Development of docking protocol for small molecules on tubulin

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Introduction

- Microtubules (MT) have gathered significant attention due to their key role in biological functions such as mitosis and axonal transport; targeting MT is a strategy for the treatment of several types of cancer and potentially neurodegenerative diseases[1].
- Due to MT's importance as drug target we intend to develop an appropriate molecular docking protocol to discover new small molecules targeting tubulin.
- We plan to evaluate the performance of several molecular docking software by re-docking known ligands and then evaluate the docked poses' reliability with Molecular Dynamics simulations[2].

Materials and Methods

So far, we have tested AutoDock4, AutoDock Vina, LeDock and DOCK. The system we chose for the docking simulation is a tubulin dimer (Fig. 1A). Several ligands in each of the eight pockets of tubulin, for a total of 30 ligands, have been re-docked with all the listed software.

All the protein structures were downloaded from the Protein Data Bank. For each ligand 100 conformations (500 with DOCK) were generated.

In Fig. 1B, 1C and 1D the Colchicine, Epothilone, and Maytansine's binding sites are respectively shown.

- In magenta, structures docked with AutoDock4;
- In orange, structures docked with AutoDock Vina;
- In yellow, structures docked with LeDock;
- In cyan, structures docked with DOCK.

The structures shown are not aligned to the crystallographic to see each software's ability to orient correctly the ligand in the binding site. To evaluate the ability to generate the correct conformation, the RMSD of the best pose with respect to the crystallographic one was calculated with AutoDockTools (ADT) and reported in Table 1. If the RMSD is lower than 2 Å we can conclude that the predicted conformation is good.

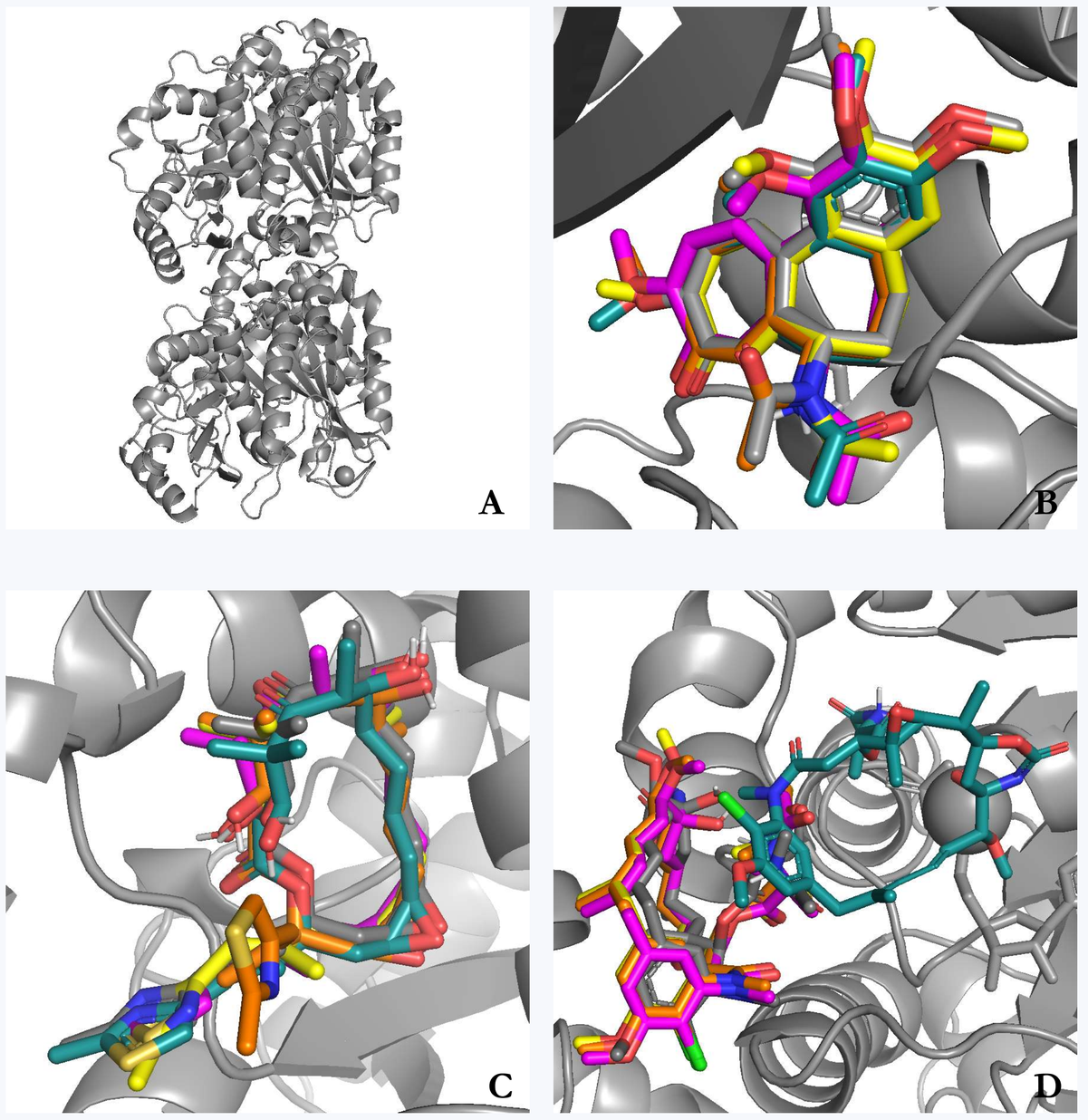

Figure 1: A) Tubulin dimer; B) Colchicine site; C) Epothilone site; D) Maytansine site

	AutoDock4	Autodock Vina	LeDock	DOCK
Colchicine	**1.296 Å**	**1.170 Å**	**1.165 Å**	**1.100 Å**
Epothilone A	**1.193 Å**	**2.875 Å**	**1.247 Å**	**0.890 Å**
Maytansine	**1.649 Å**	**1.427 Å**	**1.642 Å**	**10.466 Å**

Table 1: RMSD values of the best pose with respect to the crystallographic structure

Preliminary results and outlook

- Overall, we can see that the software tested so far can predict good structures in most of the cases, however the more flexible the ligand the worse the performance.
- AutoDock4 and DOCK obtained the lowest values, however, the maytansine docked with DOCK is slightly shifted from the crystallographic one.
- We intend to try other molecular docking software, modify the protocol and perform MD simulations for rescoring.

References

1. Steinmetz MO et al. Strategies To Hijack the Cytoskeleton. Trends Cell Biol. 2018 Oct;28(10):776-792.
2. H. Guterres and W. Im. Improving Protein-Ligand Docking Results with High-Throughput Molecular Dynamics Simulations. Journal of Chemical Information and Modeling 2020 60 (4), 2189-2198.