Improving Ligand-Ranking of AutoDock Vina by Changing the Empirical Parameters

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ABSTRACT

AutoDock Vina (Vina) achieved a very high docking-success rate, $\hat{p}$, but give a rather low correlation coefficient, R, for binding affinity with respect to experiments. This low correlation can be an obstacle for ranking of ligand-binding affinity, which is the main objective of docking simulations. In this context, we evaluated the dependence of Vina *R* coefficient upon its empirical parameters. R is affected more by changing the *gauss2* and *rotation* than other terms. The docking-success rate $\hat{p}$ is sensitive to the alterations of the *gauss1*, *gauss2*, *repulsion*, and *hydrogen bond* parameters. Based on our benchmarks, parameter set1 has been suggested to be the most optimal. The testing study over 800 complexes indicated that the modified Vina provided higher correlation with experiment $R_{\mathrm{set1}} = 0.556 \pm 0.025$ compared with $R_{\mathrm{Default}} = 0.493 \pm 0.028$ obtained by the original Vina and $R_{\mathrm{Vina\ 1.2}} = 0.503 \pm 0.029$ by Vina version 1.2. Besides, the modified Vina can be also applied more widely, giving $R \geq 0.500$ for 32/48 targets, compared with the default package, giving $R \geq 0.500$ for 31/48 targets. In addition, validation calculations for 1036 complexes obtained from version 2019 of PDBbind refined structures showed that the set1 of parameters gave higher correlation coefficient ($R_{\mathrm{set1}} = 0.621 \pm 0.016$) than the default package ($R_{\mathrm{Default}} = 0.552 \pm 0.018$) and Vina version 1.2 ($R_{\mathrm{Vina\ 1.2}} = 0.549 \pm 0.017$). The version of Vina with set1 of parameters can be downloaded at https://github.com/sontungngo/mvina. The outcomes would enhance the ranking of ligand-binding affinity using Autodock Vina.

Introduction

The ligand-binding process is one of the most important issues in biology.[1] These processes are mostly associated with noncovalent chemical reactions between inhibitors and protein targets.[2] In particular, the process can be mimicked using computational approaches,[3,4] which plays a tremendous role in computer-aided drug design (CADD).[5] Accurate determination of ligand-binding affinity and pose of a small compound to an enzyme target are of great importance because they will reduce the cost and time for therapy development.[5-7] Therefore, numerous computational approaches were advanced to carry out these tasks.[8,9] In terms of accuracy and required computing resources, these approaches can be roughly arranged into three groups: low accuracy and small consumption of central processing unit (CPU) time; medium in both accuracy and required CPU time; and accurate and precise approaches which require a large amount of computing resources. The first group involves molecular docking[10-13] and quantitative structure-activity relationship (QSAR) approaches.[10-15] The second group includes fast pulling of ligand (FPL),[16,17] umbrella sampling (US),[3,18,19] implicit ligand theory,[20,21] linear interaction energy,[22-25] and molecular mechanism/Poisson-Boltzmann surface area (MM/PBSA),[26-28] approaches. The last group contains free energy perturbation (FEP),[29,30] thermodynamics integration (TI),[31,32] and non-equilibrium molecular dynamics simulations (NEMD).[33,34] Moreover, enhanced sampling techniques are also implemented into perturbation simulations to obtain more accurate results.[35-38] However, these approaches would consume a huge amount of CPU time.

In order to calculate the binding free energy of a ligand to an enzyme, molecular dynamics (MD) simulations were normally used to generate the equilibrium complex conformations, which would be then employed as inputs into binding free energy investigations.[39,40] Normally, the docking pose would be used as starting structure of MD simulations. Therefore, molecular docking approaches are initially performed to preliminary estimate the ligand-binding pose and affinity.[41,42] Moreover, molecular docking approaches have also been used for screening a large database of compounds,[43,44] which may consist of several millions of compounds such as ZINC,[45] ChEMBL,[46] PubChem,[47] etc. Therefore, although their accuracy is not very high, molecular docking approaches play an important role in CADD.[48]

