Hidden Markov Models

Scott Pegg, Ph.D.

BMI203 May 18, 2004

Where we're going today

- Probability notation & theory
- Markov & his chains
- What's a Hidden Markov Model?
- What does it have to do with biology?
- What can I do with one? How?
- I'm confused, where do I learn more?

Probability Theory

The Basics

P(A) = probability of event A

P(X=x) = probability of variable X having value x

$0 \leqslant P(X) \leqslant 1$

Joint Probability

P(A, B) = probability of event A and B occurring

Conditional Probability

P(A | B) = probability of event A occurring, given that B has already occurred

Probability Theory

Marginal Probability

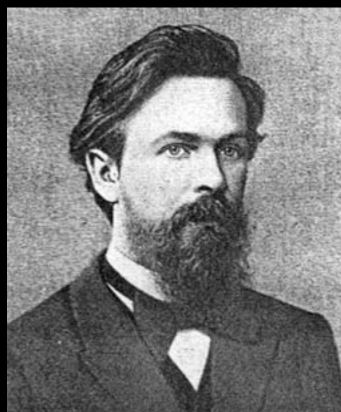
$$P(A,B) = P(A|B)\,P(B)$$

$$P(A) = \sum_{B} P(A,B) = \sum_{B} P(A|B)\,P(B)$$

Bayes' Theorem

$$P(A|B) = \frac{P(B|A)\,P(A)}{P(B)}$$

Markov who?



Andrei Andreyevich Markov
1856 - 1922
St. Petersburg, Russia

Grigory Yefimovich Rasputin
1871 - 1916
St. Petersburg, Russia

Markov Process

A process in which the state at time *t* depends upon the state at times *t-1, t-2,…, t-k*

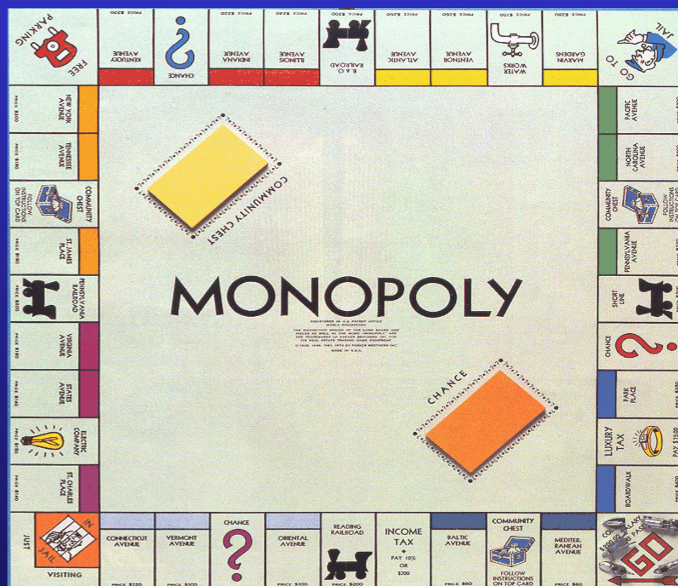
k^{th} order Markov process

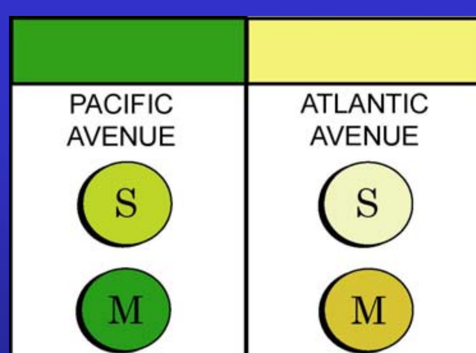
Most often, we're interested in a first order model

aka 'Markov chain'

A set of states $\mathbf{S} = \{S^0, S^1, \ldots, S^N\}$
such that
$P(S^{t+1} | S^t) = P(S^{t+1} | S^0 S^1 \ldots S^t)$

A first-order Markov process





Start on a property

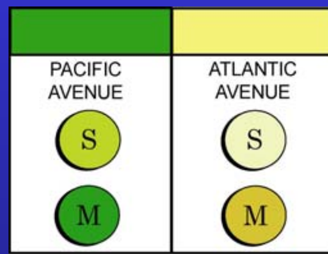
repeat until bored:

Flip that property's 'S' coin, record the result

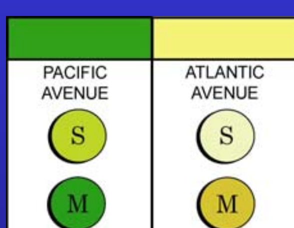
Flip that property's 'M' coin,

If the result is "heads", move to other property

If the result is "tails", stay in current property



S	$P(H) = 0.8$	$P(T) = 0.2$
S	$P(H) = 0.4$	$P(T) = 0.6$
M	$P(H) = 0.3$	$P(T) = 0.7$
M	$P(H) = 0.5$	$P(T) = 0.5$



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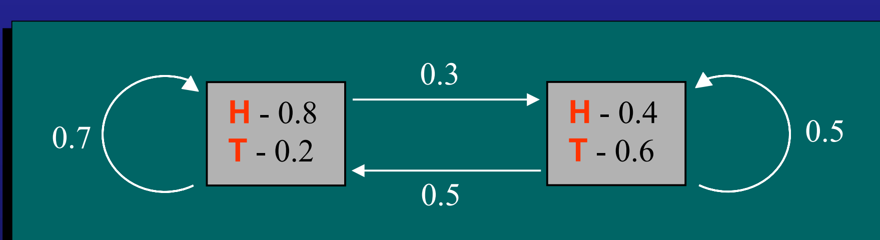
M	$P(H) = 0.5$	$P(T) = 0.5$

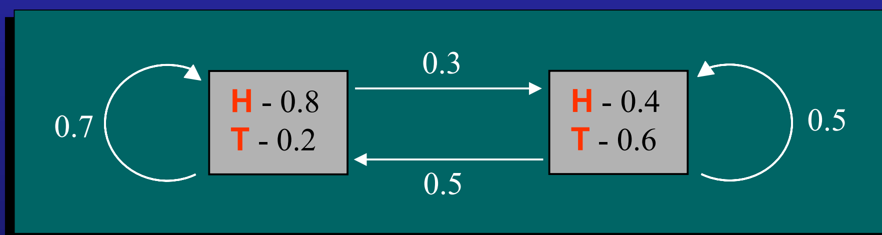
Markov Model



At the end of the game, I have a string of symbol observations

...THHTTHHTHTHHTHTHHTHT...

But I no longer remember what state (Monopoly property) each symbol was emitted from…



A “Hidden” Markov Model

HMMs in Biology

In biology, we often see strings of symbols

GCACCGTTAGGACAGGA

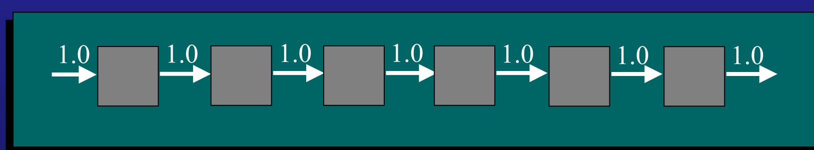
YLRNGYITSGYPLMFLHLL

And often in related groups

GCACCGTTAGGACAGGA
GGACCATTACGGCGGCA
CCAGCGTATCCGCAACA

We build HMMs which could generate them...

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	A	A	A	G
C	T	G	A	T	G
C	T	G	A	A	G



The easiest architecture is to have each column be a state.

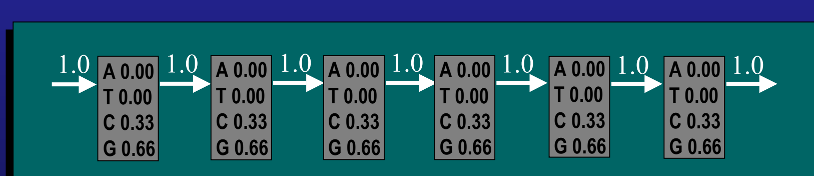
G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	A	A	A	G
C	T	G	A	T	G
C	T	G	A	A	G

C(**A**)	0	5	1	5	4	0
C(**T**)	0	0	0	1	2	0
C(**C**)	2	1	2	0	0	0
C(**G**)	3	0	3	0	0	6

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	A	A	A	G
C	T	G	A	T	G
C	T	G	A	A	G

P(**A**)	0.00	0.83	0.16	0.83	0.66	0.00
P(**T**)	0.00	0.00	0.00	0.16	0.33	0.00
P(**C**)	0.33	0.16	0.33	0.00	0.00	0.00
P(**G**)	0.66	0.00	0.50	0.00	0.00	1.00

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	A	A	A	G
C	T	G	A	T	G
C	T	G	A	A	G



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G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	-	A	A	G
C	T	-	A	T	G
C	T	-	A	A	G

What if there are gaps?

