## 10-701 <br> Machine Learning

## Hidden Markov models (HMMs)

## What's wrong with Bayesian networks

- Bayesian networks are very useful for modeling joint distributions
- But they have their limitations:
- Cannot account for temporal / sequence models
- DAG's (no self or any other loops)


## This is not a valid Bayesian network!



## Hidden Markov models

- Model a set of observation with a set of hidden states
- Robot movement

Observations: range sensor, visual sensor
Hidden states: location (on a map)

- Speech processing

Observations: sound signals
Hidden states: parts of speech, words

- Biology

Observations: DNA base pairs
Hidden states: Genes

## Hidden Markov models

- Model a set of observation with a set of hidden states
- Robot movement

Observations: range sensor, visual sensor
Hidden states: location (on a map)

1. Hidden states generate observations
2. Hidden states transition to other hidden states

## Examples: Speech processing



## Example: Biological data



ATGAAGCTACTGTCTTCTATCGAACAAGCATGCG ATATTTGCCGACTTAAAAAGCTCAAG TGCTCCAAAGAAAAACCGAAGTGCGCCAAGTGT CTGAAGAACAACTGGGAGTGTCGCTAC TCTCCCAAAACCAAAAGGTCTCCGCTGACTAGG GCACATCTGACAGAAGTGGAATCAAGG CTAGAAAGACTGGAACAGCTATTTCTACTGATTTT TCCTCGAGAAGACCTTGACATGATT

## Contents

Preface ..... page ix
Introduction ..... 1
Sequence similarity, homology, and alignment ..... 2
1.2 Overview of the book ..... 2
1.3 Probabilities and probabilistic models ..... 4
1.4 Further reading ..... 10
Pairwise alignment ..... 12
Introduction ..... 12
2.1 $\quad$ Introduction ..... 13
2.3 Alignment algorithms ..... 17
Dynamic programming with more complex models ..... 28
Heuristic alignment algorithms ..... 32
Linear space alignments ..... 34
Significance of scores ..... 36
Deriving score parameters from alignment data ..... 41
Further reading ..... 45
Markov chains and hidden Markov models ..... 46
Markov chains ..... 48
Hidden Markov models ..... 51
Parameter estimation for HMMs ..... 62
HMM model structure ..... 68
More complex Markov chains ..... 72
Numerical stability of HMM algorithms ..... 77
Further reading ..... 79
Pairwise alignment using HMMs ..... 80
Pair HMMs ..... 81
4.2 The full probability of $x$ and $y$, summing over all paths ..... 87
4.3 Suboptimal alignment ..... 89
4.4 The posterior probability that $x_{i}$ is aligned to $y_{j}$ ..... 91
4.5 Pair HMMs versus FSAs for searching ..... 95
4.6
Further reading ..... 98
Profile HMMs for sequence families ..... 100
Ungapped score matrices ..... 102
Adding insert and delete states to obtain profile HMMs ..... 102
Deriving profile HMMs from multiple alignments ..... 105
Searching with profile HMMs ..... 108
Profile HMM variants for non-global alignments ..... 113
More on estimation of probabilities ..... 115
Optimal model construction ..... 122
Weighting training sequences ..... 124
Further reading ..... 132
Multiple sequence alignment methods ..... 134
What a multiple alignment means ..... 135
Scoring a multiple alignment ..... 137
Multidimensional dynamic programming ..... 141
Progressive alignment methods ..... 143
Multiple alignment by profile HMM training ..... 149
Further reading ..... 159
Building phylogenetic trees ..... 160
The tree of life ..... 160
Background on trees ..... 161
Making a tree from pairwise distances ..... 165
Parsimony ..... 173
Assessing the trees: the bootstrap ..... 179
Simultaneous alignment and phylogeny ..... 180
Further reading ..... 188
Appendix: proof of neighbour-joining theorem ..... 190
Probabilistic approaches to phylogeny ..... 192
Introduction ..... 192
8.2 Probabilistic models of evolution ..... 193 ..... 197
8.4 Using the likelihood for inference ..... 205
215
Towards more realistic evolutionary models
224
224
8.6 Comparison of probabilistic and non-probabilistic methods
8.6 Comparison of probabilistic and non-probabilistic methods ..... 231

## Example: Gambling on dice outcome

- Two dices, both skewed (output model).
- Can either stay with the same dice or switch to the second dice (transition mode).



