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Systematic Assessment of Different Computational Approaches for Prediction of Toxic Effects of Chemical Structures

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Approximately 20% of failures in the late drug development are caused by occurrences of toxicities and adverse drug reactions (ADR). Animal trials are currently the major method for determining the possible toxic effects of drug candidates. However, as an alternative, several traditional chemoinformatics approaches such as Quantitative Structure Activity Relationship modeling, ligand- and structure-based approaches, have been proposed to perform well *in silico* thus enabling the reduction of cost, time and animal experiments. Molecular similarity analysis in alliance with identification of toxic fragments was reported to show promising performance in prediction of rodent oral toxicity [1,2]. Furthermore, pharmacophore models (toxicophores) were reported to indicate possible toxicity targets associated with adverse drug effects. Predicting the *in vitro* effects solely based on structural descriptors has also received great attention in recent years.

Here, we describe different computational approaches and their intrinsic limitations while comparing their performance across data sets provided in the Tox21 Data Challenge 2014. In particular, we examine different methodologies including analysis of toxic fragments, pan assay interface compound substructures and toxicophore mapping. Additionally, a case study consisting two different drugs having similar toxic class effects can cause similar ADR that result from sharing similar toxicological pathways or networks has been reported [3]. Proper understanding of tissue specificity is necessary to detect relevant genes and pathways in a specific organ and to identify the key nodes underlying the organ-specific safety profile of a particular drug.

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We acknowledge the funding from DFG, GRK 1172,GRK 1360, Innovative Toxicology for the Reductionof Animal Experimentation (e:ToP), Immunotox Project (BMBF) [031A268B].