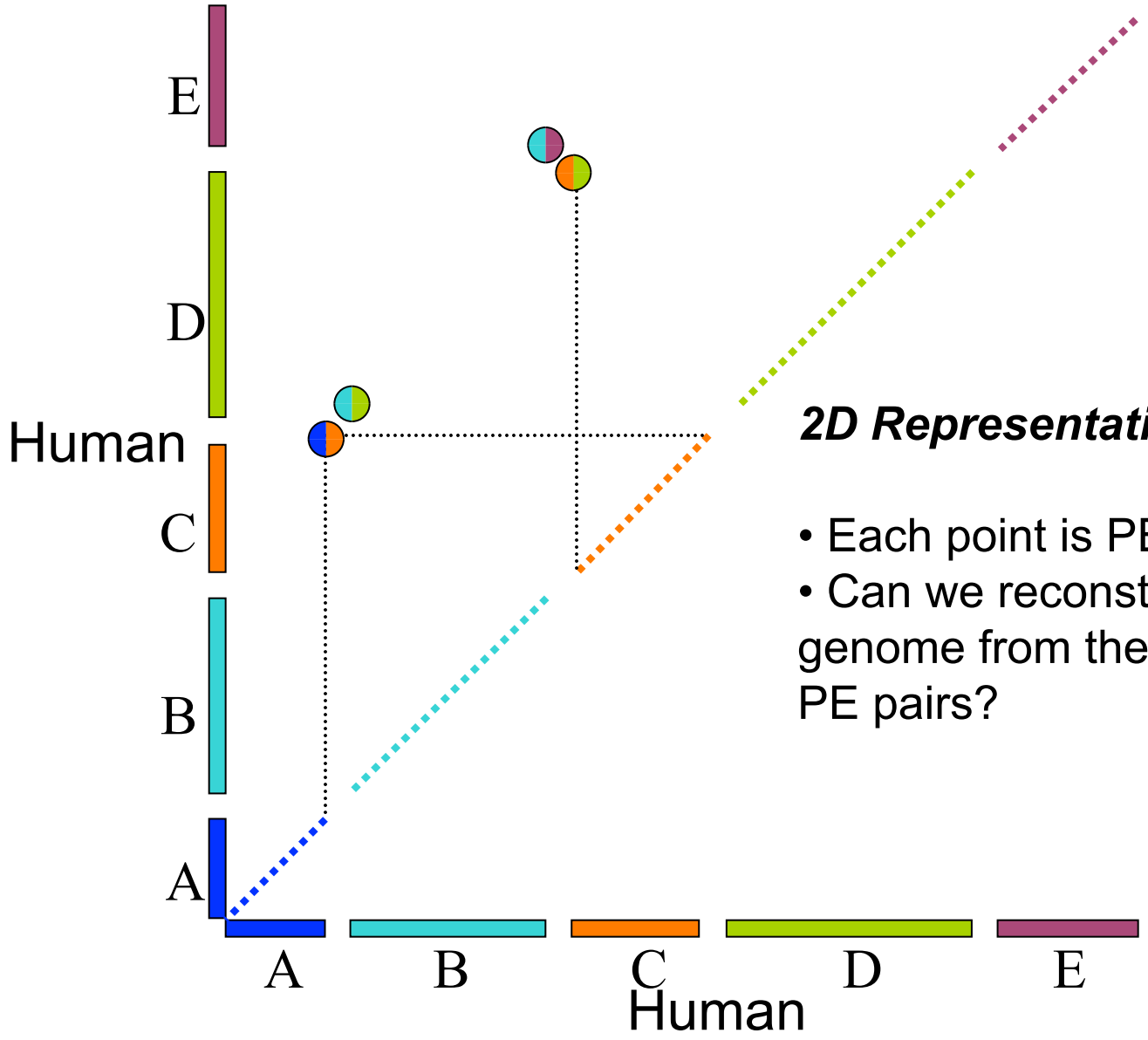

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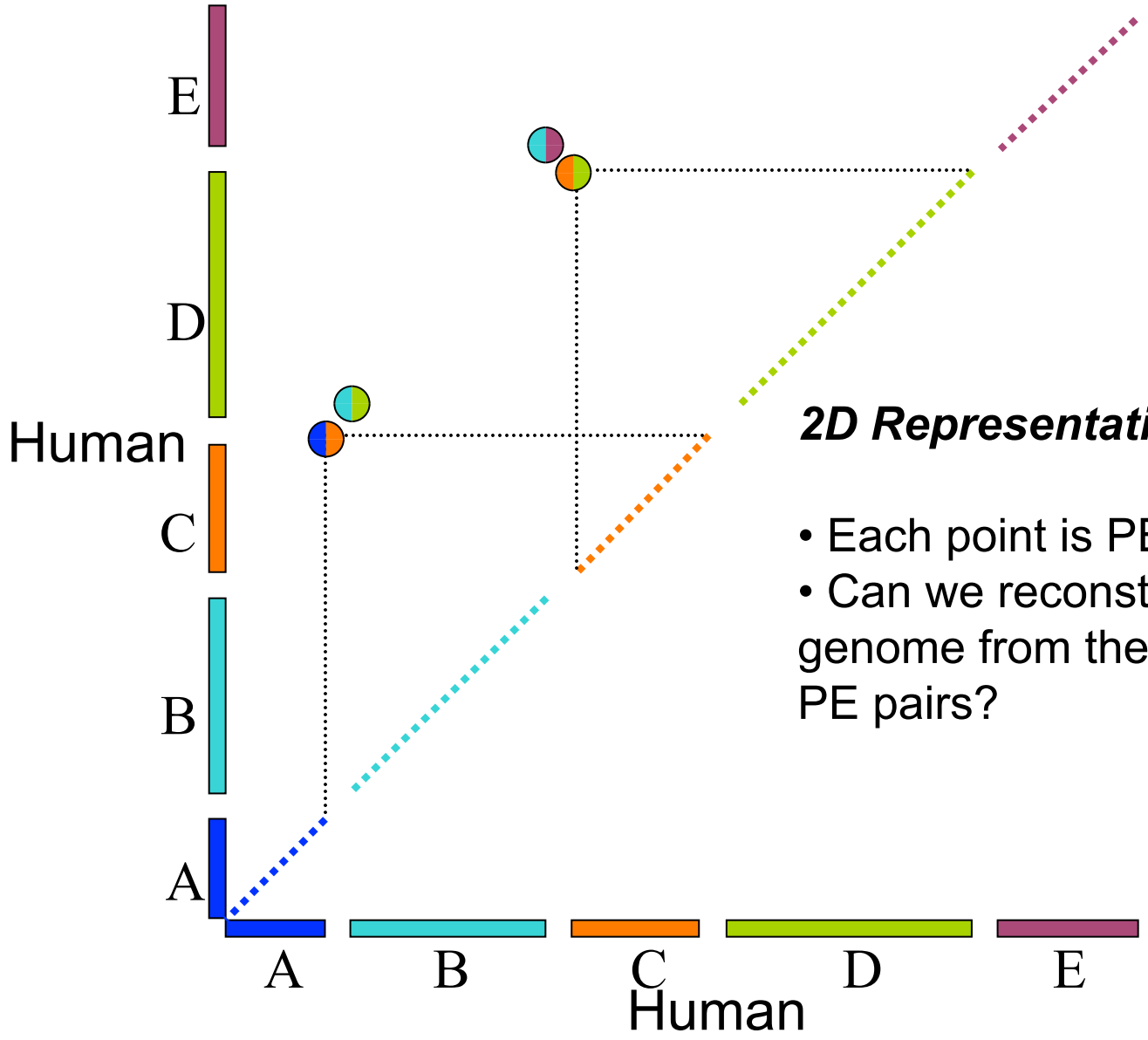

