Computer Simulation of Developmental Processes and Toxicities

Thomas B. Knudsen, PhD
Developmental Systems Biologist
US EPA, National Center for Computational Toxicology
Chemical Safety for Sustainability Research Program
knudsen.thomas@epa.gov

Scope of the Problem

▶ **Problem:** Too many chemicals (~80K) in production and/or the environment to test each for DevTox by traditional animal-based methods (cost, time, 3Rs).

▶ **HTS profiling:** newer automated high-throughput screening (HTS) assays to efficiently profile chemical-biological interactions in vitro.

▶ **ToxCast:** Stemina's DevTox QuickPredict human stem assay predicts 18% of the 1065 chemicals tested as positive for DevTox (~180 chemicals, 90% BA) [in preparation].

▶ **Challenge:** determinants of teratological outcomes are complex:
  1) nature of exposure
  2) dosimetry
  3) initiating mechanisms
  4) genetic susceptibility
  5) stage vulnerability.

pregnant mother is the exposure unit

placental metabolism & dynamics change during pregnancy

chemicals interact with biological systems wired for change

variation by species (e.g., thalidomide)

embryogenesis is critically dependent on cellular dynamics

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Embryogenesis is an orchestration of complex cell behaviors

EMBRYONIC CELL BEHAVIORS

cell growth & death
differentiation & function
cell motility & adhesion
clocks & organizers
genetic signals & responses
ECM synthesis & remodeling

CONSEQUENCES OF DISRUPTION

incorrect cell number
missing cell types
disorganization
chaos and ataxia
dysregulation
loss of mechanical properties

How can we model this complexity for developmental toxicity?

# Using the new HTS data streams to model DevTox

▶ **<u>Hypothesis:</u>** computer models that recapitulate embryology can be used analytically (to understand) and theoretically (to predict) developmental hazards.

▶ **<u>Approach:</u>** design, development, and implementation of computational models that integrate toxicological data with knowledge of the embryo.

▶ **<u>Application:</u>** 'Virtual Embryo' - a novel way to predictively model the complexity of development for exposure-based hazard assessment.

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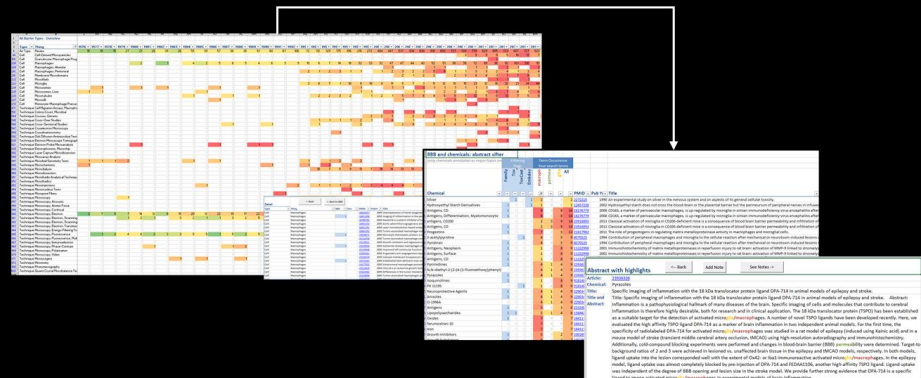
Anatomical homeostasis in a self-regulating Virtual Embryo

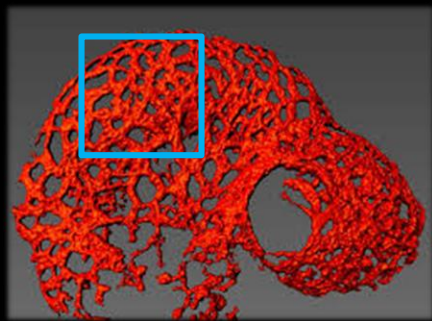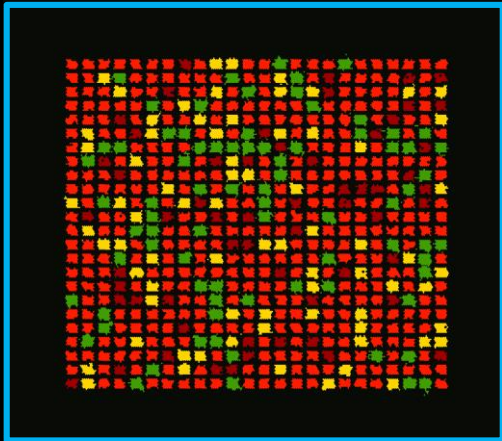*Mouse Morula*
SOURCE: Science Photo Library
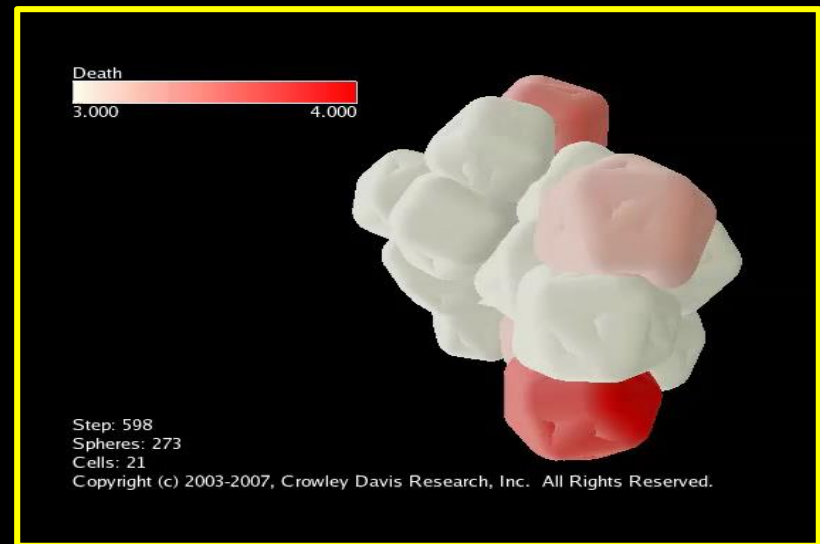
SOURCE: Andersen, Newman and Otter (2006) Am. Assoc. Artif. Intel.

