Distance Dependent Scoring Function for Describing Protein−Ligand Intermolecular Interactions

Natalia Artemenko*

Institute of Biotechnology, University of Helsinki, FI-00014, Helsinki, Finland

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A new empirical scoring function has been developed to estimate the binding affinity of a protein−ligand complex with known three-dimensional structure. The scoring function includes a small number of physicochemical descriptors and a large number of quasi-fragmental descriptors. The first group of descriptors is chosen from the following set: (1) the number of close nonbonded contacts, (2) a score for 'metal-atom' interactions, (3) the number of flexible bonds, (4) van der Waals interaction energy, and (5) electrostatic interaction energy. A training set of 288 'protein−ligand' complexes was used to develop the scoring function. The key benefit of this approach is that it reduces the computational complexity while maintaining similar predictive ability to existing methods (average for independent test sets is 2−2.2 kcal/mol). The quasi-fragmental descriptors provide a unique and novel way of accurately representing physical interactions, compared to using physicochemical ones alone.

INTRODUCTION

The rapid growth of the availability of structural information for protein−ligand complexes has fueled the continued development and enhancement of statistical scoring functions for estimating the binding free energy of putative protein−ligand complexes. The majority of the scoring functions can be divided into energy-based and rule-based[1] methods. The first group allows the contributions of different forms of interaction (e.g., hydrophobic, steric, Coulombic) between the target (enzyme/receptor/protein) and a ligand[2−8] to be estimated.

Different SAR based (Structure−Activity Relationships) approaches can be applied to generate statistics for the number of different contacts and their importance.[9,10] Currently, there are three types of scoring functions in common use: empirical,[2,11] knowledge/regression-based,[12−16] and force-field based.[17] Very often, in empirical approaches, interaction terms, derived from a weighted combination of structural parameters, help to estimate the binding affinity of the protein−ligand complexes. These additive terms represent a combination of enthalpic and entropic thermodynamic effects in the binding process. To reproduce experimentally determined affinities of a given training set, many researchers have derived the weights using multivariate regression methods. For instance, to estimate the free energy of binding complexes Böhm[2,5] used the following: (1) the free energy from the number of hydrogen bonds, (2) the rotatable bonds in the ligand, (3) ion-pair interactions, (4) hydrophobic and π-stacking interactions of aromatic groups, and (5) lipophilic interactions. Murray et al. proposed a simple empirical scoring function to estimate lipophilic and metal−ligand binding contributions as well as penalizing flexibility and hydrogen bonds.[3] This function gave a cross-validated error of around 2 kcal/mol for their training sets. Wang et al. proposed a similar scoring function with 11 parameters.[4] In this method, the root-mean-square (rms) error for a training set containing 170 protein−ligand complexes was 1.5 kcal/mol. Oprea et al. combined Coulomb and van der Waals interactions together with heuristics descriptors—the number of pairwise contacts between the atoms of the protein and the ligand.[6]

Intrinsically, empirical scoring functions have important advantages, in that they are simple to compute and so models can be built in real time. Conversely, this kind of function has inherent restrictions as their performance is totally dependent on the quality and quantity of the training sets on which they are based.

This article proposes a new empirical scoring function based on a combination of quasi-fragmental descriptors and physicochemical terms.[2−6] [A quasi-fragmental descriptor is an analog of a typical fragmental description, which characterizes the interatomic distance for a number of atomic pairs where the first atom belongs to a ligand and the second one belongs to a protein.] The quasi-fragmental descriptors describe the pairwise statistics of interatomic distances, while the physicochemical ones have been taken from previous work.[2−6]

METHODS

Descriptor Types. In this work, all protein−ligand complexes were classified in terms of interatomic distances that were represented as the number of pairs of atoms that were within 6 Å of each other, where the first one belongs to a ligand and the second one belongs to a protein. The atoms and their bonds were classified according to the *AMBER* force field. Using our source database, the numbers of times that each pair (descriptor) occurs in each protein−ligand complex were counted and entered into a matrix. Each row of the matrix corresponds to a certain protein−ligand complex, while each column corresponds to a quasi-

* Corresponding author e-mail: artemenn@tcd.ie.

