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Diacylglycerol O-acyltransferase-1 (DGAT1) is an integral membrane protein that uses acyl-coenzyme A (acyl-CoA) and diacylglycerol (DAG) to catalyze the formation of triacylglycerides (TAG). At a fictional step of TAG biosynthesis process, the acyl transfer reaction occurs between the activated carboxylate group of the fatty acid and the free hydroxyl group on the glycerol backbone of DAG. How the two substrates access to their binding sites and interact with DGAT1 remains elusive. This study aims to determine the structural basis of DGAT1’s substrate recognition by investigating each substrate’s pathway to bind to the catalytic site. We employed a variety of computational methods to study the interaction of DGAT1 with acyl-CoA and DAG. Our simulations of DGAT1-bound systems show several possible pathways of DAG molecules toward the reaction chamber. In addition, an extended simulation using Anton reveals a more plausible binding conformation between DAG and Acyl-CoA at the interior of the reaction chamber. The bound Acyl-CoA’s fatty acid lines up with the headgroup of DAG entered from the cytosol leaflet. Based on their close proximity, we were able to convert them to TAG and coenzyme to study beyond TAG synthesis process. Various behaviors on both substrates are observed, including ligand flip, rotation of the tag. Our findings will provide a better understanding of DGAT1’s activities with two main substrates during its biochemical events by identifying their distinct movement and interaction.

2543-Pos
Molecular mechanisms for strengthening E-cadherin adhesion using a monoclonal antibody
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E-cadherin (Ecad) is an essential adhesive and tumor suppressor protein; the adhesive state of Ecad is an important determinant of cancer metastatic potential. We have previously shown that the functional state of Ecad can be modified by the monoclonal antibody 19A11, which has applications in constraining cancer metastasis. However, the molecular mechanism for 19A11 activation is unclear. Here, we provide detailed analysis of Ecad structural changes induced by 19A11 binding. We show that 19A11 binds to first and second extracellular domain of Ecad, near its calcium-binding sites. Molecular dynamics simulations indicate a novel binding conformation of Ecad induced by 19A11. Using steered molecular dynamics simulations, we show that in the presence of 19A11, Ecad interacts with a higher force and longer lifetime. Finally, we use Atomic Force Microscope measurements to confirm that 19A11 strengthens Ecad homophilic binding at the single molecular level.

2544-Pos
Characterizing the roles of chemo-mechanical couplings in the differential behavior of SARS-CoV-1 and SARS-CoV-2 spike glycoprotein
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The highly contagious severe acute respiratory syndrome (SARS) coronavirus-2 (CoV-2) is a form of SARS-CoV-1 which broke out as an epidemic in 2003. SARS-CoV-1 and SARS-CoV-2 spike proteins share similarities in sequence identity and binding patterns to human angiotensin-converting enzyme 2 (ACE2) receptor. Despite these similarities, SARS-CoV-2 spike protein has a higher infectivity rate and an increasing intensity with emergence of new mutated variants, raising concerns about the efficacies of the vaccines. As such, in addition to studies discussing the binding mechanism of RBD to ACE2, it is expedient to explore the events prior to the binding of RBD-ACE2 in comparison to SARS-CoV-1. We propose that this can lead to design and possible modifications of therapeutic agents that can inhibit the binding as such prevent the spread of COVID-19 irrespective of mutating variations. For our study, we have used cryogenic electron microscopy (Cryo-EM) structures of active and inactive models of SARS-CoV-1 and 2. Our research discusses the conformational changes and differences seen through electrostatic interactions in SARS-CoV-1 and SARS-CoV-2 prior to ACE2 binding, and considers hot spots regions outside the RBD that could be contributing to the transmissible difference of SARS-CoV-1 and 2. Furthermore, we investigate several SARS-CoV-2 variants for observation of similar or different behaviors. From our initial analysis, we found that within the RBD, salt bridge interactions formed in conserved residues of SAR-CoV-2 (R273-D290, R338-D357) are more stable than in SARS-CoV-1 (K258-D277, R315-D564). We observe same patterns with hydrogen bond networks. Our impression is that this is possible because the active model of SARS-CoV-1 undergoes a conformational change in which the RBD moves toward the N-terminal domain (NTD) (D24-K365) forming a semi-closed state.

2545-Pos
Probing the role of non-specific interactions in promoting functional protein-protein complexes
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Cellular function hinges on the recognition and binding of interaction partners in the correct configuration. At low endogenous concentrations, the likelihood of two interaction partners encountering each other is diffusion-limited. Further, in order to perform a function, the interaction partners must reorient structurally to the correct configurations before they diffuse away from each other. This results in an interesting question – could biomolecular interactions have evolved to tune the kinetics of complex formation? A hierarchy of interactions, specific and promiscuous, are known to influence biomolecular interactions. Using a coarse-grained polymer description for biomolecules, we probe how an interplay between promiscuous (non-specific) and specific interactions could drive the dynamics of complex formation and maturation. In our simulations, we probe how this interplay could influence the propensity of the interaction of polymers (with a central specific interaction core) to form complexes stabilized by specific interactions. We observed that altering the non-specific interactions, the fraction of non-specifically interacting beads in the polymers, and the interacting polymer types affects the self-assembled states, suggesting an optimal range of interactions where the mature complexes form. Our study provides a mechanistic basis for the narrow range of non-specific interaction strengths that promote functional protein-protein complex formation.

2546-Pos
Additivity in the helix-coil transition of alpha-helical peptides with varying length
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The mechanical unfolding of alanine-rich helices with various lengths and sequences has been characterized using Adaptive Steered Molecular Dynamics (ASMD). We have found that the potential of mean force (PMF) and hydrogen bonding profiles for these various helices exhibit a correspondence between different chains, and the required energetics for the overall unfolding process is additive with respect to the chain length. [Biophys J, 120, 2009 (2021)] Polyalanine peptides were used to guide the hypotheses because of their high helix propensity for helical formation, and the low computational cost needed to simulate them. A synthesized polypeptide Ac-Yi(AEAKAKA)F-NH2 (EK peptide) and a natural alpha-helical peptide a2N (1–17) were used to test the generality of the observations. These alanine-rich peptides unfolded in a similar fashion that their alpha-helical contacts were lost in turn and formed polyproline II (pPII) structure successively. Polyproline II (pPII) structure was also formed afterwards and not released immediately upon the stretch. Based on our findings, the helix-coil transition for alanine-rich peptides was mainly dependent on breaking the backbone hydrogen bonds instead of the chain lengths or the specificity of residues. Moreover, these results also provide insights into the folding/unfolding pathways as well as stability for the alpha-helix structure in proteins in general.

2547-Pos
Going through changes: effect of phosphorylation on secondary structure preference and dipole-dipole interactions in model peptides
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Intrinsically disordered proteins (IDPs) are enriched in polar and charged amino acids and lack a single, well-defined tertiary structure. IDPs are frequently the targets of post-translational modifications (PTMs) which can affect protein folding or stability, activity, susceptibility to degradation, and function. Phosphorylation is one of the most common PTMs and occurs on serine, threonine, and tyrosine residues. Hyperphosphorylation of some IDPs is associated with disease states, such as the tau protein in Alzheimer’s disease and α-synuclein in Parkinson’s disease. However, the mechanism by which phosphorylation modulates protein structure and dynamics, specifically the electronic interplay between the negatively charged sidechain and the