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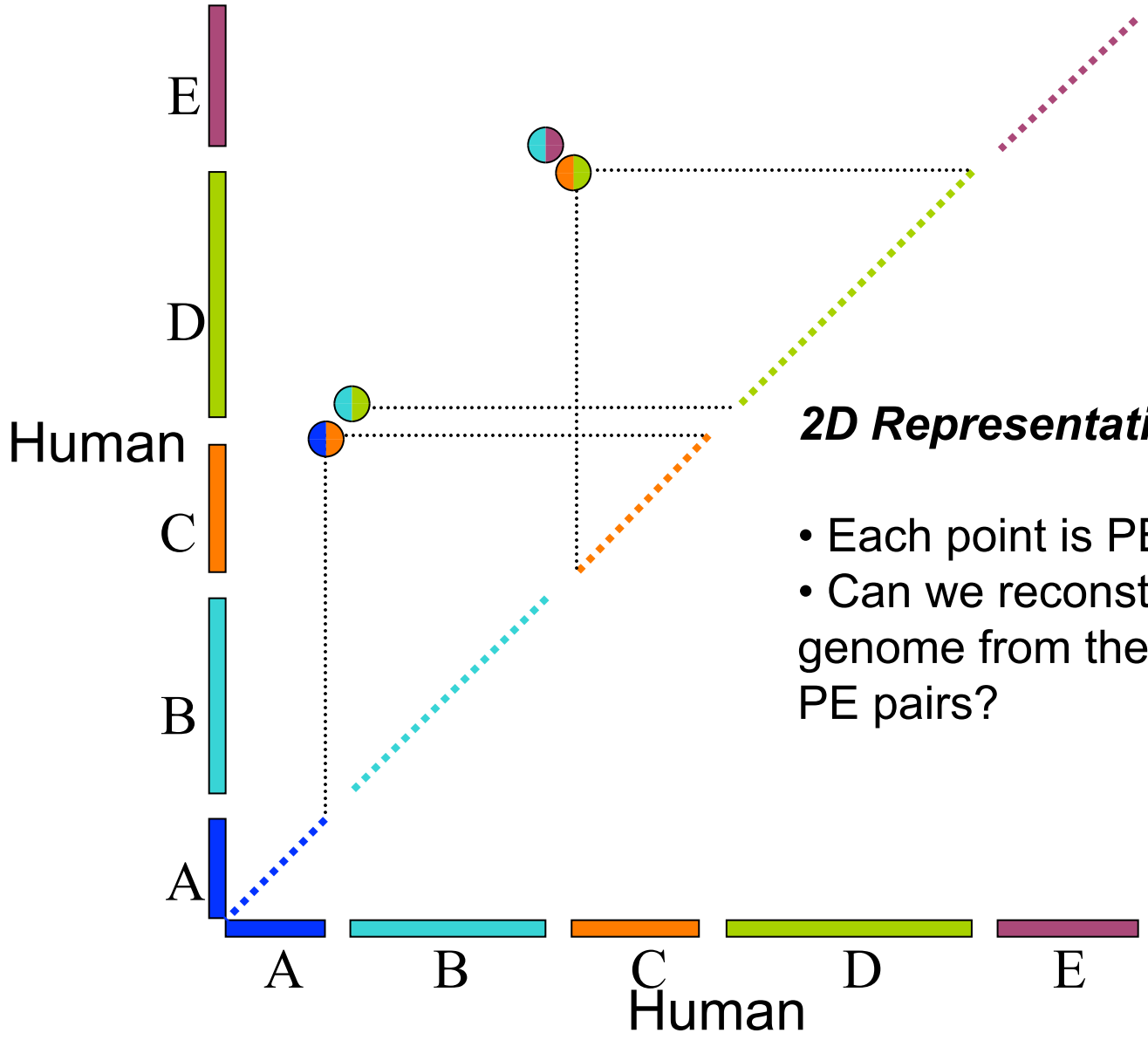