Cellular Agent-Based Model
(angiogenesis)

VEGF165
MMPs
VEGF121
**sFlit1**
TIE2
CXCL10
CCL2

- **Endothelial Stalk**
- **Endothelial Tip**
- **Mural Cell**
- **Inflammatory Cell**

- CompuCell3D modeling environment (Indiana University – J Glazier)

- steppables for distinct cell behaviors (growth, proliferation, apoptosis, differentiation, polarization, motility, ECM, signal secretion, …)

- rules coded in Python for cellular 'agents' that have autonomy as individual models

- agents interact in shared microenvironment and self-organize into emergent phenotypes

- models run differently each time (stochastic) and each run reveals one possible solution

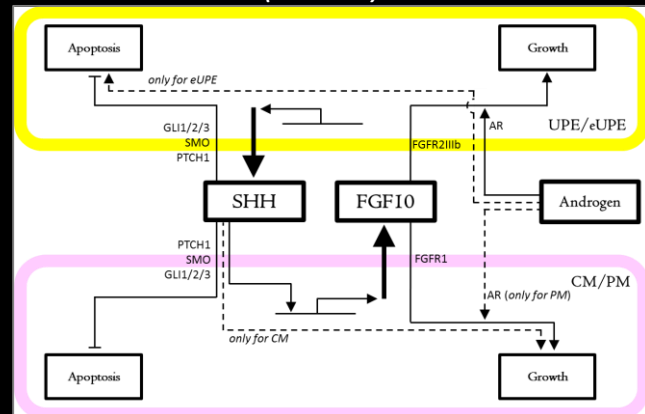# **Virtual Genital Tubercle Development:** urethral closure

Embryonic GT
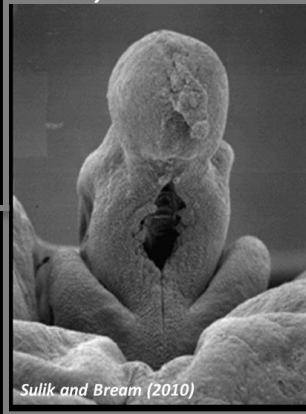
Abstracted GT
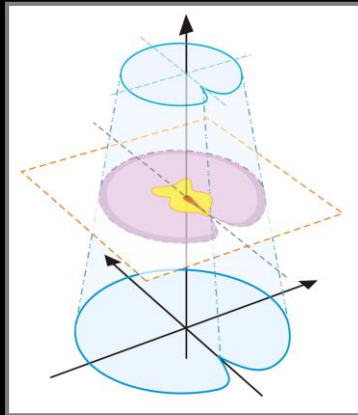
Control Network (mouse)

Sulik and Bream (2010)

ABM simulation for sexual dimorphism (mouse GD13.5 – 17.5)
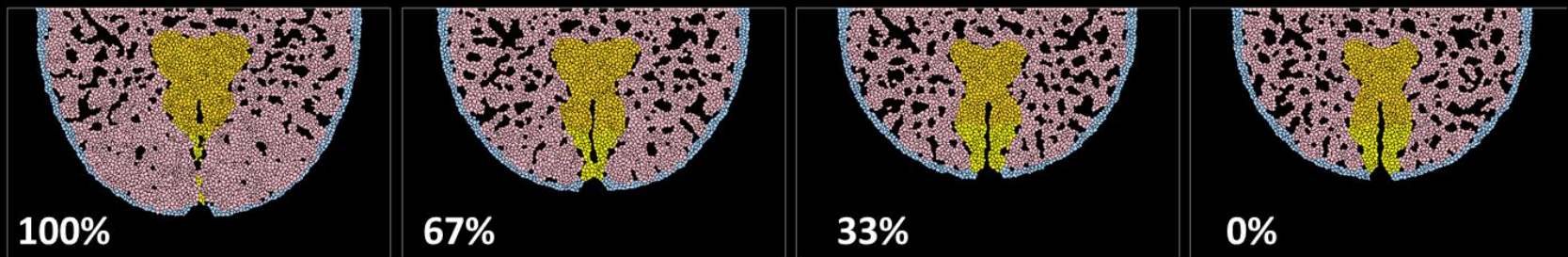

