SORBONNE UNIVERSITÉ

MEET-U

Upstream - Team 6

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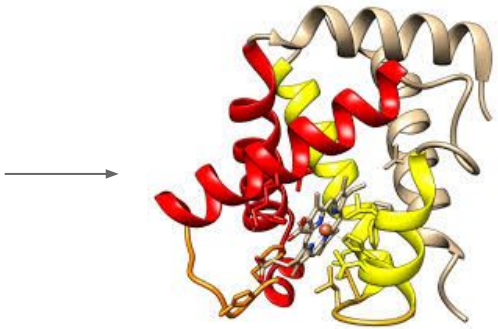
Final Presentation

January 2019



LCQB

Context

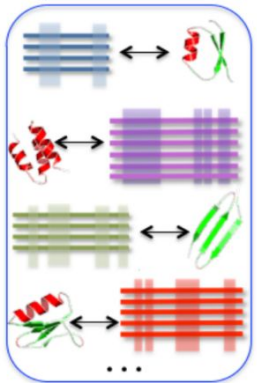
Goal

Find best templates for a target protein.

Expected output

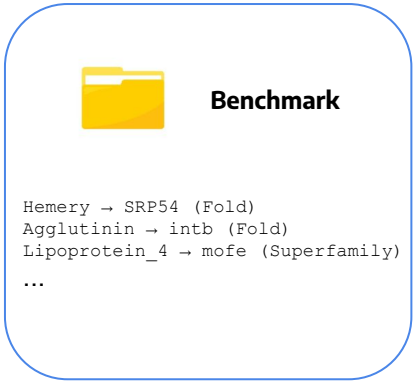
Profile-Profile Alignment file and Scoring

Data supplied



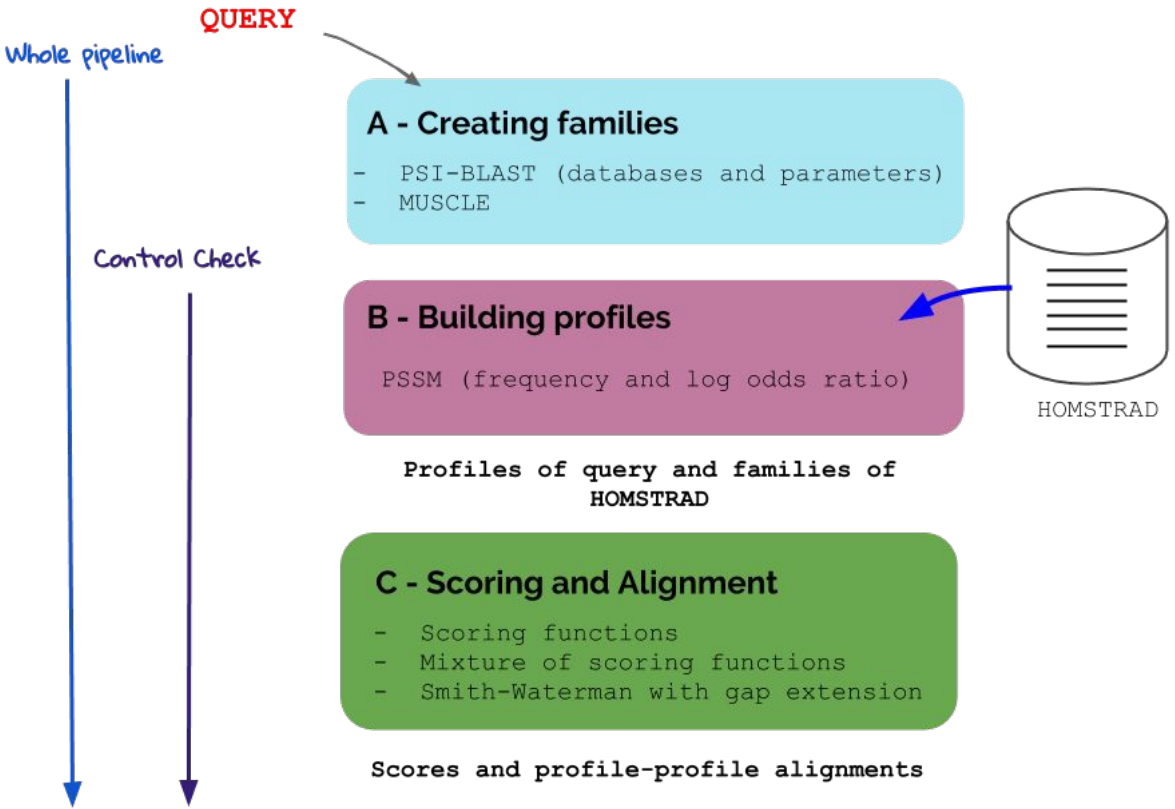
HOMSTRAD Database (reduced to 405)

