An Improved LGA for Protein-Ligand Docking Prediction

Chun-Wei Tsai*, Jui-Le Chen† ‡ , and Chu-Sing Yang†
*Department of Applied Geoinformatics, Chia Nan University of Pharmacy & Science, Tainan, Taiwan, R.O.C.
† The Institute of Computer and Communication Engineering, Electrical Engineerin,
National Cheng Kung University, Tainan, Taiwan, R.O.C.
‡ Department of Digital Multimedia Design, Tajen University, Pingtung, Taiwan, R.O.C.
Email: cwtsai0807@gmail.com, reler@mail.tajen.edu.tw, csyang@ee.ncku.edu.tw

***Abstract*—Since the high computational cost of the structure-based protein-Ligand docking prediction is one of the major problems in designing new drugs, many researchers keep looking for a high performance search algorithm to find the workable directions to drug design as well as a simulator platform being able to test and verify the new drugs. In this paper, an improved version of Lamarckian genetic algorithm (ILGA) is first presented for enhancing the performance of LGA by using pattern reduction to reduce the computation cost and using tabu search to increase the search diversity to further find the better results. In addition, the proposed algorithm is also applied to a well-known simulator platform (AutoDock) to evaluate the performance of the proposed algorithm. The simulation results show that the proposed algorithm can enhance the performance of ILGA in terms of convergence performance especially for highly flexible ligands.**

keyword: Protein-Ligand docking prediction, AutoDock, Lamarckian genetic algorithm.

I. Introduction

Drug design is very important work for human health because it is known that designing a useful drug is the way in fighting against various diseases such as preventing and curing diseases. The ligand-based and structure-based drug designs are two of the most important methods for modern drug design [1], [2]. Different from ligand-based drug design (IBDD) which uses the indirect drug design method to derive drugs, structure-based drag design (SBDD) uses direct drug design method to create possible candidate drugs. This kind of drug design, SBDD [3], usually can be used to predict the interactions between small drug molecules and protein receptor complexes, and now, it is one of the well-known computer-aided drug design methods. This prediction method is based on theoretical computing method and molecular modeling to establish the three-dimensional structure for designing a new drug molecule which has good binding activity with receptors.

One of the important reasons that many studies [4] focused on molecular docking with computer-aided SBDD method is that the time in lab for the new drug development of pharmaceutical compounds method can be reduced. Before the docking process, the active site of target protein can first be searched and then the binding energy for relative space between molecules can be calculated. The lower binding energy is the greater binding activity which can also provide better drug efficiency. For the docking method, it is used to predict if "protein" combining with "small molecule ligand" [1] will be a stable complex conformation or not [5]. To evaluate the performance of the prediction method, the score function is used for measuring the results of the binding energy between protein and ligand. Among the search process, the protein-ligand docking method will try to locate the position of ligand in the active sites of translation, rotation direction, and conformation of protein receptors.

In [6], Chen et al. pointed out that the score function and efficient search algorithm were the most important parts of a good and effective docking method. The score function is a free energy formula for representing the binding interaction between protein and ligand. A good score function should precisely show the result quality found by search algorithm. For the protein-ligand docking problem, the major concern is to find out the lowest energy conformation for finding where the main binding orientation is. For the search algorithm, the score function is used for estimating binding energy as well as guide it to the trend the search directions that have high probability to get better result that the others.

Due to the search space of possible conformations being very large, how to reduce the computation time becomes a very important research issue. In addition, because it is a NP-problem [7], an high performance search method is required for speeding up the search process. That is why many search methods for reducing the computation time have been presented to solve the docking problem [8]. The heuristic algorithm, of course, is one of the efficient ways solving this problem [9]. Recently, various heuristic algorithms (i.e, simulated annealing(SA) [10] and genetic algorithm [11], [12] have been proposed for protein-ligand docking problems because they provide a fast way to search for the approximate solution comparing with the brute force search algorithms.

Because the heuristic algorithm only can obtain the approximate solutions[2] which are close to the global optimal solution, the balance between the computation cost and solution quality becomes one of the most important problems for the heuristic algorithms. In this paper, the focus is not only on developing a good search process in a limited number of time (computation

[1]Ligands mean the drug molecules in this paper.
[2]The heuristic algorithm is no guarantee can find the optimization solution.

cost), but also on stably getting closer to the best solution for the binding location.

A modified Lamarckian genetic algorithm called improved Lamarckian genetic algorithm (ILGA) is presented in this paper to solve the docking problem for the rigid protein and flexible drug molecules. Moreover, the proposed algorithm is also applied to the AutoDock4 system [13] as the docking processing environment and existing energy scoring function.

