ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF PROTEIN AND LIGAND-BASED DOCKING PROTOCOLS THROUGH PROTEIN PHOSPHATASE SLINGSHOT HOMOLOG 2 COMPLEX

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ABSTRACT

Background: A molecular docking study (Feb-2021 to March-2022) is used to investigate the interactions between the two molecules. These interactions may be covalent, hydrogen, or Van der Waals forces. Various web-based and stand-alone tools have been discovered for molecular docking analysis.

Objective: In this study, we performed a comparison between web-based and stand-alone docking tools to evaluate the accuracy.

Methods: Five web-based tools i) Dockthor, ii) Patchdock, iii) RPBA Web, iv) Swissdock, v) Patinum and two stand-alone tools1) Autodock Vina & 2) Hex were selected for the evaluation of the tool`s accuracy in term of best conformations with minimum binding energies. Protein phosphatase Slingshot homolog 2, SSH2 (PDBID: 2NT2) and four of its related proteins were used as the key proteins in this study. Ligands and Proteins interacting with SSH2 in the Novel signalling pathway were investigated through above mentioned tools.

Results: Score based analysis of two stand-alone tools and five docking web servers was done and a comparison table was formulated for comprehensive analysis on score based and RMSD values-based results.

Conclusion: Comparative evaluation of protein and ligand-based docking protocols through protein phosphatase slingshot homolog 2 complex done

Key Words: Stand-Alone tool, Docking, Analysis, Accuracy, Dockthor, Patchdock, RPBA Web, Swissdock, Patinum, SSH2, PDBID, 2NT2

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INTRODUCTION

Molecular Docking (MD) is an approach which is used for predicting alignment of a molecule with respect to another molecule.[1] This results in a stable complex which in turn helps for identifying binding affinity among the molecules. It means MD is useful for highlighting strength as well as type of the signal produced.[2] MD is one of the most popular techniques used in predicting structure-based drug design.[3] Docking may be Self-docking either Cross docking.[4] Self-Docking is a technique in which same types of two molecules are docked with each other like protein-protein docking while Cross Docking is a technique in with different types of two molecules are docked with each other like Protein-ligand and Antigen-Antibody docking.[4,5] Stand-alone docking tools are molecular conformational

imitation software. These software particularly effective for protein-ligand docking protocols and can be used as a desktop application on a personal computer with some personal computer requirements while docking web *servers* are online servers whose users/operator can easily run to gain predicted/foreseen complex structures with individual proteins & ligands, where experimental binding information and co-evolutionary data from structures or sequences may be used with the help of visualizer and online on the docking web servers.[6] Docking results are evaluated on the basis of docking energy, rmsd value and docking interactions.[7] Most excellent solution as stated to the docking results except it is not forever the probable that reproduces the same investigational binding orientation.[8]

METHODS

Protein phosphatase Slingshot homolog 2 Complex and proteins involved in novel signaling pathways in correspondence with SSH2 molecule was acquired from the Protein Data Bank (PDB) https://www.rcsb.org/ to test the docking programs.[9] Pathways specified ligands were extracted from ligand databases like the PubChem database https://pubchem.ncbi.nlm.nih.gov.

All docking experiments were performed on different Docking stand-alone tools and docking web servers within the freedom of platforms like window and Linux10.[7,10] System equipped with Core i7-7500U @ 2.7 GHZ, 2.90GHZ with 8GB of RAM.

Software used for comparative analysis of docking stand-alone tools and web servers study include:

1. Two stand-alone docking tools used for MD.
   - AutoDock Vina for docking.
   - Hex for docking.
2. Five docking web servers used for MD.
   - Dockthor.
   - Patchdock.
   - RPBA Web.
   - Swissdock.
   - Patinum
3. BIOVIA Discovery Studio Visualizer
4. The PyMOL Molecular Graphic System 2.4.0.
5. LigPlus for 2D view analysis.

