Function-based virtual screening using machine learning and single ligand dynamic interaction data

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G-protein coupled receptors (GPCRs) are one of the most important targets in drug discovery thanks to their role as signaling transducer in multiple key biological processes. The binding of a ligand in the orthosteric pocket influences intracellular signaling. Agonists bind the receptor and trigger its signaling, while antagonists inhibit it.

Binding mode information from experimental structures has often been used in virtual screening to filter or rescore docking poses [1]. Interaction similarity not only allows to distinguish between active and inactive molecules, but it has also been shown to distinguish between agonists and antagonists. While successful, this approach is limited by the inherently static nature of crystallographic data [2], to overcome it we developed a new method leveraging binding mode information extracted from molecular dynamics (MD) simulations [3].

Machine learning, specifically one class classification, was used to identify key interactions from MD simulations. The classifiers were trained to identify binding modes comparable to the ones in the training set, while discarding anomalous ones. The model can be used to postprocess docking results, selecting poses where the molecule forms key interactions, while discarding non-relevant ones.

As a proof of concept this method was used to identify known agonists of the β2 adrenergic receptor against known antagonists, and experimentally validated inactive molecules [3]. This approach was further tested on multiple GPCRs to determine its limits and advantages when applied to receptors of different nature or using as reference ligands with a different pharmacological profile.

Bibliography:

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