CSE 427

Markov Models and Hidden Markov Models

http://upload.wikimedia.org/wikipedia/commons/b/ba/Calico_cat

Dosage Compensation and X-Inactivation

2 copies (mom/dad) of each chromosome 1-22

Mostly, both copies of each gene are expressed

E.g., A B O blood group defined by 2 alleles of 1 gene

Women (XX) get double dose of X genes (vs XY)?

So, early in embryogenesis:

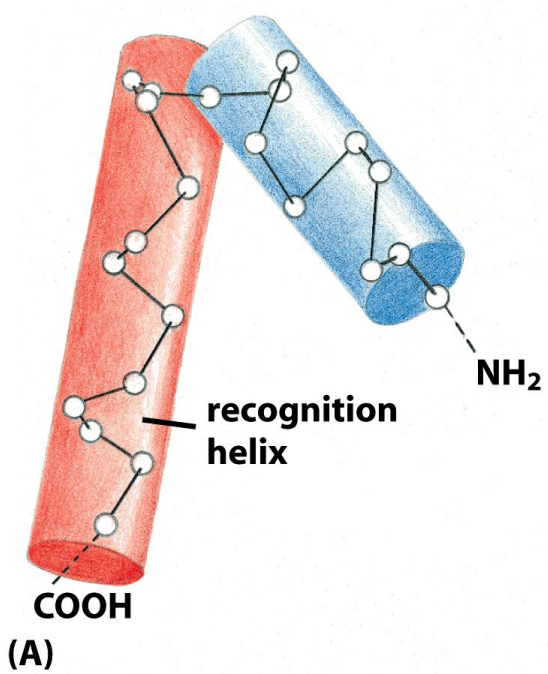
- One X randomly inactivated in each cell
- Choice maintained in daughter cells

} How?

Calico: a major coat color gene is on X

Reminder: Proteins "Read" DNA

E.g.:



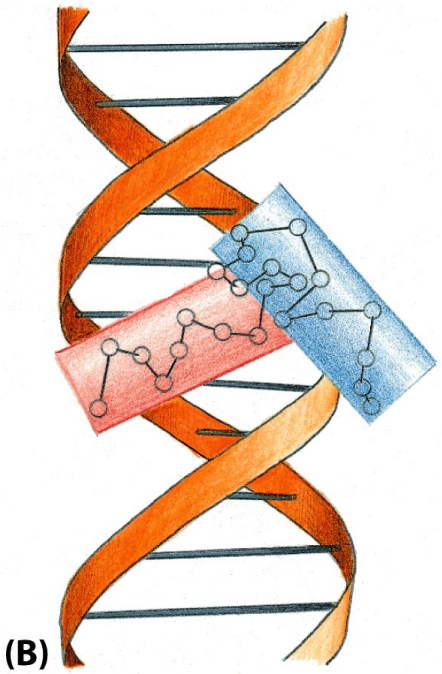


Figure 7-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

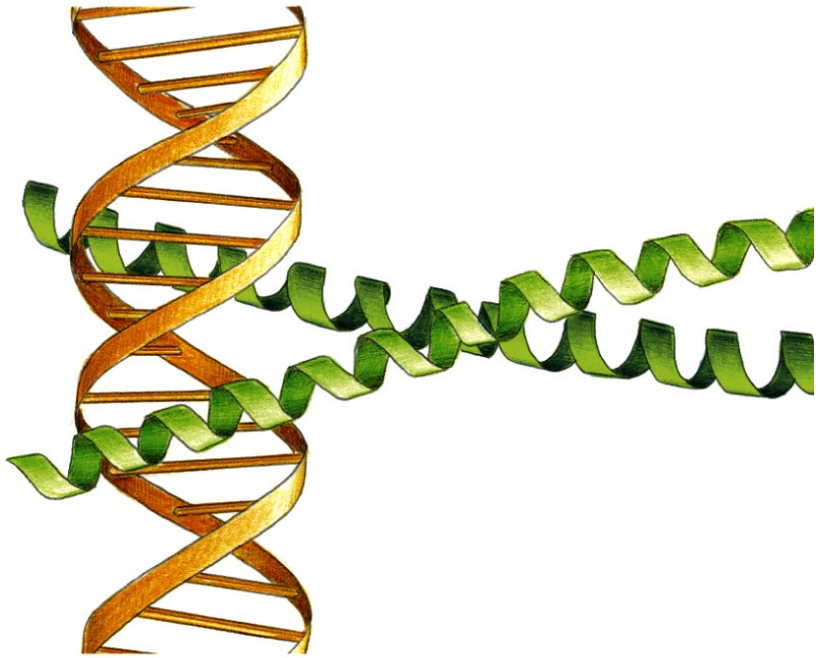


Figure 7-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Down in the Groove

Different patterns of hydrophobic methyls, potential H bonds, etc. at edges of different base pairs. They're accessible, esp. in major groove

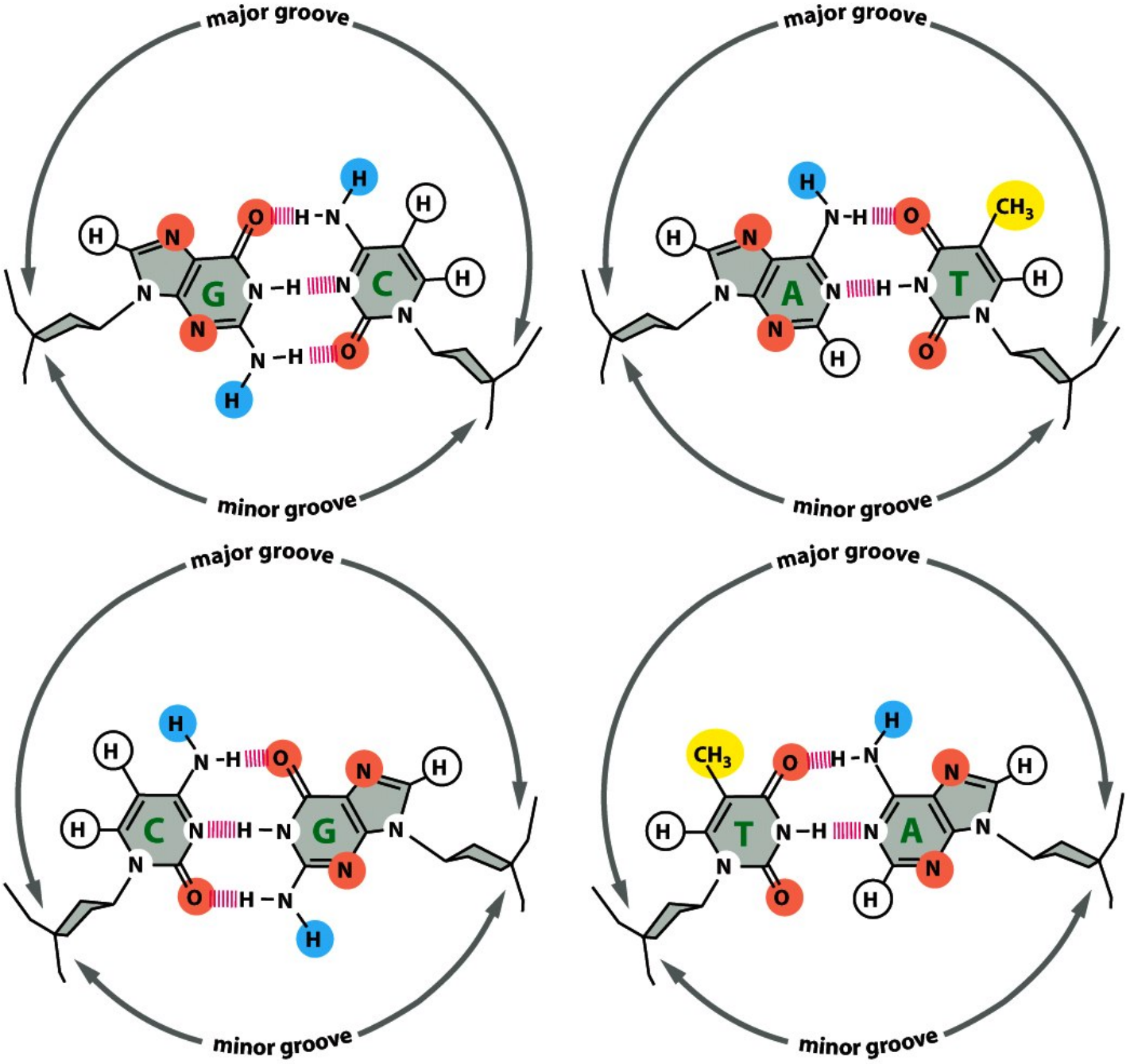
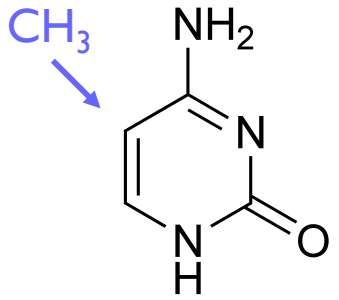


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

DNA Methylation

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

C of CpG is often (70-80%) methylated in mammals i.e., CH_3 group added (both strands)



cytosine

Same Pairing

Methyl-C alters major groove profile (∴ TF binding), but not base-pairing, transcription or replication

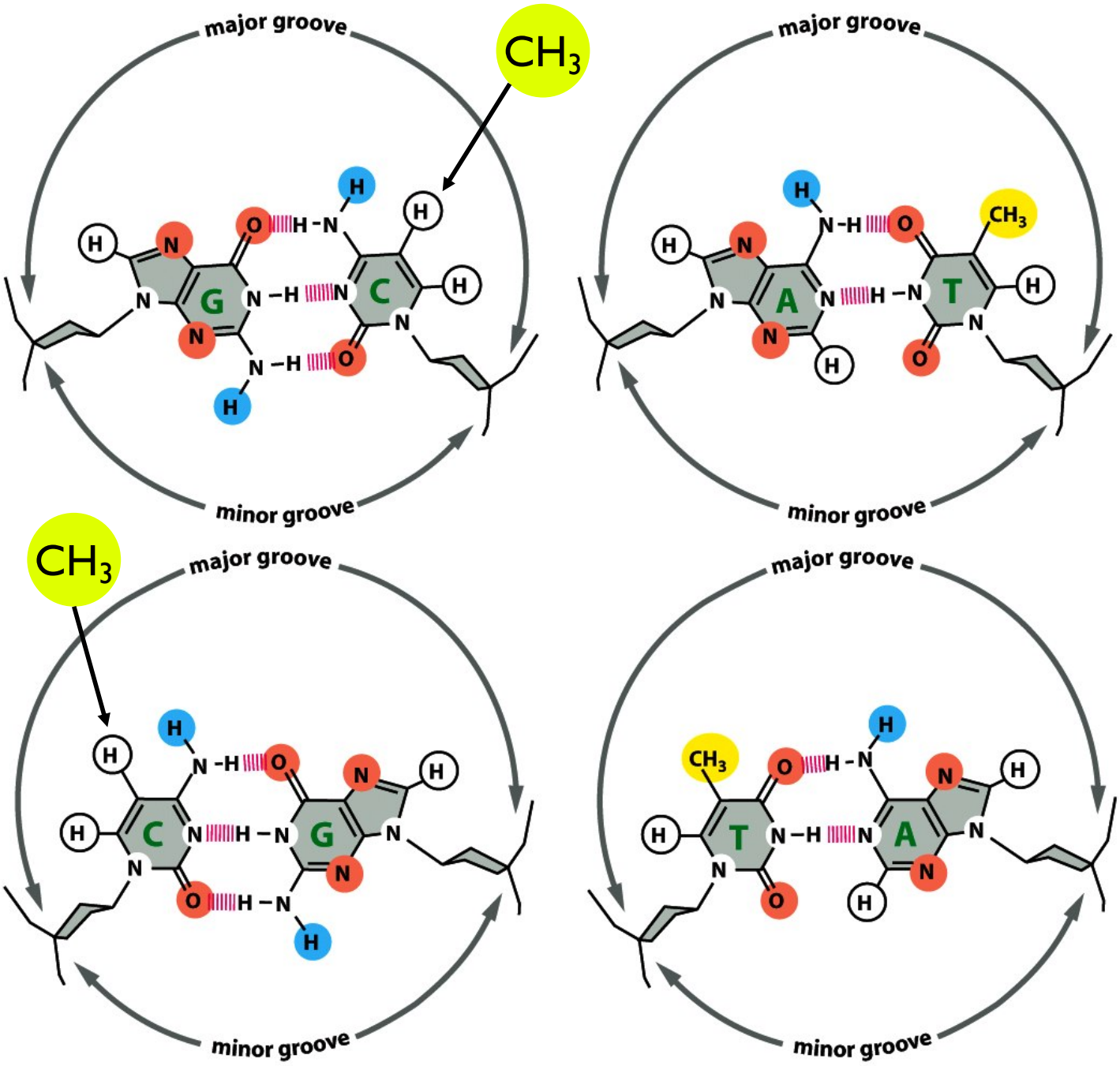
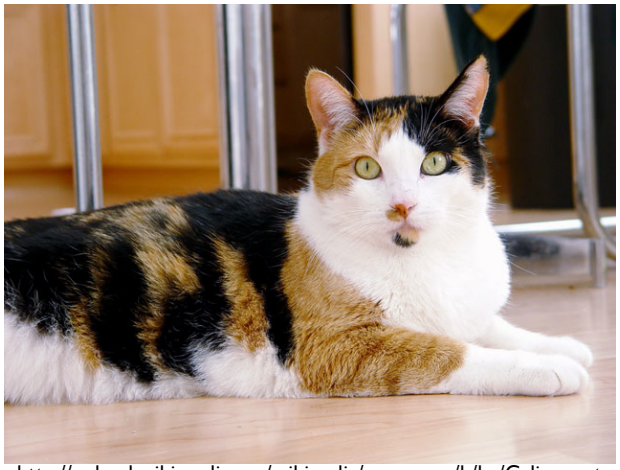


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Calico Cats



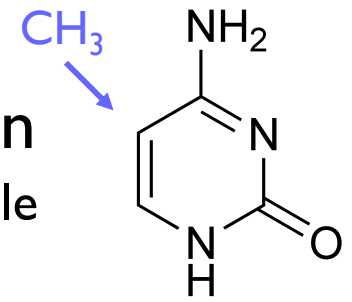
http://upload.wikimedia.org/wikipedia/commons/b/ba/Calico_cat

Calico cat story: patchwork coat-color in some female cats partially explained by X-inactivation

And heavily methylating the inactive X is part of the mechanism of X-inactivation

And methylation is broadly important for other reasons, and sculpts the genome…

DNA Methylation–Why



cytosine

In vertebrates, it generally silences transcription

(Epigenetics) X-inactivation, imprinting, repression of mobile elements, cancers, aging, and developmental differentiation

E.g., if a stem cell divides, one daughter fated to be liver, other kidney, need to

(a) Turn off liver genes in kidney & vice versa, and

(b) Remember that through subsequent cell divisions

How? One way:

(a) Methylate genes, esp. promoters, to silence them

(b) After ÷, DNA methyltransferases convert hemi- to fully-methylated (not trivial: deleting methyltransferase is embrionic-lethal in mice)

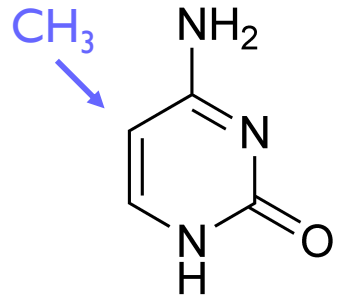
Major exception: promoters of "housekeeping" genes

"CpG Islands"

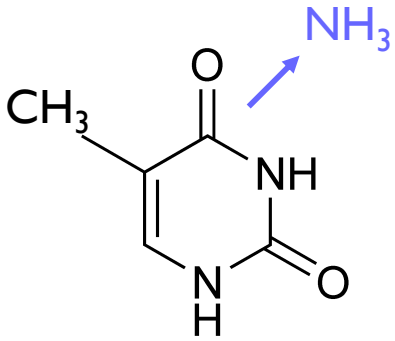
Methyl-C mutates to T relatively easily

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

BUT in some regions (e.g. active promoters), CpGs 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 (say, CpG/GpC>50%)
- More C & G than elsewhere, too (say, C+G>50%)
- 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 (see also online reading page):

Eddy, "What is a hidden Markov model?" Nature Biotechnology, 22, #10 (2004) 1315-6.

Durbin, Eddy, Krogh and Mitchison, "Biological Sequence Analysis", Cambridge, 1998 (esp. chs 3, 5)

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: Previous models we've talked about assume *independence* of nucleotides in different positions - definitely unrealistic.

Markov models allow us to relax that assumption.

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:

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

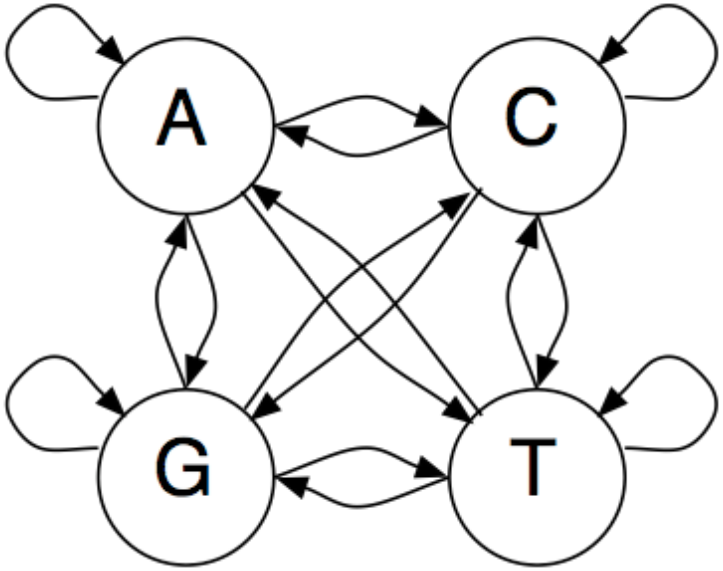
i-1 (left) k typically ≪ i-1 (right)

Example 1: Uniform random ACGT } 0th order

Example 2: Weight matrix model } 0th order

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

A Markov Model (1st order)

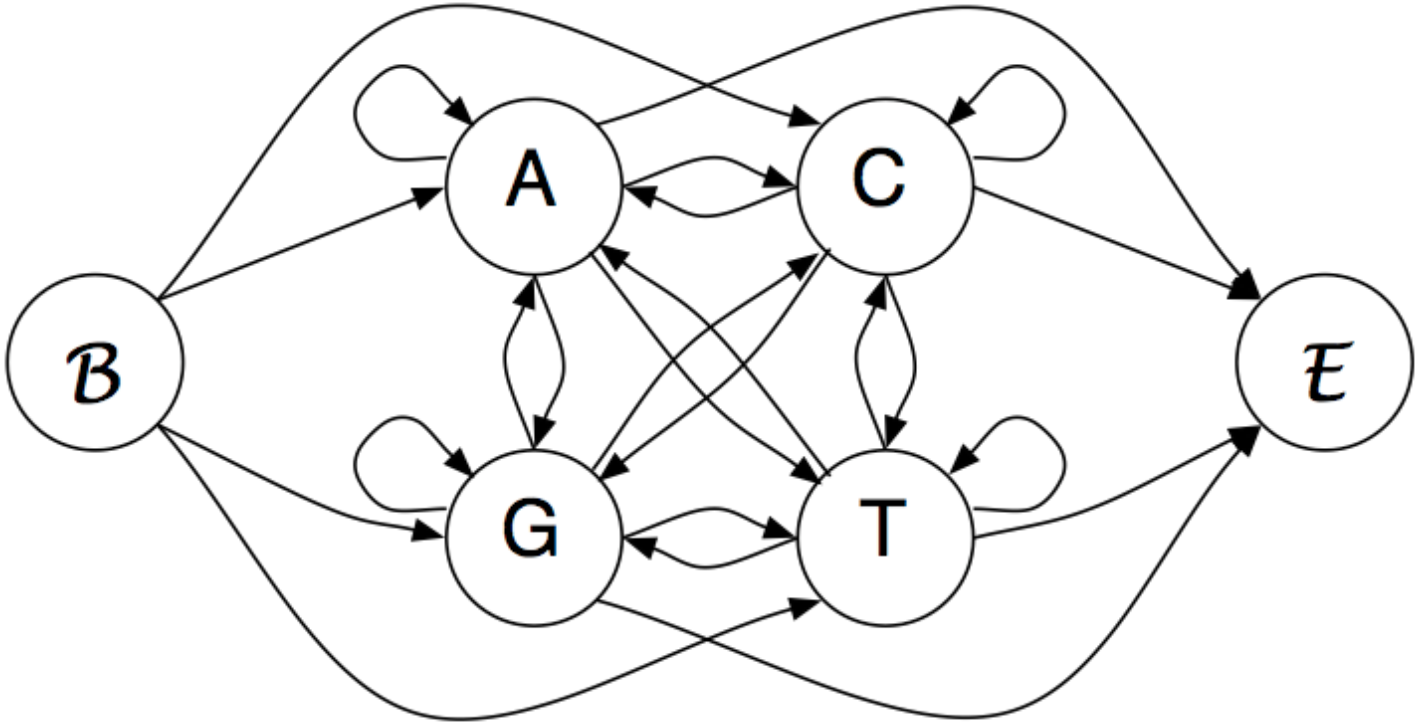


States: A,C,G,T

Emissions: corresponding letter

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

A Markov Model (1st order)



States: A,C,G,T

Emissions: corresponding letter

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

Begin/End states

Pr of emitting sequence *x*

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

law of probability ("chain rule")