Web Sites accessed for the research work are;

1. https://www.rcsb.org/ (Protein data Bank)
2. https://pubchem.ncbi.nlm.nih.gov/ (PubChem)
3. https://scholar.google.com/ (Google Scholar)
4. https://string-db.org/ (String Database)

The docked results stored and visualized using PyMol tool for the interaction study. This analysis finds the best docking tools and web servers which can be used in drug discovery.[11]. This analysis was used for comparative study.[4,12] Basically, the best rating association were selected whenever essential ligand compliance though the all docking systems like, docking gear and net servers projected some arrangements in each docking run.[13] The docking rankings from the several docking systems were in comparison & nonstop, for this reason the base gadgets and the principles of docking ratings vary a few of the exceptional docking structures.[14] Therefore, the docking results of predictable protein - ligand complexes were associated to the docking outputs of marked macromolecules. Root-mean-square deviation values were calculated to make public the difference among the ligand three dimensions coordinates (x, y & z) from the solid crystal and semifinal shapes of ligands are forecasted by using a docking algorithm.[13,15] After gaining the root-mean-square deviation value at baseline, mean the root-mean-square deviation value is zero (0), it denoted that, the method that the finalized the result acquired by the docking algorithms as the protein-ligand coordinates (x, y & z) within the solid crystal shape[13 & 16]. Here the given prediction became classified as a success and powerful while the rmsd became 2 Å or smaller.

Three initial ligand conformities have been confirmed many times for given ligand-protein complexes and for this reason many dockings were executed on every docking platform separately. The average binding sites size became now not comparable among AutoDock Vina and Hex though the binding sites shapes and these binding sites were different/ distinct among docking.[6,7, 17] In AutoDock Vina the scale of the binding website online was measured at least rectangle of the encompassing spheres. The least quadrangle near by the spheres for AutoDock vina became no longer identical as the binding website for HEX. Since in contrast to binding site shapes and the size of binding sites shapes are essential for every docking platform. Differences of binding sites shape and size would may be slow down with the docking.[19] Nevertheless, changing the binding sites is an entirely not easy venture. As shape essential differs of the docking structures right at this time, changes for evenhandedness are almost unworkable inside the binding site. Finally, no modification is available for the docking binding site because the scheme of least binding sites became nicely-described as viable. We accept as true with that this technique is truthful enough to examine the docking effects from all docking systems.[20] AutoDock Vina was the quickest and took approximately the much less amount of time to manner the ligand-protein complex as

Hex and different docking web servers' platforms. Typically, most computation times had been one of a kind. Maximum time in Hex was 4 instances longer than that in AutoDock vina. Thus, the docking times and settings had been now not alike many of the all docking platforms. In unit time, protein-ligand complexes were not frequently processed. The root-mean-square deviation values among the solid crystal and projected structures are extensively used to validate the ideal docking function was established with the help of the docking recreation.[20] Frequently, root-mean-square deviation of two Å or lesser is measured as the precise docking function as the declaration in an X-ray solid crystal configuration assessment is 2 Å and higher exactness than the declaration of the examination is incomprehensible. Indeed, visual inspection executed via PyMol to categorize all ligands with root-mean-square deviation values a lesser amount of than 2.5 Å as having moreover docking cause and counted as success of docking. Docking interactions are also cross inspected by way of PLIP internet server to categorize all ligands root-mean-square deviation values. Thus, the root-mean-square deviation isn't always the quality however simplest a nice scheme for put side by side docking scheme while a numeral of protein-ligand complexes is route.[13,20]

RESULTS

AutoDock vina 1.1.2 is constructed on a genetic set of rules /optimization Algorithms and an adaptive neighborhood search approach. As we know, genetic algorithm is an approach of natural selection to seek the appropriate results. The effects are given within the form of energy rankings (kcal/mol) inside distance from first-class mode. Which comprise all interacting foresees like van der waals force, electrostatic force and loss of entropy within the ligand plus the diversity of hydrogen bonds (any types of bonds).[12] The docking scoring feature entirely depend upon the intermolecular forces of the molecular force area. Since AutoDock Vina 1.1.2 has predefined default setting intended for docking. AutoDock vina produces fine and accurate effects for the given complexes. As "Docking Accuracy is 2 Å (50-60%)", "Docking Speed is Very Fast", "Docking Time is 40 Sec - 1 Min", "Recovery Time is 02-03 Sec", "Efficiency Rate is 53% to 80%" and "False Rate is 20% to 47%".

