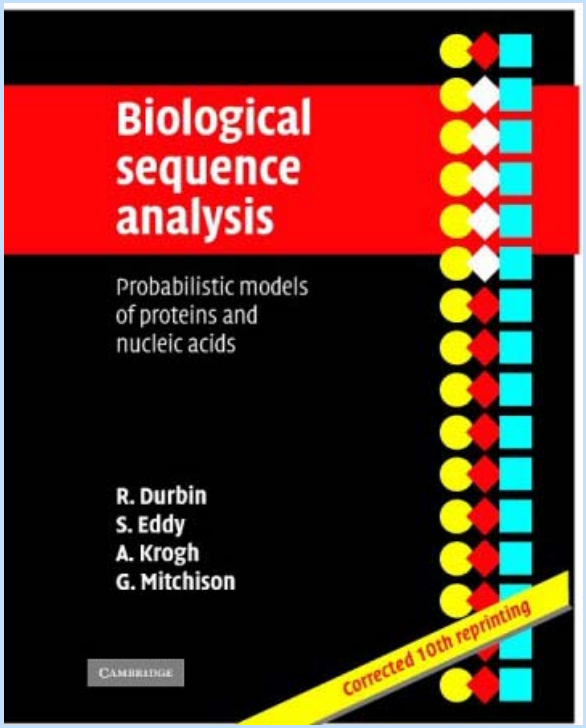
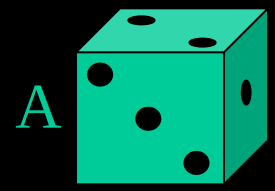
Hidden Markov Models



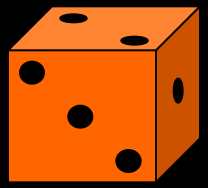
Main source: Durbin et al.,
"Biological Sequence Alignment"
(Cambridge, '98)

The occasionally dishonest casino



A

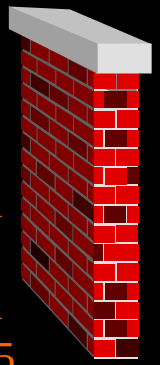
$P_A(1)$ =
$P_A(2)$ =
… = 1/6



$P_{A->B}$ =
$P_{B->A}$ =
1/10

B

$P_B(1)$=0.1
…
$P_B(5)$=0.1
$P_B(6)$ =0.5



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Can we tell when the loaded die is used?

Example - CpG islands

- **CpG islands**:
  - DNA stretches (100~1000bp) with frequent CG pairs (contiguous on same strand).
  - Rare, appear in significant genomic parts.
- **Problem (1)**: Given a short genome sequence, decide if it comes from a CpG island.

Preliminaries: Markov Chains

(S, A, p)

- S: State set
- p: Initial state prob. vector $\{p(x_1=s)\}$ [alternatively, use a begin state]
- A: Transition prob. matrix $a_{st} = P(x_i=t \mid x_{i-1}=s)$

Assumption: $X=x_1 \ldots x_n$ is a random process with *memory length 1*, i.e.: $\forall s_i \in S$

$P(x_i=s_i \mid x_1=s_1,\ldots,x_{i-1}=s_{i-1}) = P(x_i=s_i \mid x_{i-1}=s_{i-1}) = a_{s_{i-1},s_i}$

- Sequence probability:

$$P(X) = p(x_1) \cdot \Pi_{i=2\ldots L} a_{x_{i-1},x_i}$$

Markov Models

- - Transition probs for non-CpG islands
- + Transition probs for CpG islands

-	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

+	A	C	G	T
A	0.180	0.274	0.425	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

CpG islands: Fixed Window

- **Problem (1):** Given a short genome sequence X, decide if it comes from a CpG island.

- **Solution**: Model by a Markov chain. Let
  - a^+_{st}: transition prob. in CpG islands,
  - a^-_{st}: transition prob. outside CpG islands.

  Decide by log-likelihood ratio score:

$$score(X) = \log \frac{P(X \mid CpG-island)}{P(X \mid non-CpG-island)} = \sum_{i=1}^{n} \log \frac{a^+_{x_{i-1},x_i}}{a^-_{x_{i-1},x_i}}$$

$$bits\_score(X) = \frac{1}{n} \sum_{i=1}^{n} \log_2 \frac{a^+_{x_{i-1},x_i}}{a^-_{x_{i-1},x_i}}$$

Discrimination of sequences via Markov Chains

48 CpG islands, tot length ~60K nt. Similar non-CpG.

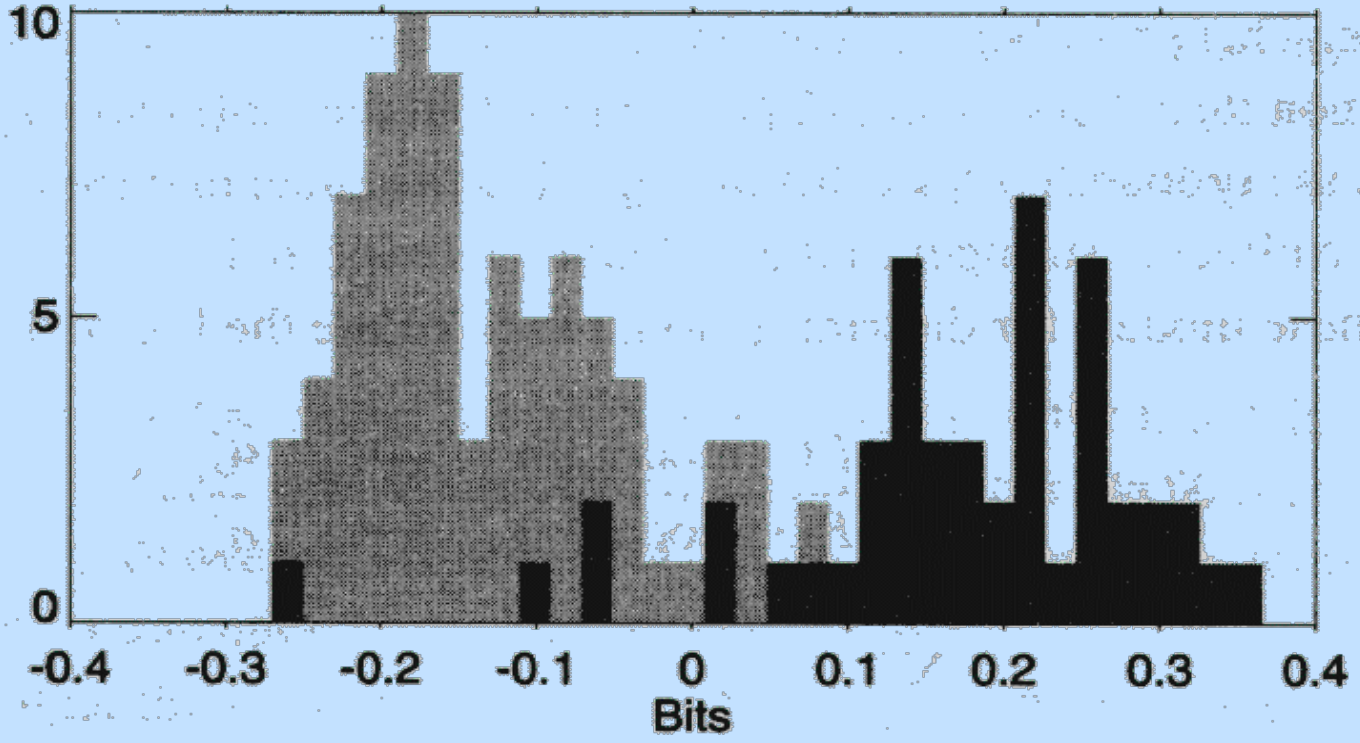


Figure 3.2 *The histogram of the length-normalised scores for all the sequences. CpG islands are shown with dark grey and non-CpG with light grey.*

Durbin et. al, Fig. 3.2

CpG islands – the general case

- **Problem(2):** Detect CpG islands in a long DNA sequence.
- **Naive Solution - Sliding windows**: $\forall 1 \leq k \leq L-l$,
  - window: $X^k = (x_{k+1},\ldots,x_{k+l})$
  - score: $score(X^k)$
  - positive score $\Rightarrow$ potential CpG island

Disadvantage: what is the length of the islands? How do we identify transitions?

