CSE P 527

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.:

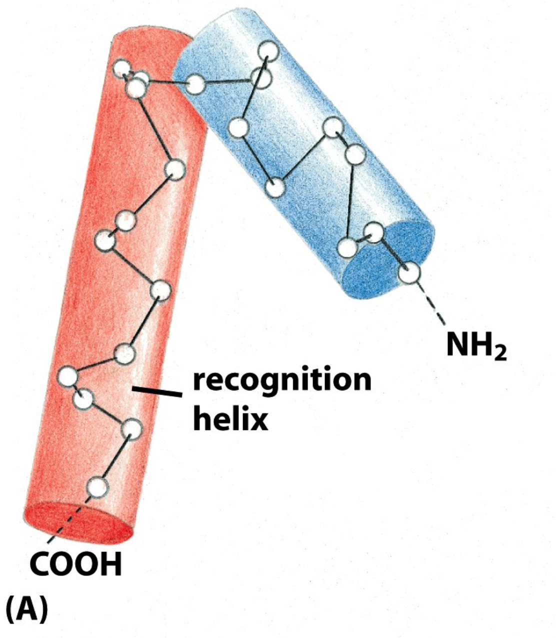


Figure 7-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

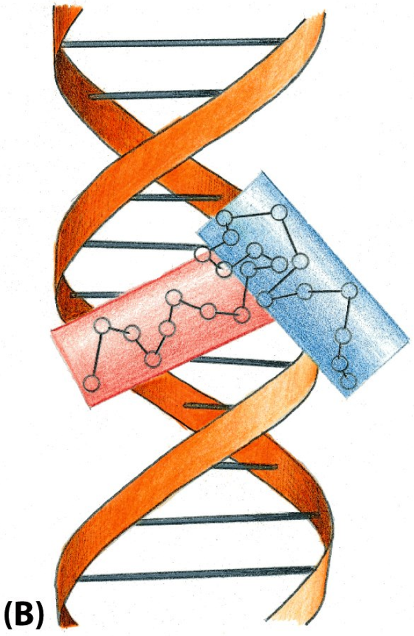
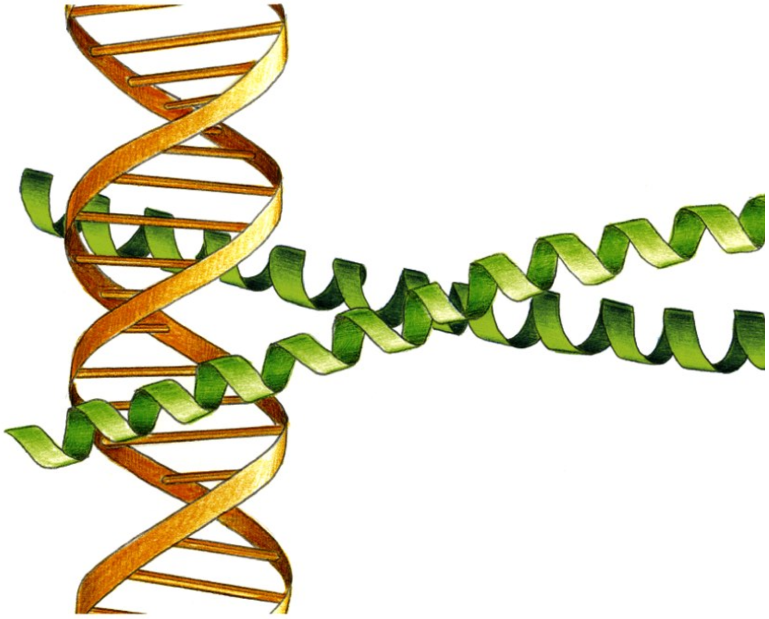
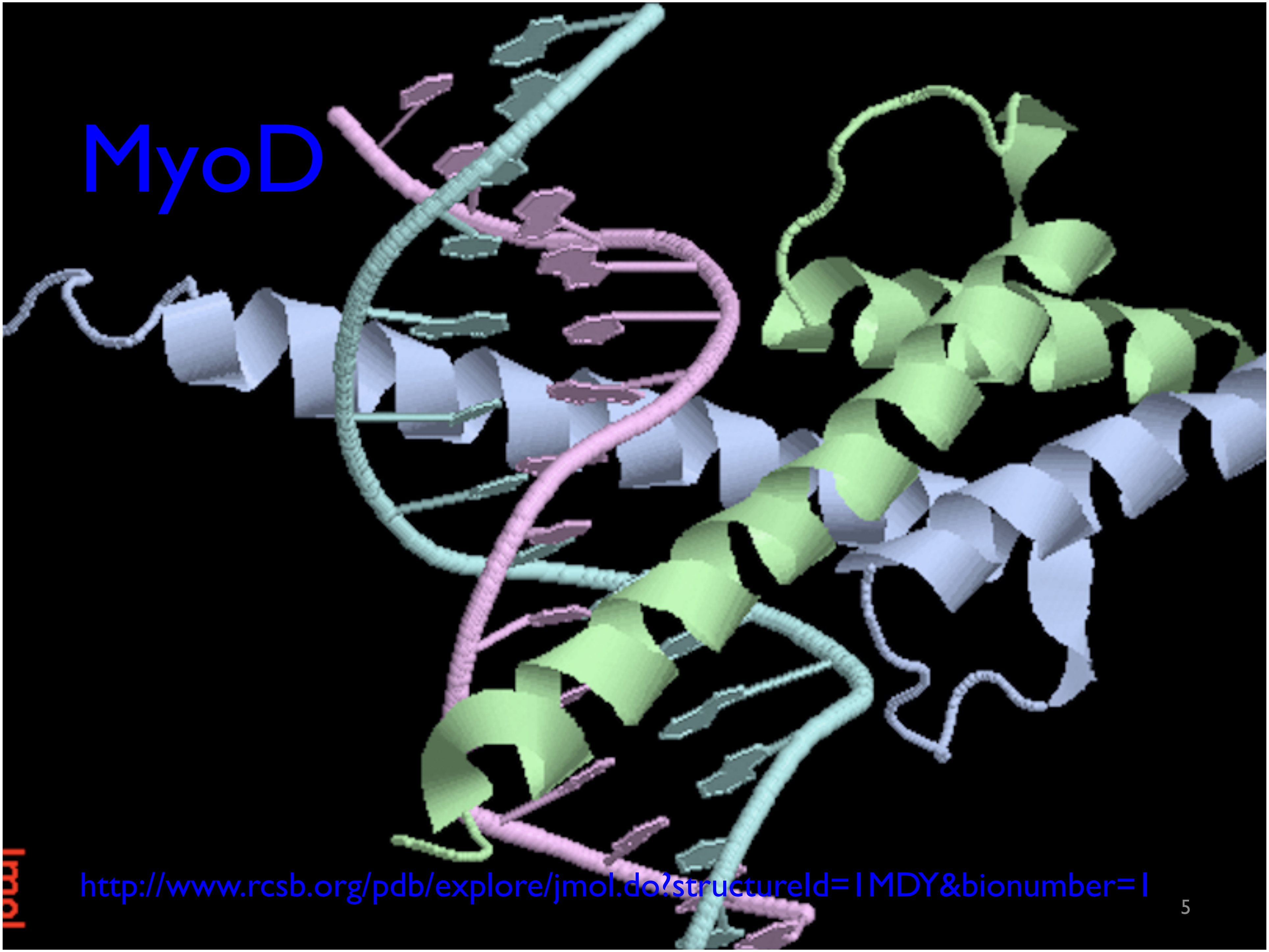


Figure 7-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)



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

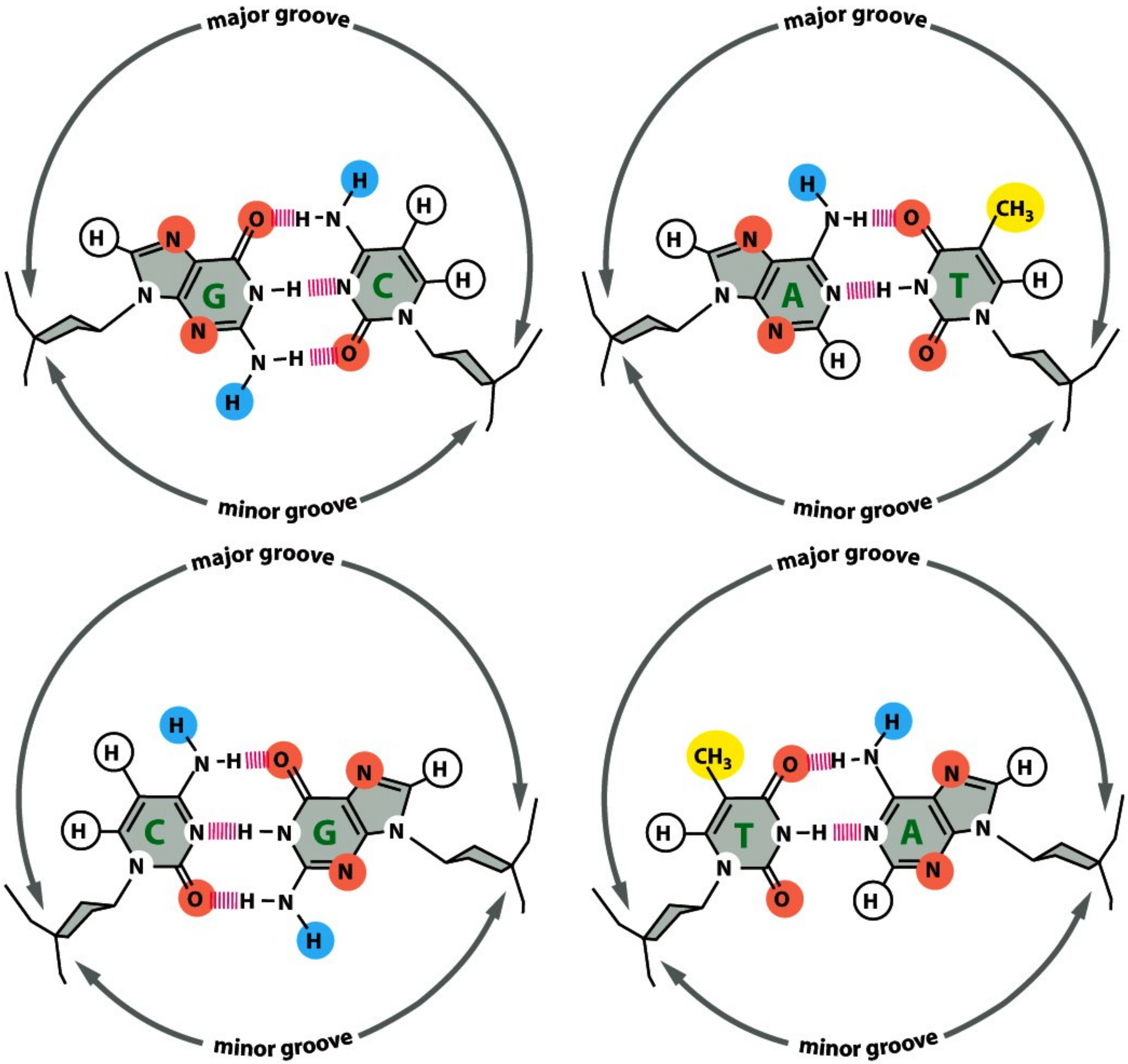
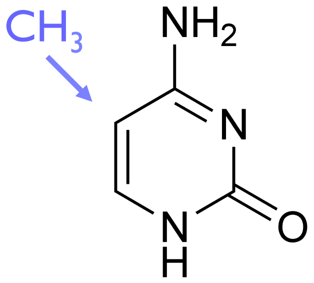


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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