Longer run time isn't always constantly essential to crop better results. Any additional change in parameter settings for docking is requisite to attain the quality outcomes in given time for docking technique. This change manner in complex task and creates unfairness on the grounds that a consumer can more successfully alter a familiar program.

Table 1: Comparison among Docking tools & web servers' output with parameters

COMPARISON OF DOCKING OUTPUT

Docking Output		Docking Tools		Docking Web Servers				
Protein	**Ligands**	**Autodock Vina**	**Hex Docking**	**Dockthor**	**Patchdock**	**RPBS Web Portal**	**Swiss Dock**	**Platinum**
2nt2	Confomer3D_CID_1024	-7.9 Kcal/mol	-309.3 Kcal/mol	-14.235 Kcal/mol	5404 Kcal/mol	-5.94000 Kcal/mol	-7.35 Kcal/mol	355.76 Kcal/mol
	Confomer3D_CID_675	-5.3 Kcal/mol	-179.23 Kcal/mol	-64.174 Kcal/mol	2752 Kcal/mol	-5.93000 Kcal/mol	-7.87 Kcal/mol	184.11 Kcal/mol
	Confomer3D_CID_107758	-6.7 Kcal/mol	-258.16 Kcal/mol	143.993 Kcal/mol	4430 Kcal/mol	-5.90000 Kcal/mol	-8.89 Kcal/mol	339.47 Kcal/mol
	Confomer3D_CID_5957	-7.6 Kcal/mol	-272.04 Kcal/mol	-145.883 Kcal/mol	4696 Kcal/mol	-5.96000 Kcal/mol	-9.59 Kcal/mol	335.18 Kcal/mol
	Structure2D_CID_153450105	Not Docked	-354.91 Kcal/mol	-145.883 Kcal/mol	5048 Kcal/mol	-5.96000 Kcal/mol	-6.98 Kcal/mol	349.30 Kcal/mol
	Docking Speed	Very Fast	Normal	Slow	Fast	Normal	Very Slow	Excellent
	Accuracy Rate	2 Å (50-60%)	1-8 Å	10 Å (60%)	Less Then 5 Å	0.87 Å	2 Å (70%)	≤ 2 Å
	Docking Time	40 Sec- 1 Min	4 - 7 Min	9 - 11 Min	2 - 3 Min	6 – 8 Min	71 - 75 Min	20- 40 Sec
	Recovery Time	02-03 Sec	02-03 Sec	02-03 Sec	07-08 Sec	04-06 Sec	01-03 Sec	03-05 Sec

Table 2: Comparison of Docking tools and web servers' output RMSD values

Docking Output		Docking Tools		Docking Web Servers				
Protein	**Ligands**	**Autodock Vina**	**Hex Docking**	**Dockthor**	**Patchdock**	**RPBS Web Portal**	**Swiss Dock**	**Platinum**
2nt2	Confomer3D_CID_1024	2.4, 2.5, 2.5, 2.8 (Å)	2.29, 2.86 (Å)	1.8, 1.9, 2.6, 3.5 (Å)	1.66, 2.29, 2.66, 2.79 (Å)	2.6 (Å)	2.8, 2.9, 3.0, 3.4, 3.5 (Å)	2.6 (Å)
	Confomer3D_CID_675	2.0, 2.4, 2.5, 2.5 (Å)	2.29, 3.09 (Å)	1.5, 1.7, 3.0, 3.2 (Å)	1.66, 2.29, 2.66, 3.17 (Å)	1.1 (Å)	2.7, 2.9, 3.2, 3.4, 3.5 (Å)	1.1 (Å)
	Confomer3D_CID_107758	2.0, 2.4, 2.5, 2.5 (Å)	2.29, 2.32 (Å)	1.8, 2.7, 2.8, 2.9,3.5 (Å)	1.66, 2.29, 2.60, 2.66 (Å)	2.3, 2.6, 3.0,3.2, 4.0 (Å)	2.5, 2.9, 3.1, 3.5, 3.6 (Å)	2.3, 2.6, 3.0,3.3 (Å)
	Confomer3D_CID_5957	2.0, 2.4, 2.5, 2.5 (Å)	2.29, 2.57 (Å)	1.9, 2.6, 2.9, 3.3,3.5 (Å)	1.66, 2.29, 2.66, 3.41 (Å)	2.2, 3.5 (Å)	2.1, 3.0, 3.1, 3.5, 3.6 (Å)	2.1, 2.2, 3.0,3.5 (Å)
	Structure2D_CID_153450105	Not Docked	2.29, 2.99 (Å)	1.9, 2.6, 2.7, 2.9,3.3 (Å)	1.66, 2.29, 2.66 (Å)	Not Docked	2.3, 2.4, 2.6, 3.1, 3.2 (Å)	Not Docked

