[P41] Automatic Discovery of Molecular Graph Patterns Inhibiting Multiple Drug Transporters

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The clinical importance of efflux and uptake transporters in drug disposition is widely acknowledged, and membrane transporter anomalies or drug-drug interactions are the basis for certain clinical disorders. Computational models could predict undesirable effects that are based on drug transporter interactions, and statistical models like quantitative structure-activity relationships and pharmacophores have been proposed [1]. Several works have been conducted in chemoinformatics to extract the frequent substructures from a dataset of graphs and to link them to a biological activity. However, in the recent years more attention has been dedicated to the discovery of patterns that are not only frequent but also "significant" [2]. In this study we have considered datasets containing compounds represented by 2D molecular graphs and split in two classes according to their ability to inhibit a transporter activity. We propose a method for computing the representative subsets of frequent patterns which occur more frequently in the inhibitors versus the non-inhibitors (figure 1). The extracted patterns are characterized by their contrast between these two classes. This method applied on three transporters (OCT2, P-gP and OATP) has allowed to identify molecular graph patterns (i) inhibiting one or several transporters at a time, or (ii) not inhibiting any transporter of interest. This automatic knowledge discovery provides new information to build prediction models and/or to assist expert examination.

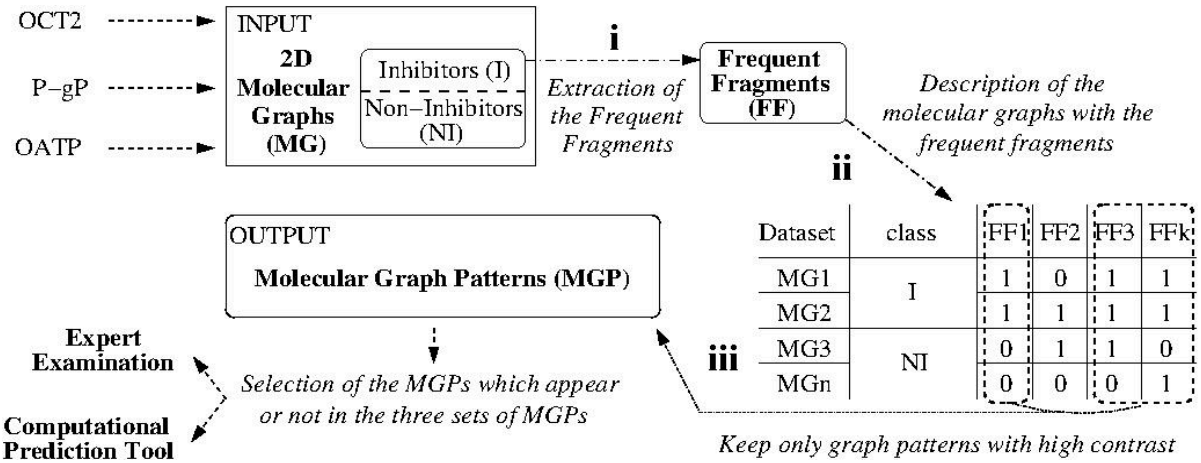

Figure 2. Extraction of the Molecular Graph Patterns

[1] Kido, Y.; Matsson, P.; Giacomini, K. M. J. Med. Chem., 54 (2011), 4548–4558.
[2] Cuissart, B.; Poezevara, G.; Crémilleux, B.; Lepailleur, A.; Bureau, R. Emerging Patterns as Structural Alerts for Computational Toxicology in Contrast Data Mining: Concepts, Algorithms and Applications; Dong, G.; Bayley, J.; Taylor & Francis Group; 2012; 259-270.