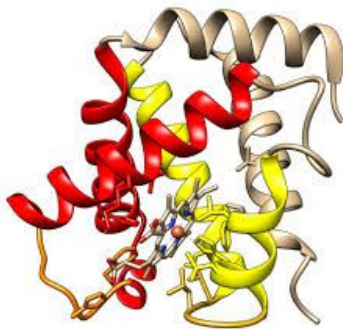# SORBONNE UNIVERSITÉ

Final Presentation

January 2019

MEET-U

Upstream - Team 6

Yasser **Mohseni Behbahani**

Bénédicte **Colnet**

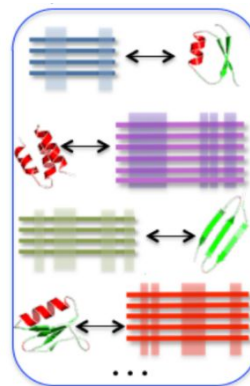Gabriela **Lobinska**

Irène Mauricette **Mendy**

Amandine **Sandri**

LCQB

Goal

Find best templates for a target protein.

Expected output

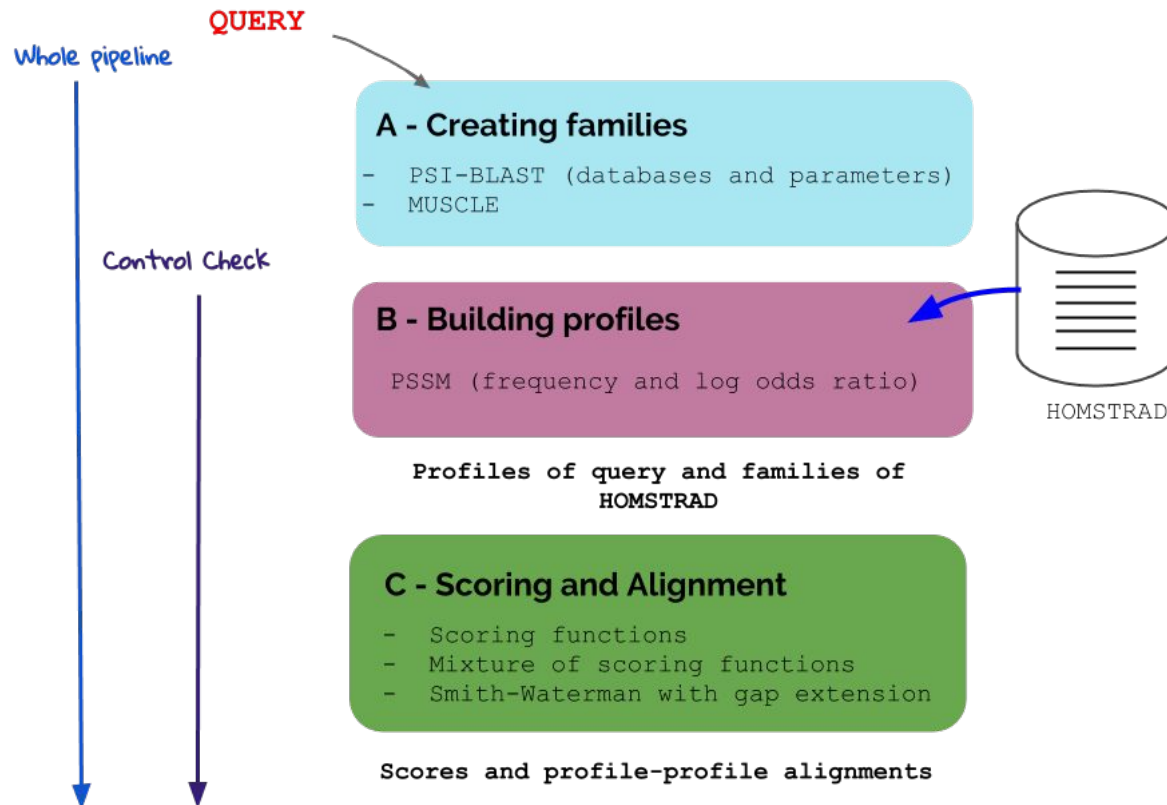Profile-Profile Alignment file and Scoring

Data supplied

Benchmark

```
Hemery → SRP54 (Fold)
Agglutinin → intb (Fold)
Lipoprotein_4 → mofe (Superfamily)
…
```