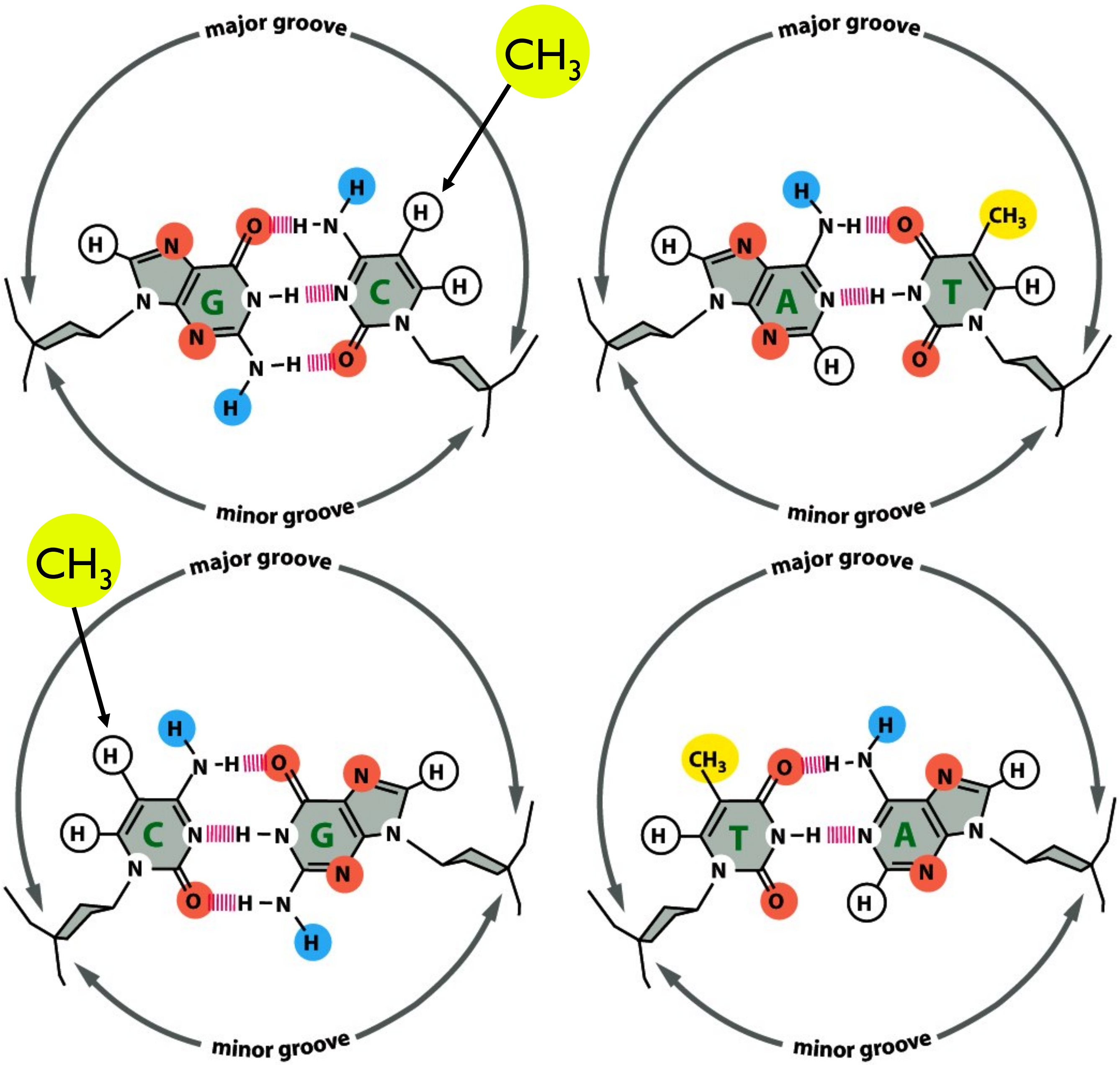
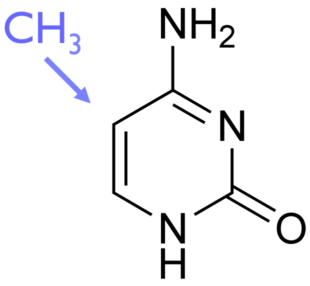


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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 an embryonic 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)

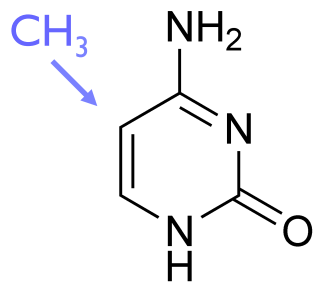
Major exception: promoters of housekeeping genes

“CpG Islands”

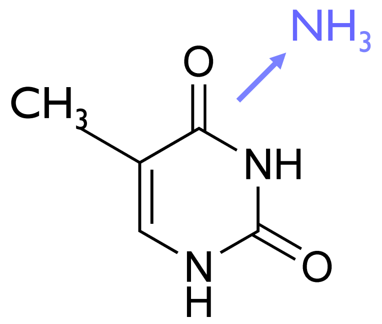
Methyl-C mutates to T relatively easily

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 – sometimes a useful approximation, but in many cases definitely unrealistic.

Markov Chains

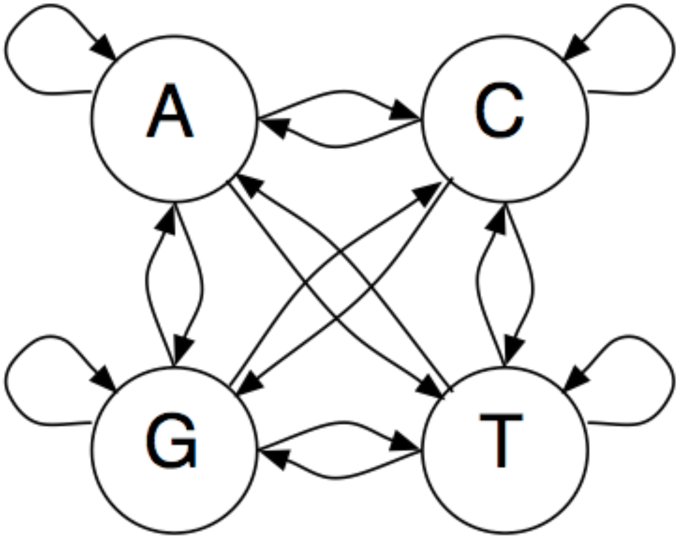
A sequence $x_1, x_2, \ldots$ of random variables is a *k-th order Markov chain* if, for all *i*, *i*th value is independent of all but the previous *k* values:

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

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

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

A Markov Model (1st order)

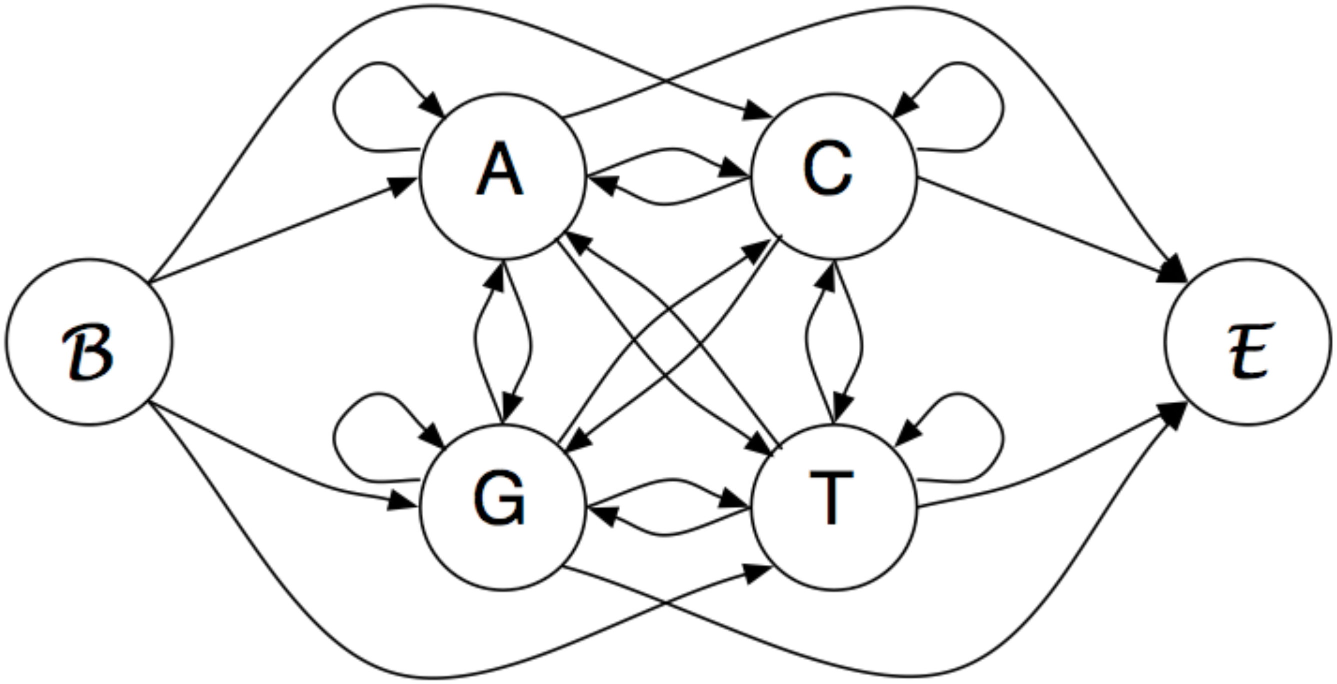


States: A,C,G,T

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

Begin/End states

Pr of emitting sequence *x*

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

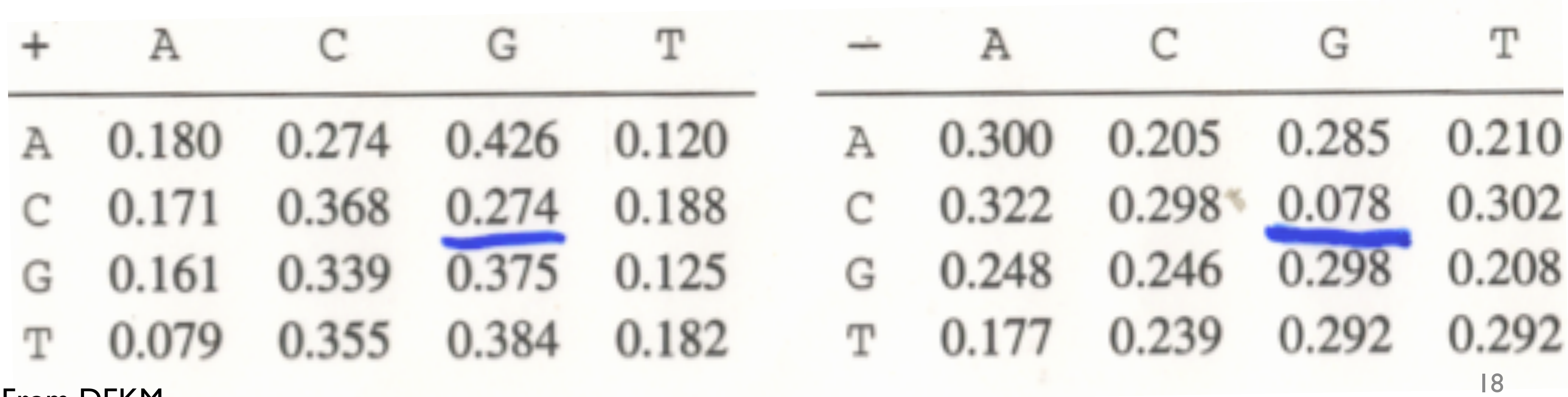
law of probability
("chain rule")

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:



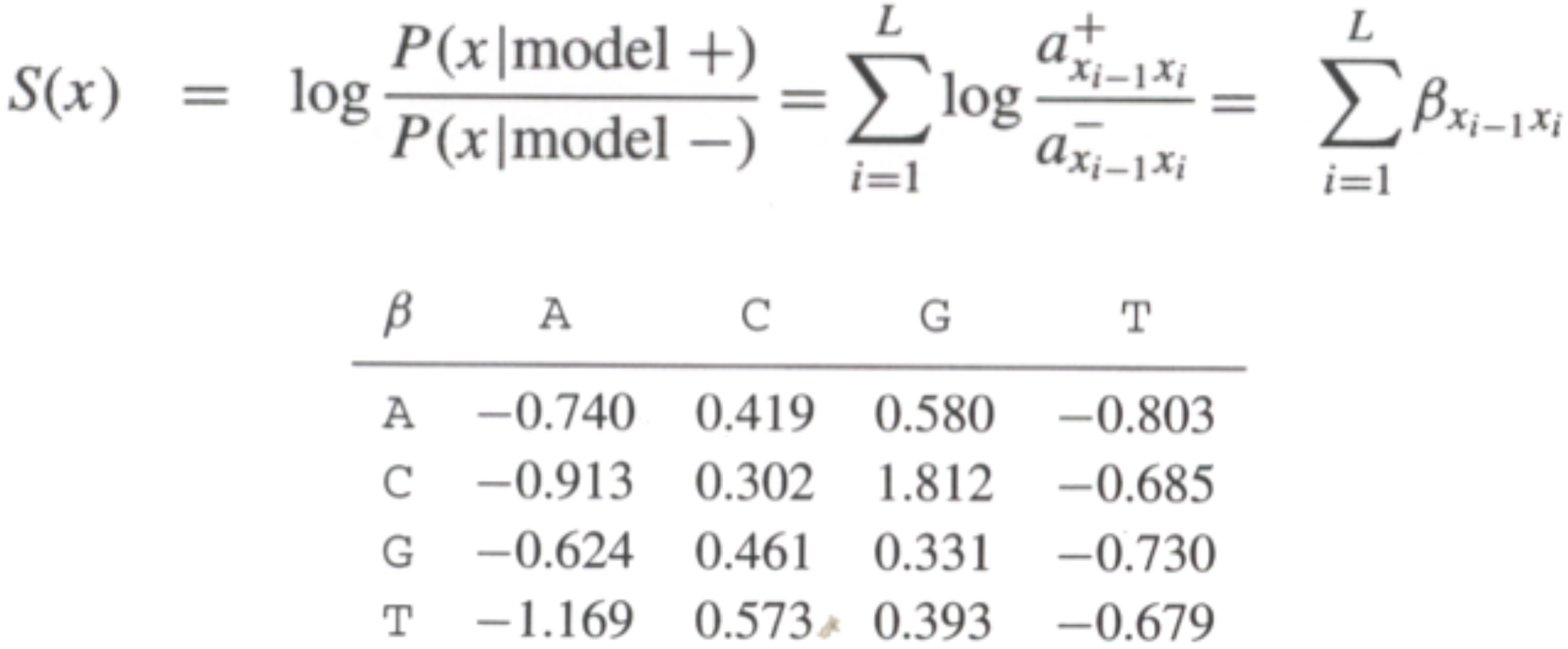
+	A	C	G	T
A	0.180	0.274	0.426	0.120
C	0.171	0.368	0.274	0.188
G	0.161	0.339	0.375	0.125
T	0.079	0.355	0.384	0.182

−	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



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

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

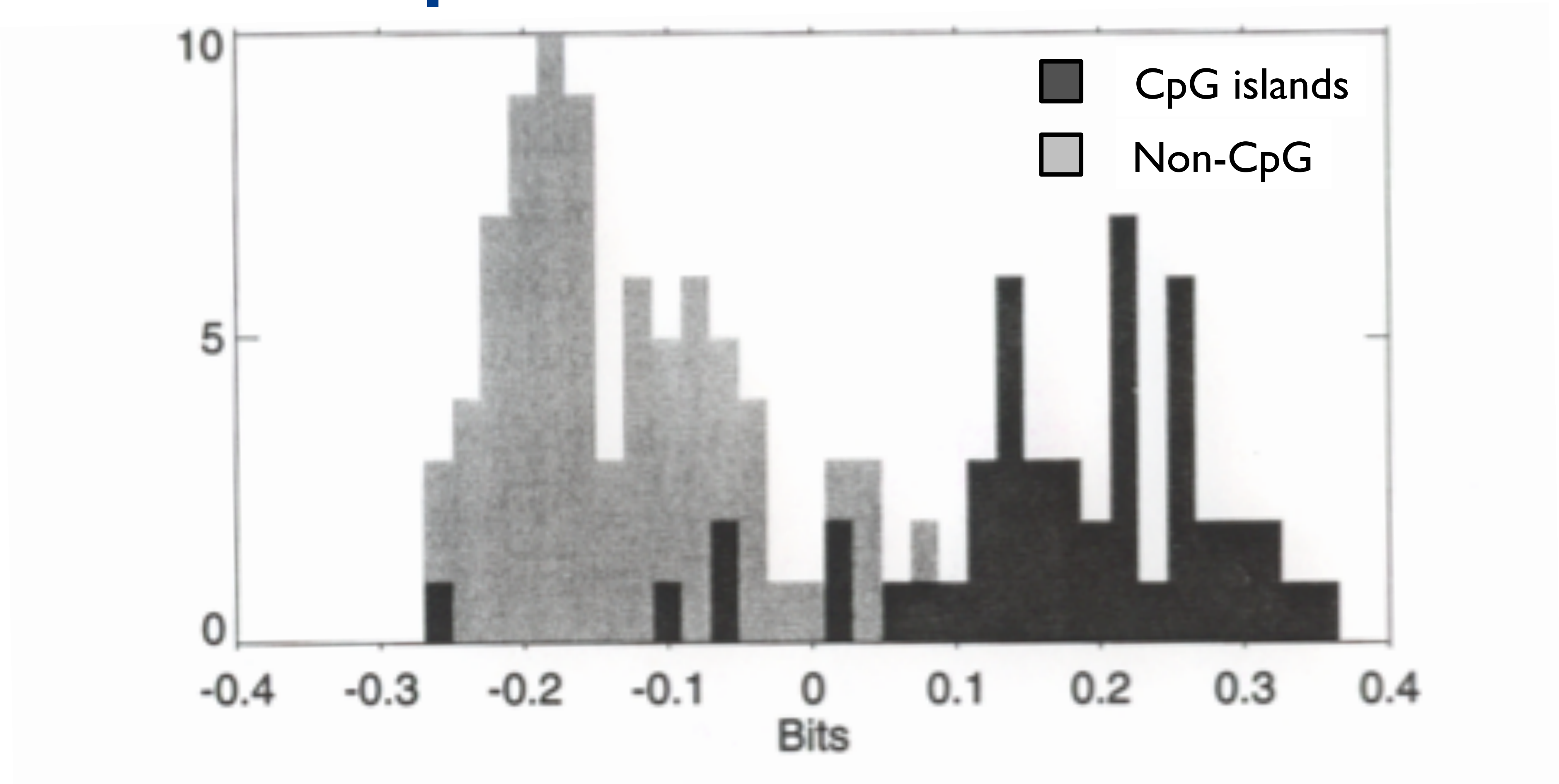


Figure 3.2 *Histogram of length-normalized scores.*

From DEKM

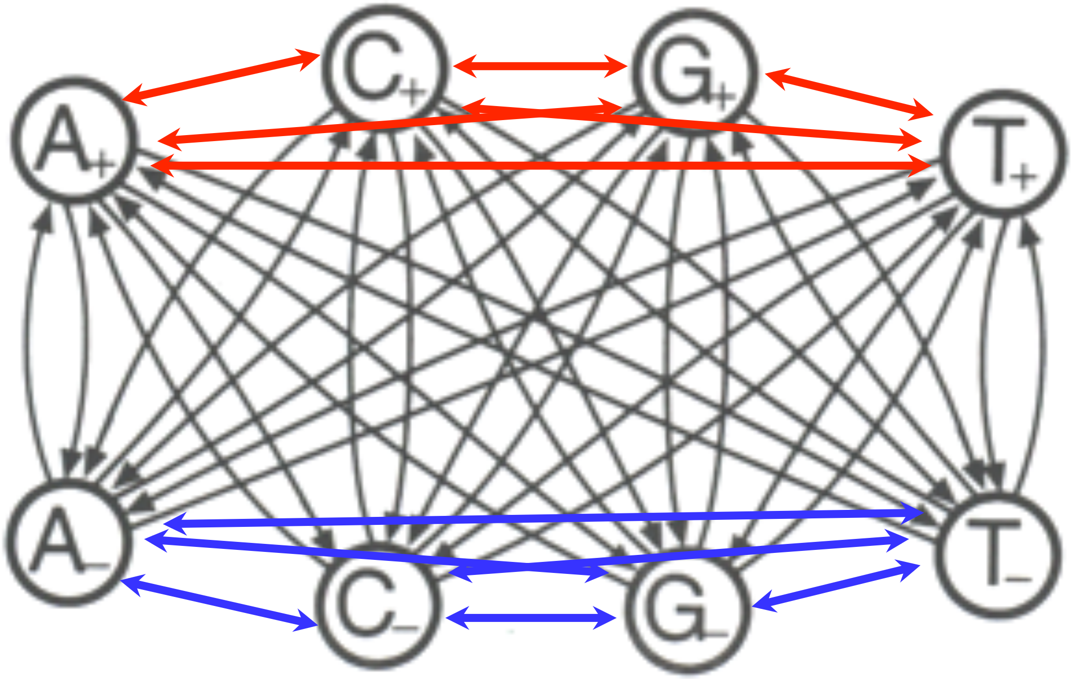
Questions

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



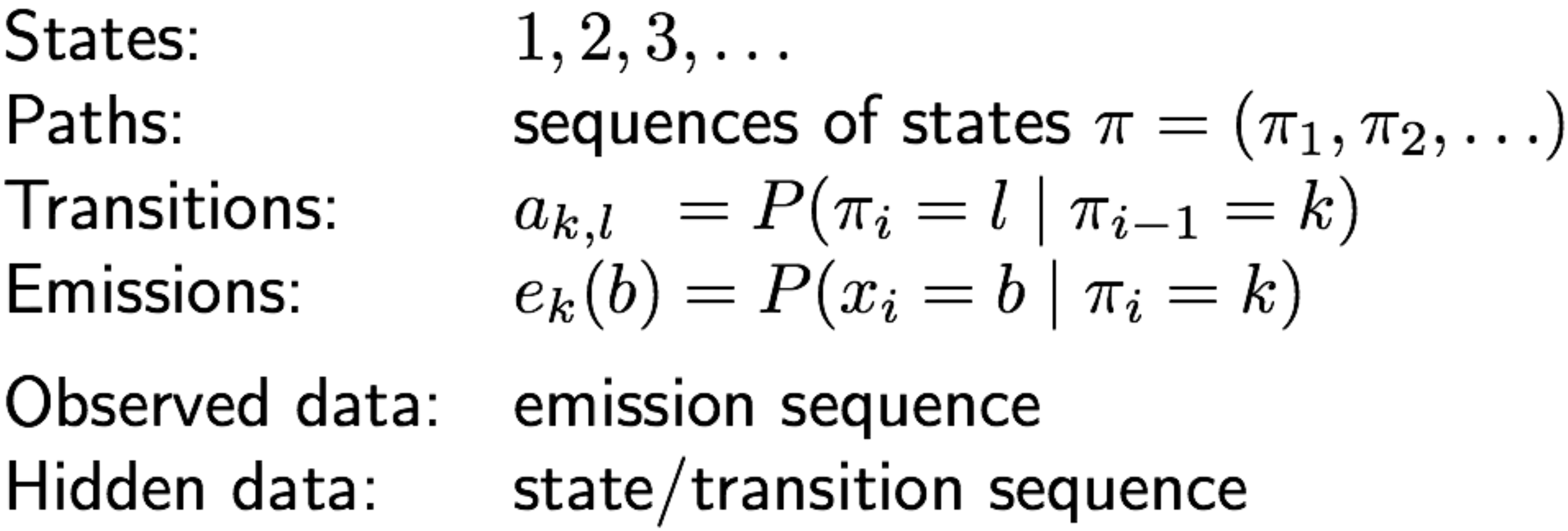
} CpG + model

} CpG – model

Emphasis is “Which (hidden) state?” not “Which model?”

