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 1-23

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.:

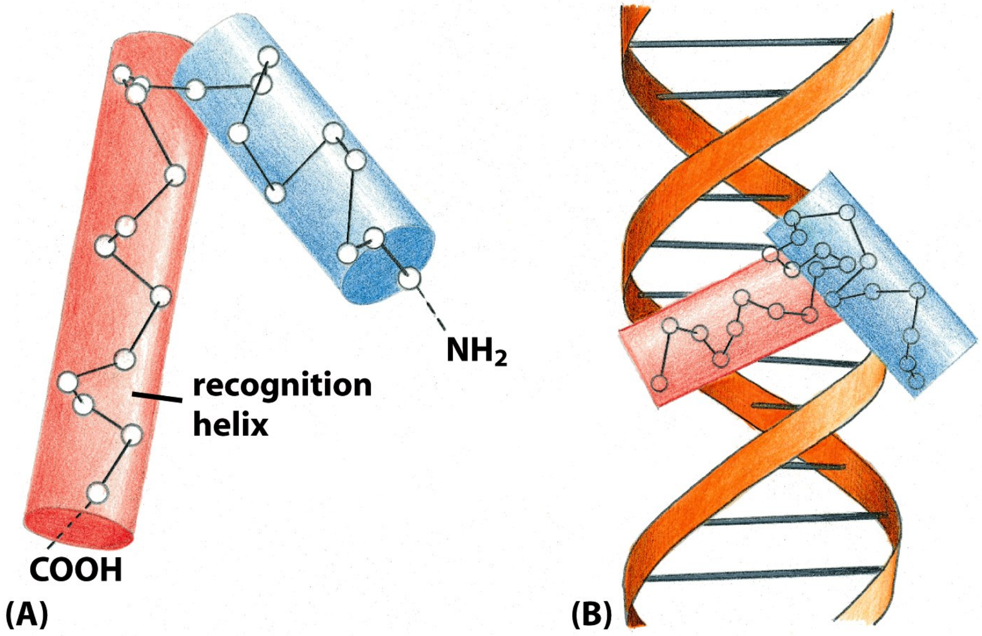
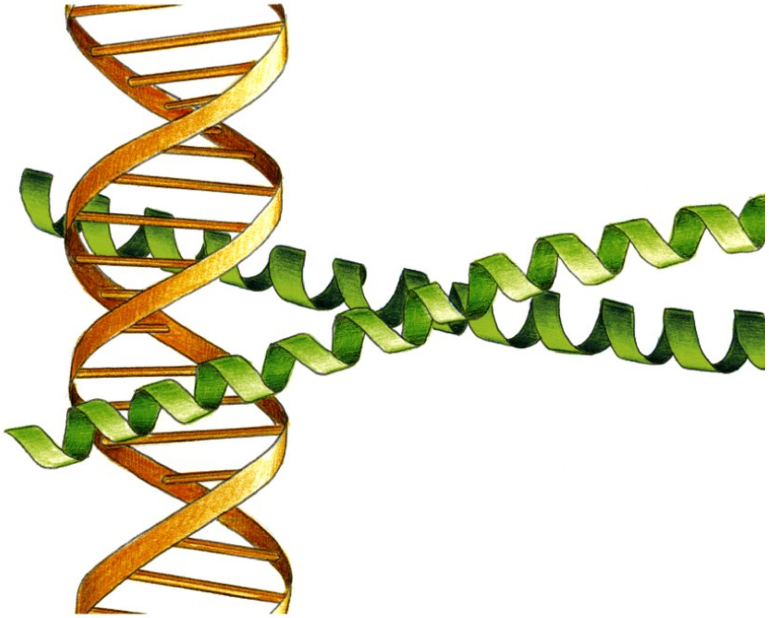
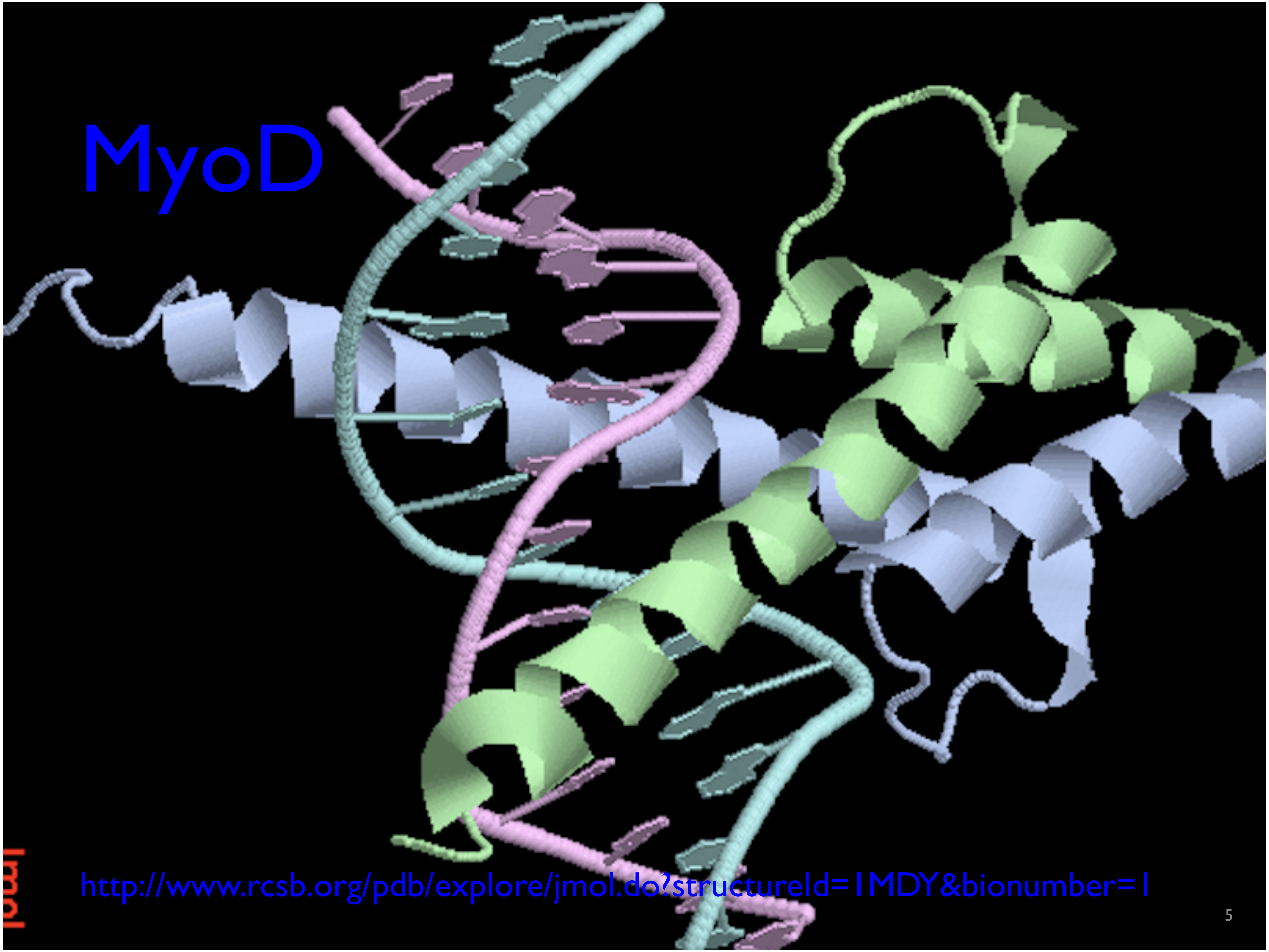


Figure 7-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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



MyoD



http://www.rcsb.org/pdb/explore/jmol.do?structureId=1MDY&bionumber=1

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

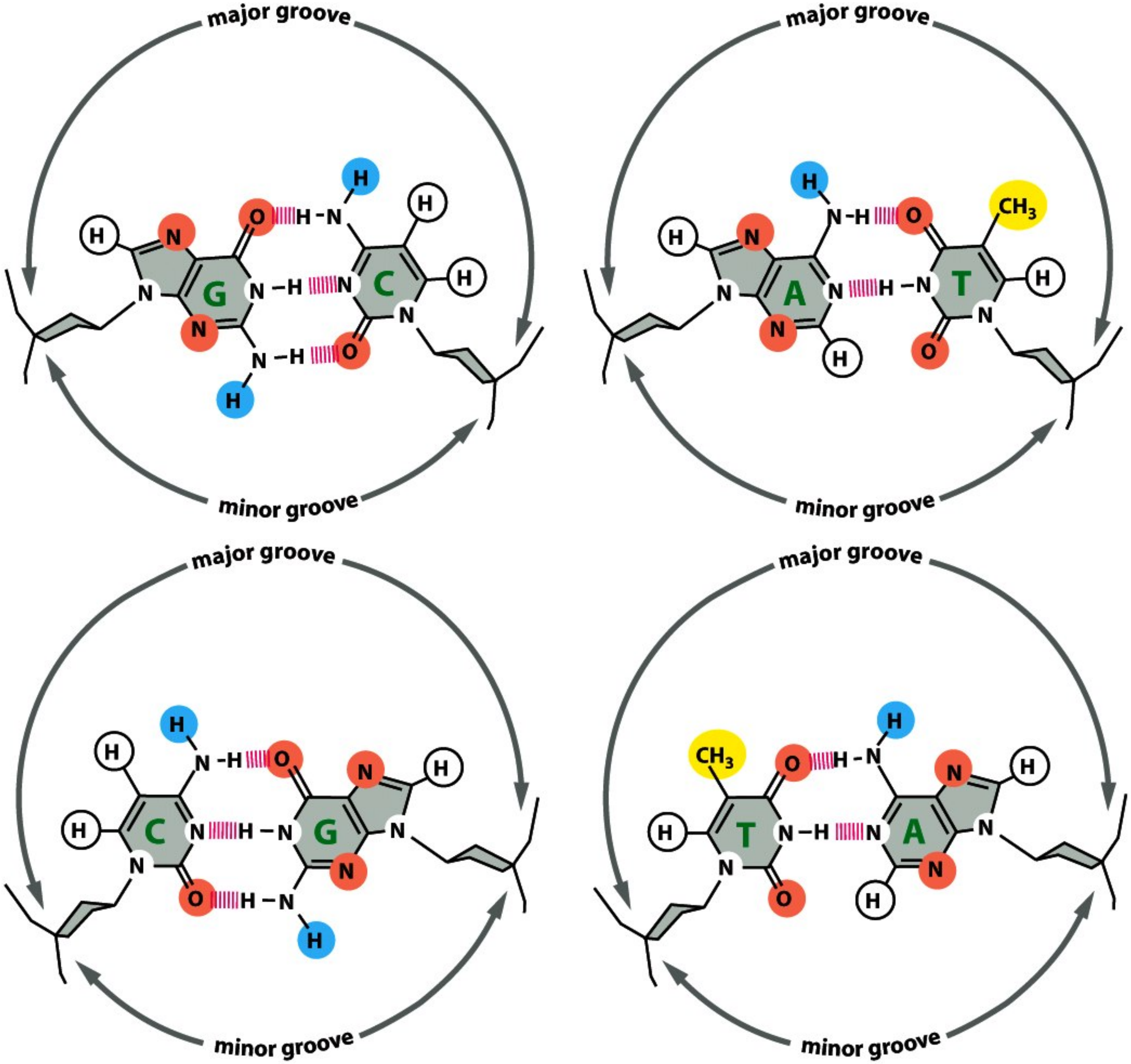
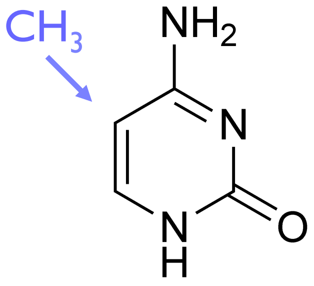


