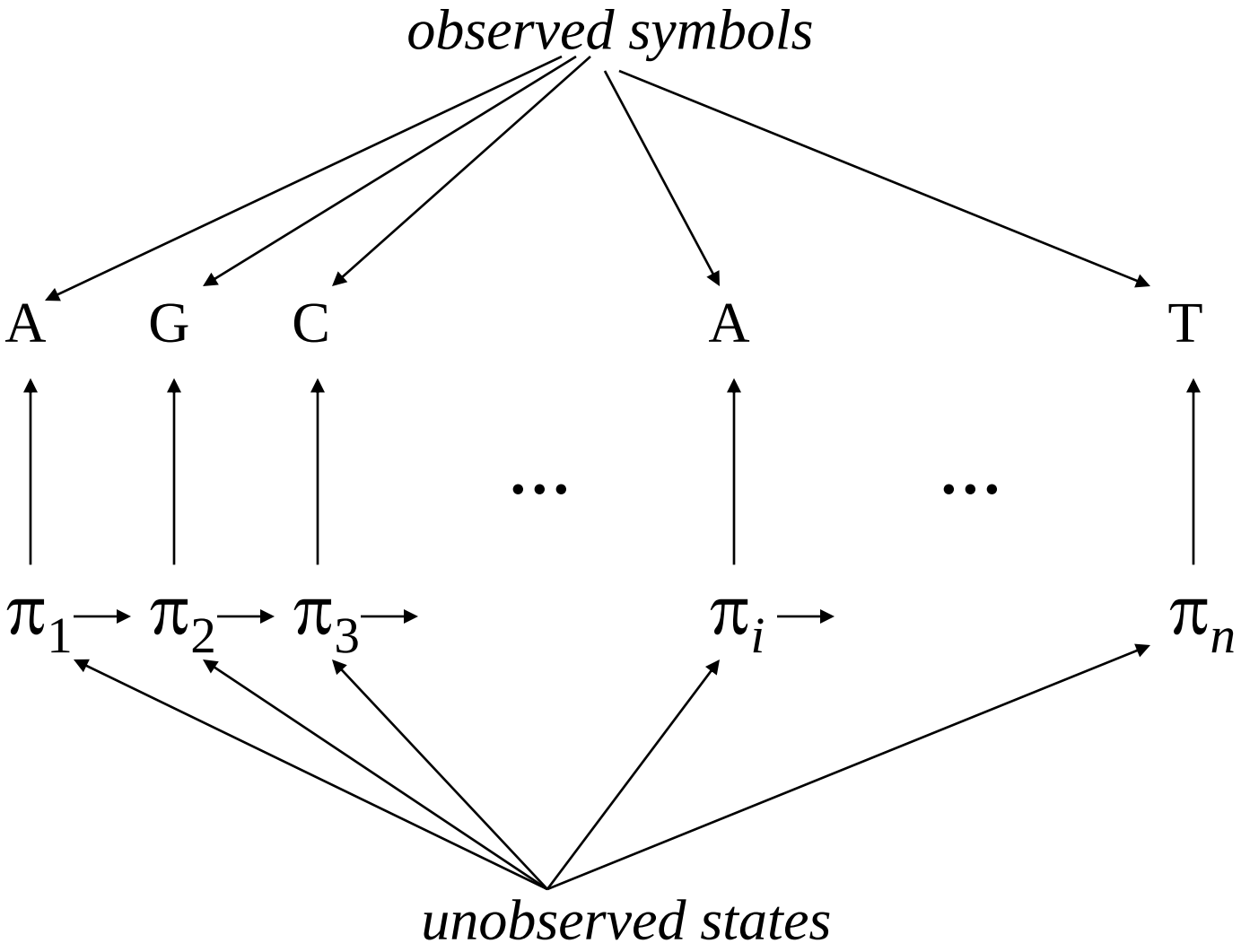
Lecture 12

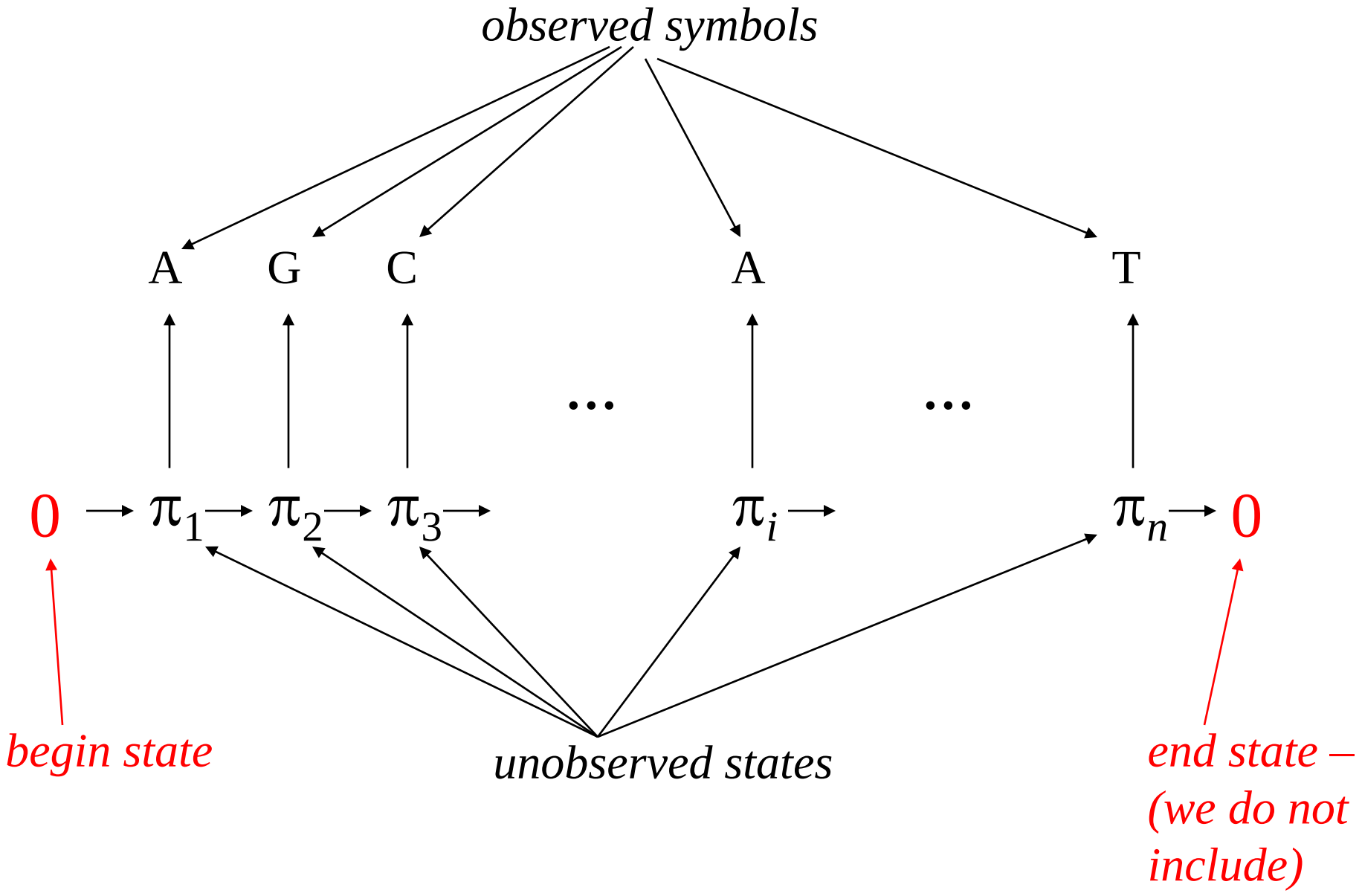
- Hidden Markov Models
  - Intro & Definitions
  - Examples

Hidden Markov Models

- Probability models for sequences of *observed symbols*, e.g.
  - nucleotide or amino acid residues
  - aligned pairs of residues
  - aligned set of residues corresponding to leaves of an underlying evolutionary tree
  - angles in protein chain (structure modelling)
  - sounds (speech recognition)

- Assume a sequence of "*hidden*" (unobserved) *states* underlies each observed symbol sequence
- Each state "*emits*" symbols (one symbol at a time)
- States may correspond to underlying "reality" we are trying to infer, e.g.
  - unobserved biological feature:
    - (positions within) a site
  - rate of evolution
  - protein structural element
  - speech phoneme


observed symbols
A
G
C
A
T
...
...
π_1
π_2
π_3
π_i
π_n
unobserved states


observed symbols
A
G
C
A
T
0
π_1
π_2
π_3
π_i
π_n
0
begin state
unobserved states
end state – (we do not include)

Advantages of HMMs

- Flexible –gives reasonably good models in wide variety of situations
- Computationally efficient
- Often interpretable:
  - hidden states can correspond to biological features.
  - can find most probable sequence of hidden states
    = biological “parsing” of residue sequence.

