HERD: The Highest Expected Reward Decoding for HMMs with Application to Recombination Detection

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Sequence annotation

Label each symbol in the input sequence by its function

Example: Finding genes (protein-coding regions) in DNA

Input: DNA sequence $X = x_1, \ldots, x_n$

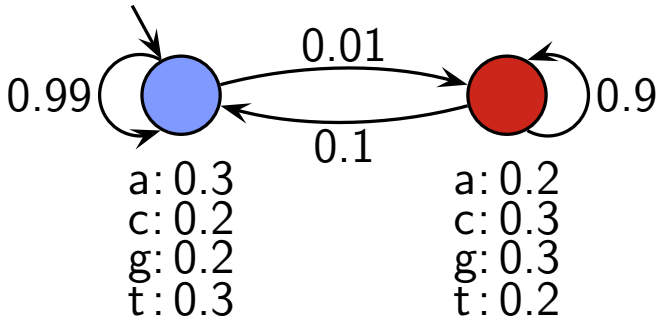
```
tgggcgtatttgcgctagtgttgggtgttccgctgtgctgttttccgtcatggctcgca
gtaaactacctttccagcgcctggtgcgcgagattgcgcaggactttaaaacagacctgc
acatccagctcgcccgccgcatccgcggagagagggcgtgattactgtggtctctctgac
```

Output: sequence of labels (colors) $A = a_1, \ldots, a_n$

red: protein coding, blue: non-coding

```
tgggcgtatttgcgctagtgttgggtgttccgctgtgctgttttccgtcatggctcgca
gtaaactacctttccagcgcctggtgcgcgagattgcgcaggactttaaaacagacctgc
acatccagctcgcccgccgcatccgcggagagagggcgtgattactgtggtctctctgac
```

Hidden Markov models (HMMs)



Sequence: $\{a, c, g, t\}^*$

$$X = x_1, x_2, \ldots, x_n$$

Annotation: $\{\blacksquare, \blacksquare\}^*$

$$A = a_1, a_2, \ldots, a_n$$

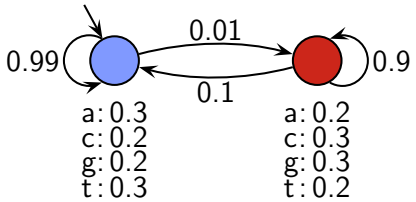
tatttagcgtcttctatcatccaatcactgcactttacacactataaatagagcagctca
tgggcgtatttgcgctagtgttgggtgttccgctgtgctgttttccgtcatggctcgca
ctaagcaaactgctcggaagtctactggtggcaaggcgccacgcaaacagttggccacta

HMM defines $P(X, A)$ for strings X and annotations A:

$$\begin{aligned} P(X, A) &= P(a_1)P(x_1|a_1)P(a_1 \to a_2)P(x_2|a_2)\cdots \\ &\quad P(a_{n-1} \to a_n)P(x_n|a_n) \end{aligned}$$

Viterbi algorithm [Forney 1973]

Input: string $X = x_1, \ldots, x_n$ and an HMM




```
tatttagcgtcttctatcatccaatcactgcactttacacactataaatagagcagctca
tgggcgtatttgcgctagtgttgggtgttccgctgtgctgttttccgtcatggctcgca
ctaagcaaactgctcggaagtctactggtggcaaggcgccacgcaaacagttggccacta
```

Goal: Find **the most probable annotation** $A^* = \arg\max_A P(X, A)$

```
tatttagcgtcttctatcatccaatcactgcactttacacactataaatagagcagctca
tgggcgtatttgcgctagtgttgggtgttccgctgtgctgttttccgtcatggctcgca
ctaagcaaactgctcggaagtctactggtggcaaggcgccacgcaaacagttggccacta
```

Simple dynamic programming

$O(n|E|)$ time (n = sequence length, $|E|$ = number of transitions)

This talk

- Viterbi is not the only algorithm for decoding HMMs
- Our new method: HERD, the highest expected reward decoding
- Motivated by application to HIV recombination detection

Gain function [Hamada et al. 2009]

$G(A, A')$ measures accuracy of A wrt. correct annotation A'

Examples:

Identity: score 1 iff A completely correct, 0 otherwise

Pointwise: score +1 for every correct label in A

Boundary: score +1 for every correct boundary, $-\gamma$ for incorrect boundary

	Identity	Pointwise	Boundary
$A =$  $A' =$ 	1	5	4
$A =$  $A' =$ 	0	4	$3-\gamma$

Optimizing expected gain

Goal: find annotation A that maximizes

$$E_{A'|X}[G(A, A')] = \sum_{A'} G(A, A')P(A'|X)$$

Identity gain function: Viterbi algorithm

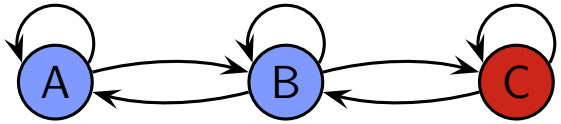
Pointwise gain function: Posterior decoding (forward-backward)

