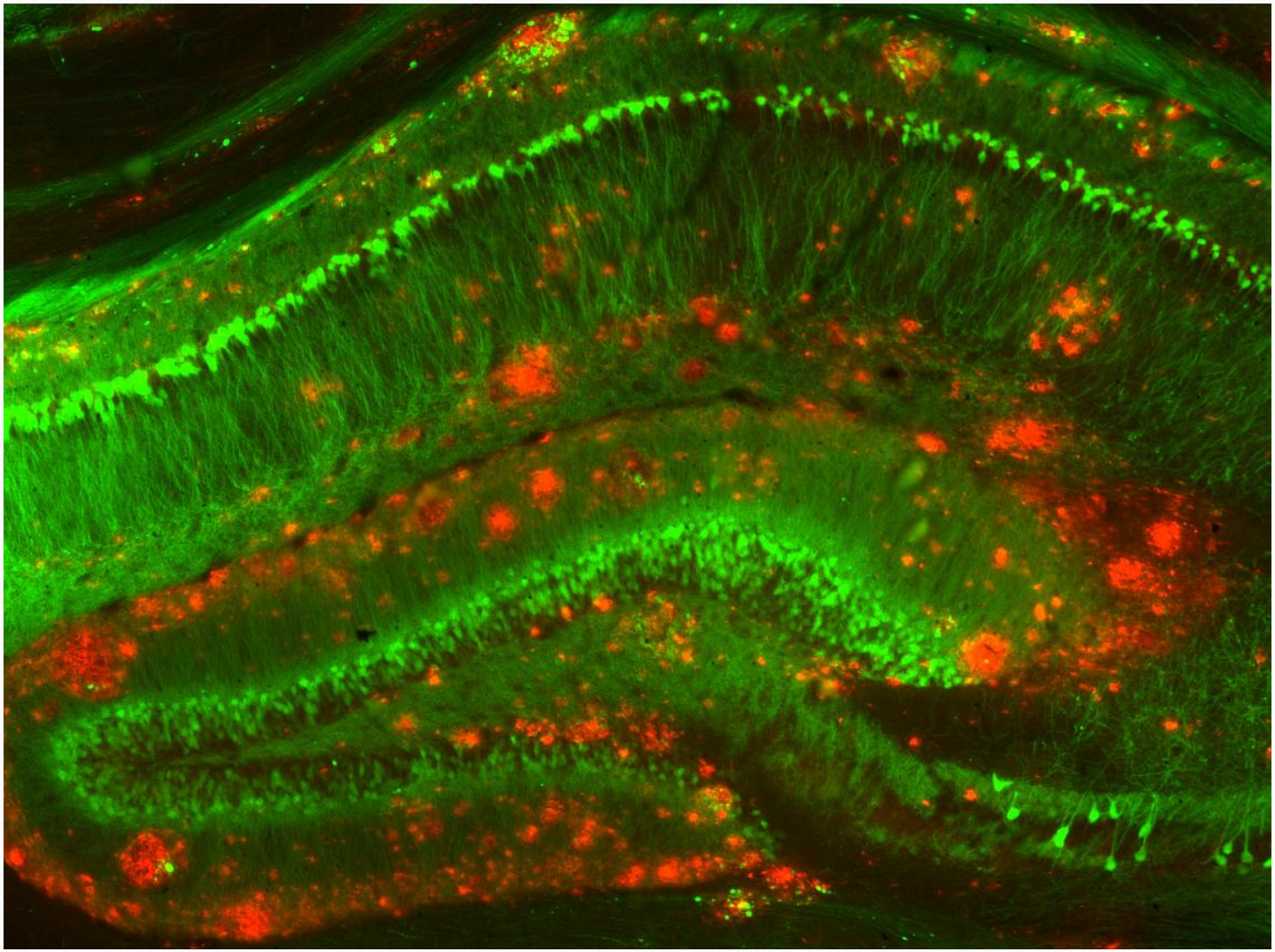
AmyloGram:a novel predictor of amyloidogenicity

