# Multiple Whole Genome Alignment

BMI/CS 776

www.biostat.wisc.edu/bmi776/

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# Goals for Lecture

the key concepts to understand are the following

- the large-scale multiple-alignment task
- progressive alignment
- breakpoint identification
- undirected graphical models
- minimal spanning trees/forests

# *Multiple* Whole Genome Alignment: Task Definition

**Given**

- a set of $n > 2$ genomes (or other large-scale sequences)

**Do**

- Identify all corresponding positions between all genomes, allowing for substitutions, insertions/deletions, and *rearrangements*.

# The MLAGAN Method

[Brudno et al., *Genome Research*, 2003]

Given: $k$ genomes $X^1$ , ... , $X^k$, guide tree $T$

for each pair of genomes $X^i$ , $X^j$

*anchors*($i, j$) = find_anchors($X^i, X^j$)

*align* = progressive_alignment($T$, *anchors*)

for each genome $X^i$ // iterative refinement

*anchors* = segments of $X^i$ with high scores in *align*

*align* = LAGAN(*align* - $X^i$, $X^i$, *anchors*) // realign $X^i$

progressive_alignment($T$, *anchors*)

if $T$ is not a leaf node

*align_left* = progressive_alignment($T$.*left, anchors*)

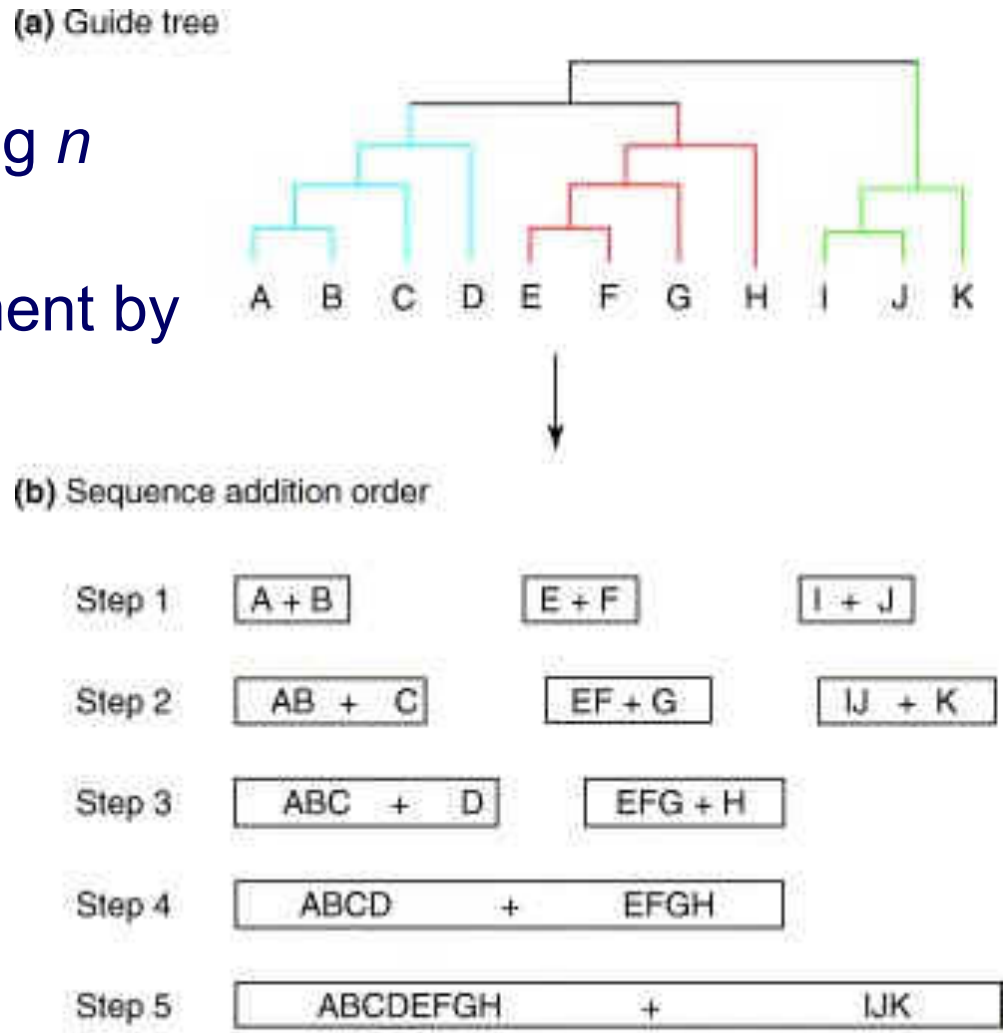
*align_right* = progressive_alignment($T$.*right, anchors*)

*align* = LAGAN(*align_left, align_right, anchors*)

return *align*

# Progressive Alignment

- given a *guide tree* relating *n* genomes
- construct multiple alignment by performing *n*-1 pairwise alignments

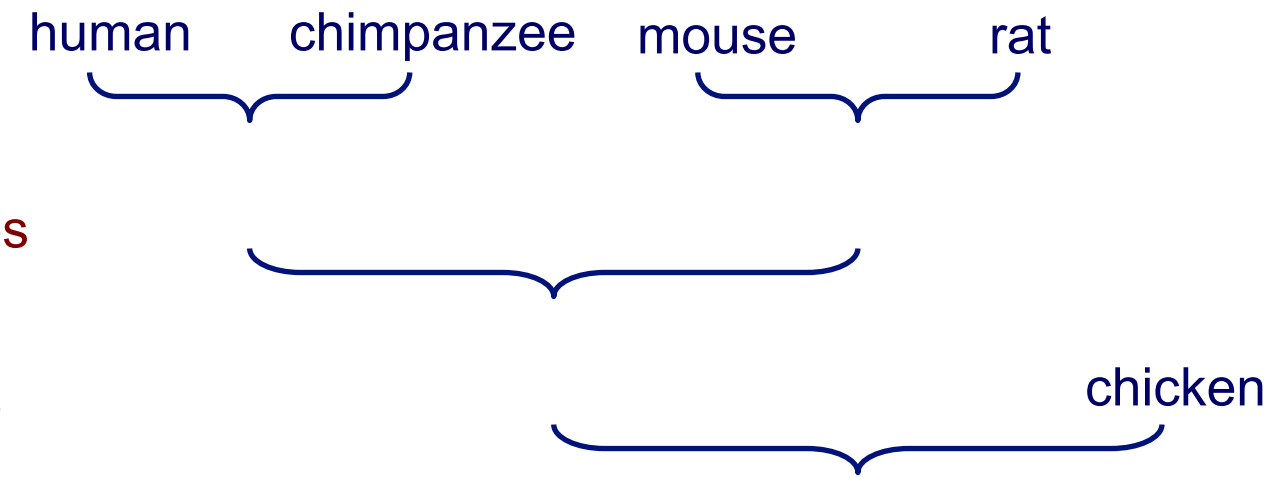


# Progressive Alignment: MLAGAN Example

align pairs of sequences

align multi-sequences (alignments)

align multi-sequence with sequence



# Progressive Alignment: MLAGAN Example

suppose we're aligning the multi-sequence X/Y with Z

1. anchors from X-Z and Y-Z become anchors for X/Y-Z
2. overlapping anchors are reweighted
3. LIS algorithm is used to chain anchors

