Phd results in a cooperativity switch and consequent strong operon repression, enabling context-specific modulation of the transcription output to the regulatory process.The regulation of transcription of TA modules by conditional cooperativity has strong implications in the formation and frequency of persister cells. Variations of this theme are likely a common mechanism in the autoregulation of bacterial operons that involve intrinsically disordered regions.

1562-Plat
Integrated View of Internal Friction in Unfolded Proteins from Single-Molecule FRET, Contact Quenching, Theory, and Simulations
Andrea Soranno[1,2], Andrea Holla[2], Fabian Dingfelder[2], Daniel Nettels[2], Dmitrii E. Makarov[3], Benjamin Schuler[2].
[1]Department of Biochemistry and Molecular Biophysics, Washington University in St Louis, St Louis, MO, USA, [2]Biochemistry Department, University of Zurich, Zurich, Switzerland, [3]Department of Chemistry and Biochemistry and Institute for Computational Engineering and Sciences, University of Texas at Austin, Austin, TX, USA.
The dynamics of proteins, which are essential for both folding and function, are known to be strongly dependent on solvent viscosity or friction. However, an increasing number of experiments have demonstrated the importance of a contribution to protein dynamics independent of solvent friction. Such 'internal friction' has been detected at all stages along the folding reaction. Even in unfolded and intrinsically disordered proteins, internal friction has a large influence, as demonstrated with several experimental techniques and in simulations. However, these methods probe different length- and timescales and have thus been used to illuminate different facets of internal friction in diverse molecular systems. To obtain an integrated and quantitative understanding, we apply the combination of two complementary experimental techniques, theory, and simulations to one system, unfolded protein L. We use single-molecule Förster resonance energy transfer (FRET) to measure the global reconfiguration dynamics of the chain, and photoinduced electron transfer (PET), a contact-based method, to quantify the rate of loop formation between two residues. This combination enables us to probe unfolded-state dynamics on different length scales, corresponding to different parts of the intramolecular distance distributions. Both FRET and PET measurements indicate that internal friction dominates unfolded-state dynamics at low denaturant concentration, and both are in remarkably good agreement with recent large-scale molecular dynamics simulations employing a new water model. The simulations indicate that both hydrogen bond formation and dihedral angle rotation are correlated with the presence of internal friction. Theoretical models of polymer dynamics allow us to quantitatively relate the contribution of internal friction in the two types of experiments with simulations and thus provide a coherent picture of internal friction in unfolded proteins.

1563-Plat
Escaping the Water Cage: Protein Intramolecular Vibrations and the Dynamical Transition
Mengyang Xu, Katherine A. Niessen, Yanting Deng, Nigel S. Michki, Andrea G. Markelz.
Department of Physics, University at Buffalo, SUNY, Buffalo, NY, USA.
The protein dynamical transition is the remarkable increase in the average atomic root mean squared displacement (RMSD) in the 180-220 K range. The effect is associated with the onset of anharmonic motions critical to biological function. However evidence of the actual biological relevance of the dynamical transition is inconsistent. While for some proteins, function ceases below the dynamical transition, for other proteins the dynamical transition appears to have no effect. Here we report measurements that suggest the difference arises from the dependence of function on large scale conformational change, and specifically the reliance on long range vibrations to access these structural changes. The dynamical transition has been extensively observed using X-ray, neutron scattering, NMR and terahertz absorption spectroscopy [1,2], with the results indicating it arises from thermally activated solvent motions. Those techniques measure all motions contributing to the RMSD including both localized motions and intramolecular vibrations. To isolate the vibrations and examine how the dynamical transition impacts them, we use a new technique, anisotropy terahertz microscopy (ATM) [3]. This unique method suppresses the background from the localized motions giving unprecedented access to the long range motions that enable large scale conformational changes. ATM measurements of lysozyme anisotropic optical absorbance in the 150-300 K temperature range show that the resonant vibrational bands rapidly increase in intensity at the dynamical transition, and surprisingly blue shift with increasing temperature, in contrast to the expected anharmonicity. The measurements demonstrate that the surrounding solvent below the dynamical transition acts as a frozen cage preventing the vibrations necessary for functional conformational change. This solvent slaving of the long range vibrations potentially impacts protein structural stability and vulnerability to structural disorder. This work was supported by NSF (DBI 1556359 and MCB 1616529), and DOE DE-SC0016317. 1. Doster,W., et al. *Phys.Rev.Lett*., 2010.104(9):098101. 2. Niessen,K., et al. *Biophys.Rev*., 2015.7,201. 3. Acbas,G., et al. *Nat.Commun*., 2014.5,3076.

