

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

**Molecular Dynamics Modeling of a Biotoxin in Various
Temperature and pH Environments and Another Protein
Interacting with Small Molecules**

By

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There has been a long history to use classical molecular dynamics in investigating the properties of biomolecular systems. As a supplement to experimental methods, it has provided invaluable insight into the properties and mechanism of proteins and other macro-molecular systems which are hard or impossible to investigate by regular in vitro experiments. In the thesis, we used classical molecular dynamics to study botulinum and PDZ domains (a common domain shared by post synaptic density protein, Drosophila disc large tumor suppressor, and zonula occuldens-1 protein) in detail. Botulinum neurotoxins type A (BoNT/A) are highly potent toxins, but are also useful in the treatment of illnesses. We studied the properties of BoNT/A at various temperatures and pH values in order to understand its toxicity and structure variations. The pH values of the environment of BoNT/A were modeled by changing the protonation states of certain titratable residue groups. Our results show that certain parts of the protein are active at acidic pH environments or at high temperatures. The protein is more stable in neutral environments at normal human body temperature; whereas, at high temperature, the protein is more stable in acidic environments. The Dishevelled (Dvl) PDZ domain is believed to play an essential role in the canonical and noncanonical Wnt signaling pathways, which are involved in embryo development as well as in tumorigenesis. Also, it binds directly to Frizzled (Fz) receptors. An organic molecule (NSC668036) from the National Cancer Institute small-molecule library has been identified to be able to bind to the Dvl PDZ domain. Molecular dynamic simulation was used to analyze the binding between them in detail.

Date: August 3, 2007

Time: 10:00 AM

Place: Math Tower 1-122

Program: Physics and Astronomy

Dissertation Advisor: Prof. Yuefan Deng