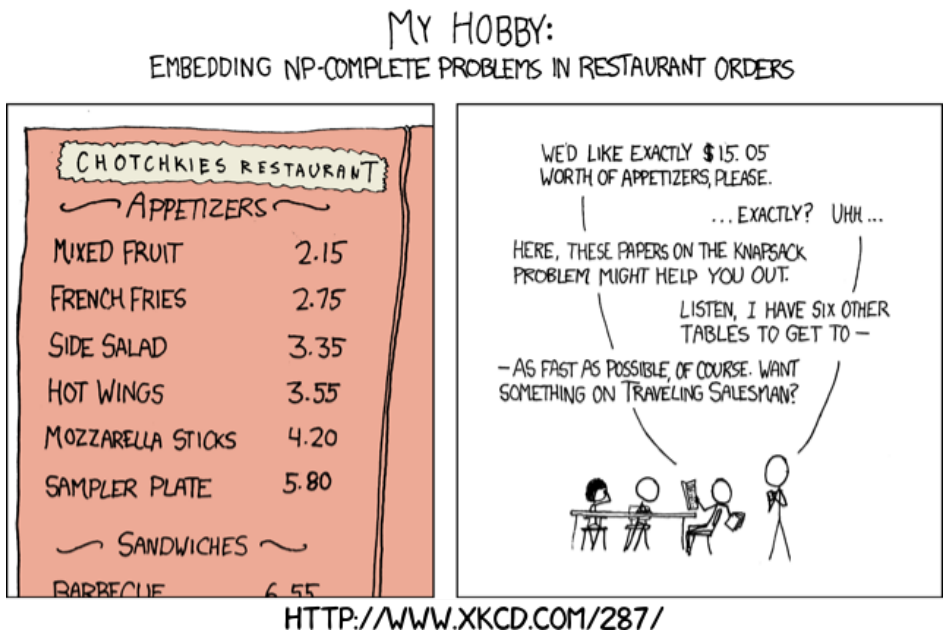
Heuristic Approaches

Mark Voorhies

5/5/2017



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- If evolution is uniform over time, then PAM matrices for larger evolutionary steps can be generated by multiplying PAM1 by itself (so, higher numbered PAM matrices represent greater evolutionary distances).
- The BLOSUM matrices were determined from automatically generated ungapped alignments. Higher numbered BLOSUM matrices correspond to *smaller* evolutionary distances. BLOSUM62 is the default matrix for BLAST.

Motivation for scoring matrices

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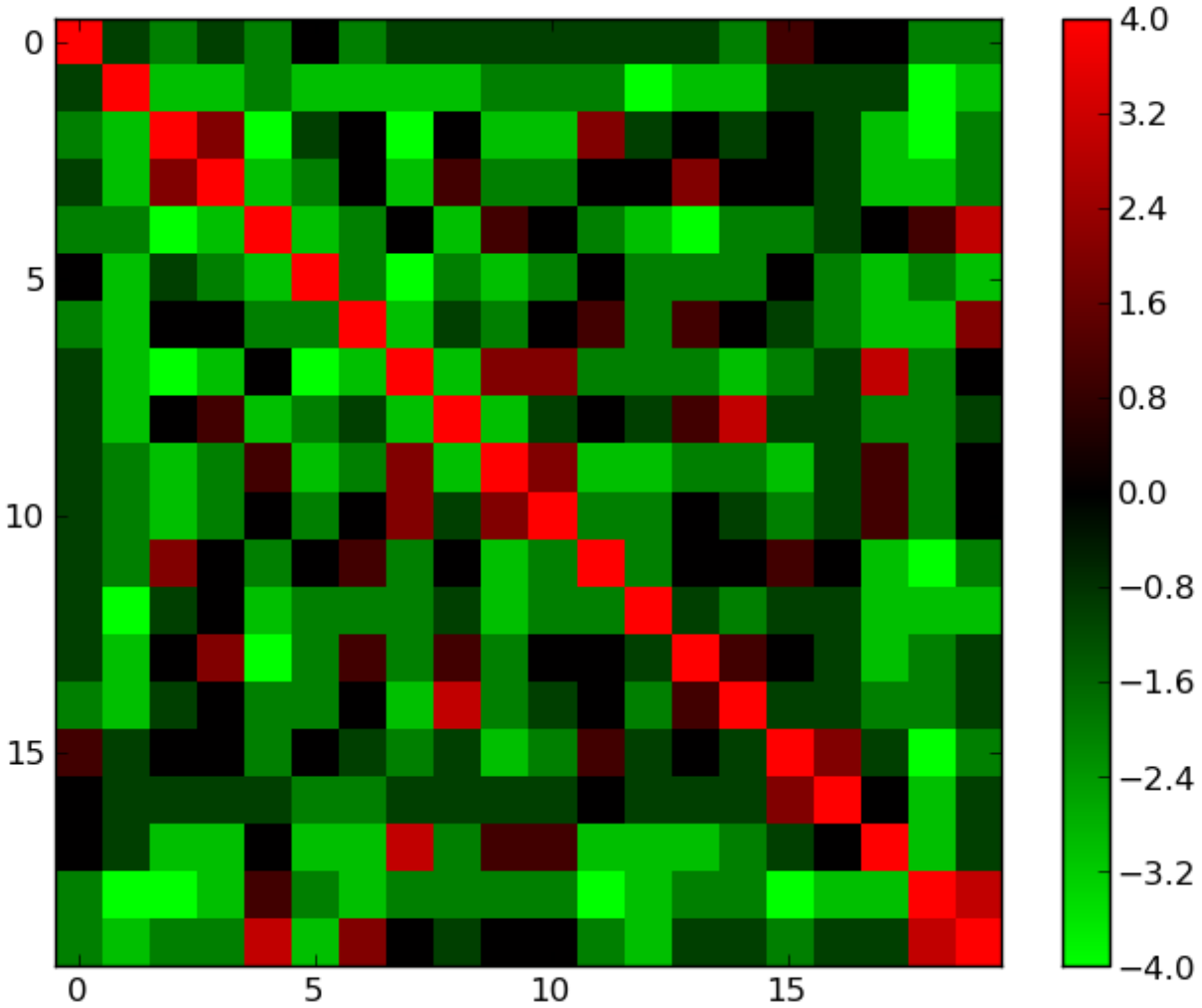
Log odds (LOD) score:

