Lecture 23:
Hidden Markov Models

Chapter 11
Dinucleotide Frequency

- Consider all 2-mers in a sequence
  \{AA, AC, AG, AT, CA, CC, CG, CT, GA, GC, GG, GT, TA, TC, TG, TT\}
- Given 4 nucleotides:
  each with probability of occurrence is \(\approx \frac{1}{4}\).
  Thus, one would expect that the probability of occurrence of any given dinucleotide is \(\approx \frac{1}{16}\).
- However, the frequencies of dinucleotides in DNA sequences vary widely.
- In particular, CG is typically underrepresented
  (frequency of CG is typically < \(\frac{1}{16}\))
Example

- From a 291829 base sequence

<p>| | | | |</p>
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<tr>
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<tbody>
<tr>
<td>AA</td>
<td>0.120214646984</td>
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<td>0.056108392614</td>
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<tr>
<td>AC</td>
<td>0.055409350713</td>
<td>GC</td>
<td>0.037792809463</td>
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<tr>
<td>AG</td>
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<td>GG</td>
<td>0.043357731266</td>
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<tr>
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<td>0.083425853585</td>
<td>GT</td>
<td>0.046828954041</td>
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<tr>
<td>CA</td>
<td>0.074369148950</td>
<td>TA</td>
<td>0.077206436668</td>
</tr>
<tr>
<td>CC</td>
<td>0.044927148868</td>
<td>TC</td>
<td>0.056207766218</td>
</tr>
<tr>
<td>CG</td>
<td>0.008179475581</td>
<td>TG</td>
<td>0.063698479926</td>
</tr>
<tr>
<td>CT</td>
<td>0.066857875186</td>
<td>TT</td>
<td>0.096567155996</td>
</tr>
</tbody>
</table>

- Expected value 0.0625
- CG is 7 times smaller than expected
Why so few CGs?

• CG is the least frequent dinucleotide because C in CG is easily methylated. And, methylated Cs are easily mutated into Ts.

• However, methylation is suppressed around genes and transcription factor regions

• So, CG appears at relatively higher frequency in these important areas

• These localized areas of higher CG frequency are called CG-islands

• Finding the CG islands within a genome is among the most reliable gene finding approaches
CG Island Analogy

- The CG islands problem can be modeled by a toy problem named "The Fair Bet Casino"
- The outcome of the game is determined by coin flips with two possible outcomes: Heads or Tails
- However, there are two different coins
  - A Fair coin: Heads and Tails with same probability $\frac{1}{2}$.
  - The Biased coin: Heads with prob. $\frac{3}{4}$, Tails with prob. $\frac{1}{4}$. 
The “Fair Bet Casino” (cont’d)

- Thus, we define the probabilities:
  - $P(H \mid \text{Fair}) = P(T \mid \text{Fair}) = \frac{1}{2}$
  - $P(H \mid \text{Bias}) = \frac{3}{4}, P(T \mid \text{Bias}) = \frac{1}{4}$
  - The crooked dealer doesn’t want to get caught switching between coins, so he does so infrequently
  - Changes between Fair and Biased coins with probability 10%
The Fair Bet Casino Problem

• **Input:** A sequence $x = x_1x_2x_3\ldots x_n$ of coin tosses made by some combination of the two possible coins ($F$ or $B$).

• **Output:** A sequence $\pi = \pi_1 \pi_2 \pi_3\ldots \pi_n$, with each $\pi_i$ being either $F$ or $B$ indicating that $x_i$ is the result of tossing the Fair or Biased coin respectively.
Problem...

**Fair Bet Casino Problem**

Any observed outcome of coin tosses could have been generated by either coin, or any combination.

But, all coin exchange combinations are not equally likely. What coin exchange combination has the highest probability of generating the observed series of tosses?

