Virtual Embryo: Cell-Agent Based Modeling of Developmental Processes and Toxicities

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Science Context

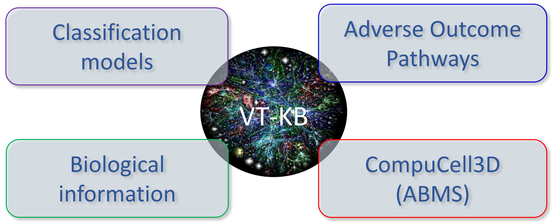
(1) Spatial regulation of cellular dynamics is fundamental to morphological development. As such, chemical disruption of spatial dynamics is a determinant of developmental toxicity.

(2) Incorporating spatial dynamics into AOPs for developmental toxicity is desired but constrained by the lack of a suitable computational environment for *in silico* embryogenesis.

(3) EPA's 'Virtual Embryo' provides a heuristic platform that translates *in vitro* data from ToxCast bioactivity profiles into probabilities of a predicted adverse outcome.

Disclaimer: this poster does not reflect EPA policy.

Approach and Integration



Classification models. Identify relevant molecular features from high-throughput screening (HTS) ToxCast data.

Adverse Outcome Pathways (AOPs). Elucidate evidence-based links between molecular initiating event and apical endpoint.

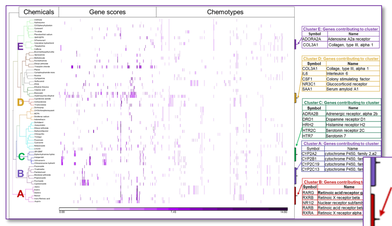
Biological information. Information mining and extraction from the extant literature → virtual tissue knowledgebase (VT-KB).

CompuCell3D. Agent-based modeling and simulation (ABMS) of morphogenetic (agents = cells):
- heterogeneous interactions that enable emergent organization;
- logistical dynamics of optimality (normal phenotype).

Model outputs. Mechanistic analysis of system fragility and fault tolerance to chemical lesion(s) → 'cybermorphs':
- define the criticality of misbehaving cells in an AOP;
- unravel spatial dynamics of morphogenetic-toxicological events;
- translate concentration response → point of departure (PoD).

Case Studies and Results

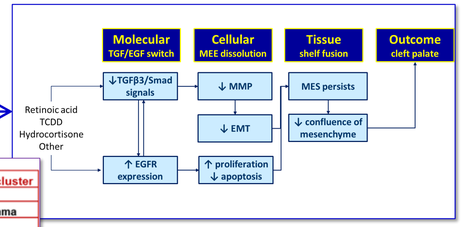
FY16: Modeling Cleft Palate: *"bringing an AOP to life"*



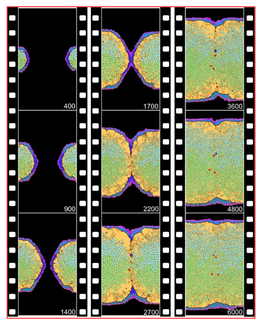
Classification model based on 63 cleft palate teratogens in ToxCast

Cluster B: Genes contributing to cluster

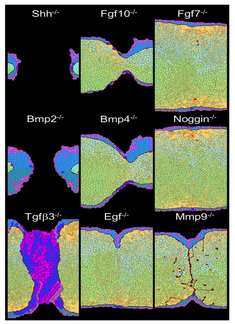
Symbol	Name
RARG	Retinoic acid receptor gamma
RXRB	Retinoic X receptor beta
NR1I2	Nuclear receptor subfamily 1, I2
RARB	Retinoic acid receptor beta
RXRA	Retinoic X receptor alpha



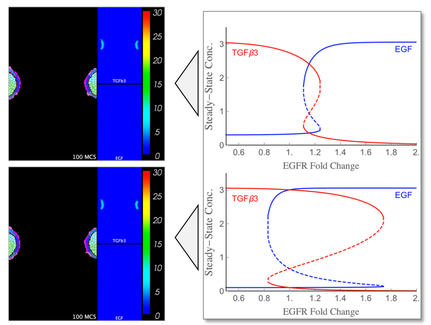
AOP for Medial Edge Epithelial (MEE) seam breakdown



ABMS: MEE seam breakdown

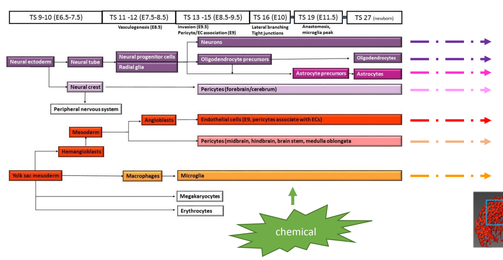


Cybermorphs: hacking the control network

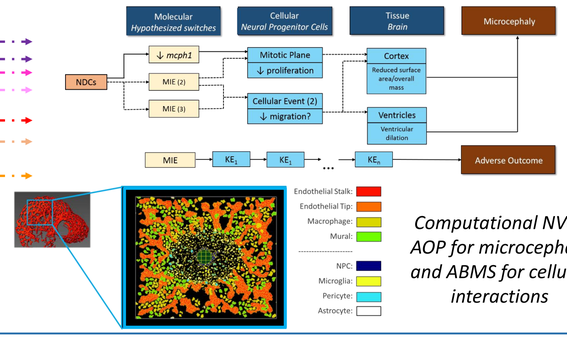


Modeling Retinoic Acid exposure: tipping points linked to manipulation of the hysteresis switch

FY17: Modeling the Neurovascular Unit (NVU): *"logistical dynamics of developmental toxicity"*



Developmental ontology of the Blood-Brain Barrier (BBB): toward a classification model for BBB development linked to chemical effects on microglial signaling.

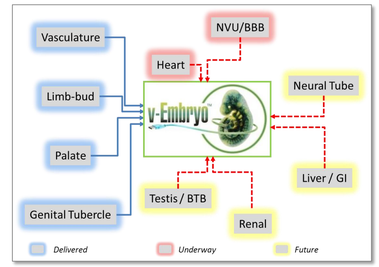


Computational NVU: AOP for microcephaly and ABMS for cellular interactions

Anticipated Products/Impacts

Virtual Embryo Products:

- ABMS delivered for angiogenesis [1], urethrogenesis [2], palatogenesis [3], and limb outgrowth [4] (FY14-16).
- ABMS underway for neurovascular development (FY17) and heart development (FY18).
- Design, development and implementation of a Virtual Tissue Laboratory System infrastucture (*leidos*) will enable high-performance computing and engage translation.



Impacts:

- Biologically-relevant *in silico* models translate mechanistic information generated at a basic level of research (ToxCast) into recognizable phenotypes (cybermorphs) predicted at a higher level.
- Systems represented dynamically bring AOPs to 'life,' which in a Children's Environmental Health setting can be used for mechanism-specific developmental toxicity as part of an Integrated Testing Strategy for rapid screening purposes.

References

1. Kleinstreuer N, Dix D, Rountree M, Baker N, Sipes N, Reif D, Spencer R, and Knudsen T (2013) A computational model predicting disruption of blood vessel development. PLoS Comput Biol 9(4): e1002996.
2. Leung MC, Sipes NS, Baker NC, Wolf CJ, Abbott BA, Seifert AW, Hutson MS, Darney SP, Spencer RM and Knudsen TB (2016) Computational embryology and predictive toxicology of hypospadias. Reprod Toxicol 64: 151-161.
3. Hutson MS, Leung MCK, Spencer RM, Baker NC and Knudsen TB (2016) Computer modeling and simulation of palatal fusion and disruption. Chem Res Toxicol (submitted, in revision).
4. Ahir B, DeWoskin RS, Baker NC, Spencer RM and Knudsen TB (2017) Developmental toxicity simulated in a dynamic virtual embryo model of early limb-bud outgrowth. (in preparation).