Michał Burdukiewicz[1], Piotr Sobczyk[2], Stefan Rödiger[3], Paweł Mackiewicz[1] and Małgorzata Kotulska[4]

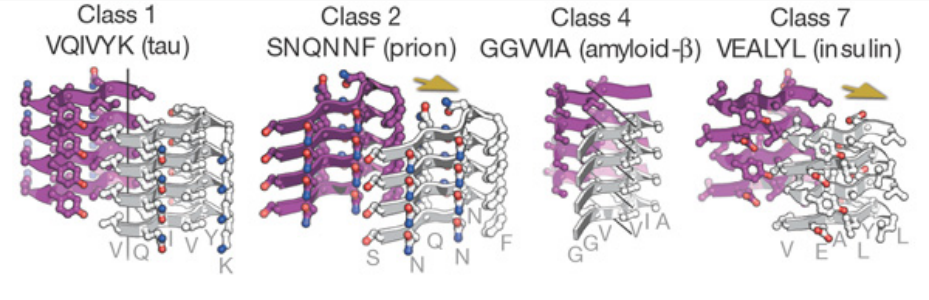
[1]University of Wrocław, Department of Genomics,
[2]Wrocław University of Science and Technology, Faculty of Pure and Applied Mathematics,
[3]Brandenburg University of Technology Cottbus-Senftenberg, Institute of Biotechnology,
[4]Wrocław University of Science and Technology, Department of Biomedical Engineering

Amyloids

Proteins associated with various neurodegenerative disorders (e.g., Alzheimer's, Parkinson'a's, Creutzfeldta-Jakob'a's diseases) creating harmful aggregates.



The aggregation of amyloids is initiated by 6- to 15-residue segments called hot spots, diverse subsequences that form unique zipper-like β-structures.

