Maximum Likelihood of Evolutionary Trees is Hard

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Joint work with Tamir Tuller

Challenging Basic Science Questions (1)

- Creation and evolution of the universe.

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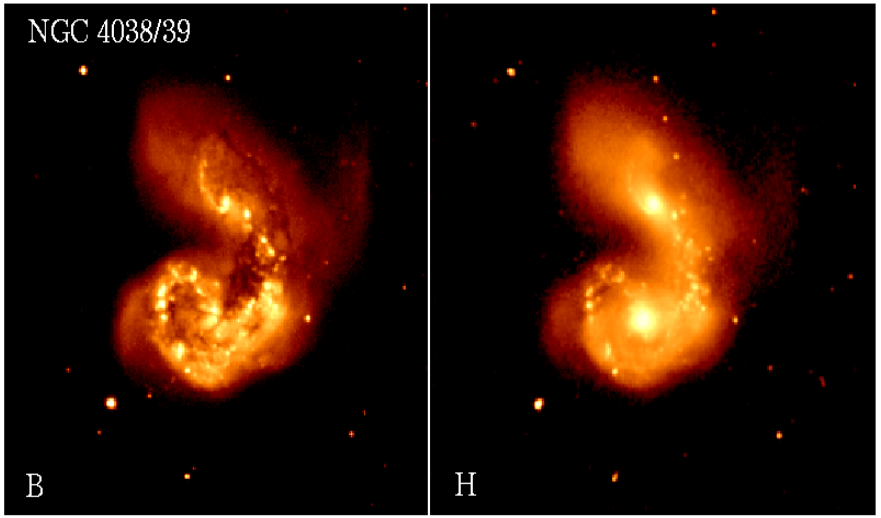

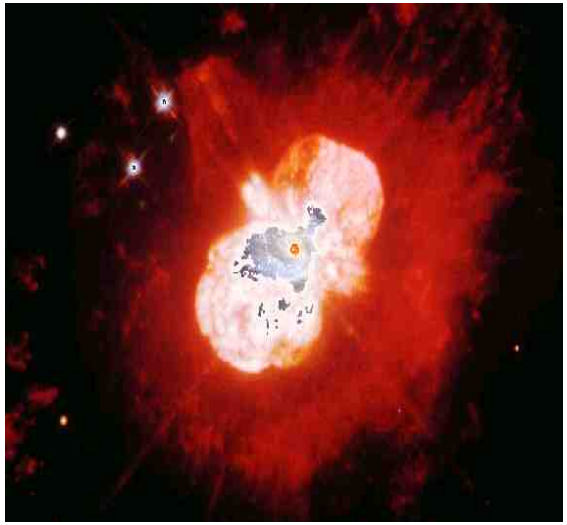

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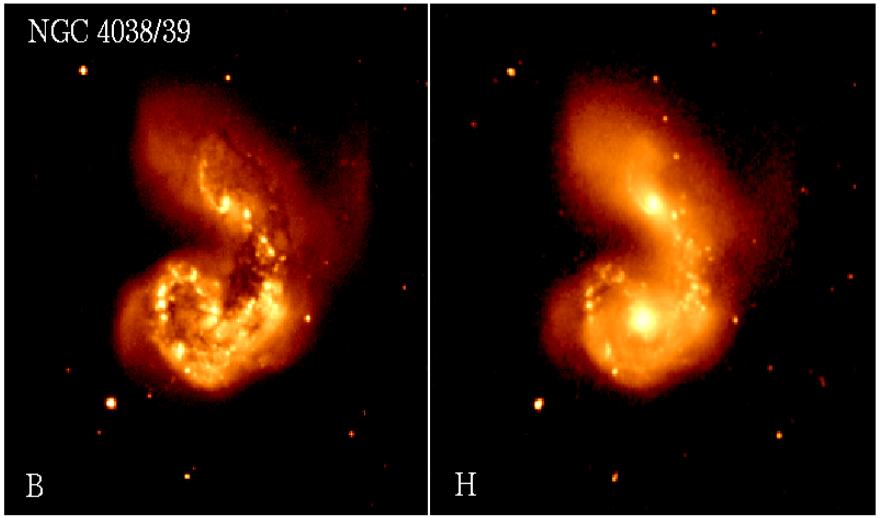

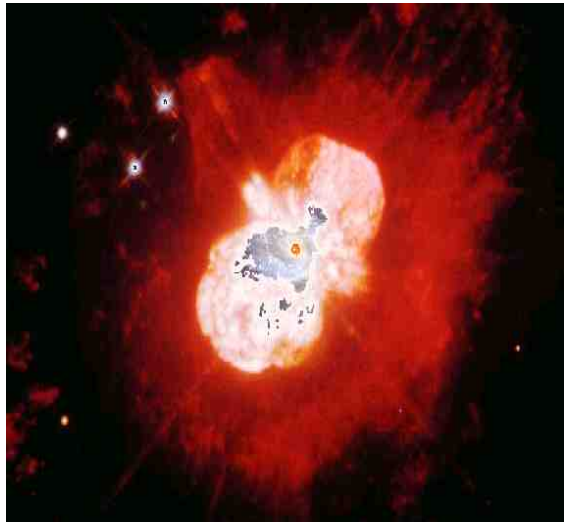

- Fascinating, but not topic of talk.

