CSE P 590 A

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.:

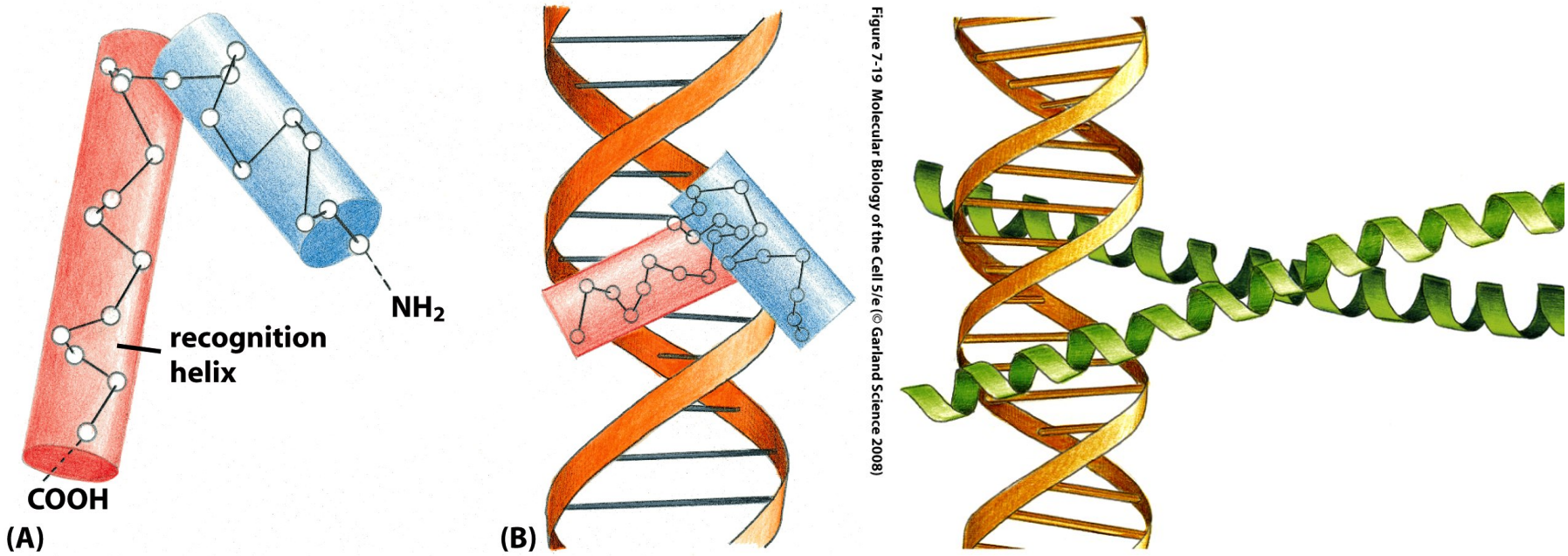


Figure 7-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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

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

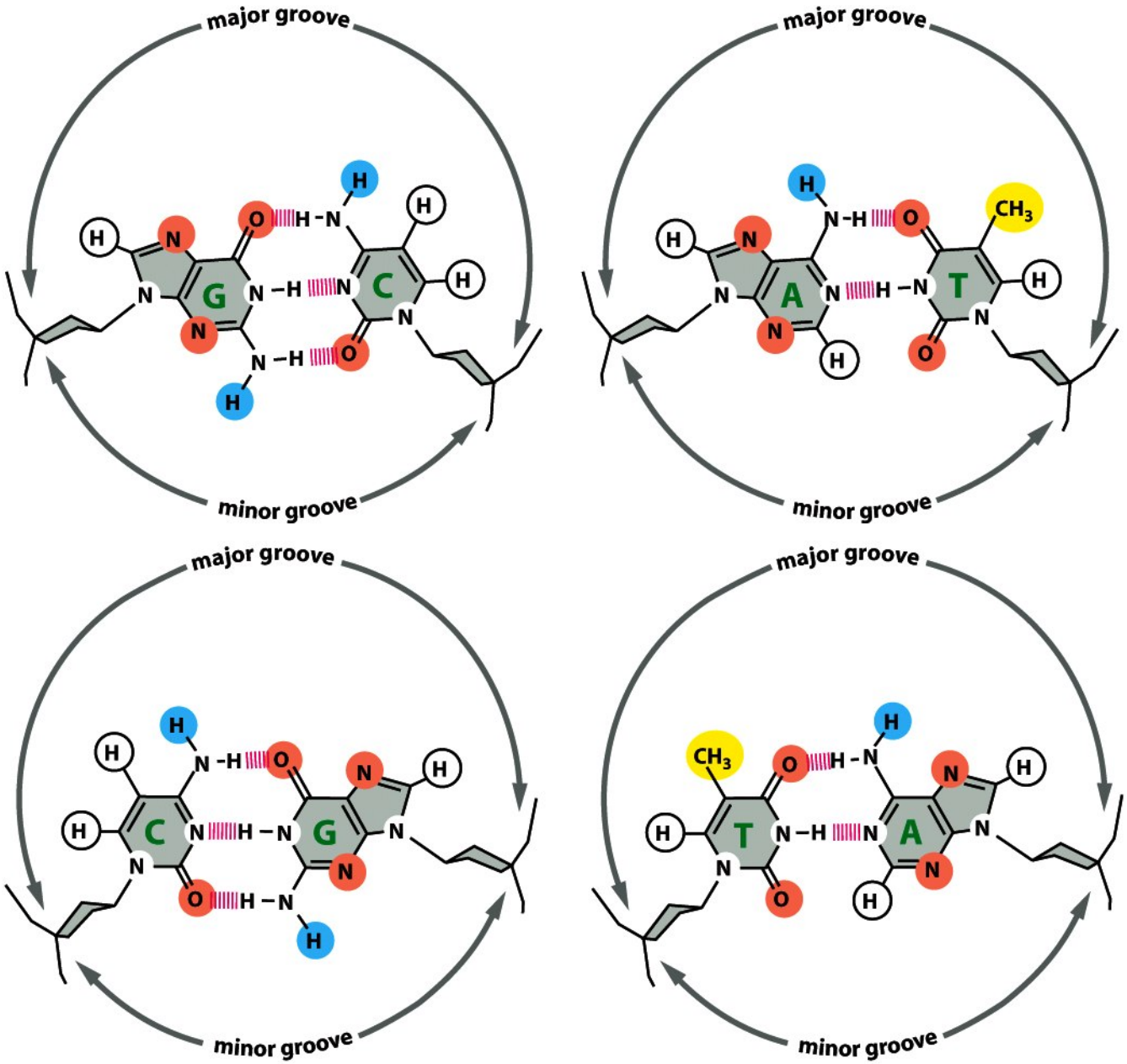
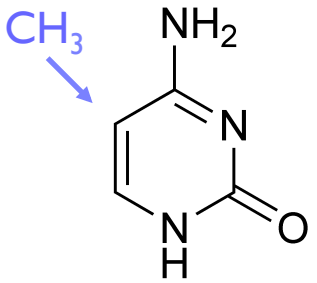


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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

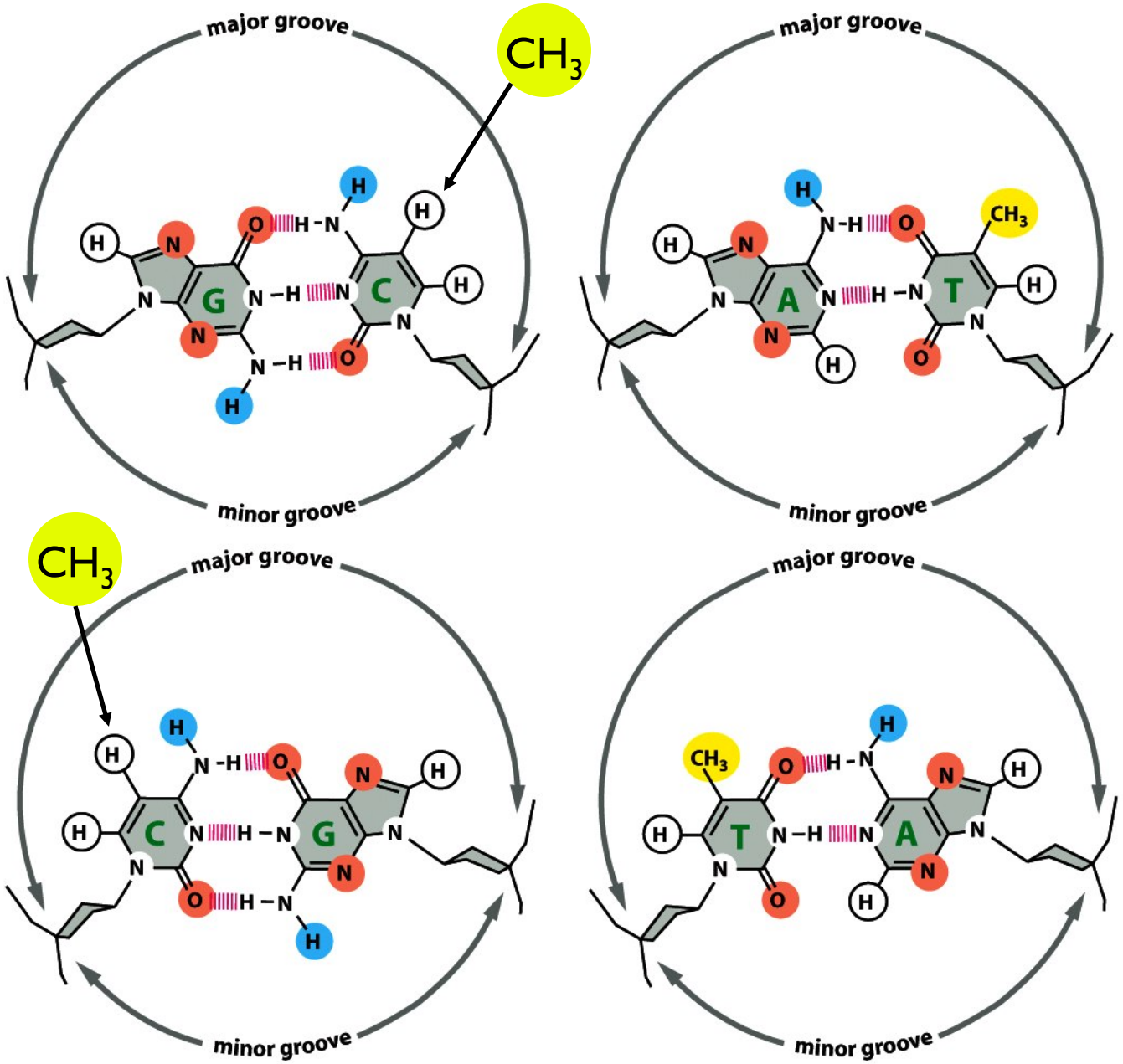
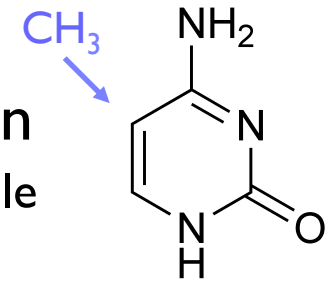


Figure 7-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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)

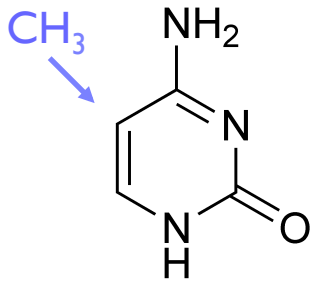
Major exception: promoters of housekeeping genes

"CpG Islands"

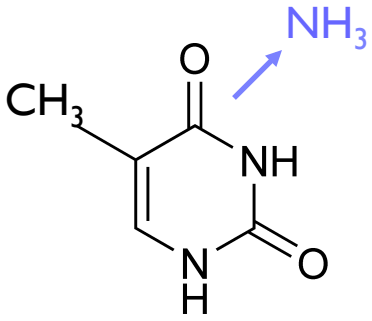
Methyl-C mutates to T relatively easily

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:

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

i-i

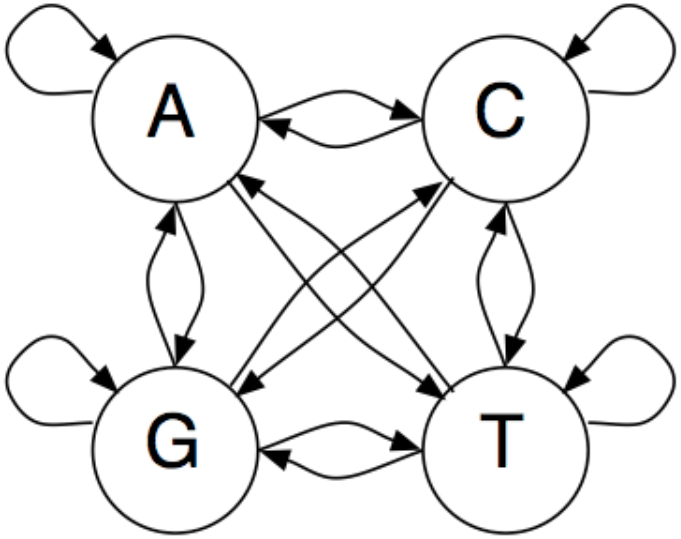
k typically ≪ i-1

Example 1: Uniform random ACGT } 0th order

Example 2: Weight matrix model

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

A Markov Model (1st order)

