2015

Modeling ATP-Binding Cassette G2 (ABCG2) Substrate Specificity

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Modeling ATP-Binding Cassette G2 (ABCG2) Substrate Specificity  
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Abstract

- Cancer estimates for USA in 2015:
  - 1.6 million new cases, 
  - half a million deaths [1]
  - majority of deaths due to resistance to chemotherapy [2]
- ATP-binding cassette (ABC) efflux transporters (e.g., ABCG2) 
  - overexpressed in chemotherapy-resistant cancer cells
  - Anticancer drugs are prone to efflux
- What we need:
  - identify substrate and non-substrate chemotypes 
  - gain a structural understanding of the efflux mechanism

Aim: Understand ABCG2 structure and function

Introduction

Why are certain compounds effluxed while others are not?

Method

Discrimination Analysis

Target property = ax + by + cz + k

Where:

a, b & c are correlation coefficients
x, y & z are independent properties

Non-Linear SVM method used for this study.

References

(1) American Cancer Society "facts and figures 2015"  
www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index  
(3) Hazai, E. et al. BMC Bioinformatics 2013, 14, 130.
(B) Sugimoto et al. Mol Cancer Ther 2003, 2(1): 105-112

Descriptors Used

<table>
<thead>
<tr>
<th>Our Model</th>
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</thead>
<tbody>
<tr>
<td>LogP (I)</td>
</tr>
<tr>
<td>Length (II)</td>
</tr>
<tr>
<td>Width (III)</td>
</tr>
<tr>
<td>Binding Energy (IV)</td>
</tr>
<tr>
<td>Atom Count (V)</td>
</tr>
<tr>
<td>Radius of Gyration (VI)</td>
</tr>
</tbody>
</table>

Results

Our models are significantly better (p<0.01)

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>FS</th>
<th>FNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3] 68.9 ± 4.9%</td>
<td>71.2 ± 7.1%</td>
<td>65.9 ± 14.8%</td>
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<tr>
<td>This work 75.6 ± 4.7%</td>
<td>76.2 ± 6.5%</td>
<td>72.5 ± 11.1%</td>
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<td>Atom count 66.4 ± 5.2%</td>
<td>68.9 ± 7.1%</td>
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<tr>
<td>Binding energy 68.5 ± 5.4%</td>
<td>67.9 ± 5.8%</td>
<td>73.4 ± 13.9%</td>
</tr>
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<td>Radius of Gyration 64.8 ± 4.7%</td>
<td>65.9 ± 5.9%</td>
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<tr>
<td>Length 65.3 ± 6.3%</td>
<td>67.7 ± 7.8%</td>
<td>50.2 ± 26.4%</td>
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<tr>
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<td>66.3 ± 6.5%</td>
<td>59.8 ± 23.1%</td>
</tr>
<tr>
<td>LogP 65.8 ± 6.1%</td>
<td>67.6 ± 7.2%</td>
<td>58.9 ± 26.3%</td>
</tr>
</tbody>
</table>

B: fraction of substrates predicted correctly;  
FNS: fraction of non-substrates predicted correctly; 
Accuracy: fraction of dataset correctly predicted; Values shown in table represent Mean ± Standard Deviation of external validation set from 100 runs of SVM.

Discussion

- SVM model capable of discriminating between substrates and nonsubstrates with a median accuracy of 76.05% and an Interquartile range of 7.04%.
- Accuracy highly dependent on composition of training, test and external validation sets.
- Insights into efflux mechanism – role of Arg482 in substrate recognition suggested by significant difference in binding energy between substrates and non substrates.

Implications

- Discriminant models are noisy – understanding of the structural mechanism of efflux might lead to better models.
- More experimental data needed – might make for a better predictive model.

Future directions

- Glean structural information on ABCG2-mediated efflux to improve model.

Acknowledgements

This work was funded by the Mary Louise Andrews Award from the Virginia Academy of Science.