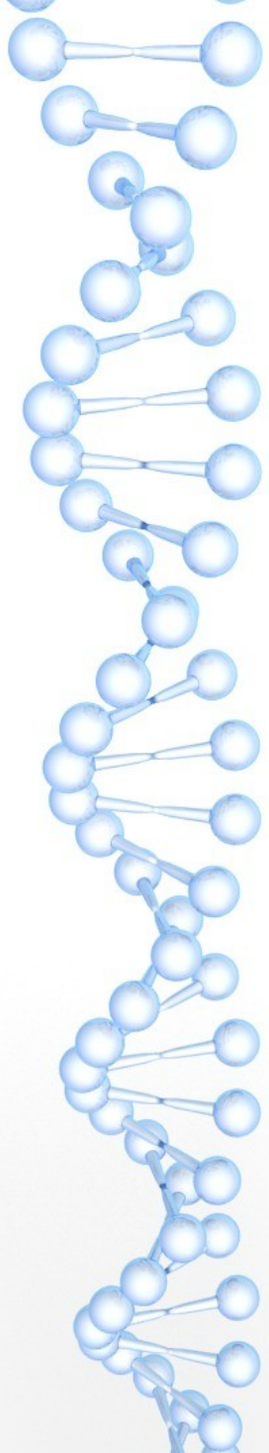
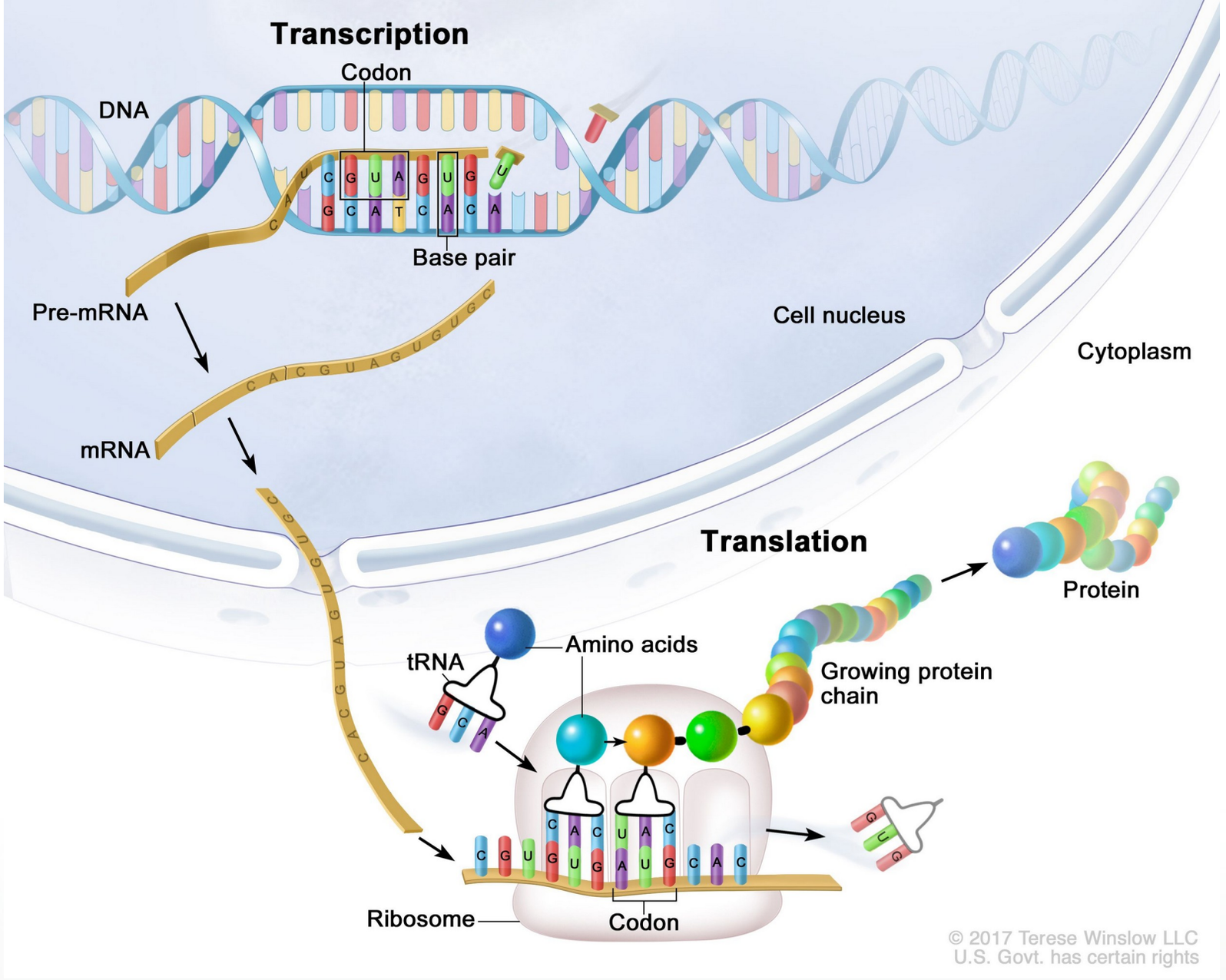