AutoDock Vina (Vina)[49] is a free open-source application providing the ligand-binding affinity and pose rapidly.[50] Vina is broadly used in the scientific community with more than 10,000 citations since released in 2010 (WebofKnowledge). In particular, Vina was built with an empirical scoring function including the Gaussian steric interaction, repulsion, hydrogen bond, hydrophobic, and torsion metrics.[49] Moreover, the docking package was implemented with the parallel computing capability, which makes Vina docking calculation run very fast.[51] Furthermore, the application also attracts large number of users since it is very user-friendly.[52] However, although Vina rapidly converges and adopts a large docking-success rate, the correlation between estimated and experimental binding free energy is low ($R < 0.5$).[51] Due to the limitation, it is hard to rank the top-lead ligands based on the ligand-binding affinity. Therefore, in this work, the dependence of Vina performance on empirical parameters was assessed to search for optimal set of parameters which enhance correlation of docking with respect to experiment. The task is of great interest, especially due to the widespread of Vina to estimate binding affinities and poses of various substrates to biomolecular targets.[53-57] In particular, 800 available ligands were redocked to their corresponding receptors using Vina with different empirical parameters. The list of complexes was reported in the previous study.[51] The dependence of Vina performance on individual empirical parameters was then clarified. Based on the observation, three sets of empirical parameters were proposed. The performance of the Vina with modified parameters on 800 complexes[51] was tested. Besides, 1315 available inhibitors were also redocked to the corresponding receptors in order to validate the obtained results. In addition, the AutoDock Vina 1.2 (Vina 1.2),[58] new version of AutoDock Vina, was also performed to compare with the obtained results. It should be noted that Vina 1.2 can use AutoDock4 scoring function, but in this work only Vina scoring function was employed for all docking calculations. The optimal empirical parameters would help rank the ligand-binding affinity more accurately.

Materials and Methods

Complex Structures and Topologies

The complex conformations were download from the Protein Data Bank (PDB) according to the previous work[51] and also reported in detail in the Supporting Information. The topological PDBQT files for rigid receptors and flexible ligands were generated via AutoDockTools with more details in the Supporting Information.[11] In particular, the Gasteiger-Marsili method was employed to calculate atomic charges.[59,60]

Molecular Docking Simulations

Vina was employed to redock several ligands to their corresponding receptors. In particular, the docking application was performed by using the globally searching exhaustiveness of 8, which corresponds to the default option. The maximum energy difference, which is the difference between the best and worst docking modes, was chosen as 7 kcal mol^{-1}.[51] The docking grid was selected to be $20 \times 20 \times 20$ Å, in which the grid center was the ligand center of mass (cf. Figure 1). Only one docking conformation corresponding to the lowest docked energy was recorded. Besides that, the Vina 1.2, new docking approaches, expanded force field, and python bindings,[58] was also performed with the same docking parameters of Vina to compare with the obtained results.

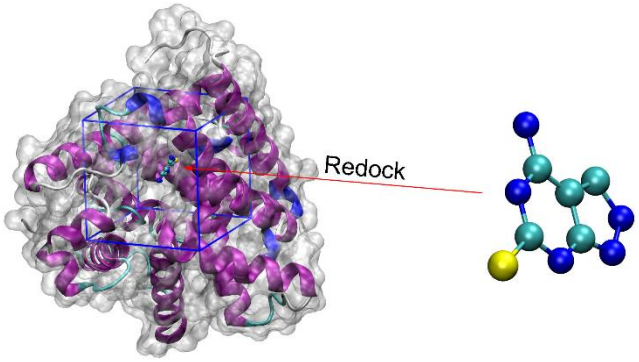

Figure 1. Ligand was redocked to the binding site of the enzyme using Vina with various empirical parameters. The center of mass of the experimental binding ligand was used as the grid center using AutoDockTools.

Structural Analysis

The root-mean-square deviation (RMSD) of non-hydrogen atoms between docked and experimental poses was determined using GROMACS tools.[61] The calculated error of correlation coefficient, docking-success rate, and root-mean-square error (RMSE) was estimated by using 1,000 bootstrapping samples.[62] The computed error of ligand-binding free energy and RMSD was the standard error of the mean.

Results and discussion

According to the previous assessment,[51] Vina rapidly converges since the accuracy insignificantly increased upon changing the globally searching exhaustiveness from 8 to 56 or 400, which corresponds to *short*, *medium*, and *long* options.[51] Moreover, it should be noted that increasing the exhaustiveness causes at least ca. 7 times increase in the CPU time. It thus is hard to use *medium* or *long* options when screening a large database of compounds that consists of several thousand/million elements. Therefore, the default or the *short* docking option is widely used to complete the task. In this context, we redock available inhibitors to the corresponding targets using the *short* option as mentioned above. Furthermore, as mentioned above, Vina is an empirical approach which uses six parameters including *gauss1*, *gauss2*, *repulsion*, *hydrophobic*, *hydrogen bond*, and *rotation* terms to calculate the contribution of the Gaussian steric interaction, repulsion, hydrogen bond, hydrophobic, and torsion terms.[49] In order to assess Vina performance dependence upon empirical parameters, we changed the individual parameter by 10% at each iteration (cf. Table S1 of the Supporting Information), while all the other parameters were kept at default values. In particular, the four parameters *gauss1*, *repulsion*, *hydrophobic*, and *hydrogen bond* were thus changed in the range from -50 to +50 % with respect to the default values. The *gauss2*, and *rotation* parameters were varied in the range from -50 to +150 and -90 to +50 % of the parameters, respectively. Besides, although the docking of 800 ligands to corresponding receptors was previously completed using the original Vina, we also redocked these complexes via the unchanged docking application. Three new sets of empirical parameters were then proposed upon the understanding about the change of docking results via the alteration of empirical parameters, which are named set1, set2, and set3. Therefore, 78 versions of Vina having different empirical parameters were compiled to redock ligands to receptors.