if 1st order MC

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

From DEKM

Discrimination/Classification

Log likelihood ratio of CpG model vs background model

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

Input seq

Prev slide

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

From DEKM

CpG Island Scores

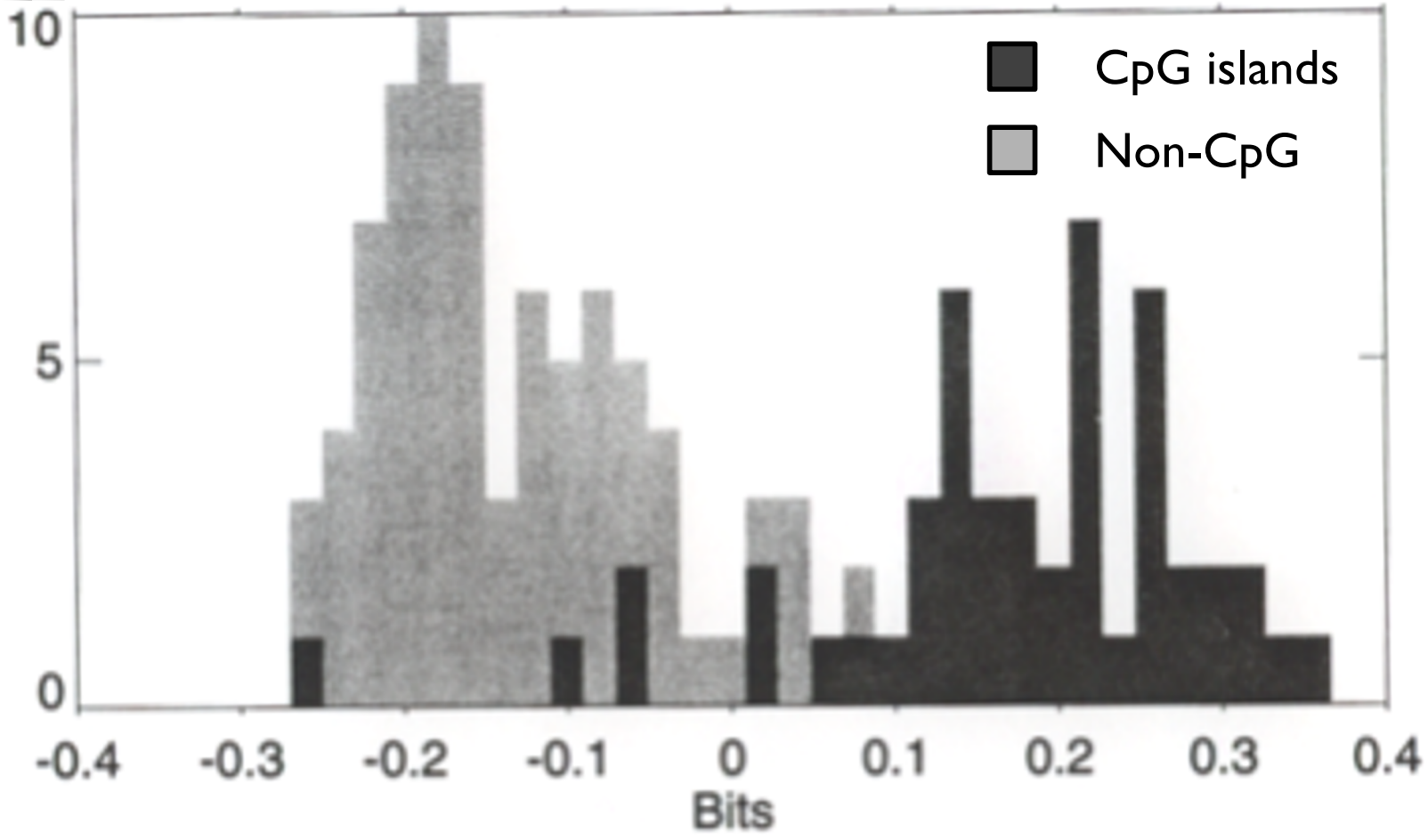
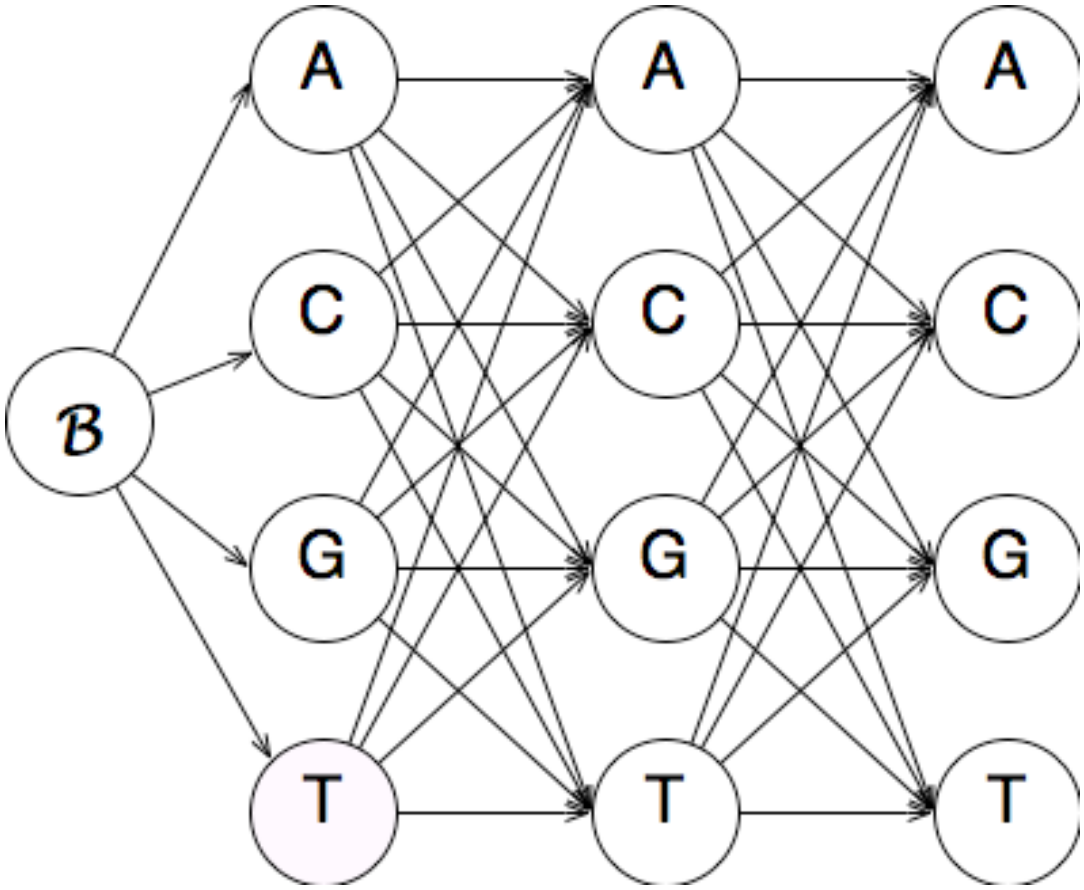


Figure 3.2 *Histogram of length-normalized scores.*

Aside: 1st Order "WMM"



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)

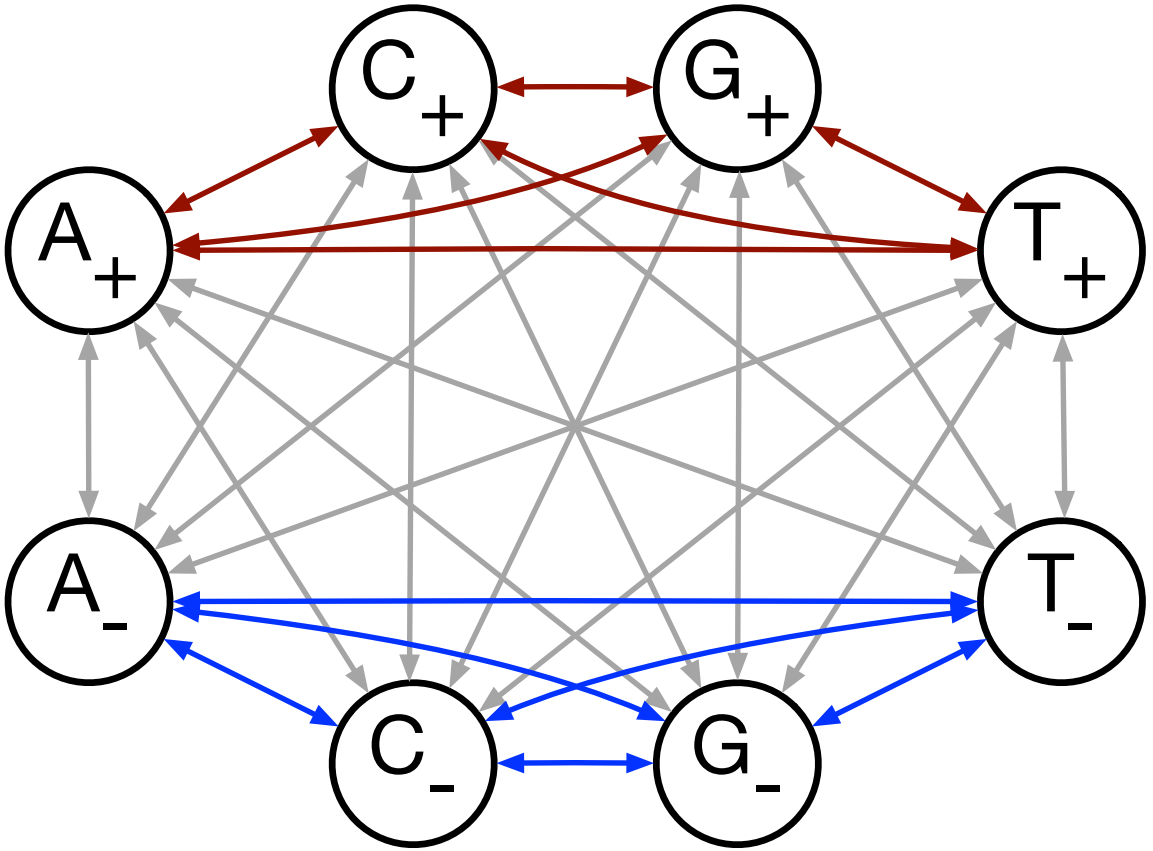
Approach 1: score 100 bp (e.g.) windows

Pro: simple

Con: arbitrary, fixed length, inflexible

Approach 2: *combine* +/- models.

Combined Model



} CpG + submodel

} CpG – submodel

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

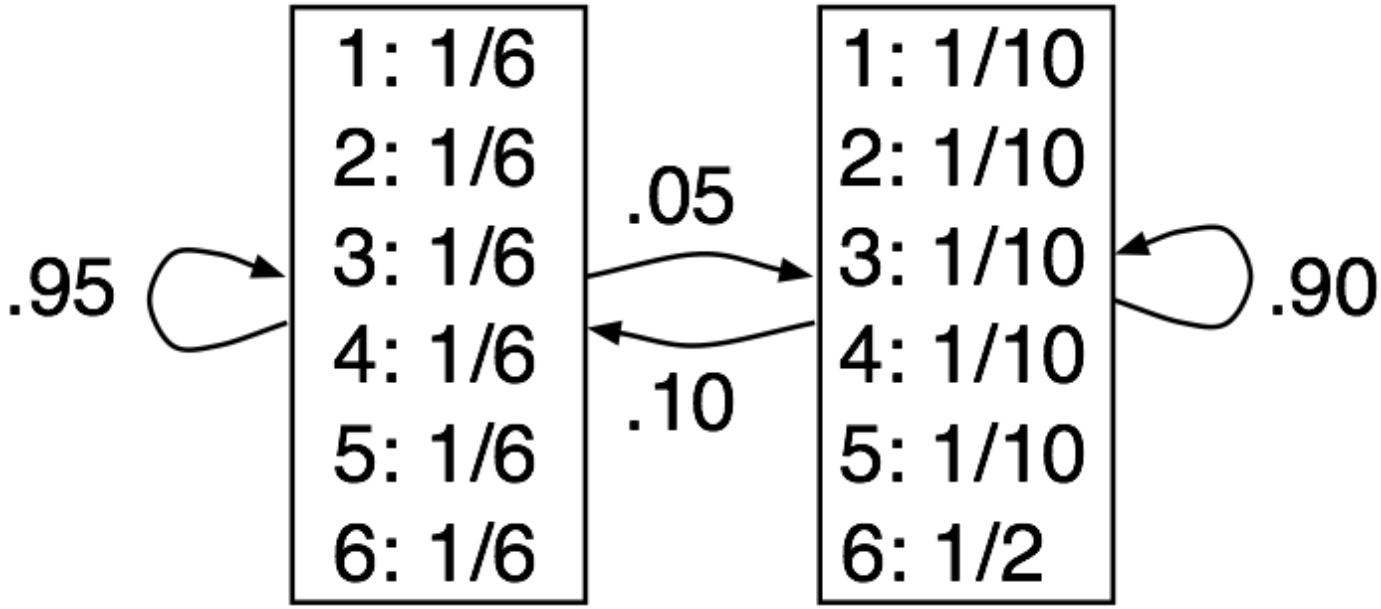
Hidden Markov Models

(HMMs; Claude Shannon, 1948)

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    315116246466442453113216311641521336251445436316566266666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

Figure 3.5

Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

Inferring hidden stuff

Joint prob 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

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

Etc.

