Comparative Study of Evolutionary Algorithms for Protein-Ligand Docking Problem on the AutoDock

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Abstract. AutoDock is a widely used simulation platform for Protein-ligand docking which is a simulator to provide the field of computer-aided drug design (CADD) with conveniences. Protein-ligand docking establishes docking models and study interaction between the receptor and the ligand, as a part of the most important means in drug development. Protein-ligand docking problem is of great significance to design more effective and ideal drugs. The experiments are simulated on AutoDock with six weighted algorithms such as Lamarckian genetic algorithm, a genetic algorithm with crossover elitist preservation, artificial bee colony algorithm, ABC_DE_based hybrid algorithm, fireworks algorithm, and monarch butterfly optimization. The diversity of search function constructed by different evolutionary algorithms for separate receptors and ligands is applied and analyzed. Performances of distinct search functions are given according to convergence speed, energy value, hypothesis test and so on. This can be of great benefit to future protein-ligand docking progress. Based on the work, appearances are found that performances of the same algorithm vary with different problems. No universal algorithms are having the best performance for diverse problems. Therefore, it is important how to choose an appropriate approach according to characteristics of problems.

Keywords: Evolutionary computation · Swarm intelligence · Protein-ligand docking · Search function

1 Introduction

In developing period of drug design, inefficiency and high cost is becoming increasingly problematic. Computer-aided drug design (CADD) steps up the process and opens up ideas of drug design as a basis. An indispensable part of CADD is protein-ligand docking. Protein-ligand docking is a practical approach for CADD. The simulation process makes use of the characteristics of receptors and the interaction between receptors and molecules to solve the problem [1–3]. To combine small molecules with protein macromolecules, the position of small molecules should be reasonably adjusted, the ideal location and interaction of the combination is detected according to the complementary principle of docking, and finally a stable complex conformation is

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obtained. The purpose is to find the best binding sites between ligands and receptors [4].

Steps to solve the protein-ligand docking problem on the simulation platform contain the scoring function and the search algorithm. The scoring function evaluates the energy value of different conformations, which is used to evaluate the binding conformation of ligands and receptors computer simulations predicted. In the process of docking, the binding affinity between ligand and receptor is supposed to be obtained accurately. As the basis of optimization, the scoring function can be directly an adaptive value in the optimization algorithm [5–8]. Scoring function is the key to optimization problems and plays an important role in the results of molecular docking and virtual screening.

Evolutionary algorithms construct the search algorithms. Some researchers have improved these methods on efficiency. Morris published in the paper [9–11] introduces genetic algorithm with Lamarck on the platform of AutoDock (Lamarckian genetic algorithm, LGA) to solve the docking problem [12]. Guan B in the paper [13] proposed a genetic algorithm with crossover elitist preservation (CEPGA) to solve the protein-ligand problem. Some researchers released some modified swarm intelligence algorithms to the protein-ligand problem such as the artificial bee colony algorithm (ABC) [14], ABC_DE_based hybrid algorithm (ADHDOCK) [15]. Evolutionary algorithms are widely applied in many fields, such as data analysis and network optimization [16–20]. Some swarm intelligence algorithms also have good performance in the search process such as fireworks algorithm (FWA) [21], monarch butterfly optimization (MBO) [22].

The AutoDock platform simulates algorithms [23] to settle protein-ligand docking problem. Algorithms have their advantages in different test cases. In this paper, six algorithms are carried out on AutoDock to make a fair comparison, such as LGA, CEPGA, ABC, ADHDOCK, FWA and MBO. Results of solving protein-ligand docking problems of algorithms are calculated and analyzed such as convergence speed, energy value, and hypothesis test. According to analysis, search algorithms have respective advantages and disadvantages in settling the protein-ligand docking problem.

2 Materials and Methods

2.1 Simulation Platform

AutoDock is a universal simulation software for protein-ligand docking. Many researchers study the protein-ligand docking problem on this platform. AutoDock is an open source molecular simulation software developed and maintained by the Olson laboratory at the Scripps Research Institute [23]. The taken version is AutoDock 4.2.

In this study, AutoDock simulates the protein-ligand docking process. The optimal combination location needs to consider the geometric structure matching of the protein and the ligand and the energy value of the combined position. AutoDock evaluates the resulting conformation and searches for a suitable conformation. The platform uses a

specific scoring function to make an evaluation. The search algorithm constructed by the evolutionary computation algorithm searches for the optimal solution.