$$s(i,j) = \log \frac{q_{ij}}{p_i p_j}$$

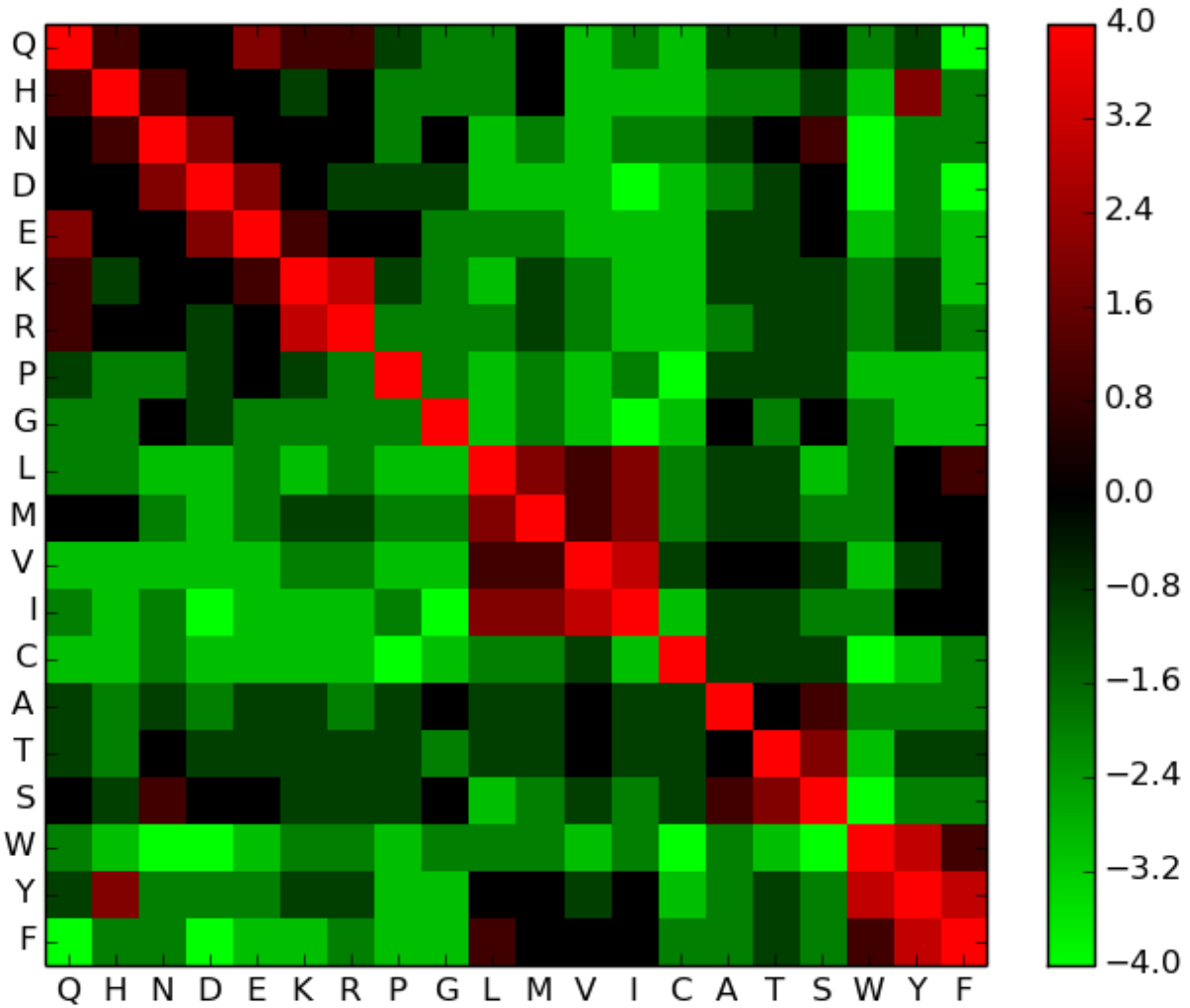
BLOSUM45 in alphabetical order



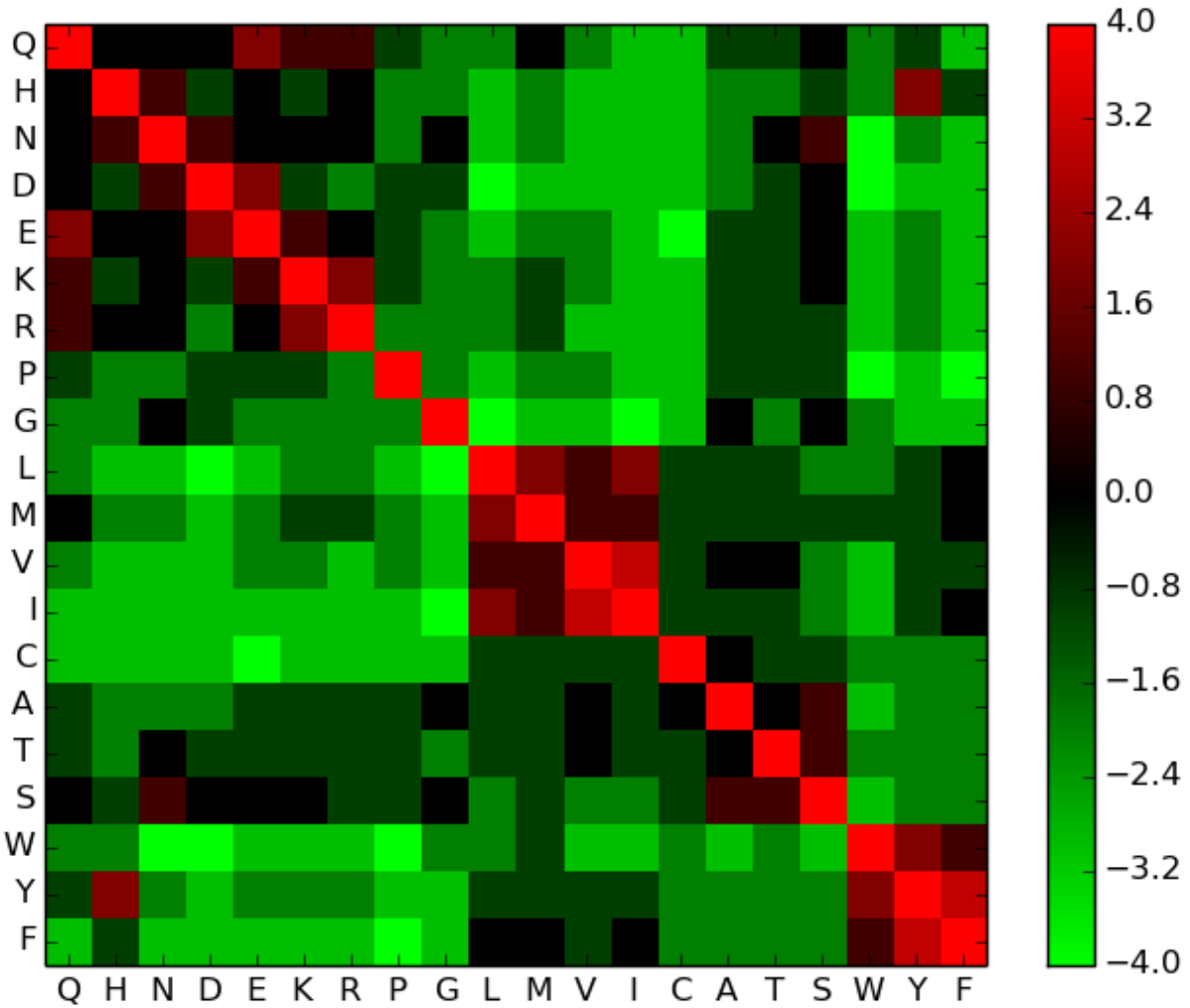
Clustering amino acids on log odds scores

```
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])
```

