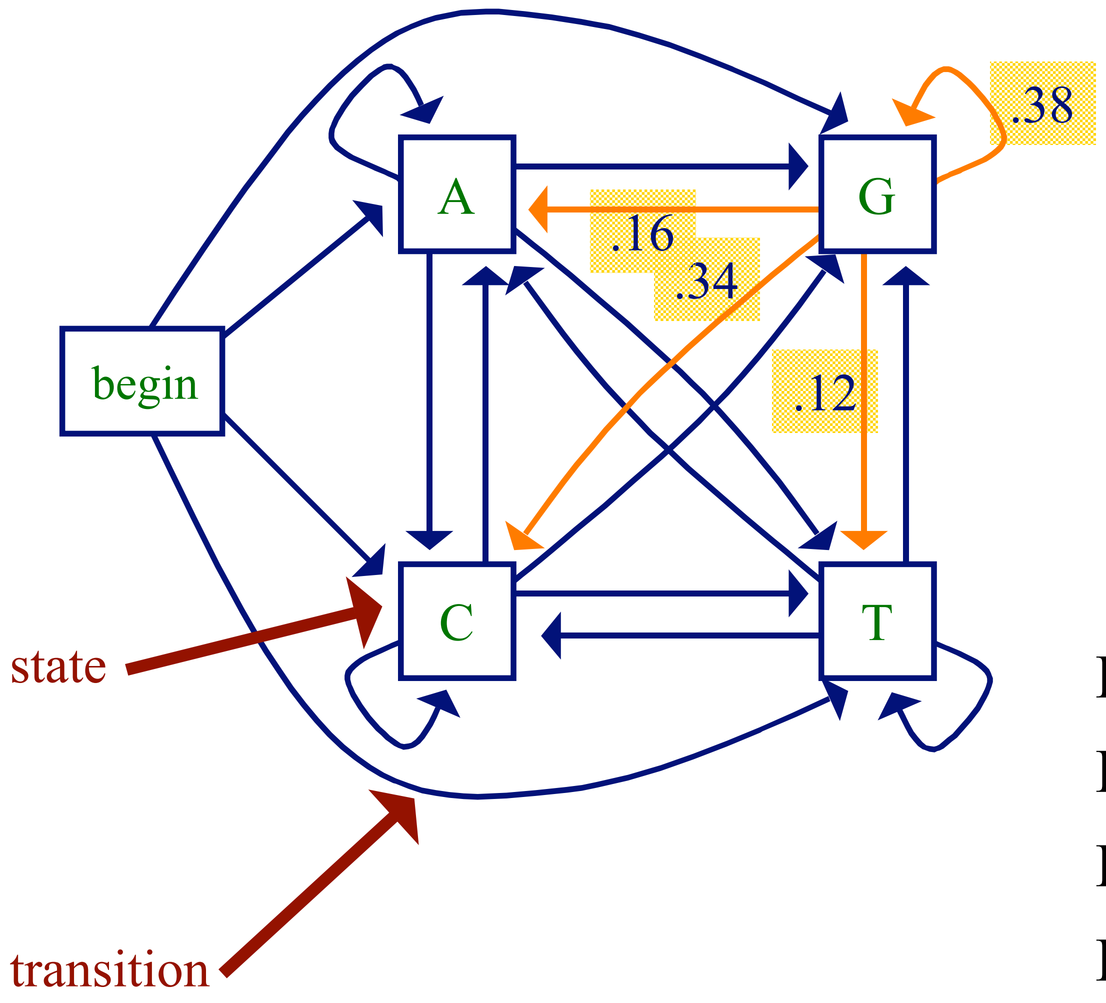
Markov Chain Models

(Slides courtesy of Dr. Mark Craven)

Motivation for Markov Models in Computational Biology

- there are many cases in which we would like to represent the statistical regularities of some class of sequences
  - genes
  - various regulatory sites in DNA (e.g. where RNA polymerase and transcription factors bind)
  - proteins in a given family
- Markov models are well suited to this type of task

A Markov Chain Model



transition probabilities

$$\Pr(x_i = a \mid x_{i-1} = g) = 0.16$$

$$\Pr(x_i = c \mid x_{i-1} = g) = 0.34$$

$$\Pr(x_i = g \mid x_{i-1} = g) = 0.38$$

$$\Pr(x_i = t \mid x_{i-1} = g) = 0.12$$

Markov Chain Models

- a Markov chain model is defined by
  - a set of states
    - some states *emit* symbols
    - other states (e.g. the *begin* state) are *silent*
  - a set of transitions with associated probabilities
    - the transitions emanating from a given state define a distribution over the possible next states

Markov Chain Models

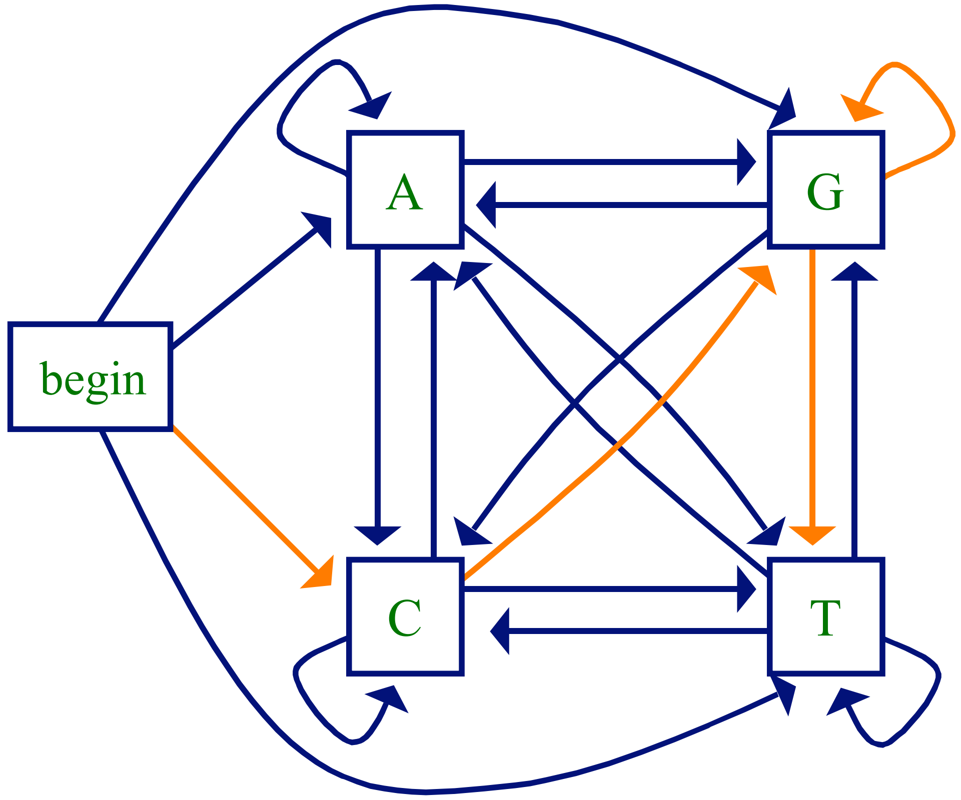
- given some sequence *x* of length *L*, we can ask how probable the sequence is given our model
- for any probabilistic model of sequences, we can write this probability as

$$\Pr(x) = \Pr(x_L, x_{L-1}, \ldots, x_1)$$
$$= \Pr(x_L | x_{L-1}, \ldots, x_1) \Pr(x_{L-1} | x_{L-2}, \ldots, x_1) \ldots \Pr(x_1)$$

- key property of a (1st order) Markov chain: the probability of each x_i depends only on the value of x_{i-1}

$$\Pr(x) = \Pr(x_L | x_{L-1}) \Pr(x_{L-1} | x_{L-2}) \ldots \Pr(x_2 | x_1) \Pr(x_1)$$
$$= \Pr(x_1) \prod_{i=2}^{L} \Pr(x_i | x_{i-1})$$

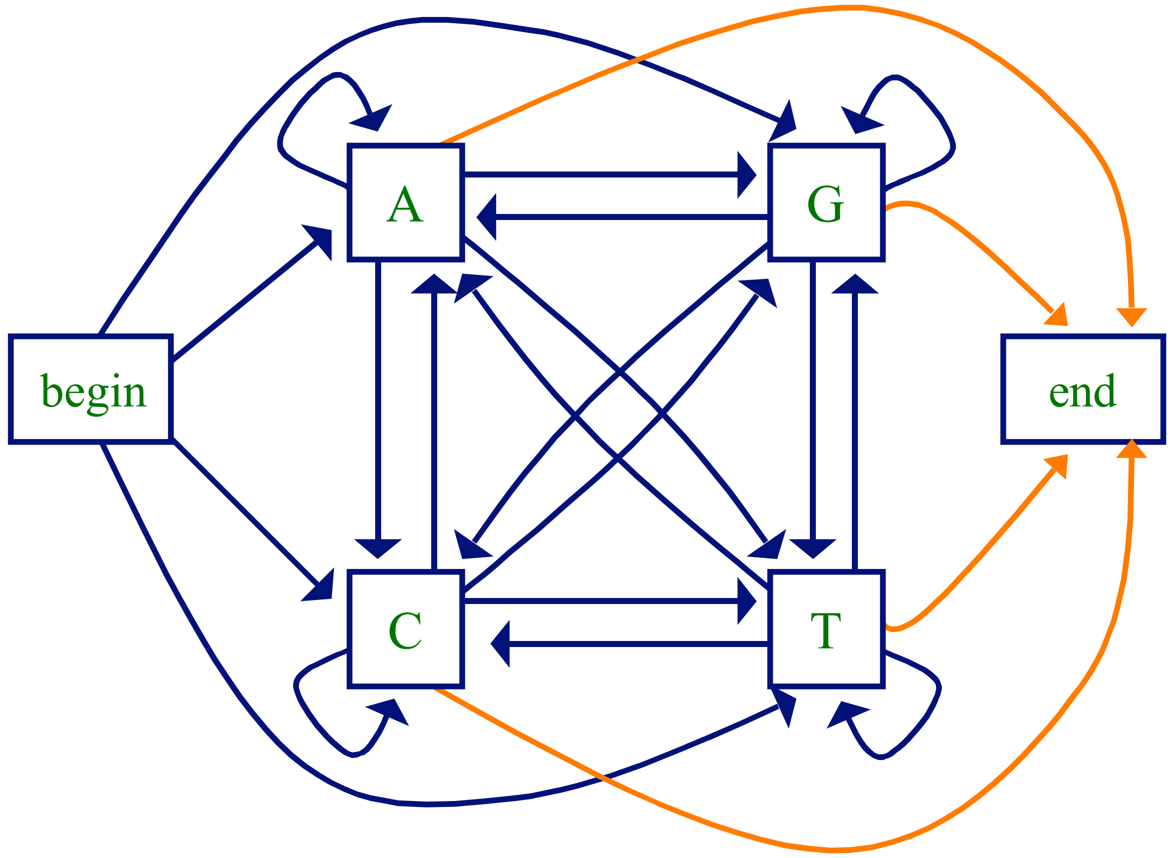
The Probability of a Sequence for a Given Markov Chain Model



$$\Pr(cggt) = \Pr(c)\Pr(g \mid c)\Pr(g \mid g)\Pr(t \mid g)$$

Markov Chain Models

- can also have an *end* state; allows the model to represent
  - a distribution over sequences of different lengths
  - preferences for ending sequences with certain symbols



