Lecture 22:
Perfect Phylogeny

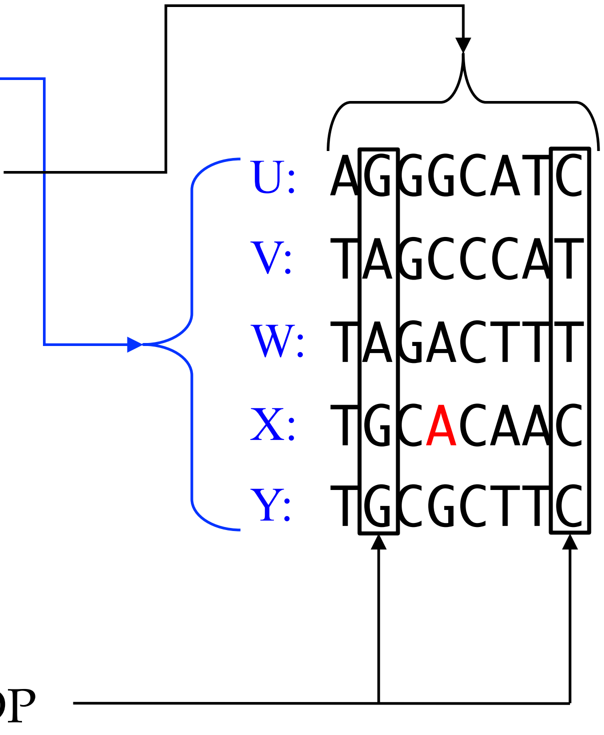
Not in textbook

Outline

- Thus far
  - distance-based evolutionary trees
    - Additive guarantees that the tree would reproduce all pairwise distances, but not all distance matrices are additive
    - Sequences → Distances ~~→~~ Sequences
  - character-based evolutionary trees
    - Trees directly from sequences
    - The most general version is hard (Large parsimony)
- Infinite Sites Model
- Perfect Phylogeny
- Local vs Global Phylogenetic Trees

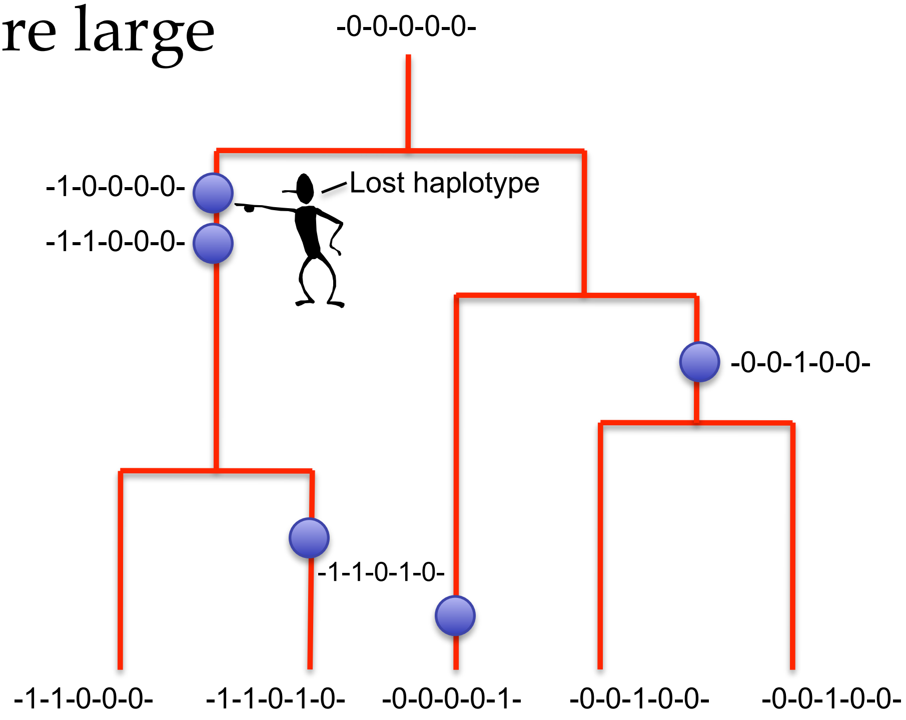
Character State Matrix M

- M has *n* rows (samples)
- M has *m* columns (characters)
- M_{ij} denotes the state object *i* has for character *j*
- Sequence Diversity Patterns (SDPs) often reoccur



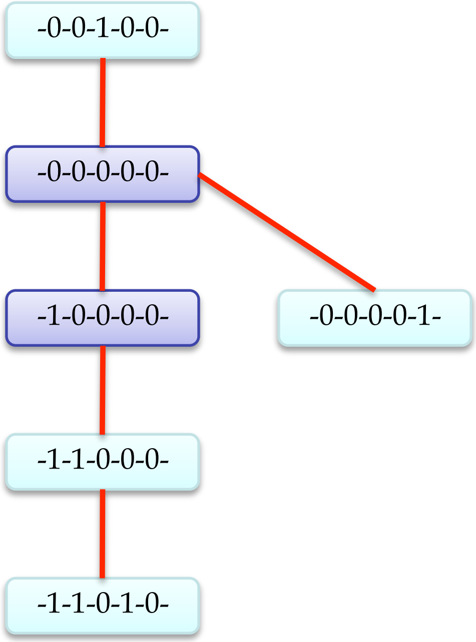
Infinite Sites Model

- Assumes mutations are rare events
- Assumes DNA sequences are large
- Multiple mutations at the same site are extremely rare
- Infinite Sites Model assumes that multiple mutations never occur at the same sequence position
- Thus, all states are "Binary" or "Biallelic"



A Different Kind of Tree

- Unrooted "Perfect Phylogeny" Tree
- Nodes correspond to sample sequences (haplotypes), both current and ancestral
- Edges correspond to actual mutations (SNPs)
- Removal of an edge creates a bipartition (each part is distinguished by a character at some position)
- SDPs can occur multiple times, and their frequency can be used as a edge weight



- Tree leaves correspond to mutations (allele variants) that are unique to a sequence, i.e. a SDP with only one minority allele instance, *private*