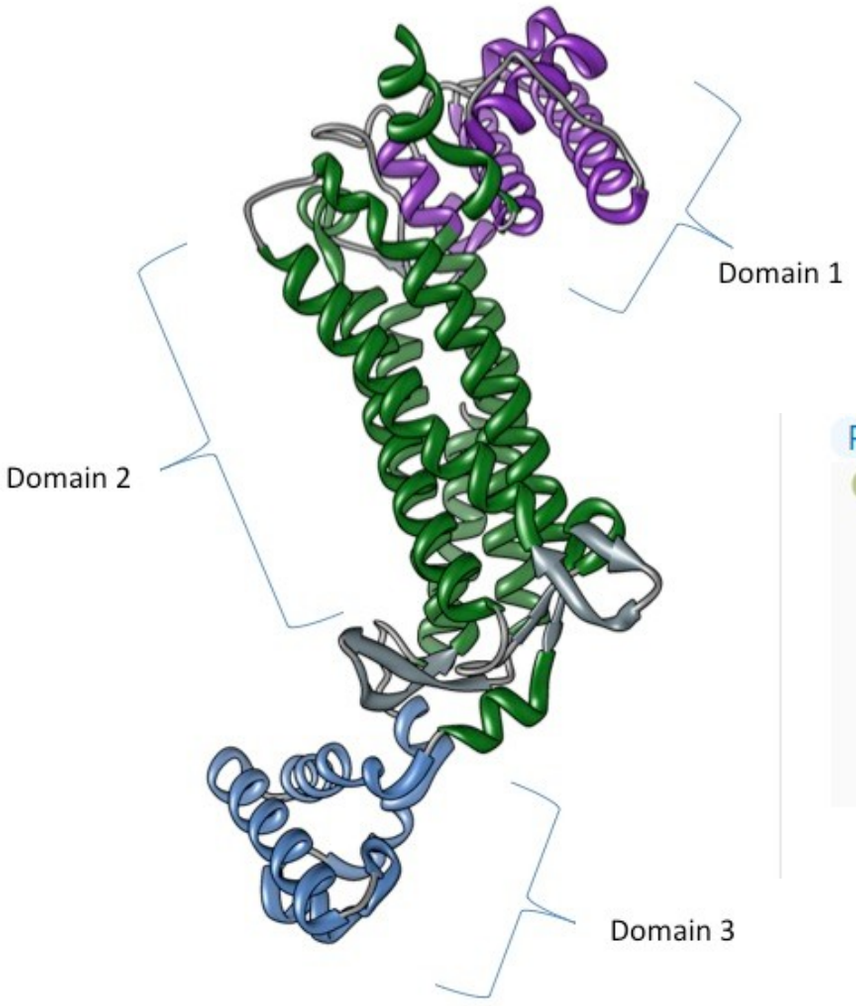
SVEUČILIŠTE U ZAGREBU
Fakultet elektrotehnike i računarstva

Implementacija skrivenih Markovljevih modela u domenskoj klasifikaciji proteinskih sekvenci

- **Pristupnik**: Domagoj Sviličić (0036540224)
- **Mentor**: doc. dr. sc. Krešimir Križanović



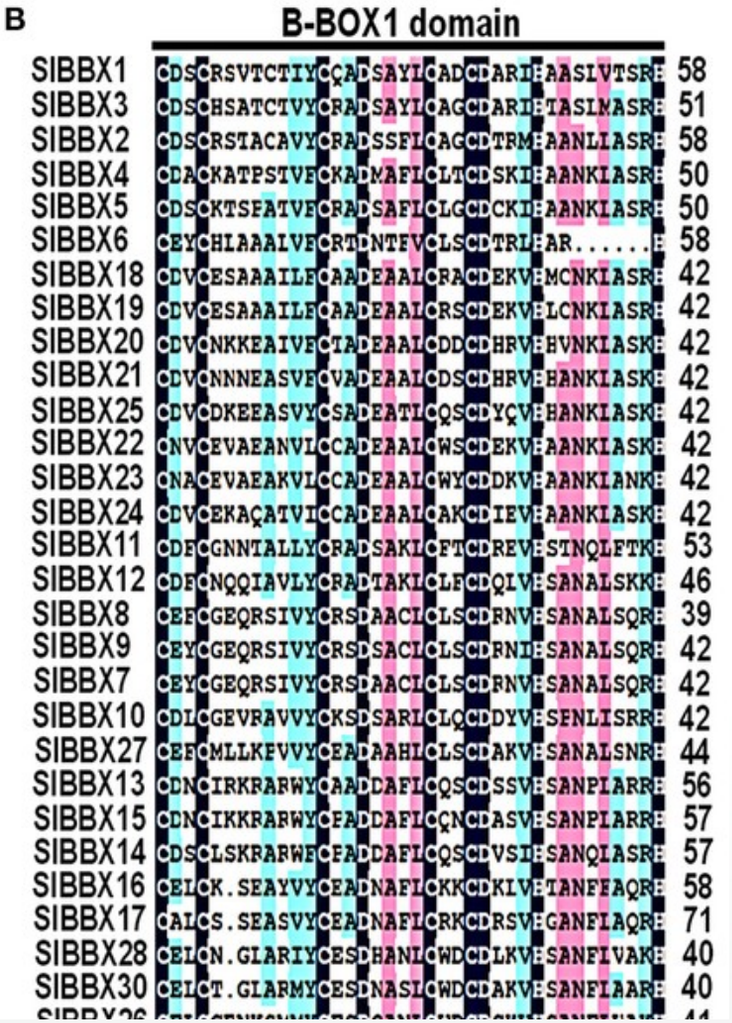
A – Alanin
C – Cistein
D – Asparaginska kiselina
E – Glutaminska kiselina
F – Fenilalanin
G – Glicin
H – Histidin
I – Izoleucin
K – Lizin
L – Leucin
M – Metionin
N – Asparagin
P – Prolin
Q – Glutamin
R – Arginin
S – Serin
T – Treonin
V – Valin
W – Triptofan
Y – Tirozin



CILJ: Odrediti koje se domene pojavljuju na nepoznatoj proteinskoj sekvenci kako bi predvidjeli potencijalne funkcije dotičnog proteina (biotehnologija, medicina, farmacija)