Markov Chain Notation

- the transition parameters can be denoted by $a_{x_{i-1}x_i}$ where

$$a_{x_{i-1}x_i} = \Pr(x_i \mid x_{i-1})$$

- similarly we can denote the probability of a sequence *x* as

$$a_{\mathrm{B}x_1} \prod_{i=2}^{L} a_{x_{i-1}x_i} = \Pr(x_1) \prod_{i=2}^{L} \Pr(x_i \mid x_{i-1})$$

where $a_{\mathrm{B}x_1}$ represents the transition from the *begin* state

Example Application

- CpG islands
  - CG dinucleotides are rarer in eukaryotic genomes than expected given the marginal probabilities of C and G
  - but the regions upstream of genes are richer in CG dinucleotides than elsewhere – *CpG islands*
  - useful evidence for finding genes
- could predict CpG islands with Markov chains
  - one to represent CpG islands
  - one to represent the rest of the genome

Estimating the Model Parameters

- given some data (e.g. a set of sequences from CpG islands), how can we determine the probability parameters of our model?
- one approach: *maximum likelihood estimation*
  - given a set of data D
  - set the parameters θ to maximize

$$\Pr(D \mid \theta)$$

  - i.e. make the data D look likely under the model

Maximum Likelihood Estimation

- suppose we want to estimate the parameters Pr(a), Pr(c), Pr(g), Pr(t)
- and we're given the sequences

  accgcgctta

  gcttagtgac

  tagccgttac
- then the maximum likelihood estimates are

$$\Pr(a) = \frac{6}{30} = 0.2 \qquad \Pr(g) = \frac{7}{30} = 0.233$$

$$\Pr(c) = \frac{9}{30} = 0.3 \qquad \Pr(t) = \frac{8}{30} = 0.267$$

Maximum Likelihood Estimation

- suppose instead we saw the following sequences

  gccgcgcttg

  gcttggtggc

  tggccgttgc

- then the maximum likelihood estimates are

$$\Pr(a) = \frac{0}{30} = 0 \qquad \Pr(g) = \frac{13}{30} = 0.433$$

$$\Pr(c) = \frac{9}{30} = 0.3 \qquad \Pr(t) = \frac{8}{30} = 0.267$$

do we really want to set this to 0?

A Bayesian Approach

- instead of estimating parameters strictly from the data, we could start with some prior belief for each
- for example, we could use *Laplace estimates*

$$\Pr(a) = \frac{n_a + 1}{\sum_i (n_i + 1)}$$

pseudocount

- where n_i represents the number of occurrences of character *i*

- using Laplace estimates with the sequences

gccgcgcttg

gcttggtggc

tggccgttgc

$$\Pr(a) = \frac{0 + 1}{34}$$

$$\Pr(c) = \frac{9 + 1}{34}$$

A Bayesian Approach

- a more general form: *m-estimates*

$$\Pr(a) = \frac{n_a + p_a m}{\left(\sum_i n_i\right) + m}$$

prior probability of *a*

number of "virtual" instances

- with m=8 and uniform priors

gccgcgcttg

gcttggtggc

tggccgttgc

$$\Pr(c) = \frac{9 + 0.25 \times 8}{30 + 8} = \frac{11}{38}$$

Estimation for 1st Order Probabilities

- to estimate a 1st order parameter, such as Pr(*c*|*g*), we count the number of times that *g* follows the history *c* in our given sequences

