Protein dynamics

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Protein dynamics | molecular dynamics | conformational ensemble | protein structure-dynamics-function relationships

1. Introduction

Proteins are known to be dynamical entities, performing their function as an ensemble of diverse conformations rather than a single static structure. Protein dynamics is a highly complex phenomenon comprising numerous contributions from motions with different mechanisms of action and happening with diverse timescales and amplitudes (**Figure 1**) that highly depend on the system and the local environment. Subangstrom vibrations of covalent bonds represent the fastest of those movements. The exploration of various rotamers of side-chains and fluctuations of the protein backbone involve nontrivial moves that span the space of several angstroms. In protein cores, such moves can require several nanoseconds to execute due to the necessity to synchronize with changes in surrounding residues[3][4][5]. Many conformational changes involve slower and more prominent coordinated movements of several residues in a sequence that manifests as, for example, gating movement executed by loops surrounding the active sites of many proteins[6]. In ligand binding and unbinding events, especially when the binding site is deeply buried in the protein structure, ligands often have to travel tens of angstroms. Such a transport process requires a series of systematic adjustments of protein side-chains and backbones along the traversed paths that might take up hundreds of milliseconds to occur[7]. Among the slowest principal motions performed by proteins are highly organized collective translocations of whole domains, starting on microsecond timescales and with amplitudes reaching nanometers. Finally, the most extensive conformational change transpires during the protein (un)folding processes, which can take hours and even days[8][9][10].

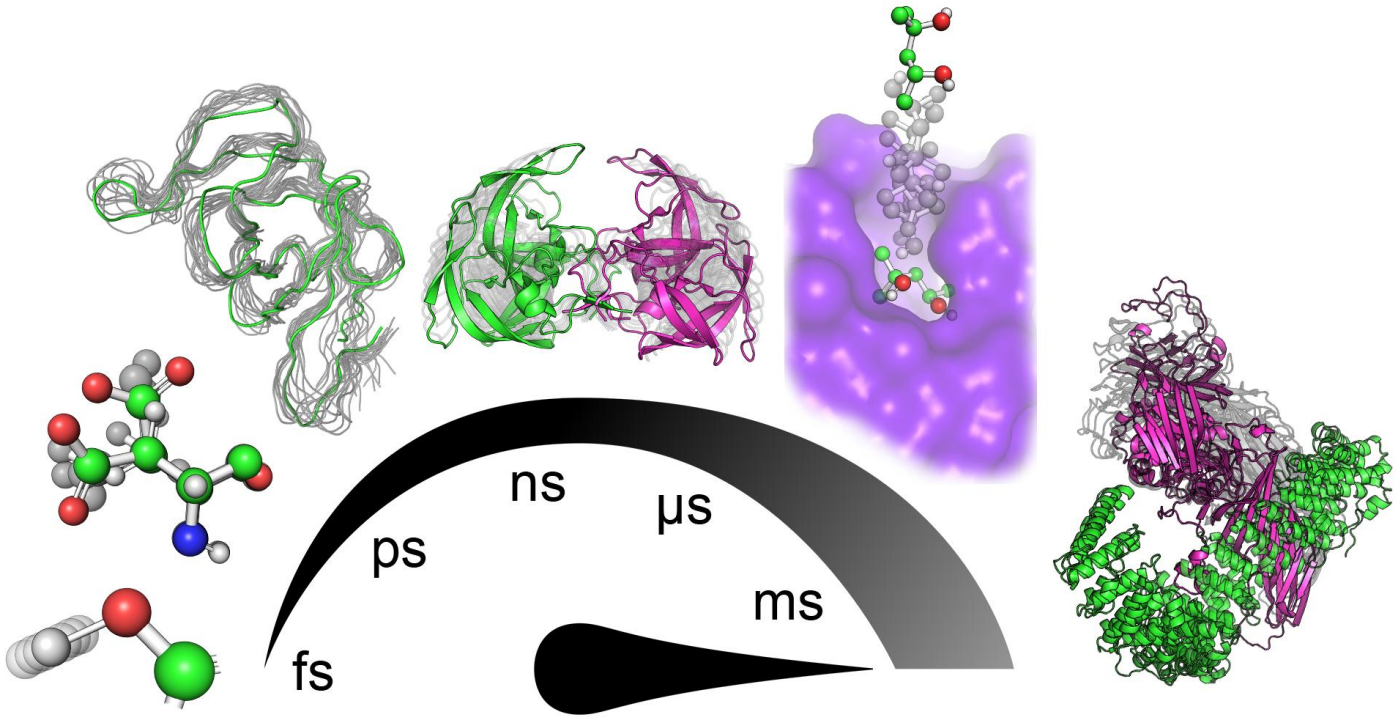

Figure 1. Hierarchy of principal motions in protein dynamics. From left to right: bond vibrations (fs–ps), side-chain rotations (ps–ns), backbone fluctuations (ns), loop motion/gating (ns–ms), ligand binding/unbinding events (>100 ns), and collective domain movement (>μs).

At present, continuous development of experimental techniques enables investigation of protein dynamics by methods such as: solution nuclear magnetic resonance (NMR) capable of capturing protein motions on broad timescales, fluorescence spectroscopy, or time-resolved macromolecular crystallography (X-ray)[8][9]. Furthermore, due to availability of enormous amount of high-quality three-dimensional (3D) protein structures obtained by NMR, X-ray, cryogenic electron microscopy (Cryo-EM), homology modeling, or hybrid-approaches, computational biophysical methods are progressively more applied to study protein motions at the atomic resolution, the most prominent being molecular dynamics (MD) simulation and normal mode analyses (NMA)[10][13].

When we consider the reliable simulation of protein dynamics as an essential component, it is natural to resort to the MD simulation technique as a golden standard to investigate the conformational behavior of a protein. Nowadays, various MD simulation protocols can be utilized to deliver insights into protein dynamics on millisecond timescales with the growing utilization of graphics processing unit (GPU)-enabled parallelism, development of more efficient software, enhanced sampling methods (high-throughput MD, Gaussian accelerated MD, etc.) and approximated models (e.g. coarse-graining), gradually making such simulations even more affordable[14][15][16][17][18][19][20][21].

2. Discussion

Despite all these improvements, MD simulations are not without errors in reproducing a realistic protein ensemble and, hence their experimental confirmation is necessary. Among the major limitations is the accuracy of force fields used to calculate interatomic interactions and the tractable sampling of the ensemble discussed above. The quality of traditionally applied force fields is intrinsically limited by numerous approximations like the lack of particular interaction types[22], neglect of electronic polarizability[23], and fixed protonation states of titrable residues[24]. At the expense of increased computational demands, some of those limitations can be partially overcome by improving potential models[25], resorting to polarizable force fields[26], and constant pH simulations[27]. Nonetheless, even without these advances, MD simulations relying on the latest force fields have been shown to reach chemical accuracy in their predictions for many different scenarios[28][29][30]. It is worth noting, including protein dynamics is crucial for design and re-design tasks, and as a recent trend, was described in recent review[31].

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