many globular proteins. For example, a simple mutation can produce marked effects at distal sites via undefined pathways for a conventionally non-allosteric protein. There are reconciling evidences on allostery mechanisms for the 'induced-fit' scheme and the 'population-shift' theory, where dynamics plays an essential role in allosteric regulations. We develop a dynamics criterion to determine possible allostery in general proteins: Given two distinctive conformational states, dynamical fluctuations and correlations, either amongst the distant functional motifs or different subunits, can be accounted for by the conformational transitions between them. If the dynamics correlations result in both correlated and anti-correlated modes of motions (Figure 1), allosteric cooperativity will occur simultaneously.

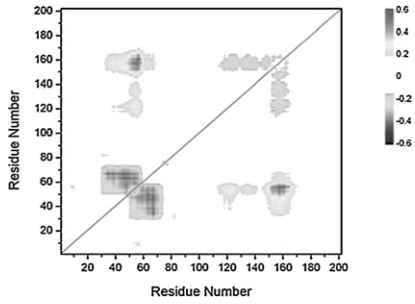

Figure 1. Difference matrix of dynamic correlations in protein - the *Aquifex* AdK case: red, a correlated motion; blue, an anti-correlated motion; and red (blue) regions correspond to same (opposite) direction distortions. The presence of both positive and negative correlations indicates the existence of an allosteric cooperativity during conformational changes, as was proved by NMR experiments.

2201-Pos Board B171
Dynamics of Intra- and Inter-Helix Contact Formation
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The ubiquitous nature of the helical fold and its characteristic physical properties make it one of the first candidates for studies of secondary structure formation in polypeptides, and the thermodynamics of helix formation is a common topic in many classical biophysics textbooks. However, though there is general agreement on the features of the equilibrium properties of the coil-to-helix transition, both experimental and theoretical studies have provided widely varying estimates of helix formation rates from tens of picoseconds to microseconds. We present results of recent molecular simulations of several helix-forming peptides that permit the quantitative study of both intra- and inter-helical contacts in polypeptides. This analysis of local, site-specific formation of intra- and inter-chain interactions is necessary for any quantitative modeling of the elementary steps of secondary and tertiary structure formation in protein folding, and it allows direct comparison to data from recent infrared vibrational spectroscopy studies.

2202-Pos Board B172
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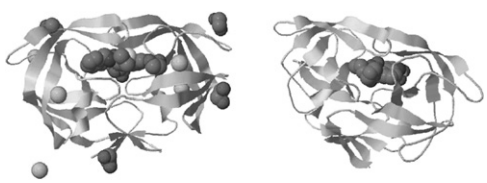
HIV-1 protease is a crucial protein during HIV infection. Protease inhibitors bind to a ''Pocket'' of this dimer and prevent its further activity, thus reducing the spread of HIV virus. However, HIV-1 protease has a high genetic variability, which generates diversity of the virus and often causes a serious problem of the emergence of drug-resistant mutants. In this research, instead of using a traditional measure of ''genetic distance'', the structural dynamic changes due to mutation is built to associated with the drug resistance of the HIV-1 protease. Traditional normal-mode analysis for biomolecules is the linear dynamic analysis near their equilibrium. However, the transition of protein state is usually highly nonlinear. Here we employ an amino acid specific GO model to investigate the nonlinear molecular dynamics changes due to the protease sequence mutations. The current results show that the mutations have obvious effects on the soft modes of the HIV protease. The reason for the drug-resistance can be clarified from our further analysis of the relationship between the soft modes change and the drug-resistance.



2203-Pos Board B173
Force Spectroscopy of the Iron Atom in Heme Proteins
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Nuclear resonance vibrational spectroscopy (NRVS) selectively reveals the complete vibrational density of states (VDOS) of a Mössbauer probe nucleus within a protein. Frequency moments of the VDOS determine effective force constants for ^{57}Fe at the active sites of cytochrome c (cyt *c*) and deoxymyoglobin (Mb). The *stiffness* measures the force needed to displace the Fe with the other atoms fixed, and probes the nearest neighbor interactions with the Fe. The stiffness of the low spin Fe environment in cyt *c* greatly exceeds that for the high spin Fe in Mb, reflecting the shorter Fe–N bonds to the heme. Moreover, a significant stiffness decrease upon oxidation of cyt *c* tracks the longer Fe–S bond to Met 80 in the oxidized protein. Quantitative comparison with ^{57}Fe/^{54}Fe frequency shifts suggests that Fe-L vibrations contribute to the Raman signal of cyt *c* recorded in resonance with the heme Soret band. The *resilience* measures the force needed to displace the Fe with the surrounding atoms free to respond, and determines the magnitude of the thermal fluctuations of the Fe on a time scale determined by the experimental energy resolution (ca. 4 ps for the results reported here). Quantitative agreement with the temperature-dependent mean squared displacement determined from independent Mössbauer measurements confirms longstanding assumptions that vibrational motion dominates thermal fluctuations of the heme Fe below the well-known dynamical transition at ca. 200 K and identifies THz frequencies below 100 cm^{-1} as the dominant contribution. The resilience increases significantly for cyt *c* with respect to Mb, which we attribute to the increased number of covalent links between heme and peptide in the former protein. Molecular dynamics simulations reproduce the increased resilience of cyt *c*, but find no significant change with oxidation state.

