Computational and mathematical challenges involved in very large-scale phylogenetics

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Species phylogeny

From the Tree of the Life Website,
University of Arizona
How did life evolve on earth?

An international effort to understand how life evolved on earth

Biomedical applications: drug design, protein structure and function prediction, biodiversity

Phylogenetic estimation is a “Grand Challenge”: millions of taxa, NP-hard optimization problems

• Courtesy of the Tree of Life project
The CIPRES Project
(Cyber-Infrastructure for Phylogenetic Research)
www.phylo.org

This project is funded by the NSF under a Large ITR grant

• **ALGORITHMS and SOFTWARE**: scaling to millions of sequences (open source, freely distributed)

• **MATHEMATICS/PROBABILITY/STATISTICS**: Obtaining better mathematical theory under complex models of evolution

• **DATABASES**: Producing new database technology for structured data, to enable scientific discoveries

• **SIMULATIONS**: The first million taxon simulation under realistically complex models

• **OUTREACH**: Museum partners, K-12, general scientific public

• **PORTAL** available to all researchers
Step 1: Gather data

S1 = AGGCTATCAGCTGACCTCCA
S2 = TAGCTATCAGCGACCGC
S3 = TAGCTGACCGGC
S4 = TCACGACCCGACA
Step 2: Multiple Sequence Alignment

S1 = AGGCTATCACCTGACCTCCA
S2 = TAGCTATCAGACCGC
S3 = TAGCTGACCGC
S4 = TCACGACCGACA

S1 = -AGGCTATCACCTGACCTCCA
S2 = TAG-CTATCAC--GACCGC--
S3 = TAG-CT-------GACCGC--
S4 = --------TCAC--GACCGACA
Step 3: Construct tree

S1 = AGGCTATCACCTGACCTCCA  S1 = -AGGCTATCACCTGACCTCCA
S2 = TAGCTATCACGACCGC  S2 = TAG-CTATCAC--GACCGC--
S3 = TAGCTGACCGC  S3 = TAG-CT-------GACCGC--
S4 = TCACGACCGACA  S4 = -------TCAC--GACCGACA
Performance criteria

- Estimated alignments are evaluated with respect to the true alignment. Studied both in simulation and on real data.

- Estimated trees are evaluated for “topological accuracy” with respect to the true tree. Typically studied in simulation.

- Methods for these problems can also be evaluated with respect to an optimization criterion (e.g., maximum likelihood score) as a function of running time. Typically studied on real data.
Observations

• The best current multiple sequence alignment methods can produce **highly inaccurate alignments on large datasets** (with the result that trees estimated on these alignments are also inaccurate).

• The fast (polynomial time) methods produce **highly inaccurate trees** for many datasets.

• Heuristics for NP-hard optimization problems often produce highly accurate trees, but can take **months** to reach solutions on large datasets.
This talk

- Part 1: Improving the topological accuracy of polynomial time phylogeny reconstruction methods (and *absolute fast converging* methods)
- Part 2: Improving heuristics for NP-hard optimization problems (getting better solutions faster)
- Part 3: Simultaneous Alignment and Tree estimation (SATe)
- Part 4: Conclusions
Part 1: Improving polynomial time methods (and absolute fast converging methods)
DNA Sequence Evolution

-3 mil yrs
-2 mil yrs
-1 mil yrs
today
Markov models of single site evolution

Simplest (Jukes-Cantor):

- The model tree is a pair \( (T,\{e,p(e)\}) \), where \( T \) is a rooted binary tree, and \( p(e) \) is the probability of a substitution on the edge \( e \).
- The state at the root is random.
- If a site changes on an edge, it changes with equal probability to each of the remaining states.
- The evolutionary process is Markovian.