Challenging Basic Science Questions (2)

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- In this talk we'll discuss certain computational aspects of this problem.

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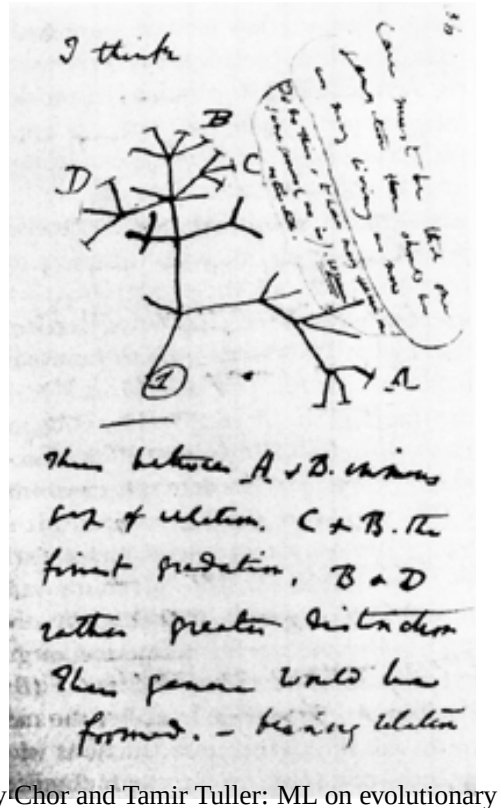

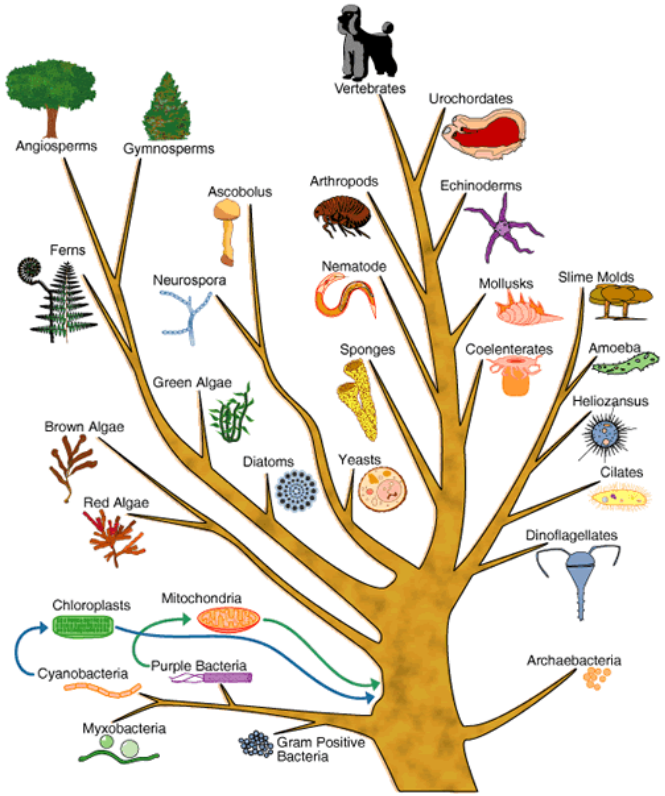

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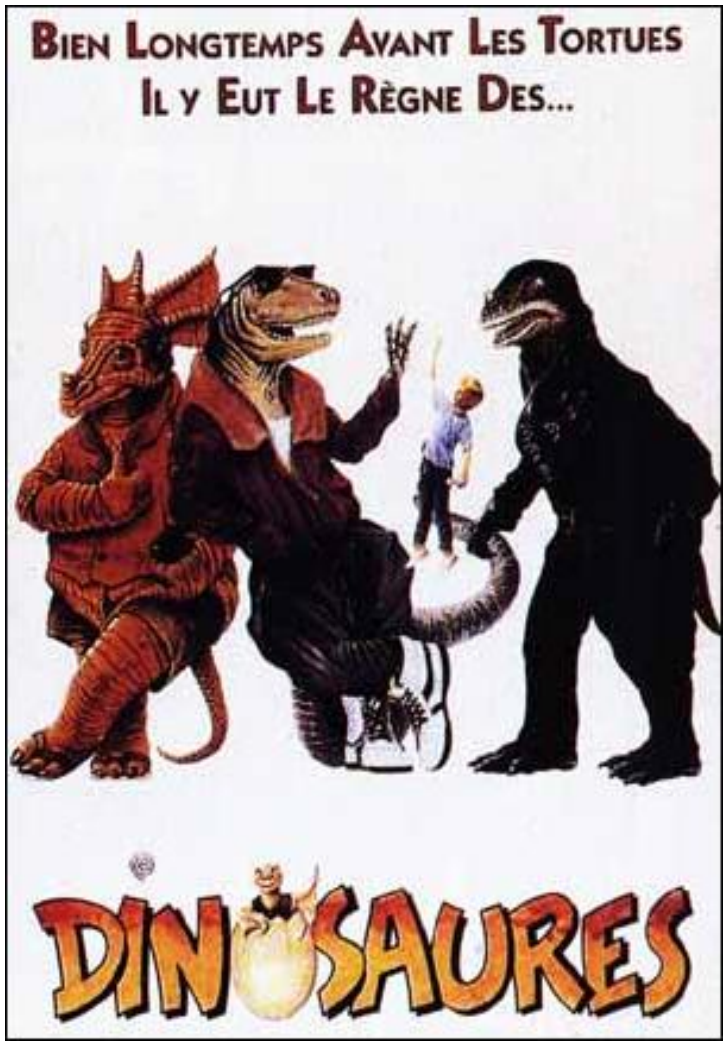