As mentioned above, the docking study using default empirical parameters was reproduced to compare with modified versions and the results were mentioned in the Supporting Information 2. The Pearson correlation coefficient between docked and experimental values is of $R_{\mathrm{Default}} = 0.493 \pm 0.028$, which is in good agreement with the previous work,

$R_{\mathrm{Vina}}^{\mathrm{short}} = 0.489 \pm 0.027$.[51] The docking-success rate which is defined as having RMSD less than 0.2 nm is of $\hat{p} = 86 \pm 1$ %, which is larger than that reported in the previous reports using the *long* option, $\hat{p} = 81$ %. It should be noted that the *long* option used the exhaustiveness of 400, which is required ca. 50 times longer computing time than the *short* option. The polar hydrogens were not automatically added to complexes in the previous work could be the cause of the smaller $\hat{p}$. However, the correlation coefficients were insignificantly changed. Besides, the average of binding energies over 800 complexes is of $\Delta G_{\mathrm{Default}} = -8.60 \pm 0.06$ kcal mol^{-1}, which is smaller than that from the previous study, $\Delta G_{\mathrm{Vina}}^{short} = -7.75 \pm 0.06$.[51] The difference between theoretical and experimental results is of $\delta = 0.62$ kcal mol^{-1}. The outcome implies that the *hydrogen bond* parameter has a stronger effect on docking pose and docking energy than on docking accuracy.

The docking simulations using various empirical parameters, which were mentioned in Table S1 of the Supporting Information, were performed. The docking results were described in the Supporting Information 2. Moreover, the docking performance was determined via the correlation coefficient analyses, in which the estimated values of R were shown in Table S2 of the Supporting Information. Furthermore, in the first steps, we have changed all of empirical parameters in the range from -50 to +50 % of their default values. The dependence of R upon the empirical parameters were shown in Figure 2. Interestingly, the R value is not sensitive to the change of the *gauss1* and *hydrophobic* parameters since it gives a relative deviation to the original one ($R_{\mathrm{Default}} = 0.493$) by amounts of 6 and 3 %, respectively. The R_{gauss1} reached the maximum value of 0.513 ± 0.028 correspondings to the $gauss1 = -0.049811$ (+40%), the difference from the original Vina only is 4%. Besides, the alteration of the *hydrophobic* metric turns the $R_{hydrophobic}$ ranging from 0.492 to 5.08. The largest value of $R_{hydrophobic}$ thus differs the R_{Default} by an amount of 3%. Moreover, the obtained results suggested that the coefficient, R, is more sensitive with the change of the *repulsion* and *hydrogen bond* terms. In particular, the $R_{repulsion}$ ranges from 0.472 ± 0.027 to 0.510 ± 0.027 and $R_{hydrogen\ bond}$ ranges from 0.447 ± 0.030 to 0.508 ± 0.026 corresponding to relative variation of 8 and 12 %, respectively. However, the maximum value of $R_{repulsion}$ and $R_{hydrogen\ bond}$ only differ from the R_{Default} by 3%, respectively.

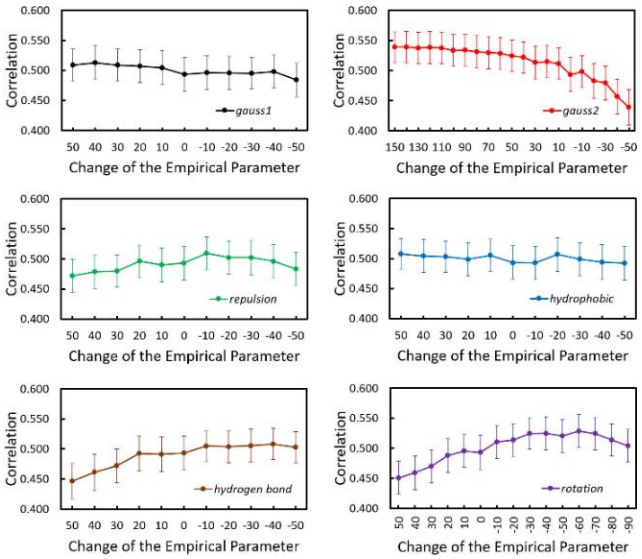

Figure 2. The correlation coefficient between docked and experimental binding free energy upon the changing of empirical parameters.

