Dose-response analysis for gene-expression data

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Date and Time: 29.11.2021 at 16:15 via Zoom

Matt Wheeler: A Bayesian's Thoughts on Toxicogenomic Data

Abstract:

Toxicogenomic dose-response data provide unique challenges to statisticians and toxicologists when estimating a point of departure. Unlike univariate hazards that can be analyzed with conventional univariate dose-response modeling techniques, modeling transcription level dose-response curves using the same univariate approaches for tens of thousands of genes to produce a single organism-wide PoD is not appropriate. At the minimum, issues arise when using these methods to describe gene PoDs; that is, it is difficult to say what any single molecular-level change means at the organism or pathway level. Clustering methods may be preferred. Additionally, genes respond in groups, and any single dose-response model ignores correlations; thus, correlative models are more appropriate and would allow for pooling information between genes. Something that is not presently done. Moreover, as there are many modeled dose-responses, we should be wary of errant observations and use robust estimation methods, including Bayesian model averaging, to describe the dose-response relationships. Finally, developing research pipelines tailored to an individual Toxicologists' experiment is impossible due to current software limitations. This talk looks at these and other issues giving solutions to some and current research paths for others.

Scott S. Auerbach: Current Practices in Genomic Dose Response Analysis

Abstract:

In its current form genomic dose response analysis (GDRA) entails the application of traditional benchmark dose modeling to functional omic data (e.g., transcriptomics and metabolomics). In the context of toxicology, the purpose of GDRA is to estimate the potency of effect on all definable molecular processes (e.g., pathways, gene ontology biological functions) and subsequently to identify the critical molecular effect to serve as a molecular point of departure (mPOD) in a qualitative risk assessment process. Current practice of GDRA entails 3 steps.

First is a prefiltering process which is intended to identify omic features that respond to treatment. Often this entails the combined application of a trend test and an effect size filter. The prefilter step serves the purpose of reducing the computational burden in the subsequent dose-response modeling process and more importantly reduces false discovery. The second step in the process entails fitting multiple parametric dose response models to the features passing the prefilter. The goal of this step is to identify the single best model that describes the shape of the dose response (i.e., the best fit model). The best fit model for each feature is then used incombination with a predefined level of response (Benchmark response (BMR); typically, 1 standard deviation change relative to control) to estimate its potency of response to chemical treatment, i.e., its benchmark dose (BMD). In the final step the best models are filter for quality (i.e., how well they describe the data) and are then passed into predefined groups of features. In the case of transcriptomics, these groups are typically pathways (e.g., P53 pathway) or gene ontologies (e.g., fatty acid metabolism). Once populated with adequately fit features the groups are filtered to identify those that are deemed to be "activated" (i.e., adequately populated with dose-responsive features). Composite BMD estimates are then determined for each "activated" group. Typically, this entails determining the median BMD of all the dose responsive features in a group. This approach to GDRA has yielded results in which the BMD of the most sensitive gene set (in the case of transcriptomics), aka mPOD, from a short term in vivo genomic dose response study provides a relatively accurate estimate of apical potency from longer, more resource intensive guideline toxicological assessments. Hence there is interest in using this approach to enhance the efficiency of risk assessment.