Applying In Silico Toxicity Models Across the Tox21 Chemical Universe

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In day-to-day life, people are continuously exposed to many chemicals through different exposure routes. Ideally, regulators will leverage all available toxicity information to make regulatory decisions on chemicals that will protect human health. Traditional toxicity testing relies on in vivo methods that are time-consuming, resource-intensive, and of questionable relevance to humans. Many available computational models can be applied to predict human toxicity for research and regulatory purposes to reduce time and resource expenditure. The goal of this collaboration was to apply and benchmark such models to the Tox21 chemical set. This set comprises approximately 10,000 chemicals including drugs, consumer products, and pesticides that have been tested in high-throughput screening assays in the U.S. Tox21 program. We applied three models to this chemical set to predict carcinogenicity and drug-induced liver injury. DeepCarc and DeepDILI are deep learning models that integrate five conventional machine learning algorithms into a neural network to generate probabilistic predictions for carcinogenicity and liver injury, respectively. We also applied carcinogenicity and mutagenicity models from the JANUS project (https://www.vegahub.eu/portfolio-item/janus/). We evaluated the confidence of each prediction as well as characterizing each model's applicability domain. Performance of all models was compared and physicochemical and structural properties of predicted active chemicals were defined. Our results suggest that these computational models can be used to rapidly screen large chemical libraries to prioritize potentially hazardous substances for further evaluation. Project was funded by NIEHS under Contract No. HHSN273201500010C.