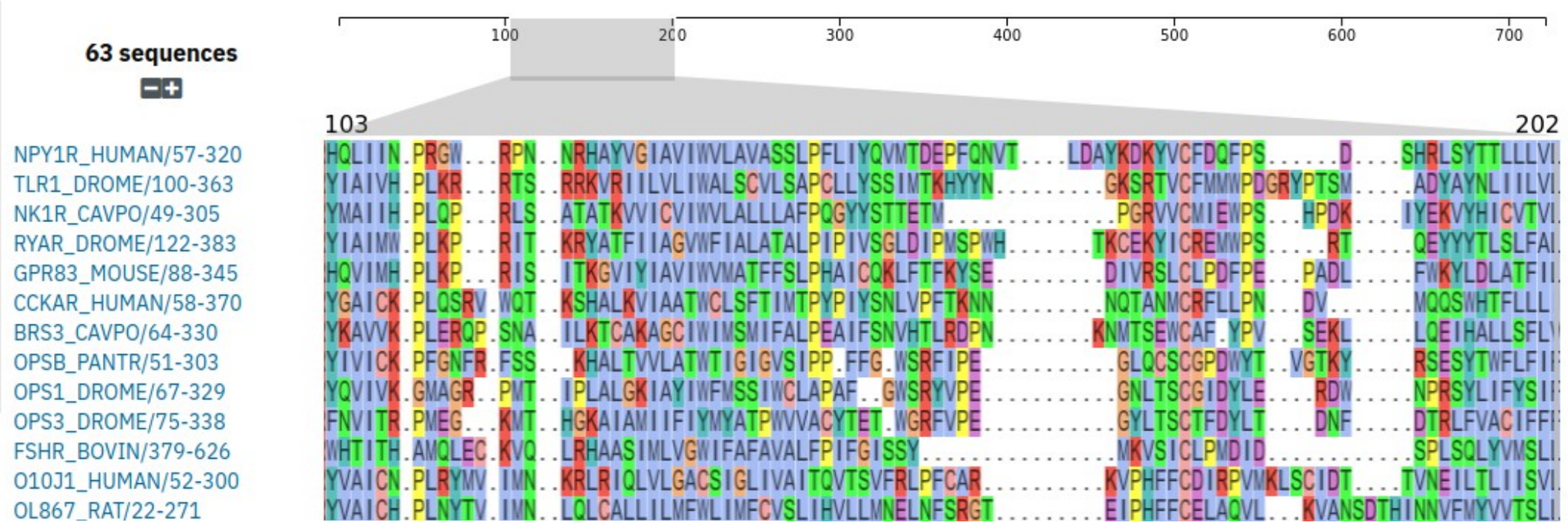
Domena - podniz proteinske sekvence odgovoran za pojedinu funkciju

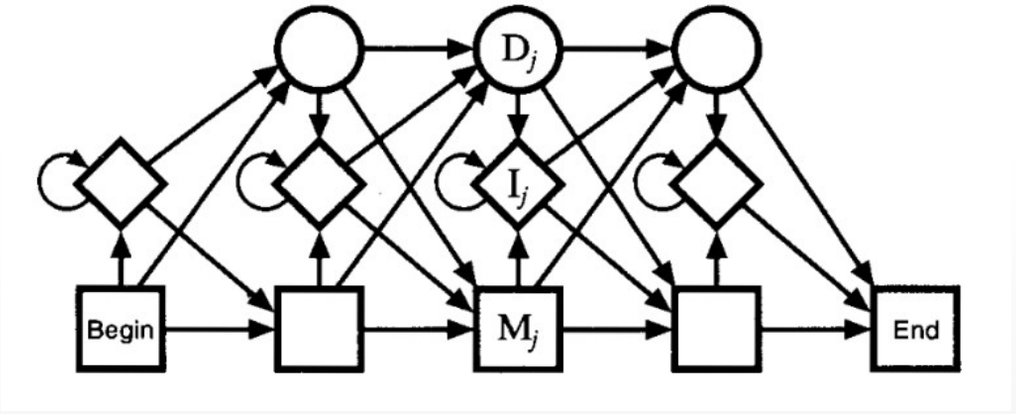
Proteinska sekvenca: ACDRYXGFPNMHCDKLVLKNDFSPYWTARYW...



- **M**ultiple **S**equence **A**lignment (MSA) algoritam
- „Seed alignment” - skup poravnatih reprezentativnih podnizova koji predstavljaju jednu proteinsku domenu (Pfam baza)
- Praćenje redosijeda i frekvencije aminokiselina po pozicijama

Konstrukcija profilnog HMM-a





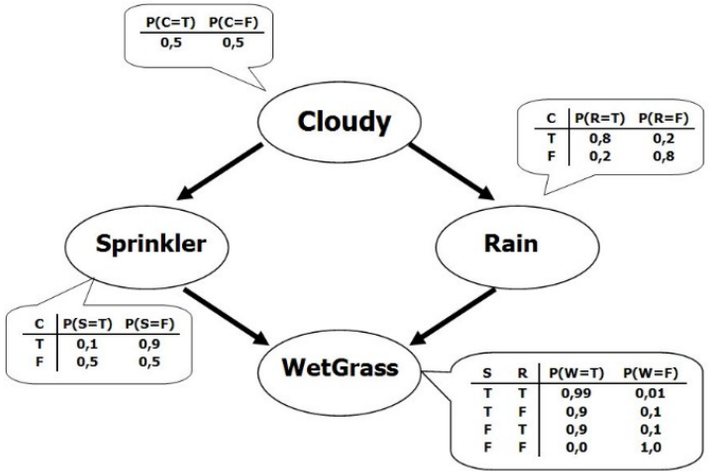
M – Match (podudaranje)

