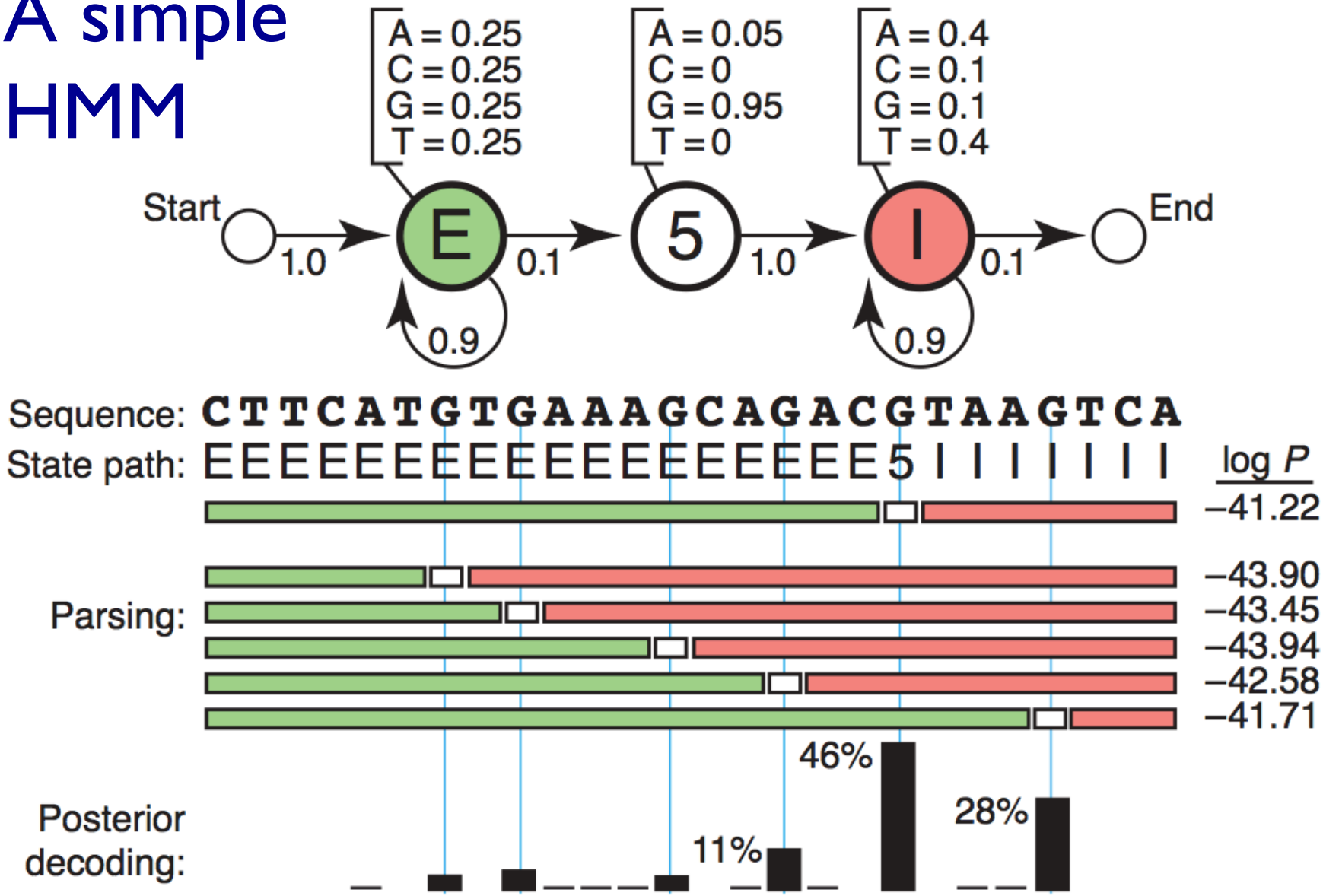
Genome 559

Hidden Markov Models

A simple HMM



Eddy, Nat. Biotech, 2004

Notes

Probability of a given a state path and output sequence is just product of emission/transition probabilities

If state path is *hidden*, you need to consider *all* possible paths (usually exponentially many). E.g., find:

- Total probability of a given seq (sum over all paths)
- Probability of the most probable single path

"Dynamic programming" algorithms similar to seq alignment can solve these problems relatively quickly

Viterbi: Most probable path

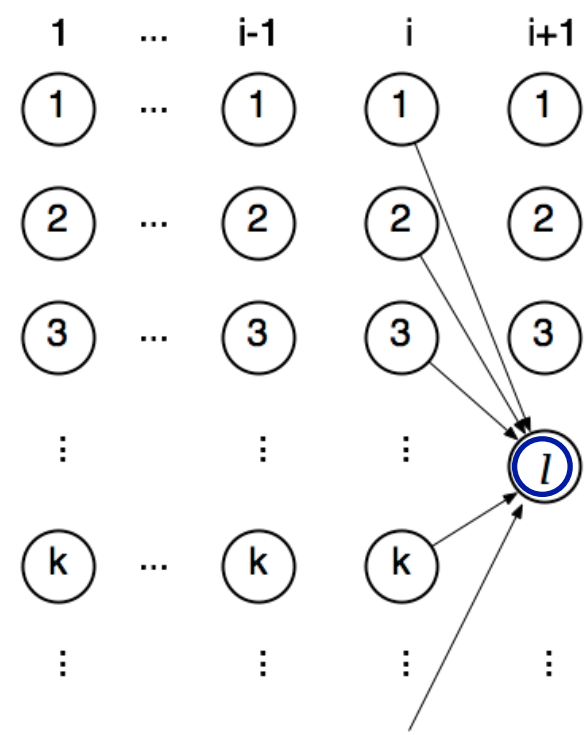
C	A	G	A	T
.25	$.25^2*.9$	$.25^3*.9^2$	$.25^4*.9^3$	$.25^5*.9^4$
0	$.25*.1*.05$	$.25^2*.9*.1*.95$	$.25^3*.9^2*.1*.05$	0
0	0	$.25*.1*.05*.1$	$.25^2*.9*.1*.95*.9*.4$ $.25*.1*.05*.1*.9*.4$	…

The Viterbi Algorithm

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

Initialize:

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



General case:

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

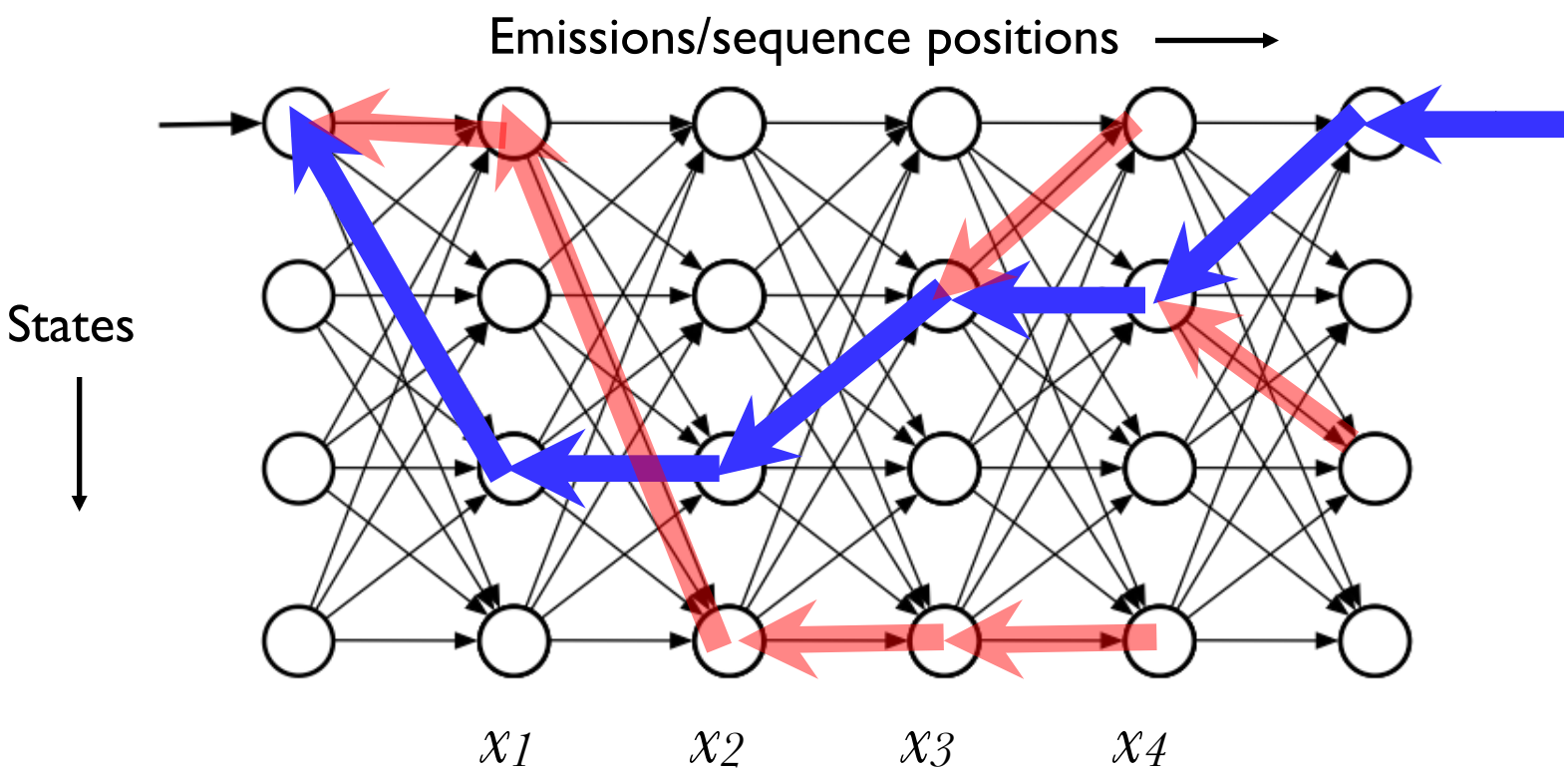
Viterbi Traceback

Above finds *probability* of best path

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

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

Viterbi Traceback



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

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

An Application: Protein Alignments

```
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       FFGGGGGGGGGGGGGGGGGG     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
```

WMM might be a good model of the marked blocks, but what about the gaps??

Profile Hmm Structure

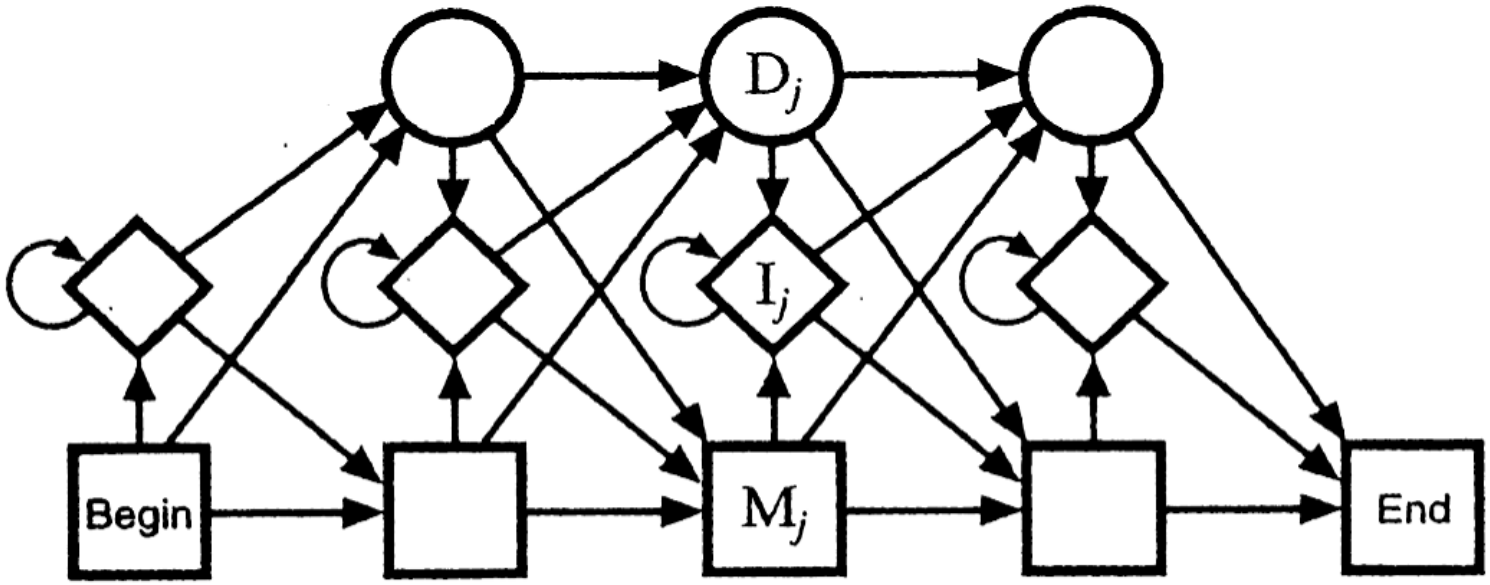


Figure 5.2 *The transition structure of a profile HMM.*

M_j: Match states (20 emission probabilities)