- using Laplace estimates with the sequences

gccgcgcttg

gcttggtggc

tggccgttgc

$$\Pr(a \mid g) = \frac{0+1}{12+4} \qquad \Pr(a \mid c) = \frac{0+1}{7+4}$$

$$\vdots$$

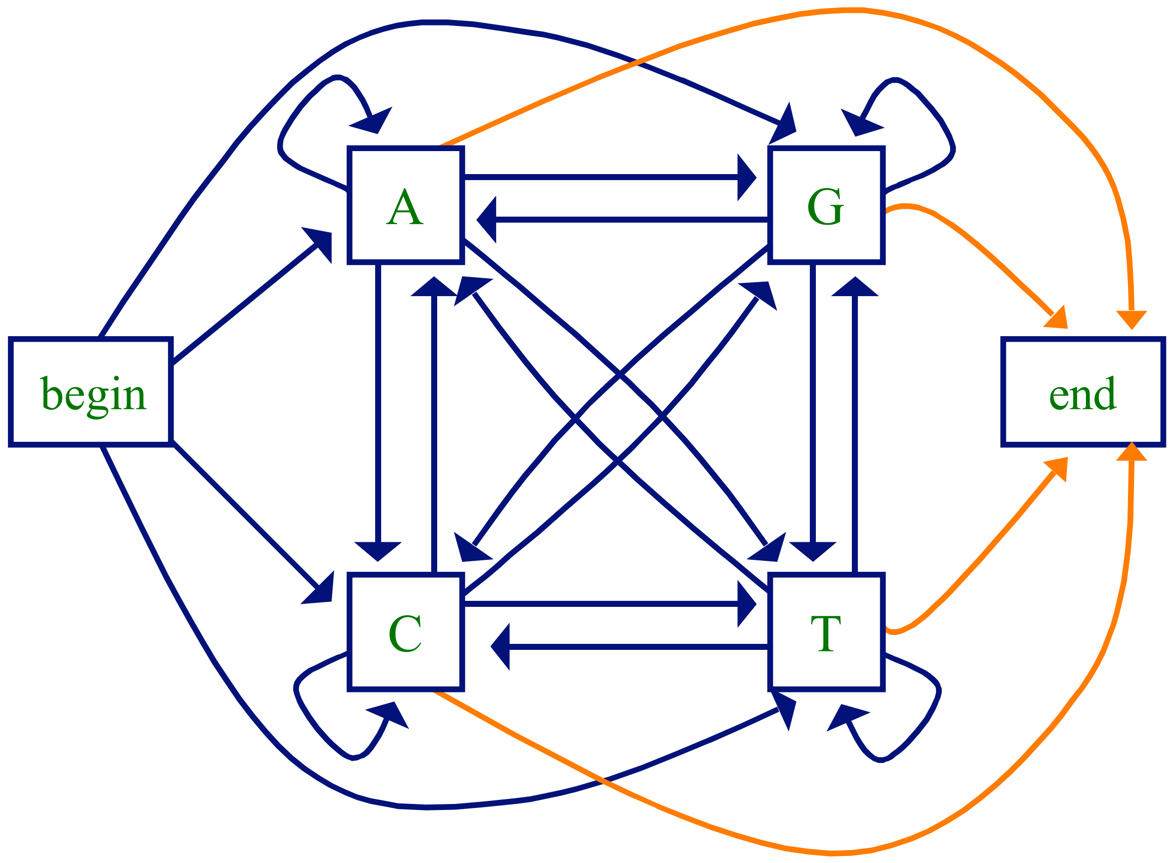
$$\Pr(c \mid g) = \frac{7+1}{12+4}$$

$$\Pr(g \mid g) = \frac{3+1}{12+4}$$

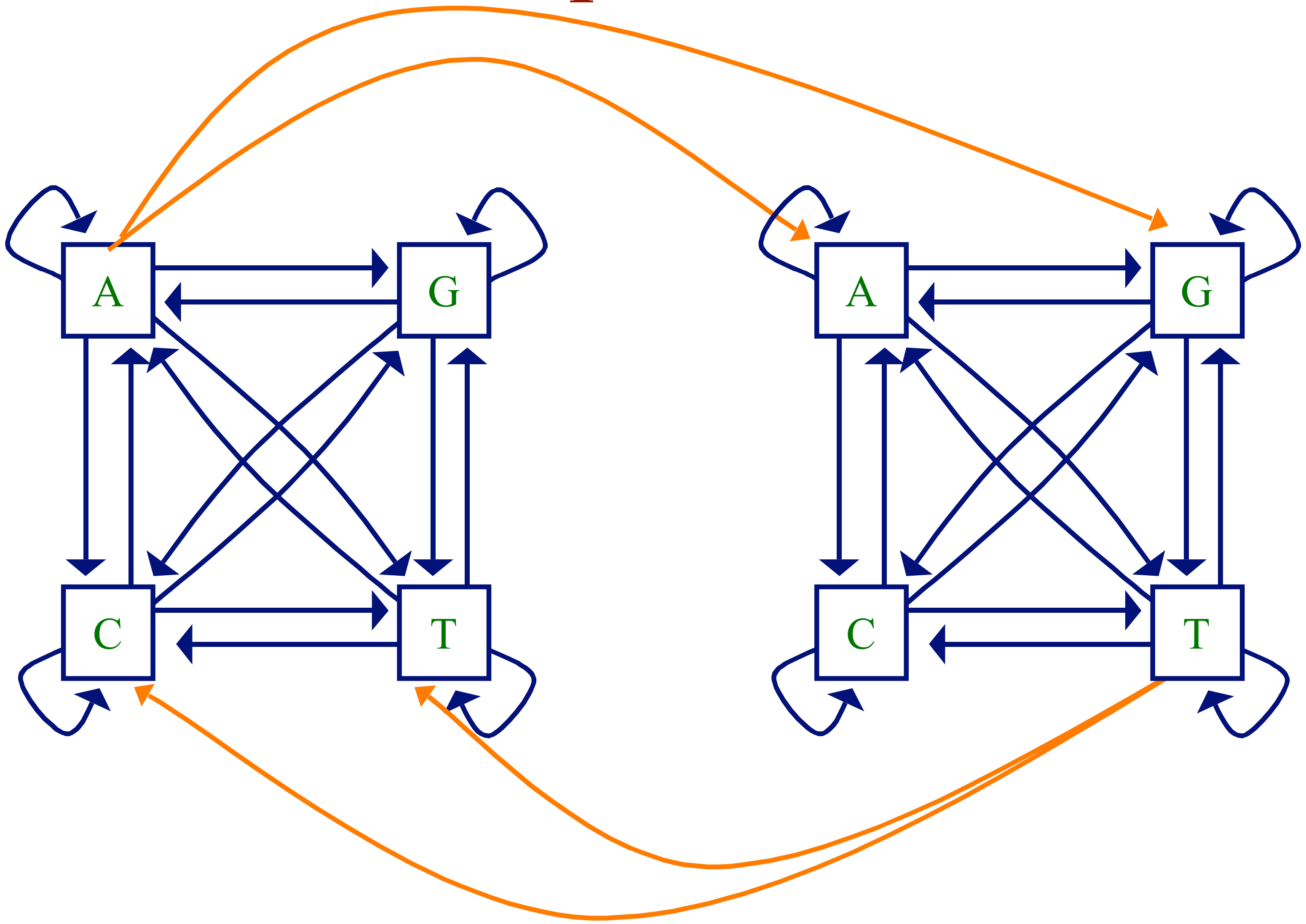
$$\Pr(t \mid g) = \frac{2+1}{12+4}$$

Markov Chain Models

- can also have an *end* state; allows the model to represent
  - a distribution over sequences of different lengths
  - preferences for ending sequences with certain symbols



A Simple HMM



- given say a *T* in our input sequence, which state emitted it?

Hidden State

- we'll distinguish between the *observed* parts of a problem and the *hidden* parts
- in the Markov models we've considered previously, it is clear which state accounts for each part of the observed sequence
- in the model above, there are multiple states that could account for each part of the observed sequence
  - this is the hidden part of the problem

The Parameters of an HMM

- as in Markov chain models, we have transition probabilities

$$a_{kl} = \Pr(\pi_i = l \mid \pi_{i-1} = k)$$

probability of a transition from state *k* to *l*

π represents a path (sequence of states) through the model

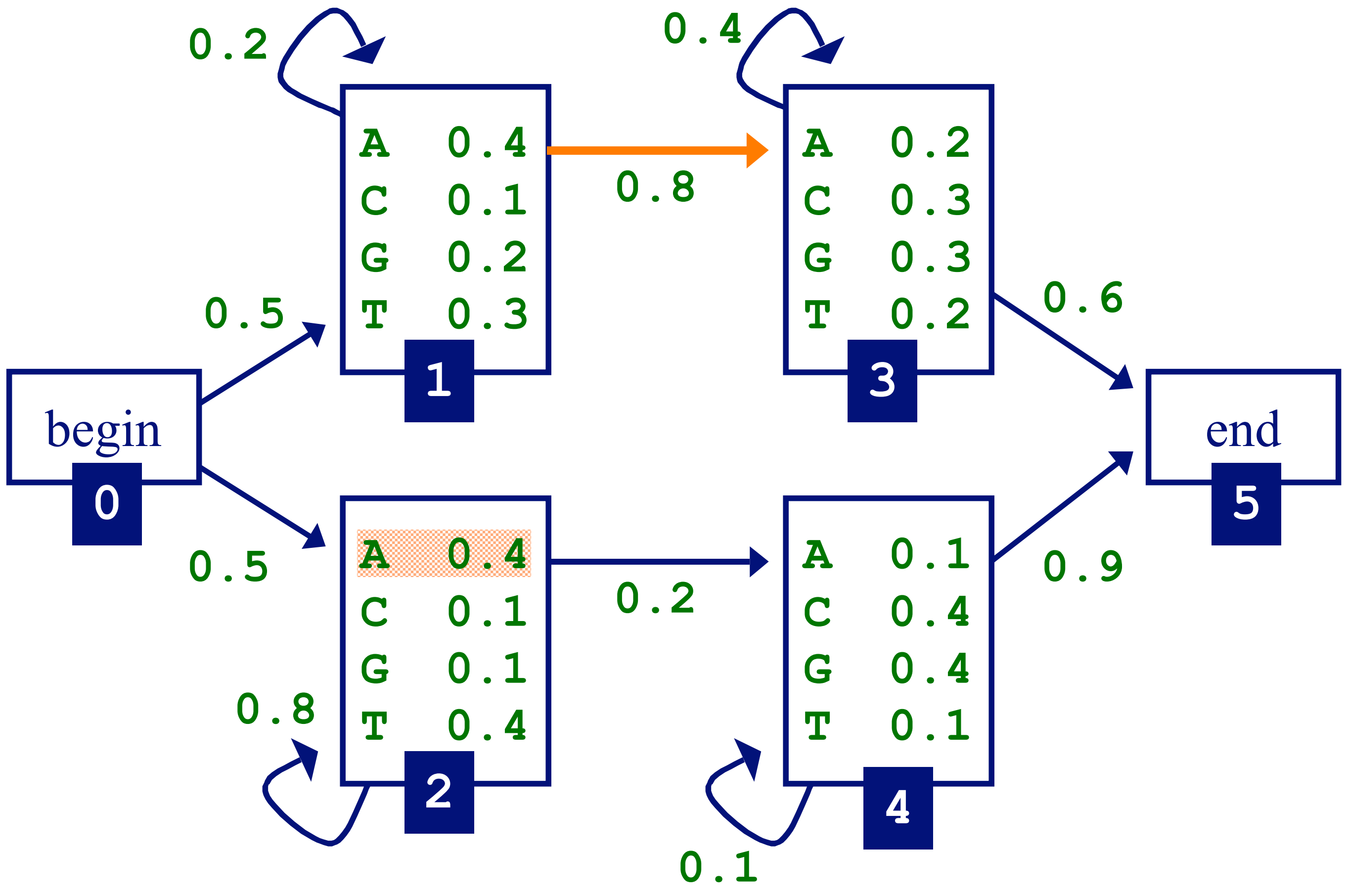
- since we've decoupled states and characters, we might also have emission probabilities

$$e_k(b) = \Pr(x_i = b \mid \pi_i = k)$$

probability of emitting character b in state *k*

A Simple HMM

a_{13}	probability of a transition from state 1 to state 3
$e_2(A)$	probability of emitting character *A* in state 2



Three Important Questions

- How likely is a given sequence?

  the Forward algorithm

- What is the most probable “path” for generating a given sequence?

  the Viterbi algorithm

- How can we learn the HMM parameters given a set of sequences?

  the Forward-Backward (Baum-Welch) algorithm

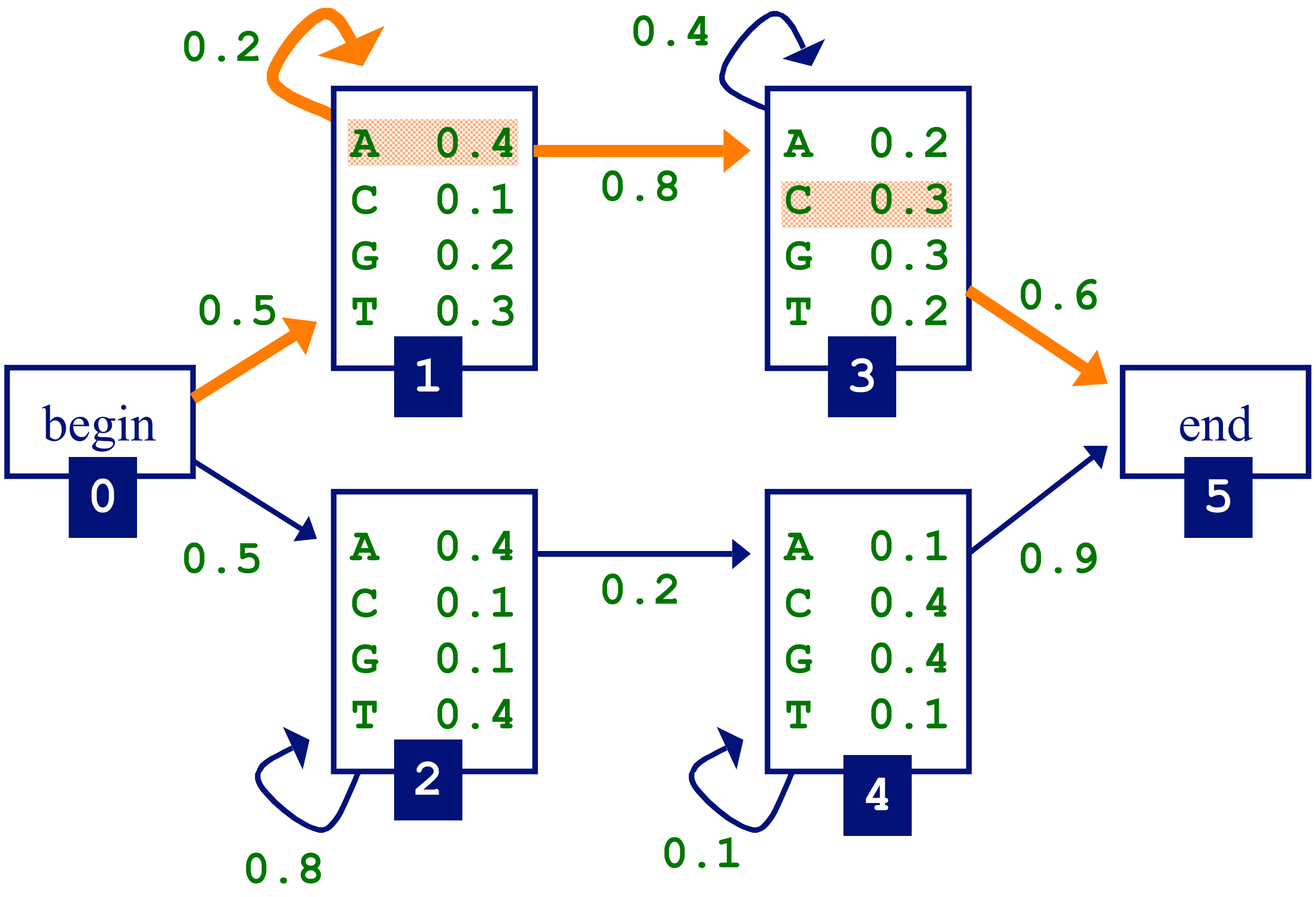
How Likely is a Given Sequence?