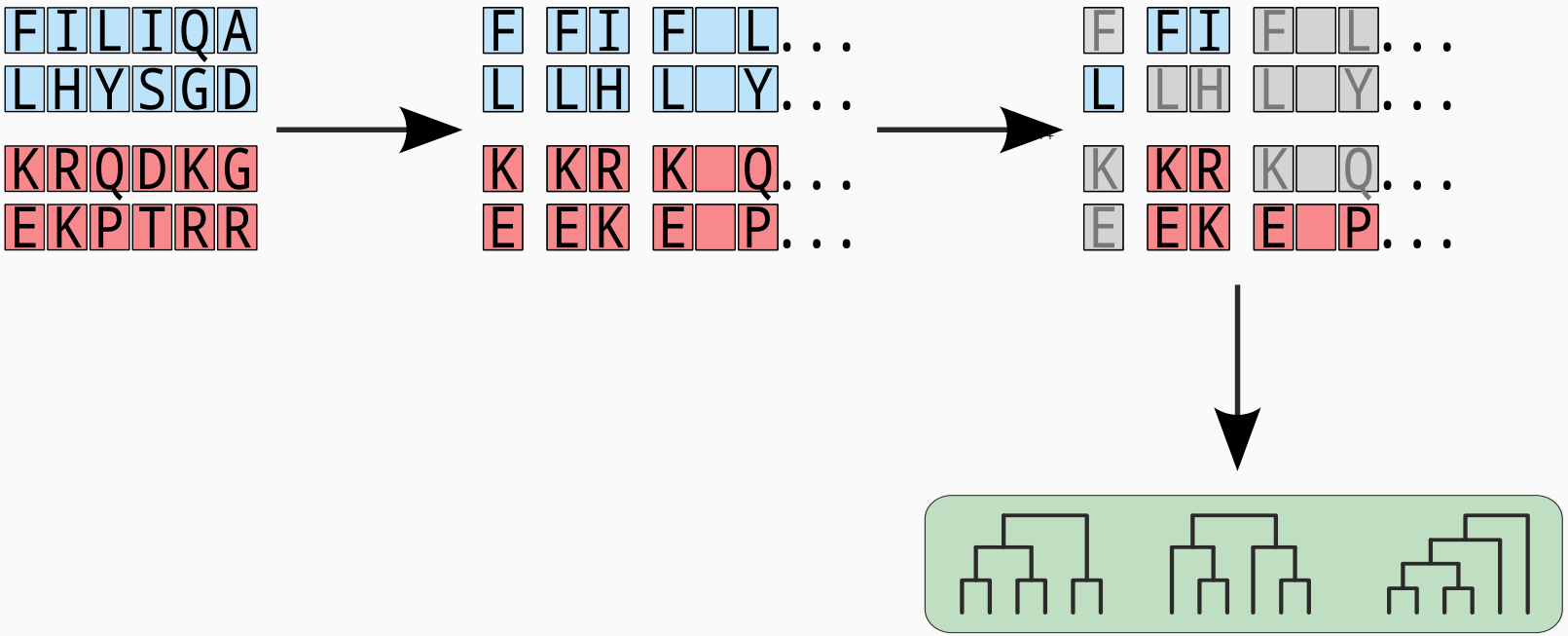


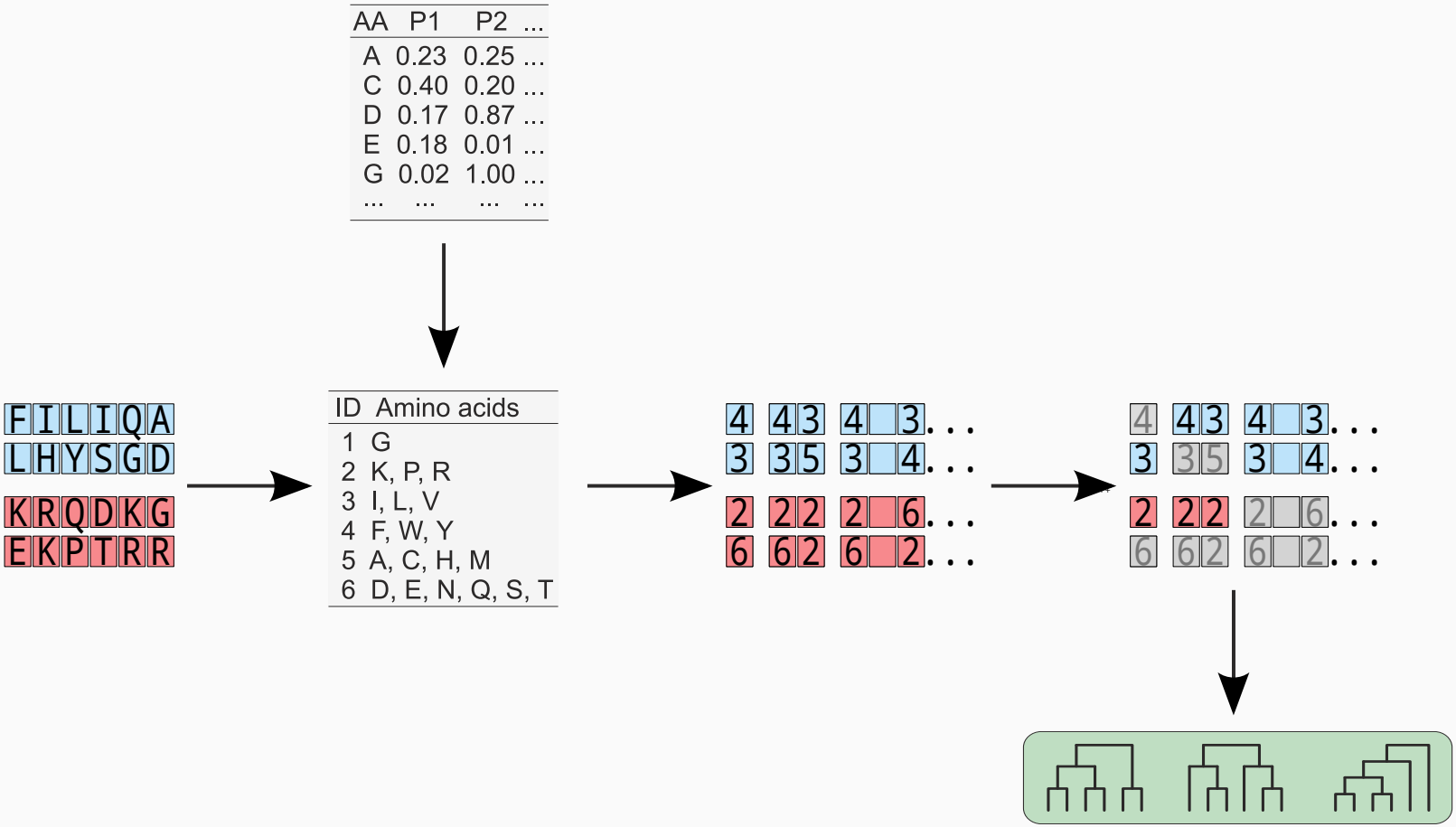
Sawaya et al. (2007)

