Multi-Break Rearrangements: from Circular to Linear Genomes

Max Alekseyev

University of South Carolina

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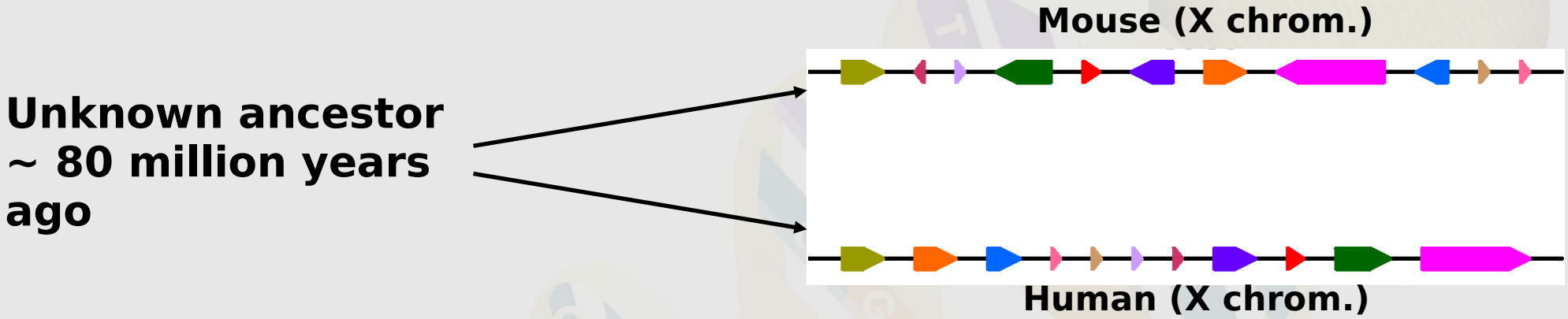
Genome Rearrangements



- What is the evolutionary scenario for transforming one genome into the other?
- Are there any rearrangement hotspots in mammalian genomes?

Random Breakage Model (RBM)

- **Random Breakage Model** (*Ohno, 1970*): Genomic architectures are shaped by rearrangements that occur randomly.

- *Nadeau & Taylor, 1984* gave first convincing arguments in favor of the RBM

- The random breakage hypothesis was embraced by biologists and has become *de facto* theory of chromosome evolution.

- RBM implies that there is no rearrangement hotspots

Rebuttal of RBM

- ✔ Pevzner & Tesler, *PNAS 2003*, rejected RBM in favor of **Fragile Breakage Model (FBM)** that postulates existence of *rearrangement hotspots* and *vast breakpoint reuse*.

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- ✔ *Sankoff & Trinh, 2004, presented arguments against Fragile Breakage Model:* ***"… we have shown that breakpoint re-use of the same magnitude as found in Pevzner and Tesler, 2003 may very well be artifacts in a context where NO re-use actually occurred."***

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- ✔ *Peng et al., 2006,* found an error in Sankoff-Trinh arguments: ***"If Sankoff & Trinh fixed their ST-Synteny algorithm, they would confirm rather than reject Pevzner-Tesler's Fragile***

Random Breakage Model: Controversy Continues...

The rebuttal of the RBM led to a split among researchers:

- ✔ *Kikuta et al., 2007:* ***"... the Nadeau and Taylor hypothesis is not possible for the explanation of synteny in general."***
- ✔ *Ma et al., 2006:* ***"Simulations ... suggest that this frequency of breakpoint reuse is approximately what one would expect if breakage was equally likely for every genomic position ..."***

Recent studies supporting Fragile Breakage Model:

- ✗ *van der Wind, 2004*
- ✗ *Bailey, 2004*
- ✗ *Zhao et al., 2004*
- ✗ *Murphy et al., 2005*
- ✗ *Hinsch & Hannenhalli, 2006*
- ✗ *Ruiz-Herrera et al., 2006*
- ✗ *Yue & Haaf, 2006*
- ✗ *Mehan et al., 2007*

Random Breakage Model and Complex Rearrangements

- Sankoff, *2006*, claims that some complex rearrangement operations (like transpositions) may cause an appearance of fragile regions in the Pevzner-Tesler analysis.

- The rebuttal of RBM does not apply when there is a significant presence of complex rearrangements (in fact, that was acknowledged in Pevzner & Tesler, *PNAS 2003*).

Random Breakage Model Debate: Algorithmic Challenge

- ✔ Algorithmic theory for transpositions remains undeveloped, thus, making analysis of breakpoint reuse difficult.

- ✔ We bypass this challenge by introducing more general multi-break rearrangements and solving the multi-break distance problem.

- ✔ The standard rearrangement operations (reversals, translocations, fusions, and fissions) make *2 breaks* in a genome and glue the resulting pieces in a new order.

- ✔ *k*-Break rearrangement operation makes *k breaks* in a genome and glues the resulting pieces in a new order. Transpositions represent 3-breaks.

Random Breakage Model Debate: Our Contribution

- ✔ **Algorithmic analysis of k-breaks**. The duality theorem for the multi-break distance problem and a linear-time algorithm for the computing multi-break distance.
  (**Theoretical Computer Science, 2007**)

- ✔ **Analysis of breakpoint re-use in the case of k-breaks**. For $k=3$ (the most relevant case in evolutionary studies), we showed that even if *3*-break rearrangements were frequent, the Pevzner-Tesler argument against RBM still stands.
  (**PLoS Computational Biology, 2007**)

Multi-Breaks and Linear Genomes: Algorithmic Challenges

- ✔ The above results address the case of circular genomes (in which every chromosome is circular) but not the (more relevant) case of linear genomes.
- ✔ Multi-break rearrangements in linear genomes are much harder to analyze than in circular genomes.
- ✔ This work extends results from Alekseyev & Pevzner, *Theor. Comput. Sci. 2007* and *PLoS Comput. Biol. 2007*, to linear genomes.

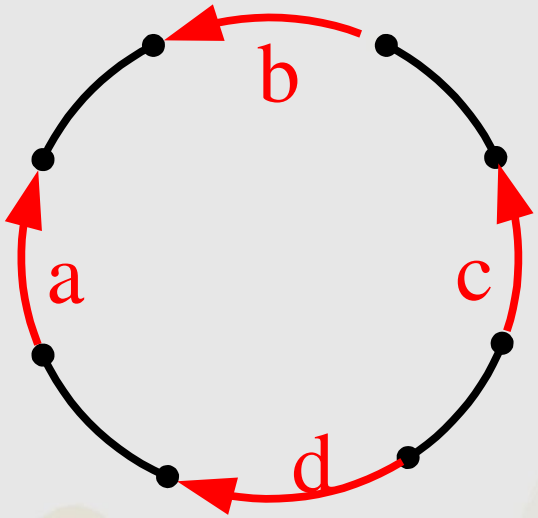
Genome Rearrangements

Genomic Distance Story

- **Genomic Distance** between two genomes is the minimum number of *reversals*, *translocations*, *fusions*, and *fissions* required to transform one genome into the other.