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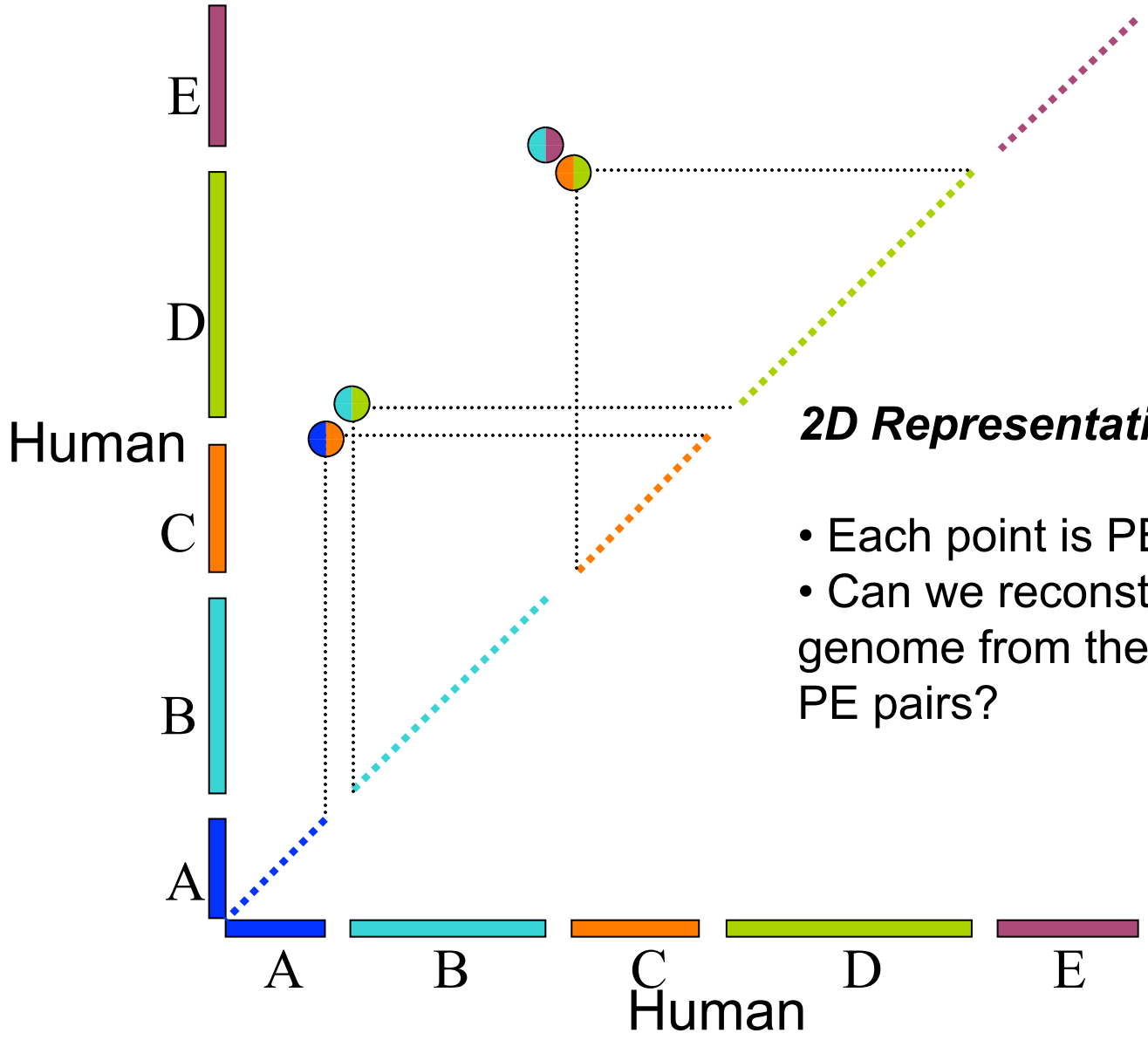

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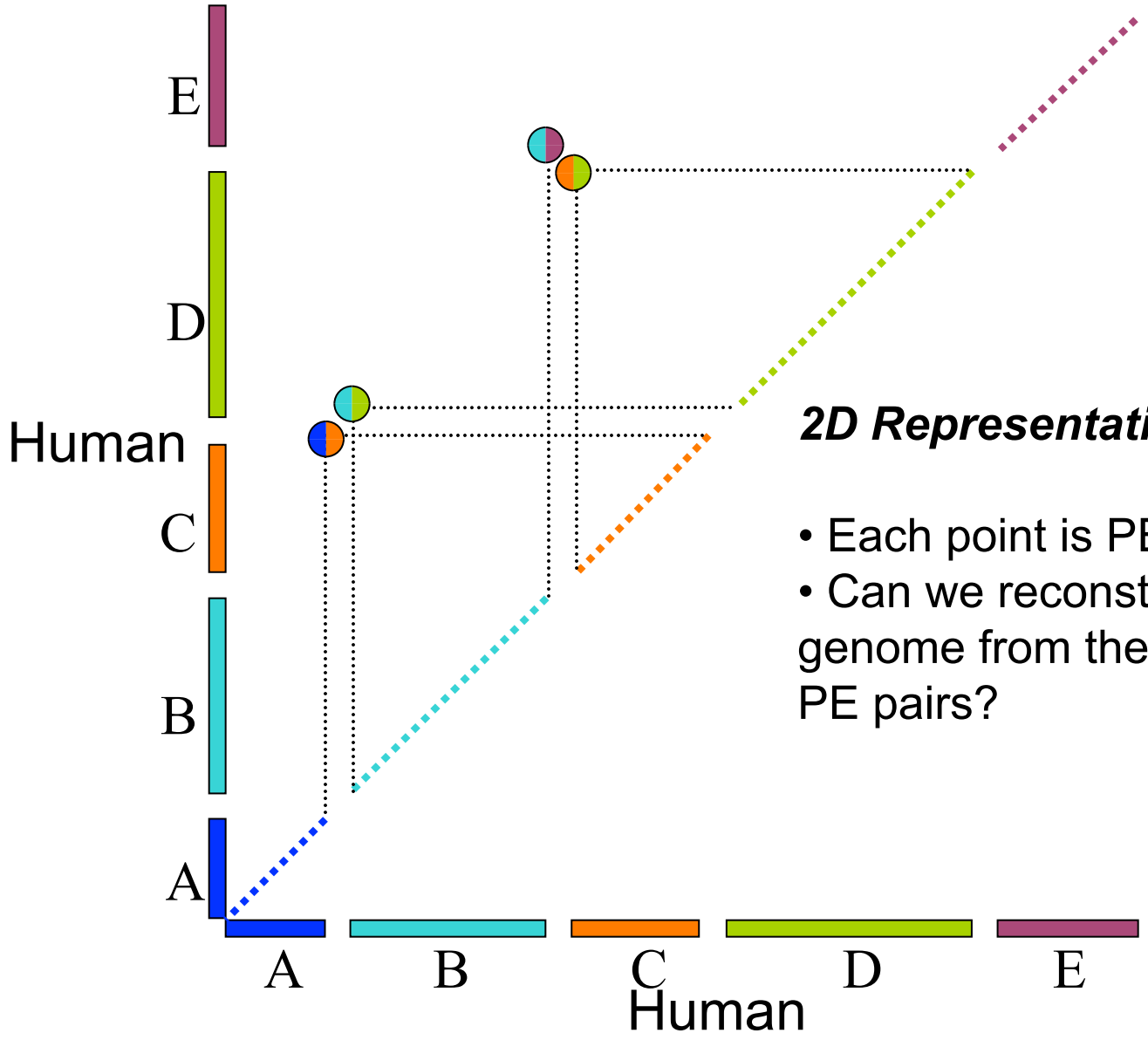

