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Talk Invited Invited Talk

Probing the Landscape of Proteins via Linear Response Theory

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Functional proteins have highly complex structures, remaining mainly unmodified as a result of a multitude of mutations, yet their energy surface going through significant changes upon perturbing specific regions. How the various accessible states are populated may be manipulated by short and long-range modifications in the structure; alternatively, the dynamical control may differ without any significant structural variation. In this study, we analyze the *h. influenzae* Ferric binding protein (FBP), using computational perturbation/response techniques [1, 2, 3]. We consider the folded protein as a network of its amino acids with links between residues in close proximity. Using linear response theory, we reproduce residue-by-residue structural changes [3] as determined from the X-ray structures of the ligand-free and ligand-bound forms. We perturb the protein in three different initial conformations: (i) the apo form; (ii) the holo form with only the protein (Fe^{+3} stripped from the data); (iii) the holo form where the Fe is treated as an additional node of the network. By sequentially inserting directed forces on single-residues along the chain [1] and recording the resulting relative changes in the atomic coordinates, we find that for the predominant number of the cases the residue-by-residue structural changes as determined from the X-ray structures are faithfully reproduced (correlation coefficient larger than 0.9). Moreover, these changes are reversible, unless a ligand that introduces a few new interactions is also present in the model. The latter observations are explained by the incessant sampling of several conformational states - including that of the bound form - in the presence of fluctuating forces provided by the environment. Shifts in the energy landscapes are only induced once a ligand that stabilizes certain conformations is integrated to the system. To provide further understanding of how the protein operates structurally, we concentrate on the few residues that give high correlations in the presence of the ligand. These include residues that are either (i) in the fixed domain that support the ferric binding region, or, (ii) residues that are located in the moving domain loops that display the largest amount of displacement upon binding. Thus, it is possible to manipulate the bound form of the protein towards the unbound form only by either directly perturbing Fe binding residues, or by controlling the distant loops that show large displacements upon binding. The latter are particularly interesting in that they are positively charged residues, providing chloride ion binding locations - chloride has been proposed as a possible controlling agent for the release of Fe^{+3}. We find that, by perturbing any one of these residues in a collection of directions spherically symmetric around it, the residues around the Fe^{+3} that are located at the tip of the cap that opens the exit of Fe^{+3} are made to operate in a coherent fashion. On the other hand, directly perturbing Fe^{+3}, as well as many of the other residues destroys this coherence. The techniques developed are generalizable to the study of the thermodynamic response expected of many protein molecules including the analysis of very large proteins as well as domain motions.

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[1] C. Baysal and A.R. Atilgan, Proteins, 2001. 45(1): p. 62-70.

[2] M. Ikeguchi et al., Proteins, 2001. 45(1): p. 62-70.

[3] L.S. Yilmaz and A.R. Atilgan, J. Chem. Phys., 2000. 113(10): p. 4454-4464.