**Decoding Problem**
P(x | fair coin) vs. P(x | biased coin)

- Suppose first, that the dealer never exchanges coins.
- Some definitions:
  - P(x | Fair): prob. of the dealer generating the outcome $x$ using the *Fair* coin.
  - P(x | Biased): prob. of the dealer generating outcome $x$ using the *Biased* coin.
\[ P(x \mid \text{fair coin}) \text{ vs. } P(x \mid \text{biased coin}) \]

1. \[ P(x \mid \text{Fair}) = P(x_1...x_n \mid \text{Fair}) = \prod_{i=1,n} p(x_i \mid \text{Fair}) = (1/2)^n \]

2. \[ P(x \mid \text{Biased}) = P(x_1...x_n \mid \text{Biased coin}) = \prod_{i=1,n} p(x_i \mid \text{Biased}) = (3/4)^k (1/4)^{n-k} = 3^k / 4^n \]

– Where \( k \) is the number of Heads in \( x \).
When is a sequence equally likely to have come from the Fair or Biased coin?

\[ P(x | \text{Fair}) = P(x | \text{Biased}) \]

\[ \frac{1}{2^n} = \frac{3^k}{4^n} \]

\[ 2^n = 3^k \]

\[ n = k \log_2 3 \]

- when \( k = n / \log_2 3 \) \( (k \sim 0.63 \, n) \)

- So when the number of heads is greater than 63% the dealer most likely used the biased coin
Log-odds Ratio

- We can define the \textit{log-odds ratio} as follows:

\[
\log_2(\frac{P(x | \text{Fair})}{P(x | \text{Biased})}) = \sum_{i=1}^{k} \log_2(\frac{p(x_i | \text{Fair})}{p(x_i | \text{Biased})}) = n - k \log_2 3
\]

- The log-odds ratio is a means (threshold) for deciding which of two alternative hypotheses is most likely.

- “Zero-crossing” measure; if the log-odds ratio $> 0$ then the numerator is more likely, if it is $< 0$ then the denominator is more likely, they are equally likely if the log-odds ratio $= 0$
Consider a sliding window of the outcome sequence. Find the log-odds for this short window.

Disadvantages:
- the length of CG-island (appropriate window size) is not known in advance
- different window sizes may classify the same position differently
Key Elements of this Problem

- There is an unknown, *hidden*, state for each observation (Was the coin the Fair or Biased?)
- Outcomes are modeled probabilistically:
  - \( P(H \mid \text{Fair}) = P(T \mid \text{Fair}) = \frac{1}{2} \)
  - \( P(H \mid \text{Bias}) = \frac{3}{4}, \ P(T \mid \text{Bias}) = \frac{1}{4} \)
- Transitions between states are modeled probabilistically:
  - \( P(\pi_i = \text{Biased} \mid \pi_{i-1} = \text{Biased}) = a_{BB} = 0.9 \)
  - \( P(\pi_i = \text{Biased} \mid \pi_{i-1} = \text{Fair}) = a_{FB} = 0.1 \)
  - \( P(\pi_i = \text{Fair} \mid \pi_{i-1} = \text{Biased}) = a_{BF} = 0.1 \)
  - \( P(\pi_i = \text{Fair} \mid \pi_{i-1} = \text{Fair}) = a_{FF} = 0.9 \)
Hidden Markov Model (HMM)

- A generalization of this class of problem
- Can be viewed as an abstract machine with $k$ hidden states that emits symbols from an alphabet $\Sigma$.
- Each state has its own probability distribution, and the machine switches between states according to this probability distribution.
- While in a certain state, the machine makes 2 decisions:
  - What state should I move to next?
  - What symbol - from the alphabet $\Sigma$ - should I emit?
Why “Hidden”?

- Observers can see the emitted symbols of an HMM but have no ability to know which state the HMM is currently in.

- Thus, the goal is to infer the most likely hidden states of an HMM based on the given sequence of emitted symbols.

HHHTHTHHTTTTHTHTHHTHTHTHTTHT
BBBBFFFFFFFFFFFFFFFFFFFFBBBBFFFF?
HMM Parameters

\( \Sigma \): set of emission characters.

Ex.: \( \Sigma = \{0, 1\} \) for coin tossing

(0 for Tails and 1 Heads)

\( \Sigma = \{1, 2, 3, 4, 5, 6\} \) for dice tossing

\( Q \): set of hidden states, emitting symbols from \( \Sigma \).

