with experimental data in overall size, cross-section area, and molecular weight.

1097-Pos Board B7
Molecular Insights into Aβ Oligomers and their Interactions with Lipid Bilayers
Xiang Yu, Qiuming Wang, Jun Zhao, Chao Zhao, Jie Zheng.
Amyloid-β (Aβ) oligomers exhibit many distinct structural morphology at the early aggregate stage, some of which are biological relevant to the pathogenesis of Alzheimer's disease (AD). Considerably less is known about the molecular structure of Aβ oligomers and their relation to amyloid fibril formation and amyloid neurotoxicity. In this work, we develop a computational platform including conformational search, structural optimization, potential energy evaluation, and all-atom molecular dynamics (MD) to predict and model a series of atomic structures of Aβ oligomers (i.e. micelles, globulomers, triangulars, annulars, and linears) in solution. Simulation results show that although different oligomers are assembled by distinct peptide packing, the formation of these Aβ oligomers is mainly driven by hydrophobic interactions largely involving hydrophobic C-terminal residues and central hydrophobic cluster residues of $L_{17}VFFA_{21}$ at the N-terminal. We further study the interactions of Aβ oligomer with lipid bilayers to examine membrane-damaging effects by varying oligomers, lipid compositions, cholesterol contents, and position and orientation of Aβ relative to lipid bilayers. Simulation results reveal that Aβ-lipid interactions are greatly enhanced as cholesterol contents and anionic headgroups of lipids increase, highlighting electrostatic interactions are dominated force to control Aβ adsorption and orientation on the lipid bilayers. Several Aβ adsorption scenarios coupled with energetic and structural analysis will be discussed. In addition, due to the complex nature of cell membranes, we also alternatively employ self-assembled monolayers as model systems to study the aggregation and conformational changes of Aβ peptides using an integrated simulation and experimental approach. The complementary results from simulations and experiments will provide valuable insights into structural transition and underlying driving forces from aqueous solution to lipid/SAM surfaces, as well as Aβ-membrane interactions, which are essential for understanding the origin of the toxicity of Aβ oligomers.

1098-Pos Board B8
Establishing a Reference State for Studying the Aggregation Kinetics of Polyglutamine Containing Systems
Scott L. Crick, Rohit V. Pappu.
Nine different neurodegenerative diseases including Huntington's disease are associated with the aggregation of proteins containing polyglutamine expansions. Studies of homopolymeric polyglutamine have been important for understanding how and why polyglutamine should be prone to aggregation. There is currently a discrepancy between conclusions from theory and computation versus interpretations of experimental data for homopolymeric polyglutamine. We propose that this discrepancy originates in the effects of intermolecular electrostatic interactions from the flanking lysines in constructs of the form KKQ_NKK, which are most commonly used for *in vitro* experiments on polyglutamine. Although the lysines are used to enhance polyglutamine solubility, the working assumption is that they do not alter polyglutamine conformations or aggregation mechanisms.
We have performed systematic tests on the effects of flanking lysines on aggregation mechanisms of polyglutamine. Data from a collection of independent experiments based on fluorescence anisotropy, atomic force microscopy, thioflavin T fluorescence, and light scattering provide unequivocal evidence supporting the strong modulating effects of lysines on the mechanisms of polyglutamine aggregation. The extent and nature of modulation depends on polyglutamine length and the number of lysines. Borrowing from the colloidal literature, it appears that the lysines convert the mechanism of polyglutamine aggregation from being diffusion-limited aggregation (DLA) to reaction-limited aggregation (RLA). We were able to unmask the effects of lysines on polyglutamine aggregation with quantitative studies on the effect of titration of mono/divalent phosphate anions on aggregation rates and aggregate morphologies.
This work is leading toward a convergent reference state for the aggregation of homopolymeric polyglutamine. This is helping us redefine the role of biologically relevant flanking sequences on polyglutamine aggregation and in controlling aggregation-related neurodegeneration. Our studies suggest that naturally occurring flanking sequences protect functionally relevant, aggregation-prone polyglutamine-rich tracts from aggregation.