Idea: Use Markov chains as before, with additional (hidden) states

Hidden Markov Model (HMM)

Finite set of states, capable of emitting symbols.
Example:
$Q = \{A_+, C_+, G_+, T_+, A_-, C_-, G_-, T_-\}$

Alphabet of symbols
Example: {A, C, G, T}

$M=(\Sigma, Q, \Theta)$

- $\Theta=(A,E)$
- A: Transition prob. a_{kl} $\forall k,l \in Q$
- E: Emission prob. $e_k(b)$ $\forall k \in Q$, $b \in \Sigma$

path $\Pi=\pi_1,\ldots,\pi_n$ (sequence of states - simple Markov chain; convention: π_0 - begin, π_{L+1} - end)

Given sequence $X = (x_1,\ldots,x_L)$:

- $a_{kl} = P(\pi_i=l \mid \pi_{i-1}=k)$,
- $e_k(b) = P(x_i=b \mid \pi_i=k)$

$$P(X,\Pi) = a_{\pi_0,\pi_1} \cdot \Pi_{i=1\ldots L} e_{\pi_i}(x_i) \cdot a_{\pi_i,\pi_{i+1}}$$

Ex.: express $P(X,\Pi)$ in terms of counts

Viterbi's Decoding Algorithm
(finding most probable state path)

Want: path Π maximizing $\mathbf{P(X, \Pi)}$

$v_k(i)$ = prob. of most probable path ending in state k at step i.

Init: $v_0(0) = 1$; $v_k(0)=0 \ \forall k>0$

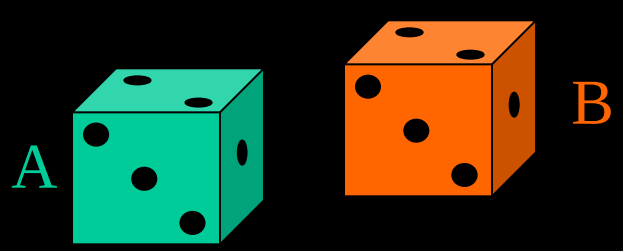
Step: $v_k(i+1)=e_k(x_{i+1})\cdot\max_l\{v_l(i)\cdot a_{lk}\}$

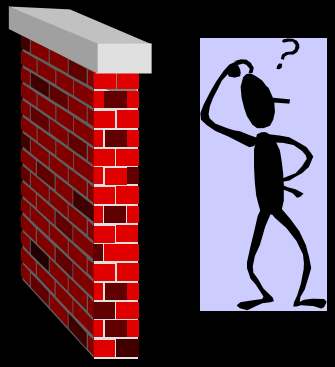
End: $P(X, \Pi^*) = \max_l\{v_l(L) \cdot a_{l0}\}$

Time complexity: $O(Ln^2)$ for n states, L steps

Can find Π^* using back pointers.

The occasionally dishonest casino (2)





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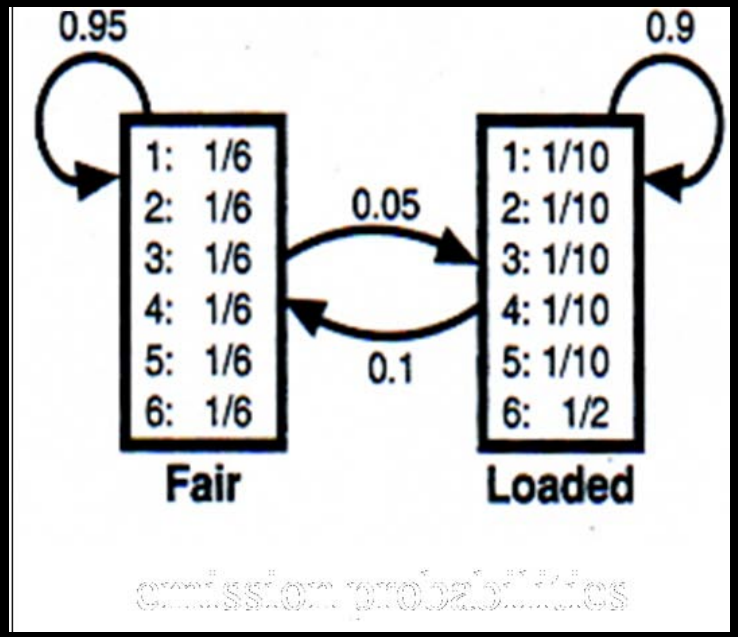
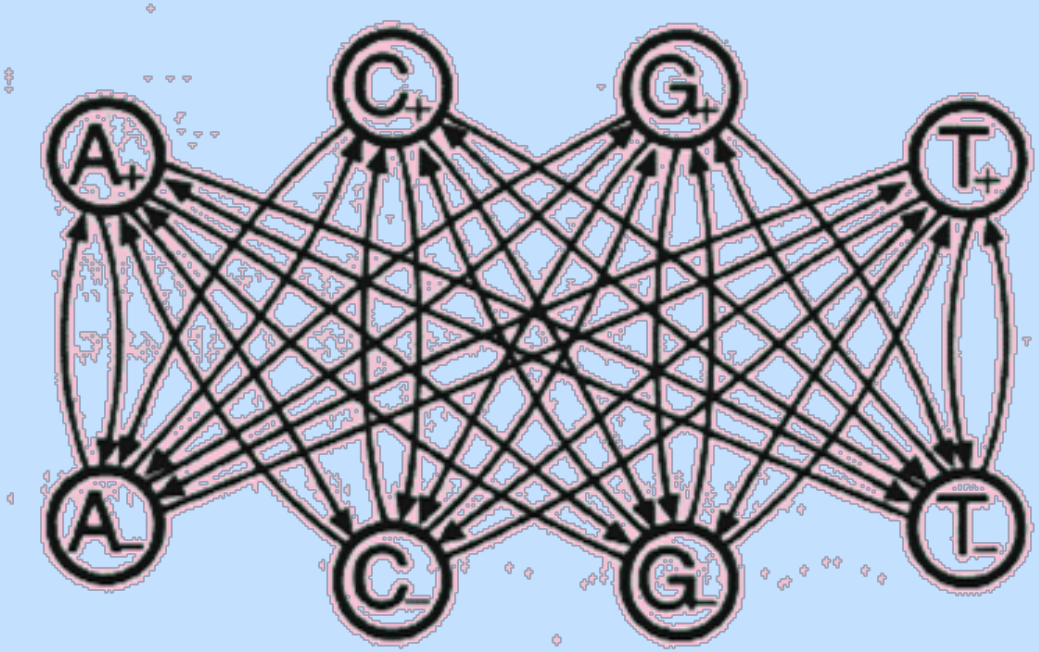


The occasionally dishonest casino (2)

HMM for CpG Islands

- States: A_+ C_+ G_+ T_+ A_- C_- G_- T_-
- Symbols: A C G T A C G T
- Path $\Pi=\pi_1,\ldots,\pi_n$: sequence of states



+	A	C	G	T
A	0.180	0.274	0.425	0.120
C	0.171	0.368	0.274	0.188
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C	0.322	0.298	0.078	0.302
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transition prob.

http://www.cs.huji.ac.il/~cbio/handouts/class4.ppt

Posterior State Probabilities

Goal: calculate $P(\pi_i=k \mid X)$

- **Our strategy:**
- $P(X, \pi_i=k) =$

  $= P(x_1,\ldots,x_i, \pi_i=k) \cdot P(x_{i+1},\ldots,x_L \mid x_1,\ldots,x_i, \pi_i=k)$

  $= P(x_1,\ldots,x_i, \pi_i=k) \cdot P(x_{i+1},\ldots,x_L \mid \pi_i=k)$
- $P(\pi_i=k \mid X) = P(\pi_i=k, X) / P(X)$

➔Need to compute these two terms - and P(X)

Forward Algorithm

Goal: calculate $P(X) = \Sigma_{\Pi} P(X, \Pi)$

Approximation: take max path Π^* from Viterbi alg.