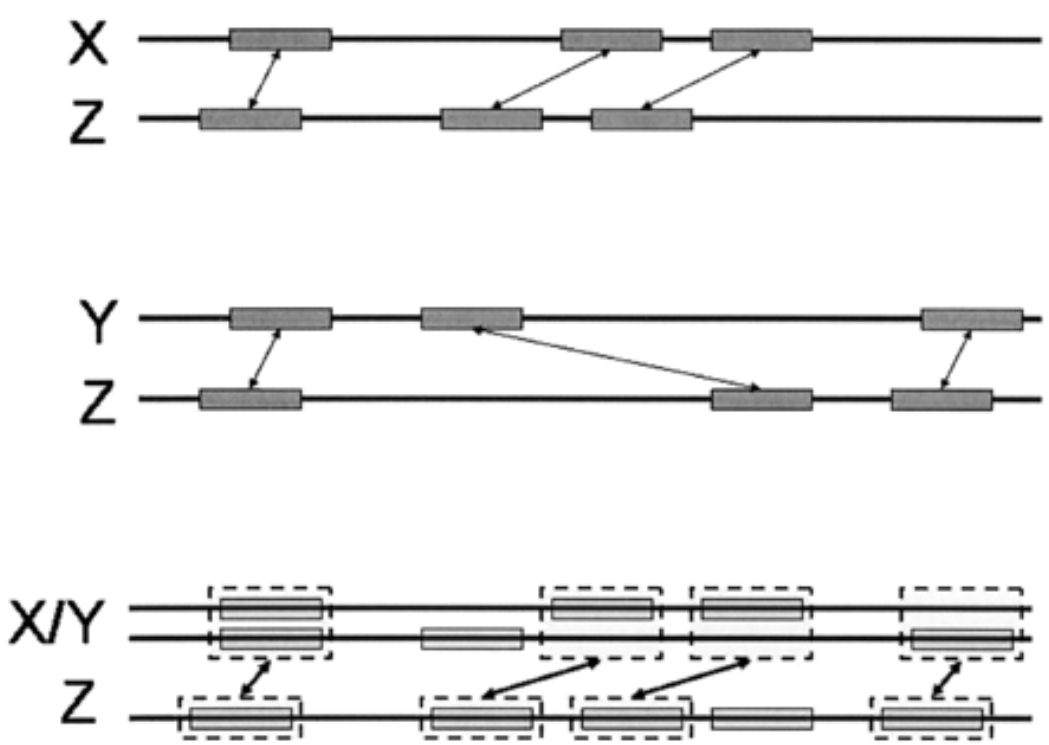
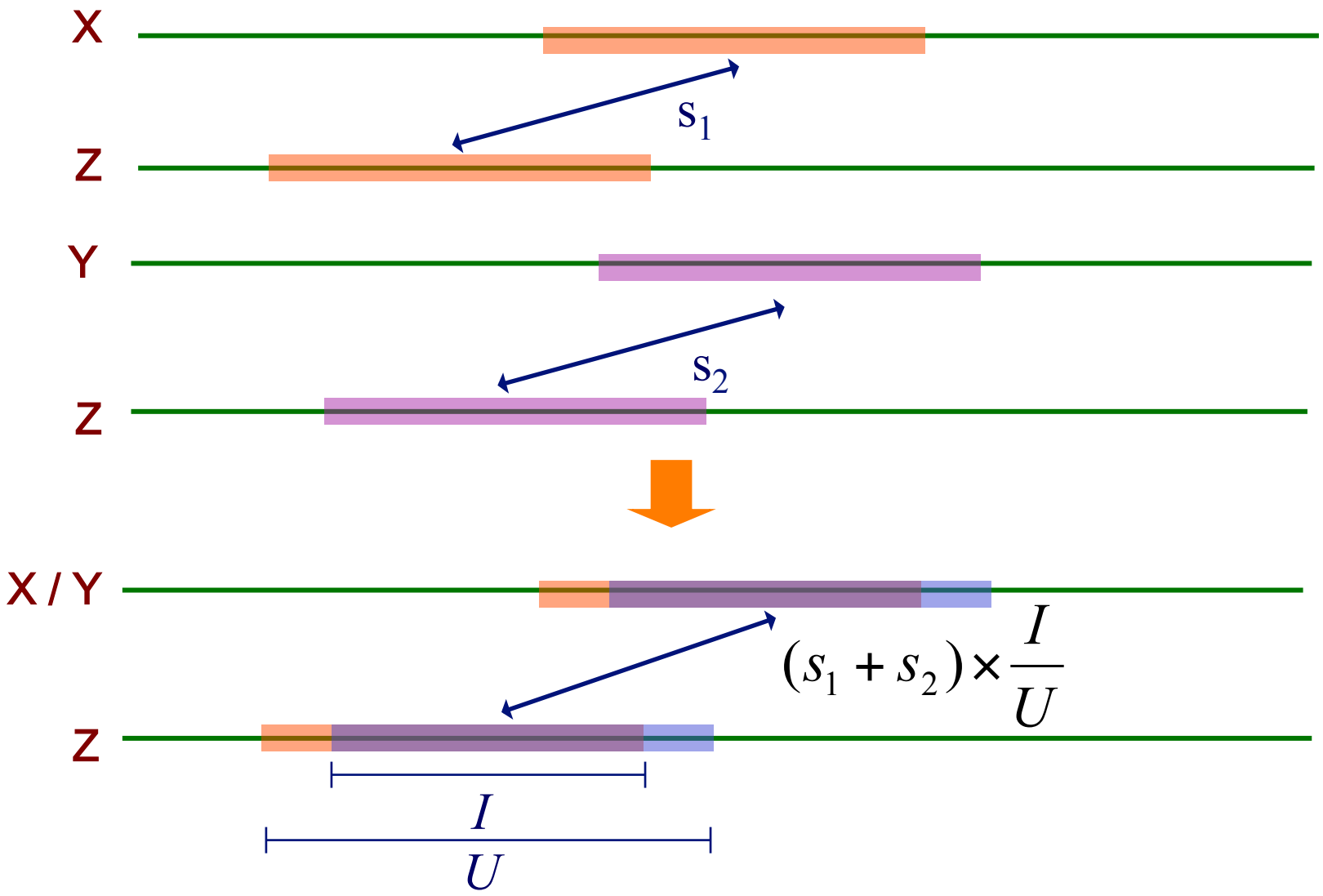
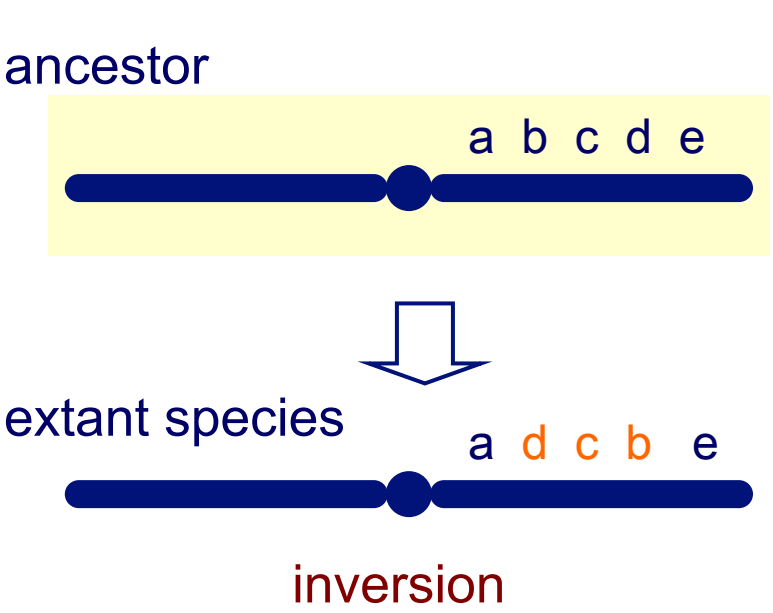


