1263-Pos Board B33
Membrane Bound Organization of Blood Coagulation Factor VIII Forms
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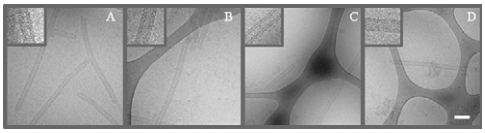
Blood hemostasis is a delicate balance between plasma proteins (coagulation factors) forming active membrane-bound complexes. Understanding their assembly is fundamental for the cure of blood disorders, such as hemophilia and thrombosis. To this goal we design suitable lipid nano-platforms supporting coagulation complexes and allowing extensive structure-functional studies required for successful nano-drug design. We aim to study the membrane-bound organization of Factor VIII (FVIII) forms, as organized onto lipid nanotubes (LNT) by combining Cryo-electron microscopy (Cryo-EM) with biophysical methods. Here we present our preliminary Cryo-EM results of the membrane-bound organization of two recombinant FVIII forms: human full length (hrFVIII-FL) and porcine - B domain deleted (prFVIII-BDD) at different lipid composition.
Cryo-electron micrographs of **A, B.** hrFVIII-FL and **C, D.** prFVIII-BDD organized onto LNT at low and high phsophatedylcholine (PS) concentration, respectively. Scale bar 100 nm. *This work is supported by an American Heart Association: Grant, 10SDG3500034.



1264-Pos Board B34
Estimation of Residue-Residue Coevolution using Direct Coupling Analysis Identifies Many Native Contacts Across a Large Number of Domain Families
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[1]Univ. Cal. San Diego, La Jolla, CA, USA, [2]Human Genetics Foundation, Torino, Italy, [3]Institute for Scientific Interchange, Torino, Italy, [4]Harvard Medical School, Boston, MA, USA, [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [6]Politecnico di Torino, Torino, Italy, [7]Rice University, Houston, TX, USA, [8]Université Pierre et Marie Curie, Paris, France.
It has long been suggested that correlations among amino acid compositions at different sequence positions can be exploited to infer spatial contacts within the three dimensional structures of proteins. Here we develop a computationally efficient implementation of Direct Coupling Analysis, termed mean field DCA (mfDCA), which has the ability to disentangle direct and indirect correlations and allows us to evaluate the accuracy of contact estimation for a large number of protein domains, based purely on sequence information. mfDCA produces a large number of correctly predicted contacts, reconstructing the global structure of contact maps for many of the protein domains examined. In addition to this, our results capture clear signals beyond intra-domain residue contacts, for instance, alternative protein conformations, ligand-mediated residue couplings, and inter-domain interactions in protein multimers. Our findings suggest that inferred contacts by mfDCA can be utilized as a reliable guide in computational estimates of alternative protein conformations, protein complex formation, and even de novo domain structure prediction. This can be accomplished provided the existence of a large number of homologous sequences which are becoming available in large quantities due to recent advances in next generation genome sequencing.

1265-Pos Board B35
Structure Prediction of a Cellulose Synthase Protein and the Effect of Mutations
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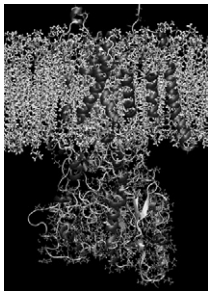
Cellulose synthases (CesAs) are the proteins responsible for the polymerization of cellulose from glucose. They are integral membrane proteins that contain multiple transmembrane helices and a cytoplasmic catalytic domain. Due to the fact that CesAs are found on the membrane and that it is difficult to crystallize such proteins, the structure of CesAs has not been determined and the exact enzymatic mechanism is unknown. We used a combination of protein structure prediction servers and molecular dynamics simulations to predict catalytic domain of cotton CesA. The globular catalytic region from this gene revealed to contain a stretch of beta sheets flanked by a UDP-glucose binding site. The predicted structure explains well the effect of point mutations that generally characterized by dwarfism, reduction in cellulose crystallinity, and reduced root elongation. Moreover, we predicted the overall position of CesA towards the membrane that may be linked to the extrusion of the cellulose from the catalytic region to the exterior of the cell. Supported as a part of the Center of Lignocellulose Structure and Formation under DOE Award DE-SC0001090.



1266-Pos Board B36
Where do Proteins Fit in the Structural Classification of Condensed Matter?
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In this work, we use Bond Orientational Order Parameters(BOOP)[1] as the universal descriptors of local packing in proteins. To classify proteins as a distinct family, this local view is combined with a global one which is portrayed by translational order parameters and the free volume distribution. We find that the organization of first coordination shells carries strong signatures of close packed crystalline order in BOOP space. We also show that proteins exhibit no icosahedral bond orientational order at the heavy-atom level and at coarse grained level where residue packing is considered. Close packedness is characterized by the space filling ratio of 0.74048 and is achieved through stacking of hexagonal arrays. Depending on stacking order, this creates Face Centered Cubic(FCC) and Hexagonal Close Packed(HCP) crystals as well as an infinite variety of FCC-HCP mixtures. Using radial distribution formalism, we show that protein-crystal correspondence is strictly local and it extends up-to second nearest neighbors. Due to local correspondence, arbitrarily stacked systems capture protein properties as accurate as ideal crystals.
In passing from bulk crystals to proteins we propose a robust route which randomly distributes free volume pockets in a close packed lattice. Remarkably, our results suggests that such protein-like structures automatically possess an exponential size distribution of free volume. This is in accordance with Cohen-Turnbull theory of dense liquids and glasses[2]. We conclude that proteins constitute a unique glassy phase with no icosahedral order.
1. Steinhardt, P.J., D.R. Nelson, and M. Ronchetti, *Bond-orientational order in liquids and glasses.* Physical Review B, 1983. **28**(2): p. 784.
2. Cohen, M.H. and D. Turnbull, *Molecular Transport in Liquids and Glasses*. Vol. 31. 1959: AIP. 1164-1169.

1267-Pos Board B37
Analysis of Conformational Dynamics Associated with TNFR1 Signaling by Live-Cell FRET and Computational Modeling
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Tumor necrosis factor receptor 1 (TNFR1) is the prototypical member of the TNFR superfamily which upon ligand binding, initiates a cell's inflammatory response. There are two available crystal structures of TNFR1. The first is of an un-liganded homo-dimer. The second, of TNFR1 in complex with its ligand lymphotoxin-α (LT-α), is a trimeric complex. Observations in cells show that upon binding ligand TNFR1 forms high molecular weight oligomeric clusters. These complexes have been imagined as a regular hexagonal lattice of the trimeric complexes that form through interactions at the dimer-interface. Our computational analysis comparing the two crystal structures reveals that ligand binding does not alter the homodimerization interaction motif or deform the receptor monomer. Thus, the conformational change associated with TNFR1 signaling across the membrane, and how it relates to the formation of clusters, has remained unknown. To address this issue, we have performed computational normal mode analysis of the TNFR1 dimer and found that the lowest frequency mode represents a previously undescribed opening motion that causes the cytosolic domains to separate upon ligand binding and network formation. Computational analysis then guided the identification of several point mutations expected to either stabilize or destabilize the predicted conformations. Accordingly, we have used live-cell FRET to test our predictions regarding the conformational changes in the receptor.