I – Insert (umetanje)

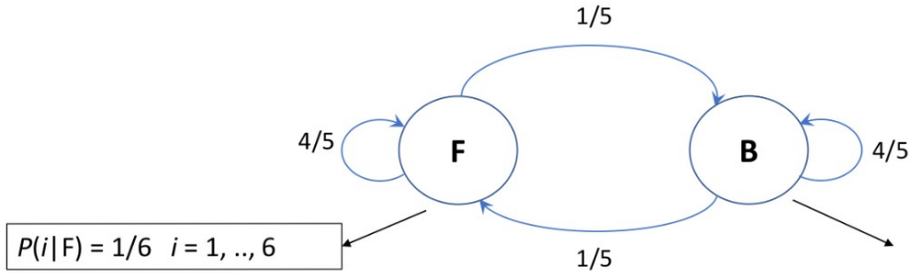
D – Delete (brisanje)

HMM-Hidden **M**arkov **M**odel

Bayesovska mreža vs. HMM



- modelira kauzalne odnose



$S = \{F, B\}$

$E = \begin{pmatrix} 1/6 & 1/6 & 1/6 & 1/6 & 1/6 & 1/6 \\ 1/10 & 1/10 & 1/10 & 1/10 & 1/10 & 1/2 \end{pmatrix}$

$\Pi = \{1/2 , 1/2\}$

$O = \{1, 2, 3, 4, 5, 6\}$

$A = \begin{pmatrix} 4/5 & 1/5 \\ 1/5 & 4/5 \end{pmatrix}$

- modelira slijed skrivenih stanja i vidljivih promatranja
- sekvencijalni podaci

HMM-algoritmi

- **Forward** (omogućuje računanje vjerojatnosti promatranog niza s obzirom na model)

- Baum Welch, Viterbi, backward algoritam

Forward algorithm:

for $i \in S$ // *initialization*

$\alpha_0(i) = \pi_i \cdot e_{io_0}$

for $t = 1$ ***to*** T

for $i \in S$

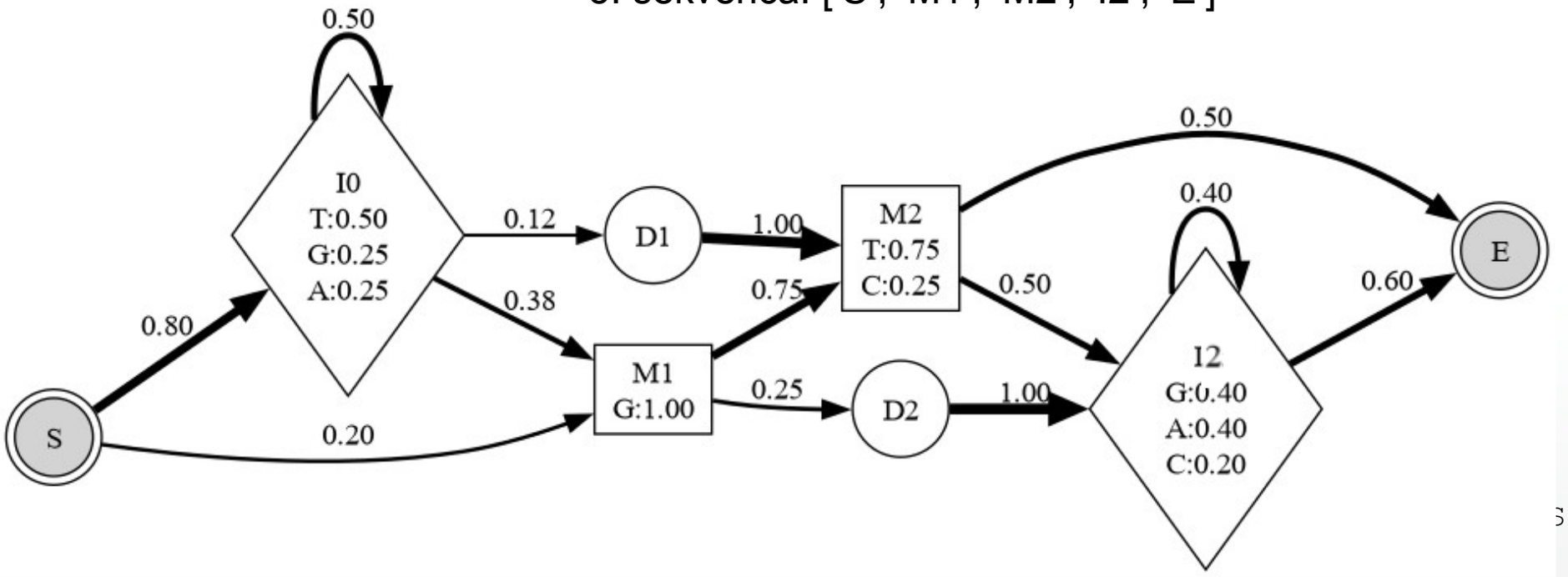
$\alpha_t(i) = e_{io_t}(\sum_{j \in S} \alpha_{t-1}(j) a_{ji})$ // *prob. at time t and state i emitting* e_{io_t}