Boundary gain function: [Gross et al. 2007]

The choice of gain function is application-dependent

More complex HMMs

May have more states of the same color



Annotation: a set of state paths

$$P(\blacksquare\square\square\square) = P(CBBB) + P(CBBA) + P(CBAB) + P(CBAA)$$

$$P(\blacksquare\blacksquare\blacksquare\blacksquare) = P(CCCC)$$

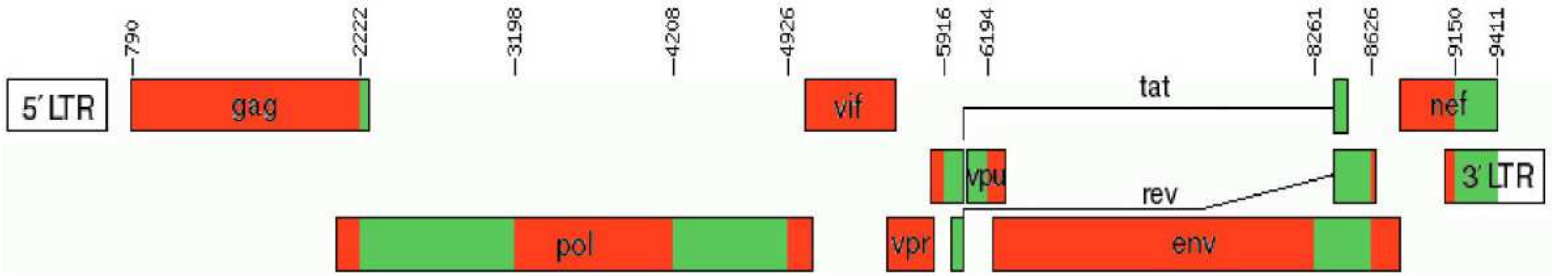
- Viterbi algorithm finds **the most probable state path**,
  not the most probable annotation
- Finding most probable annotation is NP-hard
  [Lyngso and Pedersen, 2002]
- Pointwise and boundary gain functions can be optimized efficiently

Our application: HIV recombination detection

Different subtypes of HIV (A, B, C, . . .)

Sometimes genomes recombine

Labels: one for each subtype



Source: Schultz et al 2006; subtypes A and G

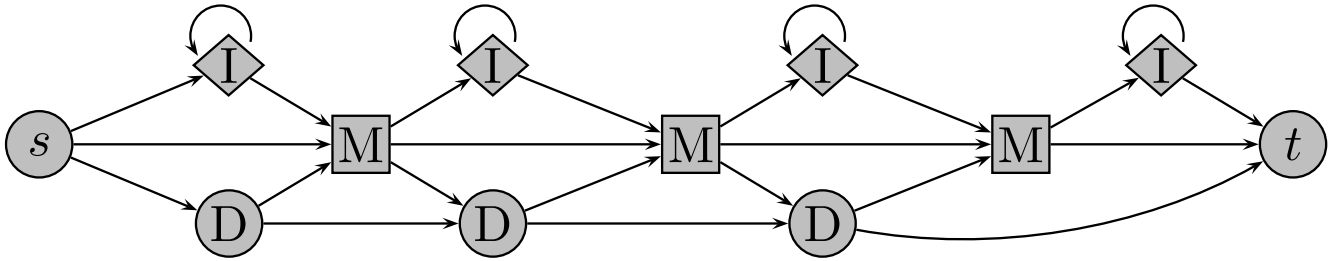
Jumping HMMs for HIV recombination detection

[Schultz et al 2006]