HMMs: Formal Definition

- Alphabet $\mathcal{B} = \{b\}$ of *observed symbols*
- Set $\mathcal{S} = \{k\}$ 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.

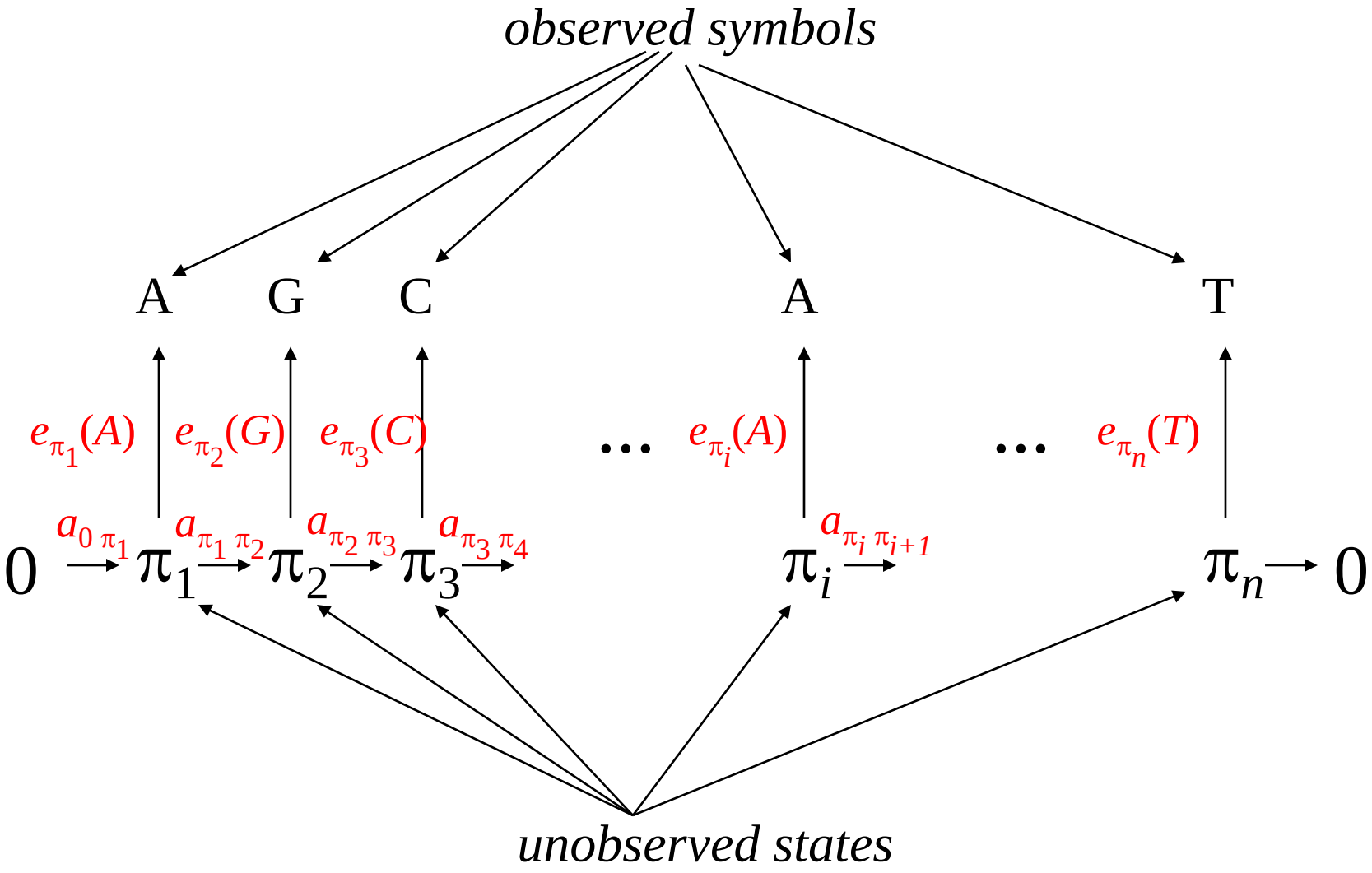
  – Model *topology* is the # of states, and ***allowed*** (i.e. $a_{kl} \neq 0$) transitions.

