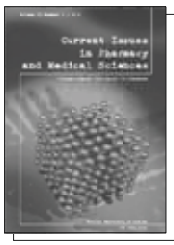

2012 Curr. Issues Pharm. Med. Sci. Vol. 25, No. 1

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
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Comparison of two molecular docking programs: the accuracy of ligand pose prediction

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ABSTRACT

The study was perform to compare the output of two different docking programs (Molegro Vritual Docker and AutoDock) in simulation of ligand-receptor interactions for and $_2$ adrenergic receptors. The exactness of the predicted ligand positions was estimated on the basis of the thirteen known crystallographic structures of the ligand-receptor complexes taken from the PDB database. Significant differences in docking results obtained by using both tested programs were observed. The overall RMSD-based scoring suggests that the procedures and algorithms implemented in AutoDock lead to slightly better results.

Keywords: docking, $_2$ adrenergic receptors, molecular modeling, binding site

INTRODUCTION

The use of the specialized software to help in understanding the nature of biochemical reactions is a common practice nowadays. One of the fields in which such aid is greatly beneficial is the simulation of ligand–receptor interactions. For that purpose, many tools and solutions were developed, including numerous computer applications. These programs differ in many aspects. They use different data formats, offer varying tools and provide solutions in different forms. They also often provide varying results.

The aim of this study was to compare the performance of Molegro Virtual Docker (MVD) [3] and AutoDock 4.0 [2] softwares for docking a chosen set of ligand–receptor pairs. Both these programs are widely known and commonly used in our projects for docking simulations and offer a wide range of settings to choose from while preparing the docking studies. Moreover, they also claim to give optimal results.

The docking r esults were compared with the experimentally determined structures of ligand-receptor complexes, including â$_1$ and â$_2$ adrenergic receptors [1].

METHODS

Models of $_1$ and $_2$ adrenergic receptors ($_1$-AR and $_2$-AR, respectively) were obtained from the Protein Data Bank database at www.pdb.org. All of the protein structures were crystallized with corresponding ligands. The ligand structures are presented in Table 1.

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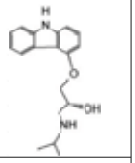
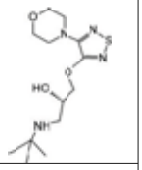
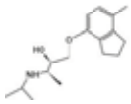
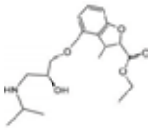
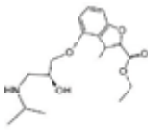
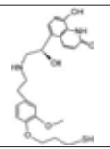
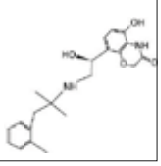
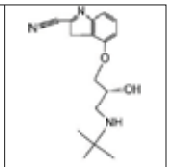
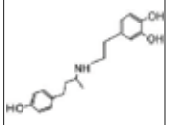
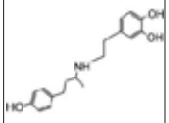
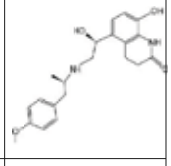
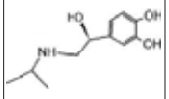
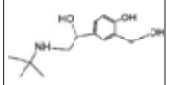
Table 1. Ligand-receptor complexes used in the research

Receptor type	pdb code	Systematic name	Ligand	Structure
$_2$-AR	2rh1	(2S)-1-(9H-Carbazol-4-yloxy)-3-(isopropylamino)propan- 2-ol	(S)-Carazolol	
	3d4s	(2S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol	Timolol	
	3ny8	(2S,3S)-1-[(7-methyl-2,3-dihydro-1H-inden-4-yl)oxy]-3-(propan-2-ylamino)butan-2-ol	ICI-118,551	
	3ny9	ethyl 4-{[(2S)-2-hydroxy-3-(propan-2-ylamino)propyl]oxy}-3-methyl-1-benzofuran-2-carboxylate	n/a	
	3nya	(2S)-1-(propan-2-ylamino)-3-[2-(prop-2-en-1-yl)phenoxy]propan-2-ol	alprenolol	
	3pds	8-hydroxy-5-[(1R)-1-hydroxy-2-[2-[3-methoxy-4-(3-sulfanylpropoxy)phenyl]ethylamino]ethyl]-1H-quinolin-2-one	FAUC50 (covalently linked to the receptor)	
	3p0g	5-hydroxy-8-[(1R)-1-hydroxy-2-{[2-methyl-1-(2-methylphenyl)propan-2-yl]amino}ethyl]-2H-1,4-benzoxazin-3(4H)-one	BI-167107	

