Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ribonucleoprotein core packing observed near a unique 5-fold vertex in the expanded TCV particle. This 5-fold vertex is the specific point of egress for the genomic RNA into the host. Far from being passively package contents, our results highlight an active role of the genomic RNA-protein core as an environmental sensor which controls capsid uncoating and RNA release.

2207-Pos

Comparing structural ensembles with DiffNets helps explain the activation mechanism of the SARS-CoV-2 protein NSP16

Michael D. Ward.
Washington University School of Medicine, Saint Charles, MO, USA.

Understanding the structural determinants of a protein's biochemical properties, such as enzymatic activity, is a major challenge in biology and medicine. Comparing computer simulations of protein variants with different biochemical properties is an increasingly powerful means to drive progress. However, success often hinges on dimensionality reduction algorithms for simplifying the complex ensemble of structures each variant adopts. Unfortunately, common algorithms rely on potentially misleading assumptions about what structural features are important, such as emphasizing larger geometric changes over smaller ones. Here we present DiffNets, self-supervised autoencoders that avoid such assumptions, and automatically identify the relevant features, by requiring that the low-dimensional representations they learn are sufficient to predict the biochemical differences between protein variants. For example, DiffNets automatically identify subtle structural signatures that predict the relative stabilities of β-lactamase variants and duty ratios of myosin isoforms. Additionally, we use DiffNets to compare simulations of NSP16, a SARS-CoV-2 protein, in its monomeric form (inactive) and in complex with NSP10 (active) to understand how it becomes activated, and ultimately plays a role in immune evasion. Further, DiffNets help us identify a cryptic pocket in NSP16 that opens when NSP16 adopts inactive structural configurations. Therefore, targeting this site with a small molecule promises to inhibit the activity of this enzyme.

2208-Pos

Unraveling SARS-CoV-2 spike protein activation pathway reveals unprecedented cryptic pockets

Hisham M. Dokainish[1], Suyong Re[2], Takaharu Mori[1], Chigusa Kobayashi[3], Jaewoon Jung[3], Yuji Sugita[1].
[1]RIKEN, Wako, Japan, [2]National Institutes of Biomedical Innovation, Health, and Nutrition, Osaka, Japan, [3]RIKEN, Kobe, Japan.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents an immediate threat to global health. Spike (S) protein on the surface of SARS-CoV-2 has been recognized as a primary antigenic target for viral neutralization and vaccine development. S-protein consists of trimeric polypeptide chains heavily glycosylated and undergoes large conformational changes of its receptor binding domain (RBD) during the activation. Structural studies have shown more than 300 S-protein conformations, which include inactive down, one-RBD-up (one-up), two-RBDs-up (two-up), and three-RBDs-up (three-up) states, while little is known about the intermediate structures and mechanisms of the structural transitions. Here, we performed atomistic molecular dynamics (MD) simulations based on an enhanced conformational sampling method to explore a wide conformational space of S-protein in solution. Starting from either down or one-up cryo-EM structures, we observed multiple transitions between down, one-up, one-open, and two-up-like conformations, suggesting the intrinsic flexibility and dynamics of RBDs of S-protein regardless of its binding to antibodies or ACE2 receptor in human host cells. Three key glycans attached at N165, N234, N343 play essential roles in the structural transitions. Larger conformational fluctuations were observed in the simulations of S-protein and a monomeric S-protein without glycosylation, suggesting that the glycans greatly reduce the number of available conformations of S-protein. As consistent with single-molecule FRET experiments, two intermediate structures between down and one-up were found and they reveal unprecedented cryptic pockets that might be targeted to stabilize down conformation, hindering ACE2 binding and subsequently cell entry o. Modelling S-protein and different classes of antibodies interactions shows that glycan shielding is the weakest in one-open conformation. Indeed, such inherent dynamics and flexibility of S-protein shall be considered for rational design of antiviral drugs and vaccine developments.

2209-Pos

Transcriptional factors control their diffusion on DNA by modulating their dynamics

Rama Reddy Goluguri[1], Mourad Sadqi[2], Victor Munoz[2].
[1]Stanford University, Stanford, CA, USA, [2]Bioengineering, University of California Merced, Merced, CA, USA.

