which is an extension of independent component analysis (ICA) techniques, is a more realistic encoding of protein fluctuations and atomic coupling since its basis vectors capture, in addition to variance, higher-order spatial statistics. QAA benefits from relaxing the constraint of orthogonality in basis vectors (e.g., PCA) or assumptions of Gaussian deviations. This coupling between the basis vectors from QAA allows one to elucidate how 'fast' and 'slow' motions in ubiquitin allow it to bind to different substrates with high specificity. Conclusions: QAA is a novel approach to organize and visualize conformational landscape spanned by a protein. QAA naturally characterizes long-tailed distributions and separates conformational clusters with exceptional clarity when projected onto the novel representation space. The transitions we observe in ubiquitin signal biologically important structural shifts and highlight meaningful energetic barriers in the underlying energy landscape.

1225-Pos

An Electrohydrodynamic Model and Extensive MD Simulations Agree on the Positional and Intra-Residual Relaxations Up to Sub-Microsecond Dynamics

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Our recent simulations have indicated that the number of water molecules within a cutoff distance of each residue scales linearly with protein depth. At physiological temperatures, while the translational memory of water molecules around a residue is proportional to its depth, the orientational memory is independent of the residues position[1]. These corroborate the recently reported result that water density fluctuations around hydrophobic surfaces are considerably larger than those near hydrophilic surfaces[2].

We develop an efficient, simple model that characterizes protein dynamics both at picosecond and sub-microsecond timescales[3], which are coupled through conformational motions and catalysis[4]. Our approach is based on our earlier two-degree-of-freedom model, coupling the protein's fluctuations to the vicinal layer[5]. It proves to be efficient in estimating dynamic transitions in different solvents. The model emanates from geometric Brownian motion, similar in spirit to those including hydrodynamic interactions[6]. In our formulation, however, the traditional intra-molecular interactions are coupled to an electrostatic field that increases the flexibility of the regions in contact with hydrophobic residues, and almost exhibits a decoupled dynamics from hydrophilic regions where the solvent friction term dominates. We derive analytically the decay of the positional fluctuations and the relaxation of the distances between the residues which are not in direct contact.

We have performed 200ns MD simulations both above and below the dynamic transitions of lysozyme and myoglobin to validate our analytical results. We obtain a remarkable agreement between simulations and our model for the decay time of both positional fluctuations and intra-residual distances.

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1226-Pos

Trade-Off Between Localization and Expression Levels in Flagellar Pole Development of the Bacterium Caulobacter Crescentus

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The bacterium Caulobacter crescentus is a model organism for cell cycle regulation and development. Upon division Caulobacter differentiates into two phenotypically distinct cells, a sessile stalked cell and a motile swarmer cell. Throughout the Caulobacter cell cycle, the localization of several key proteins is highly regulated. In this study, we address the importance of spatial localization in signal transduction and development using synthetic redesign of protein localization coupled with mathematical modeling. Development at the flagellar pole is controlled by the response regulator DivK, whose phosphorylation state is controlled by the histidine kinase DivJ and the phosphatase PleC. PleC localizes to the swarmer cell pole, while DivJ localizes at the stalked pole. To address the importance of localization, To address this question, we have constructed strains with a variety of PleC and DivJ localization patterns, including delocalization and mislocalization to the opposite pole. To determine whether phenotypic changes can be explained purely on the basis of altered localization, we have developed a mathematical model that suggests that flagellar pole development does not rely critically on precise localization of DivJ and PleC, and that developmental defects due to complete mislocalization of PleC can be compensated for by overexpression. Our results indicate that localization is not absolutely necessary for some cellular functions, but that localized proteins enhance the robustness of the system to fluctuations.

1227-Pos

Free Energy Profiles of Large Scale Protein Conformational Changes

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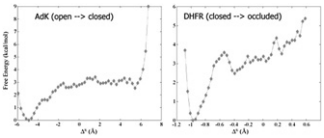
The function of many enzymes requires a transformation between widely different conformational states. Often simulations of all-atom models are not capable of determining the transformation between experimentally known end states because of the large system size and wide range of these conformational changes. However, the characterization of such transition pathways using coarse-grained models can identify significant features such as free energy barriers. In this study we employed a Monte Carlo simulation framework where bond lengths and bond angles are preserved in order to generate an initial pathway along the change in RMSD connecting these end point conformations. Within this framework, rotatable dihedral bonds along the main chain and side chain serve as the effective degrees of freedom. We then sampled conformations for each of the intermediates along this pathway without bias. The resulting conformations were combined in order to calculate the free energy profiles for these conformational changes in different proteins. These profiles yield realistic free energy barriers and indicate the degree to which conformational change is coupled to ligand binding in these enzymes.



1228-Pos

A20 Negative Feedback Regulates Period of NF-KB Oscillations

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The nuclear-cytoplasmic shuttling of NF-κB is characterized by damped oscillations of the nuclear concentration with a time period of around 1.5 hours. The NF-κB network contains several feedback loops modulating the overall response of NF-κB activity. While IκBα is known to drive and IκBϵ is know to dampen the oscillations the precise role of A20 negative feedback remains to be elucidated. Here we propose a reduced model of the NF-κB system focusing on three negative feedback loops (IκBα, IκBϵ and A20) which capture the experimentally observed responses in wild-type and knockout cells. We find that A20, like IκBϵ, efficiently dampens the oscillations although through a distinct mechanism. In addition however we have discovered a new functional role of A20 by which it controls the oscillation period of nuclear NF-κB. The design based on three nested feedback loops allows an exploration of different oscillatory responses where both period and amplitude decay can be modified. Based on these results we predict that adjusting the expression level of A20, by e.g. siRNA, the period can be changed from 1h to 3h.

1229-Pos

Systematically Defining Coarse-Grained Representations of Large Biomolecular Complexes

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Various biomolecular complexes are involved in many important biological processes. For example, the ribosome is a very large RNA-protein assembly that plays a central role in protein biosynthesis. Microtubules serve as a structural component of the cytoskeleton. It would be difficult to use large-scale atomistic molecular dynamics (MD) simulations to study the functional motions of these systems because of computational expense, and furthermore, high resolution atomic structures for such complexes may not even be available. Therefore various coarse-grained (CG) approaches have attracted rapidly growing interest, which enable simulations of large biomolecular complexes over longer effective timescales than MD simulations. We have developed a novel and systematic method for constructing CG representations of arbitrarily complex biomolecules, in order to preserve the large-scale and functionally relevant essential dynamics (ED) at the CG level. In the ED-CG scheme, the essential dynamics can be captured from principal component analysis (PCA) of a MD trajectory, elastic network model (ENM) of a single atomic structure, or a low-resolution cryo-electron microscopy density map. The method has been applied to the E. coli. ribosome and a microtubule to characterize CG models with different resolutions. The results illustrate that functionally important essential dynamics can still be captured even with aggressive coarse-graining.