

Effects of Structure Minimization on The Docking Score and Docking Time During Computational Analysis Using the Chimera Software

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Abstract

Drug discovery through computational analysis has revolutionized drug discovery. The process has comparatively reduced the time taken to develop and bring a drug into the market. Several steps are essential to be able to get results of the ligand receptor interaction(docking). Minimization is one of the steps in drug discovery. Although this step has been highlighted a step of in docking preparation, the docking can take place with or without the process. In this paper, the impact of the step on the docking scores and the time taken between the initiation of the docking process and the popping up of the docking results were examined. The results were analyzed and it was concluded that the depending of the molecule the minimization process has an impact on the docking time as well as the docking score. Recommendations were made that the minimization step should be evaluated on a case-to-case basis. This would hence reduce the time wastage associated with ligand minimization for a ligand that the process is not necessary and improve results.

Keywords: drug discovery; chimera; avogadro; minimization; docking; docking score

Introduction

Drug discovery is a complex process aimed at finding and creating new drugs for effective management of diseases (Sadeghi & Keyvanpour, 2021). It has been estimated that bringing a new drug into the market world need at least 10-17 years on average with an expenditure of about \$0.8- \$1.5 billion (Sadeghi & Keyvanpour, 2021). The process begins with identifying and confirming potential treatment the targets and concludes with the approval of a new medication for use in clinical settings (Drews, 2000). Computational analysis is one of the methods of drug discovery (Hung & Chen, 2014). Computational drug analysis is a method that molecules are attached to their targets including enzymes and transporter receptors through simulations (Hung & Chen, 2014). Due to the expensive nature of the drug discovery process caused by the screening of molecules with less chances of the having the desired outcomes, computational analysis is becoming a preferred method if drug discovery (Kapetanovic, 2008). Computational analysis reduces the number of molecules to few molecules with the potential properties to serve as candidates for a potential drug (Leelananda & Lindert, 2016). This reduces the time used and the cost that is associated with the drug

discovery process (Shaker et al., 2021) (Drews, 2000). This method has been used successfully to bring drugs into the such as atazanavir, indinavir. saquinavir, and ritonavir (HIV)-1-inhibiting drugs), raltitrexed (an anticancer), and norfloxacin (antibiotic) (Shaker et al., 2021).

Computational analysis can be divided into two. Structure based drug discovery (SBDD) and ligand-based drug discovery (LBDD) (Brogi, 2019) Ligand based screening allows analysis of similar looking ligands to be determine which has the best properties (Kapetanovic, 2008). This approach relies on the notion that the structures of a ligand and its receptor's binding site ought to fit together seamlessly, demonstrating complementarity (Guido et al., 2012). Online tools such as SwissSimilarity, uses canonical smiles of available drugs to generate molecules with almost similar structures to the parent compound (Zoete et al., 2016). SBDD is a continuation of LBDD. Structure-based drug discovery is based on the computational analysis of the three-dimensional structure of the target protein (Nascimento, 2023). This can be obtained from online databases such as Protein Data Bank. By docking the molecules obtained from LBDD, the researcher can be able to determine the binding affinities of the molecules and

the protein targets. The process uses algorithms to predict the binding poses and affinities of ligands within the binding site of the target protein (Butt et al., 2020). To execute structure-based screening effectively, access to the three-dimensional structure of the target protein is imperative, which can be obtained via experimental methods like X-ray crystallography or homology modeling. Docking algorithms, molecular dynamics simulations, and free energy calculations are frequently employed in structure-based virtual screening to refine predictions and gain insights into ligand-protein interactions (Aziz et al., 2023). This method is used complementary to the LBDD to give out more information about the molecules and their targets (Blundell, 1996).