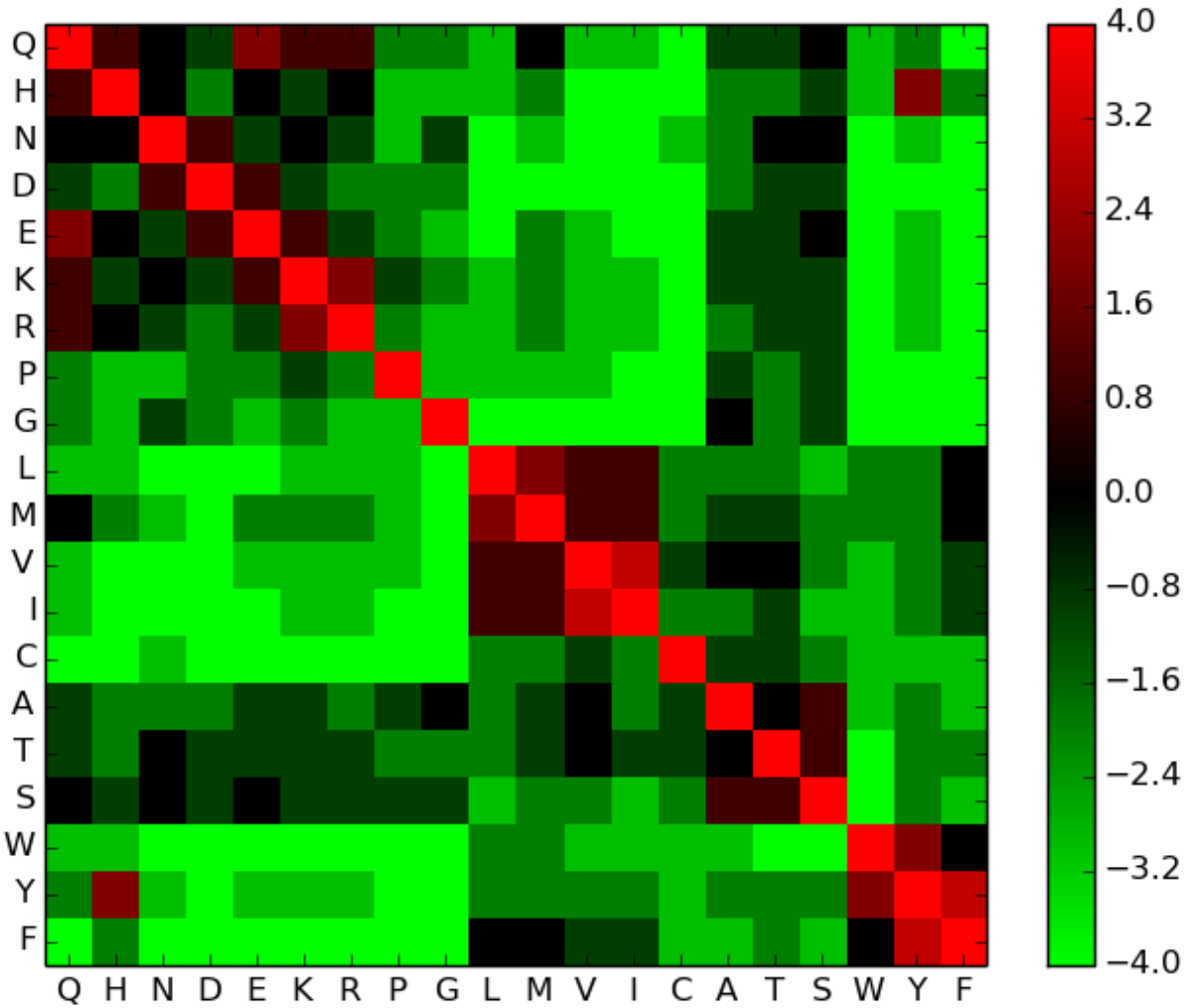
BLOSUM45 – maximum linkage clustering



BLOSUM62 with BLOSUM45 ordering



BLOSUM80 with BLOSUM45 ordering



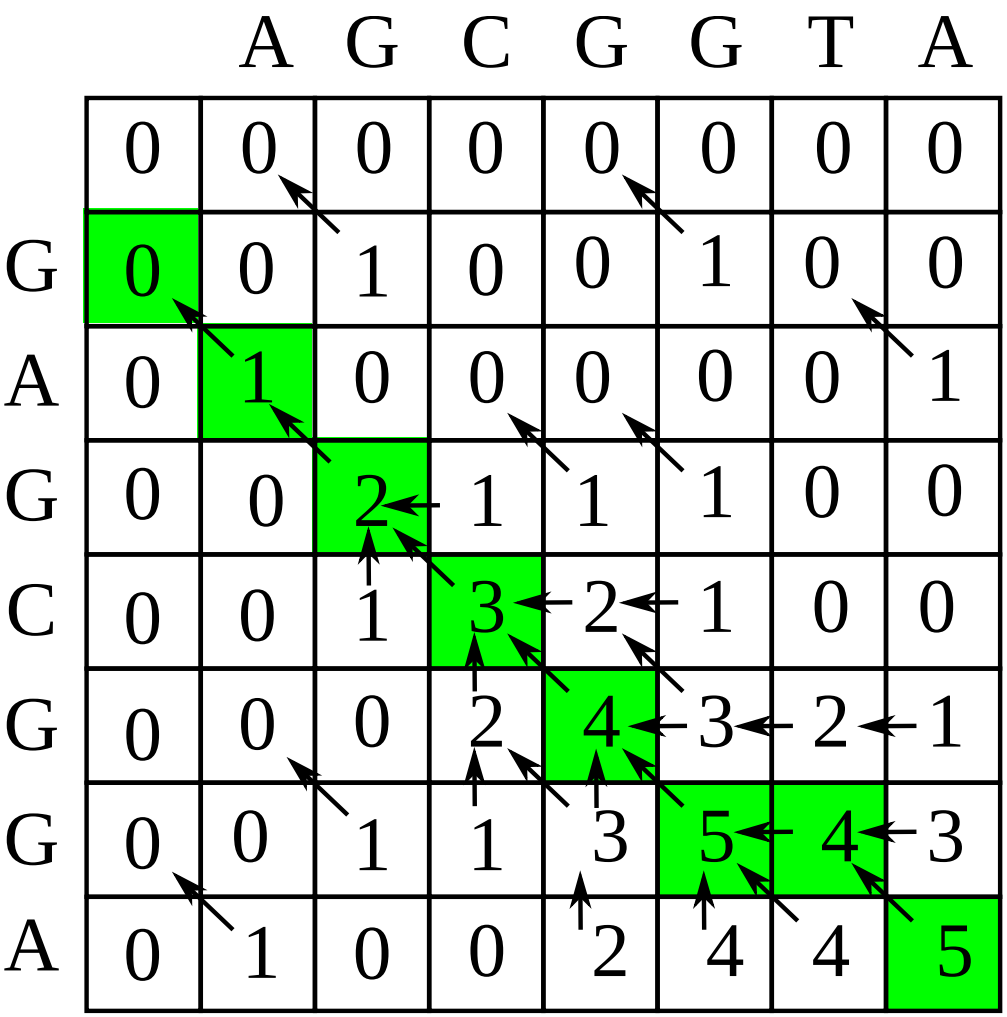
Smith-Waterman

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

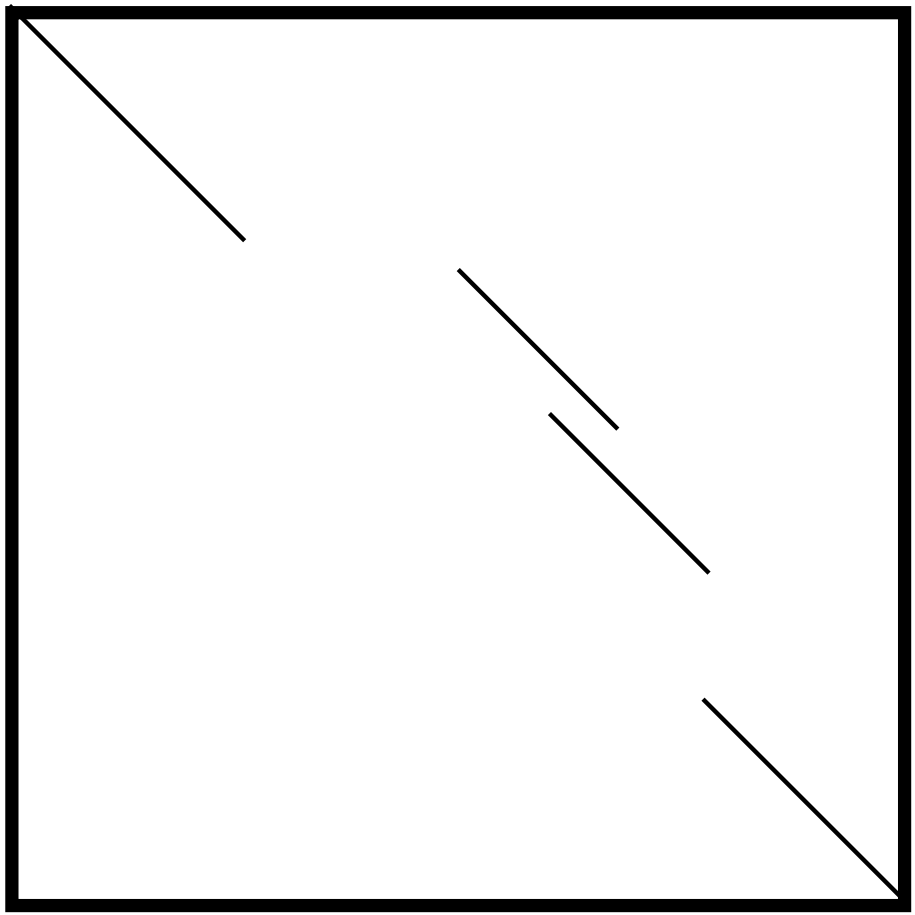


Basic Local Alignment Search Tool

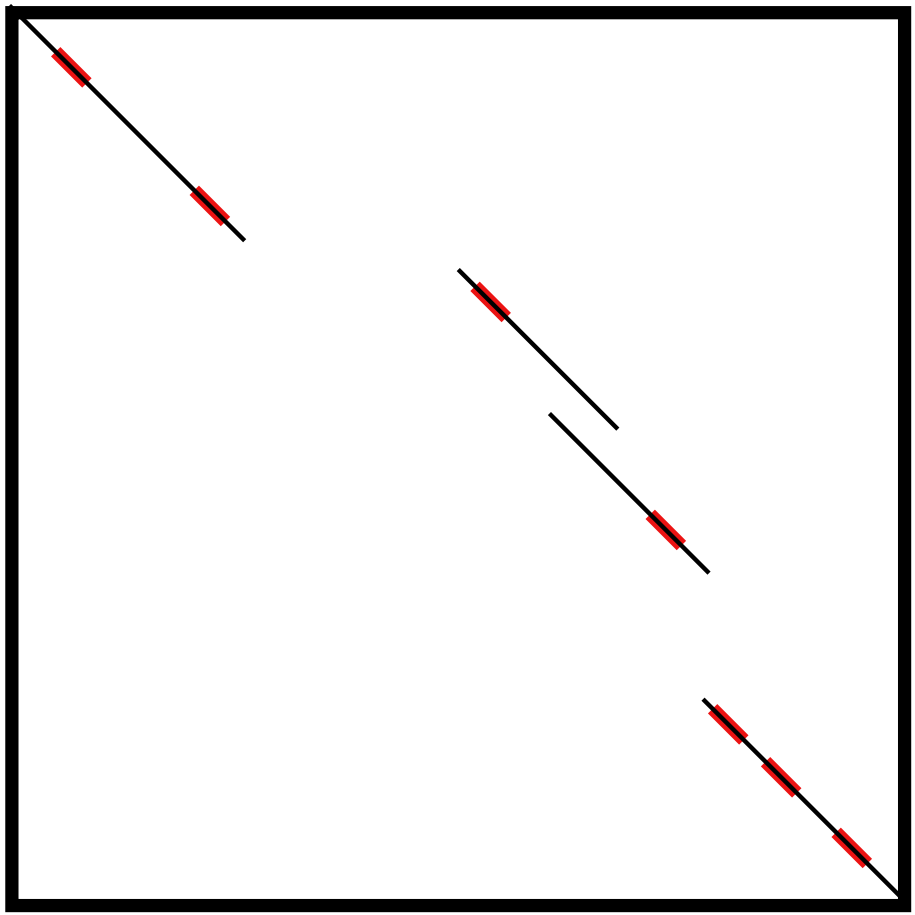
Why BLAST?

- 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.

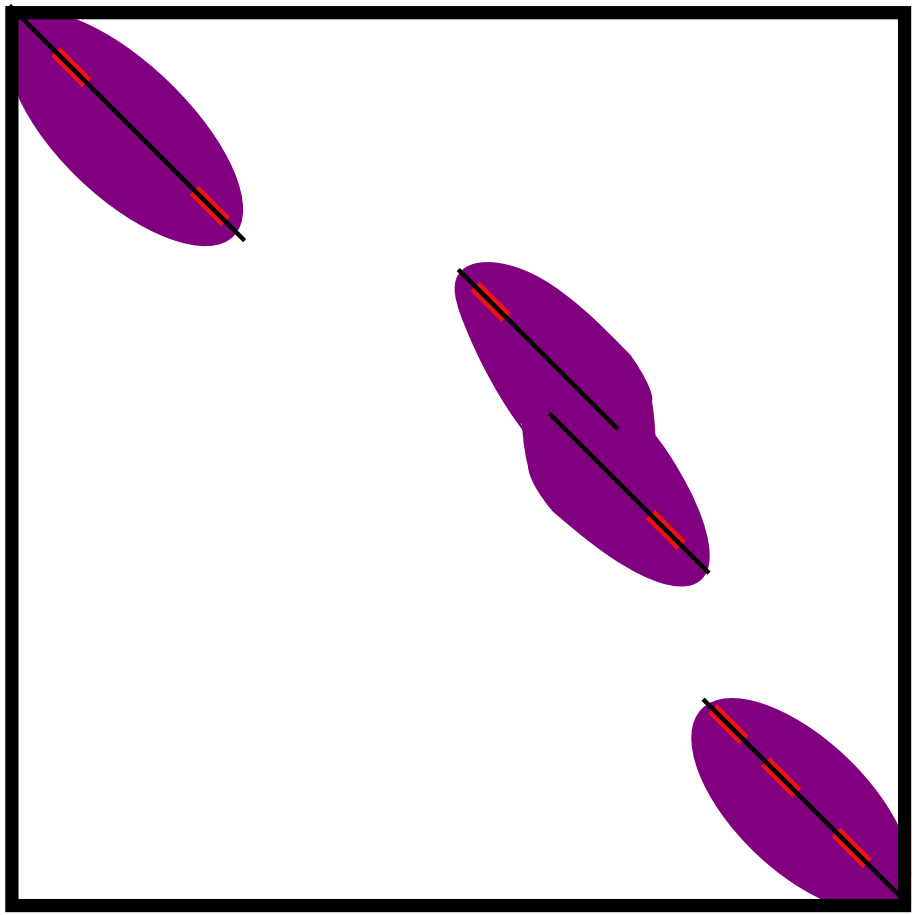
BLAST: A quick overview



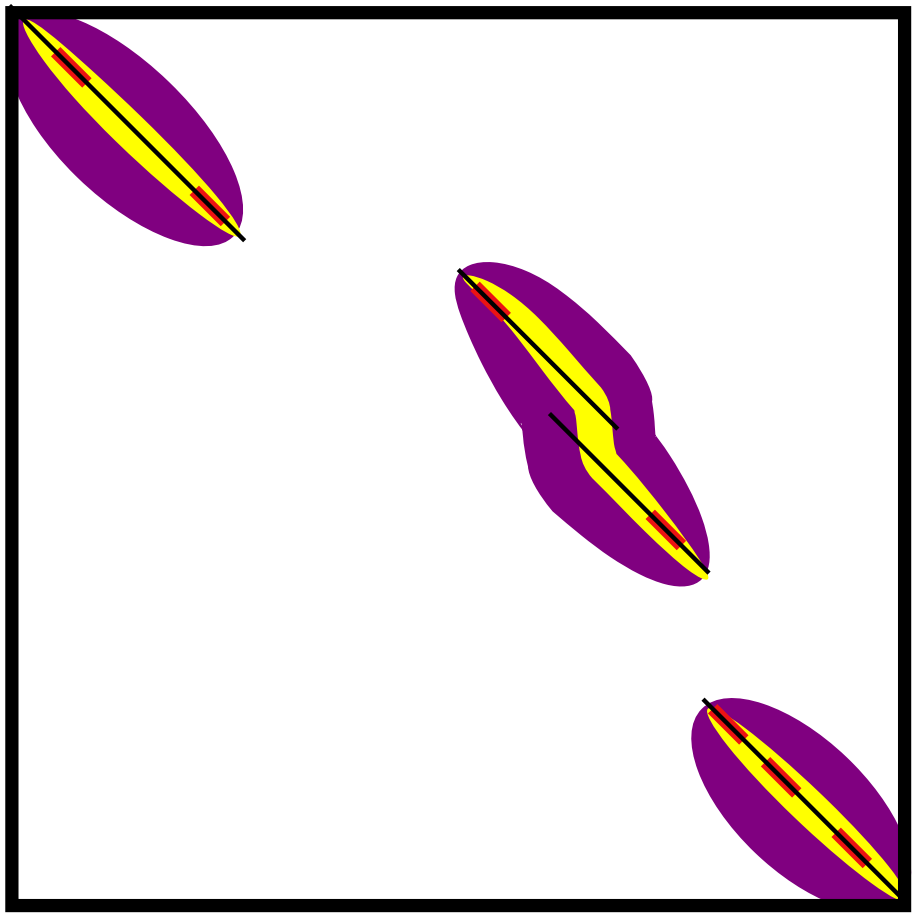
BLAST: Seed from exact word hits



BLAST: Myers and Miller local alignment around seed pairs



BLAST: High Scoring Pairs (HSPs)