2204-Pos Board B174
Extracting Non-Gaussian Modes of Motion from the Principal Components of Gramicidin A
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We have performed principal component analysis (PCA) on the trans-membrane channel gramicidin A in a membrane environment using atomistic molecular dynamics simulations. A systematic examination of all the principal components reveals a clear power law structure across the entire eigenvalue spectrum, with distinct scaling regimes for both the heavy-atom backbone as well as the side chains. Deviations from the scaling trends reveal groups of components which have symmetric but non-Gaussian distributions over the trajectory, and these correspond to anomalous diffusion in the mean square deviation over six orders of magnitude in time. The largest PCs are super-diffusive while certain groups of short PCs are sub-diffusive. We quantify the directions of collective displacement for many of the long and short PCs, and propose an extension of PCA which yields a set of apparently functional modes where many atoms move together in a uniform direction. The dominant super-diffusive mode exhibits coherent motion of the (lipid-bound) hydrophobic turns at the junction of the monomers, moving out of phase with the outermost (surface-bound) hydrophilic turns and preserving the conductive connection along the water wire at the centre of the channel. In the second super-diffusive mode, the two innermost hydrophobic turns of each monomer move out of phase with each other at the monomer junction, possibly gating the channel. The sub-diffusive modes at shorter spatial scales are associated with hydrogen-bonded groups. Our results suggest that there is information relevant to the description of protein dynamics and statistical mechanics in the entire PCA spectrum, and not just the largest few PCs as conventionally analyzed.

2205-Pos Board B175
Modeling the Open-to-closed Transition of Adenylate Kinase: All-atom Molecular Dynamics Simulations and a Double-Well Network Model
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An intrinsic property of protein is the ability to undergo conformational changes upon ligand binding. In this work, we study Adenylate Kinase (AKE), an important enzyme controlling the balance of ATP in prokaryotic cells. X-ray crystallography indicates that AKE has two distinct conformations, open and closed, depending on whether it is bound with substrates (ATP and AMP). Conformation difference in AKE can be determined by the relative position of two separate domains, the lid domain and the NMP binding domain, to the core. In this work, all-atom molecular dynamics (MD) simulations and coarse-grained modeling are used to elucidate the effects of ligand binding on AKE conformation. Results based on four 100ns all-atom trajectories indicate that ATP binding induced the closing of lid domain and suggest that the relative population between closed to open structure is increased. The closing

of NMP binding domain, however, is found to be more specific and may require a timescale longer than 100ns to close. The mechanical property of a hinge region is found to correlate with lid closing; residues in this region may be mutated to alter the rate of conformational change and hence enzyme catalysis. This prediction agrees well with the results of recent single molecule experiments. Using a double-well network coarse-grained model, multiple pathways of open-to-closed transition can be found. Motions of lid-domain and NMP binding domain are not concerted and may be treated as two distinct events. This picture is different from the result of using elastic network model and agrees better with atomistic simulations. In addition to open-to-closed transition, solvation structures and intrinsic mechanical properties of AKE are also characterized to identify key residues that may control the conformational change of AKE from mechanical perspectives.

2206-Pos Board B176

Inferring Maps of Forces Inside Cell Membrane Microdomains

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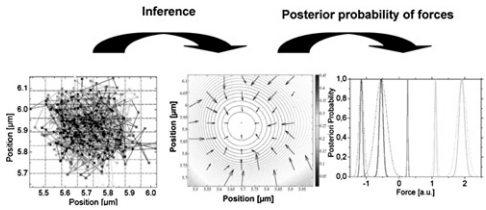
Mapping of the forces acting on biomolecules in cell membranes has spurred the development of effective labels, e.g. organic fluorophores and nanoparticles, to track trajectories of single biomolecules. Standard methods use particular statistical observables, namely the mean square displacement (MSD), to extract cues on the underlying dynamics. Yet, MSD is not an appropriate tool to access force fields and becomes easily a biased estimator in the presence of positioning noise. Here, we introduce **general inference methods** to fully exploit information hidden in the experimental trajectories, providing sharp estimates for the forces and the diffusion coefficients within membrane microdomains. Rapid and reliable convergence of the inference scheme is demonstrated on trajectories generated numerically with realistic parameters. The inference method is then applied to **infer forces and potentials** acting on the receptor of the ϵ-toxin labelled by lanthanide-ion nanoparticles. Results show a constant diffusivity inside a complex force field confining the receptor inside a specific domain, and may lead to new modelling of the membrane.
Our scheme is applicable to any labelled biomolecule and to other types of force fields, and results presented here show its general relevance to the issue of membrane compartmentation.



