

KS3 - Christodoulos Floudas (Princeton University - USA)

Overcoming the Key Challenges in De Novo Protein Design: Enhancing Computational Efficiency and Incorporating True Backbone Flexibility

Abstract:

Proteins serve as vital components in our cellular makeup and perform many biological functions that are essential for sustaining life. An important feature which determines the functionality of a protein is the form of its three-dimensional structure. Elucidated protein structures can also serve as templates for the de novo protein design which is of major importance in structure-based drug design and plays a pivotal role in the scientific challenge/roadmap: sequence to structure to function.

The primary objective in de novo protein design is to determine the amino acid sequences which are compatible with specific template backbone structures that may be rigid or flexible. It is of fundamental importance since it addresses the mapping of the space of amino acid sequences to known protein folds or postulated/putative protein folds. It is also of significant practical importance since it can lead to the improved design of inhibitors, design of novel sequences with better stability, design of catalytic sites of enzymes, and drug discovery.

The first part of this presentation will provide a motivation for the de novo protein design problem with flexible backbone template structures and an overview of the advances and limitations of the existing approaches. The second part will introduce a novel two stage approach which takes into account explicitly the flexibility of the templates. The first stage addresses the in silico sequence selection problem. The second stage addresses the fold specificity by performing structure prediction calculations using atomistic level force fields and the first principles approach, Astro-Fold. The probabilities of each sequence to fold specifically to the flexible templates are calculated. The theoretical prediction results for several systems that include variants of Compstatin, human beta defensins, and C3a will be presented.