Protein Structure

332-Pos Board B211

Protein Structure Initiative-Materials Repository (PSI-MR): An Open Shared Public Resource for Structural Genomic Plasmids

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The Protein Structure Initiative Materials Repository (PSI-MR; http://www.hip.harvard.edu/PSIMR) was established in 2006 at the Harvard Institute of Proteomics (HIP) with the mission of providing centralized storage and distribution of information and samples for the 100,000 protein expression plasmids created by PSI researchers. These plasmids are an invaluable resource that allows the research community to dissect the biological function of proteins whose structures have been identified by the PSI. Researchers can search for and request clones in the PSI collection through the Plasmid Information Database (PlasmID: http://plasmid.med.harvard.edu/PLASMID). PSI plasmids are linked to the PSI Structural Genomic Knowledgebase (PSI KB) which facilitates cross-referencing of a particular plasmid to protein annotations and experimental data. Thus far over 25,000 PSI plasmids are in process at the MR, and nearly 9,000 are already available from PlasmID. In addition to distributing materials, the MR has sought to simplify the MTA process in order to decrease the time it takes for institutions to deposit or receive plasmids. To achieve this goal, the MR pioneered two documents, the depositor's agreement, which sets forth the terms enabling the MR to distribute deposited plasmids from outside institutions, and the expedited process MTA, which eliminates the need for researchers to wait for their institutions to sign an MTA. In the future, the MR will maintain a similar scope and mission of continuing to make PSI plasmids and data available to researchers and increasing the expedited MTA network so that researchers can receive PSI plasmids without delay.

333-Pos Board B212

From The Polymer Nature Of Proteins To The Evolution Of Protein Function

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We develop a new view on evolution of protein function which is based on the key role of a polymer nature of protein polypeptide chains in determining structure and evolution of proteins. Polypeptide backbone flexibility establishes a restriction on the size and shape of basic structural units of proteins. These elements, closed loops, are formed by the returns of the protein backbone and have a characteristic size of 25-35 amino acid residues. The closed loops also possess elementary functions, which they bring together in the protein globule forming a functional site. An elementary function is defined by one or few residues involved into function, and it is encoded in the sequence of the loop by the specific signature. Biological function of the globule is built as a combination of few elementary functions which provide necessary sequence of chemical reactions occurring in the functional site. Our model delineates connections between different protein structures based on partitioning them into elementary functional loops (closed loops with a functional signature). The computational procedure for deriving sequence/structure prototypes of elementary functional loop seeks for the primordial prototypes of contemporary elementary functional loops. By considering prototypes of elementary functional loops and their presence in various protein folds, we create a graph of evolutionary connection between different protein functions. We demonstrate, for the first time, that it is possible to reconstruct how biological functions of contemporary proteins emerged as a combination of elementary nes. We explore an evolution protein function and show how current diversity of proteins evolved by utilizing elementary functional loops. We plan to use our model in theoretical predictions of outcomes from the directed evolution experiments and in the de novo design of protein folds with desirable biological function.

334-Pos Board B213

Predictions of Protein Circular Dichroism Calculated by the Dipole Interaction Model and Compared to Synchrotron Radiation Circular Dichroism Experiments

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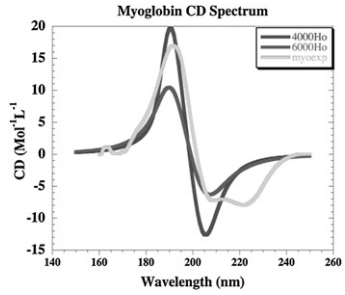
The determination of accurate secondary, tertiary and quaternary structures of macromolecules is vital for the study of intra- and interbimolecular interactions important for drug discovery, probing enzyme mechanisms and other functional protein complexes. Despite the recent advances in protein structural determination methods like X-ray crystallography, there is still a need to evaluate the accuracy of the model structures used in macromolecular interaction prediction. This is especially important where accurate three dimensional structures of the proteins are absent. Synchrotron radiation circular dichroism (SRCD) is an emerging technique sensitive not only to secondary structure but also teriary and quatertary structure. Theoretical calculations of circular dichroism (CD) using the dipole interaction model have successfully predicted CD for a variety of peptides and monomeric proteins. Herein, the dipole interaction model predicts CD for proteins in monomeric, dimmeric or tetrameric forms and is compared to experimental SRCD spectra. This is an attempt to evaluate the homology models. Preliminary results show comparable CD spectra between the dipole interaction model predictions and SRCD data for small proteins like myoglobin.



335-Pos Board B214

New Spin Label Designed for Double Electron-Electron Resonance Distance Measurements in the Liquid Nitrogen Temperature Range

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Double electron-electron resonance (DEER) measurements of interspin distances in biomolecules are restricted by the spin echo dephasing rates of the paramagnetic centers. Faster dephasing rates limit the longest distance that can be measured and the precision with which the distribution of distances can be measured. Because of the temperature dependence of dephasing rates for currently-used spin labels, the optimum temperature for DEER measurements is 50 to 60 K, which requires the use of liquid helium as the cryogen. A new spin label has been synthesized and characterized, with a structure that is analogous to the commonly-used synthetic peptide TOAC, except that the gem-dimethyl groups are replaced by spirocyclohexyl groups. Because of the absence of methyl groups, the spin echo dephasing rates for this new spin label in 1:1 water glycerol remains approximately independent of temperature up to about 130 K. The spin lattice relaxation rates for the new probe are sufficiently faster at 130 K to compensate for the changes in Boltzmann populations, so the signal-to-noise, longest distance that can be measured, and accuracy of determination of distance distributions in DEER experiments with this probe will be as favorable at 130 K as for currently-used probes at 50 to 60 K. These results indicate that it will be possible to perform DEER experiments with the substantially less expensive liquid nitrogen. Supported by NIH NIBIB EB002807(Denver), NSF CHE-0718117 (Nebraska), NSF/DOE under Grant No. CHE-0087817 and DOE under Contract No. W-31-109-Eng-38 (Indiana).

336-Pos Board B215

Ensemble Dynamics with Orientational NMR Restraints in Solution and Membrane Environments

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We have recently developed various restraint potentials for residual dipolar coupling in solution NMR [1] as well as dipolar coupling and chemical shift in solid-state NMR [2]. In principle, NMR observables are time- and ensemble-averaged, thus the structure determination needs to be based on the average property of an ensemble rather than the collection of multiple independent structure determination. In this work, we have further formulated and implemented the ensemble-average orientational restraint potentials, such as residual dipolar coupling (RDC), dipolar coupling, and peptide plane chemical shift, to explore the flexible nature of proteins embedded in such experimental observables. We will present the numerical accuracy of our implementation as a function of number of replicas during ensemble dynamics and illustrate the efficacy of ensemble dynamics in exploring protein structure and dynamics in solution and membrane environments.

337-Pos Board B216

Molecular Dynamics Simulations Of Escherichia coli Acyl Carrier Protein Containing Fatty Acyl Derivatives

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Acyl carrier protein (ACP) in bacteria and plants is an essential co-factor protein in fatty acid biosynthesis that shuttles covalently bound fatty acyl