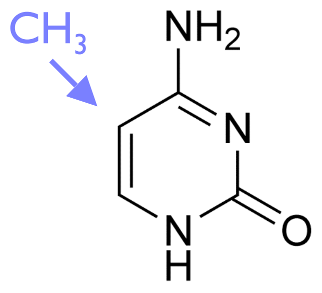
CSE 527
Lectures 11-12

Markov Models and Hidden Markov Models

DNA Methylation

CpG - 2 adjacent nts, same strand (not Watson-Crick pair; "p" mnemonic for the phosphodiester bond of the DNA backbone)



cytosine

C of CpG is often (70-80%) methylated in mammals i.e., CH3 group added (both strands)

Why? Generally silences transcription. X-inactivation, imprinting, repression of mobile elements, some cancers, aging, and *developmental differentiation*

How? DNA methyltransferases convert hemi- to fully-methylated

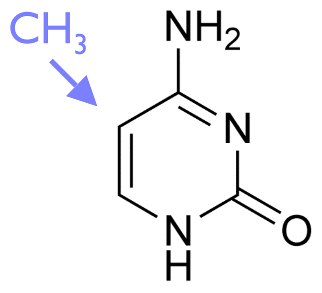
Major exception: promoters of housekeeping genes

“CpG Islands”

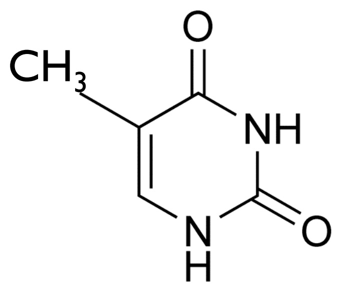
Methyl-C mutates to T relatively easily

Net: CpG is less common than expected genome-wide: f(CpG) < f(C)*f(G)

BUT in promoter (& other) regions, CpG remain unmethylated, so CpG → TpG less likely there: makes “CpG Islands”; often mark gene-rich regions



cytosine



thymine

CpG Islands

- CpG Islands
  - More CpG than elsewhere
  - More C & G than elsewhere, too
  - Typical length: few 100 to few 1000 bp
- Questions
  - Is a short sequence (say, 200 bp) a CpG island or not?
  - Given long sequence (say, 10-100kb), find CpG islands?

Markov & Hidden Markov Models

References:

Durbin, Eddy, Krogh and Mitchison, “Biological Sequence Analysis”, Cambridge, 1998

Rabiner, "A Tutorial on Hidden Markov Models and Selected Application in Speech Recognition," Proceedings of the IEEE, v 77 #2,Feb 1989, 257-286

Independence

A key issue: All models we've talked about so far assume *independence* of nucleotides in different positions - definitely unrealistic.

Markov Chains

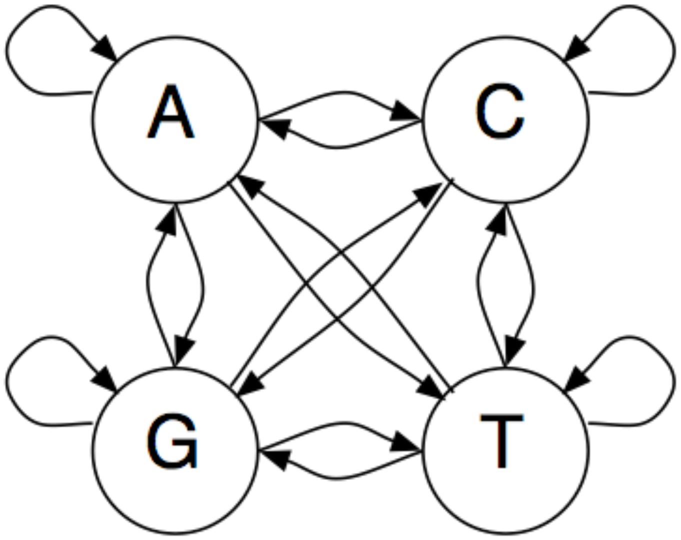
A sequence $x_1, x_2, \ldots$ of random variables is a *k-th order Markov chain* if, for all *i*, *i*^th^ value is independent of all but the previous *k* values:

$$P(x_i \mid x_1, x_2, \ldots, x_{i-1}) = P(x_i \mid x_{i-k}, x_{i-k+1}, \ldots, x_{i-1})$$

Example 1: Uniform random ACGT
Example 2: Weight matrix model
$\Big\}$ 0th order

Example 3: ACGT, but ↓ Pr(G following C)
$\Big\}$ 1st order

A Markov Model (1st order)

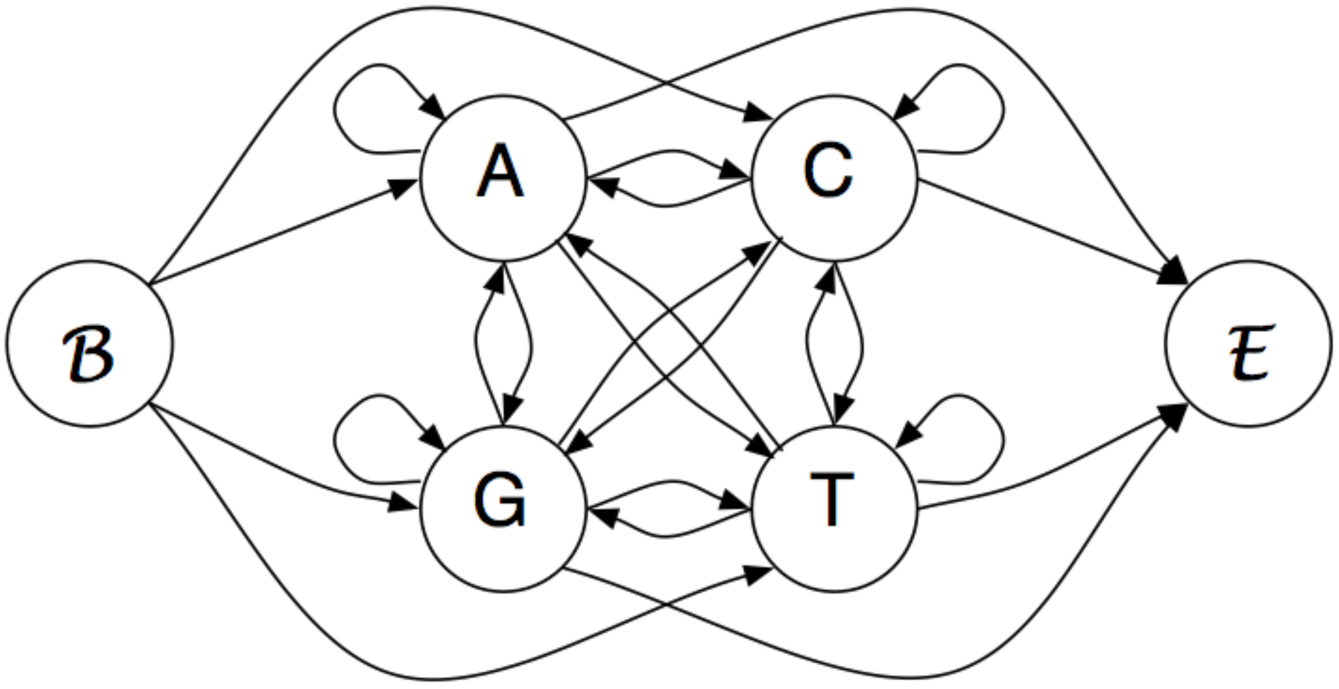


States: A,C,G,T

Emissions: corresponding letter

Transitions: $a_{st} = P(x_i = t \mid x_{i-1} = s)$ $\longleftarrow$ 1st order

A Markov Model (1st order)



States:	A,C,G,T
Emissions:	corresponding letter
Transitions:	$a_{st} = P(x_i = t \mid x_{i-1} = s)$

$\mathcal{B}$egin/$\mathcal{E}$nd states

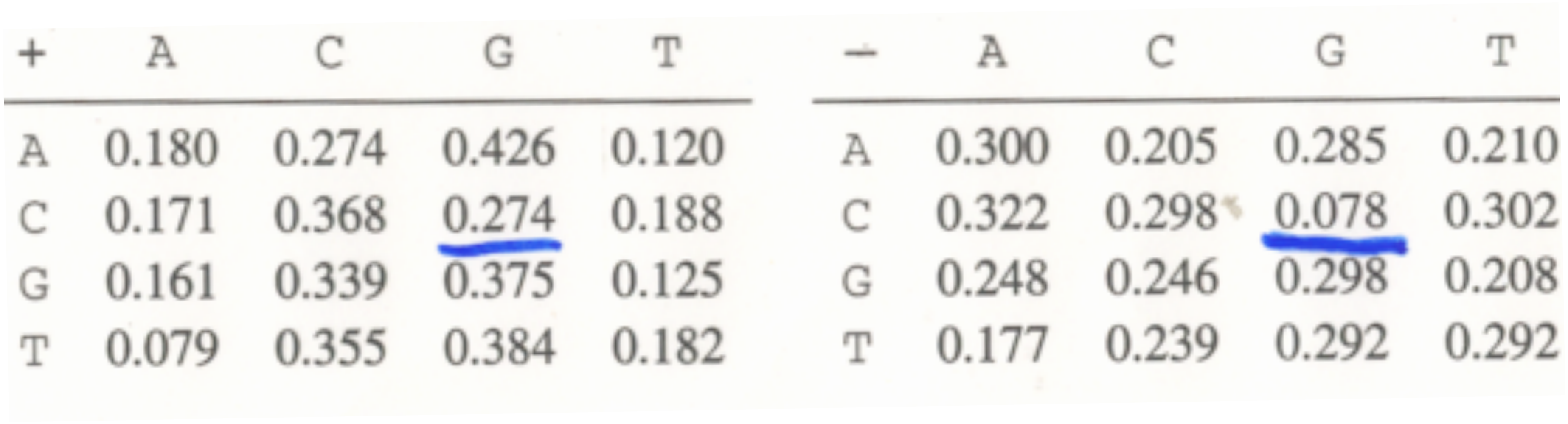
Pr of emitting sequence *x*

$$\begin{aligned}
x &= x_1\ x_2\ \ldots\ x_n \\
P(x) &= P(x_1, x_2, \ldots, x_n) \\
&= P(x_1) \cdot P(x_2 \mid x_1) \cdots P(x_n \mid x_{n-1}, \ldots, x_1) \\
&= P(x_1) \cdot P(x_2 \mid x_1) \cdots P(x_n \mid x_{n-1}) \\
&= P(x_1) \prod_{i=1}^{n-1} a_{x_i, x_{i+1}} \\
&= \prod_{i=0}^{n-1} a_{x_i, x_{i+1}} \qquad \text{(with Begin state)}
\end{aligned}$$

