Profile Hidden Markov Models

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Artificial Intelligence for Bioinformatics

Profile HMM (Haussler et al., 1993)

Motivation

- Biological sequences are typically grouped into families with a certain functionality
- A relevant task is that of detecting whether a target sequence belongs to a certain family
- This could be done aligning the sequence to each of the sequences from the family
- However, pairwise alignments alone can miss cases of distantly related sequences
- A better way to detect such relationship would be:
    1. building a model of the family
    2. testing whether the target sequence is compatible with the model

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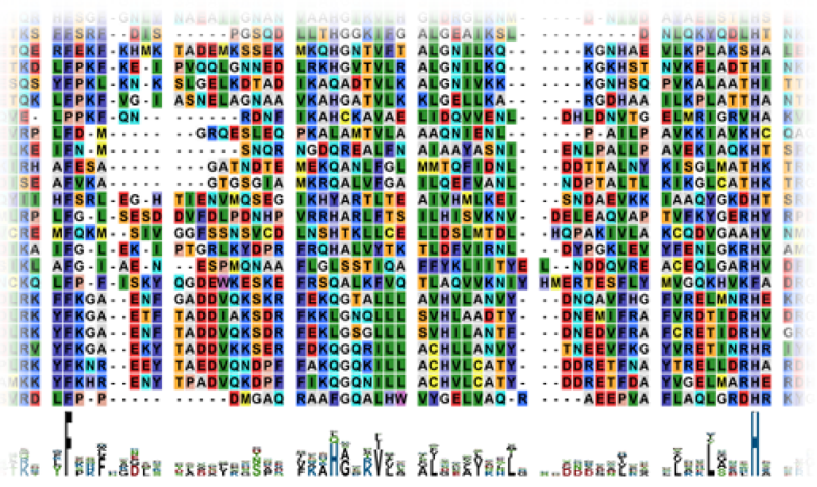
Multiple alignments

- A multiple alignment consists of the simultaneous alignment of a set of sequences
- All sequences from a certain family could be aligned to form a multiple alignment representing the family
- The family model should be a compact probabilistic representation of such multiple alignment

