Protein Dynamics Simulations Using Coarse-Grained Models

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Abstract Simulations of protein dynamics may work on different levels of molecular detail. The levels of simplification (coarse-graining) may concern different simulation aspects, including protein representation, interaction schemes or models of molecular motion. So-called coarse-grained (CG) models offer many advantages, unreachable by classical simulation tools, as demonstrated in numerous studies of protein dynamics. Followed by a brief introduction, we present example applications of CG models for efficient predictions of biophysical mechanisms. We discuss the following topics: mechanisms of chaperonin action, mechanical properties of proteins and their complexes, membrane proteins, protein-protein interactions and intrinsically unfolded proteins. These areas illustrate the opportunities for practical applications of CG simulations.

1 Introduction

The steady increase in computational power constantly sets new limits in simulations of biomolecular dynamics [164]. Nevertheless, the majority of biologically relevant protein dynamic processes remain beyond the reach of atomistic Molecular Dynamics (MD), the classical simulation tool. In such cases, the introduction of properly designed simplifications that capture relevant physical features can be the only option, or incomparably cheaper than atomistic MD, to better understand macromolecular processes [64].

A variety of purely theoretical models for analyzing the dynamic properties of proteins have been proposed [109, 171]. Nevertheless they appeared to be rather

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limited in their predictions. This is due to the complicated nature of proteins and rules governing their structure. Compared to purely analytical methods, the molecular simulation approach is better suited to handling protein complexity. Presently, molecular simulations represent a powerful and the most widely used theoretical approach for the understanding of protein dynamics [64, 99, 117].

1.1 CG Simulation Models

The most direct computational approach to protein dynamics prediction is simulation of a dynamic system of interest. A simplified simulation model of proteins is probably the earliest example of CG approach in structural biology, developed in the mid-1970s [91]. Since that time the field has grown tremendously, branching out in many variants of protein representation, models of interactions and sampling techniques (Fig. 1). Interestingly, recent estimates indicate a noticeable increase in the number of studies that rely on CG simulations [155]. This significant rise is perhaps related to a growing number of experimentally solved structures of large biomolecules (or their complexes), too big to be reasonably addressed by all-atom simulations.

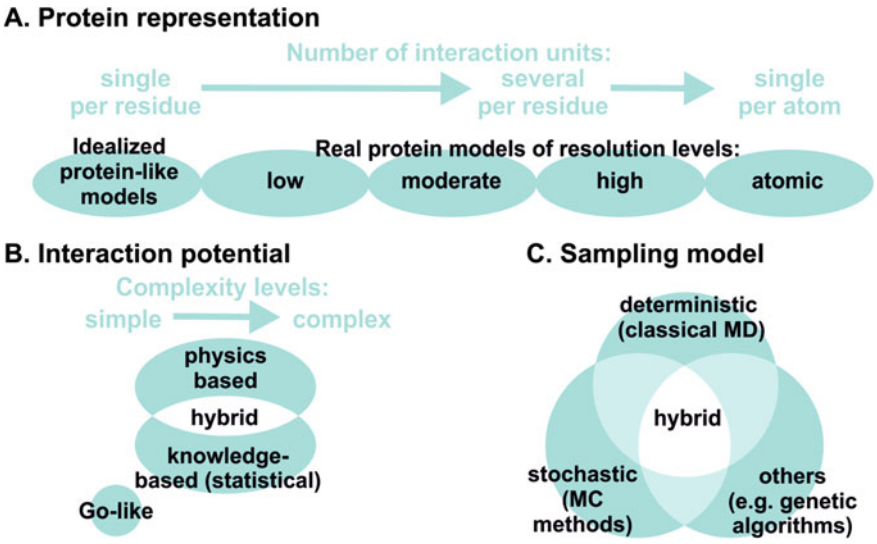

Fig. 1 Conceptual components of CG protein simulation models and their variants: **a** protein representation, **b** interaction schemes (Go-like potentials are protein specific, i.e., native interactions are favored to assure the lowest energy for the native conformation, and are used individually or in combination with non-protein specific: physics- or knowledge based schemes), **c** sampling model. This diagram applies either to continuous-space or discrete (lattice) models. For detailed review of these variants and coarse-graining levels, refer to [64]

A number of mean-resolution CG models have been developed for protein structure prediction [64, 71]. Some of them enable efficient simulation of dynamic processes. A typical example is the CABS model [72], which acronym stands for the united atoms representing a single residue in a protein chain (CA—alpha carbon of the main chain, B—beta carbon, and S—the center of side group). Thus, in the CABS model, a single amino acid is represented by 2–4 (depending on the side-chain size) interaction centers, and one of them (C-alpha) is placed into a high-resolution lattice. The interaction scheme is based on mean-force potentials derived by the statistical analysis of known protein structures. In spite of the fact that the interaction scheme is obtained only from known crystallographic structures related to completely random protein chains, protein dynamics processes (folding, unfolding, folding upon binding, diffusion, flexibility of folded structures etc.) simulated by the CABS method are qualitatively correct [23, 51, 52, 63, 65, 66, 67, 85]. These qualitatively correct results, not trivial to obtain, show that interaction patterns of unfolded (or partially unfolded) proteins are quite similar to the interactions seen in fully folded structures. The lattice representation of CABS proteins significantly increases the speed of conformational updates. Simulation processes are controlled by the Monte Carlo (MC) scheme: random series of local conformational transitions. This pseudo-random Monte Carlo process does not describe accurately ultra-short-time motions and ranges of a few angstroms, although longer-time (and space) dynamics is essentially identical with the dynamics observed for continuous space models [52, 53, 72]. The coarse-graining of CABS enables very fast derivation of its low resolution structures from high resolution atomistic coordinates, and what is more important quite accurate all-atom structures could be very rapidly re-computed from CABS coordinates [63, 65, 87, 86].

1.2 From CG to All-Atom Structures: Multiscale Modeling

One of the major future tasks of CG dynamics studies is the design of methods for the reliable and efficient transition between simplified and atomic resolution levels [132], as the element of multiscale methodologies. The idea of multiscale modeling is efficient computation on a CG scale to send it to the detailed all-atom simulation, or vice versa [68]. Obviously, the CG model used in the multiscale methods must produce physically realistic coarse-grain protein structures. Even if it is fulfilled, it is a non-trivial problem to add all-atom details to CG structures to produce physically realistic all-atom counterparts [63]. It has been demonstrated in applications to protein folding CG trajectories that reliable and efficient transitions between CG and atomic resolution are feasible [46, 65]. Finally, it is accepted that one of the most promising future directions is to develop approaches that can minimize the difference between the simplified and atomic models [58].

2 Applications in Structural Biology

In this section, we discuss several recent examples of CG modeling, including our reports and other published literature. The section covers the following actively studied tasks of protein dynamics: mechanisms of chaperonin action, mechanical properties of proteins, protein-protein interactions, membrane proteins and intrinsically unfolded proteins. Most of our own examples of CG simulations described below were done using the CABS CG modeling tool [72]. Numerous CABS applications have been also reviewed elsewhere [64, 68].

2.1 Testing Mechanisms of Macromolecular Dynamics via Simple Models: Chaperonin Action

Complex macromolecular processes can be generalized to very simple concepts and tested computationally on a very general level. This is the case of the studies of chaperonin action. Chaperonin and its protein substrate is a very large protein complex whose dynamic processes are way beyond the reach of classical dynamics simulation models. Over the past 20 years a significant number of studies, both experimental and theoretical, have been pursued to understand how chaperonins (like GroEL) facilitate protein folding processes in the cell.

Many theoretical models have been proposed focusing either on the passive (aggregation prevention) or active (folding promotion) possible roles of chaperonins [55]. A number of CG simulation studies investigated the effect of confinement on protein folding using very simplistic [178], simple lattice [11], off lattice C-alpha based and Go-like [121, 156] or more realistic [5] models. Another aspect of chaperonin action, namely the effect of interactions of the protein substrate with the surface of chaperonin cavity, was also a subject of numerous CG simulations studies using lattice [11] and off-lattice [54] models. For broad, recent reviews covering the use of CG models in chaperonin action studies, see [55, 102].

Probably the most popular theoretical model which provides explanation of the chaperonin active role is the Iterative Annealing Model (IAM). In this model chaperonin promotes the protein substrate folding by sequential unfolding of misfolding traps through their hydrophobic interactions with cage walls. Just very recently, we have attempted to test the IAM hypothesis using a de novo CABS modeling approach employing a non-specific (without the Go-like approximation) knowledge-based interaction scheme [67]. Importantly, in most (if not all, as described by Lucent et al. [102]), simulation studies testing various chaperonin models on real (i.e. not too much simplified) protein substrates, a common simplified interaction model was used: the Go-like model. Therefore, in contrast to earlier simulation studies, the CABS model did not preclude transient conformers stabilized by non-native interactions (Fig. 2).

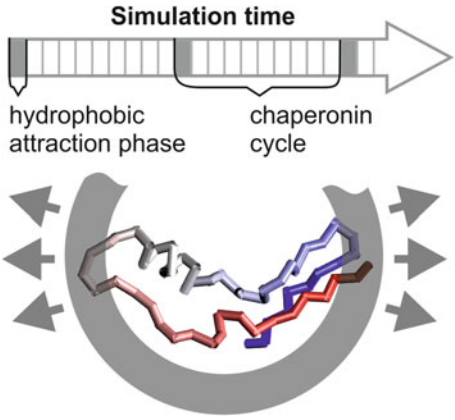

Fig. 2 A simple chaperonin model used in protein folding studies with the CG CABS model [67]. The chaperonin cage was simulated as a sphere with a thick wall of variable hydrophobicity. In the basic state the walls are inert for 9/10 of the simulation time. Periodically (see the simulation timescale above in the Figure) the walls became hydrophobic, attracting the encapsulated protein chain with a strength typical for hydrophobic interactions within folded proteins (according to the CABS force field)

The CABS simulation results showed that periodic distortion of the simulated proteins by hydrophobic chaperonin interactions promotes rapid folding and leads to a decrease in folding temperature. According to the observed mechanism of folding promotion, chaperonin prevents kinetically trapped conformations. This is contrary to the so far accepted interpretation of the IAM model suggesting not the prevention but rather the unfolding action from already trapped conformations. Interestingly, the analysis of the folding trajectories enables general observation of chaperonin-induced modulation of the observed folding mechanisms from nucleation–condensation to more framework-like. All these observations are in good agreement with the experimental data on chaperonin-bound protein substrates, generally indicating an ensemble of compact and locally expanded states lacking stable tertiary interactions.

It is worth to mention that theoretical studies of chaperonin-mediated folding may have important conceptual applications in other fields [102] e.g. in the development of structure-refinement software or in the construction of chaperonin-like molecules designed for specific biotech and medical applications. We have to emphasize that we are only at the beginning of the understanding of how chaperonins work. As pointed out by Lucent et al. [102], so far most theoretical and experimental research focused on GroEL, a specific prokaryotic chaperonin. Since chaperonins exhibit apparently different modes of action in prokaryotic and eukaryotic organisms, the investigation of these differences may be essential for the complete understanding of underlying mechanisms and protein folding itself. This challenging issue has already been addressed by a very simple lattice model [50].

