Describing & Modeling Patterns
Patterns in DNA Sequences

- **Signals in DNA sequence control events**
  - Start and end of genes
  - Start and end of introns
  - Transcription factor binding sites (regulatory elements)
  - Ribosome binding sites

- **Detection of these patterns are useful for**
  - Understanding gene structure
  - Understanding gene regulation
Motifs in DNA Sequences

- Given a collection of DNA sequences of promoter regions, describe the transcription factor binding sites (also called regulatory elements).
  
  Example:

http://www.lecb.ncifcrf.gov/~toms/sequencelogo.html
Motifs in DNA Sequences

Fig. 1. Some aligned sequences and their sequence logo. At the top of the figure are listed the 12 DNA sequences from the P1 and P2 control regions in bacteriophage lambda. These are bound by both the cI and cro proteins [16]. Each even numbered sequence is the complement of the preceding odd numbered sequence. The sequence logo, described in detail in the text, is at the bottom of the figure. The cosine wave is positioned to indicate that a minor groove faces the center of each symmetrical protein. Data which support this assignment are given in reference [17].
More Motifs in *E. Coli* DNA Sequences

http://www.lecb.ncifcrf.gov/~toms/sequencelogo.html
E. coli Ribosome binding sites

http://www.lecb.ncifcrf.gov/~toms/sequencelogo.html
Other Motifs in DNA Sequences: Human Splice Junctions

http://www.lecb.ncifcrf.gov/~toms/sequencelogo.html
Motifs

http://weblogo.berkeley.edu/examples.html
Pattern: Representations

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

TAGGTAAGT

[Diagram showing sequence alignments and logo formats]
### Profiles

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Profiles

Profile entries:
\[ P_{ij} = \ln \left( \frac{f_{ij}}{b_i} \right) \]

Zero counts:
\[ f_{ij} = \frac{c_{ij} + \alpha b_i}{n + \alpha} \]

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Relative Frequencies

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

2/9/15
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

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How to distinguish?

- **Compute**

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

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**Score(GCAC)**

= $0.461 - 0.913 + 0.419$

< 0.

**GCAC not from CpG island.**

**Score(GCTC)**

= $0.461 - 0.685 + 0.573$

> 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

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\[
P(A^+|A^+) \quad P(T^+|T^+) \quad P(C^+|C^+) \quad P(G^+|G^+)
\]
CpG Island + in an ocean of −
First order Hidden Markov Model

$P(A^+|A^+)$

$P(C^+|G^+)$

$P(G^-|C^-)$

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 $\Theta$, emitted sequence $S$
  
  **Output:** Most Probable Path $\Pi$

  **How:** Viterbi’s Algorithm (Dynamic Programming)

  Define $\Pi[i,j] = \text{MPP for first } j \text{ characters of } S \text{ ending in state } i$
  
  Define $P[i,j] = \text{Probability of } \Pi[i,j]$
  
  Compute state $i$ with largest $P[i,j]$.
Profiles

Profile entries:
\[ P_{ij} = \ln \left( \frac{f_{ij}}{b_i} \right) \]

Zero counts:
\[ f_{ij} = \frac{(c_{ij} + \alpha b_i)}{(n + \alpha)} \]

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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]

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<td>Br MerR</td>
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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

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 transition probability arrows and emitting symbols that correspond to the states.
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/
- GENEWISE http://www.ebi.ac.uk/Wise2/
- META-MEME http://metameme.sdsc.edu/
- BLOCKS http://www.blocks.fhcrc.org/

- Read more about Profile HMMs at
  - http://www.csb.yale.edu/userguides/seq/hmmer/docs/node9.html
How to model Pairwise Sequence Alignment

LEAPVE
LAPVIE

Pair HMMs
- Emit pairs of symbols
- Emission probs?
- Related to Sub. Matrices

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

How to model Pairwise Local Alignments with gaps?
Standard HMM architectures

Linear Architecture

[Diagram of a linear architecture with nodes labeled Start, Main1, Main2, Main3, Delete1, Delete2, Delete3, Insert1, Insert2, Insert3, Insert4]
Standard HMM architectures

Loop Architecture

[Diagram of Loop Architecture]
Standard HMM architectures

Wheel Architecture
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 $\Theta$
- **Criteria:** ML criterion
  - maximize $P(S | M, \Theta)$  HOW???

Problem 6: DESIGN QUESTION

- **Input:** Training Sequence $S$
- **Output:** Choose model structure $M$, and compute the parameters $\Theta$
  - No reasonable solution
  - Standard models to pick from
Iterative Solution to the LEARNING QUESTION (Problem 5)

- Pick initial values for parameters $\Theta_0$

- **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 $\Theta$

- **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.
G-Protein Couple Receptors

- Transmembrane proteins with 7 α-helices and 6 loops; many subfamilies
- Highly variable: 200-1200 aa in length, some have only 20% identity.
- [Baldi & Chauvin, ’94] HMM for GPCRs
- HMM constructed with 430 match states (avg length of sequences); Training: with 142 sequences, 12 iterations
GPCR - Analysis

- Compute main state entropy values
  \[ H_i = -\sum_a e_{ia} \log e_{ia} \]

- For every sequence from test set (142) & random set (1600) & all SWISS-PROT proteins

  Compute the negative log of probability of the most probable path \( \pi \)

  \[ \text{Score}(S) = -\log(P(\pi \mid S, M)) \]
GPCR Analysis
Figure 8.1: Entropy Profile of the Emission Probability Distributions Associated with the Main States of the HMM After 12 Cycles of Training.
Figure 8.2: Scores (Negative Log-likelihoods of Optimal Viterbi Paths). Represented sequences consist of 142 GPCR training sequences, all sequences from the SWISS-PROT database of length less than or equal to 2000, and 220 randomly generated sequences with same average composition as the GPCRs of length 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800 (20 at each length). The regression line was obtained from the 220 random sequences. The horizontal distances in the histogram correspond to normalized scores (6).
Applications of HMM for GPCR

- **Bacteriorhodopsin**
  - Transmembrane protein with 7 domains
  - But it is not a GPCR
  - Compute score and discover that it is close to the regression line. **Hence not a GPCR.**

- **Thyrotropin receptor precursors**
  - All have long initial loop on **INSERT STATE 20.**
  - Also clustering possible based on distance to regression line.
HMMs – Advantages

- Sound statistical foundations
- Efficient learning algorithms
- Consistent treatment for insert/delete penalties for alignments in the form of locally learnable probabilities
- Capable of handling inputs of variable length
- Can be built in a modular & hierarchical fashion; can be combined into libraries.
- Wide variety of applications: Multiple Alignment, Data mining & classification, Structural Analysis, Pattern discovery, Gene prediction.
HMMs – Disadvantages

- Large # of parameters.
- Cannot express dependencies & correlations between hidden states.
References