Determination of an Appropriate Surface for the Transition from Brownian Dynamics to Molecular Dynamics in Sialic Acid Binding to Neuraminidase

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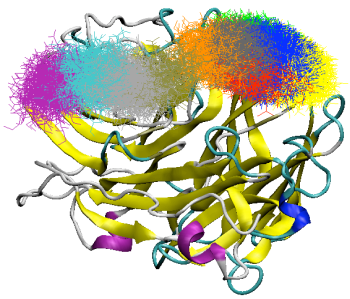
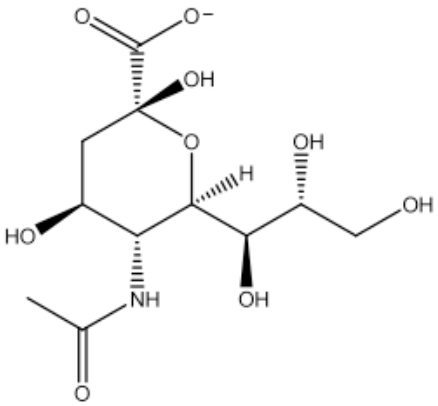
It is estimated that over 200,000 people annually are hospitalized in the U.S. alone due to the influenza virus. To facilitate the release of nascent virus from infected host cells, the viral protein neuraminidase must bind to and cleave sialic acid moieties from cell surface receptors. To increase current understanding of this process, our lab seeks to calculate the association rate constants of sialic acid binding to both the secondary site of neuraminidase, whose function is currently unknown, and the active site of neuraminidase. To accurately calculate association rate constants of sialic acid binding to neuraminidase, our lab is developing a methodology utilizing Brownian Dynamics (BD) and Molecular Dynamics (MD) coupled via a Markov chain. BD is used when the molecules are relatively separated while MD is used when the molecules are in close proximity. Simulations switch from BD to MD when they encounter a predefined "transition surface". For this surface, we have preliminary chosen an 18.5 Å by 11 Å ellipse centered around the secondary and active sites. Using BD, approximately 7000 approaches of the ligand to this surface were simulated. For this surface, nearly 90% of the sialic acids approached over the active site, compared to about 10% at the secondary site. We observed four primary orientations of the sialic acids and have classified them by the sialic acid functional group nearest the neuraminidase: carboxylate, amide, aliphatic chain, and the ring hydroxyl closer to the amide (See figure below). Over the active site, the ligand orientational distribution was approximately 40% carboxylate, 40% amide, 17% aliphatic, and 3% ring hydroxyl. Ligands that were over the secondary site were distributed approximately 25% carboxylate, 70% amide, 4% aliphatic chain, and 1% ring hydroxyl. Future work will include varying the ellipse size to better characterize the approach of the ligands. Practically, a surface that balances good BD statistics but limits MD computational time is optimal.



The 6976 ligands grouped by where they hit the 18.5 Å by 11 Å ellipse above a monomer of neuraminidase.



Sialic Acid