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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

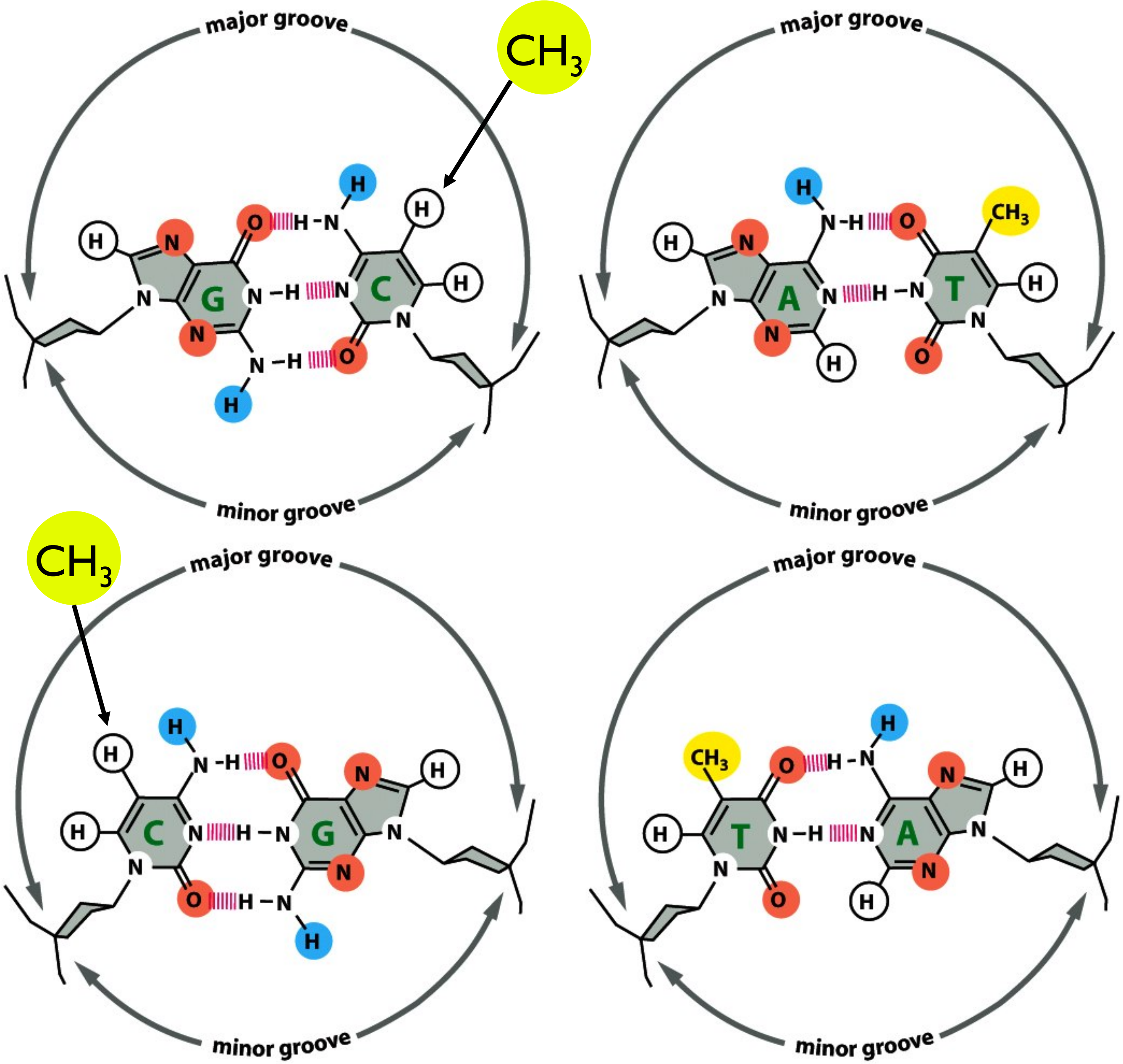
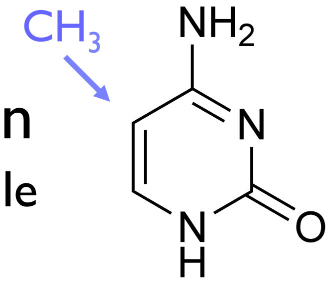


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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,

(b) remember that through subsequent divisions

How? One way:

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

(b) after ÷, DNA methyltransferases convert hemi- to fully-methylated (& deletion of methyltransferase is embrionic-lethal in mice)

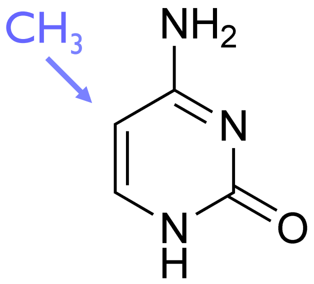
Major exception: promoters of housekeeping genes

“CpG Islands”

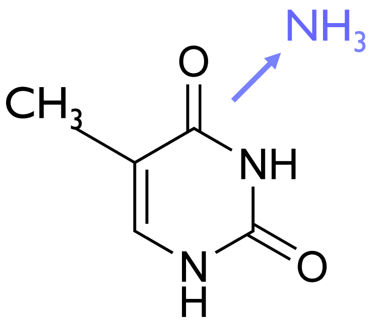
Methyl-C mutates to T relatively easily

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

BUT in some regions (e.g. active promoters), 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 (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 Chains

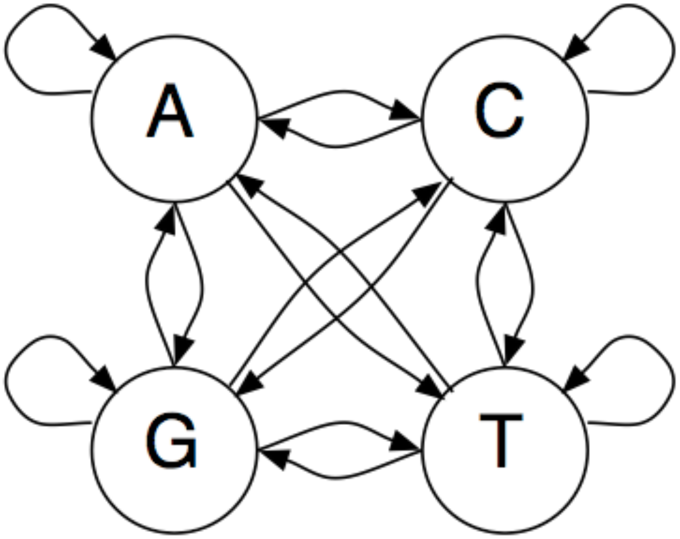
A sequence $x_1, x_2, \ldots$ of random variables is a *k-th order Markov chain* if, for all *i*, *i*th value is independent of all but the previous *k* values:

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

$$\left.\begin{array}{l}\text{Example 1: Uniform random ACGT}\\ \text{Example 2: Weight matrix model}\end{array}\right\} \text{0th order}$$

$$\left.\text{Example 3: ACGT, but} \downarrow \text{Pr(G following C)}\right\} \text{1st order}$$

A Markov Model (1st order)

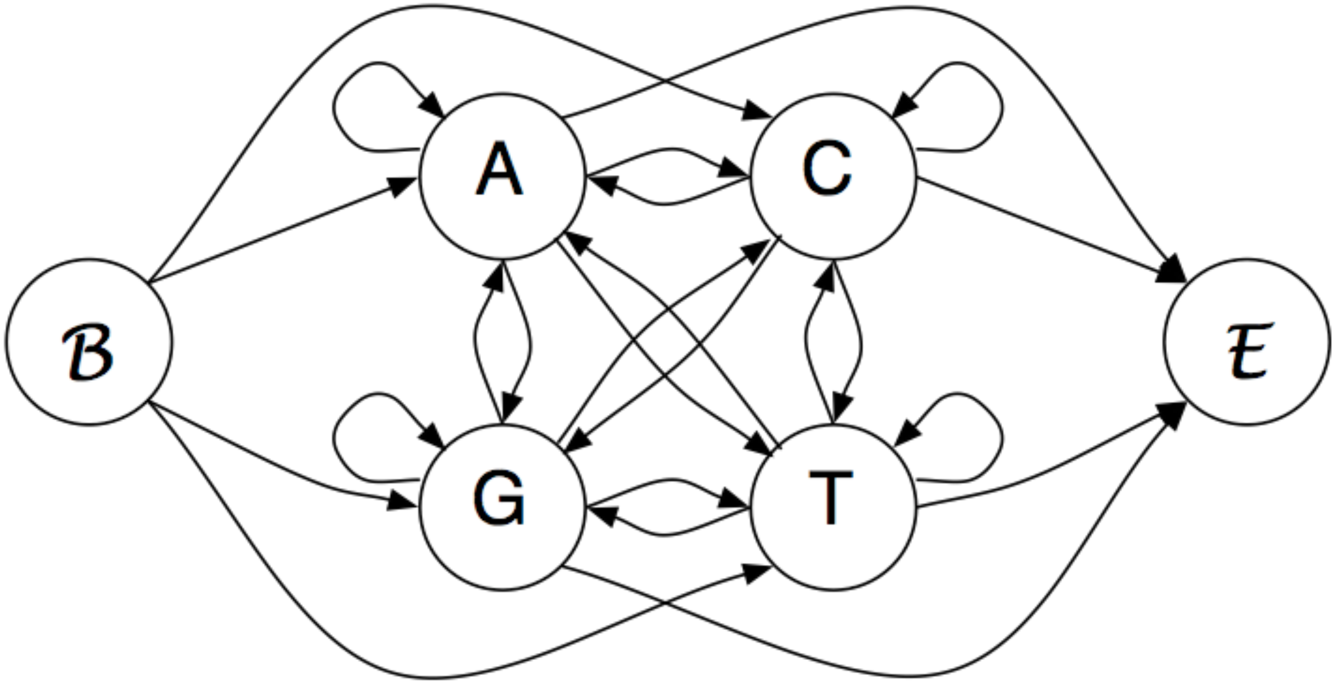


States: A,C,G,T

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

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

Pr of emitting sequence *x*

$$\begin{aligned} x &= x_1\; x_2\; \ldots\; x_n \\ P(x) &= P(x_1, x_2, \ldots, x_n) \end{aligned}$$

law of probability ("chain rule")

$$\begin{aligned} &= P(x_1)\cdot P(x_2 \mid x_1)\cdots P(x_n \mid x_{n-1}, \ldots, x_1) \end{aligned}$$