The story is significantly different when the alteration of the *gauss2* and *rotation* parameters were induced. These two terms are most influential to the correlation coefficient. When changing from -50 to +50 % of the default value, the corresponding correlation coefficient R_{gauss2} and $R_{rotation}$ range from $0.439 \pm .030$ to 0.524 ± 0.024 and 0.451 ± 0.027 to 0.525 ± 0.028, which correspond to relative deviations of 17 and 15 %, respectively. The maximum values of R_{gauss2} and $R_{rotation}$ differ from the R_{Default} by amounts of 6 and 6 %, respectively. Interestingly, although changing *gauss2* and *rotation* terms significantly increase the correlation coefficient, their influence are in the opposite direction. In particular, the R value tends to grow when the *rotation* parameter is decreased. On the other hand, the metric raises upon the increase of the *gauss2* term. Because the R values still increase upon the decreasing and increasing of the *gauss2* and *rotation* terms, respectively, the *gauss2* metric was increased to -0.012890 (+150%) of the parameter and the *rotation* value was decreased to 0.006431 (-90%) as mentioned in Table S1 of the Supporting Information. The obtained R_{gauss2} and $R_{rotation}$ depending the changes was also described in Figure 2 and Table S2 of the Supporting Information. When the *rotation* parameter was gradually reduced, $R_{rotation}$ reached the maximum value, 0.529 ± 0.028, when the *rotation* value is of 0.025722 (-60%). Besides, R_{gauss2} reached a maximum value of 0.539 ± 0.026, when the *gauss2* term was of -0.012374 (+140%).

Overall, the improvement is significant since the maximum value of R_{gauss2} and $R_{rotation}$ differ from the R_{Default} by amounts of 9% and 7%, respectively.

The average of the docking energies among protein-ligand complexes was mentioned in Table S3 of the Supporting Information. In particular, the average value of ΔG_{Dock} was linearly dependent on the change of empirical parameters. Especially, the average binding free energies are most sensitive to the change of the *gauss2* parameter, which is in good agreement with the observation that R is mostly sensitive to the change of the *gauss2* parameter. The lowest $\Delta G_{\mathrm{Dock}} = -16.43 \pm 0.12$ kcal mol^{-1} was observed when the *gauss2* parameter was assigned as -0.012890 (+150%). Besides, the highest $\Delta G_{\mathrm{Dock}} = -6.01 \pm 0.04$ kcal mol^{-1} was obtained when the *gauss2* parameter was reduced by an amount of 50% (-0.002578) of the default parameter. Moreover, the difference between docked and experimental data is associated with the RMSE, which was mentioned in Figure 3 and Table S4 of the Supporting Information. In particular, the RMSE was sensitive with the change of the *gauss1*, *gauss2* and *rotation* parameters, whereas the RMSE varies from 0.65 to 5.48 kcal mol^{-1}. RMSE curves reached the minimum values, when the *gauss1*, *gauss2* and *rotation* metrics are of -0.042695 (+20%), -0.005672 (+10%) and 0.046768 (-20%), respectively.

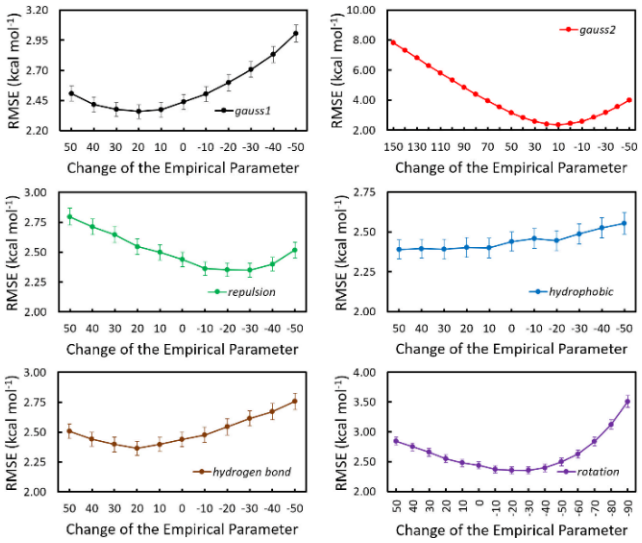

Figure 3. RMSE of docking energies compared with the respective experiments. The results were obtained when the empirical parameters were altered. The computed error was estimated using 1000 rounds of the bootstrapping analysis.

