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Are there Fragile Regions in the Human Genome? *Combinatorial Algorithms*

Phillip Compeau and Pavel Pevzner

Bioinformatics Algorithms: an Active Learning Approach

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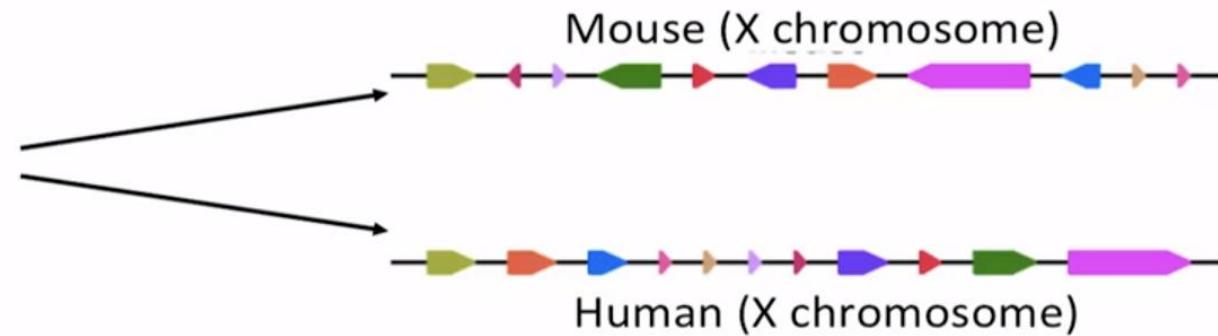
focusing on the question, how to transform
man into mice.

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Genome Rearrangements

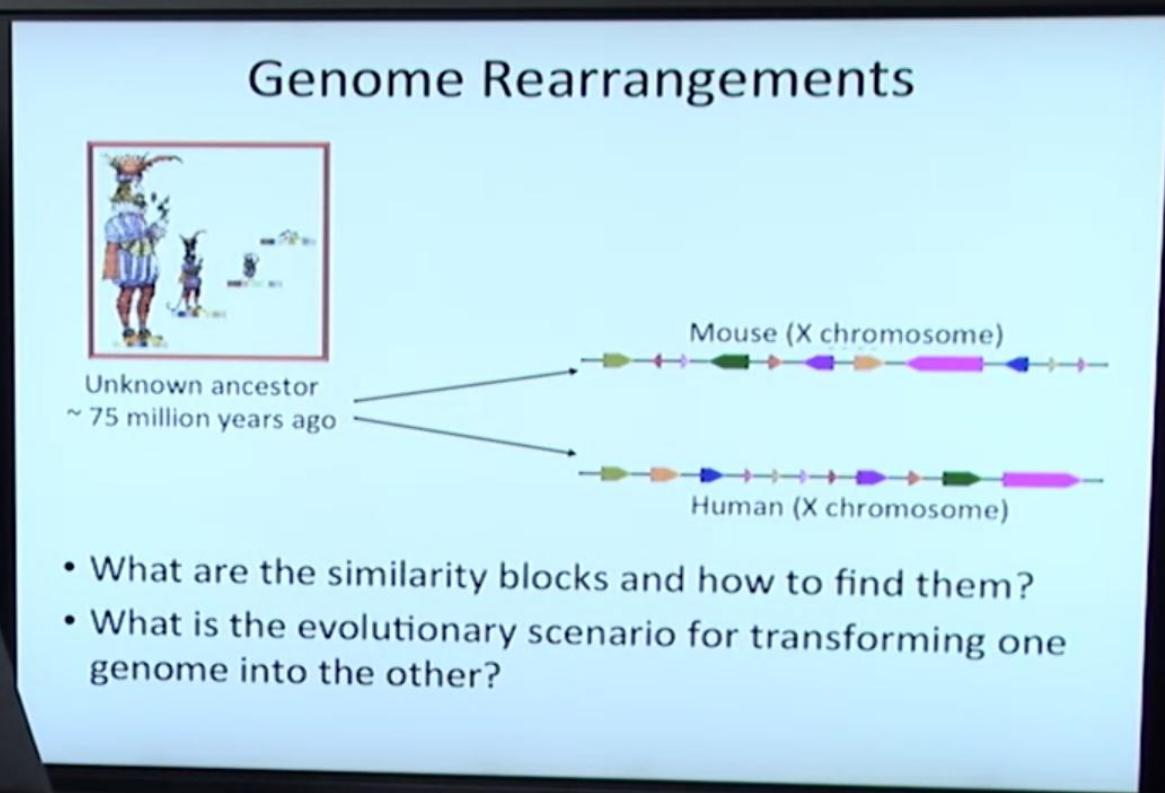


Unknown ancestor
~ 75 million years ago



- What are the similarity blocks and how to find them?
- What is the evolutionary scenario for transforming one genome into the other?
transforming mouse X chromosome into human X chromosome.

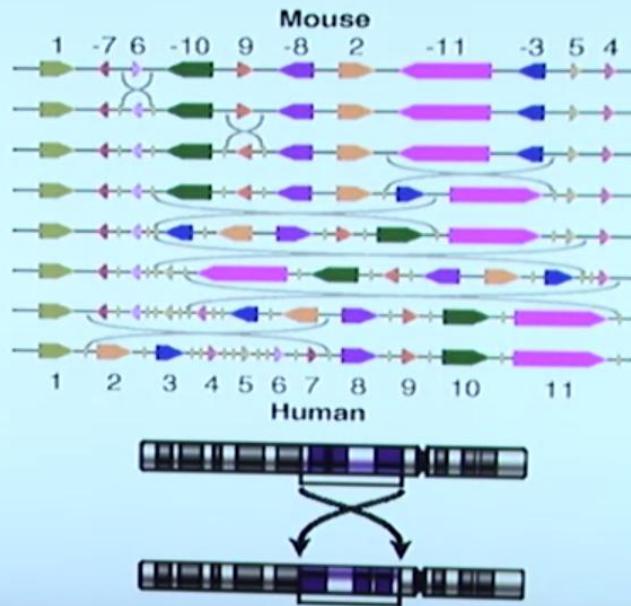
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are arranged differently in mouse and human.

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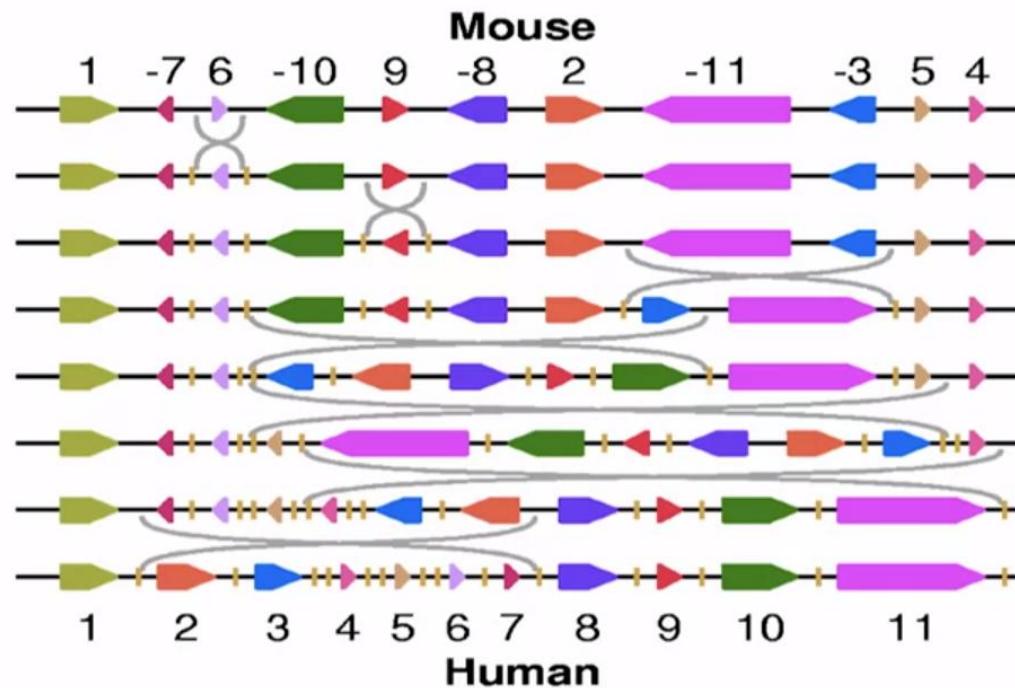
Transforming Mice into Men



as we show in this slide.
Now nature doesn't use this

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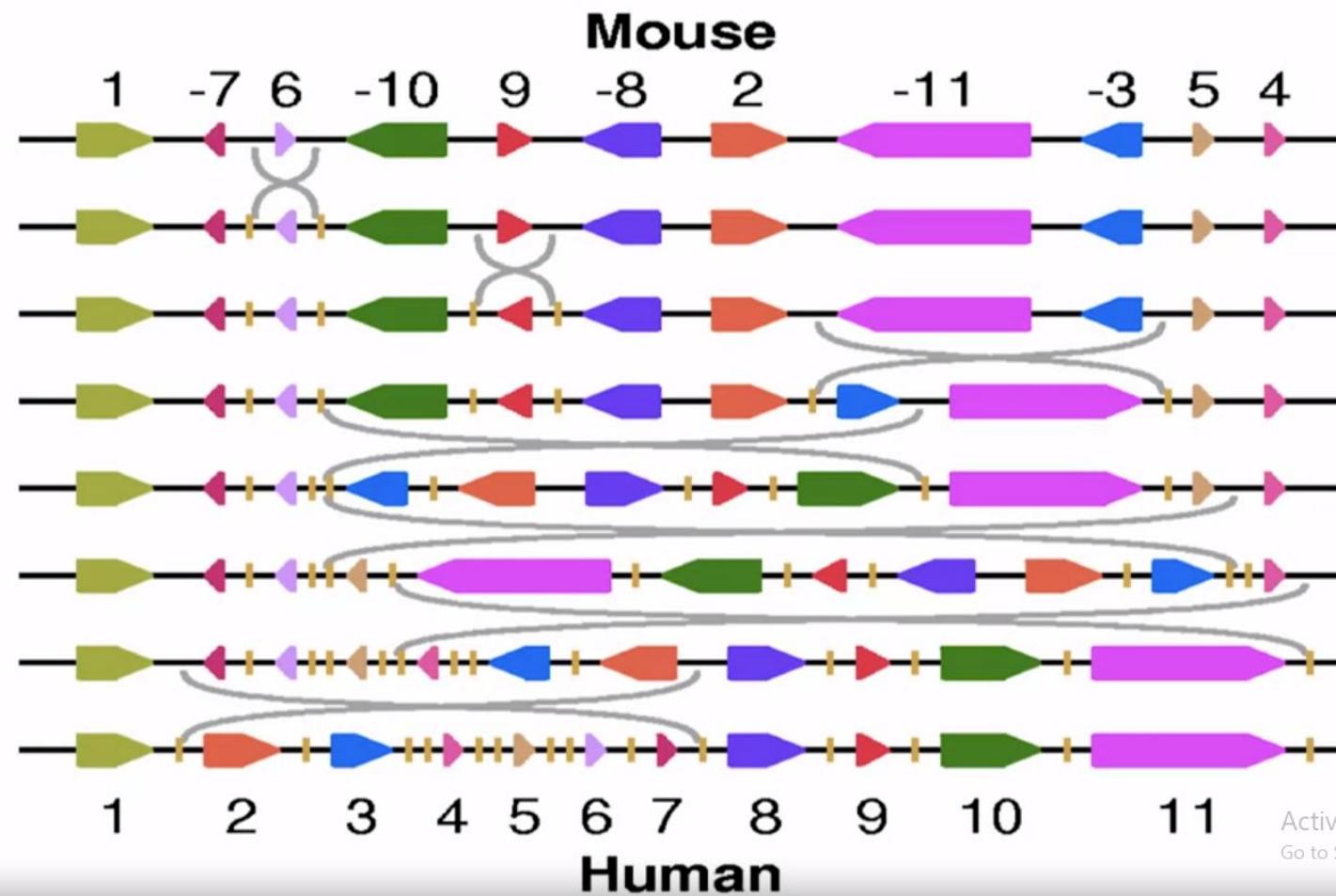
Transforming Mice into Men



by step of what this particular
evolutionary

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Human-Mouse Transformation Accomplished!



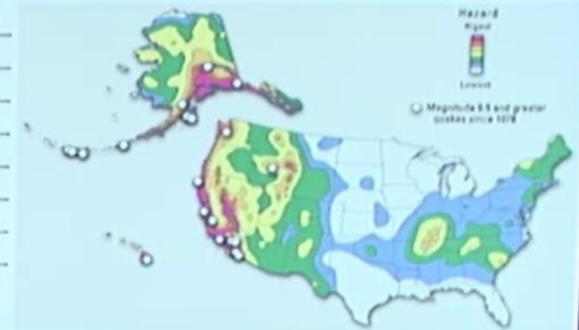
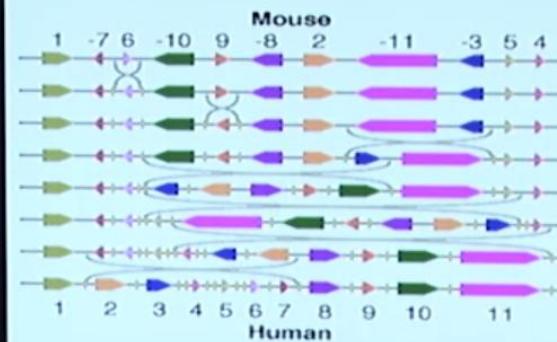
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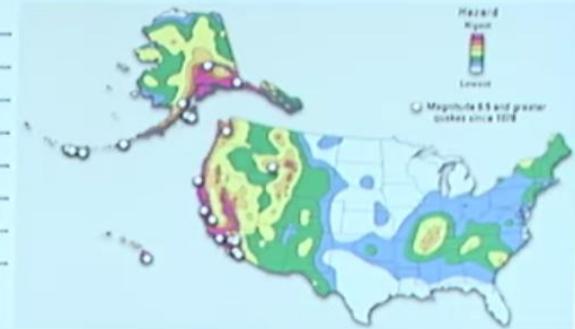
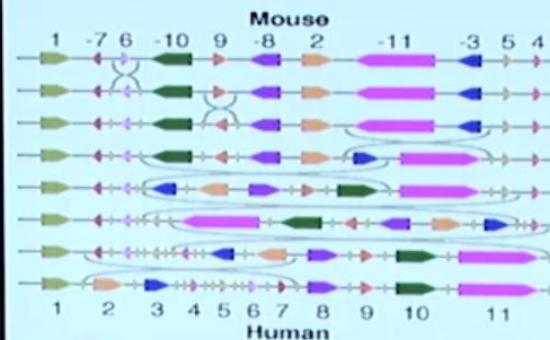
English

Evolutionary Earthquakes



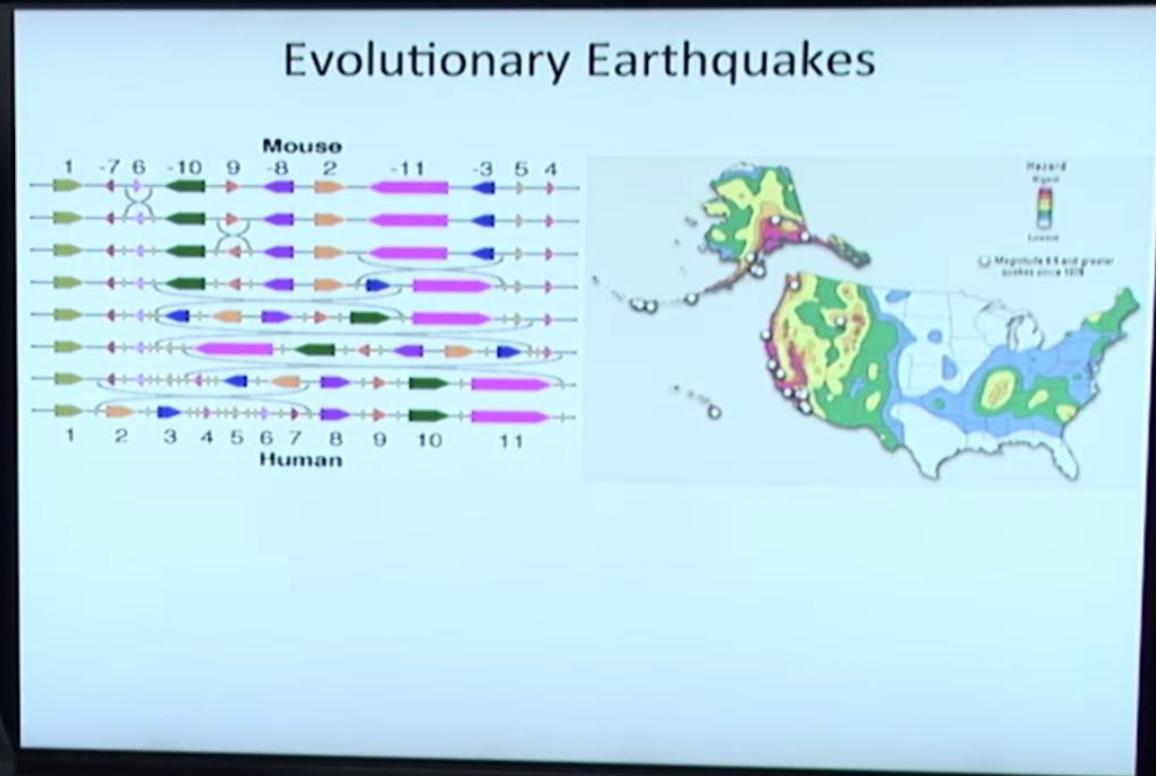
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Evolutionary Earthquakes



