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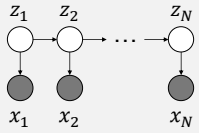
BTRY 4840/6840, CS 4775
Computational Genetics and Genomics



September 18, 2018

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Announcements

- Problem set 2 due in one week
- Fill out survey on my office hours:
  - Currently 83% say they can attend 4:30-5:30pm, ≤50% for other times

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Today's lecture

- Continuing Hidden Markov models (HMMs)
  - Viterbi algorithm
  - Forward algorithm
  - Forward/backward algorithm
  - Posterior state probabilities and posterior decoding

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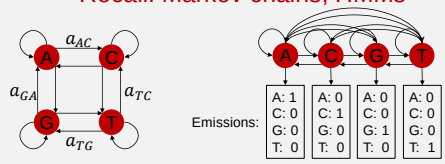
Recall: Markov chains, HMMs



- Difference between Markov chain, Hidden Markov model (HMM):
  - In Markov chain, states are observable, states unobservable in HMM
  - Both have: states, initial probabilities, transition probabilities
  - HMM has emission probabilities

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Hidden Markov models
CpG island example

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Biology background: CpG dinucleotide

- Dinucleotide sequence CG is typically written CpG
  - p for phosphate (between bases in DNA backbone): emphasizes this is dinucleotide, not base pairing
  - Can also talk about GC content: % G or C nucelotides in region, not dinucleotides
- CpG dinucleotides:
  - Cytosine in CpGs are often methylated
  - When methylated, have high rate of C→T mutations
    - Methylation: addition of methyl group (in this case to cytosine)
    - In mammals, 70-80% of CpG cytosines are methylated
  - Consequently CpGs are rarer in genome than expected

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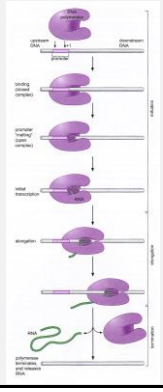
Gene promoter

- Gene promoter is:
  - Sequence where transcription is initiated
    - May or may not be transcribed, but near transcription start site (TSS)
  - Between ~100-1000 bp long
  - Subsequence bound by transcription factors:
    - A protein (i.e., product of a gene) that binds a specific DNA sequence
    - Recruits RNA polymerase, and thus controls the rate of transcription
      - In eukaryotes, often works in tandem with other elements (activators, repressors, others)



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Biology background: CpG islands

- Methylation is suppressed in promoters, other regions of the genome
- Such regions have high rate of: CpG, GC content
  - Called CpG islands
- Problems:
  - Given short sequence, is it from a CpG island?
  - Given (long) genome sequence, locate CpG islands (regions with likely biological importance)
- How would you address the first question?

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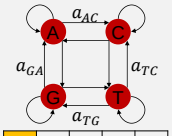
Can train Markov chains for CpG island / not



+	A	C	G	T
A	.180	.274	.426	.120
C	.171	.368	.274	.188
G	.161	.339	.375	.125
T	.079	.355	.384	.182

-	A	C	G	T
A	.300	.205	.285	.210
C	.322	.298	.078	.302
G	.248	.246	.298	.208
T	.177	.239	.292	.292

- Suppose we were given data labeled as *CpG island* or *not CpG island*
- Could use this to train a model
  - That is, set the parameters in the model based on the data
- Approach: use two Markov chains
  In CpG island: + model; not island: - model
- How would you assign transition probabilities in these DNA Markov chains?

Is MLE

$a_{kl}^{+} = \frac{c_{kl}^{+}}{\sum_{l'} c_{kl'}^{+}}, c_{kl}^{+}$ dinucleotide counts

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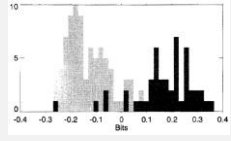
Have two opposite models: want to classify

- Can compute likelihood of a given input sequence under both models: $P(\boldsymbol{x}|\text{model}+)$, $P(\boldsymbol{x}|\text{model}-)$
- How should we discriminate between these?
- Use log-odds ratio:

$$S(x) = \log\frac{P(\boldsymbol{x}|\text{model}+)}{P(\boldsymbol{x}|\text{model}-)} = \sum_{i=1}^{N} \log\frac{a_{x_{i-1}x_i}^{+}}{a_{x_{i-1}x_i}^{-}}$$