\( Q = \{F,B\} \) for coin tossing
HMM Parameters (cont’d)

A = (a_{kl}): a \ |Q| \times |Q| \ matrix of probability of changing from state k to state l. Transition matrix

\[ a_{FF} = 0.9 \quad a_{FB} = 0.1 \]
\[ a_{BF} = 0.1 \quad a_{BB} = 0.9 \]

E = (e_k(b)): a \ |Q| \times |\Sigma| \ matrix of probability of emitting symbol b while being in state k. Emission matrix

\[ e_F(0) = \frac{1}{2} \quad e_F(1) = \frac{1}{2} \]
\[ e_B(0) = \frac{1}{4} \quad e_B(1) = \frac{3}{4} \]
HMM for Fair Bet Casino

- The *Fair Bet Casino* in HMM terms:
  - $\Sigma = \{0, 1\}$ (0 for *Tails* and 1 *Heads*)
  - $Q = \{F, B\}$ – *F* for Fair & *B* for Biased coin.

- Transition Probabilities $A$, Emission Probabilities $E$

<table>
<thead>
<tr>
<th></th>
<th>Fair</th>
<th>Biased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Biased</td>
<td>0.1</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Tails(0)</th>
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</thead>
<tbody>
<tr>
<td>Fair</td>
<td>$\frac{1}{2}$</td>
<td>$\frac{1}{2}$</td>
</tr>
<tr>
<td>Biased</td>
<td>$\frac{1}{4}$</td>
<td>$\frac{3}{4}$</td>
</tr>
</tbody>
</table>
HMM model for the Fair Bet Casino Problem
Hidden Paths

- A path $\pi = \pi_1 \ldots \pi_n$ in the HMM is defined as a sequence of hidden states.
- Consider path $\pi = \text{FFFFBBBBBFFFF}$ and sequence $x = 01011101001$

$$x = \begin{pmatrix} 0 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 0 & 0 & 1 \end{pmatrix}$$

$$\pi = \begin{pmatrix} F & F & F & F & B & B & B & B & B & B & F & F & F \end{pmatrix}$$

$$P(x_i|\pi_i) = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} & \frac{3}{4} & \frac{3}{4} & \frac{3}{4} & \frac{1}{4} & \frac{3}{4} & \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \end{pmatrix}$$

$$P(\pi_{i-1} \rightarrow \pi_i) = \begin{pmatrix} \frac{1}{2} & \frac{9}{10} & \frac{9}{10} & \frac{1}{10} & \frac{9}{10} & \frac{9}{10} & \frac{1}{10} & \frac{9}{10} & \frac{1}{10} & \frac{9}{10} & \frac{9}{10} \end{pmatrix}$$

- Probability that $x_i$ was emitted from state $\pi_i$
- Transition probability from state $\pi_{i-1}$ to state $\pi_i$
**P(x | π) Calculation**

- **P(x | π):** Probability that sequence $x$ was generated by the path $π$:

\[
P(x | π) = P(π_0 → π_1) \cdot \prod_{i=1}^{n} P(x_i | π_i) \cdot P(π_i → π_{i+1})
\]

\[
= a_{π_0, π_1} \cdot \prod e_{π_i} (x_i) \cdot a_{π_i, π_{i+1}}
\]
Decoding Problem

- **Goal**: Find an optimal hidden path of state transitions given a set of observations.

- **Input**: Sequence of observations $x = x_1 \ldots x_n$ generated by an HMM $M(\Sigma, Q, A, E)$

- **Output**: A path that maximizes $P(x \mid \pi)$ over all possible paths $\pi$. 
How do we solve this?

• Brute Force
  – Approach:
    • Enumerate every possible path
    • Compute \( P(x_{1..n} \mid \pi_{1..n}) \) for each one
    • Keep track of the most probable path
  – How many possible paths are there for \( n \) observations?