Unrooted Trees

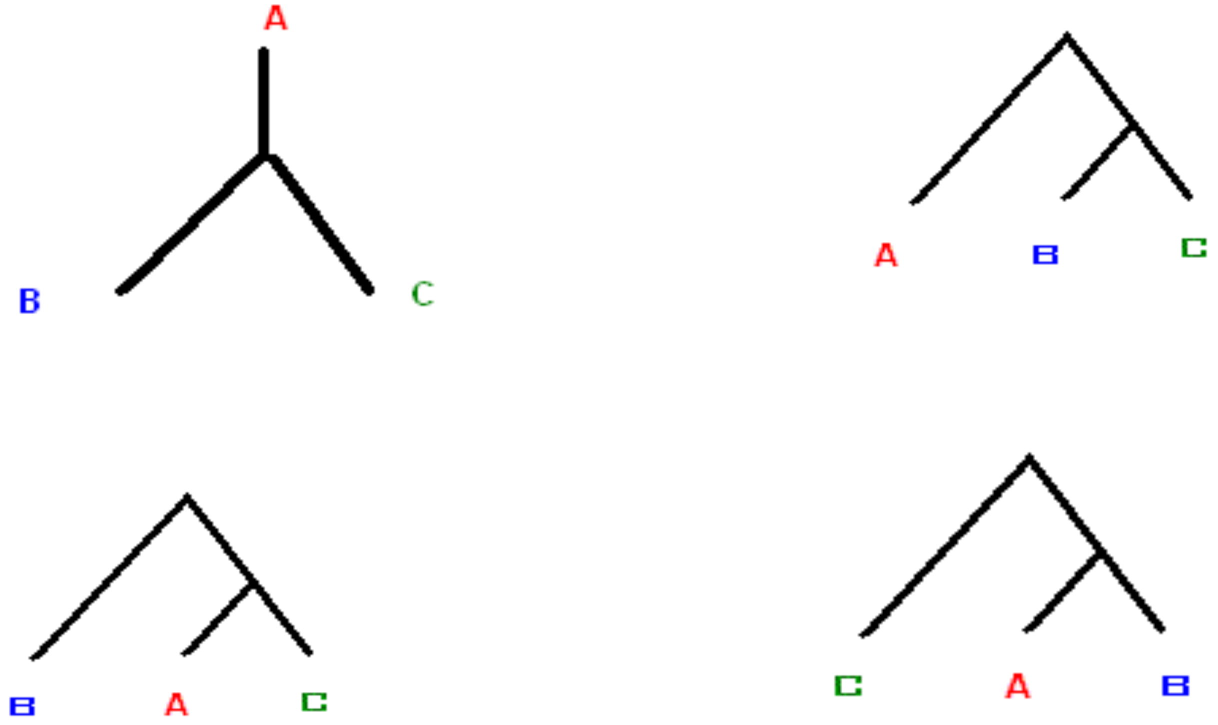
- Unrooted phylogenetic trees are less specific than evolutionary trees
- The edges are undirected, thus the direction from ancestor to descendent are unknown
- All but one leaf, however, and possibly all leafs (if the root is an interior node) must be descendents
- Slightly fewer labeled unrooted trees than labeled rooted tree

$$uT(n) = \frac{(2n-4)!}{2^{n-2}(n-2)!} \qquad \text{vs} \qquad T(n) = \frac{(2n-3)!}{2^{n-2}(n-2)!}$$

- Moreover, any node can be an "observed" sample in a phylogenetic tree whereas only leaf nodes are observed an evolutionary tree

Unrooted Binary Tree

Three different evolutionary (rooted) trees that are consistent with a common phylogenetic (unrooted) tree

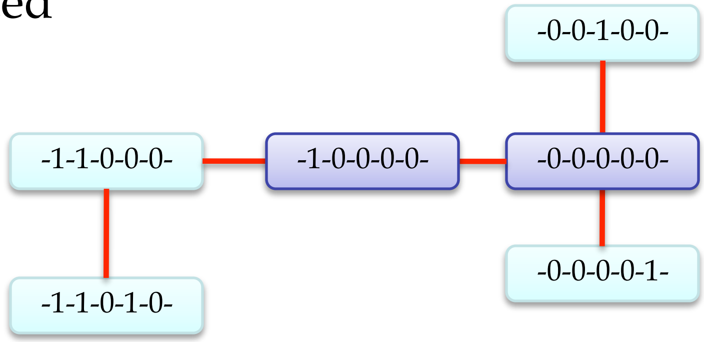


Building a Phylogenetic Tree

- Assume we only have direct access to *current* haplotypes
- Construct a pair-wise distance matrix between haplotypes using Hamming distances
- Add smallest edge between all nodes which do not introduce a loop
- If the smallest distance is greater than 1 add d-1 "hidden" nodes between the pair so that adjacent nodes have a hamming distance of 1
- Augment the distance matrix with the new nodes and claim the introduced edges
- Repeat finding the smallest distance, and augmenting until the graph is connected

	S_1	S_2	S_3	S_4	S_5
H_1	**1**	**1**	**0**	**0**	**0**
H_2	**1**	**1**	**0**	**1**	**0**
H_3	**0**	**0**	**0**	**0**	**1**
H_4	**0**	**0**	**1**	**0**	**0**

	H_2	H_3	H_4	H_A	H_B
H_1	⊘	3	**3**	**2**	⊘
H_2		4	**4**	**3**	2
H_3			**2**	⊘	2
H_4				⊘	2
H_A					⊘


-0-0-1-0-0-

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-0-0-0-0-1-

Four-Gamete Test

- Our tree construction method will not work for any arbitrary set of character sequences; it only works for those that satisfy the assumptions of the infinite sites model
- Under the assumption of the infinite sites model all SNP pairs exhibit the property no more that 3 out of the possible 4 allele combinations occur
- Direct consequence of only one mutation per site
- Showing that all SNP pair combinations satisfy the four gamete test is a *necessary* and *sufficient* condition for there to exist a perfect phylogeny tree

	S_1	S_2	S_3	S_4	S_5
H_1	1	1	0	0	0
H_2	1	1	0	1	0
H_3	0	0	0	0	1
H_4	0	0	1	0	0

Questions

- Does there exist SDPs that are compatible with all others?