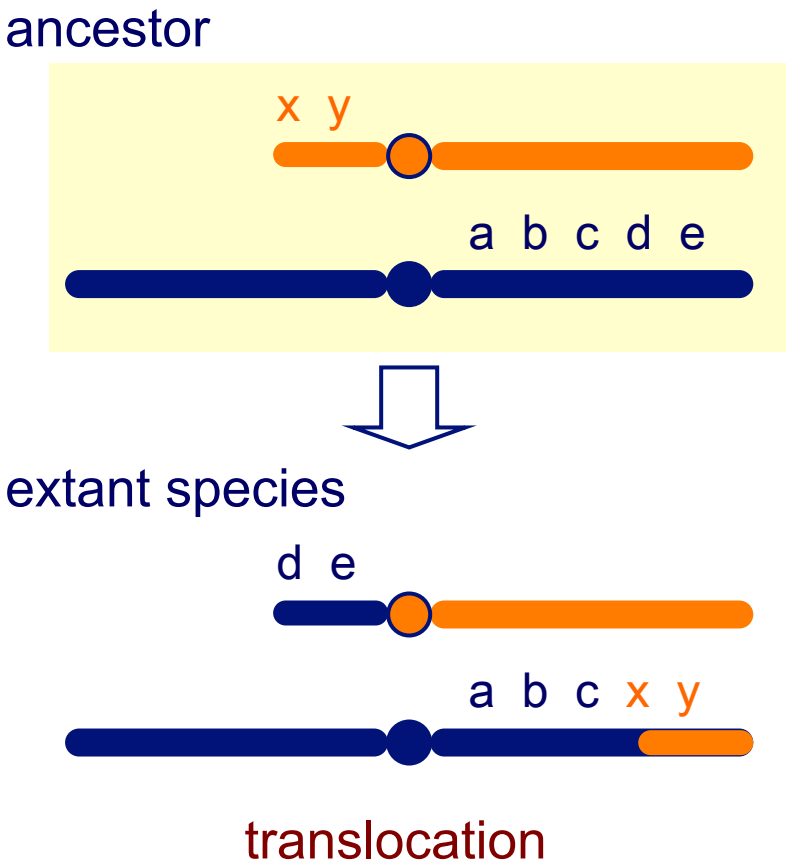

Figure from: Brudno et al. *Genome Research*, 2003

# Reweighting Anchors in MLAGAN



# Genome Rearrangements

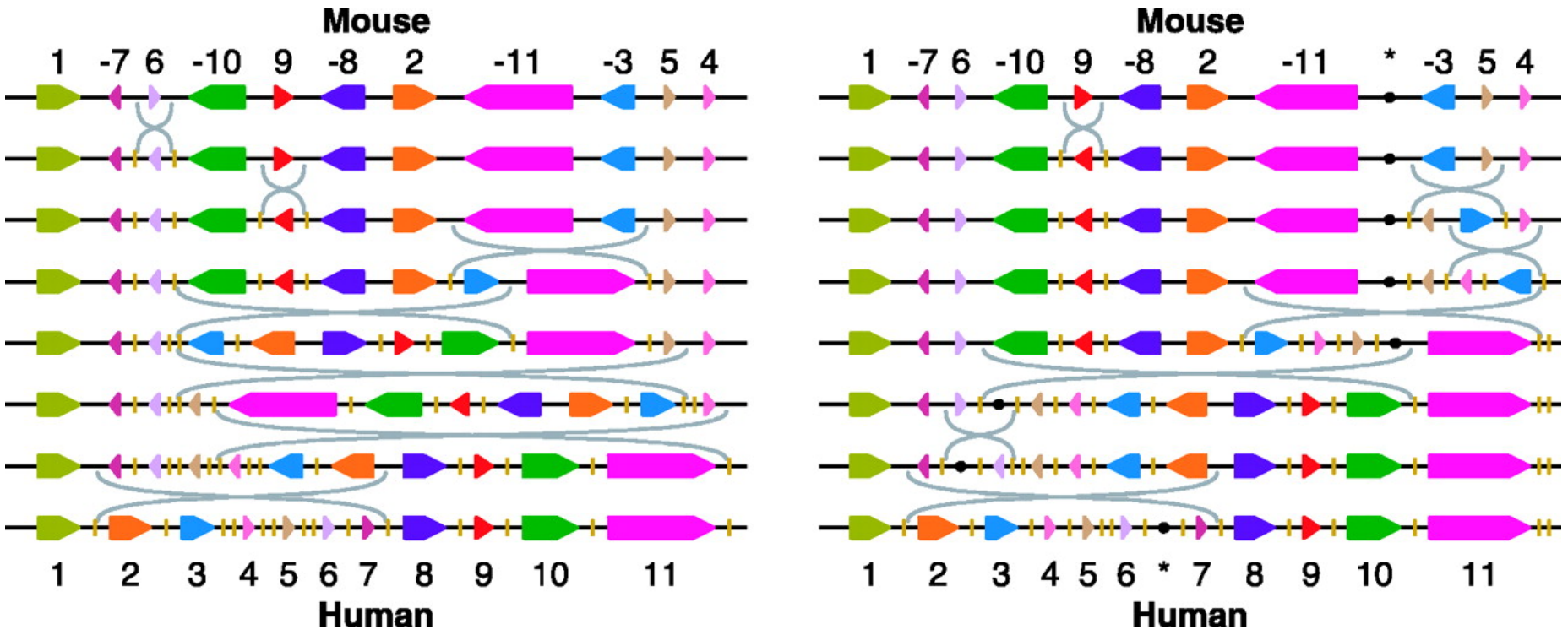



- can occur within a chromosome or across chromosomes
- can have combinations of these events

# Genome Rearrangement Example: Mouse vs. Human X Chromosome

Figure from: Pevzner and Tesler. *PNAS*, 2003




- each colored block represents a syntenic region of the two chromosomes
- the two panels show the two most parsimonious sets of rearrangements to map one chromosome to the other

# The Mauve Method

[Darling et al., *Genome Research*, 2004]

Given: $k$ genomes $X^1$ , ... , $X^k$

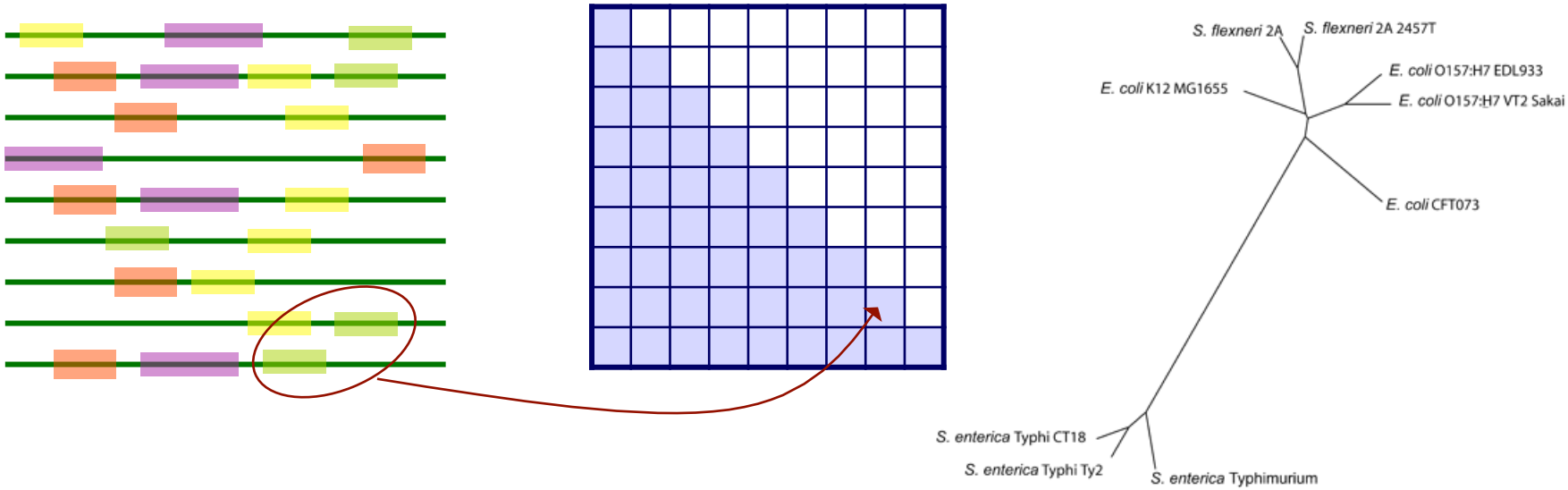
1. find multi-MUMs (MUMs present in 2 or more genomes)
2. calculate a guide tree based on multi-MUMs
3. find LCBs (sequences of multi-MUMs) to use as anchors
4. do recursive anchoring within and outside of LCBs
5. calculate a progressive alignment of each LCB using guide tree

* note: no LIS step!

# 2. Calculating the Guide Tree in Mauve

- unlike MLAGAN, Mauve calculates the guide tree instead of taking it as an input

1. find multi-MUMs in sequences
2. calculate pairwise distances
3. run neighbor-joining to get guide tree



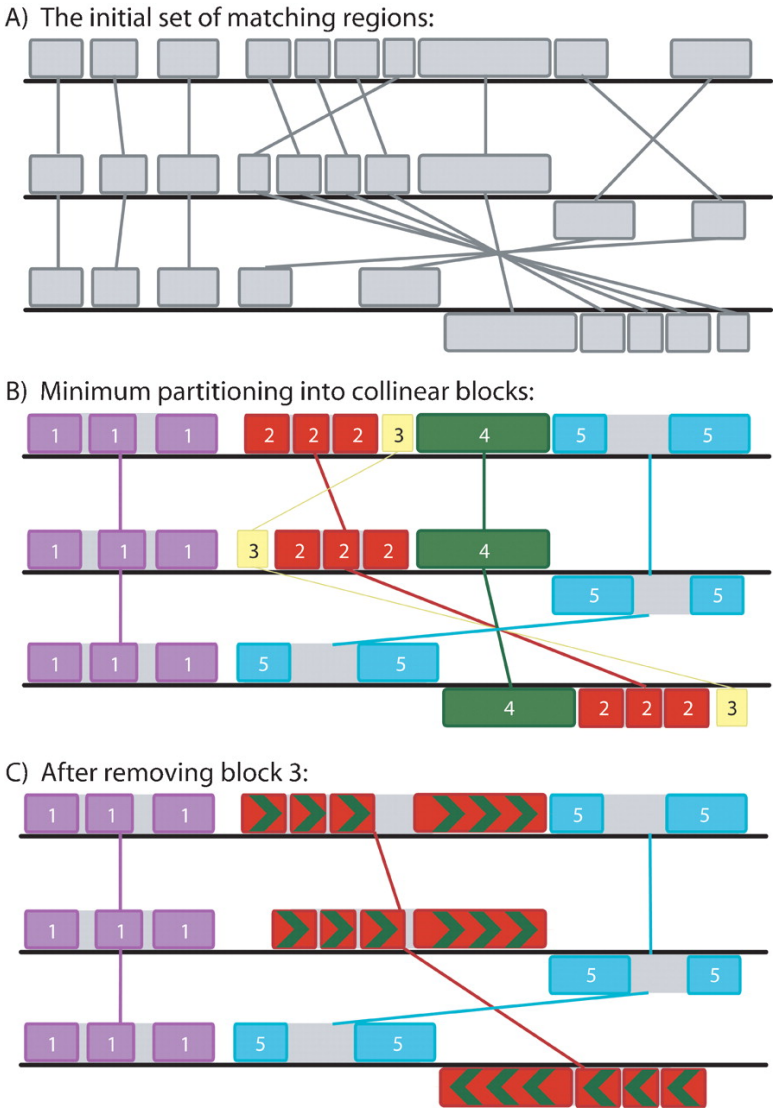

- distance between two sequences is based on fraction of sequences shared in multi-MUMs