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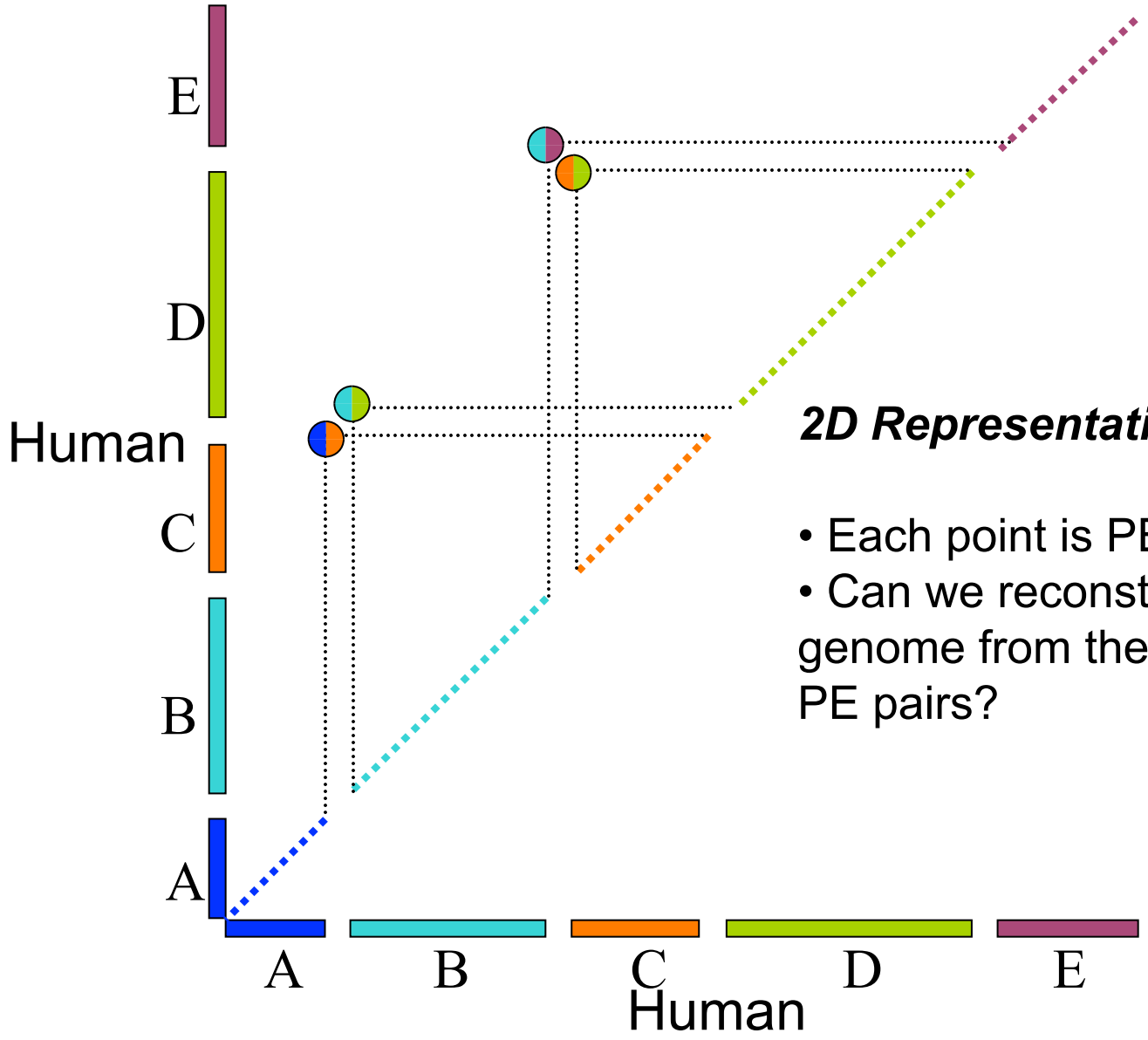

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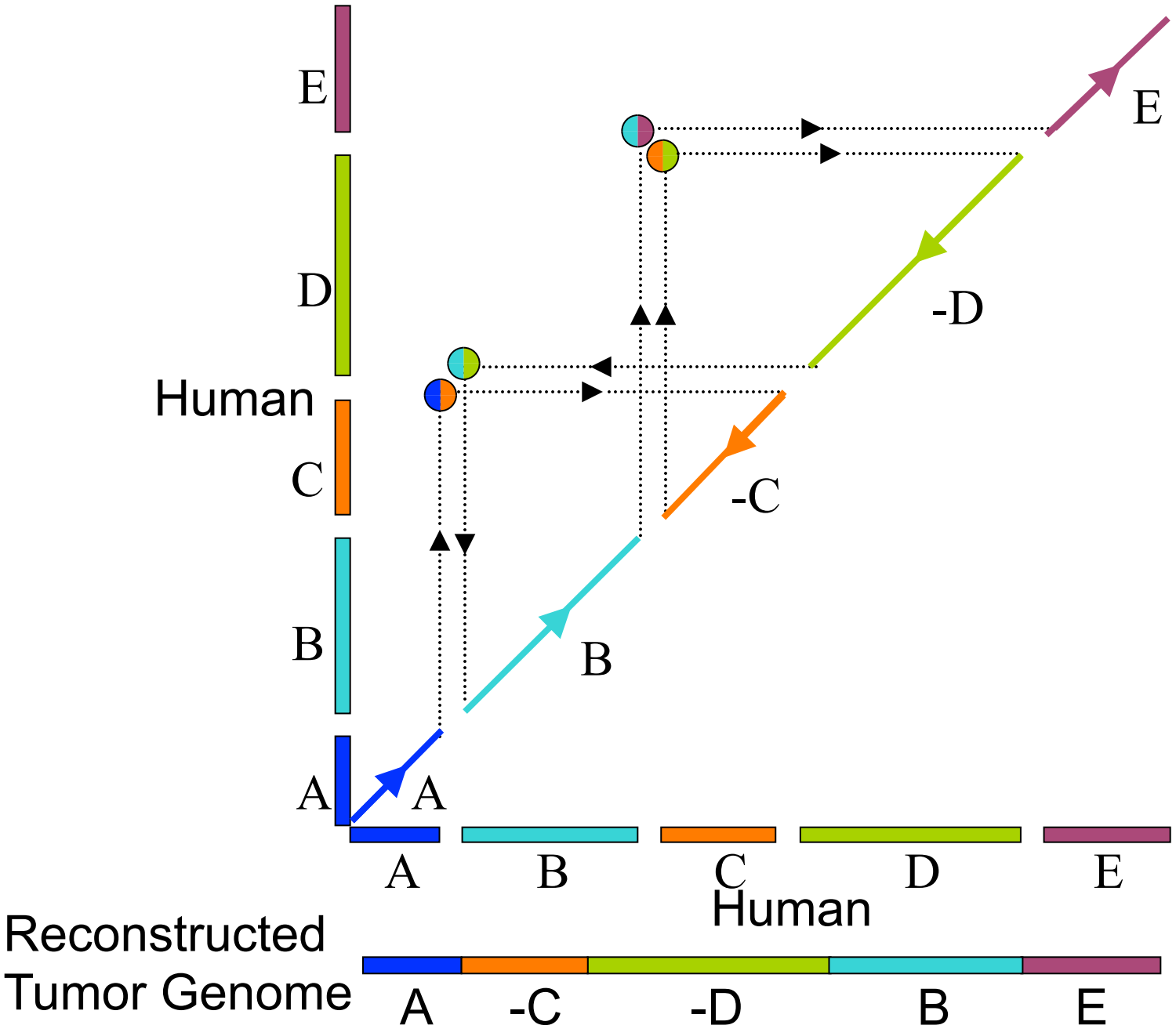
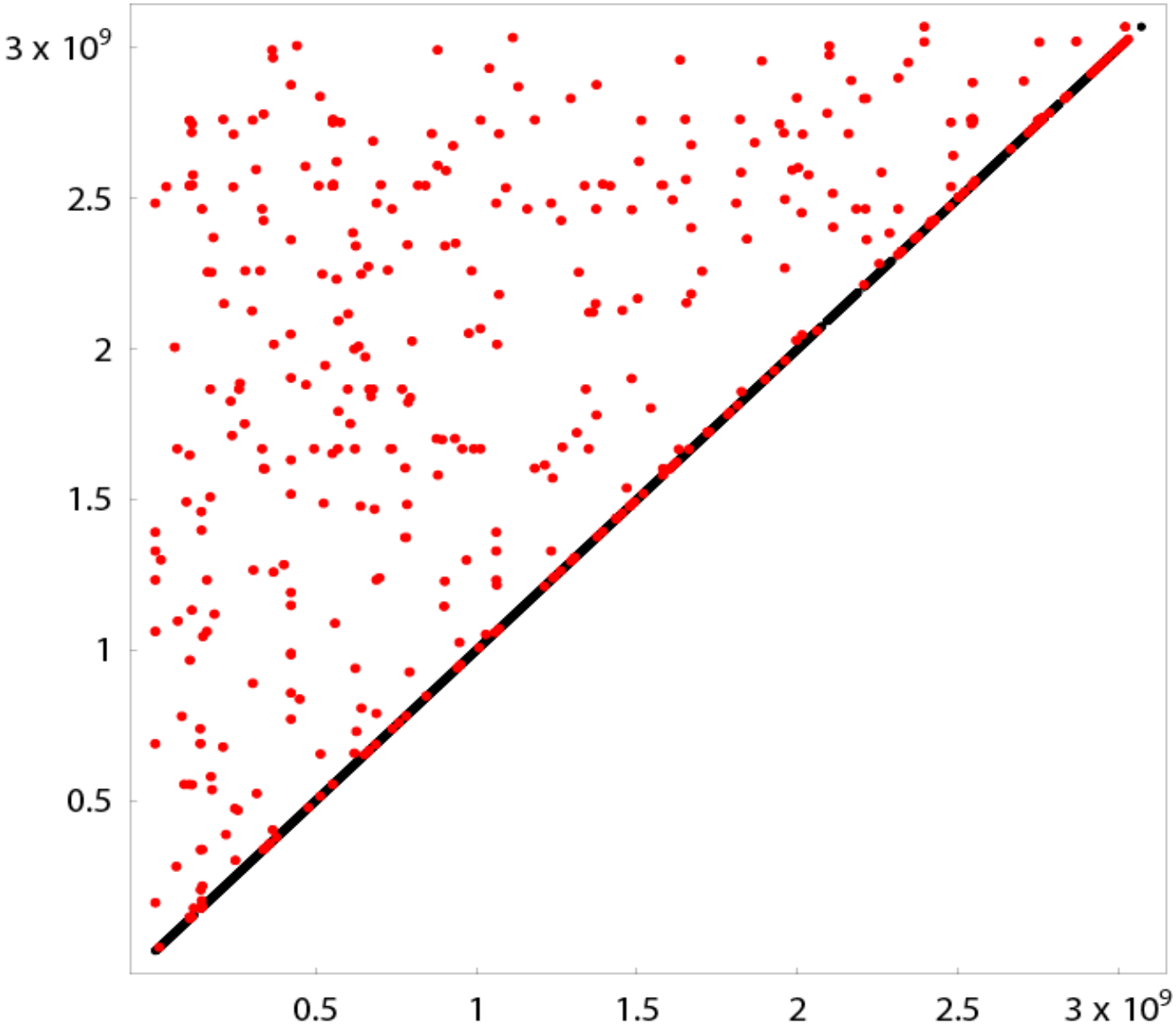

E
D
Human
C
B
A
A
B
C
D
E
-D
-C
B
E
A
B
C
D
E
Human
Reconstructed
Tumor Genome
A
-C
-D
B
E

Real data noisy and incomplete!