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

from lecture 3:

- Conditional probabilities (as on the previous slide) can be used to define a ***first-order Markov model*** (or ***Markov chain model***) for sequence probabilities:

$$P(s_1\, s_2\, s_3 \cdots s_n)$$
$$\equiv P(s_1)\, P(s_2 \mid s_1)\, P(s_3 \mid s_2) \;\cdots\; P(s_n \mid s_{n-1})$$


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)

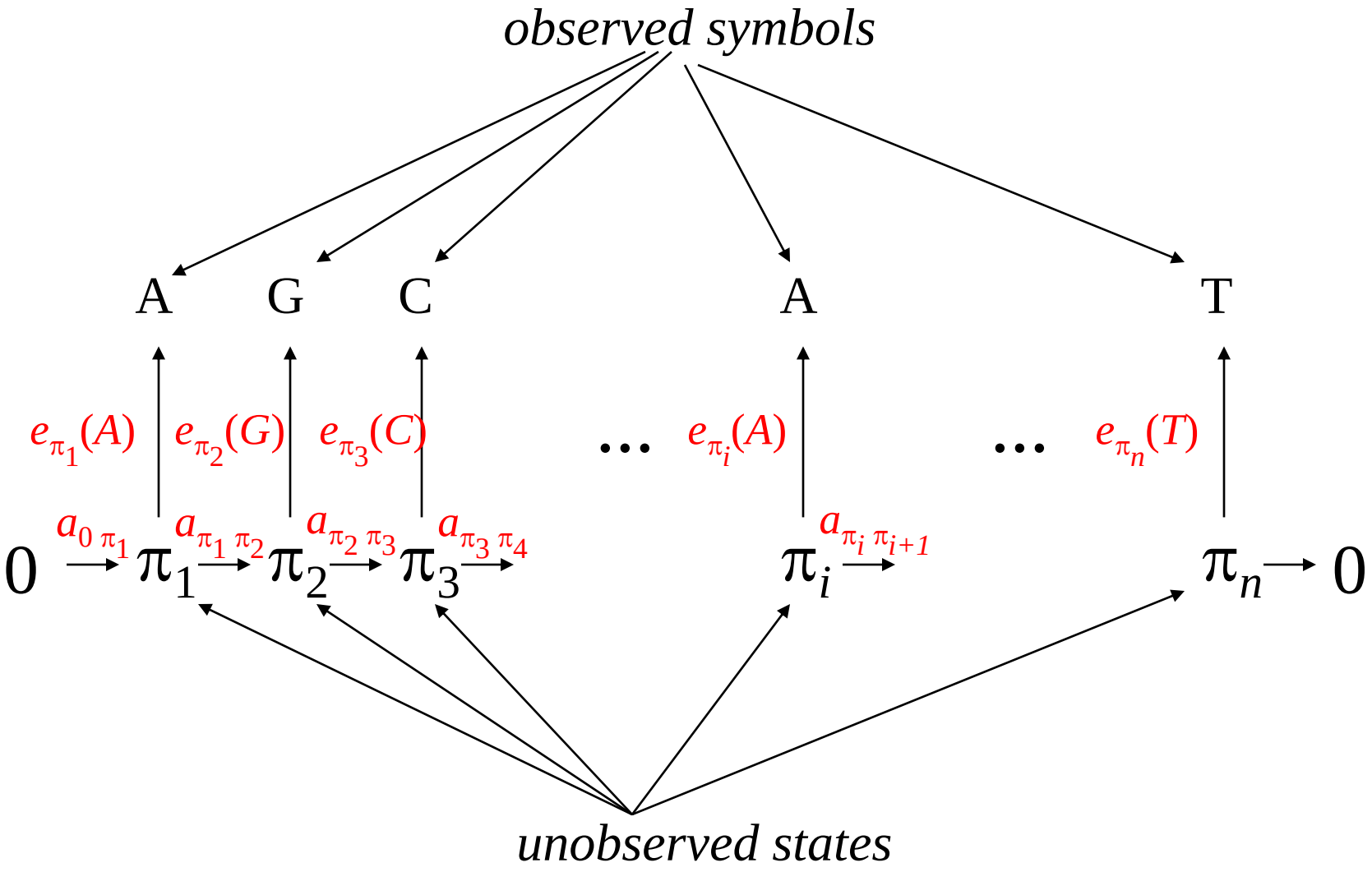
  (begin and end states do not emit symbols)

