Algorithms for HMMs

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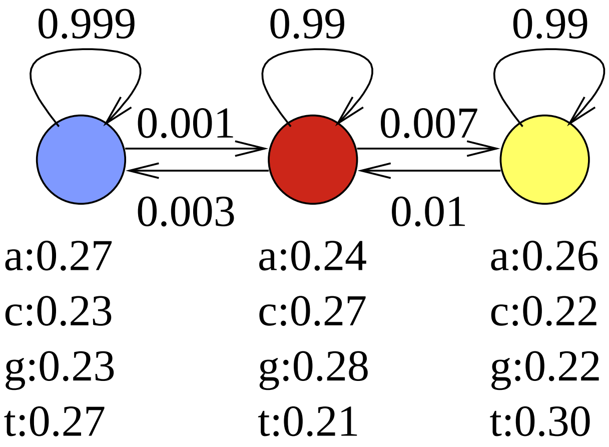
Recall: HMM (hidden Markov model, skrytý Markovov model)

model (HMM) → random DNA sequence S, random annotation A (similar to real DNA)

$\Pr(S, A)$ – probability that the model generates pair (S, A).



Assume the model starts in the blue state

$$\Pr(\mathsf{acag}) = 0.27 \cdot 0.001 \cdot 0.27 \cdot 0.99 \cdot 0.24 \cdot 0.99 \cdot 0.28 = 4.8 \cdot 10^{-6}$$

$$\Pr(\mathsf{acag}) = 0.27 \cdot 0.999 \cdot 0.23 \cdot 0.999 \cdot 0.27 \cdot 0.999 \cdot 0.23 = 0.0038$$

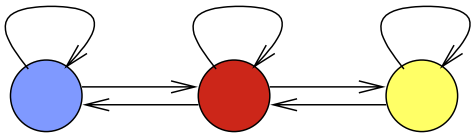
Another toy example: weather

- Period of low atmospheric pressure: mostly raining
- Period of high atmospheirc pressure: mostly sunny

Each period typically lasts several days

Exercise: Represent by an HMM

Recall: Parameters of HMMs (notation)



Sequence $S = S_1, \ldots, S_n$

Annotation $A = A_1, \ldots, A_n$

Model parameters:

Transition probability $a(u, v) = \Pr(A_{i+1} = v | A_i = u)$,

Emission probability $e(u, x) = \Pr(S_i = x | A_i = u)$,

Starting probability $\pi(u) = \Pr(A_1 = u)$.

a	🟥	🟨	🟦
🟥	0.99	0.007	0.003
🟨	0.01	0.99	0
🟦	0.001	0	0.999

e	a	c	g	t
🟥	0.24	0.27	0.28	0.21
🟨	0.26	0.22	0.22	0.30
🟦	0.27	0.23	0.23	0.27

The resulting probability:

$$\Pr(A, S) = \pi(A_1)e(A_1, S_1) \prod_{i=2}^{n} a(A_{i-1}, A_i)e(A_i, S_i)$$

Viterbi algorithm

For a given HMM and sequence S,
find the most probable annotation (state path)
$A = \arg\max_A \Pr(A, S) = \arg\max_A \Pr(A \mid S)$

Any ideas?

Recall our example:

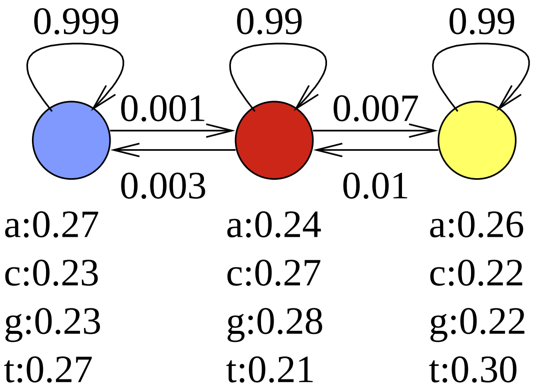
$$\Pr(\text{acag}) = 0.27 \cdot 0.001 \cdot 0.27 \cdot 0.99 \cdot 0.24 \cdot 0.99 \cdot 0.28 = 4.8 \cdot 10^{-6}$$

$$\Pr(\text{acag}) = 0.27 \cdot 0.999 \cdot 0.23 \cdot 0.999 \cdot 0.27 \cdot 0.999 \cdot 0.23 = 0.0038$$

Viterbi algorithm

Find the most probable state path $A = \arg\max_A \Pr(A, S)$

Subproblem $V[u,i]$: probability of the most probable state path generating $S_1 S_2 \ldots S_i$ and ending in state u



$V[u,i]$	a	c	a	g
🟥				
🟨				
🟦				

Viterbi algorithm

Subproblem $V[u,i]$: probability of the most probable state path generating $S_1S_2\dots S_i$ and ending in state u

Recurrence?