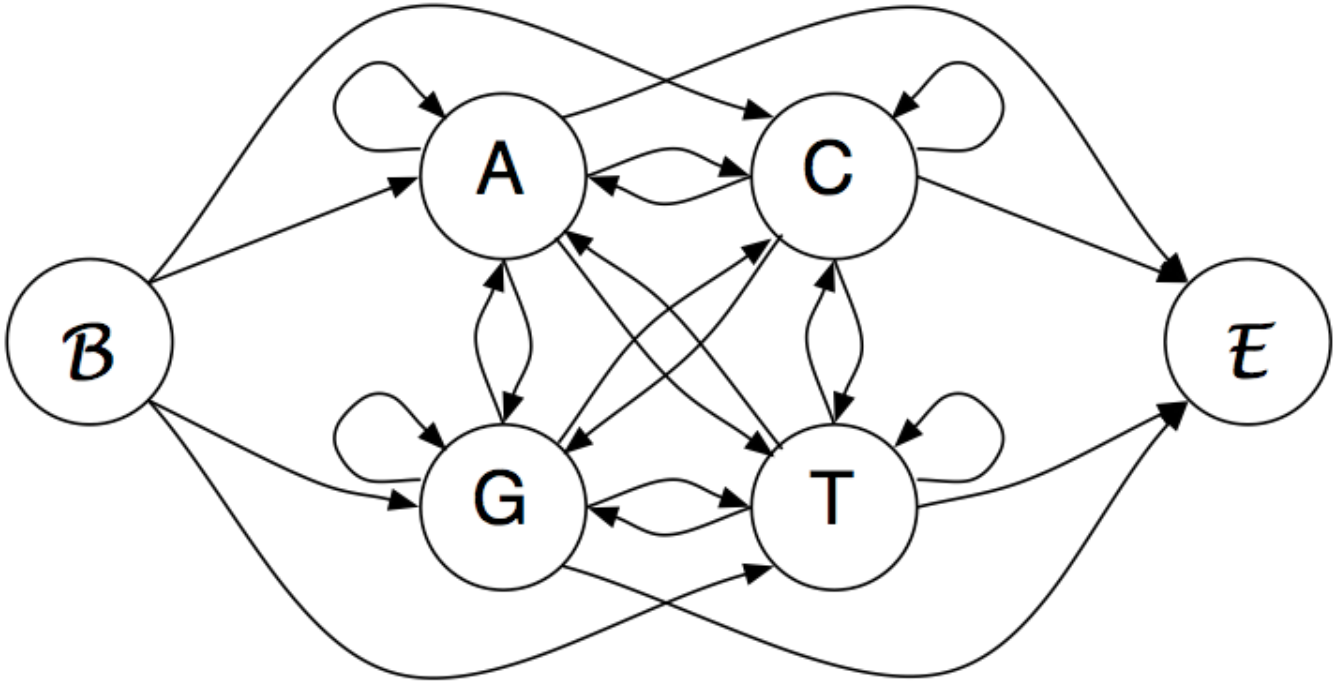


States: A,C,G,T

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*

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

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

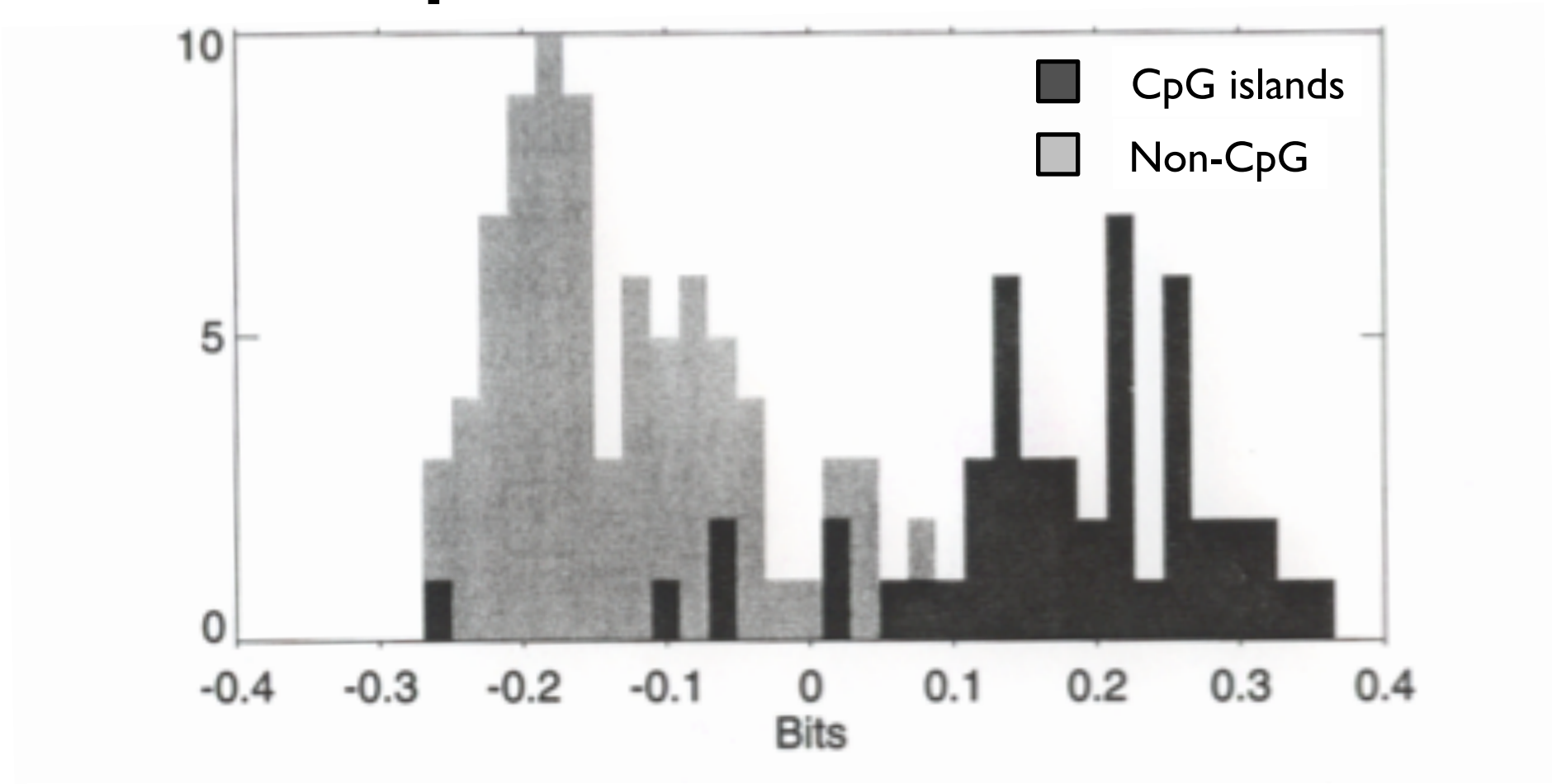


Figure 3.2 *Histogram of length-normalized scores.*

From DEKM

What does a 2nd order Markov Model look like?

3rd order?

Questions

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

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

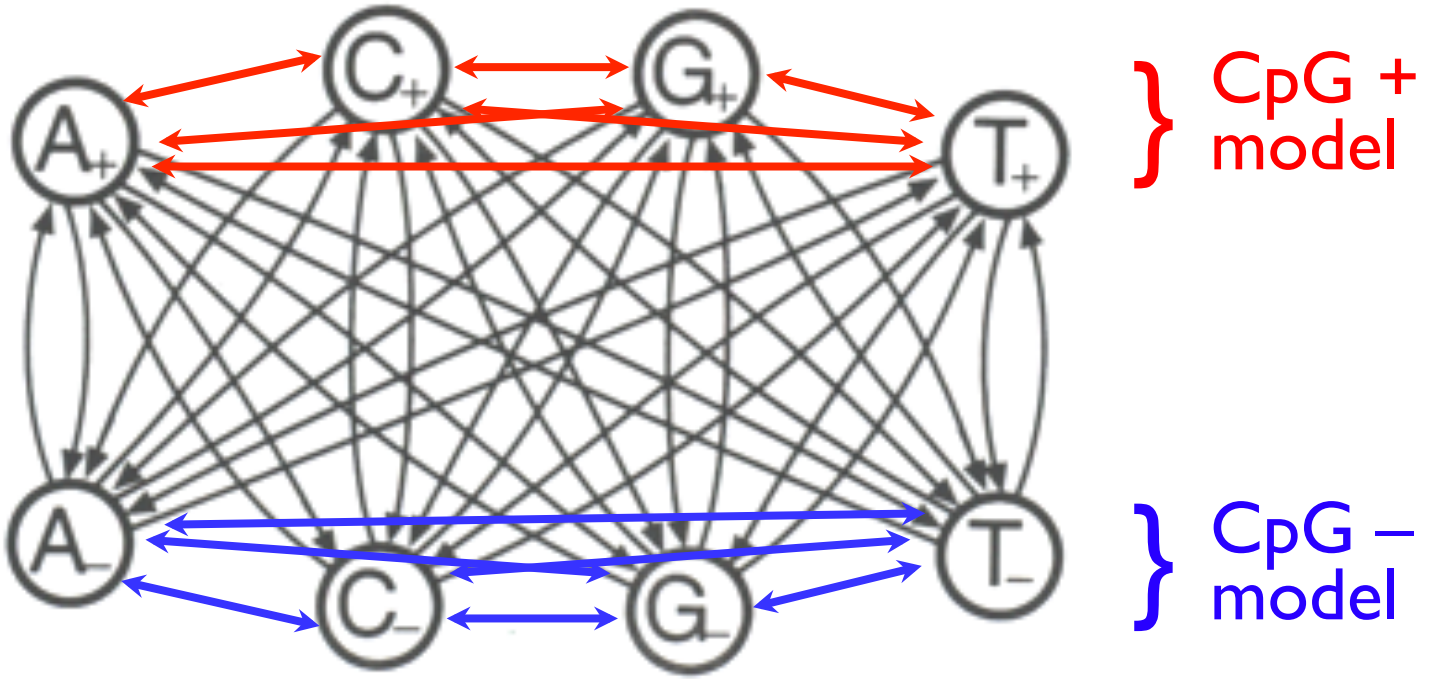
Approach 1: score 100 bp (e.g.) windows

Pro: simple

Con: arbitrary, fixed length, inflexible

Approach 2: *combine* +/- models.

Combined Model



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

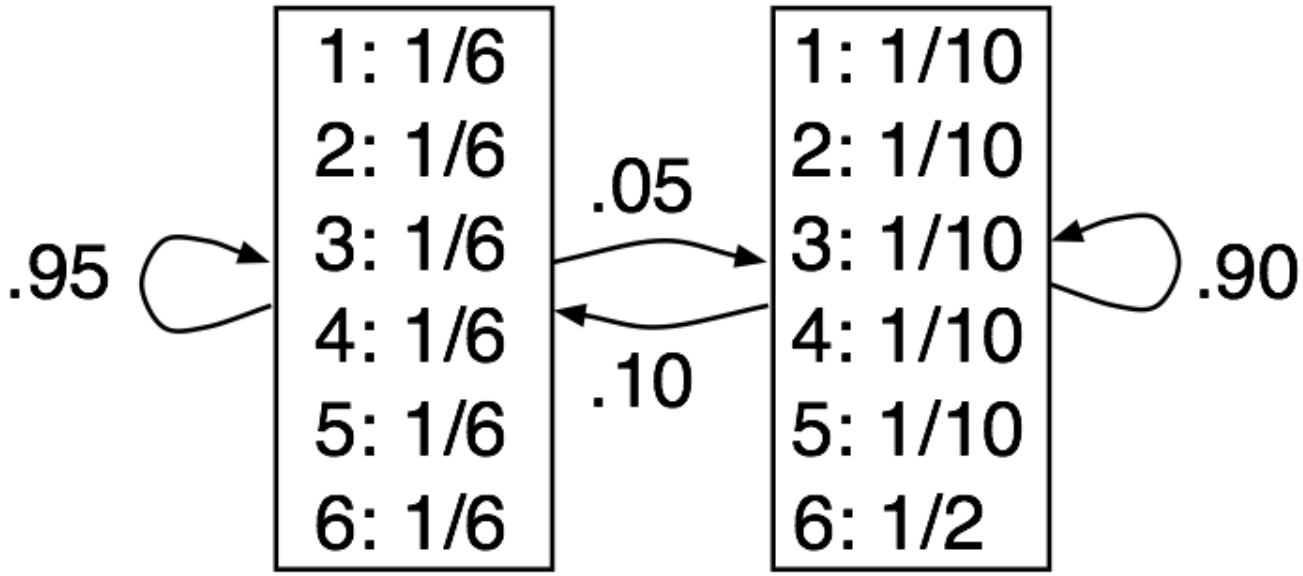
Hidden Markov Models

(HMMs; 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    315116246446644245311321631164152133625144543631656626566666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFFLLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

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

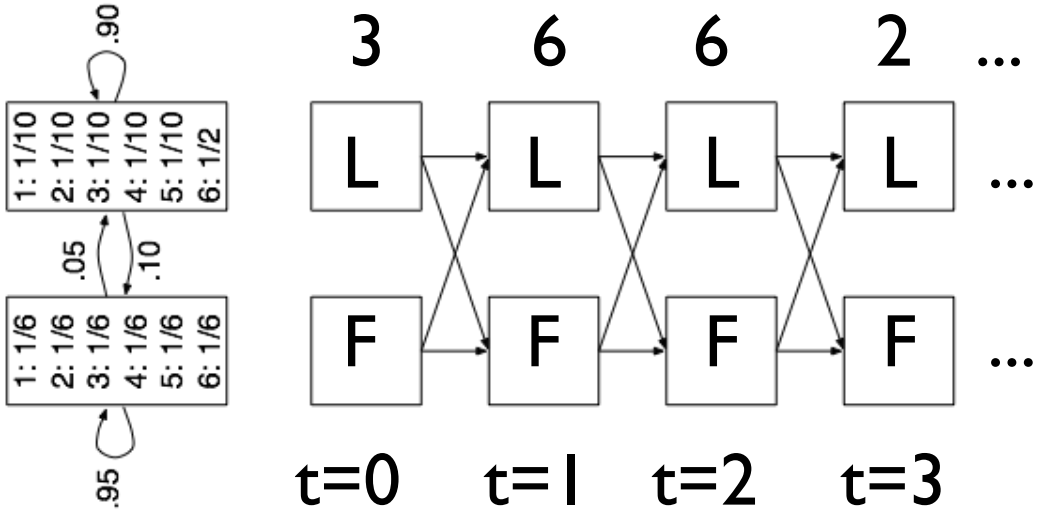
Possibly there are 10^{99} paths of prob 10^{-99}