As mentioned above, the binding poses of ligands to receptors via molecular docking simulations also play an important role since they would be used as initial conformations of MD-refined simulations,[63-65] and results of binding free energy calculations via MD simulations are often sensitive to the difference of binding conformations of complexes.[66] Indeed, the computational binding structure is more fitting to the native binding shape meaning that the estimating binding free energy is more accurate. Consequently, the better docking pose is the shape that is more fitting to the experimental binding conformation.[67] The MD-refined simulations would be faster to reach the stabilized conformations. The consumption of computing resources would be thus reduced. Therefore, the successful-docking rate, $\hat{p}$, was carefully investigated, in which the RMSD of non-hydrogen atoms between docked and experimental structures were assessed (cf. Figure 4 and Table S5 of the Supporting Information). It should be noted that a successfully-docked shape normally is the docked structure having RMSD to the respective experimental shape less than 0.2 nm.[68] However, in this work, we also assessed the successful-docking rate with a RMSD cutoff of 0.15, 0.10, and 0.05 nm.[51]

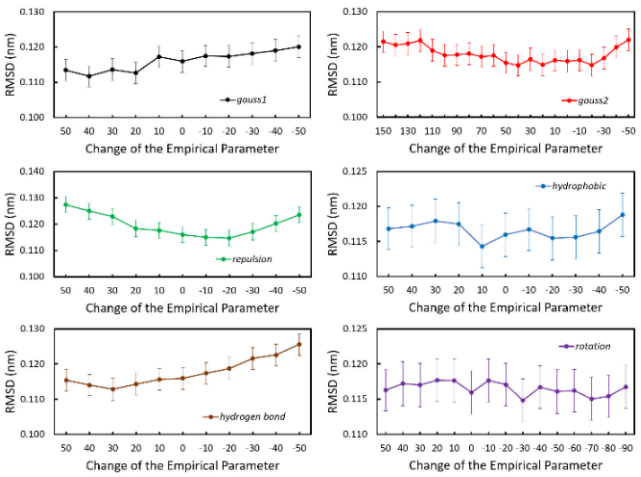

Figure 4. The dependence of RMSD upon the change of the empirical parameters. The computed error is the standard error of the mean.

The original Vina adopted a mean RMSD of 0.116 ± 0.003 nm compared to the respective experiments. The docking- success rate with an RMSD cutoff of 0.20 nm is of $\hat{p} = 86 \pm 1$ %. Besides, the modified Vina formed a mean RMSD ranging from 0.112 ± 0.003 to 0.127 ± 0.003 nm, resulting in adopting $\hat{p}$ value in the range from 82 ± 1 to 88 ± 1 % corresponding with the *repulsion* and *gauss1* terms of 1.260368 (+50%) and -0.049811 (+40%), respectively. In

particular, the dependence on alteration in the empirical parameters of $\hat{p}$ with an RMSD cutoff of 0.20 nm was fully reported in Figure 5 and Table S6 of the Supporting Information. It should be noted that the estimated mean values of RMSD are well correlated with the successful-docking rate. The smaller the mean value of RMSD is the larger the docking-success rate is. Moreover, $\hat{p}$ reached its largest value of 6%, when the *hydrogen bond* term was altered within their respective ranges. The observation is in good agreement with discussion above. The $\hat{p}_{hydrogen\ bond}$ value reached the largest values when the *hydrogen bond* metric is of -0.763671 (+30%). The $\hat{p}$ is not sensitive to the change of the *hydrophobic* parameter since the value varies within a range of <1% only. Furthermore, changing the *gauss1* term provides the largest docking-success rate $\hat{p}_{gauss1}$ of 88 ± 1 %. The alteration of *repulsion* and *hydrophobic* terms do not enlarge the R value. Other parameters including *gauss2*, *hydrogen bond*, and *rotation* metrics only formed the maximum value $\hat{p} = 87\% \pm 1\%$. Furthermore, when the other cutoff was applied including 0.15, 0.10, and 0.05 nm, the $\hat{p}$ metric became more sensitive to the *gauss1, gauss2, repulsion,* and *hydrogen bond* terms and insensitive to the *hydrophobic* and *rotation* terms (cf. Tables S7-S9 and Figures S2-S4 of the Supporting Information). Consequently, the *repulsion* metric dominates over all of the metrics in influencing the successful-docking rate, which $\hat{p}$ was changed in the range from 4 to 6 % upon the modification of the *repulsion* term.

