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Problem: Inverse docking as a platform to elucidate mechanisms defining adverse reactions to drugs

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Description of the problem:

Clinical applications and development of drugs is often hindered by adverse drug reactions (ADRs). The ADRs contribute to over 30% of failures in the late stages of drug development, incur high costs due to the drug-related mortality and undesirable side-effects and result in drug attrition. The ADRs are learned from preclinical toxicity studies, clinical trials, and post-marketing clinical reports of healthcare professionals. The information from these sources is relatively expensive to obtain and incomplete as it does not provide insights into the underlying molecular-level mechanisms. Recent work suggests that many ADRs are induced through an interaction of a drug with proteins, which include both the therapeutic and non-therapeutic (off-targets) drug targets.

The elucidation of ADRs requires as inverse docking-based approach, i.e., a given compound is screened against all potential off-targets (on a structural proteome scale) to find all off-targets that interact with the compound and as a results potentially trigger the ADRs. Conventional (non-computational) methods for identification of the off-targets rely on an in vitro counterscreen of a given compound against a large set of enzymes and receptors. The in-silico methods are more cost and time effective and, most importantly, they also provide insights into molecular mechanisms of the protein-drug interactions.

This problem concerns development of a computational solution that encompasses a bioinformatics-driven methodology for the discovery of compound–off-target interactions on the structural proteome-wide scale and a framework for validation and interpretation of the discovered off-targets against known and suspected physiological side-effects.

The main drawback of traditional proteome-wide analysis is the computational expense. One docking experiment takes between few minutes and few days depending on the complexity of the interaction and the size of the compound and the target. At the same time, in the case of our problem the total number of potential off-targets will exceed 11,000. There are two existing inverse docking methods, but both of them have a number of substantial drawbacks that prevent from their direct application. Our solution will be divided into three phases: 1) binding site prediction; 2) molecular docking; and 3) validation and interpretation of the predicted off-targets. The main challenges are scaling into the large size of the set of all potential off-targets and the interpretation of the predictions.

The proposed problem constitutes an attractive extension to the existing drug discovery and development pipeline. The discovered insights into the molecular mechanisms concerning ADRs will provide information that could be used to reduce ADRs by either designing novel variants of the existing drugs or by taking additional precautions when using the old ones.