COMPARISON OF POPULAR FORCE FIELDS FOR MOLECULAR MODELING OF PROTEINS APPLIED TO ICE BINDING OF THE *TENEBRIO MOLITOR* ANTIFREEZE PROTEIN

Nathan Odendahl (Valeria Molinero)
Department of Chemistry

Ice Binding Proteins (IBPs) are a class of proteins that affect the melting and freezing temperatures of ice. While substantial research has been conducted to understand the properties of IBPs, experimental and molecular dynamics simulations have not satisfactorily explained the mechanism of the irreversible binding of protein to ice. Parallel rows of threonine residues play an important role in the activity of hyperactive proteins. Past experimental and computational studies show a peculiar stability of the protein structure and rigidity of the two rows of threonine. The hydroxyl groups on the two threonine rows are known to closely match the dimensions of hexagonal ice, but what about this geometry allows a protein to bind irreversibly to ice? To investigate this mechanism, we use molecular dynamics simulations to examine the *Tenebrio molitor* antifreeze protein (TmAFP), which is generally representative of the family of hyperactive antifreeze proteins. In particular, when designing simulations of these proteins, force field parameters that govern the molecular system must be examined closely to ensure an accurate physical representation. We survey four common protein system force fields, two each from the CHARMM and AMBER families. Trials using AMBER force fields (ff12SB and ff14SB) as well as one newer CHARMM force field (CHARMM36) are not able to accurately mimic the ice binding face, and simulations with these force fields fail to dock with ice. An older CHARMM force field, CHARMM22, is able to reproduce threonine rigidity. We measured hydroxyl distances between neighboring threonine residues and the threonine dihedral angles with each force field and demonstrate that the experimentally observed rigidity is mimicked only in the simulations using CHARMM22. Further, a simulation with CHARMM22 shows successful binding of the TmAFP with ice, while an identical simulation with AMBER ff12SB does not bind. We propose that the threonine rigidity is essential to ice binding, and that the hardness of the CHARMM22 force field offers sufficient rigidity. Future simulations must therefore use a force field able to reproduce this rigidity, as in CHARMM22.