## A Hidden Markov model

- A set of states $\left\{\mathrm{s}_{1} \ldots \mathrm{~s}_{\mathrm{n}}\right\}$
- In each time point we are in exactly one of these states denoted by $\mathrm{q}_{\mathrm{t}}$
- $\Pi_{i}$, the probability that we start at state $\mathrm{s}_{\mathrm{i}}$
- A transition probability model, $\mathrm{P}\left(\mathrm{q}_{\mathrm{t}}=\mathrm{s}_{\mathrm{i}} \mid \mathrm{q}_{\mathrm{t}-1}=\mathrm{s}_{\mathrm{j}}\right)$
- A set of possible outputs $\Sigma$
- At time $t$ we emit a symbol $\sigma \in \Sigma$
- An emission probability model, $p\left(o_{t}=\sigma \mid s_{i}\right)$



## The Markov property

- A set of states $\left\{\mathrm{s}_{1} \ldots \mathrm{~s}_{\mathrm{n}}\right\}$
- In each time point we are in exactly one of these states denoted by $\mathrm{q}_{\mathrm{t}}$
- $\Pi_{\mathrm{i}}$, the probability that we start at state $\mathrm{s}_{\mathrm{i}}$
- A transition probability model, $\mathrm{P}\left(\mathrm{q}_{\mathrm{t}}=\mathrm{s}_{\mathrm{i}} \mid \mathrm{q}_{\mathrm{t}-1}=\mathrm{s}_{\mathrm{j}}\right)$

An important aspect of this definition is the Markov property: $\mathrm{q}_{\mathrm{t}+1}$ is conditionally independent of $\mathrm{q}_{\mathrm{t}-1}$ (and any earlier time points) given $q_{t}$
More formally $P\left(q_{t+1}=s_{i} \mid q_{t}=s_{j}\right)=P\left(q_{t+1}=s_{i} \mid q_{t}=s_{j}, q_{t-1}=s_{j}\right)$


## What can we ask when using a HMM?

A few examples:

- "What dice is currently being used?"
- "What is the probability of a 6 in the next role?"
- "What is the probability of 6 in any of the next 3 roles?"



## Inference in HMMs

$Q$ represents a set of state $\mathbf{Q}=\left\{\mathbf{s}_{1}, \mathbf{s}_{2} \ldots \mathrm{~s}_{\mathrm{t}}\right\}$

- Computing $P(Q)$ and $P\left(q_{t}=s_{i}\right)$
- If we cannot look at observations
- Computing $P(Q \mid O)$ and $P\left(q_{t}=s_{i} \mid O\right)$
- When we have observation and care about the last state only
- Computing $\operatorname{argmax}_{\mathrm{Q}} \mathrm{P}(\mathrm{Q} \mid \mathrm{O})$
- When we care about the entire path


## What dice is currently being used?

- We played $t$ rounds so far
- We want to determine $P\left(q_{t}=A\right)$
- Lets assume for now that we cannot observe any outputs (we are blind folded)
- How can we compute this?



## $P\left(q_{t}=A\right) ?$

- Simple answer:

Lets determine $P(Q)$ where $Q$ is any path that ends in $A$ $Q=q_{1}, \ldots q_{t-1}, A$
$P(Q)=P\left(q_{1}, \ldots q_{t-1}, A\right)=P\left(A \mid q_{1}, \ldots q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}=\right.$
$P\left(A \mid q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}\right)=\ldots=P\left(A \mid q_{t-1}\right) \ldots P\left(q_{2} \mid q_{1}\right) P\left(q_{1}\right)$
Markov property!

