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Correlation Studies of *HEPT* Derivatives Using Swarm Intelligence and Support Vector Machines

Luckhana Lawtrakul* and **Chakguy Prakasvudhisarn***

Department of Common and Graduate Studies and School of Manufacturing Systems and Mechanical Engineering, Sirindhorn International Institute of Technology (SIIT), Thammasat University, P.O. Box 22 Thammasat Rangsit Post Office, Pathumthani 12121, Thailand

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Summary. Two novel algorithms based on particle swarm optimization (PSO) and support vector machine (SVM) have been employed to obtain predictive QSAR models of anti-HIV-1 activity of *HEPT* derivatives. The results obtained by using the adopted PSO and SVM for structure-activity correlation determination were in close agreement with previous multiple linear regression models, which are reasonably satisfying, based on both statistical significance and predictive ability.

Keywords. Particle swarm optimization; Support vector machine; HIV-1 reverse transcriptase; QSAR.

Introduction

HIV-1 reverse transcriptase (RT) is one of the enzymes responsible for the replication of HIV-1. Therefore, the inhibition of this key biochemical event in the viral life cycle provides the most attractive target for anti-AIDS drug development [1]. A large number of HIV-1 RT inhibitors, both nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), have been designed, some of which are extensively used in anti-AIDS chemotherapy. Although many drugs are currently available, the search for new HIV-1 RT inhibitors is still going on, because of the induced resistance most of these drugs cause [2, 3]. The quantitative structure-activity relationships (QSAR) represent one of the most effective computational approaches for investigation of inhibition mechanism. QSAR analysis can indicate which features of a given molecule correlate with its activity, thus making it possible to design new and more potent compounds with enhanced biological

* Corresponding authors. E-mails: luckhana@siit.tu.ac.th, chakguy@siit.tu.ac.th

activities. Some successful QSAR approaches in predicting affinity of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (*HEPT*) analogues have been reported by our group and others [4–10]. *HEPT* is one of the most and selective non-nucleoside drugs, discovered by *Miyasaka* and coworkers [11]. Due to its high specificity and less toxicity, this inhibitor is a promising candidate for the treatment of AIDS and has been extensively studied for many years [12–14].

In our previous studies, QSAR of the *HEPT* analogues indicated that the anti-HIV-1 activities could be significantly described by structural parameters derived from quantum chemistry calculations [4–6]. These descriptors explain the role of electronic and molecular properties on the HIV-1 inhibitory potency. In addition the 3D-QSAR results based on CoMFA technique revealed that also steric interactions have to be taken into account for the explanation of the experimental data. These models use multiple linear regression (MLR) analysis to derive the relationship between the features of the molecule and its activity. In other words, an approximating function that fits the shape or general trend of the data without necessarily passing through any particular point is obtained. Normally, some criterion must be devised to establish a basis for the fit. That is, the approximating function obtained minimizes the discrepancy between the data points and the predicted values. A widely used technique for accomplishing this task is the least-squares regression. One of its useful extensions is MLR, which is used to determine an approximating function of two or more independent variables. However, MLR possesses a statistical disadvantage of normal distribution assumption. This may limit its applications or make it more difficult to use.

In recent years, there has been a lot of interest in studying two novel approaches; particle swarm optimization (PSO) and support vector machines (SVM) in the applications of structural bioinformatics and chemical process problems. They may be applied, for example, in the task assignment (or mapping) problem, convergence analysis and parameter selection for dynamical analysis in chemical process, *etc.* [15–19]. Interestingly, PSO together with neural network techniques was also used in the construction of QSAR models with good predictive capabilities [20–22]. SVMs have been used in a range of pattern recognition and classification problems such as protein folding recognition [23], protein structural class prediction [24], protein function classification [25], QSAR, and other pharmaceutical and biomedical analyses [26, 27].