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
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- k: Correction for similar, overlapping hits
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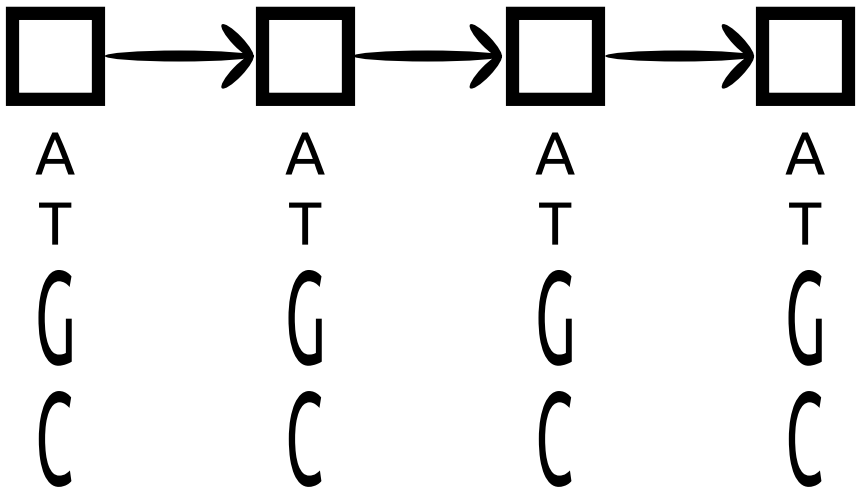
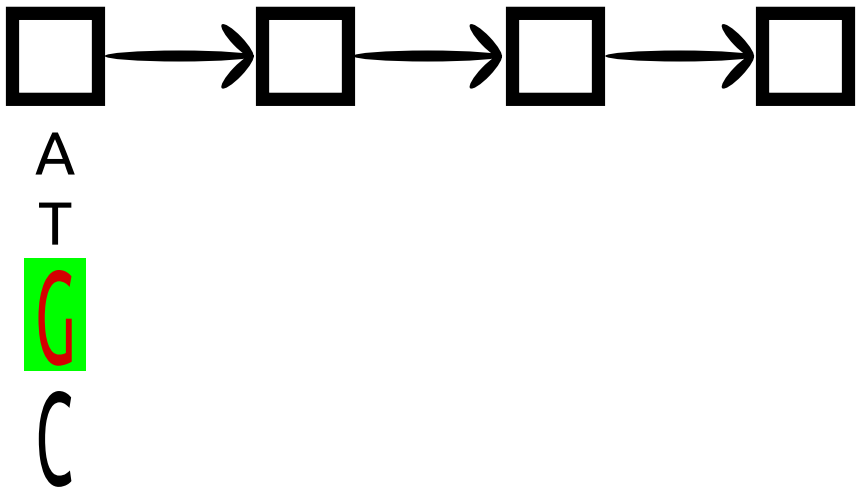
$$p = 1 - e^{-E}$$

(If you care about the difference between E and p, you're already in trouble)

0^{th} order Markov Model



1^{st} order Markov Model



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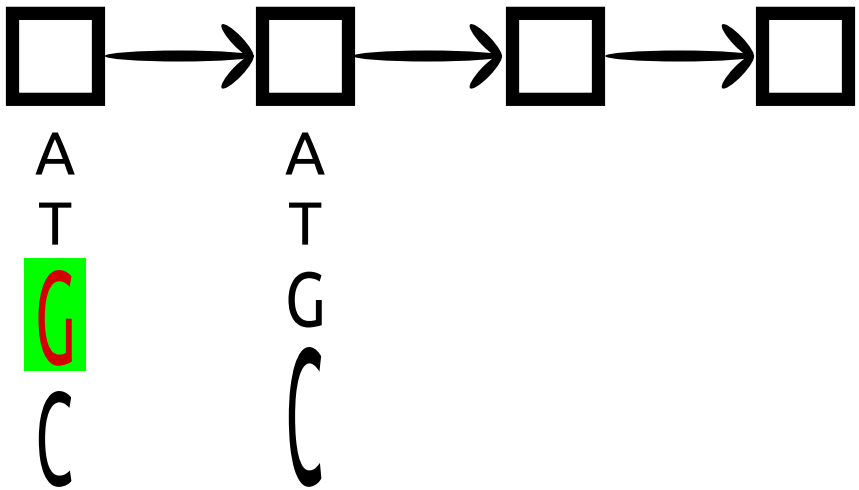

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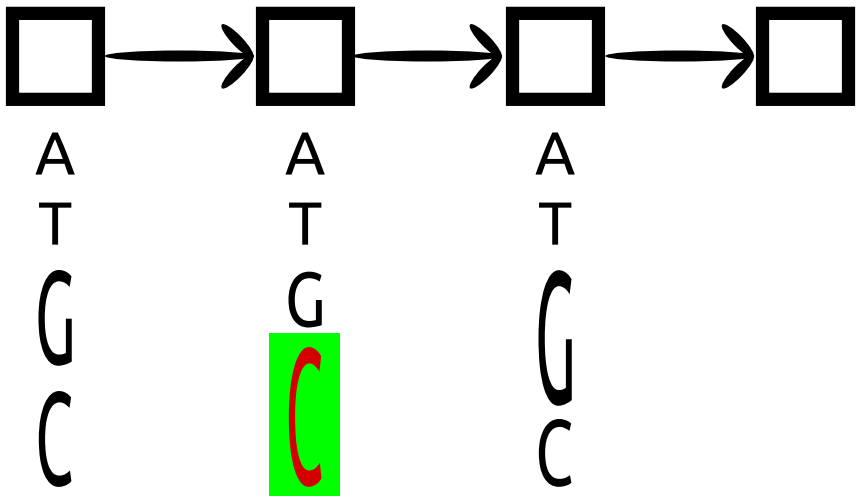
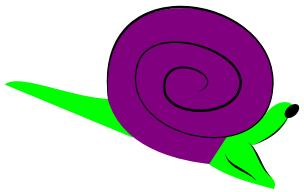
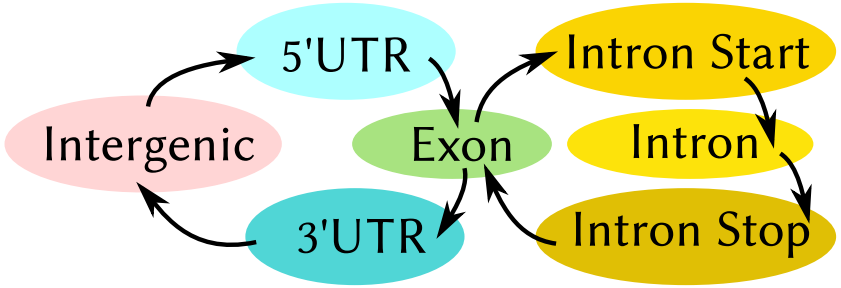


What are Markov Models good for?

- Background sequence composition
- Spam

Hidden Markov Models





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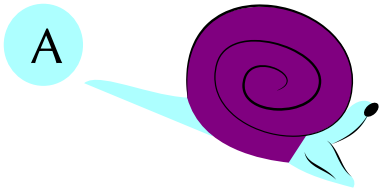

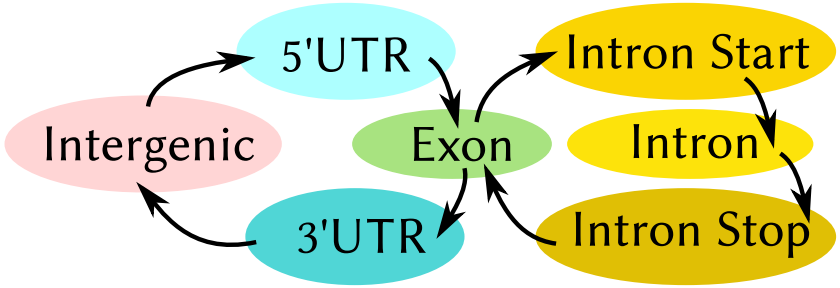

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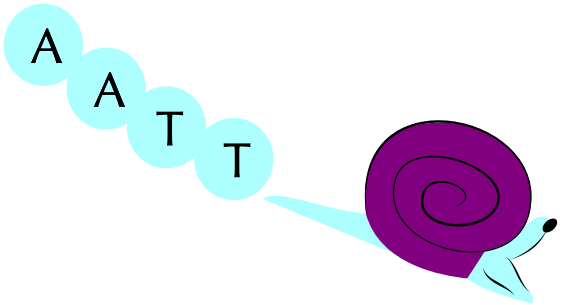

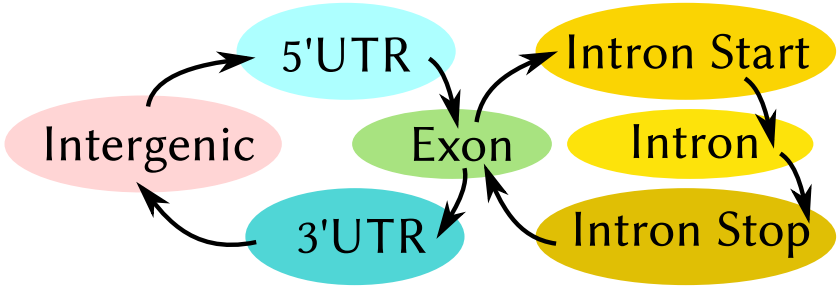

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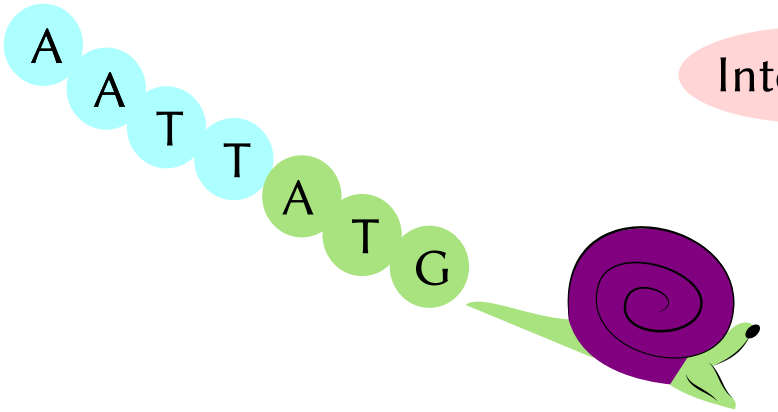