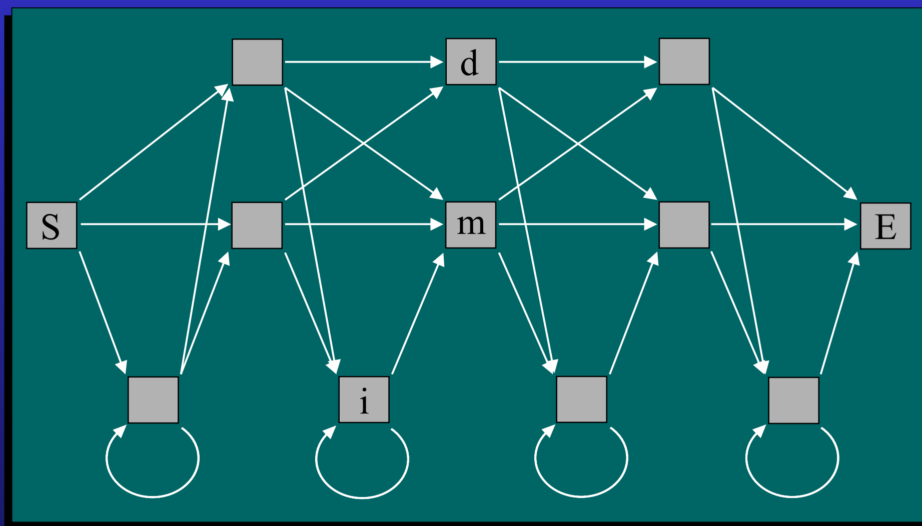
Does a gap represent an insertion or a deletion?

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	-	A	A	G
C	T	-	A	T	G
C	T	-	A	A	G

-- 1.00	delete state
A 0.00 T 0.00 C 0.66 G 0.33	match state
A 0.25 T 0.25 C 0.25 G 0.25	insert state

Instead of one state per column, we now have three!

A typical bioinformatics HMM



Three Fundamental Questions

Given a sequence of symbols and a HMM,

1. What's the most probable sequence of transitions and emissions? 'decoding'

2. How likely is this sequence given the HMM? 'likelihood'

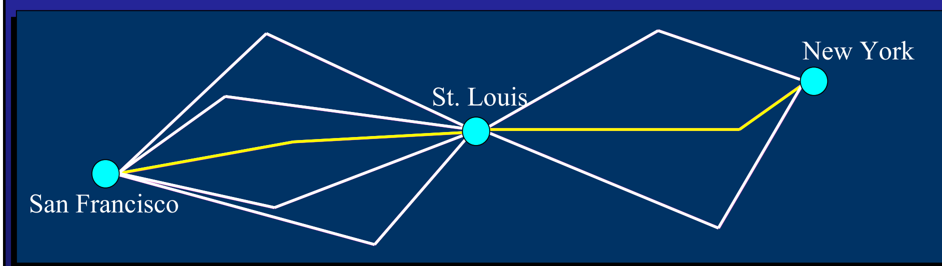
3. How should the transition and emission probabilities be updated? 'learning'

The ‘decoding’ question

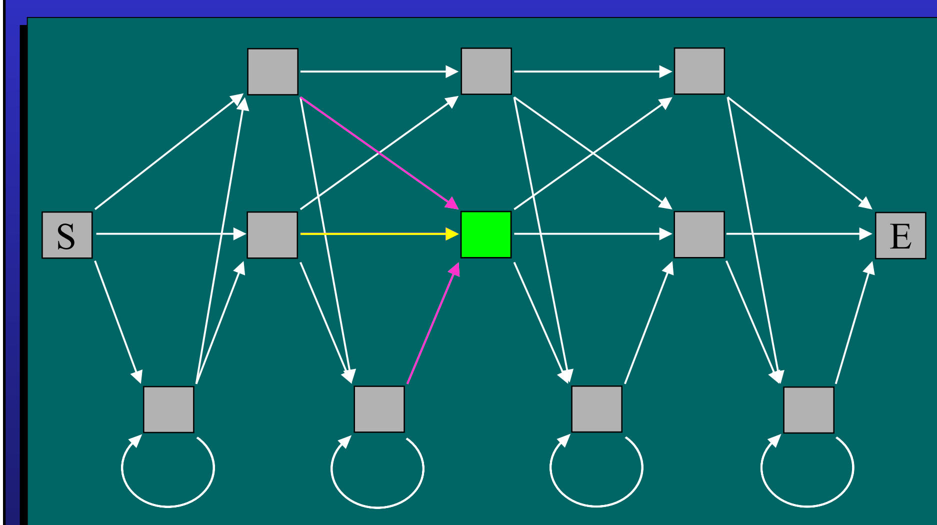
What’s the most probable sequence of transitions and emissions to produce the observed sequence of symbols?

