Hidden Markov Models
Some applications in bioinformatics
Hidden Markov models

Developed in speech recognition in the late 1960s ...

A HMM $M$ (with start- and end-states) defines a regular language $L_M$ of all the strings that $M$ can generate, i.e.

$$L_M = \{S \mid P_M(S) > 0\}$$

A run in model $M$ follows a Markovian path of states and generates a string $S$ over a finite alphabet with probability $P_M(S)$.
**Typical HMM problems**

**Annotation:** Given a model $M$ and an observed string $S$, what is the most probable path through $M$ that generates/outputs $S$

*The Viterbi algorithm. Running time $O(K^2N)$*
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**Classification:** Given a model $M$ and an observed string $S$, what is the total probability $P_M(S)$ of $M$ generating $S$

*The forward algorithm. Running time $O(K^2N)$*
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**Training:** Given a set of training strings and a model structure, find transition and emission probabilities that make the training set probable

*Hard! Use Baum-Welch or Viterbi iterative training methods ...*
Other HMM problems

**Comparison:** Given two models, what is a measure of their likeliness

*Compare entire sequence families*

**Consensus:** Given a model $M$, find the string $S$ that have the highest probability under the model

*Extract a short description of a sequence family*
History and applications of HMMs

History of HMMs

Hidden Markov Models were introduced in statistical papers by Leonard E. Baum and others in the late 1960s. One of the first applications of HMMs was speech recognition in the mid-1970s.

In the late 1980s, HMMs were applied to the analysis of biological sequences. Since then, many applications in bioinformatics...

Applications of HMMs in bioinformatics

- prediction of protein-coding regions in genome sequences
- modeling families of related DNA or protein sequences
- prediction of secondary structure elements in proteins

... and many others ...
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- ... and many others ...
Profiles and HMMs
A pairwise alignment of `acgtgtcaacgt` and `acgtcgtagcta`
Multiple Alignment

