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Editorial

Special Issue on "Computational Approaches for Protein Dynamics and Function"

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Proteins are fundamental macromolecules that sustain living organisms by performing an astonishingly wide variety of tasks. They adopt extremely diverse shapes that perform highly specific functions, achieved through temporal optimization over millions of years of evolution. Proteins usually have specific flexibility that enables them to undergo the conformational changes necessary to perform certain functions. Understanding protein flexibility and conformational dynamics is thus pivotal to determine how proteins work. In the era of advanced computing technologies, can we use computational approaches to elucidate how proteins' structures and dynamics drive their function? This Special Issue collects recent studies that employ different computational methods to answer this question.

Molecular Dynamics (MD) is regarded as the gold standard when it comes to protein dynamics. Molecular docking and virtual screening are popular computational methods to discover novel drugs and protein inhibitors. Singh et al. [1] combined docking-based virtual screening with MD simulations to find potential inhibitors of Mycobacterium tuberculosis Fatty Acid Synthase type-I (Mtb FAS-I). By screening a database of ~55,000 compounds, the authors narrowed their targets down to nine potential candidates. By carrying out short MD simulations and binding energy calculations for the nine protein–ligand complexes, the authors reduced their targets to four molecules that might act as pioneer FAS-I inhibitors, paving the way to a novel treatment for tuberculosis.

Simpler than MD simulations, Elastic Network Models (ENMs) simulate protein dynamics and flexibility by modeling the protein as a network of elastic springs, and are often used in combination with Normal Mode Analysis (NMA). Scaramozzino et al. [2] introduced a dynamic solvent effect into ENMs to more effectively reproduce X-ray fluctuations than using solvent-free ENMs. By investigating a dataset of ~1k protein structures, they showed that the highest correlation with experimental data was obtained when random perturbations were applied to the solvent-exposed surface and when water molecules were included into the ENM. These findings suggest that a tightly bound water layer is important for modulating protein flexibility, and that protein fluctuations likely originate during the bombardment of the structure by the solvent.

ENMs were also used by Tarenzi et al. [3] to decipher structure–dynamics–function relationships. ENM-NMA was applied to a dataset of 116 different proteases, and proteins were clustered together based on their "dynamic distance" in the space of normal modes. Proteins that belonged to the same sub-families, and thus, had similar sequences and functions, also had similar dynamics. Interestingly, some sub-families were also clustered together in certain cases, suggesting that they might share similar dynamic traits despite having different evolutionary origins. This method also built a basis of dynamic vectors that could describe the most important features of the large-scale motions in the dataset and was validated by MD.

Structural modeling, protein–protein docking, and Protein Contact Networks (PCNs) were used by Drago et al. [4] to analyze the interactions between the von Willebrand

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Factor (VWF) and Factor VIII belonging to the coagulation cascade. Two models of FVIII (full-length and without the B-domain) were docked with VWF. The binding energies and PCN results were subsequently analyzed to assess the stability of the FVIII-VWF interfaces and find potential allosteric pathways. The results showed that the A3-C1 domains are the preferential binding sites for VWF. This agrees with the experimental structure of efanesoctocog alfa, a novel (B-domain free) FVIII-VWF complex used in medication for hemophilia A.

The effect of ligand binding on the dynamics and allosteric pathways in human Glutathione Transferase A1 (GTSA1) was investigated by Nicolaï et al. [5]. MD simulations were carried out on apo GTSA1, and on GTSA1 bound to glutathione (GSH) or to a GS-conjugate ligand. Free-energy surfaces and 1D profiles were reconstructed based on the variability of two sets of coarse-grained angles. By looking at the differences between free-energy landscapes, the authors recognized 11 residues known to be key in ligand binding and identified 22 more that were previously unknown. Some of these residues are distant from the binding sites, highlighting the importance of long-range allosteric effects for protein-ligand interactions.

MD simulations were also used by Sogunmez and Akten [6] to analyze the dynamics of human β_2-adrenergic receptor (β_2AR) in complex with a G-protein, and its signal transmission in its fully active state. Mutual information and transfer entropy were used to infer correlations between C^{α} displacements and the rotameric states of the backbone and side-chain angles. The use of rotameric states enabled the recognition of strong correlations in almost all loop regions; the authors identified the loops as potential allosteric hot spots and highlighted the donor nature of polar residues and their importance in signal transmission.

The intertwined relationship between protein sequence, structure, dynamics, and function was broadly addressed by Orellana in a perspective article [7]. After a review of the literature, the author highlighted specific examples in which functional motions are conserved from bacteria to mammals. Emblematic of this is the mammalian proton exchanger NHE9, which shares only 20% sequence similarity with its distant bacterial homologs but exhibits a remarkably high overlap (~70–90%) in terms of functional motions, as assessed via Principal Component Analysis (PCA) of experimental ensembles and NMA. This is evidence that protein motions are a key phenotype selected during evolution. The author argues that cancer might also adopt this strategy to favor mutations that disrupt functional motions, supporting the emerging notion that disease mutations often affect protein dynamics.

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