A Novel Coevolution Data-based Approach for Computational Drug Design to Target Intrinsically Disordered Proteins

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Because traditional (experimental) methods of drug design involve trial and error, they are expensive and time-consuming. Intrinsically disordered proteins (IDPs) are structurally flexible proteins that have been observed as key players in many diseases, including Hepatitis, cancer, Alzheimer's Disease and diabetes. Little is known about the structure or function of IDPs because their structural flexibility prevents their structures from being specified experimentally by crystallography or NMR. In order to design drugs for diseases caused by IDPs, an alternative approach is required. The purpose of this project is to develop and demonstrate a cheap, fast alternative approach to generate drug candidates for diseases caused by IDPs. Here I applied a statistical coevolution analysis to obtain data about functionally important residues in IDPs, used this data to generate mutant proteins that may serve as drugs by competitive inhibition, and computationally tested the mutants for viability as drug candidates. As a proof of concept, I targeted the disordered protein hepatitis C virus NS5A and ordered protein human VAPB binding complex. The coevolution analysis was used to computationally generate variants mutated at functionally important non-binding residues in both NS5A and VAPB to produce non-functional mutants. The NS5A and VAPB mutants had very high binding site conservation (>88%), and the VAPB mutants had very high tertiary structure conservation (>99%), indicating that they are potential drug candidates. Hence I have shown that my novel statistical approach is capable of generating protein drug candidates with high potentiality, high efficiency, and low cost in comparison to traditional methods.

Awards Won:

Fourth Award of $500

American Statistical Association: Third Award of $250