- the probability that the path $\pi_0 \ldots \pi_N$ is taken and the sequence is generated: $x_1 \ldots x_L$

$$\Pr(x_1 \ldots x_L, \pi_0 \ldots \pi_N) = a_{0\pi_1} \prod_{i=1}^{L} e_{\pi_i}(x_i) a_{\pi_i \pi_{i+1}}$$

(assuming begin/end are the only silent states on path)

How Likely Is A Given Sequence?



$$\Pr(\mathrm{AAC},\pi\ ) = a_{01} \times e_1(\mathrm{A}) \times a_{11} \times e_1(\mathrm{A}) \times a_{13} \times e_3(\mathrm{C}) \times a_{35}$$

$$= 0.5 \times 0.4 \times 0.2 \times 0.4 \times 0.8 \times 0.3 \times 0.6$$

How Likely is a Given Sequence?

- the probability over *all* paths is:

$$\Pr(x_1 \ldots x_L) = \sum_{\pi} \Pr(x_1 \ldots x_L, \underbrace{\pi_0 \ldots \pi_N}_{\pi})$$

- but the number of paths can be exponential in the length of the sequence...
- the Forward algorithm enables us to compute this efficiently

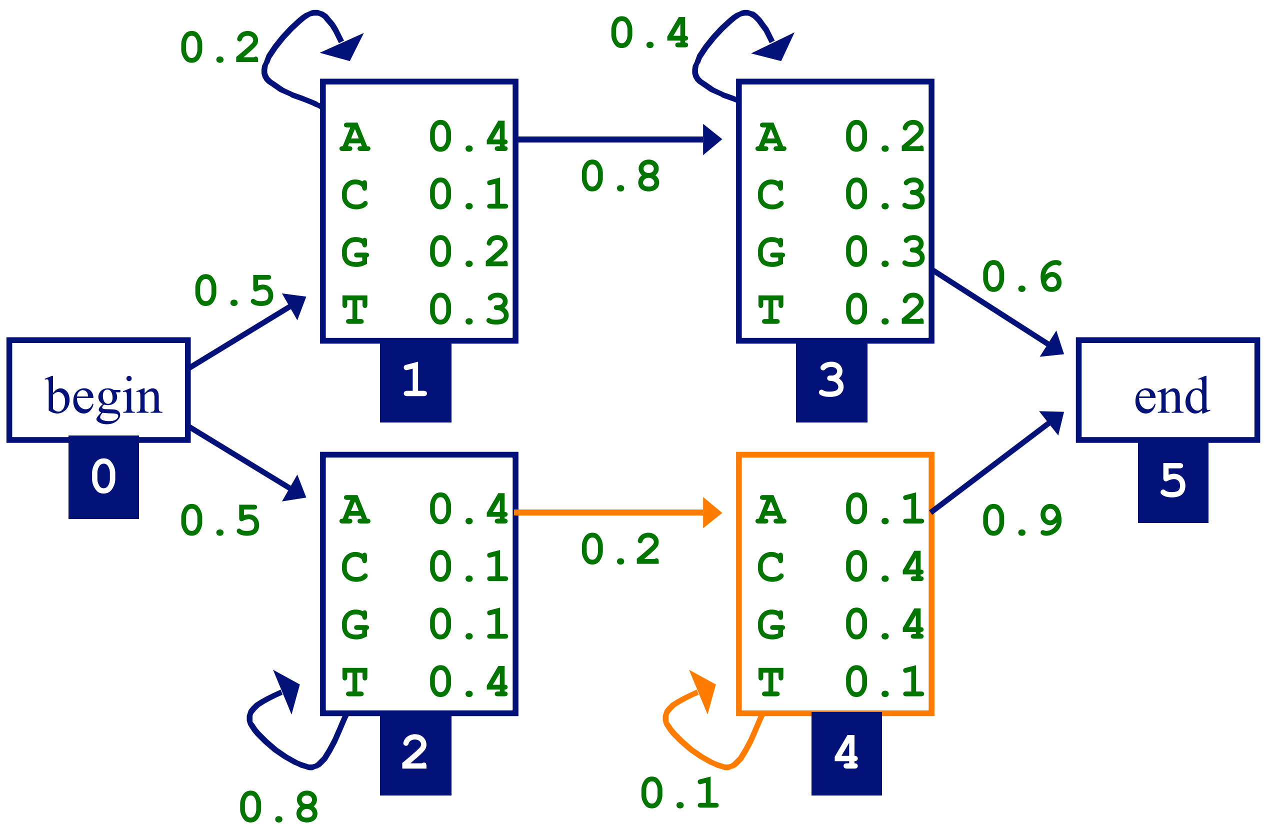
How Likely is a Given Sequence: The Forward Algorithm

- define $f_k(i)$ to be the probability of being in state *k* having observed the first *i* characters of *x*

- we want to compute $f_N(L)$, the probability of being in the end state having observed all of *x*
- can define this recursively

The Forward Algorithm

- because of the Markov property, don’t have to explicitly enumerate every path – use dynamic programming instead



- e.g. compute $f_4(i)$ using $f_2(i-1),\ f_4(i-1)$

The Forward Algorithm

- initialization:

$$f_0(0) = 1$$

probability that we're in start state and have observed 0 characters from the sequence

$$f_k(0) = 0, \quad \text{for } k \text{ that are not silent states}$$

The Forward Algorithm

- recursion for emitting states (i =1…L):

$$f_l(i) = e_l(i)\sum_k f_k(i-1)a_{kl}$$

- recursion for silent states:

$$f_l(i) = \sum_k f_k(i)a_{kl}$$

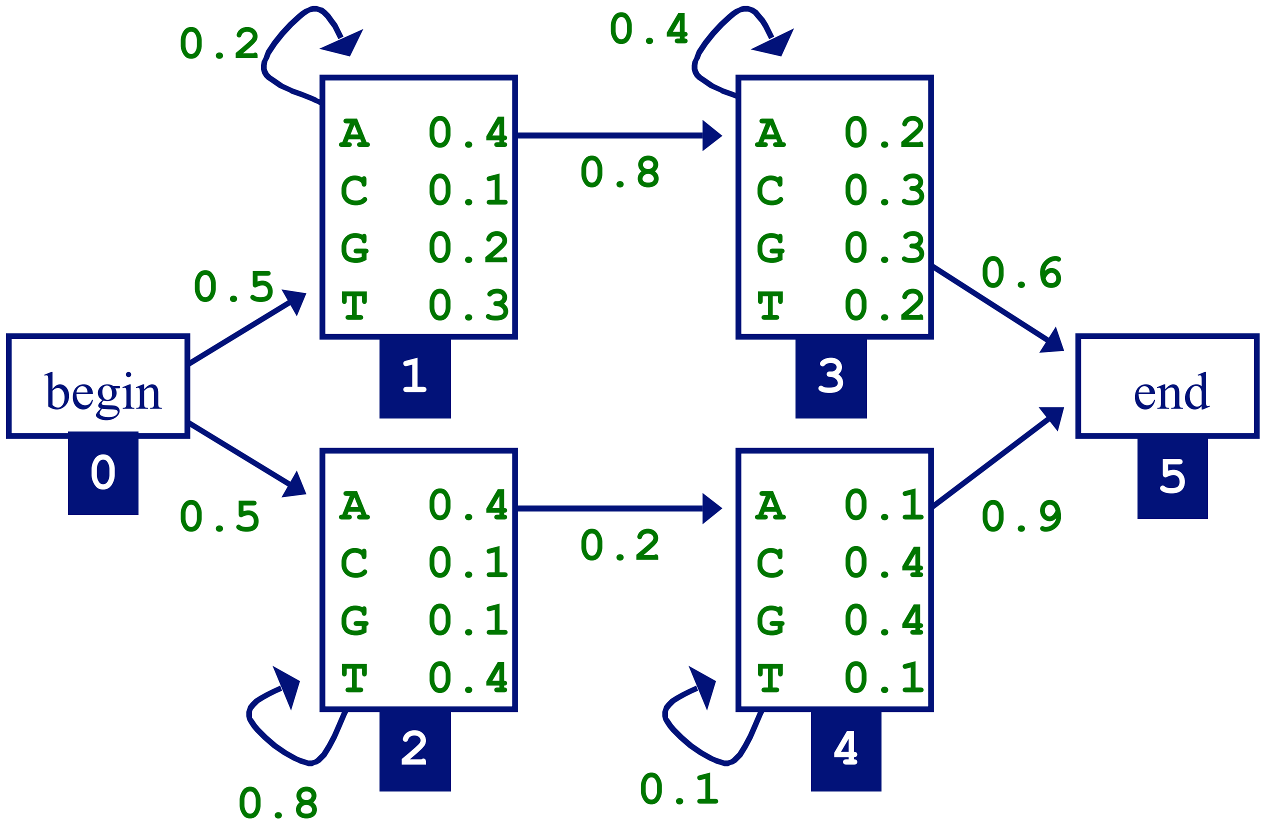
The Forward Algorithm

- termination:

$$\Pr(x) = \Pr(x_1 \ldots x_L) = f_N(L) = \sum_k f_k(L) a_{kN}$$

probability that we're in the end state and have observed the entire sequence

Forward Algorithm Example



- given the sequence x = **TAGA**

Forward Algorithm Example

- given the sequence x = TAGA
- initialization

$$f_0(0) = 1 \qquad f_1(0) = 0 \ \ldots \ f_5(0) = 0$$

- computing other values

$$f_1(1) = e_1(T) \times (f_0(0) \times a_{01} + f_1(0) a_{11}) =$$
$$0.3 \times \left(1 \times 0.5 + 0 \times 0.2\right) = 0.15$$

$$f_2(1) = 0.4 \times \left(1 \times 0.5 + 0 \times 0.8\right)$$

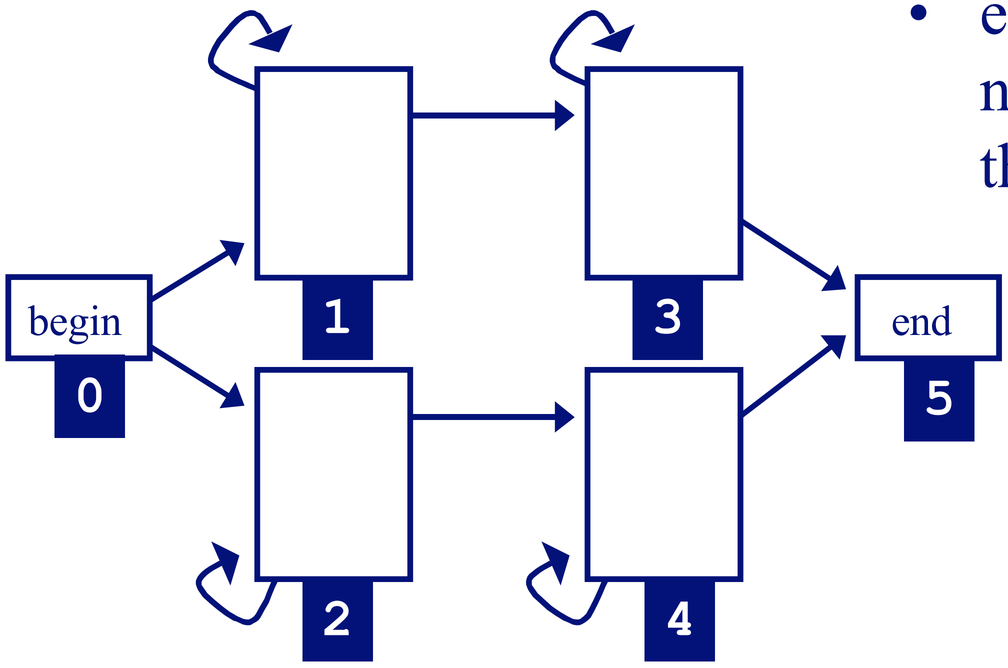
$$f_1(2) = e_1(A) \times (f_0(1) \times a_{01} + f_1(1) a_{11}) =$$
$$0.4 \times \left(0 \times 0.5 + 0.15 \times 0.2\right)$$

$$\bullet\bullet\bullet$$

$$\Pr(TAGA) = f_5(4) = (f_3(4) \times a_{35} + f_4(4) a_{45})$$

Forward Algorithm Note

- in some cases, we can make the algorithm more efficient by taking into account the minimum number of steps that must be taken to reach a state



- e.g. for this HMM, we don't need to initialize or compute the values

$$f_3(0),\ f_4(0),$$
$$f_5(0),\ f_5(1)$$

Three Important Questions

- How likely is a given sequence?
- What is the most probable "path" for generating a given sequence?
- How can we learn the HMM parameters given a set of sequences?

Finding the Most Probable Path: The Viterbi Algorithm

- define $v_k(i)$ to be the probability of the most probable path accounting for the first *i* characters of *x* and ending in state *k*

- we want to compute $v_N(L)$, the probability of the most probable path accounting for all of the sequence and ending in the end state
- can define recursively
- can use DP to find $v_N(L)$ efficiently

Finding the Most Probable Path: The Viterbi Algorithm

- initialization:

$$v_0(0) = 1$$

$$v_k(0) = 0, \quad \text{for } k \text{ that are not silent states}$$

The Viterbi Algorithm

- recursion for emitting states (i =1…L):

$$v_l(i) = e_l(x_i) \max_k \left[v_k(i-1) a_{kl} \right]$$

$$\mathrm{ptr}_l(i) = \arg\max_k \left[v_k(i-1) a_{kl} \right]$$

keep track of most probable path

- recursion for silent states:

$$v_l(i) = \max_k \left[v_k(i) a_{kl} \right]$$

$$\mathrm{ptr}_l(i) = \arg\max_k \left[v_k(i) a_{kl} \right]$$

The Viterbi Algorithm

- termination:

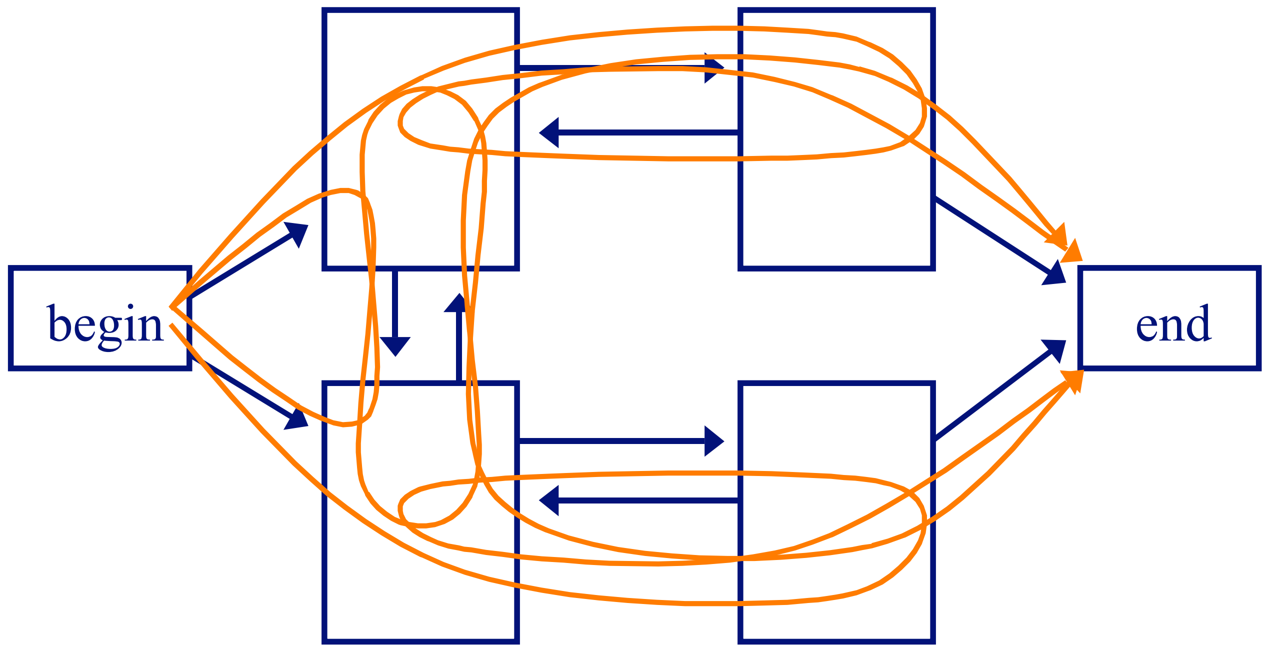
$$\Pr(x,\pi) = \max_k \left(v_k(L)a_{kN}\right)$$

$$\pi_{\mathrm{L}} = \arg\max_k \left(v_k(L)a_{kN}\right)$$

- traceback: follow pointers back starting at π_{L}

Forward & Viterbi Algorithms

- Forward/Viterbi algorithms effectively consider all possible paths for a sequence
  - Forward to find probability of a sequence
  - Viterbi to find most probable path
- consider a sequence of length 4…



Three Important Questions

- How likely is a given sequence?
- What is the most probable "path" for generating a given sequence?
- How can we learn the HMM parameters given a set of sequences?

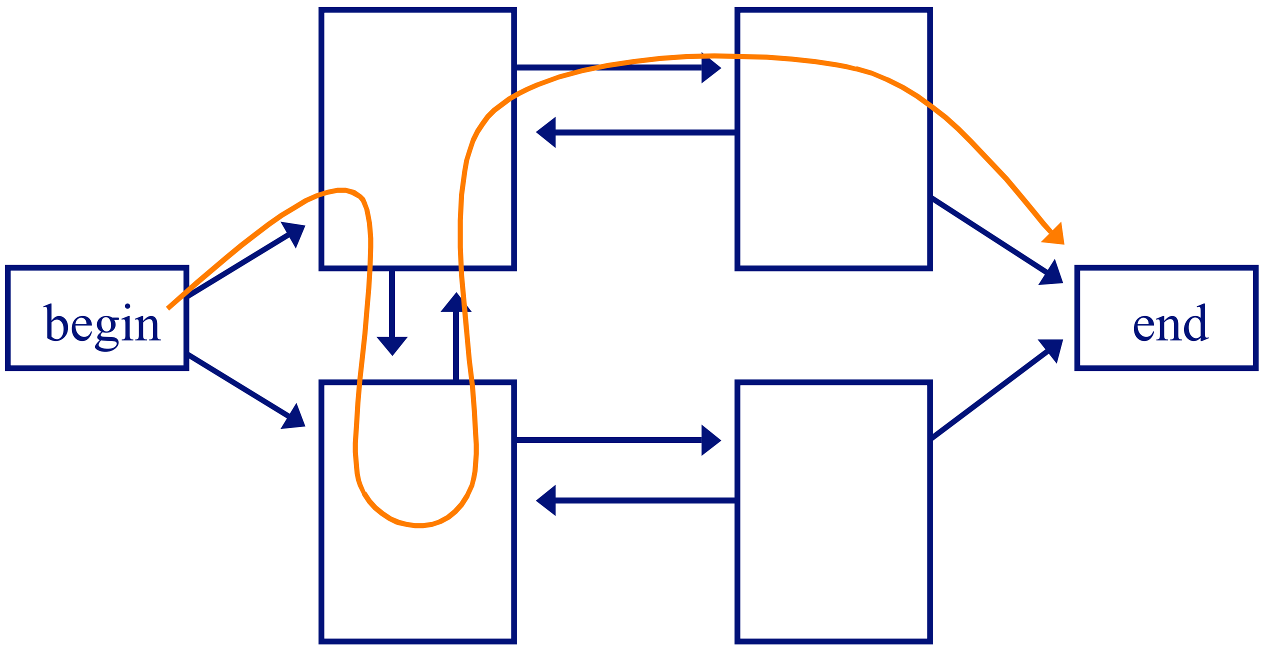
Learning Parameters

- if we know the state path for each training sequence, learning the model parameters is simple
  - no hidden state during training
  - count how often each parameter is used
  - normalize/smooth to get probabilities
  - process is just like it was for Markov chain models