Common software used include Avogadro (RRID: SCR_011958) and chimera (RRID: SCR_004097) are used in the preparation of the molecules for the docking process. There are several processes that are used to prepare the both the ligand and the target protein for the docking process. The protein is prepared by chimera by removal of all non-standard residual compounds from the structure to make it fit for ligand binding. The ligand on the other hand is prepared by both chimera (RRID: SCR_004097) and the Avogadro software. the ligand is first auto-optimized by Avogadro (RRID: SCR_011958) then minimized (adding hydrogen and charges) using chimera and then the docking process is done using the chimera software (RRID: SCR_004097) (Kamakia et al., 2023). These processes are essential in the determining the final docking scores. Computational analysis aims at reducing the time needed during drug discovery by narrowing the ligands to the few which show desirable characteristics. As described above, there are various steps used in the preparation of the ligand and the protein target before the docking process. This study analyses the process of ligand preparation. The study focuses on the ligand minimization process and the effect of the process on the docking score, the time taken to obtain the docking scores, as well as the ligand-receptor interaction. Four different compounds; Paracetamol, Losartan Suvorexant and Ibuprofen are randomly selected as subjects of the study. 5 analogues of each molecule are docked.

Objectives

- To identify compounds similar to Paracetamol, Losartan Suvorexant and Ibuprofen from the ZINC database.

- To obtain the respective protein targets.
- Prepare both the ligand (minimized and non-minimized) and the target proteins.
- To compare the docking scores and the time used for docking for the compounds.

Methodology

Identifying Compounds Similar to Paracetamol, Losartan Suvorexant and Ibuprofen from The ZINC Database

Paracetamol, Losartan Suvorexant and Ibuprofen were searched individually through PubChem online tool (RRID:SCR_004284). The respective canonical smiles were used to query the for similar compounds from the ZINC database from SwissSimilarity. The obtained compounds were saved in form of an excel file to the local storage separately.

Ligand Preparation

Individual canonical smile was used to the query the 2D structures for the canonical smiles on PubChem sketcher. The 2D structures exported to the local storage. The resulting ligands were prepared in two separate steps

Structure With Minimization: The structures were individually opened on Avogadro. The structure was then optimized using MMF94s force field with fixed atoms movable. The resultant structure was then saved in. mol format. The structure was then again opened in chimera and minimized to add hydrogen and charges. This was performed by clicking tools section on chimera, then selecting structure editing, using the steric only settings and then Gasteiger as the other residues, in the setting section The resultant structure was saved to be used in the docking

Structure Without Minimization: The same structures used above were individually opened on Avogadro. The structure was then optimized using MMF94s force field with fixed atoms movable. The resultant structure was then saved in. mol format. The resultant structure was used in the docking.

Obtaining the Respective Protein Targets

The unique protein target ID was obtained from PubChem. It was then used to query the respective protein targets were obtained from the Protein Databank (RRID:SCR_012820).The file was then downloaded and saved as a PDB file on the local folder.

Preparation of the Target Proteins

The respective target proteins were “cleaned” by removing all non-standard molecules from the structure using chimera. The structure was then saved in a PDB to be used for the docking process.

Docking

The docking process refers to where the ligands interact with the respective receptors on a simulation using the chimera software. Chimera is embedded

with AutoDock Vina (RRID: SCR_011958). The results including docking scores and the time used for docking scores were recorded. The parent ligand-receptor complex (for minimized and non-minimized structures) were analyzed using the Biovia Discovery studio (RRID: SCR_01565) to determine the interaction between the receptor and the ligand using the 2D and 3D models of the complexes.

Results

Table 1a: Docking scores for Ibuprofen unminimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock
1	100	ZINC000000113398	-7.6	9780
2	100	ZINC000000002647	-7.5	9876
3	100	ZINC000007023266	-7.8	8705
4	99.9	ZINC000036157909	-7.3	9805
5	99.9	ZINC000000395681	-7.1	8785
Ibuprofen	100		-7.6	8850

Table 1b: Docking scores for Ibuprofen minimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock
1	100	ZINC000000113398	-7.6	9943
2	100	ZINC000000002647	-7.5	8997
3	100	ZINC000007023266	-7.8	9940
4	99.9	ZINC000036157909	-7.3	9955
5	99.9	ZINC000000395681	-7.7	9820
Ibuprofen	100		-6.8	7516