Training

Max likelihood estimates for transition probabilities are just the frequencies of transitions when emitting the training sequences

E.g., from 48 CpG islands in 60k bp:



+	A	C	G	T
A	0.180	0.274	0.426	0.120
C	0.171	0.368	0.274	0.188
G	0.161	0.339	0.375	0.125
T	0.079	0.355	0.384	0.182

−	A	C	G	T
A	0.300	0.205	0.285	0.210
C	0.322	0.298	0.078	0.302
G	0.248	0.246	0.298	0.208
T	0.177	0.239	0.292	0.292

Discrimination/Classification

Log likelihood ratio of CpG model vs background model

$$S(x) = \log \frac{P(x|\text{model}+)}{P(x|\text{model}-)} = \sum_{i=1}^{L} \log \frac{a^{+}_{x_{i-1}x_i}}{a^{-}_{x_{i-1}x_i}} = \sum_{i=1}^{L} \beta_{x_{i-1}x_i}$$

β	A	C	G	T
A	−0.740	0.419	0.580	−0.803
C	−0.913	0.302	1.812	−0.685
G	−0.624	0.461	0.331	−0.730
T	−1.169	0.573	0.393	−0.679

CpG Island Scores

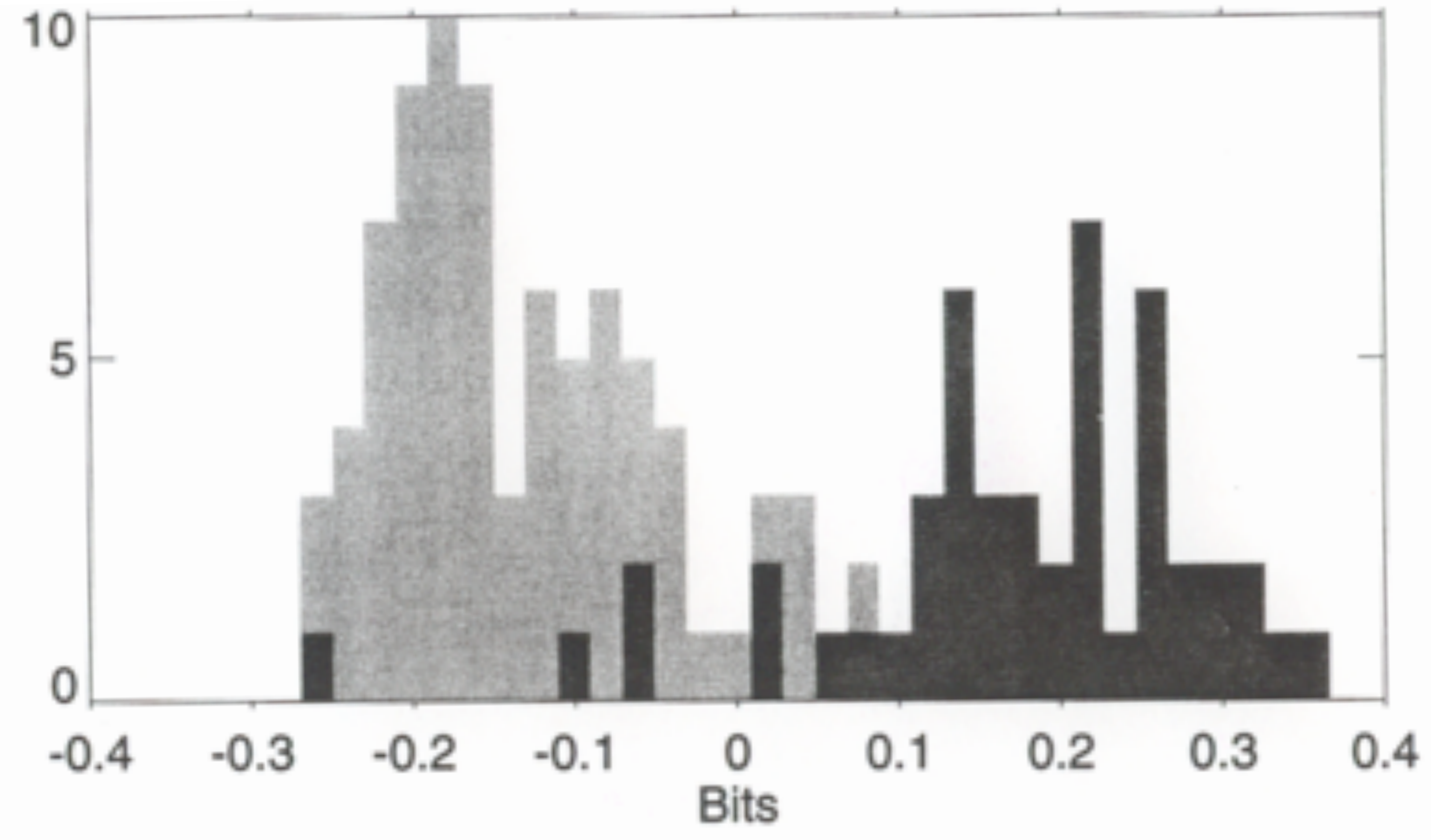
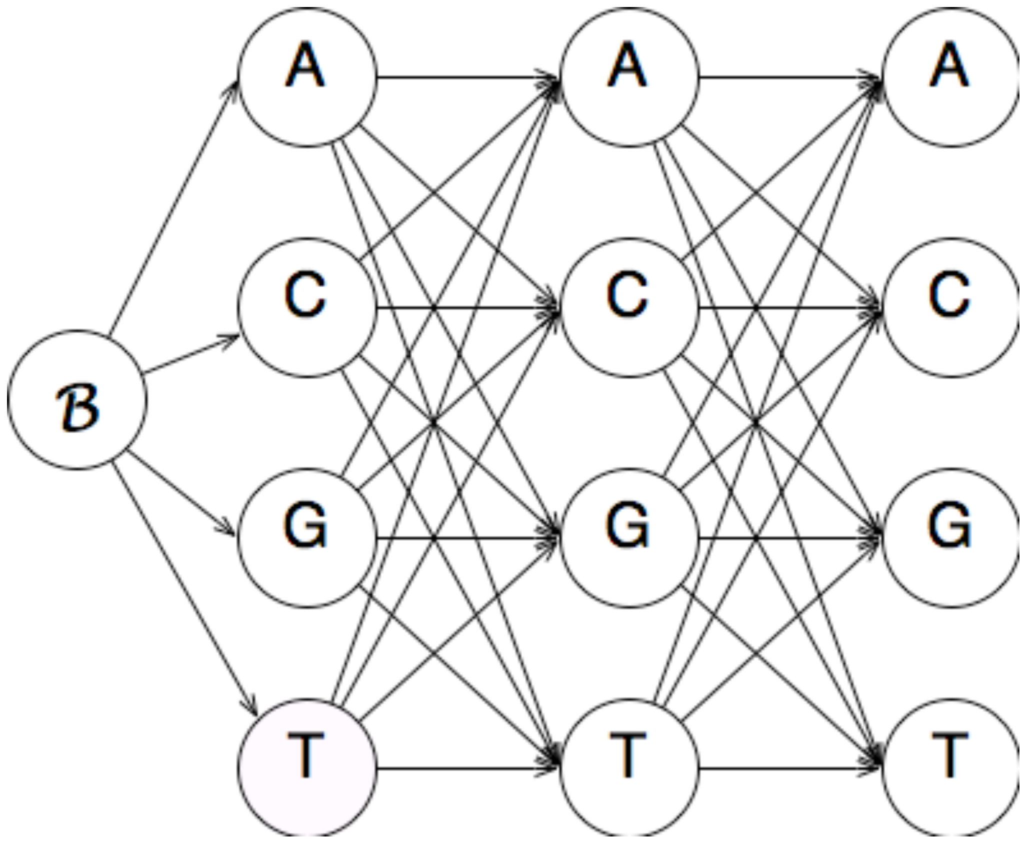


Figure 3.2 *The histogram of the length-normalised scores for all the sequences. CpG islands are shown with dark grey and non-CpG with light grey.*

Aside: 1st Order "WMM"



$$\underbrace{\qquad\qquad}_{\text{4 params}} \quad \underbrace{\qquad\qquad}_{\text{16 params}} \quad \underbrace{\qquad\qquad}_{\text{16 params}}$$