return $\sum_{i \in S} \alpha_T(i)$

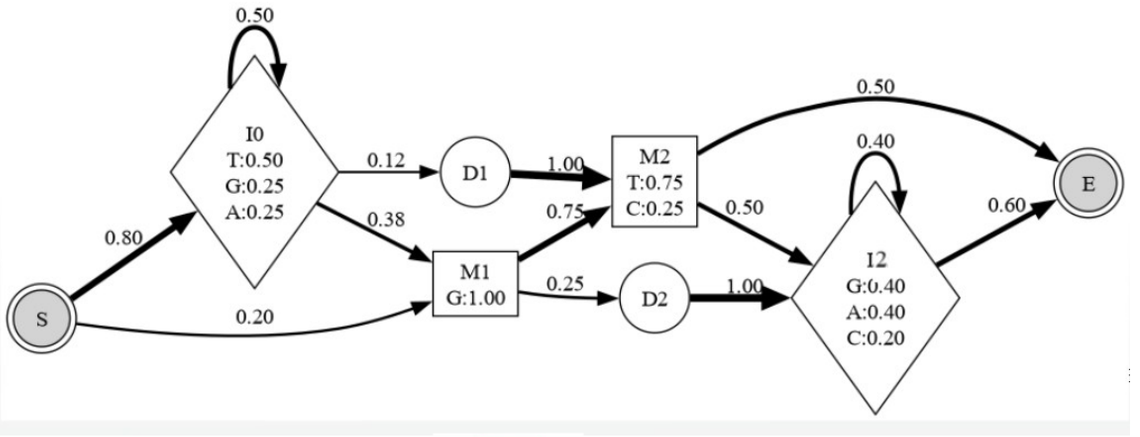
Postupak konstrukcije HMM-a

```
-GAT-T---
T---GTG--
TG-TG-GAA
--A-GC---
----GTC--
    **
```

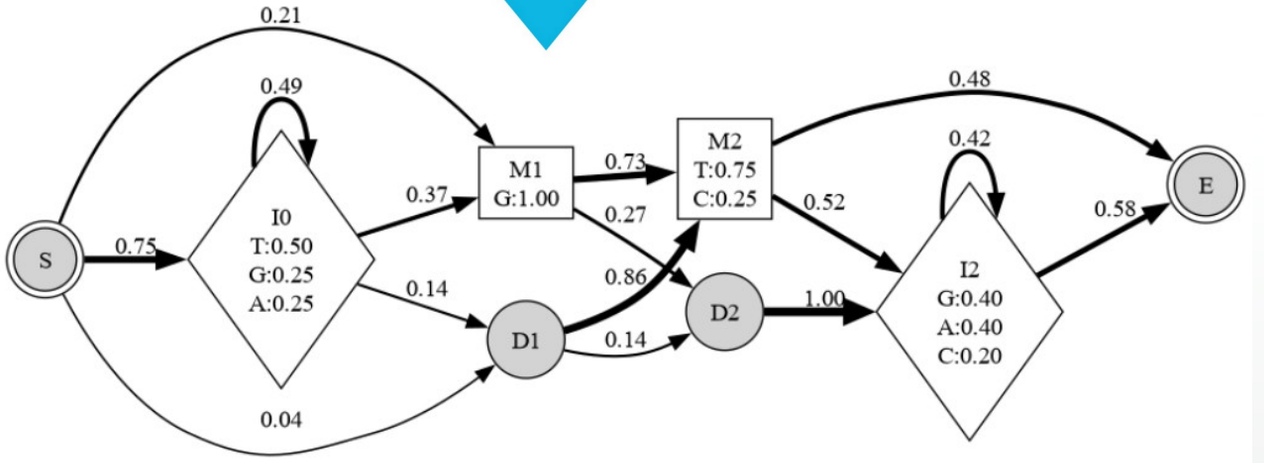
- 1. sekvenca: [’S’, ’I0’, ’I0’, ’I0’, ’D1’, ’M2’, ’E’]
- 2. sekvenca: [’S’, ’I0’, ’M1’, ’M2’, ‘I2‘, ’E’]
- 3. sekvenca: [’S’, ’I0’, ’I0’, ’I0’, ’M1’, ’D2’, ’I2’, ’I2’, ’I2’,’E’]
- 4. sekvenca: [’S’, ’I0’, ’M1’, ’M2’, ’E’]
- 5. sekvenca: [’S’, ’M1’, ’M2’, ’I2’, ’E’]



