the issue unresolved. Here, we show by a variety of biophysical approaches, including isotope-edited FTIR spectroscopy, that pE-Abeta not only has a higher alpha-helix and lower beta-sheet propensity itself but also reverses beta-sheet formation and hence fibrillogenesis of the unmodified Abeta peptide via a prion-like mechanism.These data provide a structural mechanism for pE-Abeta hypertoxicity; pE-Abeta undergoes faster nucleation due to its increased hydrophobicity, thus promoting formation of hypertoxic oligomers of partial alpha-helical structure.

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Collagen Single Fibril Elastic Modulus Measurement Technique

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We develop an experimental technique that allows precise measurement of the longitudinal component of the elastic modulus of single fibril in conditions close to in vivo. Using freshly extracted fibrils, avoiding a drying-soaking cycle and keeping deformations below 0.5%, we use a combination of optical tweezers and AFM techniques, and exploit Euler-Bernoulli elasticity theory for data analysis. We found that elastic modulus of rat tail collagen type I cannot be represented by a single quantity but rather is a distribution, significantly broader than the uncertainty of our experimental technique. Additionally, we used AFM to find variations in the fibril diameter. Since bending forces depend on the diameter to the fourth power, this variation is important for estimating the modulus. However, there still exist sources of variation that are not yet accounted for.

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Evolutionary Excursions in Quaternary Structure Space

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The assembly of individual polypeptide chains into protein complexes with diverse quaternary structures is fundamental to nearly all biological processes. Recent work has demonstrated the importance of the assembly process by showing that most complexes assemble via ordered pathways that have a strong tendency to be evolutionarily conserved (1,2). By considering protein complexes in terms of algorithmic self-assembling building blocks, we show that we can organise the vast majority of quaternary structure topologies into a simple ''Periodic Table of Protein Complexes'' that delineates possible quaternary structure space. Through analysis of the possible evolutionary transitions between quaternary structures, we can explain the relative frequencies of observed topologies and predict those which are likely to be observed in the future. Finally, we find that different evolutionary lineages have explored quaternary structure space in strikingly different ways. In particular, eukaryotes have exploited the increased flexibility of their proteomes to facilitate the assembly of complexes with more unique subunits. On the other hand, prokaryotes, with their smaller genomes, have practised coding economy by: 1) evolving protein complexes with more homomeric repeats and 2) utilising uneven subunit stoichiometries to facilitate the assembly of more diverse topologies with fewer unique components.

1. Levy ED, Erba EB, Robinson CV, Teichmann SA (2008) Assembly reflects evolution of protein complexes. Nature 453:1262-1265.
2. Marsh JA et al. (2013) Protein complexes are under evolutionary selection to assemble via ordered pathways. Cell 153:461-470.

3471-Pos Board B199

Defining Protein Complexes that Mediate Bacterial Chemotaxis by Pulsed Dipolar ESR Spectroscopy

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Bacterial chemotaxis is the process whereby cells modulate their flagella-driven motility in response to environmental cues. This widespread behavior relies upon a complex sensory apparatus composed of transmembrane receptors, histidine kinases and coupling proteins to achieve great sensitivity, gain and dynamic range in signal processing. We have applied pulsed-dipolar ESR spectroscopy (PDS) combined with site-directed spin labeling to probe the structures and mechanisms of proteins that compose these regulatory circuits. Inherent symmetries within the protein complexes require interpretation of signals from systems that contain more than two spins. Tikhonov regularization and maximum entropy refinement when combined with model simulation reproduce accurate inter-spin distance distributions from such multiply labeled species. Disulfide crosslinking and disruptive mutagenesis verify component interfaces predicted by PDS. Weak but specific interactions that produce low population aggregates relevant to complex assembly are detected by an approach that relies on magnetic dilution and baseline analysis of dipolar spectra. The resulting PDS-based models capture key architectural features of the receptor kinase arrays and the flagellar motor. Moreover, distance distributions derived from the multi- spin sites reveal changes in conformation and dynamics that accompany kinase activation and motor switching. Application to the chemotaxis system demonstrates how PDS effectively reports on key structural features of transient protein complexes and in doing so fills the resolution gap between other well-established biophysical techniques such as electron microscopy and x-ray crystallography.

3472-Pos Board B200

Interaction of Beta-Sheets to Form Aggregates and Fibrils. Theoretical and Experimental Spectroscopic Studies of Peptide Ir and Vcd Spectra

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Many peptides form aggregates and some develop fibrillar morphologies. Vibrational spectroscopic methods have been used to establish β-sheet structures underlying many of these and isotope labeling has been used to indicate parallel vs. antiparallel forms. We have developed a DFT-based calculational model of β-sheet vibrational spectra based on Ala-oligopeptides, that initially focused on IR, VCD, and Raman spectra for isolated ideal sheet structures, and have since explored its variation with structure, alignment of strands, isotope labeling, twisting of single sheets and stacking and relative rotation of multiple sheets. We have computationally simulated spectra reported in the literature for several peptides forming fibrillar structures based on our static stacked β-sheet models. With isotopic labeling we can identify the nature of the sheet formed, parallel or antiparallel, and in many cases can determine the registry between sheets. In particular, for model peptides we have prepared, our analyses of the spectra of Glu_{10} based peptides that form both regular, β1, and bifurcated H-bond , β2 sheets are analyzed in this way to show both are antiparallel in nature but the β2 is out of register by one residue, most likely in a step-wise pattern, while the β1 structure is different, but less well organized. We have extended these calculations by computing IR and VCD for structures obtained as snapshots along MD trajectories that show contributions of sidechains and other modes in qualitative agreement with experiment.

3473-Pos Board B201

Destabilizing Amyloid Fibrils by Selective Sequence Mutations Enabled by Computational Assembly of Polymorphic Structures

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The aggregation of amyloid proteins into fibrils is associated with many neurodegenerative diseases such as Alzheimer's and Type II Diabetes. Extensive research has been spent in exploring different methods to impede and inhibit amyloid aggregation. Most attempts in the literature describe methods that involve applying stress to the environment around amyloids. Varying pH levels, modifying temperature, applying pressure through protein crowding and ligand docking are classical examples of these methods. However, environmental stress usually affects molecular pathways and protein functions in the cell and is challenging to construct in vivo. In this paper, we explore a new method to destabilize amyloid proteins through mutating their amino acid sequences without stressing their environment. We've developed FibrilMutant, a software aimed at exploring sequence mutations that destabilize amyloid fibrils. It analyzes key regions of amyloid proteins and studies the effect of amino acid point mutations on fibril nucleation and aggregation. The tool identified six main regions in amyloid proteins that contribute to structural stability and generated amino acid mutations to destabilize those regions. Full length fibrils were then built from the mutated amyloid monomers and a dipolar solvent model capturing the effect of dipole-dipole interactions between water and very large molecular systems to assess their aqueous stability was used to generate energy plots. Our results validate experimental mutation data for destabilizing Amylin fibrils and reveal novel point mutations that further weaken amylin amyloid nucleation and aggregation without disrupting the native structure.

Intrinsically Disordered Proteins III

3474-Pos Board B202

Multiple Recognition Motifs Provide Rigidity to Stabilize LC8 Complexes

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Hub proteins have a large number of interacting partners and are of special importance in organizing protein-protein networks. LC8, a 10 kDa dimeric