$V[u,1] =$

$V[u,i] =$

Recall notation:

Sequence $S = S_1, \dots, S_n$, annotation $A = A_1, \dots, A_n$
Transition probability $a(u,v) = \Pr(A_{i+1} = v | A_i = u)$,
Emission probability $e(u,x) = \Pr(S_i = x | A_i = u)$,
Starting probability $\pi(u) = \Pr(A_1 = u)$.
$\Pr(A,S) = \pi(A_1)e(A_1,S_1)\prod_{i=2}^{n} a(A_{i-1},A_i)e(A_i,S_i)$

Viterbi algorithm

Subproblem $V[u,i]$: probability of the most probable state path generating $S_1 S_2 \dots S_i$ and ending in state u

Recurrence:

$V[u,1] = \pi_u \cdot e_{u,S_1}$

$V[u,i] = \max_w V[w,i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Algorithm, final answer, running time?

Recall notation:

Sequence $S = S_1, \dots, S_n$, annotation $A = A_1, \dots, A_n$

Transition probability $a(u,v) = \Pr(A_{i+1} = v | A_i = u)$,

Emission probability $e(u,x) = \Pr(S_i = x | A_i = u)$,

Starting probability $\pi(u) = \Pr(A_1 = u)$.

$\Pr(A,S) = \pi(A_1) e(A_1, S_1) \prod_{i=2}^{n} a(A_{i-1}, A_i) e(A_i, S_i)$

Viterbi algorithm (overview)

Goal: Find the most probable state path $A = \arg\max_A \Pr(A, S)$

Subproblem $V[u, i]$: probability of the most probable state path generating $S_1 S_2 \dots S_i$ and ending in state u

Recurrence:

$V[u, 1] = \pi_u \cdot e_{u,S_1}$
$V[u, i] = \max_w V[w, i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Algorithm:

```
Initialize $V[*, 1]$
for $i = 2 \dots n$ ($n$=length of $S$)
    for $u = 1 \dots m$ ($m$ =number of states)
        compute $V[u, i]$, keep best $w$ in $B[u, i]$
Maximum $V[u, n]$ over all $u$ is $\max_A \Pr(A, S)$
Retrieve the full path using matrix $B$
```

Dynamic programming in $O(nm^2)$ time

Second problem: overall probability of S

Viterbi computes $\arg\max_A \Pr(A, S)$

Now we want $\Pr(S) = \sum_A \Pr(A, S)$

Usefull e.g. to compare different models, which is more likely to produce S

Any ideas?

Recall our example:

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Forward algorithm (dopredný algoritmus)

Computes overall probability that the model emits S

$\Pr(S) = \sum_A \Pr(A, S)$

Subproblem $F[u,i]$: probability that in i steps we generate $S_1, S_2, \dots S_i$ and end in state u.

$F[u,i] = \Pr(A_i = u \wedge S_1, S_2, \dots, S_i) =$

$\sum_{A_1,\dots,A_{i-1},A_i=u} \Pr(A_1, A_2, ..., A_i \wedge S_1, S_2, ..., S_i)$

Recurrence?

$F[u,1] =$

$F[u,i] =$

Recall Viterbi recurrence:

$V[u,1] = \pi_u \cdot e_{u,S_1}$

$V[u,i] = \max_w V[w,i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Forward algorithm

Computes overall probability that the model emits S

$\Pr(S) = \sum_A \Pr(A, S)$

Subproblem $F[u, i]$: probability that in i steps we generate $S_1, S_2, \ldots S_i$ and end in state u.

Recurrence:

$F[u, 1] = \pi_u \cdot e_{u,S_1}$

$F[u, i] = \sum_w F[w, i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Recall Viterbi recurrence:

$V[u, 1] = \pi_u \cdot e_{u,S_1}$

$V[u, i] = \max_w V[w, i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Forward algorithm

Computes overall probability that the model emits S

$\Pr(S) = \sum_A \Pr(A, S)$

Subproblem $F[u, i]$**:** probability that in i steps we generate $S_1, S_2, \dots S_i$ and end in state u.

Recurrence:

$F[u, 1] = \pi_u \cdot e_{u,S_1}$

$F[u, i] = \sum_w F[w, i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Result? $\Pr(S) =$

Running time?

Forward algorithm

Computes overall probability that the model emits S

$\Pr(S) = \sum_A \Pr(A, S)$

Subproblem $F[u, i]$: probability that in i steps we generate $S_1, S_2, \dots S_i$ and end in state u.