• Is there a better approach?
  – Break the paths in two parts, \( P(x_{1..i} \mid \pi_{1..i}) \), \( P(x_{i..n} \mid \pi_{i..n}) \)
  – \( P(x_{1..n} \mid \pi_{1..n}) = P(x_{1..i} \mid \pi_{1..i}) \times P(x_{i..n} \mid \pi_{i..n}) \)
  – Will less than the highest \( P(x_{1..i} \mid \pi_{1..i}) \) ever improve the total probability?
  – Thus to find the maximum \( P(x_{1..n} \mid \pi_{1..n}) \) we need find the maximum of each subproblem \( P(x_{1..i} \mid \pi_{1..i}) \), for \( i \) from 1 to \( n \)
  – What algorithm design approach does this remind us of?
Building Manhattan for Decoding

• Andrew Viterbi developed a “Manhattan-like grid” (Dynamic programming) model to solve the Decoding Problem.

• Every choice of $\pi = \pi_1 \ldots \pi_n$ corresponds to a path in the graph.

• The only valid direction in the graph is eastward.

• This graph has $|Q|^2(n-1)$ edges.
Edit Graph for Decoding Problem

4 hidden states

6 output observations

Path with greatest probability
Decoding Problem vs. Alignment Problem

Valid directions in the alignment problem.

Valid directions in the decoding problem.
Viterbi Decoding of Fair-Bet Casino

- Each vertex represents a possible state at a given position in the output sequence
- The observed sequence conditions the likelihood of each state
- Dynamic programming reduces search space to: $|Q| + \text{transition_edges} \times (n-1) = 2 + 4 \times 5$ from naïve $2^6$
Decoding Problem

• The Decoding Problem is reduced to finding a longest path in the directed acyclic graph (DAG)

• Notes: the length of the path in this problem is defined as the product of its edges’ weights, not their sum. (But, using the log of the weights makes it a sum again!)
Decoding Problem (cont’d)

- Every path in the graph has the probability $P(x \mid \pi)$.

- The Viterbi algorithm finds the path that maximizes $P(x \mid \pi)$ among all possible paths.

- The Viterbi algorithm runs in $O(n \mid Q \mid^2)$ time.
Decoding Problem: weights of edges

The weight $w$ is given by:

\[ ??? \]
The weight $w$ is given by:

The Total probability

$$P(x | \pi) = \prod_{i=0}^{n} e^{\pi_{i+1}(x_{i+1}) \cdot a_{\pi_{i}, \pi_{i+1}}}$$
Decoding Problem: weights of edges

The weight $w$ is given by

*Each edge is a factor in the product*

$$i\text{-th term} = e^{\pi_{i+1} (x_{i+1}) \cdot a_{\pi_i, \pi_{i+1}}}$$
Decoding Problem: weights of edges

\[ i \text{-th term} = e^{\pi_i(x_i)} \cdot a_{\pi_i \pi_{i+1}} = e_{\ell}(x_{i+1}) \cdot a_{k\ell} \text{ for } \pi_i = k, \pi_{i+1} = \ell \]

The weight \( w = e_{\ell}(x_{i+1}) \cdot a_k \)

Solve for the path of highest probability

**Observation:** a prefix is also an optimal path

Where have we seen this before?
Dynamic Program’s Recursion

\[ S_{l,i+1} = \max_{k \in Q} \{ s_{k,i} \cdot \text{weight of edge between (k,i) and (l,i+1)} \} \]

\[ = \max_{k \in Q} \{ s_{k,i} \cdot a_{kl} \cdot e_l(x_{i+1}) \} \]

\[ = e_l(x_{i+1}) \cdot \max_{k \in Q} \{ s_{k,i} \cdot a_{kl} \} \]
Decoding Problem (cont’d)

- Initialization:
  - $a_{start,k} = 1/|Q|$
  - $s_{k,0} = 0$ for $k \neq \text{begin}$.

- Let $\pi^*$ be the optimal path. Then,

$$P(x | \pi^*) = \max_{k \in Q} \{s_{k,n} \cdot a_{k,end}\}$$
Viterbi for Fair Bet Casino

