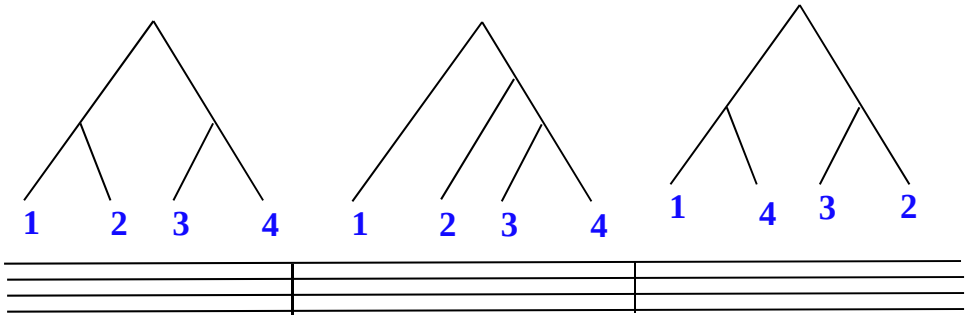
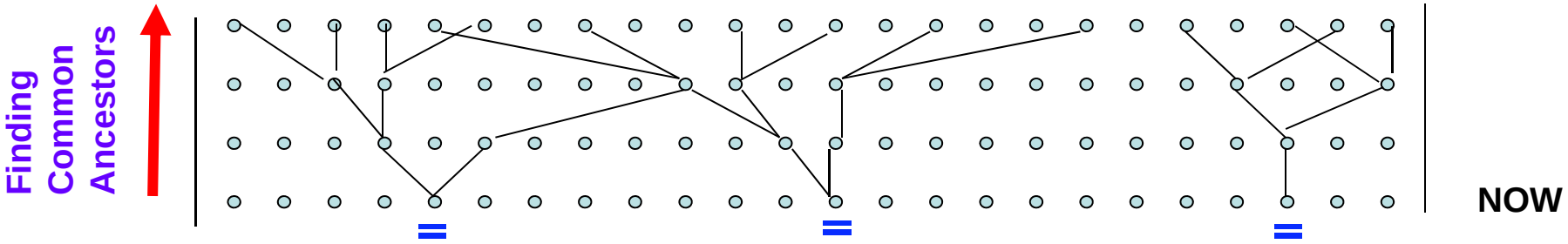
Recombination Histories & Global Pedigrees

Finding Minimal Recombination Histories



Global Pedigrees

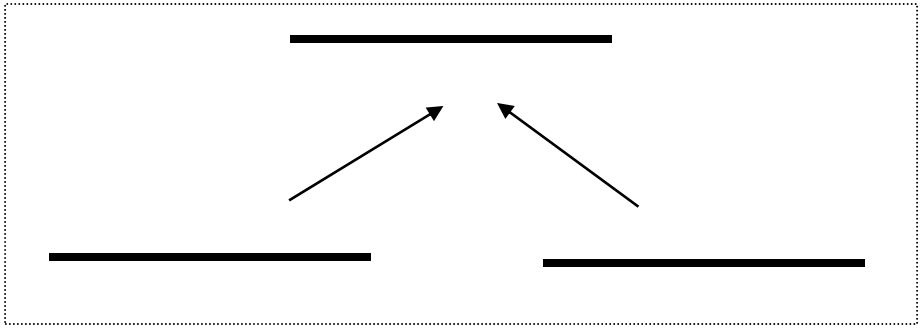


Acknowledgements

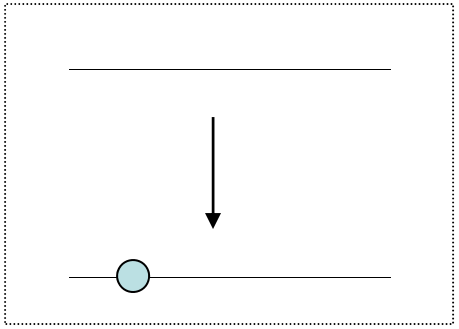
Yun Song - Rune Lyngsø - Mike Steel

Basic Evolutionary Events

Coalescent/Duplication

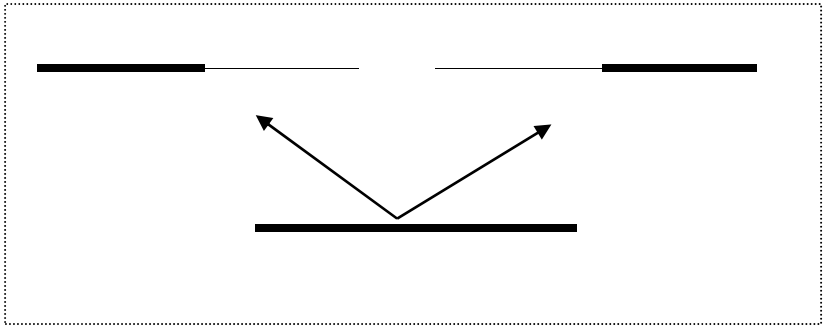


Mutation

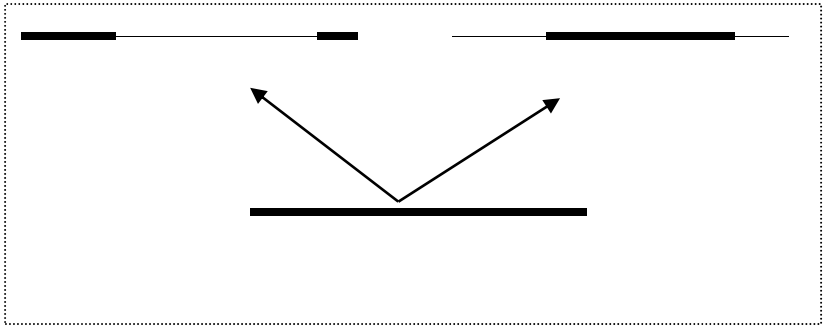


Infinite site assumption ?