Private SNPs are compatible with any other SNP

- Given N distinct haplotype sequences resulting from an infinite sites model what is minimum number of SDPs?

N-1 edges are the fewest necessary to connect N haplotypes into a “linear” tree. How many singleton SNPs occur in such a tree? 2

- Given N distinct haplotype sequences resulting from an infinite sites model what is maximum number of SDPs?

2N-3 edges, the number of edges in an unrooted tree with N leaves

Exercise

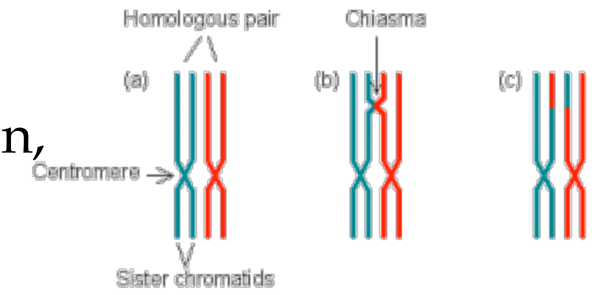
- Consider the following SNP panel

	S_1	S_2	S_3	S_4	S_5	S_5
H_1	0	0	1	0	0	1
H_2	0	0	1	0	0	0
H_3	0	1	0	0	0	0
H_4	1	0	0	0	1	0
H_5	1	0	0	1	0	0

- Satisfies the four gamete test?
- Construct the tree
- Is the SDP 11001^T possible?

Complications

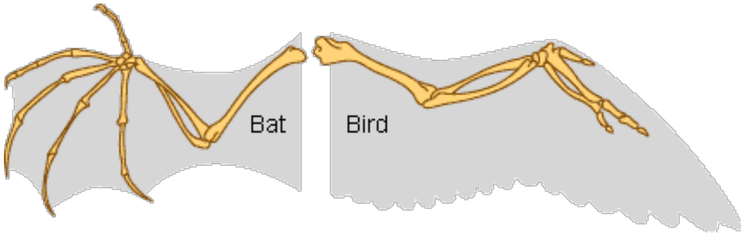
- There are two issues that limit the use of Perfect Phylogeny, both are violations of our infinite-sites model assumptions
  - In addition to mutations, haplotype diversity is generated by recombination, exchange of subsequences between haplotypes
  - Mutations reoccur at the same position (Homoplasy)



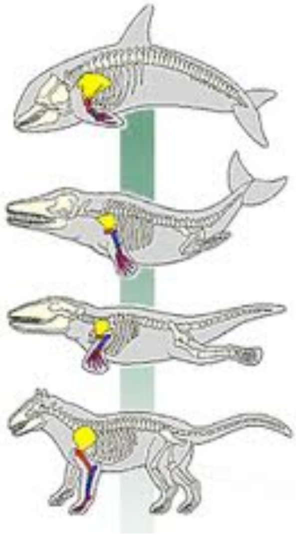
- Thus, global (over the entire genome) perfect phylogenies are rare, but local perfect phylogenies are common
- How do we locate recombinations and recurrent mutations?

Non-sequence Complications

- Evolutionary Convergence:
  - Wings on birds and bats
  - Fins on Seals and Fish

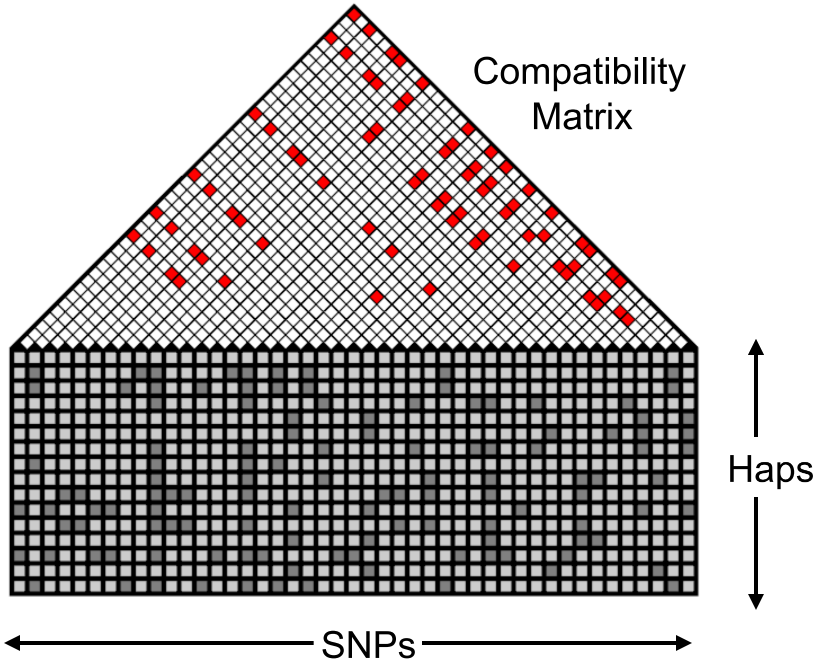


- Evolutionary Reversals:
  - Fish → Lizard→ Snake
  - Fish → Mammal →Manatee
  - (gain and later loss of legs)
- Such paths also violate the infinite sites model