The Viterbi algorithm

For any state at time *t*, there is only <u>*one*</u> most likely path to that state.



When calculating the transitions from this state to states at time t+1, one can discard the less likely paths.



The Viterbi Algorithm

Let **X** be the sequence of symbols $x_1x_2\ldots x_L$

Let $v_k(i)$ = probability of the most probable path for sequence $x_1x_2\ldots x_i$ that ends in state k

symbol index (i)

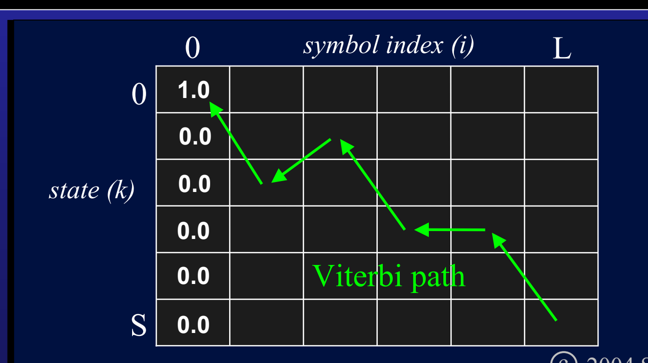
	0					L
0	**1.0**	$v_0(1)$				
	0.0					
state (k)	**0.0**					
	0.0					
	0.0					
S	**0.0**					$v_S(L)$

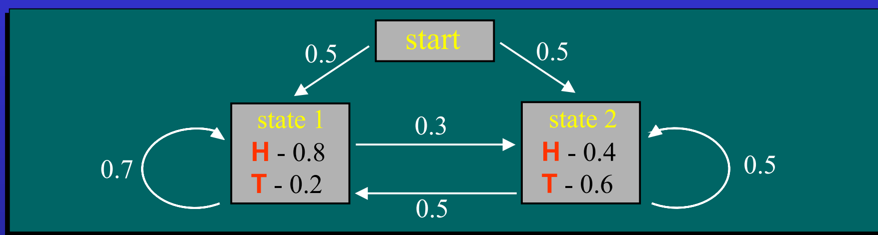
$$v_j(i+1) = e_j(x_{i+1}) \quad \max_{k \text{ in } S}\{v_k(i)\, a_{kj}\}$$

where

$e_j(x_i)$ = probability of emitting symbol x_i from state j

a_{kj} = probability of a transition from state k to state j





THHTT
0 1 2 3 4 5

$$v_j(i+1) = e_j(x_{i+1}) \quad \max_{k \text{ in } S}\{v_k(i)\, a_{kj}\}$$

$$v_2(1) \;=\; 0.6 \qquad (1.0 * 0.5) \;=\; 0.3$$

symbol index (i)

state (k)	0	1	2	3	4	5
0	**1.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
1	**0.0**	**0.10**	**0.12**	**0.0672**	**0.009408**	**0.001317**
2	**0.0**	**0.30**	**0.06**	**0.0144**	**0.012096**	**0.003629**

The Viterbi Algorithm

At the end, one has the final probability of the sequence given the most probable path,

$$P(\mathbf{X}|\pi^*) = \max_{k \text{ in } S}\ \{v_k(L)\, a_{kend}\}$$

The most probable state path π^* is recovered by simply tracing back along saved state pointers.

But there's a computational issue here…

state (k) \ symbol index (i)	0	1	2	3	4	5
0	1.0	0.0	0.0	0.0	0.0	0.0
1	0.0	0.10	0.12	0.0672	0.009408	0.001317
2	0.0	0.30	0.06	0.0144	0.012096	0.003629

underflow errors

The solution is to convert probabilites to logarithms.

Step 1: $v_{start}(0) = 0$ for all other states k, $v_k(0) = -\infty$

Step 2: $v_j(i+1) = \text{Log } e_j(x_{i+1}) + \max_{k \text{ in } S}\{v_k(i) + \text{Log } a_{kj}\}$

Step 3: $S(\mathbf{X}|\pi^*) = \max_{k \text{ in } S}\{v_k(L) + \text{Log } a_{kend}\}$

The 'decoding' answer

So what does answering the 'decoding' question give us?