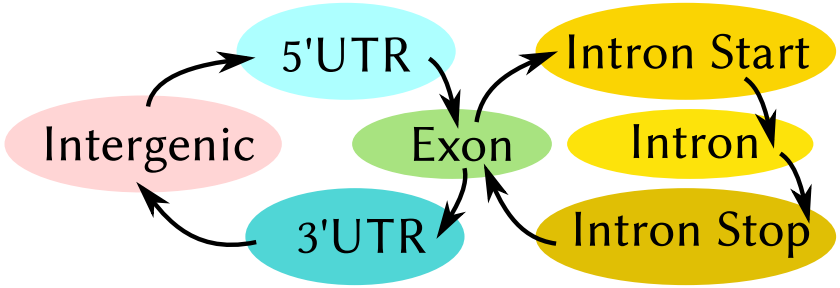

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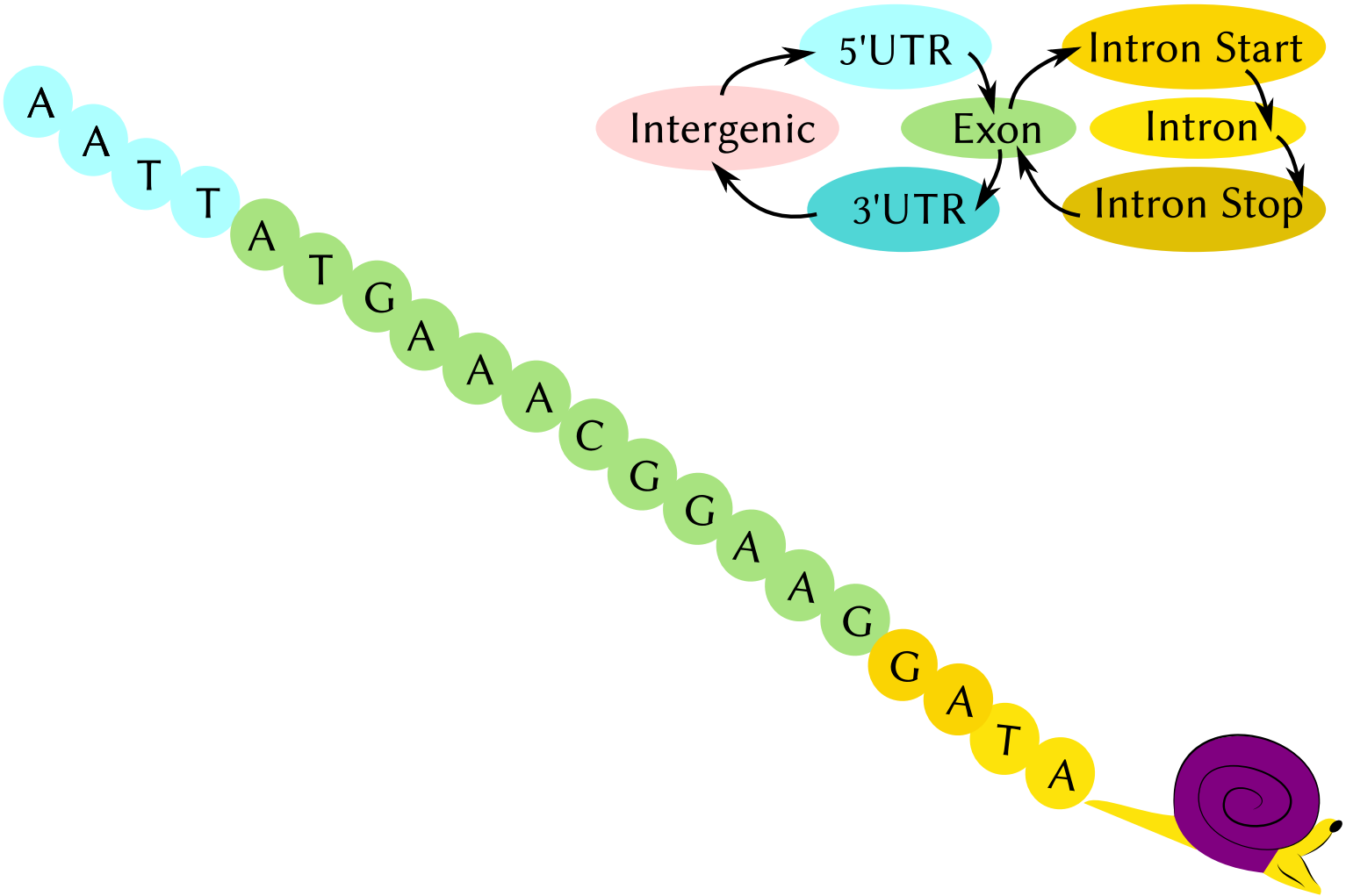

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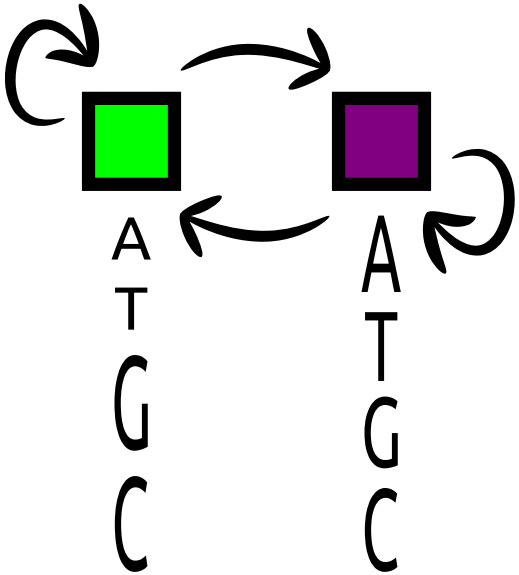
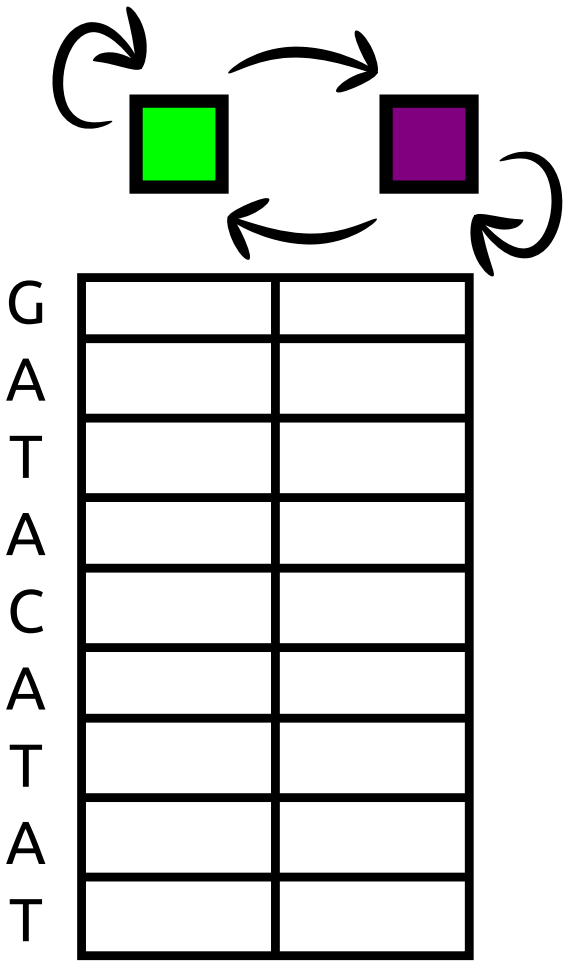


The Viterbi algorithm: Alignment



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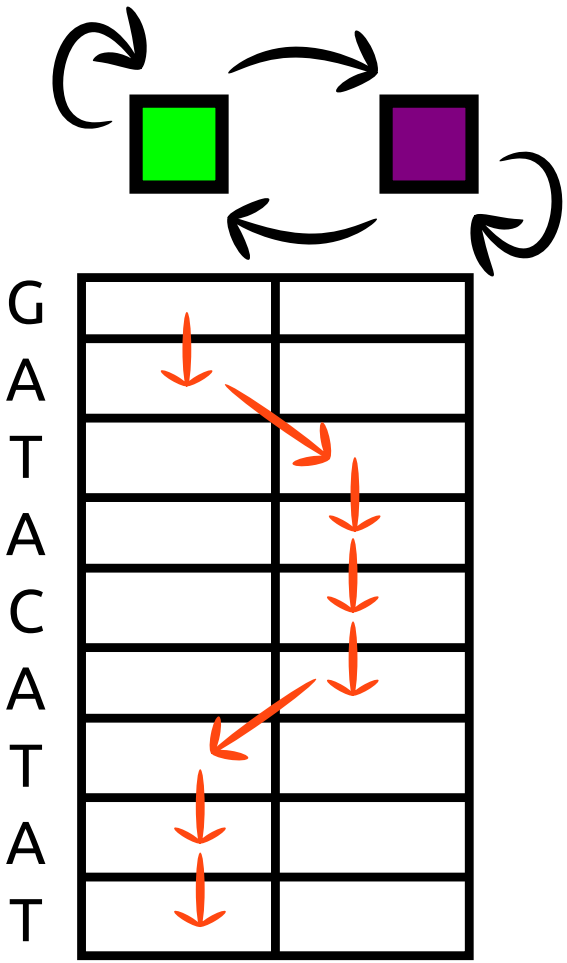
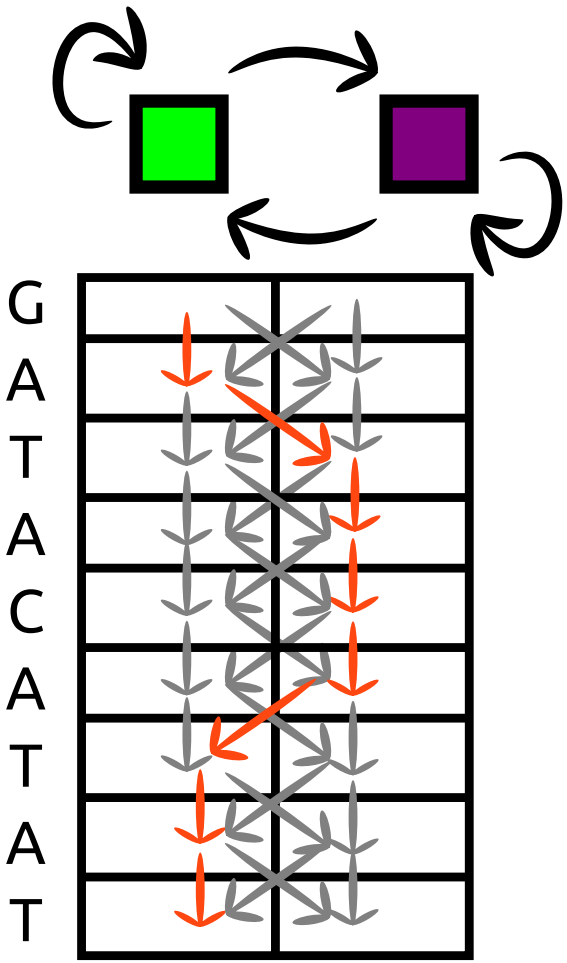


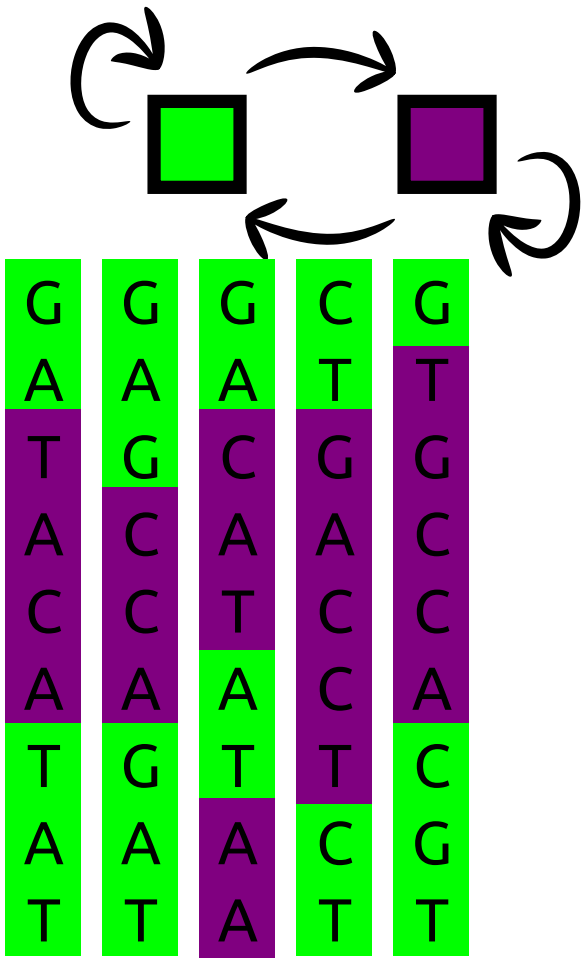
- Dynamic programming, like Smith-Waterman
- Sums *best* log probabilities of emissions and transitions (*i.e.*, multiplying independent probabilities)
- Result is most likely annotation of the target with hidden states