Recombination



Gene Conversion

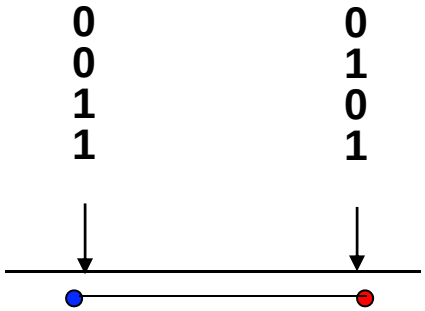


Local Inference of Recombinations

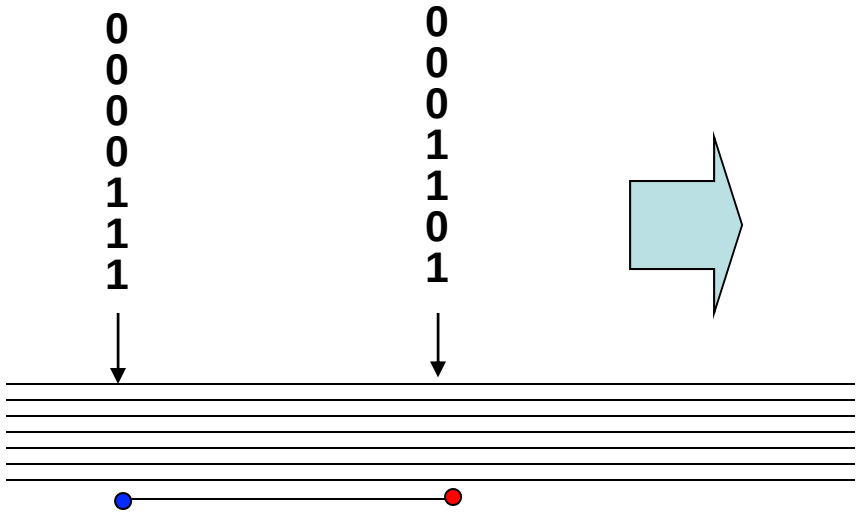
T . . . G
T . . . C
A . . . G
A . . . C

Recoding

- At most 1 mutation per column
- 0 ancestral state, 1 derived state



Incompatibility:



Four combinations

00

10

01

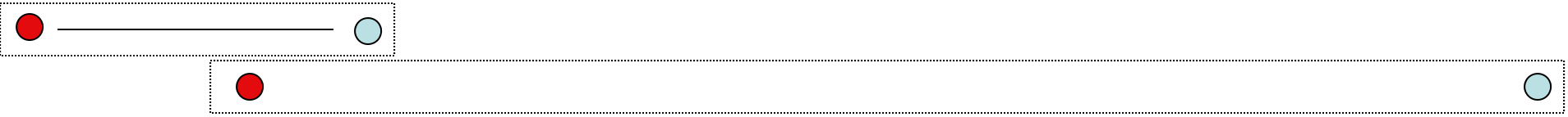
11

Myers-Griffiths (2002): **Number of Recombinations in a sample, N_R, number of types, N_T, number of mutations, N_M obeys:**

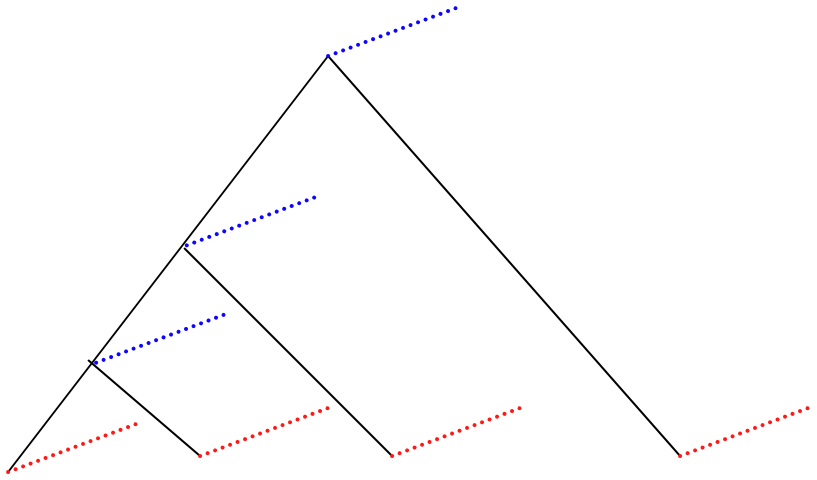
$$N_R \geq N_T - N_M - 1$$

”Observing” Recombinations: Hudson & Kaplan’s R_M

```
0 0 0 0 0 1 0 0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0
0 0 1 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0
0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0
0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1
0 0 1 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 1 0 1 0 1 1 1
0 0 1 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 0 1
1 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 0 1
1 1 1 1 1 1 0 0 1 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 0 1
```



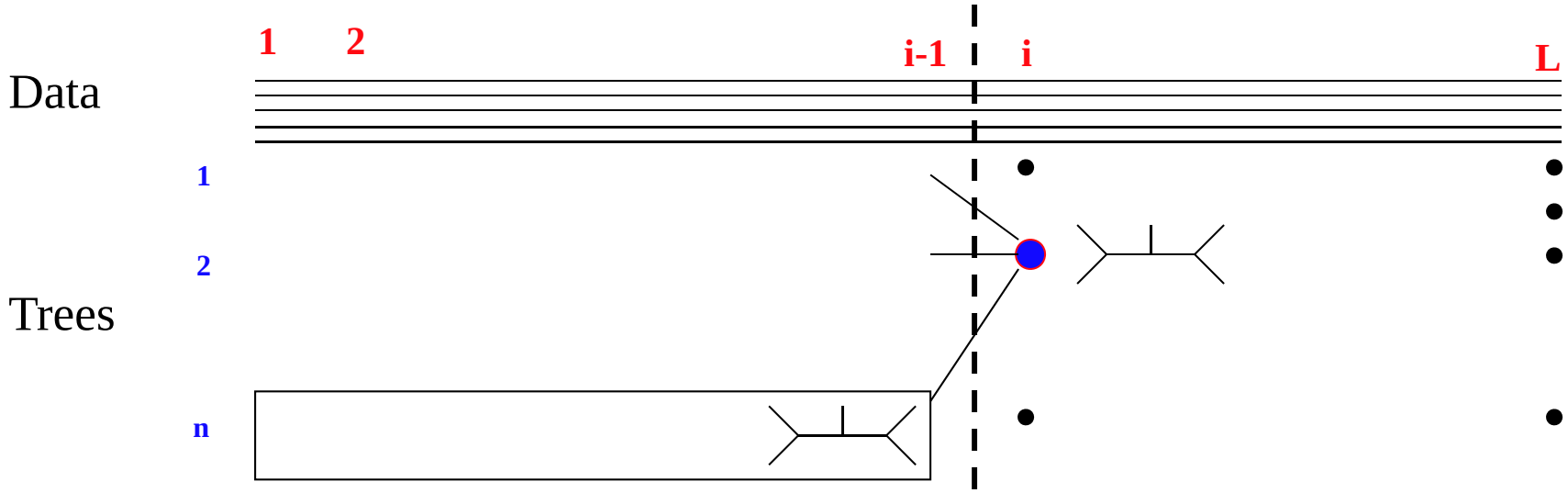
If you equate R_M with expected number of recombinations, this could be used as an estimator. Unfortunately, R_M is a gross underestimate of the real number of recombinations.



Minimal Number of Recombinations

The Kreitman data (1983): 11 sequences, 3200bp, 43(28) recoded, 9 different

Last Local Tree Algorithm:



How many local trees?