2.2 Materials

Six protein-ligand complexes [24] were chosen from the Brookhaven PDB to compare the performance of the docking techniques. Six docking problems are summarized as test cases in the following:

- HIV-1 Protease/XK263 (1hvr): The cyclic urea HIV-protease inhibitor, XK-263, has ten rotatable bonds, excluding the cyclic urea's flexibility.
- Streptavidin/Biotin (1stp): Biotin, also known as vitamin H or coenzyme R, is a water-soluble B vitamin. Streptavidin/biotin is one of the most tightly binding non-covalent complexes.
- McPC-603/Phosphocholine (2mcp): Phosphocholine is an intermediate in the synthesis of phosphatidylcholine in tissues. The recognition of phosphocholine by FabMcPC-603 is mainly because of the influence of ArgH52.
- b-Trypsin/Benzamidine (3ptb): Benzamidine is a reversible competitive inhibitor of trypsin, trypsin-like enzymes and serine proteases. The recognition of benzamidine by b-trypsin is mainly because of the polar amidine moiety and the hydrophobic benzyl ring.
- Dihydrofolate Reductase/Methotrexate (4dfr): Methotrexate is an antimetabolite that attacks proliferating tissue and selectively induces remissions in certain acute leukemias.
- Influenza Hemagglutinin/Sialic Acid (4hmg): The recognition of sialic acid by influenza hemagglutinin is chiefly because of hydrogen bonding.

2.3 Algorithm Analysis

This paper implements and runs the algorithms on the AutoDock, namely LGA, CEPGA, ABC and ADHDOCK, FWA, MBO. The test cases are the same. On the same platform, the performances of six different algorithms are equally compared. Six different evolutionary algorithms are listed below to state the principle of algorithms.

- Lamarckian Genetic Algorithm (LGA): Lamarckian genetic algorithm is coupled with the local search for the genetic algorithm. Local search refers to the current solution around an optimal solution until finding the local optimal solution algorithm. If the solution is not a local optimal solution, the local search can find the optimal solution around the solution. In the search for molecular conformation, local search has the advantage of no need for gradient information about district energy patterns, thus promoting torsional space search.
- Genetic Algorithm with Crossover Elitist Preservation (CEPGA): Good genes from parents can no longer produce good individuals through crossover operation, as original genetic algorithms do not retain the parents of the elitist individual. A crossover elitist preservation (CEP) mechanism incorporated into genetic algorithm is applied to solve protein-ligand docking problems. The crossover elitist preservation mechanism can make sure not to discard optimal solution while

speeding the operation up. In this way, the next generation will be more suitable for the competition of elitist parents and their descendants. Besides, an optimal solution in near space of current solutions which included in GA can be selected by a local search.

- Artificial Bee Colony Algorithm (ABC): The basic structure is divided into the employed bees phase, the onlooker bees phase, and the scout bees phase. The employed bees store information about the food source and share it with other bees with a certain probability. The number of employed bees is the number of food sources. An employee bee is only related to a food source. The onlooker bees observe the dance of employed bees in the hive to determine which food source to choose. Scout bees randomly search for new food sources next to the hive.
- ABC_DE_Based Hybrid Algorithm for protein–ligand docking (ADHDOCK): ABC_DE_based hybrid algorithm is an algorithm for protein–ligand docking, while integrating differential evolution algorithm (DE) and artificial bee colony algorithm (ABC). ABC and DE, two typical optimization methods that have been widely used in various fields, execute in parallel and have the same population during the present algorithm. ADHDOCK incorporates an adaptive population partition mechanism to distribute two subpopulations partition automatically to ABC and DE. On account of the reasonable allocation of computing resources, ADHDOCK is uniquely positioned to take the advantages of ABC and DE, and then avoid local optimum.
- Fireworks Algorithm (FWA): FWA presents a new search manner which searches the potential space by a stochastic explosion process within a local space. At first, N fireworks are initialized randomly. The quality is evaluated to determine the explosion amplitude and the number of sparks for each firework. And fireworks explode and generate different types of sparks within their local space. Finally, N candidate fireworks are selected among the set of candidates, which includes the newly generated sparks as well as the N original fireworks. In order to ensure diversity and balance the global and local search, the explosion amplitude and the population of the newly generated explosion sparks differ among fireworks.
- Monarch Butterfly Algorithm (MBO): MBO simulates the migration behavior of the monarch butterflies in nature. In MBO, all the monarch butterfly individuals are only idealized and located in two lands such as Southern Canada and the northern USA (land 1) and Mexico (land 2). Monarch butterflies of two positions are updated in two ways. At first, the offsprings are generated by migration operator which can be adjusted by the migration ratio. Subsequently, the positions of other butterflies are tuned by butterfly adjusting operator. In other words, the search direction of the monarch butterfly individuals in MBO algorithm is mainly determined by the migration operator and butterfly adjusting operator. Also, the migration operator and butterfly adjusting operator can be implemented simultaneously.

