Multiple Whole GenomeAlignment

BMI/CS 776
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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

Algorithms for Large-Scale MSA

- MLAGAN (Brudno et al., Stanford)
- Mauve (Darling et al., Univ. of Wisconsin)
- Mercator (Dewey and Pachter, UC Berkeley)

The MLAGAN Method

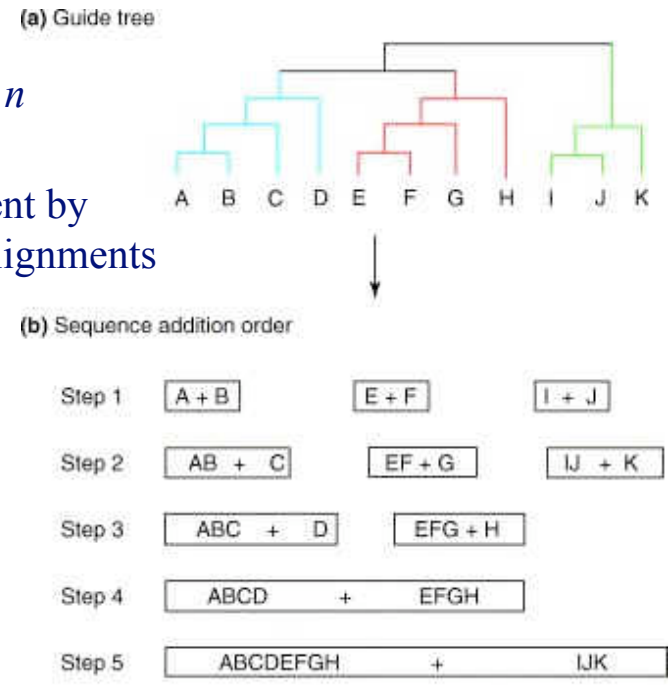
Given: k genomes X^1 , ... , X^k, guide tree T

```
for each pair of genomes X^i , X^j
    anchors = find_anchors(X^i, X^j)          // used in calls to LAGAN
align = progressive_alignment(T)
for each genome X^i                           // iterative refinement
    anchors = segments of X^i with high scores in align
    align = LAGAN(align - X^i, X^i)           // realign X^i
```

```
progressive_alignment(T)
    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)
        return align
```