2.2 *Mechanical Unfolding and Refolding of Proteins and Their Complexes*

One of the functional features of proteins is response to a wide range of applied forces. Being subjected to an applied load, proteins play key roles in cytoskeletal organization [33], mechanics [37], cellular transport [139], signaling [149] and protein degradation [44]. The required external force to unfold protein is in the order of pico-Newtons. Since the atomic force microscopy (AFM) and laser optical tweezers (LOT) techniques [105, 124, 145] detect forces in the pico-Newton range, they are useful tools for studying mechanical unfolding of biomolecules. In studies of these processes two major strategies are used. In the first technique, protein is pulled by a force ramped linearly with time, while monitoring the force (mechanical resistance) as a function of the end-to-end distance. The second strategy is based on the application of a constant force through force clamp devices. In experiments at a constant pulling speed, the total force experienced by protein is $F = k(vt-x)$, where k, v, t and x are respectively: the spring constant (stiffness) of cantilever, pulling speed, time, and displacement of the pulled amino acid from its original position. Typically, in AFM experiments k and v are in the range of 10–1000 pN and 10^{-11}–10^{-7} Å/ps, respectively. In LOT, the velocity range is similar to that of AFM, whereas the typical values of spring constant, $k = 0.001$–0.1 pN/nm. Stiffness defines the force resolution of experiment. Thus, AFM can probe unfolding of strong proteins with required Fmax of about few hundreds of pN (such as titin [124] or ubiquitin [16]), while LOT is precise enough for studying biomolecules with few tens of pN mechanical resistance (weaker proteins as well as DNA and RNA molecules [98, 147]).

Figure 3a shows the force-extension profile obtained by constant velocity stretching experiments for Ig8 titin fragment. The peaks in Fig. 3a are associated with breaking hydrogen bonds (HBs) between strands A′ and G (Fig. 3d) in single titin domains of the multidomain construction. Apart from molecular interactions studies, AFM technique can also be used to investigate the mechanical stability of proteins measured by F_{max} in the force-extension profile (note that F_{max} depends on the pulling speed logarithmically, $F_{max} \sim \ln(v)$ [31]). Measuring the mechanical stability in different solutions, one can also probe the effect of environment on hydrogen bonding [101]. The mechanical unfolding studies provide also insights into many other important issues, including: forces that drive biological processes, ligand binding affinity to proteins/receptors [34], force-induced intermediate states [35, 93, 135], the mechanical unfolding free energy landscape (FEL) of proteins [14]. The problem of FEL is considered in more detail below.

A major limitation of AFM experiments is that it cannot give the detailed characterization, at the atomic level, of conformational changes under the applied force. Computer simulations may be employed as a tool to complement experimental studies. Schulten's group used the all-atom models with an explicit water to study the mechanical unfolding of the I27 protein [100]. They deciphered in a great detail the unfolding pathway of I27 and demonstrated the existence of hump due to breaking

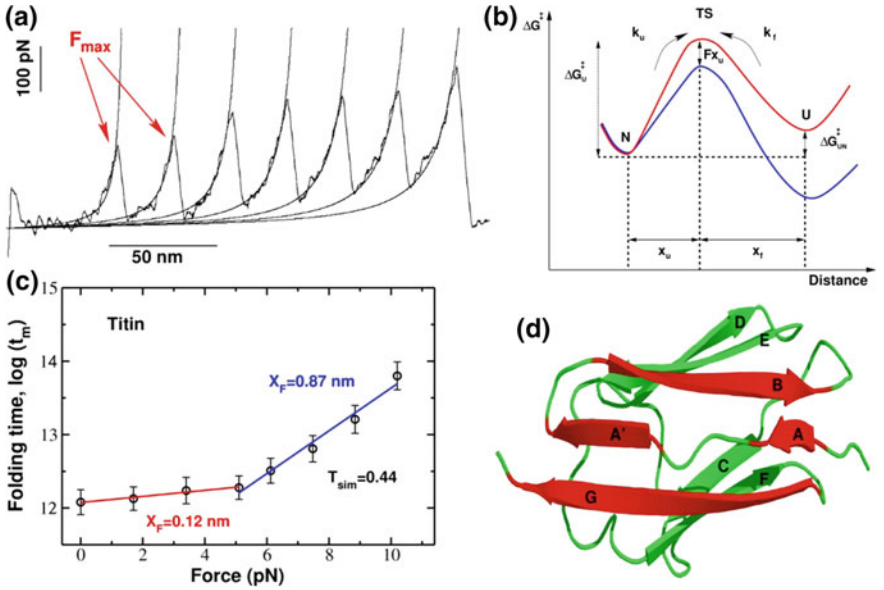

Fig. 3 **a** Force-extension profile obtained by stretching of Ig8 titin fragment (adapted from Ref. [124]). Each peak corresponds to unfolding of a single domain with maximum resisting force to stretching, F_{max}. Smooth curves are fits to the wormlike chain model. **b** Conceptual plot for the free energy landscape of protein unfolding without (red) and under (blue) the external force. An applied force lowers unfolding barrier by Fx_u increasing exponentially the unfolding rate constant (k_u), but decreasing exponentially the folding rate constant(k_f). x_u is the distance between native and transition state and x_f is the distance between transition and denatured state. **c** Distance to transition state, x_f in two different regimes for titin protein (pdb ID 1tit). The crossover from the low- to middle-force regimes occurs at $f_{switch} = \sim 5$ pN. **d** Cartoon representation of native state conformation of I27 domain (PDB code: 1tit) with eight β-strands labeled: A(4–8), A′(11–15), B(18–25), C(32–36), D(47–52), E(55–61), F(69–75), G(78–88). Importance of HBs between beta-strands marked by red color is described in the text

HBs between beta strands A and B (Fig. 3d) [101]. Mechanical unfolding of a number of proteins has been also probed by all-atom simulations with implicit solvent [115]. The major shortcoming of all-atom MD simulations is that the pulling speed is about 6 orders of magnitude higher than that used in AFM experiments. It is unclear if in silico results obtained in such extreme conditions are meaningful to understand experiments (strong forces may considerably disturb FEL), although recent studies claimed that unfolding pathways are not sensitive to pulling forces and speeds [90, 97].

The time scale discrepancy (and the related discrepancy in stretching forces required to induce unfolding) between AFM experiments and simulation can be reduced by the usage of CG models. Nowadays GPU technique allows reaching experimental pulling speeds by CG Go models [176]. CG Go models have been successfully used by many groups to study mechanical properties of proteins [2, 9, 24, 170]. Despite their simplicity, in many cases they correctly capture unfolding path-

ways, FEL and mechanical stability of proteins. For example, a complete description of mechanical unfolding pathways of single and multidomain Ubiquitin at the level of secondary structure was obtained [95]. It was shown that thermal and mechanical pathways for fibronectin type III and I27 domain are different [115]. This is because the thermal fluctuations have more global effect on entire protein and unfold the most unstable part of protein while the force should propagate protein unwinding from the points to which force is applied. Having used Go-model, mechanical unfolding pathways of protein DDFLN4 [94] and two slipknotted proteins (pdb codes—1e2i and 1p6x) [150], were shown to depend on the pulling speed.

The CG Go-models may be suitable for deciphering the FEL (Fig. 3b). Considering FEL as a function of end-to-end distance, one can use Bell-approximation [7] to estimate the distance between the native state (NS) and transition state (TS), x_u, using either the dependences of unfolding rates on the external force [7] or the dependence of force on pulling speed [31]. The distance between the NS and TS x_u (Fig. 3b), estimated by the C-alpha Go-like model [25], was in excellent agreement with experimental results [15, 76]. Furthermore, Li showed that x_u (Fig. 3b) is defined by the secondary structure content and approximately depends linearly on the contact order [83, 92], thus the helix proteins have larger distances from the native state to the transition state than beta proteins. It should be noted that the phenomenological Bell theory is based on the assumption that x_u is not moving under stretching. Recently, applying Kramers theory [81] and assuming that the distance between NS and TS is force-dependent, Dudko et al. [29] have gone beyond the Bell assumption. With the help of proposed non-linear kinetic theory [29] one can estimate not only intrinsic rate coefficient, k_u, and the distance between NS and TS, x_u, but also the unfolding barrier, ΔG_u^{++} (Fig. 3d).

One of the most successful application areas of CG Go models were estimations of the mechanical stability of proteins [13, 92, 144, 152]. It has been found that helix proteins are less stable than beta proteins and unfolding force F_{max} may be expressed as a linearly function of the contact order [119]. This is understandable because beta proteins have a larger fraction of long-range residue-residue contacts leading to higher resistance to external perturbation [83]. Using the Go models, Cieplak et al. computed F_{max} for thousands of proteins [144, 152] and have found that the mechanical clamp (resistance-determining region of a protein) of the top strongest proteins is not only consisted of hydrogen bonded β-strands being sheared during the pulling. Structures tied by disulfide bonds were found to contribute to significantly larger mechanical stability than shear-based mechanical clamps. Novel mechanical clamps were identified and classified [143, 144]. Later on, the high resistance to stretching of top 13 proteins (cysteine-slipknots) was confirmed by all-atom steered molecular dynamics (SMD) simulations [116] and observed experimentally [163]. Recently CG model was successfully applied even for proteins with non-trivial structures [150, 151], which was confirmed by experiment [45]. For a more detailed review of protein mechanostability, see Chap. 10 of this book entitled “Mechanostability of proteins and virus capsids.”

The success of CG Go models is possibly associated with the fact that the pulling starts from the native state and that these models are based on topology of the native

state. However, in particular cases one has to be careful with predictions emerging from these simple models. In the case of DDFLN4 protein, the Go model did not give the peak in the force-extension curve observed in the experiment. It was shown that the occurrence of that peak is due to non-native interactions neglected in Go model [77]. Thus, in certain cases the non-native interactions are important because non-native contacts appear in intermediate state during the unfolding process. To avoid possible artifacts associated with neglecting non-native interactions, CG models with more realistic potentials may be used. Using the CABS model [78] it was shown that non-native interactions have led to an additional intermediate state along mechanical unfolding pathway, which was previously detected in the AFM experiments [134] and in explicit-solvent all-atom simulation, but not in CG Go-model. Another example of such case is the force-induced intermediate of Ubiquitin, which was neglected in CG Go-model simulations [95], but detected by the Lund force-field [49].

Recently, Steered Molecular Dynamics (SMD) simulations have become a powerful tool to assess the strength of the molecular interactions. The idea behind using SMD simulations is that the mechanical stability, or rupture force (measured as a peak in force-extension profile), required to unbind a ligand from a receptor is related to the strength of the interaction between them [8, 26, 38, 39, 74, 75, 96, 128]. Over the last 5 years, SMD method has been implemented in many CG protein simulation packages including CABS [78], UNRES [142], AWSEM [41] and many others. With the ability of simplified models to sample longer timescales, when compared to atomistic models, application of CG models is a promising direction for studies of mechanical stability of large biomolecular complexes.

SMD simulations have been used for a wide variety of applications in the studies of biological processes and various biomolecules [90]. Going forward, SMD techniques can be used to study cell functions, where proteins are exposed to their native (crowded) environment [167]. One of the recent applications of SMD is to understand the mechanism of virus binding to its host cell [141]. Another issue of great interest is the application of SMD for studying the response of protein to periodic forces [154]. It is also worth to mention some important problems for further studies. For instance, it remains unclear if the distance between the native and transition states (distance x_u (Fig. 3c) followed from the non-linear theory [29]) depends linearly on contact order (as it was obtained in the linear Bell approximation). Generally, the deciphering FEL is done by its projection onto one-dimensional space, usually end-to-end distance. However, the validity of such approximate mapping is not always true [10], thus this issue requires further investigation.