Particle swarm optimization is a relatively new method for optimization of continuous nonlinear function developed by *Kennedy* and *Eberhart* [15]. The function is used as a criterion for selecting the best values of the decision variables. The main advantages of the PSO are that the function does not have to be twice differentiable and it embeds a mechanism that is quite robust to local optima. Another strong point of the PSO is that it is based on a very simple concept of a simplified social system and can be realized in a small computer program.

Support vector machines (SVMs) have been developed in the framework of statistical learning theory [28]. They have demonstrated excellent performance in pattern recognition [29] and in regression applications [30–32]. This theory describes the structure of the loss functions in the learning process to obtain high level of generalization by minimizing the risk. In other words, the model obtained should also work well with unseen data. This is accomplished by controlling two

factors; empirical risk and confidence interval. In addition, they are not based on any assumptions, which likely suit very well with the real world applications.

The purpose of this work is to propose new techniques for the prediction of the anti-HIV-1 activity of *HEPT* analogues based on the particle swarm optimization and the support vector machine algorithms. The PSO would be modeled to find the relationship between structural parameters of *HEPT* and its anti-HIV-1 activity by using the same criterion as MLR. That is, the proper values of structural parameters would be searched while minimizing the sum of the squares of the residual errors. Furthermore, the SVM version for regression (SVR) would be modified from the conventional form to determine the best set of parameters by adopting the quadratic loss function.

Method of Calculation

Data Set

The antiviral activities of 40 *HEPT* compounds were expressed as the effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 (EC_{50}), which the values were taken from Ref. [13]. The inhibition potency has been defined as $\log(1/EC_{50})$ in the QSAR analysis and is used as the dependent variable in the QSAR study. 35 *HEPT* derivatives were selected for the development of the models and 5 compounds were taken as test set. The chemical structures of the data set studied are given in Table 1.

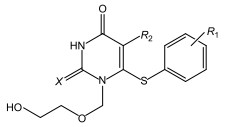
Descriptor Generation and Regression Model

To allow comparison with previous MLR approach, the input features were taken from the literature [4]. Some models were developed based on a stepwise multiple linear regression algorithm in SPSS package. The best MLR model, with both high statistical significance and high predictive ability, was presented in Table 2. It can be seen from this table that four descriptors have been found to be significant in this model. These descriptors consist of HE and MR, which are molecular descriptors; and C5 and C6, which can be considered as electronic descriptors and result from the introduction of substituent at the 5-position of the thymine ring and substitution of the 6-phenylthio moiety of *HEPT*, respectively.

Particle Swarm Optimization

The particle swarm concept is an efficient and effective multidimensional search method [33]. A population of random solutions (or particles) is first initialized. Each potential solution is also assigned a randomized velocity to probe the problem hyperspace while avoiding the local optima. Each particle can keep track of its coordinate, which is associated with the stored best value, called *pbest* (its own experience), it has achieved thus far. The overall best value, *gbest* (group's knowledge), and its location obtained so far by any particles are also recorded. At each time step, each particle moves toward its *pbest* and *gbest* locations *via* the changing velocity. The steps of the standard PSO are illustrated in Ref. [33].

Table 1. General structure of *HEPT* derivatives along with the observed and calculated values of anti-HIV-1 activity