Hidden Markov Models

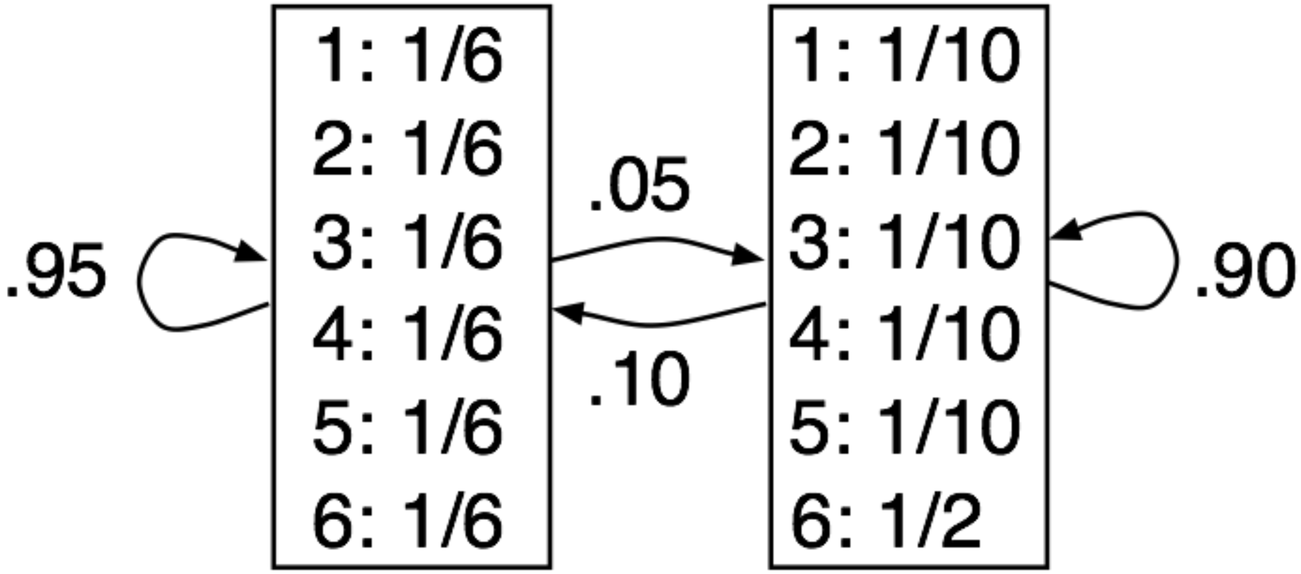
(HMMs; Claude Shannon, 1948)



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

fair die "loaded" die



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

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

occasionally swapped

```
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

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

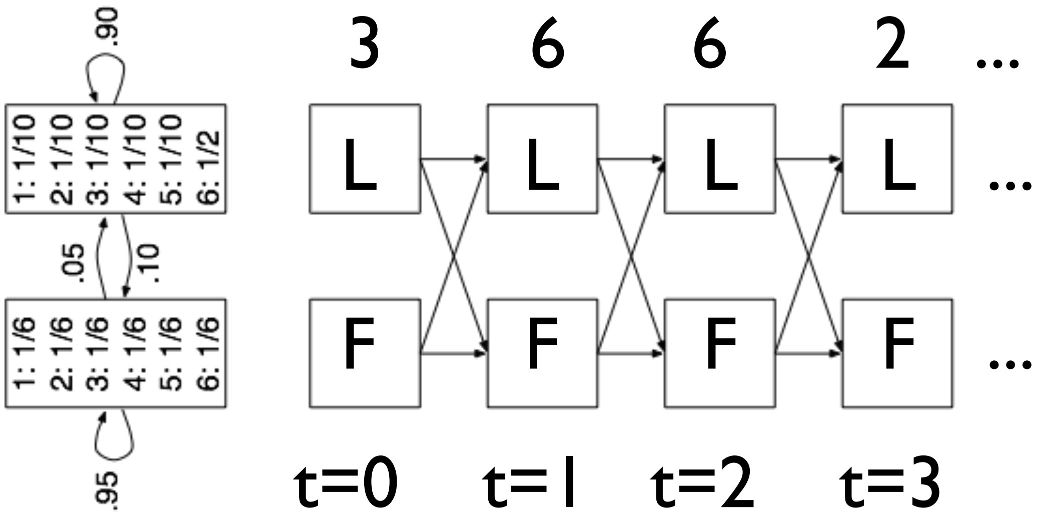
Possibly there are 10^{99} paths of prob 10^{-99}

(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

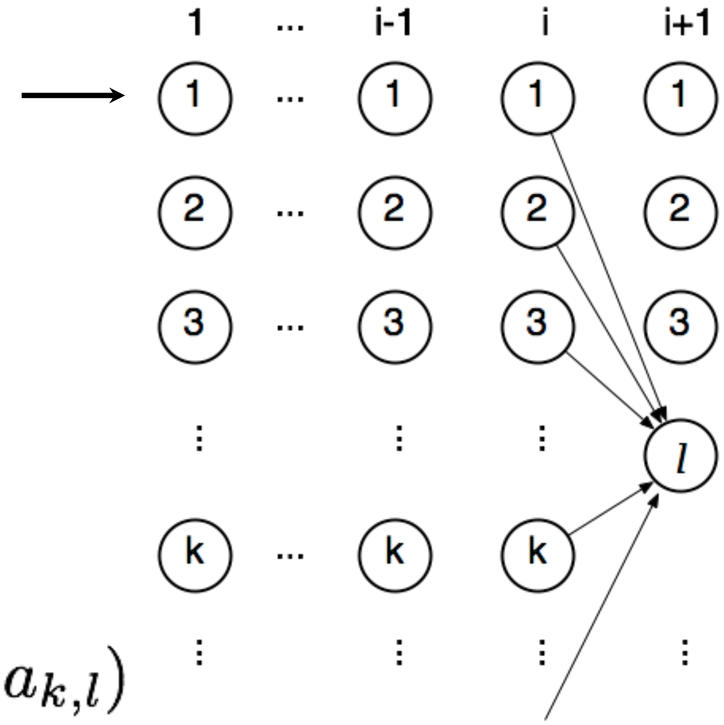
Note exponentially many paths

Viterbi

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

Initialize:

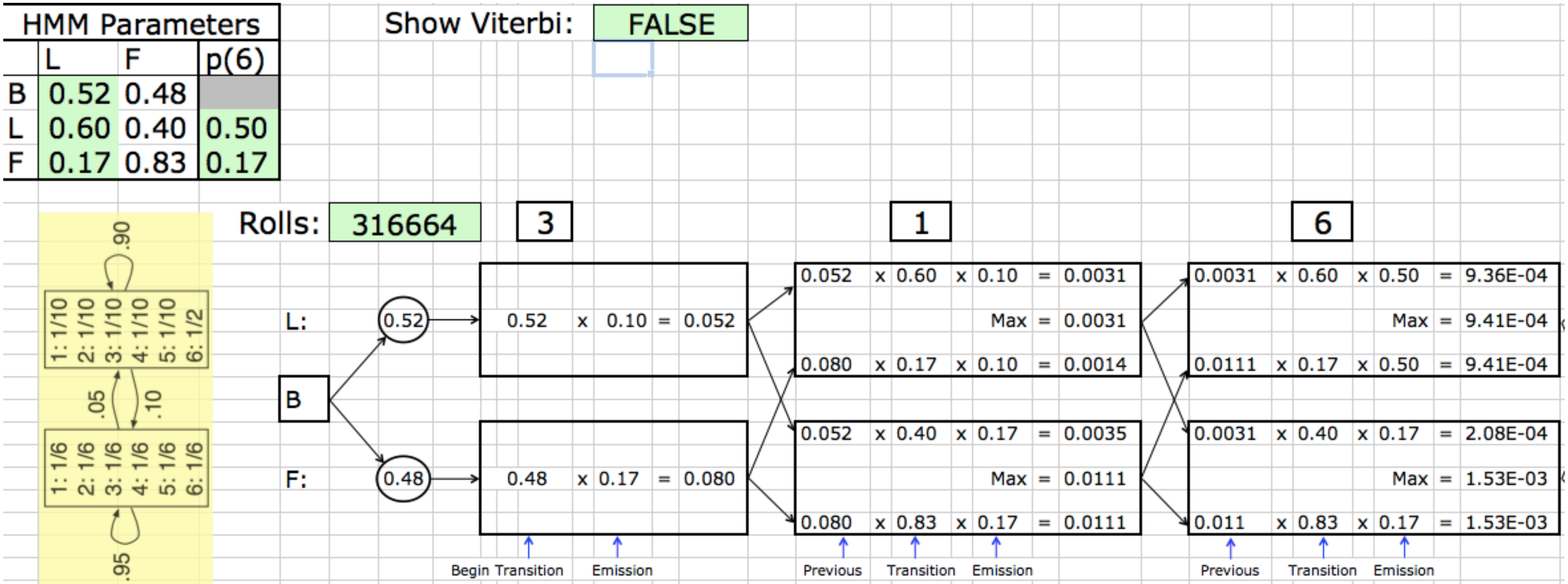
$$v_l(0) = \begin{cases} 1 & \text{if } l = Begin \text{ state} \\ 0 & \text{otherwise} \end{cases}$$



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

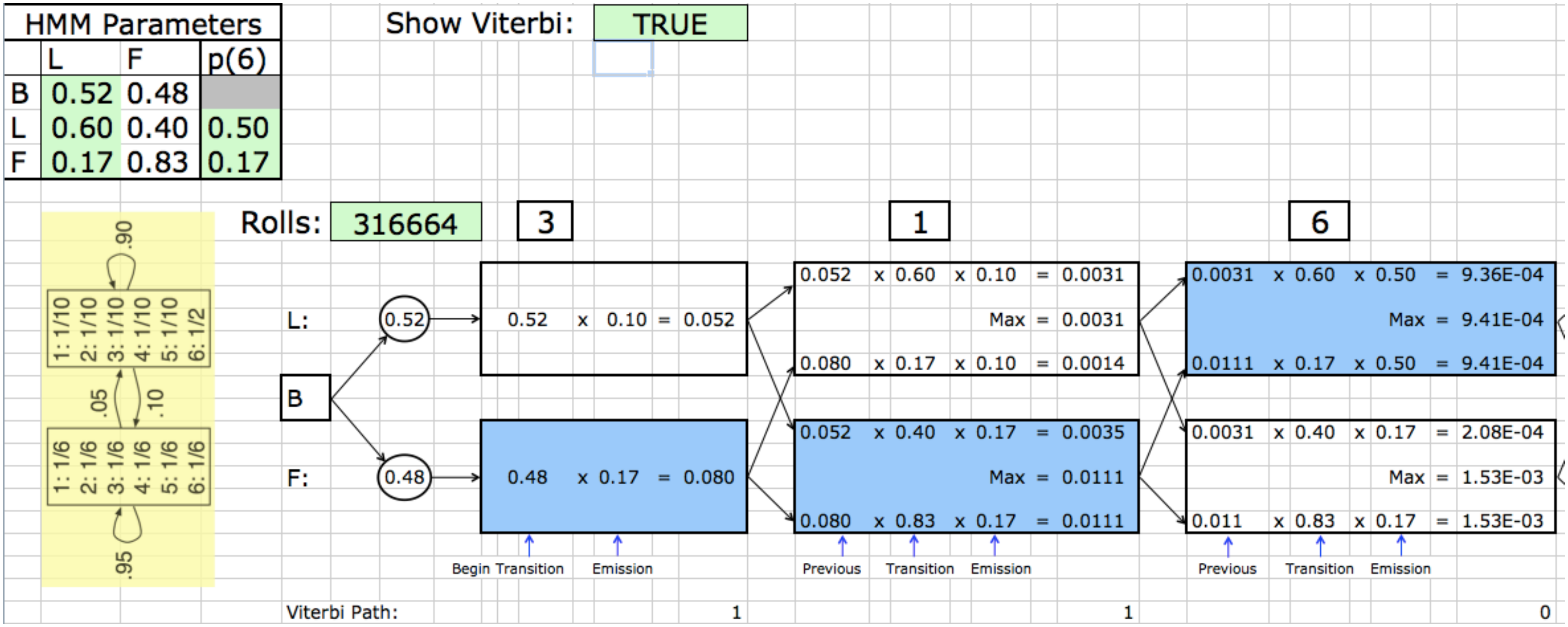
Show Viterbi: FALSE

Rolls: 316664

		3	1	6
L:	0.52	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
B				
F:	0.48	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 → 0.52 x 0.10 = 0.052

B

F: 0.48 → 0.48 x 0.17 = 0.080

Begin Transition Emission

1

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

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

Previous Transition Emission

6

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

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

Previous Transition Emission

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

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

```
Rolls   315116246446644245311321631164152133625144543631656626566666
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLL

Rolls   651166453132651245636664631636663162326455236266666625151631
Die     LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFF

Rolls   222555441666566563564324364131513465146353411126414626253356
Die     FFFFFFFFLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls   366163666466232534413661661163252562462255265252266435353336
Die     LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls   233121625364414432335163243633665562466662632666612355245242
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5

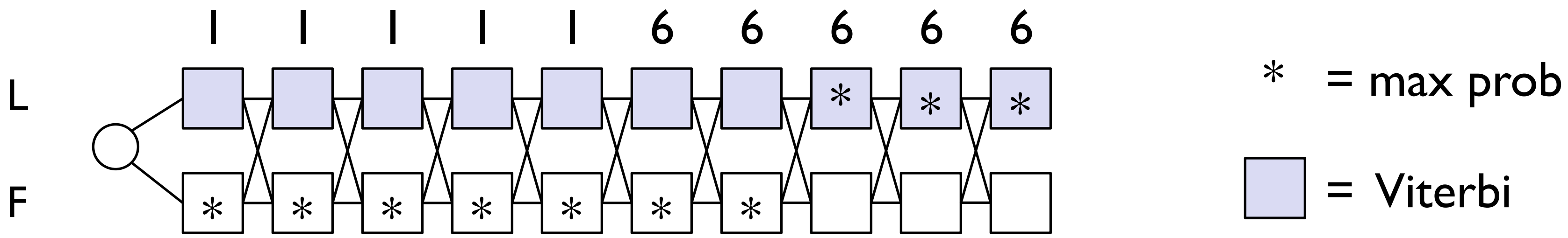
Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

From DEKM

Most probable path ≠ Sequence of most probable states

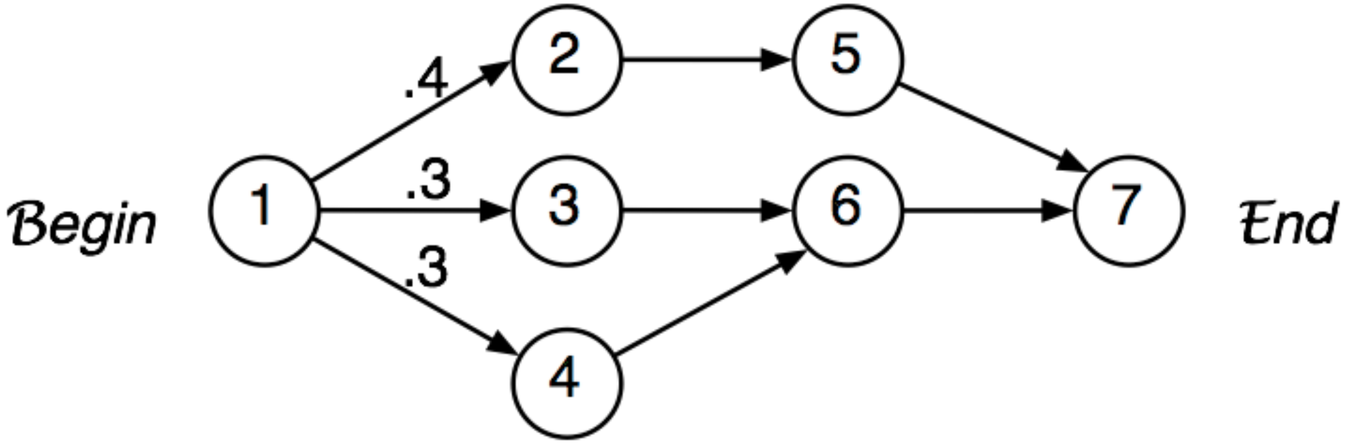
Another example, based on casino dice again

Suppose p(fair↔loaded) transitions are 10^{-99} and roll sequence is 11111…66666; 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.



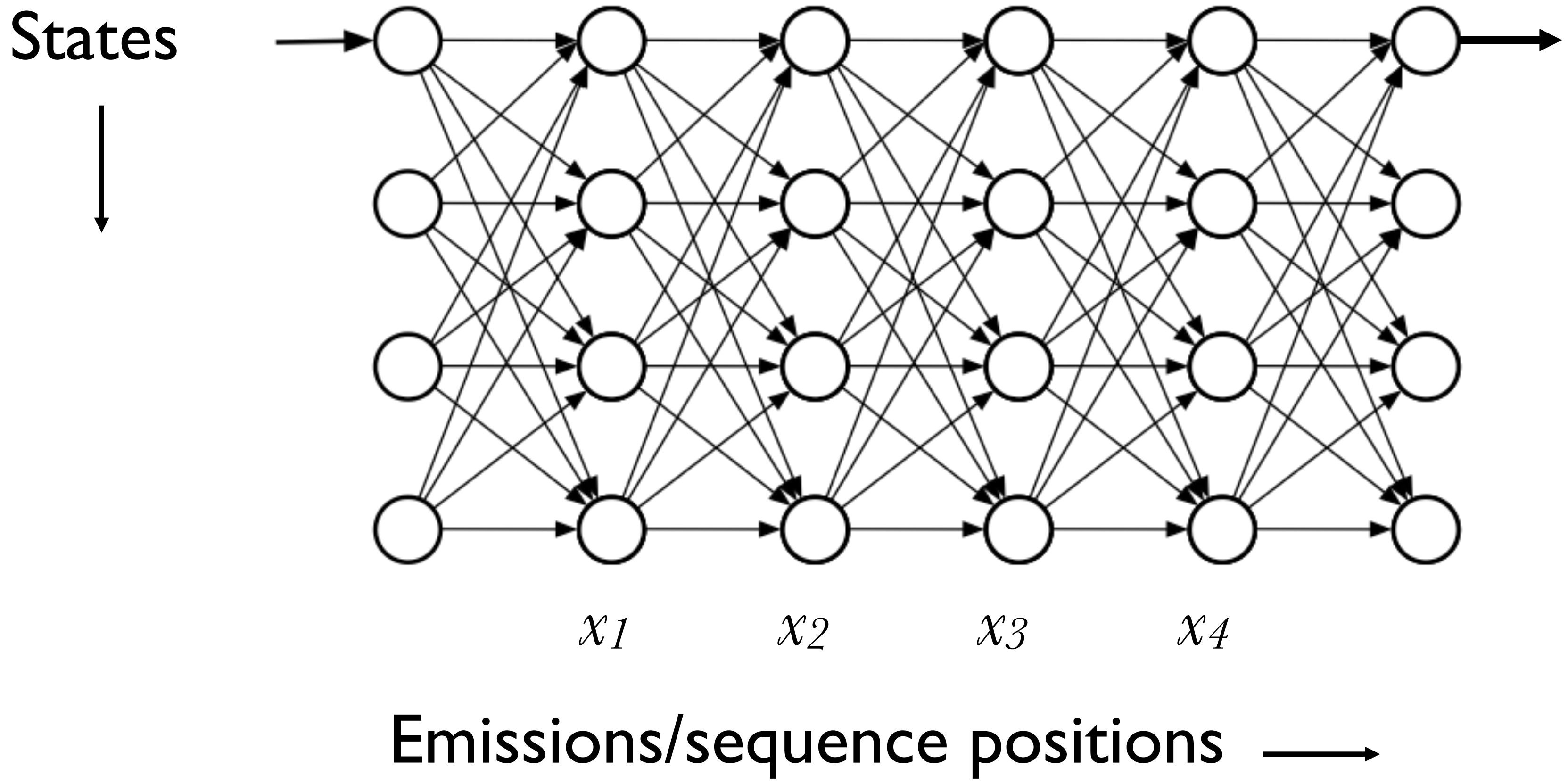
Is Viterbi "best"?

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.)

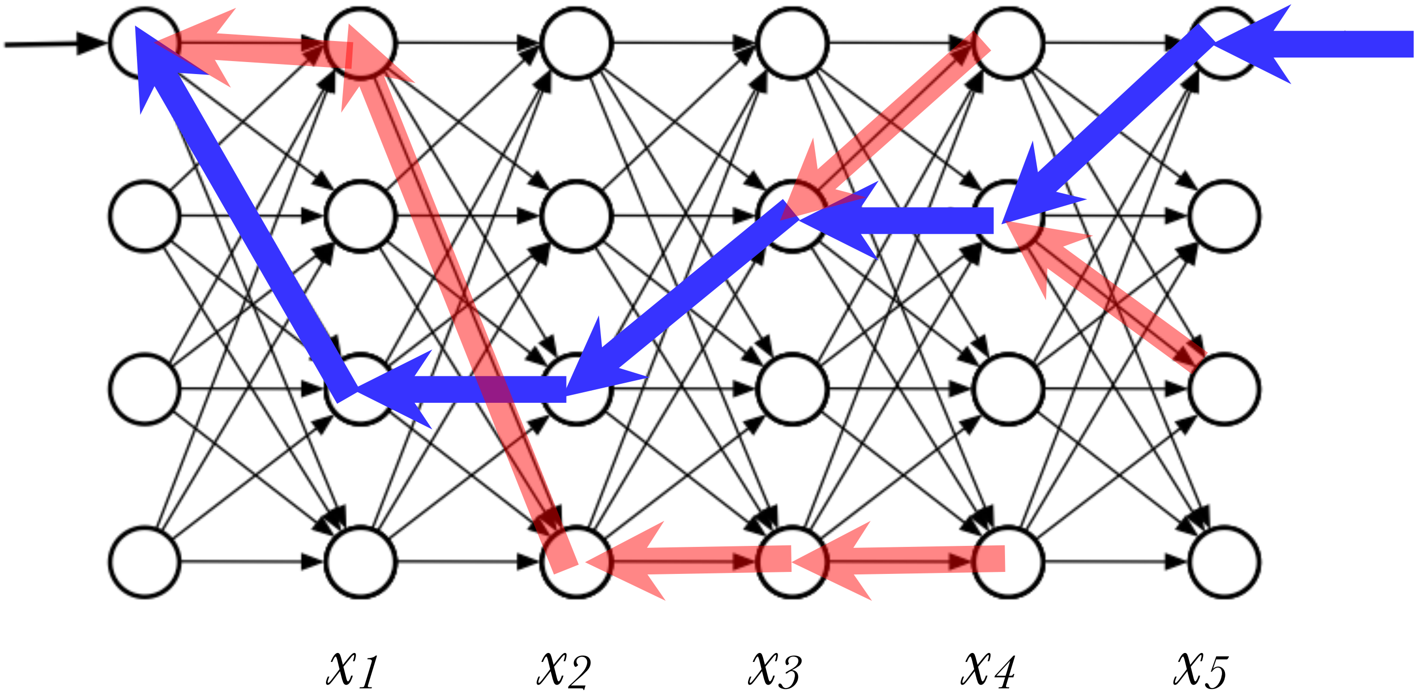
An HMM (unrolled)



