CAP 5510: Introduction to Bioinformatics

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CpG Islands

- Regions in DNA sequences with increased occurrences of substring "CG"
- Rare: typically C gets methylated and then mutated into a T.
- Often around promoter or "start" regions of genes
- Few hundred to a few thousand bases long

Problem 1:

- Input: Small sequence S
- Output: Is S from a CpG island?
  - Build Markov models: M+ and M —
  - Then compare

Markov Models

+	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

How to distinguish?

- Compute

$$S(x) = \log\left(\frac{P(x \mid M+)}{P(x \mid M-)}\right) = \sum_{i=1}^{L} \log\left(\frac{p_{x_{(i-1)}x_i}}{m_{x_{(i-1)}x_i}}\right) = \sum_{i=1}^{L} r_{x_{(i-1)}x_i}$$

r=p/m	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

Score(GCAC)
= .461-.913+.419
< 0.
GCAC not from CpG island.

Score(GCTC)
= .461-.685+.573
> 0.
GCTC from CpG island.

Problem 1:

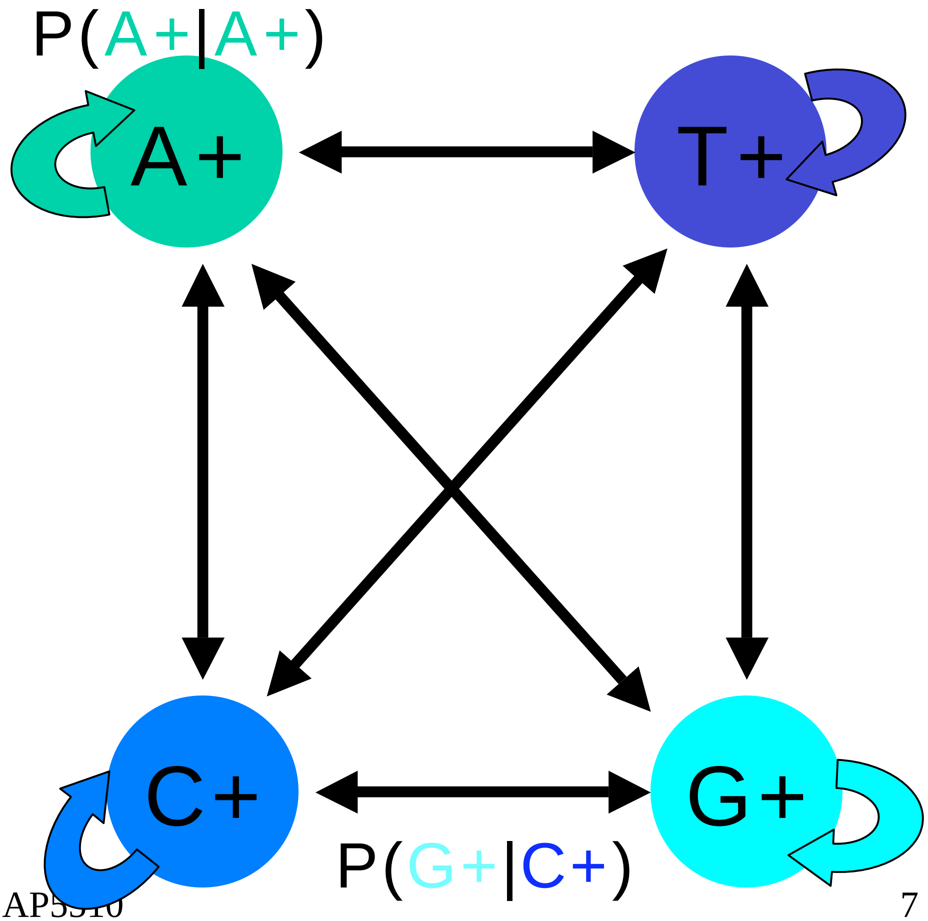
- Input: Small sequence S
- Output: Is S from a CpG island?
  - Build Markov Models: M+ & M-
  - Then compare

Problem 2:

- Input: Long sequence S
- Output: Identify the CpG islands in S.
  - Markov models are inadequate.
  - Need Hidden Markov Models.