Not justified when $\exists$ several near maximal paths

Exact alg : "Forward Algorithm"

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

- Init: $f_0(0) = 1;$ $f_k(0)=0 \ \forall k>0$
- Step: $f_k(i+1) = e_k(x_{i+1}) \cdot \Sigma_l f_l(i) \cdot a_{lk}$
- End: $P(X) = \Sigma_l f_l(L) \cdot a_{l0}$

Backward Algorithm

- $b_k(i) = P(x_{i+1},\ldots x_L \mid \pi_i=k)$
- <u>init</u>: $\forall k,\ b_k(L) = a_{k0}$
- <u>step</u>: $b_k(i) = \sum_l a_{kl}\cdot e_l(x_{i+1})\cdot b_l(i+1)$
- <u>End</u>: $P(X) = \sum_k a_{0k}\cdot e_k(x_1)\cdot b_k(1)$

Posterior State Probabilities (2)

Goal: calculate $P(\pi_i=k \mid X)$

- Recall:
  - $f_k(i) = P(x_1,\ldots,x_i\ ,\ \pi_i=k)$
  - $b_k(i) = P(x_{i+1},\ldots x_L \mid \pi_i=k)$
  - Each can be used to compute P(X)
- $P(X,\ \pi_i=k)$ =

  $= P(x_1,\ldots,x_i,\ \pi_i=k) \cdot P(x_{i+1},\ldots,x_L \mid x_1,\ldots,x_i,\ \pi_i=k)$

  $= P(x_1,\ldots,x_i,\ \pi_i=k) \cdot P(x_{i+1},\ldots,x_L \mid \pi_i=k)$

  $= f_k(i) \cdot b_k(i)$
- $P(\pi_i=k \mid X) = P(\pi_i=k, X) / P(X)$

Dishonest Casino (3)

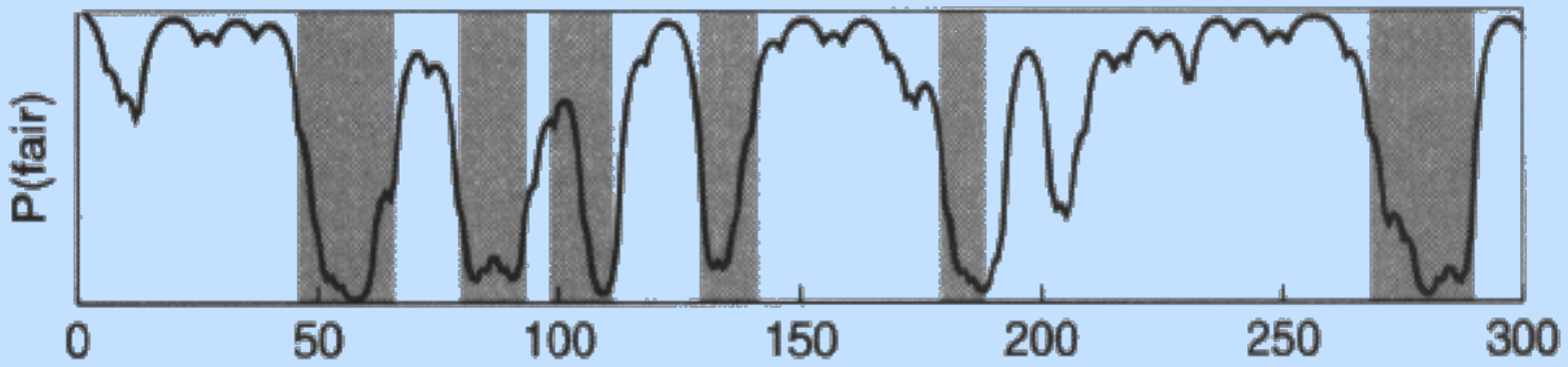


Figure 3.6 *The posterior probability of being in the state corresponding to the fair die in the casino example. The x axis shows the number of the roll. The shaded areas show when the roll was generated by the loaded die.*

Durbin et al. pp. 60

Posterior Decoding

- Now we have $P(\pi_i=k \mid X)$. How do we decode?

1. $\pi_i^* = \text{argmax}_k P(\pi_i=k \mid X)$
   - Good when interested in state at particular point
   - path of states $\pi_1^*,\ldots,\pi_L^*$ may not be legal
2. Define a function of interest $g(i)$ on the states. Compute $G(i|X) = \Sigma_k P(\pi_i=k \mid X) \cdot g(k)$
   - E.g.: $g(i)$ =1 for states in S, 0 on the rest: $G(i|X)$ is posterior prob of symbol i coming from S

e.g., CpG island
$S=\{A_+,C_+,G_+,T_+\}$

Parameter Estimation for HMMs

Log likelihood of model

Input: $X^1,\ldots,X^n$ independent training sequences

Goal: estimation of $\Theta = (A,E)$ (model parameters)

Note: $P(X^1,\ldots,X^n \mid \Theta) = \Pi_{i=1\ldots n} P(X^i \mid \Theta)$ (indep.)

$l(x^1,\ldots,x^n \mid \Theta) = \log P(X^1,\ldots,X^n \mid \Theta) = \sum_{i=1\ldots n} \log P(X^i \mid \Theta)$

Case 1 - Estimation When State Sequence is Known:

A_{kl} = #(occurred $k \to l$ transitions)

$E_k(b)$ = #(emissions of symbol b that occurred in state k)

Max. Likelihood Estimators:

- $a_{kl} = A_{kl} / \sum_{l'} A_{kl'}$
- $e_k(b) = E_k(b) / \sum_{b'} E_k(b')$

small sample, or
prior knowledge correction:

$A'_{kl} = A_{kl} + r_{kl}$

$E'k(b) = E_k(b) + r_k(b)$

- "Dirichlet priors"

Parameter Estimation in HMM

Case 2: -Estimation When States are Unknown

Input: $X^1,\ldots,X^n$ indep training sequences

- guarantees convergence
- monotone
- many local optima
- special case of EM

Baum-Welch alg. (1972):

✶ **Expectation**:

- compute expected no. of k→l state transitions: *(ex.)*

$$P(\pi_i=k,\ \pi_{i+1}=l \mid X, \Theta) = [1/P(x)] \cdot f_k(i) \cdot a_{kl} \cdot e_l(x_{i+1}) \cdot b_l(i+1)$$

$$\Rightarrow A_{kl} = \sum_j [1/P(X^j)] \cdot \sum_i f_k^j(i) \cdot a_{kl} \cdot e_l(x^j_{i+1}) \cdot b_l^j(i+1)$$

- compute expected no. of symbol b appearances in state k

$$E_k(b) = \sum_j [1/P(X^j)] \cdot \sum_{\{i \mid x^j_i=b\}} f_k^j(i) \cdot b_k^j(i)$$ *(ex.)*

✸ **Maximization**:

- re-compute new parameters from A, E using max. likelihood.

repeat (1)+(2) until improvement $\leq \varepsilon$

Profile HMMs (Haussler et al, 1993)

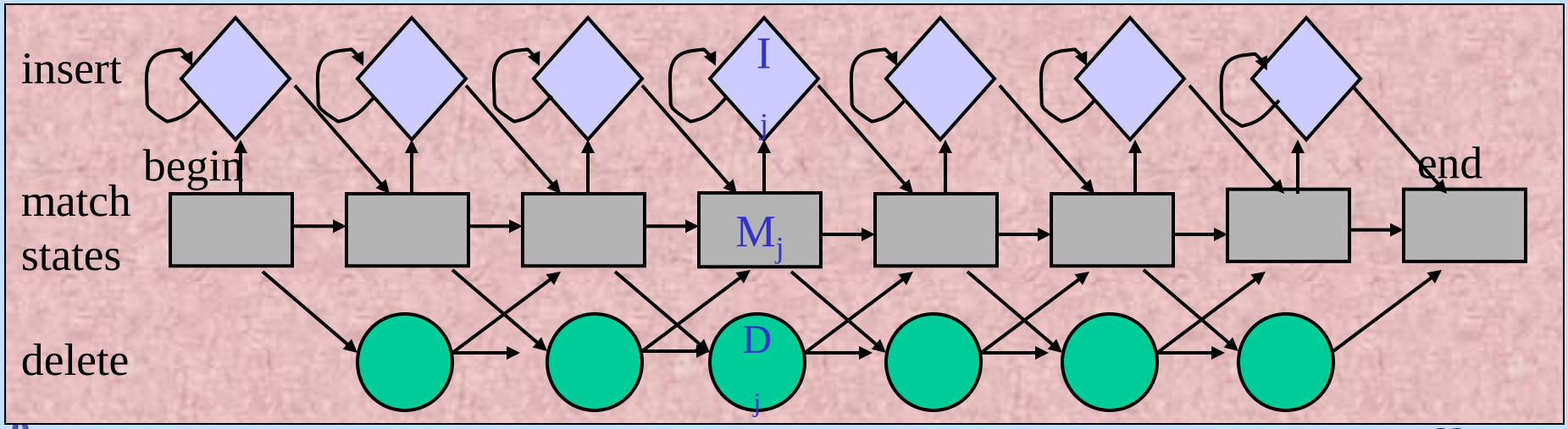
- Ungapped alignment of X against a profile M:
  - $e_i(a)$ = prob. of observing a at position i.
  - $P(X \mid M) = \Pi_{i=1\ldots L} e_i(x_i)$, or
  - $Score(X \mid M) = \sum_{i=1\ldots L} \log [e_i(x_i) / q_{x_i}]$

AG--C
A-AT-C
AG-T-C

background prob.

