Paris, France, [7]Laboratoire de Physique Statistique de l'Ecole Normale Supérieure, Paris, France.
An hydrophobic mismatch between protein length and membrane thickness can lead to a modification of protein conformation, function, and oligomerization. To study the role of hydrophobic mismatch, we have studied the change in mobility of transmembrane peptides in model bilayers. The studied peptides possess an hydrophobic helix of various length $d\pi$, and the hydrophobic thickness, h, of the bilayers can be tuned at will. For each mismatch value, using Fluorescence Recovery After Pattern Photobleaching (FRAPP), we precisely measured the diffusion coefficient D of the embedded objects and gained access to their apparent size. This enables us to observe the orientation or oligomerization state of the peptides versus their concentration, and discover that the effects of positive and negative mismatches on diffusion are highly asymmetric. For bilayers thinner than $d\pi$, the diffusion coefficient decreases and the derived characteristic sizes are larger than the peptide radii. As suggested by previous studies, the peptides should accommodate by tilting, and this scenario was confirmed by ATR-FTIR spectroscopy. As the membrane thickness increases, the value of the diffusion coefficient increases: the peptides raise (i.e. their tilt is reduced) and reach an upright position and a maximal mobility for $h \approx d\pi$. Using accessibility measurements, we show that when the membrane becomes too thick, the peptide polar heads sink into the interfacial region. Surprisingly, this "pinching" behavior does not hinder the lateral diffusion of the transmembrane peptides. But it creates interactions between the embedded peptides, and collective behaviors emerge. For low peptide concentration, the transmembrane anchorage of the peptide is broken as the bilayer is swollen. For intermediate concentrations, we observed the arrangement of small monodisperse clusters, while polydisperse macro-domains are formed at higher peptide density, leading to spontaneous and reversible formation of "vesicles".

1170-Plat
The Gating Mechanism of Yeast Aquaporin Studied by Molecular Dynamics Simulations
Gerhard Fischer[1], Urszula Kosinska-Eriksson[1],
Camilo Aponte-Santamaria[2], Madelene Palmgren[3], Cecilia Geijer[3], Kristina Hedfalk[1], Stefan Hohmann[3], Bert L. de Groot[2], Richard Neutze[1], Karin Lindkvist-Petersson[3].
[1]Department of Chemistry, Biochemistry and Biophysics, University of Gothenburg, Gothenburg, Sweden, [2]Computational Biomolecular Dynamics Group, Max Planck Institute for Biophysical Chemistry, Goettingen, Germany, [3]Department of Cell and Molecular Biology, University of Gothenburg, Gothenburg, Sweden.
Aquaporins are membrane proteins responsible for the permeation of water and other solutes through the cell membrane. They arrange in a tetrameric conformation, where each monomer acts as a highly efficient single-file water channel. The x-ray structure of the yeast aquaporin (Aqy1), recently found at a very high resolution (1.15 Angstrom), revealed the conformation of the extended N-terminus - an unusual feature within the family of aquaporins - occluding the water pore. In contrast, functional assays with spheroplast of P. pastoris showed a substantial increase in the water transport activity when Aqy1 was present compared to an assay where Aqy1 was deleted, indicating that Aqy1 is a gated water channel. Here we address the question of a putative gating mechanism of Aqy1 by using molecular dynamics simulations. Our findings suggest that Aqy1 may be regulated by both phosphorylation of a serine residue (Ser107) or membrane-mediated mechanical stress. Both possibilities lead to similar opening transitions after a local rearrangement of the residues Tyr31, Leu189, Ala190 and Val191, located in the gate of the pore. We observed that there is a principal collective motion causally involved in these gating transitions, and that is possible to attain reproducible opening events along this collective coordinate. The simulation results are therefore consistent with a mechanism in which both phosphorylation and mechanosensitive gating can trigger the channel opening. Aqy1 regulation may help yeast to survive rapid freezing and thawing, and sudden osmotic changes.

