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Adaptive variable-weighted support vector machine as optimized by particle swarm optimization algorithm with application of QSAR studies

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ABSTRACT

Representing a compound by a numerous structural descriptors becomes common in quantitative structure–activity relationship (QSAR) studies. As every descriptor carries molecular structure information more or less, it seems more advisable to investigate all the possible descriptor vectors rather than traditional variable selection when building a QSAR model. Based on particle swarm optimization (PSO) algorithm, a more flexible descriptor selection and model construction method variable-weighted support vector machine (VW-SVM) is proposed. The new strategy adopted in this paper is to weight all structural descriptors with continuous non-negative values rather than removing or reserving any ones arbitrarily. The manner of invoking PSO to seek non-negative weights of variables can be regarded as a process of searching optimized rescaling for every molecular structural descriptor. Moreover, PSO is employed to search the optimal parameters of VW-SVM model besides variable weights, enables the construction of a rational and adaptive parameter-free QSAR model according to the performance of the total model. Results obtained by investigating glycogen synthase kinase-3α inhibitors and carbonic anhydrase II inhibitors indicate VW-SVM can hold more useful structure information of compounds than other methods as optimally weighting all the descriptors, consequently leading to precisely QSAR models coupled with developed performance both in training and in prediction.

1. Introduction

As one of the most important fields in chemometrics and many other subjects such as pharmacy, quantitative structure–activity relationship (QSAR) has been receiving a series of investigations [1–4]. The main aim of QSAR studies is to establish an empirical rule or function relating structural descriptors of compounds under investigation to bioactivities or other quantitatively expressed properties. One task of QSAR study is to obtain molecular structural descriptors that can well represent a set of compounds. Nowadays, with the development of computer and information science it is easy to get hundreds of descriptors which may consist of structural, spatial, thermodynamic, electronic, topological descriptors, E-state indices, etc. Representing a compound by a numerous structural descriptors is becoming common in QSAR studies [5–8]. When building a QSAR model, abandoning some "bad" descriptor variables can improve the performance of the model, for example, helpful for reducing model complexity and enhancing model predictive ability. Whereas, it also means some risks might be carried into the model. As every descriptor carries molecular structure information more or less, it is not so advisable to discard any descriptor from a model.

The common opinions of frequently used methods for descriptor variable selection are to delete redundant variables and exclude them from a regression model [1,8]. From the view of variable weighting, it is just a strategy to weight the selected variables with values 1 and the deleted ones with 0. If continuous nonnegative values for variables are allowed, such an approach is just a special case of variable weighting. The motivation of this paper is to investigate the feasibility of weighting all the obtained descriptors with continuous non-negative values rather than simply with 0/1 weights. It is expected that the support vector machine model with weighted variables would take advantage of all the descriptors and could be followed by improved prediction performance in QSAR studies. Support vector machine (SVM) is a relatively novel machine learning technique based on statistical learning theory (SLT) principle proposed by Vapnik and co-workers in 1995 [9,10]. It boasts its structural risk minimization (RSM) principle and has desirable generalization performance. SVM has demonstrated

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good performance in model estimation problems by numerous successful applications [11–15]. It has also shown a great promise in quantitative structure–activity relation (QSAR) studies due to its ability to interpret the relationships between molecular structure and bioactivities [1,4,16–18]. Optimized variable weights can be achieved by invoking a population global stochastic optimization technique, particle swarm optimization (PSO) algorithm [19–22]. Previous studies have shown that PSO works well in different optimization problems and has relatively high efficiency in convergence to desirable optima [4,18,23,24]. Besides seeking the optimal variable weights for a variable-weight SVM (VW-SVM) model in QSAR study, PSO also can be used to search the other parameters of the model, such as penalty constant, kernel width in kernel transform for VW-SVM. The direct benefit is that it makes VW-SVM to be an adaptive parameter-free method for QSAR study, without any parameters to be adjusted. The proposed VW-SVM algorithm has been applied to two QSAR data sets, 3-anilino-4-phenylmaleimides as glycogen synthase kinase-3α (GSK-3α) inhibitors [25] and *para*-substituted aromatic sulfonamides as carbonic anhydrase II (CA II) inhibitors [26].