Table 2a: Docking scores for Paracetamol unminimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock
1	99.9	ZINC000001437230	-8.7	9743
2	99.9	ZINC000000394165	-8.1	10036
3	99.9	ZINC000000393257	-8.2	10008
4	99.8	ZINC000001596846	-7.3	10009
5	99.7	ZINC000059562238	-8.7	10052
Paracetamol	100		-6.9	7912

Table 2b: Docking scores for Paracetamol minimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Take to Dock
1	99.9	ZINC000001437230	-8.7	8222
2	99.9	ZINC000000394165	-8.7	7968
3	99.9	ZINC000000393257	-8.2	8826
4	99.8	ZINC000001596846	-7.3	10014
5	99.7	ZINC000059562238	-8.8	9050
Paracetamol	100		-6.9	8136

Table 3a: Docking scores for Losartan unminimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock (cs)
1	100	ZINC000014952767	-9.1	12660
2	99.2	ZINC000022001266	-9.1	12881
3	99.1	ZINC000077300648	-8.9	12670

4	98.5	ZINC000077300650	-8.9	126.47
5	97.3	ZINC000065743146	-9.7	17659
Losartan	100		-9.3	12789

Table 3b: Docking scores for Losartan minimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock (cs)
1	100	ZINC000014952767	-9.1	13672
2	99.2	ZINC000022001266	-9.1	13683
3	99.1	ZINC000077300648	-8.3	13656
4	98.5	ZINC000077300650	-9.1	13689
5	97.3	ZINC000065743146	-9.1	17731
Losartan	100		-9.3	12687

Table 4a: Docking scores for Suvorexant unminimized ligands.

Ligands	Percentage Similarity	Zinc ID	Docking Scores	Time Taken to Dock (cs)
1	100	ZINC000049036447	-10.5	9728
2	99	ZINC000095079930	-9.2	10759
3	99	ZINC000253476142	-9.8	9796
4	95.3	ZINC000206774725	-9.3	7831
5	95.1	ZINC00020677477	-8.8	8906
Suvorexant	100		-10.1	9757

Table 4b: Docking scores for Losartan unminimized ligands.

Ligands	Percentage Similarity	Cannonical Smile	Docking Scores	Time Taken to Dock (CS)
1	100	ZINC000049036447	-10.2	10759
2	99	ZINC000095079930	-10.0	9772
3	99	ZINC000253476142	-9.6	9789
4	95.3	ZINC000206774725	-9.2	8884
5	95.1	ZINC00020677477	-9.2	8905
Suvorexant	100		-9.2	9780

Table 5: Docking Score Analysis and Time analysis.

	Minimized Ligand			Unminimized Ligands		
	Mean	Median	Standard Deviation	Mean	Median	Standard Deviation
Ibuprofen	-7.45	-7.55	0.37	-7.48	-7.55	0.23
Paracetamol	-8.1	-8.35	0.68	-8	-8.15	0.64
Losartan	-9	-9.1	0.28	-9.17	-9.1	0.28
Suvorexant	-9.6	-9.4	0.42	-9.57	-9.55	0.68

Discussion

Minimization step is a common procedure that is used computational analysis method of drug discovery especially when using the chimera software (Otieno & Kagia, 2023). This step involves both adding hydrogens for docking preparation as well as adding charges to the ligand and the parent compound (Wang et al., 2006). This step is also important in keeping some atoms optionally fixed but has a limitation of not being able to solve large distortions in molecules (Minimize Structure, n.d.). This process is done as a docking preparation step for the ligand. Although this step is a common practice in

computational analysis using chimera, the docking process can occur with or without the step determined by the practical application obtained from the experimental data from this study. This provides a window to study the essentiality of this process and the effects it causes of various parameters on the process of computational analysis. Docking scores, time taken for the docking results to be obtained were some of the parameters analyzed in this paper. Ligands were chosen through a purposive sampling technique (Rai & Thapa, 2015). Purposive sampling is a method that is selection of samples for qualitative studies. According to this method of sampling, at a

