

## **Control Theory and Dose Response Transition in Anti-Stress Gene Regulatory Networks**

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To maintain a stable intracellular environment, cells utilize complex and specialized defense systems against a variety of external perturbations, such as electrophilic stress, heat shock, and hypoxia. Irrespective of the type of stress, many adaptive mechanisms contributing to cellular homeostasis appear to operate through gene regulatory networks that are organized into negative feedback loops. In general, the degree of deviation of the controlled variables, such as electrophiles, misfolded-proteins, and oxygen, is first detected by specialized sensor molecules, and then the signal is transduced to specific transcription factors. Transcription factors can regulate the expression of a suite of anti-stress genes, many of which encode enzymes functioning to counteract the perturbed variables. The objective of this study was to explore, using control theory and computational approaches, the theoretical basis that underlies the steady-state dose response relationship between cellular stressors and intracellular biochemical species (controlled variables, transcription factors, and gene products) in these gene regulatory networks. Our work indicated that the shape of dose response curves (linear, superlinear, or sublinear) depends on changes in the specific values of local response coefficients (gains) distributed in the feedback loop. Multimerization of anti-stress enzymes and transcription factors into homo- dimers, trimers, or even higher-order multimers, play a significant role in maintaining robust homeostasis. Moreover, our simulation noted that dose response curves for the controlled variables can transition sequentially through four distinct phases as stressor level increases: initial superlinear with lesser control, superlinear more highly controlled, linear uncontrolled, and sublinear catastrophic. Each phase relies on specific gain-changing events that come into play as stressor level increases. The low-dose region is intrinsically non-linear, and depending on the level of local gains, presence of gain-changing events, and degree of feedforward gene activation, this region can appear as superlinear, sublinear, or even J-shaped. The general dose response transition proposed here was further examined in a complex anti-electrophilic stress pathway, which involves multiple genes, enzymes, and metabolic reactions. This work would help biologists and especially toxicologists to better assess and predict the cellular impact brought about by biological stressors.

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