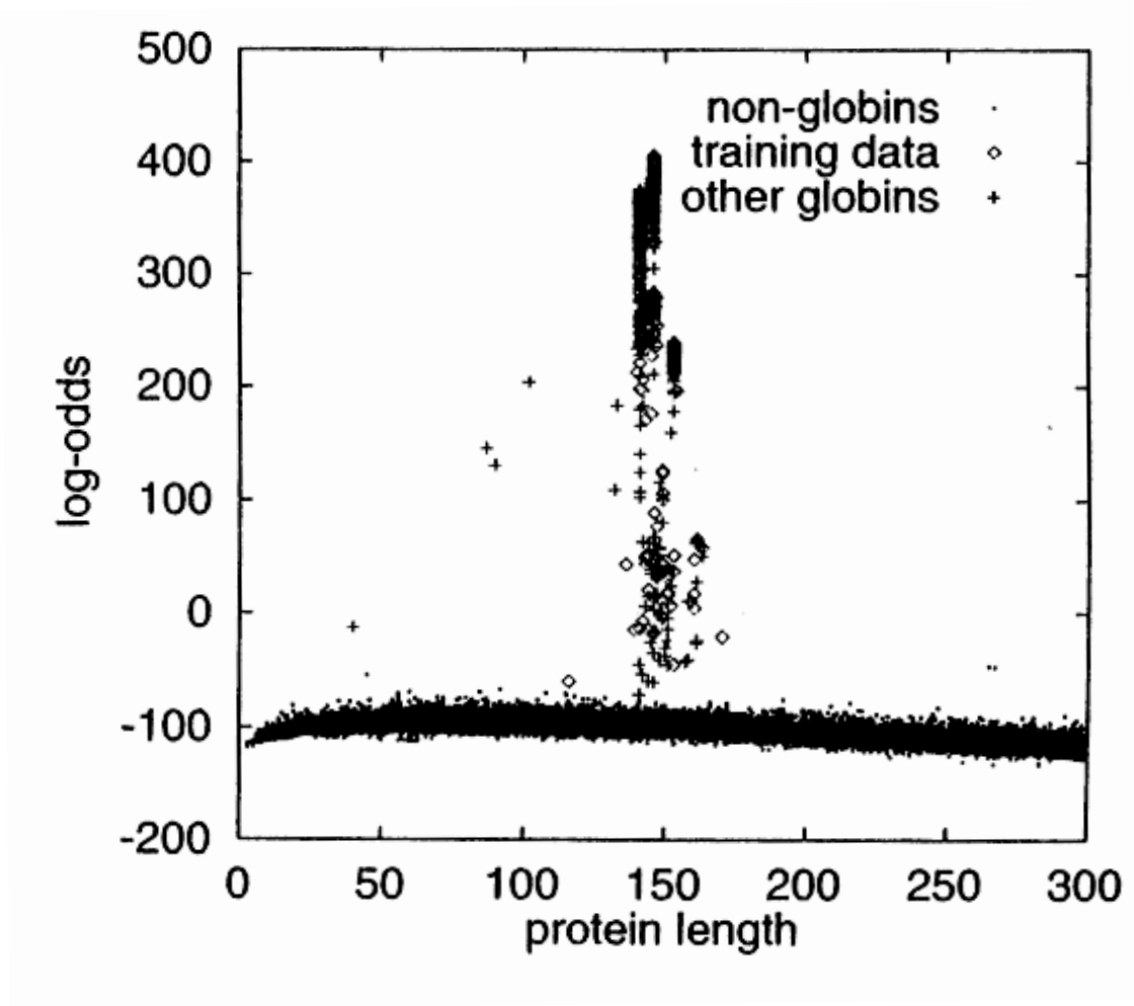
I_j: Insert states (Background emission probabilities)

D_j: Delete states (silent - no emission)

From DEKM

Odds Scores

Length-normalized log odds scores, globin model



From DEKM

HMMs in Action: Pfam

http://pfam.sanger.ac.uk/

Hand-curated "seed" multiple alignments (domains, not full-length proteins)

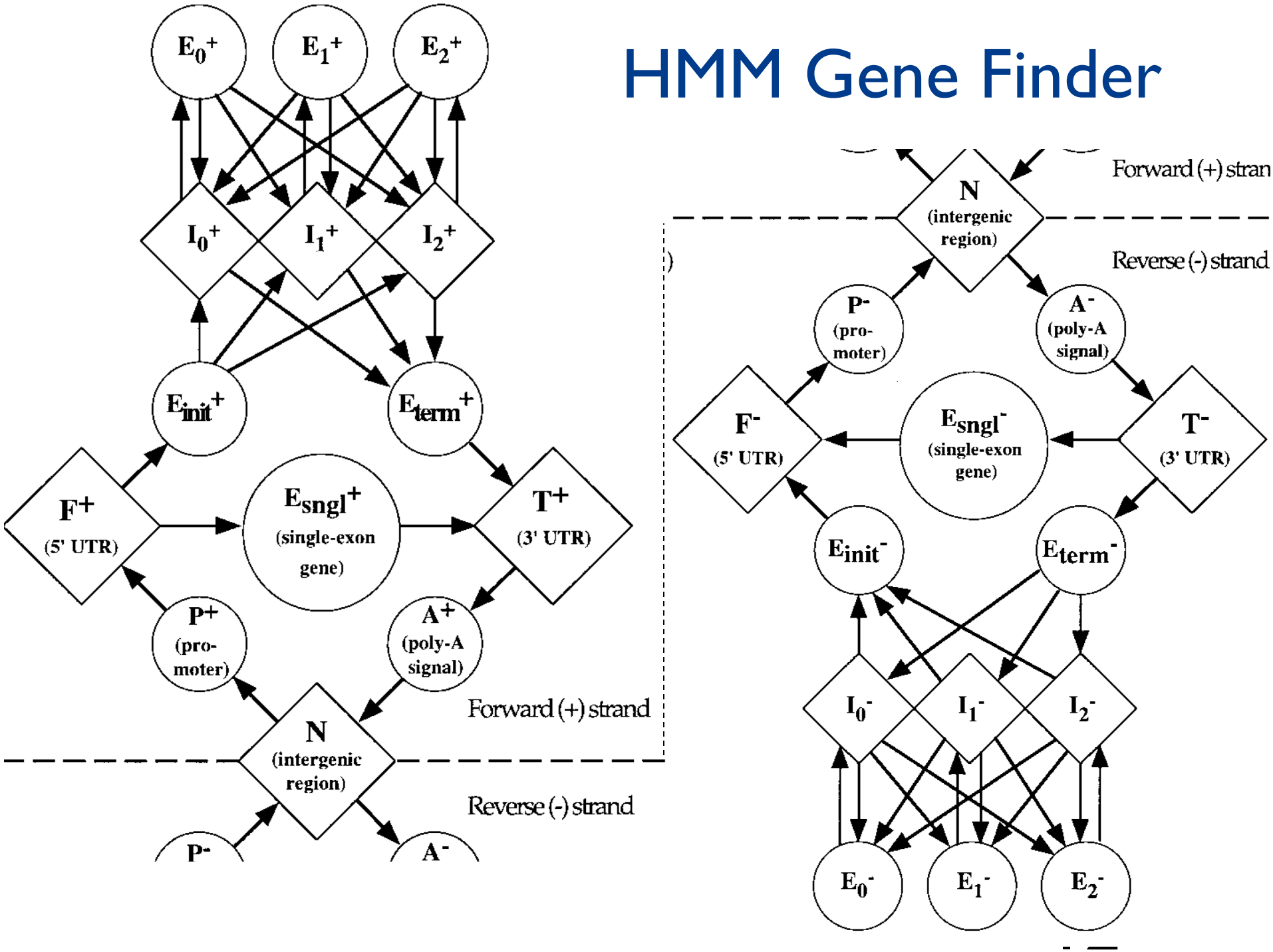
Train profile HMM from seed alignment

Hand-chosen score threshold(s)

