aggregate whereas the hydrophilic flanks prevent random aggregation and drive the system to form fibers [1,2].
Based on our atomistic simulations of the (EGAGAGA)x repeat and the hydrophilic sequences seperately, we have developed a coarse grained protein model that allows us to study fiber formation as well as certain characteristics of the mature fibers [3]. Although our model has been developed for the artificial silk protein it can also be applied for natural occurring proteins such as amyloids and may be extended to study other fiber forming proteins.
[1] Smeenk et al., Angew. Chem. Int. Ed., 2005, 44, 1968-1971
[2] Martens et al., Macromolecules, 2009, 42, 1002-1009.
[3] Schor et al. Faraday Discuss., 2010, DOI: 10.1039/b901608b

3381-Pos
The Spontaneous Aggregation of Steric Zipper Peptides Studied by Molecular Dynamics Simulations
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Recently obtained crystal structures of truncated fragments of proteins provide detailed structural insights into beta-sheet rich aggregates, known as amyloid fibrils [1,2]. The arrangement of these short model peptides revealed a common steric zipper motif in the crystalline state. Two sheets of peptide strands are interfaced by a dry and tight zipper structure with a high degree of sidechain complementarity. Combined experimental data suggests that steric zippers may represent a general feature of amyloid formation. However, a thorough understanding of the aggregation process and the structural characterization of its multitude of conformational states is still lacking.
We employ molecular dynamics simulations in an explicit solvent environment to study biomolecular aggregation at atomistic detail with the aim to unveil the energetic and structural determinants that drive the formation of amyloidogenic peptide assemblies and also stabilize the formed aggregates.
Starting from separated peptide chains with random conformations, we monitor the primary events of aggregation and find a rapid clustering of the peptides accompanied by an increased number of inter-molecular hydrogen bonds and the spontaneous formation of beta-sheet rich oligomers. Some of the peptide aggregates feature structural characteristics of the crystalline conformation (e.g. beta-sheet bilayers with dry interface), but also interconvert with conformationally distinct oligomeric states.
By mapping the conformational ensembles we were able to describe the different topologies of the system, which helps to yield insight into possible common mechanistic steps found along the aggregation pathway. The goal of our work is to fully characterize the aggregation behaviour of small model peptides and test our findings with results from /in vitro/ experiments (EM, NMR) with a particular focus on aggregation-prone sequences of tau, insulin and alpha-synuclein.
[1] Nelson et al., Nature, 2005
[2] Sawaya et al., Nature, 2007

3382-Pos
Beta-Barrel Hypothesis: Structural Insights to Oligomeric Prion Conformation
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The denaturation of prion protein (PrP) and the concurrent formation of beta-sheet rich isoform has been accredited to the etiology of the prion diseases. Accumulating biochemical evidences underline the critical role of oligomeric PrP conformations emerging from the early stage of the denaturation process. However detailed structural information on the oligomeric isoforms remains elusive, which hampers precise description of the pathological process. Recently we proposed a new structural hypothesis for the oligomeric PrP species comprised of a short PrP construct (Human PrP 175-217) based on experimental findings. We postulated that 1) monomers adopt beta-hairpin conformation and 2) assemble as beta-barrel quaternary structure. These assumptions provided a comprehensive explanation for the experimental findings suggesting beta-sheet rich structure including circular dichroism (CD) spectrum and Fourier transformed infra-red spectroscopy (FTIR) as well as the presence of disulfide bridge between CYS-179 and CYS-214. To be more specific, we constructed various beta-barrel models differing in number of monomers, intermolecular hydrogen bond pattern and side-chains facing exterior of the barrel. Those models were refined extensively using a protein structure prediction tool (Rosetta). Structural energy profile of the predicted oligomer models was consistently lower than that of native like monomer or oligomers comprised of partially denatured monomers. Also the smallest stable oligomer was predicted to be an octamer, which is in good agreement with available mass spectrometric data. Finally, we discussed a possible generality between protein denaturation and amyloidogenesis problems in general, by comparing our model with a oligomeric assembly model for the pathological amyloid beta protein (Abeta).

3383-Pos
Polymophism of A-Beta1-42 Peptide Oligomer - Membrane Interactions
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Recently, alternative propositions have been put forward to explain the pathogenesis of Alzheimer's disease with the possibility that amyloid peptides form unregulated pores or ion channels in membranes. In this study, we compared several ion channel aggregation models of with 24 Aβ1-42 peptides in a membrane environment, using Molecular Dynamics simulations. Our results indicated that like in solution, the polymorphism of Aβ1-42 oligomers also relate to possible ion conductance induced by Aβ1-42 peptides.

3384-Pos
Modeling Amyloid Oligomers with Different Structural Morphologies
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The aggregation of monomeric proteins/peptides to form ordered amyloid oligomers/fibrils is a pathogenic feature of many degenerative diseases including Alzheimer's, Parkinson's, and prion diseases. Despite of significant progress, oligomeric structures and associated toxicity at the very early stage of aggregation remain unclear. Structural knowledge of these oligomers is essential for understanding the pathology of amyloidoses and for rationally designing drugs against amyloid diseases. In this work, molecular modeling and simulations are performed to examine the conformational preference and structural characteristics of preformed oligomers with different structural morphologies (micelles, annulars, triangulars, and linears) and amyloid peptides (Abeta, hIAPP, GNNQQNY, and K3). We identify several stable oligomeric structures with different structural morphologies and sequences, delineate several common features in amyloid structures, and illustrate aggregation driving forces that stabilize these oligomeric structures. Structural comparison among different oligomers suggests that the aggregation mechanism leading to distinct morphologies and the aggregation pathways is sequence specific, due to differences in side-chain packing arrangements, intermolecular driving forces, sequence composition, and residue positions. Moreover, we are also modeling the stable A-beta oligomers on the lipid bilayers to illustrate the postulated mechanism of membrane damage associated with amyloid toxicity.

3385-Pos
A Single-Molecule Approach to Tau
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Tau is a protein associated with bundles of microtubules, while tau/tau interactions can lead to aggregates thought to underlie Alzheimer's disease. Here, we investigate the utility of a multiplexed single-molecule manipulation approach to give information on tau structure and tau/tau interactions: Previously we demonstrated the ability to perform several single molecule measurements in parallel in a multiplexed magnetic tweezers assay (Rev. Sci. Instrum. 79, 094301 (2008)), enhancing the statistical significance of the data. For testing the capability of this tool in protein folding studies, we present data on nucleic acid hairpins as a model system. We directly observe high resolution hairpin opening and closing events on several single molecule tethers simultaneously subject to the same critical force. We then describe experiments to observe the thermodynamics and kinetics of protein aggregation by i) immobilizing and studying tau in isolation then ii) studying interactions between immobilized tau with tau free in solution.

3386-Pos
Pre-Amyloid States of Islet Amyloid Polypeptide Examined by Single-Particle Fluorescence
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Islet amyloid polypeptide (IAPP or amylin) is a peptide hormone cosecreted with insulin by the pancreas that displays potent amyloidogenic activity. In vitro studies demonstrate that IAPP is capable of disrupting lipid bilayers, suggesting a possible mechanism for IAPP-induced beta-cell death in Type II Diabetes Mellitus. Of particular interest are oligomeric IAPP species, which are believed to mediate membrane leakage, as well as to be intermediates in amyloid formation. IAPP oligomers are likely to be transient and heterogeneous, and so a detailed dynamic and functional characterization of these critical structures has been challenging. We have used single-molecule Förster resonance energy transfer (FRET) to study IAPP conformations in solution; bound to model membranes; and in the presence of insulin, which exerts