- Hannenhalli and Pevzner (FOCS 1995) were first to give a polynomial-time algorithm for computing the reversal distance (between unichromosomal genomes)
- Hannenhalli and Pevzner (STOC 1995) further extended their algorithm to computing the genomic distance (between multichromosomal genomes)
- These algorithms were followed by many improvements: *Kaplan et al. 1999, Bader et al. 2001, Tannier & Sagot 2001, Tesler 2002, Ozery-Flato & Shamir 2003, Bergeron 2001-07, etc.*
- Nearly all rearrangement studies are based on the notion of the breakpoint graph introduced by Bafna and Pevzner (FOCS 1994)

Representations of Circular Chromosomes

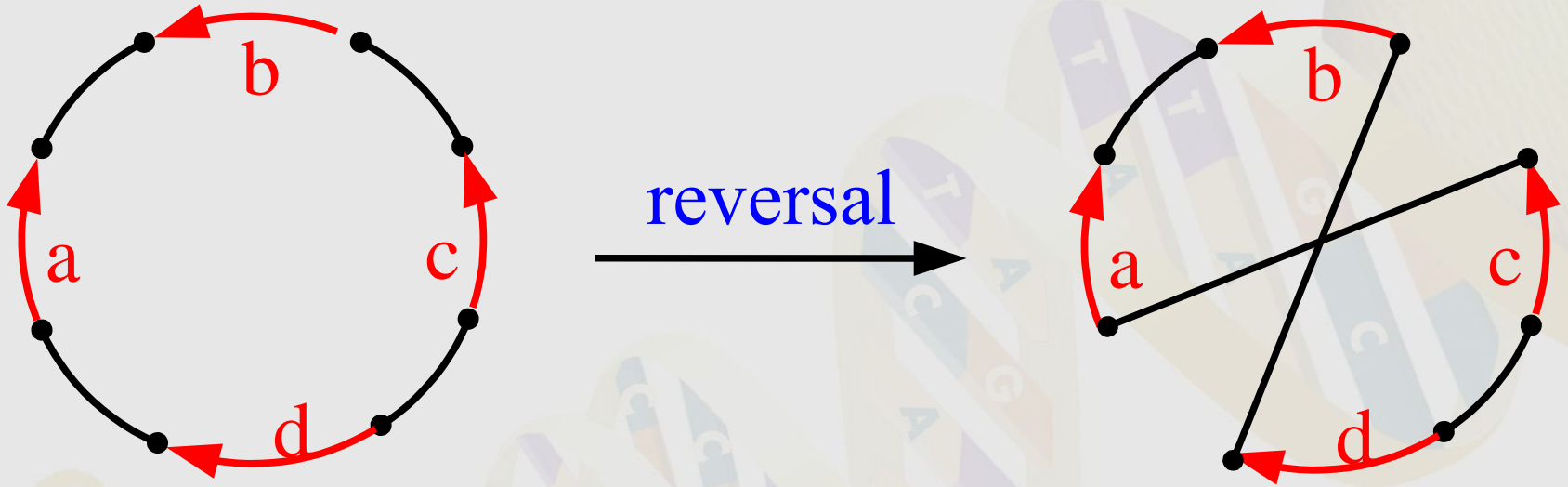


P=(+a−b−c+d)

A chromosome can be represented as:

- ✔ a cycle with directed red and undirected black edges, where red edges encode genes and adjacent genes are connected with black edges

Reversals on Circular Chromosomes

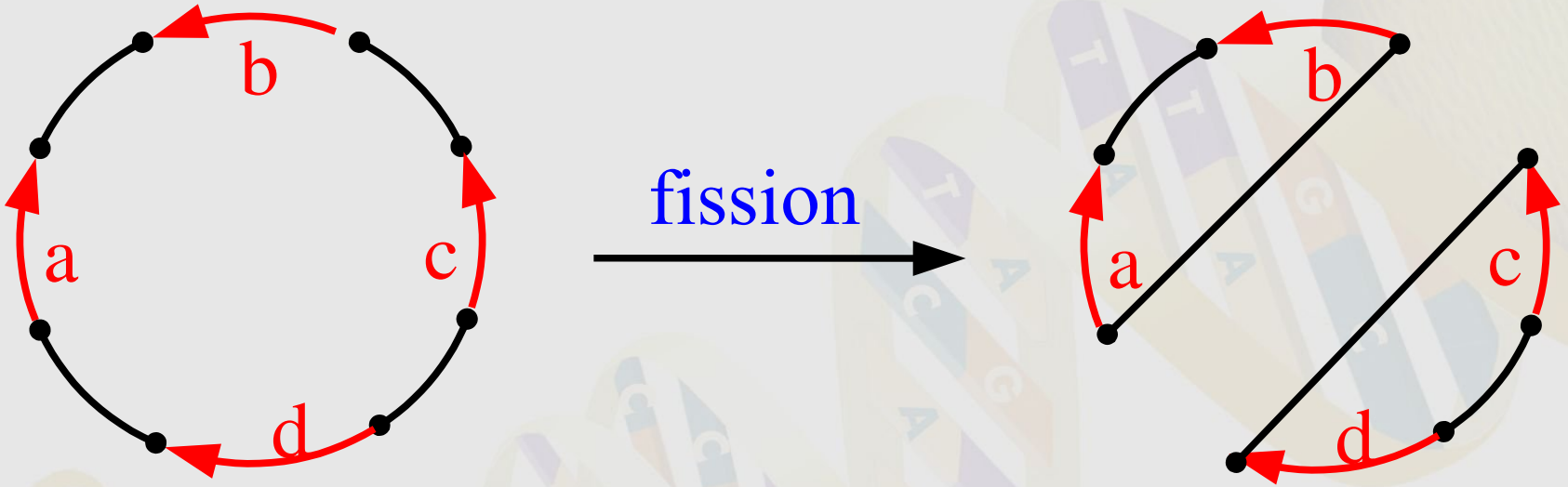


P=(+a−b−c+d)

Q=(+a−b−d+c)

