CAP 5510: Introduction to Bioinformatics
CGS 5166: Bioinformatics Tools

Giri Narasimhan

ECS 254; Phone: x3748

giri@cis.fiu.edu

www.cis.fiu.edu/~giri/teach/BioinfF18.html

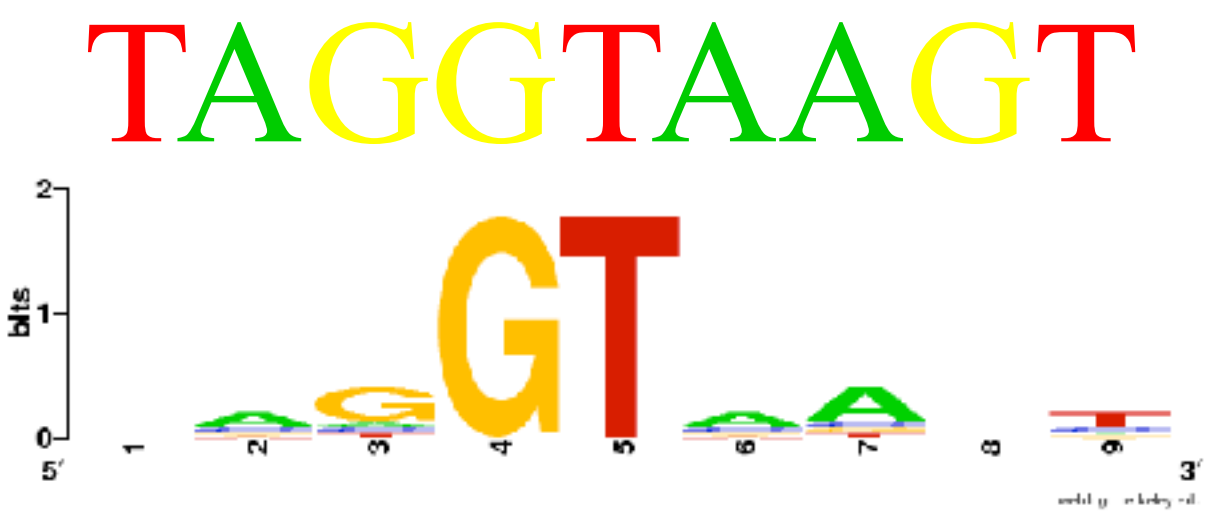
Profiles and HMMs

Pattern: Representations

GAGGTAAAC
TCCGTAAGT
CAGGTTGGA
ACAGTCAGT
TAGGTCATT
TAGGTACTG
ATGGTAACT
CAGGTATAC
TGTGTGAGT
AAGGTAAGT

TAGGTAAGT

- Alignments
- Consensus Sequences
- Logo Formats
- ...



Profiles

GAGGTAAAC
TCCGTAAGT
CAGGTTGGA
ACAGTCAGT
TAGGTCATT
TAGGTACTG
ATGGTAACT
CAGGTATAC
TGTGTGAGT
AAGGTAAGT

	1	2	3	4	5	6	7	8	9
A	3	6	1	0	0	6	7	2	1
C	2	2	1	0	0	2	1	1	2
G	1	1	7	10	0	1	1	5	1
T	4	1	1	0	10	1	1	2	6

Frequency Matrix

	1	2	3	4	5	6	7	8	9
A	.3	.6	.1	0	0	.6	.7	.2	.1
C	.2	.2	.1	0	0	.2	.1	.1	.2
G	.1	.1	.7	1	0	.1	.1	.5	.1
T	.4	.1	.1	0	1	.1	.1	.2	.6

Relative Frequencies

Profiles

GAGGTAAAC
TCCGTAAGT
CAGGTTGGA
ACAGTCAGT
TAGGTCATT
TAGGTACTG
ATGGTAACT
CAGGTATAC
TGTGTGAGT
AAGGTAAGT

	1	2	3	4	5	6	7	8	9
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C	.2	.2	.1	0	0	.2	.1	.1	.2
G	.1	.1	.7	1	0	.1	.1	.5	.1
T	.4	.1	.1	0	1	.1	.1	.2	.6