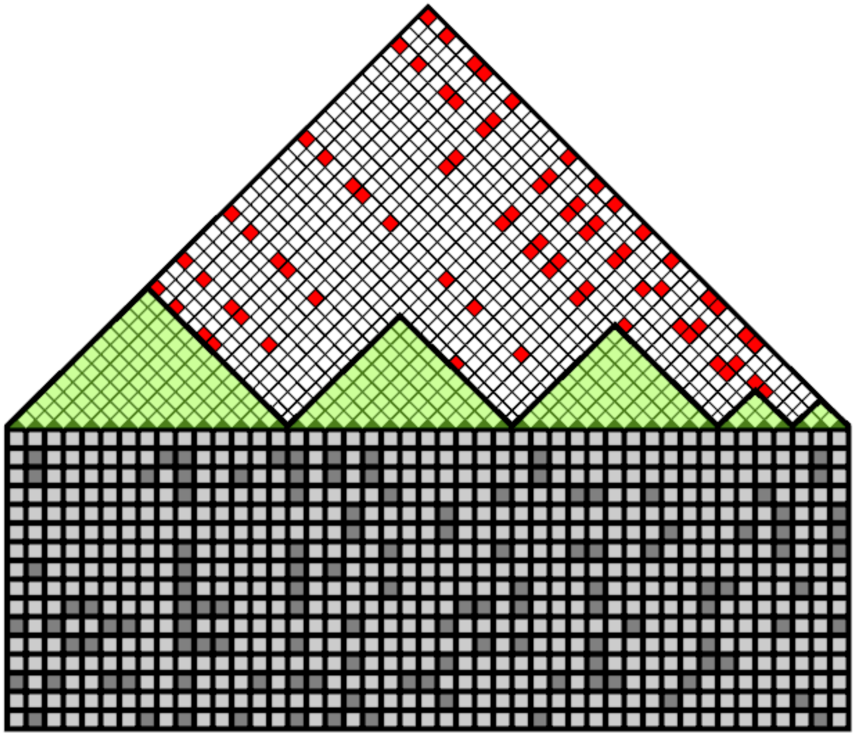
SNP Compatibility

- How do we find local genomic regions where our assumptions are valid?
- Apply 4-gamete test
- Issues
  - Can we efficiently find all compatibility intervals
  - How many intervals? (fewest necessary to cover the entire genome)
  - Unique?
  - Common properties



Algorithms

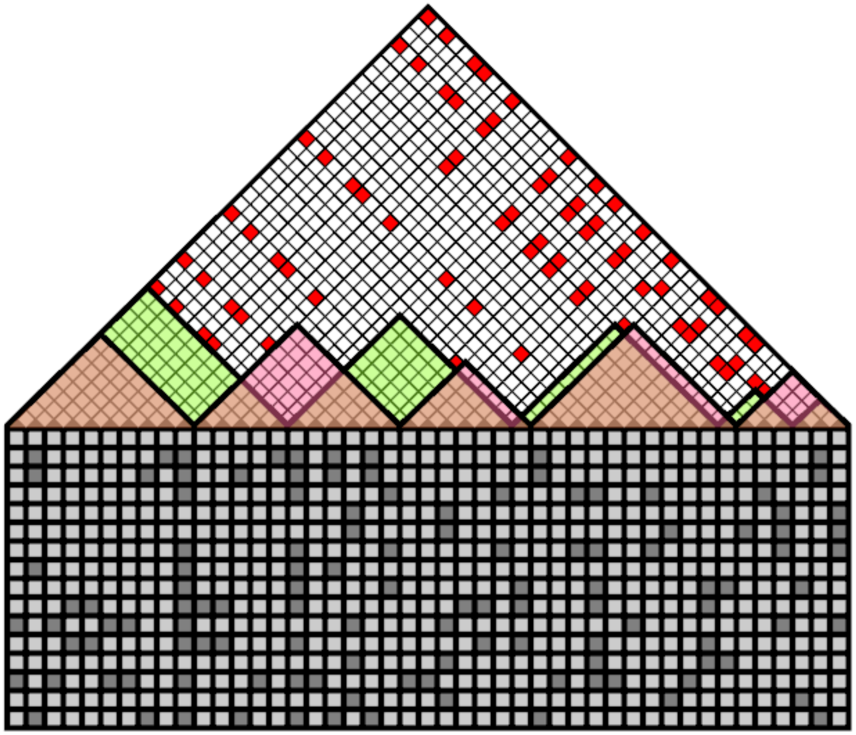
- Left-to-right scan
- Is this solution unique?



Algorithms

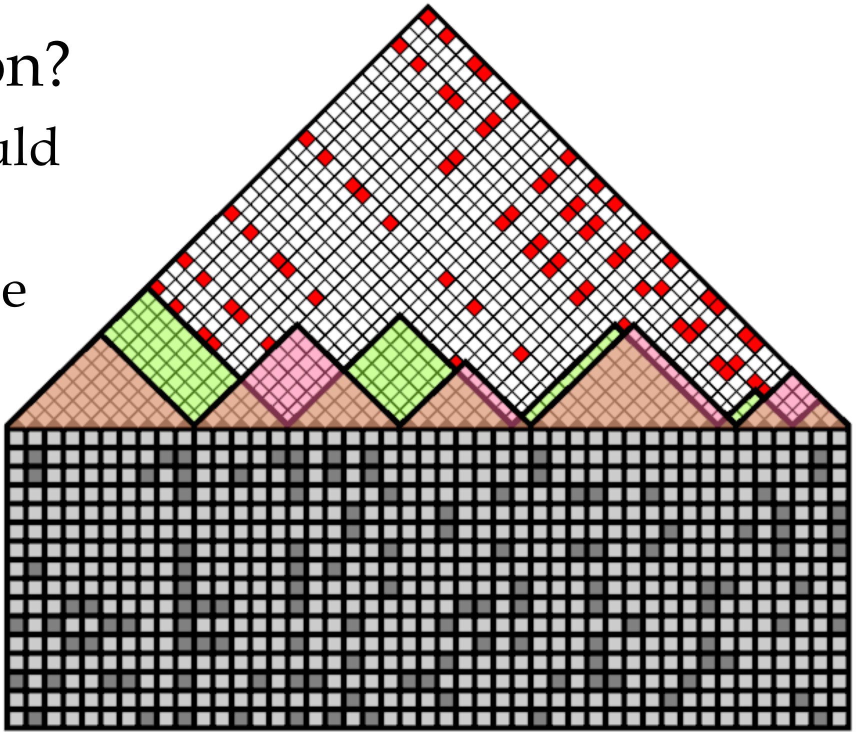
- Left-to-right scan
- Is this solution unique? **No.**
- Right-to-Left scan

- Given that the solution is not unique, which do we choose?
- The most parsimonious