2. Theory

2.1. Support vector machine (SVM)

The basic theory of SVM will be briefly reviewed in the following. Consider the problem of approximating the set of data with a linear function,

$$\mathbf{y} = \mathbf{w}^{\mathrm{T}}\mathbf{X} + b \tag{1}$$

where $\mathbf{w}$ is the weight vector to be identified in the function, and b is the threshold. The optimal regression function is given by the minimum of the cost function Φ,

$$\Phi = \frac{1}{2}\mathbf{w}^{\mathrm{T}}\mathbf{w} + C\frac{1}{I}\sum_{i=1}^{I} L_{\varepsilon}(y_i - y_{oi}) \tag{2}$$

where,

$$L_{\varepsilon}(y_i - y_{oi}) = \begin{cases} \left|y_i - y_{oi}\right| - \varepsilon & \left|y_i - y_{oi}\right| \geq \varepsilon \\ 0 & \text{otherwise} \end{cases} \tag{3}$$

is the ε-insensitive loss function measuring the error between the given observations ($\mathbf{y}_o$) and the estimated ones ($\mathbf{y}$) and ε is the tolerance zone, I is the number of the training compounds, $1/2\mathbf{w}^{\mathrm{T}}\mathbf{w}$ is used as a measure of the model complexity, defining the structure risk of a SVM model. A penalty constant C is introduced to determine the trade-off between the empirical error and the model complexity. Minimizing the cost function Φ under penalty constant C is to reduce the complexity as well as the empirical error of a model. Extension of this linear technique to nonlinear regression can be performed in a straightforward manner by substituting a so-called kernel function $K(\mathbf{x}_i, \mathbf{x})$ for the inner product $\langle \mathbf{x}_i, \mathbf{x} \rangle$. Many functions can be used as the kernel function. Gaussian radial basis function transform is frequently utilized if the knowledge of a problem dealt with is lacking, $K(\mathbf{x}_i, \mathbf{x}) = \exp(-||\mathbf{x}_i - \mathbf{x}||^2/(2\sigma^2))$.

2.2. Variable-weighted SVM (VW-SVM)

Compared with building an ordinary SVM QSAR model, variable-weight SVM attempts to extract variable information more flexibly with no descriptors removed or reserved arbitrarily. Suppose $\mathbf{X}$ is a $P \times I$ matrix with P descriptor variables for I compounds, and $\mathbf{y}$ is a vector including the corresponding dependent variable for the I samples. Not like in an ordinary SVM model, where variables in $\mathbf{X}$ are considered as making the same contribution to the QSAR model, in VW-SVM, $\mathbf{X}$ is left multiplied by a diagonal matrix diag($\mathbf{w}_{\mathrm{a}}$),

$$\mathbf{X}_{\mathbf{w}_{\mathrm{a}}} = \mathrm{diag}(\mathbf{w}_{\mathrm{a}})\mathbf{X} \tag{4}$$

where $\mathbf{w}_{\mathrm{a}}$ is a $P \times 1$ variable weighting vector with all the elements being non-negative values and diag($\mathbf{w}_{\mathrm{a}}$) is a $P \times P$ matrix whose diagonals are the elements of $\mathbf{w}_{\mathrm{a}}$. A SVM model is built between $\mathbf{X}_{\mathbf{w}_{\mathrm{a}}}$ and $\mathbf{y}$:

$$\mathbf{y} = \mathbf{w}^{\mathrm{T}}K(\mathbf{X}_{\mathbf{w}_{\mathrm{a}}}) + b \tag{5}$$

$K(\cdot)$ is the kernel function. In the present paper, a Gaussian radial basis function is used.

For prediction, the dependent variable $\mathbf{y}_{\mathrm{u}}$ of unknown compounds with measurement matrix $\mathbf{X}_{\mathrm{u}}$ is predicted as:

$$\mathbf{y}_{\mathrm{u}} = \mathbf{w}^{T}K(\mathrm{diag}(\mathbf{w}_{\mathrm{a}})\mathbf{X}_{u}) + b \tag{6}$$