## $P\left(q_{t}=A\right) ?$

- Simple answer:

1. Lets determine $P(Q)$ where $Q$ is any path that ends in $A$
$Q=q_{1}, \ldots q_{t-1}, A$
$P(Q)=P\left(q_{1}, \ldots q_{t-1}, A\right)=P\left(A \mid q_{1}, \ldots q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}\right)=$
$P\left(A \mid q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}\right)=\ldots=P\left(A \mid q_{t-1}\right) \ldots P\left(q_{2} \mid q_{1}\right) P\left(q_{1}\right)$
2. $P\left(q_{t}=A\right)=\Sigma P(Q)$
where the sum is over all sets of $t$ states that end in A

## $P\left(q_{t}=A\right) ?$

- Simple answer:

1. Lets determine $P(Q)$ where $Q$ is any path that ends in $A$
$Q=q_{1}, \ldots q_{t-1}, A$
$P(Q)=P\left(q_{1}, \ldots q_{t-1}, A\right)=P\left(A \mid q_{1}, \ldots q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}\right)=$
$P\left(A \mid q_{t-1}\right) P\left(q_{1}, \ldots q_{t-1}\right)=\ldots=P\left(A \mid q_{t-1}\right) \ldots P\left(q_{2} \mid q_{1}\right) P\left(q_{1}\right)$
2. $P\left(q_{t}=A\right)=\Sigma P(Q)$
where the sum is over all sets of $t$ sates that end in A

Q: How many sets Q are there?

A: A lot! ( $2^{t-1}$ )
Not a feasible solution

## $P\left(q_{t}=A\right)$, the smart way

- Lets define $\mathrm{p}_{\mathrm{t}}(\mathrm{i})$ as the probability of being in state $i$ at time t : $p_{t}(i)=p\left(q_{t}=s_{i}\right)$
- We can determine $p_{t}(i)$ by induction

1. $p_{1}(i)=\Pi_{i}$
2. $p_{t}(i)=$ ?

## $P\left(q_{t}=A\right)$, the smart way

- Lets define $p_{t}(i)=$ probability state $i$ at time $t=p\left(q_{t}=s_{i}\right)$
- We can determine $p_{\mathrm{t}}(\mathrm{i})$ by induction

1. $p_{1}(i)=\Pi_{i}$
2. $p_{t}(i)=\Sigma_{j} p\left(q_{t}=s_{i} \mid q_{t-1}=s_{j}\right) p_{t-1}(j)$

## $P\left(q_{t}=A\right)$, the smart way

- Lets define $p_{t}(i)=$ probability state $i$ at time $t=p\left(q_{t}=s_{i}\right)$
- We can determine $p_{t}(i)$ by induction

1. $p_{1}(i)=\Pi_{i}$
2. $p_{t}(i)=\Sigma_{j} p\left(q_{t}=s_{i} \mid q_{t-1}=s_{j}\right) p_{t-1}(j)$

This type of computation is called dynamic programming

Complexity: $\mathrm{O}\left(\mathrm{n}^{2 \star} \mathrm{t}\right)$

| Time $/$ <br> state | t 1 | t 2 | t 3 |
| :--- | :--- | :--- | :--- |
| s 1 | .3 | $\boxed{ }$ |  |
| s 2 | .7 |  |  |

Number of states in our HMM

## Inference in HMMs

- Computing $P(Q)$ and $P\left(q_{t}=s_{i}\right) \sqrt{ }$
- Computing $\mathrm{P}(\mathrm{Q} \mid \mathrm{O})$ and $\mathrm{P}\left(\mathrm{q}_{\mathrm{t}}=\mathrm{s}_{\mathrm{i}} \mid \mathrm{O}\right)$
- Computing $\operatorname{argmax}_{\mathrm{Q}} \mathrm{P}(\mathrm{Q})$


## But what if we observe outputs?

- So far, we assumed that we could not observe the outputs
- In reality, we almost always can.

| $v$ | $P(v \mid A)$ | $P(v \mid B)$ |
| :--- | :--- | :--- |
| 1 | .3 | .1 |
| 2 | .2 | .1 |
| 3 | .2 | .1 |
| 4 | .1 | .2 |
| 5 | .1 | .2 |
| 6 | .1 | .3 |



## But what if we observe outputs?

- So far, we assumed that we could not observe the outputs
- In reality, we almost a Does observing the sequence

| $v$ | $P(v \mid A)$ | $P(v \mid B)$ |
| :--- | :--- | :--- |
| 1 | .3 | .1 |
| 2 | .2 | .1 |
| 3 | .2 | .1 |
| 4 | .1 | .2 |
| 5 | .1 | .2 |
| 6 | .1 | .3 | $5,6,4,5,6,6$

Change our belief about the state?