specific point the result would tend to be similar or repetitive (Suri, 2011). Hence a specific number of samples would produce same results at a given point. For the research the sample was chosen to be 5 ligands per compound on addition to the parent compound. Docking score measures the affinity of the receptor and target ligands (Durrant & McCammon, 2011). The more negative the value the greater the interaction. Various compounds have different docking scores depending on the structural properties relative to the receptor hence different ligands would produce different docking scores on the same receptor. Auto dock vina embedded in chimera provides a virtual environment for docking to take place (Durrant & McCammon, 2011). Secondly, time taken for docking to take place is also an important factor during the process of computational analysis (Baldi, 2010). This is because the process is based on time efficiency compared to the traditional method of drug discovery (Brogi, 2019). It's hence important to study the effect of ligand minimization in time used for docking process to be completed. Time taken for docking to take place is also an important factor during the process of computational analysis (Baldi, 2010). This is because the process is based on time efficiency, the compared to the traditional method of drug discovery. The less the time the more efficient the process (Brogi, 2019). It's important to study the effect of ligand minimization in time used for docking process to be completed.

Results obtained from the above Ibuprofen studies, minimized ligands (Table 1a) and a unminimized ligands (Table 1b) produced almost similar results. Time used for docking was higher in minimized compared to unminimized ligands except for ligand 1 which showed higher docking time in unminimized ligand compared to minimized ligand. Docking scores for paracetamol are almost similar for both minimized (Table 2a) and the unminimized ligands (Table 2b) although there was no clear comparison from the tables. The time used for docking minimized and unminimized ligands, indicated that the average time for docking a minimized ligand was lower compare to the time taken for the unminimized ligands. For losartan the average docking score were higher for minimized ligands (Table 3a) compared to the unminimized ligands (Table 3b). Time used for docking to take place. Minimized ligands had a lower time need for docking to take place compared to the unminimized ligands. Suvorexant was the last ligand to be analyzed. Docking scores for the minimized

(Table 4a) and unminimized ligands (Table 4b) were analyzed as well as the time used for the docking to take place. Generally, unminimized ligands had a better docking score compared to compared to the minimized ligand (Table 4a). The time needed for docking to take place was comparatively higher in the unminimized ligands compared to the unminimized ligands. Calculation of mean median and standard deviation of the docking score and docking time (Table 5) showed that the Ibuprofen and Losartan unminimized ligands showed better results compared to the minimized ligands while Suvorexant and paracetamol minimized ligands showed better results compared to the unminimized ligand.

Conclusion

In conclusion, ligand which were minimized and unminimized were successfully docked. The docking scores and the time between the start of the docking and the popping up of the docking results in chimera was measured and used to compare between the minimized and the unminimized ligands. Comparatively, Ibuprofen and Losartan unminimized ligands showed better results compared to the minimized ligands while Suvorexant and paracetamol minimized ligands showed better results compared to the unminimized ligand.

Recommendation

Based on the analysis, structure minimization step in chimera during computational drug discovery has a selective effect on docking time and docking score based on the type of compound being studied. For compounds like ibuprofen and losartan, where minimized and unminimized ligands better results, minimization may be unnecessary, thereby saving time and computational resources. However, for compounds like suvorexant and paracetamol, where minimized ligands showed higher docking scores and more significant receptor interactions, minimization is essential. The docking time efficiency did not show consistent differences between minimized and unminimized ligands, suggesting that the need for minimization should be evaluated on a case-by-case basis. Additional studies should do to provide more data for the essentially of the minimization step. Developing a customized workflow that includes an initial assessment of minimization's impact and maintaining detailed records of docking outcomes will further refine and enhance the drug discovery process. This balanced approach ensures that

minimization is applied only when necessary, optimizing both accuracy and efficiency.

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