Computational Screening of Small Molecules for Antibacterial Agents that Target T-Box Riboswitches

Narasimhan, Shifra (School: Athens High School)

Antibiotic resistance is a growing public health challenge which affects about two million people in the U.S. annually. The search for new antibacterial agents is focusing on small drug molecules that target highly conserved regions of bacterial RNA to prevent antibiotic resistance. Of particular interest is the riboswitch, an untranslatable portion of the messenger RNA, that regulates protein synthesis in many pathogenic bacteria. This project aims to develop an effective method for computationally screening approved drug molecules to target T-Box riboswitches found in certain Gram-positive bacteria. The screening involves finding if a drug molecule stably and specifically binds to the riboswitch to turn off the bacteria's protein synthesis. A set of molecules from the National Institute of Health's NCGC pharmaceutical library, along with the T-Box riboswitch RNA, were modeled in Maestro. The stability of the binding between each molecule and the riboswitch was studied in terms of glide gscore and the number and type of chemical bonds. Glide emodel was used to determine the stablest pose of the ligand and glide gscore was used to determine relative docking stability. The results indicated that the molecules that bound most stably were binding to the bulge and hinge regions of the riboswitch. Fluorescence based assays performed (outside of this project) on a subset of the molecules indicated that the computational model needed refinement in order to provide more accurate results. Enhancement of the computational model using semi-empirical techniques is planned to augment the results provided by the glide model.

Awards Won:
Fourth Award of $500