It assigns each observed symbol to a state

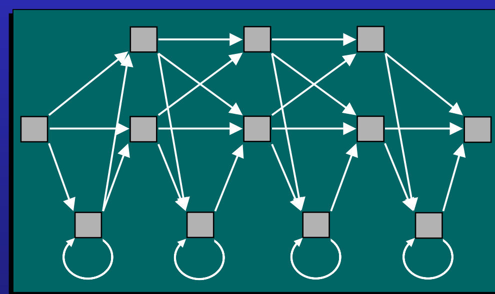
Aligning the states aligns the symbols

```
T L F A – G P G
E L F A G G P C
```

States give gap information

The 'likelihood' Question

Given a sequence of symbols and a HMM, how likely is this sequence given the HMM?



Find all of the combinations of states (ie. paths) and emissions that could generate our sequence of symbols and calculate the sum of their probabilities.

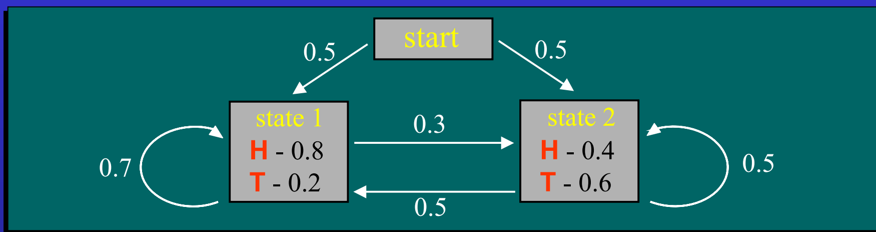
But there are an exponential number of paths!

The 'forward' Algorithm

Given the sequence of symbols **X** = $\{x_1, x_2, \ldots, x_L\}$, let $f_k(i)$ = the probability of having emitted the prefix $\{x_1, x_2, \ldots, x_i\}$ and reaching state k.

symbol index (i)

state (k)	0					L
0	**1.0**	$f_0(1)$				
	0.0					
state (k)	**0.0**					
	0.0					
	0.0					
S	**0.0**					$f_S(L)$



THHTT
0 1 2 3 4 5

$$f_j(i+1) = e_j(x_{i+1}) \sum_{k \text{ in } |\mathbf{S}|} f_k(i)\, a_{kj}$$

$$f_2(1) = 0.6\,(1.0(0.5) + 0 + 0) = 0.3$$

symbol index (i)

state (k)	0	1	2	3	4	5
0	**1.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
1	**0.0**	**0.10**	**0.176**	**0.1274**	**0.0214**	**0.0064**
2	**0.0**	**0.30**	**0.072**	**0.0355**	**0.0336**	**0.0139**

The 'forward' Algorithm

At the end of the calculation,

$$P(\mathbf{X}) = \sum_{k \text{ in } |\mathbf{S}|} f_k(L)\, a_{kend}$$

= probability of the sequence being produced by the model

The ‘backward’ Algorithm

Given the sequence of symbols $\mathbf{X} = \{x_1, x_2, \ldots, x_L\}$, let $b_k(i)$ = the probability of having emitted the suffix $\{x_{i+1}, x_{i+2}, \ldots, x_L\}$ and reaching state k.

symbol index (i)

	0					L
0	$b_0(0)$					a_{0S}
						a_{1S}
state (k)						a_{2S}
						•
						•
S					$b_S(L\text{-}1)$	a_{SS}

The ‘backward’ Algorithm

Fill in the table backwards, using the recurrence relation

$$b_j(i) = \sum_{k \text{ in } |\mathbf{S}|} a_{jk}\; e_k(x_{i+1})\; b_k(i+1)$$

At the end

$$P(\mathbf{X}) = \sum_{k \text{ in } |\mathbf{S}|} a_{\text{start } k}\; e_k(x_1)\; b_k(1)$$

= probability of the sequence being produced by the model

Which way do I go?

For P(**X**), you can go forward or backward.

Sometimes, however, you want to know which state was the most likely to have produced any given symbol. To figure this out, we go both ways.