Progressive Alignment

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

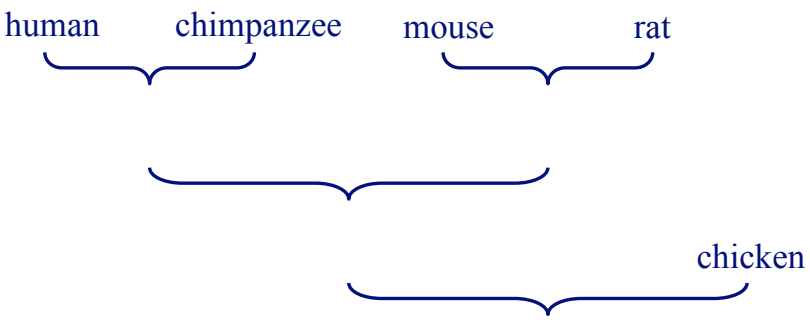


Progressive Alignment: MLAGAN Example

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

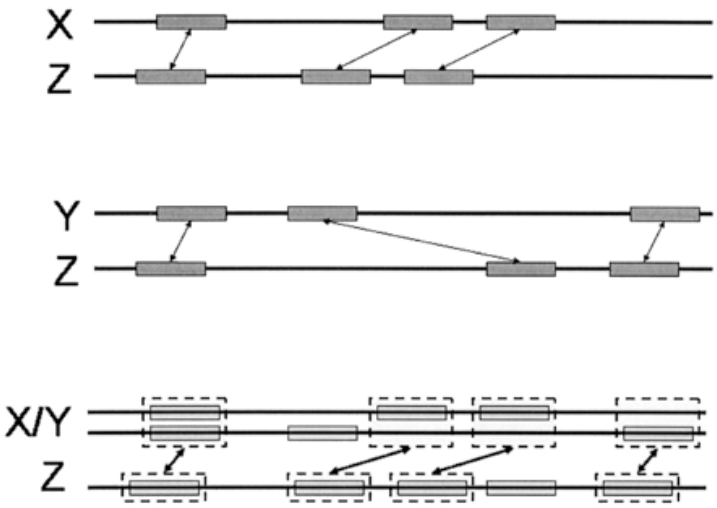
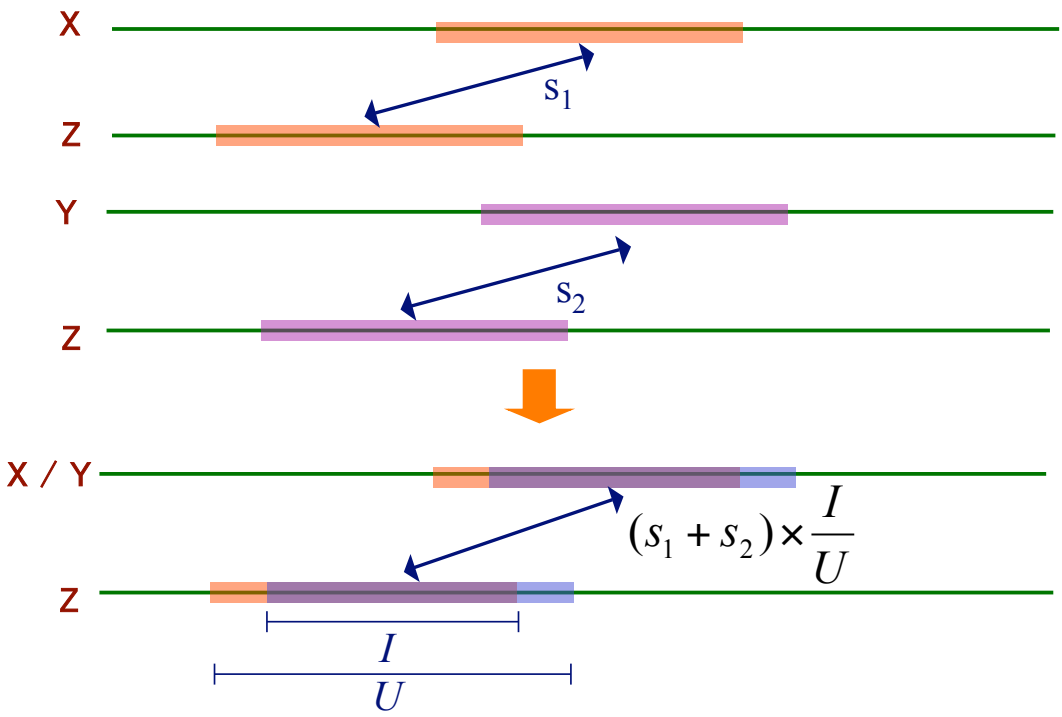
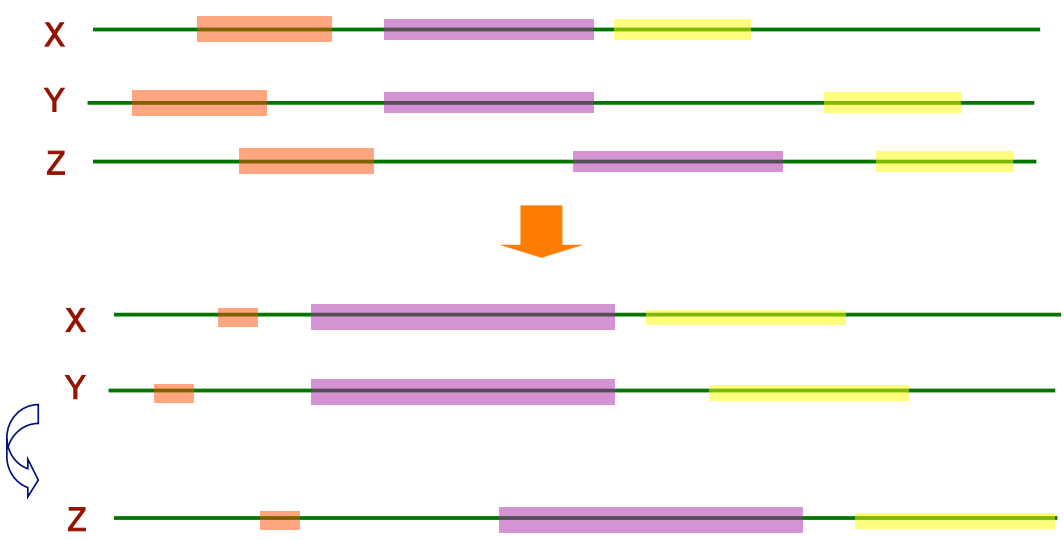


Figure from: Brudno et al. *Genome Research*, 2003

Reweighting Anchors in MLAGAN



Iterative Refinement in MLAGAN



- remove a given sequence from multiple alignment
- re-determine anchors
- realign sequence using these anchors

The Mauve Method

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!