The remainder of the paper is organized as follows. Section Section II gives a brief introduction to the molecule docking and Autodock system. Section Section III describes in detail the proposed algorithm. Performance evaluation of the proposed algorithm is presented in Section Section IV. Conclusion is drawn in Section Section V.

II. Related Work

A. Molecule Docking

Molecular docking is a simulation program used for predicting receptor-ligand complex conformation where the receptor can be proteins or nucleic acid and ligand is a small molecule. Usually, the receptor of molecular docking is drugs. In the docking procedure, to calculate binding energy between receptor and ligand needs to refer to coordinates for all atoms and to collocate several parameters, such as Van der Waals (VDW), atomic radius, charge, torsional angles, intermolecular hydrogen bonds and hydrophobicity of the contact force. When the prediction of docking process is complete, it will return all the possible ligand conformations and several predicted binding sites. The simulation process of molecular docking can be regarded as the key matching problem where the lock and key are the receptor and ligand, respectively. The goal of simulation process is to adjust the positions of key and lock being matched, or to say that it will produce many possible key positions and compare all possible key positions to further choose the best location by using the standard score function.

To understand the performance of the search algorithm for ligand docking problem and find the possible drugs, a numerous software of molecular docking predictions have been presented by the academic organizations and commercial companies, such as [14], [10], [15], [16], [17], [18], [19], [20], [21], [22], [23]. The basic idea of these programs is to quickly identify new leading compounds (throughout the virtual screening process). The search results of these programs can save time for experimental syntheses or raise accuracy. Simulation accuracy can be improved by repeatedly modifying simulation parameters, then validated by real crystal structures and experimental data to obtain the generally accepted experiment. In summary, these processes attempts to find out a good drug molecule with excellent effect for the receptor which is not validated yet by a laboratory.

B. AutoDock

AutoDock [10] is an effective tool for drug designs based on structure-based protein molecule and an open free software. This tool usually considers two target molecules of proteins and ligand for docking simulations that assume the protein being rigid and the ligand being flexibility. In other words, the protein receptor is a rigidly fixed object which needs to consider how to describe the dynamic combination between the flexible ligand and receptor molecules. To determine the merits of the parameters combination that depends on the corresponding score function to evaluate means the lowest binding energy.

This software (AutoDock) provides a method that tries to find the best combination of parameters to further provide the best relative position and orientation between the protein and ligand (i.e., the lowest free energy). Three search methods, simulated annealing, genetic algorithm and Lamarckian genetic algorithm, are provided by AutoDock environment to search for possible protein-ligand binding sites. The energy function calculating the energy value between the protein and ligand molecule is used by these search algorithms to determine which conformation is the candidate with the most appropriate binding points. The details of composition formula for free energy expressions could be referred to the study of [11]. Moreover, more and more studies attempt to apply their proposed methods to AutoDock, such as PASDock [24], DEDock [9], SODock [6] and so on.

III. The Proposed Algorithm

In this section, the proposed method first describes how the ligand molecule being represented and score function as an expression of formula. Then, the details of search procedure will also be given in this section.

A. Chromosome representation

Because AutoDock is the test environment in this paper, the proposed algorithm uses the parameter settings of this environment to define and adjust the coordinates of the ligand molecule translation, orientation and conformation. These parameters contain the three-dimensional coordinates of the ligand center points, four orientation parameters and some additional special atoms, such as coal, nitrogen and hydrogen atoms whose free torsion degrees as parameters. $N + 7$ parameters (i.e., seven translation and orientation and n free torsion degrees) are used for the encoding form.

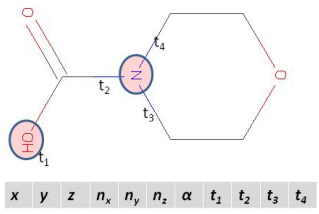


Fig. 1. Chromosome representation

As shown in Fig. 1,

- Three parameters for translation coordinates, x, y, and z, are the barycenter of ligand. As a result, the search space is a grid box space pre-specified by the user.

- The orientation of the ligand is a quadruple parameters represented by n_x, n_y, n_z, and α in the range interval $[-\pi, \pi]$. $[n_x, n_y, n_z]$ means ligand relative to the specified rotation angle of x, y, and z-axis. Although the direction of the ligand can be represented by three Euler angles, the use of the fourth parameter α can prevent *gimbal* lock problem.
- $t_1, t_2, ..., t_n$ represent the free torsion degree for some special atoms such as carbon, nitrogen and hydrogen atoms of the ligand molecule in the range interval $[-\pi, \pi]$.

