Today's Lecture: HMMs

- Definitions
- Examples
- Probability calculations
  - WDAG
  - Viterbi algorithm

HMMs: Formal Definition

- Alphabet B = {b} of *observed symbols*
- Set S = {k} of *hidden states* (usually k = 0,1, 2 ...,m; 0 is reserved for "begin" state, and sometimes also an "end" state)
- (Markov chain property): prob of state occurring at given position depends only on immediately preceding state, and is given by

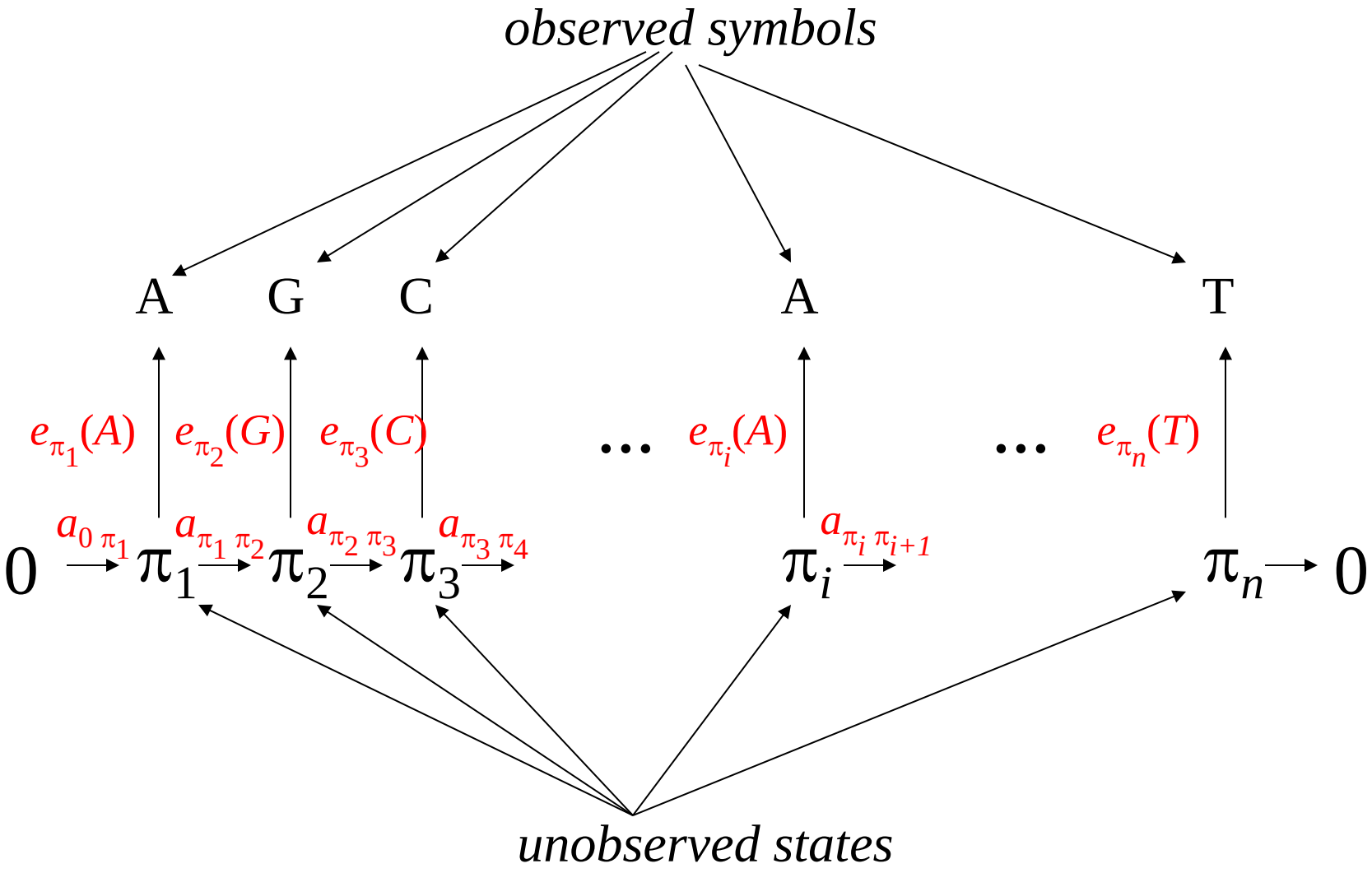
  transition probabilities (a_{kl}): a_{kl} = Prob(next state is l | curr state is k)

  $\sum_l a_{kl} = 1$, for each k.