Multiple alignment: example for the globin family



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QR  HFSGF-GNLF NAEALLGNAN LAAHGIKVLH GLDRGLKNM- ----D-NLVD ALAELSTLHS
TKS FFSRF--DIS -----PGSQD LLTHGGKIFG ALGEAIKSL- ---------D NLQKYQDLHT NK
TQE RFEKF-KHMK TADEMKSSEK MKQHGNTVFT ALGNILKQ-- ----KGNHAE VLKPLAKSHA LE
TKD LFPKF-KE-I PVQQLGNNED LRKHGVTVLR ALGNILKQ-- ----KGKHST NVKELADTHI NK
SQS YFPKL-KN-K SLGELKDTAD IKAQADTVLK ALGNIVKK-- ----KGNHSQ PVKALAATHI TT
TQK LFPKF-VG-I ASNELAGNAA VKAHGATVLK KLGELLKA-- ----RGDHAA ILKPLATTHA NT
VE- LPPKF-QN-- ------RDNF IKAHCKAVAE LIDQVVENL- --DHLDNVTG ELMRIGRVHA KV
VRP LFD-M----- --GRQESLEQ PKALAMTVLA AAQNIENL-- ----P-AILP AVKKIAVKHC QA
LKE IFN-M----- ------SNQR NGDQREALFN AIAAYASNI- --ENLPALLP AVEKIAQKHT SF
LRH AFESA----- ---GATNDTE MEKQANLFGL MMTQFIDNL- --DDTTALNY KISGLMATHK TR
LSE AFVKA----- ---GTGSGIA MKRQALVFGA ILQEFVANL- --NDPTALTL KIKGLCATHK TR
VII HFSRL-EG-H TIENVMQSEG IKHYARTLTE AIVHMLKEI- --SNDAEVKK IAAQYGKDHT SR
LRP LFG-L-SESD DVFDLPDNHP VRRHARLFTS ILHISVKNV- -DELEAQVAP TVFKYGERHY RP
CRE MFQKM--SIV GGFSSNSVCD LNSHTKLLCE LLDSLMTDL- -HQPAKIVLA KCQDVGAAHV NM
LKA IFG-L-EK-I PTGRLKYDPR FRQHALVYTK TLDFVIRNL- --DYPGKLEV YFENLGKRHV AM
LKL AFG-I-AE-N --ESPMQNAA FLGLSSTIQA FFYKLIITYE L--NDDQVRE ACEQLGARHV DF
CKQ LFP-F-ISKY QGDEWKESKE FRSQALKFVQ TLAQVVKNIY HMERTESFLY MVGQKHVKFA DR
LRK FFKGA--ENF GADDVQKSKR FEKQGTALLL AVHVLANVY- --DNQAVFHG FVRELMNRHE KR
LRK YFKGA--ETF TADDIAKSDR FKKLGNQLLL SVHLAADTY- --DNEMIFRA FVRDTIDRHV DR
LRK YFKGA--ENF TADDVQKSDR FEKLGSGLLL SVHILANTF- --DNEDVFRA FCRETIDRHV GR
LRV YFKGA--EKY TADDVKKSER FDKQGQRILL ACHLLANVY- --TNEEVFKG YVRETINRHR IY
LRK YFKNR--EEY TAEDVQNDPF FAKQGQKILL ACHVLCATY- --DDRETFNA YTRELLDRHA RD
MKK YFKHR--ENY TPADVQKDPF FIKQGQNILL ACHVLCATY- --DDRETFDA YVGELMARHE RD
VRD LFP-P----- -----DMGAQ RAAFGQALHW VYGELVAQ-R ----AEEPVA FLAQLGRDHR KY
```

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Dealing with ungapped regions

- Large portions of multiple alignments for a protein family consist of ungapped sequences of residues
- Each position in such regions has a certain amino-acid *profile*, representing the frequencies with which each amino-acid occurs in the column of the alignment
- By normalizing such profiles, it is possible to derive a probability of observing a certain residue *in that position*.

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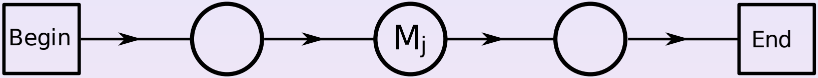

Probabilistic model for ungapped regions

- Each position in the region can be modelled with a match state with position specific emission probabilities
- The whole region can be modelled as a sequence of match states, with transitions only between successive states
- Beginning and end of the region can be modelled with special non-emitting begin and end states

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Dealing with gaps

- Gaps in the alignment tend to occur at certain positions (i.e. gaps align columnwise)
- Gaps can be dealt with by modelling the two type of corresponding modifications:
    - insertions of a sequence of residues
    - deletions of a sequence of residues

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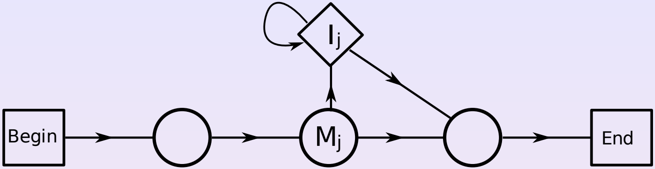

Probabilistic model with insertions

- An insertion should be modelled with a specific insertion state *I* (represented as a diamond)
- As insertions in different positions have different probabilities, transition probabilities should be position specific
- An insertion state should also have a self transition to account for insertions of sequences of residues
- Emission probabilities could instead be set for all insertion states equal to the background probability q_a of observing a certain amino-acid *a* in an arbitrary sequence.

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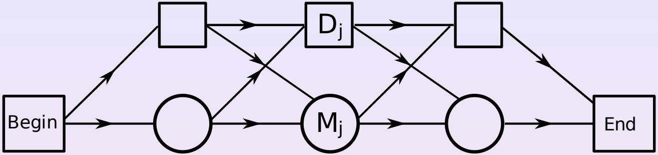
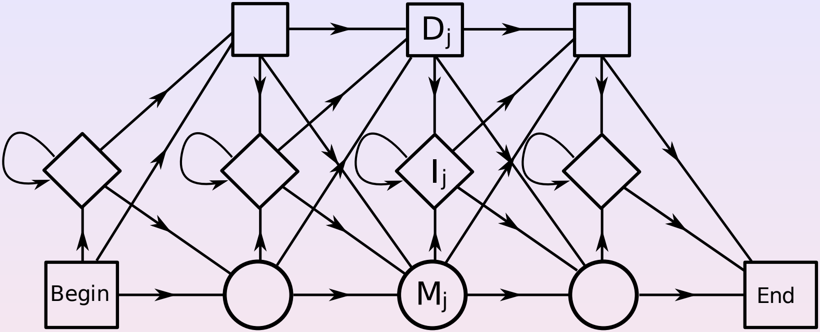


Probabilistic model with deletions

- Deletions should be modelled as special *silent* states *D* which do not emit symbols (represented as a square)
- Allowing self transitions as in insertions would complicate inference algorithms
- Sequences of deletions are instead modelled as sequences of deletion states
- This also allows to specify different transition probabilities between deletion states

Profile HMM: full model



Note

- We allow direct transitions between insertion and deletion states
- These situations are quite rare, but leaving such transitions out would give zero probability to these cases

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Parameter estimation

- We assume a multiple alignment profile for the family of interest is available (created with multiple alignment algorithms, possibly relying on 3D information)
- We need to estimate transition probabilities between states, and emission probabilities for match states (those for insertion states are set to background probabilities for arbitrary sequences)
- We first decide which positions in the alignment correspond to match states, and which to insertions or deletions:
  - A reasonable approach is that if half of the column elements in a position are gaps, the position is **not** a match state
- This allows to turn our alignment in a fully observed set of training examples: probabilities can be estimated from counts

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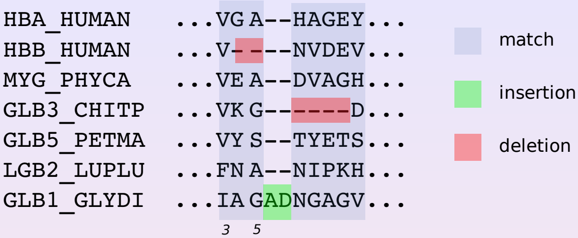