androgen

SHH field
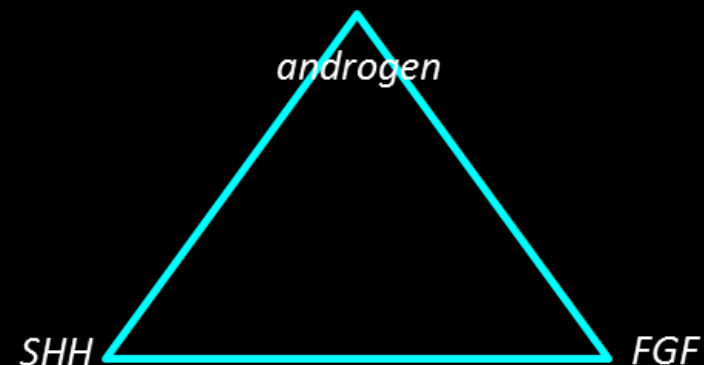
FGF10 field

no androgen

Urethral Closure: complex process disrupted in 'hypospadias'

- Driven by urethral endoderm (contact, fusion apoptosis) and androgen-dependent effects on preputial mesenchyme (proliferation, condensation, migration) via FGFR2-IIIb.
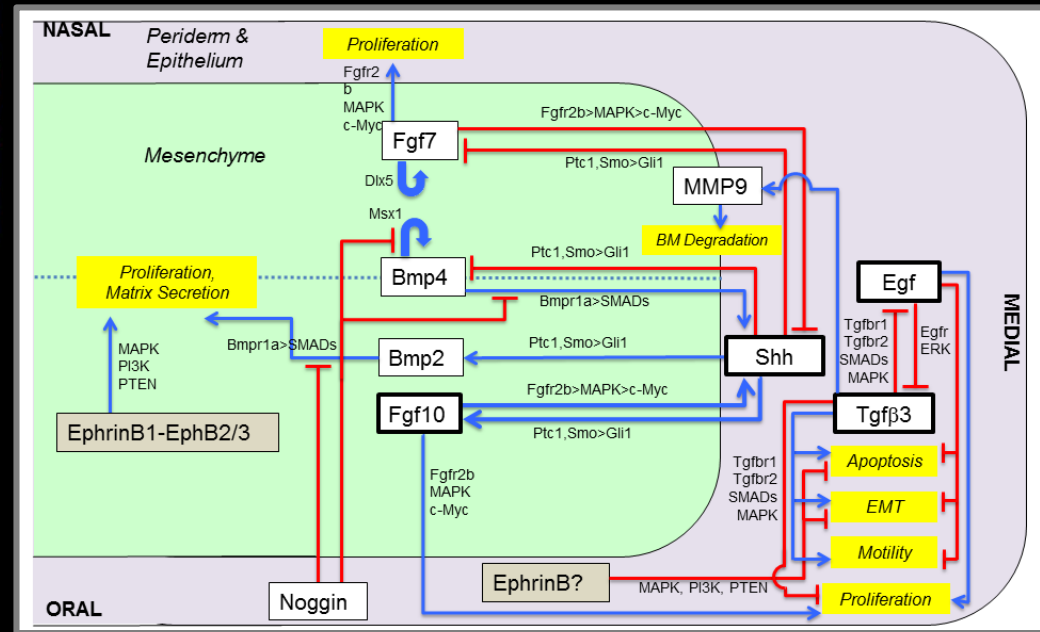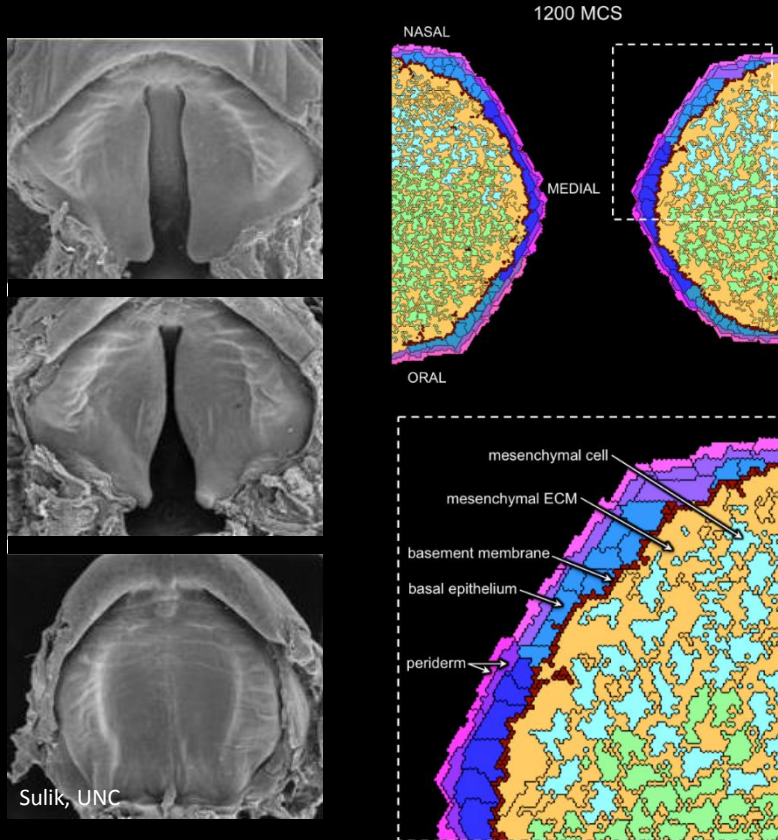

