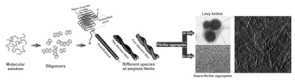
fibrillar deposits known as Lewy bodies and neurites are distinct signatures of Parkinson's disease. We demonstrate the hierarchical self-assembly of aS fibrils into mesoscopic structures in vitro. The morphology of these structures is well-defined and depends on the physicochemical conditions at which the aggregates are formed. The observed phenomenon seems to be governed by the interplay between long ranged repulsion and short ranged attraction. Once the multiple negative charges on the fibrils are sufficiently screened at high enough salt concentration or neutrilized at appropriate pH level the electrostatic repulsion is minmized allowing the short range attraction (hydrophobic) to take over and drive the fibrils into supra-fibrillar assemblies. Our findings suggest that the balance between those two types of interaction is not only crucial for the initiation of the self-assembly process but it also controls the morphology and finite size of the supra-fibrillar aggregates giving rise to a rich phase behavior.



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Structural Basis for the Prion-Like Mavs Filaments in Antiviral Innate Immunity

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Mitochondrial anti-viral signaling (MAVS) protein is a critical adaptor required for innate immune responses against RNA viruses. In virus-infected cells MAVS forms prion-like aggregates to activate antiviral signaling cascades, but the structural mechanism underlying such aggregation is unknown. Here we report cryo-electron microscopic structures of the helical filaments formed by both the N- terminal caspase activation and recruitment domain of MAVS and a truncated MAVS lacking its C-terminal transmembrane domain. Both structures display a left-handed three-stranded helical filament, revealing specific interfaces between individual subunits that are dictated by electrostatic interactions between neighboring strands and conserved hydrophobic interactions within each strand. Point mutations at multiple locations of these two interfaces impaired filament formation and antiviral signaling. Super-resolution imaging of virus-infected cells revealed the spatial features of rod-shaped MAVS clusters on mitochondria. These results elucidate the structural mechanism of MAVS polymerization, and explain how an α-helical domain uses distinct chemical interactions to form self-perpetuating filaments.

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Amyloids: Connecting from Single Fibril Mechanics to Macroscopic Rheology

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Nearly all proteins and peptides have the ability to self-assemble into amyloids when they are denatured. These highly ordered nanofibrils exhibit superior mechanical properties, which are relatively insensitive to their protein amino acid sequence. This makes them attractive candidates for applications in materials science and food industry. However, their remarkable stability constitutes a problem in the context of amyloid-related diseases, where amyloids accumulate in tissues. Despite the wide interest in amyloids, the understanding and description of their mechanical properties is still limited. Our goal was to investigate both the micromechanics of individual fibrils and the emergent mechanics of networks on the mesoscopic scale.

We will show macroscopic rheology and laser tweezer microrheology of the viscoelastic properties of amyloids formed from hen egg white lysozyme (HEWL). The macroscopic rheology of the networks will depend both on the stiffness of the fibrils and the energetics of their interactions. Therefore we show for the first time for the same system also measurements of the high bending rigidity based on fluorescence microscopy of single, fluctuating fibrils in solution. The high persistence length was further confirmed using atomic force microscopy (AFM) imaging. With laser tweezer microrheology we show the local properties of fibrils in networks. By using rheology in combination with small-angle neutron scattering (rheo-SANS), we show that the shear-thinning response results from fibril alignment. In conclusion, our results give a comprehensive description of the mechanical properties of single amyloid fibrils as well as networks of fibrils.

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Recognition of Amyloidogenic Segments Based on Site Specific Aminoacid Pairwise Correlations

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Amyloids are proteins forming aberrant intramolecular contact sites characteristic of fibrils instead of functional structure. Recent studies show that only short segments of aminoacids can be responsible for amyloidogenic properties. Here we propose an original machine learning method for classification of biological sequences based on discovering a segment with a discriminative pattern of correlations between sequence elements. The pattern is based on location of correlated pairs of elements in the window. The algorithm first recognizes the most relevant training segment in each positive training instance. Then the classification is based on maximal differences between correlation matrix of the relevant segments in positive training sequences and the matrix from negative training segments. The method was applied for recognition of amyloidogenic fragments in aminoacid sequences. It was trained on available datasets of hexapeptides with the amyloidogenic classification, using 5 or 6-residue sliding windows. Depending on the choice of training and testing datasets, area under curve of receiver operating characteristic (AUC ROC) of the method obtained the value up to 0.80 for experimental, and 0.95 for computationally generated (3D profile) datasets. The method reveals the characteristic correlation pattern of the data. Moreover, the method finds the segments with the strongest classification pattern, also in long training sequences. The method, applied to the problem of recognition of amyloidogenic segments, showed a good potential for various classification bioinformatical problems.

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Elongation of Murine Prion Protein Amyloid-Like Fibrils: Effect of Temperature and Denaturant Concentration

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Prion protein (PrP) plays a big role in a number of lethal neurological diseases, known as transmissible spongiform encephalopaties. These disorders are associated with aggregation of normal cellular prion protein (PrP^{C}) into pathogenic beta-sheet-rich prion isoform (PrP^{Sc}). Although majority of suspected cases of human prion diseases are sporadic, prions are mostly known because of their infectivity. Infectious nature of prion diseases is based on the ability of PrP^{Sc} to self-replicate by converting PrP^{C} into same pathogenic isoform. One of possible mechanisms of pathogenic prion structure replication is elongation of amyloid-like fibrils. Deeper insight into mechanism of mammalian prion fibril elongation may be important for better understanding of proteinaceous infectivity.Here we studied elongation of murine prion protein fibrils. Due to quiescent conditions, we can avoid most of nucleation processes (such as primary nucleation and fragmentation of fibrils), means the observed rate of fibrillation should be very similar to the rate of elongation. As observed rates at different temperatures give a good enough correlation when plotted in Arrhenius coordinates it is possible to estimate activation energies of fibril elongation under different conditions. We did experiments at a range of guanidinium hydrochloride (GuHCl) concentrations and were able to determine two different activation energies representing fibril elongation using folded PrP and unfolded PrP.

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Pyroglutamylated Amyloid-Beta Peptide Reverses Cross Beta-Sheets by a Prion-Like Mechanism

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The amyloid hypothesis causatively relates the extracellular fibrillar deposits of amyloid beta peptide (Abeta) to the Alzheimer's disease (AD). More recent data, however, identify the intracellular oligomers as the major cytotoxic entities. Pyroglutamylated Abeta (pE-Abeta) is present in AD brains and exerts augmented neurotoxicity by an unknown mechanism. The hypertoxicity of pE-Abeta is believed to result from its higher beta-sheet propensity and faster conversion into fibrils. While this concept is based on a set of experimental results, others have reported similar beta-sheet contents in unmodified and pE-Abeta, and even slower aggregation of pE-Abeta as compared to unmodified Abeta, leaving