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fragmental descriptor. Therefore, the content of each cell (*i*, *j*) equals the number of atomic pairs corresponding to the descriptor *j* characterizing the complex *i*.

For convenience, each quasi-fragmental descriptor has been named by the following form: <a type of atom in a ligand>_<a type of atom in a protein>_<the lower boundary value of distance interval>_<the upper boundary value of distance interval>. For instance, descriptor CT_OS_5.0_5.5 corresponds to two atoms, where the first one belongs to a ligand and has *AMBER* type *CT*, the second one belongs to the protein and has *AMBER* type *OS*, while the distance in the range from 5.0 to 5.5 Å reflects the boundary points of the interval.

Correlated components were removed from the initial descriptor set by requiring that each descriptor occurs more than three times per set. Each protein−ligand complex was characterized by binding (dissociation) constant K_d as its attribute.

A number of physicochemical descriptors were added to the descriptor matrix as columns. These additional descriptors were as follows: (1) the number of close nonbonding contacts (K_{vdW}), (2) a score for 'metal−atom' interactions (MLB), (3) the number of flexible bonds (N_{fb}), van der Waals interaction energy (estimated by the Lennard-Jones potential) (E_{vdW}), and (4) electrostatic interaction energy in a vacuum ($Elstat_1$) and at a specified distance ($Elstat_2$).

The following expression was used to count the number of close nonbonding contacts[4]

$$K_{vdW} = \sum_i \sum_j VB(d_{ij}) \tag{1}$$

$$VB(d_{ij}) = \begin{cases} = 1, & d_{ij} < r_i + r_j - 0.60 \text{ Å} \\ = 0, & d_{ij} \geq r_i + r_j - 0.60 \text{ Å} \end{cases} \tag{2}$$

where r_i and r_j are the van der Waals radii of ligand and protein atoms, respectively, and d_{ij} is the distance between the *i*th atom in the ligand and the *j*th atom in the protein.

The metal−ligand interactions were computed in accordance with the formula[3]

$$K_{ML} = \sum_i \sum_j \text{MLB}(d_{ij}) \tag{3}$$

$$\text{MLB}(d_{ij}) = \begin{cases} = 1.0, & d < 2.2 \text{ Å} \\ = 1 - (d - 2.2)/0.4, & 2.2 \text{ Å} \leq d < 2.6 \text{ Å} \\ = 0, & d \geq 2.6 \text{ Å} \end{cases} \tag{4}$$

The number of flexible bonds is composed of the number of acyclic sp^3-sp^3 and sp^3-sp^2 single bonds excluding rotatatable terminal −OH, $-CH_3$, or $-NH_2$ groups. The flexibility of the cyclic part of ligands was ignored.

The formulas for computing the energy of van der Waals interactions are the following:[6]

$$E_{vdW} = \sum_{ij \in vdW} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right] \tag{5}$$

$$A_{ij} = \left(\frac{r_i}{2} + \frac{r_j}{2} \right)^{12} \cdot \sqrt{\epsilon_i \cdot \epsilon_j} \tag{6}$$

$$B_{ij} = 2 \cdot \left(\frac{r_i}{2} + \frac{r_j}{2} \right)^{6} \cdot \sqrt{\epsilon_i \cdot \epsilon_j} \tag{7}$$

The original formula[6] was used to calculate the electrostatic interaction energy

$$E_{EP} = \sum_{i<j} \frac{q_i \cdot q_j}{\epsilon \cdot R_{ij}} \tag{8}$$

where q_i and q_j are the local atomic charges of the ligand and protein, respectively. A semiempirical quantum-chemical method AM1 is deemed to be highly suitable for the computation of the local atomic charges of ligands (q_i), whereas standard RESP (Restrained ElectroStatic Potential) charges fitted to an ab initio 6-31G* wave function better suits for protein atoms. All charges were computed by using the *HyperChem*[18] program. The computation process uses a 'distance-dependent' ϵ[18].