It can be seen from Eq. (4) that if $\mathbf{w}_{\mathrm{a}}$ is a vector with all the elements being 1, the above model is the same as an ordinary SVM model built with the whole descriptor set. If $\mathbf{w}_{\mathrm{a}}$ just consists of 0 and 1, a SVM model with variable selection is obtained, where the descriptor variables in $\mathbf{X}$ corresponding to 1s in $\mathbf{w}_{\mathrm{a}}$ are reserved and those corresponding to 0s are removed. It can be concluded that a SVM model with whole descriptor set or variable selection are just special cases of variable weighting. Thus, variable weighting SVM is expected to be more flexible and rational. The question is how to determine the variable weighting vector $\mathbf{w}_{\mathrm{a}}$. Since the present method is oriented to improve the comprehensive performance of a regression QSAR model, variables are weighted to enhance the training of a calibration set and the prediction of an independent validation set as well, by minimizing the following objective function:

$$Re = \sqrt{\frac{\mathrm{RSSC} + \mathrm{RSSV}}{I + I_{\mathrm{v}}}} \tag{7}$$

where RSSC is the sum of squared residual of the original calibration set and RSSV is the sum of squared residual of the independent validation set. The former guaranteed the precision of the model and the latter ensured the generalization ability of the model. I and I_{v} are the size of calibration set and validation set, respectively.

According to Eq. (7), the global optimization algorithm, particle swarm optimization is used to optimize the variable weighting vector $\mathbf{w}_{\mathrm{a}}$. As the same as in an ordinary SVM, other parameters should be determined for a VW-SVM model. The parameters $\mathbf{w}$ and b can be easily obtained by solving a quadratic programming problem. The other ones, such as penalty constant C, tolerance zone ε and kernel width σ in a Gaussian function kernel transform are optimized by PSO as well as the variable weights $\mathbf{w}_{\mathrm{a}}$.

2.3. Particle swarm optimization (PSO)

PSO [19–22] is an evolutionary computation technique, derived from simulating the behavior of birds searching food. As a popular optimization tool, PSO has been widely used in the training of artificial neural networks, function optimization and other genetic algorithm areas. In PSO, the potential solutions called particles fly through the problem space by following the current optimum particles. Each particle keeps track of its coordinate in the problem space which is associated with the best solution (fitness) it has achieved so far. This value is called personal best position (pBest) for particle i represented as $\mathbf{p}_{\mathrm{i}} = (p_{i1}, p_{i2}, \ldots, p_{iD})$. Another best value that is tracked by the particle swarm optimizer is the best value obtained so far by all particles in the solution space, called global best position (gBest) which is represented as $\mathbf{p}_{\mathrm{g}} = (p_{g1}, p_{g2}, \ldots, p_{gD})$. Each particle updates its velocity $\mathbf{v}_i = (v_{i1}, v_{i2}, \ldots, v_{iD})$ and position $\mathbf{x}_i = (x_{i1}, x_{i2}, \ldots, x_{iD})$ by tracking these two best values according to

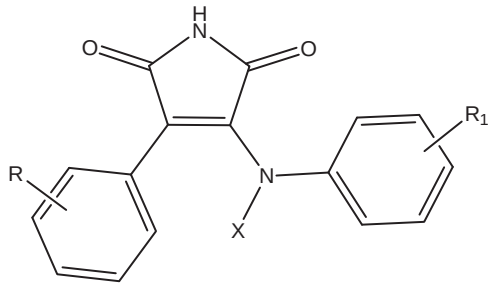

Fig. 1. Molecular basic structure of 3-anilino-4-phenylmaleimides as GSK-3α inhibitors.

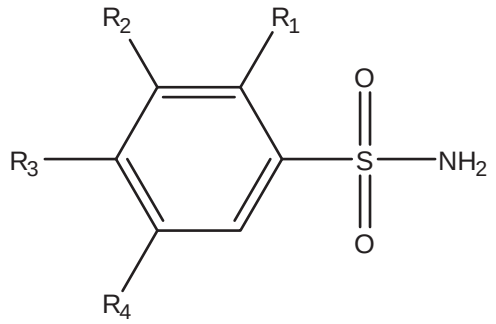

Fig. 2. Molecular basic structure of *para*-substituted aromatic sulfonamides as CA II inhibitors.

