Comparative Gene Finding (abridged)

BMI/CS 776

www.biostat.wisc.edu/bmi776/

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Goals for Lecture

Key concepts:

- Related genomes as an additional source of evidence for gene finding
- Pair hidden Markov models
- Extending GENSCAN to emits pairs of observed variables

Why Use Comparative Methods?

- Genes are among the most conserved elements in the genome
  - use conservation to help infer locations of genes
- Some signals associated with genes are short and occur frequently in the genome
  - use conservation to eliminate false candidate sites from consideration

TWINSCAN

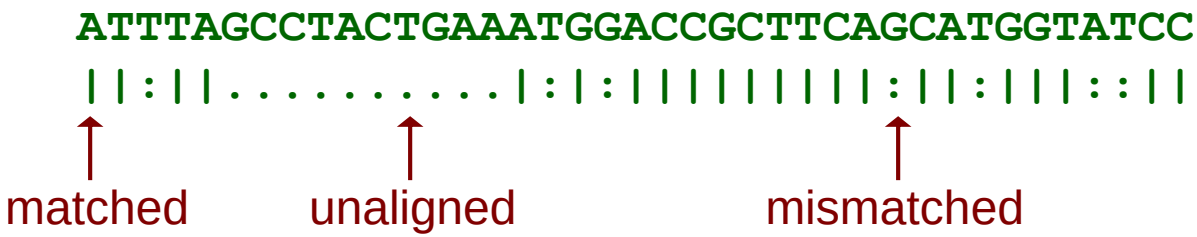
Korf et al., *Bioinformatics* 2001

- Extend GENSCAN using pre-computed conservation

- Prediction with TWINSCAN
  given: a sequence to be parsed, x
  using BLAST, construct a conservation sequence, c
  have HMM simultaneously parse (using Viterbi) x and c

Conservation Sequences in TWINSCAN

- Before processing a given sequence, TWINSCAN first computes a corresponding *conservation sequence*



- Based on BLAST matches sorted by alignment score

Conservation Sequence Example

input sequence

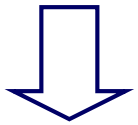
```
ATTTAGCCTACTGAAATGGACCGCTTCAGCATGGTATCC
```

significant BLAST matches ordered from best to worst

```
ATGGACCGCTTCAGC
|:|:|||||||||:|
ACGCACCGCTTCATC

AGCATGGTATCC
||:|:|||::||
AGAAGGGTCACC

ATTTA
||:||
ATCTA
```



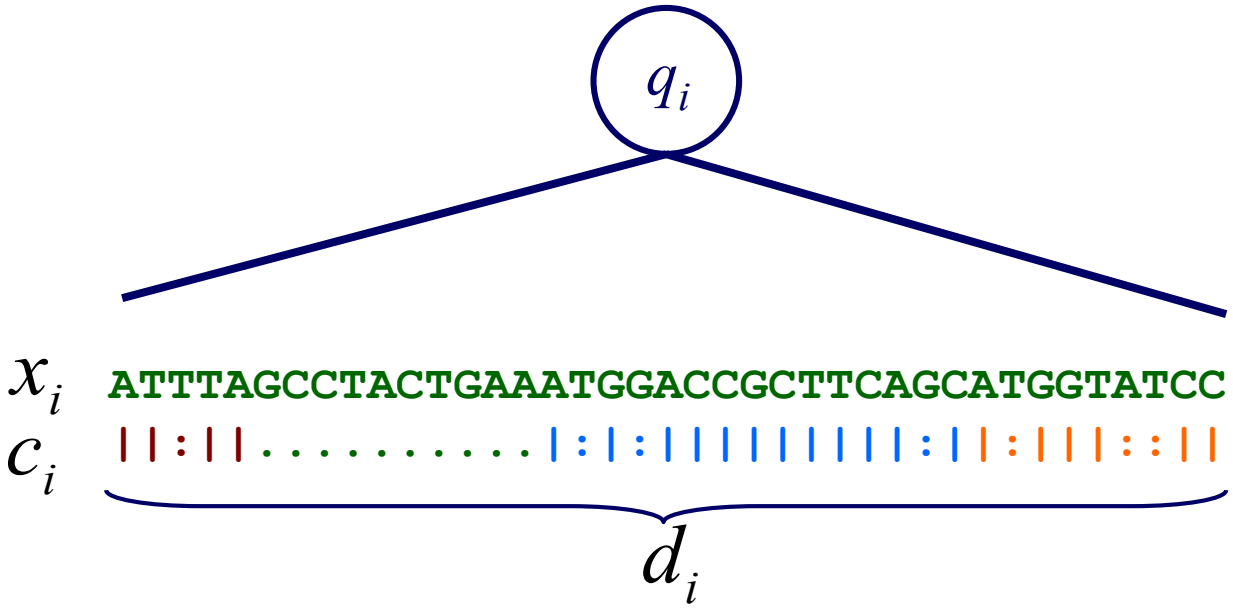
resulting conservation sequence

```
ATTTAGCCTACTGAAATGGACCGCTTCAGCATGGTATCC
||:||..........|:|:|||||||||:||:|||::||
```

