943-Symp
Spatial Dynamics and Control of Cell Differentiation
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Understanding regulatory networks requires taking into account their controls and their spatiotemporal dynamics. We are probing these in experiments on the C. elegans germ line that target organ-level regulation of differentiation, and that leverage image segmentation workflows we have developed. In this talk I will explore the role of Notch signaling as a control of the germline regulatory network, and the role of diffusion in shaping the dynamics of the network. These are first steps towards our final goal of gaining a systems-level understanding of the C. elegans germline regulatory network.

PLATFORM Q: Protein Dynamics

944-Plat
Using Molecular Simulations to Understand Allosteric Inhibition of the Hepatitis C Virus RNA Polymerase
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The Hepatitis C Virus (HCV) affects more than 100 million people around the world. About a quarter of infected individuals will eventually contract chronic liver ailments and may suffer severe complications such as liver failure. There is no known cure for this disease and few effective treatments exist. The HCV RNA-dependent RNA polymerase (RdRp) is currently a target for small molecule therapeutics due to its importance in replicating the viral genome. Several allosteric inhibitors of RdRp have been identified which bind to the enzyme outside of the active site at which nucleotides are incorporated into newly synthesized RNA. While their mechanism is as yet unknown, these inhibitors have been suggested to act by preventing a conformational change in RdRp which is necessary to initiate RNA replication. We hypothesize that one can understand the nature of allosteric inhibition by using molecular simulations to study the dynamics of the enzyme, both in a free state and bound to different inhibitors. We seek to delineate the link between ligand binding and functionally important conformational fluctuations of RdRp by observing the structural coupling which results from the internal motions of the enzyme. In addition to answering fundamental questions regarding the mechanism by which allosteric effects can occur, these studies may provide information which can aid in the development of novel and more effective RdRp inhibitors.

945-Plat
Domain Fluctuations Enable Catalytic Activity in Phosphoglycerate Kinase?
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The biological function of enzymes is often related to large-scale domain movements. The configuration changes are observed by methods like x-ray crystallography, which give a static image of the protein structure in the crystal confinement. The question is, if these configuration changes are due to the substrate binding or if they are also related to the crystal packing which favors specific configurations. The structure of a protein in solution can deviate from the crystal structure but the protein has also the ability to fluctuate between different configurations. Are these fluctuations important for protein function?
Phosphoglycerate kinase (PGK) has a widely open domain structure with a hinge near to the active center between the two domains. The hypothesis of a substrate-induced configuration change, was first proposed by Banks et al. based on the comparison of crystal structures.
We have recently investigated the domain dynamics of PGK (1). Structural analysis by small angle neutron scattering revealed that the structure of the holoprotein in solution is more compact as compared to the crystal structure, but would not allow the functionally important phosphoryl transfer between the substrates, if the protein would be static. Brownian large scale domain fluctuations on a timescale of 50 ns was revealed by neutron spin echo spectroscopy. In particular, the domain movements facilitate a close encounter of the key residues in the active center to build the active configuration. The observed dynamics shows that the protein has the flexibility to allow fluctuations and displacements that seem to enable function. The presence of the substrates increases the rigidity, which is deduced from a faster dynamics with smaller amplitude.
(1) in press: Inoue et al., Large Domain Fluctuations on 50-ns Timescale Enable Catalytic Activity in Phosphoglycerate Kinase, Biophysical Journal (2010), doi:10.1016/j.bpj.2010.08.017

946-Plat
Coarse-Grained and Atomistic Modeling of Anisotropic Atomic Fluctuations in Protein Crystal Structures
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Protein atomic fluctuations can be probed by x-ray crystallography in the form of Anisotropic Displacement Parameters (ADP). In this study, we assess the accuracy of different coarse-grained and atomistic models that include protein-environment interactions in a protein crystal in comparison with experimental ADPs. We use a coarse-grained Elastic Network Model (ENM) with three different boundary conditions (see figure) to model protein-environment interactions, and an atomistic model using a CHARMM force-field. For a large list of high-resolution protein crystal structures, we find that optimal ADP modeling is achieved by weak protein-environment interactions as compared to internal interactions within a protein structure. Therefore, the internal dynamics of a protein is only weakly perturbed by crystal packing. We also find no improvement in the accuracy of ADP modeling by using the atomistic model over the coarse-grained ENM.

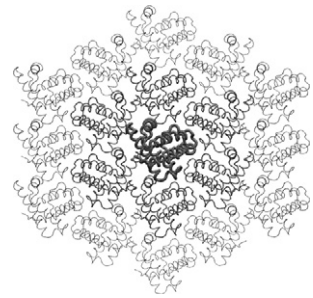

Figure. A protein-environment system constructed from a protein crystal of oxy-myoglobin (PDB code: 1a6m) with the main protein in red, the nearest neighbors in green, and the next nearest neighbors in blue. The main protein and the nearest neighbors are unconstrained while the next nearest neighbors are fixed.

947-Plat
Interconversion of Functional Motions Between Mesophilic and Thermophilic Adenylate Kinases
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Dynamic properties are functionally important in many proteins, including the enzyme adenylate kinase (AK), for which two small domains (LID and NMP) close over the larger CORE domain; the reverse (opening) motion limits the rate of catalytic turnover. Here, we compare our previously published coarse-grained (double-well G[[Unable to Display Character: ō]]) simulation of mesophilic AK from *E. coli* (AKmeso) to simulations of thermophilic AK from *Aquifex aeolicus* (AKthermo) in terms of the critical rigid-body, backbone dihedral, and contact motions in open, closed, and transition state (TS) ensembles. Like AKmeso, AKthermo follows a LID-first closure pathway in the presence of ligand, but the amplitude of LID rigid-body motions in the O ensemble decreases significantly. Backbone unfolding in O and/or TS ensembles decreases significantly relative to AKmeso in most of the interdomain hinges and within LID. In contact space, the TS of AKthermo has a weaker CORE-LID interface but a stronger contact network surrounding the CORE-NMP interface than the TS of AKmeso. A ''heated'' simulation of AKthermo at 375K and the simulation of AKmeso at 300K show similar conformational ensembles, both in the amplitude of CORE-LID motions in O ensemble and in the flexibility of some hinge regions, which supports the corresponding states hypothesis. Furthermore, mutation of 7 prolines unique to AKthermo to the corresponding residues from AKmeso more fully shifts the dynamics toward the more flexible behavior of AKmeso in most of the key hinges and even in some regions distant from any mutation. However, some prolines in AKthermo appear to strengthen or even substitute for nearby contacts from AKmeso so that local flexibility increases excessively upon mutating the proline. Finally, this mutagenic framework can inform the rational design of functionally important dynamics and allostery in other proteins toward engineering novel biological control systems.

948-Plat
Dynasome: How Does Protein Structure and Function Relate to Dynamics?
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Background: Proteins have been very successfully classified according to amino acid sequence or structure, which enabled improved prediction of function. In this study, we carried this idea one step further and developed a minimally biased scheme to compare and classify proteins purely according to their motion patterns. This approach is based on the notion that proteins, which fold into often recurring structural motives might also be exhibiting a distinct