Relative Frequencies

	1	2	3	4	5	6	7	8	9
A	0.14	0.72	-0.61	-1.43	-1.43	0.72	0.86	-0.16	-0.61
C	-0.16	-0.16	-0.61	-1.43	-1.43	-0.16	-0.61	-0.61	-0.16
G	-0.61	-0.61	0.86	-0.61	-1.43	-0.61	-0.61	0.57	-0.61
T	0.38	-0.61	-0.61	-1.43	1.19	-0.61	-0.61	-0.16	0.72

Profiles

Profile entries:

$$P_{ij} = \ln (f_{ij}/b_i)$$

Zero counts:

$$f_{ij} = (c_{ij}+\alpha b_i)/(n+\alpha)$$

	1	2	3	4	5	6	7	8	9
A	.3	.6	.1	0	0	.6	.7	.2	.1
C	.2	.2	.1	0	0	.2	.1	.1	.2
G	.1	.1	.7	1	0	.1	.1	.5	.1
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Relative Frequencies

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http://coding.plantpath.ksu.edu/profile/

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

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

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:

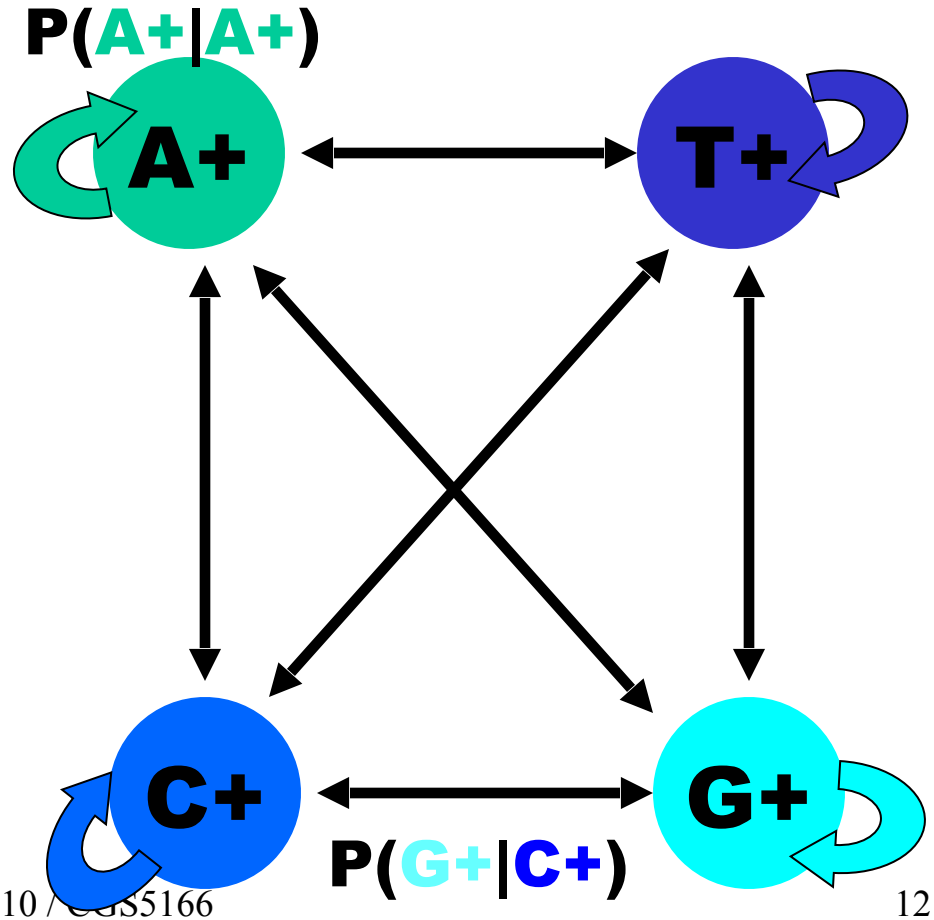
- Input: Small sequence S
- Output: Is S from a CpG island?
  - Build Markov Models: M+ & M-
  - Then compare

