

[P2] Reduction of False Positives in Structure-Based Virtual Screening when Receptor Plasticity is Considered

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Structure-based virtual screening for selecting potential drug candidates is usually challenged by how numerous false positives in a molecule library are excluded when receptor plasticity is considered. In this study, based on the binding energy landscape theory, a hypothesis that a true binder can bind to different conformations of the binding site favorably was put forth, and related strategies to defeat this challenge were devised; reducing false positives when receptor plasticity is considered. The receptors in the study are the influenza A nucleoprotein and the bacterial actin MreB. The structural flexibility of influenza A nucleoprotein and MreB were explored by molecular dynamics simulations. The resultant distinctive structures and the respective crystal structures were used as receptor models in docking exercises in which two binding sites of the influenza A nucleoprotein and one binding site of MreB were targeted with molecule libraries using the GOLD software. In each case, the intersection ligands that were listed in the top-ranked molecules from all receptor models were selected. Such selection strategy successfully distinguished high-affinity and low-affinity control molecules added to the molecule libraries. Crystal structures of MreB in complex with molecules selected by this strategy support our hypothesis. This work provides an applicable approach for reducing false positives and selecting true ligands from molecule libraries.

Keywords: virtual screening; receptor plasticity; false positives; docking; GOLD