In addition to mechanical unfolding studies, CG models can be used to characterize the refolding kinetics of proteins in a presence of external force [80, 131]. Many proteins in human body that are being subjected to a wide range of mechanical forces face challenges to reach their native states. The question of how an external force affects the protein refolding remains to be clarified. Single-molecular manipulation experiments have demonstrated that the refolding of protein under small force can be probed by force-clamp technique [32]. If the quenched force is smaller than equilibrium critical force separating folded and unfolded states, protein refolds into native state. Typical time scales for protein folding in the absence of applied external

force varies from microseconds to hours [82]. Note that underlying dynamics of the protein refolding process under force can occur on timescales that are a few orders of magnitude slower compared to conventional folding process. This is because in the presence of external force, f, the refolding times exponentially increase with f [7]. Thus, only CG models can be effectively used to study refolding process under external load. Using CG Go-model, Kouza and coworkers [80] studied the impact of the external force from 0 to 14 pN on protein refolding pathways of several proteins. It was found that there are two force regimes for refolding of titin with different distance to transition state, x_f (Figs. 1b and 1c). In the first or low force regime, the refolding pathways were in close agreement with the thermal ones. However, the simulation values of x_f obtained in this force range did not agree with the experimental ones. The results obtained for x_f in the second force regime are in good agreement with experiments (Fig. 1c) [80]. This implies that force-clamp experiments are being carried out in the second force regime (Fig. 1c) where the pathways are not the same as thermal ones. Only if the quench force is smaller than f_{switch}, the thermal folding pathway can be probed by force-clamp experiments. This result calls for a caution in interpreting results of single-molecular manipulation experiments.

2.3 *Dynamics of Protein-Protein Interactions*

Dynamics of protein-protein interactions is extremely demanding in terms of computational power, when using classical atomistic modeling tools. As demonstrated in numerous works, CG models allow for efficient exploration of the thermodynamics and kinetics of protein complexes [36, 60, 62, 114, 130]. For example, Kim and Hummer [60] investigated binding affinities of Vps27 complexes with ubiquitin attached to the membrane, where folded domains were rigid and linkers between them were flexible. They used a C-alpha model with various variants of potentials for interactions between domains, linker movement and the protein-membrane complex. Predicted binding affinities, for various modeled complexes, were in good agreement with the experimental data. Furthermore, conformations of some ubiquitin complexes were predicted with very good precision (DRMS < 2 Å).

Interestingly, accurate values of binding affinities could also be determined with a more simplified model [36]. In this case the Brownian dynamics of the Barnase-Barstar complex was derived with a model in which three amino acids were represented by one bead. Computed kinetic data of the association process corresponded well with the experiment.

The binding of a protein coactivator to an enzyme is a class of extremely important processes, usually difficult to study due to relatively high protein rearrangements. The characterization of such processes has recently been the aim of CG simulation studies [28, 84]. In one of them, Kurcinski and Kolinski [84] applied the CABS model to describe the activation of the Retinoid X Receptor (RXR) by 9-cis retinoic acid and the TRAP220 coactivator. They focused on specific transition states. The results agreed well with the experimental data and a two-stage sequential reaction

mechanism could be suggested. Interestingly, the simulations were conducted with a fully flexible peptide coactivator (11 residues) and a moderately flexible receptor (238 residues) whose conformation was restrained to the vicinity of its experimental structure (see Fig. 4 for the scheme of the multistage procedure). The resulting extent of conformational sampling was incomparably larger than with any classic all-atom simulations.

Apart from the possibility to use restraints from experimental structures to maintain the protein fold we can also use an elastic network model (ENM) as was done by Hall and Sansom [43]. In this study proper structures of the Cohesin (162 residues)-Dockerin (60 residues) complex were predicted with a CG-Molecular Dynamics (CG-MD) model in which each amino acid was represented by four beads. Ca. 80% of interfacial residues were identified correctly and two various ways of ligand binding were identified which agreed well with the results of experimental data.

With regard to the large-scale dynamics of protein systems, another promising and presently active field is CG dynamics of actin filaments [12, 21]. Because of the scale of the system, it is extremely challenging to simulate myosin binding to actin filaments by all-atom MD. A multiscale model [157] enabled the observation of the

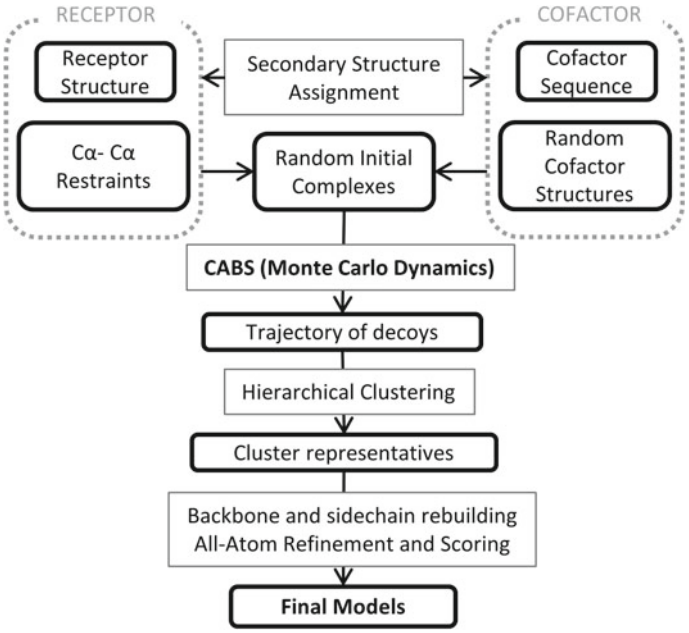

Fig. 4 Multiscale procedure for the description of binding between the Retinoid X Receptor (RXR) and the peptide (TRAP220) cofactor using CABS CG dynamics [84]. The procedure starts from the generation of input data for a receptor and a protein cofactor. In the next step, the receptor and the cofactor are put together in many random configurations, subsequently subjected to CABS CG simulation. Various types of data stored along the procedure are shown in bold frames, while the applied computational methods in thin frames

myosin motor and an insight into its action. In this case, three levels of coarse-graining were introduced: chains of secondary structure elements, domains and molecules. The movement of each component was simulated by Brownian Dynamics. A more detailed, physicochemical view of the myosin-actin complex was recently obtained with a CG simulation model [114] in which each bead represented a single amino acid. In this case conclusions regarded also more general thermodynamic aspects of protein-protein association.

Another popular and important protein-protein dynamics issue, in which diverse levels of coarse-graining are applied, is protein aggregation. All-atom MD simulations in explicit solvent can provide insights about early stages of aggregation process of short peptides derived from full-length amyloidogenic proteins [6, 73, 79, 111, 158]. Larger complexes and longer timescales can be accessed using CG models. In the simplest CG models, a single unit (cuboid [175] or tube [4]) represents the whole peptide, while in the most detailed models each amino acid consists of a few pseudo-atoms [20, 103, 107, 110, 125, 168]. Many practical applications of CG models have been outlined in recent reviews [64, 108]. Dramatic progress has been recently achieved in the CG modeling of large polyprotein complexes (made up of many copies of the same or different proteins) [130]. In their review, Saunders and Voth present two general classes of CG methods: mapping methods that transfer information from one level to another only during parameterization and bridging methods that connect different scales of representation during simulation.

The major challenge in modeling of protein interaction dynamics seems to be as that outlined in the reviews of the performance of protein docking techniques [162, 174, 22]. Namely, it is the treatment of substantial conformational changes. CG simulation models offer perhaps the most prospective means for modeling of extensive backbone dynamics in the nearest future.

2.4 Dynamics of Membrane Proteins

Membrane proteins play an important role in cell biology. They are responsible for signaling, molecular transport across lipid bilayers, maintaining cell structural stability and control of cell-cell interactions. Although 20 to 30% of all ORFs are predicted to encode membrane proteins, less than 1% of all known 3D protein structures account for membrane proteins [112]. Moreover, those proteins are embedded in different types of lipid bilayers. The interaction with lipids is essential for both protein function (e.g. can affect integral membrane protein activity [89]) and membrane properties such as hydrophobic thickness or lipid composition [48]. The complex nature of membrane-protein systems makes CG Molecular Dynamics (CG-MD) simulations a valuable approach to the investigation of dynamics, structure-function relationship and stability of membrane–protein systems [64]. One of the best performing, and probably the most recognized, CG-MD approaches is based on the MARTINI force field [104] that uses four-to-one atom mapping. Only four main types of interaction sites are defined: polar (P), non-polar (N), apolar (C), and charged (Q). Each particle

type has a number of subtypes allowing accurate representation of solvent, protein and membrane structures. This approach enables treatment of very large systems (corresponding to systems consisting of more than 500,000 atoms) and offers timescales above 100 μs which are far beyond the scope of classical all-atom-MD. The method was successfully applied by Sansom and co-workers for the prediction of protein positions within lipid bilayers [136]. Self-assembly CG-MD simulations, starting from a protein surrounded by randomly positioned water and lipid molecules, were conducted for 91 different protein systems. The resulting structures gave insights into direct protein-lipid interactions, membrane distortion around different proteins and localization of proteins in the lipid bilayers, in agreement with experimental data (see Fig. 5).

CG-MD simulations applying the MARTINI force field were also used for the investigation of helix associations and dimerization of membrane proteins. Sengupta and coworkers conducted a set of CG-MD simulations, each lasting 25 μs, to study the association mechanism of glycophorin A and two disruptive mutants, T87F and

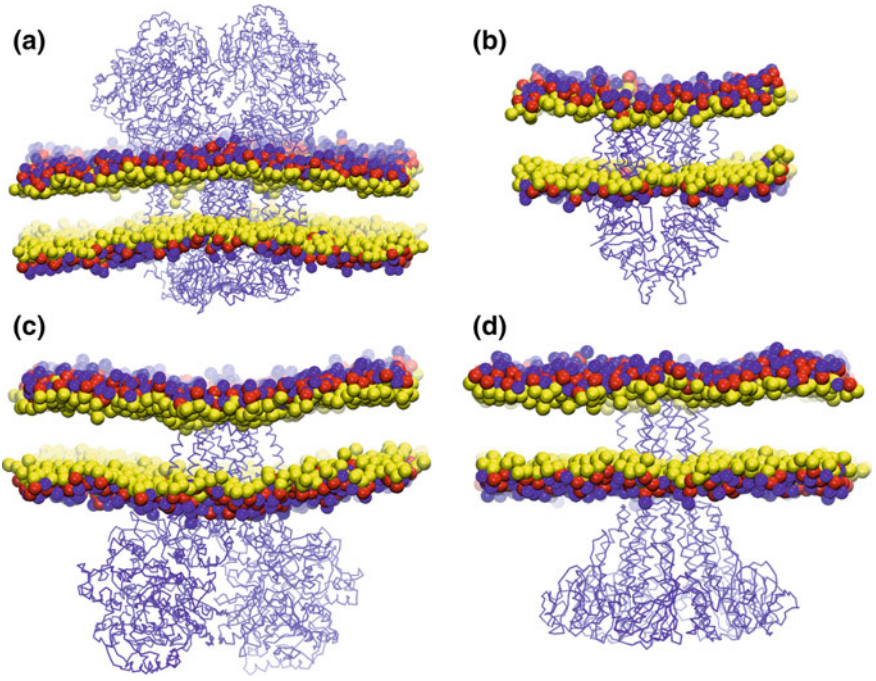

Fig. 5 Final structures from self-assembly CG-MD simulations, starting from a protein surrounded by randomly positioned water and lipid molecules [129]. The figure presents the results of four simulations: A—cytochrome bc1 complex, B—putative metal-chelating ABC transporter, C—quinol-fumarate reductase and D—Mg^{2+} transporter. Water, ion and DPPC lipid tail particles are excluded for clarity. The backbone trace of the protein is shown in blue. The particle colors are: phosphate in DPPC lipid headgroups: red; glycerol linker in the lipid: yellow; choline in PC headgroups: blue. Picture created based on materials available in the CG Database [129]

a triple mutant of the GxxxG motif (G79LG83LG86L), embedded in a DPPC lipid membrane model [138]. In each case, dimers formed within the first 5 μs. The wild-type dimer packed in a right-handed manner, and the structure was consistent with the native structures defined by NMR studies [146]. The analysis of free energy profiles reveals that two dimers formed by mutated peptides were less stable, by about 8–10 kJ mol^{-1} as a result of the disruption of a lipid bilayer surrounding the protein and less efficient helix-helix packing [138]. The observed differences became only apparent after extensive sampling, which indicates the importance of long microsecond simulation time scales.