Problem 2:

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

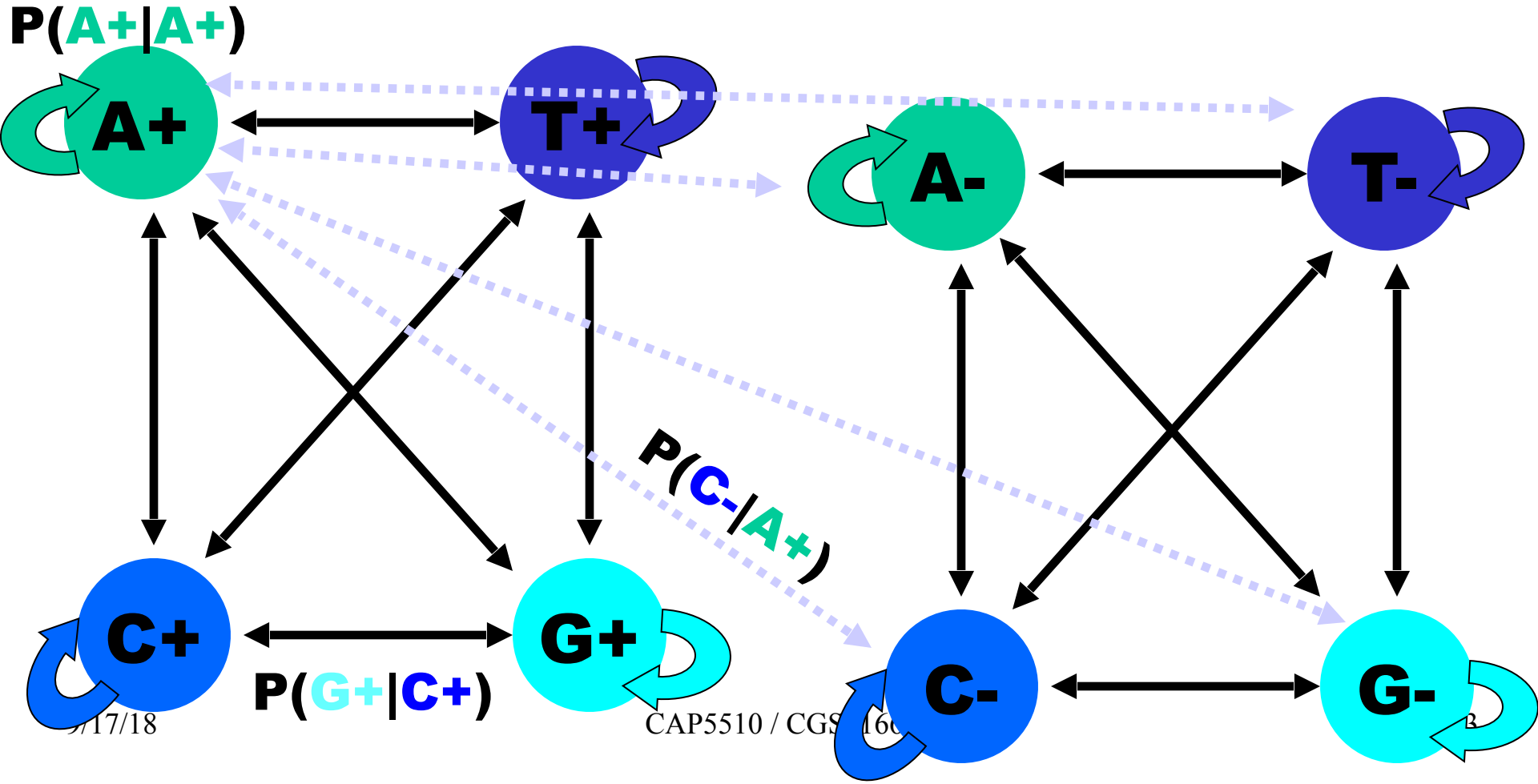
Markov Models

+	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



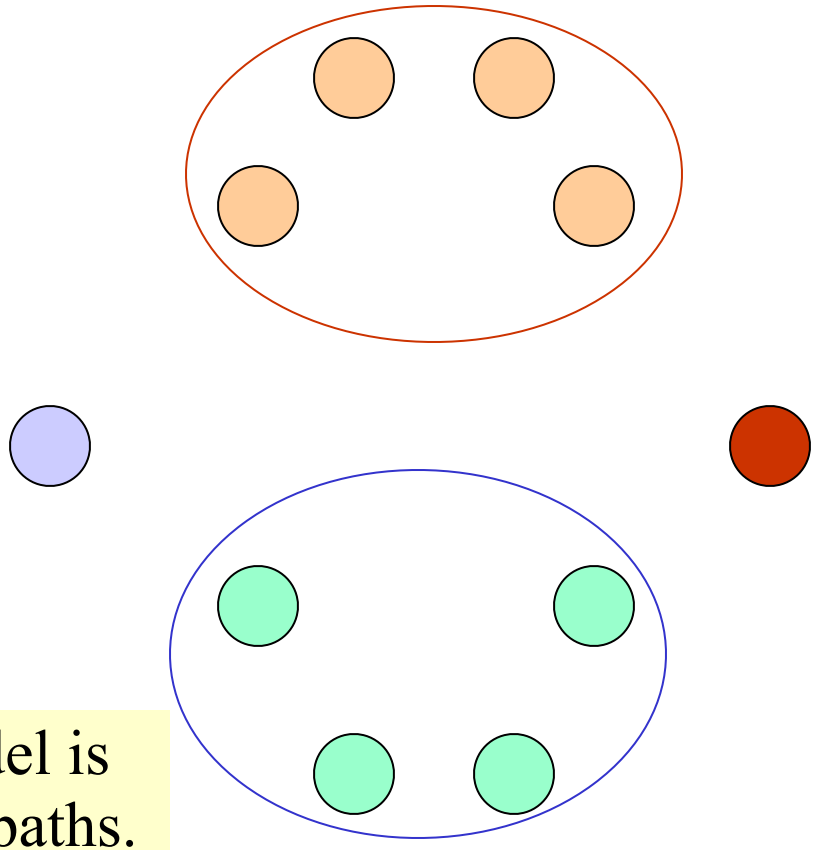
CpG Island + in an ocean of –
First order Hidden Markov Model

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 $\Pi[i,j]$ = MPP for first j characters of S ending in state i

Define P[i,j] = Probability of $\Pi[i,j]$

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

Profiles

Profile entries:

$$P_{ij} = \ln (f_{ij}/b_i)$$

Zero counts:

$$f_{ij} = (c_{ij}+\alpha b_i)/(n+\alpha)$$

	1	2	3	4	5	6	7	8	9
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T	0.38	-0.61	-0.61	-1.43	1.19	-0.61	-0.61	-0.16	0.72

Profiles; Position Weight Matrix (PWM); Position-Specific Scoring Matrix (PSSM)

