Mechanistic modeling of developmental defects through computational embryology

Abstract #409

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WC10 – Seattle, August 22, 2017

DISCLOSURES

FUNDING:

US EPA/ORD Chemical Safety for Sustainability (CSS) Research Program

Contracts GS-35F-4550G (ASA) and 261D0054 (Leidos)

EPA/ORD/NCCT contract EP-D-13-053 with Vala Sciences

EPA/ORD/NCCT contract EP-D-13-055 with Stemina Biomarker Discovery

EPA/ORD/NCCT contract EP-D-13-056 with ArunA Biomedical

Organotypic Culture Models for Predictive Toxicology Centers (EPA/STAR)

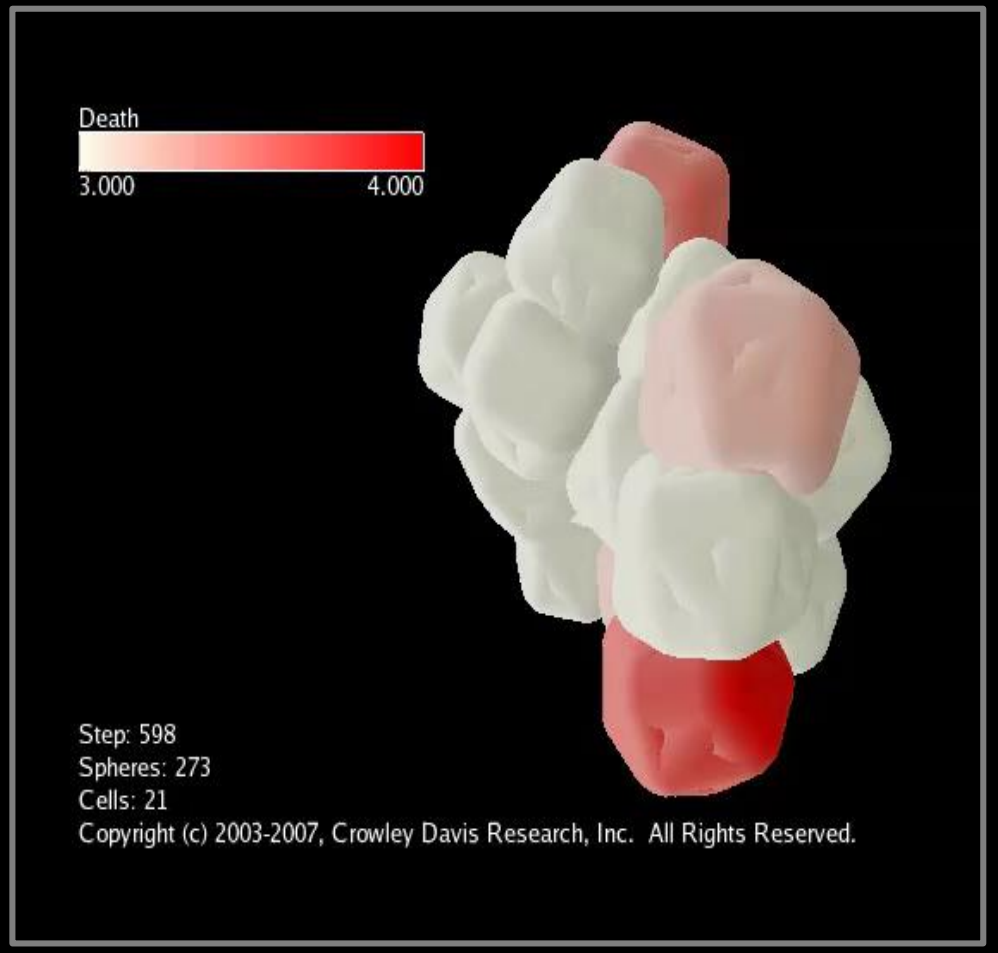
This research is funded by U.S. EPA - Science To Achieve Results (STAR) Program Grant #

DISCLAIMER: The views expressed are those of the presenter and do not reflect Agency policy.

CONFLICTS OF INTEREST: none to disclose.

Anatomical homeostasis in a self-regulating Virtual Embryo

Mouse Morula
SOURCE: Science Photo Library



SOURCE: Andersen, Newman and Otter (2006) Am. Assoc. Artif. Intel.

Breathing life into a ‘Virtual Embryo’

- CompuCell3D is an open source C++ software environment for solving biocomplexity problems - developed by James Glazier and colleagues at Indiana University.

- Mathematically integrates kinematic (chemical fields) with dynamic (cellular response) for cell-autonomous ‘agents’ that interact in a shared microenvironment.

- Control systems are transparently encapsulated with Python and dynamically-loaded at runtime to execute steppables for individual cell behaviors and extracellular forces:

  - cell growth, proliferation, adhesion, differentiation, polarization, motility, apoptosis, …
  - ECM synthesis, reaction-diffusion gradients, clocks, mechanical boundaries, fluid flow, …

- The simulation self-organizes into phenotypes that reflect emergent properties of the system as a possible solution to specific cellular lesions.

In a nutshell …

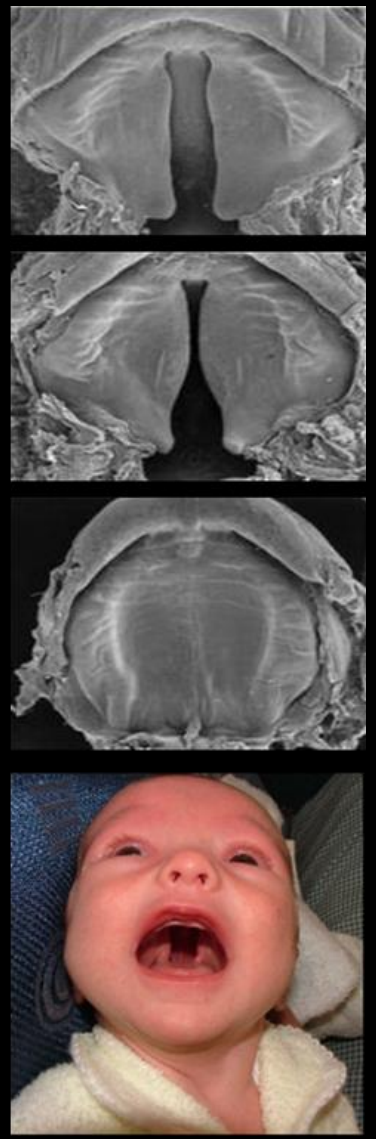
- Large data streams from ToxCast provide an alternative testing paradigm but require computational models to integrate HTS data with biological understanding.

