Conference title: IUTOX – MEXICO2016
Workshop Title: "Developmental toxicology, Different Models, Different endpoints'"
Date: October 3-5, 2016
Location: Merida, Yucatan, Mexico

"Computer Simulation of Developmental Processes and Toxicities"

Thomas B. Knudsen, PhD

National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC USA 27711

Standard practice for assessing developmental toxicity is the observation of apical endpoints (intrauterine death, fetal growth retardation, structural malformations) in pregnant rats/rabbits following exposure during organogenesis. Recapitulating the complexity of embryogenesis poses a challenge for the translation of high-throughput screening (HTS) data, captured by ToxCast/Tox21 in human cell-based assays, into predictive models of developmental toxicity. Utilizing an open source CompuCell3D.org modeling platform, we constructed cellular agent-based models from the known biology of several different embryological systems. These embryologically-inspired computer models were structured to recapitulate the kinematics of complex cell signaling networks and to simulate critical developmental transitions, including: VEGF-mediated angiogenesis (angiodysplasia), androgen-mediated urethral closure (hypospadias), TGFb-mediated tissue fusion (cleft palate), and retinoid-mediated limb outgrowth (ectrodactyly). The simulation models are numerically responsive to perturbation, hence amenable to various computational methods of data processing for translating real (HTS) or synthetic (what-if) chemical effects data to mode of action, point of departure, and genetic and early lifestage susceptibilities. These models are now being applied to the diversity of assays used to assess developmental toxicity in EPA's ToxCast program. For example, a newly added metabolomics-based platform that predicts the exposure-based potential for developmental toxicity (pDT) in a human system with ~83% accuracy (Stemina) yielded a hit on 138 ToxCast chemicals (~13% of the 1065 chemicals tested to date). A heuristic computational intelligence framework that recapitulates the kinematics of dynamical cell signaling networks in the embryo translates these in vitro predictions into system-specific developmental toxicity. Together with exposure-based methods, these in silico models yield a probabilistic assessment for chemical effects based solely on ToxCast data for toxicity at various stages of embryo-fetal development. (This work does not reflect EPA policy).