## $P\left(q_{t}=A\right)$ when outputs are observed

- We want to compute $P\left(q_{t}=A \mid O_{1} \ldots O_{t}\right)$
- For ease of writing we will use the following notations (commonly used in the literature)
- $a_{j, i} \equiv P\left(q_{t}=s_{i} \mid q_{t-1}=s_{j}\right)$
- $b_{i}\left(o_{t}\right)=P\left(o_{t} \mid s_{i}\right)$

Emission probability

## $P\left(q_{t}=A\right)$ when outputs are observed

- We want to compute $P\left(q_{t}=A \mid O_{1} \ldots O_{t}\right)$
- Lets start with a simpler question. Given a sequence of states $Q$, what is $P\left(Q \mid O_{1} \ldots O_{t}\right)=P(Q \mid O)$ ?
- It is pretty simple to move from $P(Q \mid O)$ to $P\left(q_{t}=A \mid O\right)$
- In some cases $P(Q \mid O)$ is the more important question
- Speech processing
- NLP


## $P(Q \mid O)$

- We can use Bayes rule:


Easy, $\mathrm{P}(\mathrm{O} \mid \mathrm{Q})=\mathrm{P}\left(\mathrm{o}_{1} \mid \mathrm{q}_{1}\right) \mathrm{P}\left(\mathrm{o}_{2} \mid \mathrm{a}_{2}\right) \ldots \mathrm{P}\left(\mathrm{o}_{\mathrm{t}} \mid \mathrm{q}_{\mathrm{t}}\right)$

## $P(Q \mid O)$

- We can use Bayes rule:


Easy, $P(Q)=P\left(q_{1}\right) P\left(q_{2} \mid q_{1}\right) \ldots P\left(q_{t} \mid q_{t-1}\right)$

## $P(Q \mid O)$

- We can use Bayes rule:

$$
P(Q \mid O)=\frac{P(O \mid Q) P(Q)}{P(O)}
$$

## $\mathrm{P}(\mathrm{O})$

- What is the probability of seeing a set of observations:
- An important question in it own rights, for example classification using two HMMs
- Define $\alpha_{t}(i)=P\left(o_{1}, o_{2} \ldots, o_{t} \wedge q_{t}=s_{i}\right)$
- $\alpha_{t}(i)$ is the probability that we:

1. Observe $o_{1}, o_{2} \ldots, o_{t}$
2. End up at state i

How do we compute $\alpha_{t}(i)$ ?

## Computing $\alpha_{t}(i)$

$$
\alpha_{t}(i)=P\left(o_{1}, o_{2} \ldots, o_{t} \wedge q_{t}=s_{i}\right)
$$

- $\alpha_{1}(i)=P\left(o_{1} \wedge q_{1}=i\right)=P\left(o_{1} \mid q_{1}=s_{i}\right) \Pi_{1}$

We must be at a state in time $t$

Markov property

## Example: Computing $\alpha_{3}(B)$

- We observed 2,3,6
$\alpha_{1}(A)=P\left(2 \wedge q_{1}=A\right)=P\left(2 \mid q_{1}=A\right) \Pi_{A}=.2^{*} .7=.14, \alpha_{1}(B)=.1^{*} .3=.03$
$\alpha_{2}(A)=\Sigma_{j=A, B} b_{A}(3) a_{j, A} \alpha_{1}(j)=.2^{*} .8^{*} .14+.2^{*} .2^{*} .03=0.0236, \alpha_{2}(B)=0.0052$
$\alpha_{3}(B)=\Sigma_{j=A, B} b_{B}(6) \mathrm{a}_{\mathrm{j}, \mathrm{B}} \alpha_{2}(\mathrm{j})=.3^{\star} .2^{\star} .0236+.3^{*} .8^{\star} .0052=0.00264$
$\Pi_{A}=0.7$
$\Pi_{b}=0.3$

| V | $\mathrm{P}(\mathrm{V} \mid \mathrm{A})$ | $\mathrm{P}(\mathrm{V} \mid \mathrm{B})$ |
| :--- | :--- | :--- |
| 1 | .3 | .1 |
| 2 | .2 | .1 |
| 3 | .2 | .1 |
| 4 | .1 | .2 |
| 5 | .1 | .2 |
| 6 | .1 | .3 |