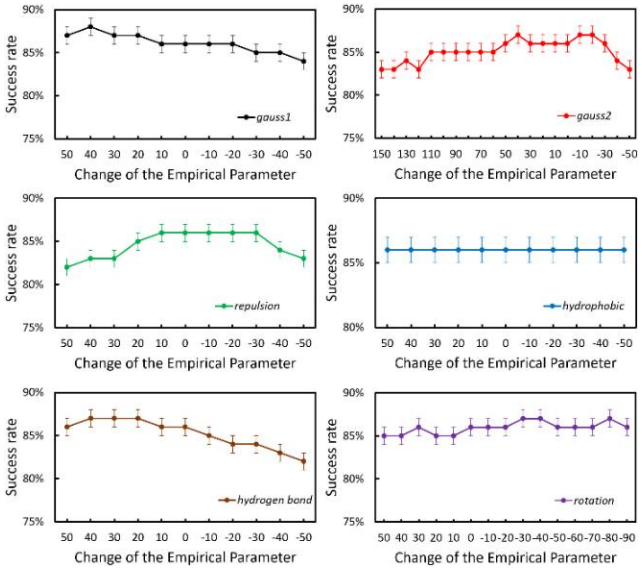

Figure 5. Changing of the docking-success rate, $\hat{p}$, upon the alteration of the empirical parameters with an RMSD cutoff of 0.20 nm. The computed error was calculated via 1000 rounds of the bootstrapping analysis.

Considering the overall influence of empirical parameters on the Vina results, we proposed three sets of empirical parameters, which were shown in Table 1. In particular, over three sets of parameters, the *gauss1* term was selected as -0.049811 (+40%) since both R_{gauss1} and $\hat{p}$ reached the maximum values with the corresponding parameters compared to the original one (Figure 5). The *gauss2* term was chosen as -0.007218 (+40%) for set1 and set2 of parameters, because the R_{gauss2} formed an appropriate value, which is larger than the original one by an amount of 6%, and the $\hat{p}$ term achieved the largest amount of 87%. In set3, the *gauss2* parameter was selected as -0.007734 (+50%) since the obtained R_{gauss2} and $\hat{p}_{gauss2}$ are almost the same as the corresponding values of set1 and set2. Moreover, the *repulsion* parameter was of 0.756221 (-10%) for set1 and set2 of empirical parameters, because the modified Vina adopted the largest correlation coefficient (0.510 ± 0.027). In set3, the *repulsion* term was picked as 0.672196 (-20%) since the $\hat{p}$ value reached the largest amount (Figure 5). The *hydrophobic* term was -0.028055 (-20%) for three sets since the docking package formed the maximum value of $R_{hydrophobic} = 0.507 \pm 0.028$. Besides, interestingly, the $\hat{p}_{hydrophobic}$ is slightly increased corresponding to this *hydrophobic* term (Figure 5). Furthermore, in set1 and set2, the *hydrogen bond* metric was changed to -0.352463 (-40%) due to forming the strongest correlation to the experiments. However, in set3, the *hydrogen bond* value was chosen as -0.528695 (-10%), because the R value was increased but the $\hat{p}$ metric was insignificantly decreased (cf. Figure 2 and Figure 5). Finally, in set1 of empirical parameters, the *rotation* term was 0.025722 (-60%), because the accuracy of the result was maximized with a value of $R_{rotation} = 0.529 \pm 0.028$ (Figure 2). Besides, the *rotation* parameter of set2 and set3 was selected as 0.012861 (-80%) since the modified Vina formed the largest successful-docking rate, 87 ± 1 %, and appropriate correlation coefficient, 0.514 ± 0.027, (Figure 2).

Table 1. Proposed Sets of Empirical Parameters.

N0	Parameter	Set1	Set2	Set3	Default[a]
1	*gauss1*	-0.049811	-0.049811	-0.049811	-0.035579
2	*gauss2*	-0.007218	-0.007218	-0.007734	-0.005156
3	*repulsion*	0.756221	0.756221	0.672196	0.840245
4	*hydrophobic*	-0.031562	-0.031562	-0.031562	-0.035069
5	*hydrogen bond*	-0.469951	-0.469951	-0.528695	-0.587439
6	*rotation*	0.025722	0.012861	0.012861	0.058460

[a]The default empirical parameters were reported in the previous study.[49]

Three modified Vina with various sets of empirical parameters were performed over 800 complexes, in which these complexes were reported in the previous work.[51] The obtained results are displayed in Table 2 and Figure 6. The detailed results were shown in Supporting Information 2. Interestingly, according to the selection of empirical parameters, the increase of the correlation coefficient depends on set1, set2, and set3, in which the obtained coefficients are of $R_{set1} = 0.556 \pm 0.025$, $R_{set2} = 0.551 \pm 0.026$, and $R_{set3} = 0.536 \pm 0.028$, respectively. The obtained correlations are significantly larger than that of the original Vina ($R_{\mathrm{Default}} = 0.493 \pm 0.028$). Moreover, the performance of AutoDock Vina 1.2 (Vina 1.2),[58] a new version of Vina supporting the AutoDock4.2 scoring function, was also assessed and reported in Table 2 and the Supporting Information 2. Although the Vina 1.2 with $R_{\mathrm{Vina\ 1.2}} = 0.503 \pm 0.029$ provides a more accurate ranking than the original Vina, $R_{\mathrm{Default}} = 0.493 \pm 0.028$, the modified Vina formed a larger correlation coefficient (Table 2). Furthermore, because, as mentioned above, the modified parameters were chosen by maximizing the correlation coefficient, the obtained $\hat{p}$ values of modified packages were slightly decreased (cf. Table 2).