- Solves all subproblems implied by emitted subsequence
- How likely is the best path? \(0.006\)
- What is it? FFBFFF

```
<table>
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<th>i</th>
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<th>3</th>
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<td>4</td>
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</tr>
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\(F\) and \(B\) are the terminal states.
Viterbi Algorithm

- Rather than addition Viterbi uses multiplication.
- Convert edge weights to logs, and then it is back to addition, which has another advantage.
- The value of the product can become extremely small, which leads to underflow.
- Logs avoid underflow.

\[ s_{k,i+1} = \log e_i(x_{i+1}) + \max_{k \in Q} \{s_{k,i} + \log(a_{kl})\} \]
Given: a sequence of coin tosses generated by an HMM.

Goal: find the most probable coin that the dealer was using at a particular time.

\[ P(\pi_i = k \mid x) = \frac{P(x, \pi_i = k)}{P(x)} \]

- Probabilities of all paths in state k at i
- Probability of sequence over all paths
Illustrating the difference

\begin{align*}
\text{x} &= \text{THHH} \\
p &= FFFFF (0.0228) \\
     &\quad BFFFF (0.0013) \\
     &\quad FBFF (0.0004) \\
     &\quad BBFF (0.0019) \\
     &\quad FFBF (0.0004) \\
     &\quad BFFB (0.0000) \\
     &\quad FBFF (0.0006) \\
     &\quad BBFF (0.0028) \\
     &\quad FFFB (0.0038) \\
     &\quad BFFB (0.0002) \\
     &\quad FBFB (0.0006) \\
     &\quad BBFB (0.0003) \\
     &\quad FBBF (0.0003) \\
     &\quad BBFB (0.0085) \\
     &\quad BBBB (0.0384) \\
\text{P(x)} &= 0.0877 \\
\end{align*}

\begin{align*}
\text{x} &= \text{THHH} \\
p &= FFFFF (0.0228) \\
     &\quad FBBF (0.0004) \\
     &\quad FFFB (0.0038) \\
     &\quad FBB (0.0000) \\
     &\quad BFF (0.0000) \\
     &\quad BFB (0.0002) \\
     &\quad BFB (0.0003) \\
     &\quad FBB (0.0006) \\
     &\quad FB (0.0003) \\
     &\quad BB (0.0085) \\
     &\quad BF (0.0019) \\
     &\quad BB (0.0028) \\
     &\quad BB (0.0003) \\
     &\quad BB (0.0384) \\
\text{P(x)} &= 0.0877 \\
\end{align*}

\begin{align*}
P(\pi_2 = F | x) &= 0.0345/0.0877 = 0.3936 \\
P(\pi_2 = B | x) &= 0.0532/0.0877 = 0.6064
\end{align*}
Forward Algorithm

- Defined $f_{k,i}$ (forward probability) as the probability of emitting the prefix $x_1...x_i$ and reaching the state $\pi = k$.

- The recurrence for the forward algorithm is:

$$f_{k,i} = e_k(x_i) \cdot \sum_{l \in Q} f_{l,i-1} \cdot A_{lk}$$

- Same as Viterbi except with summation instead of Max
Backward Algorithm

• However, forward probability is not the only factor affecting $P(\pi_i = k|x)$.

• The sequence of transitions and emissions that the HMM undergoes between $\pi_i$ and $\pi_{i+1}$ also affect $P(\pi_i = k|x)$. 
Backward Algorithm (cont’d)

• Backward probability $b_{k,i} \equiv$ the probability of being in state $\pi_i = k$ and emitting the suffix $x_{i+1} \ldots x_n$.

• The backward algorithm’s recurrence:

$$b_{k,i} = \sum_{l \in \Omega} e_l(x_{i+1}) \cdot b_{l,i+1} \cdot a_{kl}$$

This is the same as computing the probability of a specific path (slide 22) or suffix in this case except the initial probability is not $\frac{1}{2}$. 
Backward-Forward Algorithm

- The probability that the dealer used a biased coin at any moment \( i \) is as follows:

\[
P(\pi_i = k|x) = \frac{P(x, \pi_i = k)}{P(x)} = \frac{f_k(i) \cdot b_k(i)}{P(x)}
\]
HMM Parameter Estimation

• So far, we have assumed that the transition and emission probabilities are known.

• However, in most HMM applications, the probabilities are not known. It’s very hard to estimate the probabilities.

