Heuristic Approaches

Mark Voorhies

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http://www.xkcd.com/287/

MY HOBBY:
EMBEDDING NP-COMPLETE PROBLEMS IN RESTAURANT ORDERS
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Motivation for scoring matrices

Frequency of residue $i$:

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Ratio of observed to expected frequency:

$$\frac{q_{ij}}{p_i p_j}$$

Log odds (LOD) score:

$$s(i, j) = \log q_{ij}$$
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BLOSUM45 in alphabetical order
import networkx as nx

try:
    import Pycluster
except ImportError:
    import Bio.Cluster as Pycluster

class ScoreCluster:
    def __init__(self, S, alpha_aa = "ACDEFGHIKLMNPQRSTVWY"):
        """Initialize from numpy array of scaled log odds scores."""
        (x,y) = S.shape
        assert(x == y == len(alpha_aa))

        # Interpret the largest score as a distance of zero
        D = max(S.reshape(x**2)) - S

        # Maximum-linkage clustering, with a user-supplied distance matrix
        tree = Pycluster.treecluster(distancematrix = D, method = "m")

        # Use NetworkX to read out the amino-acids in clustered order
        G = nx.DiGraph()
        for (n,i) in enumerate(tree):
            for j in (i.left, i.right):
                G.add_edge(-(n+1),j)

        self.ordering = [i for i in nx.dfs_preorder(G, -len(tree)) if(i >= 0)]
        self.names = ".".join(alpha_aa[i] for i in self.ordering)
        self.C = self.permute(S)

    def permute(self, S):
        """Given square matrix S in alphabetical order, return rows and columns of S permuted to match the clustered order."""
        return array([[S[i][j] for j in self.ordering] for i in self.ordering])
BLOSUM45 – maximum linkage clustering

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BLOSUM62 with BLOSUM45 ordering
BLOSUM80 with BLOSUM45 ordering
The implementation of local alignment is the same as for global alignment, with a few changes to the rules:

- Initialize edges to 0 (no penalty for starting in the middle of a sequence)
- The maximum score is never less than 0, and no pointer is recorded unless the score is greater than 0 (note that this implies negative scores for gaps and bad matches)
- The trace-back starts from the highest score in the matrix and ends at a score of 0 (local, rather than global, alignment)

Because the naive implementation is essentially the same, the time and space requirements are also the same.
## Smith-Waterman

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Why BLAST?

- Fast, heuristic approximation to a full Smith-Waterman local alignment
- Developed with a statistical framework to calculate expected number of false positive hits.
- Heuristics biased towards “biologically relevant” hits.
BLAST: A quick overview
BLAST: Seed from exact word hits
BLAST: Myers and Miller local alignment around seed pairs
Karlin-Altschul Statistics

\[ E = kmne^{-\lambda S} \]

- **E**: Expected number of “random” hits in a database of this size scoring at least \( S \).
- **S**: HSP score
- **m**: Query length
- **n**: Database size
- **k**: Correction for similar, overlapping hits
- **\( \lambda \)**: Normalization factor for scoring matrix
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\[ p = 1 - e^{-E} \]

(If you care about the difference between \( E \) and \( p \), you’re already in trouble)
0th order Markov Model

A → A → A → A
T → T → T → T
G → G → G → G
C → C → C → C
1st order Markov Model
1st order Markov Model

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1\textsuperscript{st} order Markov Model

\[ \text{Graph of Markov Model} \]

- Node labels: A, T, G, C
- Transitions: A \rightarrow A \rightarrow A \rightarrow A
- States: A, T, G, C

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What are Markov Models good for?

- Background sequence composition
- Spam
Hidden Markov Models

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The Viterbi algorithm: Alignment
The Viterbi algorithm: Alignment

- Dynamic programming, like Smith-Waterman
- Sums best log probabilities of emissions and transitions (i.e., multiplying independent probabilities)
- Result is most likely annotation of the target with hidden states
The Forward algorithm: Net probability

- Probability-weighted sum over all possible paths
- Simple modification of Viterbi (although *summing* probabilities means we have to be more careful about rounding error)
- Result is the probability that the observed sequence is explained by the model
- In practice, this probability is compared to that of a null model (e.g., random genomic sequence)
If we have a set of sequences with known hidden states (e.g., from experiment), then we can calculate the emission and transition probabilities directly.
Training an HMM

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Otherwise, they can be iteratively fit to a set of unlabeled sequences that are known to be true matches to the model.
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- If we have a set of sequences with known hidden states (e.g., from experiment), then we can calculate the emission and transition probabilities directly.
- Otherwise, they can be iteratively fit to a set of unlabeled sequences that are known to be true matches to the model.
- The most common fitting procedure is the Baum-Welch algorithm, a special case of expectation maximization (EM).
Profile Alignments: Plan 7

(Image from Sean Eddy, PLoS Comp. Biol. 4:e1000069)
Profile Alignments: Plan 7 (from Outer Space)

(Image from Sean Eddy, PLoS Comp. Biol. 4:e1000069)
Rigging Plan 7 for Multi-Hit Alignment

(Image from Sean Eddy, PLoS Comp. Biol. 4:e1000069)
HMMer3 speeds

Eddy, PLoS Comp. Biol. 7:e1002195
HMMer3 sensitivity and specificity

Eddy, PLoS Comp. Biol. 7:e1002195
- Can emit from both sides → base pairs
- Can duplicate emitter → bifurcations
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Homework

- Keep working on your dynamic programming code.