Posters

Protein Aggregates I

1091-Pos Board B1
Characterization of the Aggregation Pathway for a 20-mer of GNNQQNY using Coarse-Grained and All-Atom Representations
Jessica Nasica-Labouze, Massimiliano Meli, Philippe Derreumaux, Giorgio Colombo, Normand Mousseau.
The formation of amyloid fibrils is associated with numerous neurodegenerative diseases such as Alzheimer's, Parkinson's, the Prion disease but also with diseases such as diabetes mellitus. Little is known about the aggregation dynamics of amyloid proteins and a detailed atomic characterization of this process is necessary to better understand their toxicity mechanism. More than 20 short amyloid peptides fragments have been identified to have the ability to drive an entire protein into an amyloid fibrillar state. In particular, the amyloid peptide GNNQQNY from the budding yeast's Prion protein Sup35 has been observed to form fibrils by X-ray crystallography. The main structural element of those GNNQQNY fibrils is a cross-β structure consisting of two parallel β-sheet stacked in-register, with side-chains interdigitating between the sheets to provide stability to the structure. We have conducted a computational study of the GNNQQNY peptide aggregation mechanism by replica-exchange molecular dynamics, using first a coarse-grained potential (OPEP) followed by an all-atom refinement of the side-chains using GROMACS. This combination of numerical methods allows us to accelerate the sampling and thus study bigger systems over longer time scales compared to the other numerical methods generally used. Here, we have investigated the aggregation process of the trimer, dodecamer and 20-mer GNNQQNY, starting from random conformations, and our simulations show a rich diversity of structural arrangements for aggregates of all sizes. For the 20-mer, we observe the formation of 3 to 4-stranded building blocks that assemble in various orientations to form transiently fibril-like structures or more disordered globular oligomers, showing a rich polymorphism.

1092-Pos Board B2
Statistical Mechanical Approach to Protein Aggregations
John Schreck, Jian-Min Yuan.
We introduce a simple quasi-one-dimensional model for protein aggregation in thermal equilibrium using 'Zimm-Bragg'-like partition functions, but for monomer, oligomer, proto-fibril, and fibrils. We study the oligomer concentrations starting with dimers up to dodecahedrons. Recent ion mobility coupled with mass spectroscopy studies have suggested that the Aβ(1-42) peptide may have a hexamer para-nucleus, potentially a toxic oligomer, which eventually matures into a full-fibril. The peptide Aβ(1-40) is thought to aggregate into fibrils from a different pathway than that of Aβ(1-42). Using a modified Ising-like model on an m × N, lattice, where m is finite, we are studying the aggregation of Aβ(1-42) peptides beginning with a hexamer para-nucleus and a dodecahedron structure. For comparison, we are studying the Aβ(1-40) peptide with dimers and tetramers as the building oligomers. Explicitly, we write down a transfer matrix for oligomer, proto-fibril and fibrillar concentrations in terms of Zimm-Bragg-like initiation and propagation parameters for each concentration. Using standard statistical mechanical techniques, the partition function is solved using transfer matrices, and thermodynamic properties can thus be obtained.

1093-Pos Board B3
Paucity of Amyloid Nuclei Defy Isolation and Toxicity Evaluation
Mirco Sorci, Whitney Silkworth, Timothy Gehan, Georges Belfort.
The molecular rearrangement of soluble proteins into fibers is a common attribute of amyloid diseases: Alzheimer's disease, Parkinson's disease, spongiform encephalopathies (including mad cow disease), and other prion diseases. In the past century considerable progress has been made in characterizing amyloid diseases, but the connection between amyloidosis and the disease is still unclear: Contradictory reports suggest that the fibrils and/or the oligomer precursors cause toxicity. The debate is still open.
Here, we offer the first attempt to ''reverse-estimate'' the concentrations of nuclei, starting from a distribution of fibril lengths. Assuming the nucleation model is valid, with a few reasonable assumptions, a fibril length distribution and a set of seeding experiments, we estimated the in vitro concentration of nuclei for the model hormone, recombinant human insulin, to be in the picomolar range. Fibril lengths are measured with an atomic force microscope and seeding shows that fibrils of different lengths exhibit similar growth rates. Because of their propensity to form aggregates (non-ordered) and fibrils (ordered), this very low concentration could explain the difficulty in fractionating, isolating and blocking nuclei toxicity. Moreover, this theoretical approach, based on our measurements and a structural fibril model recently published by David Eisenberg's group at UCLA, is general and could be used for other amyloid proteins.

