

## Combining Bioinformatics and Computational Modeling for Discovery of Critical Regulatory Pathways in Neurodevelopmental Toxicity

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Systems biology relies on the integration of disparate datasets to gain novel insights. Our research has focused on development of computational approaches allowing for efficient integration and analysis at the molecular level. Through utilization of the growing gene expression and sequence databases, exploration of common mechanisms of neurodevelopmental disorders and neurodevelopmental toxicity in the context of critical regulatory pathways is possible. These techniques have been useful in elucidating gene regulatory relationships critical for the development of the forebrain, a sensitive target for many neurodevelopmental toxicants. Algorithms based on Bayesian statistics are particularly well suited for identifying gene regulatory networks (GRNs). First, by combining results from microarray analysis after either gain of function (whole embryo electroporation) or transgenic loss of function of the proneural bHLH genes *Ngn2* and *Mash1*, potential target genes for these critical regulators of neurogenesis are identified. Novel co-factors and co-regulators, including CREB, Tcf/Lef, Pou-domain containing transcription factors, *Sox9*, and *Mef2a*, are predicted through a bioinformatic characterization of conserved regulatory elements in promoter regions of target genes. Application of a Bayesian based network analysis results in a GRN predicting optimal connectivity between putative targets, co-factors, and co-regulators. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin TCDD induced neurodevelopmental toxicity is then analyzed in the context of this regulatory network, identifying critical molecular targets. This approach demonstrates integration of experimentation with bioinformatics can provide an efficient guide for both hypothesis testing and hypothesis generation.

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