Network Motif Basis of Threshold Responses

Qiang Zhang[1], Sudin Bhattacharya[1], Rory B. Conolly[2], Harvey J. Clewell III[1], Norb E. Kaminski[3], and Melvin E. Andersen[1]

[1]*Institute for Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Durham, NC 27709, USA*

[2]*Integrated Systems Toxicology Division, NHEERL, USEPA, Durham, NC 27711, USA*

[3]*Pharmacology & Toxicology, Michigan State University, East Lansing, MI 48824, USA*

There has been a long-running debate over the existence of thresholds for adverse effects. The difficulty stems from two fundamental challenges: (i) statistical analysis by itself cannot prove the existence of a threshold, i.e., a dose below which there is no effect; and (ii) there has been little progress in developing a more mechanistic understanding of how threshold phenomena might arise. We believe that mechanistic evidence for the existence of thresholds has to come from studying the underlying biological networks as nonlinear dynamical systems. We computationally analyzed the abilities of several intracellular biochemical network motifs to generate threshold responses. These motifs include proportional and integral feedback control, incoherent feedforward control, saddle-node, pitchfork, and transcritical bifurcations, and ultrasensitivity. For each motif, we present mathematical models to illustrate the basis for threshold responses. We conclude that integral feedback, feedforward and transcritical bifurcations can generate thresholds. Other motifs, such as proportional feedback and ultrasensitivity, can give rise to "threshold-like" responses where the low-dose region has a nonzero slope that may not differ significantly from zero slope. Feedforward control can also produce nonmonotonic responses. In addition, we show that variability in biological parameters does not necessarily obscure thresholds and linearize population-averaged dose responses. In conclusion, thresholds can be understood at the level of network motifs, the study of which is necessary for the emerging, toxicity pathway-based approach for chemical safety assessment. *This is an abstract or a proposed presentation and does not necessarily reflect USEPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.*