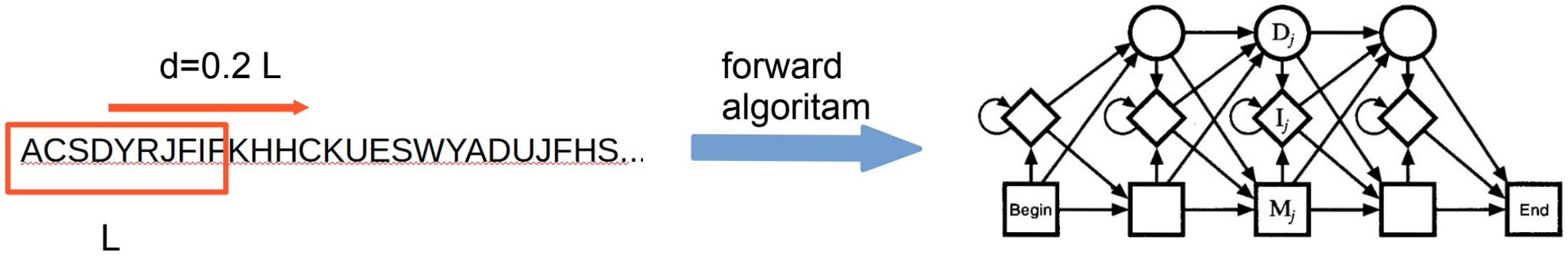
Laplaceovo zaglađivanje



$$P(x|y) = \frac{N(x,y) + \alpha}{N(y) + \alpha \cdot |X|}$$



Korištenje posmačnog prozora



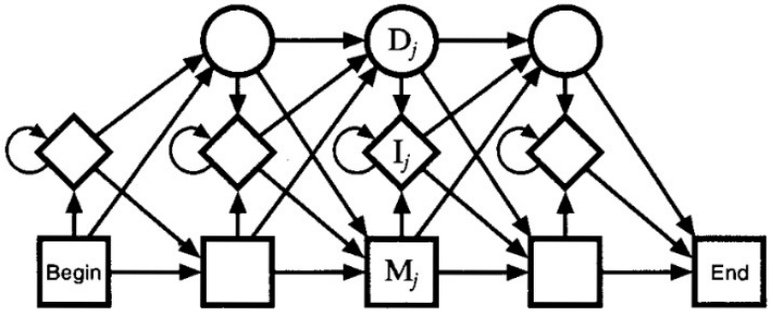
- duljina prozora pojedinog HMM-a određena preko prosječne duljine slučajno generirane sekvence (Viterbi)
- posmak prozora jednak je 20% duljine prozora

Postupak klasifikacije

1) Konstrukcija 10 profilnih HMM-a iz 10 pripadnih „seed alignment” prikaza različitih domena poravnatih MSA algoritmom
2) Nepoznatu proteinsku sekvencu ispitujemo prolaskom posmačnog prozora za svaki od 10 profilnih HMM-ova
3) Sadržaj posamčnog prozora pri svakom pomaku prosljeđujemo forward algoritmu i računamo log-odds
4) Najveći log-odds daje HMM koji je konstruiran nad „seed” poravnanjem odgovarajuće domene koja je pronađena u sekvenci