Reversals replace two black edges with two other black edges

Fissions



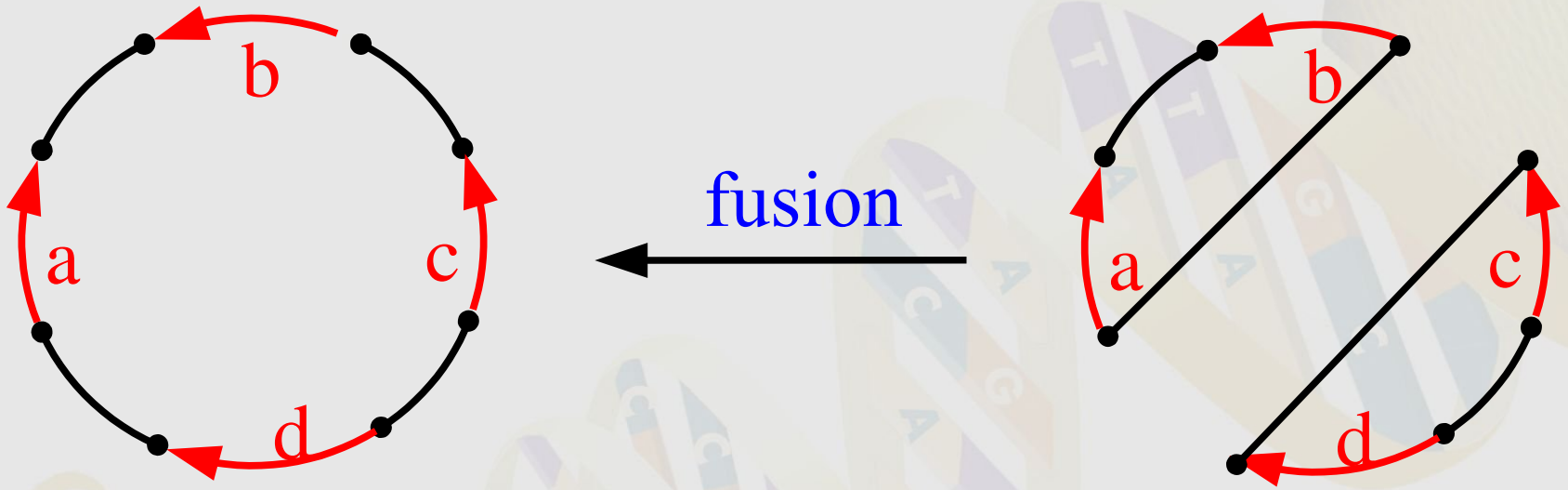
P=(+a−b−c+d)

Q=(+a−b)(−c+d)

Fissions split a single cycle (chromosome) into two.

Fissions replace two black edges with two other black edges.

Translocations / Fusions



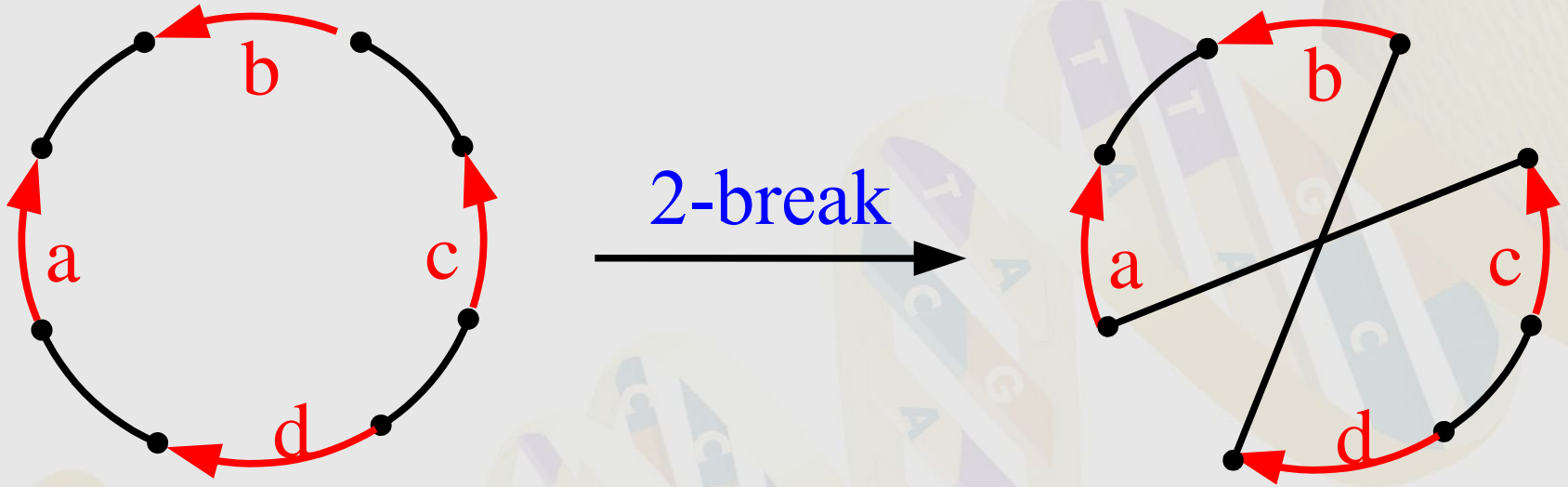
P=(+a−b−c+d)

Q=(+a−b)(−c+d)

Translocations/Fusions transform two cycles (chromosomes) into a single one.

They also replace two black edges with two other black edges.

2-Breaks



P=(+a−b−c+d)

Q=(+a−b−d+c)

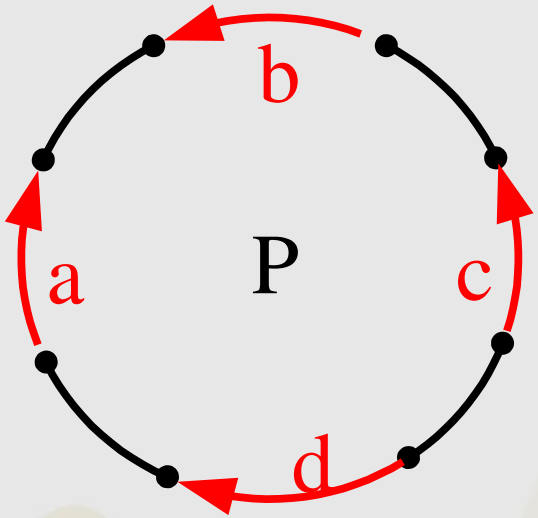
2-Break replaces *any pair* of black edges with another pair forming matching on the same 4 vertices.
Reversals, translocations, fusions, and fissions represent all different types of 2-breaks.

2-Break Distance

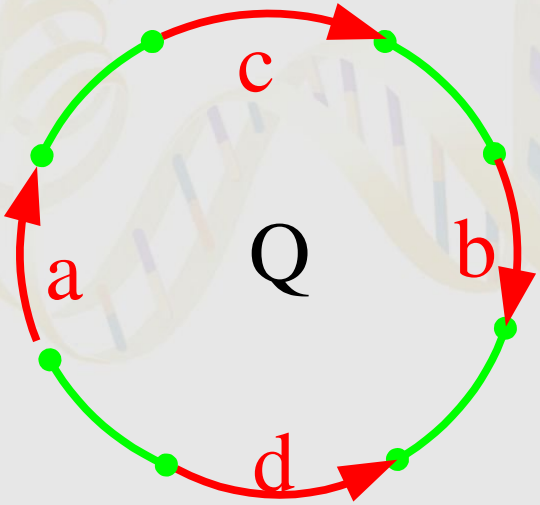
- The **2-Break distance** $d_2(P,Q)$ between circular genomes P and Q is the minimum number of 2-breaks required to transform P into Q.

- In difference from the genomic distance (between linear genomes), the 2-break distance (between circular genomes) is easy to compute.