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

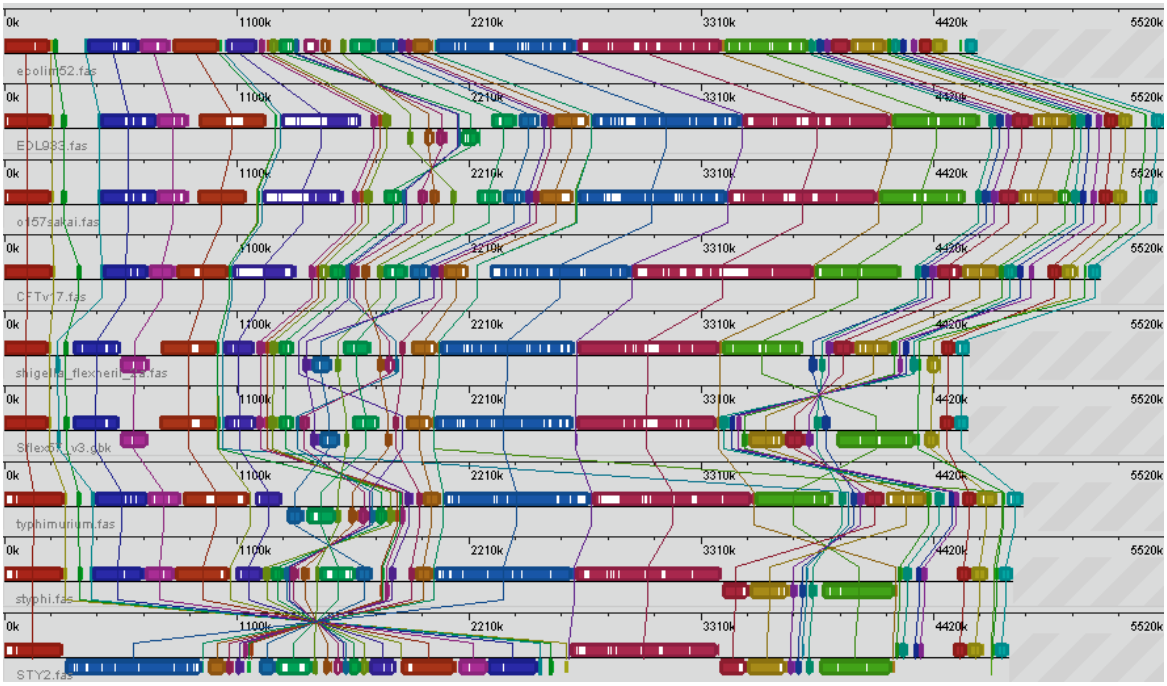
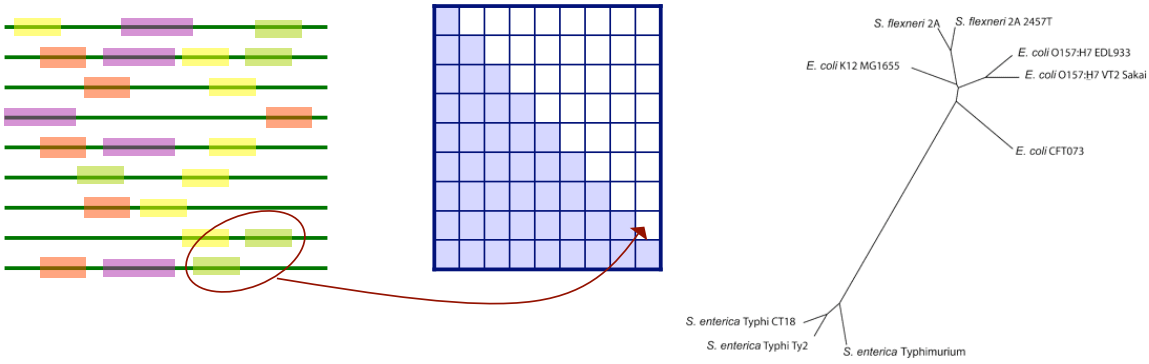


Figure courtesy of Aaron Darling

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;