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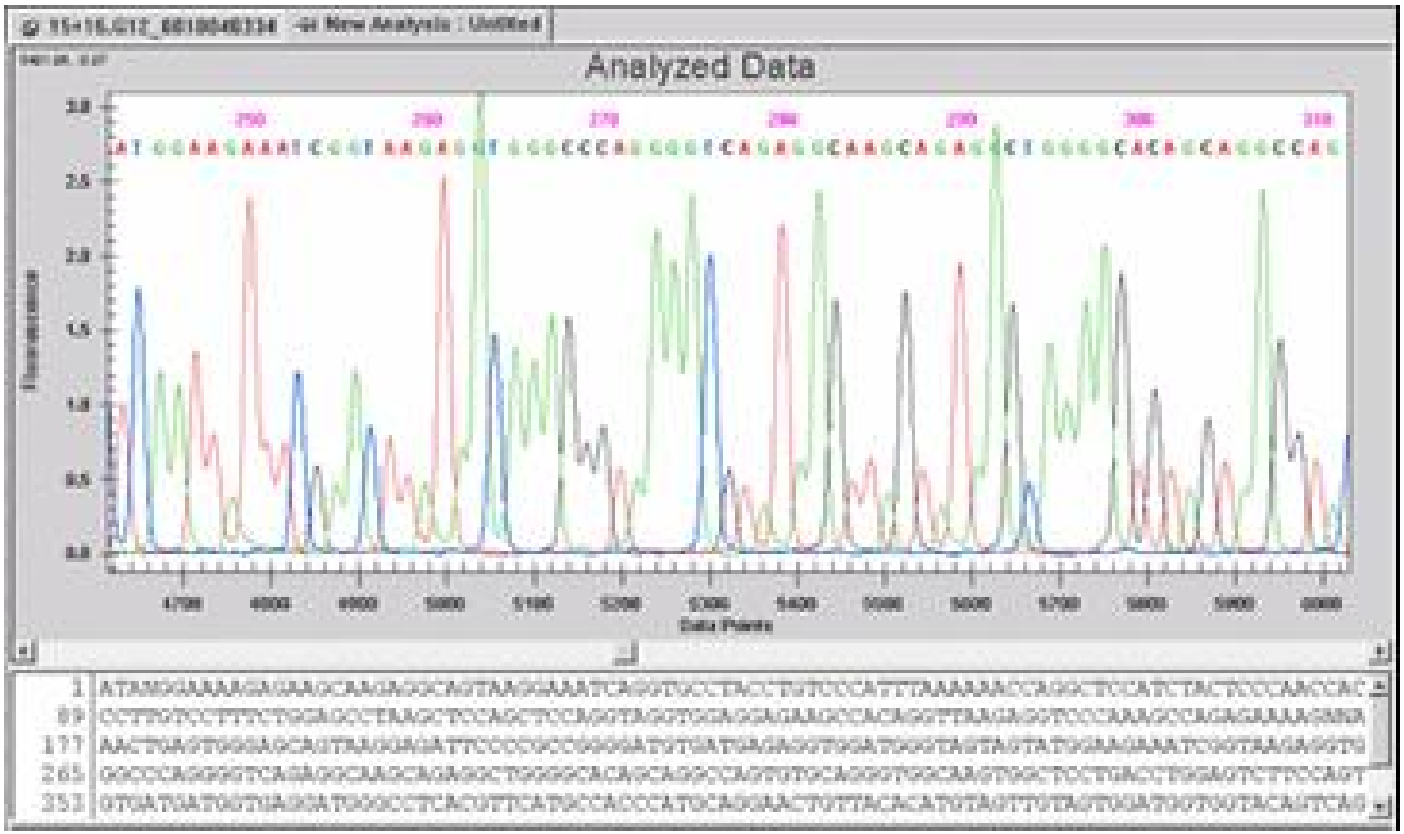

Phylogeny Reconstruction Methods

- Maximum Parsimony.
- Maximum Likelihood.
- These two are most popular, and are widely used by practitioners, among sequence based methods for phylogenetic reconstruction.

Maximum Parsimony: Definition

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Goal: Find a tree $T = (V, E)$ and an internal assignment such that total number of changes, $\sum_{e \in E} d_e$ is minimized.

Each d_e is number of unequal sites along edge e. It depends on the internal assignment a, and input pattern t at two ends of the edge.

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Maximum Likelihood: Definition (2)

$$L(\text{ data} \mid T, \text{edge parameters}) \triangleq \sum_{\text{internal assignments}} \prod_{\text{edges}} p^{d_e}(1-p)^{\ell - d_e} \ .$$

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- A well defined objective function to maximize.
- Termed average likelihood by Penny and Steel.
- Widely used in practice.

Complexity of Reconstruction

- Both MP and ML have well-defined objective functions
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  $\Longrightarrow$ Reconstruction is a computational problem.
- Number of trees over n leaves is exponential in n
  $\Longrightarrow$ Cannot exhaustively search all trees.

