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Identification of Privileged Atom-Types in Substrates of the ABC-Transporter ABCB1 (P-gp) by Random Forest Classification

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The ABC-transporter ABCB1 (P-glycoprotein) is a drug efflux pump playing an important role in the transport route of drugs through tissue barriers, protection against xenobiotics, and in cancer drug resistance. Due to this, ABCB1 is notorious for limiting bioavailability of various chemical and functional unrelated drugs.

The aim of this study is to develop *in-silico* models that provide rapid and cost-effective screening tools for the classification of ABCB1 substrates/non-substrates. Besides good classification performance, the identification of critical structural features that render molecules as ABCB1 substrates is one of the main issues of this investigation. In this study a total number of 2374 compounds retrieved from three different resources are subjected to modelling. The first data set is constituted from the literature, the second data set is compiled from the NCI60 screen [1], and additionally a highly diverse collection of compounds from the Boehringer Ingelheim Austria (BIA) research facility is used as the third data source. The chemical structures of these compounds are encoded by 166 MACCS-atom-type count descriptors. For model generation we use Breiman`s random forest algorithm [2].

The obtained models show classification accuracies of more than 80% for the individual data sets as well as for the merged data set in 10-fold crossvalidation. Analysing the most important descriptors contributing to these high quality models reveals that atom-types reflecting H-bonding properties (e.g. C=0), aromatic structures, and N-containing rings are preferentially found in the substrates class.

The detailed information on privileged atom-types of ABCB1 substrates retrieved in this study might improve the ongoing efforts to “design-in” or “design-out” ABCB1-related substrate properties in further hit-to-lead optimization campaigns.

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[1] Szakács G, Annereau JP, Lababidi S, Shankavaram U, Arciello A, Bussey KJ, Reinhold W, Guo Y, Kruh GD, Reimers M, Weinstein JN, Gottesman MM. Predicting drug sensitivity and resistance: Profiling ABC transporter genes in cancer cells. Cancer Cell. 2004; 6: 129–137. doi:10.1016/j.ccr.2004.06.026

[2] Breiman L. Random Forests. Mach Learn. 2001; 45: 5–32. doi:10.1023/A:1010933404324