Automated Quantitative Toxicogenomic Dose-response Modeling

Authors: Lyle D. Burgoon[1], Darrell R. Boverhof[2], Timothy R. Zacharewski[1,2]
[1]Toxicogenomic Informatics and Solutions, LLC, United States
[2]Department of Biochemistry & Molecular Biology, National Food Safety & Toxicology Center, Center for Integrative Toxicology, United States

Keywords: dose-response modeling, toxicogenomic, automated modeling

Toxicogenomics applied to dose-response studies yields hundreds of putative biomarkers of exposure and toxicity. Phenotypic anchoring, functional annotation, and pathway analysis may distinguish differential gene expression associated with toxicity from adaptive responses or exposure indicators, allowing investigators to identify and develop novel quantitative mechanistically-based biomarkers of toxicity that can be used clinically or in population studies to more accurately monitor and assess risk. Typically linear or other low-dose extrapolation models are used to identify points of departure. Manually fitting these mathematical models is difficult and time-consuming, especially when many toxicogenomic responses (e.g., differential gene expression) do not exhibit sigmoidal, linear, or exponential dose-response characteristics. To facilitate high throughput model-fitting, we developed the ToxResponseModeler, a Java application capable of fitting: 1) sigmoidal, 2) linear, 3) quadratic, 4) exponential, and 5) modified guassian function models. The ToxResponseModeler identifies the most suitable model for each gene using the particle swarm optimization algorithm (PSO) to identify the optimal set of parameters to model the response of interest. The best fitting models are then compared, and the optimal model is chosen for each gene based on the Euclidean distance between the model predicted and observed data. Doses can then be calculated at n^{th} percent effective dose (ED_n) including points of departure, using the optimal model. Vehicle-based points of departure are also calculated based on the intersections of the 95% or 99% confidence intervals for the vehicle and dose-response data. Collectively, this yields a point of departure with a known confidence interval, based on measurement variance. The utility of ToxResponseModeler is demonstrated using published toxicogenomic dose-response data from the livers of TCDD treated C57Bl/6 mice.

This work has been supported in part by NIEHS Superfund grant P42 ES04911.

Point of Contact:
Lyle Burgoon
Chief Executive Officer
Toxicogenomic Informatics and Solutions, LLC
PO Box 27482
Lansing, MI 48909
517-882-0080
burgoonL@txisLLC.com