- **Unrooted** $\dfrac{(2n-2)!}{2^{n-1}(n-1)!}$
- **Coalescent** $\dfrac{n!\ (n-1)!}{2^{n-1}}$

How many neighbors?

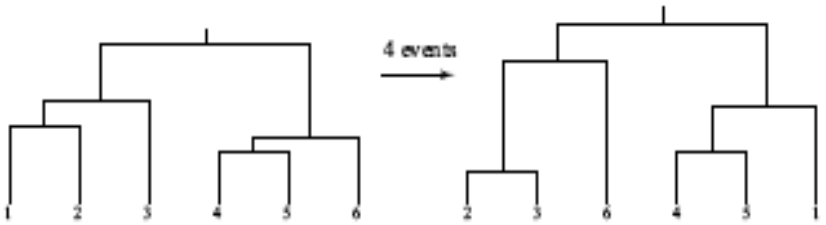
$$3n^2 - 13n + 14$$

$$\sim n^3$$

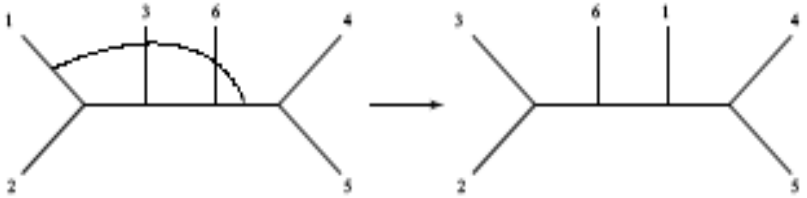
Bi-partitions

Metrics on Trees based on subtree transfers.

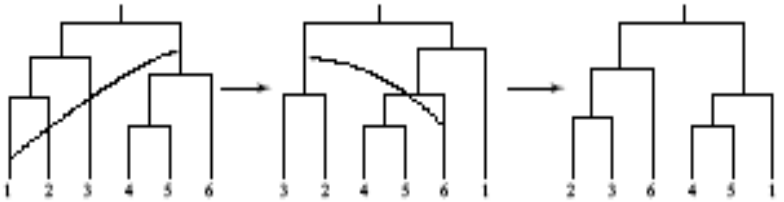
Trees including branch lengths



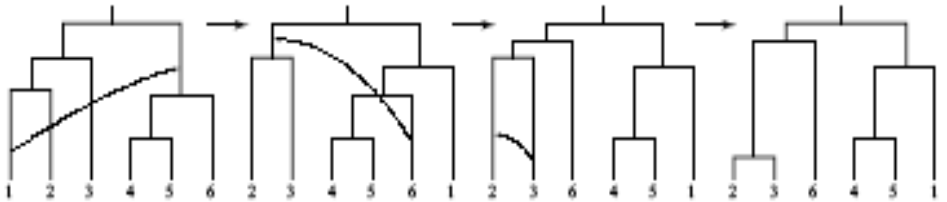
Unrooted tree topologies



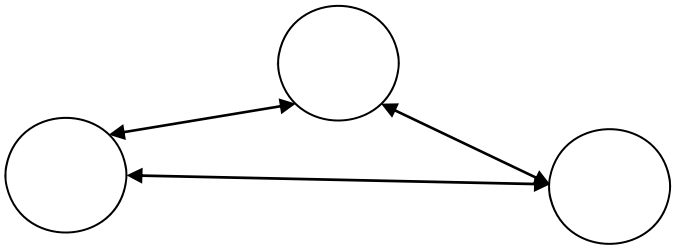
Rooted tree topologies



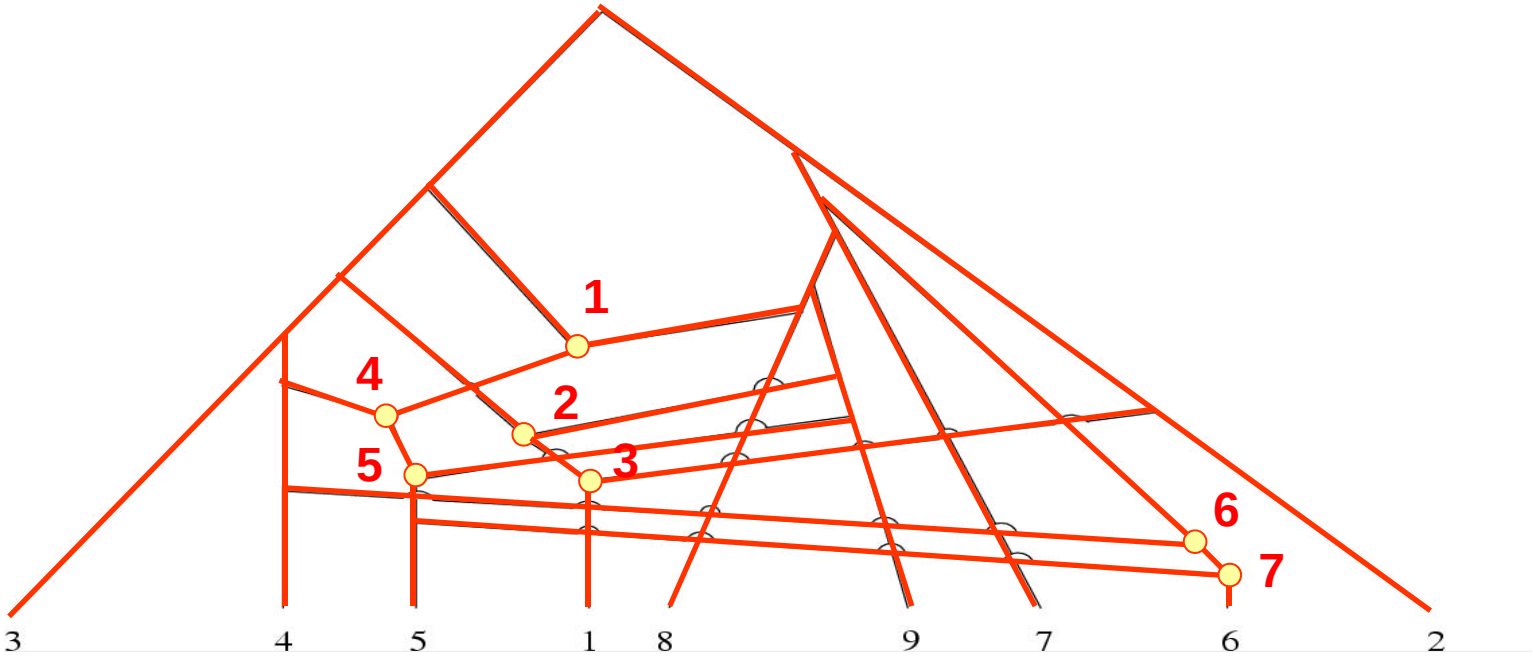
Tree topologies with age ordered internal nodes