- indels:

AG---C



Profile HMMs

- Gapped alignment of X against a profile M:

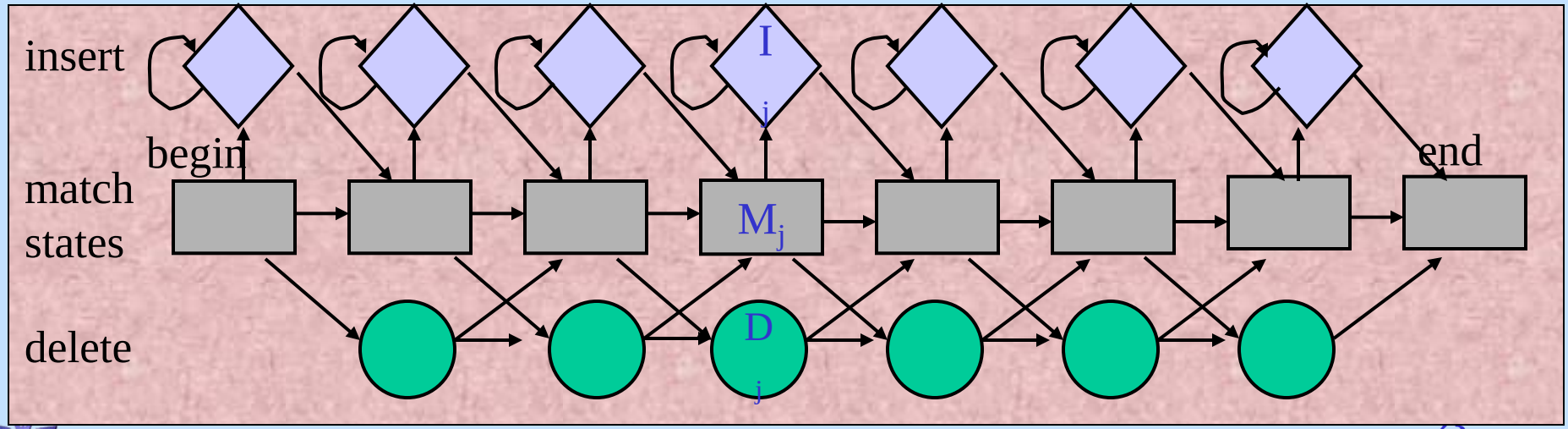
assume $e_{I_j}(a) = q_a$ (backgroud prob.)

$\Rightarrow$ gap of length k contributes to log-odds:

$$\log(a_{M_j,I_j}) + \log(a_{I_j,M_{j+1}}) + (k-1) \cdot \log(a_{I_j,I_j})$$

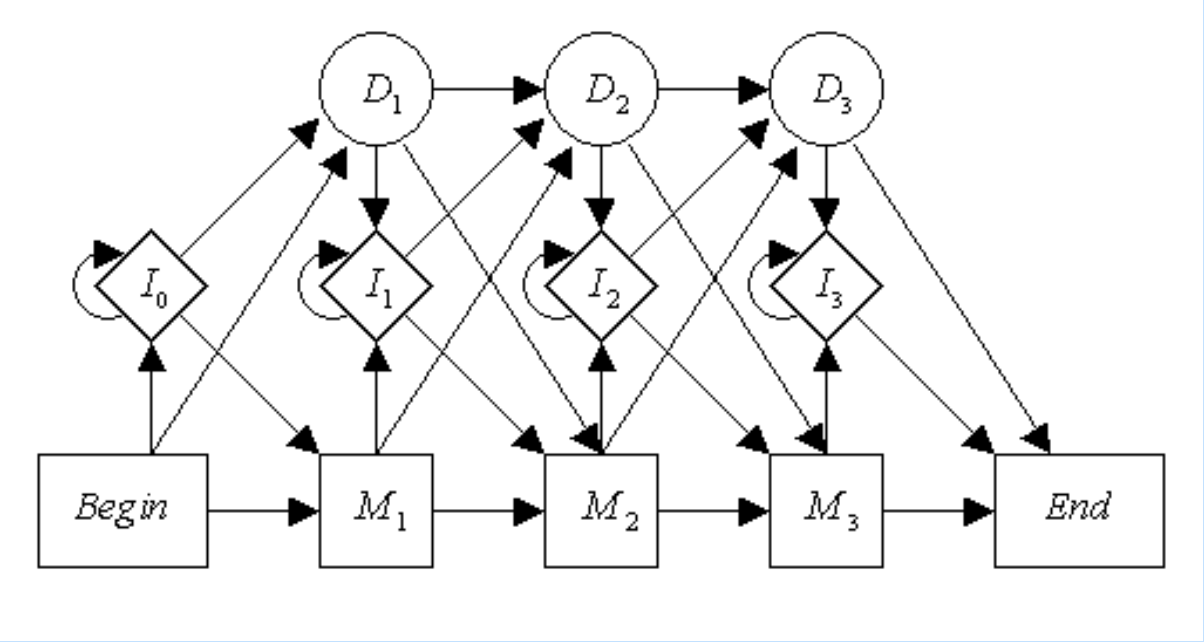
{ gap open } (gap extension)

No log odds contribution from the emission



Profile HMM

- Transition Probabilities
  - *Mi → Mi+1*
  - *Mi → Di+1*
  - *Mi → Ii*
  - *Ii → Mi+1*
  - *Ii → Ii*
  - *Ii → Di+1*
  - *Di → Di+1*
  - *Di → Mi+1*
  - *Di → Ii*
- Emission probabilities
  - $M_i \rightarrow a$
  - $I_i \rightarrow a$



http://www.cs.huji.ac.il/~cbio/handouts/Class6.ppt

Example

- Suppose we are given the aligned sequences

```
**---*
AG---C
A-AT-C
AG-AA-
--AAAC
AG---C
```

  - Suppose also that the "match" positions are marked…

Calculating A, E

count transitions and emissions:

transitions

	0	1	2	3
M-M				
M-D				
M-I				
I-M				
I-D				
I-I				
D-M				
D-D				
D-I				

```
**---*
AG---C
A-AT-C
AG-AA-
--AAAC
AG---C
```

emissions

	0	1	2	3
A				
C				
G				
T				
A				
C				
T				
G				

Calculating A, E

count transitions and emissions:

transitions

	0	1	2	3
M-M	4	3	2	4
M-D	1	1	0	0
M-I	0	0	1	0
I-M	0	0	2	0
I-D	0	0	1	0
I-I	0	0	4	0
D-M	-	0	0	1
D-D	-	1	0	0
D-I	-	0	2	0

```
**---*
AG---C
A-AT-C
AG-AA-
--AAAC
AG---C
```

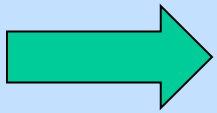
emissions

	0	1	2	3
A	-	4	0	0
C	-	0	0	4
G	-	0	3	0
T	-	0	0	0
A	0	0	6	0
C	0	0	0	0
T	0	0	1	0
G	0	0	0	0

Estimating **Maximum Likelihood** probabilities using fractions

emissions

	0	1	2	3
A	-	4	0	0
C	-	0	0	4
G	-	0	3	0
T	-	0	0	0
A	0	0	6	0
C	0	0	0	0
T	0	0	1	0
G	0	0	0	0

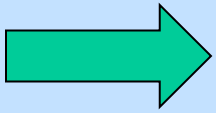


	0	1	2	3
A	-	1	0	0
C	-	0	0	1
G	-	0	1	0
T	-	0	0	0
A	.25	.25	.86	.25
C	.25	.25	0	.25
T	.25	.25	.14	.25
G	.25	.25	0	.25

Estimating ML probabilities (contd)