And these endpoints, after a reversal happens, may actually

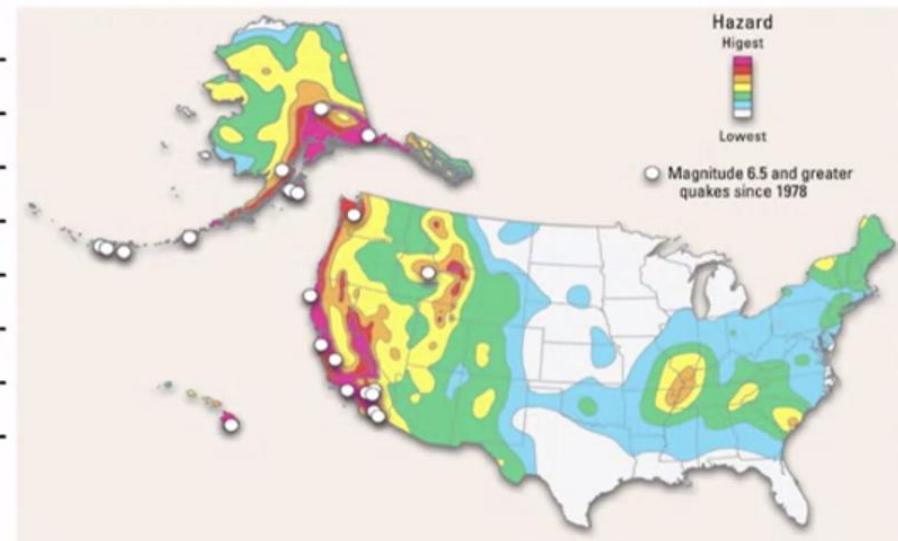
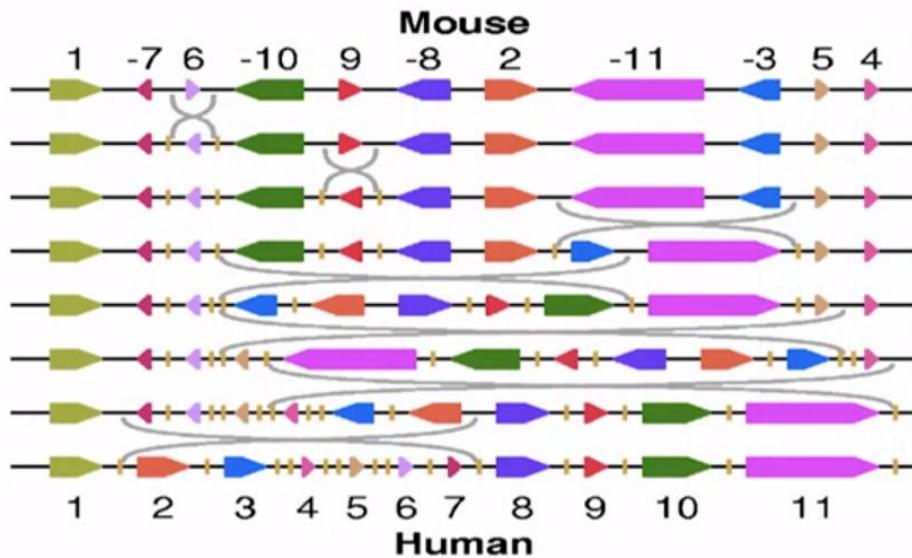
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the influence of the wrong transcription factor, thus disrupting gene regulations.

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Evolutionary Earthquakes

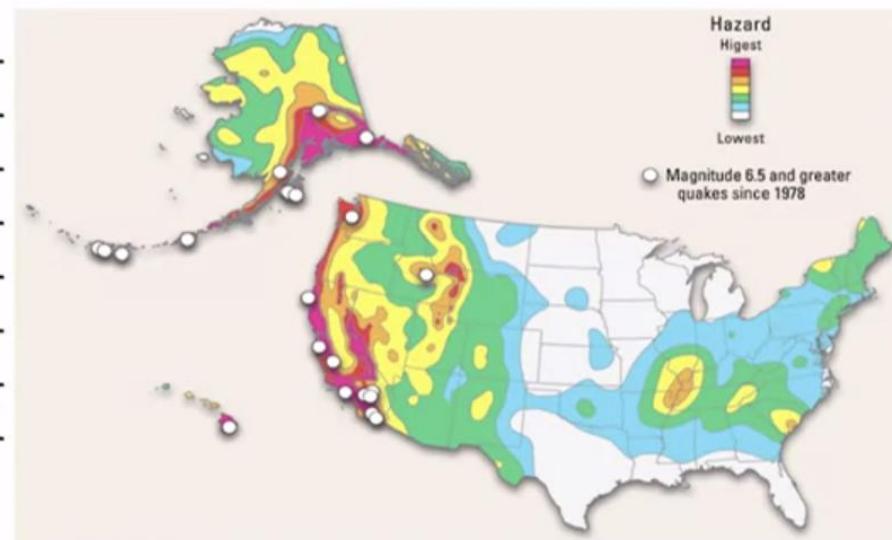
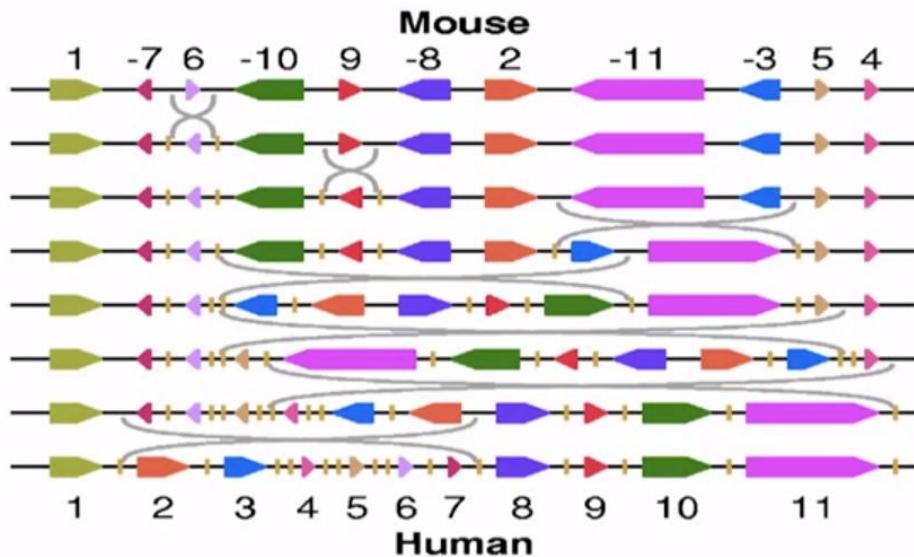


Are there any rearrangement hotspots in mammalian genomes?

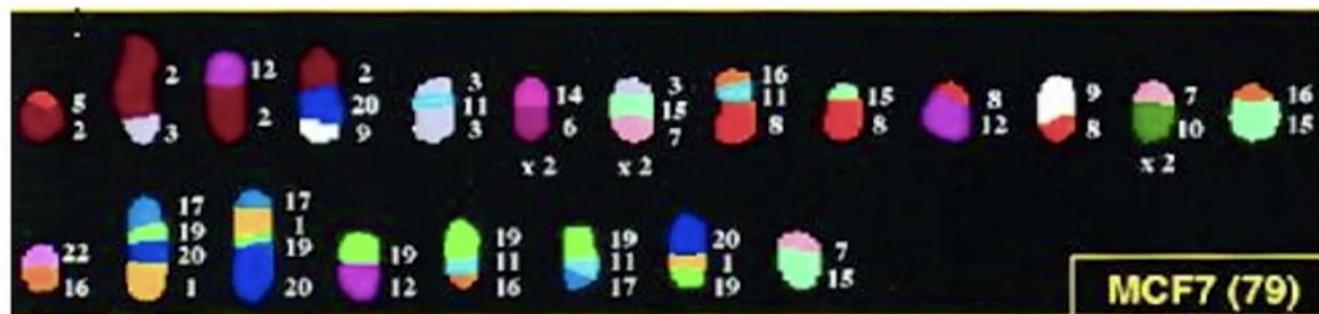
Are there any rearrangement hotspots or
fragile regions in mammalian genomes

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Evolutionary Earthquakes

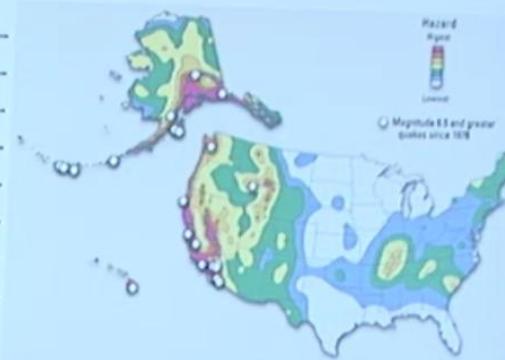
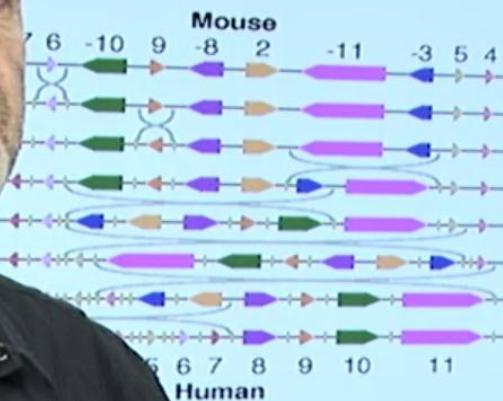


Are there any rearrangement hotspots in mammalian genomes?



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Evolutionary Earthquakes



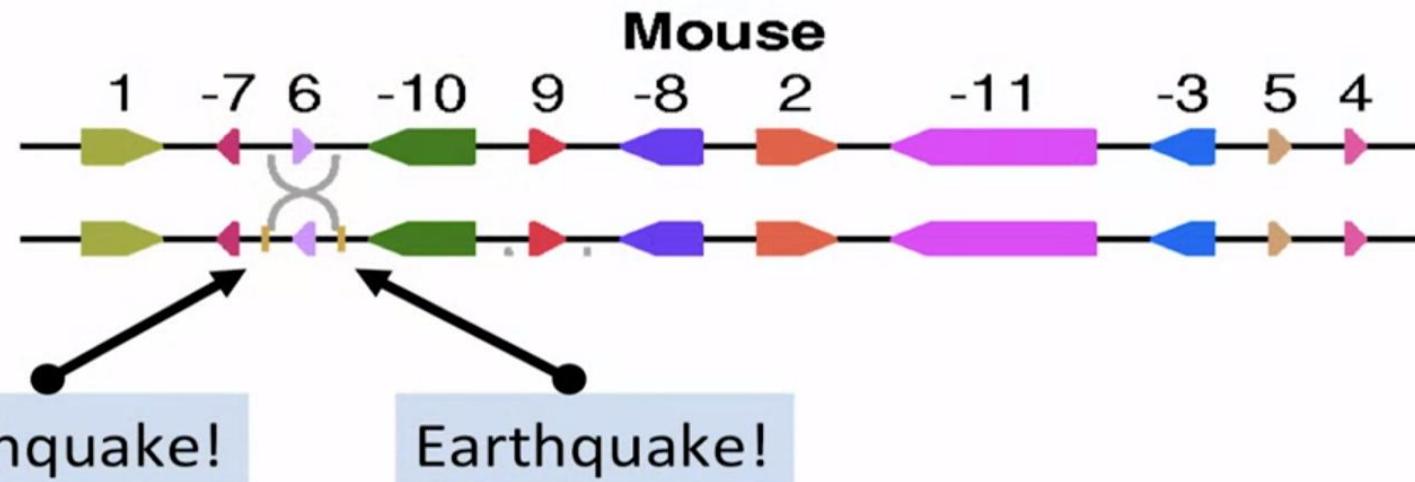
Rearrangement hotspots in mammalian genomes?



in mammalian evolutions, correlate with human rearrangement hotspots

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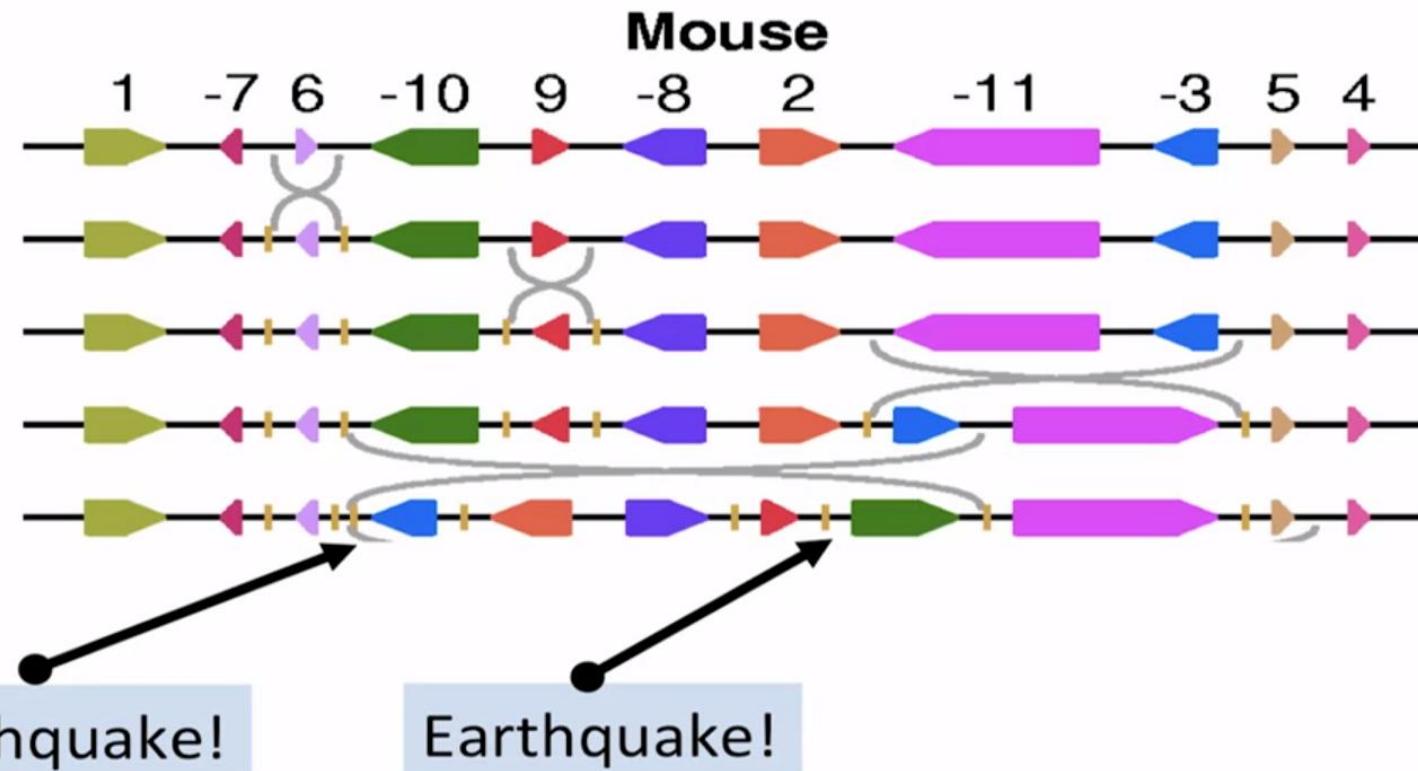
Are There Any Rearrangement Hotspots in This Scenario?



So this is how our first reversal.
And there

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Are There Any Rearrangement Hotspots in This Scenario?



Next one, two more earthquakes.

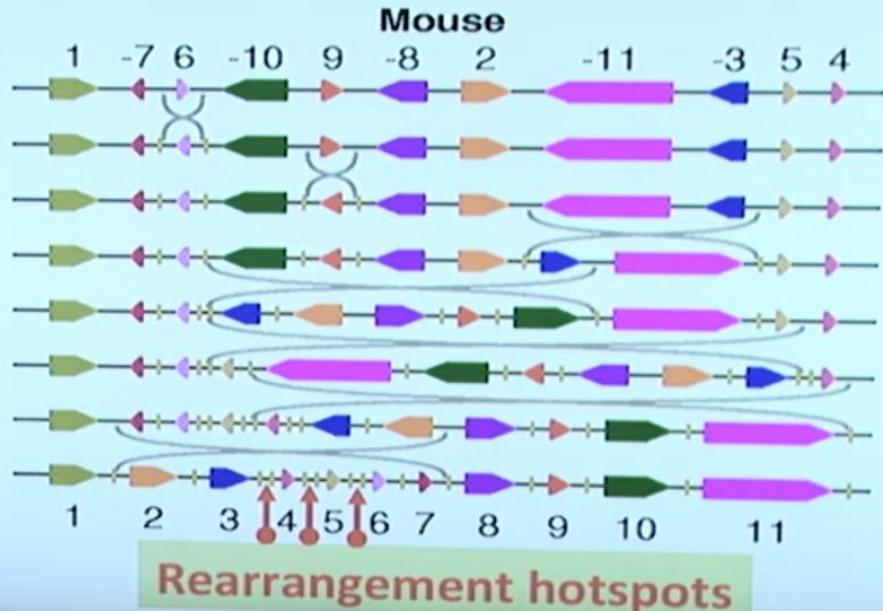
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streaks in the same regions, this is a
rearrangement hotspot.