100%   67%   33%   0%

Leung et al. (2016) *Reproductive Toxicology*

Androgenization (n = 10 sims)	Closure Index
100%	0.80
67%	0.57
33%	0.13
0%	0.07

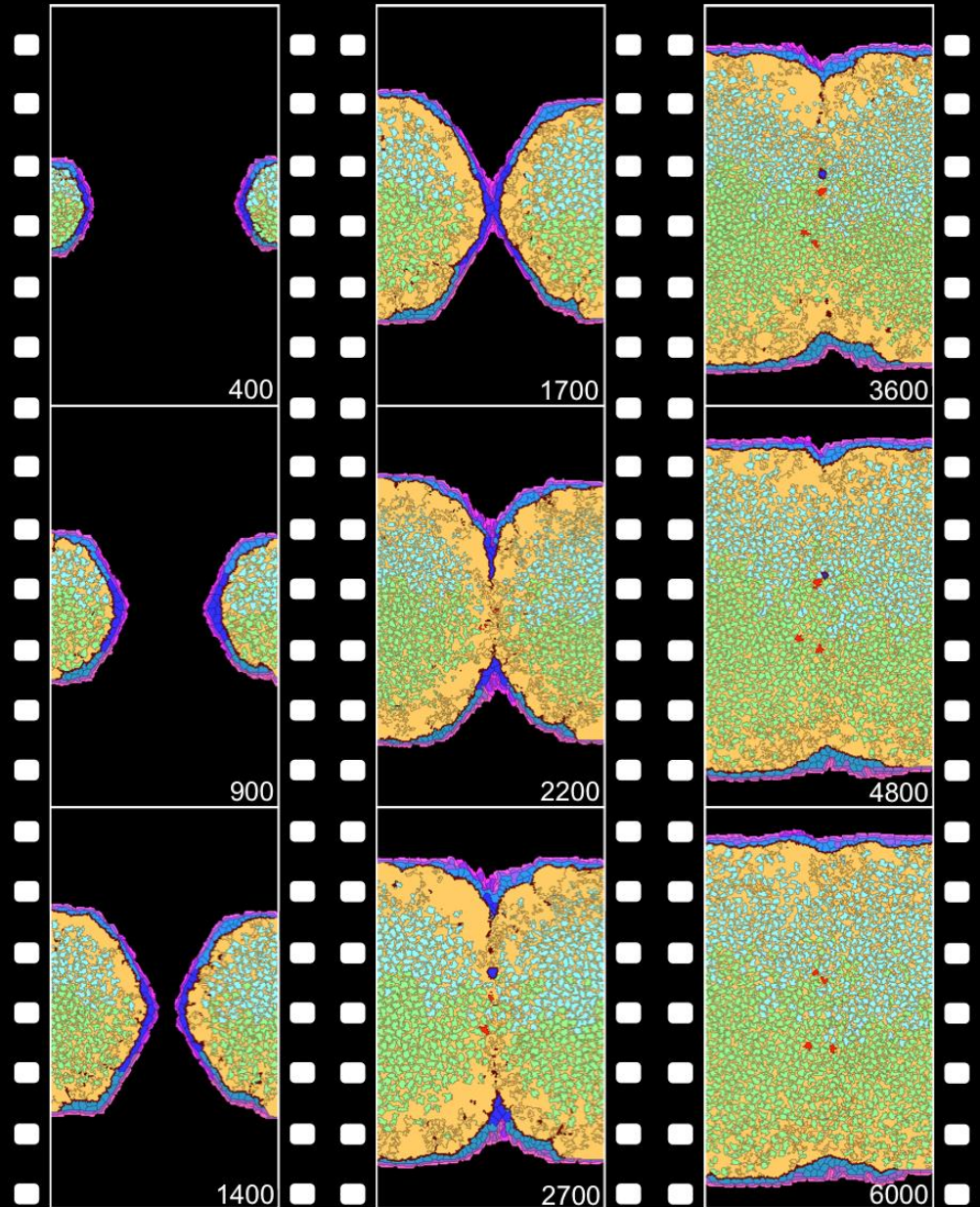androgen

SHH   FGF

Virtual Palate Development: medial edge fusion

Sulik, UNC