Aim

Analize structure of hot spots and create a novel predictor of amyloids.

- Which motifs are associated with amyloidogenicity?
- Does amyloidogenicity depend on the exact sequence of amino acids?


FILIQA
LHYSGD
KRQDKG
EKPTRR
F FI F L...
L LH L Y...
K KR K Q...
E EK E P...
F FI F L...
L LH L Y...
K KR K Q...
E EK E P...


AA P1 P2 ...
A 0.23 0.25 ...
C 0.40 0.20 ...
D 0.17 0.87 ...
E 0.18 0.01 ...
G 0.02 1.00 ...
... ...
F I L I Q A
L H Y S G D
K R Q D K G
E K P T R R
ID Amino acids
1 G
2 K, P, R
3 I, L, V
4 F, W, Y
5 A, C, H, M
6 D, E, N, Q, S, T
4 4 3 4 3 . . .
3 3 5 3 4 . . .
2 2 2 2 6 . . .
6 6 2 6 2 . . .
4 4 3 4 3 . . .
3 3 5 3 4 . . .
2 2 2 2 6 . . .
6 6 2 6 2 . . .

Reduced amino acid alphabets

- 17 measures handpicked from AAIndex database
  - size of residues,
  - hydrophobicity,
  - solvent surface area,
  - frequency in β-sheets,
  - contactivity.
- 524 284 amino acid reduced alphabets with different level of amino acid alphabet reduction (three to six amino acid groups).

Quick Permutation Test

Informative n-grams are usually selected using permutation tests.

During a permutation test we shuffle randomly class labels and compute a defined statistic (e.g. information gain). Values of statistic for permuted data are compared with the value of statistic for original data.

$$\text{p-value} = \frac{N_{T_P > T_R}}{N}$$

$N_{T_P > T_R}$: number of cases, where T_P (permuted test statistic) has more extreme values than T_R (test statistic for original data).

N: number of permutations.

