Week 4, Class 2:
Multiple Sequence Alignment

CS 426
Fall 2003

Me

Paul Chew

- Email: chew@cs.cornell.edu
- Office: 494 Rhodes
- Office Hours: MWF 11:15 to noon

- Research Area: Computational Geometry

Recall: Multiple Sequence Alignment (MSA)

- Goal is to find a common alignment of several sequences
- Provides more information that pairwise alignment
  - Can match a single protein against entire family
- Useful to…
  - Distinguish evolutionary relationships
  - Discover *important* parts of a protein family

```
TFAA--LSK
ALSA--LSD
ALSN--LSD
MSSMKDLSG
ELKP--LAQ
```

MSA is NP-Complete

- To find the best alignment we typically measure
  - Sum of pairwise distances within each column
  - Distances are measured using a scoring matrix (e.g., BLOSUM or PAM)
- Best alignment can be found using Dynamic Programming
  - But requires time $\Theta(n^k)$ for k sequences of length n

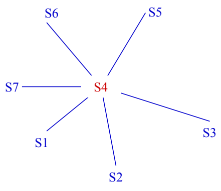
- MSA using Sum-of-Pairs is known to be NP-complete

- For an NP-complete problem
  - If a fast (polynomial time) algorithm is ever found then all NP-complete problems have fast algorithms
- Most researchers believe that no polynomial time algorithm exists
  - Goal becomes: find a reasonable approximation to the exact solution

Recall: Center Star Method

- Choose one sequence to be the *center*
- Align each of the other sequences with this center sequence
- Try each sequence as the center to find the one with the least cost: $\Sigma_{i\neq c}D(S_c,S_i)$

- Produces an approximation whose sum-of-pairs cost is < twice optimal
  - d(.,.), the scoring matrix, must satisfy the Triangle Inequality

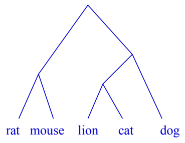


Phylogenetic Tree Alignment

- Phylogenetic tree = evolutionary tree

- *If* you know the phylogenetic tree for your sequences
  - The cost for an alignment is $\Sigma_{(i,j)\in E}D(S_i,S_j)$ where E is the set of edges in the tree

- Note that the Center Star Method is just using a particularly bad phylogenetic tree



- Unfortunately
  - The multiple alignment is often needed to *derive* the phylogenetic tree
  - Usually, we don't know the sequences for the internal nodes

Consensus Representations

- Goal: Build a single string that somehow *represents* an entire set, ***S***, of strings
- There are 2 related ideas that are candidates for such a string
  - the *Steiner string*
  - the *consensus string* of the *optimal consensus multiple alignment*
- The *Steiner string*, S*, is the string that minimizes the consensus error
  - The *consensus error* for string T is $\Sigma_{S \in \boldsymbol{S}} D(S,T)$
- Note that the Steiner string is not necessarily a member of ***S***
- Note also that the definition of Steiner string does not depend on a multiple alignment (although a Steiner string *induces* a multiple alignment)

The Consensus String of a Multiple Alignment

- The *consensus string* S_M derived from multiple alignment *M* is the concatenation of the consensus characters for each column of *M*
  - The *consensus character* for column i is the character that minimizes the summed distance to it from all the characters in column i

```
A B A
A B -
- B A
C A -
-----
A B A
```

The Optimal Consensus Multiple Alignment

- The *optimal consensus multiple alignment* is the alignment that minimizes the sum of the column errors
  - The *column error* is the sum of distances from the consensus character to each character in that column
- One can show that
  - The multiple alignment induced by the Steiner string is the same as the *optimal consensus multiple alignment*
  - The consensus string of the *optimal consensus multiple alignment* is (once spaces are removed) the same as the Steiner string
- Unfortunately, we have no way to determine the Steiner string (although we can approximate within a factor of 2 using the center-star string)

How is MSA Actually Done?

- The Center Star Method
  - Produces a result with a provable bound
  - But it's not often used in practice because it doesn't work as well as other methods
- Technique that is commonly used
  - Iterative pairwise alignment (see below)
- Additional methods
  - Repeated-motif methods
  - Hidden Markov models (more on this later in the course)

Iterative Pairwise Alignment

- In simplest form
  - Add strings one at a time to a growing multiple alignment
  - The string chosen is the one *closest* to some string already in the multiple alignment
- This is basically
  - a Minimum Spanning Tree (when using edit distance) or
  - a Maximum Spanning Tree (when using similarity scores)
- There are lots of variations on this idea
- We are using the Minimum Spanning Tree as a way to *cluster* the strings
- There are many clustering methods; each one leads to a somewhat different method for multiple alignment
- For some methods we must compute the distance between a sequence and a *set* of sequences

Summarizing a Group of Sequences: the Profile

- For a multiple alignment of length n, a *profile* is a table of size $|\Sigma \cup \{-\}| \times n$
  - Each entry shows the frequency of a symbol within a column
  - Σ is the alphabet (in our case, the 20 amino acids)

```
A B A
A B -
- B A
C A -
```

	Col 1	Col 2	Col 3
A	0.50	0.25	0.50
B	0.00	0.75	0.00
C	0.25	0.00	0.00
-	0.25	0.00	0.50

Aligning a String to a Profile

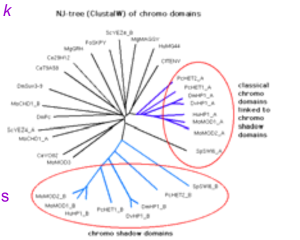
- Dynamic Programming can be used just as it is for pairwise comparisons
- We use a weighted sum of s-values when comparing a letter to a profile-column
  - s(.,.) is the scoring matrix used for pairwise comparisons
- Profile to profile comparisons can be done similarly

- Example
  - Suppose
    - s(A,A) = 2
    - s(A,B) = s(A,-) = -1
    - s(A,C) = -2
  - Then A matched to column 1 scores 0.5(2) + 0.25(-1) + 0.25(-2) = 0.25

	Col 1	Col 2	Col 3
A	0.50	0.25	0.50
B	0.00	0.75	0.00
C	0.25	0.00	0.00
-	0.25	0.00	0.50

A Multiple Alignment Package: ClustalW

- Basic outline of algorithm
  - Calculate the C(k,2) [i.e., *k choose 2*] pairwise alignment scores
  - Use a neighbor-joining algorithm to build a tree based on the distances
  - Distances are updated using string/string, string/profile, and profile/profile comparisons
- Actual algorithm includes many ad-hoc rules (e.g., weighting, different scoring matrices, and special gap scores)



http://www.uib.no/aasland/chromo/chromo-tree.gif