Table 2. Calculated Metrics of the Modified Vina in Comparison with the Original Version.[a]

N0	Package	R	ΔG_{Dock}	$RMSD$	$\hat{p}$
1	**set1**	0.556 ± 0.025	-12.88 ± 0.11	0.119 ± 0.003	84 ± 1
2	**set2**	0.551 ± 0.026	-17.77 ± 0.17	0.120 ± 0.003	83 ± 1
3	**set3**	0.536 ± 0.028	-15.44 ± 0.14	0.118 ± 0.003	85 ± 1
4	**Default**	0.493 ± 0.028	-8.60 ± 0.06	0.116 ± 0.003	86 ± 1
5	**Vina 1.2**	0.503 ± 0.029	-8.60 ± 0.06	0.115 ± 0.003	87 ± 1

[a]The unit of ΔG_{Dock} and RMSD is kcal mol^{-1} and nm, respectively. The computed error of ΔG_{Dock} and RMSD is standard error of the mean. The $\hat{p}$ value was calculated within a cutoff 0.2 nm.

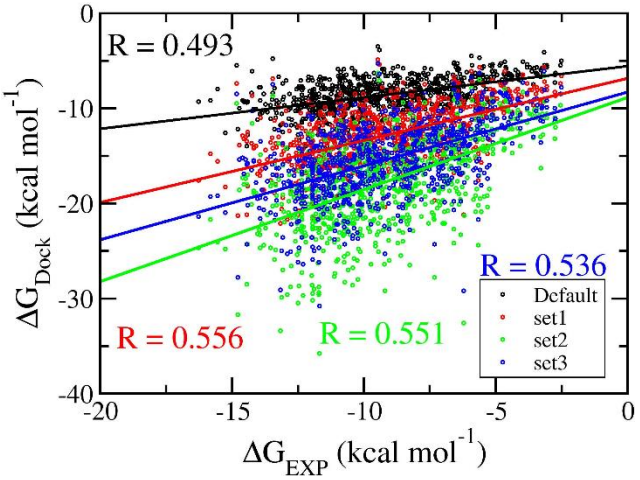

Figure 6. Correlation coefficients between original/modified Vina versus experiments. The results were obtained over 800 complexes, which were listed in the previous work.[51]

The influence of modified empirical parameters on individual enzymic targets was also evaluated and the results were shown in Table S10 of the ESI. For Vina with the default parameters, 31 out of 48 targets have correlation higher than 0.5 ($R_{\mathrm{Default}} \geq 0.500$) whereas with set1 parameters the number of targets having $R_{set1} \geq 0.500$ is 32 out of 48. Besides, Vina with set2 and set3 increase further that number to 33 out of 48 targets. This clearly indicates the new sets of empirical parameters gives higher correlation with respect to experiment. It is a critical increase because when screening a large number of ligands, we first need to know more accurately the ranking of ligand-binding affinity.

In addition, a further validating investigation of the performance of the modified Vina with the difference of empirical parameters was performed in comparison with the original one. 1036 complexes from the version 2019 of PDBbind refined structures, which were mentioned in Supporting Information, were redocked by using the original and modified Vina package. The obtained results were mentioned in Table 3 and Figure 7. All of the modified versions of Vina formed larger correlation coefficients compared with the original one ($R_{\mathrm{Default}} = 0.543 \pm 0.020$) and the Vina 1.2 version ($R_{\mathrm{Vina\ 1.2}} = 0.540 \pm 0.020$). The obtained R of modified Vina ranges from 0.591 ± 0.018 to 0.617 ± 0.017. Vina with set1 parameters adopted the largest coefficient of $R_{set1} = 0.617 \pm 0.017$. Moreover, the docking-success rates were reduced, which range from 79 ± 1 to 81 ± 1 % in comparison with the default package, $\hat{p}_{\mathrm{Default}} = 84 \pm 1$ %, and the 1.2 version, $\hat{p}_{\mathrm{Vina\ 1.2}} = 83 \pm 1$ %,.