Hutson et al. (2016) submitted

SHH FGF10 FGF7

BMP2 BMP4 NOGGIN

100 MCS TGFb3 EGF MMP
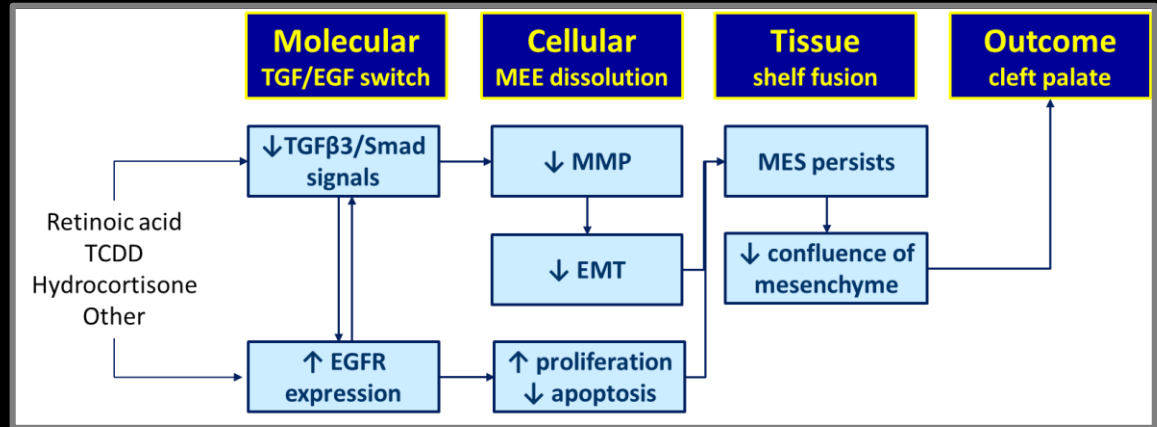
10

ABM for Fusion

Jin and Ding (2006) Development
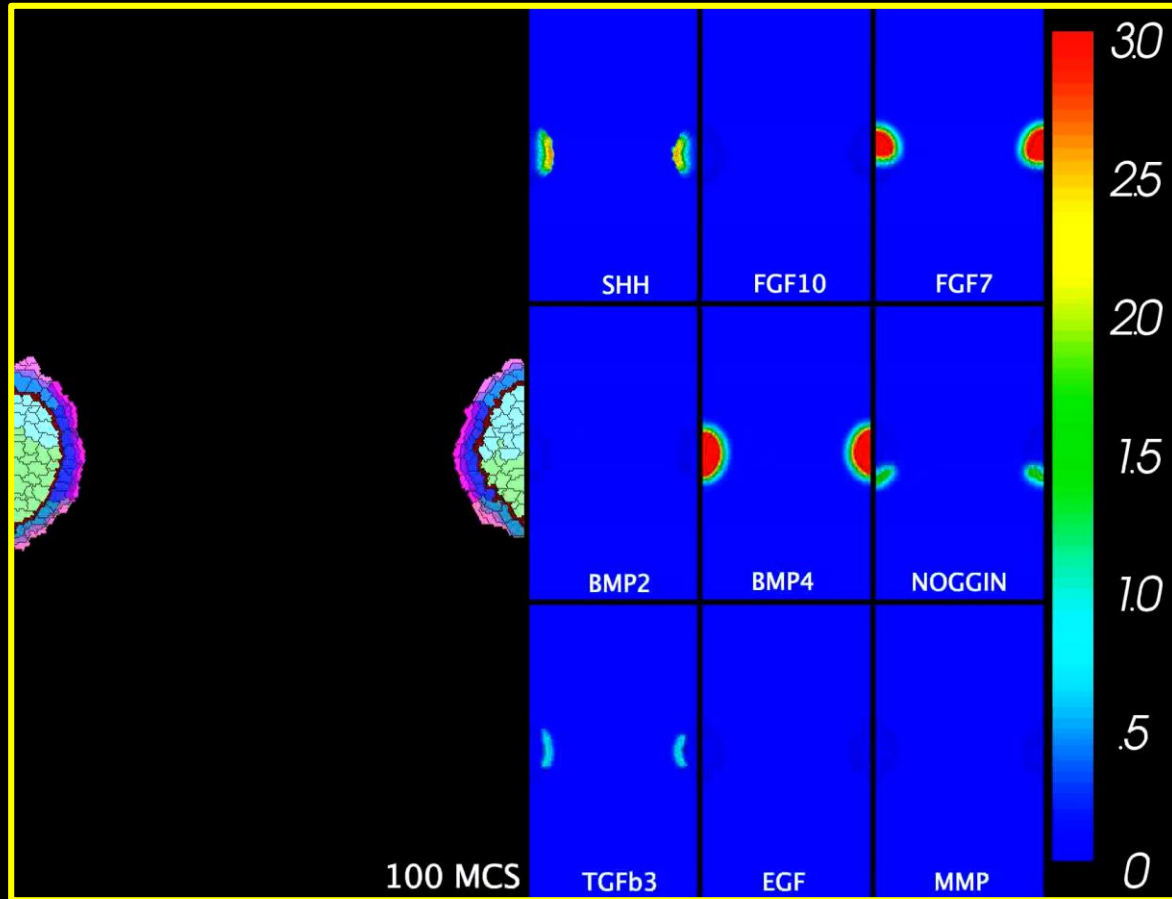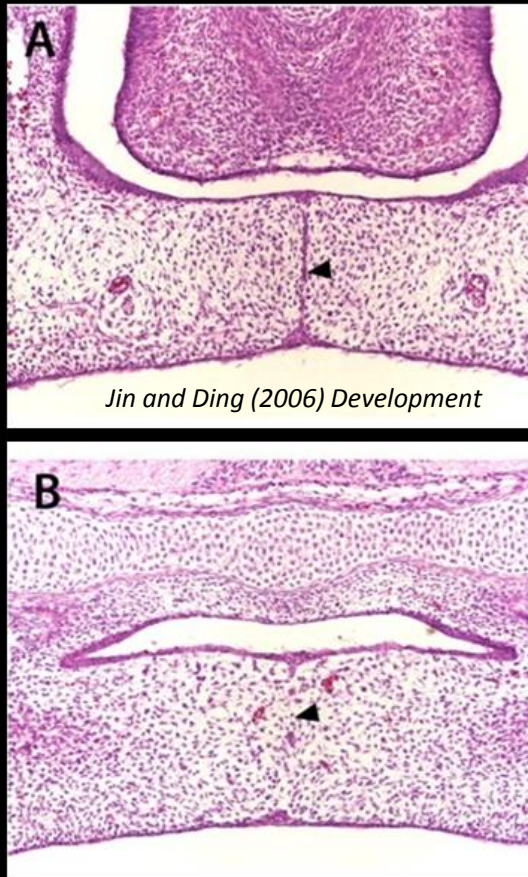
Hacking the Control Network:

in silico knockouts → Cybermorphs

Shh⁻/⁻   Fgf10⁻/⁻   Fgf7⁻/⁻

Bmp2⁻/⁻   Bmp4⁻/⁻   Noggin⁻/⁻

Tgfβ3⁻/⁻   Egf⁻/⁻   Mmp9⁻/⁻

| **Molecular** TGF/EGF switch	**Cellular** MEE dissolution	**Tissue** shelf fusion	**Outcome** cleft palate
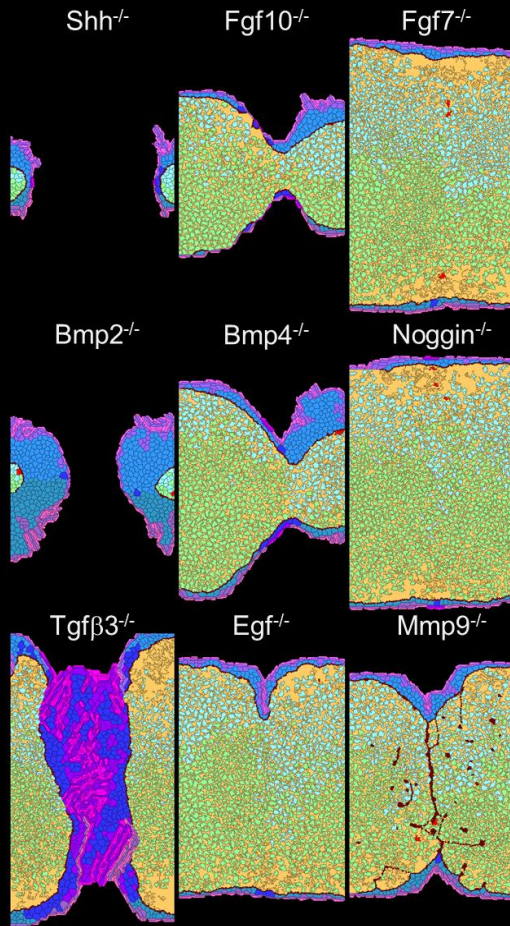
Fusion Switch

- TGFβ3 triggers apoptosis, epithelial-mesenchymal transition, and retraction to break down the midline seam.

- EGF has the opposite effect, maintaining epithelial proliferation and survival.

