Profile HMMs for Sequence Families

COMP 571
Luay Nakhleh, Rice University

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Sequence Families

- Functional biological sequences typically come in families
- Sequences in a family have diverged during evolution, but normally maintain the same or a related function
- Thus, identifying that a sequence belongs to a family tells about its function

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HMM Profile

- Consensus modeling of the family using a probabilistic model
- Built from a given multiple alignment (assumed to be correct)

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Sequences from a Globin Family

Alignment of 7 globins

The 8 alpha helices are shown as A-H above the alignment

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Ungapped Score Matrices

- A natural probabilistic model for a conserved region would be to specify independent probabilities $e_i(a)$ of observing amino acid a in position i
- The probability of a new sequence x according to this model is

$$\mathbf{P}(x|M) = \prod_{i=1}^{L} e_i(x_i)$$

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Log-odds Ratio

- We are interested in the ratio of the probability to the probability of x under the random model

$$S = \sum_{i=1}^{L} \log \frac{e_i(x_i)}{q_{x_i}}$$

Position specific score matrix (PSSM)

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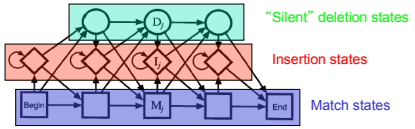
Adding Indels to Obtain a Profile HMM



Profile HMMs generalize pairwise alignment

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Deriving Profile HMMs from Multiple Alignments

- Essentially, we want to build a model representing the consensus sequence for a family, rather than the sequence of any particular member
- Non-probabilistic profiles and profile HMMs

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Non-probabilistic Profiles

- Gribskov, McLachlan, and Eisenberg 1987
- No underlying probabilistic model, but rather assigned position specific scores for each match state and gap penalty
- The score for each consensus position is set to the average of the standard substitution scores from all the residues in the corresponding multiple sequence alignment column

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Non-probabilistic Profiles

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```
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...
              **  *****
```

The score for residue 'a' in column 1 → $\frac{5}{9}s(\mathrm{V},a)+\frac{1}{9}s(\mathrm{F},a)+\frac{1}{9}s(\mathrm{I},a)$

s(a,b) : standard substitution matrix

Non-probabilistic Profiles

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- They also set gap penalties for each column using a heuristic equation that decreases the cost of a gap according to the length of the longest gap observed in the multiple alignment spanning the column

Problem with the Approach

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- If we had an alignment with 100 sequences, all with a cysteine (C), at some position, the probability distribution for that column for an "average" profile would be exactly the same as would be derived from a single sequence
- Doesn't correspond to our expectation that the likelihood of a cysteine should go up as we see more confirming examples

Similar Problem with Gaps

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```
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...
              ***  *****
```

Scores for a deletion in columns 2 and 4 would be set to the same value

More reasonable to set the probability of a new gap opening to be higher in column 4

Basic Profile HMM Parameterization

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- A profile HMM defines a probability distribution over the whole space of sequences
- The aim of parameterization is to make this distribution peak around members of the family
- Parameters: probabilities and the length of the model

Model Length

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- A simple rule that works well in practice is that columns that are more than half gap characters should be modeled by inserts

Probability Values

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$$a_{k\ell} = \frac{A_{k\ell}}{\sum_{\ell'} A_{k\ell'}} \qquad e_k(a) = \frac{E_k(a)}{\sum_{a'} E_k(a')}$$

k, ℓ : indices over states

$a_{k\ell}, e_k(a)$: transition and emission probabilities

$A_{k\ell}, E_k(a)$: transition and emission frequencies

Problem with the Approach

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- Transitions and emissions that don't appear in the training data set would acquire zero probability (would never be allowed)
- Solution: add pseudo-counts to the observed frequencies
- Simples pseudo-count is Laplace's rule: add one to each frequency