1094-Pos Board B4
Monte Carlo Simulation of Protioglican-Collagen Fibrils
James Kruczek, C. Brad Bennett, W.G. Matthews, D.A. Rabson, Sagar A. Pandit.
Proteoglycans play a key role in fibril organization. Proteoglycans bind to the surfaces of collagen fibrils affecting their arrangement. A statistical model was constructed to determine the thermodynamics of proteoglycan-connected collagen fibrils that can be used to understand the formation of collagenous tissues. This model was found to be similar to a clock model. A Metropolis Monte-Carlo algorithm generated sample states of the collagen fibrils for different densities of proteoglycan, at different temperatures. Heat capacities, energies, displacements, and other properties were calculated from these states. The data show areas of interest and a possible phase transition at different temperatures depending on the density.

1095-Pos Board B5
Molecular Modeling of Amyloid Oligomers and their Interactions with Membranes
Jie Zheng, Xiang Yu, Jun Zhao, Qiuming Wang, Chao Zhao.
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, we model and identify a series of stable oligomeric structures with different structural morphologies (micelles, annulars, triangulars, globulomers, and linears) for various amyloid peptides (Abeta, hIAPP, GNNQQNY, and K3). Some common structural characteristics and underlying driving force stabilizing these oligomers are delineated. More importantly, we further examine the interactions of these stable oligomers with lipid bilayers to illustrate two postulated mechanisms of membrane damage (membrane thinning vs. ion channel) associated with amyloid toxicity.

1096-Pos Board B6
Molecular Dynamics Simulations of Human Islet Amyloid Polypeptide (IAPP) Oligomers and their Interactions with Lipid Bilayers
Jun Zhao, Xiang Yu, Chao Zhao, Qiuming Wang, Jie Zheng.
Human islet amyloid polypeptide (hIAPP) is a main component of amyloid plaques found in the pancreas of approximately 90% of typeII diabetes patients and hIAPP oligomers are major toxic species responsible for pancreatic islet β-cell dysfunction. But, molecular structures of these oligomers remain elusive. In this work, base on recent solid-state NMR, mass-per-length, and AFM data, we modeled series of hIAPP oligomers with different β-layers (one, two, and three-layers), morphologies (linear-like and annular-like), symmetries (symmetry and asymmetry), and associated interfaces using molecular dynamics simulations. For linear-like structures, three distinct interfaces formed by C-terminal-C-terminal β-sheet (CC), N-terminal-N-terminal β-sheet (NN), and C-terminal-N-terminal β-sheet (CN) are identified to drive multiple cross-β-layers laterally associated together to form different amyloid organizations via different intermolecular interactions, in which the CC interface is dominated by polar interactions, the NN interface by hydrophobic interactions, and the CN interface by mixed polar and hydrophobic interactions. Overall structural stability of the proposed hIAPP oligomers is a result of delicate balance between maximization of favorable peptide-peptide interactions at the interfaces and optimization of solvation energy with globular structure. Different hIAPP oligomeric models indicate a general and intrinsic nature of amyloid polymorphism, driven by different interfacial sidechain interactions. Furthermore, we propose two annular hIAPP structures (CNpNC and NCpCN) embedded in the DMPC lipid bilayers to examine the ion-channel mechanism. The CNpNC model is well maintained in the lipid bilayer with high selectivity of chlorine ions, while the pore structure of the NCpCN model is completed blocked in the lipid bilayers, leading to no selectivity of any ions. This result suggests a preferential conformation for hIAPP ion-channel related to their neurotoxicity. All proposed models are compatible