Applying In Silico Toxicity Models Across the Tox21 Chemical Universe

S. Lee[1], A. Borrel[2], Kim To[2], Ting Li[3], Zhichao Liu[3], Weida Tong[3], E. Benfenati[4], A. Roncaglioni[4], A. Manganaro[5], K. Mansouri[6], N. Kleinstreuer[6]

[1]Duke University, Durham, NC, United States; [2]Inotiv, RTP, NC, United States; [3]National Center for Toxicological Research, FDA, Jefferson, AR, USA; [4]Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; [5]KODE, Pisa, Italy;[6]NIH/NIEHS/DTT/PTB/NICEATM, RTP, NC, United States

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 chemical use that will protect human health. Traditional toxicity testing generally 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 toxicity to reduce time and resources required for research and regulatory purpose. The goal of this collaboration is to apply and benchmark 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 the carcinogenicity and mutagenicity models from the “Joining environmental, ecotoxicological and toxicological Assessment of chemical substances with Non-testing methods within a Unified Screening” (JANUS) project. Confidence of each prediction was analyzed along with characterizing each model’s applicability domain. Performance of all models was compared and physicochemical properties of predicted active chemicals were defined. We found that the DeepCarc and JANUS models predicted a majority of the Tox21 compounds to have low carcinogenicity concern and DeepDILI predicted most to have a low risk of liver injury. The DeepCarc model predicted only 88 compounds to have a carcinogenicity probability greater than 0.9, whereas the JANUS carcinogenicity model predicted 263 chemicals as carcinogenic with high confidence. Structural analysis of compounds predicted to be carcinogenic in both models showed that most of them had low molecular weights, with a median weight of 105 g/mol for chemicals identified by DeepCarc and 183 g/mol for chemicals identified by JANUS. The DeepDILI model predicted 1,773 compounds to have a liver injury probability greater than 0.9. These chemicals had a higher molecular weight, with a median weight equal to 270 g/mol. For reference the full Tox21 chemical set has a median molecular weight equal to 231 g/mol. Our results suggest that these computational models can be used to rapidly screen large chemical libraries to prioritize potentially hazardous substances for further evaluation.

This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. The authors declare there exists no real or conflict of interest.

Keywords: QSAR, in vitro and alternatives, bioinformatics