Improved Protein-Ligand Binding with DINC Web Server

Hall-Swan S[1], Kavraki L[2], Devaurs D[2]

1. Tufts University, Medford MA
2. Department of Computer Science, Rice University, Houston TX

Abstract

Computational molecular docking tools are used to predict protein-ligand binding modes, which is important in drug discovery and design. Most tools are designed for small ligands, but large ligands, such as peptides, are also important. Peptides can be used to modify protein-protein interactions, and thus are possible treatments for various diseases, including cancer immunotherapy treatments involving the Major Histocompatibility Complex (MHC). Computational methods are needed for predicting the docking modes of peptides, as there are too many peptides to be tested experimentally. DINC is a meta docking tool that incrementally docks overlapping fragments of a ligand using AutoDock, a popular docking tool, therefore allowing it to predict binding modes of ligands that are too large to be efficiently analyzed using other tools. We hope to improve DINC's performance by integrating different docking tools, in both the sampling and scoring of the ligand fragments. Improving DINC's accuracy will allow obtaining better predictions, while improving DINC's efficiency will allow virtual screening of more peptides at once.

Background

Computational Molecular Docking

Computational molecular docking tools are used to predict protein-ligand binding modes, which is important in drug discovery and design. These tools can be used to dock flexible ligands to a target protein, for example, in the process of finding which ligands are potentially good inhibitors of this protein. This saves time and money by narrowing down the list of potential inhibitors to ligands with the highest binding affinity, thus decreasing the number of ligands that must be tested experimentally in the lab. There are a number of molecular docking tools available, but most are designed for small ligands with 12 or fewer rotating bonds [2]. Using more rotational bonds increases computational time and produces less accurate results [1], so there is a need for better tools for large ligands, like peptides, for pharmaceutical uses like cancer immunotherapy.

Cancer Immunotherapy

Large ligands like peptides and peptidomimetics can be used to modify protein-protein interactions, and thus are possible treatments for various diseases, including cancer immunotherapy treatments. Cancer immunotherapy relies on the Major Histocompatibility Complex (MHC) protein, which can trigger a T-cell immune response from cancerous cells by displaying peptides (i.e., fragments of proteins produced in the cell) on the cell surface [2]. Predicting which peptides will bind MHC proteins is critical for evaluating potential immunotherapy targets. Computational methods are needed for predicting the docking modes of peptides, as there are too many to be tested experimentally.

DINC

DINC (Docking INCrementally) is a meta docking tool that was designed to solve the problems of docking larger ligands. It is a meta docking tool that incrementally docks overlapping fragments of a ligand, with each fragment containing 6 rotatable bonds [2]. The

current version of DINC uses the popular docking tool AutoDock to dock each fragment. Previous work has shown that DINC is faster and more efficient than AutoDock alone when used to dock larger ligands, but DINC is not always more accurate than AutoDock, especially when docking large peptides [2]. In this project, we explored a couple ways of improving DINC's performance.

Methods

We created two alternate versions of DINC to improve the tool. The first version, DINC-Vina, replaces AutoDock with Vina for both the sampling and scoring parts of the algorithm. The second version, DINC-Hybrid, uses consensus scoring for each fragment. Each fragment is docked using AutoDock and the output conformations are ranked by binding energy according to AutoDock's scoring function. Then, the conformations are rescored by Vina's scoring functions and given ranks based on those binding energies. The two ranks are summed to find the overall rank of the conformation, and the top ranks are used in the next iteration of DINC.

We performed a preliminary assessment of each version of DINC with redocking experiments. Redocking experiments use a known ligand-protein pair and compare the docking program's results with the known crystal structure of the ligand. We used the crystal structure whose code is 4d0d in the protein databank. This complex contains a peptide with 26 rotational bonds bound to a major histocompatibility complex (MHC) protein. We compared the top scoring binding modes from each version of DINC, looking at the binding energy and RMSD (root mean square distance) as compared to the original crystal structure of 4d0d.

Results

The results from the preliminary assessment show that the two new versions of DINC perform better than the original DINC, especially with regard to the RMSD of the docked ligand (Figures 1, 2, 3). The output RMSD was lower in DINC-Vina than DINC, and even lower in DINC-hybrid. Both DINC-Vina and DINC-Hybrid's top scoring conformations had RMSD $\leq$ 4Å.

Figures

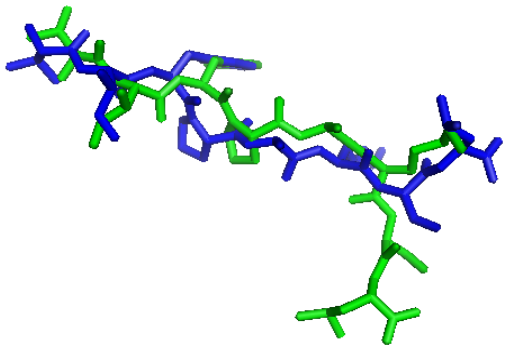

Figure 1. The top scoring output conformation from DINC (blue) compared to the original crystal structure of the ligand (green). The output has a binding energy of -12.20 kcal/mol and RMSD of 4.30Å.

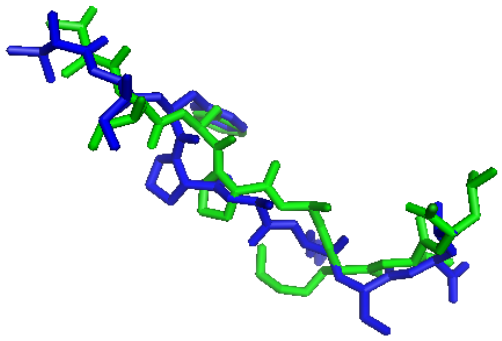

Figure 2. The top scoring output conformation from DINC-Vina (blue) compared to the original crystal structure of the ligand (green). The output has a binding energy of -13.30 kcal/mol and RMSD of 3.15Å.

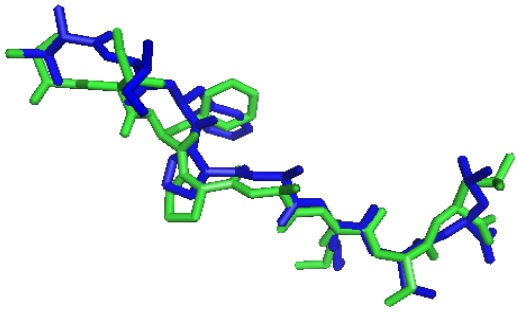

Figure 3. The top scoring output conformation from DINC-Hybrid (blue) compared to the original crystal structure of the ligand (green). The output has a binding energy of -10.51 kcal/mol according to AutoDock and -15.24 kcal/mol according to Vina, and its RMSD is 1.98Å.

Discussion

From the preliminary results, we can see that DINC can be improved to dock larger ligands. Based on these results, there is more improvement with DINC-hybrid, but more benchmarking must be done to confirm this. Going forward, we expect similar results to these preliminary findings, and thus we believe that DINC with Vina will benefit researchers working on improving cancer immunotherapy. Improving DINC's accuracy will allow obtaining better predictions, while improving DINC's efficiency will allow the virtual screening of more peptides at once.

References

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