3 Materials and Methods

3.1 Parameters Setting

In the process of performance testing, each algorithm must be reasonably set the parameters. LGA, CEPGA, ABC, ADHDOCK, FWA and MBO are compared at the AutoDock platform. The initial population is set as 50. These algorithms terminate when the energy function evaluations reach 1.5×10^6 for each run. The AutoDock platform runs every search algorithms 20 times to solve given test cases. The search algorithm is evaluated the docking results by analyzing the convergence, stability and hypothesis testing.

3.2 Convergence Analysis

According to set iterations, the energy value obtained by the algorithm is used to determine the convergence of the algorithm. Figure 1 is the convergence diagrams of the six algorithms for each test case.

The slope of ADHDOCK and ABC in Fig. 1(a) is the smallest, which is at the better convergence position and gets lowest energy value. Moreover, LGA converges slowly and finds the energy close to the lowest. In Fig. 1(b), the slope and the energy value of ABC are in good agreement with our expectation. With the increasing of iterations, results of LGA are approaching the lowest. The convergence rate of CEPGA and FWA is moderate, while the result is relatively high. In Fig. 1(c), the energy value of MBO is getting better as the number of iterations increases and MBO gets the best energy finally. The convergence rate of other algorithms is moderate. In Fig. 1(d), the slope of MBO is stable which can prevent from falling into the local optimal solution early, and MBO has the lowest energy. The convergence rate of all the algorithms in Fig. 1(e) is relatively equal. LGA gets better results. In Fig. 1(f), the convergence rate of LGA is the slowest. ABC get the best energy value whose results change distinctly with the number of iterations increasing. The convergence rate and the solution quality of the same algorithm differ in different test cases.

3.3 Algorithm Stability Analysis

Figure 2 shows box plots for each test case. The minimum, the first quartile, the median, the third quartile, the maximum and the outliers of the energy values are calculated to mark on the box plot. The range from the minimum to the maximum shows the variation range of data. The interquartile range shows the likely variation range. The outliers are points out of the range. The protein-ligand docking problem is an optimization problem in need of minimum value. When the shown value or the median value is lower, the algorithm has better solving performance. The box plot with smaller range shows that the algorithm has stability.

According to Figures, the median energy value of ADHDOCK is the lowest in Fig. 2(a) and its minimum energy value is lowest. In Fig. 2(b), ABC finds smaller energy value and the range of ABC is also smallest. In Fig. 2(c), the minimum energy of MBO is lowest. The median energy of ADHDOCK is lowest. The range of CEPGA