A multiscale MD approach (combining CG-MD and all-atom-MD simulations) was used by Kalli and coworkers [57] to explore the formation of an aIIb/b3 integrin TM helix hetero-dimer in the DPPC membrane model. CG-MD simulations were performed using high-throughput methodology [42] which enabled automatic running of multiple self-assembly simulations and statistical analysis over an ensemble of approximately 100 structures. Dimer formation usually occurred within a few hundred nanoseconds of CG-MD. The resulting dimers were submitted to further assessment and refinement using all-atom-MD simulation. Comparing the final structure of the modeled dimer with the available aIIb/b3 integrin NMR structure (PDB ID: 2K9 J [88]) yields a Cα rmsd of 2.2 Å for the TM region, a similar crossing angle of $30 \pm 3°$ and a helix-helix interface created by the same residues. The results indicate that a purely computational based approach may result in hetero-dimer formation with an accuracy similar to the NMR method.

Recently, Periole and coworkers applied large-scale CG-MD simulations to study the energetics of the receptor-receptor dimer interface of the G protein coupled receptor (GPCR), rhodopsin [118]. The procedure involved self-assembly simulations of multiple copies of rhodopsin embedded into a lipid membrane over time scales ranging from 10 to 100 μs. During the simulations the potentials of mean force (PMFs) were computed for pairs of rhodopsin molecules along different interfaces. The resulting data pointed to the most stable rhodopsin-rhodopsin conformation involving a symmetrical Helix1/Helix8 interface. The observed interface was also in agreement with recent cross-linking experiments [69] and EM density maps [126]. This approach based on extensive CG-MD simulations may also be used to investigate homo- and hetero-dimer interfaces of other members of the GPCR family.

The above examples illustrate some of the CG-MD methods which use the MARTINI force field applied in the studies of membrane-protein systems. A wide variety of other CG methods currently exist and new force fields are being developed [3, 59, 61, 120, 148, 179]. Recently, an extension of CABS coarse-grained model to modeling the effect of membrane environment (CABS-membrane [120]) has been applied to ab initio folding simulations of 10 short helical membrane proteins. The CABS-membrane simulations started from random protein conformations, situated outside the membrane environment, and allowed for full flexibility of the modeled proteins during their spontaneous insertion into the membrane. In the obtained trajectories, models close to the experimental membrane structures were found (see Fig. 6). Another class of approaches is based on combination of CG models with the Gaussian network model (GNM) and/or the anisotropy elastic network model (ANM).

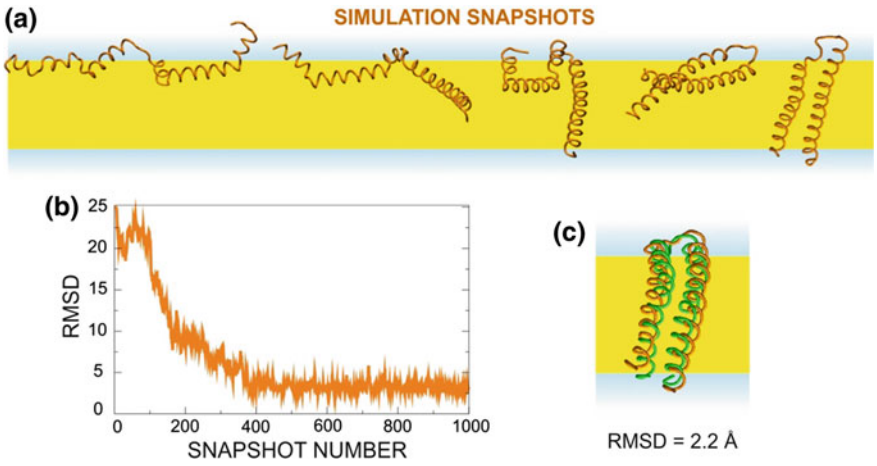

Fig. 6 Membrane insertion and folding of 1A91 protein observed in CABS-membrane ab initio simulations [120]. **a** example simulation snapshots illustrating the insertion and folding mechanism, **b** evolution of the RMSD values (reflecting similarity to the experimental structure) vs simulation time, **c** comparison of the highest accuracy model obtained in the simulations (RMSD = 2.2 Å) with the experimental structure (colored in green)

These methods were used to investigate the mechanism of L-arginine (Arg)/agmatine (Agm) antiporter (AdiC) [18] and prediction of functional motions of outer membrane transporter and signal transducer FecA [137].

Despite the limitations of CG models, united-atom representation and simplification of energy function, there is a growing need for improving CG computational methods to be used to study the function and dynamics of large and complex protein-membrane systems. Nevertheless, CG based methods are rapidly advancing and may become invaluable tools for the exploration of some fundamental events that are otherwise still not reachable by biochemical experiments.

2.5 Intrinsically Unfolded Proteins

Over the last decades, the thermodynamically stable conformation of a protein was usually treated as the state responsible for biological functions. Nevertheless, at the end of the 20th century the research community realized that intrinsically disordered proteins (IDP) or proteins with intrinsically disordered regions (IDR) are ubiquitous in nature and they can retain their functionality [40, 106, 160, 161, 172]. Conformational studies of these proteins are experimentally extremely challenging [30], particularly due to their large structural heterogeneity and aggregation tendency. With the boom of IDP studies, computer simulation models have emerged as useful tools for the description of IDP conformational ensembles [17, 122, 123]. As

the effective search of the conformational space is the major advantage of the CG models, they can be used as methods of choice for possibly the broadest sampling of conformational disorder.

Owing to their flexibility, disordered proteins have increased tendency of forming protein-protein complexes. During binding, as compared to folded structures, they can form a far larger number of interaction contacts. This theory is called the "fly-casting mechanism" and it was illustrated by Shoemaker et al. [140] who investigated the kinetics of IDP binding to the receptor using their free energy functional based on a simplified scheme of amino acid contacts.

Nevertheless, CG simulations of pKID-KIX complexes [47] indicated that the increased binding affinity can be caused not only by the greater capture radius of IDPs. The kinetic analysis of this process was based on simulations using the CG Go model with the continuum C-alpha chain representation and compared with available experimental data for various ordered and disordered complexes. Interestingly, it was found that the coupling of folding with binding of IDPs leads to a significant reduction in the binding free-energy barrier. This work also discusses roles of other structural factors important for this particular association.

Abeln and Frenkel analyzed other aspects of how intrinsically disordered regions (IDRs) can influence the protein association process using Monte Carlo (MC) simulation on cubic lattice with C-alpha representation [1]. The simulation results provided intriguing insights into the effect of IDRs on protein structure. The authors indicated that proteins with hydrophobic binding motifs without neighboring IDRs tend to aggregate and consequently form amyloids.

The ability to fold upon binding of some IDPs has been extensively studied using CG simulation models [27, 159, 165, 166, 169]. A multiscale model was used to generate the pathway of IDP folding induced by binding to its receptor [169]. The method included a step of CG simulation with C-alpha representation and optimal path calculation at an atomic level. The binding process was simulated as fully flexible and the role of non-native interactions was stressed. In other studies [165, 166] the authors characterized an ensemble of transition states of p27Kip1 protein binding to a rigid structure of a cyclin A—Cdk2 complex. In this case a knowledge-based potential was utilized to investigate some aspects of the folding mechanism of this protein. Intrinsically disordered proteins frequently serve as flexible linkers of protein domains. CG modeling of such systems was reviewed by Zhou [177].

Similarly to protein structure prediction, IDP modeling approaches can be divided into de novo methods (based on the prediction power of the method) and those utilizing sparse experimental data. The CG C-alpha model of Norgaard et al. [113] was designed to simulate disordered proteins and parametrized using data from nuclear magnetic resonance spin-labeling experiments on the $\Delta 131\Delta$ fragment of Staphylococcal nuclease. Importantly, such an approach can be used by utilizing data from MD trajectories or other experiments.

Interestingly, 2D lattice models have been recently used to explain the worse performance of sequence-based disorder prediction methods for smaller proteins (or segments) than for larger ones. Such a simple simulation model enabled a novel

insight into the basic determinants of protein disorder: amino acid composition and chain length [153].

As shown above, CG models, even very simplistic ones, provided many important facts for the description of IDP and IDR dynamics. However, the potential of CG modeling does not seem to be sufficiently exploited in the field [64], perhaps because of the relatively recent interest in the area.

3 Conclusions and Perspectives

An obvious advantage of CG protein simulations is that larger protein systems can be studied and longer timescales can be assessed than it is possible using atomic-resolution MD [64, 117]. Apart from expanding the limits, the speed-up benefit of CG models brings many new opportunities for the design of some extensive 'in silico experiments' [155], such as: comparative dynamics for a large set of proteins [156], comprehensive mutation analysis [70], scanning parameters of a simulation model to see how it affects simulation results [173] or construction of databases by high-throughput simulation protocols [19].

CG protein modeling has already a history of a few decades. The last decade showed a dramatic increase in CG modeling studies of large biomolecules [64, 155]. We can expect that this trend will continue in the foreseeable future, since atomic-resolution MD is far too slow for studies of many practical problems. The current need for computer-enhanced studies of large biomolecules is mostly due to the recent growth of experimental data of structural biology that require rapid interpretation and validation of emerging hypotheses [56, 117].

In this chapter, we described recent applications of CG simulations to some representative and important topics of protein dynamics. The work demonstrates the utility of CG modeling in understanding real biological problems. As shown, there are many variants of CG simulation tools and many successful strategies in which CG models are an important component. Future developments are expected to include CG models in unified/integrative structure modeling procedures utilizing a wide range of experimental and computational techniques [64, 127, 133]. Consequently, the integration of protein CG models together with CG models for other molecules (lipids, nucleic acids, carbohydrates) as well as CG models with atomic MD (so-called multiscale approach) should be the focus of further research.