the following equations:

$$v_{id}(\text{new}) = w \times v_{id}(\text{old}) + c_1 \times r_1 \times (p_{id} - x_{id}) + c_2 \times r_2 \times (p_{gd} - x_{id}) \quad (8)$$

$$x_{id}(\text{new}) = x_{id}(\text{old}) + \mu \times v_{id}(\text{new}) \quad (9)$$

where w is an inertia weight which is brought into Eq. (8) to balance the global search and local search, r_1 and r_2 are random numbers between 0 and 1. Two positive constants, c_1 and c_2, called learning factors are introduced, and generally both take the integer value 2. In Eq. (9), μ is the time parameter determining the different flying times for each particle. The particle swarm optimization concept consists of, at each time step, changing the velocity of each particle toward its *p*Best and *g*Best locations. Acceleration is weighted by a random term, with separate random numbers being generated for acceleration toward *p*Best and *g*Best locations.

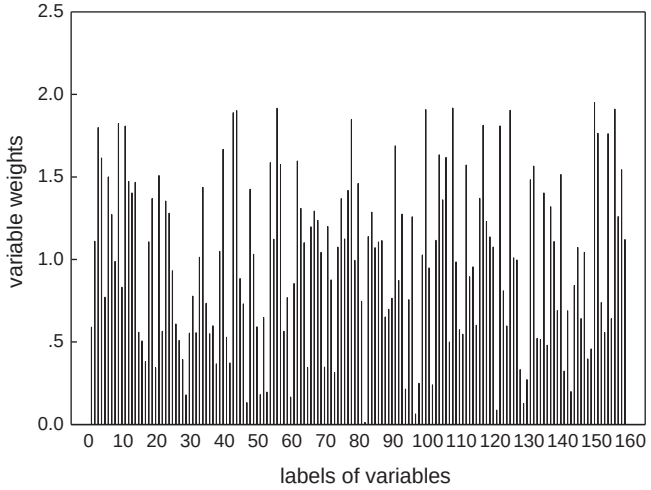

Fig. 4. The optimal weights of each descriptor variables in GSK-3α inhibitor data set.

In this paper, PSO is employed to search the optimal solution of VW-SVM by minimizing the objective function Re as the fitness function. Each particle is encoded as a real string representing the variable weights ($\mathbf{w}_a$), kernel width (σ), penalty constant (C) and tolerance zone (ε). With the movement of the particles in the problem space, the optimal solution with minimum value of the objective function Re will be obtained. Optimizing the parameters of SVM model relating the variable weights synergistically keeps the model from getting trapped into local optima and improves the model performance, also enables VW-SVM to be an adaptive parameter-free modeling technique for QSAR study.

3. Data sets

3.1. Glycogen synthase kinase-3α (GSK-3α) inhibitor data set

Glycogen synthase kinase-3α (GSK-3α) was recently found to be an attractive target for the treatment of Alzheimer's disease due to its dual action in the formation of both amyloid plaques and neurofibrillary tangles [27–30]. It is also a viable target for many other diseases, such as type 2 diabetes. In this paper, a set of 67

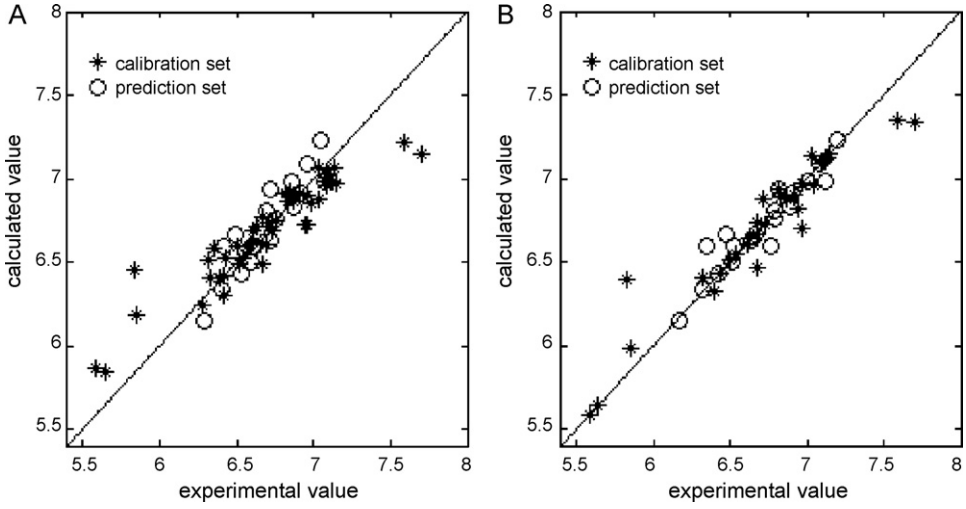

Fig. 3. (A) Calculated versus experimental values of the activities of GSK-3α inhibitors using ordinary SVM modeling. (B) Calculated versus experimental values of the activities of GSK-3α inhibitors using VW-SVM modeling.