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)

Training an HMM



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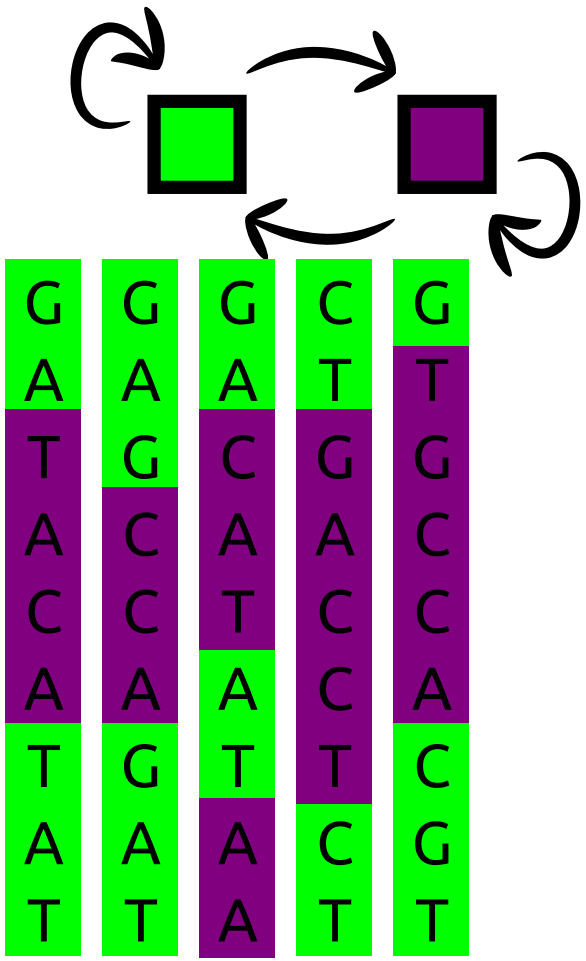

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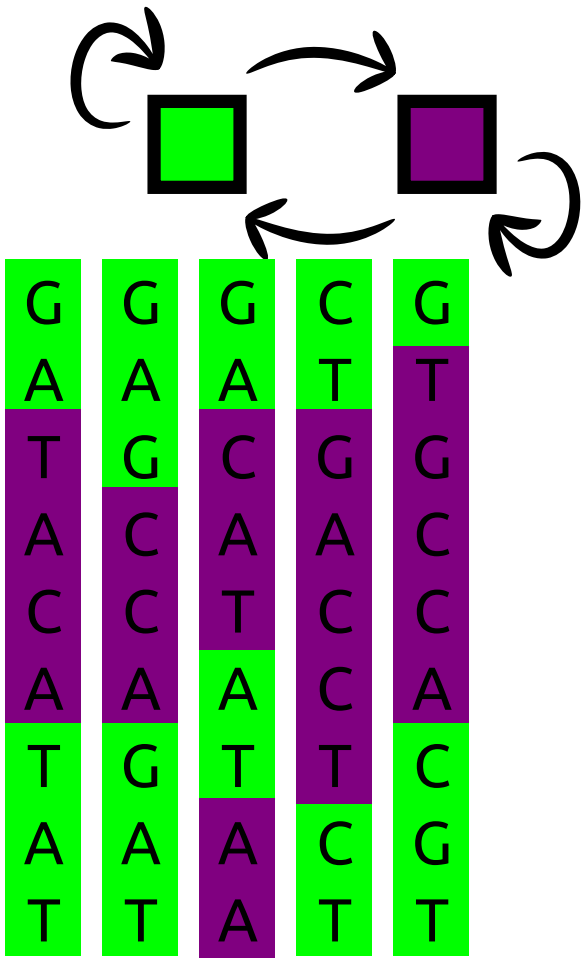
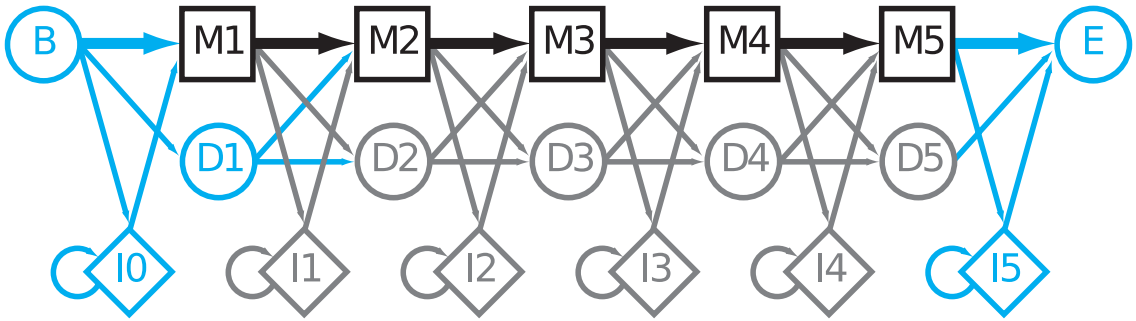


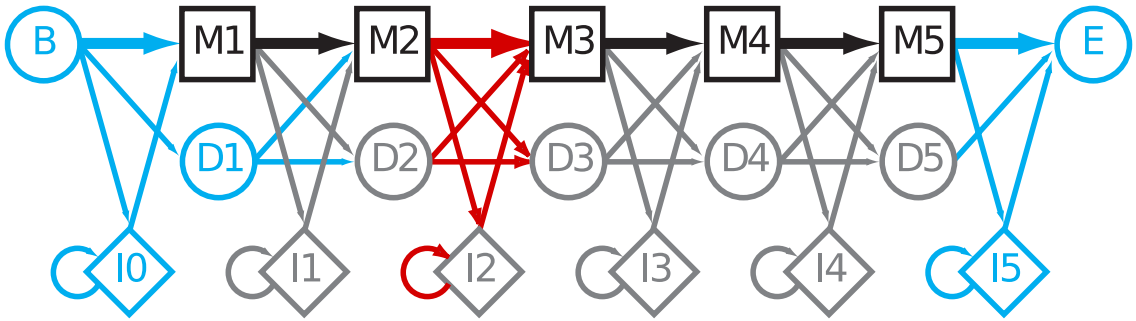
- If we have a set of sequences with known hidden states (*e.g.*, from experiment), then we can calculate the emission and transition probabilities directly
- Otherwise, they can be iteratively fit to a set of unlabeled sequences that are known to be true matches to the model
- The most common fitting 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)



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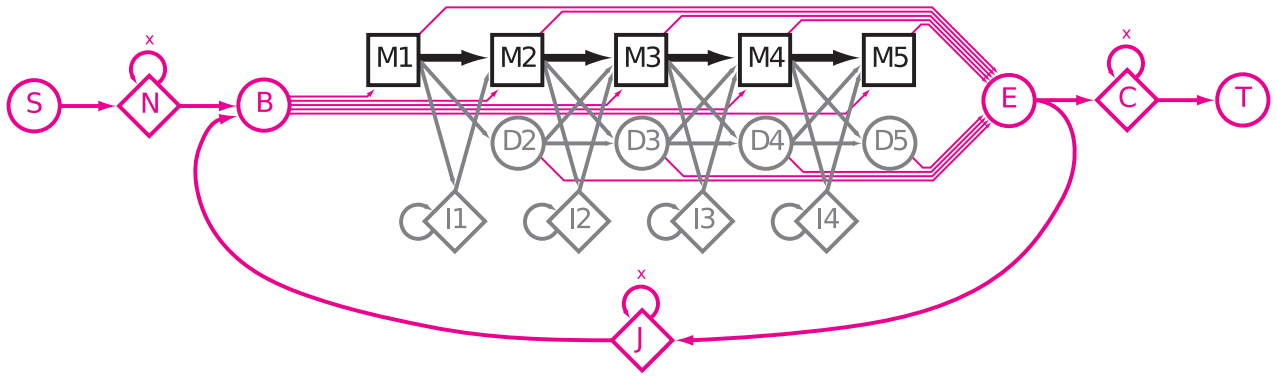
Rigging Plan 7 for Multi-Hit Alignment