- if we don’t know the path for each training sequence, how can we determine the counts?
  - key insight: estimate the counts by considering every path weighted by its probability

Learning without Hidden State

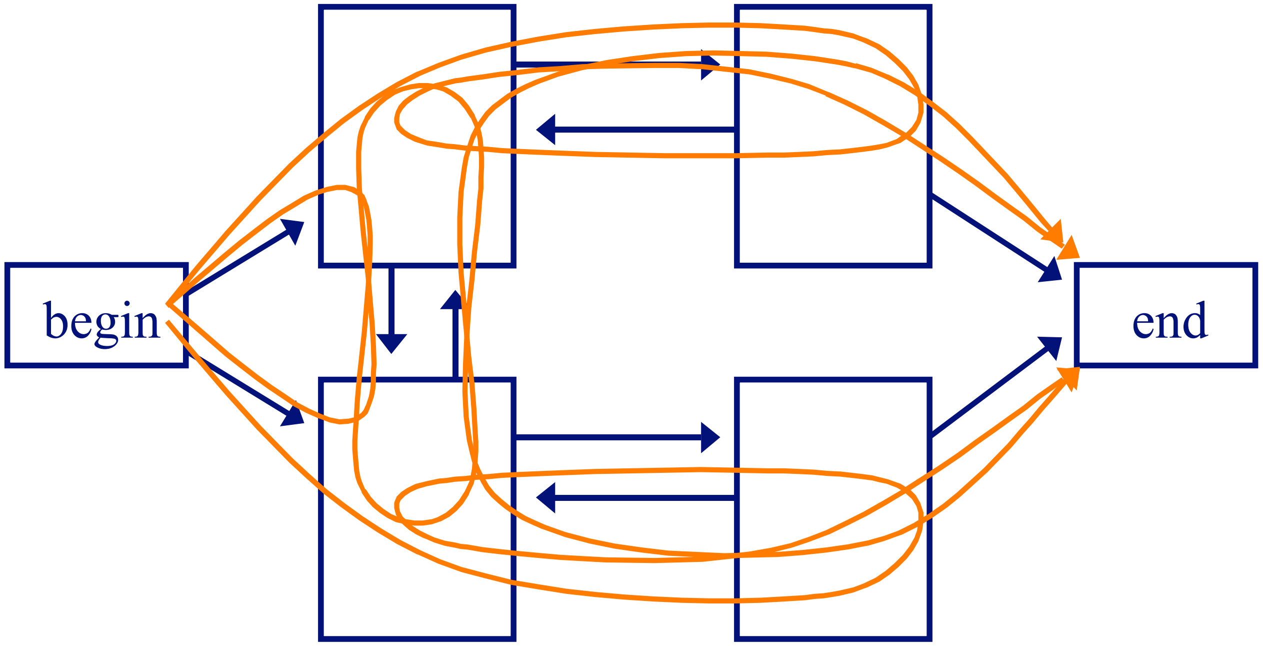
- learning is simple if we know the correct path for each sequence in our training set



- estimate parameters by counting the number of times each parameter is used across the training set

Learning with Hidden State

- if we don't know the correct path for each sequence in our training set, consider all possible paths for the sequence



- estimate parameters through a procedure that counts the <u>expected</u> number of times each parameter is used across the training set

Learning Parameters: The Baum-Welch Algorithm

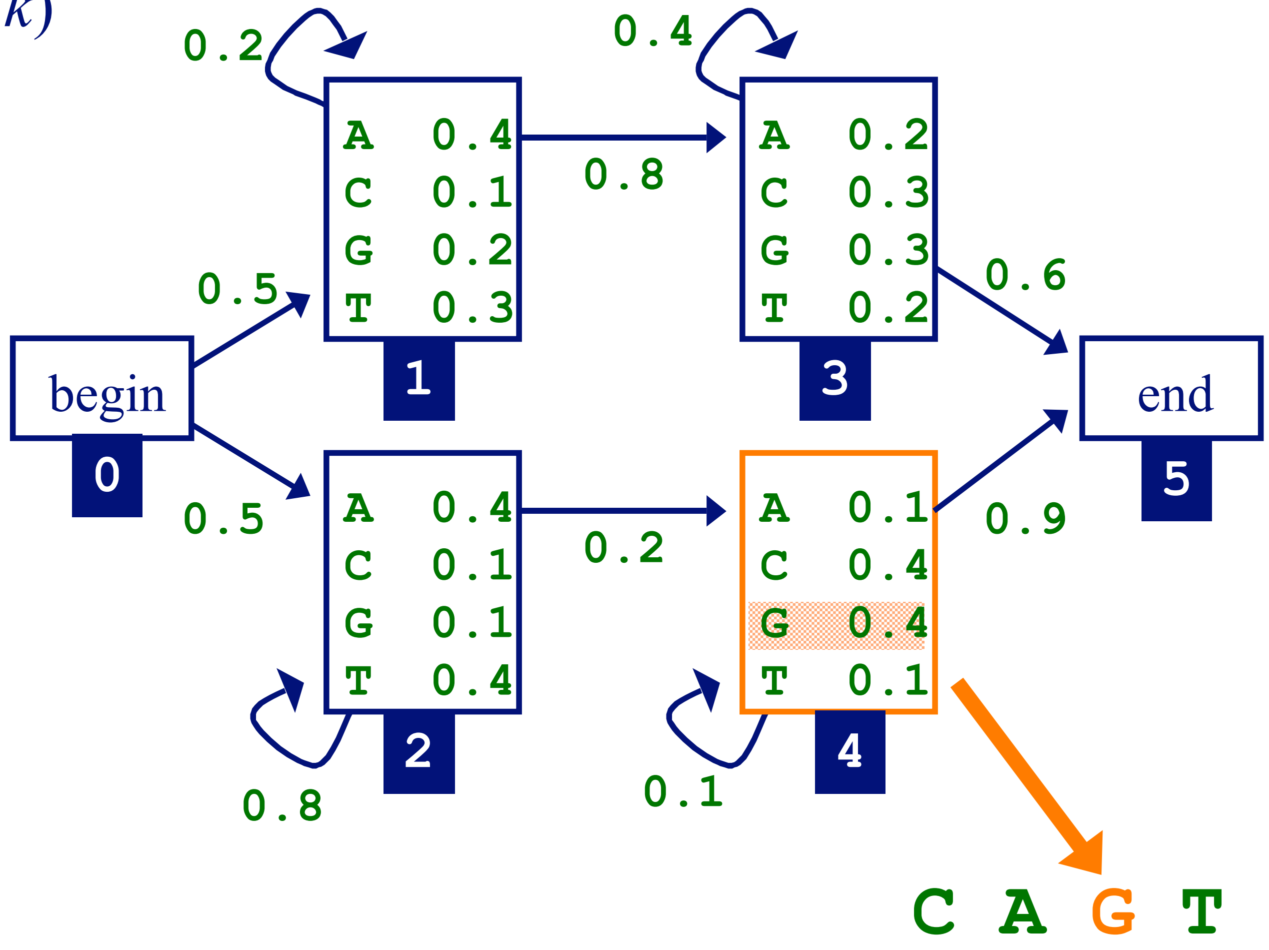
- *a.k.a* the Forward-Backward algorithm
- an *Expectation Maximization* (EM) algorithm
  - EM is a family of algorithms for learning probabilistic models in problems that involve hidden state
- in this context, the hidden state is the path that best explains each training sequence

Learning Parameters: The Baum-Welch Algorithm

- algorithm sketch:
  - initialize parameters of model
  - iterate until convergence
    - calculate the *expected* number of times each transition or emission is used
    - adjust the parameters to *maximize* the likelihood of these expected values