+



21 queries → Best hit HOMSTRAD

Strategy


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

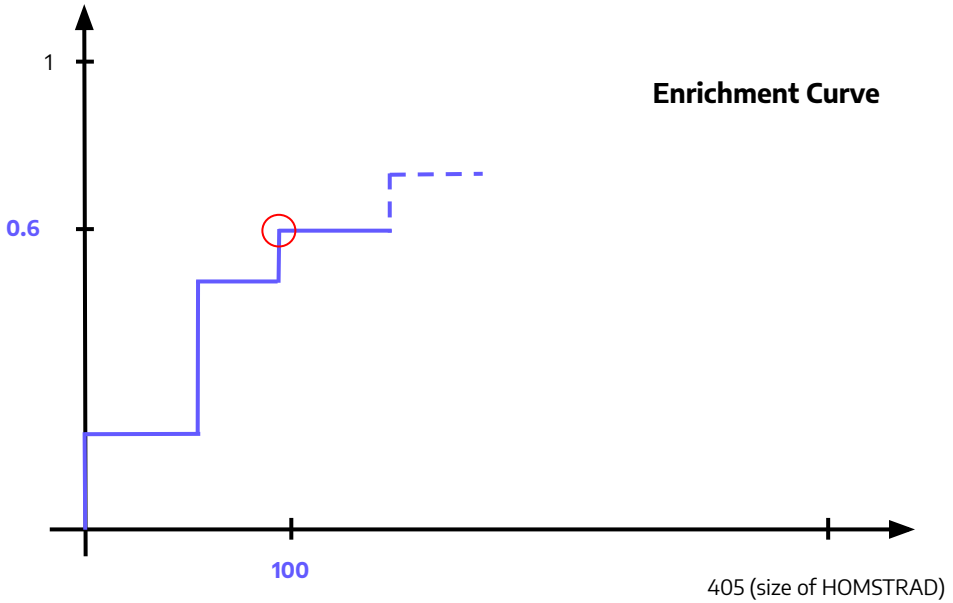
Assess the quality of the scoring

Benchmark

21 queries → Best hit HOMSTRAD

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

Plot the enrichment curve
```



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

```
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       Launch the pipeline
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```
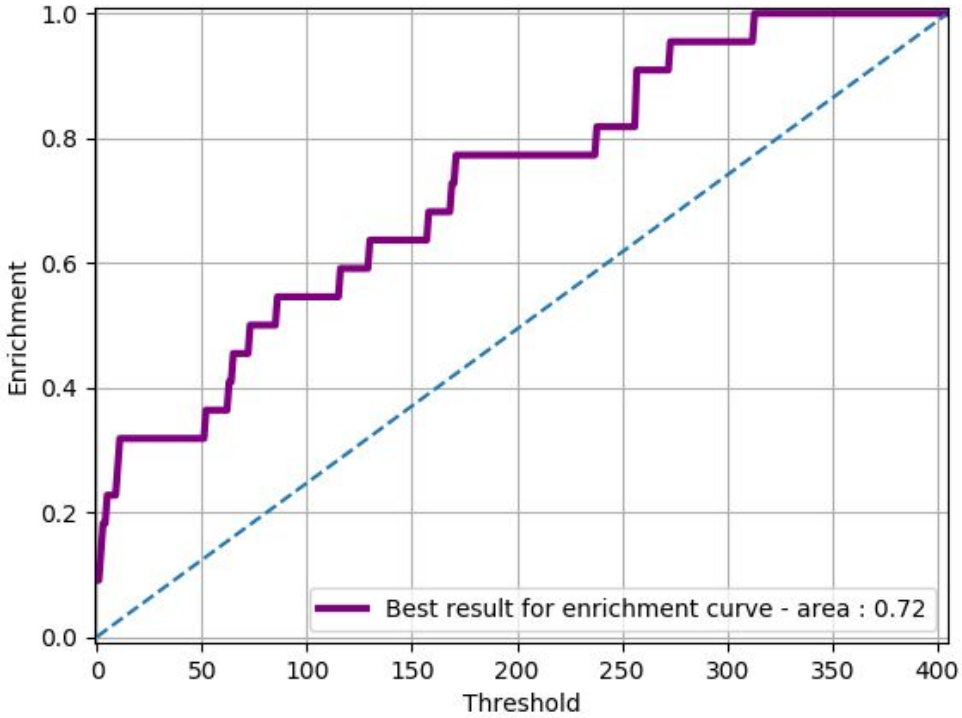



