CSCE 471/871 Lecture 3: Markov Chains and Hidden Markov Models

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Outline

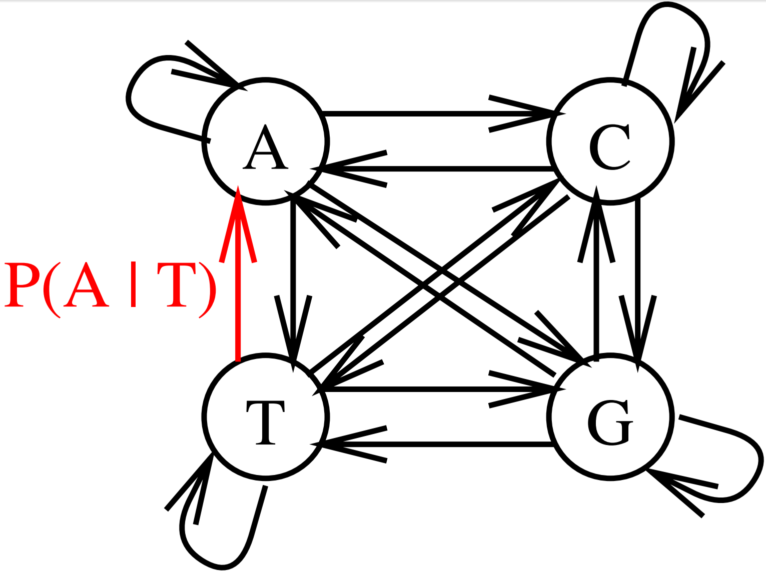
- Markov chains
- Hidden Markov models (HMMs)
  - Formal definition
  - Finding most probable state path (Viterbi algorithm)
  - Forward and backward algorithms
- Specifying an HMM
  - State sequence known
  - State sequence unknown
  - Structure

- Focus on nucleotide sequences
- The sequence “CG” (written “CpG”) tends to appear more frequently in some places than in others
- Such CpG islands are usually 10^2–10^3 bases long
- Questions:
  1. Given a short segment, is it from a CpG island?
  2. Given a long segment, where are its islands?

Modeling CpG Islands

- Model will be a CpG generator
- Want probability of next symbol to depend on current symbol
- Will use a standard (non-hidden) Markov model
  - Probabilistic state machine
  - Each state emits a symbol

Modeling CpG Islands (2)



The Markov Property

- A first-order Markov model (what we study) has the property that observing symbol $\mathbf{x}_i$ while in state π_i depends only on the previous state π_{i-1} (which generated $\mathbf{x}_{i-1}$)
- Standard model has 1-1 correspondence between symbols and states, thus

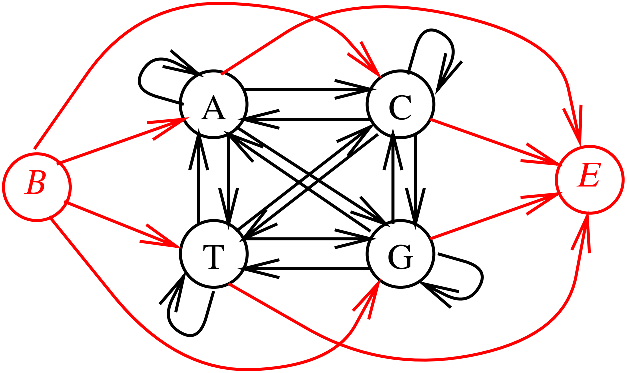
$$P(\mathbf{x}_i \mid \mathbf{x}_{i-1}, \ldots, \mathbf{x}_1) = P(\mathbf{x}_i \mid \mathbf{x}_{i-1})$$

and

$$P(\mathbf{x}_1, \ldots, \mathbf{x}_L) = P(\mathbf{x}_1) \prod_{i=2}^{L} P(\mathbf{x}_i \mid \mathbf{x}_{i-1})$$

Begin and End States

- For convenience, can add special "begin" (B) and "end" (E) states to clarify equations and define a distribution over sequence lengths
- Emit empty (null) symbols $\mathbf{x}_0$ and $\mathbf{x}_{L+1}$ to mark ends of sequence



Markov Chains for Discrimination

- How do we use this to differentiate islands from non-islands?
- Define two Markov models: islands ("$+$") and non-islands ("$-$")
  - Each model gets 4 states (A, C, G, T)
  - Take training set of known islands and non-islands
  - Let c_{st}^+ = number of times symbol t followed symbol s in an island:

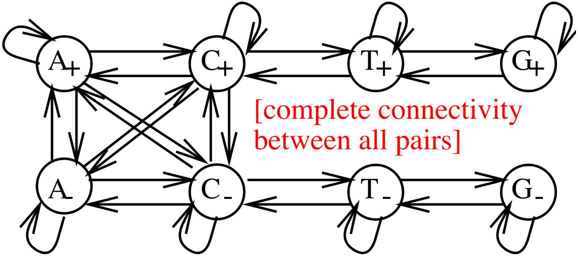
$$\hat{P}^+(t \mid s) = \frac{c_{st}^+}{\sum_{t'} c_{st'}^+}$$

- Example probabilities in [Durbin et al., p. 51]
- Now score a sequence $X = \langle \mathbf{x}_1, \ldots, \mathbf{x}_L \rangle$ by summing the log-odds ratios:

$$\log\left(\frac{\hat{P}(X \mid +)}{\hat{P}(X \mid -)}\right) = \sum_{i=1}^{L+1} \log\left(\frac{\hat{P}^+(\mathbf{x}_i \mid \mathbf{x}_{i-1})}{\hat{P}^-(\mathbf{x}_i \mid \mathbf{x}_{i-1})}\right)$$

Hidden Markov Models

- Second CpG question: Given a long sequence, where are its islands?
  - Could use tools just presented by passing a fixed-width window over the sequence and computing scores
  - Trouble if islands' lengths vary
  - Prefer single, unified model for islands vs. non-islands

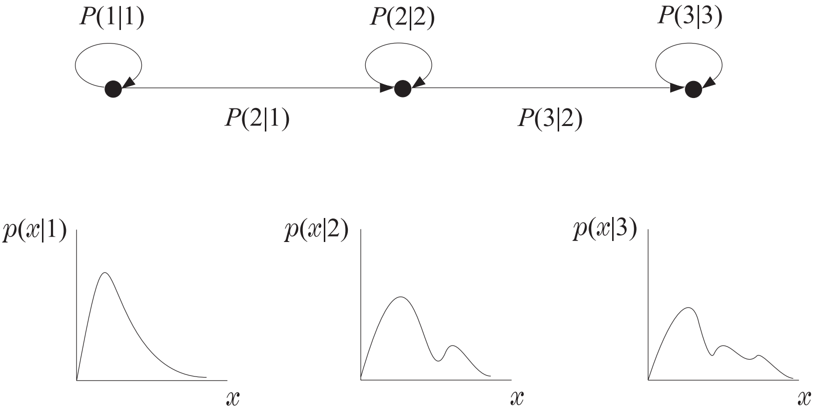


- Within the $+$ group, transition probabilities similar to those for the separate $+$ model, but there is a small chance of switching to a state in the $-$ group

What's Hidden in an HMM?

- No longer have one-to-one correspondence between states and emitted characters
  - E.g., was C emitted by C_+ or C_-?
- Must differentiate the symbol sequence X from the state sequence $\pi = \langle \pi_1, \ldots, \pi_L \rangle$
  - State transition probabilities same as before: $P(\pi_i = \ell \mid \pi_{i-1} = j)$ (i.e., $P(\ell \mid j)$)
  - Now each state has a prob. of emitting any value: $P(\mathbf{x}_i = \mathbf{x} \mid \pi_i = j)$ (i.e., $P(\mathbf{x} \mid j)$)

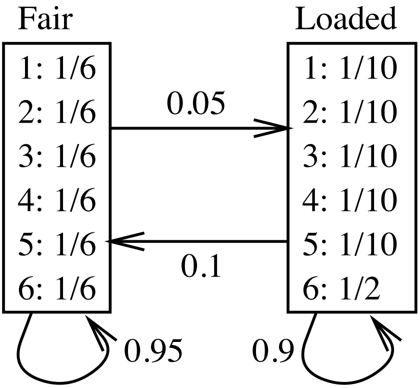
What's Hidden in an HMM? (2)



[In CpG HMM, emission probs discrete and $= 0$ or 1]

Example: The Occasionally Dishonest Casino

- Assume that a casino is typically fair, but with probability 0.05 it switches to a loaded die, and switches back with probability 0.1



- Given a sequence of rolls, what's hidden?

The Viterbi Algorithm

- Probability of seeing symbol sequence X and state sequence π is

$$P(X, \pi) = P(\pi_1 \mid 0) \prod_{i=1}^{L} P(\mathbf{x}_i \mid \pi_i) \, P(\pi_{i+1} \mid \pi_i)$$

- Can use this to find most likely path:

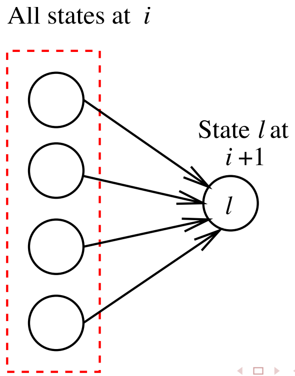
$$\pi^* = \operatorname*{argmax}_{\pi} P(X, \pi)$$

  and trace it to identify islands (paths through "$+$" states)
- There are an exponential number of paths through chain, so how do we find the most likely one?