  – Usually, many transition probabilities are set to 0.

  – Model *topology* is the # of states, and *allowed* (i.e. $a_{kl} \neq 0$) transitions.

  Sometimes omit begin state, in which case need *initiation probabilities* (p_k) for sequence starting in a given state


observed symbols
A
G
C
A
T
$e_{\pi_1}(A)$
$e_{\pi_2}(G)$
$e_{\pi_3}(C)$
…
$e_{\pi_i}(A)$
…
$e_{\pi_n}(T)$
$a_{0\,\pi_1}$
$a_{\pi_1\,\pi_2}$
$a_{\pi_2\,\pi_3}$
$a_{\pi_3\,\pi_4}$
$a_{\pi_i\,\pi_{i+1}}$
0
π_1
π_2
π_3
π_i
π_n
0
unobserved states

- Prob that symbol occurs at given sequence position depends only on hidden state at that position, and is given by

  emission probabilities:

  $e_k(b)$ = Prob(observed symbol is b | curr state is k)

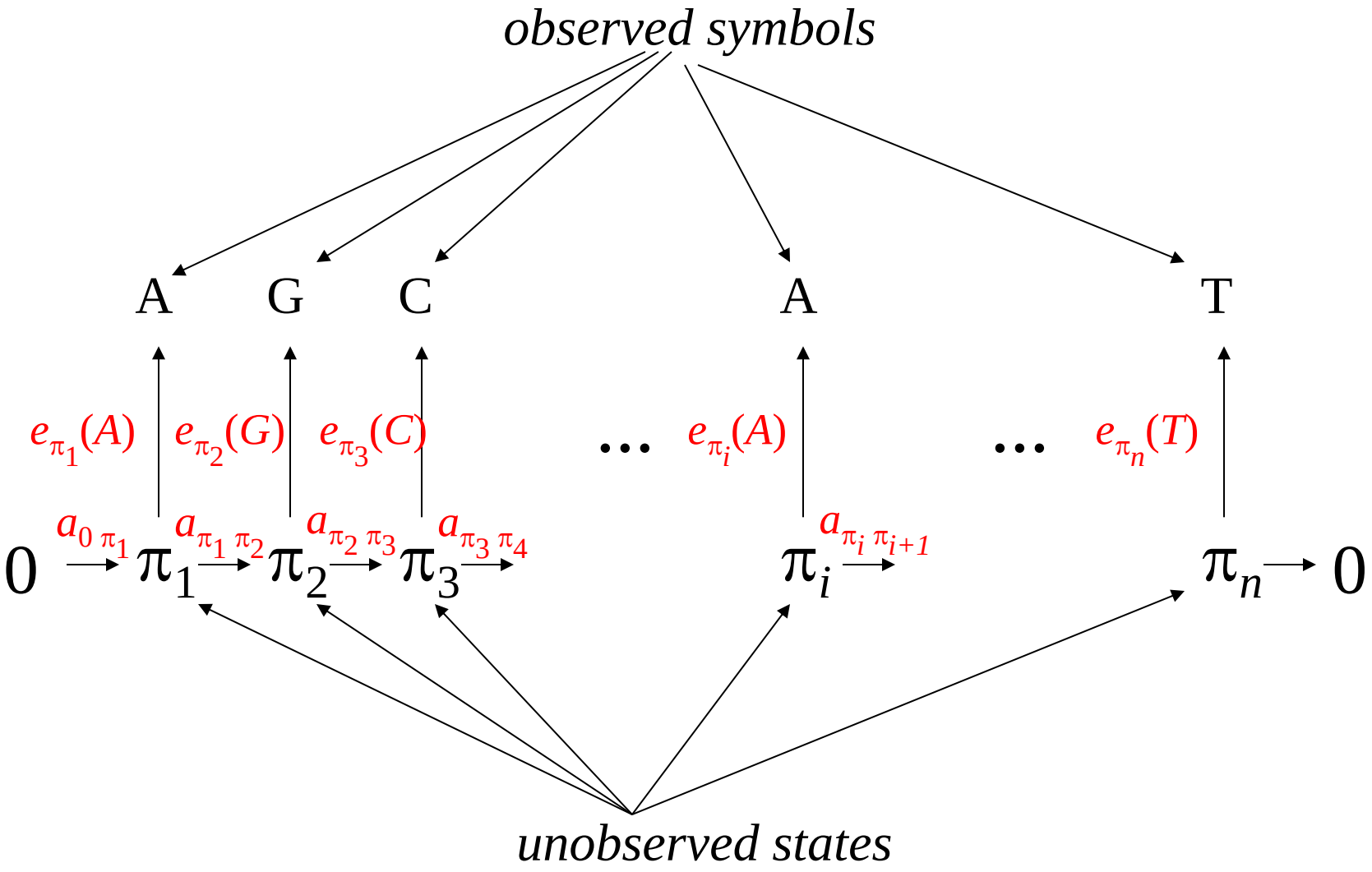
  (begin and end states do not emit symbols)