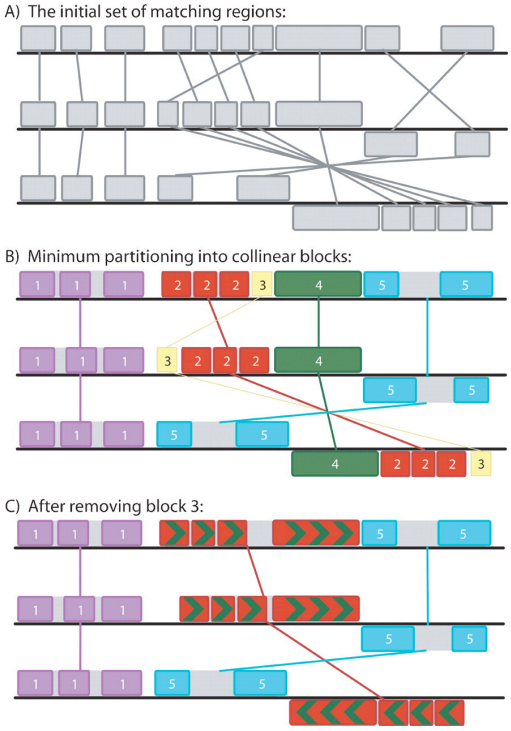
- distance between two sequences is based on fraction of sequences shared in multi-MUMs

3. Selecting Anchors: Finding Local Collinear Blocks

repeat

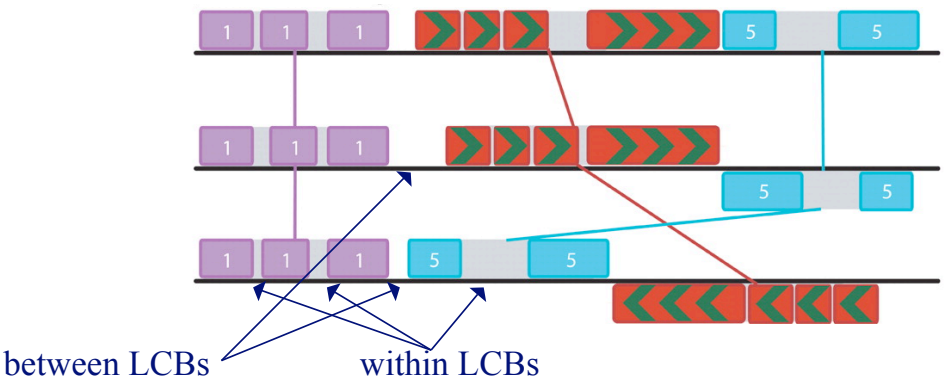
- partition set of multi-MUMs, M into collinear blocks
- find minimum-weight collinear block(s)
- remove minimum weight block(s) if they're sufficiently small