http://coding.plantpath.ksu.edu/profile/

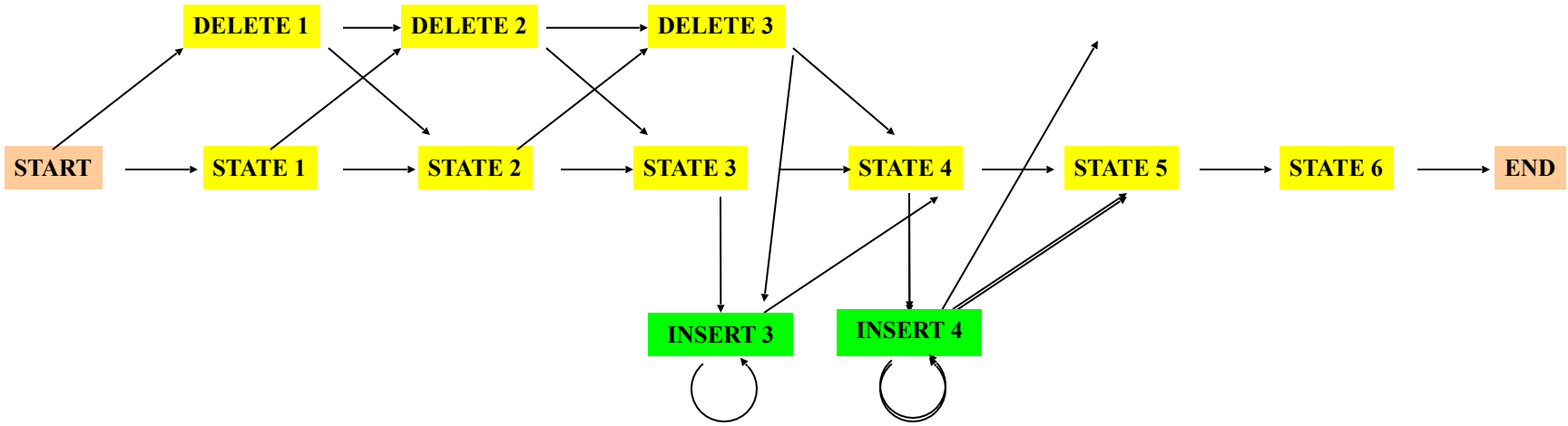
Profile HMMs

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

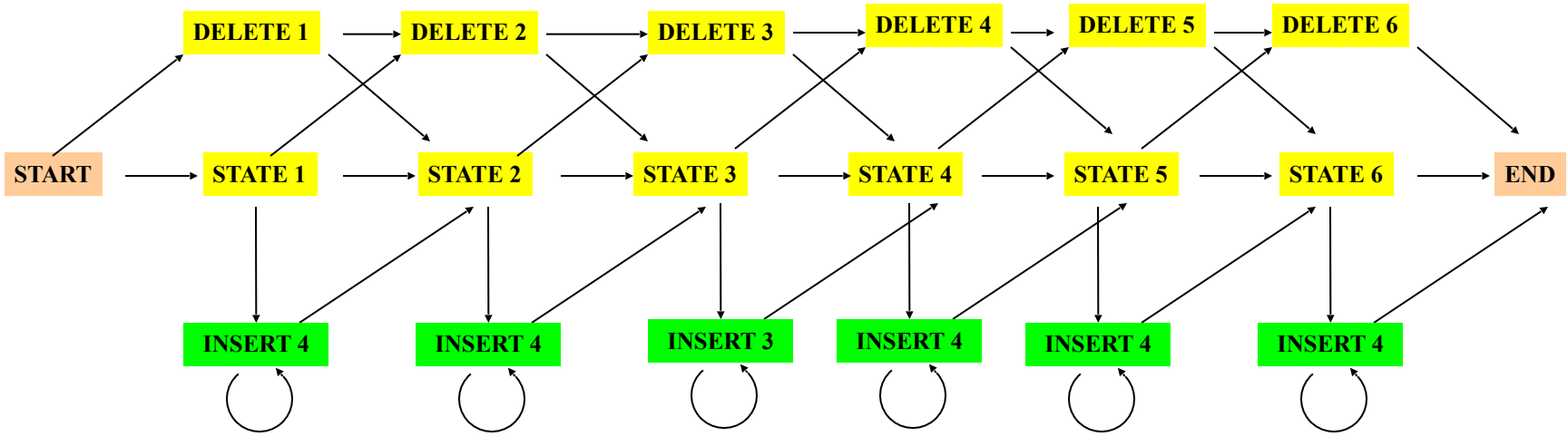
Location in Seq.	Sequence 1	2	3	4	5	6		Protein Name
14	G	V	S	A	S	A		Ka RotR
32	G	V	S	E	M	T		Ec DeoR
33	G	V	S	P	G	T		Ec RpoD
76	G	A	G	I	A	T		Ec TrpR
178	G	C	S	P	R	T		Ec CAP
205	C	L	S	P	S	R		Ec AraC
210	C	L	S	P	S	R		St AraC
13	G	V	N	K	E	T		Br MerR

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.