States

Emissions/sequence positions

Viterbi: best path to each state

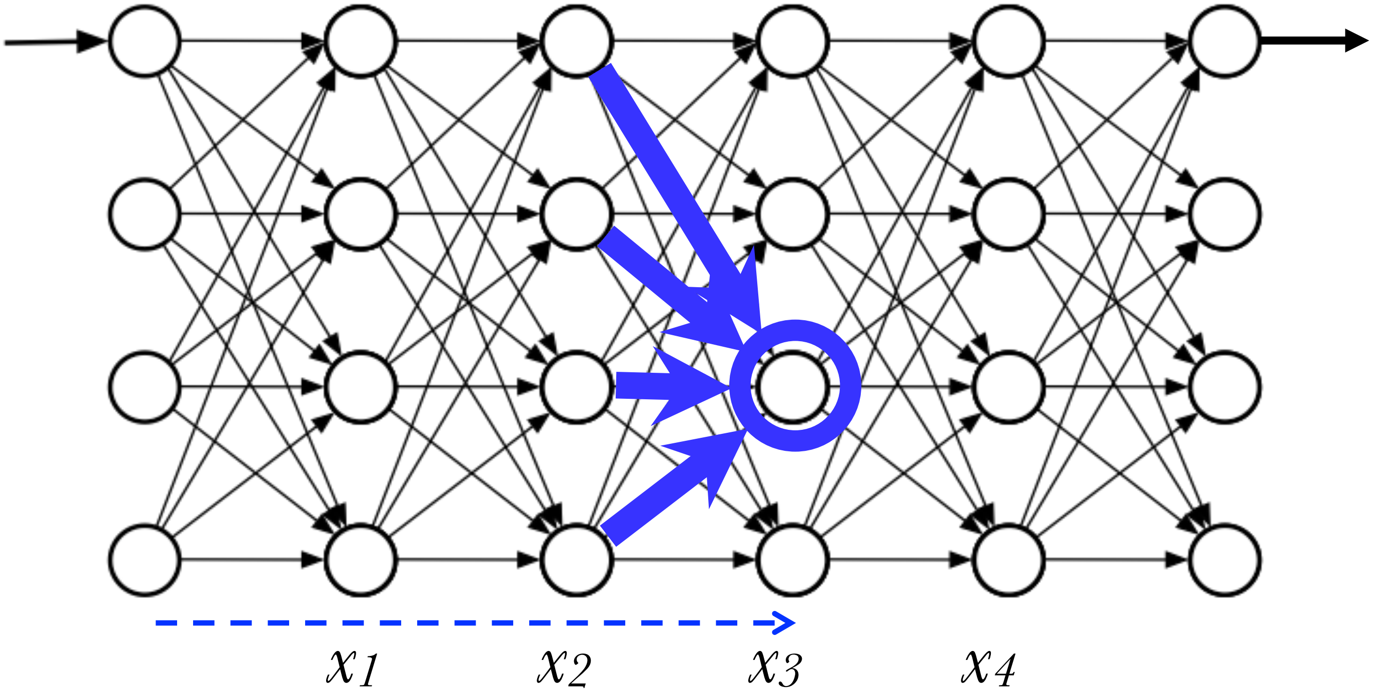


Viterbi *score:* $$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

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



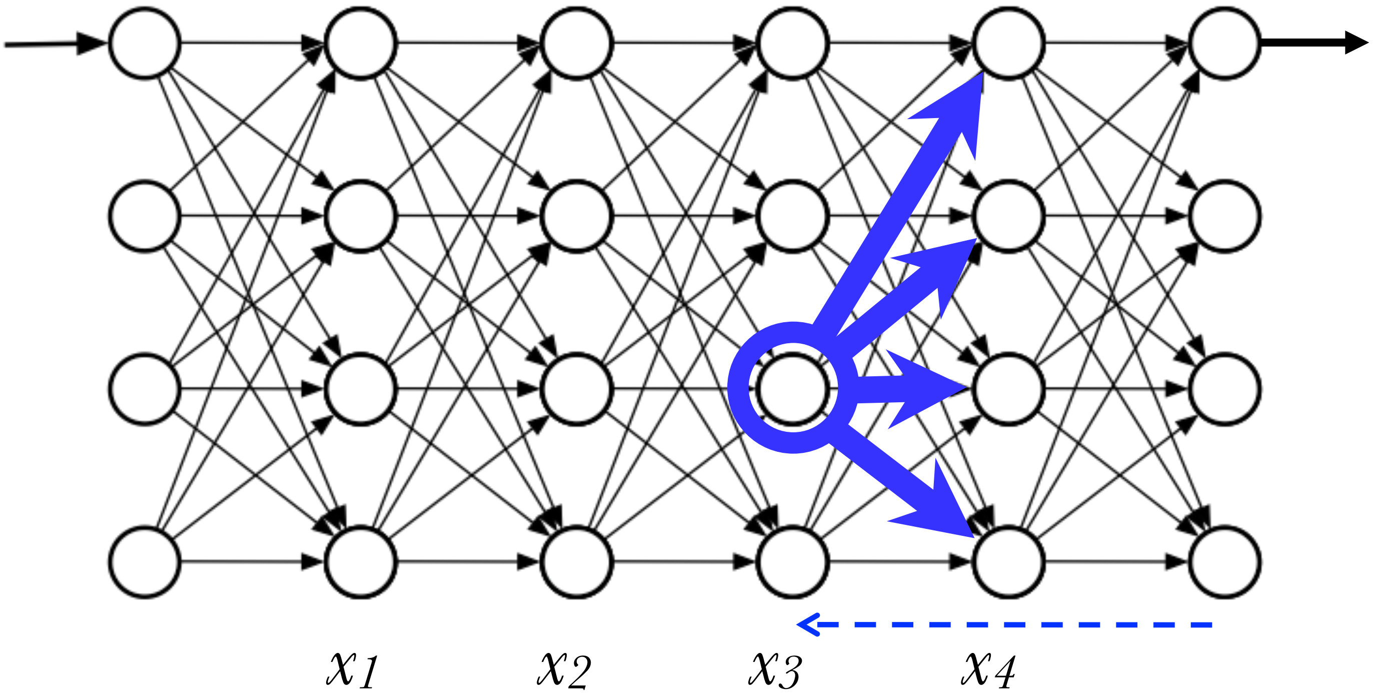
$$f_k(i) \triangleq P(x_1 \ldots x_i,\ \pi_i = k)$$

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

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

The Backward Algorithm

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



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

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

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

In state *k* at step *i* ?

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

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

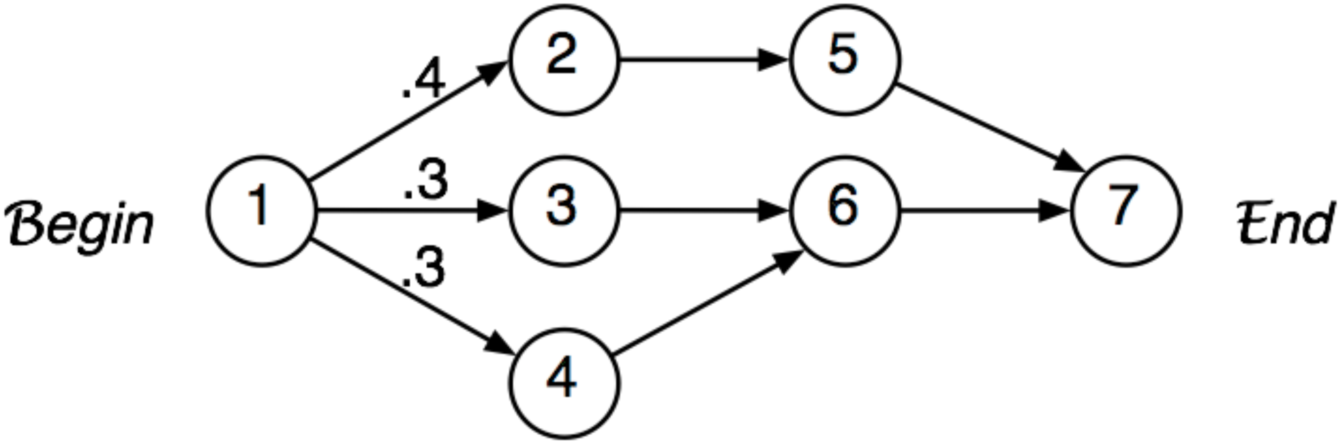
The *posterior* probability of being in state *k* at time *i*

Posterior Decoding, I

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

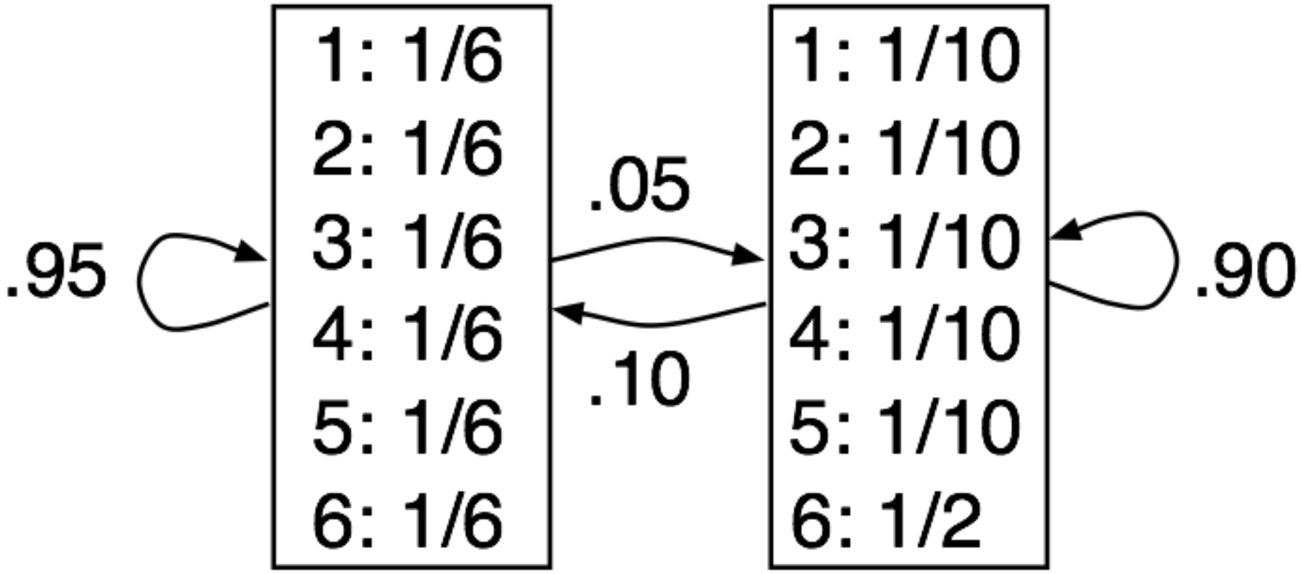
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

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     LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls   233121625364414432335163243633665562466662632666612355245242
Die     FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi FFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

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

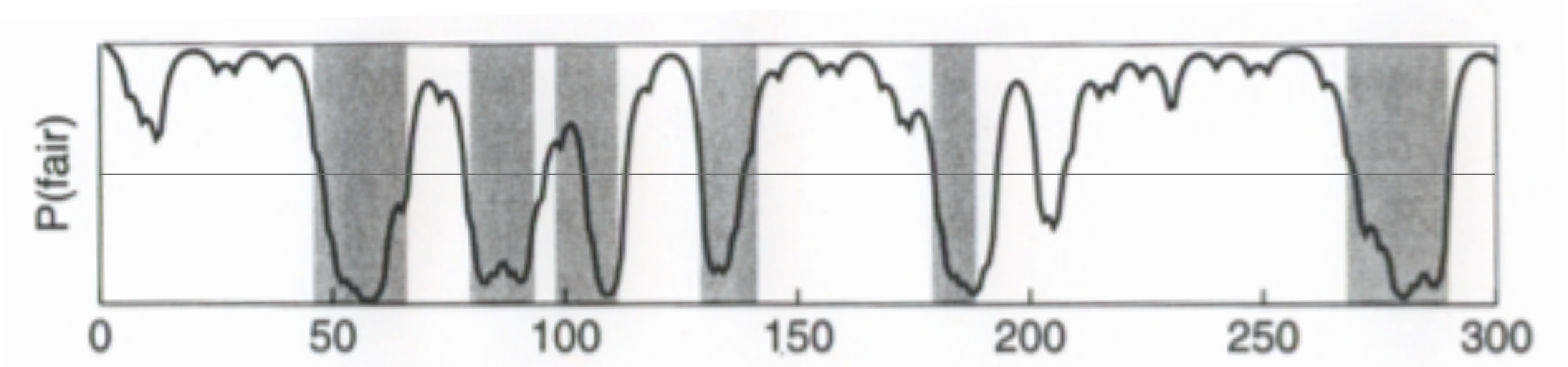


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

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

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

+ 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.)