B. Score function

AutoDock uses an empirical energy function as the score function to evaluate the ligand molecular docking conformation which is suitable or not for binding area of receptor. AutoDock uses an empirical energy function as the score function to evaluate the ligand molecular docking conformation being suitable or not for binding area of receptor.

A set of candidate solutions, X, can be expressed as the total energy of the protein-ligand interaction and the sum of the internal energy for both ligand and protein.

$$minEtotal(X) = E_v + E_h + E_e + E_i + E_d, \quad (1)$$

where E_v, E_h and E_e are used for the interaction forces of intermolecular namely Van der Waals forces, hydrogen bond and electronic potential energy; E_i is represented as the internal attraction of ligand and protein molecules; and E_d is the desolvation of binding area meaning the performance for hydrophobic. Note that, the details of Eq. (1) can be referred to study of [11].

C. Search Procedure

1. Randomly generate an initial population $S = S_1, S_2, ..., S_n$
2. While the termination criterion is not met
3. For $i = 0$ to g_n
4. Evaluate the fitness value f_i of each chromosome S_i
5. Select the fitter chromosomes to reproduce
6. Perform the crossover and mutation operators to generate population S'
7. Find the best solution of S' but not in Tabu list to perform the SW local Search
8. If $(i > 2)$
9. Perform pattern reduction procedure to detect and compress
10. Add Gaussian random number $\sigma(0, 1)$ to adjust common genes of S'
11. EndIf
12. EndFor
13. EndWhile

Fig. 2. Outline of detection operator of ILGA.

Fig. 2 shows that, in addition to basic operators of simple genetic algorithm (i.e., initialization, selection, reproduction, crossover and mutation), the ILGA uses the advantages of GA, local search and pattern reduction (PR) [25] to search for global optimum, fine-tune the final result and reduce common computations to speed up the computation time, respectively. However, for structure-based protein-ligand docking prediction problems, the quality (i.e., accuracy of the final result) is more important than reducing the computation time of the whole search process. Because most research for solving this problem generally performs their search methods for a certain number of iterations (such as 250,000 iterations) to find the better result by using the evaluating score function to further find the best binding active site and conformation of ligand molecular in the vast search space, the proposed algorithm employs the PR which does not only speed up the iterative process closer to the optimal solution, but also avoid convergence being too fast. Moreover, because fast convergence of search algorithm will degrade the diversity of search solutions which may let it fall into local optimal, the proposed method attempts that during the PR process, the solution in each group will be maintained for the PR gene cluster with a certain interval [-1,1] of the Gaussian random value. Trying to let the common gene cluster maintain a certain diversity is due to the random number and avoid many computing resources being consumed.

D. The ILGA with Local Search

Because most heuristic algorithms do not guarantee that they can find the local optimum solution in each iteration, the local search algorithm is one of the most effective methods to fine-tune the solution to further improve the quality of end result. That is why local search is widely applied to improving the search ability of heuristic algorithm, i.e., combining it with genetic algorithms. In AutoDock, LGA is a hybrid method which integrates genetic algorithm for global search with the Solis and Wets (SW) [26] algorithm for local search that is provided with features for directed and self-adjustment step length. Of course, SW algorithm is also used as a local search in the proposed algorithm.

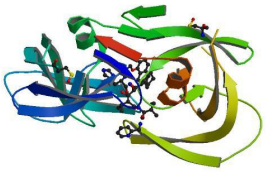
To avoid search the same solution for multiple times, the proposed algorithm integrates the concept of the tabu search [27] into local search operator to prevent repeated evaluations. More precisely, the proposed algorithm will check if the solution (common gene) is compressed by pattern reduction and listed in the Tabu list at first or not. If it is listed in the tabu list, the proposed algorithm will find out the solution not in the list at overall sequence checking to perform search operation. In other words, it is a method to disturb the genes that have similar structures and may let the search fall into local minima. This method then can be used for increasing the search diversity with a certain number of iterations for the local search and the probability of finding the optimal solution.

IV. Simulation Results

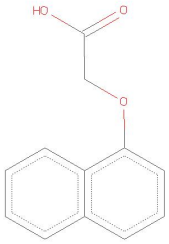
In this paper, the performance of the proposed algorithm is evaluated by using it to solve the protein-ligand docking problem. All the empirical analyses are conducted on an IBM X3400 machine with 2.0 GHz Xeon CPU and 8GB of memory using CentOS 5.0 running Linux 2.6.18. Moreover, all the programs are written in C++ and compiled using g++ (GNU C++ compiler).