Gene regulation requires transcription factors to efficiently recognize their target DNA site. Efficient recognition of target sequence is achieved by a facilitated diffusion process that combines 3D diffusion and 1D diffusive motions along the DNA, which are enabled by weak electrostatic (non-specific) interactions. The protein is presumed to scan the DNA while bound non-specifically, and lock into the specific binding site once it's encountered. The mechanism by which a single domain protein alternates rapidly between these two binding modes is however unknown. Many eukaryotic transcription factors are intrinsically disordered or marginally stable, and their folding dynamics consistent with downhill folding scenario. The functional implications that such marginal stability and downhill folding behavior have for eukaryotic transcription factors are not known. Here we studied the binding dynamics of *Drosophila* Engrailed homeodomain (EnHD) to the lambda phage DNA at the single-molecule level using optical tweezers to mechanically control the DNA and confocal fluorescence microscopy to track EnHD on DNA. To determine the role of EnHD conformational dynamics on its DNA scanning properties we investigated the wild-type and two variants that differ in their folding properties: a hyper stable EnHD produced by Barrick group by consensus design, and a destabilizing single-point mutant that is known to be intrinsically disordered. In our single-molecule tracking experiments we see a strong correlation between the overall DNA scanning speed of the EnHD variant and its conformational flexibility. These observations make the very first link between conformational flexibility and DNA scanning function of eukaryotic TFs. We conclude that these observations stem from the downhill folding behavior of EnHD, which allows it to sample more extended, search competent conformations, that result in fast DNA scanning, and to quickly lock into a binding-competent state upon encountering the target site.

2210-Pos

Accelerated cyclic peptide ensemble generation using reservoir REMD

Shawn C.C. Hsueh, Steven S. Plotkin.
Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada.

Cyclic peptides have been widely used as potential therapeutics and scaffolded antigens due to their ability to bias the conformation to the desired structure using just a few amino acids. Although many tools have been developed to perform cyclic peptide structure prediction, there is little discussion on the ensemble generation of the cyclic peptides. We found that conventional molecular dynamics (MD) simulation is insufficient to sample the ensemble of small cyclic peptides (<10 amino acids), likely due to energy barriers rooted in the ring-like conformational constraint. As a result, accelerated MD methods are required to sample a complete ensemble. In this study, an accelerated MD method, reservoir replica exchange MD (R-REMD), is implemented in GROMACS-4.6.7, and applied on three small cyclic peptide model systems (i.e., cyclo-(CGHHQKLVG), cyclo-(CGPRRARSG), and oxytocin (CYIQNCPLG)). We found that R-REMD can significantly accelerate the ensemble generation of cyclo-(CGHHQKLVG) compared to normal REMD, but cannot accelerate cyclo-(CGPRRARSG) or oxytocin. Furthermore, the former model system was found to have a larger RMSD auto-correlation time than the latter two from separate conventional MD simulations. As a result, RMSD auto-correlation time may be a good indicator of whether R-REMD should be used rather than REMD for cyclic peptides. Thus, this research provides R-REMD to the GROMACS community and benchmarks R-REMD on cyclic peptide systems for the first time.

2211-Pos

Hydration-water and membrane lipids modulate G-protein-coupled receptor activation

Nipuna Weerasinghe[1], Steven D.E. Fried[1], Andrey V. Struts[1,2], Suchithranga M.D.C. Perera[1], Michael F. Brown[1,3].
[1]Department of Chemistry and Biochemistry, University of Arizona, Tucson, AZ, USA, [2]Laboratory of Biomolecular NMR, St. Petersburg State University, St. Petersburg, Russian Federation, [3]Department of Physics, University of Arizona, Tucson, AZ, USA.

G-protein-coupled receptors (GPCRs) are responsible for transducing signals across lipid membranes in cells and are the largest family of targets (∼40%) for currently approved drugs. They exist as dynamic conformational ensembles with multiple inactive and active conformational substates described by an energy landscape model. We investigated ways in which the receptor hydration level and lipid bilayer composition influence the activation of the archetypical GPCR rhodopsin by quantifying the shift in the metarhodopsin equilibrium in native and POPC recombinant membranes by different polyethylene glycol osmolyte solutions. Our results show a flood of ∼90 water molecules into the rhodopsin interior during photoactivation, forming a solvent-swollen Meta-II active state. Dehydrating conditions favored inactive Meta-I through the efflux