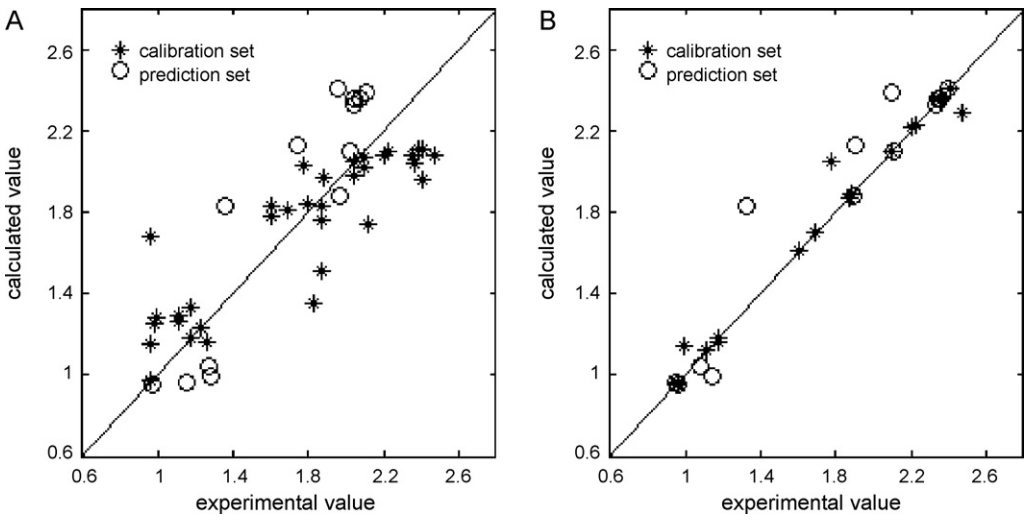

Fig. 5. (A) Calculated versus experimental values of the activities of CA II inhibitors using ordinary SVM modeling. (B) Calculated versus experimental values of the activities of CA II inhibitors using VW-SVM modeling.

3-anilino-4-phenylmaleimides as the GSK-3α inhibitors reported by Sivaprakasam et al. [25] is applied to test the feasibility of the proposed VW-SVM method. Molecular basic structure of 3-anilino-4-phenylmaleimides is presented in Fig. 1. The inhibitory activities of GSK-3α are expressed as IC_{50} values, which are the concentrations of compounds that would produce a 50% decrease in the cytopathic effect. The activity data taken from Ref. [25] are converted to the logarithmic scale [pC (mM)] and used as the response variable. Besides four indicator variables used by Sivaprakasam et al. [25], a series of molecular descriptors representing the chemical structure has been calculated using a Materials Studio 4.0 software system, including spatial, thermodynamic, topological descriptors, E-state indices, etc. Each compound is described by 159 structural descriptors.

3.2. Carbonic anhydrase II (CA II) inhibitor data set

Carbonic anhydrases (CAs) occupy a special place among the metallo-enzymes extensively studied in the last decade [31–36]. These enzymes are ubiquitous in all kingdoms such as *Archaea*, *Bacteria*, algae, green plants as well as superior animals including vertebrates. CAs were proved to be very important as they are involved in crucial physiological processes, connected with the catalysis of the reversible hydration of carbonic dioxide to bicarbonate and a proton, as these chemical species are important in many physiological processes, such as metabolizing tissues and excretion sites, secretion of electrolytes in a variety of tissues and organs, pH regulation and homeostasis, biosynthetic reactions (gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, tumorigenicity, and many other physiologic or pathologic processes [31–36]. Due to their important role, inhibition of these enzymes by carbonic anhydrase inhibitors (CAIs) may be exploited for the design of therapeutic agents useful in the management and prevention of many diseases [34–36]. In higher vertebrates, including humans, 15 different isozymes were described among which the cytosolic CA II is physiologically one of the most important isoforms [31,32].