Method - Smith & Waterman

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

		F	A	T	C	A	T	Y
	0	0	0	0	0	0	0	0
T	0	0	0	5	0	0	5	0
C	0	0	0	0	14	8	2	3
A	0	0	4	0	8	18	12	6
G	0	0	0	2	2	12	16	10
S	0	0	0	5	1	6	17	14
F	0	6	0	0	3	0	11	20
A	0	0	10	4	0	7	5	14

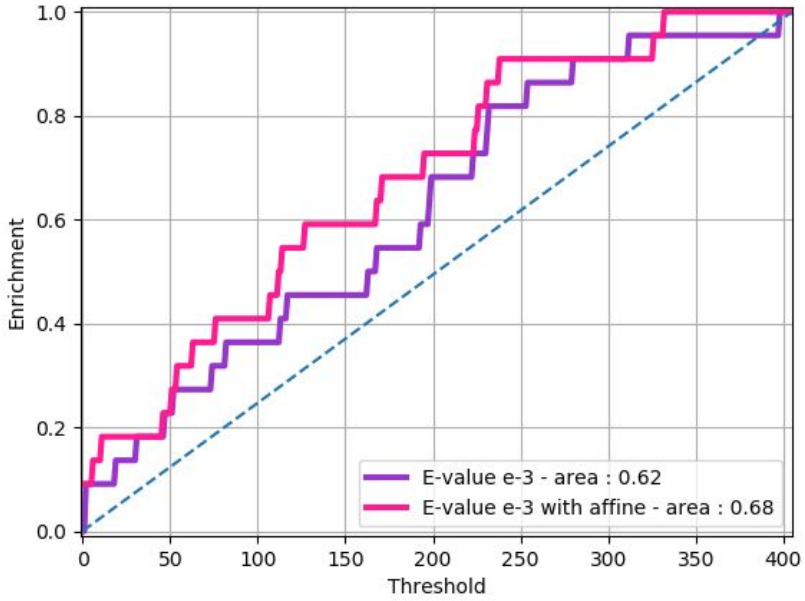
Source: Wikipedia

```
FATCA-TY
|||  ::
TCAGSFA
```