- Note that
  - there are no *direct* dependencies between observed symbols in the sequence, however
  - there are *indirect* dependencies implied by state dependencies

Where do the parameters come from?

- Can either
  - *define* parameter values *a priori*, or
  - *estimate* them from training data (observed sequences of the type to be modelled).
- Usually one does a mixture of both –
  - model topology is defined (some transitions set to 0), but
  - remaining parameters estimated

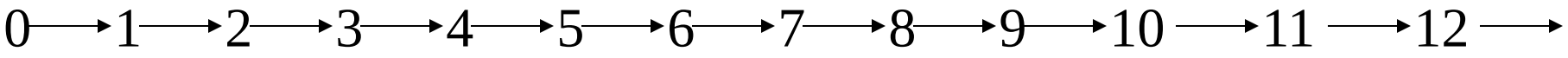
Hidden Markov Model



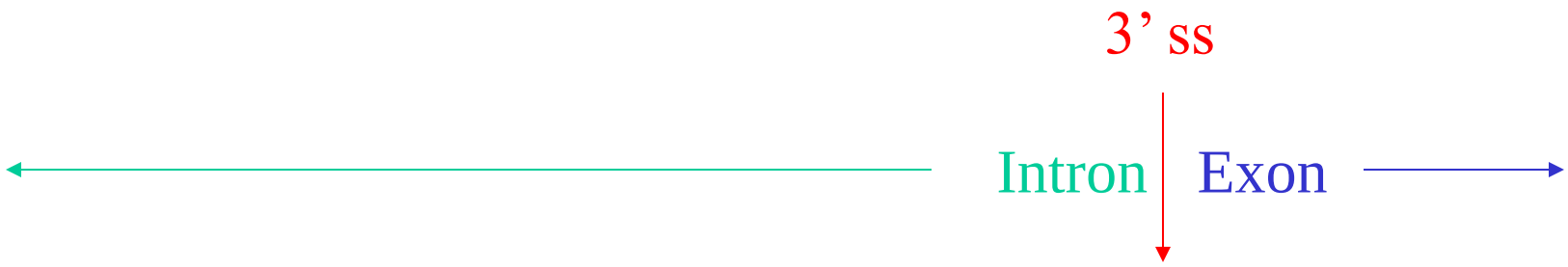
HMM Examples

- Site models:
  - "states" correspond to positions (columns in the tables). state i transitions only to state $i+1$:
    - $a_{i,i+1} = 1$ for all i;
    - all other a_{ij} are 0
  - emission probabilities are position-specific frequencies: values in frequency table columns

Topology for Site HMM: ‘allowed’ transitions (transits with non-zero prob – all are 1)



