Implementation of A Webserver for Ensemble Docking with SARS-CoV-2 Proteins
by Mauricio M. Rigo

Abstract: The consequences of COVID-19 pandemic have been disastrous, and efforts are currently being made to find a vaccine and new medications. The Main protease (Mpro), a SARS-CoV-2 protein involved in viral gene expression and replication, is being used as one of the targets in several molecular docking studies for drug design. However, despite more than 150 crystallographic Mpro structures being available in the Protein Data Bank (PDB), most efforts are focused on one single structure, ignoring the Mpro flexibility. In addition, Mpro binding site is formed by a dimer, but most molecular docking studies have taken into account only one of the protomers. Here we present a method that accounts for the role of both protomers in determining the flexibility of the Mpro binding site in solution. We have incorporated this approach in a webserver (DINC-COVID) that can be broadly used by practitioners with different expertise. The DINC-COVID webserver provides binding modes that account for the flexibility of both the ligand and receptor. For that, three Mpro ensembles with highly diverse conformations were constructed based on crystal structures and molecular dynamics simulation. Representative ensemble conformations were selected with a combination of dimensionality reduction and clustering. The sampling of the ligand is performed with Autodock Vina, and the output conformations are ranked using AutoDock Vina, AutoDock4, and Vinarodo scoring functions. The best binding modes for each scoring function are chosen, and the resulting complexes are returned. As validation, DINC-COVID was able to reproduce 36 near-native binding modes complexes during self-docking, as evidenced by the low mean RMSD (only 1.4 Å) between the binding modes and the ligand crystal structure. In addition, different receptor conformations contributed to the lower energy binding modes in different ensemble docking experiments. These results highlight the potential of DINC-COVID to identify completely novel binding modes, and to reveal yet unknown candidate inhibitors for SARS-CoV-2 Mpro. The webserver is available at dinc-covid.kavrakilab.org. This work was funded by the National Science Foundation (NSF), by the Cancer Prevention & Research Institute of Texas (CPRIT), by the National Council for Scientific and Technological Development (CNPq, Brazil), and by Rice University funds.