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

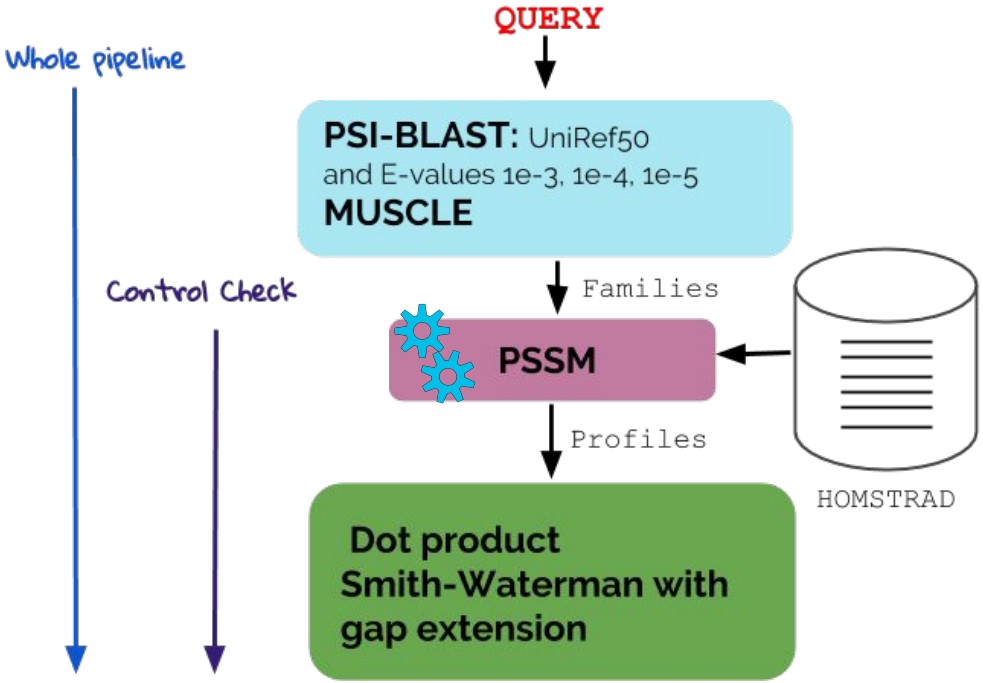
match = dot product of the profile's columns