Baum-Welch Training

AKA "the forward-backward alg"

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

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

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

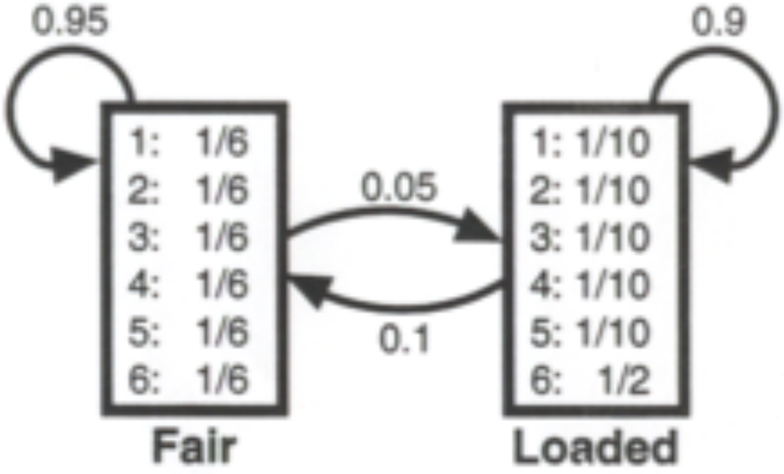
Estimated # of $k \to l$ transitions $\hat{A}_{k,l}$ on *set* of seqs x^j

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

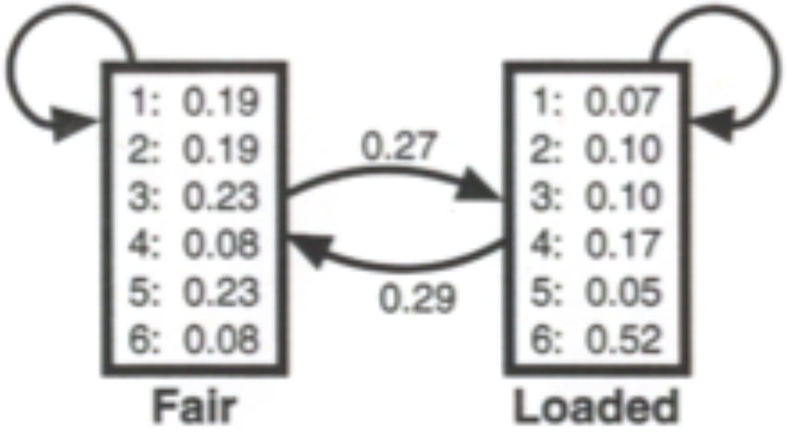
New estimate $\hat{a}_{k,l} \;=\; \dfrac{\hat{A}_{k,l}}{\sum_l \hat{A}_{k,l}}$

Emissions: similar

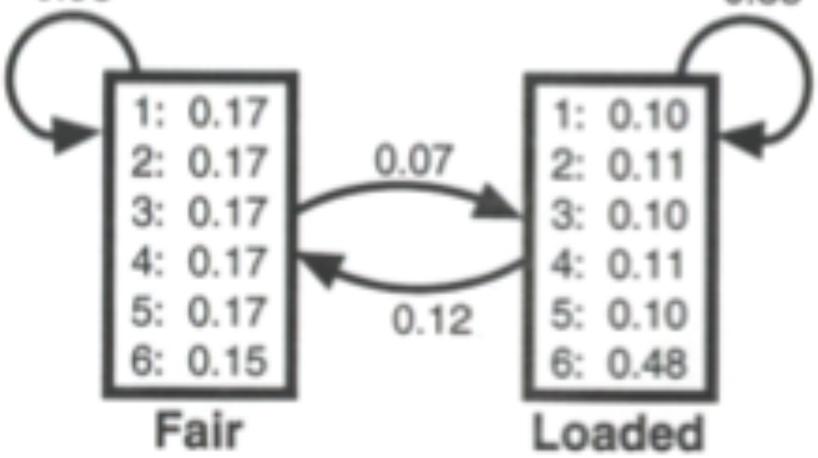
True Model



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,...

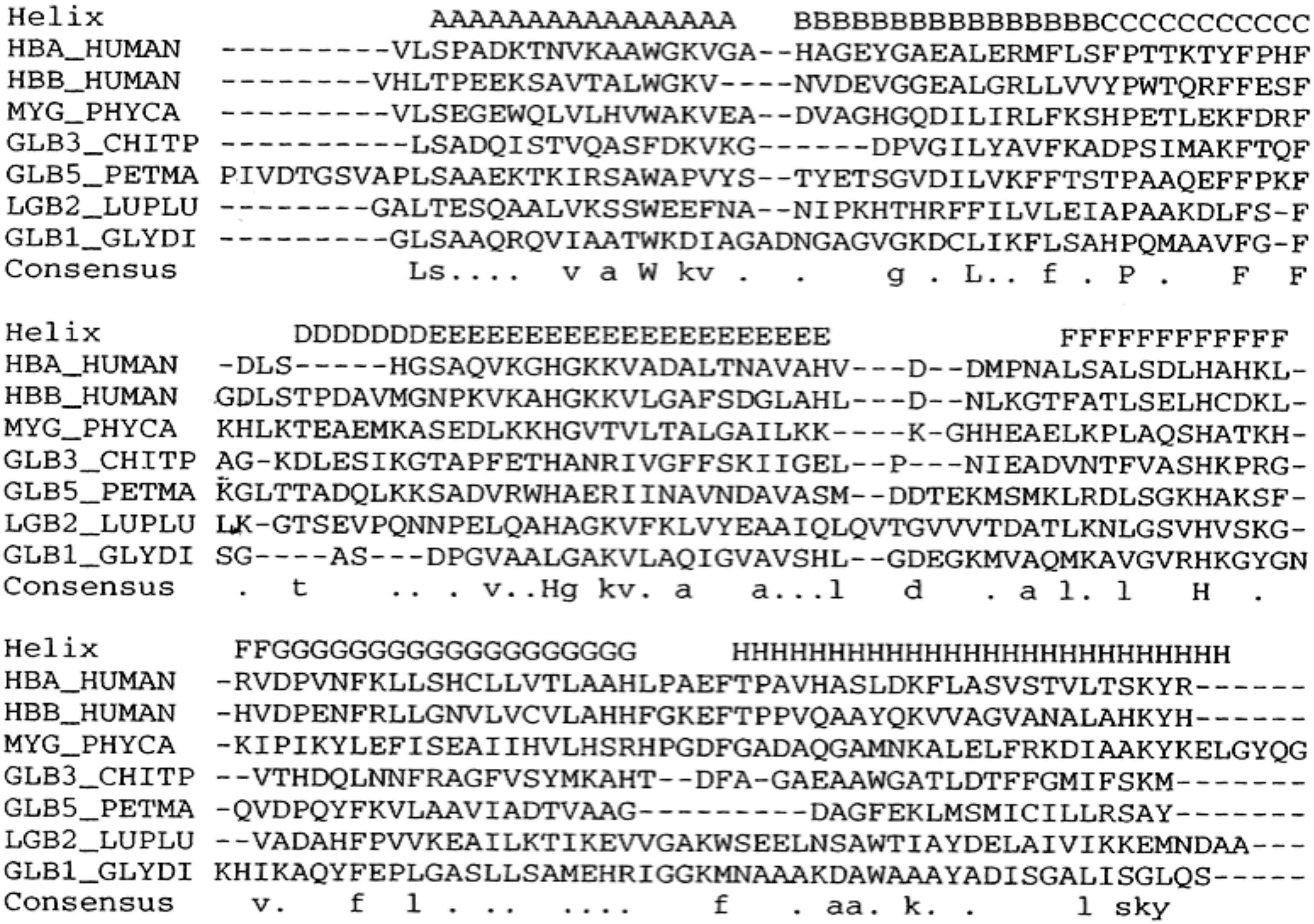
Identifying family very useful: suggests function, etc.

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

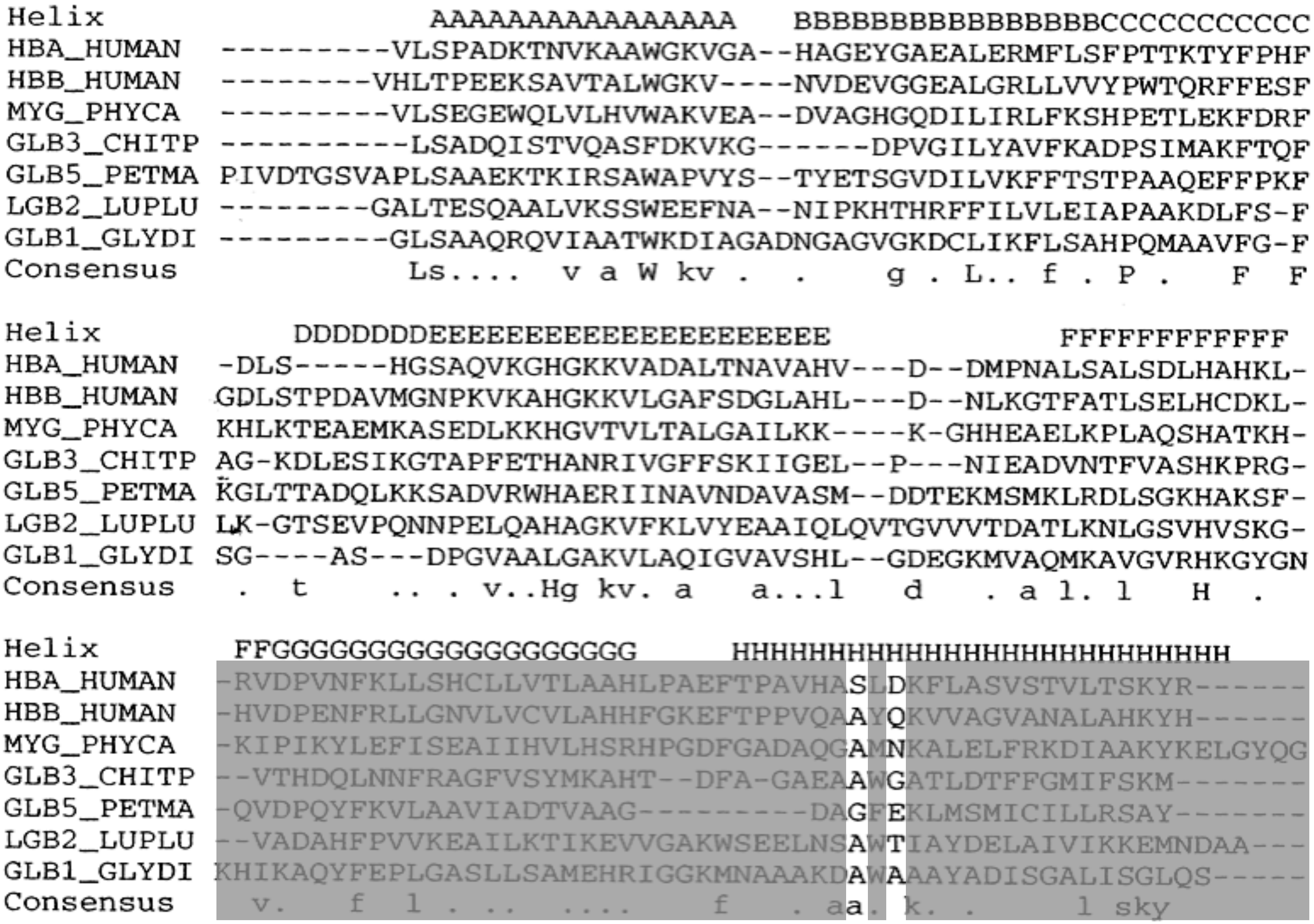


```
Helix                  AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBBCCCCCCCCCCC
HBA_HUMAN   ---------VLSPADKTNVKAAWGKVGA--HAGEYGAEALERMFLSFPTTKTYFPHF
HBB_HUMAN   --------VHLTPEEKSAVTALWGKV----NVDEVGGEALGRLLVVYPWTQRFFESF
MYG_PHYCA   ---------VLSEGEWQLVLHVWAKVEA--DVAGHGQDILIRLFKSHPETLEKFDRF
GLB3_CHITP  ----------LSADQISTVQASFDKVKG------DPVGILYAVFKADPSIMAKFTQF
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?