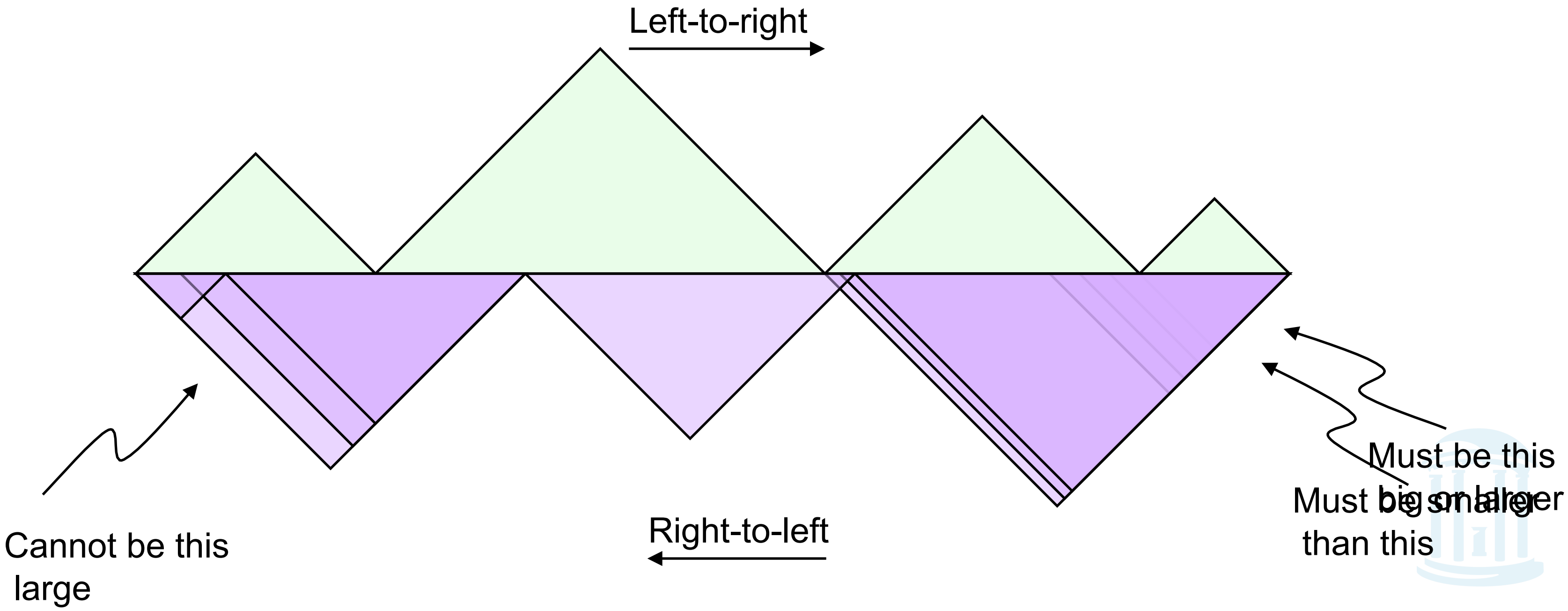
Algorithms

- Questions
  - Of all scans, which has the fewest intervals?
  - Is there a solution with fewer intervals?
- What is a better solution?
  - Clearly the intervals could be larger
  - What is the maximal size of the intervals?



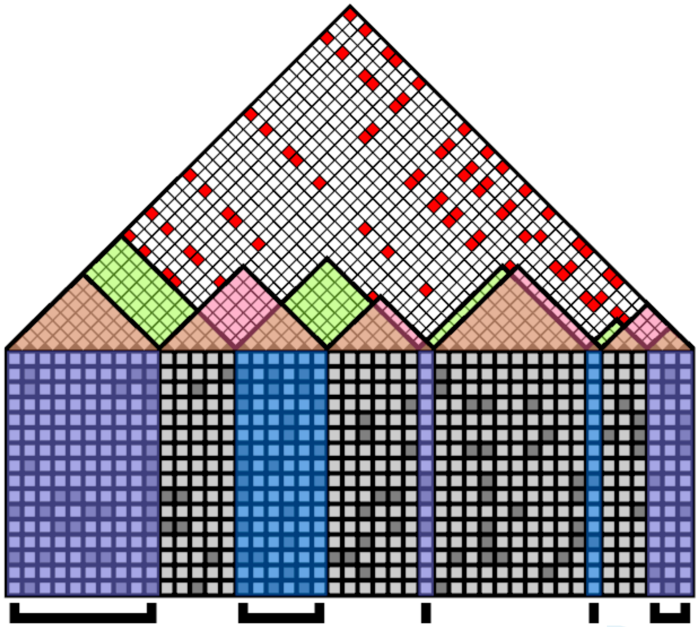
Algorithms

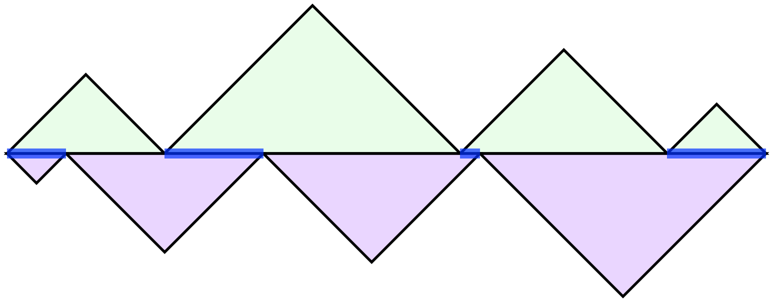
- Theorem
  - Left-to-right and right-to-left scans have the same number of intervals, *k*
  - *k* is the minimum number of intervals possible