Hex 8.0.0 is based on an FFT algorithm. He has complex scoring functions with many predefined parameter settings. As "Docking Accuracy is 1.8 Å", "Docking Speed is Normal", "Docking Time is 4 - 7 Min", "Recovery Time is 02-03 Sec", "Efficiency Rate is <20 for Four of the Seven Targets (60%)" and "False Rate is <20 for Three of the Seven Targets (40%)".

Dockthor gave results in the form of energy within total energy, vdw energy and elec energy. For selected parameters, "Docking Accuracy is 10.0 Å (60%)", "Docking Speed is Slow", "Docking Time is 9-11 Min", "Recovery Time is 02-03 Sec", "Efficiency Rate is 70%" and "False Rate is 30%". While Patchdock gave results in the form of scoring. "Docking Accuracy is Less than 5 Å", "Docking Speed is Fast", "Docking Time is 2-3 Min", "Recovery Time is 07-08 Sec", "Efficiency Rate is 60%" and "False Rate is 40%".RPBA Web gave us result in the form of energy with number of rotatable bonds, "Docking Accuracy is 0.87 Å", "Docking Speed is Normal", "Docking Time is 6-8 Min", "Recovery Time is 04-06 Sec", "Efficiency Rate is 71%" and "False Rate is 29%".Swiss Dock gave us result in the form of full fit mesentery (kcal/mol) and estimated energy(kcal/mol). "Docking Accuracy is 2 Å (70%)", "Docking Speed is Very Slow", "Docking Time is 71-75 Min", "Recovery Time is 01-03 Sec", "Efficiency Rate is 57%" and "False Rate is 47%". At last, Patinum gave result in the form of match and mismatch. "Docking Accuracy is ≤ 2 Å", "Docking Speed is Excellent", "Docking Time is 20 - 40 Sec", "Recovery Time is 03-05 Sec", "Efficiency Rate is ≥ 88%" and "False Rate is ≥10 %".

Score based analysis of two stand-alone tools and five docking web servers was done and a comparison table was formulated for comprehensive analysis on score based and RMSD values-based results.

DISCUSSION

At the earlier stage in 2004 eight docking tools was used for protein-ligand docking and database screening. We were used two standalone tools and five docking web servers. After 2004, in 2006 TarFisDock online web server used for the searching the interactions of molecules (698 Protein molecules) while we were used Dockthor, Patchdock, RPBA Web, Swissdock. Patinum web servers for molecular interactions. At the next in 2007, structure dependent virtual screening is executed by molecular docking on three standalone docking tools. We were used Swissdock, which is provide more structure dependent interactions. One step toward 2012, recognition of small chemical molecules is important step for the development of online docking web servers. We were used five docking web servers for the comparative study. Furthermore in 2015 five docking platform studied for the use of molecular docking. We were also used two standalone tools with five docking web servers for better achievement. At the next stage in 2017, Protein-Protein and Protein-DNA/RNA interaction recreation is priceless by involving the molecular docking. Our experiments were protein-protein and protein-Ligands based interactions. Any more in 2018, the performance of six docking tools was compared for repeating experimental binding method and main subclass of Protein- Protein relation build the projection of Dn Symmetry for the matching of

symmetric protein. We were used two standalone tools and five docking web servers in respect of their efficiency and accuracy. In 2020, HDOCK server was used for template-based modeling, efficient forecast and Molecular docking.