A. Parameter settings and datasets

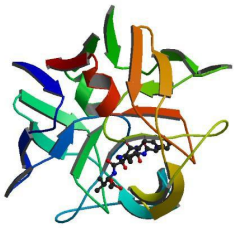
The experimental data used to evaluate the performance of the proposed algorithm include four protein-ligand sets for docking simulations. Each molecular data source is accessed from the RCSB Protein Data Bank database (http://www.pdb.org). These structure diagrams for both protein and ligand molecules are shown in Fig. 3.



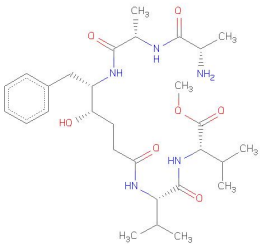
(a) PDB ID(1hiv)



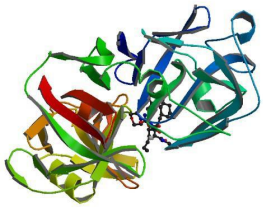
(b) ligand(NOA) for 1hiv



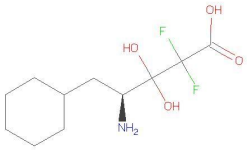
(a) PDB ID(1aaq)



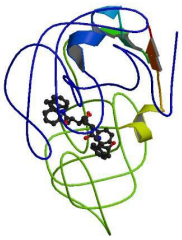
(b)ligand(PSI)for 1aaq



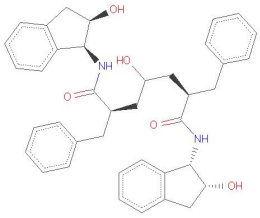
(a) 1epo



(b) igand(CFH)for 1epo



(a) 4phv



(b) ligand(VAC)for 4phv

Fig. 3. Structure diagrams for both protein and ligand molecule.

The description data type for ligand and protein receptor use the AutoDock PDBQ format and these are made by using AutoDock Tools at the preparation phase. On one side, the document of ligand with operation steps are shown as following. (1) The coordinates for all atoms in the ligand molecule are extracted from the PDB format file which describes protein receptor. (2) Adding the hydrogen atoms, the charge and combine the non-polarity hydrogen atoms. (3) Define the root node of the ligand and the bond type being twist. On the other side, the document of protein receptor molecules for data format are as follows. (1) To remove the water molecules, ligands, and the metal ion which is not a part of binding sites. (2) To edit incomplete atoms. (3) Adding the hydrogen atoms, the charge and combine the non-polarity hydrogen atoms. (4) To distribute the solvent parameters. The execution environment parameter settings for ILGA simulation is shown in Table I.

TABLE I
SIMULATION RESULTS

Simulation Runs	30
Population size	50
Crossover rate	1
Mutation rate	0.02
Crossover method	Arithmetic method
Stop criteria (max generation no./ max evaluation counts)	max gens. = 5000 max eval. = 250000

B. Results

Tables II and III use two different viewpoints to evaluate the AutoDock simple GA (sGA), LGA and ILGA. Table II shows that the experimental results of ILGA (RMSD) is better than sGA and LGA when performing the same iterations. By using the variance information of these results, the final result of ILGA is smaller than it of LGA method. In other words, this experimental result shows that the proposed method is more stable than the sGA and LGA.

Table III uses another viewpoint to compare the ILGA, sGA and LGA that t he computing time of the proposed algorithm is less than it of the sGA and LGA when setting a condition of result quality for sGA, LGA and ILGA. In summary, these two experimental results show that ILGA method can enhance both time consumption and solution quality in comparison with traditional methods (sGA and LGA) for search results. In summary, these two experimental results show that ILGA method can enhance both time consume and solution quality to compare with traditional methods (sGA and LGA) for search results.

The Fig. 4 for the comparison of convergence of sGA, LGA and the proposed method (ILGA). Fig. 4(a) for the complete results of the convergence process indicates the proposed method for both convergence rate and solution quality being superior to other types of GA-based approach. Fig. 4(b) is a detailed comparison for the three methods, which more clearly shows the method of this study mentioned early in the convergence can be achieved very close to the optimal solution, while the other two methods still need more computing time to achieve the same result.