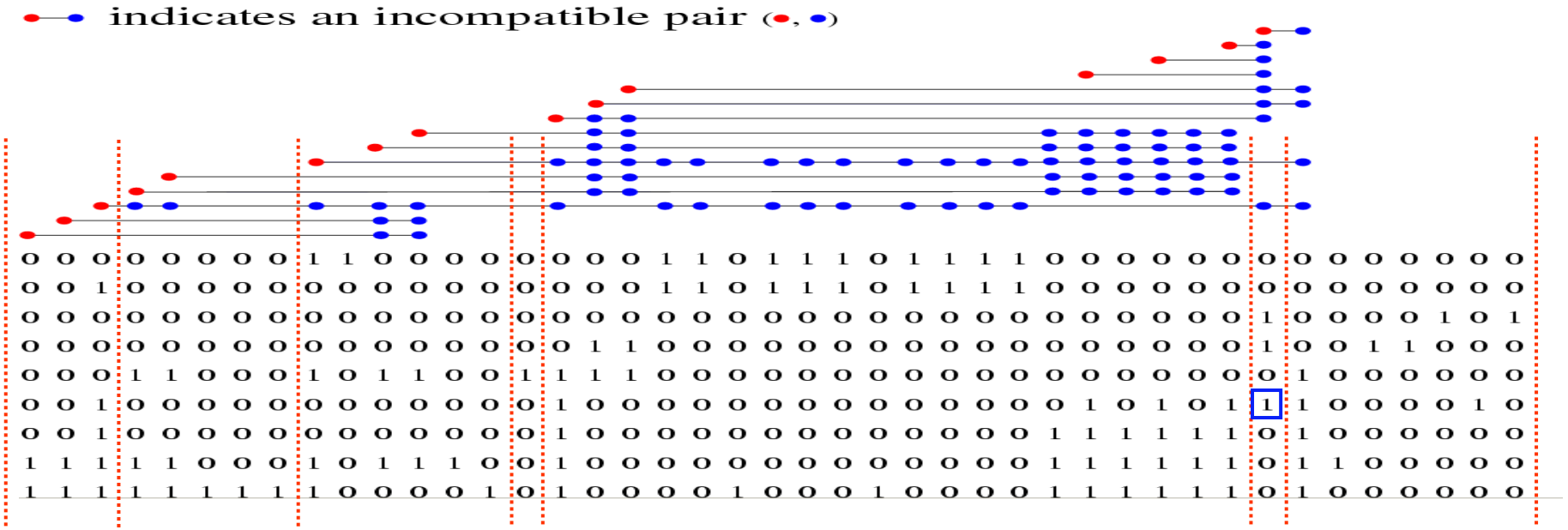


Pretending the **easy** problem (unrooted) is the **real** problem (age ordered), causes violation of the triangle inequality:



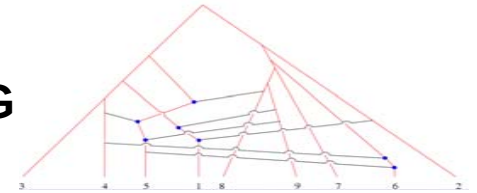
Due to Yun Song



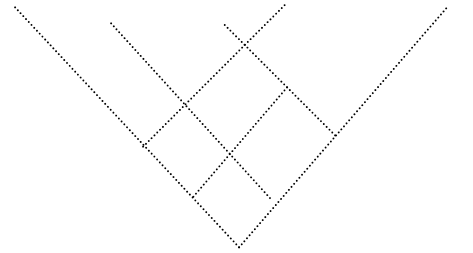


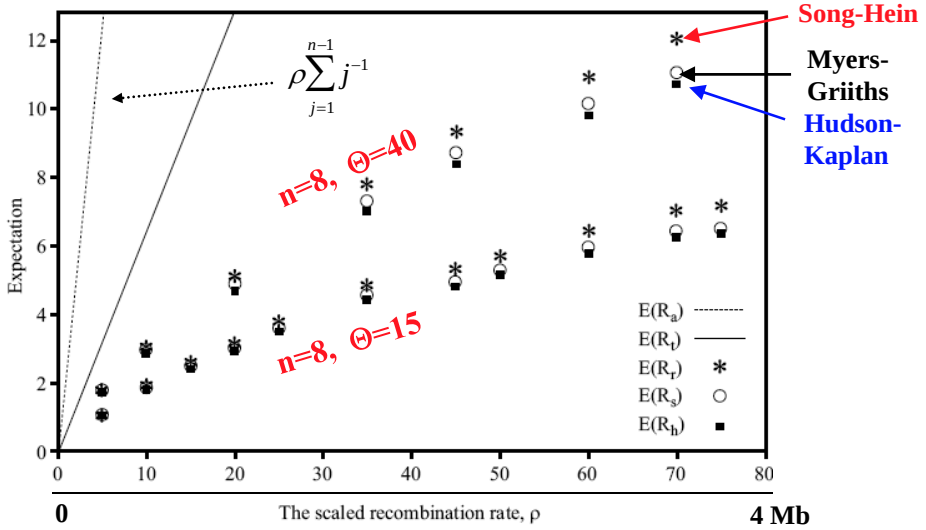
minARGs: Recombination Events & Local Trees

