the molecular behavior during the trajectory is a substantial challenge that has received relatively little attention. Here, we introduce the sigma-r plot, a plot of the standard deviation of intermolecular distances as a function of that distance. This representation of global dynamics contains within a single, one-dimensional plot, the average range of motion between pairs of atoms within a macromolecule. Comparison of sigma-r plots calculated from 10 nsec trajectories of proteins representing the four major SCOP fold classes indicates significant diversity of dynamic behaviors which are recognizably different among the four classes. Differences in domain structure and molecular weight also produce recognizable features in sigma-r plots, reflective of differences in global dynamics. Plots generated from trajectories with progressively increasing simulation time reflect the increased sampling of the structural ensemble as a function of time. Single amino acid replacements can give rise to changes in global dynamics detectable through comparison of sigma-r plots. Dynamic behavior of substructures can be monitored by careful choice of interatomic vectors included in the calculation. Comparison between the sigma-r plots calculated from MD simulations and from wide angle x-ray solution scattering data is also feasible with the potential for providing direct experimental tests of the approximations required for coarse-grained MD simulations. These examples provide demonstrations of the utility of the sigma-r plot to provide a simple measure of the global dynamics of a macromolecule.

1897-Pos Board B34

Computational Modeling of the FcαRI Receptor Binding in the Fcα Domain of the Human Antibody IgA: Corse-Grained Molecular Dynamics (MD) Methods

Manori Jayasinghe[1], Monica T. Posgai[2], Sam Tonddast-Navaei[3], George M. Ibrahim[4], George Stan[3], Andrew B. Herr[5].
[1]Mathematics physics and computer science, University of Cincinnati Blue ash college, Blue Ash, OH, USA, [2]School of Medicine, University of Cincinnati, Cincinnati, OH, USA, [3]Department of Chemistry, University of Cincinnati, Cincinnati, OH, USA, [4]Department of Medical Sciences, University of Toronto, Toronto, Toronto, ON, Canada, [5]Department of Molecular Genetics, Biochemistry & Microbiology, University of Cincinnati college of Medicine, Cincinnati, OH, USA.

FcαRI receptor binding in the Fcα domain of the antibody IgA triggers immune effector responses such as phagocytosis, antibody-dependent cell-mediated cytotoxicity, respiratory burst and cytokine release in eukaryotic cells. Fcα is a dimer of heavy chains of the IgA antibody and each Fcα heavy chain which consisted of two immunoglobulin constant domains, C_H2 and C_H3, can bind one FcαRI molecule at the C_H2-C_H3 interface forming a 2:1 stoichiometry which is unique to the human IgA. Experimental evidences confirmed that FcαRI binding to the Fcα C_H2-C_H3 junction altered the kinetics of HAA lectin binding at the distant IgA1 hinge and distant Fab region.

Given the importance of residues near the C_H2-C_H3 junction for receptor binding that were predicted experimentally by binding energetic analysis, our focus in this computational research was to understand the conformational changes and the residue-pairs in long-range communication which co-ordinate the receptor binding dynamics of the Fcα dimer complex.

We computed the principal collective motions by using the corse-grained structure based molecular dynamics trajectories performed on the high resolution crystal structure of Fcα-FcαRI 2:1complex of PDB ID 1OW0 to understand the functional dynamics in Fcα. We used three distinct Fcα conformations namely free Fcα, Fcα-FcαRI 1:1 asymmetric and Fcα-FcαRI 2:1 symmetric complexes to comparatively study the functional dynamics induced upon receptor binding.

Our findings confirmed that FcαRI binding, either in asymmetric or symmetric complex with Fcα, propagated long-range conformational changes across the Fc domains, potentially also impacting the hinge and Fab regions.

Key words: IgA antibody, single-basin structure-based coarse grain MD simulation, principal component modes, long-range interaction, ligand-induced conformational changes

1898-Pos Board B35

Computer-Aided Drug Discovery Approach Finds Calcium Sensitizer of Cardiac Troponin

Steffen Lindert[1], Monica X. Li[2], Brian Sykes[2], J. Andrew McCammon[1].
[1]UCSD, La Jolla, CA, USA, [2]University of Alberta, Edmonton, AB, Canada.