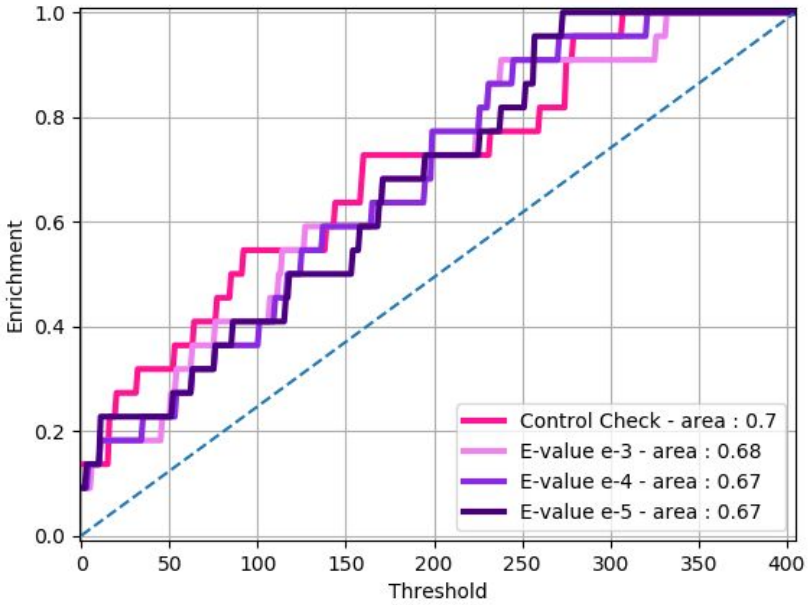
Method - Smith & Waterman



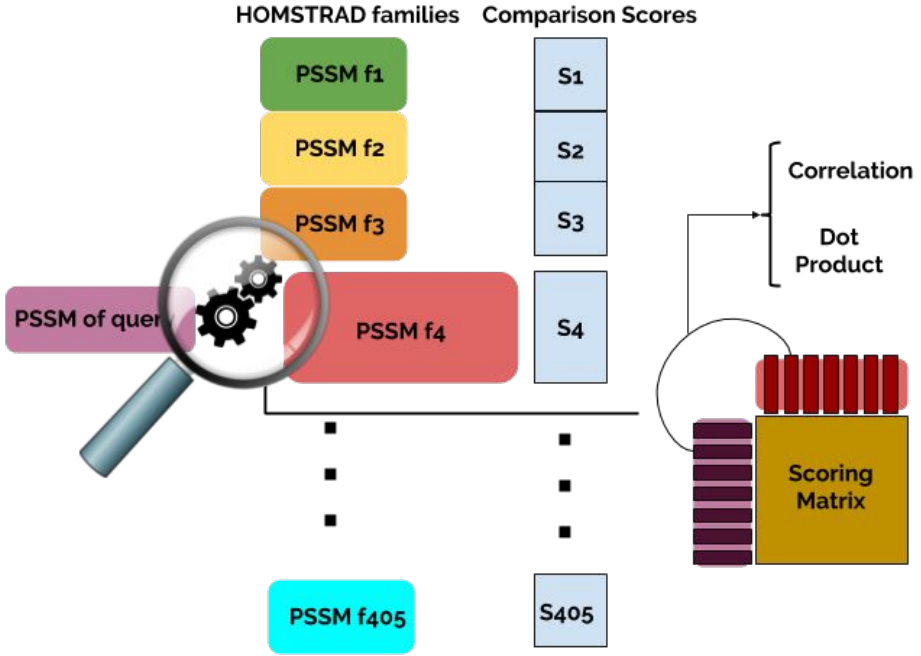

```
Query       3    AGLPVIMCLKSNNHQKYLRYQSDNIQQYGLLQFSADKILDPLAQFEVEPS------KTYDGLVHIKSRYTNKYLVRWSPNHYWITASANEPDENKSNWA----CTLFKPLYVEEGNMK-KVRLLHVQLGHYTQNYTVGGSFVSYLFAESSQIDTGSKDVFHVID-    151
Template    1    ---ATWTCINQQLEDKRLLYSQAKAE--------SNSHHAPLSDGKTGSSYPHWFTNGYDG--------NGKLIKGRTPIKFGKADCDRPPKHSQNGMGKDDHYLLEFPTFPDGHDYKFDSKKPKENPGPARVIYT----YPNKVFCGIVAHQRGNQGDLRLCSH    149
```

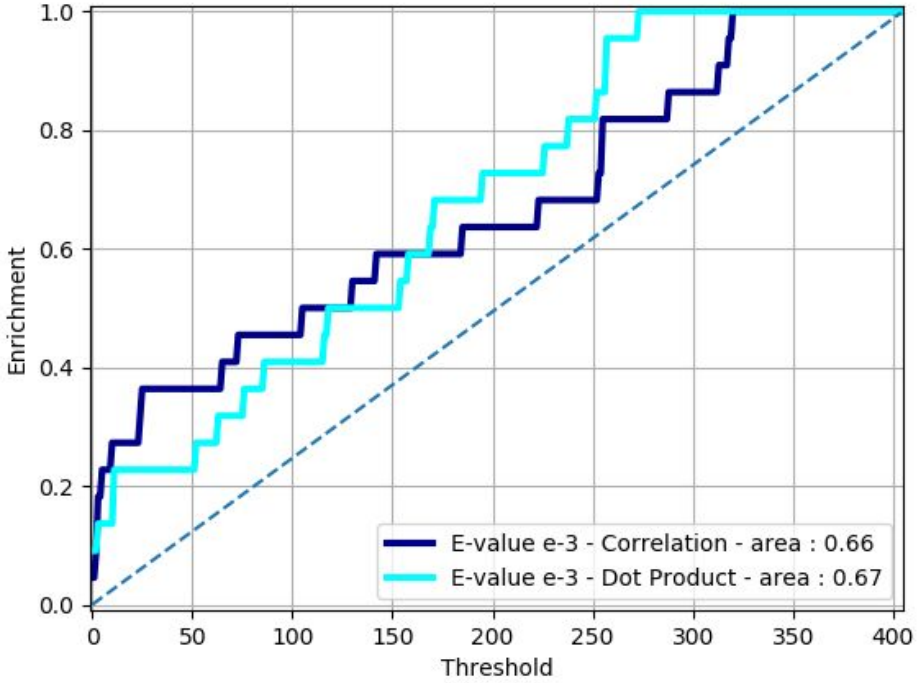
Method - Evaluation of Profile Construction