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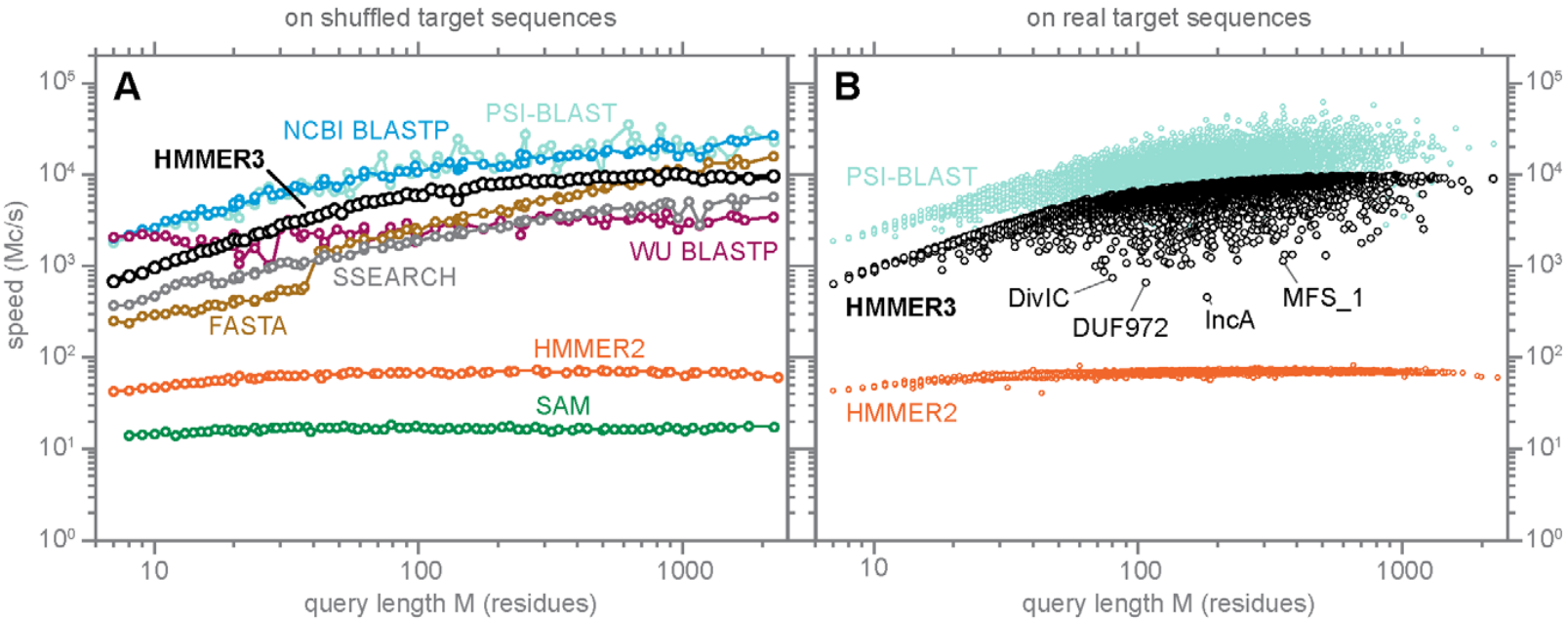
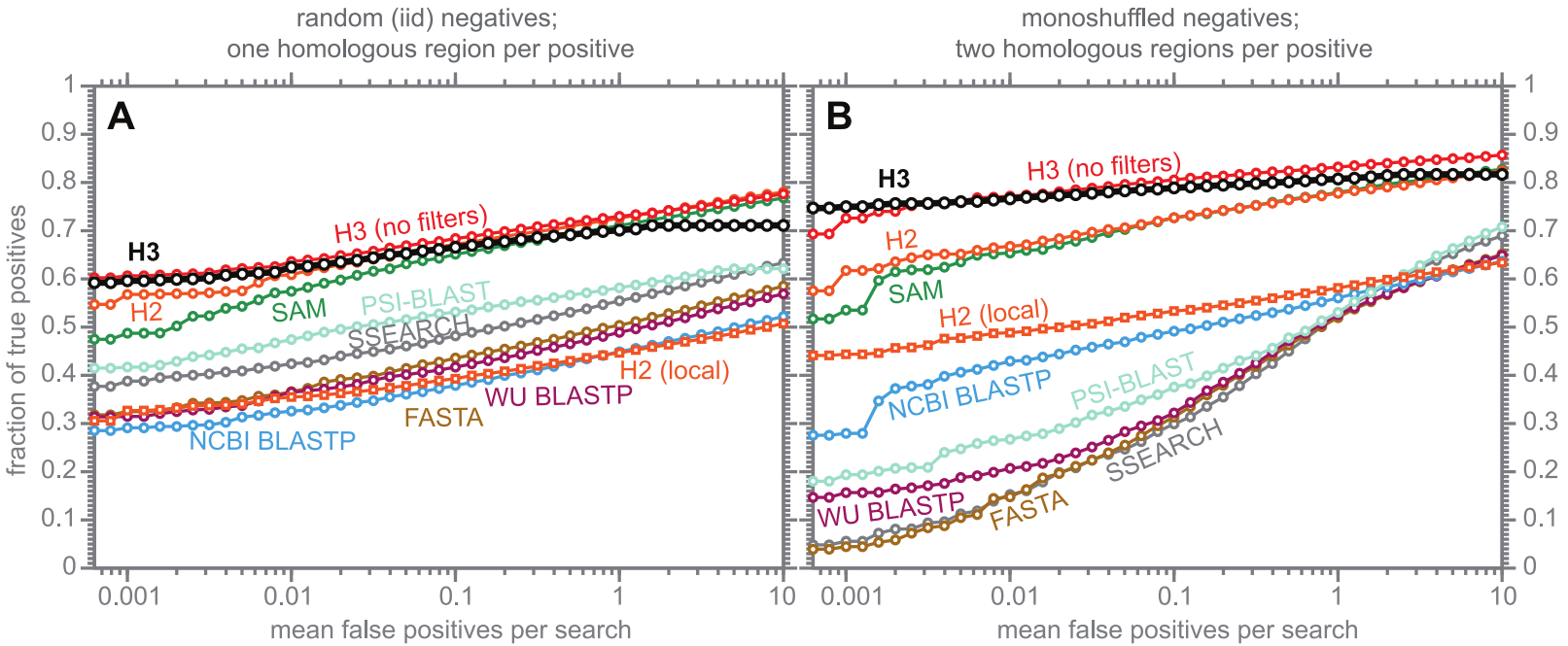
HMMer3 speeds



Eddy, PLoS Comp. Biol. 7:e1002195

HMMer3 sensitivity and specificity



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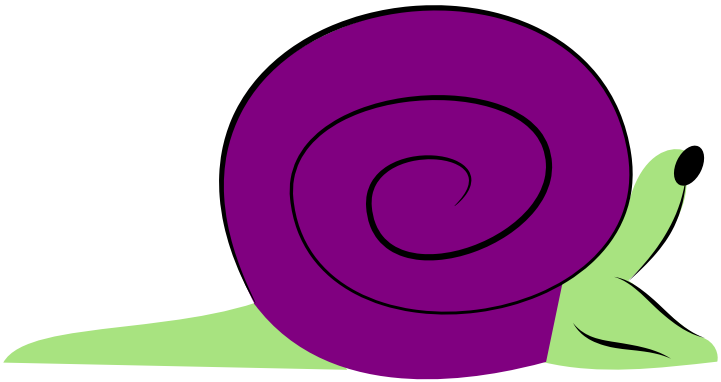
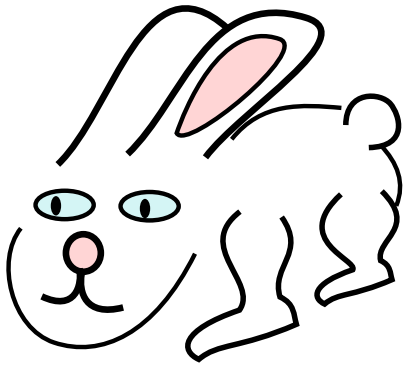
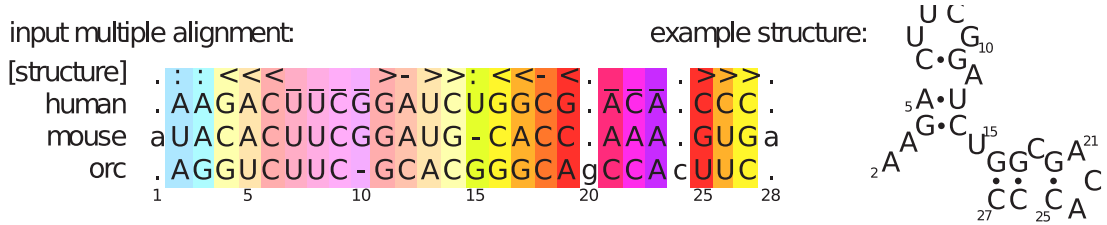
Stochastic Context Free Grammars

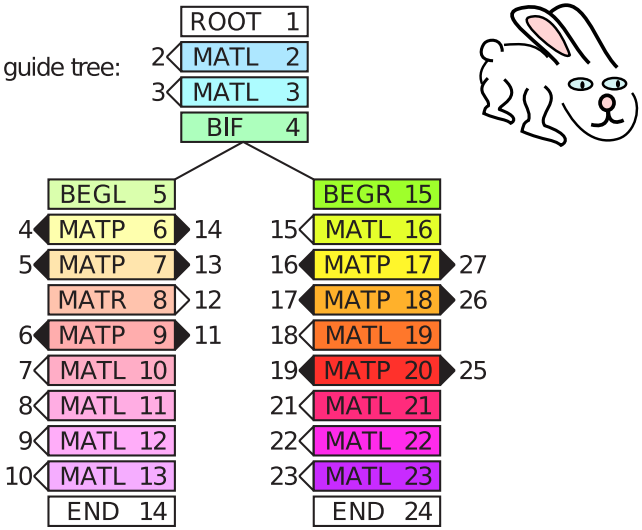




- Can emit from both sides $\rightarrow$ base pairs
- Can duplicate emitter $\rightarrow$ bifurcations

INFERNAL/Rfam





Modified from the INFERNAL User Guide – Nawrocki, Kolbe, and Eddy

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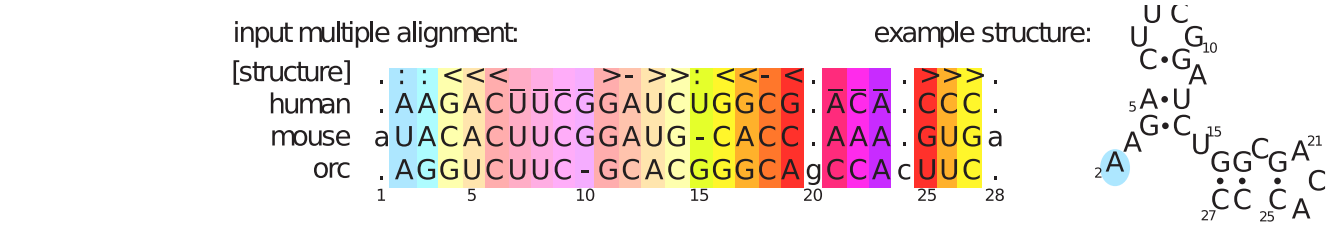

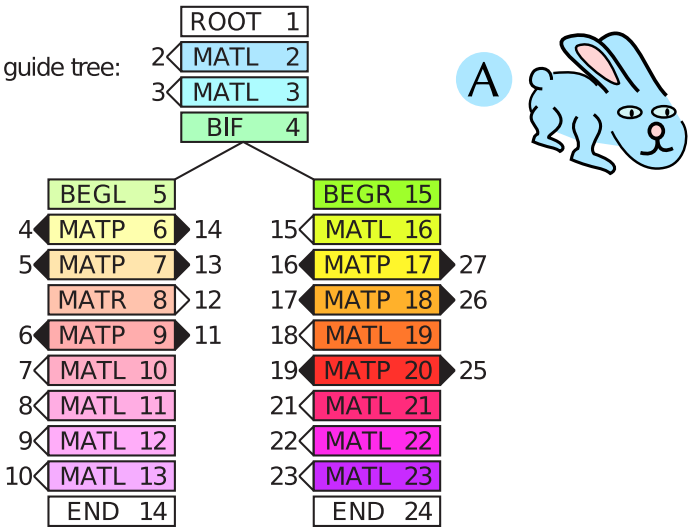

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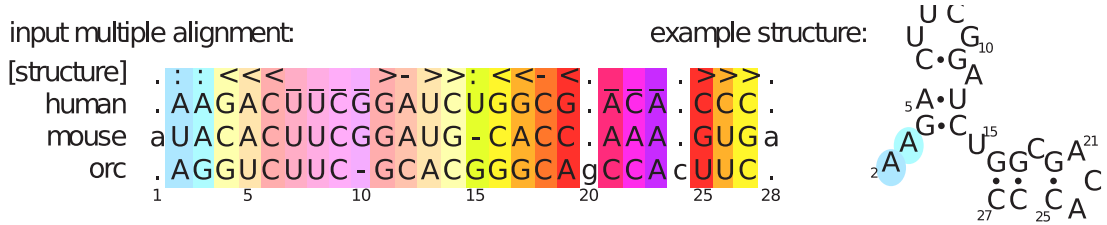