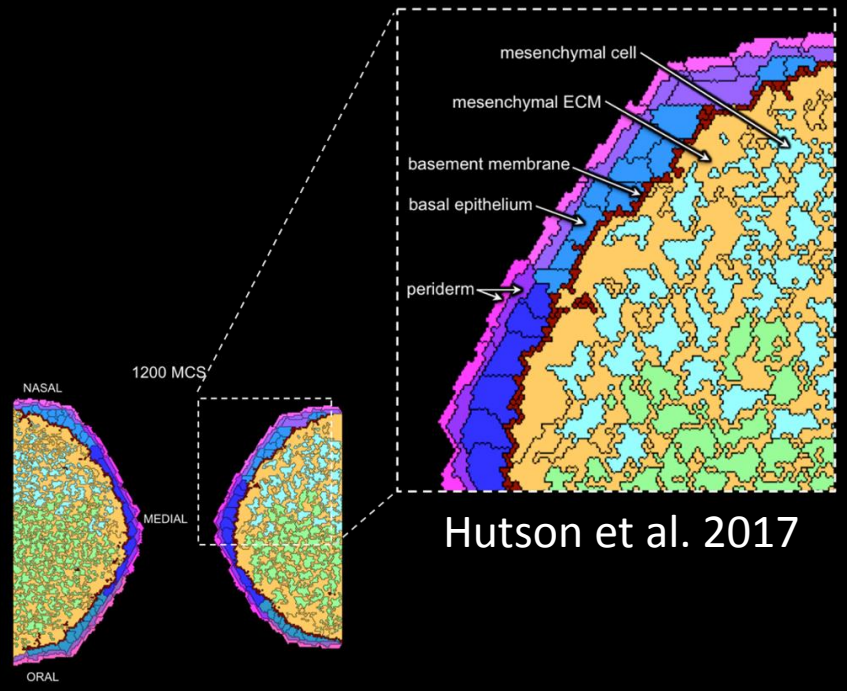
- We are building and testing **Agent-Based Models** (ABMs) of human development that can be executed *in silico* with the CompuCell3D to:

  - reconstruct tissue development cell-by-cell and interaction-by-interaction;
  - qualitative prediction of virtual phenotypes (cybermorphs);
  - impute ToxCast data into a virtual-tissue computer simulation;
  - and return quantitative predictions of teratogenicity.

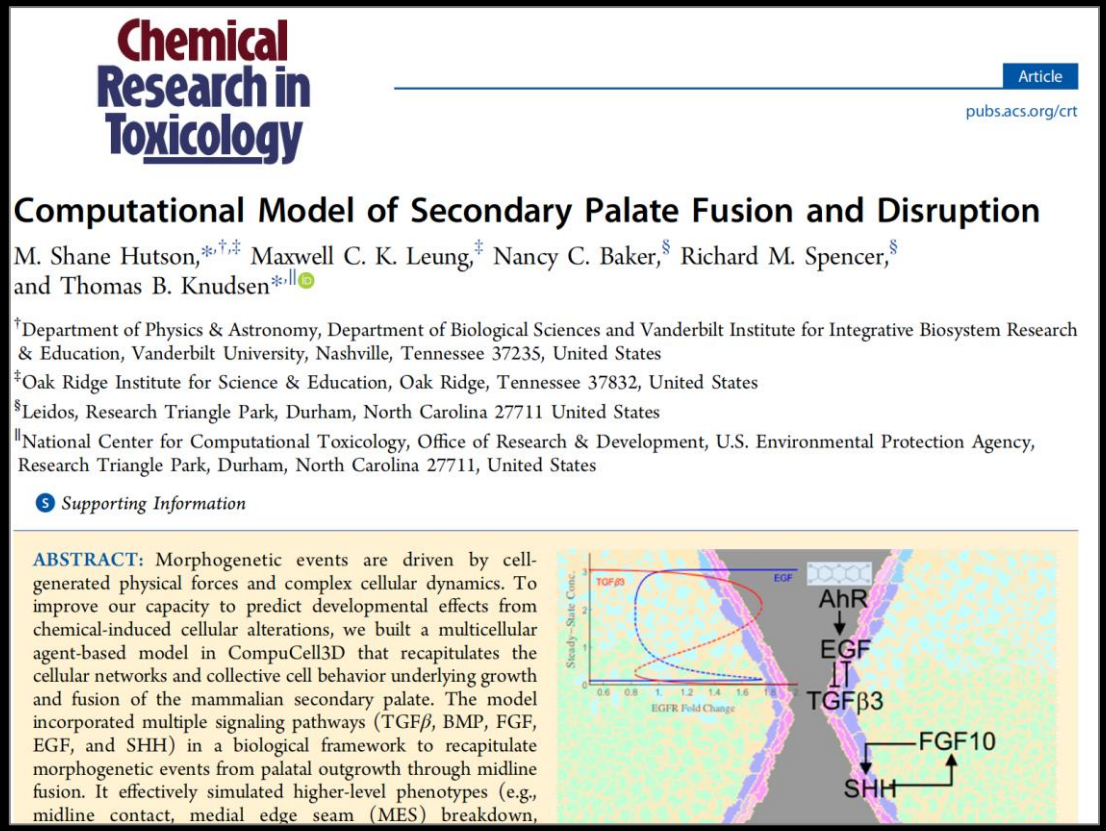
- These simulations provide a systems-based approach that is 3R's-compliant and amenable to forward-engineer and reverse-engineer developmental toxicity.