More complex models (such as the General Markov model) are also considered, often with little change to the theory.
Distance-based Phylogenetic Methods

**TRUE TREE**

**INFERRED TREE**

**DNA SEQUENCES**

S₁: ACAATTAGAAC  
S₂: ACCCTTAGAAC  
S₃: ACCATTCGAAC  
S₄: ACCAGACCAAC

**DISTANCE MATRIX**

<table>
<thead>
<tr>
<th></th>
<th>S₁</th>
<th>S₂</th>
<th>S₃</th>
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<tr>
<td>S₄</td>
<td>0</td>
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</tr>
</tbody>
</table>
FN: false negative  
(missing edge)  
FP: false positive  
(incorrect edge)  

50% error rate
Neighbor joining has poor performance on large diameter trees \cite{Nakhleh2001}

**Simulation study** based upon fixed edge lengths, K2P model of evolution, sequence lengths fixed to 1000 nucleotides.

Error rates reflect proportion of incorrect edges in inferred trees.
Theorem: Neighbor joining (and some other distance-based methods) will return the true tree with high probability provided sequence lengths are exponential in the diameter of the tree (Erdos et al., Atteson).
Statistical consistency, exponential convergence, and absolute fast convergence (afc)
A two-phase procedure which reduces the sequence length requirement of methods. The DCM phase produces a collection of trees, and the SQS phase picks the “best” tree.

The “base method” is applied to subsets of the original dataset. When the base method is NJ, you get DCM1-NJ.
Graph-theoretic divide-and-conquer (DCM’s)

- Define a triangulated (i.e. chordal) graph so that its vertices correspond to the input taxa.
- Compute a decomposition of the graph into overlapping subgraphs, thus defining a decomposition of the taxa into overlapping subsets.
- Apply the “base method” to each subset of taxa, to construct a subtree.
- Merge the subtrees into a single tree on the full set of taxa.
DCM (cartoon)
Some properties of chordal graphs

• Every chordal graph has at most $n$ maximal cliques, and these can be found in polynomial time: *Maxclique* decomposition.

• Every chordal graph has a vertex separator which is a maximal clique: *Separator-component* decomposition.

• Every chordal graph has a perfect elimination scheme: *enables us to merge correct subtrees and get a correct supertree back, if subtrees are big enough.*
DCM1 Decompositions

**Input:** Set $S$ of sequences, distance matrix $d$, threshold value $q \in \{d_{ij}\}$

1. Compute threshold graph

   $$ G_q = (V, E), V = S, E = \{(i, j) : d(i, j) \leq q\} $$

2. Perform minimum weight triangulation (note: if $d$ is an additive matrix, then the threshold graph is provably chordal).

**DCM1 decomposition:** Compute maximal cliques
DCM1-boosting distance-based methods
[Nakhleh et al. ISMB 2001]

Theorem:
DCM1-NJ converges to the true tree from polynomial length sequences
However,

- The best phylogenetic accuracy tends to be from computationally intensive methods (and most molecular phylogeneticists prefer these methods).
- Unfortunately, these approaches can take weeks or more, just to reach decent local optima.

- Conclusion: *We need better heuristics for NP-hard optimization methods!* 
Part 2: Improved heuristics for NP-hard optimization problems

- Rec-I-DCM3: Roshan, Williams, Moret, and Warnow
- Part of the CIPRES software distribution and portal
Standard problem: Maximum Parsimony
(Hamming distance Steiner Tree)

- **Input:** Set $S$ of $n$ aligned sequences of length $k$
- **Output:** A phylogenetic tree $T$
  - leaf-labeled by sequences in $S$
  - additional sequences of length $k$ labeling the internal nodes of $T$

such that $\sum_{(i,j)\in E(T)} H(i, j)$ is minimized.
Maximum parsimony (example)

• **Input**: Four sequences
  – ACT
  – ACA
  – GTT
  – GTA

• **Question**: which of the three trees has the best MP scores?
Maximum Parsimony

MP score = 5

MP score = 7

MP score = 4

Optimal MP tree
Maximum Parsimony: computational complexity

Optimal labeling can be computed in linear time $O(nk)$

MP score = 4

Finding the optimal MP tree is $NP$-hard
Maximum Likelihood (ML)

• Given: stochastic model of sequence evolution (e.g. Jukes-Cantor) and a set S of sequences
• Objective: Find tree T and parameter values so as to maximize the probability of the data.

