However, within the same topological structural framework, the C-clade gp120 exhibits coupled motions that are slightly different from those observed for B-clade. Network analysis indicates that the communities in C-clade gp120 differ the most from B-clade gp120. Even though, gp120 from these clades are structurally similar, spatially distant sites may differentially influence conformational motions to modulate the antibody escape in a clade specific manner.

1245-Pos Board B155
Capturing the Initial Autocatalytic Maturation Mechanism of HIV-1 protease at Atomic Resolution
S. Kashif Sadiq, Gianni De Fabritiis.
The first and critical step of HIV virion maturation is the autocatalysis of a pseudo-folded partially dimerized viral protease, each monomer embedded in a Gag-Pol polyprotein precursor. Although the first stage of autocatalysis is thought to be protease N-terminal intra-molecular cleavage, a basic structural understanding of this process remains elusive.
Here, we have performed an ensemble of 1000 all-atom, explicit solvent, molecular dynamics simulations with an aggregate sampling time of 100 microseconds in order to capture and describe the initial auto-binding event of HIV-1 protease in atomic detail. Our method uses the ACEMD molecular dynamics code, deployed on GPUGrid, a volunteer based distributed computing infrastructure. We have used this strategy to characterize the conformational kinetics and energetic landscape of mature HIV-1 protease, reproducing the conformers of the flexible beta-hairpin flaps that modulate active site access. This implicates conformational selection as the principal ligand-binding mechanism for the enzyme.
Applying this methodology to the immature protease, comprising a single extended and initially unbound N-terminal, results in several auto-binding events, with the lytic peptide bond converging within cleavage distance of the catalytic aspartic acid dyad in the active site. Furthermore, the flaps of the protease open to guide the extended chain into the active site, whilst the process is largely orchestrated by conserved residues. Our study thus confirms that N-terminal auto-binding is possible under conditions of thermodynamic equilibrium on a timescale of 100 microseconds. As the equilibrium process occurs rarely under the timescale investigated, we employ metadynamics simulations to determine the energetic landscape.
The first stage of the molecular mechanism of HIV-1 protease auto-binding, reported here, is crucial for a better understanding of viral maturation and provides a structural basis for a new and potentially resistance-proof allosteric anti-retroviral inhibitor strategy.

1246-Pos Board B156
Nonspecific Protein Adsorption Requires Large Adhesive Domains on the Surface
Lei Shen, **Xiaoyang Zhu**.
We study the dynamics of protein adsorption using nm - μm scale patterns involving hydrophobic domains in hydrophilic matrices. We report the discovery of a critical requirement on the sizes of adhesive pads for protein adsorption: the area of each adhesive pad must be more than two orders of magnitude larger than the footprint of a protein molecule before irreversible adsorption occurs. We attribute this to the minimal surface area sampled by a mobile protein molecule in a precursor state before irreversible adsorption occurs.

1247-Pos Board B157
Fast Dynamics of Protein Preservation in Sugar Glasses
David S. Simmons, Marcus T. Cicerone, Jack F. Douglas.
Encapsulation in sugar-based glasses has long been employed to stabilize proteins against low temperatures and dehydration. However, the molecular origins of this effect have been unclear, and it fails to adequately preserve over one third of protein-based drugs. Recent experimental results have indicated that preservation time is strongly correlated with short-time dynamics of the glass. Accordingly, we employ molecular dynamics to investigate interrelations between several fast dynamic phenomena in glasses in order to elucidate the precise molecular origin of their preservative effect. Our results emphasize the presence of a post-inertial relaxation that exhibits unusual time scaling and that appears to be closely linked to the Debye-Waller factor, a caging size parameter that has been shown to strongly predict preservation quality. Longer-time relaxation of the glass, which is expected to intermediate between fast dynamics and long-time preservation effects, is shown to possess at least two relevant time scales: the first is a caging relaxation between distinct particles; and the second is a structural relaxation related to particle diffusion.