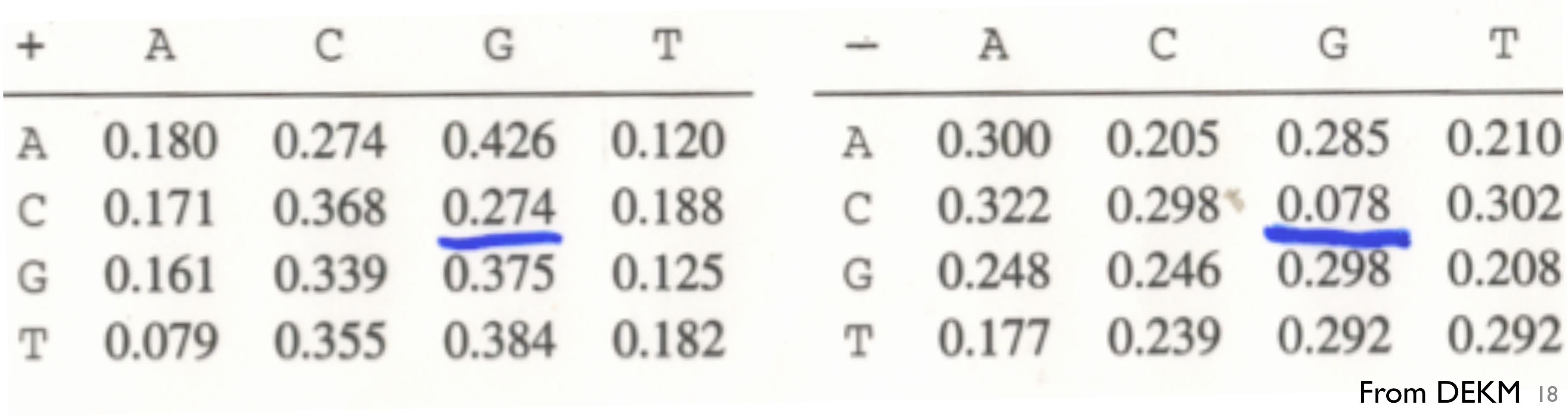
if 1st order MC

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

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

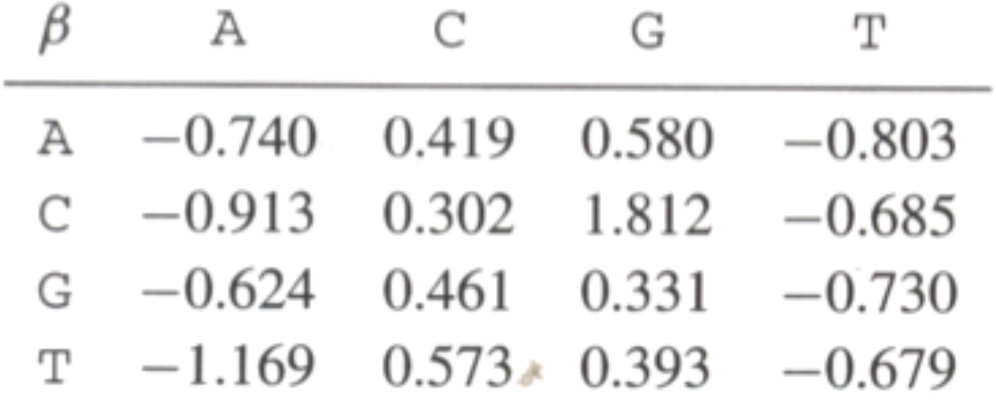
−	A	C	G	T
A	0.300	0.205	0.285	0.210
C	0.322	0.298	0.078	0.302
G	0.248	0.246	0.298	0.208
T	0.177	0.239	0.292	0.292

From DEKM

Discrimination/Classification

Log likelihood ratio of CpG model vs background model

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



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

From DEKM

CpG Island Scores

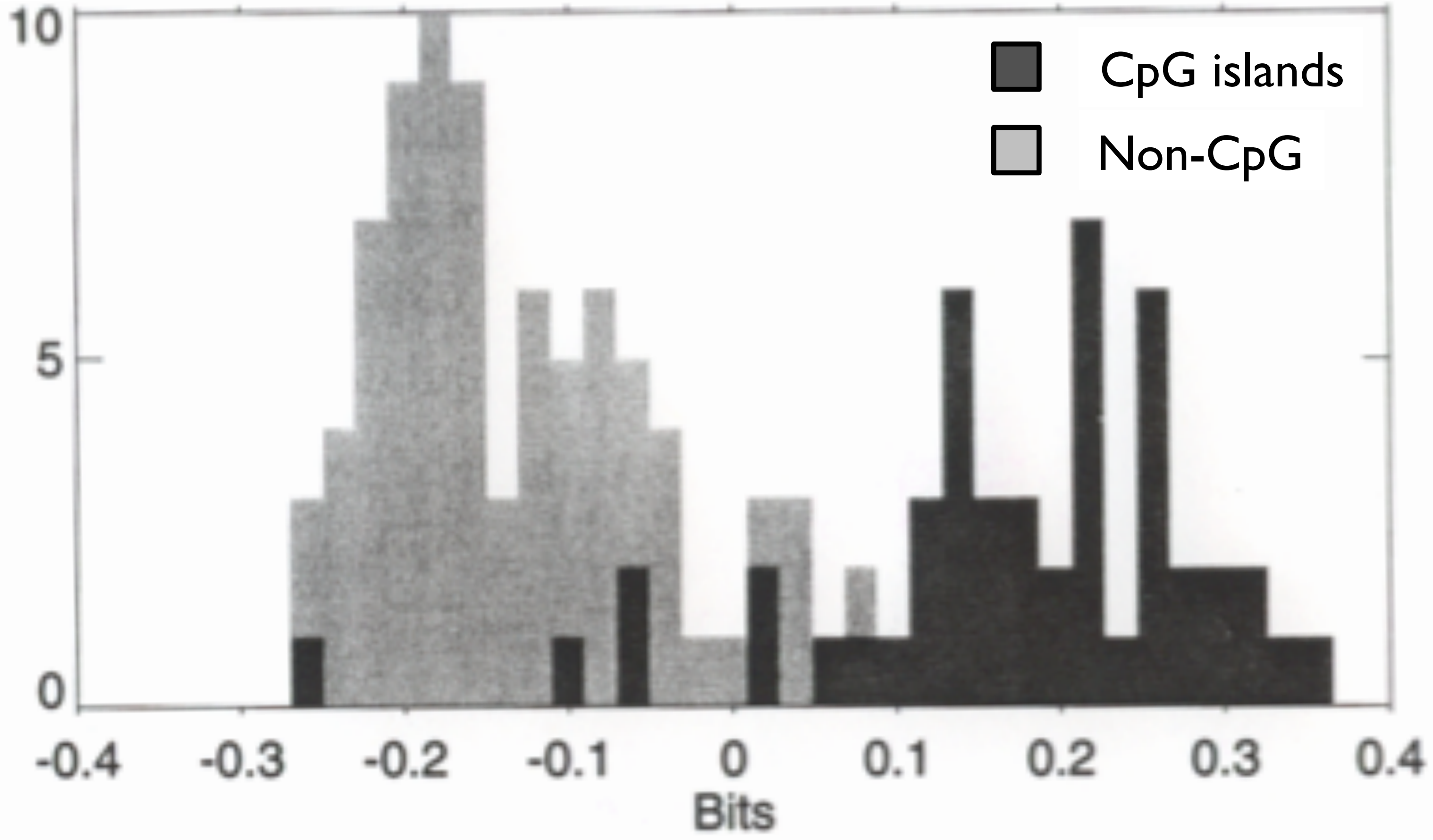


Figure 3.2 *Histogram of length-normalized scores.*

From DEKM

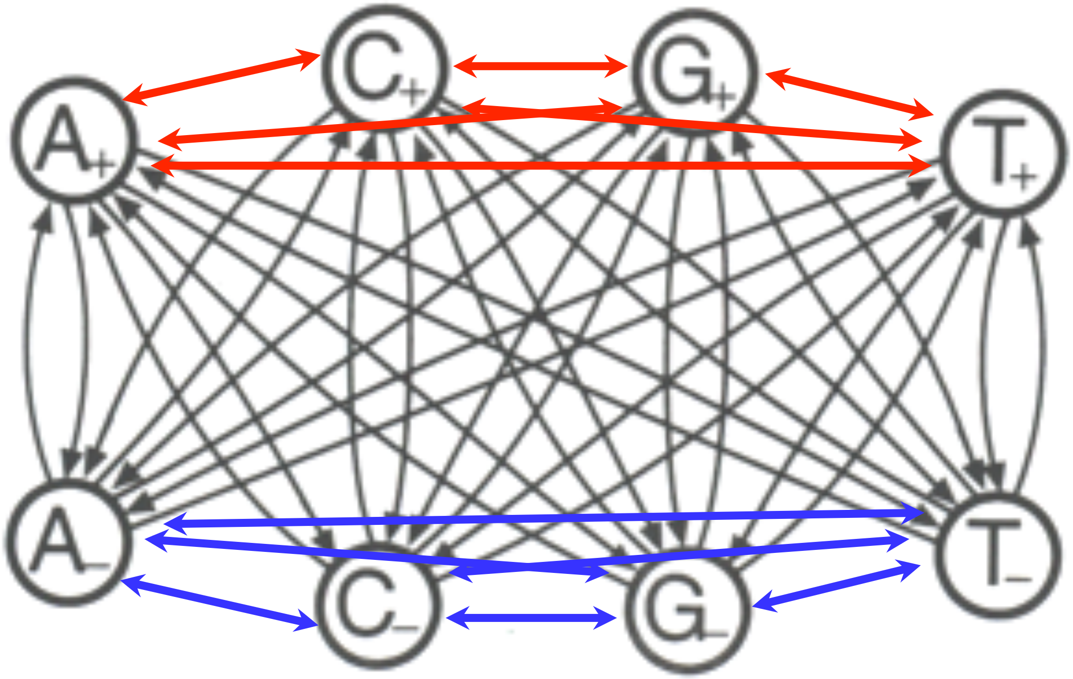
Questions

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 + model

} CpG – model

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

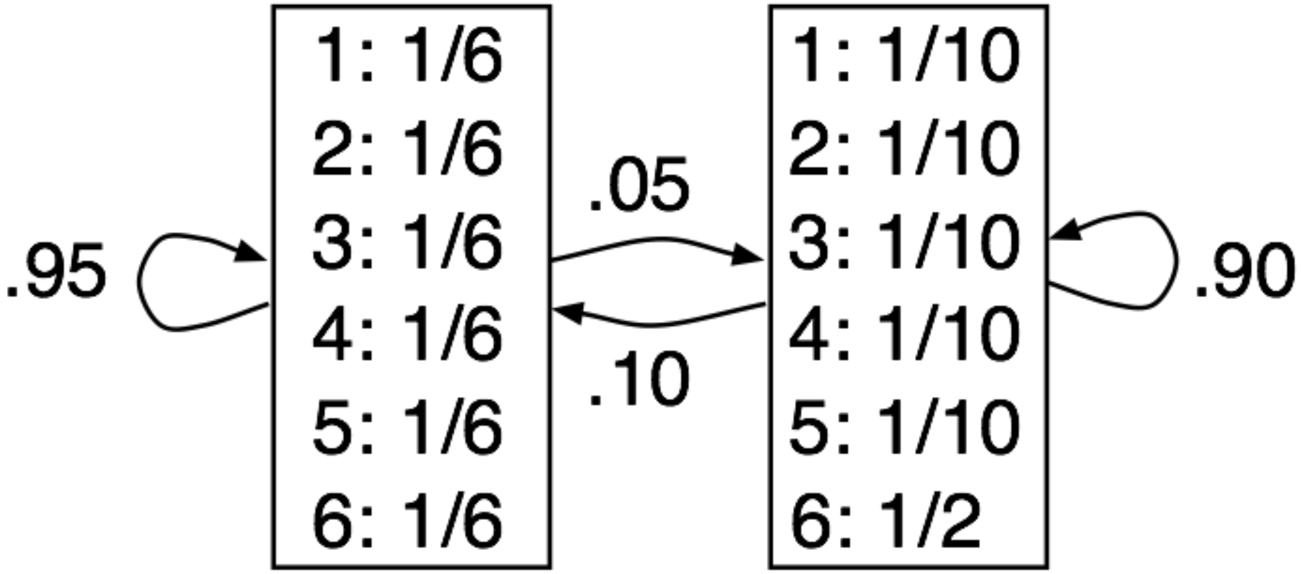
Hidden Markov Models

(HMMs; Claude Shannon, 1948)