Two Genomes as Black-Red and Green-Red Cycles

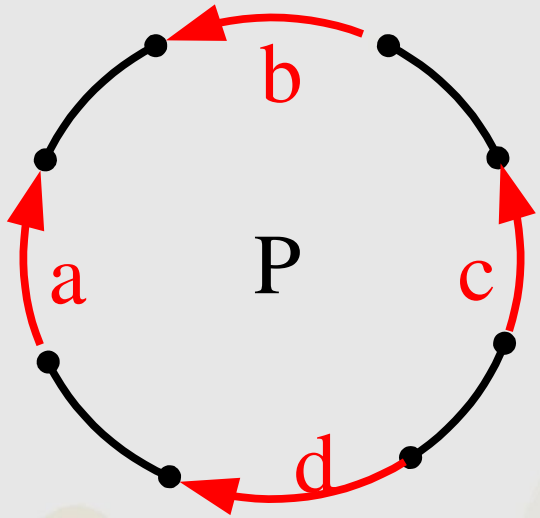


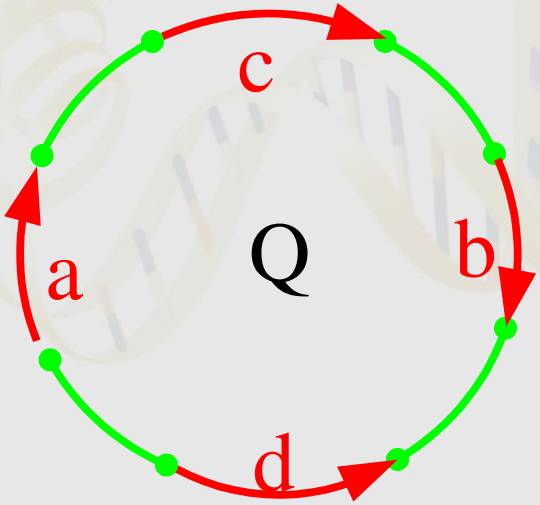
P=(+a−b−c+d)

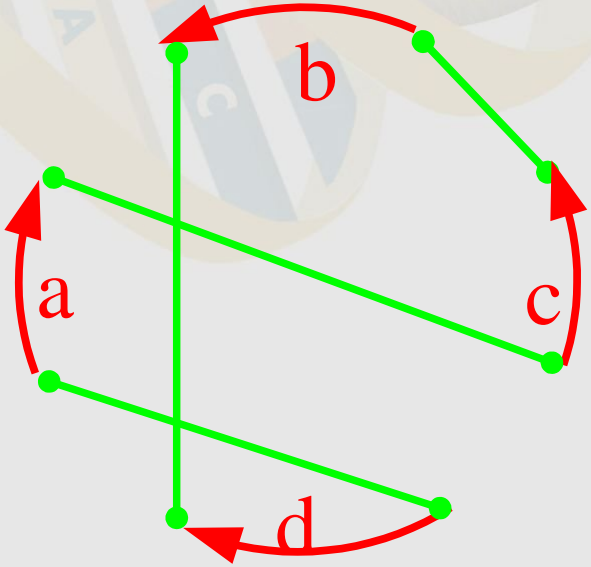


Q=(+a+c+b−d)

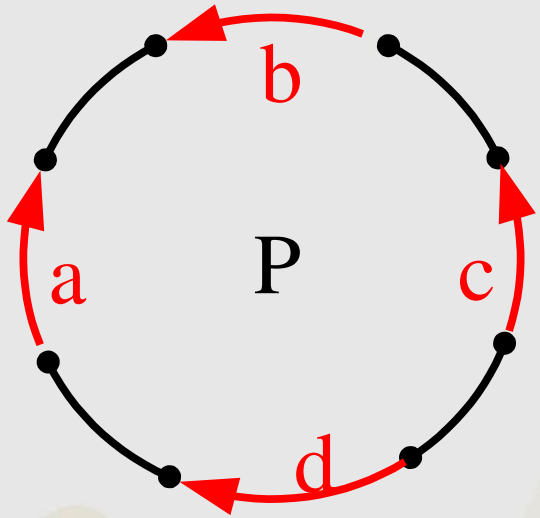
Rearranging Q in the P order

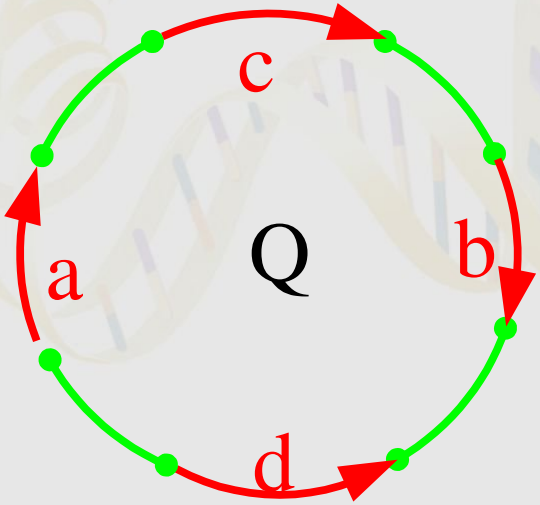




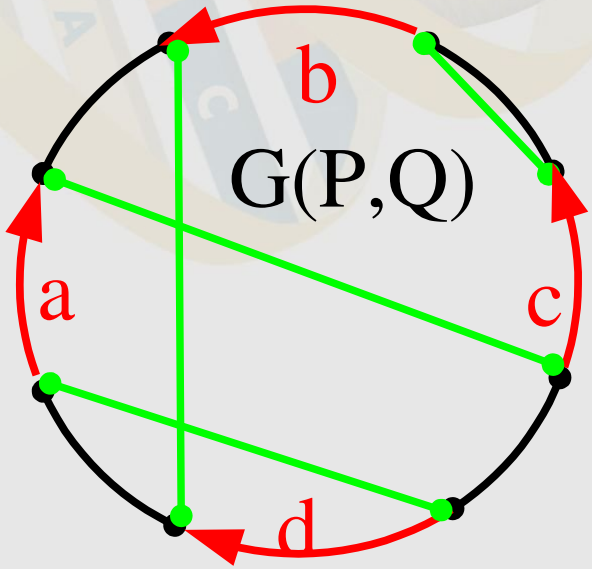


New Interpretation of the Breakpoint Graph: Gluing Red Edges with the Same Labels





Breakpoint Graph

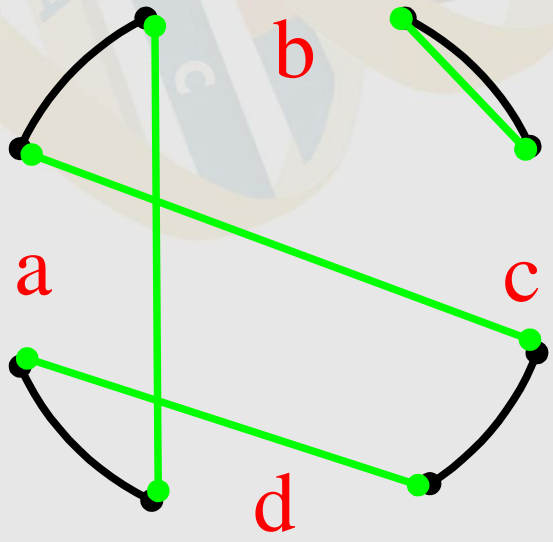


Black-Green Cycles

- Number of black-green cycles in the breakpoint graph:

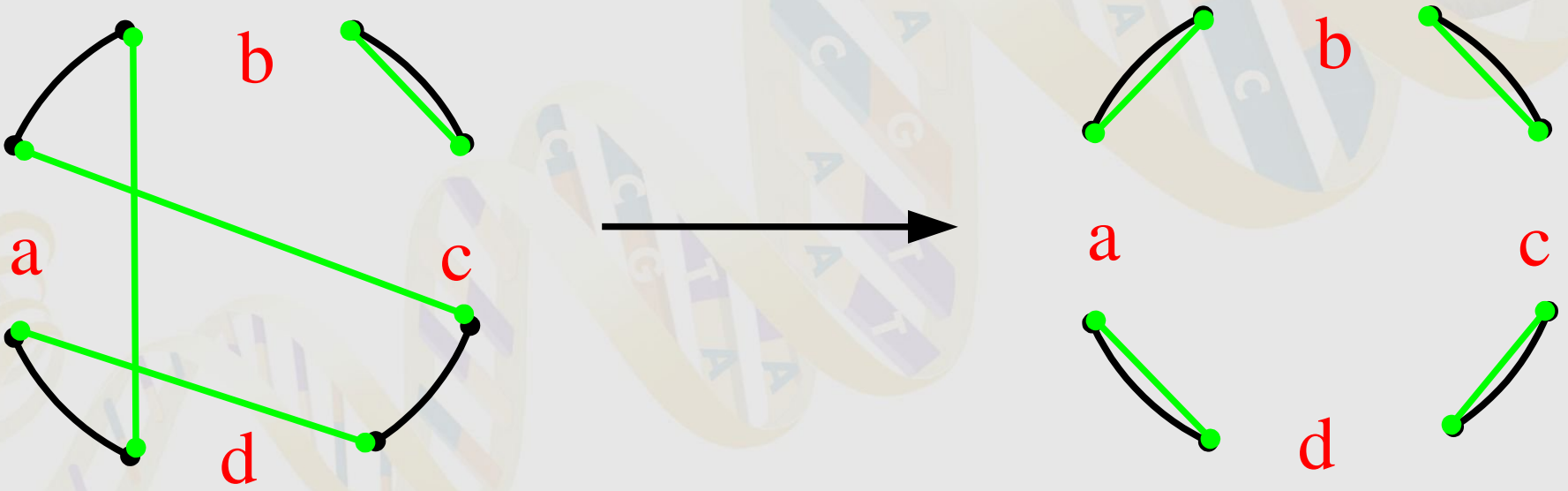
  cycle(P,Q)

  is the key parameter in computing the 2-break distance.



Rearrangements Change Cycles

Transforming genome Q into genome P by 2-breaks corresponds to transforming black-green cycles in G(P,Q) into *trivial cycles* in G(P,P).



cycle(P,Q)=2 cycles

cycle(P,P)= 4 *trivial* cycles

Sorting by 2-Breaks

$$Q=Q_0 \xrightarrow{\text{2-breaks}} Q_1 \rightarrow \ldots \rightarrow Q_d=P$$

$$G(P,Q) \rightarrow G(P,Q_1) \rightarrow \ldots \rightarrow G(P,P)$$

cycle(P,Q) cycles → ... → |P| cycles

# of black-green cycles increased by |P| - cycle(P,Q)

How much each 2-break can contribute to this increase?

Each 2-Break Increases #Cycles by at Most 1

A 2-Break:

- ✔ adds 2 new black edges and thus **creates** at most **2 new** cycles (containing two new black edges)
- ✔ removes 2 black edges and thus **destroys** at least **1 old** cycle (containing two old edges):

change in the number of cycles: $\Delta cycle \leq 2\text{-}1=1$.

2-Break Distance

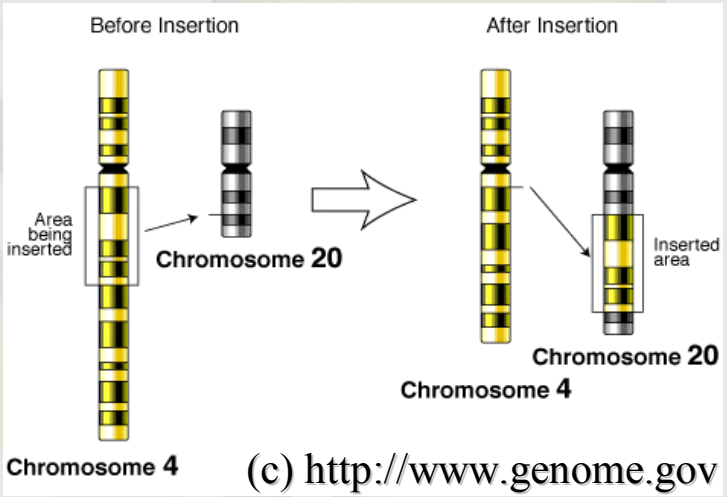
- ✔ Any 2-Break increases the number of cycles by at most one (**Δcycle $\leq$ 1**)
- ✔ Any non-trivial cycle can be split into two cycles with a 2-break (**Δcycle = 1**)
- ✔ Every sorting by 2-break must increase the number of cycles by **|P| - cycle(P,Q)**
- ✔ The **2-Break Distance** between genomes P and Q:

$$d_2(P,Q) = |P| - cycle(P,Q)$$

(cp. *Yancopoulos et al., 2005, Bergeron et al., 2006*)

Transpositions

- **Sorting by Transpositions:**
  Given two genomes, find the shortest sequence of transpositions transforming one genome into the other