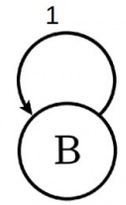
Računanje log-odds vrijednosti

Profilni HMM za neku domenu



forward algoritam

Pozadinski trivijalni model

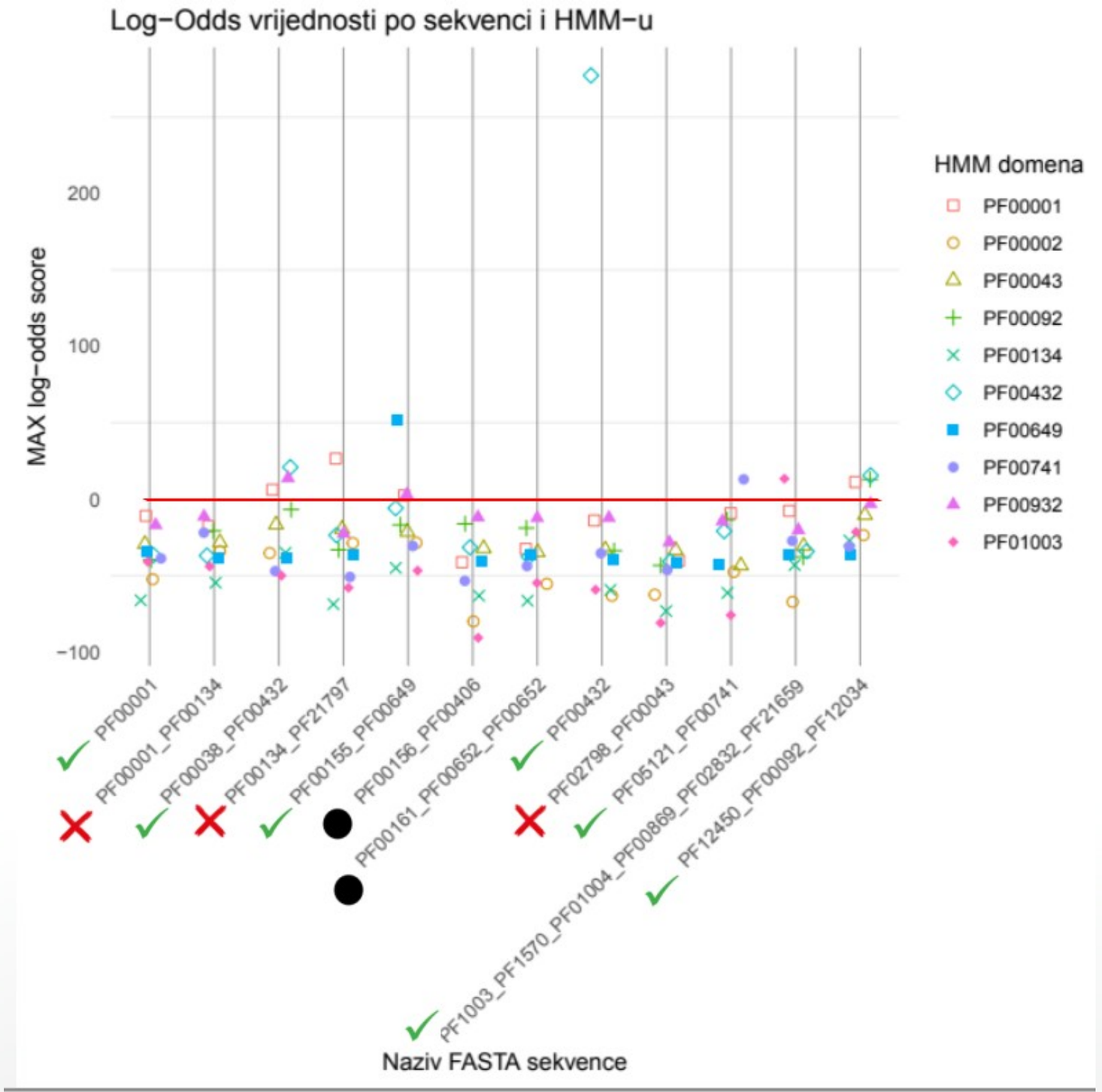


A	1/20
C	1/20
...	
Y	1/20

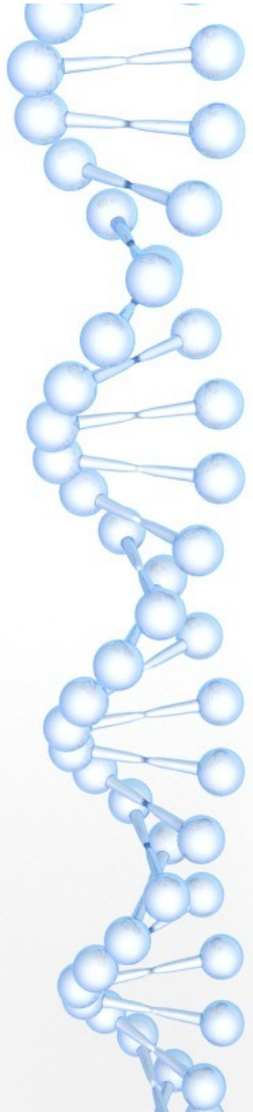
forward algoritam

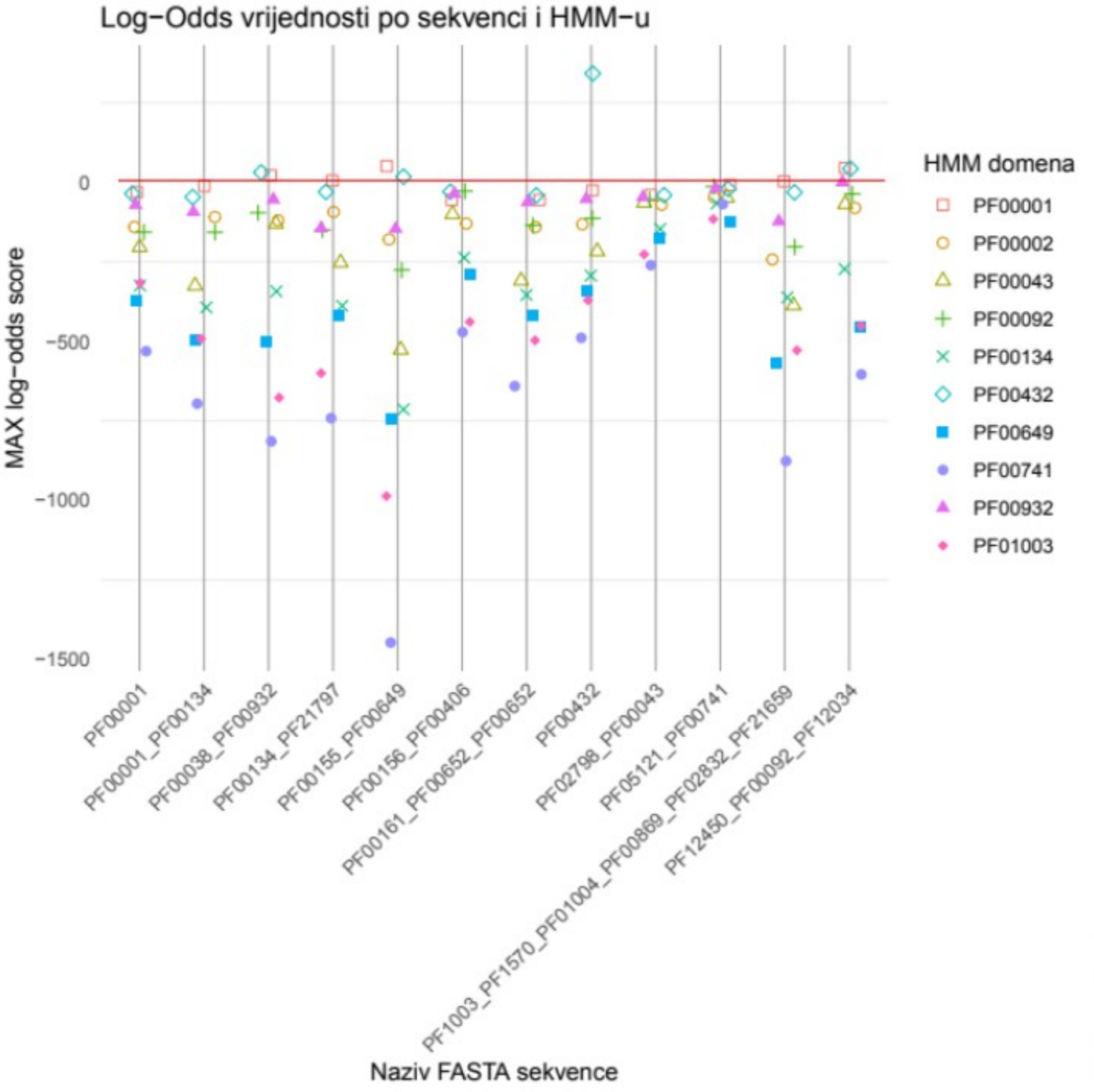
$$\text{log-odds} = \log(P(X|HMM)) - \log(P(X|pozadinski\ model))$$