Intrinsically Disordered Proteins II

1248-Pos Board B158
α-Synuclein Interactions with Hsp70
Elizabeth Middleton, Elizabeth Rhoades.
α-Synuclein (αS) is an intrinsically disordered neuronal protein that forms amyloid fibers in Parkinson's disease (PD). Hsp70 is an ATP-dependent molecular chaperone that may inhibit and reverse protein misfolding. It has been shown that Hsp70 can inhibit αS aggregation and mediate αS toxicity in some model systems, as well as promote degradation of soluble αS. There is, however, conflicting evidence as to whether Hsp70 interacts directly with monomeric or oligomeric αS. Moreover, there is very little information on how Hsp70 may modulate interactions between αS and lipid membranes, an area of interest because it is thought that oligomeric αS may cause neuronal cell death through direct interactions with cellular membranes. In this work, binding of wildtype and pathological αS monomers and oligomers to Hsp70 was measured by fluorescence correlation spectroscopy to detect the direct interaction between αS and Hsp70. In addition, the effect of Hsp70 on αS membrane binding was observed to probe the mechanism of reduced αS toxicity in the presence of Hsp70.

1249-Pos Board B159
Intrinsically Disordered Protein Regions Modeled as Isolated Entities Commonly Adopt Ensembles of Collapsed, Globular Conformations
Albert H. Mao, Rohit V. Pappu.
Intrinsically disordered proteins (IDPs) adopt an ensemble of conformations under native physiological conditions. Despite their lack of folded structure, they perform important physiological functions and are predicted to constitute around 30% of eukaryotic proteomes. The success of disorder prediction using a protein's primary structure suggests that the propensity for disorder is encoded in the amino acid sequence. Previously, we found that net charge per residue segregates IDP sequences along a globule-to-coil transition and speculated that the polymeric characters of an IDP conformational ensemble could be predicted using only physicochemical properties derived from its amino acid composition. We tested these predictions by studying over 100 intrinsically disordered regions (IDRs) extracted from the DisProt database using atomistic Metropolis simulations in ABSINTH implicit solvent. For most of these IDRs, which exhibit low absolute net charge per residue, simulation results agreed with predictions of a collapsed, globular conformational ensemble. However, the expected swelling with higher absolute net charge per residue was only observed for positively charged IDRs. Here, we explore possible mechanisms and provide a physicochemical basis for the asymmetric behavior of sequences rich in anionic residues (aspartate and glutamate) versus those rich in cationic residues (arginine and lysine). Additionally, we discuss the functional consequences of sequence patterning in IDPs.
Supported by grants 5T32GM008802 from the NIH National Institute of General Medical Sciences and MCB 0718924 from the National Science Foundation.

1250-Pos Board B160
Computational Epigenetics: Molecular Dynamics Simulations of the Structure of HP1 Bound to a Variably Modified Histone Tail
George V. Papamokos, George Tziatzos, Anastasia Politou,
Demetrios Papageorgiou, Spyros Georgatos, Efthimios Kaxiras.
Post-translational modifications (PTMs) occurring in the intrinsically unstructured ''tails'' of the core histones are thought to function as transducers of epigenetic signals. Two of those, methylation of Lys9 and phosphorylation of Ser10 in histone H3 have been proposed to affect chromatin compaction and chromatin opening, respectively. Furthermore their combination has been suggested to function as a ''binary switch'', which controls the reversible association of the nucleosome with heterochromatin protein 1 (HP1). However, despite significant advances in the field, the exact role of such methyl/phos switches remains controversial.
To understand better how PTMs operate in the context of an intrinsically unstructured protein, we studied the interaction between HP1 and an assortment of differentially modified H3 tails by molecular dynamics simulations performed for sufficiently long times (1μs). The model system used in our studies is the complex formed between the chromodomain of HP1 and a hexapeptide from the H3 tail, mono-, di- and trimethylated at Lys9, in the presence/absence of Ser10 phosphorylation.
Our computational analysis identifies novel structural determinants involved in H3-HP1 interactions and highlights the crucial role of H3 residues other than Lys9 and Ser10 in the association-dissociation mechanism. These results complement existing functional information on the structure and dynamics of chromatin complexes and underscore the significance of modifiable sequence motifs extending beyond the level of simple methyl/phos switches and including more complex patterns of PTMs.