Cores

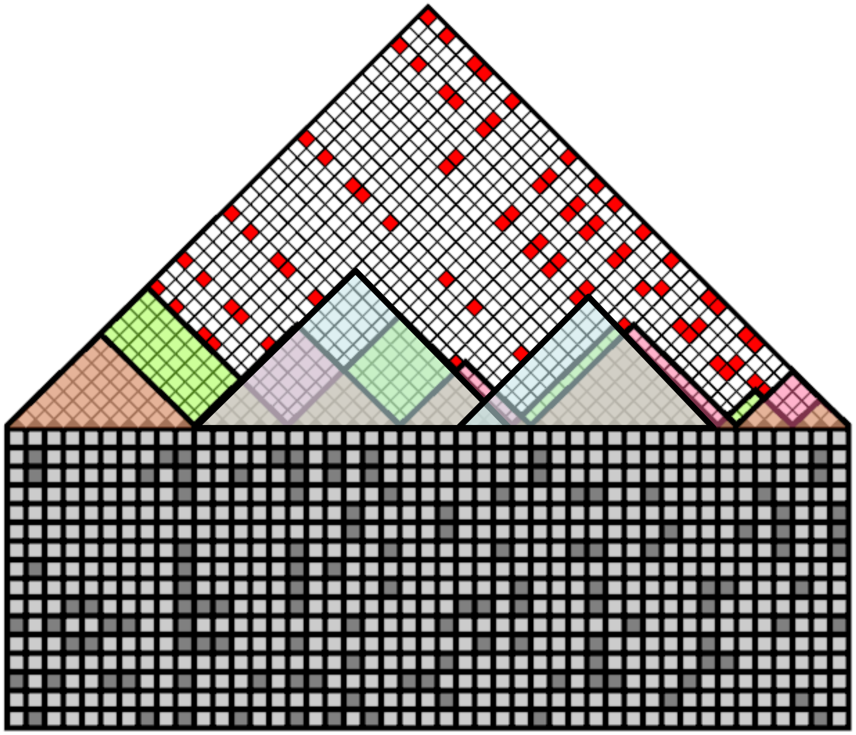
- The interval overlaps tell us something important
  - Pair the L-R and R-L scan intervals from left to right. The overlap of these pairs are the interval cores.
  - The i th *core* essentially is the SNPs that the i th interval of the L-R and R-L scan agree should be included in the i th interval of any minimal set of intervals
- A refinement of Parsimonious:
  - Use this to find the minimal set of maximally-sized intervals





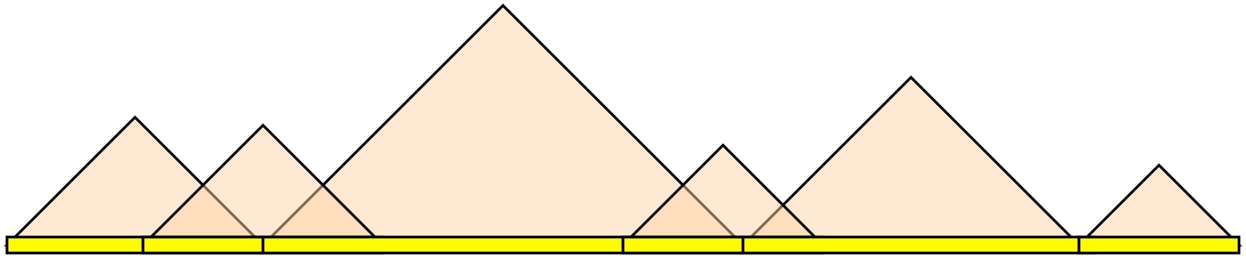
Uber Scan

- But first, lets backup momentarily
  - The left-to-right scan found a minimal set of non-overlapping intervals
  - Can we find the set of all intervals of maximal size?
  - These were clearly not found in our left-to-right or right-to-left scans



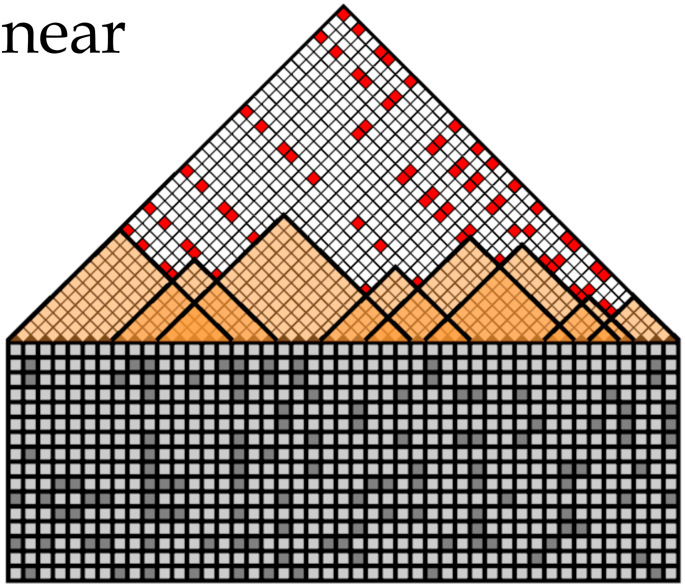
Uber Scan

- Simple modification to the left-to-right scan algorithm
  - Instead of restarting when an incompatibility is found, only remove a portion of it
  - Specifically remove everything before (in the scanning direction) and including the closest newly introduced incompatibility
  - Open a new interval starting at the first SNP in the queue
  - Continue as before



Uber Scan

- Properties
  - Will contain more than the minimal number of intervals, *k*
  - Each interval is maximal in size (bounded on each side by an incompatibility)
  - Maintains a linear runtime



Max-*k* cover

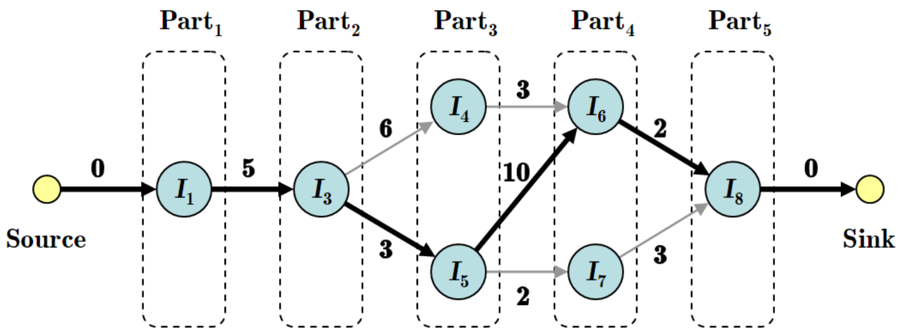
- Minimal set of *k* maximally-sized intervals
  - Must be a subset of the Uber scan, since Uber includes all intervals of maximal size
  - Search all subsets of size k?

$$\binom{|Uber|}{k}$$

    - No. Combinatorial Explosion
    - Instead restructure the problem as a graph problem