Modeling Sequences in TWINSCAN

- Each state "emits" two sequences
  - the given DNA sequence, x
  - the conservation sequence, c
- Treats them as conditionally independent given the state

$$\Pr(q_i, d_i, x_i, c_i) \approx \Pr(d_i \mid q_i)\ \Pr(x_i \mid q_i, d_i)\ \Pr(c_i \mid q_i, d_i)$$



SLAM

Pachter et al., *RECOMB* 2001

- Doesn't require a pre-computed alignment
- Combine generalized HMM (GENSCAN) and pair HMM
  - GPHMM

- Prediction with SLAM

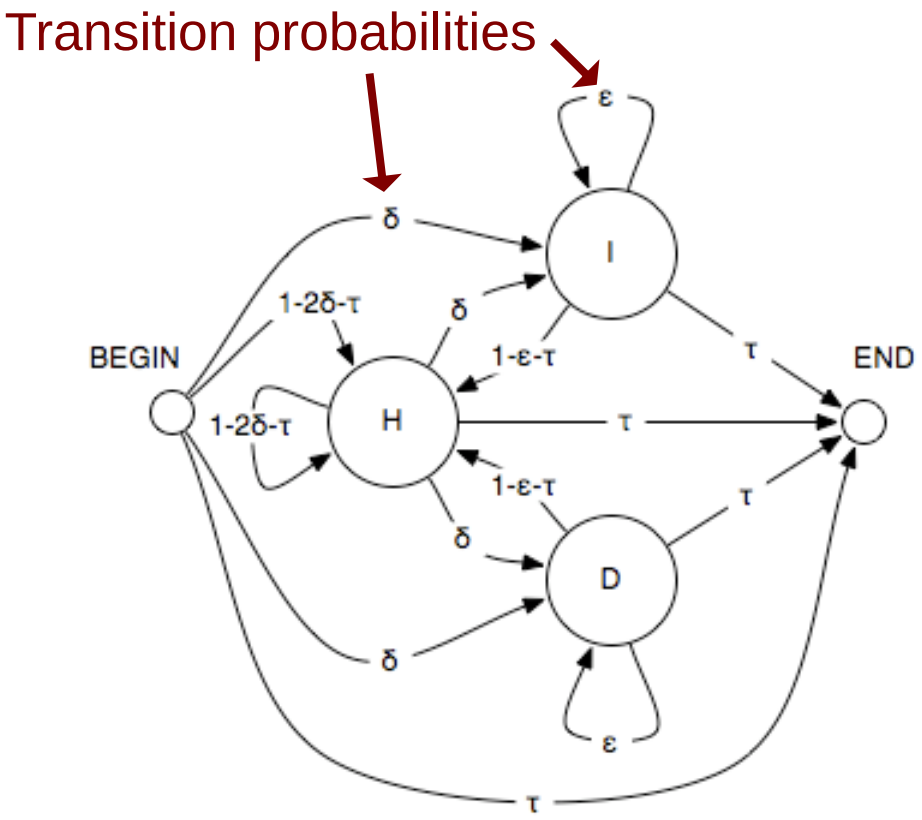
  given: a pair of sequences to be parsed, x and y