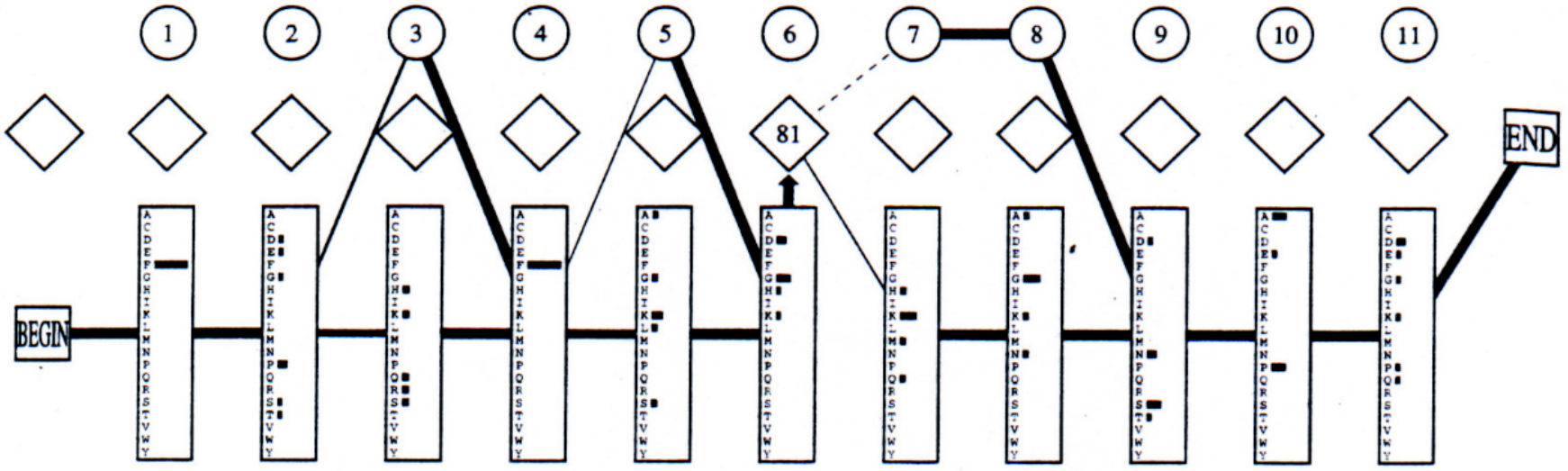
transitions

	0	1	2	3
M-M	4	3	2	4
M-D	1	1	0	0
M-I	0	0	1	0
I-M	0	0	2	0
I-D	0	0	1	0
I-I	0	0	4	0
D-M	-	0	0	1
D-D	-	1	0	0
D-I	-	0	2	0



	0	1	2	3
M-M	.8	.75	.66	1.0
M-D	.2	.25	0	0
M-I	0	0	.33	0
I-M	.33	.33	.28	.33
I-D	.33	.33	.14	.33
I-I	.33	.33	.57	.33
D-M	-	0	0	1
D-D	-	1	0	0
D-I	-	0	1	0

HMM from multiple alignment…

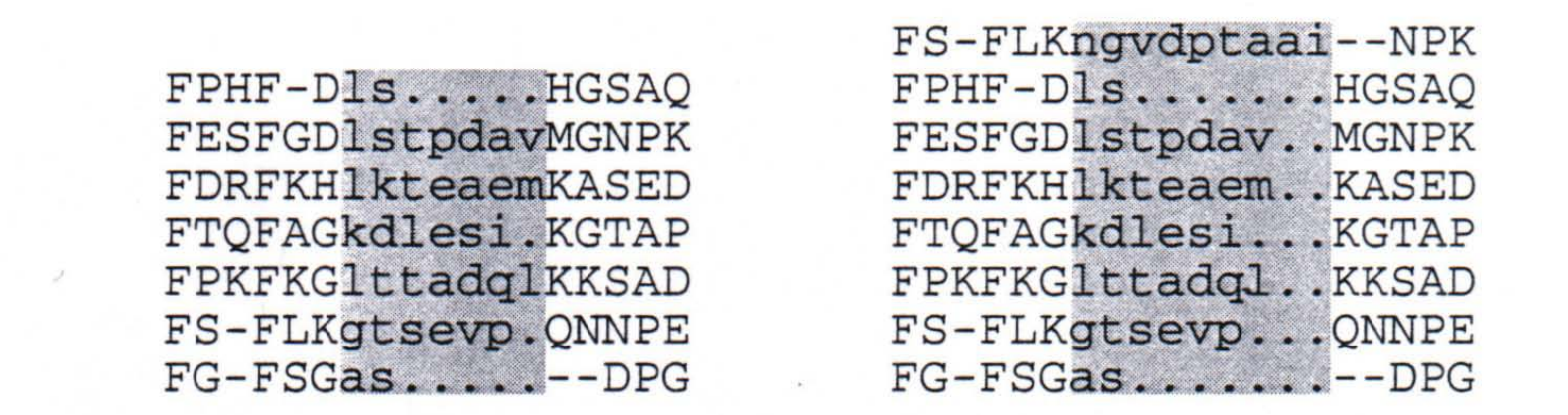



```
FPHF-DLS-----HGSAQ
FESFGDLSTPDAVMGNPK
FDRFKHLKTEAEMKASED
FTQFAG-KDLESIKGTAP
FPKFKGLTTADQLKKSAD
FS-FLK-GTSEVPQNNPE
FG-FSG----AS---DPG
```

Shade: insert

.. and multiple alignment from a given HMM

- Align each sequence to the profile separately



- Right: a new sequence realigend with the model
- Inserts are unaligned.

Searching with Profile HMMs

Compute: $\log \frac{P(X|Model)}{P(X|random)}$

$\Pi_i q_{x_i}$

$V_j^M(i)$: log odds of best path matching $x_1,\ldots,x_i$ to submodel up to level j, ending with x_i emitted by state M_j

$V_j^I(i)$: same, ending with x_i emitted by state I_j

$V_j^D(i)$: score for best path ending in D_j after x_i has been emitted (and x_{i+1} has not been emitted yet)

- $V_j^M(i) = \log [e_{Mj}(x_i) / q_{xi}] + \max \{ V_{j-1}^M(i-1)+\log(a_{Mj-1,Mj}), V_{j-1}^I(i-1)+\log(a_{Ij-1,Mj}), V_{j-1}^D(i-1)+\log(a_{Dj-1,Mj}) \}$

- $V_j^I(i) = \log [e_{Ij}(x_i) / q_{xi}] + \max \{ V_j^M(i-1)+\log(a_{Mj-1,Ij}), V_j^I(i-1)+\log(a_{Ij,Ij}), V_j^D(i-1)+\log(a_{Dj,Ij}) \}$

- $V_j^D(i) = \max \{V_{j-1}^M(i)+\log(a_{Mj-1,Dj}), V_{j-1}^I(i)+\log(a_{Ij-1,Dj}), V_{j-1}^D(i)+\log(a_{Dj-1,Dj}) \}$

Training a profile HMM from unaligned sequences

- choose length of the profile HMM, initialize parameters
- train the model using Baum-Welch
- obtain MA with the resulting profile as before.

(Formulas inlc. forward/backward – in handout)

An Illustrative Study

"HMMs in Computational Biology", Krogh, Brown, Mian, Sjoalnder, Haussler '93

- Globin experiment:
  - Heme-containing proteins, involved in the storage and transport of oxygen
  - 625 globins from Swissprot, ave. legnth 145AA
  - Training set: 400 sequences
  - Built model and ran it against test globins and all Swissprot proteins (25K).

Representative globins

```
Helix                AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBBCCCCCCCCCCCC    DDDDDDDEE
HBA_HUMAN  ---------VLSPADKTNVKAAWGKVGA--HAGEYGAEALERMFLSFPTTKTYFPHF-DLS-----HGSA
HBB_HUMAN  --------VHLTPEEKSAVTALWGKV----NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNP
MYG_PHYCA  ---------VLSEGEWQLVLHVWAKVEA--DVAGHGQDILIRLFKSHPETLEKFDRFKHLKTEAEMKASE
GLB3_CHITP ----------LSADQISTVQASFDKVKG------DPVGILYAVFKADPSIMAKFTQFAG-KDLESIKGTA
GLB5_PETMA PIVDTGSVAPLSAAEKTKIRSAWAPVYS--TYETSGVDILVKFFTSTPAAQEFFPKFKGLTTADQLKKSA
LGB2_LUPLU --------GALTESQAALVKSSWEEFNA--NIPKHTHRFFILVLEIAPAAKDLFS-FLK-GTSEVPQNNP
GLB1_GLYDI ---------GLSAAQRQVIAATWKDIAGADNGAGVGKDCLIKFLSAHPQMAAVFG-FSG----AS---DP

Helix      EEEEEEEEEEEEEEEEEE            FFFFFFFFFFFF  FFGGGGGGGGGGGGGGGGGG
HBA_HUMAN  QVKGHGKKVADALTNAVAHV---D--DMPNALSALSDLHAHKL--RVDPVNFKLLSHCLLVTLAAHLPAE
HBB_HUMAN  KVKAHGKKVLGAFSDGLAHL---D--NLKGTFATLSELHCDKL--HVDPENFRLLGNVLVCVLAHHFGKE
MYG_PHYCA  DLKKHGVTVLTALGAILKK----K-GHHEAELKPLAQSHATKH--KIPIKYLEFISEAIIHVLHSRHPGD
GLB3_CHITP PFETHANRIVGFFSKIIGEL--P---NIEADVNTFVASHKPRG---VTHDQLNNFRAGFVSYMKAHT--D
GLB5_PETMA DVRWHAERIINAVNDAVASM--DDTEKMSMKLRDLSGKHAKSF--QVDPQYFKVLAAVIADTVAAG----
LGB2_LUPLU ELQAHAGKVFKLVYEAAIQLQVTGVVVTDATLKNLGSVHVSKG---VADAHFPVVKEAILKTIKEVVGAK
GLB1_GLYDI GVAALGAKVLAQIGVAVSHL--GDEGKMVAQMKAVGVRHKGYGNKHIKAQYFEPLGASLLSAMEHRIGGK

Helix       HHHHHHHHHHHHHHHHHHHHHHHHH
HBA_HUMAN  FTPAVHASLDKFLASVSTVLTSKYR------
HBB_HUMAN  FTPPVQAAYQKVVAGVANALAHKYH------
MYG_PHYCA  FGADAQGAMNKALELFRKDIAAKYKELGYQG
GLB3_CHITP FA-GAEAAWGATLDTFFGMIFSKM-------
GLB5_PETMA -----DAGFEKLMSMICILLRSAY-------
LGB2_LUPLU WSEELNSAWTIAYDELAIVIKKEMNDAA---
GLB1_GLYDI MNAAAKDAWAAAYADISGALISGLQS-----
```

