staphylococcal nuclease following a number of point mutations. These studies serve as a first step in developing the ability to quantitatively rank the energies of designed protein constructs.

290-Pos Board B45
Effect of Intracellular Loop 3 on Intrinsic Dynamics of Human β2-Adrenergic Receptor
Ozer Ozcan[1], Arzu Uyar[1], Pemra Doruker[1], **Ebru Demet Akten**[2].
[1]Bogazici University, Istanbul, Turkey, [2]Kadir Has University, Istanbul, Turkey.
To understand the effect of the long intracellular loop 3 (ICL3) on the intrinsic dynamics of human β2-adrenergic receptor, molecular dynamics (MD) simulations were performed on two different models, both of which were based on the inactive crystal structure in complex with carazolol (after removal of carazolol and T4-lysozyme). In the so-called loop model, the ICL3 region that is missing in available crystal structures was modeled as an unstructured loop of 32-residues length, whereas in the clipped model, the two open ends were covalently bonded to each other. The latter model without ICL3 was taken as a reference, which has also been commonly used in recent computational studies. Each model was embedded into POPC bilayer membrane with explicit water and subjected to a 1 μs molecular dynamics (MD) simulation at 310 K. After around 600 ns, the loop model started a transition to a "very inactive" conformation, which is characterized by a further movement of the intracellular half of transmembrane helix 6 (TM6) towards the receptor core, and a close packing of ICL3 underneath the membrane completely blocking the G-protein's binding site. Concurrently, the binding site at the extracellular part of the receptor expanded slightly with the Ser207-Asp113 distance increasing to 18 Å from 11 Å, which was further elaborated by docking studies. The essential dynamics analysis indicated a strong coupling between the extracellular and intracellular parts of the intact receptor, implicating a functional relevance for allosteric regulation. In contrast, no such transition to the "very inactive" state, nor any structural correlation, was observed in the clipped model without ICL3. Furthermore, elastic network analysis using different conformers for the loop model indicated a consistent picture on the specific ICL3 conformational change being driven by global modes.

291-Pos Board B46
Conformational Sampling and Structure Prediction of Multi-Loops in Proteins using Distance-Guided Sequential Chain-Growth Monte Carlo Method
Ke Tang[1], Jinfeng Zhang[2], Jie Liang[1].
[1]Bioengineering, University of Illinois at Chicago, Chicago, IL, USA, [2]Statistics, Florida State University, Tallahassee, FL, USA.
Protein loops are critical to their overall biochemical functions. The irregularity and flexibility of loops make their structures difficult to determine experimentally and challenging to model computationally. As loops are often in spatial proximity and interact with each other, modeling multiple loops simultaneously is an especially challenging task for protein structure prediction. We have developed a new method called Multi-loops Distance-guided Sequential chain-GROwth Monte Carlo (m-DiSGRO) for conformational sampling and structure prediction of multi-loop regions in protein. m-DiSGRO simultaneously grows interacting loops. Our method successfully achieves an average minimum RMSD of 1.43 angstrom and an average lowest energy RMSD of 2.78 angstrom for 36 pairs of interacting protein loops of the total length ranging from 12 residues to 24 residues, with a mean length of 18. Our method also succeeded in modeling multi-loops in beta-barrel membrane protein. For the outer-membrane protein G (OmpG) with 3 interacted loops of a total length of 12 + 12 + 10 =34 residues, the minimal RMSD and lowest energy RMSD conformations of the loop region compared to the native structure is only 2.51 angstrom and 2.65 angstrom, respectively.

292-Pos Board B47
Structural Properties of Membrane Inserted Fusion Peptide from Influenza Virus Analysed by Molecular Simulation
Diana Lousa, Bruno L. Victor, Carlos Fernandez, Cláudio M. Soares.
ITQB-UNL, Oeiras, Portugal.
Influenza virus is responsible for worldwide outbreaks of flu, causing hundreds of thousands of deaths every year, which rise to millions in pandemic years. In order to infect the host cells, influenza virus promotes the fusion of the viral and host membranes. This process is mediated by hemagglutinin (HA), a glycoprotein located on the surface of the viral envelope. Influenza HA has a highly conserved N-terminal domain, comprising ~20 residues, which inserts into the host membrane. This region is critical for destabilizing target membranes during the fusion process and is known as fusion peptide (FP).
To elucidate the molecular determinants that lead to the destabilization of biological membranes by the FP, we used a molecular dynamics (MD) approach.

