Multiple Whole Genome Alignment

BMI/CS 776
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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)
- a method for scoring the similarity of a pair of characters

Do

- construct global alignment: identify matches between genomes as well as various non-match features

The MLAGAN Method

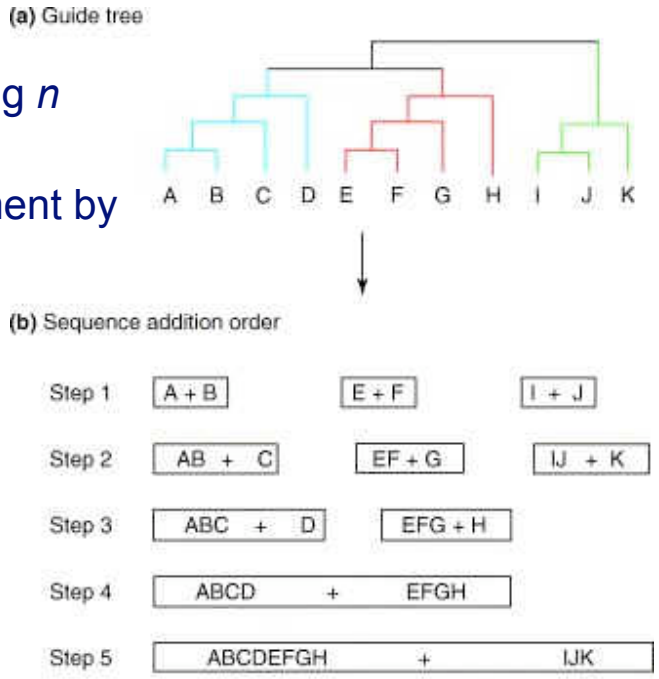
[Brudno et al., *Genome Research*, 2003]

Given: k genomes $X^1, \ldots, X^k$, 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*)
        align_right = progressive_alignment(T.*right*)
        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