Automatic classification/alignment of all other protein sequences

11912 families in Pfam 24.0, 10/2009 (covers ~75% of proteins)

HMM Gene Finder



HMM Summary

Search

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

Model building

- Typically fix architecture (e.g. profile HMM), then
- Learn parameters – the Baum-Welch Algorithm

Scoring

- Odds ratio to background

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

A very widely used tool for biosequence analysis

Many variants on all of these points

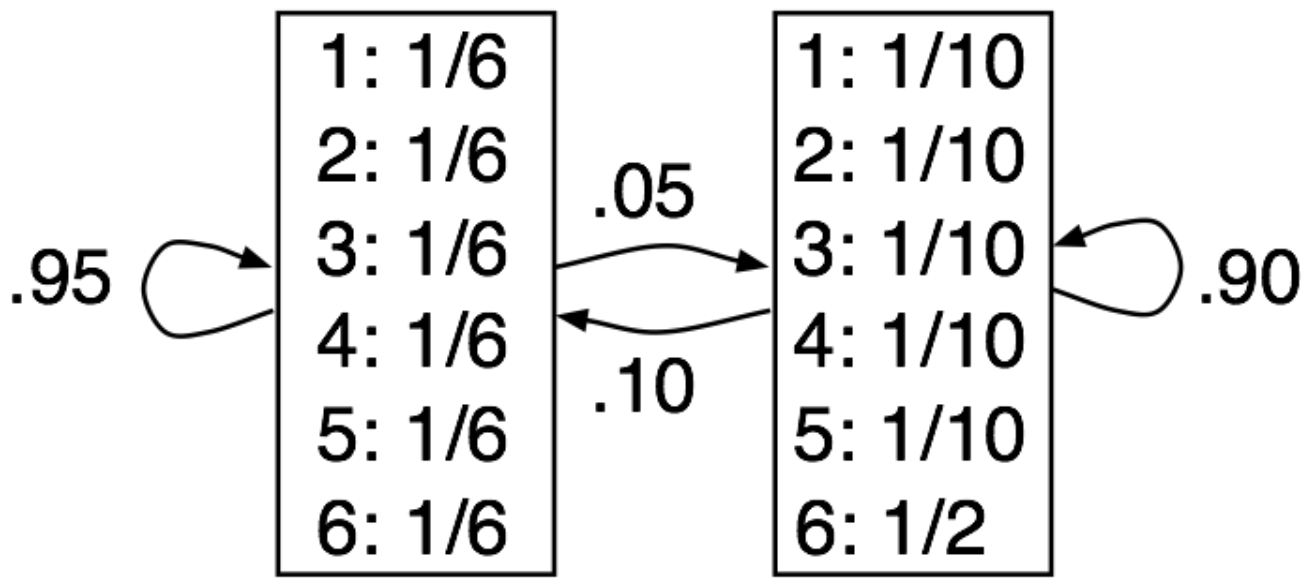
Hidden Markov Models

(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



```
Rolls    3151162464466442453113216311641521336251445436316566266666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLL

Rolls    6511664531326512456366646316366631623264552362666666251516 31
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    2225554416665665635643243641315134651463534111264146262533 56
Die      FFFFFFFFLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    3661636664662325344136616611632525624622552652522664353533 36
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    2331216253644144323351632436336655624666626326666123552452 42
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

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

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

The Viterbi Algorithm: The most probable path

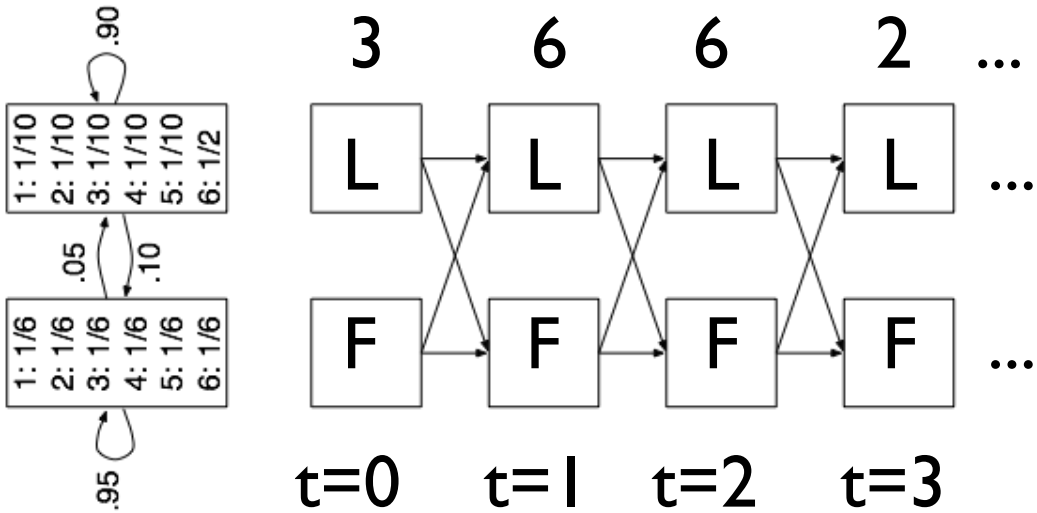
Viterbi finds: $\pi^* = \arg\max_{\pi} P(x, \pi)$

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

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

Key problem: exponentially many paths π

Unrolling an HMM



Conceptually, sometimes convenient

Note exponentially many paths

```
Rolls    3151162464466442453113216311641521336251445436316566266666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLL

Rolls    6511664531326512456366646316366631623264552362666666251516 31
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    2225554416665665635643243641315134651463534111264146262533 56
Die      FFFFFFFFLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    3661636664662325344136616611632525624622552652522664353533 36
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    2331216253644144323351632436336655624666626326666123552452 42
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Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
```

Figure 3.5

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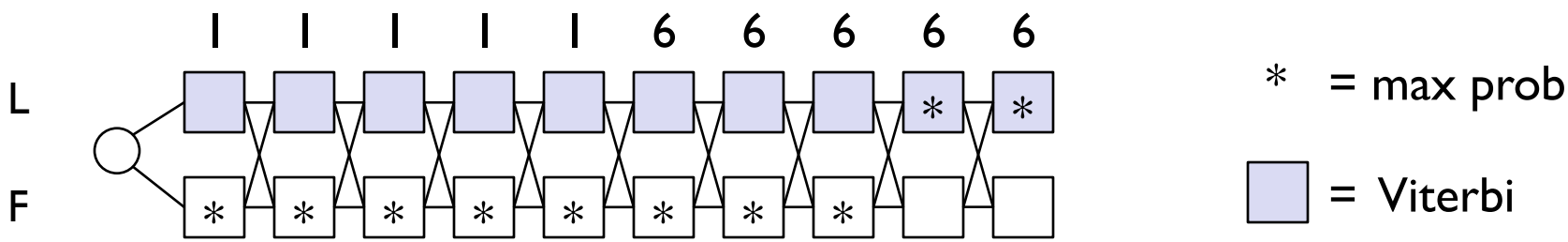