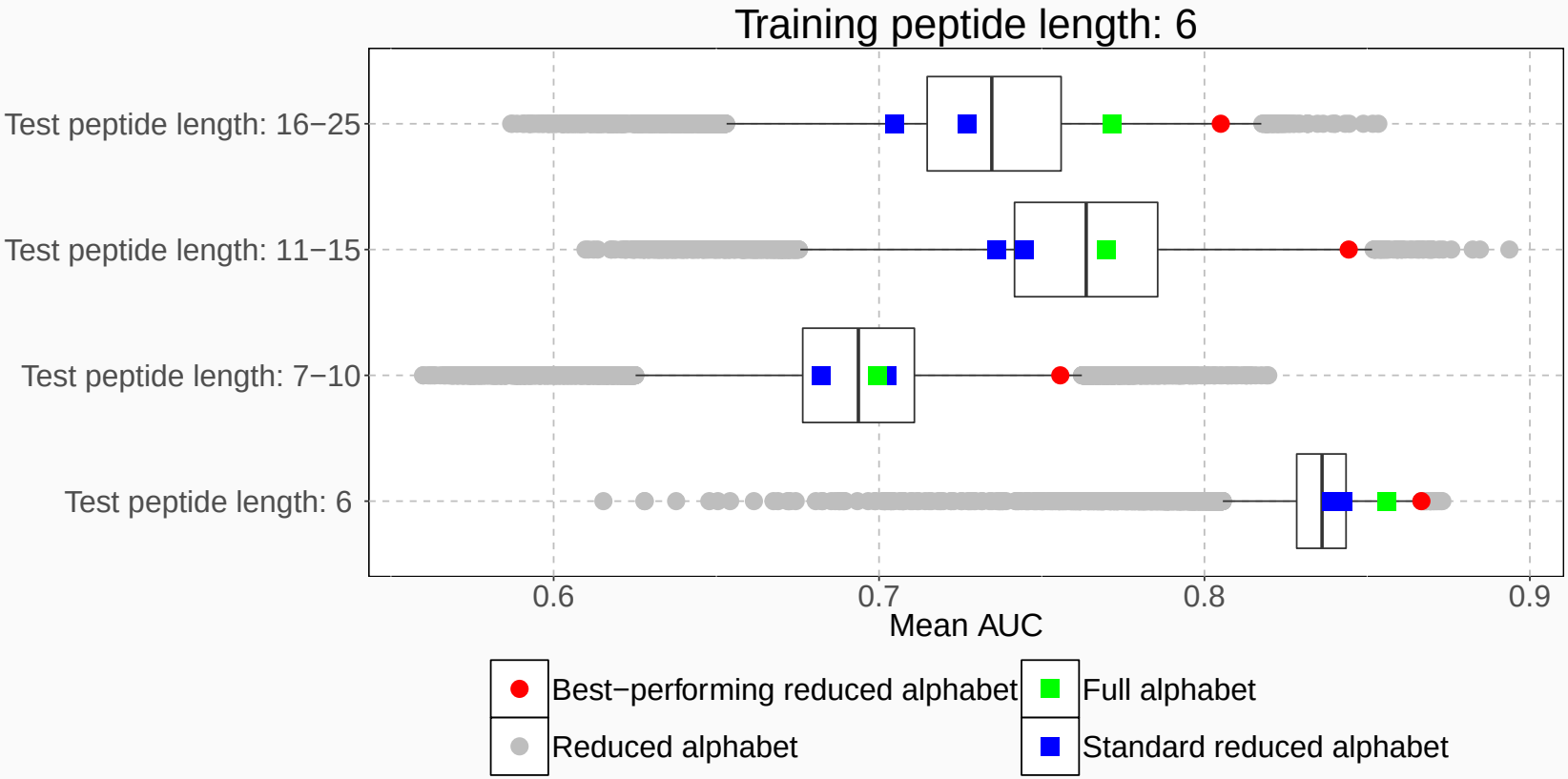
QuiPT

Quick **P**ermutation **T**est is a fast alternative to permutation tests for n-gram data. It also allows precise estimation of p-value.

QuiPT is avaible as part of the **biogram** R package.