Platform Y: Protein Dynamics I

1171-Plat
Protein Similarity Derived Solely from Molecular Dynamics
Philip C. Biggin, Rune Lyngsø, Jotun Hein, Márton Münz.
Oxford University, Oxford, United Kingdom.
The dynamic motions of many proteins are central to their function. It therefore follows that the dynamic requirements of a protein are evolutionary constrained. In order to assess and quantify this, one needs to compare the dynamic motions of different proteins. Comparing the dynamics of distinct proteins may also provide insight into how protein motions are modified by variations in sequence and, consequently, by structure. The optimal way of comparing complex molecular motions is, however, far from trivial. The majority of comparative molecular dynamics studies performed to date relied upon prior sequence or structural alignment to define which residues were equivalent in 3-dimensional space. Here we discuss an alternative methodology for comparative molecular dynamics that does not require any prior alignment information. We show it is possible to align proteins based solely on their dynamics and that we can use these dynamics-based alignments to quantify the dynamic similarity of proteins. Our method was tested on 10 representative members of the PDZ domain family. As a result of creating pairwise dynamics-based alignments of PDZ domains, we have found evolutionarily conserved patterns in their backbone dynamics. We compare the results to other recently developed methods.

1172-Plat
Structure Fluctuations in Proteins and their Relationship to Amino Acid Propensities
Anatoly M. Ruvinsky[1], Ilya A. Vakser[2].
[1]Center for Bioinformatics, The University of Kansas, Lawrence, KS, USA, [2]Center for Bioinformatics and Department of Molecular Biosciences, The University of Kansas, Lawrence, KS, USA.
The spectrum and scale of fluctuations in protein structures affect the range of cell phenomena, including stability of protein structures or their fragments, allosteric transitions and energy transfer. The study presents a statistical-thermodynamic analysis of relationship between the sequence composition and the distribution of residue fluctuations in protein-protein complexes [1]. A one-node-per-residue elastic network model accounting for the nonhomogeneous protein mass distribution and the inter-atomic interactions through the renormalized inter-residue potential is developed. Two factors, a protein mass distribution and a residue environment, were found to determine the scale of residue fluctuations. Surface residues undergo larger fluctuations than core residues, showing agreement with experimental observations. Ranking residues over the normalized scale of fluctuations yields a distinct classification of amino acids into three groups: (i) highly fluctuating - Gly, Ala, Ser, Pro and Asp, (ii) moderately fluctuating - Thr, Asn, Gln, Lys, Glu, Arg, Val and Cys (iii) weakly fluctuating - Ile, Leu, Met, Phe, Tyr, Trp and His. The structural instability in proteins possibly relates to the high content of the highly fluctuating residues and a deficiency of the weakly fluctuating residues in irregular secondary structure elements (loops), chameleon sequences and disordered proteins. Strong correlation between residue fluctuations and the sequence composition of protein loops supports this hypothesis. Comparing fluctuations of binding site residues (interface residues) with other surface residues shows that, on average, the interface is more rigid than the rest of the protein surface and Gly, Ala, Ser, Cys, Leu and Trp have a propensity to form more stable docking patches on the interface. The findings have broad implications for understanding mechanisms of protein association and stability of protein structures.
1. A.M. Ruvinsky and I.A. Vakser. arXiv:0907.5021v1

1173-Plat
Direct Observation of Ligand Dynamics in Cytochrome *C* Using Time-Resolved FTIR Spectroscopy
Joerg Zimmermann, Megan C. Thielges, Floyd E. Romesberg.
The Scripps Research Institute, La Jolla, CA, USA.
Horse heart cytochrome *c* (cyt c) has emerged as a paradigm for the study of protein folding. The folding of reduced cyt *c* induced by photodissociation of CO from the CO-bound unfolded protein has been studied extensively. Following a nanosecond light pulse, four transitions have been resolved with time constants of approximately 1-5, 50-100, 200-500, and 1000-10,000 μs. While originally thought to be associated with CO rebinding to two different partially folded states of cyt *c*, the two slower process are now understood to reflect the bimolecular reassociation of CO followed by religation of the His18, which by the base elimination mechanism is induced to dissociate after CO photolysis. Thus, the two slower time constants turn out not to report on protein folding, but instead reflect the complexity of heme ligation. The two faster time constants have been attributed to ligation at the heme center by protein side chains. Here, to unambiguously determine the post-photodissociation steps involving CO, we monitored the CO vibration following photodissociation with step-scan FT IR spectroscopy. We find that like the slower timescale processes, the 50-100 μs timescale process is associated not with protein dynamics, but with CO ligand dynamics. The data clearly demonstrate that whatever the origins of the spectral changes, they clearly involve CO rebinding or changes in the environment of an already bound CO ligand. In addition to these fast dynamics, we also find multi-phasic CO rebinding on timescales of 1-100 s. The dependence of the associated amplitudes on denaturant concentration suggests that a unique species exists at intermediate denaturant concentrations, consistent with a folding-unfolding process of the protein driven by CO dissociation. This may