From DEKM

Most probable path ≠ Sequence of most probable states

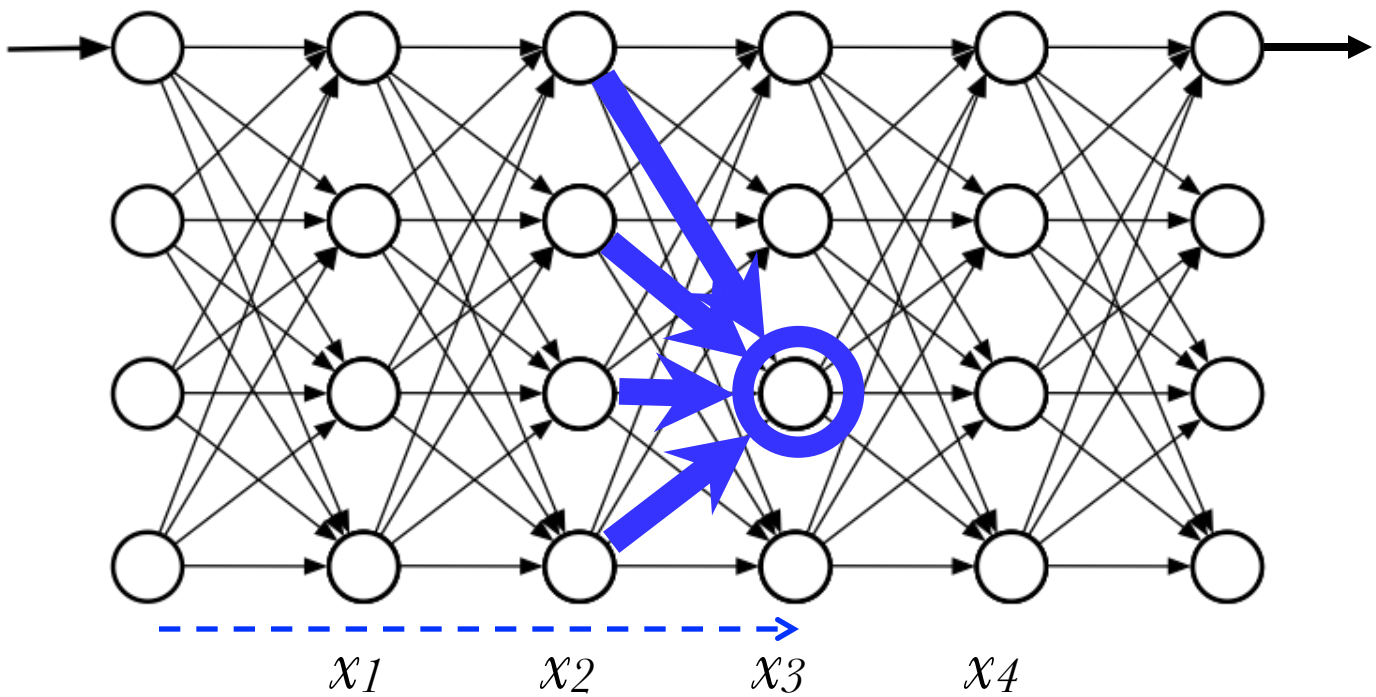
Another example, based on casino dice again

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.



The Forward Algorithm

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



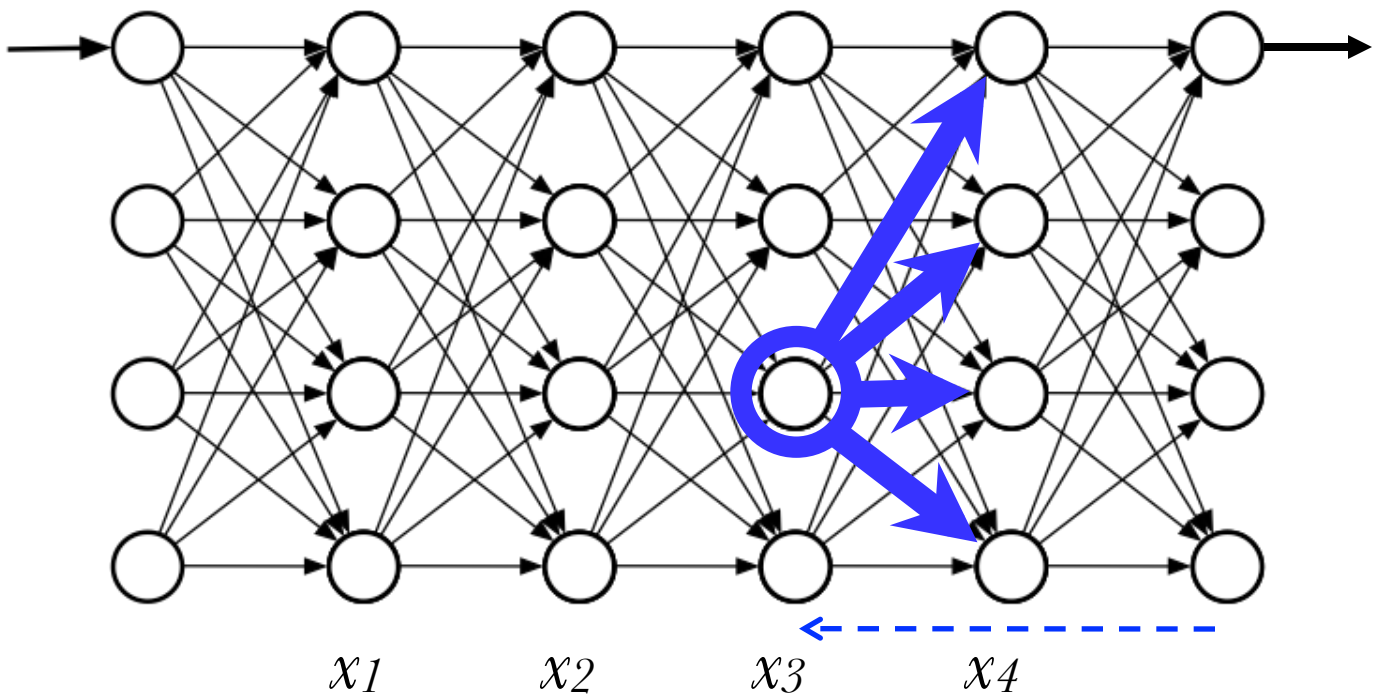
$$f_k(i) \triangleq P(x_1 \ldots x_i,\ \pi_i = k)$$

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

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

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* ?

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