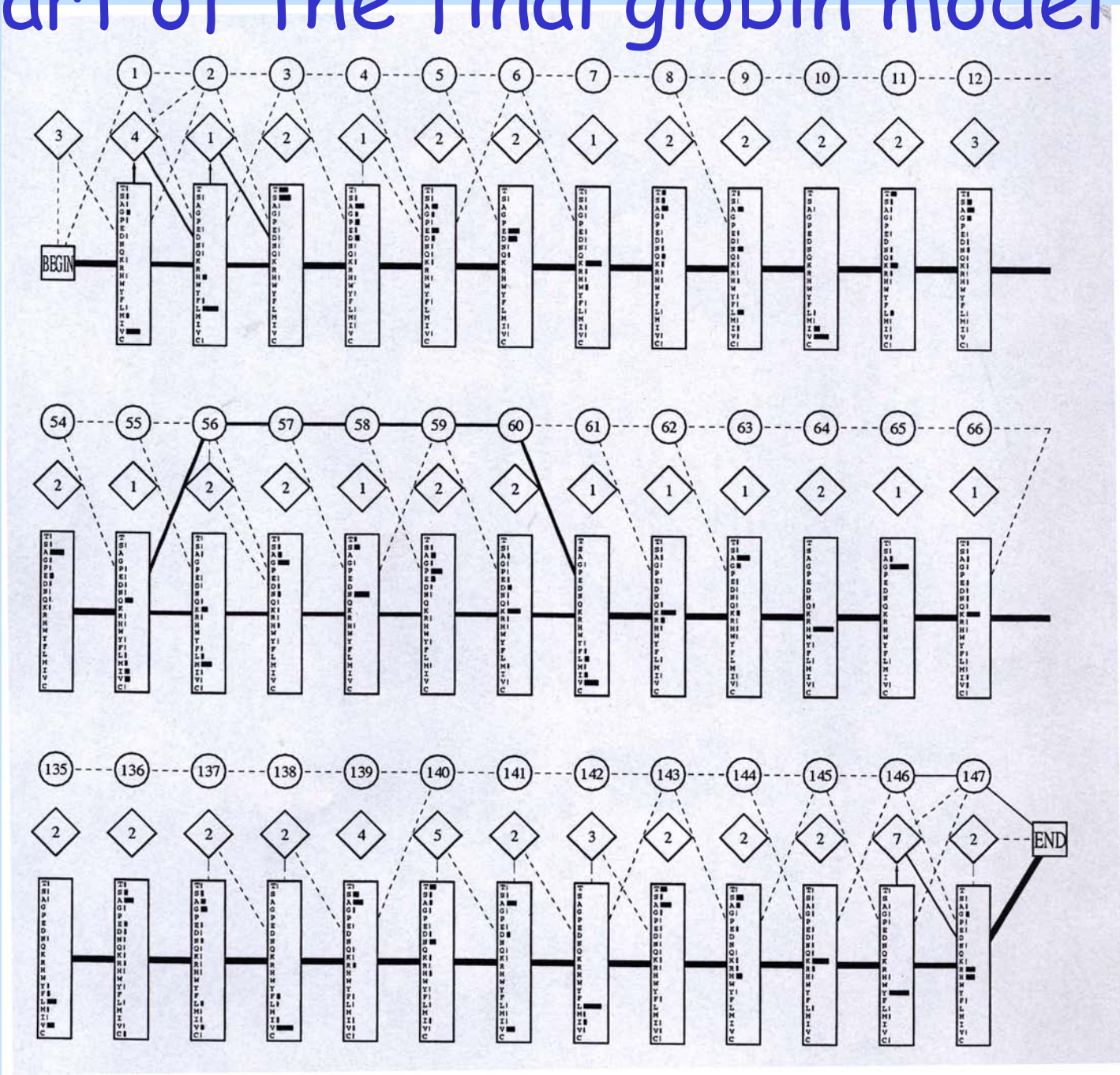
Alignment from Bashford et al 87

A-H: alpha helices

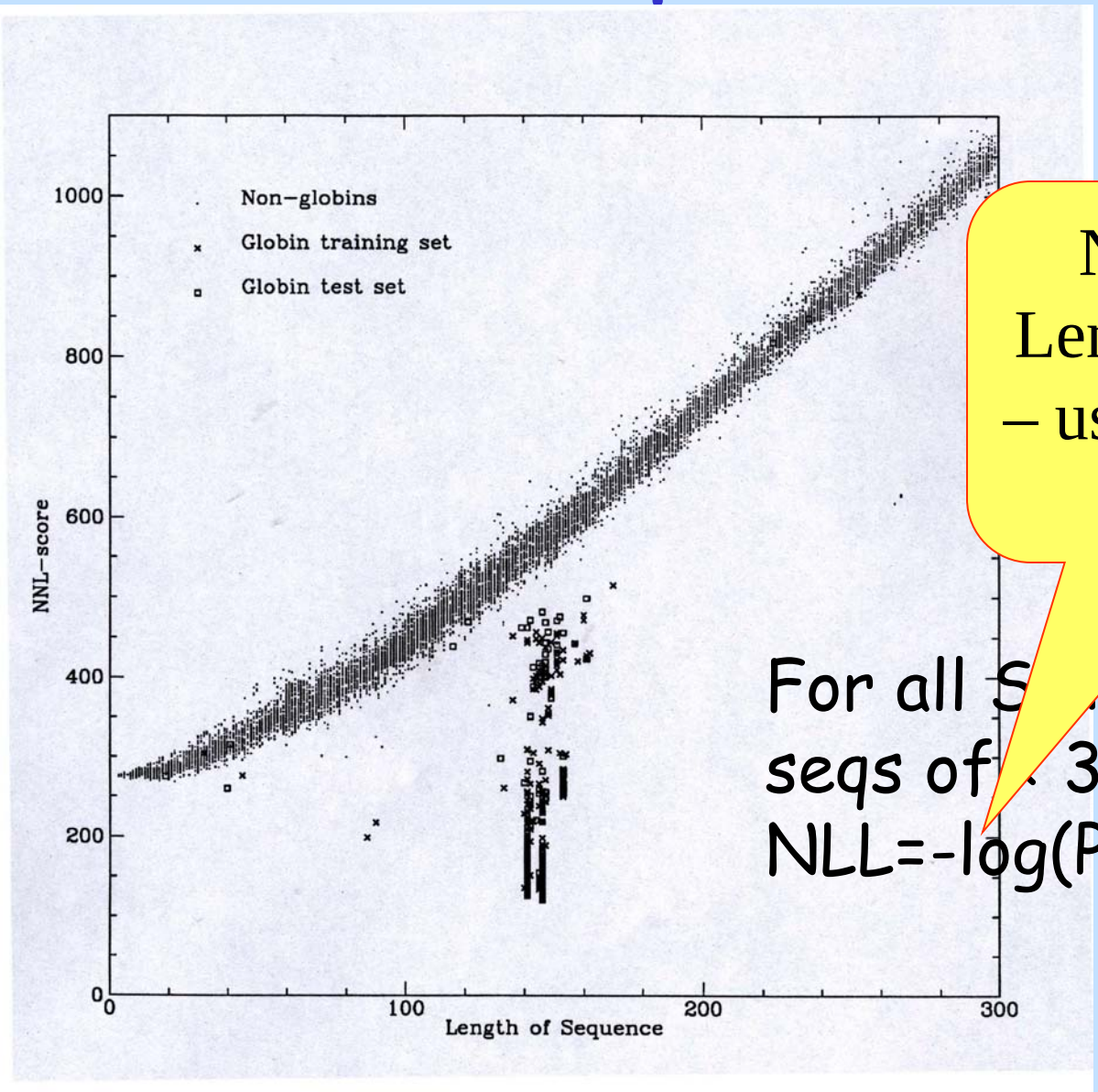
Realignment by trained HMM

```
Helix                AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBBCCCCCCCCCCCC    DDDDDDDEE
                     ****************+   ++++++++++++++++++++++++++++           +
HBA_HUMAN  V.........LSPADKTNVKAAWGKVGA..HAGEYGAEALERMFLSFPTTKTYFPHF-DLSHGSAQ----
HBB_HUMAN  Vh........LTPEEKSAVTALWGKV--..NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNP
MYG_PHYCA  V.........LSEGEWQLVLHVWAKVEA..DVAGHGQDILIRLFKSHPETLEKFDRFKHLKTEAEMKASE
GLB3_CHITP -.........LSADQISTVQASFDKV--..KGDPVG--ILYAVFKADPSIMAKFTQF-AGKDLESIKGTA
GLB5_PETMA PivdtgsvapLSAAEKTKIRSAWAPVYS..TYETSGVDILVKFFTSTPAAQEFFPKFKGLTTADQLKKSA
LGB2_LUPLU Ga........LTESQAALVKSSWEEFNA..NIPKHTHRFFILVLEIAPAAKDLF-SFLKGTSEVPQ-NNP
GLB1_GLYDI G.........LSAAQRQVIAATWKDIAGadNGAGVGKDCLIKFLSAHPQMAAVF-GF----SGASD---P

Helix      EEEEEEEEEEEEEEEEEE            FFFFFFFFF   FFFFFGGG GGGGGGGGGGGGGGGG
           +******************            *********           ***************+
HBA_HUMAN  -VKGHGKKVADALTNAVAHVDD.....MPNALSALSDLHA...HKLRVDPV.NFKLLSHCLLVTLAAHLP
HBB_HUMAN  KVKAHGKKVLGAFSDGLAHLDN.....LKGTFATLSELHC...DKLHVDPE.NFRLLGNVLVCVLAHHFG
MYG_PHYCA  DLKKHGVTVLTALGAILKKKGH.....HEAELKPLAQSHA...TK-HKIPIkYLEFISEAIIHVLHSRHP
GLB3_CHITP PFETHANRIVGFFSKIIGELPN.....IEADVNTFVASHK...PR-GVTHD.QLNNFRAGFVSYMKAH--
GLB5_PETMA DVRWHAERIINAVNDAVASMDDtek..MSMKLRDLSGKHA...KSFQVDPQ.YFKVLAAVIADTVAA---
LGB2_LUPLU ELQAHAGKVFKLVYEAAIQLQVtgvvvTDATLKNLGSVHV...SK-GVADA.HFPVVKEAILKTIKEVVG
GLB1_GLYDI GVAALGAKVLAQIGVAVSHLGDegk..MVAQMKAVGVRHKgygNK-HIKAQ.YFEPLGASLLSAMEHRIG

Helix        HHHHHHHHHHHHHHHHHHHHHHHHH
             ++++++++++++++++++++++++
HBA_HUMAN  AEFTPAVHASLDKFLASVSTVLTSKY......R
HBB_HUMAN  KEFTPPVQAAYQKVVAGVANALAHKY......H
MYG_PHYCA  GDFGADAQGAMNKALELFRKDIAAKYkelgyqG
GLB3_CHITP TDF-AGAEAAWGATLDTFFGMIFSKM......-
GLB5_PETMA GD------AGFEKLMSMICILLRSAY......-
LGB2_LUPLU AKWSEELNSAWTIAYDELAIVIKKEMnda...A
GLB1_GLYDI GKMNAAAKDAWAAAYADISGALISGLq.....S
```