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References

1. Abeln, S., Frenkel, D.: Disordered flanks prevent peptide aggregation. PLoS Comput. Biol. **4**, e1000241 (2008). https://doi.org/10.1371/journal.pcbi.1000241
2. Arad-Haase, G., et al.: Mechanical unfolding of acylphosphatase studied by single-molecule force spectroscopy and MD simulations. Biophys. J. **99**, 238–247 (2010). https://doi.org/10.1016/j.bpj.2010.04.004
3. Arkhipov, A., Freddolino, P.L., Schulten, K.: Stability and dynamics of virus capsids described by coarse-grained modeling. Structure **14**, 1767–1777 (2006). https://doi.org/10.1016/j.str.2006.10.003
4. Auer, S., Meersman, F., Dobson, C.M., Vendruscolo, M.: A generic mechanism of emergence of amyloid protofilaments from disordered oligomeric aggregates. PLoS Comput. Biol. **4**, e1000222 (2008). https://doi.org/10.1371/journal.pcbi.1000222
5. Baumketner, A., Jewett, A., Shea, J.E.: Effects of confinement in chaperonin assisted protein folding: rate enhancement by decreasing the roughness of the folding energy landscape. J. Mol. Biol. **332**, 701–713 (2003). https://doi.org/10.1016/S0022-2836(03)00929-X
6. Baumketner, A., Shea, J.E.: The structure of the Alzheimer amyloid beta 10–35 peptide probed through replica-exchange molecular dynamics simulations in explicit solvent. J. Mol. Biol. **366**, 275–285 (2007)
7. Bell, G.I.: Models for the specific adhesion of cells to cells. Science **200**, 618–627 (1978)
8. Bernetti, M., Cavalli, A., Mollica, L.: Protein-ligand (un)binding kinetics as a new paradigm for drug discovery at the crossroad between experiments and modelling. Medchemcomm **8**, 534–550 (2017). https://doi.org/10.1039/c6md00581k
9. Best, R.B., Hummer, G.: Protein folding kinetics under force from molecular simulation. J. Am. Chem. Soc. **130**, 3706–3707 (2008). https://doi.org/10.1021/ja0762691
10. Best, R.B., Paci, E., Hummer, G., Dudko, O.K.: Pulling direction as a reaction coordinate for the mechanical unfolding of single molecules. J. Phys. Chem. B **112**, 5968–5976 (2008). https://doi.org/10.1021/Jp075955j
11. Betancourt, M.R., Thirumalai, D.: Exploring the kinetic requirements for enhancement of protein folding rates in the GroEL cavity. J. Mol. Biol. **287**, 627–644 (1999). https://doi.org/10.1006/jmbi.1999.2591
12. Bindschadler, M.: Modeling actin dynamics. Wiley Interdisciplinary Rev. Syst. Biol. Med. **2**, 481–488 (2010). https://doi.org/10.1002/wsbm.62
13. Brockwell, D.J., et al.: Pulling geometry defines the mechanical resistance of a beta-sheet protein (vol 10, pg 731, 2003). Nat. Struct. Biol. **10**, 872–872 (2003). https://doi.org/10.1038/nsb1003-872b
14. Bustamante, C., Chemla, Y.R., Forde, N.R., Izhaky, D.: Mechanical processes in biochemistry. Annu. Rev. Biochem. **73**, 705–748 (2004). https://doi.org/10.1146/annurev.biochem.72.121801.161542
15. Caraglio, M., Imparato, A., Pelizzola, A.: Pathways of mechanical unfolding of FnIII(10): low force intermediates. J. Chem. Phys. **133**, 065101 (2010). https://doi.org/10.1063/1.3464476
16. Carrion-Vazquez, M., Li, H., Lu, H., Marszalek, P.E., Oberhauser, A.F., Fernandez, J.M.: The mechanical stability of ubiquitin is linkage dependent. Nat. struct. Biol. **10**, 738–743 (2003). https://doi.org/10.1038/nsb965
17. Chan, H.S., Zhang, Z., Wallin, S., Liu, Z.: Cooperativity, local-nonlocal coupling, and nonnative interactions: principles of protein folding from coarse-grained models. Annu. Rev. Phys. Chem. **62**, 301–326 (2011). https://doi.org/10.1146/annurev-physchem-032210-103405

18. Chang, S., Hu, J.P., Lin, P.Y., Jiao, X., Tian, X.H.: Substrate recognition and transport behavior analyses of amino acid antiporter with coarse-grained models. Mol. BioSyst. **6**, 2430–2438 (2010). https://doi.org/10.1039/c005266c
19. Chetwynd, A.P., Scott, K.A., Mokrab, Y., Sansom, M.S.: CGDB: a database of membrane protein/lipid interactions by coarse-grained molecular dynamics simulations. Mol. Membr. Biol. **25**, 662–669 (2008). https://doi.org/10.1080/09687680802446534
20. Chiricotto, M., Tran, T.T., Nguyen, P.H., Melchionna, S., Sterpone, F., Derreumaux, P.: Coarse-grained and all-atom simulations towards the early and late steps of amyloid fibril formation. Isr. J. Chem. **57**, 564–573 (2017)
21. Chu, J.W., Voth, G.A.: Coarse-grained modeling of the actin filament derived from atomistic-scale simulations. Biophys. J. **90**, 1572–1582 (2006). https://doi.org/10.1529/biophysj.105.073924
22. Ciemny, M.P., Kurcinski, M., Kamel, K., Kolinski, A., Nawsad, A., Schueler-Furman, O., Kmiecik, S.: Protein–peptide docking: opportunities and challenges. Drug Discov. Today. **23**, 1530–1537 (2018)
23. Ciemny, M.P., Debinski, A., Paczkowska, M., Kolinski, A., Kurcinski, M., Kmiecik, S.: Protein-peptide molecular docking with large-scale conformational changes: the p 53-MDM2 interaction. Sci. Rep. **6**, 37532 (2016). https://doi.org/10.1038/srep37532
24. Cieplak, M., Hoang, T.X., Robbins, M.O.: Folding and stretching in a go-like model of titin. Proteins **49**, 114–124 (2002). https://doi.org/10.1002/prot.10087
25. Clementi, C., Nymeyer, H., Onuchic, J.N.: Topological and energetic factors: what determines the structural details of the transition state ensemble and "en-route" intermediates for protein folding? An investigation for small globular proteins. J. Mol. Biol. **298**, 937–953 (2000). https://doi.org/10.1006/jmbi.2000.3693
26. Colizzi, F., Perozzo, R., Scapozza, L., Recanatini, M., Cavalli, A.: Single-molecule pulling simulations can discern active from inactive enzyme inhibitors. J. Am. Chem. Soc. **132**, 7361–7371 (2010). https://doi.org/10.1021/ja100259r
27. De Sancho, D., Best, R.B.: Modulation of an IDP binding mechanism and rates by helix propensity and non-native interactions: association of HIF1alpha with CBP. Mol. BioSyst. **8**, 256–267 (2012). https://doi.org/10.1039/c1mb05252g
28. Di Fenza, A., Rocchia, W., Tozzini, V.: Complexes of HIV-1 integrase with HAT proteins: multiscale models, dynamics, and hypotheses on allosteric sites of inhibition. Proteins: Struct. Funct. Bioinf. **76**, 946–958 (2009). https://doi.org/10.1002/prot.22399
29. Dudko, O.K., Hummer, G., Szabo, A.: Intrinsic rates and activation free energies from single-molecule pulling experiments. Phys. Rev. Lett. **96**, 108101 (2006). https://doi.org/10.1103/PhysRevLett.96.108101
30. Eliezer, D.: Biophysical characterization of intrinsically disordered proteins. Curr. Opin. Struct. Biol. **19**, 23–30 (2009). https://doi.org/10.1016/j.sbi.2008.12.004
31. Evans, E., Ritchie, K.: Dynamic strength of molecular adhesion bonds. Biophys. J. **72**, 1541–1555 (1997). https://doi.org/10.1016/S0006-3495(97)78802-7
32. Fernandez, J.M., Li, H.B.: Force-clamp spectroscopy monitors the folding trajectory of a single protein. Science **303**, 1674–1678 (2004). https://doi.org/10.1126/science.1092497
33. Fletcher, D.A., Mullins, R.D.: Cell mechanics and the cytoskeleton. Nature **463**, 485–492 (2010). https://doi.org/10.1038/nature08908
34. Florin, E.L., Moy, V.T., Gaub, H.E.: Adhesion forces between individual ligand-receptor pairs. Science **264**, 415–417 (1994). https://doi.org/10.1126/science.8153628
35. Fowler, S.B., et al.: Mechanical unfolding of a titin Ig domain: structure of unfolding intermediate revealed by combining AFM, molecular dynamics simulations, NMR and protein engineering. J. Mol. Biol. **322**, 841–849 (2002). https://doi.org/10.1016/S0022-2836(02)00805-7
36. Frembgen-Kesner, T., Elcock, A.H.: Absolute protein-protein association rate constants from flexible, coarse-grained brownian dynamics simulations: the role of intermolecular hydrodynamic interactions in Barnase-Barstar association. Biophys. J. **99**, L75–L77 (2010). https://doi.org/10.1016/j.bpj.2010.09.006

37. Granzier, H.L., Labeit, S.: The giant protein titin: a major player in myocardial mechanics, signaling, and disease. Circ. Res. **94**, 284–295 (2004). https://doi.org/10.1161/01.res.0000117769.88862.f8
38. Grubmuller, H., Heymann, B., Tavan, P.: Ligand binding: Molecular mechanics calculation of the streptavidin biotin rupture force. Science **271**, 997–999 (1996). https://doi.org/10.1126/science.271.5251.997
39. Gu, J.F., Li, H.X., Wang, X.C.: A self-adaptive steered molecular dynamics method based on minimization of stretching force reveals the binding affinity of protein-ligand complexes. Molecules **20**, 19236–19251 (2015). https://doi.org/10.3390/molecules201019236
40. Habchi, J., Tompa, P., Longhi, S., Uversky, V.N.: Introducing protein intrinsic disorder. Chem. Rev. **114**, 6561–6588 (2014). https://doi.org/10.1021/cr400514h
41. Habibi, M., Rottler, J., Plotkin, S.S.: As simple as possible but not simpler: on the reliability of protein coarse-grained models. Biophys. J. **112**, 176a–176a (2017)
42. Hall, B.A., Chetwynd, A.P., Sansom, M.S.: Exploring peptide-membrane interactions with coarse-grained MD simulations. Biophys. J. **100**, 1940–1948 (2011). https://doi.org/10.1016/j.bpj.2011.02.041
43. Hall, B.A., Sansom, M.S.P.: Coarse-grained MD simulations and protein–protein interactions: the Cohesin–Dockerin system. J. Chem. Theory Comput. **5**, 2465–2471 (2009). https://doi.org/10.1021/ct900140w
44. Hanson, P.I., Whiteheart, S.W.: AAA + proteins: have engine, will work. Nat. Rev. Mol. Cell Biol. **6**, 519–529 (2005). https://doi.org/10.1038/nrm1684
45. He, C., Genchev, G.Z., Lu, H., Li, H.: Mechanically untying a protein slipknot: multiple pathways revealed by force spectroscopy and steered molecular dynamics simulations. J. Am. Chem. Soc. **134**, 10428–10435 (2012). https://doi.org/10.1021/ja3003205
46. Heath, A.P., Kavraki, L.E., Clementi, C.: From coarse-grain to all-atom: toward multiscale analysis of protein landscapes. Proteins **68**, 646–661 (2007). https://doi.org/10.1002/prot.21371
47. Huang, Y., Liu, Z.: Kinetic advantage of intrinsically disordered proteins in coupled folding-binding process: a critical assessment of the "Fly-Casting" mechanism. J. Mol. Biol. **393**, 1143–1159 (2009). https://doi.org/10.1016/j.jmb.2009.09.010
48. Hunte, C.: Specific protein-lipid interactions in membrane proteins. Biochem. Soc. Trans. **33**, 938–942 (2005). https://doi.org/10.1042/BST20050938
49. Irback, A., Mitternacht, S., Mohanty, S.: Dissecting the mechanical unfolding of ubiquitin. Proc Natl Acad Sci U S A **102**, 13427–13432 (2005). https://doi.org/10.1073/pnas.0501581102
50. Jacob, E., Horovitz, A., Unger, R.: Different mechanistic requirements for prokaryotic and eukaryotic chaperonins: a lattice study. Bioinformatics **23**, i240–i248 (2007). https://doi.org/10.1093/bioinformatics/btm180
51. Jamroz, M., Kolinski, A., Kmiecik, S.: CABS-flex: server for fast simulation of protein structure fluctuations. Nucleic Acids Res. **41**, W427–W431 (2013). https://doi.org/10.1093/nar/gkt332
52. Jamroz, M., Kolinski, A., Kmiecik, S.: CABS-flex predictions of protein flexibility compared with NMR ensembles. Bioinformatics **30**, 2150–2154 (2014). https://doi.org/10.1093/bioinformatics/btu184
53. Jamroz, M., Orozco, M., Kolinski, A., Kmiecik, S.: Consistent view of protein fluctuations from all-atom molecular dynamics and coarse-grained dynamics with knowledge-based force-field. J. Chem. Theor. Comput. **9**, 119–125 (2013). https://doi.org/10.1021/ct300854w
54. Jewett, A.I., Baumketner, A., Shea, J.E.: Accelerated folding in the weak hydrophobic environment of a chaperonin cavity: creation of an alternate fast folding pathway. Proc Natl Acad Sci U S A **101**, 13192–13197 (2004). https://doi.org/10.1073/pnas.0400720101
55. Jewett, A.I., Shea, J.E.: Reconciling theories of chaperonin accelerated folding with experimental evidence. Cell. Mol. Life Sci. **67**, 255–276 (2009)