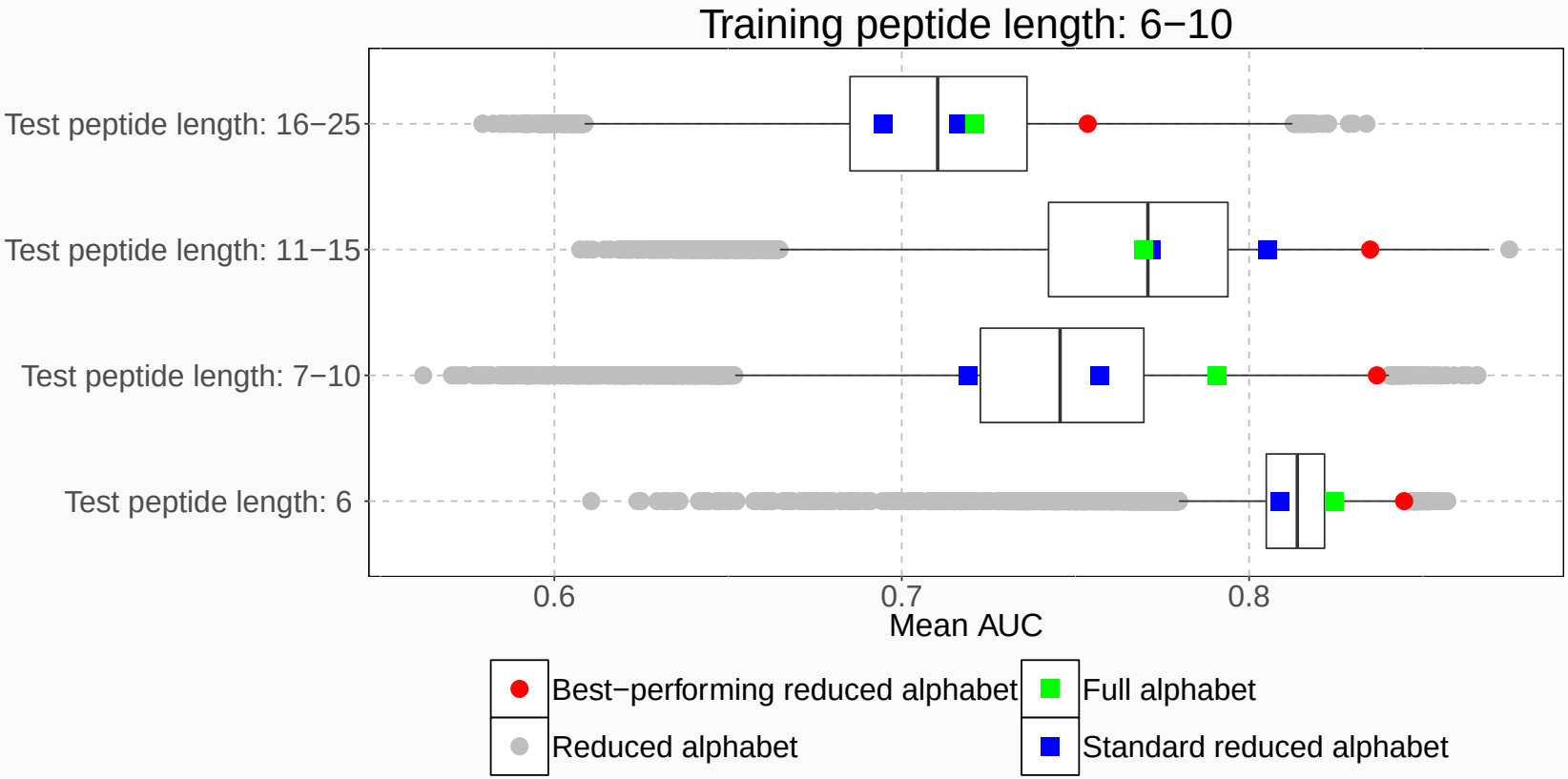
Results

Cross-validation



Hinges of boxes correspond to the 0.25 and 0.75 quartiles. The bar inside the box represents the median. The gray circles correspond to the reduced alphabets with the AUC outside the 0.95 confidence interval.