2207-Pos Board B177

Probe of flexibility and conformational heterogeneity in Zn-cytochrome c (Zn-cyt c) folding by Three-Pulse Photon Echo Peak Shift (3PEPS) Spectroscopy

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We investigated the dynamics and conformational heterogeneity of Zn-cyt c with 3PEPS, a type of femtosecond nonlinear spectroscopy that is used to quantify the spectrum of sub-nanosecond protein motions and the inhomogeneous broadening of the system. Wavelength-dependent measurements were performed on the Soret transitions of the folded state, the guanidine hydrochloride unfolded state (4.5 M), and the state at the midpoint (2.5 M) of the denaturant titration. The measurements resolve a substantial increase in the inhomogeneous broadening of the Soret band upon unfolding, as expected due to an increase in conformational diversity upon unfolding. Unexpectedly, the inhomogeneous broadening of the midpoint state is greater than that of the unfolded state. This observation is consistent with the Soret band spectrum, which first broadens, then attains a maximum width at the midpoint, and finally narrows, as the denaturant concentration is increased. A two-state folding model is used to quantitatively model the 3PEPS results. In this model, the homogeneous linewidth of the folded and unfolded states is identical, the piecosecond dynamics of the unfolded conformer are slightly slower, the inhomogeneous broadening of the unfolded state is 33% larger than that of the folded state, and the midpoint is a 1:1 mixture of the folded and unfolded states. Numerical results are consistent with the experimental data. Interestingly, biophysical techniques often resolve multimodal conformational distributions, whereas ultrafast spectroscopic measurements are not modeled with the functional forms of the inhomogeneous distribution function (IDF) obtained from these experiments. Our work is therefore significant because it represents the first instance in which a multimodal IDF, rather than the traditionally assumed Gaussian form, is quantitatively reconciled with a set of ultrafast spectroscopic measurements on protein conformers.

2208-Pos Board B178

Evaluation Of Three Transition Pathway Modeling Techniques In Capturing Structural Intermediates In F1 Atpase, Myosin, Kinesin, And Chaperonin Groel

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Computer modeling of conformational transitions aims to predict the order of structural events in a functioning molecular machine. Here we evaluate 3 transition pathway modeling techniques — mixed elastic network model (MENM)[1], Min-Action-Path[2] and adiabatic morphing[3]. We will assess their accuracy in capturing structural intermediates during the transitions in four ATPase-based molecular machines (F_1 ATPase, myosin, kinesin, and chaperonin GroEL), for which abundant structural data are available for validation. We will map transition pathways and experimental structures to a 2D plane spanned by two reaction coordinates that assess the progress of transition at the active site and the force-generating component, respectively. These techniques are found to perform differently in qualitatively capturing the order of structural events in agreement with the structural data (see Figure).

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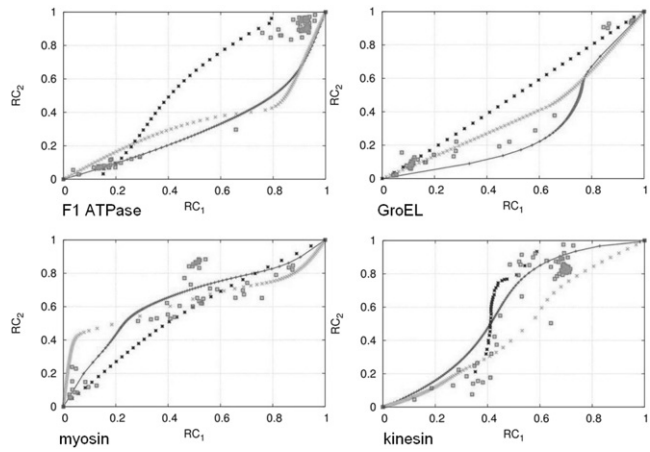

Figure. Transition pathways predicted by MENM (+), Min-Action-Path (×) and adiabatic morphing (*) compared with experimental structures (square).

2209-Pos Board B179

Self Assembly Of AOT Reverse Micelles With/without Peptides

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We are interested in understanding the dynamics and stability of proteins under confinement. To study the reverse micelle formation process and the peptide dynamics inside reverse micelle we performed molecular dynamics simulations for two AOT reverse micelle self-assembly systems, one without peptides and the other with two octa-peptides (AKAAAKA). The self-assembled systems are water-in-oil micro-emulsion systems, and each of them has a 200 ns long simulation time. The other three components of the systems are sodium ions, water and isooctane. The water to surfactant ratio for both of the systems is 6. Reverse micelles form in a quick, spontaneous way. The peptides get encapsulated during the self-assembly and are located at the inner face of the reverse micelle close to the AOT surfactants. The two peptides adopt different conformations, unfolded and alpha-helical, respectively. The peptides are encapsulated in separate reverse micelles. The encapsulated peptides have high coordination with AOT head groups and sodium ions. They experienced low hydration environment and showed much slower dynamics inside the reverse micelle. We find that the dynamics of peptides inside reverse micelle is very different from that in bulk water.

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