Notation:

$\max_x F(x)$ = the maximum y-value attained by F()

$\arg\max_x F(x)$ = the x-value where that occurs

The Viterbi Algorithm: The most probable path

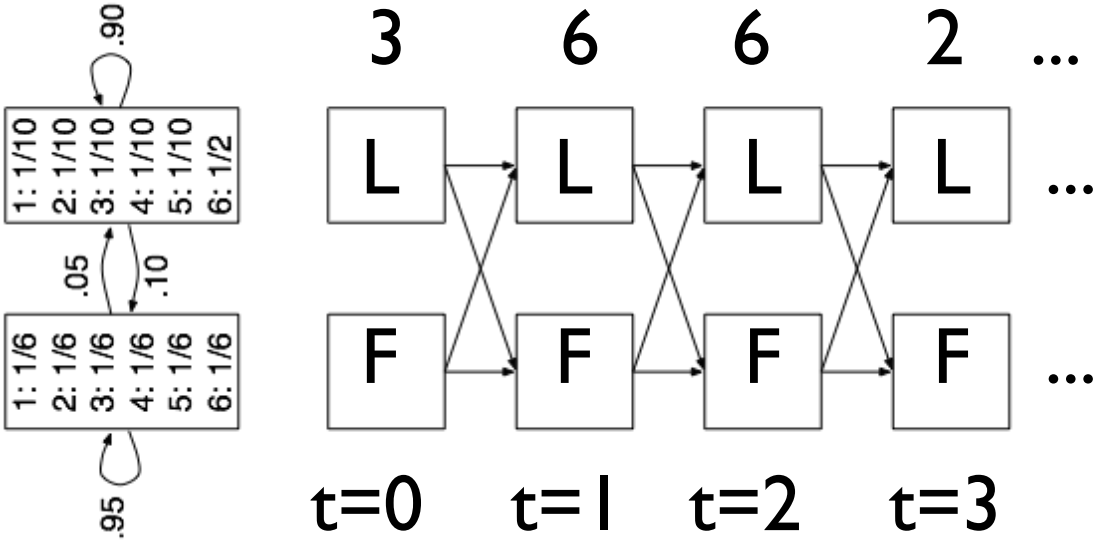
Viterbi finds: $\pi^* = \arg\max_{\pi} P(x, \pi)$

Possibly there are 10^{99} paths of prob 10^{-99}
(If so, non-Viterbi approaches may be preferable.)

More commonly, one path (+ slight variants) dominate others; Viterbi finds that

Key problem: exponentially many paths π

Unrolling an HMM



Conceptually, sometimes convenient

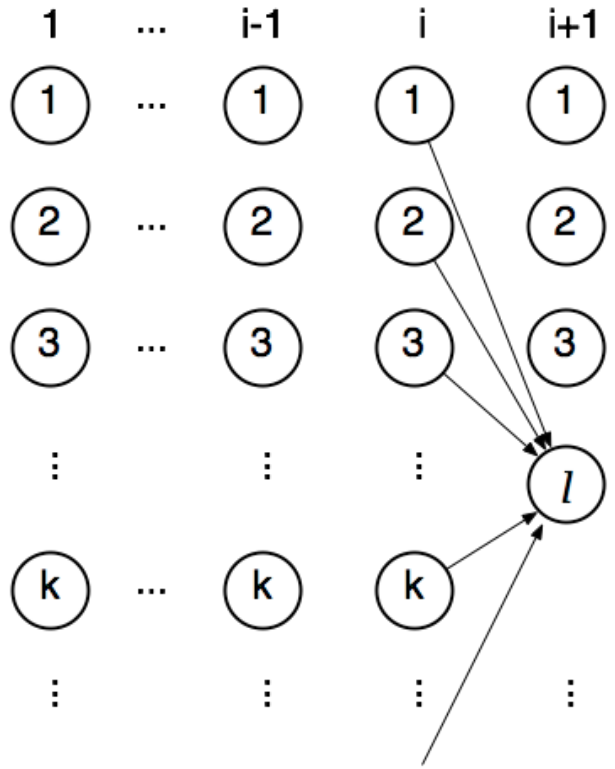
Note exponentially many paths

Viterbi

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

Initialize:

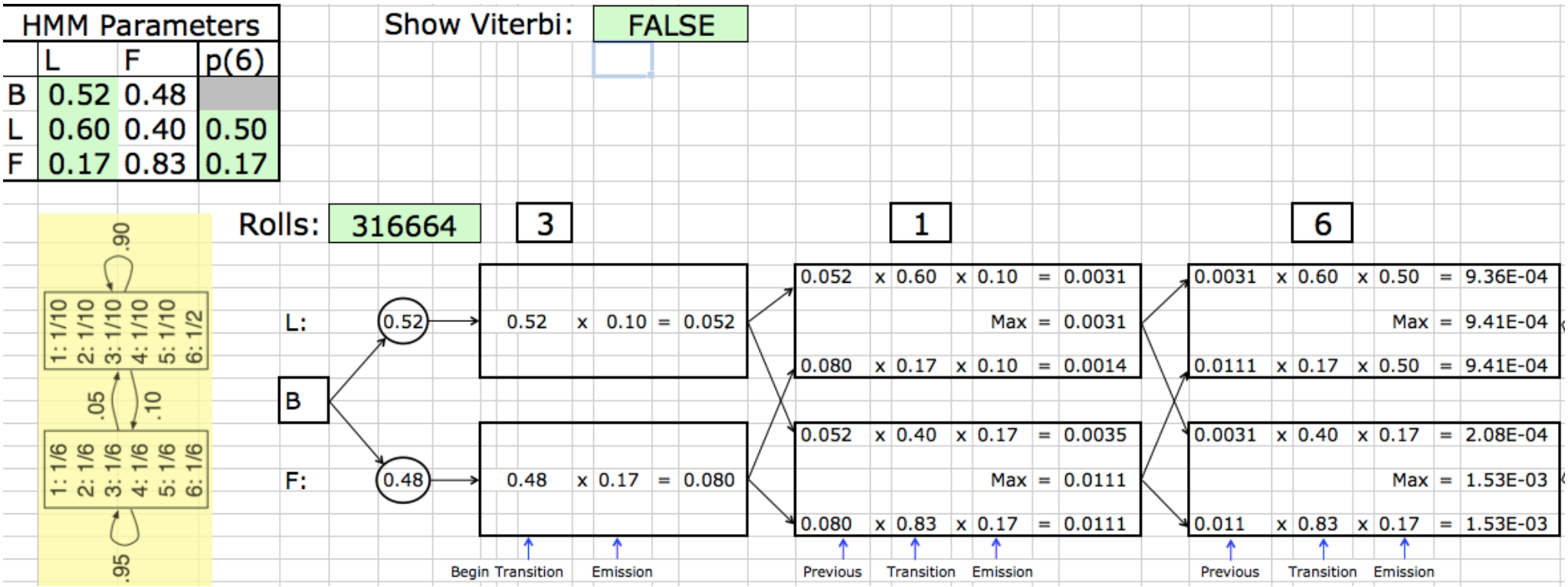
$$v_l(0) = \begin{cases} 1 & \text{if } l = Begin \text{ state} \\ 0 & \text{otherwise} \end{cases}$$



General case:

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

HMM Casino Example

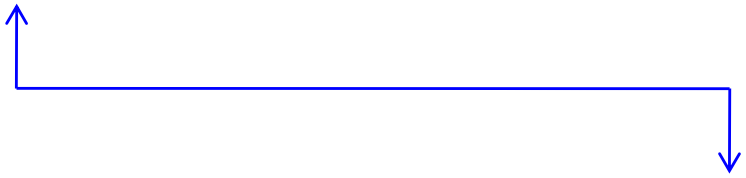


(Excel spreadsheet on web; download & play…)