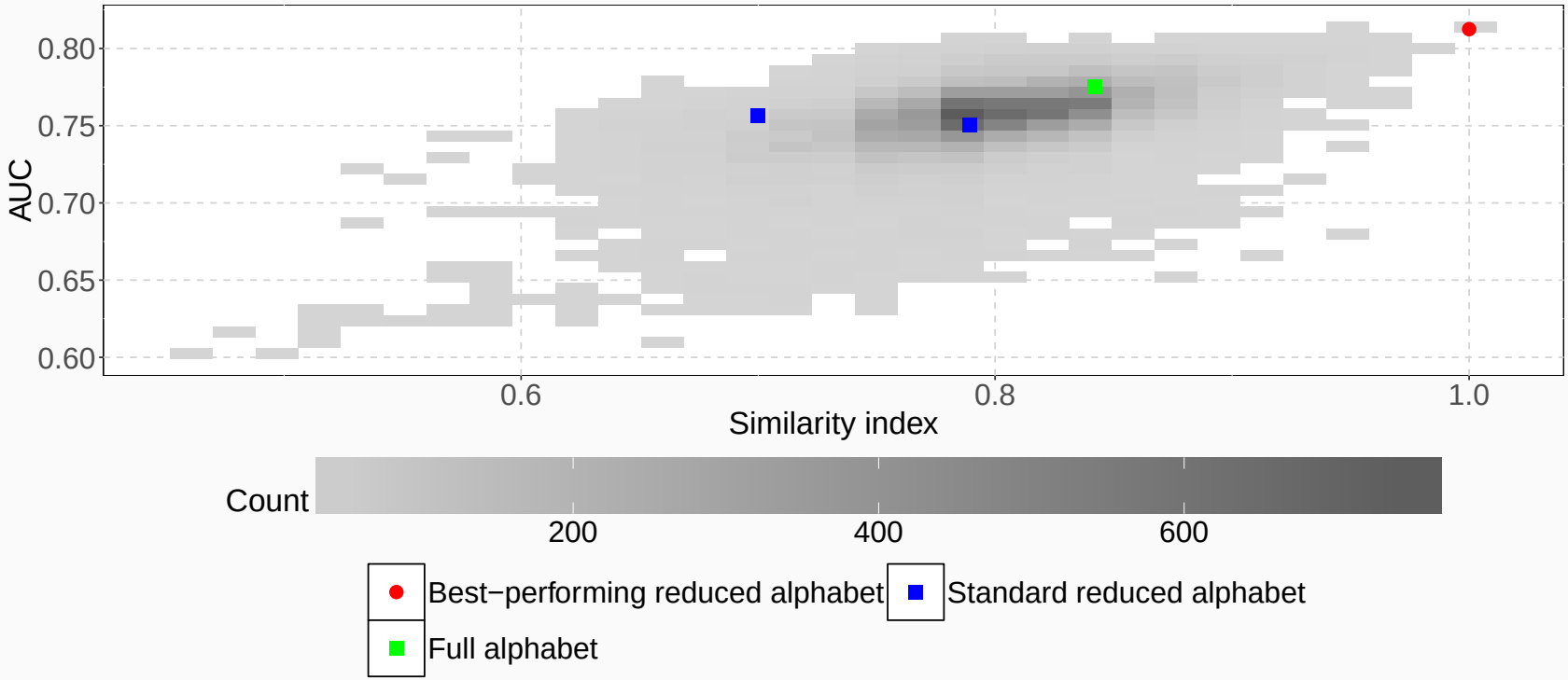
Cross-validation



Hinges of boxes correspond to the 0.25 and 0.75 quartiles. The bar inside the box represents the median. The gray circles correspond to the reduced alphabets with the AUC outside the 0.95 confidence interval.

Is the best-performing reduced amino alphabet associated with amyloidogenicity?