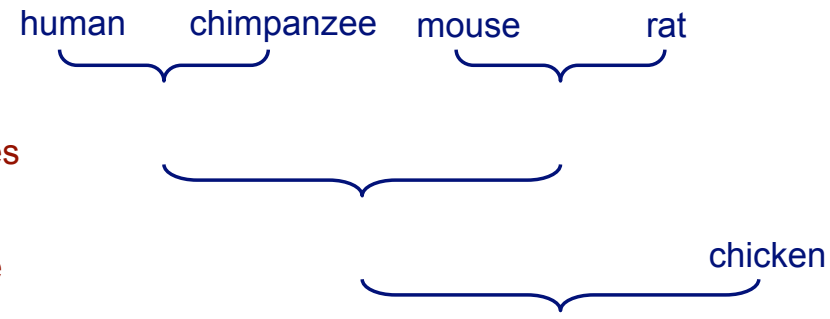


Progressive Alignment: MLAGAN Example

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

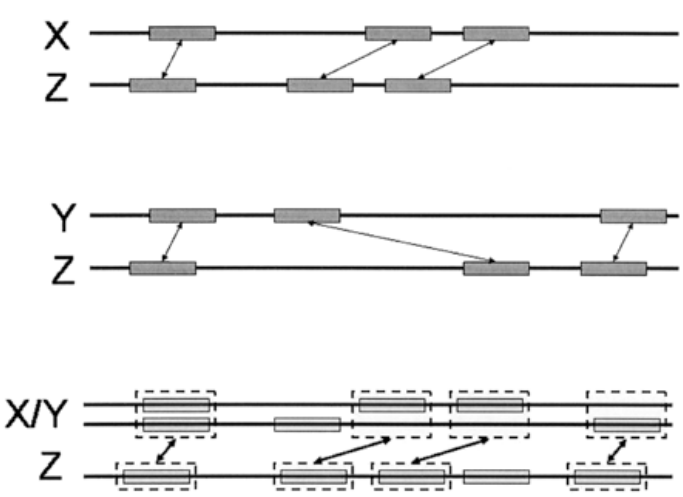
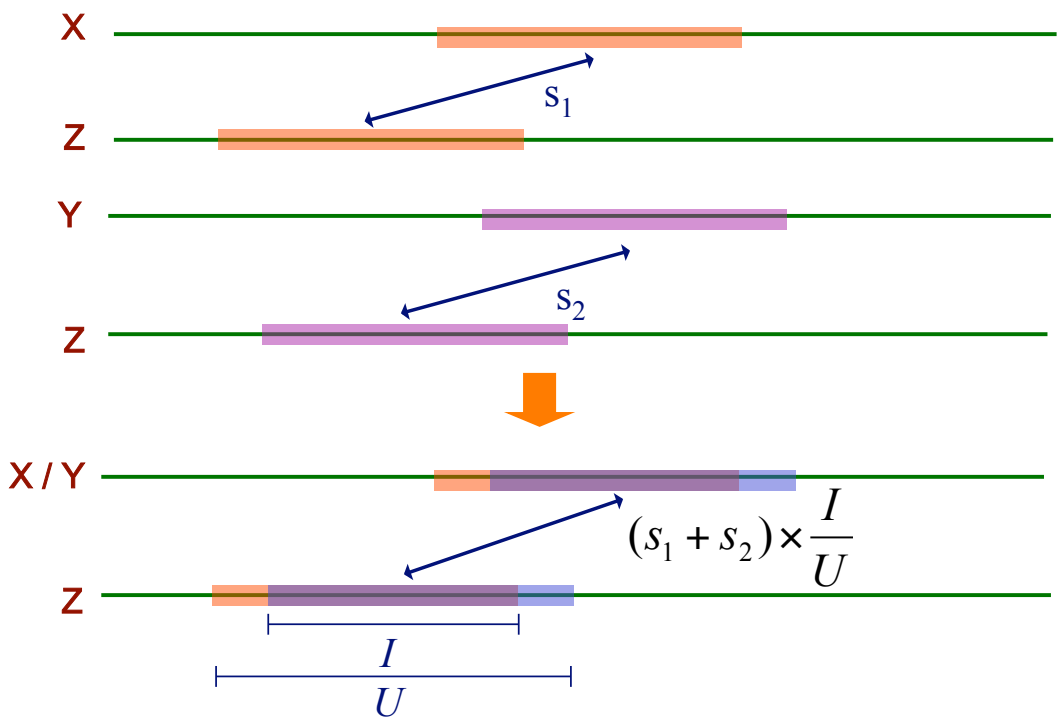
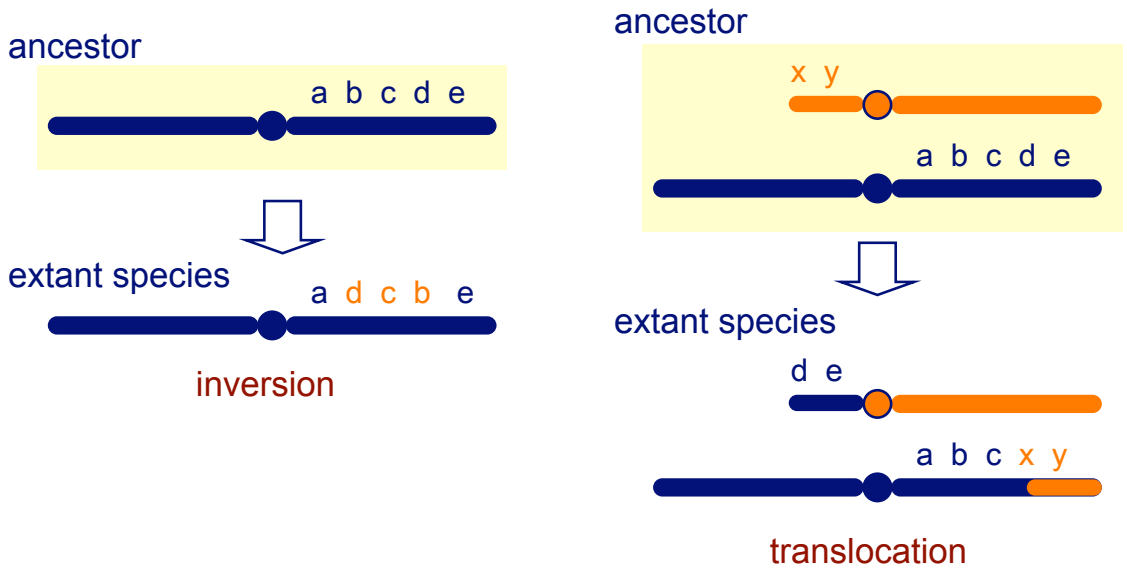