```
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           DDDDDDDEEEEEEEEEEEEEEEEEEEEEE           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

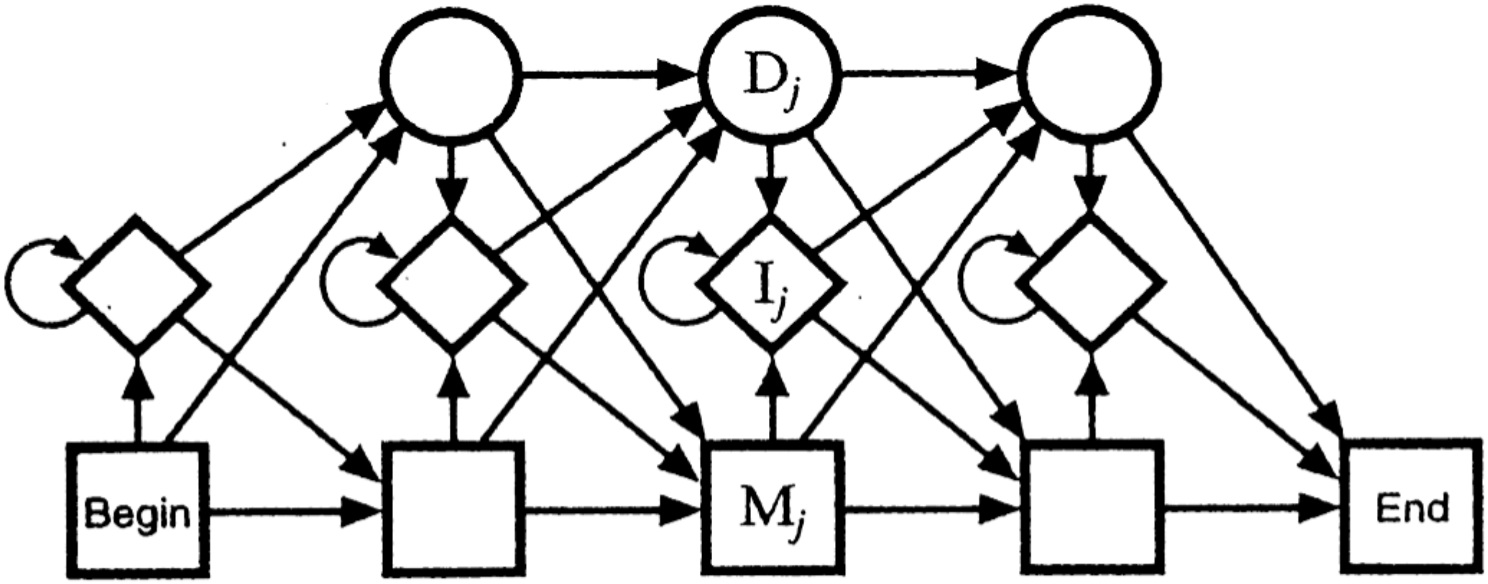


Figure 5.2 *The transition structure of a profile HMM.*

Mj: Match states (20 emission probabilities)

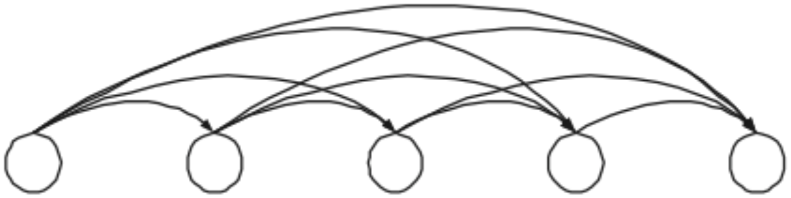
Ij: Insert states (Background emission probabilities)

Dj: Delete states (silent - no emission)

From DEKM

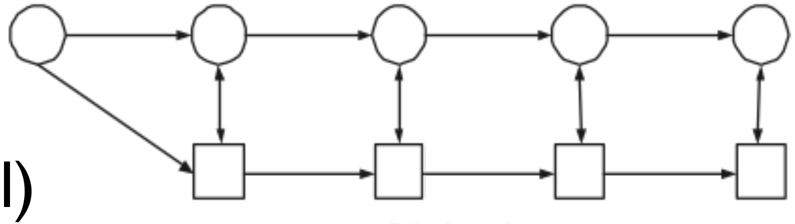
Silent States

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

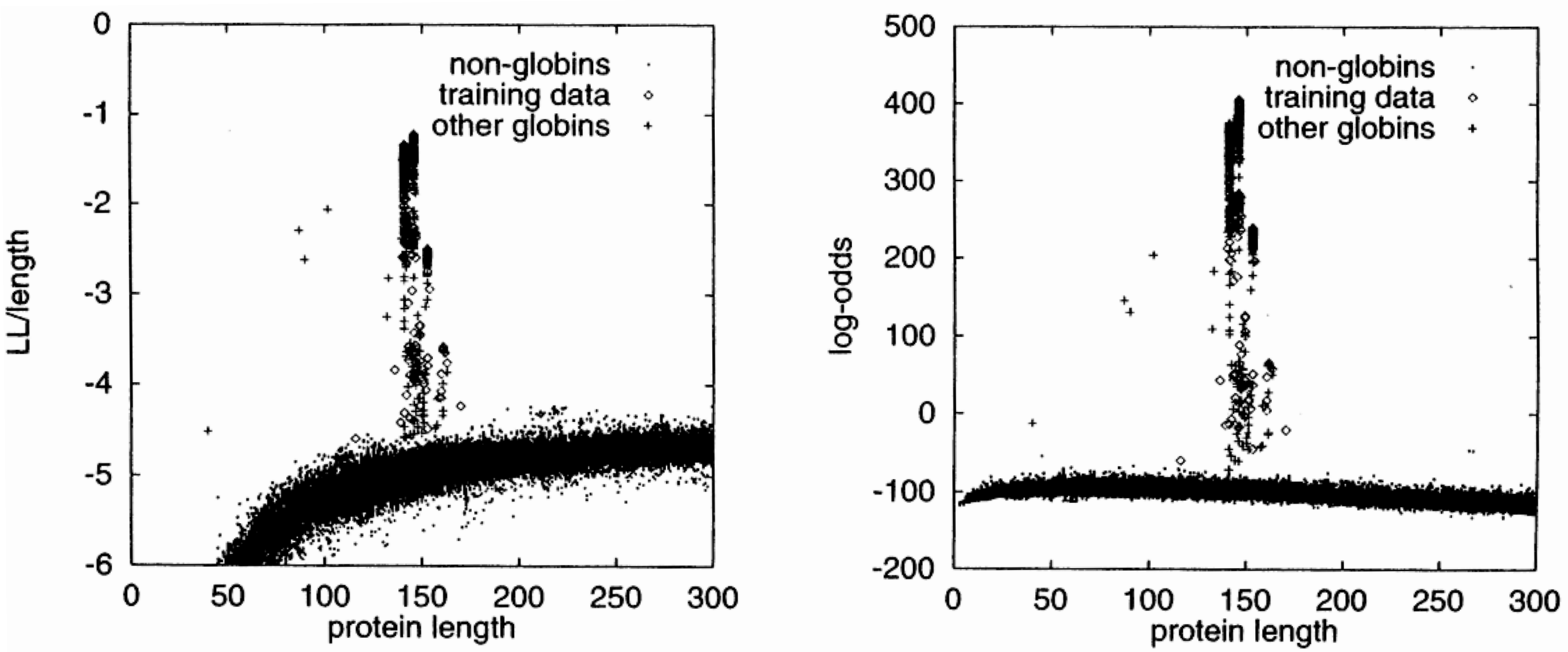


Figure 5.5 *To the left the length-normalized LL score is shown as a function of sequence length. The right plot shows the same for the log-odds score.*

From DEKM

Z-Scores

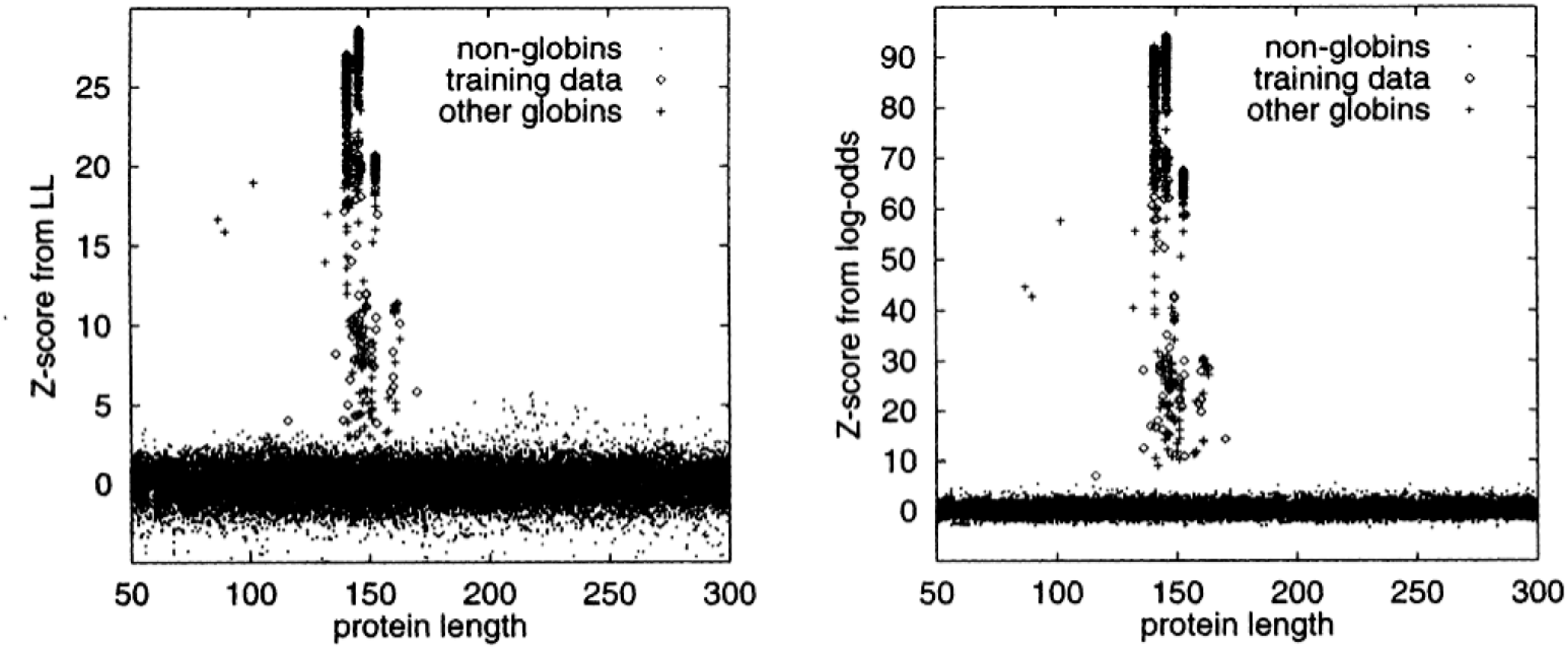


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

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 ≥ 1 domain of ~75% of human proteins)
- Pfam 27.0 (March 2013, 14831 families; ≈ 90%)
- Pfam 29.0 (Dec 2015, 16295 families)

refinements

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.

refinements

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.

refinements

Model structure

Define it as well as you can.

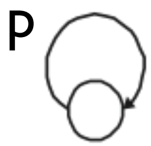
In principle, you can allow all transitions and hope to learn their probabilities from data, but it usually works poorly – too many local optima

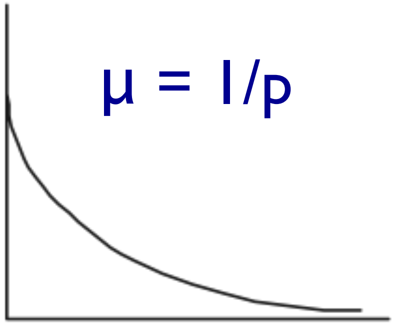
refinements

Duration Modeling

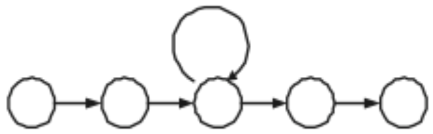
Self-loop duration:

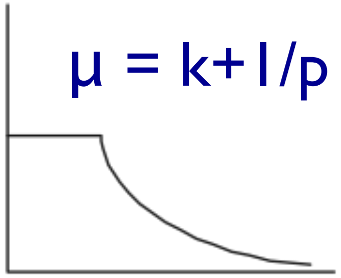
geometric $p^n(1-p)$



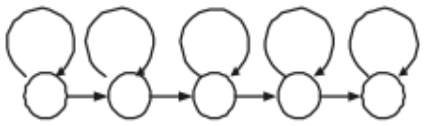


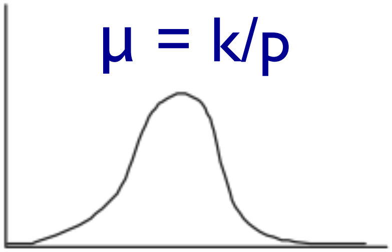
min, then geometric





“negative binomial”





More general: possible (but slower)

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, …)

A very widely used tool for biosequence analysis

- *(and many other applications)*