No.	R_1	R_2	X	$\log(1/EC_{50})$	MLR	PSO	SVM
1	2-*Me*	*Me*	O	4.149	5.103	5.102	5.147
2	2-Cl	*Me*	O	3.886	5.081	5.080	5.063
3	2-NO_2	*Me*	O	3.854	3.833	3.832	3.793
4	2-O*Me*	*Me*	O	4.721	5.163	5.162	5.147
5	3-*Et*	*Me*	O	5.569	5.461	5.460	5.540
6	3-*t-Bu*	*Me*	O	4.921	6.691	6.690	6.825
7	3-CH_2OH	*Me*	O	3.535	3.998	3.998	3.986
8	3-CF_3	*Me*	O	4.347	5.642	5.641	5.623
9	3-F	*Me*	O	5.482	4.738	4.737	4.714
10	3-Cl	*Me*	O	4.886	4.955	4.954	4.966
11	3-NO_2	*Me*	O	4.469	3.621	3.621	3.648
12	3-O*Me*	*Me*	O	4.658	4.819	4.818	4.812
13	3,5-Me_2	*Me*	O	6.585	6.433	6.432	6.466
14	3,5-Cl_2	*Me*	O	5.886	5.435	5.434	5.476
15	3,5-Me_2	*Me*	S	6.658	6.416	6.415	6.528
16	3-COO*Me*	*Me*	O	5.102	4.745	4.744	4.747
17	3-CO*Me*	*Me*	O	5.137	5.029	5.028	5.038
18	4-CO*Me*	*Me*	O	3.959	4.765	4.764	4.797
19	3-COOH	*Me*	O	3.454	3.544	3.543	3.452
20	3-CN	*Me*	O	5.000	4.434	4.433	4.387
21	H	$CH_2CH{=}CH_2$	O	5.602	6.382	6.379	6.306
22	H	COO*Me*	O	5.181	5.417	5.416	5.364
23	H	CONH*Ph*	O	4.745	4.337	4.337	4.407
24	H	*Et*	S	6.959	6.177	6.176	6.192
25	H	*i-Pr*	S	7.229	7.396	7.394	7.362
26	3,5-Me_2	*i-Pr*	S	8.301	8.439	8.437	8.539
27	3,5-Cl_2	*Et*	S	7.367	7.358	7.357	7.445
28	H	*Et*	O	6.921	6.154	6.152	6.181
29	H	*Pr*	O	5.469	6.047	6.045	6.046
30	H	*i-Pr*	O	7.201	6.984	6.982	6.926
31	3,5-Me_2	*Et*	O	7.886	7.335	7.333	7.377
32	3,5-Me_2	*i-Pr*	O	8.569	7.695	7.693	7.674
33	3,5-Cl_2	*Et*	O	7.854	6.578	6.577	6.628
34	H	*Me*	O	5.155	4.506	4.505	4.494
35	H	*Me*	S	6.009	5.160	5.159	5.203
Prediction Set							
36	3,5-Me_2	*Et*	S	8.108	7.581	7.580	7.670
37	3-*Me*	*Me*	O	5.585	5.391	5.390	5.415
38	3-OH	*Me*	O	4.086	4.397	4.395	4.274
39	4-NO_2	*Me*	O	3.721	3.613	3.612	3.559
40	4-OH	*Me*	O	3.558	3.762	3.761	3.612

Table 2. Best MLR, PSO, and SVM models for prediction of anti-HIV-1 activity

Descriptor[a]	Notation	Coefficients		
		MLR	PSO	SVM
(1) hydration energy (kcal/mol)	HE	0.198	0.198	0.213
(2) molar refractivity	MR	0.093	0.093	0.100
(3) atomic net charge of carbon-5 of thymine ring	C5	45.797	45.737	40.143
(4) atomic net charge of carbon-6 of thymine ring	C6	38.482	38.443	34.573
constant		14.418	14.403	12.946
the correlation coefficient for the model	r	0.869	0.869	0.869
the standard deviation	s	0.743	0.743	0.745
the F value	F	23.169	23.169	23.027

[a] Parameter values of compounds and the regression coefficient of MLR were taken from Ref. [4]

Particles' velocities on each dimension are clamped to a maximum velocity, $V_{\max}$, to control the exploration ability of particles. The acceleration constants c_1 and c_2 represent the weighing of the stochastic terms that pull each particle toward *pbest* and *gbest* positions. They are normally set to 2.0 to give it a mean of 1 for the cognition and social parts, so that the particles would thoroughly search the settled regions [34]. As a result, the search space is statistically shrunk through iterations. This resembles a local search algorithm. In contrast, the first part helps expand the search space so that the particles can explore new areas. This implies a global search ability of the PSO. An inertia weight w is then introduced into Eq. (1) as shown below to balance between the global and local search abilities; where i is the ith particle, d is the dimension of hyperspace (or number of variables), c_1 and c_2 are positive constants, and rand( ) is a random value generated by a uniform random function on the interval (0.0, 1.0).

$$V[i][d] = w * V[i][d] + c_1 * rand(\ ) * (pbestx[i][d] - presentx[i][d]) + c_2 * rand(\ ) * (pbestx[gbest][d] - persentx[i][d]) \quad (1)$$

$$presentx[i][d] = presentx[i][d] + V[i][d] \quad (2)$$

These stochastic factors allow the particles to explore new space and avoid possible local optima. Logically, the PSO should possess more exploitation ability at the beginning to find a good region, then more exploration ability to refine search within it. Simply, w could be a positive linear or nonlinear function of time, which has a high value at the beginning and gradually lower later on. This is also a contribution to improve convergence rate.

To derive the relationship between features of the molecule and its activity while minimizing their discrepancy, the PSO was used to minimize the sum of squared errors between the experimental data and the predicted values. Hence, the function for the PSO is the minimization of $\sum_{i=1}^{n} {e_i}^2$ or $\sum_{i=1}^{n} (y_i - \hat{y}_i)^2$ where y_i represents the ith value of the experimental data and $\hat{y}_i$ represents the estimated ith value. Hence, $y_i = \log (1/EC_{50})_i$ and $\hat{y}_i = w_1\mathrm{HE}_i + w_2\mathrm{MR}_i + w_3\mathrm{C5}_i + w_4\mathrm{C6}_i + b$. The best values of w_1, w_2, w_3, w_4, and b are iteratively searched by a group of particles through the problem hyperspace.

Support Vector Machines

Support vector machines represent a relatively new type of learning machine. The main advantage is their good generalization properties [28]. The initial work is focused on optical character recognition [29]. They are recently extended to cover applications in regression and time series predictions [30–32].

In regression problems, the ε-insensitive loss function is commonly incorporated with SVMs (ε-SVR). It was proposed by *Vapnik* [28] to approximate targets y_i with a resulted function $f(\mathbf{x})$. The function is obtained by utilizing ε-insensitive loss function creating sparseness in the support vectors. This means that $f(\mathbf{x})$ is allowed to vary at most ε deviation from the target and is as flat as possible simultaneously. If the deviations are larger than *a priori* ε specified, this implies a bad fit and this function is proportionally penalized with *a priori* constant C. This constant C determines the trade off between the training errors and model complexity.

Consider the problem of approximating the following set of data $\{(\mathbf{x}_1, y_1), \ldots, (\mathbf{x}_l, y_l)\} \subset \Re^n \times \Re$ with linear function $f(\mathbf{x}) = \langle \mathbf{w}, \mathbf{x} \rangle + b$, where $\mathbf{w} \in \Re^n, b \in \Re$, and $\langle ., . \rangle$ represents dot product. Minimum flatness of $f(\mathbf{x})$ is accomplished by searching the smallest $\mathbf{w}$. A widely used formulation is minimization of $\|\mathbf{w}\|^2$. Hence, the formulation of ε-SVR can be described by Eq. (3) subject to $y_i - \langle \mathbf{w}, \mathbf{x}_i \rangle - b \leq \varepsilon + \xi_i, \langle \mathbf{w}, \mathbf{x}_i \rangle + b - y_i \leq \varepsilon + \xi_i^*, \xi_i, \xi_i^* \geq 0$.

$$\min \frac{1}{2}\|\mathbf{w}\|^2 + C\sum_{i=1}^{l}(\xi_i + \xi_i^*) \tag{3}$$

Everything above ε is captured in slack variables ξ_i and everything below $-\varepsilon$ is captured in slack variables ξ_i^*, which is penalized in the objective function with *a priori C*. The ε-insensitive loss function [28], $|\xi|_\varepsilon$, is defined by Eq. (4).

$$|\xi|_\varepsilon = \begin{cases} 0; & \text{if } |f(\mathbf{x}) - y| < \varepsilon \\ |f(\mathbf{x}) - y| - \varepsilon; & \text{otherwise} \end{cases} \tag{4}$$

This loss function is a slightly more general than the following loss-function $L(y, f(\mathbf{x})) = |y - f(\mathbf{x})|$ which is used in the least modulus method to minimize the empirical risk [23]. The ε-insensitive loss function is depicted in Fig. 1.

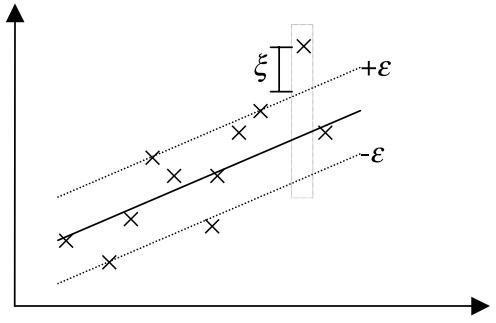


Fig. 1. The soft margin tube of Eq. (4); differences between the regression line and data points (crosses) contained inside two dashed lines are considered as zeroes

The above optimization problem (3) can be more easily solved in its dual form. Using the *Lagrang*ian multipliers and the *Karush-Kuhn-Tucker* (*KKT*) conditions to determine the *Wolfe* dual, the following dual problem can be obtained Eq. (5) subject to $\sum_{i=1}^{l}(\alpha_i - \alpha_i^*) = 0$ and $\alpha_i, \alpha_i^* \in [0, C], i = 1, \ldots, l$.

$$\max -\frac{1}{2}\sum_{i=1}^{l}\sum_{j=1}^{l}(\alpha_i - \alpha_i^*)(\alpha_j - \alpha_j^*)\langle \mathbf{x}_i, \mathbf{x}_j\rangle - \varepsilon\sum_{i=1}^{l}(\alpha_i + \alpha_i^*) + \sum_{i=1}^{l} y_i(\alpha_i - \alpha_i^*) \tag{5}$$

The so-called support vector expansion **w** can be obtained as follows (Eq. (6)) and the approximating function is given by Eq. (7).

$$\mathbf{w} = \sum_{i=1}^{l}(\alpha_i - \alpha_i^*)\mathbf{x}_i \tag{6}$$

$$f(\mathbf{x}) = \sum_{i=1}^{l}(\alpha_i - \alpha_i^*)\langle \mathbf{x}_i, \mathbf{x}\rangle + b \tag{7}$$

Using the *KKT* conditions, the bias b can be computed as shown by Eq. (8).

$$\begin{aligned} b &= y_i - \langle \mathbf{w}, \mathbf{x}_i\rangle - \varepsilon \quad \text{for } \alpha_i \in (0, C) \\ b &= y_i - \langle \mathbf{w}, \mathbf{x}_i\rangle + \varepsilon \quad \text{for } \alpha_i^* \in (0, C) \end{aligned} \tag{8}$$

In addition to *a priori* constant C, ε must also be specified in advance. Based on the results of MLR analyses, the data set used suit very well with the least-squares function. For this reason, the *Gauss*ian loss function, $(y - f(\mathbf{x}))^2$, should be selected to enhance the results of SVR. Therefore, the solution is given by Eq. (9) subject to $\sum_{i=1}^{l}(\alpha_i - \alpha_i^*) = 0$ and $\alpha_i, \alpha_i^* \in [0, C],\ i = 1, \ldots, l$.