Figure from: Brudno et al. *Genome Research*, 2003

Reweighting Anchors in MLAGAN



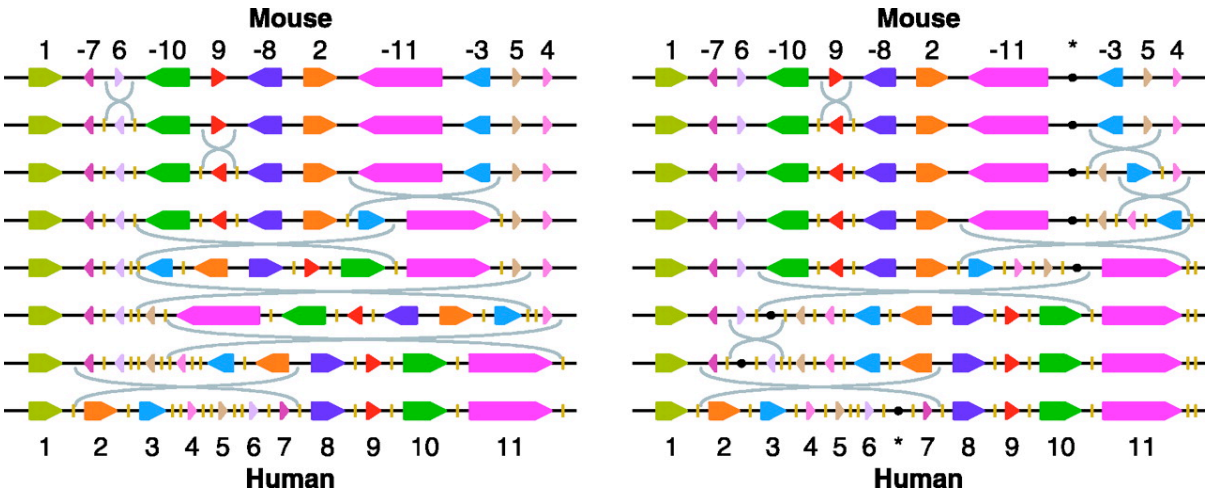
Genome Rearrangements



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

Genome Rearrangement Example: Mouse vs. Human X Chromsome

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 $X^1, \ldots, X^k$

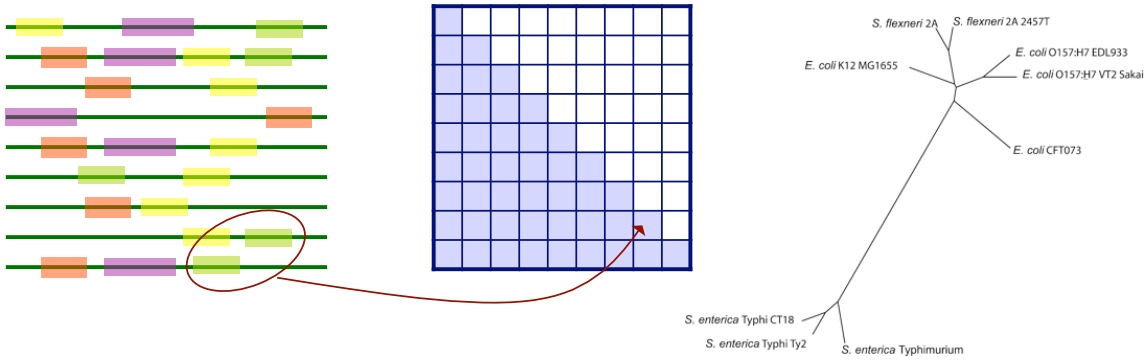
1. find multi-MUMs (MUMs present in 2 or more genomes)
2. calculate a guide tree based on multi-MUMs
3. find LCBs (sequences of multi-MUMs) to use as anchors
4. do recursive anchoring within and outside of LCBs
5. calculate a progressive alignment of each LCB using guide tree

* 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



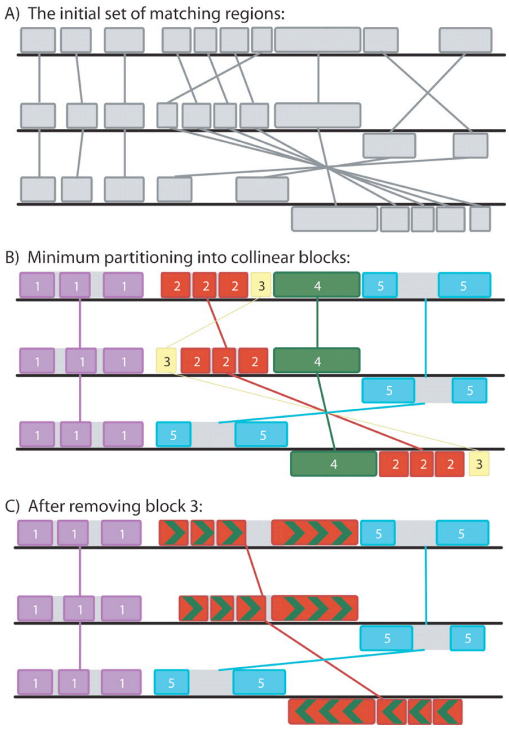
- distance between two sequences is based on fraction of sequences shared in multi-MUMs

