Use of mutual information theory to decipher the impacts of multiple stressors from molecular through whole-organism level effects.

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The complex nature of multiple stressor effects in biological systems requires new approaches for integrating and drawing inferences from highly diversified data sets. In the present study, we leverage a multiple-stressors investigation in the Western fence lizard (WFL, *Sceloporus occidentalis*) where combinations of climate change and habitat degradation related stressors including malarial parasitism, decreased basic resource (food) availability and exposure to chemical contamination (trinitrotoluene, TNT) were investigated in laboratory bioassays. Resulting datasets from this work include 29 toxicological endpoints ranging from whole organism level effects to blood chemistry parameters for single-stressor and pairwise-stressor exposures. In concert, microarray-based transcript expression datasets were also generated based on these bioassays to provide effects assessment at the molecular and metabolic pathway-level of organization. The data sets were merged and standardized using z-scores and then the popular mutual information theory based algorithm “context likelihood of relatedness” and a new in-house algorithm “R_REVEAL” were utilized to reverse engineer the network-based relationships among transcription factors, protein-coding genes, protein levels in blood serum and ultimately, whole organism-level effects. An illustrative example of analysis results was identification of high network interconnectivity between genes involved in heme metabolic pathways and blood-hemoglobin levels in TNT exposures. Specifically, expression of genes involved in hemoglobin genesis increased in TNT exposures due to TNT-induced red blood cell RBC lysis and subsequent anemia. Additional components of this network included genes involved in hematopoiesis where gene expression was again increased. The overall response indicates a compensatory response to RBC loss where the molecular machinery of the organism has been engaged to produce new RBCs to mitigate anemia. Additional stressors (food limitation and malarial infection) tended to reduce this overall response. This and several other network-based observations will be presented to illustrate the utility of mutual information theory for providing insights given complex multi-stressor, multi-dimensional datasets.