until minimum-weight block is not small enough

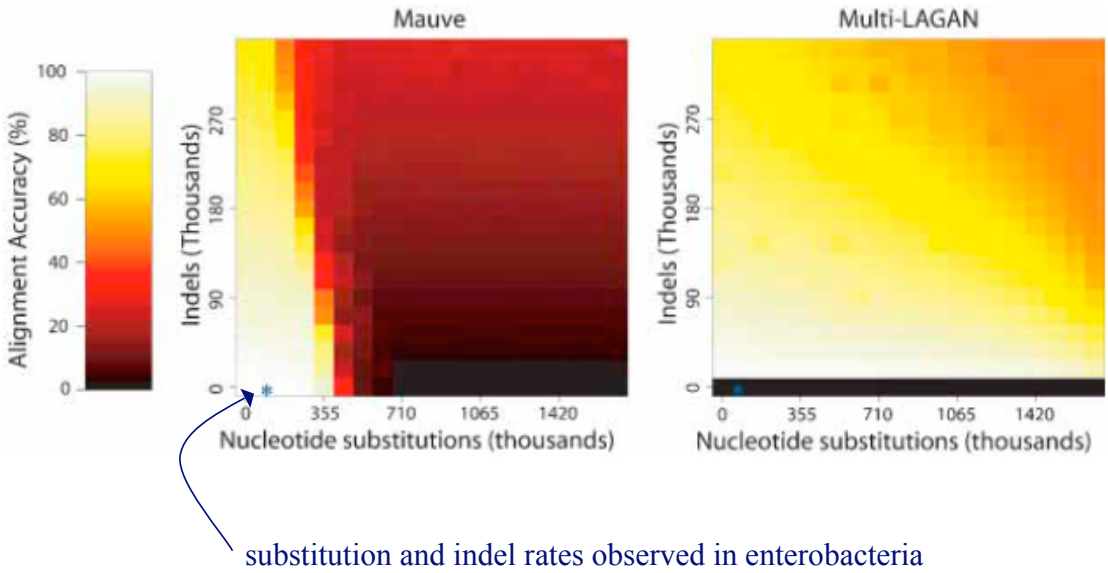


4. and 5. Recursive Anchoring and Gapped Alignment

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



Mauve vs. MLAGAN: Accuracy on Simulated Genome Data



substitution and indel rates observed in enterobacteria

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

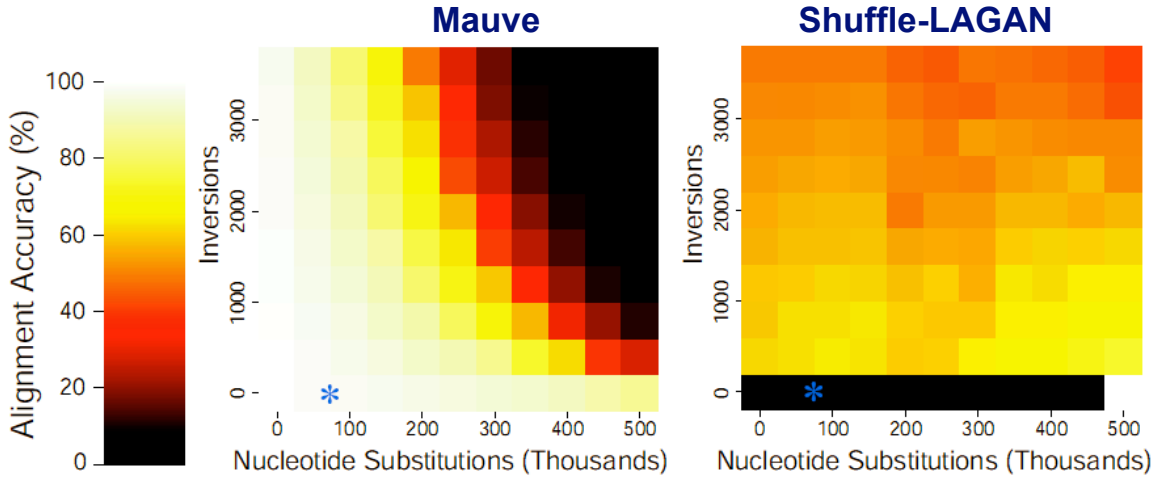
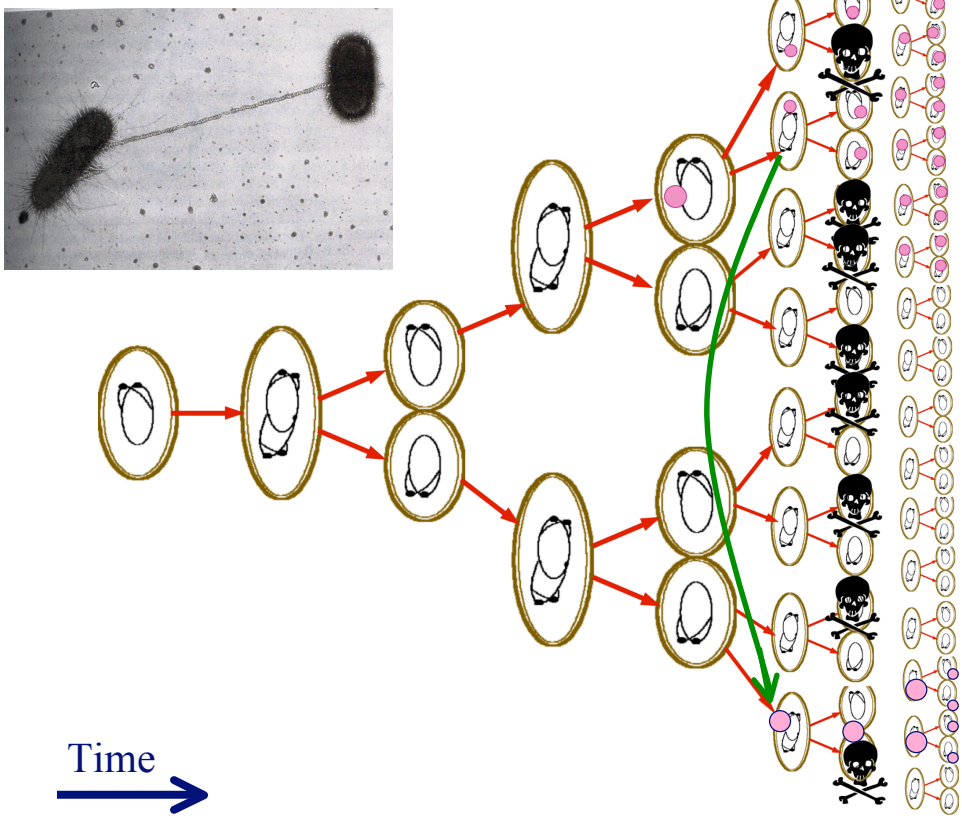
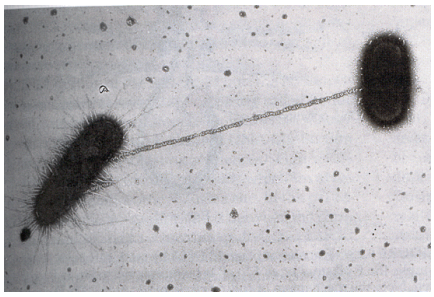