(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

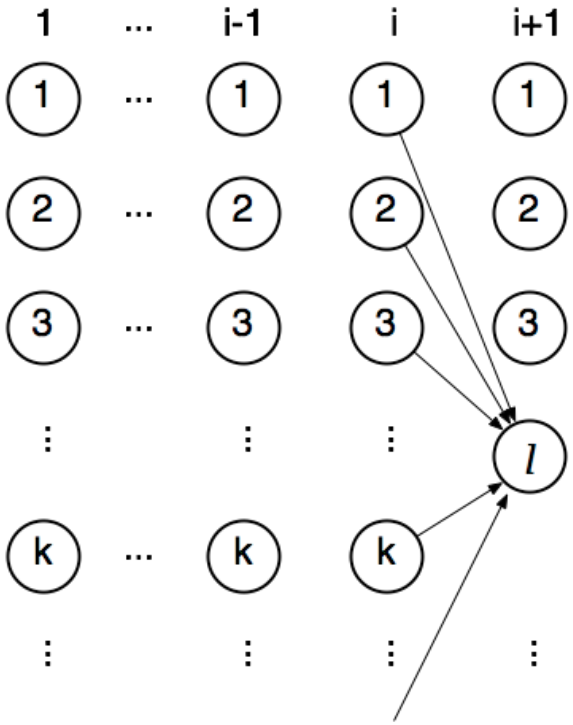
Note exponentially many paths

Viterbi

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

Initialize:

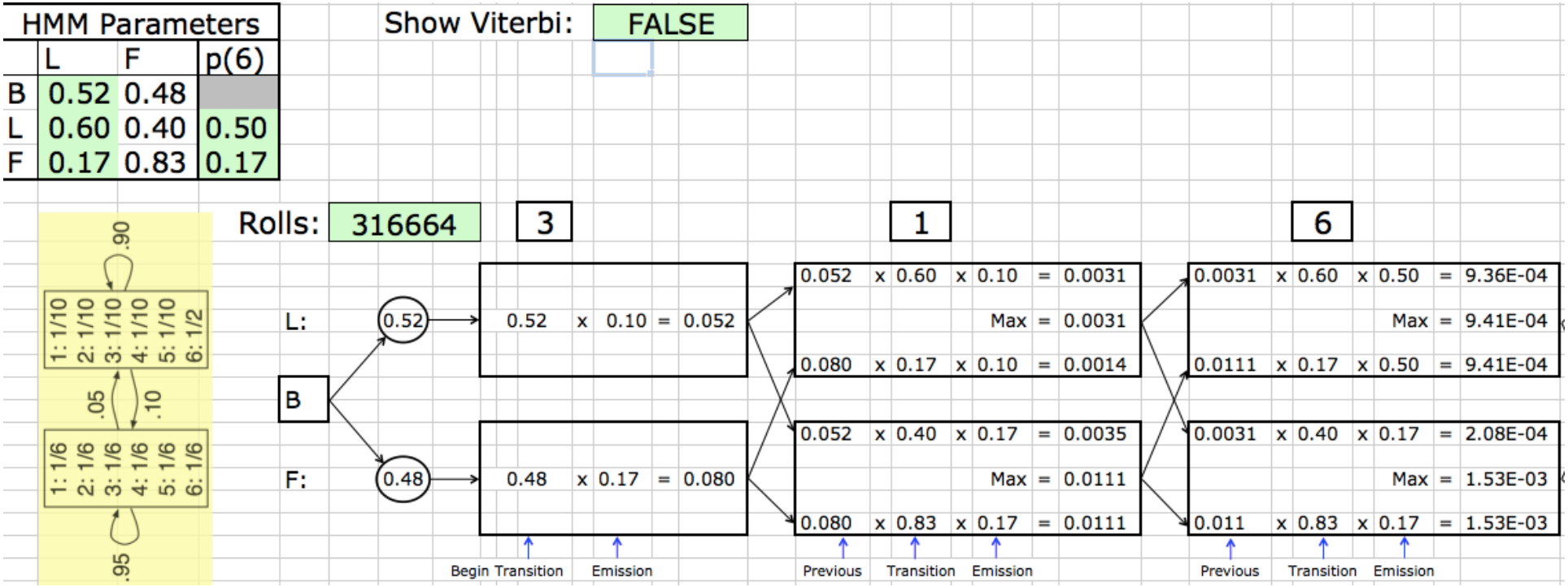
$$v_l(0) = \begin{cases} 1 & \text{if } l = B\text{egin state} \\ 0 & \text{otherwise} \end{cases}$$



General case:

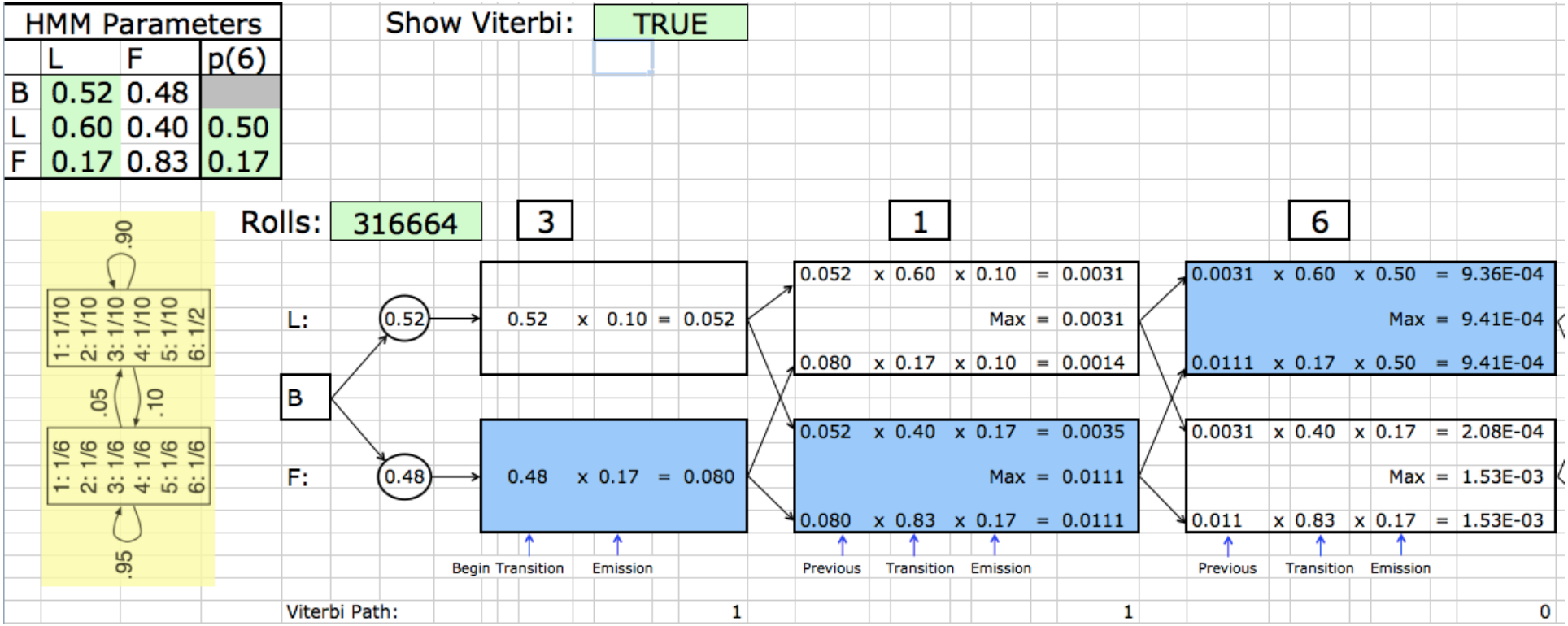
$$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

HMM Casino Example



(Excel spreadsheet on web; download & play…)

HMM Casino Example

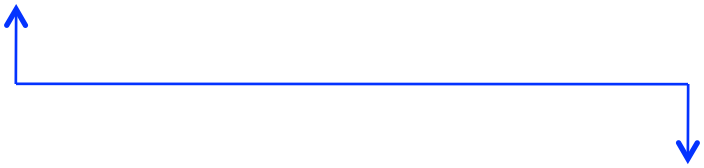


(Excel spreadsheet on web; download & play…)