  find approximate alignment of x and y

  run constrained Viterbi to have HMM simultaneously parse and align x and y

Pair Hidden Markov Models

- Each non-silent state emits one or a pair of characters

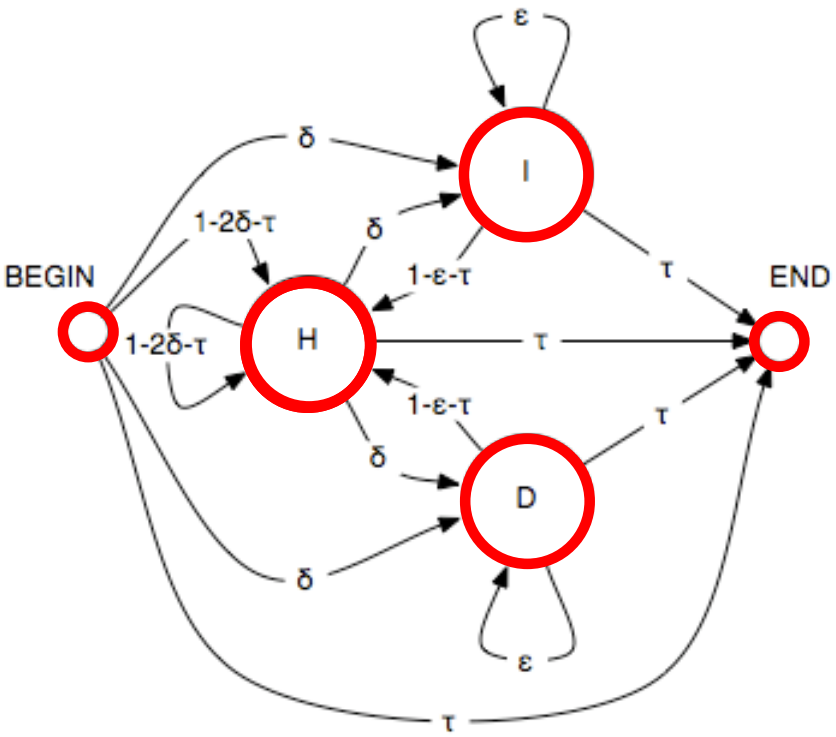


H: homology (match) state

I: insert state

D: delete state

PHMM Paths = Alignments



sequence 1: **AAGCGC**
sequence 2: **ATGTC**

hidden: **B H H I I H D H E**
observed: **A A G C G C**
A T G T C

Generalized Pair HMMs

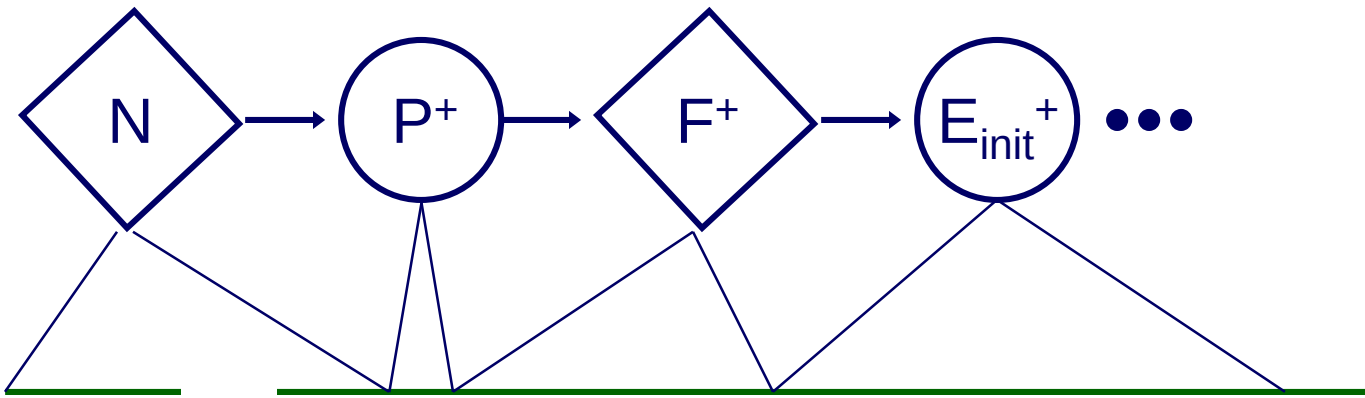
- Represent a parse π, as a sequence of states and a sequence of associated lengths for each input sequence

sequence of hidden states

$\vec{q} = \{q_1, q_2, \ldots, q_n\}$

$\vec{d} = \{d_1, d_2, \ldots, d_n\}$

$\vec{e} = \{e_1, e_2, \ldots, e_n\}$



pair of duration times generated by hidden state

may be gaps in the sequences

TWINSCAN vs SLAM

- Both use multiple genomes to predict genes
- Both use generalized HMMs
- TWINSCAN
  - takes as an input a genomic sequence, and a conservation sequence computed from an informant genome
  - models probability of both sequences; assumes they're conditionally independent given the state
  - predicts genes only in the genomic sequence
- SLAM
  - takes as input two genomic sequences
  - models joint probability of pairs of aligned sequences
  - can simultaneously predict genes and compute alignments

- More detailed slides in Spring 2015 syllabus
  - https://www.biostat.wisc.edu/bmi776/spring-15/syllabus.html