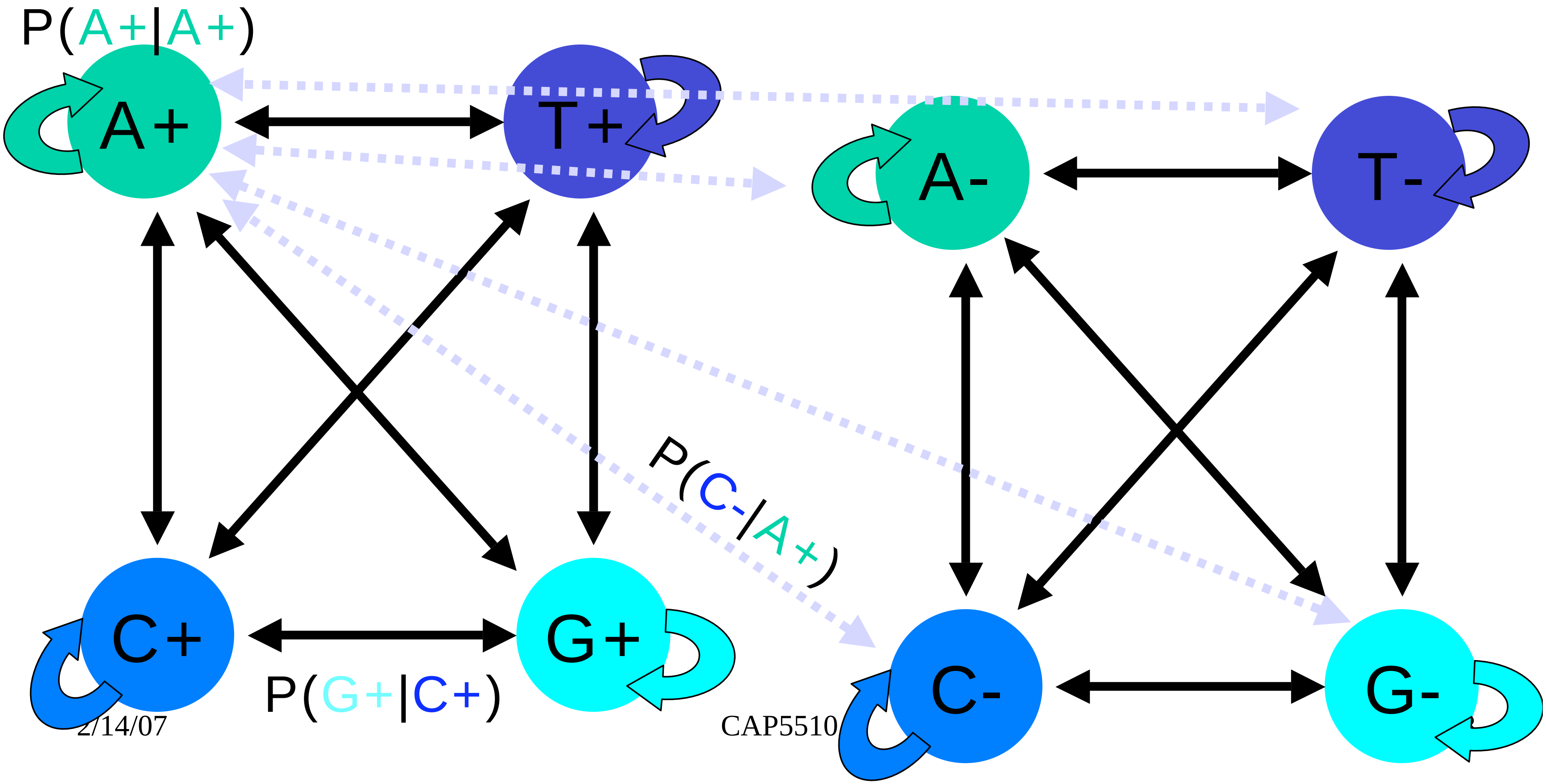
Markov Models

+	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



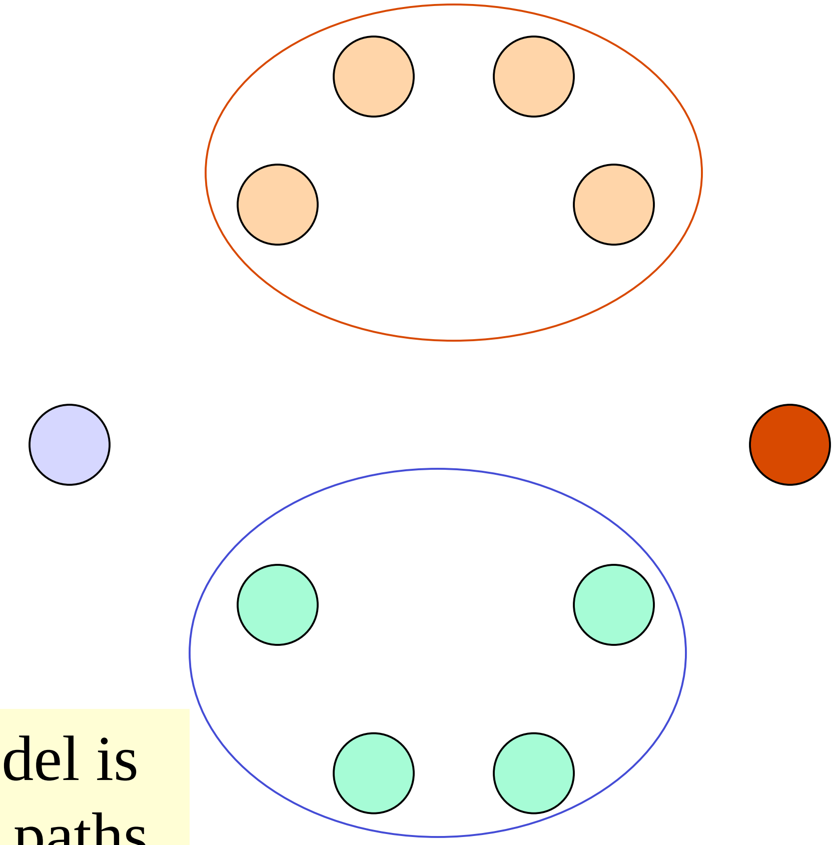
CpG Island + in an ocean of –
First order **Hidden** Markov Model

MM=16, HMM= 64 transition probabilities (adjacent bp)



Hidden Markov Model (HMM)

- States
- Transitions
- Transition Probabilities
- Emissions
- Emission Probabilities



- What is hidden about HMMs?

Answer: The path through the model is hidden since there are many valid paths.

How to Solve Problem 2?

- Solve the following problem:

Input: Hidden Markov Model M,

parameters Θ, emitted sequence S

Output: Most Probable Path Π

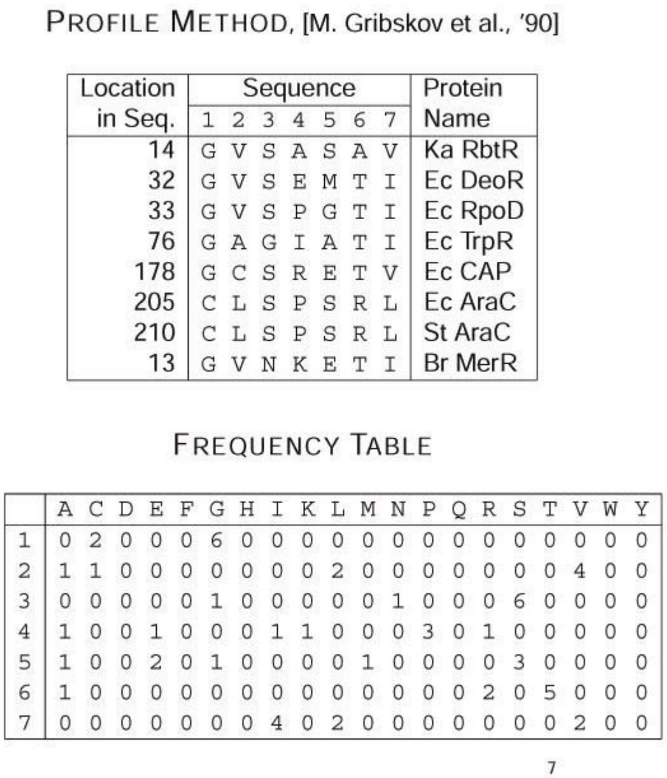
How: Viterbi's Algorithm (Dynamic Programming)

