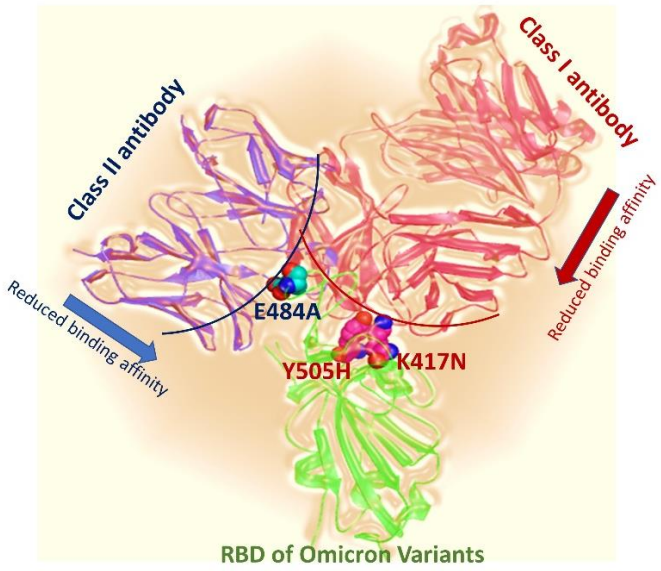
Computational Biology

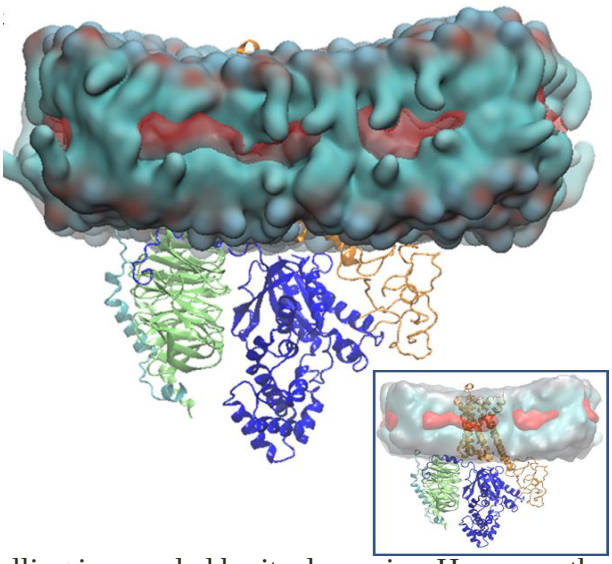
Dr. Sandipan Chakraborty uses GPU-enabled high-performance computation as a tool to understand the structure and dynamics of biological macromolecules and biopolymers. Using extensive all-atom molecular dynamics simulation and novel algorithms for free energy landscape computations, he does computational microscopy to elucidate the structural rationale of the functional dynamics of proteins and protein complexes. The structural insights obtained from computer simulations are used for structure-guided rational engineering of proteins with improved function and stability. Also, he works on computer-aided drug discovery/repurposing to identify new lead molecules against different targets of therapeutic significance and characterize the mechanism of drug action. The active areas of research in his lab are:

Host-Virus interaction

Using evolutionary bioinformatics and high-performance computation, we are working to understand the host-viral interaction of pathogenic coronaviruses. Our current research interest is SARS-CoV2. We have decoded the human ACE2 receptor usage trait that enables the coronaviruses to spill over to humans. SARS-CoV2 is evolutionarily divergent from other human ACE2-user CoVs. We also developed a mutant-screening platform that can identify fitness-enhancing mutations in the spike proteins. The expertise and platform developed at DRILS can be used to understand pathogenicity and perform disease surveillance for other tropical viruses. We also use immunoinformatics and binding free energy calculations to explore antigen-antibody interactions involving viral proteins. We demonstrated that all the omicron variants attain class I and class II antibodies escape abilities by incorporating mutations at the hotspot residues for each specific class of antibody. We intend to use advanced computations to explore the efficacy of approved antibodies against emerging viral variants.

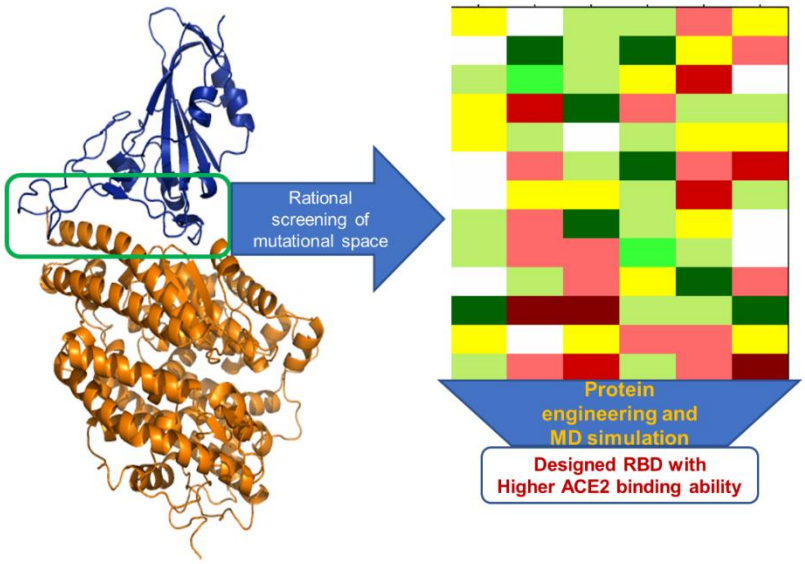


Mechanism of GPCR activation



GPCRs (G-protein coupled receptors) are an amazing signal transducer that relays the signal from the extracellular ligand-binding cavity to the intracellular G-protein regulatory sites to initiate cellular signalling. One of the well-studied GPCRs is the human serotonin1A receptor. Postsynaptic serotonin1A receptors are essential in controlling mood, cognition and memory. The serotonin1A receptor signalling is mediated through the Gi/o protein. The receptor is also a major drug target in neuropsychiatric diseases like anxiety, depression, Parkinson's disease and schizophrenia. Molecular basis for GPCR signalling is encoded by its dynamics. However, the structural elucidation of the dynamic transitions which govern the receptor activity and function remains completely lacking due to the lack of serotonin1A structures in different conformational states. We resolved the full-length structure of serotonin1A receptor coupled with the G-proteins and decoded the mechanism of ligand binding and membrane cholesterol on the dynamics of intracellular loops (ICL) and the G-protein coupling efficiency using GPU-accelerated atomistic simulations. We aim to employ Exa scale computation to understand GPCR organization and dynamics in response to different ligand-driven activation.

Protein engineering

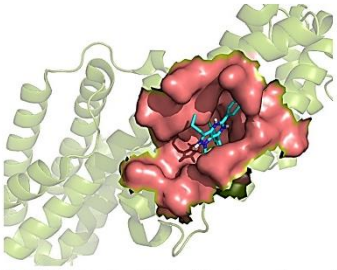


We have developed a multi-tier comprehensive SARS-CoV-2 mutation screening platform combining MM/GBSA, extensive molecular dynamics simulations, and steered molecular dynamics to identify RBD mutants with enhanced ACE2 binding capability. We have designed a RBD which shows significantly higher ACE2 binding abilities than wild-type and SARS-CoV2 variant RBD. We are now working on the development of a protein subunit vaccine based on SARS-CoV-2 spike RBD. We are using epitope-grafting to engineer the B-cell and T-cell epitopes to produce human ACE2-specific RBD-based antigen that can bypass existing immunity but induce long-term immune memory. We intend to use immunoinformatics, molecular dynamics simulations and computational protein engineering to rationally engineer

proteins for improved function, antibody engineering with broader neutralizing abilities, and biologics discovery.

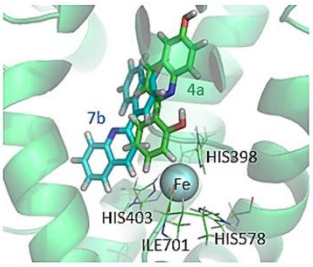
Mechanism of drug action against targets of therapeutic importance

We have integrated advanced techniques of macromolecular simulation and rare event sampling to augment our medicinal chemistry and structure-guided drug discovery initiatives. Macromolecular simulations in combination with computer-aided drug discovery/repurposing has been used to identify new lead molecules against different targets of therapeutic significance and structurally characterize the mechanism of drug action.



DRL1398 docked into Chorismate mutase

Using computer-aided drug discovery and atomistic simulation, we are working on the development of multi-target inhibitors for Alzheimer's disease, specific inhibitor of 12R-Lox for psoriasis and other skin related inflammatory diseases, Chorismate mutase for MDR-TB and many more.



Specific inhibitor of 12R-LOX