Figure courtesy of Aaron Darling

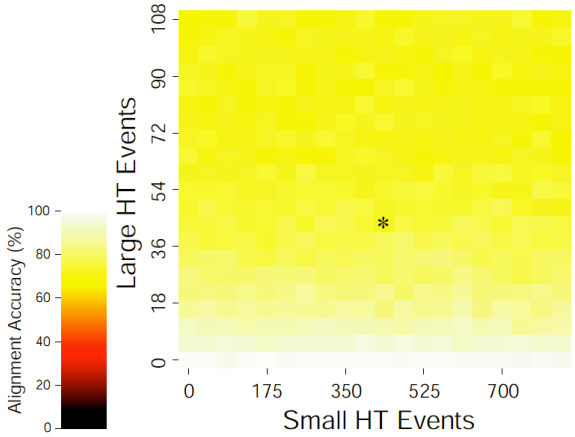
Evolution with *Horizontal Transfer*



Mauve Accuracy on Simulated Enterobacteria-like Data



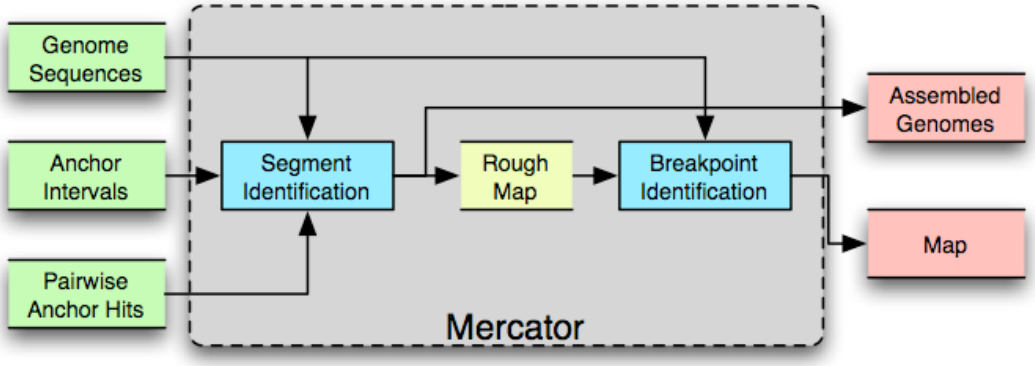
- data here include horizontal transfers



- 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

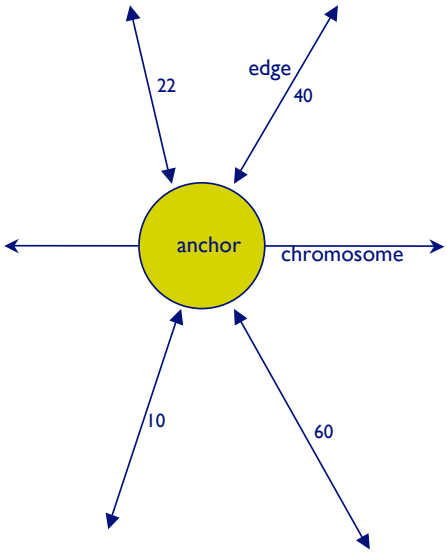
Mercator



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

Establishing Anchors Representing Orthologous Segments

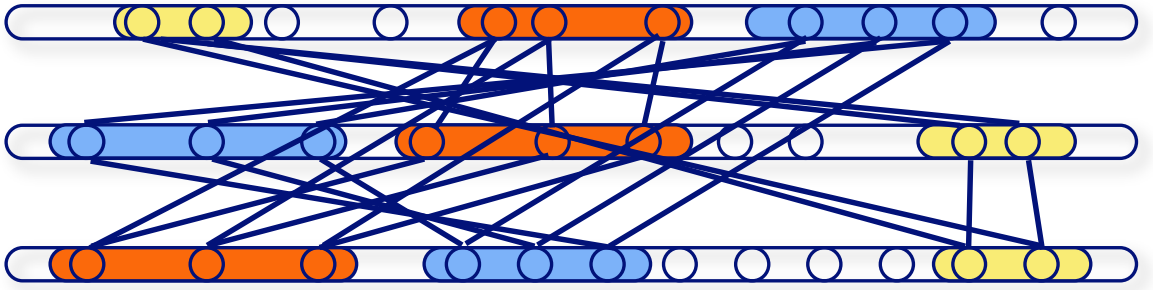
- anchors can correspond to genes, exons or MUMS
- e.g., may do all-vs-all pairwise comparison of genes
- construct graph with anchors as vertices and high-similarity hits as edges (weighted by alignment score)



