SESSION 1D

FRONTIERS IN PEPTIDE AND PROTEIN SCIENCE

Session Moderator: Rachel Klevit, Biochemistry
MGH 228
12:30 PM to 2:15 PM

* Note: Titles in order of presentation.

Inhibition of a D*e Novo* Synthetic Amyloidogenic Peptide's Aggregation by Naturally Occuring Amyloids
Charles Haoyi Lin, Senior, Biology (Molecular, Cellular & Developmental), Biochemistry
UW Honors Program
Mentor: Valerie Daggett, Bioengineering

Amyloid diseases are characterized by the aggregation and buildup of proteins in vital tissues and organs. Insoluble β-sheet amyloid fibrils were previously thought to be the major underlying cause of tissue degeneration and cell death. However, recent experimental evidence suggests that soluble oligomers, which form during protein aggregation and before polymerization into fibrils, are the principal cause of toxicity in mammalian cells. These toxic oligomeric protein assemblies are believed to share a common sequence-independent secondary protein backbone structure known as α-sheet. This project proposes the investigation of a synthetic peptide known as AP3 that is capable of forming toxic oligomers and β-sheet amyloid fibrils. This peptide was *de novo* designed with a completely randomized sequence which preserves the underlying chirality that produces α-sheet character leading to its exhibition of amyloidogenic properties under acidic conditions. Furthermore, AP3 aggregation was shown to be inhibited by three naturally occuring amyloid proteins implicated in their respective dieseases: Amyloid Beta (Alzheimer's), IAPP (Type II Diabetes), and Transthyretin (Cardiac Amyloidosis). Analysis using dot-blot assays, soluble oligomer binding assays (SOBA), and BLITz assays will provide additional insight into the behavioral, binding, and kinetic properties of AP3. Upon further evaluation, we aim to demonstrate the ability of AP3 to serve as a synthetic model for naturally occuring amyloids and provide a better understanding of amyloidogenesis as well as the interactions between amyloidogenic species. This research will prove useful in the creation of more effective amyloid inhibitors and treatments for amyloid diseases.

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Wrangler: Toward Improved Peptide Design
Jennifer Ann (Jenny) Ferina, Senior, Bioengineering
UW Honors Program
Mentor: Valerie Daggett, Bioengineering
Mentor: Matthew Childers, Bioengineering

While there is an abundance of computational tools for protein design, the vast majority of them focus on static structures. Data for the most probable rotamers of an amino acid are often obtained from mining its appearances across crystal structures, which do not take into account the native dynamics or conditions of a protein. Additionally, conformational secondary structure propensities are often derived from the frequency that an amino acid appears within a certain range of dihedral backbone angles in static structures. However, these data do not emulate realistic conditions, because proteins are dynamic and surrounded by solvent; thus, incorporation of dynamic data should improve the design process. Wrangler, our in-house software for peptide design, integrates dynamic data for both rotamers and secondary structure propensities. The data are obtained from molecular dynamics (MD) simulations in explicit water, taking into account interactions with surrounding solvent to better sample the most probable conformations. Several amyloid peptide aggregation inhibitors were designed using Wrangler's scoring metrics to validate the software. These inhibitors were shown via MD simulations to better retain secondary structure than our current standards. Future work involves synthesizing the peptides in the wet lab to determine whether they experimentally perform better than our current inhibitors.

POSTER SESSION 4

MGH 241, Easel 135

4:00 PM to 6:00 PM

Molecular Dynamics Simulations of the Membrane-Bound Digylocysolated Human Prion Protein and Bovine Oligomer Reveal Insights into Infectious Prion Propagation

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UW Honors Program
Mentor: Valerie Daggett, Bioengineering
Mentor: Matthew Childers, Bioengineering

Prion diseases occur from the misfolding of the Prion Protein cellular form (PrP^C) under low pH conditions to the infectious scrapie species (PrP^Sc), which can aggregate further into insoluble fibrils. Previous studies have demonstrated that along with other amyloid oligomers, the prion scrapie oligomers cause neurotoxicity by disrupting the membrane, increasing its permeability and affecting calcium ion influx; however, the molecular mechanism for this effect is unknown. Molecular Dynamics simulations were performed to gain insight into the molecular mechanism of PrP^Sc-induced misfolding of PrP^C and oligomer toxicity in a membrane environment. The system was composed of the hexameric bovine PrP^Sc spiral model oligomer and the di-glycosylated human PrP^C attached to a POPC membrane via a glycophosphatidylinositol (GPI) anchor. Prior unpublished membrane simulations of this system have suggested that PrP^Sc induced PrP^C conformational changes as well as significant membrane disruption from oligomer-binding. Here we confirm and build upon these earlier studies demonstrating the reproducibility and robustness of oligomer binding affinity by varying the proximity of the oligomer to the membrane, providing key insight into infectious scrapie propagation and PrP^Sc cellular toxicity.

POSTER SESSION 4

MGH 241, Easel 134

4:00 PM to 6:00 PM

Investigating the Early Unfolding Pathways of the SH3 Protein Domain

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UW Honors Program
Mentor: Valerie Daggett, Bioengineering
Mentor: Matthew Childers, Bioengineering

For many globular proteins, the sequence and native structure are known. However, less is understood about how a string of amino acids folds into a functional protein. Experimental study of folding presents challenges due to the transience and variability of folding/unfolding transition states and intermediates. Alternatively, computational study of unfolding can provide significant insight into folding. Here, molecular dynamics simulations have been used to study the unfolding pathways of the SH3 domain structural family and to investigate the factors that determine the path and outcome. To separate folding determinants from amino acid sequence, 17 SH3 proteins were chosen with an average sequence identity of only 27%. Six unfolding simulations were performed for each protein, and the unfolding transition state ensemble was identified by locating the large, rapid conformational changes that signal the start of unfolding. Contact analysis was used to characterize the structure of the transition states ensembles. Two general pathways at the transition state were identified, distinguished based on the specific β-sheet structure lost at the transition state. In the first, more populated pathway contacts in the β-sheet containing the N- and C- terminal β-strands were lost while the second pathway was defined by structure loss in the other β-sheet. Though many of the investigated proteins went through both pathways in different simulations, most showed a clear bias towards one pathway. This work demonstrates that similar protein structures can fold through different pathways. The bias of many SH3 proteins towards one folding pathway also suggests the presence of some elements of primary structure that direct folding. Further investigation of the SH3 domain may yield 'rules' that determine the structure and folding pathway of the domain, and these rules may inform the study of other, similar proteins.