Minimal ARG

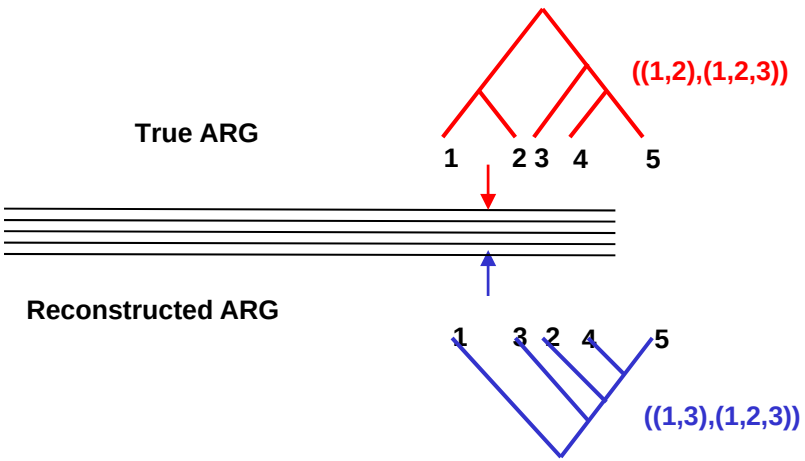


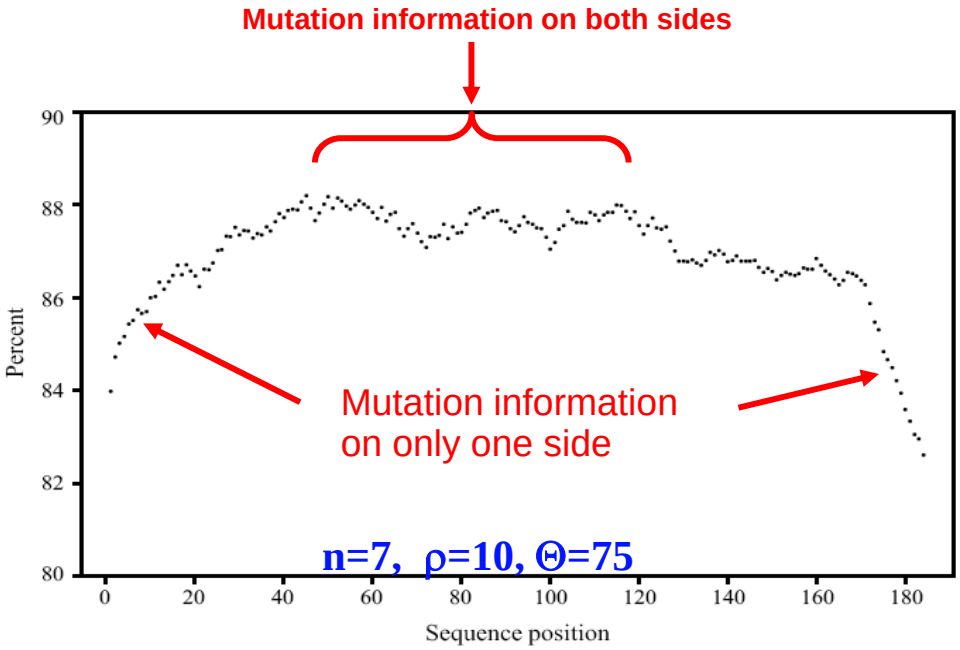
True ARG



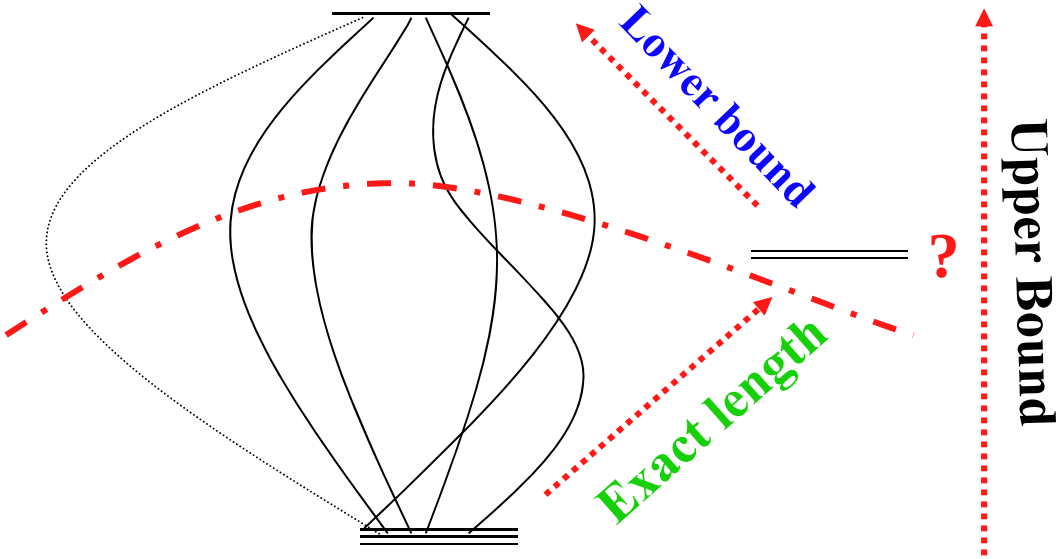


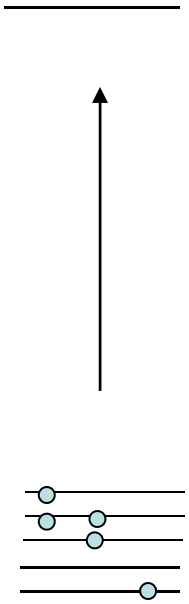
$E_{70}(R) = 132$ $E_{70}(R_{visible}) = 46$





Counting + Branch and Bound Algorithm

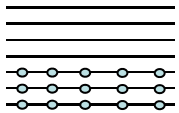




289920

k	k-recombination neighborhood
0	3
1	91
2	1314
3	8618
4	30436
5	62794
6	78970
7	63049
8	32451
9	10467
10	1727

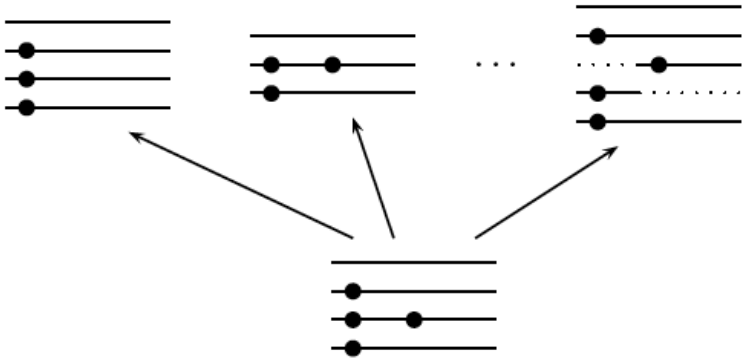
	Number of segregating sites			
n	2	3	4	5
2	30	573	16 875	689 175
3	108	6 286	743 387	149 861 079
4	330	62 589	32 482 009	35 523 729 489
5	866	445 137	893 479 326	4 938 627 635 669
6	2 143	3 302 506	29 521 615 942	962 962 451 049 968
7	4 611	17 409 443	568 860 072 916	91 812 561 254 804 105
8	9 728	98 432 218	13 273 296 248 617	
9	18 378	420 106 717	195 515 335 378 914	
10	34 552	1 917 604 869		
11	59 577	6 985 275 356		



