Predicting the impact of point mutation on Protein Structure
Mentor: Dr. Zoé Lacroix
Location: Scientific Data Management Lab. Room GWC 443

Amino acid substitution is now considered as a major constraint on protein evolvability, while it was previously admitted that most positions can tolerate drastic sequence changes, provided the fold is conserved (see review by Tokuriki and Stawfik, 2009). Actually, mutations affect stability and stability affects evolution. The level of deleterious mutations can be as high as one third. Therefore, the prediction of the effects of residue substitution can be of great help in wet labs. Due to evolution, the number of stabilizing mutations is smaller than for destabilizing ones. One must mention that a stabilizing mutation is not necessarily related to an improved efficiency of the mutated protein, as far as function is concerned. Sometimes, a more stable structure results in an increased rigidity, while the function requires a certain level of flexibility. This is the case, for instance, with the enzyme catalysis (Worth et al., 2011). Therefore, it seems reasonable to place a threshold of 2 kcal/mol in either ways of $\Delta\Delta G$ (stabilizing or destabilizing) in order to claim a putative malfunction. Mutations in conserved positions usually cause large stability decreases.

In this project, we aim at improving our current consensus method taking an average of various stability analyses to predict the impact of point mutation on protein structure (see SPROUTS at http://sprouts.rpbs.univ-paris-diderot.fr/ and Lonquety et al., 2009). The current method focuses only on the thermodynamic contribution to stability, which can be considered as acceptable for small and medium size proteins (500 AA maximum length). We wish to explore how other methods such as the prediction of Most Interacting Residues (MIR) can improve the prediction on the impact of mutation.


To apply, a student must contact Dr. Lacroix at zoe.lacroix@asu.edu with a resume up-to-date and a letter of motivation (stipulating the reasons why you are interested by the project, if you have prior knowledge of the problems addressed, if you are interested to participate in a cross-disciplinary project, etc.)