Define Π[i,j] = MPP for first j characters of S ending in state i

Define P[i,j] = Probability of Π[i,j]

- **Compute state i with largest P[i,j].**

Profile Method



PROFILE METHOD, [M. Gribskov et al., '90]

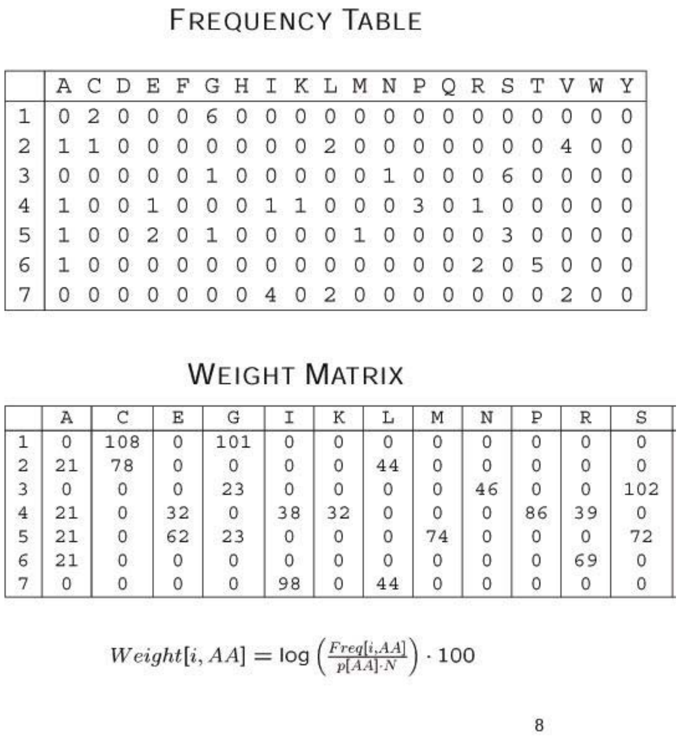
Location	Sequence							Protein
in Seq.	1	2	3	4	5	6	7	Name
14	G	V	S	A	S	A	V	Ka RbtR
32	G	V	S	E	M	T	I	Ec DeoR
33	G	V	S	P	G	T	I	Ec RpoD
76	G	A	G	I	A	T	I	Ec TrpR
178	G	C	S	R	E	T	V	Ec CAP
205	C	L	S	P	S	R	L	Ec AraC
210	C	L	S	P	S	R	L	St AraC
13	G	V	N	K	E	T	I	Br MerR

FREQUENCY TABLE

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
1	0	2	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	4	0	0
3	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	6	0	0	0	0
4	1	0	0	1	0	0	0	1	1	0	0	0	3	0	1	0	0	0	0	0
5	1	0	0	2	0	1	0	0	0	0	1	0	0	0	0	3	0	0	0	0
6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	5	0	0	0
7	0	0	0	0	0	0	0	4	0	2	0	0	0	0	0	0	0	2	0	0

7

Profile Method



FREQUENCY TABLE

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
1	0	2	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	4	0	0
3	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	6	0	0	0	0
4	1	0	0	1	0	0	0	1	1	0	0	0	3	0	1	0	0	0	0	0
5	1	0	0	2	0	1	0	0	0	0	1	0	0	0	0	3	0	0	0	0
6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	5	0	0	0
7	0	0	0	0	0	0	0	4	0	2	0	0	0	0	0	0	0	2	0	0

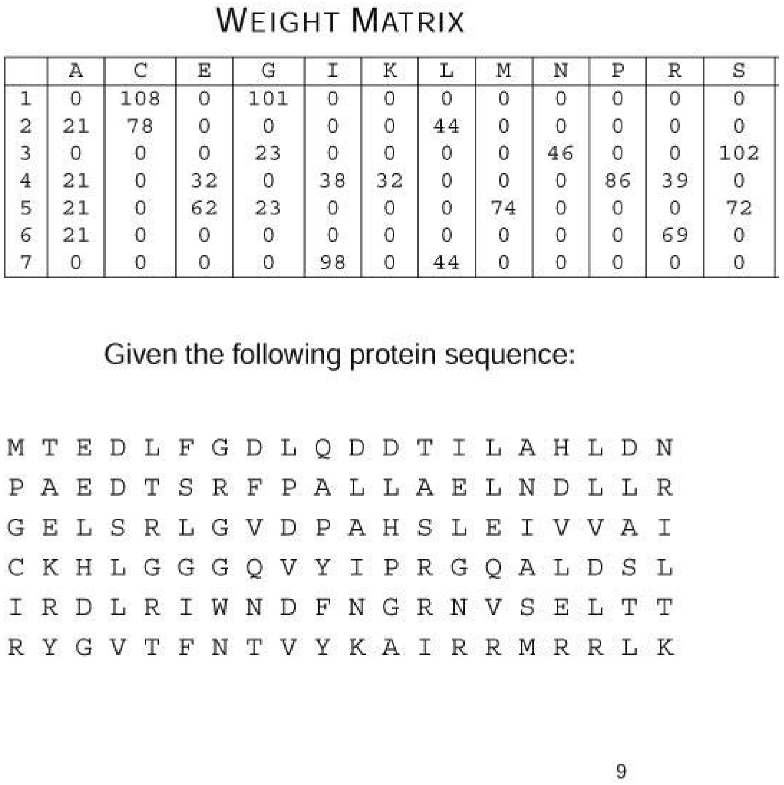
WEIGHT MATRIX

	A	C	E	G	I	K	L	M	N	P	R	S
1	0	108	0	101	0	0	0	0	0	0	0	0
2	21	78	0	0	0	0	44	0	0	0	0	0
3	0	0	0	23	0	0	0	0	46	0	0	102
4	21	0	32	0	38	32	0	0	0	86	39	0
5	21	0	62	23	0	0	0	74	0	0	0	72
6	21	0	0	0	0	0	0	0	0	0	69	0
7	0	0	0	0	98	0	44	0	0	0	0	0

$$Weight[i, AA] = \log\left(\frac{Freq[i,AA]}{p[AA]\cdot N}\right) \cdot 100$$

8

Profile Method



WEIGHT MATRIX

	A	C	E	G	I	K	L	M	N	P	R	S
1	0	108	0	101	0	0	0	0	0	0	0	0
2	21	78	0	0	0	0	44	0	0	0	0	0
3	0	0	0	23	0	0	0	0	46	0	0	102
4	21	0	32	0	38	32	0	0	0	86	39	0
5	21	0	62	23	0	0	0	74	0	0	0	72
6	21	0	0	0	0	0	0	0	0	0	69	0
7	0	0	0	0	98	0	44	0	0	0	0	0