# 3. Selecting Anchors: Finding Local Collinear Blocks

repeat

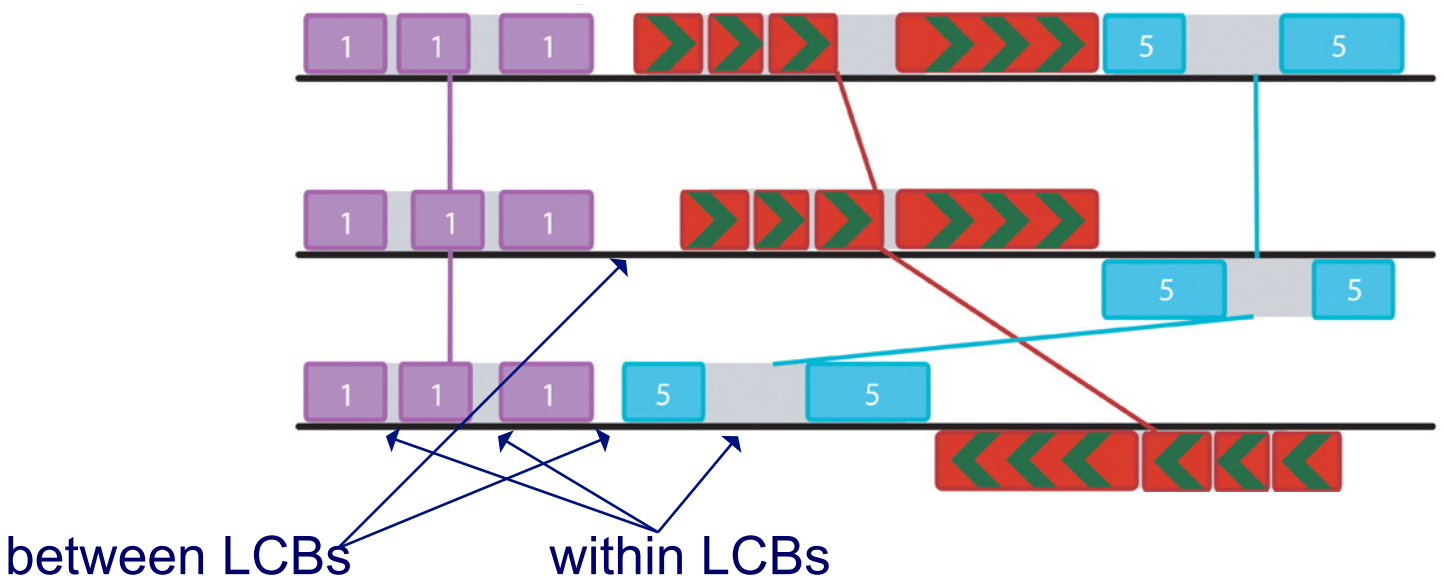
- partition set of multi-MUMs, M into collinear blocks
- find minimum-weight collinear block(s)
- remove minimum weight block(s) if they're sufficiently small

until minimum-weight block is not small enough

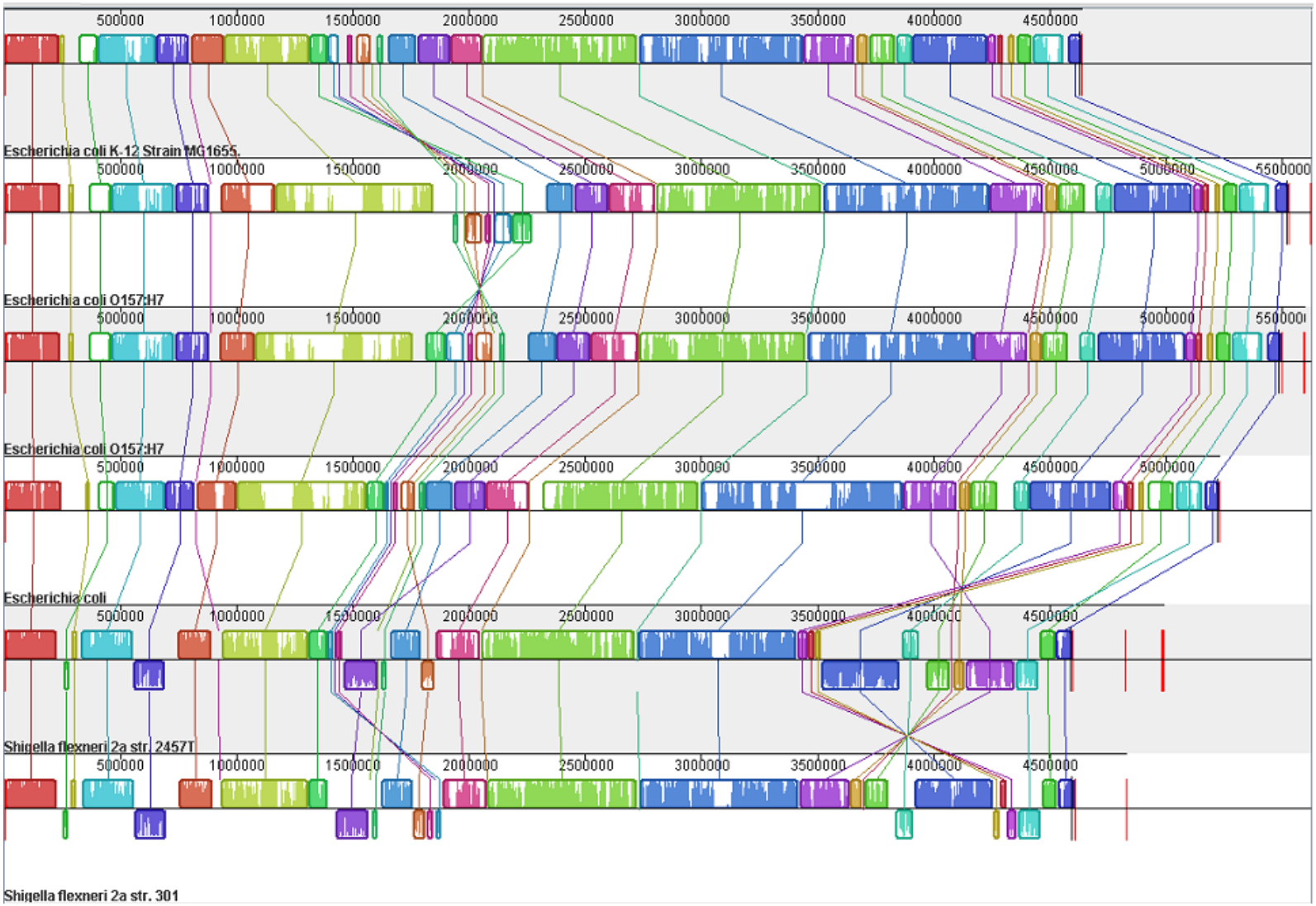


# 4. and 5. Recursive Anchoring and Gapped Alignment

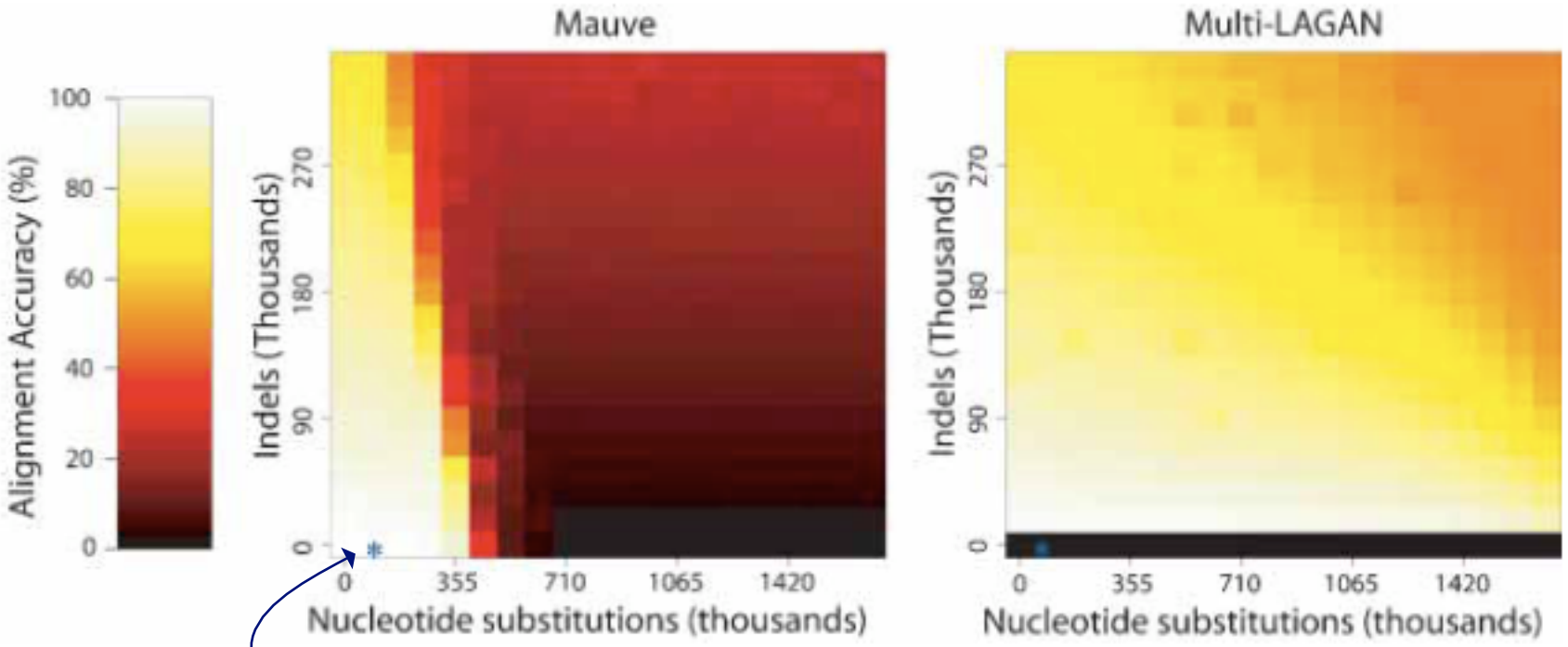
- recursive anchoring (finding finer multi-MUMs and LCBs) and standard alignment (CLUSTALW) are used to extend LCBs



