

N-gram analysis of amyloid data

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Amyloids are short proteins associated with the number of clinical disorders, for example Alzheimer's or Creutzfeldt-Jakobs diseases. Despite being variable in size, amino acid composition and structure, all amyloidogenic sequences form cytotoxic aggregates [BU15]. The hallmark trait of amyloids is the presence of characteristic short sequences of amino acids, called hot-spots, amyloids can create zipper-like -structures [F12]. Although studies investigating properties of amyloidogenic sequences were already conducted, the newly established AmyLoad data base facilitates large-scale analysis of amyloids [WK15].

Among commonly acclaimed methods of predicting amyloids, only FISH Amyloid [GK14] focuses more deeply on the putative motifs of hot spots. To expand its model by considering longer and more complicated motifs, we used n-gram analysis. N-grams (k-mers) are vectors of n characters derived from input sequences. Although they constitute a powerful tool for biological sequence analysis, they suffer greatly from the dimensionality curse. To deal with the abovementioned problem, we created biogram software [BSL15]. Aside from essential functionalities, like efficient data storage, we also implemented a feature selection method. QuiPT (Quick Permutation Test) uses several filtering criteria such as information gained to choose significant features. To speed up the computation and allow precise estimation of small p-values, QuiPT performs an exact test instead of a large number of permutations.

Moreover, we aggregate amino acids into bigger groups based on their physicochemical properties important in the aggregation of amyloids. It not only reduces dimensionality of the problem, but preserves relationships between residues. Since it is still unclear which properties are exactly the most important for amylogenicity, we compare classifiers trained on different amino acid aggregations. The n-gram model, trained on the data from AmyLoad database, is validated through simple yet accurate amyloid prediction framework using random forests. The preliminary analysis of the amyloidogenic sequences yield not only new insight on the structure of the hot spots, but facilitated prediction of amyloids. The mean AUC of the classifier committee in 5-fold crossvalidation was 0.89.

The predictor of amyloidogenic sequences is accessible as a web-server (ADRES).

References

- [BSL15] Michał Burdukiewicz, Piotr Sobczyk, and Chris Lauber. *biogram: analysis of biological sequences using n-grams*, 2015. R package version 1.2.
- [BU15] Leonid Breydo and Vladimir N. Uversky. Structural, morphological, and functional diversity of amyloid oligomers. *FEBS letters*, July 2015.
- [F12] Marcus Fndrich. Oligomeric Intermediates in Amyloid Formation: Structure Determination and Mechanisms of Toxicity. *Journal of Molecular Biology*, 421(45):427–440, August 2012.
- [GK14] Paweł Gasior and Małgorzata Kotulska. FISH Amyloid – a new method for finding amyloidogenic segments in proteins based on site specific co-occurrence of aminoacids. *BMC Bioinformatics*, 15(1):54, February 2014.
- [WK15] Paweł P. Wozniak and Małgorzata Kotulska. AmyLoad: website dedicated to amyloidogenic protein fragments. *Bioinformatics (Oxford, England)*, June 2015.
- [WSTT14] Ian Walsh, Flavio Seno, Silvio C. E. Tosatto, and Antonio Trovato. PASTA 2.0: an improved server for protein aggregation prediction. *Nucleic Acids Research*, 42(W1):W301–W307, July 2014.