```
HBA_HUMAN     ...VG A--HAGEY...
HBB_HUMAN     ...V- ---NVDEV...
MYG_PHYCA     ...VE A--DVAGH...
GLB3_CHITP    ...VK G------D...
GLB5_PETMA    ...VY S--TYETS...
LGB2_LUPLU    ...FN A--NIPKH...
GLB1_GLYDI    ...IA GADNGAGV...
                 3   5
```

▨ match

🟩 insertion

🟥 deletion

Parameter estimation: examples

- Non-zero emission probabilities for match state M_3:

$$e_{M_3}(V) = 5/7 \quad e_{M_3}(F) = 1/7 \quad e_{M_3}(I) = 1/7$$

- Non-zero transition probabilities from match state M_3:

$$a_{M_3 M_4} = 6/7 \quad a_{M_3 D_4} = 1/7$$

- Non-zero transition probabilities from match state M_5:

$$a_{M_5 M_6} = 5/7 \quad a_{M_5 I_5} = 1/7 \quad a_{M_5 D_6} = 1/7$$

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Parameter estimation: adding pseudocounts

- All transitions and emissions never observed in the multiple alignment will be set to zero using only counts.
- This can be a problem if an unsufficient number of examples is available (i.e. always)
- A simple solution consists of adding a non-zero prior probability for any transition or emission, to be combined to the counts observed on data
- Such prior probability can be thought of coming from *pseudocounts* of hypothetical observations of emissions/transitions
- The simplest pseudocount (Laplace smoother) consists of adding a single hypothetical observation of any possible emission/transition