

Ligand-Based Models for the Isoform Specificity of Cytochrome P450 Substrates

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In silico prediction of ADMET (absorption, distribution, metabolism, elimination, and toxicity) properties is expected to detect and eliminate compounds with inappropriate pharmacokinetic properties at an early stage of the drug discovery process. A central step in the ADMET process is drug metabolism. Metabolic stability, drug toxicity, and drug-drug interactions have to be considered.

Oxidation reactions mediated by cytochrome P450 isoforms play a crucial role in phase I of the human metabolism of xenobiotics. Here, we report on the isoform specificity for CYP3A4, CYP2D6, and CYP2C9 substrates.[1] The influence of the descriptors used for structure representation and the impact of the modeling method on the predictability of the models will be discussed. A thorough CV (cross-validation) scheme is presented to assess the reliability of the models. Furthermore, the prediction of a more diverse and larger external validation data set with an accuracy of up to 83% underlines the validity of the models.

It will be shown that the random selection of a test set can be rather misleading to assess the predictability of a classification model (Figure 1).

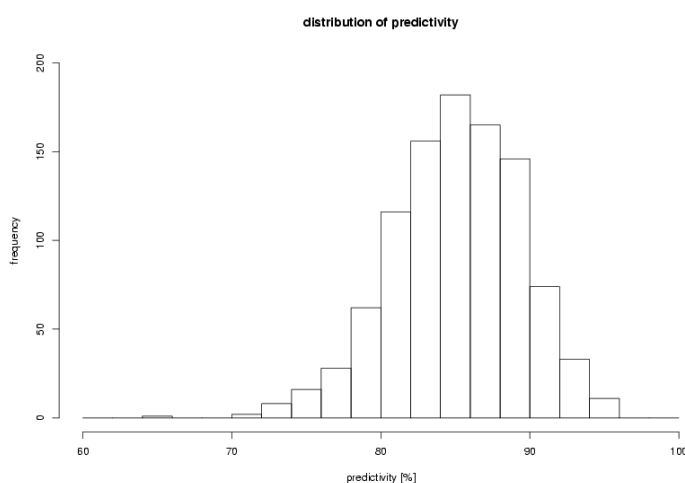


Figure 1: Distribution of the predictability for 1000 randomly selected test data sets.

A classification model for the isoform specificity is implemented in the application isoCYP.[2,3]

1. Terfloth, L.; Bienfait, B.; Gasteiger, J. Ligand-Based Models for the Isoform Specificity of Cytochrome P450 3A4, 2D6, and 2C9 Substrates. *J. Chem. Inf. Model.* **2007**, *47*, 1688-1701.
2. The software package isoCYP is available from Molecular Networks GmbH, Erlangen, Germany. <http://www.molecular-networks.com> (accessed Feb 24, 2008).
3. A Web service of isoCYP is available from Molecular Networks GmbH, Erlangen, Germany. http://www.molecular-networks.com/online_demos/cyp450 (accessed Feb 24, 2008).