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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

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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

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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.