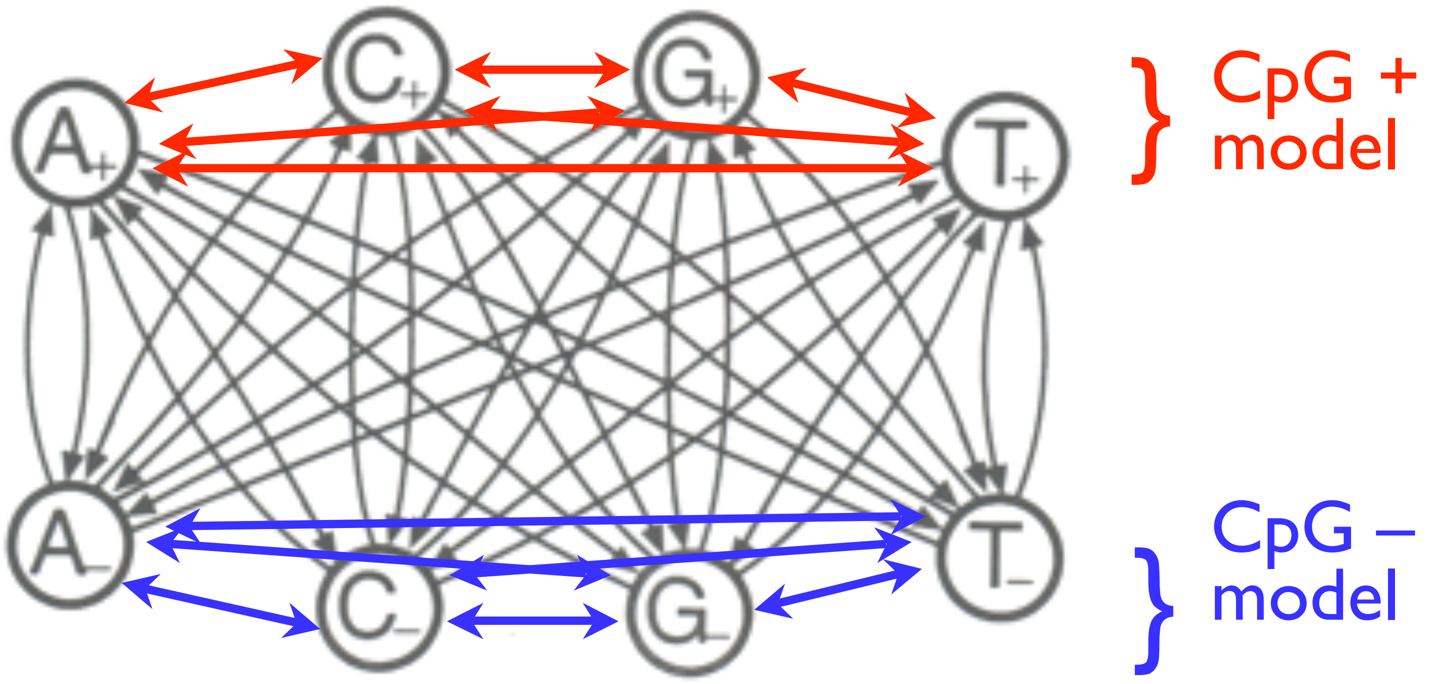
Questions

Q1: Given a *short* sequence, is it more likely from feature model or background model? Above

Q2: Given a *long* sequence, where are the features in it (if any)

- Approach 1: score 100 bp (e.g.) windows
    - Pro: simple
    - Con: arbitrary, fixed length, inflexible
- Approach 2: *combine* +/- models.

Combined Model



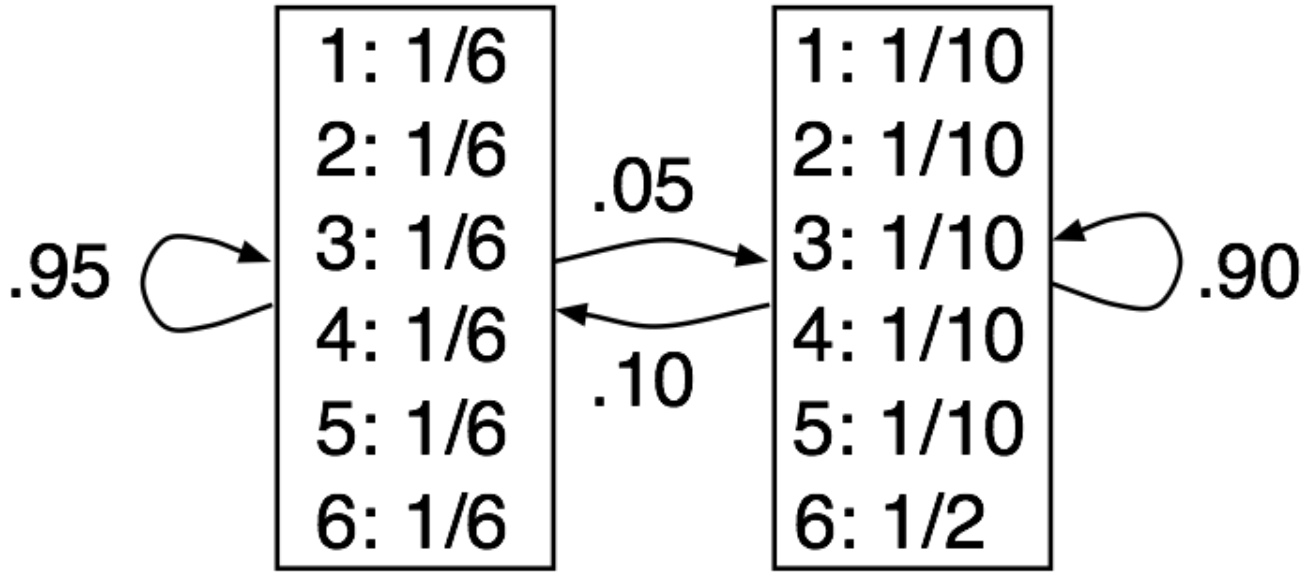
Emphasis is "Which (hidden) state?" not "Which model?"

Hidden Markov Models (HMMs)

States:	$1, 2, 3, \ldots$
Paths:	sequences of states $\pi = (\pi_1, \pi_2, \ldots)$
Transitions:	$a_{k,l} = P(\pi_i = l \mid \pi_{i-1} = k)$
Emissions:	$e_k(b) = P(x_i = b \mid \pi_i = k)$
Observed data:	emission sequence
Hidden data:	state/transition sequence

The Occasionally Dishonest Casino

1 fair die, 1 "loaded" die, occasionally swapped



```
Rolls   315116246446644245311321631164152133625144543631656626566666
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLL

Rolls   651166453132651245636664631636663162326455236266666625151631
Die     LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFF

Rolls   222555441666566563564324364131513465146353411126414626253356
Die     FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls   366163666466232534413661661163252562462255265252266435353336
Die     LLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls   233121625364414432335163243633665562466662632666612355245242
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5 *The numbers show 300 rolls of a die as described in the example. Below is shown which die was actually used for that roll (F for fair and L for loaded). Under that the prediction by the Viterbi algorithm is shown.*

Inferring hidden stuff

Joint probability of a given path π & emission sequence *x*:

$$P(x,\pi) = a_{0,\pi_1} \prod_{i=1}^{n} e_{\pi_i}(x_i) \cdot a_{\pi_i,\pi_{i+1}}$$

But π is hidden; what to do? Some alternatives:

Most probable single path

$$\pi^* = \arg\max_{\pi} P(x,\pi)$$

Sequence of most probable states

$$\hat{\pi}_i = \arg\max_{k} P(\pi_i = k \mid x)$$

The Viterbi Algorithm: The most probable path

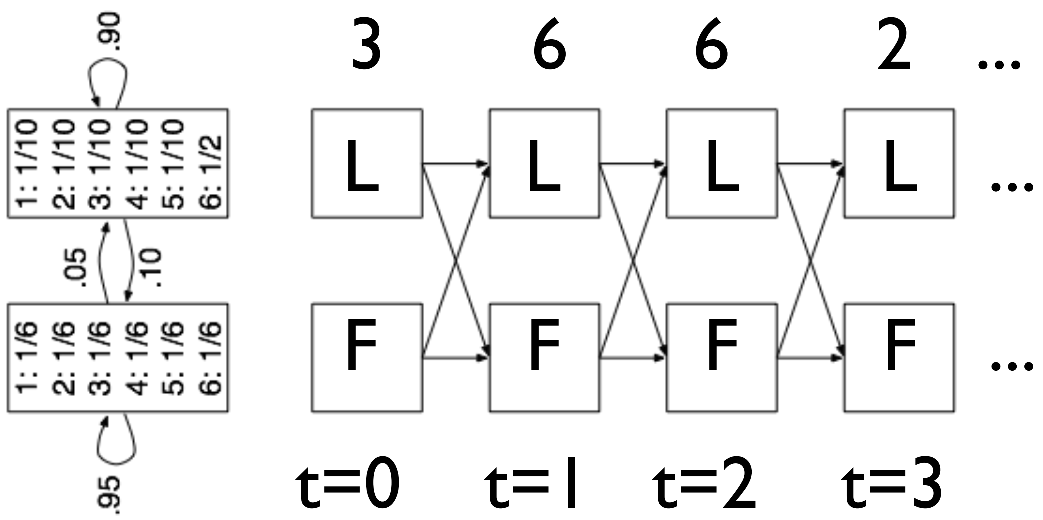
Viterbi finds: $\pi^* = \arg\max_{\pi} P(x, \pi)$

Possibly there are 10^{99} paths of prob 10^{-99}

More commonly, one path (+ slight variants) dominate others.
(If not, other approaches may be preferable.)

Key problem: exponentially many paths π

Unrolling an HMM



Conceptually, sometimes convenient

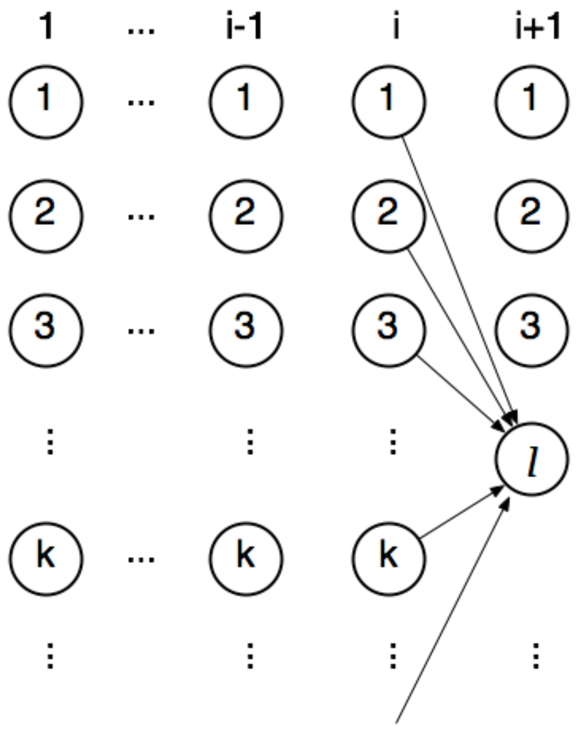
Note exponentially many paths

Viterbi

$v_l(i) =$ probability of the most probable path emitting $x_1, x_2, \ldots, x_i$ and ending in state l

Initialize:

$$v_l(0) = \begin{cases} 1 & \text{if } l = \textit{Begin} \text{ state} \\ 0 & \text{otherwise} \end{cases} \longrightarrow$$



General case:

$$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

Viterbi Traceback

Above finds *probability* of best path

To find the path itself, trace *backward* to the state *k* attaining the max at each stage

