Irreversible binders design using molecular docking: the Reactive Docking method

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The identification of molecules capable of binding selectively to biologically relevant targets is generally a non-trivial task. Challenges may come from the search of the optimal binders in the chemical space, but also from the experimental confirmation of the binding event itself together with the identification of robust biological assays for assessing the activity. Complexity further increases when designing molecules capable of targeting protein-protein interactions (PPI) [1], or orphan proteins for which a phenotype is not known yet. In order to address these hard challenges, in recent years there has been a great interest in the use of covalent binders (or suicide inhibitors [2]). Molecules capable of irreversible binding simplify considerably the hit identification because of the initial low-affinity required to binding, and the capability of altering considerably the biological activity of the target, simplifying the clarification of its role in unknown/undiscovered biological pathways.
Using AutoDock [3], we have designed a special docking protocol called "Reactive Docking"[4] which is specifically tailored to model irreversible binding events. The protocol is fully predictive, allowing the identification of the preferred reaction sites on the protein surface, as well as the identification of which molecules are more likely to react with a given residue. Its implementation allows to screen reactive ligand libraries against large number of targets in a high-throughput fashion, and has been successfully applied in a proteomic-wide studies[4].

Rerefences

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