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



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

```
Rolls    315116246446644245311321631164152133625144543631656626566666
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLL

Rolls    651166453132651245636664631636663162326455236266666625151631
Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
Viterbi  LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFF

Rolls    222555441666566563564324364131513465146353411126414626253356
Die      FFFFFFFFLLLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFLL
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

Rolls    366163666466232534413661661163252562462255265252266435353336
Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
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Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

Figure 3.5

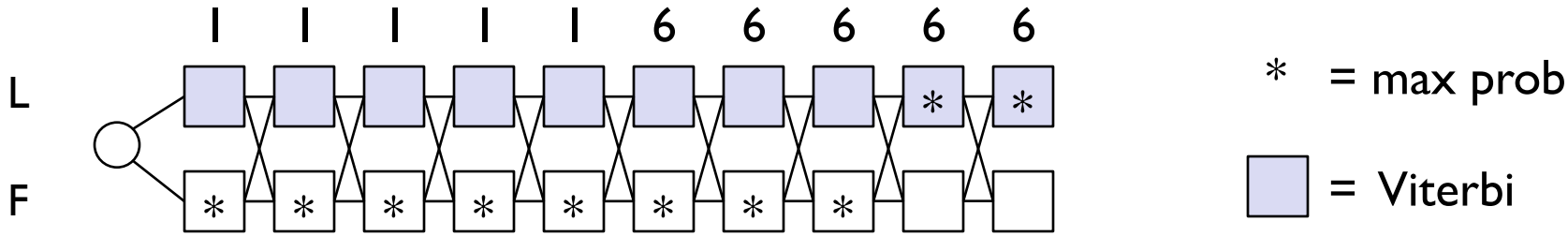
Rolls: Visible data–300 rolls of a die as described above.
Die: Hidden data–which die was actually used for that roll (F = fair, L = loaded).
Viterbi: the prediction by the Viterbi algorithm is shown.

From DEKM

Most probable path ≠ Sequence of most probable states

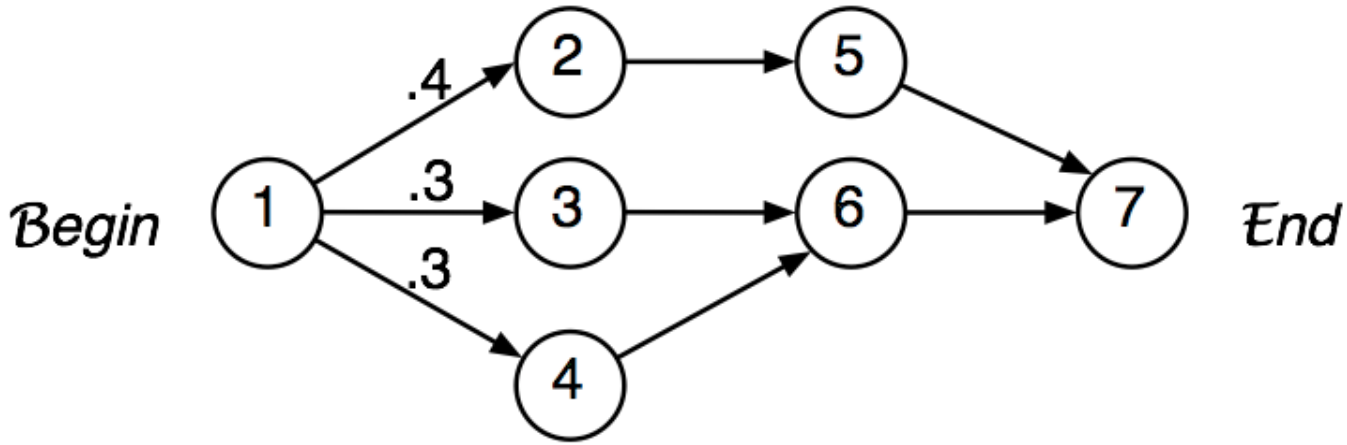
Another example, based on casino dice again

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"?

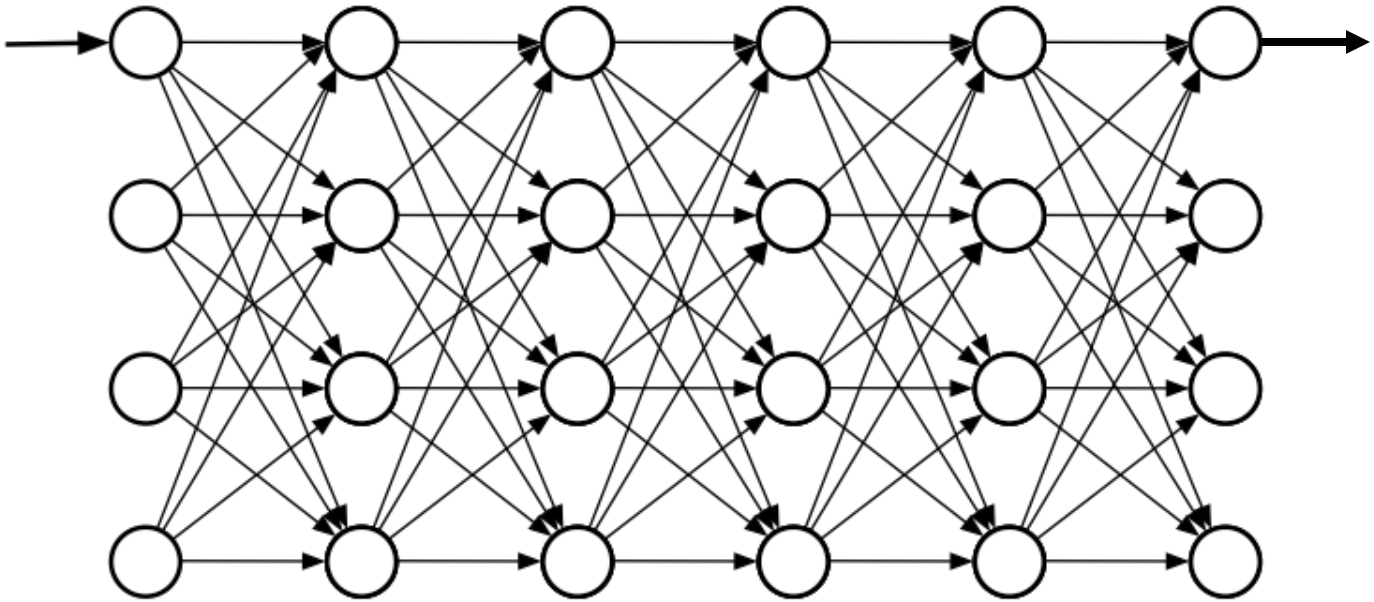
Viterbi finds $\pi^* = \arg\max_{\pi} P(x, \pi)$



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.)

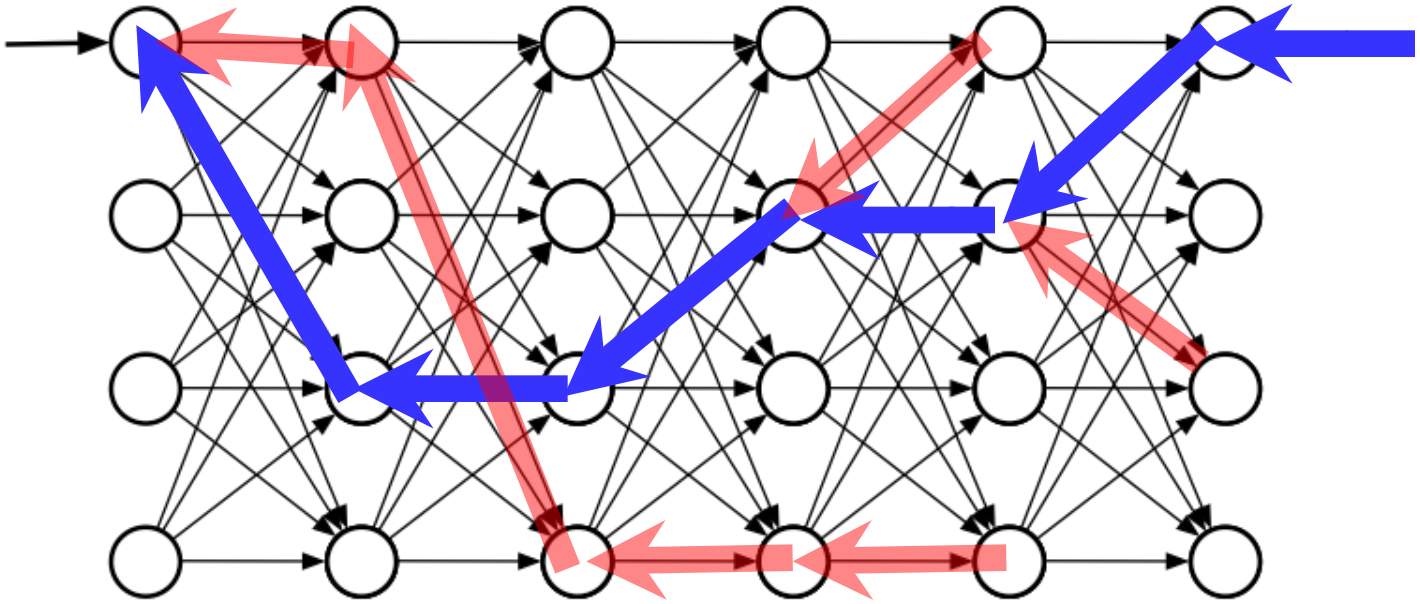
An HMM (unrolled)

States



Emissions/sequence positions

Viterbi: best path to each state



Viterbi *score*:

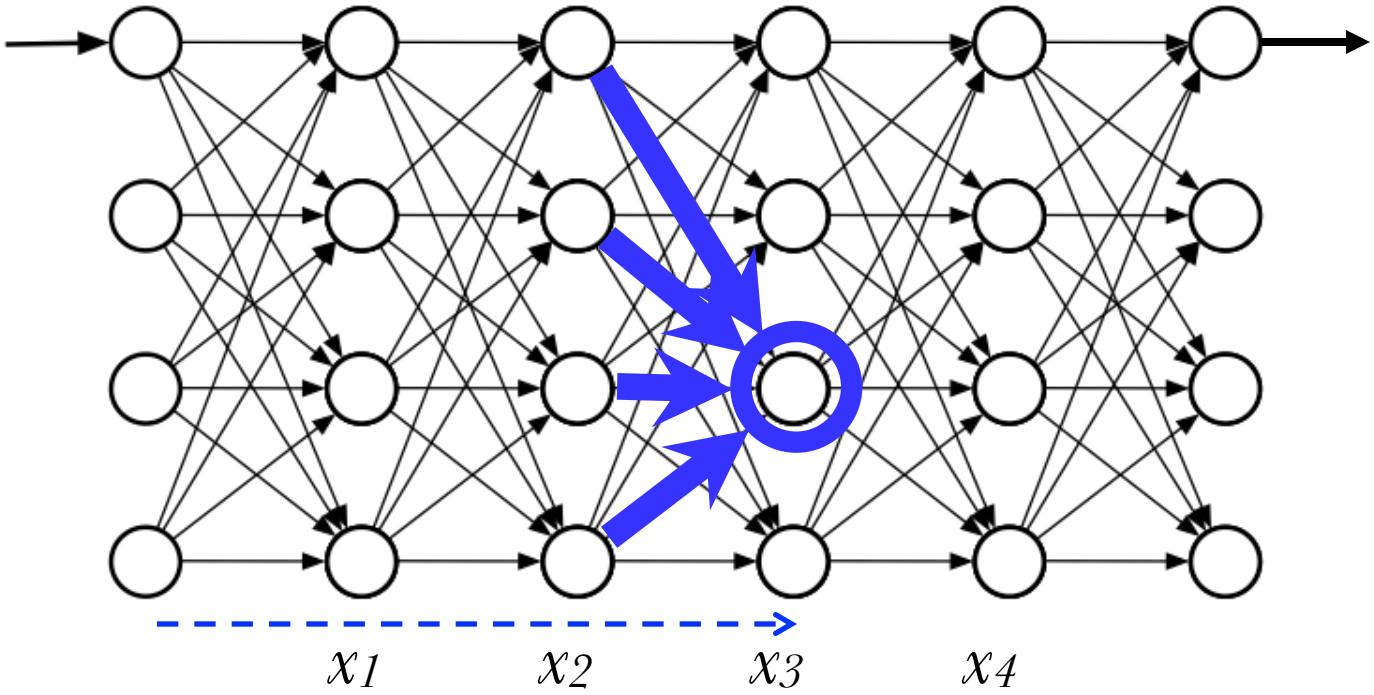
$$v_l(i+1) = e_l(x_{i+1}) \cdot \max_k (v_k(i)\, a_{k,l})$$

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



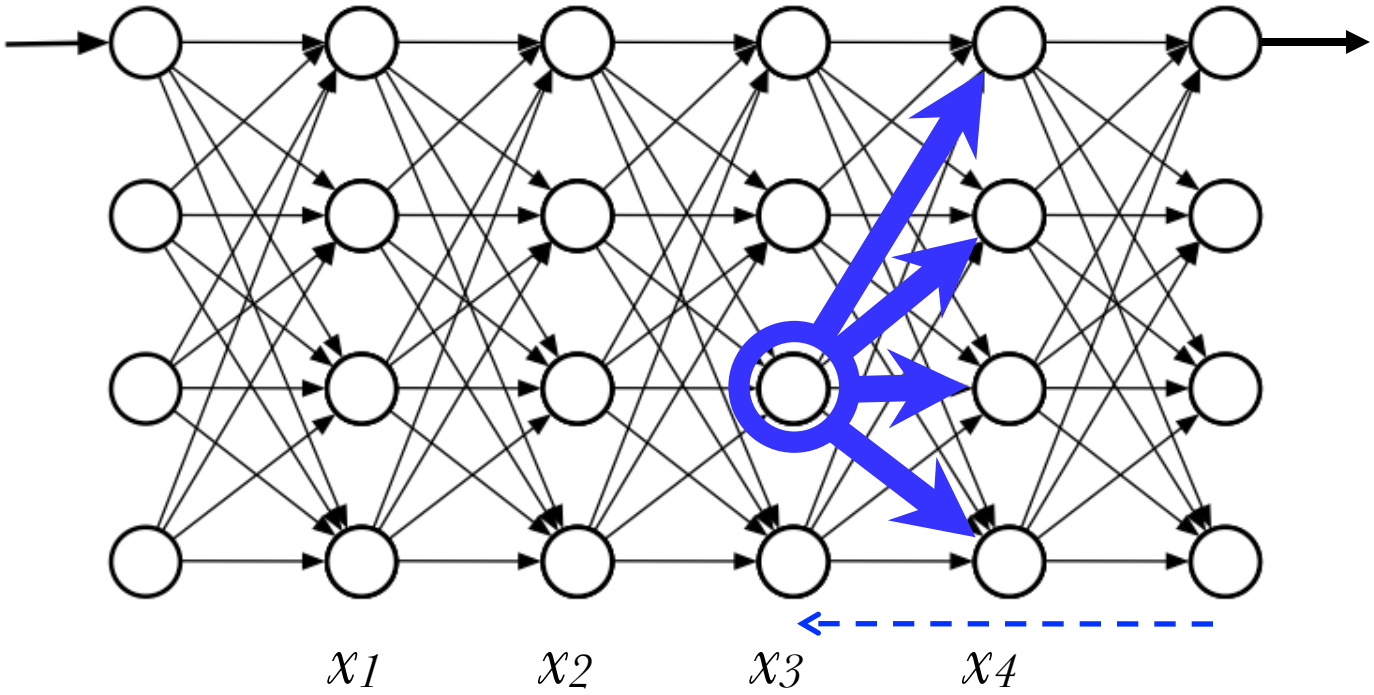
$$f_k(i) \triangleq P(x_1 \ldots x_i,\ \pi_i = k)$$

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

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

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* ?

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

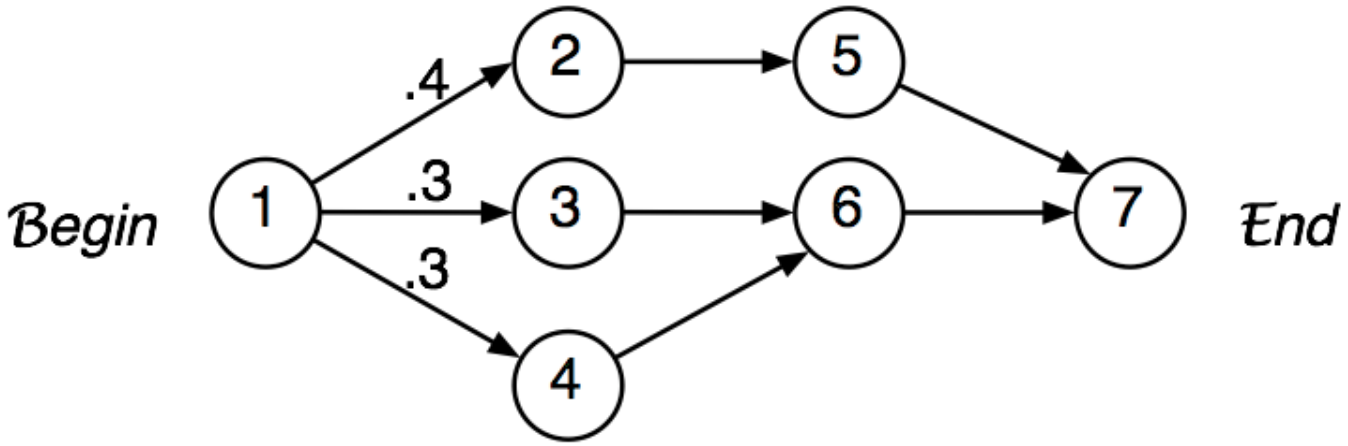
$$
P(\pi_i = k \mid x) \;=\; \frac{P(x, \pi_i = k)}{P(x)} \;=\; \frac{f_k(i) \cdot b_k(i)}{P(x)}
$$

Posterior Decoding, I

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

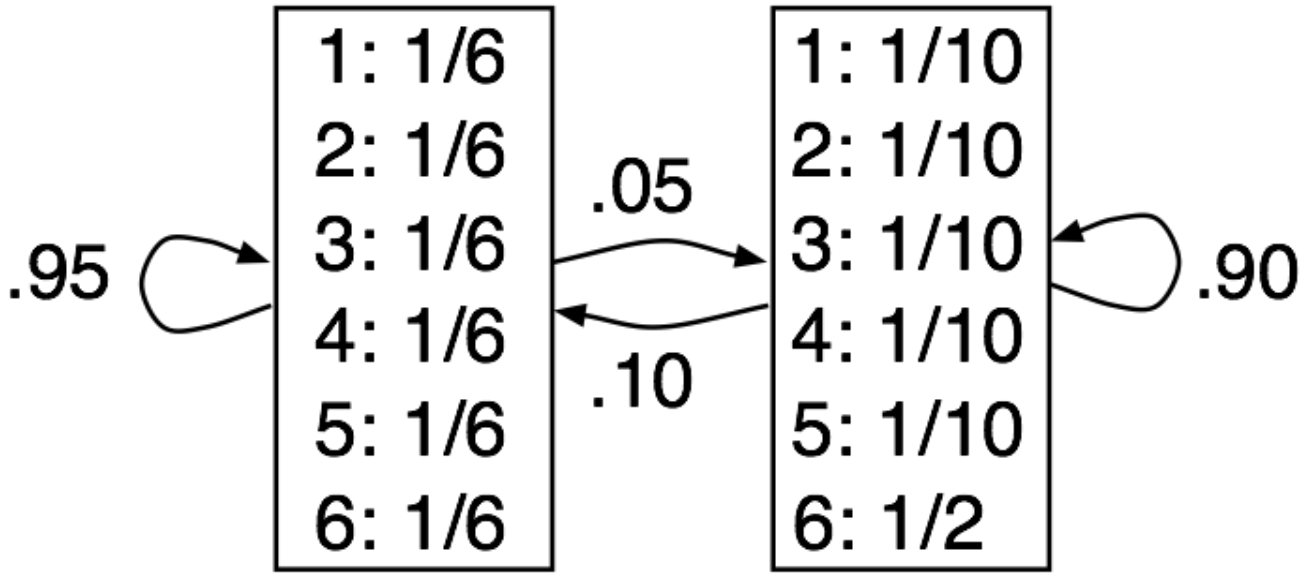
$$\hat{\pi}_i = \arg\max_k P(\pi_i = k \mid x)$$

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



The Occasionally Dishonest Casino

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



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Die      LLLLLLFFFFFFFFFFFFLLLLLLLLLLLLLLLLFFFLLLLLLLLLLLLLLFFFFFFFFF
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Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFL

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Die      LLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi  LLLLLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

Rolls    233121625364414432335163243633665562466662632666612355245242
Die      FFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFFF
Viterbi  FFFFFFFFFFFFFFFFFFFFFFFFFFFFLLLLLLLLLLLLLLLLLLLLLLFFFFFFFFFF
```