# Mauve Alignment of 9 Enterobacteria (*Shigella and E. coli*)



# Mauve vs. MLAGAN: Accuracy on Simulated Genome Data



# Mauve vs. LAGAN: Accuracy on Simulated Genome Data with Inversions

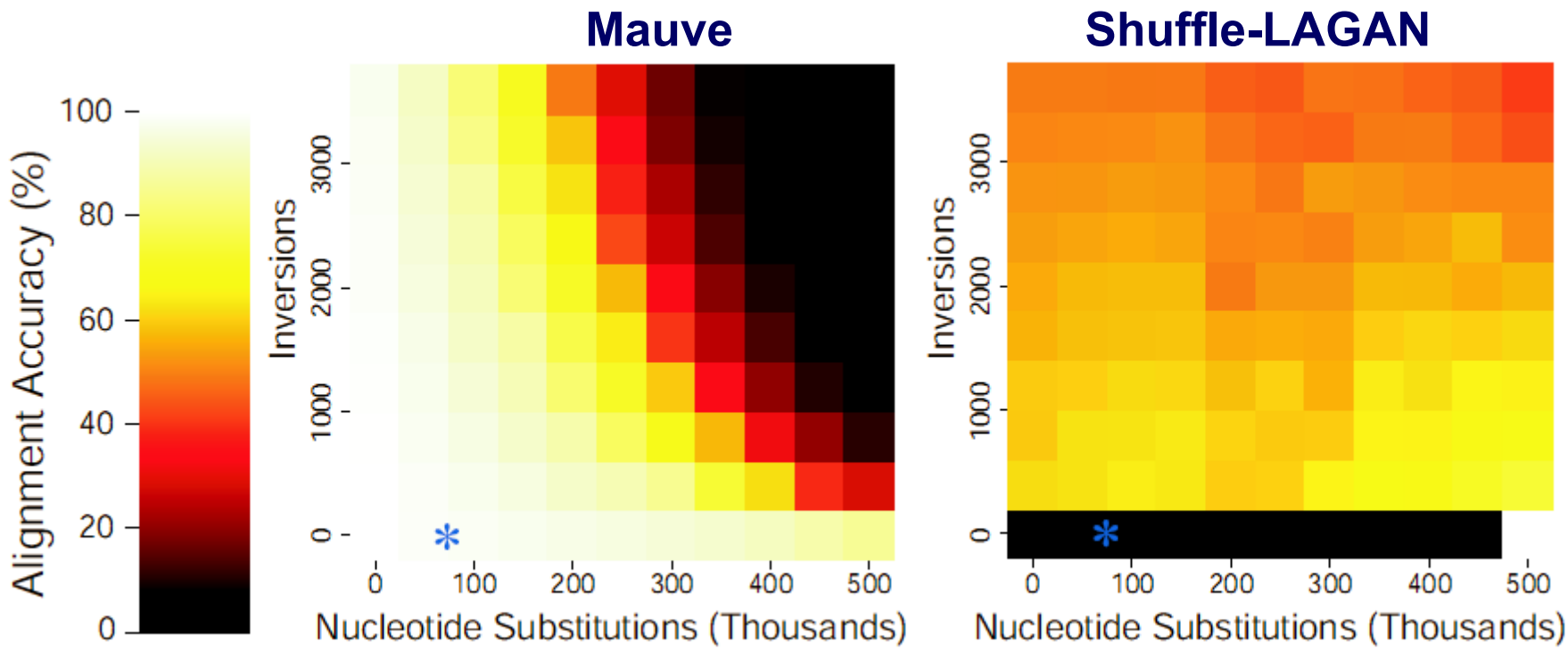
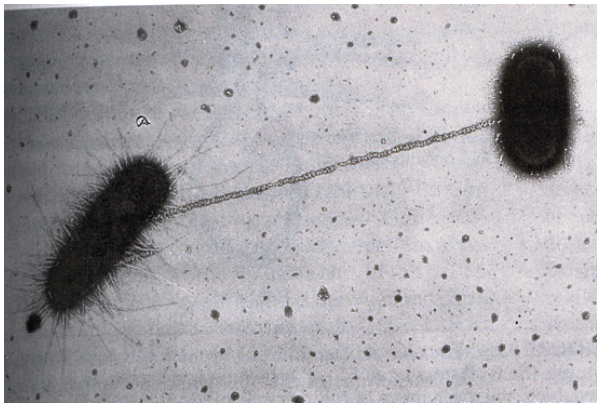
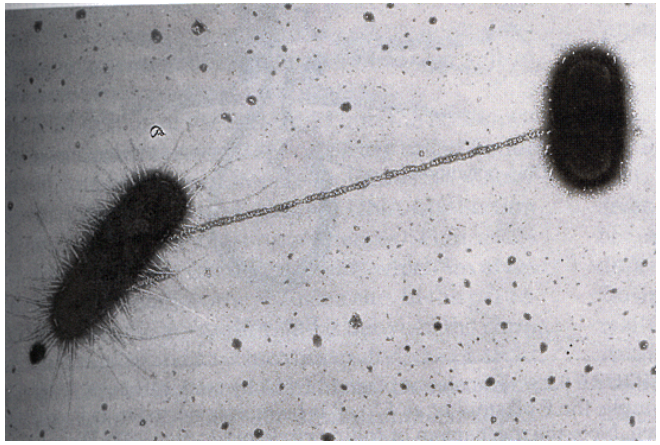



Figure courtesy of Aaron Darling

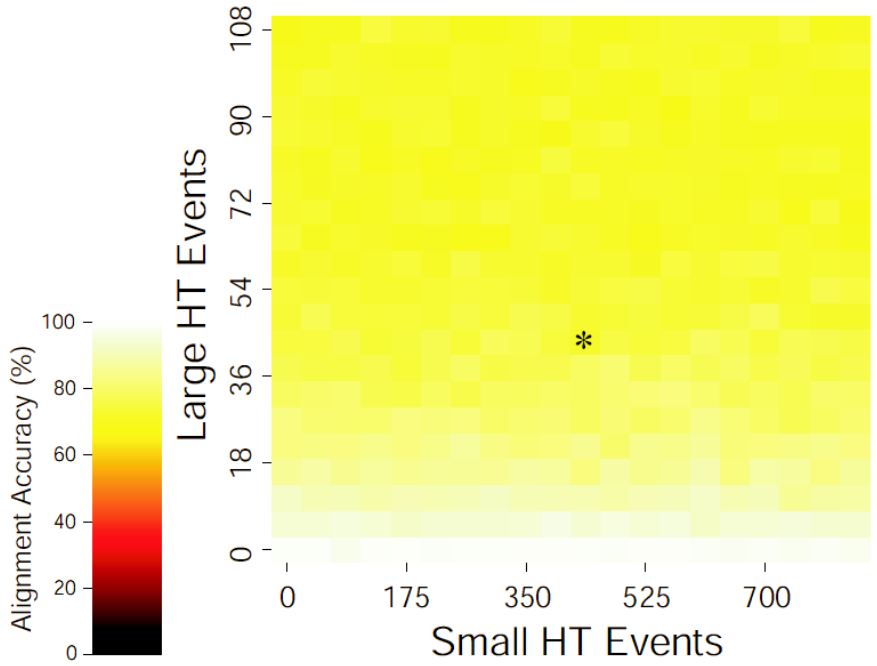
# Evolution with *Horizontal Transfer*



# Mauve Accuracy on Simulated Enterobacteria-like Data



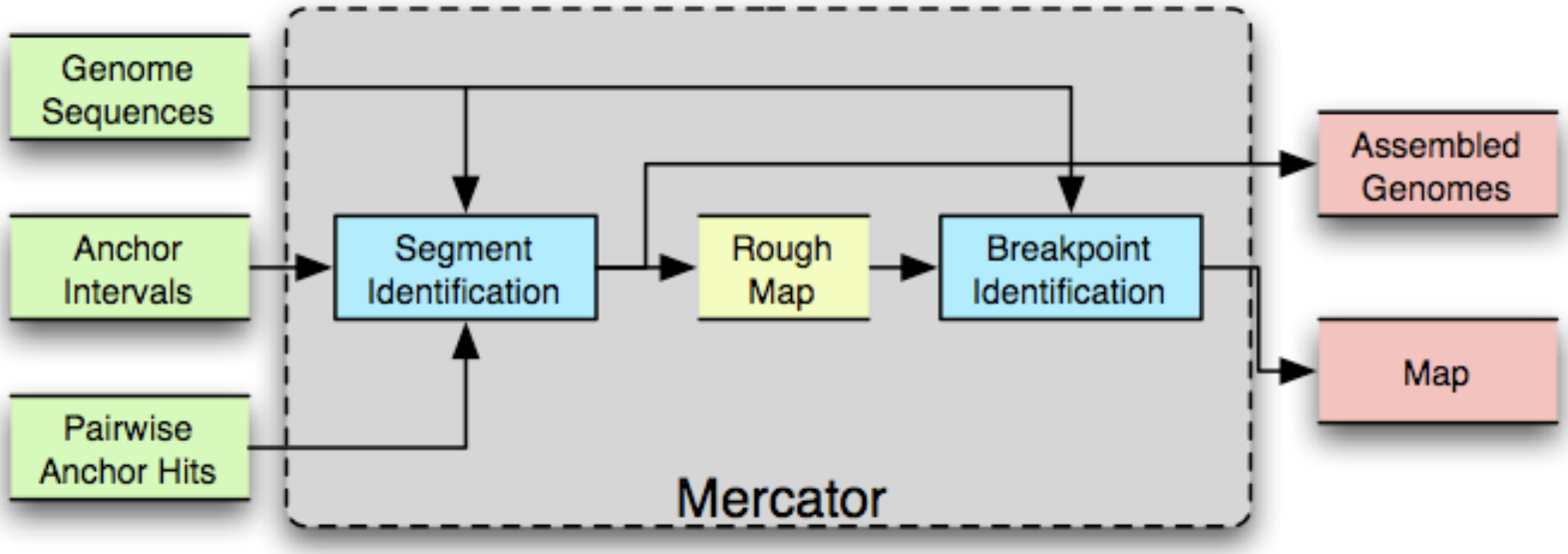
- data here include horizontal transfers