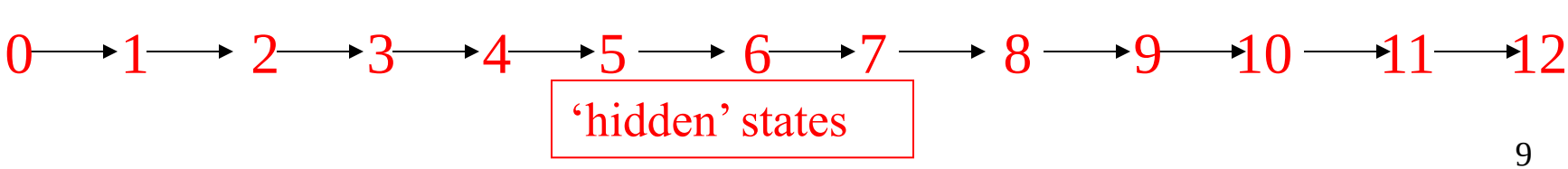
HMM for *C. elegans* 3' Splice Sites



A	3276	3516	2313	476	67	757	240	8192	0	3359	2401	2514
C	970	648	664	236	129	1109	6830	0	0	1277	1533	1847
G	593	575	516	144	39	595	12	0	8192	2539	1301	1567
T	3353	3453	4699	7336	7957	5731	1110	0	0	1017	2957	2264
CONSENSUS	W	W	W	T	T	t	C	A	G	r	w	w

Emission probabilities

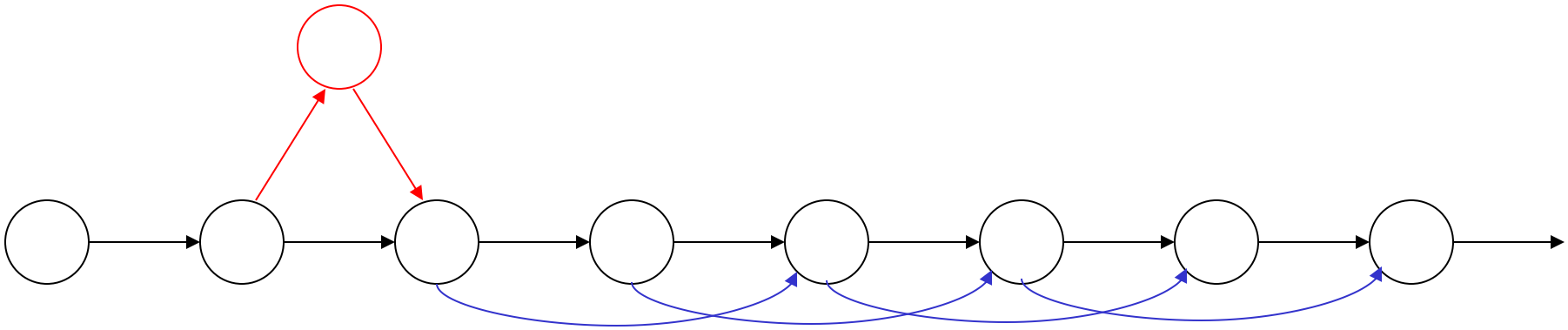
A	0.400	0.429	0.282	0.058	0.008	0.092	0.029	1.000	0.000	0.410	0.293	0.307
C	0.118	0.079	0.081	0.029	0.016	0.135	0.834	0.000	0.000	0.156	0.187	0.225
G	0.072	0.070	0.063	0.018	0.005	0.073	0.001	0.000	1.000	0.310	0.159	0.191
T	0.409	0.422	0.574	0.896	0.971	0.700	0.135	0.000	0.000	0.124	0.361	0.276



- Can expand model to allow omission of nuc at some positions by including other (downstream) transitions (or via “silent states”)
- Can allow insertions by including additional states.
- transition probabilities no longer necessarily 1 or 0