Rough Orthology Map

k-partite graph with edge weights

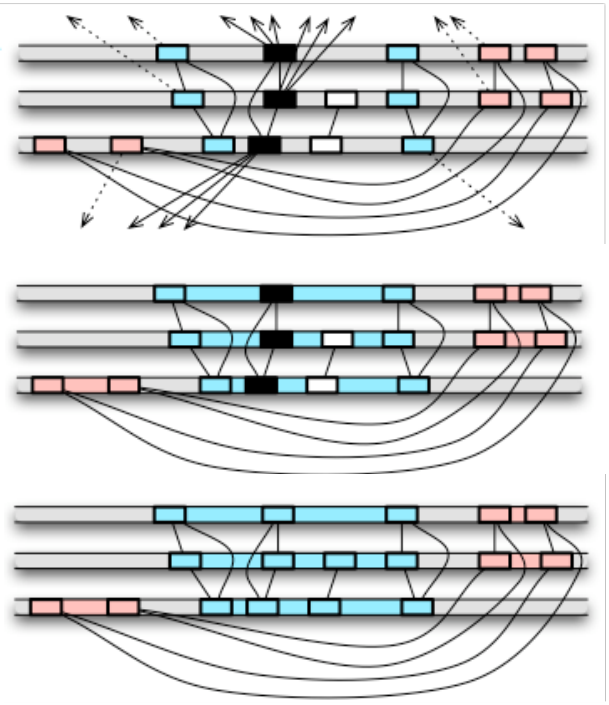
vertices = anchors, edges = sequence similarity



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 $\geq i$
  - join colinear cliques into *segments*
  - filter edges not consistent with significant segments

Mercator Example



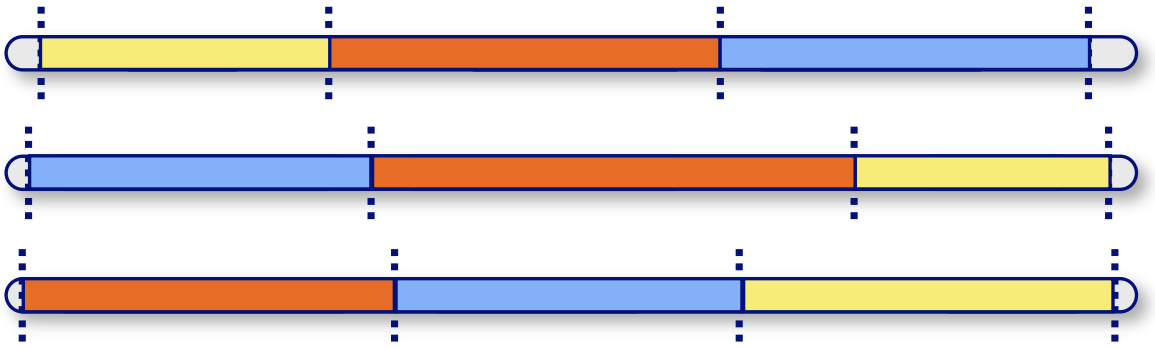
repetitive elements (black anchors) are identified
3-cliques (red and blue anchors) are found

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

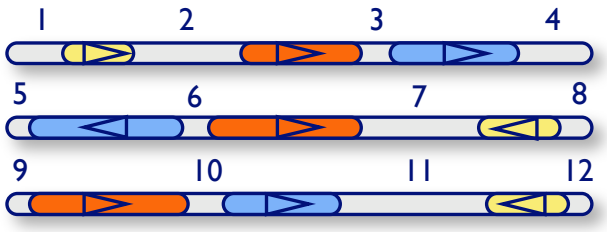
2-cliques are found and incorporated into segment