3. Selecting Anchors: Finding Local Collinear Blocks

repeat

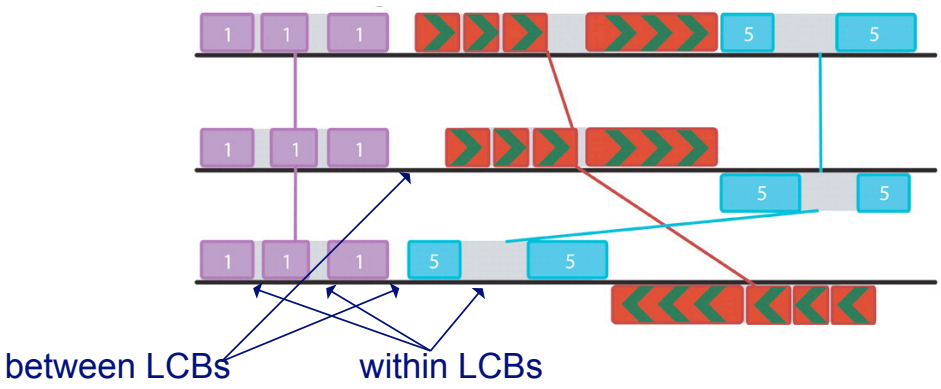
- partition set of multi-MUMs, M into collinear blocks
- find minimum-weight collinear block(s)
- remove minimum weight block(s) if they're sufficiently small