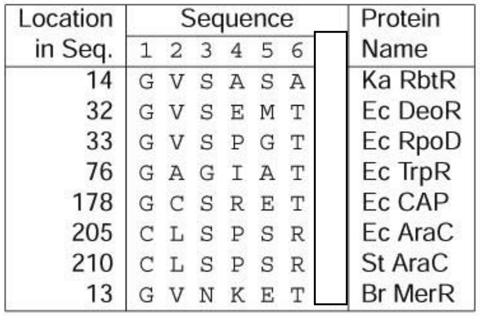
Given the following protein sequence:

```
M T E D L F G D L Q D D T I L A H L D N
P A E D T S R F P A L L A E L N D L L R
G E L S R L G V D P A H S L E I V V A I
C K H L G G G Q V Y I P R G Q A L D S L
I R D L R I W N D F N G R N V S E L T T
R Y G V T F N T V Y K A I R R M R R L K
```

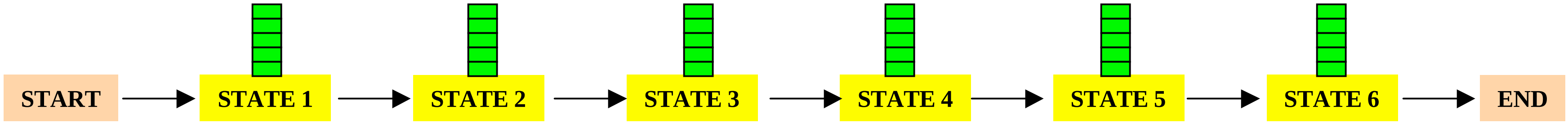
9

Profile HMMs

PROFILE METHOD, [M. Gribskov et al., '90]

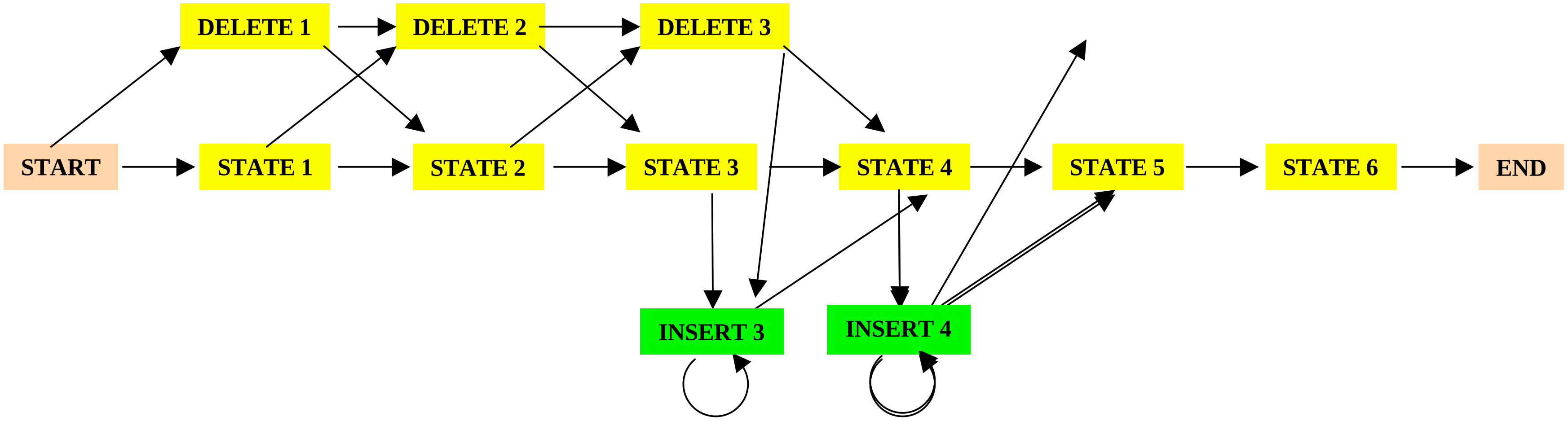


Location in Seq.	Sequence 1	2	3	4	5	6	Protein Name
14	G	V	S	A	S	A	Ka RbtR
32	G	V	S	E	M	T	Ec DeoR
33	G	V	S	P	G	T	Ec RpoD
76	G	A	G	I	A	T	Ec TrpR
178	G	C	S	R	E	T	Ec CAP
205	C	L	S	P	S	R	Ec AraC
210	C	L	S	P	S	R	St AraC
13	G	V	N	K	E	T	Br MerR