Our Major Question

Is ML Computationally Intractable?

- MP known for almost 20 years to be computationally intractable [Day *et al.*, 1986, translation from vertex cover] .
- No such result has been found for ML to date.
- Tuffley and Steel (1997): Relations between likelihood and parsimony.
- Addario-Berry *et al.* (2003): Ancestral ML is hard.
- Still, no cigar (and not even close).

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This work:
ML is computationally hard (NP complete)
$\Longrightarrow$ No such algorithm exists (unless P=NP).

Intractability Proof: The Big Picture

Efficiently translate vertex cover (VC) to ML.

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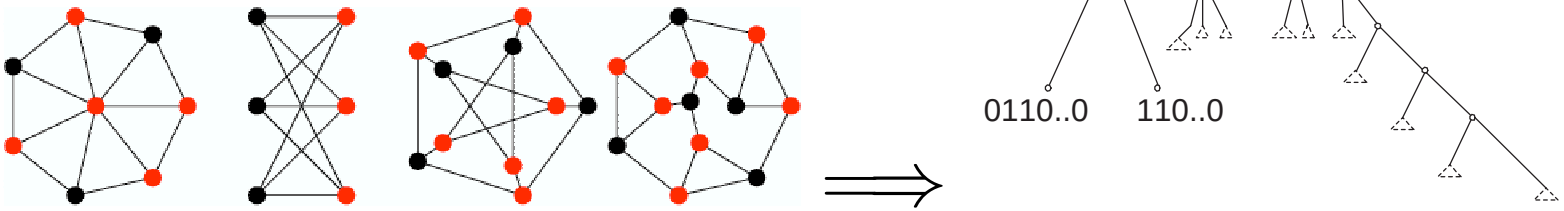

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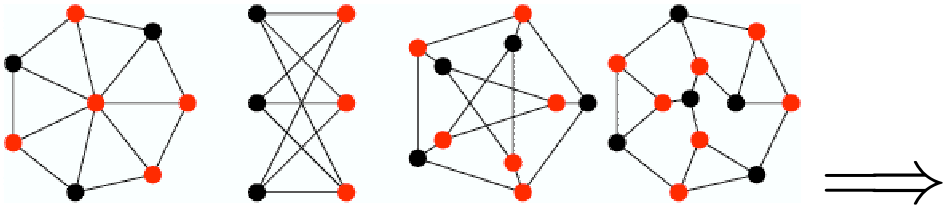

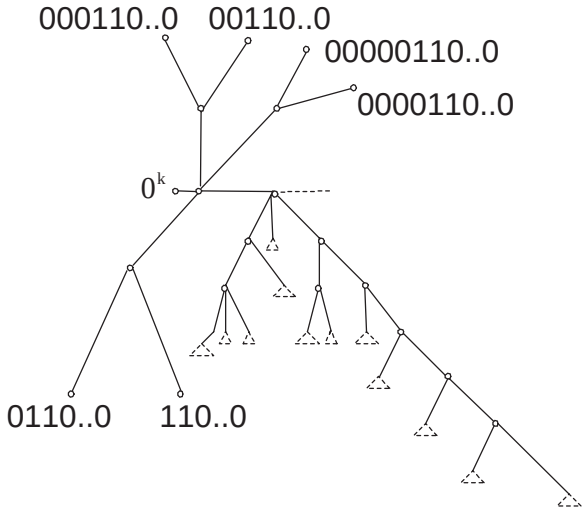

"Translation" means

- Small cover $\Longrightarrow$ Large likelihood.
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Vertex Cover in Graphs

Given a graph (V, E)

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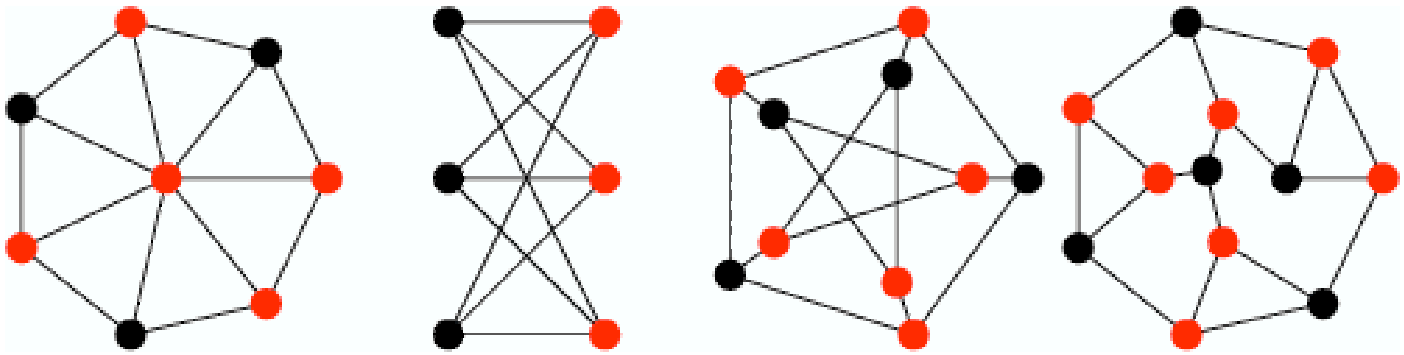