Further selected docking stand-alone tools and online docking web servers will compare for the Comparative Evaluation of Protein and Ligand Based Docking Protocols. For this purpose, six parameters are selected. Which are "Docking Accuracy", "Docking Speed", "Docking Time", "Recovery Time", "Efficiency Rate" and "False Rate". Protein-Protein docking performed with some tools and servers for observing behavior variations of tools and server's protein-protein docking. Also supporting the Protein-Ligand docking results.

In this study comparative evaluation of protein and ligand-based docking protocols are focused rather than improvement of correct ligands. A criterion is the docking scores of the docking complexes, when accurately the same docking runs are recurring. AutoDock Vina showed no score differences within the same setting, difference of score occur by changing the settings. AutoDock Vina moreover has a characteristic to carry out docking with known protein objectives. These constant runs in AutoDock Vina are suitable for docking platforms users. These could result in terrible valuation if the docking platforms are forced to compute ratings for self-doubting compounds, seeing that first the protein-ligands complex which acquired docking consequences by way of all docking platforms were used for the assessment on this observe. Hex may want to spend extra time for the other compounds than AutoDock Vina. The docking structures will cause diverse docking results whenever the identical docking circumstances. As docking postures are predictable for numbers of ligands, influence due to the use of accidental facts isn't always severe considering the fact that this sort of prediction may be effortlessly repeated. Binding sites that are larger logically than normal sizes generate additional dispersal of the docking poses and ratings, because there are greater progressions of autonomy for the ligand configurations. Finally, docking calculations are normally much less consistent for larger active sites/ binding sites. Dissimilarities within the docking notches absolutely associated with the sizes of entire complex (binding sites), this association become extensively less in Hex. AutoDock Vina was the nice in prediction amongst the tested platforms, as anticipated.

On the other hand, hydrogen bonds and further unlike molecular foresees inking a ligand molecule with a protein molecule can't be determined efficaciously with root-mean-square deviation of two Å. In reality, all the docking tools and web servers confirmed exceptional docking ratings, regardless of the fact that the docking configurations have been like. Docking platforms can provide the precise molecular interactions in that root-mean-square deviation range, after that the docking score ought to be the equal most of a hit instance despite the fact that the anticipated docking poses fluctuate. Actually, AutoDock Vina also establish the right ligands when root-mean-square deviation values have been extra than 2 Å. If we repeat the docking many times, we might accomplish improved docking outcome as illustrate above. Consequently, it was not single doubt that the usage of 10 or extra preface conformations of a ligands created higher docking results

For seeing efficiency and accuracy five parameters was selected and inside the docking set, dockings had been repeated more than three times. When we repeated the docking more than three times, all configurations created dispersion. Docking pose predictions, 68% docking predictions have been within 2-4 Å from the high-quality root-mean-square deviation in every protein-ligand structure by any docking platform. In short about 30% of the re-docking / repeated docking consequences have been attractive extraordinary. All settings of the systems led to huge distributions of the docking positions. For ranking the applicants of ligand configurations, the docking rates are essential for the docking platforms. Frequently docking ratings have been inside 10 factors from the top docking rating expected by using every docking platform, when the dockings were repeated numerous instances. However, the docking ratings from the 05-factor variety have been much less than the contradictory docking settings. Which maybe because of the reality that the computational instant needed by means of AutoDock Vina is no longer than those essential by means of the contradictory docking platforms. Docking structures discover the top docking positions mainly depend upon the scores and positions of the docking need to be the identical regardless of the fact that the docking pose are in contrast. Thus, the docking structures aren't final results the quality consequences each time for the reason that docking consequences are discrete in both the root-mean-square deviation and docking ranking. In cause of larger molecule (ligand) has extra levels of autonomy in its configurations and as an outcome more dispersal within the docking score and level can be predictable. On the other hand, AutoDock Vina changed into now not that truthful. Universally, the differentiation connecting the first-rate and the least in root-mean-square deviation and level changed into certainly associated with the sizes of the active sites/binding sites. Thus, AutoDock Vina is ideal at locating the pleasant docking scored conformation continuously. In docking web servers "Swiss Dock" and "Pathdock" gave efficient result in regard of efficiency and accuracy.

CONCLUSION

Comparative evaluation of protein and ligand-based docking protocols through protein phosphatase slingshot homolog 2 complex done. In which two standalone tools and five docking web servers was used in respect of their efficiency and accuracy.

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