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Problem 2: locate CpG islands in sequence

- Given (long) genome sequence, locate CpG islands
- How?
  - Could divide up sequence into 100 bp windows, compute log odds scores, call windows with positive scores CpG islands
  - Not ideal:
    - Why 100 bp? CpG islands vary in length
    - In general won't start/end at window boundary
- Instead: use hidden Markov model
  - Observed DNA is derived from some underlying hidden biological process that impacts the DNA sequence we do see
  - Can incorporate Markov models that give expected frequency of dinucleotides between bases within CpG islands/non-island

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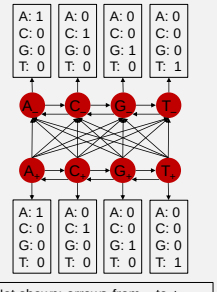
CpG island hidden Markov model



Not shown: arrows from – to + some arrows between +/– states

- Can merge the two Markov models, make states hidden
  - States get relabeled, with +, –
  - Both "emit" A,C,G,T
- Transition probabilities:
  - Based on those in Markov chains, but need probability of switching: + to – and – to +
- Why such a large number of states?
  - Why not use only two: +/ – ?
  - Need memory of previous nucleotide to model dinucleotides

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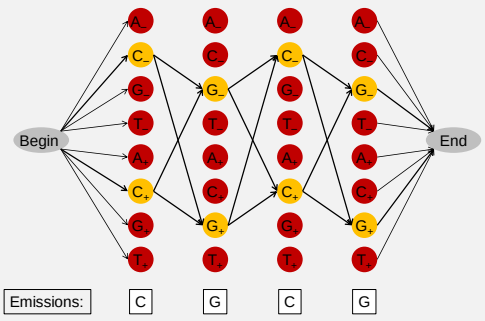
Numerous possible paths through states



Want to know most likely state path for given observed sequence

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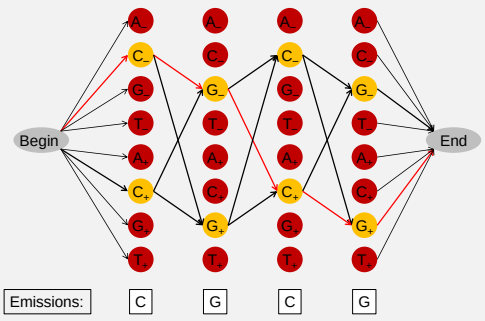
What if the path was given to us?



Easy to calculate probability of path/observations (e.g., loaded/fair die earlier)

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How do we find the most likely path?

- Can compute probability of a given path, how can we find the best one?
- Dynamic programming!
  - Highest probability path to a given state is product of:
    a) Highest probability path to all previous states (subproblem)
    b) Transition probability to from previous state to given state
    c) Emission probability
- Viterbi algorithm / Viterbi decoding
  - Terminology: HMM decoding: path of states that produce some sequence (note: not necessarily *correct* path)

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Hidden Markov models

Viterbi decoding: maximum likelihood path

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Goal: maximum likelihood decoding

- Want to maximize joint probability $P(\boldsymbol{x}, \boldsymbol{z})$ over $\boldsymbol{z}$
  - Recall: $\boldsymbol{x}$ – sequence of observations; $\boldsymbol{z}$ – sequence of states
- For $\boldsymbol{x}, \boldsymbol{z}$ given, we have:

$$P(\boldsymbol{x}, \boldsymbol{z}) = a_{0z_1} \cdot e_{z_1}(x_1) \cdot \prod_{i=2}^{N} e_{z_i}(x_i) \cdot a_{z_{i-1}z_i}$$

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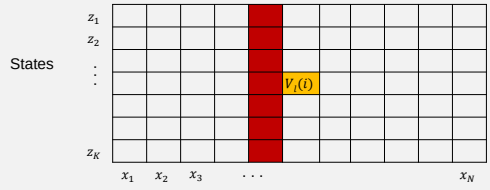
Viterbi algorithm summary



- Let $V_k(i-1)$ be the probability of the highest probability path to state k, up to observation x_{i-1}
- Assume we know $V_k(i-1)$, for all k
  How do we get $V_l(i)$ for a given l?

$$V_l(i) = e_l(x_i) \cdot \max_k (V_k(i-1) \cdot a_{kl})$$

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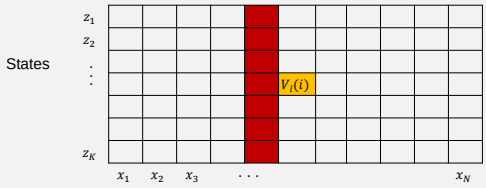
Viterbi algorithm



- Initialization: $V_k(1) = a_{0k}e_k(x_1) = P(z_1 = k)P(x_1|z_1 = k)$
- Iteration: $V_i(i) = e_i(x_i) \cdot \max_k(V_k(i-1) \cdot a_{kl})$
- Final value: $\max_{\boldsymbol{z}} P(\boldsymbol{x}, \boldsymbol{z}) = \max_k V_k(N)$
- How do we get path? Trace back: keep back pointers to max
- Runtime, Space complexity: $O(K^2N)$, $O(KN)$, respectively

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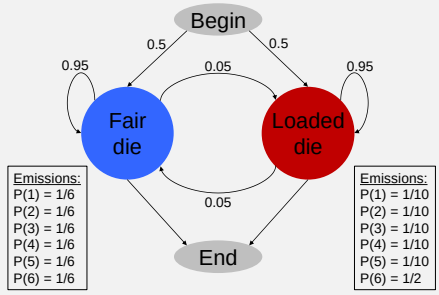
Example: occasionally dishonest casino



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Example: Viterbi path for dishonest casino

- 300 rolls generated by sampling Markov chain
- Viterbi decoding shown – what do you notice?

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Desired uses of HMMs (highlighted done)

- Evaluation:
  - **Given**: observed $\boldsymbol{x}$ and HMM specification
    Question: what is the joint probability of $\boldsymbol{x}$ and a given $\boldsymbol{z}$?
    Question: what is the likelihood of $\boldsymbol{x}$ based on the HMM?
- Decoding:
  - **Given**: observed $\boldsymbol{x}$ and HMM
    Question: what sequence of hidden states produced $\boldsymbol{x}$?
  - Viterbi decoding: most likely hidden state sequence
  - Posterior probability of hidden states: probability of each state z_i producing each x_i
    - Technically not a decoding: not path of states, but probabilities
- Learning:
  - **Given**: observed $\boldsymbol{x}$ and HMM without complete probabilities
    Question: what emission, transition probabilities produced $\boldsymbol{x}$?

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Hidden Markov models

What is the likelihood of the data $P(\boldsymbol{x})$ based on a given parameterization of an HMM?

Forward algorithm

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Law of total probability gives $P(\boldsymbol{x})$

- Want to know the probability that the data was generated by the model
- From law of total probability, have:

$$P(\boldsymbol{x}) = \sum_{\boldsymbol{z}} P(\boldsymbol{x}, \boldsymbol{z})$$

- We know how to compute:
  - $P(\boldsymbol{x}, \boldsymbol{z})$ for a given $\boldsymbol{z}$: multiply transition, emission probabilities
  - $\max_{\boldsymbol{z}} P(\boldsymbol{x}, \boldsymbol{z})$: Viterbi algorithm
- How do we compute $P(\boldsymbol{x})$?
  - Exponential number of paths
  - Could just use Viterbi to approximate, but that's only one path
  - ➢ Dynamic programming still works

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Forward probability

- Will compute iteratively
- Let $f_k(i) = P(x_1, \ldots, x_i, z_i = k)$: forward probability
- Given $f_j(i-1)$ at some step, the following holds:

$$f_k(i) = e_k(x_i) \sum_{j=1}^{K} f_j(i-1) \cdot a_{jk}$$

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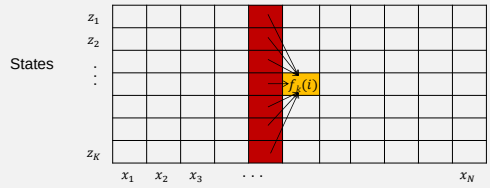
Forward probability calculation