56. Jung, J., Mori, T., Kobayashi, C., Matsunaga, Y., Yoda, T., Feig, M., Sugita, Y.: GENESIS: a hybrid-parallel and multi-scale molecular dynamics simulator with enhanced sampling algorithms for biomolecular and cellular simulations. Wiley Interdisciplinary Rev. Comput. Mol. Sci. **5**, 310–323 (2015). https://doi.org/10.1002/wcms.1220
57. Kalli, A.C., Hall, B.A., Campbell, I.D., Sansom, M.S.: A helix heterodimer in a lipid bilayer: prediction of the structure of an integrin transmembrane domain via multiscale simulations. Structure **19**, 1477–1484 (2011). https://doi.org/10.1016/j.str.2011.07.014
58. Kamerlin, S.C., Vicatos, S., Dryga, A., Warshel, A.: Coarse-grained (multiscale) simulations in studies of biophysical and chemical systems. Annu. Rev. Phys. Chem. **62**, 41–64 (2011). https://doi.org/10.1146/annurev-physchem-032210-103335
59. Kar, P., Gopal, S.M., Cheng, Y.M., Panahi, A., Feig, M.: Transferring the PRIMO coarse-grained force field to the membrane environment: simulations of membrane proteins and helix-helix association. J. Chem. Theor. Comput. **10**, 3459–3472 (2014). https://doi.org/10.1021/ct500443v
60. Kim, Y.C., Hummer, G.: Coarse-grained models for simulations of multiprotein complexes: application to ubiquitin binding. J. Mol. Biol. **375**, 1416–1433 (2008). https://doi.org/10.1016/j.jmb.2007.11.063
61. Kim, B.L., Schafer, N.P., Wolynes, P.G.: Predictive energy landscapes for folding alpha-helical transmembrane proteins. Proc. Natl. Acad. Sci. U S A **111**, 11031–11036 (2014). https://doi.org/10.1073/pnas.1410529111. 1410529111 [pii]
62. Kim, Y.C., Tang, C., Clore, G.M., Hummer, G.: Replica exchange simulations of transient encounter complexes in protein-protein association. Proc. Natl. Acad. Sci. U S A **105**, 12855–12860 (2008). https://doi.org/10.1073/pnas.0802460105
63. Kmiecik, S., Gront, D., Kolinski, A.: Towards the high-resolution protein structure prediction. Fast refinement of reduced models with all-atom force field. BMC Struct. Biol. **7**, 43 (2007). https://doi.org/10.1186/1472-6807-7-43
64. Kmiecik, S., Gront, D., Kolinski, M., Wieteska, L., Dawid, A.E., Kolinski, A.: Coarse-grained protein models and their applications. Chem. Rev. **116**, 7898–7936 (2016). https://doi.org/10.1021/acs.chemrev.6b00163
65. Kmiecik, S., Gront, D., Kouza, M., Kolinski, A.: From coarse-grained to atomic-level characterization of protein dynamics: transition state for the folding of B domain of protein A. J. Phys. Chem. B **116**, 7026–7032 (2012). https://doi.org/10.1021/jp301720w
66. Kmiecik, S., Kolinski, A.: Folding pathway of the b1 domain of protein G explored by multiscale modeling. Biophys. J. **94**, 726–736 (2008). https://doi.org/10.1529/biophysj.107.116095
67. Kmiecik, S., Kolinski, A.: Simulation of chaperonin effect on protein folding: a shift from nucleation-condensation to framework mechanism. J. Am. Chem. Soc. **133**, 10283–10289 (2011). https://doi.org/10.1021/ja203275f
68. Kmiecik, S., Jamroz, M., Kolinski, A.: Multiscale approach to protein folding dynamics. In: Kolinski, A. (ed.) Multiscale Approaches to Protein Modeling, pp. 281–293. Springer, New York (2011). https://doi.org/10.1007/978-1-4419-6889-0_12
69. Knepp, A.M., Periole, X., Marrink, S.J., Sakmar, T.P., Huber, T.: Rhodopsin forms a dimer with cytoplasmic helix 8 contacts in native membranes. Biochemistry **51**, 1819–1821 (2012). https://doi.org/10.1021/bi3001598
70. Koga, N., Takada, S.: Folding-based molecular simulations reveal mechanisms of the rotary motor F1-ATPase. Proc. Natl. Acad. Sci. U S A **103**, 5367–5372 (2006). https://doi.org/10.1073/pnas.0509642103
71. Kolinski, A., Skolnick, J.: Reduced models of proteins and their applications. Polymer **45**, 511–524 (2004). https://doi.org/10.1016/j.polymer.2003.10.064
72. Kolinski, A.: Protein modeling and structure prediction with a reduced representation. Acta Biochim. Pol. **51**, 349–371 (2004). doi: 035001349
73. Kouza, M., Banerji, A., Kolinski, A., Buhimschi, I.A., Kloczkowski, A.: Oligomerization of FVFLM peptides and their ability to inhibit beta amyloid peptides aggregation: consideration as a possible model. Phys. Chem. Chem. Phys. **19**, 2990–2999 (2017)

74. Kouza, M., Banerji, A., Kolinski, A., Buhimschi, I.A., Kloczkowski, A.: Role of Resultant Dipole Moment in Mechanical Dissociation of Biological Complexes. Molecules **23**, 1995 (2018)
75. Kouza, M., Co, N.T., Li, M.S., Kmiecik, S., Kolinski, A., Kloczkowski, A., Buhimschi, I.A.: Kinetics and mechanical stability of the fibril state control fibril formation time of polypeptide chains: A computational study. J. Chem. Phys. **148**, 215106 (2018)
76. Kouza, M., Hu, C.K., Li, M.S.: New force replica exchange method and protein folding pathways probed by force-clamp technique. J. Chem. Phys. **128**, 045103 (2008). https://doi.org/10.1063/1.2822272
77. Kouza, M., Hu, C.K., Zung, H., Li, M.S.: Protein mechanical unfolding: importance of non-native interactions. J. Chem. Phys. **131**, 215103 (2009). https://doi.org/10.1063/1.3272275
78. Kouza, M., Jamroz, M., Gront, D., Kmiecik, S., Kolinski, A.: Mechanical unfolding of DDFLN4 studied by coarse-grained knowledge-based CABS model. TASK Quaterly **18**, 373–378 (2014)
79. Kouza, M., Co, N.T., Nguyen, P.H., Kolinski, A., Li, M.S.: Preformed template fluctuations promote fibril formation: Insights from lattice and all-atom models. J. Chem. Phys. **142** (2015). doi: Artn 145104. https://doi.org/10.1063/1.4917073
80. Kouza, M., Lan, P.D., Gabovich, A.M., Kolinski, A., Li, M.S.: Switch from thermal to force-driven pathways of protein refolding. J. Chem. Phys. **146** (2017b). doi: Artn 135101. https://doi.org/10.1063/1.4979201
81. Kramers, H.A.: Brownian motion in a field of force and the diffusion model of chemical reactions. Physica **7**(7), 284–303 (1940). https://doi.org/10.1016/S0031-8914(40)90098-2
82. Kubelka, J., Hofrichter, J., Eaton, W.A.: The protein folding 'speed limit'. Curr. Opin. Struct. Biol. **14**, 76–88 (2004)
83. Kumar, S., Li, M.S.: Biomolecules under mechanical force. Phys. Rep.-Rev. Sect. Phys. Lett. **486**, 1–74 (2010). https://doi.org/10.1016/j.physrep.2009.11.001
84. Kurcinski, M., Kolinski, A.: Theoretical study of molecular mechanism of binding TRAP220 coactivator to Retinoid X Receptor alpha, activated by 9-cis retinoic acid. J. Steroid Biochem. Mol. Biol. **121**, 124–129 (2010). https://doi.org/10.1016/j.jsbmb.2010.03.086
85. Kurcinski, M., Kolinski, A., Kmiecik, S.: Mechanism of folding and binding of an intrinsically disordered protein as revealed by ab initio simulations. J. Chem. Theor. Comput. **10**, 2224–2231 (2014). https://doi.org/10.1021/ct500287c
86. Kurcinski, M., Oleniecki, T., Ciemny, M.P., Kuriata, A., Kolinski, A., Kmiecik, S. CABS-flex standalone: a simulation environment for fast modeling of protein flexibility. Bioinformatics, bty685 (2018).
87. Kuriata, A., Gierut A.M., Oleniecki, T., Ciemny, M.P., Kolinski, A., Kurcinski, M., Kmiecik, S. CABS-flex 2.0: a web server for fast simulations of flexibility of protein structures. Nucl. Acids Res. W1: W338–W343 (2018).
88. Lau, T.L., Kim, C., Ginsberg, M.H., Ulmer, T.S.: The structure of the integrin alphaIIb-beta3 transmembrane complex explains integrin transmembrane signalling. EMBO J. **28**, 1351–1361 (2009). https://doi.org/10.1038/emboj.2009.63
89. Lee, A.G.: How lipids affect the activities of integral membrane proteins. BBA-Biomembr. **1666**, 62–87 (2004). https://doi.org/10.1016/j.bbamem.2004.05.012
90. Lee, E.H., Hsin, J., Sotomayor, M., Comellas, G., Schulten, K.: Discovery through the computational microscope. Structure **17**, 1295–1306 (2009). https://doi.org/10.1016/j.str.2009.09.001
91. Levitt, M., Warshel, A.: Computer simulation of protein folding. Nature **253**, 694–698 (1975). https://doi.org/10.1038/253694a0
92. Li, M.S.: Secondary structure, mechanical stability, and location of transition state of proteins. Biophys. J. **93**, 2644–2654 (2007). https://doi.org/10.1529/biophysj.107.106138
93. Li, L., Huang, H.H., Badilla, C.L., Fernandez, J.M.: Mechanical unfolding intermediates observed by single-molecule force spectroscopy in a fibronectin type III module. J. Mol. Biol. **345**, 817–826 (2005). https://doi.org/10.1016/j.jmb.2004.11.021