HOMSTRAD Database (reduced to 405)   21 queries → Best hit HOMSTRAD

QUERY

Whole pipeline

Control Check

A - Creating families

- PSI-BLAST (databases and parameters)
- MUSCLE

B - Building profiles

PSSM (frequency and log odds ratio)

HOMSTRAD

Profiles of query and families of HOMSTRAD

C - Scoring and Alignment

- Scoring functions
- Mixture of scoring functions
- Smith-Waterman with gap extension

Scores and profile-profile alignments

Results & Assessment method

Goal

Assess the quality of the scoring

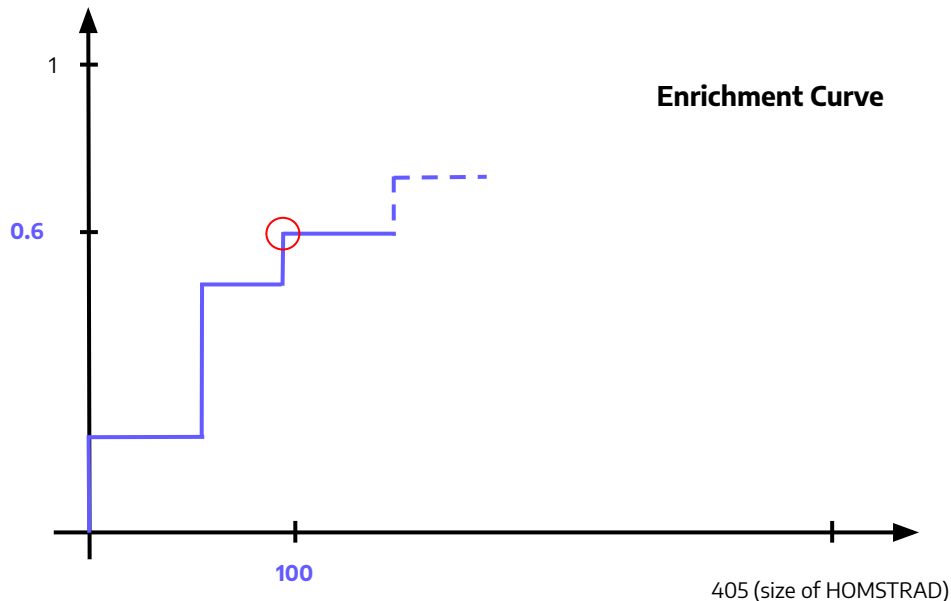### Benchmark

21 queries → Best hit HOMSTRAD

```
For each query
      Launch the pipeline
      Register the ranking

Plot the enrichment curve
```

Enrichment Curve

Meaning : In the top 100 (25%) of the HOMSTRAD database, 60% of the hits are found

Results & Assessment method

Goal

Assess the quality of the scoring

Benchmark

21 queries → Best hit HOMSTRAD

```
For each query
        Launch the pipeline
        Register the ranking

Plot the enrichment curve
```
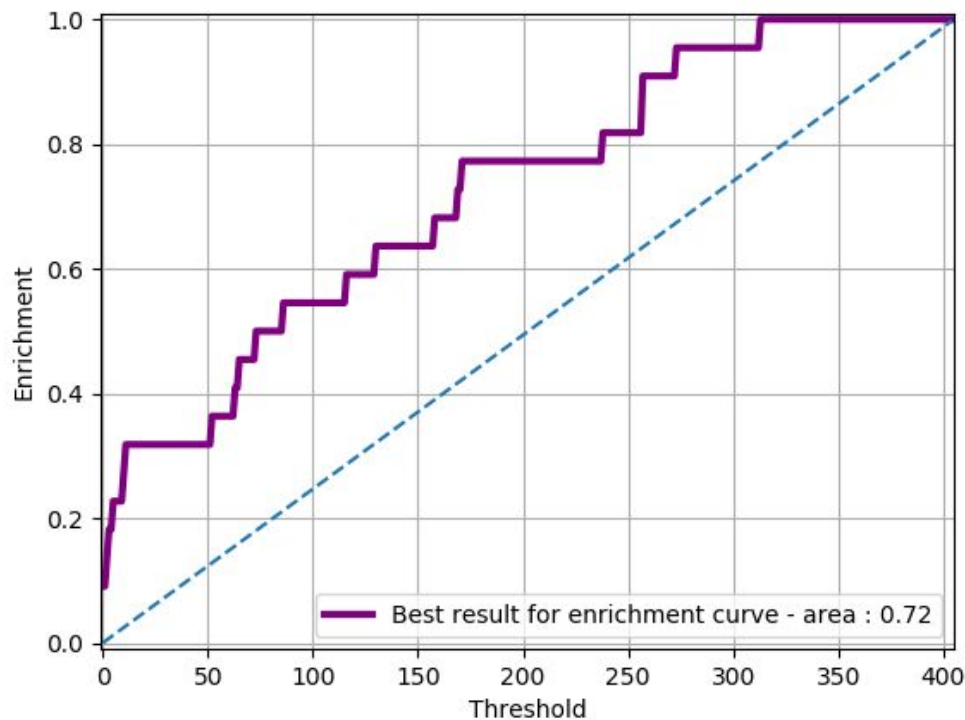
Classic Smith & Waterman