Insertions & Deletions in Site Model

insertion state



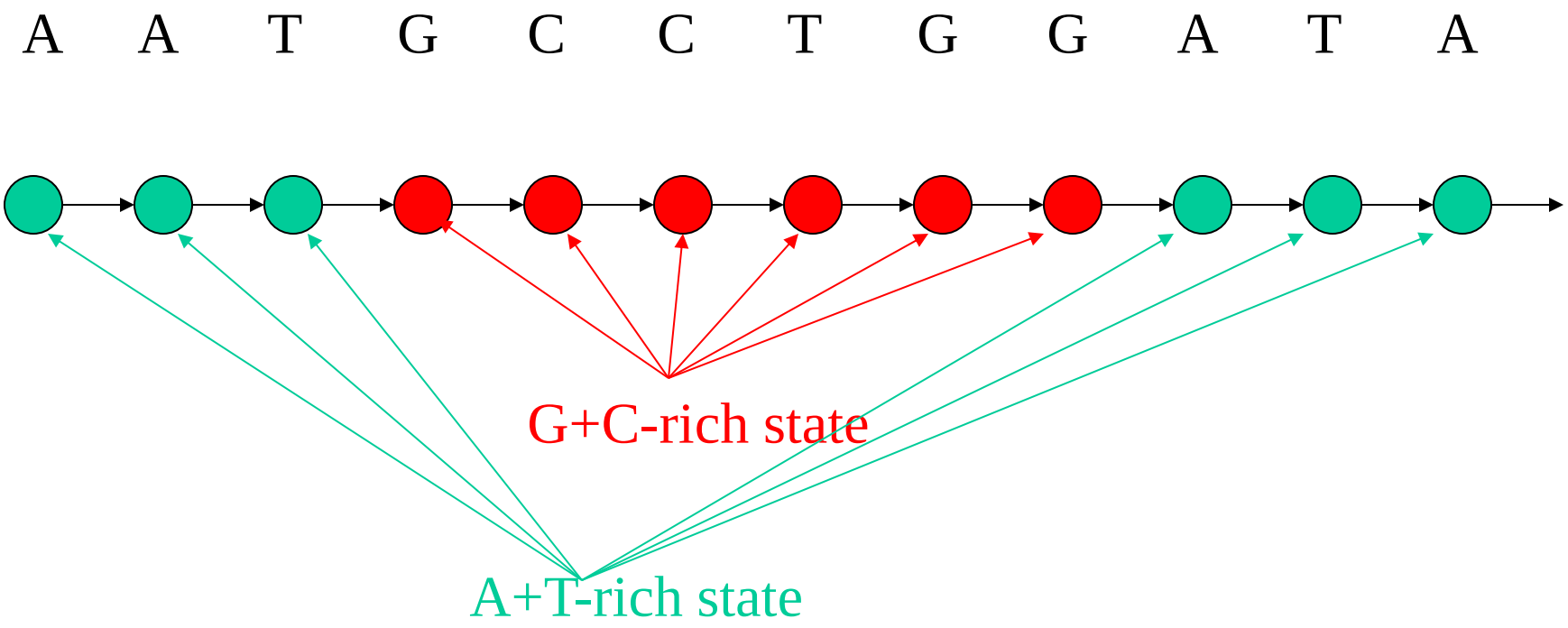
other transitions correspond
to deletions