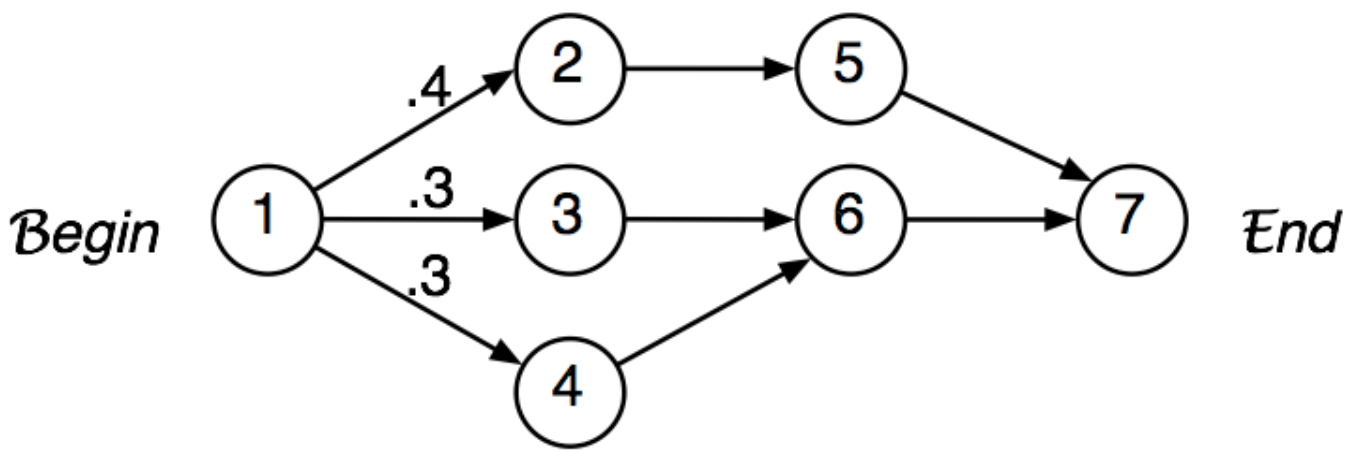
$$
P(\pi_i = k \mid x) \;=\; \frac{P(x, \pi_i = k)}{P(x)} \;=\; \frac{f_k(i) \cdot b_k(i)}{P(x)}
$$

Posterior Decoding, I

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

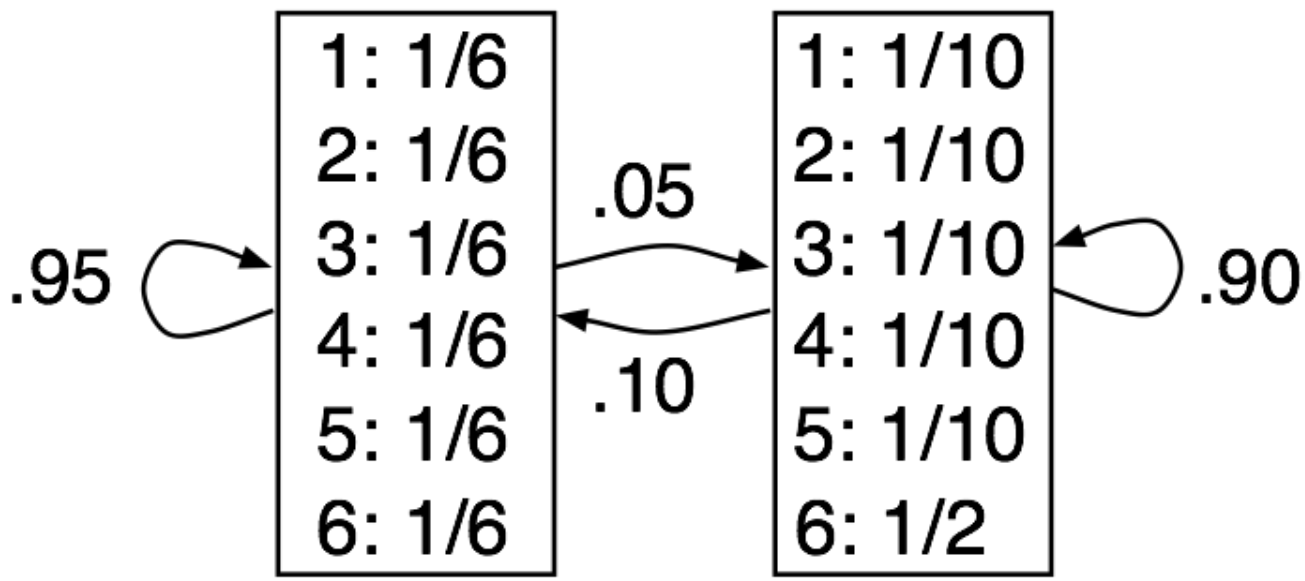
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

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



The Occasionally Dishonest Casino

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



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From DEKM

Posterior Decoding

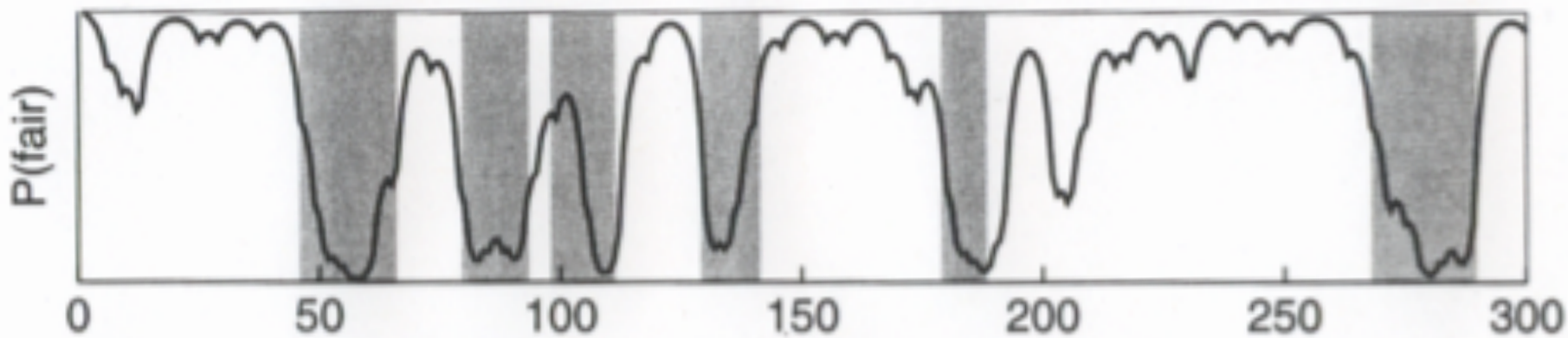


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