1. Reconstructing tissue development: *cleft palate as an example*





Hutson et al. 2017



Chemical Research in Toxicology

Article

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Computational Model of Secondary Palate Fusion and Disruption

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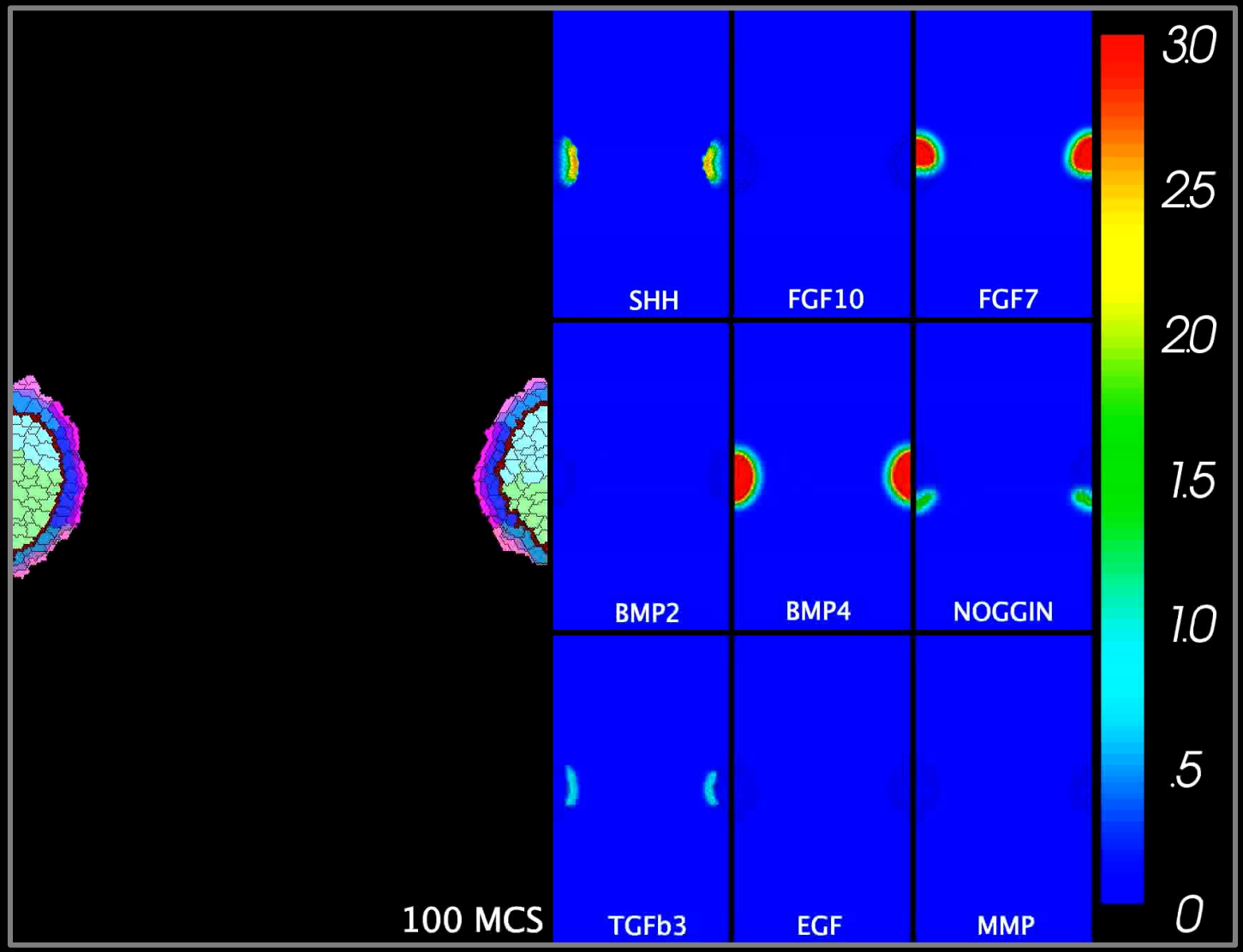
Supporting Information