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

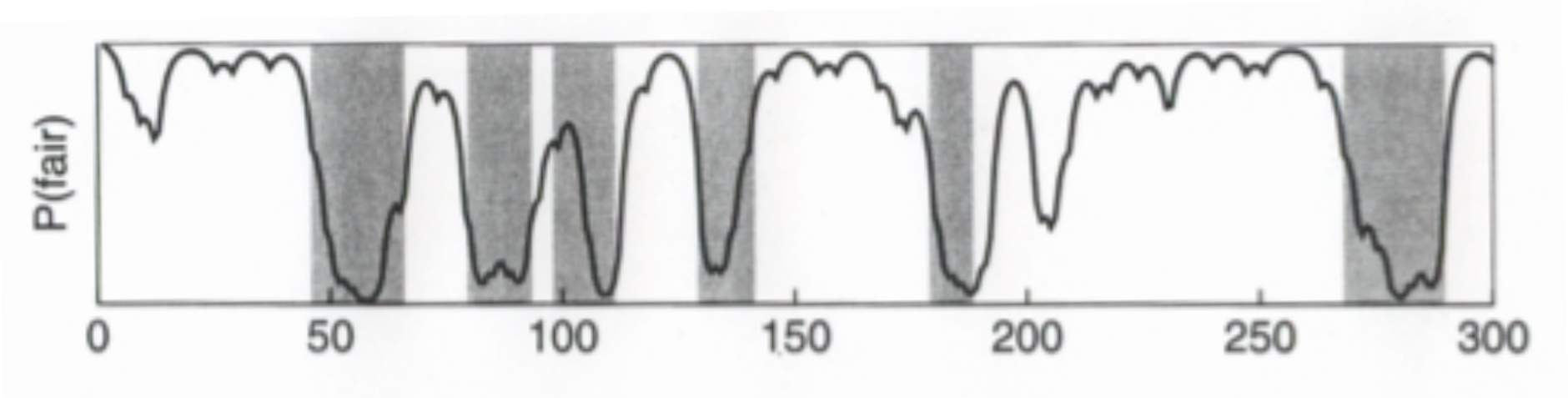


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

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:
Found 46 of 48
plus 121 "false positives"

Post-process:
46/48
67 false pos

Posterior Decoding:
same 2 false negatives
plus 236 false positives

46/48
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

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

$$e_k(b) = \ldots$$

+ 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

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

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

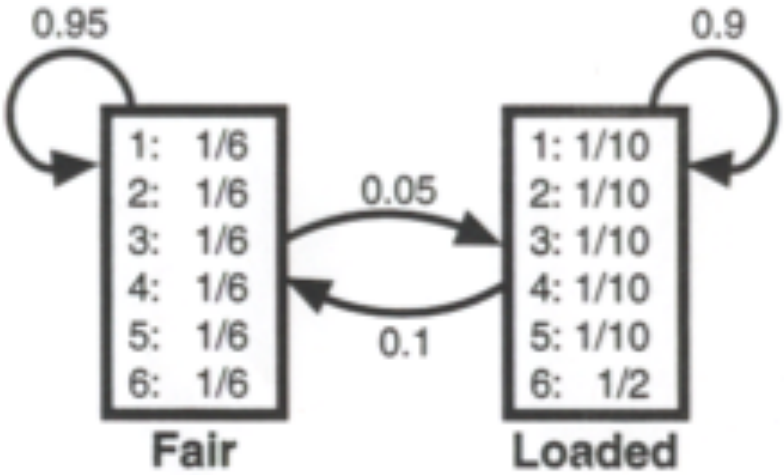
Estimated # of $k \to l$ transitions $\hat{A}_{k,l}$

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

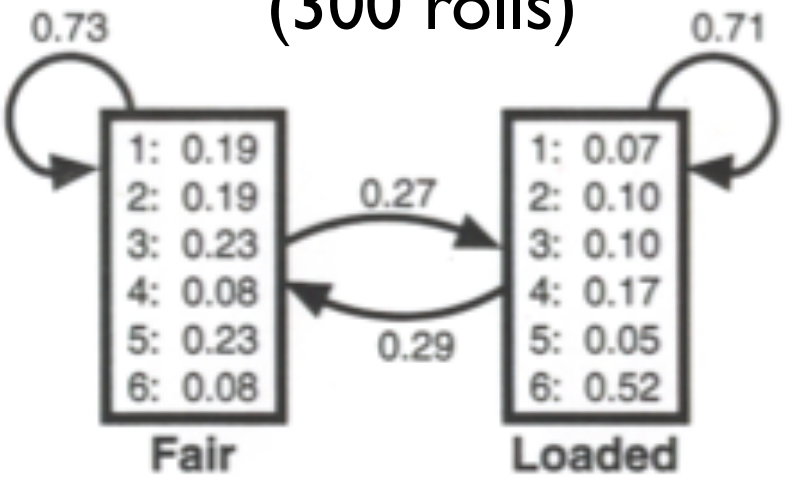
New estimate $\hat{a}_{k,l} = \dfrac{\hat{A}_{k,l}}{\sum_l \hat{A}_{k,l}}$

Emissions: similar

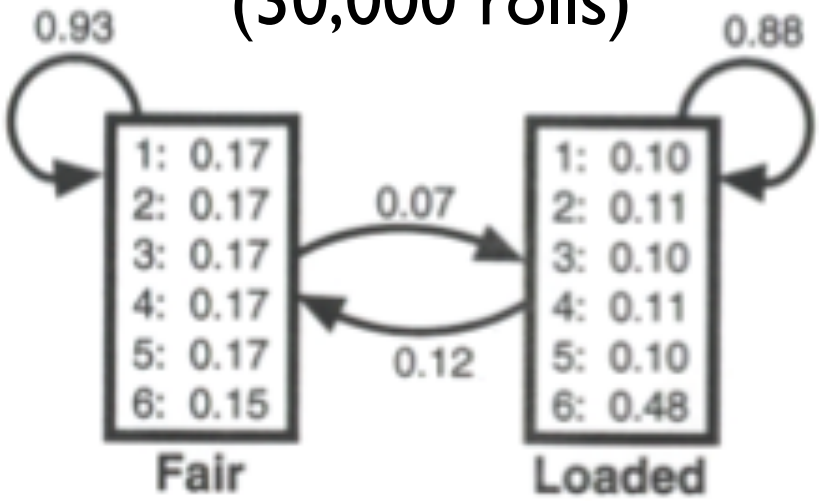
True Model



B-W Learned Model (300 rolls)



B-W Learned Model (30,000 rolls)



Log-odds (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/

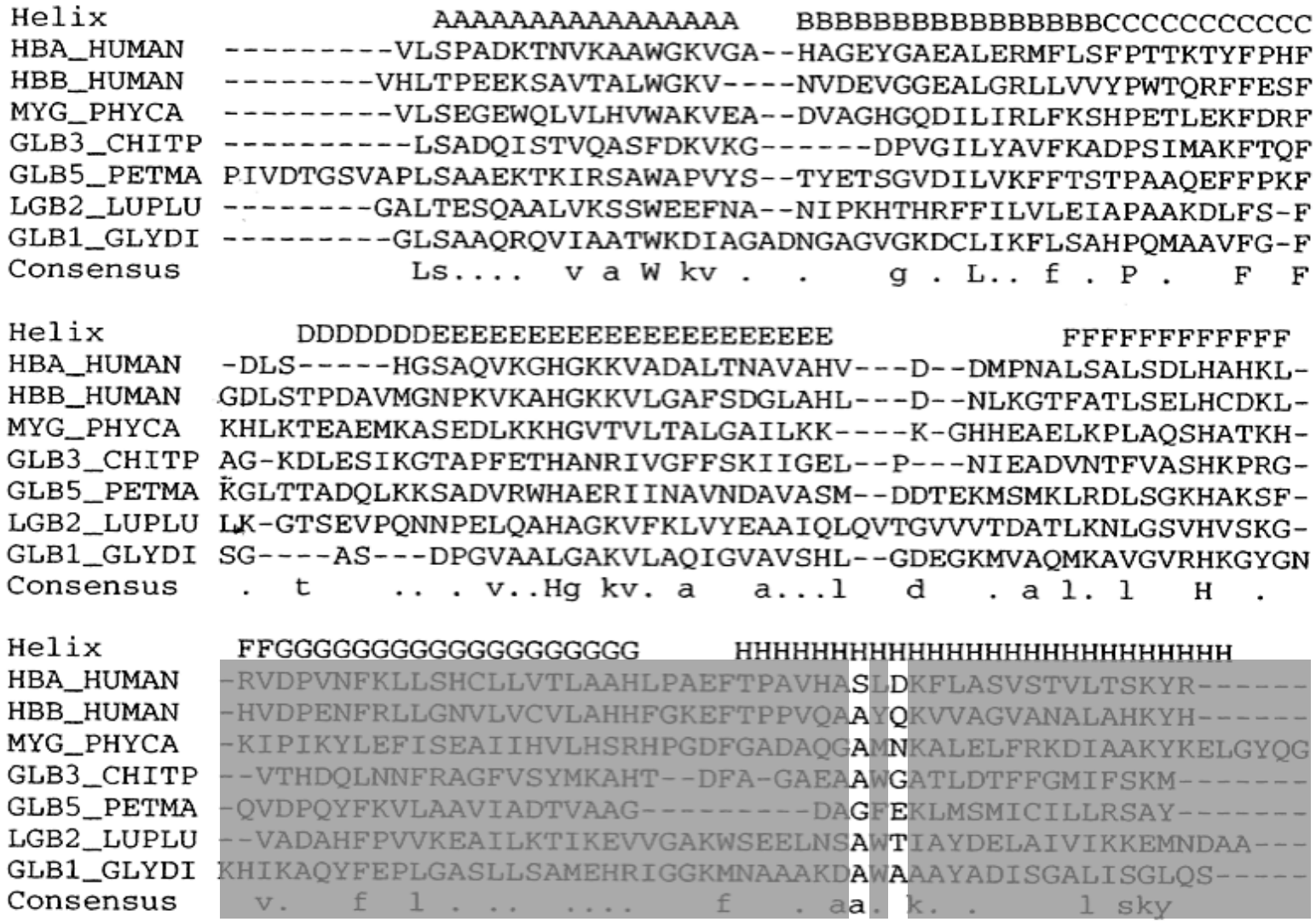
Proteins fall into families, both across & within species

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

Identifying family very useful: suggests function, etc.

So, search & alignment are both important

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

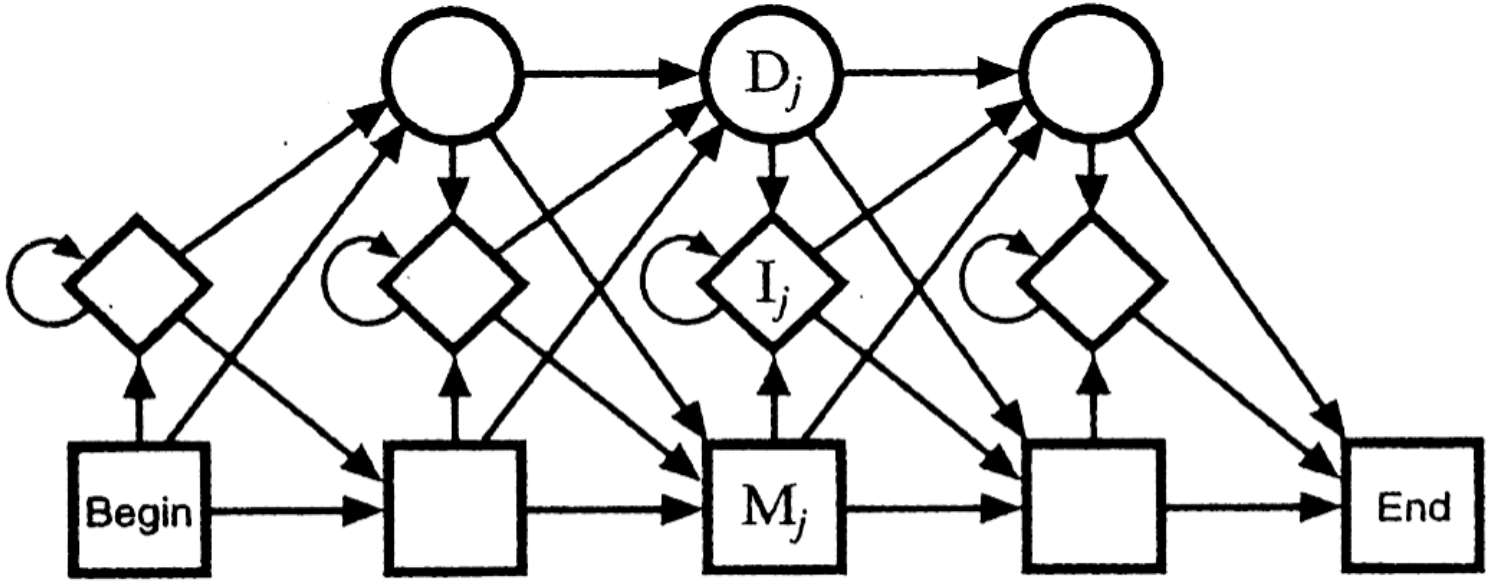


Figure 5.2 *The transition structure of a profile HMM.*

M_j: Match states (20 emission probabilities)

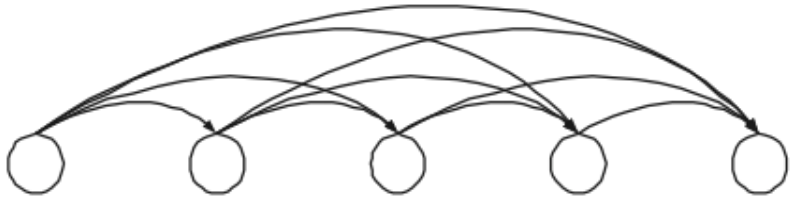
I_j: Insert states (Background emission probabilities)

D_j: Delete states (silent - no emission)