Method - Correlation vs Dot Product





Method - Correlation vs Dot Product

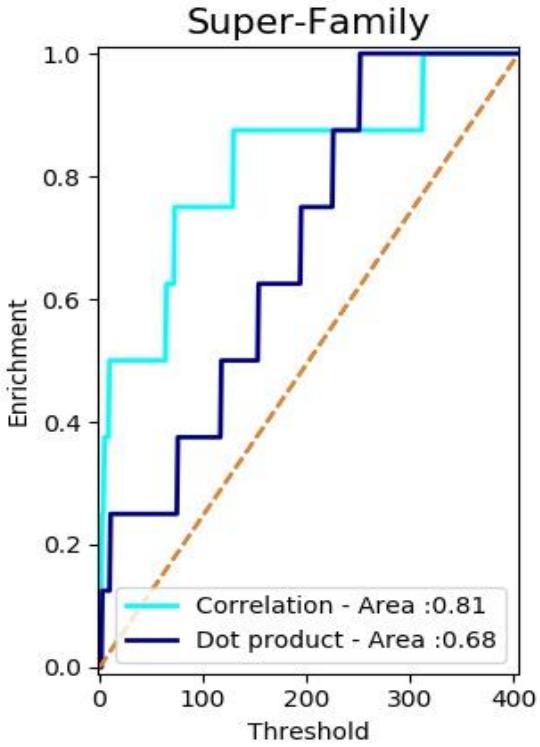
Benchmark

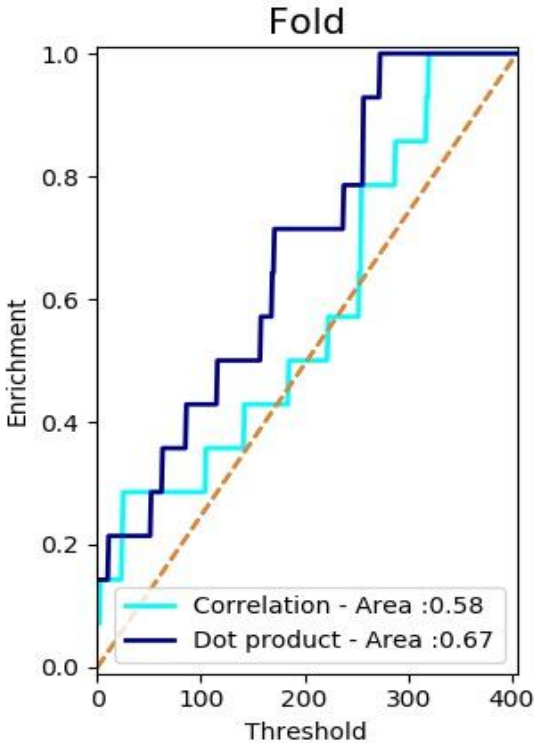
21 queries → Best hit HOMSTRAD
Either Superfamily & Family (8) or Fold (13) hit