Part of the final globin model



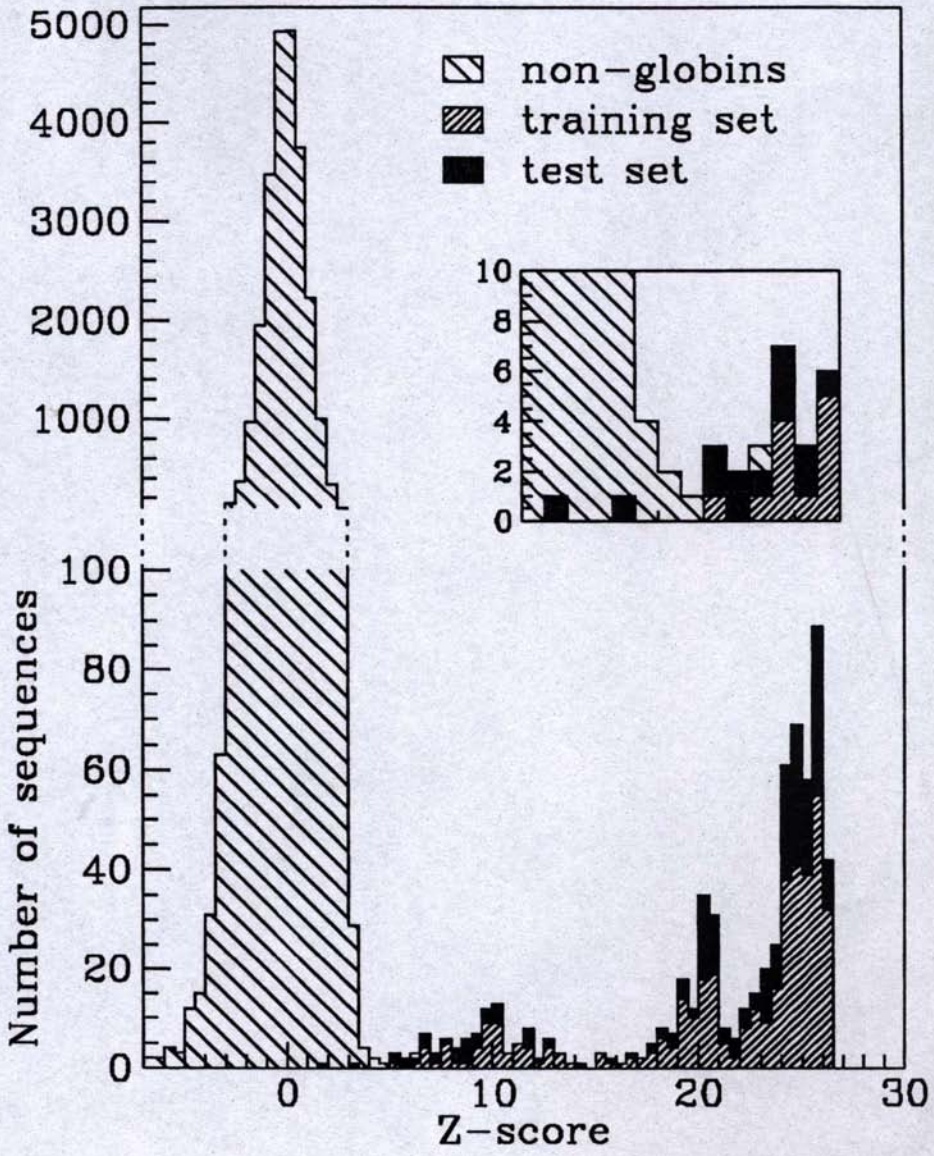
Score vs sequence length



Negative LL.
Length dependent – using log odds is preferable

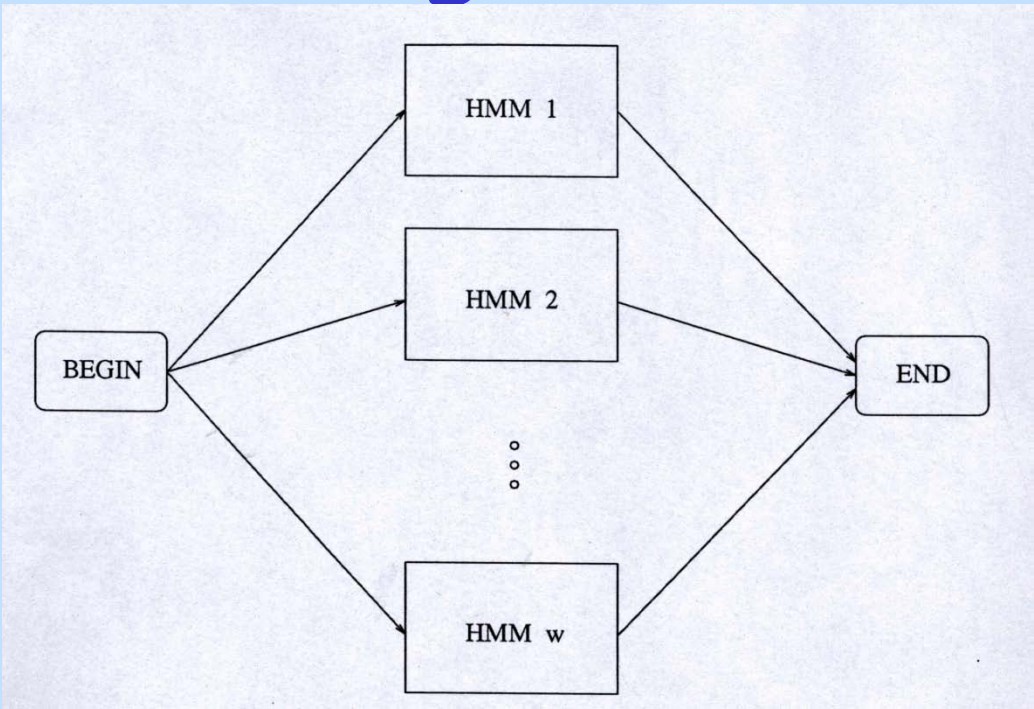
For all Swissprot seqs of ≤ 300AA
NLL=-log(P(seq|model))