- Classic version: one gap penalty
- Affine Gap extension: one penalty for opening a gap sequence, and one penalty for extending an existing gap

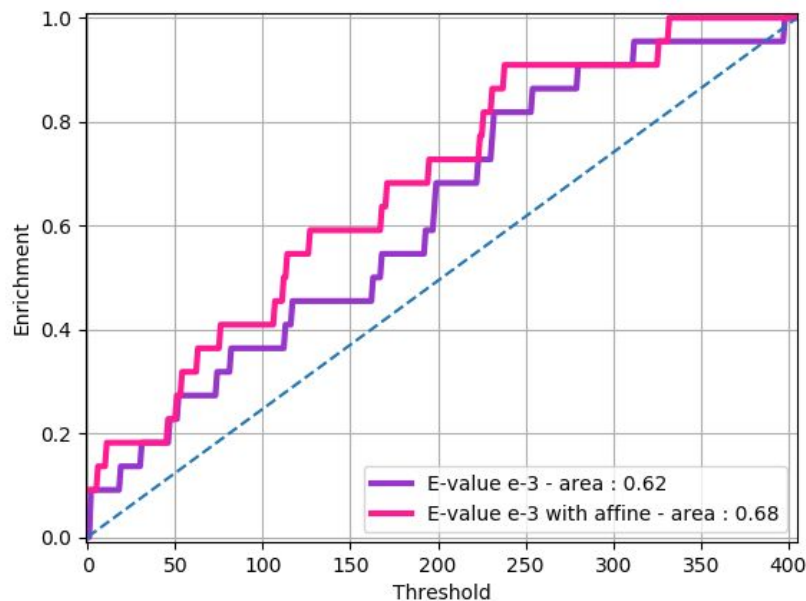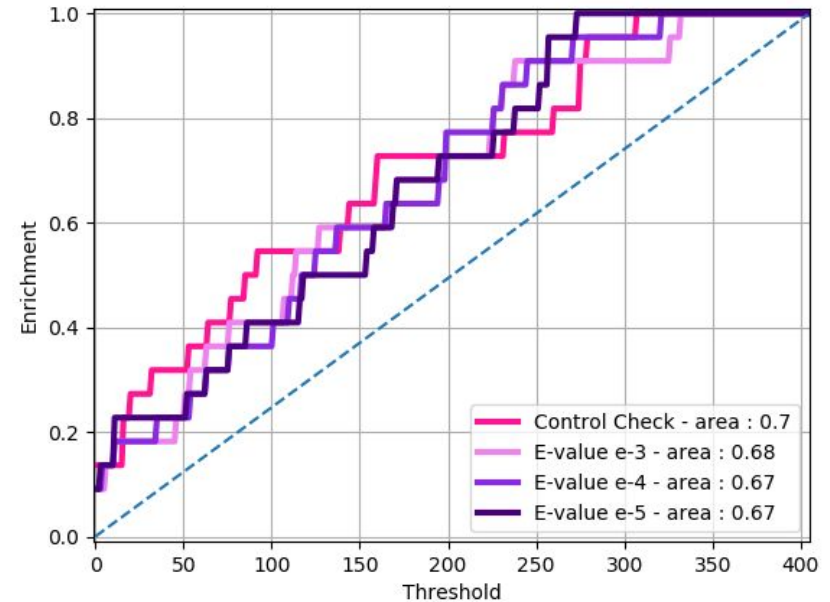# Affine gap is more biologically plausible