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

Superfamily
- Probably common ancestry
- Homology
- Sequence similarity

Family
- Pairwise sequence similarity > 25%



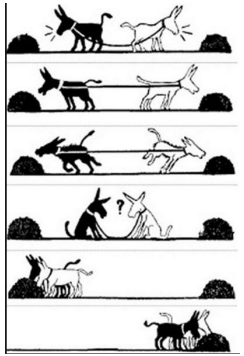


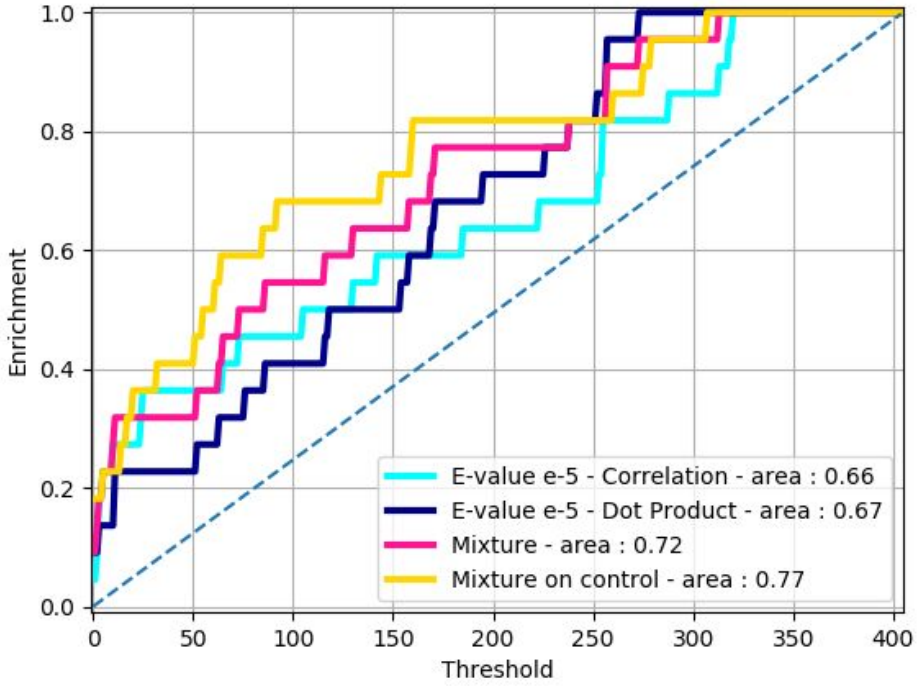
Method - Mixture of Scoring Functions

Dot product
... better on Fold

Correlation
... better on superfamily

Mixture of scoring





Results

Prediction for the 11 sequences

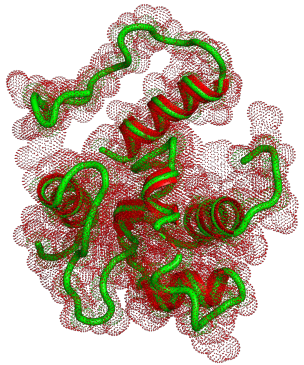
Mysterious query ID	Best hit template
trQ6HKV8 (BT9727_1481)	BRCT
trQ6HLB4 (BT9727_1323)	END
feuA (BT9727_3483)	neur_chan_memb
G1G14-4353	pot
recN (BT9727_3916)	COX1
G1G14-3311 (BT9727_3234)	PCI1
scdA (BT9727_1971)	PABP
hmp (BT9727_1331)	zf-CCHC
mfd (BT9727_0048)	COX1
celB (BT9727_4888)	Ribosomal_L12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



To go forward

- Despite the good quality of the profiles created, parameters improvement is still required (e-value, database, gap penalties, scoring functions)

- Super-family and Fold types→ influence scoring function performance

- Fold detection Improvement through:
- Mixture classification approach (test on benchmark already positive)
- Secondary structure prediction information

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

Annexe 2 - Strategy Requirements

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

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

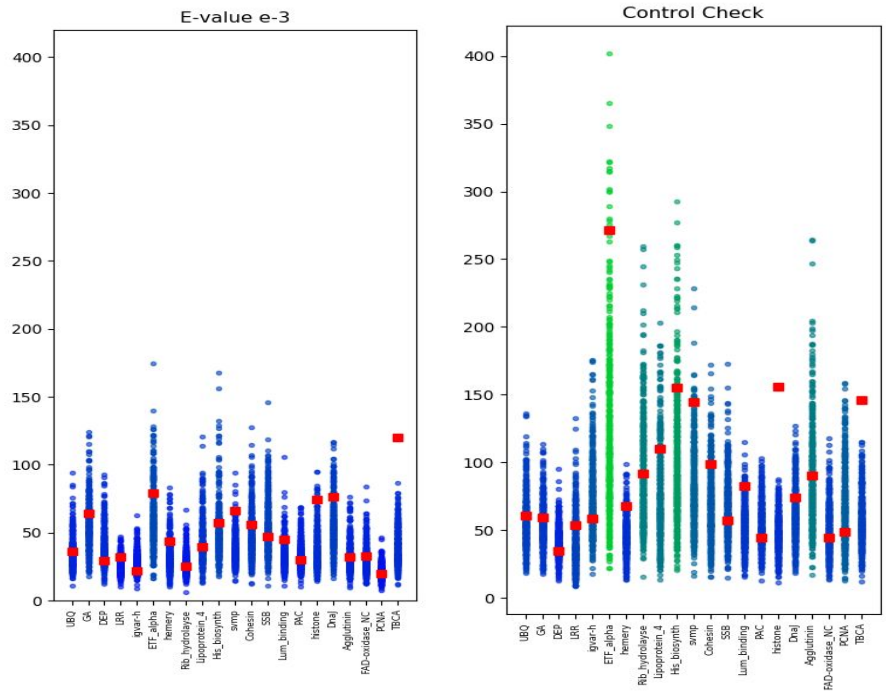
  → Profile Creation method (PSSM, HMM…)

