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Evaluation of QSAR and ligand enzyme docking for the identification of ABCB1 substrates

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Introduction

The ABC transporter superfamily is one of the largest and abundant families of proteins. The ABC transporter P-glycoprotein (ABCB1, P-gp), a polyspecific protein has demonstrated its function as a transporter of hydrophobic drugs as well as transporting lipids, steroids and metabolic products. Its role in multidrug resistance (MDR) and pharmacokinetic profile of clinically important drug molecules has been widely recognised. Figure below shows X-Ray crystal structures of P-glycoprotein that are available in the Protein Data Bank (PDB) with various binding sites of this polyspecific transporter enzyme.

Methods

Dataset: The p-gp inhibition class published by Matsson et al (2009) [1] consisting of 54 inhibitors (IC50 <50 μM) and 69 non-inhibitors. Dataset was split randomly into a training set of 98 compounds for building models and a validation set of 25 for testing the model accuracy.

Molecular Descriptors: ACD Labs/Log D Suite Version 12.0 and Molecular Operating Environment (MOE), 2012.10 were used to calculate molecular properties.

Docking: Docking of compounds was carried out using the Dock application in MOE software. Compounds were docked into the X-ray structures of mouse P-gp 3GSU and 3G61 [2] extracted from Protein Data Bank. Docking experiments included four different binding sites on 3GSU protein [2].

Statistical Analysis: Results from docking experiments (scores) and molecular descriptor calculations were analysed using data mining tools including CART, boosted trees and Support Vector Machine (Statistica 11.0).

Results

Optimization of CART, SVM and Boosted trees

Conclusion

Docking performance was better using the 3G61 structure of P-gp. The most important feature for binding to P-gp was lipophilicity. Use of lipophilicity and docking scores in Support Vector Machine leads to the most accurate prediction model in comparison with the models based on docking scores only. On the other hand, optimization of CART, SVM and BT without the use of docking scores may produce similar or better results (in case of boosted trees). A model generated using BT was identified as the best model, with a prediction accuracy of 88%. Mathews correlation coefficient of 0.77 and Youden’s J index of 0.80 for the test set.

References


An example docking pose: Chlorprotixene docked to P-gp 3G61

Significance of docking scores using selected CART, iCART and SVM models; ACC= Accuracy; MCC= Mathews Correlation Coefficient

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters given</th>
<th>Parameters selected by analysis</th>
<th>Training Set</th>
<th>Validation Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>CART 1</td>
<td>Docking scores + molecular descriptors</td>
<td>QZ59rrr, log D, log D10</td>
<td>0.71</td>
<td>0.49</td>
</tr>
<tr>
<td>CART 2</td>
<td>Docking scores + molecular descriptors</td>
<td>QZ59rrr, log D, log D10</td>
<td>0.76</td>
<td>0.48</td>
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<tr>
<td>CART 1</td>
<td>QZ59rrr (manually selected) + molecular descriptors</td>
<td>QZ59rrr, log D, log D10</td>
<td>0.83</td>
<td>0.66</td>
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<tr>
<td>CART 2</td>
<td>QZ59rrr (manually selected) + molecular descriptors</td>
<td>QZ59rrr, log D, log D10</td>
<td>0.85</td>
<td>0.71</td>
</tr>
<tr>
<td>SVM</td>
<td>Docking scores + molecular descriptors</td>
<td>QZ59rrr, log D, log D10</td>
<td>0.76</td>
<td>0.55</td>
</tr>
</tbody>
</table>

ACC= Accuracy ; MCC= Mathews Correlation Coefficient; SE= Sensitivity; SP= Specificity

Optimized parameters for CART, iCART and SVM models

Selected Models:

<table>
<thead>
<tr>
<th>Model</th>
<th>Train set</th>
<th>Validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td>CART</td>
<td>ACC = 0.94</td>
<td>MCC = 0.88</td>
</tr>
<tr>
<td>BT</td>
<td>ACC = 1.00</td>
<td>MCC = 0.88</td>
</tr>
<tr>
<td>SVM</td>
<td>ACC = 0.85</td>
<td>MCC = 0.69</td>
</tr>
</tbody>
</table>

An example docking pose: Chlorprotixene docked to P-gp 3G61