94. Li, M.S., Kouza, M.: Dependence of protein mechanical unfolding pathways on pulling speeds. J. Chem. Phys. **130**, 145102 (2009). https://doi.org/10.1063/1.3106761
95. Li, M.S., Kouza, M., Hu, C.K.: Refolding upon force quench and pathways of mechanical and thermal unfolding of ubiquitin. Biophys. J. **92**, 547–561 (2007). https://doi.org/10.1529/biophysj.106.087684
96. Li, M.S., Mai, B.K.: Steered molecular dynamics-a promising tool for drug design. Curr. Bioinform. **7**, 342–351 (2012)
97. Lichter, S., Rafferty, B., Flohr, Z., Martini, A.: Protein high-force pulling simulations yield low-force results. PLoS ONE **7**, e34781 (2012). https://doi.org/10.1371/journal.pone.0034781
98. Liphardt, J., Onoa, B., Smith, S.B., Tinoco Jr., I., Bustamante, C.: Reversible unfolding of single RNA molecules by mechanical force. Science **292**, 733–737 (2001). https://doi.org/10.1126/science.1058498
99. Liu, X., Shi, D., Zhou, S., Liu, H., Yao, X.: Molecular dynamics simulations and novel drug discovery. Expert Opin. Drug Discov. **13**, 23–37 (2018). https://doi.org/10.1080/17460441.2018.1403419
100. Lu, H., Isralewitz, B., Krammer, A., Vogel, V., Schulten, K.: Unfolding of titin immunoglobulin domains by steered molecular dynamics simulation. Biophys. J. **75**, 662–671 (1998)
101. Lu, H., Schulten, K.: The key event in force-induced unfolding of Titin's immunoglobulin domains. Biophys. J. **79**, 51–65 (2000). https://doi.org/10.1016/S0006-3495(00)76273-4
102. Lucent, D., England, J., Pande, V.: Inside the chaperonin toolbox: theoretical and computational models for chaperonin mechanism. Phys. Biol. **6**, 015003 (2009). https://doi.org/10.1088/1478-3975/6/1/015003
103. Malolepsza, E., Boniecki, M., Kolinski, A., Piela, L.: Theoretical model of prion propagation: a misfolded protein induces misfolding. Proc. Natl. Acad. Sci. USA **102**, 7835–7840 (2005)
104. Marrink, S.J., Tieleman, D.P.: Perspective on the Martini model. Chem. Soc. Rev. **42**, 6801–6822 (2013). https://doi.org/10.1039/c3cs60093a
105. Marszalek, P.E., Lu, H., Li, H., Carrion-Vazquez, M., Oberhauser, A.F., Schulten, K., Fernandez, J.M.: Mechanical unfolding intermediates in titin modules. Nature **402**, 100–103 (1999). https://doi.org/10.1038/47083
106. Mittag, T., Kay, L.E., Forman-Kay, J.D.: Protein dynamics and conformational disorder in molecular recognition. J. Mol. Recognit. **23**, 105–116 (2010). https://doi.org/10.1002/jmr.961
107. Morriss-Andrews, A., Shea, J.E.: Simulations of protein aggregation: insights from atomistic and coarse-grained models. J. Phys. Chem. Lett. **5**, 1899–1908 (2014). https://doi.org/10.1021/jz5006847
108. Morriss-Andrews, A., Shea, J.E.: Computational studies of protein aggregation: methods and applications. Annu. Rev. Phys. Chem. **66**, 643–666 (2015). https://doi.org/10.1146/annurev-physchem-040513-103738
109. Munoz, V., Henry, E.R., Hofrichter, J., Eaton, W.A.: A statistical mechanical model for beta-hairpin kinetics. Proc. Natl. Acad. Sci. U S A **95**, 5872–5879 (1998). https://doi.org/10.1073/pnas.95.11.5872
110. Nasica-Labouze, J., et al.: Amyloid beta protein and Alzheimer's Disease: when computer simulations complement experimental studies. Chem. Rev. **115**, 3518–3563 (2015)
111. Nguyen, P.H., Li, M.S., Stock, G., Straub, J.E., Thirumalai, D.: Monomer adds to preformed structured oligomers of A beta-peptides by a two-stage dock-lock mechanism. Proc. Natl. Acad. Sci. U.S.A. **104**, 111–116 (2007). https://doi.org/10.1073/Pnas.0607440104
112. Nilsson, J., Persson, B., von Heijne, G.: Comparative analysis of amino acid distributions in integral membrane proteins from 107 genomes. Proteins **60**, 606–616 (2005). https://doi.org/10.1002/prot.20583
113. Norgaard, A.B., Ferkinghoff-Borg, J., Lindorff-Larsen, K.: Experimental parameterization of an energy function for the simulation of unfolded proteins. Biophys. J. **94**, 182–192 (2008). https://doi.org/10.1529/biophysj.107.108241
114. Okazaki, K.-I., Sato, T., Takano, M.: Temperature-enhanced association of proteins due to electrostatic interaction: a coarse-grained simulation of Actin-Myosin binding. J. Am. Chem. Soc. **134**, 8918–8925 (2012). https://doi.org/10.1021/ja301447j

115. Paci, E., Karplus, M.: Unfolding proteins by external forces and temperature: the importance of topology and energetics. Proc. Natl. Acad. Sci. U S A **97**, 6521–6526 (2000). https://doi.org/10.1073/pnas.100124597
116. Peplowski, L., Sikora, M., Nowak, W., Cieplak, M.: Molecular jamming–the cystine slipknot mechanical clamp in all-atom simulations. J. Chem. Phys. **134**, 085102 (2011). https://doi.org/10.1063/1.3553801
117. Perilla, J.R., et al.: Molecular dynamics simulations of large macromolecular complexes. Curr. Opin. Struct. Biol. **31**, 64–74 (2015). https://doi.org/10.1016/j.sbi.2015.03.007
118. Periole, X., Knepp, A.M., Sakmar, T.P., Marrink, S.J., Huber, T.: Structural determinants of the supramolecular organization of G protein-coupled receptors in bilayers. J. Am. Chem. Soc. **134**, 10959–10965 (2012). https://doi.org/10.1021/ja303286e
119. Plaxco, K.W., Simons, K.T., Baker, D.: Contact order, transition state placement and the refolding rates of single domain proteins. J. Mol. Biol. **277**, 985–994 (1998). https://doi.org/10.1006/jmbi.1998.1645
120. Pulawski, W., Jamroz, M., Kolinski, M., Kolinski, A., Kmiecik, S.: Coarse-Grained simulations of membrane insertion and folding of small helical proteins using the CABS model. J. Chem. Inf. Model. **56**, 2207–2215 (2016). https://doi.org/10.1021/acs.jcim.6b00350
121. Rathore, N., Knotts, T.A.T., de Pablo, J.J.: Confinement effects on the thermodynamics of protein folding: Monte Carlo simulations. Biophys. J. **90**, 1767–1773 (2006). https://doi.org/10.1529/biophysj.105.071076
122. Rauscher, S., Gapsys, V., Gajda, M.J., Zweckstetter, M., de Groot, B.L., Grubmuller, H.: Structural ensembles of intrinsically disordered proteins depend strongly on force field: a comparison to experiment. J. Chem. Theor. Comput. **11**, 5513–5524 (2015). https://doi.org/10.1021/acs.jctc.5b00736
123. Rauscher, S., Pomès, R.: Molecular simulations of protein disorder. This paper is one of a selection of papers published in this special issue entitled "Canadian Society of Biochemistry, Molecular & Cellular Biology 52nd Annual Meeting—Protein Folding: Principles and Diseases" and has undergone the Journal's usual peer review process. Biochem. Cell Biol. **88**, 269–290 (2010). https://doi.org/10.1139/o09-169
124. Rief, M., Gautel, M., Oesterhelt, F., Fernandez, J.M., Gaub, H.E.: Reversible unfolding of individual titin immunoglobulin domains by AFM. Science **276**, 1109–1112 (1997). https://doi.org/10.1126/science.276.5315.1109
125. Rojas, A., Liwo, A., Browne, D., Scheraga, H.A.: Mechanism of fiber assembly: treatment of a beta peptide aggregation with a coarse-grained united-residue force field. J. Mol. Biol. **404**, 537–552 (2010)
126. Ruprecht, J.J., Mielke, T., Vogel, R., Villa, C., Schertler, G.F.: Electron crystallography reveals the structure of metarhodopsin I. EMBO J. **23**, 3609–3620 (2004). https://doi.org/10.1038/sj.emboj.7600374
127. Russel, D., Lasker, K., Phillips, J., Schneidman-Duhovny, D., Velazquez-Muriel, J.A., Sali, A.: The structural dynamics of macromolecular processes. Curr. Opin. Cell Biol. **21**, 97–108 (2009). https://doi.org/10.1016/j.ceb.2009.01.022
128. Rydzewski, J., Nowak, W.: Ligand diffusion in proteins via enhanced sampling in molecular dynamics. Phys. Life Rev. (2017). https://doi.org/10.1016/j.plrev.2017.03.003
129. Sansom, M.S., Scott, K.A., Bond, P.J.: Coarse-grained simulation: a high-throughput computational approach to membrane proteins. Biochem. Soc. Trans. **36**, 27–32 (2008). https://doi.org/10.1042/BST0360027
130. Saunders, M.G., Voth, G.A.: Coarse-graining of multiprotein assemblies. Curr. Opin. Struct. Biol. **22**, 144–150 (2012). https://doi.org/10.1016/j.sbi.2012.01.003
131. Schafer, K., Oestereich, M., Gauss, J., Diezemann, G.: Force probe simulations using a hybrid scheme with virtual sites. J. Chem. Phys. **147** (2017)
132. Scheraga, H.A., Khalili, M., Liwo, A.: Protein-folding dynamics: overview of molecular simulation techniques. Annu. Rev. Phys. Chem. **58**, 57–83 (2007). https://doi.org/10.1146/annurev.physchem.58.032806.104614