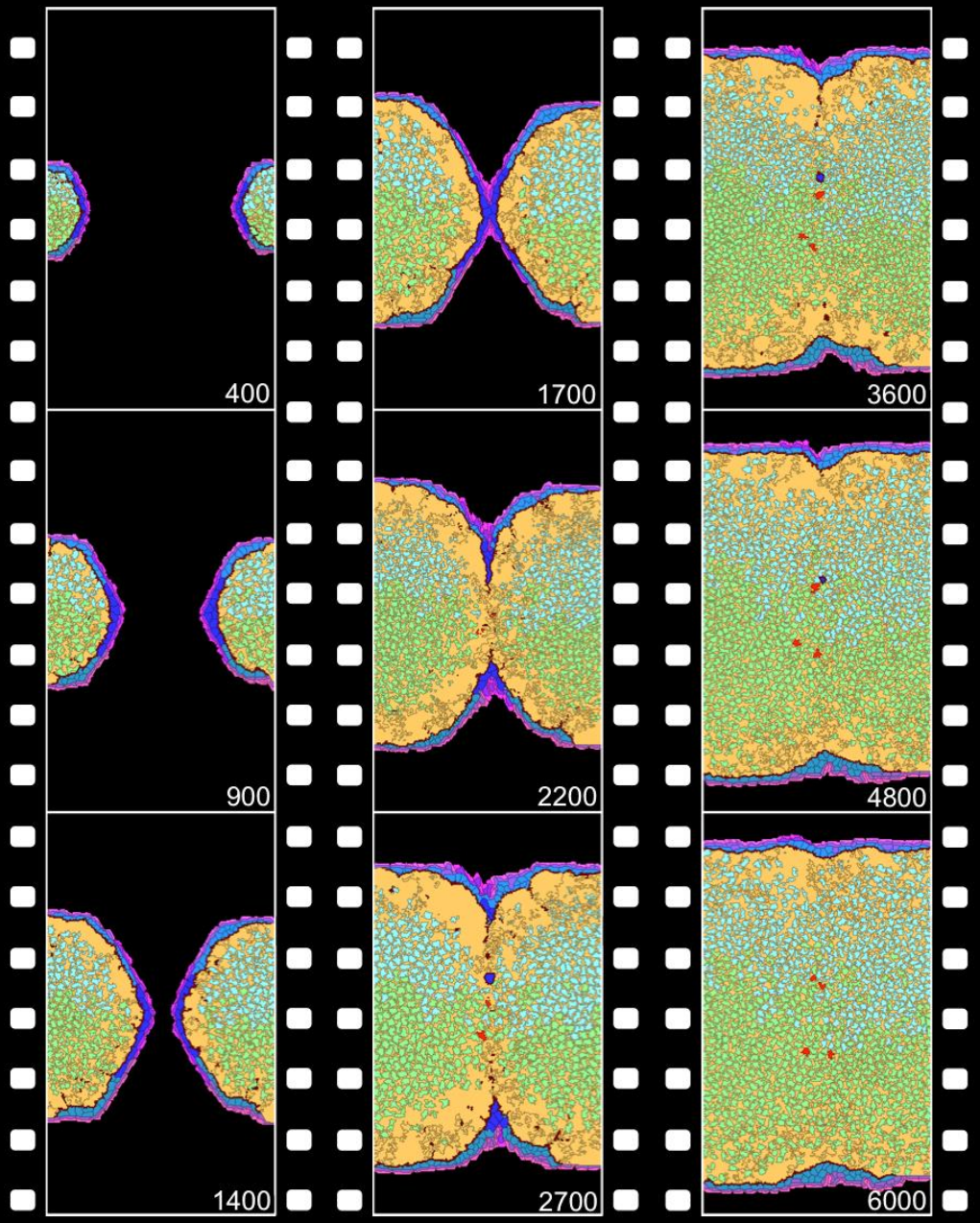
ABSTRACT: Morphogenetic events are driven by cell-generated physical forces and complex cellular dynamics. To improve our capacity to predict developmental effects from chemical-induced cellular alterations, we built a multicellular agent-based model in CompuCell3D that recapitulates the cellular networks and collective cell behavior underlying growth and fusion of the mammalian secondary palate. The model incorporated multiple signaling pathways (TGFβ, BMP, FGF, EGF, and SHH) in a biological framework to recapitulate morphogenetic events from palatal outgrowth through midline fusion. It effectively simulated higher-level phenotypes (e.g., midline contact, medial edge seam (MES) breakdown,

- Most prevalent craniofacial birth defect (annually ~7000 newborns in the USA), linked to the disruption of outgrowth and fusion of the embryonic palatal processes.