A generalization of pairwise alignment, comparison of multiple sequence which makes it possible to identify weaker similarities
<table>
<thead>
<tr>
<th>Protein</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCK_HUMAN/80-135</td>
<td>IIVVALYDYEAIH...HEDLSFQKGDQMVLEESG...EWKARSLATR...KEGYIPSNYVARV</td>
</tr>
<tr>
<td>LYN_HUMAN/65-120</td>
<td>DIVVALYPYGTH...PDDLSFKKGEHMKVLEEHG...EWKAKSLTIT...KEGFIPSNYVAKL</td>
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<tr>
<td>BLK_MOUSE/54-109</td>
<td>RFVVALFDYAAN...DRDLQVGLKEGQLQVRSTG...DWMARLSVTVG...REGVPSNFVPV</td>
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<tr>
<td>SR64_DROME/98-154</td>
<td>RRVVAVLYDYSQRD...ESDLRSFKGDREVDITTSDE...DWWRVVNLTR...QEGPLINFVAEE</td>
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<tr>
<td>CRKL_HUMAN/126-181</td>
<td>EYVRTLYDFPSQ...ADELLPDDKGEILVEKHEQ...QWSSARNKDG...RVGMIPVYVEK</td>
</tr>
<tr>
<td>NCK1_HUMAN/193-250</td>
<td>HVVQALYPFSSSN...DEELNCFEKGDMVIEKEFDE...PEWVKCRKING...MVGLVPKNYTVV</td>
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<tr>
<td>MY53_YEAST/1124-1181</td>
<td>PKFEEAAYDFPSG...SSEELPLKQGDIFISREDPS...GWSLAKLDDLS...KEGVNPVAYMPY</td>
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<tr>
<td>ABL_DROME/207-263</td>
<td>QLFVALYDFQAGG...ENQLSLKKEQVRILSYNSK...GEWCEAHSDSGN...VGNWPSNYVTPL</td>
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<tr>
<td>ABL1_HUMAN/64-119</td>
<td>NLFAVLYDFVASG...DNTLSITKGKLRGYNHNN...GEWCEAQTKNQ...QGWPSNYITPV</td>
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<tr>
<td>SPK1_DUGTI/36-92</td>
<td>YMVKAKYKYAASS...DSTDIFEEKEIMYVEQFDE...FLWLVKVQKDN...KEGLVPSNSYKQ</td>
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<td>SS81_YEAST/303-359</td>
<td>YKAKALEYDADDAYEISFQNEILQVDSE...WVKARRANG...ETGIIPSNYQVLI</td>
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<tr>
<td>DRK_DROME/1-56</td>
<td>MEAIKHDFSATA...DDELRSFKRTQLKILNMDDE...SNWYRAELDGK...EGLIPSNYEMK</td>
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<tr>
<td>SEM5_CAEEL/1-56</td>
<td>MEAAEAFDFQAGS...PDELSFKRGTNLKLNKSDE...PHWNAELDGK...EGFIPSNYRI</td>
</tr>
<tr>
<td>CSK_CHICK/12-68</td>
<td>TEICAYHNFGHTA...EQLDFPSKGDVTLTSTICK...PNWYAKAKNNV...REGIPAYNVQK</td>
</tr>
<tr>
<td>NCK1_HUMAN/5-59</td>
<td>VVVVAKFDFYVAQQ...EQLDIIKNNKRLWLLDSDKS...WWRVRNSMN...KTFGPFPSYVERK</td>
</tr>
<tr>
<td>SPCA_DROME/973-1027</td>
<td>ECVVAVLYDYTEKS...PREVSMMKGDVLTLNSNNK...DWMKVEVN...RQGFVFPAAYTKK</td>
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<tr>
<td>SPCA_HUMAN/980-1034</td>
<td>QRMYLIALFDQARS...PREVMTSKGDVLTLSSINS...DWMKVEAA...HGIVPAAYVRRL</td>
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<tr>
<td>SCD2_SCHPO/27-84</td>
<td>KVIRALYDTARK...ATEVSAKGFDDHVIGREND...KAWYEVNPAAG...TRGFVFPSYFEI</td>
</tr>
<tr>
<td>BEM1_YEAST/75-130</td>
<td>KVIVKAYSQAT...SKYLSMEEGFFYVSDEKD...WYKASNPSG...KEGVPKTYFEVF</td>
</tr>
<tr>
<td>SLC1A_YEAST/72-130</td>
<td>KKVRAIYDYEQVQNADEELTHFNDEFVFDVFFDKDA...DLWLVKSTVSN...EFGFSPANYVPE</td>
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<tr>
<td>RSG1_BOVIN/279-336</td>
<td>RRVARAILPTVDP...DIEISLFKGDVFVHEIERED...WMWTVNLRTD...EQGIIEDLYEEEV</td>
</tr>
<tr>
<td>YKA7_CAEEL/194-250</td>
<td>PYGIAKFDYAPA...EEDSRMLGRGTDYSLJKVD...EWFYGENQNQR...TFGFVPSYLDK</td>
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<tr>
<td>STE6_SCHPO/3-58</td>
<td>FQTAAIDYENSS...NRPSFLKFSA5T3LTVVELED...GWCDGICSE...KRGWFPSICDSS</td>
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<tr>
<td>NCF1_HUMAN/159-213</td>
<td>QTYRMAIDYETKS...GEMALSTGDVEVEKSES...GWWFCMQKA...KRGNIPASFLEPL</td>
</tr>
<tr>
<td>NCF2_HUMAN/229-283</td>
<td>EPHYVAIKAYTAVE...GEDSERLEGAEVEHVIKLD...GEWVIRKKDD...VTFYFPSMLQK</td>
</tr>
<tr>
<td>SCD2_SCHPO/126-183</td>
<td>LFGVQVFDFLEEAA...PDELEIKAAIEATIARSH...EWLVKAPMRGL...GLPLIFSLQF</td>
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<tr>
<td>BEM1_YEAST/158-215</td>
<td>LAYAVLYDFKAEK...ADELTYVGENFICAHNC...EWFIAKPGRLG...GGLVPVPFVS</td>
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<tr>
<td>SLA1_YEAST/356-413</td>
<td>KRGIVQYDQAMESA...QDLTIKSQGKYVLDKKS...KDWNMQLVDSG...KSLGVPQFIEPV</td>
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<tr>
<td>NCF2_HUMAN/243-297</td>
<td>EAHRVLFGFVPF...KEELQVMPGNNIFVFLKKGND...NWATVMFN...QKGLVPCNYLEP</td>
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<tr>
<td>BOI2_YEAST/46-105</td>
<td>PMXIAINEYFKRM...EDELMKFPDKDKEIVTDDEEKDSYWFGNRNLTDN...EGLYPVFVTQK</td>
</tr>
<tr>
<td>BZZ1_YEAST/496-553</td>
<td>GKNKVLYAYVQKD...DDEITTPGDKISLVDARTG...SGWTKINNDDTG...ETGLVPTYIRIS</td>
</tr>
</tbody>
</table>
The aim of **profile analysis** is to identify highly conserved regions/motifs of multiple alignments.