- Initialization: $f_k(1) = a_{0k} e_k(x_1) = P(z_1 = k) P(x_1 | z_1 = k)$
- Iteration: $f_k(i) = e_k(x_i) \cdot \sum_{j=1}^{K} f_j(i-1) \cdot a_{jk}$
- Final value: $P(\boldsymbol{x}) = \sum_{k=1}^{K} f_k(N)$
- Runtime, Space complexity: $O(K^2 N)$, $O(KN)$, respectively

No trace back: not about one path

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Applications of forward algorithm

- Forward probabilities are used in:
  - Forward-backward algorithm to compute posterior probability of each state
  - Posterior decoding
  - Unsupervised learning via Baum-Welch
  - Sampling a state path from the distribution $P(\boldsymbol{z}|\boldsymbol{x})$
- In principle can use $P(\boldsymbol{x})$ to compare two different HMMs, but in practice this is uncommon
  - Instead, one chooses hidden states and sets parameters (transition/emission probabilities) from theory or via learning

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Desired uses of HMMs (highlighted done)

- Evaluation:
  - **Given**: observed $\boldsymbol{x}$ and HMM specification
    Question: what is the joint probability of $\boldsymbol{x}$ and a given $\boldsymbol{z}$?
    Question: what is the likelihood of $\boldsymbol{x}$ based on the HMM?
- Decoding:
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  - Viterbi decoding: most likely hidden state sequence
  - Posterior probability of hidden states: probability of each state z_i producing each x_i
    - Technically not a decoding: not path of states, but probabilities
- Learning:
  - **Given**: observed $\boldsymbol{x}$ and HMM without complete probabilities
    Question: what emission, transition probabilities produced $\boldsymbol{x}$?

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Hidden Markov models

What is $P(z_i = k|\boldsymbol{x})$?

Forward-backward algorithm

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Computing $P(z_i = k|\boldsymbol{x})$

- Want $P(z_i = k|\boldsymbol{x})$
- By definition of conditional probability, we have

$$P(z_i = k|\boldsymbol{x}) = \frac{P(\boldsymbol{x}, z_i = k)}{P(\boldsymbol{x})}$$

  - Forward probability gives $P(\boldsymbol{x})$
  - How do we compute the numerator?

$$\begin{aligned} P(\boldsymbol{x}, z_i = k) &= P(x_1, \ldots, x_i, z_i = k) P(x_{i+1}, \ldots, x_N | x_1, \ldots, x_i, z_i = k) \\ &= P(x_1, \ldots, x_i, z_i = k) P(x_{i+1}, \ldots, x_N | z_i = k) \\ &= f_k(i) \cdot \underbrace{P(x_{i+1}, \ldots, x_N | z_i = k)}_{b_k(i)} \end{aligned}$$

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Backward probability

- Similar to forward probability, but calculated using observed data *after* a given step i
- Let $b_k(i) = P(x_{i+1}, \ldots, x_N | z_i = k)$: backward probability
- Given $b_k(i+1)$ at some step, the following holds:

$$b_k(i) = \sum_{l=1}^{K} a_{kl} \cdot e_l(x_{i+1}) \cdot b_l(i+1)$$

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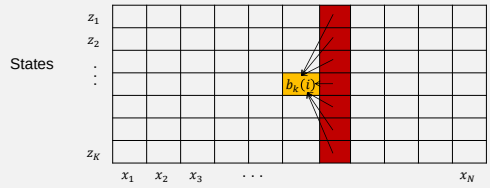
Backward probability calculation



- Initialization: $b_k(N) = a_{k0}$ (typically 1)
- Iteration: $b_k(i) = \sum_{l=1}^{K} a_{kl} \cdot e_l(x_{i+1}) \cdot b_l(i+1)$
- Note: $b_k(i)$ does not include emission probability for step i
- Final value: $P(\boldsymbol{x}) = \sum_{k=1}^{K} a_{0k} e_k(x_1) b_k(1)$

Analogous to forward
- Computes $P(\boldsymbol{x})$
- No trace back

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Final notes

- Summary:
  - Hidden Markov models: very general framework for analyzing data from a given model
    - Viterbi algorithm
    - Forward algorithm