133. Schlick, T., Collepardo-Guevara, R., Halvorsen, L.A., Jung, S., Xiao, X.: Biomolecularmodeling and simulation: a field coming of age. Q. Rev. Biophys. **44**, 191–228 (2011). https://doi.org/10.1017/S0033583510000284
134. Schwaiger, I., Kardinal, A., Schleicher, M., Noegel, A.A., Rief, M.: A mechanical unfolding intermediate in an actin-crosslinking protein. Nat. Struct. Mol. Biol. **11**, 81–85 (2004)
135. Schwaiger, I., Kardinal, A., Schleicher, M., Noegel, A.A., Rief, M.: A mechanical unfolding intermediate in an actin-crosslinking protein. Nat. Struct. Mol. Biol. **11**, 81–85 (2004). https://doi.org/10.1038/nsmb705
136. Scott, K.A., Bond, P.J., Ivetac, A., Chetwynd, A.P., Khalid, S., Sansom, M.S.: Coarse-grained MD simulations of membrane protein-bilayer self-assembly. Structure **16**, 621–630 (2008). https://doi.org/10.1016/j.str.2008.01.014
137. Sen, T.Z., Kloster, M., Jernigan, R.L., Kolinski, A., Bujnicki, J.M., Kloczkowski, A.: Predicting the complex structure and functional motions of the outer membrane transporter and signal transducer FecA. Biophys. J. **94**, 2482–2491 (2008). https://doi.org/10.1529/biophysj.107.116046
138. Sengupta, D., Marrink, S.J.: Lipid-mediated interactions tune the association of glycophorin A helix and its disruptive mutants in membranes. Phys. Chem. Chem. Phys. **12**, 12987–12996 (2010). https://doi.org/10.1039/c0cp00101e
139. Serohijos, A.W., Chen, Y., Ding, F., Elston, T.C., Dokholyan, N.V.: A structural model reveals energy transduction in dynein. Proc. Natl. Acad. Sci. U S A **103**, 18540–18545 (2006). https://doi.org/10.1073/pnas.0602867103
140. Shoemaker, B.A., Portman, J.J., Wolynes, P.G.: Speeding molecular recognition by using the folding funnel: the fly-casting mechanism. Proc. Natl. Acad. Sci. **97**, 8868–8873 (2000). https://doi.org/10.1073/pnas.160259697
141. Sieben, C., et al.: Influenza virus binds its host cell using multiple dynamic interactions. Proc. Natl. Acad. Sci. U S A **109**, 13626–13631 (2012). https://doi.org/10.1073/pnas.1120265109
142. Sieradzan, A.K., Jakubowski, R.: Introduction of steered molecular dynamics into UNRES coarse-grained simulations package. J. Comput. Chem. **38**, 553–562 (2017)
143. Sikora, M., Cieplak, M.: Mechanical stability of multidomain proteins and novel mechanical clamps. Proteins **79**, 1786–1799 (2011). https://doi.org/10.1002/prot.23001
144. Sikora, M., Sulkowska, J.I., Witkowski, B.S., Cieplak, M.: BSDB: the biomolecule stretching database. Nucleic Acids Res. **39**, D443–D450 (2011). https://doi.org/10.1093/nar/gkq851
145. Simmons, R.M., Finer, J.T., Chu, S., Spudich, J.A.: Quantitative measurements of force and displacement using an optical trap. Biophys. J. **70**, 1813–1822 (1996). https://doi.org/10.1016/S0006-3495(96)79746-1
146. Smith, S.O., et al.: Implications of threonine hydrogen bonding in the glycophorin A transmembrane helix dimer. Biophys. J. **82**, 2476–2486 (2002). https://doi.org/10.1016/S0006-3495(02)75590-2
147. Smith, S.B., Cui, Y., Bustamante, C.: Overstretching B-DNA: the elastic response of individual double-stranded and single-stranded DNA molecules. Science **271**, 795–799 (1996). https://doi.org/10.1126/science.271.5250.795
148. Spijker, P., van Hoof, B., Debertrand, M., Markvoort, A.J., Vaidehi, N., Hilbers, P.A.: Coarse grained molecular dynamics simulations of transmembrane protein-lipid systems. Int. J. Mol. Sci. **11**, 2393–2420 (2010). https://doi.org/10.3390/ijms11062393
149. Stossel, T.P., Condeelis, J., Cooley, L., Hartwig, J.H., Noegel, A., Schleicher, M., Shapiro, S.S.: Filamins as integrators of cell mechanics and signalling. Nat. Rev. Mol. Cell Biol. **2**, 138–145 (2001). https://doi.org/10.1038/35052082
150. Sulkowska, J.I., Sulkowski, P., Onuchic, J.N.: Jamming proteins with slipknots and their free energy landscape. Phys. Rev. Lett. **103**, 268103 (2009). https://doi.org/10.1103/PhysRevLett.103.268103
151. Sulkowska, J.I., Sulkowski, P., Szymczak, P., Cieplak, M.: Untying knots in proteins. J. Am. Chem. Soc. **132**, 13954–13956 (2010). https://doi.org/10.1021/Ja102441z
152. Sulkowska, J.I., Cieplak, M.: Mechanical stretching of proteins - a theoretical survey of the protein data bank. J. Phys.-Condens. Mat. **19** (2007). https://doi.org/10.1088/0953-8984/19/28/283201

153. Szilagyi, A., Gyorffy, D., Zavodszky, P.: The twilight zone between protein order and disorder. Biophys. J. **95**, 1612–1626 (2008). https://doi.org/10.1529/biophysj.108.131151
154. Szymczak, P., Janovjak, H.: Periodic forces trigger a complex mechanical response in ubiquitin. J. Mol. Biol. **390**, 443–456 (2009). https://doi.org/10.1016/j.jmb.2009.04.071
155. Takada, S.: Coarse-grained molecular simulations of large biomolecules. Curr. Opin. Struct. Biol. **22**, 130–137 (2012). https://doi.org/10.1016/j.sbi.2012.01.010
156. Takagi, F., Koga, N., Takada, S.: How protein thermodynamics and folding mechanisms are altered by the chaperonin cage: molecular simulations. Proc. Natl. Acad. Sci. U.S.A. **100**, 11367–11372 (2003). https://doi.org/10.1073/pnas.1831920100
157. Taylor, W.R., Katsimitsoulia, Z.: A coarse-grained molecular model for actin-myosin simulation. J. Mol. Graph. Model. **29**, 266–279 (2010). https://doi.org/10.1016/j.jmgm.2010.06.004
158. Thirumalai, D., Reddy, G., Straub, J.E.: Role of water in protein aggregation and amyloid polymorphism. Acc. Chem. Res. **45**, 83–92 (2012). https://doi.org/10.1021/ar2000869
159. Turjanski, A.G., Gutkind, J.S., Best, R.B., Hummer, G.: Binding-induced folding of a natively unstructured transcription factor. PLoS Comput. Biol. **4**, e1000060 (2008). https://doi.org/10.1371/journal.pcbi.1000060
160. Uversky, V.N.: Introduction to intrinsically disordered proteins (IDPs). Chem. Rev. **114**, 6557–6560 (2014). https://doi.org/10.1021/cr500288y
161. Uversky, V.N., Gillespie, J.R., Fink, A.L.: Why are "natively unfolded" proteins unstructured under physiologic conditions? Proteins: Struct. Funct. Bioinf. **41**, 415–427 (2000). https://doi.org/10.1002/1097-0134(20001115)41:3%3c415:aid-prot130%3e3.0.co;2-7
162. Vajda, S., Kozakov, D.: Convergence and combination of methods in protein-protein docking. Curr. Opin. Struct. Biol. **19**, 164–170 (2009). https://doi.org/10.1016/j.sbi.2009.02.008
163. Valbuena, A., et al.: On the remarkable mechanostability of scaffoldins and the mechanical clamp motif. Proc. Natl. Acad. Sci. U S A **106**, 13791–13796 (2009). https://doi.org/10.1073/pnas.0813093106
164. Vendruscolo, M., Dobson, C.M.: Protein dynamics: Moore's law in molecular biology. Curr. Biol. **21**, R68–R70 (2011). https://doi.org/10.1016/j.cub.2010.11.062
165. Verkhivker, G.M.: Protein conformational transitions coupled to binding in molecular recognition of unstructured proteins: Deciphering the effect of intermolecular interactions on computational structure prediction of the p27Kip1 protein bound to the cyclin A–cyclin-dependent kinase 2 complex. Proteins: Struct. Funct. Bioinf. **58**, 706–716 (2005). https://doi.org/10.1002/prot.20351
166. Verkhivker, G.M., Bouzida, D., Gehlhaar, D.K., Rejto, P.A., Freer, S.T., Rose, P.W.: Simulating disorder–order transitions in molecular recognition of unstructured proteins: where folding meets binding. Proc. Natl. Acad. Sci. **100**, 5148–5153 (2003). https://doi.org/10.1073/pnas.0531373100
167. Vogel, V., Sheetz, M.: Local force and geometry sensing regulate cell functions. Nat. Rev. Mol. Cell Biol. **7**, 265–275 (2006). https://doi.org/10.1038/nrm1890
168. Wang, Y.M., Latshaw, D.C., Hall, C.K.: Aggregation of A beta(17-36) in the presence of naturally occurring phenolic inhibitors using coarse-grained simulations. J. Mol. Biol. **429**, 3893–3908 (2017)
169. Wang, J., Wang, Y., Chu, X., Hagen, S.J., Han, W., Wang, E.: Multi-scaled explorations of binding-induced folding of intrinsically disordered protein inhibitor IA3 to its target enzyme. PLoS Comput. Biol. **7**, e1001118 (2011). https://doi.org/10.1371/journal.pcbi.1001118
170. West, D.K., Olmsted, P.D., Paci, E.: Mechanical unfolding revisited through a simple but realistic model. J. Chem. Phys. **124** (2006). https://doi.org/10.1063/1.2185100
171. Wolynes, P.G., Onuchic, J.N., Thirumalai, D.: Navigating the folding routes. Science **267**, 1619–1620 (1995). https://doi.org/10.1126/science.7886447
172. Wright, P.E., Dyson, H.J.: Intrinsically unstructured proteins: re-assessing the protein structure-function paradigm. J. Mol. Biol. **293**, 321–331 (1999). https://doi.org/10.1006/jmbi.1999.3110

173. Yao, X.Q., Kenzaki, H., Murakami, S., Takada, S.: Drug export and allosteric coupling in a multidrug transporter revealed by molecular simulations. Nat. Commun. **1**, 117 (2010). https://doi.org/10.1038/ncomms1116
174. Zacharias, M.: Accounting for conformational changes during protein-protein docking. Curr. Opin. Struct. Biol. **20**, 180–186 (2010). https://doi.org/10.1016/j.sbi.2010.02.001
175. Zhang, J., Muthukumar, M.: Simulations of nucleation and elongation of amyloid fibrils. J. Chem. Phys. **130**, 035102 (2009). https://doi.org/10.1063/1.3050295
176. Zhmurov, A., Dima, R.I., Kholodov, Y., Barsegov, V.: Sop-GPU: accelerating biomolecular simulations in the centisecond timescale using graphics processors. Proteins **78**, 2984–2999 (2010). https://doi.org/10.1002/prot.22824
177. Zhou, H.-X.: Polymer models of protein stability, folding, and interactions†. Biochemistry **43**, 2141–2154 (2004). https://doi.org/10.1021/bi036269n
178. Zhou, H.X., Dill, K.A.: Stabilization of proteins in confined spaces. Biochemistry **40**, 11289–11293 (2001). https://doi.org/10.3410/f.1002736.29765
179. Zhou, J., Thorpe, I.F., Izvekov, S., Voth, G.A.: Coarse-grained peptide modeling using a systematic multiscale approach. Biophys. J. **92**, 4289–4303 (2007). https://doi.org/10.1529/biophysj.106.094425