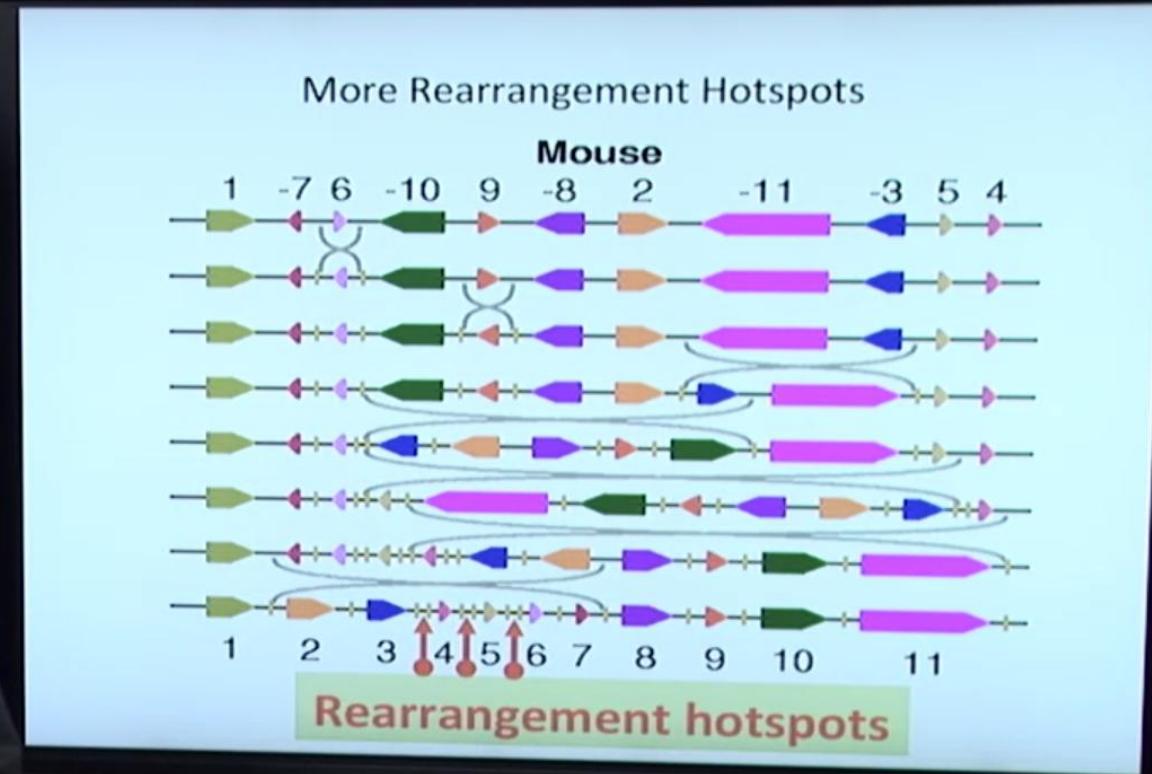
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More Rearrangement Hotspots



where there will multiply repeated earthquakes in

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streaks in the same regions, this is a rearrangement hotspot.

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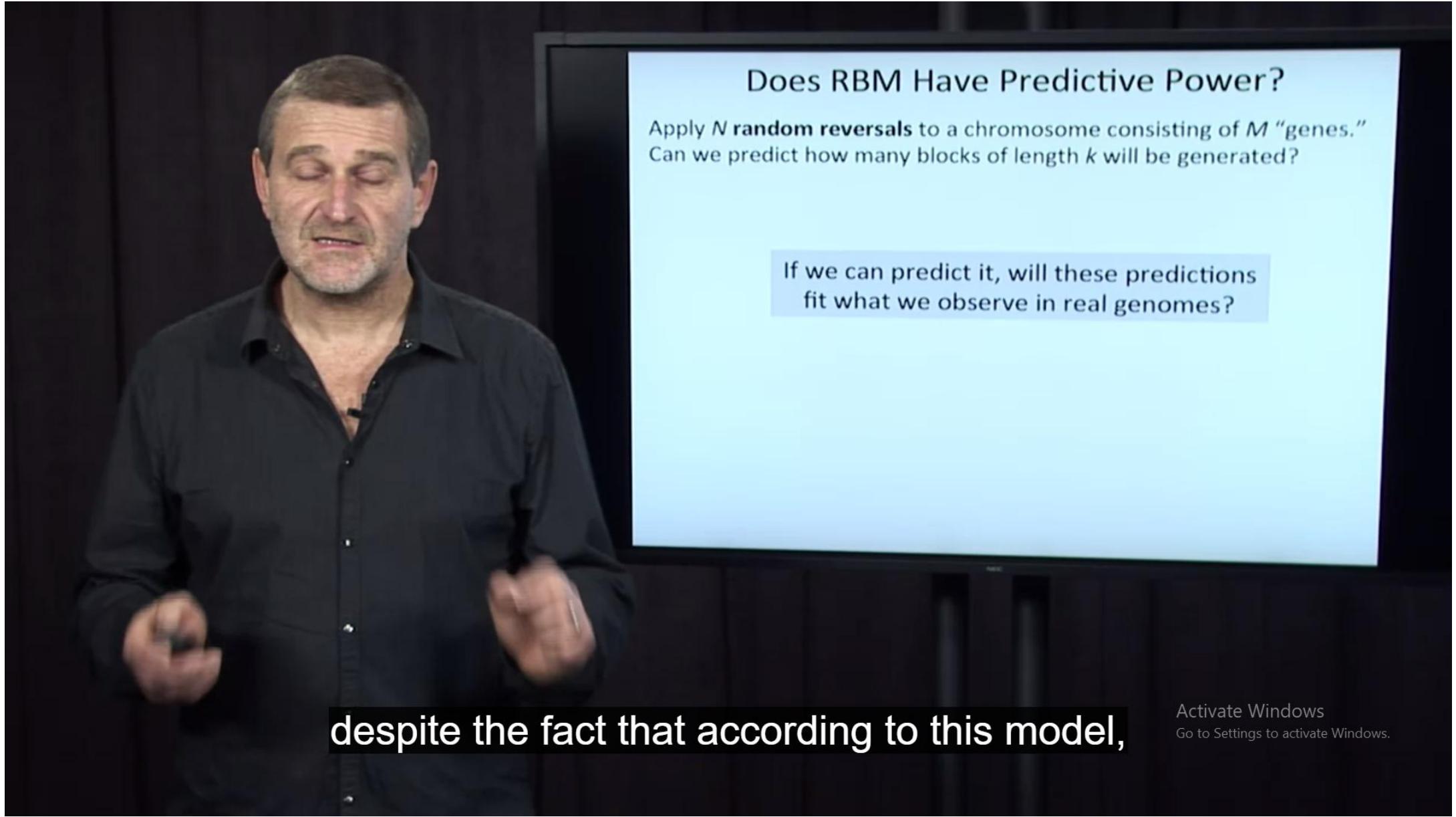
with a random breakage model of chromosome evolution.

Random Breakage Model of Chromosome Evolution

- *Susumu Ohno, 1973*: Rearrangements occur at random positions (no fragile regions).
- *Nadeau & Taylor, 1984*: the first statistical arguments in favor of the Random Breakage Model (RBM).



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Does RBM Have Predictive Power?

Apply N **random reversals** to a chromosome consisting of M "genes."
Can we predict how many blocks of length k will be generated?

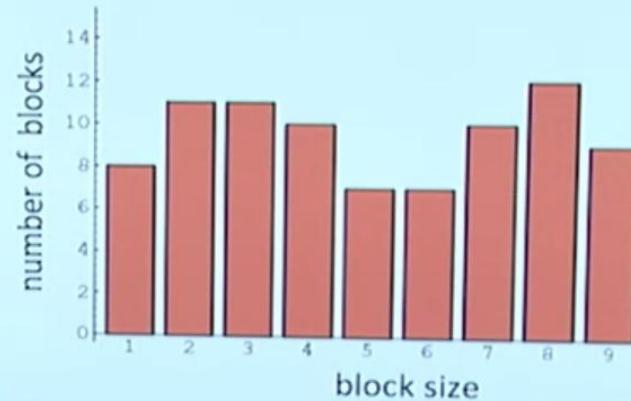
If we can predict it, will these predictions
fit what we observe in real genomes?

despite the fact that according to this model,

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Does RBM Have Predictive Power?

Apply N **random reversals** to a chromosome consisting of M "genes."
Can we predict how many blocks of length k will be generated?

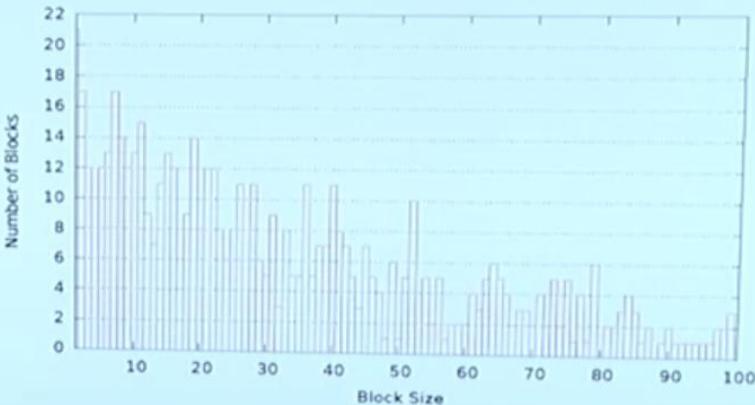


For example, what would you expect after
applying N random reversals

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Does RBM Have Predictive Power?

Apply N **random reversals** to a chromosome consisting of M "genes."
Can we predict how many blocks of length k will be generated?

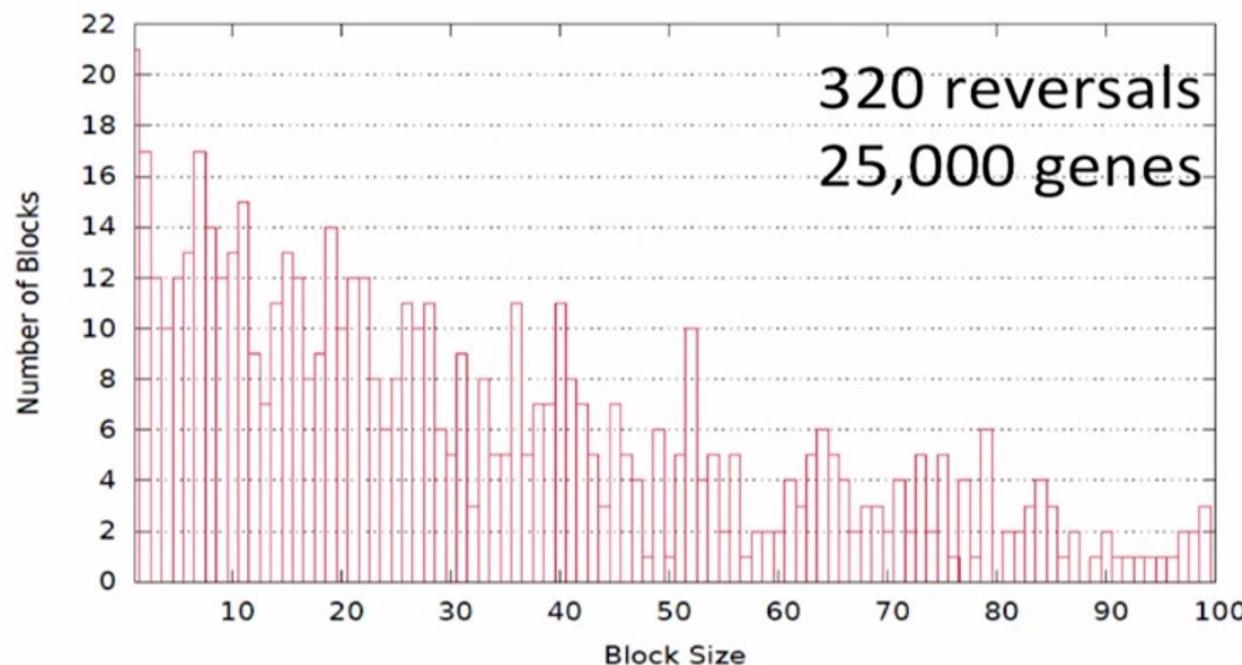


will be variable.
It turned out that we expect

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Does RBM Have Predictive Power?

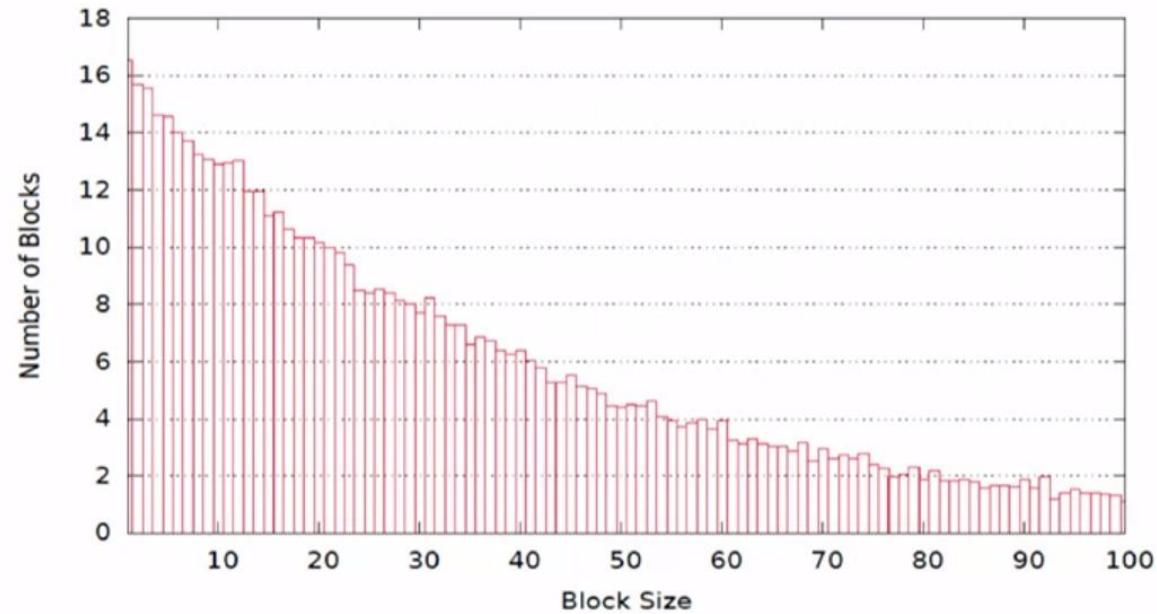
Apply N **random reversals** to a chromosome consisting of M “genes.”
Can we predict how many blocks of length k will be generated?



Despite the fact that reversals occur at random positions, we can predict (roughly) how many blocks of each length will be generated!

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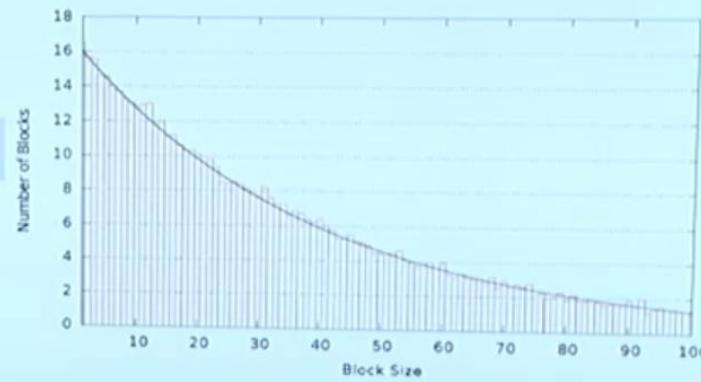
Histogram of Synteny Block Lengths (averaged over 100 simulations)



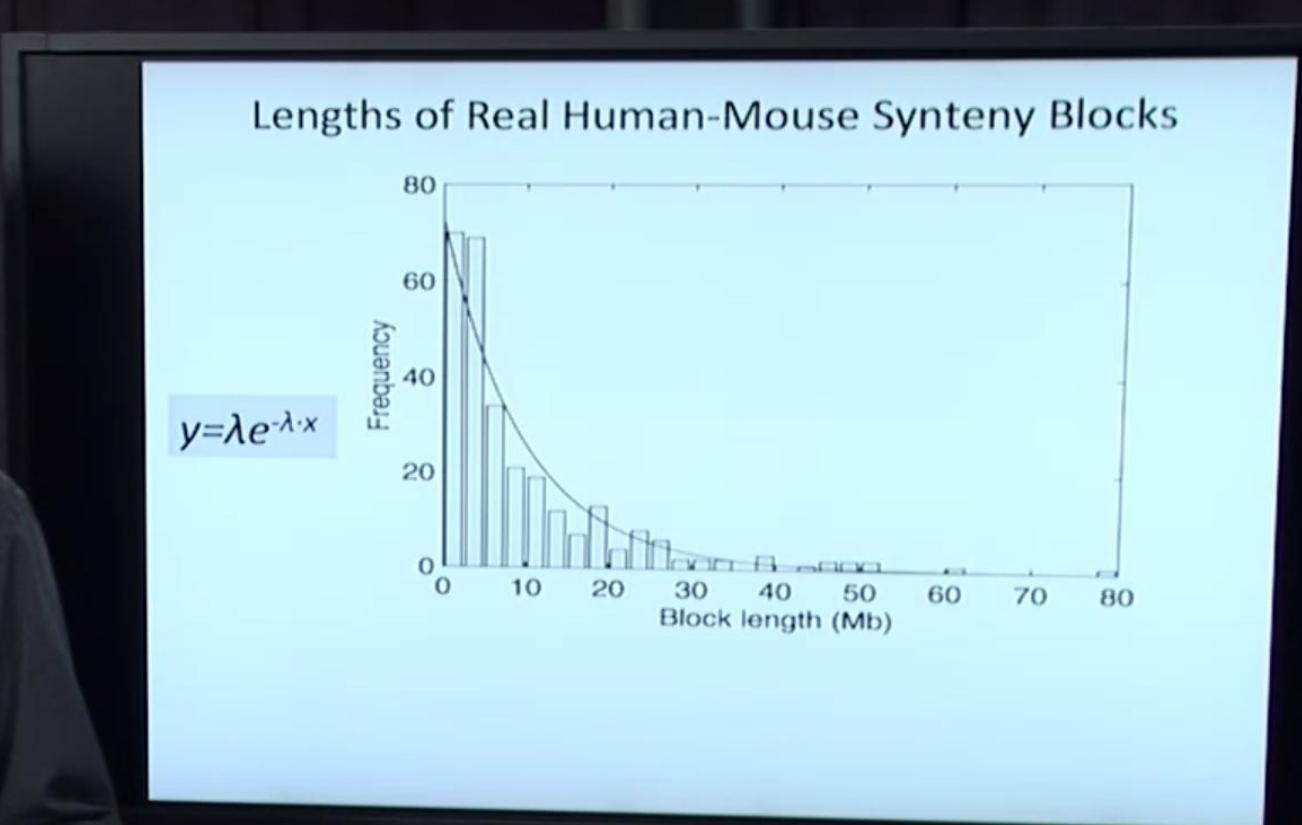
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Exponential Distribution (simulated data)