A **profile** is a summary of the region/motif (sequence family) in terms of column specific substitution and gap statistics.

A **profile** can be used to test if a new sequence has the characteristics of the region by “aligning” it to the profile.
## Multiple alignments and profiles

An aligned sequence family or “region of interest”

<table>
<thead>
<tr>
<th>. . .</th>
<th>ACA</th>
<th>### ATG</th>
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<tr>
<td>. . .</td>
<td>TCA</td>
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Multiple alignments and profiles

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A “classic” profile summarizing the sequence family

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**ACAATTC** is the consensus sequence
Multiple alignments and profiles

An aligned sequence family or “region of interest”

```
... ACA --- ATG ...
... TCA ACT ATC ...
... ACA C-- AGC ...
... AGA --- ATC ...
... ACC G-- ATC ...
```

The frequency $f_{ij}$ of symbol $i$ in column $j$.

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A   C   A   A   -   -   -   A   T   C
Multiple alignments and profiles

Position-specific score matrix

A profile can be used to decide if a new sequence looks like to profiled motifs, i.e. fits the profile ...

How well does G fits column 9?

“Fit of G to column 9” = \( f_{G9} \) / “background frequency of G” = 0.2 / 0.25 = 0.8

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**How well does G fits column 9?**

"Fit of G to column 9" = \( f_{G9} / \) "background frequency of G" = 0.2 / 0.25 = 0.8

**How well does ACAACTAGG fit the profile?**

"Fit of ACAACTAGG" = (0.8/0.25) * (0.8/0.25) * ... * (0.2/0.25) = 42.95

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A: C: A: A: -: -: -: -: A: T: C

A probabilistic HMM based model of a sequence family related by substitutions, insertions and deletions.

Advantages: Focus on modeling. Algorithms for determining if the profile fits a new sequence (forward) and matching against the profile (Viterbi) are immediately available Parameters can be estimated by well founded statistical theory ...
Constructing a profile HMMs

Length of model equals length of consensus sequence
Constructing a profile HMMs

Length of model equals length of consensus sequence
Constructing a profile HMMs

Problem: Insertions are only possible between position 3 and 4?

Length of model equals length of consensus sequence

Match states
Constructing a profile HMMs

**Problem:** Insertions are only possible between position 3 and 4?

**Solution:** Add insert-states ...

Length of model equals length of consensus sequence
Constructing a profile HMMs

**Problem:** Model cannot match short sequences?

**Problem:** Insertions are only possible between position 3 and 4?

**Solution:** Add insert-states ...

Length of model equals length of consensus sequence
Problem: Model cannot match short sequences?

Solution: Add delete-states ...

Length of model equals length of consensus sequence
Length of model equals length of consensus sequence
Profile HMM

Consists of Match-, Insert-, and Delete-states. A run generates a sequence (DNA or protein). The hidden path of states explains how the generated sequence relates to the sequence family ...
Applications of profile HMMs

Database searching / classification

Using the **Forward algorithm** we can compute the total probability of a sequence being generated by the model, i.e. belongs to the sequence family. Can be used to **classify unknown sequences** as belonging to the family ...

Multiple alignment / annotation

Using the **Viterbi algorithm** we can compute the most likely path through the model that generates a sequence, i.e. the most likely alignment of the sequence against the sequence family. Can be used to build multiple alignments ...
Profile HMM

Consists of **Match**-, **Insert**-, and **Delete**-states. A run generates a sequence (DNA or protein). The hidden path of states explains how the generated sequence relates to the sequence family ...

**Seq:** N B L S  
**Path:** Begin – M1 – I2 – D2 – M3 – M4 - End
Pfam

Pfam is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains and families. For each family in Pfam you can ...

Look at multiple alignments
View protein domain architectures
Examine species distribution
Follow links to other databases
View known protein structures

http://pfam.sanger.ac.uk
How to handle silent-states?
Viterbi algorithm (with silent states)

\[
\max_{s} \mathbf{P} \left( s \right) = R_{\text{vit}} \left[ |s|, \text{End} \right]
\]

where

\[
R_{\text{vit}} \left[ i, \text{p} \right] = \max \left\{ R_{\text{vit}} \left[ i, \text{q} \right] \cdot P \left( \text{q} \rightarrow \text{p} \right) \right\}
\]

\[
R_{\text{vit}} \left[ i, \text{p} \right] = \max \left\{ R_{\text{vit}} \left[ i-1, \text{q} \right] \cdot P \left( \text{q} \rightarrow \text{p} \right) \right\} \cdot P \left( s[i] \mid \text{q}_i \right)
\]