Viterbi Traceback

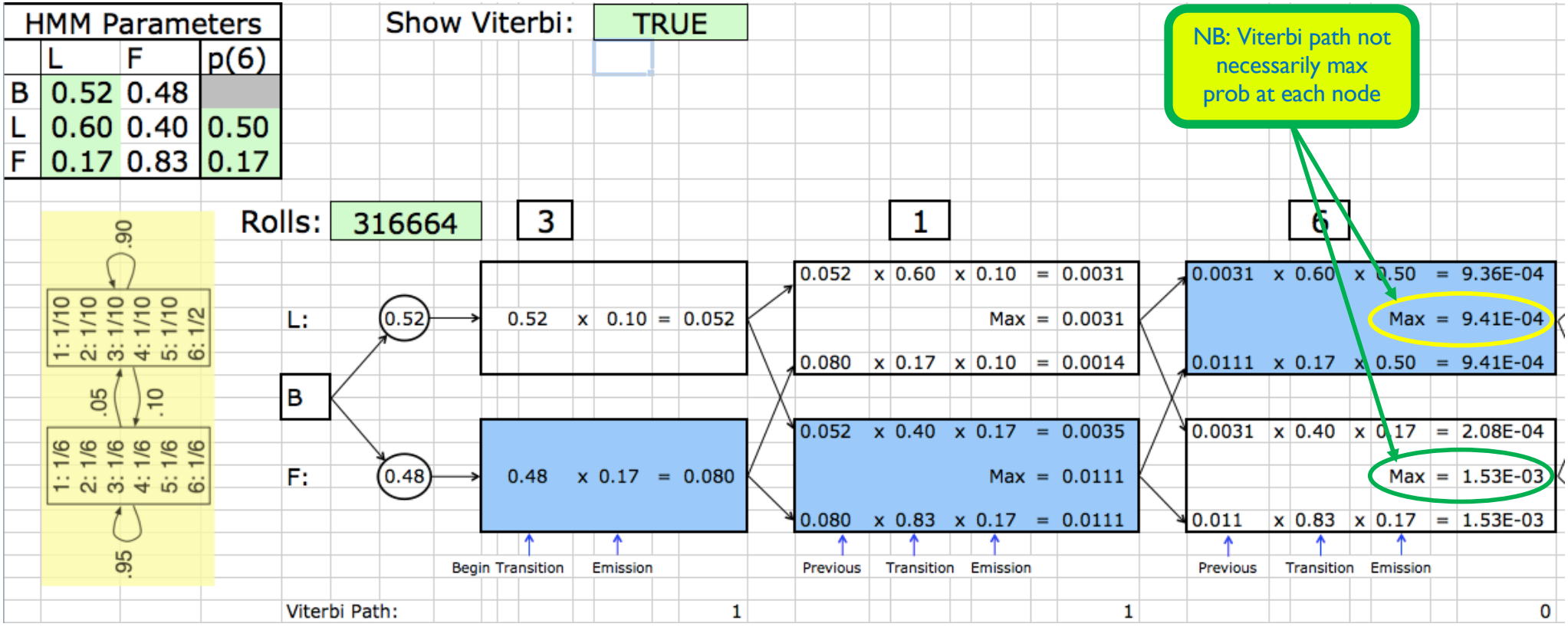
Above finds *probability* of best path

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



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

HMM Casino Example



(Excel spreadsheet on web; download & play…)

```
Rolls    315116246466442453113216311641521336251445436316566266666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFLLLLLLLLLLLLLLLLFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

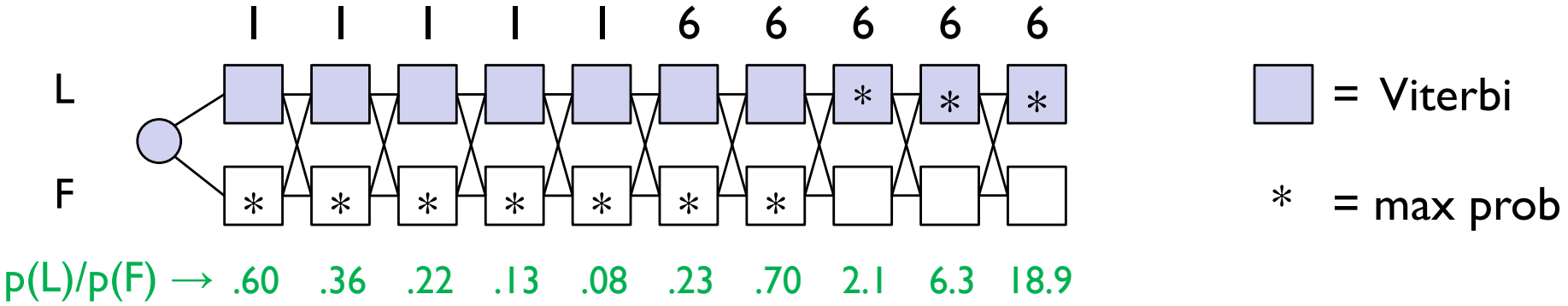
Figure 3.5

Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

Most probable path ≠ Sequence of most probable states

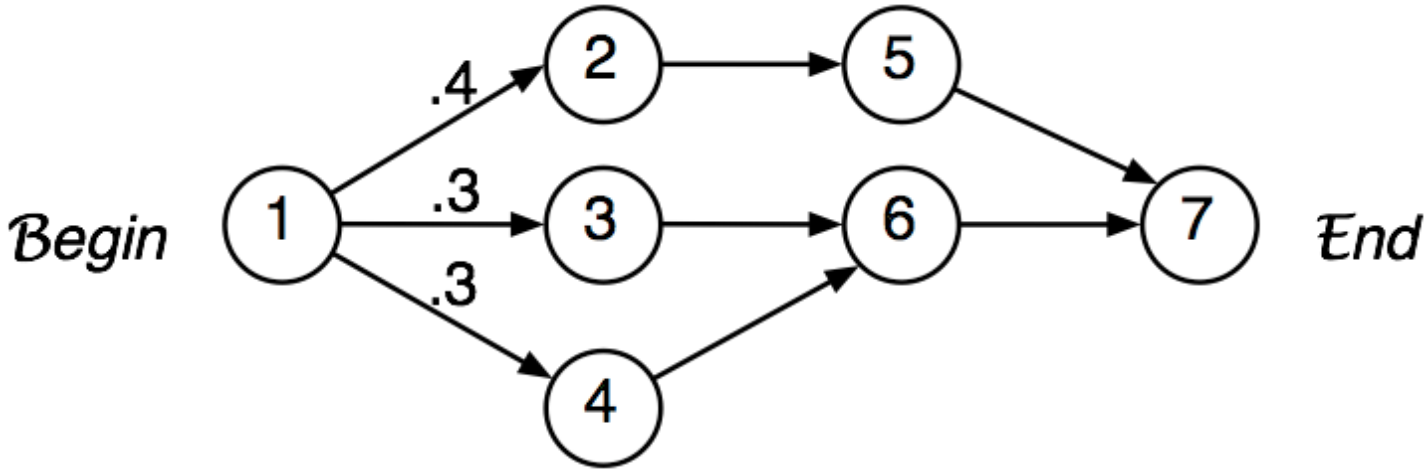
Another example, based on casino dice again:

Suppose p(fair ⟷ loaded) transitions are 10^{-99} and roll sequence is 1111166…666; then fair state is more likely all through 1's & into the run of 6's, but eventually loaded wins, and the improbable F → L transitions make Viterbi = *all* L.



Is Viterbi "best"?

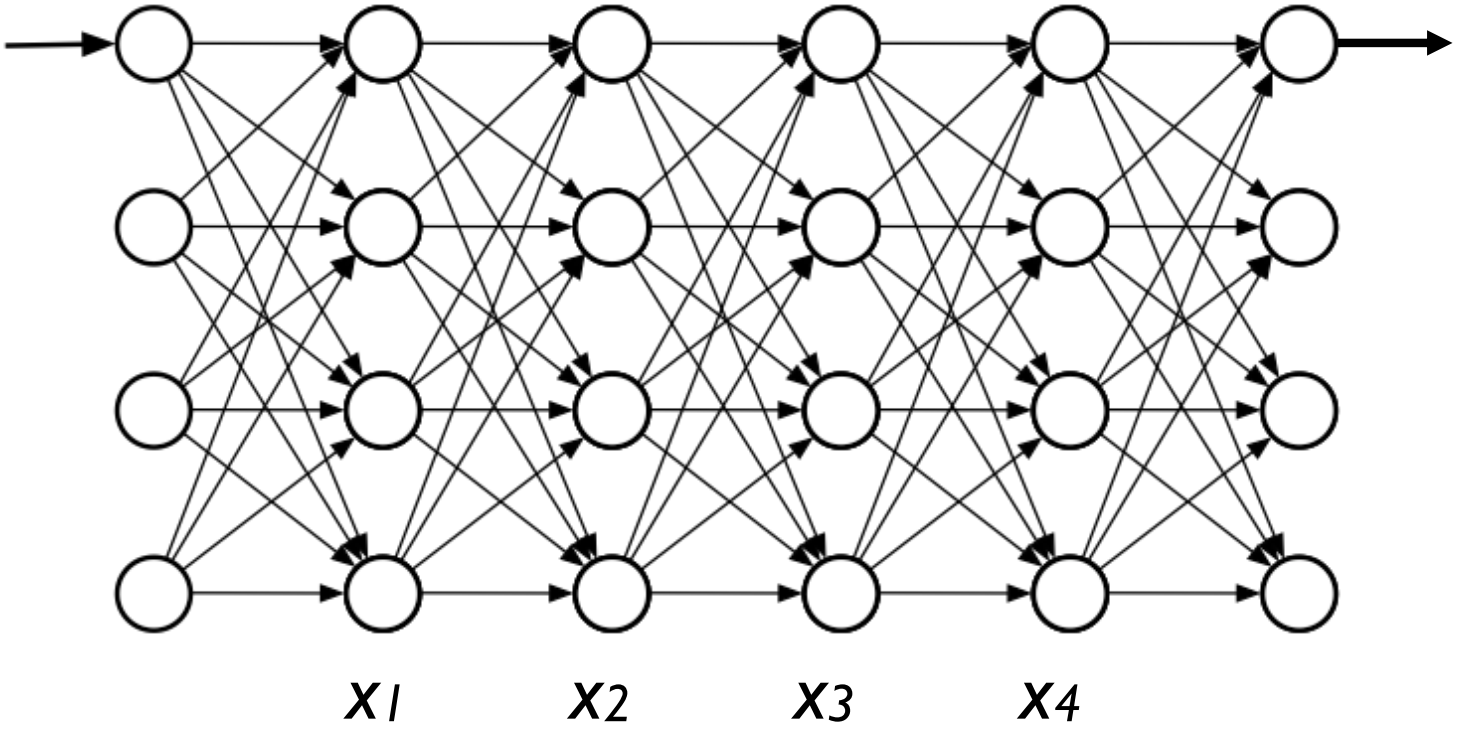
Viterbi finds $\pi^* = \arg\max_{\pi} P(x, \pi)$



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.)

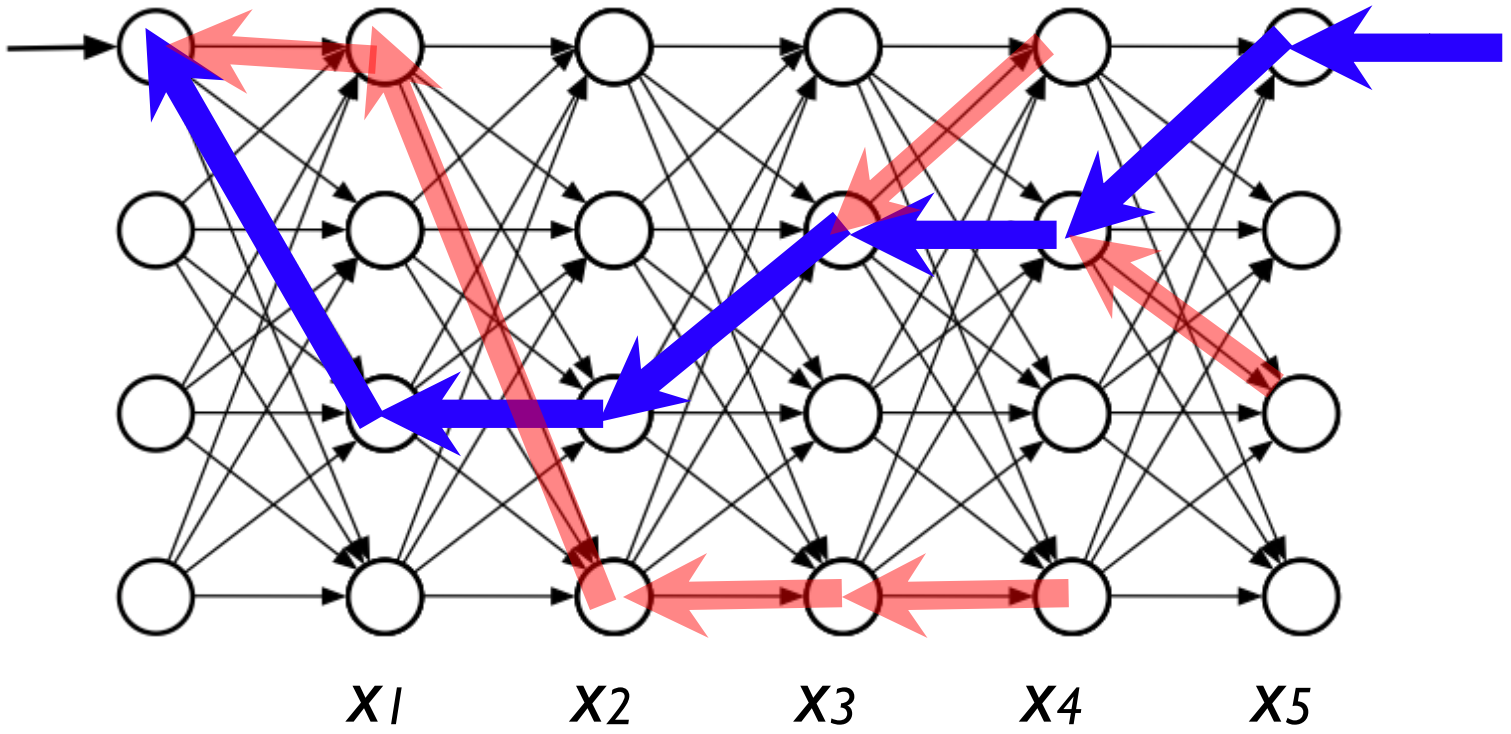
An HMM (unrolled)

States



Emissions/sequence positions

Viterbi: best path to each state



Viterbi *score:*

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

Viterbi *path*[R]*:*

$$back_l(i+1) = \arg\max_k (v_k(i)\, a_{k,l})$$

Another Q: What's P(x)?

Given an HMM and a sequence x, Viterbi finds the single path π having the greatest probability of emitting x (and implicitly finds that probability $P(x, \pi)$)

