MetaPies, an annotated database for metabolism analysis and prediction: results and future perspectives

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Drug metabolism with its many enzymes and reactions is a key factor in early ADMET screens for the selection of promising drug candidates, but its success depends on the reliability of available tools. With a view to supporting metabolic screening, our first objective was to generate a metabolism database offering an overview of the compared quantitative importance of biotransformation reactions and related enzymes in the metabolism of drugs and other xenobiotics. Thus, a meta-analysis of the literature was performed with 903 papers selected according to predefined criteria. These papers reported experimental metabolic data on 1171 different substrates, namely 747 drugs and 424 other xenobiotics. These substrates yielded a total of 6767 different metabolites (5.78 per substrate). Each metabolite was annotated and classified according to the metabolic reaction that generated it and the enzyme family that catalysed the reaction.
In order to investigate the physico-chemical profile of the collected molecules, the second objective is to compute property spaces for substrates and metabolites of each enzyme family, said property spaces being defined by average and range values for a set of representative molecular properties. This analysis should evidence significant differences between such property spaces thus emphasizing that each enzyme family recognizes substrates and produces metabolites with well-defined and poorly overlapping molecular properties. Lastly, the third objective will be to develop a metabolism prediction approach based firstly on a substructure search to find similar substrates and resulting metabolites. The reliability of the retrieved hits will be validated by considering how well a substrate and its predicted metabolites fall within the corresponding enzyme's property spaces. Database handling and property space calculations are here carried out by VEGA ZZ[1,2], an in-house freely available suite of programs which includes specific features for managing and interrogating chemical databases as well as for property space calculations. Moreover, the novel VEGA ZZ release includes enhanced user-friendly "point & click" graphic interfaces, which are commonly exploited in Windows-based PCs, and which should help the users to handle complex problems in a simple and productive way. Not to mentioned that the included features allow the computational performances to be optimized by exploiting the grid-computing as supported by recent multicore-architectures.

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[1] A. Pedretti, L. Villa, G. Vistoli, "VEGA: A versatile program to convert, handle and visualize molecular structure on Windows-based PCs", J. Mol. Graph., Vol. 21, 47-49 (2002).
[2] A. Pedretti, L. Villa, G. Vistoli, "VEGA - An open platform to develop chemo-bio-informatics applications, using plug-in architecture and script programming", J.C.A.M.D., Vol. 18, 167-173 (2004).