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MACHINE LEARNING APPROACH TO STUDY DRUG-INDUCED HEPATOTOXICITY THROUGH GENE EXPRESSION PROFILING

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Abstract

Liver is the primary organ responsible for drug metabolization and absorption, many currently and normally used drugs could affect the liver adversely. Hepatotoxicity caused by drugs, in particular idiosyncratic reactions, is a major challenge to the pharmaceutical industry and physicians. Toxicology aims at identifying toxicity in drugs, toxicogenomics on the other hand, integrates genome technologies into toxicology studies including those related to drug discovery. The application of new technologies in pharmacogenomics and toxicogenomics research offers the potential to identify risk factors and clarify the pathogenesis of idiosyncratic hepatotoxicity. Biotech scientists are now applying genome technologies to toxicology research to better understand the effects of drugs on human liver. Development of efficient drugs with both requirements, lower cost and lower toxicity due to the effects of chemicals and xenobiotics on cell function remains a challenge that can be overcome by combining biotechnology and bioinformatics. High throughput screening of thousands of genes and hundreds of compounds have largely influenced the fields of pharmacology and toxicology. For years, it has been shown that gene expression profiling can be used to identify the mechanisms that underlie the potential toxicity of chemicals. However, even with these technologies the data mining process is the real challenge. In this work, we present a computational approach to study toxicogenomic patterns through gene profiles over time. Genes are ranked based on large absolute or relative amounts of change over time as a function of the drug concentration in relation to their replicate variances. We use gene expression data from the Japanese toxicogenomics project (TGP), a 5-year project that was completed in 2007. The TGP data contains a collection of 17,657 Affymetrix™ microarrays from both in vitro and animal samples interrogating 131 compounds used in many already available drugs.

Performing an integrated analysis of gene expression changes with traditional toxicity allows us to extend the search using a mathematical and computational approach to identify gene signatures that are predictive or coincident with toxicologic patterns.

References

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