The original Vina adopted the larger value $\hat{p}_{\mathrm{Default}}$ compared to the modified packages (cf. Table 3) possibly because the version 2009 of PDBbind refined complexes were used to train the empirical parameters of the original Vina.[49] The set1 parameters formed a slight decrease of $\hat{p}$ term ($\hat{p}_{set1} = 81 \pm 1$ %). However, reaching a higher correlation coefficient is the most important since docking simulations were mainly used to relatively rank the ligand-binding affinity (as mentioned above). Furthermore, the modified Vina systameticaly overestimates the binding free energy. Although it is not an important issue since docking simulations were mainly used to relatively rank the ligand-binding affinity, Vina with set1 parameters formed the smallest difference between docking and experimental energy compared with the other modified Vina versions (Table 3). Overall, we may assume that set1 is the most appropriate since it stably forms the largest R and appropriate $\hat{p}$ over various groups of complexes.

Table 3. Calculated Results of the Modified Vina Compared with the Original Version.[a]

N0	Package	R	ΔG_{Dock}	$RMSD$	$\hat{p}$
1	**set1**	0.617 ± 0.017	-14.48 ± 0.11	0.131 ± 0.004	81 ± 1
2	**set2**	0.607 ± 0.018	-20.54 ± 0.18	0.135 ± 0.004	79 ± 1
3	**set3**	0.591 ± 0.018	-17.71 ± 0.15	0.127 ± 0.003	81 ± 1
4	**Default**	0.543 ± 0.020	-9.29 ± 0.06	0.119 ± 0.003	84 ± 1
5	**Vina 1.2**	0.540 ± 0.020	-9.25 ± 0.06	0.120 ± 0.003	83 ± 1

[a]The unit of ΔG_{Dock} and RMSD is kcal mol^{-1} and nm, respectively. The computed error of ΔG_{Dock} and RMSD is standard error of the mean. The $\hat{p}$ value was calculated within a cutoff 0.2 nm.

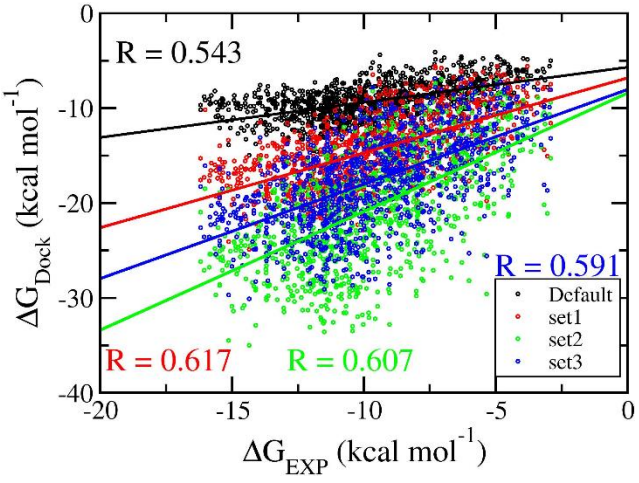

Figure 7. Correlation coefficients between original/modified Vina versus experiments. The results were obtained over 1036 complexes from PDB refine structures.

Conclusions

AutoDock Vina is not only fast but also gives a large docking-success rate. However, low correlation of docking energy with respect to experiment is a major weakness of Vina. Normally, docking simulations were mostly employed to relatively rank the ligand-binding affinity. The correlation coefficient is thus considered more important than the other metrics. In this work, we have evaluated the dependence of docking performance on the changes in empirical parameters. Although changing of six parameters alters the obtained correlation coefficient R, the *gauss2* and *rotation* terms form more effects. Moreover, the docking-success rate $\hat{p}$ are sensitive to the alteration of the *gauss1*, *gauss2*, and *repulsion* parameters.

Three sets of empirical parameters were proposed including set1 (more priority for R), set2 (keep a balance between R and $\hat{p}$), and set3 (more priority for $\hat{p}$) based on the knowledge on the dependence of Vina on individual empirical parameters. The testing study of three modified Vina over 800 complexes was then carried out. The obtained correlation coefficients were significantly larger than that by the original and 1.2 versions. Therefore, the Vina with proposed sets of parameters can provide better ranking for ligand binding affinity. Moreover, all of the modified versions formed appropriate correlation coefficients ($R > 0.500$) for ≥ 32 targets, where the corresponding number provided by the original Vina is 31 only. Therefore, the Vina with proposed sets of parameters can apply wider compared with the default parameters.

Validating investigations over 1036 complexes from the version 2019 of PDBbind refined structures were also performed. The obtained correlation of three modified Vina was significantly larger than the original one suggesting that the docking approach with proposed parameters can rank ligand-binding affinity with more accuracy. Besides, we have suggested that set1 parameters are more appropriate than set2 and set3 parameters.

Acknowledgments

This research was funded by Foundation for Science and Technology Development of Ton Duc Thang University (FOSTECT), website:

http://fostect.tdtu.edu.vn, under Grant FOSTECT.2019B.08.

Keywords: AutoDock Vina, Empirical Parameter, Modified Vina, Binding Affinity, Screening

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