ABM for palatal outgrowth and fusion

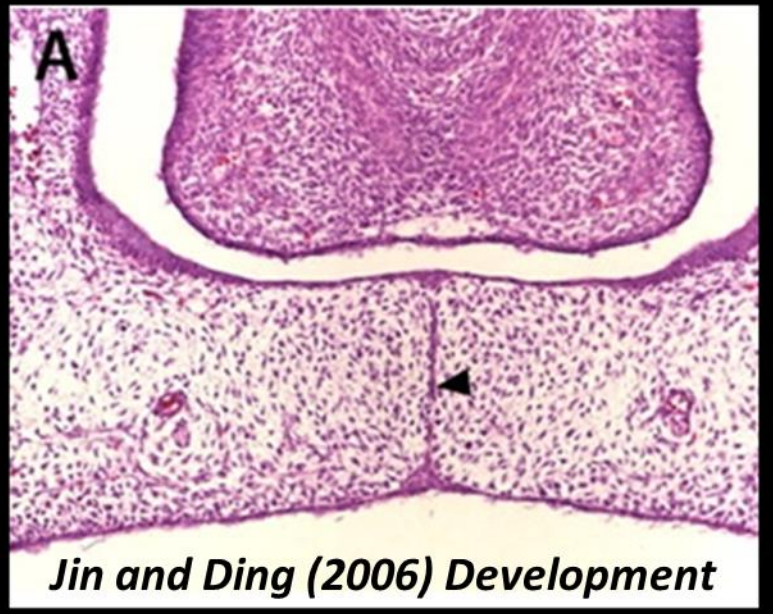


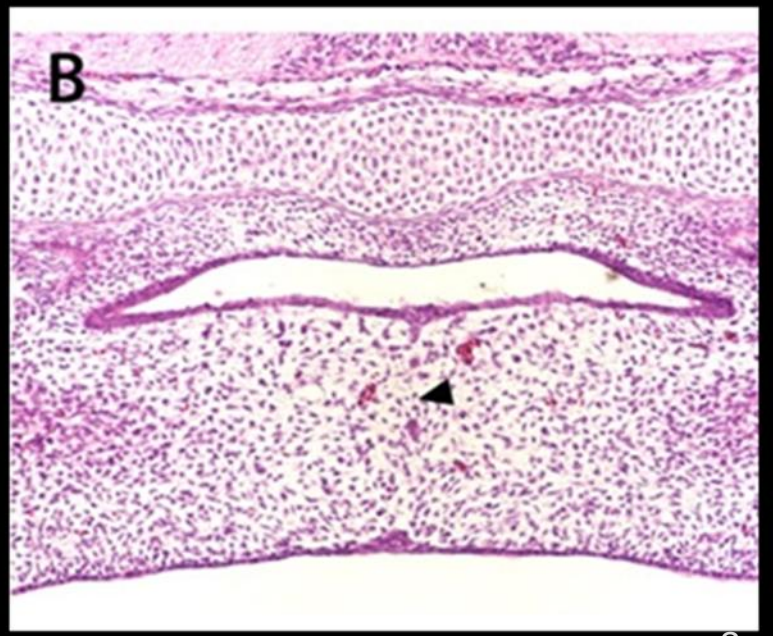
Hutson et al. (2017) Chem Res Toxicol



in silico

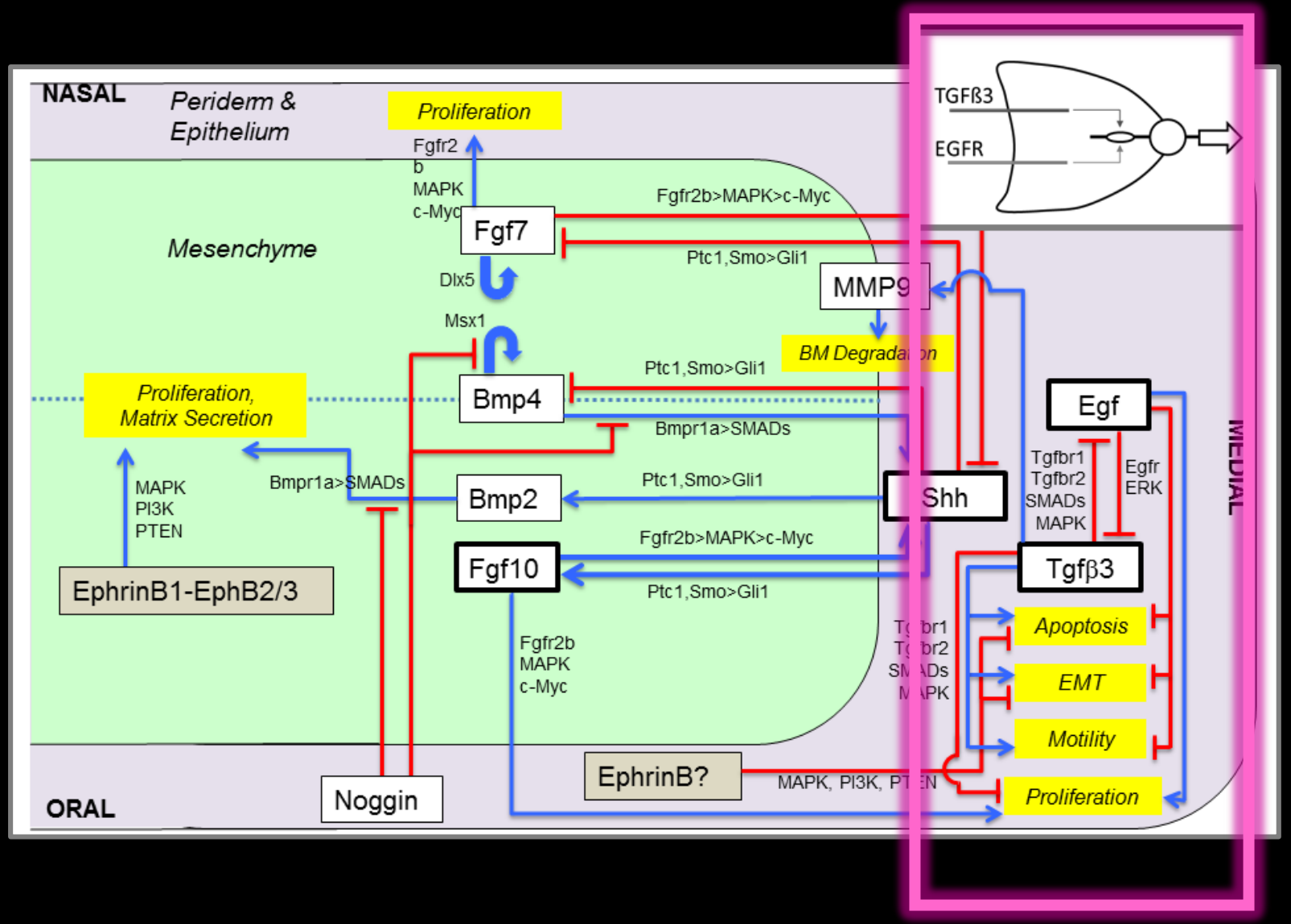