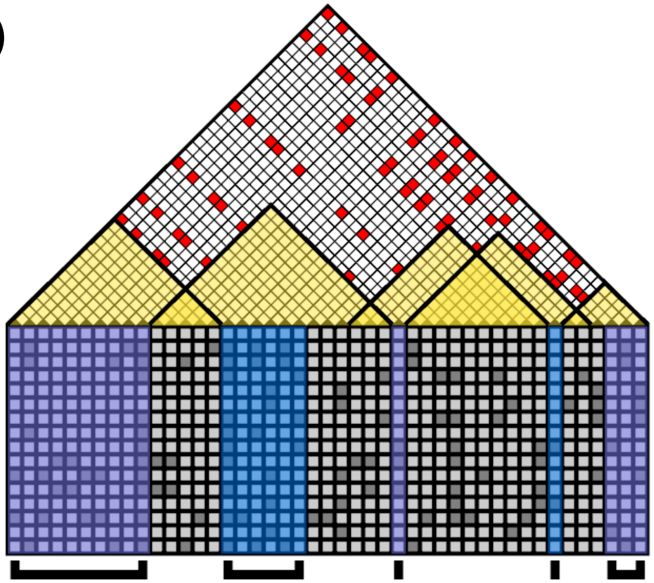
Max-*k* cover

- Minimal set of *k* maximally-sized intervals
  - We know any minimal set must include the cores
  - Find all intervals from the Uber scan that overlap each core
  - Construct a *k*-partite graph
    - Vertices are intervals
    - Edges are weighted with the amount of overlap
  - Solve for maximal path (dynamic program)



Max-*k* cover

- Properties
  - May not be unique
  - Theoretical runtime $O(ku)$, where u is the number of intervals in Uber scan
  - In practice, we never see more than 3 intervals in any part, thus $O(k)$

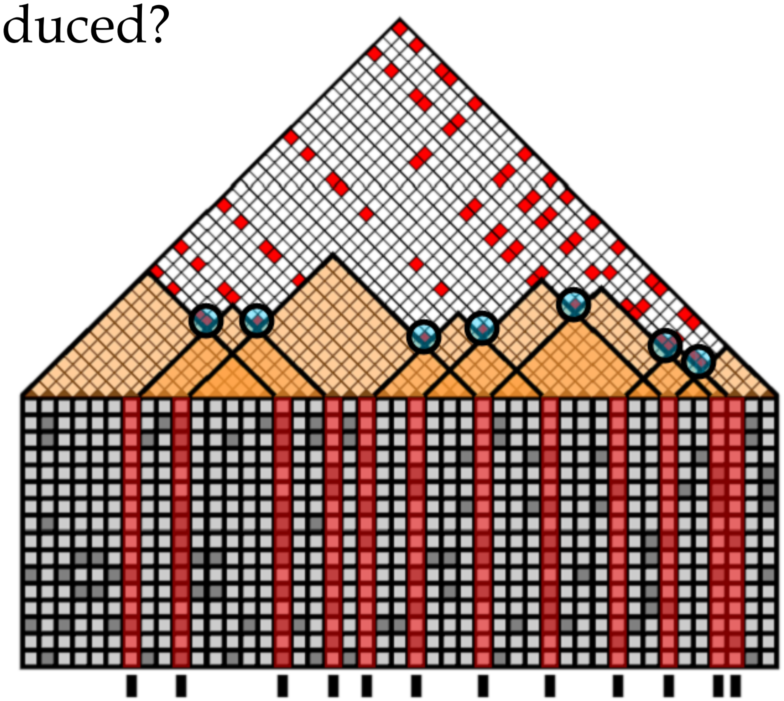


Uses

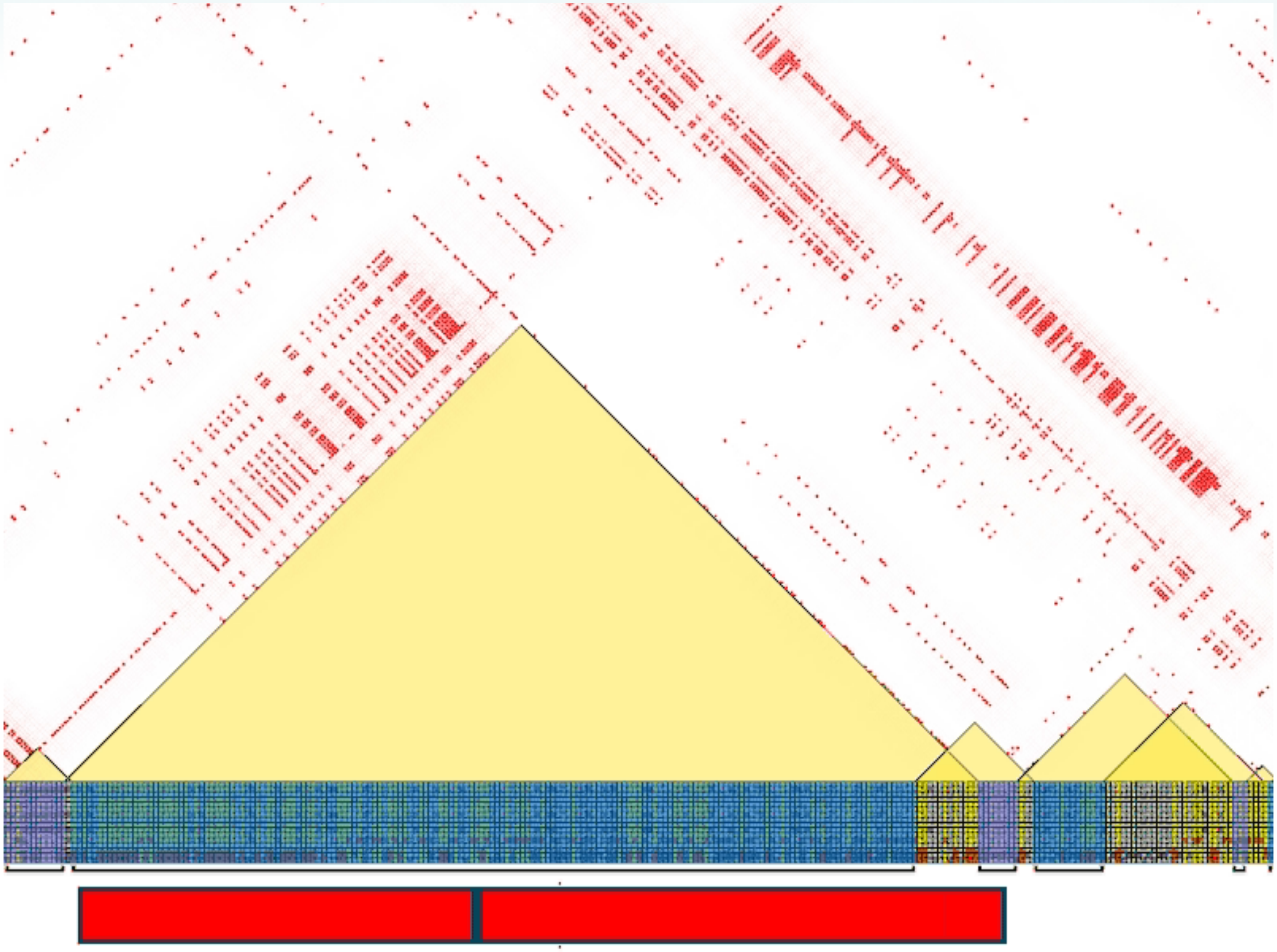
- Phylogeny trees
  - Represent the data with the fewest possible trees
  - Maximal intervals provide maximal support for each tree
- Recombination
  - *k* gives us a lower bound on the minimum number of recombinations needed to make the dataset
  - Although, not very tight
  - But it scales to large datasets