$$y = \lambda e^{-\lambda \cdot x}$$



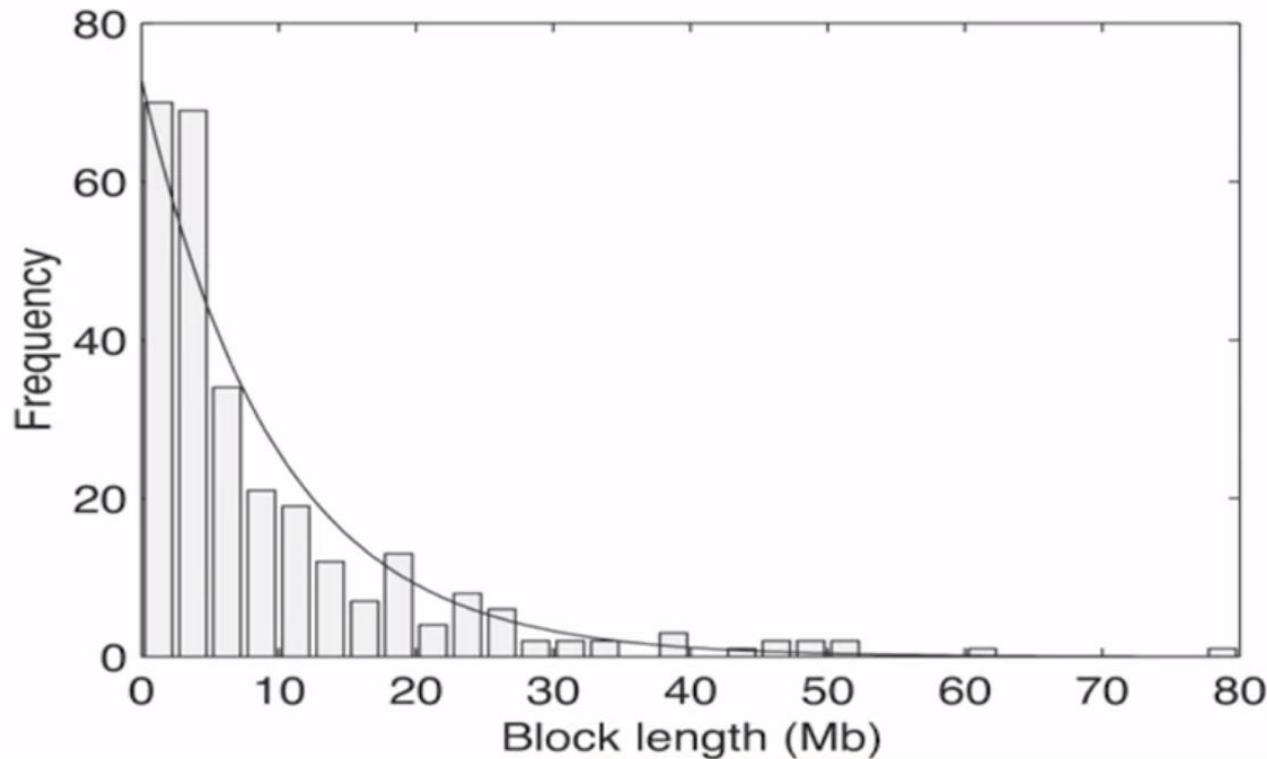
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Lengths of Real Human-Mouse Synteny Blocks

$$y = \lambda e^{-\lambda \cdot x}$$



1990s: RBM was embraced by biologists and has become *de facto* theory of chromosome evolution.
embraced by biologists and has become de
facto theory of chromosome evolution.

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Are There Fragile Regions in the Human Genome?

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Are There Fragile Regions in the Human Genome?

- Transforming Men into Mice
- **Sorting by Reversals**
- Breakpoint Theorem
- Rearrangements in Tumor Genomes
- 2-Breaks
- Breakpoint Graphs
- 2-Break Distance Theorem
- Rearrangement Hotspots in the Human Genome
- Synteny Block Construction

Transforming Men into Mice

- **Sorting by Reversals**
- Breakpoint Theorem
- Rearrangements in Tumor Genomes
- 2-Breaks

Breakpoint Graphs

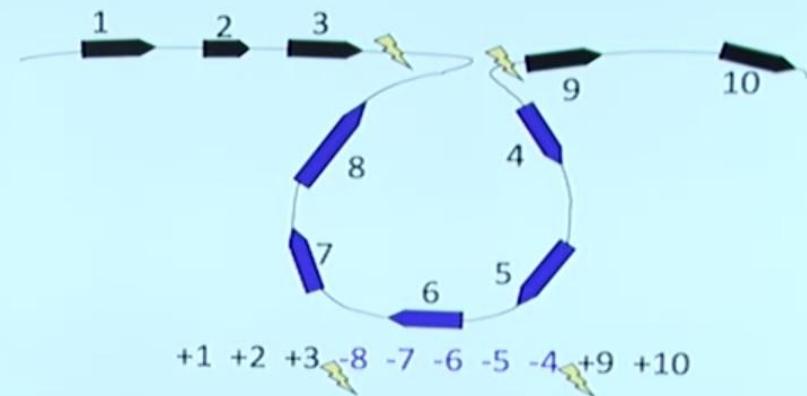
- 2-Break Distance Theorem
- Rearrangement Hotspots in the Human Genome
- Synteny Block Construction

We'll now talk about the algorithmic
problem of sorting by reversals.

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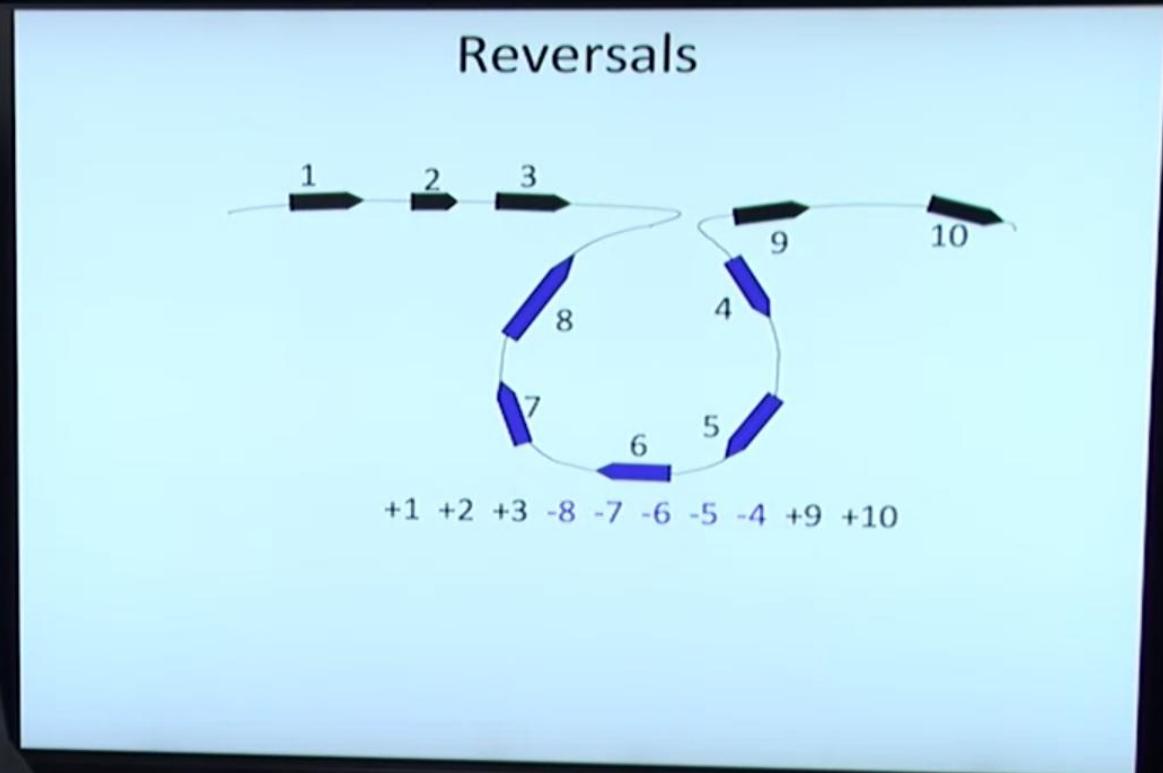
Reversals



The reversal introduced two *breakpoints* (disruptions in gene order).

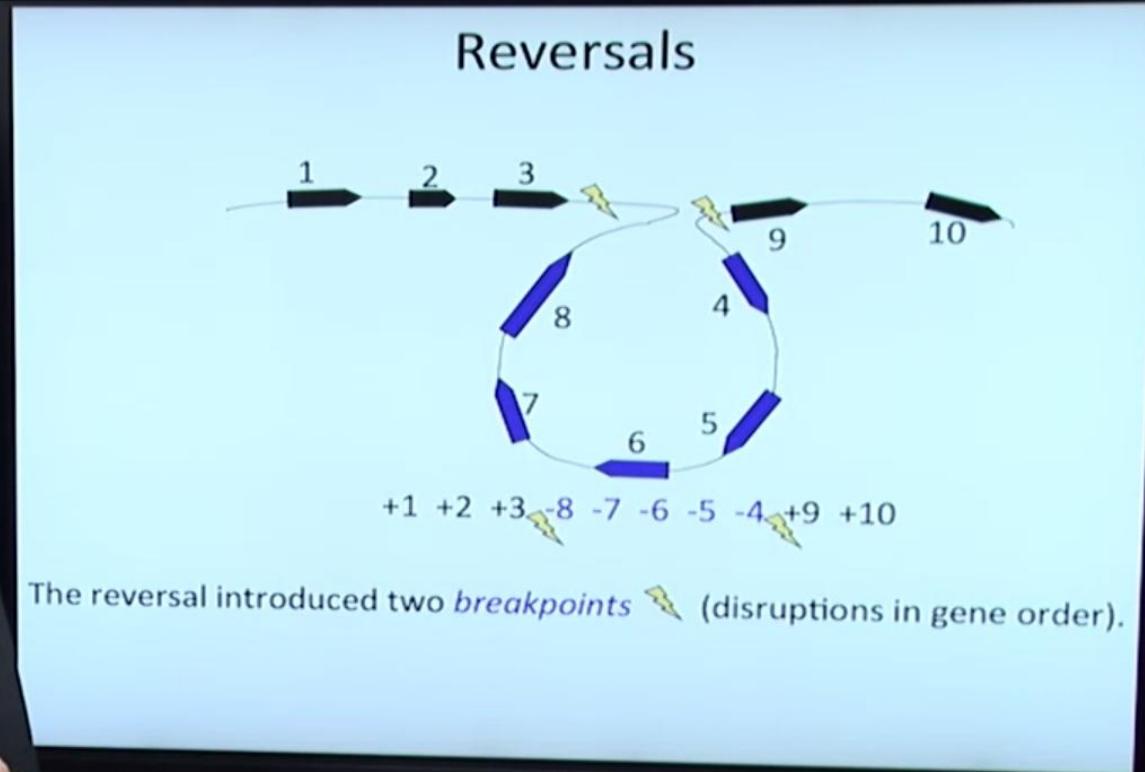
a new order as shown on this slide.
And as a result, the

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a new order as shown on this slide.
And as a result, the

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reversal introduces two breakpoints,
disruptions in the gene order.

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Rearrangement Scenario with 5 Reversals

Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	2	3	4	5	6	7	8	1
Step 3:	2	3	4	5	6	7	8	-1
Step 4:	-8	-7	-6	-5	-4	-3	-2	-1
Step 5:	1	2	3	4	5	6	7	8

So let's take a look at one of the possible rearrangement scenarios.

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Rearrangement Scenario with 4 Reversals

Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

that transforms the same permutation into identity with just four reversals.

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Rearrangement Scenario with 4 Reversals

Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

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Rearrangement Scenario with 4 Reversals

Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

Reversal distance: the minimum number of reversals to transform one permutation into another.

for transforming one genome into another
because

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Sorting by 4 Reversals

Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

Reversal Distance Problem: Calculate the reversal distance between two permutations.

- **Input:** Two permutations.
- **Output:** The reversal distance between them.

problem of calculating the reversal distance

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Sorting by 4 Reversals

Step 0: $2 \ -4 \ -3 \ 5 \ -8 \ -7 \ -6 \ 1$

Step 1: $2 \ 3 \ 4 \ 5 \ -8 \ -7 \ -6 \ 1$

Step 2: $-5 \ -4 \ -3 \ -2 \ -8 \ -7 \ -6 \ 1$

Step 3: $-5 \ -4 \ -3 \ -2 \ -1 \ 6 \ 7 \ 8$

Step 4: $1 \ 2 \ 3 \ 4 \ 5 \ 6 \ 7 \ 8$

Sorting by Reversals Problem: Calculate the reversal distance between a permutation and the identity permutation ($+1 +2 \dots +n$).

- **Input:** A permutation P .
- **Output:** The reversal distance between P and the identity permutation.

Sorting by 4 Reversals

Step 0: $2 \ -4 \ -3 \ 5 \ -8 \ -7 \ -6 \ 1$
Step 1: $2 \ 3 \ 4 \ 5 \ -8 \ -7 \ -6 \ 1$
Step 2: $-5 \ -4 \ -3 \ -2 \ -8 \ -7 \ -6 \ 1$
Step 3: $-5 \ -4 \ -3 \ -2 \ -1 \ 6 \ 7 \ 8$
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Sorting by Reversals Problem: Calculate the reversal distance between a permutation and the identity permutation ($+1 +2 \dots +n$).

- **Input:** A permutation P .
- **Output:** The reversal distance between P and the identity permutation.

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Greedy Sorting by Reversals



(+1 -7 +6 -10 +9 -8 +2 -11 -3 +5 +4)

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Greedy Sorting by Reversals



(+1 **-7** +6 -10 +9 -8 **+2** -11 -3 +5 +4)
(+1 **-2** +8 -9 +10 -6 +7 -11 -3 +5 +4)

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Greedy Sorting by Reversals



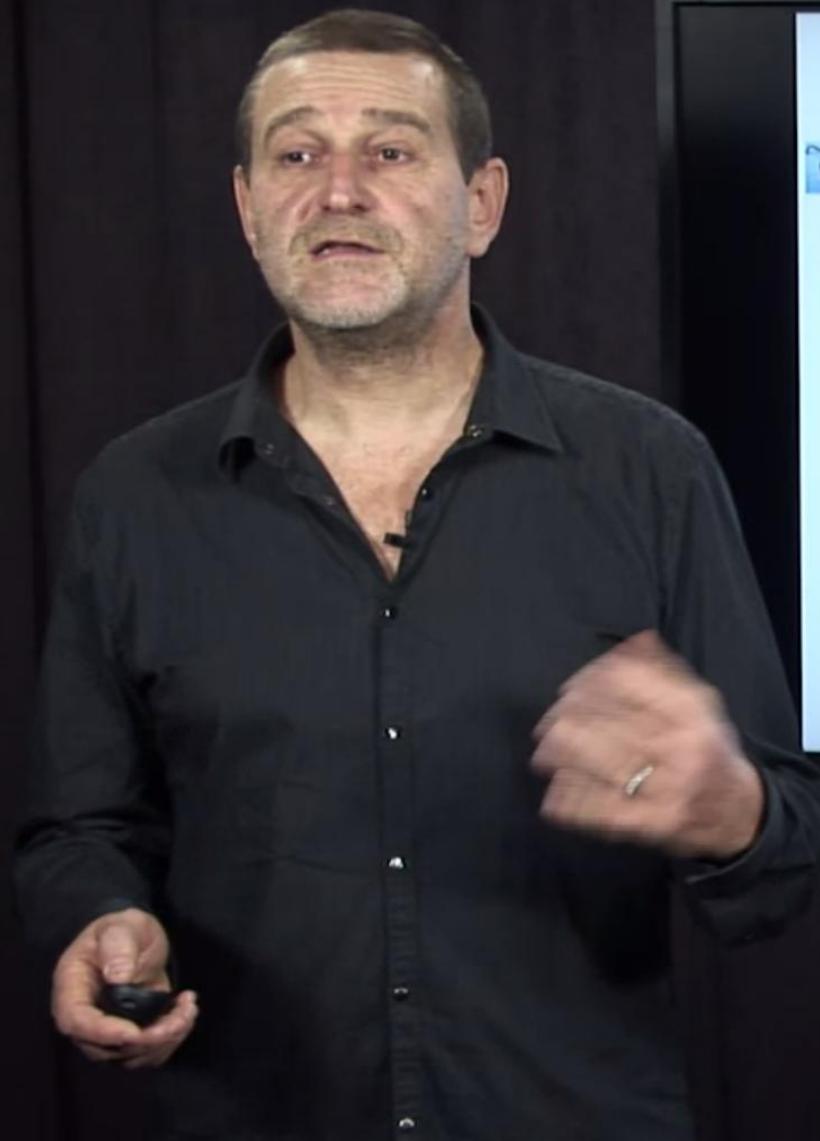
(+1 **-7** **+6** **-10** **+9** **-8** **+2** **-11** **-3** **+5** **+4**)
(+1 **-2** **+8** **-9** **+10** **-6** **+7** **-11** **-3** **+5** **+4**)
(+1 **+2** **+8** **-9** **+10** **-6** **+7** **-11** **-3** **+5** **+4**)

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Greedy Sorting by Reversals



(+1 -7 +6 -10 +9 -8 +2 -11 -3 +5 +4)
(+1 -2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +3 +11 -7 +6 -10 +9 -8 +5 +4)



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Greedy Sorting by Reversals



(+1 -7 +6 -10 +9 -8 +2 -11 -3 +5 +4)
(+1 -2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +3 +11 -7 +6 -10 +9 -8 +5 +4)
(+1 +2 +3 -4 -5 +8 -9 +10 -6 +7 -11)

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Greedy Sorting by Reversals

(+1 -7 +6 -10 +9 -8 +2 -11 -3 +5 +4)
(+1 -2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +8 -9 +10 -6 +7 -11 -3 +5 +4)
(+1 +2 +3 +11 -7 +6 -10 +9 -8 +5 +4)
(+1 +2 +3 -4 -5 +8 -9 +10 -6 +7 -11)
(+1 +2 +3 +4 -5 +8 -9 +10 -6 +7 -11)
(+1 +2 +3 +4 +5 +8 -9 +10 -6 +7 -11)
(+1 +2 +3 +4 +5 +6 -10 +9 -8 +7 -11)
(+1 +2 +3 +4 +5 +6 -7 +8 -9 +10 -11)
(+1 +2 +3 +4 +5 +6 +7 +8 -9 +10 -11)
(+1 +2 +3 +4 +5 +6 +7 +8 +9 +10 -11)

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Are there Fragile Regions in the Human Genome?

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- **Breakpoint Theorem**
- Rearrangements in Tumor Genomes
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Adjacencies and Breakpoints

+3 +4 +5 -12 -8 -7 -6 +1 +2 +10 +9 -11 +13 +14

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Adjacencies and Breakpoints

+3  +4  +5 -12 -8 -7 -6 +1 +2 +10 +9 -11 +13 +14
in order

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Adjacencies and Breakpoints

+3  +4  +5  -12 -8 -7 -6 +1 +2 +10 +9 -11 +13 +14
out of order

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Adjacencies and Breakpoints

+3  +4  +5  -12  -8  -7 -6 +1 +2 +10 +9 -11 +13 +14
in order
despite being inverted

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Adjacencies and Breakpoints

+3  +4  +5  -12  -8  -7 -6 +1 +2 +10 +9 -11 +13 +14
in order
despite being inverted

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Adjacencies and Breakpoints

-4 +5 -12 -8 -7 -6 +1 +2 +10 +9 -11 +13 +14

Activate Windows
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Adjacencies and Breakpoints

+3  +4  +5  -12  -8  -7  -6  +1  +2  +10  +9  -11  +13  +14

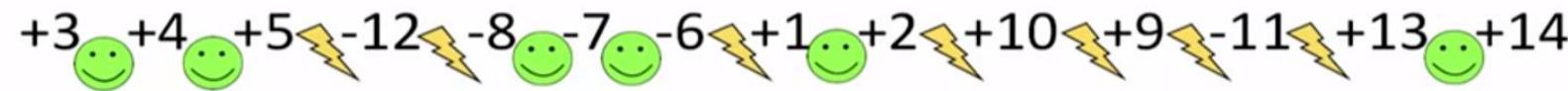
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Adjacencies and Breakpoints



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Adjacencies and Breakpoints



Activate Windows
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Adjacencies and Breakpoints



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Adjacencies and Breakpoints

0 +3 +4 +5 -12 -8 -7 -6 +1 +2 +10 +9 -11 +13 +14 15

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Adjacencies and Breakpoints



$$\text{adjacencies}(P) + \text{breakpoints}(P) = |P| + 1$$



Adjacencies and Breakpoints



$$\text{adjacencies}(P) + \text{breakpoints}(P) = |P| + 1$$



What is the number of breakpoints in the identity permutation $(+1 +2 \dots +n)$?

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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>								
Step 0:	<u>2 -4 -3 5 -8 -7 -6 1</u> 6								
Step 1:	2 3 4 5 -8 -7 -6 1								
Step 2:	-5 -4 -3 -2 -8 -7 -6 1								
Step 3:	-5 -4 -3 -2 -1 6 7 8								
Step 4:	1 2 3 4 5 6 7 8								

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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>							
Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

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Step 4:	1	2	3	4	5	6	7	8

How many breakpoints can be eliminated by a single reversal?

Hint:



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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>							
Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

How many breakpoints can be eliminated by a single reversal?

Breakpoint Theorem: Reversal distance $\geq \text{breakpoints}(P)/2$

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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>							
Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

How many breakpoints can be eliminated by a single reversal?

Breakpoint Theorem: Reversal distance $\geq \text{breakpoints}(P)/2$

Activate Windows
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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>							
Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

How many breakpoints can be eliminated by a single reversal?

Breakpoint Theorem: Reversal distance $\geq \text{breakpoints}(\mathcal{P})/2$

the number of breakpoints by two, but you can check that

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Sorting by Reversals as Breakpoint Elimination

	<i>breakpoints(P)</i>							
Step 0:	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4:	1	2	3	4	5	6	7	8

How many breakpoints can be eliminated by a single reversal?

Breakpoint Theorem: Reversal distance $\geq \text{breakpoints}(\mathcal{P})/2$

intricacies of the polynomial algorithm
for sorting by reversals.

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Press Esc to exit full screen

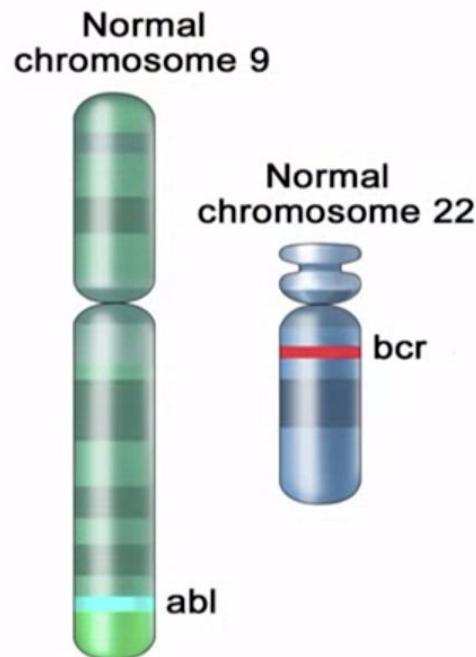
Are There Fragile Regions in the Human Genome?

- Transforming Men into Mice
- Sorting by Reversals
- Breakpoint Theorem
- **Rearrangements in Tumor Genomes**
- 2-Breaks
- Breakpoint Graphs
- 2-Break Distance Theorem
- Rearrangement Hotspots in the Human Genome
- Synteny Block Construction

So far, we have been talking about
rearrangements in unichromosomal genomes.

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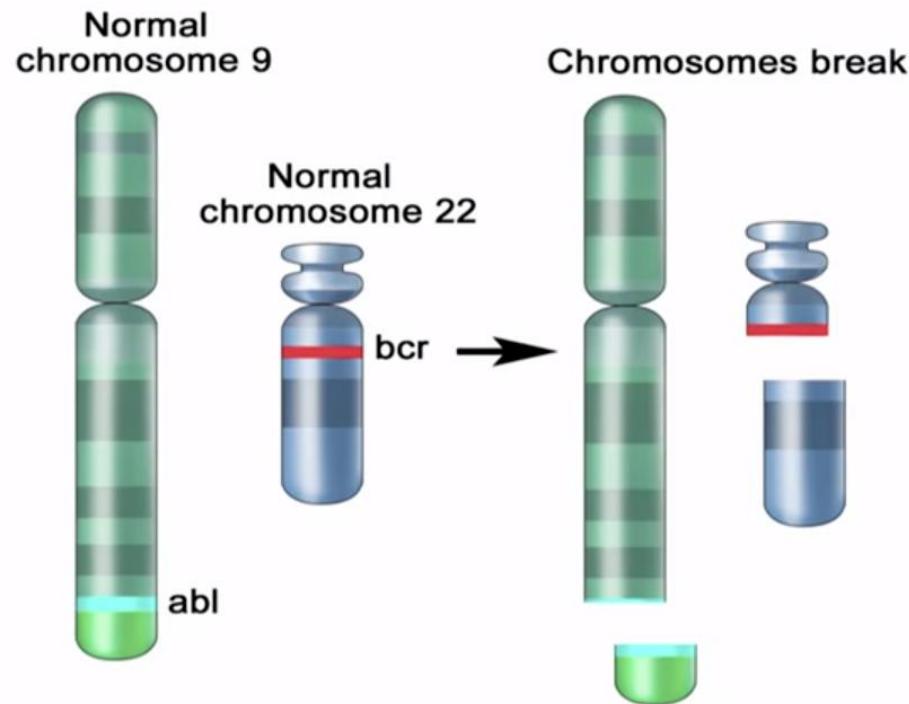
Philadelphia Chromosome



So these are normal

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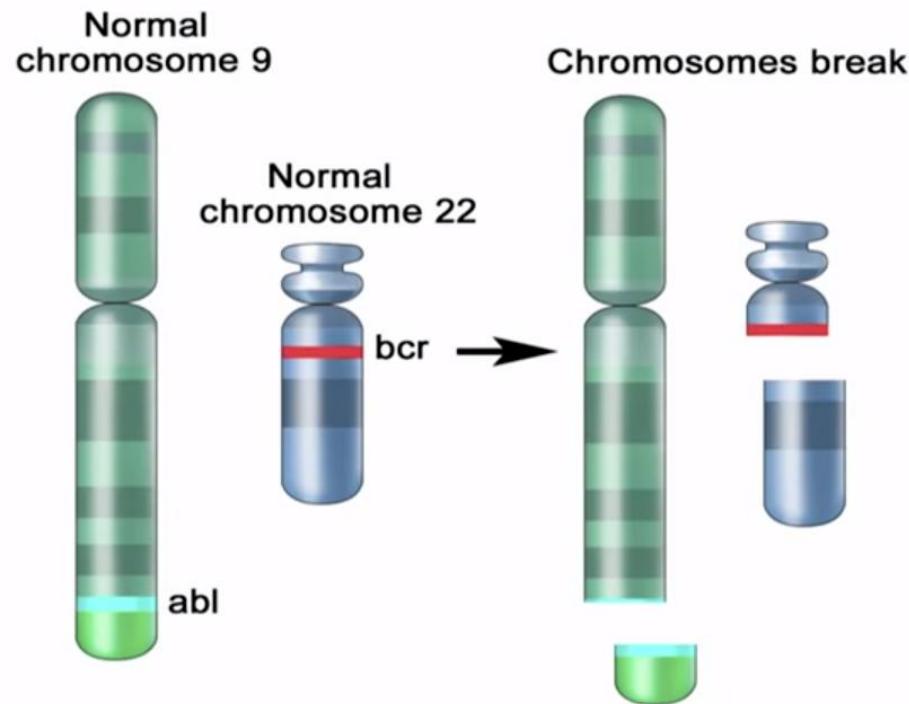
Philadelphia Chromosome



Now, consider a break in two places on

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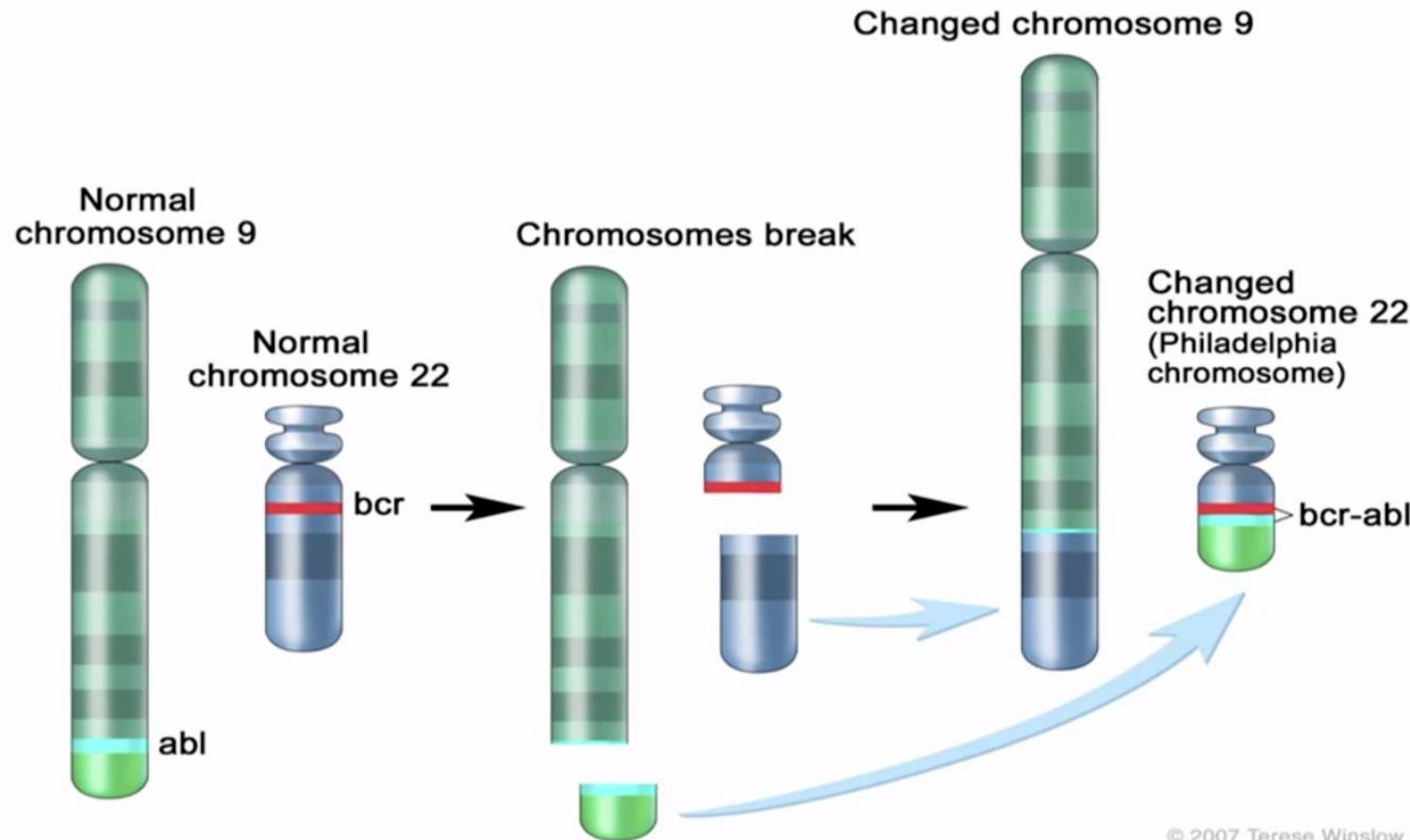
Philadelphia Chromosome



each of these chromosomes that
separate each chromosome into two.

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Philadelphia Chromosome

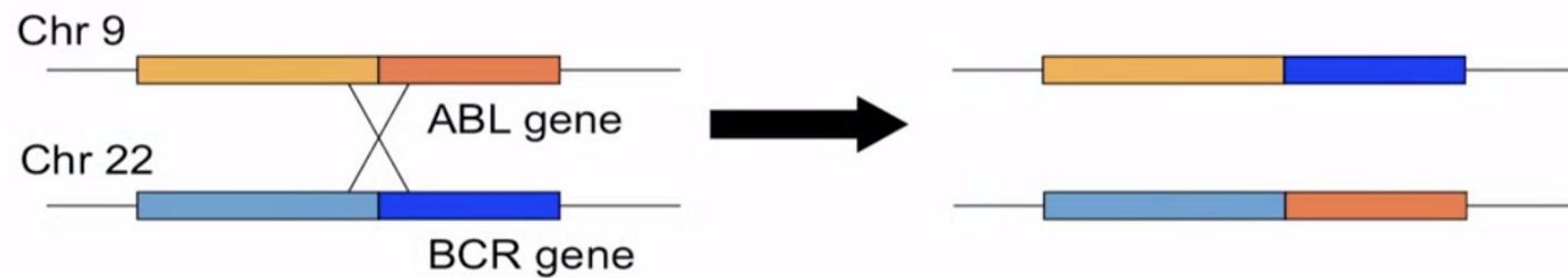


a new order resulting in new chimeric
Oncogenic bcr-abl fusion gene.
chromosomes.
biomarker for chronic myeloid leukemia (CML)

© 2007 Terese Winslow
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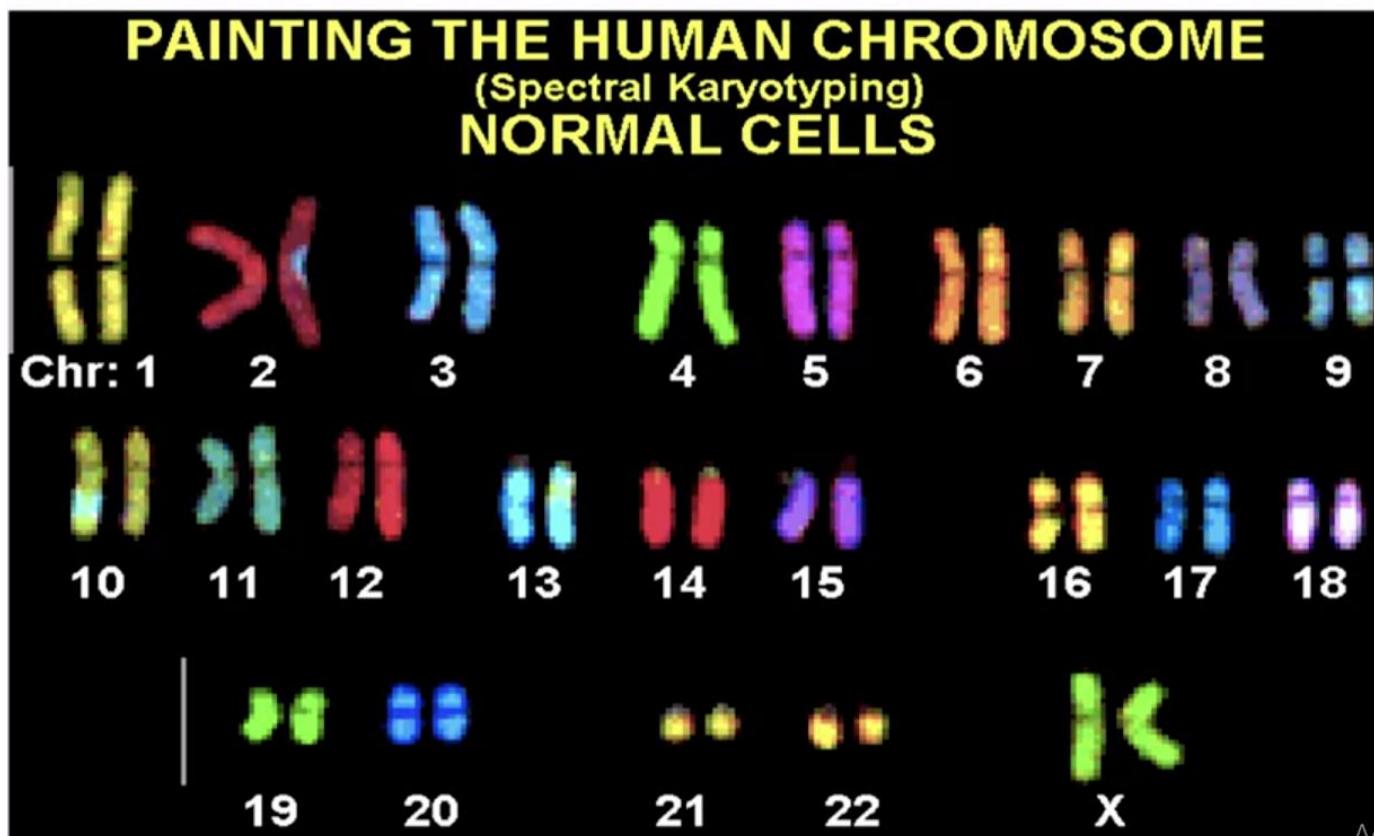
Translocations