(figure from www.cc.ioc.ee/jus/gtglossary/assets/vertex_cover.gif)

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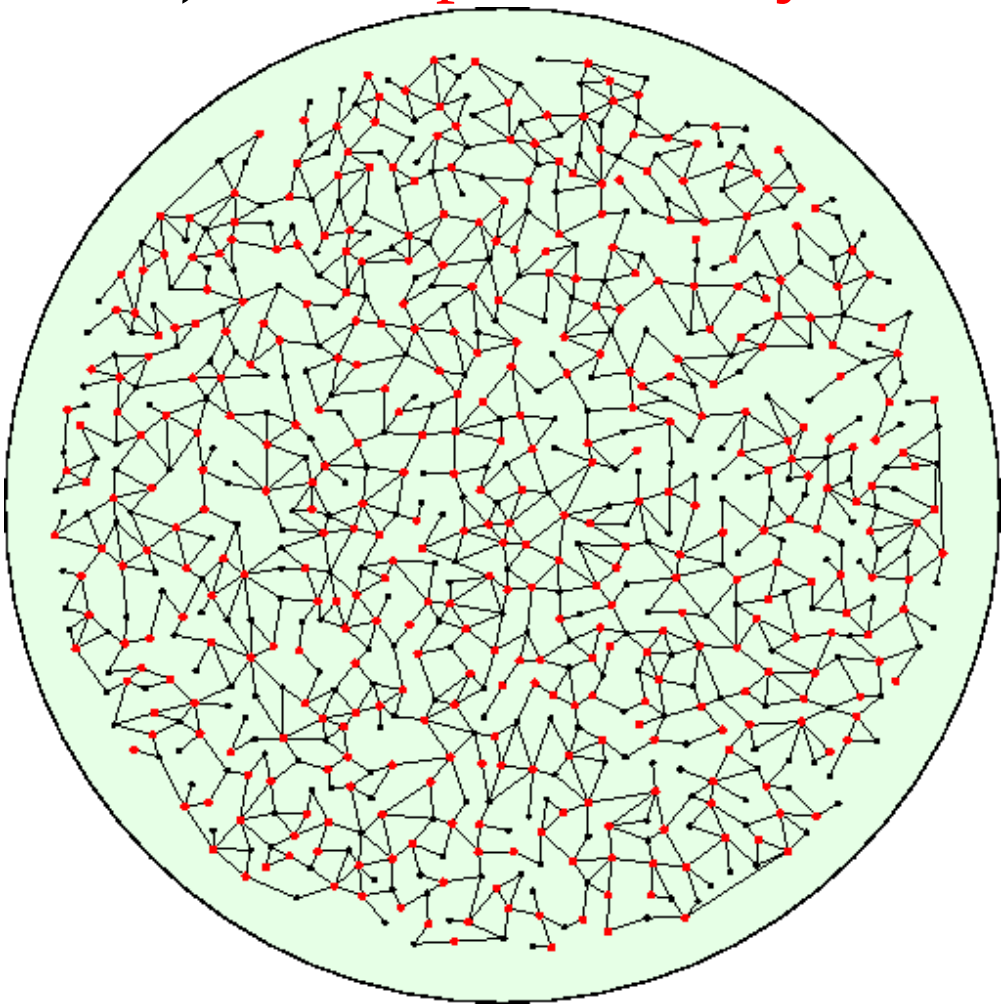

(figure from http://wwwbrauer.in.tum.de/gruppen/theorie/hard/vc1.png)

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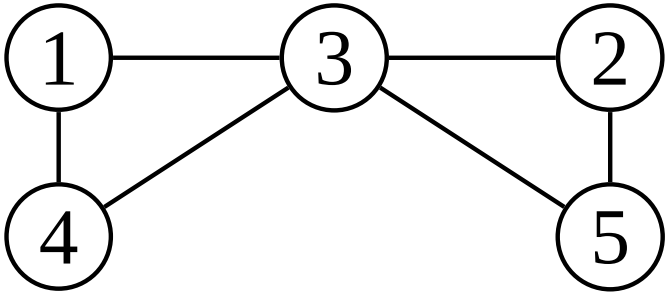
Notice: Yes/No question.

Translating VC to ML

The following graph, with 5 vertices and 6 edges



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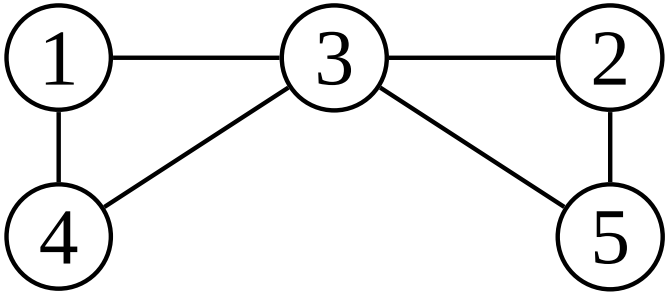

Translates to

A set with 7 binary sequences, each of length 5:

```
00000  10100  10010  01100
       01001  00110  00101
```

