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Workshop: "Advancing Computational and Systems Toxicology for the effective design of safer chemical and pharmaceutical products"

Computational Systems Toxicology: recapitulating the logistical dynamics of cellular response networks in virtual tissue models

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Translating *in vitro* data and biological information into a predictive model for human toxicity poses a significant challenge. This is especially true for complex adaptive systems such as the embryo where cellular dynamics are precisely orchestrated in space and time. Computer cell agent-based models (ABMs) that incorporate the logistical dynamics of complex signaling networks built in CompuCell3D can be wired to recapitulate key morphogenetic events. An array of embryologically-inspired ABMs or 'virtual embryo' provides an approach to *in silico* generation of developmental phenotypes or 'cybermorphs' by electronically manipulating the underlying biological network. By imputing toxicity profiles from *in vitro* assays on key genes, pathways or cellular behaviors, a series of concentration-response curves may be translated into predicted adverse outcomes for developmental toxicity. This provides a novel approach to translate concentration-response profiles from high-throughput screening (HTS) libraries such as ToxCast/Tox21 into a probabilistic prediction of developmental toxicity. Combinations can be tested *in silico* for cumulative or aggregate exposures as well as chemical-interactions with nonchemical stressors. Model outputs to date include quantitative predictions of effects on VEGF-mediated angiogenesis (angiodysplasia), androgen-mediated urethral closure (hypospadias), and TGFß-mediated tissue fusion (cleft palate). Other virtual tissue models underway include the limb-bud (phocomelia), endocardial cushion (valvulo-septal defects), and neurovascular unit (microcephaly). Disclaimer: This abstract does not reflect EPA policy.