

Computational Investigation of Dose Response for MAPK-Regulated Steroid Hormone-Mediated Gene Expression

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The possibility that environmental chemicals can disrupt normal functions of the endocrine system is a public health and regulatory concern. Translating this concern into quantitative assessments of potential human health risks requires knowledge of the shapes of dose-response curves, particularly in regions of low-incidence that are of greatest public health concern. In this project we developed computational models of biochemical networks that control steroid hormone-mediated gene expression. The models encode hypothesis about the topology (i.e., the maps of connections between interacting molecules) and the regulatory control structures of these networks. A major focus of this project was on the classical pathway for steroid hormone-mediated gene expression and on the role of mitogen activated protein kinase (MAPK) mediated protein phosphorylation processes as a co-regulator of steroid-hormone regulated gene expression. The project used various computational models, including stochastic differential equations and Boolean networks, to investigate how these phosphorylation events modulate the dose response for steroid receptor-mediated gene expression. The integrated models dissected the effect of each individual network component on dose responses in terms of amplification, sensitivity, and shape. These networks showed quite complex dose-response behaviors, including binary switching, that have been seen experimentally. These complex behaviors, in turn, produced complexities in dose-response curves and challenges for human health risk assessment. This project also developed software tools for visualization of the outputs of the computational model. Just as laboratory results are examined visually at the level of Western Blots and red-green plots from gene array experiments, so simulations of biochemical networks can be visualized in the same way and thereby facilitate communication between experimental and computational biologists.

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Presentations

Breen, M. S., Zeng, Y., Zhang, Q., McDougal, J. N., Shi, P., and Conolly, R. B. (2006). Chemically-induced skin irritation: Computational model of intracellular signaling pathways that mediate

Zhang, Q., Mundy, W., and Conolly, R. (2006). Dynamics of extracellular signal-regulated kinase (ERK) activation in developing cerebellar granule cells (CGS): a systems biology-oriented study. *The Toxicologist* 90(S-1): 433. (Abstract 2116).

Peer-reviewed publication(s):

Zhang, Q., Andersen, M. E., and Conolly, R. B. (2006). Binary gene induction and protein expression in individual cells. *Theor. Biol. Med. Model.* 3: 18.

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