Improved Protein-Ligand Binding with DINC Web Server

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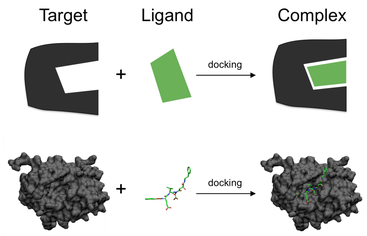
Computational Molecular Docking

- Predict protein-ligand binding modes
- Fast and cheap screening before experimentally testing protein-ligand binding
- Most tools designed for small ligands with 12 or fewer rotational bonds [1]



Sampling: Generates possible docked conformations of a particular ligand

Scoring: Calculates the binding energy and ranks the conformations

DINC – Docking INCrementally

- Designed to solve problems with docking larger ligands

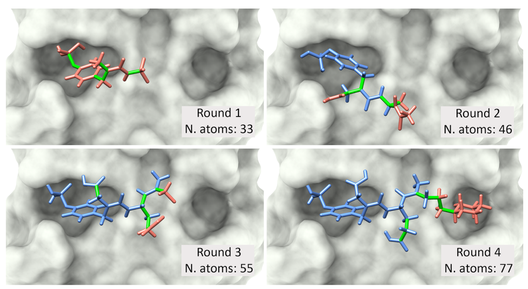


Fig 1. showing the incremental docking method of DINC.

- Current version of DINC uses AutoDock to dock each fragment

Problem:

Previous work has shows DINC to be more efficient than AutoDock alone, but not always more accurate when it comes to large peptides [2]

References

[1]Dhanik, A., & Kavraki, L. E. (2012). Protein-Ligand Interactions: Computational Docking. *ELS*. doi:10.1002/9780470015902.a0004105.pub2

[2] Dhanik, A., Mcmurray, J. S., & Kavraki, L. E. (2013). DINC: A new AutoDock-based protocol for docking large ligands. *BMC Structural Biology, 13*(Suppl 1). doi:10.1186/1472-6807-13-s1-s11

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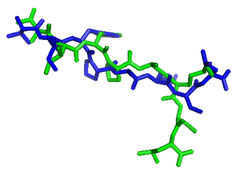
Improving DINC to dock large peptides

Method 1: DINC-Vina

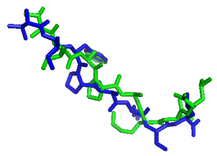
Replace AutoDock with Vina, a potentially more powerful tool



DINC output

Binding Energy: -12.20 kcal/mol

all atom RMSD: 4.30Å



DINC-Vina output

Binding Energy: -13.30 kcal/mol

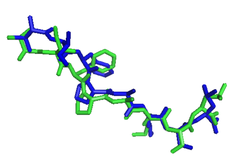
all atom RMSD: 3.15Å

Original crystal structure in blue, docked ligand in green

Method 2: DINC-Hybrid

Implement consensus scoring with scoring functions from AutoDock and Vina

- Uses AutoDock to sample and score
- Rescores output binding modes with Vina
- Ranks conformations by binding energy based on each scoring function, then sums the ranks



DINC-Hybrid output

Binding Energy:

-10.51 kcal/mol (AutoDock) or

-15.24 kcal/mol (Vina)

all atom RMSD: 1.98Å

Original crystal structure in blue, docked ligand in green

Evaluations

- The two versions of DINC with Vina are more accurate than DINC with AutoDock

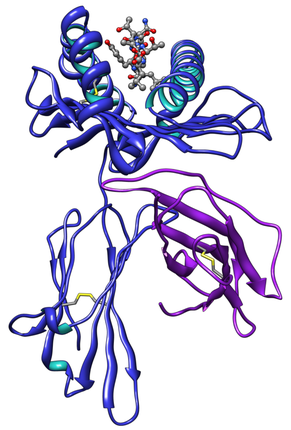
Further testing

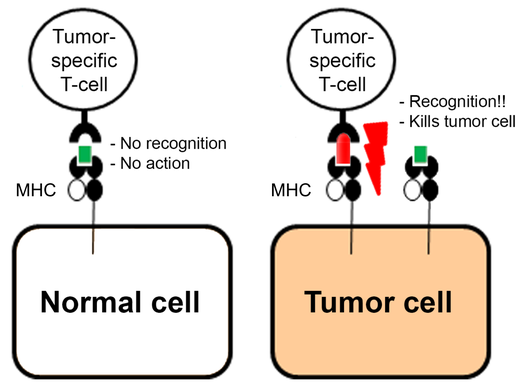
- Benchmarking of each version of DINC with many more ligands to assess performance

Application to Cancer Immunotherapy

Major Histocompatibility Complex (MHC) [2]

- Binds peptides from cell and displays them on cell surface
- T-cells recognize peptides from cancerous cells, triggering an immune response
- Predicting which peptides will bind MHC proteins is critical for evaluating potential immunotherapy targets





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