1564-Plat
Facilitator Models of Weak Binding in Protein-Protein Interactions
Seyit Kale, Madeleine Strickland, Alan Peterkofsky, Nico Tjandra, Jian Liu.
NHLBI, National Institutes of Health, Bethesda, MD, USA.
Pairwise interactions are intuitive to our understanding on protein-ligand binding; however *in vivo* this is rarely true. Most intracellular proteins operate in a highly cooperative manner to perform tasks ranging from metabolic turnover to intricate signaling regulation. In some cases, one substrate needs to simultaneously interact with more than one binding partner to carry out faithful signal transductions. While one of these binding partners is the determinant of such signal transduction, it can share very similar tertiary structure with the other but might differ in functional role and abundance. Motivated by this observation, we explore the physical consequences of the mere steric presence of a non-specific ligand, the ''competitor'', crowding the surface of a ''target'' ligand. The specific interaction occurs between the protein and the ''target'' ligand, which explores the same surface as well, albeit for its unique binding site. A simple lattice model incorporating these elements along with the natural rules of exclusion and hopping reveals the regimes for when recruitment (turnover) or residence (transition state stabilization) are favored. Exploration of the search dynamics of the two ligands along the protein surface provides further insight.

Platform: Membrane Structure I: Cholesterol

1565-Plat
Polyphenol Alkyl Ester Inhibits Membrane Cholesterol Domain Formation Through an Antioxidant Mechanism Based, in Nonlinear Fashion, on Chain Length
Samuel Sherratt[1], Pierre Villeneuve[2], Robert Jacob[1], Erwann Durand[2], R. Preston Mason[1,3].
[1]Elucida Research, Beverly, MA, USA, [2]CIRAD, UMRIATE, Montpellier, France, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
Under conditions of oxidative stress, cholesterol aggregates into discrete membrane bilayer domains that precipitate the formation of extracellular crystals, a hallmark feature of the advanced atheroma in cardiovascular disease. Molecular intervention using membrane-directed antioxidants, such as polyphenolic esters, alkylated to increase their lipophilicity and bioavailability, may reduce cholesterol domain formation and associated pathology. In this study, we tested the effects of rosmarinic acid (R0) and rosmarinic esters, with alkyl chain lengths ranging from 4 to 16 carbons (R4-R16), on membrane lipid oxidation and cholesterol domain formation. Model membranes were prepared as binary mixtures of dilinoleoylphosphatidylcholine and cholesterol (at a cholesterol-to-phospholipid mole ratio of 0.6:1), in the absence or presence of each of the various rosmarinic compounds, and exposed to oxidative conditions for up to 72 hr. Changes in lipid hydroperoxide (LOOH) and cholesterol domain formation were measured using iodometric and small angle x-ray diffraction approaches, respectively. Rosmarinic acid and the various esters were observed to have differential effects on LOOH formation based on alkyl chain length. R8 had the greatest antioxidant effect, reducing LOOH levels by 60 $\pm$ 18% as compared to vehicle. R8 also inhibited cholesterol domain formation. By contrast, R0 and R16 failed to inhibit LOOH formation (6 $\pm$ 19% reduction, 5 $\pm$ 13% increase compared to vehicle, respectively), resulting in cholesterol domain formation. These data indicate that the membrane antioxidant potential of rosmarinic acid esters is dependent, in a nonlinear manner, on alkyl chain length. The mechanism for this effect is attributed to the influence of alkyl chain length on the optimal depth of the polyphenols into the lipid bilayer. These findings provide insight into novel atheroprotective benefits of polyphenol esters that are dependent on their membrane location.

1566-Plat
Is the Site of Influenza Virus Assembly and Budding Enriched with Cholesterol and Sphingolipids?
Mary L. Kraft[1], Ashley N. Yeager[1], Peter K. Weber[2], Joshua Zimmerberg[3].
[1]Chem & Biomol Engr, University of Illinois, Urbana, IL, USA, [2]Glenn T. Seaborg Institute, Lawrence Livermore National Laboratory, Livermore, CA, USA, [3]Program in Physical Biology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA.