J Comput Aided Mol Des (2013) 27:1067–1073
DOI 10.1007/s10822-013-9697-8

Combined QSAR and molecule docking studies on predicting P-glycoprotein inhibitors

Wen Tan · Hu Mei · Li Chao · Tengfei Liu · Xianchao Pan · Mao Shu · Li Yang

Received: 2 July 2013 / Accepted: 2 December 2013 / Published online: 10 December 2013

Abstract P-glycoprotein (P-gp) is an ATP-binding cassette multidrug transporter. The over expression of P-gp leads to the development of multidrug resistance (MDR), which is a major obstacle to effective treatment of cancer. Thus, designing effective P-gp inhibitors has an extremely important role in the overcoming MDR. In this paper, both ligand-based quantitative structure–activity relationship (QSAR) and receptor-based molecular docking are used to predict P-gp inhibitors. The results show that each method achieves good prediction performance. According to the results of tenfold cross-validation, an optimal linear SVM model with only three descriptors is established on 857 training samples, of which the overall accuracy (Acc), sensitivity, specificity, and Matthews correlation coefficient are 0.840, 0.873, 0.813, and 0.683, respectively. The SVM model is further validated by 418 test samples with the overall Acc of 0.868. Based on a homology model of human P-gp established, Surflex-dock is also performed to give binding free energy-based evaluations with the overall accuracies of 0.823 for the test set. Furthermore, a consensus evaluation is also performed by using these two methods. Both QSAR and molecular docking studies indicate that molecular volume, hydrophobicity and aromaticity are three dominant factors influencing the inhibitory activities.

Keywords P-glycoprotein · Inhibitor · Support vector machine · Surflex-dock · Prediction

Introduction

During the last decades, a major obstacle to the effective treatment of cancer is multidrug resistance (MDR) [1, 2]. MDR is a phenomenon whereby tumor cells exposed to one cytotoxic agent develop cross-resistance to a range of structurally and functionally unrelated compounds [3–6]. One of the most important mechanisms underlying MDR is cellular overproduction of P-glycoprotein (P-gp) [7–9]. Shtill et al. [10] attempted to influence the over expression of P-gp on molecular levels, but the results turned out to be less effective. So the most promising and alternative way is the development of P-gp inhibitors. However, the polyspecificity of P-gp in recognizing inhibitors make it difficult to design effective candidate compounds [11].

Ligand-based and receptor-based prediction methods are two methodologies for predicting and designing P-gp inhibitors [12]. As a traditional ligand-based method, Quantitative Structure–Activity Relationship (QSAR) has been extensively applied in predicting biological activity/function. Although many qualitative or quantitative prediction models have been proposed for screening P-gp inhibitors, low predictive power or poor interpretability remains a major obstacle [13–15]. On the other hand, receptor-based methods, e.g. molecular docking, allow

Electronic supplementary material The online version of this article (doi:10.1007/s10822-013-9697-8) contains supplementary material, which is available to authorized users.

W. Tan · H. Mei (✉) · L. Yang
Key Laboratory of Biorheological Science and Technology, Ministry of Education, Chongqing 400044, China
e-mail: meihu@cqu.edu.cn

W. Tan · H. Mei · X. Pan · L. Yang
College of Bioengineering, Chongqing University, Chongqing 400044, China

L. Chao · T. Liu · M. Shu
School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, China

investigation of ligand-receptor interactions in atomic details when high-resolution structures of receptors are available. However, this method usually generates a large number of potentially false positive results. Up to date, few docking studies on P-gp inhibitors are reported due to the lack of crystal structures of P-gp [16–18].

As discussed above, ligand-based and receptor-based prediction methods are complementary to each other. Ligand-based QSAR method always give relatively higher prediction accuracy (Acc) for a given class of compounds, while molecular docking can not only give quantitative or qualitative evaluation of ligand binding affinity by empirical or semi-empirical scoring functions, but also provide atomic details on ligand-receptor interactions. Therefore, in this paper, QSAR and molecular docking are combined to predict P-gp inhibitors. The results show that both QSAR and molecular docking achieve good prediction performance. Furthermore, a consensus evaluation reinforces the confidence to the prediction of the optimal SVM model.

Materials and methods

Dataset

A data set of 1,275 compounds, including 666 P-gp inhibitors and 609 non-inhibitors was derived from the dataset constructed by Broccatelli et al. [19]. 857 training samples (393 inhibitors and 464 non-inhibitors) and 418 test samples (273 inhibitors and 145 non-inhibitors) were chosen in accordance with the literature [19]. It should be noted that the compounds with molecular weight >700 are explicitly excluded in this dataset. So it should be very careful to employ the QSAR model established in this paper to predict compounds with molecular weight >700.

Structural description

The molecular descriptors were calculated by using PreADMET (v2.0) program (http://preadmet.bmdrc.org). First, all compounds were optimized by Sybyl 8.1 software [20] with Tripos force field and MMFF94 partial charge. Total 1,081 descriptors were obtained including 102 constitutional descriptors, such as atom counts, bond counts, electronic and pharmacophore features, 342 topological (2D) descriptors, such as Burden eigenvalues, topological indices and information content descriptors, and 637 conformational (3D) descriptors including Randic profiles, surface area descriptors and potential energy etc. All parameters in PreADMET were set as default.

Then, the resulting 1,081 descriptors were screened by variance and correlation analysis. After removing 741 descriptors with relative standard deviation (SD/mean) less than 1.5 and 233 multi-correlated descriptors, 87 descriptors were retained for SVM modeling.

SVM modeling

SVM has been successfully applied to a wide range of computational biology fields [21–24]. The key point of SVM is to classify objects in a high-dimensional space and find an optimum separation hyperplane that gives the largest minimum distance to nearest data points [25]. Especially for a small dataset, this optimum separation hyperplane can maximize SVM's ability to predict the correct classes of new compounds [12]. Herein, SVM was implemented by Libsvm [26] software, and only linear kernel was adopted in consideration of model interpretability. The kernel function of linear kernel is given below:

$$K(x, x_i) = x \cdot x_i \tag{1}$$

All descriptors were normalized by unit length [Eq (2)] before SVM modeling. The prediction power of SVM classier is evaluated by Acc, sensitivity (Sen), precision (Pre), specificity (Spe), area under receiver operating characteristics curve (AUC), enrichment (ER), F-measure, and the Matthews correlation coefficient (MCC). The equations of *F-measure* is given in Eq (3):

$$x_i^{'} = x_i / \|x\| \tag{2}$$

where x_i' is the normalized value, x_i is the original value, $\|x\|$is the Euclidean length of the vector x.

$$F - measure = \frac{2Pre \times Sen}{Pre + Sen} \tag{3}$$

Homology modeling

Due to the absence of crystal structure of human P-gp, homology modeling was used to generate a 3-D structure for docking studies. The amino acid sequence of human P-gp (Accession code: P08183) was obtained from the Universal Protein Resource (http://www.uniprot.org). The BLAST program was used to search a template in Protein Data Bank (PDB). The Blosum scoring matrix was selected with a gap penalty of 10 and a gap extension penalty of 0.05. Homology modeling was performed by Modeller 9v4 [27] program with default settings. The stereochemical quality of resulting P-gp homology models were assessed by Procheck program [28].

Surflex-dock

Surflex-dock is a fully automatic flexible molecular docking algorithm based on molecular similarity and an empirical-based scoring function [29, 30]. The docking

score, expressed in *-lg* (K_d) units, consists of hydrophobic, polar, electrostatic, repulsive, entropic, and solvation terms. Surflex-dock has proved to be one of the most effective docking methods, which can effectively decrease false positive results [30, 31]. Prior to docking, all 1,275 ligands were optimized by Tripos force field and MMFF94 partial charges. Herein, the "thresh" and "bloat" were set to 0.5 and 1 for generation of a protomol, and the number of additional starting conformations and resulting docking poses were set to 5 and 20, respectively.

Results and discussion

SVM modeling

An optimal linear SVM model with 87 descriptors is determined by tenfold cross-validation. For 857 training samples (Fig. 1a) and 418 test samples (Fig. 1b), the overall Acc, Sen, Spe, and AUC are 0.892, 0.890, 0.854, 0.942 and 0.852, 0.971, 0.628, 0.928, respectively. In order to decrease model complexity, the descriptors with small weight coefficients are eliminated in a backward manner until prediction performance is unacceptable. Total five SVM models are retained for further analysis, of which the prediction performance is shown in Fig. 1. The list of descriptors and corresponding weights are given in supplement information (Table S1–S5).

It can be seen that all the SVM models achieve good performance on 857 training samples, of which the Acc, Sen, Spe, Pre, and AUC are larger than 0.80 (Fig. 1a). For 418 test samples, the overall performance is also satisfactory, especially when the Sen is concerned (Fig. 1b). It is obviously that the SVM model with three descriptors is the best of all. The three descriptors involved are HTv (H total index weighted by atomic van der Waals volume), MLOGP (Moriguchi octanol–water partition coefficient), and HOMT (Total harmonic oscillator model of aromaticity index) [32]. It can be also observed that the weights of HTv, MLOGP, and HOMT are increased significantly in the process of variable screening.

To enhance the model's interpretability, this SVM model is further optimized by substituting HTv with more meaningful Molvolume (molecular volume) descriptor. From Fig. 1, it can be observed that the overall performance of the two models is equivalent to each other. The detailed performance of this optimized SVM model is shown in Tables 1 and 2. The weight coefficients of Molvolume, MLOGP, and HOMT descriptors are 50.49, 26.63 and 22.88 respectively. Therefore, it can be deduced that molecular volume, hydrophobicity, and aromaticity are the key factors for the inhibitory activities. The X-ray structure of mouse P-gp also reveals a large hydrophobic binding site packed with a number of aromatic residues.

Figure 2 is the sample distribution in the chemical space of the three descriptors. It can be seen that most active samples are distributed in the top right corner of the structural space, while most inactive samples in the bottom left corner. The sample distribution suggests that the three descriptors are qualified for discriminating active samples from inactive ones. Overall, in comparison with earlier studies [19, 33], this optimal SVM model is simple, predictive, and interpretable.

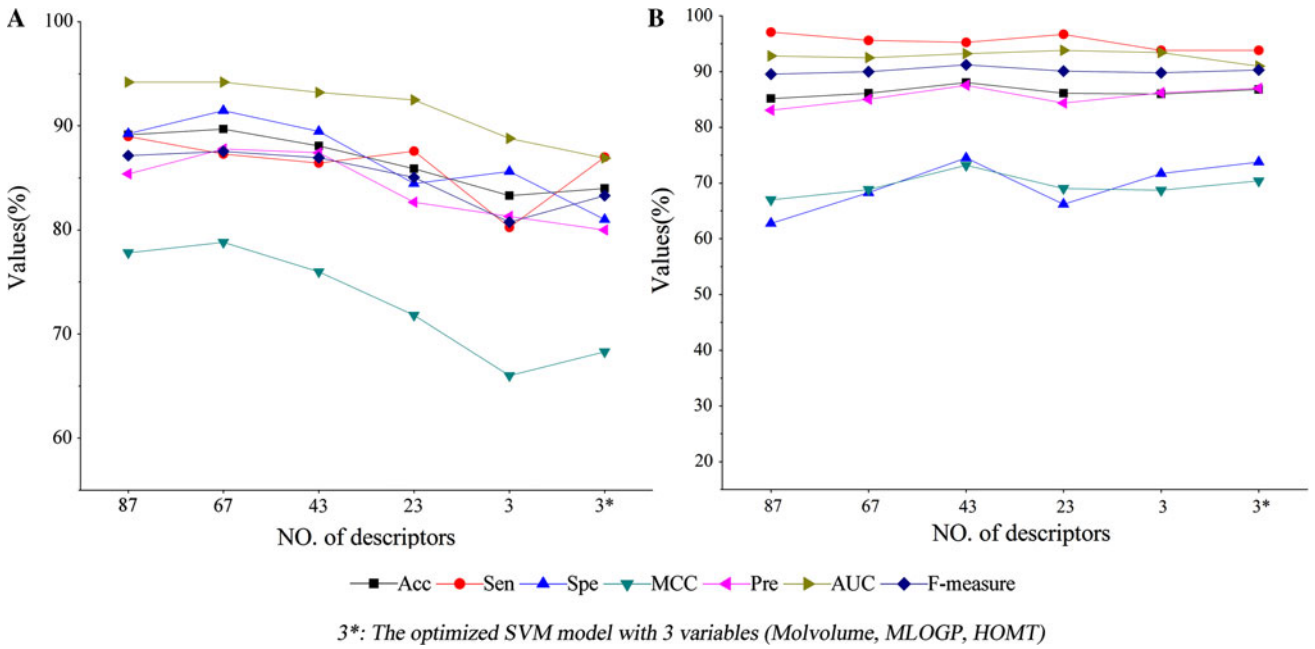

Fig. 1 The prediction performance of SVM models on the training (**a**) and test (**b**) sets

Table 1 The prediction performance on the training set

Models	TP	TN	FP	FN	Acc	Pre	Sen	Spe	MCC	AUC	ER
SVM[a]	343	377	87	50	0.840	0.798	0.873	0.813	0.683	0.873	1.7
Docking score	271	375	89	122	0.754	0.753	0.690	0.808	0.503	0.820	1.6
SVM-Docking score[b]	26,148	30,519	4,431	540	0.8490	0.89449	0.86721	0.911873	0.780697	–	1.98

[a] $C = 44.8169$, $\varepsilon = -0.07006$

[b] The performance on the 651 training samples with the consistent results

Table 2 The prediction performance on the test set

Models	TP	TN	FP	FN	Acc	Pre	Sen	Spe	MCC	AUC	ER
SVM	256	107	38	17	0.868	0.871	0.938	0.738	0.704	0.911	1.3
Docking score	228	116	29	45	0.823	0.887	0.835	0.800	0.621	0.883	1.4
SVM-Docking score[a]	220	92	14	9	0.931	0.940	0.961	0.868	0.839	–	1.4

[a] The performance on the 335 test samples with the consistent results

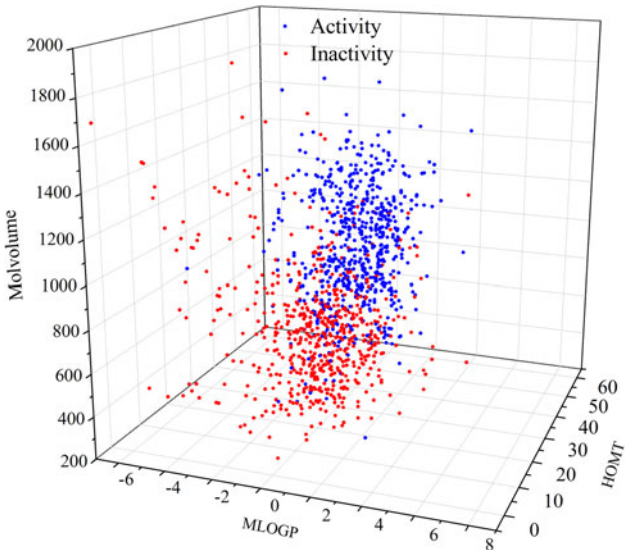

Fig. 2 The sample distribution in the chemical space of Molvolume, MLOGP, and HOMT variables

Homology modeling

The crystal structure of murine P-gp (PDB code: 3G61, Chain A) with a sequence identity of 87 % is selected as a template for 3-D homology modeling of human P-gp. Total 20 homology models of P-gp are generated by Modeller 9v4. The homology model with the lowest discrete optimized protein energy (Fig. 3a) is further evaluated by Procheck program. The results show that about 95.4 % residues are in most favored and additionally allowed region, and that about 3.4 and 1.2 % of the residues in generously allowed and disallowed region, respectively. Further investigation indicates that the residues in the disallowed regions are mainly located in the nucleotide binding domains (NBD). The overall G-factor of this optimal model is −0.22 (−0.17 for dihedrals, −0.33 for covalent), which indicates a high-quality model [34].

Surflex-dock

P-gp belongs to the ATP-binding cassette superfamily of transporters. P-gp is composed of two homologous halves, each half containing one transmembrane domain (TMD) and one NBD, separated by a flexible linker region [35, 36]. Each TMD consists of six potential transmembrane helices. The 6 + 6 transmembrane helices of the two halves form the transportation channel of substrate excretion. The channel is determined as the competitive binding site of inhibitors and used for the following docking studies. Figure 3b is the Connolly surface of this transportation channel projected by lipophilic properties. It is clear to see that the channel contains predominantly hydrophobic residues. The ATP binding site is located in NBD, and is composed of many conserved motifs, such as Walker A, Walker B, C-loop, D-loop, and H-loop etc. [37, 38] (Fig. 3c).

Figure 4 is a receiver operating characteristic (ROC) curve of the total scores of 857 training samples. The area under the ROC curve is 0.82, which indicates high predictive capability. According to Youden index, a measure for evaluating biomarker effectiveness [39], the total score of 6.595 is selected as an optimal threshold. This docking score maps to the largest Youden index 0.498. According to this threshold, the Acc, Sen and Spe for 857 training samples are 0.754, 0.690, and 0.808, respectively (Table 1). For the 418 test samples, the Acc, Sen, and Spe are 0.823, 0.835, and 0.800, respectively (Table 2).

From the predicted results by these two methods, it can be observed that about 77.3 % of the whole samples,

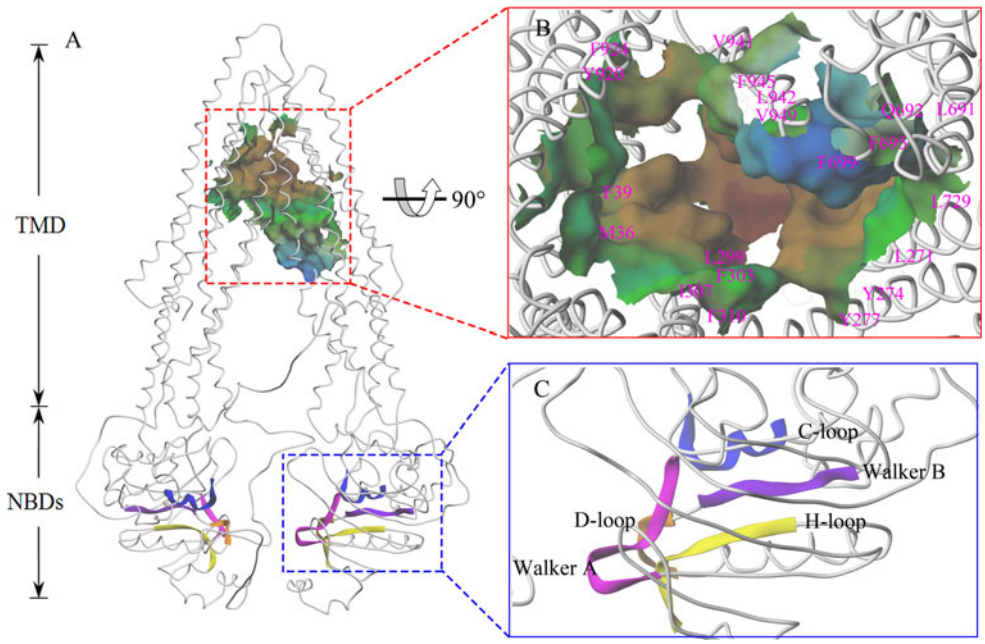

Fig. 3 The homology model of human P-gp. **a**: The homology model of human P-gp (side view); **b**: Antapical view of the Connolly surface of the transportation channel (*Brown*: hydrophobic, *Blue*: hydrophilic); **c**: Conserved motifs in NBD (*Magenta*: Walker A; *Purple*: Walker B; *Blue*: C-loop; *Orange*: D-loop; *Yellow*: H-loop)

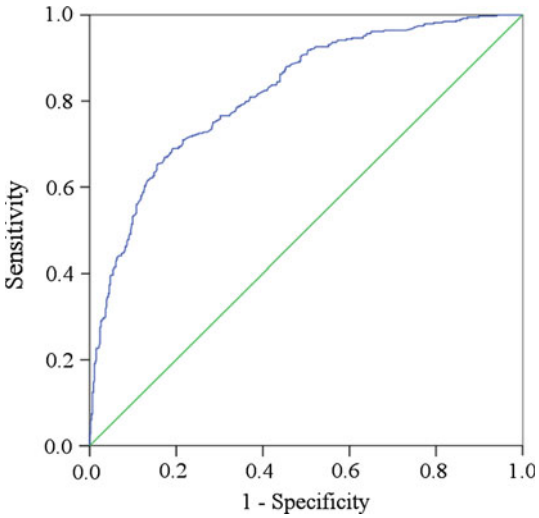

Fig. 4 The ROC curve of the docking scores

namely 651 training samples and 335 test samples, get consistent predicted classes. The Acc, Sen, and Spe are 0.890, 0.867, 0.911 for 651 training samples (Table 1), and 0.931, 0.961, 0.868 for 335 test samples (Table 2), respectively. Undoubtedly, the consistent results reinforce the confidence to the prediction of the SVM model.

Key residues for the binding of P-gp inhibitors

To investigate key residues for the binding of inhibitors, the top 100 P-gp inhibitors and 100 non-inhibitors are selected in descending and ascending order of the total scores, respectively. The occurrence frequencies of the residues within 3Å distance to the optimal conformers of the 100 inhibitors and 100 non-inhibitors are shown in Fig. 5. It is obvious that there is significant difference in the sum of residue's occurrence frequencies between the cases of inhibitors and non-inhibitors. As we know, the number of residue's occurrence frequencies can in some degree reflect the size of ligand volume. Therefore, it can be also inferred that molecular volume is an important factor affecting the binding affinities of P-gp inhibitors.

The results show that Phe945, Tyr274, Phe303, Phe699, Phe695, Gln692, Leu271, Leu729, Phe39, and Val949 are very important for the binding of P-gp inhibitors, of which the occurrence frequency are 92, 90, 89, 89, 88, 79, 71, 67, 65, and 52, respectively. Furthermore, all residues, except Gln692 (hydrophilic) and Tyr274 (neutral), are hydrophobic, which indicates that hydrophobicity interaction is another important factor affecting the binding of P-gp inhibitors. This conclusion is consistent with the results of the SVM model and earlier research [40]. Besides, the docking results also show that Gln692 and Tyr274 are mainly involved in H-bond interactions with P-gp inhibitors.

For 100 non-inhibitors, Tyr274, Gln692, Leu271, Phe695, Asn688, Leu729, Phe945, Met953, Leu691, and Phe303 are relatively important, of which the occurrence frequencies are 51, 49, 48, 41, 36, 35, 31, 31, 29, and 27, respectively. In comparison with the case of 100 P-gp inhibitors, significant decrease in the occurrence frequencies of Phe699, Phe303, Phe695, Phe945, and Phe39 is detected which indicates their important roles in the binding of P-gp inhibitors. Earlier studies [41] also show that position 699^{Phe}, 303^{Ile}, and 695^{Val} are also important ligand binding sites of mouse P-gp.

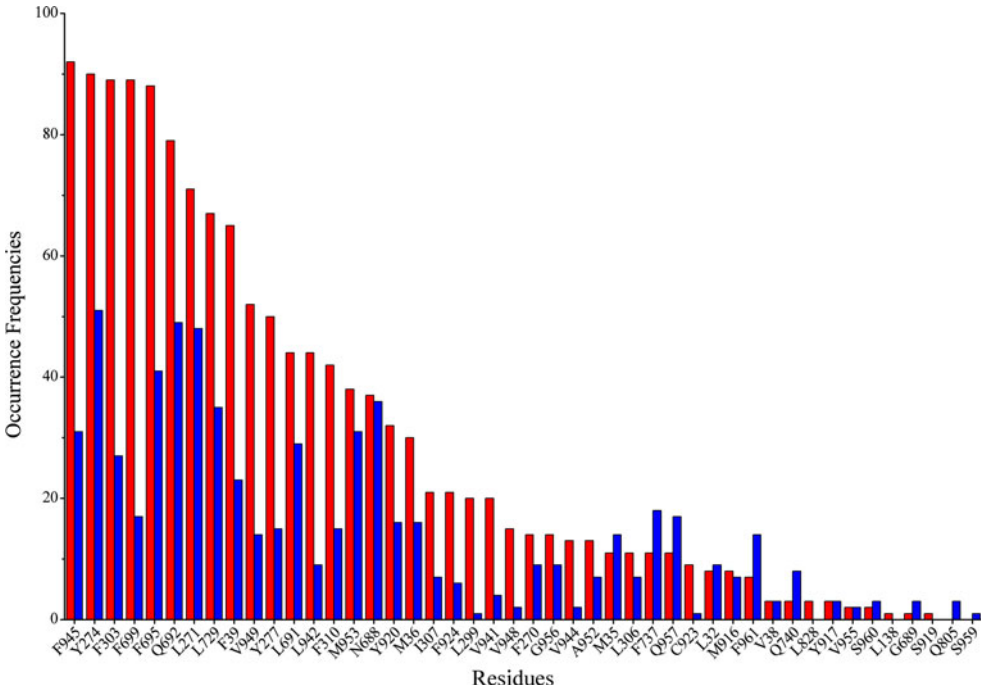

Fig. 5 The histogram of occurrence frequencies of the residues within 3Å distance to the ligands. (*Red*: residues within 3Å distance to the 100 P-gp inhibitors; *Blue*: residues within 3Å distance to the 100 non-inhibitors)

Conclusion

By using only three descriptors, an optimal SVM prediction model of P-gp inhibitors is established with the overall Acc of 0.840 for 857 training samples and 0.868 for 418 test samples. Compared with the existing prediction models, the SVM model constructed in this paper is very simple, predictive, and interpretable. The results indicate that the molecular volume is the primary factor influencing the activities of P-gp inhibitors, followed by Moriguchi octanol–water partition coefficient and total harmonic oscillator model of aromaticity index.

Based on the optimal homology model of human P-gp, molecular docking is also performed by using Surflex-dock method. The results show that the total score of Surflex-dock is also a good predictor of P-gp inhibitors. Then, a consensus evaluation is carried out by employing these two prediction methods. The results show about 77.3 % samples get consistent prediction results.

Beside, the occurrence frequencies of the residues within 3Å distance is also statistically analyzed for the 100 P-gp inhibitors and 100 non-inhibitors selected. The docking results prove further that molecular volume, hydrophobicity and aromaticity are three dominant factors influencing the inhibitory activities. The docking results also indicate that Phe699, Phe303, Phe695, Phe945, and Phe39 may provide important binding sites for P-gp inhibitors. Due to the absence of high-resolution X-ray structure of P-gp, a comprehensive understanding of mechanism of the competitive inhibition still need further study.

Acknowledgments This research was supported by the National Natural Science Foundation of China (No 61073135) and the "111" project of "Introducing Talents of Discipline to Universities".

References

1. Nobili S, Landini I, Mazzei T, Mini E (2012) Overcoming tumor multidrug resistance using drugs able to evade P-glycoprotein or to exploit its expression. Med Res Rev 32(6):1220–1262
2. Wu C-P, Ohnuma S, Ambudkar SV (2011) Discovering natural product modulators to overcome multidrug resistance in cancer chemotherapy. Curr Pharm Biotechnol 12(4):609
3. Alexiou GA, Goussia A, Kyritsis AP, Tsiouris S, Ntoulia A, Malamou-Mitsi V, Voulgaris S, Fotopoulos AD (2011) Influence of glioma's multidrug resistance phenotype on 99mTc-tetrofosmin uptake. Mol Imag Biol 13(2):348–351
4. Li W, Samra DA, Merzaban J, Khashab NM (2013) P-glycoprotein targeted nanoscale drug carriers. J Nanosci Nanotechnol 13(2):1399–1402
5. Gong J, Jaiswal R, Mathys J-M, Combes V, Grau G, Bebawy M (2012) Microparticles and their emerging role in cancer multidrug resistance. Cancer Treat Rev 38(3):226–234
6. Zhao L, Sun Y, Li X, Jin X, Xu Y, Guo Z, Liang R, Ding X, Chen T, Wang S (2011) Multidrug resistance strength of the novel multidrug resistance gene HA117: compared with MRP1. Med Oncol 28(4):1188–1195
7. Nobili S, Landini I, Mazzei T, Mini E (2011) Overcoming tumor multidrug resistance using drugs able to evade P-glycoprotein or to exploit its expression. Med Res Rev 32:1220–1262
8. Xiong X-B, Lavasanifar A (2011) Traceable multifunctional micellar nanocarriers for cancer-targeted co-delivery of MDR-1 siRNA and doxorubicin. ACS Nano 5(6):5202–5213
9. Wang X, Li J, Wang Y, Koenig L, Gjyrezi A, Giannakakou P, Shin EH, Tighiouart M, Chen Z, Nie S (2011) A folate receptor-targeting nanoparticle minimizes drug resistance in a human cancer model. ACS Nano 5(8):6184–6194

10. Shtil AA (2001) Signal transduction pathways and transcriptional mechanisms as targets for prevention of emergence of multidrug resistance in human cancer cells. Curr Drug Targets 2(1):57–77
11. Liu M, Hou T, Feng Z, Li Y (2012) The flexibility of P-glycoprotein for its poly-specific drug binding from molecular dynamics simulations. J Biomol Struct Dyn (ahead-of-print):1–18
12. Bikadi Z, Hazai I, Malik D, Jemnitz K, Veres Z, Hari P, Ni ZL, Loo TW, Clarke DM, Hazai E, Mao QC (2011) Predicting P-glycoprotein-mediated drug transport based on support vector machine and three-dimensional crystal structure of P-glycoprotein. PLoS ONE 6(10):e25815
13. Muller H, Pajeva IK, Globisch C, Wiese M (2008) Functional assay and structure-activity relationships of new third-generation P-glycoprotein inhibitors. Bioorg Med Chem 16(5):2448–2462
14. Pajeva IK, Globisch C, Wiese M (2009) Combined pharmacophore modeling, docking, and 3D QSAR studies of ABCB1 and ABCC1 transporter inhibitors. Chem Med Chem 4(11):1883–1896
15. Chen L, Li Y, Zhao Q, Peng H, Hou T (2011) ADME evaluation in drug discovery. 10. Predictions of P-glycoprotein inhibitors using recursive partitioning and naive Bayesian classification techniques. Mol Pharm 8(3):889–900
16. Sirisha K, Shekhar MC, Umasankar K, Mahendar P, Sadanandam A, Achaiah G, Reddy VM (2011) Molecular docking studies and in vitro screening of new dihydropyridine derivatives as human MRP1 inhibitors. Bioorg Med Chem 19(10):3249–3254
17. Klepsch F, Chiba P, Ecker GF (2011) Exhaustive sampling of docking poses reveals binding hypotheses for propafenone type inhibitors of P-glycoprotein. PLoS Comput Biol 7(5):e1002036
18. Becker JP, Depret G, Van Bambeke F, Tulkens PM, Prevost M (2009) Molecular models of human P-glycoprotein in two different catalytic states. BMC Struct Biol 9:3
19. Broccatelli F, Carosati E, Neri A, Frosini M, Goracci L, Oprea TI, Cruciani G (2011) A novel approach for predicting P-glycoprotein (ABCB1) inhibition using molecular interaction fields. J Med Chem 54(6):1740–1751
20. Sybyl 8.1; Tripos Inc.: St. Louis M, USA, 2008; Available online: http://www.tripos.com
21. Kalita MK, Nandal UK, Pattnaik A, Sivalingam A, Ramasamy G, Kumar M, Raghava GPS, Gupta D (2008) CyclinPred: a SVM-based method for predicting cyclin protein sequences. PLoS ONE 3(7):e2605
22. Pan XC, Mei H, Xie JA, Lu J, Wang Q, Zhang YL, Tan W (2012) Prediction of TAP binding affinity of peptide and selection specificity using VHSE descriptors. Chem J Chin Univ-Chin 33(11):2556–2562
23. Xie JA, Mei H, Lu J, Pan XC, Wang Q, Zhang YL (2012) Studies on the prediction of selective cleavage sites and cleavage profile of proteasome using VHSE amino acid descriptor. Acta Chim Sinica 70(3):318–324
24. Zhang YL, Mei H, Wang Q, Xie JA, Lv J, Pan XC, Tan W (2012) Peptide binding specificities of HLA-B*5701 and B*5801. Sci China-Life Sci 55(9):818–825
25. Noble WS (2006) What is a support vector machine? Nat Biotechnol 24(12):1565–1567
26. Chang C–C, Lin C-J (2011) LIBSVM: a library for support vector machines. ACM Trans Intell Syst Technol (TIST) 2(3):27
27. Šali A, Webb B, Madhusudhan M, Shen M, Marti-Renom M, Eswar N, Alber F, Topf M, Oliva B, Fiser A (2008) MODELLER. A program for protein structure modeling. Version 9v4, University of California, San Francisco, CA
28. Laskowski RA, MacArthur MW, Moss DS, Thornton JM (1993) PROCHECK: a program to check the stereochemical quality of protein structures. J Appl Crystallogr 26(2):283–291
29. Jain AN (2003) Surflex: fully automatic flexible molecular docking using a molecular similarity-based search engine. J Med Chem 46(4):499–511
30. Wu B, Sun J, Cheng SP, Gu JD, Li AM, Zhang XX (2011) Comparative analysis of binding affinities between styrene and mammalian CYP2E1 by bioinformatics approaches. Ecotoxicology 20(5):1041–1046
31. Kellenberger E, Rodrigo J, Muller P, Rognan D (2004) Comparative evaluation of eight docking tools for docking and virtual screening accuracy. Proteins 57(2):225–242
32. Kruszewski J, Krygowski TM (1972) Definition of aromaticity basing on the harmonic oscillator model [J]. Tetrahedron Lett 13(36):3839–3842
33. Poongavanam V, Haider N, Ecker GF (2012) Fingerprint-based in silico models for the prediction of P-glycoprotein substrates and inhibitors. Bioorg Med Chem 20:5388–5395
34. Jensen AR (1999) The g factor: the science of mental ability. Psicothema 11(2):445–446
35. C-l Chen, Chin JE, Ueda K, Clark DP, Pastan I, Gottesman M, Roninson I (1986) Internal Duplication and Homology with Bacterial Transport Proteins in the mdr1 (P-Glycoprotein). Cell 47:381–389
36. Hrycyna CA, Airan LE, Germann UA, Ambudkar SV, Pastan I, Gottesman MM (1998) Structural flexibility of the linker region of human P-glycoprotein permits ATP hydrolysis and drug transport. Biochemistry 37(39):13660–13673
37. Singh DV, Godbole MM, Misra K (2013) A plausible explanation for enhanced bioavailability of P-gp substrates in presence of piperine: simulation for next generation of P-gp inhibitors. J Mol Model 19(1):227–238
38. Kim IW, Peng XH, Sauna ZE, FitzGerald PC, Xia D, Muller M, Nandigama K, Ambudkar SV (2006) The conserved tyrosine residues 401 and 1044 in ATP sites of human P-glycoprotein are critical for ATP binding and hydrolysis: evidence for a conserved subdomain, the A-loop in the ATP-binding cassette. Biochemistry (Mosc) 45(24):7605–7616
39. Perkins NJ, Schisterman EF (2006) The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 163(7):670–675
40. Tarcsay A, Keseru GM (2011) Homology modeling and binding site assessment of the human P-glycoprotein. Future Med Chem 3(3):297–307
41. Aller SG, Yu J, Ward A, Weng Y, Chittaboina S, Zhuo R, Harrell PM, Trinh YT, Zhang Q, Urbatsch IL, Chang G (2009) Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. Science 323(5922):1718–1722