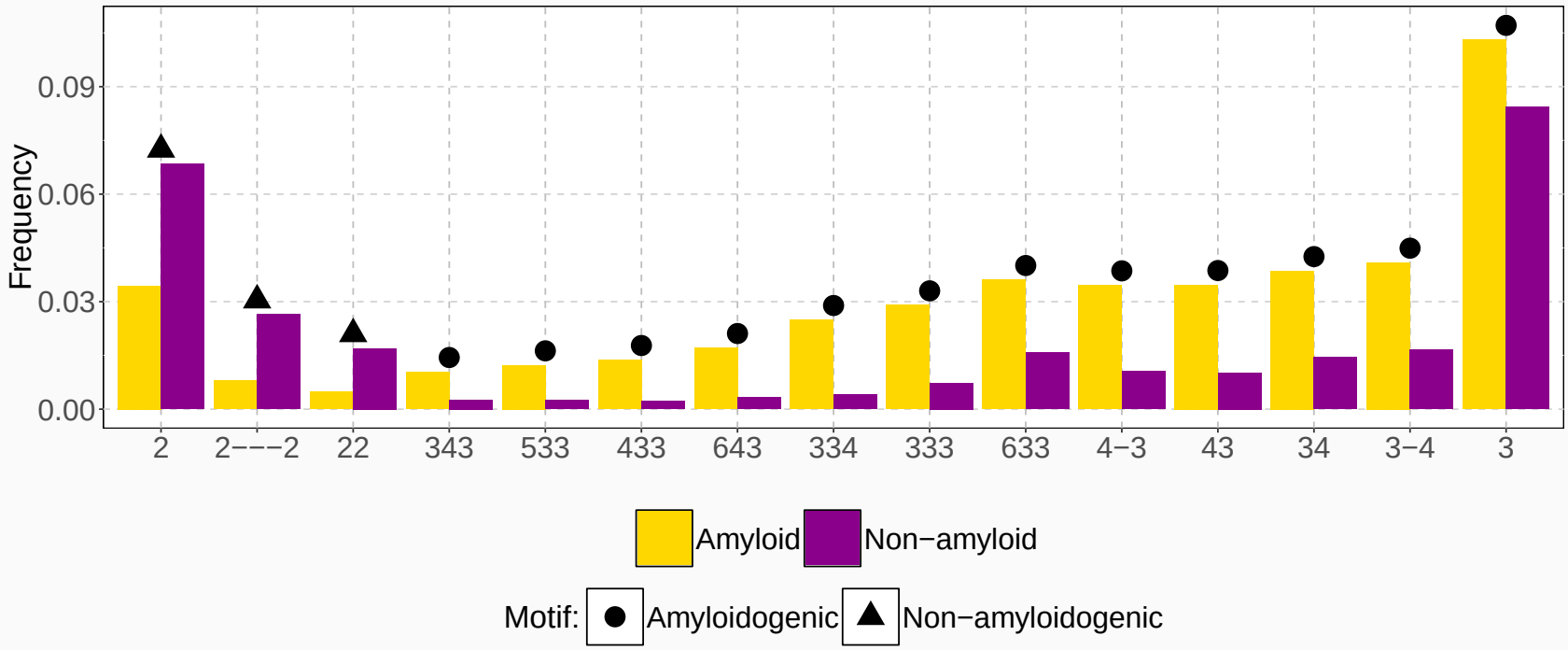
Similarity index



Similarity index (Stephenson and Freeland, 2013) measures the similarity between two reduced alphabets (1 - identical, 0, totally dissimilar).

Are informative n-grams found by QuiPT associated with amyloidogenicity?

Informative n-grams



Out of 65 the most informative n-grams, 15 (23%) were also found in the motifs validated experimentally (Paz and Serrano, 2004).

Is performance of the AmyloGram, the classifier based on the best-performing reduced amino acid alphabet, also adequate on the independent dataset?

Benchmark results

Classifier	AUC	MCC
AmyloGram	**0.8972**	**0.6307**
PASTA 2.0(Walsh et al., 2014)	0.8550	0.4291
FoldAmyloid (Garbuzynskiy et al., 2010)	0.7351	0.4526
APPNN (Família et al., 2015)	0.8343	0.5823

The predictor based on the best-performing alphabet, called AmyloGram, was benchmarked against the most popular tools for the detection of amyloid peptides using an external data set *pep424*.

Summary

We identified a group of reduced amino acid alphabets which capture properties of amyloids.

Our algorithm was also capable of extracting n-gram associated with amyloidogenicity, partially confirming experimental results.

Our software is available as a web-server: `smorfland.uni.wroc.pl/amylogram`.

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References

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