States:	$1, 2, 3, \ldots$
Paths:	sequences of states $\pi = (\pi_1, \pi_2, \ldots)$
Transitions:	$a_{k,l} \quad = P(\pi_i = l \mid \pi_{i-1} = k)$
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



.95

1: 1/6
2: 1/6
3: 1/6
4: 1/6
5: 1/6
6: 1/6

.05

.10

1: 1/10
2: 1/10
3: 1/10
4: 1/10
5: 1/10
6: 1/2

.90

```
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      FFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

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.

From DEKM

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

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

Etc.

The Viterbi Algorithm: The most probable path

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

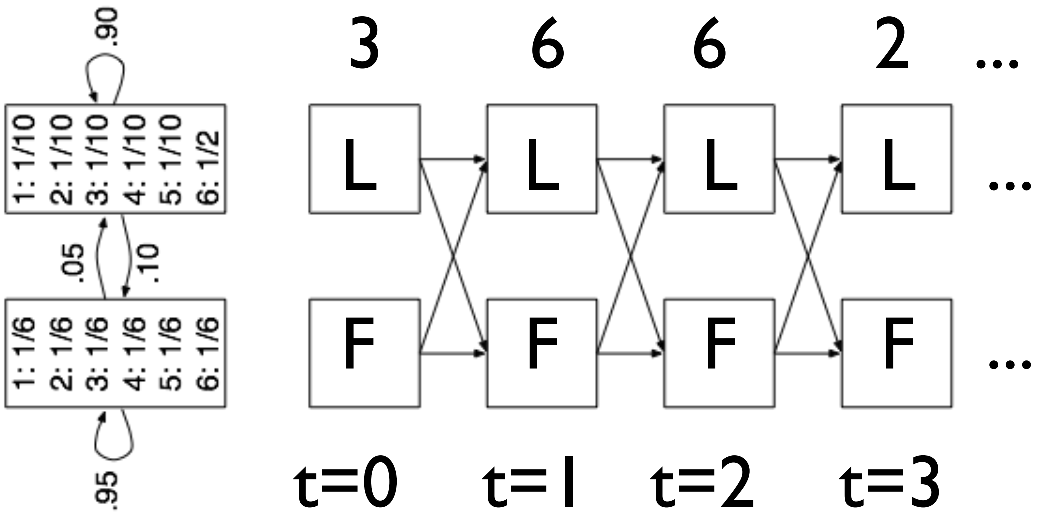
Possibly there are 10^{99} paths of prob 10^{-99}

(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

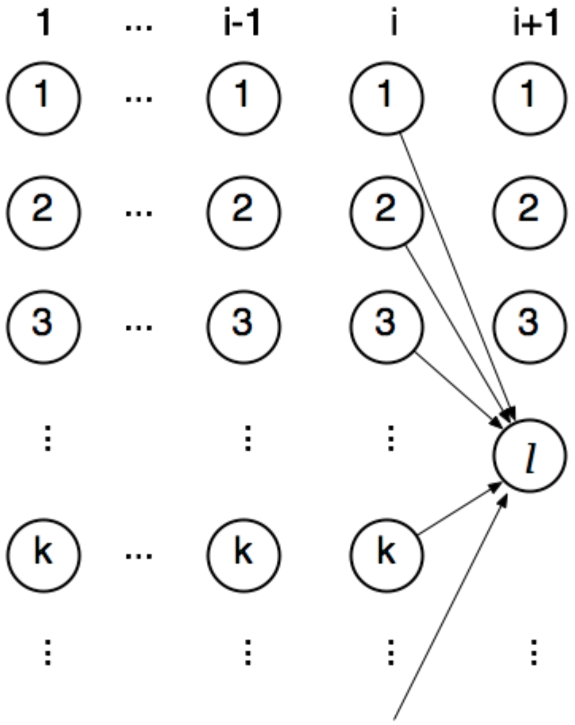
Note exponentially many paths

Viterbi

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

Initialize:

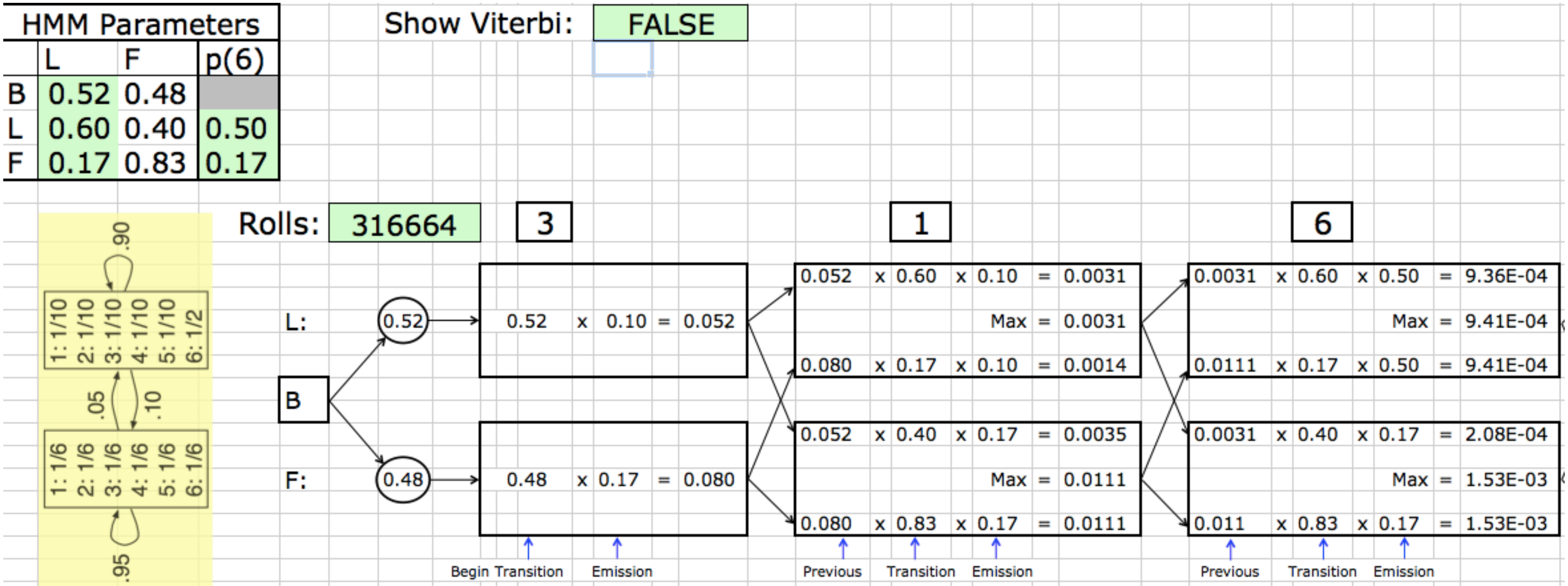
$$v_l(0) = \begin{cases} 1 & \text{if } l = Begin \text{ state} \\ 0 & \text{otherwise} \end{cases} \longrightarrow$$



General case:

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

HMM Casino Example



HMM Parameters

	L	F	p(6)
B	0.52	0.48	
L	0.60	0.40	0.50
F	0.17	0.83	0.17

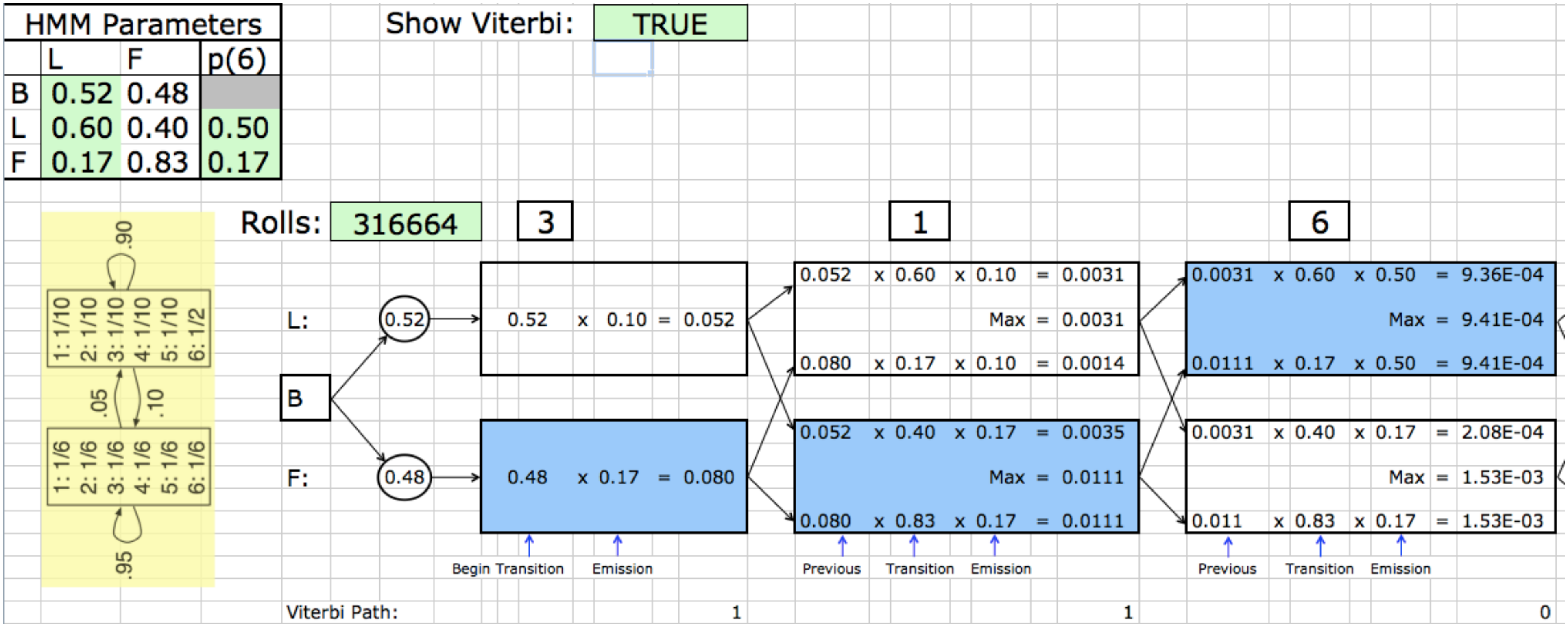
Show Viterbi: FALSE

Rolls: 316664

	3	1	6
L:	0.52 x 0.10 = 0.052	0.052 x 0.60 x 0.10 = 0.0031 Max = 0.0031 0.080 x 0.17 x 0.10 = 0.0014	0.0031 x 0.60 x 0.50 = 9.36E-04 Max = 9.41E-04 0.0111 x 0.17 x 0.50 = 9.41E-04
F:	0.48 x 0.17 = 0.080	0.052 x 0.40 x 0.17 = 0.0035 Max = 0.0111 0.080 x 0.83 x 0.17 = 0.0111	0.0031 x 0.40 x 0.17 = 2.08E-04 Max = 1.53E-03 0.011 x 0.83 x 0.17 = 1.53E-03
	Begin Transition Emission	Previous Transition Emission	Previous Transition Emission

(Excel spreadsheet on web; download & play…)

HMM Casino Example



HMM Parameters			
	L	F	p(6)
B	0.52	0.48	
L	0.60	0.40	0.50
F	0.17	0.83	0.17

Show Viterbi: TRUE

Rolls: 316664

3

L: 0.52 x 0.10 = 0.052

F: 0.48 x 0.17 = 0.080

1

L:
0.052 x 0.60 x 0.10 = 0.0031
Max = 0.0031
0.080 x 0.17 x 0.10 = 0.0014

F:
0.052 x 0.40 x 0.17 = 0.0035
Max = 0.0111
0.080 x 0.83 x 0.17 = 0.0111

6

L:
0.0031 x 0.60 x 0.50 = 9.36E-04
Max = 9.41E-04
0.0111 x 0.17 x 0.50 = 9.41E-04

F:
0.0031 x 0.40 x 0.17 = 2.08E-04
Max = 1.53E-03
0.011 x 0.83 x 0.17 = 1.53E-03

Viterbi Path: 1 1 0

(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

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

```
Rolls    315116246446644245311321631164152133625144543631656626566666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFLLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5

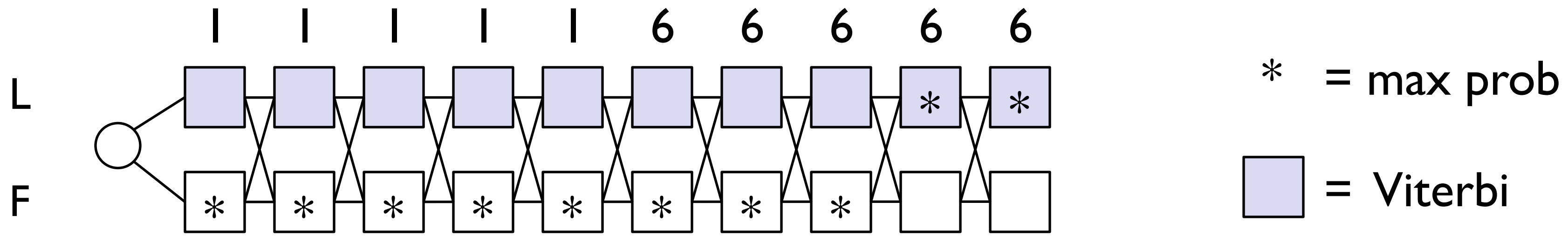
Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

From DEKM

Most probable path ≠ Sequence of most probable states

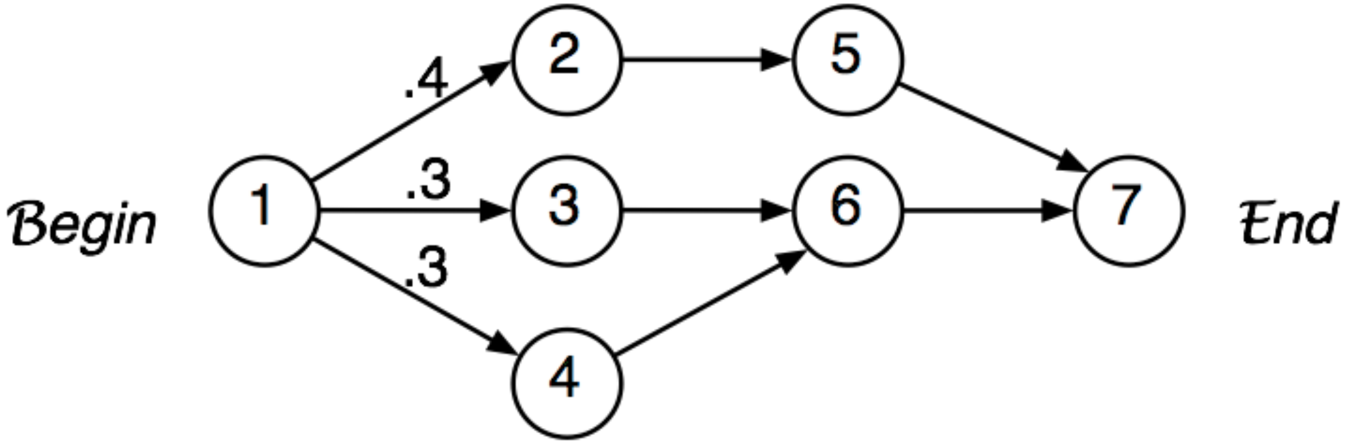
Another example, based on casino dice again

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



Is Viterbi "best"?

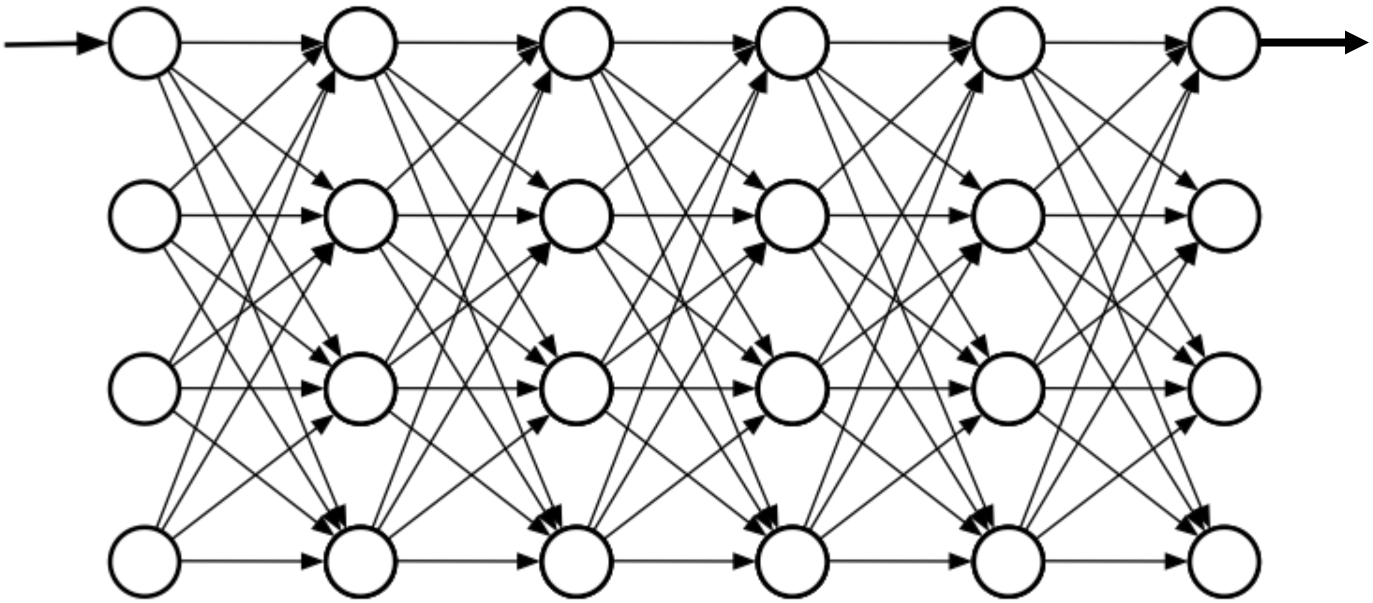
Viterbi finds $\pi^* = \arg\max_\pi P(x, \pi)$



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)