$$\min \frac{1}{2}\sum_{i=1}^{l}\sum_{j=1}^{l}(\alpha_i - \alpha_i^*)(\alpha_j - \alpha_j^*)\langle \mathbf{x}_i, \mathbf{x}_j\rangle + \frac{1}{2C}\sum_{i=1}^{l}(\alpha_i^2 - (\alpha_i^*)^2) - \sum_{i=1}^{l}(\alpha_i - \alpha_i^*)y_i \tag{9}$$

The values of HE_i, MR_i, $\mathrm{C5}_i$, and $\mathrm{C6}_i$ would be entered as inputs $\mathbf{x}_i$ and $\mathbf{x}_j$. The values of $\log(1/EC_{50})_i$ were taken into the SVR model by y_i. This least-squares support vector machine then attempts to determine the best values of w_1, w_2, w_3, w_4, and b.

Results and Discussions

The SVR and the PSO based regression methods were implemented in MATLAB. The published data from *Hannongbua et al.* [4] were used to train the proposed methods for predicting anti-HIV-1 activity of *HEPT* derivatives.

The PSO is a very simple search algorithm that was found to be effective for optimizing a wide range of functions. The objective here is to establish a mathematical relationship between the biological activity (output) and descriptors (four

inputs: HE, MR, C5, and C6) by formulating them as an optimization problem and then using the PSO to determine coefficients involved.

Initially, the relationship between the dependent and independent variables was found to be linear. Its MLR model and explanatory parameters were also presented in Table 2. The hydration energy (HE) is the molecular parameter which represents for solvent–solvent cavity term, solute–solvent *van der Waals* term, and solute–solvent electrostatic polarization term. The fit of the three-dimensional structure and the complementary of the surface properties of an inhibitor to its binding site are conditions for its biological activity. Another one, equally important, is that the inhibitor has to reach this binding site. The *HEPT* compounds displaying a high HE, binding more tightly to the solvent molecules than those with a low HE, diffuse slower through the biological environment to the receptor target. The electrostatic polarizability induced by the HE can help to facilitate correct orientation of the inhibitor molecules for the first contact at the binding site. Electrostatic interactions are considered to be important forces, due to their relative strength, among the atomic variables within the thymine ring, C5 and C6 were found to play an important role in the correlation equation. The value of atomic charges distribution of C5 and C6 are the results from the introduction of R2 and R1 substituents of *HEPT*. The significance of molar refractivity (MR) term in QSAR equations has been correlated with polarizability, lipophilicity, molar volume, and steric bulk. The larger the polar part of a molecule is, the larger its MR value will be. A positive sign of MR in a QSAR equation can be explained by binding of the substituents to a polar surface.

Several hundreds of molecular descriptors could be generated in QSAR studies. In QSARs, the number of compounds with the biological activity values is usually small compared with the number of structural descriptors. If the number of descriptors is too large compared to the sample size, this may result in over-fitting and underestimation of model error. The 4 selected parameters in the models derived from 35 *HEPT* compounds may not be sufficient to completely explain relationship between the *HEPT* structural descriptors and biological activity. This leads to the differences between experimentally and calculated biological values. However increasing the number of descriptors results in either reducing the stability of the model or even bringing the insignificance independent variables into the model due to the limited number of compounds in this study.

The initial population size was chosen such that it was large enough to cover the search space within the iteration limit based on the trial runs and literature. The population size of 40 particles was then selected. Again based on the trial runs, the maximum number of iterations was simply fixed at 300, after which the particle with the best performance was picked as the solution. Clearly from Fig. 2, the PSO has very fast convergence. The total error calculated, e, decreases extremely quickly about 10–15 iterations as illustrated in the closer look of total error decreasing in Fig. 2. Afterward, the curve appears almost flat. Hence, the maximum iteration number of 300 was sufficient. The weight parameter, w, was initially set at 0.9 and linearly reduced to 0.4 [35]. $V_{\max}$ was set at about 10–20% of the dynamic range of the variable on each dimension [33]. Lastly, the minimum and maximum positions were chosen such that they were large enough in each dimension to represent the suitable corresponding search spaces. They should