Translocation in CML yields Philadelphia chromosome:

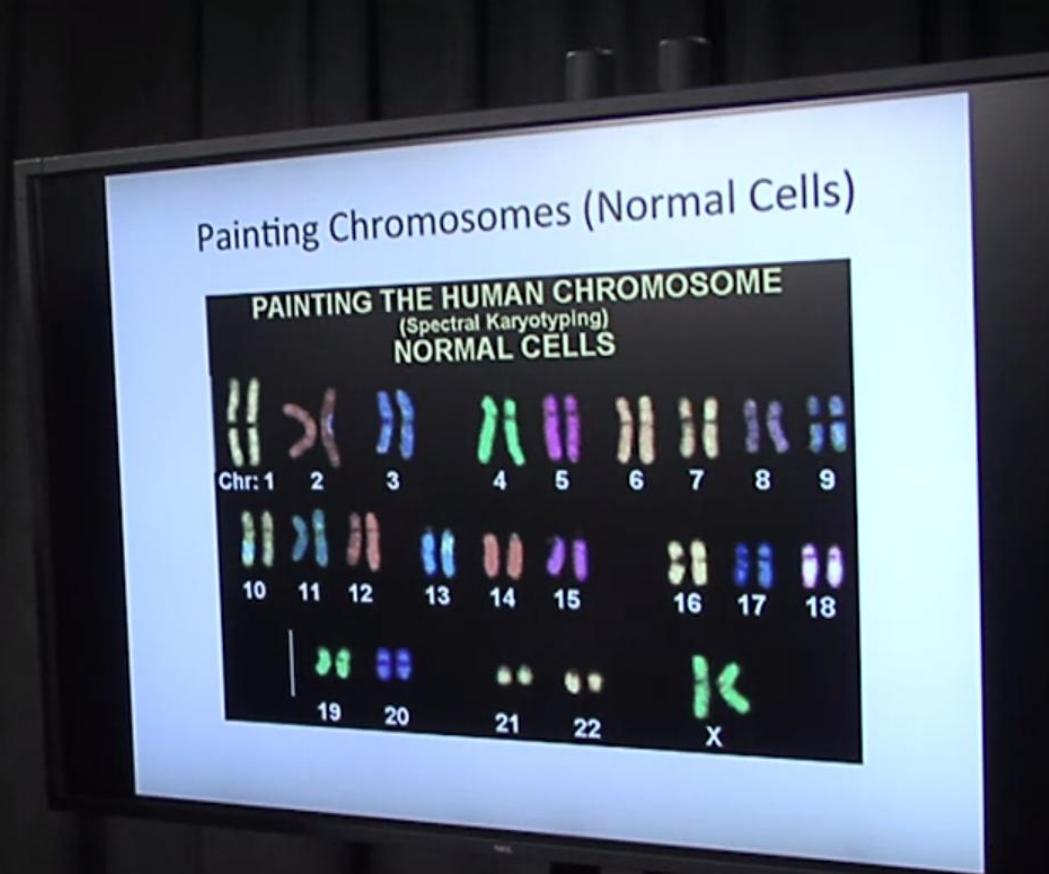


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Painting Chromosomes (Normal Cells)



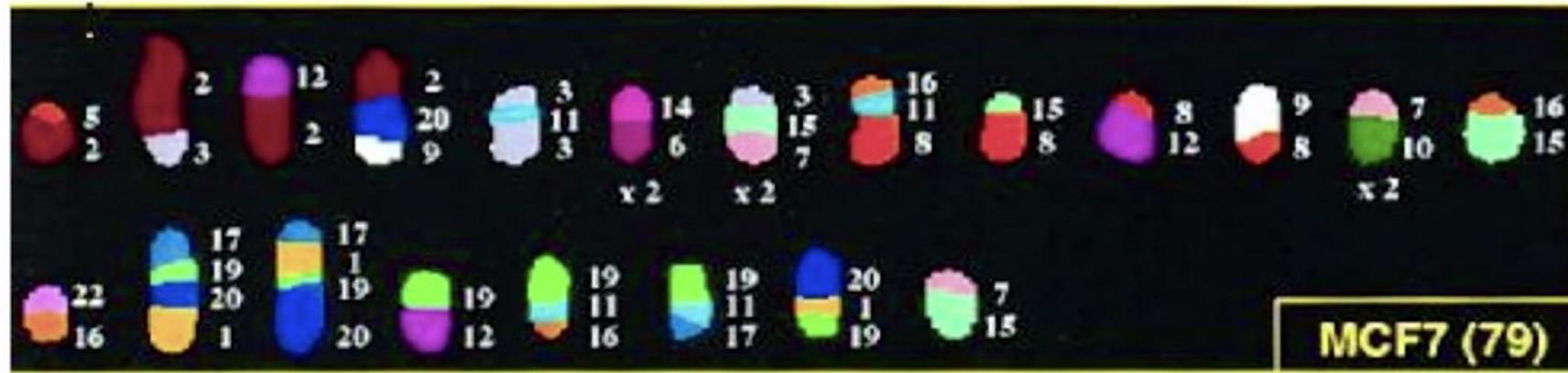
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Activate Windows
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Painting Chromosomes (Tumor Cells)

- MCF7 is human breast cancer cell line:



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Painting Chromosomes (Tumor Cells)

- MCF7 is human breast cancer cell line:



A karyogram showing the chromosomal rearrangements in MCF7 tumor cells. The chromosomes are arranged in two rows, with pairs labeled x 2. The chromosomes are color-coded and labeled with their corresponding human chromosome numbers. The karyogram shows various rearrangements, including inversions and translocations. In the bottom right corner, a green box contains the text "MCF7 (79)".

What sequence of rearrangements has produced MCF7?

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Rearrangements in Multichromosomal Genomes

translocations

Before translocation

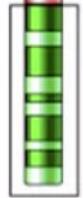


Chromosome 20

After translocation



Derivative Chromosome 20



Chromosome 4

$(+5 +9 +4 +8)$
 $(-6 -1 +7 -2)$

Chromosome 4

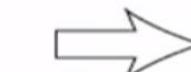
$(+5 +9 +7 -2)$
 $(-6 -1 +4 +8)$

fusions and fissions



Chromosome 4

Chromosome 20



$(1 2 3 4 5)$

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$(1 2)$
 $(3 4 5)$



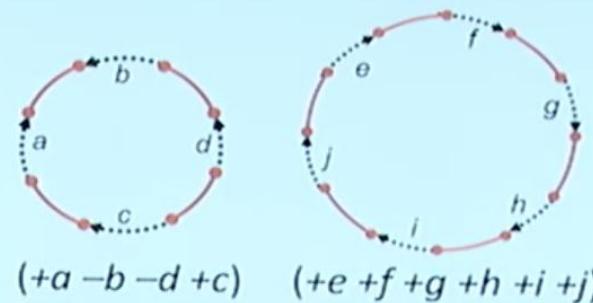
Are There Fragile Regions in the Human Genome?

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- Breakpoint Graphs
- 2-Break Distance Theorem
- Rearrangement Hotspots in the Human Genome
- Synteny Block Construction

to address their question of how

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From Linear to Circular Chromosomes

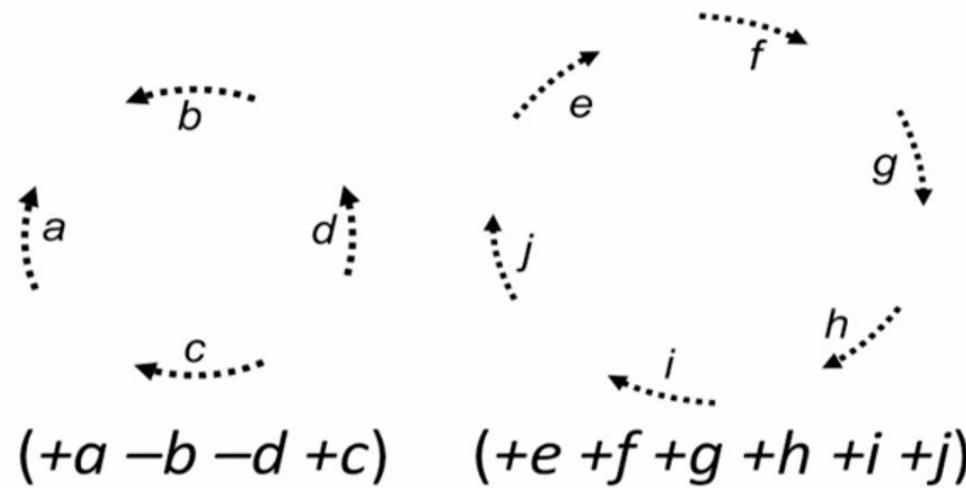


Black directed edges represent synteny blocks.
Red undirected edges connect adjacent synteny blocks.

two cycles.

These cycles, important, they have

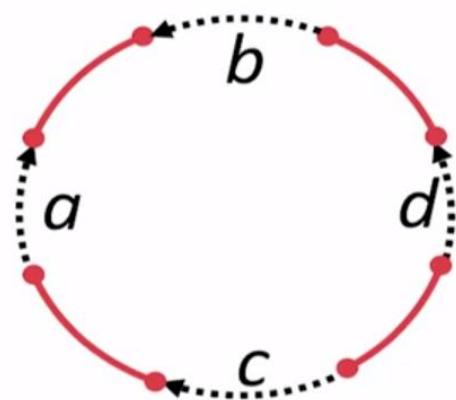
From Linear to Circular Chromosomes



Black directed edges represent synteny blocks.

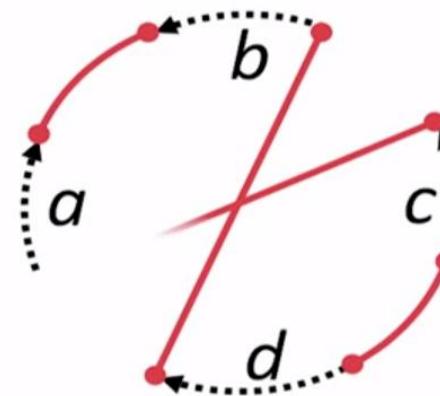
For example, +a, -b, -d, +c
will be arranged as four edges

Equivalent Representations of a Circular Genome



$$Q = (+a - b - d + c)$$

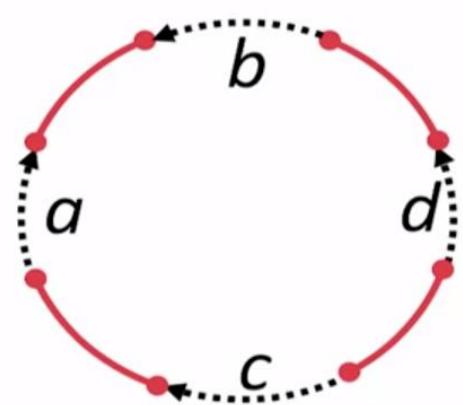
=



$$Q = (+a - b - d + c)$$

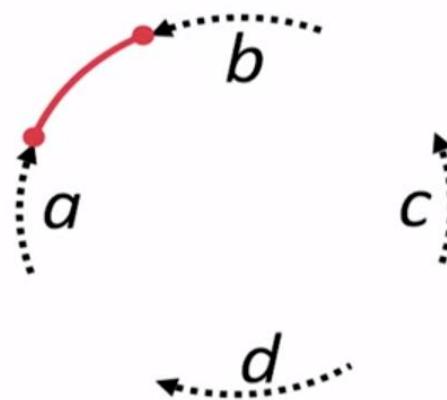
And after -d, we should go to +c,
and finally to +a.

Equivalent Representations of a Circular Genome



$$Q = (+a - b - d + c)$$

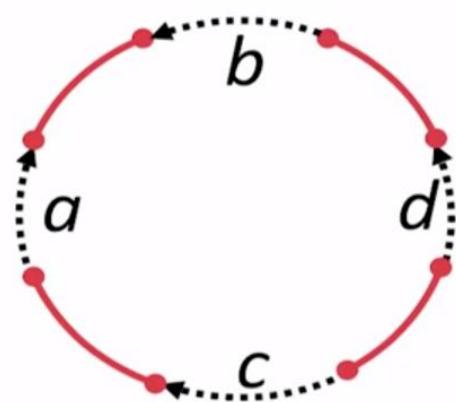
=



$$Q = (+a - b - d + c)$$

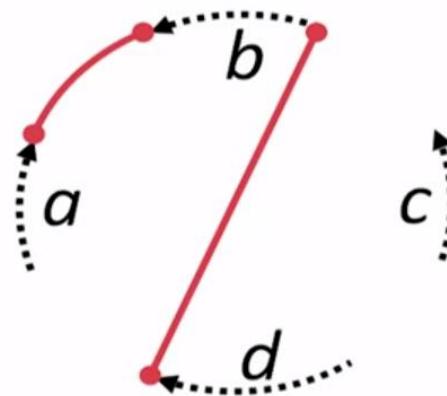
That's what we do.
After -b,

Equivalent Representations of a Circular Genome



$$Q = (+a - b - d + c)$$

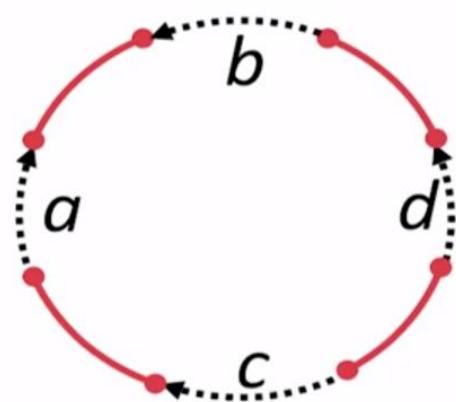
=



$$Q = (+a - b - d + c)$$

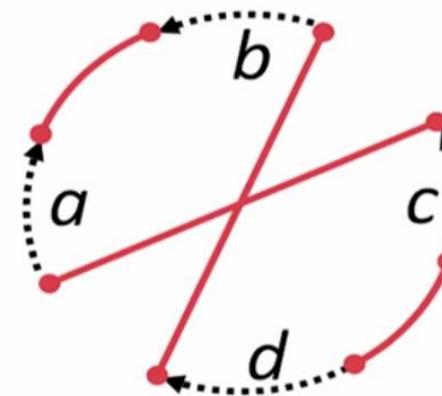
you should go to $-d$, that's what we do.

Equivalent Representations of a Circular Genome



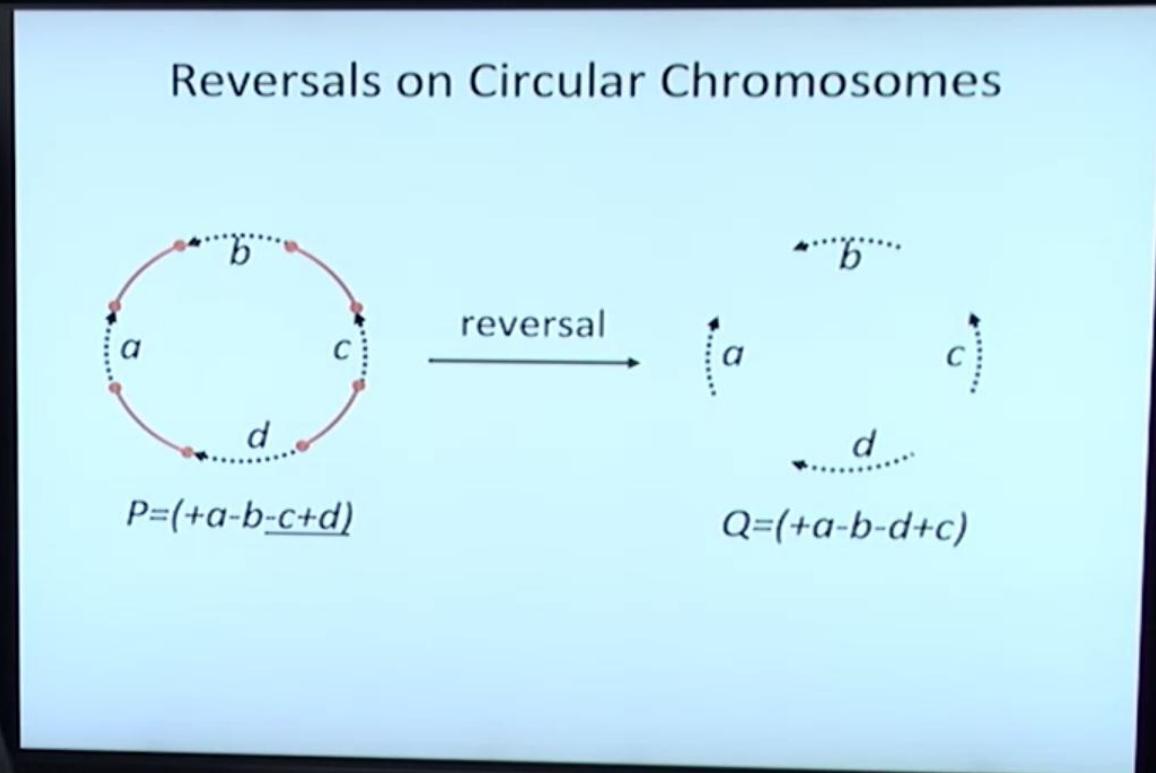
$$Q = (+a - b - d + c)$$

=



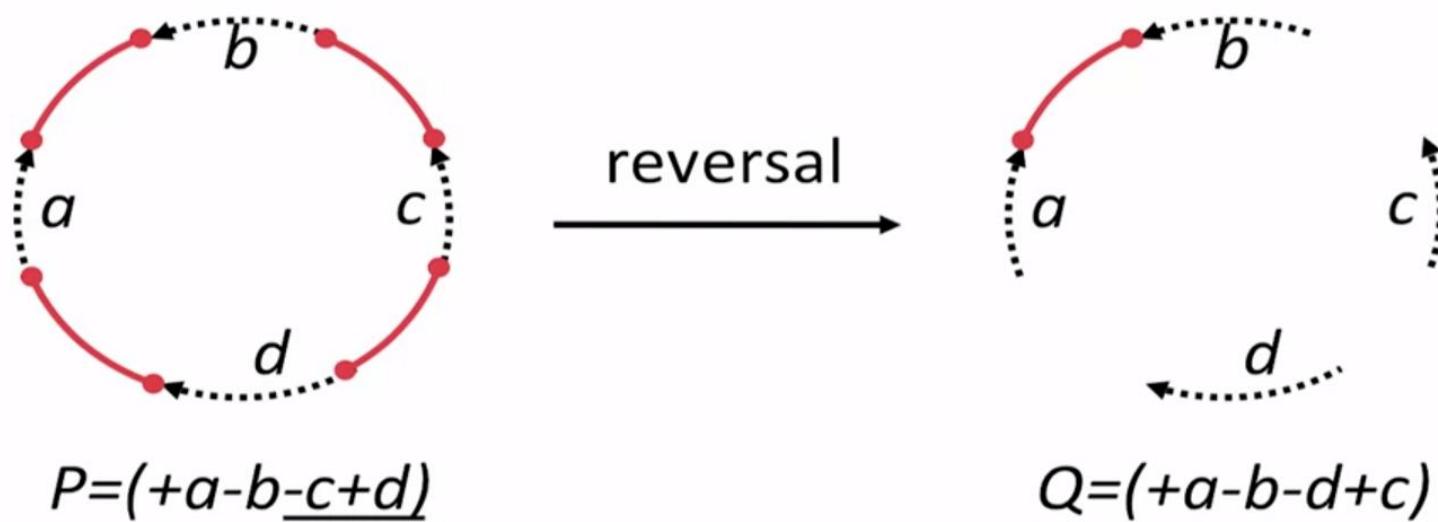
$$Q = (+a - b - d + c)$$

And after $-d$, we should go to $+c$,
and finally to $+a$.