$_1$-AR	2vt4	4-{[(2S)-3-(tert-butylamino)-2-hydroxypropyl]oxy}-3H-indole-2-carbonitrile	n/a	
	2y00	4-[2-[[(2R)-4-(4-hydroxyphenyl)butan-2-yl]amino]ethyl]benzene-1,2-diol	Dobutamine	
	2y01	4-[2-[[(2R)-4-(4-hydroxyphenyl)butan-2-yl]amino]ethyl]benzene-1,2-diol	Dobutamine	
	2y02	8-hydroxy-5-[(1R)-1-hydroxy-2-[[(2R)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]-1H-quinolin-2-one	Carmoterol	
	2y03	4-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol	Isoprenaline	
	2y04	(RS)-4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol	Salbutamol	

Models were prepared using Yasara 11.2.15. Both water molecules and cofactors were removed from the structures. One essential ligand molecule from the binding site per model was extracted from the file to be used for docking simulations. The initial ligand position from the crystallized model served as a reference molecule for RMSD (root-mean-square deviation) calculations.

Docking was performed using Molegro 2010.4.2.0 and AutoDock 4.0 software. Molegro Vitrual Docker generates a series of docking poses and arranges them using energy based criterion and the embedded scoring function (MolDock score). The process includes docking of flexible ligands into rigid targets of â$_1$ and â$_2$ adrenergic receptors models. The docking space was limited and centered on the binding site using a sphere with a radius of 10Ĺ. Blind docking was carried out with the following settings:

- numbers of runs = 100,
- maximal number of poses = 10,
- maximal number of iterations = 1500,
- algorithm = MolDock SE.

Afterwards, the docking results were collected in a table. For each molecule, the five complexes with lowest energy were selected. For these complexes, MolDock Score, Rerank Score, RMSD and HBond values were calculated. Also, the selected five poses were visually observed and best positions were chosen. This helped to create an additional mean of comparison to the reference ligands.

The AutoDock 4.0 software was employed to conduct the second set of docking simulations for the studied protein-ligand complexes. The software consists of AutoGrid and AutoDock scripts and graphical user interface AutoDockTools. To be used for docking, it was necessary to save the protein and ligand molecules as .pdbqt files. Afterwards, the docking grid was prepared to compute the affinity potential grids using specific atomic probes for each atom type. The number of grid points was calculated individually for each model with default settings, and it did not exceed 25 in any axis. One grid point was equal to 0.375 Å. The grid box position was centered in the binding site depending on the protein structure.

The following parameters were set to be used for the docking parameter file:

- number of runs = 100,
- search algorithm type = Genetic,
- maximum number of evaluations = Long,
- type of output = Lamarckian.

The docking process was conducted using standard autogrid4 and AutoDock4 syntax.

RESULTS

The docking results acquired from both AutoDock 4.0 and Molegro Virtual Docker are presented in Table 2.