1099-Pos Board B9
Crowding Alone Cannot Account for Cosolute Effects on Amyloid Aggregation
Shahar Sukenik, Regina Politi, Assaf Friedler, Daniel Harries.
Amyloid fiber formation is a specific form of protein aggregation, often resulting from the misfolding of native proteins. Recent experiments showed a reduction in fibrillation halftimes for amyloid-forming peptides in the presence of cosolutes that are preferentially excluded from proteins and peptides. This effect has previously been attributed to the large volume excluded by inert cellular solutes, sometimes termed ''macromolecular crowding''. A different family of cosolutes that are commonly used as osmoprotectants by cells (termed osmolytes) exhibited in several instances an inhibitory effect on amyloid formation. To learn more about the difference in action between these two groups of cosolutes, we studied a model peptide that can fold to a stable monomeric β-hairpin conformation, but under certain solution conditions aggregates to form amyloid fibrils. We found that, in the presence of polyols (acting as osmolytes) and polyethylene glycols (crowders), the monomeric β-hairpin conformation was stabilized with respect to the unfolded state. Stabilization free energy was linear with solute concentration, and grew with crowder molecular volume as would also be predicted by molecular crowding models. Once aggregation was initiated and followed by ThT fluorescence, transmission electron microscopy, and CD spectroscopy, the polyols glycerol and sorbitol increased the lag time for fibril formation and elevated the amount of aggregated peptide at equilibrium, in a cosolute size and concentration dependent manner. However, fibrillation rates remained almost unaffected by a wide range of molecular weights of soluble polyethylene glycols. This difference in effect between the two cosolute groups cannot be accounted for by the purely entropic excluded volume interactions that are responsible for crowding. We therefore suggest that other forces, enthalpic by nature, may contribute to the cosolute effects acting on amyloid formation.

1100-Pos Board B10
Transmembrane β-Barrel Topology Model for Alzheimer's β-Amyloid (Aβ) Ion Channels
Hyunbum Jang, Fernando Teran Arce, Srinivasan Ramachandran, Ricardo Capone, Ratnesh Lal, Ruth Nussinov.
We modeled Alzheimer's amyloidβ (Aβ) ion channel in a β-barrel-like organization embedded in a lipid bilayer using explicit molecular dynamics (MD) simulations. The β-barrel motif is common in transmembrane toxin pores, typically consisting of a monomeric chain that forms a circular β-sheet with antiparallel β-strands stabilized by the connecting loops. In our simulations, Aβ barrels consist of multimeric chains forming two β-sheets arranged by parallel β-strands, where the strands of each monomer are connected by a turn. Our conceptual designs of Aβ barrels employ the U-shaped *β-strand-turn-β-strand* peptides using currently available NMR-based coordinates for $Aβ_{17-42}$ (known as p3) and $Aβ_{9-42}$ (called N9) peptides. Recently, it has been demonstrated that the N-terminal truncated Aβ peptides are capable of forming ion-permeable channels and their morphologies are consistent with atomic force microscopy (AFM) images of full-length $Aβ_{1-42}$ channels. Since no experimental coordinates for the membrane embedded structure of full-length $Aβ_{1-42}$ are currently available, we generated two U-shaped $Aβ_{1-42}$ peptides from both p3 and N9 peptides through an extension of their N-termini by adapting the NMR-based coordinates of solution structure of $Aβ_{1-16}$. In good agreement with AFM images and previous modeling, all Aβ barrels, including p3, N9, and $Aβ_{1-42}$ barrels break into heterogeneous, loosely-associated mobile β-sheet subunits, verifying that membranes do not support intact β-sheet conformations. The subunits appear mobile and allow unregulated, hence toxic, ion flux. In the Aβ channels, the presence of β-barrel-like conformation and the formation of ion-permeable barrels with hybrid monomer conformation suggest that Aβ barrel is a populated polymorphic variant of Aβ channels.
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1101-Pos Board B11
Amyloid Nucleation: Evidence for Nucleating Cores within Unstructured Protein Aggregates
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Despite significant progress investigating the self-assembly of amyloid-forming materials, our understanding of the fundamental mechanisms and structural pathways involved in this phenomenon remains limited. Detailed