It is believed that the scoring function, which describes the binding process in protein−ligand complexes, can be represented as a combination of several components, some of which can be of little or no importance. The group of components used were as follows: (1) the contribution of van der Waals interactions within the complexes; (2) the contribution of metal−ligand binding; (3) the deformation effects that were defined by the number of flexible bonds; (4) the contribution of electrostatic interactions; and (5) structural and steric information for the bonded complexes.

To generate the descriptor matrix the following special conditions have to be specified: (1) the distance range; (2) the interval step used for the generation of quasi-fragmental descriptors within a chosen range; and (3) whether to include or exclude overlapping descriptors. A distance range of 1 to 6 Å and interval steps of 0.5 Å, 1.0 Å, and 1.5 Å were chosen. Descriptor sets both including and excluding overlaps were considered.

Training Set. Training, validation, and test sets were chosen from the source database of 288 protein−ligand complexes with known dissociation (binding) constants (see the Supporting Information). The training, validation, and test sets were chosen to contain 80%, 10%, and 10% of complexes, respectively. To generate a variety of data sets this division was repeated 10 times so that each complex occurred at least once in the validation and test subsets.

The complexes were taken from the Brookhaven Protein Data Bank (PDB).[19] To ensure the accuracy, only structures with a resolution better than 3.2 Å were used. The binding constants for these complexes were taken from previous works[2−6,20−23] and, for convenience, were represented in the form of the negative logarithm of dissociation constants, i.e., pK_d. The pK_d values in this set range from 0.47 to 13.96. Since a large number of descriptors appeared to be strongly correlated with each other, only a subset of descriptors, with mutual correlation coefficients not exceeding 0.97, was used for the remaining statistical analysis.

During the preprocessing stage all organic ligands that had no covalent bonds with protein molecules of the complexes were extracted and classified using the *AMBER* force field classification. Attention was paid to only organic ligands, all counterions were excluded from consideration, whereas the metal atoms were considered to be fragments of protein

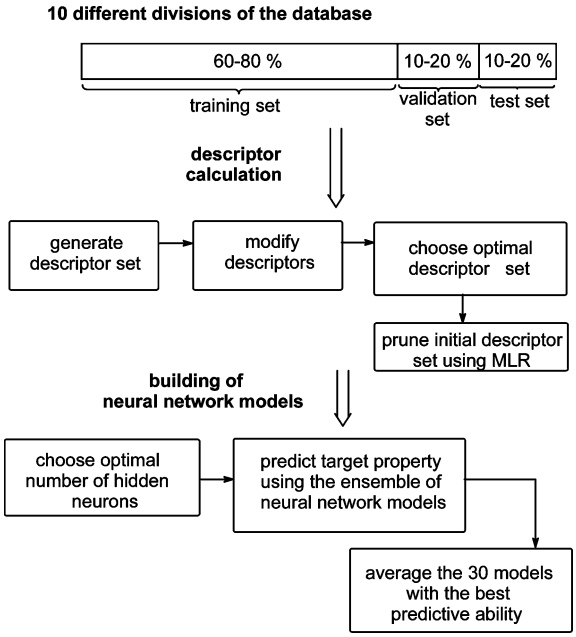

Figure 1. Algorithm of QSAR modeling.

molecules. The *AMBER* force field classification was also used for the construction of quasi-fragmental descriptors.

Statistical Analysis. Two statistical methods—stepwise multiple linear regression (MLR) and feed-forward neural networks with back-propagation error learning method (BPNN)—formed the basis of our modeling.