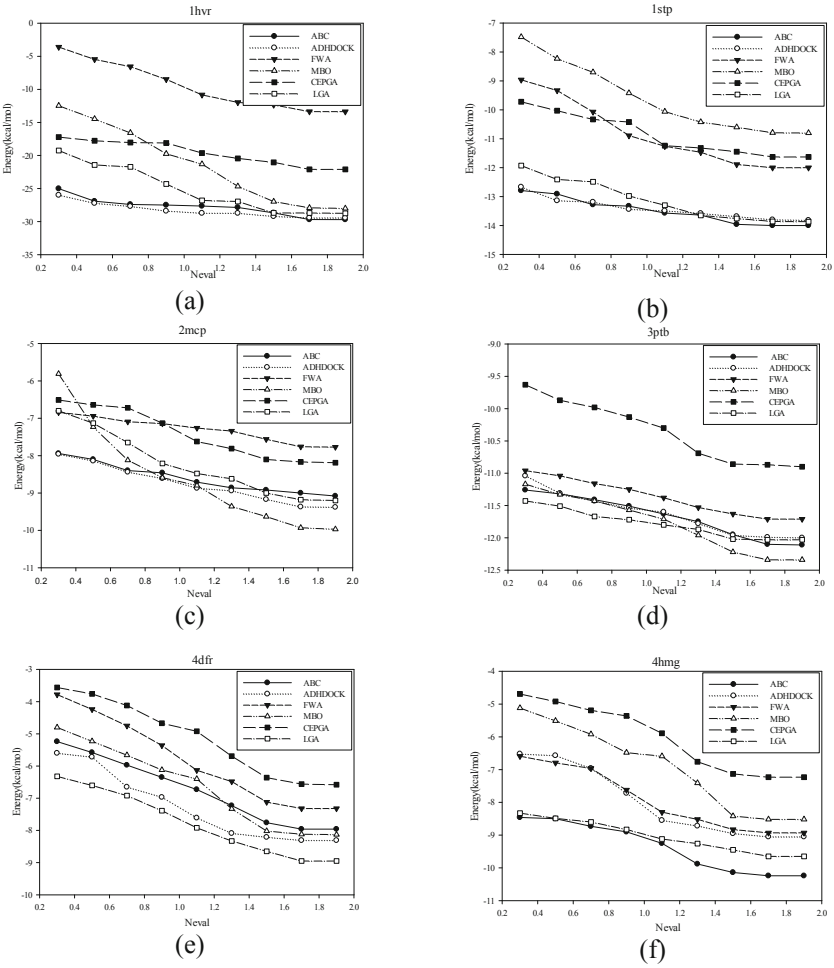

Fig. 1. This figure shows the convergence graphs of the six algorithms for each test case. Neval is the number of iterations of the function, and the ordinate is the energy value generated by the docking of the function after iterating specified times.: (a) Convergence diagram of 1hvr; (b) Convergence diagram of 1stp; (c) Convergence diagram of 2mcp; (d) Convergence diagram of 3ptb; (e) Convergence diagram of 4dfr; (f) Convergence diagram of 4hmg.

is the smallest while its results are not good. In Fig. 2(d), MBO gets lowest energy. The range of values of ABC is smallest in Fig. 2(e). And LGA has lowest energy. The median energy of ADHDOCK is lowest. In Fig. 2(f), the median and minimum of the energy of ABC are lowest. The range of FWA is the smallest while its result is not good. It is observed that the distribution of the same algorithm is different for different test cases.

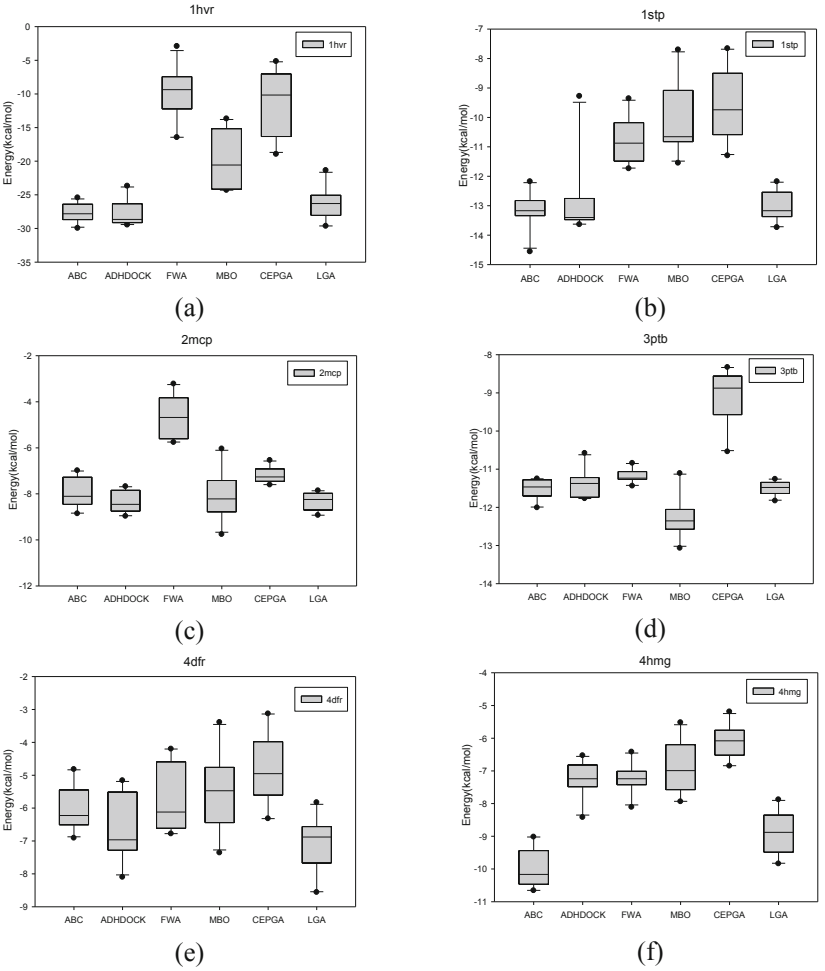

Fig. 2. This figure shows the box plots for each test case. (a) Box plot of 1hvr; (b) Box plot of 1stp; (c) Box plot of 2mcp; (d) Box plot of 3ptb; (e) Box plot of 4dfr; (f) Box plot of 4hmg.