Source: Wikipedia

In our version, **profile-profile alignment**

match = dot product of the profile's columns

Method - Smith & Waterman

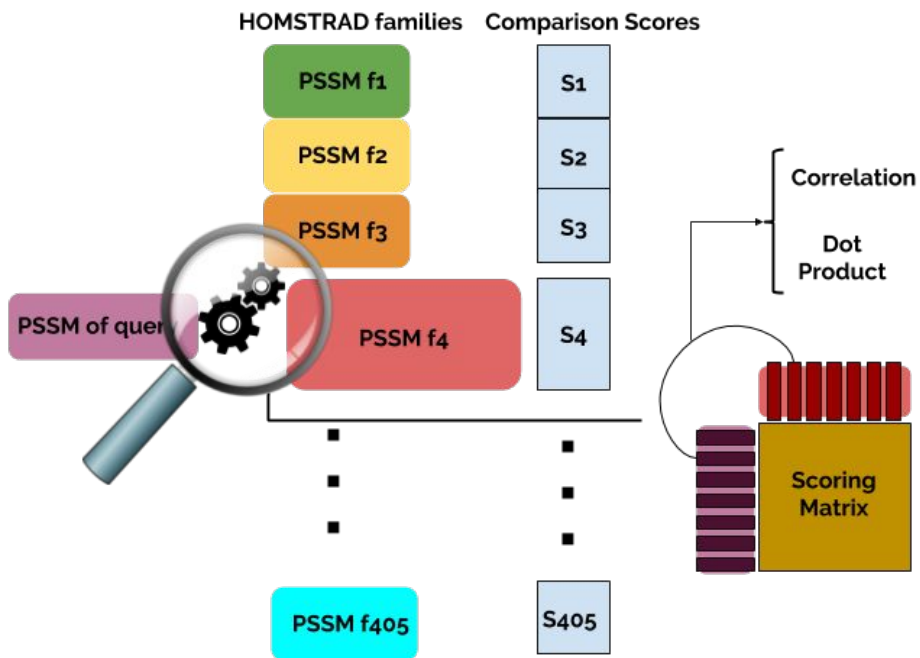# Method – Correlation vs Dot Product
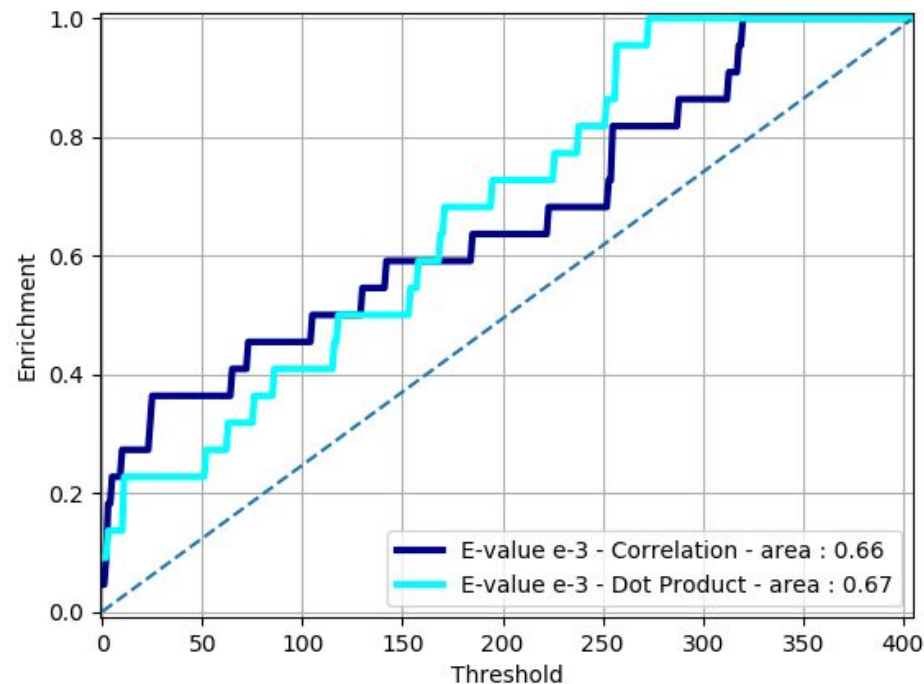
Benchmark