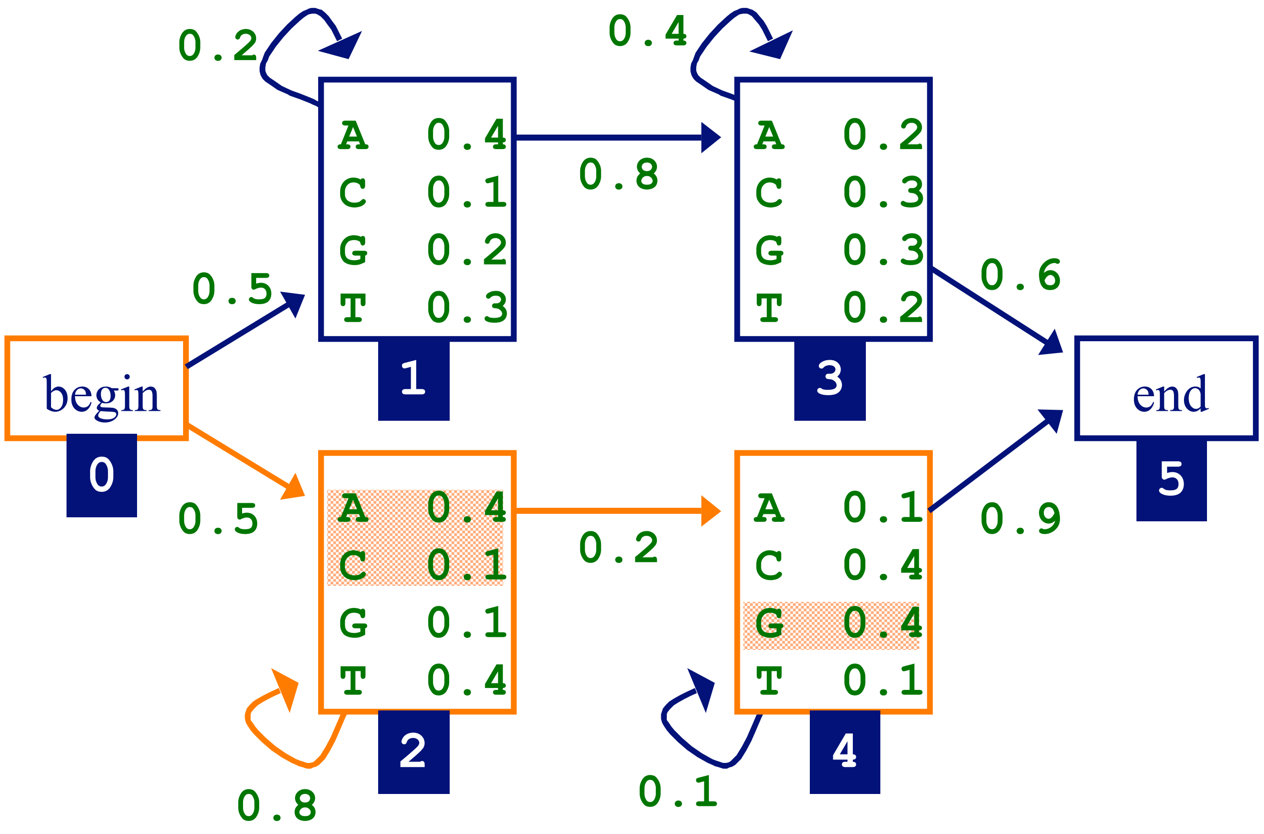
The Expectation Step

- we want to know the probability of producing sequence *x* with the *i* th symbol being produced by state *k* (for all *x*, *i* and *k*)



The Expectation Step

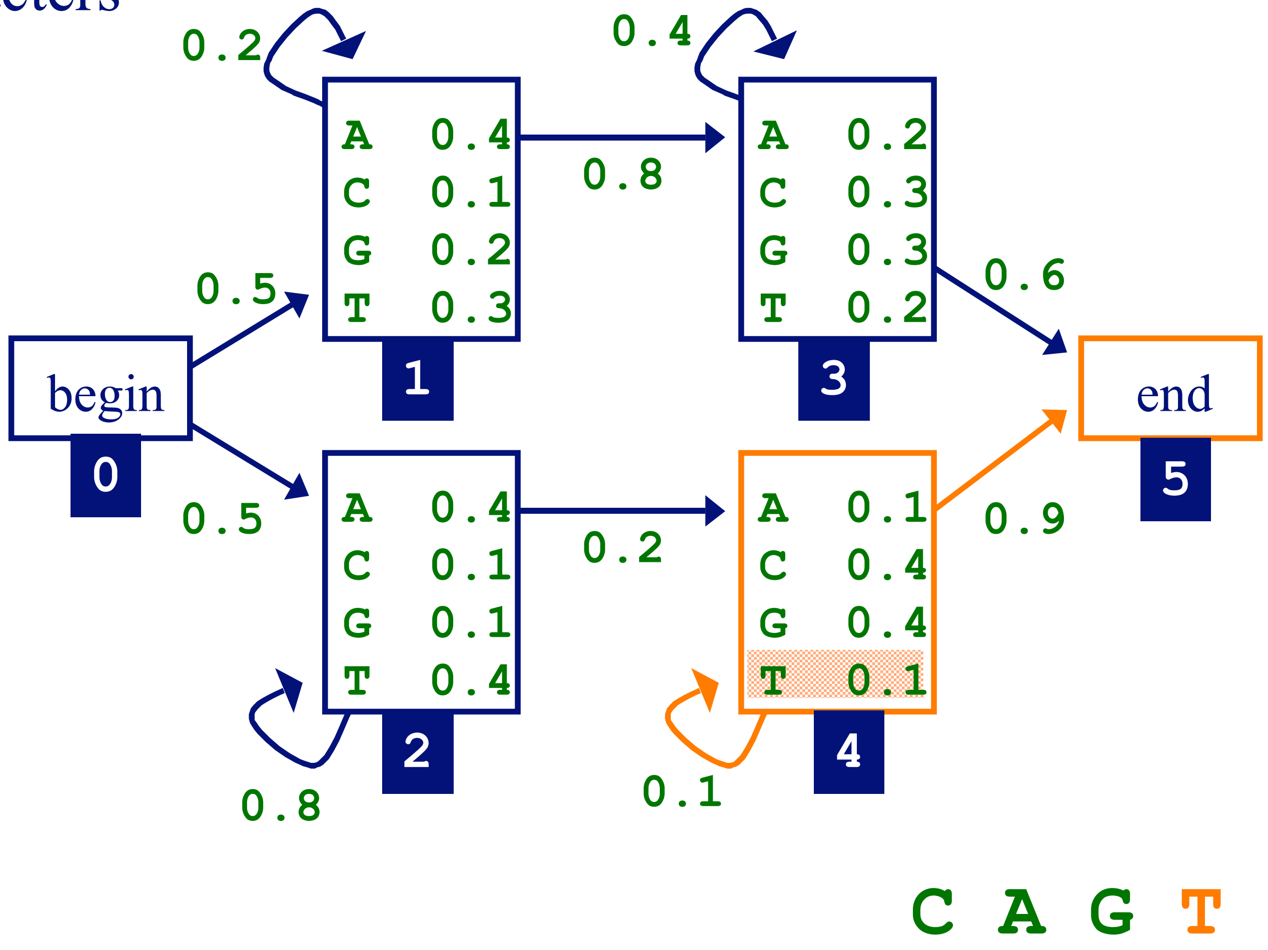
- the forward algorithm gives us $f_k(i)$, the probability of being in state *k* having observed the first *i* characters of *x*



C A G T

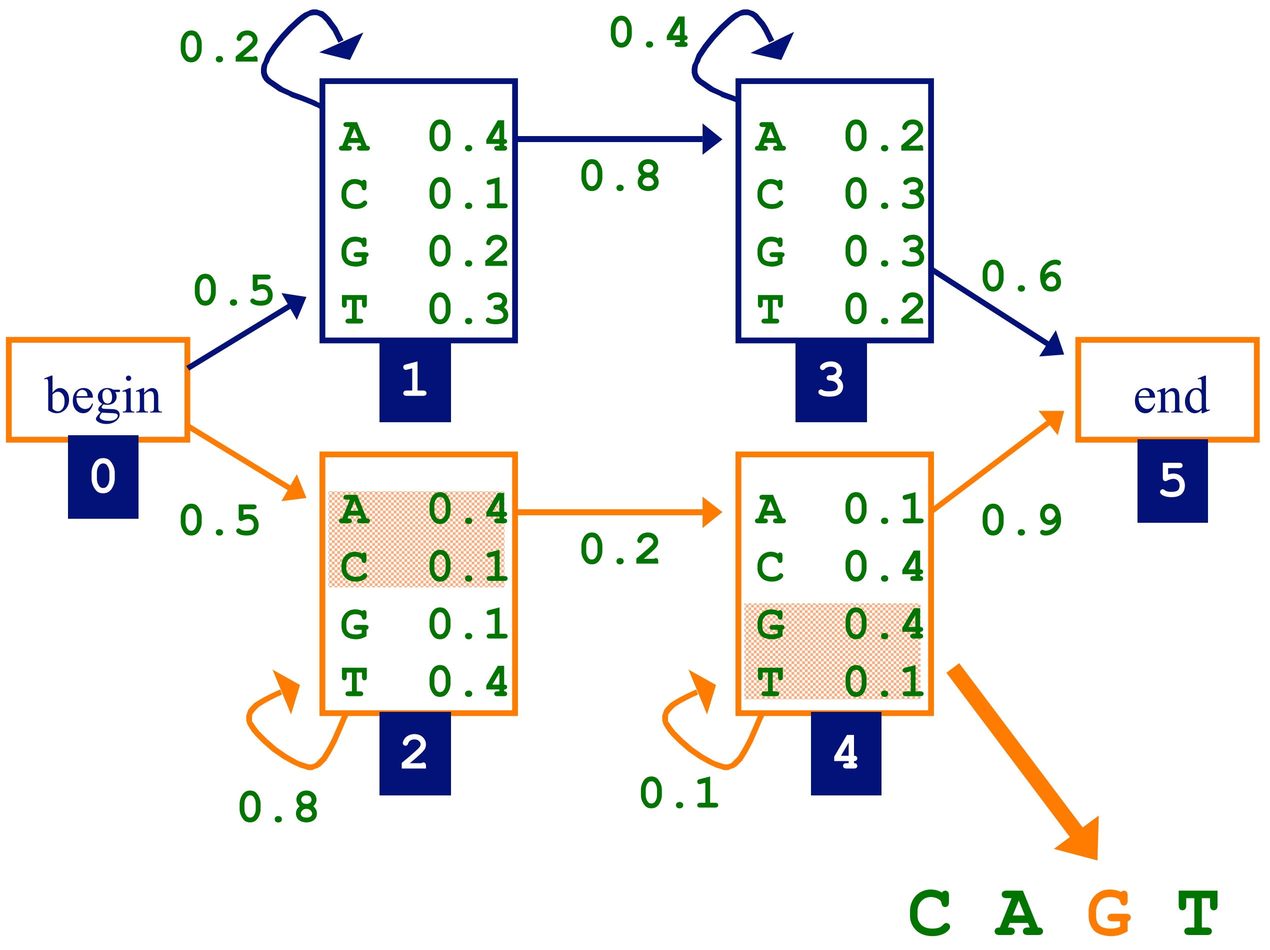
The Expectation Step

- the *backward algorithm* gives us $b_k(i)$, the probability of observing the rest of x, given that we're in state *k* after *i* characters



The Expectation Step

- putting forward and backward together, we can compute the probability of producing sequence *x* with the *i* th symbol being produced by state *q*