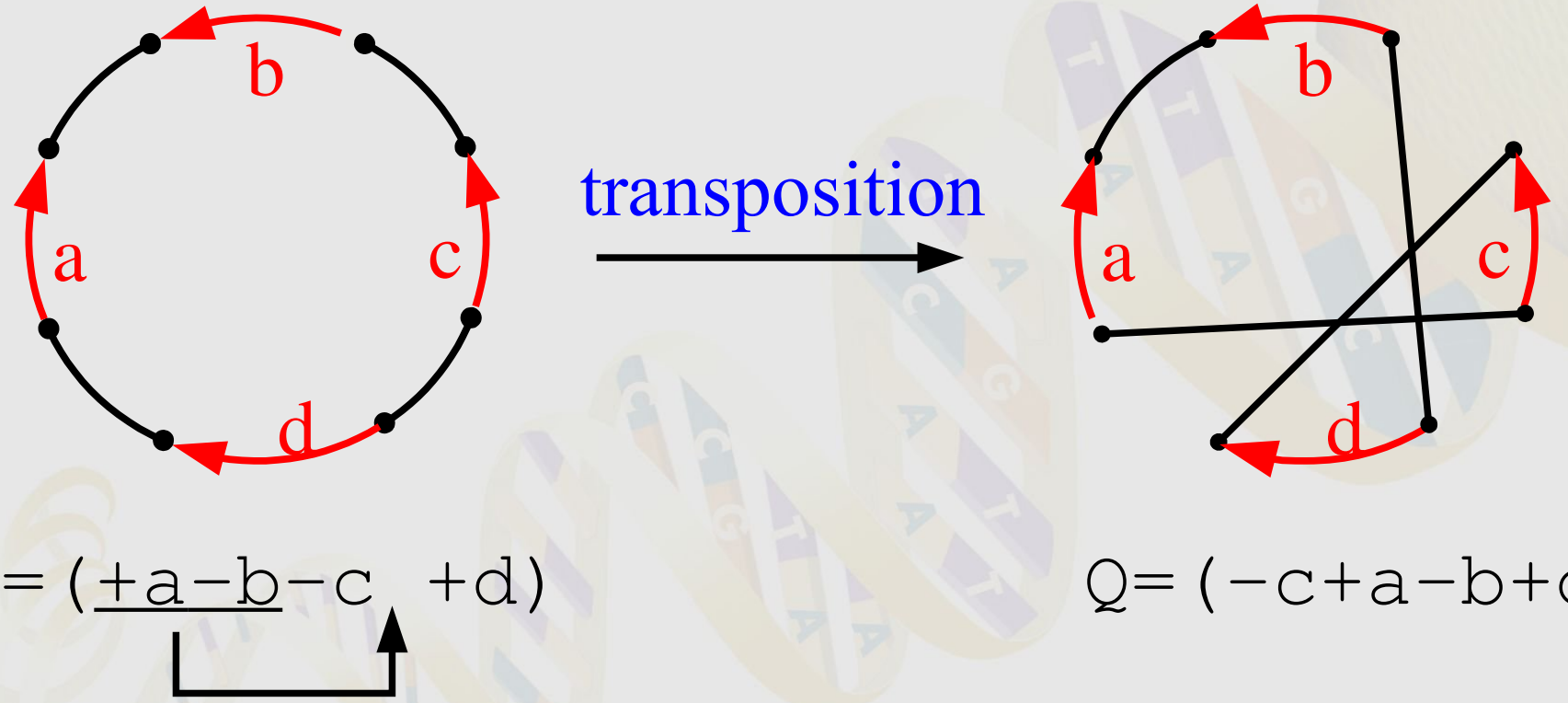


- First 1.5-approximation algorithm was given by Bafna and Pevzner (*SODA 1995*)

- Recent achievement: 1.375-approximation algorithm due to Elias and Hartman (*WABI 2005*)

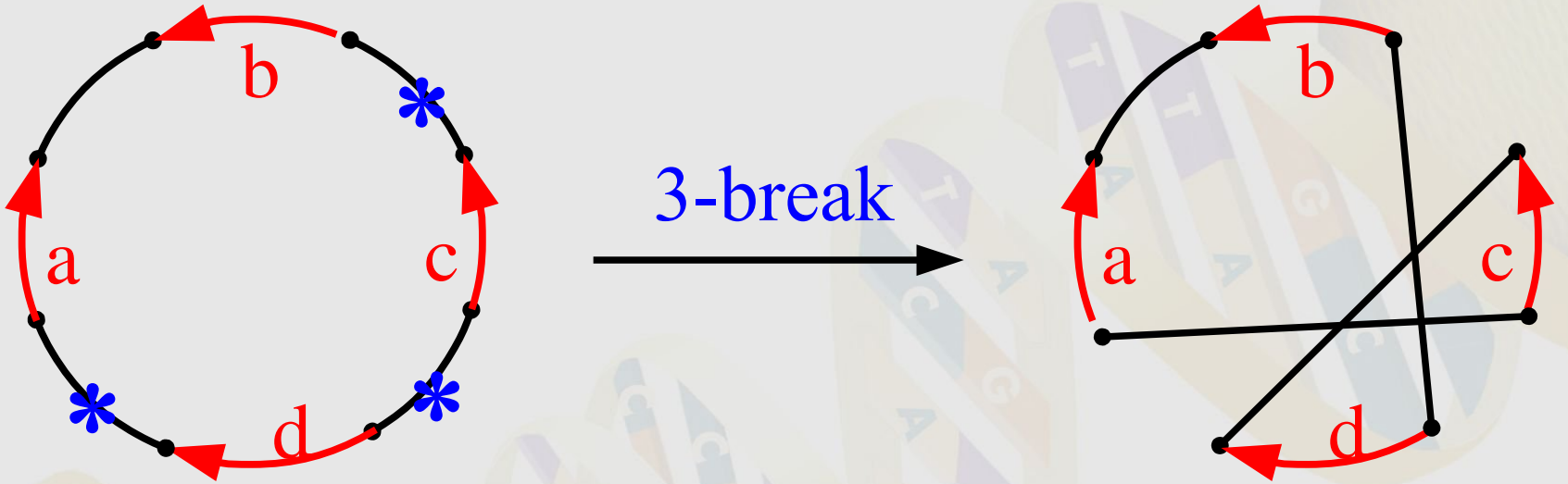
- The complexity status remains unknown

Transpositions



Transpositions cut off a segment of one chromosome and insert it at some position in the same or another chromosome

3-Breaks



P=(+a−b−c+d)

Q=(−c+a−b+d)

3-Break replaces *any triple* of black edges with another triple forming matching on the same 6 vertices.

Transpositions are 3-Breaks.

3-Break Distance

- The **3-Break Distance** $d_3(P,Q)$ between genomes P and Q is the minimum number of 3-Breaks required to transform P into Q.

- 3-Break Distance between genomes P and Q (*TCS07*):

$$d_3(P,Q) = (|P| - cycle^{odd}(P,Q)) / 2$$

k-Break Distance

- Exact formulas for $\mathbf{d_k(P,Q)}$ becomes complex as k grows, e.g.:

Corollary 2. *The 4-break distance between a black matching P and a gray matching Q is*

$$d_4(P, Q) = \left\lceil \frac{|P| - c_1(P, Q) - \lfloor c_2(P, Q)/2 \rfloor}{3} \right\rceil$$

where $c_i(P, Q)$ is the number of black-gray cycles containing i modulo 3 black edges.

Corollary 3. *The 5-break distance between a black matching P and a gray matching Q is*

$$d_5(P, Q) = \left\lceil \frac{|P| - c_1(P, Q) - \min\{c_2(P, Q), c_3(P, Q)\} - \lfloor \max\{0, c_3(P, Q) - c_2(P, Q)\}/3 \rfloor}{4} \right\rceil$$

where $c_i(P, Q)$ is the number of cycles containing i modulo 4 black edges.

