Siemens Competition
Math : Science : Technology
Regional Finalist

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Project Title: *A Novel Method of Targeting Intrinsically Disordered Proteins for Drug Discovery: Application to Cancer and Tuberculosis* (Computer Science)

For treating many diseases, it is necessary to target intrinsically disordered proteins (IDPs) that constantly change their tertiary structure, unlike other protein targets of drugs. However, IDPs are difficult to target because their constantly changing structure makes it difficult for drugs to bind to them. IDPs are hubs of protein-protein interaction networks, and their mutation leads to complex neurodegenerative and infectious disorders. In this research, we develop a novel method to block the interactions of the IDP by finding drugs that bind to the IDP's protein partners in place of the IDP. An IDP protein partner is another protein, often ordered, that binds to the IDP. These drugs out-compete the IDP for effective inhibition. This research integrates biomimicry and support vector machines (SVMs) to determine effective inhibitors of IDP interactions.

The proposed method compares the drug to the IDP binding site using forty-eight 3D descriptors, which are condensed into four 3D similarity features. These features are used as inputs to the SVM classifier. The SVM is trained on more than seventeen hundred drugs from bioassay data on two oncogenes and a Tuberculosis enzyme, and predicted test set cases with more than 90% accuracy.

Furthermore, we validate the classifier through application to Thrombin, a protein promoting tumor metastasis which has FDA approved inhibitors. The classifier ranked an approved Thrombin inhibitor as having the greatest activity out of nearly three thousand FDA approved drugs. We apply the classifier and docking simulations to find novel inhibitors of the Tuberculosis EmbR protein, which plays a key part in bacterial drug resistance. A number of drugs were identified with antibacterial activity against Tuberculosis and related bacteria. This method is further applicable to identifying drugs with activity against other deadly viruses, like Marburg virus and Ebola.