until minimum-weight block is not small enough

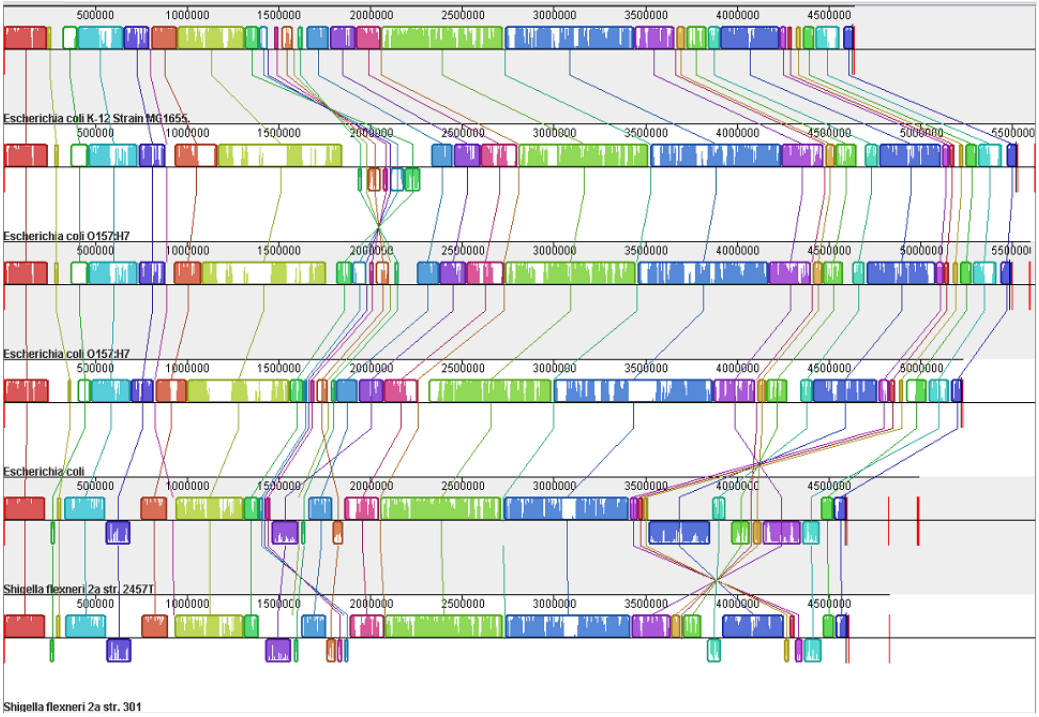


4. and 5. Recursive Anchoring and Gapped Alignment

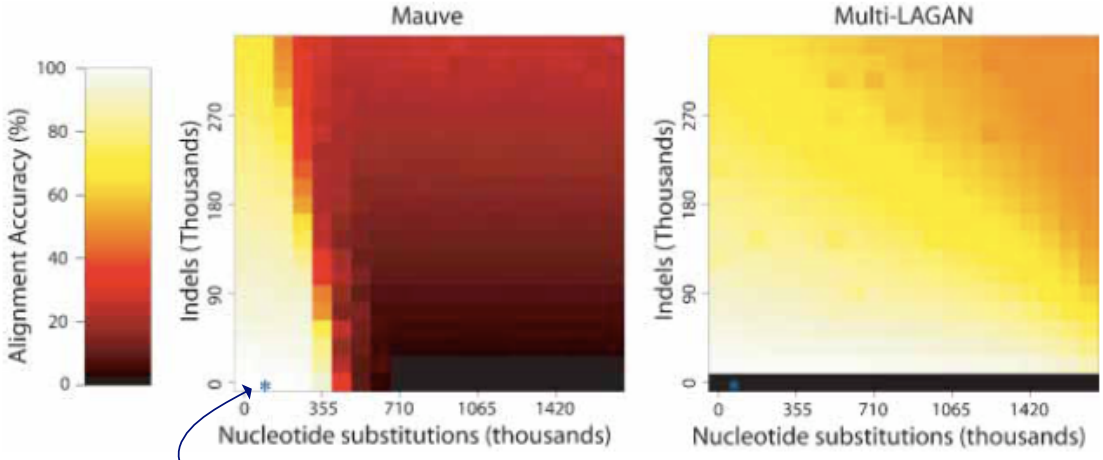
- recursive anchoring (finding finer multi-MUMs and LCBs) and standard alignment (CLUSTALW) are used to extend LCBs



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



Mauve vs. MLAGAN: Accuracy on Simulated Genome Data



substitution and indel rates observed in enterobacteria

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

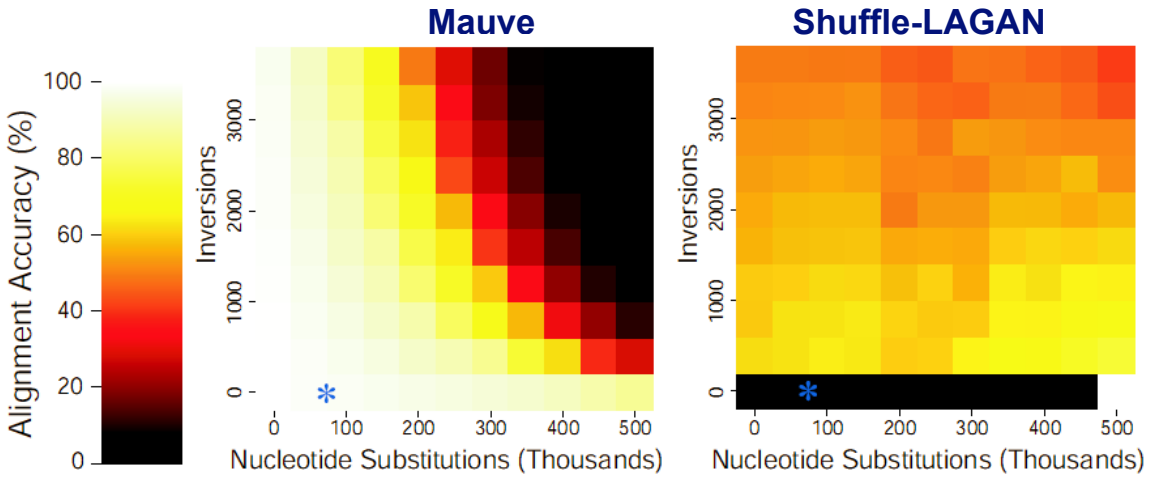
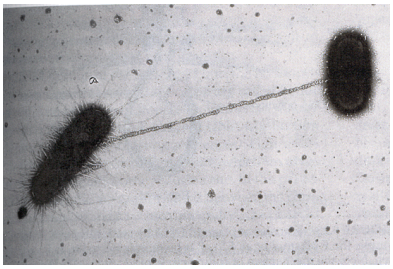
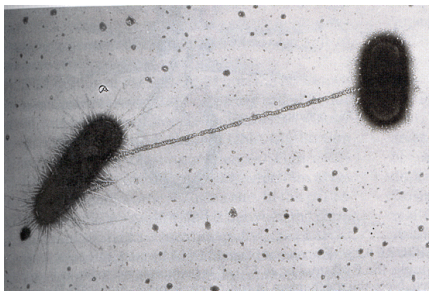