```
Rolls   315116246446644245311321631164152133625144543631656626566666
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLL

Rolls   651166453132651245636664631636663162326455236266666625151631
Die     LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls   222555441666566563564324364131513465146353411126414626253356
Die     FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

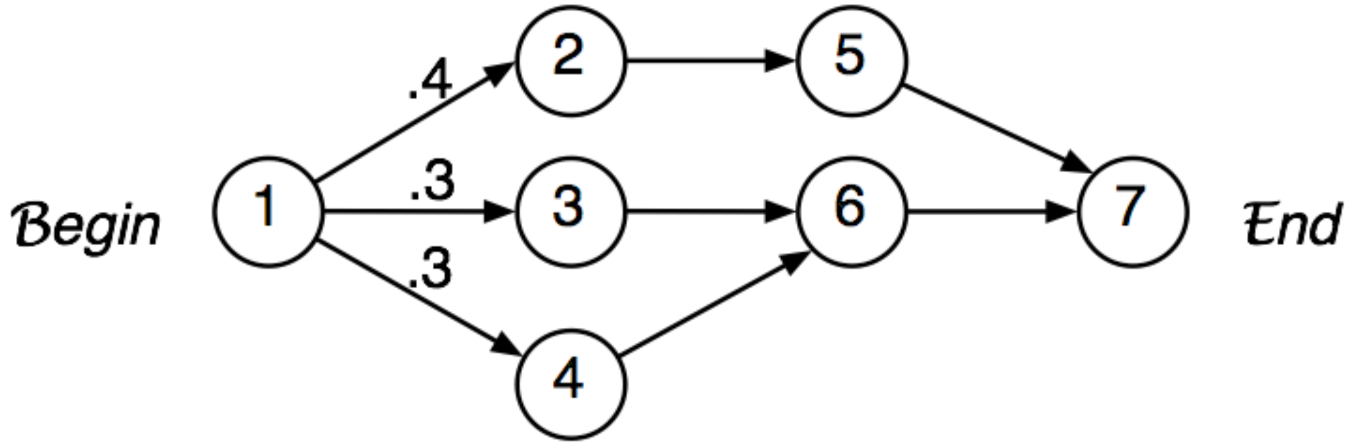
Rolls   366163666466232534413661661163252562462255265252266435353336
Die     LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls   233121625364414432335163243633665562466662632666612355245242
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5 *The numbers show 300 rolls of a die as described in the example. Below is shown which die was actually used for that roll (F for fair and L for loaded). Under that the prediction by the Viterbi algorithm is shown.*

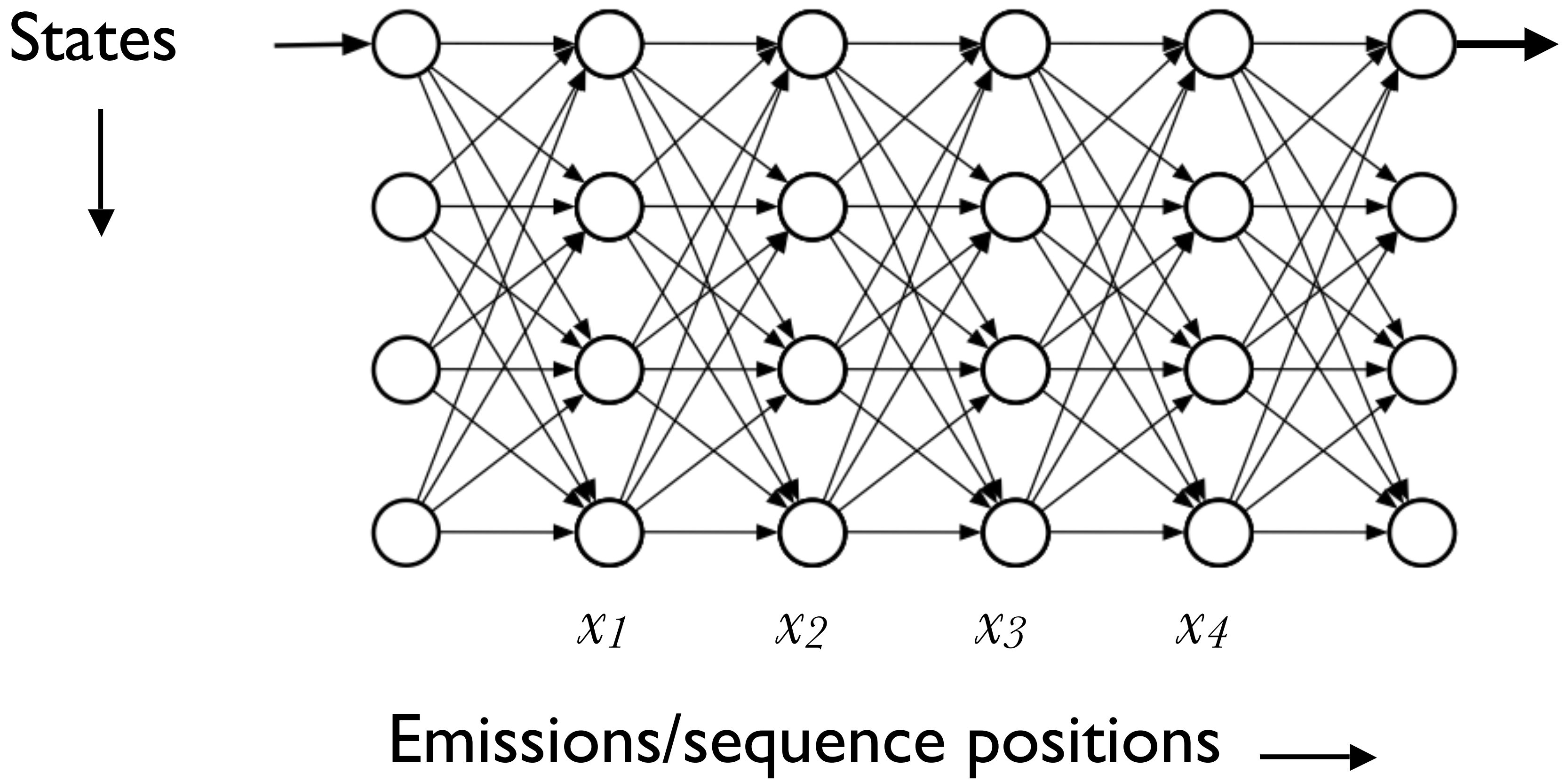
Is Viterbi “best”?

Viterbi finds $\pi^* = \arg\max_{\pi} P(x, \pi)$

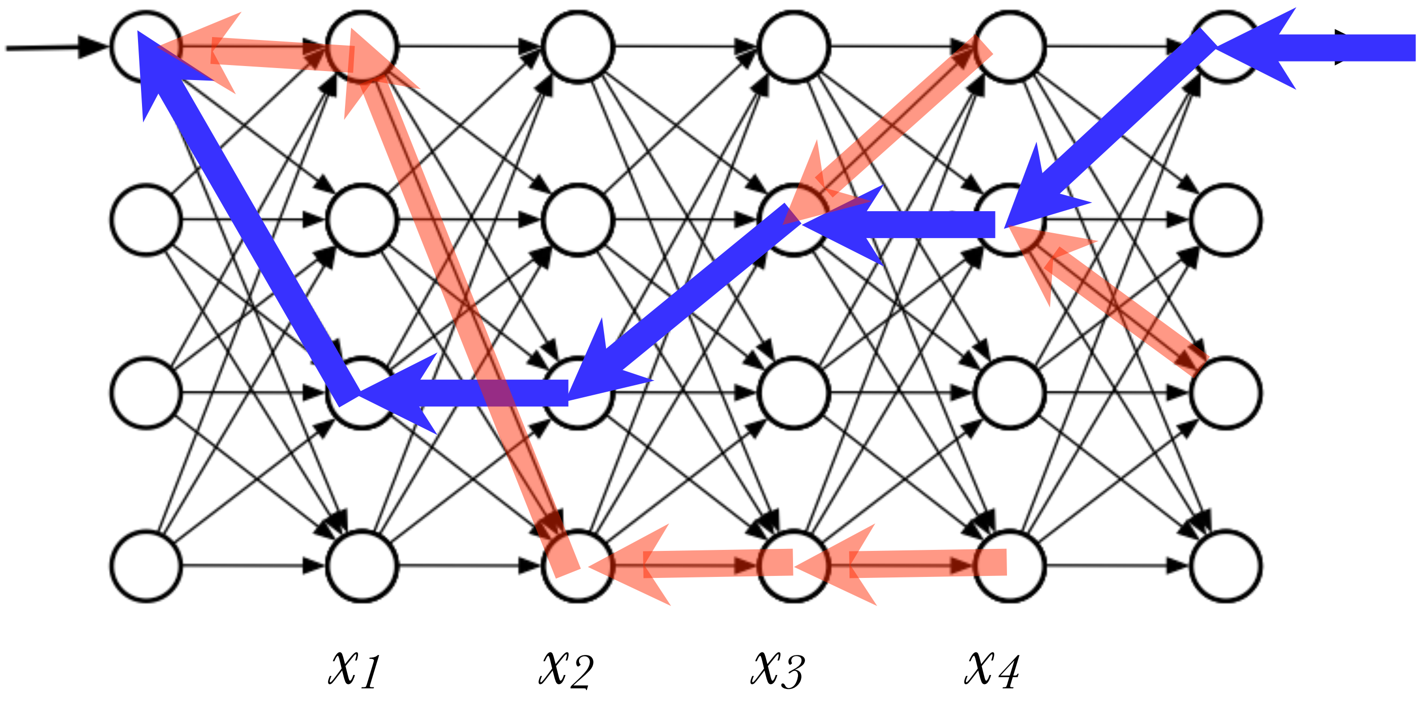


Most probable (Viterbi) *path* goes through 5, but most probable *state* at 2nd step is 6
(I.e., Viterbi is not the only interesting answer.)