- We estimate that the formula for the 20-break distance contains over 1,500 terms.
- We effectively solved the k-break distance problem for an arbitrary k (TCS07).

From Circular Genomes to Linear Genomes

Circularization of Linear Genomes

- Graph of a genome P with n linear chromosomes consist of n alternating black-red paths with 2n endpoints.
- If we introduce an arbitrary perfect black matching on these 2n endpoints, the resulting graph will represent a circular genome, called circularization or closure of P.
- Rearrangements in a linear genome correspond to 3-breaks in its closure.

Rearrangement Distance between Linear Genomes

- The k-break distance between closures gives a lower bound for the rearrangement distance between linear genomes P and Q:

$$d_k^{linear}(P,Q) \geq \max_{P'} \min_{Q'} d_k(P',Q')$$
$$d_k^{linear}(P,Q) \geq \max_{Q'} \min_{P'} d_k(P',Q')$$

where P' and Q' vary over all possible closures of P and Q respectively.

Rearrangement Distance between Human and Mouse

- Solving this max-min problem for *Human* and *Mouse* genomes:

  $d_2^{linear}(H,M) \geq 233$

  $d_3^{linear}(H,M) \geq 137$

- The genomic distance between Human and Mouse is $d_2^{linear}(H,M) = 245$ (Pevzner & Tesler, *Genome Res. 2003*).

Complex Rearrangements and Breakpoint Re-use

Transforming Circularized Mouse into Human by 3-Breaks

$$\text{Mouse}=Q_0 \xrightarrow{\text{3-breaks}} Q_1 \rightarrow \ldots \rightarrow Q_d=\text{Human}$$

$$d = d_3(Human, Mouse) = 139$$

- ✔ Each 3-break makes 3 breaks, hence the total number of breaks in this transformation is 3*139 = 417.
- ✔ 417 is much larger than 281 (the observed number of breakpoints between *Human* and *Mouse* genomes), implying that there is high breakpoint re-use inconsistent with RBM.

Transforming Circularized Mouse into Human by 3-Breaks

$$\text{Mouse}=Q_0 \xrightarrow{\text{3-breaks}} Q_1 \rightarrow \ldots \rightarrow Q_d=\text{Human}$$

$$d = d_3(Human, Mouse) = 139$$

- Each 3-break makes 3 breaks, hence the total number of breaks in this transformation is 3*139 = 417.

- **OOPS!** Some of these 3-breaks may be actually 2-breaks making only 2 breaks each.
  If every 3-break in the series were a 2-break then the total number of breaks is 2*139=278 < 281, in which case there could be no breakpoint re-uses at all.

Minimum Number of Breaks

Problem. Given two genomes P and Q, find a series of k-breaks transforming P into Q and making the *smallest number of breaks*.

Theorem. Any series of k-breaks transforming a genome P into a genome Q makes at least $\mathbf{d_k(P,Q)+d_2(P,Q)}$ breaks.

Theorem. There exists a series of $\mathbf{d_3(P,Q)}$ 3-breaks transforming P into Q and making $\mathbf{d_3(P,Q)+d_2(P,Q)}$ breaks.

$d_2(Human,Mouse) = 246$

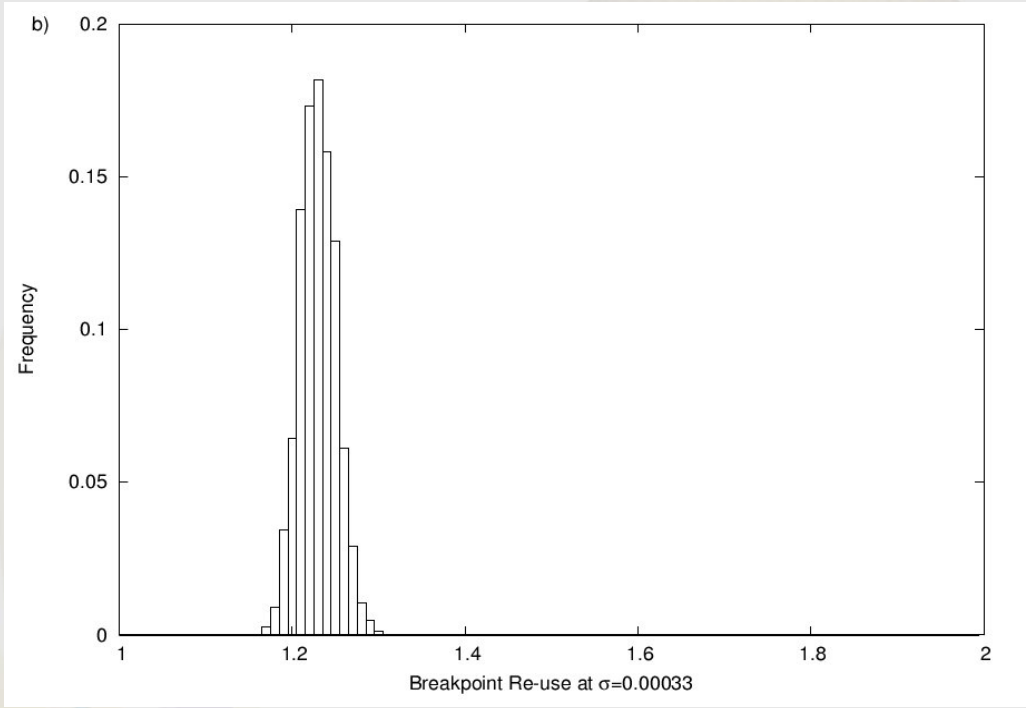
$d_3(Human,Mouse) = 139$

minimum number of breaks = 385

Breakpoint Re-use between Human and Mouse Genomes

- Any transformation of *Mouse* into *Human* genome with 3-breaks requires at least 385 (370 in the linear case) breaks, while there are 281 break-points.

- So, there are at least 385-281=104 breakpoint re-uses (re-use rate 1.37) which is significantly higher than statistically expected in RBM.



- Mean = 1.23
- Standard deviation = 0.02
- Maximum breakpoint reuse rate = 1.33 (observed once in 100,000 simulations)

Breakpoint Re-use between Linear Genomes

- The number of breaks in a series of rearrangements transforming a linear genome P into a linear genome Q is bounded as:

$$\#\text{breaks}(P,Q) \geq \max_{P'} \min_{Q'} d_2(P',Q') + d_3(P',Q')$$

$$\#\text{breaks}(P,Q) \geq \max_{Q'} \min_{P'} d_2(P',Q') + d_3(P',Q')$$

  where P' and Q' vary over all possible closures of P and Q respectively.

- This max-min problem was solved exactly.