- ToxCast profiling for 63 cleft palate teratogens pointed to ~10 bioactivity clusters (eg, retinoid, glucocorticoid, GPCR, …).
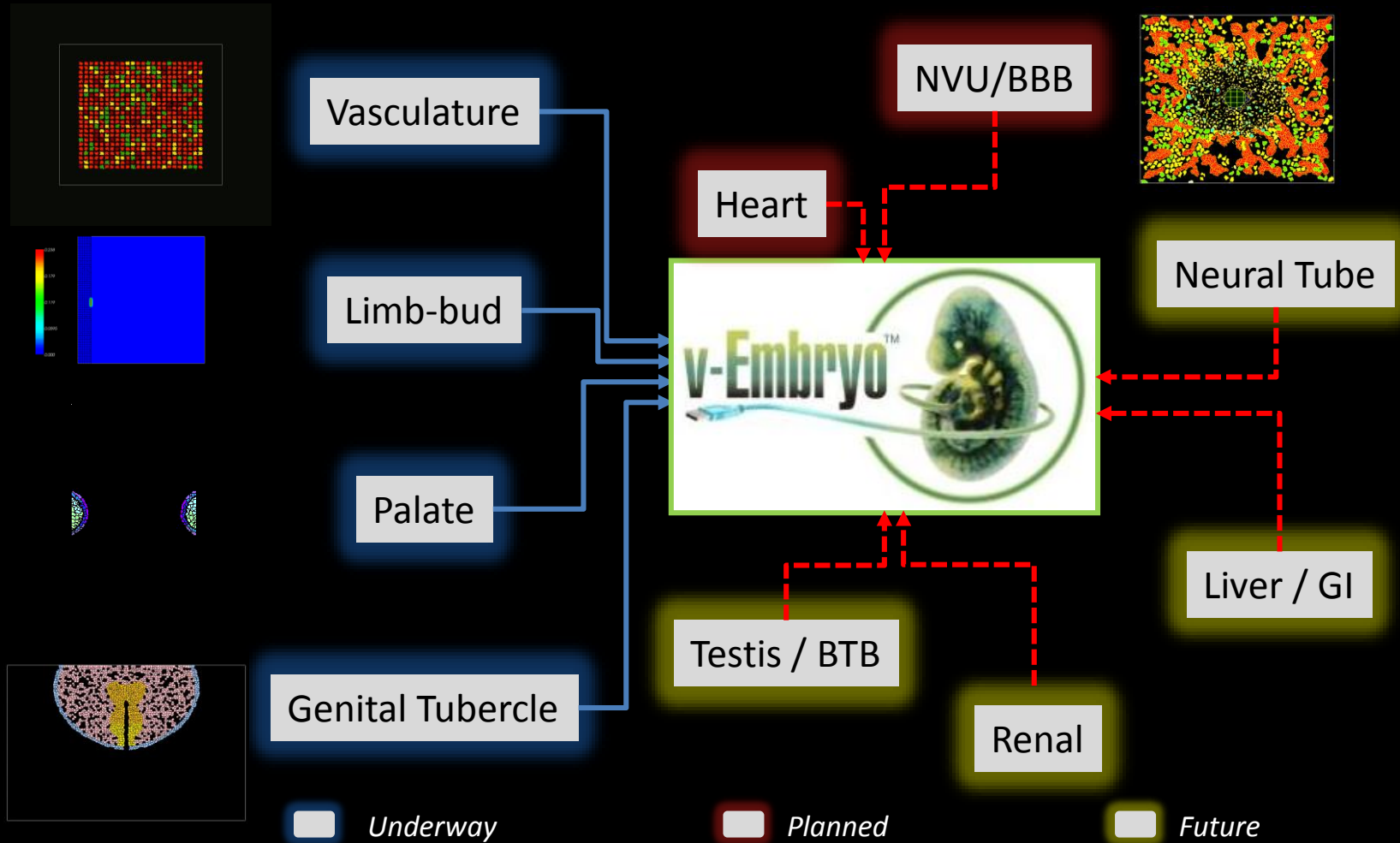
TGF-EGF circuit dynamics:
modeling acute exposure to retinoic acid
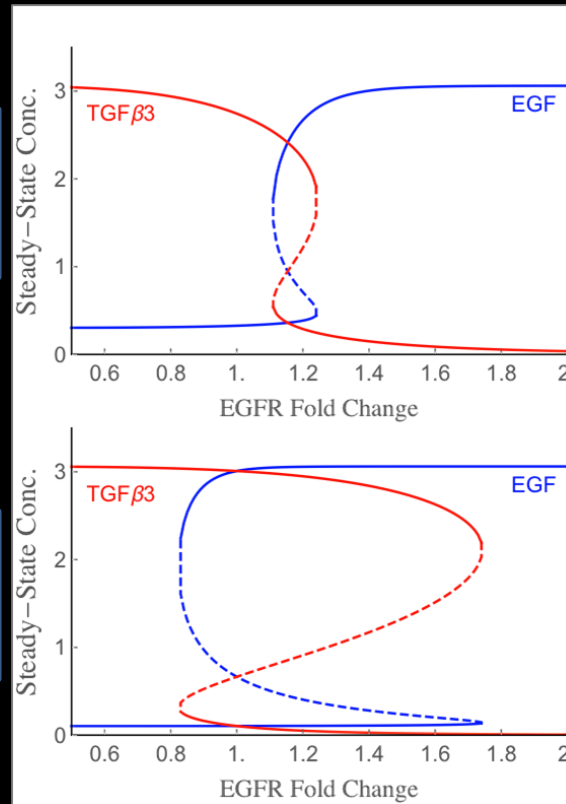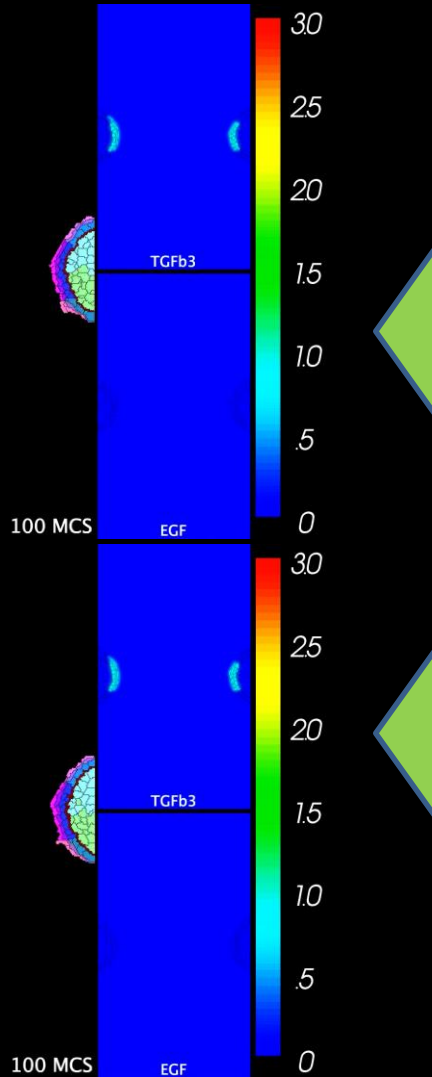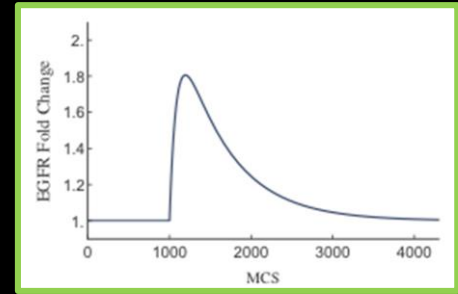
tipping point >1.8x (n=24)
(reversible)