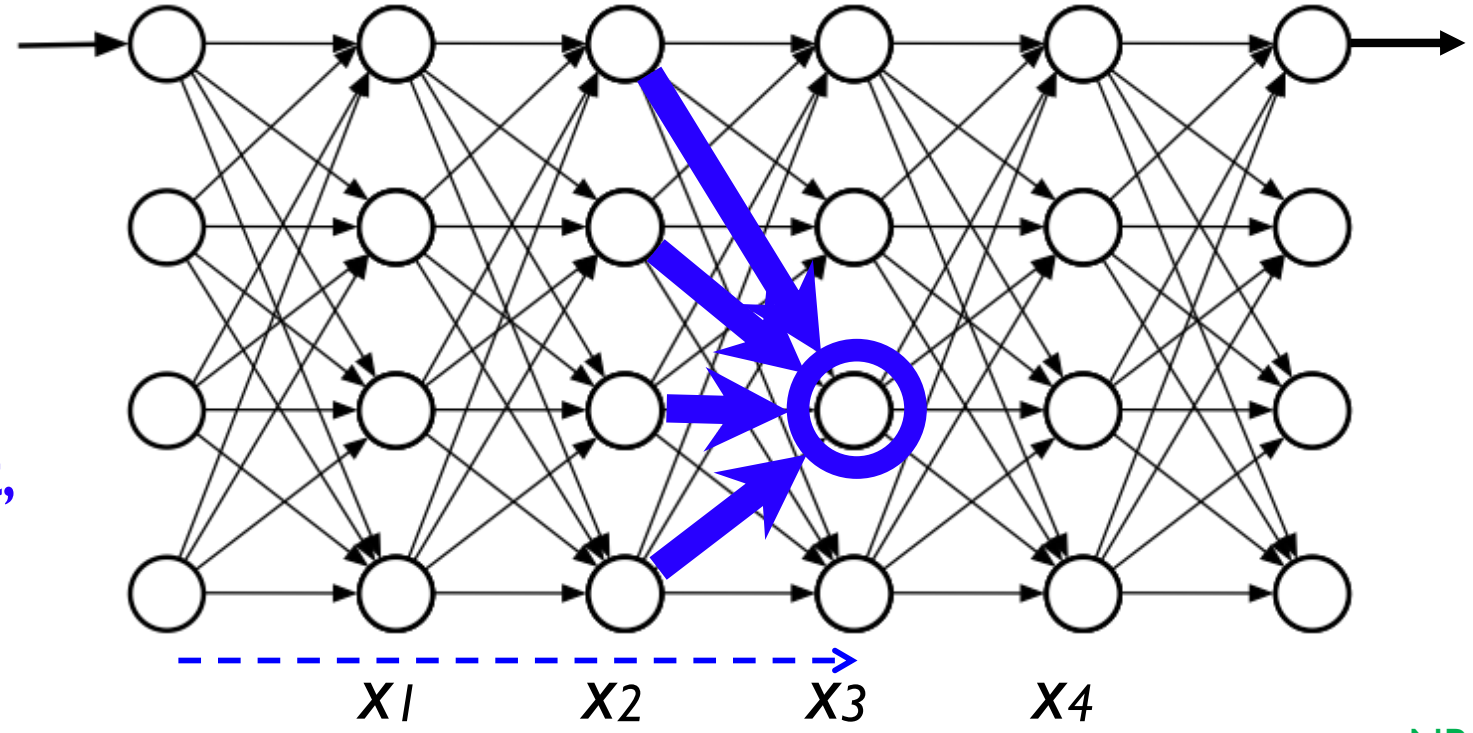
What if I don't care about π? E.g., what is the probability $P(x)$ of emitting x, on *some* path?

Of course, $P(x) = \sum_{\pi} P(x, \pi)$, i.e. sum over all paths, but exponentially many, so nontrivial …

Answer to this and related Qs is easiest to think about by focusing on intermediate states

The Forward Algorithm

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



NB: Joint

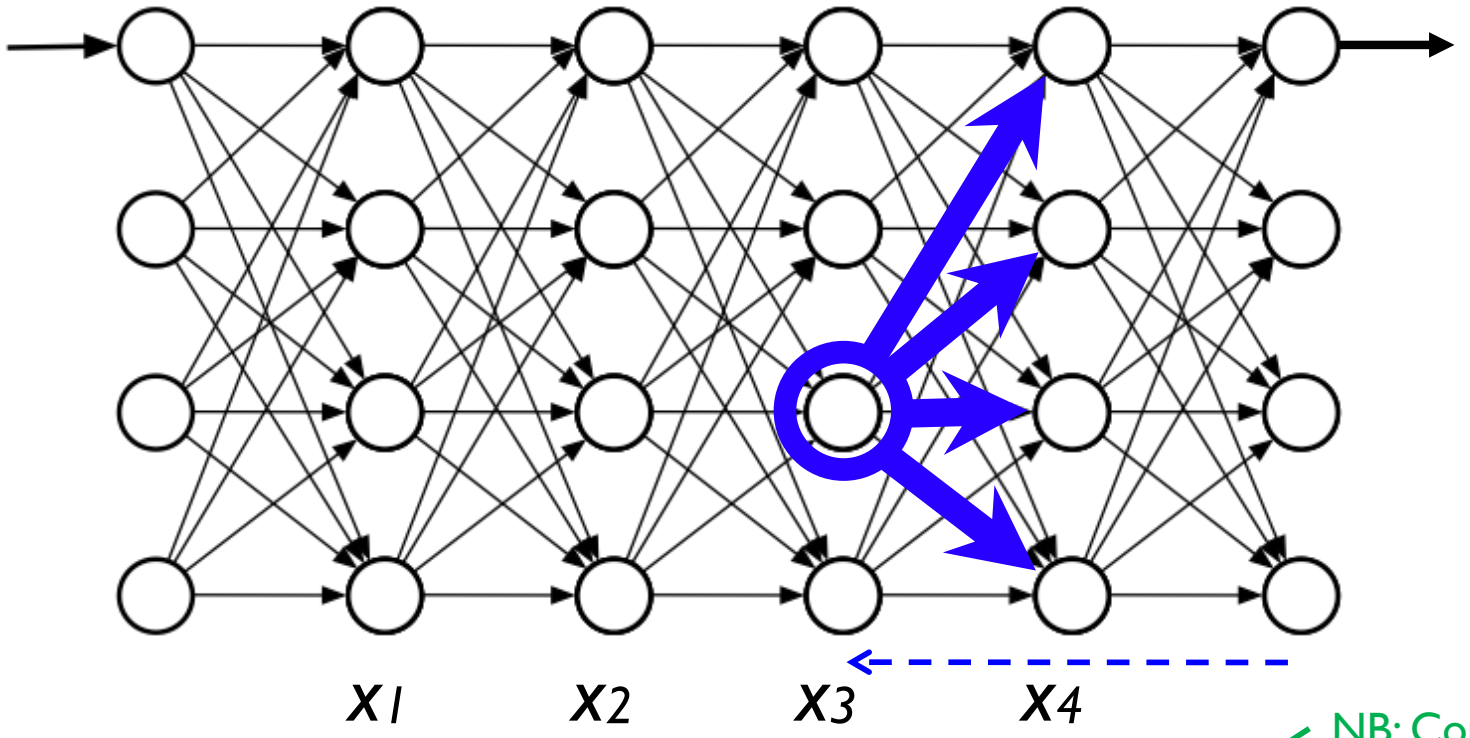
$$f_k(i) \triangleq P(x_1 \ldots x_i,\ \pi_i = k)$$

$$f_l(i+1) = e_l(x_{i+1}) \sum_k f_k(i) a_{k,l}$$

$$P(x) = \sum_\pi P(x,\pi) = \sum_k f_k(n) a_{k,end}$$

The Backward Algorithm

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



NB: Conditional

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

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

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

[& P(x) = $b_{start}(0)$]

In state *k* at step *i* ?

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

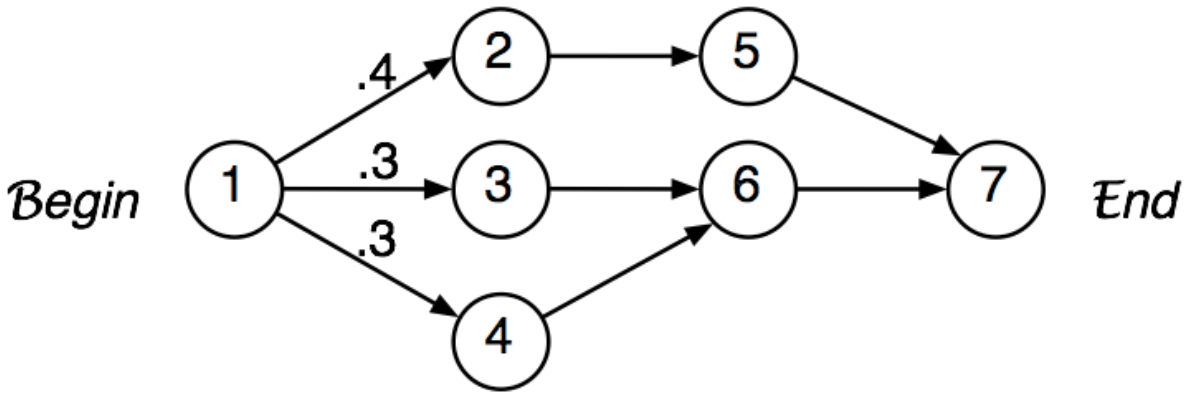
$$
P(\pi_i = k \mid x) \;=\; \frac{P(x, \pi_i = k)}{P(x)} \;=\; \frac{f_k(i) \cdot b_k(i)}{P(x)}
$$

Posterior Decoding, 1

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

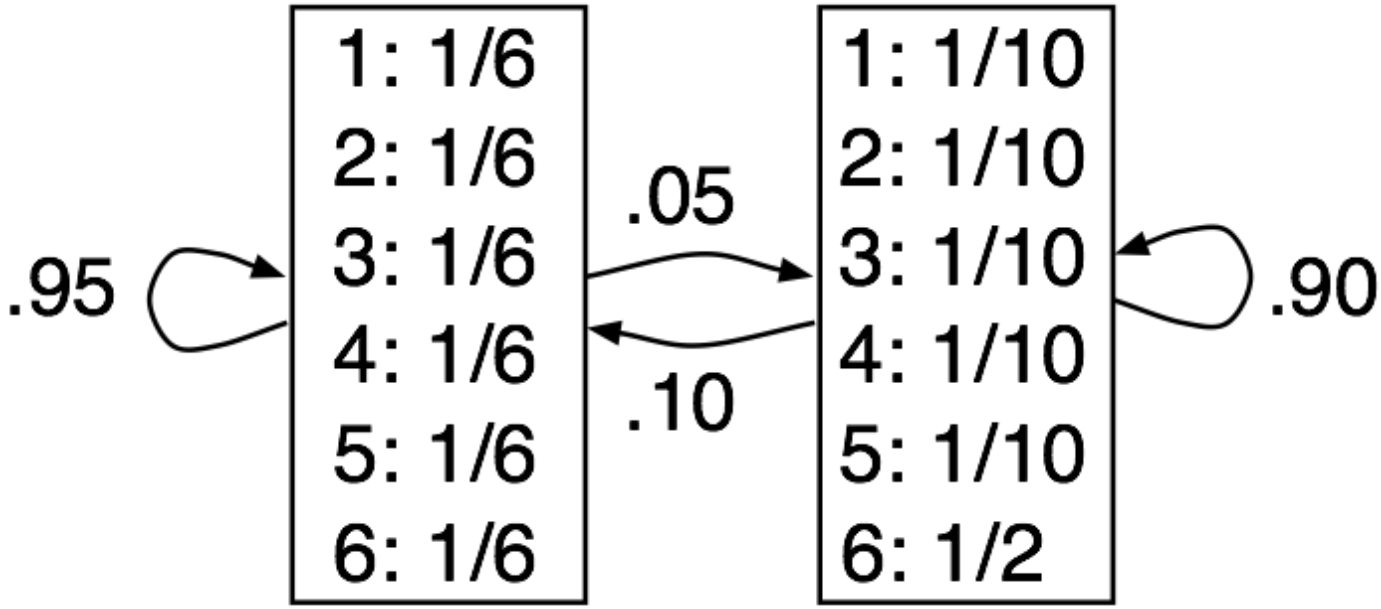
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

Note: the most likely sequence of states (a path) ≠
the sequence of most likely states.
That may even be an illegal path! (E.g. 1,2,6,7 below)



The Occasionally Dishonest Casino

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