We want to know

$P(\pi_i = k \mid \mathbf{X})$ = the probability of state i being k given the sequence of symbols **X**

Matching a symbol with a state

We start by breaking $P(\mathbf{X}, \pi_i = k)$ into two parts,

$$P(\mathbf{X}, \pi_i = k) = \underbrace{P(x_1, \ldots x_i, \pi_i = k)}_{\text{front}} \; \underbrace{P(x_{i+1}, \ldots, x_L \mid \pi_i = k)}_{\text{back}}$$

$$= f_k(i) \cdot b_k(i)$$

$$P(\pi_i = k \mid \mathbf{X}) = \frac{P(\mathbf{X}, \pi_i = k)}{P(\mathbf{X})} = \frac{f_k(i) \; b_k(i)}{P(\mathbf{X})}$$

Underflow Problems Again

Once again we've got a potential underflow problem.

This time, however, we can't just convert to Logs.

$$f_j(i+1) = e_j(x_{i+1}) \sum_{j \text{ in } |\mathbf{S}|} f_k(i)\, a_{kj}$$

Instead we scale the values,

$$\tilde{f}_j(i) = \frac{f_j(i)}{\prod_{n=1}^{i} s_n}$$

Scaling

The iteration equations become

$$\tilde{f}_j(i+1) = \frac{1}{S_{i+1}} e_k(x_{i+1}) \sum_{j \text{ in } |\mathbf{S}|} \tilde{f}_k(i)\, a_{kj}$$

$$\tilde{b}_j(i+1) = \frac{1}{S_i} \sum_{j \text{ in } |\mathbf{S}|} a_{kj}\; \tilde{b}_k(i)\;\; e_k(x_{i+1})$$

How do we choose s_i?

Such that $\sum_j f_j(i) = 1$

so $\quad s_{i+1} = \sum_j e_j(x_{i+1}) \sum_k f_k(i)\, a_{kj}$

The ‘likelihood’ answer

So what does answering the ‘likelihood’ question give us?

It tells us how well our observed sequence fits our model.

When the HMM is trained on a set of homologous sequences, the likelihood is a measure of whether our new sequence belongs to this family of sequences.

So how do we train an HMM on a set of sequences?

The ‘learning’ question

How should the transition and emission probabilities be updated given new sequences of symbols?

We are given n sequences $\{\mathbf{X}^{(1)}, \mathbf{X}^{(2)}, \ldots, \mathbf{X}^{(n)}\}$ of lengths $L^{(1)}, L^{(2)}, \ldots, L^{(n)}$

which were generated from HMM $M(\boldsymbol{\Psi}, \mathbf{S}, \theta)$.

We want to assign values to θ that maximize the probabilities of our sequences given the model.

The ‘learning’ question

Since the sequences are assumed to have been generated independently,

$$P(\mathbf{X}^{(1)},\ldots,\mathbf{X}^{(n)} \mid \theta) = \prod_{i=1}^{n} P(\mathbf{X}^{(i)} \mid \theta)$$

We’re multiplying small numbers again…

$$\begin{aligned}\text{Score}\,(\mathbf{X}^{(1)},\ldots,\mathbf{X}^{(n)} \mid \theta) &= \text{Log } P(\mathbf{X}^{(1)},\ldots,\mathbf{X}^{(n)} \mid \theta) \\ &= \sum_{i=1}^{n} \text{Log } P(\mathbf{X}^{(i)} \mid \theta)\end{aligned}$$

Our goal is to find θ^* such that

$$\theta^* = \underset{\theta}{\text{argmax}} \{ \text{Score}\,(\mathbf{X}^{(1)},\ldots,\mathbf{X}^{(n)} \mid \theta) \}$$

Maximum Likelihood Estimators

Say we know the state sequences $\Pi^{(1)}, \ldots, \Pi^{(n)}$ for each sequence of symbols $\mathbf{X}^{(1)}, \ldots \mathbf{X}^{(n)}$.

We can simply count

A_{kj} = # of transitions from state k to state j

$E_k(b)$ = # of times symbol b was emitted from state k

Our Maximum Likelihood Estimators are then

$$a_{kj} = \frac{A_{kj}}{\sum_{q \text{ in } \mathbf{S}} A_{kq}} \qquad e_k(b) = \frac{E_k(b)}{\sum_{\sigma \text{ in } \Psi} E_k(\sigma)}$$

Maximum Likelihood Estimators

But there's a potential problem here…

$$a_{kj} = \frac{A_{kj}}{\sum_{q \text{ in } S} A_{kq}} \qquad e_k(b) = \frac{E_k(b)}{\sum_{\sigma \text{ in } \Psi} E_k(\sigma)}$$

possible zero denominators (especially when the number of sequences is small).