Herein, a set of 47 *para*-substituted aromatic sulfonamides and their biological activities as CA II inhibitors [26] are also studied using the proposed method. Molecular basic structure of *para*-substituted aromatic sulfonamides as CA II inhibitors and the substituent sites are presented in Fig. 2. All the 47 compounds in the data set are characterized by 158 descriptors produced by Materials Studio 4.0.

All the algorithms used in this paper are written in Matlab 5.3 and run on a personal computer (Intel Pentium processor 4/2.80 GHz 1 GB RAM).

4. Results and discussion

4.1. Glycogen synthase kinase-3α (GSK-3α) inhibitor data set

For comparisons, besides the proposed VW-SVM, stepwise regression followed by multiple linear regression (MLR) or ordinary SVM also employed to model the activities of 3-anilino-4-phenylmaleimides as the GSK-3α inhibitors. The total 67 samples are split into a calibration set with 32 samples, a validation set with 16 samples and a prediction set with 19 samples by DUPLEX method [37] for VW-SVM. For stepwise regression with MLR or an ordinary SVM, the calibration set and the validation set are combined together as a new calibration set and used for training the models. The final results of the three methods are listed in Table 1. The correlation coefficient for the calibration set trained by MLR is 0.9724 but 0.8076 for the prediction set, and the root mean square error (RMSE) is 0.0982 for the calibration set but 0.2564 for the prediction set. Obviously, MLR gives a depressed performance in prediction. To achieve the optimal model parameters for ordinary SVM, Monte Carlo cross-validation (MCCV) is invoked to determine the kernel width σ and penalty constant C. The model of SVM gives a correlation coefficient of 0.9328 and a RMSE of 0.1790 for the calibration set and a correlation coefficient of 0.8974 and a RMSE of 0.1223 for the prediction set. The correlation between the calculated and the observed values of GSK-3α inhibitor activities is shown in Fig. 3A. Although ordinary SVM exhibits an advanced performance compared with MLR, a correlation coefficient of 0.8974 and a RMSE of 0.1223 for the prediction set reveal the prediction of the model could be not very satisfactory as well.

To be an adaptive modeling method, whole of the parameters of VW-SVM including the variables weights, kernel width σ, penalty constant C and tolerance zone ε are optimized by PSO algorithm via minimizing the objective function defined in Eq. (7). The optimal weights of each descriptor variables can been found in Fig. 4. It can be seen that different descriptor variables are differently weighted as expected. With the optimal variable weights, a correlation coefficient for calibration set of 0.9537 is obtained by VW-SVM and that for the prediction set is 0.9403, and the RSS is 0.1507 and 0.0976 for calibration and prediction sets, respectively. The correlation between the calculated and the experimental values of activities

Table 1
Results of QSAR analysis of GSK-3α inhibitor data using VW-SVM compared with those obtained by MLR and ordinary SVM.

Data set	*R* (correlation coefficient)			RMSE (root mean squared error)		
	MLR	SVM	VW-SVM	MLR	SVM	VW-SVM
Calibration set	0.9724	0.9328	0.9537	0.0982	0.1790	0.1507
Prediction set	0.8076	0.8974	0.9403	0.2564	0.1223	0.0976

Table 2
Results of QSAR analysis of CA II inhibitor data using VW-SVM compared with those obtained by MLR and ordinary SVM.

Data set	*R* (correlation coefficient)			RMSE (root mean squared error)		
	MLR	SVM	VW-SVM	MLR	SVM	VW-SVM
Calibration set	0.9031	0.8781	0.9888	0.2172	0.2579	0.0773
Prediction set	0.7850	0.8706	0.9595	0.3100	0.2914	0.1777

is shown in Fig. 3B. Compared with MLR and ordinary SVM, VW-SVM provides even better performance for both the calibration set and the prediction set, exhibiting that the proposed algorithm has better precision in modeling and superior generalization in prediction. Since the weight values of most of the descriptors are more than 0 as shown in Fig. 4, it can been concluded that most of the descriptors of 3-anilino-4-phenylmaleimides contribute a quantity of structure information to the QSAR model. Much more descriptors are included into the calibration model and thus useful information carried by them would be retained for training and prediction. A flexible variable selection is realized, which improves the performance of a model straightforwardly.