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

Results (1) - Control Check of Profiles Construction

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



Parameter Optimization

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

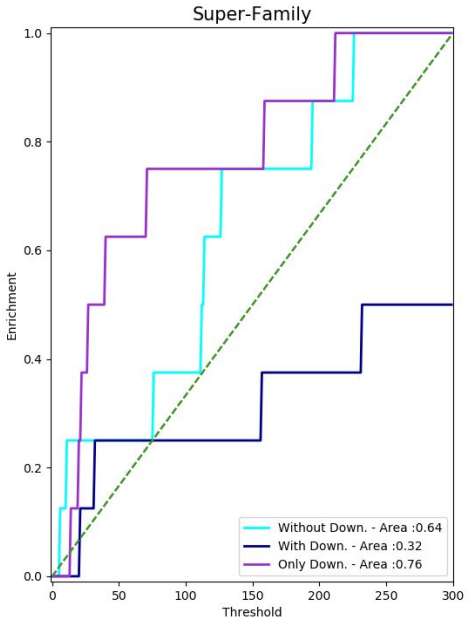
Results (4) Downstream evaluation

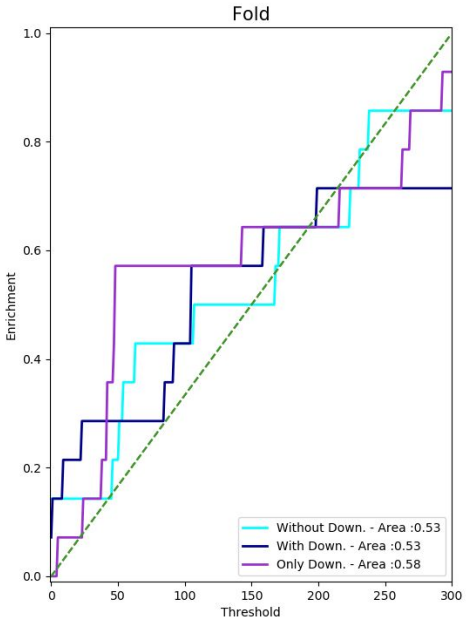
Final ranking scores with downstream program combination

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

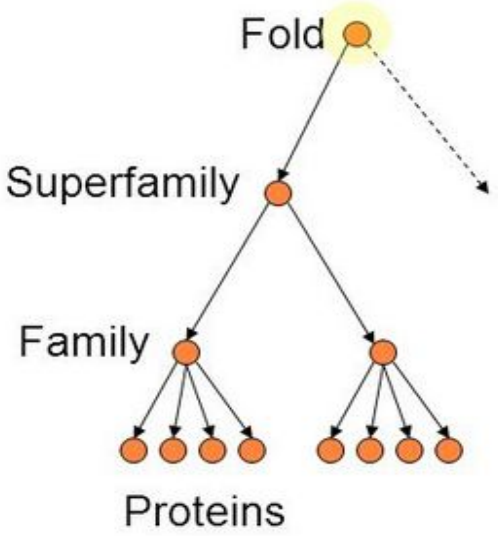
→ Superfamily: Poorer results with upstream & downstream combination

→ hypothesis: Overfitting during learning on Orion dataset





Fold and Superfamily



Picture from Morten Nielsen, CBS, BioCentrum, DTU