Recurrence:

$F[u, 1] = \pi_u \cdot e_{u,S_1}$

$F[u, i] = \sum_w F[w, i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Result $\Pr(S) = \sum_u F[u, n]$

Running time $O(nm^2)$

Third problem: probability that S_i was generated in state u

$\Pr(A_i = u \mid S) = \frac{\Pr(A_i=u,S)}{\Pr(S)}$
$\Pr(A_i = u, S) = \sum_{A:A_i=u} \Pr(A, S)$

Compute this by a combination of forward and backward algorithms

$F[u,i]$: probability that in i steps we generate $S_1, S_2, \dots S_i$ and end in state u.

$B[u,i]$: probability that if we start at u at position i, we will generate $S_{i+1} \dots, S_n$ in the next steps

$\Pr(A_i = u, S) = F[u,i] \cdot B[u,i]$

Backward algorithm (spätný algoritmus)

Forward algorithm $F[u,i]$: probability that in i steps we generate $S_1, S_2, \ldots S_i$ and end in state u.

$F[u,1] = \pi_u \cdot e_{u,S_1}$
$F[u,i] = \sum_w F[w,i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Backward algorithm $B[u,i]$: probability that if we start at u at position i, we will generate $S_{i+1} \ldots, S_n$ in the next steps

How to compute $B[u,i]$?

Backward algorithm (spätný algoritmus)

Forward algorithm $F[u,i]$: probability that in i steps we generate $S_1, S_2, \ldots S_i$ and end in state u.

$F[u,1] = \pi_u \cdot e_{u,S_1}$
$F[u,i] = \sum_w F[w,i-1] \cdot a_{w,u} \cdot e_{u,S_i}$

Backward algorithm $B[u,i]$: probability that if we start at u at position i, we will generate $S_{i+1} \ldots, S_n$ in the next steps

$B[u,n] = 1$
$B[u,i] = \sum_w F[w,i+1] \cdot a_{u,w} \cdot e_{w,S_{i+1}}$

Exercise: How to use matrix B to compute $\Pr(S)$?

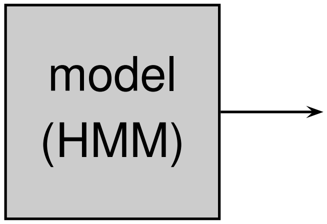
Posterior decoding

Using forward/backward we can compute
$\Pr(A_i = u \,|\, S)$ for each u and i (posterior probabilities of states)
in $O(nm^2)$ overall time

We can also select A such that $A_i = \max_i \Pr(A_i = u \,|\, S)$
Advantage: This takes into account suboptimal state paths
Disadvantage: $\Pr(A \,|\, S)$ can be zero or very low

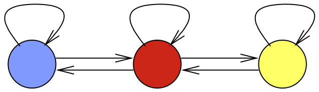
Another option: use posterior probabilities to assign confidence to parts of prediction from Viterbi

Recall: Finding genes with HMMs



model (HMM) → random DNA sequence S, random annotation A
(similar to real DNA)

$\Pr(S, A)$ – probability that the model generates pair (S, A).

- **Determine states and transitions of the model:** by hand based on your knowledge about the gene structure 
- **Parameter training:** emission and transition probabilities are determined based on the real sequences with known genes (**training set**)
- **Use:** for a new sequence S, find the most probable annotation
  $A = \arg\max_A \Pr(A|S)$
  Viterbi algorithm in $O(nm^2)$ (dynamic programming)

Parameter training

- States and allowed transitions typically manually
- Probabilities of transition, emission, starting usually automatically from training adata
- More complex models with more parameters need more training data

  Otherwise **overfitting**: model fits training data very well but behaves poorly on unseen examples
- To test acurracy of the model use a separate testing set not used for training.

HMM parameter training from annotated sequences

Input: state diagram of the model and a training set of sequences and state paths $(S^{(1)}, A^{(1)}), (S^{(2)}, A^{(2)}), \ldots$

Goal: choose parameters maximalizing their likelihood in the model $\arg\max_{a,e,\pi} \prod_i \Pr(S^{(i)}, A^{(i)} | a, e, \pi)$

This is achieved by using observed frequencies

Fir example $a_{u,v}$: find all occurrences of state u and find out how often is it followed by v