21 queries → Best hit HOMSTRAD
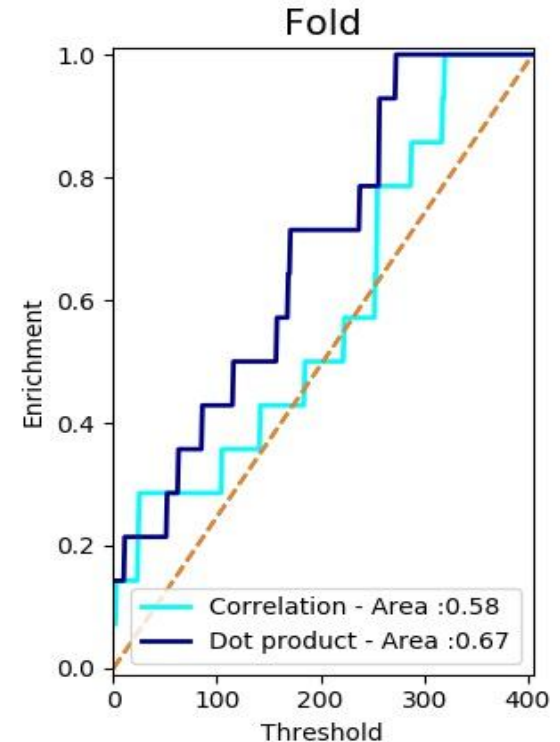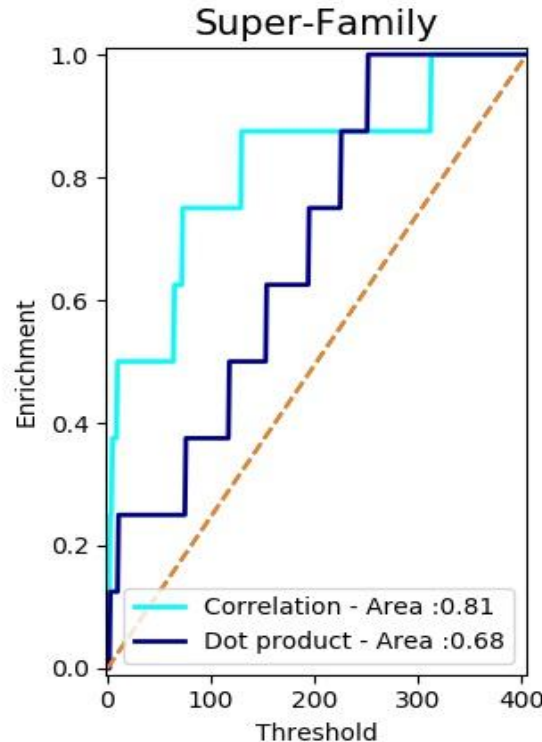Either Superfamily & Family (8) or Fold (13) hit

Fold
- Major structural similarity
- SSE's in similar arrangement

Superfamily
- Probably common ancestry
- Homology
- Sequence similarity

Family
- Pairwise sequence similarity > 25%

Method – Mixture of Scoring Functions

Dot product

... better on Fold

Correlation

... better on superfamily

Mixture of scoring
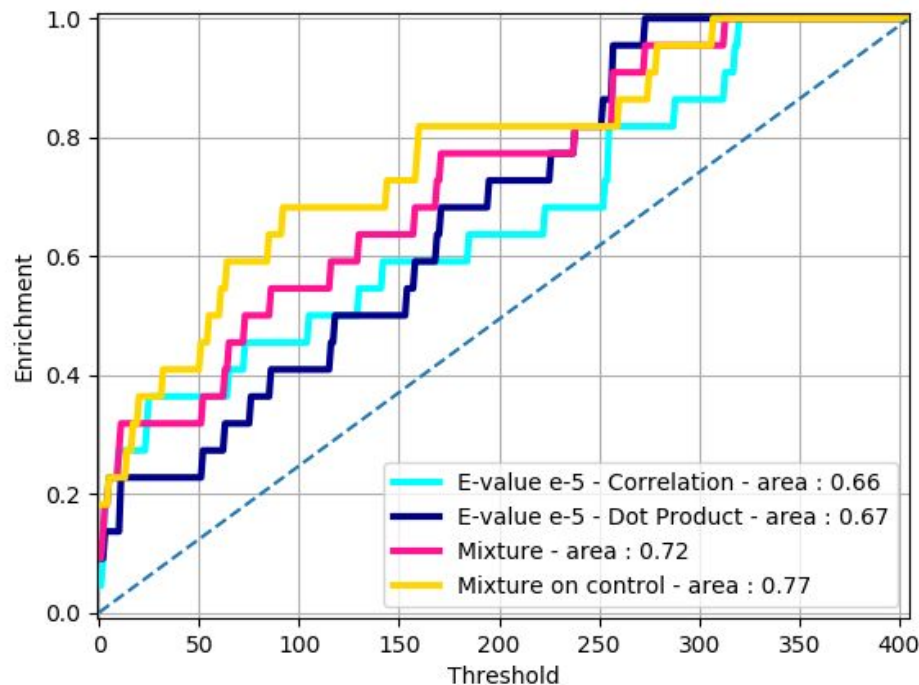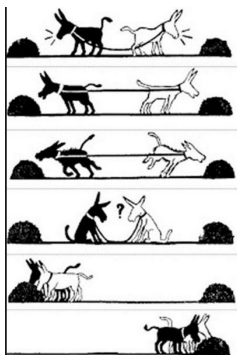
Prediction for the 11 sequences