Yields the Viterbi algorithm that computes (the probability of) the most likely path that generates a string \( S \).
Forward algorithm (with silent states)

\[
P(s) = R_{fw} \left[ \left\lfloor s, \text{End} \right\rfloor \right]
\]

where

\[
R_{fw} \left[ i, p \right] = \sum_{q} \left\{ R_{fw} \left[ i, q \right] \cdot P \left( q \rightarrow p \right) \right\}
\]

\[
R_{fw} \left[ i, p \right] = \sum_{q} \left\{ R_{fw} \left[ i - 1, q \right] \cdot P \left( q \rightarrow p \right) \right\} \cdot P \left( s[i] \mid q \right)
\]

Yield the forward algorithm that computes the total probability of generating string S.
Pair HMMs
To computationally find an optimal alignment, we must:

1. Define the cost of an alignment (typically a sub cost and a gap cost)
2. Define an optimal alignment (typically an alignment of max (or min) cost)
3. Construct an efficient algorithm for computing an optimal alignment
Computing an optimal alignment

Cost of an optimal alignment of $A[1..i]$ and $B[1..j]$

\[
\text{Cost}(i, j) = \max \begin{cases} 
\text{Cost}(i-1, j-1) + \text{subcost}(A[i], B[j]) \\
\text{Cost}(i-1, j) + \text{gapcost} \\
\text{Cost}(i, j-1) + \text{gapcost} \\
0 \text{ if } i=0 \text{ and } j=0
\end{cases}
\]

To compute the score of an optimal alignment of $A[1..n]$ and $B[1..m]$, fill out an $(n+1) \times (m+1)$ table cf. above recursion.

The optimal alignment score is in entry $(n,m)$. 
Pairwise alignment using HMMs

A Pair-HMM generates an alignment of two sequences and a state path. The emission distributions are either over:
- Pairs of symbols
- A symbol from either sequence (implicitly paired with a gap)

Pair-HMM generating alignments with ‘affine gap-cost’

Generating an alignment:
State path = B M M X M Y Y M M E
x = x₁ x₂ x₃ x₄ - - x₅ x₆
y = y₁ y₂ - y₃ y₄y₅y₆y₇
Algorithm: Viterbi algorithm for pair HMMs

Initialisation:
\[ v^M(0, 0) = 1. \text{ All other } v^*(i, 0), v^*(0, j) \text{ are set to 0.} \]

Recurrence: \( i = 1, \ldots, n, j = 1, \ldots, m; \)
\[ v^M(i, j) = p_{x_i y_j} \max \left\{ (1 - 2\delta - \tau)v^M(i - 1, j - 1), (1 - \varepsilon - \tau)v^X(i - 1, j - 1), (1 - \varepsilon - \tau)v^Y(i - 1, j - 1) \right\}; \]
\[ v^X(i, j) = q_{x_i} \max \left\{ \delta v^M(i - 1, j), \varepsilon v^X(i - 1, j) \right\}; \]
\[ v^Y(i, j) = q_{y_j} \max \left\{ \delta v^M(i, j - 1), \varepsilon v^Y(i, j - 1) \right\}. \]

Termination:
\[ v^E = \tau \max(v^M(n, m), v^X(n, m), v^Y(n, m)). \]
Pairwise alignment using HMMs

Algorithm: Viterbi algorithm for pair HMMs

Initialisation:
\[ v^M(0, 0) = 1. \text{ All other } v^*(i, 0), v^*(0, j) \text{ are set to } 0. \]

Recurrence: \( i = 1, \ldots, n, j = 1, \ldots, m; \)
\[
v^M(i, j) = p_{x_i y_j} \max \left\{ (1 - 2\delta - \tau)v^M(i - 1, j - 1), (1 - \varepsilon - \tau)v^X(i - 1, j - 1), (1 - \varepsilon - \tau)v^Y(i - 1, j - 1) \right\}
\]

\[
v^X(i, j) = q_x_i \max \left\{ \delta v^M(i - 1, j), \varepsilon v^X(i - 1, j) \right\}
\]

\[
v^Y(i, j) = q_{y_j} \max \left\{ \delta v^M(i, j - 1), \varepsilon v^Y(i, j - 1) \right\}
\]

Termination:
\[ v^E = \tau \max(v^M(n, m), v^X(n, m), v^Y(n, m)). \]

Note similarities with the “traditional” non-HMM based solution.

Running time?