- 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



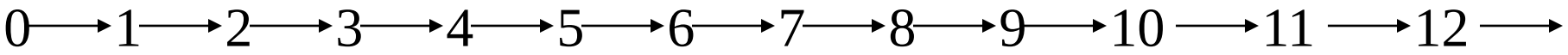
HMM examples: 1-state HMMs

- single state, emitting residues with specified freqs:
  = ‘background’ 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

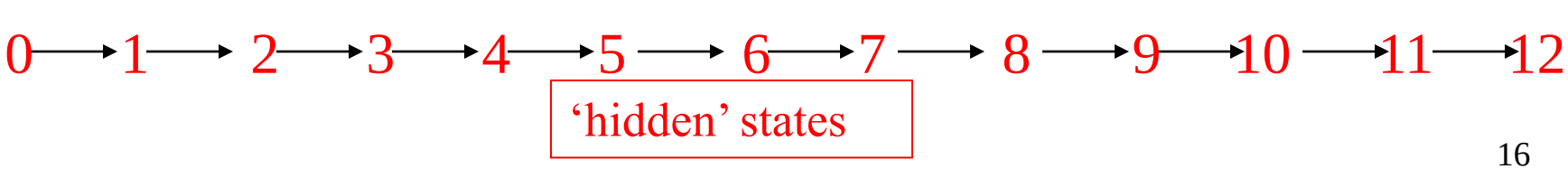


HMM for *C. elegans* 3' Splice Sites

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

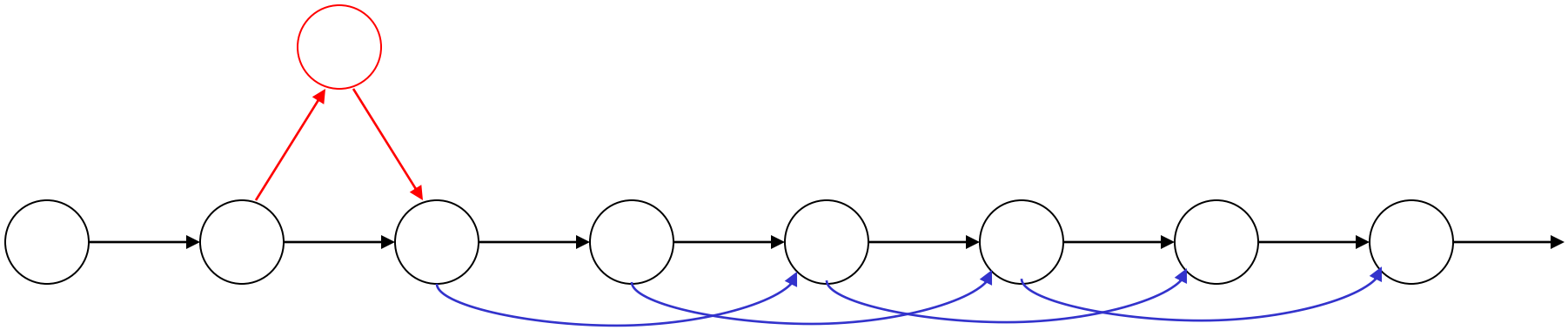
A	0.400	0.429	0.282	0.058	0.008	0.092	0.029	1.000	0.000	0.410	0.293	0.307
C	0.118	0.079	0.081	0.029	0.016	0.135	0.834	0.000	0.000	0.156	0.187	0.225
G	0.072	0.070	0.063	0.018	0.005	0.073	0.001	0.000	1.000	0.310	0.159	0.191
T	0.409	0.422	0.574	0.896	0.971	0.700	0.135	0.000	0.000	0.124	0.361	0.276



– 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 then no longer necessarily 1 or 0