Table 2. Results of the docking procedures

PDB code	AutoDock		MVD	
	Free energy of binding [kcal/mol]	RMSD [Ĺ]	MolDock Score [kJ/mol]	RMSD [Å]
2rh1	-11.32	0.95	-143.44	1.56
	-11.29	0.99	-140.77	1.76
	-11.28	0.93	-139.56	5.81
	-11.24	0.95	-138.07	1.40
	-11.24	0.93	-136.31	1.11
3d4s	-8.46	0.48	-134.07	0.63
	-8.46	0.44	-128.18	1.32
	-8.43	0.48	-123.95	0.74
	-8.42	0.41	-122.35	4.76
	-8.42	0.57	-121.27	4.73
3ny8	-9.24	1.22	-113.44	13.11
	-9.20	1.03	-110.92	11.53
	-7.50	1.86	-108.78	11.52
	-6.64	3.79	-108.23	10.55
	-6.60	4.27	-104.39	1.77
3ny9	-10.80	0.82	-157.70	6.35
	-7.29	2.40	-153.13	1.26
	-6.76	2.25	-144.13	1.12
	-6.74	4.51	-144.05	10.52
	-6.46	3.37	-136.76	9.84
3nya	-8.61	1.96	-107.43	11.48
	-8.50	1.95	-107.10	10.55
	-8.53	0.85	-105.69	11.98
	-8.41	0.89	-104.90	11.49
	-8.40	0.79	-104.17	2.72
3pds	-10.00	1.78	-164.54	11.86
	-9.51	2.45	-161.09	9.71
	-8.54	4.24	-160.40	7.81
	-8.19	4.03	-159.80	10.38
	-7.82	1.68	-159.02	8.46
3p0g	-12.04	1.25	-150.74	2.03
	-9.25	3.57	-147.20	1.52
	-8.59	2.12	-144.77	0.67
	-8.54	2.12	-140.40	1.83
	-8.53	3.35	-139.29	1.22
2vt4	-8.60	1.06	-133.21	0.91
	-8.59	1.02	-133.15	1.53
	-6.75	3.95	-125.12	6.11
	-6.75	3.97	-123.25	6.16
	-5.28	3.15	-122.41	5.16
2y00	-7.68	0.95	-131.21	7.62
	-7.37	2.31	-124.46	0.83
	-7.24	2.46	-123.51	9.35
	-6.48	3.40	-121.37	9.53
	-6.37	2.77	-118.45	5.41

2y01	-7.26	1.21	-122.73	11.79
	-7.16	2.17	-121.89	9.33
	-6.86	2.50	-121.41	13.07
	-6.17	2.84	-117.95	5.54
	-5.48	3.11	-115.09	9.88
2y02	-10.02	0.55	-146.69	6.15
	-8.24	2.12	-138.28	7.41
	-8.13	2.63	-137.50	3.77
	-7.66	2.80	-134.86	1.39
	-7.56	2.94	-131.24	4.42
2y03	-7.51	0.73	-87.65	1.27
	-7.45	0.76	-86.25	2.04
	-7.43	0.74	-84.12	2.61
	-7.42	0.78	-83.81	5.32
	-7.38	0.79	-82.84	1.11
2y04	-6.44	1.44	-98.27	5.45
	-6.40	1.32	-95.50	1.32
	-6.39	1.29	-93.95	0.61
	-5.91	2.39	-93.42	2.61
	-5.71	2.31	-90.93	2.31

It can be seen that AutoDock 4.0 performed better for structures: 2rh1, 2vt4, 2y01, 2y02, 2y03, 3d4s, 3ny8, 3ny9, 3nya, 3pds. However, MVD gave better results for 2y00, 2y04, 3p0g. For all cases, AutoDock 4.0 provided an answer that could be called satisfactory. On the other hand, MVD failed to dock the ligand to the proteins 2y01, 3nya and 3pds. At the same, it was hard to decide if the docking result was acceptable and whether these were really the best or not. An interesting example of such a case can be seen in Fig. 1. This is the case of docking to the 2vt4 protein. The correct position is outlined in green. The red and yellow positions represent, accordingly, the RMSD values of 0,91 Å and 1,53 Å, respectively. As one can see, both rings are docked quite well, while in the latter case, the chain is rotated.