An application of the BPNN method for QSAR studies usually involves the determination of the optimal number of hidden neurons and building an ensemble of models, which should be combined to obtain a reliable prediction. The latter requirement stems from the fact that different neural network models give slightly different final solutions. Therefore, it is necessary to average the predictions in order to obtain reproducible results. In addition, development of any statistical model should involve supervision over its predictive ability, which is usually achieved by using a cross-validation procedure. In the case of neural networks such supervision is usually achieved by preventing "overtraining". This is usually implemented by (1) dividing a whole set of compounds into a training set (which is directly used for training neural network) and a "validation" set (which is used to monitor a predictive performance of neural network model in the course of its training) and (2) choosing a neural network model that corresponds to the lowest prediction error estimated for the validation set. However, since information from the validation set is used to choose a model (and, hence, is implicitly present in the model), the true predictive performance of the model cannot be estimated by the error on the validation set. Therefore, to assess the predictive ability of the model it is necessary to use an additional "test" set of compounds. It should be noted that this methodology, of using three different sets of compounds for building neural network models, is especially important for the case of QSAR/QSPR descriptors (e.g., fragmental or quasi-fragmental descriptors), since their large number may easily lead to "overtraining".

Model Building. The following scheme was used to build the models (as done in previous articles[24−26] and illustrated in Figure 1). A data set containing information on 288 protein−ligand complexes with known dissociation constants was split into three subsets: a training set (80% of the complexes), a validation set (10% of the complexes), and a test set (10% of the complexes). This division was performed 10 times in such a way that each complex occurred at least once in the validation and test subsets. In this study several initial descriptor sets were used. These sets were generated using a variety of interval steps and inclusion or exclusion of overlapping ranges, as described above. For each subdivision, the initial descriptor subset, used for training, was pruned using a MLR procedure. For each iteration of the MLR process, a new descriptor is chosen so as to maximize the reduction of the root-mean-square (rms) error computed when the model is applied to the validation set. The MLR process was carried out for each of the 10 divisions, resulting in a different number of descriptors each time. The results were averaged together to generate a representative value for the predictive ability of the models. Finally, the 10 pruned descriptor sets were used to do further neural network analysis employing *BPNN*.

Table 1. Statistical Parameters for Regression Models

divisions	no. of selected descriptors	R	rms_{train}	rms_{valid}	rms_{pred}
first	9	0.752	1.60	1.61	1.47
second	4	0.686	1.78	1.31	1.64
third	8	0.766	1.51	2.01	2.03
fourth	21	0.851	1.26	1.95	1.77
fifth	5	0.720	1.71	1.71	1.56
sixth	8	0.745	1.55	1.60	2.08
seventh	38	0.916	0.96	1.49	1.93
eighth	2	0.571	1.98	1.78	1.74
ninth	12	0.782	1.49	1.48	1.61
10th	16	0.836	1.33	1.70	2.05
average	***12.3 ± 7.6***	***0.762***	***1.52***	***1.67***	***1.79***

Next, for each of the 10 divisions, 8 groups of neural network models were generated, using 4 to 11 hidden neurons. To eliminate biases, each group of networks contains 10 models generated from the same data, for which the statistical parameters were averaged. Therefore, 100 neural network models were built for each number of hidden neurons, and the overall number of neural network models was 800 for each initial descriptor set. The network was trained to achieve the minimum rms error on the validation set. These rms error values were used to determine the optimal number of hidden neurons. Finally, the statistical parameters were averaged for the 30 best models (with the lowest rms errors on the validation sets) with the chosen number of hidden neurons.

Results. Final results of our linear regression models are shown in Table 1. The average correlation coefficient equalled 0.7625, the average rms error on the training sets was 1.52 units of pK, while the average rms error on the prediction sets was 1.79 units of pK.

The resulting 10 descriptor sets, selected by MLR, were used for further neural network analysis. During the analysis 10 neural network models were built for each division and for each number of hidden neurons in the range of 4 to 11. During the MLR training process the selection of additional descriptors was terminated when no additional descriptor could further reduce the rms error.