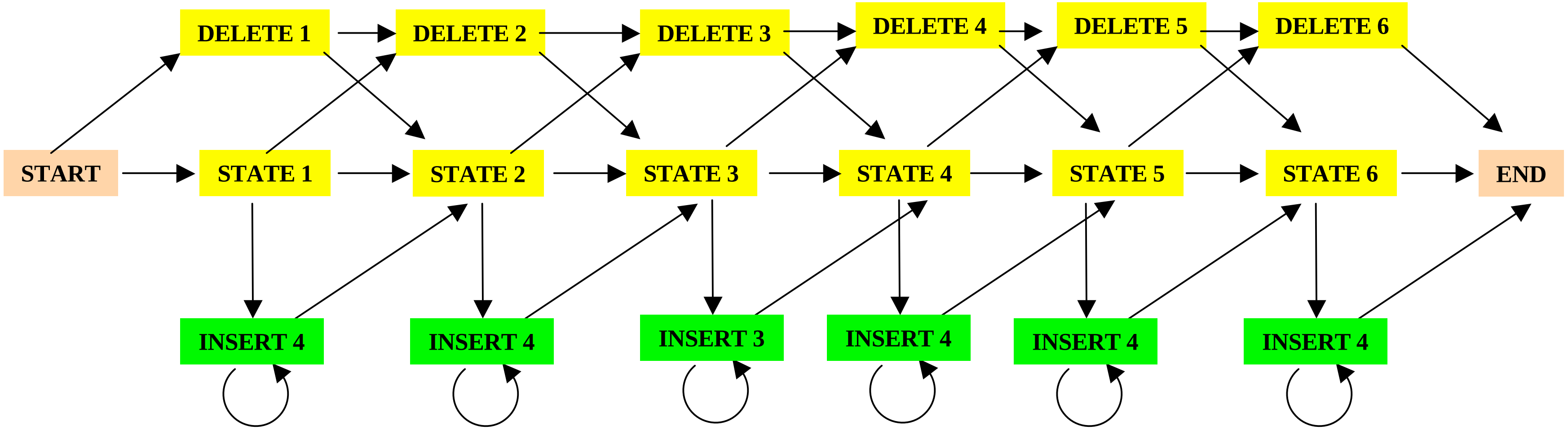


Profile HMMs with InDels

- Insertions
- Deletions
- Insertions & Deletions



Profile HMMs with InDels

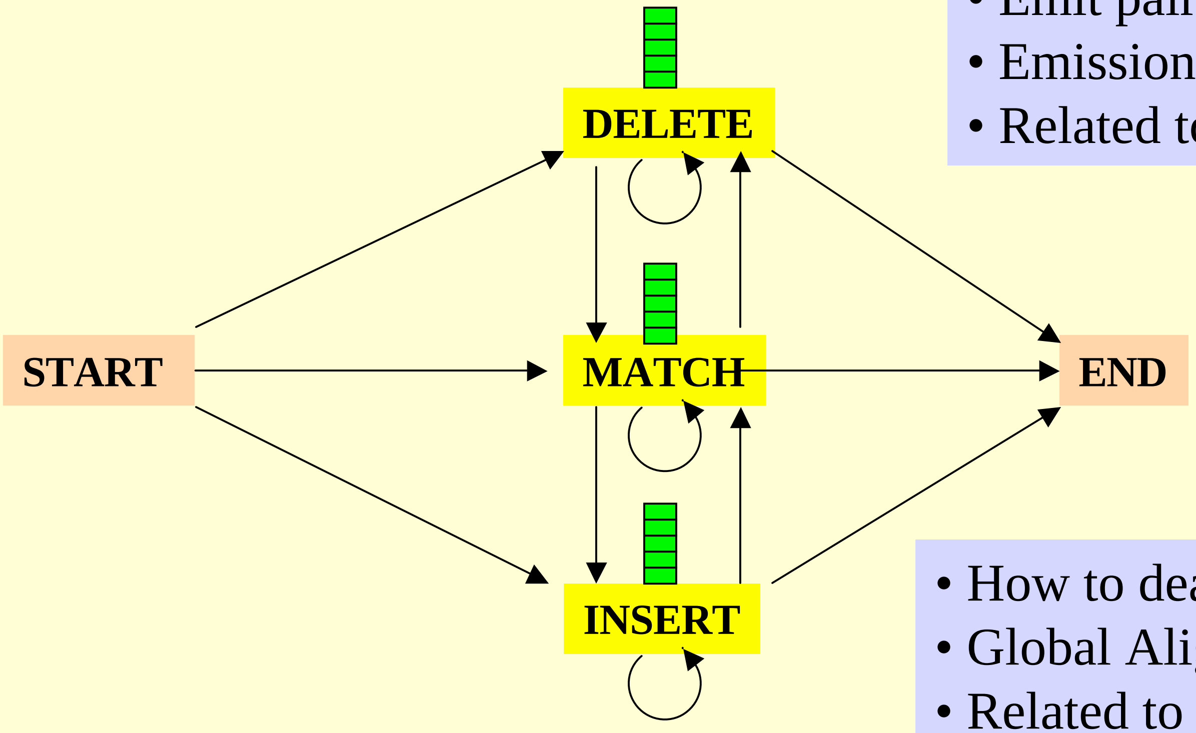


Missing transitions from DELETE j to INSERT j and from INSERT j to DELETE j+1.

How to model Pairwise Sequence Alignment

LEAPVE

LAPVIE

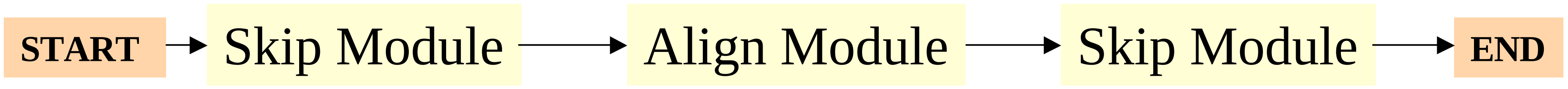


Pair HMMs

- Emit pairs of synbols
- Emission probs?
- Related to Sub. Matrices

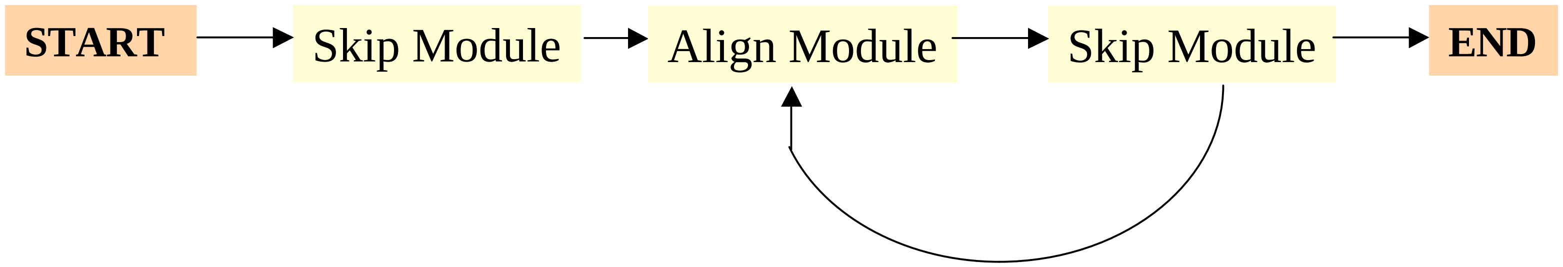
- How to deal with InDels?
- Global Alignment? Local?
- Related to Sub. Matrices

How to model Pairwise Local Alignments?