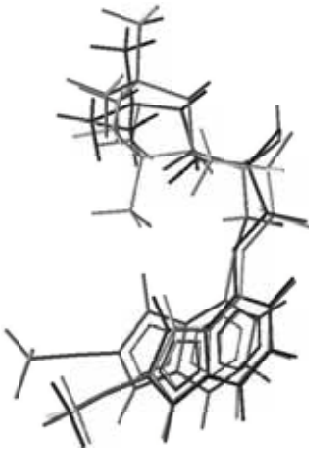


Fig. 1. Positions of the ligand docked to 2vt4 protein, calculated by MVD. The experimentally determined position of the ligand is presented in green. The red and yellow positions represent the RMSD values of 0.91 Å and 1.53 Å, respectively. Protein models were removed for clarity

Another interesting example is presented in Fig. 2a. In this case, it was impossible to achieve the goal of docking the ligand by MVD. The RMSD values of the positions range from 9.33 Å (yellow), to 13.07 Å (blue). Notice that no correct alignment was made, even in regard to the rings. On the other hand, AutoDock had no problems in achieving the correct docking position, which can be seen in Fig. 2b. This situation also occurs in the case of 3ny8.

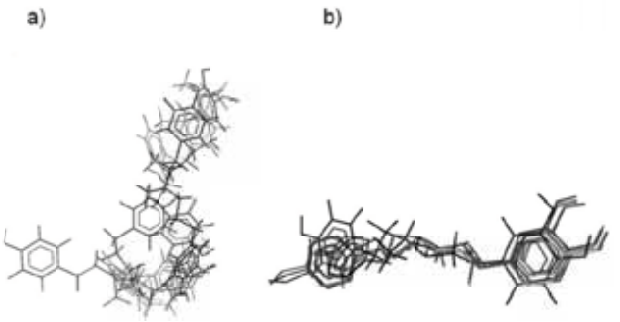


Fig. 2. Positions of the ligand docked to 2y01 protein calculated by MVD (left) and by AutoDock (right). The experimentally determined positions of the ligand are presented in green. The other positions are docked incorrectly in the case of MVD, or close to the correct position for the AutoDock-based results

MVD software in some cases failed to determine the best position based on its scoring function. Such an example is presented in Fig 3. This is the case of the protein 3ny9. The position marked in green is the experimentally determined position. The red position was chosen by the software, based on its scoring function. The yellow and green positions are, accordingly, placed as the second and third best. After examining this case, it may be concluded that actually the second (yellow) position is the best. This opinion agrees with the fact that the RMSD value of the second position is the lowest of all.

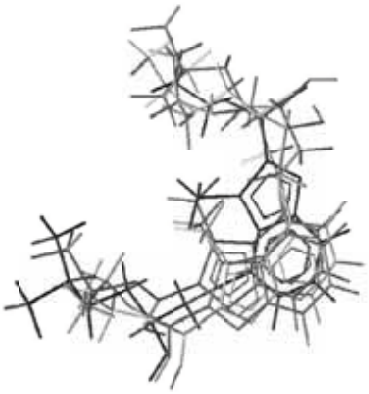


Fig. 3. Positions of the ligand docked to 3ny9 protein calculated by Molegro. The experimentally determined position of the ligand is presented in green

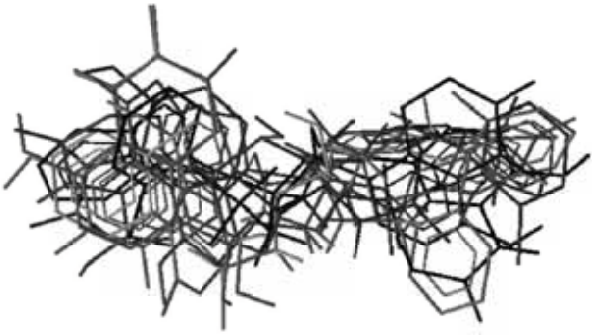


Fig. 4. Positions of the ligand docked to the 3p0g protein calculated by AutoDock4.0. The experimentally determined position of the ligand is presented in green

Applying the default scoring function in the AutoDock4.0 software did not always give correct results. This was apparent in the case of the 3p0g and 3nya proteins. The docking process also failed to give good results in the first case, where no position overlaps with the whole ligand in Fig. 4. In the latter case, the scoring function picked the blue position (RMSD 1,96 Å) over the yellow position (RMSD 0,85 Å) which can be seen in Fig. 5.