Mysterious query ID	Best hit template
trQ6HKV8 (BT9727_1481)	BRCT
trQ6HLB4 (BT9727_1323)	END
feuA (BT9727_3483)	neur_chan_memb
G1G14-4353	pot
recN (BT9727_3916)	COX1
G1G14-3311 (BT9727_3234)	PCI1
scdA (BT9727_1971)	PABP
hmp (BT9727_1331)	zf-CCHC
mfd (BT9727_0048)	COX1
celB (BT9727_4888)	Ribosomal_L12
arcD (BT9727_0754)	hormone5

To go forward

- Despite the good quality of the profiles created, parameters improvement is still required (e-value & database)

- Further analysis on scoring method (euclidean distance, spearmann correlation, ect.)

- Fold detection Improvement

  → Secondary structure prediction information & Hydrophobicity instead of sequence

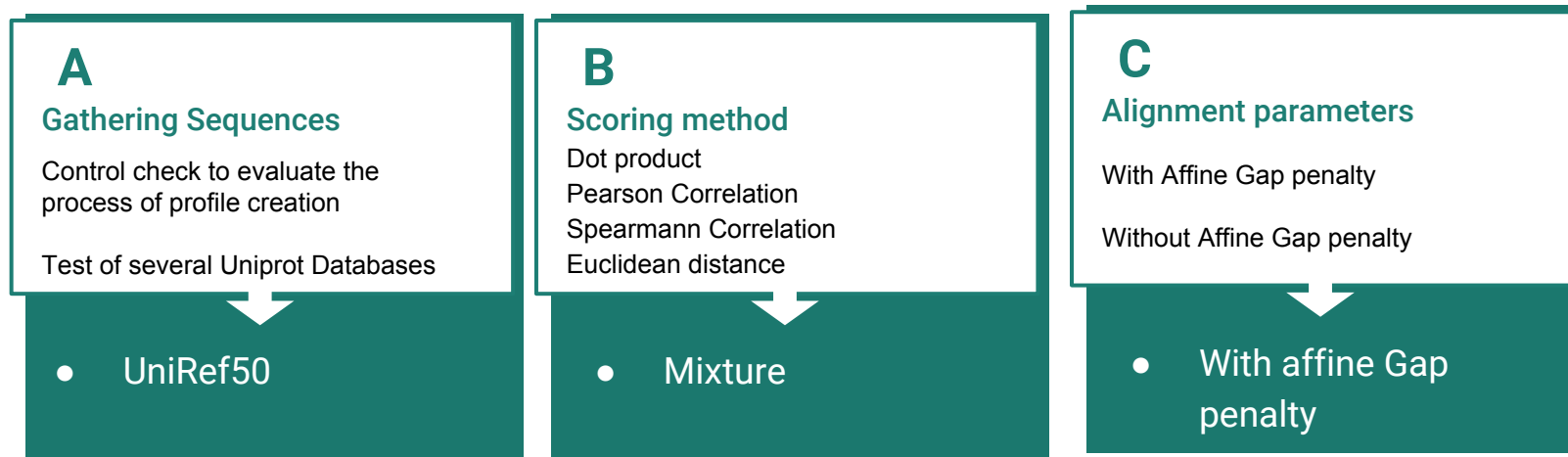 → Mixture classification approach (test on benchmark already positive)
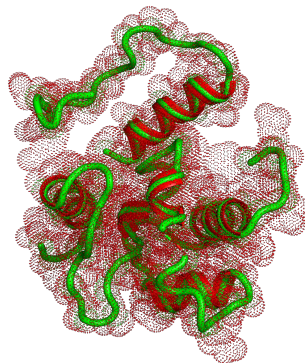
References

[1] Moult J., Pedersen J. T., Judson R., and Fidelis K. A large-scale experiment to assess protein structure prediction methods. Proteins, 23, 1995.