An HMM (unrolled)



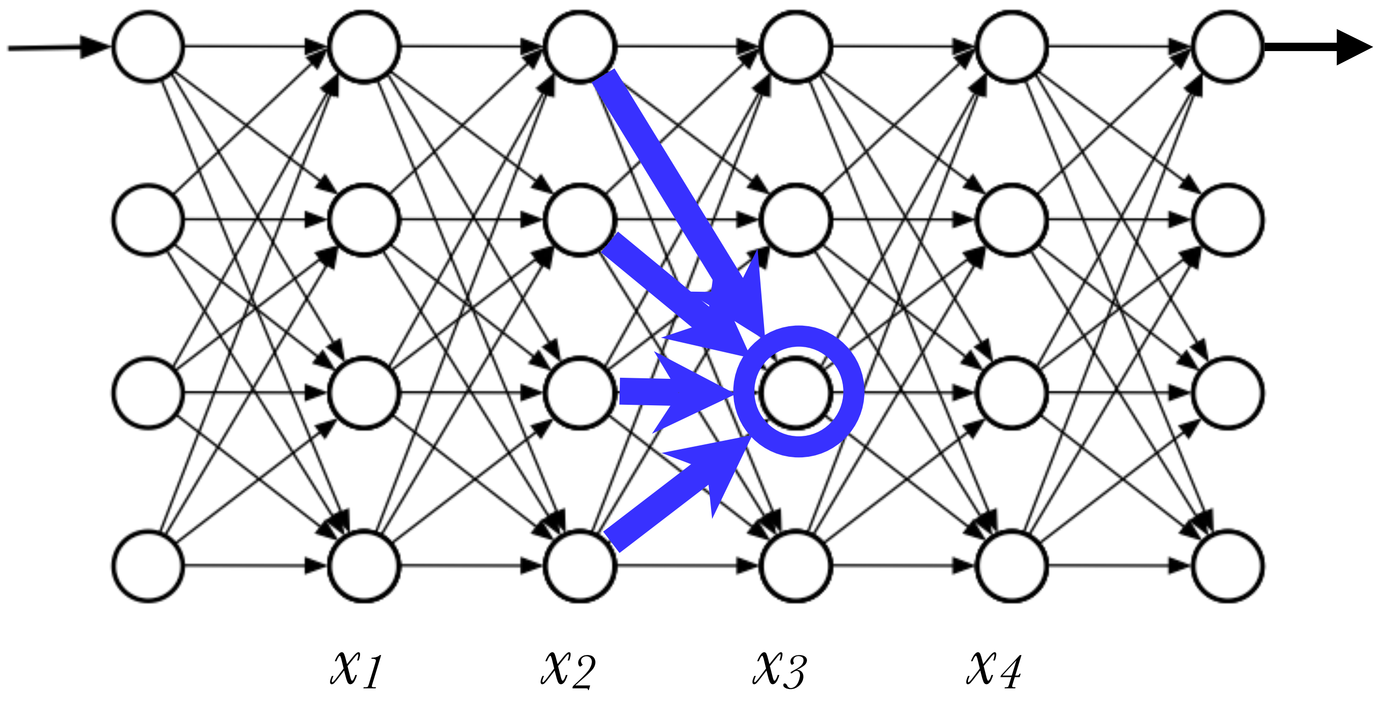
Viterbi: best path to each state



$$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

The Forward Algorithm

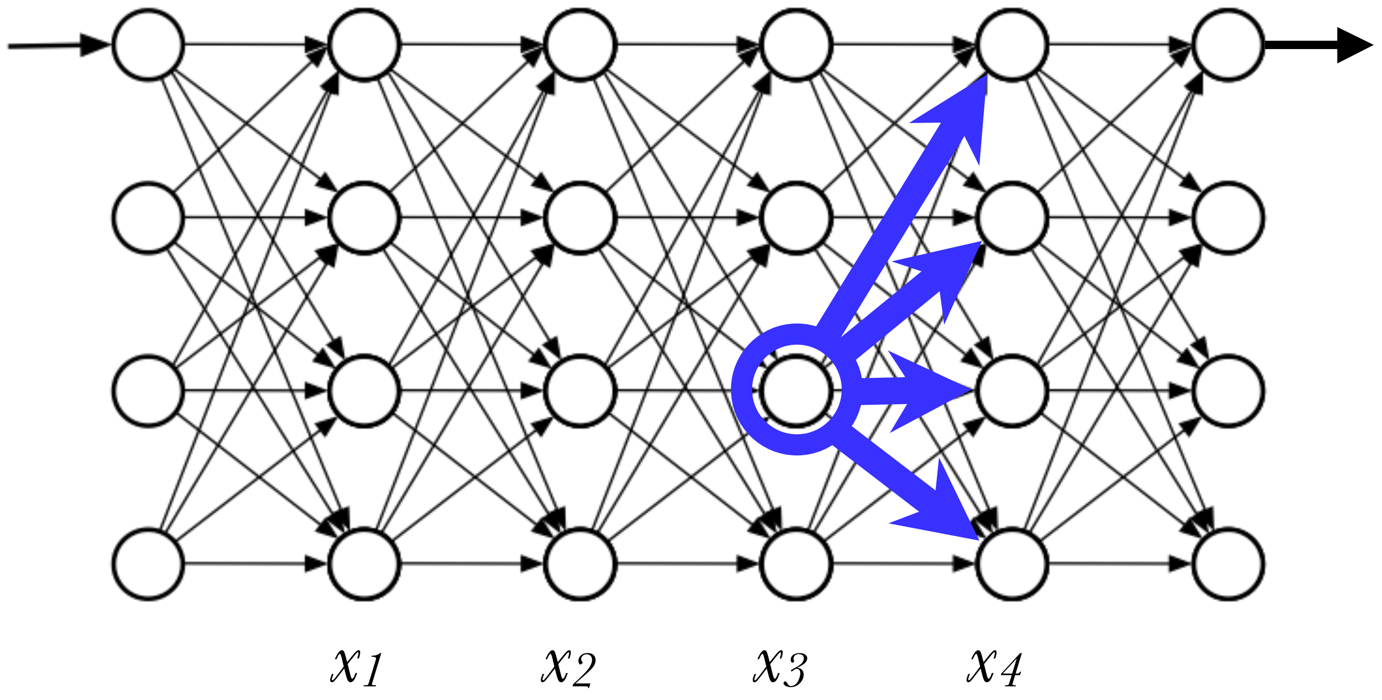
For each state/time, want *total* probability of all paths leading *to* it, with given emissions



$$
\begin{aligned}
f_k(i) &= P(x_1 \ldots x_i,\ \pi_i = k) \\
f_l(i+1) &= e_l(x_{i+1}) \textstyle\sum_k f_k(i) a_{k,l} \\
P(x) &= \textstyle\sum_\pi P(x,\pi) = \sum_k f_k(n) a_{k,0}
\end{aligned}
$$

The Backward Algorithm

Similar: for each state/time, want total probability of all paths *from* it, with given emissions, *conditional* on that state.



$$b_k(i) \triangleq P(x_{i+1} \cdots x_n \mid \pi_i = k)$$

$$b_k(i) = \sum_l a_{k,l}\, e_l(x_{i+1})\, b_l(i+1)$$

$$b_k(n) = a_{k,0}$$

In state *k* at step *i* ?

$$
\begin{aligned}
&P(x,\ \pi_i = k) \\
&\quad = \quad P(x_1, \ldots, x_i,\ \pi_i = k) \cdot P(x_{i+1}, \ldots, x_n \mid x_1, \ldots, x_i,\ \pi_i = k) \\
&\quad = \quad P(x_1, \ldots, x_i,\ \pi_i = k) \cdot P(x_{i+1}, \ldots, x_n \mid \pi_i = k) \\
&\quad = \quad f_k(i) \cdot b_k(i)
\end{aligned}
$$

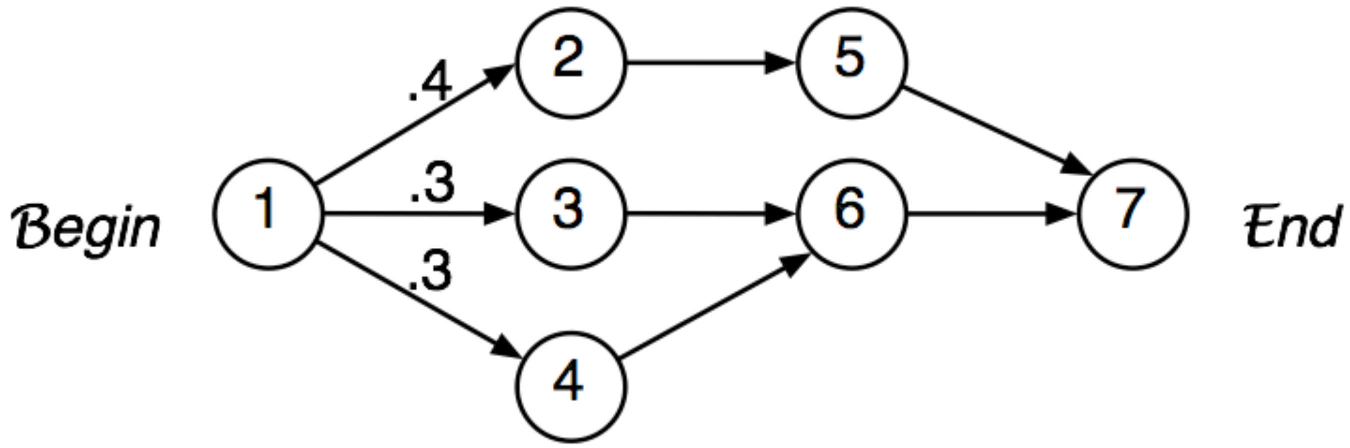
$$
P(\pi_i = k \mid x) \; = \; \frac{P(x, \pi_i = k)}{P(x)} \; = \; \frac{f_k(i) \cdot b_k(i)}{P(x)}
$$

Posterior Decoding, I

Alternative 1: what's the most likely state at step *i*?