From DEKM

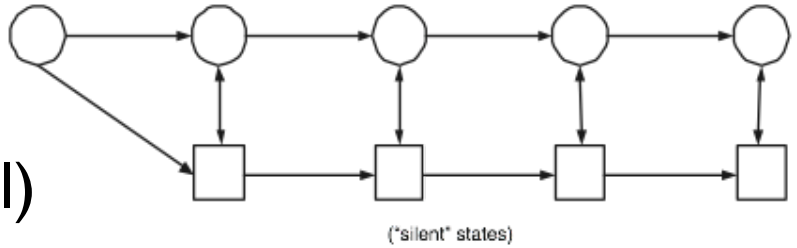
Silent States

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

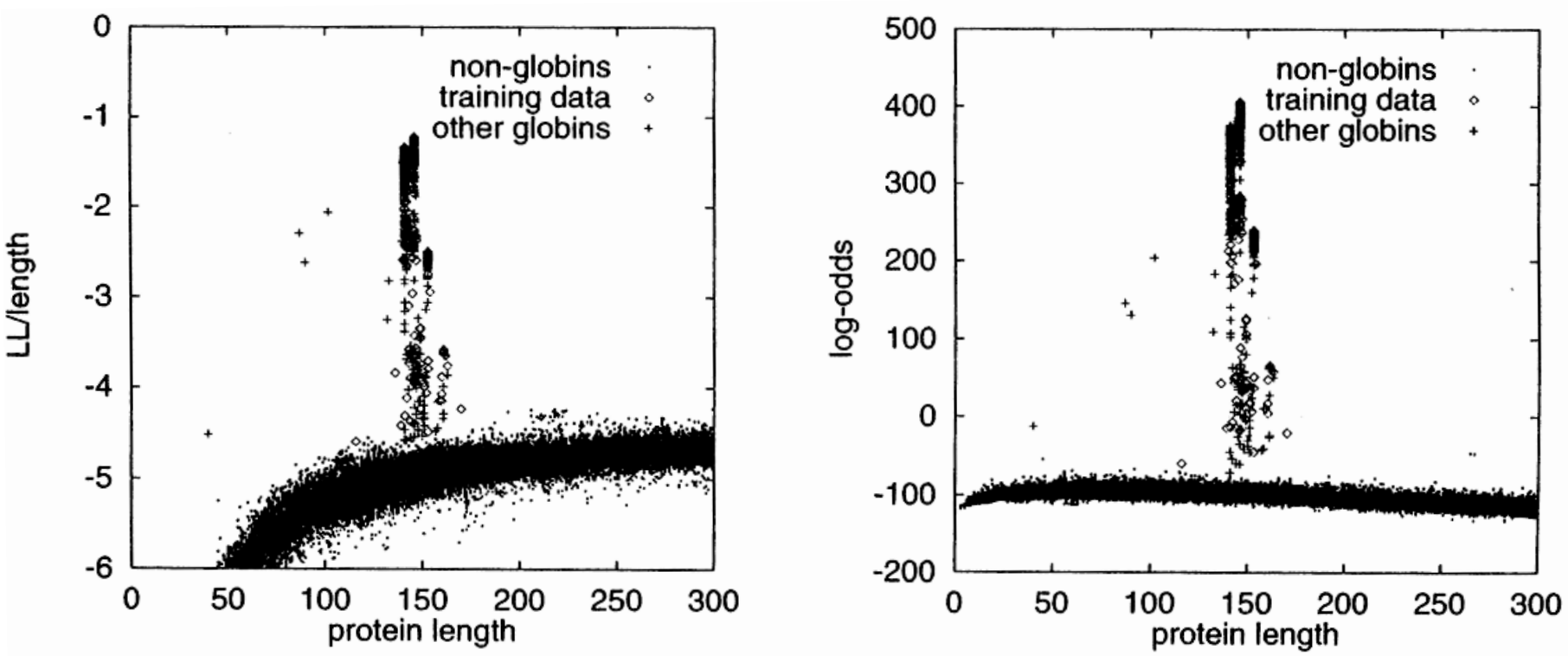


Figure 5.5 *To the left the length-normalized LL score is shown as a function of sequence length. The right plot shows the same for the log-odds score.*

From DEKM

Z-Scores

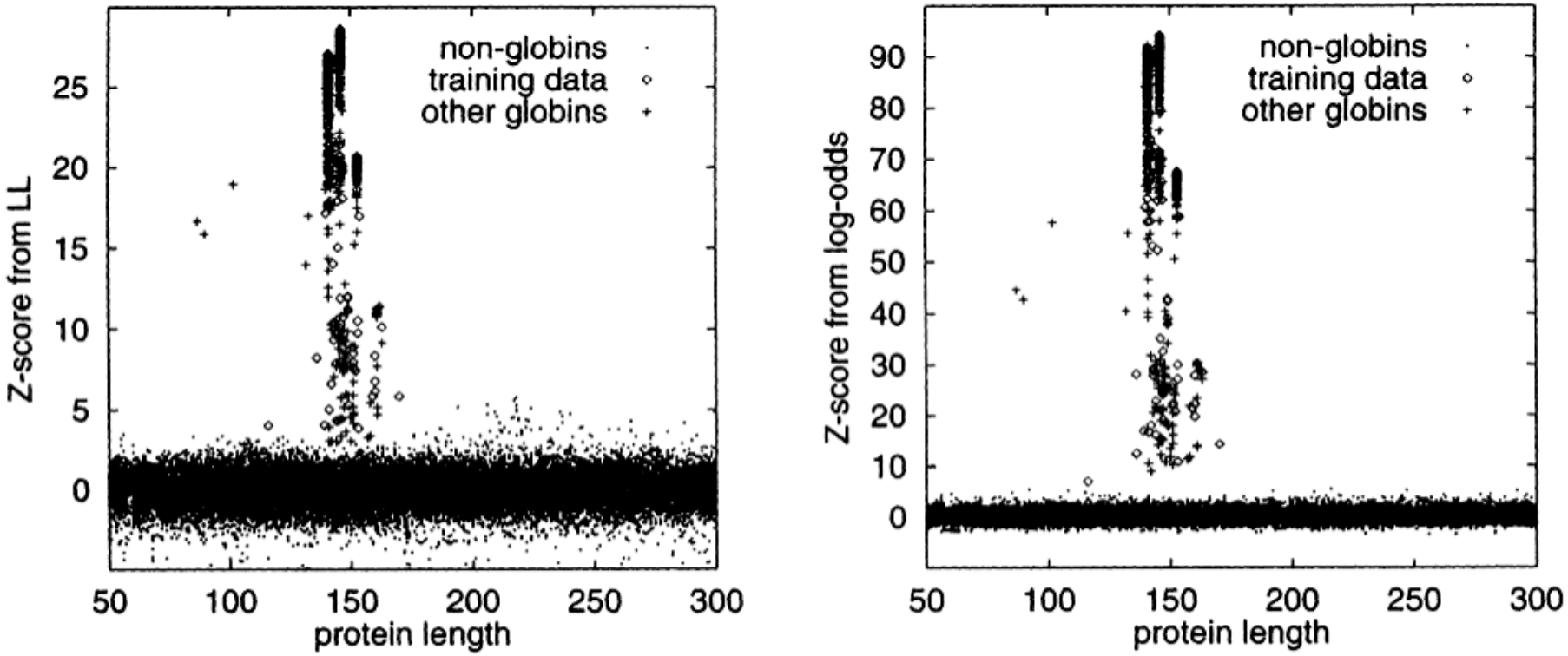


Figure 5.6 *The Z-score calculated from the LL scores (left) and the log-odds (right).*

From DEKM

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%)

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)

refinements

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

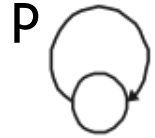
Define it as well as you can.

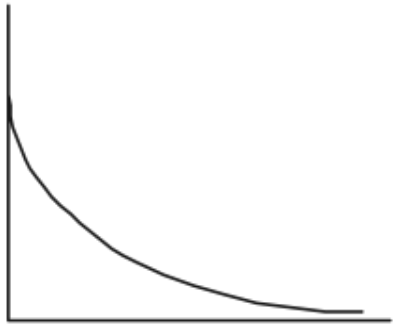
In principle, you can allow all transitions and hope to learn their probabilities from data, but it usually works poorly – too many local optima

refinements

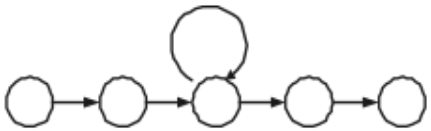
Duration Modeling

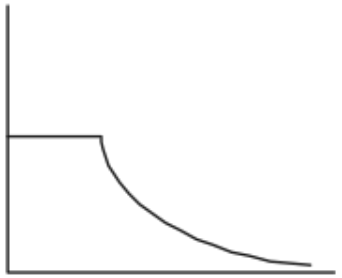
Self-loop duration:
geometric $p^n(1-p)$



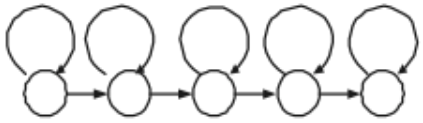


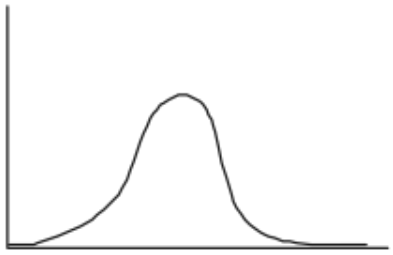
min, then geometric





"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", but Viterbi-based

HMM Summary (cont.)

Search:

- Viterbi or forward

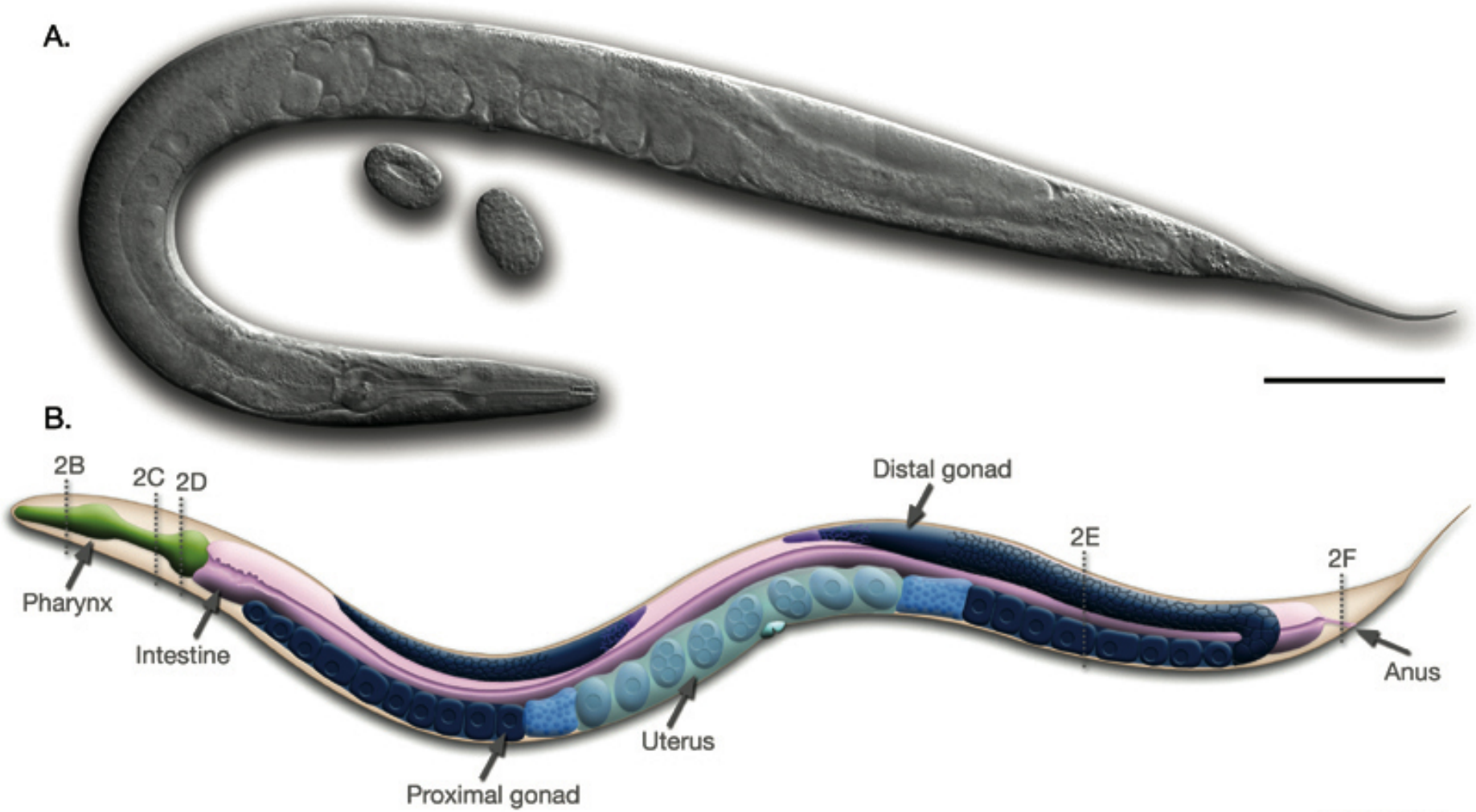
Scoring:

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

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

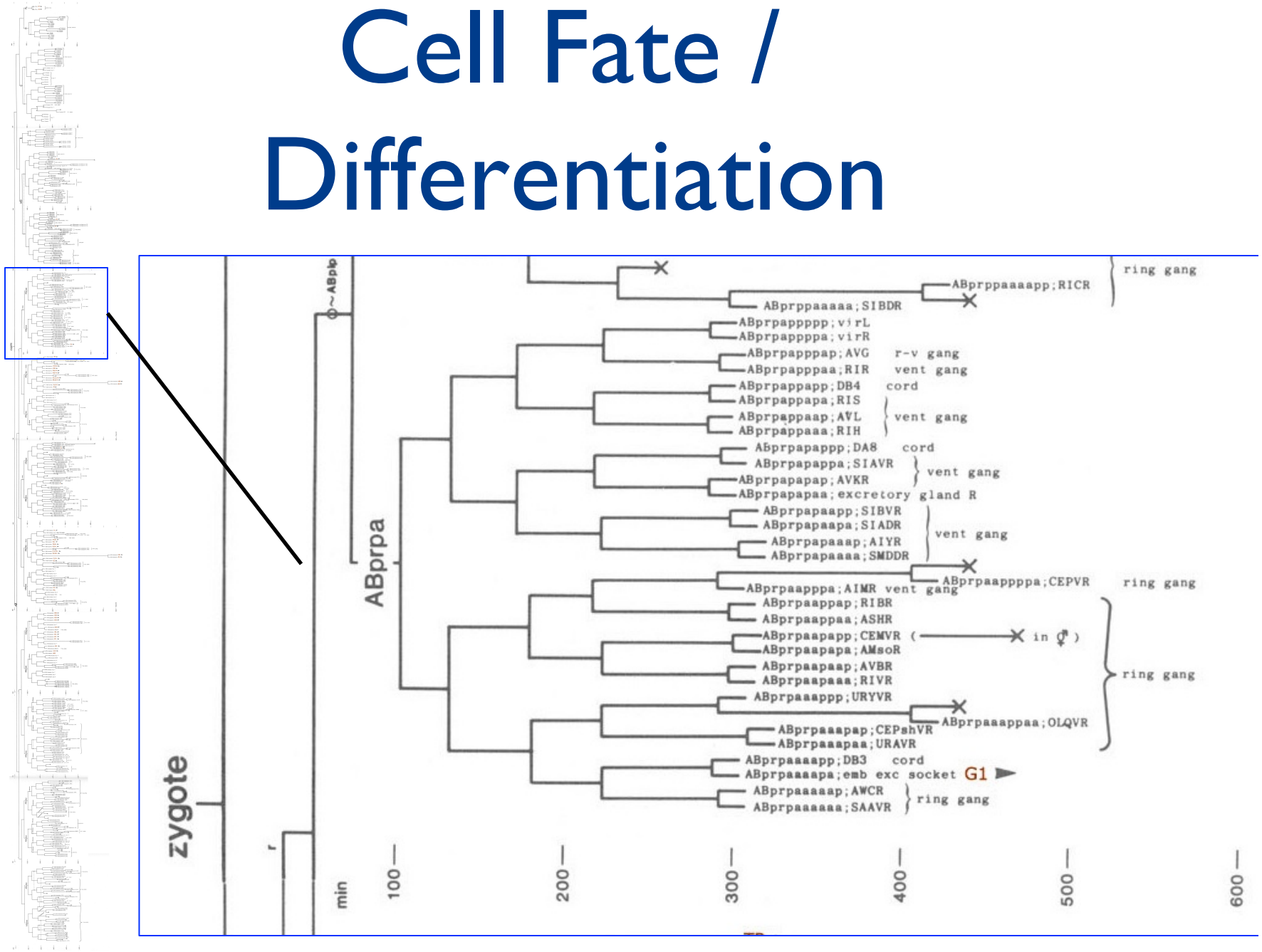
A very widely used tool for biosequence analysis

Caenorhabditis elegans



IntroFig1

Cell Fate / Differentiation



Differentiation

Once a cell differentiates, how does it know to stay that way?

- "Epigenetics"
- Methylation is a large part of the story
- Chromatin modification is another part

Chromatin

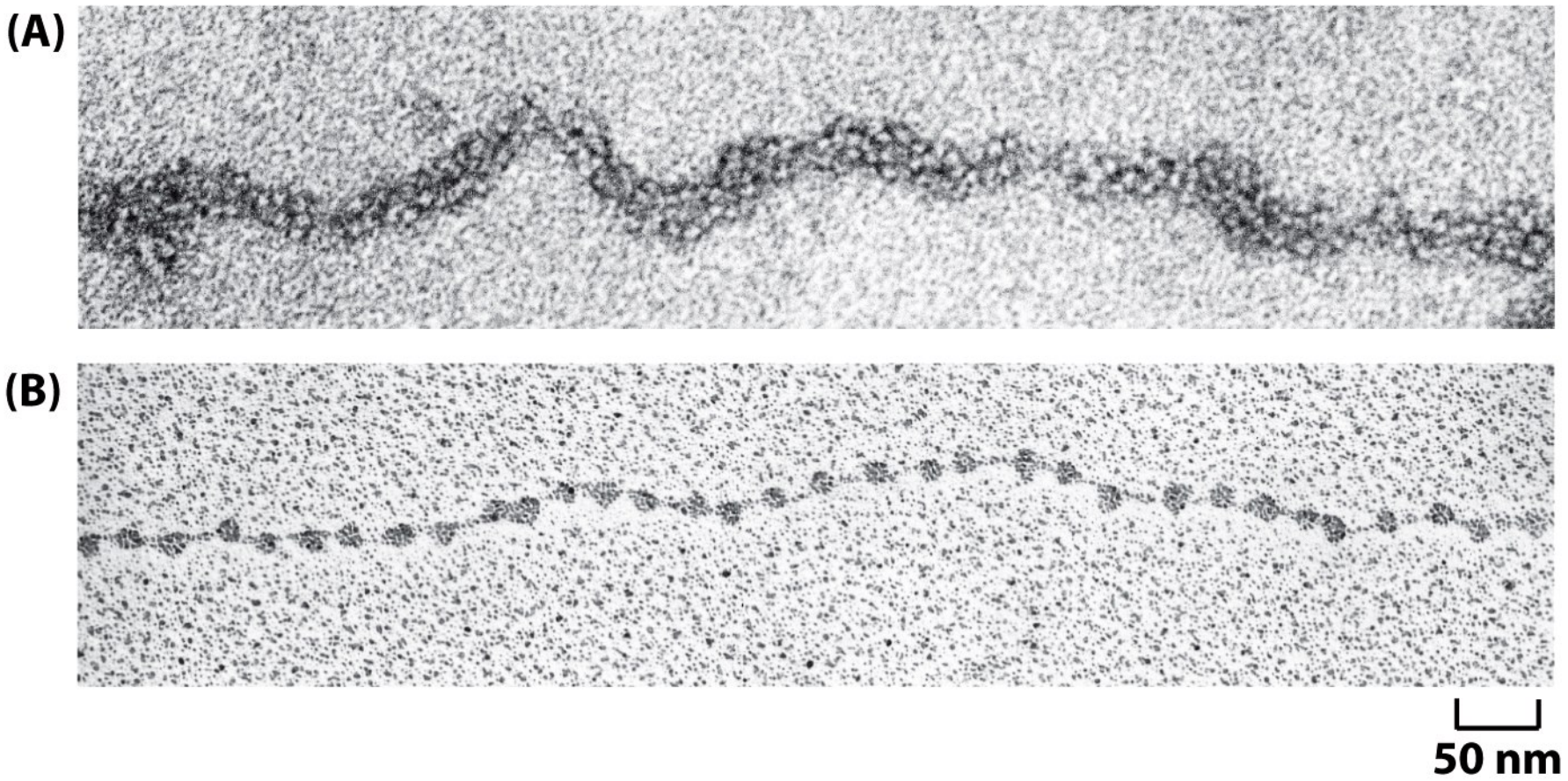
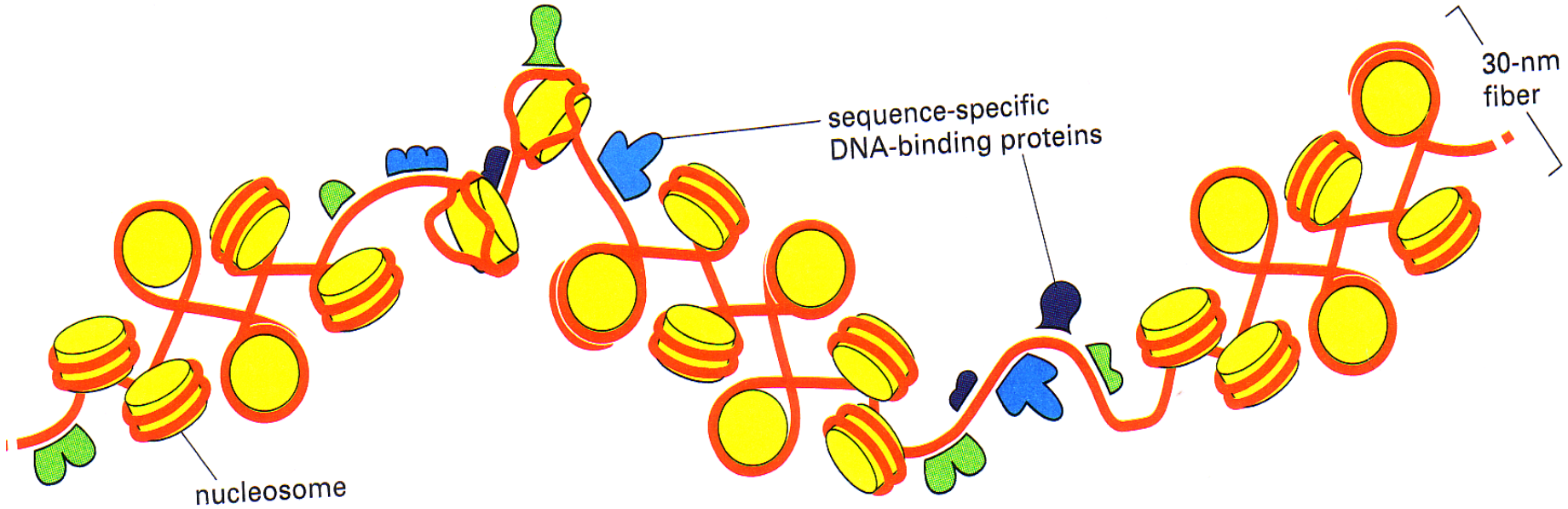


Figure 4-22 Molecular Biology of the Cell 5/e (© Garland Science 2008)


sequence-specific
DNA-binding proteins
30-nm
fiber
nucleosome

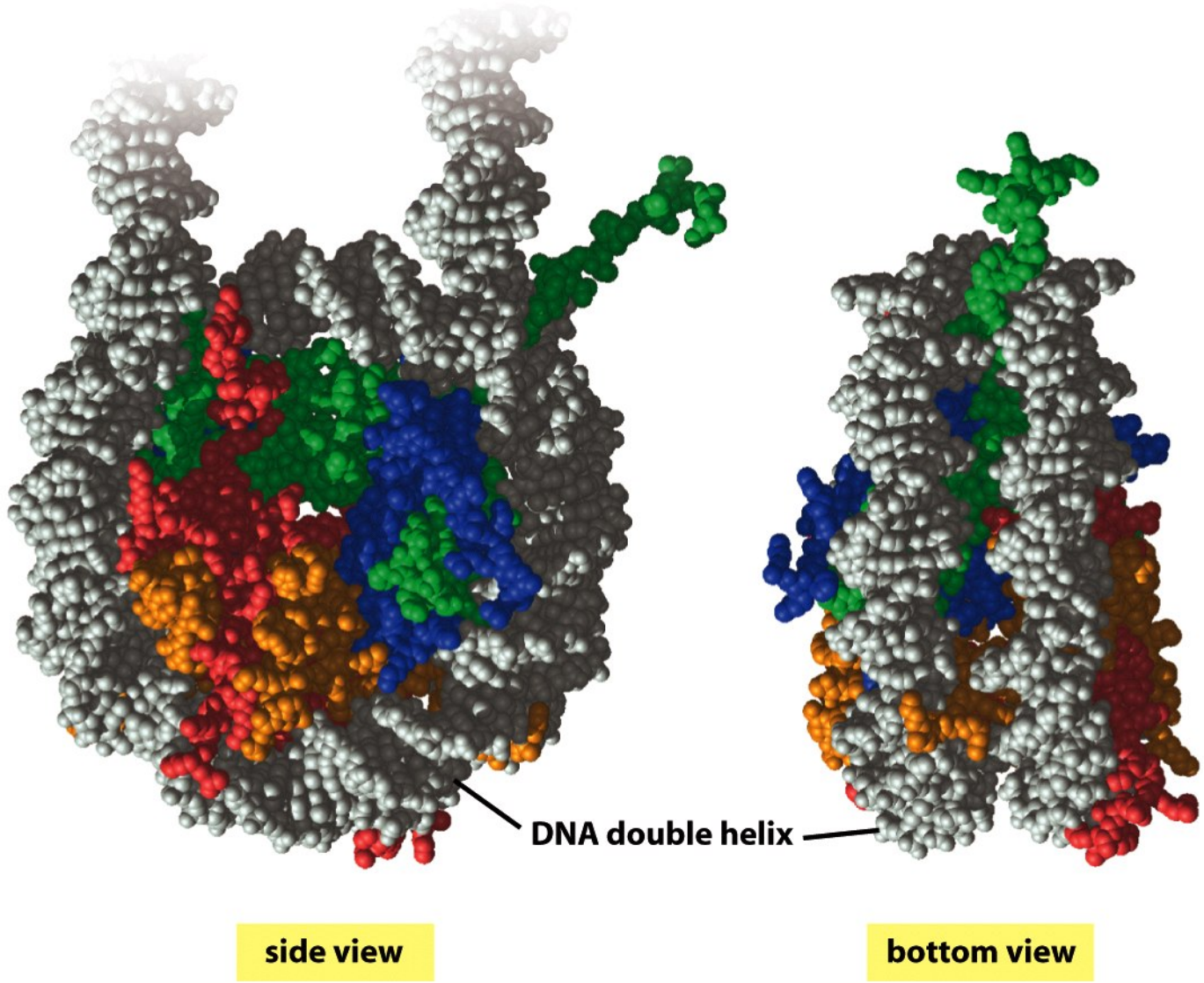
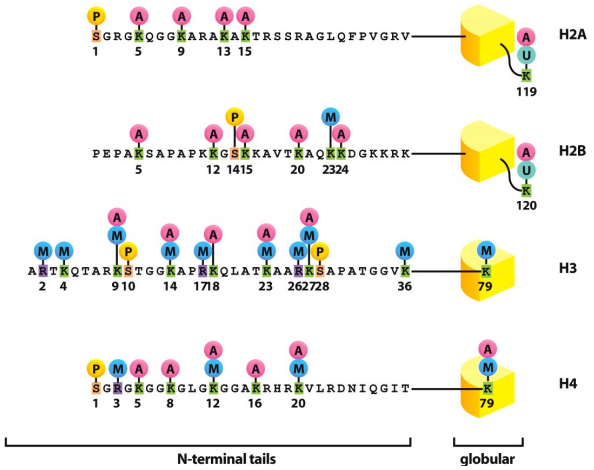