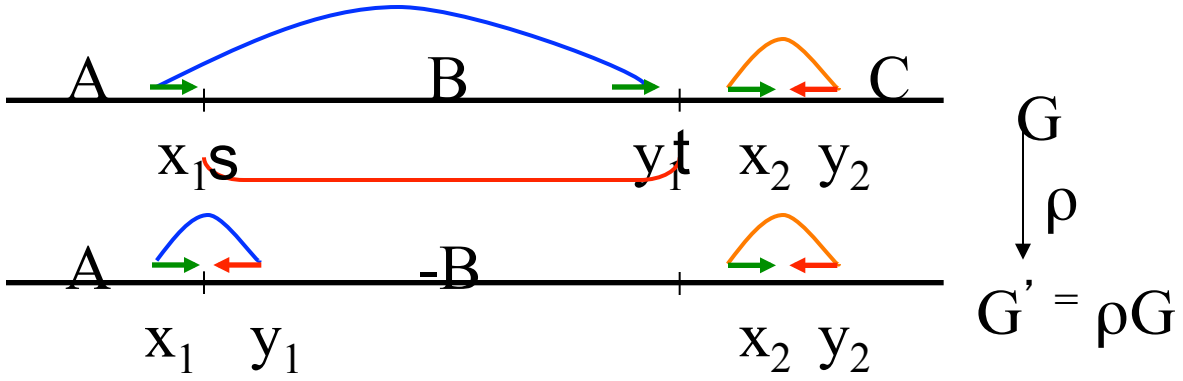


Reconstruction of Tumor History

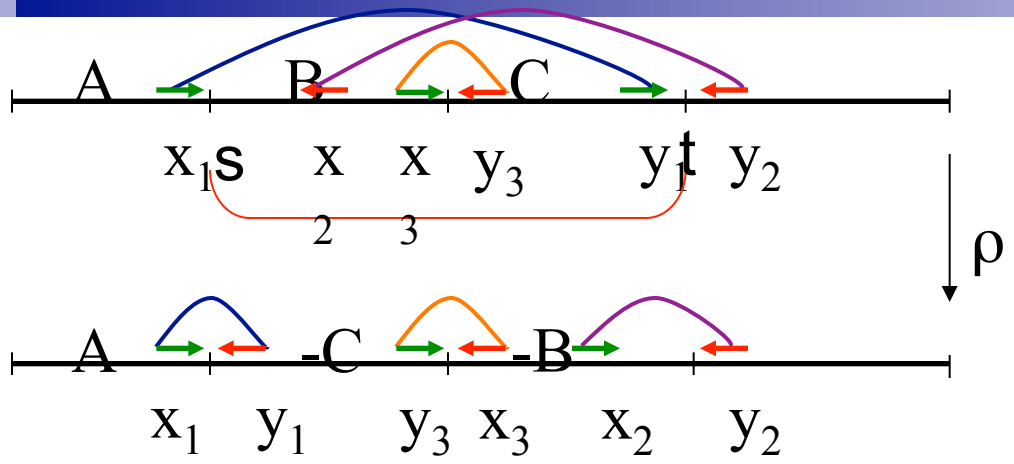
- Use knowledge of known rearrangement mechanisms
  - **e.g. inversions, translocations, etc.**
- Find *simplest* explanation for data, given these mechanisms.
- Motivation: *Sorting by Reversals*

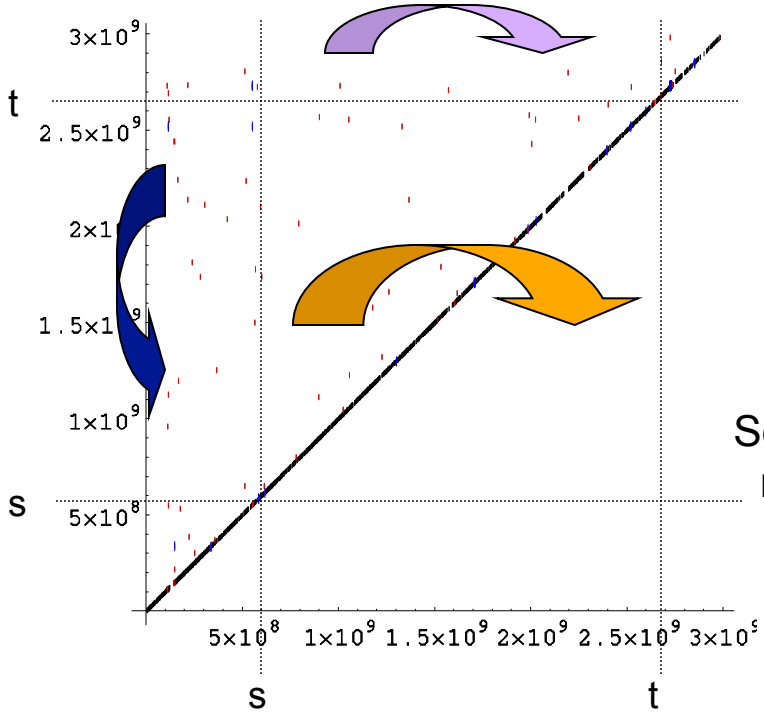
PE Sorting Problem

- **G** = [0,*M*], unichromosomal genome.
- Reversal $\rho_{s,t}(x) = \begin{cases} x, & \text{if } x < s \text{ or } x > t, \\ \boldsymbol{t - (x - s)}, & \textbf{otherwise.} \end{cases}$

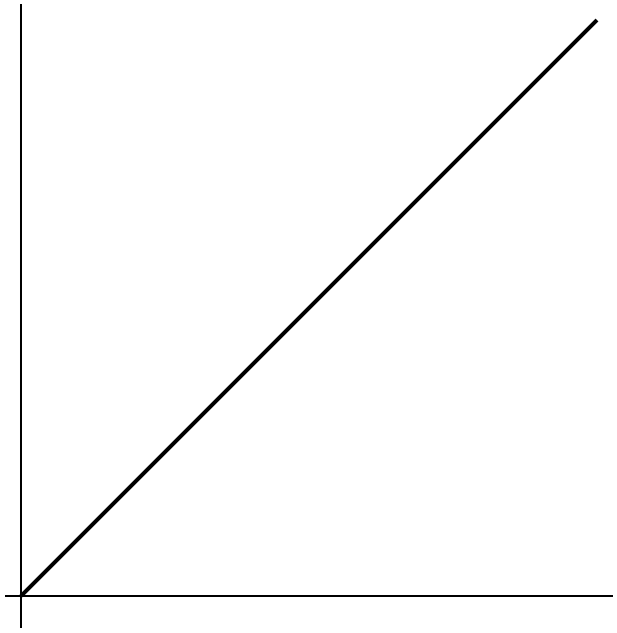


Given: PE pairs $(x_1, y_1), \ldots, (x_n, y_n)$
Find: Minimum number of reversals $\rho_{s1,t1}, \ldots, \rho_{sn,\,tn}$ such that if $\rho = \rho_{s1,t1} \cdots \rho_{sn,\,tn}$ then $(\rho\, x_1, \rho\, y_1), \ldots, (\rho\, x_n, \rho\, y_n)$ are valid PE pairs.