Examples (cont'd) – 1-state HMMs

- single state, emitting residues with specified freqs:
  = 'background' model

Examples (cont'd) – 2-state HMMs

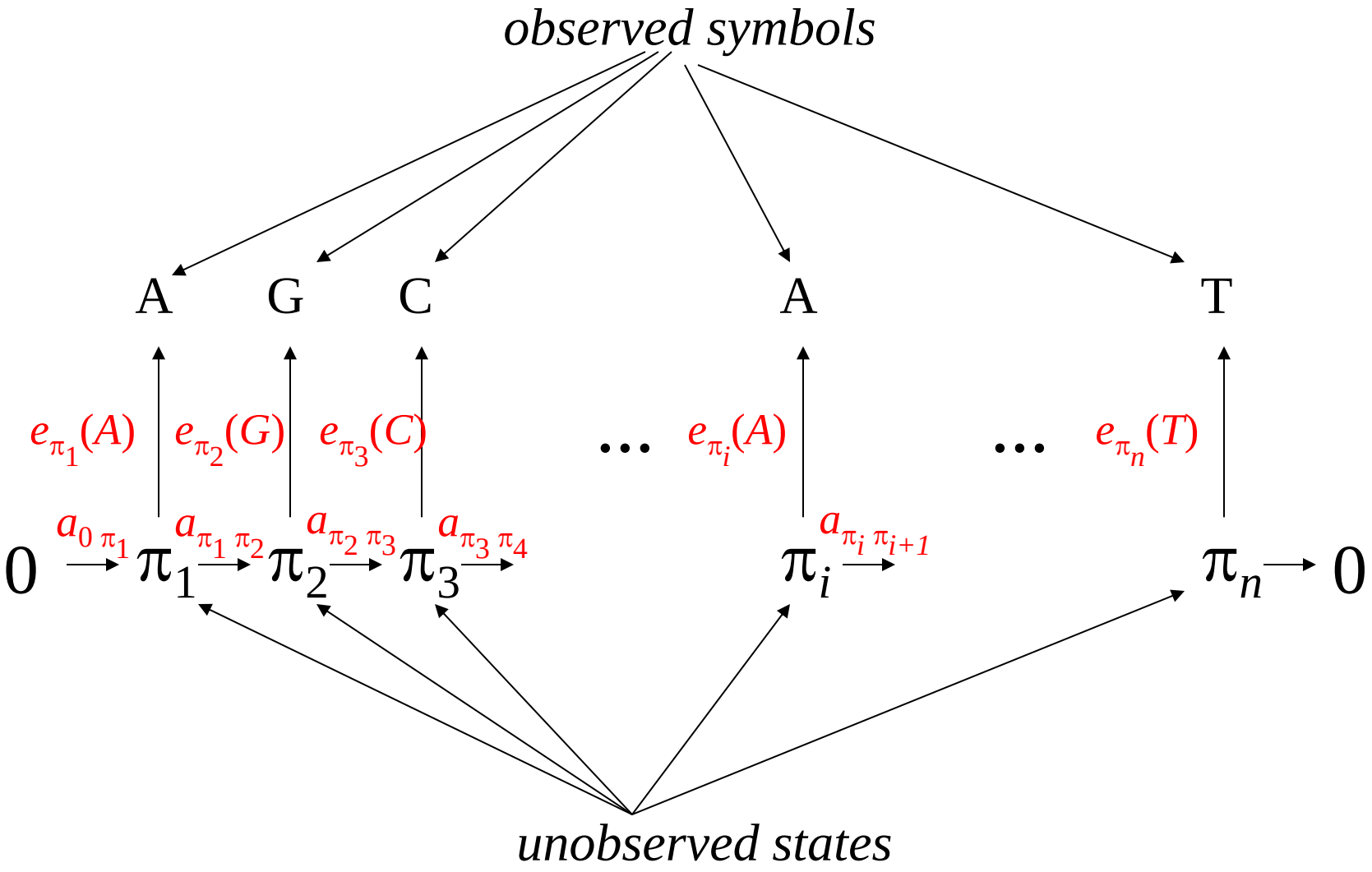
- if a_{11} and a_{22} are small (close to 0), and
  a_{12} and a_{21} are large (close to 1),
  then get (nearly) periodic model with period 2; e.g.
  - dinucleotide repeat in DNA, or
  - (some) beta strands in proteins.
- if a_{11} and a_{22} large, and
  a_{12} and a_{21} small,
  then get models of alternating regions of different compositions (specified by emission probabilities), e.g.
  - higher vs. lower G+C content regions (RNA genes in thermophilic bacteria); or
  - hydrophobic vs. hydrophilic regions of proteins (e.g. transmembrane domains).


A A T G C C T G G A T A
G+C-rich state
A+T-rich state

2-state HMMs

- Can find most probable state decomposition ('Viterbi path') consistent with observed sequence
- Advantages over linked-list dynamic programming method (lecture 3) for finding high-scoring segments:
  - That method assumes you *know* appropriate parameters to find targeted regions; HMM method can *estimate* parameters.
  - HMM (easily) finds multiple segments
  - HMM can attach *probabilities* to alternative decompositions
  - HMM generalization to > 2 *types* of segments is easy – just allow more states!
- Disadvantage:
  - Markov assumption on state transitions implies geometric distribution for lengths of regions -- may not be appropriate