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

	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

Z-Scores

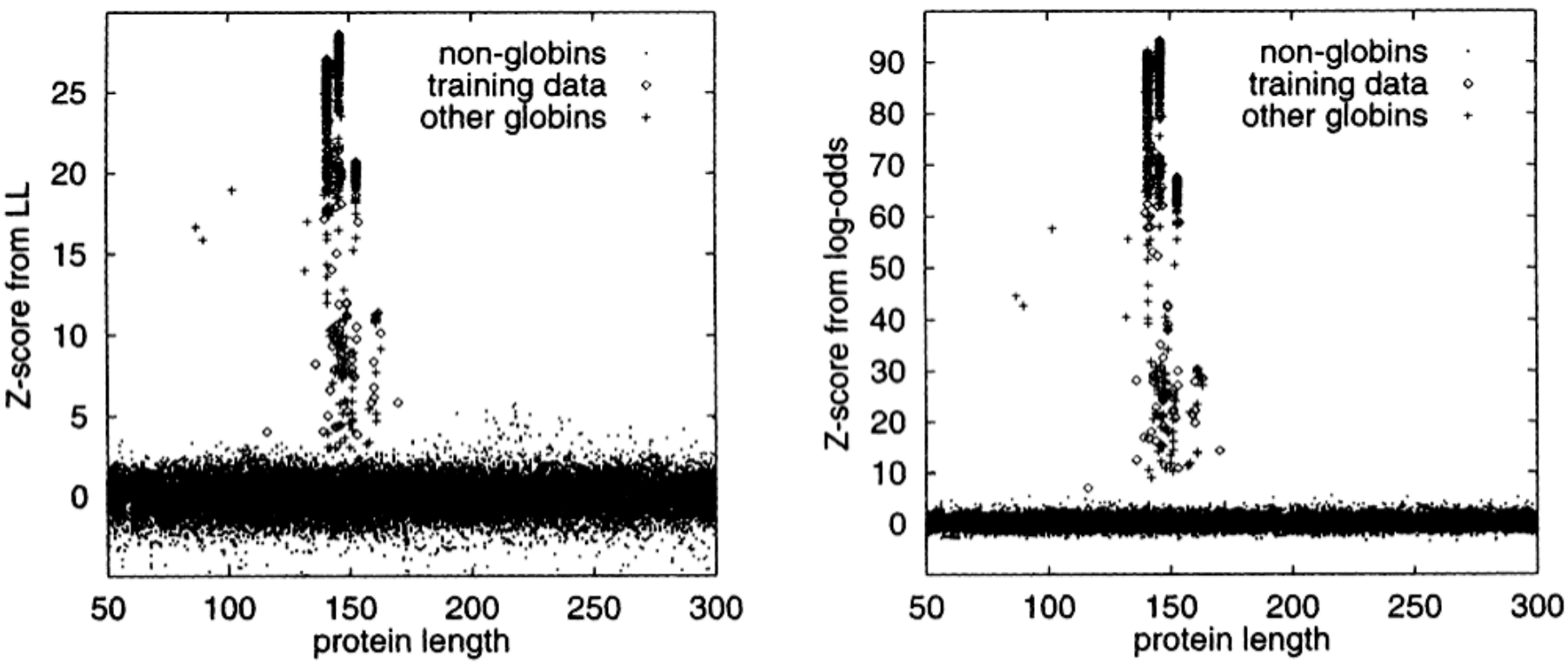
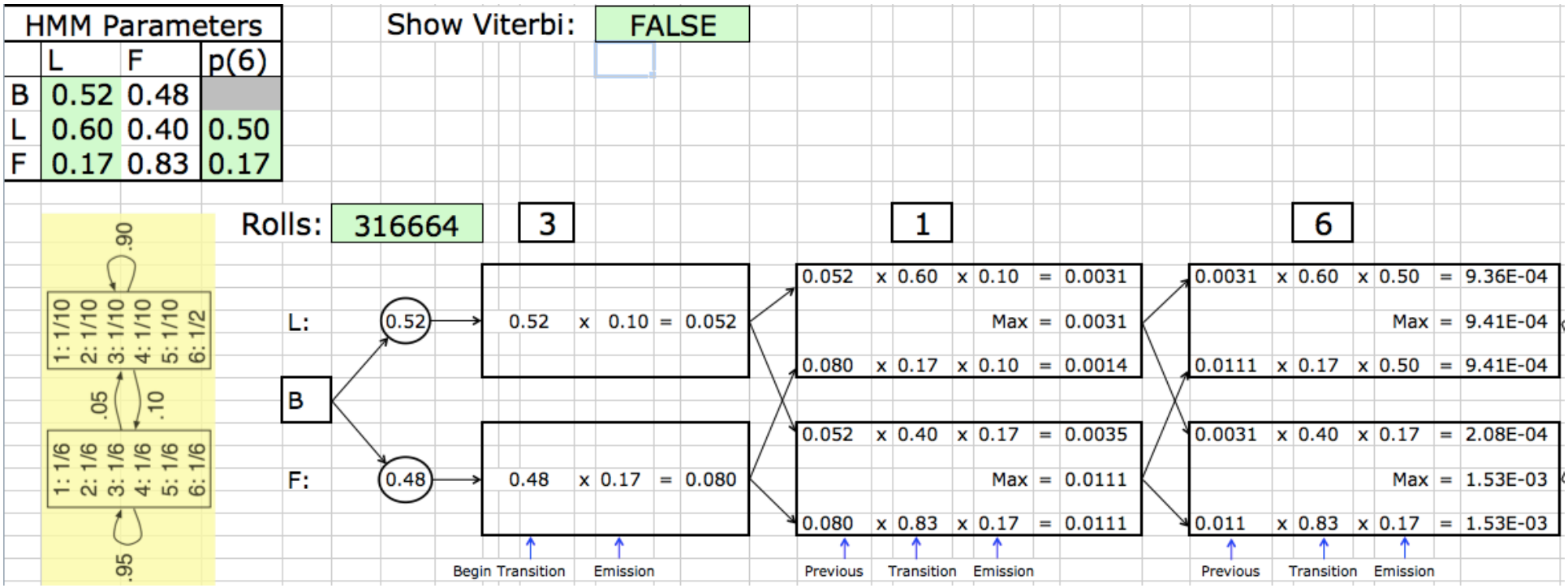


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

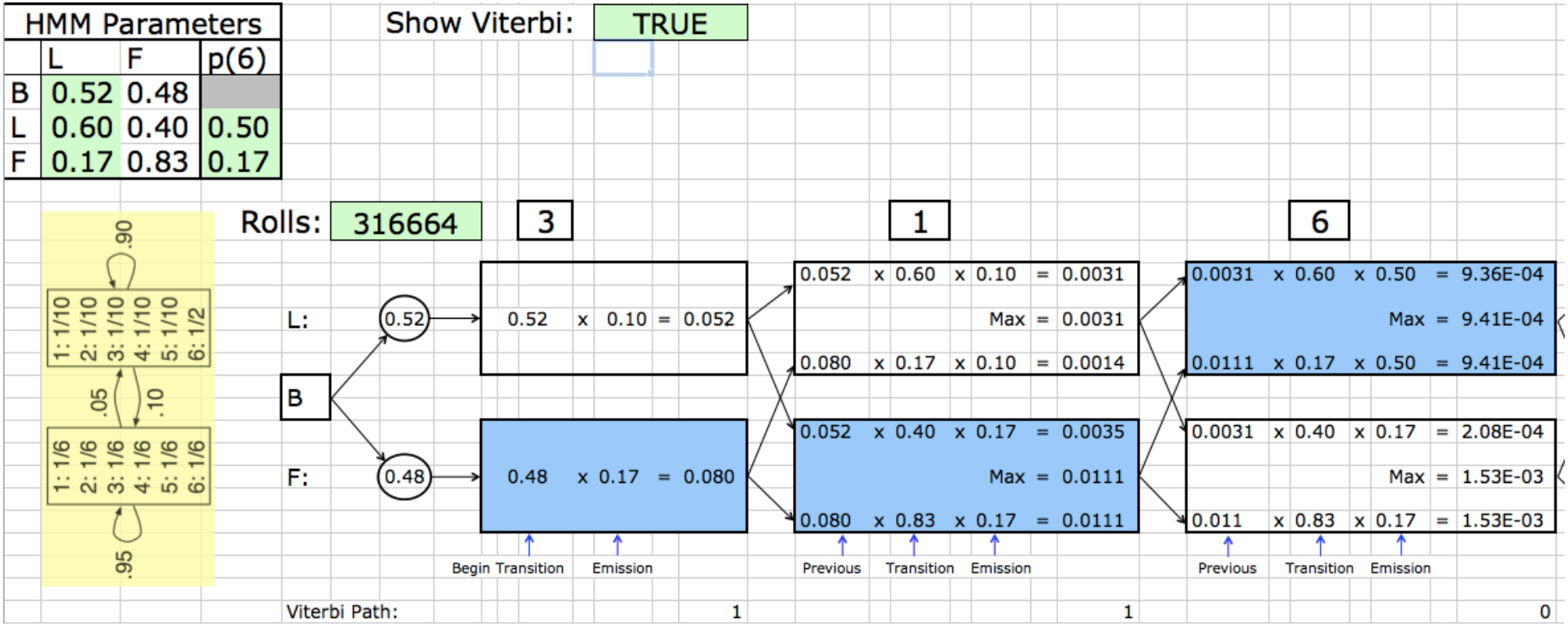
From DEKM

HMM Casino Example



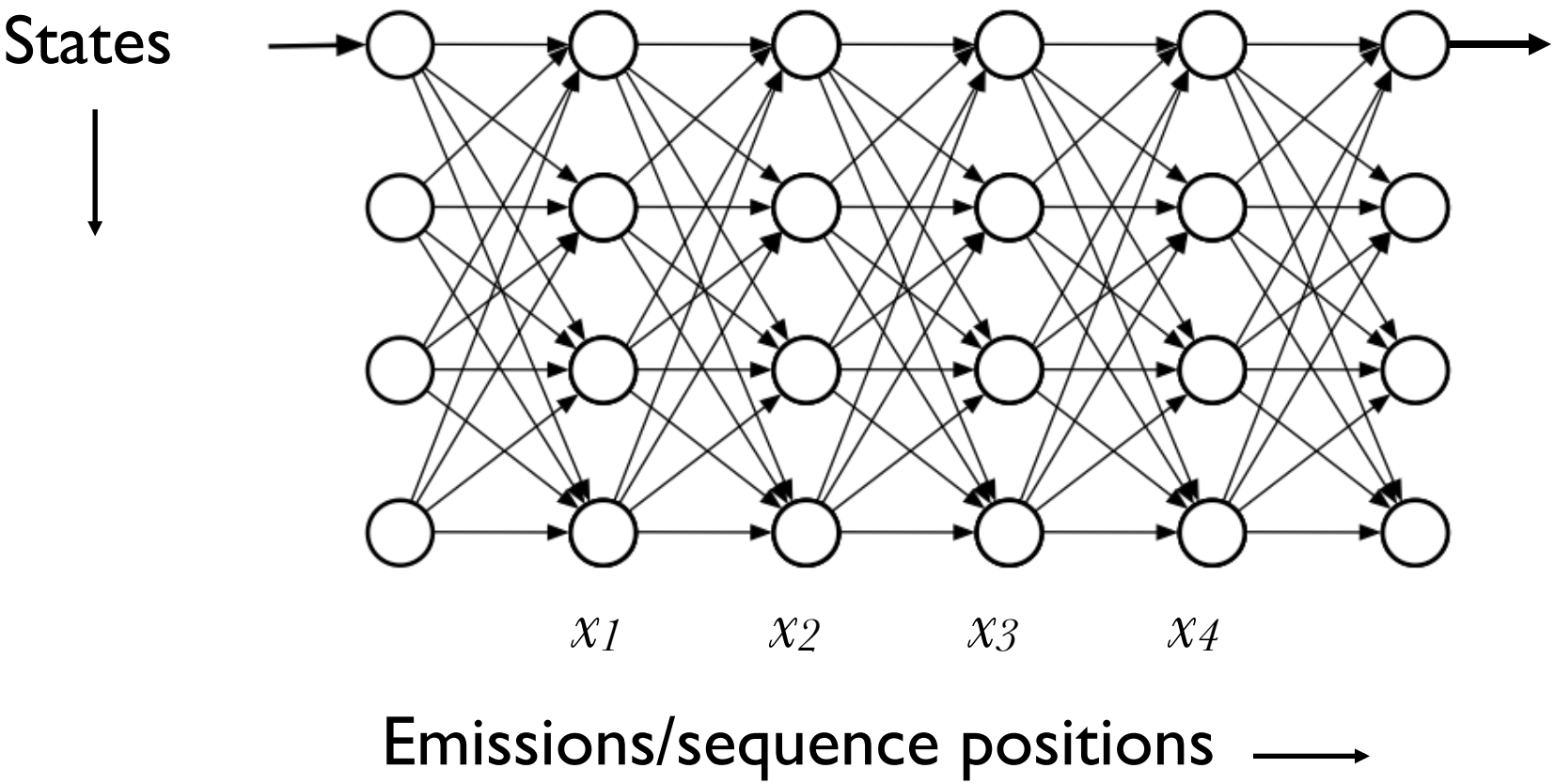
(Excel spreadsheet on web; download & play…)

HMM Casino Example



(Excel spreadsheet on web; download & play…)

An HMM (unrolled)



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

One very successful approach: profile HMMs