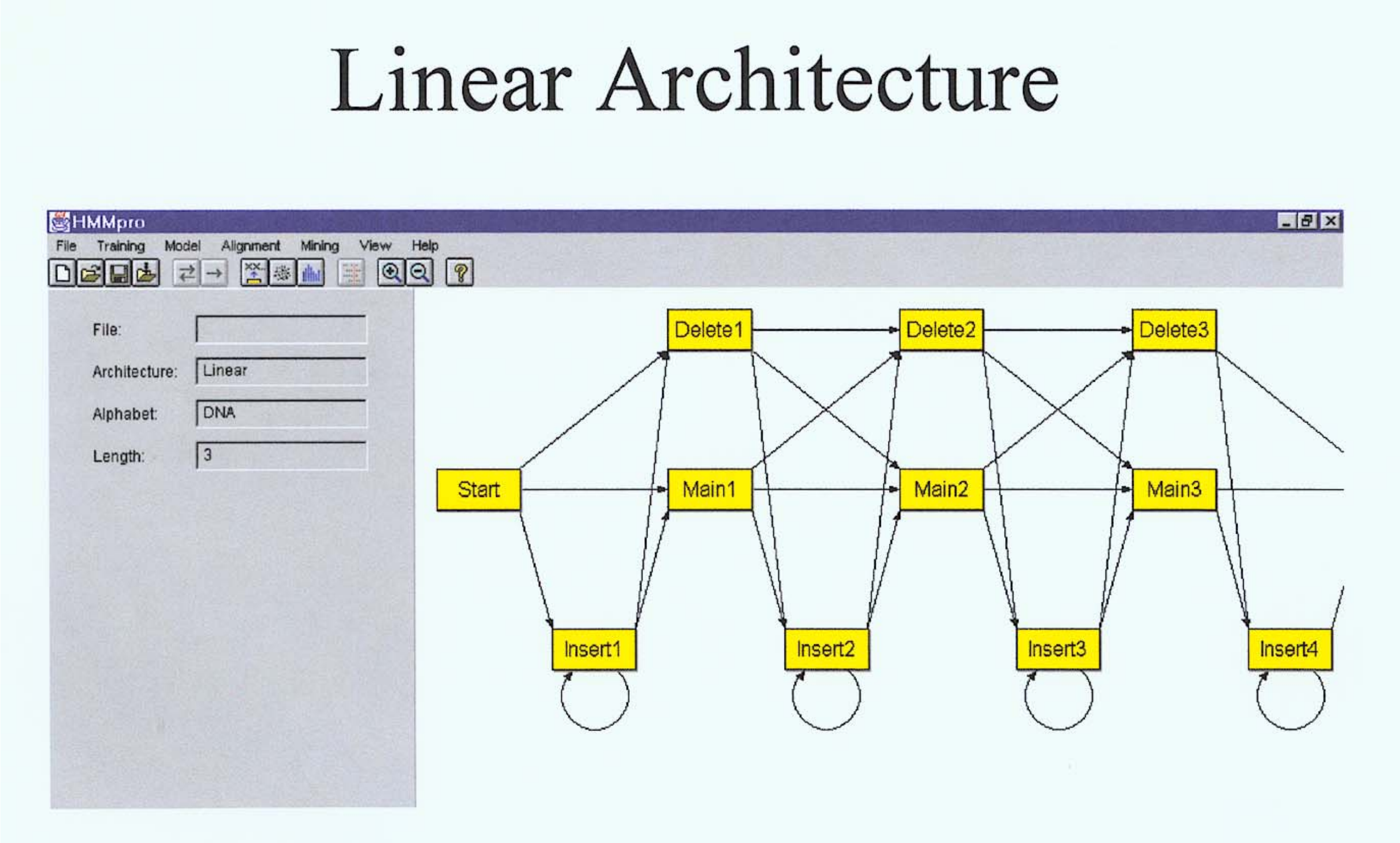
START → Skip Module → Align Module → Skip Module → END

How to model Pairwise Local Alignments with gaps?