HMM parameter training from unannotated sequences

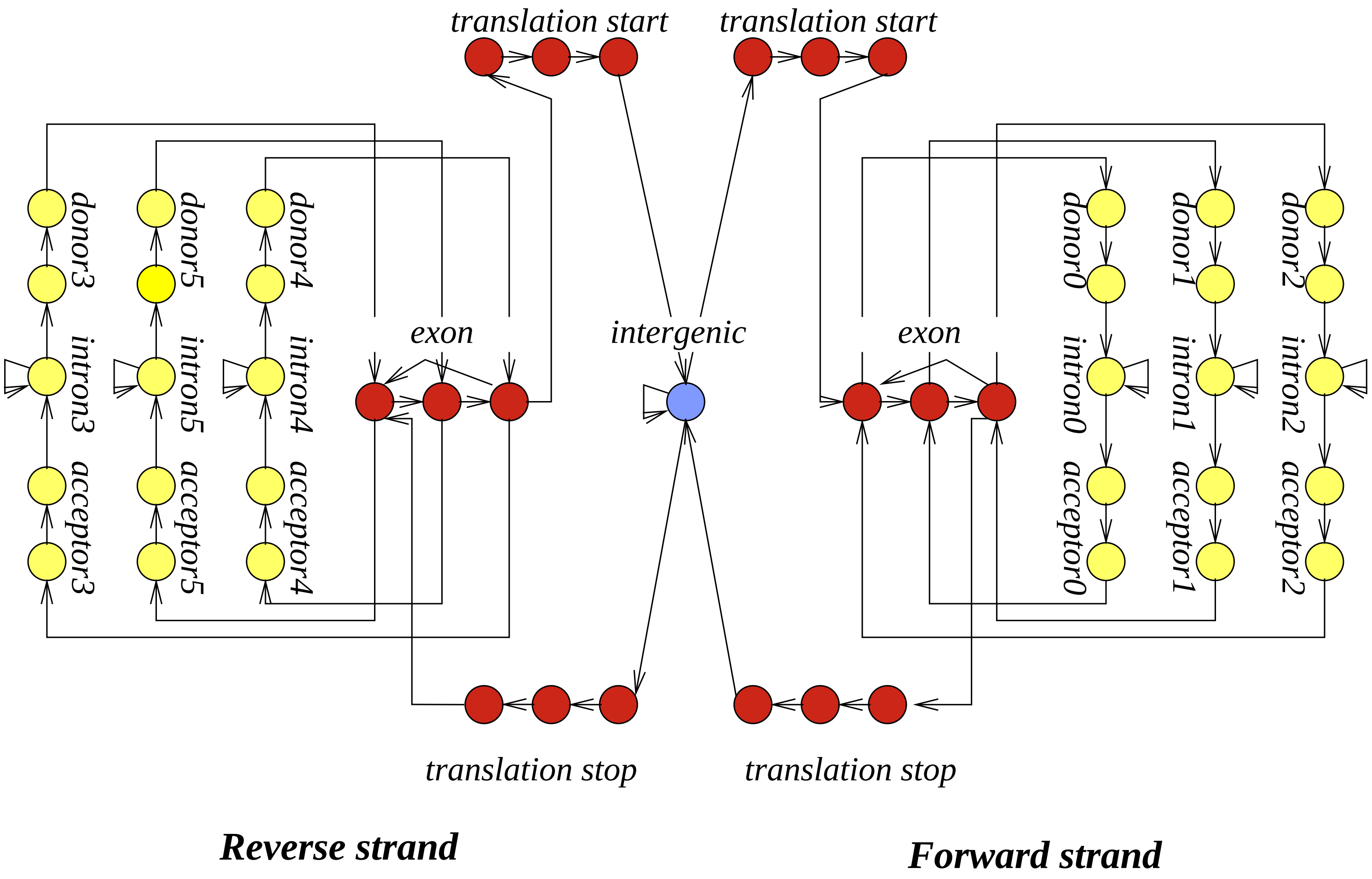
Input: state diagram of the model and a training set of sequences $S^{(1)}, S^{(2)}, \ldots$, state paths $A^{(1)}$ unknown

Goal: choose parameters maximalizing their likelihood in the model $\arg\max_{a,e,\pi} \prod_i \Pr(S^{(i)}|a, e, \pi)$

Baum-Welch algorithm (version of expectation maximization, EM).
Iterative heuristic algorithm improving parameters until convergence.
Each iteration forward and backward algorithms

Designing state diagram of HMM

We have seen example of gene finding



Two examples

- How would you modify gene finding HMM so that intergenic regions have length at least 10?
  What about lengths of introns and exons?

- Create a model of prokaryotic genes without introns
  which are grouped into operons,
  each operon starting with a promoter containing sequence
  TATAAT 10bp before transcription start.
  Genes in an operon are separated by short untranslated regions.
  Operons are separated by some untranscribed regions.