Laplace Correction

$$A'_{kj} = A_{kj} + r_{kj}$$
$$E'_k(b) = E_k(b) + r_k(b)$$

Where r_{kj} and $r_k(b) = 1$

(or contain a priori knowledge)

The Baum-Welch Algorithm

What if we don't know the state sequences?

In this case, finding the optimal parameter values (θ^*) is NP-complete

But we can use an iterative algorithm to get close…

Step 1: Assign initial values to θ

The Baum-Welch Algorithm

Step 2a: Compute the expected number of transitions from state k to state j

$$P(\pi_i=k, \pi_{i+1}=j \mid \mathbf{X}, \theta) = \frac{f_k(i)\ a_{kj}\ e_j(x_{i+1})\ b_j(i+1)}{P(X)}$$

so the expected value is

$$A_{kj} = \sum_{h=1}^{n} \left[\frac{1}{P(X^{(h)})} \sum_{i=1}^{L^{(h)}} f_k^{(h)}(i)\ a_{kj}\ e_j(x_{i+1}^{(h)})\ b_j^{(h)}(i+1) \right]$$

n = number of sequences in **X**
L = length of sequence $X^{(h)}$

The Baum-Welch Algorithm

Step 2b: Compute the expected number of emissions of symbol b from state k

$$E_k(b) = \sum_{h=1}^{n} \left[\frac{1}{P(X^{(h)})} \sum_{i \mid X_i^{(h)} = b} f_k^{(h)}(i)\ b_k^{(h)}(i) \right]$$

Step 3: Recalculate a_{kj} and $e_k(b)$ using the values of A_{kj} and $E_k(b)$ using the maximum likelihood estimators.

The Baum-Welch Algorithm

Step 4: Calculate

$$\text{Score}\,(\mathbf{X}^{(1)},\ldots,\mathbf{X}^{(n)} \mid \theta) = \sum_{i=1}^{n} \text{Log}\;P(\mathbf{X}^{(i)} \mid \theta)$$

If the improvement is less than some threshold *t*, then stop. Else, go back to step 2.

We're guaranteed to converge, since the function is monotonically increasing and the logs of probabilities are bounded by zero.

There's no guarantee, however, of finding the global maximum, so in general you repeat several times with different initial values of θ.

Choosing initial parameter values

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	-	A	A	G
C	T	-	A	T	G
C	T	-	A	A	G

How do I account for unobserved symbols?

Choosing initial parameter values

We can add a pseudocount

Laplace Correction $A'_{kj} = A_{kj} + r_{kj}$

Or we can assume there's a background probability for each symbol.

Where can we get these probabilities?

Substitution matrix

This implies that all columns of the alignment come from the same distribution.

G	T	G	A	A	G
G	T	C	A	A	G
G	C	C	T	T	G
G	T	-	A	A	G
C	T	-	A	T	G
C	T	-	A	A	G

A better method is to consider each column as having been generated from a distribution of symbols

Dirichlet mixtures

Brown, Hughey, Krogh, Mian, Sjolander, & Haussler (1993) "Using Dirichlet Mixture Priors to Derive Hidden Markov Models for Protein Families", ISMB93
http://citeseer.ist.psu.edu/brown93using.html

HMM architecture

How do we choose the state architecture in the first place?

