P06-09: Computational modelling of integrated stress response and oxidative stress response for cellular adversity predictions

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Purpose: Adverse Outcome Pathway (AOPs) provide a conceptual understanding of mechanistic events occurring at multiple levels of biological organization. An AOP network is a sequence of Key Events (KE), based on their biological causality events are categorised into: Molecular Initiating Event (MIE), and Adverse Outcome (AO). The intuitive linear representation of events makes it an easy to adapt tool for regulatory toxicological assessment. In AOP development cycle, the initial hypothesis and proposed structure provide the backbone of the AOP. The AOPs backbone is further strengthen by the structured evidence gathered through literature resources, *in-vitro* and *in-vivo* experiments and by integration of information from peer-reviewed databases. Finding evidence for specific event, their assessment with selective Weight of Evidence (WoE) method, and harmonized integration with other information resources is a repetitive and expert driven task. To address this challenge, we propose an ontology driven text-mining tool which assists in automated extraction, followed by assessment and curation of textual mechanistic evidence from literature, reports and biological databases.

Methods: AOP-Bot is built on top of multiple components of ontology-based information extraction system. Multiple existing entity extraction systems, using rule-based and machine learning methods, have been reviewed and integrated in the "Bio Annotator" framework. In this approach, identified genes, protein, chemicals, disease, and species are normalized using the grounding system. The grounding system is built on top of biomedical ontologies such as Gene Ontology (GO), Disease Ontology (DO), HGNC, CHEBI and controlled vocabularies reflecting commonly used AOP terminology etc. Grounded entities are then integrated into a unified semantic representation, supporting linkage to existing data and use of background knowledge in subsequent analysis. Normalized entities are converted into vector form using pre-trained Word2vec model on PubMed and PMC corpora to recommend related entities. Relation between the entities is mapped based on the concept of co-occurrence and enriched with peer-reviewed databases such as KEGG, Signor, Wiki-Pathway, String, CTD etc. Extracted evidence are stored in databases, which can be further visualized by interactive network and facilitate the curation by the community.

Results: This tool provide AOP developers with a platform to generate hypothesis and gather evidence for hypothesis from various literature and biological databases. It is a community-driven tools, where endorsed evidence will be stored and given more weightage. AOP-Bot also provides a robust framework for the developer community to integrate the customized tools and curated database. The evidence database will also complement the available AOP-help finder tool with evidence weighting. AOP-bot will be catalogued as third-party tools of AOP-Wiki to provide evidence rich network.

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Computational modelling of integrated stress response and oxidative stress response for cellular adversity predictions

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Drug Induced Liver Injury (DILI) is a major problem for the drug development industry. We urgently need new methods to predict DILI early in the drug development process with high accuracy and without using animals. Computational approaches have the potential to contribute to this challenge because they can make predictions and increase mechanistic understanding. Exposure of cells to toxic compounds activates various cellular stress pathways and activity within these pathways is known to contribute to DILI. Therefore, computational models of stress pathway activity based on experimental measurements could be an important step in the improvement of adversity predictions. Because compounds rarely induce only a single stress pathway, such computational models may need to take interactions between different stress pathways into account.

We initially focussed on Nitrofurantoin, an antibiotic that is known to cause DILI and activates both the integrated stress response (ISR) and the oxidative stress response (OSR). We developed a computational model describing the protein dynamics of previously published data on HepG2 GFP-reporter cell lines for ATF4, CHOP, NRF2 and SRXN1 that were exposed to 6, 30, 60 and 120 μM of Nitrofurantoin for up to 60 hours. We modelled the compound kinetics using measurements of Nitrofurantoin in medium. Additionally, the model could describe ATP and GSH data that were generated in separate experiments, under the condition that GSH production was ATP dependent. To investigate the generalisability of this model we applied it to data of the same cell lines exposed to various concentrations of Diclofenac (10, 50.5, 101, 202, 404 μM) and Ketoconazole (6.5, 33 and 66 μM), both of which invoke the OSR and ISR. To correctly simulate the data of these compounds, only a limited number of parameters required adaptation, suggesting that a large part of the downstream response is compound independent.

We have also developed a computational model to relate cellular adversity quantitatively to ISR/OSR protein dynamics. Using Annexin V measurements in the same dataset we quantified the amount of healthy and apoptotic cells over time. Using the OSR-ISR model as input, we could correctly simulate the cellular adversity after exposure to the mentioned compounds. In conclusion, our analysis shows that the various developed models could become part of a novel pipeline of methods for DILI prediction.

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Chemical Effect Predictor: A tool to predict chemical toxicity using a multi-scale network

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Characterising the toxicity of chemicals and drugs in humans is not only important in the field of drug discovery but also for the development of new methods for chemical risk assessment. Currently, most of the predictive methods are addressed to a specific adverse effect or toxicity endpoint. Moreover, these methods are a "black box", providing limited insights into the mechanisms of toxicity of chemicals. System and network-based methods are suitable approaches to analysing and explaining how chemicals and drugs perturb biological systems. In this context, we present the Chemical Effect Predictor (CEP), a tool that leverages a multiscale biological network for the prediction of toxicity of compounds and the generation of mechanistic hypotheses for their mode of action. The model is based on a network that integrates different layers of information, such as associations among compounds, proteins, diseases, and biological processes. For each compound and disease, we compute network diffusion profiles, which