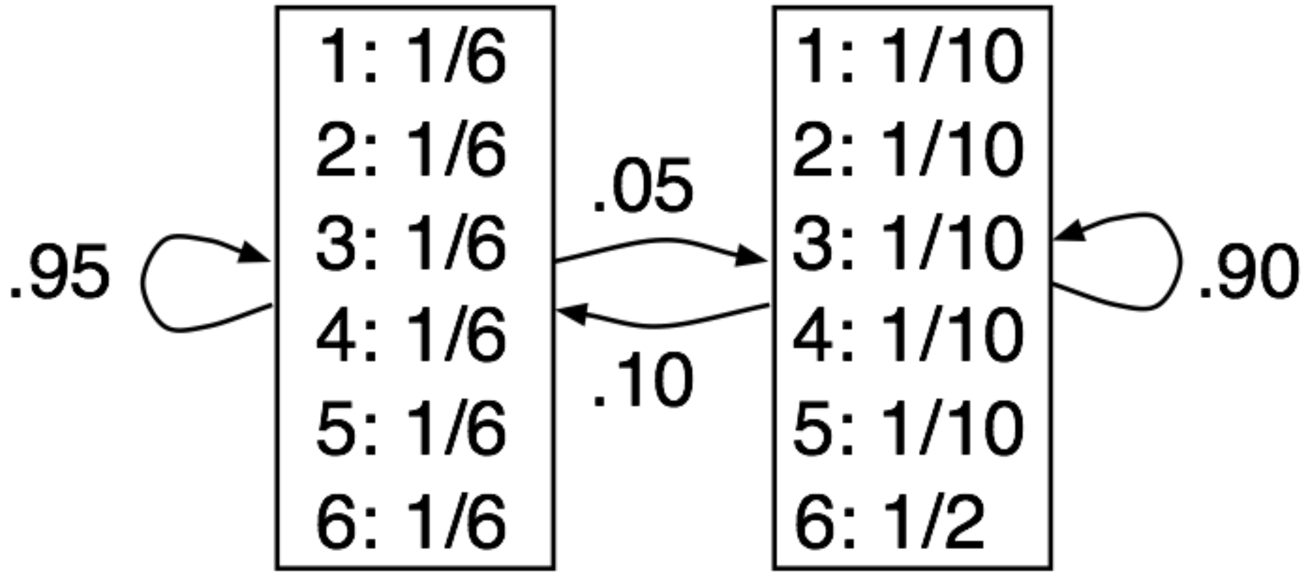
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

Note: the sequence of most likely states ≠ the most likely sequence of states. May not even be legal!



The Occasionally Dishonest Casino

1 fair die, 1 “loaded” die, occasionally swapped



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Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
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Rolls   651166453132651245636664631636663162326455236266666625151631
Die     LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls   222555441666566563564324364131513465146353411126414626253356
Die     FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

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Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

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Posterior Decoding

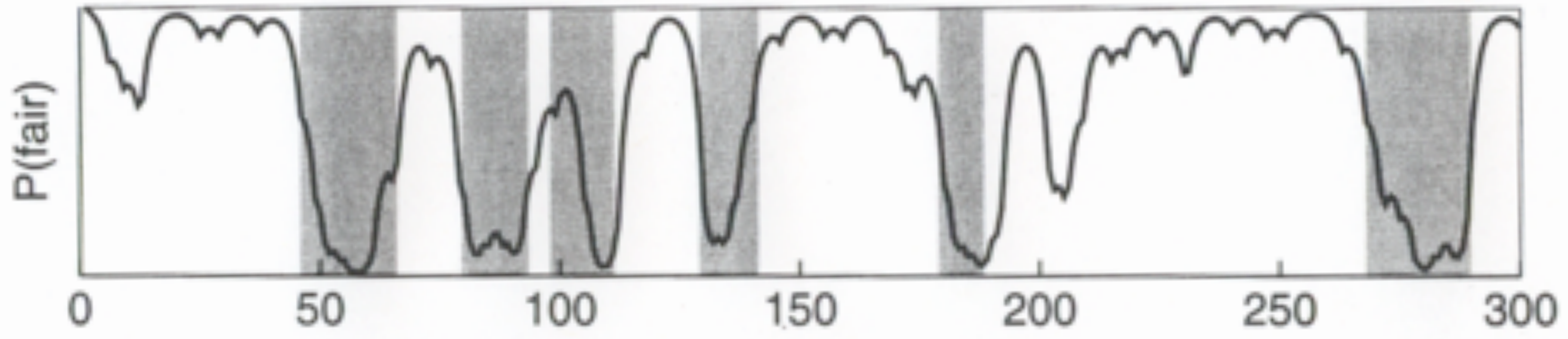


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

Posterior Decoding, II

Alternative 1: what's most likely state at step *i* ?

$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

Alternative 2: given some function *g(k)* on states, what's its expectation. E.g., what's probability of "+" model in CpG HMM (*g*(*k*)=1 iff *k* is "+" state)?

$$G(i \mid x) = \sum_k P(\pi_i = k \mid x) \cdot g(k)$$

CpG Islands again

Data: 41 human sequences, totaling 60kbp, including 48 CpG islands of about 1kbp each

Viterbi:	Post-process:
Found 46 of 48	46/48
plus 121 “false positives”	67 false pos
Posterior Decoding:	
same 2 false negatives	46/48
plus 236 false positives	83 false pos

Post-process: merge within 500; discard < 500

Training

Given model topology & training sequences, learn transition and emission probabilities

If π known, then MLE is just frequency observed in training data

$$\begin{aligned} a_{k,l} &= \frac{\text{count of } k \rightarrow l \text{ transitions}}{\text{count of } k \rightarrow \text{anywhere transitions}} \quad \longleftarrow \text{+ pseudocounts?} \\ e_k(b) &= \ldots \end{aligned}$$

If π hidden, then use EM:

given π, estimate θ; given θ estimate π. $\Big\}$ 2 ways

Viterbi Training

given π, estimate θ; given θ estimate π

Make initial estimates of parameters θ

Find Viterbi path π for each training sequence

Count transitions/emissions on those paths, getting new θ

Repeat

Not rigorously optimizing desired likelihood, but still useful & commonly used.

(Arguably good if you're doing Viterbi decoding.)

Baum-Welch Training

given θ, estimate π ensemble; then re-estimate θ

$$P(\pi_i = k,\ \pi_{i+1} = l \mid x, \theta)$$

$$= \frac{f_k(i \mid \theta)\ a_{k,l}\ e_l(x_{i+1})\ b_l(i+1 \mid \theta)}{P(x \mid \theta)}$$

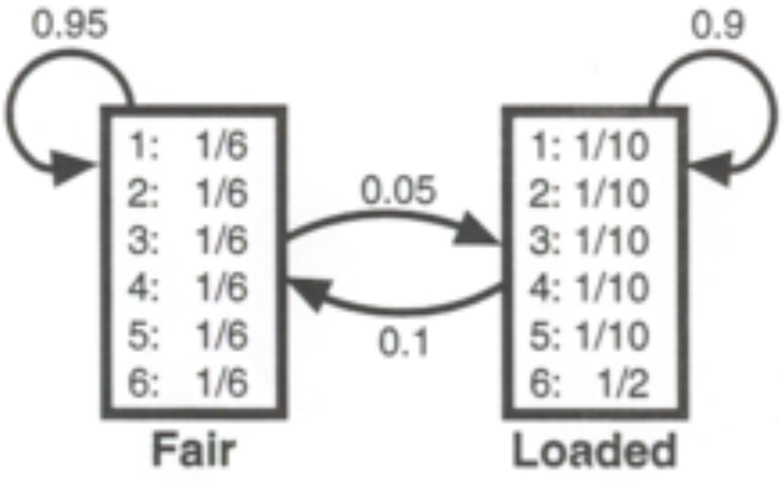
Estimated # of $k \rightarrow l$ transitions $\hat{A}_{k,l}$

$$= \sum_{\text{training seqs } x^j} \sum_i P(\pi_i = k,\ \pi_{i+1} = l \mid x^j, \theta)$$

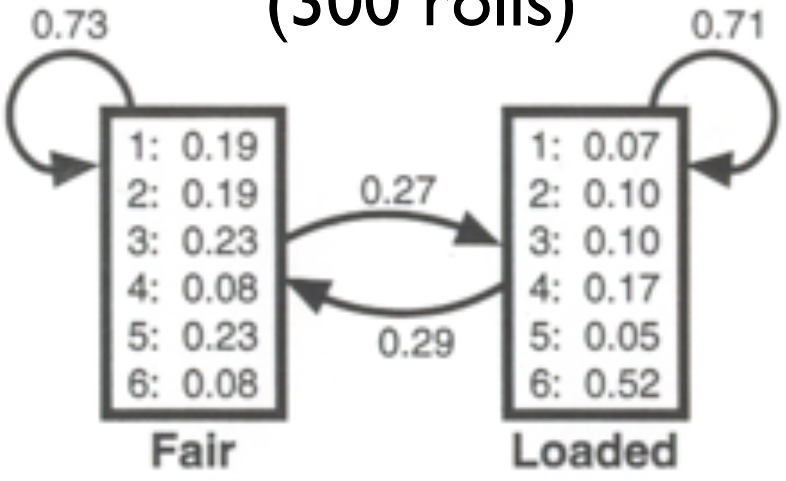
New estimate $\hat{a}_{k,l} = \dfrac{\hat{A}_{k,l}}{\sum_l \hat{A}_{k,l}}$

Emissions: similar

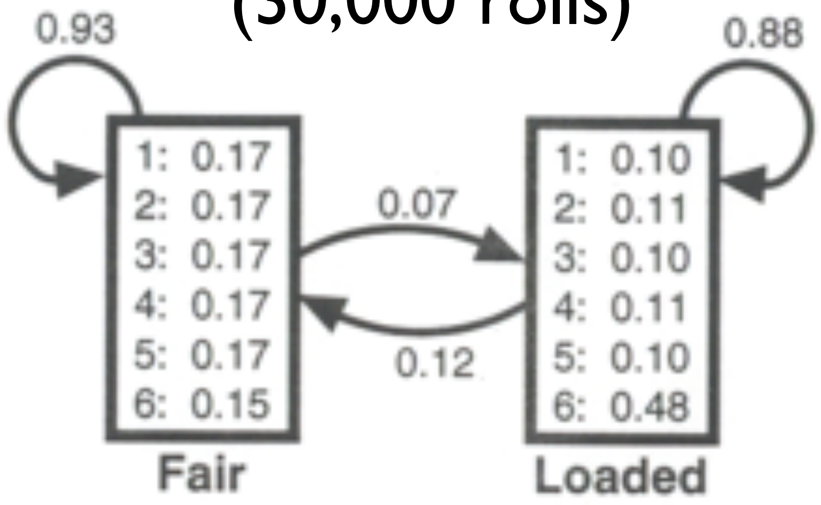
True Model



B-W Learned Model (300 rolls)



B-W Learned Model (30,000 rolls)



Log-odds per roll

True model	0.101 bits
300-roll est.	0.097 bits
30k-roll est.	0.100 Bits

(NB: overfitting)

HMM Summary

Viterbi – best single path (max of products)

joint vs conditional probs

Forward – Sum over all paths (sum of products)

Backward – similar

Baum-Welch – Training via EM and forward/backward (aka the forward/backward algorithm)

Viterbi training – also "EM", but Viterbi-based

HMMs in Action: Pfam

Proteins fall into families, both across & within species

Ex: Globins, GPCRs, Zinc Fingers, Leucine zippers,...