Example

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```
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...
               ***  *****
```

$e_{M_1}(\mathrm{V}) = 6/27, e_{M_1}(\mathrm{I}) = e_{M_1}(\mathrm{F}) = 2/27$

$e_{M_1}(a) = 1/27$ for all residue types a other than V, I, F

$a_{M_1M_2} = 7/10, a_{M_1D_2} = 2/10$ and $a_{M_1I_1} = 1/10$

Example: Full Profile HMM

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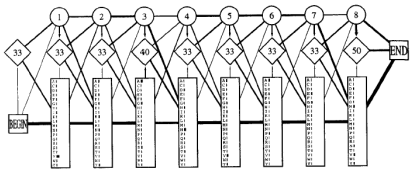

Searching with Profile HMMs

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- One of the main purposes of developing profile HMMs is to use them to detect potential membership in a family
- We can either use Viterbi algorithm to get the most probable alignment or the forward algorithm to calculate the full probability of the sequence summed over all possible paths

Viterbi Algorithm

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$$V_j^{\mathrm{M}}(i) = \log \frac{e_{\mathrm{M}_j}(x_i)}{q_{x_i}} + \max \begin{cases} V_{j-1}^{\mathrm{M}}(i-1) + \log a_{\mathrm{M}_{j-1}\mathrm{M}_j}, \\ V_{j-1}^{\mathrm{I}}(i-1) + \log a_{\mathrm{I}_{j-1}\mathrm{M}_j}, \\ V_{j-1}^{\mathrm{D}}(i-1) + \log a_{\mathrm{D}_{j-1}\mathrm{M}_j}; \end{cases}$$

$$V_j^{\mathrm{I}}(i) = \log \frac{e_{\mathrm{I}_j}(x_i)}{q_{x_i}} + \max \begin{cases} V_j^{\mathrm{M}}(i-1) + \log a_{\mathrm{M}_j\mathrm{I}_j}, \\ V_j^{\mathrm{I}}(i-1) + \log a_{\mathrm{I}_j\mathrm{I}_j}, \\ V_j^{\mathrm{D}}(i-1) + \log a_{\mathrm{D}_j\mathrm{I}_j}; \end{cases}$$

$$V_j^{\mathrm{D}}(i) = \max \begin{cases} V_{j-1}^{\mathrm{M}}(i) + \log a_{\mathrm{M}_{j-1}\mathrm{D}_j}, \\ V_{j-1}^{\mathrm{I}}(i) + \log a_{\mathrm{I}_{j-1}\mathrm{D}_j}, \\ V_{j-1}^{\mathrm{D}}(i) + \log a_{\mathrm{D}_{j-1}\mathrm{D}_j}. \end{cases}$$

Forward Algorithm

$$
\begin{aligned}
F_j^{\mathrm{M}}(i) &= \log \frac{e_{\mathrm{M}_j}(x_i)}{q_{x_i}} + \log\big[a_{\mathrm{M}_{j-1}\mathrm{M}_j} \exp\big(F_{j-1}^{\mathrm{M}}(i-1)\big) \\
&\quad + a_{\mathrm{I}_{j-1}\mathrm{M}_j} \exp\big(F_{j-1}^{\mathrm{I}}(i-1)\big) + a_{\mathrm{D}_{j-1}\mathrm{M}_j} \exp\big(F_{j-1}^{\mathrm{D}}(i-1)\big)\big]; \\
F_j^{\mathrm{I}}(i) &= \log \frac{e_{\mathrm{I}_j}(x_i)}{q_{x_i}} + \log\big[a_{\mathrm{M}_j\mathrm{I}_j} \exp\big(F_j^{\mathrm{M}}(i-1)\big) \\
&\quad + a_{\mathrm{I}_j\mathrm{I}_j} \exp\big(F_j^{\mathrm{I}}(i-1)\big) + a_{\mathrm{D}_j\mathrm{I}_j} \exp\big(F_j^{\mathrm{D}}(i-1)\big)\big]; \\
F_j^{\mathrm{D}}(i) &= \log\big[a_{\mathrm{M}_{j-1}\mathrm{D}_j} \exp\big(F_{j-1}^{\mathrm{M}}(i)\big) + a_{\mathrm{I}_{j-1}\mathrm{D}_j} \exp\big(F_{j-1}^{\mathrm{I}}(i)\big) \\
&\quad + a_{\mathrm{D}_{j-1}\mathrm{D}_j} \exp\big(F_{j-1}^{\mathrm{D}}(i)\big)\big].
\end{aligned}
$$

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Questions?

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