Toxicity Prediction Tools for Endocrine Disruption

Melissa A. Pasquinelli, Stephen Little, and James Rabinowitz, National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC

Experiments have shown that some classes of environmental chemicals act as agonists or antagonists of hormone receptors. We are developing a predictive tool using molecular modeling that can be used to screen for endocrine disrupting effects. This tool will aid the Agency in prioritizing data requirements for risk assessment. A key step is to determine whether these chemicals bind to hormone receptors, and if so, what the strength of the interaction is between the chemical and the receptor. Computational docking methods provide this type of insight. We can then study how this interaction impacts the function of the receptor and hence the toxicological mechanisms of these chemicals. A challenge for predictive methods in toxicology is the danger of false negatives. High-throughput computational docking methods commonly used in drug discovery yield too many false negatives to be a reliable predictive tool for toxicology. We have found that the false negative rate can be minimized by including sufficient protein flexibility during the docking calculations using the Induced Fit program. As a test case, we cross-docked the ligands and receptors from a series of crystal structures of the estrogen receptor (ER), including structures with estradiol bound (1GWR) and the antagonist tamoxifen bound (2BJ4). Rigid protein docking algorithms yield a false negative by predicting no binding of tamoxifen to the 1GWR structure of ER. However, when some protein flexibility is included for 1GWR, tamoxifen can bind properly in the ER binding site, and this structure compares well to the 2BJ4 structure. This tool was then applied to a set of experimentally tested environmental chemicals and produced a significant reduction in the false negative rate. The inclusion of protein flexibility dramatically increases computational cost, so its usefulness in high-throughput docking is limited. Potential methods for overcoming these limitations while conserving the accuracy will be discussed. *This abstract does not necessarily reflect EPA policy.*