- small HT events have little effect compared to large HT events
- when scored on regions conserved in all 9 taxa, accuracy is always > 98%

Figures courtesy of Aaron Darling

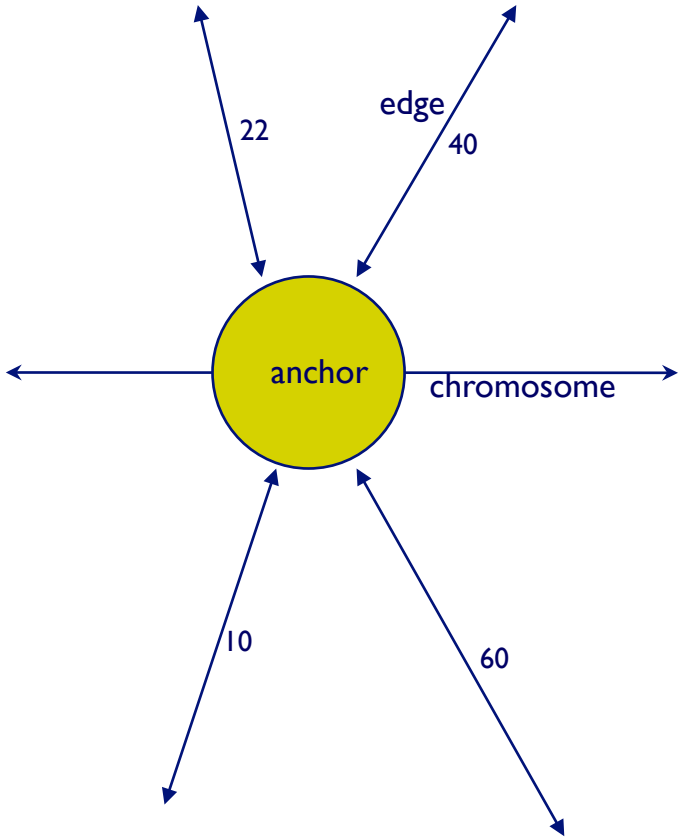
# Mercator




- orthologous segment identification: graph-based method
- breakpoint identification: refine segment endpoints with a graphical model

# Establishing Anchors Representing Orthologous Segments

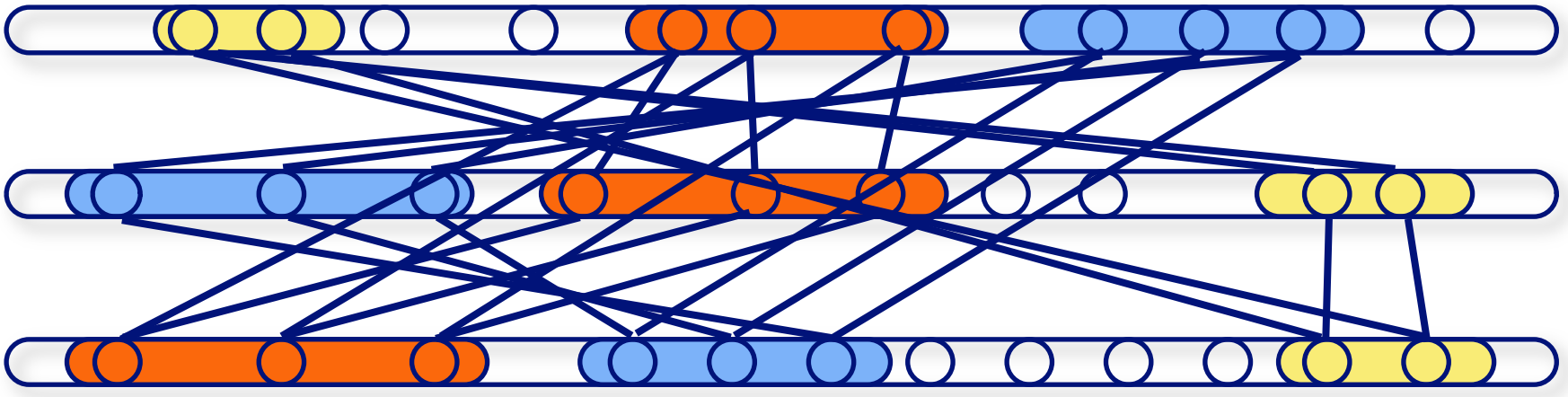
- anchors can correspond to genes, exons or MUMS
- e.g., may do all-vs-all pairwise comparison of genes
- construct graph with anchors as vertices and high-similarity hits as edges (weighted by alignment score)



# Rough Orthology Map

k-partite graph with edge weights

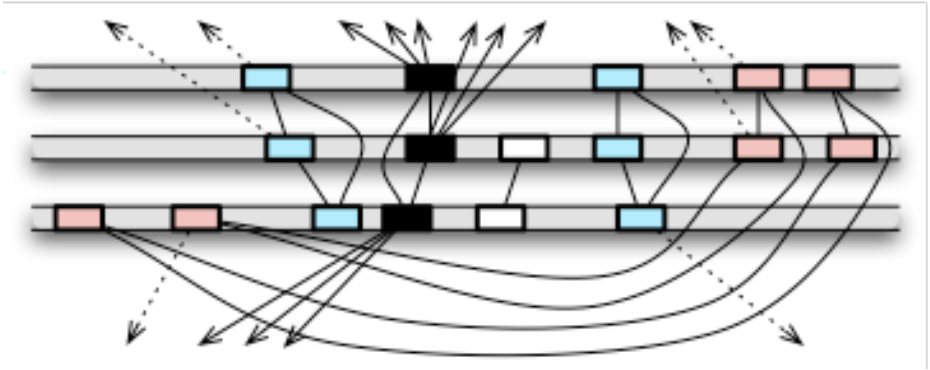
vertices = anchors, edges = sequence similarity



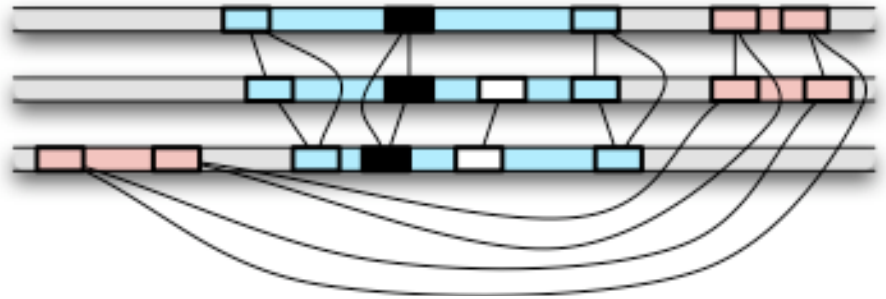
# Greedy Segment Identification

- for *i* = k to 2 do
  - identify repetitive anchors (depends on number of high-scoring edges incident to each anchor)
  - find “best-hit” anchor cliques of size ≥ *i*
  - join colinear cliques into *segments*
  - filter edges not consistent with significant segments

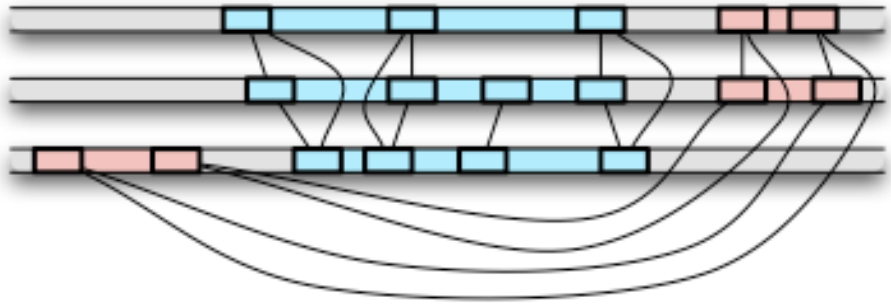
# Mercator Example



repetitive elements (black anchors) are identified; 3-cliques (red and blue anchors) are found