Identifying family very useful: suggests function, etc.

So, search & alignment are both important

One very successful approach: profile HMMs

```
Helix                 AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBBCCCCCCCCCCC
HBA_HUMAN  ---------VLSPADKTNVKAAWGKVGA--HAGEYGAEALERMFLSFPTTKTYFPHF
HBB_HUMAN  --------VHLTPEEKSAVTALWGKV----NVDEVGGEALGRLLVVYPWTQRFFESF
MYG_PHYCA  ---------VLSEGEWQLVLHVWAKVEA--DVAGHGQDILIRLFKSHPETLEKFDRF
GLB3_CHITP ----------LSADQISTVQASFDKVKG------DPVGILYAVFKADPSIMAKFTQF
GLB5_PETMA PIVDTGSVAPLSAAEKTKIRSAWAPVYS--TYETSGVDILVKFFTSTPAAQEFFPKF
LGB2_LUPLU --------GALTESQAALVKSSWEEFNA--NIPKHTHRFFILVLEIAPAAKDLFS-F
GLB1_GLYDI ---------GLSAAQRQVIAATWKDIAGADNGAGVGKDCLIKFLSAHPQMAAVFG-F
Consensus            Ls....  v a W kv .  .    g . L.. f . P .   F  F

Helix          DDDDDDDEEEEEEEEEEEEEEEEEEEEE            FFFFFFFFFFFF
HBA_HUMAN  -DLS-----HGSAQVKGHGKKVADALTNAVAHV---D--DMPNALSALSDLHAHKL-
HBB_HUMAN  GDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHL---D--NLKGTFATLSELHCDKL-
MYG_PHYCA  KHLKTEAEMKASEDLKKHGVTVLTALGAILKK----K-GHHEAELKPLAQSHATKH-
GLB3_CHITP AG-KDLESIKGTAPFETHANRIVGFFSKIIGEL--P---NIEADVNTFVASHKPRG-
GLB5_PETMA KGLTTADQLKKSADVRWHAERIINAVNDAVASM--DDTEKMSMKLRDLSGKHAKSF-
LGB2_LUPLU LK-GTSEVPQNNPELQAHAGKVFKLVYEAAIQLQVTGVVVTDATLKNLGSVHVSKG-
GLB1_GLYDI SG----AS---DPGVAALGAKVLAQIGVAVSHL--GDEGKMVAQMKAVGVRHKGYGN
Consensus   .  t    .. . v..Hg kv. a   a...l   d   . a l. l   H  .

Helix       FFGGGGGGGGGGGGGGGGGGG     HHHHHHHHHHHHHHHHHHHHHHHHHH
HBA_HUMAN  -RVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR------
HBB_HUMAN  -HVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH------
MYG_PHYCA  -KIPIKYLEFISEAIIHVLHSRHPGDFGADAQGAMNKALELFRKDIAAKYKELGYQG
GLB3_CHITP --VTHDQLNNFRAGFVSYMKAHT--DFA-GAEAAWGATLDTFFGMIFSKM-------
GLB5_PETMA -QVDPQYFKVLAAVIADTVAAG---------DAGFEKLMSMICILLRSAY-------
LGB2_LUPLU --VADAHFPVVKEAILKTIKEVVGAKWSEELNSAWTIAYDELAIVIKKEMNDAA---
GLB1_GLYDI KHIKAQYFEPLGASLLSAMEHRIGGKMNAAAKDAWAAAYADISGALISGLQS-----
Consensus    v.   f  l . ..  ....    f   . aa. k. .     l sky
```

Alignment of 7 globins. A-H mark 8 alpha helices.

Consensus line: upper case = 6/7, lower = 4/7, dot=3/7.

Could we have a profile (aka weight matrix) w/ indels?

Profile Hmm Structure

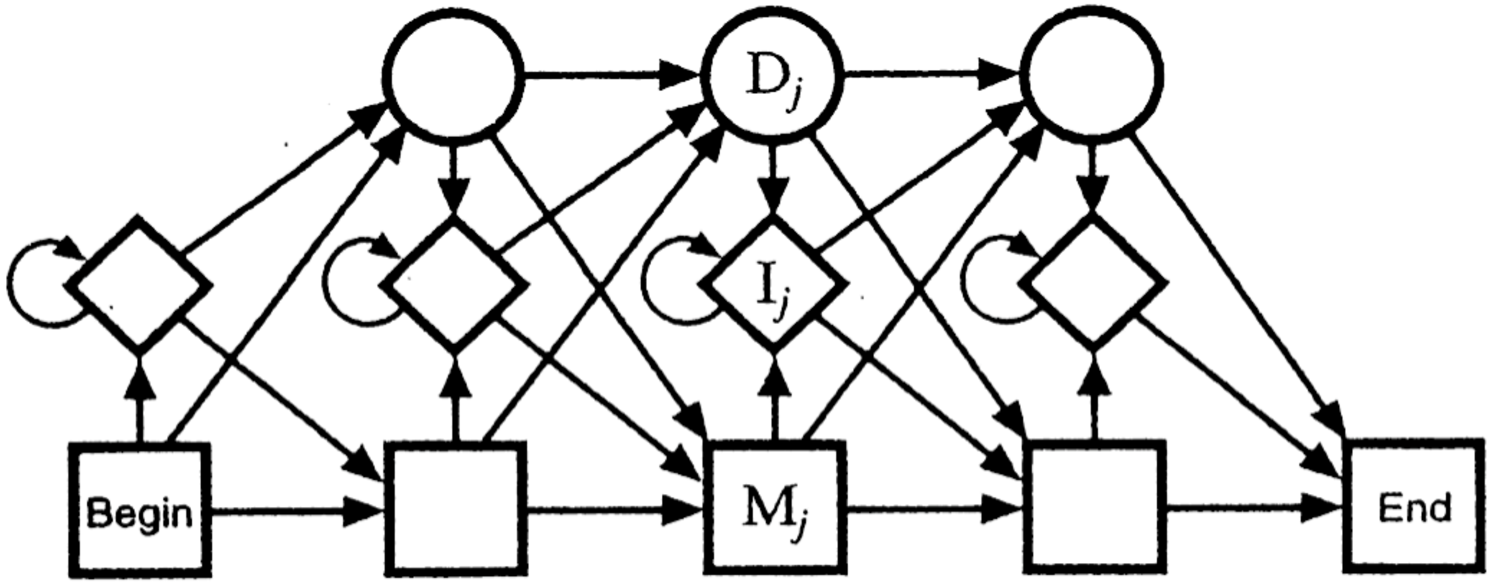
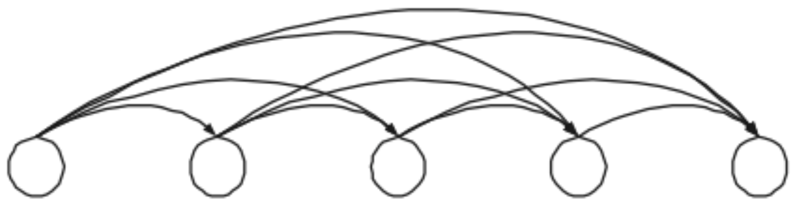


Figure 5.2 *The transition structure of a profile HMM.*

M_j:	Match states (20 emission probabilities)
I_j:	Insert states (Background emission probabilities)
D_j:	Delete states (silent - no emission)

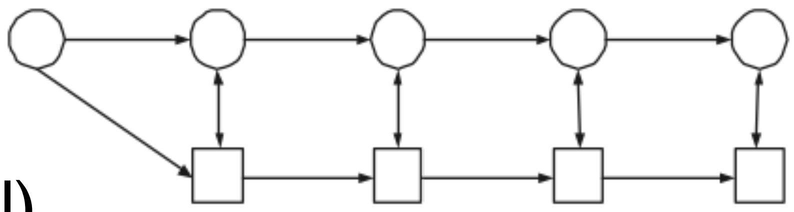
Silent States

Example: chain of states, can skip some



Problem: many parameters.

A solution: chain of "silent" states; fewer parameters (but less detailed control)



Algorithms: basically the same.