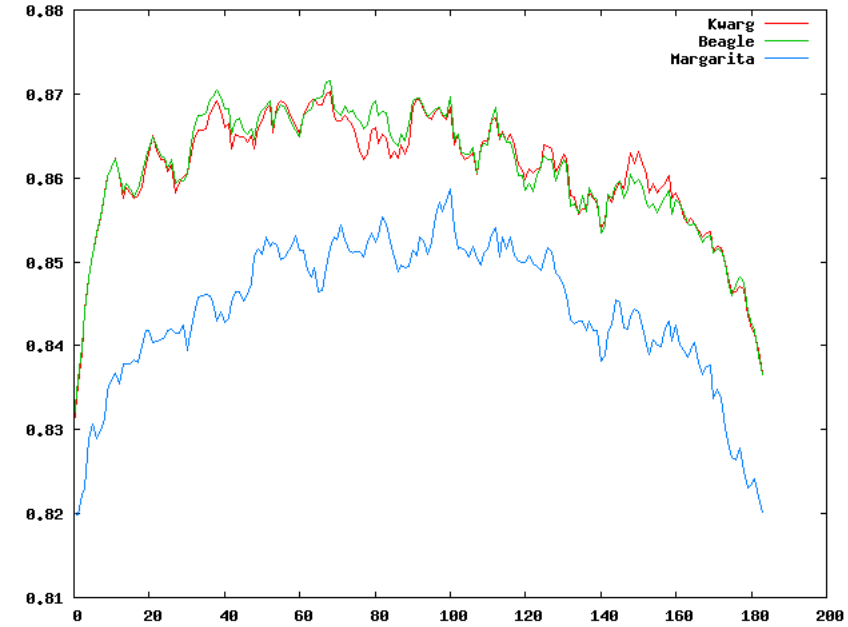
Song, Y.S., Lyngsø, R.B. & Hein, J. (2006) Counting all possible ancestral configurations of sample sequences in population genetics. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 3(3), 239–251

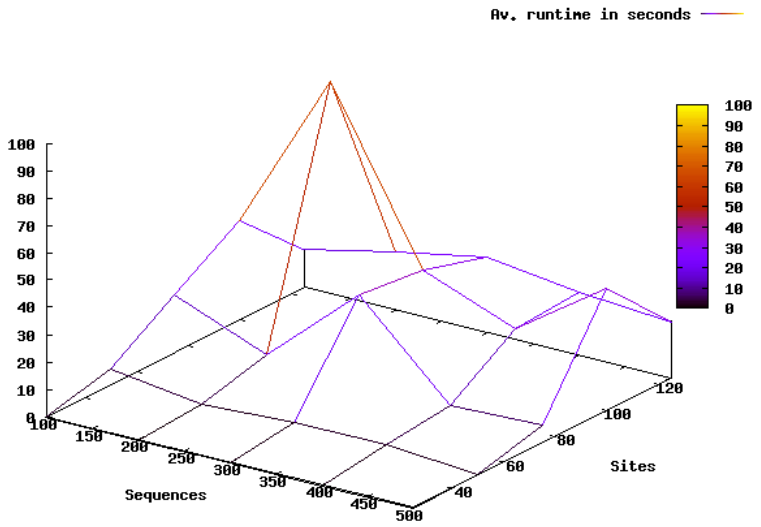
Lyngsø, R.B., Song, Y.S. & Hein, J. (2008) Accurate computation of likelihoods in the coalesc recombination via parsimony. Lecture Notes in Bioinformatics: Proceedings of RECOMB 2008 463–477

BB & Heuristic minimal ancestral recombination graphs



Beagle	Margarita	Kwarg
Try each in turn until shortest route is determined	Just follow road seeming to lead in the right direction	Choice based on location of next crossroads