Analyzing the errors present when applying the groups of neural network models to the validation sets indicates that 9 hidden neurons is optimal (Figure 2). In addition, for each

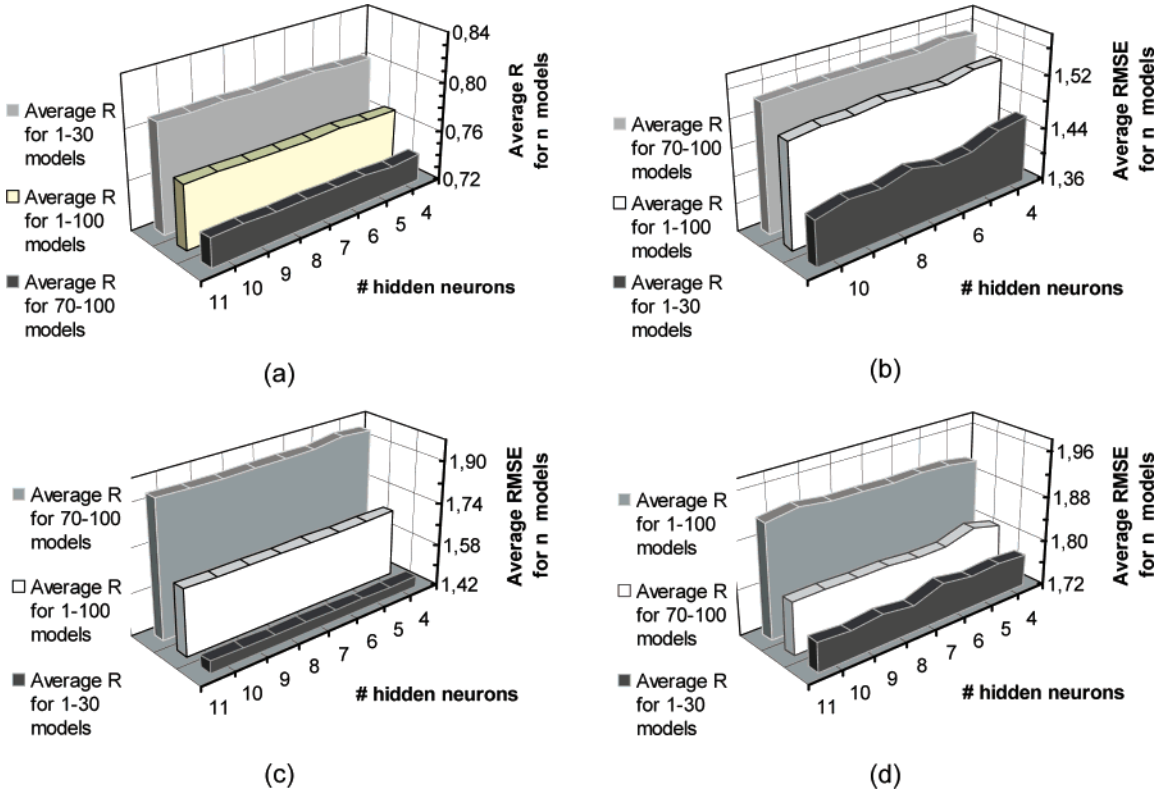

Figure 2. The variations of the average statistical parameters depending on the number of hidden neurons for (a) the average correlation coefficient for the training sets; (b) the average rms error for the training sets; (c) the average rms error for the validation sets; and (d) the average rms error for the external test sets.