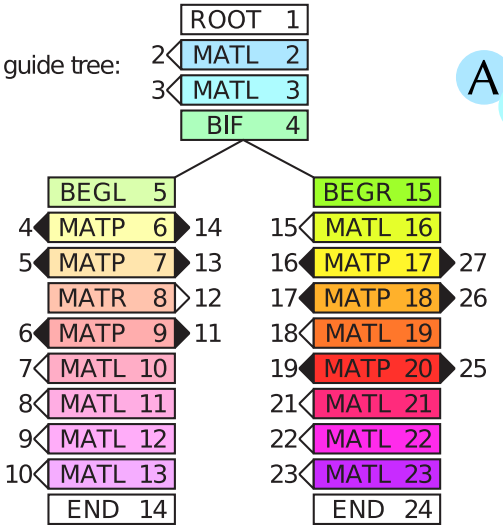

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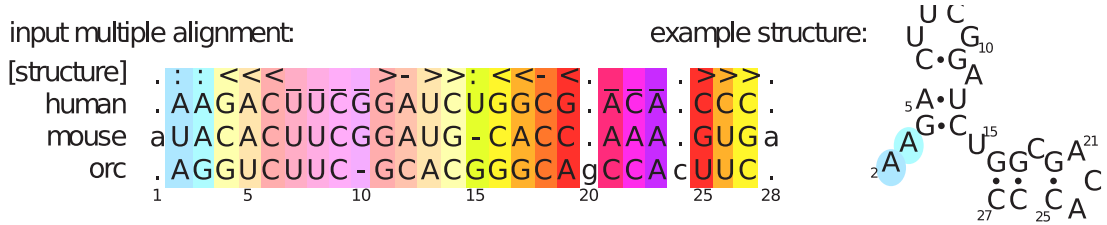

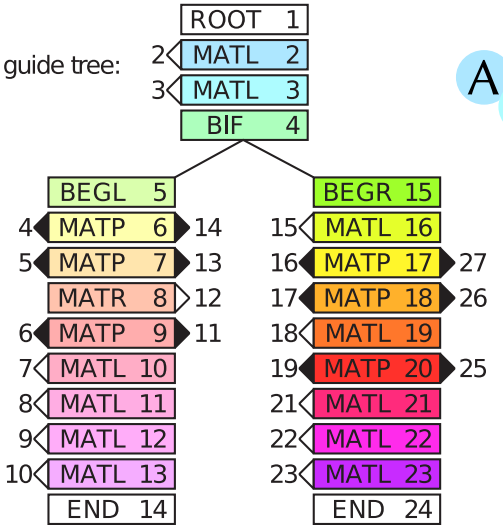

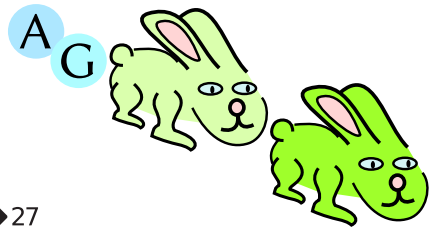

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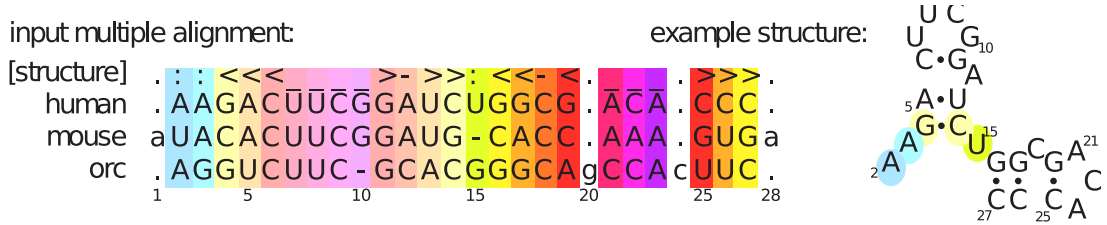

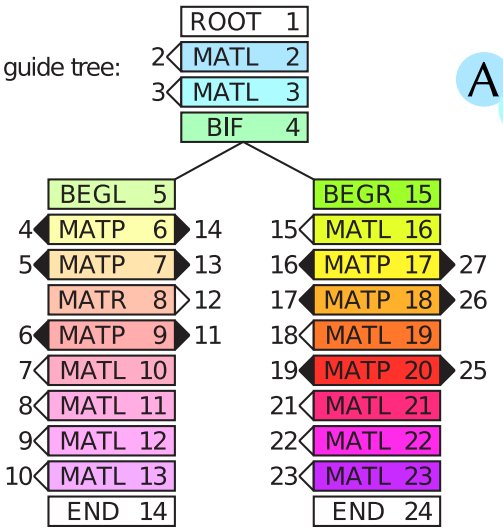

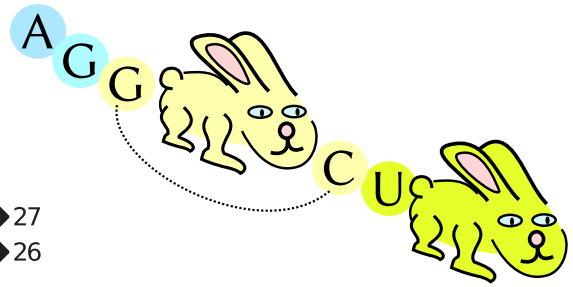

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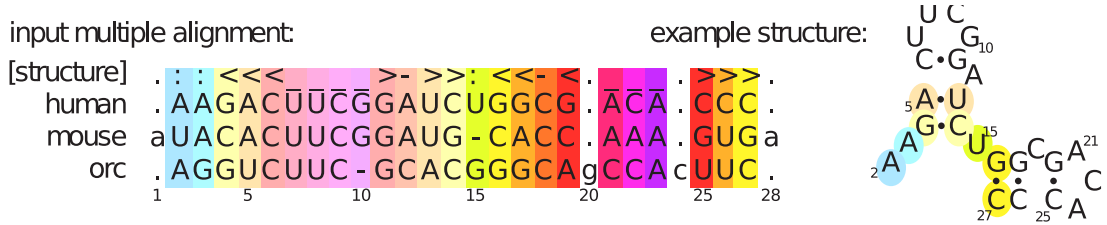

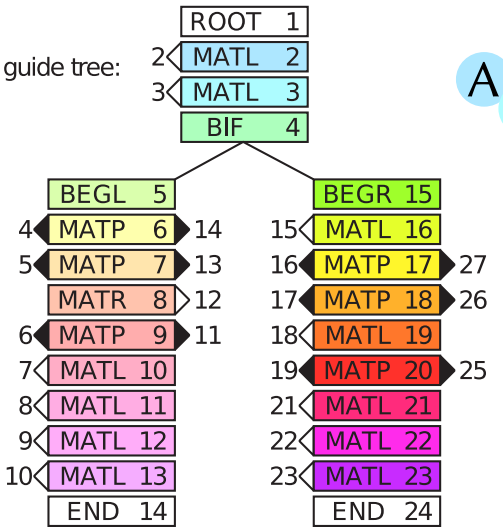

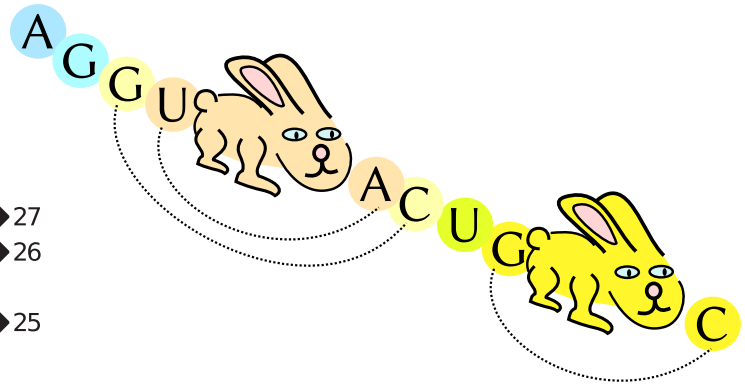

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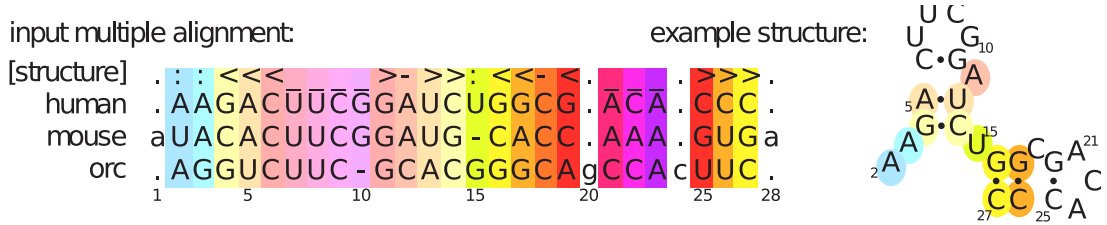

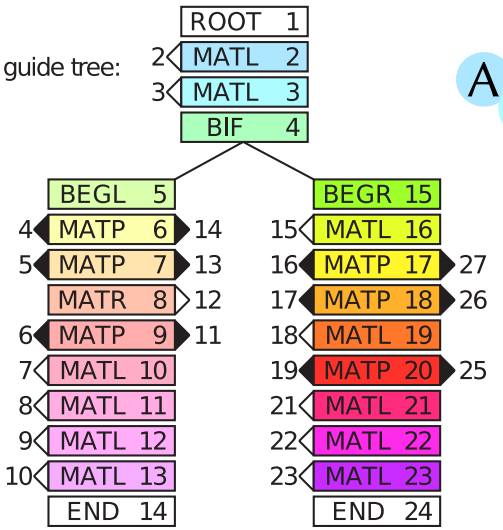

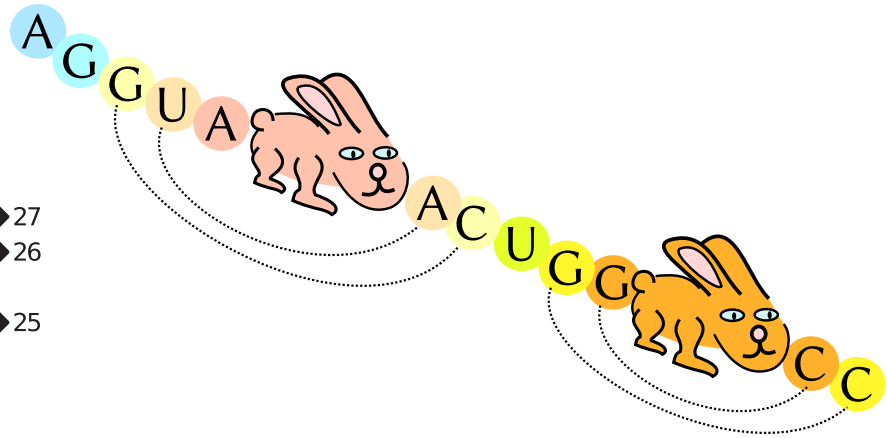

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Homework

- Keep working on your dynamic programming code.