Translating VC to ML

- If G has n vertices and m edges, will construct $m+1$ binary sequences, each of length n.
- One sequence is all zeroes.
- For every edge $(i,j) \in E$, have the sequence

$$\overbrace{\underbrace{00..00}_{i-1}1\underbrace{00..00}_{j-i-1}1\underbrace{00..00}_{n-j}}^{n}$$

Canonical Trees: Definition

1. Tree has an internal node (called the "root") with 0 length edge to the all zero leaf.
2. All leaves are at distance one or two from the root.
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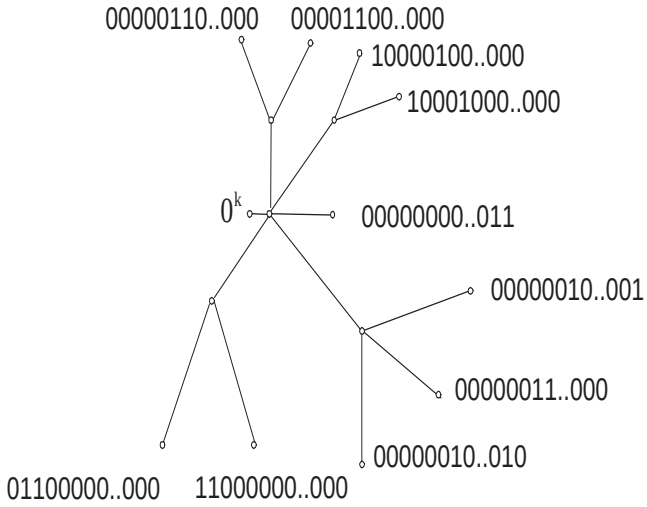
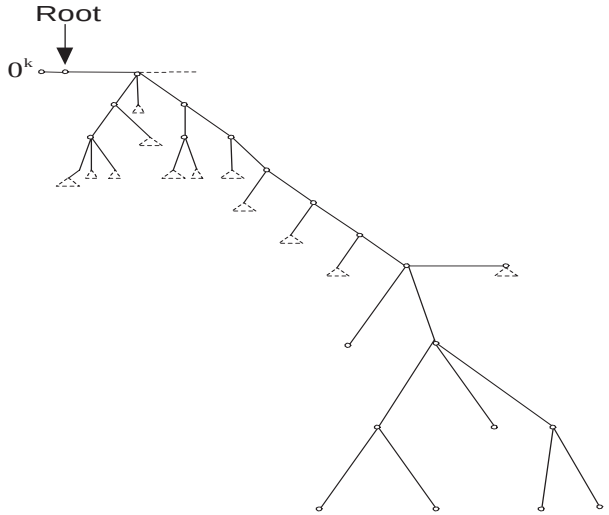


Yes



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Canonical Trees and Vertex Covers

[Day, 1986]: A canonical tree with degree d at root exists

G has a cover of size d.

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Given a canonical tree T with $m+1$ leaves labelled by sequences from S. Let d denote the degree of the root. Then for the optimal edge lengths p^*,

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So as $n \to \infty$,

$$\frac{-\log(L)}{(m+d)\log(n)} \to 1 \ .$$

Do We Have the Desired Proof?

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Seems to imply

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Take it easy. There is a problem here:
ML tree need not be canonical!