Breakpoint Re-use between Human and Mouse

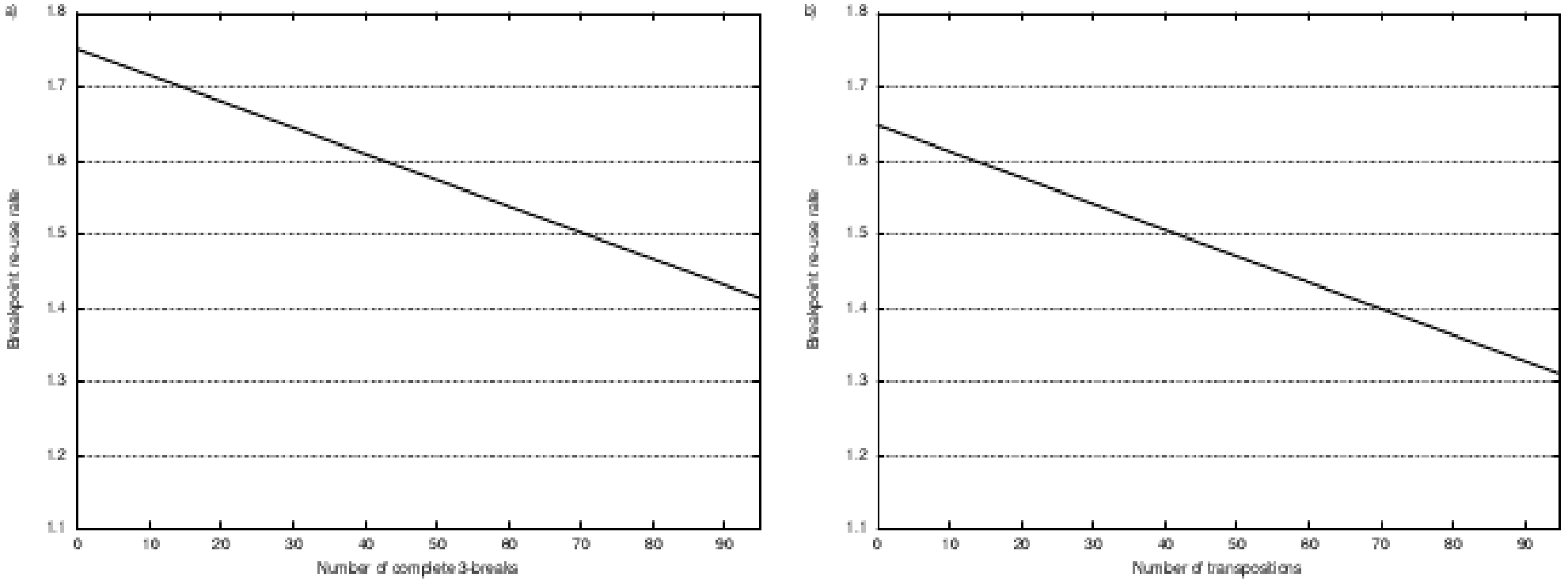


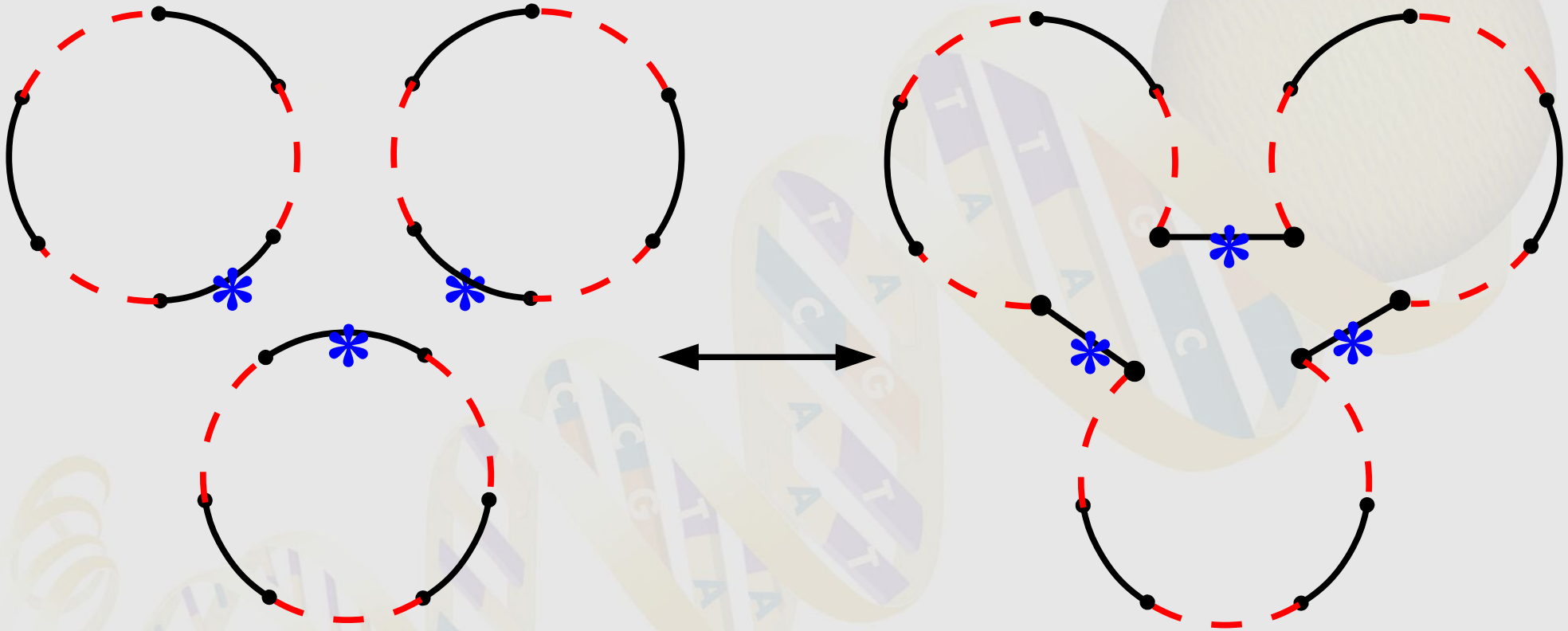
Fig. 3: The lower bound on the breakpoint re-use rate for human and mouse genomes based on 281 synteny blocks from [40]. The lower bound is represented as a function of a) the number of complete 3-breaks in a series of 3-breaks between the circularized human and mouse genomes. (Reproduced from [2]). b) the number of transpositions in a series of rearrangements between the linear human and mouse genomes.

Open Problem

- ✔ Multi-break distance problem for linear genomes


Thank You!

3-Breaks include 3-Way Fusions and Fissions



3-Breaks can merge three chromosomes into a single one as well as split a single chromosome into three ones.

3-Break Distance: Focus on Odd Cycles

- 3-break can increase the number of *odd* cycles (i.e., cycles with odd number of black edges) by at most 2 ($\Delta cycle^{odd} \leq 2$)

- A non-trivial *odd* cycle can be split into three *odd* cycles with a 3-break ($\Delta cycle^{odd} = 2$)

- An *even* cycle can be split into two *odd* cycles with a 3-break ($\Delta cycle^{odd} = 2$)

- *3-Break Distance* between genomes P and Q:

$$d_3(P,Q) = (|P| - cycle^{odd}(P,Q)) / 2$$