The Viterbi Algorithm (2)

- Assume that we know (for all k) $v_k(i)$ = probability of most likely path ending in state k with observation $\mathbf{x}_i$
- Then

$$v_\ell(i+1) = P(\mathbf{x}_{i+1} \mid \ell) \max_k \{v_k(i) \, P(\ell \mid k)\}$$



The Viterbi Algorithm (3)

Given the formula, can fill in table with dynamic programming:

- $v_0(0) = 1$, $v_k(0) = 0$ for $k > 0$
- For $i = 1$ to L; for $\ell = 1$ to M (# states)
  - $v_\ell(i) = P(\mathbf{x}_i \mid \ell)\ \max_k\{v_k(i-1)\, P(\ell \mid k)\}$
  - $\mathrm{ptr}_i(\ell) = \mathrm{argmax}_k\{v_k(i-1)\, P(\ell \mid k)\}$
- $P(X, \pi^*) = \max_k\{v_k(L)\, P(0 \mid k)\}$
- $\pi_L^* = \mathrm{argmax}_k\{v_k(L)\, P(0 \mid k)\}$
- For $i = L$ to 1
  - $\pi_{i-1}^* = \mathrm{ptr}_i(\pi_i^*)$

To avoid underflow, use $\log(v_\ell(i))$ and add

The Forward Algorithm

Given a sequence X, find $P(X) = \sum_{\pi} P(X, \pi)$

Use dynamic programming like Viterbi, replacing max with sum, and $v_k(i)$ with $f_k(i) = P(\mathbf{x}_1, \ldots, \mathbf{x}_i, \pi_i = k)$ (= prob. of observed sequence through $\mathbf{x}_i$, stopping in state k)

- $f_0(0) = 1, f_k(0) = 0$ for $k > 0$
- For $i = 1$ to L; for $\ell = 1$ to M (# states)
  - $f_\ell(i) = P(\mathbf{x}_i \mid \ell) \sum_k f_k(i-1) \, P(\ell \mid k)$
- $P(X) = \sum_k f_k(L) \, P(0 \mid k)$

To avoid underflow, can again use logs, though exactness of results compromised (Section 3.6)

The Backward Algorithm

Given a sequence X, find the probability that $\mathbf{x}_i$ was emitted by state k, i.e.,

$$P(\pi_i = k \mid X) = \frac{P(\pi_i = k, X)}{P(X)}$$

$$= \frac{\overbrace{P(\mathbf{x}_1, \ldots, \mathbf{x}_i, \pi_i = k)}^{f_k(i)} \; \overbrace{P(\mathbf{x}_{i+1}, \ldots, \mathbf{x}_L \mid \pi_i = k)}^{b_k(i)}}{\underbrace{P(X)}_{\text{computed by forward alg}}}$$

Algorithm:

- $b_k(L) = P(0 \mid k)$ for all k
- For $i = L - 1$ to 1; for $k = 1$ to M (# states)
  - $b_k(i) = \sum_\ell P(\ell \mid k)\, P(\mathbf{x}_{i+1} \mid \ell)\, b_\ell(i+1)$

Example Use of Forward/Backward Algorithm

Define $g(k) = 1$ if $k \in \{\text{A}_+, \text{C}_+, \text{G}_+, \text{T}_+\}$ and 0 otherwise

Then $G(i \mid X) = \sum_k P(\pi_i = k \mid X)\, g(k) =$ probability that $\mathbf{x}_i$ is in an island

For each state k, compute $P(\pi_i = k \mid X)$ with forward/backward algorithm

Technique applicable to any HMM where set of states is partitioned into classes

- Use to label individual parts of a sequence

Specifying an HMM

- Two problems: defining structure (set of states) and parameters (transition and emission probabilities)
- Start with latter problem, i.e., given a training set $X_1, \ldots, X_N$ of independently generated sequences, learn a good set of parameters θ
- Goal is to maximize the (log) likelihood of seeing the training set given that θ is the set of parameters for the HMM generating them:

$$\sum_{j=1}^{N} \log(P(X_j; \theta))$$

When State Sequence Known

- Estimating parameters when e.g., islands already identified in training set
- Let $A_{k\ell}$ = number of $k \to \ell$ transitions and $E_k(b)$ = number of emissions of b in state k

$$P(\ell \mid k) = A_{k\ell} \Big/ \left(\sum_{\ell'} A_{k\ell'} \right)$$

$$P(b \mid k) = E_k(b) \Big/ \left(\sum_{b'} E_k(b') \right)$$

When State Sequence Known (2)