## Where we are

- We want to compute $\mathrm{P}(\mathrm{Q} \mid \mathrm{O})$
- For this, we only need to compute $\mathrm{P}(\mathrm{O})$
- We know how to compute $\alpha_{\mathrm{t}}(\mathrm{i})$

From now its easy

$$
\begin{aligned}
& \alpha_{t}(i)=P\left(o_{1}, o_{2} \ldots, o_{t} \wedge q_{t}=s_{i}\right) \\
& \text { so } \\
& P(O)=P\left(o_{1}, o_{2} \ldots, o_{t}\right)=\Sigma_{i} P\left(o_{1}, o_{2} \ldots, o_{t} \wedge q_{t}=s_{i}\right)=\Sigma_{i} \alpha_{t}(i)
\end{aligned}
$$

note that

$$
\begin{aligned}
& \mathrm{p}\left(\mathrm{q}_{\mathrm{t}}=\mathrm{s}_{\mathrm{i}} \mid \mathrm{o}_{1}, \mathrm{o}_{2} \ldots, \mathrm{o}_{\mathrm{t}}\right)=\frac{\alpha_{\mathrm{t}}(\mathrm{i})}{\sum_{\mathrm{j}} \alpha_{\mathrm{t}}(\mathrm{j})} \\
& \mathrm{P}(\mathrm{~A} \mid \mathrm{B})=\mathrm{P}(\mathrm{~A} \wedge \mathrm{~B}) / P(B)
\end{aligned}
$$

## Complexity

- How long does it take to compute $\mathrm{P}(\mathrm{Q} \mid \mathrm{O})$ ?
- $P(Q): O(t)$
- $\mathrm{P}(\mathrm{O} \mid \mathrm{Q}): \mathrm{O}(\mathrm{t})$
- $\mathrm{P}(\mathrm{O}): \mathrm{O}\left(\mathrm{n}^{2} \mathrm{t}\right)$


## Inference in HMMs

- Computing $P(Q)$ and $P\left(q_{t}=s_{i}\right) \sqrt{ }$
- Computing $P(Q \mid O)$ and $P\left(q_{t}=s_{i} \mid O\right) \sqrt{ }$
- Computing $\operatorname{argmax}_{\mathrm{Q}} \mathrm{P}(\mathrm{Q})$


## Most probable path

- We are almost done ...
- One final question remains

How do we find the most probable path, that is $Q^{*}$ such that

$$
\mathrm{P}\left(\mathrm{Q}^{*} \mid \mathrm{O}\right)=\operatorname{argmax}_{\mathrm{Q}} \mathrm{P}(\mathrm{Q} \mid \mathrm{O}) ?
$$

- This is an important path
- The words in speech processing
- The set of genes in the genome
- etc.


## Example

- What is the most probable set of states leading to the sequence:

$$
1,2,2,5,6,5,1,2,3 ?
$$

$$
\begin{aligned}
& \Pi_{\mathrm{A}}=0.7 \\
& \Pi_{\mathrm{b}}=0.3
\end{aligned}
$$

| v | $\mathrm{P}(\mathrm{v} \mid \mathrm{A})$ | $\mathrm{P}(\mathrm{v} \mid \mathrm{B})$ |
| :--- | :--- | :--- |
| 1 | .3 | .1 |
| 2 | .2 | .1 |
| 3 | .2 | .1 |
| 4 | .1 | .2 |
| 5 | .1 | .2 |
| 6 | .1 | 0.8 |

## Most probable path <br> $\arg \max _{Q} P(Q \mid O)=\arg \max _{Q} \frac{P(O \mid Q) P(Q)}{P(O)}$ <br> $$
=\arg \max _{Q} P(O \mid Q) P(Q)
$$