Hidden Markov Model



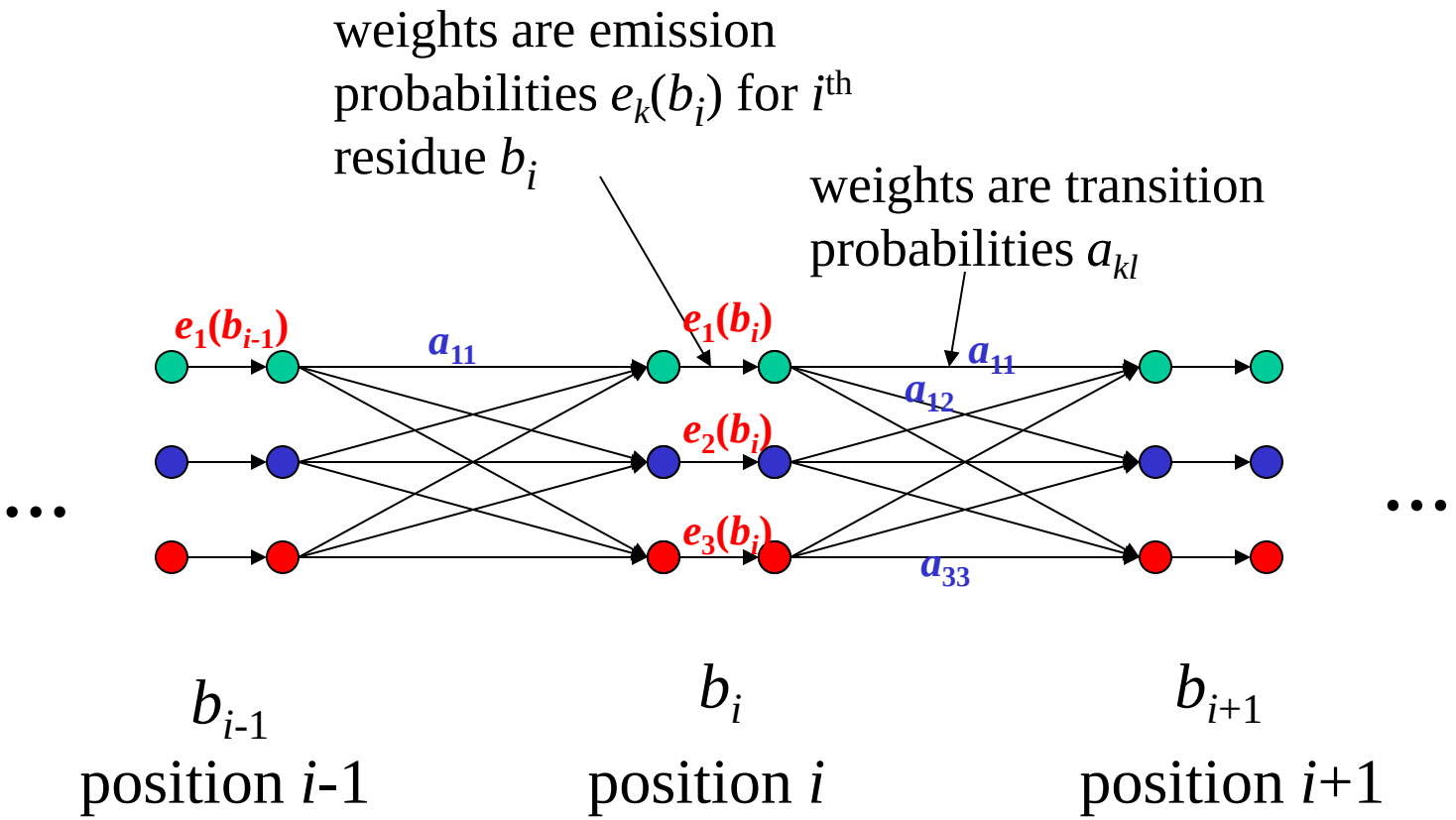
HMM Probabilities of Sequences

- Prob of sequence of states $\pi_1\pi_2\pi_3 \ldots \pi_n$ is
  $a_{0\pi_1} a_{\pi_1\pi_2} a_{\pi_2\pi_3} a_{\pi_3\pi_4} \ldots a_{\pi_{n-1}\pi_n}$.
- Prob of seq of observed symbols $b_1 b_2 b_3 \ldots b_n$,
  conditional on state sequence is
  $e_{\pi_1}(b_1) e_{\pi_2}(b_2)\, e_{\pi_3}(b_3) \ldots e_{\pi_n}(b_n)$
- Joint probability = $a_{0\pi_1} \prod_{i=1}^{n} a_{\pi_i\pi_{i+1}}\, e_{\pi_i}(b_i)$
  (define $a_{\pi_n\pi_{n+1}}$ to be 1)
- (Unconditional) prob of observed sequence
  = sum (of joint probs) over all possible state paths
  - not practical to compute directly, by 'brute force'! We will use dynamic programming.