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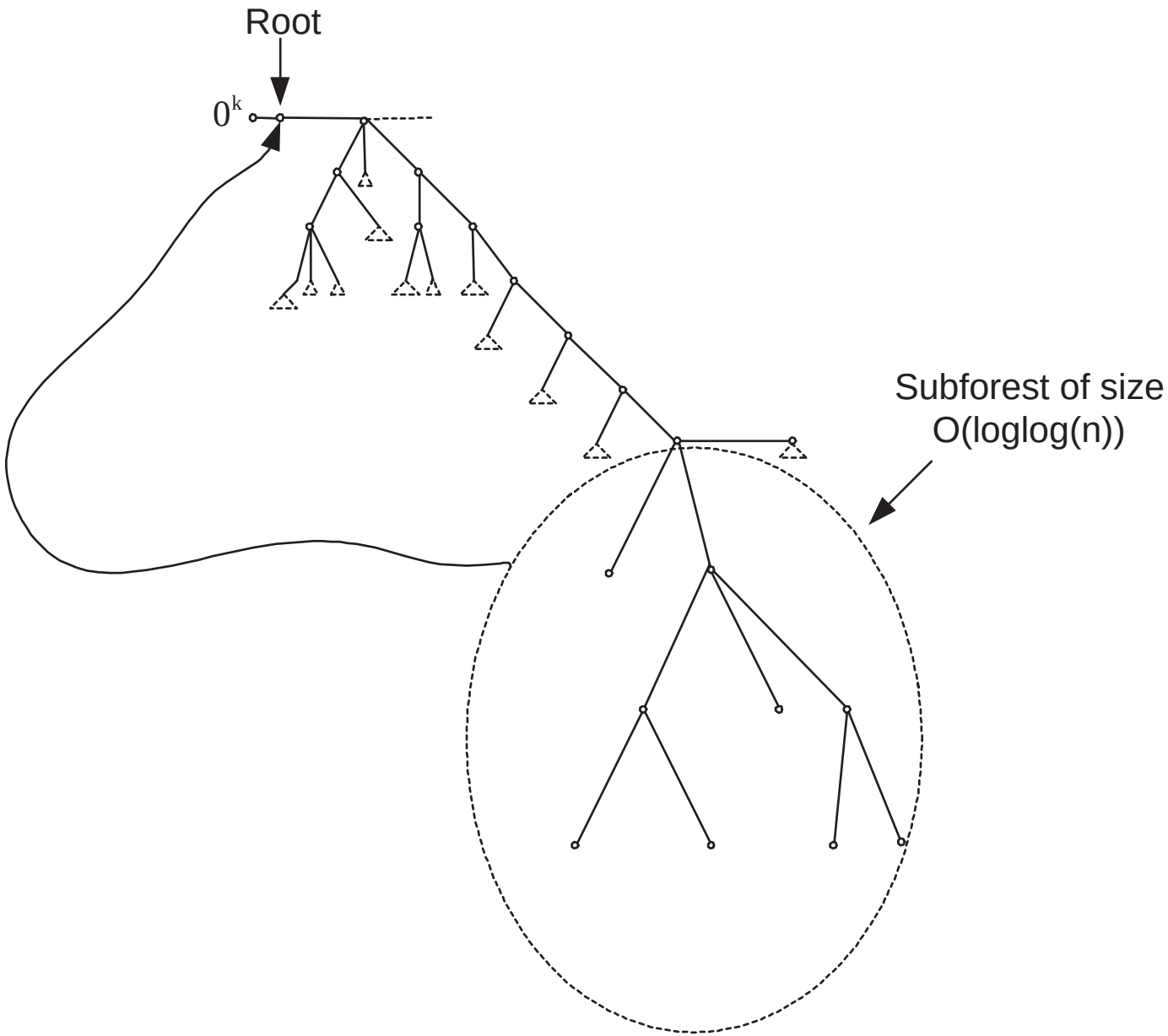
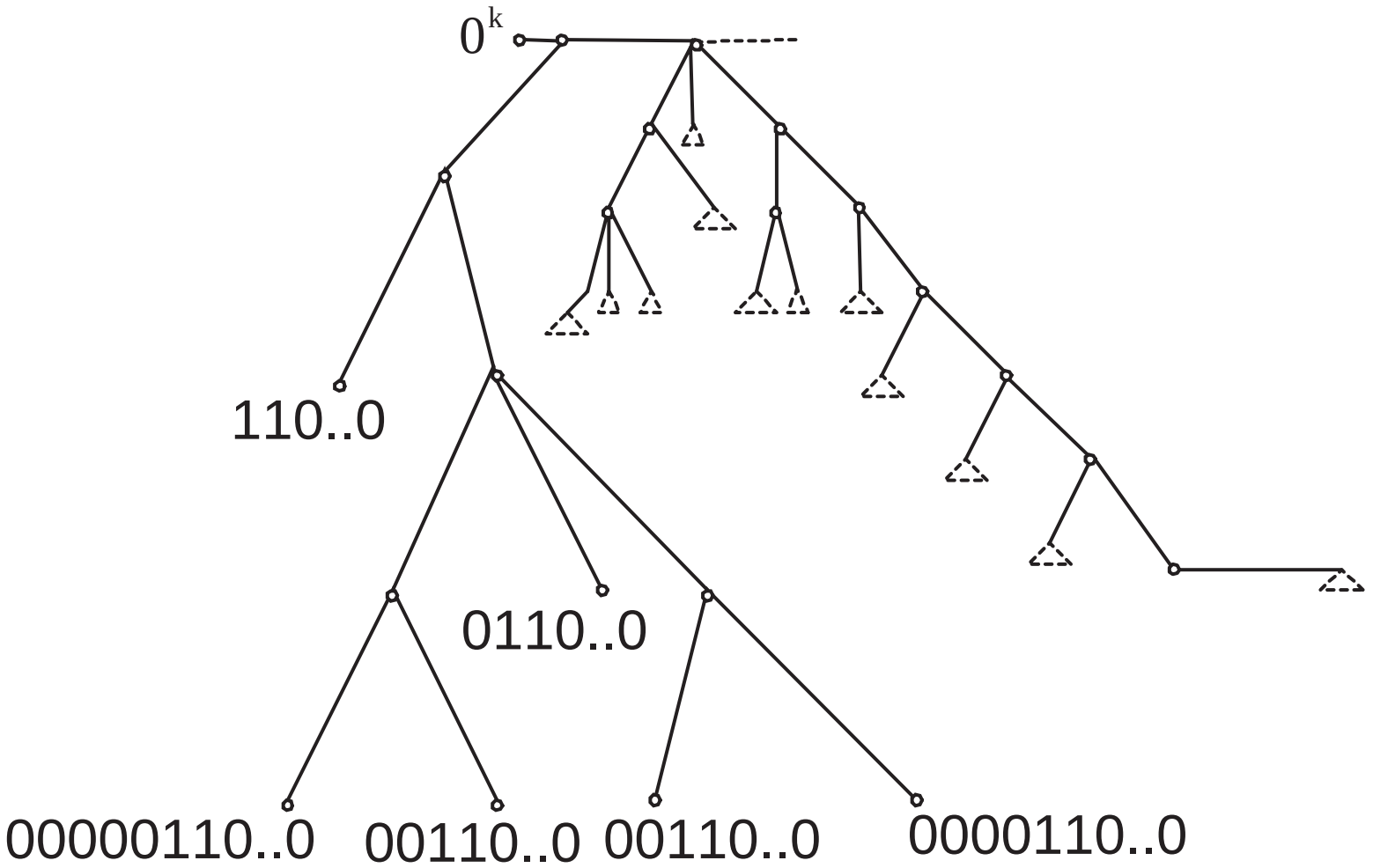
- So accumulated loss in log likelihood is small.

