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 TGFβ-mediated tissue fusion (cleft palate). Other virtual tissue models underway include the limb-bud (phocomelia), endocardial cushion (valvulo-septal defects), and neurovascular unit (microcephaly).

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