GT-Arbeitskreis Computational Toxicology

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The Adverse Outcome Pathway (AOP) framework aims to formalize knowledge on how molecular initiating events are linked to adverse outcomes, through key events on different biological levels. However, often the underlying toxicity mechanisms are not completely understood and the relationship between changes on the molecular or cellular level and the adverse outcome are largely qualitative.

We aim to derive events in Drug-Induced Liver Injury (DILI) and quantify the association between these events in a data-driven manner. To do so, we use data from the TG-GATEs database which contains information from single- and repeat-dose studies in rats on 156 compounds out of which many are known to be hepatotoxic. First, the dysregulation of individual genes, cellular pathways and serum marker levels is computed and sequences describing these changes over time are formulated for each compound-dose combination. We then derive events and cascades which are frequently observed in adverse conditions using sequential pattern mining and investigate association rules which provide insights on which events or a combination thereof are predictive for histopathology at a later timepoint. Among others, this identified fatty acid metabolism and NFkB signalling as events which are often followed by hepatic necrosis and inflammation, respectively.

Overall, this analysis aspires to contribute towards a quantitate AOP for DILI by deriving mechanistic information on events preceding DILI, including their strength of association and longitudinal order.