We performed simulations with the wild type and four different FP mutants: G1V, W14A, G4A/G8A/G16A/G20A, and G12A/G13A, which are known or expected to have an impaired fusogenic activity. Our aim is to understand how these mutations affect the conformational distribution of the peptide and its ability to destabilize the membrane.
Given that lipid membranes are very viscous, it is difficult to obtain reasonable sampling using standard MD. Therefore, in addition to standard MD simulations, we also performed bias-exchange metadynamics simulations, both in water and in a DMPC membrane. These simulations enable us to compare the energy landscapes of the wild type and mutant peptides and explain how these mutations affect the fusogenic ability of the peptide.

293-Pos Board B48
Modeling the Structural Properties of the Transmembrane Peptide of Influenza Hemagglutinin in a Membrane Bilayer
Bruno L. Victor, António M. Baptista, **Cláudio M. Soares**.
ITQB-UNL, Oeiras, Portugal.
Like all enveloped viruses, influenza virus enters the host cell by fusing its membrane with the host membrane, in a process mediated by the hemagglutinin (HA) glycoprotein. HA is a homotrimeric protein comprised by a soluble part (which contains the receptor binding site and the fusion peptide) and a transmembrane (TM) peptide. The TM peptide attaches the protein to the viral membrane and is also thought to play a role in the fusion process. Although this peptide has been gaining considerable attention in recent years, its 3D structure and the molecular determinants of membrane insertion remain unknown.
To analyze the structural determinants of membrane insertion of the TM peptide, we simulated this peptide in the presence of a DMPC bilayer [1]. We observed that the peptide adopts a mainly helical conformation and inserts in the membrane with a tilt angle of ~64°. Simulations with mutant forms of the TM peptide revealed that mutations of Trp 24 and Tyr 5 found in the C-terminal and N-terminal regions, respectively, affect the helicity and consequently the peptide arrangement inside the membrane bilayer. Since HA is a trimer, we also performed simulations with three copies of the TM peptide embedded in a membrane. The simulations showed that the three peptides assemble in a triangular arrangement that approximately matches the positions where they should attach to the available crystallographic structure of the soluble part of HA.
1. B. L. Victor, A. M. Baptista and C. M. Soares, J Chem Inf Model, 2012, 52, 3001-3012.

294-Pos Board B49
The Amyloid Precursor Protein Maintains an Ideal&Alpha-Helical Conformation in the Lipid Bilayer
Thomas Lemmin, Mitko Dimitrov, Patrick Fraering, Matteo Dal Peraro.
EPFL, Lausanne, Switzerland.
The Amyloid Precursor Protein (APP) is a type-I transmembrane glycoprotein present at the neuronal synapse. The proteolytic cleavage by γ-secretase produces amyloid-β (A&β) peptides of different lengths, the deposition of which is an early indicator of Alzheimer's disease (AD). At present, there is no consensus on the conformation of the APP transmembrane (TM) domain at the biological membrane. Although structures have been determined by nuclear magnetic resonance (NMR) in detergent micelles, their conformation is markedly different. Here we show by using molecular simulations that the APP-TM region systematically prefers a straight helical conformation once embedded in a membrane bilayer. APP-TM is highly flexible however, and its secondary structure is strongly influenced by the surrounding lipid environment. This behavior is confirmed when analyzing in silico the atomistic APP-TM population observed by residual dipolar couplings and double electron-electron resonance (DEER) spectroscopy. These structural and dynamic features are probably critical in the proteolytic processing of APP by the γ-secretase enzyme, as suggested by mutants mimicking influencing the APP flexibility that shows a relevant increase in the production of A&β38 compared to physiological A&β40 peptides.
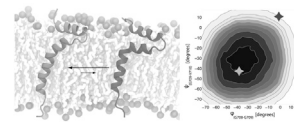
295-Pos Board B50
Conformation and Aggregation of Peptides at Interfaces
Mehmet Sayar.
Koc University, Istanbul, Turkey.
Conformation of proteins and peptides are not solely determined by their sequence, but are also strongly dependent on the environmental conditions. In addition to factors like salt concentration or pH, the environment presented by the surrounding molecules also play a major role in the conformational preference of proteins and peptides. In this study, we perform a comparative study on the conformational behavior of peptides in bulk vs. at an interface. The interface can be a macroscopic air/water interface or a nanoscale interface presented