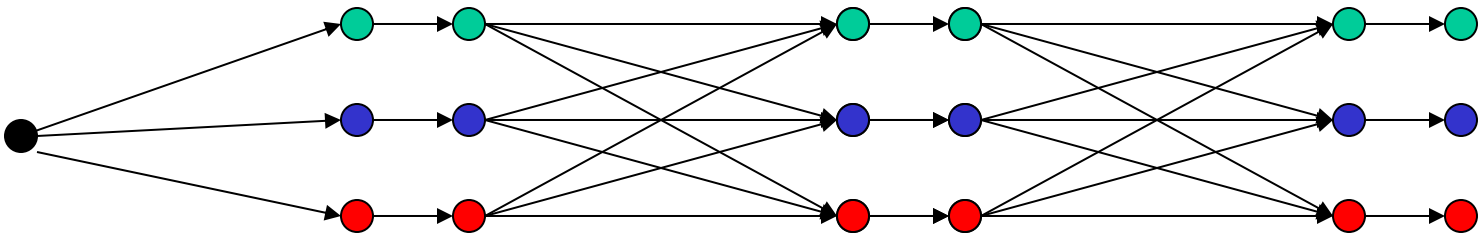
Computing HMM Probabilities

- WDAG structure for sequence HMMs:
  - for i^{th} position in seq (i = 1, ... n), have 2 nodes for each state:
    - total # nodes = $2ns + 1$, where n = seq length, s = # states
  - Pair of nodes for a given state at i^{th} position is connected by an *emission* edge
    - Weight is the emission prob for i^{th} observed residue.
    - Can omit node pair if emission prob = 0.
  - Have *transition* edges connecting (right-hand) state nodes at position i with (left-hand) state nodes at position i+1
    - Weights are transition probs
    - Can omit edges with transition prob = 0.

WDAG for 3-state HMM, length *n* sequence



Beginning of Graph



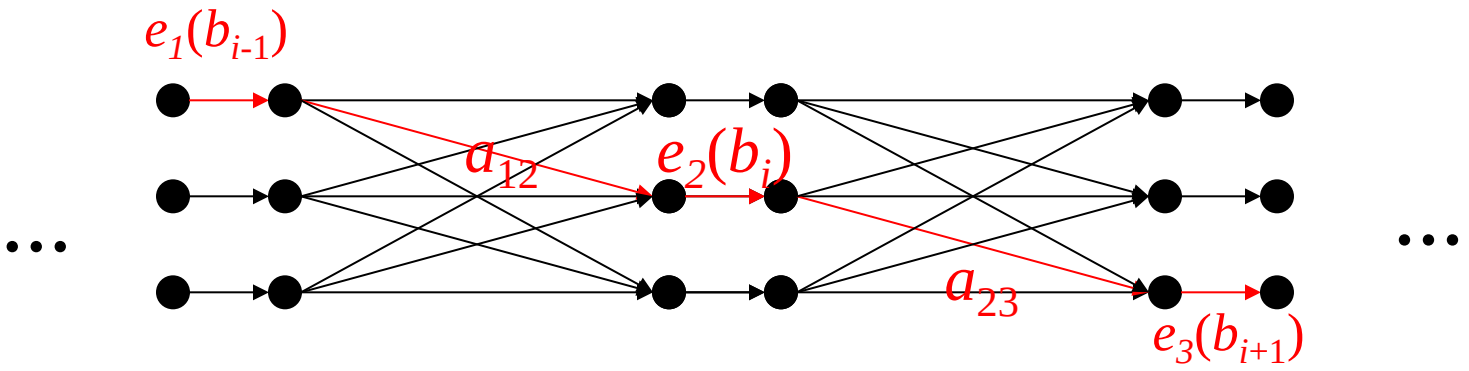
b_1 b_2 b_3

begin state position 1 position 2 position 3

- ***Paths*** through graph from begin node to end node correspond to *sequences of states*
- ***Product weight*** along path
  = *joint probability* of state sequence & observed symbol sequence
- Sum of (product) path weights, over all paths,
  = *probability of observed sequence*
- Sum of (product) path weights over
  - all paths going through a particular node, or
  - all paths that include a particular edge,

  divided by prob of observed sequence,
  = *posterior probability* of that edge or node
- ***Highest-weight path*** = *highest probability state sequence*

Path Weights



- By general results on WDAGs, can use dynamic programming to find highest weight path:

  = "Viterbi algorithm" to find highest probability path (most probable "parse")

  – in this case can use log probabilities & sum weights

  – (N.B. paths are constrained to begin at the begin node!)

The Viterbi path is
the *most probable parse*!