We will use the following definition:

$$
\delta_{t}(i)=\max _{q_{1} \ldots q_{t-1}} p\left(q_{1} \ldots q_{t-1} \wedge q_{t}=s_{i} \wedge O_{1} \ldots O_{t}\right)
$$

In other words we are interested in the most likely path from 1 to $t$ that:

1. Ends in $\mathrm{S}_{\mathrm{i}}$
2. Produces outputs $\mathrm{O}_{1} \ldots \mathrm{O}_{\mathrm{t}}$

## Computing $\delta_{t}(\mathrm{i})$

$$
\begin{aligned}
& \delta_{1}(i)=p\left(q_{1}=s_{i} \wedge O_{1}\right) \\
& \quad=p\left(q_{1}=s_{i}\right) p\left(O_{1} \mid q_{1}=s_{i}\right) \\
& \quad=\pi_{i} b_{i}\left(O_{1}\right)
\end{aligned}
$$

$$
\delta_{t}(i)=\max _{q_{1} \ldots q_{t-1}} p\left(q_{1} \ldots q_{t-1} \wedge q_{t}=s_{i} \wedge O_{1} \ldots O_{t}\right)
$$

Q: Given $\delta_{t}(\mathrm{i})$, how can we compute $\delta_{\mathrm{t}+1}(\mathrm{i})$ ?
A: To get from $\delta_{t}(\mathrm{i})$ to $\delta_{\mathrm{t}+1}(\mathrm{i})$ we need to

1. Add an emission for time $\mathrm{t}+1\left(\mathrm{O}_{\mathrm{t}+1}\right)$
2. Transition to state $\mathrm{s}_{\mathrm{i}}$

$$
\begin{aligned}
& \delta_{t+1}(i)=\max _{q_{1} \ldots q_{t}} p\left(q_{1} \ldots q_{t} \wedge q_{t+1}=s_{i} \wedge O_{1} \ldots O_{t+1}\right) \\
& \quad=\max _{j} \delta_{t}(j) p\left(q_{t+1}=s_{i} \mid q_{t}=s_{j}\right) p\left(O_{t+1} \mid q_{t+1}=s_{i}\right) \\
& \quad=\max _{j} \delta_{t}(j) a_{j, i} b_{i}\left(O_{t+1}\right)
\end{aligned}
$$

## The Viterbi algorithm

$$
\begin{aligned}
& \delta_{t+1}(i)=\max _{q_{1} \ldots q_{t}} p\left(q_{1} \ldots q_{t} \wedge q_{t+1}=s_{i} \wedge O_{1} \ldots O_{t+1}\right) \\
& \quad=\max _{j} \delta_{t}(j) p\left(q_{t+1}=s_{i} \mid q_{t}=s_{j}\right) p\left(O_{t+1} \mid q_{t+1}=s_{i}\right) \\
& \quad=\max _{j} \delta_{t}(j) a_{j, t} b_{i}\left(O_{t+1}\right)
\end{aligned}
$$

- Once again we use dynamic programming for solving $\delta_{\mathrm{t}}(\mathrm{i})$
- Once we have $\delta_{t}(\mathrm{i})$, we can solve for our $\mathrm{P}\left(\mathrm{Q}^{*} \mid \mathrm{O}\right)$

By :
$P\left(Q^{*} \mid O\right)=\operatorname{argmax}_{Q} P(Q \mid O)=$
path defined by $\operatorname{argmax}_{\mathrm{j}} \delta_{\mathrm{t}}(\mathrm{j})$,

## Inference in HMMs

- Computing $P(Q)$ and $P\left(q_{t}=s_{i}\right) \sqrt{ }$
- Computing $P(Q \mid O)$ and $P\left(q_{t}=s_{i} \mid O\right) \sqrt{ }$
- Computing $\operatorname{argmax}_{Q} P(Q)$


## What you should know

- Why HMMs? Which applications are suitable?
- Inference in HMMs
- No observations
- Probability of next state w. observations
- Maximum scoring path (Viterbi)

