Cybermedia Center, Osaka University

Virtual Screening for High Specificity Inhibitors of SSH-2

Joshua Wei
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Overview

- Dual Specificity Phosphatases or DSPs are characterized for their ability to dephosphorylate phospho-tyrosine and phospho-serine/threonine.
- Finding specific inhibitors of DSPs like SSH-2 have potential in drugs to combat Alzheimer's and certain cancers.
- The top 1% of the highest ranked inhibitors of SSH-2 are docked against other DSPs to determine specificity
- However, some DSPs were only recently modeled, such as by past PRIME students, and require loop optimization and energy minimization to improve their structure.

Week 1: Optimizing Models of Dual Specificity Phosphatases

- A list of previously generated models was worked through to determine best candidates for screening
- First two DSPs suitable for modeling optimization were DUSP 19 and PRL-2
- Loop optimization has been successful, though significant improvement as a result has not been observed
- Accuracy of the models were judged by MolProbity, online structural model assessment program
- Olivia is running dock for DUSP19. I should have PRL-2 docking by tomorrow.

Future Plans

- Future plans included looking into ways to display and utilize Modeller's DOPE score function to determine best locations for loop minimization.
- We attempted to write script to generate scores, but had problems with python not recognizing Modeller module. Reinstallation may be required.
- We are still trying to determine the best method to optimize models. Options include loop modeling then energy minimization or vice versa
- As docking gets underway, we will begin to look more into ways to determine specific inhibitors through pharmacophore generation and comparison.

Cultural Exploration!