model, four statistical attributes were noted: the correlation coefficient averaged over the training sets and the average rms errors for three kinds of sets (training, validation, and prediction). In our case, the average rms error on training sets was 1.52 units of p*K*, on the validation sets it was 1.67 units of p*K*, and on the test sets it was 1.92 units of p*K*. Data from the test sets took part in neither the model building nor the model evaluation. Therefore, the rms errors, for test sets, could be used to correctly determine the predictive efficiency of the models. Further analyses computed the errors for all three sets evaluated in such a manner. Averaging results for each individual compound or complex across the ensemble of neural network models decreased the prediction error. To prove these hypotheses, the average rms error, across the 100 neural network models (containing 9 hidden neurons), was computed for each complex in the database. As a result, the rms error became 1.33 units of p*K* on the training sets, 1.67 units of p*K* on the validation sets, and 1.93 units of p*K* on the test sets. It is obvious that only a slight improvement was achieved in the predictive ability of the averaged model. The 30 best neural network models, corresponding to the lowest validation error, were analyzed. After evaluating these models across all 3 sets the rms error became 1.29 units of p*K* on training sets, 1.46 units of p*K* on validation sets, and 1.77 units of p*K* on test sets. The parameters for both resulting models are compared in Table 2, which also contains statistical parameters averaged over 30 and 100 models.

As indicated in Table 2, the best neural network model composition (the last row in Table 2 and Figure 2) provided a correlation coefficient of 0.8474, an rms error of 1.28 units p*K* on the training sets, 1.45 units p*K* on the validation sets, and 1.77 units p*K* on test sets. These neural network results

Table 2. Average Statistical Parameters for Different Sets of Regression and Neural Network Models

model type	R_{av}	rms_{train}	rms_{valid}	rms_{pred}
MLR	0.7625	1.52	1.67	1.79
averaged parameters over 100 neural network models	0.7713	1.52	1.67	1.92
averaged parameters based on individual contributions over 100 neural network models	0.8531	1.33	1.67	1.93
averaged parameters over 30 neural network models	0.8071	1.43	1.46	1.77
averaged parameters based on individual contributions over 30 NN models	0.8474	1.28	1.45	1.77

are better than those seen with linear regression modeling (the first row in Table 2). The fact that nonlinear models perform better demonstrates the existence of nonlinearities in structure-binding affinity relationships for a diverse set of "protein−ligand" complexes.

DISCUSSION

This research has shown that the fragmental approach is a universal methodology for predicting different parameters of chemical compounds. In turn, QSAR techniques are used to find connections between the physicochemical descriptors of a ligand and its activity. The main advantage of using structural fragments is that they are easy for chemists to use and interpret. The presented scoring function provides a predictive ability in the range 1.5−1.9 pK_d or 2−2.5 kcal/mol and an rms error of 1.0−1.5 pK_d or 1.4−2 kcal/mol (Figure 3) on training sets. This is comparable to others.[4,17,20,22,27] Meanwhile, the predictive ability of the models generated by MacKerell[17] et al. and Tao[20] et al. is slightly

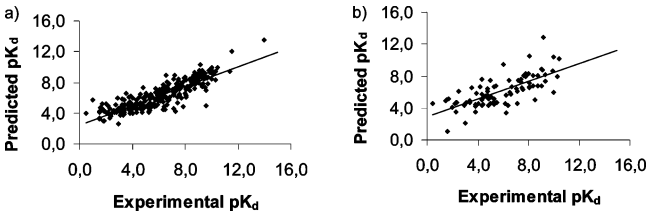

Figure 3. Experimental vs average predicted values of dissociation constants for protein−ligand complexes for the (a) training set and the (b) external prediction set.

better (7.3 kJ/mol = 1.74 kcal/mol); however, they utilize a smaller training set (containing 82 protein−ligand complexes compared to the 288 used in this study) which would be less diverse and so easier to model. Wang[4,27] et al. also used a smaller training set (170 complexes), and, in addition, the van der Waals radii for a number of atoms were specially optimized to increase the predictive ability. As a result, they reported a predictive ability about 1.16 pK_d (6.6 kcal/mol), but again the training set was less diverse and the method used is more computationally expensive. Recently, the *k*-nearest neighbor algorithm has been used with a quantitative structure-binding affinity relationship methodology[28] on a diverse set of complexes (264) which is similar to the presented one (288). This model was based on simplified descriptors, derived from Pauling's atomic electronegativities. The derived statistical parameters of the model, trained using 118 complexes, were comparable to this method.