[2] G. Wang and R. Dunbrack. Scoring profile-to-profile sequence alignments. Protein science : a publication of the Protein Society, 13:1612–26, 07 2004. doi: 10.1110/ps.03601504.

Annexe 1 – Method

A

Gathering Sequences

Control check to evaluate the process of profile creation

Test of several Uniprot Databases

- UniRef50

B

Scoring method
Dot product
Pearson Correlation
Spearmann Correlation
Euclidean distance

- Mixture

C

Alignment parameters

With Affine Gap penalty

Without Affine Gap penalty

- With affine Gap penalty

- **Profile comparison**
  → requires a **scoring method**
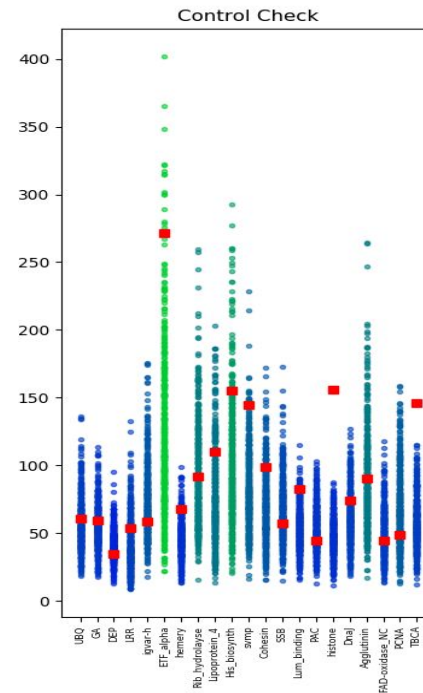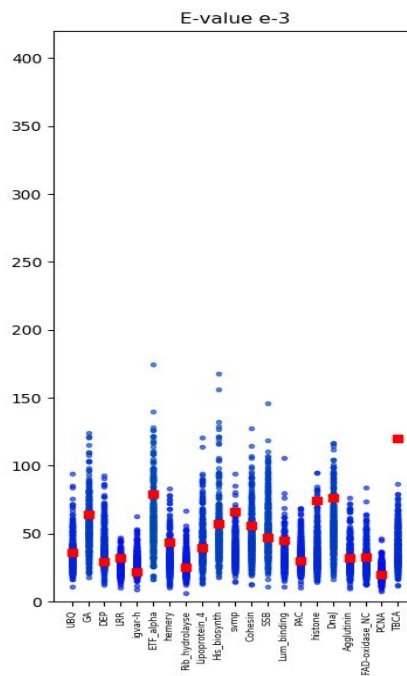
B

A

C

- **Profile creation**
  → requires **Protein Database** selection

  → Profile Creation method (PSSM, HMM…)

- **Profile alignment**
  → requires **strategic alignment algorithm**

Evaluation of process of profile creation method (2)

- Running profile comparison on **provided** MSA and **our** MSA

- Scores are more spread for the **provided** MSA comparing to **our** MSA

Gap penalties optimization

- Use of Smith-Waterman algorithm to align profiles

- Optimization for dot product and correlation comparison methods

Parameters	Value	Bibliography value [2]
Gap opening penalty Dot Product	12	0.07
Gap extension penalty Dot Product	1	0.005
Zero Shift Dot Product	-0.03	-0.05
Gap opening penalty Correlation	5	1.39
Gap extension penalty Correlation	0.5	0.07
Zero Shift Correlation	-0.2	-0.21

Table 1: Optimized parameters for scoring functions

→ Improvements of the scores with gap penalties

Final ranking scores with downstream program combination

→ Downstream program uses machine learning on 3 scores (DOPE, H-P and Alignments scores)

→ Superfamily: Poorer results with upstream & downstream combination

→ hypothesis: Overfitting during learning on Orion dataset