Figure courtesy of Aaron Darling

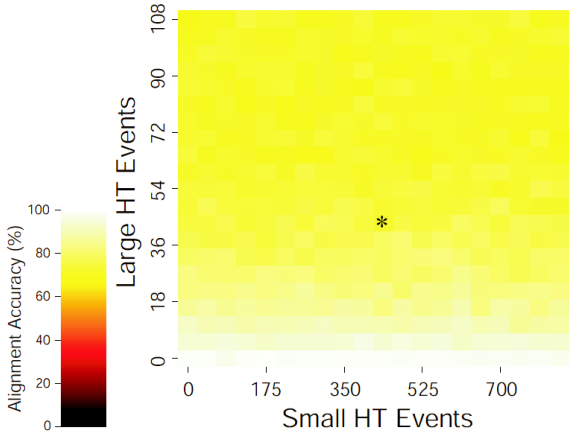
Evolution with *Horizontal Transfer*



Mauve Accuracy on Simulated Enterobacteria-like Data



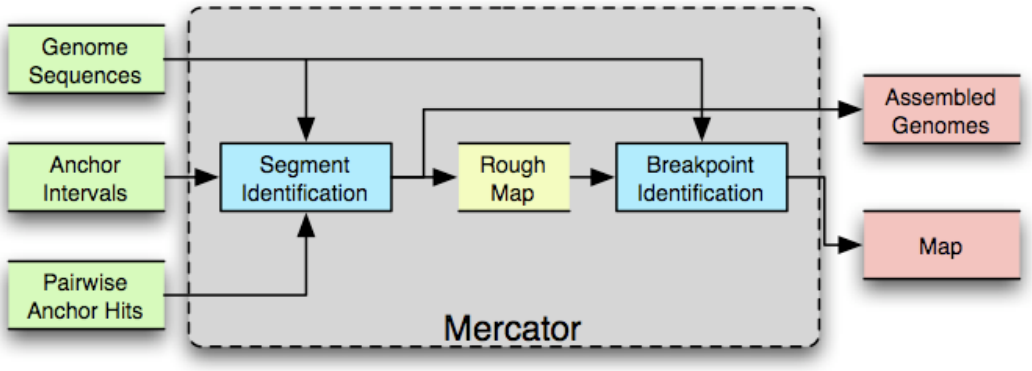
- data here include horizontal transfers



- 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

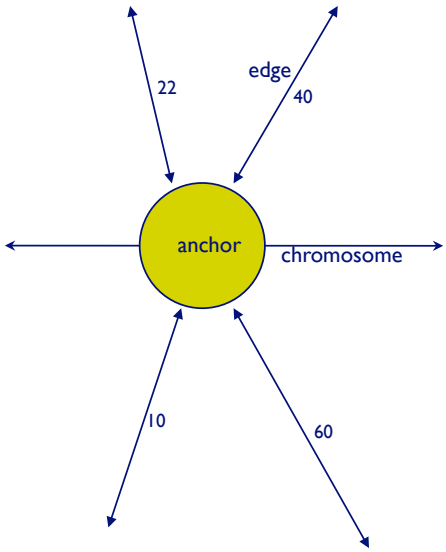
Mercator



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

Establishing Anchors Representing Orthologous Segments

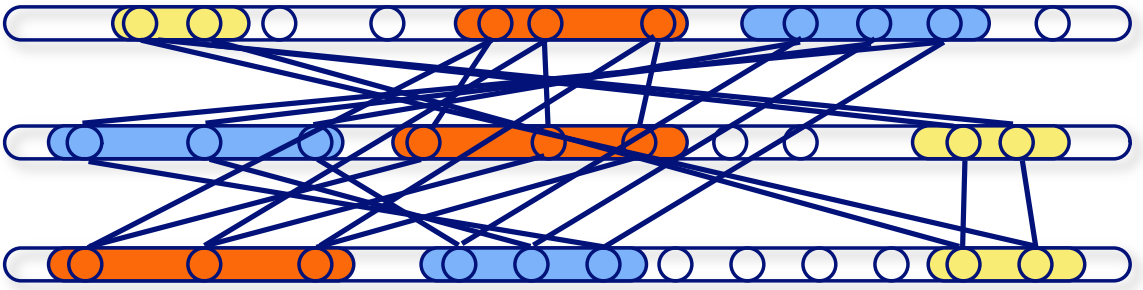
- anchors can correspond to genes, exons or MUMS
- e.g., may do all-vs-all pairwise comparison of genes
- construct graph with anchors as vertices and high-similarity hits as edges (weighted by alignment score)



Rough Orthology Map

k-partite graph with edge weights

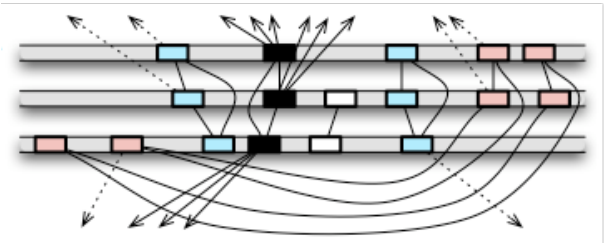
vertices = anchors, edges = sequence similarity