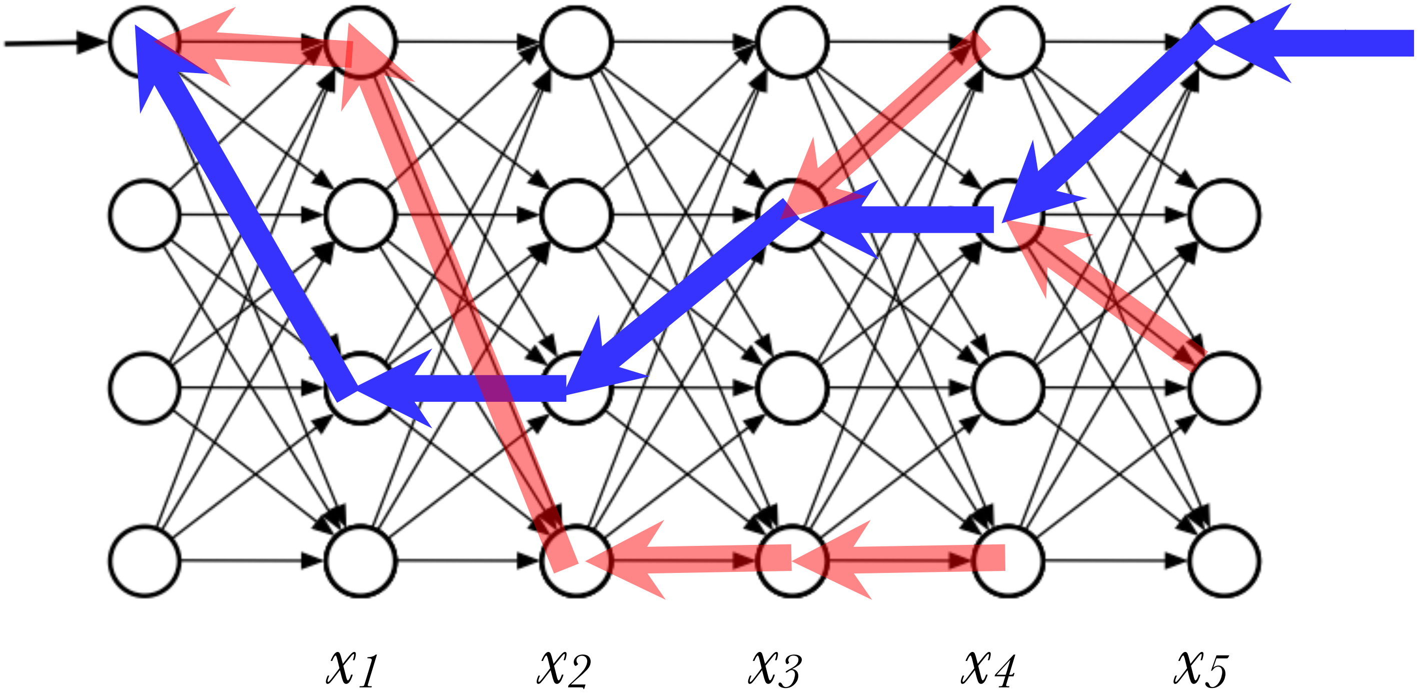
States



x_1 x_2 x_3 x_4

Emissions/sequence positions

Viterbi: best path to each state

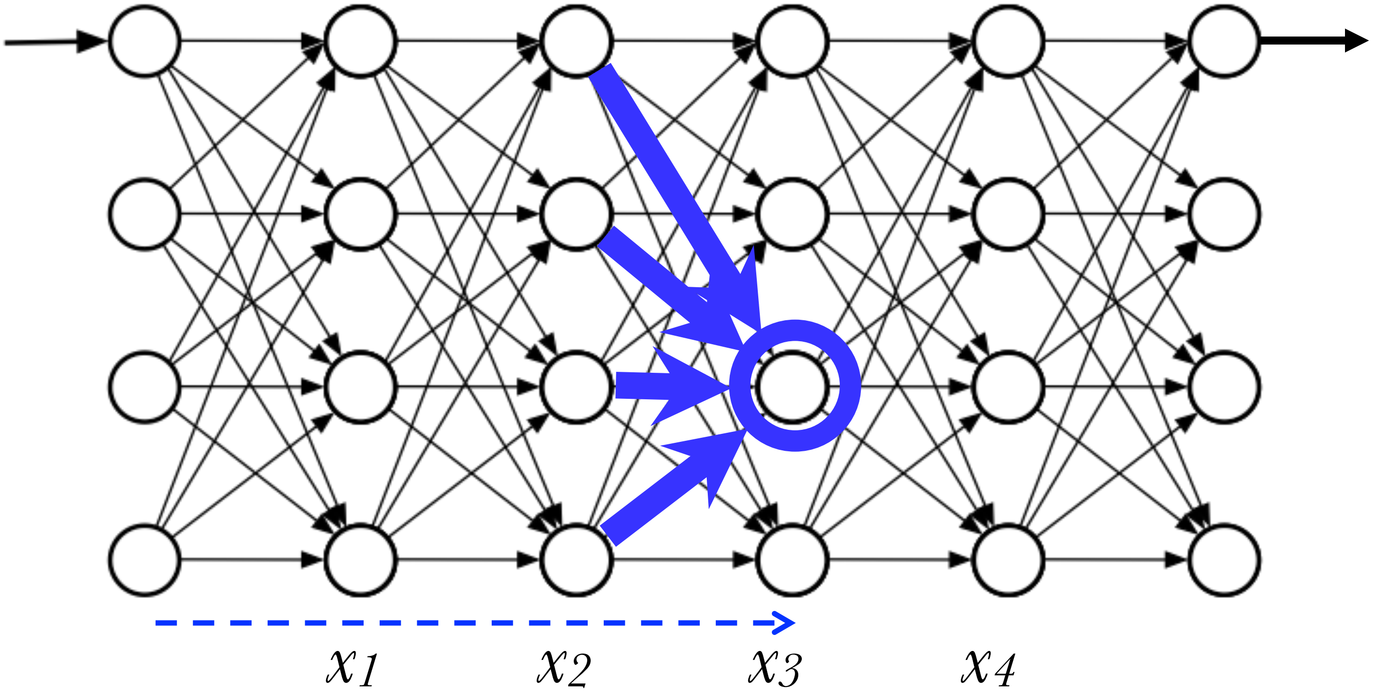


Viterbi *score:* $$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

Viterbi *path*^{R}: $$back_l(i+1) = \arg\max_k (v_k(i)\, a_{k,l})$$

The Forward Algorithm

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



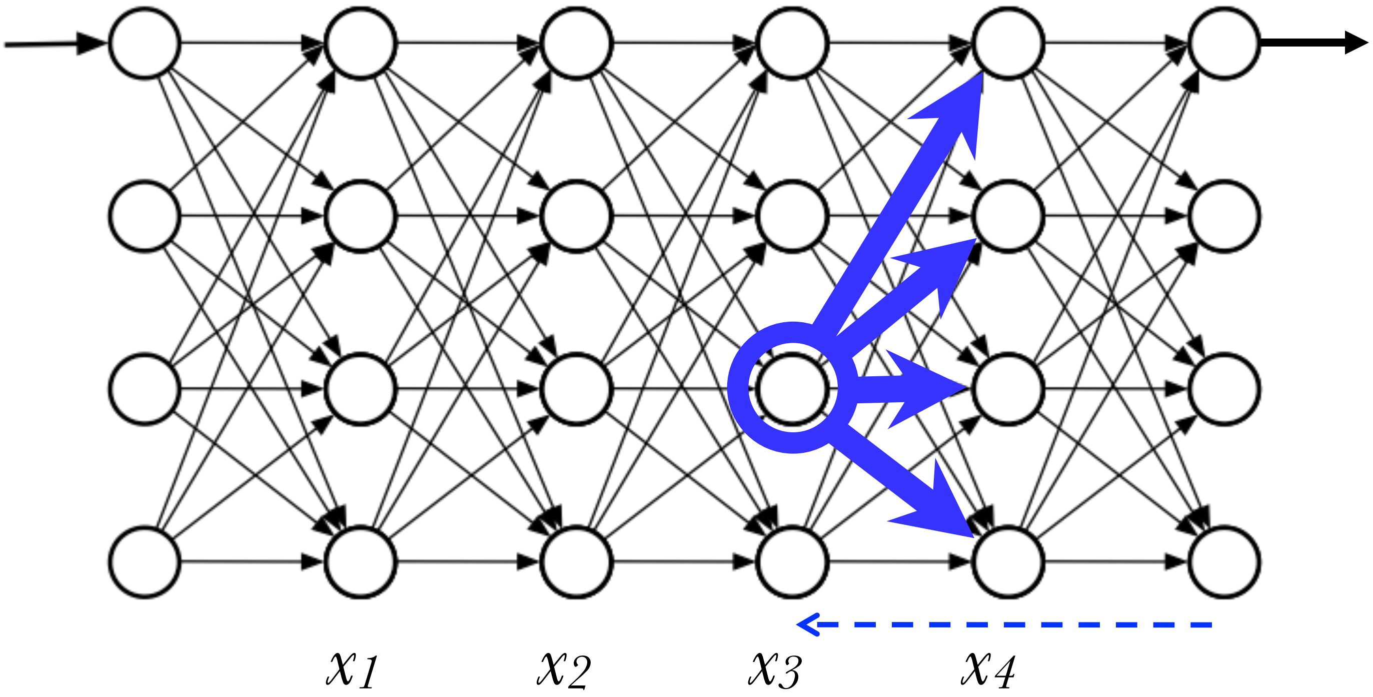
$$f_k(i) \triangleq P(x_1 \ldots x_i,\ \pi_i = k)$$

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

$$P(x) = \textstyle\sum_\pi P(x,\pi) = \textstyle\sum_k f_k(n) a_{k,0}$$

The Backward Algorithm

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



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

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

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

In state *k* at step *i* ?

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

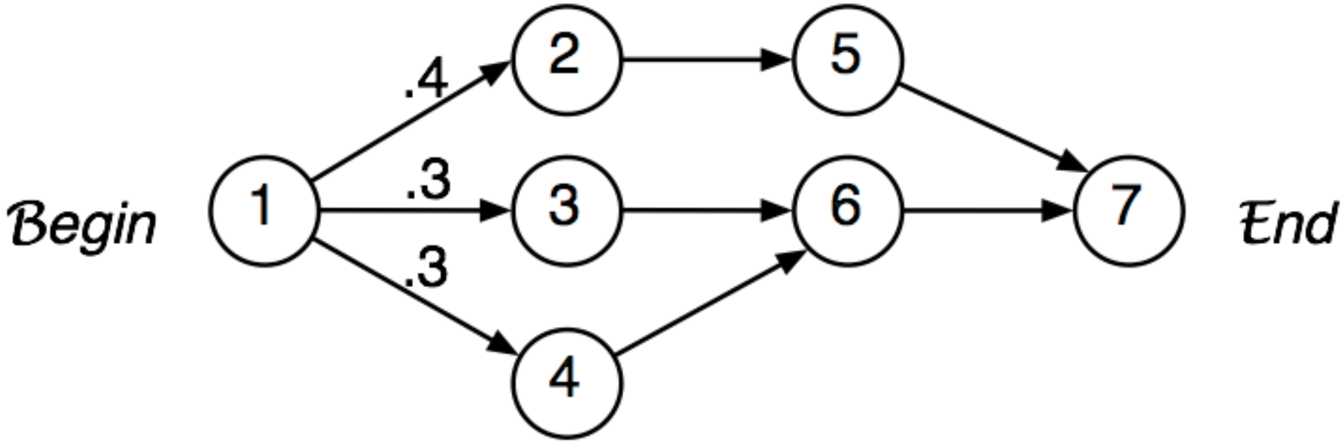
$$
P(\pi_i = k \mid x) \ = \ \frac{P(x, \pi_i = k)}{P(x)} = \frac{f_k(i) \cdot b_k(i)}{P(x)}
$$

Posterior Decoding, I

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

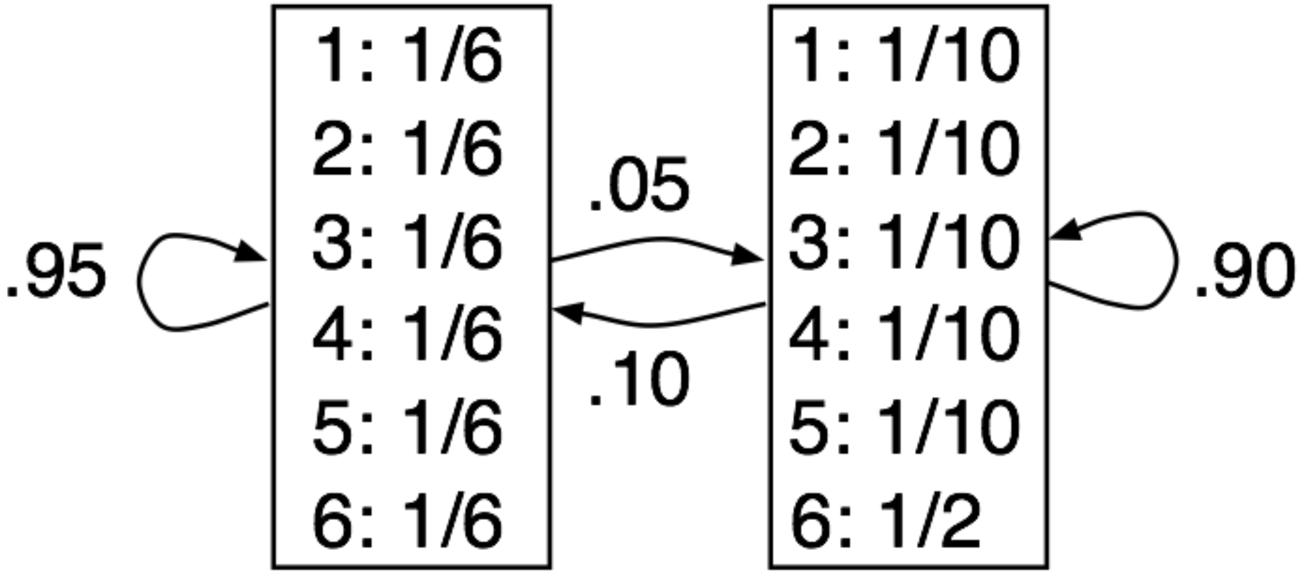
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