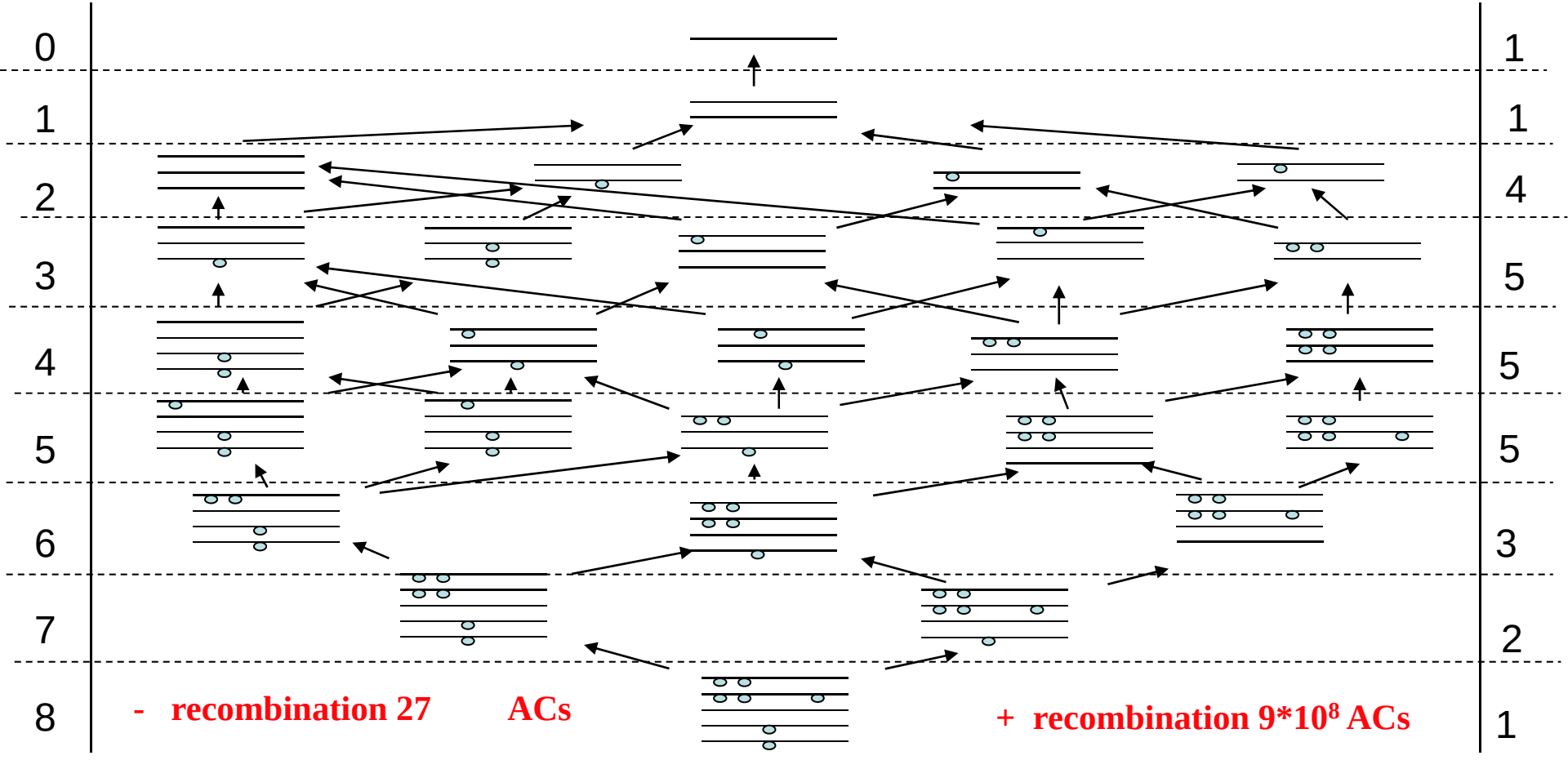


The Griffiths-Ethier-Tavare Recursions

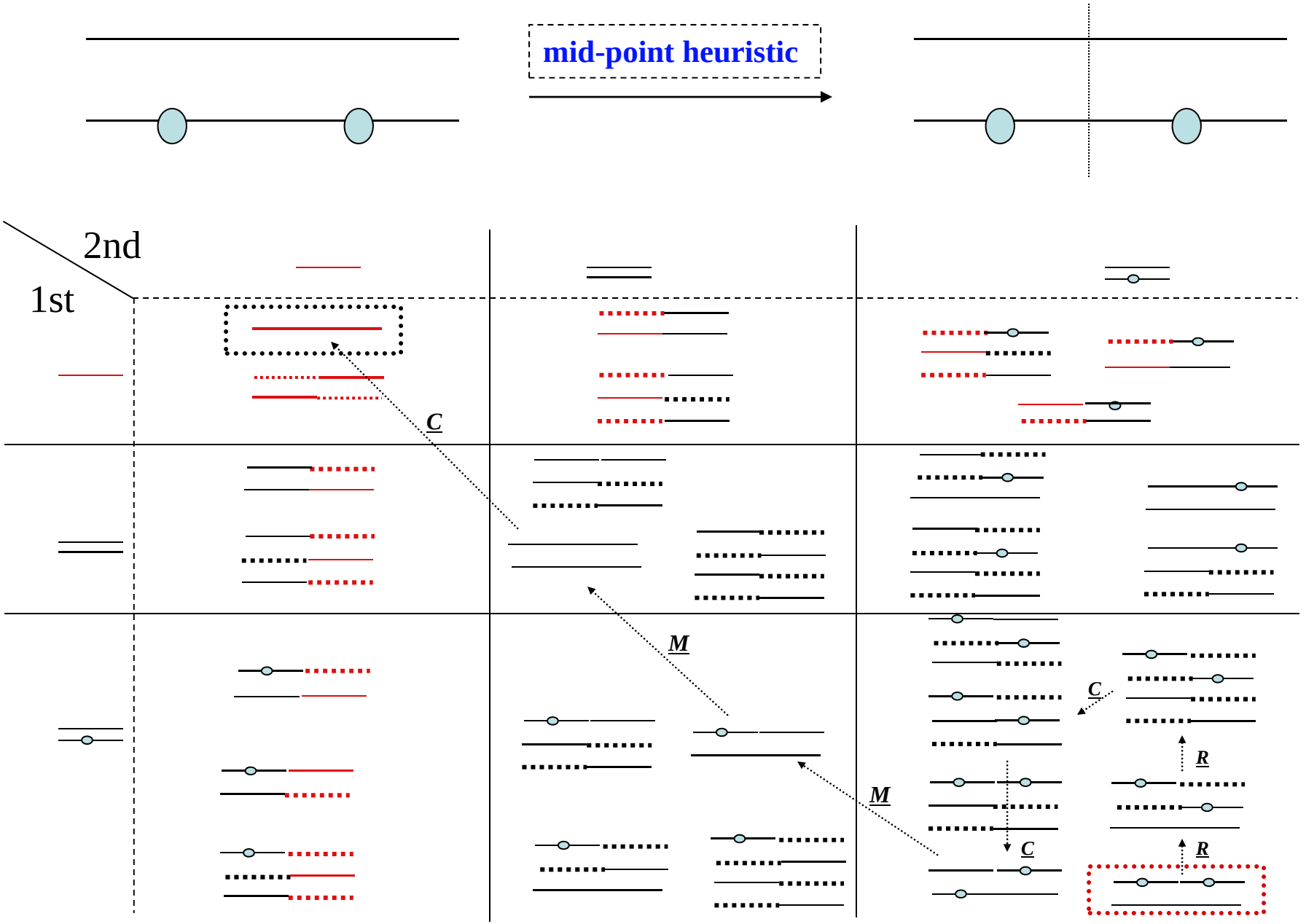
No recombination: Infinite Site Assumption
Ancestral State Known

History Graph: Recursions Exists
No cycles

Possible Histories without Recombination for simple data example



Ancestral configurations to 2 sequences with 2 segregating sites

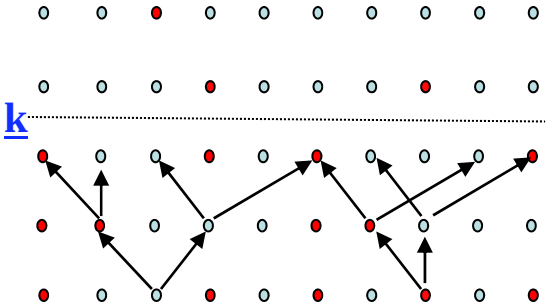


	0-ARG	1-ARG	2-ARG
	5 states	+15 states	+10 states
Θ,ρ = 2, 0	0.148	0.148	0.148
Θ,ρ = 1, 1	0.037	0.082	0.090
Θ,ρ = 2, 2	0.032	0.074	0.085

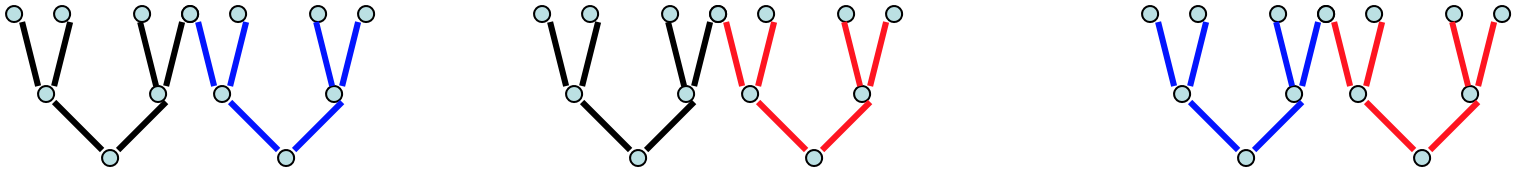
Reconstructing global pedigrees: Superpedigrees