HMM for Sequence Alignment

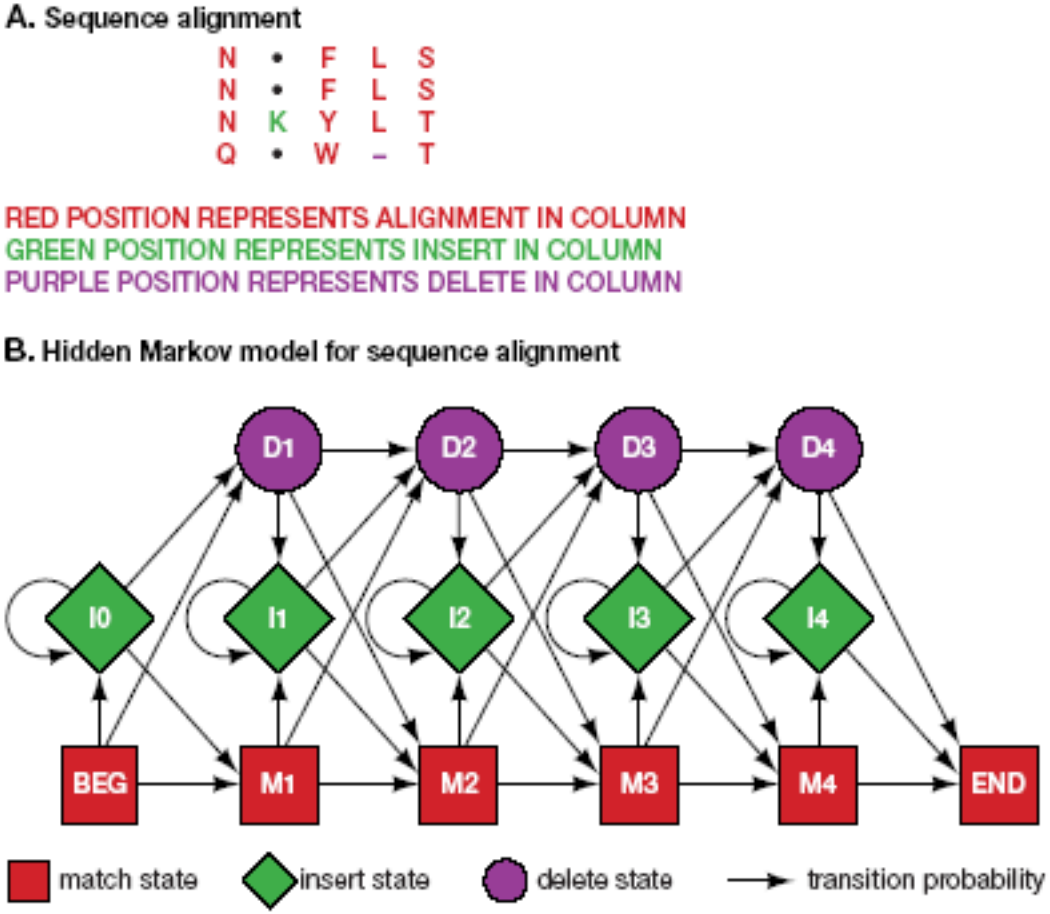


FIGURE 5.16. Relationship between the sequence alignment and the hidden Markov model of the alignment (Krogh et al. 1994). This particular form for the HMM was chosen to represent the sequence, structural, and functional variation expected in proteins. The model accommodates the identities, mismatches, 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

Profile HMM Software

- HMMER http://hmmer.wustl.edu/
- SAM http://www.cse.ucsc.edu/research/compbio/sam.html
- PFTOOLS http://www.isrec.isb-sib.ch/ftp-server/pftools/
- HMMpro http://www.netid.com/html/hmmpro.html
- GENEWISE http://www.ebi.ac.uk/Wise2/
- PROBE ftp://ftp.ncbi.nih.gov/pub/neuwald/probe1.0/
- META-MEME http://metameme.sdsc.edu/
- BLOCKS http://www.blocks.fhcrc.org/
- PSI-BLAST http://www.ncbi.nlm.nih.gov/BLAST/newblast.html

- Read more about Profile HMMs at
  - http://www.csb.yale.edu/userguides/seq/hmmer/docs/node9.html