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Significance of Sub-pico-newton Forces on the Folding-Unfolding of TrpZip2 β-Hairpin

Significance of Sub-pico-newton Forces on the Folding-Unfolding of TrpZip2 β-Hairpin

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It is mandatory for proteins to attain a unique three-dimensional fold to perform their designated functions in living systems.[1] The folding mechanism of proteins is often affected by various factors, which include a significant contribution from the solvent environments and the subtle mechanical forces they impart. For example, the thermal motion of the solvent could easily impart tens of piconewtons of force on the protein.[2] Again, living cells are subjected to mechanical tensions owing to pressure gradients and mechanical translocations. These mechanical strain often causes perturbation to the protein structure, which enables them to perform various functions like transportation and enzymic activity. The structural aberrations caused by these forces can directly affect the folding-unfolding mechanism of the proteins inside the living systems. TrpZip2, a 12-residue model β-Hairpin protein, is schematized here to assess the folding-unfolding process under the influence of a mechanical bias.

The effect of forces on the protein folding-unfolding was studied using metadynamics simulation under no external force and a 30 pN external bias. 30 pN was chosen in such a way that the protein does experience a net effective force, yet preserving the morphology of TrpZip2. We found that in both null external force and 30 pN bias, TrpZip2 exhibited a zip-out mechanism for folding-unfolding, but the folding pathways in both scenarios were distinctive. The hairpin turn showed high stability in the presence and absence of external force, thereby initiating the folding process. Most importantly, the cause of the diverse behavior of TrpZip2 towards folding-unfolding was found to be the existence of wide conformations that can be achieved via different trapped intermediates while experiencing irregular forces surrounding them.[3]

Figure1: Different folding pathways of TrpZip2 hairpin with no external bias and 30 pN external bias.

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Aggregation Rate of Amyloid Beta Peptides is Controlled by Beta-Content in Monomeric State and Mechanical Stability of Fibrillar Structure

Aggregation Rate of Amyloid Beta Peptides is Controlled by Beta-Content in Monomeric State and Mechanical Stability of Fibrillar Structure

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The formation of the fibrillar structure and oligomers of amyloid proteins/peptides is believed to be associated with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc. Since the rate of aggregation can influence neurotoxicity, the search for key factors controlling this rate is of paramount importance. Recently, evidence has been found that the rate of protein aggregation is related to the mechanical stability of the fibrillar structure and the content of beta in the monomeric state in such a way that the higher the mechanical stability or the beta content, the faster the formation of fibrils. However, this conclusion was supported by limited data.

In this report, we extend the previous study to a larger dataset, including the wild type of Aβ42 peptide and its 20 mutants, whose aggregation rate was measured experimentally. Using all-atom steered molecular dynamics (SMD) and conventional molecular dynamics (CMD) simulations, we can access the mechanical stability of the fibril structure and the beta content in the monomeric state. Our result supports the hypothesis that mechanical stability and beta content are related to the aggregation rate. Since estimation of the aggregation rate using all-atom simulations is nearly forbidden by current computational capabilities, our result is useful for predicting it based on information obtained from CMD for monomers and SMD simulations for fibrils, which are computationally feasible.

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Symmetry-Breaking Mechanisms of the SARS-CoV-2 Main Protease

Symmetry-Breaking Mechanisms of the SARS-CoV-2 Main Protease

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The coronavirus 3C-like main protease (MPro) – an essential target of COVID-19 drugs – has approximately half of the activity and an asymmetric dimer structure at certain pH, suggesting that only one catalytic site is active at a time. However, the mechanism that leads to this asymmetry is unknown. Prior to the COVID-19 pandemic, previous modeling studies that investigated the asymmetry of MPro were only about 148 ns long. In the last few years, several groups have produced much longer simulations of MPro and released them to the public for detailed analysis. Here, we analyze a 100-microsecond simulation produced by D.E. Shaw Research (DESRES) and a series of trajectories with an aggregate time of 2.9-millisecond produced by Folding@Home to investigate the mechanism by which asymmetry emerges. The D.E. Shaw simulation reveals a domino chain initiated by breaking the salt-bridge Arg4*-Glu290 that propagates to alternate conformations of the catalytic sites. Markov state model analysis of the Folding@Home simulations reveals that transitions between active and inactive conformations in two subunits are reversible and that one subunit is preferentially in an active conformation.

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Cocktail of REGN Antibodies Binds More Strongly to SARS-CoV-2 Than Its Components, But The Omicron Variant Reduces Its Neutralizing Ability

Cocktail of REGN Antibodies Binds More Strongly to SARS-CoV-2 Than Its Components, But The Omicron Variant Reduces Its Neutralizing Ability

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A promising approach to combat Covid-19 infections is the development of effective antiviral antibodies that target the SARS-CoV-2 spike protein. Understanding the structures and molecular mechanisms underlying the binding of antibodies to SARS-CoV-2 can contribute to quickly achieving this goal. Recently, a cocktail of REGN10987 and REGN10933 antibodies was shown to be an excellent candidate for the treatment of Covid-19. Here, using all-atom steered molecular dynamics and coarse-grain umbrella sampling we examine the interactions of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein with REGN10987 and REGN10933 separately as well as together. Both computational methods show that REGN10933 binds to RBD more strongly than REGN10987. Importantly, the cocktail binds to RBD (simultaneous binding) more strongly than its components. The dissociation constants of REGN10987-RBD and REGN10933-RBD complexes calculated from the coarse-grained simulations are in good agreement with the experimental data. Thus, REGN10933 is probably a better candidate for treating Covid-19 than REGN10987, although the cocktail appears to neutralize the virus more efficiently than

REGN10933 or REGN10987 alone. REGN10987's association with RBD is driven by van der Waals interactions, while the electrostatic interactions dominate in the case of REGN10933 and the cocktail. We also studied the effectiveness of these antibodies on the two most dangerous variants Delta and Omicron. Consistent with recent experimental reports, our results confirmed that the Omicron variant reduces the neutralizing activity of REGN10933, REGN10987, and REGN10933+REGN10987 with the K417N, N440K, L484A, and Q498R mutations playing a decisive role, while the Delta variant slightly changes their activity.

Keywords: SARS-CoV-2, RBD, Covid-19, REGN-COV2, REGN10933, REGN10987, antibody cocktail, SMD simulation, Coarse-grained simulation, Delta variant, Omicron variant.