in vivo

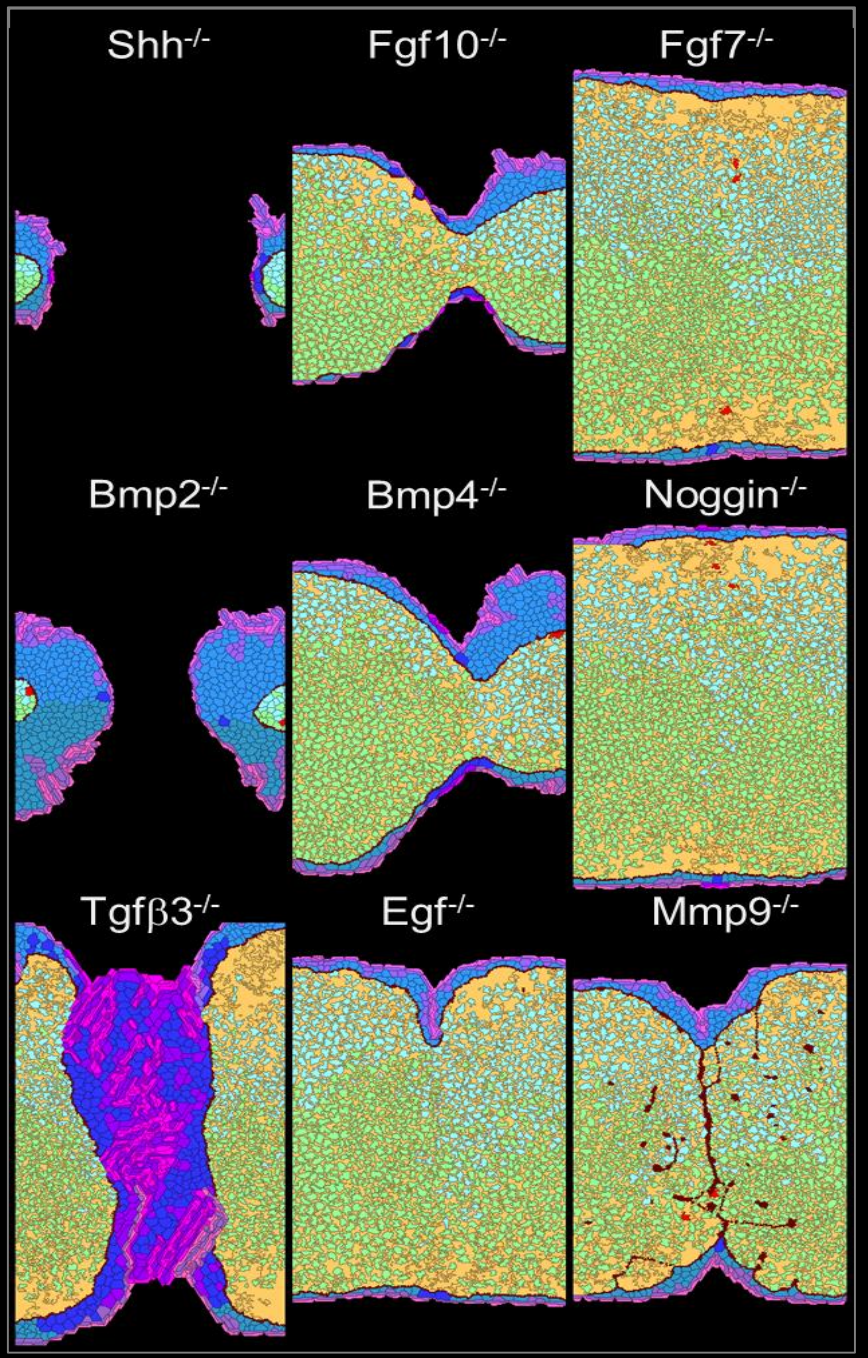




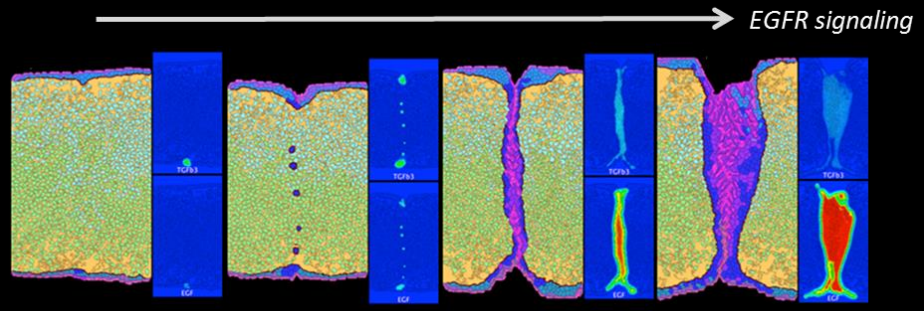
2. Qualitative prediction of phenotype

hacking the control network → 'Cybermorphs'



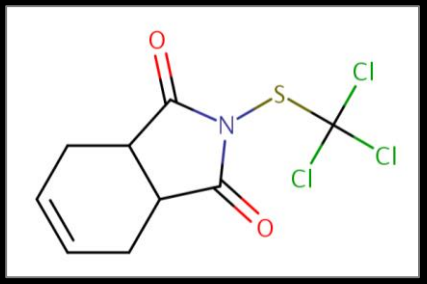


3. Imputing ToxCast data into the model

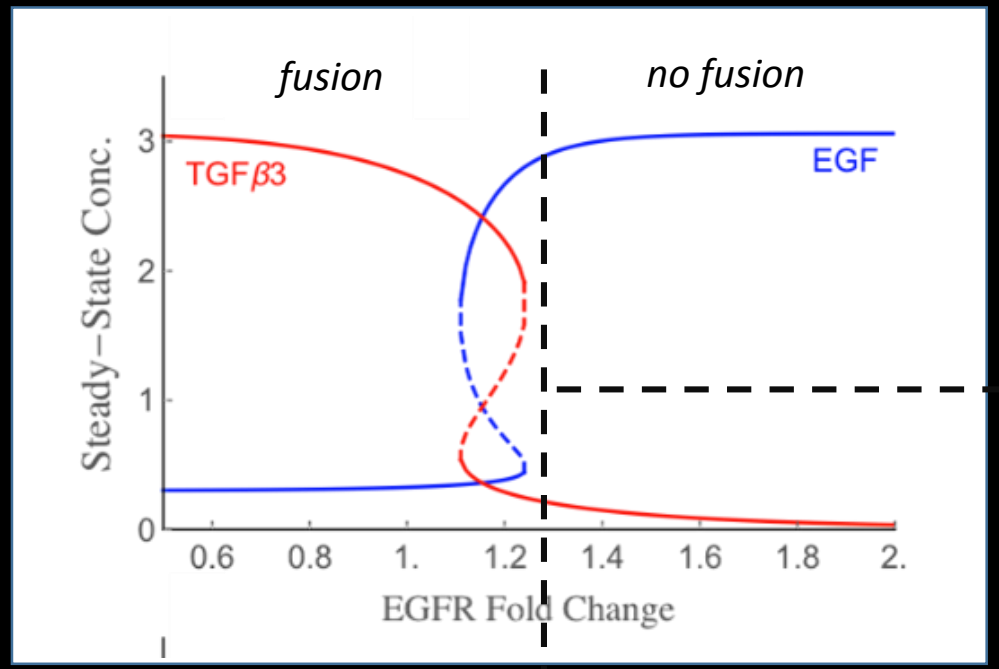


Captan

ToxRefDB NOAEL = 10 mg/kg/day
(rabbit) LOAEL = 30 mg/kg/day

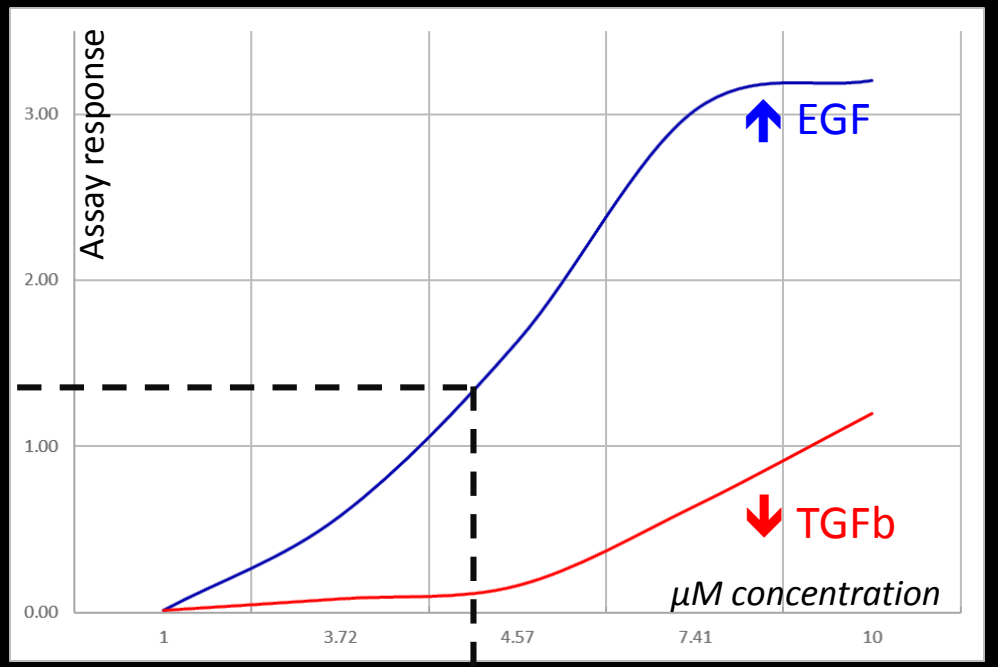


Switch dynamics



virtual tipping point ~1.2x EGFR

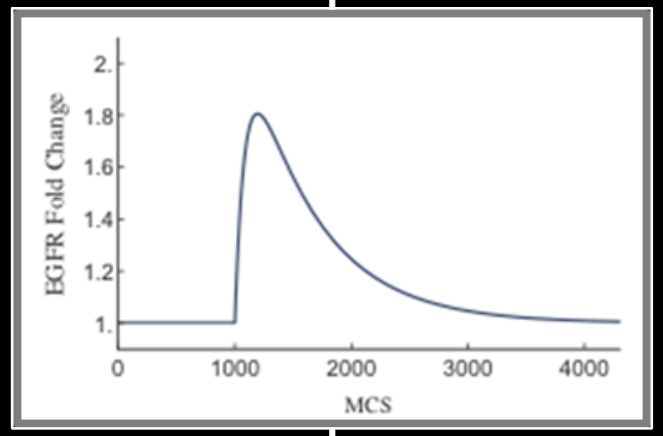
ToxCast dose response



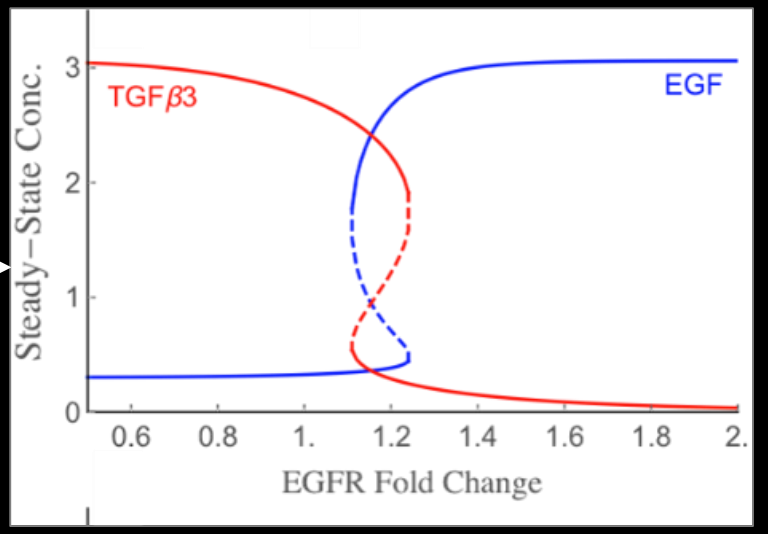
tipping point ~ 4 µM Captan

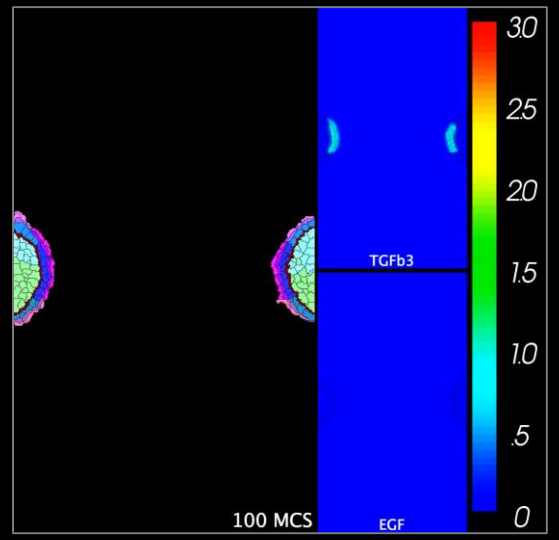
4. Quantitative prediction of teratogenicity: *messin' with the switch*