Using Profile HMM’s

- Search
  - Forward or Viterbi
  - Scoring
    - Log likelihood (length adjusted)
    - Log odds vs background
    - Z scores from either

$\left.\begin{array}{l} \\ \\ \\ \end{array}\right\}$ next slides

- Alignment
  - Viterbi

Likelihood vs Odds Scores

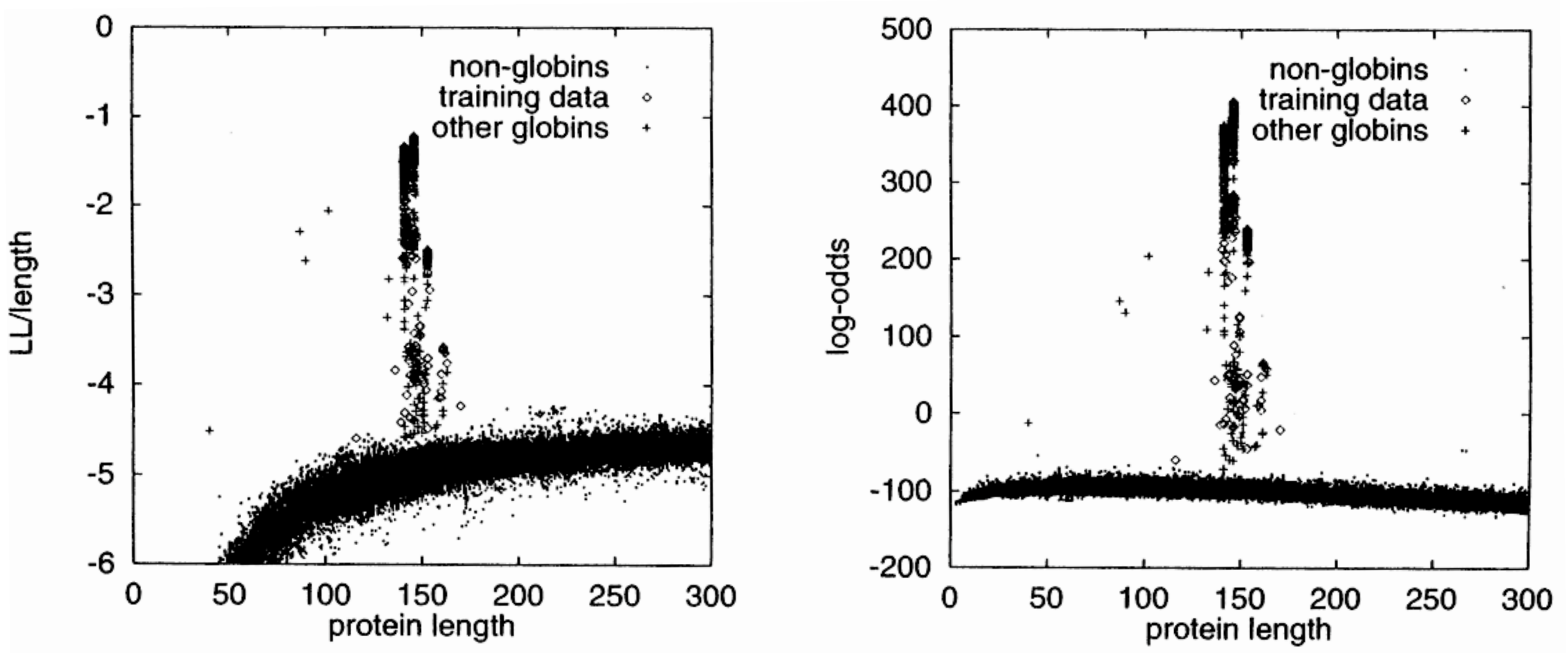


Figure 5.5 *To the left the length-normalized LL score is shown as a function of sequence length. The right plot shows the same for the log-odds score.*

Z-Scores

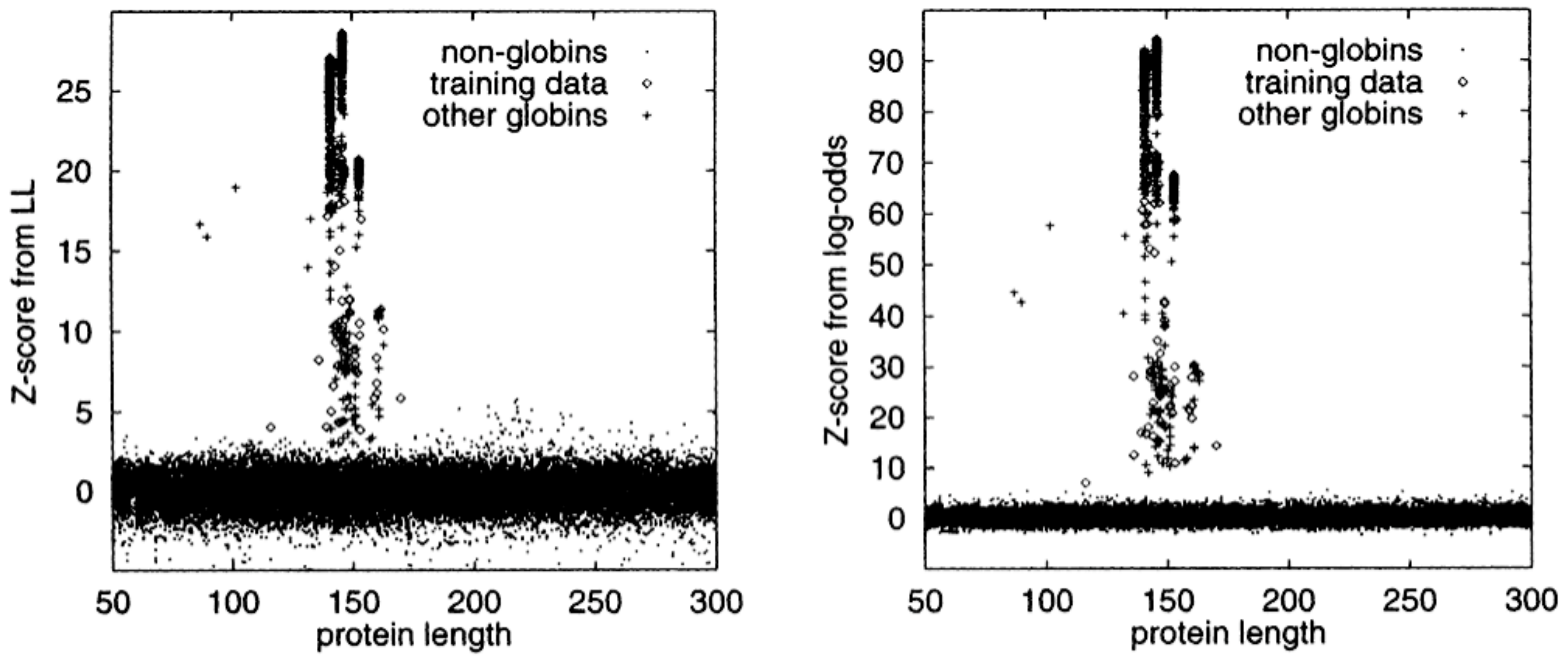


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

Pfam Model Building

Hand-curated “seed” multiple alignments

Train profile HMM from seed alignment

Hand-chosen score threshold(s)

Automatic classification/alignment of all other protein sequences

7973 families in Rfam 18.0, 8/2005 (covers ~75% of proteins)

Model-building refinements

Pseudocounts (count = 0 common when training with 20 aa's)

$$e_i(a) = \frac{C_{i,a} + A \cdot q_a}{\sum_a C_{i,a} + A}, \quad A \sim 20, \; q_a = \text{ background}$$

(~50 training sequences)

Pseudocount "mixtures", e.g. separate pseudocount vectors for various contexts (hydrophobic regions, buried regions,...)

(~10-20 training sequences)

More refinements

Weighting: may need to down weight highly similar sequences to reflect phylogenetic or sampling biases, etc.

Match/insert assignment: Simple threshold, e.g. "> 50% gap ⇒ insert", may be suboptimal. Can use forward-algorithm-like dynamic programming to compute max *a posteriori* assignment.

Numerical Issues

Products of many probabilities → 0

For Viterbi: just add logs

For forward/backward: also work with logs, but you need sums of products, so need "log-of-sum-of-product-of-exp-of-logs", e.g., by table/interpolation

Keep high precision and perhaps scale factor

Working with log-odds also helps.

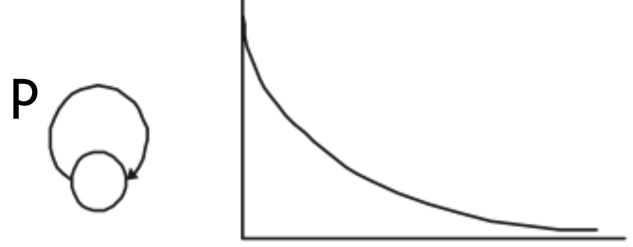
Model structure

Define it as well as you can.

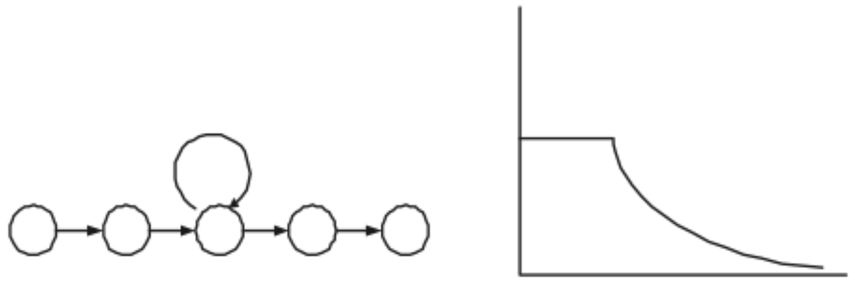
In principle, you can allow all transitions and hope to learn their probabilities from data, but it usually works poorly – too many local optima

Duration Modeling

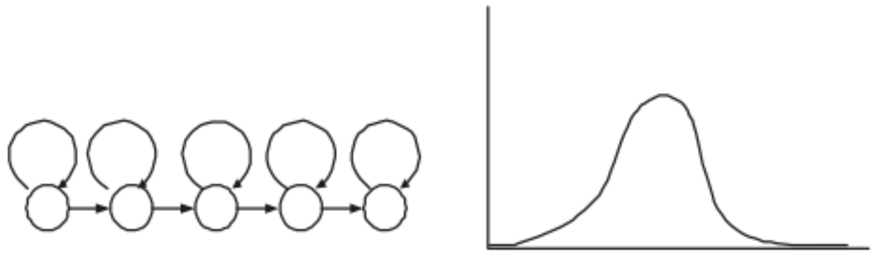
Self-loop duration:
  geometric pn(1-p)



min, then geometric



“negative binomial”



More general: possible (but slower)