Be careful if little training data available

- E.g., an unused state k will have undefined parameters
- Workaround: Add pseudocounts $r_{k\ell}$ to $A_{k\ell}$ and $r_k(b)$ to $E_k(b)$ that reflect prior biases about probabilities
- Increased training data decreases prior's influence
- [Sjölander et al. 96]

The Baum-Welch Algorithm

- Estimating parameters when state sequence unknown
- Special case of expectation maximization (EM) alg
- Start with arbitrary $P(\ell \mid k)$ and $P(b \mid k)$, and use to estimate $A_{k\ell}$ and $E_k(b)$ as expected number of occurrences given the training set[1]:

$$A_{k\ell} = \sum_{j=1}^{N} \frac{1}{P(X_j)} \sum_{i=1}^{L} f_k^j(i)\, P(\ell \mid k)\, P(\mathbf{x}_{i+1}^j \mid \ell)\, b_\ell^j(i+1)$$

(Prob. of transition from k to ℓ at position i of sequence j, summed over all positions of all sequences)

$$E_k(b) = \sum_{j=1}^{N} \sum_{i:\mathbf{x}_i^j = b} P(\pi_i = k \mid X_j) = \sum_{j=1}^{N} \frac{1}{P(X_j)} \sum_{i:\mathbf{x}_i^j = b} f_k^j(i)\, b_k^j(i)$$

[1] Superscript j corresponds to jth train example

The Baum-Welch Algorithm (2)

$$A_{k\ell} = \sum_{j=1}^{N} \frac{1}{P(X_j)} \sum_{i=1}^{L} f_k^j(i)\, P(\ell \mid k)\, P(\mathbf{x}_{i+1}^j \mid \ell)\, b_\ell^j(i+1)$$

$$E_k(b) = \sum_{j=1}^{N} \sum_{i:\mathbf{x}_i^j=b} P(\pi_i = k \mid X_j) = \sum_{j=1}^{N} \frac{1}{P(X_j)} \sum_{i:\mathbf{x}_i^j=b} f_k^j(i)\, b_k^j(i)$$

- Use these (& pseudocounts) to recompute $P(\ell \mid k)$ and $P(b \mid k)$
- After each iteration, compute log likelihood and halt if no improvement

HMM Structure

How to specify HMM states and connections?

States come from background knowledge on problem, e.g., size-4 alphabet, $+/-$, $\Rightarrow 8$ states

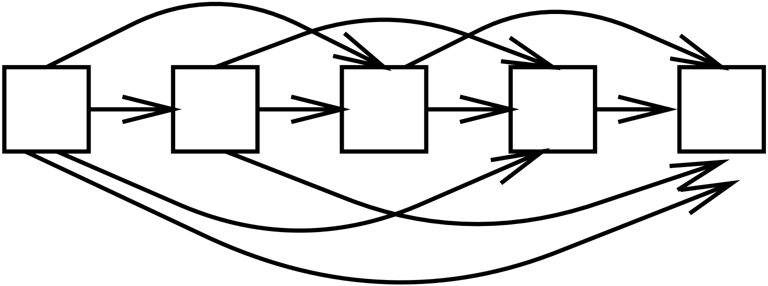
Connections:

- Tempting to specify complete connectivity and let Baum-Welch sort it out
- Problem: Huge number of parameters could lead to local max
- Better to use background knowledge to invalidate some connections by initializing $P(\ell \mid k) = 0$
  - Baum-Welch will respect this

Silent States

May want to allow model to generate sequences with certain parts deleted

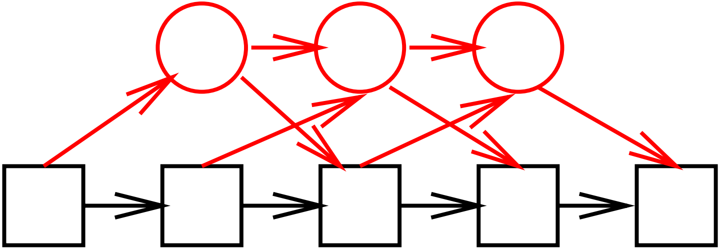
- E.g., when aligning sequences against a fixed model, some parts of the input might be omitted



Problem: Huge number of connections, slow training, local maxima

Silent States (2)

- Silent states (like begin and end states) don't emit symbols, so they can "bypass" a regular state



- If there are no purely silent loops, can update Viterbi, forward, and backward algorithms to work with silent states [Durbin et al., p. 72]
- Used extensively in profile HMMs for modeling sequences of protein families (aka multiple alignments)