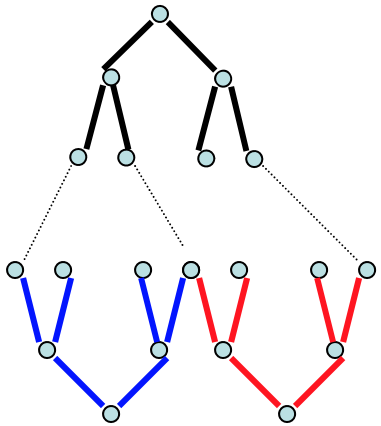
Steel and Hein, 2006

The gender-labeled pedigrees for all pairs defines global pedigree



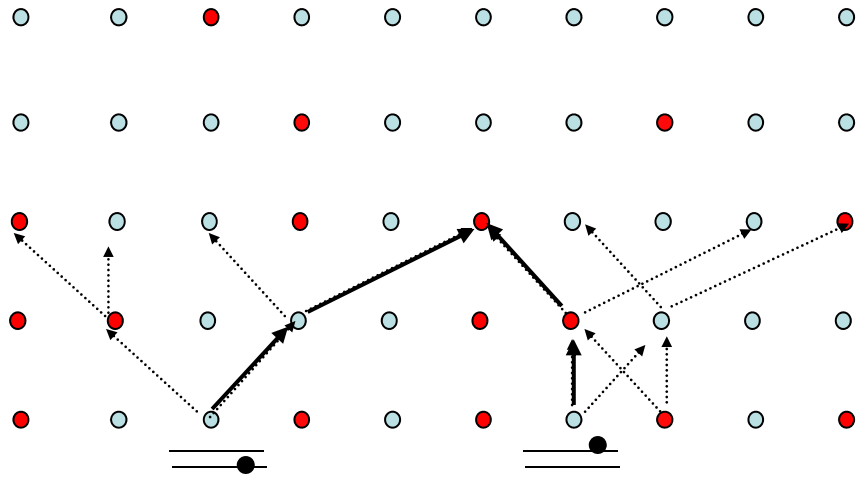
Gender-unlabeled pedigrees don't!!





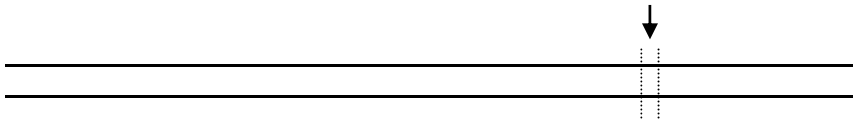
Steel, M. & Hein, J. (2006) Reconstructing pedigrees: a combinatorial perspective. Journal of Theoretical Biology, 240(3), 360–367

Benevolent Mutation and Recombination Process



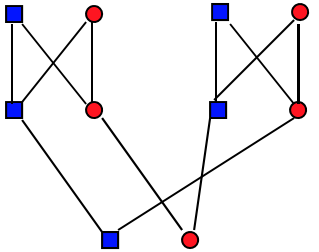
Genomes with ρ and μ/ρ --> infinity

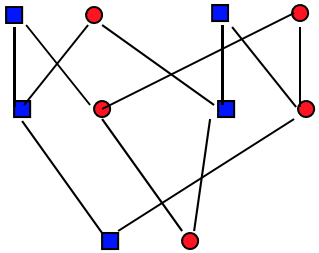
ρ – recombination rate, μ – mutation rate



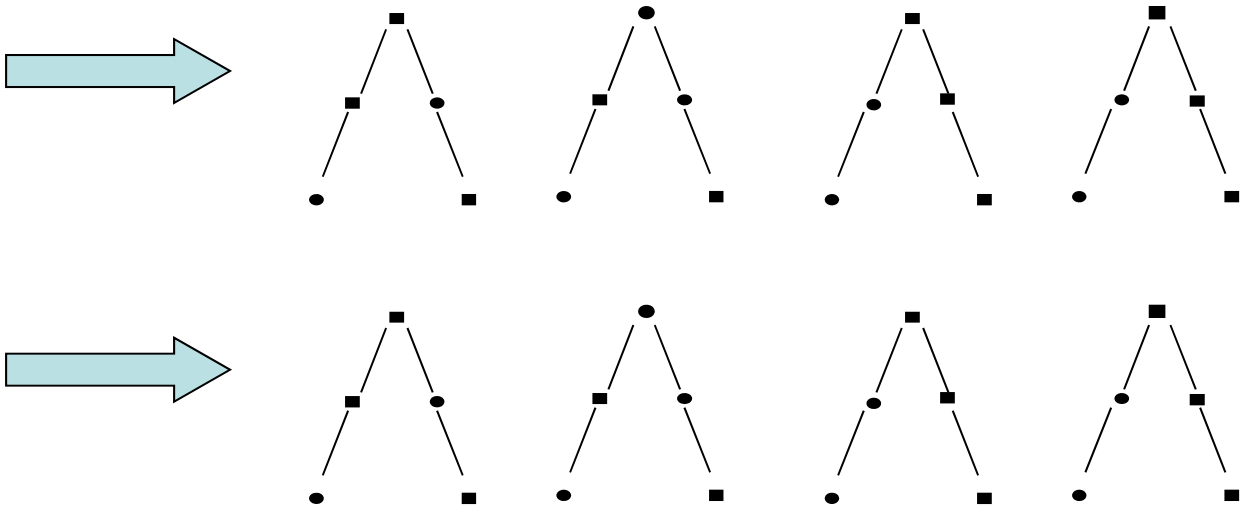
- **All embedded phylogenies are observable**
- **Do they determine the pedigree?**

Counter example:





Embedded phylogenies:



Infinite Sequences: From ARG to Pedigree

What can you observe from data (infinite sequences)?

A. The ARG?

B. Sequence of neighbor pairs of local trees with recombination points

Going to neighbor triples, quadruples,.., be more restrictive than pairs?

C. Sequence of local trees?

D. Set of local trees?

E. Set/Sequences of local unrooted tree topologies?

F. Set/Sequences of local bipartitions? (neighbor pairs…

Given A/B/C/D/E above how much does that constrain set of pedigrees

How many pedigrees are compatible with A/B/C/D/E varying over data?

Infinite Sequences: From ARG to Pedigree

What can you observe from data (infinite sequences)?

A. The ARG? ⇒

B. Sequence of pairs of local trees with recombination points

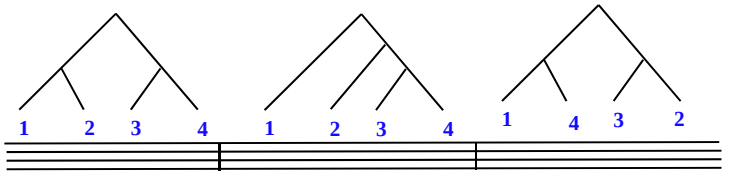
Going to triples, quadruples,.., be more restrictive than pairs?

C. Sequence of local trees?

D. Set of local trees?

E. Set/Sequences of local unrooted tree topologies?

F. Set/Sequences of bipartitions



Motivation

- **Inferring/Reconstructing Evolutionary Histories of Sequences**
- **Inferring parameters in the Evolutionary Process Generating Sequences**
- **Understanding why the problem is computationally hard.**

Overview

- **Bounds on Recombinations in Data Sets**
- **Minimal Histories**
  - **Spatial Algorithm**
  - **Temporal Algorithm**
- **Digression: Other Spatial/Temporal Algorithms**
- **Number of Ancestral States**
- **Likelihood calculations on the ε-ARG.**
- **Pedigrees and the ARG.**

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