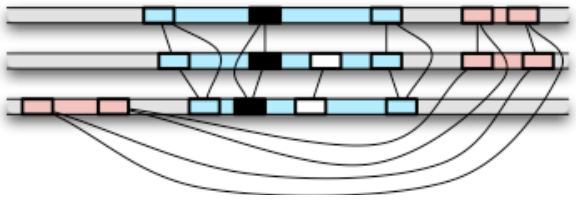
Greedy Segment Identification

- 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

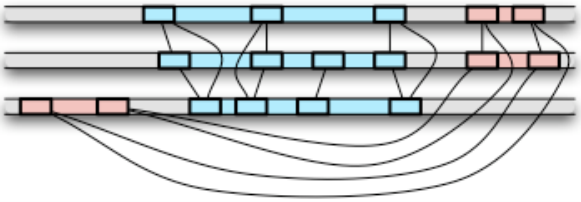
Mercator Example



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



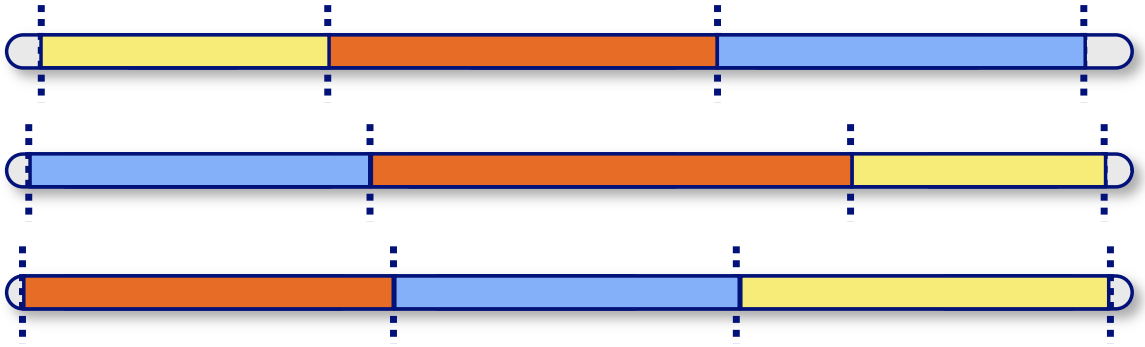
segments are formed by red and blue anchors; inconsistent edges are filtered



2-cliques are found and incorporated into segments

Refining the Map: Finding Breakpoints

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

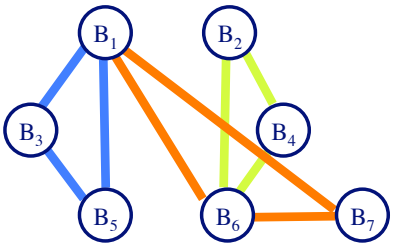


- Mercator finds breakpoints by using inference in an *undirected graphical model*

Undirected Graphical Models

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

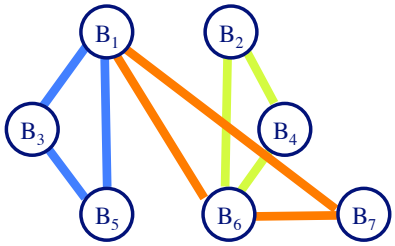
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$



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

Undirected Graphical Models

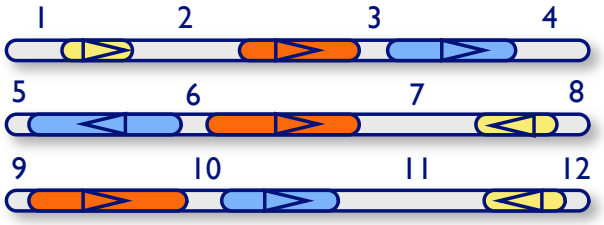
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$

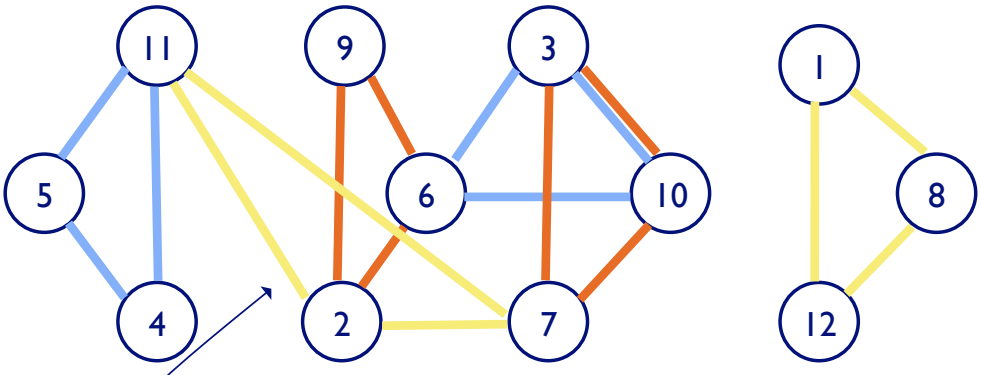


for the given graph:

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

The Breakpoint Graph





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

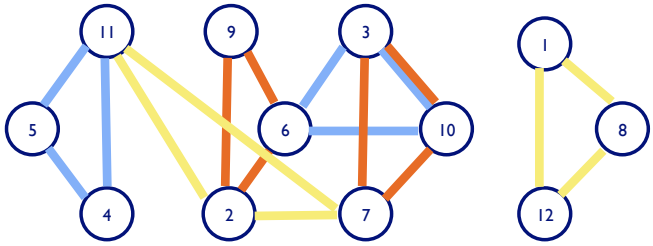
Breakpoint Undirected Graphical Model

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

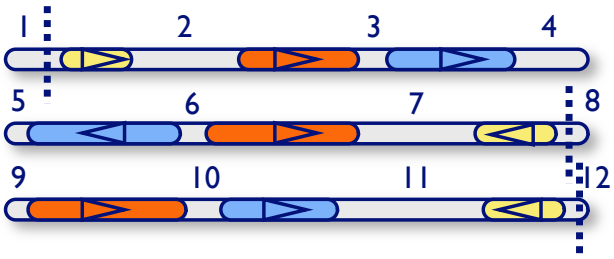
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$

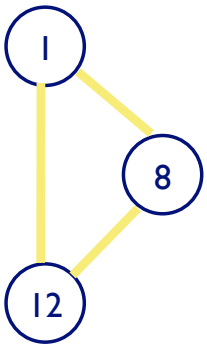
configuration of breakpoints

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



Breakpoint Undirected Graphical Model

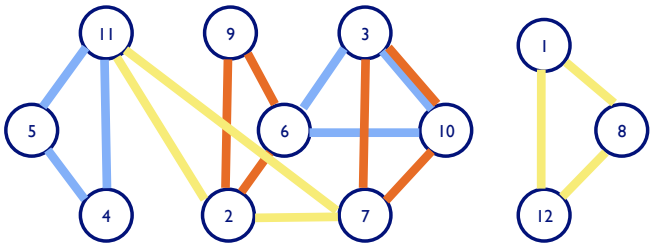




- the possible values for a variable indicate the possible coordinates for a breakpoint
- the potential for a clique is a function of the alignment score for the breakpoint regions split at the breakpoints $\mathbf{b}_C$

Breakpoint Undirected Graphical Model

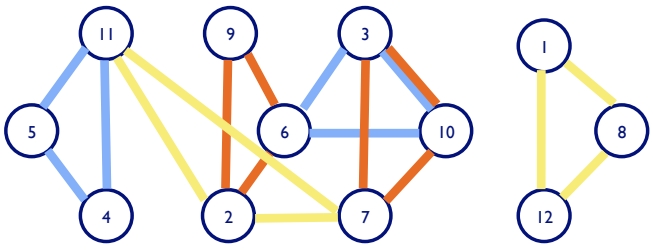
$$p(\mathbf{b}) = \frac{1}{Z} \prod_{C \in cliques} \psi_C(\mathbf{b}_C)$$



- *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

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



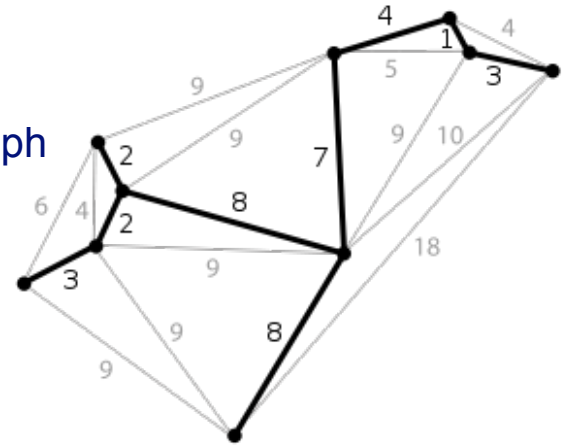
- assign potentials, based on pairwise alignments, to edges only

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

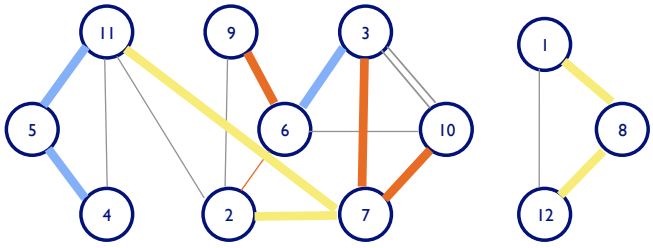
- eliminate edges by finding a *minimum spanning forest*, where edges are weighted by phylogenetic distance

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 or 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)