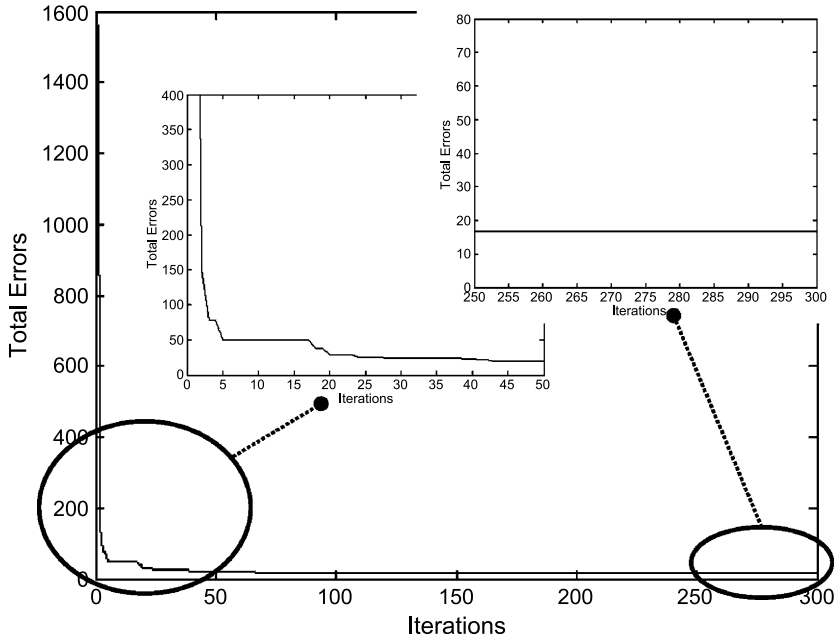


Fig. 2. Total error decreasing during training with the closer look of total error decreasing from 0–50 iterations and from 250–300 iterations

ensure that the search spaces are never violated and the solutions obtained are always valid.

The support vector machines (SVMs), an excellent regression technique, were also studied in this work. Since the data applied in *Hannongbua et al.* [4] showed strong linear relationships and the measure used was r^2, the cost function for SVM was then changed from ε-insensitive loss function to quadratic function. That is, $L(y,f(\mathbf{x})) = (y - f(\mathbf{x}))^2$ and the use of kernel was not required. The upper bound C was kept large enough by being set at 1000000 to prevent any α_i and α_i^* from reaching the upper bound at the optimal solution. The above optimization model was then solved by using a quadratic programming in MATLAB.

The predictions of anti-HIV-1 activity of *HEPT* derivatives and the coefficients obtained from PSO and SVM are depicted in Tables 1 and 2, respectively. The comparison is also made against the MLR results. Clearly, the results obtained by using the adopted PSO and SVM for structure-activity correlation determination were found to be comparable with previously published reference values, which are reasonably satisfying, based on both statistical significance and predictive ability.

Conclusion

This research demonstrated that the PSO and the SVM could be applied to find QSAR models. The PSO based algorithm is very simple, fast, and quite robust to local optima. In addition, there is no requirement for differentiable function. The results obtained clearly show that the PSO is quite competitive in performance with those of SVM and MLR. Comparably, the models determined by the SVM are also

in close agreement with those of the other two. Even though the SVM may be a little more complex in concept, its parameters can be set deterministically and easily.

The modified PSO and SVM may be extended for the variables selection in MLR, PLS (partial least-squares), and GAs (genetic algorithms) modeling. The optimizer such as PSO may be suitable for such task. As for SVM, the kernel tricks or mapping functions will probably be the logical solutions for these non-linear features, therefore SVM should be applied to the original data set with several kernels to display the relative importance of each selected descriptor in the final set of QSAR models.

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