Profile HMM for each subtype

— represents multiple alignment of sequences in the subtype

— match, insert, delete state for each alignment column

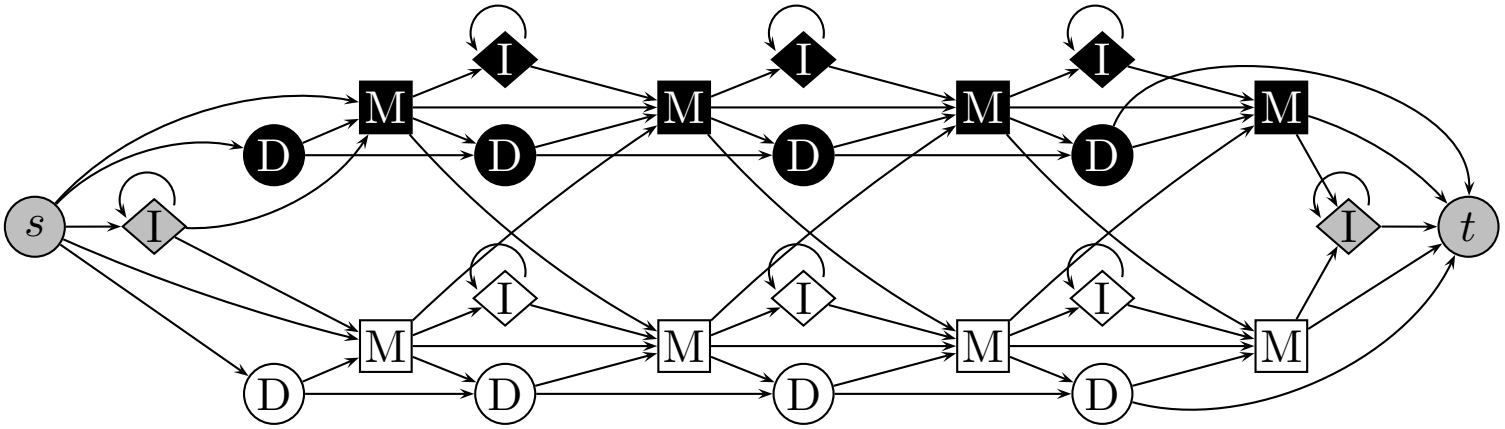



```
TTTTGGCTGAGGCAATGAGCCAAGCAACAAATGC
TTTTGGCCGAGGCAATGAGTCAAGCA---AATTC
TTTTGGCTGAGGCAATGAGCCAAGCA---AATAC
```

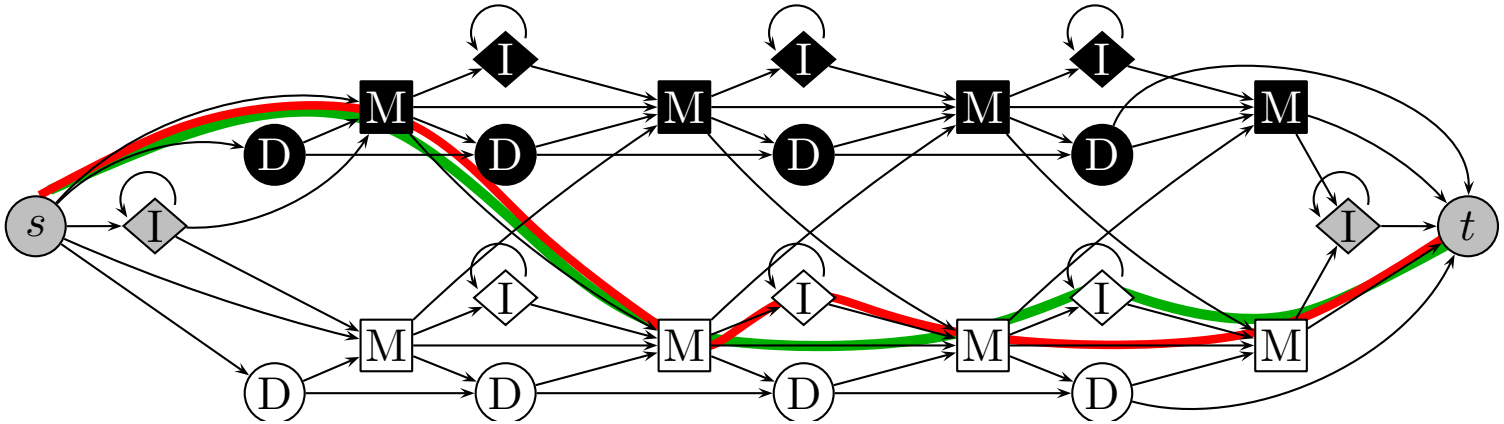
Jumping HMMs for HIV recombination detection (cont.)