Insertions & Deletions in Site Model

insertion state



other transitions correspond
to deletions

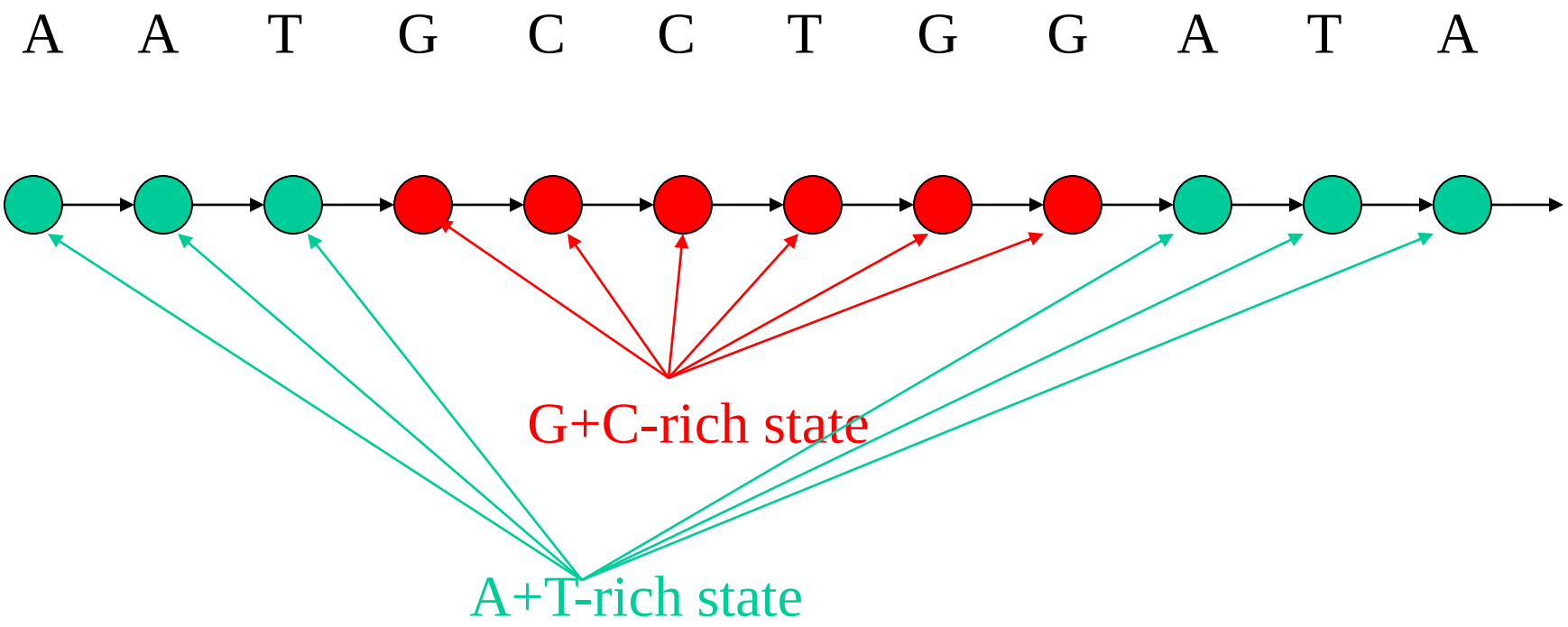
HMM examples (in Durbin *et al.*)

- protein families (like site models – but important to allow insertions & deletions)
- Pair HMMs
- protein structure (symbols emitted are structural elements)

HMM examples: 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).

Closely related to D-segment method (lecture 7)!


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

HMM examples: Markov models

- Ordinary Markov chain model:
  - states = observed symbols
  - emission probs = 1 or 0
  - transition probs = prob of observing a symbol, given the preceding one.
- Order *k* Markov model
  - states = length *k* words (e.g. $b_1 b_2 \ldots b_k$)
  - (unique) symbol emitted by $b_1 b_2 \ldots b_k$ is b_k
  - transition prob from $b_1 b_2 \ldots b_k$ to $c_1 c_2 \ldots c_k$ is non-zero only if
    - $c_1 c_2 \ldots c_{k-1} = b_2 b_3 \ldots b_k$, in which case it is
      $P(b_{k+1} | b_1 b_2 \ldots b_k)$ where $b_{k+1} = c_k$

from lecture 3:

- Similarly, one can define an a ***order-k Markov model*** in which the probability of s_i is conditional on $s_{i-k} \cdots s_{i-2}\, s_{i-1}$

  (i.e. the k preceding residues)

- Note that the required number of parameters is exponential in k
- The ***independence model*** (which is usually good enough for us!) = the ***order-0 Markov model***