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



.95

1: 1/6
2: 1/6
3: 1/6
4: 1/6
5: 1/6
6: 1/6

.05

.10

1: 1/10
2: 1/10
3: 1/10
4: 1/10
5: 1/10
6: 1/2

.90

```
Rolls   315116246446644245311321631164152133625144543631656626566666
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLL

Rolls   651166453132651245636664631636663162326455236266666625151631
Die     LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls   222555441666566563564324364131513465146353411126414626253356
Die     FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls   366163666466232534413661661163252562462255265252266435353336
Die     LLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls   233121625364414432335163243633665562466662632666612355245242
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

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.

From DEKM

Posterior Decoding

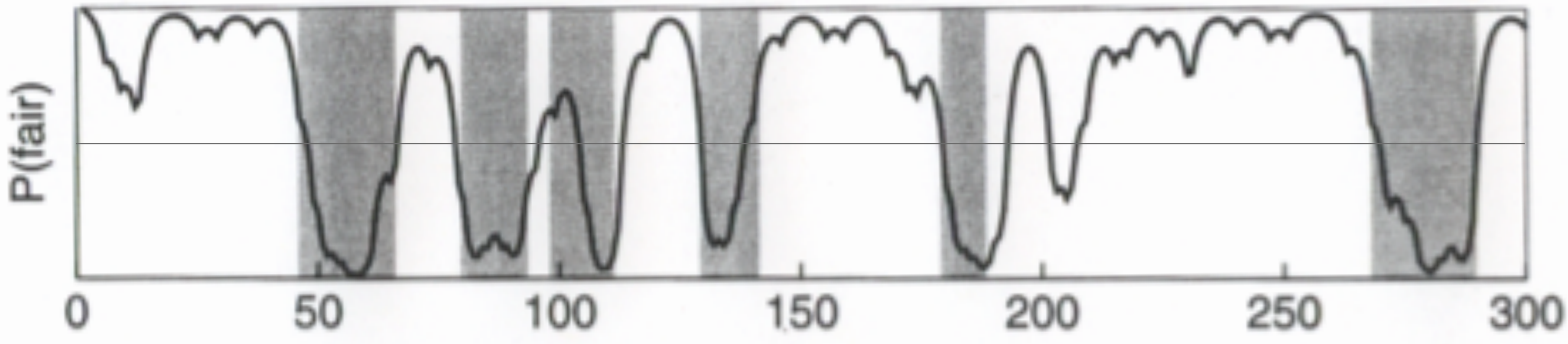


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

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

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

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

← + pseudocounts?

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

Viterbi Training

given π, estimate θ; given θ estimate π; 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.)

AKA "the forward-backward alg"

Baum-Welch Training

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

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

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

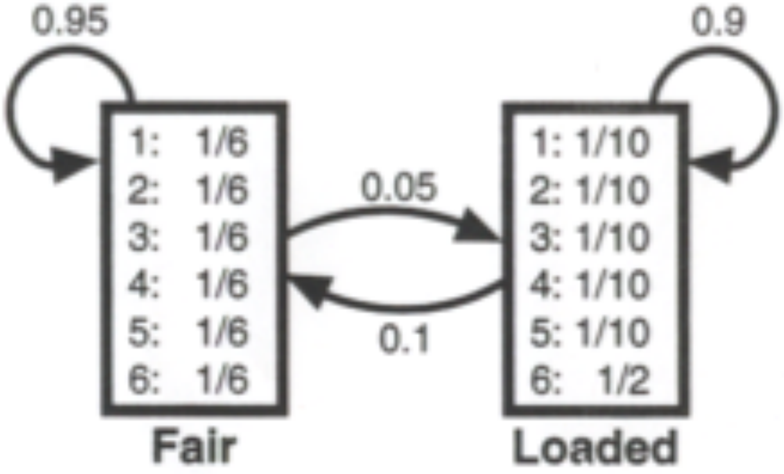
Estimated # of $k \rightarrow l$ transitions $\hat{A}_{k,l}$ on *set* of seqs x^j

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

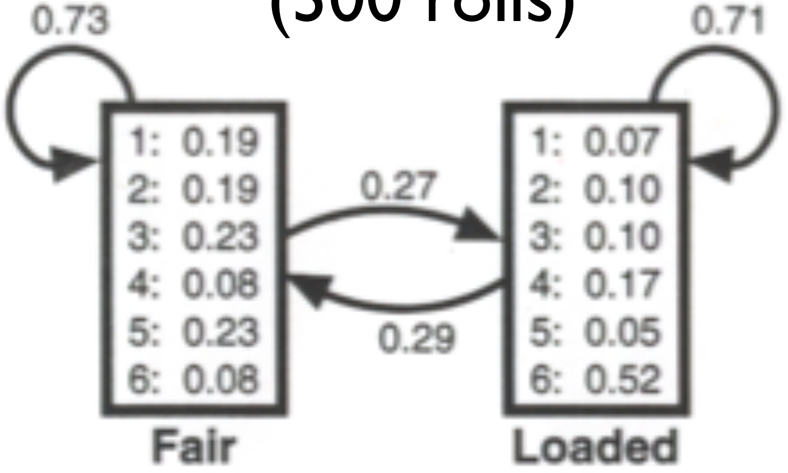
New estimate $\hat{a}_{k,l} = \dfrac{\hat{A}_{k,l}}{\sum_l \hat{A}_{k,l}}$

Emissions: similar

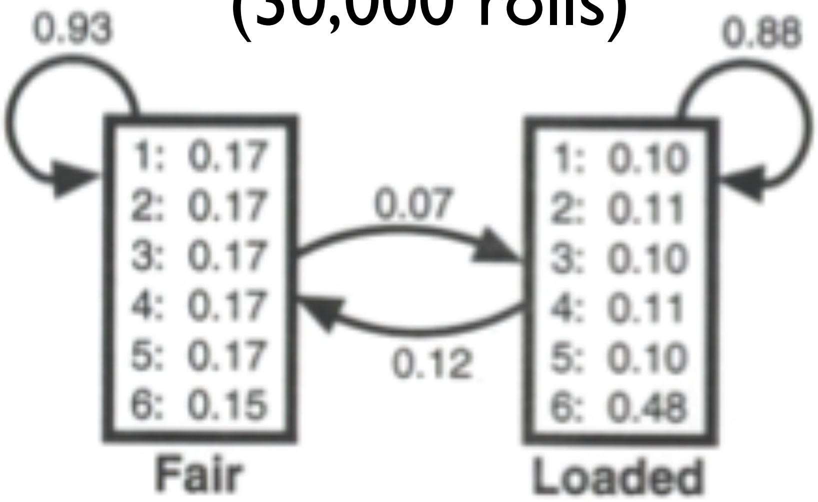
True Model



B-W Learned Model (300 rolls)