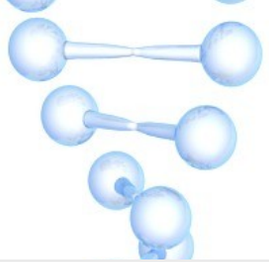
Analiza rezultata



Analiza rezultata – bez korištenja posmačnog prozora

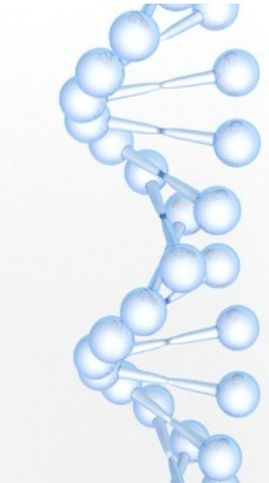




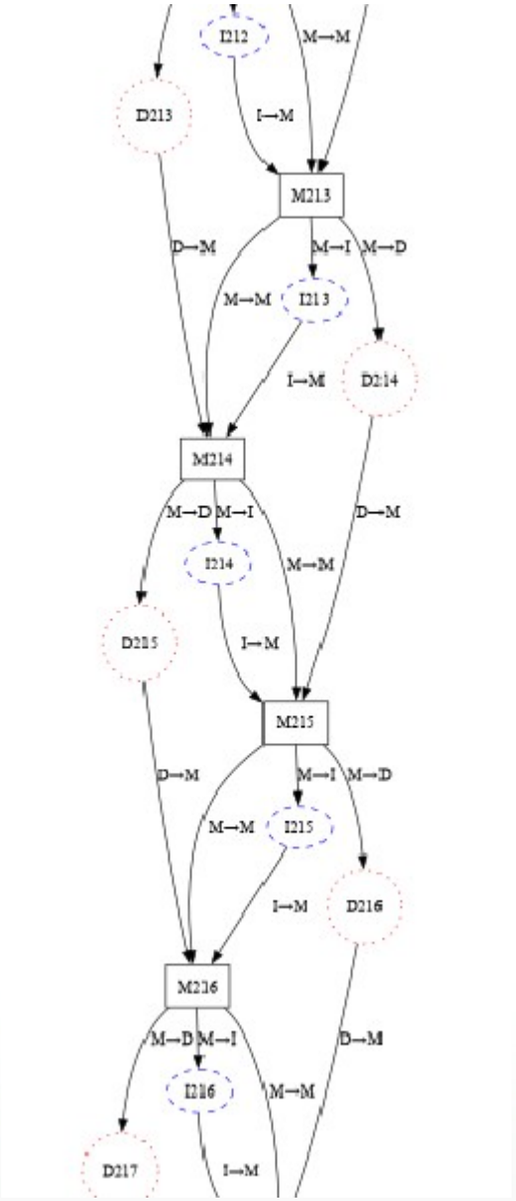


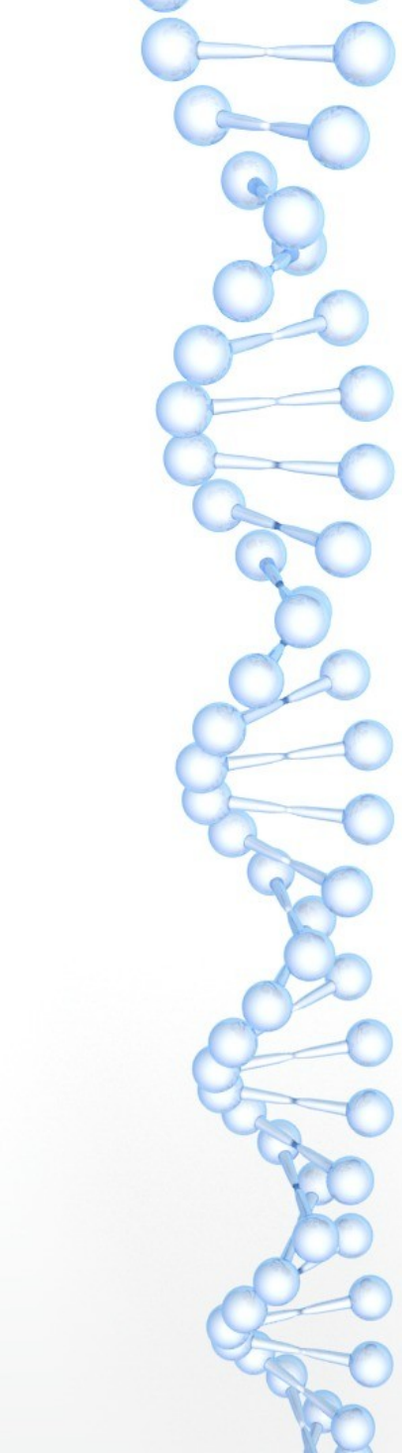
HMMER

```
#                                                                            --- full sequence --- -------------- this domain -------------
# target name        accession   tlen query name           accession   qlen   E-value  score  bias   #  of  c-Evalue  i-Evalue  score  bias
#------------------- ---------- ----- -------------------- ---------- ----- --------- ------ ----- --- --- --------- --------- ------ -----
7tm_1                PF00001.26   260 A0A821XNW9           -            782   1.4e-62  197.6  12.8   1   2   1.4e-62   1.4e-62  197.6  12.8
receptor (rhodopsin family)
7tm_1                PF00001.26   260 A0A821XNW9           -            782   1.4e-62  197.6  12.8   2   2      0.18      0.18   -2.7   2.2
receptor (rhodopsin family)
#
# Program:         hmmscan
# Version:         3.4 (Aug 2023)
# Pipeline mode:   SCAN
# Query file:      A0A821XNW9.fa
# Target file:     binaries/PF00001.hmm
# Option settings: hmmscan --domtblout rezultati.tbl binaries/PF00001.hmm A0A821XNW9.fa
# Current dir:     /home/domagoj/Desktop/Seminar2_Implementation_of_Hidden_Markov_Models_in_the_Phylogenetic_Classification_of_Protein_Sequer
# Date:            Fri May 16 12:37:25 2025
# [ok]
```



HMMER-
vizualizacija HMM-a





Zaključak

- HMM-ovi – pogodni za ugradnju vanjskog domenskog znanja
- mogućnost treniranja na inicijalno malim količinama podataka
- ovisnost evaluacije o eksperimentalnom postavu