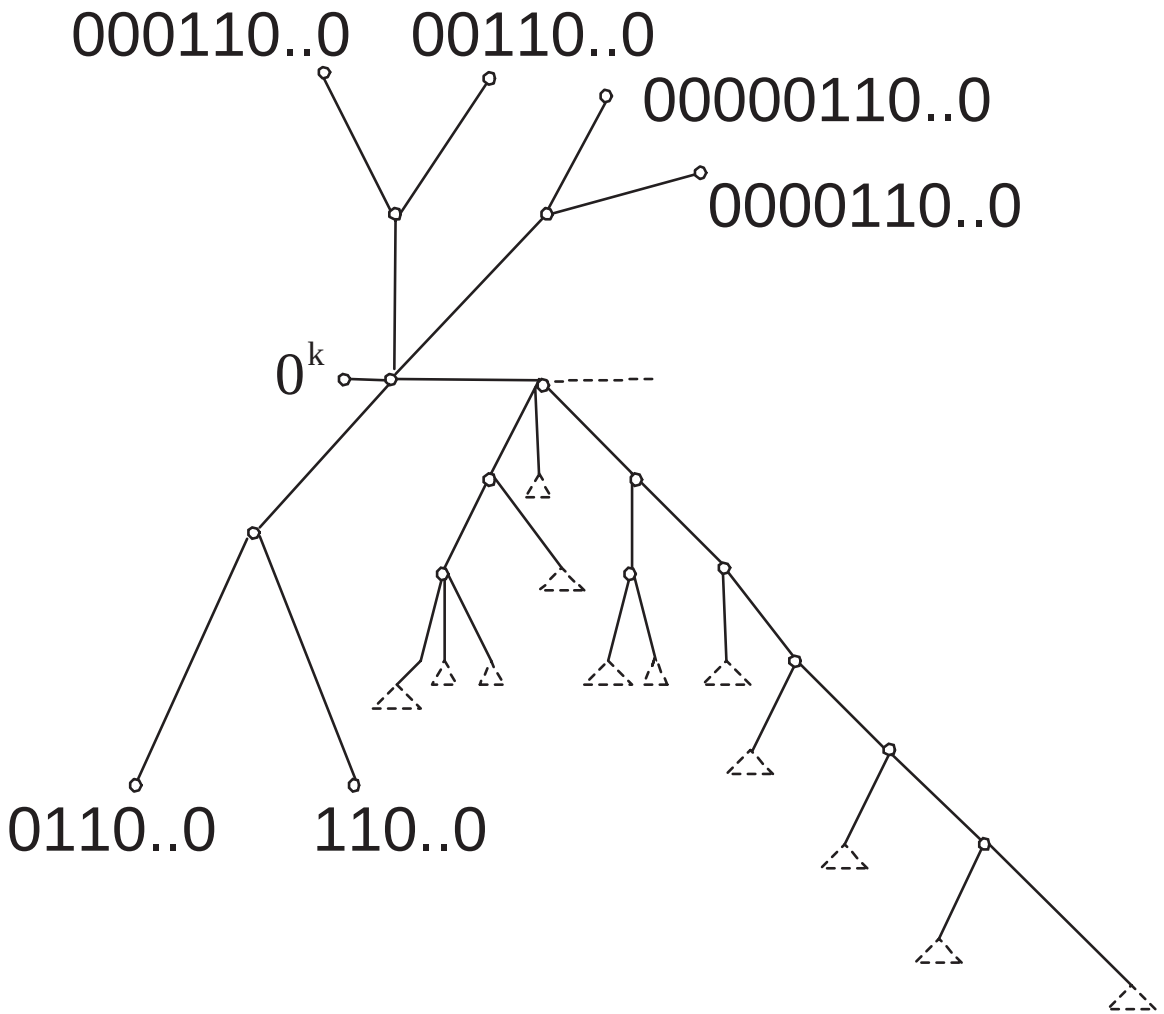
(Step 1) Identify a Small SubForest



(Step 2) Uproot and Relocate to Root



(Step 3) Rearange in ”Canonical Way”



Parsimony–Likelihood Relations

- Can show that parsimony of small subtree worsens by only B ($B < 8^4$) if plug all zero sequence to root of subforest. (Require G has bounded degree 3 – technical, not a problem.)
- Using the deep results of Tuffley and Steel (1997),
- This implies that decrease in log likelihood is at most $B \log n$.
- Number of modifications at most $n/\log\log n$.
- Total decrease at most $Bn \log n/\log\log n$.
- Small enough to establish desired result. ♠

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- Hardness of Gap VC by Berman and Karpinski, 1999.
- Translate this to bound $D = -(m + \frac{m_1+m_2}{2}) \cdot \log n$ on the log likelihood.

Hardness Conclusion

- Maximum likelihood of phylogenetic tree is computationally intractable
- No magic bullet!

Open Problems and Further Research

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