Preferred by some systematists, but even harder than MP in practice.
Approaches for “solving” MP (and other NP-hard problems in phylogeny)

1. Hill-climbing heuristics (which can get stuck in local optima)
2. Randomized algorithms for getting out of local optima
3. Approximation algorithms for MP (based upon Steiner Tree approximation algorithms).
Problems with current techniques for MP

Shown here is the performance of a TNT heuristic maximum parsimony analysis on a real dataset of almost 14,000 sequences. (“Optimal” here means best score to date, using any method for any amount of time.) Acceptable error is below 0.01%.
Rec-I-DCM3: a new technique (Roshan et al.)

- Combines a new decomposition technique (DCM3) with recursion and iteration, to produce a novel approach for escaping local optima
- Demonstrated here on MP (maximum parsimony), but also implemented for ML and other optimization problems
The DCM3 decomposition

**Input**: Set $S$ of sequences, and guide-tree $T$

1. Compute *short subtree* graph $G(S,T)$, based upon $T$
2. Find clique separator in the graph $G(S,T)$ and form subproblems

DCM3 decompositions
(1) can be obtained in $O(n)$ time (the short subtree graph is *triangulated*)
(2) yield small subproblems
(3) can be used iteratively
Iterative-DCM3
Rec-I-DCM3 significantly improves performance (Roshan et al.)

Comparison of TNT to Rec-I-DCM3(TNT) on one large dataset
Part 3: Multiple sequence alignment

- SATe (Simultaneous Alignment and Tree estimation)
- Developers: Liu, Nelesen, Linder, and Warnow
- unpublished
Multiple Sequence Alignment

AGGCTATCACCTGACCTCCA  -AGGCTATCACCTGACCTCCA
TAGCTATCACGACCGC  TAG-CTATCAC--GACCGC--
TAGCTGACCGC  TAG-CT--------GACCGC--

Notes:
1. We insert gaps (dashes) to each sequence to make them “line up”.
2. Nucleotides in the same column are presumed to have a common ancestor (i.e., they are “homologous”).
Indels and substitutions at the DNA level

...ACGGTGCAGTTACCA...
Indels and substitutions at the DNA level

...ACGGTG\textcolor{cyan}{G}CAGT\textcolor{green}{T}ACCA...
Indels and substitutions at the DNA level

Deletion  Mutation

...ACGGTGCA...GTTACCA...

...ACCAGTCA...CACCA...
The true multiple alignment is:

...ACG GTG CAG TTACCA...

...AC----CAGT CACCA...
Basic observations about standard two-phase methods

- Clustal is the standard multiple alignment method used by systematists.
- However, many new MSA methods improve on ClustalW, with ProbCons and MAFFT the two best MSA methods.
- The best current two-phase techniques are obtained by computing maximum likelihood trees on ProbCons or MAFFT alignments (joint work with Wang, Leebens-Mack, and dePamphilis - unpublished).
New method: SATe
(Simultaneous Alignment and Tree estimation)

• Developers: Warnow, Linder, Liu, Nelesen, and Zhao.

• Basic technique: iteratively propose alignments (using various techniques), and compute maximum likelihood trees for these alignments.

• Unpublished.
Simulation study

• 100 taxon model trees, 1000 sites at the root
• DNA sequences evolved with indels and substitutions (using ROSE).
• We vary the gap length distribution, probability of gaps, and probability of substitutions, to produce 8 model conditions: models 1-4 have “long gaps” and 5-8 have “short gaps”.
• We compare SATe to maximum likelihood trees (using RAxML) on various alignments (including the true alignment), each method limited to 24 hours.
Error rates refer to the proportion of incorrect edges.
Errors in estimating alignments

- Normalized number of columns in the estimated alignment relative to the true alignment.
Summary of SATe

- SATe produces more accurate trees than the best current two-phase method, especially when the evolutionary process has many gap events.

- SATe alignments do not compress the data (“over-align”) as much as standard MSA methods, most of which are based upon progressive alignment.
Future work

• Our current research is focused on extending SATe to estimate maximum likelihood under models that include gap events.

• Evolution is more complex than just indels and substitutions: we need methods that can handle genome rearrangements and duplications.
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