3.4 Hypothesis Test Results

On six test cases, compared algorithms run for 20 times. Table 1 demonstrates the hypothesis test results. The difference factor p-value determines the quality of the result. In the experiment, α is settled as 0.05. If p-value < 0.05, the current algorithm is superior to the compared algorithm. If p-value > 0.95, the current algorithm is inferior to the compared algorithm. If $0.05 <$ p-value < 0.95, it shows that the performance of the two algorithms is not very different on this test case.

Some phenomena can be seen through the results of the hypothesis test. For 1hvr, ADHDOCK is better than four compared algorithms. For 1stp, ADHDOCK is better than three compared algorithms. For 4hmg, ABC is better than four compared

Table 1. Results of hypothesis tests

PDB		ABC	ADHDOCK	FWA	MBO	CEPGA	LGA
1hvr	ABC	–	0.443	0.016	0.054	0.007	0.003
	ADHDOCK	0.562	–	0.019	0.009	0.009	0.005
	FWA	1	1	–	1	0.702	0.998
	MBO	0.947	0.905	0.021	–	0.012	0.020
	CEPGA	1	1	0.299	1	–	0.998
	LGA	1	0.996	0.018	0.997	0.003	–
1stp	ABC	–	0.342	0.001	0.002	0.001	0.348
	ADHDOCK	0.665	–	0.001	0.001	0.002	0.605
	FWA	1	0.999	–	0.475	0.142	1
	MBO	0.998	0.989	0.528	–	0.179	0.998
	CEPGA	0.999	0.997	0.857	0.822	–	0.996
	LGA	0.650	0.396	0.001	0.002	0.001	–
2mcp	ABC	–	0.768	0.001	0.368	0.001	0.933
	ADHDOCK	0.231	–	0.001	0.170	0.001	0.881
	FWA	0.999	1	–	0.987	0.007	0.999
	MBO	0.630	0.832	0.013	–	0.004	0.956
	CEPGA	0.999	1	1	1	–	1
	LGA	0.063	0.116	0.002	0.005	0.003	–
3stp	ABC	–	0.353	0.004	0.006	0.001	0.731
	ADHDOCK	0.647	–	0.067	0.194	0.001	0.787
	FWA	0.997	0.934	–	0.732	0.190	0.999
	MBO	0.944	0.806	0.267	–	0.007	0.986
	CEPGA	1	1	1	1	–	1
	LGA	0.268	0.216	0.001	0.732	0.003	–
4dfr	ABC		0.053	0.205	0.018	0.001	0.749
	ADHDOCK	0.948		0.613	0.138	0.004	0.998
	FWA	0.796	0.388		0.170	0.028	0.909
	MBO	0.984	0.862	0.827		0.095	0.999
	CEPGA	0.999	0.996	0.971	0.138		1
	LGA	0.250	0.002	0.009	0.170	0.001	
4hmg	ABC	–	0.014	0.036	0.014	0.005	0.490
	ADHDOCK	0.986	–	0.969	0.429	0.502	1
	FWA	0.962	0.030	–	0.057	0.001	1
	MBO	0.985	0.570	0.945	–	0.523	0.999
	CEPGA	0.995	0.495	0.999	0.470	–	1
	LGA	0.510	0.032	0.005	0.004	0.001	–

algorithms. ABC is better than three compared algorithms for 1hvr, 1stp, and 3stp. For 1hvr, MBO is better than three compared algorithms. For 1stp, 2mcp, 4df, and 4hmgr, LGA is better than three compared algorithms. Accordingly, from results of the hypothesis test, there is not an algorithm better than others for given six test cases.

4 Results Discussion

The primary purpose of this paper is to explore the differences between different evolutionary algorithms in protein-ligand docking. The research shows that search functions constructed by different evolutionary algorithms can achieve satisfactory results respectively under different environments or requirements. In study as mentioned, the results of algorithms are different due to the change of problems. Under parameter setting above, ADHDOCK has highlighted performance for 1hvr, ABC has good performance for 1stp and 4hmg, MBO is best for 2mcp and 3ptb, LGA has good performance for 4dfr. Evaluations of algorithms on six protein-ligand complexes are different.

In general, the experiments show that affected search functions check molecular pairs. Performances of algorithms vary with test cases to be solved.

5 Conclusions

Experiments mentioned above demonstrate that different search functions have different effects on respective problems. For every algorithm solving protein-ligand problem, it can perform pretty well in some cases while it has terrible performance in other cases. Consequently, there are no multipurpose algorithms concerning different test cases. Presented algorithms have apparent advantages in specified problems, not in common use. Therefore, it is vital to choose a suited method which is implemented on the same simulation platform to solve protein-ligand problem.

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