tipping point ~1.5x (n=16)
(non-reversible)

Toward a Virtual Embryo

Vasculature

Limb-bud

Palate

Genital Tubercle

NVU/BBB

Heart

v-Embryo™

Neural Tube

Liver / GI

Testis / BTB

Renal

Underway   *Planned*   *Future*

Special Thanks

- Sid Hunter – NHEERL / ISTD
- Max Leung –
- Nicole Kleinstreuer – NICEATM (NIH / NIEHS)
- Nisha Sipes – NCCT
- Richard Spencer –
- Nancy Baker – Leidos / NCCT
- Tamara Tal – NHEERL / ISTD
- Ed Carney – Dow Chemical Company
- Tuula Heinonen – U Tampere / FICAM
- Jessica Palmer – Stemina Biomarker Discovery
- James Glazier – Indiana U / STAR
- Shane Hutson – Vanderbilt U / STAR
- Kate Saili – NCCT
- Todd Zurlinden – NCCT
- Richard Judson – NCCT
- Imran Shah – NCCT
- RS Thomas – Director, NCCT
- Kevin Crofton – NCCT
- John Cowden – NCCT/CSS
- Tina Bahadori – CSS
- Jill Franzosa - CSS

Integrating biological activity and exposure in the U.S. EPA's ToxCast Program. RS Thomas
S6: Innovations in the Human Health Risk Assessment of Uxmal 6 room, Mon 2:30-4:30

science in ACTION
INNOVATIVE RESEARCH FOR A SUSTAINABLE FUTURE

Virtual Tissue Models: Predicting How Chemicals Impact Human Development

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

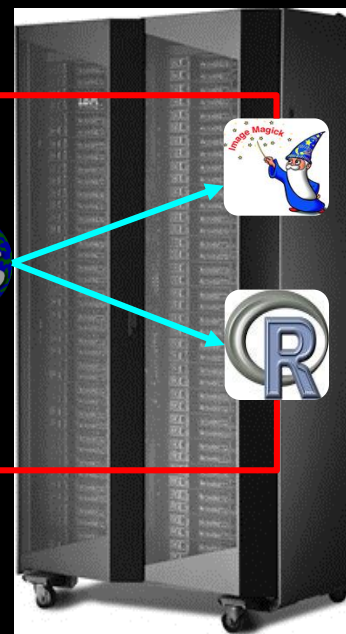National Center for Computational Toxicology

Virtual Tissues Laboratory System

Virtuoso
Web Services and Queries

HPC
Massively-parallel simulation

Video or 3D Results

VTKB
CC3D simulations
ToxCastDB
Bionetworks
Literature mining
Provenance

CC 3D

Data Analysis

BIO 2 RDF