Prediction of xenobiotics metabolism in human

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***Short Abstract* — Xenobiotic metabolism in humans is catalyzed by a few enzymes with broad substrate specificities, which provide the overall broad chemical specificity for nearly all xenobiotics that human encounter. Xenobiotic metabolism are classified into functional group biotransformations. Based on bona fide reactions and negative examples for each reaction class, support vector machine (SVM) classifiers are built. The input to SVM is a set of atomic and molecular features to define the electrostatic, steric, energetic, geometrical and topological environment of the atoms in the reaction center under the molecule. Results show that the overall sensitivity and specificity of classifiers is around 87%.**

I. Purpose

Biotransformation is the process whereby a substance, usually a foreign compound (xenobiotic), is chemically transformed in the body to form a metabolite or a variety of metabolites. Chemical transformations can activate a xenobiotic rendering it toxic, or can alter a xenobiotic to a non-toxic species. Xenobiotic metabolism is accomplished by a limited number of enzymes that exhibit broad substrate specificities. These enzymes conduct limited types of biotransformations. Numerous efforts have been made to predict the site of metabolism in xenobiotics metabolism. These systems can be roughly divided into two categories: local and global systems. Local predictive methods are applicable to relatively simple biological systems such as a single enzyme or a single mechanism. Global systems are designed to provide a global view of the metabolism of a given compound at the organism level. Current global systems models xenobiotics metabolism using reaction rules, which are designed to genaralize functional group transformations that occur in known reactions. These rules can provide reasonable prediction of all possible metabolite formation. However, they commonly predict many more metabolites than that are observed experimentally.

We proposed a global system for xenobitoics metabolism prediction by combining reaction rules and machine learning. Using a complete set of xenobiotics metabolism enzymes, we identify 6276 unique human xenobiotics reactions from Symyx's Metabolite database. The reaction sets include 7058 unique metabolites used as substrates or products. The 7058 compounds can be viewed as set of currently known xenobiotics and their metabolites that human can exposure. The 6276 unique reactions defined the possible fate of these compounds. We defined 43 reaction rules based on functional group biotransformations, which can cover almost all of the 6276 reactions. For a given compound, these rules defined all possible biotransformations. For each reaction rule, we designed a classifier to separate the real and putative reaction centers. For each reaction rule, the reaction center can be well defined, and is represented as a molecular substructure pattern using SMARTs. Using the SMARTS patterns, we identified potential reaction centers for each reaction class using the 7058 compounds. Each set of potential reaction centers was divided into negative and positive examples. A match to a reaction center pattern was considered to be a positive example if the match was recorded in 6276 reactions to be a reaction center in the type of reaction associated with the reaction center pattern. Otherwise, the match was considered to be a negative example. More than 54 atomic properties were used to model the topological, geometrical, electronic and steric environment of the atoms in the molecule, and more than 81 molecular properties were used to model the shape, surface, energy, and charge distribution of the molecule. Support Vector Machines were used to separate the positive and negative examples for each reaction class. Results based on both cross validation and blind testing show that the overall sensitivity and specificity of classifiers is around 85%. The classifiers can enhance the accuracy to rank the possibility of metabolite formation.

II. Conclusion

Global classification models are proposed to predict the fate of xenobiotics in humans. The methods represent a step toward the development of computational tools that can predict xenobiotic metabolism pathways in humans.

References

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