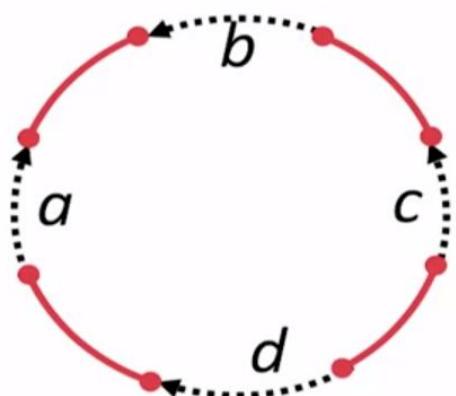
Now let's try to figure out how a reversal looks like in terms of these graphs.

Reversals on Circular Chromosomes



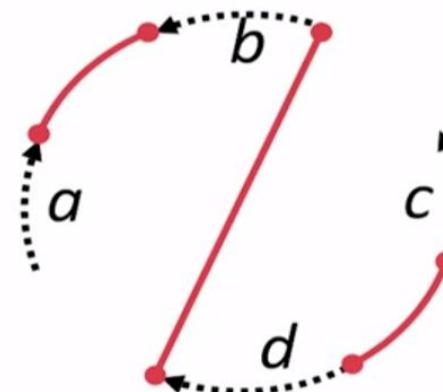
Well, after $+a$ we should go to $-b$,
after $-b$ we should go to $-d$

Reversals on Circular Chromosomes



$$P = (+a - b - \underline{c} + d)$$

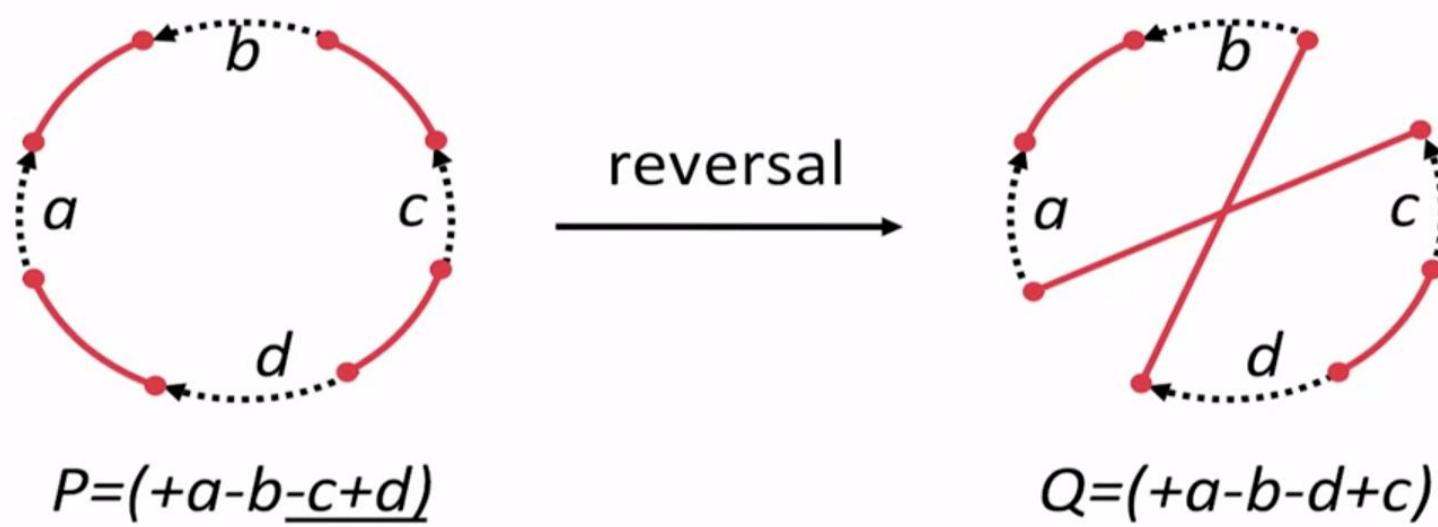
reversal



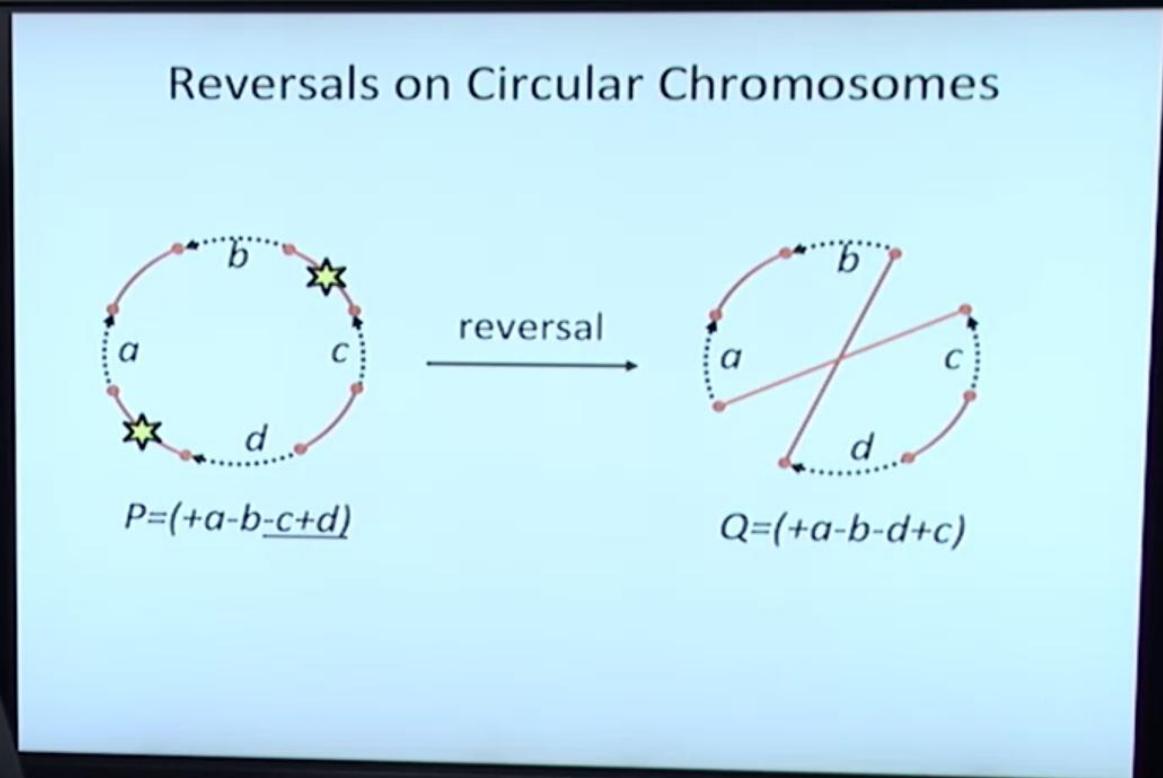
$$Q = (+a - b - d + c)$$

after $-d$ we should go to $+c$
and finally from $+c$ we should go to $+a$

Reversals on Circular Chromosomes

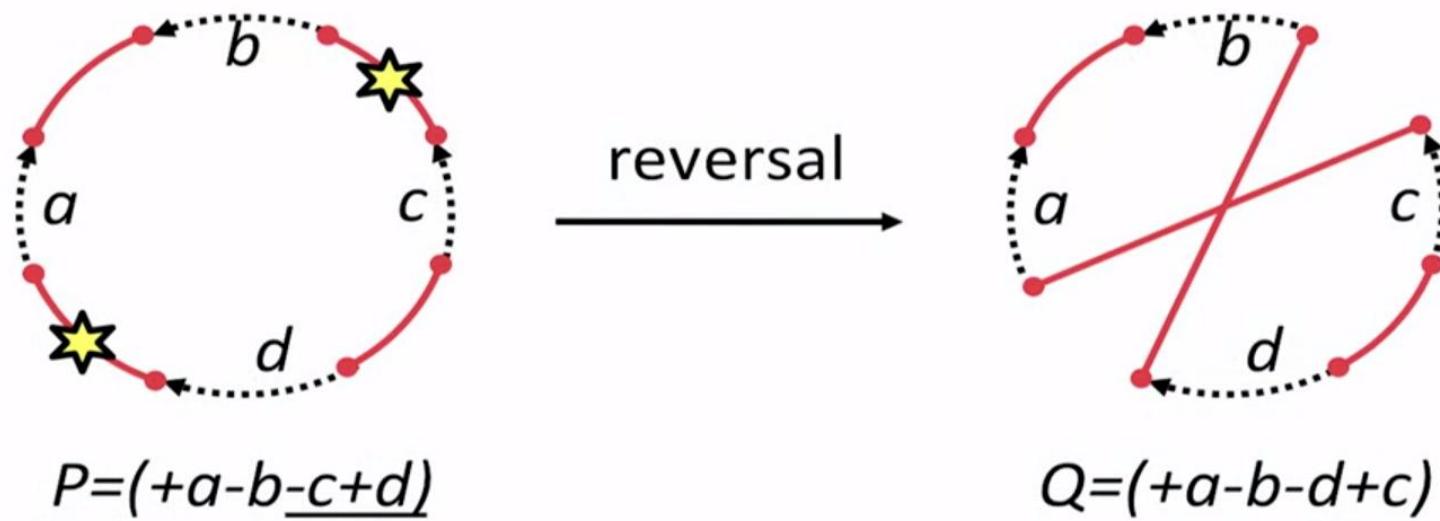


So, therefore a transformation of genome P



two red edges.
And it adds two new red edges.

Reversals on Circular Chromosomes

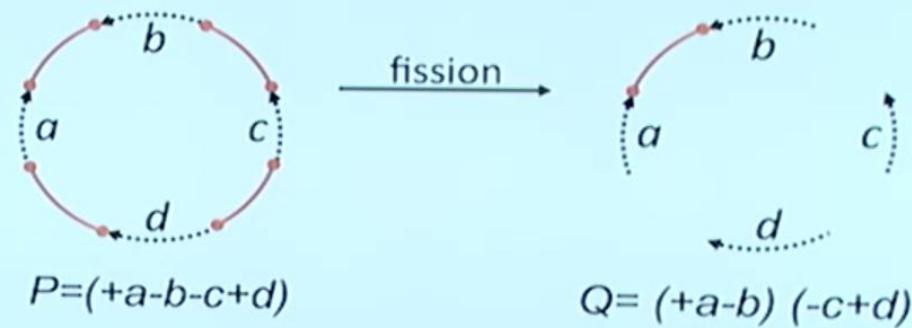


A reversal deletes two red edges and replaces them by two other red edges (on the same 4 nodes)

**It deletes two red edges and replaces them
by two other red edges on the same**



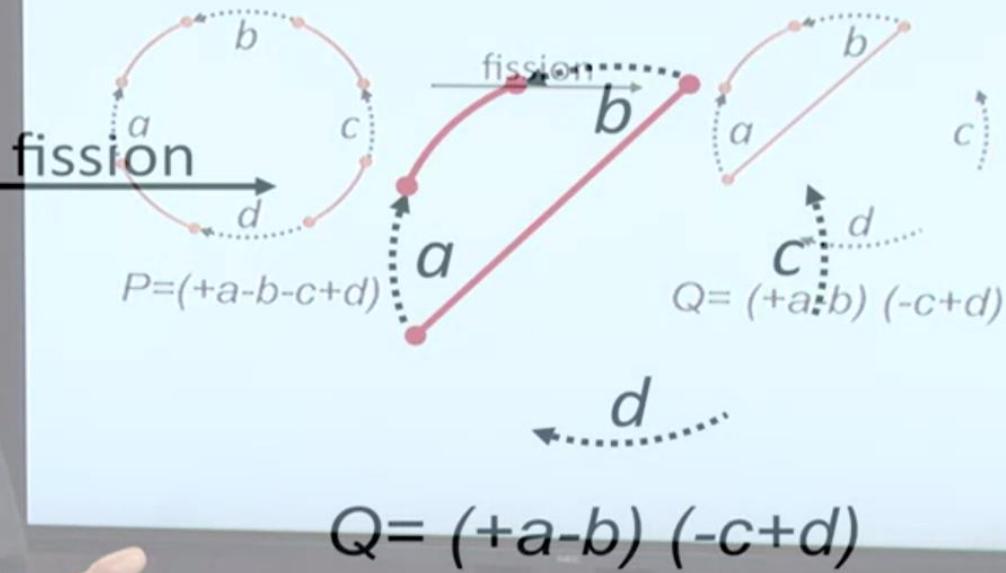
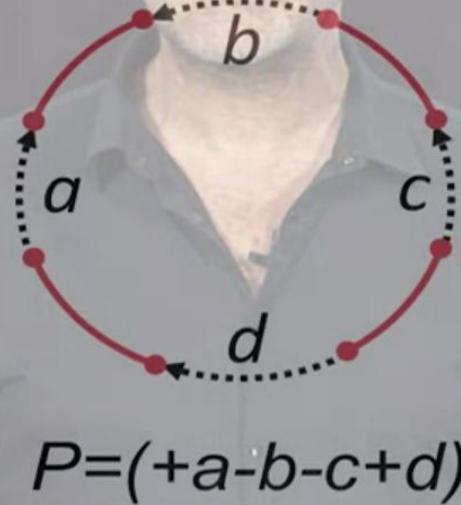
Fusion/Fission as Replacement of Two Red Edges



and from $-b$, we should go to $+a$,
so it will look like this.

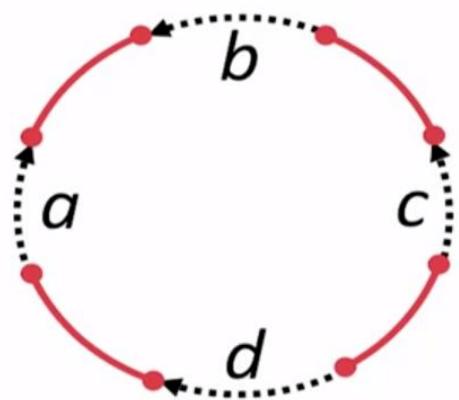
Fusion/Fission as Replacement of Two Red Edges

Fusion/Fission as Replacement of Two Red Edges



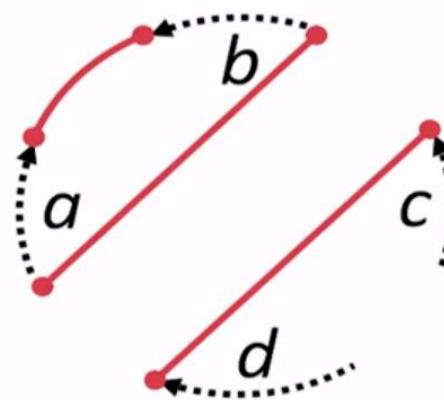
and from $-b$, we should go to $+a$,
so it will look like this.