B-W Learned Model (30,000 rolls)



Log-odds (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.sanger.ac.uk/

Proteins fall into families, both across & within species

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

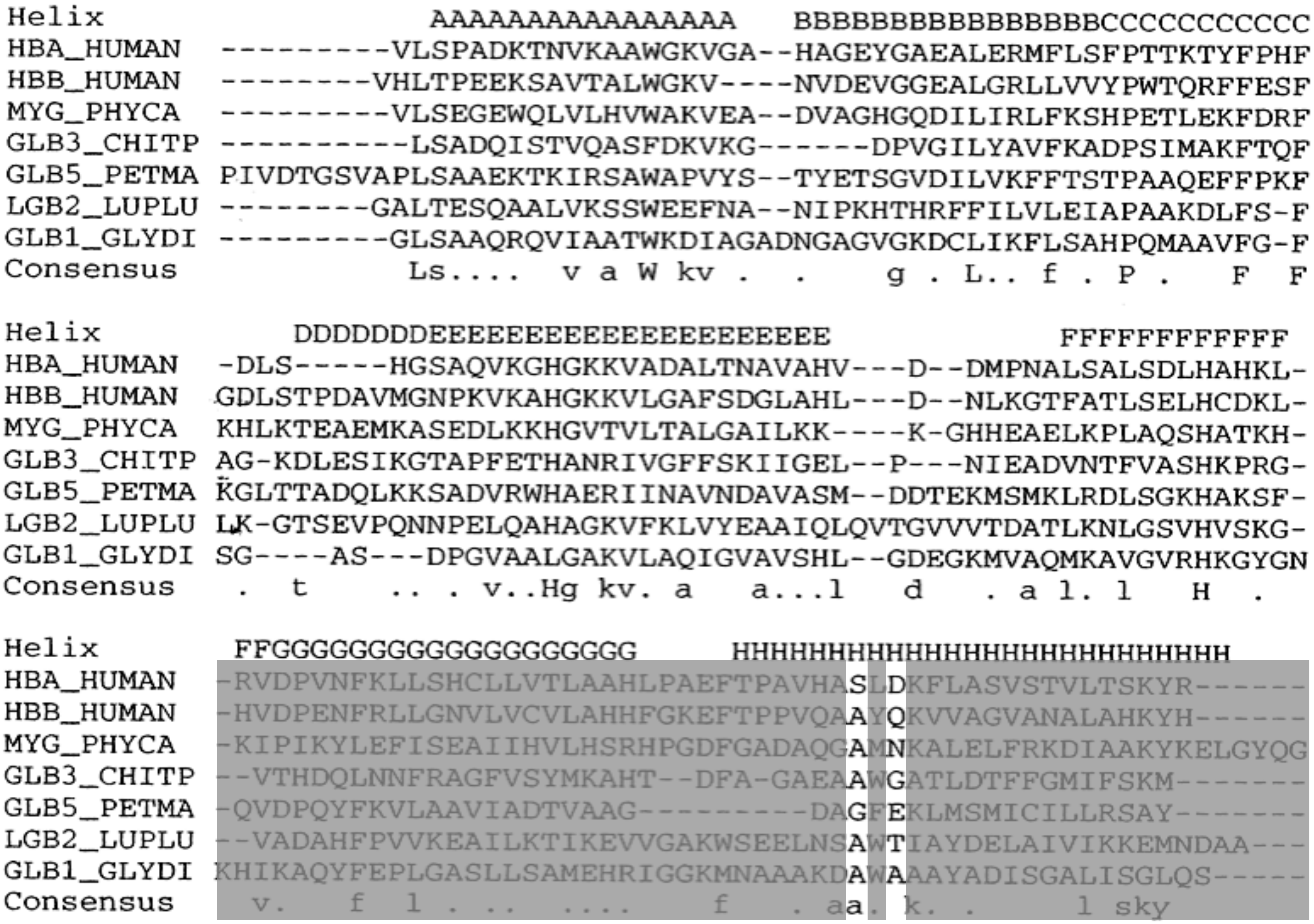
Identifying family very useful: suggests function, etc.

So, search & alignment are both important

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

A. There is more info in *multiple* examples

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

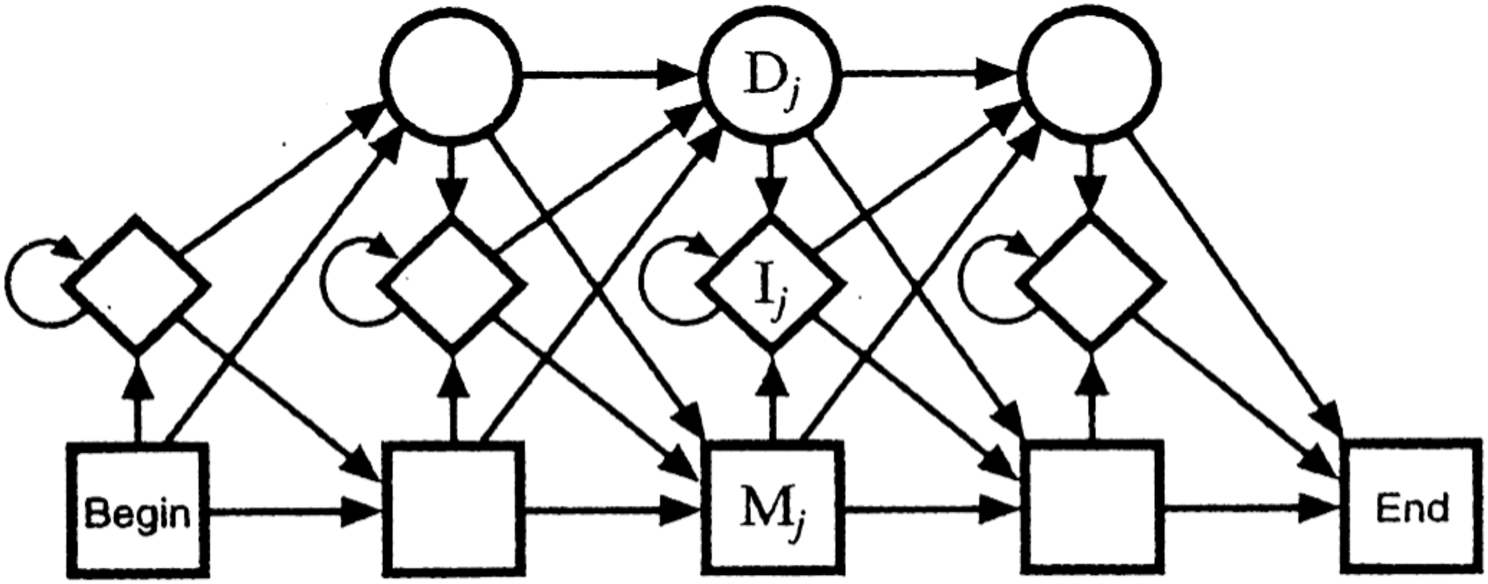


Figure 5.2 *The transition structure of a profile HMM.*

M$_j$: Match states (20 emission probabilities)

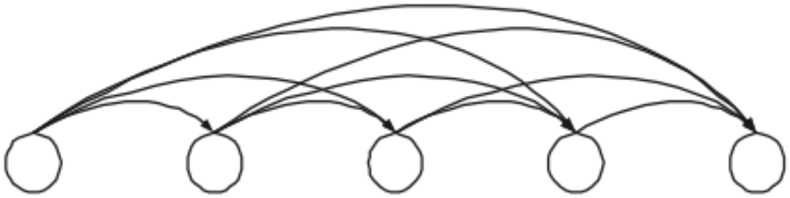
I$_j$: Insert states (Background emission probabilities)

D$_j$: Delete states (silent - no emission)

From DEKM

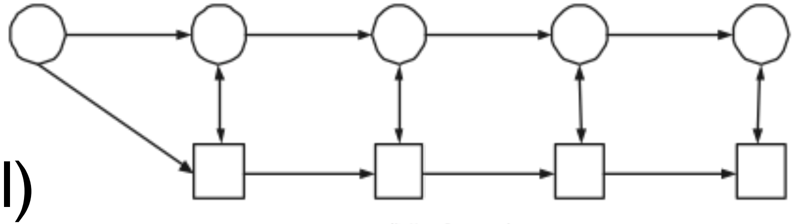
Silent States

Example: chain of states, can skip some



Problem: many parameters.

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



(“silent” states)

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

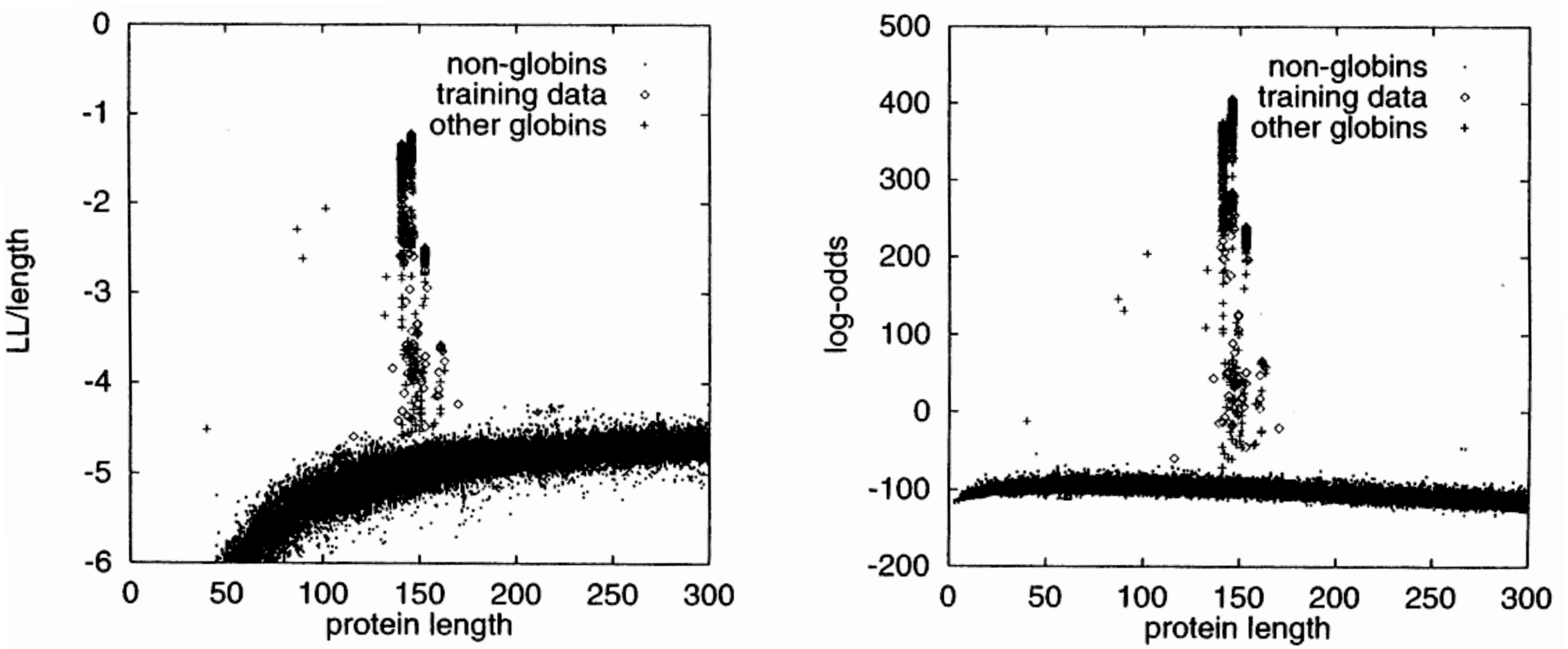


Figure 5.5 *To the left the length-normalized LL score is shown as a function of sequence length. The right plot shows the same for the log-odds score.*

From DEKM

Z-Scores

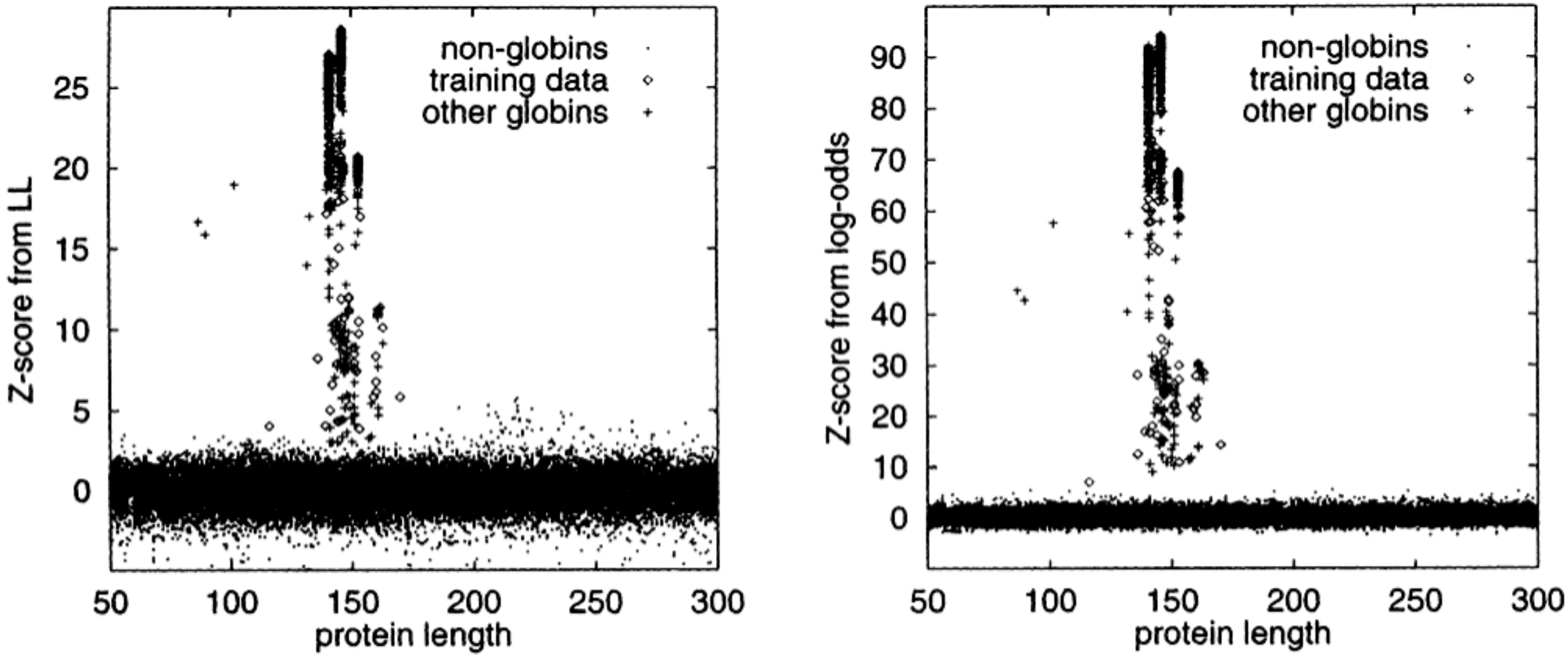


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

From DEKM

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

Pfam 25.0 (March 2011, 12273 families; covers ~75% of human proteins)

Pfam 27.0 (March 2013, 14831 families; ≈ 90%)

HMM Summary

Inference

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

joint vs
conditional probs

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”, but Viterbi-based

HMM Summary (cont.)

Search:

- Viterbi or forward

Scoring:

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

Excellent tools available (SAM, HMMer, Pfam, …)

A very widely used tool for biosequence analysis