The presented model achieves error levels lower than that achieved using the recent 'conformer focusing' theory, as presented by Tirado-Rives and Jorgensen.[16] These methods try to model the properties of the physical structure, whereas the presented method simply learns the relationship between a complex structure and the desired property. This ability allows the model to implicitly exploit as of yet unknown or unexplored controlling factors and, therefore, allows the system to produce a potentially better model.

The current study demonstrates that using quasi-fragmental descriptors, for model creating, led to the exclusion of physicochemical descriptors (e.g., the number of close nonbonding contacts and flexible bonds, a score for 'metal-atom' interactions, van der Waals interaction energy, and electrostatic interaction energy) from the selected descriptor sets.

The selection of a set of linearly independent and statistically significant descriptors by stepwise MLR consists of the several rules. The first descriptor, that is selected, must correlate with the predicted property in the best way and provide the minimum rms error on the validation set (for a single descriptor). The quality of this correlation derives from the functional dependence of the predicted property on the selected descriptor. At the next step, another descriptor, correlated with the difference between predicted and expected (experimental) values in the best way, should be selected. These steps should be repeated until the rms error cannot be reduced further. As a result, the final descriptor set corresponds to a statistical model providing the minimal rms error on the validation set.

Table 3 shows the most important descriptors, which are present in at least half of the models built from the initial descriptor set. The most utilized descriptors for the modeling are CT_CT_5.0_5.5 and CA_CA_5.5_6.0. Other descriptors

Table 3. Most Frequently Selected Descriptors for Generating Models

descriptors	the no. of models
CT_CT_5.0_5.5	30
CA_CA_5.5_6.0	20
N_N2_5.5_6.0	20
CA_N2_5.0_5.5	20
OS_N3_5.0_5.5	20
N*_CA_5.5_6.0	20
N_{fb}	10

in the table include the most typical atoms for amino acid residues and organic compounds. The last descriptor in this list (N_{fb}) is the number of flexible bonds. The list of the most important descriptors can be expanded by including several interesting descriptors reflecting the contributions of the nitrogen−oxygen noncovalent bond around 3 Å (e.g., N_O_2.5_3.0, O2_N_2.8_3.3, and OS_N_2.8_3.3 describing hydrogen bonds). Another interesting descriptor, less important than those in Table 3, is P_CC_4.5_5.0, which demonstrates the importance of carbon−phosphorus binding at the given distance.

CONCLUSION

This research has compared models, constructed using quasi-fragmental descriptors, to known protein−ligand complexes. It has indicated that the absence of physicochemical descriptors, from the set of selected descriptors (due to their low statistical significance), indicates at least *an implicit equivalence between quasi-fragmental descriptors and physicochemical ones*. Quasi-fragmental descriptors may replace many typical physicochemical terms in a 'protein−ligand' system. This substitution simplifies descriptor generation both in terms of time and processing complexity.

Moreover, the choice of descriptors is crucial to the quality of the model. It is important to know that the quasi-fragmental approach has proven to be more effective, in describing the physical interactions within protein−ligand system, than using physicochemical descriptors alone. This fact is shown by the statistical analysis of different descriptor sets in this paper. The rms error, on test and validation sets, is decreased by replacing physicochemical descriptors with quasi-fragmental ones.

To date, physicochemical descriptors such as the number and energy of hydrogen bonds and lipophilic and rotational energy have not been explored. Using these kinds of descriptors may further improve the predictive ability of our scoring function.

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Supporting Information Available: List of proteins included the training, validation, and test sets containing a brief 'protein−ligand complex' annotation, the pK_d value, and the resolution factor for each complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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