START → Skip Module → Align Module → Skip Module → END

Standard HMM architectures



Linear Architecture

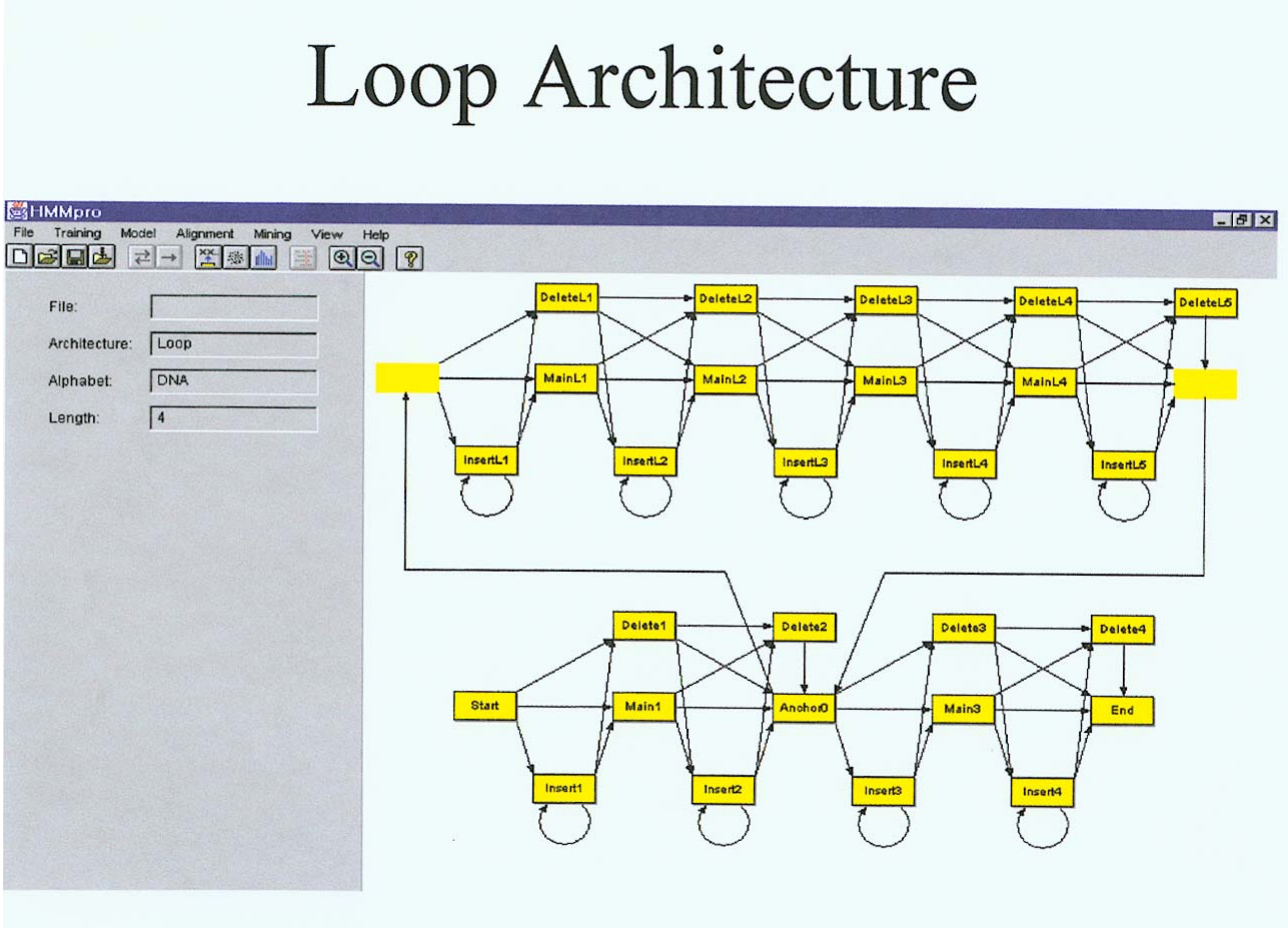
File:

Architecture: Linear

Alphabet: DNA

Length: 3

Standard HMM architectures



Loop Architecture

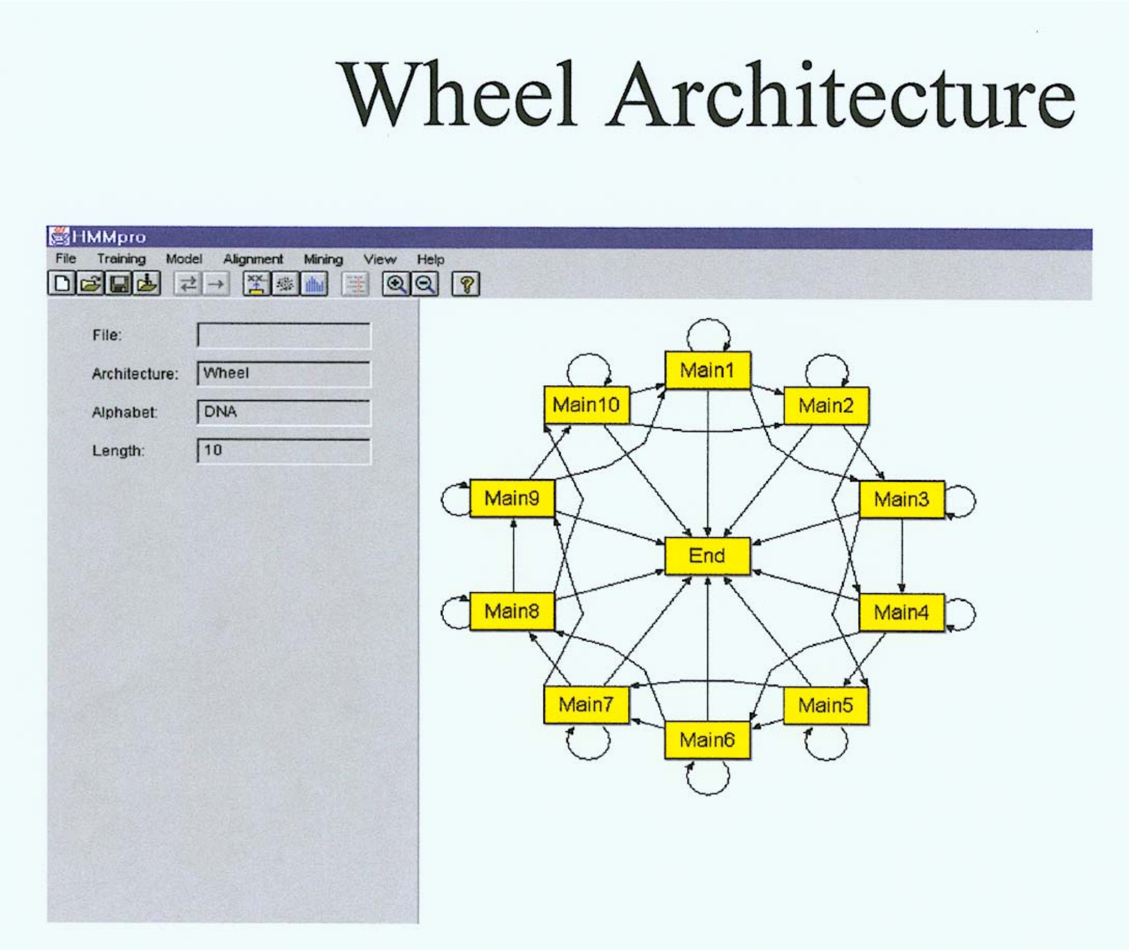
File:

Architecture: Loop

Alphabet: DNA

Length: 4

Standard HMM architectures



Wheel Architecture

File:

Architecture: Wheel

Alphabet: DNA

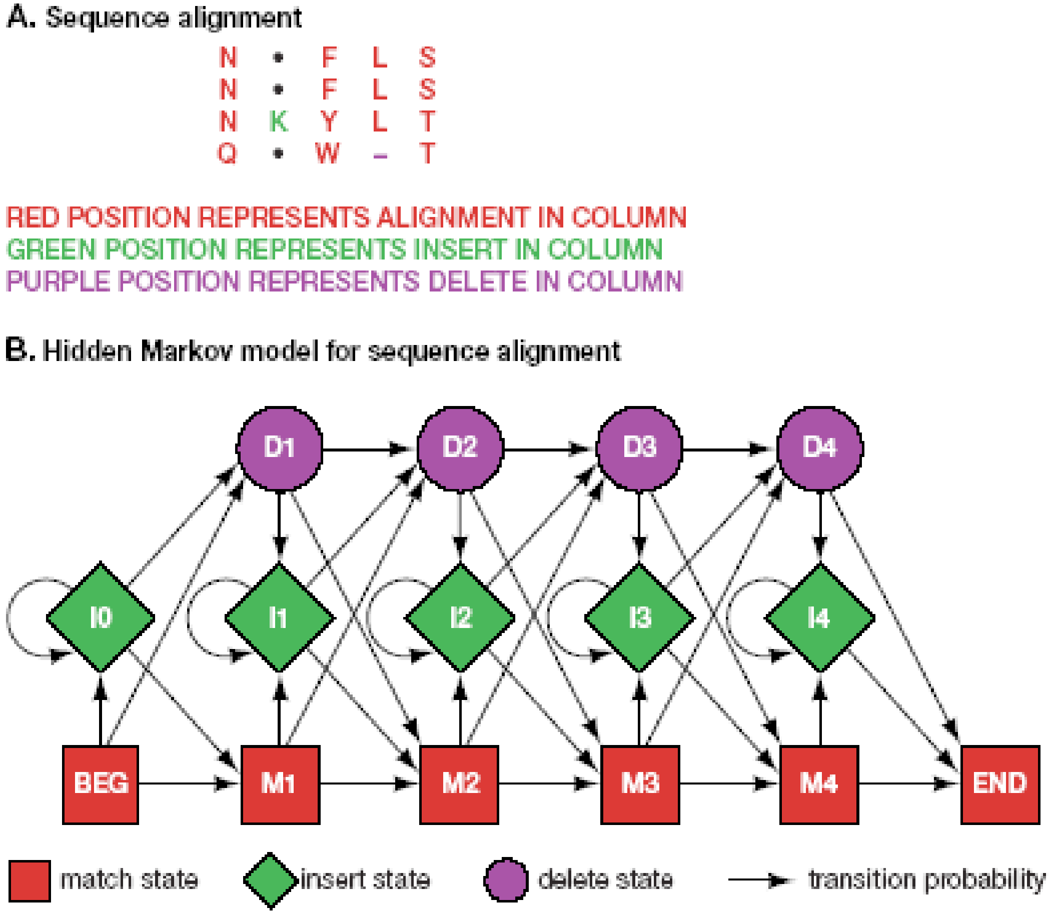
Length: 10

Profile HMMs from Multiple Alignments

```
HBA_HUMAN    VGA--HAGEY
HBB_HUMAN    V----NVDEV
MYG_PHYCA    VEA--DVAGH
GLB3_CHITP   VKG------D
GLB5_PETMA   VYS--TYETS
LGB2_LUPLU   FNA--NIPKH
GLB1_GLYDI   IAGADNGAGV
```

Construct Profile HMM from above multiple alignment.

HMM for Sequence Alignment



A. Sequence alignment

```
N  •  F  L  S
N  •  F  L  S
N  K  Y  L  T
Q  •  W  –  T
```

RED POSITION REPRESENTS ALIGNMENT IN COLUMN
GREEN POSITION REPRESENTS INSERT IN COLUMN
PURPLE POSITION REPRESENTS DELETE IN COLUMN

B. Hidden Markov model for sequence alignment

FIGURE 5.16. Relationship between the sequence alignment and the hidden Markov model of the alignment (Krogh et al. 1994). This particular form for the HMM was chosen to represent the sequence, structural, and functional variation expected in proteins. The model accommodates the identities, mismatches, insertions, and deletions expected in a group of related proteins. (*A*) A section of an msa. The illustration shows the columns generated in an msa. Each column may include matches and mismatches (*red* positions), insertions (*green* positions), and deletions (*purple* positions). (*B*) The HMM. Each column in the model represents the possibility of a match, insert, or delete in each column of the alignment in *A*. The HMM is a probabilistic representation of a section of the msa. Sequences can be generated from the HMM by starting at the beginning state labeled BEG and then by following

Problem 3: LIKELIHOOD QUESTION

- Input: Sequence S, model M, state i
- Output: Compute the probability of reaching state i with sequence S using model M
  - Backward Algorithm (DP)

Problem 4: LIKELIHOOD QUESTION

- Input: Sequence S, model M
- Output: Compute the probability that S was emitted by model M
  - Forward Algorithm (DP)

Problem 5: LEARNING QUESTION

- Input: model structure M, Training Sequence *S*
- Output: Compute the parameters Θ
- Criteria: ML criterion
  - maximize P(*S* | M, Θ)   HOW???

Problem 6: DESIGN QUESTION

- Input: Training Sequence *S*
- Output: Choose model structure M, and compute the parameters Θ
  - No reasonable solution
  - Standard models to pick from

Iterative Solution to the LEARNING QUESTION (Problem 5)

- Pick initial values for parameters Θ_0
- Repeat

    Run training set S on model M

    Count # of times transition $i \Rightarrow j$ is made

    Count # of times letter x is emitted from state i

    Update parameters Θ

- Until (some stopping condition)

Entropy

- Entropy measures the variability observed in given data.

$$E = -\sum_{c} p_c \log p_c$$

- Entropy is useful in multiple alignments & profiles.

- Entropy is max when uncertainty is max.