4.2. Carbonic anhydrase II (CA II) inhibitor data set

The same model building methods are used for the CA II inhibitor data, stepwise regression followed by MLR or ordinary SVM, and VW-SVM optimized using PSO. Before VW-SVM modeling, DUPLEX method is employed to divide the data set into three subsets, 22 samples for a calibration set, 12 samples for a validation set and 13 samples for a prediction set. And for training a MLR model or an ordinary SVM model, the calibration set and the validation set are combined as a new calibration set. Table 2 summarizes the statistical results. MLR gives a correlation coefficient of 0.9031 and a RMSE of 0.2172 for the calibration set and a correlation coefficient of 0.7850 and a RMSE of 0.3100 for the prediction set. The results, especially the prediction results reveal the relationship between the molecular structures of *para*-substituted aromatic sulfonamides and their biological activities is failed to be represented. A correlation between the results calculated by ordinary SVM and the observed values of bioactivities is shown in Fig. 5A. Ordinary SVM brings an enhanced prediction performance than MLR. A correlation coefficient of 0.8706 and a RMSE of 0.2914 for the calibration set are obtained. However, the modeling and prediction precision is still too low.

To improve the QSAR model, VW-SVM algorithm is applied to predict the inhibitory activity of *para*-substituted aromatic sulfonamides. The weights of all the descriptors in VW-SVM are revealed in Fig. 6. As well, different descriptors are differently weighted with continuous non-negative values. Individual descriptors obtain the weights close to 0, indicating the descriptors that have no or very slight contribution to training the QSAR model are well selected. With the optimal weights for the descriptors, the correlation coefficient of VW-SVM is 0.9888 for the calibration set and 0.9595 for the prediction set. The correlation between the calculated and the experimental values of biological activities is exhibited in Fig. 5B. Compared with ordinary SVM as shown in Fig. 5A, VW-SVM improves the performance of the QSAR model further. The latter provides higher correlation coefficients and lower root mean squared errors. A RMSE obtained by VW-SVM is 0.0773 for the calibration set and 0.1777 for the prediction set, both much smaller than those of ordinary SVM. Once more, the results of different methods demonstrate the weighting whole descriptor variables using PSO is beneficial for improving the training and prediction performance of a QSAR model.

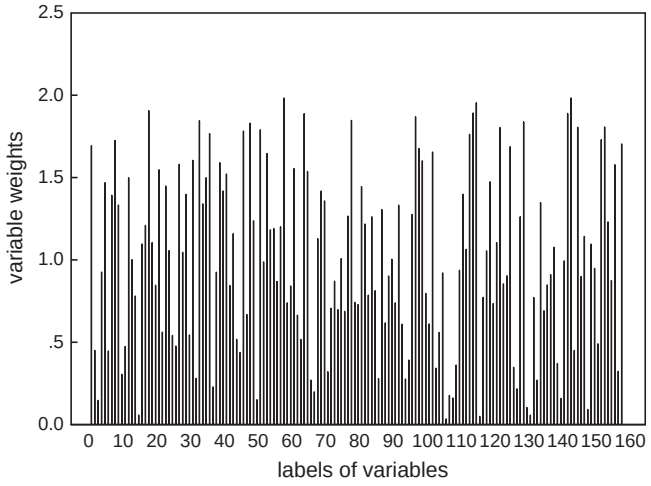

Fig. 6. The optimal weights of each descriptor variables in CA II inhibitor data set.

5. Conclusion

In this paper, the idea of variable weighting is incorporated into SVM for QSAR study, and PSO optimized variable-weighted SVM is proposed. Weighting descriptor variables is to avoid dropping any useful information that might be caused by removing or reserving any descriptor arbitrarily, carrying out a more flexible and rational variable selection than simple ones. The use of PSO makes VW-SVM possible for adaptive synergetic optimization of all parameters including variable weights according to the performance of the total model. The performance of VW-SVM is evaluated using two QSAR data sets which reveals the proposed method is a useful modeling technique for QSAR study, with improved performance both in model training and in prediction as compared to the traditional variable selection methods coupled with MLR or ordinary SVM.

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