```
Rolls    315116246466442453113216311641521336251445436316566266666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5

Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

Posterior Decoding

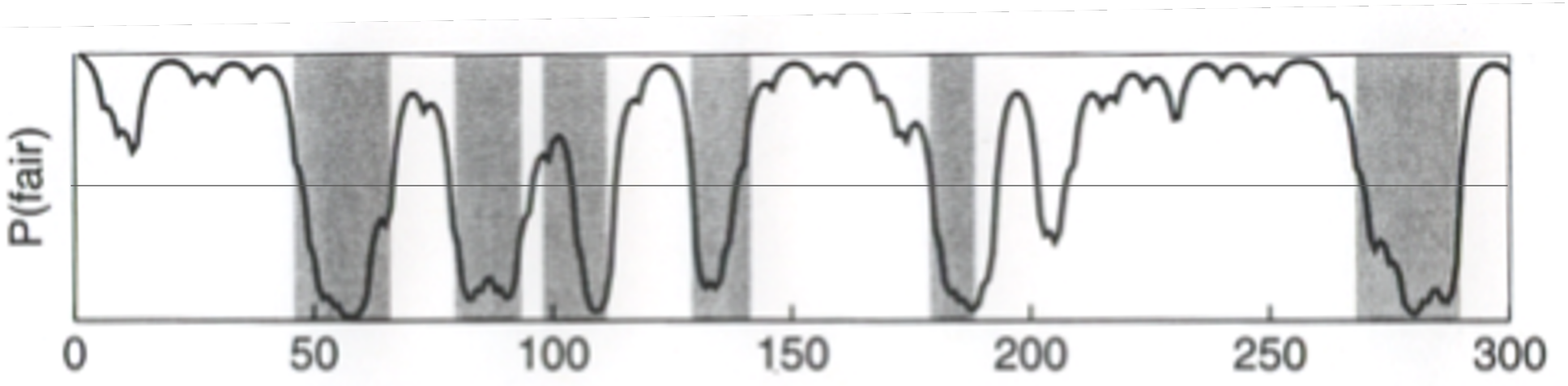


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

From DEKM

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

	Post-process:
Viterbi:	
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

$$a_{k,l} = \frac{\text{count of } k \to l \text{ transitions}}{\text{count of } k \to \text{anywhere transitions}}$$

$$e_k(b) = \ldots$$

+ pseudocounts?

If π hidden, then use EM:
given θ, estimate π; given π estimate θ; repeat } 2 ways

Viterbi Training

given θ, estimate π; given π estimate θ; repeat

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.)

(And see note about "classification EM," ~#45 in MLE-EM slides.)

AKA "the forward-backward alg"

Baum-Welch Training

EM: given θ, estimate *π ensemble*; then re-estimate θ

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

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

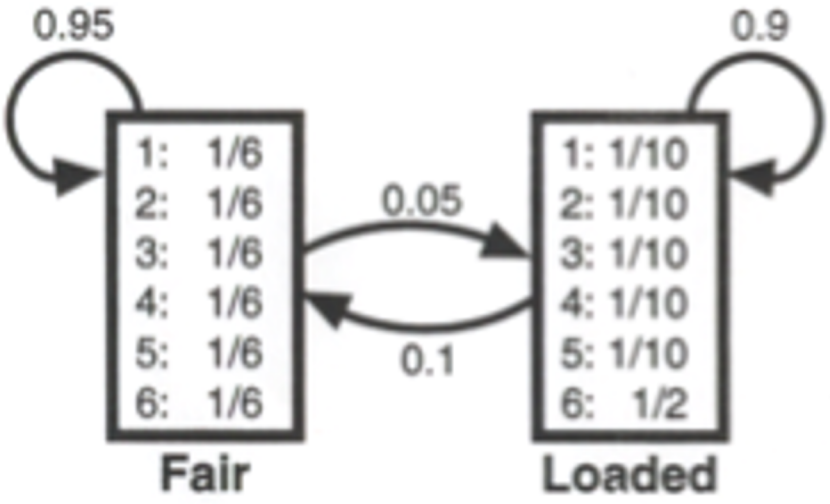
Estimated # of $k \to l$ transitions $\hat{A}_{k,l}$ on *set* of seqs x^j

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

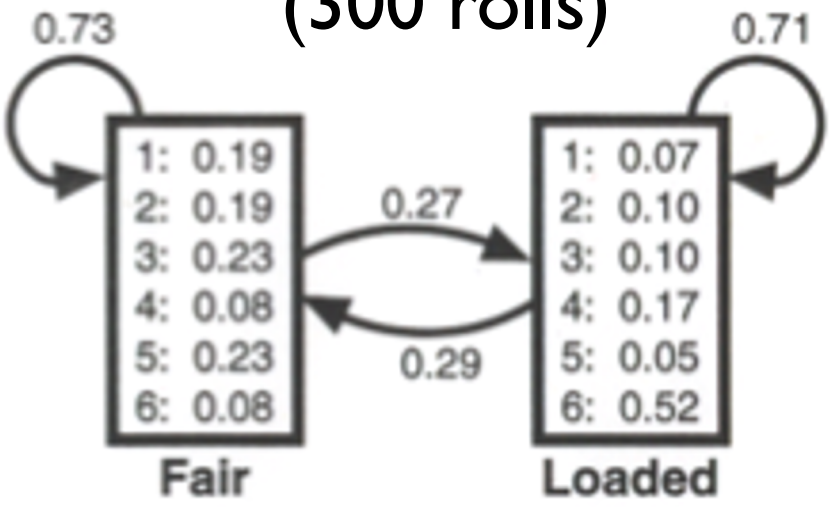
New estimate $\hat{a}_{k,l} = \frac{\hat{A}_{k,l}}{\sum_l \hat{A}_{k,l}}$

Emissions: similar

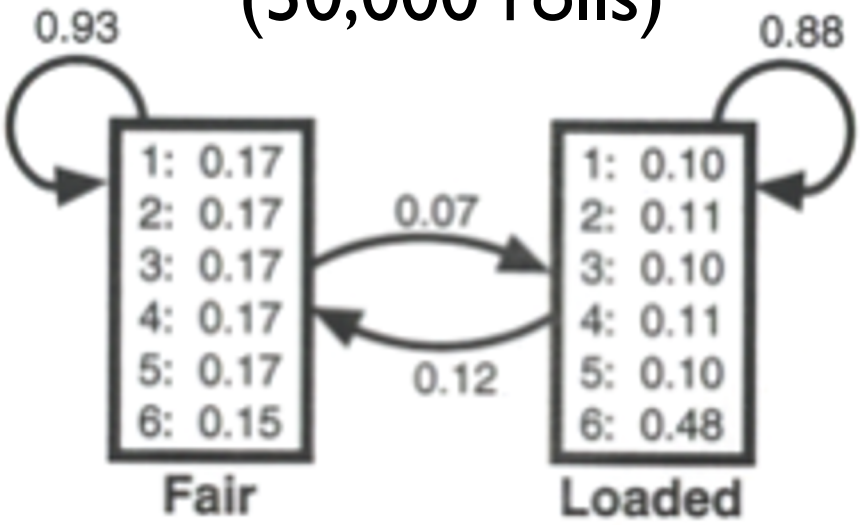
True Model



B-W Learned Model (300 rolls)



B-W Learned Model (30,000 rolls)



Log-odds (vs all F) per roll

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

(NB: overestimated)

From DEKM

HMMs in Action: Pfam

http://pfam.xfam.org

Proteins fall into families, across & within species

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

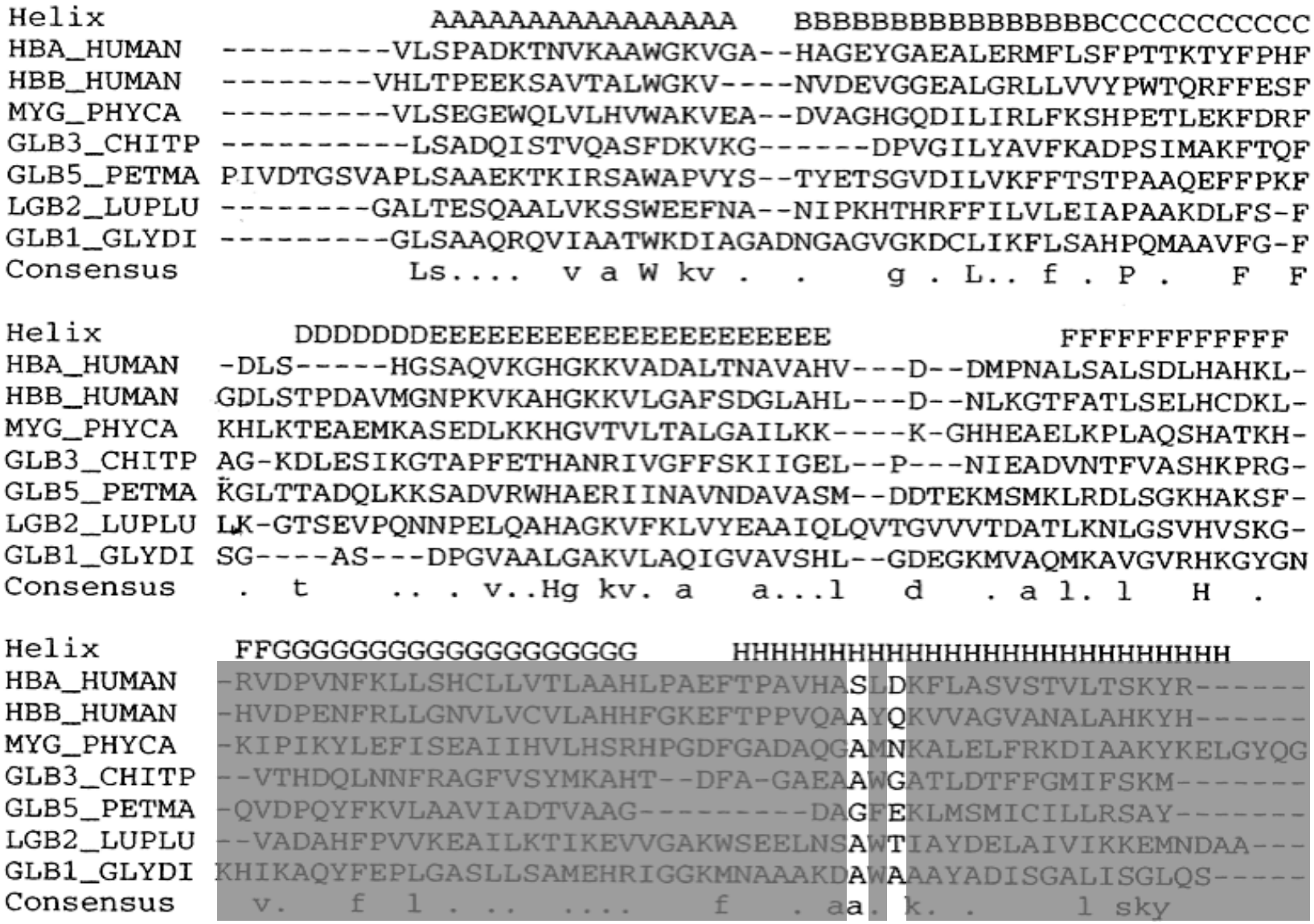
Identifying family very useful: suggests function, etc.