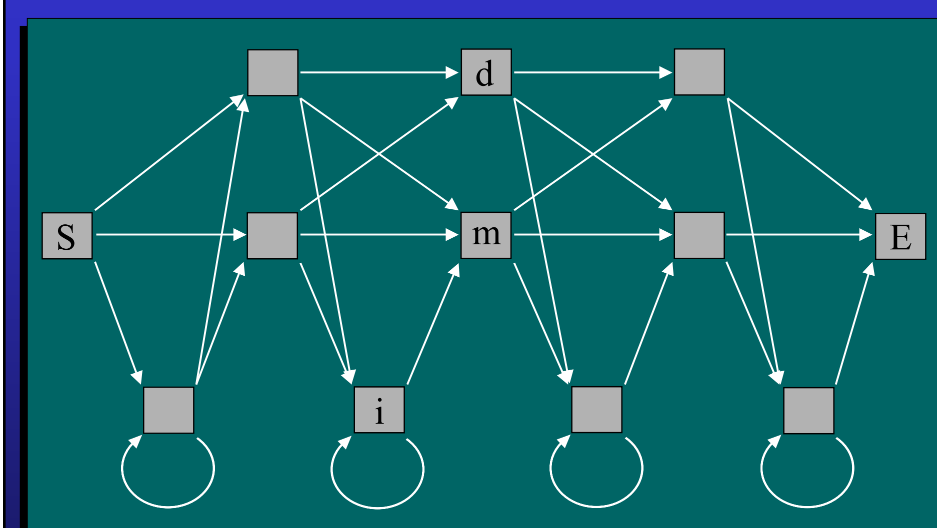
Use what's intuitive and what's worked

Algorithms to 'learn' the architecture exist

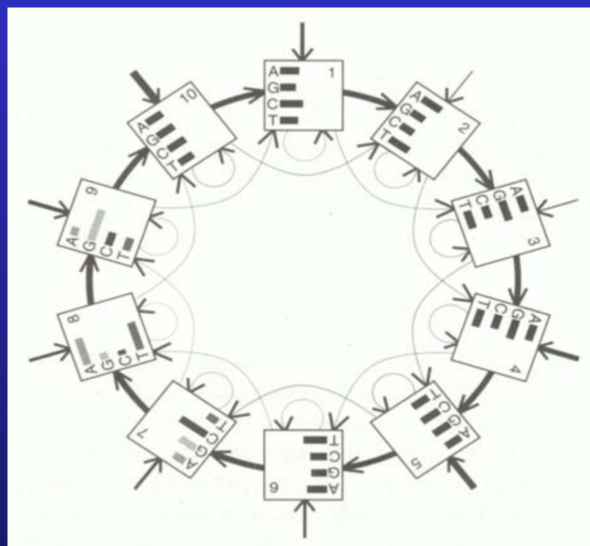
Slow

Unclear if they find an optimal structure

A typical bioinformatics HMM

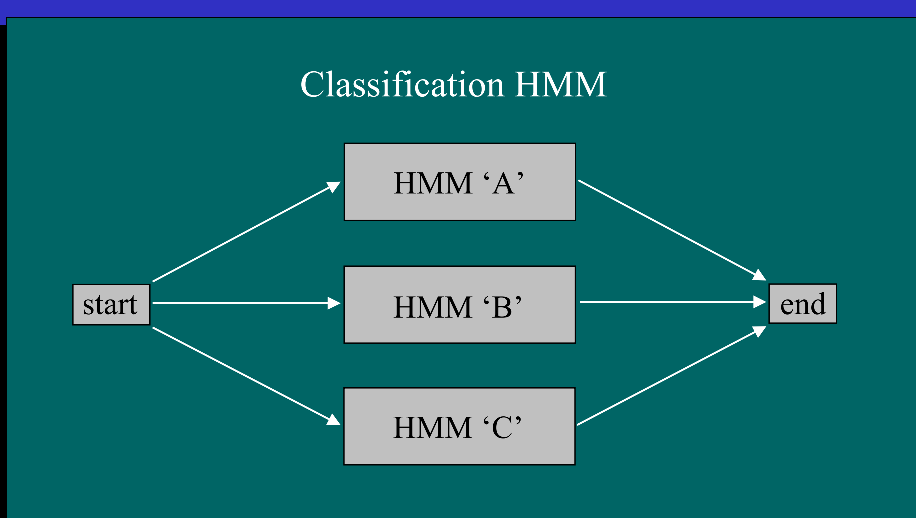


HMM architecture variants



Baldi & Brunak, Bioinformatics: The Machine Learning Approach, MIT Press, 1998

HMM architecture variants



HMMs in Bioinformatics

- Sequence classification
- Remote homology detection
- Multiple sequence alignment
- General pattern recognition

Benefits & Limitations

What are the benefits to using HMMs?

- Solid basis in probability theory
- Relatively fast algorithms
- Multiple uses
- Can be made modular

What are the limitations when using HMMs?

- Need examples to train the model
- First order approximation may miss long-range interactions

Some HMM Packages

HMMR & Pfam - Sean Eddy (Sanger Centre)

HMMR is an HMM package
Pfam is a curated database of HMMs trained on protein domains

SAM - David Haussler (U.C. Santa Cruz)

SAM = Sequence Alignment and Modelling System

HMMpro - Baldi & Chauvin (NetID, Inc.)

Takeaway

- Basic Probability Theory
- Markov Chains
- Hidden Markov Models
- 3 basic questions of HMMs
  - Decoding - Viterbi
  - Likelihood - forward & backward
  - Learning - Baum-Welch
- Uses, costs & benefits of using HMMs

Some HMM References

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