

NCCT POST-DOCTORAL PROJECT DESCRIPTION

Project Number:	NCCT-09-09
Location:	Research Triangle Park, NC
Title of Project:	Understanding the Sources and Impact of Uncertainty in Predictive Models of Toxicity from the ToxCast™ Program
Brief Description of Research Project:	<p>The goal of the EPA ToxCast™ program is the prediction and understanding of environmental chemical toxicity. At the core is an effort to build predictors of a chemical's propensity to produce various kinds of toxicity. Predictors so far have been statistical models such as would be derived from machine learning methods (regression, neural networks, support vector machines, etc.) but may well be informed by more biological considerations in the future. The inputs to the predictors are parameters such as IC50s derived from a wide range of <i>in vitro</i>, high-throughput screening (HTS) biological assays. The predictors themselves are trained on data for a set of environmental chemicals with animal toxicity studies. Summaries of the results of the <i>in vivo</i> animal toxicity studies are used as the targets for training the predictors. A major issue with this approach is a lack of understanding of the variability inherent in the experimental results, <i>in vitro</i> and <i>in vivo</i>, and how that affects the usefulness of the resulting models.</p> <p>Ultimately, ToxCast™ results will be used for prioritizing chemicals for further testing, and potentially for more quantitative risk assessment purposes. It is critical for such applications that the uncertainties of ToxCast™ outputs be quantified. While the naïve output of a predictor may be a ranking of chemicals in terms of their predicted propensity to cause a given toxicity, when uncertainty is properly taken into account, that ranking may turn into a partial ranking, or a set of rankings and associated weights (e.g., the most likely ranking of chemicals A – D may be 1,2,3,4; while an almost equally supported ranking is 1,3,2,4; in this example, the data do not really distinguish the order of B and C relative to this sort of toxicity).</p> <p>Uncertainty arises in ToxCast™ from three components: through the HTS assays, both through biological variability and the measurement process; through uncertainty about the quantitative characterization of whole-animal toxicity, and uncertainty about the predictors themselves, which are derived from a kind of fitting process. The goal of this project is to quantify and understand all three sources of uncertainty, using a combination of conventional statistical methods, and mechanistic models to characterize biological variability, variability introduced by the measurement processes, and uncertainty about the choice of prediction model.</p>
High Priority Research Area:	Computational Toxicology
Projected duration of appointment:	3 years; with option to extend up to 4 years.
Educational requirements:	Ph. D. in applied mathematics, statistics, physics, biomedical engineering, computational/systems/quantitative biology or toxicology, or related field.

Specialized training and/or experience preferred:	Statistical or probabilistic quantitative methods, informatics, biological modeling, comfort with programming and large scale simulation.
Scientific contact/Principal Investigators*	<p><u>Name: R. Woodrow Setzer</u> <u>Email: setzer.woodrow@epa.gov</u> <u>Name: Richard Judson</u> <u>Email: judson.richard@epa.gov</u> Link to Biosketches: http://www.epa.gov/ncct/organization.html</p>