[Schultz et al 2006]

- Profile HMM for each subtype
- Profiles connected by jumping transitions



Annotation issues in jumping HMMs



State path: alignment of sequence to subtype profiles

Annotation: segments of input emitted by subtype profiles

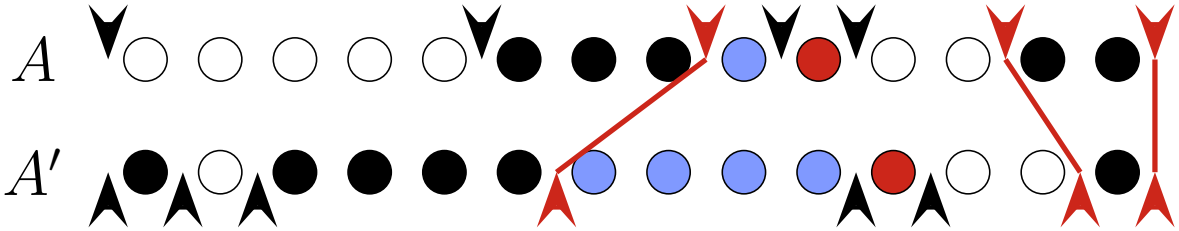
- Many state paths for each annotation
- Many annotations with slightly shifted boundaries

Change the objective function for decoding

HERD: highest expected reward decoding

Boundaries are **buddies** if they are closer than W,

and their flanking regions have the same colors and overlap



gain: $+3 - 4\gamma$

Our gain function $G(A, A')$:

+1 for each boundary in A with a buddy in A'

$-\gamma$ for each boundary without a buddy

Appropriate for recombination detection

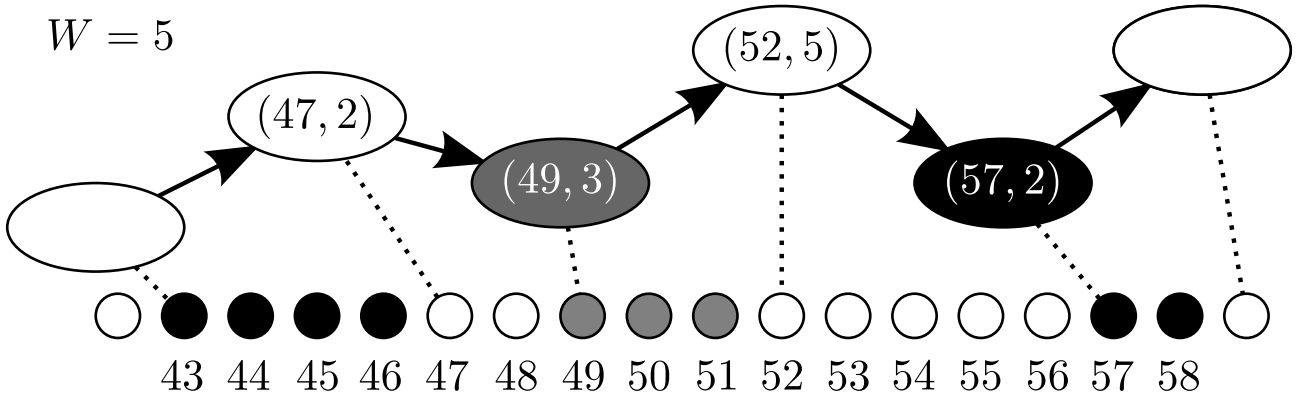
Similar gain function [Brown and Truszkowski 2010]:

score 1 if all boundaries have a buddy

HERD: highest expected reward decoding

Our gain function can be optimized in $O(nW|E| + nW^2C^2)$:

- Compute $P(a_{i...j} = c_1^{j-i}c_2 \,|\, X)$ by a modified forward/backward alg.
- Compute expected gain at each potential boundary
- Find the highest-weight path in a DAG



Comparison on HIV recombination data

Algorithm	% bases correct	Feature sp.	Feature sn.
Artificial recombinants, $P_j = 10^{-5}$			
HERD $W = 10, \gamma = 1$	95.5%	62.1%	57.6%
HERD $W = 1, \gamma = 0.1$	81.3%	37.2%	29.3%
Viterbi	96.3%	51.8%	48.2%
Posterior	95.8%	60.4%	57.7%
No recombination			
HERD, $W = 10, \gamma = 1, P_j = 10^{-9}$	100.0%	100.0%	100.0%
HERD, $W = 10, \gamma = 1, P_j = 10^{-5}$	93.7%	83.9%	83.9%
Viterbi, $P_j = 10^{-9}$ or $P_j = 10^{-5}$	100.0%	100.0%	100.0%

Conclusion

- Many options for decoding HMMs
- Choice application dependent (gain function)
- Some choices lead to NP-hard problems
- Our gain function appropriate for recombination detection, polynomial-time algorithm
- Problem: how to choose parameters, e.g. W and γ
- Possible extensions:
  – closer buddies score more
  – combine with reward for correct bases
- **http://compbio.fmph.uniba.sk/herd/**