V. CONCLUSION

This study presents a hybrid search algorithm which combines genetic algorithms, local search method and pattern reduction to improve the accuracy and reduce the computation cost for protein-ligand docking in structure-based drug design. It attempts to design an efficient GA-based method with pattern reduction to reduce duplication and unnecessary calculations. By using pattern reduction method, this heuristic algorithm not only can shorten computing time to solve such problems, but also can focus on getting better solution quality. For future research, the heuristic algorithm based on the proposed method applying to the protein-ligand docking will be developed. Then

TABLE II
AVERAGE RESULTS OF SGA, LGA AND ILGA WITH ACCURACY COMPARISON

	sGA				LGA				ILGA			
PDB	Energy	RMSD	Succ.[a]	Time[b]	Energy	RMSD	Succ.[a]	Time[b]	Energy	RMSD	Succ.[a]	Time[b]
1hiv	-4.12	11.61	0.00	37.39	-4.45	10.36	0.00	37.46	-17.85	4.31	0.24	37.41
1aaq	-3.92	9.34	0.00	16.20	-4.32	8.73	0.01	16.05	-16.44	3.03	0.38	16.12
1epo	-7.41	7.72	0.04	17.17	-7.81	7.32	0.04	17.26	-12.26	6.53	0.09	17.13
4phv	-11.56	7.53	0.10	17.24	-12.35	7.03	0.10	17.19	-16.13	2.37	0.31	17.21

[a]Succ.: The rate of successful docking (RMSD less than 2.0Å).
[b]Time : Average execution time in second per run.

TABLE III
AVERAGE RESULTS OF SGA, LGA AND ILGA WITH TIME CONSUME COMPARISON

	sGA				LGA				ILGA			
PDB	Energy	RMSD	Succ.[a]	Time[b]	Energy	RMSD	Succ.[a]	Time[b]	Energy	RMSD	Succ.[a]	Time[b]
1hiv	-4.39	10.42	0.00	47.46	-4.45	10.36	0.00	37.46	-6.64	9.24	0.13	20.51
1aaq	-4.24	8.92	0.00	16.57	-4.32	8.73	0.01	16.05	-6.14	6.52	0.27	13.40
1epo	-7.78	7.34	0.04	17.59	-7.81	7.32	0.04	17.26	-9.32	7.10	0.07	11.29
4phv	-11.74	7.91	0.08	18.21	-12.35	7.03	0.10	17.19	-13.13	6.73	0.16	9.72

[a]Succ.: The rate of successful docking (RMSD less than 2.0 Å).
[b]Time : Average execution time in second per run.

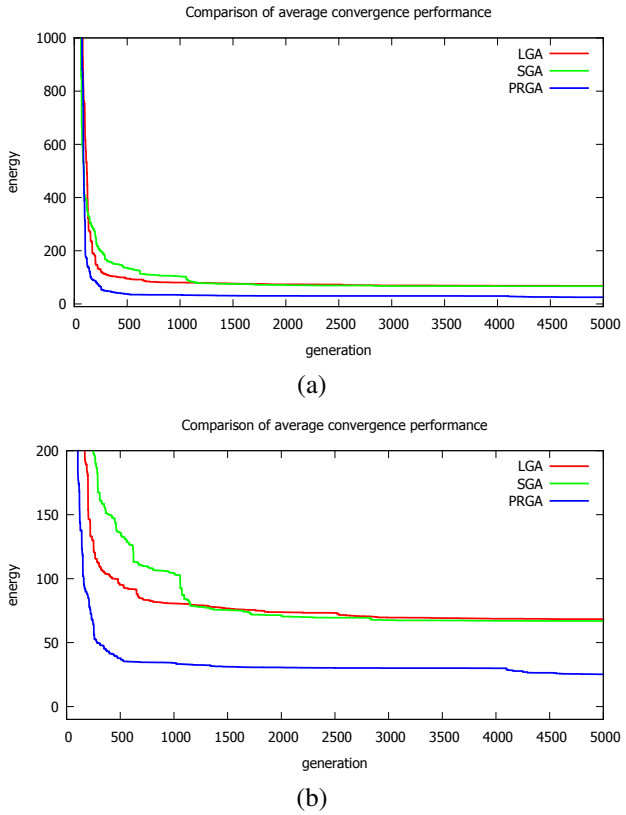


Fig. 4. Comparison of average convergence performance for protein(hsgl)-ligand(ind)

the current algorithm will be further designed and modified so that it can present more effective detection on evaluating repeats in order to reduce a lot more computing time.

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