Critical SNPs

- How stable are these intervals?
  - If we remove any given SNP, will the minimal number of intervals needed, *k*, be reduced?
- Algorithm
  - – Only consider the flagging SNPs of the Uber intervals
    - Intervals are bounded by incompatibilities. Unless they are removed, the interval cannot change size



Some Context

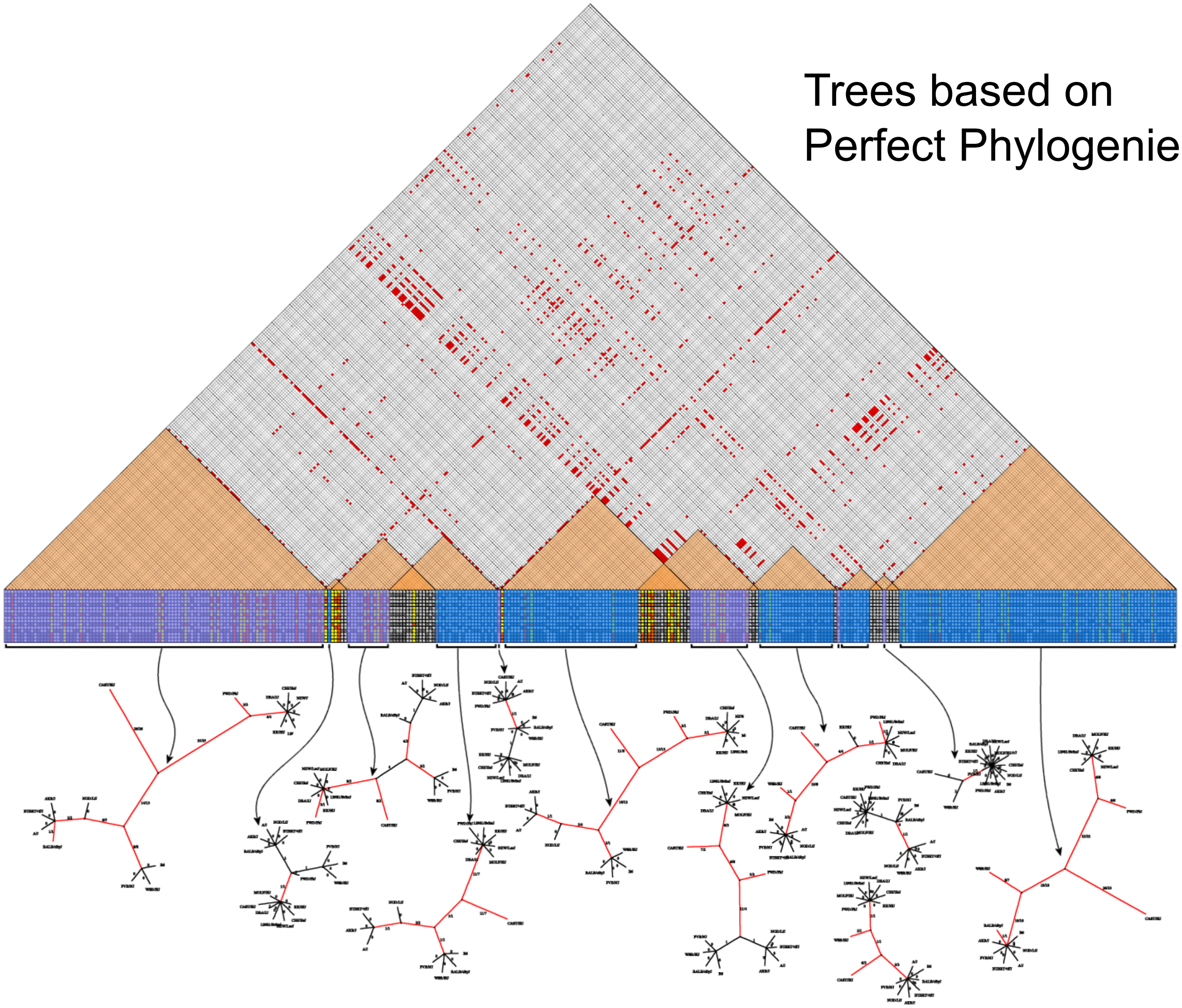


346866 of 689472 Perlegen SNPs on Chr 1, 60 Billion pairwise relationships, >7.5 GBytes

Chromosome 14

15059098-15230790

Trees based on Perfect Phylogenies



Local to Global Trees

- Given a forest of local phylogeny trees, how do we construct a global tree?
- Generally, by combining tree metrics (Sum of distances from *i* to *j*) across all trees and then applying either neighbor joining or UPMGA
- Evolution is more complicated than a simple tree
  - Common introgressions near species splits
  - Gene flows when branches interact