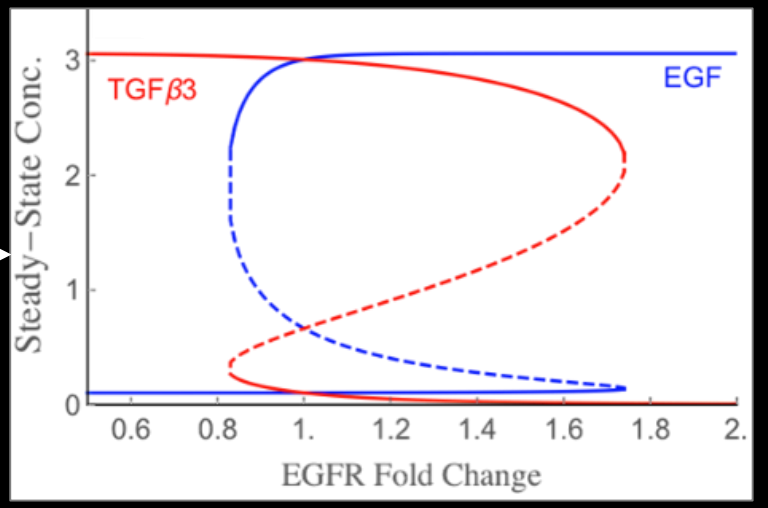
narrow bifurcation zone

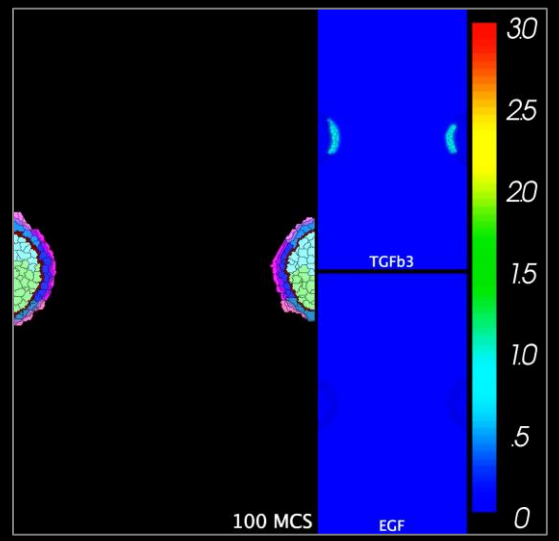


broad bifurcation zone



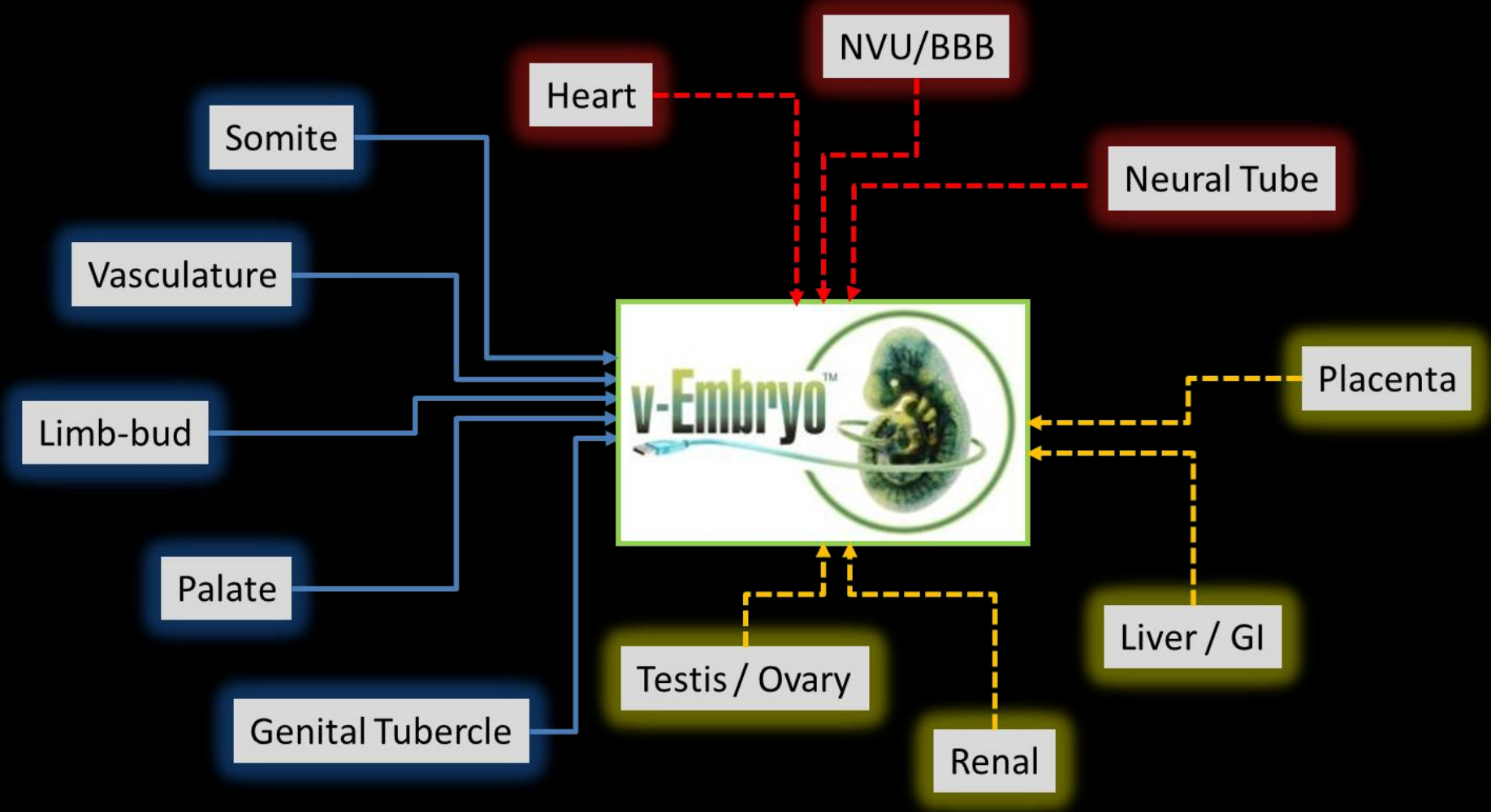






SOURCE: Brophy and Voight (2014) Nature

Grand Challenge: *a predictive virtual embryo - how far must 'computational embryology' advance to predict developmental toxicity in lieu of animal testing?*



Special Thanks

Todd Zurlinden – NCCT
Kate Saili – NCCT
Nancy Baker – Leidos / NCCT
Richard Spencer – ARA / EMVL
Sid Hunter – EPA/NHEERL
Barbara Abbott – EPA/NHEERL
David Belair – EPA/NHEERL
Shane Hutson – Vanderbilt U / STAR
James Glazier – Indiana U / STAR

http://www2.epa.gov/sites/production/files/2015-08/documents/virtual_tissue_models_fact_sheet_final.pdf