So, search & alignment are both important

Q. Why not just use Blast/Smith-Waterman?

A. There is more info in *multiple* examples (e.g., psiBLAST)

One very successful approach: profile HMMs



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

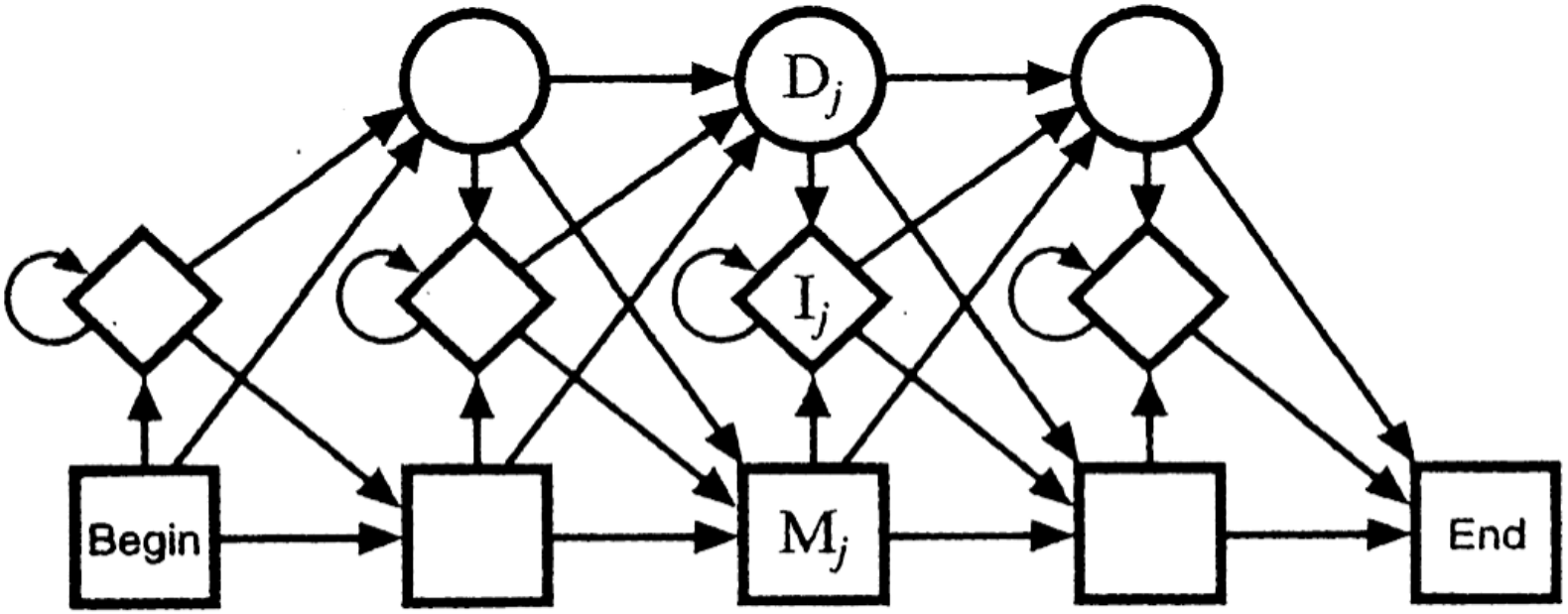


Figure 5.2 *The transition structure of a profile HMM.*

M_j: Match states (20 emission probabilities)

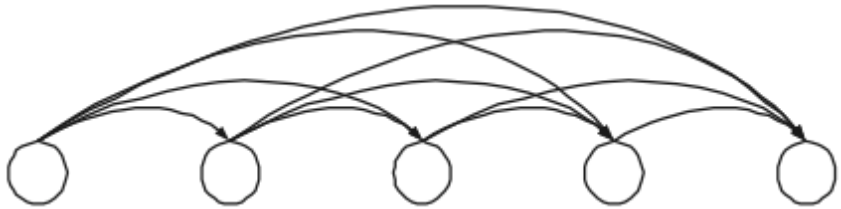
I_j: Insert states (Background emission probabilities)

D_j: Delete states (silent - no emission)

From DEKM

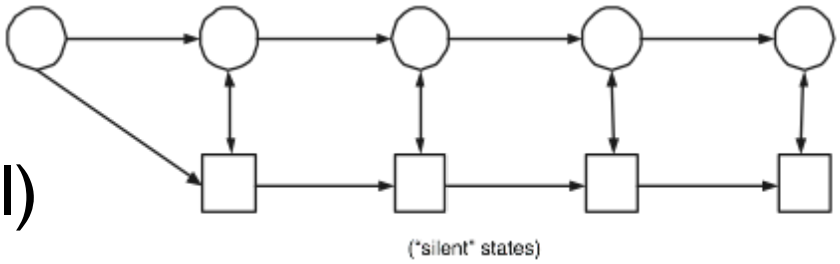
Silent States

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

} next slides

- Alignment
  - Viterbi

Likelihood vs Odds Scores

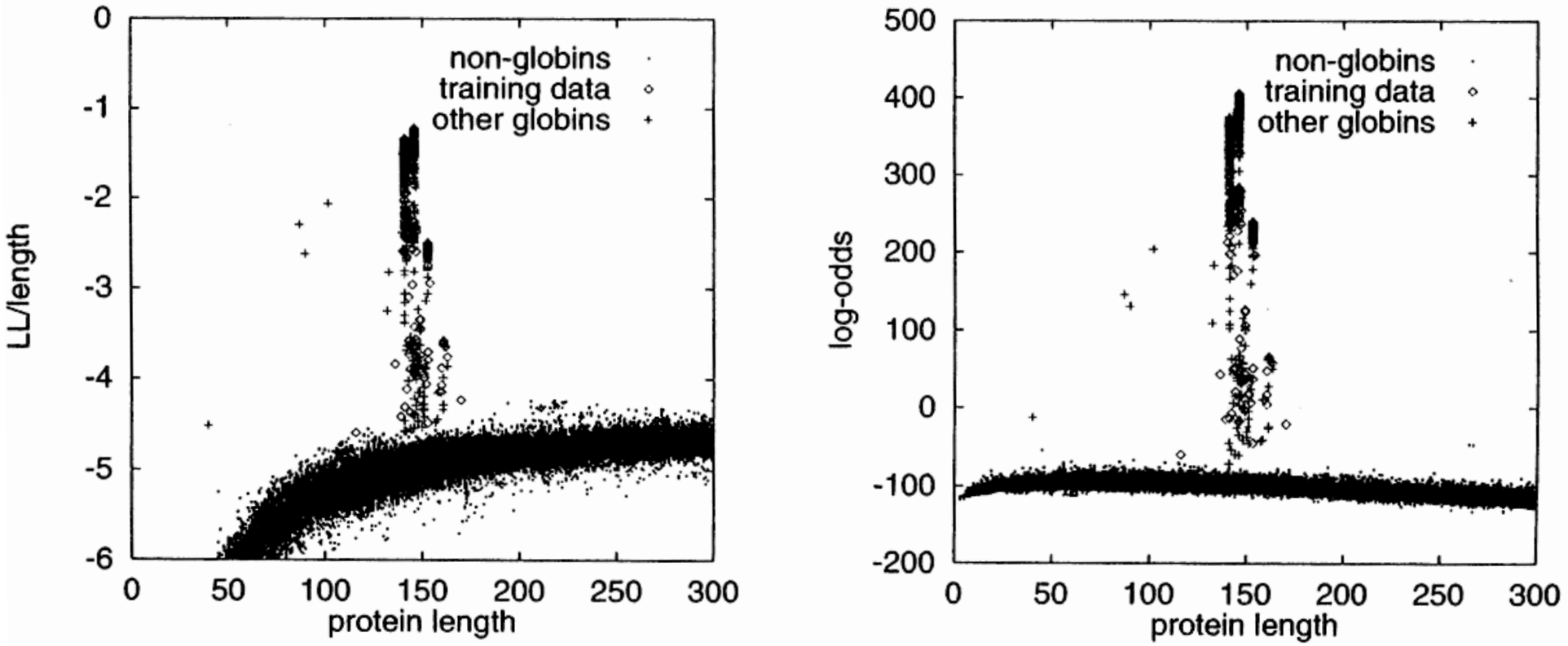


Figure 5.5 *To the left the length-normalized LL score is shown as a function of sequence length. The right plot shows the same for the log-odds score.*

From DEKM

Z-Scores

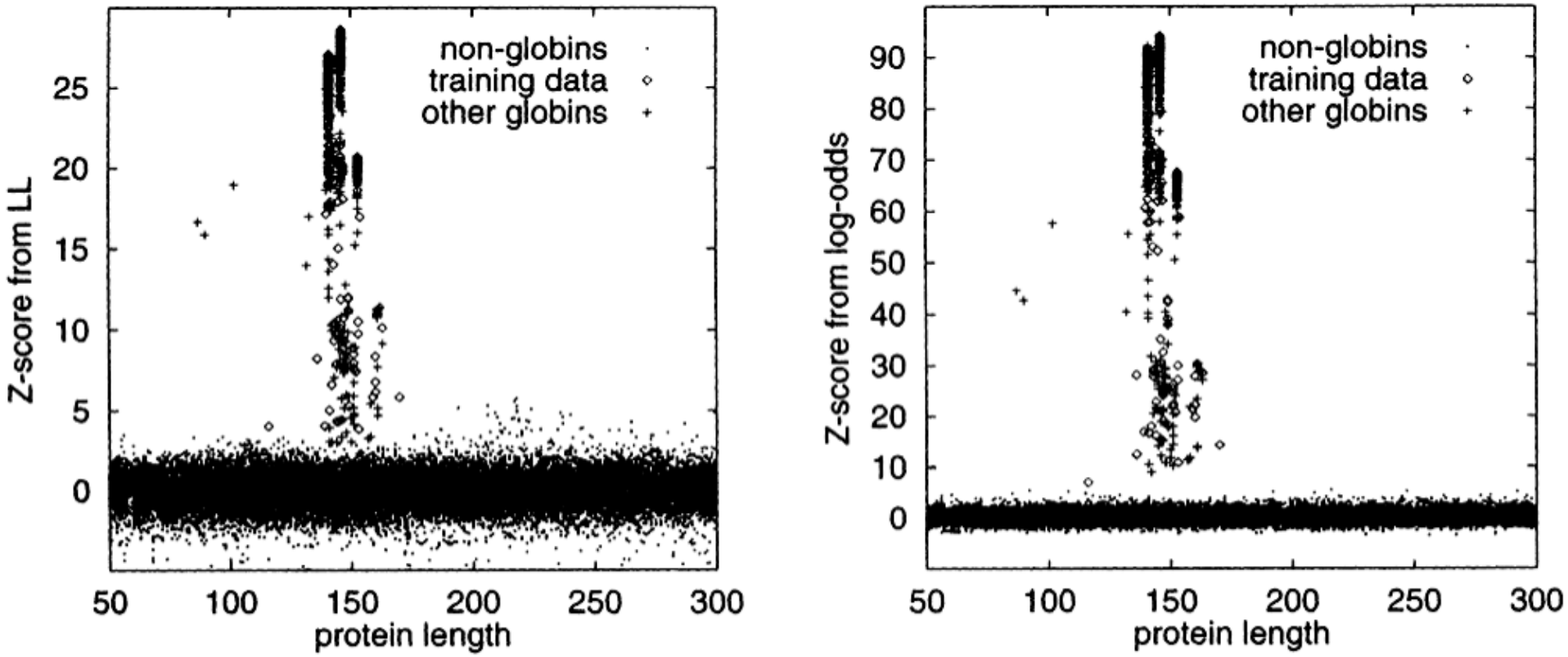


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

From DEKM

http://xfam.org

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

Version	Date	#Families	Coverage
25.0	3/2011	12273	75
27.0	3/2013	14831	90
31.0	3/2017	16712	
32.0	9/2018	17929	
33.1	5/2020	18259	

% of human proteins containing ≥ 1 PFAM domain

HMM Summary

joint vs conditional probs

Inference

- Viterbi – best single path (max of products)
- Forward – sum over all paths (sum of products)
- Backward – similar
- Posterior decoding

Model building

- Semi-supervised – typically fix architecture (e.g. profile HMM), then learn parameters
- Baum-Welch – training via EM and forward/backward (aka the forward/backward algorithm)
- Viterbi training – also "EM-like", but Viterbi-based

HMM Summary (cont.)

Search:

- Viterbi or forward

Scoring:

- Odds ratio to background
- Z-score
- E-values, etc., too

Excellent tools available (HMMer, Pfam, …)

Very widely used for bioseq analysis (& elsewhere)