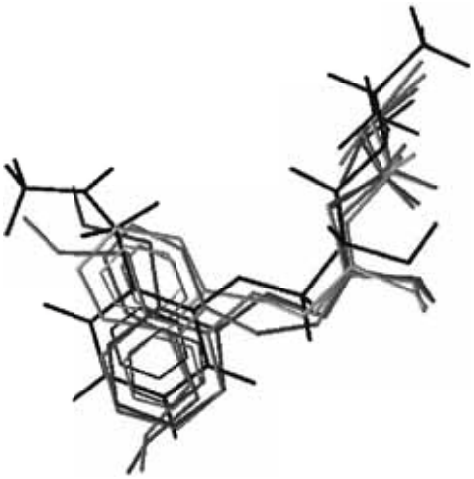


Fig. 5. Positions of the ligand docked to 3nya protein calculated by AutoDock 4.0. The experimentally determined position of the ligand is presented in green

DISCUSSION

Finding the sources of better applicability for the tested programs is not an easy task, due to both their complexity and the numerous differences displayed between the computational techniques applied by them. Both tested programs use different empirical force fields to express the strength of interactions in the ligand-receptor systems; they also use different search algorithms. Interestingly, the MVD scoring function (MolDock Score) does not necessarily correspond to the true binding affinity. In the case of AutoDock, the binding free energy can be estimated and is comparable with the available experimental data.

One can also notice that AutoDock uses slightly more sophisticated interactions parameters, compared to MVD. Some of the more significant differences are:

1. AutoDock computes Coulombic interactions applying Gasteiger atomic partial charges. MVD has implemented a simple scheme including three types of charges for oxygen and nitrogen atoms.
2. Piecewise Linear Potential (PLP) [4] is used in MVD to account for the steric interactions and for hydrogen bonding. This PLP is, however, based on the same parameters for all atom-atom pairs. Analogical interactions in AutoDock are expressed by the Lennard-Jones 6-12 potential, whereas the corresponding parameters are taken from the AMBER force field. This means that more atom types are taken into account.
3. Finally, AutoDock accounts for the presence of water and the solvation effect (although indirectly). Namely, the desolvation potential based on the volume of atoms that surround a given atom and shield it from solvent, is calculated. No analogical procedure is implemented in MVD. This may be especially important in the case of ligand-adrenergic receptor systems, as the recent molecular modeling studies show that interactions with water molecules contribute significantly to the overall ligand-envi- ronment interactions, even in the case of bound ligands. The amino acid residues creating the binding cavity are also exposed to contact with water. Therefore, salvation effects are assumed to be essential in the studied systems.
4. Although both MVD and AutoDock default search algorithms have some features in common (e.g. they both are 'genetic'-type algorithms), only the AutoDock algorithm considers the unbound states (conformations) of the ligand and receptor (this is necessary for calculating the solvation effects, for instance).

All these differences and their combinations can influence the obtained results and be responsible for the varying effectiveness of both programs. The choice of a suitable program should therefore be based not only on the exactness of the results, but also on other factors, such as the available time and the computational resources, as well as the specificity of the addressed problem.

Concluding, the overall results suggest that RMSD value should not exceed 1 Å for a position to be considered as correct. In more complex cases, both tested programs had problems in proposing a reasonable answer. What is more, in some cases, it was apparent that RMSD is more reliable than scoring functions when it comes to finding the best results. In most cases, the positions with the lowest RMSD values also had the lowest energies, but this did not always hold true. Overall, AutoDock 4.0 gave better results, but used significantly more time and processing power to solve the given problems.

ACKNOWLEDGMENT

The work was supported by the TEAM research program founded by the Foundation for Polish Science.

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