The Expectation Step

- first, we need to know the probability of the *i* th symbol being produced by state *k,* given sequence *x*

$$\Pr(\pi_i = k \mid x)$$

- given this we can compute our expected counts for state transitions, character emissions

The Expectation Step

- the probability of of producing *x* with the *i* th symbol being produced by state *k* is

$$\Pr(\pi_i = k, x) = \Pr(x_1 \ldots x_i, \pi_i = k) \times \Pr(x_{i+1} \ldots x_L \mid \pi_i = k)$$

- the first term is $f_k(i)$, computed by the forward algorithm
- the second term is $b_k(i)$, computed by the backward algorithm

The Backward Algorithm

- initialization:

$$b_k(L) = a_{kN}$$

for states with a transition to *end* state

The Backward Algorithm

- recursion (*i* =*L…1*):

$$b_k(i) = \sum_l \begin{cases} a_{kl} b_l(i), & \text{if } l \text{ is silent state} \\ a_{kl} e_l(x_{i+1}) b_l(i+1), & \text{otherwise} \end{cases}$$

The Backward Algorithm

- termination:

$$\Pr(x) = \Pr(x_1 \ldots x_L) = \sum_l \begin{Bmatrix} a_{0l} b_l(0), & \text{if } l \text{ is silent state} \\ a_{0l} e_l(x_1) b_l(1), & \text{otherwise} \end{Bmatrix}$$

The Expectation Step

- now we can calculate the probability of the *i* th symbol being produced by state *k*, given *x*

$$\Pr(\pi_i = k \mid x) = \frac{\Pr(\pi_i = k, x)}{\Pr(x)}$$

$$= \frac{f_k(i) b_k(i)}{\Pr(x)}$$

$$\boxed{= \frac{f_k(i) b_k(i)}{f_N(L)}}$$

The Expectation Step

- now we can calculate the expected number of times letter c is emitted by state k
- here we've added the superscript j to refer to a specific sequence in the training set

$$n_{k,c} = \underbrace{\sum_{x^j}}_{\text{sum over sequences}} \left[\frac{1}{\Pr(x^j)} \underbrace{\sum_{\{i \mid x_i^j = c\}}}_{\text{sum over positions where } c \text{ occurs in x}} f_k^j(i) b_k^j(i) \right]$$

The Expectation Step

- and we can calculate the expected number of times that the transition from *k* to *l* is used

$$n_{k\to l} = \sum_{x^j} \frac{\sum_i f_k^j(i) a_{kl} e_l(x_{i+1}^j) b_l^j(i+1)}{\Pr(x^j)}$$

- or if *l* is a silent state

$$n_{k\to l} = \sum_{x^j} \frac{\sum_i f_k^j(i) a_{kl} b_l^j(i)}{\Pr(x^j)}$$

The Maximization Step

- Let $n_{k,c}$ be the expected number of emissions of *c* from state *k* for the training set
- estimate new emission parameters by:

$$e_k(c) = \frac{n_{k,c}}{\sum_{c'} n_{k,c'}}$$

- just like in the simple case
- but typically we'll do some "smoothing" (e.g. add pseudocounts)

The Maximization Step

- let $n_{k\rightarrow l}$ be the expected number of transitions from state k to state l for the training set
- estimate new transition parameters by:

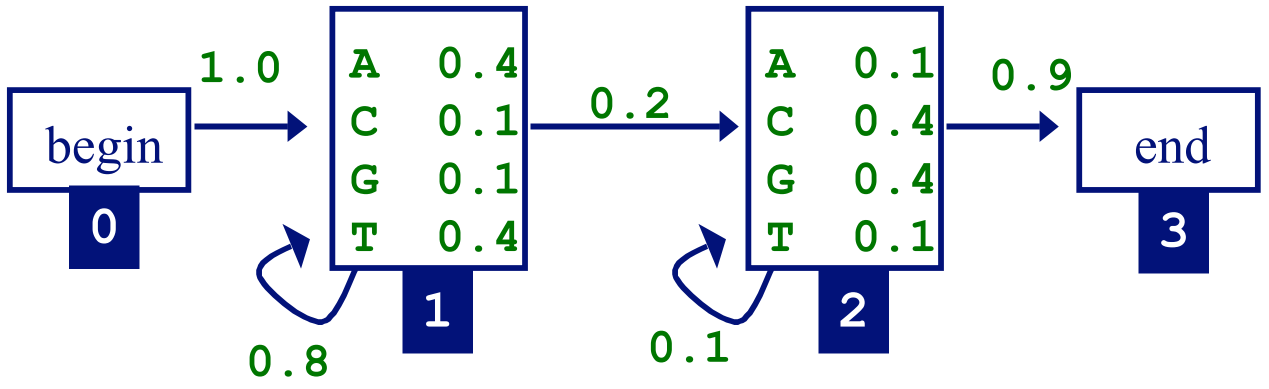
$$a_{kl} = \frac{n_{k\rightarrow l}}{\sum_m n_{k\rightarrow m}}$$

The Baum-Welch Algorithm

- initialize the parameters of the HMM
- iterate until convergence
  - initialize $n_{k,c}$, $n_{k \to l}$ with pseudocounts
  - **E-step**: for each training set sequence *j* = 1…*n*
    - calculate $f_k(i)$ values for sequence *j*
    - calculate $b_k(i)$ values for sequence *j*
    - add the contribution of sequence *j* to $n_{k,c}$, $n_{k \to l}$
  - **M-step**: update the HMM parameters using $n_{k,c}$, $n_{k \to l}$

Baum-Welch Algorithm Example

- given
  - the HMM with the parameters initialized as shown
  - the training sequences **TAG, ACG**



- we'll work through one iteration of Baum-Welch

Baum-Welch Example (Cont)

- determining the forward values for TAG

$$f_0(0) = 1$$

$$f_1(1) = e_1(T) \times a_{01} \times f_0(0) = 0.4 \times 1 = 0.4$$

$$f_1(2) = e_1(A) \times a_{11} \times f_1(1) = 0.4 \times 0.8 \times 0.4 = 0.128$$

$$f_2(2) = e_2(A) \times a_{12} \times f_1(1) = 0.1 \times 0.2 \times 0.4 = 0.008$$

$$f_2(3) = e_2(G) \times \left(a_{12} \times f_1(2) + a_{22} \times f_2(2)\right) = \\ 0.4 \times (0.0008 + 0.0256) = 0.01056$$

$$f_3(3) = a_{23} \times f_2(3) = 0.9 \times 0.01056 = 0.009504$$

- here we compute just the values that represent events with non-zero probability
- in a similar way, we also compute forward values for ACG

Baum-Welch Example (Cont)

- determining the backward values for TAG

$$b_3(3) = 1$$

$$b_2(3) = a_{23} \times b_3(3) = 0.9 \times 1 = 0.9$$

$$b_2(2) = a_{22} \times e_2(G) \times b_2(3) = 0.1 \times 0.4 \times 0.9 = 0.036$$

$$b_1(2) = a_{12} \times e_2(G) \times b_2(3) = 0.2 \times 0.4 \times 0.9 = 0.072$$

$$b_1(1) = a_{11} \times e_1(A) \times b_1(2) + a_{12} \times e_2(A) \times b_2(2) =$$
$$0.8 \times 0.4 \times 0.072 + 0.2 \times 0.1 \times 0.036 = 0.02376$$

$$b_0(0) = a_{01} \times e_1(T) \times b_1(1) = 1.0 \times 0.4 \times 0.02376 = 0.009504$$

- here we compute just the values that represent events with non-zero probability
- in a similar way, we also compute backward values for ACG

Baum-Welch Example (Cont)

- determining the expected emission counts for state 1

	contribution of TAG		contribution of ACG		pseudocount
$n_{1,A} =$	$\dfrac{f_1(2)b_1(2)}{f_3(3)}$	$+$	$\dfrac{f_1(1)b_1(1)}{f_3(3)}$	$+$	1
$n_{1,C} =$			$\dfrac{f_1(2)b_1(2)}{f_3(3)}$	$+$	1
$n_{1,G} =$					1
$n_{1,T} =$	$\dfrac{f_1(1)b_1(1)}{f_3(3)}$			$+$	1

*note that the forward/backward values in these two columns differ; in each column they are computed for the sequence associated with the column

Baum-Welch Example (Cont)

- determining the expected transition counts for state 1 (not using pseudocounts)

contribution of TAG

contribution of ACG

$$n_{1\to 1} = \frac{f_1(1)a_{11}e_1(A)b_1(2)}{f_3(3)} + \frac{f_1(1)a_{11}e_1(C)b_1(2)}{f_3(3)}$$

$$n_{1\to 2} = \frac{f_1(1)a_{12}e_2(A)b_2(2) + f_1(2)a_{12}e_2(G)b_2(3)}{f_3(3)} + \frac{f_1(1)a_{12}e_2(C)b_2(2) + f_1(2)a_{12}e_2(G)b_2(3)}{f_3(3)}$$

- in a similar way, we also determine the expected emission/transition counts for state 2

Baum-Welch Example (Cont)

- determining probabilities for state 1

$$e_1(A) = \frac{n_{1,A}}{n_{1,A} + n_{1,C} + n_{1,G} + n_{1,T}}$$

$$e_1(C) = \frac{n_{1,C}}{n_{1,A} + n_{1,C} + n_{1,G} + n_{1,T}}$$

M

$$a_{11} = \frac{n_{1\to 1}}{n_{1\to 1} + n_{1\to 2}}$$

$$a_{12} = \frac{n_{1\to 2}}{n_{1\to 1} + n_{1\to 2}}$$

Markov Models Summary

- we considered models that varied in terms of order, in/homogeneity, hidden state
- three DP-based algorithms for HMMs: Forward, Backward and Viterbi
- we discussed three key tasks: learning, classification and segmentation
- the algorithms used for each task depend on whether there is hidden state (correct path known) in the problem or not

Comments on Markov Models

- there are many successful applications in computational biology
  - gene recognition and associated subtasks
  - protein family modeling
  - motif modeling
  - etc.
- there are many variants of the models/algorithms we considered here (some of these are covered in BMI/CS 776)
  - fixed length motif models
  - semi-markov models
  - stochastic context free grammars
  - Gibbs sampling for learning parameters