Figure 4-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Histone Codes



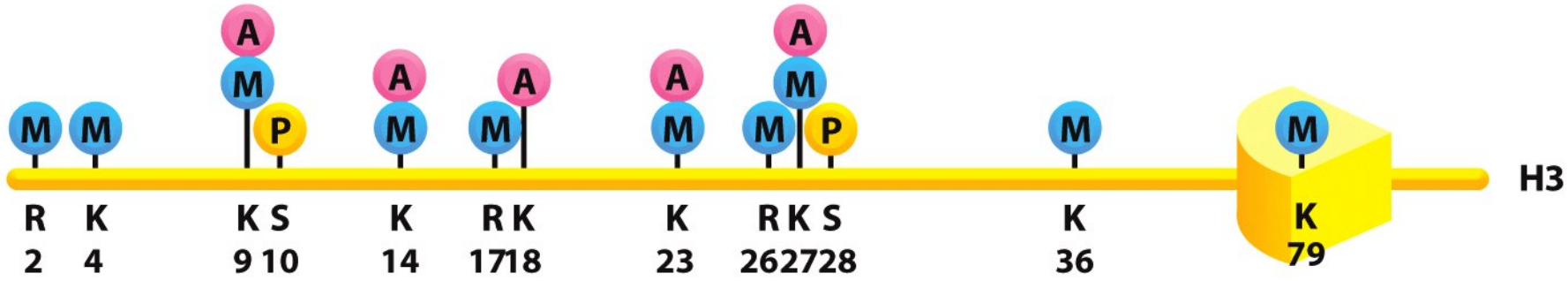


Figure 4-44a Molecular Biology of the Cell 5/e (© Garland Science 2008)

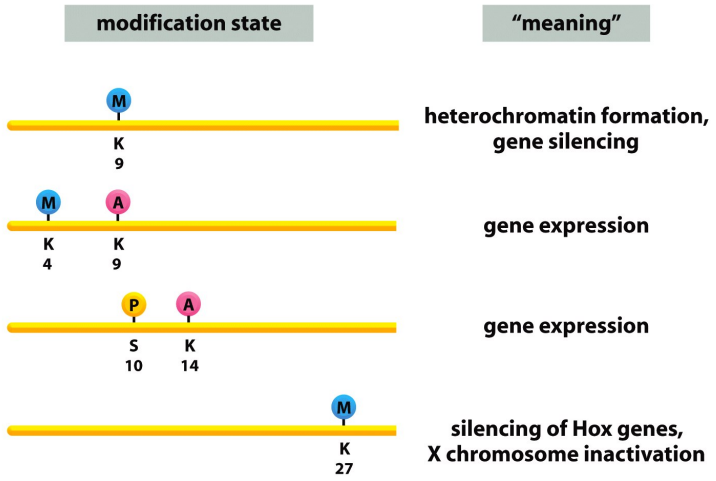


Figure 4-44b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Differentiation

- Once a cell differentiates, how does it know to stay that way?
  - Methylation is a large part of the story
  - Chromatin modification is another part
  - Positive autoregulation of genes is another
    - TF A turns self on (+ others) maintaining A identity
- Consequences:
  - Can't regrow body parts (but salamanders can…)
  - Can't clone (easily)

Stem Cells

Reservoirs of partially undifferentiated cells in many tissues in the body

Replenish/replace dead/damaged cells

Huge therapeutic potential

Best source? Embryonic tissue

⇒ ethical issues

What about cell cultures

⇒ many are basically tumors

Cloning

Need to “undo” all the epigenetic marking added during differentiation, quench the feedback markers, etc.

Dolly the sheep

OCT 3/4 (Octamer binding transcription factor 3/4)

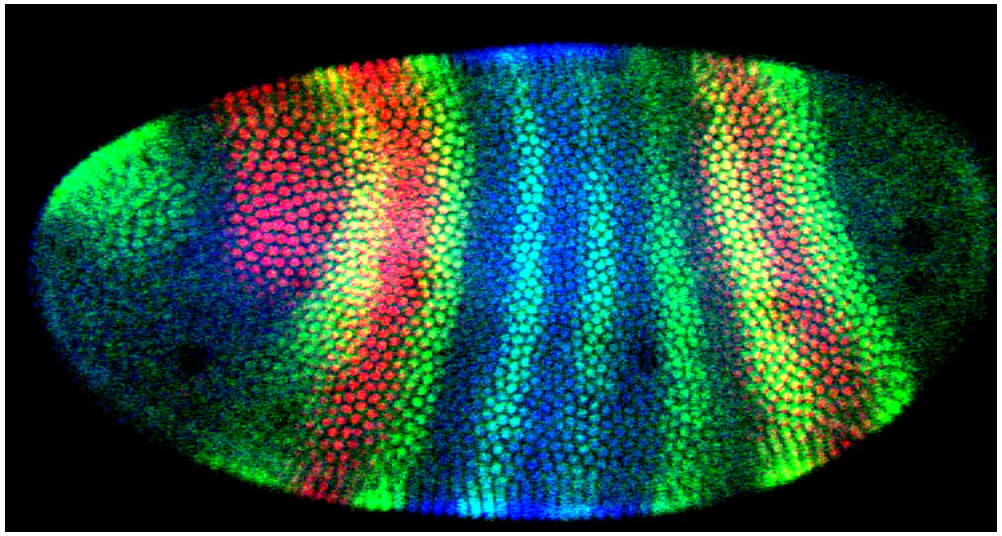
Transcription factor that binds to the octamer motif (5'-ATTTGCAT-3'). Forms a trimeric complex with SOX2 on DNA and controls the expression of a number of genes involved in embryonic development such as YES1, FGF4, UTF1 and ZFP206. Critical for early embryogenesis and for embryonic stem cell pluripotency.

http://www.uniprot.org/uniprot/Q01860

SOX2 (SRY-related high-mobility-group (HMG)-box protein 2)

Transcription factor that forms a trimeric complex with OCT4 on DNA and controls the expression of a number of genes involved in embryonic development such as YES1, FGF4, UTF1 and ZFP206. Critical for early embryogenesis and for embryonic stem cell pluripotency

http://www.uniprot.org/uniprot/P48431



Klf4 (kruppel-like factor 4)

Zinc-finger transcription factor. Contains 3 C2H2-type zinc fingers. May act as a transcriptional activator. Binds the CACCC core sequence. May be involved in the differentiation of epithelial cells and may also function in the development of the skeleton and kidney.

http://www.uniprot.org/uniprot/O43474

MYC (Myc proto-oncogene)

Basic helix-loop-helix transcription factor. Binds DNA both in a non-specific manner and also specifically recognizes the core sequence 5'-CAC[GA]TG-3'. Seems to activate the transcription of growth-related genes. Efficient DNA binding requires dimerization with another bHLH protein. Binds DNA as a heterodimer with MAX. Interacts with TAF1C, SPAG9, PARP10, JARID1A and JARID1B.

http://www.uniprot.org/uniprot/P01106

Stem Cells Again

Great recent progress in making equiv of embryonic stem cells from adult tissues

Takahashi & Yamanaka, *Cell*, 2006

Key? Transfect genes for those 4 transcription factors!

Issues

Myc is a proto-oncogene

Long term stability of derived cells with unnatural expression of these genes is unclear

Delivery: Retro virus

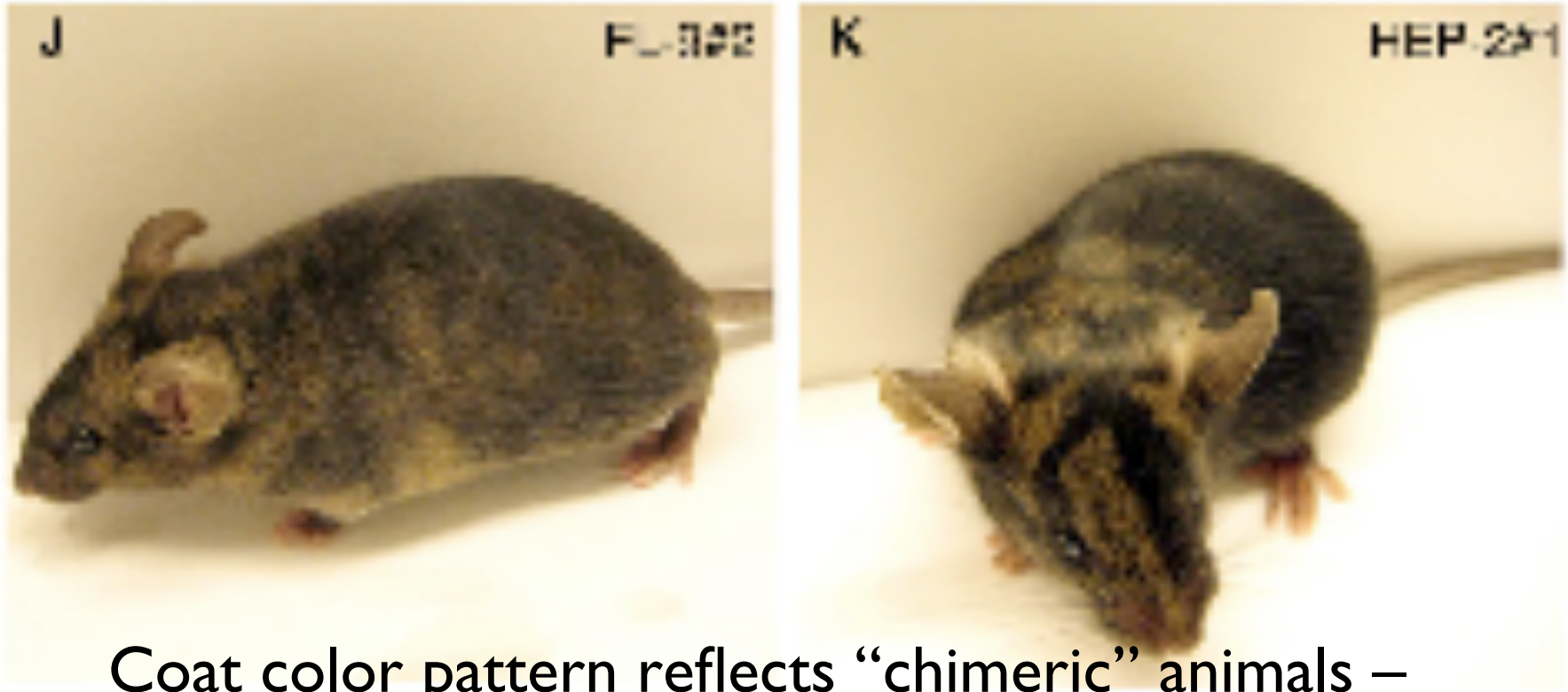
may do damage during integration

Recent Progress

2007: Some other gene combinations work, without Myc

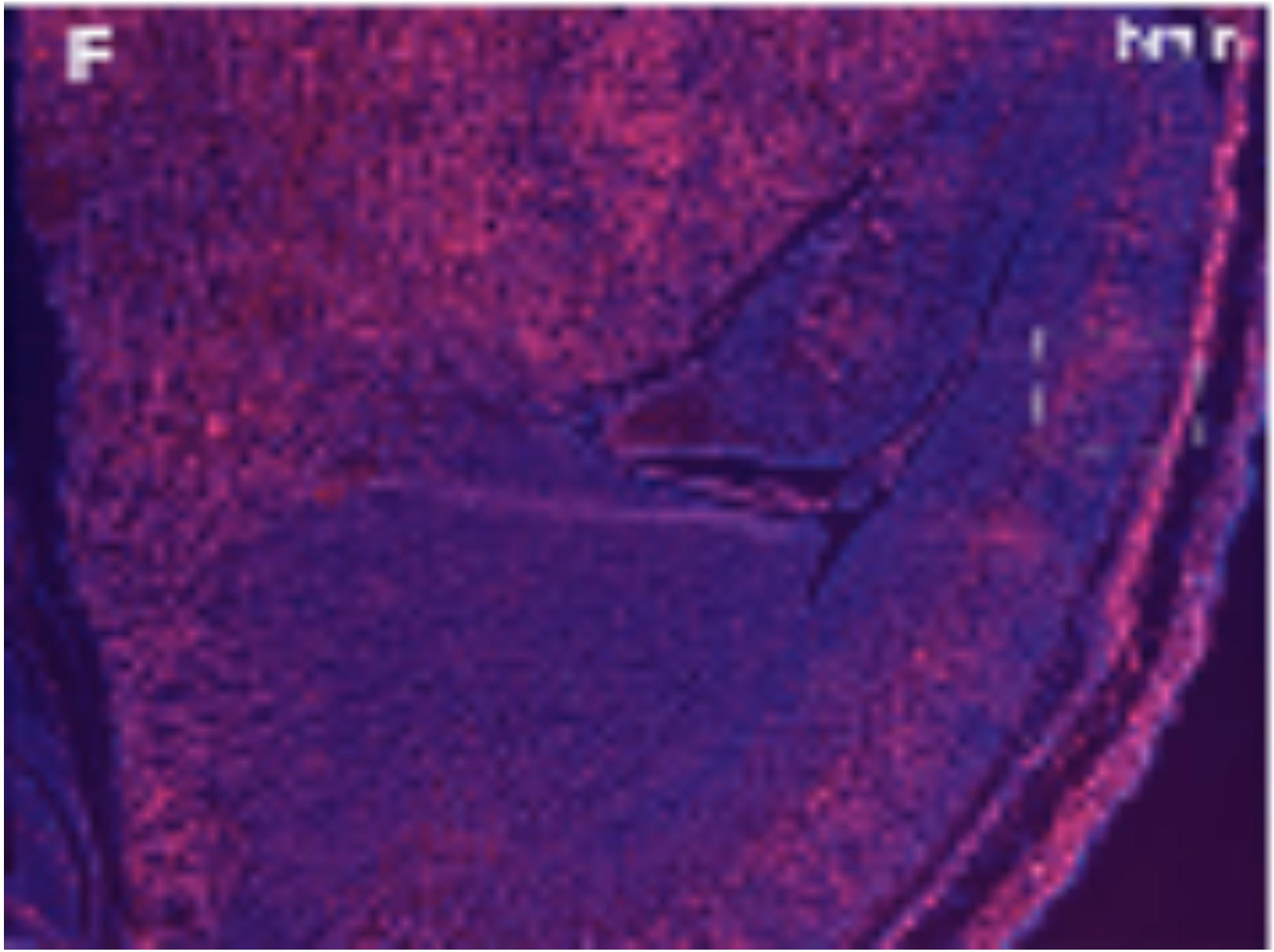
2008: Can use adenoviruses

E.g., Stadtfeld, Nagaya, Utikal, Weir, Hochedlinger, *Science*, Sept 2008.



Coat color pattern reflects “chimeric” animals – otherwise normal, but mosaic of “induced pluripotent stem cells” & normal cells, grown from embryonic fusion

Stadtfeld, *et al.*, 2008



Ditto in brain section Stadtfeld, *et al.*, 2008