Generation of Machine-Learning Models to Anticipate Endocrine Disruption

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Endocrine disruption is a major focus of toxicology research, and thus human estrogen and androgen receptors are key targets of interest. Downstream effects of receptor activation are difficult to anticipate without expensive, time-consuming *in vitro and in vivo* testing, so the Environmental Protection Agency (EPA) has prioritized alternative methods. Recently, the EPA has used high-throughput ToxCast/Tox21 screening data across relevant targets and processes to construct mathematical models capable of predicting the likelihood of estrogen or androgen pathway agonism/antagonism of a chemical. One limitation of these studies is the requirement of *in vitro* data for prediction; in contrast, machine learning methods are capable of prospective prediction from molecular structure alone. Particularly, Bayesian machine learning models (BMLMs) have shown broad applicability to drug discovery and toxicology applications. The current study describes the generation and evaluation of several groups of BMLMs using androgen and estrogen receptor data, including *in vitro* ToxCast/Tox21 data, EPA mathematical model output scores, and binary data considering bioactivity and cytotoxicity. Group performance was evaluated by cross-referencing external predictions of *in vitro* and *in vivo* reference chemicals. These predictions were evaluated to produce an overall active/inactive classification for each chemical, and classifications were then compared to the results reported by mathematical model studies published by the EPA. BMLM prediction accuracies ranged from 86-93% for reference chemicals of androgen and estrogen receptors, for both agonist and antagonist action. Exploration of other machine learning algorithms, including deep learning, was conducted on training datasets for further comparison. This study demonstrates that prospective prediction using ToxCast/Tox21 assays is achievable at the same level of accuracy seen in recent EPA publications, on the basis of molecular structure alone.