Defects in the contractile machinery can lead to heart failure. Weakened contraction of the heart will lead to diminished blood supply of the organs in the human body. Thus, in the fight against heart failure, therapeutics that have the ability to increase the contractile power of the heart are urgently needed. One possible route of action to improve heart contractile power is increasing the calcium sensitivity of the thin filament. From a pharmaceutical standpoint, calcium sensitizers have the distinct advantage of not altering cardiomyocyte calcium levels and thus have lower potential for side effects. Small chemical molecules have been shown to bind to the interface between cTnC and the cTnI switch peptide and exhibit calcium sensitizing properties, possibly by stabilizing cTnC in an open conformation. Building on existing structural data of a known calcium sensitizer bound to cardiac troponin, we devised a combined computational and experimental drug discovery approach. We used Molecular Dynamics to sample a range of troponin structure conformations and accounted for receptor flexibility by running virtual screens into several conformational states. The most promising compounds were then tested using solution NMR titration assays. We were able to identify a novel calcium sensitizer 4-(4-(2,5-dimethylphenyl)-1-piperazinyl)-3-pyridinamine (NCI147866) which binds to cTnC and the cTnC-$cTnI_{147\text{-}163}$ complex. Its presence increased the affinity of switch peptide to cTnC by approximately a factor of two. This action was comparable to that of known levosimendan analogues and served as an excellent starting point for targeted compound improvement aimed at higher affinity and calcium sensitization.

1899-Pos Board B36

A Coarse-Grained Langevin Equation for Protein Dynamics: Global Anisotropy and a Mode Approach to Local Complexity

Jeremy T. Copperman, Marina G. Guenza.
Physics, University of Oregon, Eugene, OR, USA.

We utilize a multi-scale approach where molecular dynamic simulations are performed to obtain quantitative structural averages used as input to a coarse-grained Langevin Equation for Protein Dynamics, which can be solved analytically. The approach describes proteins as fundamentally semiflexible objects collapsed into the free energy well representing the folded state. The normal mode analytical solution to this Langevin equation naturally separates into global modes describing the fully anisotropic tumbling of the macromolecule as a whole, and internal modes which describe local fluctuations about the folded structure. Complexity in the configurational free energy landscape around the folded state of the macromolecule leads to a renormalization of the internal modes, while the global modes provide a basis set in which the dipolar orientation and global anisotropy can be accounted for when comparing to experiments. Fundamental to this approach is the inclusion of internal dissipation which is absent in any rigid-body hydrodynamical modeling scheme. This simple approach predicts the dynamics of both global rotational diffusion and internal motion from the picosecond to the nanosecond regime, and is quantitative when compared to time correlation functions calculated from molecular dynamic simulations and in good agreement with Nuclear Magnetic Resonance relaxation experiments. Results for several well-characterized globular proteins are presented, suggesting our method describes the relevant dynamics around the global minimum well. Use of non-equilibrium simulation techniques such as metadynamics to sample the full free-energy landscape of the protein, and extension of the theoretical treatment to describe the dynamics into the biologically interesting microsecond to millisecond regime, will be discussed.

1900-Pos Board B37

Looking at Estrogen Receptor from Small Angles

Sichun Yang, Wei Huang, Krishna M. Ravikumar.
Center for Proteomics and Department of Pharmacology, Case Western Reserve University, Cleveland, OH, USA.

The estrogen receptor (ERα) functions as a hormone-activated transcription factor. The protein is multidomain and highly flexible. To date, however, it remains unclear how various domains interact with one another within the functional ER homodimer. Here, we show via a computational-experimental study that binding of ligand and DNA can allosterically act on the ER's domain-domain organizations and interactions. First, a set of putative conformations are identified from enabling simulations that search exhaustively all possible domain-domain interactions. Second, multiple major conformations are identified on the basis of experimental synchrotron-based measurements using SAXS and footprinting data that are best-interpreted by computational results from simulations. Finally, data from chemical cross-linking are used to verify the identified ER conformations in solution. This tight integration of multi-technique measurements provides unique insight into the function of ER that dynamically changes its conformations in response to ligand and DNA binding, both of which play critical roles in the development and progression of breast cancer.

1901-Pos Board B38

Study of Proton Transfer in Escherichia Coli Photolyase

Meng Zhang[1], Zheyun Liu[2], Jiang Li[3], Lijuan Wang[3], Dongping Zhong[3].
[1]Biophysics, The Ohio State University, Columbus, OH, USA, [2]Chemistry and Biochemistry, The Ohio State University, Columbus, OH, USA, [3]Physics, The Ohio State University, Columbus, OH, USA.

Photolyase is a flavoenzyme which utilizes blue-light energy to repair UV-light damaged DNA. The catalytic cofactor of photolyase, flavin adenine