• Parameter estimation is much harder than state estimation
HMM Parameter Estimation (cont’d)

- Let $\Theta$ be a vector containing all of the unknown transition and emission probabilities.
- Given training sequences $x^1, \ldots, x^m$, let $P(x \mid \Theta)$ be the max. prob. of $x$ given the assignment of param.’s $\Theta$.
- Then our goal is to find

$$\max_\Theta \prod_{j=1}^{m} P(x_i \mid \Theta)$$
• If hidden states were known, we could use our training data to estimate parameters

\[ a_{kl} = \frac{A_{kl}}{\sum_{q \in Q} A_{kq}} \quad e_k(b) = \frac{E_k(b)}{\sum_{\sigma \in \Sigma} E_k(\sigma)} \]

• In all likelihood we wouldn’t be given the hidden state sequence, \( \pi \), but only the observed output stream, \( x \)

• An alternative is to make an intelligent guess of \( \pi \), use the equations above to estimate parameters, then run Viterbi to estimate the hidden state, then reestimate the parameters and repeat until the state assignments or parameter values converge.

• Such iterative approaches are called Expectation Maximization (EM) methods of parameter estimation
Profile Alignment using HMMs

- Distant species of functionally related sequences may have weak pairwise similarities with known species, and thus fail individual pairwise significance tests.
- However, they may have weak similarities with many known species.
- The goal is to consider sequences at once. (Multiple alignment)
- Related sequences are often better represented by a consensus profile that any multiple alignment.
Profile Representations

Aligned DNA sequences can be represented by a $4 \cdot n$ profile matrix reflecting the frequencies of nucleotides in every aligned position.

\[
\begin{array}{llllllll}
A & .72 & .14 & 0 & 0 & .72 & .72 & 0 & 0 \\
T & .14 & .72 & 0 & 0 & 0 & .14 & .14 & .86 \\
G & .14 & .14 & .86 & .44 & 0 & .14 & 0 & 0 \\
C & 0 & 0 & .14 & .56 & .28 & 0 & .86 & .14 \\
\end{array}
\]

Protein families can be represented by a $20 \cdot n$ profile representing frequencies of amino acids.
HMM Alignment

• One method of performing sequence comparisons to a profile is to use a HMM
• Emission probabilities, $e_i(a)$, from the profile
• Transition probabilities from our match-mismatch matrix $\delta_{ij}$.
• Or we can explicitly represent the insertion and deletion states
Profile HMM

A profile HMM
States of Profile HMM

- Match states $M_1\ldots M_n$ (plus begin/end states)
- Insertion states $I_0I_1\ldots I_n$
- Deletion states $D_1\ldots D_n$

- Assumption:
  
  $$e_{I_j}(a) = p(a)$$

  where $p(a)$ is the frequency of the occurrence of the symbol $a$ in all the sequences.
Transition Probabilities in Profile HMM

- \( \log(a_{MI}) + \log(a_{IM}) = \text{gap initiation penalty} \)

- \( \log(a_{II}) = \text{gap extension penalty} \)
Profile HMM Alignment

- Define $v^M(j)(i)$ as the logarithmic likelihood score of the best path for matching $x_1 \ldots x_i$ to profile HMM ending with $x_i$ emitted by the state $M_j$.

- $v^I(j)(i)$ and $v^D(j)(i)$ are defined similarly.
Profile HMM Alignment: Dynamic Programming

\[ v^{M_j}(i) = \log \left( \frac{e_{M_j}(x_i)}{p(x_i)} \right) + \max \begin{cases} 
  v^{M}_{j-1}(i-1) + \log(a_{M_{j-1},M_j}) \\
  v^{I}_{j-1}(i-1) + \log(a_{I_{j-1},M_j}) \\
  v^{D}_{j-1}(i-1) + \log(a_{D_{j-1},M_j}) 
\end{cases} \]

\[ v^{I_j}(i) = \log \left( \frac{e_{I_j}(x_i)}{p(x_i)} \right) + \max \begin{cases} 
  v^{M}_{j}(i-1) + \log(a_{M_j, I_j}) \\
  v^{I}_{j}(i-1) + \log(a_{I_j, I_j}) \\
  v^{D}_{j}(i-1) + \log(a_{D_j, I_j}) 
\end{cases} \]
A path through an edit graph and the corresponding path through a profile HMM