for non-equilibrium backbone dynamics; as the thiyl radicals separate under the influence of backbone motion, their recombination rate decreases, so that observation of the transient thiyl absorbance provides access to backbone dynamics. Unlike fluorescence or triplet quenching experiments, which often are used for the study of polypeptide dynamics, this method observes processes far from equilibrium, and has no intrinsic limitation of the accessible time scale.

The encounter probability of the thiyl radicals was found to decay with time following a power law $t^{-0.94}$ which is incompatible with simple diffusion. Thus, the relative motion of the radicals is affected by the dynamics of the connecting backbone, resulting in an unusual power law for the re-encounter probability which could be described as (fractal) diffusion in a reduced non-integer dimensional space. The scaling law was found to extend over the full experimental time window, covering nine orders of magnitude in time (1 ps to 1 ms), although very different processes govern backbone motion on these different time scales. Furthermore, the same scaling law was observed in a folding protein having secondary and tertiary structure, in simple model peptides forming only secondary structure, and in a protein under unfolding conditions, indicating an intrinsic behaviour of the polypeptide backbone itself.

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Mobility of a Loop of a B. subtilis Carboxylesterase and its Effect on Substrate Conversion

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Carboxylesterases (CEs) are ubiquitous enzymes responsible for the detoxification of xenobiotics. CEs can metabolize and hydrolyze a variety of esterified drugs, including the anticancer agent CPT-11. The specificity of CEs for a particular substrate or inhibitor depends on the enzyme's molecular structure and the dynamics of conformational substructures when a substrate is bound. We have used a series of biophysical techniques to understand differences in substrate selectivity of CEs. First, we used molecular dynamics simulations (MD) and normal mode analysis (NMA) to identify the loop region of high fluctuation in a CE from B. subtilis. Second, we calculated the root-mean-square deviation (RMSD) from both MD and NMA trajectory data. Then we used these RMSD data along with its secondary structure to make correlations with enzyme activity. Meanwhile, we generated a series of mutations at specific amino acid residues that are located near this flexible loop region in order to restrict its mobility. Then we measured enzyme activity of these mutant CEs and compared them with the wild type. Our hypothesis is that the molecular dynamics of this enzyme is correlated with substrate conversion efficiency for selected CEs. These experiments provide the first data toward testing this hypothesis.

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Reality's A Drag: Accounting For Friction In Simple Protein Models

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Elastic network models (ENMs) are widely used for studying the global equilibrium dynamics of proteins because they predict motions on timescales that are generally inaccessible to molecular dynamics (MD) simulations. Although the slowest motions predicted by in vacuo ENMs have repeatedly shown to correlate well with experiment, the timescales of these motions do not. Here we develop a simple algorithm for scaling the characteristic timescales of slow motions predicted by an ENM to reflect the true timescales of the molecular motions. Using MD trajectories on the order of tens of nanoseconds, we calculate ideal friction constants for Langevin models of three proteins. We then demonstrate that the difference between the slowest vibrational frequencies predicted by the Langevin model and those predicted by an in vacuo ENM can be explained through simple physical arguments. We provide an expression for scaling the normal mode frequencies of an in vacuo ENM to realistic values and discuss the utility of our results in combining ENMs with MD simulations to predict large-scale protein dynamics.

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Coupling Of Solvent And Protein Dynamics: Mossbauer And Incoherent Neutron Scattering From Dielectric Relaxation Data

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A wide variety of protein dynamics are accounted for by two classes of solvent processes: the bulk-solvent viscosity and hydration-shell dynamics. In glass-forming solvents the bulk viscosity arises from the well-characterized microscopic alpha relaxation; in liquid solvents that freeze the alpha process is essentially molecular reorientation. In past work we showed that the solvent alpha relaxation determines the activation enthalpy of alpha-slaved protein motions.

We have now measured the dielectric spectrum of the hydration-shell dynamics in myoglobin solutions as a function of hydration, temperature and frequency. These hydration-shell data and a minimal model of protein-solvent coupling predict the temperature- and hydration-dependence of the Mossbauer effect. Furthermore, we show agreement between incoherent neutron scattering data and our measurements of hydration dynamics.

These improvements in understanding protein-solvent dynamical coupling will be discussed in terms of earlier work describing the slaving of many protein functional motions to the solvent alpha-process and the slaving of protein folding. We demonstrate that many enthalpy barriers to protein motion arise almost entirely from solvent dynamical processes.

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A Detailed Comparison Between The NMR Ensemble, Two X-ray Models And Computational Predictions Of Motions For A Designed Sugar Binding Protein

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Coarse-grained elastic network models with single point representation of amino acids are becoming increasingly popular for describing conformational flexibility and equilibrium dynamics of proteins. In particular, the Gaussian network model (GNM) predictions have been fairly successful in interpreting the residue-level root-mean-square variations in residue positions inferred from NMR ensembles of structural models for a given protein and the fluctuations in residue positions indicated by crystallographic B-factors. Here, we carried out a detailed analysis for a designed sugar binding protein whose structure was solved in two crystal forms by X-ray crystallography and by NMR. Comparison with experimental data and results from molecular dynamics simulations confirm that the GNM predicts well the equilibrium dynamics of this protein and correlates better with the NMR derived data than crystallographic B-factors. The results further stipulate the importance of examining multiple structures determined by different methods as well as performing both analytical and numerical studies, toward gaining an accurate understanding of the type and range of conformational motions accessible to a given protein under native state conditions.

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Molecular Dynamics Simulations of Phosphorylation-induced Conformational Transitions in the *Mycobacterium tuberculosis* Response Regulator PrrA

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Phosphorylation-mediated activation of response regulators (RRs) is predominantly used by microorganisms as a central strategy in the regulatory activities of their two-component systems, the underlying molecular mechanisms are however far from fully understood. In this work we have conducted molecular dynamics simulations of the phosphorylation-induced conformational transitions in the *Mycobacterium tuberculosis* RR, PrrA, to obtain the dynamical details that are relevant to the RR activation. From the full-length structure of unphosphorylated PrrA we generated a computational model for the phosphorylated PrrA state by changing the phospho-accepting aspartic acid Asp-58 in the regulatory domain to the phosphoaspartate phos-Asp-58. The resultant structural relaxations were simulated through a rapid sampling of protein motions using a conformation-biased all heavy-atom potential energy function without explicit solvent. Marked structural rearrangements have been observed across the interdomain interface of the phosphorylated PrrA, manifesting the global effect of the local phosphorylation upon a single residue of aspartate. Such changes have also been found to involve the domain-crossing motions that disrupt the hydrophilic and hydrophobic interactions within the interdomain space and thus transform PrrA from a compact structure to a more extended conformation featuring a wider domain-domain separation and a more exposed transactivation loop. These simulated motions reflect the essential early-stage activation dynamics for the relief of the inhibitory role of the regulatory domain in PrrA. In effect, each more extended PrrA becomes more suited to interact with DNA and RNA polymerase; the activation of many proteins also shifts the population-equilibrium of PrrA towards more active states, therefore leading to a phosphorylation-enhanced allosteric regulation for the control of transcription.