The Effect of Starting Location and Orientation on Molecular Dynamics Simulations as Applied to the Influenza Neuraminidase- Sialic Acid System.

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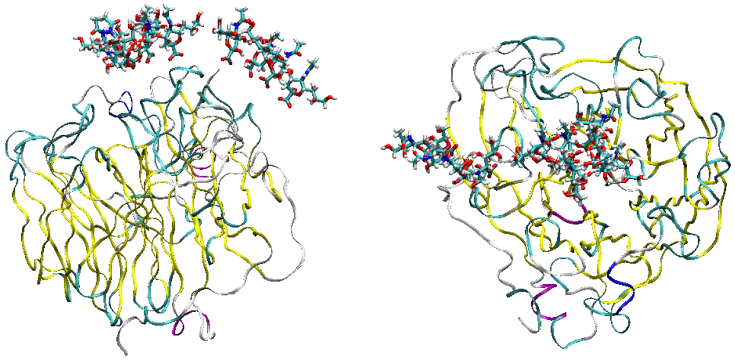
One successful drug pathway for combating the influenza virus is to inhibit the catalytic activity of influenza neuraminidase. Inhibitors such as peramivir, zanamivir (Relenza®), and oseltamivir (Tamiflu®) compete with terminal cell-surface receptor sialic acid moieties for access to neuraminidase's binding site. To understand the efficacy of these drugs, it is important to understand the pathways and kinetics of the protein-ligand binding. Previous research on the association kinetics of influenza neuraminidase and sialic acid ligands relied solely on Brownian dynamics (BD) modeling. While BD is time efficient, it relies upon many approximations that make it less accurate for close-range simulations. Our research aims to improve the balance between the time efficiency of BD simulations while retaining the accuracy of molecular dynamics (MD) simulations. To determine the effect of starting configuration on the results of MD simulations, we used many different starting positions and orientations— as provided by previous BD modeling— and assessed the binding kinetics and spatial distribution of the ligands.



Side and top views of the distribution of starting coordinates.