ably exists in structure determination. Indeed, we find the level of degeneracy of modes is proportional to the density of modes in the vibrational spectrum. This means that for modes at the same frequency, degeneracy is more severe for larger proteins. Degeneracy exists also in modes of coarse-grained models, but to a less extent than those of all-atom models. In closing, we discuss the implications of the degeneracy of normal modes – how it will affect how normal modes are to be used in various normal modes-based applications.

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Statistical Physics of the Causality and Energetics in Allosteric Communication

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Allostery is one of the pervasive mechanisms through which proteins in living systems carry out enzymatic activity, cell signaling, and metabolism control. The effective modeling of protein function regulation requires a synthesis of the thermodynamic and structural views of allostery. We present here a structure-based statistical mechanical model of allostery, allowing to observe causality of communication between regulatory and functional sites and to estimate per-residue free energy changes. Based on the notions of ligand free and ligand occupied systems in the context of protein harmonic representation, corresponding sets of characteristic normal modes are obtained and used as inputs for the allosteric potential. The latter quantifies mean elastic work exerted on a residue because of the local motion of its neighbors. Subsequently, in a statistical mechanical framework the entropic contribution to allosteric free energy of a residue is directly calculated from the comparison of the conformational ensembles in the ligand free and occupied systems. The method is a systematic approach for analyzing the energetics of allosteric communication based on a single structure, and its feasibility was tested on a variety of allosteric proteins particularly heterogeneous in terms of size, topology, and degree of oligomerization. The allosteric free energy calculations show diversity of ways and complexity of scenarios existing in the phenomenology of allosteric causality and communication. Achieving the discriminative power between agonist and antagonists and developing computational techniques for on-demand design of desired allosteric effectors are among the major goals of future theoretical studies towards allosteric drug design.

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Spectrus: A Dimensionality Reduction Approach for Identifying Dynamical Domains in Protein Complexes from Limited Structural Datasets

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Large scale movements in proteins often arise from the relative displacements of few quasi-rigid domains which ought to be identifiable by comparing alternative conformers. Two major obstacles of domain partitioning strategies are: (i) the sensitive dependence of domain definitions on the number of available conformers or the partitioning algorithm and (ii) the lack of objective criteria for establishing the correct number of quasi-rigid domains. We show that significant advancements on both fronts can be made by resorting to the spectral dimensional-reduction of the distance fluctuation matrix of amino acids pairs. The strategy, implemented in an algorithm called SPECTRUS, is applicable to single proteins or very large complexes, such as ion channels and viral capsids, and can robustly pinpoint their innate quasi-rigid domains: very consistent partitions have been obtained using thousands of conformers or just a couple of alternative structures (and even a single structure, by using elastic networks). The returned partitions provide valuable insight into the functional mechanics of the considered molecules.

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Mode Localization in the Cooperative Dynamics of Protein Recognition

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The biological function of proteins is encoded in their structure and expressed through the mediation of their dynamics. But how do the random thermal motions of a folded protein in the picosecond timescale propagate to become emergent biological processes? Our approach is a novel theoretical method, the Langevin Equation for Protein Dynamics (LE4PD), which takes the structural ensemble of a protein as input and projects the dynamics analytically. Both simulation-derived and experimental NMR conformers are the input structural ensembles for the LE4PD. The model is solved in a set of diffusive modes which span a vast range of timescales from the picosecond to the microsecond regime. Local fluctuations initiate biologically relevant pathways as they cooperatively enhance the dynamics in specific regions in the protein. The slowest, most collective motion localizes directly to highly conserved regions involved in binding partner recognition and active-site regulation. The picture that emerges is a dynamically heterogenous protein where biologically active regions provide energetically-comparable conformational states that can be trapped by a reacting partner. Starting from the static structural ensemble of a protein, the LE4PD predicts where specific regions in the protein three-dimensional structure become dynamically active at a given timescale and how allosteric dynamics are enhanced or suppressed upon binding. We analyze this mechanism as we calculate the dynamics of monomeric and dimerized HIV protease, and free Insulin Growth Factor II Receptor (IGF2R) domain 11 and its IGF2R:IGF2 complex, and other examples. The diffusive mode rendition precisely indicates the position inside the primary sequence of these energetically-guided local fluctuations, allowing us to predict which parts of the protein will lead the kinetics of biologically relevant processes.

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Tuning Allostery in Random Spring Networks

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Allostery in proteins is the process by which the binding of a ligand to one site affects activity at a second distant site. Inspired by this biological process, we have developed a method to tune random spring networks to exhibit allostery-like behavior. We show that allosteric communication does not require the transmission of stresses nor a single narrow communication pathway between sites. This communication also does not depend on the existence of a zero-frequency mode, although the displacements typically correspond to a single low-frequency mode for protein-scale system sizes. The behavior of these networks can be reproduced in macroscopic experimental systems in both two and three dimensions.

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Revealing the Mechanism for Conformational Changes from Structurally Rich Ensembles

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Conformational changes in proteins are essential to their biological functions, from allosteric regulation to signal propagation. However, the transient nature of the intermediates along transition pathways hampers their experimental detection, making the mechanisms underlying these processes highly elusive. Here, applying an innovative combination of Principal Component Analysis (PCA) of experimental ensembles and coarse-grained simulations [1], we dissect the essential motions orchestrating biological functions for the highly studied ion channel GLIC. This prokaryotic protein, which has been solved in different functional states along the gating cycle, is a prototype for the Pentameric Ligand-Gated Ion Channels (PLGICs) that mediate synaptic communication. We show how the Principal Components (PCs) of the GLIC ensemble decode the core motions common to all the current structures, providing mathematical reaction coordinates to cluster them and reveal clearly the interconnecting pathways. Modeling GLIC as an elastic network in a Langevin simulation, we generate smooth trajectories between end-points that visit spontaneously multiple intermediate states along the transition, providing a realistic description of the mechanism. Finally, by direct analysis of the correlated motions along the dominant PCs we unveil an elegant mechanism to propagate information from the binding site throughout the protein [2]. Our approach provides a powerful and general theoretical framework to study conformational changes and synthetize the rich structural information deposited currently in the Protein Data Bank.

1.Orellana L., Yoluk O., Orozco M., Lindahl E. Revealing conformational transition pathways by analysis of structurally rich X-ray ensembles and coarse-grained simulations (2015) (submitted)
2.Fenwick R.B.*, Orellana L.*, Esteban-Martín S., Orozco M., Salvatella X. Correlated motions are a fundamental property of beta-sheets. Nature Communications (2014); 5: 4070. http://dx.doi.org/10.1038/ncomms5070 * Shared First Authorship