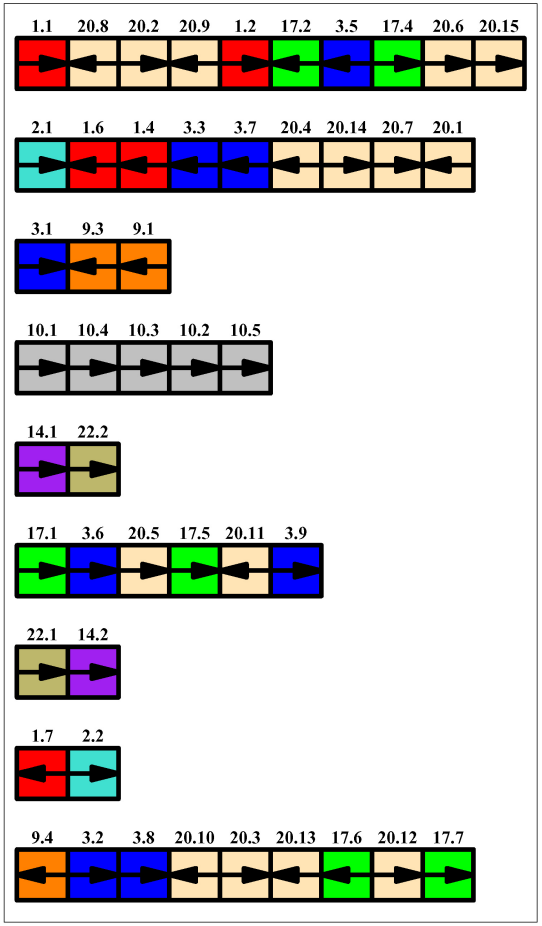




Sequence of reversals.



All ES pairs valid.

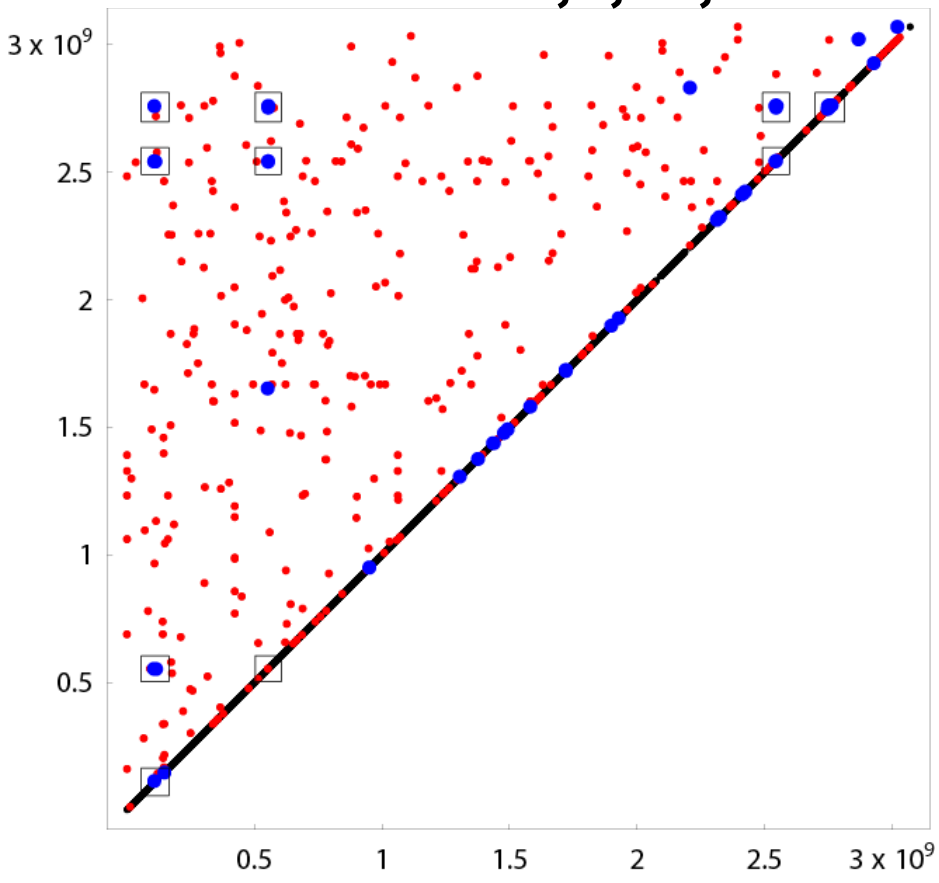


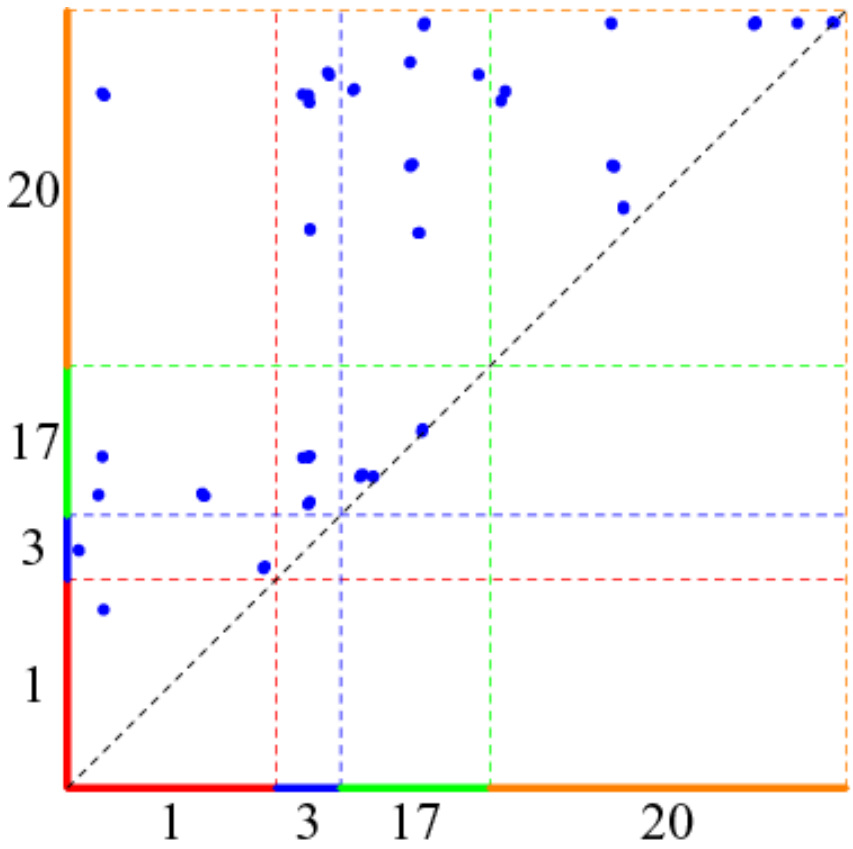
Human chromosomes → MCF7 chromosomes

5 inversions
15 translocations
Raphael et al.

Complications with MCF7:

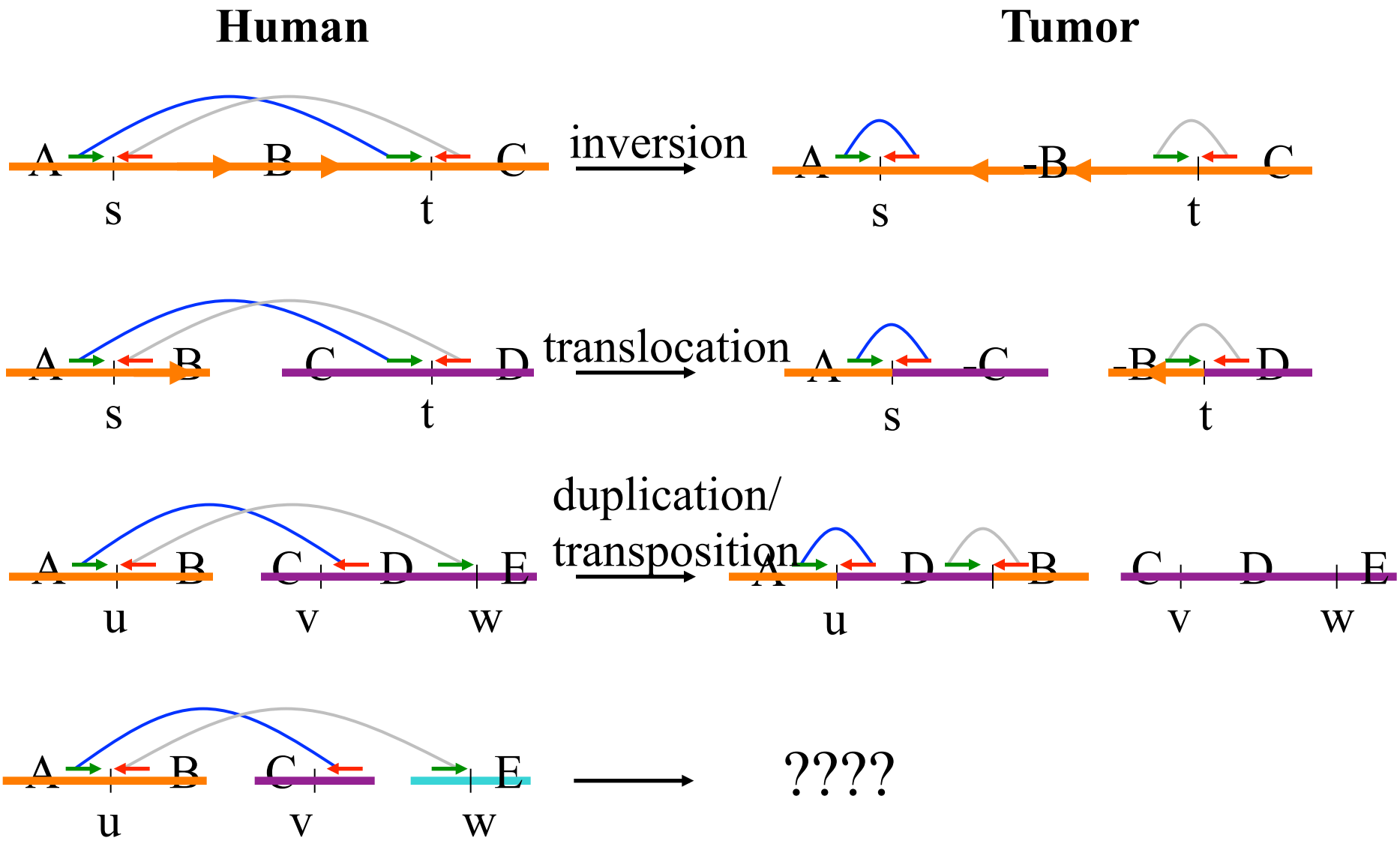
Chromosomes 1,3,17, 20



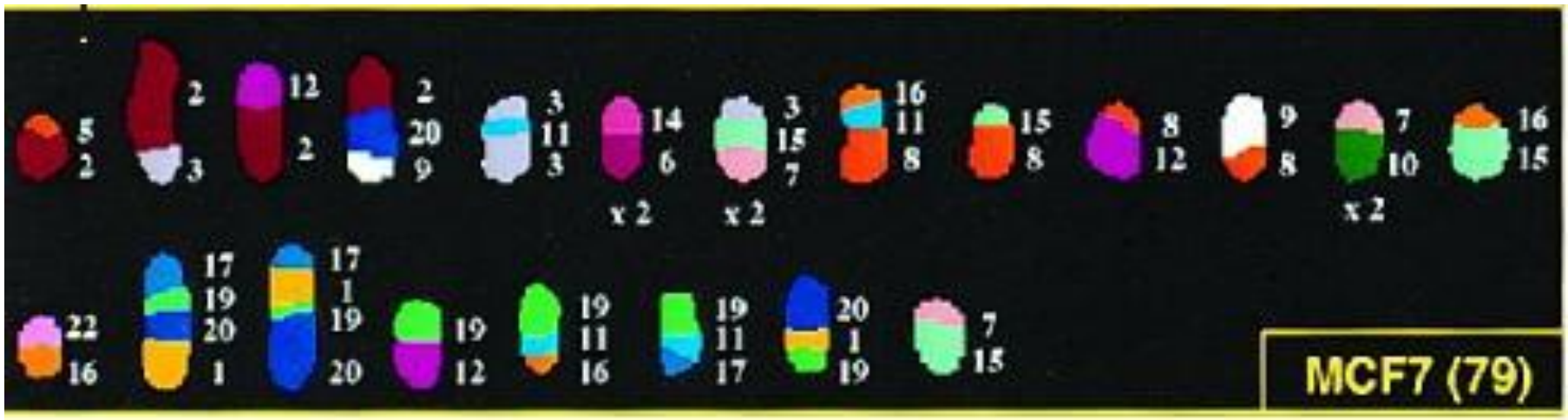


33/70 clusters
Total length: 31Mb

Rearrangement Signatures



Complex Tumor Genomes



Structure of Duplications in Tumors?

- Duplicated segments may co-localize
  (Guan et al. *Nat.Gen.*1994)

Human genome

Tumor genome

- Mechanisms not well understood.

Tumor Amplisomes