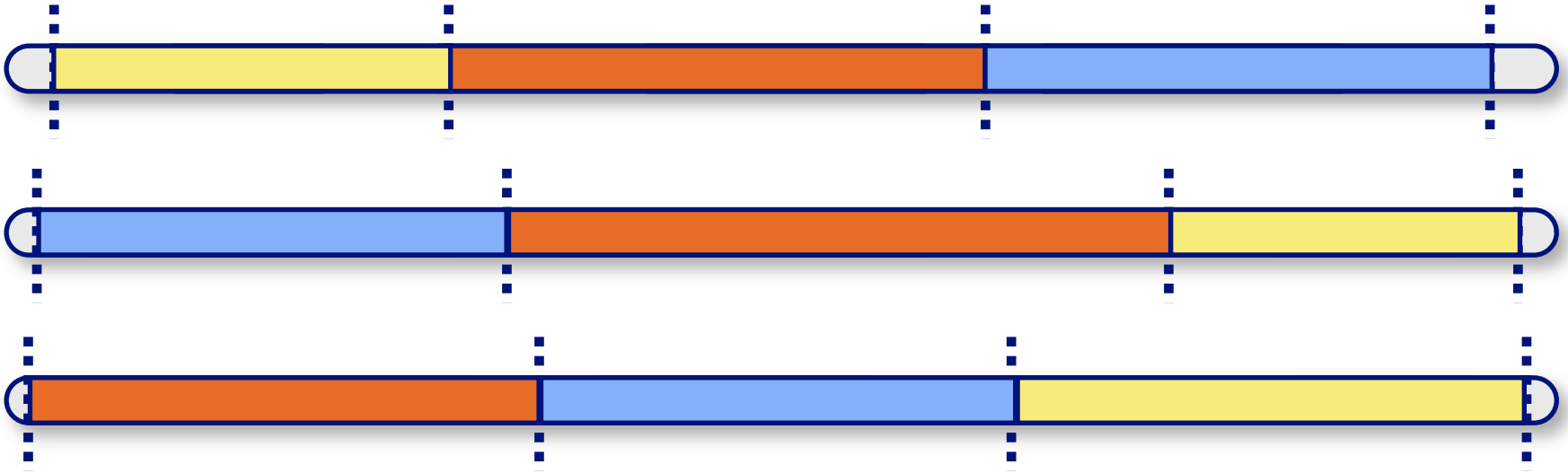
segments are formed by red and blue anchors; inconsistent edges are filtered



2-cliques are found and incorporated into segments

# Refining the Map: Finding Breakpoints

- *breakpoints*: the positions at which genomic rearrangements disrupt colinearity of segments

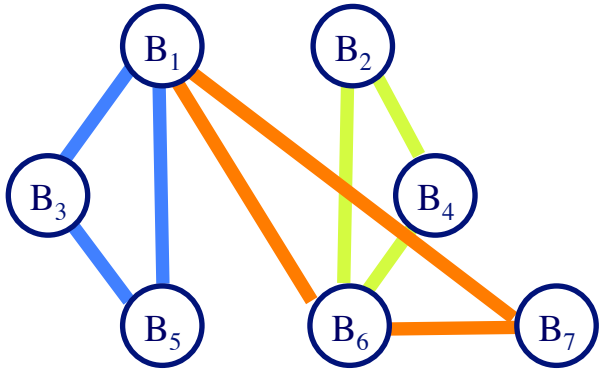


- Mercator finds breakpoints by using inference in an *undirected graphical model*

# Undirected Graphical Models

- an undirected graphical model represents a probability distribution over a set of variables using a factored representation

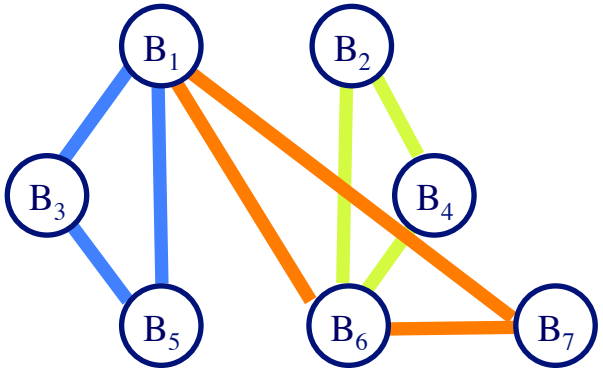
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$




| | |
|---|---|
| $B_i$ | random variable |
| $\mathbf{b}$ | assignment of values to all variables |
| $\mathbf{b}_C$ | assignment of values subset of variables in $C$ |
| $\psi_C$ | function (called a potential) representing the "compatibility" of a given set of values |
| $Z$ | normalization term |

# Undirected Graphical Models

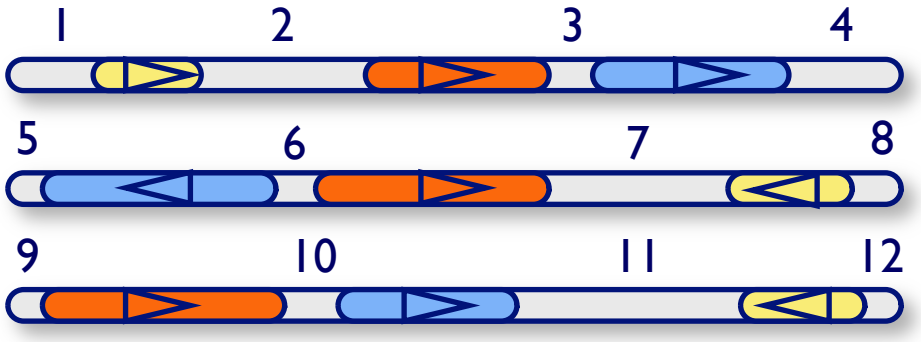
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$

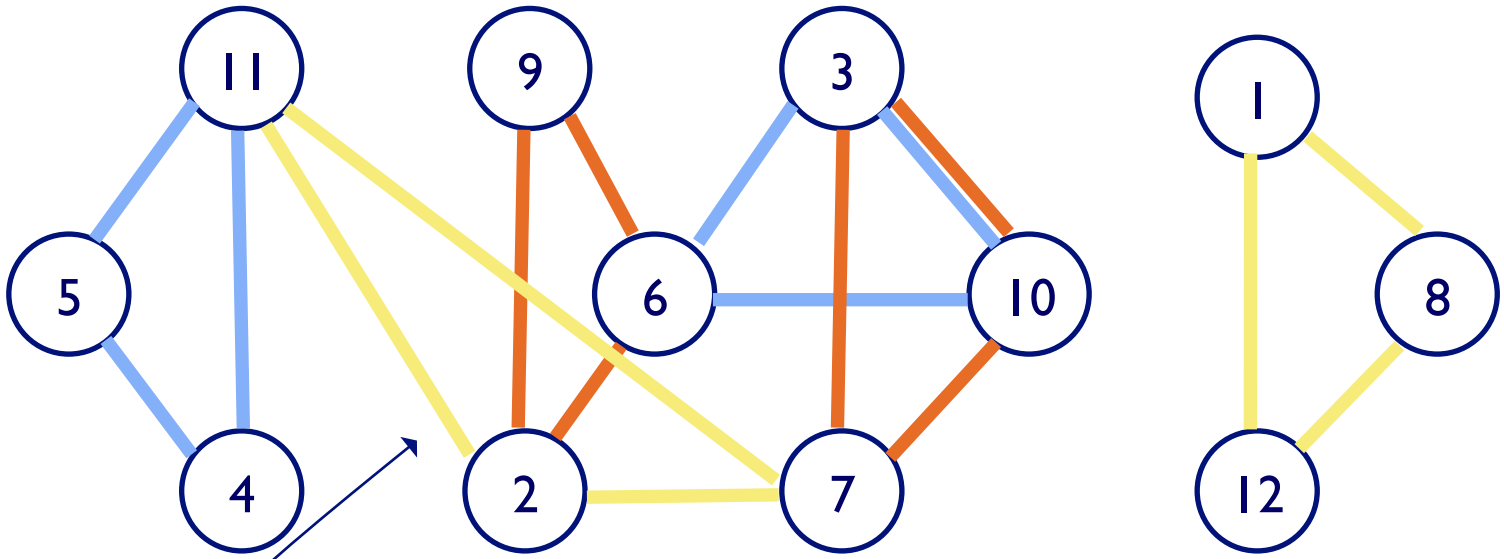



for the given graph:

$$p(\mathbf{b}) = \frac{1}{Z}\ \psi_1(b_1,b_3,b_5)\ \psi_2(b_1,b_6,b_7)\ \psi_3(b_2,b_4,b_6)$$

# The Breakpoint Graph




some prefix of region 2 and some prefix of region 11 should be aligned

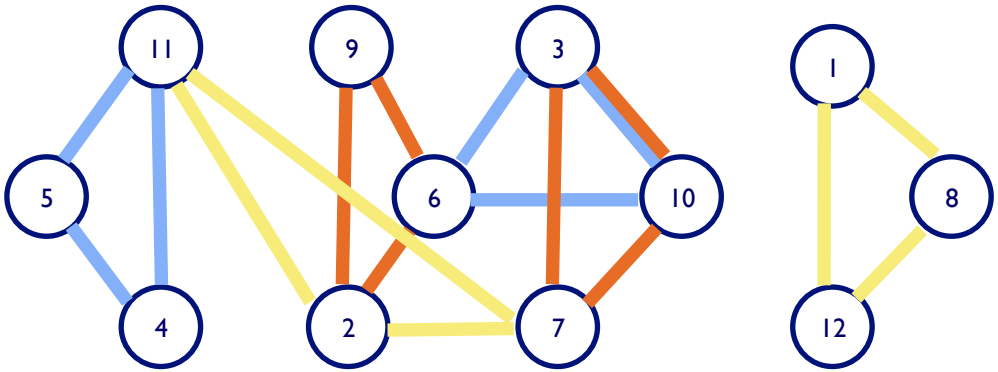
# Breakpoint Undirected Graphical Model

- Mercator frames the task of finding breakpoints as an inference task in an undirected graphical model

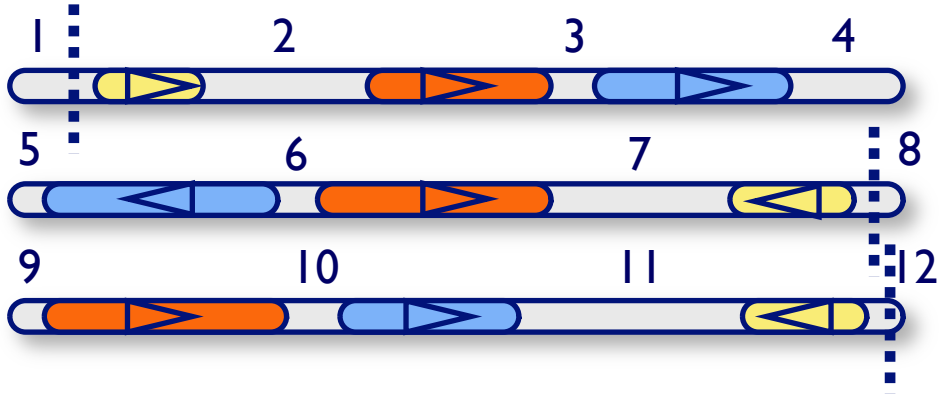
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$

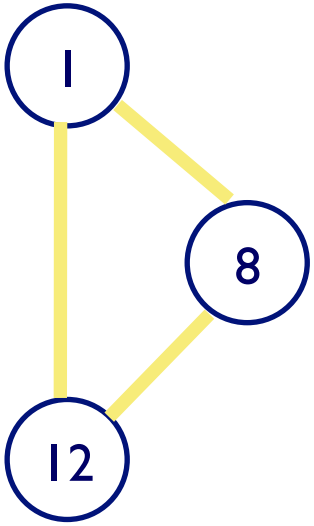
configuration of breakpoints

potential function representing score of multiple alignment of sequences in clique $C$ for breakpoints in $b$



# Breakpoint Undirected Graphical Model

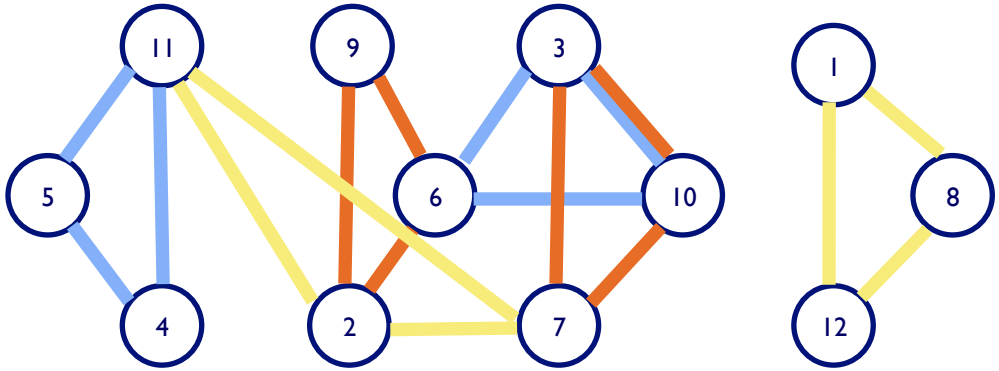



- the possible values for a variable indicate the possible coordinates for a breakpoint
- the potential for a clique is a function of the alignment score for the breakpoint regions split at the breakpoints $\mathbf{b}_C$

# Breakpoint Undirected Graphical Model

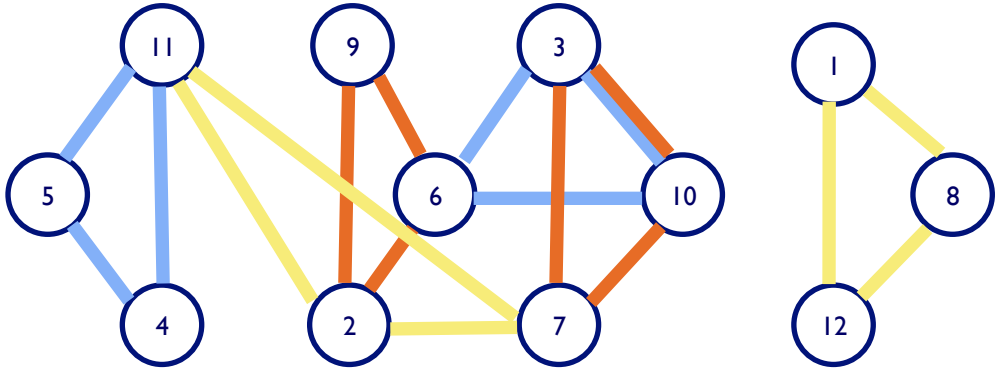
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$




- *inference task*: find most probable configuration $\mathbf{b}$ of breakpoints
- not tractable in this case
  - graph has a high degree of connectivity
  - multiple alignment is difficult
- so Mercator uses several heuristics

# Making Inference Tractable in Breakpoint Undirected Graphical Model

$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$



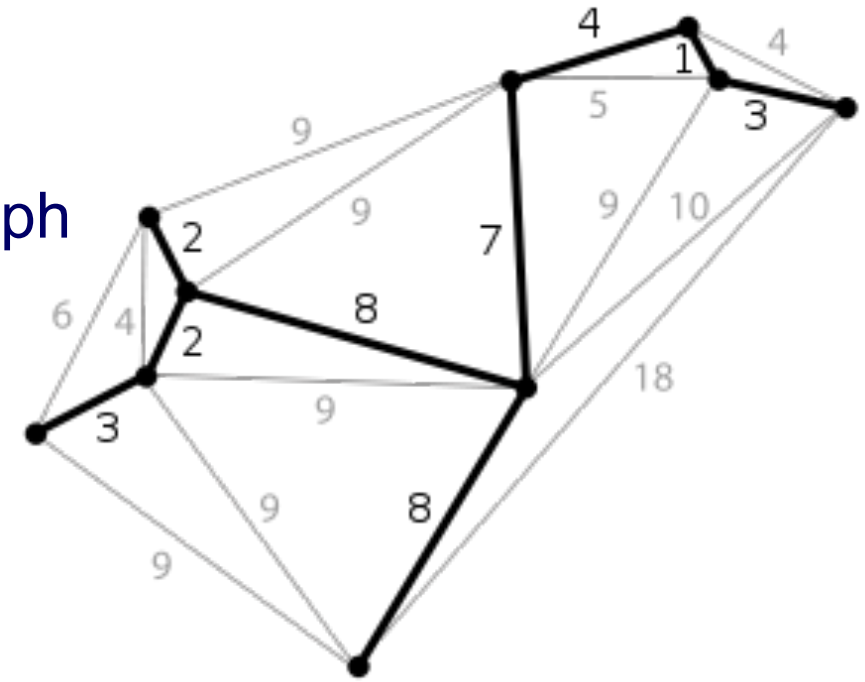

- assign potentials, based on pairwise alignments, to edges only

$$p(\mathbf{b}) = \frac{1}{Z} \prod_{(i,j) \in edges} \psi_{i,j}(b_i, b_j)$$

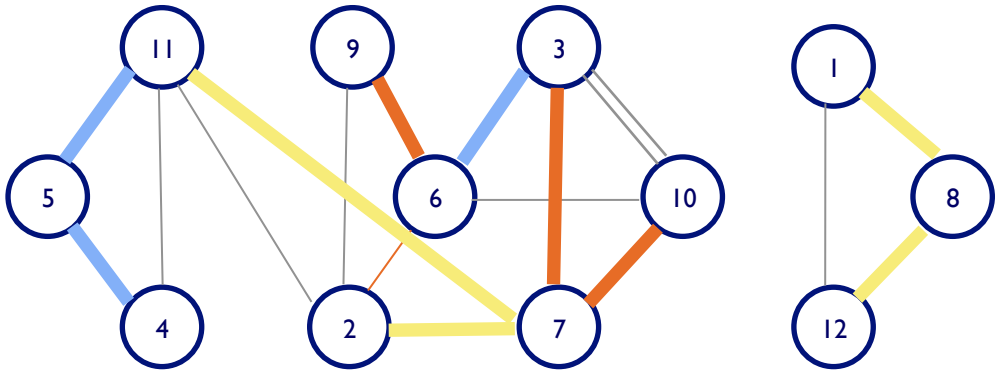
- eliminate edges by finding a *minimum spanning forest*, where edges are weighted by phylogenetic distance

# Minimal Spanning Forest

- *minimal spanning tree*: a minimal-weight tree that connects all vertices in a graph




- *minimal spanning forest*: a set of MSTs, one for each connected component



# Breakpoint Finding Algorithm

1. construct breakpoint segment graph
2. weight edges with phylogenetic distances
3. find minimum spanning tree/forest
4. perform pairwise alignment for each edge in MST
5. use alignments to estimate $\psi_{i,j}(b_i, b_j)$
6. perform max-product inference (similar to Viterbi) to find maximizing $b_i$

# Comments on Whole-Genome Alignment Methods

- employ common strategy
  - find seed matches
  - identify (sequences of) matches to anchor alignment
  - fill in the rest with standard methods (e.g. DP)
- vary in what they (implicitly) assume about
  - the distance of sequences being compared
  - the prevalence of rearrangements
- involve a lot of heuristics
  - for efficiency
  - because we don't know enough to specify a precise objective function (e.g. how should costs should be assigned to various rearrangements)