“Determining Patterns of Cross-Interactions between Amyloid Proteins”

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Amyloid proteins are characterized by their ability to form fibrils. These fibrils are often associated with the development of several diseases, the most well-known of which include Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis (ALS), Huntington’s disease, and type 2 diabetes. The formation of fibrils by amyloid proteins, which originally exist in a different, non-fibrillar form, is usually triggered by additional factors such as mutations within the protein, interactions with other molecules, or specific environmental conditions.

The aim of our study was to predict the impact of interactions with other proteins, which exhibit similar properties, on the changes in their tendency to form fibrils. Of particular interest are interactions between human proteins and amyloids originating from outside the human organism, especially the so-called functional bacterial amyloids. The term *functional* refers here solely to their role in bacterial physiology, where they support growth and vital processes, for example by enabling the formation of a protective biofilm. The same proteins, when introduced into the human body, may adversely affect the ability of human proteins to form harmful fibrils and thus contribute to disease development. A confirmed example of such an effect is the interaction of bacterial amyloids, produced by certain gut-dwelling species, with the human protein α-synuclein, which is involved in the development of Parkinson’s disease. These interactions may facilitate its misfolding and thereby promote disease progression.

The project aimed to discover and describe the rules governing interactions between various amyloid proteins forming fibrillar structures, and to use this knowledge to develop an algorithm and software capable of predicting such interactions without the need for costly and time-consuming laboratory experiments. As a result, among others, the world’s only database of amyloid interactions – *AmyloGraph* – was created. Based on these data, the software *PACT (Prediction of Amyloid Cross-interaction by Threading)* was developed and made publicly available to model potential interactions between fibril-forming proteins. This method was used to predict and test previously unknown interactions between human and bacterial proteins. Experiments demonstrated that cross-interactions with other proteins can accelerate, slow, or inhibit the aggregation of amyloid proteins. The potential involvement of amyloid interactions in neurodegenerative diseases, particularly Parkinson’s and Alzheimer’s diseases, was also analyzed. The study further revealed functional amyloid signaling patterns that enable microorganisms to regulate the aggregation process.

The knowledge gained during the project can be used to better understand and control protein aggregation processes occurring in disease development, as well as in drug design and materials science. This will contribute to the development of the scientific discipline of biomedical engineering and related fields.

The project resulted in the publication of more than a dozen articles in leading scientific journals, three doctoral dissertations (two more in the pipeline), presenting the developed algorithms, computational software, and databases, as well as experimental results. The project also contributed to the habilitation application for one person.

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