Z-score distribution



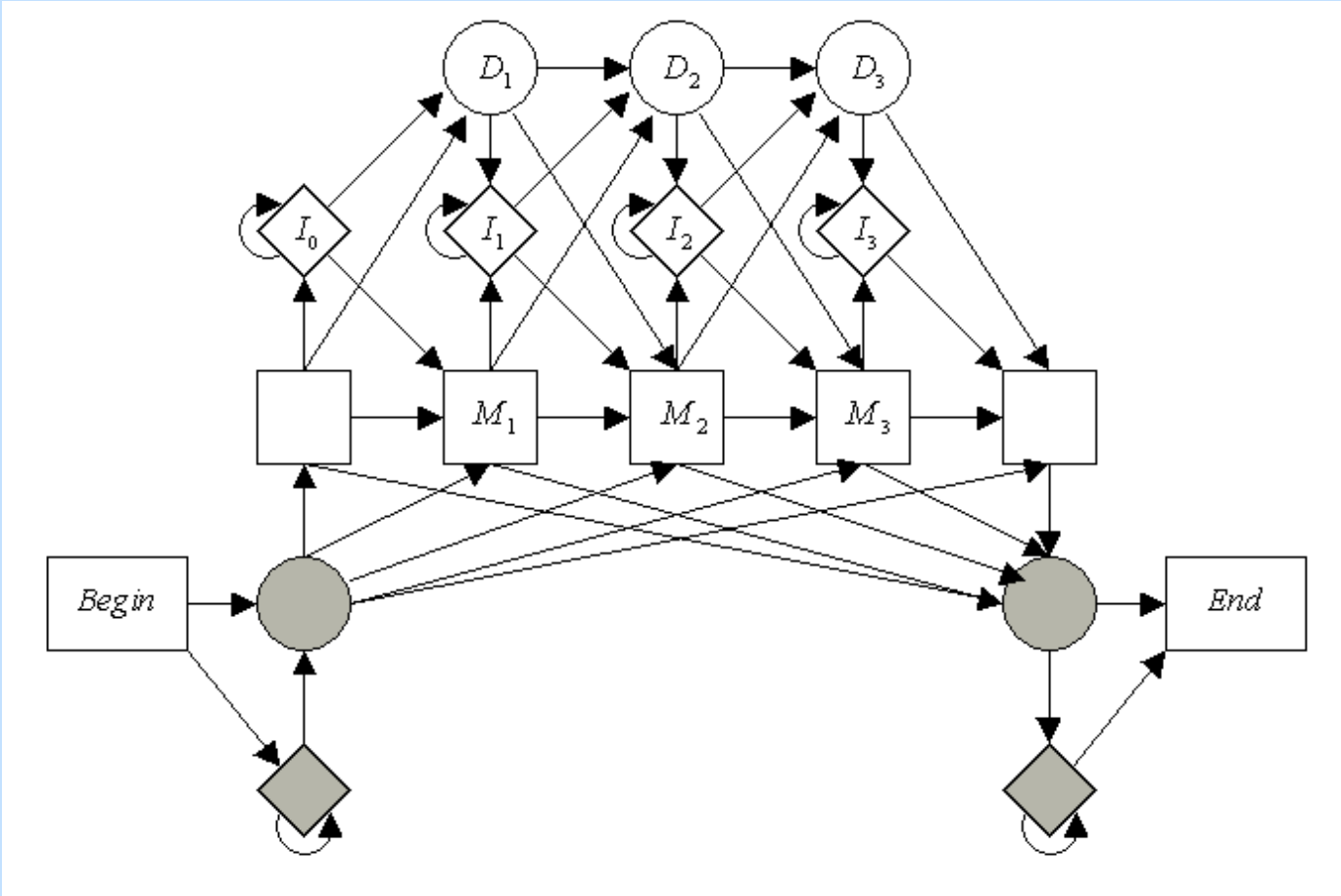
- Z-score: (S-E(S)) / sd(S)
- On ~25K proteins, cutoff 5 misses 2/628 globins with no fp

Discovering subfamilies



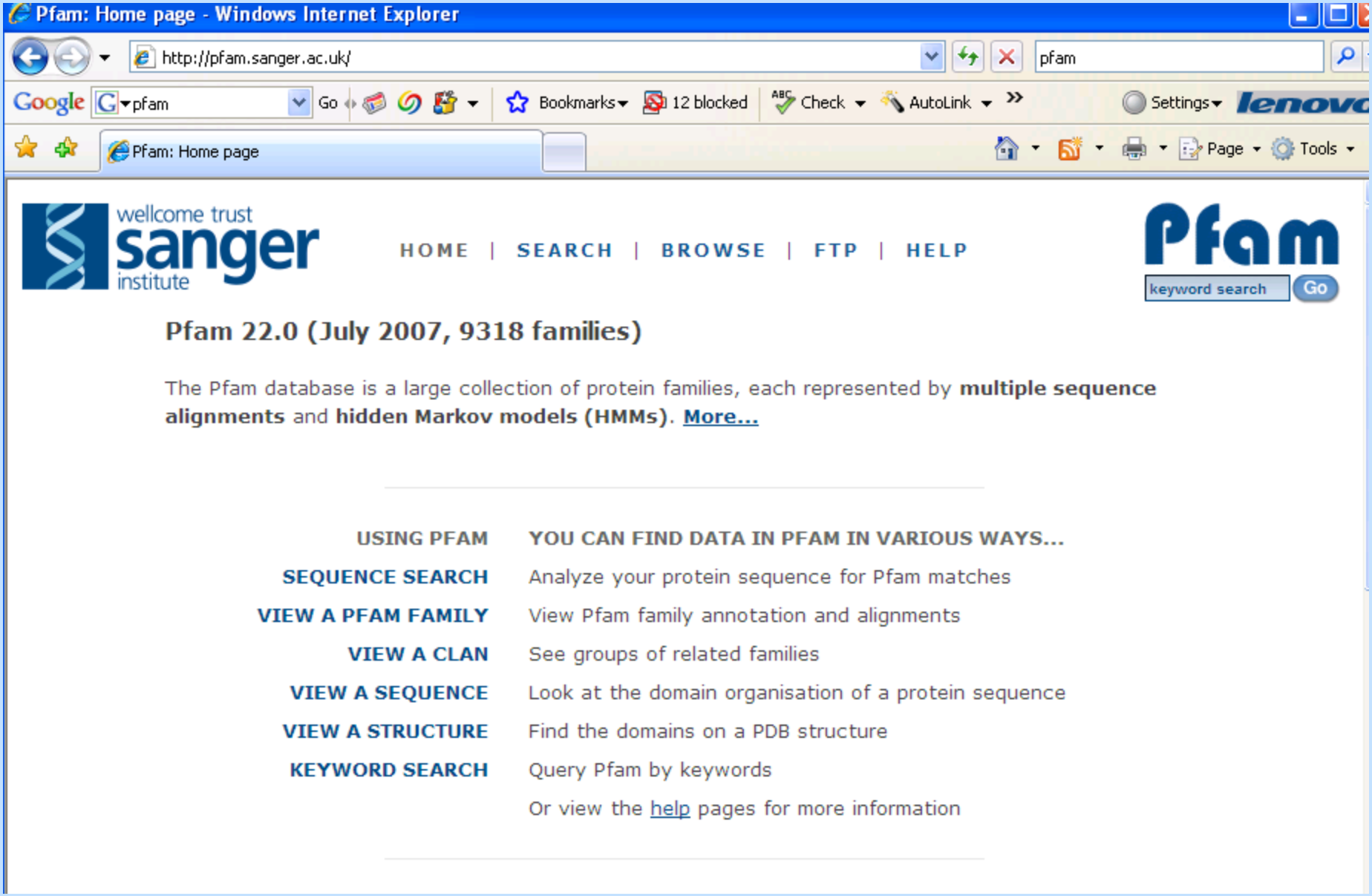
- 10 component HMM. Training set: 628 globins. Classified each sequence using the model.
- Generated 7 nonempty clusters, with ~560 falling into 4 "biologically meaningful" clusters.

Local alignment in HMM



Add flanking states for regions of unaligned seq.

Durbin et al. Ch. 5.5


Pfam: Home page - Windows Internet Explorer
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12 blocked
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