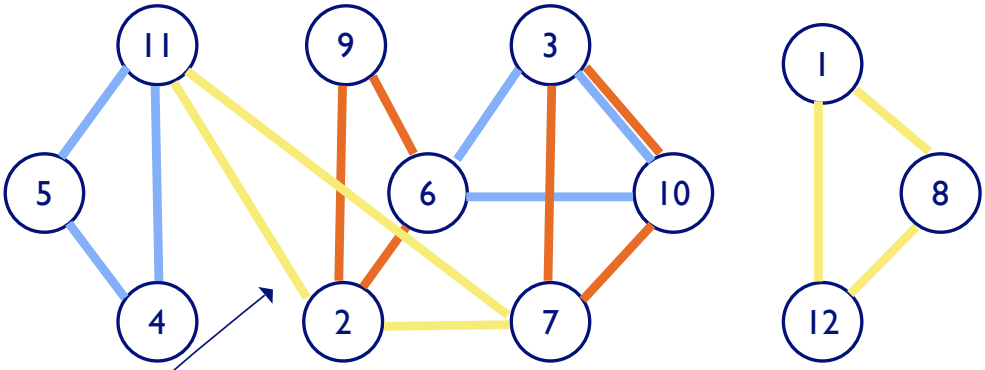
Refining the Map: Finding Breakpoints

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



The Breakpoint Graph





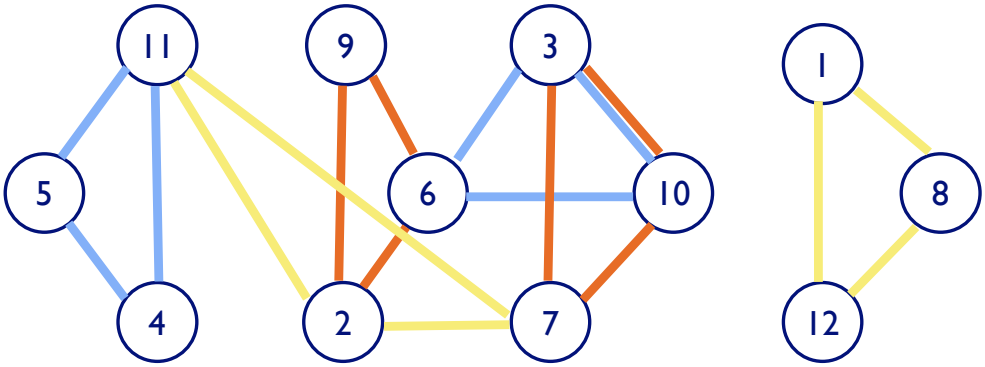
some prefix of region 2 and some prefix of region 11 should be aligned

Breakpoint Undirected Graphical Model

b: configuration of breakpoints

$\psi_{B_C}(b_C)$: probability of multiple alignment of clique B_C

$$p(b) = \frac{1}{Z} \prod_{C \in \mathcal{C}} \psi_{B_C}(b_C)$$



Breakpoint Undirected Graphical Model

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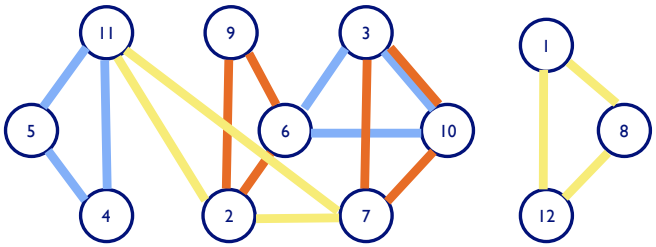
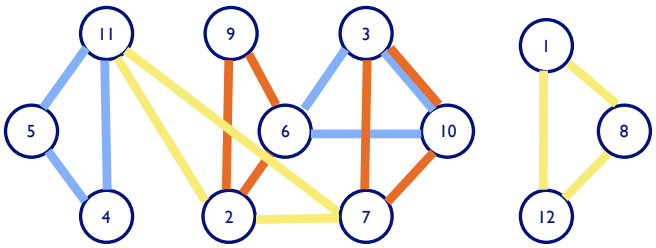


- *inference task*: find most probable configuration *b* of breakpoints
- not tractable in this case

Making Inference Tractable in Breakpoint Undirected Graphical Model

$$p(b) = \frac{1}{Z} \prod_{C \in \mathcal{C}} \psi_{B_C}(b_C)$$



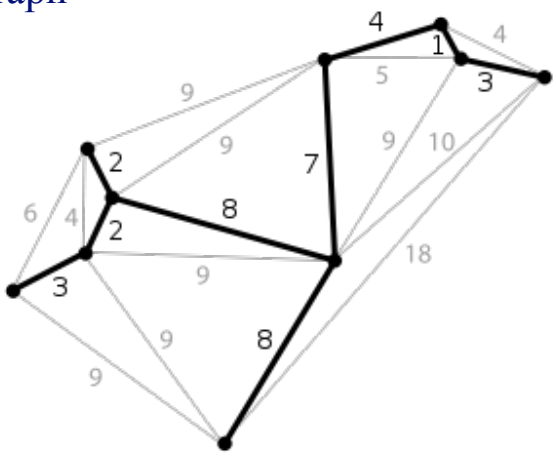
- assign potentials, based on pairwise alignments, to edges only

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

- 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 MAP inference 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)