Fusion/Fission as Replacement of Two Red Edges



$$P = (+a - b - c + d)$$

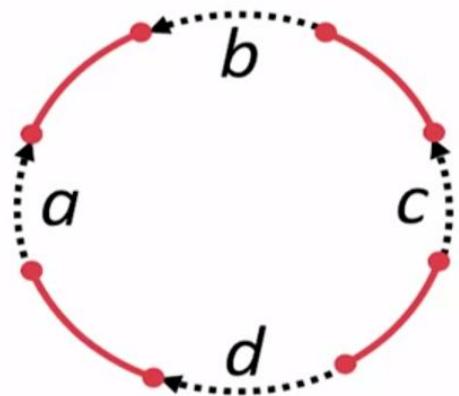
fission



$$Q = (+a - b) (-c + d)$$

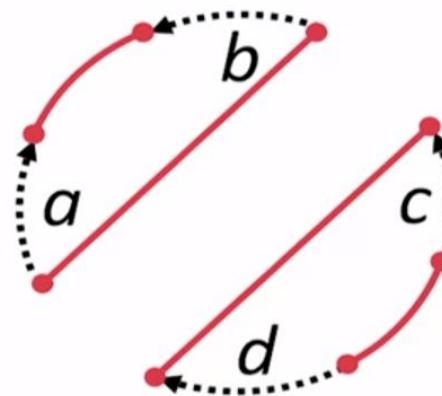
And also from -c

Fusion/Fission as Replacement of Two Red Edges



$$P = (+a - b - c + d)$$

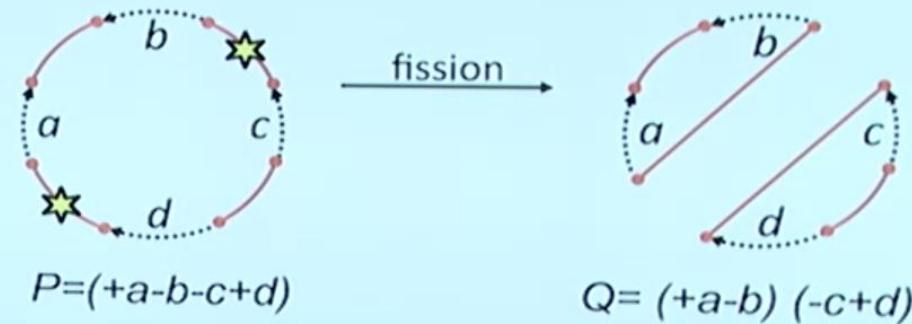
fission



$$Q = (+a - b) (-c + d)$$

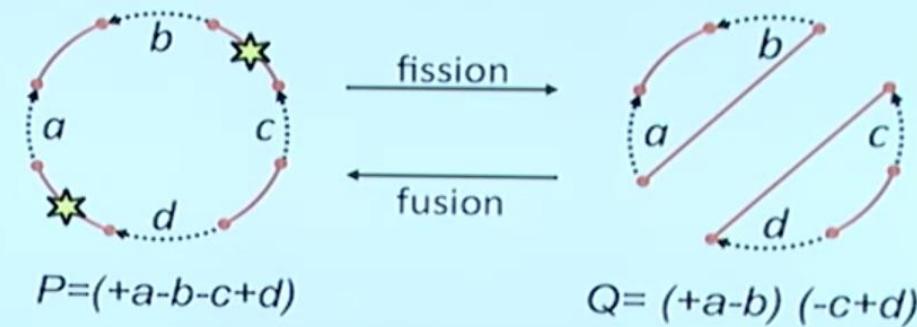
So you see that geometrically also a

Fusion/Fission as Replacement of Two Red Edges

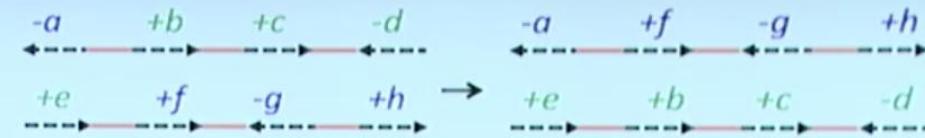


Once again, we remove two red edges and add two new red edges.

Fusion/Fission as Replacement of Two Red Edges

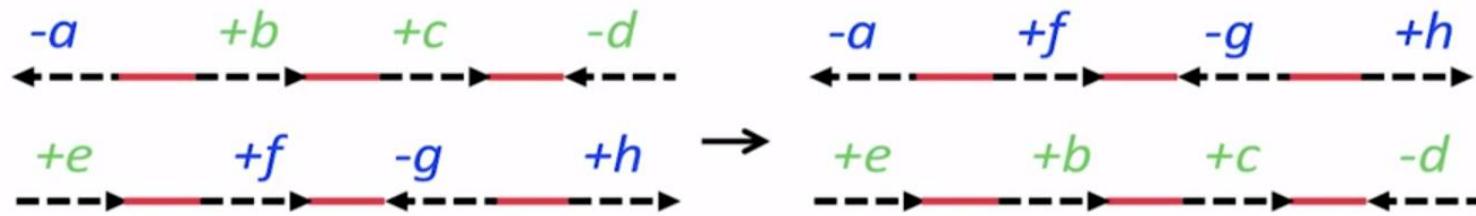


in the case of fusion, the reverse operation, we would



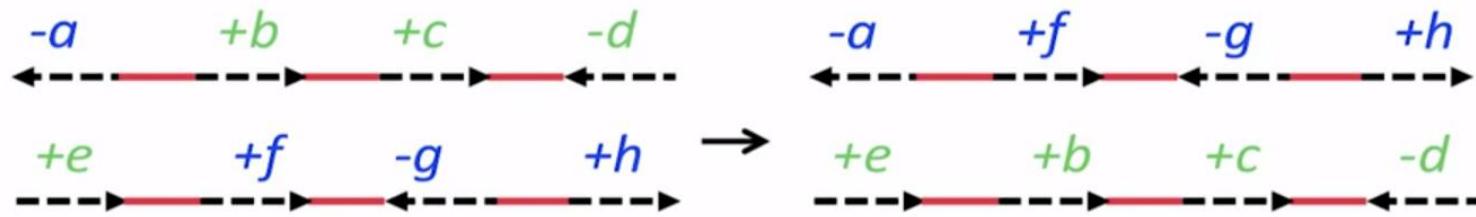
Translocation on linear chromosomes

It's the same story.
Here are two linear chromosomes that after

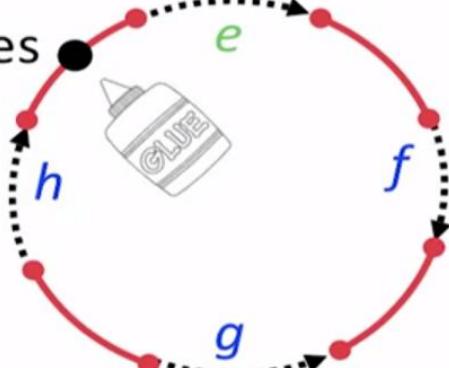


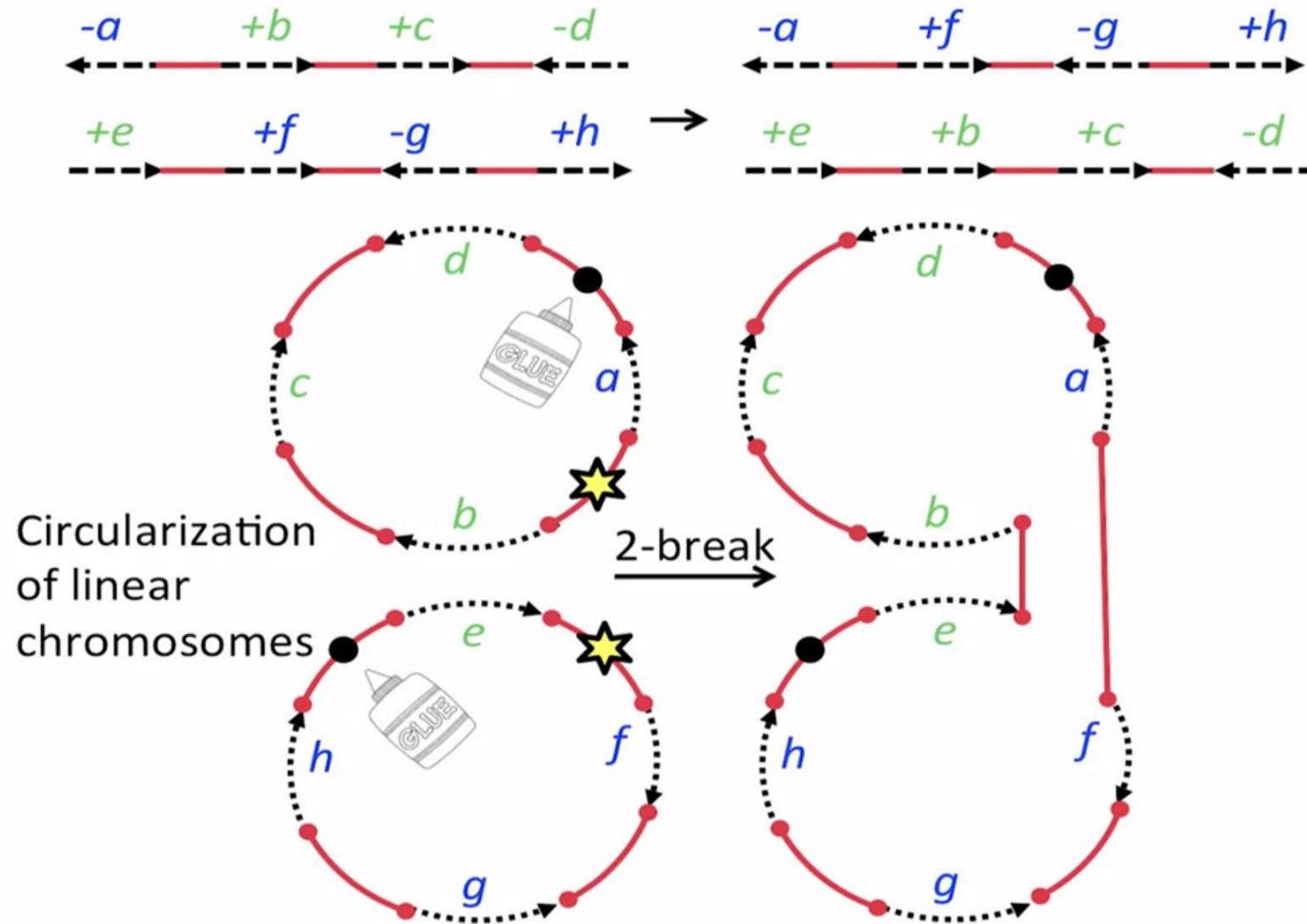
Circularization
of linear
chromosomes

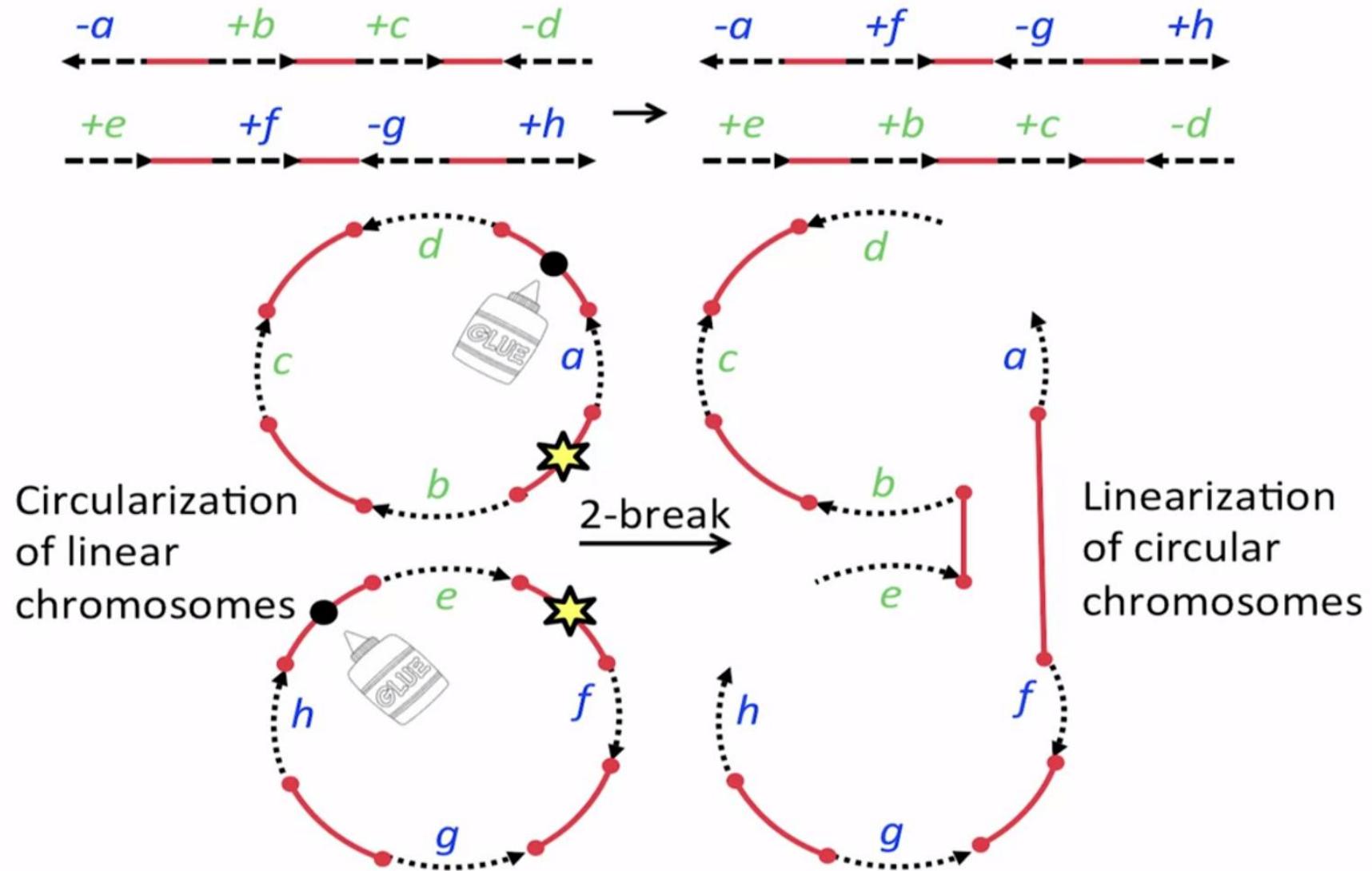
Let's circularize them by just gluing the
ends using one of the red edges.

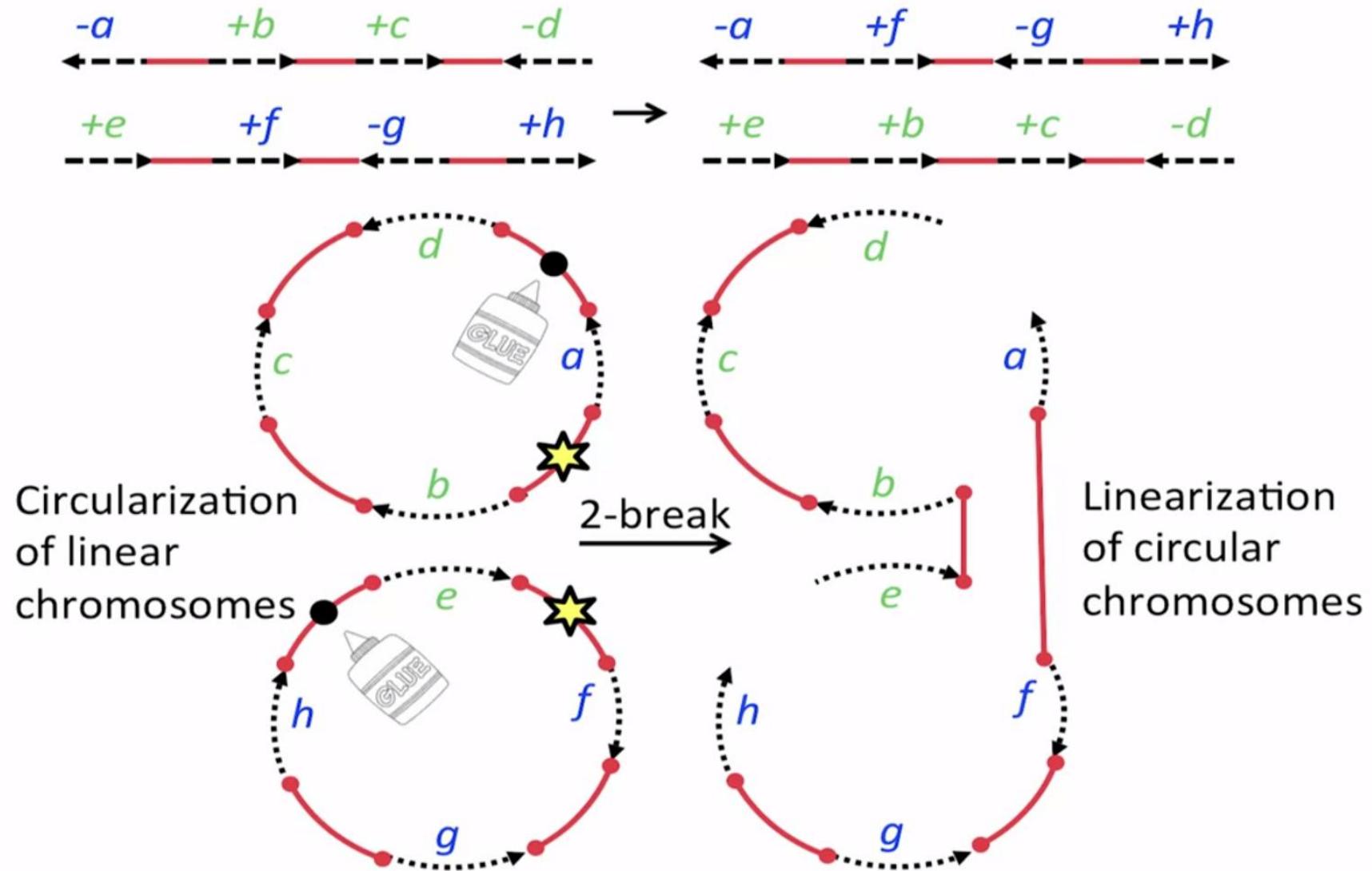


Circularization
of linear
chromosomes









2-Break Distance

2-Break distance $d(P, Q)$:

minimum number of 2-breaks transforming genome P into genome Q

2-Break Distance Problem. Find the 2-break distance between two genomes.

- **Input.** Two genomes on the same set of synteny blocks.
- **Output.** The 2-break distance between these genomes.