Exploring the binding pathways of zanamivir to wild-type neuraminidase using molecular dynamics and MM/GBSA

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Neuraminidase (NA) is a viral enzyme essential to the influenza replication cycle. To facilitate nascent viral release, NA cleaves terminal sialic acid moieties from host cell surface receptors. Treatment with zanamivir, an FDA approved NA inhibitor, is an effective way to slow the progression of an influenza infection. Treatments like this, however, have led to the rise of antiviral drug resistance through mutations of NA that allow for selective binding to sialic acid but not to NA inhibitors. To investigate the molecular mechanisms that allow for NA's selective ligand binding, we have focused on the binding kinetics of zanamivir to the NA enzyme, elucidating protein-ligand interactions that effect ligand binding. To this end, we have employed a multi-scale methodology comprising multiple computational methods: Brownian dynamics, which takes into account long-range electrostatic interactions that influence the diffusional approach of ligands, molecular dynamics (MD), which samples proximal protein-ligand motion, and free energy analysis (Molecular Mechanics/Generalized Born Surface Area - MM/GBSA), which interprets the MD results. MM/GBSA free energies are computed for each saved MD configuration. Together, these methods give the complete binding trajectories of zanamivir, allowing for a deeper understanding of zanamivir's thermodynamic interactions with viral NA.